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(73)专利权人 阿迪塞特生物公司
地址 美国加利福尼亚州门洛帕克市
(72)发明人 米拉·彼尔高棉
加利特·丹克贝尔 约拉姆·瑞特
伊兰·贝尔 卡莲·仙尼克
耶尔·特布尔(艾尔巴茨)
耶尔·雪帕贝(塞里)
列乌特·埃雷尔西格尔
雷蒙特·奥伦
德罗尔希姆尔·阿利雪克费斯
(74)专利代理机构 上海翼胜专利商标事务所(普通合伙) 31218
代理人 翟羽
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(54)发明名称

具有高亲和性和优良特异性的类TCR抗体结合域的亲和性实体及其用途

(57)摘要

本发明提供多种具有类T细胞受体(TCRL)结合域的亲和性结合实体及其使用方法。更具体地,所述多个组合物结合HLA-A2/WT1+、HLA-A2/MAGE-A4、HLA-A2/MAGE-A9、HLA-A2/PAP或HLA-A2/TyrD+的细胞,因此可用于诊断和治疗。

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1.一种亲和性结合实体，其特征在于，所述亲和性结合实体能够以人类主要组织兼容性复合体(MHC)限定的方式结合HLA-A2/$TyrD_{369-377}$，其中所述亲和性结合实体包括抗原结合区域，所述抗原结合区域包括多个N端至C端排列的互补性决定区(CDR)序列：

CDR1	重链(HC)	SEQ ID NO: 309	SYGVH
CDR2	HC	SEQ ID NO: 310	VIWAGGTTNYNSALMS
CDR3	HC	SEQ ID NO: 311	DGHFHFDF
CDR1	轻链(LC)	SEQ ID NO: 303	RASDIIYSNLA ；
CDR2	LC	SEQ ID NO: 304	AATNLAA 及
CDR3	LC	SEQ ID NO: 305	QHFWGSSIS

或其中所述亲和性结合实体包括抗原结合区域，所述抗原结合区域包括多个N端至C端排列的互补性决定区(CDR)序列：

CDR1	重链(HC)	SEQ ID NO: 293	TSGMGVS
CDR2	HC	SEQ ID NO: 294	HIYWDDDKRYNPSLKS
CDR3	HC	SEQ ID NO: 295	KDYGSSFYAMHY
CDR1	轻链(LC)	SEQ ID NO: 287	KASQDIHNYIA
CDR2	LC	SEQ ID NO: 288	YTSTLQP 及
CDR3	LC	SEQ ID NO: 289	LQYDNLWT 。

2.如权利要求1的所述亲和性结合实体，其特征在于，所述亲和性结合实体选自于由抗体、嵌合抗原受体(CAR)和T细胞受体(TCR)组成的群组。

3.如权利要求1所述的亲和性结合实体，其特征在于，所述亲和性结合实体是抗体。

4.如权利要求1所述的亲和性结合实体，其特征在于，所述亲和性结合实体是TCR。

5.如权利要求1所述的亲和性结合实体，其特征在于，所述亲和性结合实体是CAR。

6.如权利要求1所述的亲和性结合实体，其特征在于，所述亲和性结合实体是可溶性实体。

7.如权利要求3所述的亲和性结合实体，其特征在于，所述亲和性结合实体是人源化抗体。

8.如权利要求1或3所述的亲和性结合实体，其特征在于，所述亲和性结合实体包含治疗部分。

9.如权利要求1所述的亲和性结合实体，其特征在于，所述亲和性结合实体包括可检测部分。

10.如权利要求2或3所述的亲和性结合实体，其特征在于，所述抗体为单链抗体，双特异性抗体或全长度的抗体。

11.一种分离的多核苷酸，其特征在于，所述多核苷酸包括核酸序列，用以编码如权利要求1至10任一项所述的亲和性结合实体。

12.一种表达载体，其特征在于，所述表达载体包括如权利要求11所述的多核苷酸，所述多核苷酸可操作地连接至顺式作用的调控组件。

13.一种细胞，其特征在于，所述细胞包括如权利要求11所述的多核苷酸，或如权利要求12所述的表达载体。

14.一种药物组合物，其特征在于，所述药物组合物包含如权利要求1至10任一项所述的亲和性结合实体、如权利要求12所述的表达载体，或如权利要求13所述的细胞。

15.一种利用权利要求1至10任一项所述的亲和性结合实体、权利要求12所述的表达载体或权利要求13所述的细胞制备用于治疗黑色素瘤或胶质母细胞瘤的药物的应用。

具有高亲和性和优良特异性的类TCR抗体结合域的亲和性实体及其用途

[0001] 技术领域及背景技术

[0002] 本发明在其一些实施例中有关于多个亲和性结合实体，所述亲和性结合实体包括具有高亲和性和优良特异性的一类TCR抗体结合域及其用途。

[0003] 肿瘤和病毒感染的多个细胞被多个$CD8^+$细胞毒性T细胞识别，作为回应，所述多个$CD8^+$细胞毒性T细胞被活化以消灭这些细胞。为了能被活化，所述克隆型T细胞受体(TCR)需要遇到由所述细胞膜表面的主要组织兼容性复合物(MHC)分子所表现的一特定的胜肽抗原。多个细胞经过恶性转化或病毒感染后表现衍生自多个肿瘤相关抗原或多个病毒蛋白在所述细胞的多个第一类MHC分子上。因此，多个疾病特异性MHC-肽复合物对于多个免疫治疗方法是多个理想的目标。一种这样的方法将多个TCR对于MHC肽复合物的所述独特的优异特异性但低固有亲和性变换成具有对多个肿瘤或病毒表位赋有一类TCR特异性的多个高亲和性可溶性抗体分子。所述多个抗体，称为多个TCR抗体，被开发为一新类别的免疫治疗药物，所述免疫治疗药物能够靶向多个肿瘤和病毒感染的细胞，并且介导它们的特异性杀伤。除了它们的多个治疗能力外，类TCR抗体被开发为针对癌症和多个传染病的多个诊断试剂，以及作为研究第一类MHC抗原的表现的多个有价值的研究工具。

发明内容

[0004] 根据本发明的一些实施例的一个方面，提供了一种亲和性结合实体，所述亲和性结合实体包括一抗原结合区域，所述抗原结合区域包括多个N端至C端排列的互补性决定区(CDR)序列：

[0005]

CDR1	重链(HC)	SEQ ID NO: 309	SYGVH
CDR2	HC	SEQ ID NO: 310	VIWAGGTTNYNSALMS
CDR3	HC	SEQ ID NO: 311	DGHFHFDF
CDR1	轻链(LC)	SEQ ID NO: 303	RASDIIYSNLA
CDR2	LC	SEQ ID NO: 304	AATNLAA
CDR3	LC	SEQ ID NO: 305	QHFWGSSIS

[0006] 所述亲和性结合实体能够以一人类主要组织兼容性复合体(MHC)限定的方式结合HLA-A2/$TyrD_{369-377}$。

[0007] 根据本发明的一些实施例的一个方面，提供了一种亲和性结合实体，所述亲和性结合实体包括一抗原结合区域，所述抗原结合区域包括多个N端至C端排列的互补性决定区(CDR)序列：

[0008]

CDR1	重链(HC)	SEQ ID NO: 293	TSGMGVS
CDR2	HC	SEQ ID NO: 294	HIYWDDDKRYNPSLKS
CDR3	HC	SEQ ID NO: 295	KDYGSSFYAMHY
CDR1	轻链(LC)	SEQ ID NO: 287	KASQDIHNYIA
CDR2	LC	SEQ ID NO: 288	YTSTLQP
CDR3	LC	SEQ ID NO: 289	LQYDNLWT

[0009] 所述亲和性结合实体能够以一MHC限定的方式结合HLA-A2/TyrD$_{369-377}$。

[0010] 根据本发明的一些实施例的一个方面，提供了一种亲和性结合实体，所述亲和性结合实体包括一抗原结合区域，所述抗原结合区域包括多个N端至C端排列的互补性决定区(CDR)序列：

[0011]

CDR1	HC	SEQ ID NO: 325	SYDMS
CDR2	HC	SEQ ID NO: 326	YMSSGGGTYYPDTVKG
CDR3	HC	SEQ ID NO: 327	HDEITNFDY
CDR1	LC	SEQ ID NO: 319	RASQSISNSLH
CDR2	LC	SEQ ID NO: 320	YASQSIS
CDR3	LC	SEQ ID NO: 321	QQSYSWPLT

[0012] 所述亲和性结合实体能够以一MHC限定的方式结合HLA-A2/WT1$_{126-134}$。

[0013] 根据本发明的一些实施例的一个方面，提供了一种亲和性结合实体，其特征在于，所述亲和性结合实体包括一抗原结合区域，所述抗原结合区域包括多个N端至C端排列的互补性决定区(CDR)序列：

[0014]

CDR1	HC	SEQ ID NO: 341	GYWIE
CDR2	HC	SEQ ID NO: 342	EILPGSGGTNYNEKFKG
CDR3	HC	SEQ ID NO: 343	DSNSFTY
CDR1	LC	SEQ ID NO: 335	SVSSSVDYIH
CDR2	LC	SEQ ID NO: 336	STSILAS
CDR3	LC	SEQ ID NO: 337	QQRSSYT

[0015] 所述亲和性结合实体能够以一MHC限定的方式结合HLA-A2/MAGE-A4$_{328-343}$。

[0016] 根据本发明的一些实施例的一个方面，提供了一种亲和性结合实体，所述亲和性结合实体包括一抗原结合区域，所述抗原结合区域包括多个N端至C端排列的互补性决定区(CDR)序列：

[0017]

CDR1	HC	SEQ ID NO: 357	FSSSWMN
CDR2	HC	SEQ ID NO: 358	RIYPGDGDTNYNEKFKG
CDR3	HC	SEQ ID NO: 359	EATTVVAPYYFDY
CDR1	LC	SEQ ID NO: 351	RASENIYRNLA
CDR2	LC	SEQ ID NO: 352	AATNLAD
CDR3	LC	SEQ ID NO: 353	QHFWGTPLT

[0018] 所述亲和性结合实体能够以一MHC限定的方式结合HLA-A2/MAGE-A9$_{344-359}$。

[0019] 根据本发明的一些实施例的一个方面，提供了一种亲和性结合实体，所述亲和性结合实体包括一抗原结合区域，所述抗原结合区域包括多个N端至C端排列的互补性决定区(CDR)序列：

[0020]

CDR1	HC	SEQ ID NO: 373	DYNMD
CDR2	HC	SEQ ID NO: 374	DINPNYDTTTYNQKFKG
CDR3	HC	SEQ ID NO: 375	RNYGNYVGFDF
CDR1	LC	SEQ ID NO: 367	KASQRVNNDVA
CDR2	LC	SEQ ID NO: 368	YASNRYT
CDR3	LC	SEQ ID NO: 369	QQDYSSPFT

[0021] 所述亲和性结合实体能够以一MHC限定的方式结合HLA-A2/PAP$_{360-375}$。

[0022] 根据本发明的一些实施例，所述亲和性结合实体选自于由一抗体、一嵌合抗原受

体(CAR)和一T细胞受体(TCR)组成的群组。

[0023] 根据本发明的一些实施例,所述亲和性结合实体是一抗体。

[0024] 根据本发明的一些实施例,所述亲和性结合实体是一TCR。

[0025] 根据本发明的一些实施例,所述亲和性结合实体是一CAR。

[0026] 根据本发明的一些实施例,所述亲和性结合实体是一可溶性实体。

[0027] 根据本发明的一些实施例,所述亲和性结合实体是一人源化抗体。

[0028] 根据本发明的一些实施例,所述亲和性结合实体包含一治疗部分。

[0029] 根据本发明的一些实施例,所述亲和性结合实体包括一可检测部分。

[0030] 根据本发明的一些实施例,所述抗体为一单链抗体,一双特异性抗体或一全长度的抗体。

[0031] 根据本发明的一些实施例的一个方面,提供了一种分离的多核苷酸,所述多核苷酸包括一核酸序列,用以编码所述亲和性结合实体。

[0032] 根据本发明的一些实施例的一个方面,提供了一种表达载体,所述多核苷酸可操作地连接至一顺式作用的调控组件。

[0033] 根据本发明的一些实施例的一个方面,提供了一种细胞,所述细胞包括所述多核苷酸,或所述表达载体。

[0034] 根据本发明的一些实施例的一个方面,提供了一种药物组合物,所述药物组合物包含所述亲和性结合实体、所述载体,或所述细胞。

[0035] 根据本发明的一些实施例的一个方面,提供了一种检测一癌细胞的方法,所述方法包括:在允许免疫复合物形成的条件下,使所述抗体与所述细胞接触,其中所述免疫复合物的存在或所述免疫复合物的一水平用以指示出所述癌细胞。

[0036] 根据本发明的一些实施例的一个方面,提供了一种在需要检测和治疗癌症的一主体中检测和治疗癌症的方法,其特征在于,所述方法包括:

[0037] (a)根据所述方法侦测所述主体中多个癌细胞的存在;

[0038] (b)当侦测到多个癌细胞时,判断所述主体具有癌症;及

[0039] (c)给予所述主体一抗癌疗法。

[0040] 根据本发明的一些实施例的一个方面,提供了一种在需要检测和治疗癌症的一主体中检测和治疗癌症的方法,所述方法包括:在允许免疫复合物形成的条件下,使所述主体的一细胞与所述抗体接触,其中所述免疫复合物的存在或所述免疫复合物的一水平用以指示出所述癌症。

[0041] 根据本发明的一些实施例,所述细胞是一皮肤细胞。

[0042] 根据本发明的一些实施例的一个方面,提供了一种治疗癌症的方法,所述方法包括:给予有需要的一主体一治疗有效数量的所述亲和性结合实体、所述载体或所述细胞,从而治疗癌症。

[0043] 根据本发明的一些实施例的一个方面,提供了一种用以制备治疗癌症的药物的应用,所述应用使用所述亲和性结合实体、所述载体或所述细胞。

[0044] 根据本发明的一些实施例,所述亲和性结合实体用于TyrD时,所述癌症选自于由黑色素瘤和胶质母细胞瘤所组成的群组。

[0045] 根据本发明的一些实施例,所述亲和性结合实体用于威尔姆氏肿瘤蛋白1(WT1)

时，所述癌症选自于由慢性髓细胞性白血病、多发性骨髓瘤(MM)、急性淋巴细胞性白血病(ALL)、急性骨髓/骨髓性白血病(AML)、骨髓发育异常综合症(MDS)、间皮瘤、卵巢癌、胃肠癌，例如结肠直肠癌腺癌、甲状腺癌、乳腺癌、肺癌(例如非小细胞肺癌)、黑色素瘤、骨肉瘤、子宫内膜癌、前列腺癌和胶质瘤。

[0046] 根据本发明的一些实施例，所述亲和性结合实体用于黑色素瘤相关抗原4(MAGE-A4)时，所述癌症选自黑色素瘤、卵巢癌、T细胞白血病/淋巴瘤(例如ATLL)、睾丸癌、头颈癌、膀胱癌及食道癌。

[0047] 根据本发明的一些实施例，所述亲和性结合实体用于黑色素瘤相关抗原9(MAGE-A9)时，所述癌症选自于由肾细胞癌、膀胱癌、乳腺癌及肝细胞癌所组成的群组。

[0048] 根据本发明的一些实施例，所述亲和性结合实体用于前列腺性酸性磷酸酶(PAP)时，所述癌症选自于由前列腺癌所组成的群组。

[0049] 除非另加说明，否则本文所使用的所有技术术语和/科学术语都具有与本发明所属领域的普通技术人员通常所理解的相同的含意。虽然本发明的实施例可以通过类似或等同于本发明的实施例所述的任何方法和物质实施或测试，本发明的实施例、列举的方法和/或物质已在下面描述。在冲突的情况下，将以本专利说明书包括定义以控制。此外，物质、方法和实施例仅是举例性质，并且不必然用以限制。

附图说明

[0050] 在此描述的本发明的一些实施例仅通过举例的方式并参考附图描述，通过详细说明附图具体的参考资料，应当强调所示的细节仅为举例，用以说明本发明实施例的目的。基于这点，结合所述附图及描述使对本领域技术人员能清楚的实施本发明的实施例。

[0051] 在附图中：

[0052] 图1：靶向多个HLA-A2/酪氨酸酶复合物的类TCR抗体的表面结合亲和性测定。所述多个纯化的IgG通过抗小鼠或人类的IgG间接地固定在所述表面等离子共振(SPR)的传感芯片上。分析物是由大肠杆菌表达的多个scHLA-A2复合物的体外重新折叠所产生的多个纯化的重组单链HLA-A2/酪氨酸酶复合物。

[0053] 图2：通过丙氨酸扫描对于多个类TCR抗体的表位特异性测定。所述酪氨酸酶胜肽序列的多个位置1、2、3、4、5、6、7和8被取代为丙氨酸，所述多个丙氨酸(Ala)突变胜肽被合成，并且以一浓度的10^{-4}至10^{-5}摩尔浓度加至多个T2细胞抗原呈现细胞(APC)中在37℃中12小时。通过流式细胞技术取得在一浓度的10微克/毫升的类TCR抗体下的结合，以及测量通过平均荧光强度所测量的结合强度，并且与野生型(WT)的天然酪氨酸酶胜肽的所述结合强度进行比较。每个Ala取代的位置的所述相对影响被评估为WT胜肽的所述结合的百分比。

[0054] 图3：多个类TCR抗体D11和D7与加有酪氨酸酶胜肽的多个T2APC以及多个对照组HLA-A2限定胜肽的结合。多个T2细胞被加入一浓度的10^{-4}至10^{-5}摩尔浓度的酪氨酸酶胜肽以及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用巯基化藻红蛋白(PE)标记的二级抗小鼠IgG所监测。单克隆抗体(MAb)BB7.2被用来监测HLA-A2的表达，以平均荧光强度(MFI)表示。

[0055] 图4：多个类TCR抗体D11和D7与加有酪氨酸酶胜肽以及多个对照组HLA-A2限定胜肽的多个T2APC的结合。多个T2细胞被加入一浓度的10^{-4}至10^{-5}摩尔浓度的酪氨酸酶胜肽以

及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG所监测。MAb BB7.2被用来监测HLA-A2的表达，以平均荧光强度(MFI)表示。

[0056] 图5：类TCR抗体D11与加有酪氨酸酶胜肽以及多个对照组HLA-A2限定胜肽的多个T2APC的结合。多个T2细胞被加入一浓度的10^{-4}至10^{-5}摩尔浓度的酪氨酸酶胜肽以及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG所监测。MAb BB7.2被用来监测HLA-A2的表达，以平均荧光强度(MFI)表示。

[0057] 图6：类TCR抗体D7与加有酪氨酸酶胜肽以及多个对照组HLA-A2限定胜肽的多个T2APC的结合。多个T2细胞被加入一浓度的10^{-4}至10^{-5}摩尔浓度的酪氨酸酶胜肽以及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG所监测。MAb BB7.2被用来监测HLA-A2的表达，以平均荧光强度(MFI)表示。

[0058] 图7：类TCR抗体MC1与加有酪氨酸酶胜肽以及多个对照组HLA-A2限定胜肽的多个T2APC的结合。多个T2细胞被加入一浓度的10^{-4}至10^{-5}摩尔浓度的酪氨酸酶胜肽以及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG所监测。MAb BB7.2被用来监测HLA-A2的表达，以平均荧光强度(MFI)表示。

[0059] 图8：类TCR抗体MC1与表达HLA-A2和酪氨酸酶的黑色素瘤细胞的结合。通过流式细胞技术利用二级PE标记的抗人类IgG监测多个黑色素瘤细胞与类TCR抗体MC1的结合。MAb BB7.2被用来监测HLA-A2的表达，以平均荧光强度(MFI)表示。

[0060] 图9：类TCR抗体MC1与HLA-A2+以及酪氨酸酶呈阳性或阴性的多个细胞的结合。通过流式细胞技术利用二级PE标记的抗人类IgG监测表达HLA-A2以及酪氨酸酶呈阳性或阴性的多个肿瘤细胞与类TCR抗体MC1的结合。MAb BB7.2被用来监测HLA-A2的表达，以平均荧光强度(MFI)表示。

[0061] 图10：多个类TCR抗体D11和D7与HLA-A2+以及酪氨酸酶呈阳性或阴性的多个细胞的结合。通过流式细胞技术利用二级PE标记的抗小鼠IgG监测表达HLA-A2以及酪氨酸酶呈阳性或阴性的多个肿瘤细胞与类TCR抗体MC1的结合。MAb BB7.2被用来监测HLA-A2的表达，以平均荧光强度(MFI)表示。

[0062] 图11：多个类TCR抗体D11和D7与HLA-A2+以及酪氨酸酶呈阴性的多个细胞的结合。通过流式细胞技术利用二级PE标记的抗小鼠IgG监测表达HLA-A2以及酪氨酸酶呈阴性的多个肿瘤细胞与类TCR抗体MC1的结合。MAb BB7.2被用来监测HLA-A2的表达，以平均荧光强度(MFI)表示。

[0063] 图12：多个类TCR抗体D11和D7和MC1与HLA-A2+以及酪氨酸酶呈阳性或阴性的多个细胞的多个对比性结合。通过流式细胞技术利用二级PE标记的抗小鼠IgG监测表达HLA-A2以及酪氨酸酶呈阳性或阴性的多个肿瘤细胞与类TCR抗体D11、D7以及MC1的结合。

[0064] 图13：类TCR抗体D11与HLA-A2+/酪氨酸酶呈阴性的多个正常原代细胞的结合。多个正常原代细胞的组织学来源如标示，通过流式细胞技术利用二级PE标记的抗小鼠IgG监测表达HLA-A2以及酪氨酸酶呈阴性的多个肿瘤细胞与类TCR抗体D11的结合。MAb BB7.2被用来监测HLA-A2的表达。

[0065] 图14：类TCR抗体D11与HLA-A26/酪氨酸酶呈阴性的多个正常原代细胞的结合。多个正常原代细胞的组织学来源如标示，通过流式细胞技术利用二级PE标记的抗小鼠IgG监测表达HLA-A2以及酪氨酸酶呈阴性的多个肿瘤细胞与类TCR抗体D11的结合。

[0066] 图15:类TCR抗体D7与HLA-A2+/酪氨酸酶呈阴性的多个正常原代细胞的结合。多个正常原代细胞的组织学来源如标示,通过流式细胞技术利用二级PE标记的抗小鼠IgG监测表达HLA-A2以及酪氨酸酶呈阴性的多个肿瘤细胞与类TCR抗体D7的结合。

[0067] 图16:BB7.2与多个正常原代细胞的结合。多个正常原代细胞的组织学来源如标示,通过流式细胞技术利用MAb BB7.2及二级PE标记的抗小鼠IgG监测多个正常原代细胞的组织学来源的HLA-A2的表达。

[0068] 图17:多个类TCR抗体MC1,D11及D7与多个正常外周血单个核细胞(PBMCs)的结合。通过PCR鉴定PBMCs的HLA-A2同源或杂合性的特性。利用二级PE标记的抗小鼠IgG监测多个类TCR抗体的结合。

[0069] 图18:类TCR抗体D11的选择性的总结。通过利用PE标记的抗小鼠IgG监测HLA-A2+抗原呈阳性以及阴性的多个细胞与类TCR抗体D11的结合。+/-表示通过PCR所测量的酪氨酸酶的信使核糖核酸(mRNA)的基因表达。MAb BB7.2被用来监测HLA-A2的表达。

[0070] 图19:类TCR抗体D7选择性的总结。通过利用PE标记的抗小鼠IgG监测HLA-A2+抗原呈阳性以及阴性的多个细胞与类TCR抗体D7的结合。+/-表示通过PCR测得的酪氨酸酶mRNA的基因表达。MAb BB7.2被用来监测HLA-A2的表达。

[0071] 图20:多个类TCR抗体MC1,D11及D7与加有酪氨酸酶胜肽以及相似于酪氨酸酶的多个HLA-A2限定胜肽的多个T2APC结合。多个T2细胞被加入一浓度的10^{-4}摩尔浓度的酪氨酸酶胜肽以及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG所监测。

[0072] 图21:类TCR抗体D11与加有多个相似于酪氨酸酶胜肽的多个HLA-A2限定胜肽的多个T2APC结合。多个T2细胞被加入一浓度的10^{-5}摩尔浓度的酪氨酸酶胜肽以及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG所监测。MAb BB7.2的结合确保胜肽的加入效率的测量。

[0073] 图22:类TCR抗体D11与多个加有相似于酪氨酸酶胜肽的多个HLA-A2限定胜肽的多个T2APC结合。多个T2细胞被加入一浓度的10^{-5}摩尔浓度的酪氨酸酶胜肽以及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG所监测。MAb BB7.2的结合确保胜肽的加入效率的测量。

[0074] 图23:类TCR抗体D11与加有多个相似于酪氨酸酶胜肽的多个HLA-A2限定胜肽的多个T2APC结合。多个T2细胞被加入一浓度的10^{-5}摩尔浓度的酪氨酸酶胜肽以及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG所监测。MAb BB7.2的结合确保胜肽的加入效率的测量。

[0075] 图24:类TCR抗体D11与加有相似于酪氨酸酶的多个HLA-A2限定胜肽的多个T2APC结合。多个T2细胞被加入一浓度的10^{-5}摩尔浓度的酪氨酸酶胜肽以及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG所监测。MAb BB7.2的结合确保胜肽的加入效率的测量。

[0076] 图25:类TCR抗体D7与加有相似于酪氨酸酶的多个HLA-A2限定胜肽的多个T2APC结合。多个T2细胞被加入一浓度的10^{-5}摩尔浓度的酪氨酸酶胜肽以及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG所监测。MAb BB7.2的结合确保胜肽的加入效率的测量。

[0077] 图26:类TCR抗体D7与加有相似于酪氨酸酶的多个HLA-A2限定胜肽的多个T2APC结合。多个T2细胞被加入一浓度的10^{-5}摩尔浓度的酪氨酸酶胜肽以及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG所监测。MAb BB7.2的结合确保胜肽的加入效率的测量。

[0078] 图27:类TCR抗体D7与加有相似于酪氨酸酶的多个HLA-A2限定胜肽的多个T2APC结合。多个T2细胞被加入一浓度的10^{-5}摩尔浓度的酪氨酸酶胜肽以及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG所监测。MAb BB7.2的结合确保胜肽的加入效率的测量。

[0079] 图28:类TCR抗体D7与丙氨酸扫描后所辨识的加有相似于酪氨酸酶的多个HLA-A2限定胜肽的多个T2APC结合。多个T2细胞加入一浓度的10^{-5}摩尔浓度的酪氨酸酶胜肽以及多个所标示的胜肽在37℃中12小时,所述酪氨酸酶胜肽以及多个所标示的胜肽是根据D7的表位识别特异性从多个Ala突变胜肽中所筛选的。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG所监测。MAb BB7.2的结合确保胜肽的加入效率的测量。

[0080] 图29:靶向多个HLA-A2/WT1复合物的类TCR抗体B47B6的表面结合亲和性测定。多个纯化的IgG通过抗小鼠或人类的IgG间接地固定在所述表面等离子共振(SPR)的传感芯片上。分析物是由大肠杆菌表达的多个scHLA-A2复合物的体外重新折叠所产生的多个纯化的重组单链HLA-A2/WT1复合物。

[0081] 图30:多个类TCR抗体B47和ESK1与加有WT1HLA-A2限定胜肽的多个T2APC的结合。多个T2细胞被加入一浓度的10^{-4}至10^{-5}摩尔浓度的酪氨酸酶胜肽以及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用PE标记的抗小鼠IgG(用于B47)或人类IgG(用于ESK1)所监测。MAb BB7.2被用来监测HLA-A2的表达,以平均荧光强度(MFI)表示。

[0082] 图31:多个类TCR抗体B47和ESK1与加有WT1胜肽以及多个对照组HLA-A2限定胜肽的多个T2APC的结合。多个T2细胞被加入一浓度的10^{-4}摩尔浓度的WT1胜肽以及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG(用于B47)或人类IgG(用于ESK1)所监测。MAb BB7.2被用来监测HLA-A2的表达,以平均荧光强度(MFI)表示。

[0083] 图32:多个类TCR抗体B47和ESK1与加有多个相似于WT1胜肽的HLA-A2限定胜肽的多个T2APC的结合。多个T2细胞被加入一浓度的10^{-4}至10^{-5}摩尔浓度的WT1胜肽以及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG(用于B47)或人类IgG(用于ESK1)所监测。MAb BB7.2的结合确保胜肽的加入效率的测量。

[0084] 图33:类TCR抗体B47与加有WT1胜肽或多个对照组HLA-A2限定胜肽的T2APCs的结合。多个T2细胞被加入一浓度的10^{-4}摩尔浓度的WT1胜肽以及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG所监测。MAb BB7.2的结合确保胜肽的加入效率的测量。

[0085] 图34:类TCR抗体B47与加有相似于WT1胜肽的HLA-A2限定胜肽的多个T2APC的结合。多个T2细胞被加入一浓度的10^{-4}至10^{-5}摩尔浓度的WT1胜肽以及多个所标示的胜肽在37℃中12小时。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG(用于B47)或人类IgG(用于ESK1)所监测。MAb BB7.2的结合确保胜肽的加入效率的测量。

[0086] 图35:多个类TCR抗体B47和ESK1与表达或不表达WT1的HLA-A2呈阳性的多个细胞

的结合。结合是通过流式细胞技术利用二级PE标记的抗小鼠IgG(用于B47)或人类IgG(用于ESK1)所监测。MAb BB7.2被用来监测HLA-A2的表达。

[0087] 图36:类TCR抗体B47的选择性的总结。通过利用PE标记的抗小鼠IgG监测HLA-A2+抗原呈阳性以及阴性的多个细胞与类TCR抗体B47的结合。+/-表示通过PCR测得的WT1mRNA的基因表达。MAb BB7.2被用来监测HLA-A2的表达。

[0088] 图37:通过丙氨酸扫描对于多个类TCR抗体的表位特异性测定。所述WT1胜肽序列的多个位置1、3、4、5、7和8被取代为丙氨酸,所述多个丙氨酸(Ala)突变胜肽被合成,并且加至多个抗原呈现细胞(APC)中。通过流式细胞技术取得类TCR抗体ESK1的结合,以及测量通过平均荧光强度所测量的结合强度,并且与野生型(WT)的天然WT1胜肽的所述结合强度进行比较。每个Ala取代的位置的所述相对影响被评估为WT胜肽的所述结合的百分比。数据来自Dao等人《科学转化医学》5:176ra33(2013)。

[0089] 图38:多个类TCR抗体D11、D7和生物素化的MC1与加有酪氨酸酶胜肽以及相似于酪氨酸酶的多个HLA-A2限定胜肽的多个T2APC的结合,S17至S23为丙氨酸为基础的多个相似性胜肽。多个T2细胞被加入一浓度的10^{-5}摩尔浓度的酪氨酸酶胜肽以及多个所标示的胜肽在37℃中12小时。多个细胞被在一浓度的10微克/毫升的多个类T细胞受体(TCRL)抗体染色后接着利用二级PE标记的链霉亲和素/抗小鼠IgG,并且通过流式细胞技术分析,以平均荧光强度(MFI)表示。

[0090] 图39:多个类TCR抗体D11、D7和MC1与加有酪氨酸酶胜肽以及相似于酪氨酸酶的多个HLA-A2限定胜肽的多个T2APC的结合,KIAA0355、S7、S17至S23为丙氨酸为基础的多个相似性胜肽。多个T2细胞被加入一浓度的10^{-5}摩尔浓度的酪氨酸酶胜肽以及多个所标示的胜肽在37℃中12小时。多个细胞被一浓度的10微克/毫升的多个TCRL抗体染色后接着利用二级PE标记的链霉亲和素/抗小鼠IgG,并且通过流式细胞技术分析,以平均荧光强度(MFI)表示。

[0091] 图40A至C:多个类TCR抗体D11(图40A),D7(图40B)和生物素化的MC1(图40C)与HLA-A2+,酪氨酸酶抗原呈阳性或阴性的细胞的结合。通过qPCR对表达HLA-A2的多个肿瘤和正常原代细胞测试酪氨酸酶mRNA的表达。多个肿瘤细胞被一浓度的10微克/毫升的多个TCRL抗体染色后接着利用二级PE标记的链霉亲和素/抗小鼠IgG,并且通过流式细胞技术分析,以平均荧光强度(MFI)表示。

[0092] 图41:由具有一个抗CD-3臂及一个D11臂的双特异性(BS)TCRL对于HLA-A2+/酪氨酸酶+(阳性)以及HLA-A2+/酪氨酸酶-(阴性)的多个细胞株的杀灭,所述TCRL称为Tyr D11BS TCRL。将Tyr D11BS TCRL与黑色素瘤HLA-A2+/酪氨酸酶+的多个细胞以及HLA-A2+/酪氨酸酶-的对照组肿瘤细胞培养在一起,多个细胞与所述Tyr D11BS TCRL以及从多个健康个体中分离的多个未活化(naïve)PBMC以10:1E:T的比率(10:1效应物:标靶的比率)培养24小时,通过乳酸脱氢酶(LDH)释放测试测定细胞毒性。

[0093] 图42:由Tyr D11对于HLA-A2+/酪氨酸酶-的多个正常原代细胞的杀灭,将BS D11与作为对照组的黑色素瘤HLA-A2+/酪氨酸酶+的多个细胞以及HLA-A2+/酪氨酸酶-的多个正常原代细胞细胞培养在一起,多个细胞与所述Tyr D11BS TCRL以及从多个健康个体中分离的多个未活化PBMC以10:1E:T的比率(10:1效应物:标靶的比率)培养24小时。

[0094] 图43:由Tyr D7BS TCRL对于HLA-A2+/酪氨酸酶+以及HLA-A2+/酪氨酸酶-的多个

细胞株的杀灭，将D7BS与黑色素瘤HLA-A2+/酪氨酸酶+的多个细胞以及HLA-A2+/酪氨酸酶-的多个对照组肿瘤细胞培养在一起，多个细胞与所述Tyr D7BS以及从多个健康个体中分离的多个未活化PBMC以10:1E:T的比率(10:1效应物:标靶的比率)培养24小时。

[0095] 图44：由D7BS对于HLA-A2+/酪氨酸酶-的多个正常原代细胞的杀灭，将D7BS与作为对照组的黑色素瘤HLA-A2+/酪氨酸酶+的多个细胞以及HLA-A2+/酪氨酸酶-的多个正常原代细胞细胞培养在一起，多个细胞与所述Tyr D11BS TCRL以及从健康个体中分离多个的多个未活化PBMC以10:1E:T的比率(10:1效应物:标靶的比率)培养24小时。

[0096] 图45显示了D7BS在预防NOD/SCID小鼠中的S.C.501A黑色素瘤的肿瘤形成的体内功效。

[0097] 图46：多个类TCR抗体生物素化ESK1和B47B6与加有WT1胜肽以及多个其它HLA-A2限定胜肽的多个T2APC的结合。多个T2细胞被加入一浓度的10^{-5}摩尔浓度的WT1胜肽以及多个所标示的胜肽在37℃中12小时。多个细胞被一浓度的10微克/毫升的多个TCRL抗体染色后接着利用二级PE标记的链霉亲和素/抗小鼠IgG，并且通过流式细胞技术分析，以平均荧光强度(MFI)表示。

[0098] 图47：多个类TCR抗体生物素化ESK1和B47B6与加有WT1胜肽以及相似于WT1的多个HLA-A2限定胜肽的多个T2APC的结合。S2、S6及S7为多个丙氨酸为基础的相似性胜肽。S11为一不规则肽(heteroclitic peptide)。多个T2细胞被加入一浓度的10^{-5}摩尔浓度的WT1胜肽以及多个所标示的胜肽在37℃中12小时。多个细胞被一浓度的10微克/毫升的多个TCRL抗体ESK1和B47B6染色后接着利用二级PE标记的链霉亲和素/抗小鼠IgG，并且通过流式细胞技术分析，以平均荧光强度(MFI)表示。

[0099] 图48：通过SPR的亲和性-靶向多个HLA-A2/WT1复合物的类TCR抗体ESK1和B47B6的表面结合亲和性测定。纯化的重组的生物化的单链HLA-A2/WT1复合物是由大肠杆菌表达的多个scHLA-A2复合物的体外重新折叠所产生，所述HLA-A2/WT1复合物与中性亲和素(NeutrAvidin)间接地固定在SPR的传感芯片上。纯化的ESK1和B47B6TCRL的多个抗原结合域(Fab)作为多个分析物。

[0100] 图49：通过丙氨酸扫描突变来测定表位特异性。所述在多个位置1、2、3、4、5、7、8和9具有丙氨酸取代的多个突变的WT1胜肽被合成并以一浓度的10^{-5}摩尔浓度加至多个T2细胞抗原呈现细胞(APC)中于37℃下12小时。多个细胞被一浓度的10微克/毫升的类TCR抗体B47B6染色，并且通过流式细胞技术分析。每个Ala取代的位置的所述相对影响以结合野生型胜肽的百分比表达。

[0101] 图50：多个类TCR抗体B47和ESK1与HLA-A2+以及WT1mRNA呈阳性或阴性的多个细胞的结合。通过qPCR对表达HLA-A2的多个肿瘤细胞进行WT1的mRNA表达的测试。多个肿瘤细胞被10微克/毫升的多个TCRL抗体ESK1和B47B6染色后接着利用二级PE标记的链霉亲和素，以平均荧光强度(MFI)表示。亦表示mRNA的表达的数据以及双特异性形式(具有抗CD3)的多个抗体对细胞的杀灭，如本文所述。

[0102] 图51A：通过比较B47B6BS与ESK1BS对HLA-A2+/WT1+和HLA-A2+/WT1-的多个正常原代细胞的杀灭。将B47B6BS和ESK1BS与HLA-A2+/WT1+或HLA-A2+/WT1-的正常原代细胞培养在一起，多个细胞与所述B47B6BS或ESK1BS以及与从多个健康个体中分离的多个未活化PBMC以10:1E:T的比率培养24小时。通过乳酸脱氢酶(LDH)释放测试测定细胞毒性。

[0103] 图51B:通过比较B47B6BS与ESK1BS对HLA-A2+/WT1+和HLA-A2+/WT1-的多个细胞株的杀灭。将B47B6BS和ESK1BS与HLA-A2+/WT1+或HLA-A2+/WT1-的多个肿瘤细胞培养在一起,多个细胞与所述B47B6BS或ESK1BS以及从与多个健康个体中分离的未活化PBMC以10:1E:T的比率培养24小时(#F3-格式-其中所述抗分化簇3(CD3)的单链变异区(scFv)片段与所述Fab的所述轻链可变区域轻链恒定区(VLCL)融合)。

[0104] 图52:类TCR抗体C106B9与加有MAGE-A4$_{230-239}$(也被称为MAGE-A4胜肽)胜肽以及多个其它HLA-A2限定胜肽的结合。多个T2细胞被加入一浓度的10^{-5}摩尔浓度的MAGE-A4以及多个所标示的胜肽在37℃中12小时。多个细胞被10微克/毫升的多个TCRL抗体C106B9染色后接着利用二级PE标记的抗小鼠IgG,并且通过流式细胞技术分析,以平均荧光强度(MFI)表示。

[0105] 图53:类TCR抗体C106B9与加有MAGE-A4胜肽以及多个相似于MAGE-A4的HLA-A2限定胜肽的结合。多个T2细胞被加入10^{-5}摩尔浓度的MAGE-A4以及多个所标示的胜肽在37℃中12小时。多个细胞被一浓度的10微克/毫升的多个TCRL抗体C106B9染色后接着利用二级PE标记的抗小鼠IgG,并且通过流式细胞技术分析。

[0106] 图54:通过SPR的亲和性-靶向多个HLA-A2/MAGE-A4复合物的类TCR抗体C106B9的表面结合亲和性测定。纯化的重组的生物素化的HLA-A2/MAGE-A4复合物是由大肠杆菌表达的多个scHLA-A2复合物的体外重新折叠所产生,所述HLA-A2/MAGE-A4复合物与中性亲和素间接地固定在SPR的传感芯片上。纯化的C106B9TCRL Fab作为所述分析物。

[0107] 图55:通过丙氨酸扫描突变来测定表位特异性。所述在多个位置1、2、3、4、5、7、8和9具有丙氨酸取代的所述多个突变的MAGE-A4胜肽被合成,多个可能的锚定位置由一灰色的星表示。所述多个天然及突变的MAGE-A4胜肽以一浓度的10^{-5}摩尔浓度加至多个T2细胞抗原呈现细胞(APC)中于37℃下12小时。多个细胞被一浓度的10微克/毫升的类TCR抗体C106B9染色,并且通过流式细胞技术分析,多个细胞加入多个突变以及野生型胜肽的MFI值被比较,每个Ala取代的位置的所述相对影响以结合野生型胜肽的百分比表达。

[0108] 图56:类TCR抗体C106B9与HLA-A2+以及MAGE-A4抗原呈阳性或阴性的多个细胞的结合。通过qPCR确认在多个细胞中MAGE-A4的mRNA的表达。多个肿瘤细胞被10微克/毫升的C106B9染色后接着利用二级PE标记的抗小鼠抗体,以平均荧光强度(MFI)表示。亦表示mRNA的表达的数据以及双特异性形式(具有抗CD3)的多个抗体对细胞的杀灭,如本文所述。

[0109] 图57:由C106B9BS对于HLA-A2+/MAGE-A4+以及HLA-A2+/MAGE-A4-的多个细胞株的杀灭,将C106B9BS与HLA-A2+/MAGE-A4+的多个细胞以及对照组的HLA-A2+/MAGE-A4-的多个细胞培养在一起,多个细胞与所述C106B9BS以及从多个健康个体中分离的多个未活化PBMC以10:1E:T的比率培养24小时。

[0110] 图58:由C106B9BS对于HLA-A2+/MAGE-A4-的多个正常原代细胞株的杀灭,将C106B9BS与HLA-A2+/MAGE-A4-的多个正常原代细胞培养在一起,多个细胞与所述C106B9BS以及从多个健康个体中分离的多个未活化PBMC以10:1E:T的比率培养24小时。

[0111] 图59:MAGE-A4BS C106B9BS在预防NOD/SCID小鼠中的S.C.黑色素瘤的肿瘤形成的体内功效。

[0112] 图60:类TCR抗体F184C7与加有MAGE-A9$_{223-231}$胜肽(也被称为MAGE-A9胜肽)以及多个其它HLA-A2限定胜肽的结合。多个T2细胞被加入10^{-5}摩尔浓度的MAGE-A9以及多个所标示

的胜肽在37℃中12小时。多个细胞被一浓度的10微克/毫升的多个TCRL抗体F184C7染色后接着利用二级PE标记的抗小鼠IgG,并且通过流式细胞技术分析,以平均荧光强度(MFI)表示。

[0113] 图61:类TCR抗体F184C7与加有MAGE-A9胜肽以及多个相似于MAGE-A9的HLA-A2限定胜肽的结合。S8为一以丙氨酸为基础的相似性胜肽。多个T2细胞被加入10^{-5}摩尔浓度的MAGE-A9以及多个所标示的胜肽在37℃中12小时。多个细胞被一浓度的10微克/毫升的多个TCRL抗体F184C7染色后接着利用二级PE标记的抗小鼠IgG,并且通过流式细胞技术分析,以平均荧光强度(MFI)表示。

[0114] 图62:通过丙氨酸扫描突变来测定表位特异性。所述在多个位置2、3、4、5、6、7、8和9具有丙氨酸取代的所述多个突变MAGE-A9胜肽被合成。所述多个Ala突变以及天然胜肽以一浓度的10^{-5}摩尔浓度被加至多个T2细胞抗原呈现细胞(APC)中于37℃下12小时。多个细胞被一浓度的10微克/毫升的类TCR抗体B47B6染色,并且通过流式细胞技术分析。每个Ala取代的位置的所述相对影响以结合野生型胜肽的百分比表达。

[0115] 图63:类TCR抗体F184C7与多个HLA-A2+的正常原代细胞的结合。多个正常原代细胞被10微克/毫升的多个TCRL抗体F184C7染色后接着是二级PE标记的抗小鼠抗体,以平均荧光强度(MFI)表示。

[0116] 图64:类TCR抗体D10A3与加有$PAP_{112-120}$胜肽(也被称为PAP胜肽)以及多个其它HLA-A2限定胜肽的结合。多个T2细胞被加入一浓度的10^{-5}摩尔浓度的PAP以及多个所标示的胜肽在37℃中12小时。多个细胞被10微克/毫升的多个TCRL抗体C106B9染色后接着利用二级PE标记的抗小鼠IgG,并且通过流式细胞技术分析,以平均荧光强度(MFI)表示。

[0117] 图65:类TCR抗体D10A3与加有PAP胜肽以及多个相似于PAP的HLA-A2限定胜肽的结合。多个T2细胞被加入一浓度的10^{-5}摩尔浓度的PAP以及多个所标示的胜肽在37℃中12小时。多个细胞被10微克/毫升的多个TCRL抗体D10A3染色后接着利用二级PE标记的抗小鼠IgG,并且通过流式细胞技术分析,以平均荧光强度(MFI)表示。

[0118] 图66:通过丙氨酸扫描突变来测定表位特异性。所述在多个位置1、3、4、6、7、8和9具有丙氨酸取代的多个突变的PAP胜肽被合成并以一浓度的10^{-5}摩尔浓度加至多个T2细胞抗原呈现细胞(APC)中于37℃下12小时。多个细胞被一浓度的10微克/毫升的类TCR抗体D10A3染色,多个细胞加入多个突变以及野生型胜肽的MFI值被比较,每个Ala取代的位置的所述相对影响以结合野生型胜肽的百分比表达。

[0119] 图67:类TCR抗体D10A3与多个HLA-A2+的正常原代细胞的结合。多个正常原代细胞被10微克/毫升的多个TCRL抗体D10A3染色后接着利用二级PE标记的抗小鼠抗体,以平均荧光强度(MFI)表示。

[0120] 图68:D11抗体的多个氨基酸和多个核酸(SEQ ID NO:280-295)。

[0121] 图69:D7抗体的多个氨基酸和多个核酸(SEQ ID NO:296-311)。

[0122] 图70:B47B6抗体的多个氨基酸和多个核酸(SEQ ID NO:312-327)。

[0123] 图71:C106B9抗体的多个氨基酸和多个核酸(SEQ ID NO:328-343)。

[0124] 图72:F184C7抗体的多个氨基酸和多个核酸(SEQ ID NO:344-359)。

[0125] 图73:D10A3抗体的多个氨基酸和多个核酸(SEQ ID NO:360-375)。

具体实施例

[0126] 本发明在其一些实施例中有关于多个亲和性结合实体，所述亲和性结合实体包括具有高亲和性和优良特异性的一类TCR抗体结合域及其用途。

[0127] 在详细解释本发明的至少一个实施例之前，应当理解本发明不一定限定于本发明在以下描述的细节或所举例的多个实施例。本发明能够以其他实施例或以各种方法来实施或应用。

[0128] 类T细胞受体(TCR)(TCRL)被赋予针对多个肿瘤表位的一类TCR特异性。不同于对MHC肽抗原复合物表现出低亲和性的多个TCR，多个TCRL的特性是即使所述多个TCRL的可溶性形式也具有亲和性。TCRL被开发为一新颖的治疗类别用于靶向多个肿瘤细胞并介导它们的特异性杀伤。此外，所述多个抗体是多个有价值的研究试剂，允许了人类第一类胜肽-MHC的配体表达以及TCR-胜肽-MHC的多个相互作用的研究。

[0129] 本发明人现在已经通过一费力的筛选和实验辨识了多个新颖的TCRL，所述多个新颖的TCRL对TyrD-HLA-A2(D7及D11)，WT1-HLA-A2(B47)，MAGE-A4-HLA-A2(C106B9)，MAGE-A9-HLA-A2(F184C7)以及PAP(D10A3)。表现出史无前例的优良特异性，所述多个抗体的所述多个CDR可以被植入在任何亲和性结合实体中，例如具有一效应活性(例如，CAR和TCR)。

[0130] 因此，根据本发明的一些实施例的一个方面，提供了一种亲和性结合实体，所述亲和性结合实体包括一抗原结合区域，所述抗原结合区域包括多个N端至C端排列的互补性决定区(CDR)序列：

[0131]

CDR1	重链(HC)	SEQ ID NO: 309	SYGVH
CDR2	HC	SEQ ID NO: 310	VIWAGGTTNYNSALMS
CDR3	HC	SEQ ID NO: 311	DGHFHFDF
CDR1	轻链(LC)	SEQ ID NO: 303	RASDIIYSNLA
CDR2	LC	SEQ ID NO: 304	AATNLAA
CDR3	LC	SEQ ID NO: 305	QHFWGSSIS

[0132] 所述亲和性结合实体能够以一人类主要组织兼容性复合体(MHC)限定的方式结合HLA-A2/$TyrD_{369-377}$。

[0133] 根据本发明的一些实施例的一个方面，提供了一种亲和性结合实体，所述亲和性结合实体包括一抗原结合区域，所述抗原结合区域包括多个N端至C端排列的互补性决定区(CDR)序列：

[0134]

CDR1	重链(HC)	SEQ ID NO: 293	TSGMGVS
CDR2	HC	SEQ ID NO: 294	HIYWDDDKRYNPSLKS
CDR3	HC	SEQ ID NO: 295	KDYGSSFYAMHY
CDR1	轻链(LC)	SEQ ID NO: 287	KASQDIHNYIA
CDR2	LC	SEQ ID NO: 288	YTSTLQP
CDR3	LC	SEQ ID NO: 289	LQYDNLWT

[0135] 所述亲和性结合实体能够以一MHC限定的方式结合HLA-A2/$TyrD_{369-377}$。

[0136] 根据本发明的一些实施例的一个方面，提供了一种亲和性结合实体，所述亲和性结合实体包括一抗原结合区域，所述抗原结合区域包括多个N端至C端排列的互补性决定区(CDR)序列：

[0137]

CDR1	HC	SEQ ID NO: 325	SYDMS
CDR2	HC	SEQ ID NO: 326	YMSSGGGTYYPDTVKG
CDR3	HC	SEQ ID NO: 327	HDEITNFDY
CDR1	LC	SEQ ID NO: 319	RASQSISNSLH
CDR2	LC	SEQ ID NO: 320	YASQSIS
CDR3	LC	SEQ ID NO: 321	QQSYSWPLT

[0138] 所述亲和性结合实体能够以一MHC限定的方式结合HLA-A2/WT1$_{126-134}$。

[0139] 根据本发明的一些实施例的一个方面，提供了一种亲和性结合实体，其特征在于，所述亲和性结合实体包括一抗原结合区域，所述抗原结合区域包括多个N端至C端排列的互补性决定区(CDR)序列：

[0140]

CDR1	HC	SEQ ID NO: 341	GYWIE
CDR2	HC	SEQ ID NO: 342	EILPGSGGTNYNEKFKG
CDR3	HC	SEQ ID NO: 343	DSNSFTY
CDR1	LC	SEQ ID NO: 335	SVSSSVDYIH
CDR2	LC	SEQ ID NO: 336	STSILAS
CDR3	LC	SEQ ID NO: 337	QQRSSYT

[0141] 所述亲和性结合实体能够以一MHC限定的方式结合HLA-A2/MAGE-A4$_{328-343}$。

[0142] 根据本发明的一些实施例的一个方面，提供了一种亲和性结合实体，所述亲和性结合实体包括一抗原结合区域，所述抗原结合区域包括多个N端至C端排列的互补性决定区(CDR)序列：

[0143]

CDR1	HC	SEQ ID NO: 357	FSSSWMN
CDR2	HC	SEQ ID NO: 358	RIYPGDGDTNYNEKFKG
CDR3	HC	SEQ ID NO: 359	EATTVVAPYYFDY
CDR1	LC	SEQ ID NO: 351	RASENIYRNLA
CDR2	LC	SEQ ID NO: 352	AATNLAD
CDR3	LC	SEQ ID NO: 353	QHFWGTPLT

[0144] 所述亲和性结合实体能够以一MHC限定的方式结合HLA-A2/MAGE-A9$_{344-359}$。

[0145] 根据本发明的一些实施例的一个方面，提供了一种亲和性结合实体，所述亲和性结合实体包括一抗原结合区域，所述抗原结合区域包括多个N端至C端排列的互补性决定区(CDR)序列：

[0146]

CDR1	HC	SEQ ID NO: 373	DYNMD
CDR2	HC	SEQ ID NO: 374	DINPNYDTTTYNQKFKG
CDR3	HC	SEQ ID NO: 375	RNYGNYVGFDF
CDR1	LC	SEQ ID NO: 367	KASQRVNNDVA
CDR2	LC	SEQ ID NO: 368	YASNRYT
CDR3	LC	SEQ ID NO: 369	QQDYSSPFT

[0147] 所述亲和性结合实体能够以一MHC限定的方式结合HLA-A2/PAP$_{360-375}$。

[0148] 本文所使用的一“T细胞受体样抗体”或“TCRL”是指与一HLA限定胜肽抗原复合的一MHC结合的一抗体。TCRL与所述TCRL标靶的结合具有一MHC限定的特异性。在缺少所述复合胜肽下，所述TCRL抗体不与所述MHC结合，以及在所述MHC的一缺少下，所述抗体在不与所述胜肽结合。

[0149] 本文所使用的“结合(binding)”或“结合(binds)”是指抗体-抗原形式的结合，其中通常是，在临床相关的TCRL的情况下，通过表面等离子体共振分析(SPR)测定，在K_D低于20纳摩尔浓度的范围内。

[0150] 所述抗原结合域与所述抗原结合域的抗原的所述亲和性是使用所述抗体的所述可溶性形式来测定，所述抗体的所述抗原结合域的所述多个CDR是从所述抗体的所述可溶性形式所衍生。对于亲和性评估，所述抗原是使用所述抗原的可溶性形式，例如，如下文进一步描述的一单链MHC胜肽复合物。

[0151] 如本文所使用，术语“K_D”是指所述抗原结合域与所述抗原结合域的相对应的抗原之间的所述平衡解离常数。

[0152] 应当理解，所述亲和性结合实体的所述亲和性是通过多个CDR测定。然而，所述亲和力可以使用本领域已知的多个方法来改善，例如亲和性成熟。

[0153] 本文所用的“亲和性结合实体”是指一结合部分，所述结合部分以比起对于一非特定抗原更高的一亲和性结合至一特定抗原，，并且赋有一亲和性至少10^{-6}摩尔浓度，如通过本领域已知的多个测试所测定，包含表面等离子体共振技术(SPR)。

[0154] 根据一具体的实施方案，所述亲和性为500纳摩尔浓度-0.5纳摩尔浓度，100纳摩尔浓度-1纳摩尔浓度，50纳摩尔浓度-1纳摩尔浓度，20纳摩尔浓度-1纳摩尔浓度，10纳摩尔浓度-1纳摩尔浓度。

[0155] 所述亲和性部分可以选自由TCR，CAR-T以及抗体所组成的所述群组。

[0156] 根据一具体的实施方案，所述亲和性结合实体是一抗体。尽管与其它亲和性结合实体相比，所述多个抗体的参考文献较详细，本实施方案的所述描述不应被解释为限制性的，本发明平等地与本文所述的多个结合实体相关，特别是在下文进一步描述的所述细胞治疗的意义上。

[0157] 本发明中使用的术语“抗体”包含多个完整分子及所述完整分子的多个功能片段，例如Fab、F(ab’)2、Fv、scFv、dsFv或多个单域分子，例如VH和VL，所述多个功能片段能够以一MHC限制的形式与一抗原的一表位结合。作为一个更基本的陈述，所述术语“抗体”目的在于包含任何亲和性结合实体，所述亲和性结合实体以一MHC限定的特异性与一表现在一细胞表面上的分子结合。因此，本发明的一些实施例的所述抗体的多个CDR可以被植入在多个人工分子中，例如T细胞受体或多个CAR，如下文进一步描述。

[0158] 用于实施本发明一些实施例的多个合适的抗体片段包含一免疫球蛋白轻链(本文称为”轻链”)的一互补决定区域(CDR)、一免疫球蛋白重链(本文中称为”重链”)的一互补决定区域、一轻链可变区域、一重链可变区域、一轻链、一重链、一Fd片段，以及所述多个抗体片段基本上包括轻链和重链，例如一Fv区、一单链Fv(scFv)、一双硫键所稳定的Fv(dsFv)、一Fab，一Fab’和一F(ab’)2。

[0159] 如本文所使用，术语“互补决定区域”或“CDR”可互相转换使用以指出在所述多个重链和轻链多肽的所述可变区域内发现的所述多个抗原结合区。一般地，多个抗体在每个所述VH(CDR HI或HI；CDR H2或H2；以及CDR H3或H3)中包括三个CDR；以及三个在每个所述VL(CDR LI或LI；CDR L2或L2；and CDR L3或L3)中。所述多个CDR序列的多个例子被提供给根据以下实施例I制备的D7和D11-TCRL。另外的实施例包括WT1B47B6、MAGE-A4C106B9、MAGE-A9F184C7、PAP D10A3(如图68-73所示)。

[0160] 一特定抗体中的所述氨基酸残基的构成一可变区域或一CDR的所述身份可以使用在本领域中已知的方法来测定，并且包括例如由Kabat等人定义的序列变异性的方法(参见例如Kabat等人，1992，《免疫相关的蛋白序列》，第5版，公共健康服务，国家卫生研究院，华盛顿特区)，所述结构环区域的位置如Chothia等人所定义(参见例如Chothia等人，《自然》342:877-883，1989)，使用牛顿的分子的AbM抗体模拟软件(现在是Accelrys®，参见Martin等人，1989，《美国国家科学院院报》86:9268；以及全球的网站万维网站www.bioinf-org.uk/abs)在Kabat和Chothia之间的折衷，如由接触定义所定义的可用的复杂晶体结构(参见MacCallum等人)，《分子生物学杂志》262:732-745，1996)，所述“构型定义”(参见，例如Makabe等人，《生物化学杂志》283:1156-1164，2008)以及IMGT[LeFRanc MP等人(2003)用于免疫球蛋白和T细胞受体的多个可变区域和Ig超家族的个类V区域的IMGT独特编号，《发育和比较免疫学》27:55-77]。

[0161] 如本文所使用，所述“多个可变区域”和“多个CDR”可以指由本领域已知的任何方法包括方法的组合所定义的多个可变区域和多个CDR。

[0162] 根据一具体的实施例，所述多个CDR是根据Kabat等人(同上)的来测定。

[0163] 多个功能性抗体片段包括轻链和重链的整个或基本上整个的可变区域，被定义为如下：

[0164] (1)Fv，被定义为由所述轻链(VL)的所述可变区域以及所述重链(VH)的可变区域所组成的一基因工程片段，以双链表达；

[0165] (2)单链Fv(“scFv”)，一基因工程的单链分子，包含所述轻链的所述可变区域和所述重链的所述可变区域，所述基因工程的单链分子通过一合适的多肽连接子作为一基因融合的单链分子。

[0166] (3)双硫键所稳定的Fv(“dsFv”)，一基因工程的抗体，包含所述轻链的所述可变区和所述重链的所述可变区，所述基因工程的抗体通过一基因工程的双硫键连接。

[0167] (4)Fab，一抗体分子的一片段包含一抗体分子的一单价抗原结合部分；所述抗体分子的片段可通过以所述木瓜蛋白酶处理整个抗体以产出所述完整的所述轻链和所述重链的所述Fd片段来获得，所述重链的所述Fd片段由所述可变区域及所述重链的所述Fd片段的CH1区域所组成；

[0168] (5)Fab’，一抗体分子的一片段包含一抗体分子的单价抗原结合部分，所述抗体分子的片段可通过胃蛋白酶处理整个抗体来获得，然后减小(每抗体分子获得两个Fab’片段)；

[0169] (6)F(ab’)2，一抗体分子的一片段包含一抗体分子的一单价抗原结合部分，所述F(ab’)2可通过所述酶胃蛋白酶处理整个抗体来获得(即，由两个双硫键保持在一起的多个Fab’片段的一个二聚体)；以及

[0170] (7)多个单域抗体或纳米体由对于抗原具有足够亲和性的单个VH或VL区域所组成。

[0171] 生产多个多克隆和单克隆抗体的多个方法以及所述多个多克隆和单克隆抗体的多个片段在本领域中是已知的(参见例如参见Harlow和Lane，《抗体：一实验室手册》，冷泉港实验室，纽约，1988，在此引入作为参考资料)。

[0172] 生产多个多克隆和单克隆抗体的方法以及所述多个多克隆和单克隆抗体的片段

在本领域中是已知的(参见例如参见Harlow和Lane,《抗体:一实验室手册》,冷泉港实验室,纽约,1988,在此引入作为参考资料)。

[0173] 根据本发明一些实施例的多个抗体片段可以通过所述抗体的蛋白水解或者通过在大肠杆菌或多个哺乳动物细胞(例如中国仓鼠卵巢细胞培养或其它蛋白表达系统)里的DNA编码所述片段的表达来制备。多个抗体片段可通过多个常规方法通过胃蛋白酶或木瓜蛋白酶切割多个整个抗体来获得。例如,多个抗体片段可通过胃蛋白酶对多个抗体的酶切来生产,以提供的一5S片段表示为F(ab')。所述片段可以使用一硫醇还原剂进一步切割所述片段,以及可选地用于由多个双硫键的裂解所产生的多个所述巯基的一阻挡基团来产生多个3.5S的Fab'单价片段。替代地,使用胃蛋白酶的一酶切产生两个单价Fab'片段和Fc片段。所述多个方法描述在例如由Goldenberg,美国专利号4,036,945和4,331,647,以及所述多个专利包含的多个引用,所述多个专利的整体是以引用的方式并入本文中。另参见Porter,R.R.[《生化杂志》73:119-126(1959)]。其它切割抗体的多个方法,例如多个重链的分离以形成多个单价轻-重链片段、多个片段的进一步切割、或其它酶的、也可以使用多个化学技术或遗传技术,只要所述多个片段结合至被所述完整抗体所辨识的所述抗原。

[0174] 多个Fv片段包括多个VH和VL链的一联结。所述联结可以是非共价的,如Inbar等人所描述[《美国国家科学院院报》69:2659-62(19720)]中所述。替代地,所述多个可变链可通过分子间的一双硫键连接或通过多个化学物质如戊二醛交联。优选地,所述多个Fv片段包括由一胜肽连接子连接的多个VH和VL链。所述多个单链抗原结合蛋白(sFv)是通过构建一结构基因包含多个DNA序列编码由一寡核苷酸连接的所述多个VH和VL区域来制备。所述结构基因被插入在一表达载体中,所述表达载体随后被引入一宿主细胞例如大肠杆菌中,所述多个重组宿主细胞合成一单个多肽链,所述单个多肽链具有一连接符桥接所述两个V域。用于生产sFvs的多个方法描述在例如[Whitlow和Filpula,《方法》2:97-105(1991);Bird等人,《科学》242:423-426(1988);Pack等人,《生物/科学》11:1271-77(1993);以及美国专利号4,746,778,所述专利的全文以引用的方式并入本文中。

[0175] 一抗体片段的另一种形式是一胜肽,所述胜肽编码一单一互补决定区域(CDR),多个CDR胜肽("多个最小识别单元")可通过构建编码感兴趣的一抗体的所述CDR的多个基因获得。所述多个基因是由,例如通过利用所述聚合酶链式反应从多个抗体产生细胞的RNA合成所述可变区域来制备。参见例如Larrick和FRy[《方法》,2:106-10(1991)]。

[0176] 多个非人类(例如:鼠类)抗体的多个人源化形式是多个免疫球蛋白、多个免疫球蛋白链或所述多个免疫球蛋白链的多个片段(例如Fv、Fab、Fab'、F(ab')分支2或其它抗原结合子序列)的多个嵌合分子,所述多个人源化形式含有最小的来源于非人类免疫球蛋白的序列。多个人源化抗体包含多个人类免疫球蛋白(受体抗体),其中所述多个人类免疫球蛋白内的形成所述受体的一互补决定区域(CDR)的多个残基被替换为从多个非人类物种(供体抗体)例如小鼠、大鼠或兔子的一CDR的多个残基,所述非人类物种的多个残基具有所需特异性、亲和性和容量。在一些例子下,所述人类免疫球蛋白的多个Fv框架残基被替换为相对应的多个非人类残基。多个人源化抗体还可以包括多个在所述受体抗体和所述引入的CDR中都没有发现的残基或多个框架序列,所述受体抗体中也不在导入的CDR或骨架序列中发现的残基。一般而言,所述人源化抗体可能基本上包含全部中的至少一个,并且典型地包括两个,多个可变区域,其中所有或基本上所有的CDR区域对应于一非人类免疫球蛋白的所

述多个CDR区域，以及所有或基本上所有的FR区域对应于一非人类免疫球蛋白共有序列的所述多个FR区域。所述人源化抗体理想地还包括一免疫球蛋白恒定区(Fc)的至少一部分，典型地，一人类免疫球蛋白的一免疫球蛋白恒定区(Fc)的至少一部分(Jones等人，《自然》，321:522-525(1986)；Riechmann等人，《自然》，332:323-329(1988)；以及Presta，《结构生物学的目前观点》，2:593-596(1992)]。

[0177] 用于人源化多个非人类抗体的多个方法在本领域中是已知的。通常，一人源化抗体具有从非人类的一来源中引入的一个或多个氨基酸残基。所述多个非人类氨基酸残基经常被称为多个引入残基，所述多个引入残基通常是从一引入的可变区域中取得。人性化可以基本上按照Winter及多个同事的所述方法[Jones等人，《自然》，321:522-525(1986)；Riechmann等人，《自然》，332:323-329(1988)；Verhoeyen等，《科学》，239:1534-1652(1988)]，通过用啮齿类的多个CDR或多个CDR序列代替一人类抗体的所述相对应的序列。因此，这种人源化抗体是多个嵌合抗体(美国专利号4,816,567)，其中基本上小于一完整的人类可变区域已被来自于一非人类物种的所述相对应的序列取代。实际上，多个人源化抗体通常是多个人类抗体，其中一些CDR残基和可能地一些FR残基是被来自于多个啮齿类抗体中的多个类似位点的多个残基所取代。

[0178] 多个人类抗体亦可以使用本领域已知的各种技术来生产，包括多个噬菌体展示库[Hoogenboom和Winter，《分子生物杂志》，227:381(1991)；Marks等人，《分子生物杂志》，222:581(1991)]，Cole等人和Boerner等人的所述多个技术也可用于多个人类单克隆抗体的所述制备[Cole等人，《单克隆抗体和癌症治疗》，Alan R.Liss，第77页(1985)和Boerner等人，《免疫杂志》，147(1):86-95(1991)]。同样地，多个人类抗体可以通过将人类免疫球蛋白基因座引入多个转基因动物来制备，例如，所述多个内源性免疫球蛋白基因已被部分地或完全地去活化的多个小鼠。在挑战上，观察到人类抗体的产生，所述人类抗体在所有方面都非常类似于在人类中所看到的所述抗体，包含基因重排，组合和抗体库。所述方法描述在例如美国专利号5,545,807；5,545,806；5,569,825；5,625,126；5,633,425；5,661,016中，以及在以下的多个科学出版物中：Marks等人，《生物/科技杂志》:779-783(1992)；Lonberg等人，《自然》368:856-859(1994)；Morrison，《自然》368 812-13(1994)；Fishwild等人，《自然生物技术》14,845-51(1996)；Neuberger，《自然生物技术》14:826(1996)；以及:Lonberg和Huszar，《国际免疫评论》13,65-93(1995)。

[0179] 在一实施例中，所述抗体是一全长抗体，本发明的一抗体的所述多个重链和所述多个轻链可以是全长(例如：一抗体可以包含至少一个，以及优选两个完整的重链和至少一个或两个完整的轻链)或可以包括一抗原结合部分(一Fab，F(ab')分支2，Fv或一单链Fv片段(“scFv”)。在其它实施例中，所述抗体的重链恒定区是选自于例如IgG1、IgG2、IgG3、IgG4、IgM、IgA1、IgA2、IgD和IgE。在一些实施例中，所述免疫球蛋白的同种型选自IgG1、IgG2、IgG3和IgG4，更具体地，IgG1(例如人类的IgG1)或IgG4(例如，人类的IgG4)。所述抗体类型的选择将取决于所述抗体被设计去引发的免疫效应的功能。

[0180] 本文还涵盖了多个抗体的多个双特异性配置。一种双特异性单克隆抗体(BsMAb，BsAb)是一种人工蛋白，所述人工蛋白由两种不同单克隆抗体的片段所组成，因此与两种不同类型的抗原结合。根据一特定的实施例，所述BsMAb被设计成同时结合到一细胞毒性细胞(例如，使用一类似于CD3的受体)以及一标靶例如将被摧毁的一肿瘤细胞(在下文中进一步

描述)。

[0181] 如本文所使用的短语“嵌合抗原受体(CAR)”是指一重组或合成分子,所述重组或合成分子把对一所需抗原的抗体为基础的特异性结合至一T细胞受体活化的细胞内区域,以生产对所述特异性抗原表现出细胞免疫活性的一嵌合蛋白。

[0182] 如本文所使用的短语“T细胞受体”或“TCR”是指重组T细胞受体的可溶性以及非可溶性形式。

[0183] 如本文所使用的短语“MHC(或HLA)限定胜肽”是指潜在地表现在一MHC分子上的一胜肽。所述胜肽可以通过“湿式”实验室程序例如质谱法或通过计算机模拟分析来侦测。一表现有MHC(或HLA)的胜肽是指在体外或体内进行确认的由一MHC分子表现的一胜肽。

[0184] 根据一具体的实施例,所述MHC限定胜肽是来自于WT1以及所述亲和性结合实体包括B47B6的所述多个CDR。

[0185] 根据一具体的实施例,所述MHC限定胜肽是来自于TyrD以及所述亲和性结合实体包括D7或D11的所述多个CDR。

[0186] 根据一具体的实施例,所述MHC限定胜肽是来自于WT1以及所述亲和性结合实体包括C106B9的所述多个CDR。

[0187] 根据一具体的实施例,所述MHC限定胜肽是来自于MAGE-A9以及所述亲和性结合实体包括F184C7的所述多个CDR。

[0188] 根据一具体的实施例,所述MHC限定胜肽是来自于PAP以及所述亲和性结合实体包括D10A3的所述多个CDR。

[0189] 所述上面提到的多个亲和性结合实体的多个CDR描述在图68-73中。

[0190] 只要保持或甚至改善所述相相应的标靶的所述结合亲和性和可选地特异性,也考虑到多个同源性序列,例如,至少90%的同源性,95%的同源性或甚至至少99%的同源性。

[0191] 因此,根据本发明的一方面,提供了一分离的多核苷酸,所述多核苷酸包含一核酸序列编码本文所述的所述亲和性结合实体。

[0192] 本发明还提供了一表达载体,包括可操作地连接至一顺式作用的调控组件的多核苷酸。

[0193] 本发明的一些实施例的所述核酸构建体(本文也称为一”表达载体”)包含多个附加序列,所述多个附加序列赋予所述载体适合于在多个原核生物、多个真核生物,或优选地两者(例如:多个穿梭载体)中复制和整合。此外,多个典型的克隆载体也可以包含一转录和翻译的起始序列,转录和翻译终止子以及一多腺苷酸化信号。作为示例,所述多个构建体将会典型地包含一5’LTR,一tRNA结合位点,一种包装信号,一种第二链DNA合成的来源,以及一3’LTR或3’LTR的一部分。

[0194] 本发明一些实施例的所述核酸构建体典型地包含一信号序列用于从一宿主细胞分泌或表现所述亲和性结合实体,其中所述抗体位于所述宿主细胞中。优选地,用于所述目的的所述信号序列是一哺乳动物信号序列。

[0195] 所述真核启动子典型地包含两种类型的识别序列,所述TATA盒以及多个上游启动子。所述TATA盒,位于所述转录起始位点的上游的25-30个碱基对,被认为参与指引RNA聚合酶开始RNA合成。所述其它上游启动子组件测定转录启动后的所述速率。

[0196] 优选地,本发明一些实施例的所述核酸构建体所使用的所述启动子在所转化的所

述特定细胞群中是活化的。多个细胞类型特异性和/或组织特异性启动子的多个例子包含个启动子组件，例如肝脏特异性的白蛋白[Pinkert等人，(1987)《基因和发展》1:268-277]、多个淋巴特异性启动子[Calame等人，(1988)《免疫学进展》43:235-275]；在多个T细胞受体的多个特定启动子中[Winoto等人，(1989)《欧洲分子生物学组织》8:729-733]和多个免疫球蛋白；[Banerji等人(1983)《细胞》33729-740]，多个神经元特异性启动子，例如所述神经丝启动子[Byrne等人，(1989)《美国国家科学院院刊》86:5473-5477]，多个胰腺特异性启动子[Edlunch等人，(1985)《科学》230:912-916]或多个乳腺特异性启动子，例如所述牛奶乳清蛋白启动子(美国专利号4,973,316以及欧洲申请公开号264,166)。

[0197] 多个增强子组件可以从多个链接的同源或异源启动子刺激转录至1,000倍。当多个增强子位于转录起始位点的下游或上游时是活化的。来源于多个病毒的许多增强子组件具有一广泛的宿主范围并且在各种组织中是活性的。例如，所述SV40早期基因增强子适用于许多细胞类型。适用于本发明一些实施例的其它增强子/启动子组合物包含衍生自多瘤病毒，人类或鼠类巨细胞病毒(CMV)，衍生自各种逆转录病毒，例如鼠白血病病毒，鼠或金肉瘤病毒和HIV的所述长末端重复。参见，《多个增强子和真核表达》，冷泉港出版社，冷泉港，纽约1983，所述《多个增强子和真核表达》在此引入作为参考文献。

[0198] 在所述表达载体的所述构建中，所述启动子优选地位于与所述异源转录起始位点大致相同的距离处，如在所述启动子的天然设置中的所述转录起始位点。然而，如本领域已知的，在不丧失启动子功能的情况下，所距离的一些变化是可以容许的。

[0199] 多聚腺苷酸序列还可以被加入所述表达载体中，以提高TCRL mRNA转录的所述效率。需要两个不同的序列组件用于精确和有效的多聚腺苷酸化：多个富有GU或U的序列位于所述多聚腺苷酸位点的下游以及一高度保守序列的6个核苷酸，AAUAAA，位于上游的11-30个核苷酸。适用于本发明一些实施例的终止和多个多腺苷酸化信号包括来源于SV40的所述多个终止和多个多腺苷酸化信号。

[0200] 除了已经描述的所述多个组件，本发明一些实施例的所述表达载体通常可以包含其它特化的组件以增加多个克隆核酸的所述表达水平或促进携带所述重组DNA的多个细胞的所述辨识。例如，许多动物病毒含有多个DNA序列促进所述病毒基因体在多个允许的细胞类型中的所述额外的染色体复制。只要通过所述质体上携带的个基因或所述宿主细胞的所述基因体提供多个适当的因子，那么带有所述多个病毒复制子的质体可被游离性的复制。

[0201] 所述载体可以包括或不包括一真核复制子。如果一真核复制子存在，则使用所述适当的可选择标记在真核细胞中扩增所述载体。如果所述载体不包括一真核复制子，则不可能有游离性的扩增。相反，所述重组DNA整合到所述设计的细胞的所述基因组中，其中所述基因组是所述启动子指导所需核酸的表达的地方。

[0202] 还提供了多个细胞，所述细胞包括本文所述的多个多核苷酸/多个表达载体。

[0203] 所述多个细胞通常地被挑选用于多个重组蛋白的高表达(例如，多个细菌，植物或真核细胞，例如，多个CHO，HEK-293细胞)，但当例如将所述TCRL的所述多个CDR被植入在所述多个细胞中一T细胞受体或CAR时，也可以是具有一特异性免疫效应活性的多个宿主细胞(例如，多个T细胞或NK细胞)。如下文进一步的描述。

[0204] 所述亲和性结合实体的所述高特异性赋于它特别适合于多个诊断和治疗应用。

[0205] 因此，根据本发明的一个方面，提供了检测表现有一感兴趣的HLA限定胜肽抗原的

一细胞的一方法。所述方法包括连接所述细胞与本发明的具有对所述感兴趣的HLA限定胜肽抗原的特异性的所述亲和性结合实体(例如,抗体)接触。所述接触是在允许免疫复合的形成的多个条件下进行,其中所述免疫复合物或所述免疫复合物的水平的一表现指示所述细胞表现有感兴趣的所述HLA限定胜肽抗原。

[0206] 本文所使用的术语“侦测(detecting)”是指“侦测(detecting)”、“感知(perceiving)"、“揭露(uncovering)"、“揭发(exposing)"、“形象化(visualizing)"或“辨认(identifying)"一细胞的动作。所述精确的检测方法依赖于所述可检测部分(在本文中也称为可辨识部分),所述抗体如本文进一步所述与所述可检测部分结合在一起。

[0207] 根据本发明的所述多个教示可以把多个单一细胞用作多个细胞。例如,所述多个细胞可以来自任何生物样本,例如细胞株,初代(例如肿瘤培养物)以及多个细胞样本,例如多种外科检体,包括切口或切除检体,细针吸取物等。活组织检查的多个方法在本领域中是已知的。

[0208] 上述检测方法可用于多个疾病的所述诊断,通过以上所述HLA胜肽复合物的疾病的诊断以的正常表现或不同组织的分布来确定。

[0209] 本文所使用的术语“诊断(diagnosing)”是指对一疾病进行一分类,测定一疾病的一严重程度(等级或阶段),监测进展,预测所述疾病的一结果和/或恢复的多个前景。

[0210] 所述对象可以是正在进行一例行的健康检查的一健康对象(例如,人类)。替代地,所述受试者可能处于所述疾病的风险。另外,替代地,所述方法可用于监测治疗的功效。

[0211] 所述TCRL可以包括例如,结合至一可识别部分。替代地或另外地,所述TCRL(或一复合物包含相同的TCRL)可以间接地辨识,例如通过使用一种二级抗体。

[0212] 所述接触可以在体外(即在一细胞株,多个原代细胞中),体内或体内进行。

[0213] 如上所述,本发明的方法在多个条件之下足以形成一免疫复合物(例如,本发明的所述多个抗体和与所述MHC复合的所述胜肽之间的一复合物,通常在所述多个细胞未被裂解时);所述多个条件(例如,多个合适的浓度,多个缓冲液,多个温度,多个反应时间)以及优化所述多个条件的方法是本领域技术人员已知的,并且在此公开了多个例子。

[0214] 本发明的所述多个亲和性结合实体(例如,抗体)特别适用于所述癌症的治疗。

[0215] 本文所使用的术语“癌症”定义为由多个异常细胞的所述快速和不受控的生长所表现的疾病。多个癌细胞可以局部地扩散或通过所述血流和淋巴系统到所述身体的其它部位。

[0216] 所述癌症可以是一血液恶性肿瘤,一实体瘤、原发或转移性肿瘤。各种癌症的多个例子包含但不限于乳腺癌、前列腺癌、卵巢癌、子宫颈癌、皮肤癌、胰腺癌、结肠直肠癌、肾癌、肝癌、脑癌、淋巴瘤、慢性淋巴细胞性白血病(CLL)、白血病、肺癌等。可通过本发明的一些实施例的所述方法治疗的多个额外的非限制性例子提供在以上的表1。

[0217] 多个可以被治疗的癌症包括没有血管化的肿瘤,或不是基本上血管化的,以及多种血管化的肿瘤。所述癌症可以包括多种非固态肿瘤(例如多个血液肿瘤,例如,白血病和淋巴瘤)或可包括多种实体瘤。本发明的所述多个抗体治疗的癌症类型包含但不限于,癌症、胚瘤及肉瘤,以及一些白血病或淋巴瘤、良性和恶性肿瘤,以及恶性肿瘤,例如肉瘤、癌症和黑色素瘤。还包括多种成人肿瘤/癌症和多种儿科肿瘤/癌症。

[0218] 多种血液癌症是所述血液或骨髓的多种癌症。血液学(或造血)的癌症的例子包含

白血病，包含急性白血病(例如急性淋巴细胞性白血病、急性髓细胞性白血病、急性骨髓性白血病和成髓细胞性白血病、早幼粒细胞性白血病、骨髓单核细胞性白血病、单核细胞性白血病和红白血病)、慢性白血病、(如慢性髓细胞(粒细胞)白血病、慢性粒细胞白血病和慢性淋巴细胞性白血病)、真性红细胞增多症、淋巴瘤、霍奇金病、非霍奇金淋巴瘤(懒惰的、高品位的形式)、多发性骨髓瘤、瓦尔登斯特伦巨球蛋白血症、重链病、骨髓增生异常综合征、毛细胞白血病和骨髓增生异常综合征。

[0219] 多个实体瘤是通常是不包含囊肿或多个液体区域的多个异常组织。多种实体瘤可以是良性或恶性。不同类型的实体瘤被命名为形成它们的多个细胞的所述类型(例如多种肉瘤、多种癌症和多种淋巴瘤)。多个实体瘤的多个例子，例如多种多肉瘤和多种癌，包含纤维肉瘤、粘液肉瘤、脂肪肉瘤、软骨肉瘤、骨肉瘤、滑膜肉瘤、间皮瘤和肉瘤，尤因氏瘤，平滑肌肉瘤，横纹肌肉瘤，结肠癌，淋巴恶性肿瘤，胰腺癌，乳腺癌，肺癌，卵巢癌，前列腺癌，肝细胞癌，鳞状细胞癌，基底细胞癌，腺癌，汗腺癌，甲状腺髓样癌、甲状腺乳头状癌、肾上腺皮脂腺癌、乳头状癌、乳头状腺癌、髓样癌、支气管癌，肾细胞癌、肝癌、胆管癌、绒毛膜上皮癌、威尔姆氏瘤、宫颈癌、睾丸肿瘤、睾丸精原细胞瘤、膀胱癌、黑色素瘤、以及中枢神经系统肿瘤(例如胶质瘤(例如脑干胶质瘤和混合性胶质瘤)，胶质母细胞瘤(也被称为多形性胶质母细胞瘤)星形细胞瘤，中枢神经系统(CNS)淋巴瘤、生殖细胞瘤、髓母细胞瘤，神经鞘瘤、颅咽管瘤，室管膜瘤、松果体瘤、血管母细胞瘤，听神经瘤，少突胶质细胞瘤、神经母细胞瘤，脑膜瘤，视网膜母细胞瘤和脑转移瘤)。

[0220] 根据本发明的一些实施例，所述病理为一实体瘤。

[0221] 根据本发明的一些实施例，本发明的一些实施例的方法所制备的药物的结果具有一抗肿瘤作用。

[0222] 本文所使用的术语“抗肿瘤效应”，是指一种生物效应，所述生物效应可通过肿瘤体积的一减少，所述肿瘤细胞数目的一减少，所述转移数目的一减少，寿命的一增加，或与癌性病症相关的各种生理症状的改善来表现。一“抗肿瘤效应”也可以通过本发明的所述药物在第一线预防肿瘤发生的能力来表现。

[0223] 根据具体的实施方案，当所述亲和性结合实体是用于酪氨酸酶(TyrD)时，所述癌症是选自于由黑色素瘤和胶质母细胞瘤所组成的所述群组。

[0224] 根据一具体的实施方案，当所述亲和性结合实体是用于WT1时，所述癌症是选自：

[0225] 表1

[0226]

白血病
多发性骨髓瘤(MM)
急性淋巴细胞白血病(ALL)
急性髓细胞性白血病(AML)
骨髓增生异常综合征(MDS)
间皮瘤
卵巢癌
胃肠道癌症，如大肠癌、腺癌、甲状腺癌
乳腺癌
肺癌(如非小细胞肺癌)

黑色素瘤
骨肉瘤
子宫内膜癌

[0227] 根据具体的实施方案，当所述亲和性结合实体是用于MAGE时，所述癌症是选自：

[0228] 表2

[0229]

MAGE-A4
卵巢癌
T 细胞白血病/淋巴瘤（例如，ATLL）
肉瘤
睾丸癌
头颈癌
膀胱癌

[0230]

食管癌。

[0231] 表3

[0232]

MAGE-A9
肾细胞癌
膀胱癌
乳腺癌
原发性肝细胞癌。

[0233] 根据一具体的实施方案，当所述亲和性结合实体是用于PAP时，所述癌症是前列腺癌。

[0234] 所述上面的多个分类皆与诊断及治疗有关。

[0235] 测定本发明的所述免疫复合物的存在或水平取决于所述抗体所附着的所述可检测部分。

[0236] 可用于本发明的多个可检测部分的多个例子包含但不限于多个放射性同位素，多个磷光化学品，多个化学发光化学品，多个荧光化学品，多个酶，多个荧光多肽和多个表位标记。所述可检测部分可以是一结合对的一组成，所述组成可通过所述组成与所述结合对以及可直接观察的一标签的一额外的构件的相互作用来辨识。在一例子中，所述结合对的所述组成是通过一相应的标记抗体所辨识的一抗原。在一个例子中，所述标签是一荧光蛋白或一酶产生一比色反应。

[0237] 多个可检测部分的其它例子包含由正电子发射断层扫描(PET)以及磁共振成像(MRI)可检测的所述多个可检测部分，所有所述可检测部分都是本领域技术人员已知的。

[0238] 当所述可检测部分是一多肽时，所述免疫标记(即与所述可检测部分偶联的所述抗体)可通过多个重组手段来生产，或化学合成，可通过例如，使用多个固相胜肽合成技术以定义的顺序对一个或多个氨基酸残基的所述逐步加入。使用重组DNA技术(其中编码所述TCRL的所述多核苷酸被转录地融合所述可检测部分)可与本发明抗体结合的多肽可检测部分的例子包含多个荧光多肽，多个磷光多肽，多个酶和多个表位标记。

[0239] 替代地，本发明的所述多个抗体的一可检测部分的一化学连接可以使用任何合适的化学键，直接或间接的，如通过一肽键(当可检测部分为一多肽时)，或通过一中间连接组件的共价键，例如一连接子胜肽或其它化学部分，例如一有机聚合物来进行。所述多个嵌合胜肽可以通过在所述多个胜肽的所述羧基(C)或氨基(N)末端上的键合来连接，或通过键合至多个内部的化学基团例如直链，支链或环状侧链，内部的碳或氮原子等。本领域普通技术人员可以容易地辨别和制备所述多个修饰的胜肽，使用已知的胜肽合成方法和/或多个胜肽的共价键。美国专利号3,940,475、4,289,747和4,376,110中详细地提供了对多个抗体的荧光标记的描述。

[0240] 用于偶联两个胜肽部分的示例性方法在下文描述：

[0241] SPDP偶联：

[0242] 可以使用本领域技术人员已知的任何SPDP偶联方法。例如，在一个示例性实施例中，使用如下所述的Cumber等人的方法的一修饰(1985年，《酶学方法》112:207-224)。

[0243] 一胜肽，例如一可辨识的或治疗部分，(1.7毫克/毫升)与一过量10倍的SPDP(在乙醇中50毫摩尔浓度)混合，所述抗体在20毫摩尔浓度的磷酸钠，0.10摩尔浓度的氢氧化钠(NaCl)pH 7.2中与一过量25倍的SPDP混合，并且每一个反应放置例如，室温下3小时。然后用PBS对所述反应透析。

[0244] 所述胜肽被还原，例如与50毫摩尔浓度的DTT在室温下1小时。通过G-25管柱(高达5%的样品/管柱体积)在磷酸二氢钾(KH_2PO_4)pH 6.5下的平衡，将所述被还原的胜肽与所述SPDP-抗体以一摩尔比为1:10抗体:胜肽结合，并在4℃放置过夜以形成一胜肽-抗体偶联物。

[0245] 戊二醛偶联：

[0246] 一胜肽(例如，一可辨识或治疗部分)与一抗体的偶联可以通过本领域技术人员已知的使用戊二醛的多个方法来实现。例如，在一个示例性实施例中，使用在下面描述的G.T.Hermanson(1996“抗体修饰和偶联，在生物偶联技术，学术出版社，圣地亚哥)的所述偶联的方法。

[0247] 所述抗体和所述胜肽(1.1毫克/毫升)与一过量10倍的具0.05%戊二醛的0.1摩尔浓度的磷酸盐及0.15摩尔浓度的氯化钠(pH6.8)溶液相混合，并允许在室温反应2小时。0.01m赖氨酸可以被加入以阻断多个过量的位点。反应后，使用以PBS(10%v样品/管柱体积)平衡的G-25管柱移除所述过量的戊二醛。

[0248] 碳二亚胺偶联：

[0249] 一胜肽与一抗体的偶联可通过本领域技术人员已知的多个方法使用一脱水剂例如一种碳二亚胺来实现。最优选地，所述碳二亚胺在4-二甲基氨基吡啶的存在之下使用。正如本领域技术人员所已知的，碳二亚胺的偶联可用于在胜肽的一羧基与一抗体的一羟基之间形成一共价键(导致一酯键的形成)，或一抗体的一氨基基团(导致一酰胺键的形成)或一抗体的一巯基(导致一硫代酯键的形成)。

[0250] 同样地，碳二亚胺偶联可用于在一抗体的一碳基团与所述胜肽的一羟基、氨基或巯基之间形成多个相似的共价键。参见，通常地，J.March，《高级有机化学:反应的机理和结构》，pp.349-50&372-74(3d ed.)，1985。通过说明，并非限制，所述胜肽使用一种一碳二亚胺，例如如二环己基碳化二亚胺，通过一共价键与一与所述抗体偶联。通常地参见，

B.Neises等人的所述多个偶联方法(1978,《应用化学》,国际英文版,17:522;A.Hassner等人(1978,《四面体通讯》4475);E.P.Boden等人(1986,《有机化学期刊》50:2394)和L.J.Mathias(1979,《合成》561)。所述免疫复合物的水平可以与来自一非患病对象的一对照组样品进行比较,其中免疫复合物形成的上升调节是黑色素瘤的指示。优选地,所述对象是例如与人类相同的物种,优选地与相同的年龄,重量,性别等互相匹配。应当理解,所述对照组样品也可以来自所述相同的对象的一健康组织,在疾病进展之前或疾病缓解之后。

[0251] 根据一具体实施例,所述侦测是由FACS实现。

[0252] 如上所述,本发明的所述多个亲和性结合实体,例如,抗体也可用于多个治疗中,其中所述抗体包括一治疗部分。

[0253] 所述治疗部分可以是所述抗体的一组成部分,例如,在一整个抗体的情况下,所述Fc区活活抗体依赖性细胞介导的细胞毒性作用(ADCC)。ADCC是一种细胞介导的免疫防御机制,其中通过所述免疫系统的一效应细胞主动地裂解一标靶细胞,所述标靶细胞的多个膜-表面抗原已被多个特定的抗体结合。这是多个抗体作为所述体液免疫反应的一部分的多个机制之一,可以起到限制和包含感染的作用。经典的ADCC由多个自然杀伤(NK)细胞所介导,多个巨噬细胞,多个嗜中性粒细胞和多个嗜酸性粒细胞也可以介导ADCC。例如,多个嗜酸性粒细胞可以通过IgE介导的ADCC杀灭已知为蠕虫的一些寄生虫。由于ADCC依赖于一先前的抗体反应,ADCC是所述适应性免疫反应的一部分。

[0254] 替代地或额外地,所述抗体可以是一双特异性抗体,其中所述治疗部分是一T细胞接合物,例如一个抗CD3抗体或一个抗CD16a,替代地,所述治疗部分可以是一个抗免疫检查点分子(抗PD-1)。

[0255] 替代地或额外地,所述抗体可以连接到一异源治疗部分(如上述多个偶联的方法)。所述治疗部分可以是,例如一细胞毒性部分、一毒性部分、一细胞因子部分、一药物。

[0256] 所述抗体可以是一可溶的或非可溶的形式。

[0257] 多个非可溶的形式可以是那些包含所述抗体的多个CDR的一分子被锚定至或被表现至一细胞或一颗粒上(后者可用于治疗以及多个诊断应用)。

[0258] 所述多个细胞的例子包括多个免疫细胞,多个T细胞,多个B细胞,多个树突细胞,细胞因子诱导的杀伤细胞(CIK),自然杀伤T细胞(NKT),自然杀伤细胞(NK)(自体,同种异体,异种的)。

[0259] 根据一具体的实施例,所述抗体(或实际上所述抗体的CDR)形成一嵌合抗原受体(CAR)(如上所述)或一人工T细胞受体。因此,编码这样的一分子的一多核苷酸被导入至感兴趣的一细胞中。

[0260] 根据本发明的一些实施例,所述细胞是一T细胞,一自然杀伤细胞,在一标靶细胞上发挥效应物的杀伤作用的一细胞,在效应T细胞上进行一抑制作用的一细胞,具有一效应物的杀伤功能的一设计的细胞或具有一抑制功能的一设计的细胞。

[0261] 根据本发明的一些实施例,所述细胞是一T细胞,或αβT细胞或γδT细胞。

[0262] 根据本发明的一些实施例,所述细胞是一自然杀伤(NK)细胞。

[0263] 根据本发明的一些实施例,所述自然杀伤细胞用于标靶向癌症

[0264] 根据本发明的一些实施例,所述T细胞是一细胞毒性T细胞(效应T细胞)。

[0265] 根据本发明的一些实施例,细胞毒性T细胞(效应T细胞)用于治疗多个癌症抗原。

[0266] 根据本发明的一些实施例，所述细胞毒性T细胞用于治疗由一癌症引起或相关的一病理。

[0267] 根据本发明的一些实施例，所述T细胞包括一Treg细胞)。

[0268] 根据本发明的一些实施例，所述T细胞包括CD3T细胞

[0269] 根据本发明的一些实施例，所述T细胞包括CD4T细胞。

[0270] 根据本发明的一些实施例，所述T细胞包括CD8T细胞。

[0271] 根据本发明的一些实施例，所述抗原结合域包括一单链Fv(scFv)分子。

[0272] 本发明的所述CAR分子的所述细胞质区域(也称为“细胞内信号区域”)负责所述免疫细胞中的所述多个正常效应功能的至少一者，其中所述CAR已经被置入所述免疫细胞中。

[0273] 所述术语“效应物功能”是指一细胞的一特定功能。一T细胞的效应功能，例如，可以是细胞溶解的活性或帮助的活性包含所述多个细胞因子的分泌。因此，所述术语“细胞内信号区域”指的是一蛋白的所述部分，其中所述部分将执行器功能信号转换并引导所述细胞进行一专用功能。尽管通常可以使用所述整个细胞内信号区域，但在许多情况下不需要使用所述整个链。在使用所述细胞内信号区域的一截短部分的程度上，只要所述截短部分转导所述效应功能信号，所述截短部分可用于代替所述完整的链。因此所述术语细胞内信号区域表示包含足以转导效应功能信号的胞内信号域的任何的截短部分。

[0274] 用于本发明的所述CAR分子中的多个细胞内信号区域的多个例子包含所述T细胞受体(TCR)的所述多个细胞质序列以及多个共同受体，在抗原与受体接合后，所述共同受体协同引发的信号转导，以及所述多个序列的任何衍生物或变异体，以及具有相同功能的能力的任何的合成序列。

[0275] 已知仅通过所述TCR所产生的多个信号不足以完全活化所述T细胞，并且还需要一个二级或共刺激的信号。因此，T细胞的活化可以由两个不同种类的胞质信号序列来介导：那些通过所述TCR引发的抗原依赖性的主要活化方法(多个主要的细胞质信号序列)的方法以及那些以一抗原无关的方式进行提供一个二级或共刺激的信号(多个二级细胞质信号序列)的方法。

[0276] 多个初级细胞质信号序列以一刺激方式或以一抑制方式调节所述TCR复合物的主要的活化。以一刺激方式起作用的多个主要细胞质信号序列可包含多个信号基序，所述多个信号基序是已知为多个免疫受体酪氨酸为基础的活化基序(ITAMs)。

[0277] ITAM的多个例子具备主要用于本发明的多个主要细胞质信号序列包含那些衍生自TCR zeta、FcR gamma、CD3gamma、CD3delta、CD3epsilon、CD5、CD22、CD79a、CD79b及CD66d的ITAM。特别优选的是，本发明的所述CAR中的细胞质信号分子包括衍生自CD3zeta的一细胞质信号序列。

[0278] 在一优选实施例中，所述CAR的细胞质区域可以被设计成包括所述CD3-zeta信号区域本身或与结合于在适用于本发明的CAR的背景下任何其它所需的(多个)细胞质区域。例如，所述CAR的所述细胞质区域可以包括一CD3zeta链部分及一共刺激信号区域。所述共刺激信号区是指所述CAR的一部分包括一共刺激分子的所述细胞内区域。一个共刺激分子是除了一抗原受体或多个淋巴细胞对一抗原的一有效应答所需的所述抗原受体的配体以外的一细胞表面分子。所述多个分子的多个例子包含CD27、CD28、4-1BB(CD137)、OX40、CD30、CD40、PD-1、ICOS、淋巴细胞功能相关抗原-1(LFA-1)、CD2、CD7、LIGHT、NKG2C、B7-H3以

及与CD83特异性结合的一配体等。因此，虽然本发明主要以4-1BB作为所述共刺激信号组件，其它共刺激组件均在本发明的范围内。

[0279] 根据本发明的一些实施例，所述细胞内区域包括一共刺激信号区和一zeta链部分。所述共刺激信号区域是指所述CAR分子的一部分包括一共刺激分子的所述细胞内区域。多个共刺激分子是除多个抗原受体或多个淋巴细胞对抗原的一有效反应所需的多个抗原受体的配体以外的多个细胞表面分子。

[0280] 本文所使用的“共刺激配体”，包含在一抗原呈现细胞[例如，一aAPC(人工抗原呈现细胞)，树突状细胞，B细胞等]上的一分子，所述分子特异性地结合在T细胞上的一同源的共刺激分子，从而提供一信号，除了由例如，一TCR/CD3复合物与加有胜肽的一MHC分子的结合所提供的所述主信号之外，介导一T细胞反应，包含但不限于，增殖、活化、分化等。一共刺激配体可以包括但不限于，CD7、B7-1(CD80)、B7-2(CD86)，PD-L1、PD-L2、4-1BBL、OX40L、诱导性的共刺激配体(ICOS-L)、细胞间粘附分子(ICAM-1)、CD 30L、CD40、CD70、CD83、HLA-G、MICA、MICB、HVEM、淋巴毒素beta受体、3/TR6、ILT3、ILT4、HVEM、结合Toll配体的受体的一激动剂或抗体以及具体结合B7-H3的一配体。一种共刺激配体也包括，尤其是，与表现在一T细胞上的一共刺激分子特异性结合的一抗体，例如但不限于CD27、CD28、4-1BB、OX40、CD30、CD40、PD-1、ICOS、淋巴细胞功能相关抗原-1(LFA-1)、CD2、CD7、光、NKG2C、B7-H3以及与CD83特异性结合的一配体。

[0281] 一“共刺激分子”是指在T细胞上的所述同源结合配偶体，所述同源结合配偶体与一共刺激配体特异性结合，从而介导所述T细胞的一共刺激应答，例如但不限于，增殖。多个共刺激分子包含但不限于一第一类MHC分子，BTLA及一Toll配体受体。

[0282] 本文所使用的一“共刺激信号”是指一信号结合于一初级信号，例如TCR/CD3连接，导致T细胞增殖和/或多个关键分子的上升调节或下降调节。

[0283] 术语“刺激”是指一主要的反应，通过一刺激分子(例如，一TCR/CD3复合物)结合其同源的配体所引发，所述主要的反应是是通过介导一信号转导事件，例如但不限于，通过所述TCRCD3复合物的信号转导。刺激可以介导一些分子的改变的表达，例如TGF-β的下降调节，和/或多个细胞骨架结构的重组等。

[0284] 一“刺激分子”，如本文所使用的术语，表示在一T细胞上的一分子特异性结合于表现在一抗原呈现细胞上的一同源的刺激配体。

[0285] 一“刺激分子”，如本文所使用的术语，表示一配体在当表现在一抗原呈现细胞(例如，aAPC，一树突细胞、一B细胞等)上时可特异性地结合于在T细胞上的一同源结合配偶体(本文称为一“刺激分子”)，通过所述T细胞通过介导一初级反应，包含但不限于，激活，引发一免疫反应，增殖等。多个刺激配体在本领域中是已知的，并且尤其是包括，并且加有一胜肽的一第一类MHC分子、一抗CD3抗体、一超激动剂抗cd28抗体和一超激动剂抗cd2抗体。

[0286] 关于所述细胞质区域，本发明一些实施例的所述CAR分子可以设计成包括所述CD28和/或4-1BB的信号区域本身或与结合于在适用于本发明的CAR的背景下任何其它所需的(多个)细胞质区域。在本发明一些实施例的CAR分子的环境中是有用的。在一个实施例中，所述CAR的所述胞质域可以被设计为进一步包括CD3-zeta的所述信号区域。例如，所述CAR的胞质区域可以包含但不限于CD3-zeta，4-1BB及CD28的多个信号模块及多个组合。

[0287] 根据本发明的一些实施例，所述细胞内区域包括至少一种，例如，至少两个，至少

三个，至少四个，至少五个，例如，至少六个选自于由CD3ζ(CD247、CD3z)、CD28、41BB、ICOS、OX40和CD137所组成的群组中的所述多个多肽。

[0288] 根据本发明的一些实施例，所述细胞内区域包括所述CD3ζ-链[CD247分子，也称为“CD3-zeta”和”CD3z”;Genbank登录号NP_000725.1和NP_93170.1]，所述CD247分子是来自多个内源性TCR的所述主变送器的信号。

[0289] 根据本发明的一些实施例，所述细胞内区域包括各种共刺激蛋白受体在所述CAR的所述胞质尾部以提供额外的多个信号至所述T细胞(第二代CAR)例子包含但不限于CD28[例如Genbank登录号NP_001230006.1、NP_001230007.1、NP_006130.1]，4-1BB[肿瘤坏死因子受体超级家族，成员9(TNFRSF 9)，也称为“CD137”，例如Genbank登录号NP_001552.2]，以及ICOS[诱导型T细胞共刺激剂，例如Genbank登录号NP_036224.1]。多个临床前研究表示，所述第二代CAR设计提高了多个T细胞的所述抗肿瘤活性。

[0290] 根据本发明的一些实施例，所述细胞内区域包括多个信号区域，如CD3z-CD28-41BB或CD3z-CD28-OX40，以进一步增强效力。所述术语”OX40”是指肿瘤坏死因子受体超级家族，成员4(TNFRSF4)，例如Genbank登录号NP_003318.1(多个“第三代”CAR)。

[0291] 根据本发明的一些实施例，所述细胞内区域包括CD28-CD3z，CD3z，CD28-CD137-CD3z。所述术语”CD137”是指肿瘤坏死因子受体超级家族，成员9(TNFRSF9)，例如Genbank登录号NP_001552.2。

[0292] 根据本发明的一些实施例，当所述CAR分子被设计用于一自然杀伤细胞时，则所述信号区域可以是CD28和/或CD3ζ。

[0293] 所述跨膜区域可以是从一天然或从一合成的来源获得。在所述来源是天然的情况下，所述区域可以是来源于任何膜结合或跨膜蛋白。本发明中特定用途的多个跨膜区域可衍生自(即至少包括所述(多个)跨膜区域的)T细胞受体的所述alpha、beta或zeta链、CD28、CD3epsilon、CD45、CD4、CD5、CD8、CD9、CD16、CD22、CD33、CD37、CD64、CD80、CD86、CD134、CD137、CD154。替代地，所述跨膜区域可以是合成的，在这种情况下所述跨膜区域主要包括疏水残基例如亮氨酸和缬氨酸。优选地，在一合成的跨膜区域的每一端可发现一苯丙氨酸、色氨酸和缬氨酸的三联体。可选地，一种短的寡-或多肽连接物，优选地在2和10个氨基酸长度之间可以在跨膜区域和所述CAR的所述细胞质信号区域之间形成所述连接。一甘氨酸-丝氨酸双联体提供了一特别适合的连接子。

[0294] 根据本发明的一些实施例，本发明的一些实施例的CAR分子中包括的所述跨膜区域是天然地相关于所述CAR的所述多个区域中的其中一者的一跨膜区域。根据本发明的一些实施例，所述跨膜区域可以通过氨基酸取代来筛选或修饰，以避免所述多个区域结合于所述相同或不同的表面膜蛋白的所述多个跨膜区域，以最小化与所述受体复合物的其它成员的多个相互作用。

[0295] 根据一些实施例，在CAR分子的所述细胞外区域和所述跨膜区域之间，或在所述细胞质区域与所述CAR分子的所述跨膜区域之间，可包含一间隔区域。如本文所使用，术语“间隔区域”一般表示任何的寡-或多肽，所述寡-或多肽将所述跨膜区域链接到所述多肽链中的所述细胞外区域或所述细胞质区域。一间隔区域可包括多达300个氨基酸，优选地10至100个氨基酸，以及最优选地25至50个氨基酸。

[0296] 根据本发明一些实施例的一个方面，本发明提供了一种在有需要的一主体中治疗

癌症的方法，包括给予所述主体所述亲和性结合实体，从而在所述主体中治疗所述癌症的。

[0297] 还提供了所述亲和性结合实体的一种用途，如本文所定义的一药物的所述制备，用于治疗一病理例如，癌症。

[0298] 所述TCRL的所述筛选将会自然依赖于所述TCRL在病理中的表现。多个示例性的TCRL及所述TCRL与多个病理的关联被提供在上表中。

[0299] 术语“治疗”是指抑制，预防或阻止一病理(疾病，紊乱或病症)的发展和/或导致一病理的所述减少，缓解或回复。本领域技术人员将理解，可以使用各种方法和测试来取得一病理的所述发展，相似地，各种方法和分析可用于取得一病理的减少，缓解或回归。

[0300] 如本文所使用，术语“受试者”包括多个哺乳动物，优选地在患有所述病理的任何年龄的人类。

[0301] 本发明一些实施例的所述多个抗体本身可以被给药至一生物体，或在与合适的多种载体或多种赋形剂混合的一药物组合物中。

[0302] 本文所使用的一“药物组合物”是指在此描述的一种或多种所述活性成分与其它化学成分例如生理学上合适的多种载体和多种赋形剂的制备。一药物组合物的所述目的是促进一化合物至一生物体的给药。

[0303] 本文中的术语“活性成分”是指用于负责所述生物学效应的所述抗体。

[0304] 在下文中，短语“生理上可接受的载体”和“药学上可接受的载体”可互换使用，用于指出一载体或一稀释剂不会对一生物体造成显着的刺激，并且不会妨碍所给予的化合物的所述生物学活性和多个性质。一佐剂被包含在所述多个短语之下。

[0305] 本文的术语“赋形剂”是指一惰性物质被加入至一药物组合物中以进一步促进活性成分的给药。赋形剂的多个例子，不限于，包括碳酸钙，磷酸钙，各种糖类和淀粉的类型，多种纤维素衍生物，明胶，植物油以及多种聚乙二醇。

[0306] 用于制备和多个药物的给药的技术可在《雷明顿药物科学》麦克出版公司，伊斯顿，宾夕法尼亚州，最新版本中找到，作为参考文献引入在此。

[0307] 多个合适的给药途径可以，例如包括口腔、直肠、粘膜、尤其是经鼻、肠或胃肠外给药，包含肌内，皮下和髓内注射以及鞘内注射，直接心空内，心内，例如，进入右或左心室腔、进入共同的冠状动脉、静脉内、腹膜内、鼻内或眼内注射。

[0308] 多种常规方法用于药物递送给中枢神经系统(CNS)包括：多个神经外科策略(例如，脑内注射或脑室内输注)；所述试剂的分子操纵(例如，一嵌合融合蛋白的制备，所述嵌合融合蛋白包括一运输胜肽，所述运输胜肽对一内皮细胞表面分子具有一亲和力，以结合自身不能穿越血脑屏障(BBB)的一试剂)试图利用其中一个BBB的所述内源性运输途径；多个药理学策略被设计为增加一试剂的脂溶性(例如，偶联多个水溶性试剂与多个脂质或胆固醇载体)；以及通过超渗透破坏而暂时破坏bbb的完整性(由将一甘露醇溶液注入所述颈动脉或一生物活性剂如血管紧张胜肽的所述使用)。然而，所述多个策略中的每一者都具有多个限制，例如与一侵入性外科手术相关的所述固有风险，由在所述内源传输系统中固有的限制所施加的一尺寸限制，多个潜在的不期望的生物性副作用与一嵌合分子的全身给药相关联，所述嵌合分子包含一可能在CNS外活化的载体基序，以及在所述脑部的BBB被破坏的多个区域内的脑损伤的所述可能风险，这使得所述方法成为一次等优选的递送方法。

[0309] 替代地，可以以局部而非全身的方式给予所述药物组合物，例如，通过将所述药物

组合物直接注射到一患者的一组织区域中。

[0310] 所述术语“组织”是指一生物体的一部分被设计成执行一功能或多个功能。多个例子包括，但不限于，脑组织、视网膜、皮肤组织、肝组织、胰腺组织、骨、软骨、结缔组织、血液组织、肌肉组织、心脏组织脑组织、血管组织、肾组织、肺组织、性腺组织、造血组织。

[0311] 本发明一些实施例的多个药物组合物可以通过本领域已知的方法制备，例如，通过常规的混合、溶解、制粒、糖衣、喷雾、乳化、包封、截留或冻干的多个过程。

[0312] 因此，根据本发明的一些实施方式所使用的多个药物组合物可以以常规方式使用一种或多种生理上可接受的载体来配制，所述载体包含多个赋形剂和多个助剂，所述多个赋形剂和多个助剂促进所述活性成分在用于药学上的制备上的过程，适当的配方取决于所选择的所述给药途径。

[0313] 对于注射，所述药物组合物的所述多个活性成分可以配制成多个水溶液，优选地在生理地相容的缓冲液中，如Hank’s溶液，林格氏溶液或生理盐缓冲液。对于粘膜给药，在所述配方中使用适合所述即将被渗透的屏障的多个渗透剂。所述多个渗透剂在本领域中是已知的。

[0314] 对于口服给药，所述药物组合物可以通过将所述多个活性化合物与本领域已知的多个药学上可接受的载体结合而容易地配制。所述多个载体使得所述药物组合物可以配制成片剂、丸剂、锭剂、胶囊剂、液体、凝胶、糖浆剂、浆料、悬浮液等，用于一患者的口服摄取。用于口服的多个药物制剂可使用一固体赋形剂来制备，可选地研磨所得到的混合物，如果需要，在加入多个合适的辅料后，加工成多个片剂或多个糖衣核心。多个合适的赋形剂，特别是，填料例如多种糖类，包括乳糖、蔗糖、甘露醇或山梨糖醇；纤维素制剂例如，玉米淀粉、大米淀粉、马铃薯淀粉、明胶、黄蓍胶、甲基纤维素、羟丙基甲基纤维素、甲基纤维素钠，和/或多种生理上可接受的聚合物，如聚乙烯吡咯烷酮(PVP)。如果需要，可以加入多种崩解剂，例如交联的聚乙烯吡咯烷酮、琼脂或海藻酸或所述海藻酸的盐类例如海藻酸钠。

[0315] 多个糖衣核心具有多个合适的涂层。为此目的，多种浓缩糖溶液可以被使用，所述多种浓缩糖溶液可任选地含有阿拉伯树胶、滑石(talc)、聚乙烯吡咯烷酮、卡波普凝胶、聚乙二醇、二氧化钛、漆溶液以及合适的有机溶剂或多个溶剂混合物。多种染料或多种颜料可以被加入至所述多个片剂或糖衣涂层中，用于辨识或表征多个活性化合物剂量的不同组合。

[0316] 可用于口服的药物组合物，包含由明胶制成的多个推入式胶囊以及由明胶和一增塑剂，例如甘油或山梨糖醇所制成的软的、密封的胶囊。所述多个推入式胶囊可以含有所述活性成分混合于填充剂例如乳糖、粘合剂例如淀粉、润滑剂如滑石粉或硬脂酸镁以及，可选地稳定剂。在多个软胶囊中，所述多个活性成分可以溶解或悬浮在一合适的液体中，如脂肪油、液体石蜡或多种液体聚乙二醇。此外，可以加入稳定剂。用于口服给药的所有配方应具有适合于所选择的给药途径的剂量。

[0317] 对于口腔给药，所述组合物可以采用常规方式所配制的多个片剂或多个锭剂的形式。

[0318] 为了通过鼻部吸入，根据本发明一些实施例所使用的所述多个活性成分在使用来自于一加压包装的气溶胶喷雾的形式，或使用合适的推进剂例如二氯二氟甲烷、三氯氟甲烷、二氯四氟乙烷或二氧化碳的喷雾器下被方便地递送。在加压气雾剂的情况下，所述剂量

单位可以通过提供用于输送一计量的数量的一阀门来测定。用于一分配器的胶囊和盒例如,明胶可以被配制成含有所述化合物的一粉末混合物以及一合适的粉末基质例如乳糖或淀粉。

[0319] 本文所述的药物组合物可配制成用于胃肠外给药,例如,通过静脉注射或连续输注。用于注射的多个配方可以以单位剂量形式呈现,例如在安瓿或多个多剂量容器中,与任选地,一加入的防腐剂。所述多个组合物可以是油性或水性载体中的悬浮液、溶液或乳液,并且可以包含多个配制剂,例如悬浮剂、稳定剂和/或分散剂。

[0320] 用于肠胃外给药的多个药物组合物包含在水溶性形式的所述活性制剂的多个水溶液。额外地,可将所述多个活性成分的悬浮液制备为合适的油性或以水为基底的注射悬浮液。多种合适的亲脂性溶剂或多种载体包括多种矿物油例如芝麻油,或多个合成脂肪酸酯例如油酸乙酯,多种甘油三酯或多种脂质体。水性注射悬浮液可含有增加所述悬浮液的粘度的多种物质,例如羧甲基纤维素钠,山梨糖醇或葡聚糖。可选地,所述悬浮液也可含有多个合适的稳定剂或增加所述多个活性成分的所述溶解度的试剂以允许所述多个高度浓缩的溶液的制备。

[0321] 替代地,所述活性成分在使用前可以是粉末形式,用于构成一合适的载体,例如,无菌、无热原的水为基底的溶液。

[0322] 本发明一些实施例的所述药物组合物也可以被配制成多个直肠组合物例如多种栓剂或多种滞留灌肠剂,例如,多个常规的栓剂基质,例如可可脂或其它甘油酯。

[0323] 适用于本发明一些实施例的背景中的多个药物组合物包含多个成分,其中所述多个有效成分以一能有效达到预期目的的数量被包含。更具体地,一治疗有效数量是指多个活性成分(TCRL抗体)的数量有效地预防,缓解或改善一病症的症状(例如,癌症)或延长所述被治疗对象的存活。

[0324] 一治疗有效数量的测定是完全在本领域技术人员的能力内,特别是根据本文所提供的所述详细内容。

[0325] 对于本发明的方法中使用的任何制剂,所述治疗有效数量或剂量可以最初地从多个体外和细胞培养测试中估计。例如,可以在多个动物模型中配制一剂量以获得一期望的浓度或滴度。所述信息可用于更准确地测定人类中的有用剂量。

[0326] 本文所述的多个活性成分的毒性和治疗功效可通过在体外、在多种细胞培养或多种实验动物的多个标准药物过程来测定。从所述多个体外和细胞培养测试以及动物研究中所获得的所述数据可用于配制用于人类的剂量的一范围。所述剂量可以根据所采用的所述剂型以及所使用的所述给药途径而变化。所述确切的配方,给药途径和剂量可以通过所述个别的医生根据患者的状况来选择。(参见例如,Fingl等人,1975,在“药物的药理学基础”中,第一章,第一页)。

[0327] 剂量的数量和间隔可以被单独调节以提供所述活性成分中的TCRL(所述TCRL组织)的水平足以诱导或抑制所述生物效应(最小的有效浓度,MEC)。用于每种制剂中的所述MEC将会不同,但是可以从体外数据中估计。实现MEC所需的剂量将取决于个体的特征和给药途径。多个侦测测试可用于测定多个血浆浓度。

[0328] 根据待治疗的所述病症的所述严重程度和反应性,给药可以是一单次或一多次的给药,持续从数天至数周的持续时间,或直至达到治愈或治疗疾病状态。

[0329] 当然，被给予的一组合物的数量将取决于所述被治疗的对象，所述痛苦的所述严重程度，所述给药方式，所述处方医生的所述判断等。

[0330] 如果需要，本发明的一些实施例的多个组合物也可以被提供在一包装或一分配器装置中，例如一FDA批准的套组(诊断的或治疗的)，所述套组可含有一种或多种含有活性成分的单位剂型。所述包装可以例如包括金属或塑料箔，例如一泡罩包装。所述包装或分配器装置可伴有用于给药的多个指示。所述包装或分配器也可以伴有与所述容器相关的一注意事项，所述容器是在由一政府机构监管规定的药品的制造，使用或出售的形式，所述注意事项反映了所述多个成分或人或兽医管理机构的所述形式的批准。例如，所述注意事项，可以是由美国食品和药物管理局批准的用于多个处方药物或多个处方药物的批准的产品插入物。多个组合物包括还可以制备配制在兼容性药物载体中的本发明的一制剂，被放置在一适当的容器中，并且被标记用于治疗一指示的状况，如上面的进一步的详细描述。

[0331] 可以预期到在本申请成熟的一专利寿命期间，将开发出许多相关的TCRLs；所述术语TCRLs的范围意在包括所有类似的先前技术。

[0332] 如本文所使用的术语“约”指±10％。

[0333] 术语“包括(comprises)”、“包括(comprising)”、“包括(includes)”、“包含(including)”、“具有(having)”及其词形变化是指“包括但不限于”。

[0334] 术语“由…组成(consisting of)”意思是“包括及不限于”。

[0335] 术语“基本上由.....组成(essentially consisting of)”是指组合物、方法或结构可包括额外的成分、步骤及/或部件，但只有当额外的成分、步骤及/或部件实质上不改变所要求保护的组合物、方法或结构的基本特征及新特征。

[0336] 本文所使用的单数型式“一”、“一个”及“至少一”包括复数引用，除非上下文另有明确规定。例如，术语“一化合物”或“至少一种化合物”可以包括多个化合物，包括其混合物。

[0337] 在整个本申请中，本发明的各种实施例可以以一个范围的型式存在。应当理解，以一范围型式的描述仅仅是因为方便及简洁，不应理解为对本发明范围的硬性限制。因此，应当认为所述的范围描述已经具体公开所有可能的子范围以及该范围内的单一数值。例如，应当认为从1到6的范围描述已经具体公开子范围，例如从1到3，从1到4，从1到5，从2到4，从2到6，从3到6等，以及所数范围内的单一数字，例如1、2、3、4、5及6，此不管范围为何皆适用。

[0338] 每当在本文中指出数值范围，是指包括所指范围内的任何引用的数字(分数或整数)。术语，第一指示数字及第二指示数字″之间的范围”及第一指示数字″到”第二指示数字″的范围″在本文中可互换，并指包括第一及第二指示数字，及其间的所有分数及整数。

[0339] 如本文所用的术语「方法(method)」指的是用于完成一特定任务的方式(manner)，手段(means)，技术(technique)和程序(procedures)，包括但不限于，那些方式，手段，技术和程序，其是已知的，或是从已知的方式，手段，技术或程序很容易地被化学，药理，生物，生化及医学领域从业者所开发。

[0340] 如本文所用，术语″治疗″包括终止，基本上抑制，减慢或逆转病症的进程，基本上改善病症的临床或心理症状或基本上预防病症的临床或心理症状的出现。

[0341] 当参考多个特定的序列列表时，所述参考将被理解为还包括基本上与所述参考的互补序列相对应的多个序列，所述序列包括多个次要的序列变化，由于例如多个定序误差，

多个克隆误差或碱基替换，碱基缺失或碱基添加所引起的其他改变所导致，所述多个变化的所述频率在小于五十分之一个核苷酸中，在小于一百分之一个核苷酸中，或者，替代地，在小于二百分之一个核苷酸中，在小于五百分之一个核苷酸中，或在小于一千分之一个核苷酸中，或者，在小于五千分之一个核苷酸中，或者，在小于一万分之一个核苷酸中。

[0342] 可以理解，本发明的某些特征，为了清楚阐明，描述在独立的实施例的上下文中，也可以是在一单一实施例中以组合提供。相反，本发明的各种特征，为了简明，在一单一实施例的上下文中描述，也可以单独或以任何合适的子组合或以适合于本发明的任何其它描述的实施方式来提供。在各种实施例的上下文中描述的部分特征不应被认为是那些实施例的主要特征，除非该实施例在没有这些组件的情况下不运作。

[0343] 下面的实施例中描述了本发明的各种实施例和方面，并且如权利要求部分中所要求的，在下面的实施例中发现了实验支持。

[0344] 多个例子

[0345] 现在参考以下多个多个例子，所述多个例子与上述的多个描述以一非限制性的方式一起示出了本发明的一些实施例。

[0346] 通常地，本文所使用的术语和用于本发明中的所述实验室方法包括分子，生物化学，微生物以及重组DNA技术。所述多个技术在文献中被彻底解释。参见，例如，“分子克隆：实验室手册”Sambrook等人，(1989)；“分子生物学当前议定书”卷一至三，Ausubel，R.M.，ed.(1994)；Ausubel等人，“分子生物学当前议定书”，JohnWileyandSons，Baltimore，Maryland(1989)；Perbal，“分子克隆实用指南”，JohnWiley&Sons，NewYork(1988)；Watson等人，“重组DNA”，美国科学书籍，纽约；Birren等人(eds)“基因组分析：实验室手册系列”，卷一至四，冷泉港实验室出版社，纽约(1998)；在美国专利号4,666,828；4,683,202；4,801,531；5,192,659及5,272,057所阐述的方法；“细胞生物学：实验室手册”，卷一至三，Cellis，J.E.，ed.(1994)；由FReshney，Wiley-Liss的“动物细胞培养-基本技术手册”，纽约(1994)，ThirdEdition；“免疫学中的现行协议”卷一至三，ColiganJ.E.，ed.(1994)；Stites等人(eds)，“基础免疫学和临床免疫学”(第八版)，Appleton&Lange，Norwalk，CT(1994)；Mishell和Shiigi(eds)，“细胞免疫学中的多个选择方法”，W.H.Freeman and Co.，纽约(1980)；现有的免疫分析在专利和科学文献中有广泛的描述。参见，例如，美国专利号3,791,932；3,839,153；3,850,752；3,850,578；3,853,987；3,867,517；3,879,262；3,901,654；3,935,074；3,984,533；3,996,345；4,034,074；4,098,876；4,879,219；5,011,771和5,281,521；"寡核苷酸合成"Gait，M.J.，ed.(1984)；“核酸杂交"Hames，B.D.，和Higgins S.J.，eds.(1985)；"转录和翻译"Hames，B.D.，and Higgins S.J.，eds.(1984)；"动物细胞培养"Freshney，R.I.，ed.(1986)；"固定化细胞和酶"IRL出版社，(1986)；"分子克隆的一实用指南"Perbal，B.，(1984)and"酶学方法"卷1-317，学术出版社；"PCR协议：方法和应用指南"，学术出版社，圣地亚哥，加利福尼亚州(1990)；Marshak等人，"蛋白质纯化和鉴定策略-实验室课程手册"CSHL出版社(1996)；所有所述多个文献都以引用的方式并入本文中。在本文献中提供了其它的一般参考文献。在所述多个文献中的所述多个步骤被认为在本领域中是已知的，并为了读者的方便提供。这里所包含的所有信息都以引用的方式并入本文中。

[0347] 多个常用的材料和方法

[0348] 生物素化的单链MHC胜肽复合物的制备

[0349] 多个单链MHC(scMHC)[3]-胜肽复合物是在异丙基β-D-硫代半乳糖苷(IPTG)的诱导下从大肠杆菌中的多个包涵体里的体外重新折叠产生。简单地说，一scMHC，包含所述β_2-微球蛋白的以及所述HLA-A2基因的所述多个细胞外区域通过一柔性连接子连接彼此，所述scMHC被设计以在所述C端包含用于位点特异性生物素化的BirA辨识序列(scMHC-BirA)。在如所述的胜肽的存在下进行体外重新折叠。通过阴离子交换Q-Sepharose色谱(GE Healthcare Life Sciences)分离和纯化正确折叠的多个MHC-胜肽复合物，然后使用所述BirA酶(亲和性)进行位点特异性的生物素化，用于生产多个单链MHC胜肽复合物的一更详细的描述提供在Denkberg等人(2002)PNAS，99:9421-9426中。

[0350] 流式细胞技术

[0351] 多个T-B杂化T2细胞被无血清的RPMI 1640培养基清洗，用含有10^{-4}至10^{-5}摩尔浓度的酪氨酸酶$_{369-377}$YMDGTMSQV(SEQ ID NO:1)/WT1$_{126-134}$(RMFPNAPYL，SEQ ID NO:141)胜肽/MAGE-A4$_{230-239}$SEQ ID NO:176/MAGE-A9$_{223-231}$203/PAP$_{112-120}$SEQ ID NO:230的胜肽或相关的多个对照组胜肽(列于下表15中)的培养基孵育过夜。使用多个加有胜肽的T2细胞上的HLA-A2-结合抗体BB7.2的MFI与未加载的多个T2细胞(>1)的MFI之间的比率来验证胜肽加载效率，数据不示出。

[0352] 多个T2或原代细胞或细胞株(10^6)与10微克/毫升的特定抗体(Ab)(有或无生物素化)在4℃下培养1小时，接着与PE标记的抗小鼠/人/链霉亲和素Ab在4℃下培45分钟，应当理解，抗小鼠二级抗体或链霉亲和素的工作得到与D11和B47B6的相似的结果。最后对细胞进行清洗和分析：

[0353] FACS 1:

[0354] 机器:BD FACS calibur

[0355] 分析软件:CELLQuest

[0356] FACS 2:

[0357] 机器:Beckman Coulter NAVIOS

[0358] 分析软件:Kaluza第1.3版

[0359] 使用所述杂交瘤技术生产HLA-A2/酪氨酸酶369-377/WT1$_{126-134}$/MAGE-A4$_{230-239}$/MAGE-A9$_{223-231}$/PAP$_{112-120}$的多个类TCR抗体

[0360] 通过5-6次HLA-A2-胜肽复合物50微克/小鼠的注射使HHD小鼠被免疫化。前2-3次的注射加入QuilA佐剂被皮下给药。通过从对上述复合物免疫的小鼠中分离的多个脾细胞与NSO骨髓瘤细胞的融合产生多个杂交瘤克隆(如前面所述的Weidanz等人2011，《国际免疫学评论》30:328-340)，以及通过如下所述的多个差异性ELISA试验进行筛选和分离。例如，对于多个酪氨酸酶TCRL的筛选，使用所述相关的多个TyrD369-377胜肽HLA-A2复合物并与所述非相关的多个p68-DDX5对照组胜肽(SEQ ID NO:2YLLPAIVHI)HLA-A2配合物相比较。具有多个纯化的HLA-A2-Tyr复合物以及显示其它HLA-A2-限定胜肽(表15)的对照组HLA-A2复合物的ELISA被用于筛选多个特异性克隆，多个分离的杂交瘤克隆被亚克隆以及被定序。两个克隆906-11-D11(称为D11，图68)和905-2-D7(称为D7，图69)被描述。

[0361] 杂交瘤在HAT DMEM或无血清的DCCM2培养基中生长直到汇合＞80％并且收集上清液。纯化的IgG是通过使用蛋白A管柱作亲和层析从培养上清液分离。所述纯化的蛋白的SDS-PAGE分析显示出均质的，纯的IgG具有预期的分子量为约150千道尔顿。

[0362] 整个IgG Ab的构建

[0363] 所述多个H和L Fab基因(仅用于MC1)被克隆以用来表达,如人类IgG1κAb分别进入所述多个真核表达载体pOptiVEC以及pcDNA3.3-TOPO中。每个穿梭表达载体携带了一个不同的基因选择(对于pOptiVEC,所述DHFR/HT-以及对于pcDNA3.3,遗传霉素)。通过使用所述FreeStyle MAX反应剂(Invitrogen)在悬浮培养中将所述两种构建体的共转染至所述二氢叶酸还原酶(DHFR)缺陷型的衍生自多个DG44细胞的中国仓鼠卵巢(CHO)来促进表达。在共转染后,细胞培养在选择性培养基中。与具有酪氨酸酶369-377胜肽的对多个JY T2细胞特异性反应的克隆被调整至在0.5%的血清中生长,并且使用蛋白A亲和层析被进一步地纯化。所述纯化的蛋白的SDS-PAGE分析显示出均质的、纯的IgG具有预期的分子量为～150千道尔顿。

[0364] 具有上清液或纯化的多个Ab的ELISA

[0365] 通过使用多个生物素化的scMHC胜肽复合物的ELISA测定各个上清液或多个纯化的TCRL抗体的所述结合特异性。将Maxi sorp 96孔洞的ELISA盘子(Nunc#442404)被涂上牛血清白蛋白-生物素(1微克/孔洞)过夜。在被清洗后,将所述多个盘子用链霉亲和素(1微克/孔洞)放置(1小时,室温),大量地清洗,并且再用0.25微克的MHC/胜肽配合物放置(1小时,室温)。将所述多个盘子在室温下用PBS/2%脱脂牛奶被封闭30分钟,随后在室温下用1毫克/孔洞的上清液或纯化的多个TCRL抗体放置1小时。在清洗后,所述多个盘子放置有用HRP-偶联/抗人类或小鼠Ab。采用TMB四甲基联苯胺试剂(DAKO,S1599)进行侦测,所述多个HLA-A2-限定胜肽用于所述纯化的上清液或纯化的多个TCRL抗体的多个特异性测试。

[0366] Proteon XPR36表面等离子体共振(SPR)的结合分析

[0367] IgG类TCR抗体的固定化在25℃呈垂直方向的一通用层介质(GLM)芯片(Bio-Rad实验室,赫拉克勒斯,加利福尼亚州,美国)上进行,所述连续的运行缓冲液为PBST(10毫摩尔浓度的磷酸钠,150毫摩尔浓度的氯化钠,0.005%Tween 20,pH7.4)。用50微升的0.04摩尔浓度的N-乙基-N'-(3-二甲氨基丙基)碳二亚胺(EDC)和0.01摩尔浓度的N-羟基硫代琥珀酰亚胺(磺基-nhs)的一混合物在30微升/分钟的一流速下活化五个通道,将所述抗小鼠或人类IgG/NeutrAvidin稀释在10毫摩尔浓度的乙酸钠缓冲液pH4.5直到一最终浓度25微克/毫升,以及在150微升被注射后紧接着150微升的1摩尔浓度的乙醇胺盐酸盐pH8.5的一注射。所述IgG TCRL抗体/纯化的单链重组HLA-A2/酪氨酸酶/WT1/MAGE-A4/MAGE-A9/PAP复合体配体在PBST中稀释至5-10微克/毫升,以及90微升以30微升/分钟的一流速下以垂直方向注射。所述第六通道维持空着以作为一参考。所述分析物纯化的单链重组HLA-A2/酪氨酸酶/WT1/MAGE-A4/MAGE-A9/PAP复合物/Fab TCRL抗体被(75微升于50微升/分钟)使用五个不同的浓度(1000、500、250、125以及625纳摩尔浓度)于所述ProteOn的所述水平方向注入,在所述第六通道中同时注入运行的缓冲液,用于双重参考以校正所述实验期间所述多个捕获的抗体从所述芯片传感器表面的损失。所有的结合传感图是使用整合的ProteOn管理器(Bio-Rad实验室,赫拉克勒斯,美国)软件中收集,处理及分析。多条结合曲线是使用所述朗缪尔模型描述1:1结合化学计量来拟合,或使用所述朗缪尔和质量转移限制模型。

[0368] 多个功能性分析

[0369] LDH-释放测试

[0370] 在一非放射性细胞毒性测试使用CytoTox96® (Promega)测定双特异性TCRL复

位向标靶细胞杀伤，所述测试定量地测量乳酸脱氢酶(LDH)，一种在细胞溶解后释放的酶。以一种10分钟偶联酶法测量多个培养上清液中释放的LDH，导致一四唑鎓盐(INT)的所述转化变成一红甲类产物。所述产生的颜色数量与多个裂解的细胞的所述数量成比例。

[0371] 具体地，多个标靶细胞和多个效应细胞被清洗，计数以及重新悬浮在无酚红的cRPMI培养基(1％FBS)中。将多个标靶细胞被调整至一细胞密度每毫升$2.5X10^5$个细胞，并且所述多个反应细胞至一细胞密度每毫升$2.5X10^6$个细胞。40微升(1×10^4细胞)的多个标靶细胞被培养在一96孔V型盘子中。以最高测试浓度制备所述双特异性TCRL测试试剂的一个五倍浓缩液，所述浓缩液在不含酚红的培养基中连续稀释十分之一以得到其它测试的浓度。然后将所述双特异性TCRL以每孔洞20微升加到所述测试盘子中的所述多个标靶细胞中以给予多个最终指示的滴定量。然后将含有所述多个标靶细胞的所述测试的盘子与所述双特异性TCRL混合于37℃/5％CO_2下培养20分钟，在培养后，40微升的多个效应细胞($1X10^5$细胞)被加到每个洞孔中，产生一效应物以10:1(E:T)的比率，多个对照组孔洞被单独地设置多个效应细胞以计算标靶自发释放，以及多个标靶细胞与最终的80微克/毫升的洋地黄以计算出最大的释放。每个条件以三重复在一最终体积100微升进行测定。将所述盘子在37℃/5％CO_2下培养24小时。在培养期后，所述盘子在700x g下离心5分钟，并且从每一个孔洞中转移50微升至一96孔洞平底Maxisorb盘子(Nunc)中的所述对应的孔洞中，按照制造商的多个说明，使用CytoTox96®测试缓冲液重新构成所述CytoTox96®基质混合物，以及将50微升加入到所述盘子的每个孔洞中。所述盘子被铝箔覆盖，并且在室温放置10分钟。然后在一盘子读取器中记录在490纳米的所述吸亮度。然后使用以下公式计算细胞毒性百分比：特异性裂解＝[(实验-自发效应体-标靶效应物)/(目标最大值-目标自发值)]x 100。用于杀灭试验的多个PBMC是从多个健康志愿者分离，并且具有所有监管的IRB的多个批准及多个书面同意。使用所述Lymphoprep技术分离多个效应PBMC。

[0372] 多个肿瘤细胞株和多个正常的原代细胞

[0373] 多个细胞株A375(黑色素瘤)、U2OS(骨肉瘤)、TCCSUP(膀胱癌)和Fib(纤维母细胞)在补充有10％FBS的完整DMEM中培养(全部由GIBCO提供)。501A、SKMel5、Mewo和1938(黑色素瘤)、Saos2(骨肉瘤)、Panc1(胰腺癌)、J82和UMUC3(膀胱)、H1703(非小细胞肺腺癌)、JVM2(覆盖细胞淋巴瘤)、IM9(多发性骨髓瘤)、U266(骨髓瘤)以及SW620(结直肠癌)培养在补充有10％FBS的完整RPMI中(全部由GIBCO提供)。Malme3m(黑色素瘤)、JEKO1(套细胞淋巴瘤)、SET2(必需的血小板抑制剂)以及BV173(B细胞前体白血病)培养在补充有20％FBS的完整RPMI中(全部由GIBCO提供)，thp-1(AML)培养在补充有10％FBS的完整RPMI中(全部由GIBCO提供)和0.05毫摩尔浓度的beta-巯基乙醇(由Thermo-fisher提供)。OVCAR-3(卵巢腺癌)培养在补充有20％FBS的完整RPMI中和0.01毫克/毫升的牛胰岛素(由Sigma提供)。所有细胞株保持在37℃在7.5％CO2的一湿润的空气中以及购自美国模式培养物保藏所。

[0374] 多个正常的原代肝细胞，多个心脏肌细胞，多个成骨细胞，多个星形细胞，多个支气管上皮细胞，多个结肠平滑肌细胞，多个中皮细胞和多个肾上皮细胞是从Sciencell取得，并且根据所述制造商的多个说明进行培养。所有细胞株保持在37℃在7.5％CO2的一湿润的空气中。

[0375] 在Expi293系统中的多个可溶性重组Fab Ab的表达和纯化

[0376] TyrD11和D7的所述VH-CH1和VL-CL基因、MAGE-A4C106B9、WT1B47B6和ESK1IgGs被

克隆在所述真核表达载体pcDNA3.4中用于表达为Fab,His-tag被连接到CH1区域的所述C-末端。

[0377] 通过所述Fectamine转染试剂(Life technologies)将所述两种构建体(重链和轻链)共转染在Expi293表达培养液中的所述多个Expi293F人类细胞(二者都是所述Expi293表达系统的多个组成)中来促进表达。在共转染后,多个细胞被培养6天。在6天后,多个细胞在700x g下离心5分钟。离心后,所述含有D11、D7、C106B9、B47B6或ESK1Fab的所述上清液从多个细胞中移除并且通过0.22μ过滤器。然后将所述上清液用PBS透析过夜。

[0378] 通过金属亲和管柱(Talon)纯化所述D11、D7、C106B9、B47B6或ESK1Fab重组蛋白,并且用PBS透析过夜。所述纯化的D11、D7、C106B9、B47B6或ESK1Fab在还原和非还原的SDS-PAGE上分析。

[0379] 在Expi 293系统中的多个双特异性TCRL的构建,表达和纯化

[0380] TyrD11和D7的所述VH-CH1和VL-CL基因,WT1B47B6和ESK1和MAGE-A4C106B9,IgGs被克隆所述真核表达载体pcDNA3.4中以用于作为双特异性(BS)于(多个序列如图68-70中所示,ESK1的多个序列可从WO 2015/0761取得)。对于Tyr D11,WT1B47B6和ESK1和MAGE-A4C106B9的所述轻链载体,抗CD3(克隆UCHT1)scFv被连接到所述VL区的所述N-末端(BS格式3,#F3)。对于所述重链载体,His-tag被连接到所述CH1区域的所述C末端。对于Tyr D7,抗CD3(克隆UCHT1)scFv被连接到重链的所述VH区的所述N-末端(BS格式1,#1)以及His-tag被连接到所述CH1区域的所述C-端。

[0381] 通过所述Fectamine转染试剂(Life technologies)将所述两种构建体共转染在Expi293表达培养液中的所述多个Expi293F人类细胞(二者都是所述Expi293表达系统的多个组成)中来促进表达。在共转染后,多个细胞被培养6天。在6天后,多个细胞在700x g下离心5分钟。离心后,所述含有所述多个TCRL双特异性抗体的所述上清液从多个细胞中移除并且通过0.22微米的过滤器。然后将所述上清液用PBS透析过夜。

[0382] 所述多个BS-TCRL的多个重组蛋白是通过金属亲和性(Talon)和尺寸排阻色谱法(Superdex 200 10/300GL GE)的两个步骤纯化。所述多个纯化的BS-TCRL在SDS-PAGE上分析。

[0383] 多个体内测试

[0384] 对于501A黑色素瘤细胞株(ATCC,马纳萨斯弗吉尼亚州,美国)

[0385] 多个细胞被培养在补充有10％胎牛血清(GIBCO,沃尔瑟姆马萨诸塞州,美国)的RPMI 1640生长培养基(GIBCO,沃尔瑟姆马萨诸塞州,美国)中。

[0386] 人类外周血单个核细胞(PBMC)是使用多个SepMateTM-50管子(Stemcell)从多个健康捐赠者中制备的。

[0387] 在第0天,多个8-10周岁的雌性NOD/SCID小鼠(Envigo,以色列;n＝6-8)在一单侧被皮下注射(s.c.)$5x10^6$个的501A黑色素瘤细胞,+/-$25x10^6$个PBMC(效应体:肿瘤细胞的比率5:1)在最终体积0.25毫升的磷酸缓冲溶液(PBS)中;D7双特异性TCRL(0.1毫克/千克)或载体(PBS)以一最终体积为0.2ml在s.c.注射后1小时静脉注射(i.v)给药,包含四个额外的剂量,每24小时给药。

[0388] 对于A375黑色素瘤细胞株(ATCC,马纳萨斯弗吉尼亚州,美国)

[0389] 多个细胞被培养在补充有10％胎牛血清(GIBCO,沃尔瑟姆马萨诸塞州,美国)的

RPMI 1640生长培养基(GIBCO,沃尔瑟姆马萨诸塞州,美国)中。

[0390] 使用一快速膨胀指南(REP)从人类外周血单个核细胞(PBMC)制备多个活化的CD8T细胞,使用SepMateTM-50管子(Stemcell)从健康的捐赠者的外周血液中制造多个非活化(Naïve)的PBMC,接着使用Dynabeads® Untouched™人类CD8T细胞套组(Invitrogen)使CD8T细胞富集,所述多个纯化的CD8T细胞的活化在预涂有对抗CD3(OKT3)和CD28的多个单克隆抗体的锥形瓶中进行,在补充有10%FBS和100IU/毫升的人类IL-2的培养基中72小时,活化的多个细胞会在补充有10%FBS,3000IU/毫升的IL-2,30毫克/毫升的OKT3以及$2x10^8$的受辐射的PBMC。

[0391] 在第0天,8-10周岁的雌性NOD/SCID小鼠(Envigo,以色列;n=6-8)在一单侧被皮下注射(s.c.)$5x10^6$个的A375黑色素瘤细胞,+/-$10x10^6$个REP CD8T细胞(效应:肿瘤细胞的比率2:1)在最终体积0.25毫升的磷酸缓冲溶液(PBS);MAGE-A4C106B9双特异性TCRL(0.1毫克/千克)、WT1B47B6双特异性TCRL(0.1毫克/千克)或载体(PBS)以一最终体积为0.2ml在s.c.注射后1小时静脉注射(i.v)给药,包含四个额外的剂量,每24小时给药。

[0392] 在所述两种情况(501A和A375)中以多个游标卡尺在两种垂直尺寸上对多个肿瘤每星期测量两次,以下公式计算出肿瘤体积:$width\ x\ \left(\frac{length}{2}\right)^2\ x\ 3.14$

[0393] 本研究中使用的其它TCRL抗体

[0394] 在WO 2008/120202中描述了MC1的生成。

[0395] ESK1的所述生产(Dao T、Yan S、Veomett N、Pankov D、Zhou L、Korontsvit T、Scott A、Whitten J、Maslak P、Casey E、Tan T、Liu H、Zakhaleva V、Curcio M、Doubrovina E、O'Reilly RJ、Liu C、Scheinberg DA,《用治疗性人抗体靶向细胞内WT1癌基因产物》,《科学转化医学》,2013年3月13日;5(176):176ra33)。因此ESK1是根据所述公开的序列WO 2015/07761,ESK1全长的VH-SEQ ID NO:128和ESK1全长的VL-SEQ ID NO:130在WO 2015/070061的序列列表通过合成基因合成产所生的,所述抗体作为IgG使用上面所述Expi293系统在多个HEK293细胞中生产,并且通过使用蛋白A管柱作亲和层析从多个培养上清液纯化。

[0396] 多个核酸的提取

[0397] 根据所述制造商的多个说明以RNeasy Plus Mini(Qiagen)从$1*10^6$至$5*10^6$个细胞培养的细胞中萃取总RNA。

[0398] cDNA合成

[0399] 根据所述制造商的多个说明以SuperScript® III第一链合成系统(Invitrogen)利用寡dT以及随机六聚体(1:1)的结合,从1-5微克的RNA合成cDNA。F或定量PCR,以H_2O将cDNA稀释成1:5。

[0400] 常规PCR(PCR)

[0401] 所述多个PCR循环条件为在95℃中2分钟,接着40个循环的在95℃中20秒、在60℃中1分钟,以及在72℃中1分钟。所述PCR结束在一最终的延长在72℃中10分钟。根据制造商的多个说明,用KAPA HiFi PCR套组(Kapa Biosystems)进行多个反应。

[0402] 以下多个引子被使用:

[0403] TYR_S:TTAGCAAAGCATACCATCA(SEQ ID NO:3)和TYR_AS:CCAGACAAAGAGGTCATAA

(SEQ ID NO:4)

[0404] 对于酪氨酸酶表达(预期产物大小:117个碱基对)和WT1_s:AGGCTGCAATAAGAGATA(SEQ ID NO:5)和WT1_AS:TTCGCTGACAAGTTTTAC(SEQ ID NO:6)用于WT1表达(预期的产物大小:188个碱基对)。

[0405] 为了可视化所述多个扩增产物,将10微升的样品与2微升的6x加载缓冲液(New England Biolabs)混合,并且在1.5%琼脂糖凝胶中进行电泳,以溴化乙锭对多个DNA标记物(New England Biolabs)染色。在ImageQuant LAS4000(GE Healthcare Life Sciences)上测定所述多个PCR产物带的存在和强度。

[0406] 定量PCR(qPCR)

[0407] 根据所述制造商的多个说明,采用TaqMan基因表达主要混合物在一ABI7300仪器(Applied Biosystems)上进行定量PCR。即时PCR的所述多个周期条件为在95℃中10分钟,接着40个循环的在95℃中15秒,以及在60℃中1分钟。用于即时PCR的多个探针是从Applied Biosystems上购买;在5'末端,将它们偶联至所述氟铬FAM。使用以下多个测试(多个引物和多个探针):对于TYR(cat#Hs00165976)、对于MAGE A4(cat#Hs00751150),对于WT1(cat#Hs01103751)。Beta-肌动蛋白被作为一看家基因用于标准化(cat#Hs99999903)。

[0408] 本研究中使用的多个胜肽

[0409]

表 4 – 丙氨酸扫瞄 - TyrD

胜肽的名字	胜肽-HLA-A2 序列	SEQ ID NO:
TyrD-A1	AMDGTMSQV	104
TyrD-A2	YADGTMSQV	105
TyrD-A3	YMAGTMSQV	106
TyrD-A4	YMDATMSQV	107
TyrD-A5	YMDGAMSQV	108
TyrD-A6	YMDGTASQV	109
TyrD-A7	YMDGTMAQV	110
TyrD-A8	YMDGTMSAV	111
TyrD-A9	YMDGTMSQA	112

[0410]

表 5 – 多个相似的胜肽 - TyrD

胜肽的名字	胜肽-HLA-A2 序列	SEQ ID NO:	相似于
Tyrosinase D (Tyrosinase PEptide)	YMDGTMSQV	113	
Tyrosinase N	YMNGTMSQV	114	
*KIAA0355	YMDNVMSEV	115	TyrD
KPNA1	VMDSKIVQV	116	TyrD
GPLD1	LMNGTLKQV	117	TyrD

[0411]

TyrD-S1	SQDGTRSQV	118	TyrD
TyrD-S2	VMDTTKSQV	119	TyrD
TyrD-S3	GMDGTQQQI	120	TyrD
TyrD-S4	GMVGTMTEV	121	TyrD
TyrD-S5	MMDATFSAV	122	TyrD
TyrD-S6	QMDPTGSQL	123	TyrD
*TyrD-S7	SMDGSMRTV	124	TyrD
TyrD-S8	WMDGIASQI	125	TyrD
TyrD-S9	YLEGILSQV	126	TyrD
TyrD-S10	YMAIKMSQL	127	TyrD
TyrD-S11	YMDAVVSLV	128	TyrD
TyrD-S12	YMDGTNRRI	129	TyrD
TyrD-S13	YMDPSTYQV	130	TyrD
TyrD-S14	YMLGTNHQL	131	TyrD
TyrD-S15	YMPGTASLI	132	TyrD
TyrD-S16	YMRETRSQL	133	TyrD
*TyrD-S17	MMDGAMGYV	134	TyrD
*TyrD-S18	NMDSFMAQV	135	TyrD
*TyrD-S19	QMDFIMSCV	136	TyrD
*TyrD-S20	YEDLKMYQV	137	TyrD
*TyrD-S21	YMDTIMELV	138	TyrD
*TyrD-S22	YTDLAMSTV	139	TyrD
*TyrD-S23	YVDFVMSSV	140	TyrD

[0412] *丙氨酸为基础的相似的多个胜肽

[0413]

	表 6 - 多个相似的胜肽 - WT1		
胜肽的名字	胜肽-HLA-A2 序列	SEQ ID NO:	相似于
WT1 (WT1 PEptide)	RMFPNAPYL	141	
WT1-S1	LDFPNLPYL	142	WT1
*WT1-S2	RCFPNCPFL	143	WT1
WT1-S3	LMFENAAYL	144	WT1
WT1-S4	RMFPNKYSL	145	WT1
WT1-S5	RLFPNAKFL	146	WT1
*WT1-S6	RLFPNLPEL	147	WT1
*WT1-S7	RMFPTPPSL	148	WT1

[0414]

WT1-S8	RMVPRAVYL	149	WT1
WT1-S9	RMFFNGRYI	150	WT1
WT1-S10	RMLPHAPGV	151	WT1
WT1-S11	YMFPNAPYL	152	WT1
WT1-S12	AMDPNAAYV	153	WT1
WT1-S13	ICFPNAPKV	154	WT1
WT1-S14	NMFENGCYL	155	WT1
WT1-S15	NMPPNFPYI	156	WT1
WT1-S16	REMTQAPYL	157	WT1
WT1-S17	RMAPRAPWI	158	WT1
WT1-S18	RMEPRAPWI	159	WT1
WT1-S19	RMEPRAPWV	160	WT1
WT1-S20	RMFLNNPSI	161	WT1
WT1-S21	RMFQQTFYL	162	WT1
WT1-S22	RMNPNSPSI	163	WT1
WT1-S23	RQFPNASLI	164	WT1
WT1-S24	RQFPNKDAL	165	WT1
WT1-S25	RVFPWASSL	166	WT1
WT1-S26	RLFPWGNKL	167	WT1

[0415] *丙氨酸为基础的相似的多个胜肽

[0416]

表 7 -丙氨酸扫瞄 – WT1

胜肽的名字	胜肽-HLA-A2 序列	SEQ ID NO:
WT1-A1	AMFPNAPYL	168
WT1-A2	RAFPNAPYL	169
WT1-A3	RMAPNAPYL	170
WT1-A4	RMFANAPYL	171
WT1-A5	RMFPAAPYL	172
WT1-A7	RMFPNAAYL	173
WT1-A8	RMFPNAPAL	174
WT1-A9	RMFPNAPYA	175

[0417]

表 8 -多个相似的胜肽– MAGE-A4			
胜肽的名字	胜肽-HLA-A2 序列	SEQ ID NO:	相似于
MAGE-A4 (MAGE-A4 PEptide)	GVYDGREHTV	176	
MAGE-A4-S1	GLADGRTHTV	177	MAGE-A4
MAGE-A4-S2	GVSDGRWHSV	178	MAGE-A4
MAGE-A4-S4	GVYDGEEHSV	179	MAGE-A4
MAGE-A4-S5	GLYDGMEHL	180	MAGE-A4
MAGE-A4-S6	GVSDGQWHTV	181	MAGE-A4
MAGE-A4-S9	GVYAGREHFL	182	MAGE-A4
MAGE-A4-S10	GLYDGMEHLI	183	MAGE-A4
MAGE-A4-S12	ASYDGTEVTV	184	MAGE-A4
MAGE-A4-S13	AVLDGRELRV	185	MAGE-A4
MAGE-A4-S15	GLYDGIEHFM	186	MAGE-A4
MAGE-A4-S16	GLYDGPVHEV	187	MAGE-A4
MAGE-A4-S17	GVCAGREHFI	188	MAGE-A4
MAGE-A4-S18	GVYAGRPLSV	189	MAGE-A4
MAGE-A4-S19	TVYDLREQSV	190	MAGE-A4
MAGE-A4-S20	VVDDGVEHTI	191	MAGE-A4
MAGE-A4-S21	GVFDGLHTV	192	MAGE-A4

[0418]

表 9 -丙氨酸扫瞄– MAGE-A4		
胜肽的名字	胜肽-HLA-A2 序列	SEQ ID NO:
MAGE-A4-A1	AVYDGREHTV	193
MAGE-A4-A2	GAYDGREHTV	194
MAGE-A4-A3	GVADGREHTV	195
MAGE-A4-A4	GVYAGREHTV	196
MAGE-A4-A5	GVYDAREHTV	197
MAGE-A4-A6	GVYDGAEHTV	198
MAGE-A4-A7	GVYDGRAHTV	199
MAGE-A4-A8	GVYDGREATV	200

[0419]

MAGE-A4-A9	GVYDGREHAV	201
MAGE-A4-A10	GVYDGREHTA	202

[0420]

表 10 -多个相似的胜肽– MAGE-A9			
胜肽的名字	胜肽-HLA-A2 序列	SEQ ID NO:	相似于
MAGE-A9 (MAGE-A9 PEptide)	ALSVMGVYV	203	
MAGE-A9S1	ALSVLGVMV	204	MAGE-A9
MAGE-A9S3	ALSRKGIYV	205	MAGE-A9
MAGE-A9S4	ALSVMYSYL	206	MAGE-A9
MAGE-A9S6	AVSHMGVLV	207	MAGE-A9
MAGE-A9S7	LLSLMGVLV	208	MAGE-A9
*MAGE-A9S8	VLSIMGVYA	209	MAGE-A9
MAGE-A9S10	ALQVRKVYV	210	MAGE-A9
MAGE-A9S11	ALQVYGVEV	211	MAGE-A9
MAGE-A9S13	ALSVAGGFV	212	MAGE-A9
MAGE-A9S14	ALSVLGKVV	213	MAGE-A9
MAGE-A9S15	ALSVMIPAV	214	MAGE-A9
MAGE-A9S16	DLSVCSVYV	215	MAGE-A9
MAGE-A9S17	ILGVMGVDV	216	MAGE-A9
MAGE-A9S20	LLSVNGVSV	217	MAGE-A9
MAGE-A9S23	SLSPMGRYV	218	MAGE-A9
MAGE-A9S24	ALSAVMGVTL	219	MAGE-A9
MAGE-A9S25	AILLVMGVDV	220	MAGE-A9
MAGE-A9S26	ALSDHHVYL	221	MAGE-A9

[0421] *丙氨酸为基础的相似的多个胜肽

[0422]

表 11 -丙氨酸扫瞄– MAGE-A9		
胜肽的名字	胜肽-HLA-A2 序列/	SEQ ID NO:
MAGE-A9-A2	AASVMGVYV	222
MAGE-A9-A3	ALAVMGVYV	223

[0423]

MAGE-A9-A4	ALSAMGVYV	224
MAGE-A9-A5	ALSVAGVYV	225
MAGE-A9-A6	ALSVMAVYV	226
MAGE-A9-A7	ALSVMGAYV	227
MAGE-A9-A8	ALSVMGVAV	228
MAGE-A9-A9	ALSVMGVYA	229

[0424]

表 12 -多个相似的胜肽– PAP			
胜肽的名字	胜肽-HLA-A2 序列	SEQ ID NO:	相似于
PAP (PAP PEptide)	TLMSAMTNL	230	
PAP(TLM)S1	TLMSAEANL	231	PAP
PAP(TLM)S2	QLCSAMTQL	232	PAP
PAP(TLM)S3	RLMSALTQL	233	PAP
PAP(TLM)S4	GLMSLTTNL	234	PAP
PAP(TLM)S5	GLMSMATNL	235	PAP
PAP(TLM)S6	GLMSMTTNL	236	PAP
PAP(TLM)S7	LLMSISTNL	237	PAP
PAP(TLM)S8	QLPSTMTNL	238	PAP
PAP(TLM)S9	TLASSMGNL	239	PAP
PAP(TLM)S10	TLFSALTGL	240	PAP
PAP(TLM)S11	TLGSATTEL	241	PAP
PAP(TLM)S12	TLMRAMTDC	242	PAP
PAP(TLM)S13	TLMSMVANL	243	PAP
PAP(TLM)S14	TLPSAETAL	244	PAP
PAP(TLM)S15	TLPSRMTVL	245	PAP
PAP(TLM)S18	RLMSALTQV	246	PAP
PAP(TLM)S19	SIHSQMTNL	247	PAP
PAP(TLM)S20	SIMFAMTPL	248	PAP
PAP(TLM)S21	TIVAAMSNL	249	PAP
PAP(TLM)S22	TLITAMEQL	250	PAP
PAP(TLM)S23	TLTSNMSQL	251	PAP

[0425]

表 13 -丙氨酸扫瞄– PAP		
胜肽的名字	胜肽-HLA-A2 序列	SEQ ID NO:
PAP A1	ALMSAMTNL	252
PAP A3	TLASAMTNL	253
PAP A4	TLMAAMTNL	254
PAP A6	TLMSAATNL	255
PAP A7	TLMSAMANL	256
PAP A8	TLMSAMTAL	257
PAP A9	TLMSAMTNA	258

[0426]

表 14-通过 MS 在多个正常的必需组织发现的多个相似的胜肽			
胜肽的名字	胜肽序列/SEQ ID NO:	基因	通过 MS 发现的多个相似的胜肽所在的多个正常的必需组织
KPNA1	VMDSKIVQV/259	KPNA1,KPNA5,KPNA6	肾上腺、膀胱、脑皮质、脑、脑、结肠、心、肠、肾、肝、肺、间皮、神经、垂体、视网膜、脊髓、颈、脂肪、乳腺、十二指肠、食道、胆囊、卵巢、胰腺、前列腺、皮肤、脾脏、胃、睾丸、子宫

[0427]

WT1-S10	RMLPHAPGV/260	HDAC1,HDAC2	肾上腺、膀胱、脑皮质、脑、脑、结肠、心、肠、肾、肝、肺、间皮、神经、垂体、视网膜、脊髓、颈、脂肪、乳腺、十二指肠、食道、胆囊、卵巢、胰腺、前列腺、皮肤、脾脏、胃、睾丸、子宫
WT1-S12	AMDPNAAYV/261	SERPINA6	肝
WT1-S22	RMNPNSPSI/262	ERH	结肠，肠，肾，肺，十二指肠，胆囊，子宫
MAGE-A4-S1	GLADGRTHTV/263	THBS3	结肠，内皮，肠，肾，间皮，神经，垂体，十二指肠，胃
MAGE-A4-S16	GLYDGPVHEV/264	DPYSL4	脑，小脑，脑，脑，肠，肺，前列腺，脾脏
MAGE-A4-S21	GVFDGLHTV/265	BTD	脑皮质、肠、肾、肝、肺、间皮、视网膜、乳腺、十二指肠、胃、睾丸、子宫
MAGE-A9-S26	ALSDHHVYL/266	ALDOC	肾上腺、膀胱、脑、脑、脑、脑、结肠、

[0428]

			内皮、心脏、肠、肾、肝、肺、间皮、神经、垂体、视网膜、脊髓颈、乳腺、十二指肠、食道、前列腺皮肤、脾脏、胃、睾丸、子宫。
PAP-S3	RLMSALTQL/267	DAB2IP	脑、小脑、脑皮质、脑、脑、结肠、心、肠、肾、肺、间皮、神经、视网膜、脊髓、颈部、脂肪、乳腺、十二指肠、前列腺、脾脏、子宫
PAP-S18	RLMSALTQV/268	RASAL2	膀胱、脑小脑、脑皮质、脑、脑、结肠、内皮、心脏、肠、肾、肝、肺、间皮、神经、垂体、视网膜、脊髓、颈、脂肪、乳腺、十二指肠、食道、胆囊、卵巢、前列腺、皮肤、脾脏、胃、睾丸、子宫

[0429]

表 15－ 多个对照组胜肽		
胜肽	胜肽-HLA-A2 序列	SEQ ID NO:
MART1(26)	ELAGIGILTV	269
CMV	NLVPMVATV	270
Gag	SLYNTVATL	271
Tyrosinase D	YMDGTMSQV	272
WT-1	RMFPNAPYL	273
MAGE-A4	GVYDGREHTV	274
PAP	TLMSAMTNL	275
MAGE-A9	ALSVMGVYV	276
SSX-2	KASEKIFYV	277
NY-ESO	SLLMWITQC	278
UHRF1	TLFDYEVRL	279

[0430] 实施例1：

[0431] 对于HLA-A2/酪氨酸酶的多个类TCR抗体

[0432] 对HLA-A2/酪氨酸369-377具有类TCR特异性的多个Abs＝的分离

[0433] MHC-TyrD369-377复合物的生产-本发明人进行的之前的研究显示使用多个大型抗体噬菌体库来产生对肿瘤及多个病毒T细胞表位具有胜肽特异性，HLA-A2限定的特异性的多个重组抗体。所述多个分子被称为多个类TCR抗体。为了生产对所述HLA-A2/TyrD369-377复合物具有一特异性的多个抗体，使用一单链MHC构建体生产表现有所述酪氨酸酶胜肽(Tyrosinase$_{369-377}$YMDGTMSQV，SEQ ID NO:1)的重组胜肽-HLA-A2复合物。通过5-6次HLA-A2-胜肽复合物50微克/小鼠的注射使多个HHD小鼠被免疫化。前2-3次的注射加入QuilA佐剂被皮下给药。通过从多个被免疫化的小鼠中分离的多个脾细胞与多个NSO骨髓瘤细胞的融合产生多个杂交瘤克隆(如前面所述的Weidanz等人2011，《国际免疫学评论》30:328-340)，以及通过如下所述的多个差异性ELISA试验进行筛选和分离。具有多个纯化的HLA-A2-Tyr复合物以及显示其它HLA-A2-限定胜肽(表15)的对照组HLA-A2复合物的ELISA被用于筛选多个特异性克隆，多个分离的杂交瘤克隆被亚克隆以及被定序。两个克隆906-11-D11(称为D11，图68)和905-2-D7(称为D7，图69)被描述。

[0434] 对于HLA-A2/酪氨酸酶369-377具有特异性的多个类TCR抗体的特性

[0435] 为了测定所述多个分离的类TCR抗体的所述表面亲和性，使用了表面等离子体共振(SPR)结合分析，通过抗小鼠或人类的IgG把所述多个分离的纯化的IgG类TCR抗体间接地固定在所述表面等离子共振(SPR)的传感芯片上。所述分析物是在各种浓度下的所述纯化的单链重组HLA-A2/酪氨酸酶复合物。如图1所示，SPR分析的所述多个传感图显示出针对所述HLA-A2/酪氨酸酶特异性的多个类TCR抗体克隆MC1、D11和D7的相似的亲和性，带有对应MC1和D11为4.1纳摩尔浓度，D7为3.8纳摩尔浓度。所述多个结果表明，全部三个类TCR抗体克隆对所述特异性HLA-A2/胜肽复合物都表现出相似的高亲和性的4纳摩尔浓度。

[0436] 为了研究所述多个分离的类TCR抗体对所述酪氨酸酶369-377胜肽的所述优良胜肽表位特异性，进行了丙氨酸扫瞄，在所述丙氨酸扫瞄中，所述胜肽中的多个特定的残基被突变为丙氨酸，并且通过将所述多个突变的胜肽加在多个T2抗原呈现细胞上以测试所述多

个TCR-样抗体与多个Ala突变胜肽的所述结合。通过流式细胞技术监测结合，当通过平均荧光强度(MFI)所测定的，多个TCR-样抗体与所述多个突变胜肽的结合的程度被用来与加有所述未突变酪氨酸酶胜肽的多个T2APC比较。所述各种Ala突变胜肽(描述在图2)的所述适当的加入是通过流式细胞技术使用BB7.2来监测，所述BB7.2是针对HLA-A2的一单克隆抗体。

[0437] 与所述天然未突变的酪氨酸酶胜肽相比，所有Ala突变胜肽被有效地加到多个T2细胞上(数据未示出)。通过利用HLA-A2-结合抗体BB7.2的MFI与未加载的多个T2细胞(>1)的MFI之间的比率来验证胜肽加载效率。如图2所示，全部三个类TCR抗体都表现出胜肽依赖性结合，因为多个特定的突变影响了所述结合，并且在多个特定胜肽位置引入Ala时，在所述类TCR抗体的结合强度中引发了一减少。所述多个结果表明，在HLA-A2加入各种Ala突变酪氨酸酶胜肽的情况下，全部三个类TCR抗体都表现出胜肽特异性及限制性的结合，表明所述多个抗体在所述多个抗体的结合性质上是相似于TCR，因此，所述多个抗体以MHC限定以及胜肽特异性的方式来结合所述MHC-胜肽复合物。

[0438] 然而，所述三个类TCR抗体在所述三个类TCR抗体的优良特异性和胜肽依赖性反应的不同是在于所述胜肽中对Ala突变敏感和受影响的结合灵敏度的位置的数量。当MC1与一单一Ala突变胜肽结合在一个位置#6时显示出90％的一显着下降，D11和D7都表现出对于D11在两个位置#3、6的一大于90％的下降，对于D11在四个位置#3、4、6、7的结合的一大于90％的减少。MC1与多个Ala突变胜肽的结合时进一步观察到在三个位置#1、3、6的一较温和但显着的一大于70％的下降4，6，7，尽管D11和D7在五胜肽残基被突变成Ala(对于D11，位置#1，2，3，4，6，以及对于D7，位置#2，3，4，6，7)时表现出一大于70％的结合的显着减少。

[0439] 总体而言，通过观察所述各种Ala突变的Tyr胜肽正确地结合Tyr特异性的类TCR抗体的能力，所述丙氨酸扫描分析揭示了D11和D7相较于MC1对多个Ala突变更受影响及敏感。根据图2中所示的所述数据，D11和D7相较于MC1在所述D11和D7的结合性质上具有更高的胜肽限制及敏感度；它们对于九个胜肽残基中的四个的Ala突变敏感(不包含多个锚定位置)，尽管MC1只有对3个位置。D11和D7在它们的结合特性上分别对第五位置七和五敏感。具体地，D11在位置#7减少了68％的所述结合，67％位置#5，59％位置#8；D7在位置#5减少了66％的所述结合，63％位置#1，63％位置#8。

[0440] 结论，Ala扫描可以被用作测定多个类TCR抗体的所述选择性和优良特异性的一手段，若表现出对Ala突变表现出越高的敏感性，可以观察到越高特异性和胜肽依赖性的结合。所述策略可用于过滤和筛选表现出更高和优化的选择性和特异性性质的所述理想的类TCR抗体如多个MHC-限定胜肽特异性结合物。

[0441] 对于HLA-A2/酪氨酸酶的多个类TCR抗体的结合选择性和特异性

[0442] 为了定性出所述多个分离的类TCR抗体的所述结合特异性，通过流式细胞技术取得所述多个纯化的IgG的所述反应性和特异性。将多个特异性或对照组胜肽加入多个T2APC中，并且与所述Ab培养，接着与PE标记的抗人类或小鼠Ab一起培养。如图3-7所示，所述MC1(图7)、D11和D7(图3至6)的多个IgG接合在加有所述酪氨酸酶胜肽的T2细胞上，但不能显着地结合在加有多个对照组胜肽的多个细胞上(表15)。对于MC1，在多个对照组胜肽上观察到非常低的背景的结合具有MCI的比率3-7(图7)，而D11和D7没有表现出任何背景结合(图3至6)。通过MAb BB7.2的结合来监测加载的胜肽呈现的程度，所述MAb BB7.2与所有的HLA-A2

胜肽复合物结合。所述多个结果表明，全部三个类TCR抗体都表现出HLA-A2-限定的胜肽特异性的结合，因为它们仅与表现所述酪氨酸酸的多个细胞上，但不与其它HLA-A2限定胜肽结合。

[0443] 为了探索所述多个HLA-A2/酪氨酸酶类TCR Ab是否能够结合在多个肿瘤细胞的所述表面上的多个内源性衍生的MHC-酪氨酸盐复合物，在来源于多个黑色素瘤患者的多株上进行流式细胞技术分析。将多个细胞与多个抗酪氨酸酶369-377/HLA-A2类TCR抗体一起培养，然后与PE标记的抗人类或抗小鼠Ab一起培养。如图8至12所示，所述多个类TCR抗体辨识出具有一非常高强度的多个酪氨酸酶-阳性和HLA-A2-阳性细胞。如此所示，表示出所述大量的HLA-A2-酪氨酸酶复合物表现在所述多个黑色素瘤细胞的所述表面。所述类TCR抗体的所述染色是非常均匀的；以针对所述酪氨酸蛋白的Ab对所述多个黑色素瘤细胞(例如624.38，及501A)的细胞内染色揭示出，在所测试每一株中的95％的所述多个细胞都表达所述酪氨酸酶蛋白(数据未示出)。在酪氨酸酶-阴性或HLA-A2-阴性细胞中没有被检测到反应性。通过各种组织来源的多种细胞株的广泛的流式细胞分析技术分析，所述多种细胞株为HLA-A2阳性，Ag(酪氨酸酶)阴性的，验证了抗酪氨酸酶/HLA-A2类TCR Abs的特异性。所述分析如图10-12所示，D11和D7的反应性也在一组正常的原代细胞包括多个内皮细胞、纤维细胞、星形细胞、肝细胞、肾细胞、心脏肌细胞、结肠肌肉和PBMC(图13-17)中被测试。没有与所述多个HLA-A2+和Tyr-的正常原代细胞的结合被观察到，而当在PBMC上测试MC1时观察到背景的结合(图17)。D11和D7对HLA-A2+/酪氨酸酶+的多个黑色素瘤细胞以及广泛的组的各种组织来源的HLA-A2+/酪氨酸酶-的细胞包括所述多个正常原代细胞的反应性的所述分析如图18-19所示。D11和D7类TCR抗体的反应性对于表达HLA-A2和所述抗原酪氨酸酶的多个黑色素瘤细胞来说是极为特异性。

[0444] 所述多个研究的所述总体结论是，所述多个类TCR Ab是特异性的，并且在当HLA等位基因与Ag的所述充分结合存在时，它们仅辨识在细胞表面上表现的所述特定胜肽-MHC复合物。然而，流式细胞技术的数据的仔细评估表示出多个结果展示出与D11和D7相比时的MC1的差异选择性。例如，对MC1与多个HLA-A2+和Tyr-细胞株HepG2，SW620以及Loucy的结合的分析，如图9所示，揭示了由MFI测得的背景的结合，然而，在所述多个细胞上的D11和D7的相似的分析揭示出没有结合(图10和12)。通过并排比较所述三个类TCR抗体在这些和另外的细胞(图12)揭示了MC1表现出与HLA-A2+/tyr+的多个黑色素瘤细胞的显着结合，但在一各式各样的HLA-A2+/Tyr-的多个细胞(SW620、Colo205、HepG2、Panc1、RPMI、DG75、Jeko1和Loucy)上具有背景的结合，而D11和D7对所述多个细胞没有表现出的任何背景的结合。

[0445] 因此，可以总结出D11和D7相较于MC1更具特异性和选择性，并且综合流式细胞技术研究以及其它分析，例如，利用一大组的不同组织来源的细胞的功能分析是多个有用工具，用于评估多个类TCR抗体的所述选择性，所述细胞表达所述合适的HLA等位基因以及是抗原呈阳性或阴性。

[0446] 为了进一步评估所述酪氨酸酶特异性的多个类TCR抗体的所述优良特异性，它们对于表现出所述天然酪氨酸酶的序列相似度的多个胜肽的反应性被评估(表5)。

[0447] 因此，当针对一特定的类TCR抗体的丙氨酸/甘氨酸扫描数据是可使用的如上所述时，进行另一轮的相似的多个胜肽的筛选。基于丙氨酸扫描，测量和评估所述胜肽抗原中的每一个氨基酸残基对于TCRL的结合的所述贡献。通过上述多个工具辨识保持所述多个关键

位置的多个相似的胜肽，并且被赋予更高的优先级。所述多个胜肽被合成并且被用于如上所述的优良特异性的评估。

[0448] 本文所述的策略结合了结合被洗脱的多个HLA胜肽的质谱分析的胜肽序列相似性的计算机模拟分析、多个胜肽数据库以及丙氨酸扫描提供了一工具盒以充分地控制多个胜肽搜索参数，多于其它工具，例如BLAST或ScanProsite所提供的。多个附加参数被采用，包括允许多个胜肽长度的范围、序列的最大允许数量或差异、HLA结合分数的所述要求。所述工具也适用于将某些氨基酸定义为等同的能力。最重要的是突显已经通过质谱分析或从数据库数据或文献发现的多个胜肽的能力。

[0449] 应用上述工具，合成三种类TCR抗体的优良特异性根据本文所述的标准选择用于评估的相似胜肽的大板(表5)。所述多个相似的胜肽已被加到多个T2APC上，并且所述多个类TCR抗体的反应性被测试。如图20所示，当在一组的相似的胜肽上测试MC1时，相较于对于天然酪氨酸酶胜肽的结合，观察到所述MC1表示出对酪氨酸酶具有序列相似度的多个胜肽例如KIAA0335和KPNA1的背景结合。然而，如图21至28所示，所述多个类TCR抗体D11和D7不结合任何从一大组的所述被分析的胜肽的相似的胜肽，包含与MC1表示出背景结合的所述KIAA0335和KPNA1胜肽的不辨识。所述多个数据证明了与MC1相比，D11和D7的所述更优异的选择性和优良特异性，并且证明了所述相似胜肽方法的所述用处以及如上所述所开发的多个工具作为多个重要的工具，当为了最佳及最理想的候选物评估一组的类TCR抗体以用于进一步评估时，评估出所述选择性和优良特异性分级。

[0450] 此外，在多个类TCR抗体的丙氨酸扫描后，多个额外的相似的胜肽已经被筛选和测试了。由于所述TyrD胜肽序列中的每一种氨基酸不可能相等地贡献对Tyr TCRL的结合，对于Tyr TCRL结合是关键的所述胜肽残基被辨别出来。一组合的多个合成胜肽被生产，其中所述TyrD九聚体中的每一个氨基酸依次地被丙氨酸取代。通过FACS分析测定Tyr TCRL与带有所述多个丙氨酸取代的多个胜肽中的一者的细胞结合的能力，并将所述多个结合结果与所述非突变胜肽获得的结合结果进行比较。与所述非突变胜肽相比，在丙氨酸取代导致在结合上的一巨大的下降的位置处的所述残基被认为是关键的。然后进行一定向的计算机模拟，以辨识仅包含所述多个关键位置基序的蛋白序列。所述多个胜肽也用于多个Tyr TCRL的特异性评估(表5S17至S23)。所述衍生自多个丙氨酸扫描分析的多个相似的胜肽被合成并加到多个T2APC细胞上，并且测试D11和D7的所述反应性。如图28所示，没有观察到所述多个胜肽的结合，从而进一步证实和增强所述多个类TCR抗体的所述优良特异性和选择性。

[0451] 实施例1A

[0452] 用于HLA-A2/酪氨酸酶的多个类TCR抗体的定性

[0453] 对HLA-A2/酪氨酸酶369-377具有类TCR特异性的多个Ab的所述优良特异性的比较

[0454] 为了定性出所述多个分离的类TCR抗体的所述结合特异性，通过流式细胞仪评估所述多个纯化的IgG的反应性和特异性(具有或不含生物素化)。在酪氨酸酶胜肽加入多个T2APC或多个对照组胜肽(表15)，并且与所述Ab(D7，D11或MC1)一起培养，接着与PE标记的链霉亲和素或PE标记的多个抗小鼠Ab一起培养。如图38所示，多个D11和D7TCRL结合加有所述酪氨酸酶胜肽的T2细胞，但没有显示与加入对照组胜肽的多个细胞的结合。相反，MC1TCRL显示与加有酪氨酸酶胜肽和作为对照组的所述不相关胜肽的多个T2细胞的结合。

[0455] 为了进一步评估所述多个D7和D11类TCR抗体的所述特异性，评估它们与对于所述

酪氨酸酶胜肽显示序列相似度的多个胜肽的反应性。所述胜肽如表5所示。

[0456] 如图39中所示，TCRL对于与酪氨酸酶胜肽(例如KIAA0335和KPNA1(表14)以及标记为S2、S4、S5、S9、S11、S13、S18、(S19、S22和S23)具有序列相似性的各种胜肽具有容易检测的结合。多个D11和D7类TCR抗体不结合任何来自于所述相同组的多个相似胜肽的所述多个胜肽。所述多个数据证实了与MC1TCRL相比，D11和D7TCRL的所述更优良的选择性和优良特异性，并且证明了所述相似胜肽方法以及如上所述所开发的多个工具的所述用处以评估多个类TCR抗体的所述选择性和优良特异性分级。

[0457] 本发明人研究了HLA-A2/酪氨酸酶的多个类TCR Ab对于内源性地显示在多个黑色素瘤细胞株的所述表面上的多个MHC-酪氨酸酶胜肽复合物的结合特异性。多个细胞与抗酪氨酸酶369-377/HLA-A2的多个类TCR抗体Ab(具有或不具有生物素化)一起培养，接着与PE标记的链霉亲和素或多个抗小鼠Ab培养。一组的肿瘤细胞及多个正常初级细胞已被定性为HLA-A2(阳性)及酪氨酸酶(阳性或阴性)的表达，被用来比较所述多个类TCR抗体的所述结合。如图40A至C所示，所述多个类TCR抗体辨识多个酪氨酸酶-阳性及HLA-A2-阳性细胞。所述多个类TCR抗体被测试在各种来源的多个HLA-A2-阳性细胞株上，所述细胞株不显示Tyr RNA表达(Tyr-阴性)。如图40A至B所示，多个D11和D7TCRL不结合所述多个细胞中的任何一种，而MC1则容易染上各种HLA-A2+/Tyr-细胞。D7和D11TCRL不表现任何与正常的原代细胞的结合，而MC1显示出与它们中的一些的可侦测的结合(图40C)。

[0458] 总体来说，与MC1TCRL相比，多个D7和D11TCRL证明了对于辨识由HLA-A2表现的酪氨酸酶胜肽的更优异的特异性及选择性。

[0459] 多个功能性分析被用来进一步定性所述多个D7和D11类TCR抗体。将多个TCRL的多个可变区融合到一个抗CD3scFv，所述抗CD3scFv可以以一双特异性的形式重新靶向多个效应T细胞以杀死肿瘤标靶细胞。如图41至44所示，D7和D11CD3双特异性类TCR抗体的多个构建体在多个人类PBMC的存在下，在体外显示了对多个黑色素瘤501A细胞的强大的细胞毒性。Panc-1，酪氨酸酶阴性细胞株作为阴性对照组，并且表现出没有细胞毒性。用多个D7和D11TCRL针对一组的多个HLA-A2+/Tyr-正常人类原代细胞没有细胞毒性被侦测到证实了它们的选择性。

[0460] 实施例1B

[0461] 在多个NOD/SCID小鼠中，D7BS TCRL在s.c.501A黑色素瘤肿瘤形成模型中的体内功效

[0462] 图45显示了在多个NOD/SCID小鼠中D7BS TCRL在s.c.501A黑色素瘤肿瘤形成模型中的体内功效。显然，所述双特异性抗体的给药完全抑制了肿瘤形成超过65天的所述实验，如通过肿瘤体积所证实。所述结果支持在本文所述的多个临床设置中TCRL的可变序列的使用。

[0463] 实施例2

[0464] 用于HLA-A2/WT1的多个类TCR抗体

[0465] 对HLA-A2/WT1具有类TCR特异性的多个Ab的分离和定性

[0466] 为了产生对所述HLA-A2/WT1复合物具有一特异性的所述多个抗体，多个重组胜肽-HLA-A2复合物被生产，所述多个重组胜肽-HLA-A2复合物使用一单链MHC构建体表现所述WT1胜肽(RMFPNAPYL，SEQ ID NO:151)。多个抗体的生产如在所述一般材料和方法以及上

述实施例1中所述，一类TCR特异性克隆称为B47(也称为B47B6)被分离以及定性(图70)。

[0467] 作为类TCR抗体结合选择性的一比较，一类TCR抗体称为ESK1，Dao T、Yan S、Veomett N、Pankov D、Zhou L、Korontsvit T、Scott A、Whitten J、Maslak P、Casey E、Tan T、Liu H、Zakhaleva V、Curcio M、Doubrovina E、O'Reilly RJ、Liu C、Scheinberg DA。

[0468] 通过表面等离子体共振(SPR)结合分析评估B47的所述结合亲和性，通过抗小鼠的IgG把所述分离的纯化的IgG类TCR抗体间接地固定在所述SPR的传感芯片。所述分析物是以各种浓度使用的所述纯化的单链重组HLA-A2/WT1复合物。如图29所示，SPR分析的所述多个传感图显示了对于所述HLA-A2/WT1特异性类TCR抗体克隆B47的一亲和性为4.4纳摩尔浓度。

[0469] 为了定性所述多个分离的类TCR抗体的所述结合特异性，通过流式细胞技术评估所述多个纯化的IgG的所述反应性和特异性。将多个T2APC加到特定的或多个对照组胜肽中(表15)并且与Ab一起培养，接着与PE标记的抗人类或小鼠Ab一起培养。如图30和31所示，B47和ESK1结合于加有所述WT1胜肽的多个T2细胞(Figure30)但不与加有多个对照组胜肽的多个细胞结合(图31)。显着性差异是B47和ESK1所观察到的所述结合强度。尽管B47强烈地结合于加有10^{-4}至10^{-5}摩尔浓度的胜肽的多个T2细胞，ESK1较弱地结合于加有10^{-4}摩尔浓度的WT1胜肽的多个T2细胞(对于ESK1的MFI 18与B47的474相比)在胜肽浓度10^{-5}摩尔浓度的B47仍然显着地结合(MFI 88)，而ESK1的结合几乎是无法检测的或非常低的(图30)。所述多个结果表明，B47的所述亲和性和结合灵敏度具有多个显着的差异，与ESK1相比，ESK1结合强度急剧下降相较于B47在胜肽浓度具有10倍下降。B47和ESK1不结合加有多个对照组HLA-A2限定胜肽的多个T2APC(图31)。所述多个结果表明，两个类TCR抗体都表现出HLA-A2-限定胜肽的特异性结合，因为它们仅与表现所述WT1的多个细胞结合，而非其它HLA-A2限定胜肽。

[0470] 为了进一步研究所述多个WT1类TCR抗体优良特异性，以上面描述的所述策略对于与计算机模拟的多个相似的胜肽的结合进行了评估。如图32和33所示，B47没有结合在一设计的小组中任何相似的胜肽(表6)。然而，如图32所示，ESK1表现出与两个相似胜肽的低背景结合。在额外的多个对照组胜肽和多个相似胜肽上评估B47(图34)。通过流式细胞技术进行所述多个类TCR抗体的进一步分析，使用是HLA-A2的并且表达或不表达所述WT1抗原的肿瘤细胞。如图35所示，所述ESK1WT1类TCR样抗体强烈地结合HLA-A2+/WT+BV173和SET2细胞，但是B47没有表现出对于所述多个细胞的任何结合至所述流式细胞技术灵敏度的水平。为了进一步研究特异性，在如通过PCR评估的HLA-A2但不表达所述WT1基因的细胞上评估ESK1和B47的所述反应性。如此所示，B47不与所述多个细胞中的任何细胞结合，而ESK1结合至被发现是WT1阴性的501、A498以及SKMEL细胞。其它WT1阴性细胞没有被ESK1结合。HLA-A2的表达的所述水平被MAb BB7.2所监测，所述MAb BB7.2辨识在所述细胞表面上的所有HLA-A2/胜肽分子。在图36示出了B47WT-特异性的类TCR抗体的结合数据的一总结。

[0471] 为了进一步研究ESK1和B47对于HLA-A2+/WT1+BV173和SET2细胞的所述结合的所述矛盾的数据，即可以通过ESK1显着地侦测到结合，而非B47，我们采用直接的生化手段来评估在所述多个细胞上的实际的WT1表现。我们采用来自于各种组织以及BV173和SET2细胞的多个HLA胜肽洗脱策略，接着是多个洗脱的胜肽的MS分析。所述多个实验的所述数据表示，在任何的所述多个MS运行的多个临床组织或多个细胞株中都没有侦测到所述WT1胜肽。

在所述BV173或SET-2细胞株的深度分析(mRNA WT1-阳性)未能检测到所述胜肽(Orbitrap或多个Q Exactive MS仪器)。通过Orbitrap MS侦测所述WT1胜肽,接着从多个T2加有胜肽的细胞直接洗脱,所述多个T2细胞被加入各种WT1胜肽浓度的10^{-5}、10^{-7}、10^{-9}摩尔浓度,并且通过所述MS在加有胜肽浓度10^{-5}和10^{-7}摩尔浓度的多个T2APC的多个洗脱液中侦测到所述胜肽,通过所述MS从加有10^{-7}摩尔浓度的胜肽的多个T2APC侦测所述胜肽对应于约250个位点/细胞的实际表达(使用所述Orbitrap MS)。

[0472] 所述多个数据举例说明了所述描述的多个结合工具对于加有胜肽的细胞的所述用处,所述加有胜肽的细胞显示了各种组织学来源的多个相似的胜肽和多个细胞,以评估多个类TCR抗体的所述特异性和选择性。

[0473] 为了进一步研究表位特异性,在所述WT1胜肽序列上进行丙氨酸扫描诱变。如图37所示,表示了仅有在所述WT1胜肽的位置1中的突变影响ESK1的所述结合强度,表示出与B47相比,ESK1的所述结合选择性和优良特异性是有限的,亦如同所述所观察到的特异性模式,如同所观察到的多个相似的胜肽,以及对于HLA-A2+/WT1-/的多个细胞。所述多个数据表示,与ESK1相比,B47的所述选择性和优良特异性是优异的,并且本文所述的所述工具箱是一有价值的工具以在多个类TCR抗体的筛选、表性以及临床前开发的过程中评估多个类TCR抗体的所述选择性和优良特异性。

[0474] 实施例2A

[0475] 用于HLA-A2/WT1的多个类TCR抗体

[0476] 对HLA-A2/WT1具有TCR样特异性的多个Ab的优良特异性的比较

[0477] 多个类TCR抗体B47和ESK1的所述选择性被比较。(Dao等人,《科学转化医学》,2013年3月13日;5(176):176ra33)。

[0478] 多个T2APC被加入特定的(WT1,SEQ ID NO:141)或多个对照组胜肽(表15)并且与B47和ESK1抗体一起培养,接着与PE标记的链霉亲和素或多个抗小鼠Ab一起培养。B47和多个ESK1TCRL两者都结合加有所述WT1胜肽的多个T2细胞,但不结合加有多个对照组胜肽的多个细胞(图46)。一组的多个相似胜肽(表6)被合成以进一步定性出所述WT1TCRL的特异性。所述B47TCRL不结合在加有任何的所述多个相似胜肽的T2细胞,而ESK1TCRL对几种相似胜肽显示出可侦测的结合(图47)。ESK1TCRL显示了结合至一衍生自HDAC2(组蛋白脱乙酰化酶2,表14)的一相似胜肽,所述相似胜肽是普遍地表现在许多正常细胞中。,WT1-S10(SEQ ID NO:151)被表现在多个正常组织中,如质谱所证实在脑、大脑皮质、心脏、肾脏、肝脏、肺、以及其它正常组织(表14)。

[0479] 通过SPR对B47和多个ESK1TCRL的结合的进一步定性显示B47的亲和性(5纳摩尔浓度)比起ESK1(200纳摩尔浓度)更强大,主要由于ESK1与多个MHC-WT1胜肽复合物的分解率较快(图48)。

[0480] 进行所述WT1胜肽的额外的丙氨酸扫描诱变以改良多个B47类TCR抗体的胜肽表位特异性(图49)。将所述多个突变胜肽加入多个T2细胞上,并且进行如上所述的结合分析。通过流式细胞技术使用针对HLA-A2的BB7.2单克隆抗体监测所述各种Ala突变的加载。

[0481] 如图49所示,在一些位置处的Ala的多个取代显着地影响B47结合至所述多个突变胜肽。B47TCRL对多个位置性的取代表现出更大的敏感度(与ESK1相比,图37)。当所述胜肽中的四个残基被突变为丙氨酸(位置1、3、4和7)时,所述B47类TCR抗体失去了＞73％的它对

表现的胜肽的结合。一第五个位置位置的敏感度可归因于位置号码5。对于B47和多个ESK1TCRL两者，位置2是关键，因为它被认为是作为所述多个胜肽在所述HLA-A2胜肽结合槽中的一锚定位置。

[0482] 在B47和ESK1TCRL之间的进一步定性和比较是在多个肿瘤细胞株和各种来源的原代细胞上进行。如图50所示，B47不结合至一组的细胞，所述一组的细胞都是HLA-A2阳性和WT1mRNA阳性或阴性的多个细胞。相反，ESK1TCRL结合至一数量的肿瘤和正常的原代细胞(全部HLA-A2+)。例如，JVM2和IM9(两者皆HLA-A2阳性和WT1阴性)以及多个正常的初级星形细胞显示出结合。细胞毒性试验使用TCRL-aCD3双特异性构建体以及多个人类PBMC显示出B47TCRL不诱导HLA-A2+/WT1+或HLA-A2+/WT1-的多个细胞的死亡，而ESK1TCRL-aCD3对一数量的细胞具有细胞毒性，包含WT-1阴性。因此，B47TCRL在所述双特异性的形式在给合以及功能性活动中皆表现出更优异的特异性，相较于ESK1，所述ESK1结合至以及重新靶向CD3T细胞至一些细胞，包含多个正常的初代细胞，不管WT-1的表达如何。

[0483] 实施例3

[0484] 对HLA-A2/MAGE-A4具有特异性的多个类TCR抗体

[0485] 实施例3A

[0486] 对HLA-A2/MAGE-A4具有特异性的TCRL的分离和定性

[0487] 为了定性所述多个分离的类TCR抗体的所述结合特异性，通过流式细胞技术评估所述多个纯化的IgG的所述反应性和特异性。在多个T2APC中加入MAGE-A4胜肽或多个对照组胜肽(表15)以及与所述TCRL Ab C106B一起培养，接着与PE标记的链霉亲和素或PE标记的多个抗小鼠Abs一起培养。如图52所示，C106B9结合加有MAGE-A4胜肽的多个T2细胞，但显示不结合加有多个对照组胜肽的多个细胞。

[0488] 为了进一步评估所述C106B9类TCR抗体的所述特异性，评估它们与对于所述MAGE-A4胜肽显示序列相似度的多个胜肽的反应性。所述胜肽如表8所示。

[0489] 如图53所示，C106B9TCRL类TCR抗体不结合任何来自于所述相同组的多个相似胜肽的所述多个胜肽。所述多个数据证明了C106B9的所述高选择性和高特异性，并且证明了所述相似胜肽方法的所述用处以及如上所述所开发的多个工具以评估出多个TCRL的所述选择性和优良特异性。

[0490] 为了测定所述多个分离的类TCR抗体的所述表面亲和性，使用了表面等离子体共振(SPR)结合分析，通过抗小鼠的IgG把所述分离的纯化的IgG类TCR抗体间接地固定在所述表面等离子共振(SPR)的传感芯片上。所述分析物是在各种浓度下的所述纯化的单链重组HLA-A2/MAGE-A4复合物。如图54所示，SPR分析的所述多个传感图显示出针对所述HLA-A2/MAGE-A4特异性的多个类TCR抗体克隆C106B9的相似的亲和性具有对应的亲和力8.8纳摩尔浓度。

[0491] 为了研究所述多个分离的类TCR抗体对所述MAGE-A4胜肽的所述优良胜肽表位特异性，进行了丙氨酸扫瞄，在所述丙氨酸扫瞄中，所述胜肽中的多个特定的残基被突变为丙氨酸，并且通过将所述多个突变的胜肽加在多个T2抗原呈现细胞上以测试所述多个类TCR抗体与多个Ala突变胜肽的所述结合(表9)。通过流式细胞技术监测结合，当通过平均荧光强度(MFI)所测定的，多个TCR-样抗体与所述多个突变胜肽的结合的程度被用来与加有所述未突变MAGE-A4胜肽的多个T2APC比较。所述各种Ala突变胜肽(描述在图2)的所述适当的

加入是通过流式细胞技术使用BB7.2来监测，所述BB7.2是针对HLA-A2的一单克隆抗体。

[0492] 与所述天然未突变的MAGE-A4相比，所有Ala突变胜肽被有效地加到多个T2细胞上(数据未示出)。如图55所示，所述类TCR抗体表现出胜肽依赖性结合，因为多个特定的突变影响了所述结合，并且在多个特定胜肽位置引入Ala时，在所述类TCR抗体的结合强度中引发了一减少。所述多个结果表明，在HLA-A2加入各种Ala突变MAGE-A4胜肽的情况下，MAGE-A4类TCR抗体表现出胜肽特异性及限制性的结合，表明所述抗体在所述抗体的结合性质上是相似于TCR，因此，所述抗体以MHC限定以及胜肽特异性的方式来结合所述MHC-胜肽复合物。

[0493] 所述C106B9类TCR抗体表现出90％的一显着下降在与Ala突变胜肽结合的四个位置#4、5、6和7。一第五个位置的敏感度可归因于位置号码2(33％的减小)。

[0494] 总体而言，所述丙氨酸扫描分析揭示了Ala扫描可以被用作测定多个类TCR抗体的所述选择性和优良特异性的一手段，若表现出对Ala突变表现出越高的敏感性，可以观察到越高特异性和胜肽依赖性的结合。所述策略可用于过滤和筛选表现出更高和优化的选择性和特异性性质的所述理想的类TCR抗体如多个MHC-限定胜肽特异性结合物。

[0495] 本发明人研究了HLA-A2/MAGE-A4的类TCR Ab对于内源性地显示在多个黑色素瘤细胞株的所述表面上的多个MHC-MAGE-A4胜肽复合物的结合特异性。多个细胞与抗MAGE-A4-HLA-A2的多个类TCR抗体Ab一起培养，接着与PE标记的链霉亲和素或多个抗小鼠Ab培养。一组的肿瘤细胞及多个正常初级细胞已被定性出HLA-A2(阳性)及MAGE-A4(阳性或阴性)的表达，被用来比较所述多个类TCR抗体的所述结合。如图56所示，所述类TCR抗体辨识低强度的MAGE-A4-阳性及HLA-A2-阳性的多个细胞。所述类TCR抗体被测试在各种来源的多个HLA-A2-阳性细胞株上，所述细胞株不显示MAGE-A4RNA表达(MAGE-A4-阴性)，这些具有一MAGE-A4/HLA-A2TCRL-双特异性的建构体的细胞的杀灭能力也被测试。如图56所示，C106B9不结合所述多个细胞中的任何一种。

[0496] 多个功能性分析被用来进一步定性所述所述C106B9类TCR抗体。将多个TCRL的多个可变区融合到一个抗CD3scFv，所述抗CD3scFv可以以一双特异性的形式重新靶向多个效应T细胞以杀死肿瘤标靶细胞。如图57所示，所述C106B9双特异性类TCR抗体的多个构建体在多个人类PBMC的存在下，在体外显示了对多个MAGE-A4阳性的细胞的强大的细胞毒性。TCCSUP和OVCAR，MAGE-A4阴性细胞株作为阴性对照组，并且表现出没有细胞毒性。如进一步在图58所示，用C106B9TCRL针对一组的多个HLA-A2+/MAGE-A4-正常人类原代细胞没有细胞毒性被侦测到证实了它们的选择性。

[0497] 实施例3B

[0498] 在多个NOD/SCID小鼠中C106B9BS TCRL在s.c.A375黑色素瘤肿瘤形成模型中的体内功效

[0499] 图59显示了在多个NOD/SCID小鼠中C106B9BS TCRL在s.c.A375黑色素瘤肿瘤形成模型中的体内功效。显然，所述双特异性抗体的给药完全抑制了肿瘤形成超过35天的所述实验，如通过肿瘤体积所证实。所述结果支持在本文所述的多个临床设置中TCRL的可变序列的使用。

[0500] 实施例4

[0501] 对HLA-A2/MAGE-A9具有特异性的多个类TCR抗体

[0502] 对HLA-A2/MAGE-A9具有特异性的TCRL的分离和定性

[0503] 为了定性所述多个分离的类TCR抗体的所述结合特异性，通过流式细胞技术评估所述多个纯化的IgG的所述反应性和特异性。在多个T2APC中加入MAGE-A9胜肽或多个对照组胜肽以及与所述TCRL Ab F184C7一起培养，接着与PE标记的链霉亲和素或PE标记的多个抗小鼠Abs一起培养。如图60所示，F184C7结合加有MAGE-A9胜肽的多个T2细胞，但显示不结合加有多个对照组胜肽的多个细胞。

[0504] 为了进一步评估所述F184C7类TCR抗体的所述特异性，它们与对于所述MAGE-A9胜肽显示序列相似度的多个胜肽的反应性被评估。所述胜肽如表10所示。

[0505] 如图61所示，F184C7TCRL类TCR抗体不结合任何来自于所述相同组的多个相似胜肽的所述多个胜肽。所述多个数据证明了F184C7的所述高选择性和高特异性，并且证明了所述相似胜肽方法的所述用处以及如上所述所开发的多个工具以评估出多个TCRL的所述选择性和优良特异性。

[0506] 为了研究所述多个分离的类TCR抗体对所述MAGE-A9胜肽的所述优良胜肽表位特异性，进行了丙氨酸扫瞄，在所述丙氨酸扫瞄中，所述胜肽中的多个特定的残基被突变为丙氨酸，并且通过将所述多个突变的胜肽加在多个T2抗原呈现细胞上以测试所述多个类TCR抗体与多个Ala突变胜肽的所述结合(表11)。通过流式细胞技术监测结合，当通过平均荧光强度(MFI)所测定的，多个TCR-样抗体与所述多个突变胜肽的结合的程度被用来与加有所述未突变MAGE-A4胜肽的多个T2APC比较。所述各种Ala突变胜肽(描述在图2)的所述适当的加入是通过流式细胞技术使用BB7.2来监测，所述BB7.2是针对HLA-A2的一单克隆抗体。

[0507] 与所述天然未突变的MAGE-A9相比，所有Ala突变胜肽被有效地加到多个T2细胞上(数据未示出)。如图62所示，所述类TCR抗体表现出胜肽依赖性结合，因为多个特定的突变影响了所述结合，并且在多个特定胜肽位置引入Ala时，在所述类TCR抗体的结合强度中引发了一减少。所述多个结果表明，在HLA-A2加入各种Ala突变MAGE-A9胜肽的情况下，所述类TCR抗体表现出胜肽特异性及限制性的结合，表明所述抗体在所述抗体的结合性质上是相似于TCR，因此，所述抗体以MHC限定以及胜肽特异性的方式来结合所述MHC-胜肽复合物。

[0508] 所述F184C7类TCR抗体表现出90％的一显着下降在与Ala突变胜肽结合的五个位置#3、5、6、7和8。

[0509] 总体而言，所述丙氨酸扫描分析揭示了Ala扫描可以被用作测定多个类TCR抗体的所述选择性和优良特异性的一手段，若表现出对Ala突变表现出越高的敏感性，可以观察到越高特异性和胜肽依赖性的结合。所述策略可用于过滤和筛选表现出更高和优化的选择性和特异性性质的所述理想的类TCR抗体如多个MHC-限定胜肽特异性结合物。

[0510] 本发明人研究了所述HLA-A2/MAGE-A9类TCR Ab对不显示MAGE-A9RNA表达的各种来源的正常原代细胞的板的结合特异性。如图63所示，F184C7TCRL不与所述多个细胞中的任何一种结合。阳性对照组是加有所述MAGE-A9胜肽的多个T2细胞，所述多个T2细胞被F184C7胜肽强烈地结合。

[0511] 实施例5

[0512] 对HLA-A2/PAP具有特异性的多个类TCR抗体

[0513] 对HLA-A2/PAP具有特异性的TCRL的分离和定性

[0514] 为了定性所述多个分离的类TCR抗体的所述结合特异性，通过流式细胞技术评估

所述多个纯化的IgG的所述反应性和特异性。在多个T2APC中加入PAP胜肽或多个对照组胜肽以及与所述TCRL Ab D10A3一起培养，接着与PE标记的链霉亲和素或PE标记的多个抗小鼠Abs一起培养。如图64所示，D10A3结合加有PAP胜肽的多个T2细胞，但显示不结合加有多个对照组胜肽的多个细胞。

[0515] 为了进一步评估所述D10A3类TCR抗体的所述特异性，评估它们与对于所述PAP胜肽显示序列相似度的多个胜肽的反应性。所述胜肽如表12所示。

[0516] 如图65所示，D10A3TCRL类TCR抗体不结合任何来自于所述相同组的多个相似胜肽的所述多个胜肽。所述多个数据证明了D10A3的所述高选择性和高特异性，并且证明了所述相似胜肽方法的所述用处以及如上所述所开发的多个工具以评估出多个TCRL的所述选择性和优良特异性。

[0517] 为了研究所述多个分离的类TCR抗体对所述PAP胜肽的所述优良胜肽表位特异性，进行了丙氨酸扫瞄，在所述丙氨酸扫瞄中，所述胜肽中的多个特定的残基被突变为丙氨酸，并且通过将所述多个突变的胜肽加在多个T2抗原呈现细胞上以测试所述多个类TCR抗体与多个Ala突变胜肽的所述结合(表13)。通过流式细胞技术监测结合，当通过平均荧光强度(MFI)所测定的，多个TCR-样抗体与所述多个突变胜肽的结合的程度被用来与加有所述未突变PAP胜肽的多个T2APC比较。所述各种Ala突变胜肽(描述在图2)的所述适当的加入是通过流式细胞技术使用BB7.2来监测，所述BB7.2是针对HLA-A2的一单克隆抗体。

[0518] 与所述天然未突变的PAP相比，所有Ala突变胜肽被有效地加到多个T2细胞上(数据未示出)。如图66所示，所述类TCR抗体表现出胜肽依赖性结合，因为多个特定的突变影响了所述结合，并且在多个特定胜肽位置引入Ala时，在所述类TCR抗体的结合强度中引发了一减少。所述多个结果表明，在HLA-A2加入各种Ala突变PAP胜肽的情况下，所述类TCR抗体表现出胜肽特异性及限制性的结合，表明所述抗体在所述抗体的结合性质上是相似于TCR，因此，所述抗体以MHC限定以及胜肽特异性的方式来结合所述MHC-胜肽复合物。

[0519] 所述D10A3类TCR抗体表现出90％的一显着下降在与Ala突变胜肽结合的三个位置#3、6和8。，还观察到与在位置#4的一Ala突变胜肽的结合的70％的减少。一第五个位置的敏感度可归因于位置号码7(45％的减少)。

[0520] 本发明人研究了所述HLA-A2/PAP类TCR Ab对不显示PAP RNA表达的各种来源的正常原代细胞的板的结合特异性。如图67所示，D10A3TCRL不与所述多个细胞中的任何一种结合。阳性对照组是加有所述PAP胜肽的多个T2细胞，所述多个T2细胞被D10A3胜肽强烈地结合。

[0521] 虽然本发明已经结合其特定实施例进行了描述，但是显而易见的是，许多备选方案，修饰以及变动对本领域技术人员来说是显而易见的。因此，本发明旨在涵盖所有落入所述权利要求的精神和范围内的所有这样的备选方案，修饰以及变动。

[0522] 在本说明书中提及的所有出版物，专利和专利申请以其整体作为参考文献并入本说明书中，在同样的程度上，所述独立的出版物、专利或专利申请案被明确地且个别地标示为以引用的方式并入本文中。此外，本申请中任何参考文献的引用或证明不应被解释为承认所述参考文献可用作本发明的现有技术。在同样的程度上，所用的章节标题，不应被认为是必要的限制。

[0001] 序列表
[0002] <110> 应用免疫科技有限公司
[0003] 彼尔高棉，米拉
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[0005] 瑞特，约拉姆
[0006] 贝尔，伊兰
[0007] 仙尼克，卡莲
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[0151] Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
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[0161] Thr Gly Asn Lys Ile Leu Val Lys Gln Ser Pro Met Leu Val Ala Tyr
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[0163] Asp Asn Ala Val Asn Leu Ser Trp Lys His Leu Cys Pro Ser Pro Leu
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[0185] 35 40 45
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[0197] <213> homo sapiens
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[0201] Thr Gly Asn Lys Ile Leu Val Lys Gln Ser Pro Met Leu Val Ala Tyr
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[0203] Asp Asn Ala Val Asn Leu Ser Cys Lys Tyr Ser Tyr Asn Leu Phe Ser
[0204] 35 40 45
[0205] Arg Glu Phe Arg Ala Ser Leu His Lys Gly Leu Asp Ser Ala Val Glu
[0206] 50 55 60
[0207] Val Cys Val Val Tyr Gly Asn Tyr Ser Gln Gln Leu Gln Val Tyr Ser
[0208] 65 70 75 80
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[0212] 100 105 110
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[0214] 115 120 125
[0215] Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro
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[0219] Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile
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[0225] Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
[0226] 210 215 220
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[0241] 65 70 75 80
[0242] Thr Ser Asn Ala Glu Cys Asp Cys Thr Pro Gly Phe His Cys Leu Gly
[0243] 85 90 95
[0244] Ala Gly Cys Ser Met Cys Glu Gln Asp Cys Lys Gln Gly Gln Glu Leu
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[0246] Thr Lys Lys Gly Cys Lys Asp Cys Cys Phe Gly Thr Phe Asn Asp Gln
[0247] 115 120 125
[0248] Lys Arg Gly Ile Cys Arg Pro Trp Thr Asn Cys Ser Leu Asp Gly Lys
[0249] 130 135 140
[0250] Ser Val Leu Val Asn Gly Thr Lys Glu Arg Asp Val Val Cys Gly Pro
[0251] 145 150 155 160

[0252] Ser Pro Ala Asp Leu Ser Pro Gly Ala Ser Ser Val Thr Pro Pro Ala
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[0254] Pro Ala Arg Glu Pro Gly His Ser Pro Gln Ile Ile Ser Phe Phe Leu
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[0256] Ala Leu Thr Ser Thr Ala Leu Leu Phe Leu Leu Phe Phe Leu Thr Leu
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[0258] Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
[0259] 210 215 220
[0260] Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
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[0262] Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
[0263] 245 250 255
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[0265] <211> 199
[0266] <212> PRT
[0267] <213> homo sapiens
[0268] <400> 14
[0269] Met Lys Ser Gly Leu Trp Tyr Phe Phe Leu Phe Cys Leu Arg Ile Lys
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[0271] Val Leu Thr Gly Glu Ile Asn Gly Ser Ala Asn Tyr Glu Met Phe Ile
[0272] 20 25 30
[0273] Phe His Asn Gly Gly Val Gln Ile Leu Cys Lys Tyr Pro Asp Ile Val
[0274] 35 40 45
[0275] Gln Gln Phe Lys Met Gln Leu Leu Lys Gly Gly Gln Ile Leu Cys Asp
[0276] 50 55 60
[0277] Leu Thr Lys Thr Lys Gly Ser Gly Asn Thr Val Ser Ile Lys Ser Leu
[0278] 65 70 75 80
[0279] Lys Phe Cys His Ser Gln Leu Ser Asn Asn Ser Val Ser Phe Phe Leu
[0280] 85 90 95
[0281] Tyr Asn Leu Asp His Ser His Ala Asn Tyr Tyr Phe Cys Asn Leu Ser
[0282] 100 105 110
[0283] Ile Phe Asp Pro Pro Pro Phe Lys Val Thr Leu Thr Gly Gly Tyr Leu
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[0285] His Ile Tyr Glu Ser Gln Leu Cys Cys Gln Leu Lys Phe Trp Leu Pro
[0286] 130 135 140
[0287] Ile Gly Cys Ala Ala Phe Val Val Val Cys Ile Leu Gly Cys Ile Leu
[0288] 145 150 155 160
[0289] Ile Cys Trp Leu Thr Lys Lys Lys Tyr Ser Ser Ser Val His Asp Pro
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[0291] Asn Gly Glu Tyr Met Phe Met Arg Ala Val Asn Thr Ala Lys Lys Ser
[0292] 180 185 190
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[0294] 195

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[0296] <211> 277

[0297] <212> PRT

[0298] <213> homo sapiens

[0299] <400> 15

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[0302] Leu Leu Leu Gly Leu Gly Leu Ser Thr Val Thr Gly Leu His Cys Val

[0303] 20 25 30

[0304] Gly Asp Thr Tyr Pro Ser Asn Asp Arg Cys Cys His Glu Cys Arg Pro

[0305] 35 40 45

[0306] Gly Asn Gly Met Val Ser Arg Cys Ser Arg Ser Gln Asn Thr Val Cys

[0307] 50 55 60

[0308] Arg Pro Cys Gly Pro Gly Phe Tyr Asn Asp Val Val Ser Ser Lys Pro

[0309] 65 70 75 80

[0310] Cys Lys Pro Cys Thr Trp Cys Asn Leu Arg Ser Gly Ser Glu Arg Lys

[0311] 85 90 95

[0312] Gln Leu Cys Thr Ala Thr Gln Asp Thr Val Cys Arg Cys Arg Ala Gly

[0313] 100 105 110

[0314] Thr Gln Pro Leu Asp Ser Tyr Lys Pro Gly Val Asp Cys Ala Pro Cys

[0315] 115 120 125

[0316] Pro Pro Gly His Phe Ser Pro Gly Asp Asn Gln Ala Cys Lys Pro Trp

[0317] 130 135 140

[0318] Thr Asn Cys Thr Leu Ala Gly Lys His Thr Leu Gln Pro Ala Ser Asn

[0319] 145 150 155 160

[0320] Ser Ser Asp Ala Ile Cys Glu Asp Arg Asp Pro Pro Ala Thr Gln Pro

[0321] 165 170 175

[0322] Gln Glu Thr Gln Gly Pro Pro Ala Arg Pro Ile Thr Val Gln Pro Thr

[0323] 180 185 190

[0324] Glu Ala Trp Pro Arg Thr Ser Gln Gly Pro Ser Thr Arg Pro Val Glu

[0325] 195 200 205

[0326] Val Pro Gly Gly Arg Ala Val Ala Ala Ile Leu Gly Leu Gly Leu Val

[0327] 210 215 220

[0328] Leu Gly Leu Leu Gly Pro Leu Ala Ile Leu Leu Ala Leu Tyr Leu Leu

[0329] 225 230 235 240

[0330] Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala His Lys Pro Pro Gly Gly

[0331] 245 250 255

[0332] Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu Gln Ala Asp Ala His Ser

[0333] 260 265 270

[0334] Thr Leu Ala Lys Ile

[0335] 275

[0336] <210> 16
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[0338] <212> PRT
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[0343] Leu Ala Leu Leu Ser Pro Gly Ala Ala Asp Phe Asn Ile Ser Ser Leu
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[0345] Ser Gly Leu Leu Ser Pro Ala Leu Thr Glu Ser Leu Leu Val Ala Leu
[0346] 35 40 45
[0347] Pro Pro Cys His Leu Thr Gly Gly Asn Ala Thr Leu Met Val Arg Arg
[0348] 50 55 60
[0349] Ala Asn Asp Ser Lys Val Val Thr Ser Ser Phe Val Val Pro Pro Cys
[0350] 65 70 75 80
[0351] Arg Gly Arg Arg Glu Leu Val Ser Val Val Asp Ser Gly Ala Gly Phe
[0352] 85 90 95
[0353] Thr Val Thr Arg Leu Ser Ala Tyr Gln Val Thr Asn Leu Val Pro Gly
[0354] 100 105 110
[0355] Thr Lys Phe Tyr Ile Ser Tyr Leu Val Lys Lys Gly Thr Ala Thr Glu
[0356] 115 120 125
[0357] Ser Ser Arg Glu Ile Pro Met Ser Thr Leu Pro Arg Arg Asn Met Glu
[0358] 130 135 140
[0359] Ser Ile Gly Leu Gly Met Ala Arg Thr Gly Gly Met Val Val Ile Thr
[0360] 145 150 155 160
[0361] Val Leu Leu Ser Val Ala Met Phe Leu Leu Val Leu Gly Phe Ile Ile
[0362] 165 170 175
[0363] Ala Leu Ala Leu Gly Ser Arg Lys
[0364] 180
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[0367] <212> PRT
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[0374] Ser Leu Phe Ala Glu Thr Ile Trp Val Thr Ala Asp Gln Tyr Arg Val
[0375] 35 40 45
[0376] Tyr Pro Leu Met Gly Val Ser Gly Lys Asp Asp Val Phe Ala Gly Ala
[0377] 50 55 60

[0378] Trp Ile Ala Ile Phe Cys Gly Phe Ser Phe Phe Met Val Ala Ser Phe
[0379] 65 70 75 80
[0380] Gly Val Gly Ala Ala Leu Cys Arg Arg Arg Ser Met Val Leu Thr Tyr
[0381] 85 90 95
[0382] Leu Val Leu Met Leu Ile Val Tyr Ile Phe Glu Cys Ala Ser Cys Ile
[0383] 100 105 110
[0384] Thr Ser Tyr Thr His Arg Asp Tyr Met Val Ser Asn Pro Ser Leu Ile
[0385] 115 120 125
[0386] Thr Lys Gln Met Leu Thr Phe Tyr Ser Ala Asp Thr Asp Gln Gly Gln
[0387] 130 135 140
[0388] Glu Leu Thr Arg Leu Trp Asp Arg Val Met Ile Glu Gln Glu Cys Cys
[0389] 145 150 155 160
[0390] Gly Thr Ser Gly Pro Met Asp Trp Val Asn Phe Thr Ser Ala Phe Arg
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[0392] Ala Ala Thr Pro Glu Val Val Phe Pro Trp Pro Pro Leu Cys Cys Arg
[0393] 180 185 190
[0394] Arg Thr Gly Asn Phe Ile Pro Leu Asn Glu Glu Gly Cys Arg Leu Gly
[0395] 195 200 205
[0396] His Met Asp Tyr Leu Phe Thr Lys Ala Gly Val Gln Trp His Asn Leu
[0397] 210 215 220
[0398] Ser Ser Leu Gln Arg Leu Pro Pro Gly Phe Lys Gly Phe Ser His Leu
[0399] 225 230 235 240
[0400] Ser Phe Gln Ser Ser Trp Asp Tyr Arg Ala Ala Ser Asn Thr Ser Ala
[0401] 245 250 255
[0402] Thr Pro Ser Thr Ala Thr Arg Gly Val Ser Arg Gly Leu Gly Leu Pro
[0403] 260 265 270
[0404] Ser
[0405] <210> 18
[0406] <211> 258
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[0408] <213> homo sapiens
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[0414] Ser Leu Phe Ala Glu Thr Ile Trp Val Thr Ala Asp Gln Tyr Arg Val
[0415] 35 40 45
[0416] Tyr Pro Leu Met Gly Val Ser Gly Lys Asp Asp Val Phe Ala Gly Ala
[0417] 50 55 60
[0418] Trp Ile Ala Ile Phe Cys Gly Phe Ser Phe Phe Met Val Ala Ser Phe
[0419] 65 70 75 80

[0420] Gly Val Gly Ala Ala Leu Cys Arg Arg Arg Ser Met Val Leu Thr Tyr
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[0422] Leu Val Leu Met Leu Ile Val Tyr Ile Phe Glu Cys Ala Ser Cys Ile
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[0424] Thr Ser Tyr Thr His Arg Asp Tyr Met Val Ser Asn Pro Ser Leu Ile
[0425] 115 120 125
[0426] Thr Lys Gln Met Leu Thr Phe Tyr Ser Ala Asp Thr Asp Gln Gly Gln
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[0428] Glu Leu Thr Arg Leu Trp Asp Arg Val Met Ile Glu Gln Glu Cys Cys
[0429] 145 150 155 160
[0430] Gly Thr Ser Gly Pro Met Asp Trp Val Asn Phe Thr Ser Ala Phe Arg
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[0432] Ala Ala Thr Pro Glu Val Val Phe Pro Trp Pro Pro Leu Cys Cys Arg
[0433] 180 185 190
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[0436] His Met Asp Tyr Leu Phe Thr Lys Gly Cys Phe Glu His Ile Gly His
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[0438] Ala Ile Asp Ser Tyr Thr Trp Gly Ile Ser Trp Phe Gly Phe Ala Ile
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[0453] 35 40 45
[0454] Pro His Met Val Gly Ile Gly Gln Asn Ser Ser Phe Asn Ser Trp Met
[0455] 50 55 60
[0456] Glu Ser Gln Phe Leu His Pro Ser Met Glu Pro Gly Gln Trp Leu Pro
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[0458] Tyr Ile Thr Ile Phe Arg Phe Thr His Ile Ile Arg Cys Val Arg Ile
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[0460] Ser Phe Leu Phe Asn Ile Pro Trp Tyr Gly Tyr Pro His Phe Val Cys
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[0462] His Ser Ser Val Ser Gly His Leu Gly Tyr Phe Tyr Leu Leu Leu Leu
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[0464] Trp Leu Val Cys Cys Glu His Arg Cys Thr Asn Ile Cys Ser Arg Gln
[0465] 130 135 140
[0466] Thr Ser Phe Lys Arg Leu Phe Leu Lys Lys Tyr Val Ser Tyr Asn Ile
[0467] 145 150 155 160
[0468] Phe Leu Leu Cys Val Glu Ser Asp Ile Ser Ile Asp Leu Glu Gly Tyr
[0469] 165 170 175
[0470] Gly Met Gly Cys Thr Asn Ile Cys Ser Arg Gln Thr Ser Phe Lys Arg
[0471] 180 185 190
[0472] Leu Phe Lys Arg Lys Tyr Arg Cys Leu Leu Asn Met Phe Leu Val Met
[0473] 195 200 205
[0474] Asn Val Glu Ser Gly Thr Asn Arg Tyr Met Glu Val Arg Arg Ala Trp
[0475] 210 215 220
[0476] Arg Gly Ser Lys Trp Glu Asp Glu Glu Asn Trp Leu Gly Ile Asp Val
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[0479] 245
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[0491] Leu Leu Thr Val Ile Ser Lys Gly Cys Ser Leu Asn Cys Val Asp Asp
[0492] 50 55 60
[0493] Ser Gln Asp Tyr Tyr Val Gly Lys Lys Asn Ile Thr Cys Cys Asp Thr
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[0495] Asp Leu Cys Asn Ala Ser Gly Ala His Ala Leu Gln Pro Ala Ala Ala
[0496] 85 90 95
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[0498] 100 105 110
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[0504] <400> 21

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[0507] Gly Phe Leu Phe Leu Leu Phe Phe Trp Leu Asp Arg Ser Val Leu Ala

[0508] 20 25 30

[0509] Lys Glu Leu Lys Phe Val Thr Leu Val Phe Arg His Gly Asp Arg Ser

[0510] 35 40 45

[0511] Pro Ile Asp Thr Phe Pro Thr Asp Pro Ile Lys Glu Ser Ser Trp Pro

[0512] 50 55 60

[0513] Gln Gly Phe Gly Gln Leu Thr Gln Leu Gly Met Glu Gln His Tyr Glu

[0514] 65 70 75 80

[0515] Leu Gly Glu Tyr Ile Arg Lys Arg Tyr Arg Lys Phe Leu Asn Glu Ser

[0516] 85 90 95

[0517] Tyr Lys His Glu Gln Val Tyr Ile Arg Ser Thr Asp Val Asp Arg Thr

[0518] 100 105 110

[0519] Leu Met Ser Ala Met Thr Asn Leu Ala Ala Leu Phe Pro Pro Glu Gly

[0520] 115 120 125

[0521] Val Ser Ile Trp Asn Pro Ile Leu Leu Trp Gln Pro Ile Pro Val His

[0522] 130 135 140

[0523] Thr Val Pro Leu Ser Glu Asp Gln Leu Leu Tyr Leu Pro Phe Arg Asn

[0524] 145 150 155 160

[0525] Cys Pro Arg Phe Gln Glu Leu Glu Ser Glu Thr Leu Lys Ser Glu Glu

[0526] 165 170 175

[0527] Phe Gln Lys Arg Leu His Pro Tyr Lys Asp Phe Ile Ala Thr Leu Gly

[0528] 180 185 190

[0529] Lys Leu Ser Gly Leu His Gly Gln Asp Leu Phe Gly Ile Trp Ser Lys

[0530] 195 200 205

[0531] Val Tyr Asp Pro Leu Tyr Cys Glu Ser Val His Asn Phe Thr Leu Pro

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[0533] Ser Trp Ala Thr Glu Asp Thr Met Thr Lys Leu Arg Glu Leu Ser Glu

[0534] 225 230 235 240

[0535] Leu Ser Leu Leu Ser Leu Tyr Gly Ile His Lys Gln Lys Glu Lys Ser

[0536] 245 250 255

[0537] Arg Leu Gln Gly Gly Val Leu Val Asn Glu Ile Leu Asn His Met Lys

[0538] 260 265 270

[0539] Arg Ala Thr Gln Ile Pro Ser Tyr Lys Lys Leu Ile Met Tyr Ser Ala

[0540] 275 280 285

[0541] His Asp Thr Thr Val Ser Gly Leu Gln Met Ala Leu Asp Val Tyr Asn

[0542] 290 295 300

[0543] Gly Leu Leu Pro Pro Tyr Ala Ser Cys His Leu Thr Glu Leu Tyr Phe

[0544] 305 310 315 320

[0545] Glu Lys Gly Glu Tyr Phe Val Glu Met Tyr Tyr Arg Asn Glu Thr Gln

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[0550] 355 360 365
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[0554] 385
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[0558] <213> homo sapiens
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[0563] 20 25 30
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[0565] 35 40 45
[0566] Pro Ile Asp Thr Phe Pro Thr Asp Pro Ile Lys Glu Ser Ser Trp Pro
[0567] 50 55 60
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[0570] Leu Gly Glu Tyr Ile Arg Lys Arg Tyr Arg Lys Phe Leu Asn Glu Ser
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[0580] Cys Pro Arg Phe Gln Glu Leu Glu Ser Glu Thr Leu Lys Ser Glu Glu
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[0594] Arg Ala Thr Gln Ile Pro Ser Tyr Lys Lys Leu Ile Met Tyr Ser Ala
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[0596] His Asp Thr Thr Val Ser Gly Leu Gln Met Ala Leu Asp Val Tyr Asn
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[0600] Glu Lys Gly Glu Tyr Phe Val Glu Met Tyr Tyr Arg Asn Glu Thr Gln
[0601] 325 330 335
[0602] His Glu Pro Tyr Pro Leu Met Leu Pro Gly Cys Ser Pro Ser Cys Pro
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[0604] Leu Glu Arg Phe Ala Glu Leu Val Gly Pro Val Ile Pro Gln Asp Trp
[0605] 355 360 365
[0606] Ser Thr Glu Cys Met Thr Thr Asn Ser His Gln Val Leu Lys Val Ile
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[0608] Phe Ala Val Ala Phe Cys Leu Ile Ser Ala Val Leu Met Val Leu Leu
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[0610] Phe Ile His Ile Arg Arg Gly Leu Cys Trp Gln Arg Glu Ser Tyr Gly
[0611] 405 410 415
[0612] Asn Ile
[0613] <210> 23
[0614] <211> 353
[0615] <212> PRT
[0616] <213> homo sapiens
[0617] <400> 23
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[1250] His Cys Leu Gly Cys Leu Ser Val Pro Pro Lys Glu Leu Arg Ala Ala
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[1252] Gly His Leu Ser Ser Pro Gly Tyr Leu Pro Ser Tyr Glu Arg Val Pro
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[1254] His Leu Pro His Pro Trp Ala Leu Cys Ala Pro
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[1258] <212> PRT
[1259] <213> homo sapiens

[1260] <400> 40
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[1268] 50 55 60
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[1301] 50 55 60

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[1309] 115 120 125
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[1314] Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly
[1315] 165 170 175
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[1336] 50 55 60
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[1340] 85 90 95
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[1354] 195 200 205
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[1381] 130 135 140
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[1385] 165 170 175

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[1387] 180 185 190
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[1402] 35 40 45
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[1422] 195 200 205
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[1428] 245 250 255
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[1430] 260 265 270
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[1450] 100 105 110
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[1460] 180 185 190
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[1470] 260 265 270
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[1503] Ile Tyr Arg Arg Arg Leu Met Lys Gln Asp Phe Ser Val Pro Gln Leu
[1504] 530 535 540
[1505] Pro His Ser Ser Ser His Trp Leu Arg Leu Pro Arg Ile Phe Cys Ser
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[1597] 660
[1598] <210> 47
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[3177] 420 425 430
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[3282] 435 440 445
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[3315] Gly Thr Ala Arg Arg Pro Gly Ala Ala Ala Ser Gly Glu Arg Asp Asp
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[3322] 180 185 190
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[3417] 195 200 205
[3418] Lys Val Tyr Gln Met Lys Ser Lys Pro Arg Gly Tyr Cys Leu Ile Ile
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[3420] Asn Asn His Asn Phe Ala Lys Ala Arg Glu Lys Val Pro Lys Leu His
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[3422] Ser Ile Arg Asp Arg Asn Gly Thr His Leu Asp Ala Gly Ala Leu Thr
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[3424] Thr Thr Phe Glu Glu Leu His Phe Glu Ile Lys Pro His Asp Asp Cys
[3425] 260 265 270
[3426] Thr Val Glu Gln Ile Tyr Glu Ile Leu Lys Ile Tyr Gln Leu Met Asp
[3427] 275 280 285
[3428] His Ser Asn Met Asp Cys Phe Ile Cys Cys Ile Leu Ser His Gly Asp
[3429] 290 295 300
[3430] Lys Gly Ile Ile Tyr Gly Thr Asp Gly Gln Glu Ala Pro Ile Tyr Glu
[3431] 305 310 315 320
[3432] Leu Thr Ser Gln Phe Thr Gly Leu Lys Cys Pro Ser Leu Ala Gly Lys
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[3435] 340 345 350
[3436] Gly Ile Pro Val Glu Thr Asp Ser Glu Glu Gln Pro Tyr Leu Glu Met
[3437] 355 360 365
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[3443] 405 410 415

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[3460] 35 40 45
[3461] Gly Ala Asp Tyr Ile Leu Leu Pro Phe Lys Lys Met Asp Phe Ser Arg
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[3466] 85 90 95
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[3474] 145 150 155 160
[3475] Arg Val Met Leu Tyr Gln Ile Ser Glu Glu Val Ser Arg Ser Glu Leu
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[3477] Arg Ser Phe Lys Phe Leu Leu Gln Glu Glu Ile Ser Lys Cys Lys Leu
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[3479] Asp Asp Asp Met Asn Leu Leu Asp Ile Phe Ile Glu Met Glu Lys Arg
[3480] 195 200 205
[3481] Val Ile Leu Gly Glu Gly Lys Leu Asp Ile Leu Lys Arg Val Cys Ala
[3482] 210 215 220
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[3484] 225 230 235 240
[3485] Ser Lys Glu Arg Ser Ser Ser Leu Glu Gly Ser Pro Asp Glu Phe Ser

[3486] 245 250 255
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[3488] 260 265 270
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[3490] 275 280 285
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[3492] 290 295 300
[3493] Lys Ala Arg Glu Lys Val Pro Lys Leu His Ser Ile Arg Asp Arg Asn
[3494] 305 310 315 320
[3495] Gly Thr His Leu Asp Ala Gly Ala Leu Thr Thr Thr Phe Glu Glu Leu
[3496] 325 330 335
[3497] His Phe Glu Ile Lys Pro His Asp Asp Cys Thr Val Glu Gln Ile Tyr
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[3502] 370 375 380
[3503] Thr Asp Gly Gln Glu Ala Pro Ile Tyr Glu Leu Thr Ser Gln Phe Thr
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[3505] Gly Leu Lys Cys Pro Ser Leu Ala Gly Lys Pro Lys Val Phe Phe Ile
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[3524] <211> 496
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[3531] 20 25 30
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[3534] Gln Glu Lys Arg Met Leu Glu Glu Ser Asn Leu Ser Phe Leu Lys Glu
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[3540] Gln Ile Ser Ala Tyr Arg Phe His Phe Cys Arg Met Ser Trp Ala Glu
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[3546] Ser Arg Ser Glu Leu Arg Ser Phe Lys Phe Leu Leu Gln Glu Glu Ile
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[3548] Ser Lys Cys Lys Leu Asp Asp Asp Met Asn Leu Leu Asp Ile Phe Ile
[3549] 165 170 175
[3550] Glu Met Glu Lys Arg Val Ile Leu Gly Glu Gly Lys Leu Asp Ile Leu
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[3552] Lys Arg Val Cys Ala Gln Ile Asn Lys Ser Leu Leu Lys Ile Ile Asn
[3553] 195 200 205
[3554] Asp Tyr Glu Glu Phe Ser Lys Gly Glu Glu Leu Cys Gly Val Met Thr
[3555] 210 215 220
[3556] Ile Ser Asp Ser Pro Arg Glu Gln Asp Ser Glu Ser Gln Thr Leu Asp
[3557] 225 230 235 240
[3558] Lys Val Tyr Gln Met Lys Ser Lys Pro Arg Gly Tyr Cys Leu Ile Ile
[3559] 245 250 255
[3560] Asn Asn His Asn Phe Ala Lys Ala Arg Glu Lys Val Pro Lys Leu His
[3561] 260 265 270
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[3565] 290 295 300
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[3567] 305 310 315 320
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[3569] 325 330 335

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[3574] Pro Lys Val Phe Phe Ile Gln Ala Cys Gln Gly Asp Asn Tyr Gln Lys
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[3576] Gly Ile Pro Val Glu Thr Asp Ser Glu Glu Gln Pro Tyr Leu Glu Met
[3577] 385 390 395 400
[3578] Asp Leu Ser Ser Pro Gln Thr Arg Tyr Ile Pro Asp Glu Ala Asp Phe
[3579] 405 410 415
[3580] Leu Leu Gly Met Ala Thr Val Asn Asn Cys Val Ser Tyr Arg Asn Pro
[3581] 420 425 430
[3582] Ala Glu Gly Thr Trp Tyr Ile Gln Ser Leu Cys Gln Ser Leu Arg Glu
[3583] 435 440 445
[3584] Arg Cys Pro Arg Gly Asp Asp Ile Leu Thr Ile Leu Thr Glu Val Asn
[3585] 450 455 460
[3586] Tyr Glu Val Ser Asn Lys Asp Asp Lys Lys Asn Met Gly Lys Gln Met
[3587] 465 470 475 480
[3588] Pro Gln Pro Thr Phe Thr Leu Arg Lys Lys Leu Val Phe Pro Ser Asp
[3589] 485 490 495
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[3597] Glu Asp Leu Ala Ser Leu Lys Phe Leu Ser Leu Asp Tyr Ile Pro Gln
[3598] 20 25 30
[3599] Arg Lys Gln Glu Pro Ile Lys Asp Ala Leu Met Leu Phe Gln Arg Leu
[3600] 35 40 45
[3601] Gln Glu Lys Arg Met Leu Glu Glu Ser Asn Leu Ser Phe Leu Lys Glu
[3602] 50 55 60
[3603] Leu Leu Phe Arg Ile Asn Arg Leu Asp Leu Leu Ile Thr Tyr Leu Asn
[3604] 65 70 75 80
[3605] Thr Arg Lys Glu Glu Met Glu Arg Glu Leu Gln Thr Pro Gly Arg Ala
[3606] 85 90 95
[3607] Gln Ile Ser Ala Tyr Arg Val Met Leu Tyr Gln Ile Ser Glu Glu Val
[3608] 100 105 110
[3609] Ser Arg Ser Glu Leu Arg Ser Phe Lys Phe Leu Leu Gln Glu Glu Ile
[3610] 115 120 125
[3611] Ser Lys Cys Lys Leu Asp Asp Asp Met Asn Leu Leu Asp Ile Phe Ile

[3612] 130 135 140
[3613] Glu Met Glu Lys Arg Val Ile Leu Gly Glu Gly Lys Leu Asp Ile Leu
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[3615] Lys Arg Val Cys Ala Gln Ile Asn Lys Ser Leu Leu Lys Ile Ile Asn
[3616] 165 170 175
[3617] Asp Tyr Glu Glu Phe Ser Lys Glu Arg Ser Ser Ser Leu Glu Gly Ser
[3618] 180 185 190
[3619] Pro Asp Glu Phe Ser Asn Gly Glu Glu Leu Cys Gly Val Met Thr Ile
[3620] 195 200 205
[3621] Ser Asp Ser Pro Arg Glu Gln Asp Ser Glu Ser Gln Thr Leu Asp Lys
[3622] 210 215 220
[3623] Val Tyr Gln Met Lys Ser Lys Pro Arg Gly Tyr Cys Leu Ile Ile Asn
[3624] 225 230 235 240
[3625] Asn His Asn Phe Ala Lys Ala Arg Glu Lys Val Pro Lys Leu His Ser
[3626] 245 250 255
[3627] Ile Arg Asp Arg Asn Gly Thr His Leu Asp Ala Gly Ala Leu Thr Thr
[3628] 260 265 270
[3629] Thr Phe Glu Glu Leu His Phe Glu Ile Lys Pro His Asp Asp Cys Thr
[3630] 275 280 285
[3631] Val Glu Gln Ile Tyr Glu Ile Leu Lys Ile Tyr Gln Leu Met Asp His
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[3637] Thr Ser Gln Phe Thr Gly Leu Lys Cys Pro Ser Leu Ala Gly Lys Pro
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[3639] Lys Val Phe Phe Ile Gln Ala Cys Gln Gly Asp Asn Tyr Gln Lys Gly
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[3642] 370 375 380
[3643] Leu Ser Ser Pro Gln Thr Arg Tyr Ile Pro Asp Glu Ala Asp Phe Leu
[3644] 385 390 395 400
[3645] Leu Gly Met Ala Thr Val Asn Asn Cys Val Ser Tyr Arg Asn Pro Ala
[3646] 405 410 415
[3647] Glu Gly Thr Trp Tyr Ile Gln Ser Leu Cys Gln Ser Leu Arg Glu Arg
[3648] 420 425 430
[3649] Cys Pro Arg Gly Asp Asp Ile Leu Thr Ile Leu Thr Glu Val Asn Tyr
[3650] 435 440 445
[3651] Glu Val Ser Asn Lys Asp Asp Lys Lys Asn Met Gly Lys Gln Met Pro
[3652] 450 455 460
[3653] Gln Pro Thr Phe Thr Leu Arg Lys Lys Leu Val Phe Pro Ser Asp

[3654] 465 470 475
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[3656] <211> 464
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[3659] <400> 70
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[3661] 1 5 10 15
[3662] Glu Asp Leu Ala Ser Leu Lys Phe Leu Ser Leu Asp Tyr Ile Pro Gln
[3663] 20 25 30
[3664] Arg Lys Gln Glu Pro Ile Lys Asp Ala Leu Met Leu Phe Gln Arg Leu
[3665] 35 40 45
[3666] Gln Glu Lys Arg Met Leu Glu Glu Ser Asn Leu Ser Phe Leu Lys Glu
[3667] 50 55 60
[3668] Leu Leu Phe Arg Ile Asn Arg Leu Asp Leu Leu Ile Thr Tyr Leu Asn
[3669] 65 70 75 80
[3670] Thr Arg Lys Glu Glu Met Glu Arg Glu Leu Gln Thr Pro Gly Arg Ala
[3671] 85 90 95
[3672] Gln Ile Ser Ala Tyr Arg Val Met Leu Tyr Gln Ile Ser Glu Glu Val
[3673] 100 105 110
[3674] Ser Arg Ser Glu Leu Arg Ser Phe Lys Phe Leu Leu Gln Glu Glu Ile
[3675] 115 120 125
[3676] Ser Lys Cys Lys Leu Asp Asp Asp Met Asn Leu Leu Asp Ile Phe Ile
[3677] 130 135 140
[3678] Glu Met Glu Lys Arg Val Ile Leu Gly Glu Gly Lys Leu Asp Ile Leu
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[3680] Lys Arg Val Cys Ala Gln Ile Asn Lys Ser Leu Leu Lys Ile Ile Asn
[3681] 165 170 175
[3682] Asp Tyr Glu Glu Phe Ser Lys Gly Glu Glu Leu Cys Gly Val Met Thr
[3683] 180 185 190
[3684] Ile Ser Asp Ser Pro Arg Glu Gln Asp Ser Glu Ser Gln Thr Leu Asp
[3685] 195 200 205
[3686] Lys Val Tyr Gln Met Lys Ser Lys Pro Arg Gly Tyr Cys Leu Ile Ile
[3687] 210 215 220
[3688] Asn Asn His Asn Phe Ala Lys Ala Arg Glu Lys Val Pro Lys Leu His
[3689] 225 230 235 240
[3690] Ser Ile Arg Asp Arg Asn Gly Thr His Leu Asp Ala Gly Ala Leu Thr
[3691] 245 250 255
[3692] Thr Thr Phe Glu Glu Leu His Phe Glu Ile Lys Pro His Asp Asp Cys
[3693] 260 265 270
[3694] Thr Val Glu Gln Ile Tyr Glu Ile Leu Lys Ile Tyr Gln Leu Met Asp
[3695] 275 280 285

[3696] His Ser Asn Met Asp Cys Phe Ile Cys Cys Ile Leu Ser His Gly Asp
[3697] 290 295 300
[3698] Lys Gly Ile Ile Tyr Gly Thr Asp Gly Gln Glu Ala Pro Ile Tyr Glu
[3699] 305 310 315 320
[3700] Leu Thr Ser Gln Phe Thr Gly Leu Lys Cys Pro Ser Leu Ala Gly Lys
[3701] 325 330 335
[3702] Pro Lys Val Phe Phe Ile Gln Ala Cys Gln Gly Asp Asn Tyr Gln Lys
[3703] 340 345 350
[3704] Gly Ile Pro Val Glu Thr Asp Ser Glu Glu Gln Pro Tyr Leu Glu Met
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[3706] Asp Leu Ser Ser Pro Gln Thr Arg Tyr Ile Pro Asp Glu Ala Asp Phe
[3707] 370 375 380
[3708] Leu Leu Gly Met Ala Thr Val Asn Asn Cys Val Ser Tyr Arg Asn Pro
[3709] 385 390 395 400
[3710] Ala Glu Gly Thr Trp Tyr Ile Gln Ser Leu Cys Gln Ser Leu Arg Glu
[3711] 405 410 415
[3712] Arg Cys Pro Arg Gly Asp Asp Ile Leu Thr Ile Leu Thr Glu Val Asn
[3713] 420 425 430
[3714] Tyr Glu Val Ser Asn Lys Asp Asp Lys Lys Asn Met Gly Lys Gln Met
[3715] 435 440 445
[3716] Pro Gln Pro Thr Phe Thr Leu Arg Lys Lys Leu Val Phe Pro Ser Asp
[3717] 450 455 460
[3718] <210> 71
[3719] <211> 235
[3720] <212> PRT
[3721] <213> homo sapiens
[3722] <400> 71
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[3724] 1 5 10 15
[3725] Glu Asp Leu Ala Ser Leu Lys Phe Leu Ser Leu Asp Tyr Ile Pro Gln
[3726] 20 25 30
[3727] Arg Lys Gln Glu Pro Ile Lys Asp Ala Leu Met Leu Phe Gln Arg Leu
[3728] 35 40 45
[3729] Gln Glu Lys Arg Met Leu Glu Glu Ser Asn Leu Ser Phe Leu Lys Glu
[3730] 50 55 60
[3731] Leu Leu Phe Arg Ile Asn Arg Leu Asp Leu Leu Ile Thr Tyr Leu Asn
[3732] 65 70 75 80
[3733] Thr Arg Lys Glu Glu Met Glu Arg Glu Leu Gln Thr Pro Gly Arg Ala
[3734] 85 90 95
[3735] Gln Ile Ser Ala Tyr Arg Val Met Leu Tyr Gln Ile Ser Glu Glu Val
[3736] 100 105 110
[3737] Ser Arg Ser Glu Leu Arg Ser Phe Lys Phe Leu Leu Gln Glu Glu Ile

[3738] 115 120 125
[3739] Ser Lys Cys Lys Leu Asp Asp Asp Met Asn Leu Leu Asp Ile Phe Ile
[3740] 130 135 140
[3741] Glu Met Glu Lys Arg Val Ile Leu Gly Glu Gly Lys Leu Asp Ile Leu
[3742] 145 150 155 160
[3743] Lys Arg Val Cys Ala Gln Ile Asn Lys Ser Leu Leu Lys Ile Ile Asn
[3744] 165 170 175
[3745] Asp Tyr Glu Glu Phe Ser Lys Glu Arg Ser Ser Ser Leu Glu Gly Ser
[3746] 180 185 190
[3747] Pro Asp Glu Phe Ser Asn Asp Phe Gly Gln Ser Leu Pro Asn Glu Lys
[3748] 195 200 205
[3749] Gln Thr Ser Gly Ile Leu Ser Asp His Gln Gln Ser Gln Phe Cys Lys
[3750] 210 215 220
[3751] Ser Thr Gly Glu Ser Ala Gln Thr Ser Gln His
[3752] 225 230 235
[3753] <210> 72
[3754] <211> 9
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[3759] <222> (1)..(9)
[3760] <223> 短胜肽
[3761] <400> 72
[3762] Ile Leu Lys Glu Pro Val His Gly Val
[3763] 1 5
[3764] <210> 73
[3765] <211> 9
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[3771] <223> 短胜肽
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[3773] Ser Leu Tyr Asn Thr Val Ala Thr Leu
[3774] 1 5
[3775] <210> 74
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[3780] <221> PEPTIDE
[3781] <222> (1)..(8)
[3782] <223> 短胜肽
[3783] <400> 74
[3784] Ile Leu Glu Pro Val His Gly Val
[3785] 1 5
[3786] <210> 75
[3787] <211> 9
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[3791] <221> PEPTIDE
[3792] <222> (1)..(9)
[3793] <223> 短胜肽
[3794] <400> 75
[3795] Gly Ile Leu Gly Phe Val Phe Thr Leu
[3796] 1 5
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[3798] <211> 252
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[3800] <213> Influenza A virus
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[3802] Met Ser Leu Leu Thr Glu Val Glu Thr Tyr Val Leu Ser Ile Val Pro
[3803] 1 5 10 15
[3804] Ser Gly Pro Leu Lys Ala Glu Ile Ala Gln Arg Leu Glu Asp Val Phe
[3805] 20 25 30
[3806] Ala Gly Lys Asn Thr Asp Leu Glu Ala Leu Met Glu Trp Leu Lys Thr
[3807] 35 40 45
[3808] Arg Pro Ile Leu Ser Pro Leu Thr Lys Gly Ile Leu Gly Phe Val Phe
[3809] 50 55 60
[3810] Thr Leu Thr Val Pro Ser Glu Arg Gly Leu Gln Arg Arg Arg Phe Val
[3811] 65 70 75 80
[3812] Gln Asn Ala Leu Asn Gly Asn Gly Asp Pro Asn Asn Met Asp Arg Ala
[3813] 85 90 95
[3814] Val Lys Leu Tyr Arg Lys Leu Lys Arg Glu Ile Thr Phe His Gly Ala
[3815] 100 105 110
[3816] Lys Glu Val Ala Leu Ser Tyr Ser Ala Gly Ala Leu Ala Ser Cys Met
[3817] 115 120 125
[3818] Gly Leu Ile Tyr Asn Arg Met Gly Ala Val Thr Thr Glu Val Ala Phe
[3819] 130 135 140
[3820] Ala Val Val Cys Ala Thr Cys Glu Gln Ile Ala Asp Ser Gln His Arg
[3821] 145 150 155 160

[3822] Ser His Arg Gln Met Val Thr Thr Thr Asn Pro Leu Ile Arg His Glu
[3823] 165 170 175
[3824] Asn Arg Met Val Leu Ala Ser Thr Thr Ala Lys Ala Met Glu Gln Met
[3825] 180 185 190
[3826] Ala Gly Ser Ser Glu Gln Ala Ala Glu Ala Met Glu Val Ala Ser Gln
[3827] 195 200 205
[3828] Ala Arg Gln Met Val Gln Ala Met Arg Ala Ile Gly Thr Pro Pro Ser
[3829] 210 215 220
[3830] Ser Ser Ala Gly Leu Lys Asp Asp Leu Leu Glu Asn Leu Gln Ala Tyr
[3831] 225 230 235 240
[3832] Gln Lys Arg Met Gly Val Gln Met Gln Arg Phe Lys
[3833] 245 250
[3834] <210> 77
[3835] <211> 584
[3836] <212> PRT
[3837] <213> Influenza A virus
[3838] <400> 77
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[3841] Arg Ile Cys Thr Gly Ile Thr Ser Ser Asn Ser Pro His Val Val Lys
[3842] 20 25 30
[3843] Thr Ala Thr Gln Gly Glu Val Asn Val Thr Gly Val Ile Pro Leu Thr
[3844] 35 40 45
[3845] Thr Thr Pro Thr Lys Ser His Phe Ala Asn Leu Lys Gly Thr Gln Thr
[3846] 50 55 60
[3847] Arg Gly Lys Leu Cys Pro Asn Cys Phe Asn Cys Thr Asp Leu Asp Val
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[3849] Ala Leu Gly Arg Pro Lys Cys Met Gly Asn Thr Pro Ser Ala Lys Val
[3850] 85 90 95
[3851] Ser Ile Leu His Glu Val Lys Pro Ala Thr Ser Gly Cys Phe Pro Ile
[3852] 100 105 110
[3853] Met His Asp Arg Thr Lys Ile Arg Gln Leu Pro Asn Leu Leu Arg Gly
[3854] 115 120 125
[3855] Tyr Glu Asn Ile Arg Leu Ser Thr Ser Asn Val Ile Asn Thr Glu Thr
[3856] 130 135 140
[3857] Ala Pro Gly Gly Pro Tyr Lys Val Gly Thr Ser Gly Ser Cys Pro Asn
[3858] 145 150 155 160
[3859] Val Ala Asn Gly Asn Gly Phe Phe Asn Thr Met Ala Trp Val Ile Pro
[3860] 165 170 175
[3861] Lys Asp Asn Asn Lys Thr Ala Ile Asn Pro Val Thr Val Glu Val Pro
[3862] 180 185 190
[3863] Tyr Ile Cys Ser Glu Gly Glu Asp Gln Ile Thr Val Trp Gly Phe His

[3864] 195 200 205
[3865] Ser Asp Asp Lys Thr Gln Met Glu Arg Leu Tyr Gly Asp Ser Asn Pro
[3866] 210 215 220
[3867] Gln Lys Phe Thr Ser Ser Ala Asn Gly Val Thr Thr His Tyr Val Ser
[3868] 225 230 235 240
[3869] Gln Ile Gly Gly Phe Pro Asn Gln Thr Glu Asp Glu Gly Leu Lys Gln
[3870] 245 250 255
[3871] Ser Gly Arg Ile Val Val Asp Tyr Met Val Gln Lys Pro Gly Lys Thr
[3872] 260 265 270
[3873] Gly Thr Ile Val Tyr Gln Arg Gly Ile Leu Leu Pro Gln Lys Val Trp
[3874] 275 280 285
[3875] Cys Ala Ser Gly Arg Ser Lys Val Ile Lys Gly Ser Leu Pro Leu Ile
[3876] 290 295 300
[3877] Gly Glu Ala Asp Cys Leu His Glu Lys Tyr Gly Gly Leu Asn Lys Ser
[3878] 305 310 315 320
[3879] Lys Pro Tyr Tyr Thr Gly Glu His Ala Lys Ala Ile Gly Asn Cys Pro
[3880] 325 330 335
[3881] Ile Trp Val Lys Thr Pro Leu Lys Leu Ala Asn Gly Thr Lys Tyr Arg
[3882] 340 345 350
[3883] Pro Pro Ala Lys Leu Leu Lys Glu Arg Gly Phe Phe Gly Ala Ile Ala
[3884] 355 360 365
[3885] Gly Phe Leu Glu Gly Gly Trp Glu Gly Met Ile Ala Gly Trp His Gly
[3886] 370 375 380
[3887] Tyr Thr Ser His Gly Ala His Gly Val Ala Val Ala Ala Asp Leu Lys
[3888] 385 390 395 400
[3889] Ser Thr Gln Glu Ala Ile Asn Lys Ile Thr Lys Asn Leu Asn Tyr Leu
[3890] 405 410 415
[3891] Ser Glu Leu Glu Val Lys Asn Leu Gln Arg Leu Ser Gly Ala Met Asn
[3892] 420 425 430
[3893] Glu Leu His Asp Glu Ile Leu Glu Leu Asp Glu Lys Val Asp Asp Leu
[3894] 435 440 445
[3895] Arg Ala Asp Thr Ile Ser Ser Gln Ile Glu Leu Ala Val Leu Leu Ser
[3896] 450 455 460
[3897] Asn Glu Gly Ile Ile Asn Ser Glu Asp Glu His Leu Leu Ala Leu Glu
[3898] 465 470 475 480
[3899] Arg Lys Leu Lys Lys Met Leu Gly Pro Ser Ala Val Glu Ile Gly Asn
[3900] 485 490 495
[3901] Gly Cys Phe Glu Thr Lys His Lys Cys Asn Gln Thr Cys Leu Asp Arg
[3902] 500 505 510
[3903] Ile Ala Ala Gly Thr Phe Asn Ala Gly Asp Phe Ser Leu Pro Thr Phe
[3904] 515 520 525
[3905] Asp Ser Leu Asn Ile Thr Ala Ala Ser Leu Asn Asp Asp Gly Leu Asp

[3906] 530 535 540
[3907] Asn His Thr Ile Leu Leu Tyr Tyr Ser Thr Ala Ala Ser Ser Leu Ala
[3908] 545 550 555 560
[3909] Val Thr Leu Met Ile Ala Ile Phe Ile Val Tyr Met Val Ser Arg Asp
[3910] 565 570 575
[3911] Asn Val Ser Cys Ser Ile Cys Leu
[3912] 580
[3913] <210> 78
[3914] <211> 566
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[3916] <213> Influenza A virus
[3917] <400> 78
[3918] Met Lys Thr Ile Ile Ala Leu Ser Tyr Ile Leu Cys Leu Val Phe Ala
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[3920] Gln Lys Leu Pro Gly Asn Asp Asn Ser Thr Ala Thr Leu Cys Leu Gly
[3921] 20 25 30
[3922] His His Ala Val Pro Asn Gly Thr Ile Val Lys Thr Ile Thr Asn Asp
[3923] 35 40 45
[3924] Gln Ile Glu Val Thr Asn Ala Thr Glu Leu Val Gln Ser Ser Ser Thr
[3925] 50 55 60
[3926] Gly Gly Ile Cys Asp Ser Pro His Gln Ile Leu Asp Gly Glu Asn Cys
[3927] 65 70 75 80
[3928] Thr Leu Ile Asp Ala Leu Leu Gly Asp Pro Gln Cys Asp Gly Phe Gln
[3929] 85 90 95
[3930] Asn Lys Lys Trp Asp Leu Phe Val Glu Arg Ser Lys Ala Tyr Ser Asn
[3931] 100 105 110
[3932] Cys Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Ser Leu Arg Ser Leu Val
[3933] 115 120 125
[3934] Ala Ser Ser Gly Thr Leu Glu Phe Asn Asn Glu Ser Phe Asn Trp Thr
[3935] 130 135 140
[3936] Gly Val Thr Gln Asn Gly Thr Ser Ser Ala Cys Lys Arg Arg Ser Asn
[3937] 145 150 155 160
[3938] Asn Ser Phe Phe Ser Arg Leu Asn Trp Leu Thr His Leu Lys Phe Lys
[3939] 165 170 175
[3940] Tyr Pro Ala Leu Asn Val Thr Met Pro Asn Asn Glu Lys Phe Asp Lys
[3941] 180 185 190
[3942] Leu Tyr Ile Trp Gly Val His His Pro Gly Thr Asp Asn Asp Gln Ile
[3943] 195 200 205
[3944] Ser Leu Tyr Ala Gln Ala Ser Gly Arg Ile Thr Val Ser Thr Lys Arg
[3945] 210 215 220
[3946] Ser Gln Gln Thr Val Ile Pro Ser Ile Gly Ser Arg Pro Arg Ile Arg
[3947] 225 230 235 240

[3948] Asp Val Pro Ser Arg Ile Ser Ile Tyr Trp Thr Ile Val Lys Pro Gly
[3949] 245 250 255
[3950] Asp Ile Leu Leu Ile Asn Ser Thr Gly Asn Leu Ile Ala Pro Arg Gly
[3951] 260 265 270
[3952] Tyr Phe Lys Ile Arg Ser Gly Lys Ser Ser Ile Met Arg Ser Asp Ala
[3953] 275 280 285
[3954] Pro Ile Gly Lys Cys Asn Ser Glu Cys Ile Thr Pro Asn Gly Ser Ile
[3955] 290 295 300
[3956] Pro Asn Asp Lys Pro Phe Gln Asn Val Asn Arg Ile Thr Tyr Gly Ala
[3957] 305 310 315 320
[3958] Cys Pro Arg Tyr Val Lys Gln Asn Thr Leu Lys Leu Ala Thr Gly Met
[3959] 325 330 335
[3960] Arg Asn Val Pro Glu Lys Gln Thr Arg Gly Ile Phe Gly Ala Ile Ala
[3961] 340 345 350
[3962] Gly Phe Ile Glu Asn Gly Trp Glu Gly Met Val Asp Gly Trp Tyr Gly
[3963] 355 360 365
[3964] Phe Arg His Gln Asn Ser Glu Gly Thr Gly Gln Ala Ala Asp Leu Lys
[3965] 370 375 380
[3966] Ser Thr Gln Ala Ala Ile Asn Gln Ile Asn Gly Lys Leu Asn Arg Leu
[3967] 385 390 395 400
[3968] Ile Gly Lys Thr Asn Glu Lys Phe His Gln Ile Glu Lys Glu Phe Ser
[3969] 405 410 415
[3970] Glu Val Glu Gly Arg Ile Gln Asp Leu Glu Lys Tyr Val Glu Asp Thr
[3971] 420 425 430
[3972] Lys Ile Asp Leu Trp Ser Tyr Asn Ala Glu Leu Leu Val Ala Leu Glu
[3973] 435 440 445
[3974] Asn Gln His Thr Ile Asp Leu Thr Asp Ser Glu Met Asn Lys Leu Phe
[3975] 450 455 460
[3976] Glu Arg Thr Lys Lys Gln Leu Arg Glu Asn Ala Glu Asp Met Gly Asn
[3977] 465 470 475 480
[3978] Gly Cys Phe Lys Ile Tyr His Lys Cys Asp Asn Ala Cys Ile Gly Ser
[3979] 485 490 495
[3980] Ile Arg Asn Gly Thr Tyr Asp His Asp Val Tyr Arg Asp Glu Ala Leu
[3981] 500 505 510
[3982] Asn Asn Arg Phe Gln Ile Lys Gly Val Glu Leu Lys Ser Gly Tyr Lys
[3983] 515 520 525
[3984] Asp Trp Ile Leu Trp Ile Ser Phe Ala Ile Ser Cys Phe Leu Leu Cys
[3985] 530 535 540
[3986] Val Ala Leu Leu Gly Phe Ile Met Trp Ala Cys Gln Lys Gly Asn Ile
[3987] 545 550 555 560
[3988] Arg Cys Asn Ile Cys Ile
[3989] 565

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[3991] <211> 466
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[3993] <213> Influenza B virus
[3994] <400> 79
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[3996] 1 5 10 15
[3997] Gly Val Leu Leu Ser Leu Tyr Val Ser Ala Ser Leu Ser Tyr Leu Leu
[3998] 20 25 30
[3999] Tyr Ser Asp Val Leu Leu Lys Phe Ser Ser Thr Lys Thr Thr Ala Pro
[4000] 35 40 45
[4001] Thr Met Ser Leu Glu Cys Thr Asn Ala Ser Asn Ala Gln Thr Val Asn
[4002] 50 55 60
[4003] His Ser Ala Thr Lys Glu Met Thr Phe Pro Pro Pro Glu Pro Glu Trp
[4004] 65 70 75 80
[4005] Thr Tyr Pro Arg Leu Ser Cys Gln Gly Ser Thr Phe Gln Lys Ala Leu
[4006] 85 90 95
[4007] Leu Ile Ser Pro His Arg Phe Gly Glu Ile Lys Gly Asn Ser Ala Pro
[4008] 100 105 110
[4009] Leu Ile Ile Arg Glu Pro Phe Val Ala Cys Gly Pro Lys Glu Cys Arg
[4010] 115 120 125
[4011] His Phe Ala Leu Thr His Tyr Ala Ala Gln Pro Gly Gly Tyr Tyr Asn
[4012] 130 135 140
[4013] Gly Thr Arg Lys Asp Arg Asn Lys Leu Arg His Leu Val Ser Val Lys
[4014] 145 150 155 160
[4015] Leu Gly Lys Ile Pro Thr Val Glu Asn Ser Ile Phe His Met Ala Ala
[4016] 165 170 175
[4017] Trp Ser Gly Ser Ala Cys His Asp Gly Arg Glu Trp Thr Tyr Ile Gly
[4018] 180 185 190
[4019] Val Asp Gly Pro Asp Asn Asp Ala Leu Val Lys Ile Lys Tyr Gly Glu
[4020] 195 200 205
[4021] Ala Tyr Thr Asp Thr Tyr His Ser Tyr Ala His Asn Ile Leu Arg Thr
[4022] 210 215 220
[4023] Gln Glu Ser Ala Cys Asn Cys Ile Gly Gly Asp Cys Tyr Leu Met Ile
[4024] 225 230 235 240
[4025] Thr Asp Gly Ser Ala Ser Gly Ile Ser Lys Cys Arg Phe Leu Lys Ile
[4026] 245 250 255
[4027] Arg Glu Gly Arg Ile Ile Lys Glu Ile Leu Pro Thr Gly Arg Val Glu
[4028] 260 265 270
[4029] His Thr Glu Glu Cys Thr Cys Gly Phe Ala Ser Asn Lys Thr Ile Glu
[4030] 275 280 285
[4031] Cys Ala Cys Arg Asp Asn Ser Tyr Thr Ala Lys Arg Pro Phe Val Lys

[4032] 290 295 300
[4033] Leu Asn Val Glu Thr Asp Thr Ala Glu Ile Arg Leu Met Cys Thr Lys
[4034] 305 310 315 320
[4035] Thr Tyr Leu Asp Thr Pro Arg Pro Asp Asp Gly Ser Ile Ala Gly Pro
[4036] 325 330 335
[4037] Cys Glu Ser Asn Gly Asp Lys Trp Leu Gly Gly Ile Lys Gly Gly Phe
[4038] 340 345 350
[4039] Val His Gln Arg Met Ala Ser Lys Ile Gly Arg Trp Tyr Ser Arg Thr
[4040] 355 360 365
[4041] Met Ser Lys Thr Asn Arg Met Gly Met Glu Leu Tyr Val Lys Tyr Asp
[4042] 370 375 380
[4043] Gly Asp Pro Trp Thr Asp Ser Asp Ala Leu Thr Leu Ser Gly Val Met
[4044] 385 390 395 400
[4045] Val Ser Ile Glu Glu Pro Gly Trp Tyr Ser Phe Gly Phe Glu Ile Lys
[4046] 405 410 415
[4047] Asp Lys Lys Cys Asp Val Pro Cys Ile Gly Ile Glu Met Val His Asp
[4048] 420 425 430
[4049] Gly Gly Lys Asp Thr Trp His Ser Ala Ala Thr Ala Ile Tyr Cys Leu
[4050] 435 440 445
[4051] Met Gly Ser Gly Gln Leu Leu Trp Asp Thr Val Thr Gly Val Asp Met
[4052] 450 455 460
[4053] Ala Leu
[4054] 465
[4055] <210> 80
[4056] <211> 565
[4057] <212> PRT
[4058] <213> Influenza C virus
[4059] <400> 80
[4060] Met Ser Asp Arg Arg Gln Asn Arg Lys Thr Pro Asp Glu Gln Arg Lys
[4061] 1 5 10 15
[4062] Ala Asn Ala Leu Ile Ile Asn Glu Asn Ile Glu Ala Tyr Ile Ala Ile
[4063] 20 25 30
[4064] Cys Lys Glu Val Gly Leu Asn Gly Asp Glu Met Leu Ile Leu Glu Asn
[4065] 35 40 45
[4066] Gly Ile Ala Ile Glu Lys Ala Ile Arg Ile Cys Cys Asp Gly Lys Tyr
[4067] 50 55 60
[4068] Gln Glu Lys Arg Glu Lys Lys Ala Arg Glu Ala Gln Arg Ala Asp Ser
[4069] 65 70 75 80
[4070] Asn Phe Asn Ala Asp Ser Ile Gly Ile Arg Leu Val Lys Arg Ala Gly
[4071] 85 90 95
[4072] Ser Gly Thr Asn Ile Thr Tyr His Ala Val Val Glu Leu Thr Ser Arg
[4073] 100 105 110

[4074] Ser Arg Ile Val Gln Ile Leu Lys Ser His Trp Gly Asn Glu Leu Asn
[4075] 115 120 125
[4076] Arg Ala Lys Ile Ala Gly Lys Arg Leu Gly Phe Ser Ala Leu Phe Ala
[4077] 130 135 140
[4078] Ser Asn Leu Glu Ala Ile Ile Tyr Gln Arg Gly Arg Asn Ala Ala Arg
[4079] 145 150 155 160
[4080] Arg Asn Gly Ser Ala Glu Leu Phe Thr Leu Thr Gln Gly Ala Gly Ile
[4081] 165 170 175
[4082] Glu Thr Arg Tyr Lys Trp Ile Met Glu Lys His Ile Gly Ile Gly Val
[4083] 180 185 190
[4084] Leu Ile Ala Asp Ala Lys Gly Leu Ile Asn Gly Lys Arg Glu Gly Lys
[4085] 195 200 205
[4086] Arg Gly Val Asp Ala Asn Val Lys Leu Arg Ala Gly Thr Thr Gly Ser
[4087] 210 215 220
[4088] Pro Leu Glu Arg Ala Met Gln Gly Ile Glu Lys Lys Ala Phe Pro Gly
[4089] 225 230 235 240
[4090] Pro Leu Arg Ala Leu Ala Arg Arg Val Val Lys Ala Asn Tyr Asn Asp
[4091] 245 250 255
[4092] Ala Arg Glu Ala Leu Asn Val Ile Ala Glu Ala Ser Leu Leu Leu Lys
[4093] 260 265 270
[4094] Pro Gln Ile Thr Asn Lys Met Thr Met Pro Trp Cys Met Trp Leu Ala
[4095] 275 280 285
[4096] Ala Arg Leu Thr Leu Lys Asp Glu Phe Ala Asn Phe Cys Ala Tyr Ala
[4097] 290 295 300
[4098] Gly Arg Arg Ala Phe Glu Val Phe Asn Ile Ala Met Glu Lys Ile Gly
[4099] 305 310 315 320
[4100] Ile Cys Ser Phe Gln Gly Thr Ile Met Asn Asp Asp Glu Ile Glu Ser
[4101] 325 330 335
[4102] Ile Glu Asp Lys Ala Gln Val Leu Met Met Ala Cys Phe Gly Leu Ala
[4103] 340 345 350
[4104] Tyr Glu Asp Phe Ser Leu Val Ser Ala Met Val Ser His Pro Leu Lys
[4105] 355 360 365
[4106] Leu Arg Asn Arg Met Lys Ile Gly Asn Phe Arg Val Gly Glu Lys Val
[4107] 370 375 380
[4108] Ser Thr Val Leu Ser Pro Leu Leu Arg Phe Thr Arg Trp Ala Glu Phe
[4109] 385 390 395 400
[4110] Ala Gln Arg Phe Ala Leu Gln Ala Asn Thr Ser Arg Glu Gly Ala Gln
[4111] 405 410 415
[4112] Ile Ser Asn Ser Ala Val Phe Ala Val Glu Arg Lys Ile Thr Thr Asp
[4113] 420 425 430
[4114] Val Gln Arg Val Glu Glu Leu Leu Asn Lys Val Gln Ala His Glu Asp
[4115] 435 440 445

[4116] Glu Pro Leu Gln Thr Leu Tyr Lys Lys Val Arg Glu Gln Ile Ser Ile
[4117] 450 455 460
[4118] Ile Gly Arg Asn Lys Ser Glu Ile Lys Glu Phe Leu Gly Ser Ser Met
[4119] 465 470 475 480
[4120] Tyr Asp Leu Asn Asp Gln Glu Lys Gln Asn Pro Ile Asn Phe Arg Ser
[4121] 485 490 495
[4122] Gly Ala His Pro Phe Phe Phe Glu Phe Asp Pro Asp Tyr Asn Pro Ile
[4123] 500 505 510
[4124] Arg Val Lys Arg Pro Lys Lys Pro Ile Ala Lys Arg Asn Ser Asn Ile
[4125] 515 520 525
[4126] Ser Arg Leu Glu Glu Glu Gly Met Asp Glu Asn Ser Glu Ile Gly Gln
[4127] 530 535 540
[4128] Ala Lys Lys Met Lys Pro Leu Asp Gln Leu Thr Ser Thr Ser Ser Asn
[4129] 545 550 555 560
[4130] Ile Pro Gly Lys Asn
[4131] 565
[4132] <210> 81
[4133] <211> 498
[4134] <212> PRT
[4135] <213> Influenza A virus
[4136] <400> 81
[4137] Met Ala Ser Gln Gly Thr Lys Arg Ser Tyr Glu Gln Met Glu Thr Asp
[4138] 1 5 10 15
[4139] Gly Glu Arg Gln Asn Ala Thr Glu Ile Arg Ala Ser Val Gly Lys Met
[4140] 20 25 30
[4141] Ile Asp Gly Ile Gly Arg Phe Tyr Ile Gln Met Cys Thr Glu Leu Lys
[4142] 35 40 45
[4143] Leu Ser Asp Tyr Glu Gly Arg Leu Ile Gln Asn Ser Leu Thr Ile Glu
[4144] 50 55 60
[4145] Arg Met Val Leu Ser Ala Phe Asp Glu Arg Arg Asn Lys Tyr Leu Glu
[4146] 65 70 75 80
[4147] Glu His Pro Ser Ala Gly Lys Asp Pro Lys Lys Thr Gly Gly Pro Ile
[4148] 85 90 95
[4149] Tyr Lys Arg Val Asp Gly Lys Trp Met Arg Glu Leu Val Leu Tyr Asp
[4150] 100 105 110
[4151] Lys Glu Glu Ile Arg Arg Ile Trp Arg Gln Ala Asn Asn Gly Asp Asp
[4152] 115 120 125
[4153] Ala Thr Ala Gly Leu Thr His Met Met Ile Trp His Ser Asn Leu Asn
[4154] 130 135 140
[4155] Asp Thr Thr Tyr Gln Arg Thr Arg Ala Leu Val Arg Thr Gly Met Asp
[4156] 145 150 155 160
[4157] Pro Arg Met Cys Ser Leu Met Gln Gly Ser Thr Leu Pro Arg Arg Ser

[4158] 165 170 175
[4159] Gly Ala Ala Gly Ala Ala Val Lys Gly Val Gly Thr Met Val Met Glu
[4160] 180 185 190
[4161] Leu Ile Arg Met Ile Lys Arg Gly Ile Asn Asp Arg Asn Phe Trp Arg
[4162] 195 200 205
[4163] Gly Glu Asn Gly Arg Lys Thr Arg Ser Ala Tyr Glu Arg Met Cys Asn
[4164] 210 215 220
[4165] Ile Leu Lys Gly Lys Phe Gln Thr Ala Ala Gln Arg Ala Met Met Asp
[4166] 225 230 235 240
[4167] Gln Val Arg Glu Ser Arg Asn Pro Gly Asn Ala Glu Ile Glu Asp Leu
[4168] 245 250 255
[4169] Ile Phe Leu Ala Arg Ser Ala Leu Ile Leu Arg Gly Ser Val Ala His
[4170] 260 265 270
[4171] Lys Ser Cys Leu Pro Ala Cys Val Tyr Gly Pro Ala Ile Ala Ser Gly
[4172] 275 280 285
[4173] Tyr Asn Phe Glu Lys Glu Gly Tyr Ser Leu Val Gly Ile Asp Pro Phe
[4174] 290 295 300
[4175] Lys Leu Leu Gln Asn Ser Gln Val Tyr Ser Leu Ile Arg Pro Asn Glu
[4176] 305 310 315 320
[4177] Asn Pro Ala His Lys Ser Gln Leu Val Trp Met Ala Cys Asn Ser Ala
[4178] 325 330 335
[4179] Ala Phe Glu Asp Leu Arg Val Leu Ser Phe Ile Arg Gly Thr Lys Val
[4180] 340 345 350
[4181] Ser Pro Arg Gly Lys Leu Ser Thr Arg Gly Val Gln Ile Ala Ser Asn
[4182] 355 360 365
[4183] Glu Asn Met Asp Thr Met Glu Ser Ser Thr Leu Glu Leu Arg Ser Arg
[4184] 370 375 380
[4185] Tyr Trp Ala Ile Arg Thr Arg Ser Gly Gly Asn Thr Asn Gln Gln Arg
[4186] 385 390 395 400
[4187] Ala Ser Ala Gly Gln Ile Ser Val Gln Pro Ala Phe Ser Val Gln Arg
[4188] 405 410 415
[4189] Asn Leu Pro Phe Asp Lys Pro Thr Ile Met Ala Ala Phe Thr Gly Asn
[4190] 420 425 430
[4191] Thr Glu Gly Arg Thr Ser Asp Met Arg Ala Glu Ile Ile Arg Met Met
[4192] 435 440 445
[4193] Glu Gly Ala Lys Pro Glu Glu Met Ser Phe Gln Gly Arg Gly Val Phe
[4194] 450 455 460
[4195] Glu Leu Ser Asp Glu Lys Ala Thr Asn Pro Ile Val Pro Ser Phe Asp
[4196] 465 470 475 480
[4197] Met Ser Asn Glu Gly Ser Tyr Phe Phe Gly Asp Asn Ala Glu Glu Tyr
[4198] 485 490 495
[4199] Asp Asn

[4200] <210> 82
[4201] <211> 498
[4202] <212> PRT
[4203] <213> Influenza A virus
[4204] <400> 82
[4205] Met Ala Ser Gln Gly Thr Lys Arg Ser Tyr Glu Gln Met Glu Thr Gly
[4206] 1 5 10 15
[4207] Gly Glu Arg Gln Asn Ala Thr Glu Ile Arg Ala Ser Val Gly Arg Met
[4208] 20 25 30
[4209] Val Gly Gly Ile Gly Arg Phe Tyr Val Gln Met Cys Thr Glu Leu Lys
[4210] 35 40 45
[4211] Leu Ser Asp Gln Glu Gly Arg Leu Ile Gln Asn Ser Ile Thr Ile Glu
[4212] 50 55 60
[4213] Arg Met Val Leu Ser Ala Phe Asp Glu Arg Arg Asn Arg Tyr Leu Glu
[4214] 65 70 75 80
[4215] Glu His Pro Ser Ala Gly Lys Asp Pro Lys Lys Thr Gly Gly Pro Ile
[4216] 85 90 95
[4217] Tyr Arg Arg Arg Asp Gly Lys Trp Val Arg Glu Leu Ile Leu Tyr Asp
[4218] 100 105 110
[4219] Lys Glu Glu Ile Arg Arg Ile Trp Arg Gln Ala Asn Asn Gly Glu Asp
[4220] 115 120 125
[4221] Ala Thr Ala Gly Leu Thr His Met Met Ile Trp His Ser Asn Leu Asn
[4222] 130 135 140
[4223] Asp Ala Thr Tyr Gln Arg Thr Arg Ala Leu Val Arg Thr Gly Met Asp
[4224] 145 150 155 160
[4225] Pro Arg Met Cys Ser Leu Met Gln Gly Ser Thr Leu Pro Arg Arg Ser
[4226] 165 170 175
[4227] Gly Ala Ala Gly Ala Ala Ile Lys Gly Val Gly Thr Met Val Met Glu
[4228] 180 185 190
[4229] Leu Ile Arg Met Ile Lys Arg Gly Ile Asn Asp Arg Asn Phe Trp Arg
[4230] 195 200 205
[4231] Gly Asp Asn Gly Arg Arg Thr Arg Ile Ala Tyr Glu Arg Met Cys Asn
[4232] 210 215 220
[4233] Ile Leu Lys Gly Lys Phe Gln Thr Ala Ala Gln Arg Ala Met Met Asp
[4234] 225 230 235 240
[4235] Gln Val Arg Glu Ser Arg Asn Pro Gly Asn Ala Glu Ile Glu Asp Leu
[4236] 245 250 255
[4237] Ile Phe Leu Ala Arg Ser Ala Leu Ile Leu Arg Gly Ser Val Ala His
[4238] 260 265 270
[4239] Lys Ser Cys Leu Pro Ala Cys Val Tyr Gly Leu Ala Val Ala Ser Gly
[4240] 275 280 285
[4241] Tyr Asp Phe Glu Arg Glu Gly Tyr Ser Leu Val Gly Ile Asp Pro Phe

[4242] 290 295 300
[4243] Arg Leu Leu Gln Asn Ser Gln Val Phe Ser Leu Ile Arg Pro Asn Glu
[4244] 305 310 315 320
[4245] Asn Pro Ala His Lys Ser Gln Leu Val Trp Met Ala Cys His Ser Ala
[4246] 325 330 335
[4247] Ala Phe Glu Asp Leu Arg Val Ser Ser Phe Ile Arg Gly Thr Arg Val
[4248] 340 345 350
[4249] Ile Pro Arg Gly Gln Leu Ser Thr Arg Gly Val Gln Ile Ala Ser Asn
[4250] 355 360 365
[4251] Glu Asn Val Glu Ala Met Asp Ser Ser Thr Leu Glu Leu Arg Ser Arg
[4252] 370 375 380
[4253] Tyr Trp Ala Ile Arg Thr Arg Ser Gly Gly Asn Thr Asn Gln Gln Arg
[4254] 385 390 395 400
[4255] Ala Ser Ala Gly Gln Ile Ser Val Gln Pro Thr Phe Ser Val Gln Arg
[4256] 405 410 415
[4257] Asn Leu Pro Phe Glu Arg Pro Thr Ile Met Ala Ala Phe Lys Gly Asn
[4258] 420 425 430
[4259] Thr Glu Gly Arg Thr Ser Asp Met Arg Thr Glu Ile Ile Arg Met Met
[4260] 435 440 445
[4261] Glu Ser Ala Arg Pro Glu Asp Val Ser Phe Gln Gly Arg Gly Val Phe
[4262] 450 455 460
[4263] Glu Leu Ser Asp Glu Lys Ala Thr Asn Pro Ile Val Pro Ser Phe Asp
[4264] 465 470 475 480
[4265] Met Ser Asn Glu Gly Ser Tyr Phe Phe Gly Asp Asn Ala Glu Glu Tyr
[4266] 485 490 495
[4267] Asp Asn
[4268] <210> 83
[4269] <211> 560
[4270] <212> PRT
[4271] <213> Influenza B virus
[4272] <400> 83
[4273] Met Ser Asn Met Asp Ile Asp Ser Ile Asn Thr Gly Thr Ile Asp Lys
[4274] 1 5 10 15
[4275] Thr Pro Glu Glu Leu Thr Pro Gly Thr Ser Gly Ala Thr Arg Pro Ile
[4276] 20 25 30
[4277] Ile Lys Pro Ala Thr Leu Ala Pro Pro Ser Asn Lys Arg Thr Arg Asn
[4278] 35 40 45
[4279] Pro Ser Pro Glu Arg Thr Thr Thr Ser Ser Glu Thr Asp Ile Gly Arg
[4280] 50 55 60
[4281] Lys Ile Gln Lys Lys Gln Thr Pro Thr Glu Ile Lys Lys Ser Val Tyr
[4282] 65 70 75 80
[4283] Lys Met Val Val Lys Leu Gly Glu Phe Tyr Asn Gln Met Met Val Lys

[4284] 85 90 95
[4285] Ala Gly Leu Asn Asp Asp Met Glu Arg Asn Leu Ile Gln Asn Ala Gln
[4286] 100 105 110
[4287] Ala Val Glu Arg Ile Leu Leu Ala Ala Thr Asp Asp Lys Lys Thr Glu
[4288] 115 120 125
[4289] Tyr Gln Lys Lys Arg Asn Ala Arg Asp Val Lys Glu Gly Lys Glu Glu
[4290] 130 135 140
[4291] Ile Asp His Asn Lys Thr Gly Gly Thr Phe Tyr Lys Met Val Arg Asp
[4292] 145 150 155 160
[4293] Asp Lys Thr Ile Tyr Phe Ser Pro Ile Lys Ile Thr Phe Leu Lys Glu
[4294] 165 170 175
[4295] Glu Val Lys Thr Met Tyr Lys Thr Thr Met Gly Ser Asp Gly Phe Ser
[4296] 180 185 190
[4297] Gly Leu Asn His Ile Met Ile Gly His Ser Gln Met Asn Asp Val Cys
[4298] 195 200 205
[4299] Phe Gln Arg Ser Lys Gly Leu Lys Arg Val Gly Leu Asp Pro Ser Leu
[4300] 210 215 220
[4301] Ile Ser Thr Phe Ala Gly Ser Thr Leu Pro Arg Arg Ser Gly Thr Thr
[4302] 225 230 235 240
[4303] Gly Val Ala Ile Lys Gly Gly Gly Thr Leu Val Asp Glu Ala Ile Arg
[4304] 245 250 255
[4305] Phe Ile Gly Arg Ala Met Ala Asp Arg Gly Leu Leu Arg Asp Ile Lys
[4306] 260 265 270
[4307] Ala Lys Thr Ala Tyr Glu Lys Ile Leu Leu Asn Leu Lys Asn Lys Cys
[4308] 275 280 285
[4309] Ser Ala Pro Gln Gln Lys Ala Leu Val Asp Gln Val Ile Gly Ser Arg
[4310] 290 295 300
[4311] Asn Pro Gly Ile Ala Asp Ile Glu Asp Leu Thr Leu Leu Ala Arg Ser
[4312] 305 310 315 320
[4313] Met Val Val Val Arg Pro Ser Val Ala Ser Lys Val Val Leu Pro Ile
[4314] 325 330 335
[4315] Ser Ile Tyr Ala Lys Ile Pro Gln Leu Gly Phe Asn Thr Glu Glu Tyr
[4316] 340 345 350
[4317] Ser Met Val Gly Tyr Glu Ala Met Ala Leu Tyr Asn Met Ala Thr Pro
[4318] 355 360 365
[4319] Val Ser Ile Leu Arg Met Gly Asp Asp Ala Lys Asp Lys Ser Gln Leu
[4320] 370 375 380
[4321] Phe Phe Met Ser Cys Phe Gly Ala Ala Tyr Glu Asp Leu Arg Val Leu
[4322] 385 390 395 400
[4323] Ser Ala Leu Thr Gly Thr Glu Phe Lys Pro Arg Ser Ala Leu Lys Cys
[4324] 405 410 415
[4325] Lys Gly Phe His Val Pro Ala Lys Glu Gln Val Glu Gly Met Gly Ala

[4326] 420 425 430
[4327] Ala Leu Met Ser Ile Lys Leu Gln Phe Trp Ala Pro Met Thr Arg Ser
[4328] 435 440 445
[4329] Gly Gly Asn Glu Val Ser Gly Glu Gly Gly Ser Gly Gln Ile Ser Cys
[4330] 450 455 460
[4331] Ser Pro Val Phe Ala Val Glu Arg Pro Ile Ala Leu Ser Lys Gln Ala
[4332] 465 470 475 480
[4333] Val Arg Arg Met Leu Ser Met Asn Val Glu Gly Arg Asp Ala Asp Val
[4334] 485 490 495
[4335] Lys Gly Asn Leu Leu Lys Met Met Asn Asp Ser Met Ala Lys Lys Thr
[4336] 500 505 510
[4337] Ser Gly Asn Ala Phe Ile Gly Lys Lys Met Phe Gln Ile Ser Asp Lys
[4338] 515 520 525
[4339] Asn Lys Val Asn Pro Ile Glu Ile Pro Ile Lys Gln Thr Ile Pro Asn
[4340] 530 535 540
[4341] Phe Phe Phe Gly Arg Asp Thr Ala Glu Asp Tyr Asp Asp Leu Asp Tyr
[4342] 545 550 555 560
[4343] <210> 84
[4344] <211> 248
[4345] <212> PRT
[4346] <213> Influenza B virus
[4347] <400> 84
[4348] Met Ser Leu Phe Gly Asp Thr Ile Ala Tyr Leu Leu Ser Leu Ile Glu
[4349] 1 5 10 15
[4350] Asp Gly Glu Gly Lys Ala Glu Leu Ala Glu Lys Leu His Cys Trp Phe
[4351] 20 25 30
[4352] Gly Gly Lys Glu Phe Asp Leu Asp Ser Ala Leu Glu Trp Ile Lys Asn
[4353] 35 40 45
[4354] Lys Arg Cys Leu Thr Asp Ile Gln Lys Ala Leu Ile Gly Ala Ser Ile
[4355] 50 55 60
[4356] Cys Phe Leu Lys Pro Lys Asp Gln Glu Arg Lys Arg Arg Phe Ile Thr
[4357] 65 70 75 80
[4358] Glu Pro Leu Ser Gly Met Gly Thr Thr Ala Thr Lys Lys Lys Gly Leu
[4359] 85 90 95
[4360] Ile Leu Ala Glu Arg Lys Met Arg Arg Cys Val Ser Phe His Glu Ala
[4361] 100 105 110
[4362] Phe Glu Ile Ala Glu Gly His Glu Ser Ser Ala Leu Leu Tyr Cys Leu
[4363] 115 120 125
[4364] Met Val Met Tyr Leu Asn Pro Glu Asn Tyr Ser Met Gln Val Lys Leu
[4365] 130 135 140
[4366] Gly Thr Leu Cys Ala Leu Cys Glu Lys Gln Ala Ser His Ser His Arg
[4367] 145 150 155 160

[4368] Ala His Ser Arg Ala Ala Arg Ser Ser Val Pro Gly Val Arg Arg Glu
[4369] 165 170 175
[4370] Met Gln Met Val Ser Ala Met Asn Thr Ala Lys Thr Met Asn Gly Met
[4371] 180 185 190
[4372] Gly Lys Gly Glu Asp Val Gln Lys Leu Ala Glu Glu Leu Gln Asn Asn
[4373] 195 200 205
[4374] Ile Gly Val Leu Arg Ser Leu Gly Ala Ser Gln Lys Asn Gly Glu Gly
[4375] 210 215 220
[4376] Ile Ala Lys Asp Val Met Glu Val Leu Lys Gln Ser Ser Met Gly Asn
[4377] 225 230 235 240
[4378] Ser Ala Leu Val Arg Lys Tyr Leu
[4379] 245
[4380] <210> 85
[4381] <211> 97
[4382] <212> PRT
[4383] <213> Influenza A virus
[4384] <400> 85
[4385] Met Ser Leu Leu Thr Glu Val Glu Thr Pro Ile Arg Asn Glu Trp Gly
[4386] 1 5 10 15
[4387] Cys Arg Cys Asn Gly Ser Ser Asp Pro Leu Ala Ile Ala Ala Asn Ile
[4388] 20 25 30
[4389] Ile Gly Ile Leu His Leu Ile Leu Trp Ile Leu Asp Arg Leu Phe Phe
[4390] 35 40 45
[4391] Lys Cys Ile Tyr Arg Arg Phe Lys Tyr Gly Leu Lys Gly Gly Pro Ser
[4392] 50 55 60
[4393] Thr Glu Gly Val Pro Lys Ser Met Arg Glu Glu Tyr Arg Lys Glu Gln
[4394] 65 70 75 80
[4395] Gln Ser Ala Val Asp Ala Asp Asp Gly His Phe Val Ser Ile Glu Leu
[4396] 85 90 95
[4397] Glu
[4398] <210> 86
[4399] <211> 281
[4400] <212> PRT
[4401] <213> Influenza B virus
[4402] <400> 86
[4403] Met Ala Asp Asn Met Thr Thr Thr Gln Ile Glu Val Gly Pro Gly Ala
[4404] 1 5 10 15
[4405] Thr Asn Ala Thr Ile Asn Phe Glu Ala Gly Ile Leu Glu Cys Tyr Glu
[4406] 20 25 30
[4407] Arg Phe Ser Trp Gln Arg Ala Leu Asp Tyr Pro Gly Gln Asp Arg Leu
[4408] 35 40 45
[4409] His Arg Leu Lys Arg Lys Leu Glu Ser Arg Ile Lys Thr His Asn Lys

[4410] 50 55 60
[4411] Ser Glu Pro Glu Asn Lys Arg Met Ser Leu Glu Glu Arg Lys Ala Ile
[4412] 65 70 75 80
[4413] Gly Val Lys Met Met Lys Val Leu Leu Phe Met Asp Pro Ser Ala Gly
[4414] 85 90 95
[4415] Ile Glu Gly Phe Glu Pro Tyr Cys Val Lys Asn Pro Ser Thr Ser Lys
[4416] 100 105 110
[4417] Cys Pro Asn Tyr Asp Trp Thr Asp Tyr Pro Pro Thr Pro Gly Lys Tyr
[4418] 115 120 125
[4419] Leu Asp Asp Ile Glu Glu Glu Pro Glu Asn Val Asp His Pro Ile Glu
[4420] 130 135 140
[4421] Val Val Leu Arg Asp Met Asn Asn Lys Asp Ala Arg Gln Lys Ile Lys
[4422] 145 150 155 160
[4423] Asp Glu Val Asn Thr Gln Lys Glu Gly Lys Phe Arg Leu Thr Ile Lys
[4424] 165 170 175
[4425] Arg Asp Ile Arg Asn Val Leu Ser Leu Arg Val Leu Val Asn Gly Thr
[4426] 180 185 190
[4427] Phe Leu Lys His Pro Asn Gly Asp Lys Ser Leu Ser Thr Leu His Arg
[4428] 195 200 205
[4429] Leu Asn Ala Tyr Asp Gln Asn Gly Gly Leu Val Ala Lys Leu Val Ala
[4430] 210 215 220
[4431] Thr Asp Asp Arg Thr Val Glu Asp Glu Lys Asp Gly His Arg Ile Leu
[4432] 225 230 235 240
[4433] Asn Ser Leu Phe Glu Arg Phe Asp Glu Gly His Ser Lys Pro Ile Arg
[4434] 245 250 255
[4435] Ala Ala Glu Thr Ala Val Gly Val Leu Ser Gln Phe Gly Gln Glu His
[4436] 260 265 270
[4437] Arg Leu Ser Pro Glu Glu Gly Asp Asn
[4438] 275 280
[4439] <210> 87
[4440] <211> 122
[4441] <212> PRT
[4442] <213> Influenza B virus
[4443] <400> 87
[4444] Met Ala Asp Asn Met Thr Thr Thr Gln Ile Glu Trp Arg Met Lys Lys
[4445] 1 5 10 15
[4446] Met Ala Ile Gly Ser Ser Thr His Ser Ser Ser Val Leu Met Lys Asp
[4447] 20 25 30
[4448] Ile Gln Ser Gln Phe Glu Gln Leu Lys Leu Arg Trp Glu Ser Tyr Pro
[4449] 35 40 45
[4450] Asn Leu Val Lys Ser Thr Asp Tyr His Gln Lys Arg Glu Thr Ile Arg
[4451] 50 55 60

[4452] Leu Ala Thr Glu Glu Leu Tyr Leu Leu Ser Lys Arg Ile Asp Asp Ser
[4453] 65 70 75 80
[4454] Ile Leu Phe His Lys Thr Val Ile Ala Asn Ser Ser Ile Ile Ala Asp
[4455] 85 90 95
[4456] Met Ile Val Ser Leu Ser Leu Leu Glu Thr Leu Tyr Glu Met Lys Asp
[4457] 100 105 110
[4458] Val Val Glu Val Tyr Ser Arg Gln Cys Leu
[4459] 115 120
[4460] <210> 88
[4461] <211> 716
[4462] <212> PRT
[4463] <213> Influenza A virus
[4464] <400> 88
[4465] Met Glu Asp Phe Val Arg Gln Cys Phe Asn Pro Met Ile Val Glu Leu
[4466] 1 5 10 15
[4467] Ala Glu Lys Ala Met Lys Glu Tyr Gly Glu Asp Leu Lys Ile Glu Thr
[4468] 20 25 30
[4469] Asn Lys Phe Ala Ala Ile Cys Thr His Leu Glu Val Cys Phe Met Tyr
[4470] 35 40 45
[4471] Ser Asp Phe His Phe Ile Asn Glu Gln Gly Glu Ser Ile Ile Val Glu
[4472] 50 55 60
[4473] Pro Glu Asp Pro Asn Ala Leu Leu Lys His Arg Phe Glu Ile Ile Glu
[4474] 65 70 75 80
[4475] Gly Arg Asp Arg Thr Met Ala Trp Thr Val Val Asn Ser Ile Cys Asn
[4476] 85 90 95
[4477] Thr Thr Gly Ala Glu Lys Pro Lys Phe Leu Pro Asp Leu Tyr Asp Tyr
[4478] 100 105 110
[4479] Lys Glu Asn Arg Phe Ile Glu Ile Gly Val Thr Arg Arg Glu Val His
[4480] 115 120 125
[4481] Ile Tyr Tyr Leu Glu Lys Ala Asn Lys Ile Lys Ser Glu Lys Thr His
[4482] 130 135 140
[4483] Ile His Ile Phe Ser Phe Thr Gly Glu Glu Met Ala Thr Lys Ala Asp
[4484] 145 150 155 160
[4485] Tyr Thr Leu Asp Glu Glu Ser Arg Ala Arg Ile Lys Thr Arg Leu Phe
[4486] 165 170 175
[4487] Thr Ile Arg Gln Glu Met Ala Ser Arg Gly Leu Trp Asp Ser Phe Arg
[4488] 180 185 190
[4489] Gln Ser Glu Arg Gly Glu Glu Thr Ile Glu Glu Arg Phe Glu Ile Thr
[4490] 195 200 205
[4491] Gly Thr Met Arg Arg Leu Ala Asp Gln Ser Leu Pro Pro Asn Phe Ser
[4492] 210 215 220
[4493] Cys Leu Glu Asn Phe Arg Ala Tyr Val Asp Gly Phe Glu Pro Asn Gly

[4494] 225 230 235 240
[4495] Tyr Ile Glu Gly Lys Leu Ser Gln Met Ser Lys Glu Val Asn Ala Arg
[4496] 245 250 255
[4497] Ile Glu Pro Phe Leu Arg Thr Thr Pro Arg Pro Ile Arg Leu Pro Asp
[4498] 260 265 270
[4499] Gly Pro Pro Cys Phe Gln Arg Ser Lys Phe Leu Leu Met Asp Ser Leu
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[4501] Lys Leu Ser Ile Glu Asp Pro Ser His Glu Gly Glu Gly Ile Pro Leu
[4502] 290 295 300
[4503] Tyr Asp Ala Ile Lys Cys Met Arg Thr Phe Phe Gly Trp Lys Glu Pro
[4504] 305 310 315 320
[4505] Ser Val Val Lys Pro His Gly Lys Gly Ile Asn Pro Asn Tyr Leu Leu
[4506] 325 330 335
[4507] Ser Trp Lys Gln Val Leu Ala Glu Leu Gln Asp Ile Glu Ser Glu Glu
[4508] 340 345 350
[4509] Lys Ile Pro Arg Thr Lys Asn Met Lys Lys Thr Ser Gln Leu Lys Trp
[4510] 355 360 365
[4511] Ala Leu Gly Glu Asn Met Ala Pro Glu Lys Val Asp Phe Asp Asp Cys
[4512] 370 375 380
[4513] Lys Asp Ile Ser Asp Leu Lys Gln Tyr Asp Ser Asp Glu Pro Glu Leu
[4514] 385 390 395 400
[4515] Arg Ser Leu Ser Ser Trp Ile Gln Asn Glu Phe Asn Lys Ala Cys Glu
[4516] 405 410 415
[4517] Leu Thr Asp Ser Ile Trp Ile Glu Leu Asp Glu Ile Gly Glu Asp Val
[4518] 420 425 430
[4519] Ala Pro Ile Glu His Ile Ala Ser Met Arg Arg Asn Tyr Phe Thr Ala
[4520] 435 440 445
[4521] Glu Val Ser His Cys Arg Ala Thr Glu Tyr Ile Met Lys Gly Val Tyr
[4522] 450 455 460
[4523] Ile Asn Thr Ala Leu Leu Asn Ala Ser Cys Ala Ala Met Asp Asp Phe
[4524] 465 470 475 480
[4525] Gln Leu Ile Pro Met Ile Ser Lys Cys Arg Thr Lys Glu Gly Arg Arg
[4526] 485 490 495
[4527] Lys Thr Asn Leu Tyr Gly Phe Ile Ile Lys Gly Arg Ser His Leu Arg
[4528] 500 505 510
[4529] Asn Asp Thr Asp Val Val Asn Phe Val Ser Met Glu Phe Ser Leu Thr
[4530] 515 520 525
[4531] Asp Pro Arg Leu Glu Pro His Lys Trp Glu Lys Tyr Cys Val Leu Glu
[4532] 530 535 540
[4533] Ile Gly Asp Met Leu Leu Arg Ser Ala Ile Gly Gln Val Ser Arg Pro
[4534] 545 550 555 560
[4535] Met Phe Leu Tyr Val Arg Thr Asn Gly Thr Ser Lys Ile Lys Met Lys

[4536] 565 570 575
[4537] Trp Gly Met Glu Met Arg Arg Cys Leu Leu Gln Ser Leu Gln Gln Ile
[4538] 580 585 590
[4539] Glu Ser Met Ile Glu Ala Glu Ser Ser Val Lys Glu Lys Asp Met Thr
[4540] 595 600 605
[4541] Lys Glu Phe Phe Glu Asn Arg Ser Glu Thr Trp Pro Ile Gly Glu Ser
[4542] 610 615 620
[4543] Pro Lys Gly Val Glu Glu Gly Ser Ile Gly Lys Val Cys Arg Thr Leu
[4544] 625 630 635 640
[4545] Leu Ala Lys Ser Val Phe Asn Ser Leu Tyr Ala Ser Pro Gln Leu Glu
[4546] 645 650 655
[4547] Gly Phe Ser Ala Glu Ser Arg Lys Leu Leu Leu Ile Val Gln Ala Leu
[4548] 660 665 670
[4549] Arg Asp Asn Leu Glu Pro Gly Thr Phe Asp Leu Gly Gly Leu Tyr Glu
[4550] 675 680 685
[4551] Ala Ile Glu Glu Cys Leu Ile Asn Asp Pro Trp Val Leu Leu Asn Ala
[4552] 690 695 700
[4553] Ser Trp Phe Asn Ser Phe Leu Thr His Ala Leu Arg
[4554] 705 710 715
[4555] <210> 89
[4556] <211> 752
[4557] <212> PRT
[4558] <213> Influenza B virus
[4559] <400> 89
[4560] Met Asn Ile Asn Pro Tyr Phe Leu Phe Ile Asp Val Pro Ile Gln Ala
[4561] 1 5 10 15
[4562] Ala Ile Ser Thr Thr Phe Pro Tyr Thr Gly Val Pro Pro Tyr Ser His
[4563] 20 25 30
[4564] Gly Thr Gly Thr Gly Tyr Thr Ile Asp Thr Val Ile Arg Thr His Glu
[4565] 35 40 45
[4566] Tyr Ser Asn Lys Gly Lys Gln Tyr Ile Ser Asp Val Thr Gly Cys Val
[4567] 50 55 60
[4568] Met Val Asp Pro Thr Asn Gly Pro Leu Pro Glu Asp Asn Glu Pro Ser
[4569] 65 70 75 80
[4570] Ala Tyr Ala Gln Leu Asp Cys Val Leu Glu Ala Leu Asp Arg Met Asp
[4571] 85 90 95
[4572] Glu Glu His Pro Gly Leu Phe Gln Ala Gly Ser Gln Asn Ala Met Glu
[4573] 100 105 110
[4574] Ala Leu Met Val Thr Thr Val Asp Lys Leu Thr Gln Gly Arg Gln Thr
[4575] 115 120 125
[4576] Phe Asp Trp Thr Val Cys Arg Asn Gln Pro Ala Ala Thr Ala Leu Asn
[4577] 130 135 140

[4578] Thr Thr Ile Thr Ser Phe Arg Leu Asn Asp Leu Asn Gly Ala Asp Lys
[4579] 145 150 155 160
[4580] Gly Gly Leu Val Pro Phe Cys Gln Asp Ile Ile Asp Ser Leu Asp Lys
[4581] 165 170 175
[4582] Pro Glu Met Ile Phe Phe Thr Val Lys Asn Ile Lys Lys Lys Leu Pro
[4583] 180 185 190
[4584] Ala Lys Asn Arg Lys Gly Phe Leu Ile Lys Arg Ile Pro Met Lys Val
[4585] 195 200 205
[4586] Lys Asp Arg Ile Thr Arg Val Glu Tyr Ile Lys Arg Ala Leu Ser Leu
[4587] 210 215 220
[4588] Asn Thr Met Thr Lys Asp Ala Glu Arg Gly Lys Leu Lys Arg Arg Ala
[4589] 225 230 235 240
[4590] Ile Ala Thr Ala Gly Ile Gln Ile Arg Gly Phe Val Leu Val Val Glu
[4591] 245 250 255
[4592] Asn Leu Ala Lys Asn Ile Cys Glu Asn Leu Glu Gln Ser Gly Leu Pro
[4593] 260 265 270
[4594] Val Gly Gly Asn Glu Lys Lys Ala Lys Leu Ser Asn Ala Val Ala Lys
[4595] 275 280 285
[4596] Met Leu Ser Asn Cys Pro Pro Gly Gly Ile Ser Met Thr Val Thr Gly
[4597] 290 295 300
[4598] Asp Asn Thr Lys Trp Asn Glu Cys Leu Asn Pro Arg Ile Phe Leu Ala
[4599] 305 310 315 320
[4600] Met Thr Glu Arg Ile Thr Arg Asp Ser Pro Ile Trp Phe Arg Asp Phe
[4601] 325 330 335
[4602] Cys Ser Ile Ala Pro Val Leu Phe Ser Asn Lys Ile Ala Arg Leu Gly
[4603] 340 345 350
[4604] Lys Gly Phe Met Ile Thr Ser Lys Thr Lys Arg Leu Lys Ala Gln Ile
[4605] 355 360 365
[4606] Pro Cys Pro Asp Leu Phe Asn Ile Pro Leu Glu Arg Tyr Asn Glu Glu
[4607] 370 375 380
[4608] Thr Arg Ala Lys Leu Lys Lys Leu Lys Pro Phe Phe Asn Glu Glu Gly
[4609] 385 390 395 400
[4610] Thr Ala Ser Leu Ser Pro Gly Met Met Met Gly Met Phe Asn Met Leu
[4611] 405 410 415
[4612] Ser Thr Val Leu Gly Val Ala Ala Leu Gly Ile Lys Asn Ile Gly Asn
[4613] 420 425 430
[4614] Lys Glu Tyr Leu Trp Asp Gly Leu Gln Ser Ser Asp Asp Phe Ala Leu
[4615] 435 440 445
[4616] Phe Val Asn Ala Lys Asp Glu Glu Thr Cys Met Glu Gly Ile Asn Asp
[4617] 450 455 460
[4618] Phe Tyr Arg Thr Cys Lys Leu Leu Gly Ile Asn Met Ser Lys Lys Lys
[4619] 465 470 475 480

[4620] Ser Tyr Cys Asn Glu Thr Gly Met Phe Glu Phe Thr Ser Met Phe Tyr
[4621] 485 490 495
[4622] Arg Asp Gly Phe Val Ser Asn Phe Ala Met Glu Leu Pro Ser Phe Gly
[4623] 500 505 510
[4624] Val Ala Gly Val Asn Glu Ser Ala Asp Met Ala Ile Gly Met Thr Ile
[4625] 515 520 525
[4626] Ile Lys Asn Asn Met Ile Asn Asn Gly Met Gly Pro Ala Thr Ala Gln
[4627] 530 535 540
[4628] Thr Ala Ile Gln Leu Phe Ile Ala Asp Tyr Arg Tyr Thr Tyr Lys Cys
[4629] 545 550 555 560
[4630] His Arg Gly Asp Ser Lys Val Glu Gly Lys Arg Met Lys Ile Ile Lys
[4631] 565 570 575
[4632] Glu Leu Trp Glu Asn Thr Lys Gly Arg Asp Gly Leu Leu Val Ala Asp
[4633] 580 585 590
[4634] Gly Gly Pro Asn Leu Tyr Asn Leu Arg Asn Leu His Ile Pro Glu Ile
[4635] 595 600 605
[4636] Ile Leu Lys Tyr Asn Ile Met Asp Pro Glu Tyr Lys Gly Arg Leu Leu
[4637] 610 615 620
[4638] His Pro Gln Asn Pro Phe Val Gly His Leu Ser Ile Glu Gly Ile Lys
[4639] 625 630 635 640
[4640] Glu Ala Asp Ile Thr Pro Ala His Gly Pro Ile Lys Lys Met Asp Tyr
[4641] 645 650 655
[4642] Asp Ala Val Ser Gly Thr His Ser Trp Arg Thr Lys Arg Asn Arg Ser
[4643] 660 665 670
[4644] Ile Leu Asn Thr Asp Gln Arg Asn Met Ile Leu Glu Glu Gln Cys Tyr
[4645] 675 680 685
[4646] Ala Lys Cys Cys Asn Leu Phe Glu Ala Cys Phe Asn Ser Ala Ser Tyr
[4647] 690 695 700
[4648] Arg Lys Pro Val Gly Gln His Ser Met Leu Glu Ala Met Ala His Arg
[4649] 705 710 715 720
[4650] Leu Arg Met Asp Ala Arg Leu Asp Tyr Glu Ser Gly Arg Met Ser Lys
[4651] 725 730 735
[4652] Glu Asp Phe Glu Lys Ala Met Ala His Leu Gly Glu Ile Gly Tyr Met
[4653] 740 745 750
[4654] <210> 90
[4655] <211> 759
[4656] <212> PRT
[4657] <213> Influenza A virus
[4658] <400> 90
[4659] Met Glu Arg Ile Lys Glu Leu Arg Asn Leu Met Ser Gln Ser Arg Thr
[4660] 1 5 10 15
[4661] Arg Glu Ile Leu Thr Lys Thr Thr Val Asp His Met Ala Ile Ile Lys

[4662] 20 25 30
[4663] Lys Tyr Thr Ser Gly Arg Gln Glu Lys Asn Pro Ala Leu Arg Met Lys
[4664] 35 40 45
[4665] Trp Met Met Ala Met Lys Tyr Pro Ile Thr Ala Asp Lys Arg Ile Thr
[4666] 50 55 60
[4667] Glu Met Ile Pro Glu Arg Asn Glu Gln Gly Gln Thr Leu Trp Ser Lys
[4668] 65 70 75 80
[4669] Met Asn Asp Ala Gly Ser Asp Arg Val Met Val Ser Pro Leu Ala Val
[4670] 85 90 95
[4671] Thr Trp Trp Asn Arg Asn Gly Pro Met Thr Asn Thr Val His Tyr Pro
[4672] 100 105 110
[4673] Lys Ile Tyr Lys Thr Tyr Phe Glu Arg Val Glu Arg Leu Lys His Gly
[4674] 115 120 125
[4675] Thr Phe Gly Pro Val His Phe Arg Asn Gln Val Lys Ile Arg Arg Arg
[4676] 130 135 140
[4677] Val Asp Ile Asn Pro Gly His Ala Asp Leu Ser Ala Lys Glu Ala Gln
[4678] 145 150 155 160
[4679] Asp Val Ile Met Glu Val Val Phe Pro Asn Glu Val Gly Ala Arg Ile
[4680] 165 170 175
[4681] Leu Thr Ser Glu Ser Gln Leu Thr Ile Thr Lys Glu Lys Lys Glu Glu
[4682] 180 185 190
[4683] Leu Gln Asp Cys Lys Ile Ser Pro Leu Met Val Ala Tyr Met Leu Glu
[4684] 195 200 205
[4685] Arg Glu Leu Val Arg Lys Thr Arg Phe Leu Pro Val Ala Gly Gly Thr
[4686] 210 215 220
[4687] Ser Ser Val Tyr Ile Glu Val Leu His Leu Thr Gln Gly Thr Cys Trp
[4688] 225 230 235 240
[4689] Glu Gln Met Tyr Thr Pro Gly Gly Glu Val Lys Asn Asp Asp Val Asp
[4690] 245 250 255
[4691] Gln Ser Leu Ile Ile Ala Ala Arg Asn Ile Val Arg Arg Ala Ala Val
[4692] 260 265 270
[4693] Ser Ala Asp Pro Leu Ala Ser Leu Leu Glu Met Cys His Ser Thr Gln
[4694] 275 280 285
[4695] Ile Gly Gly Ile Arg Met Val Asp Ile Leu Lys Gln Asn Pro Thr Glu
[4696] 290 295 300
[4697] Glu Gln Ala Val Gly Ile Cys Lys Ala Ala Met Gly Leu Arg Ile Ser
[4698] 305 310 315 320
[4699] Ser Ser Phe Ser Phe Gly Gly Phe Thr Phe Lys Arg Thr Ser Gly Ser
[4700] 325 330 335
[4701] Ser Val Lys Arg Glu Glu Glu Val Leu Thr Gly Asn Leu Gln Thr Leu
[4702] 340 345 350
[4703] Lys Ile Arg Val His Glu Gly Tyr Glu Glu Phe Thr Met Val Gly Arg

[4704] 355 360 365
[4705] Arg Ala Thr Ala Ile Leu Arg Lys Ala Thr Arg Arg Leu Ile Gln Leu
[4706] 370 375 380
[4707] Ile Val Ser Gly Arg Asp Glu Gln Ser Ile Ala Glu Ala Ile Ile Val
[4708] 385 390 395 400
[4709] Ala Met Val Phe Ser Gln Glu Asp Cys Met Ile Lys Ala Val Arg Gly
[4710] 405 410 415
[4711] Asp Leu Asn Phe Val Asn Arg Ala Asn Gln Arg Leu Asn Pro Met His
[4712] 420 425 430
[4713] Gln Leu Leu Arg His Phe Gln Lys Asp Ala Lys Val Leu Phe Gln Asn
[4714] 435 440 445
[4715] Trp Gly Val Glu Pro Ile Asp Asn Val Met Gly Met Ile Gly Ile Leu
[4716] 450 455 460
[4717] Pro Asp Met Thr Pro Ser Ile Glu Met Ser Met Arg Gly Val Arg Ile
[4718] 465 470 475 480
[4719] Ser Lys Met Gly Val Asp Glu Tyr Ser Ser Thr Glu Arg Val Val Val
[4720] 485 490 495
[4721] Ser Ile Asp Arg Phe Leu Arg Val Arg Asp Gln Arg Gly Asn Val Leu
[4722] 500 505 510
[4723] Leu Ser Pro Glu Glu Val Ser Glu Thr Gln Gly Thr Glu Lys Leu Thr
[4724] 515 520 525
[4725] Ile Thr Tyr Ser Ser Ser Met Met Trp Glu Ile Asn Gly Pro Glu Ser
[4726] 530 535 540
[4727] Val Leu Val Asn Thr Tyr Gln Trp Ile Ile Arg Asn Trp Glu Thr Val
[4728] 545 550 555 560
[4729] Lys Ile Gln Trp Ser Gln Asn Pro Thr Met Leu Tyr Asn Lys Met Glu
[4730] 565 570 575
[4731] Phe Glu Pro Phe Gln Ser Leu Val Pro Lys Ala Ile Arg Gly Gln Tyr
[4732] 580 585 590
[4733] Ser Gly Phe Val Arg Thr Leu Phe Gln Gln Met Arg Asp Val Leu Gly
[4734] 595 600 605
[4735] Thr Phe Asp Thr Ala Gln Ile Ile Lys Leu Leu Pro Phe Ala Ala Ala
[4736] 610 615 620
[4737] Pro Pro Lys Gln Ser Arg Met Gln Phe Ser Ser Phe Thr Val Asn Val
[4738] 625 630 635 640
[4739] Arg Gly Ser Gly Met Arg Ile Leu Val Arg Gly Asn Ser Pro Val Phe
[4740] 645 650 655
[4741] Asn Tyr Asn Lys Ala Thr Lys Arg Leu Thr Val Leu Gly Lys Asp Ala
[4742] 660 665 670
[4743] Gly Thr Leu Thr Glu Asp Pro Asp Glu Gly Thr Ala Gly Val Glu Ser
[4744] 675 680 685
[4745] Ala Val Leu Arg Gly Phe Leu Ile Leu Gly Lys Glu Asp Arg Arg Tyr

[4746] 690 695 700
[4747] Gly Pro Ala Leu Ser Ile Asn Glu Leu Ser Asn Leu Ala Lys Gly Glu
[4748] 705 710 715 720
[4749] Lys Ala Asn Val Leu Ile Gly Gln Gly Asp Val Val Leu Val Met Lys
[4750] 725 730 735
[4751] Arg Lys Arg Asp Ser Ser Ile Leu Thr Asp Ser Gln Thr Ala Thr Lys
[4752] 740 745 750
[4753] Arg Ile Arg Met Ala Ile Asn
[4754] 755
[4755] <210> 91
[4756] <211> 109
[4757] <212> PRT
[4758] <213> Influenza B virus
[4759] <400> 91
[4760] Met Leu Glu Pro Leu Gln Ile Leu Ser Ile Cys Ser Phe Ile Leu Ser
[4761] 1 5 10 15
[4762] Ala Leu His Phe Met Ala Trp Thr Ile Gly His Leu Asn Gln Ile Lys
[4763] 20 25 30
[4764] Arg Gly Val Asn Leu Lys Ile Gln Ile Arg Asn Pro Asn Lys Glu Ala
[4765] 35 40 45
[4766] Ile Asn Arg Glu Val Ser Ile Leu Arg His Asn Tyr Gln Lys Glu Ile
[4767] 50 55 60
[4768] Gln Ala Lys Glu Thr Met Lys Lys Ile Leu Ser Asp Asn Met Glu Val
[4769] 65 70 75 80
[4770] Leu Gly Asp His Ile Val Val Glu Gly Leu Ser Thr Asp Glu Ile Ile
[4771] 85 90 95
[4772] Lys Met Gly Glu Thr Val Leu Glu Val Glu Glu Leu Gln
[4773] 100 105
[4774] <210> 92
[4775] <211> 100
[4776] <212> PRT
[4777] <213> Influenza B virus
[4778] <400> 92
[4779] Met Asn Asn Ala Thr Phe Asn Cys Thr Asn Ile Asn Pro Ile Thr His
[4780] 1 5 10 15
[4781] Ile Arg Gly Ser Ile Ile Ile Thr Ile Cys Val Ser Leu Ile Val Ile
[4782] 20 25 30
[4783] Leu Ile Val Phe Gly Cys Ile Ala Lys Ile Phe Ile Asn Lys Asn Asn
[4784] 35 40 45
[4785] Cys Thr Asn Asn Val Ile Arg Val His Lys Arg Ile Lys Cys Pro Asp
[4786] 50 55 60
[4787] Cys Glu Pro Phe Cys Asn Lys Arg Asp Asp Ile Ser Thr Pro Arg Ala

[4788] 65 70 75 80
[4789] Gly Val Asp Ile Pro Ser Phe Ile Leu Pro Gly Leu Asn Leu Ser Glu
[4790] 85 90 95
[4791] Gly Thr Pro Asn
[4792] 100
[4793] <210> 93
[4794] <211> 498
[4795] <212> PRT
[4796] <213> Influenza A virus
[4797] <400> 93
[4798] Met Ala Ser Gln Gly Thr Lys Arg Ser Tyr Glu Gln Met Glu Thr Asp
[4799] 1 5 10 15
[4800] Gly Glu Arg Gln Asn Ala Thr Glu Ile Arg Ala Ser Val Gly Lys Met
[4801] 20 25 30
[4802] Ile Gly Gly Ile Gly Arg Phe Tyr Ile Gln Met Cys Thr Glu Leu Lys
[4803] 35 40 45
[4804] Leu Ser Asp Tyr Glu Gly Arg Leu Ile Gln Asn Ser Leu Thr Ile Glu
[4805] 50 55 60
[4806] Arg Met Val Leu Ser Ala Phe Asp Glu Arg Arg Asn Lys Tyr Leu Glu
[4807] 65 70 75 80
[4808] Glu His Pro Ser Ala Gly Lys Asp Pro Lys Lys Thr Gly Gly Pro Ile
[4809] 85 90 95
[4810] Tyr Arg Arg Val Asn Gly Lys Trp Met Arg Glu Leu Ile Leu Tyr Asp
[4811] 100 105 110
[4812] Lys Glu Glu Ile Arg Arg Ile Trp Arg Gln Ala Asn Asn Gly Asp Asp
[4813] 115 120 125
[4814] Ala Thr Ala Gly Leu Thr His Met Met Ile Trp His Ser Asn Leu Asn
[4815] 130 135 140
[4816] Asp Ala Thr Tyr Gln Arg Thr Arg Ala Leu Val Arg Thr Gly Met Asp
[4817] 145 150 155 160
[4818] Pro Arg Met Cys Ser Leu Met Gln Gly Ser Thr Leu Pro Arg Arg Ser
[4819] 165 170 175
[4820] Gly Ala Ala Gly Ala Ala Val Lys Gly Val Gly Thr Met Val Met Glu
[4821] 180 185 190
[4822] Leu Val Arg Met Ile Lys Arg Gly Ile Asn Asp Arg Asn Phe Trp Arg
[4823] 195 200 205
[4824] Gly Glu Asn Gly Arg Lys Thr Arg Ile Ala Tyr Glu Arg Met Cys Asn
[4825] 210 215 220
[4826] Ile Leu Lys Gly Lys Phe Gln Thr Ala Ala Gln Lys Ala Met Met Asp
[4827] 225 230 235 240
[4828] Gln Val Arg Glu Ser Arg Asp Pro Gly Asn Ala Glu Phe Glu Asp Leu
[4829] 245 250 255

[4830] Thr Phe Leu Ala Arg Ser Ala Leu Ile Leu Arg Gly Ser Val Ala His
[4831] 260 265 270
[4832] Lys Ser Cys Leu Pro Ala Cys Val Tyr Gly Pro Ala Val Ala Ser Gly
[4833] 275 280 285
[4834] Tyr Asp Phe Glu Arg Glu Gly Tyr Ser Leu Val Gly Ile Asp Pro Phe
[4835] 290 295 300
[4836] Arg Leu Leu Gln Asn Ser Gln Val Tyr Ser Leu Ile Arg Pro Asn Glu
[4837] 305 310 315 320
[4838] Asn Pro Ala His Lys Ser Gln Leu Val Trp Met Ala Cys His Ser Ala
[4839] 325 330 335
[4840] Ala Phe Glu Asp Leu Arg Val Leu Ser Phe Ile Lys Gly Thr Lys Val
[4841] 340 345 350
[4842] Val Pro Arg Gly Lys Leu Ser Thr Arg Gly Val Gln Ile Ala Ser Asn
[4843] 355 360 365
[4844] Glu Asn Met Glu Thr Met Glu Ser Ser Thr Leu Glu Leu Arg Ser Arg
[4845] 370 375 380
[4846] Tyr Trp Ala Ile Arg Thr Arg Ser Gly Gly Asn Thr Asn Gln Gln Arg
[4847] 385 390 395 400
[4848] Ala Ser Ala Gly Gln Ile Ser Ile Gln Pro Thr Phe Ser Val Gln Arg
[4849] 405 410 415
[4850] Asn Leu Pro Phe Asp Arg Thr Thr Val Met Ala Ala Phe Thr Gly Asn
[4851] 420 425 430
[4852] Thr Glu Gly Arg Thr Ser Asp Met Arg Thr Glu Ile Ile Arg Met Met
[4853] 435 440 445
[4854] Glu Ser Ala Arg Pro Glu Asp Val Ser Phe Gln Gly Arg Gly Val Phe
[4855] 450 455 460
[4856] Glu Leu Ser Asp Glu Lys Ala Ala Ser Pro Ile Val Pro Ser Phe Asp
[4857] 465 470 475 480
[4858] Met Ser Asn Glu Gly Ser Tyr Phe Phe Gly Asp Asn Ala Glu Glu Tyr
[4859] 485 490 495
[4860] Asp Asn
[4861] <210> 94
[4862] <211> 548
[4863] <212> PRT
[4864] <213> Human herpesvirus 5
[4865] <400> 94
[4866] Met Glu Ser Arg Gly Arg Arg Cys Pro Glu Met Ile Ser Val Leu Gly
[4867] 1 5 10 15
[4868] Pro Ile Ser Gly His Val Leu Lys Ala Val Phe Ser Arg Gly Asp Thr
[4869] 20 25 30
[4870] Pro Val Leu Pro His Glu Thr Arg Leu Leu Gln Thr Gly Ile His Val
[4871] 35 40 45

[4872] Arg Val Ser Gln Pro Ser Leu Ile Leu Val Ser Gln Tyr Thr Pro Asp
[4873] 50 55 60
[4874] Ser Thr Pro Cys His Arg Gly Asp Asn Gln Leu Gln Val Gln His Thr
[4875] 65 70 75 80
[4876] Tyr Phe Thr Gly Ser Glu Val Glu Asn Val Ser Val Asn Glu Pro Met
[4877] 85 90 95
[4878] Ser Ile Tyr Val Tyr Ala Leu Pro Leu Lys Met Leu Asn Ile Pro Ser
[4879] 100 105 110
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[5044] 210 215 220
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[5250] 260 265 270
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[5255] Leu Tyr Leu Leu Phe Asp Glu Tyr Thr Thr Ile Pro Phe Ser Leu Leu
[5256] 305 310 315 320
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[7243] gacatccaga tgacacagtc tccatcctca ctgtctgcat ctctgggagg caaagtcacc 120
[7244] atcacatgca aggcaagcca agacattcac aactatatag cttggtacca acacaagcct 180
[7245] gtaaaaggtc ctaggctgct catacattac acatctacat tacagccagg caccccatca 240
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[7271] Arg Leu Leu Ile His Tyr Thr Ser Thr Leu Gln Pro Gly Thr Pro Ser
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[7273] Arg Phe Ser Gly Ser Gly Ser Gly Arg Asp Tyr Ser Phe Ser Ile Ser
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[7276] 100 105 110
[7277] Asn Leu Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala
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[7279] Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu
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[7283] Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn
[7284] 165 170 175
[7285] Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr
[7286] 180 185 190
[7287] Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His
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[7306] aacccatccc tgaagagccg actcacaatc tccaaggata cctccagaaa ccaggtattc 300
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[7343] Gly Leu Glu Trp Leu Ala His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr
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[7345] Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Arg
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[7347] Asn Gln Val Phe Leu Lys Ile Thr Ser Val Asp Ala Ala Asp Thr Ala
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[7353] Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr
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[7355] Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu
[7356] 165 170 175
[7357] Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His
[7358] 180 185 190
[7359] Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser
[7360] 195 200 205
[7361] Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn
[7362] 210 215 220
[7363] Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro
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[7365] Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser
[7366] 245 250 255
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[7369] Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp
[7370] 275 280 285
[7371] Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr
[7372] 290 295 300
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[7374] 305 310 315 320
[7375] Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu
[7376] 325 330 335
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[7379] Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr
[7380] 355 360 365
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[7382] 370 375 380
[7383] Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln
[7384] 385 390 395 400
[7385] Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met
[7386] 405 410 415
[7387] Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys
[7388] 420 425 430
[7389] Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
[7390] 435 440 445
[7391] Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly

[7392] 450 455 460

[7393] Lys

[7394] 465

[7395] <210> 284

[7396] <211> 33

[7397] <212> DNA

[7398] <213> Artificial sequence

[7399] <220>

[7400] <221> gene

[7401] <222> (1)..(33)

[7402] <223> D11轻链CDR的核酸序列

[7403] <400> 284

[7404] aaggcaagcc aagacattca caactatata gct 33

[7405] <210> 285

[7406] <211> 21

[7407] <212> DNA

[7408] <213> Artificial sequence

[7409] <220>

[7410] <221> gene

[7411] <222> (1)..(21)

[7412] <223> D11轻链CDR的核酸序列

[7413] <400> 285

[7414] tacacatcta cattacagcc a 21

[7415] <210> 286

[7416] <211> 24

[7417] <212> DNA

[7418] <213> Artificial sequence

[7419] <220>

[7420] <221> gene

[7421] <222> (1)..(24)

[7422] <223> D11轻链CDR的核酸序列

[7423] <400> 286

[7424] ctacagtatg ataatctgtg gacg 24

[7425] <210> 287

[7426] <211> 11

[7427] <212> PRT

[7428] <213> Artificial sequence

[7429] <220>

[7430] <221> PEPTIDE

[7431] <222> (1)..(11)

[7432] <223> D11轻链CDR的氨基酸序列

[7433] <400> 287

[7434] Lys Ala Ser Gln Asp Ile His Asn Tyr Ile Ala
[7435] 1 5 10
[7436] <210> 288
[7437] <211> 7
[7438] <212> PRT
[7439] <213> Artificial sequence
[7440] <220>
[7441] <221> PEPTIDE
[7442] <222> (1)..(7)
[7443] <223> D11轻链CDR的氨基酸序列
[7444] <400> 288
[7445] Tyr Thr Ser Thr Leu Gln Pro
[7446] 1 5
[7447] <210> 289
[7448] <211> 8
[7449] <212> PRT
[7450] <213> Artificial sequence
[7451] <220>
[7452] <221> PEPTIDE
[7453] <222> (1)..(8)
[7454] <223> D11轻链CDR的氨基酸序列
[7455] <400> 289
[7456] Leu Gln Tyr Asp Asn Leu Trp Thr
[7457] 1 5
[7458] <210> 290
[7459] <211> 21
[7460] <212> DNA
[7461] <213> Artificial sequence
[7462] <220>
[7463] <221> gene
[7464] <222> (1)..(21)
[7465] <223> D11重链CDR的核酸序列
[7466] <400> 290
[7467] acttctggta tgggtgtgag c 21
[7468] <210> 291
[7469] <211> 48
[7470] <212> DNA
[7471] <213> Artificial sequence
[7472] <220>
[7473] <221> gene
[7474] <222> (1)..(48)
[7475] <223> D11重链CDR的核酸序列

[7476] <400> 291
[7477] cacatttact gggatgatga caagcgctat aacccatccc tgaagagc 48
[7478] <210> 292
[7479] <211> 36
[7480] <212> DNA
[7481] <213> Artificial sequence
[7482] <220>
[7483] <221> gene
[7484] <222> (1)..(36)
[7485] <223> D11重链CDR的核酸序列
[7486] <400> 292
[7487] aaggactacg gtagtagctt ctatgctatg cactac 36
[7488] <210> 293
[7489] <211> 7
[7490] <212> PRT
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[7492] <220>
[7493] <221> PEPTIDE
[7494] <222> (1)..(7)
[7495] <223> D11重链CDR的氨基酸序列
[7496] <400> 293
[7497] Thr Ser Gly Met Gly Val Ser
[7498] 1 5
[7499] <210> 294
[7500] <211> 16
[7501] <212> PRT
[7502] <213> Artificial sequence
[7503] <220>
[7504] <221> PEPTIDE
[7505] <222> (1)..(16)
[7506] <223> D11重链CDR的氨基酸序列
[7507] <400> 294
[7508] His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser Leu Lys Ser
[7509] 1 5 10 15
[7510] <210> 295
[7511] <211> 12
[7512] <212> PRT
[7513] <213> Artificial sequence
[7514] <220>
[7515] <221> PEPTIDE
[7516] <222> (1)..(12)
[7517] <223> D11重链CDR的氨基酸序列

[7518] <400> 295
[7519] Lys Asp Tyr Gly Ser Ser Phe Tyr Ala Met His Tyr
[7520] 1 5 10
[7521] <210> 296
[7522] <211> 705
[7523] <212> DNA
[7524] <213> Artificial sequence
[7525] <220>
[7526] <221> gene
[7527] <222> (1)..(705)
[7528] <223> D7轻链的核酸序列
[7529] <400> 296
[7530] atgagtgtgc ccactcaggt cctggggttg ctgctgctgt ggcttacaga tgccagatgt 60
[7531] gacatccaga tgactcagtc tccagcctcc ctatctgtat ctgtgggaga aactgtcacc 120
[7532] atcacatgtc gagcaagtga tattatttac agtaatttag catggtatca gcagaaacag 180
[7533] ggaaaatctc ctcagctcct ggtctatgct gcaacaaact tagcagctgg tgtgccatca 240
[7534] aggttcagtg gcagtggatc aggcacacag tattccctca agatcaatag cctgcagtct 300
[7535] gaagattttg ggacttatta ctgtcaacat ttttggggta gttcaatctc gttcggctcg 360
[7536] gggacaaagt tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 420
[7537] tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 480
[7538] cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 540
[7539] aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 600
[7540] ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 660
[7541] tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag 705
[7542] <210> 297
[7543] <211> 234
[7544] <212> PRT
[7545] <213> Artificial sequence
[7546] <220>
[7547] <221> PEPTIDE
[7548] <222> (1)..(234)
[7549] <223> D7轻链的氨基酸序列
[7550] <400> 297
[7551] Met Ser Val Pro Thr Gln Val Leu Gly Leu Leu Leu Leu Trp Leu Thr
[7552] 1 5 10 15
[7553] Asp Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser
[7554] 20 25 30
[7555] Val Ser Val Gly Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Asp Ile
[7556] 35 40 45
[7557] Ile Tyr Ser Asn Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro
[7558] 50 55 60
[7559] Gln Leu Leu Val Tyr Ala Ala Thr Asn Leu Ala Ala Gly Val Pro Ser

[7560] 65 70 75 80
[7561] Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn
[7562] 85 90 95
[7563] Ser Leu Gln Ser Glu Asp Phe Gly Thr Tyr Tyr Cys Gln His Phe Trp
[7564] 100 105 110
[7565] Gly Ser Ser Ile Ser Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg
[7566] 115 120 125
[7567] Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
[7568] 130 135 140
[7569] Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
[7570] 145 150 155 160
[7571] Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
[7572] 165 170 175
[7573] Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
[7574] 180 185 190
[7575] Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
[7576] 195 200 205
[7577] His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
[7578] 210 215 220
[7579] Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
[7580] 225 230
[7581] <210> 298
[7582] <211> 1380
[7583] <212> DNA
[7584] <213> Artificial sequence
[7585] <220>
[7586] <221> gene
[7587] <222> (1)..(1380)
[7588] <223> D7重链的核酸序列
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[7590] atggctgtcc tggtgctgtt cctctgcctg gttgcatttc caagctgtgt cctgtcccag 60
[7591] gtgcaactga aggaatcagg acctggtctg gtggcgccct cacagagcct gtccatcact 120
[7592] tgcactgtct ctgggttttc attaaccagc tatggtgtac actgggttcg ccagcctcca 180
[7593] ggaaagggtc tggagtggct gggagtaata tgggctggtg gaaccacaaa ttataattcg 240
[7594] gctctcatgt ccagactgag catcagcaga gacaactcca agagccaagt tttcttagaa 300
[7595] atgaacagtc tgcaaactga tgacacagcc atttactact gtgccagaga tggtcacttc 360
[7596] cactttgact tctggggcca aggcaccact ctcacagtct cctcagccaa aacgacaccc 420
[7597] ccatctgtct atccactggc ccctggatct gctgcccaaa ctaactccat ggtgaccctg 480
[7598] ggatgcctgg tcaagggcta tttccctgag ccagtgacag tgacctggaa ctctggatcc 540
[7599] ctgtccagcg gtgtgcacac cttcccagct gtcctgcagt ctgacctcta cactctgagc 600
[7600] agctcagtga ctgtcccctc cagcacctgg cccagcgaga ccgtcacctg caacgttgcc 660
[7601] cacccggcca gcagcaccaa ggtggacaag aaaattgtgc ccagggattg tggttgtaag 720

[7602] ccttgcatat gtacagtccc agaagtatca tctgtcttca tcttcccccc aaagcccaag 780
[7603] gatgtgctca ccattactct gactcctaag gtcacgtgtg ttgtggtaga catcagcaag 840
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[7608] tacaccattc cacctcccaa ggagcagatg gccaaggata aagtcagtct gacctgcatg 1140
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[7610] gagaactaca agaacactca gcccatcatg gacacagatg gctcttactt cgtctacagc 1260
[7611] aagctcaatg tgcagaagag caactgggag gcaggaaata ctttcacctg ctctgtgtta 1320
[7612] catgagggcc tgcacaacca ccatactgag aagagcctct cccactctcc tggtaaatga 1380
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[7614] <211> 459
[7615] <212> PRT
[7616] <213> Artificial sequence
[7617] <220>
[7618] <221> PEPTIDE
[7619] <222> (1)..(459)
[7620] <223> D7重链的氨基酸序列
[7621] <400> 299
[7622] Met Ala Val Leu Val Leu Phe Leu Cys Leu Val Ala Phe Pro Ser Cys
[7623] 1 5 10 15
[7624] Val Leu Ser Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala
[7625] 20 25 30
[7626] Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu
[7627] 35 40 45
[7628] Thr Ser Tyr Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu
[7629] 50 55 60
[7630] Glu Trp Leu Gly Val Ile Trp Ala Gly Gly Thr Thr Asn Tyr Asn Ser
[7631] 65 70 75 80
[7632] Ala Leu Met Ser Arg Leu Ser Ile Ser Arg Asp Asn Ser Lys Ser Gln
[7633] 85 90 95
[7634] Val Phe Leu Glu Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr
[7635] 100 105 110
[7636] Tyr Cys Ala Arg Asp Gly His Phe His Phe Asp Phe Trp Gly Gln Gly
[7637] 115 120 125
[7638] Thr Thr Leu Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val Tyr
[7639] 130 135 140
[7640] Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu
[7641] 145 150 155 160
[7642] Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp
[7643] 165 170 175

[7644] Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu
[7645] 180 185 190
[7646] Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser Ser
[7647] 195 200 205
[7648] Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala Ser
[7649] 210 215 220
[7650] Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys
[7651] 225 230 235 240
[7652] Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro
[7653] 245 250 255
[7654] Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr
[7655] 260 265 270
[7656] Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser
[7657] 275 280 285
[7658] Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg
[7659] 290 295 300
[7660] Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile
[7661] 305 310 315 320
[7662] Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn
[7663] 325 330 335
[7664] Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
[7665] 340 345 350
[7666] Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu
[7667] 355 360 365
[7668] Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp Phe
[7669] 370 375 380
[7670] Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala
[7671] 385 390 395 400
[7672] Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr
[7673] 405 410 415
[7674] Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly
[7675] 420 425 430
[7676] Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His
[7677] 435 440 445
[7678] Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
[7679] 450 455
[7680] <210> 300
[7681] <211> 33
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[7683] <213> Artificial sequence
[7684] <220>
[7685] <221> gene

[7686] <222> (1)..(33)
[7687] <223> D7重链CDR的核酸序列
[7688] <400> 300
[7689] cgagcaagtg atattattta cagtaattta gca 33
[7690] <210> 301
[7691] <211> 21
[7692] <212> DNA
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[7694] <220>
[7695] <221> gene
[7696] <222> (1)..(21)
[7697] <223> D7重链CDR的氨基酸序列
[7698] <400> 301
[7699] gctgcaacaa acttagcagc t 21
[7700] <210> 302
[7701] <211> 27
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[7705] <221> gene
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[7707] <223> D7轻链CDR的核酸序列
[7708] <400> 302
[7709] caacattttt ggggtagttc aatctcg 27
[7710] <210> 303
[7711] <211> 11
[7712] <212> PRT
[7713] <213> Artificial sequence
[7714] <220>
[7715] <221> PEPTIDE
[7716] <222> (1)..(11)
[7717] <223> D7轻链CDR的氨基酸序列
[7718] <400> 303
[7719] Arg Ala Ser Asp Ile Ile Tyr Ser Asn Leu Ala
[7720] 1 5 10
[7721] <210> 304
[7722] <211> 7
[7723] <212> PRT
[7724] <213> Artificial sequence
[7725] <220>
[7726] <221> PEPTIDE
[7727] <222> (1)..(7)

[7728] <223> D7轻链CDR的氨基酸序列
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[7730] Ala Ala Thr Asn Leu Ala Ala
[7731] 1 5
[7732] <210> 305
[7733] <211> 9
[7734] <212> PRT
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[7736] <220>
[7737] <221> PEPTIDE
[7738] <222> (1)..(9)
[7739] <223> D7轻链CDR的氨基酸序列
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[7741] Gln His Phe Trp Gly Ser Ser Ile Ser
[7742] 1 5
[7743] <210> 306
[7744] <211> 15
[7745] <212> DNA
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[7747] <220>
[7748] <221> gene
[7749] <222> (1)..(15)
[7750] <223> D7重链CDR的核酸序列
[7751] <400> 306
[7752] agctatggtg tacac 15
[7753] <210> 307
[7754] <211> 48
[7755] <212> DNA
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[7757] <220>
[7758] <221> gene
[7759] <222> (1)..(48)
[7760] <223> D7重链CDR的核酸序列
[7761] <400> 307
[7762] gtaatatggg ctggtggaac cacaaattat aattcggctc tcatgtcc 48
[7763] <210> 308
[7764] <211> 24
[7765] <212> DNA
[7766] <213> Artificial sequence
[7767] <220>
[7768] <221> gene
[7769] <222> (1)..(24)

[7770] <223> D7重链CDR的核酸序列
[7771] <400> 308
[7772] gatggtcact tccactttga cttc 24
[7773] <210> 309
[7774] <211> 5
[7775] <212> PRT
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[7779] <222> (1)..(5)
[7780] <223> D7重链CDR的氨基酸序列
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[7782] Ser Tyr Gly Val His
[7783] 1 5
[7784] <210> 310
[7785] <211> 16
[7786] <212> PRT
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[7788] <220>
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[7790] <222> (1)..(16)
[7791] <223> D7重链CDR的氨基酸序列
[7792] <400> 310
[7793] Val Ile Trp Ala Gly Gly Thr Thr Asn Tyr Asn Ser Ala Leu Met Ser
[7794] 1 5 10 15
[7795] <210> 311
[7796] <211> 8
[7797] <212> PRT
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[7800] <221> PEPTIDE
[7801] <222> (1)..(8)
[7802] <223> D7重链CDR的氨基酸序列
[7803] <400> 311
[7804] Asp Gly His Phe His Phe Asp Phe
[7805] 1 5
[7806] <210> 312
[7807] <211> 642
[7808] <212> DNA
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[7810] <220>
[7811] <221> gene

[7812] <222> (1)..(642)
[7813] <223> B47B6轻链的核酸序列
[7814] <400> 312
[7815] gatattgtgc tcactcagtc tccagccacc ctgtctgtga gtccaggaga tagcgtcagt 60
[7816] ctttcctgca gggccagcca aagtattagc aacagcctac actggtatca acaaaaatca 120
[7817] catgagtctc caaggcttct catcaagtat gcttcccagt ccatctctgg aatcccctct 180
[7818] aggttcagtg gcagtggatc agggacagat ttcactctca gtatcaacag tgtggagact 240
[7819] gaagattttg gaatgtattt ctgtcaacag agttacagct ggcctctcac gttcggtgct 300
[7820] gggtccaagc tggagctgaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360
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[7822] cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480
[7823] aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540
[7824] ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
[7825] tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642
[7826] <210> 313
[7827] <211> 214
[7828] <212> PRT
[7829] <213> Artificial sequence
[7830] <220>
[7831] <221> PEPTIDE
[7832] <222> (1)..(214)
[7833] <223> B47B6轻链的氨基酸序列
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[7835] Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
[7836] 1 5 10 15
[7837] Asp Ser Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Asn Ser
[7838] 20 25 30
[7839] Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu Leu Ile
[7840] 35 40 45
[7841] Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
[7842] 50 55 60
[7843] Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Thr
[7844] 65 70 75 80
[7845] Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Tyr Ser Trp Pro Leu
[7846] 85 90 95
[7847] Thr Phe Gly Ala Gly Ser Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala
[7848] 100 105 110
[7849] Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
[7850] 115 120 125
[7851] Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
[7852] 130 135 140
[7853] Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu

[7854] 145 150 155 160
[7855] Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
[7856] 165 170 175
[7857] Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
[7858] 180 185 190
[7859] Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
[7860] 195 200 205
[7861] Phe Asn Arg Asn Glu Cys
[7862] 210
[7863] <210> 314
[7864] <211> 1323
[7865] <212> DNA
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[7869] <222> (1)..(1323)
[7870] <223> B47B6重链的核酸序列
[7871] <400> 314
[7872] gaagtgcagt tggtggagtc ggggggaggc ttagtgaagc ctggagggtc cctgaaactc 60
[7873] tcctgtgcag cctctggatt cgttttcagt agctatgaca tgtcttgggt tcgccaggct 120
[7874] caggagaaga ggctggagtg ggtcgcatac atgagtagtg gtggcggcac ctactatcca 180
[7875] gacactgtga agggccgatt caccatctcc agagacaatg ccaagaacac cctgcacctg 240
[7876] caaatgagca gcctgaagtc tgaggacaca gccatgtatt actgtgcaag acatgatgag 300
[7877] attactaact ttgactactg gggccaaggc accactctca cagtctcctc agccaaaacg 360
[7878] acacccccat ctgtctatcc actggcccct ggatctgctg cccaaactaa ctccatggtg 420
[7879] accctgggat gcctggtcaa gggctatttc cctgagccag tgacagtgac ctggaactct 480
[7880] ggatccctgt ccagcggtgt gcacaccttc ccagctgtcc tgcagtctga cctctacact 540
[7881] ctgagcagct cagtgactgt cccctccagc acctggccca gcgagaccgt cacctgcaac 600
[7882] gttgcccacc cggccagcag caccaaggtg gacaagaaaa ttgtgcccag ggattgtggt 660
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[7884] cccaaggatg tgctcaccat tactctgact cctaaggtca cgtgtgttgt ggtagacatc 780
[7885] agcaaggatg atcccgaggt ccagttcagc tggtttgtag atgatgtgga ggtgcacaca 840
[7886] gctcagacgc aaccccggga ggagcagttc aacagcactt tccgctcagt cagtgaactt 900
[7887] cccatcatgc accaggactg gctcaatggc aaggagttca aatgcagggt caacagtgca 960
[7888] gctttccctg cccccatcga gaaaaccatc tccaaaacca aaggcagacc gaaggctcca 1020
[7889] caggtgtaca ccattccacc tcccaaggag cagatggcca aggataaagt cagtctgacc 1080
[7890] tgcatgataa cagacttctt ccctgaagac attactgtgg agtggcagtg gaatgggcag 1140
[7891] ccagcggaga actacaagaa cactcagccc atcatggaca cagatggctc ttacttcgtc 1200
[7892] tacagcaagc tcaatgtgca gaagagcaac tgggaggcag gaaatacttt cacctgctct 1260
[7893] gtgttacatg agggcctgca caaccaccat actgagaaga gcctctccca ctctcctggt 1320
[7894] aaa 1323
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[7896] <211> 441
[7897] <212> PRT
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[7899] <220>
[7900] <221> PEPTIDE
[7901] <222> (1)..(441)
[7902] <223> B47B6重链的氨基酸序列
[7903] <400> 315
[7904] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[7905] 1 5 10 15
[7906] Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Val Phe Ser Ser Tyr
[7907] 20 25 30
[7908] Asp Met Ser Trp Val Arg Gln Ala Gln Glu Lys Arg Leu Glu Trp Val
[7909] 35 40 45
[7910] Ala Tyr Met Ser Ser Gly Gly Gly Thr Tyr Tyr Pro Asp Thr Val Lys
[7911] 50 55 60
[7912] Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu His Leu
[7913] 65 70 75 80
[7914] Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala
[7915] 85 90 95
[7916] Arg His Asp Glu Ile Thr Asn Phe Asp Tyr Trp Gly Gln Gly Thr Thr
[7917] 100 105 110
[7918] Leu Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu
[7919] 115 120 125
[7920] Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys
[7921] 130 135 140
[7922] Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser
[7923] 145 150 155 160
[7924] Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
[7925] 165 170 175
[7926] Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp
[7927] 180 185 190
[7928] Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr
[7929] 195 200 205
[7930] Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys
[7931] 210 215 220
[7932] Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys
[7933] 225 230 235 240
[7934] Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val
[7935] 245 250 255
[7936] Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe
[7937] 260 265 270

[7938] Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu
[7939] 275 280 285
[7940] Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile Met His
[7941] 290 295 300
[7942] Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala
[7943] 305 310 315 320
[7944] Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg
[7945] 325 330 335
[7946] Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met
[7947] 340 345 350
[7948] Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro
[7949] 355 360 365
[7950] Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn
[7951] 370 375 380
[7952] Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Val
[7953] 385 390 395 400
[7954] Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr
[7955] 405 410 415
[7956] Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His Thr Glu
[7957] 420 425 430
[7958] Lys Ser Leu Ser His Ser Pro Gly Lys
[7959] 435 440
[7960] <210> 316
[7961] <211> 33
[7962] <212> DNA
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[7964] <220>
[7965] <221> gene
[7966] <222> (1)..(33)
[7967] <223> B47B6轻链CDR的核酸序列
[7968] <400> 316
[7969] agggccagcc aaagtattag caacagccta cac 33
[7970] <210> 317
[7971] <211> 21
[7972] <212> DNA
[7973] <213> Artificial sequence
[7974] <220>
[7975] <221> gene
[7976] <222> (1)..(21)
[7977] <223> B47B6轻链CDR的核酸序列
[7978] <400> 317
[7979] tatgcttccc agtccatctc t 21

[7980] <210> 318
[7981] <211> 27
[7982] <212> DNA
[7983] <213> Artificial sequence
[7984] <220>
[7985] <221> gene
[7986] <222> (1)..(27)
[7987] <223> B47B6轻链CDR的核酸序列
[7988] <400> 318
[7989] caacagagtt acagctggcc tctcacg 27
[7990] <210> 319
[7991] <211> 11
[7992] <212> PRT
[7993] <213> Artificial sequence
[7994] <220>
[7995] <221> PEPTIDE
[7996] <222> (1)..(11)
[7997] <223> B47B6轻链CDR的氨基酸序列
[7998] <400> 319
[7999] Arg Ala Ser Gln Ser Ile Ser Asn Ser Leu His
[8000] 1 5 10
[8001] <210> 320
[8002] <211> 7
[8003] <212> PRT
[8004] <213> Artificial sequence
[8005] <220>
[8006] <221> PEPTIDE
[8007] <222> (1)..(7)
[8008] <223> B47B6轻链CDR的氨基酸序列
[8009] <400> 320
[8010] Tyr Ala Ser Gln Ser Ile Ser
[8011] 1 5
[8012] <210> 321
[8013] <211> 9
[8014] <212> PRT
[8015] <213> Artificial sequence
[8016] <220>
[8017] <221> PEPTIDE
[8018] <222> (1)..(9)
[8019] <223> B47B6轻链CDR的氨基酸序列
[8020] <400> 321
[8021] Gln Gln Ser Tyr Ser Trp Pro Leu Thr

[8022] 1 5
[8023] <210> 322
[8024] <211> 15
[8025] <212> DNA
[8026] <213> Artificial sequence
[8027] <220>
[8028] <221> gene
[8029] <222> (1)..(15)
[8030] <223> B47B6重链CDR的核酸序列
[8031] <400> 322
[8032] agctatgaca tgtct 15
[8033] <210> 323
[8034] <211> 48
[8035] <212> DNA
[8036] <213> Artificial sequence
[8037] <220>
[8038] <221> gene
[8039] <222> (1)..(48)
[8040] <223> B47B6重链CDR的核酸序列
[8041] <400> 323
[8042] tacatgagta gtggtggcgg cacctactat ccagacactg tgaagggc 48
[8043] <210> 324
[8044] <211> 27
[8045] <212> DNA
[8046] <213> Artificial sequence
[8047] <220>
[8048] <221> gene
[8049] <222> (1)..(27)
[8050] <223> B47B6重链CDR的核酸序列
[8051] <400> 324
[8052] catgatgaga ttactaactt tgactac 27
[8053] <210> 325
[8054] <211> 5
[8055] <212> PRT
[8056] <213> Artificial sequence
[8057] <220>
[8058] <221> PEPTIDE
[8059] <222> (1)..(5)
[8060] <223> B47B6重链CDR的氨基酸序列
[8061] <400> 325
[8062] Ser Tyr Asp Met Ser
[8063] 1 5

[8064] <210> 326
[8065] <211> 16
[8066] <212> PRT
[8067] <213> Artificial sequence
[8068] <220>
[8069] <221> PEPTIDE
[8070] <222> (1)..(16)
[8071] <223> B47B6重链CDR的氨基酸序列
[8072] <400> 326
[8073] Tyr Met Ser Ser Gly Gly Gly Thr Tyr Tyr Pro Asp Thr Val Lys Gly
[8074] 1 5 10 15
[8075] <210> 327
[8076] <211> 9
[8077] <212> PRT
[8078] <213> Artificial sequence
[8079] <220>
[8080] <221> PEPTIDE
[8081] <222> (1)..(9)
[8082] <223> B47B6重链CDR的氨基酸序列
[8083] <400> 327
[8084] His Asp Glu Ile Thr Asn Phe Asp Tyr
[8085] 1 5
[8086] <210> 328
[8087] <211> 639
[8088] <212> DNA
[8089] <213> Artificial sequence
[8090] <220>
[8091] <221> gene
[8092] <222> (1)..(639)
[8093] <223> C106B9轻链的核酸序列
[8094] <400> 328
[8095] caaattgttc tcacccagtc tccagcaatc atgtctgcat ctccagggga gaaggtcacc 60
[8096] ataacctgca gtgtcagctc aagtgtagat tacattcact ggttccagca gaagccaggc 120
[8097] acttctccca aattctggat ttatagcaca tccatcctgg cttctggagt ccctgctcgc 180
[8098] ttcagtggca gtggatctgg gacctcttac tctctcacaa tcagccgaat ggaggctgaa 240
[8099] gatgctgcca cttattactg ccagcaaagg agtagttacc cacccacgtt cggctcgggg 300
[8100] acaaagttgg aaataaaacg ggctgatgct gcaccaactg tatccatctt cccaccatcc 360
[8101] agtgagcagt taacatctgg aggtgcctca gtcgtgtgct tcttgaacaa cttctacccc 420
[8102] aaagacatca atgtcaagtg gaagattgat ggcagtgaac gacaaaatgg cgtcctgaac 480
[8103] agttggactg atcaggacag caaagacagc acctacagca tgagcagcac cctcacgttg 540
[8104] accaaggacg agtatgaacg acataacagc tatacctgtg aggccactca caagacatca 600
[8105] acttcaccca ttgtcaagag cttcaacagg aatgagtgt 639

[8106] <210> 329
[8107] <211> 213
[8108] <212> PRT
[8109] <213> Artificial sequence
[8110] <220>
[8111] <221> PEPTIDE
[8112] <222> (1)..(213)
[8113] <223> C106B9轻链的氨基酸序列
[8114] <400> 329
[8115] Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
[8116] 1 5 10 15
[8117] Glu Lys Val Thr Ile Thr Cys Ser Val Ser Ser Ser Val Asp Tyr Ile
[8118] 20 25 30
[8119] His Trp Phe Gln Gln Lys Pro Gly Thr Ser Pro Lys Phe Trp Ile Tyr
[8120] 35 40 45
[8121] Ser Thr Ser Ile Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
[8122] 50 55 60
[8123] Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
[8124] 65 70 75 80
[8125] Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Tyr Pro Pro Thr
[8126] 85 90 95
[8127] Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala Pro
[8128] 100 105 110
[8129] Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly
[8130] 115 120 125
[8131] Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn
[8132] 130 135 140
[8133] Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu Asn
[8134] 145 150 155 160
[8135] Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser
[8136] 165 170 175
[8137] Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr
[8138] 180 185 190
[8139] Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser Phe
[8140] 195 200 205
[8141] Asn Arg Asn Glu Cys
[8142] 210
[8143] <210> 330
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[8148] <221> gene
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[8150] <223> C106B9重链的核酸序列
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[8153] tcctgcaagg ctactggcta cacattcact ggctactgga tagagtggat aaaacagagg 120
[8154] cctggacatg gccttgagtg gattggagag attttacctg gaagtggtgg tactaactac 180
[8155] aatgagaaat tcaagggcaa ggccacattc actgcacata catcctccaa cacagcctac 240
[8156] atgcaactca gcagcctgac aactgaggac tctgccatct attactgtgc aagggatagt 300
[8157] aactccttta cttactgggg ccaagggact ctggtcactg tctcttcagc caaaacgaca 360
[8158] cccccatctg tctatccact ggcccctgga tctgctgccc aaactaactc catggtgacc 420
[8159] ctgggatgcc tggtcaaggg ctatttccct gagccagtga cagtgacctg gaactctgga 480
[8160] tccctgtcca gcggtgtgca caccttccca gctgtcctgc agtctgacct ctacactctg 540
[8161] agcagctcag tgactgtccc ctccagcacc tggcccagcg agaccgtcac ctgcaacgtt 600
[8162] gcccacccgg ccagcagcac caaggtggac aagaaaattg tgcccaggga ttgtggttgt 660
[8163] aagccttgca tatgtacagt cccagaagta tcatctgtct tcatcttccc cccaaagccc 720
[8164] aaggatgtgc tcaccattac tctgactcct aaggtcacgt gtgttgtggt agacatcagc 780
[8165] aaggatgatc ccgaggtcca gttcagctgg tttgtagatg atgtggaggt gcacacagct 840
[8166] cagacgcaac cccgggagga gcagttcaac agcactttcc gctcagtcag tgaacttccc 900
[8167] atcatgcacc aggactggct caatggcaag gagttcaaat gcagggtcaa cagtgcagct 960
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[8172] agcaagctca atgtgcagaa gagcaactgg gaggcaggaa atactttcac ctgctctgtg 1260
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[8174] <210> 331
[8175] <211> 440
[8176] <212> PRT
[8177] <213> Artificial sequence
[8178] <220>
[8179] <221> PEPTIDE
[8180] <222> (1)..(440)
[8181] <223> C106B9重链的氨基酸序列
[8182] <400> 331
[8183] Gln Val Gln Leu Gln Gln Ser Gly Gly Glu Val Met Lys Pro Gly Ala
[8184] 1 5 10 15
[8185] Ser Val Lys Leu Ser Cys Lys Ala Thr Gly Tyr Thr Phe Thr Gly Tyr
[8186] 20 25 30
[8187] Trp Ile Glu Trp Ile Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
[8188] 35 40 45
[8189] Gly Glu Ile Leu Pro Gly Ser Gly Gly Thr Asn Tyr Asn Glu Lys Phe

[8190] 50 55 60
[8191] Lys Gly Lys Ala Thr Phe Thr Ala His Thr Ser Ser Asn Thr Ala Tyr
[8192] 65 70 75 80
[8193] Met Gln Leu Ser Ser Leu Thr Thr Glu Asp Ser Ala Ile Tyr Tyr Cys
[8194] 85 90 95
[8195] Ala Arg Asp Ser Asn Ser Phe Thr Tyr Trp Gly Gln Gly Thr Leu Val
[8196] 100 105 110
[8197] Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala
[8198] 115 120 125
[8199] Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu
[8200] 130 135 140
[8201] Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly
[8202] 145 150 155 160
[8203] Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp
[8204] 165 170 175
[8205] Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro
[8206] 180 185 190
[8207] Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys
[8208] 195 200 205
[8209] Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile
[8210] 210 215 220
[8211] Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro
[8212] 225 230 235 240
[8213] Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val
[8214] 245 250 255
[8215] Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val
[8216] 260 265 270
[8217] Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln
[8218] 275 280 285
[8219] Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln
[8220] 290 295 300
[8221] Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala
[8222] 305 310 315 320
[8223] Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro
[8224] 325 330 335
[8225] Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala
[8226] 340 345 350
[8227] Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu
[8228] 355 360 365
[8229] Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr
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[8231] Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr

[8232] 385 390 395 400
[8233] Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe
[8234] 405 410 415
[8235] Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His Thr Glu Lys
[8236] 420 425 430
[8237] Ser Leu Ser His Ser Pro Gly Lys
[8238] 435 440
[8239] <210> 332
[8240] <211> 30
[8241] <212> DNA
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[8245] <222> (1)..(30)
[8246] <223> C106B9轻链CDR的核酸序列
[8247] <400> 332
[8248] agtgtcagct caagtgtaga ttacattcac 30
[8249] <210> 333
[8250] <211> 21
[8251] <212> DNA
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[8255] <222> (1)..(21)
[8256] <223> C106B9轻链CDR的核酸序列
[8257] <400> 333
[8258] agcacatcca tcctggcttc t 21
[8259] <210> 334
[8260] <211> 27
[8261] <212> DNA
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[8264] <221> gene
[8265] <222> (1)..(27)
[8266] <223> C106B9轻链CDR的核酸序列
[8267] <400> 334
[8268] cagcaaagga gtagttaccc acccacg 27
[8269] <210> 335
[8270] <211> 10
[8271] <212> PRT
[8272] <213> Artificial sequence
[8273] <220>

[8274] <221> PEPTIDE
[8275] <222> (1)..(10)
[8276] <223> C106B9轻链CDR的氨基酸序列
[8277] <400> 335
[8278] Ser Val Ser Ser Ser Val Asp Tyr Ile His
[8279] 1 5 10
[8280] <210> 336
[8281] <211> 7
[8282] <212> PRT
[8283] <213> Artificial sequence
[8284] <220>
[8285] <221> PEPTIDE
[8286] <222> (1)..(7)
[8287] <223> C106B9轻链CDR的氨基酸序列
[8288] <400> 336
[8289] Ser Thr Ser Ile Leu Ala Ser
[8290] 1 5
[8291] <210> 337
[8292] <211> 9
[8293] <212> PRT
[8294] <213> Artificial sequence
[8295] <220>
[8296] <221> PEPTIDE
[8297] <222> (1)..(9)
[8298] <223> C106B9轻链CDR的氨基酸序列
[8299] <400> 337
[8300] Gln Gln Arg Ser Ser Tyr Pro Pro Thr
[8301] 1 5
[8302] <210> 338
[8303] <211> 15
[8304] <212> DNA
[8305] <213> Artificial sequence
[8306] <220>
[8307] <221> gene
[8308] <222> (1)..(15)
[8309] <223> C106B9重链CDR的核酸序列
[8310] <400> 338
[8311] ggctactgga tagag 15
[8312] <210> 339
[8313] <211> 51
[8314] <212> DNA
[8315] <213> Artificial sequence

[8316] <220>
[8317] <221> gene
[8318] <222> (1)..(51)
[8319] <223> C106B9重链CDR的核酸序列
[8320] <400> 339
[8321] gagattttac ctggaagtgg tggtactaac tacaatgaga aattcaaggg c 51
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[8323] <211> 21
[8324] <212> DNA
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[8329] <223> C106B9重链CDR的核酸序列
[8330] <400> 340
[8331] gatagtaact cctttactta c 21
[8332] <210> 341
[8333] <211> 5
[8334] <212> PRT
[8335] <213> Artificial sequence
[8336] <220>
[8337] <221> PEPTIDE
[8338] <222> (1)..(5)
[8339] <223> C106B9重链CDR的氨基酸序列
[8340] <400> 341
[8341] Gly Tyr Trp Ile Glu
[8342] 1 5
[8343] <210> 342
[8344] <211> 17
[8345] <212> PRT
[8346] <213> Artificial sequence
[8347] <220>
[8348] <221> PEPTIDE
[8349] <222> (1)..(17)
[8350] <223> C106B9重链CDR的氨基酸序列
[8351] <400> 342
[8352] Glu Ile Leu Pro Gly Ser Gly Gly Thr Asn Tyr Asn Glu Lys Phe Lys
[8353] 1 5 10 15
[8354] Gly
[8355] <210> 343
[8356] <211> 7
[8357] <212> PRT

[8358] <213> Artificial sequence
[8359] <220>
[8360] <221> PEPTIDE
[8361] <222> (1)..(7)
[8362] <223> C106B9重链CDR的氨基酸序列
[8363] <400> 343
[8364] Asp Ser Asn Ser Phe Thr Tyr
[8365] 1 5
[8366] <210> 344
[8367] <211> 642
[8368] <212> DNA
[8369] <213> Artificial sequence
[8370] <220>
[8371] <221> gene
[8372] <222> (1)..(642)
[8373] <223> F184C7轻链的核酸序列
[8374] <400> 344
[8375] gacatccaga tgactcagtc tccagcctcc ctatctgtat ctgtgggaga aactgtcacc 60
[8376] atcacatgtc gagcaagtga gaatatttac agaaatttag catggtatca gcagaaacag 120
[8377] ggaaaatctc ctcaactcct ggtccatgct gcaacaaact tagcagatgg tgtgccatca 180
[8378] aggttcagtg gcagtggatc agacacacag tattccctca agatcaacag cctgcagtct 240
[8379] gaagattttg ggaattatta ctgtcaacat ttttgggggga ctccgctcac gttcggtgct 300
[8380] gggaccaagc tggagctgaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360
[8381] tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420
[8382] cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480
[8383] aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540
[8384] ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
[8385] tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642
[8386] <210> 345
[8387] <211> 214
[8388] <212> PRT
[8389] <213> Artificial sequence
[8390] <220>
[8391] <221> PEPTIDE
[8392] <222> (1)..(214)
[8393] <223> F184C7轻链的氨基酸序列
[8394] <400> 345
[8395] Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Val Ser Val Gly
[8396] 1 5 10 15
[8397] Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Arg Asn
[8398] 20 25 30
[8399] Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val

[8400] 35 40 45
[8401] His Ala Ala Thr Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
[8402] 50 55 60
[8403] Ser Gly Ser Asp Thr Gln Tyr Ser Leu Lys Ile Asn Ser Leu Gln Ser
[8404] 65 70 75 80
[8405] Glu Asp Phe Gly Asn Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Leu
[8406] 85 90 95
[8407] Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala
[8408] 100 105 110
[8409] Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
[8410] 115 120 125
[8411] Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
[8412] 130 135 140
[8413] Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
[8414] 145 150 155 160
[8415] Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
[8416] 165 170 175
[8417] Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
[8418] 180 185 190
[8419] Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
[8420] 195 200 205
[8421] Phe Asn Arg Asn Glu Cys
[8422] 210
[8423] <210> 346
[8424] <211> 1338
[8425] <212> DNA
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[8427] <220>
[8428] <221> gene
[8429] <222> (1)..(1338)
[8430] <223> F184C7重链的核酸序列
[8431] <400> 346
[8432] caggttcagc tgcagcagtc tggacctgag atggtgaagc ctggggcctc agtgaagatt 60
[8433] ccctgcaagg cttctggcta cgcattcagt agctcctgga tgaactgggt gaagcagagg 120
[8434] cctggaaagg gtcttgagtg gattggacgg atttatcctg gagatggaga tactaactac 180
[8435] aatgagaagt tcaagggcaa ggccacactg actgtagaca aatcctccag cacagtctac 240
[8436] atgcaactca gcagcctgac atctgaggac tctgcggtct acttctgtgc aagagaggct 300
[8437] actacggtag tggccccgta ctactttgac tactggggcc aaggcaccac tctcacagtc 360
[8438] tcctcagcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgctgcccaa 420
[8439] actaactcca tggtgaccct gggatgcctg gtcaagggct atttccctga gccagtgaca 480
[8440] gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgtcctgcag 540
[8441] tctgacctct acactctgag cagctcagtg actgtcccct ccagcacctg gcccagcgag 600

[8442] accgtcacct gcaacgttgc ccacccggcc agcagcacca aggtggacaa gaaaattgtg 660
[8443] cccagggatt gtggttgtaa gccttgcata tgtacagtcc cagaagtatc atctgtcttc 720
[8444] atcttccccc caaagcccaa ggatgtgctc accattactc tgactcctaa ggtcacgtgt 780
[8445] gttgtggtag acatcagcaa ggatgatccc gaggtccagt tcagctggtt tgtagatgat 840
[8446] gtggaggtgc acacagctca gacgcaaccc cgggaggagc agttcaacag cactttccgc 900
[8447] tcagtcagtg aacttcccat catgcaccag gactggctca atggcaagga gttcaaatgc 960
[8448] agggtcaaca gtgcagcttt ccctgccccc atcgagaaaa ccatctccaa aaccaaaggc 1020
[8449] agaccgaagg ctccacaggt gtacaccatt ccacctccca aggagcagat ggccaaggat 1080
[8450] aaagtcagtc tgacctgcat gataacagac ttcttccctg aagacattac tgtggagtgg 1140
[8451] cagtggaatg ggcagccagc ggagaactac aagaacactc agcccatcat ggacacagat 1200
[8452] ggctcttact tcgtctacag caagctcaat gtgcagaaga gcaactggga ggcaggaaat 1260
[8453] actttcacct gctctgtgtt acatgagggc ctgcacaacc accatactga gaagagcctc 1320
[8454] tcccactctc ctggtaaa 1338
[8455] <210> 347
[8456] <211> 446
[8457] <212> PRT
[8458] <213> Artificial sequence
[8459] <220>
[8460] <221> PEPTIDE
[8461] <222> (1)..(446)
[8462] <223> F184C7重链的氨基酸序列
[8463] <400> 347
[8464] Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Met Val Lys Pro Gly Ala
[8465] 1 5 10 15
[8466] Ser Val Lys Ile Pro Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Ser
[8467] 20 25 30
[8468] Trp Met Asn Trp Val Lys Gln Arg Pro Gly Lys Gly Leu Glu Trp Ile
[8469] 35 40 45
[8470] Gly Arg Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Asn Glu Lys Phe
[8471] 50 55 60
[8472] Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Val Tyr
[8473] 65 70 75 80
[8474] Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
[8475] 85 90 95
[8476] Ala Arg Glu Ala Thr Thr Val Val Ala Pro Tyr Tyr Phe Asp Tyr Trp
[8477] 100 105 110
[8478] Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Lys Thr Thr Pro Pro
[8479] 115 120 125
[8480] Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met
[8481] 130 135 140
[8482] Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr
[8483] 145 150 155 160

[8484] Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro
[8485] 165 170 175
[8486] Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val
[8487] 180 185 190
[8488] Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His
[8489] 195 200 205
[8490] Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys
[8491] 210 215 220
[8492] Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe
[8493] 225 230 235 240
[8494] Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro
[8495] 245 250 255
[8496] Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val
[8497] 260 265 270
[8498] Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr
[8499] 275 280 285
[8500] Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu
[8501] 290 295 300
[8502] Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys
[8503] 305 310 315 320
[8504] Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser
[8505] 325 330 335
[8506] Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro
[8507] 340 345 350
[8508] Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile
[8509] 355 360 365
[8510] Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly
[8511] 370 375 380
[8512] Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp
[8513] 385 390 395 400
[8514] Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp
[8515] 405 410 415
[8516] Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His
[8517] 420 425 430
[8518] Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
[8519] 435 440 445
[8520] <210> 348
[8521] <211> 33
[8522] <212> DNA
[8523] <213> Artificial sequence
[8524] <220>
[8525] <221> gene

[8526] <222> (1)..(33)
[8527] <223> F184C7轻链CDR的核酸序列
[8528] <400> 348
[8529] cgagcaagtg agaatattta cagaaattta gca 33
[8530] <210> 349
[8531] <211> 21
[8532] <212> DNA
[8533] <213> Artificial sequence
[8534] <220>
[8535] <221> gene
[8536] <222> (1)..(21)
[8537] <223> F184C7轻链CDR的核酸序列
[8538] <400> 349
[8539] gctgcaacaa acttagcaga t 21
[8540] <210> 350
[8541] <211> 27
[8542] <212> DNA
[8543] <213> Artificial sequence
[8544] <220>
[8545] <221> gene
[8546] <222> (1)..(27)
[8547] <223> F184C7轻链CDR的核酸序列
[8548] <400> 350
[8549] caacattttt gggggactcc gctcacg 27
[8550] <210> 351
[8551] <211> 11
[8552] <212> PRT
[8553] <213> Artificial sequence
[8554] <220>
[8555] <221> PEPTIDE
[8556] <222> (1)..(11)
[8557] <223> F184C7轻链CDR的氨基酸序列
[8558] <400> 351
[8559] Arg Ala Ser Glu Asn Ile Tyr Arg Asn Leu Ala
[8560] 1 5 10
[8561] <210> 352
[8562] <211> 7
[8563] <212> PRT
[8564] <213> Artificial sequence
[8565] <220>
[8566] <221> PEPTIDE
[8567] <222> (1)..(7)

[8568] <223> F184C7轻链CDR的氨基酸序列
[8569] <400> 352
[8570] Ala Ala Thr Asn Leu Ala Asp
[8571] 1 5
[8572] <210> 353
[8573] <211> 9
[8574] <212> PRT
[8575] <213> Artificial sequence
[8576] <220>
[8577] <221> PEPTIDE
[8578] <222> (1)..(9)
[8579] <223> F184C7轻链CDR的氨基酸序列
[8580] <400> 353
[8581] Gln His Phe Trp Gly Thr Pro Leu Thr
[8582] 1 5
[8583] <210> 354
[8584] <211> 22
[8585] <212> DNA
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[8588] <221> gene
[8589] <222> (1)..(22)
[8590] <223> F184C7重链CDR的核酸序列
[8591] <400> 354
[8592] attcagtagc tcctggatga ac 22
[8593] <210> 355
[8594] <211> 51
[8595] <212> DNA
[8596] <213> Artificial sequence
[8597] <220>
[8598] <221> gene
[8599] <222> (1)..(51)
[8600] <223> F184C7重链CDR的核酸序列
[8601] <400> 355
[8602] cggatttatc ctggagatgg agatactaac tacaatgaga agttcaaggg c 51
[8603] <210> 356
[8604] <211> 39
[8605] <212> DNA
[8606] <213> Artificial sequence
[8607] <220>
[8608] <221> gene
[8609] <222> (1)..(39)

[8610] <223> F184C7重链CDR的核酸序列
[8611] <400> 356
[8612] gaggctacta cggtagtggc cccgtactac tttgactac 39
[8613] <210> 357
[8614] <211> 7
[8615] <212> PRT
[8616] <213> Artificial sequence
[8617] <220>
[8618] <221> PEPTIDE
[8619] <222> (1)..(7)
[8620] <223> F184C7重链CDR的氨基酸序列
[8621] <400> 357
[8622] Phe Ser Ser Ser Trp Met Asn
[8623] 1 5
[8624] <210> 358
[8625] <211> 17
[8626] <212> PRT
[8627] <213> Artificial sequence
[8628] <220>
[8629] <221> PEPTIDE
[8630] <222> (1)..(17)
[8631] <223> F184C7重链CDR的氨基酸序列
[8632] <400> 358
[8633] Arg Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Asn Glu Lys Phe Lys
[8634] 1 5 10 15
[8635] Gly
[8636] <210> 359
[8637] <211> 13
[8638] <212> PRT
[8639] <213> Artificial sequence
[8640] <220>
[8641] <221> PEPTIDE
[8642] <222> (1)..(13)
[8643] <223> F184C7重链CDR的氨基酸序列
[8644] <400> 359
[8645] Glu Ala Thr Thr Val Val Ala Pro Tyr Tyr Phe Asp Tyr
[8646] 1 5 10
[8647] <210> 360
[8648] <211> 642
[8649] <212> DNA
[8650] <213> Artificial sequence
[8651] <220>

[8652] <221> gene
[8653] <222> (1)..(642)
[8654] <223> D10A3轻链的核酸序列
[8655] <400> 360
[8656] aatattgtgc tgacccagac tcccaaattc ctgcttgtat cagcaggaga cagggtttcc 60
[8657] ataacctgca aggccagtca gcgtgtgaat aatgatgtag cttggtacca acagaagcca 120
[8658] gggcagtctc ctaaactgct gatatactat gcatccaatc gctacactgg agtccctgat 180
[8659] cgcttcactg gcagtggata tgggacggat ttcactttca ccatcagcac tgtgcaggct 240
[8660] gaagacctgg cagtttattt ctgtcagcag gattatagct ctccattcac gttcggctcg 300
[8661] gggacaaagt tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360
[8662] tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420
[8663] cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480
[8664] aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540
[8665] ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600
[8666] tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642
[8667] <210> 361
[8668] <211> 214
[8669] <212> PRT
[8670] <213> Artificial sequence
[8671] <220>
[8672] <221> PEPTIDE
[8673] <222> (1)..(214)
[8674] <223> D10A3轻链的氨基酸序列
[8675] <400> 361
[8676] Asn Ile Val Leu Thr Gln Thr Pro Lys Phe Leu Leu Val Ser Ala Gly
[8677] 1 5 10 15
[8678] Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Arg Val Asn Asn Asp
[8679] 20 25 30
[8680] Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
[8681] 35 40 45
[8682] Tyr Tyr Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
[8683] 50 55 60
[8684] Ser Gly Tyr Gly Thr Asp Phe Thr Phe Thr Ile Ser Thr Val Gln Ala
[8685] 65 70 75 80
[8686] Glu Asp Leu Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Pro Phe
[8687] 85 90 95
[8688] Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
[8689] 100 105 110
[8690] Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
[8691] 115 120 125
[8692] Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
[8693] 130 135 140

[8694] Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
[8695] 145 150 155 160
[8696] Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
[8697] 165 170 175
[8698] Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
[8699] 180 185 190
[8700] Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
[8701] 195 200 205
[8702] Phe Asn Arg Asn Glu Cys
[8703] 210
[8704] <210> 362
[8705] <211> 1332
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[8709] <221> gene
[8710] <222> (1)..(1332)
[8711] <223> D10A3重链的核酸序列
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[8713] gaggtccagc tgcaacagtt tggaactgag ctggtgaagc ctggggcttc agtgaagata 60
[8714] tcctgcaagg cttctggcta cacattcact gactacaaca tggactgggt gaagcagagc 120
[8715] catggaaaga gccttgagtg gattggagat attaatccta actatgatac tactacctac 180
[8716] aaccagaagt tcaagggaaa ggccacattg actgtagaca agtcctccag cacagcctac 240
[8717] atggagctcc gcagcctgac ttctgaggac actgcagtct tttactgtgc aagaaggaac 300
[8718] tatggtaact acgtggggtt tgacttctgg ggccaaggca ccactctcac agtctcctca 360
[8719] gccaaaacga cacccccatc tgtctatcca ctggcccctg gatctgctgc ccaaactaac 420
[8720] tccatggtga ccctgggatg cctggtcaag ggctatttcc ctgagccagt gacagtgacc 480
[8721] tggaactctg gatccctgtc cagcggtgtg cacaccttcc cagctgtcct gcagtctgac 540
[8722] ctctacactc tgagcagctc agtgactgtc ccctccagca cctggcccag cgagaccgtc 600
[8723] acctgcaacg ttgcccaccc ggccagcagc accaaggtgg acaagaaaat tgtgcccagg 660
[8724] gattgtggtt gtaagccttg catatgtaca gtcccagaag tatcatctgt cttcatcttc 720
[8725] cccccaaagc ccaaggatgt gctcaccatt actctgactc ctaaggtcac gtgtgttgtg 780
[8726] gtagacatca gcaaggatga tcccgaggtc cagttcagct ggtttgtaga tgatgtggag 840
[8727] gtgcacacag ctcagacgca accccgggag gagcagttca acagcacttt ccgctcagtc 900
[8728] agtgaacttc ccatcatgca ccaggactgg ctcaatggca aggagttcaa atgcagggtc 960
[8729] aacagtgcag ctttccctgc ccccatcgag aaaaccatct ccaaaaccaa aggcagaccg 1020
[8730] aaggctccac aggtgtacac cattccacct cccaaggagc agatggccaa ggataaagtc 1080
[8731] agtctgacct gcatgataac agacttcttc cctgaagaca ttactgtgga gtggcagtgg 1140
[8732] aatgggcagc cagcggagaa ctacaagaac actcagccca tcatggacac agatggctct 1200
[8733] tacttcgtct acagcaagct caatgtgcag aagagcaact gggaggcagg aaatactttc 1260
[8734] acctgctctg tgttacatga gggcctgcac aaccaccata ctgagaagag cctctcccac 1320
[8735] tctcctggta aa 1332

[8736] <210> 363
[8737] <211> 444
[8738] <212> PRT
[8739] <213> Artificial sequence
[8740] <220>
[8741] <221> PEPTIDE
[8742] <222> (1)..(444)
[8743] <223> D10A3重链的氨基酸序列
[8744] <400> 363
[8745] Glu Val Gln Leu Gln Gln Phe Gly Thr Glu Leu Val Lys Pro Gly Ala
[8746] 1 5 10 15
[8747] Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
[8748] 20 25 30
[8749] Asn Met Asp Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
[8750] 35 40 45
[8751] Gly Asp Ile Asn Pro Asn Tyr Asp Thr Thr Thr Tyr Asn Gln Lys Phe
[8752] 50 55 60
[8753] Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
[8754] 65 70 75 80
[8755] Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Thr Ala Val Phe Tyr Cys
[8756] 85 90 95
[8757] Ala Arg Arg Asn Tyr Gly Asn Tyr Val Gly Phe Asp Phe Trp Gly Gln
[8758] 100 105 110
[8759] Gly Thr Thr Leu Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val
[8760] 115 120 125
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[8793] Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser
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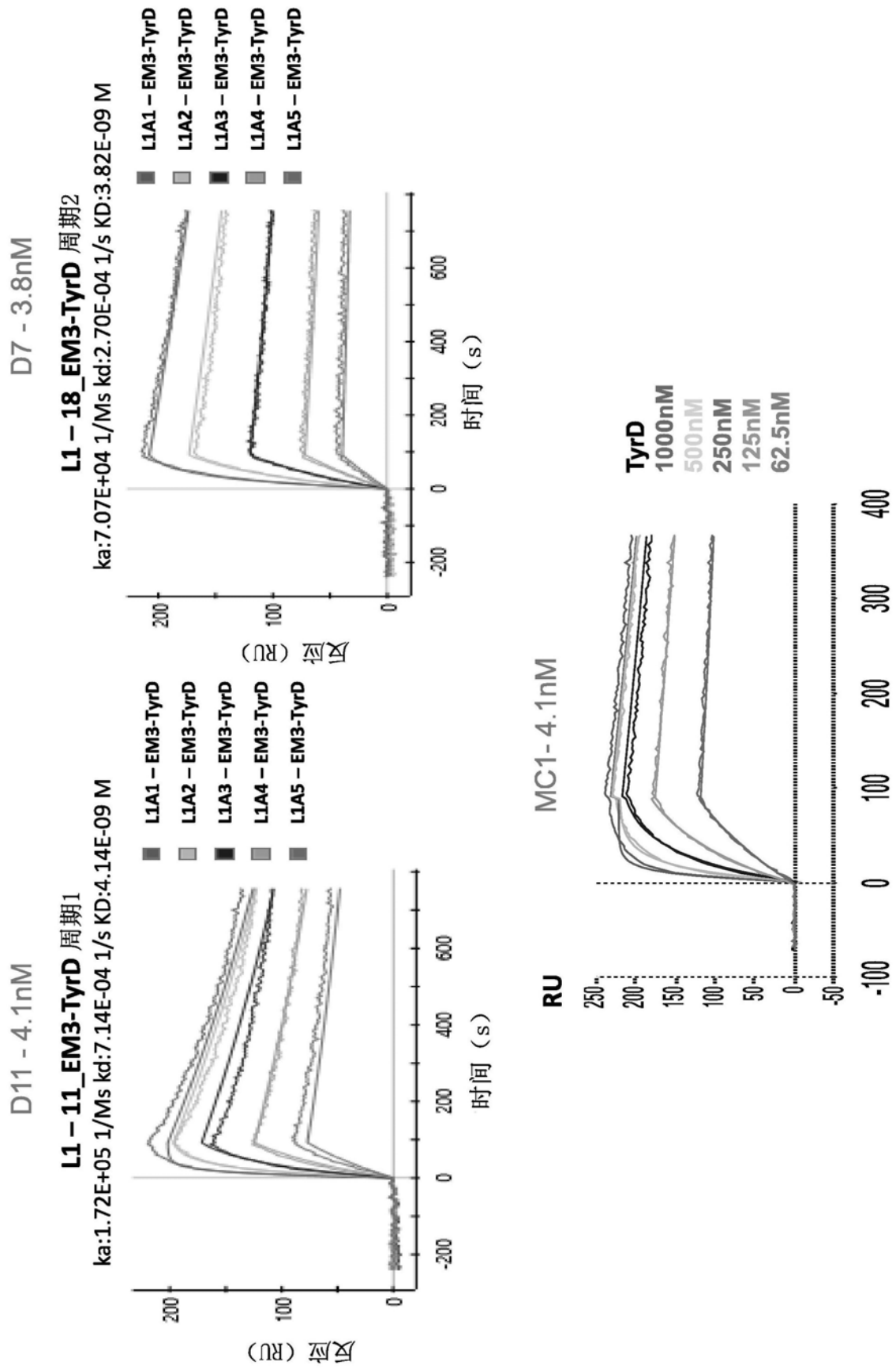
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L1 – 11_EM3-TyrD 周期1
ka:1.72E+05 1/Ms kd:7.14E-04 1/s KD:4.14E-09 M
L1A1 – EM3-TyrD
L1A2 – EM3-TyrD
L1A3 – EM3-TyrD
L1A4 – EM3-TyrD
L1A5 – EM3-TyrD
反应（RU）
时间（s）
D7 - 3.8nM
L1 – 18_EM3-TyrD 周期2
ka:7.07E+04 1/Ms kd:2.70E-04 1/s KD:3.82E-09 M
L1A1 – EM3-TyrD
L1A2 – EM3-TyrD
L1A3 – EM3-TyrD
L1A4 – EM3-TyrD
L1A5 – EM3-TyrD
反应（RU）
时间（s）
MC1- 4.1nM
RU
TyrD
1000nM
500nM
250nM
125nM
62.5nM

图1

TyrD	YMDGTMSQV
TyrD A1	AMDGTMSQV
TyrD A2 锚定位置	YADGTMSQV
TyrD A3	YMAGTMSQV
TyrD A4	YMDATMSQV
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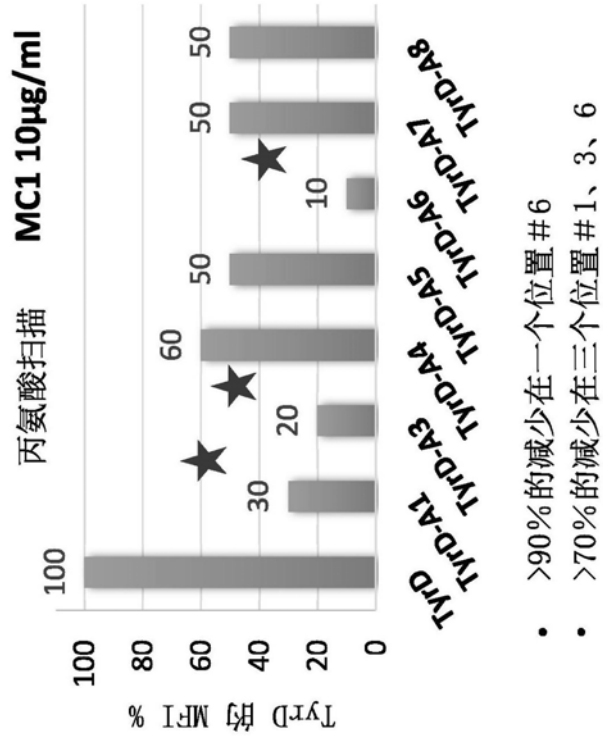
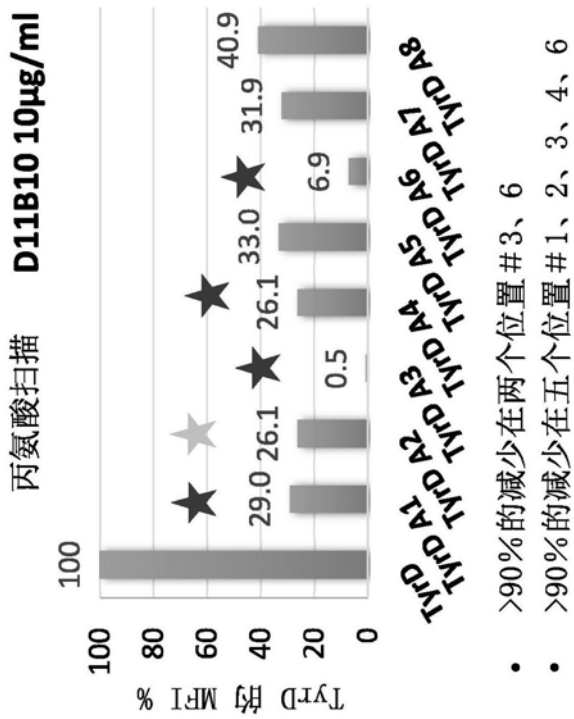




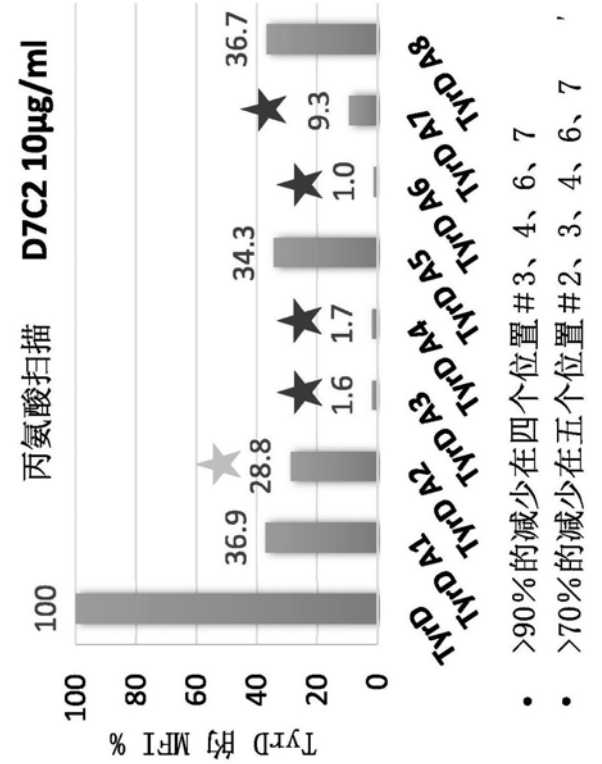
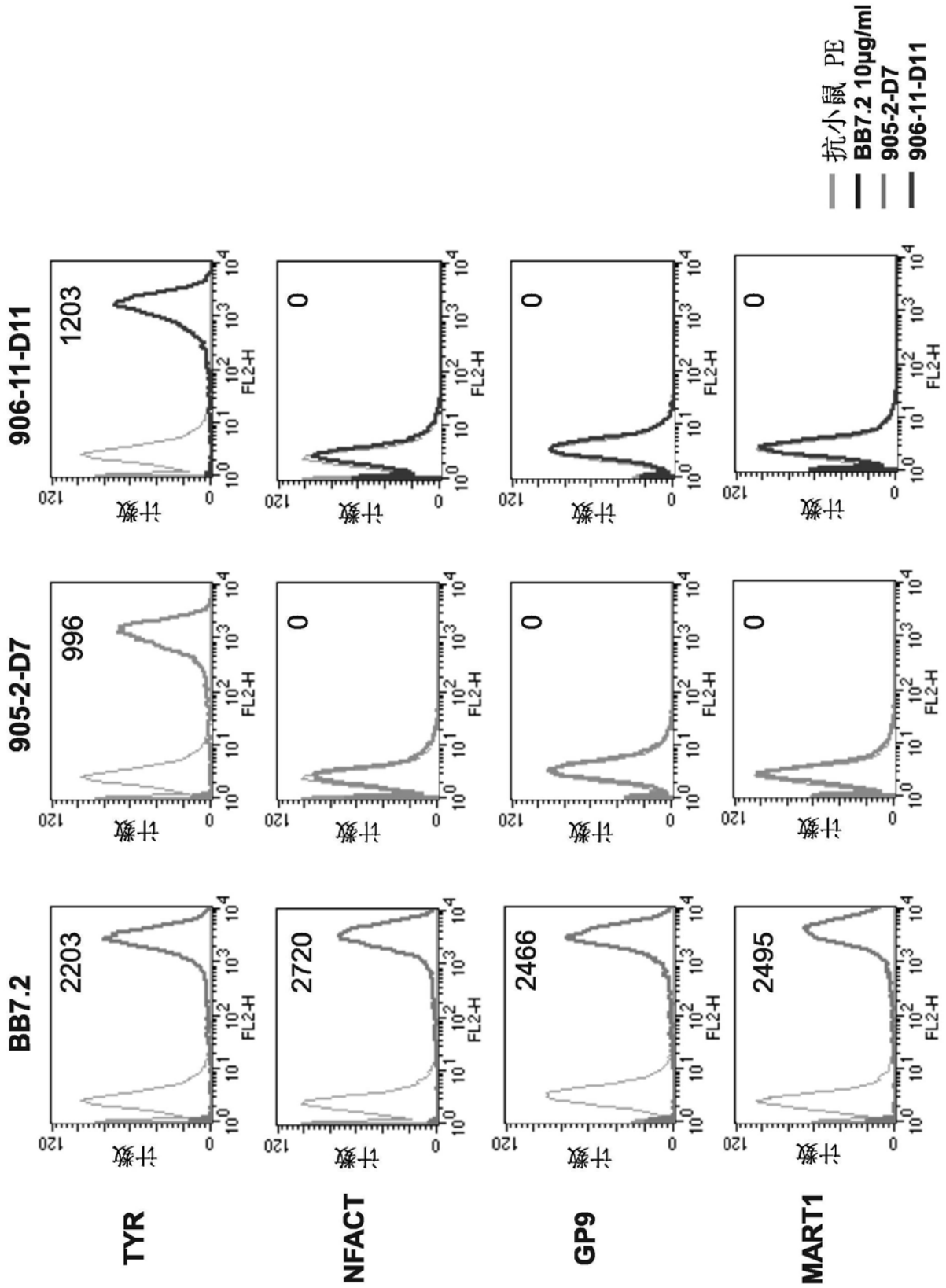


图2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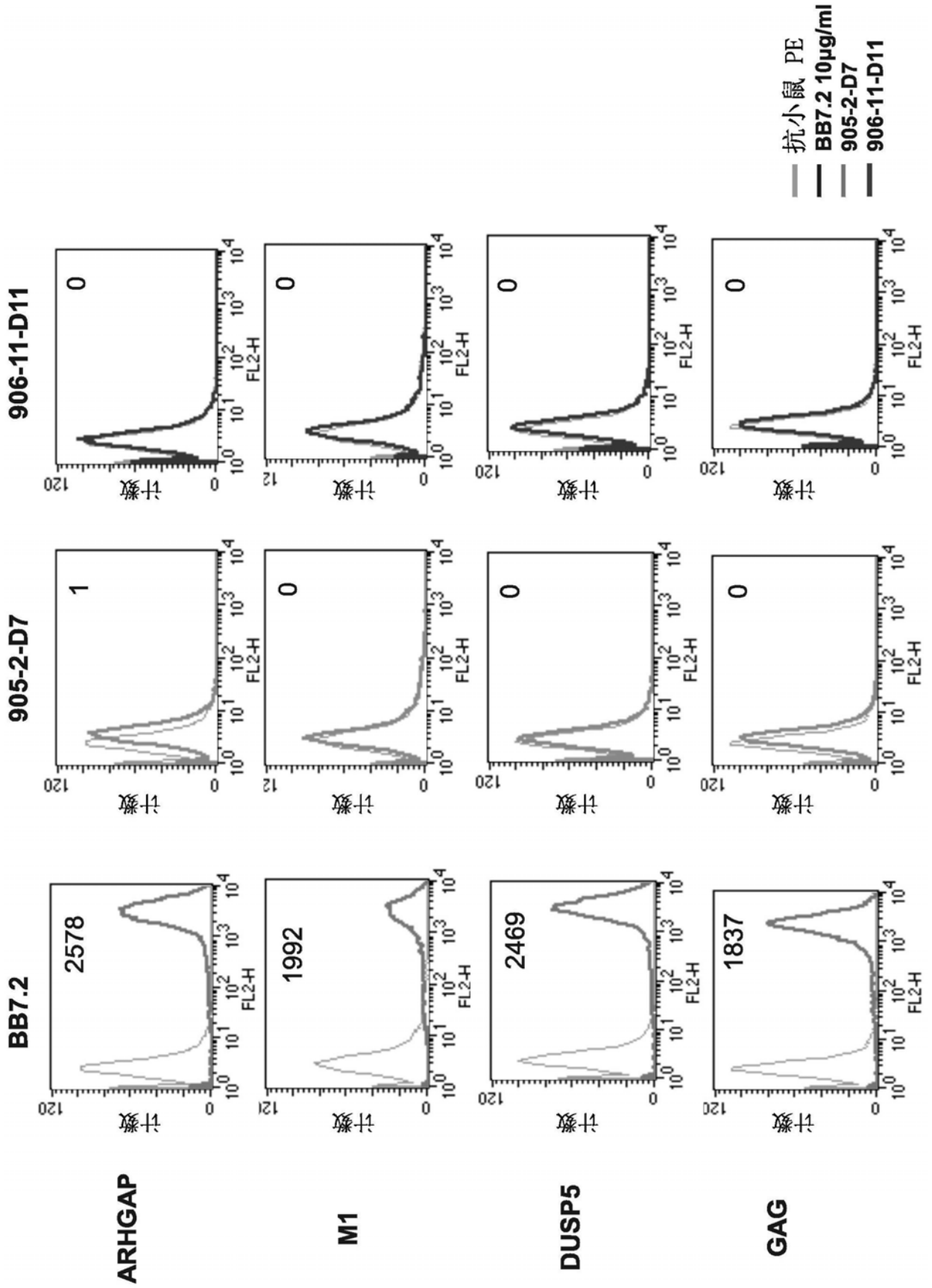
906-11-D11
BB7.2
905-2-D7
906-11-D11
TYR
NFACT
GP9
MART1
2203
996
1203
2720
0
0
0
2466
0
0
0
2495
0
0
0
计数
FL2-H

图3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906-11-D11
BB7.2
905-2-D7
906-11-D11
ARHGAP
M1
DUSP5
GAG
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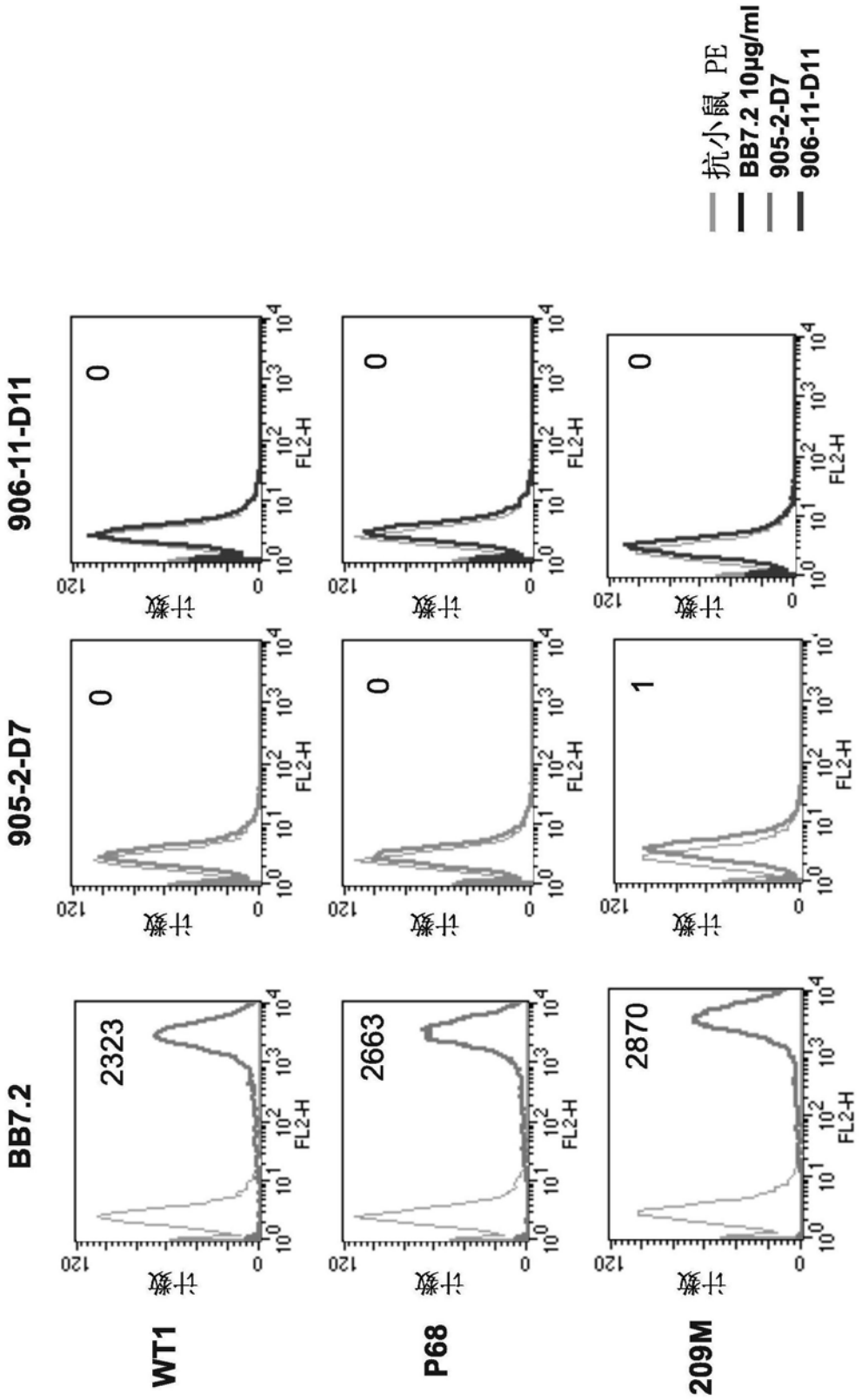
1992
0
0
2469
0
0
1837
0
0
计数
FL2-H

图3-续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906-11-D11
WT1
P68
209M
2323
2663
2870
0
0
0
0
0
1
计数
FL2-H
抗小鼠 PE
BB7.2 10μg/ml
905-2-D7
906-11-D11

图4

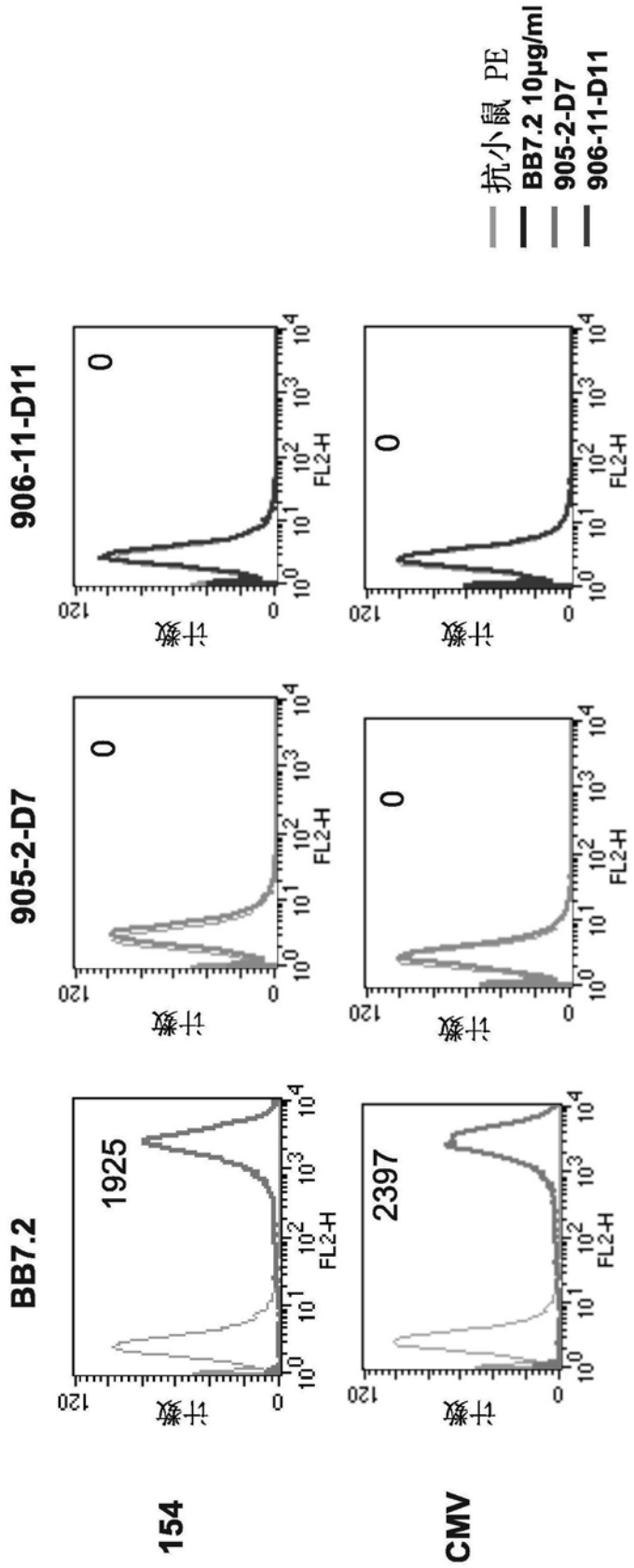

抗小鼠 PE
BB7.2 10μg/ml
905-2-D7
906-11-D11
BB7.2
905-2-D7
906-11-D11
154
CMV
1925
0
0
0
2397
0
0
0
计数
FL2-H

图4-续

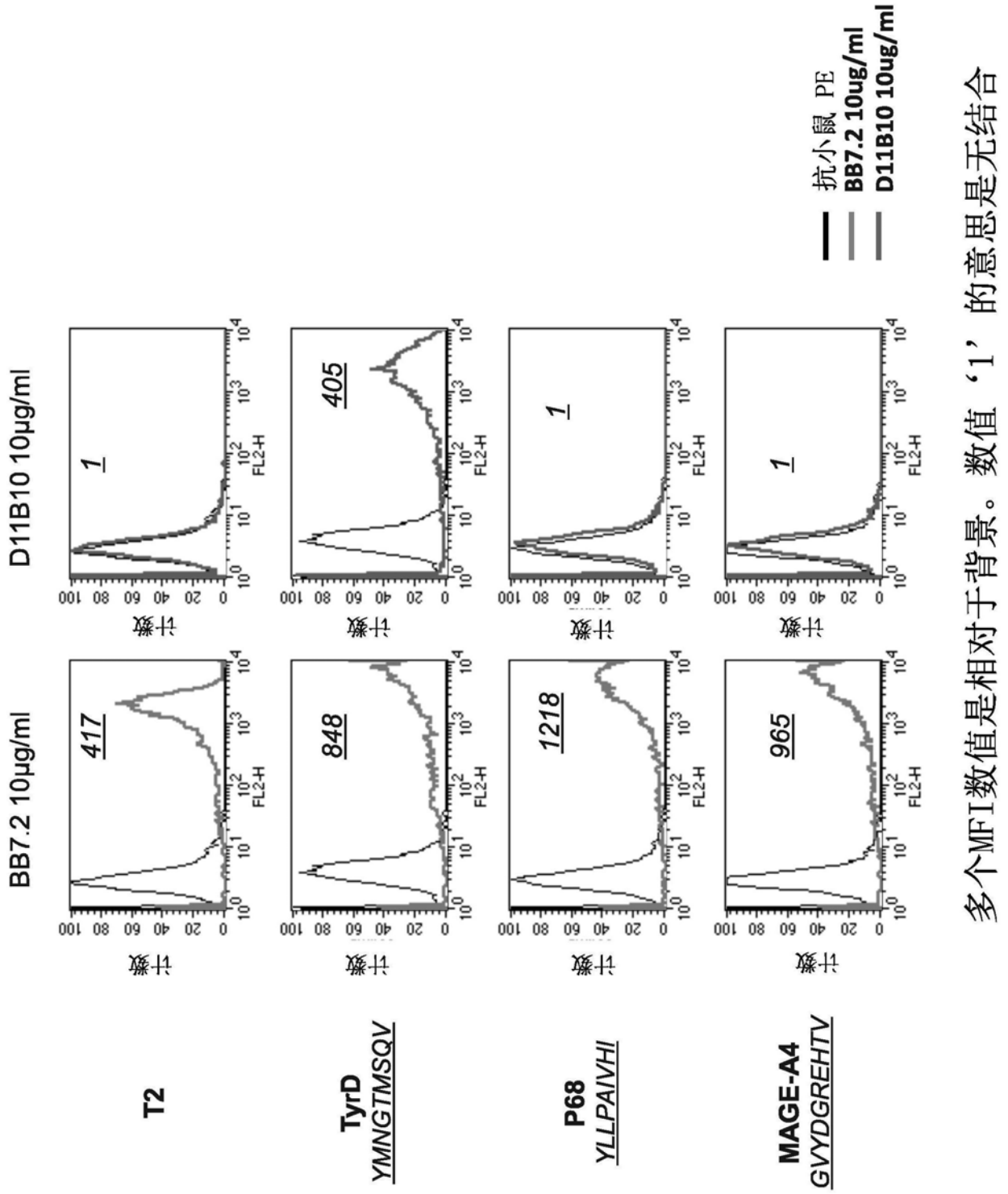

BB7.2 10μg/ml
D11B10 10μg/ml
T2
TyrD
YMNGTMSQV
P68
YLLPAIVHI
MAGE-A4
GVYDGREHTV
417
1
848
405
1218
1
965
1
计数
FL2-H
抗小鼠 PE
BB7.2 10ug/ml
D11B10 10ug/ml
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图5

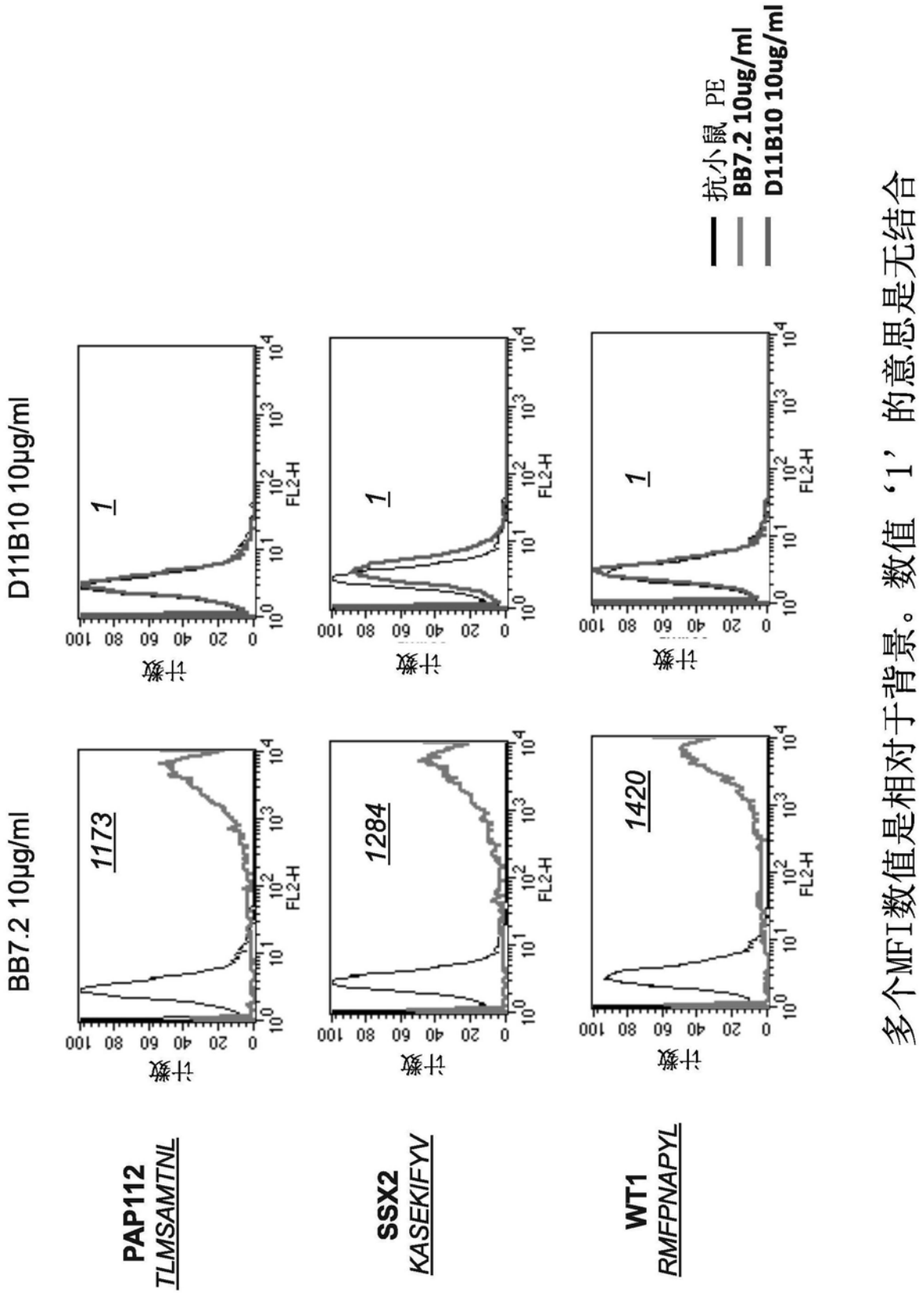
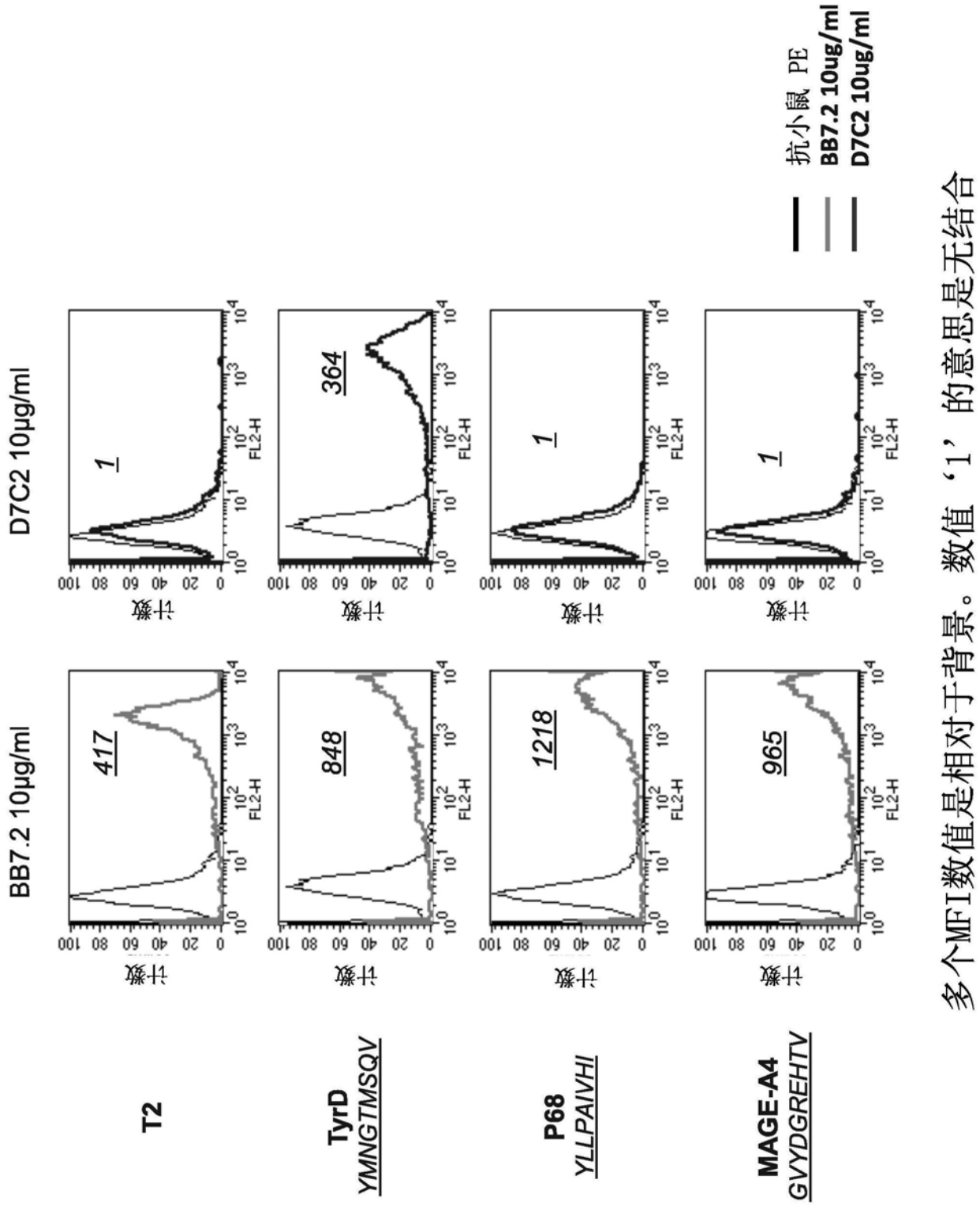

BB7.2 10μg/ml
D11B10 10μg/ml
PAP112
TLMSAMTNL
SSX2
KASEKIFYV
WT1
RMFPNAPYL
1173
1284
1420
1
计数
FL2-H
抗小鼠 PE
BB7.2 10ug/ml
D11B10 10ug/ml
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图5-续



多个MFI数值是相对于背景。数值‘1’的意思是无结合

图6

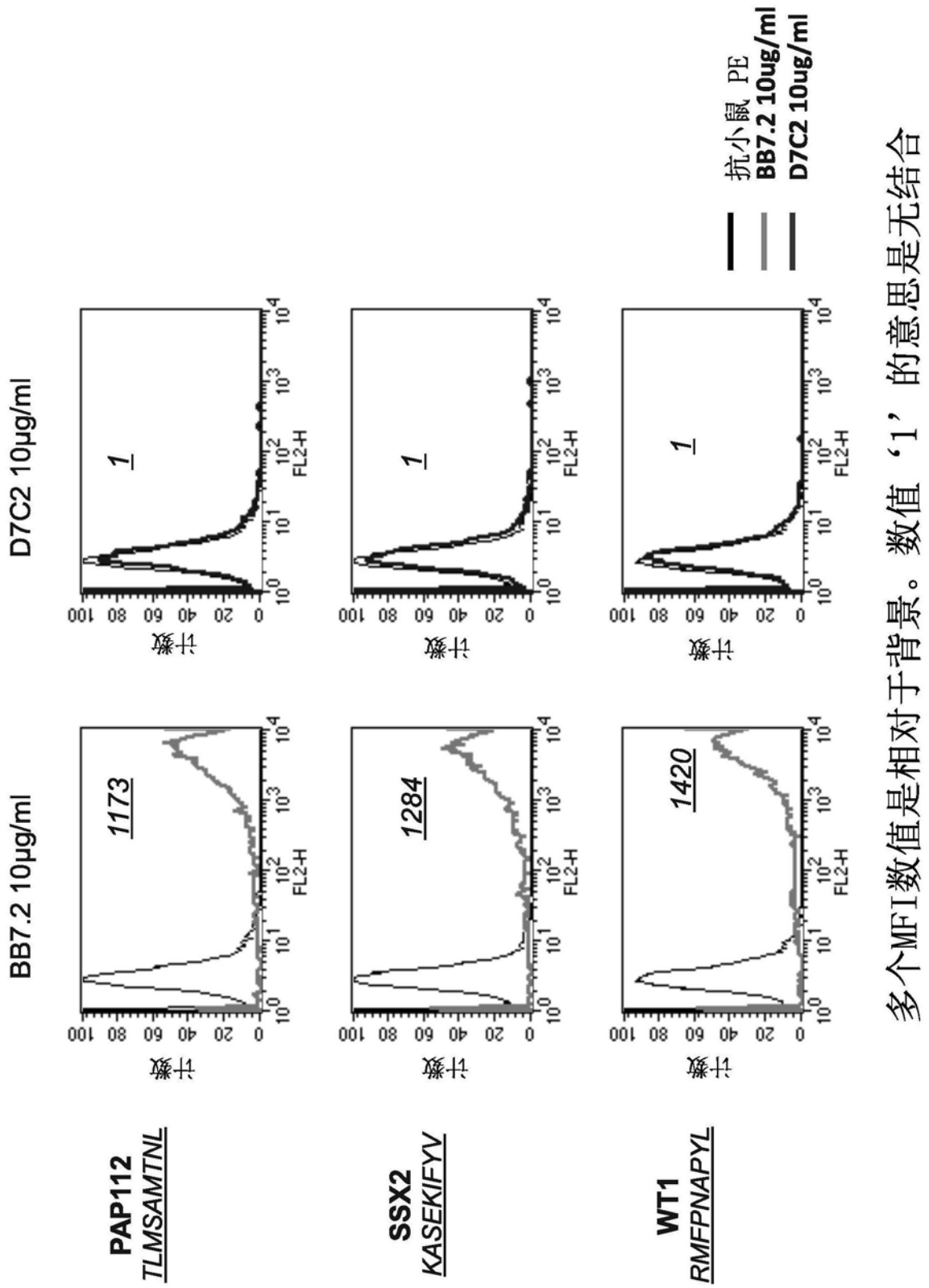

BB7.2 10μg/ml
D7C2 10μg/ml
PAP112
TLMSAMTNL
SSX2
KASEKIFYV
WT1
RMFPNAPYL
1173
1284
1420
1
计数
FL2-H
抗小鼠 PE
BB7.2 10ug/ml
D7C2 10ug/ml
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图6-续

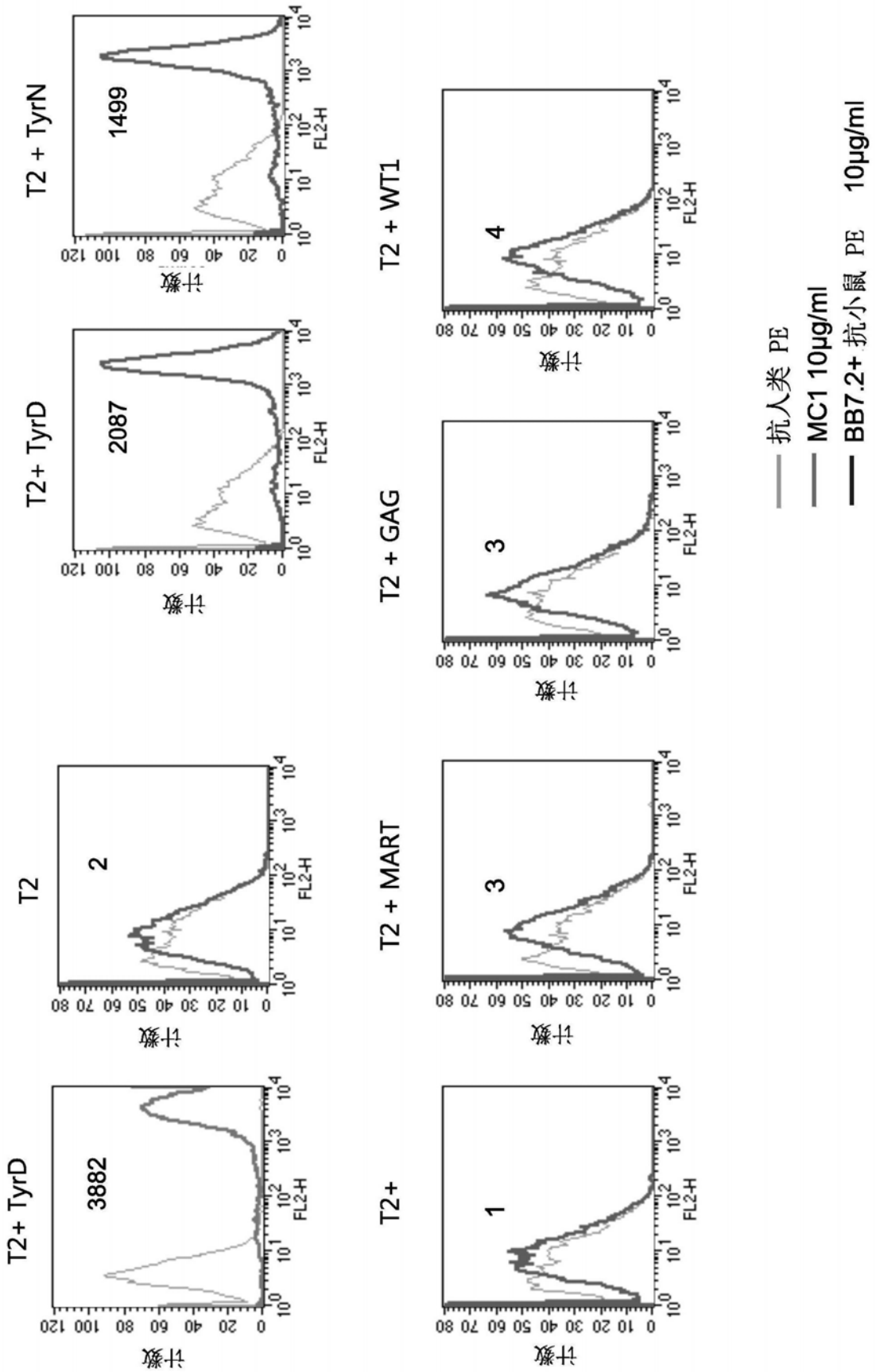

T2+ TyrD
3882
T2
2
T2+ TyrD
2087
T2 + TyrN
1499
T2+
1
T2 + MART
3
T2 + GAG
3
T2 + WT1
4
计数
FL2-H
抗人类 PE
MC1 10μg/ml
BB7.2+ 抗小鼠 PE 10μg/ml

图7

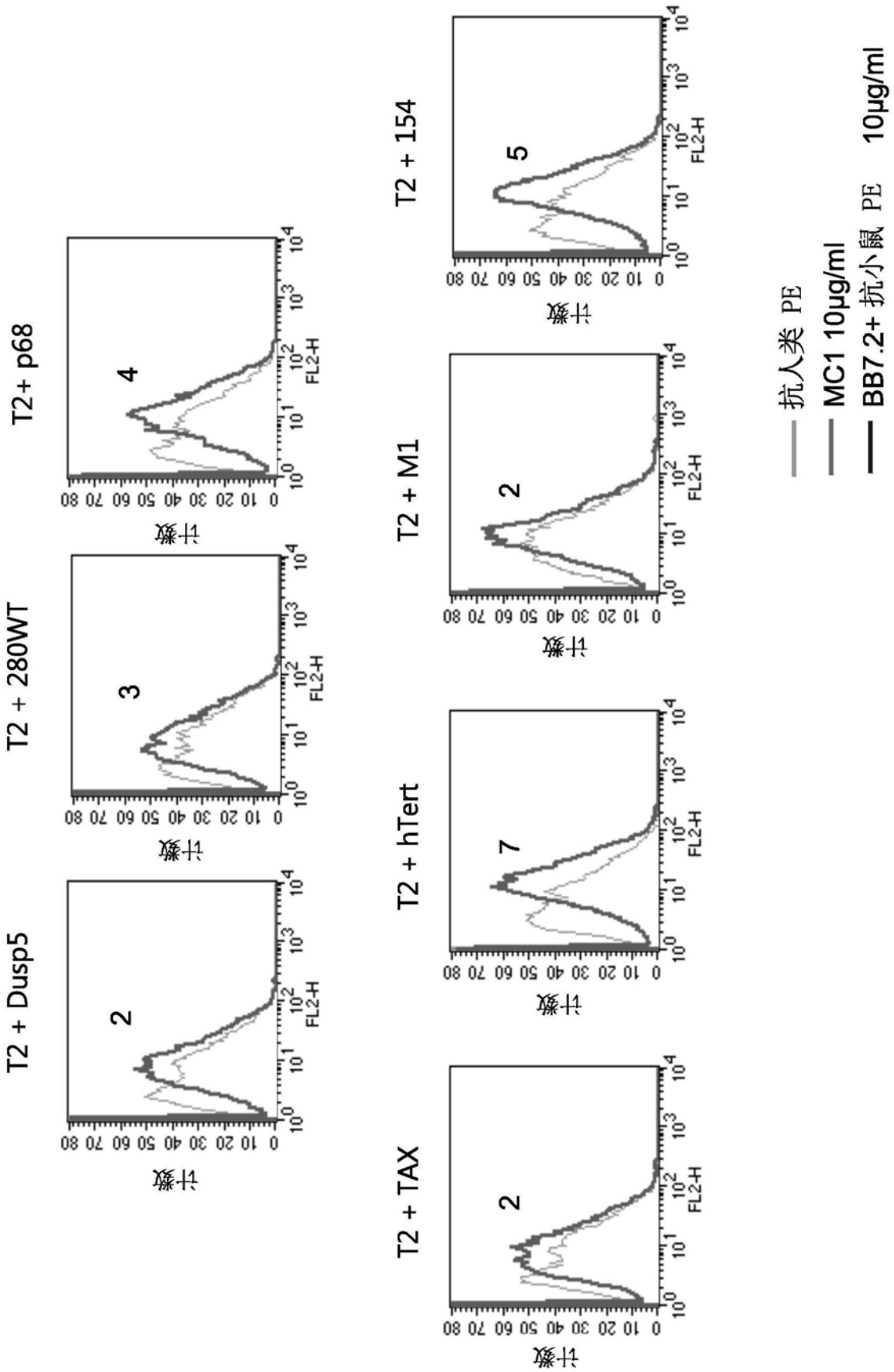

T2 + Dusp5
T2 + 280WT
T2+ p68
T2 + TAX
T2 + hTert
T2 + M1
T2 + 154
2
3
4
2
7
2
5
计数
FL2-H
抗人类 PE
MC1 10μg/ml
BB7.2+ 抗小鼠 PE 10μg/ml

图7-续

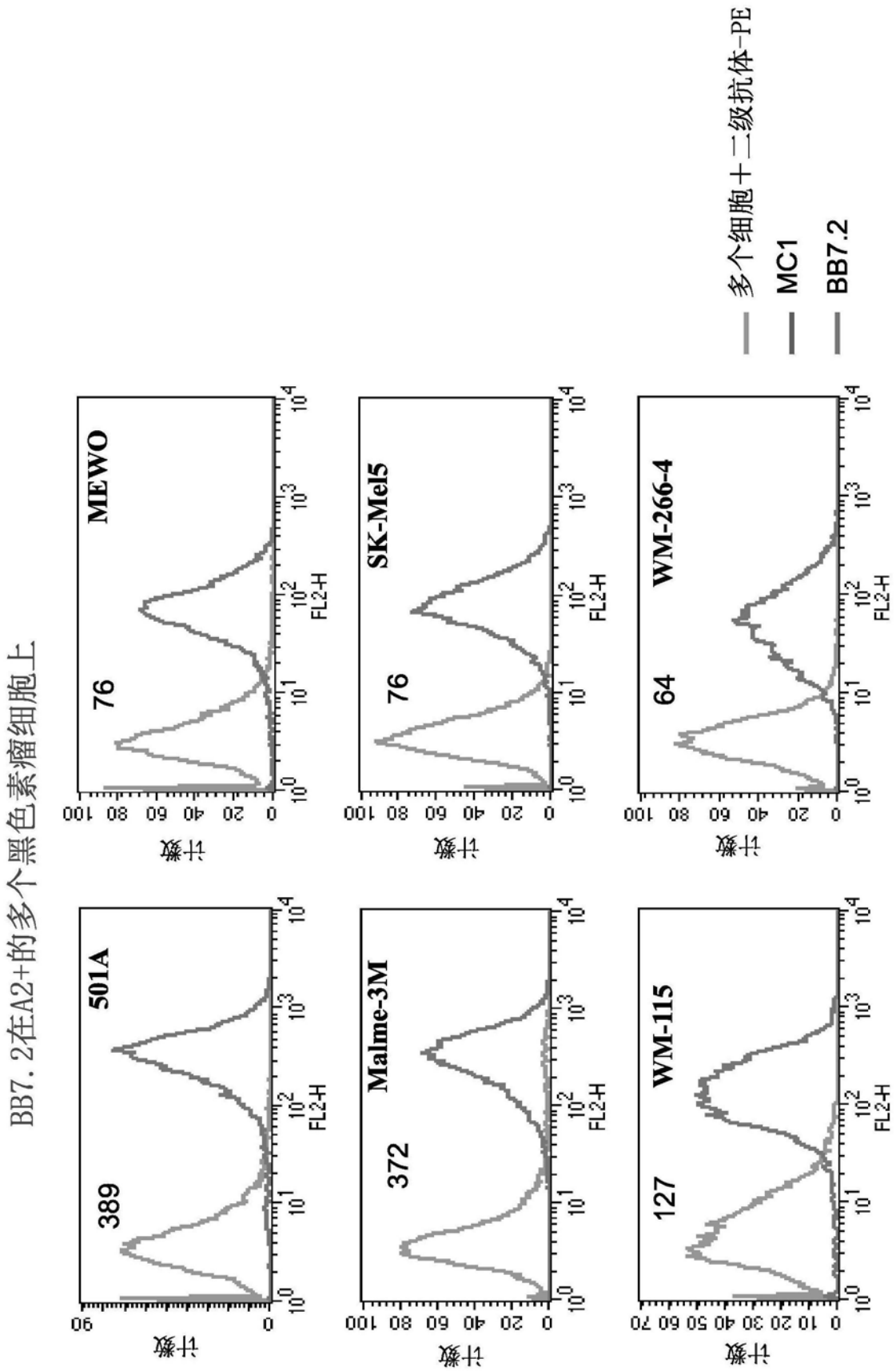

BB7.2在A2+的多个黑色素瘤细胞上
多个细胞＋二级抗体-PE
MC1
BB7.2
389
501A
76
MEWO
372
Malme-3M
76
SK-Mel5
127
WM-115
64
WM-266-4
计数
FL2-H

图8

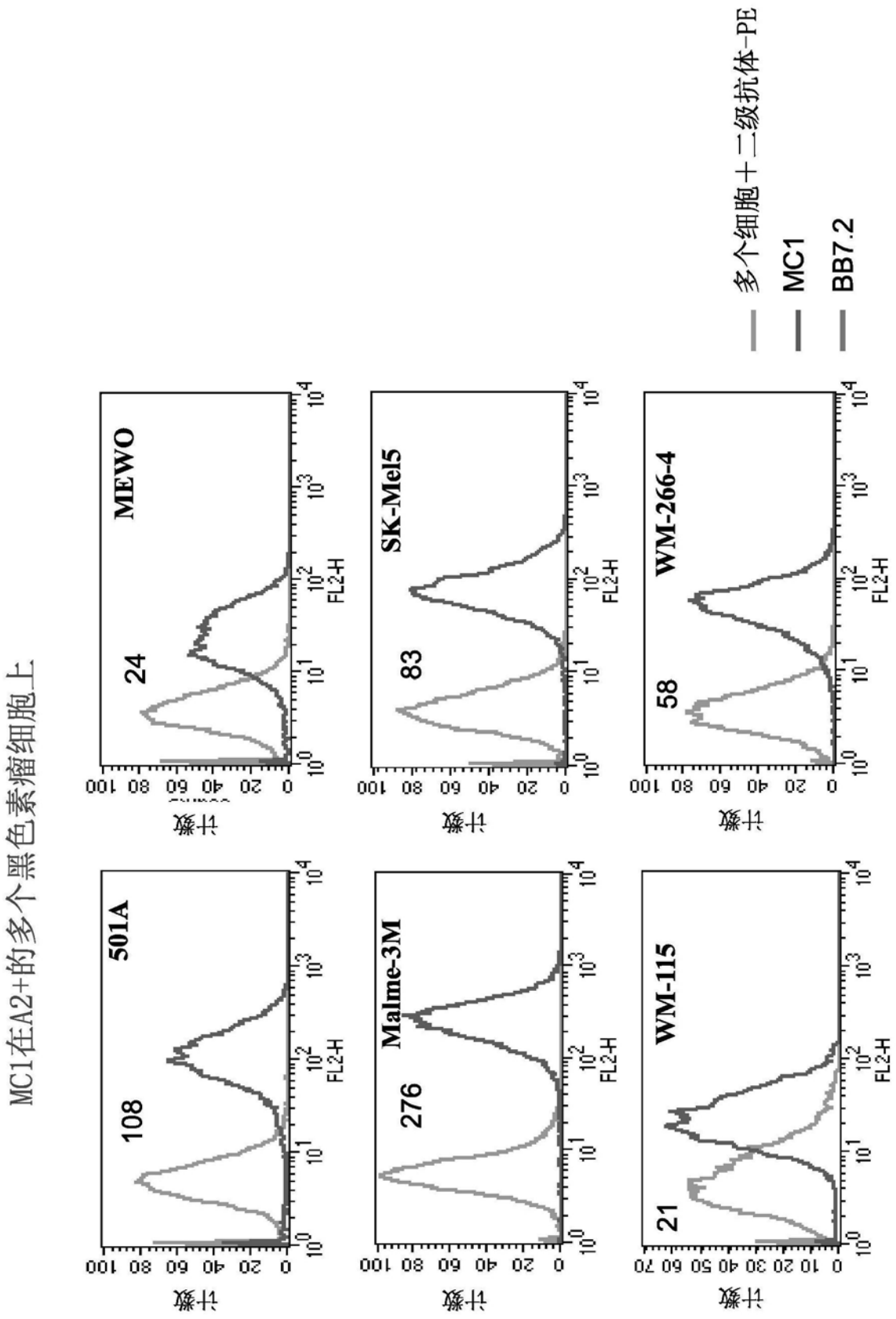

MC1在A2+的多个黑色素瘤细胞上
501A
108
MEWO
24
Malme-3M
276
SK-Mel5
83
WM-115
21
WM-266-4
58
计数
FL2-H
多个细胞+二级抗体-PE
MC1
BB7.2

图8-续

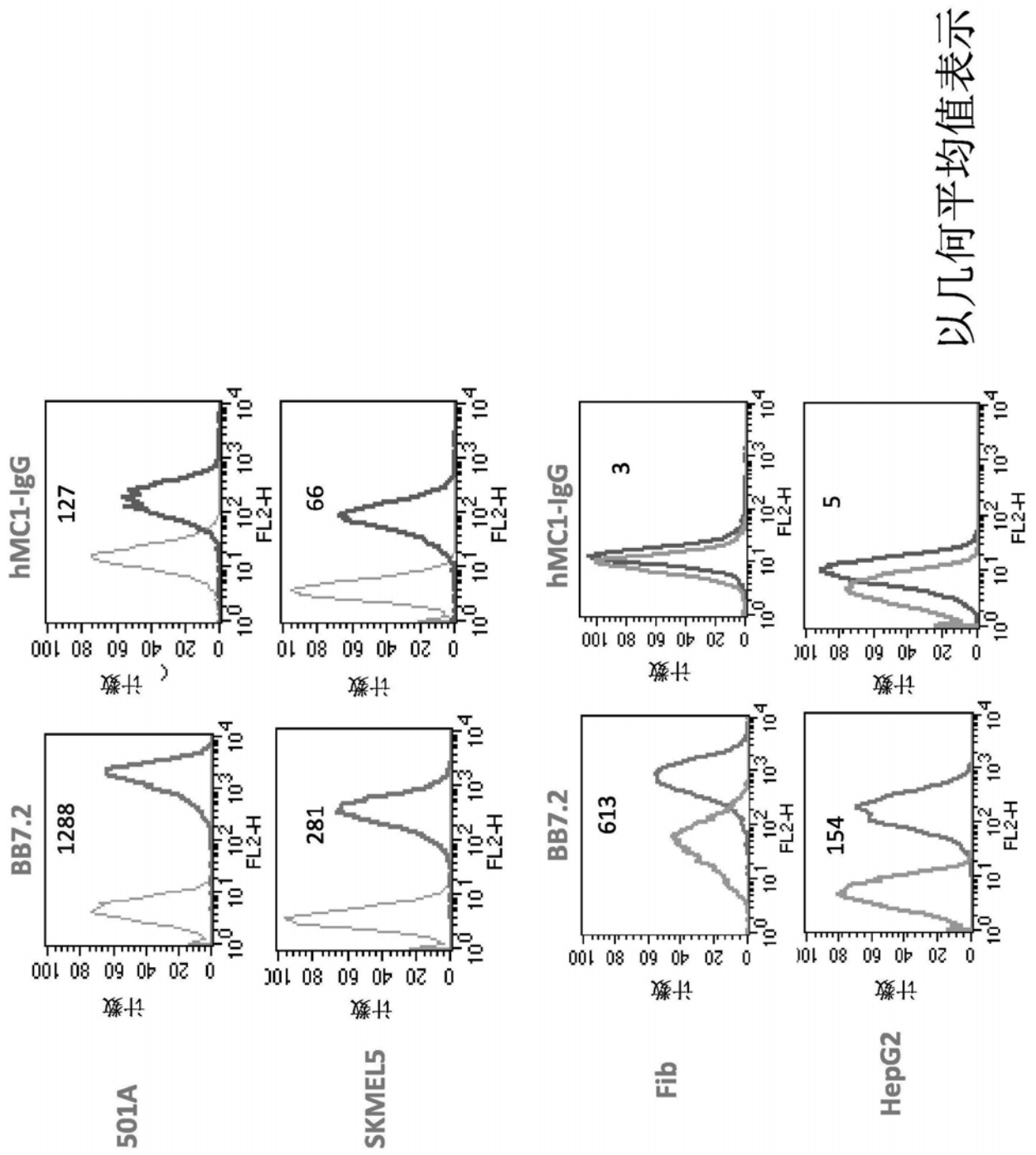

以几何平均值表示
501A
SKMEL5
Fib
HepG2
BB7.2
hMC1-IgG
1288
127
281
66
613
3
154
5
计数
FL2-H

图9

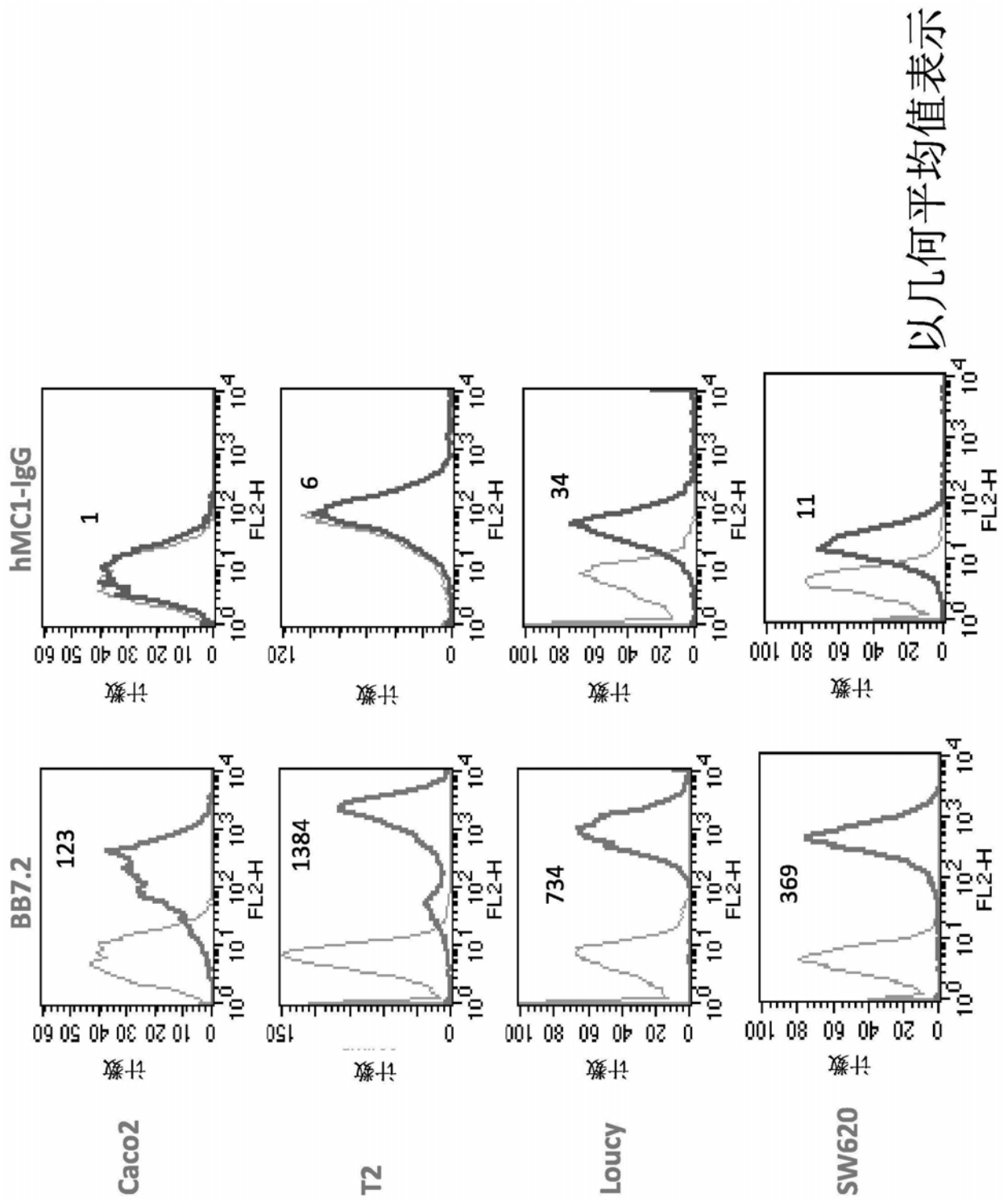

BB7.2
hMC1-IgG
Caco2
T2
Loucy
SW620
123
1
1384
6
734
34
369
11
计数
FL2-H
以几何平均值表示

图9-续

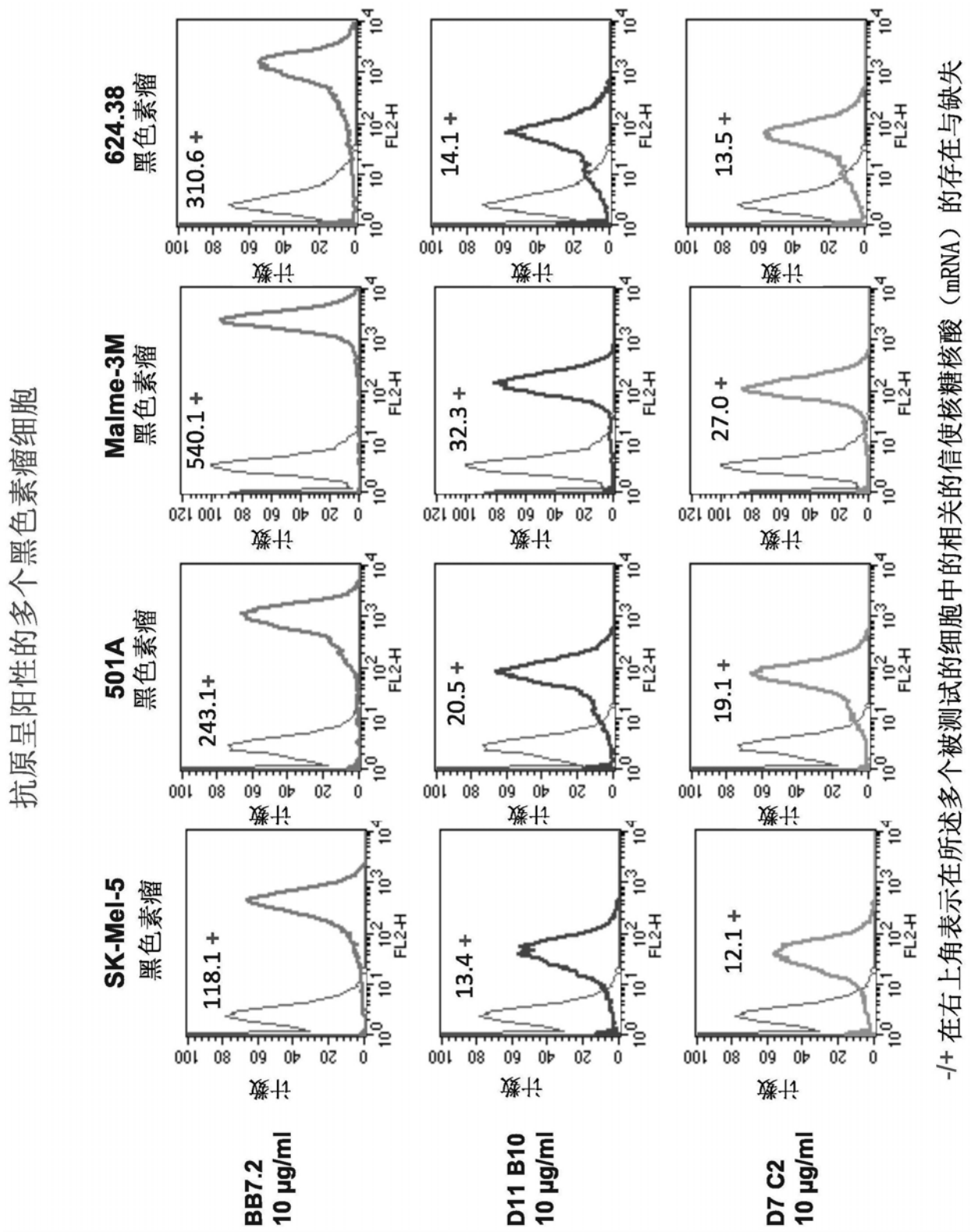

抗原呈阳性的多个黑色素瘤细胞
SK-Mel-5
黑色素瘤
501A
黑色素瘤
Malme-3M
黑色素瘤
624.38
黑色素瘤
BB7.2
10 μg/ml
D11 B10
10 μg/ml
D7 C2
10 μg/ml
118.1 +
243.1+
540.1 +
310.6 +
13.4 +
20.5 +
32.3 +
14.1 +
12.1 +
19.1 +
27.0 +
13.5 +
计数
FL2-H
-/+ 在右上角表示在所述多个被测试的细胞中的相关的信使核糖核酸（mRNA）的存在与缺失

图10

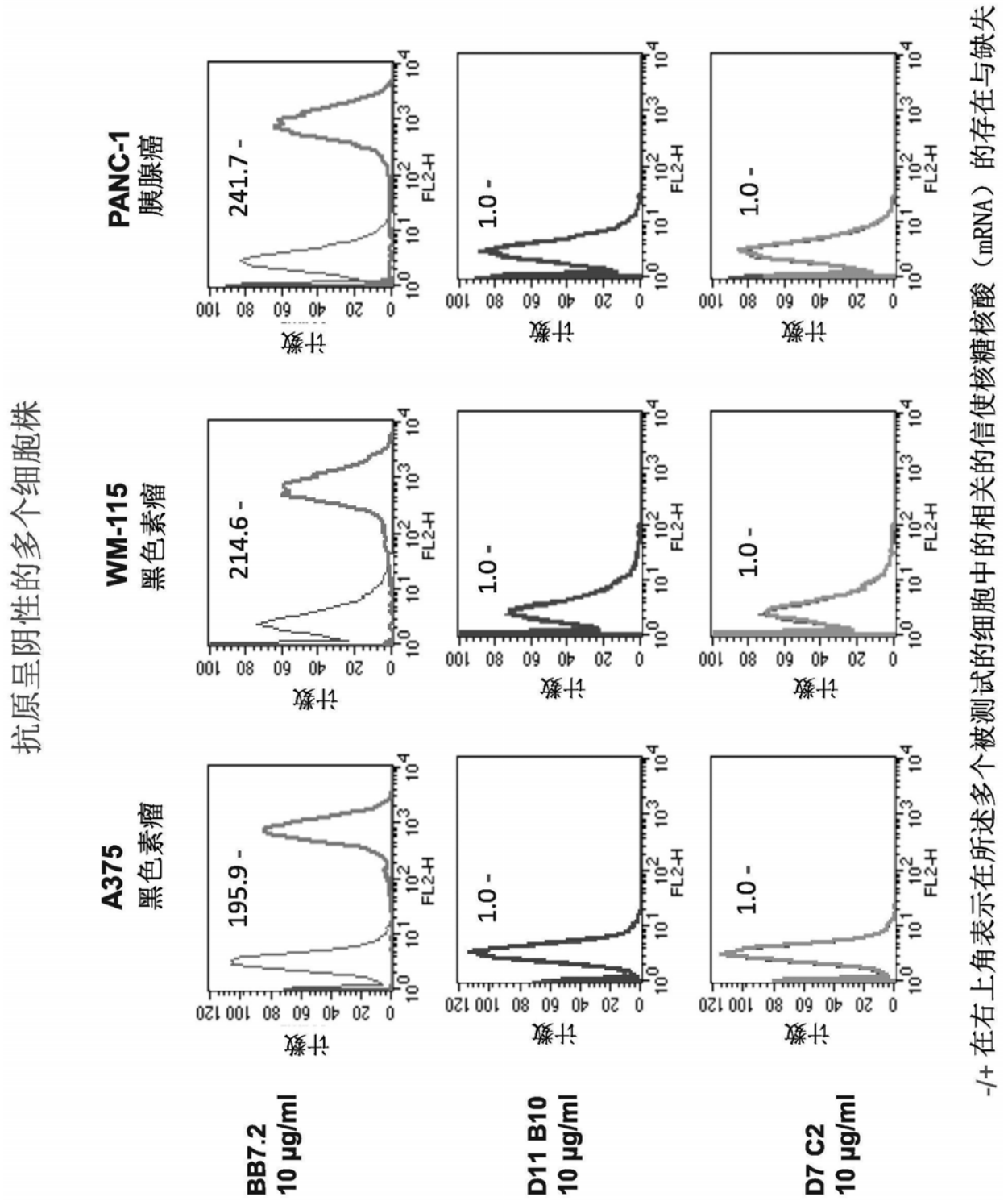
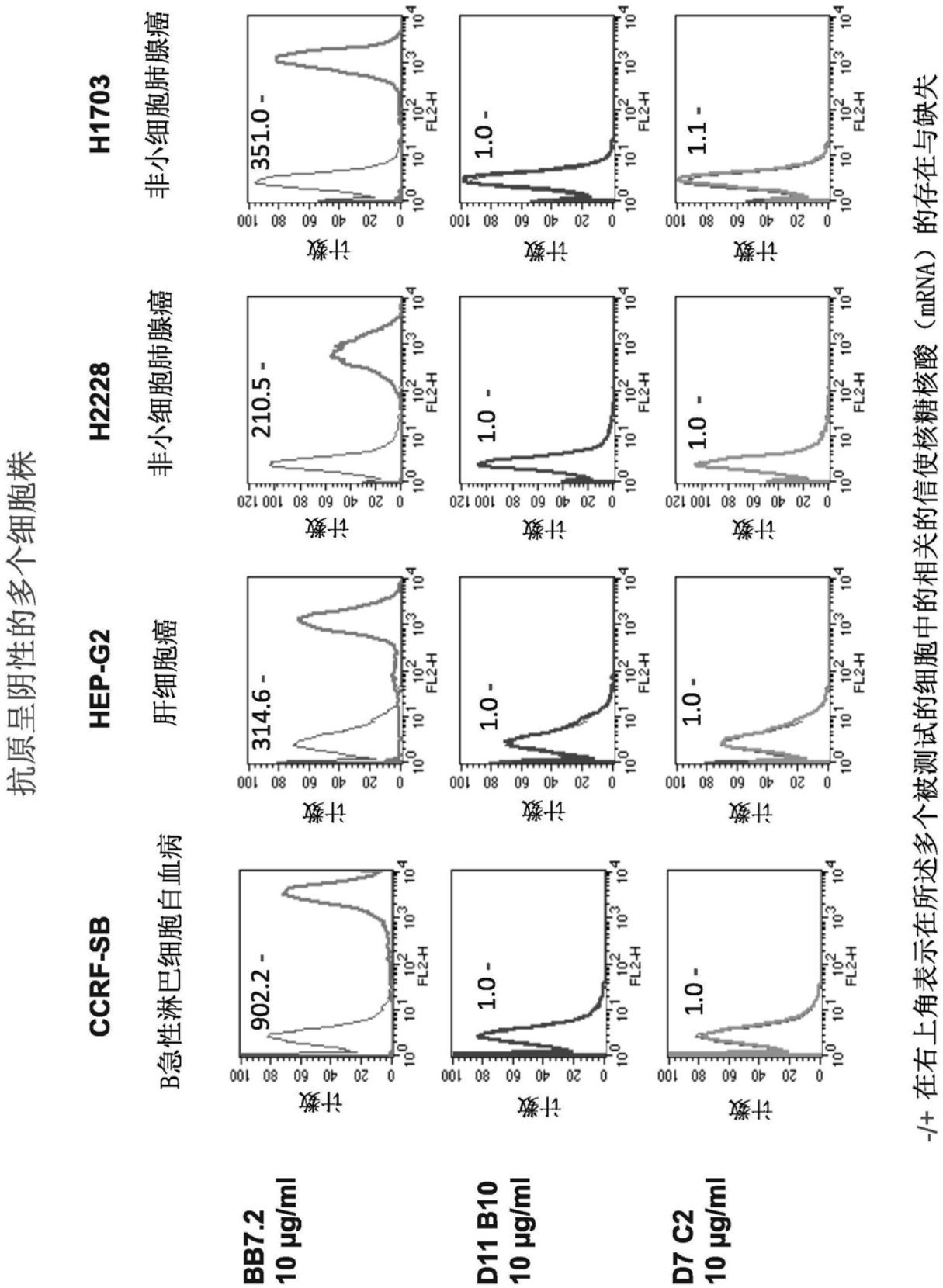

抗原呈阴性的多个细胞株
A375
黑色素瘤
WM-115
黑色素瘤
PANC-1
胰腺癌
BB7.2
10 μg/ml
D11 B10
10 μg/ml
D7 C2
10 μg/ml
195.9 -
214.6 -
241.7 -
1.0 -
1.0 -
1.0 -
1.0 -
1.0 -
1.0 -
计数
FL2-H
-/+ 在右上角表示在所述多个被测试的细胞中的相关的信使核糖核酸（mRNA）的存在与缺失

图10-续



-/+ 在右上角表示在所述多个被测试的细胞中的相关的信使核糖核酸（mRNA）的存在与缺失

图10-续

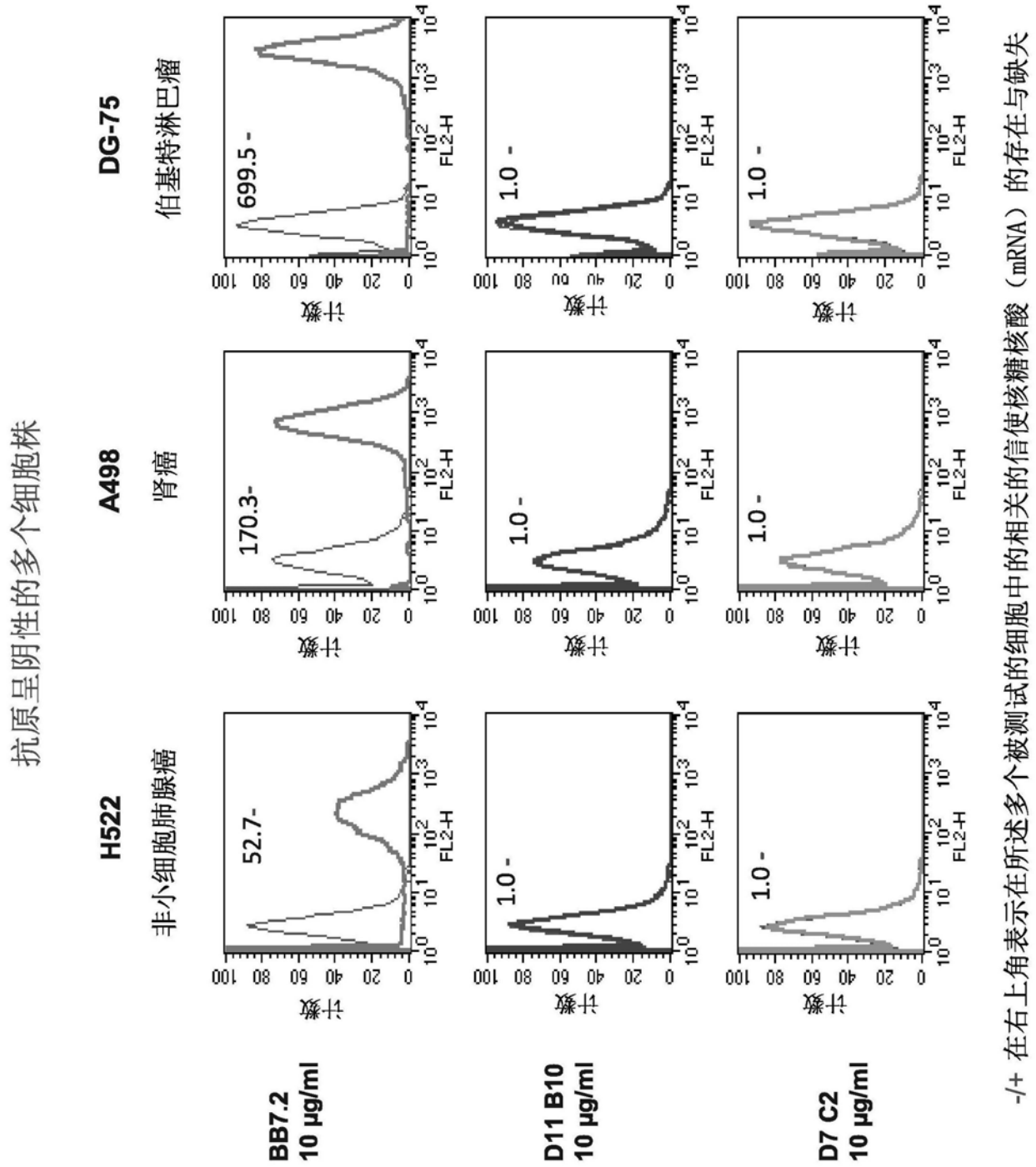

抗原呈阴性的多个细胞株
H522
非小细胞肺腺癌
A498
肾癌
DG-75
伯基特淋巴瘤
52.7-
170.3-
699.5 -
1.0 -
1.0 -
1.0 -
1.0 -
1.0 -
BB7.2
10 μg/ml
D11 B10
10 μg/ml
D7 C2
10 μg/ml
计数
FL2-H
-/+ 在右上角表示在所述多个被测试的细胞中的相关的信使核糖核酸（mRNA）的存在与缺失

图10-续

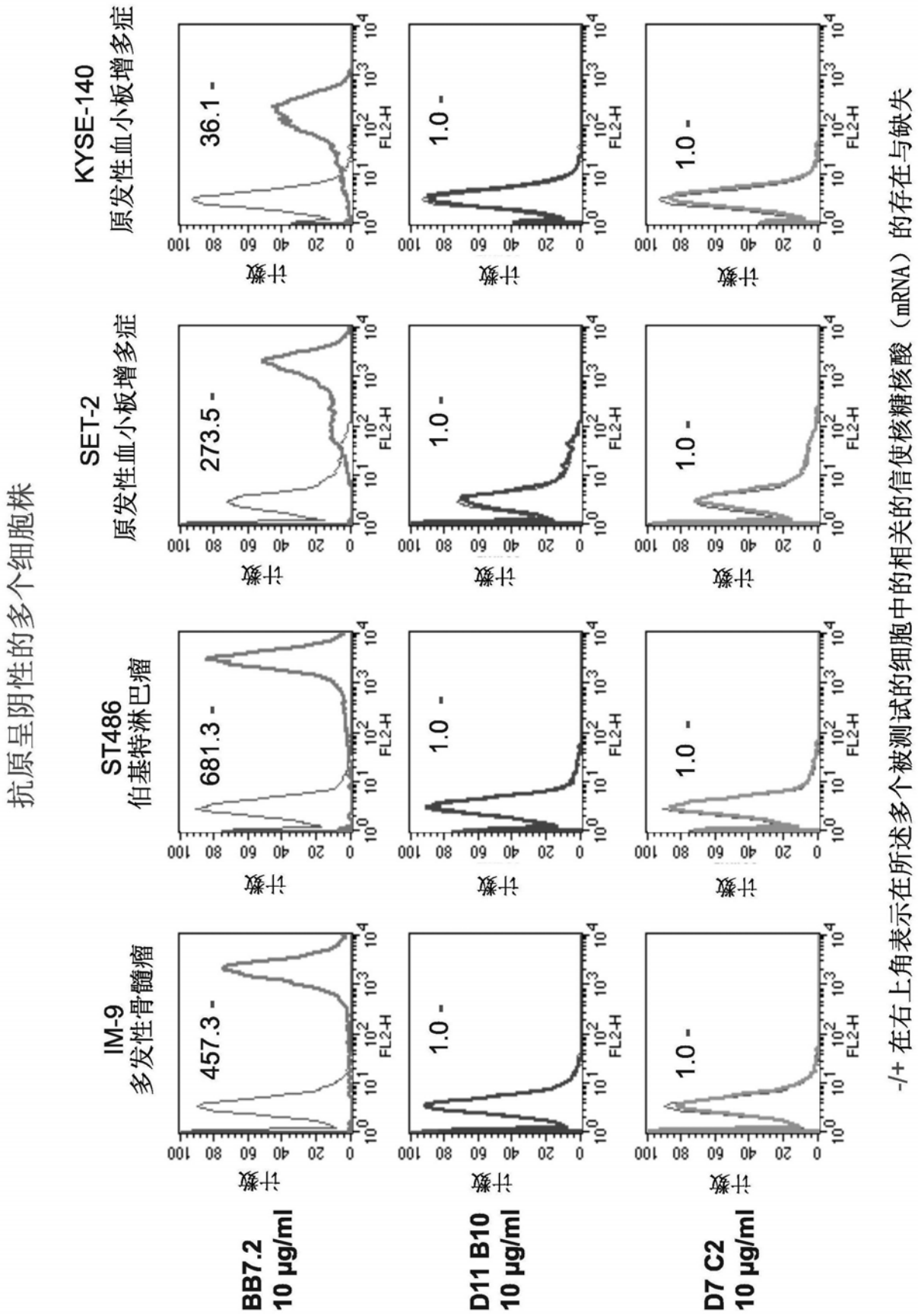

抗原呈阴性的多个细胞株
IM-9
多发性骨髓瘤
ST486
伯基特淋巴瘤
SET-2
原发性血小板增多症
KYSE-140
原发性血小板增多症
457.3 -
681.3 -
273.5 -
36.1 -
1.0 -
BB7.2
10 µg/ml
D11 B10
10 µg/ml
D7 C2
10 µg/ml
计数
FL2-H
-/+ 在右上角表示在所述多个被测试的细胞中的相关的信使核糖核酸（mRNA）的存在与缺失

图11

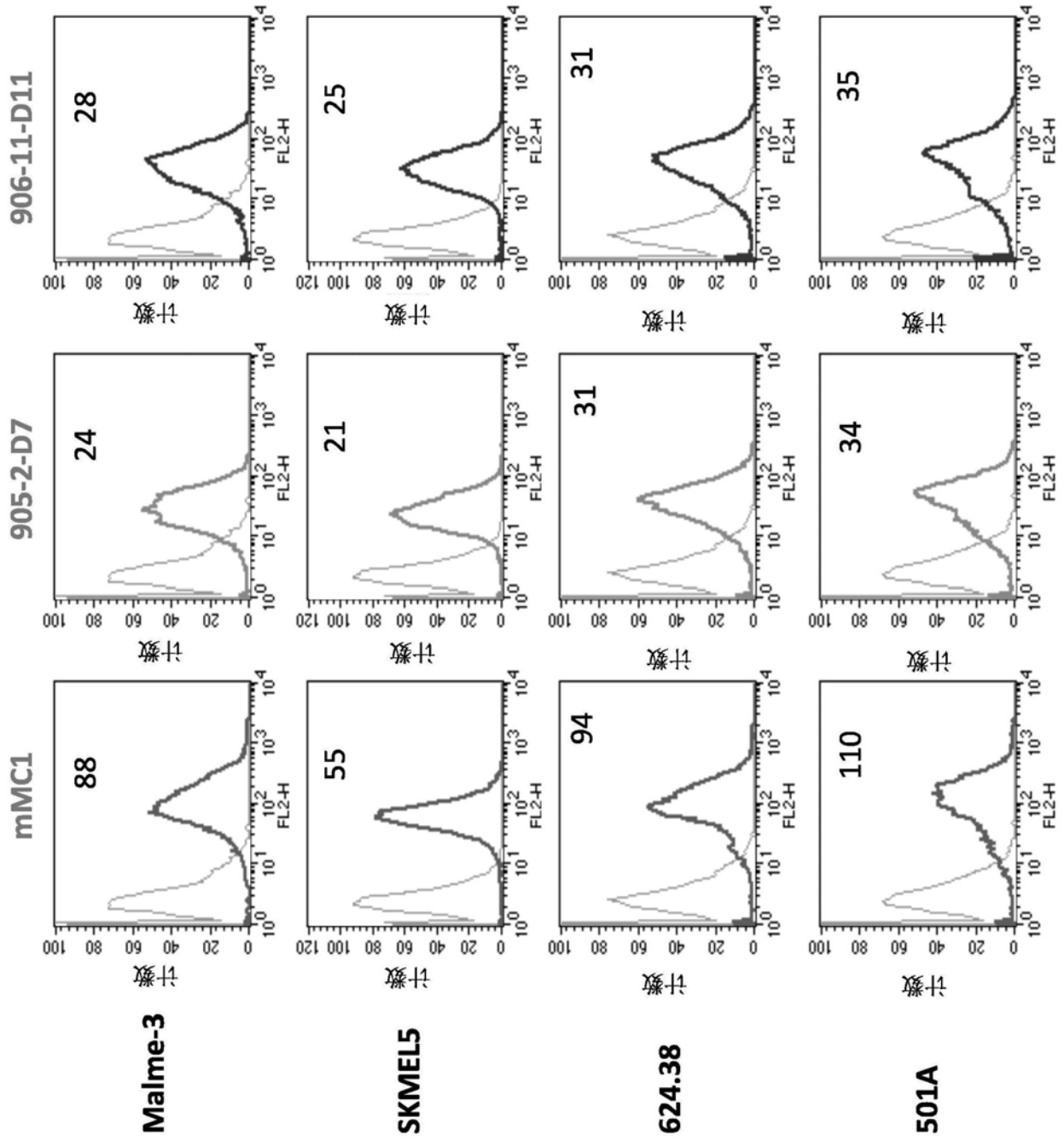

mMC1
905-2-D7
906-11-D11
Malme-3
SKMEL5
624.38
501A
88
24
28
55
21
25
94
31
31
110
34
35
计数
FL2-H

图12

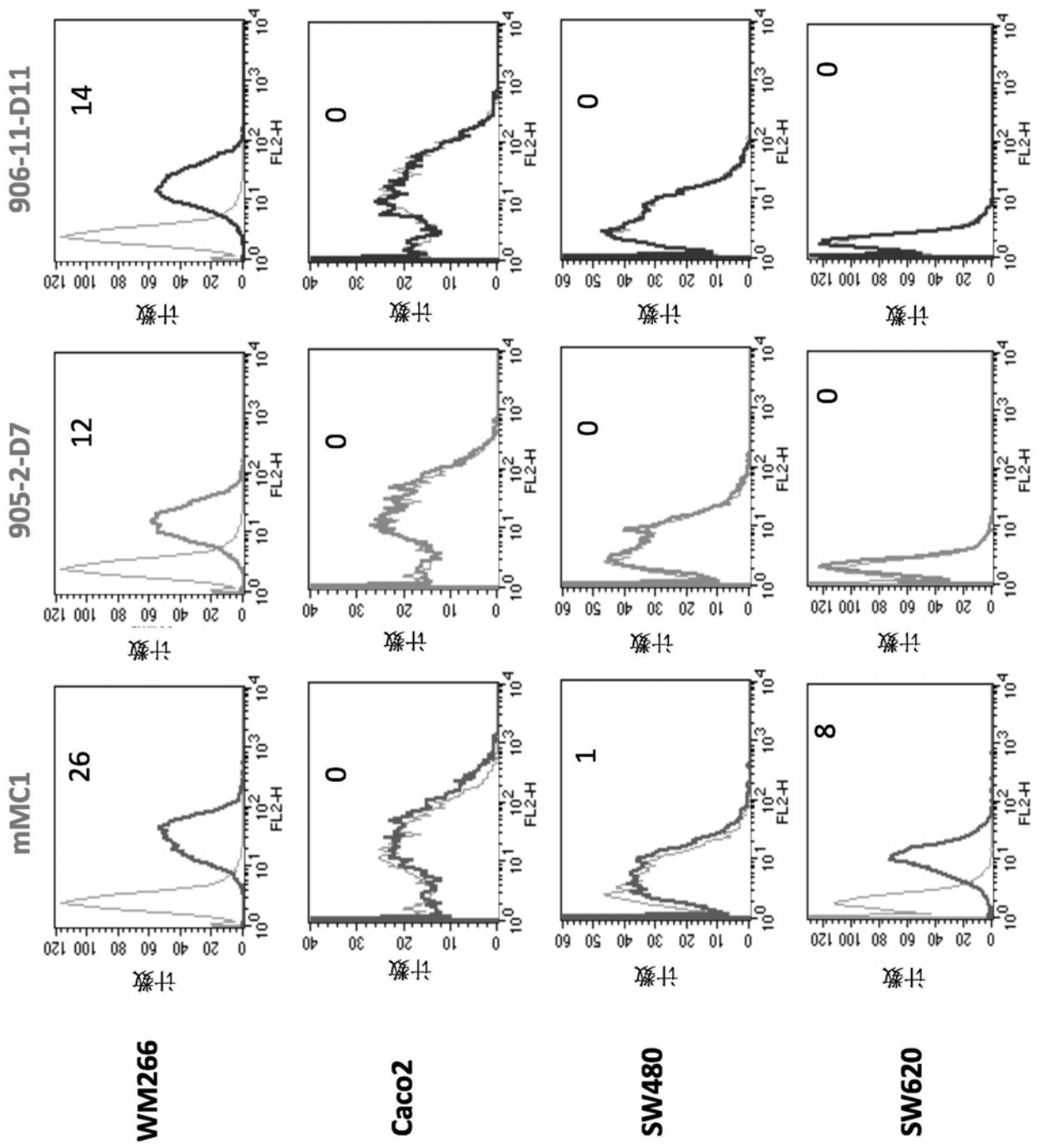

mMC1
905-2-D7
906-11-D11
WM266
Caco2
SW480
SW620
26
12
14
0
0
0
1
0
0
8
0
计数
FL2-H

图12-续

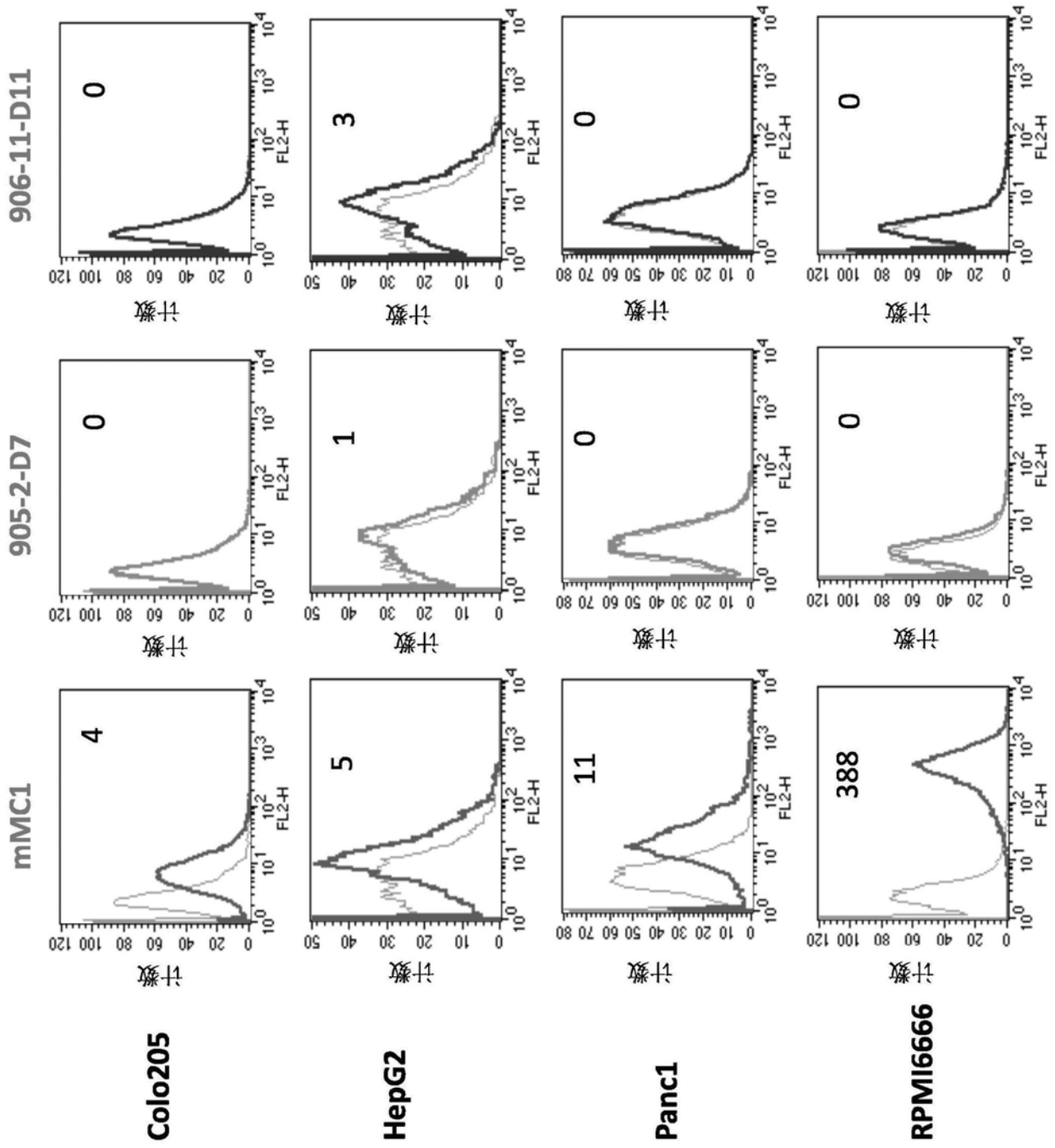

mMC1
905-2-D7
906-11-D11
Colo205
HepG2
Panc1
RPMI6666
4
0
0
5
1
3
11
0
0
388
0
0
计数
FL2-H

图12-续

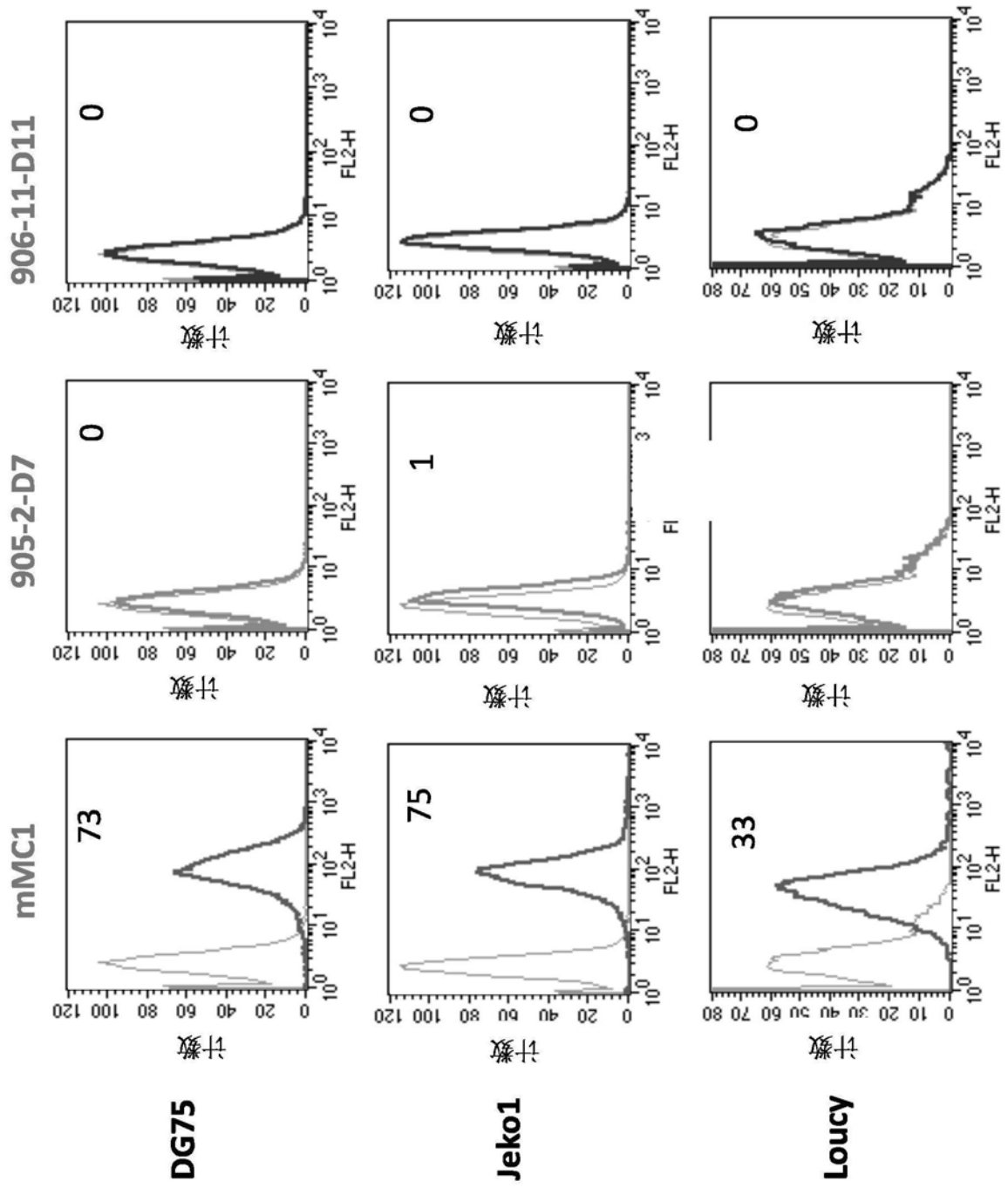


图12-续

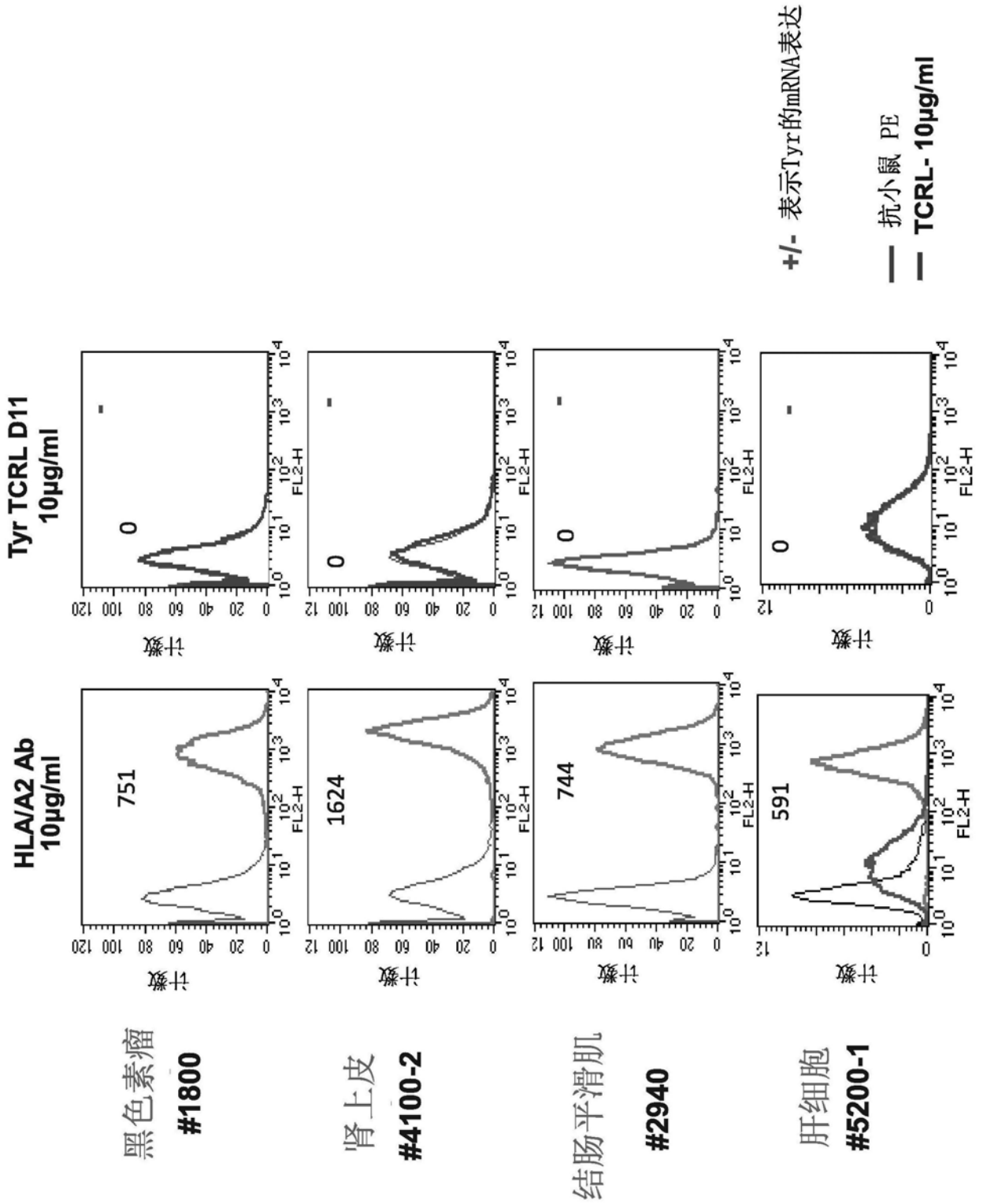

HLA/A2 Ab
10μg/ml
Tyr TCRL D11
10μg/ml
751
0
1624
0
744
0
591
0
计数
FL2-H
黑色素瘤
#1800
肾上皮
#4100-2
结肠平滑肌
#2940
肝细胞
#5200-1
+/- 表示Tyr的mRNA表达
抗小鼠 PE
TCRL- 10μg/ml

图13

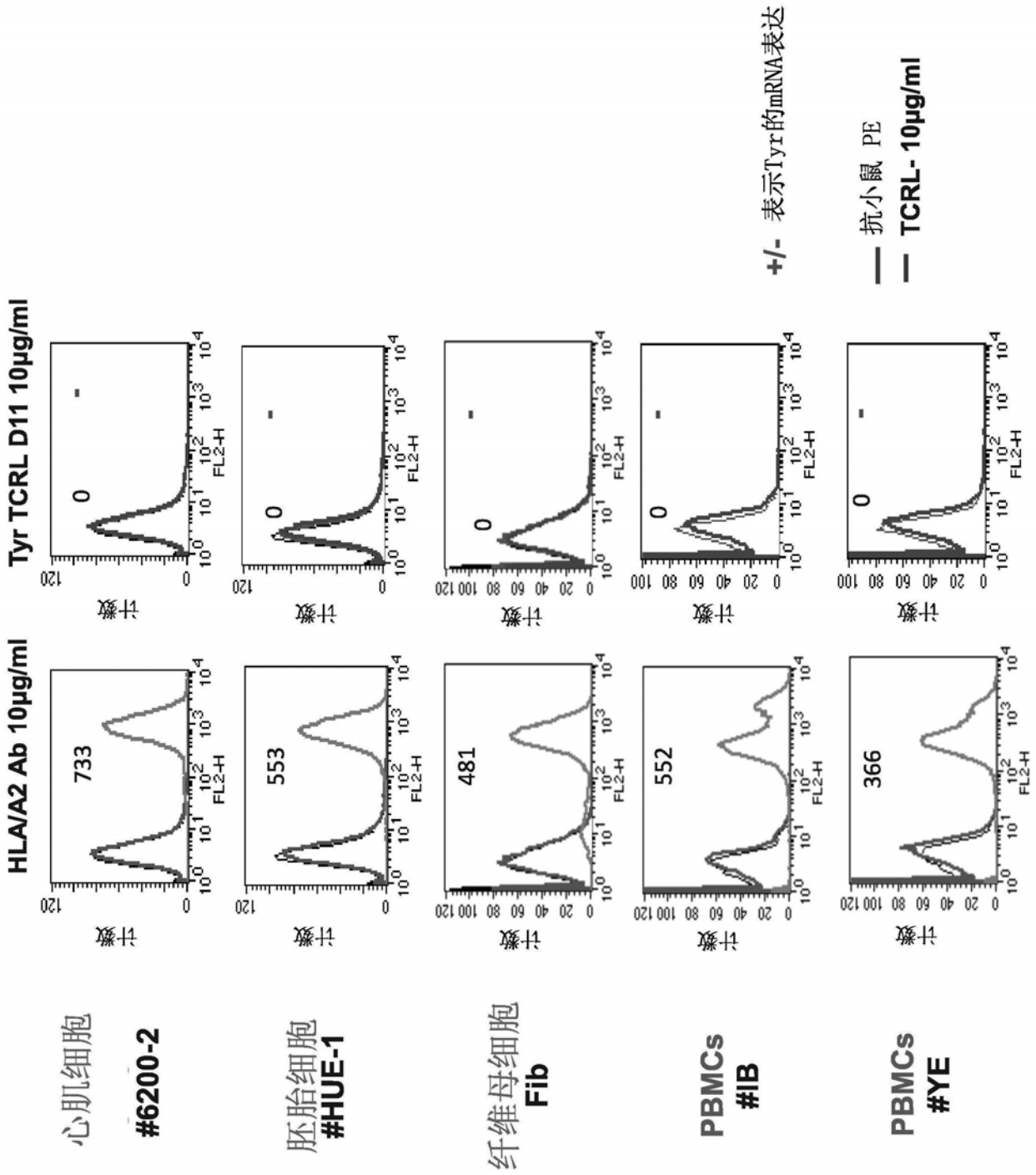

HLA/A2 Ab 10μg/ml
Tyr TCRL D11 10μg/ml
+/- 表示Tyr的mRNA表达
抗小鼠 PE
TCRL- 10μg/ml
心肌细胞
#6200-2
胚胎细胞
#HUE-1
纤维母细胞
Fib
PBMCs
#IB
PBMCs
#YE
733
553
481
552
366
0
-
计数
FL2-H

图13-续

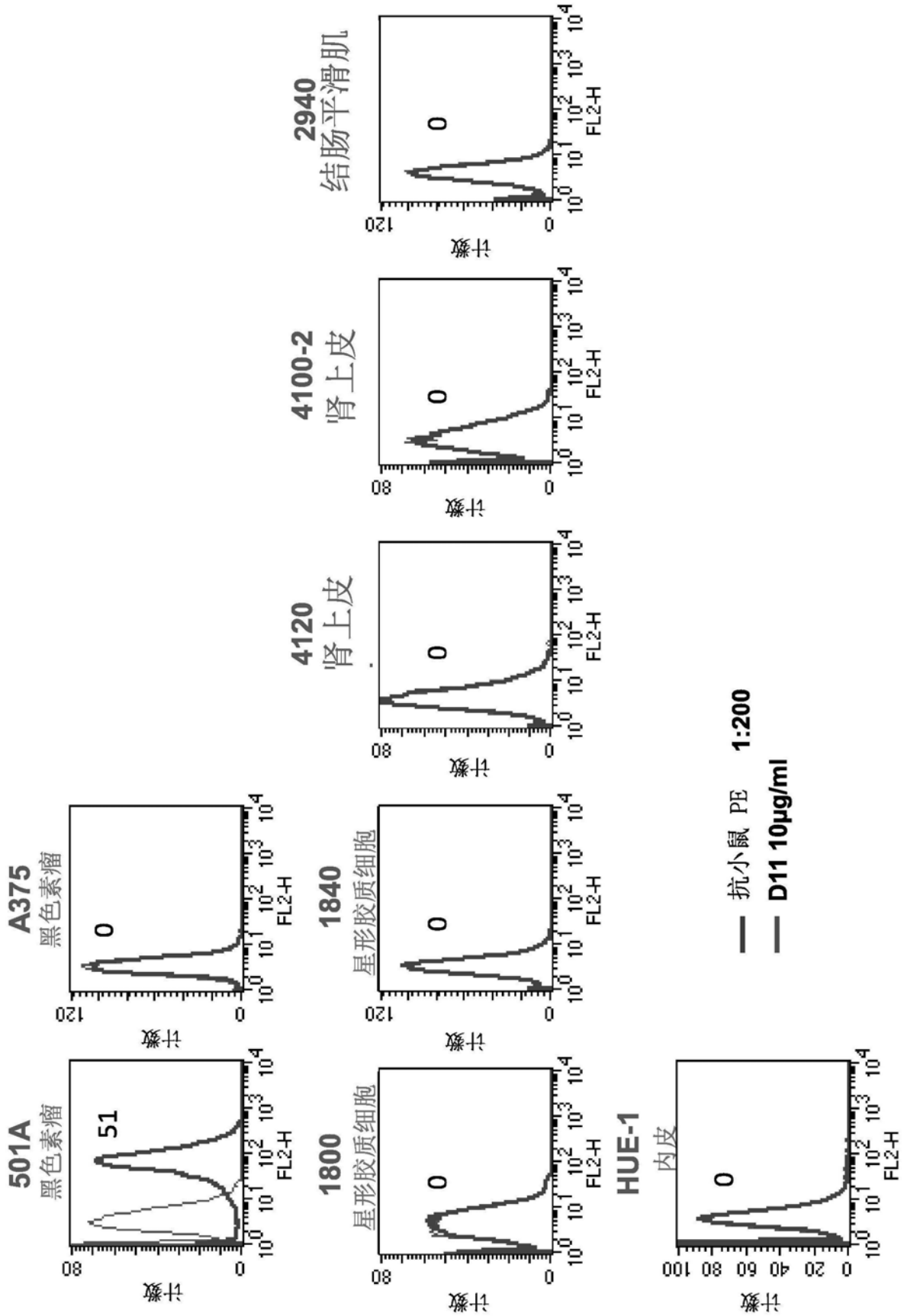

501A
黑色素瘤
51
A375
黑色素瘤
0
1800
星形胶质细胞
0
1840
星形胶质细胞
0
4120
肾上皮
0
4100-2
肾上皮
0
2940
结肠平滑肌
0
HUE-1
内皮
0
计数
FL2-H
抗小鼠 PE 1:200
D11 10μg/ml

图14

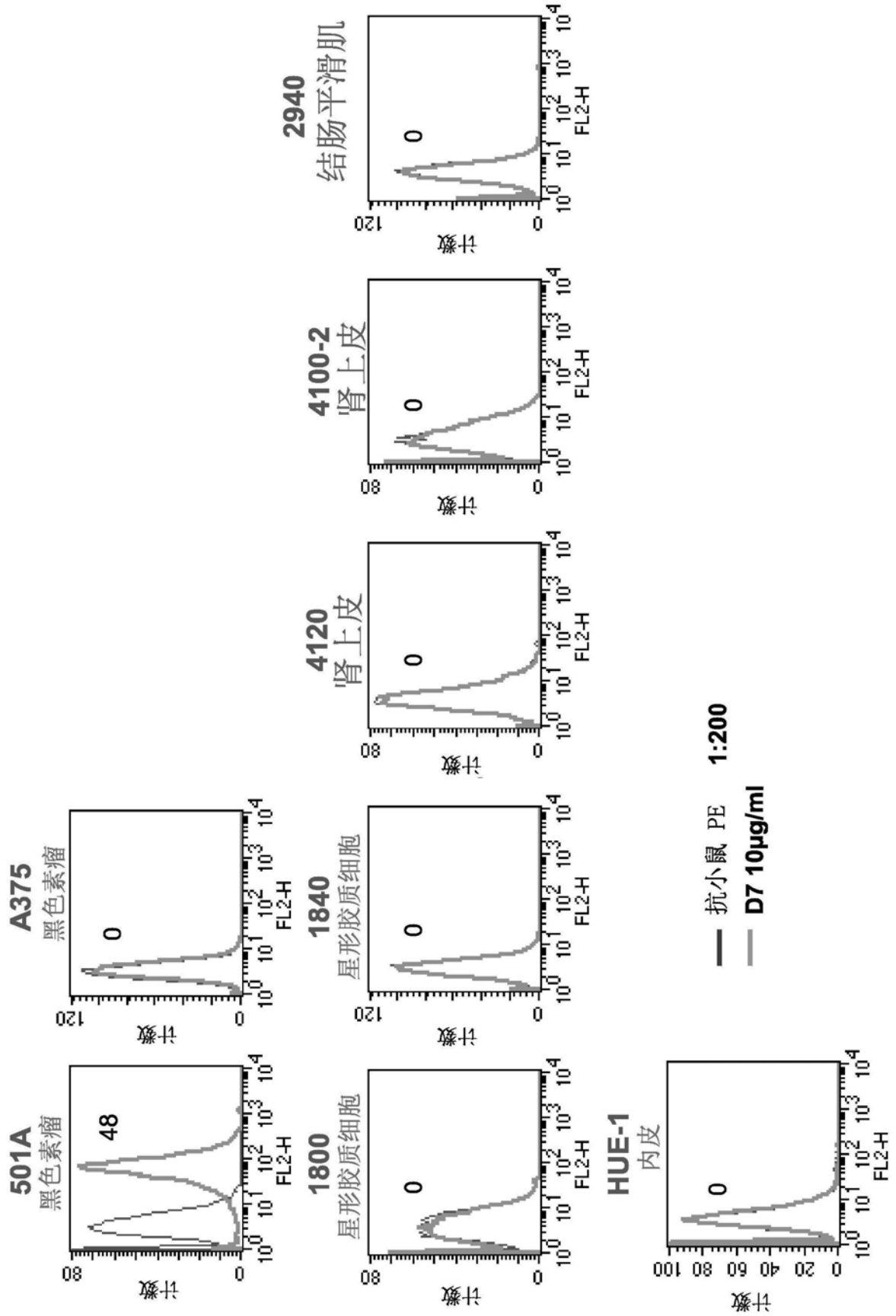

501A
黑色素瘤
48
A375
黑色素瘤
0
1800
星形胶质细胞
0
1840
星形胶质细胞
0
4120
肾上皮
0
4100-2
肾上皮
0
2940
结肠平滑肌
0
HUE-1
内皮
0
计数
FL2-H
抗小鼠 PE 1:200
D7 10μg/ml

图15

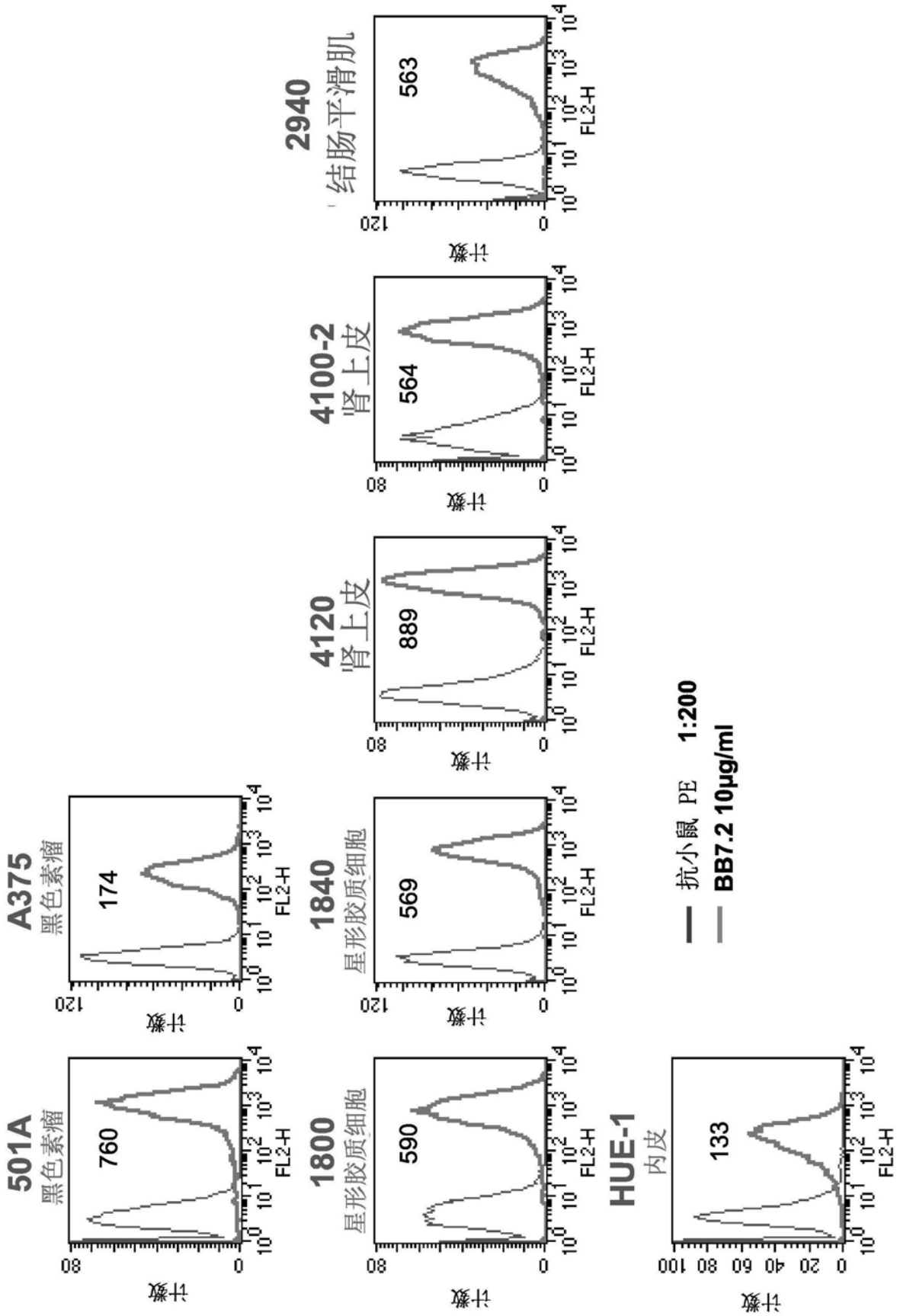

501A
黑色素瘤
760
A375
黑色素瘤
174
1800
星形胶质细胞
590
1840
星形胶质细胞
569
HUE-1
内皮
133
4120
肾上皮
889
4100-2
肾上皮
564
2940
结肠平滑肌
563
计数
FL2-H
抗小鼠 PE 1:200
BB7.2 10μg/ml

图16

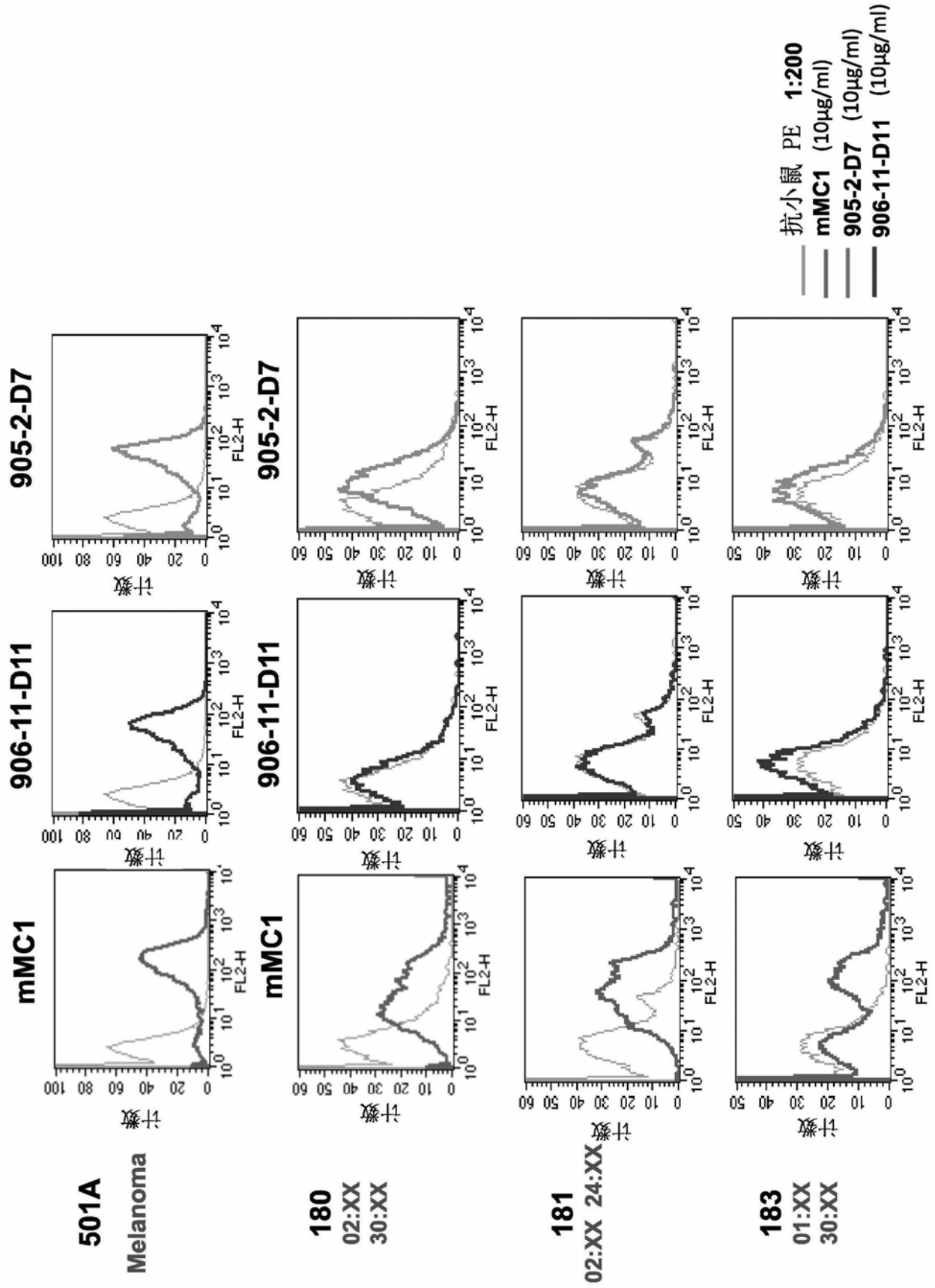

抗小鼠 PE 1:200
mMC1 (10μg/ml)
905-2-D7 (10μg/ml)
906-11-D11 (10μg/ml)
501A
Melanoma
180
02:XX
30:XX
181
02:XX 24:XX
183
01:XX
30:XX
mMC1
906-11-D11
905-2-D7
计数
FL2-H

图17

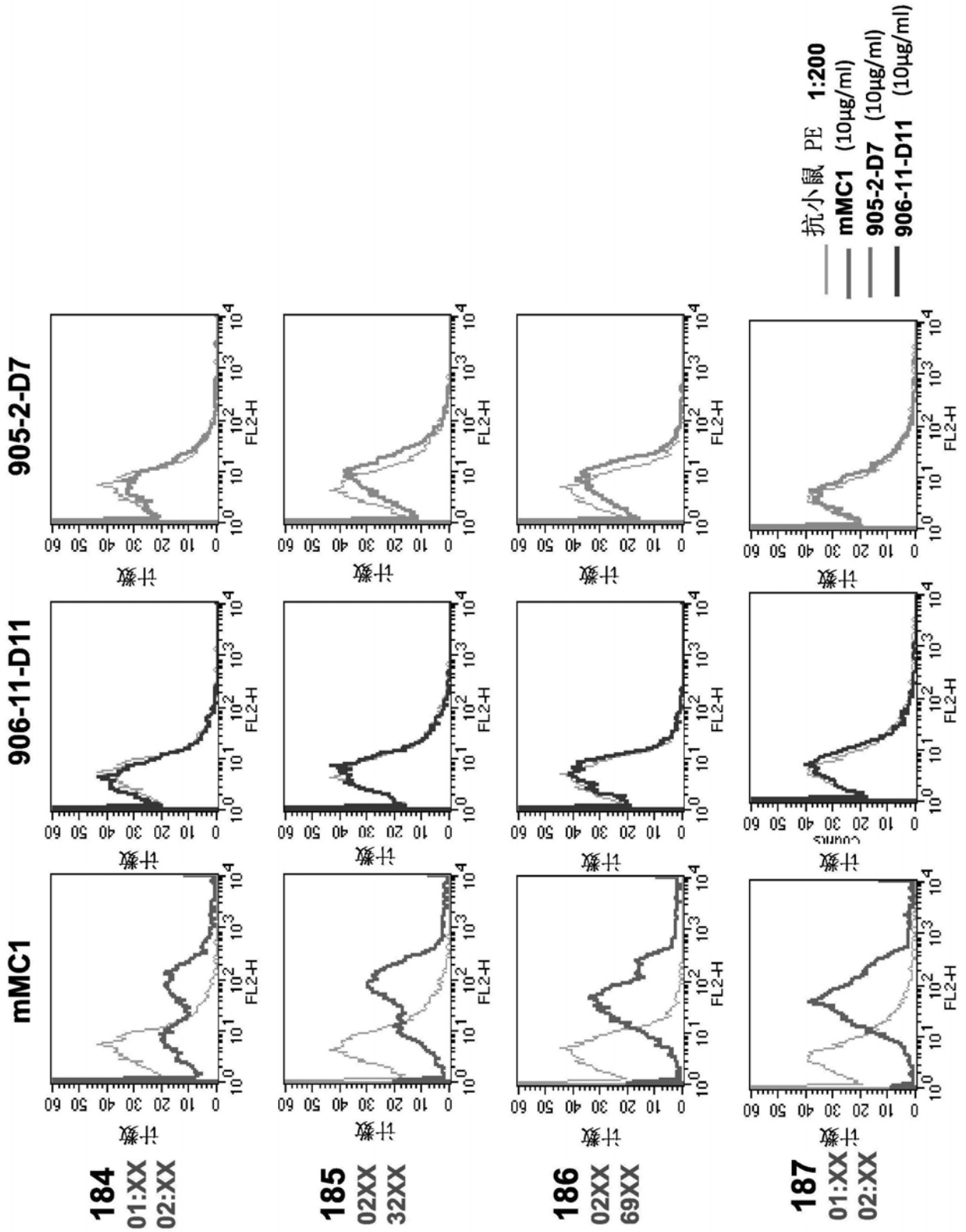

mMC1
906-11-D11
905-2-D7
184
01:XX
02:XX
185
02XX
32XX
186
02XX
69XX
187
01:XX
02:XX
计数
FL2-H
抗小鼠 PE 1:200
mMC1 (10μg/ml)
905-2-D7 (10μg/ml)
906-11-D11 (10μg/ml)

图17-续

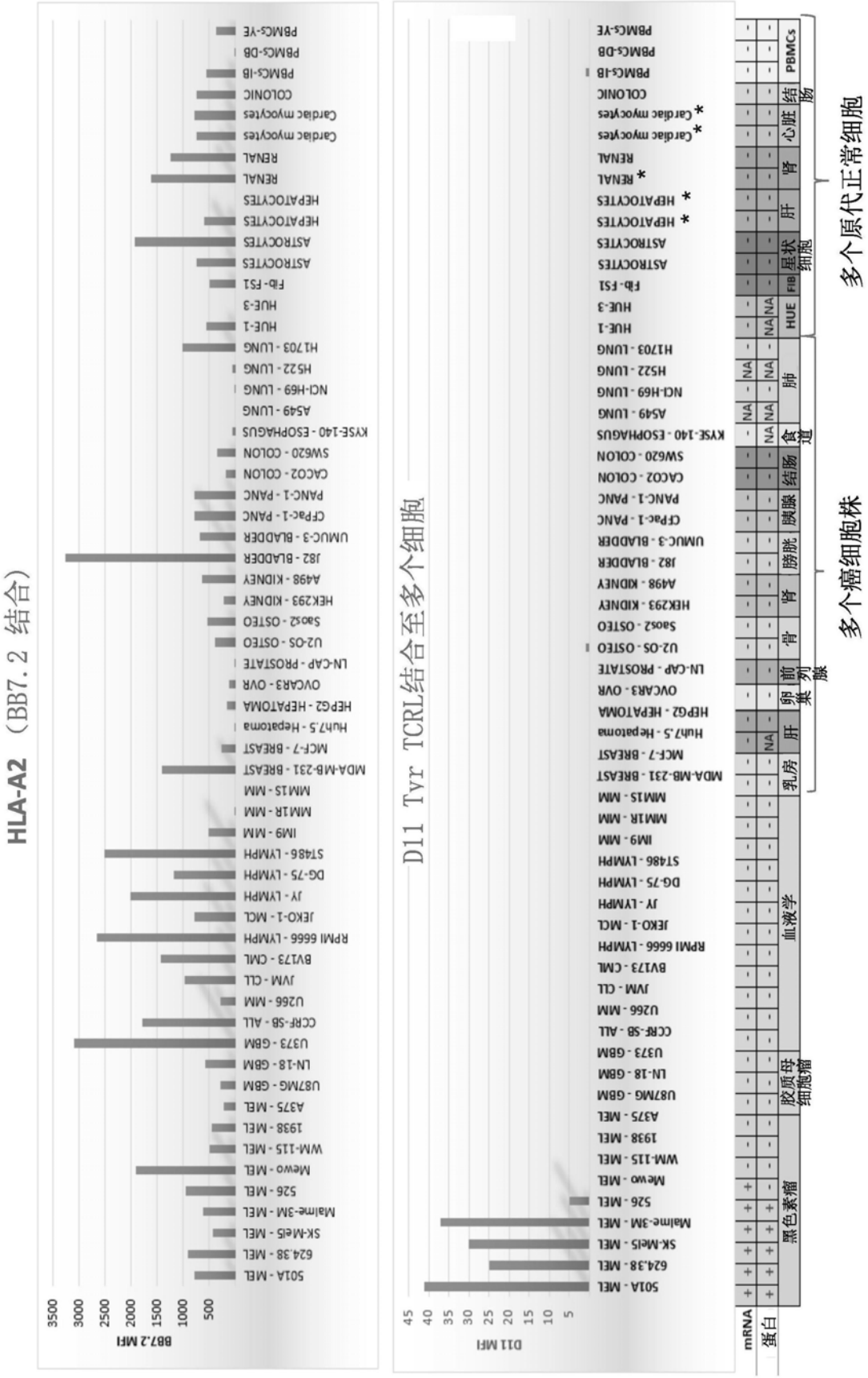

HLA-A2 （BB7.2 结合）
BB7.2 MFI
D11 Tyr TCRL结合至多个细胞
D11 MFI
mRNA
蛋白
黑色素瘤
胶质母细胞瘤
血液学
乳房
肝
卵巢
前列腺
骨
肾
膀胱
胰腺
结肠
食道
肺
HUE
FIB
星状细胞
肝
肾
心脏
结肠
PBMCs
多个癌细胞株
多个原代正常细胞

图18

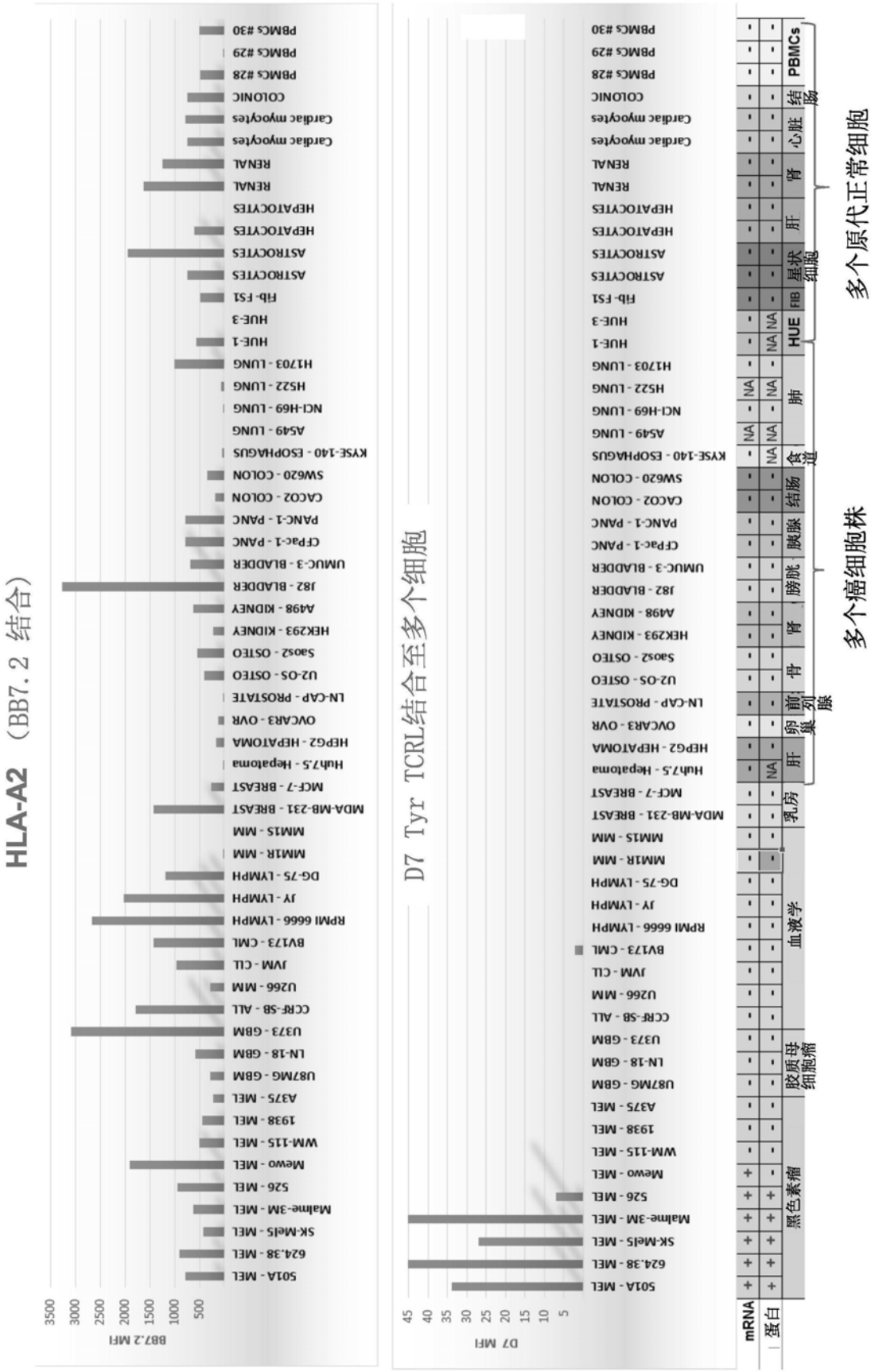

HLA-A2 (BB7.2 结合)
BB7.2 MFI
D7 Tyr TCRL结合至多个细胞
D7 MFI
mRNA
蛋白
黑色素瘤
胶质母细胞瘤
血液学
乳房
肝
卵巢
前列腺
骨
肾
膀胱
胰腺
结肠
食道
肺
HUE
FIB
星状细胞
肝
肾
心脏
结肠
PBMCs
多个原代正常细胞
多个癌细胞株

图19

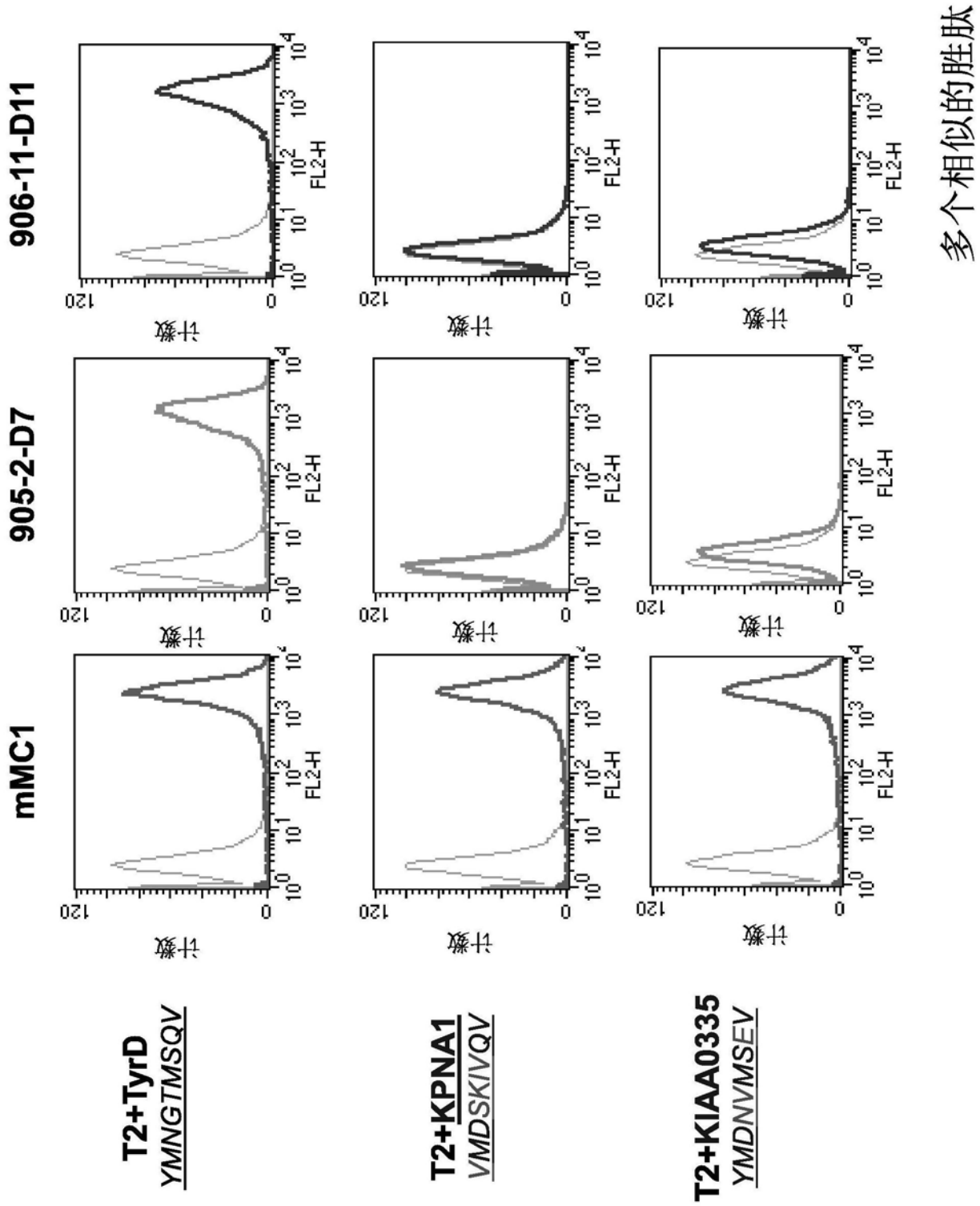

mMC1
905-2-D7
906-11-D11
T2+TyrD
YMNGTMSQV
T2+KPNA1
VMDSKIVQV
T2+KIAA0335
YMDNVMSEV
计数
FL2-H
多个相似的胜肽

图20

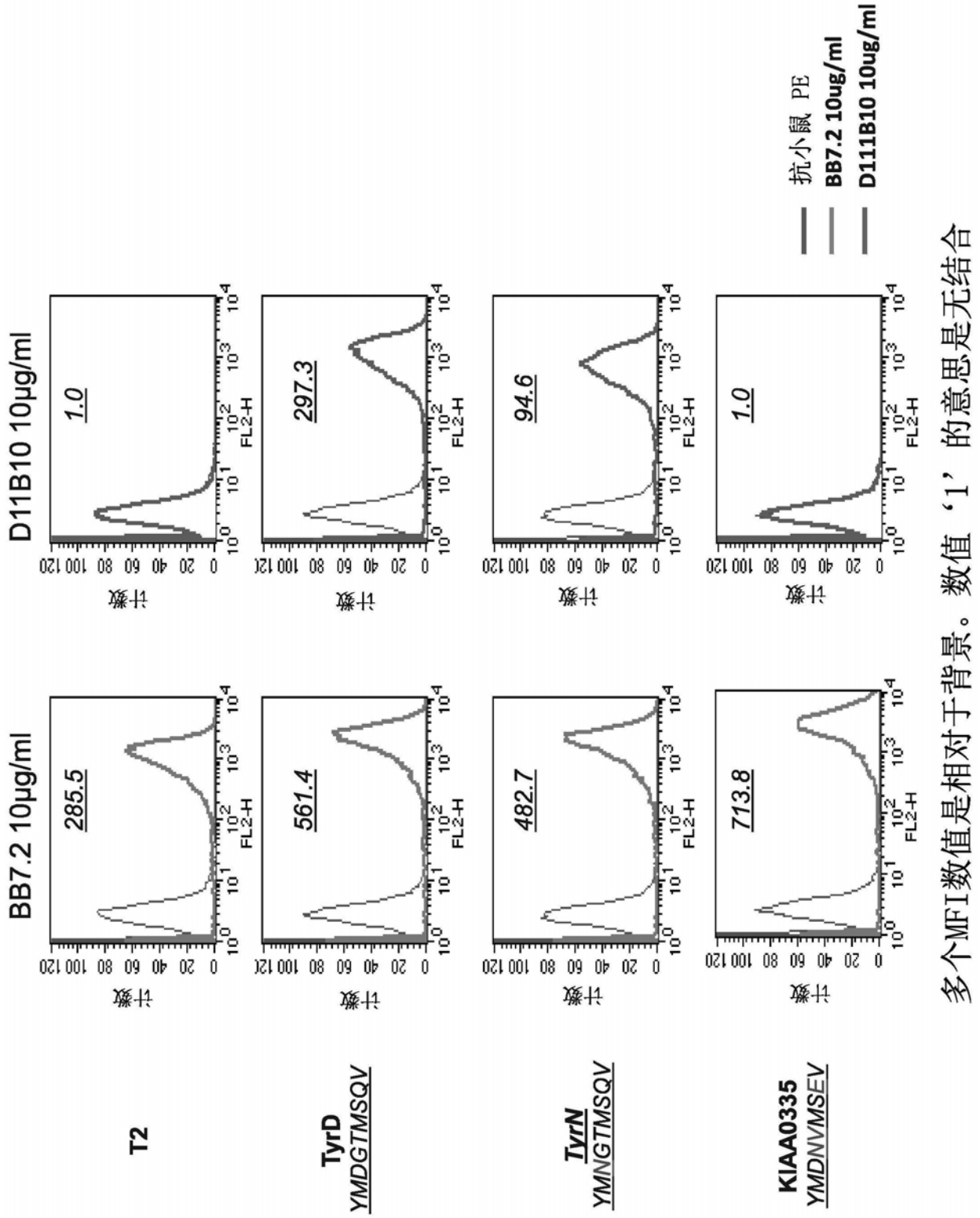

BB7.2 10μg/ml
D11B10 10μg/ml
T2
TyrD
YMDGTMSQV
TyrN
YMNGTMSQV
KIAA0335
YMDNVMSEV
285.5
561.4
482.7
713.8
1.0
297.3
94.6
1.0
计数
FL2-H
抗小鼠 PE
BB7.2 10ug/ml
D111B10 10ug/ml
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图21

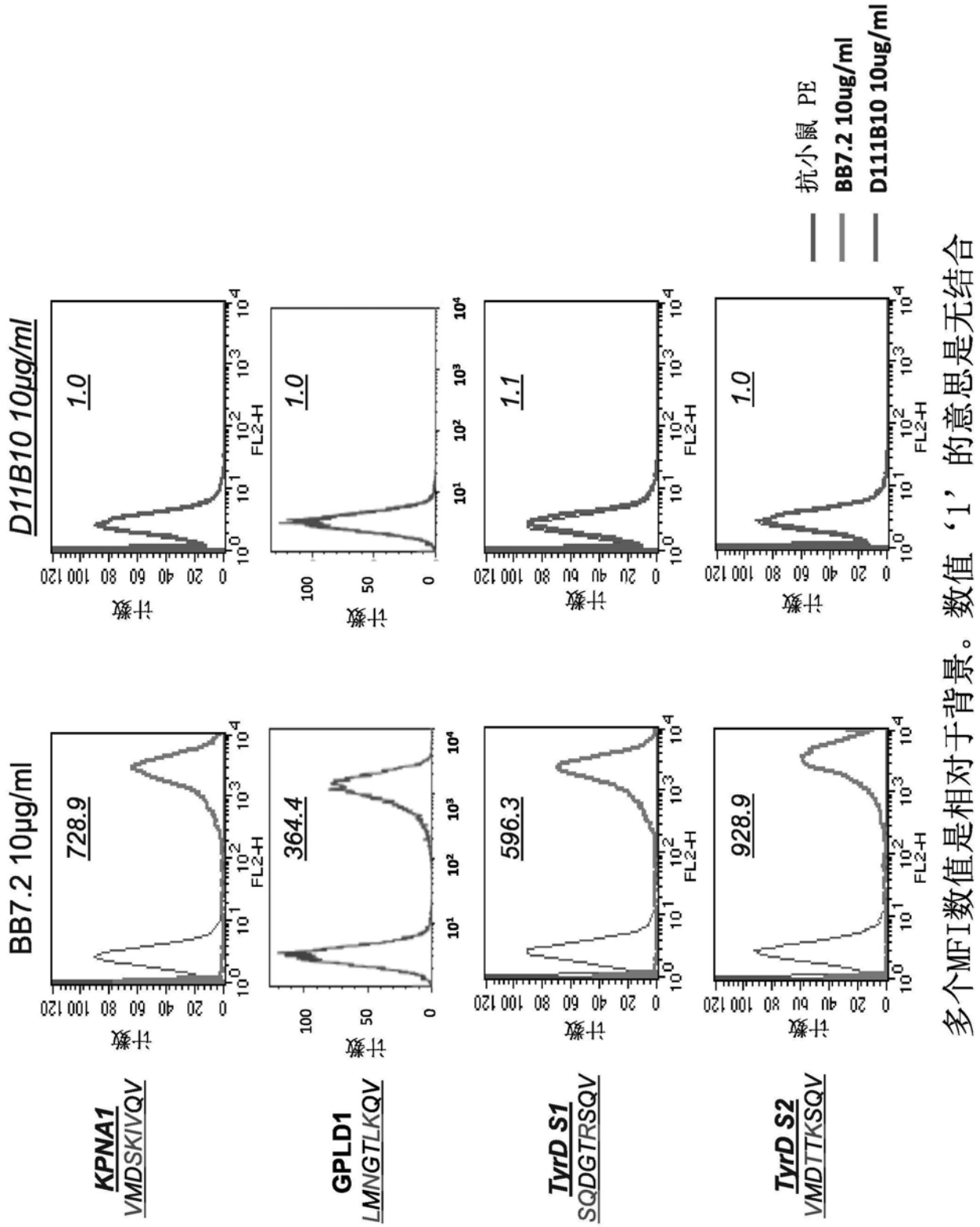

KPNA1
VMDSKIVQV
GPLD1
LMNGTLKQV
TyrD S1
SQDGTRSQV
TyrD S2
VMDTTKSQV
BB7.2 10μg/ml
D11B10 10μg/ml
728.9
364.4
596.3
928.9
1.0
1.0
1.1
1.0
计数
FL2-H
抗小鼠 PE
BB7.2 10ug/ml
D111B10 10ug/ml
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图21-续

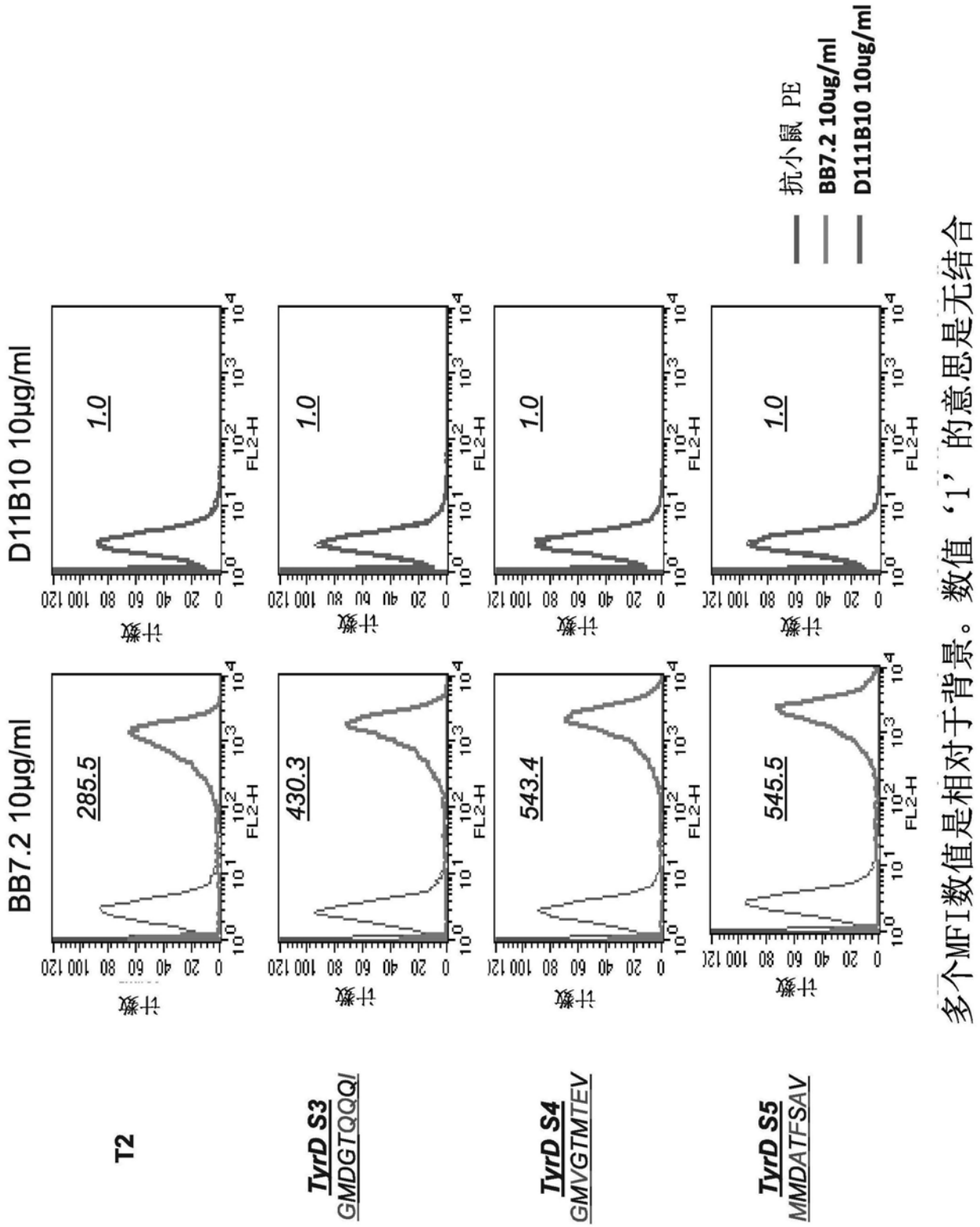

BB7.2 10μg/ml
D11B10 10μg/ml
抗小鼠 PE
BB7.2 10ug/ml
D111B10 10ug/ml
T2
TyrD S3
GMDGTQQQI
TyrD S4
GMVGTMTEV
TyrD S5
MMDATFSAV
285.5
430.3
543.4
545.5
1.0
计数
FL2-H
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图22

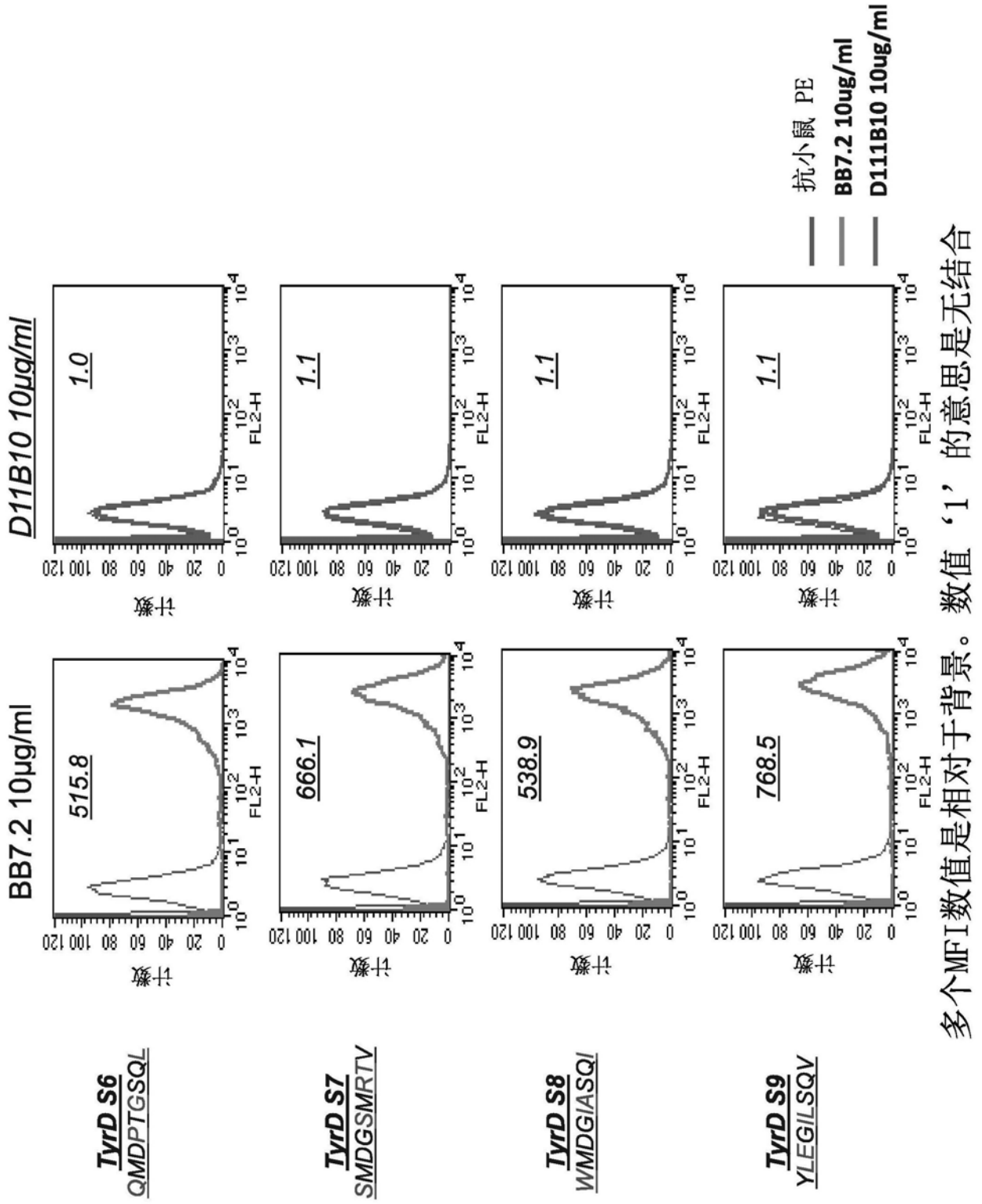

BB7.2 10μg/ml
D11B10 10μg/ml
TyrD S6
QMDPTGSQL
515.8
1.0
TyrD S7
SMDGSMRTV
666.1
1.1
TyrD S8
WMDGIASQI
538.9
1.1
TyrD S9
YLEGILSQV
768.5
1.1
计数
FL2-H
抗小鼠 PE
BB7.2 10ug/ml
D111B10 10ug/ml
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图22-续

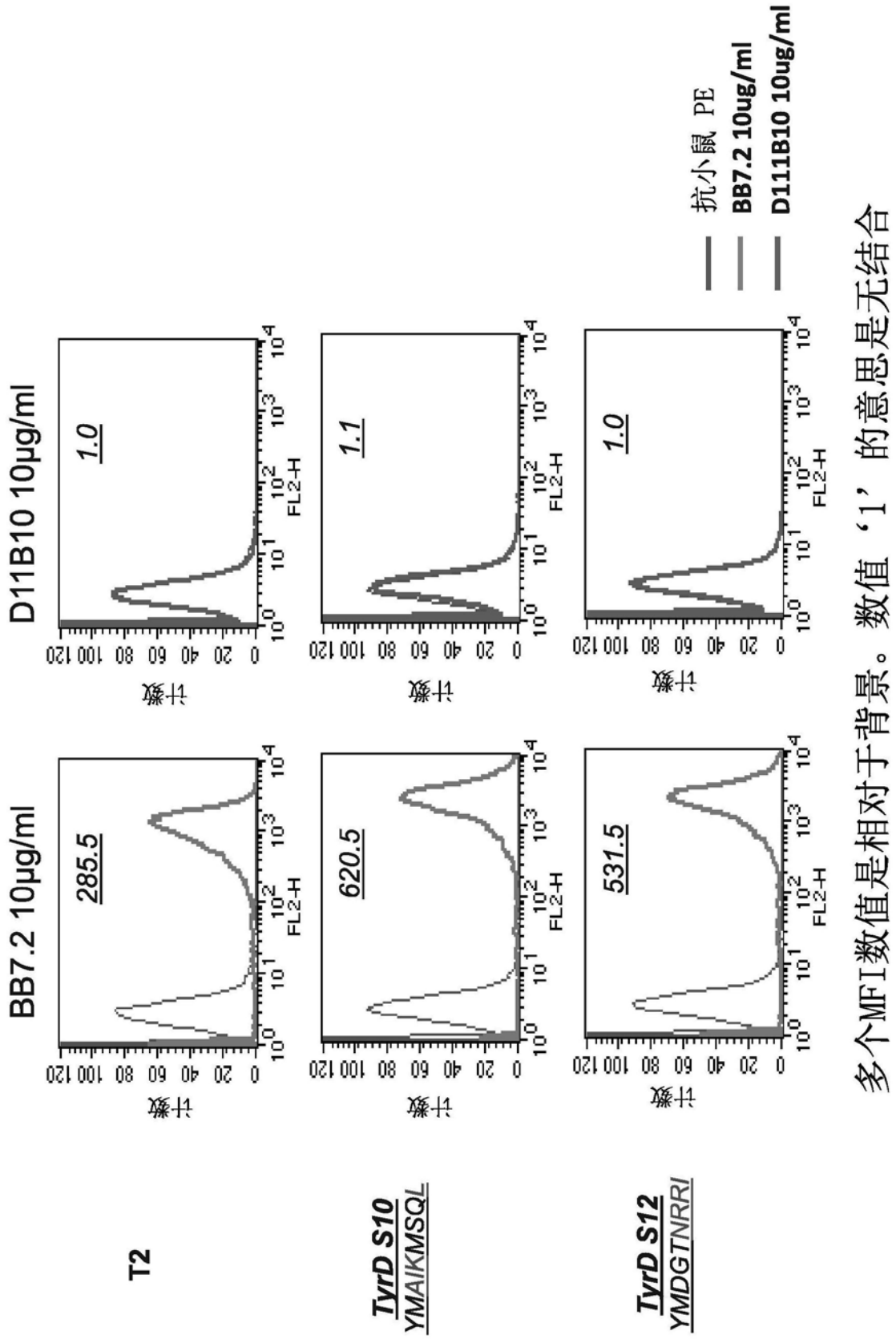

BB7.2 10μg/ml
D11B10 10μg/ml
285.5
1.0
620.5
1.1
531.5
1.0
计数
FL2-H
抗小鼠 PE
BB7.2 10ug/ml
D111B10 10ug/ml
T2
TyrD S10
YMAIKMSQL
TyrD S12
YMDGTNRRI
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图23

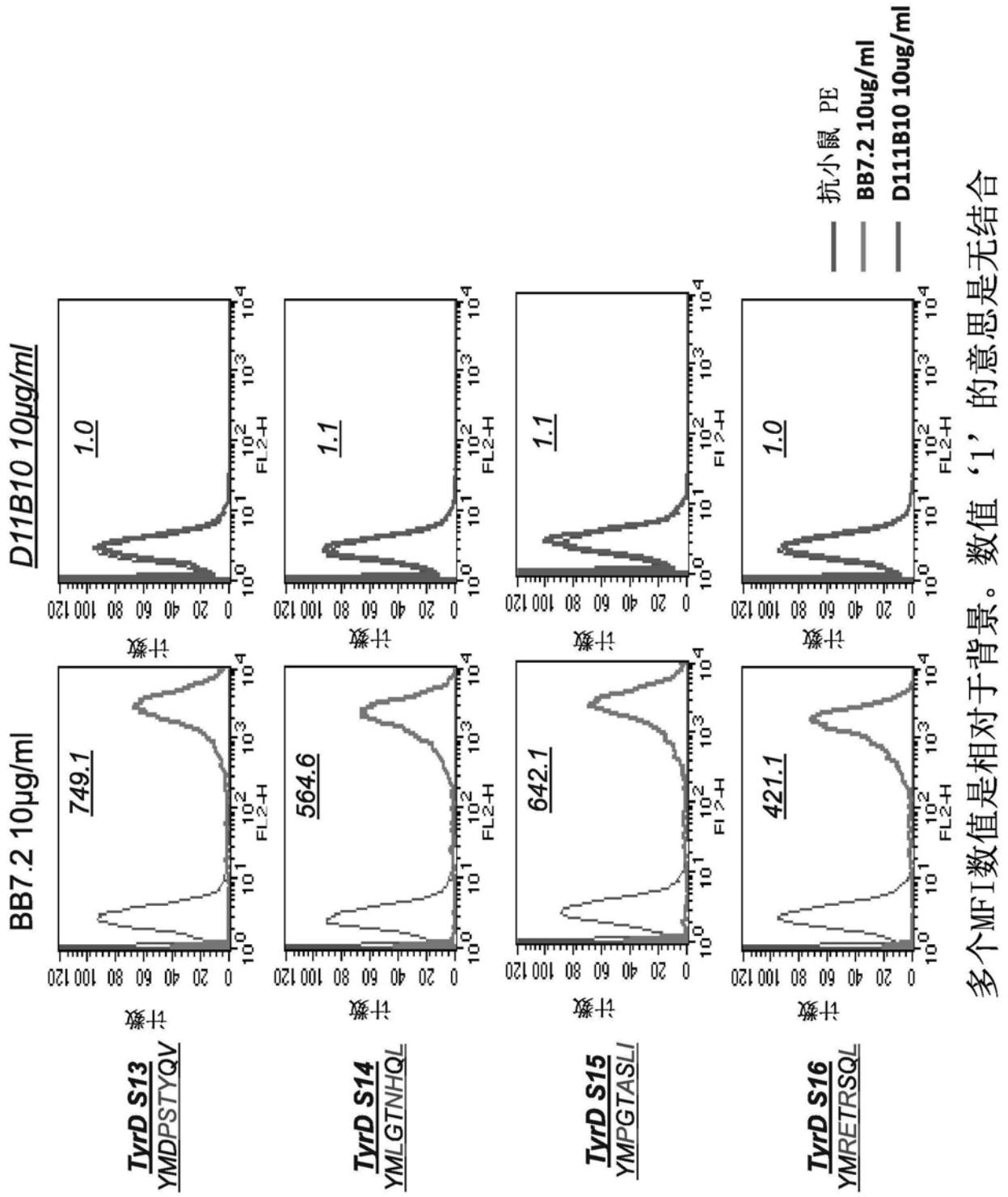

BB7.2 10μg/ml
D11B10 10μg/ml
TyrD S13
YMDPSTYQV
749.1
1.0
TyrD S14
YMLGTNHQL
564.6
1.1
TyrD S15
YMPGTASLI
642.1
1.1
TyrD S16
YMRETRSQL
421.1
1.0
计数
FL2-H
抗小鼠 PE
BB7.2 10ug/ml
D111B10 10ug/ml
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图23-续

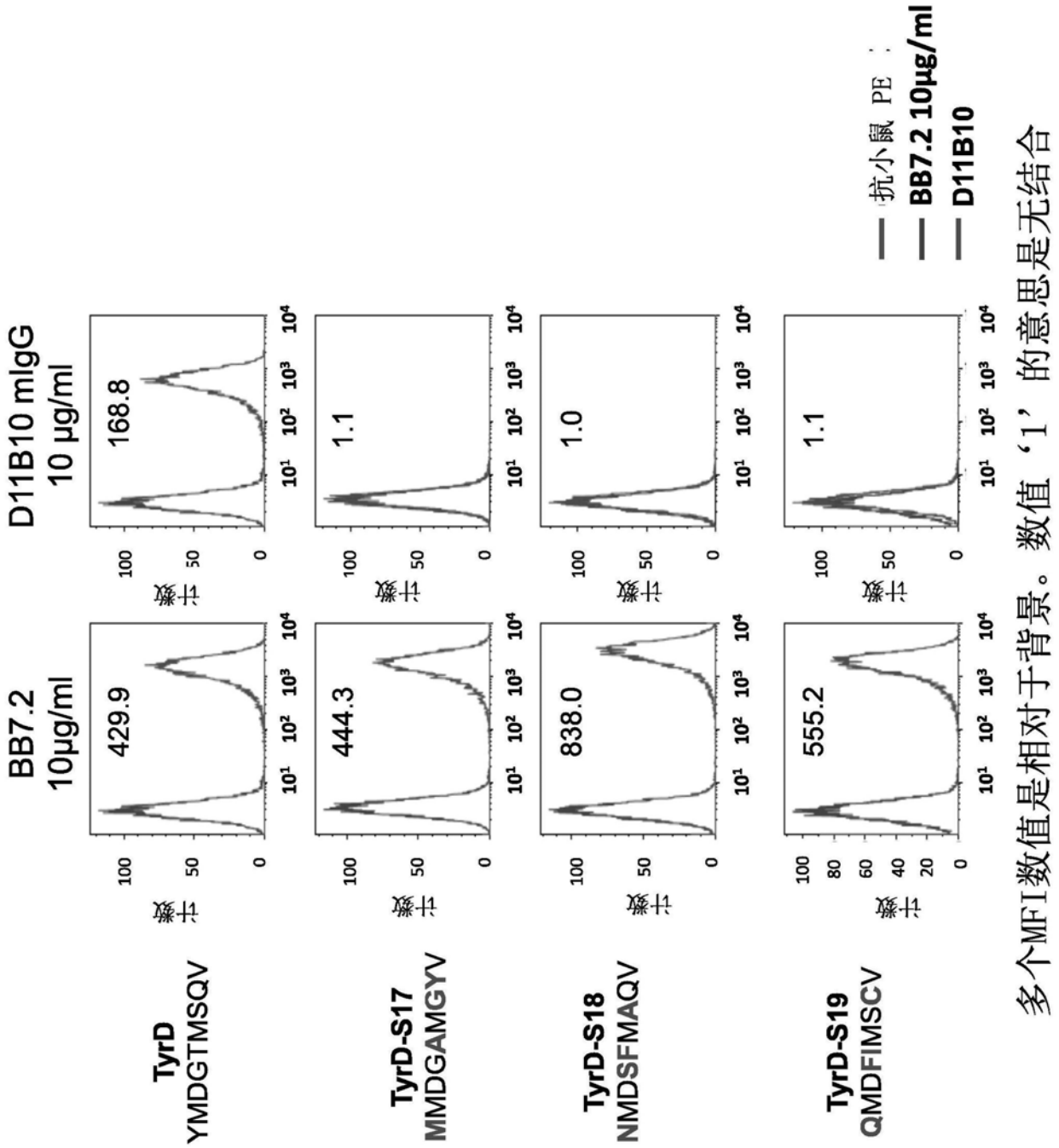

BB7.2
10μg/ml
D11B10 mIgG
10 μg/ml
TyrD
YMDGTMSQV
TyrD-S17
MMDGAMGYV
TyrD-S18
NMDSFMAQV
TyrD-S19
QMDFIMSCV
429.9
168.8
444.3
1.1
838.0
1.0
555.2
1.1
计数
抗小鼠 PE
BB7.2 10μg/ml
D11B10
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图24

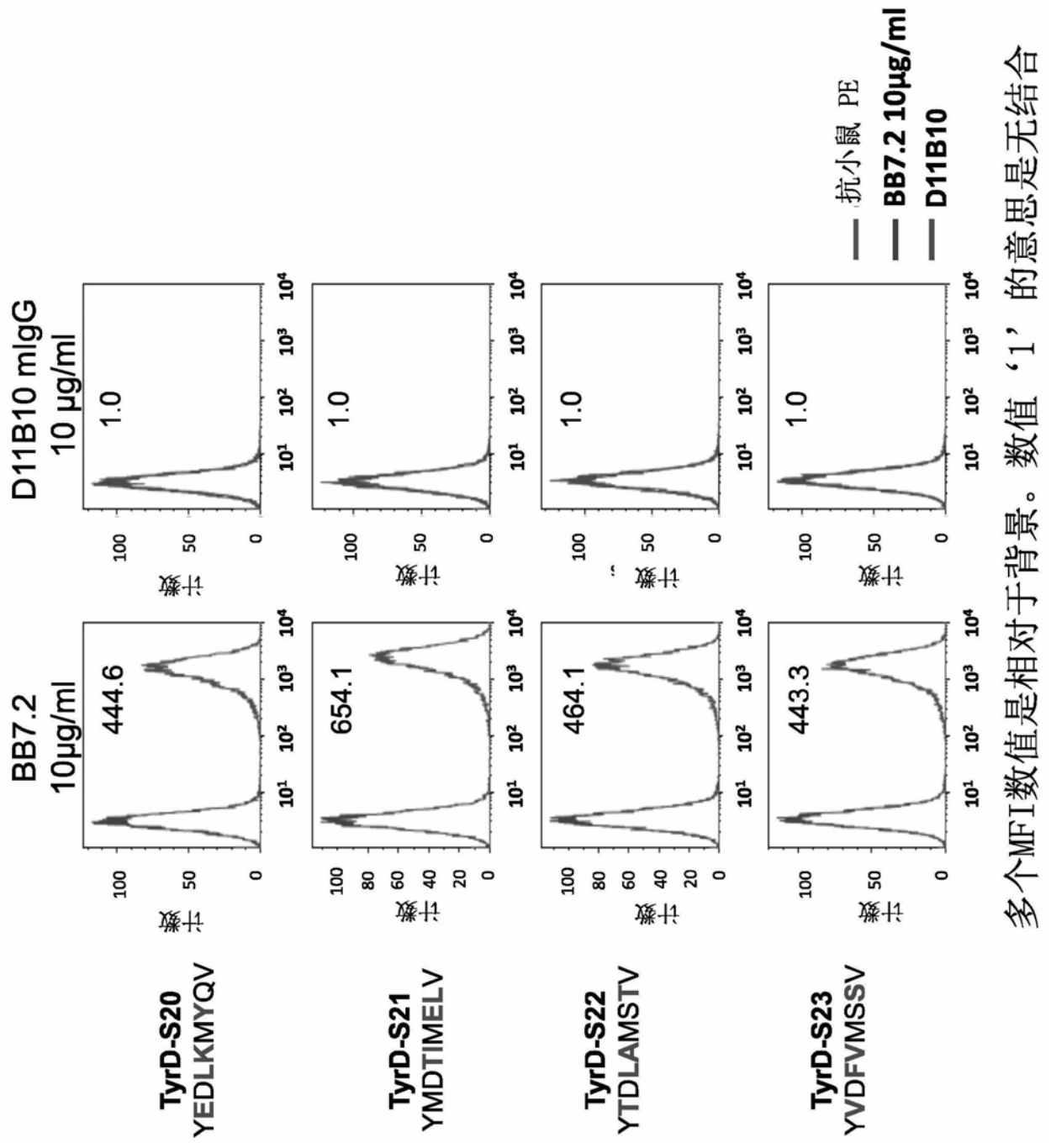

BB7.2
10μg/ml
D11B10 mIgG
10 μg/ml
TyrD-S20
YEDLKMYQV
TyrD-S21
YMDTIMELV
TyrD-S22
YTDLAMSTV
TyrD-S23
YVDFVMSSV
444.6
1.0
654.1
1.0
464.1
1.0
443.3
1.0
计数
抗小鼠 PE
BB7.2 10μg/ml
D11B10
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图24-续

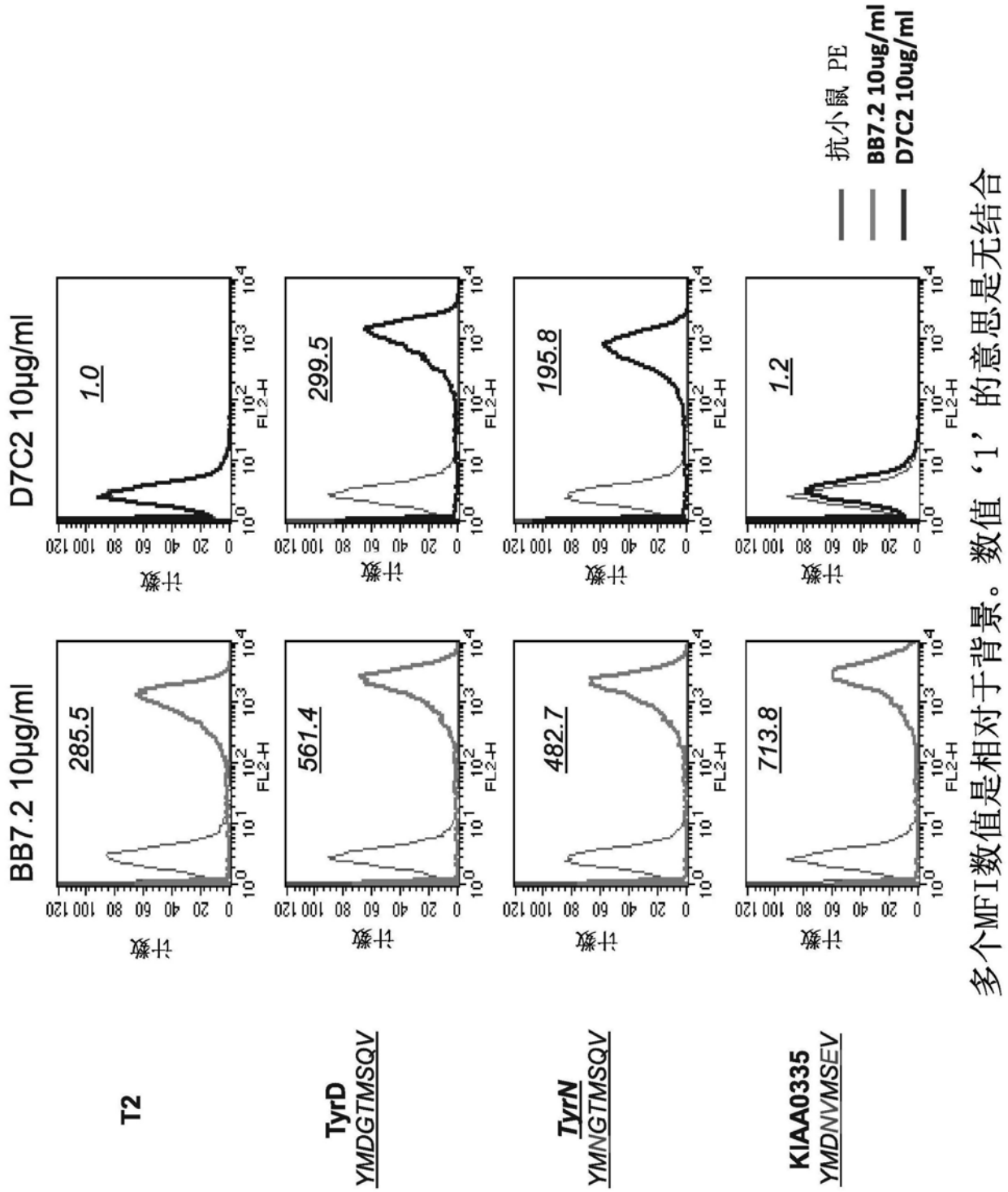

BB7.2 10μg/ml
D7C2 10μg/ml
T2
TyrD
YMDGTMSQV
TyrN
YMNGTMSQV
KIAA0335
YMDNVMSEV
285.5
561.4
482.7
713.8
1.0
299.5
195.8
1.2
计数
FL2-H
抗小鼠 PE
BB7.2 10ug/ml
D7C2 10ug/ml
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图25

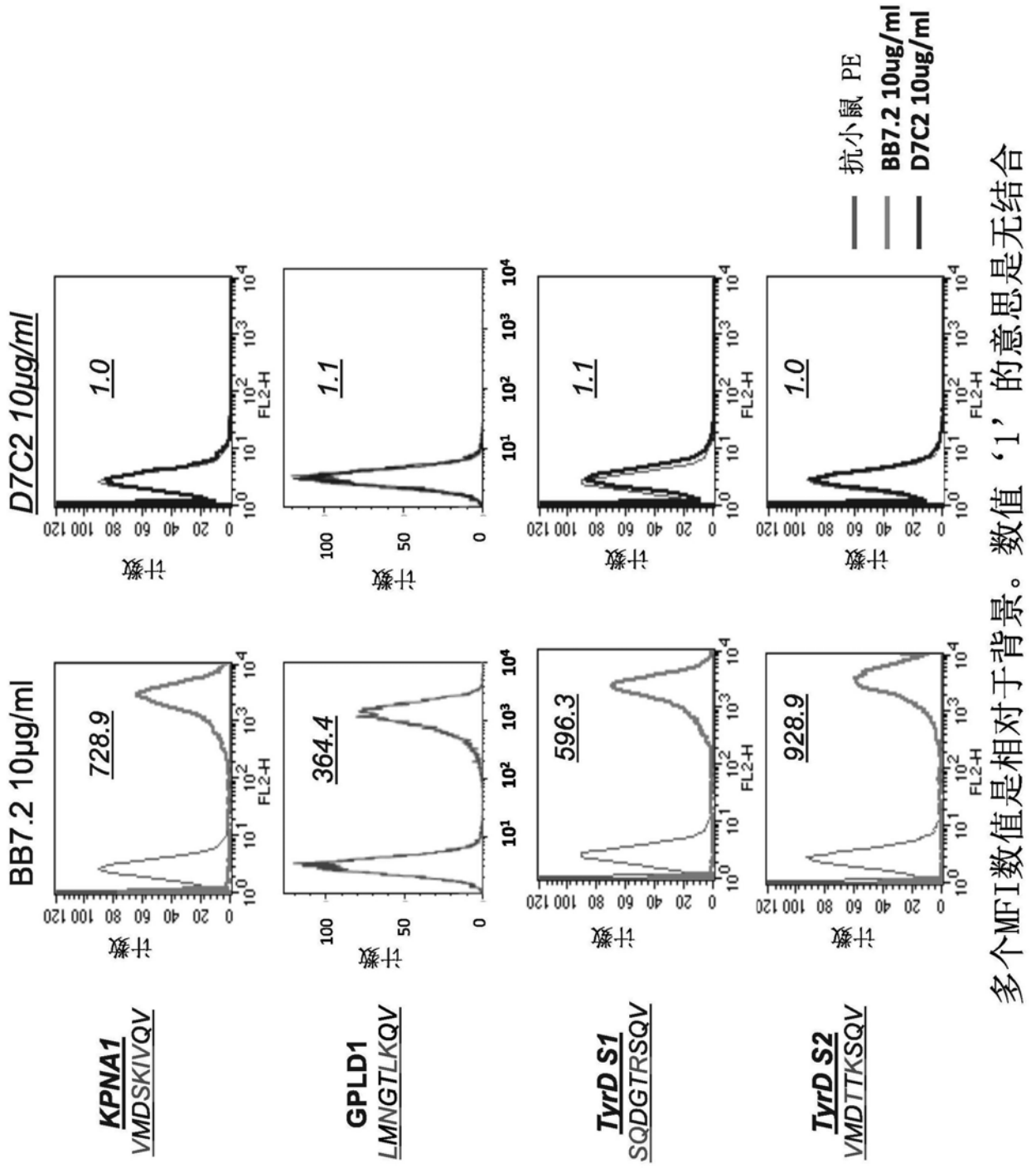

KPNA1
VMDSKIVQV
GPLD1
LMNGTLKQV
TyrD S1
SQDGTRSQV
TyrD S2
VMDTTKSQV
BB7.2 10μg/ml
D7C2 10μg/ml
728.9
364.4
596.3
928.9
1.0
1.1
1.1
1.0
计数
FL2-H
抗小鼠 PE
BB7.2 10ug/ml
D7C2 10ug/ml
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图25-续

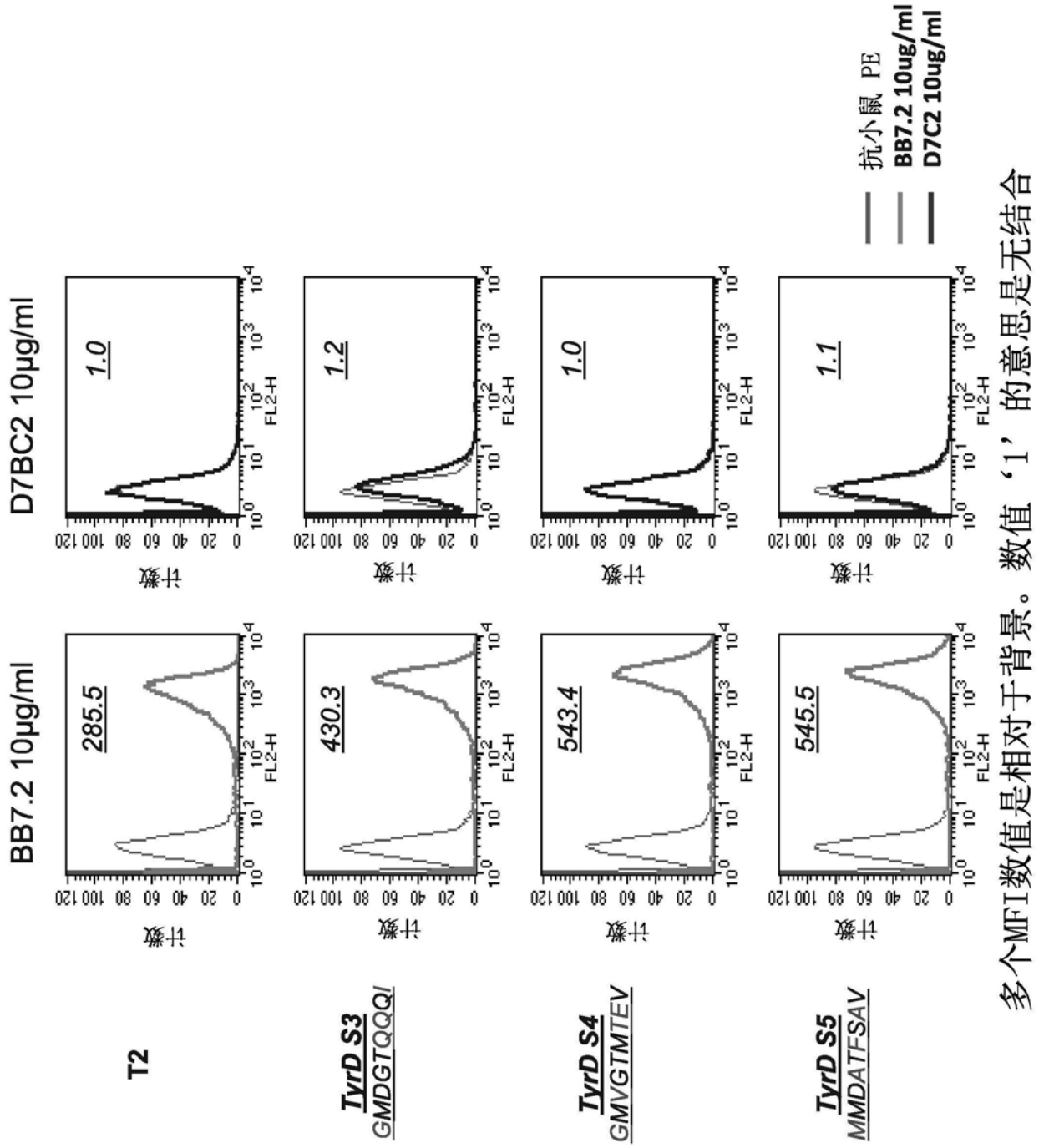

BB7.2 10μg/ml
D7BC2 10μg/ml
T2
TyrD S3
GMDGTQQQI
TyrD S4
GMVGTMTEV
TyrD S5
MMDATFSAV
285.5
430.3
543.4
545.5
1.0
1.2
1.0
1.1
计数
FL2-H
抗小鼠 PE
BB7.2 10ug/ml
D7C2 10ug/ml
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图26

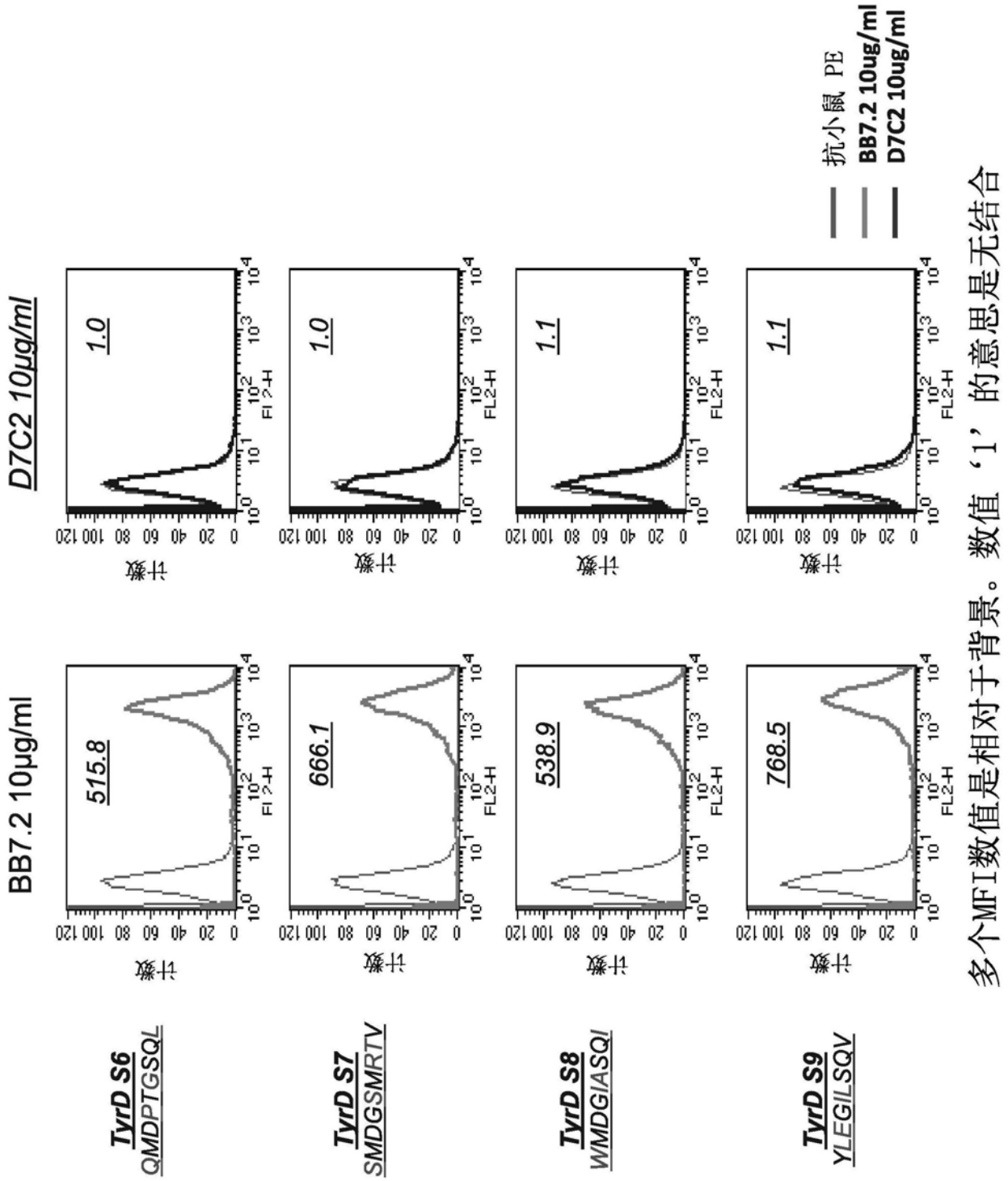

BB7.2 10μg/ml
D7C2 10μg/ml
TyrD S6
QMDPTGSQL
TyrD S7
SMDGSMRTV
TyrD S8
WMDGIASQI
TyrD S9
YLEGILSQV
515.8
1.0
666.1
1.0
538.9
1.1
768.5
1.1
计数
FL2-H
抗小鼠 PE
BB7.2 10ug/ml
D7C2 10ug/ml
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图26-续

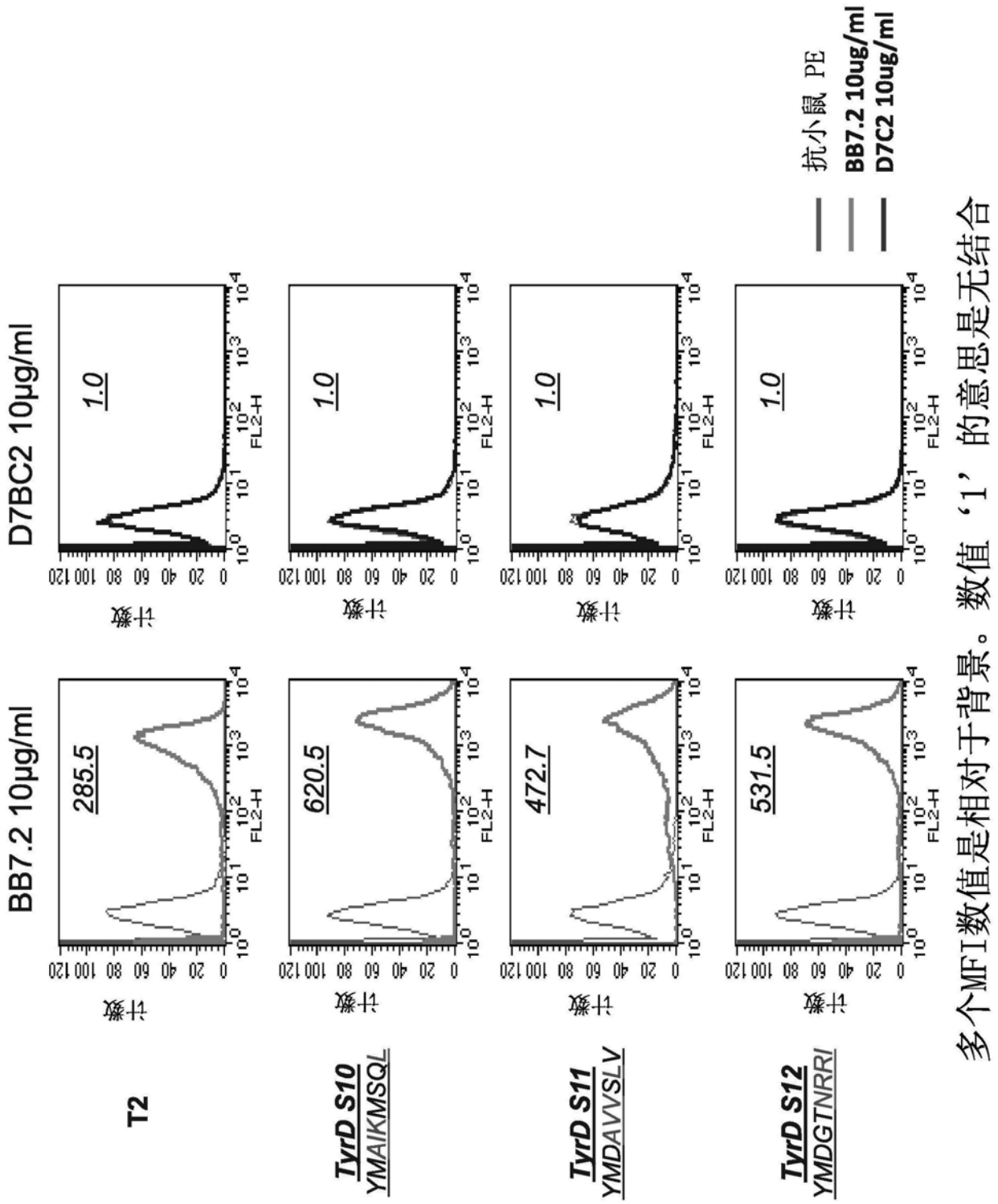

BB7.2 10μg/ml
D7BC2 10μg/ml
T2
TyrD S10
YMAIKMSQL
TyrD S11
YMDAVVSLV
TyrD S12
YMDGTNRRI
285.5
620.5
472.7
531.5
1.0
计数
FL2-H
抗小鼠 PE
BB7.2 10ug/ml
D7C2 10ug/ml
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图27

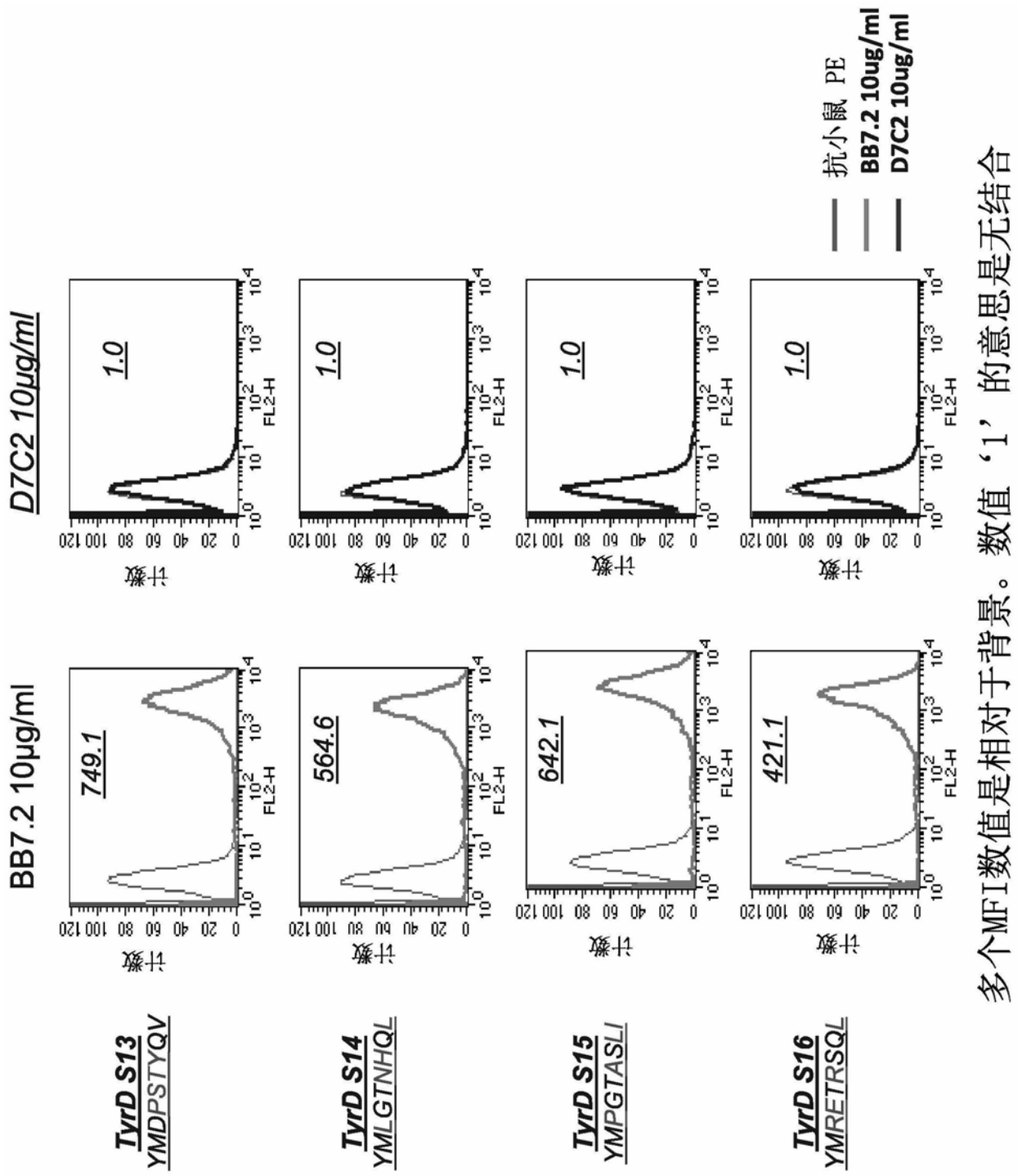

BB7.2 10μg/ml
D7C2 10μg/ml
TyrD S13
YMDPSTYQV
749.1
1.0
TyrD S14
YMLGTNHQL
564.6
1.0
TyrD S15
YMPGTASLI
642.1
1.0
TyrD S16
YMRETRSQL
421.1
1.0
计数
FL2-H
抗小鼠 PE
BB7.2 10ug/ml
D7C2 10ug/ml
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图27-续

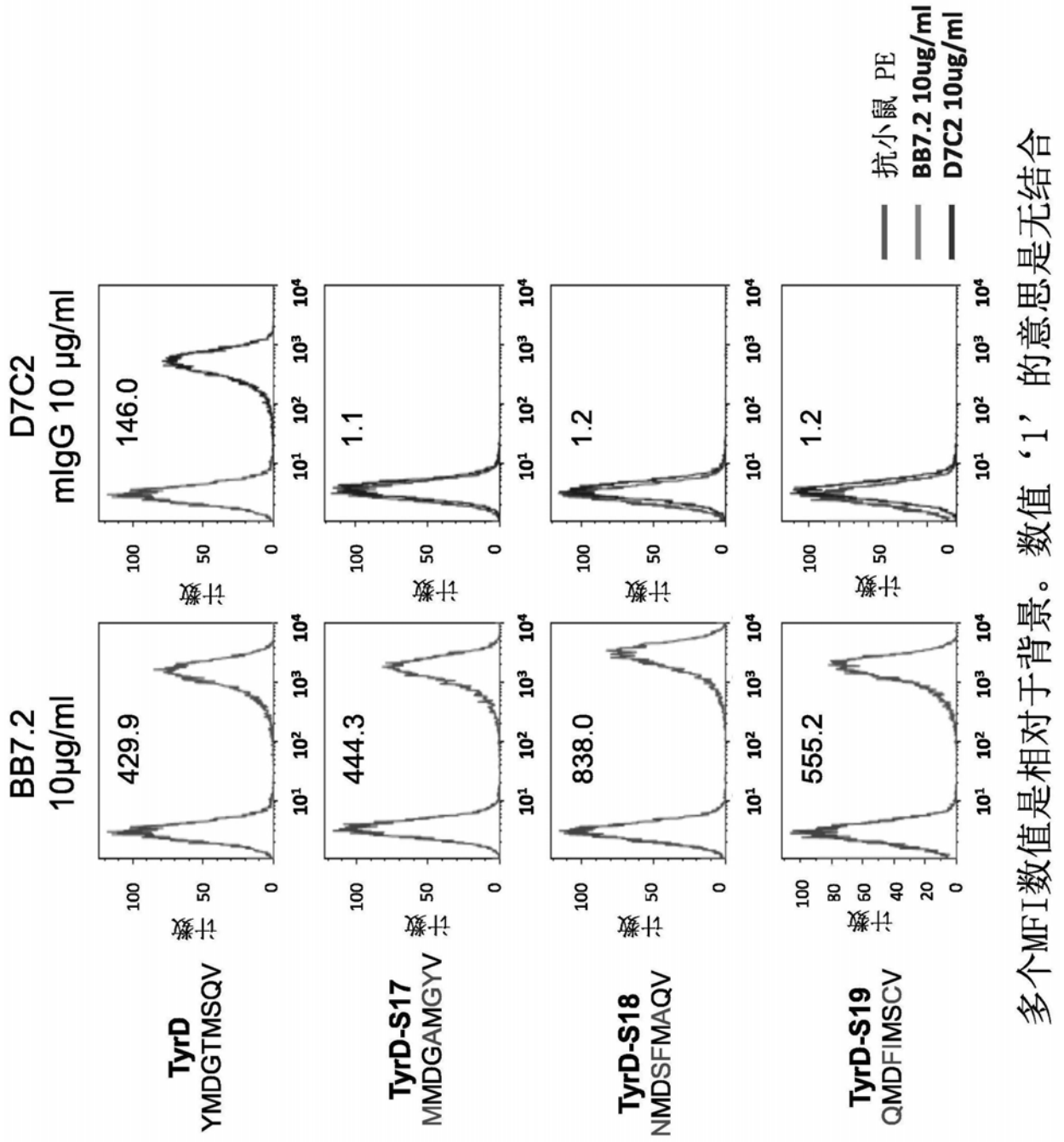

BB7.2
10μg/ml
D7C2
mIgG 10 μg/ml
TyrD
YMDGTMSQV
429.9
146.0
TyrD-S17
MMDGAMGYV
444.3
1.1
TyrD-S18
NMDSFMAQV
838.0
1.2
TyrD-S19
QMDFIMSCV
555.2
1.2
计数
抗小鼠 PE
BB7.2 10ug/ml
D7C2 10ug/ml
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图28

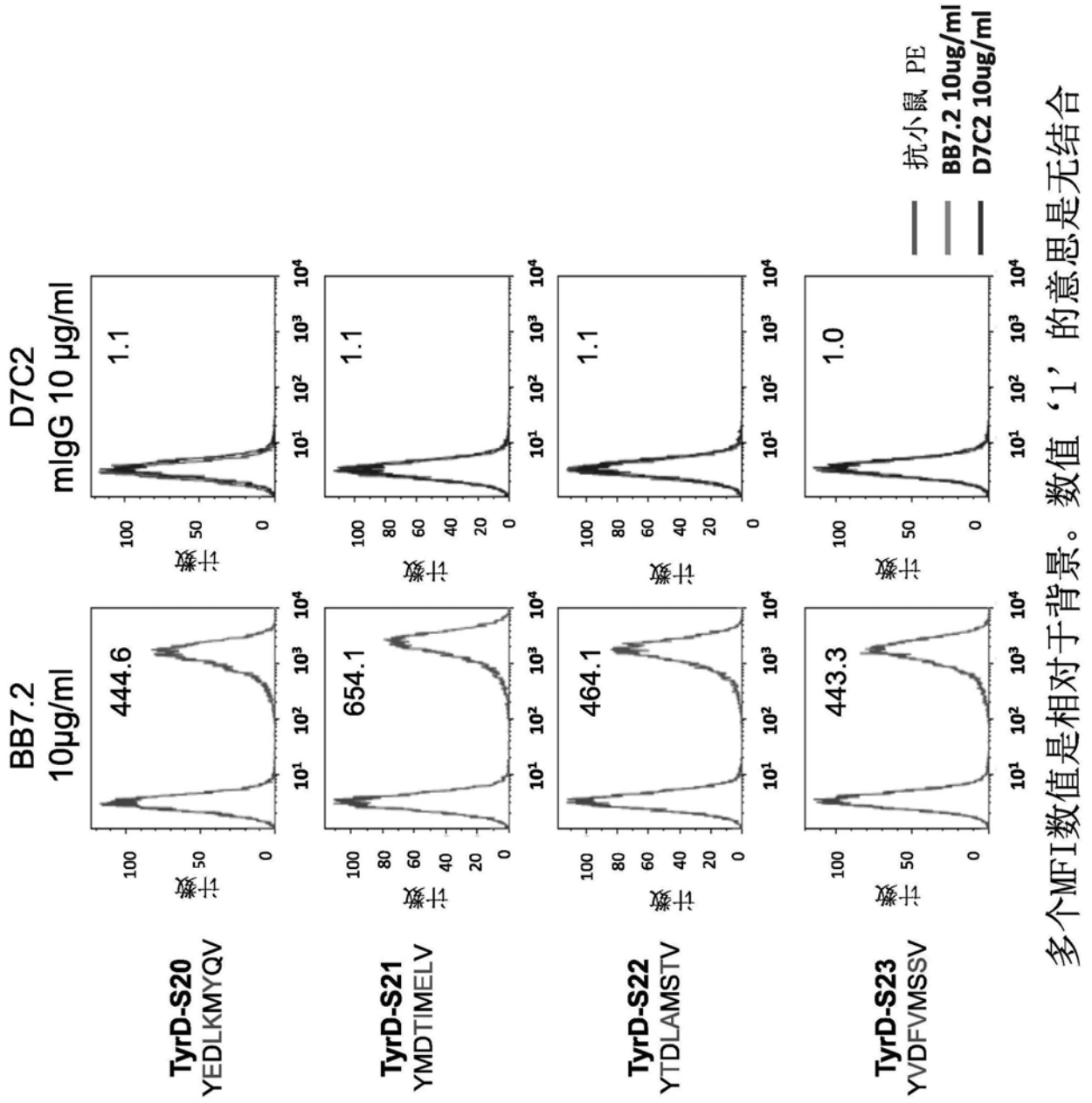

BB7.2
10μg/ml
D7C2
mIgG 10 μg/ml
TyrD-S20
YEDLKMYQV
TyrD-S21
YMDTIMELV
TyrD-S22
YTDLAMSTV
TyrD-S23
YVDFVMSSV
444.6
1.1
654.1
1.1
464.1
1.1
443.3
1.0
计数
抗小鼠 PE
BB7.2 10ug/ml
D7C2 10ug/ml
多个MFI数值是相对于背景。数值‘1’的意思是无结合

图28-续

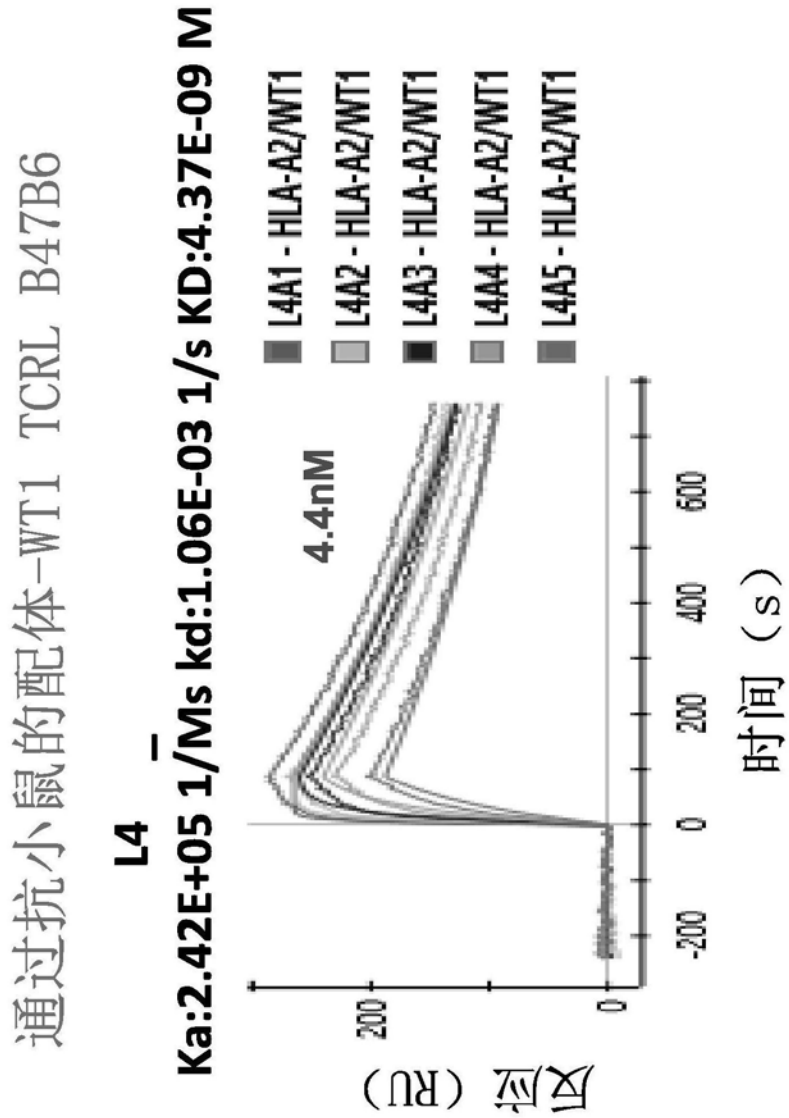
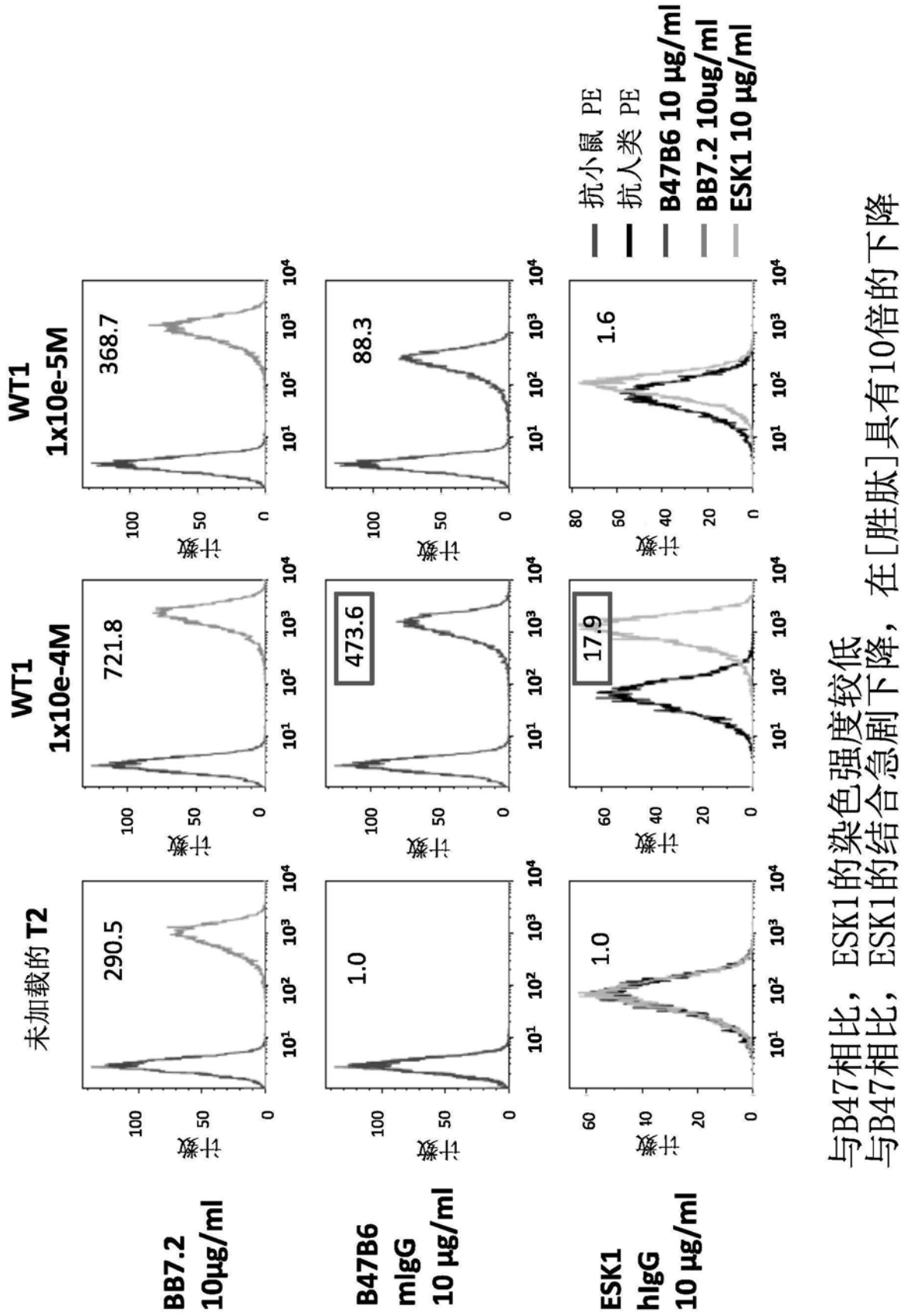

通过抗小鼠的配体-WT1 TCRL B47B6
L4
Ka:2.42E+05 1/Ms kd:1.06E-03 1/s KD:4.37E-09 M
4.4nM
L4A1 - HLA-A2/WT1
L4A2 - HLA-A2/WT1
L4A3 - HLA-A2/WT1
L4A4 - HLA-A2/WT1
L4A5 - HLA-A2/WT1
反应（RU）
200
0
-200
0
200
400
600
时间（s）

图29



与B47相比，ESK1的染色强度较低
与B47相比，ESK1的结合急剧下降，在[胜肽]具有10倍的下降

图30

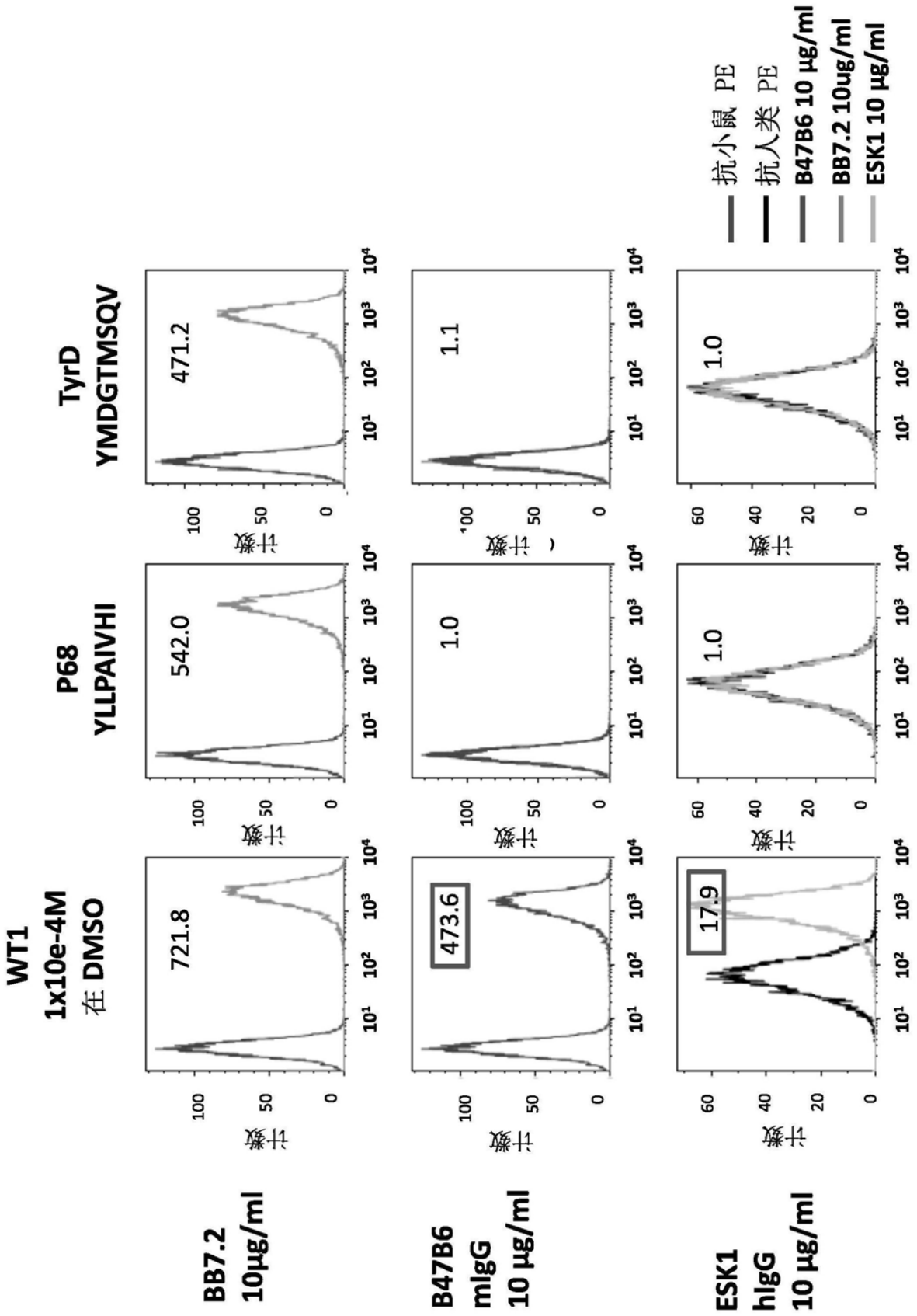

WT1
1x10e-4M
在 DMSO
P68
YLLPAIVHI
TyrD
YMDGTMSQV
BB7.2
10μg/ml
B47B6
mIgG
10 μg/ml
ESK1
hIgG
10 μg/ml
721.8
542.0
471.2
473.6
1.0
1.1
17.9
1.0
1.0
1.0
计数
抗小鼠 PE
抗人类 PE
B47B6 10 μg/ml
BB7.2 10ug/ml
ESK1 10 μg/ml

图31

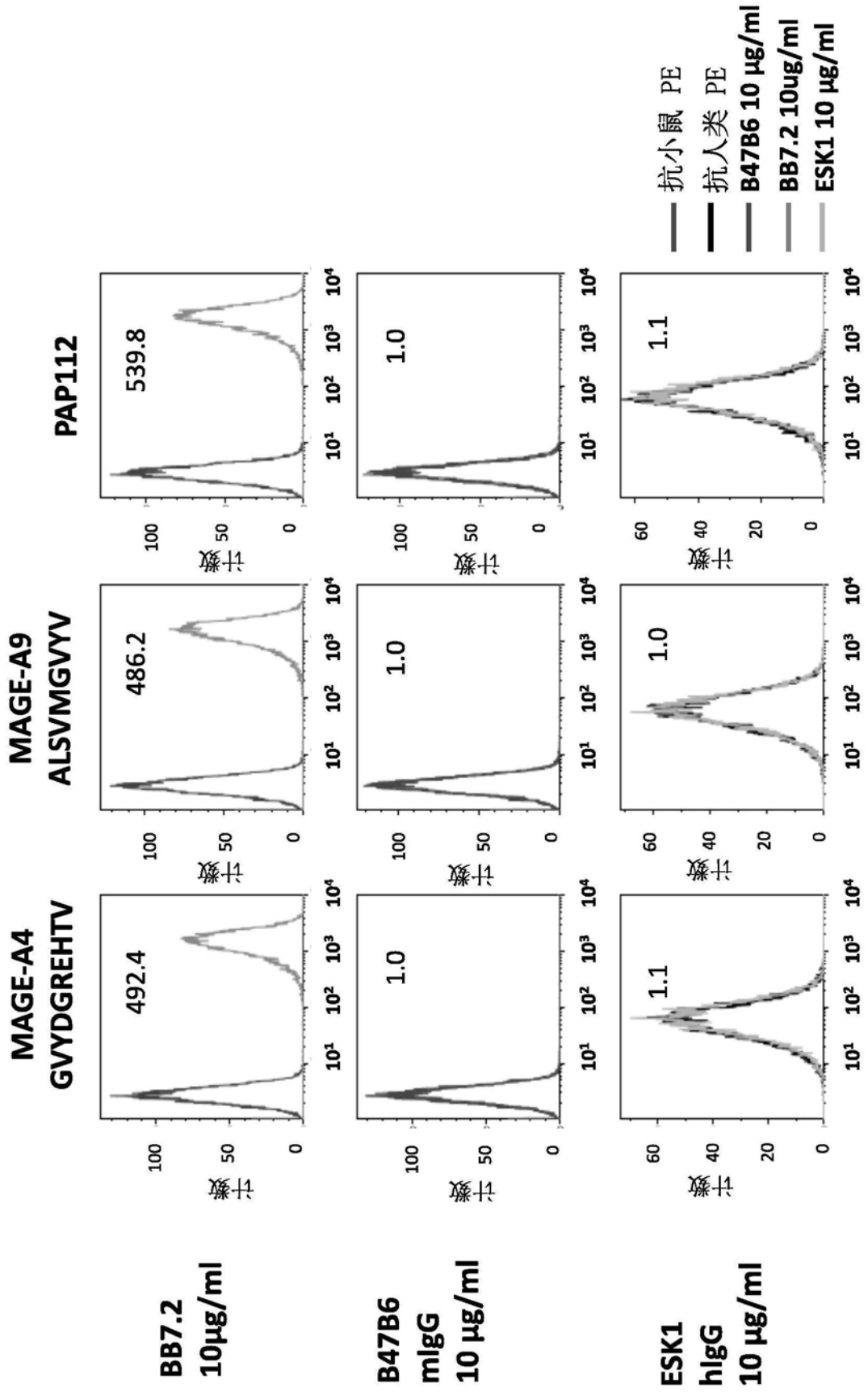

MAGE-A4
GVYDGREHTV
MAGE-A9
ALSVMGVYV
PAP112
492.4
486.2
539.8
1.0
1.0
1.0
1.1
1.0
1.1
计数
BB7.2
10μg/ml
B47B6
mIgG
10 μg/ml
ESK1
hIgG
10 μg/ml
抗小鼠 PE
抗人类 PE
B47B6 10 μg/ml
BB7.2 10ug/ml
ESK1 10 μg/ml

图31-续

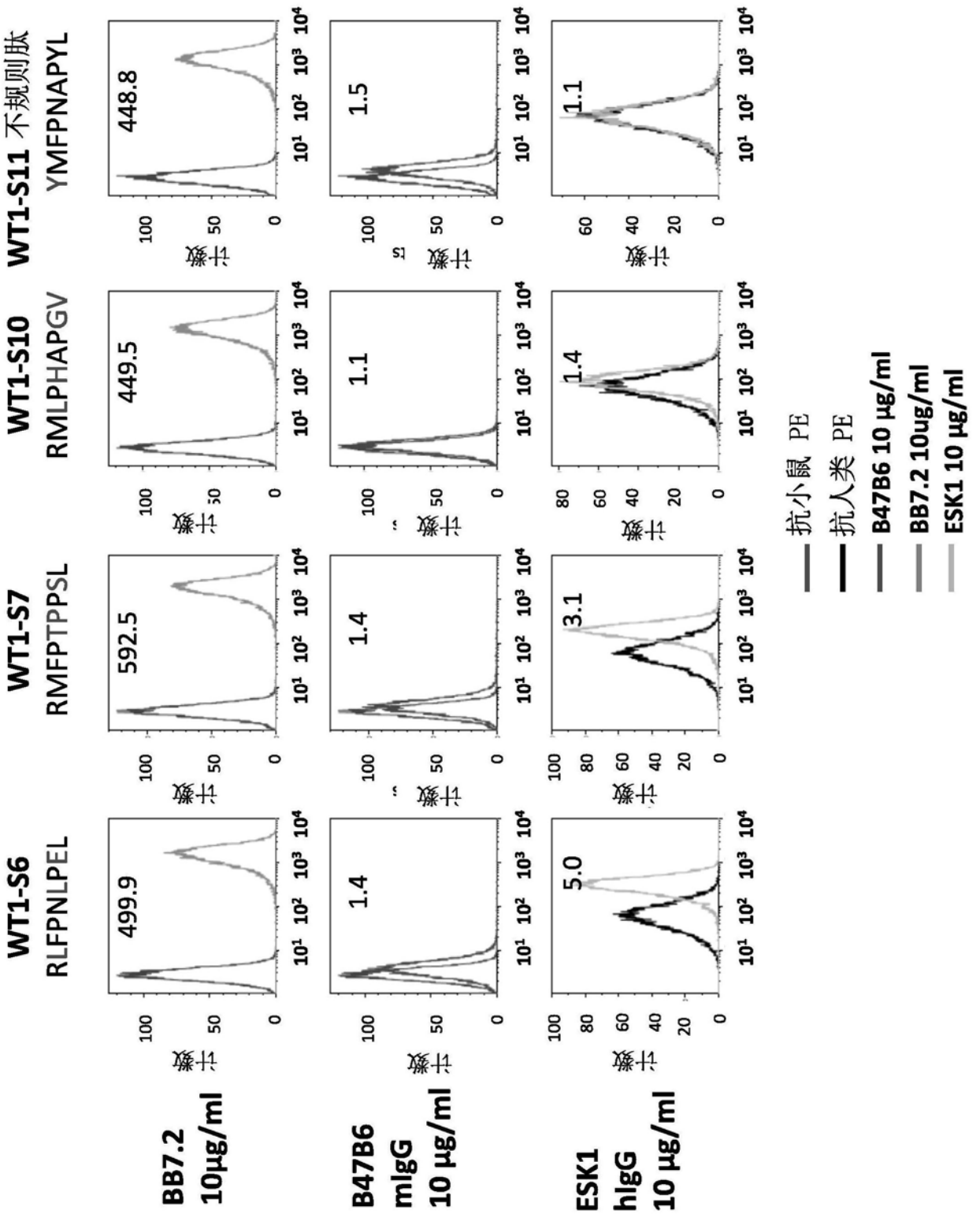

WT1-S6
RLFPNLPEL
WT1-S7
RMFPTPPSL
WT1-S10
RMLPHAPGV
WT1-S11 不规则肽
YMFPNAPYL
BB7.2
10μg/ml
B47B6
mIgG
10 μg/ml
ESK1
hIgG
10 μg/ml
499.9
592.5
449.5
448.8
1.4
1.4
1.1
1.5
5.0
3.1
1.4
1.1
计数
抗小鼠 PE
抗人类 PE
B47B6 10 μg/ml
BB7.2 10ug/ml
ESK1 10 μg/ml

图32

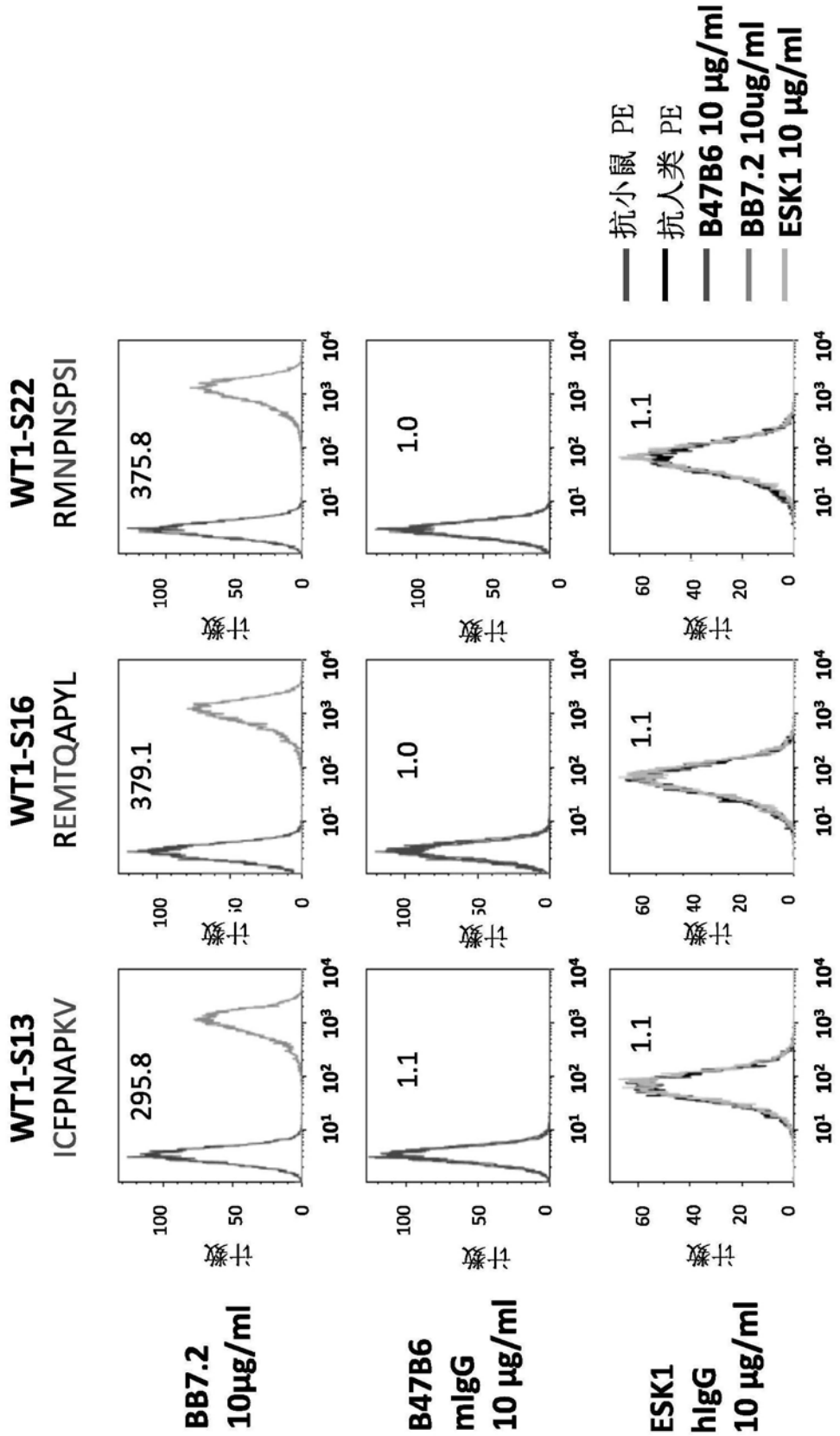

WT1-S13
ICFPNAPKV
WT1-S16
REMTQAPYL
WT1-S22
RMNPNSPSI
295.8
379.1
375.8
1.1
1.0
1.0
1.1
1.1
1.1
计数
BB7.2
10μg/ml
B47B6
mIgG
10 μg/ml
ESK1
hIgG
10 μg/ml
抗小鼠 PE
抗人类 PE
B47B6 10 μg/ml
BB7.2 10ug/ml
ESK1 10 μg/ml

图32-续

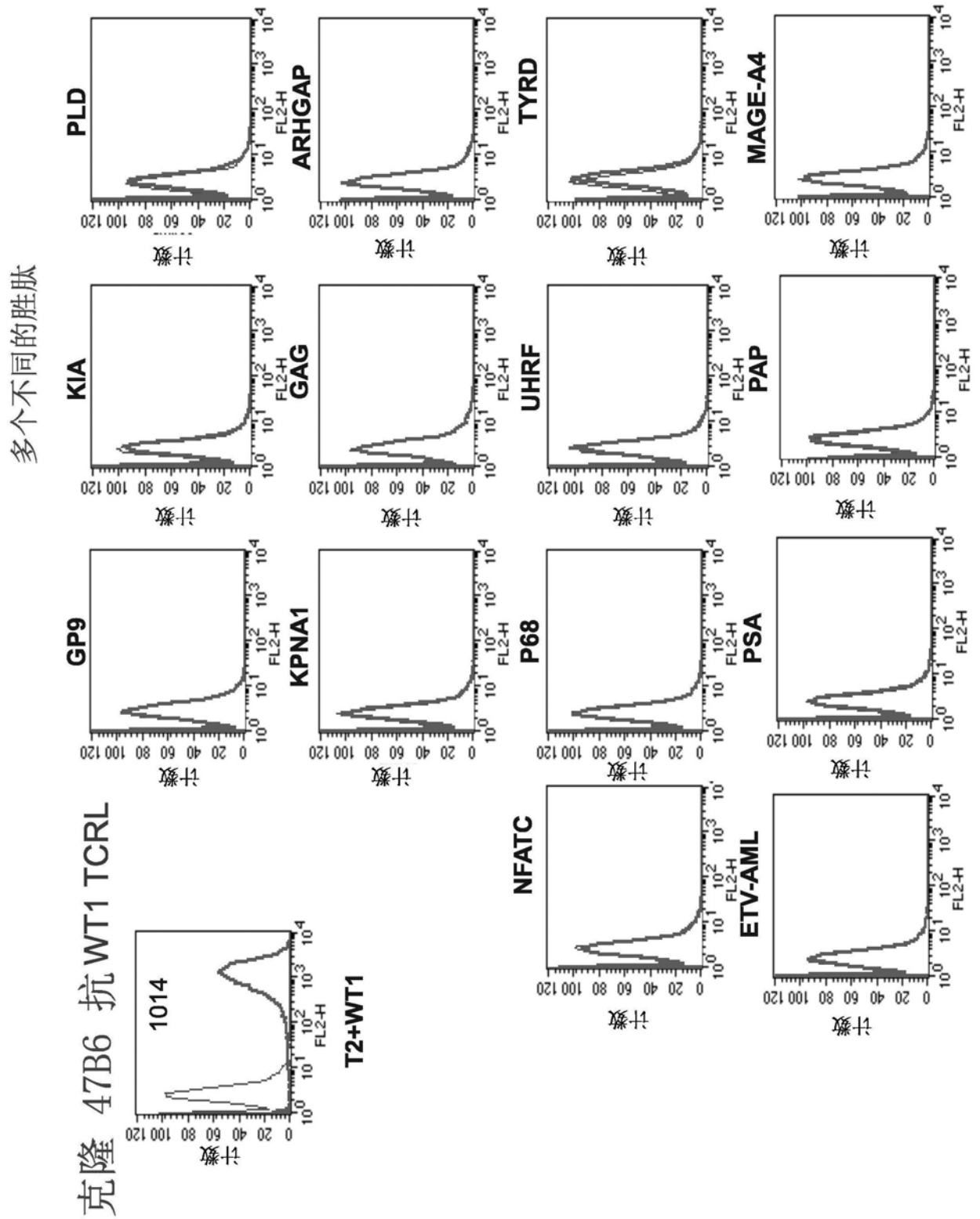
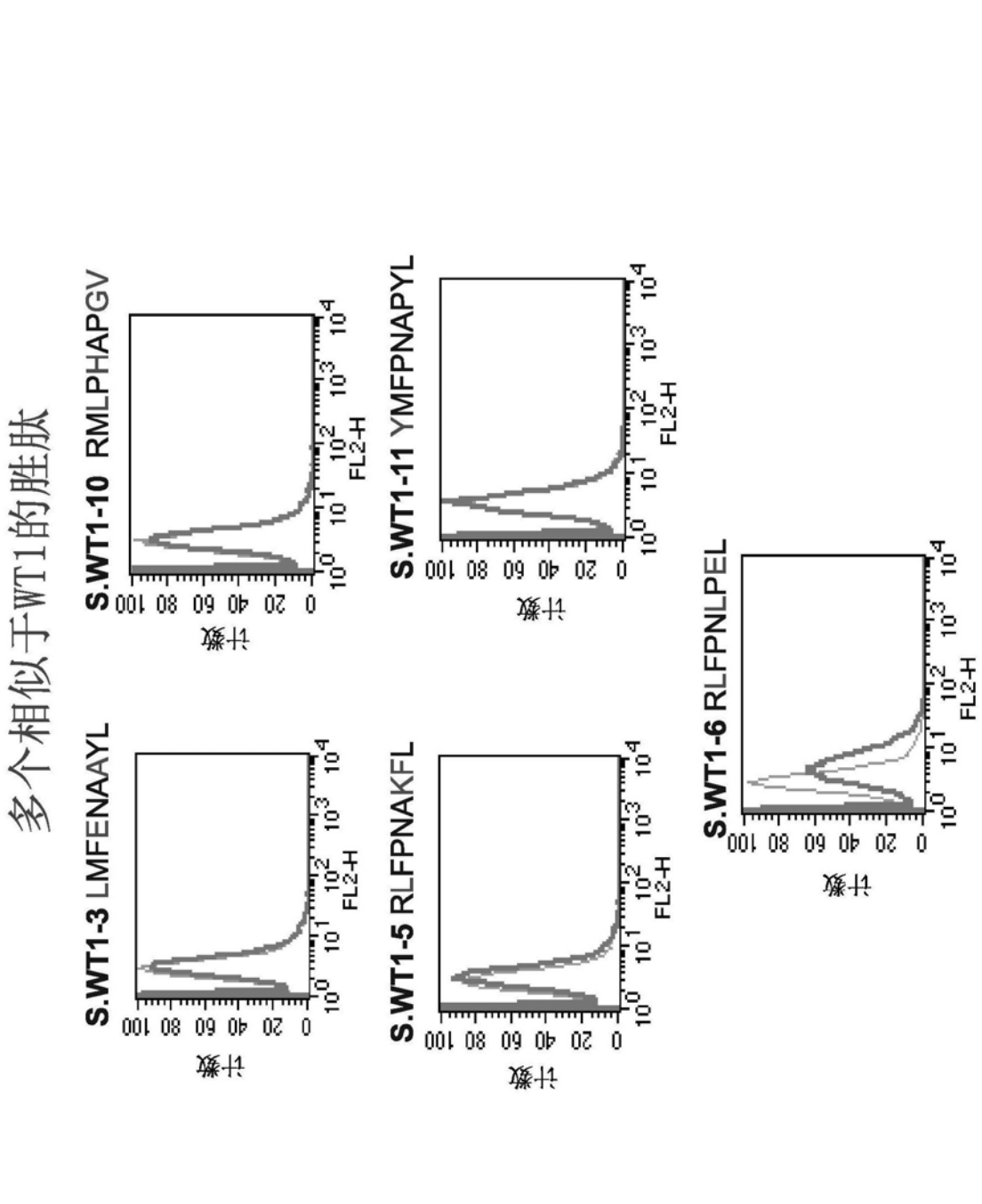

克隆 47B6 抗WT1 TCRL
多个不同的胜肽
1014
T2+WT1
GP9
KIA
PLD
KPNA1
GAG
ARHGAP
P68
UHRF
TYRD
PSA
PAP
MAGE-A4
NFATC
ETV-AML
计数
FL2-H

图33



抗WT1 TCRL仅结合多个加有WT1的细胞，它不结合其它的胜肽（14个不同的胜肽5个相似的胜肽被分析）

图33-续

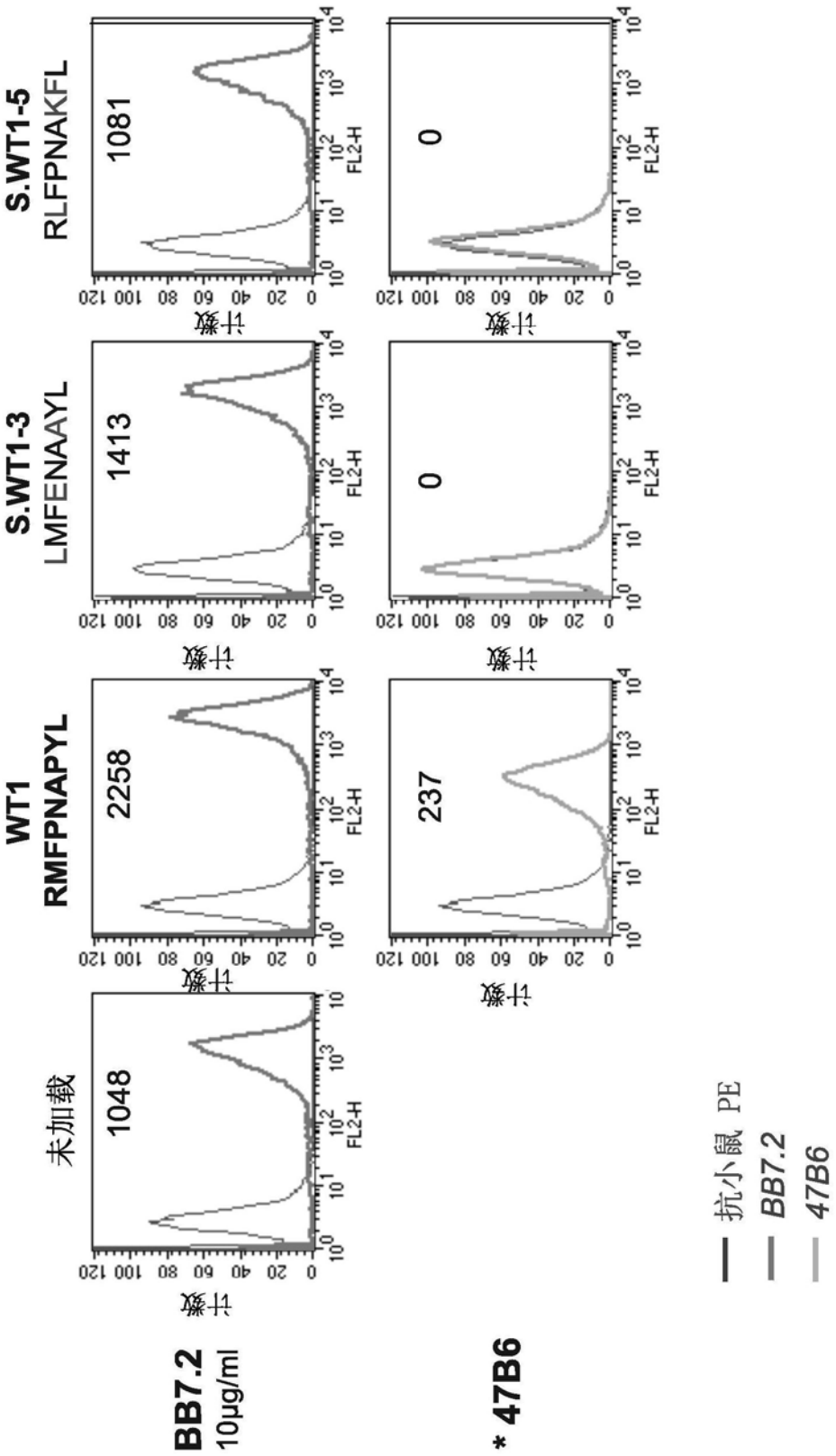

未加载
WT1
RMFPNAPYL
S.WT1-3
LMFENAAYL
S.WT1-5
RLFPNAKFL
1048
2258
1413
1081
237
0
0
计数
FL2-H
BB7.2
10μg/ml
* 47B6
抗小鼠 PE
BB7.2
47B6

图34

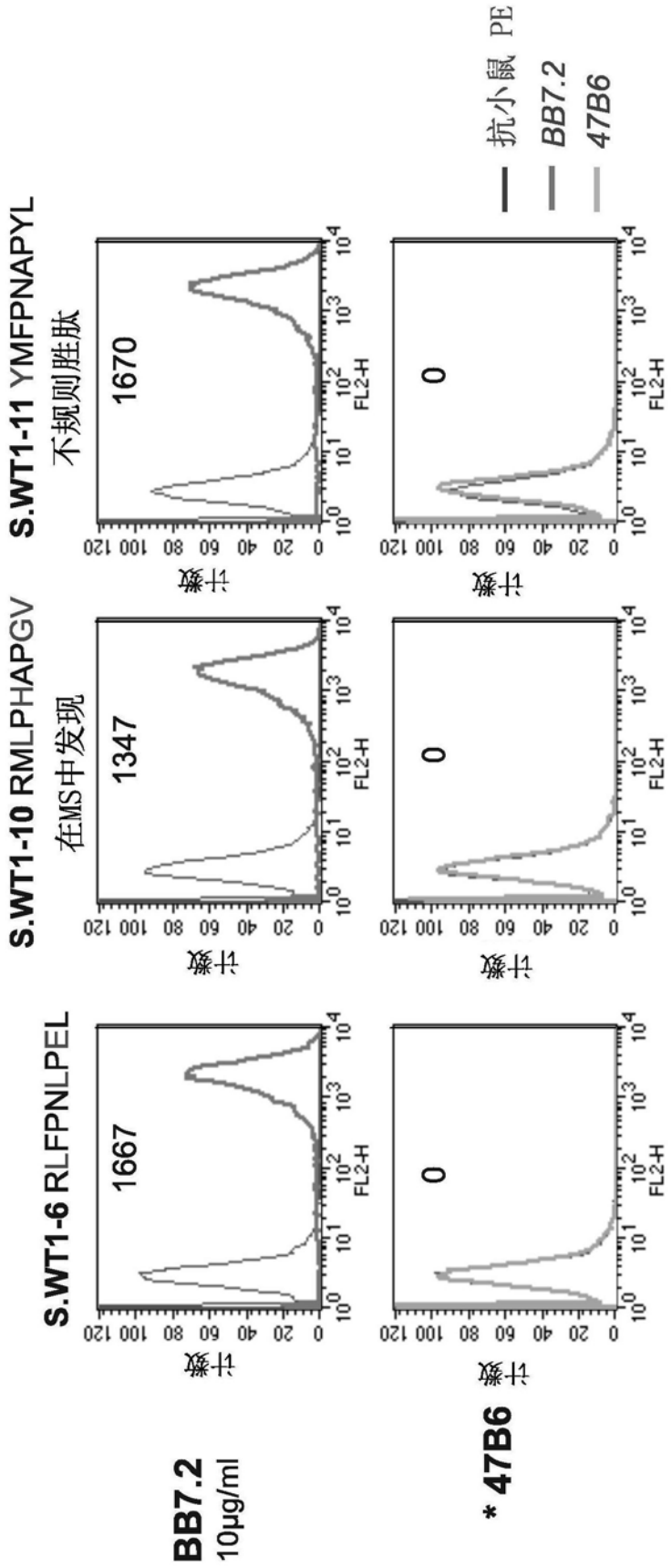

S.WT1-6 RLFPNLPEL
S.WT1-10 RMLPHAPGV
在MS中发现
S.WT1-11 YMFPNAPYL
不规则胜肽
1667
1347
1670
0
0
0
计数
FL2-H
BB7.2
10μg/ml
* 47B6
抗小鼠 PE
BB7.2
47B6

图34-续

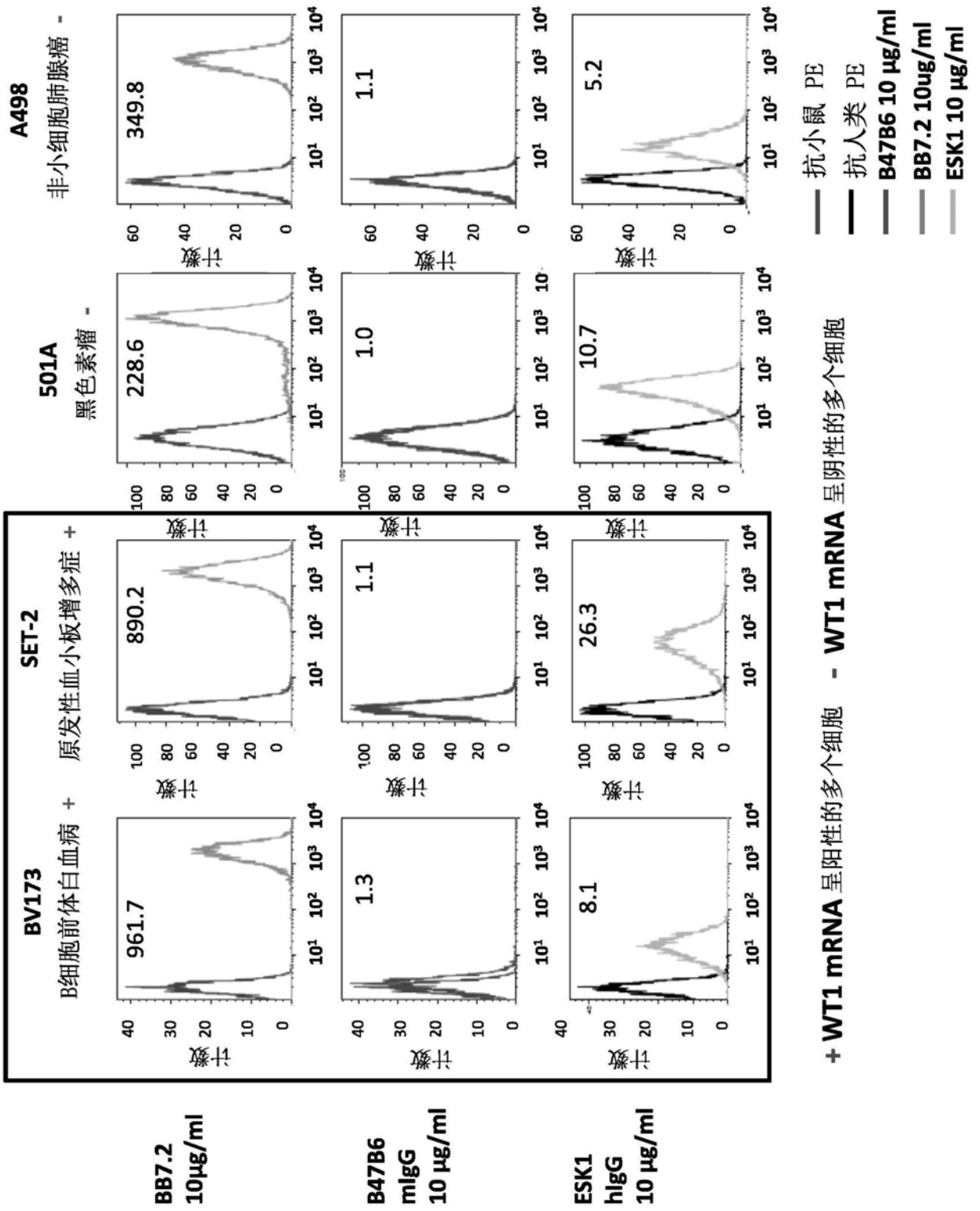

BV173
B细胞前体白血病 +
961.7
1.3
8.1
SET-2
原发性血小板增多症 +
890.2
1.1
26.3
501A
黑色素瘤 -
228.6
1.0
10.7
A498
非小细胞肺腺癌 -
349.8
1.1
5.2
计数
抗小鼠 PE
抗人类 PE
B47B6 10 μg/ml
BB7.2 10ug/ml
ESK1 10 μg/ml
+ WT1 mRNA 呈阳性的多个细胞
- WT1 mRNA 呈阴性的多个细胞
BB7.2 10μg/ml
B47B6 mIgG 10 μg/ml
ESK1 hIgG 10 μg/ml

图35

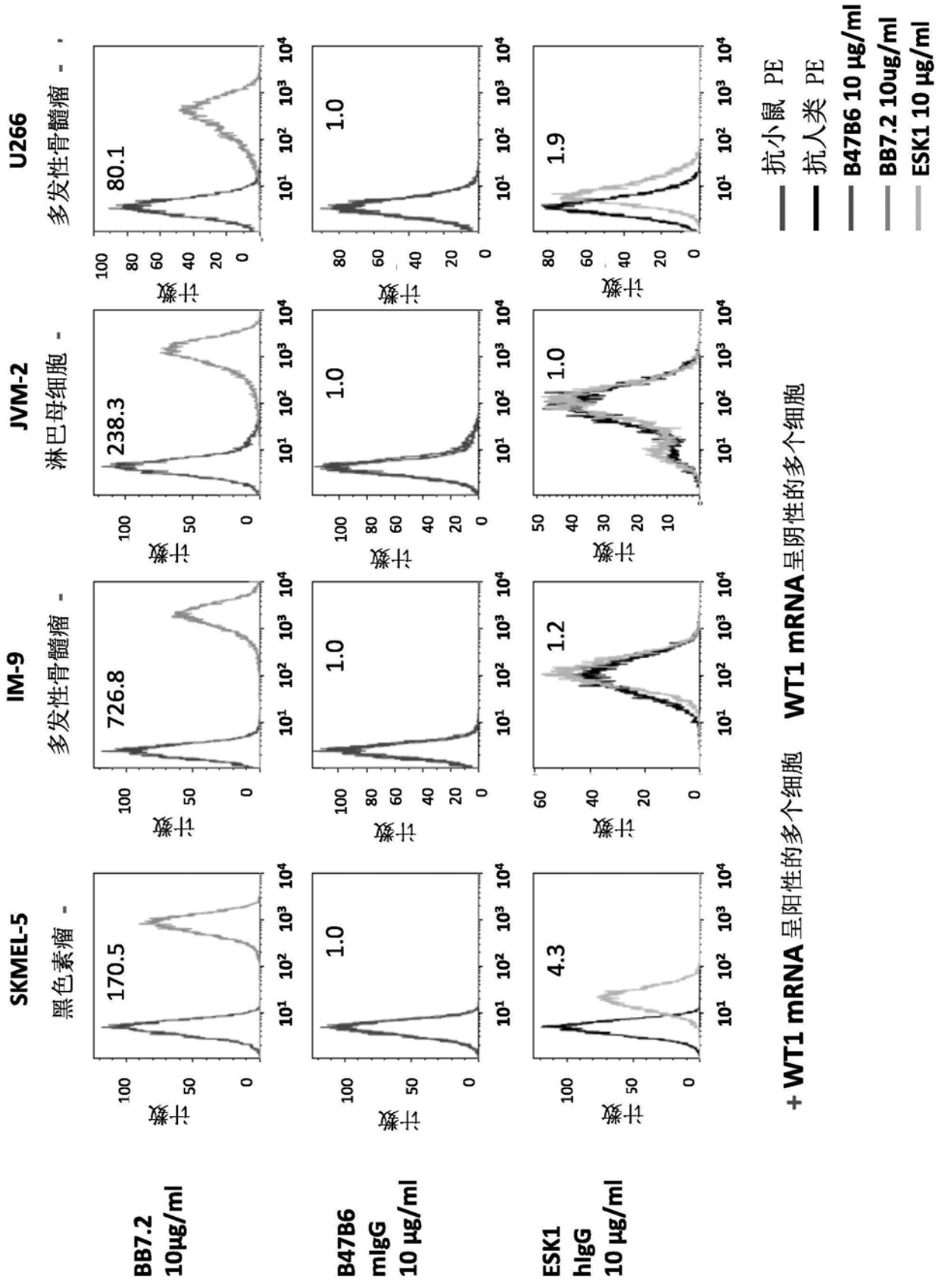

SKMEL-5
黑色素瘤 -
IM-9
多发性骨髓瘤 -
JVM-2
淋巴母细胞 -
U266
多发性骨髓瘤 - -
170.5
726.8
238.3
80.1
1.0
1.0
1.0
1.0
4.3
1.2
1.0
1.9
计数
BB7.2
10μg/ml
B47B6
mIgG
10 μg/ml
ESK1
hIgG
10 μg/ml
+ WT1 mRNA 呈阳性的多个细胞
WT1 mRNA 呈阴性的多个细胞
抗小鼠 PE
抗人类 PE
B47B6 10 μg/ml
BB7.2 10ug/ml
ESK1 10 μg/ml

图35-续

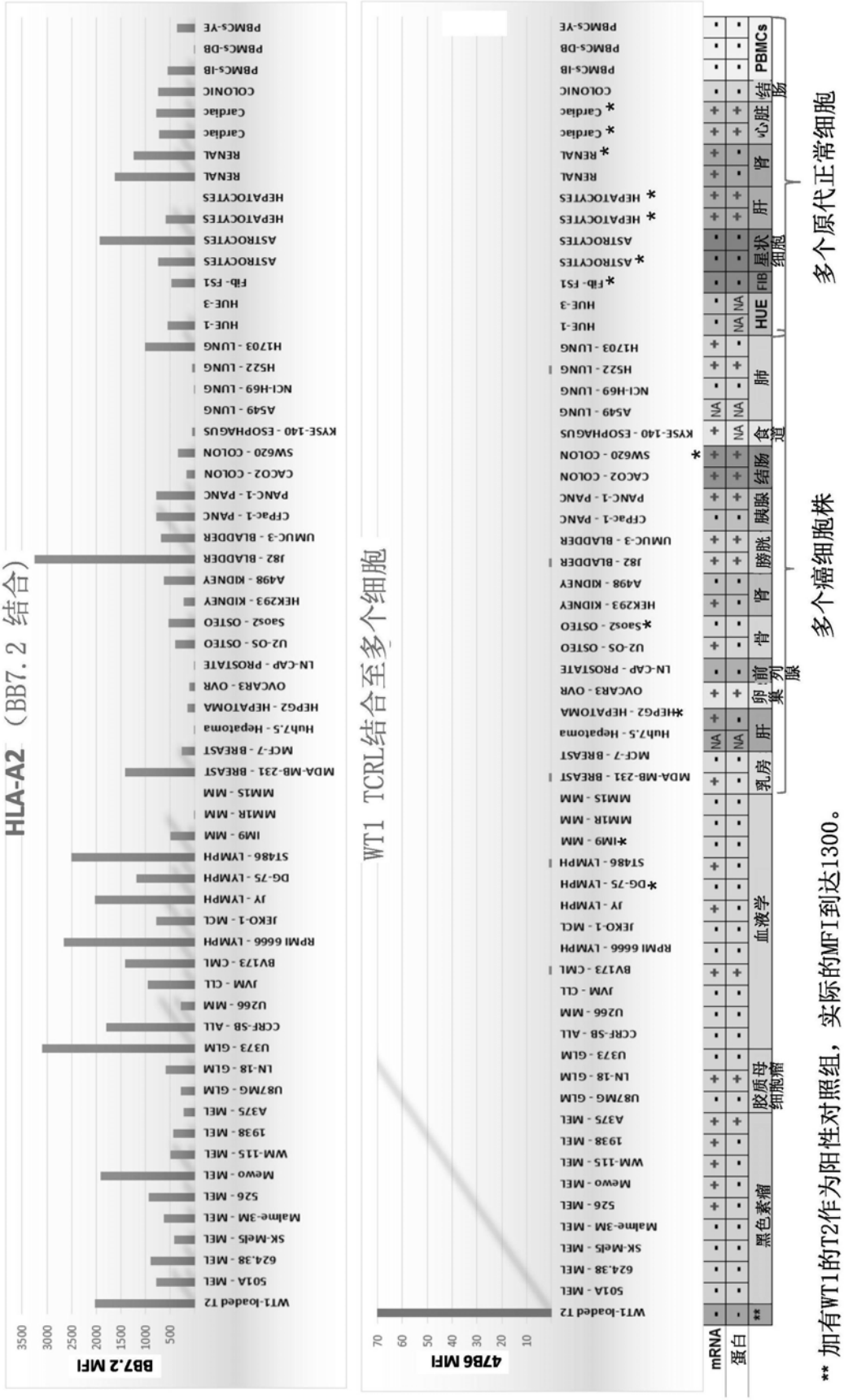
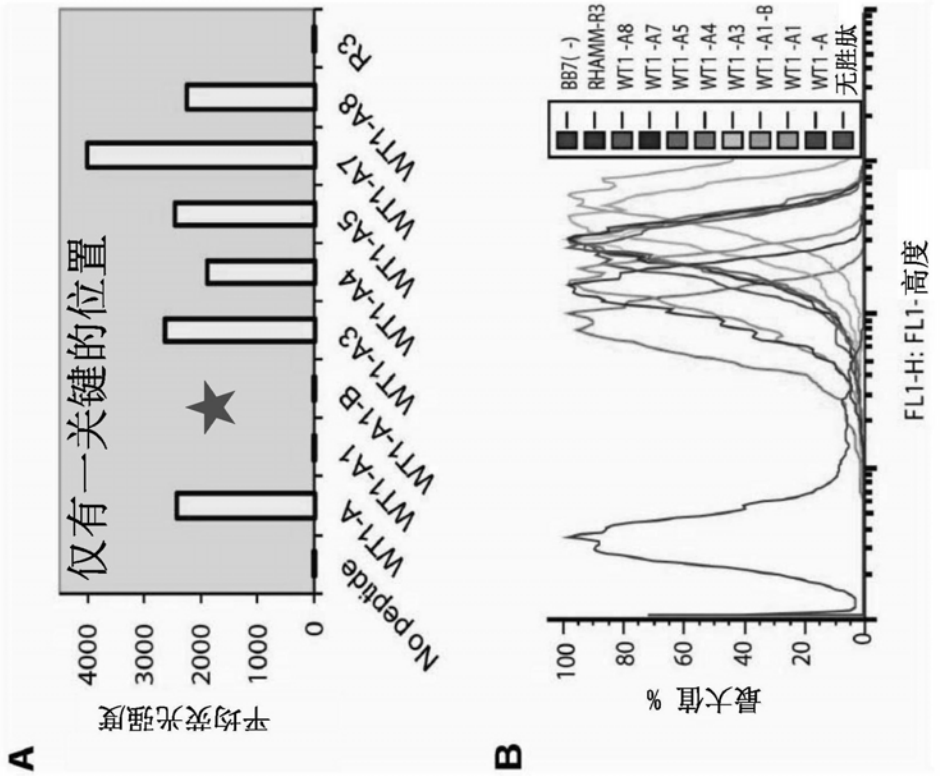

HLA-A2（BB7.2 结合）
BB7.2 MFI
WT1 TCRL结合至多个细胞
4786 MFI
mRNA
蛋白
黑色素瘤
胶质母细胞瘤
血液学
乳房
肝
卵巢
前列腺
骨
肾
膀胱
胰腺
结肠
食道
肺
HUE
FIB
星状细胞
肝
肾
心脏
结肠
PBMCs
多个原代正常细胞
多个癌细胞株
** 加有WT1的T2作为阳性对照组，实际的MFI到达1300。

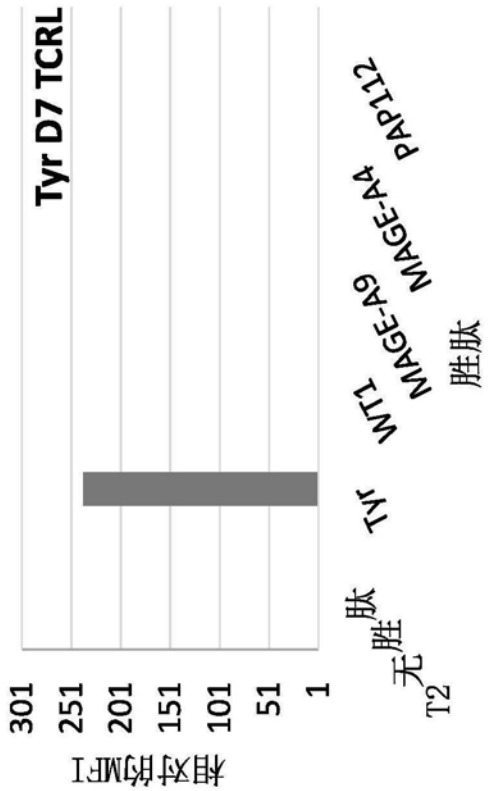
图36

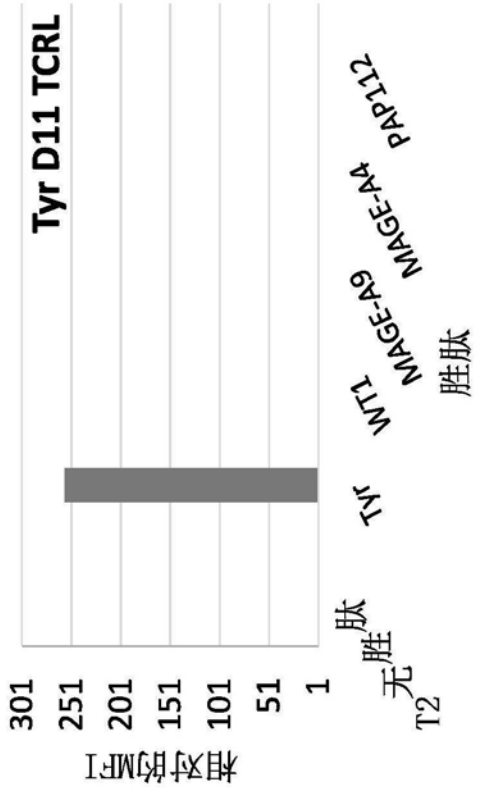


图S1. 抗原表位特异性。所述RMF胜肽序列在位置1、3、4、5、7或8被取代为丙氨酸，或在位置1取代为酪氨酸（WT1-A1B）（序列在表S1）。
（A）多个T2细胞肽脉冲了50微克/毫升的多个指示的胜肽，以及通过流式细胞技术来测量ESK1的所述结合。（B）为了显示所述多个同源的胜肽仍结合在HLA-A0201上，多个被细胞同时染上抗HLA-A2单克隆抗体，克隆BB7.2来测量所述多个胜肽对HLA-A2分子的相对结合。

Tao Dao 等人，科学转化医学 5, 176ra33 (2013)

图37


Tyr D7 TCRL
相对的MFI
301
251
201
151
101
51
1
T2
无胜肽
Tyr
WT1
MAGE-A9
MAGE-A4
PAP112
胜肽


Tyr D11 TCRL
相对的MFI
301
251
201
151
101
51
1
T2
无胜肽
Tyr
WT1
MAGE-A9
MAGE-A4
PAP112
胜肽

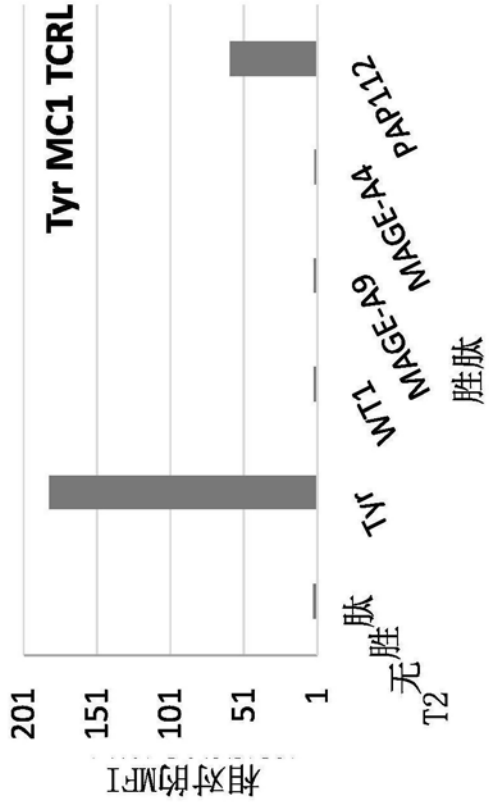
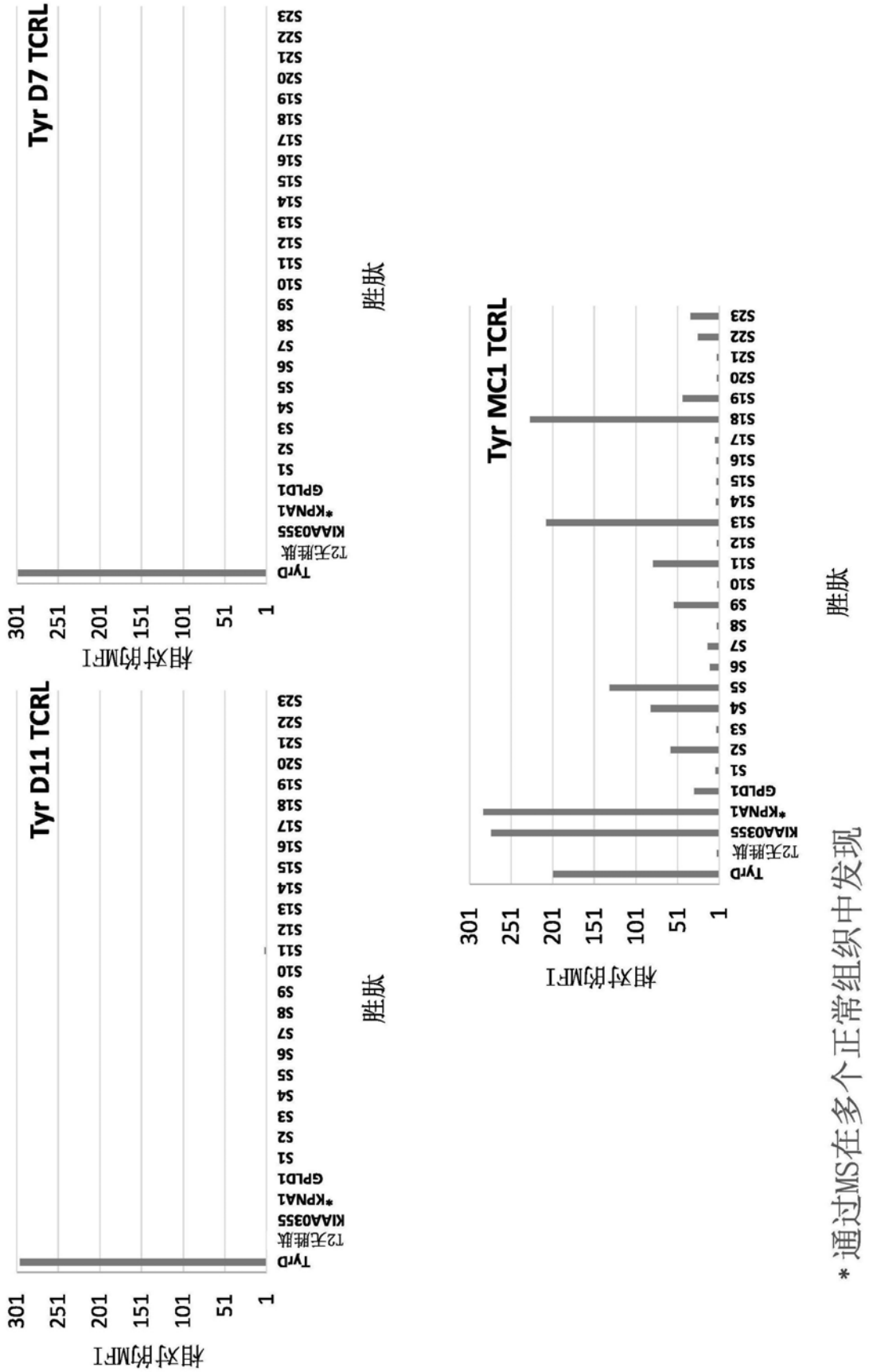

Tyr MC1 TCRL
相对的MFI
201
151
101
51
1
T2
无胜肽
Tyr
WT1
MAGE-A9
MAGE-A4
PAP112
胜肽

图38



* 通过MS在多个正常组织中发现

图39


A) Tyr D11 TCRL
相对的MFI
141
121
101
81
61
41
21
1
T2 TyrD
501A - MEL
SKMel5 - MEL
Mevo - MEL
A375
1938
U2OS
Saos-2
Panc1
J82
UMUC3
H1703
OVCAR3
JVM2
THP1
Jeko1
BV173
SET2
U266
IM9
Fib
星形胶质细胞
心肌细胞
结肠平滑肌
肾近端
肝细胞
成骨细胞 - 胫骨
支气管上皮
尿道上皮细胞
mRNA
APCs
黑色素瘤
骨
胰腺
膀胱
肺
卵巢
血液
不同来源的
多個人类原代细胞

图40A

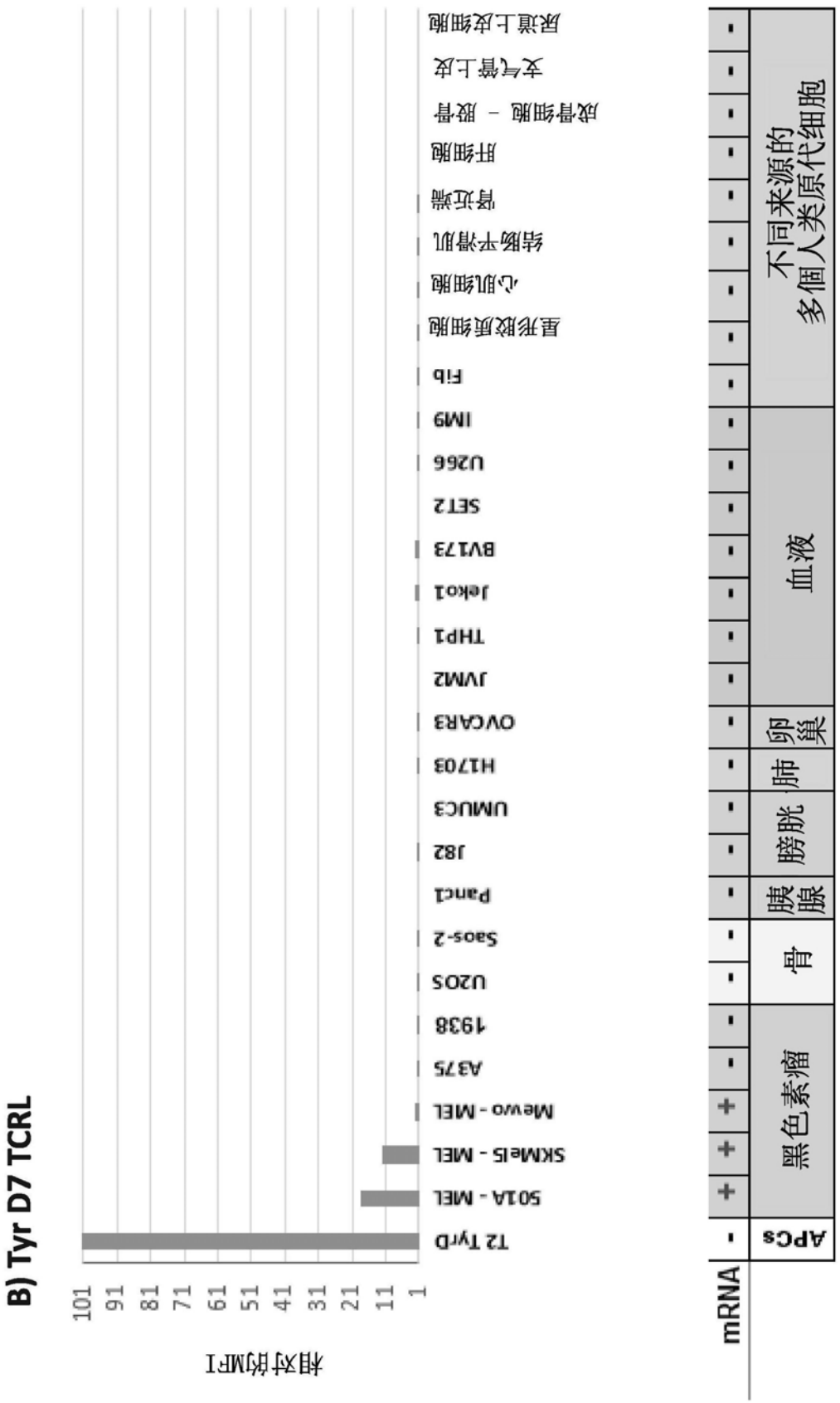

B) Tyr D7 TCRL
相对的MFI
101
91
81
71
61
51
41
31
21
11
1
T2 TyrD
501A - MEL
SKMel5 - MEL
Mevwo - MEL
A375
1938
U2OS
Saos-2
Panc1
J82
UMUC3
H1703
OVCAR3
JVM2
THP1
Jeko1
BV173
SET2
U266
IM9
Fib
星形胶质细胞
心肌细胞
结肠平滑肌
肾近端
肝细胞
成骨细胞 - 股骨
支气管上皮
尿道上皮细胞
mRNA
APCs
黑色素瘤
骨
胰腺
膀胱
肺
卵巢
血液
不同来源的
多個人类原代细胞

图40B

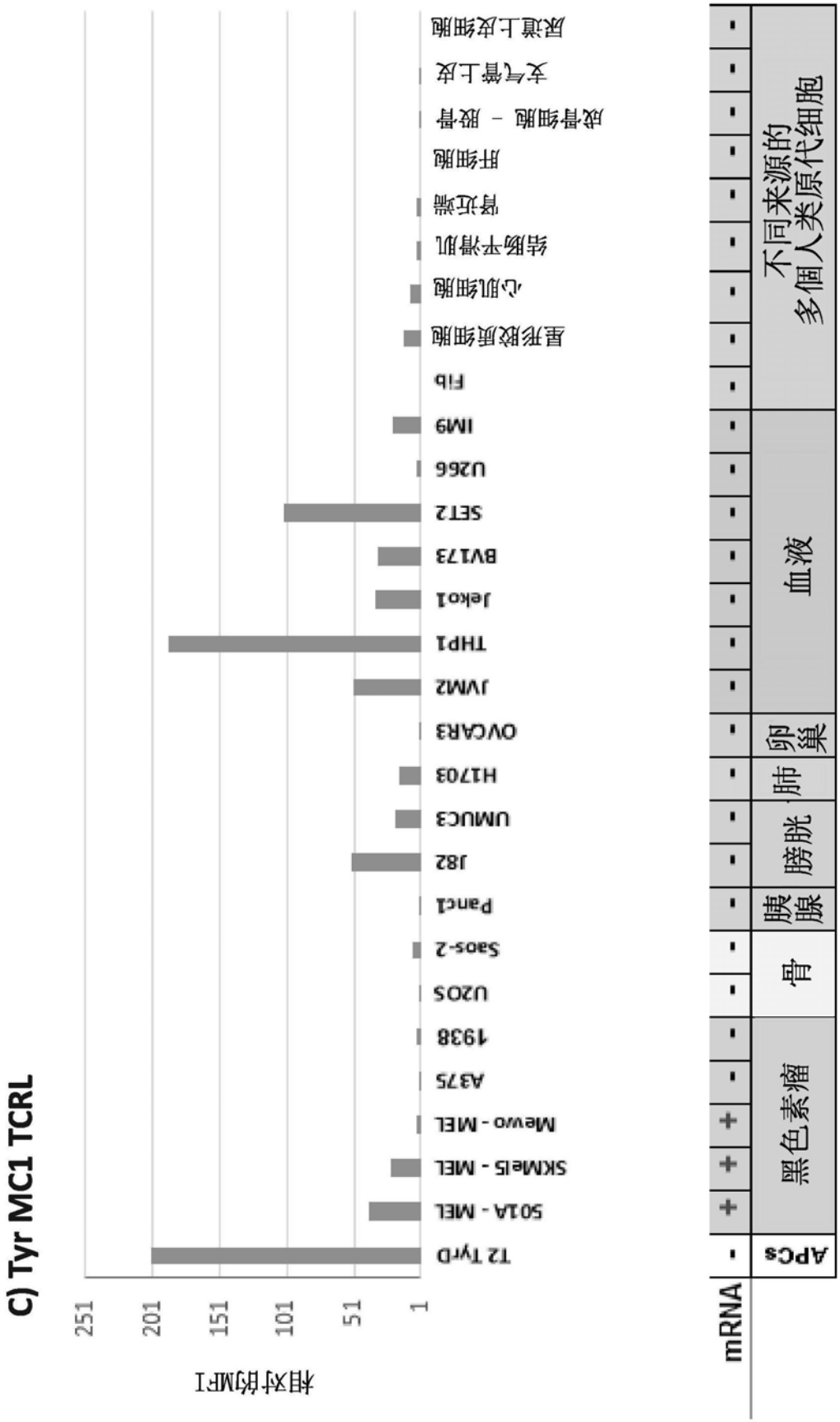

C) Tyr MC1 TCRL
相对的MFI
251
201
151
101
51
1
T2 TyrD
501A - MEL
SKMel5 - MEL
Mevwo - MEL
A375
1938
U2OS
Saos-2
Panc1
J82
UMUC3
H1703
OVCAR3
JVM2
THP1
Jeko1
BV173
SET2
U266
IM9
Fib
星形胶质细胞
心肌细胞
结肠平滑肌
肾近端
肝细胞
成骨细胞 - 股骨
支气管上皮
尿道上皮细胞
mRNA
APCs
黑色素瘤
骨
胰腺
膀胱
肺
卵巢
血液
不同来源的
多個人类原代细胞

图40C

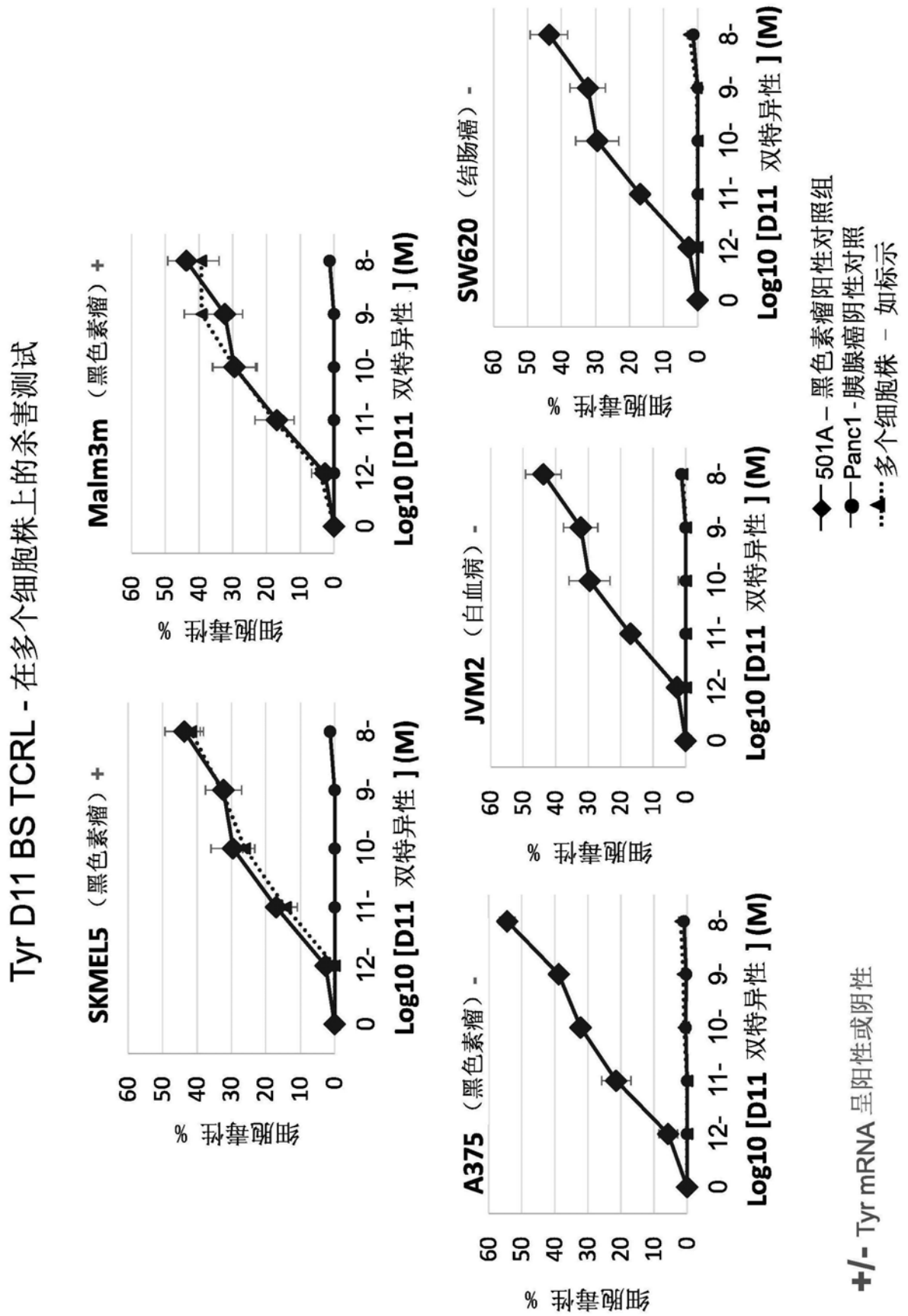

Tyr D11 BS TCRL - 在多个细胞株上的杀害测试
SKMEL5 （黑色素瘤）+
Malm3m （黑色素瘤）+
A375 （黑色素瘤）-
JVM2 （白血病）-
SW620 （结肠癌）-
细胞毒性 %
Log10 [D11 双特异性] (M)
501A – 黑色素瘤阳性对照组
Panc1 -胰腺癌阴性对照
多个细胞株 – 如标示
+/- Tyr mRNA 呈阳性或阴性

图41

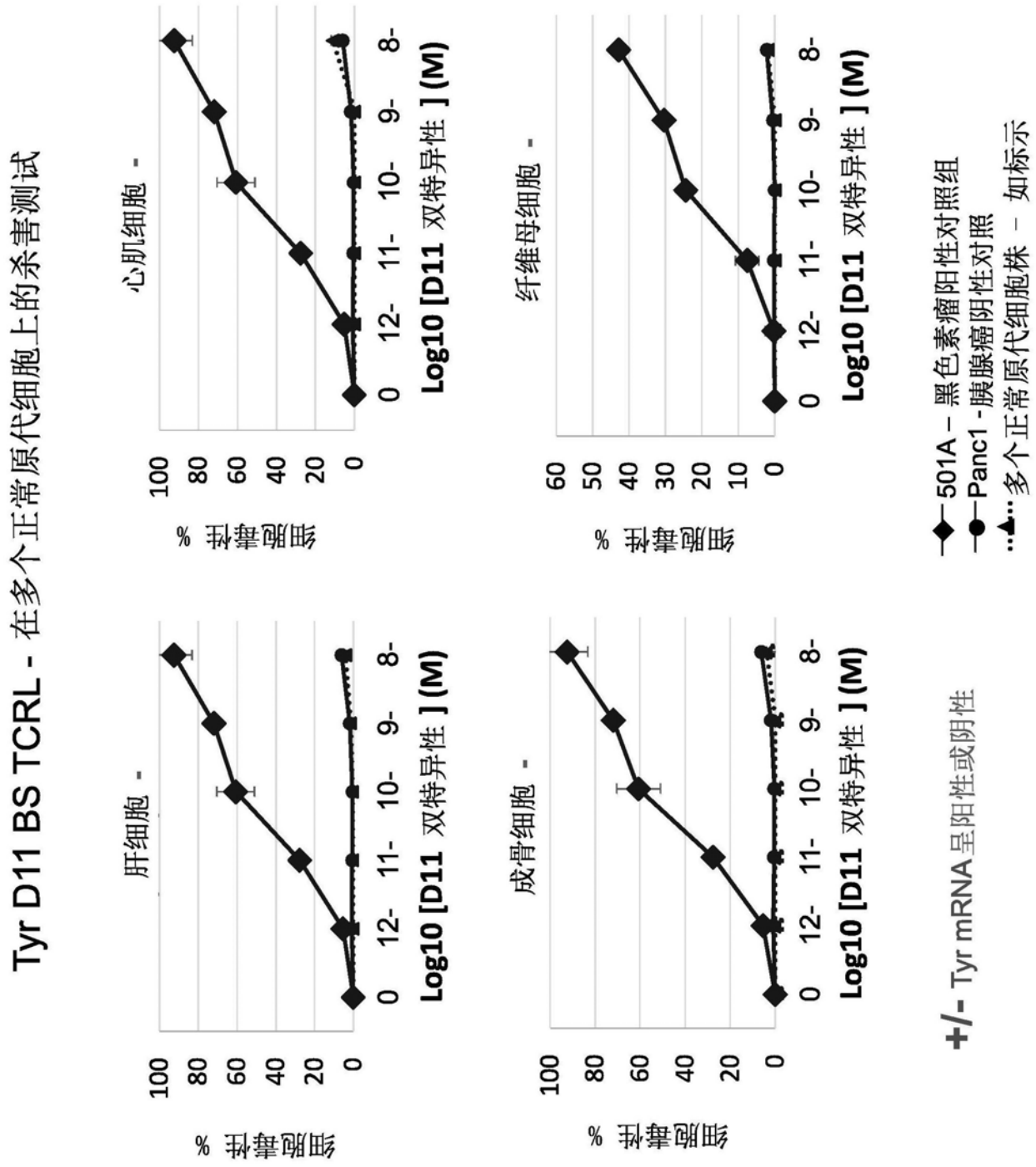

Tyr D11 BS TCRL - 在多个正常原代细胞上的杀害测试
肝细胞 -
心肌细胞 -
成骨细胞 -
纤维母细胞 -
细胞毒性 %
Log10 [D11 双特异性] (M)
501A – 黑色素瘤阳性对照组
Panc1 -胰腺癌阴性对照
多个正常原代细胞株 – 如标示
+/- Tyr mRNA 呈阳性或阴性

图42

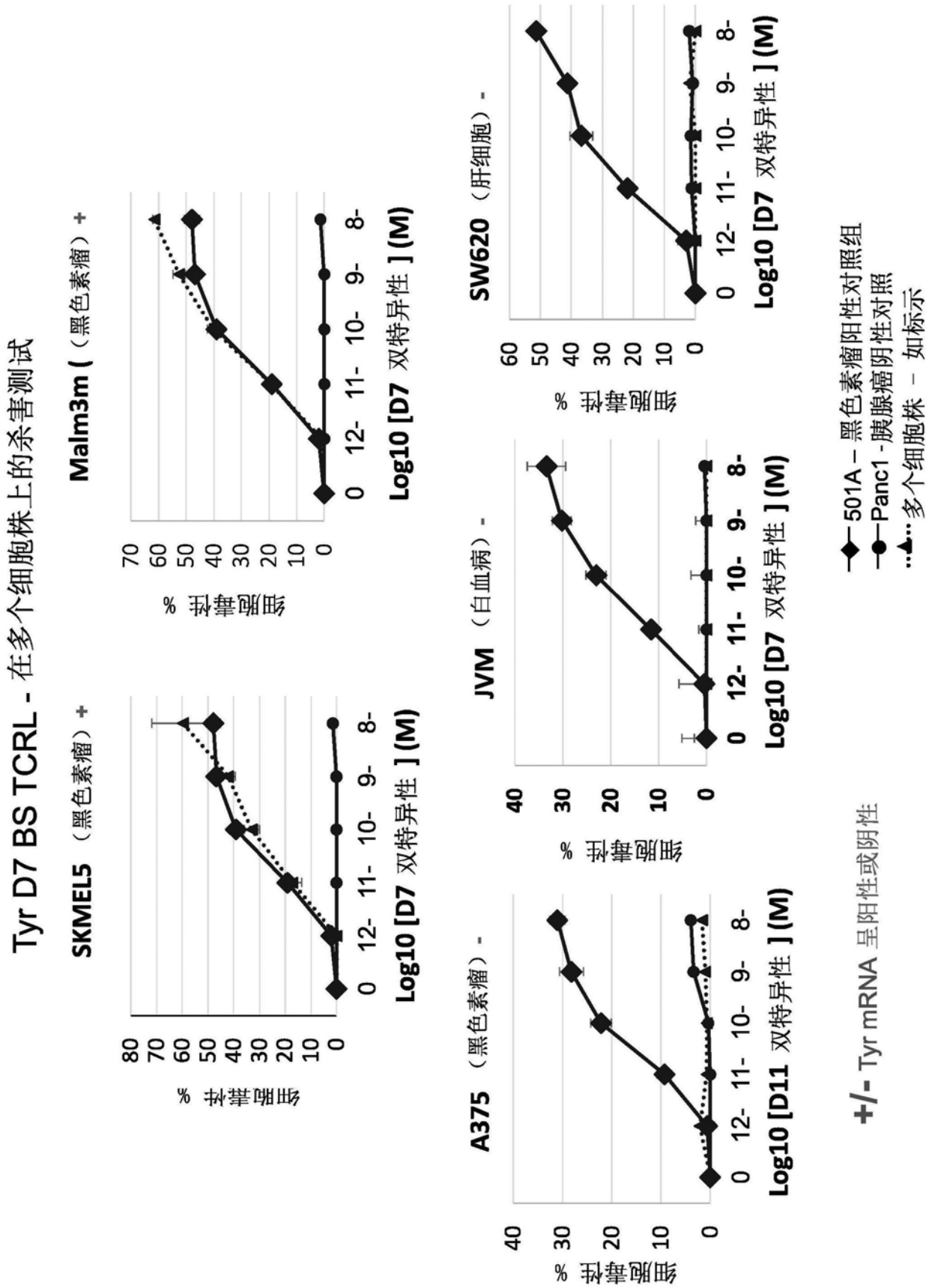

Tyr D7 BS TCRL - 在多个细胞株上的杀害测试
SKMEL5 （黑色素瘤）+
Malm3m (（黑色素瘤）+
A375 （黑色素瘤）-
JVM （白血病）-
SW620 （肝细胞）-
细胞毒性 %
Log10 [D7 双特异性] (M)
Log10 [D11 双特异性] (M)
0 12- 11- 10- 9- 8-
501A – 黑色素瘤阳性对照组
Panc1 -胰腺癌阴性对照
多个细胞株 – 如标示
+/- Tyr mRNA 呈阳性或阴性

图43

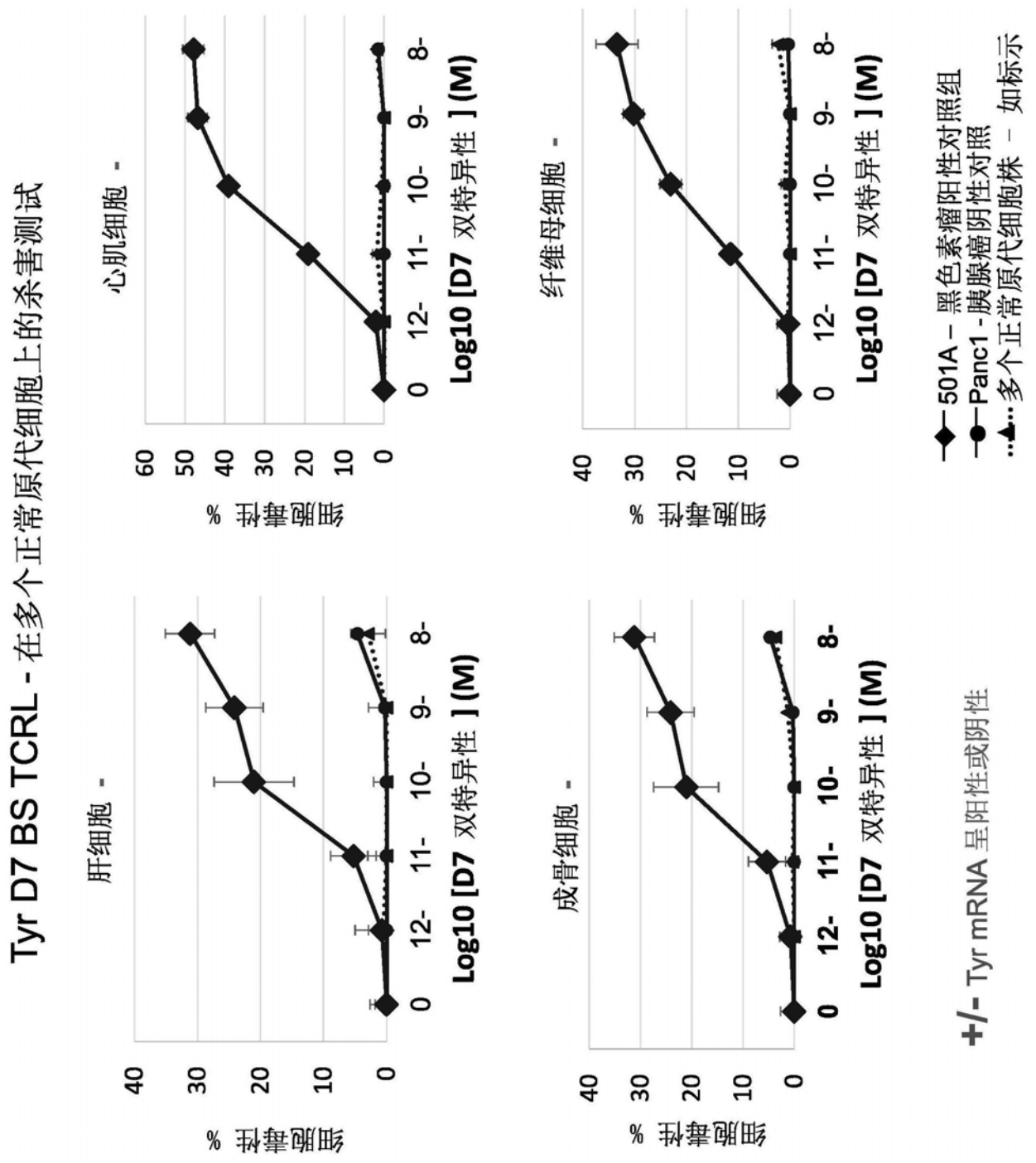

Tyr D7 BS TCRL - 在多个正常原代细胞上的杀害测试
肝细胞 -
心肌细胞 -
成骨细胞 -
纤维母细胞 -
细胞毒性 %
Log10 [D7 双特异性] (M)
0
12-
11-
10-
9-
8-
501A – 黑色素瘤阳性对照组
Panc1 - 胰腺癌阴性对照
多个正常原代细胞株 – 如标示
+/- Tyr mRNA 呈阳性或阴性

图44

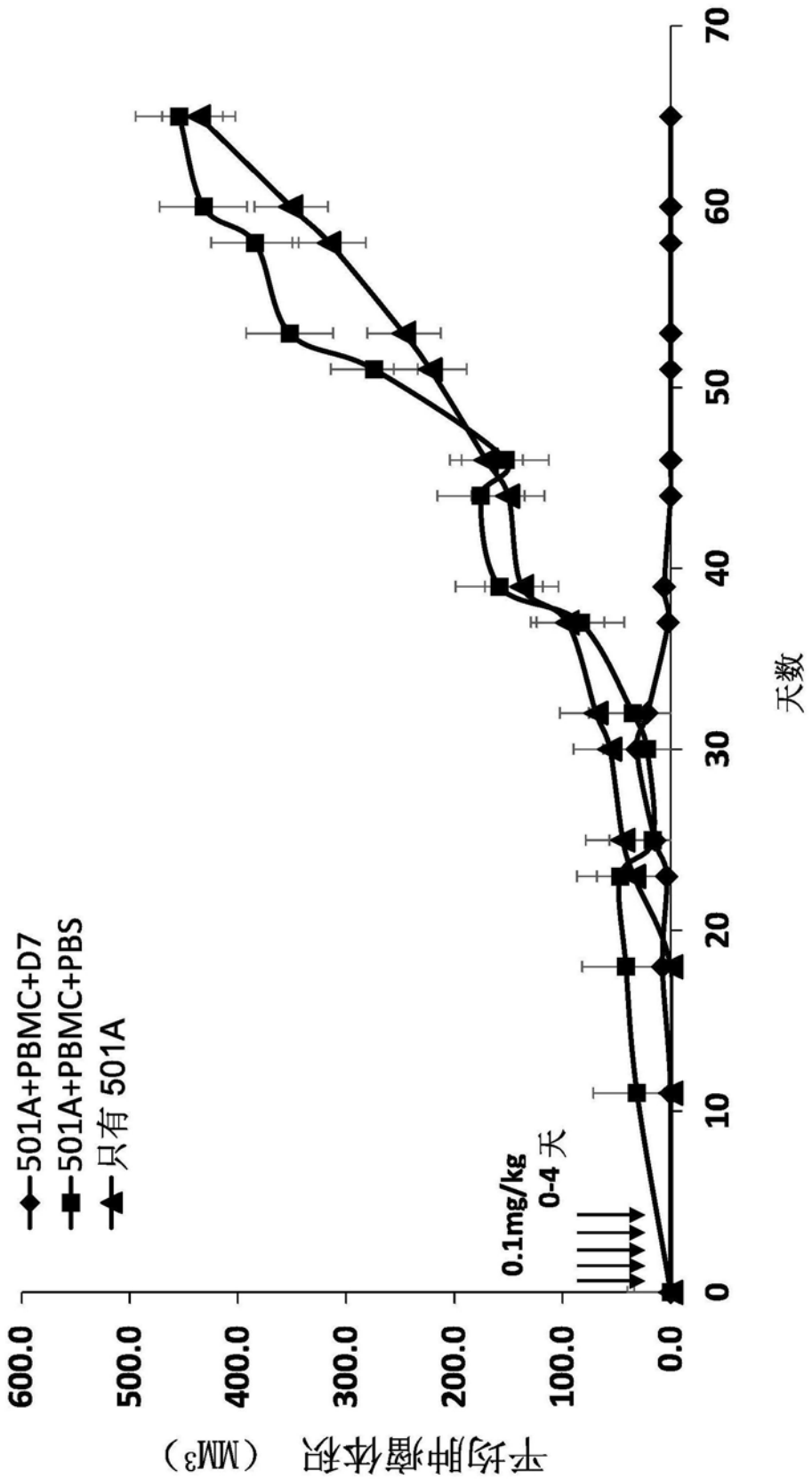

501A+PBMC+D7
501A+PBMC+PBS
只有 501A
0.1mg/kg
0-4 天
平均肿瘤体积 （MM3）
600.0
500.0
400.0
300.0
200.0
100.0
0.0
0
10
20
30
40
50
60
70
天数

图45

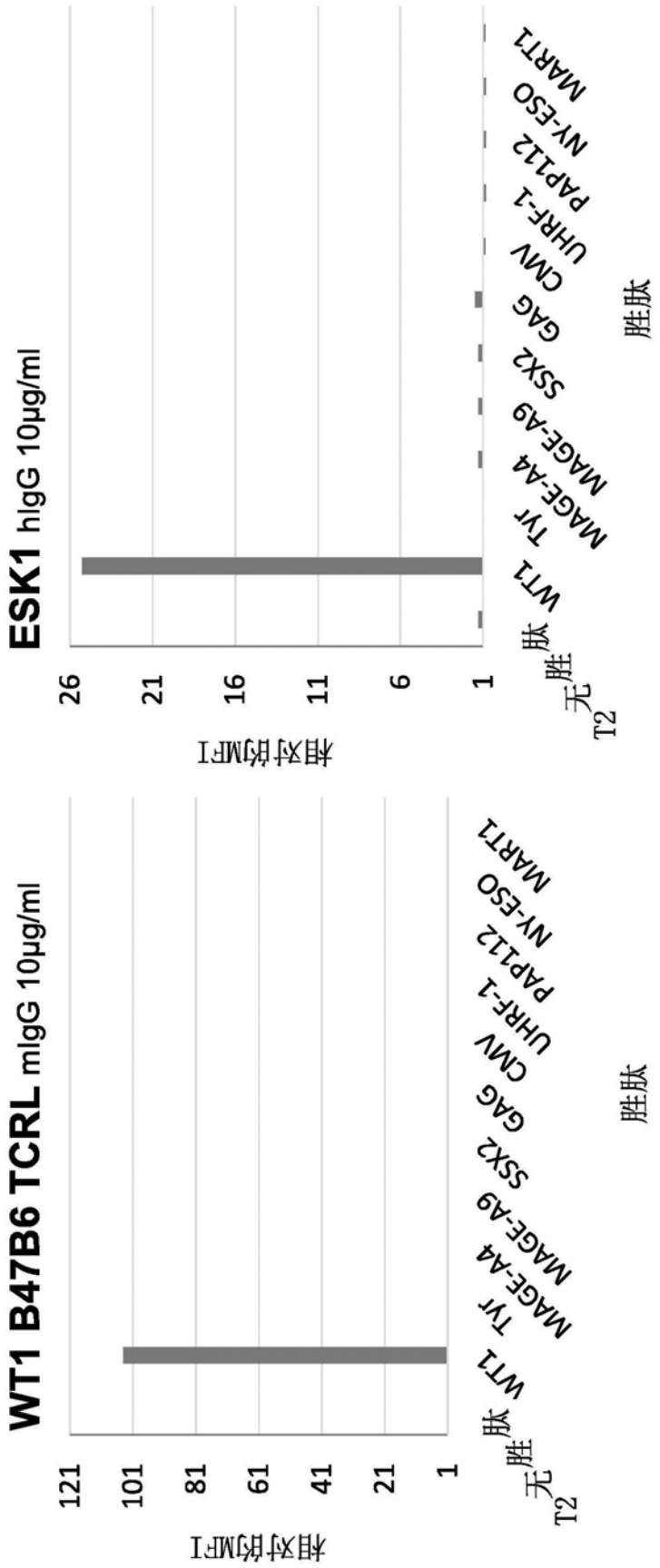

ESK1 hIgG 10μg/ml
相对的MFI
26
21
16
11
6
1
无胜肽
T2
WT1
Tyr
MAGE-A4
MAGE-A9
SSX2
GAG
CMV
UHRF-1
PAP112
NY-ESO
MART1
胜肽
WT1 B47B6 TCRL mIgG 10μg/ml
相对的MFI
121
101
81
61
41
21
1
无胜肽
T2
WT1
Tyr
MAGE-A4
MAGE-A9
SSX2
GAG
CMV
UHRF-1
PAP112
NY-ESO
MART1
胜肽

图46

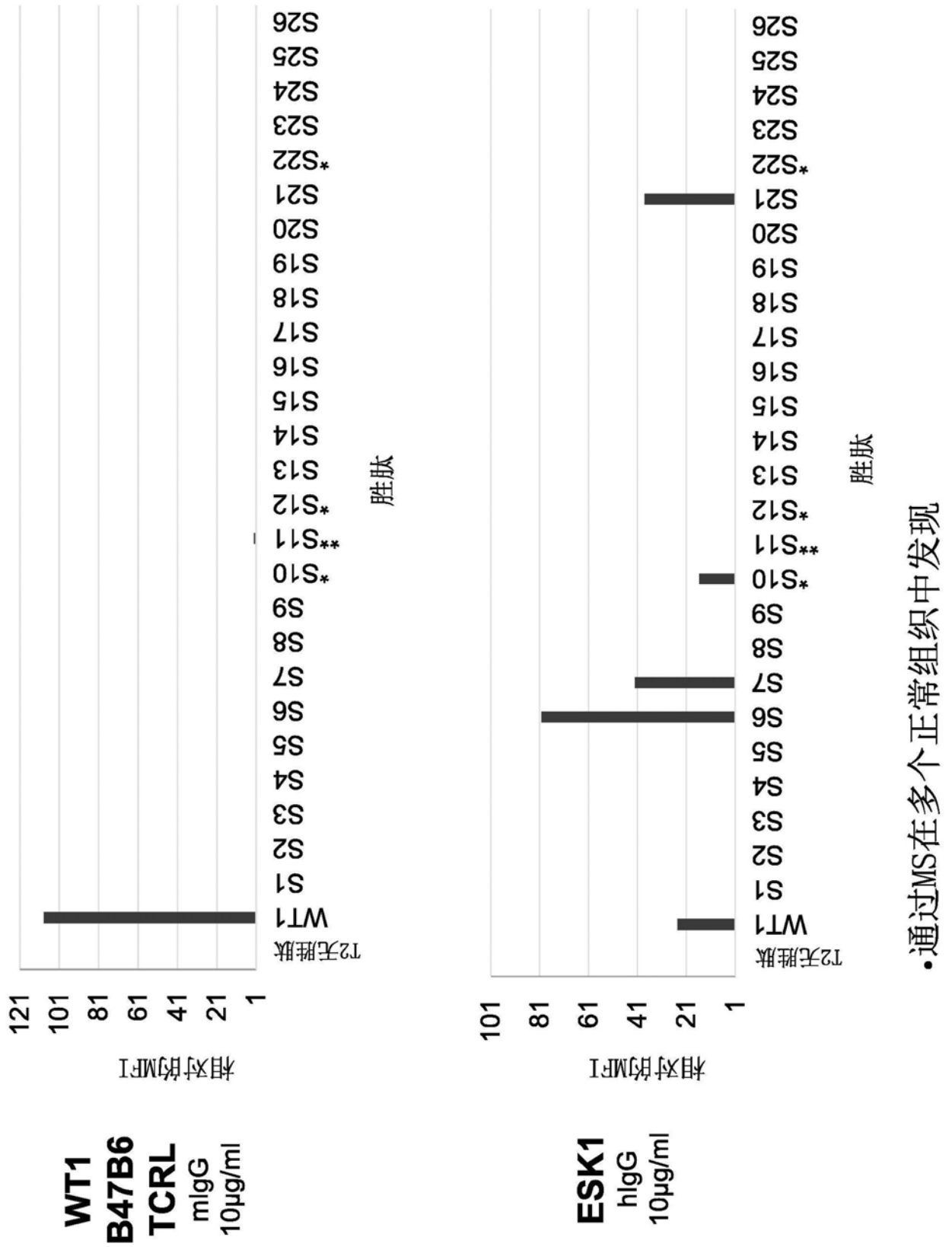

WT1
B47B6
TCRL
mIgG
10μg/ml
121
101
81
61
41
21
1
相对的MFI
T2无胜肽
WT1
S1
S2
S3
S4
S5
S6
S7
S8
S9
*S10
**S11
*S12
S13
S14
S15
S16
S17
S18
S19
S20
S21
*S22
S23
S24
S25
S26
胜肽
ESK1
hIgG
10μg/ml
101
81
61
41
21
1
相对的MFI
T2无胜肽
WT1
S1
S2
S3
S4
S5
S6
S7
S8
S9
*S10
**S11
*S12
S13
S14
S15
S16
S17
S18
S19
S20
S21
*S22
S23
S24
S25
S26
胜肽
•通过MS在多个正常组织中发现

图47

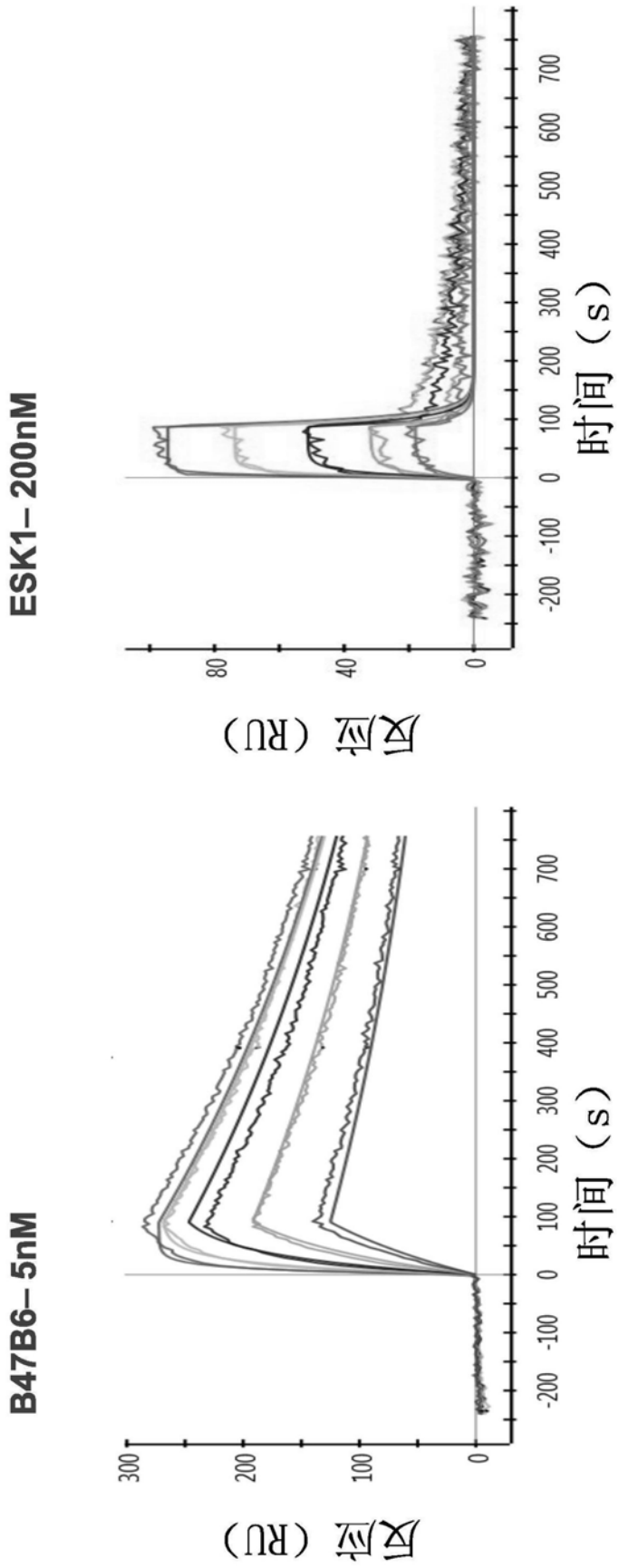

B47B6-5nM
反应（RU）
300
200
100
0
-200
-100
0
100
200
300
400
500
600
700
时间（s）
ESK1-200nM
反应（RU）
80
40
0
-200
-100
0
100
200
300
400
500
600
700
时间（s）

图48

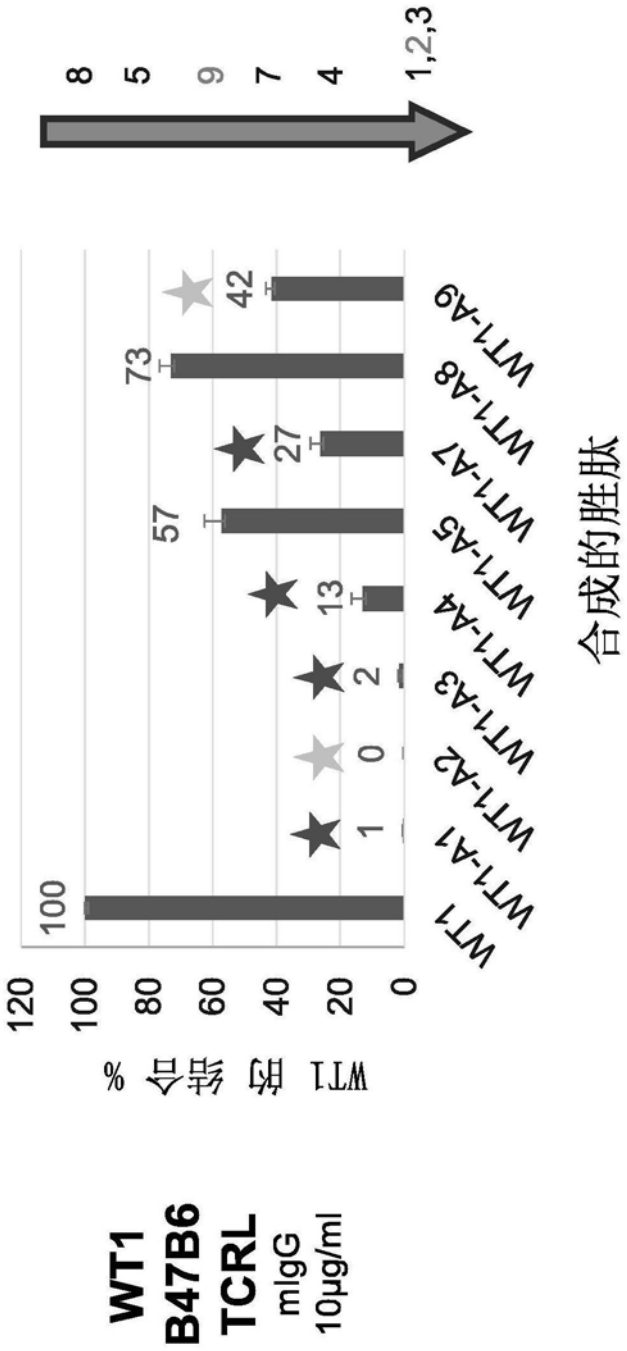

WT1
B47B6
TCRL
mIgG
10μg/ml
WT1 的结合 %
120
100
80
60
40
20
0
100
1
0
2
13
57
27
73
42
WT1
WT1-A1
WT1-A2
WT1-A3
WT1-A4
WT1-A5
WT1-A7
WT1-A8
WT1-A9
合成的胜肽
8
5
9
7
4
1,2,3

图49

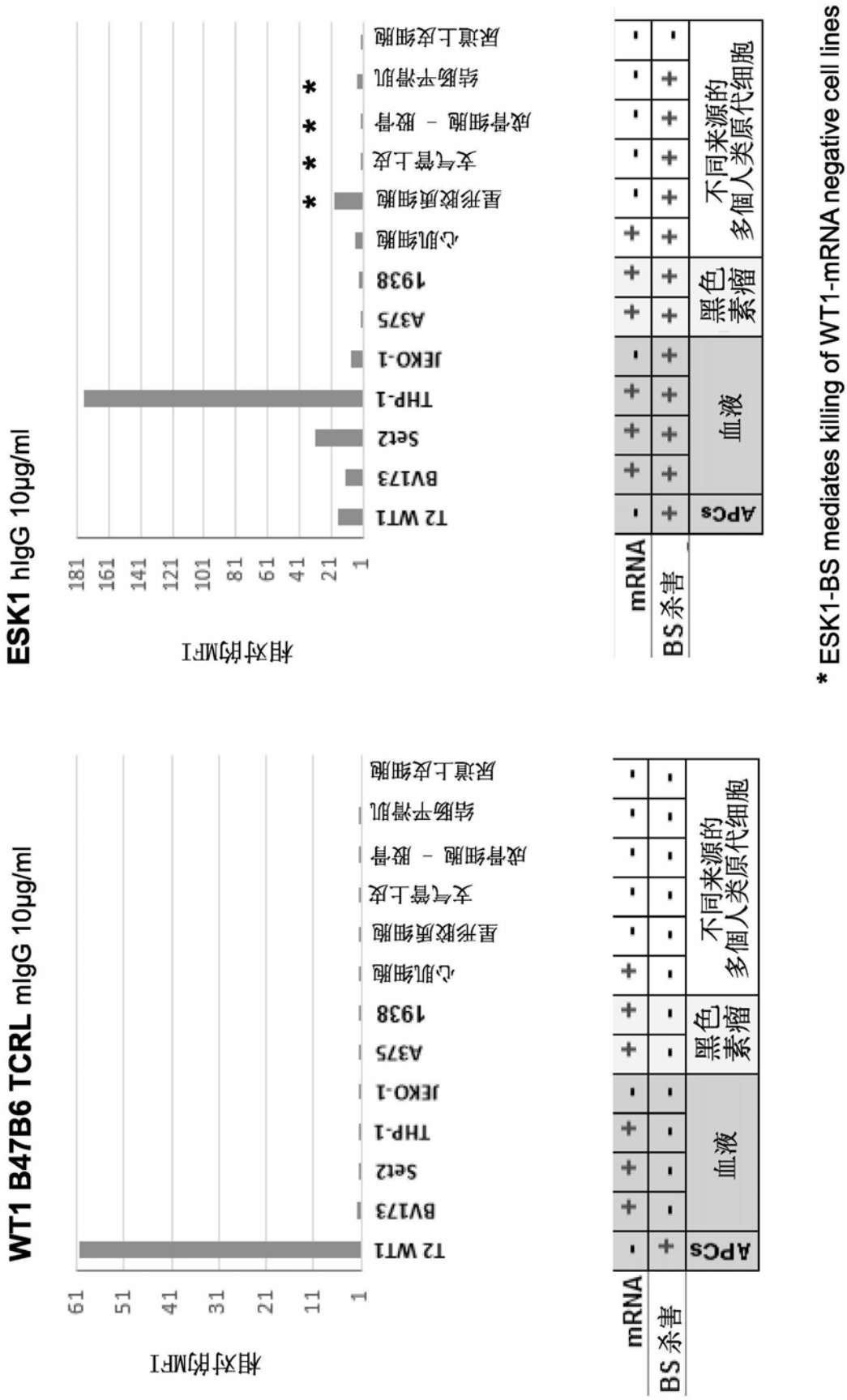

WT1 B47B6 TCRL mIgG 10μg/ml
相对的MFI
61
51
41
31
21
11
1
T2 WT1
BV173
Set2
THP-1
JEKO-1
A375
1938
心肌细胞
星形胶质细胞
支气管上皮
成骨细胞 – 胶骨
结肠平滑肌
尿道上皮细胞
mRNA
BS杀害
APCs
血液
黑色素瘤
不同来源的多個人类原代细胞
ESK1 hIgG 10μg/ml
相对的MFI
181
161
141
121
101
81
61
41
21
1
T2 WT1
BV173
Set2
THP-1
JEKO-1
A375
1938
心肌细胞
星形胶质细胞
支气管上皮
成骨细胞 – 胶骨
结肠平滑肌
尿道上皮细胞
mRNA
BS杀害
APCs
血液
黑色素瘤
不同来源的多個人类原代细胞
* ESK1-BS mediates killing of WT1-mRNA negative cell lines

图50

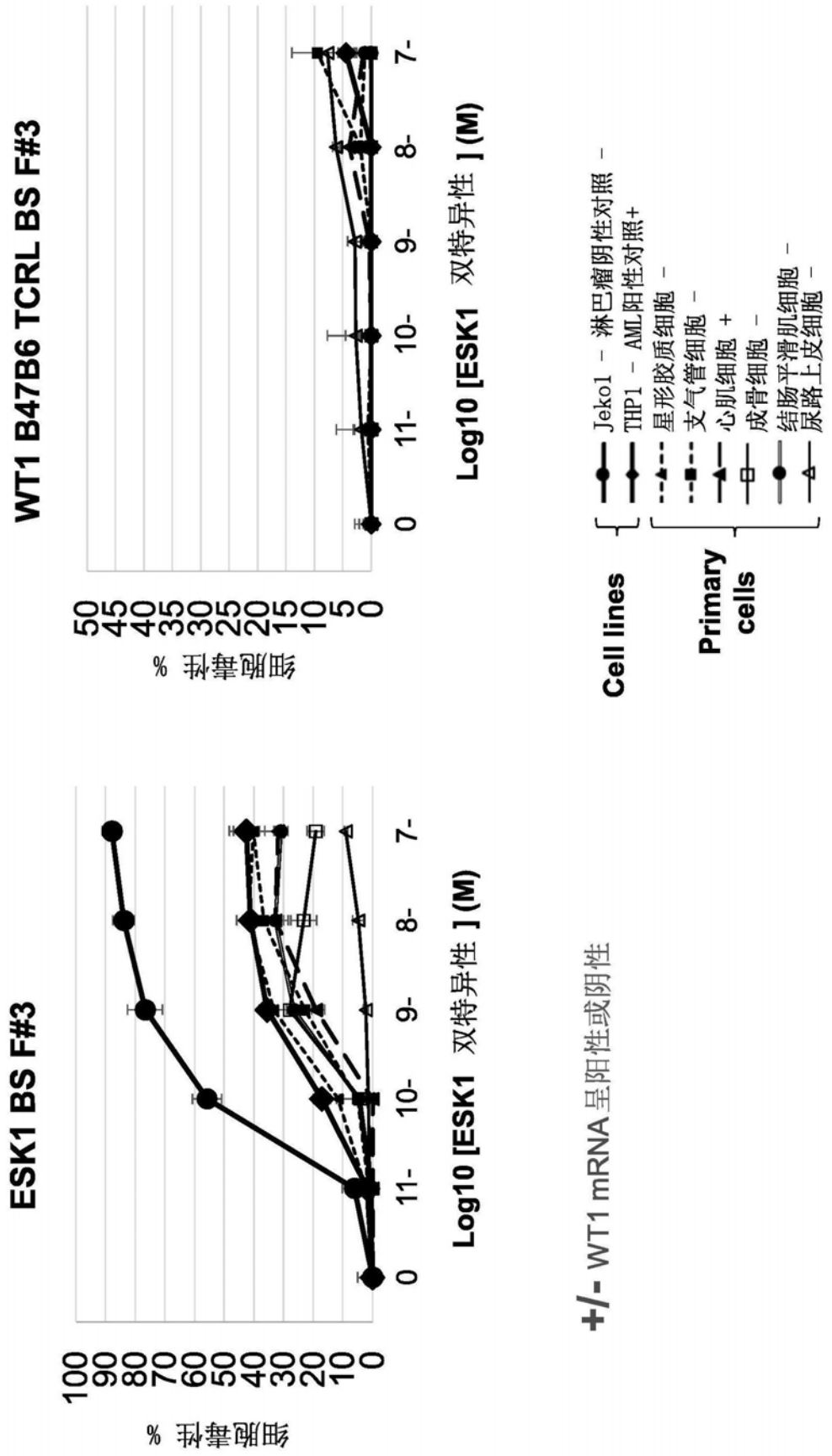

ESK1 BS F#3
细胞毒性 %
100
90
80
70
60
50
40
30
20
10
0
0
11-
10-
9-
8-
7-
Log10 [ESK1 双特异性] (M)
WT1 B47B6 TCRL BS F#3
细胞毒性 %
50
45
40
35
30
25
20
15
10
5
0
0
11-
10-
9-
8-
7-
Log10 [ESK1 双特异性] (M)
+/- WT1 mRNA 呈阳性或阴性
Cell lines
Jeko1 – 淋巴瘤阴性对照 –
THP1 – AML阳性对照+
Primary cells
星形胶质细胞 –
支气管细胞 –
心肌细胞 +
成骨细胞 –
结肠平滑肌细胞 –
尿路上皮细胞 –

图51A

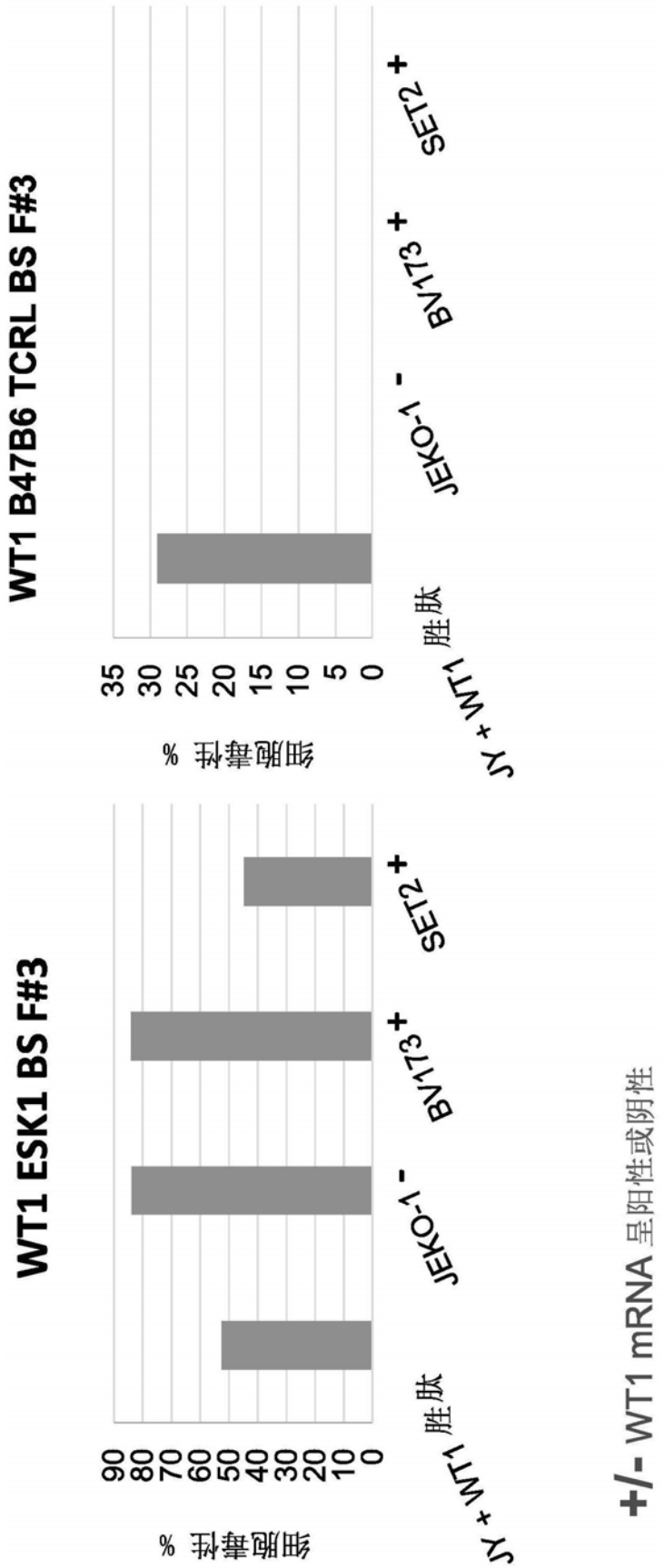

WT1 ESK1 BS F#3
细胞毒性 %
90
80
70
60
50
40
30
20
10
0
JY + WT1 胜肽
JEKO-1 -
BV173 +
SET2 +
WT1 B47B6 TCRL BS F#3
细胞毒性 %
35
30
25
20
15
10
5
0
JY + WT1 胜肽
JEKO-1 -
BV173 +
SET2 +
+/- WT1 mRNA 呈阳性或阴性

图51B

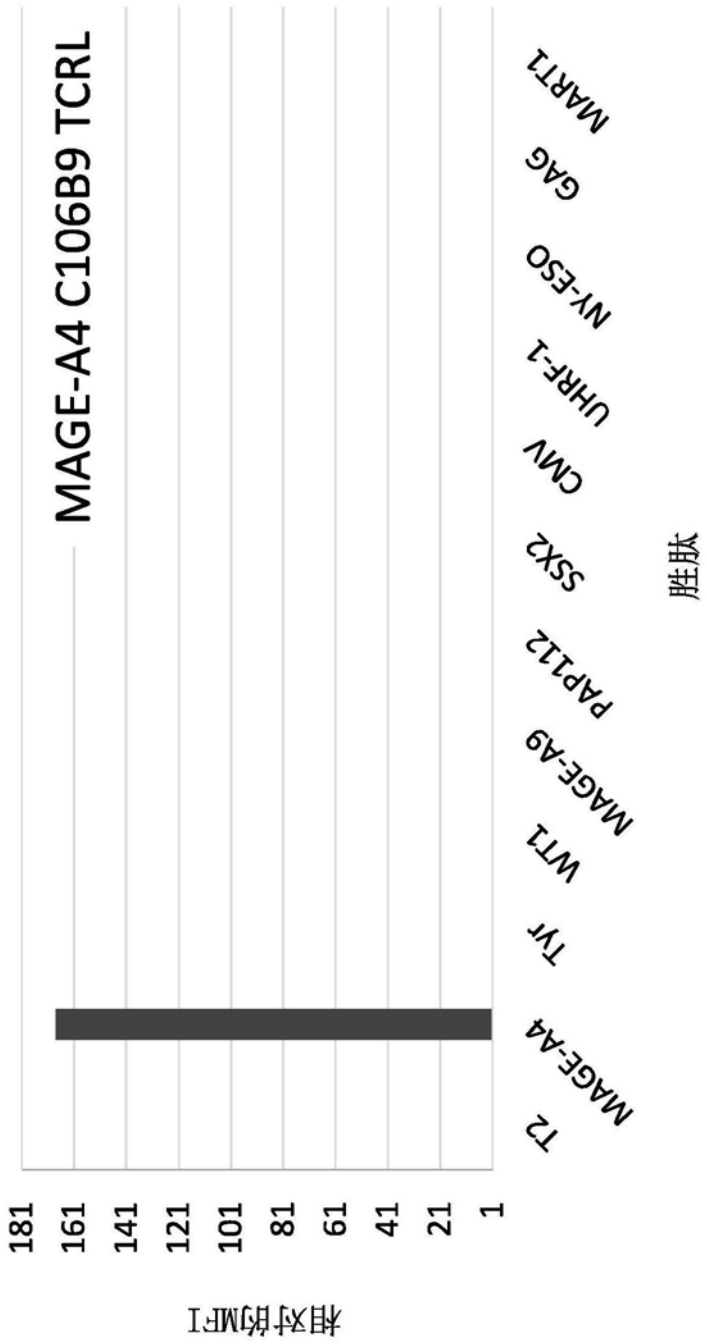

MAGE-A4 C106B9 TCRL
181
161
141
121
101
81
61
41
21
1
相对的MFI
T2
MAGE-A4
Tyr
WT1
MAGE-A9
PAP112
SSX2
CMV
UHRF-1
NY-ESO
GAG
MART1
胜肽

图52

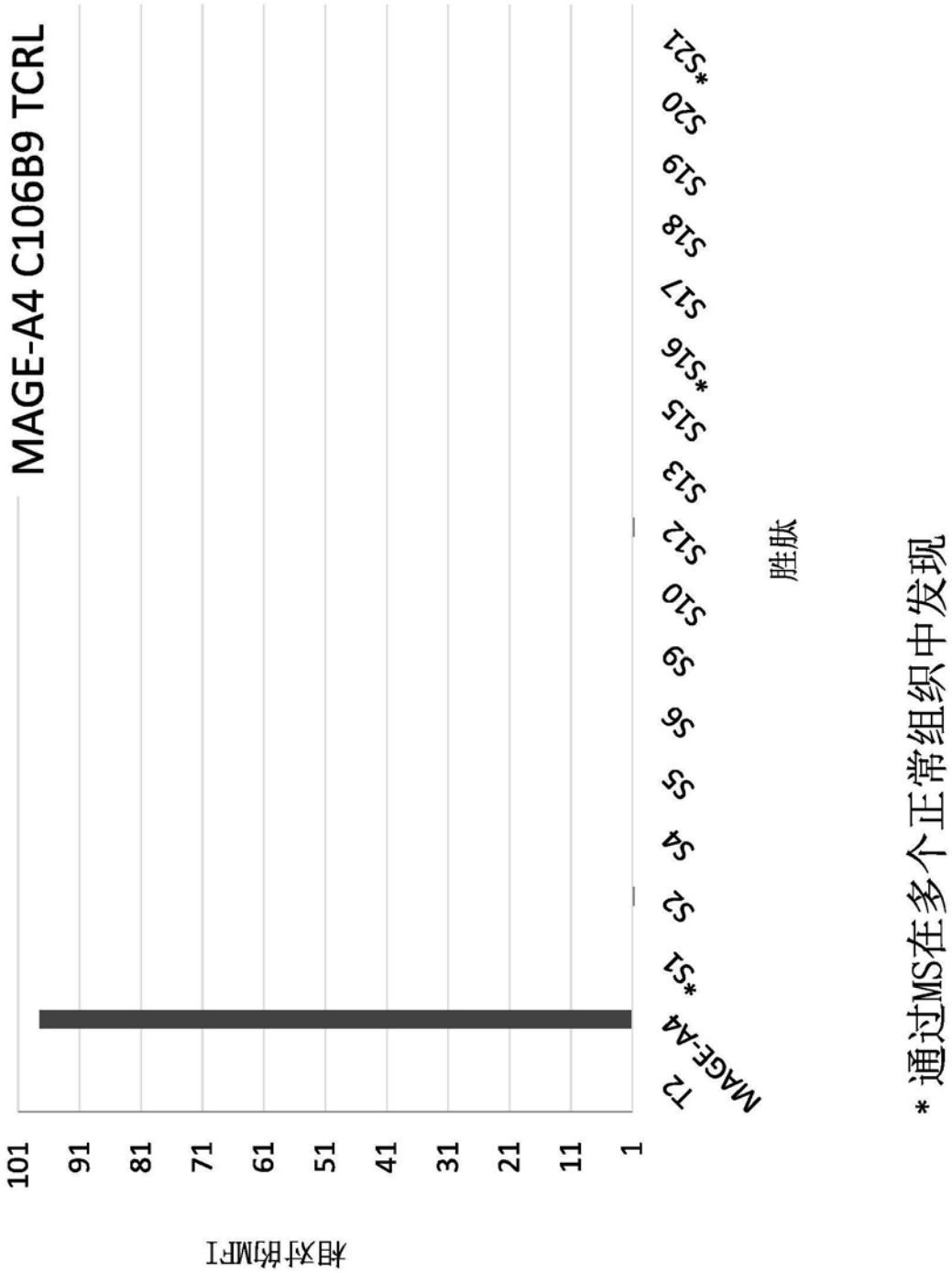

MAGE-A4 C106B9 TCRL
相对的MFI
101
91
81
71
61
51
41
31
21
11
1
T2
MAGE-A4
*S1
S2
S4
S5
S6
S9
S10
S12
S13
S15
*S16
S17
S18
S19
S20
*S21
胜肽
* 通过MS在多个正常组织中发现

图53

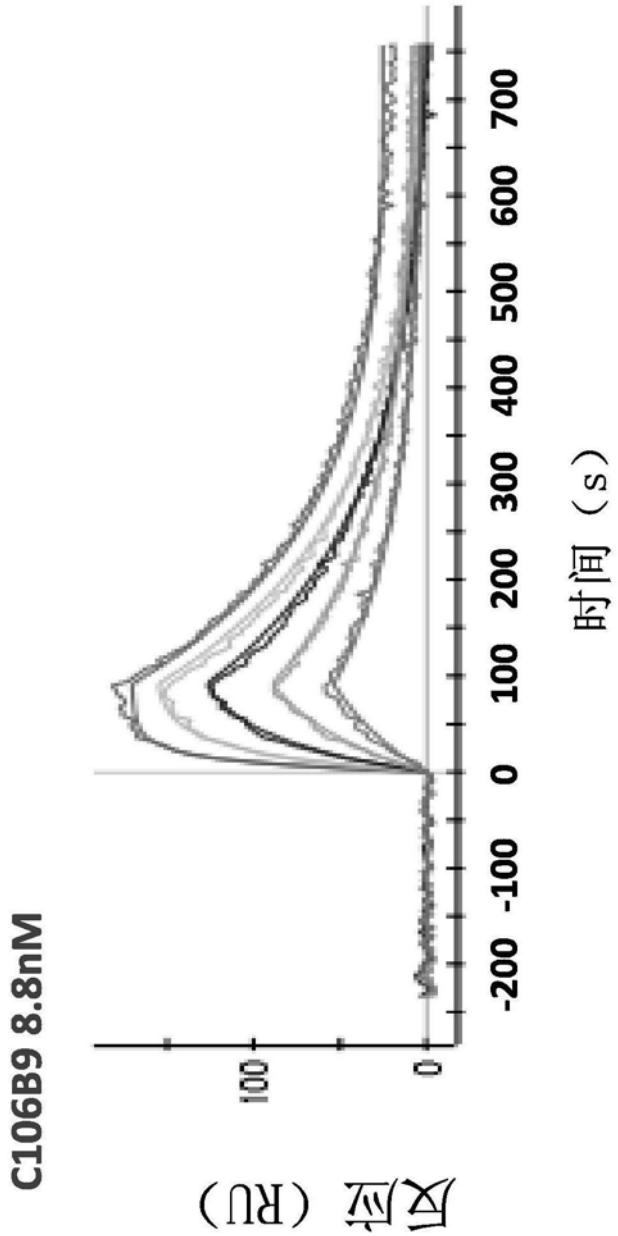


图54

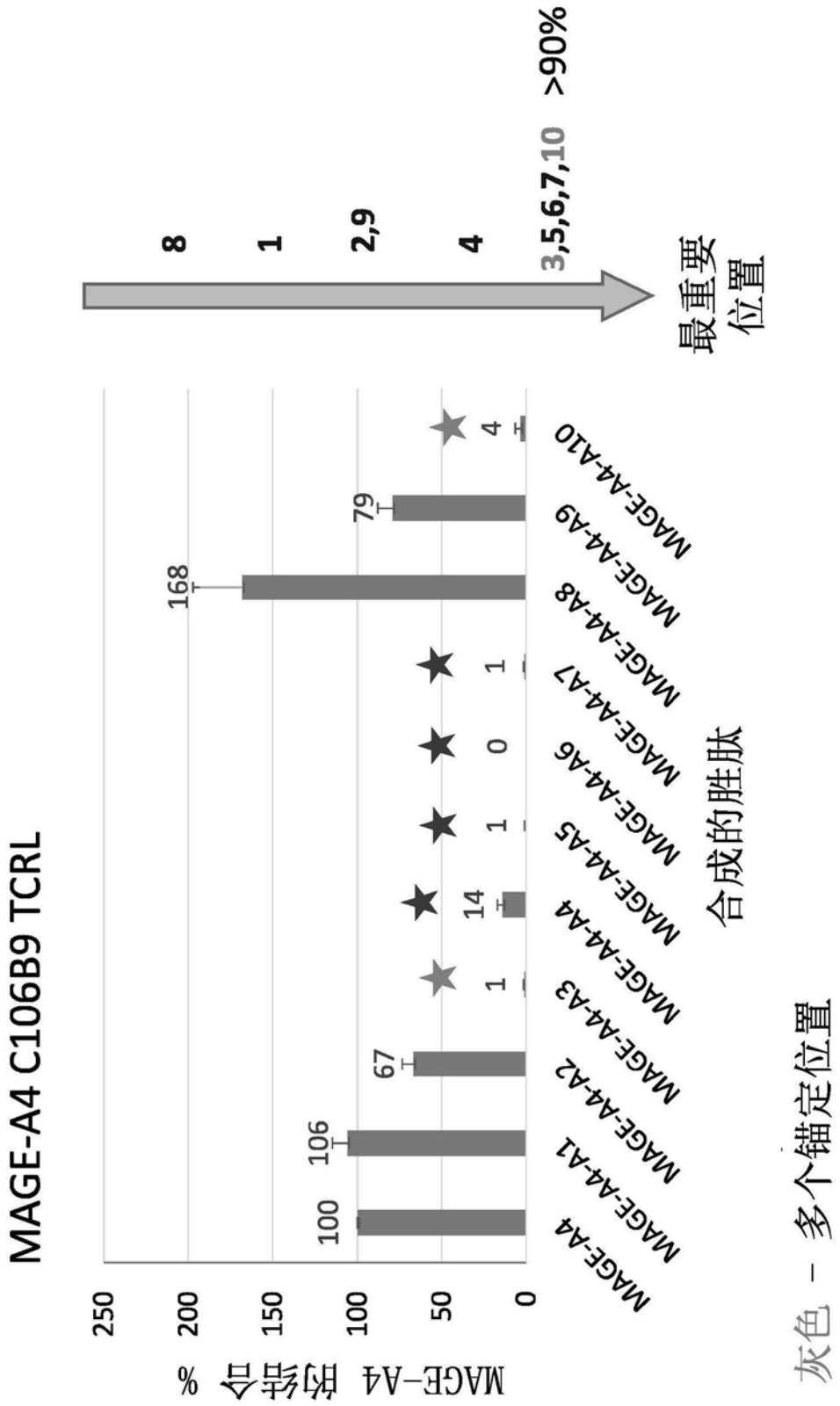

MAGE-A4 C106B9 TCRL
MAGE-A4 的结合 %
250
200
150
100
50
0
100
106
67
1
14
1
0
1
168
79
4
MAGE-A4
MAGE-A4-A1
MAGE-A4-A2
MAGE-A4-A3
MAGE-A4-A4
MAGE-A4-A5
MAGE-A4-A6
MAGE-A4-A7
MAGE-A4-A8
MAGE-A4-A9
MAGE-A4-A10
合成的胜肽
8
1
2,9
4
3,5,6,7,10
>90%
最重要位置
灰色 – 多个锚定位置

图55

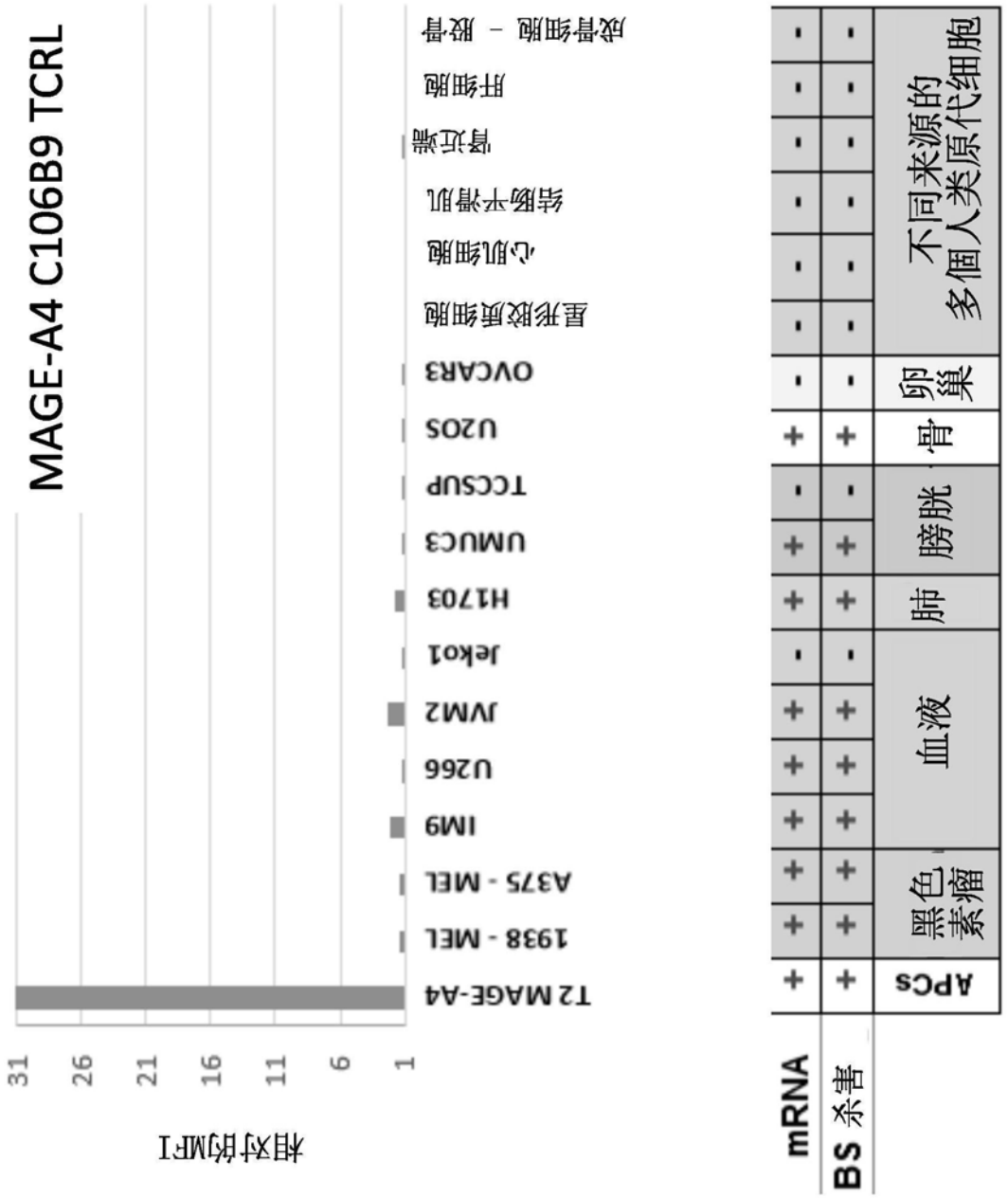

MAGE-A4 C106B9 TCRL
相对的MFI
31
26
21
16
11
6
1
T2 MAGE-A4
1938 - MEL
A375 - MEL
IM9
U266
JVM2
Jeko1
H1703
UMUC3
TCCSUP
U2OS
OVCAR3
星形胶质细胞
心肌细胞
结肠平滑肌
肾近端
肝细胞
成骨细胞 – 胶骨
mRNA
BS 杀害
APCs
黑色素瘤
血液
肺
膀胱
骨
卵巢
不同来源的多個人类原代细胞

图56

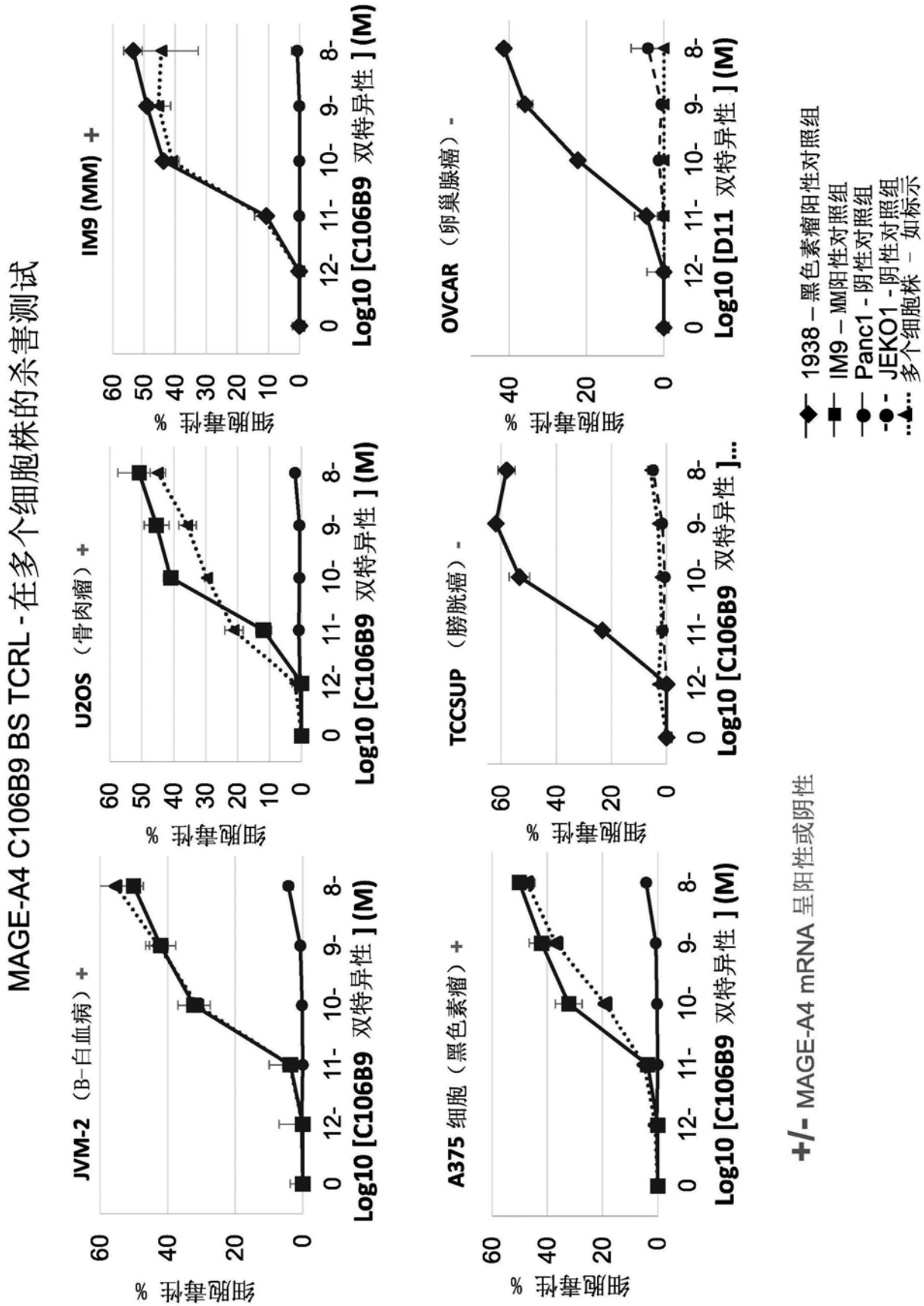

MAGE-A4 C106B9 BS TCRL - 在多个细胞株的杀害测试
JVM-2 （B-白血病）+
U2OS （骨肉瘤）+
IM9 (MM) +
A375 细胞（黑色素瘤）+
TCCSUP （膀胱癌）-
OVCAR （卵巢腺癌）-
细胞毒性 %
Log10 [C106B9 双特异性] (M)
Log10 [D11 双特异性] (M)
1938 – 黑色素瘤阳性对照组
IM9 – MM阳性对照组
Panc1 - 阴性对照组
JEKO1 - 阴性对照组
多个细胞株 – 如标示
+/- MAGE-A4 mRNA 呈阳性或阴性

图57

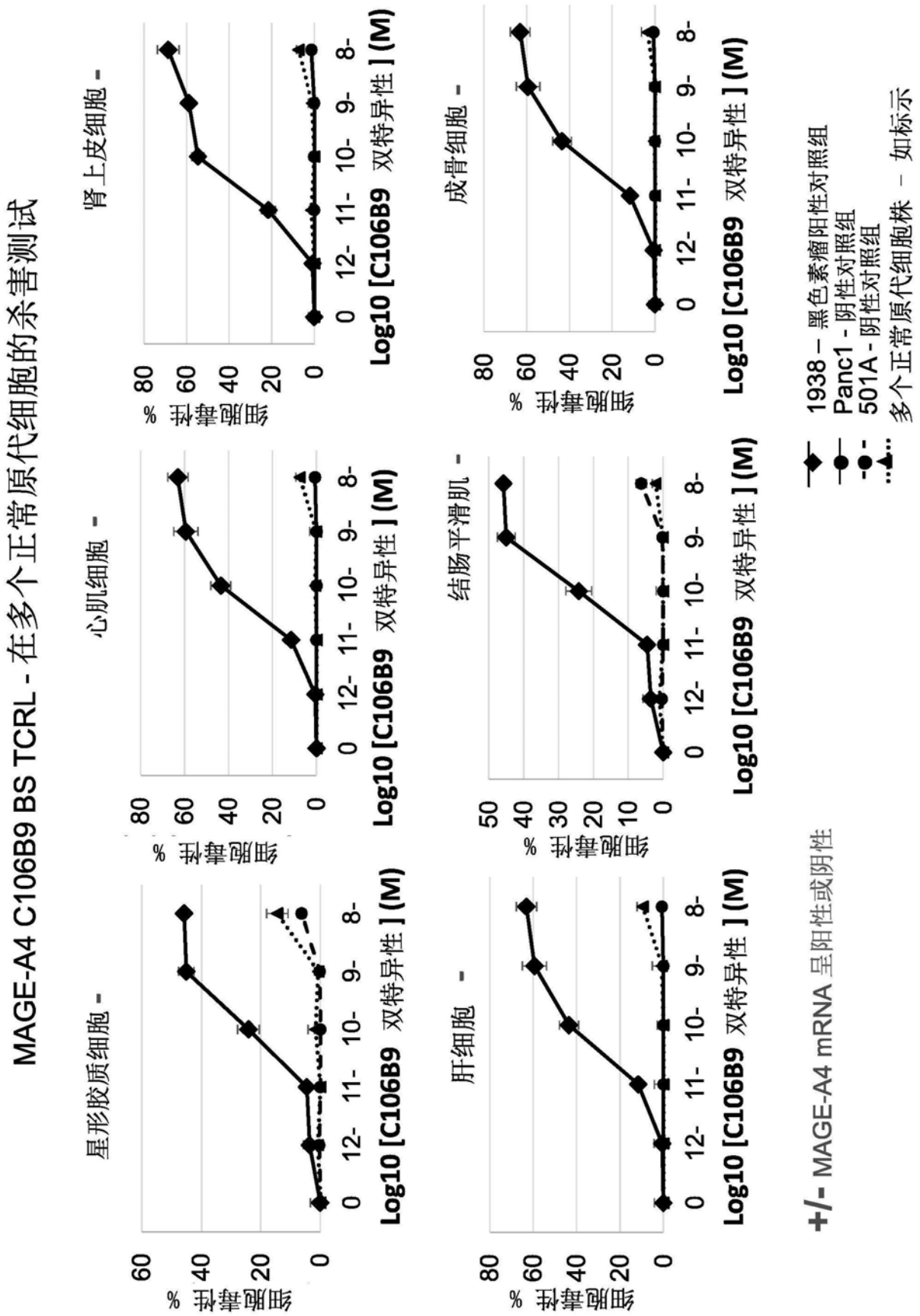

MAGE-A4 C106B9 BS TCRL - 在多个正常原代细胞的杀害测试
星形胶质细胞 -
心肌细胞 -
肾上皮细胞 -
肝细胞 -
结肠平滑肌 -
成骨细胞 -
细胞毒性 %
Log10 [C106B9 双特异性] (M)
1938 – 黑色素瘤阳性对照组
Panc1 - 阴性对照组
501A - 阴性对照组
多个正常原代细胞株 – 如标示
+/- MAGE-A4 mRNA 呈阳性或阴性

图58

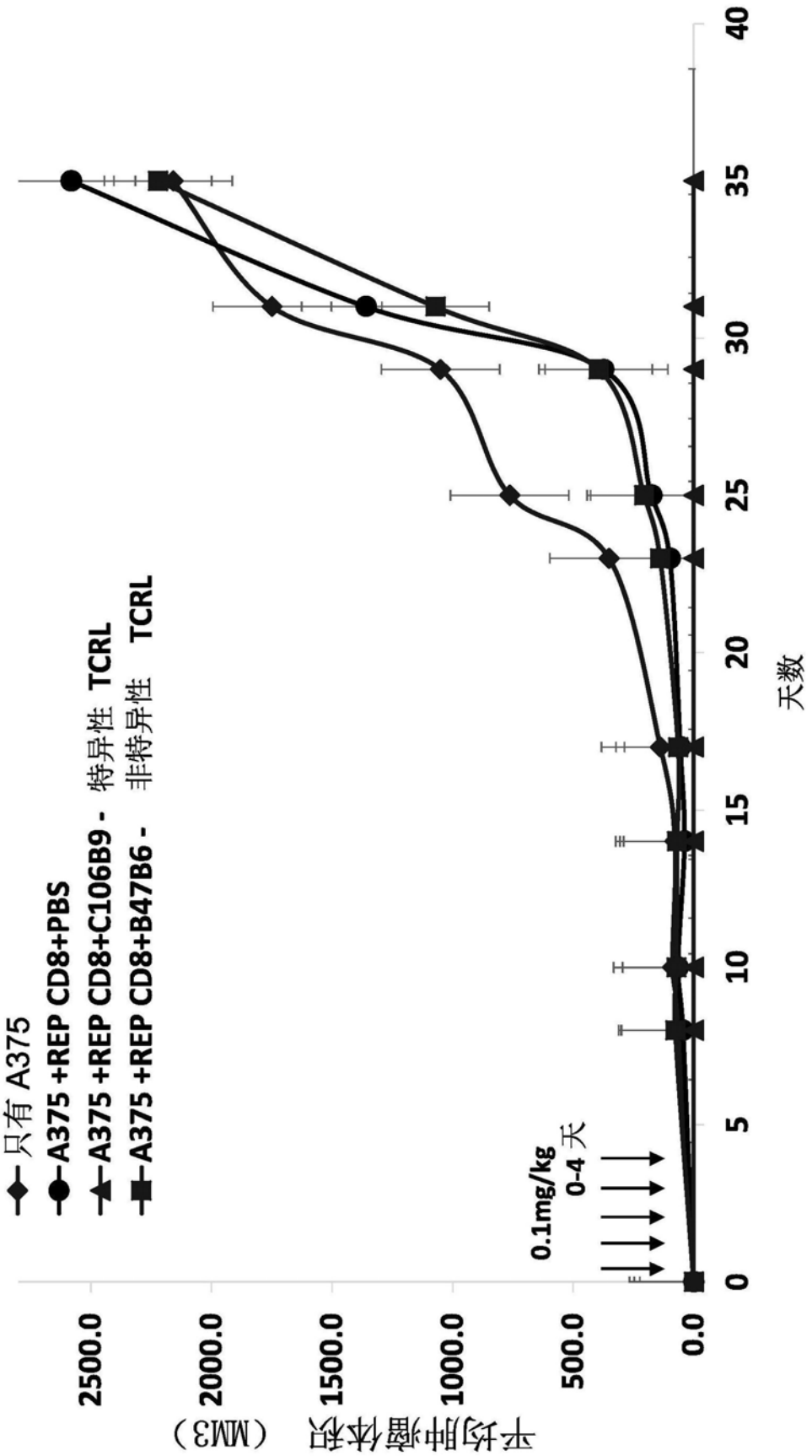

只有 A375
A375 +REP CD8+PBS
A375 +REP CD8+C106B9 - 特异性 TCRL
A375 +REP CD8+B47B6 - 非特异性 TCRL
0.1mg/kg
0-4 天
平均肿瘤体积 (MM3)
2500.0
2000.0
1500.0
1000.0
500.0
0.0
0
5
10
15
20
25
30
35
40
天数

图59


MAGE-A9 F184C7 TCRL
相对的MFI
61
51
41
31
21
11
1
MAGE-A9
T2
无胜肽
MAGE-A4
Tyr
WT1
SSX2
GAG
CMV
UHRF-1
PAP112
NY-ESO
MART1
胜肽

图60

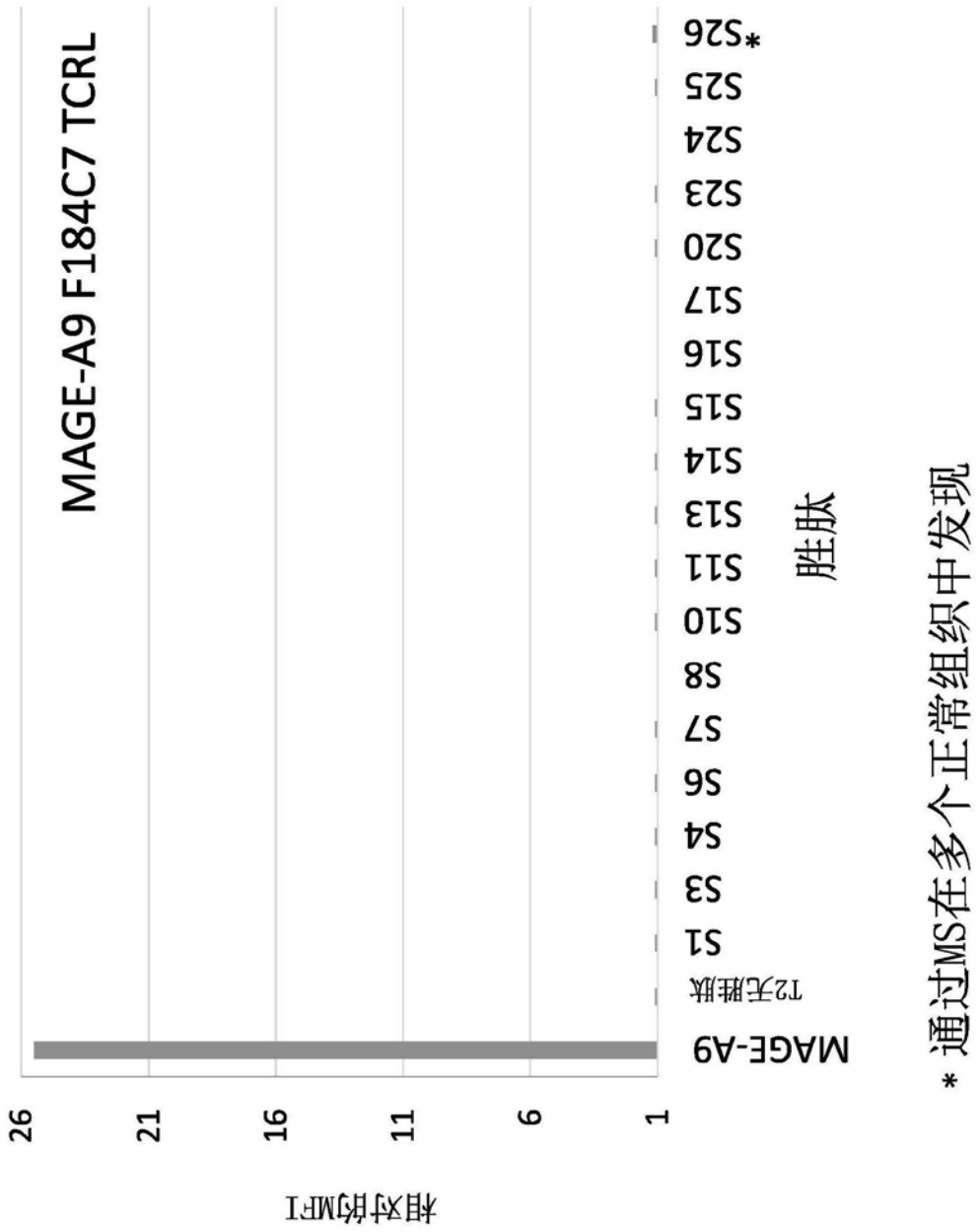

MAGE-A9 F184C7 TCRL
相对的MFI
26
21
16
11
6
1
MAGE-A9
T2无胜肽
S1
S3
S4
S6
S7
S8
S10
S11
S13
S14
S15
S16
S17
S20
S23
S24
S25
*S26
胜肽
* 通过MS在多个正常组织中发现

图61

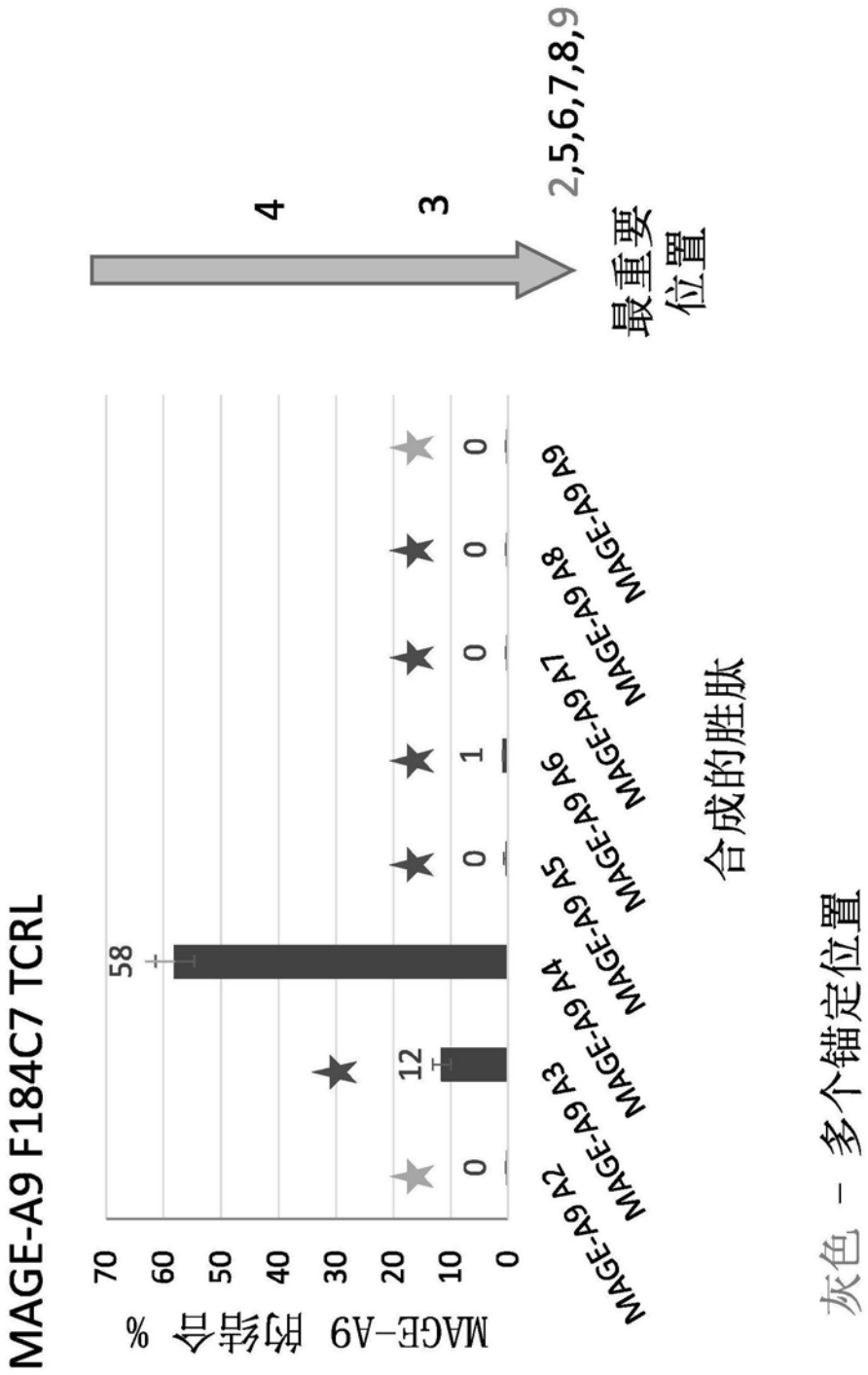

MAGE-A9 F184C7 TCRL
MAGE-A9 的结合 %
70
60
50
40
30
20
10
0
58
12
0
0
1
0
0
0
MAGE-A9 A2
MAGE-A9 A3
MAGE-A9 A4
MAGE-A9 A5
MAGE-A9 A6
MAGE-A9 A7
MAGE-A9 A8
MAGE-A9 A9
合成的胜肽
4
3
2,5,6,7,8,9
最重要位置
灰色 – 多个锚定位置

图62


MAGE-A9 F184C7 TCRL
相对的MFI
31
26
21
16
11
6
1
T2 + MAGE-A9
星形胶质细胞
心肌细胞
结肠平滑肌
支气管上皮
肾近端
肝细胞
表皮角质细胞
尿道上皮细胞
成骨细胞 - 股骨

图63

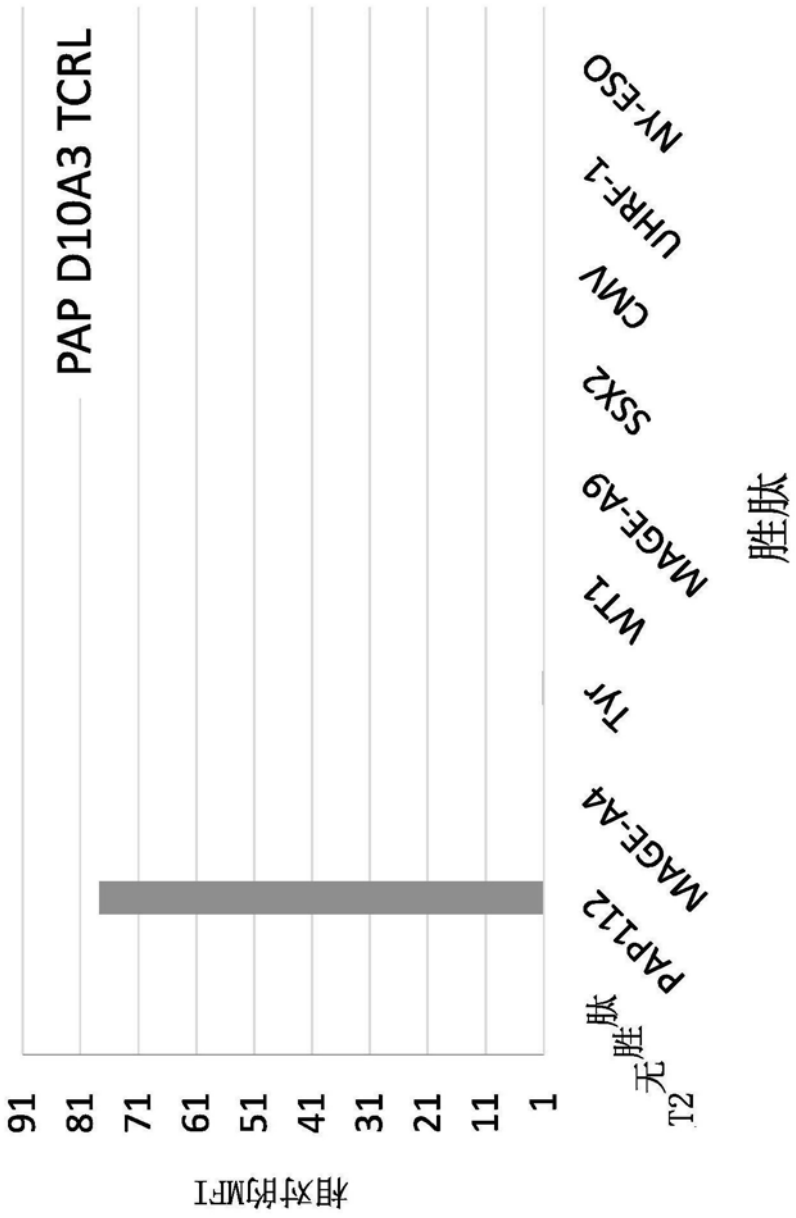

PAP D10A3 TCRL
91
81
71
61
51
41
31
21
11
1
相对的MFI
T2
无胜肽
PAP112
MAGE-A4
Tyr
WT1
MAGE-A9
SSX2
CMV
UHRF-1
NY-ESO
胜肽

图64

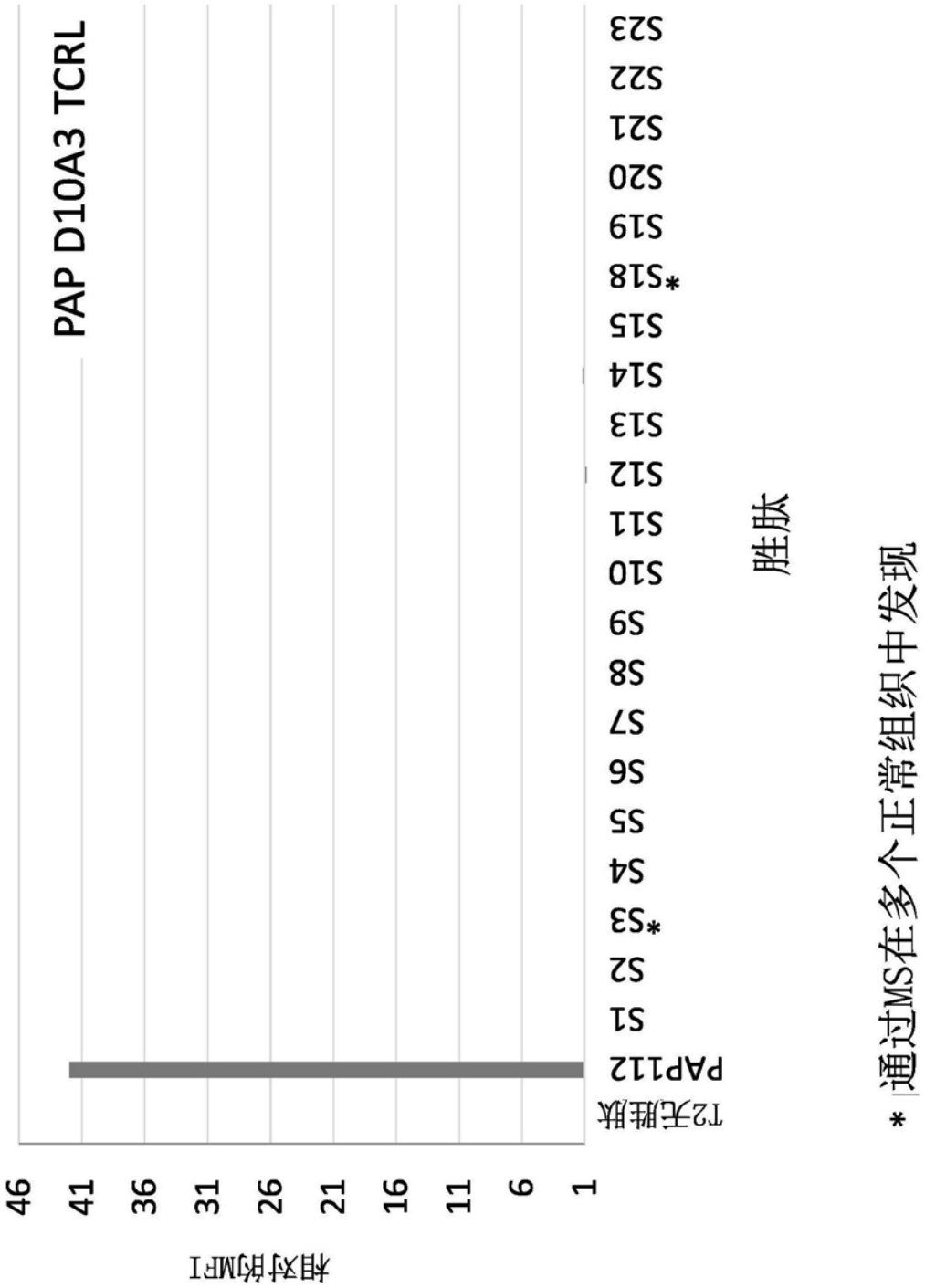

PAP D10A3 TCRL
相对的MFI
46
41
36
31
26
21
16
11
6
1
T2无胜肽
PAP112
S1
S2
*S3
S4
S5
S6
S7
S8
S9
S10
S11
S12
S13
S14
S15
*S18
S19
S20
S21
S22
S23
胜肽
* 通过MS在多个正常组织中发现

图65

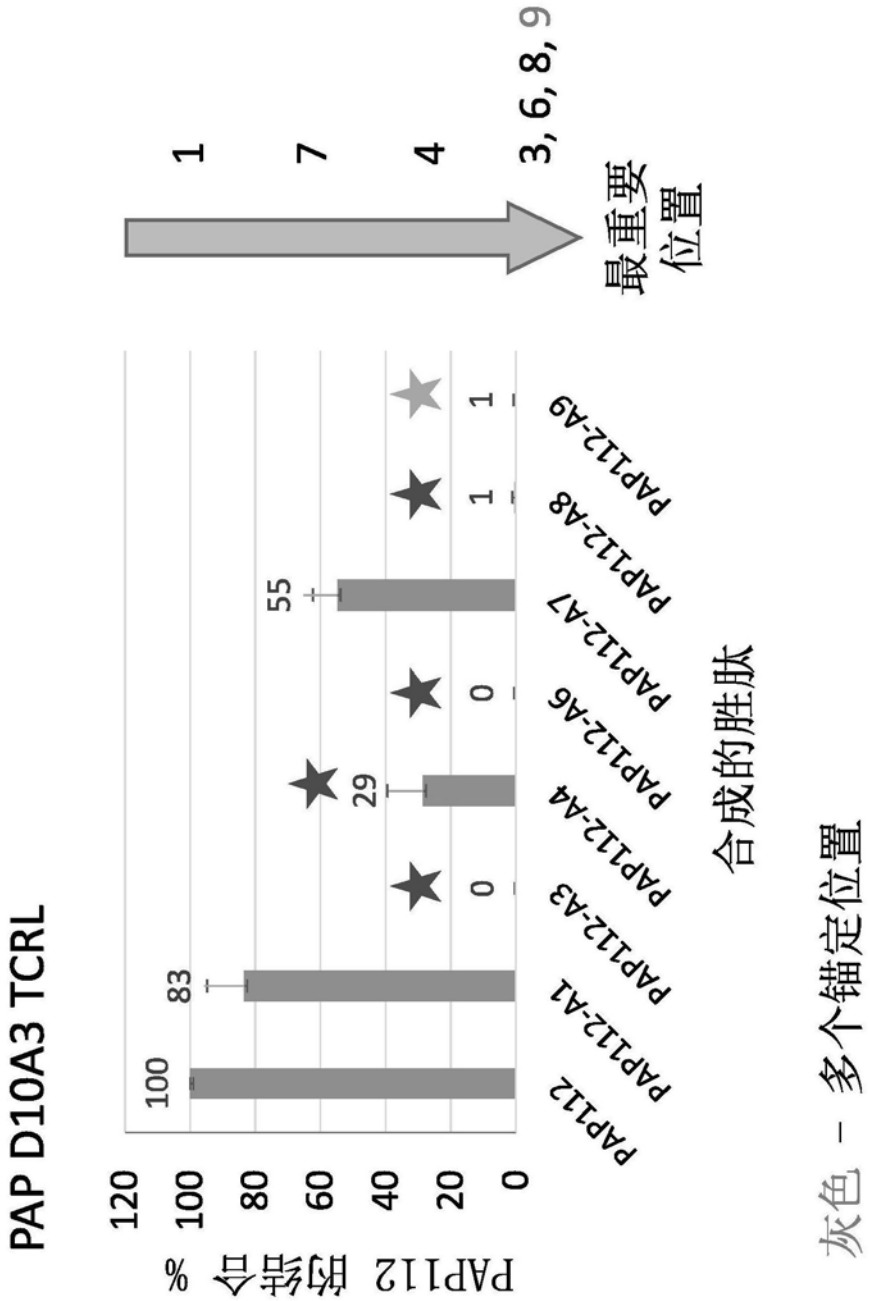

PAP D10A3 TCRL
PAP112 的结合 %
120
100
80
60
40
20
0
100
83
0
29
0
55
1
1
PAP112
PAP112-A1
PAP112-A3
PAP112-A4
PAP112-A6
PAP112-A7
PAP112-A8
PAP112-A9
合成的胜肽
1
7
4
3, 6, 8, 9
最重要位置
灰色 – 多个锚定位置

图66


PAP D10A3 TCRL
相对的MFI
46
41
36
31
26
21
16
11
6
1
T2 胜肽 112
星形胶质细胞
心肌细胞
结肠平滑肌
支气管上皮
肾近端
肝细胞
表皮角质细胞
尿道上皮细胞
成骨细胞 - 股骨

图67

906-11-D11

重链：DNA序列（1398 个碱基对）

引导序列 -FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-恒定区 - 终止密码子

ATGGACAGGCTTACTTCCTCATTCCTGCTGCTGATTGTCCCTGCATATGTCCTTTCCCAGGTAACTC
TGAAAGAGTCTGGCCCTGGGATATTGCAGCCCTCCCAGACCCTCAGTCTGACTTGTTCTTTCTCTGG
GTTTTCACTGACCACTTCTGGTATGGGTGTGAGCTGGATTCGTCAGCCTTCAGGAAAGGGTCTGGAG
TGGCTGGCACACATTTACTGGGATGATGACAAGCGCTATAACCCATCCCTGAAGAGCCGACTCACAA
TCTCCAAGGATACCTCCAGAAACCAGGTATTCCTCAAGATCACCAGTGTGGACGCTGCAGATACTGC
CACATACTACTGTGCTCGAAAGGACTACGGTAGTAGCTTCTATGCTATGCACTACTGGGGTCAAGGA
ACCTCAGTCACCGTCTCCTCAGCCAAAACGACACCCCCATCTGTCTATCCACTGGCCCCTGGATCTG
CTGCCCAAACTAACTCCATGGTGACCCTGGGATGCCTGGTCAAGGGCTATTTCCCTGAGCCAGTGAC
AGTGACCTGGAACTCTGGATCCCTGTCCAGCGGTGTGCACACCTTCCCAGCTGTCCTGCAGTCTGAC
CTCTACACTCTGAGCAGCTCAGTGACTGTCCCCTCCAGCACCTGGCCCAGCGAGACCGTCACCTGCA
ACGTTGCCCACCCGGCCAGCAGCACCAAGGTGGACAAGAAAATTGTGCCCAGGGATTGTGGTTGTAA
GCCTTGCATATGTACAGTCCCAGAAGTATCATCTGTCTTCATCTTCCCCCCAAAGCCCAAGGATGTG
CTCACCATTACTCTGACTCCTAAGGTCACGTGTGTTGTGGTAGACATCAGCAAGGATGATCCCGAGG
TCCAGTTCAGCTGGTTTGTAGATGATGTGGAGGTGCACACAGCTCAGACGCAACCCCGGGAGGAGCA
GTTCAACAGCACTTTCCGCTCAGTCAGTGAACTTCCCATCATGCACCAGGACTGGCTCAATGGCAAG
GAGTTCAAATGCAGGGTCAACAGTGCAGCTTTCCCTGCCCCCATCGAGAAAACCATCTCCAAAACCA
AAGGCAGACCGAAGGCTCCACAGGTGTACACCATTCCACCTCCCAAGGAGCAGATGGCCAAGGATAA
AGTCAGTCTGACCTGCATGATAACAGACTTCTTCCCTGAAGACATTACTGTGGAGTGGCAGTGGAAT
GGGCAGCCAGCGGAGAACTACAAGAACACTCAGCCCATCATGGACACAGATGGCTCTTACTTCGTCT
ACAGCAAGCTCAATGTGCAGAAGAGCAACTGGGAGGCAGGAAATACTTTCACCTGCTCTGTGTTACA
TGAGGGCCTGCACAACCACCATACTGAGAAGAGCCTCTCCCACTCTCCTGGTAAATGA

重链：氨基酸序列（465 个氨基酸）

引导序列 -FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-恒定区 - 终止密码子

MDRLTSSFLLLIVPAYVLSQVTLKESGPGILQPSQTLSLTCSFSGFSLTTSGMGVSWIRQPSGKGLE
WLAHIYWDDDKRYNPSLKSRLTISKDTSRNQVFLKITSVDAADTATYYCARKDYGSSFYAMHYWGQG
TSVTVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSD
LYTLSSSVTVPSSTWPSETVTCNVAHPASSTKVDKKIVPRDCGCKPCICTVPEVSSVFIFPPKPKDV
LTITLTPKVTCVVVDISKDDPEVQFSWFVDDVEVHTAQTQPREEQFNSTFRSVSELPIMHQDWLNGK
EFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQWN
GQPAENYKNTQPIMDTDGSYFVYSKLNVQKSNWEAGNTFTCSVLHEGLHNHHTEKSLSHSPGK

轻链：DNA序列（702 个碱基对）

引导序列 -FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-恒定区 - 终止密码子

ATGAGACCGTCTATTCAGTTCCTGGGGCTCTTGTTGTTCTGGCTTCATGGTGCTCAGTGTGACATCC
AGATGACACAGTCTCCATCCTCACTGTCTGCATCTCTGGGAGGCAAAGTCACCATCACATGCAAGGC
AAGCCAAGACATTCACAACTATATAGCTTGGTACCAACACAAGCCTGTAAAAGGTCCTAGGCTGCTC
ATACATTACACATCTACATTACAGCCAGGCACCCCATCAAGGTTCAGTGGAAGTGGGTCTGGGAGAG
ATTATTCCTTCAGCATCAGCAACCTGGAGCCTGAAGATATTGCAACTTATTATTGTCTACAGTATGA
TAATCTGTGGACGTTCGGTGGAGGCACCAAGCTGGAAATCAAACGGGCTGATGCTGCACCAACTGTA
TCCATCTTCCCACCATCCAGTGAGCAGTTAACATCTGGAGGTGCCTCAGTCGTGTGCTTCTTGAACA
ACTTCTACCCCAAAGACATCAATGTCAAGTGGAAGATTGATGGCAGTGAACGACAAAATGGCGTCCT
GAACAGTTGGACTGATCAGGACAGCAAAGACAGCACCTACAGCATGAGCAGCACCCTCACGTTGACC
AAGGACGAGTATGAACGACATAACAGCTATACCTGTGAGGCCACTCACAAGACATCAACTTCACCCA
TTGTCAAGAGCTTCAACAGGAATGAGTGTTAG

重链：氨基酸序列（233 个氨基酸）

引导序列 -FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-恒定区 - 终止密码子

MRPSIQFLGLLLFWLHGAQCDIQMTQSPSSLSASLGGKVTITCKASQDIHNYIAWYQHKPVKGPRLL
IHYTSTLQPGTPSRFSGSGSGRDYSFSISNLEPEDIATYYCLQYDNLWTFGGGTKLEIKRADAAPTV
SIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLT
KDEYERHNSYTCEATHKTSTSPIVKSFNRNEC

图68

重链：DNA序列（1380 个碱基对）

引导序列 -FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4- 恒定区 - 终止密码子

ATGGCTGTCCTGGTGCTGTTCCTCTGCCTGGTTGCATTTCCAAGCTGTGTCCTGTCCCAGGTGCAAC
TGAAGGAATCAGGACCTGGTCTGGTGGCGCCCTCACAGAGCCTGTCCATCACTTGCACTGTCTCTGG
GTTTTCATTAACCAGCTATGGTGTACACTGGGTTCGCCAGCCTCCAGGAAAGGGTCTGGAGTGGCTG
GGAGTAATATGGGCTGGTGGAACCACAAATTATAATTCGGCTCTCATGTCCAGACTGAGCATCAGCA
GAGACAACTCCAAGAGCCAAGTTTTCTTAGAAATGAACAGTCTGCAAACTGATGACACAGCCATTTA
CTACTGTGCCAGAGATGGTCACTTCCACTTTGACTTCTGGGGCCAAGGCACCACTCTCACAGTCTCC
TCAGCCAAAACGACACCCCCATCTGTCTATCCACTGGCCCCTGGATCTGCTGCCCAAACTAACTCCA
TGGTGACCCTGGGATGCCTGGTCAAGGGCTATTTCCCTGAGCCAGTGACAGTGACCTGGAACTCTGG
ATCCCTGTCCAGCGGTGTGCACACCTTCCCAGCTGTCCTGCAGTCTGACCTCTACACTCTGAGCAGC
TCAGTGACTGTCCCCTCCAGCACCTGGCCCAGCGAGACCGTCACCTGCAACGTTGCCCACCCGGCCA
GCAGCACCAAGGTGGACAAGAAAATTGTGCCCAGGGATTGTGGTTGTAAGCCTTGCATATGTACAGT
CCCAGAAGTATCATCTGTCTTCATCTTCCCCCCAAAGCCCAAGGATGTGCTCACCATTACTCTGACT
CCTAAGGTCACGTGTGTTGTGGTAGACATCAGCAAGGATGATCCCGAGGTCCAGTTCAGCTGGTTTG
TAGATGATGTGGAGGTGCACACAGCTCAGACGCAACCCCGGGAGGAGCAGTTCAACAGCACTTTCCG
CTCAGTCAGTGAACTTCCCATCATGCACCAGGACTGGCTCAATGGCAAGGAGTTCAAATGCAGGGTC
AACAGTGCAGCTTTCCCTGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGCAGACCGAAGGCTC
CACAGGTGTACACCATTCCACCTCCCAAGGAGCAGATGGCCAAGGATAAAGTCAGTCTGACCTGCAT
GATAACAGACTTCTTCCCTGAAGACATTACTGTGGAGTGGCAGTGGAATGGGCAGCCAGCGGAGAAC
TACAAGAACACTCAGCCCATCATGGACACAGATGGCTCTTACTTCGTCTACAGCAAGCTCAATGTGC
AGAAGAGCAACTGGGAGGCAGGAAATACTTTCACCTGCTCTGTGTTACATGAGGGCCTGCACAACCA
CCATACTGAGAAGAGCCTCTCCCACTCTCCTGGTAAATGA

重链：氨基酸序列（459 个氨基酸）

引导序列 -FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4- 恒定区 - 终止密码子

MAVLVLFLCLVAFPSCVLSQVQLKESGPGLVAPSQSLSITCTVSGFSLTSYGVHWVRQPPGKGLEWL
GVIWAGGTTNYNSALMSRLSISRDNSKSQVFLEMNSLQTDDTAIYYCARDGHFHFDFWGQGTTLTVS
SAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSS
SVTVPSSTWPSETVTCNVAHPASSTKVDKKIVPRDCGCKPCICTVPEVSSVFIFPPKPKDVLTITLT
PKVTCVVVDISKDDPEVQFSWFVDDVEVHTAQTQPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRV
NSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQWNGQPAEN
YKNTQPIMDTDGSYFVYSKLNVQKSNWEAGNTFTCSVLHEGLHNHHTEKSLSHSPGK

轻链：DNA序列（705 个碱基对）

引导序列 -FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4- 恒定区 - 终止密码子

ATGAGTGTGCCCACTCAGGTCCTGGGGTTGCTGCTGCTGTGGCTTACAGATGCCAGATGTGACATCC
AGATGACTCAGTCTCCAGCCTCCCTATCTGTATCTGTGGGAGAAACTGTCACCATCACATGTCGAGC
AAGTGATATTATTTACAGTAATTTAGCATGGTATCAGCAGAAACAGGGAAAATCTCCTCAGCTCCTG
GTCTATGCTGCAACAAACTTAGCAGCTGGTGTGCCATCAAGGTTCAGTGGCAGTGGATCAGGCACAC
AGTATTCCCTCAAGATCAATAGCCTGCAGTCTGAAGATTTTGGGACTTATTACTGTCAACATTTTTG
GGGTAGTTCAATCTCGTTCGGCTCGGGGACAAAGTTGGAAATAAAACGGGCTGATGCTGCACCAACT
GTATCCATCTTCCCACCATCCAGTGAGCAGTTAACATCTGGAGGTGCCTCAGTCGTGTGCTTCTTGA
ACAACTTCTACCCCAAAGACATCAATGTCAAGTGGAAGATTGATGGCAGTGAACGACAAAATGGCGT
CCTGAACAGTTGGACTGATCAGGACAGCAAAGACAGCACCTACAGCATGAGCAGCACCCTCACGTTG
ACCAAGGACGAGTATGAACGACATAACAGCTATACCTGTGAGGCCACTCACAAGACATCAACTTCAC
CCATTGTCAAGAGCTTCAACAGGAATGAGTGTTAG

重链：氨基酸序列（234 个氨基酸）

引导序列 -FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4- 恒定区 - 终止密码子

MSVPTQVLGLLLLWLTDARCDIQMTQSPASLSVSVGETVTITCRASDIIYSNLAWYQQKQGKSPQLL
VYAATNLAAGVPSRFSGSGSGTQYSLKINSLQSEDFGTYYCQHFWGSSISFGSGTKLEIKRADAAPT
VSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTL
TKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC

图69

WT1 B47B6 TCRL 序列

重链：DNA序列

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-恒定区

GAAGTGCAGTTGGTGGAGTCGGGGGGAGGCTTAGTGAAGCCTGGAGGGTCCCTGAAACTCTCCTGTGCAGCCTC
TGGATTCGTTTTCAGTAGCTATGACATGTCTTGGGTTCGCCAGGCTCAGGAGAAGAGGCTGGAGTGGGTCGCATA
CATGAGTAGTGGTGGCGGCACCTACTATCCAGACACTGTGAAGGGCCGATTCACCATCTCCAGAGACAATGCCAA
GAACACCCTGCACCTGCAAATGAGCAGCCTGAAGTCTGAGGACACAGCCATGTATTACTGTGCAAGACATGATGA
GATTACTAACTTTGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCAGCCAAAACGACACCCCCATCTGT
CTATCCACTGGCCCCTGGATCTGCTGCCCAAACTAACTCCATGGTGACCCTGGGATGCCTGGTCAAGGGC
TATTTCCCTGAGCCAGTGACAGTGACCTGGAACTCTGGATCCCTGTCCAGCGGTGTGCACACCTTCCCAG
CTGTCCTGCAGTCTGACCTCTACACTCTGAGCAGCTCAGTGACTGTCCCCTCCAGCACCTGGCCCAGCGA
GACCGTCACCTGCAACGTTGCCCACCCGGCCAGCAGCACCAAGGTGGACAAGAAAATTGTGCCCAGGGAT
TGTGGTTGTAAGCCTTGCATATGTACAGTCCCAGAAGTATCATCTGTCTTCATCTTCCCCCCAAAGCCCA
AGGATGTGCTCACCATTACTCTGACTCCTAAGGTCACGTGTGTTGTGGTAGACATCAGCAAGGATGATCC
CGAGGTCCAGTTCAGCTGGTTTGTAGATGATGTGGAGGTGCACACAGCTCAGACGCAACCCCGGGAGGAG
CAGTTCAACAGCACTTTCCGCTCAGTCAGTGAACTTCCCATCATGCACCAGGACTGGCTCAATGGCAAG
GAGTTCAAATGCAGGGTCAACAGTGCAGCTTTCCCTGCCCCCATCGAGAAAACCATCTCCAAAACCAAAG
GCAGACCGAAGGCTCCACAGGTGTACACCATTCCACCTCCCAAGGAGCAGATGGCCAAGGATAAAGTCAG
TCTGACCTGCATGATAACAGACTTCTTCCCTGAAGACATTACTGTGGAGTGGCAGTGGAATGGGCAGCCA
GCGGAGAACTACAAGAACACTCAGCCCATCATGGACACAGATGGCTCTTACTTCGTCTACAGCAAGCTCA
ATGTGCAGAAGAGCAACTGGGAGGCAGGAAATACTTTCACCTGCTCTGTGTTACATGAGGGCCTGCACAA
CCACCATACTGAGAAGAGCCTCTCCCACTCTCCTGGTAAA

EVQLVESGGGLVKPGGSLKLSCAASGFVFSSYDMSWVRQAQEKRLEWVAYMSSGGGTYYPDTVKGRFTISRDNAKNT
LHLQMSSLKSEDTAMYYCARHDEITNFDYWGQGTTLTVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFP
EPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVAHPASSTKVDKKIVPRDCGC
KPCICTVPEVSSVFIFPPKPKDVLTITLTPKVTCVVVDISKDDPEVQFSWFVDDVEVHTAQTQPREEQFN
STFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTC
MITDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSKLNVQKSNWEAGNTFTCSVLHEGLHNHHT
EKSLSHSPGK

轻链：DNA序列

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-恒定区

GATATTGTGCTCACTCAGTCTCCAGCCACCCTGTCTGTGAGTCCAGGAGATAGCGTCAGTCTTTCCTGCAGGGCCAGCCAAAGT
ATTAGCAACAGCCTACACTGGTATCAACAAAAATCACATGAGTCTCCAAGGCTTCTCATCAAGTATGCTTCCCAGTCCATcTCTG
GAATCCCCTCTAGGTTCAGTGGCAGTGGATCAGGGACAGATTTCACtCTCAGTATCAACAGTGTGGAGACTGAAGATTTTGGA
ATGTATTTCTGTCAACAGAGTTACAGCTGGCCTCTCACGTTCGGTGCTGGGTCCAAGCTGGAGCTGAAACGGGCTGATGCT
GCACCAACTGTATCCATCTTCCCACCATCCAGTGAGCAGTTAACATCTGGAGGTGCCTCAGTCGTGTGCT
TCTTGAACAACTTCTACCCCAAAGACATCAATGTCAAGTGGAAGATTGATGGCAGTGAACGACAAAATGG
CGTCCTGAACAGTTGGACTGATCAGGACAGCAAAGACAGCACCTACAGCATGAGCAGCACCCTCACGTTG
ACCAAGGACGAGTATGAACGACATAACAGCTATACCTGTGAGGCCACTCACAAGACATCAACTTCACCCA
TTGTCAAGAGCTTCAACAGGAATGAGTGT

图70

DIVLTQSPATLSVSPGDSVSLSCRASQSISNSLHWYQQKSHESPRLLIKYASQSISGIPSRFSGSGSGTDFTLSINSVETEDFGMYFCQQ
SYSWPLTFGAGSKLELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWT
DQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC

图70-续

C106B9 MAGE-A4 TCRL

重链：DNA序列

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-恒定区

Nuc-seq:

CAGGTTCAACTGCAGCAGTCTGGAGGTGAGGTGATGAAGCCTGGGGCCTCAGTGAAGCTTTCCTGCAAGGCTACT
GGCTACACATTCACTGGCTACTGGATAGAGTGGATAAAACAGAGGCCTGGACATGGCCTTGAGTGGATTGGAGA
GATTTTACCTGGAAGTGGTGGTACTAACTACAATGAGAAATTCAAGGGCAAGGCCACATTCACTGCACATACATCC
TCCAACACAGCCTACATGCAACTCAGCAGCCTGACAACTGAGGACTCTGCCATCTATTACTGTGCAAGGGATAGTA
ACTCCTTTACTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTTCAGCCAAAACGACACCCCCATCTGTCTATC
CACTGGCCCCTGGATCTGCTGCCCAAACTAACTCCATGGTGACCCTGGGATGCCTGGTCAAGGGCTATTT
CCCTGAGCCAGTGACAGTGACCTGGAACTCTGGATCCCTGTCCAGCGGTGTGCACACCTTCCCAGCTGTC
CTGCAGTCTGACCTCTACACTCTGAGCAGCTCAGTGACTGTCCCCTCCAGCACCTGGCCCAGCGAGACCG
TCACCTGCAACGTTGCCCACCCGGCCAGCAGCACCAAGGTGGACAAGAAAATTGTGCCCAGGGATTGTGG
TTGTAAGCCTTGCATATGTACAGTCCCAGAAGTATCATCTGTCTTCATCTTCCCCCCAAAGCCCAAGGAT
GTGCTCACCATTACTCTGACTCCTAAGGTCACGTGTGTTGTGGTAGACATCAGCAAGGATGATCCCGAGG
TCCAGTTCAGCTGGTTTGTAGATGATGTGGAGGTGCACACAGCTCAGACGCAACCCCGGGAGGAGCAGTT
CAACAGCACTTTCCGCTCAGTCAGTGAACTTCCCATCATGCACCAGGACTGGCTCAATGGCAAGGAGTTC
AAATGCAGGGTCAACAGTGCAGCTTTCCCTGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGCAGAC
CGAAGGCTCCACAGGTGTACACCATTCCACCTCCCAAGGAGCAGATGGCCAAGGATAAAGTCAGTCTGAC
CTGCATGATAACAGACTTCTTCCCTGAAGACATTACTGTGGAGTGGCAGTGGAATGGGCAGCCAGCGGAG
AACTACAAGAACACTCAGCCCATCATGGACACAGATGGCTCTTACTTCGTCTACAGCAAGCTCAATGTGC
AGAAGAGCAACTGGGAGGCAGGAAATACTTTCACCTGCTCTGTGTTACATGAGGGCCTGCACAACCACCA
TACTGAGAAGAGCCTCTCCCACTCTCCTGGTAAA

AA-seq:

QVQLQQSGGEVMKPGASVKLSCKATGYTFTGYWIEWIKQRPGHGLEWIGEILPGSGGTNYNEKFKGKATFTAHTSSN
TAYMQLSSLTTEDSAIYYCARDSNSFTYWGQGTLVTVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEP
VTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVAHPASSTKVDKKIVPRDCGCKP
CICTVPEVSSVFIFPPKPKDVLTITLTPKVTCVVVDISKDDPEVQFSWFVDDVEVHTAQTQPREEQFNST
FRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMI
TDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSKLNVQKSNWEAGNTFTCSVLHEGLHNHHTEK
SLSHSPGK

轻链

轻链：DNA序列

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-恒定区

CAAATTGTTCTCACCCAGTCTCCAGCAATCATGTCTGCATCTCCAGGGGAGAAGGTCACCATAACCTGCAGTGTCA
GCTCAAGTGTAGATTACATTCACTGGTTCCAGCAGAAGCCAGGCACTTCTCCCAAATTCTGGATTTATAGCACATCC
ATCCTGGCTTCTGGAGTCCCTGCTCGCTTCAGTGGCAGTGGATCTGGGACCTCTTACTCTCTCACAATCAGCCGAAT
GGAGGCTGAAGATGCTGCCACTTATTACTGCCAGCAAAGGAGtAGTTACCCACCCACgTTCGGCTCGGGGACAAAGT

图71

TGGAAATAAAACGGGCTGATGCTGCACCAACTGTATCCATCTTCCCACCATCCAGTGAGCAGTTAACATCTG
GAGGTGCCTCAGTCGTGTGCTTCTTGAACAACTTCTACCCCAAAGACATCAATGTCAAGTGGAAGATTGA
TGGCAGTGAACGACAAAATGGCGTCCTGAACAGTTGGACTGATCAGGACAGCAAAGACAGCACCTACAGC
ATGAGCAGCACCCTCACGTTGACCAAGGACGAGTATGAACGACATAACAGCTATACCTGTGAGGCCACTC
ACAAGACATCAACTTCACCCATTGTCAAGAGCTTCAACAGGAATGAGTGT

AA-seq:

QIVLTQSPAIMSASPGEKVTITCSVSSSVDYIHWFQQKPGTSPKFWIYSTSILASGVPARFSGSGSGTSYSLTISRMEAEDA
ATYYCQQRSSYPPTFGSGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQN
GVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC

图71-续

F184C7 MAGE A9

重链：DNA序列

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-恒定区

Nuc-seq:

CAGGTTCAGCTGCAGCAGTCTGGACCTGAGATGGTGAAGCCTGGGGCCTCAGTGAAGATTCCCTGCAAGGCTTCT
GGCTACGCATTCAGTAGCTCCTGGATGAACTGGGTGAAGCAGAGGCCTGGAAAGGGTCTTGAGTGGATTGGACG
GATTTATCCTGGAGATGGAGATACTAACTACAATGAGAAGTTCAAGGGCAAGGCCACACTGACTGTAGACAAATC
CTCCAGCACAGTCTACATGCAACTCAGCAGCCTGACATCTGAGGACTCTGCGGTCTACTTCTGTGCAAGAGAGGCT
ACTACGGTAGTGGCCCCGTACTACTTTGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCAGCCAAAACGA
CACCCCCATCTGTCTATCCACTGGCCCCTGGATCTGCTGCCCAAACTAACTCCATGGTGACCCTGGGATG
CCTGGTCAAGGGCTATTTCCCTGAGCCAGTGACAGTGACCTGGAACTCTGGATCCCTGTCCAGCGGTGTG
CACACCTTCCCAGCTGTCCTGCAGTCTGACCTCTACACTCTGAGCAGCTCAGTGACTGTCCCCTCCAGCA
CCTGGCCCAGCGAGACCGTCACCTGCAACGTTGCCCACCCGGCCAGCAGCACCAAGGTGGACAAGAAAAT
TGTGCCCAGGGATTGTGGTTGTAAGCCTTGCATATGTACAGTCCCAGAAGTATCATCTGTCTTCATCTTC
CCCCCAAAGCCCAAGGATGTGCTCACCATTACTCTGACTCCTAAGGTCACGTGTGTTGTGGTAGACATCA
GCAAGGATGATCCCGAGGTCCAGTTCAGCTGGTTTGTAGATGATGTGGAGGTGCACACAGCTCAGACGCA
ACCCCGGGAGGAGCAGTTCAACAGCACTTTCCGCTCAGTCAGTGAACTTCCCATCATGCACCAGGACTGG
CTCAATGGCAAGGAGTTCAAATGCAGGGTCAACAGTGCAGCTTTCCCTGCCCCCATCGAGAAAACCATCT
CCAAAACCAAAGGCAGACCGAAGGCTCCACAGGTGTACACCATTCCACCTCCCAAGGAGCAGATGGCCAA
GGATAAAGTCAGTCTGACCTGCATGATAACAGACTTCTTCCCTGAAGACATTACTGTGGAGTGGCAGTGG
AATGGGCAGCCAGCGGAGAACTACAAGAACACTCAGCCCATCATGGACACAGATGGCTCTTACTTCGTCT
ACAGCAAGCTCAATGTGCAGAAGAGCAACTGGGAGGCAGGAAATACTTTCACCTGCTCTGTGTTACATGA
GGGCCTGCACAACCACCATACTGAGAAGAGCCTCTCCCACTCTCCTGGTAAA

AA-seq:

QVQLQQSGPEMVKPGASVKIPCKASGYAFSSSWMNWVKQRPGKGLEWIGRIYPGDGDTNYNEKFKGKATLTVDKSS
STVYMQLSSLTSEDSAVYFCAREATTVVAPYYFDYWGQGTTLTVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCLV
KGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVAHPASSTKVDKKIVP
RDCGCKPCICTVPEVSSVFIFPPKPKDVLTITLTPKVTCVVVDISKDDPEVQFSWFVDDVEVHTAQTQPR
EEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKDK
VSLTCMITDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSKLNVQKSNWEAGNTFTCSVLHEGL
HNHHTEKSLSHSPGK

轻链：DNA序列

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-恒定区

Nuq-seq:

GACATcCAGATGACTCAGTCTCCAGCCTCCCTATCTGTATCTGTGGGAGAAACTGTCACCATCACATGTCGAGCAA
GTGAGAATATTTACAGAAATTTAGCATGGTATCAGCAGAAACAGGGAAAATCTCCTCAACTCCTGGTCCATGCTGC
AACAAACTTAGCAGATGGTGTGCCATCAAGGTTCAGTGGCAGTGGATCAGACACACAGTATTCCCTCAAGATCAA
CAGCCTGCAGTCTGAAGATTTTGGGAATTATTACTGTCAACATTTTTGGGGGACTCCGCTCACGTTCGGTGCTGGG

图72

ACCAAGCTGGAGCTGAAACGGGCTGATGCTGCACCAACTGTATCCATCTTCCCACCATCCAGTGAGCAGTT
AACATCTGGAGGTGCCTCAGTCGTGTGCTTCTTGAACAACTTCTACCCCAAAGACATCAATGTCAAGTGG
AAGATTGATGGCAGTGAACGACAAAATGGCGTCCTGAACAGTTGGACTGATCAGGACAGCAAAGACAGCA
CCTACAGCATGAGCAGCACCCTCACGTTGACCAAGGACGAGTATGAACGACATAACAGCTATACCTGTGA
GGCCACTCACAAGACATCAACTTCACCCATTGTCAAGAGCTTCAACAGGAATGAGTGT

AA-seq:
DIQMTQSPASLSVSVGETVTITCRASENIYRNLAWYQQKQGKSPQLLVHAATNLADGVPSRFSGSGSDTQYSLKINSLQ
SEDFGNYYCQHFWGTPLTFGAGTKLELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDG
SERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC

图72-续

D10A3 PAP TCRL

重链：DNA序列

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-恒定区

Nuc seq

GAGGTCCAGCTGCAACAGTTTGGAACTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGATATCCTGCAA
GGCTTCTGGCTACACATTCACTGACTACAACATGGACTGGGTGAAGCAGAGCCATGGAAAGAGCCTTGA
GTGGATTGGAGATATTAATCCTAACTATGATACTACTACCTACAACCAGAAGTTCAAGGGAAAGGCCAC
ATTGACTGTAGACAAGTCCTCCAGCACAGCCTACATGGAGCTCCGCAGCCTGACTTCTGAGGACACTGC
AGTCTTTTACTGTGCAAGAAGGAACTATGGTAACTACGTGGGGTTTGACTTCTGGGGCCAAGGCACCAC
TCTCACAGTCTCCTCAGCCAAAACGACACCCCCATCTGTCTATCCACTGGCCCCTGGATCTGCTGCCCAAA
CTAACTCCATGGTGACCCTGGGATGCCTGGTCAAGGGCTATTTCCCTGAGCCAGTGACAGTGACCTGGAA
CTCTGGATCCCTGTCCAGCGGTGTGCACACCTTCCCAGCTGTCCTGCAGTCTGACCTCTACACTCTGAGC
AGCTCAGTGACTGTCCCCTCCAGCACCTGGCCCAGCGAGACCGTCACCTGCAACGTTGCCCACCCGGCCA
GCAGCACCAAGGTGGACAAGAAAATTGTGCCCAGGGATTGTGGTTGTAAGCCTTGCATATGTACAGTCCC
AGAAGTATCATCTGTCTTCATCTTCCCCCCAAAGCCCAAGGATGTGCTCACCATTACTCTGACTCCTAAG
GTCACGTGTGTTGTGGTAGACATCAGCAAGGATGATCCCGAGGTCCAGTTCAGCTGGTTTGTAGATGATG
TGGAGGTGCACACAGCTCAGACGCAACCCCGGGAGGAGCAGTTCAACAGCACTTTCCGCTCAGTCAGTGA
ACTTCCCATCATGCACCAGGACTGGCTCAATGGCAAGGAGTTCAAATGCAGGGTCAACAGTGCAGCTTTC
CCTGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGCAGACCGAAGGCTCCACAGGTGTACACCATTC
CACCTCCCAAGGAGCAGATGGCCAAGGATAAAGTCAGTCTGACCTGCATGATAACAGACTTCTTCCCTGA
AGACATTACTGTGGAGTGGCAGTGGAATGGGCAGCCAGCGGAGAACTACAAGAACACTCAGCCCATCATG
GACACAGATGGCTCTTACTTCGTCTACAGCAAGCTCAATGTGCAGAAGAGCAACTGGGAGGCAGGAAATA
CTTTCACCTGCTCTGTGTTACATGAGGGCCTGCACAACCACCATACTGAGAAGAGCCTCTCCCACTCTCC
TGGTAAA

AA-seq:

EVQLQQFGTELVKPGASVKISCKASGYTFTDYNMDWVKQSHGKSLEWIGDINPNYDTTTYNQKFKGKATLT
VDKSSSTAYMELRSLTSEDTAVFYCARRNYGNYVGFDFWGQGTTLTVSSAKTTPPSVYPLAPGSAAQTNSM
VTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVAHPASSTK
VDKKIVPRDCGCKPCICTVPEVSSVFIFPPKPKDVLTITLTPKVTCVVVDISKDDPEVQFSWFVDDVEVH
TAQTQPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTIPPPK
EQMAKDKVSLTCMITDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSKLNVQKSNWEAGNTFTC
SVLHEGLHNHHTEKSLSHSPGK

轻链：DNA序列

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region

Nucseq:

AATATTGTGCTGACCCAGACTCCCAAATTCCTGCTTGTATCAGCAGGAGACAGGGTTTCCATAACCTGCA
AGGCCAGTCAGCGTGTGAATAATGATGTAGCTTGGTACCAACAGAAGCCAGGGCAGTCTCCTAAACTGC
TGATATACTATGCATCCAATCGCTACACTGGAGTCCCTGATCGCTTCACTGGCAGTGGATATGGGACGG

图73

ATTTCACTTTCACCATCAGCACTGTGCAGGCTGAAGACCTGGCAGTTTATTTCTGTCAGCAGGATTATAG
CTCTCCATTCACGTTCGGCTCGGGGACAAAGTTGGAAATAAAACGGGCTGATGCTGCACCAACTGTATCC
ATCTTCCCACCATCCAGTGAGCAGTTAACATCTGGAGGTGCCTCAGTCGTGTGCTTCTTGAACAACTTCT
ACCCCAAAGACATCAATGTCAAGTGGAAGATTGATGGCAGTGAACGACAAAATGGCGTCCTGAACAGTTG
GACTGATCAGGACAGCAAAGACAGCACCTACAGCATGAGCAGCACCCTCACGTTGACCAAGGACGAGTAT
GAACGACATAACAGCTATACCTGTGAGGCCACTCACAAGACATCAACTTCACCCATTGTCAAGAGCTTCA
ACAGGAATGAGTGT

AA-seq

NIVLTQTPKFLLVSAGDRVSITCKASQRVNNDVAWYQQKPGQSPKLLIYYASNRYTGVPDRFTGSGYGTD
FTFTISTVQAEDLAVYFCQQDYSSPFTFGSGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDI
NVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC

图73-续