(19)国家知识产权局

(12)发明专利

(10)授权公告号 CN 110740749 B
(45)授权公告日 2024.12.10

(21)申请号 201880031212.2
(22)申请日 2018.03.13
(65)同一申请的已公布的文献号
申请公布号 CN 110740749 A
(43)申请公布日 2020.01.31
(30)优先权数据
62/471,196 2017.03.14 US
62/636,746 2018.02.28 US
(85)PCT国际申请进入国家阶段日
2019.11.11
(86)PCT国际申请的申请数据
PCT/US2018/022230 2018.03.13
(87)PCT国际申请的公布数据
WO2018/169993 EN 2018.09.20
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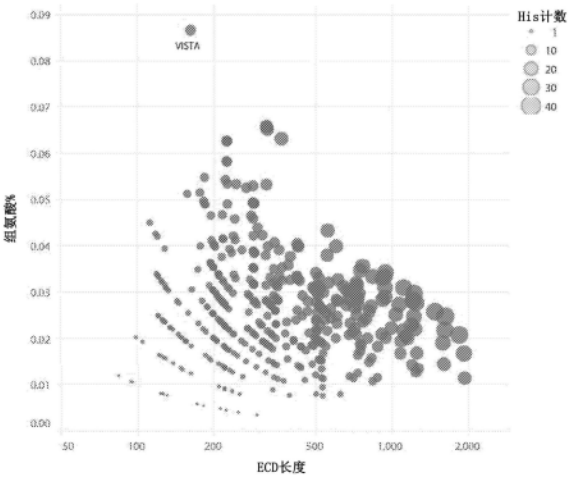
(51)Int.Cl.
A61K 39/395(2006.01)
C07K 16/28(2006.01)
C07K 16/30(2006.01)
(56)对比文件
US 2017051061 A1,2017.02.23
US 2012108455 A1,2012.05.03
Jie Deng.A New VISTA on combination therapy for negative checkpoint regulator blockade.《Journal for Immunotherapy of Cancer》.2016,第第4卷卷(第第4卷期),第1-7页.
Jie Deng.A New VISTA on combination therapy for negative checkpoint regulator blockade.《Journal for Immunotherapy of Cancer》.2016,第第4卷卷(第第4卷期),第1-7页.
审查员 吕丽珊
权利要求书2页 说明书188页
序列表323页 附图42页

(54)发明名称

在酸性pH下与VISTA结合的抗体

(57)摘要

本申请涉及在酸性pH下与含V结构域免疫球蛋白的T细胞激活抑制剂(VISTA)特异性地结合的抗体及其在癌症治疗中的用途。在一些实施方案中,所述抗体在酸性pH下与人VISTA特异性地结合,但在中性或生理pH下与人VISTA并非显著结合。



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1.一种抗体,其与含人V结构域Ig的T细胞激活抑制剂hVISTA特异性地结合,其中所述抗体包含:

轻链可变区VL和重链可变区VH,所述轻链可变区VL包含VL CDR1、CDR2和CDR3,其分别由SEQ ID NO:68的位置24-35、51-57和90-98组成,所述重链可变区VH包含VH CDR1、CDR2和CDR3,其分别由SEQID NO:55的位置26-35、50-66和99-112组成。

2.根据权利要求1所述的抗体,其中所述抗体包含含有如下氨基酸序列的VH:SEQ ID NO:55。

3.根据权利要求1所述的抗体,其中所述抗体包含含有如下氨基酸序列的VL:SEQ ID NO:68。

4.根据权利要求1所述的抗体,其中所述抗体包含含有如下氨基酸序列的VH:SEQ ID NO:55;并且其中所述抗体包含含有如下氨基酸序列的VL:SEQ ID NO:68。

5.根据权利要求1-4中任一项所述的抗体,其中所述抗体在中性或生理条件下以10^{-5}M或更大的K_D与hVISTA结合,其中中性条件是具有7.0的pH的条件,并且其中生理条件是具有7.4的pH的条件。

6.根据权利要求1-4中任一项所述的抗体,其中所述抗体在酸性条件下以10^{-7}M或更小的K_D与hVISTA结合,其中酸性条件是具有6.0至6.5的pH的条件。

7.根据权利要求1-4中任一项所述的抗体,其中所述抗体在酸性条件下以10^{-8}M或更小的K_D与hVISTA结合,其中酸性条件是具有6.0至6.5的pH的条件。

8.根据权利要求1-4中任一项所述的抗体,其中所述抗体在酸性条件下以10^{-9}M或更小的K_D与hVISTA结合,其中酸性条件是具有6.0至6.5的pH的条件。

9.根据权利要求1-4中任一项所述的抗体,其中所述抗体具有一种或多种以下性质:

a.在酸性条件下以比中性或生理条件下的K_D低至少10倍的K_D与hVISTA结合,其中酸性条件是具有6.0至6.5的pH的条件,其中中性条件是具有7.0的pH的条件,并且其中生理条件是具有7.4的pH的条件;

b.在酸性条件下以比中性或生理条件下的k_{off}低至少5倍的k_{off}与hVISTA结合,其中酸性条件是具有6.0至6.5的pH的条件,其中中性条件是具有7.0的pH的条件,并且其中生理条件是具有7.4的pH的条件;

c.在具有低于pH 7.0的pH的条件下抑制hVISTA与人T细胞的结合;

d.在具有低于pH 7.0的pH的条件下抑制hVISTA与huPSGL-1的结合;

e.抑制hVISTA与硫酸乙酰肝素蛋白多糖的结合;

f.在具有低于pH 7.0的pH的条件下抑制hVISTA与硫酸乙酰肝素蛋白多糖的结合;

g.在具有低于pH 7.0的pH的条件下刺激T细胞激活;和

h.降低VISTA介导的细胞间粘附。

10.根据权利要求1-4中任一项所述的抗体,其中所述抗体在6.0至6.5的pH条件下在hVISTA的细胞外结构域(ECD)处结合。

11.根据权利要求1-4中任一项所述的抗体,其是IgG抗体。

12.根据权利要求11所述的抗体,其是IgG1、IgG2或IgG4抗体。

13.根据权利要求12所述的抗体,其是具有S228P取代的IgG4抗体。

14.根据权利要求1-4中任一项所述的抗体,其中所述抗体是无效应子抗体。

15.根据权利要求14所述的抗体,其中所述抗体包含重链恒定区,所述重链恒定区包含1-5个降低抗体的效应子功能的突变。

16.根据权利要求1-4中任一项所述的抗体,其中所述抗体的恒定区是IgG1.3、IgG1.1或是具有P238K取代的IgG1。

17.根据权利要求1-4中任一项所述的抗体,其中所述抗体具有效应子功能。

18.根据权利要求17所述的抗体,其中所述抗体被去岩藻糖基化。

19.根据权利要求17所述的抗体,其中所述抗体包含重链恒定区,所述重链恒定区包含1-5个增强抗体的效应子功能的突变。

20.根据权利要求18所述的抗体,其中所述抗体包含重链恒定区,所述重链恒定区包含1-5个增强抗体的效应子功能的突变。

21.根据权利要求1-4中任一项所述的抗体,其是全长抗体。

22.根据权利要求1-4中任一项所述的抗体,其是抗原结合片段。

23.根据权利要求1-4中任一项所述的抗体,其是多聚抗体。

24.根据权利要求1-4中任一项所述的抗体,其与另一个分子连接。

25.根据权利要求24所述的抗体,所述另一个分子是标记或肽。

26.根据权利要求1-4中任一项所述的抗体,其是抗体药物缀合物。

27.一种核酸,其编码根据权利要求1-25中任一项所述的抗体。

28.一种组合物,其包含编码根据权利要求1-25中任一项所述的抗体的重链的核酸和编码所述抗体的轻链的核酸。

29.一种包含根据权利要求27所述的核酸或根据权利要求28所述的组合物的细胞。

30.一种制备抗体的方法,其包括在表达所述抗体的条件下培养根据权利要求29所述的细胞。

31.一种组合物,其包含根据权利要求1-26中任一项所述的抗体、根据权利要求27所述的核酸、根据权利要求28所述的组合物或根据权利要求29所述的细胞以及药学上可接受的载体。

在酸性pH下与VISTA结合的抗体

技术领域

[0001] 本申请涉及在酸性pH下与含V结构域免疫球蛋白的T细胞激活抑制剂(VISTA)特异性地结合的抗体及其在癌症治疗中的用途。

[0002] 背景技术和发明内容

[0003] 含V结构域Ig的T细胞激活抑制剂或VISTA是骨髓单核细胞和其他白细胞表达的免疫受体B7家族的共抑制成员。但是,对于VISTA抑制免疫应答的机制了解甚少。

[0004] 诸位发明人已经发现,与其他已知的免疫受体不同,VISTA可以在酸性pH下与它的反受体接合并选择性地起作用,而在生理pH(例如7.3-7.4)下具有很小的活性。因此,VISTA可以抑制酸性微环境(如肿瘤床或炎症部位)中的免疫应答,而不干扰在血液中循环或存在于未发炎、非酸性组织中的细胞。此外,诸位发明人已经发现,抗VISTA抗体可以被工程化为在酸性pH下与VISTA选择性地结合,而在生理pH下几乎不结合,这反映了VISTA自身的酸性pH选择性。相对于在生理pH下结合VISTA的抗体,这些酸性pH选择性抗体可以提供用于治疗疾病(如癌症)的期望特性。

[0005] 本公开文本涉及在酸性pH下(例如在酸性条件下)与VISTA(如人VISTA(“hVISTA”或“huVISTA”))的细胞外结构域(ECD)特异性地结合的抗体。本公开文本还涉及在酸性pH下与VISTA(如hVISTA)的细胞外结构域(ECD)特异性地结合而在中性或生理pH下几乎不结合的抗体。诸位发明人已经在本文中注意到,hVISTA-ECD氨基酸序列包含许多保守的和非保守的组氨酸残基,并且相对于其他B7家族成员和其他免疫球蛋白超家族成员,VISTA的ECD中组氨酸残基的频率异常高。(参见图1A和图1B。)在溶液中,氨基酸组氨酸的pK_a为约6.5,这意味着在pH 6.5处或更低时,蛋白质内的组氨酸残基往往是质子化的,因此带正电,而在高于pH 6.5的pH下它们越来越多地被非质子化,并且电荷呈中性。肿瘤微环境和发炎的组织通常是酸性的,因此,在这些微环境中发现的VISTA蛋白可能在其组氨酸残基处至少部分地质子化。如本文所讨论的,诸位发明人已经假设组氨酸质子化可能影响VISTA的构象、表面结构和/或电荷密度,这反过来又可能产生用于一种或多种受体-配体相互作用和抗体结合的pH特异性或pH选择性表位。使用在酸性pH下而不是中性或生理pH下结合的抗体靶向VISTA可以防止靶标介导的经由循环的和淋巴器官中存在的骨髓单核细胞的药物沉积,从而改善肿瘤微环境中的抗体PK、受体占用以及活性。在治疗方式如抗体依赖性细胞介导的细胞毒性(ADCC)、抗体依赖性细胞吞噬作用(ADCP)、补体依赖性细胞毒性(CDC)和有效载荷(抗体-药物缀合物)的递送的情况下,酸性pH选择性抗体还可以提高VISTA抗体对于肿瘤内靶细胞而非循环靶细胞的特异性。

附图说明

[0006] 在2018年2月28日提交的优先权美国临时申请号62/636,746中提供了一些附图的彩色版本。假设根据要求并支付必要的费用后美国专利商标局将提供彩色附图的副本,则可以通过本申请的公开获得此优先权申请文件。

[0007] 图1A至图1C显示,VISTA的细胞外结构域含有异常高频率的组氨酸残基,这些组氨

酸残基中有许多是保守的,并且这些组氨酸残基中至少一些可以参与受体-配体结合。图1A显示了含有免疫球蛋白结构域的蛋白质的图,其中将每种蛋白质的细胞外结构域氨基酸残基的数目绘制在x轴上,并且将每种蛋白质的细胞外结构域内组氨酸残基的频率绘制在y轴上。每个数据点的大小对应于每种蛋白质的细胞外结构域中组氨酸残基的总数。图1B显示了人、食蟹猴和小鼠VISTA的细胞外结构域的比对氨基酸序列。标记了信号肽(Sig)和跨膜结构域(TMD)序列位置。在所有三个物种中保守的组氨酸残基以粗体和下划线显示;在人和食蟹猴中保守的组氨酸残基仅以粗体显示。图1C显示了人VISTA免疫球蛋白结构域的三维结构的模型。组氨酸残基被描绘为球形和棒状痕迹。

[0008] 图2A至图2B显示了如下模型,其中VISTA的细胞外结构域中的组氨酸残基赋予了对于酸性pH而非生理pH的反受体选择性。图2A显示了在组氨酸残基中吡咯铵基团(NH)的质子化的缺乏与存在之间的平衡。溶液中组氨酸的pK_a为6.5,这表明组氨酸残基在pH 6.5或更低时与更高的pH相比更可能被质子化,因此带正电。图2B显示了如下模型,其中VISTA在酸性pH下选择性地接合与P-选择素糖蛋白配体1(PSGL-1)或其他反受体和配体(“VISTA-R”)。因此,在酸性pH下而非生理pH下与VISTA的细胞外结构域结合的抗体可能对抑制或调节VISTA活性至关重要。

[0009] 图3显示了肿瘤浸润巨噬细胞、树突细胞、嗜中性粒细胞、CD4+效应T细胞、CD4+调节性T细胞、CD8+T细胞、天然杀伤(NK)细胞和B细胞上的VISTA表面表达水平(抗VISTA抗体染色的平均荧光强度(MFI))。VISTA在许多肿瘤浸润白细胞、特别是髓样细胞上表达。肿瘤微环境通常是酸性的,使得VISTA能够接合反受体和配体。

[0010] 图4A至图4E显示了VISTA在酸性pH下与白细胞和PSGL-1选择性地结合,在中性pH下几乎不结合,并且这种结合可以被抗VISTA抗体阻断。图4A的左图显示了与激活的人CD4+T细胞结合的荧光缀合的重组VISTA多聚体的代表性直方图。从深灰色到浅灰色,填充的直方图描绘了在pH 7.0、6.5、6.4、6.3、6.1和6.0下的结合。一些直方图用其相应的pH标记。在pH 6.0下的非VISTA对照多聚体结合显示为未填充的直方图。在右图中,用曲线图表示了在不同pH下与来自两个供体的激活的人CD4+T细胞结合的VISTA(圆形)和对照(三角形)多聚体的平均MFI。图4B显示了在pH 6.0和pH 7.4下重组VISTA多聚体与外周血单核细胞(PBMC)结合的代表性直方图。从深灰色到浅灰色,填充的直方图描绘了在pH 6.0下与CD19+B细胞、CD4+T细胞、CD8+T细胞、CD56+NK细胞和CD14+单核细胞的结合。未填充的实线边界和虚线边界直方图分别描绘了在pH 7.4下与总PBMC淋巴细胞和单核细胞的结合。图4C显示了在抗VISTA阻断抗体(方形)或非VISTA特异性同种型匹配的对照抗体(圆形)的存在下重组VISTA多聚体与激活的人CD4+T细胞的代表性结合。抗体浓度以对数尺度绘制。还显示了非线性回归。三角形描绘了来自未用重组VISTA多聚体染色的激活的人CD4+T细胞的背景信号。图4D显示了在pH 6.0下重组VISTA多聚体与缺乏硫酸乙酰肝素的中国仓鼠卵巢(CHO)细胞(细胞系pGSD-677,美国典型培养物保藏中心(American Type Culture Collection))的结合的代表性二维流式细胞术图,所述细胞被转染以表达人PSGL-1。在存在和不存在图4C中所示的抗VISTA阻断抗体的情况下进行多聚体结合。重组VISTA多聚体未染色的细胞显示为对照。将PSGL-1抗体染色绘制在y轴上,并且将VISTA多聚体染色绘制在x轴上。图4E显示了在pH 6.0和pH 7.4下重组小鼠VISTA-Fc融合蛋白与小鼠脾细胞结合的代表性直方图。从深灰色到浅灰色,填充的直方图描绘了在pH 6.0下与CD8+T细胞、CD11b+髓样细胞和CD4+T细胞

的结合。未填充的直方图描绘了在pH 7.4下与总脾细胞的结合。

[0011] 图5A至图5D显示了VISTA在酸性pH下优先地介导T细胞抑制和细胞:细胞粘附,并且可以用抗VISTA阻断抗体逆转这两种作用。图5A显示了在pH6.0和7.0下在表达hVISTA的293T细胞或载体对照(绘制在y轴上)与x轴上的内源性地表达细胞表面硫酸乙酰肝素的CHO细胞之间的代表性细胞:细胞缀合物形成。图5B是在抗VISTA阻断抗体、抗VISTA非阻断抗体或同种型匹配的非VISTA特异性对照抗体的存在下相同细胞之间在pH 6.0下形成的细胞缀合物的频率的图。图5C显示了在不同pH下与表达h VISTA和抗人T细胞受体激动剂抗体OKT3的单链可变片段的293T细胞(“人工抗原呈递细胞”)共培养后,由表达NFkB萤光素酶报告基因的Jurkat(人T细胞系)细胞生成的萤光素酶活性的代表性图。将抗VISTA阻断抗体(方形)或同种型匹配的非VISTA特异性对照抗体(圆形)添加至共培养的细胞中。在图5D中,将图5A中所示的数据绘制为相对于对照,在用抗VISTA抗体处理的情况下的萤光素酶信号的增加倍数(“效应量”)。

[0012] 图6A至图6G显示了VISTA可以发现于细胞内的内体、特别是Rab11+再循环内体中,并且可以经由内体运输再循环至细胞表面和从细胞表面再循环。图6A显示了在表达人VISTA的293T细胞内VISTA、Rab5(早期内体标记物)、Rab7(晚期内体标记物)和Rab11(再循环内体标记物)的共定位。图6B显示了VISTA和Rab11在人单核细胞内的共定位。细胞内VISTA与Rab11+再循环内体共定位。与VISTA抗体相同的同种型的非VISTA结合对照抗体(“cAb”)不可检测地结合单核细胞。图6C显示了三种抗VISTA抗体在pH 7.4(黑色)、6.7(深灰色)和6(浅灰色)下与重组VISTA的结合。图6D显示了表达VISTA的急性骨髓性白血病(AML)细胞系对通过带有组织蛋白酶B敏感接头和细胞毒性有效载荷的相同的抗VISTA抗体1(倒三角形)、2(圆形)、3(方形)或非VISTA特异性对照抗体(三角形)的杀伤的易感性。将细胞活力(CellTiter-Glo LU)绘制在y轴上,并且将抗体浓度绘制在x轴上。图6E比较了抗VISTA抗体3的hVISTA结合与工程化变体(“VISTA mAb 3c”)的这种结合,后者在酸性pH下没有展现出受损的结合。图6F显示了抗体药物-缀合物测定,其比较了抗VISTA抗体3(方形)和3c(菱形)的效价。图6G显示了内体运输的示意图,其中VISTA经由早期内体和再循环内体再循环至细胞表面和从细胞表面再循环。

[0013] 图7A至图7F显示了如何设计和筛选抗VISTA抗体变体文库以获得酸性pH选择性抗体。图7A显示了在抗人VISTA抗体克隆P1-061029(缩写为‘029)的VH CDR 3中进行的氨基酸取代,以产生用于筛选的‘029文库。为了潜在地改善在酸性pH下与VISTA的富组氨酸区域的结合,文库允许取代为带负电荷的氨基酸天冬氨酸和谷氨酸以及pH响应性组氨酸。X=H、D或E。从合成中去除括号中的序列,以避免引入负值。合成了总共647个具有1-2个突变的P1-061029HCDR3的独特序列。图7B显示了‘针对酸性pH选择性抗体变体对029文库进行反复筛选和选择的程序。R表示选择轮数。图7C显示了代表性二维流式细胞术图数据,其显示了9轮选择之后的变体库。VISTA结合绘制在y轴上,并且变体抗体表达绘制在x轴上。显示了在各种抗体浓度和pH下的结合数据。图7D显示了在pH 6.0和7.4下P1-061029及其后代克隆与人VISTA结合的图。图7E显示了在pH 6.0下P1-061029及其后代克隆与人VISTA的解离速率的图。图7F显示了在pH 6.0和pH 7.4下抗体P1-068761、P1-068767和P1-061029与人VISTA的SPR结合数据。

[0014] 图8A至图8F显示了VISTA抗体P1-068761和P1-068767的酸性pH选择性细胞结合、

阻断和效应子活性。图8A和图8B显示了与异位表达人VISTA的Raji细胞结合的酸性pH选择性抗体P1-068761(图8A)和P1-068767(图8B)的平均荧光强度。在大约pH 6.0(圆形;图8A中的最高曲线)、6.1(方形;第三高的曲线)、6.2(三角形;第二高的曲线)、6.4(倒三角形;第四高的曲线,接近pH 6.1曲线)、6.6(菱形;从底部数第四条曲线)、7.0(圆形;从底部数第三条曲线)、7.2(方形;从底部数第二条曲线)和8.1(未填充的三角形;图8A中的底部曲线)下将细胞染色。用荧光缀合的抗人IgG二抗检测结合。图8C显示了在不同pH下P1-068767(圆形)和同种型匹配的非特异性对照抗体(三角形)以3125ng/mL与异位表达人VISTA的Raji细胞的结合。“pH_{50}”即失去50％的P1-068767结合的pH值为约6.6。图8D显示了与人单核细胞结合的同种型匹配的非特异性对照抗体(填充和未填充圆形分别为pH7.0和6.0)、抗VISTA mAb 2(“对照”,参见图6C,填充和未填充方形分别为pH 7.0和6.0)、P1-068761(填充和未填充三角形分别为pH 7.0和6.0)和P1-068767(填充和未填充倒三角形分别为pH 7.0和6.0)的平均荧光强度(MFI)。通过荧光缀合的抗人IgG二抗检测结合。图8E显示了通过P1-061029(方形)、P1-068761(三角形)和P1-068767(倒三角形)对在pH 6.0下重组VISTA多聚体与激活的人CD4+T细胞的结合的可比较的阻断,而非VISTA特异性对照抗体(圆形)不阻断VISTA结合。图8F显示了在生理pH下P1-068761(三角形)和P1-068767(倒三角形)在介导抗体依赖性细胞毒性(ADCC)中降低的效价。还显示了P1-061029(方形)、非VISTA特异性阳性对照抗体(圆形)和非VISTA特异性阴性对照抗体(菱形)。靶细胞的NK细胞特异性裂解以靶细胞总数的百分比形式绘制在y轴上,并且抗体浓度绘制在x轴上。还显示了非线性回归。

[0015] 图9显示了食蟹猴中酸性pH选择性抗VISTA抗体的增强的药代动力学(PK)。该图显示了在用VISTA抗体2(“对照”,圆形,参见图6C)、VISTA抗体3(“酸性pH敏感的”,方形,参见图6C)或P1-068767(三角形)处理的食蟹猴中随时间变化的血清抗体浓度。

[0016] 图10A和图10B显示了酸性pH选择性抗VISTA抗体‘761和‘767中突变的结合作用。图10A显示了在pH 7.4、pH 6.7和pH 6.0下P1-068761回复突变体的动力学结合数据以及相对于P1-068761其回复突变的位置。图10B显示了在pH7.4、pH 6.7和pH 6.0下P1-068767回复突变体的动力学结合数据以及相对于P1-068767其回复突变的位置。

[0017] 图11A至图11C显示了各种抗VISTA抗体的表位分组和定位。图11A显示了与P1-061029和VISTA抗体对照相比,P1-068761和P1-068767的VISTA表位竞争。图11B和图11C显示了与非阻断hVISTA抗体(mAb1;图11C)相比,如表14中列出的用于阻断hVISTA抗体(图11B)的所有残基的表位的表示。指示了氨基酸残基66(H)和162(A)以表示分子的取向。组氨酸残基呈灰色,并且表位残基呈黑色。

[0018] 图12A至图12C显示了以下的成像的毛细管等电聚焦(icIEF)数据:图12A:P1-061029、图12B:P1-068761和图12C:P1-068767。指示了主要种类的等电点(pI main)以及pI标记物。

[0019] 图13A和图13B显示了‘029和‘015后代克隆的可变区的比对。图13A显示了‘029及其后代克隆的可变区的氨基酸序列的比对。图13B显示了‘015及其后代克隆的可变区的氨基酸序列的比对。

具体实施方式

[0020] 定义

[0021] 在本申请中,除非另外陈述,否则“或”的使用意指“和/或”。在多个从属权利要求的上下文中,“或”的使用仅以替代方式回指多于一个前述独立或从属权利要求。术语“包含”、“包括”和“具有”在本文中可以互换使用。根据本发明,“分离的”分子是已经从其天然环境去除的分子。因此,术语“分离的”不一定反映分子已被纯化的程度。

[0022] 术语“多肽”是指氨基酸残基的聚合物,并且不限于最小长度。“蛋白质”可以包括一种或多种多肽。氨基酸残基的此类聚合物可含有天然或非天然氨基酸残基,并且包括但不限于氨基酸残基的肽、寡肽、二聚体、三聚体和多聚体。所述定义涵盖了全长蛋白质及其片段两者。所述术语还包括多肽的表达后修饰,例如糖基化、唾液酸化、乙酰化、磷酸化等。此外,用于本发明的目的,“多肽”或“蛋白质”分别指包含对天然序列的修饰如缺失、添加和取代(通常在本质上是保守的)的多肽或蛋白质,只要所述蛋白质保持所需活性即可。这些修饰可能是故意的(如通过定点诱变),或者可能是偶然的(如通过产生蛋白质的宿主的突变或由于PCR扩增引起的错误)。蛋白质可以包括两种或更多种多肽。

[0023] “VISTA”是含V结构域免疫球蛋白的T细胞激活蛋白的抑制剂的缩写,它是免疫检查点调节剂的B7家族的成员。VISTA也称为PD-1同源物(PD1H)、B7-H5、C10orf54、ESC-1的分化(Dies-1)、血小板受体Gi24前体和死亡结构域1α(DD1α)。本文中的术语“hVISTA”或“huVISTA”是指人VISTA蛋白。hVISTA(包含其信号肽)的氨基酸序列在SEQ ID NO:1中提供,而不含信号肽的序列在SEQ ID NO:2中提供。(参见下面的序列表。)VISTA的细胞外结构域或“ECD”或“VISTA-ECD”是指VISTA蛋白的位于细胞外空间中的部分,这在hVISTA的情况下包含SEQ ID NO:2的氨基酸1-162。(另参见图1B。)hVISTA的“IgV结构域”部分包含SEQ ID NO:2的残基5-135。

[0024] 术语“前导肽”或“前导序列”是指位于多肽的N末端的氨基酸残基的序列,所述序列促进多肽从哺乳动物细胞的分泌。前导序列可以在从哺乳动物细胞输出多肽后被裂解,从而形成成熟蛋白。前导序列可以是天然的或合成的,并且与它们所附接的蛋白质可以是异源的或同源的。

[0025] 本文中术语“抗体”或“Ab”以最广义使用,并且涵盖各种抗体结构,包括但不限于单克隆抗体、多克隆抗体、多特异性抗体(例如双特异性抗体)和抗体片段,只要它们展现出所需的抗原结合活性即可。如本文所用,所述术语是指包含至少重链的互补决定区(CDR)1、CDR2和CDR3以及至少轻链的CDR1、CDR2和CDR3的分子,其中所述分子能够与抗原结合。术语抗体包括但不限于能够结合抗原的片段,如Fv、单链Fv(scFv)、Fab、Fab’和$(Fab')_2$。术语抗体还包括但不限于嵌合抗体、人源化抗体、人抗体以及各种物种(如小鼠、食蟹猴等)的抗体。

[0026] 术语“重链”或“HC”是指包含至少重链可变区、具有或不具有前导序列的多肽。在一些实施方案中,重链包含重链恒定区的至少一部分。术语“全长重链”是指包含重链可变区和重链恒定区、具有或不具有前导序列并且具有或不具有C末端赖氨酸(K)的多肽。

[0027] 术语“重链可变区”或“VH”是指包含重链的重链互补决定区(CDR)1、框架区(FR)2、CDR2、FR3和CDR3的区域。在一些实施方案中,重链可变区还包含FR1的至少一部分和/或FR4的至少一部分。如下所述,在一些实施方案中,重链CDR1包含本文中VH SEQ ID NO的残基26-35;重链CDR2包含本文中VH SEQ ID NO的残基50-66,并且重链CDR3包含本文中VH SEQ ID NO的残基99-110。在其他实施方案中,如果指定的话,则重链CDR1对应于Kabat残基31至

35;重链CDR2对应于Kabat残基50至65;并且重链CDR3对应于Kabat残基95至102。参见例如Kabat Sequences of Proteins of Immunological Interest(1987和1991,NIH,贝塞斯达,马里兰州)。在一些实施方案中,重链CDR如在本文中,如在下面的序列表或表2中所指定。

[0028] 术语“轻链”或“LC”是指包含至少轻链可变区、具有或不具有前导序列的多肽。在一些实施方案中,轻链包含轻链恒定区的至少一部分。术语“全长轻链”是指包含轻链可变区和轻链恒定区、具有或不具有前导序列的多肽。

[0029] 术语“轻链可变区”或“VL”是指包含轻链CDR1、FR2、HVR2、FR3和HVR3的区域。在一些实施方案中,轻链可变区也包含FR1和/或FR4。如下所述,在一些实施方案中,轻链CDR1包含本文中的VL SEQ ID NO的残基24-35;轻链CDR2包含本文中的VL SEQ ID NO的残基51-57,并且轻链CDR3包含本文中的VL SEQ ID NO的残基90-98。在其他实施方案中,如果指定的话,则轻链CDR1对应于Kabat残基24至34;轻链CDR2对应于Kabat残基50至56;并且轻链CDR3对应于Kabat残基89至97。参见例如Kabat Sequences of Proteins of Immunological Interest(1987和1991,NIH,贝塞斯达,马里兰州)。在一些实施方案中,轻链CDR如本文中,如在序列表中所指定。

[0030] “嵌合抗体”是指如下抗体,其中重链和/或轻链的一部分衍生自特定来源或物种,而重链和/或轻链的其余部分衍生自不同来源或物种。在一些实施方案中,嵌合抗体是指包含至少一个来自第一物种(如小鼠、大鼠、食蟹猴等)的可变区和至少一个来自第二物种(如人、食蟹猴等)的恒定区的抗体。在一些实施方案中,嵌合抗体包含至少一个小鼠可变区和至少一个人恒定区。在一些实施方案中,嵌合抗体包含至少一个食蟹猴可变区和至少一个人恒定区。在一些实施方案中,嵌合抗体的所有可变区均来自第一物种,而嵌合抗体的所有恒定区均来自第二物种。

[0031] “人源化抗体”是指如下抗体,其中非人可变区的框架区中的至少一个氨基酸已被来自人可变区的相应氨基酸替代。在一些实施方案中,人源化抗体包含至少一个人恒定区或其片段。在一些实施方案中,人源化抗体是Fab、scFv、$(Fab')_2$等。

[0032] 如本文所用,“人抗体”是指在人中产生的抗体、在包含人免疫球蛋白基因的非人动物(如XenoMouse®)中产生的抗体、以及使用体外方法(如噬菌体展示)选择的抗体,其中抗体库是基于人免疫球蛋白序列。

[0033] 如本文所用,“VISTA抗体”或“抗VISTA抗体”是指在至少某些条件(如酸性pH)下与VISTA特异性地结合的抗体。在一些实施方案中,所述抗体可以是“huVISTA抗体”或“抗huVISTA抗体”,指示其在至少某些条件下(如在酸性pH下)与人VISTA蛋白特异性地结合。例如,可以将与VISTA的细胞外结构域(ECD)特异性地结合的VISTA抗体称为“VISTA-ECD抗体”。

[0034] 在一些实施方案中,与中性和/或生理pH相比,在酸性pH下抗体可以与VISTA以更高的亲和力结合。在一些实施方案中,所述抗体可以在酸性pH下与VISTA以更高的亲和力结合,并且在中性和/或生理pH下仅可以忽略不计地或非特异性地结合。

[0035] 针对抗体与蛋白质(例如VISTA-ECD蛋白)结合的“K_D”或“解离常数”是抗体与蛋白质(例如VISTA-ECD蛋白)的亲和力或特异性结合的量度。较低的K_D指示与较高的K_D相比改善的结合或亲和力。K_D由对于抗体和多肽的“解离速率”或k_{off}或k_d与“缔合速率”或k_{on}或k_a之间

的比率组成。解离速率和缔合速率是系统中两个结合配偶体缔合和解离的速率。因此,较慢的解离速率(其中缔合速率保持大致恒定)导致较高的总体亲和力,从而导致较低的K_D。如本文所使用,特定值"或更小"的k_{off}指示k_{off}或"解离速率"如所指定或比指定的速率慢。

[0036] 术语"特异性结合"或"特异性地结合"或类似术语表示对于两个多肽(如抗体及其多肽靶标)的结合的K_D小于在相同条件下存在的两个随机多肽之间的该值。换言之,K_D较小是由于系统中多肽的非特异性聚集而导致的。

[0037] 在一些实施方案中,抗体在特定pH下或pH范围内特异性地结合VISTA-ECD蛋白。本文中的"酸性"pH通常是指小于7.0的pH,"碱性"pH通常是指高于7.0的pH,并且"中性"pH通常是指约7.0的pH。本文中的"生理pH"是指正常(即非癌性)生理条件下的pH,例如7.35至7.45或7.3至7.4,如约7.4。在两个分子(如VISTA和VISTA结合配偶体或VISTA和T细胞)的结合的上下文中使用的本文中的短语,如"在酸性条件下结合"或"在生理条件下结合"等,分别是指在酸性pH下结合和在生理pH下结合。

[0038] 当提及"阻断"或"抑制"配体(或受体)或竞争抗体与单独的或在细胞上的受体(或配体)的结合时,如果与对照相比存在统计学上显著的总体减少(例如50%或更大的总体减少,例如75%、80%、85%、90%、95%或更大的总体减少),则结合被阻断。例如,"抗VISTA阻断抗体"是可以在至少某些条件下(如在酸性pH下)阻断VISTA与PSGL-1或另一种VISTA配体或受体或硫酸乙酰肝素蛋白多糖的结合。

[0039] 如本文所用,"肿瘤模型"是指体内临床前测定,其可以用于研究VISTA-ECD抗体的生物学活性,并且包括异种移植物或天然小鼠肿瘤测定系统。在一些情况下,肿瘤模型可以允许追踪用抗体处理后的肿瘤大小或生长,和/或追踪肿瘤中免疫细胞(如特定类型的T细胞或NK细胞)的存在,以确定抗体是否已经触发或增强免疫应答。

[0040] 如本文所用,术语"免疫刺激剂"是指通过充当免疫刺激分子(包括共刺激分子)的激动剂或充当免疫抑制分子的拮抗剂来刺激免疫系统的分子,其包括共抑制分子。免疫刺激分子或免疫抑制分子可以是免疫检查点调节剂,如VISTA或另一种B7家族成员或如下文进一步描述的另一种分子。免疫刺激剂可以是生物剂(如抗体或抗体片段)、其他蛋白质或疫苗,或者可以是小分子药物。""免疫刺激分子"包括起到增强、刺激、诱导或以其他方式"开启"免疫应答的作用的受体或配体。如本文所定义的免疫刺激分子包括共刺激分子。"免疫抑制分子"包括起到减轻、抑制、阻抑或以其他方式"关闭"免疫应答的作用的受体或配体。如本文所定义的免疫抑制分子包括共抑制分子。此类免疫刺激和免疫抑制分子可以是例如在免疫细胞(如T细胞)上发现的或在参与先天免疫的细胞(如NK细胞)上发现的受体或配体。

[0041] 关于肽、多肽或抗体序列的"氨基酸序列同一性百分比(%)"和"同源性"定义为在用以实现最大百分比序列同一性并且不将任何保守取代视为序列同一性的一部分而比对序列和引入缺口(如果需要)后,候选序列中与特定肽或多肽序列中的氨基酸残基相同的氨基酸残基的百分比。用于确定氨基酸序列同一性百分比的比对可以以本领域熟知的多种方式来实现,例如,使用公众可获得的计算机软件,如BLAST、BLAST-2、ALIGN或MEGALIGNTM(DNASTAR)软件。本领域技术人员可以确定用于测量比对的适当参数,包括为了在被比较的序列的全长上实现最大比对所需要的任何算法。

[0042] 术语"触发"或"增强"是指任何事件的起始或增加(如蛋白质配体结合)或任何生

物活性(如免疫应答)或表型特征的起始或增加,或者是指该活性或特征的发生率、程度或可能性的增加。“触发”或“增强”是指与参考相比,活性、功能和/或量的开始或增加。所述触发或增强不必是完全的。例如,在某些实施方案中,“增强”意指引起总体增加20%或更大的能力。在另一个实施方案中,“增强”意指引起总体增加50%或更大的能力。在又另一个实施方案中,“增强”意指引起总体增加75%、85%、90%、95%或更大的能力。

[0043] 术语“抑制”(“inhibition”或“inhibit”)更通常地指任何事件的减少或停止(如蛋白质配体结合)或任何表型特征的减少或停止或该特征的发生率、程度或可能性的减少或停止。“降低”或“抑制”是指与参考相比,活性、功能和/或量的降低或阻滞。所述抑制或降低不必是完全的。例如,在某些实施方案中,“降低”或“抑制”意指引起总体减少20%或更大的能力。在另一个实施方案中,“降低”或“抑制”意指引起总体减少50%或更大的能力。在又另一个实施方案中,“降低”或“抑制”意指引起总体降低75%、85%、90%、95%或更大的能力。

[0044] 如本文所用,“治疗”涵盖用于人中的疾病的治疗剂的任何给予或施用,并且包括抑制疾病或疾病或一种或多种疾病症状的进展、抑制或减缓疾病或其进展或其症状中的一种或多种、阻止其发展、部分或完全地减轻疾病或其症状中的一种或多种或防止疾病的一种或多种症状的复发。

[0045] 术语“受试者”和“患者”在本文可互换地用于指人。

[0046] 术语“有效量”或“治疗有效量”是指对于治疗受试者中的疾病或障碍以例如部分或完全地减轻一种或多种症状有效的药物的量。在一些实施方案中,有效量是指在必需剂量下并且持续必需的时间有效实现所需治疗或预防结果的量。

[0047] 术语“癌症”在本文中用于指展现出异常高水平的增殖和生长的细胞群。癌症可以是良性的(也称为良性肿瘤)、恶性前的或恶性的。癌细胞可以是实体癌细胞或白血病癌细胞。术语“肿瘤生长”在本文中用于指由一个或多个包含癌症的细胞的增殖或生长,这引起癌症的大小或程度的相应增加。

[0048] 适用于本文的治疗方法的癌症的例子包括但不限于癌、淋巴瘤、母细胞瘤、肉瘤和白血病。此类癌症的更具体的非限制性例子包括鳞状细胞癌、小细胞肺癌、垂体癌、食道癌、星形细胞瘤、软组织肉瘤、非小细胞肺癌(包括鳞状细胞非小细胞肺癌)、肺腺癌、肺鳞状癌、腹膜癌、肝细胞癌、胃肠癌、胰腺癌、胶质母细胞瘤、子宫颈癌、卵巢癌、肝癌、膀胱癌、肝细胞瘤、乳腺癌、结肠癌、结直肠癌、子宫内膜或子宫癌、唾液腺癌、肾癌、肾细胞癌、肝癌、前列腺癌、外阴癌、甲状腺癌、肝癌、脑癌、子宫内膜癌、睾丸癌、胆管癌、胆囊癌、胃癌、黑色素瘤和各种类型的头颈癌(包括头和颈的鳞状细胞癌)。

[0049] 与一种或多种其他治疗剂“组合”给予包括同时(并行)给予和以任何顺序连续(依次)给予。

[0050] “药学上可接受的载体”是指用于与治疗剂一起使用的无毒固体、半固体或液体填充剂、稀释剂、包囊材料、配制助剂或本领域中常规的载体,它们共同包含用于给予至受试者的“药物组合物”。药学上可接受的载体在使用的剂量和浓度下对接受者无毒,并且与配制品的其他成分相容。药学上可接受的载体适用于所用配制品。例如,如果要口服给予治疗剂,则载体可以是凝胶胶囊。如果要皮下给予治疗剂,则理想的是载体对皮肤无刺激性,并且不会引起注射部位反应。

[0051] “化学治疗剂”是可用于治疗癌症的化学化合物。可在本文的方法中给予的化学治疗剂的例子包括但不限于烷基化剂,如噻替派和Cytoxan®环磷酰胺;烷基磺酸酯,如白消安、英丙舒凡和哌泊舒凡;氮杂环丙烷,如苯佐替派(benzodopa)、卡波醌、美妥替哌(meturedopa)和乌瑞替哌(uredopa);乙烯亚胺和甲基蜜胺类(methylamelamines),包括六甲蜜胺、三乙撑蜜胺(triethylenemelamine)、三乙撑磷酰胺(trietylenephosphoramide)、三乙撑硫代磷酰胺(triethiylenethiophosphoramide)和三羟甲基蜜胺(trimethylolomelamine);多聚乙酰(尤其是布拉他辛(bullatacin)和布拉他辛酮(bullatacinone));喜树碱(包括合成类似物拓扑替康);苔藓抑素;海洋抑素(callystatin);CC-1065(包括其阿多来新、卡折来新和比折来新合成类似物);隐藻素类(cryptophycins)(特别是隐藻素1和隐藻素8);尾海兔素;多拉司他汀(duocarmycin)(包括合成类似物、KW-2189和CB1-TM1);艾榴塞洛素(eleutherobin);水鬼蕉碱(pancratistatin);匍枝珊瑚醇(sarcodictyin);海绵抑制素(spongistatin);氮芥(例如苯丁酸氮芥)、萘氮芥、氯磷酰胺(chlorophosphamide)、雌氮芥、异环磷酰胺、二氯甲基二乙胺、盐酸氧化氮芥(mechlorethamine oxide hydrochloride)、美法仑、新恩比兴、苯芥胆甾醇(phenesterine)、松龙苯芥、曲磷胺、尿嘧啶氮芥;亚硝基脲例如卡莫司汀、氯脲菌素、福莫司汀、洛莫司汀、尼莫司汀和雷莫司汀(ranimnustine);抗生素,如烯二炔抗生素(例如卡奇霉素、尤其是卡奇霉素γ1I和卡奇霉素ωI1(参见例如Agnew,Chem Intl.Ed.Engl.,33:183-186(1994));达尼霉素(dynemicin),包括达尼霉素A;双磷酸盐,如氯膦酸盐;埃斯波霉素(esperamicin);以及新制癌菌素发色团和相关的色蛋白烯二炔抗生素发色团)、紫苏素(aclacinomysins)、放线菌素D(actinomycin)、土霉素(authramycin)、偶氮丝氨酸(azaserine)、博来霉素、放线菌素C(cactinomycin)、卡拉比星(carabicin)、洋红霉素(carminomycin)、嗜癌霉素(carzinophilin)、色霉素(chromomycinis)、更生霉素、柔红霉素、地托比星(detorubicin)、6-重氮基-5-氧代-L-正亮氨酸、Adriamycin®阿霉素(包括吗啉代-阿霉素、氰基吗啉代-阿霉素、2-吡咯啉-阿霉素和脱氧阿霉素)、表柔比星、依索比星(esorubicin)、伊达比星(idarubicin)、麻西罗霉素(marcellomycin)、丝裂霉素(如丝裂霉素C)、霉酚酸、诺加霉素、橄榄霉素(olivomycins)、培洛霉素(peplomycin)、泛霉素(potfiromycin)、嘌呤霉素、三铁阿霉素(quelamycin)、罗多比星(rodorubicin)、链黑菌素(streptonigrin)、链脲菌素(streptozocin)、杀结核菌素(tubercidin)、乌苯美司(ubenimex)、净司他丁(zinostatin)、佐柔比星(zorubicin);抗代谢物,如甲氨蝶呤和5-氟尿嘧啶(5-FU);叶酸类似物,如二甲叶酸(denopterin)、甲氨蝶呤、蝶罗呤、三甲曲沙;嘌呤类似物,如氟达拉滨、6-巯基嘌呤、硫咪嘌呤(thiamiprine)、硫鸟嘌呤;嘧啶类似物,如安西他滨、阿扎胞苷、6-氮杂尿苷、卡莫氟(carmofur)、阿糖胞苷、双脱氧尿苷、去氧氟尿苷(doxifluridine)、依诺他滨(enocitabine)、氟尿苷;雄激素,如卡普睾酮(calusterone)、丙酸甲雄烷酮(dromostanolone propionate)、环硫雄醇(epitiostanol)、美雄烷(mepitiostane)、睾内酯;抗肾上腺素,如氨鲁米特(aminoglutethimide)、米托坦(mitotane)、曲络司坦(trilostane);叶酸补充剂,如叶酸;醋葡醛内酯;醛磷酰胺糖苷(aldophosphamide glycoside);氨基酮戊酸(aminolevulinic acid);恩尿嘧啶(eniluracil);安吖啶(amsacrine);贝斯布西(bestrabucil);比生群(bisantrene);依达

曲酯(edatraxate);去氧胺(defofamine);秋水仙胺(demecolcine);地吖醌(diaziquone);依法磷酸(elfornithine);依利醋氨;埃博霉素(epothilone);依托格鲁(etoglucid);硝酸镓(gallium nitrate);羟基脲;香菇多糖;氯尼达明(lonidainine);美登木素生物碱(maytansinoids),如美登素(maytansine)和安丝菌素;米托胍腙(mitoguazone);米托蒽醌(mitoxantrone);莫吡坦(mopidanmol);二胺硝吖啶(nitraerine);喷司他丁(pentostatin);蛋氨氮芥(phenamet);吡柔比星(pirarubicin);洛索蒽醌(losoxantrone);鬼臼酸(podophyllinic acid);2-乙酰肼;丙卡巴肼(procarbazine);PSK®多糖复合物(JHS天然产物,Eugene,OR);丙亚胺(razoxane);根霉素(rhizoxin);西佐喃(sizofiran);锗螺胺(spirogermanium);替奴佐酸(tenuazonic acid);三亚胺醌(triaziquone);2,2',2″-三氯三乙胺;单端孢霉烯(trichothecenes)(尤其是T-2毒素、维拉库林A(verracurin A)、漆斑菌素A(roridin A)和胺癸叮(anguidine);乌拉坦(urethan);长春地辛(vindesine);达卡巴嗪(dacarbazine);甘露醇氮芥;二溴甘露醇;二溴卫矛醇;哌泊溴烷(pipobroman);加息托星(gacytosine);阿糖胞苷("Ara-C");环磷酰胺;噻替派;紫杉烷,例如Taxol®紫杉醇(Bristol-Myers Squibb Oncology,普林斯顿,新泽西州)、Abraxane®紫杉醇的无克列莫佛的白蛋白工程化的纳米粒子配制品(American Pharmaceutical Partners,Schaumberg,伊利诺伊州)和Taxotere®多西他赛(Rhône-Poulenc Rorer,Antony,法国);苯丁酸氮芥(chloranbucil);Gemzar®吉西他滨;6-硫鸟嘌呤;巯基嘌呤;甲氨蝶呤;铂类似物,如顺铂、奥沙利铂和卡铂;长春碱;铂;依托泊苷(VP-16);异环磷酰胺;米托蒽醌;长春新碱;Navelbine®长春瑞滨;诺肖林(novantrone);替尼泊苷;依达曲沙(edatrexate);柔红霉素;氨基蝶呤;希罗达(xeloda);伊班膦酸盐(ibandronate);伊立替康(Camptosar,CPT-11)(包括伊立替康与5-FU和甲酰四氢叶酸的治疗方案);拓扑异构酶抑制剂RFS 2000;二氟甲基鸟氨酸(difluorometlhylornithine,DMFO);维A酸(retinoids),如视黄酸;卡培他滨;考布他汀(combretastatin);甲酰四氢叶酸(LV);奥沙利铂,包括奥沙利铂治疗方案(FOLFOX);降低细胞增殖的PKC-α、Raf、H-Ras、EGFR(例如厄洛替尼(Tarceva®))和VEGF-A的抑制剂以及上述任何一种的药学上可接受的盐、酸或衍生物。

[0052] 可以在本文的方法中给予的其他非限制性示例性化学治疗剂包括起到调节或抑制对癌症的激素作用的抗激素剂(如抗雌激素和选择性雌激素受体调节剂(SERM)),包括例如他莫昔芬(包括Nolvadex®他莫昔芬)、雷洛昔芬(raloxifene)、屈洛昔芬、4-羟基他莫昔芬、曲奥昔芬(trioxifene)、雷洛昔芬(keoxifene)、LY117018、奥那司酮(onapristone)和Fareston®托瑞米芬(toremifene);抑制酶芳香酶的芳香酶抑制剂,所述酶调节肾上腺中的雌激素产生,所述芳香酶抑制剂例如4(5)-咪唑、氨鲁米特、Megase®醋酸甲地孕酮(megestrol acetate)、Aromasin®依西美坦(exemestane)、福美斯坦(formestanie)、法倔唑(fadrozole)、Rivisor®伏罗唑(vorozole)、Femara®来曲唑(letrozole)和Arimidex®阿那曲唑(anastrozole);和抗雄激素,如氟他胺、尼鲁米特、比卡鲁胺、亮丙瑞林和戈舍瑞林;以及曲沙他滨(troxacitabine)(1,3-二氧戊烷核苷胞嘧啶类似物);反义寡

核苷酸,特别是那些抑制参与异常细胞增殖的信号传导途径中的基因表达的反义寡核苷酸,例如PKC-α、Ralf和H-Ras;核酶,如VEGF表达抑制剂(例如Angiozyme®核酶)和HER2表达抑制剂;疫苗,如基因疗法疫苗,例如Allovectin®疫苗、Leuvectin®疫苗和Vaxid®疫苗;Proleukin®rIL-2;Lurtotecan®拓扑异构酶1抑制剂;Abarelix®rmRH;以及上述任何一种的药学上可接受的盐、酸或衍生物。

[0053] “抗血管生成剂”或“血管生成抑制剂”是指直接或间接地抑制血管生成、血管发生或不期望的血管通透性的小分子量物质、多核苷酸(包括例如抑制性RNA(RNAi或siRNA))、多肽、分离的蛋白、重组蛋白、抗体或其缀合物或融合蛋白。应当理解,抗血管生成剂包括那些结合血管生成因子或其受体并阻断血管生成因子或其受体的血管生成活性的药剂。例如,可以在本文方法中给予的抗血管生成剂可以包括抗体或针对血管生成剂的其他拮抗剂,例如针对VEGF-A(例如贝伐单抗(Avastin®))或VEGF-A受体(例如KDR受体或Flt-1受体)的抗体、抗PDGFR抑制剂(如Gleevec®(甲磺酸伊马替尼))、阻断VEGF受体信号传导的小分子(例如PTK787/ZK2284、SU6668、Sutent®/SU11248(苹果酸舒尼替尼)、AMG706或在例如国际专利申请WO2004/113304中描述的那些)。抗血管生成剂还包括天然血管生成抑制剂,例如血管抑素、内皮抑素等。参见例如Klagsbrun和D'Amore(1991)Annu.Rev.Physiol.53:217-39;Streit和Detmar(2003)Oncogene 22:3172-3179(例如表3列出了恶性黑色素瘤的抗血管生成疗法的);Ferrara和Alitalo(1999)Nature Medicine 5(12):1359-1364;Tonini等人(2003)Oncogene 22:6549-6556(例如表2列出了已知的抗血管生成因子);和Sato(2003)Int.J.Clin.Oncol.8:200-206(例如表1列出了临床试验中使用的抗血管生成剂)。

[0054] 如本文所用,“生长抑制剂”是指在体外或体内抑制细胞(如表达VEGF的细胞)的生长的化合物或组合物。因此,可以在本文的方法中给予的生长抑制剂可以是显著降低S期细胞(如表达VEGF的细胞)的百分比的生长抑制剂。生长抑制剂的例子包括但不限于阻断细胞周期进程(在S期以外的地方)的药剂,如诱导G1阻滞和M期阻滞的药剂。经典的M期阻断剂包括长春花(长春新碱和长春碱)、紫杉烷和拓扑异构酶II抑制剂(如阿霉素、表柔比星、柔红霉素、依托泊苷和博来霉素)。那些阻滞G1的药剂也渗透到S期阻滞中,例如DNA烷化剂(如他莫昔芬、泼尼松、达卡巴嗪、甲氧乙胺、顺铂、甲氨蝶呤、5-氟尿嘧啶和阿糖胞苷)。进一步的信息可发现于Mendelsohn和Israel编,The Molecular Basis of Cancer,第1章,Murakami等人的标题为“Cell cycle regulation,oncogenes,and antineoplastic drugs”(W.B.Saunders,费城,1995),例如第13页。紫杉烷(紫杉醇和多西他赛)是均源自紫杉树的抗癌药。源自欧洲紫杉的多西他赛(Taxotere®,Rhone-Poulenc Rorer)是紫杉醇(Taxol®,Bristol-Myers Squibb)的半合成类似物。紫杉醇和多西他赛促进来自微管蛋白二聚体的微管的组装,并通过防止解聚作用稳定微管,这导致细胞中的有丝分裂的抑制。

[0055] 术语“抗肿瘤组合物”是指包含至少一种活性治疗剂的可用于治疗癌症的组合物。治疗剂的例子包括但不限于例如化学治疗剂、生长抑制剂、细胞毒性剂、辐射疗法中使用的药剂、抗血管生成剂、癌症免疫治疗剂、凋亡剂、抗微管蛋白剂和治疗癌症的其他药剂、如抗HER-2抗体、抗CD20抗体、表皮生长因子受体(EGFR)拮抗剂(例如酪氨酸激酶抑制剂)、HER1/

EGFR抑制剂(例如厄洛替尼(Tarceva®)、血小板衍生生长因子抑制剂(例如Gleevec®(甲磺酸伊马替尼))、COX-2抑制剂(例如塞来昔布)、干扰素、CTLA4抑制剂(例如、抗CTLA抗体伊匹木单抗(YERVOY®))、PD-1或PD-L1抑制剂(例如

OPDIVO®、KEYTRUDA®、TECENTRIQ®、BAVENCIO®、

IMFINZI®)、TIM3抑制剂(例如抗TIM3抗体)、细胞因子、与以下靶标:ErbB2、ErbB3、ErbB4、PDGFR-β、BlyS、APRIL、BCMA、CTLA4、TIM3或VEGF受体中的一种或多种结合的拮抗剂(例如中性抗体)、TRAIL/Apo2和其他生物活性和有机化学剂等。其组合也包含在本公开文本中。

[0056] 在酸性pH下与VISTA-ECD特异性地结合的抗体

[0057] 由于VISTA在其ECD中具有大量的组氨酸残基,因此与中性pH、特别是接近作为组氨酸的pK_a的pH 6.5相比,其折叠和整体结构以及可用于配体(如抗体)的结合的表面在酸性pH下可能不同。由于肿瘤微环境通常是酸性的,对于在那些微环境中与VISTA结合,抗体可能需要在酸性pH下与VISTA特异性结合,其中至少一些表面组氨酸残基更可能被质子化。

[0058] 下面的序列表分别提供了具有或不具有信号肽的人VISTA(hVISTA)的氨基酸序列(SEQ ID NO:1和SEQ ID NO:2(成熟hVISTA))。信号肽组成SEQ ID NO:1的氨基酸残基1-32。细胞外结构域(ECD)由SEQ ID NO:2的氨基酸残基1-162组成。IgV结构域组成SEQ ID NO:1的氨基酸残基37-167和SEQ ID NO:2的氨基酸残基5-135。茎区域在SEQ ID NO:1的氨基酸残基172-194和SEQ ID NO:2的氨基酸残基136-162处;跨膜结构域在SEQ ID NO:1的氨基酸残基195-216和SEQ ID NO:2的氨基酸残基163-184处。SEQ ID NO:1的氨基酸残基187和SEQ ID NO:2的155(粗体且加下划线)可以是D或E,其代表hVISTA中的多态性。该残基用粗体、加下划线显示。因此,SEQ ID NO:1和SEQ ID NO:2在该残基处包含两种人多态性。VISTA的ECD中的组氨酸残基是加灰色阴影的。

[0059] 抗VISTA抗体(Ab)可以在酸性pH下与VISTA-ECD或其片段(例如所述片段包含VISTA的IgV结构域或来自hVISTA的包含例如SEQ ID NO:2的氨基酸20-95、20-70、35-70、35-95、35-127或37-125的区域)特异性地结合。在某些实施方案中,Ab在小于pH 7.0的pH下与VISTA-ECD蛋白特异性地结合。在某些实施方案中,Ab在小于pH 6.8的pH下与VISTA-ECD蛋白特异性地结合。在某些实施方案中,Ab在小于pH 6.5的pH下与VISTA-ECD蛋白特异性地结合。在某些实施方案中,Ab在小于pH 6.3的pH下与VISTA-ECD蛋白特异性地结合。在某些实施方案中,Ab在小于pH 6.0的pH下与VISTA-ECD蛋白特异性地结合。在某些实施方案中,Ab在小于pH 5.8的pH下与VISTA-ECD蛋白特异性地结合。在某些实施方案中,Ab在小于pH 5.5的pH下与VISTA-ECD蛋白特异性地结合。在某些实施方案中,Ab在小于pH 5.3的pH下与VISTA-ECD蛋白特异性地结合。在某些实施方案中,Ab在小于pH5.0的pH下与VISTA-ECD蛋白特异性地结合。

[0060] 某些Ab在pH 5.0-pH 7.0范围内的pH下与VISTA-ECD蛋白特异性地结合。某些Ab在pH 5.0-pH 6.5范围内的pH下与VISTA-ECD蛋白特异性地结合。某些Ab在pH 5.0-pH 6.0范围内的pH下与VISTA-ECD蛋白特异性地结合。某些Ab在pH 5.5-pH 7.0范围内的pH下与VISTA-ECD蛋白特异性地结合。某些Ab在pH 5.5-pH 6.5范围内的pH下与VISTA-ECD蛋白特异性地结合。某些Ab在pH 6.0-6.5范围内的pH下与VISTA-ECD蛋白特异性地结合。

[0061] 本文还提供了在6.5或更低的pH下以10^{-6}M或更小的K_D与VISTA-ECD蛋白(如hVISTA-ECD或其片段,所述片段包含VISTA的IgV结构域或来自hVISTA的包含例如SEQ ID NO:2的氨基酸20-95、20-70、35-70、35-95、35-127或37-125的区域)结合的Ab。在一些实施方案中,Ab以10^{-7}M或更小的K_D结合。在一些实施方案中,Ab以10^{-8}M或更小的K_D结合。在一些实施方案中,Ab以10^{-9}M的K_D结合。在一些实施方案中,Ab以10^{-10}M或更小的K_D结合。例如,Ab可以在6.5或更低的pH下以10^{-8}M或更小的K_D与VISTA-ECD蛋白结合。

[0062] 本文还提供了如下Ab,其在6.0-6.5的pH范围内以10^{-6}M或更小的K_D与VISTA-ECD蛋白结合。在一些实施方案中,Ab以10^{-7}M或更小的K_D结合。在一些实施方案中,Ab以10^{-8}M或更小的K_D结合。在一些实施方案中,Ab以10^{-9}M的K_D结合。在一些实施方案中,Ab以10^{-10}M或更小的K_D结合。例如,Ab可以在6.5或更低的pH下例如在6.0-6.5的pH范围内以10^{-7}M或更小的K_D与VISTA-ECD蛋白结合。此外,Ab可以在6.5或更低的pH下例如在6.0-6.5的pH范围内以10^{-8}M或更小的K_D与VISTA-ECD蛋白结合。Ab可以在6.5或更低的pH下例如在6.0-6.5的pH范围内以10^{-9}M或更小的K_D与hVISTA-ECD结合。

[0063] 本文还提供了在6.5或更低的pH下与VISTA-ECD蛋白(如hVISTA-ECD或其片段,所述片段包含VISTA的IgV结构域或来自hVISTA的包含例如SEQID NO:2的氨基酸20-95、20-70、35-70、35-95、35-127或37-125的区域)特异性地结合的Ab,其中在25℃或37℃下k_{off}为$10^{-5}s^{-1}$或更小。在一些实施方案中,Ab在25℃或37℃下具有$10^{-4}s^{-1}$或更小的k_{off}。在一些实施方案中,Ab在25℃或37℃下具有2 $10^{-4}s^{-1}$或更小的k_{off}。在一些实施方案中,Ab在25℃或37℃下具有5 $10^{-4}s^{-1}$或更小的k_{off}。在一些实施方案中,Ab在25℃或37℃下具有7 $10^{-4}s^{-1}$或更小的k_{off}。在一些实施方案中,Ab在25℃或37℃下具有$10^{-3}s^{-1}$或更小的k_{off}。在一些实施方案中,Ab在25℃或37℃下具有2 $10^{-3}s^{-1}$或更小的k_{off}。在一些实施方案中,Ab在25℃或37℃下具有5 $10^{-3}s^{-1}$或更小的k_{off}。在一些实施方案中,Ab在25℃或37℃下具有7 $10^{-3}s^{-1}$或更小的k_{off}。在一些实施方案中,Ab在25℃或37℃下具有$10^{-2}s^{-1}$或更小的k_{off}。在一些实施方案中,Ab在25℃或37℃下具有$10^{-1}s^{-1}$或更小的k_{off}。例如,Ab可以在6.5或更低的pH下以在25℃或37℃下$10^{-3}s^{-1}$或更小的k_{off}与VISTA-ECD蛋白特异性地结合。Ab可以在6.5或更低的pH下以在25℃或37℃下$10^{-3}s^{-1}$或更小的k_{off}与hVISTA-ECD蛋白特异性地结合。此外,Ab可以在6.5或更低的pH下以在25℃或37℃下$10^{-2}s^{-1}$或更小的k_{off}与VISTA-ECD蛋白特异性地结合。

[0064] 本文提供了例如在6.5或更低的pH下与VISTA-ECD蛋白(如hVISTA-ECD或其片段,所述片段包含VISTA的IgV结构域或来自hVISTA的包含例如SEQ ID NO:2的氨基酸20-95、20-70、35-70或35-95、35-95、35-127或37-125的区域)结合的Ab,其中(i)K_D为10^{-6}M或更小、10^{-7}M或更小、10^{-8}M或更小、10^{-9}M或更小或10^{-10}M或更小并且(ii)k_{off}速率为$10^{-5}s^{-1}$或更小、10^{-4}(或2、5或7 10^{-4})s^{-1}或更小、10^{-3}(或2、5或7 10^{-4})s^{-1}或更小、$10^{-2}s^{-1}$或更小或$10^{-1}s^{-1}$或更小,如例如在25℃或37℃下所测量的。例如,Ab可以在6.5或更小的pH下与VISTA-ECD蛋白结合,其中K_D为10^{-7}M或更小并且k_{off}速率为$10^{-3}s^{-1}$或更小,如例如在25℃或37℃下所测量的。Ab可以在6.5或更小的pH下与VISTA-ECD蛋白结合,其中K_D为10^{-8}M或更小并且k_{off}速率为$10^{-3}s^{-1}$或更小,如例如在25℃或37℃下所测量的。Ab可以在6.5或更小的pH下与VISTA-ECD蛋白结合,其中K_D为10^{-8}M或更小并且k_{off}速率为$10^{-2}s^{-1}$或更小,如例如在25℃或37℃下所测量的。例如,Ab可以在6.5或更小的pH下与hVISTA-ECD结合,其中K_D为10^{-7}M或更小并且k_{off}速率为$10^{-3}s^{-1}$或更小,如例如在25℃或37℃下所测量的。Ab可以在6.5或更小的pH下与hVISTA-

ECD结合,其中K_D为10^{-9}M或更小并且k_{off}速率为$10^{-3}s^{-1}$或更小,如例如在25℃或37℃下所测量的。Ab可以在6.5或更小的pH下与hVISTA-ECD结合,其中K_D为10^{-9}M或更小并且k_{off}速率为$10^{-2}s^{-1}$或更小,如例如在25℃或37℃下所测量的。Ab可以在6.5或更小的pH下与hVISTA-ECD结合,其中K_D为10^{-8}M或更小并且k_{off}速率为10^{-4}(或2、5或7 10^{-4})s^{-1}或更小,如例如在25℃或37℃下所测量的。Ab可以在6.5或更小的pH下与hVISTA-ECD结合,其中K_D为10^{-8}M或更小并且k_{off}速率为10^{-5}(或2、5或7 10^{-5})s^{-1}或更小,如例如在25℃或37℃下所测量的。Ab可以在6.5或更小的pH下与hVISTA-ECD结合,其中K_D为10^{-9}M或更小并且k_{off}速率为10^{-4}(或2、5或7 10^{-4})s^{-1}或更小,如例如在25℃或37℃下所测量的。Ab可以在6.5或更小的pH下与hVISTA-ECD结合,其中K_D为10^{-9}M或更小并且k_{off}速率为10^{-5}(或2、5或7 10^{-5})s^{-1}或更小,如例如在25℃或37℃下所测量的。

[0065] 本文提供了例如在6.5或更小的pH下以在25℃或37℃下$10^{4}M^{-1}s^{-1}$或更高的k_{on}与VISTA-ECD蛋白特异性地结合的Ab。在一些此类实施方案中,Ab可以以$10^{5}M^{-1}s^{-1}$或更高的k_{on}结合。在一些此类实施方案中,Ab可以以$10^{6}M^{-1}s^{-1}$或更高的k_{on}结合。在一些此类实施方案中,Ab可以以$10^{7}M^{-1}s^{-1}$或更高的k_{on}结合。例如,Ab可以在6.5或更低的pH下与VISTA-ECD蛋白结合,其中k_{on}为$10^{6}M^{-1}s^{-1}$或更高,如例如在25℃或37℃下所测量的。例如,Ab可以在6.5或更低的pH下与hVISTA的ECD结合,其中k_{on}为$10^{6}M^{-1}s^{-1}$或更高,如例如在25℃或37℃下所测量的。

[0066] 本文提供了例如在6.5或更低的pH下与VISTA-ECD蛋白结合的Ab,其中(i)K_D为10^{-6}M或更小、10^{-7}M或更小、10^{-8}M或更小、10^{-9}M或更小或10^{-10}M或更小,并且(ii)k_{on}为$10^{4}M^{-1}s^{-1}$或更高、$10^{5}M^{-1}s^{-1}$或更高、$10^{6}M^{-1}s^{-1}$或更高、$10^{7}M^{-1}s^{-1}$或更高,如例如在25℃或37℃下所测量的。例如,Ab可以在6.5或更低的pH下与VISTA-ECD蛋白结合,其中K_D为10^{-7}M或更小并且k_{on}速率为$10^{6}M\ s^{-1}$或更高,如例如在25℃或37℃下所测量的。例如,Ab可以在6.5或更低的pH下与VISTA-ECD蛋白结合,其中K_D为10^{-8}M或更小并且k_{on}速率为$10^{6}M\ s^{-1}$或更高,如例如在25℃或37℃下所测量的。例如,Ab可以在6.5或更低的pH下与hVISTA-ECD结合,其中K_D为10^{-7}M或更小并且k_{on}速率为$10^{6}M\ s^{-1}$或更高,如例如在25℃或37℃下所测量的。例如,Ab可以在6.5或更低的pH下与hVISTA-ECD结合,其中K_D为10^{-8}M或更小并且k_{on}速率为$10^{6}M\ s^{-1}$或更高,如例如在25℃或37℃下所测量的。

[0067] 在一些实施方案中,Ab可以在6.5或更低的pH下与VISTA-ECD蛋白结合,其中K_D为10^{-7}M或更小以及其中k_{off}为$10^{-5}s^{-1}$或更小、2 $10^{-5}s^{-1}$或更小、5$10^{-5}s^{-1}$或更小、7 $10^{-5}s^{-1}$或更小、$10^{-4}s^{-1}$或更小、2 $10^{-4}s^{-1}$或更小、5 $10^{-4}s^{-1}$或更小、7 $10^{-4}s^{-1}$或更小、$10^{-3}s^{-1}$或更小、2 $10^{-3}s^{-1}$或更小、5 $10^{-3}s^{-1}$或更小、7 $10^{-3}s^{-1}$或更小、$10^{-2}s^{-1}$或更小或$10^{-1}s^{-1}$或更小,如例如在25℃或37℃下所测量的。在一些实施方案中,Ab可以在6.5或更低的pH下与VISTA-ECD蛋白结合,其中K_D为10^{-9}M或更低以及其中k_{off}为$10^{-5}s^{-1}$或更小、$10^{-4}s^{-1}$或更小、$10^{-3}s^{-1}$或更小、$10^{-2}s^{-1}$或更小或$10^{-1}s^{-1}$或更小,如例如在25℃或37℃下所测量的。在一些此类实施方案中,Ab可以在6.5或更低的pH下与VISTA-ECD蛋白结合,其中K_D为10^{-10}M或更小以及其中k_{off}为$10^{-5}s^{-1}$或更小、$10^{-4}s^{-1}$或更小、$10^{-3}s^{-1}$或更小、$10^{-2}s^{-1}$或更小或$10^{-1}s^{-1}$或更小,如例如在25℃或37℃下所测量的。

[0068] 在一些实施方案中,Ab可以在6.5或更低的pH下与VISTA-ECD蛋白结合,其中K_D为10^{-7}M或更小以及其中k_{on}为$10^{4}M^{-1}s^{-1}$或更高、$10^{5}M^{-1}s^{-1}$或更高、$10^{6}M^{-1}s^{-1}$或更高、$10^{7}M^{-1}s^{-1}$或更

高,如例如在25℃或37℃下所测量的。在一些实施方案中,Ab可以在6.5或更低的pH下与VISTA-ECD蛋白结合,其中K_D为10^{-8}M或更小以及其中k_{on}为$10^4M^{-1}s^{-1}$或更高、$10^5M^{-1}s^{-1}$或更高、$10^6M^{-1}s^{-1}$或更高、$10^7M^{-1}s^{-1}$或更高,如例如在25℃或37℃下所测量的。在一些实施方案中,Ab可以在6.5或更低的pH下与VISTA-ECD蛋白结合,其中K_D为10^{-9}M或更小以及其中k_{on}为$10^4M^{-1}s^{-1}$或更高、$10^5M^{-1}s^{-1}$或更高、$10^6M^{-1}s^{-1}$或更高、$10^7M^{-1}s^{-1}$或更高,如例如在25℃或37℃下所测量的。在一些此类实施方案中,Ab可以在6.5或更低的pH下与VISTA-ECD蛋白结合,其中K_D为10^{-10}M或更小以及其中k_{on}为$10^4M^{-1}s^{-1}$或更高、$10^5M^{-1}s^{-1}$或更高、$10^6M^{-1}s^{-1}$或更高、$10^7M^{-1}s^{-1}$或更高,如例如在25℃或37℃下所测量的。

[0069] 在一些实施方案中,Ab可以在6.5或更低的pH下与VISTA-ECD蛋白结合,其中K_D为10^{-7}M或更小以及其中k_{off}为$10^{-5}s^{-1}$或更小、$10^{-4}s^{-1}$或更小、$10^{-3}s^{-1}$或更小、$10^{-2}s^{-1}$或更小或$10^{-1}s^{-1}$或更小,如例如在25℃或37℃下所测量的,并且k_{on}为$10^4M^{-1}s^{-1}$或更高、$10^5M^{-1}s^{-1}$或更高、$10^6M^{-1}s^{-1}$或更高、$10^7M^{-1}s^{-1}$或更高,如例如在25℃或37℃下所测量的。在一些实施方案中,Ab可以在6.5或更低的pH下与VISTA-ECD蛋白结合,其中K_D为10^{-8}M或更小以及其中k_{off}为$10^{-5}s^{-1}$或更小、$10^{-4}s^{-1}$或更小、$10^{-3}s^{-1}$或更小、$10^{-2}s^{-1}$或更小或$10^{-1}s^{-1}$或更小,如例如在25℃或37℃下所测量的,并且k_{on}为$10^4M^{-1}s^{-1}$或更高、$10^5M^{-1}s^{-1}$或更高、$10^6M^{-1}s^{-1}$或更高、$10^7M^{-1}s^{-1}$或更高,如例如在25℃或37℃下所测量的。在一些实施方案中,Ab可以在6.5或更低的pH下与VISTA-ECD蛋白结合,其中K_D为10^{-9}M或更小以及其中k_{off}为$10^{-5}s^{-1}$或更小、$10^{-4}s^{-1}$或更小、$10^{-3}s^{-1}$或更小、$10^{-2}s^{-1}$或更小或$10^{-1}s^{-1}$或更小,如例如在25℃或37℃下所测量的,并且k_{on}为$10^4M^{-1}s^{-1}$或更高、$10^5M^{-1}s^{-1}$或更高、$10^6M^{-1}s^{-1}$或更高、$10^7M^{-1}s^{-1}$或更高,如例如在25℃或37℃下所测量的。在一些此类实施方案中,Ab可以在6.5或更低的pH下与VISTA-ECD蛋白结合,其中K_D为10^{-10}M或更小以及其中k_{off}为$10^{-5}s^{-1}$或更小、$10^{-4}s^{-1}$或更小、$10^{-3}s^{-1}$或更小、$10^{-2}s^{-1}$或更小或$10^{-1}s^{-1}$或更小,如例如在25℃或37℃下所测量的,并且k_{on}为$10^4M^{-1}s^{-1}$或更高、$10^5M^{-1}s^{-1}$或更高、$10^6M^{-1}s^{-1}$或更高、$10^7M^{-1}s^{-1}$或更高,如例如在25℃或37℃下所测量的。

[0070] 还如上所述,在一些上述实施方案中,VISTA-ECD蛋白是hVISTA-ECD或hVISTA-ECD的一部分(例如IgV结构域)。在一些上述实施方案中,Ab可以与包含SEQ ID NO:2的氨基酸20-95的表位特异性地结合。在一些上述实施方案中,Ab可以与包含SEQ ID NO:2的氨基酸20-70的表位特异性地结合。在一些上述实施方案中,Ab可以与包含SEQ ID NO:2的氨基酸35-95的表位特异性地结合。在一些上述实施方案中,Ab可以与包含SEQ ID NO:2的氨基酸35-70的表位特异性地结合。在一些上述实施方案中,表位是三维表位,其不仅包含SEQ ID NO:2的上述部分:残基20-95、20-70、35-95或35-70中的一个,而且还包含SEQ ID NO:2的另一部分,如SEQ ID NO:2的残基95-105。在某些实施方案中,Ab与WO 2015/097536中描述的Ab所结合的hVISTA的表位结合。例如,Ab可以与WO 2015/097536中披露的Ab竞争或交叉竞争与hVISTA的结合。在某些实施方案中,Ab与人VISTA的构象表位结合。在某些实施方案中,Ab与如下构象表位结合,所述构象表位包含或存在于人VISTA的SEQ ID NO:2的残基103-111和SEQ ID NO:2的136-146内。在某些实施方案中,Ab与如下构象表位结合,所述构象表位包含或存在于人VISTA的SEQ ID NO:2的残基24-36、54-65和100-102内。在某些实施方案中,Ab与如下构象表位结合,所述构象表位包含人VISTA的FG环中的氨基酸残基。在一些实施方案中,Ab与包含SEQ ID NO:2的氨基酸残基35至127和/或37-125的多肽结合。在一些实施方案中,Ab与包含SEQ ID NO:2的氨基酸残基350-127的VISTA ECD多肽或其部分结合,但

抗体不结合或以降低的亲和力结合包含氨基酸取代的VISTA ECD多肽或其部分,其中所述取代(1)是以下氨基酸残基之一的取代:T35、Y37、K38、T39、Y41、R54、T61、F62、Q63、L65、H66、L67、H68、H69、F97、L115、V117、I119、H121、H122、S124、E125、R127和SEQ ID NO:2或(2)是以下氨基酸残基之一的取代:Y37、T39、R54、F62、Q63、H66、L115、V117、I119、S124或E125。在一些实施方案中,抗VISTA抗体具有与本文所述,例如实施例中所述的抗体相同的结合特征(或显著相同的结合特征)。

[0071] 上述抗体中的一些可能根据pH值而显示对于VISTA-ECD蛋白的不同结合亲和力。在酸性条件下(例如在pH 6.5下或更低)与VISTA-ECD蛋白特异性地结合的某些Ab,在中性和/或碱性pH下还以相似的亲和力特异性地结合VISTA-ECD蛋白(即它们是"泛结合剂")。例如,一些此类Ab可以在pH 6.5和pH 7.0下以10^{-7}M或更小的K_D与VISTA-ECD蛋白结合(在例如25℃或37℃的恒定温度下),使得pH 6.5下的K_D在pH 7.0下的K_D的1.5倍内。一些此类Ab可以在pH 6.5和pH 7.0下以10^{-8}M或更小的K_D与VISTA-ECD蛋白结合(在例如25℃或37℃的恒定温度下),使得pH 6.5下的K_D在pH 7.0下的K_D的1.5倍内。一些此类Ab可以在pH 6.5和pH 7.0下以10^{-8}M或更小的K_D与hVISTA-ECD蛋白结合(在例如25℃或37℃的恒定温度下),使得pH 6.5下的K_D在pH 7.0下的K_D的1.5倍内。

[0072] 在酸性条件下(例如在pH 6.5下或更低)与VISTA-ECD蛋白特异性地结合的某些Ab,可以在中性、生理和/或碱性条件下以较低亲和力结合VISTA-ECD蛋白("pH敏感性结合剂"或"pH敏感性Ab")。在酸性条件下(例如在pH 6.5下或更低)与VISTA-ECD蛋白特异性地结合的某些Ab,可以在中性、生理和/或碱性条件下具有不明显的例如几乎检测不到的与VISTA-ECD蛋白的结合。例如,在一些实施方案中,Ab可以在pH 6.5下以10^{-8}M或更小的K_D并且在pH 7.0和/或pH 7.4下以大于10^{-8}M的K_D与VISTA-ECD蛋白结合。在一些此类实施方案中,Ab可以在pH 6.5下以10^{-8}M或更小的K_D并且在pH 7.0和/或pH 7.4下以大于pH 6.5下K_D的1.5倍的K_D与VISTA-ECD蛋白结合。在某些实施方案中,提供了与VISTA-ECD蛋白特异性地结合的pH敏感性Ab,其中在pH 6.5下的K_D比在pH 7.0下低至少1.5倍、2倍、5倍、10倍、20倍、50倍、100倍、300倍、500倍、1000倍或5000倍(在例如25℃或37℃的恒定温度下)。例如,在一些情况下Ab与VISTA-ECD蛋白结合,其中相对于pH 7.0和/或pH 7.4或更高,K_D在pH 6.0下至少小1.5倍、2倍、5倍、10倍、20倍、50倍、100倍、300倍、500倍、1000倍或5000倍(在例如25℃或37℃的恒定温度下)。

[0073] 在某些实施方案中,Ab与VISTA-ECD蛋白特异性地结合,其中k_{off}在酸性条件下低于在中性、生理或碱性条件下的k_{off}。在某些实施方案中,提供了在酸性条件下与VISTA-ECD蛋白结合的Ab,其中在pH 6.5下的k_{off}比pH 7.0和/或pH 7.4下的k_{off}低至少1.5倍、2倍、5倍、10倍、20倍、50倍、100倍或1000倍,如例如在25℃或37℃下所测量的。换言之,解离速率在酸性pH下比在中性pH下慢。例如,在一些实施方案中,Ab与VISTA-ECD蛋白特异性地结合,其中相对于pH 7.0和/或pH 7.4,k_{off}速率在pH 6.0下低至少1.5倍、2倍、5倍、10倍、20倍、50倍、100倍或1000倍,如例如在25℃或37℃下所测量的。在某些实施方案中,提供了与VISTA-ECD蛋白结合的Ab,其中在pH 6.5下的k_{off}比pH 7.4下的K_{off}低至少1.5倍、2倍、5倍、10倍、20倍、50倍、100倍或1000倍,如例如在25℃或37℃下所测量的。在一些实施方案中,Ab与VISTA-ECD蛋白特异性地结合,其中相对于pH 7.4,在pH 6.0下的k_{off}速率低至少1.5倍、2倍、5倍、10倍、20倍、50倍、100倍或1000倍,如例如在25℃或37℃下所测量的。在某些实施方

案中,提供了与VISTA-ECD蛋白结合的Ab,其中在pH 6.0-6.5下的k_{off}比在pH 7.0-7.4下的k_{off}低至少1.5倍、2倍、5倍、10倍、20倍、50倍、100倍或1000倍,如例如在25℃或37℃下所测量的。

[0074] 在某些实施方案中,Ab与VISTA-ECD蛋白特异性地结合,其中相对于中性、生理或碱性条件,k_{on}在酸性条件下较高。在某些实施方案中,提供了在酸性条件下与VISTA-ECD蛋白结合的Ab,其中在pH 6.5下的k_{on}比在pH 7.0和/或pH 7.4下的k_{on}高至少2倍、5倍、10倍、20倍、50倍、100倍或1000倍,如例如在25℃或37℃下所测量的。例如,在一些实施方案中,Ab与aVISTA-ECD蛋白特异性地结合,其中k_{on}在pH 6.0下比在pH 7.0和/或pH 7.4下高至少2倍、5倍、10倍、20倍、50倍、100倍或1000倍,如例如在25℃或37℃下所测量的。

[0075] 在某些实施方案中,Ab在至少一个组氨酸残基例如SEQ ID NO:1中的His 98被质子化的pH下与VISTA-ECD蛋白特异性地结合。在某些实施方案中,Ab在ECD中大多数组氨酸残基被质子化的pH下与VISTA-ECD蛋白特异性地结合,所述pH预期为pH 6.5或更低,例如在pH 6.0与pH 6.5之间。

[0076] 本文还涵盖相对于酸性pH,在中性、生理或碱性pH下以更高的亲和力与VISTA-ECD蛋白特异性地结合的Ab,条件是结合亲和力在酸性pH下依然很高。例如,Ab可以在pH 6.5和pH 7.0下均以10^{-8}M或更小的K_D与VISTA-ECD蛋白结合,但Ab在pH 7.0下以比在pH 6.5下低至少1.5倍、2倍、5倍、10倍、20倍、50倍、100倍、300倍、500倍、1000倍的K_D结合。

[0077] 本文还涵盖具有此部分的以上一个或多个特性的Ab。上述特性(如特定的K_D、k_{off}、k_{on}、特异性表位)不应孤立对待。因此,Ab可以与包含上述SEQ ID NO:2的区域之一的表位结合,并且也可以具有如上所述的泛结合或pH敏感性或pH选择性结合特性,如通过不同pH下的K_D、k_{off}或k_{on}的行为中的一个或多个所示。

[0078] 在任何上述实施方案中,Ab可以是例如全长抗体(即,包含全长重链(具有或不具有C末端赖氨酸)和全长轻链)或抗原结合片段(如Fab片段、Fab'片段,$(Fab')_2$片段、scFv片段、Fv片段),或者Ab可以是嵌合抗体、人源化抗体或人抗体,或者Ab可以是双特异性或多特异性抗体。

[0079] 可以使用几种不同的方法来测定抗体在给定pH下与VISTA-ECD蛋白的结合程度。例如,通过表面等离子共振(SPR),如通过BIACORE®测定。一种示例性的SPR测定包括使用固定化捕获试剂(例如,使用Biacore®抗人Fc捕获试剂盒、GE Healthcare目录号BR-1008-39或Biacore®抗小鼠捕获试剂盒、GE Healthcare目录号BR-1008-39)在CM4传感器芯片上捕获一种或几种抗体,并使以浓度系列的VISTA抗原作为分析物流动,以测定在具有所需pH的运行缓冲液中的结合动力学和亲和力。在一个实施方案中,以30uL/min的流速、最多四分钟缔合时间和最多十分钟解离时间,注射在0.1nM至500nM范围内的两至五种浓度(例如0.1nM、1nM、10nM、100nM、500nM)下的VISTA。在结合周期之间,按照制造商的相应捕获试剂盒的说明书再生捕获表面。使用参考流动池和空白注射对所有数据进行双重参考。使用Biacore® T200评估软件,将具有简单1:1动力学的数据拟合至具有质量转移的Langmuir结合模型。也可以使用实施例中描述的SPR方法。

[0080] 可以使用在其表面表达VISTA ECD多肽、PSGL-1或硫酸乙酰肝素的细胞测定Ab对VISTA ECD多肽的亲和力,所述方法包括流式细胞术,并且其中在给定的pH(例如pH 6.5或

更低)下测定Ab与细胞结合的VISTA-ECD的结合。示例性的流式细胞术测定包括以下内容:将293T细胞或异位表达hVISTAECD的其他细胞重悬于由HBSS+1％BSA组成的、调节至所需pH(例如用MES调节至pH 6.0或用HEPES调节至pH 7.4)的缓冲液中。将抗hVISTA的Ab(例如人IgG)从约20μg/mL开始连续稀释,并与重悬的细胞在4℃下孵育30分钟。然后将细胞用相同的缓冲液洗涤两次以保持所需的pH(例如pH为6.0或7.4),并与识别一抗(例如人IgG)且在降低的pH下稳定的荧光团缀合的二抗孵育。然后像以前一样洗涤细胞,并立即将其获取在BD Fortessa或其他流式细胞仪上,但不固定。可以如实施例中所述测定Ab对VISTAECD多肽的亲和力。

[0081] 在某些实施方案中,与hVISTA ECD结合的Ab阻断例如在细胞上hVISTA与其结合配偶体(例如VISTA受体)的结合。抑制或阻断可以是100％或至少99％、95％、90％、85％、80％、75％或50％。在某些实施方案中,Ab在酸性pH(例如pH 6.5或更低)下与VISTA-ECD蛋白结合,并且将VISTA与其结合配偶体的结合抑制至少50％,如至少75％、80％、85％、90％、95％或100％。在某些实施方案中,Ab在低于pH 7.0的pH下与VISTA-ECD蛋白特异性地结合并将VISTA与其结合配偶体的结合抑制至少50％。在某些实施方案中,Ab在低于pH 6.8的pH下与VISTA-ECD蛋白特异性地结合且将VISTA与其结合配偶体的结合抑制至少50％。在某些实施方案中,Ab在低于pH 6.5的pH下与VISTA-ECD蛋白特异性地结合且将VISTA与其结合配偶体的结合抑制至少50％。在某些实施方案中,Ab在低于pH 6.3的pH下与VISTA-ECD蛋白特异性地结合且将VISTA与其结合配偶体的结合抑制至少50％。在某些实施方案中,Ab在低于pH 6.0的pH下与VISTA-ECD蛋白特异性地结合且将VISTA与其结合配偶体的结合抑制至少50％。在某些实施方案中,Ab在低于pH 5.8的pH下与VISTA-ECD蛋白特异性地结合且将VISTA与其结合配偶体的结合抑制至少50％。在某些实施方案中,Ab在低于pH 5.5的pH下与VISTA-ECD蛋白特异性地结合且将VISTA与其结合配偶体的结合抑制至少50％。在某些实施方案中,Ab在低于pH 5.3的pH下与VISTA-ECD蛋白特异性地结合且将VISTA与其结合配偶体的结合抑制至少50％。在某些实施方案中,Ab在低于pH 5.0的pH下与VISTA-ECD蛋白特异性地结合且将VISTA与其结合配偶体的结合抑制至少50％。

[0082] 某些Ab在pH 5.0-pH 7.0范围内的pH下与VISTA-ECD蛋白特异性地结合并将VISTA与其结合配偶体的结合抑制至少50％。某些Ab在pH 5.0-pH 6.5范围内的pH下与VISTA-ECD蛋白特异性地结合并将VISTA与其结合配偶体的结合抑制至少50％。某些Ab在pH 5.0-pH 6.0范围内的pH下与VISTA-ECD蛋白特异性地结合并将VISTA与其结合配偶体的结合抑制至少50％。某些Ab在pH5.5-pH 7.0范围内的pH下与VISTA-ECD蛋白特异性地结合并将VISTA与其结合配偶体的结合抑制至少50％。某些Ab在pH 5.5-pH 6.5范围内的pH下与VISTA-ECD蛋白特异性地结合并将VISTA与其结合配偶体的结合抑制至少50％。某些Ab在pH 6.0-6.5范围内的pH下与VISTA-ECD蛋白特异性地结合并将VISTA与其结合配偶体的结合抑制至少50％。可以如实施例中所述来测定结合的抑制。

[0083] VISTA结合配偶体可以是PSGL-1,如人PSGL-1。人PSGL-1同种型的序列在本文中以SEQ ID NO:3-10提供。它也可以是例如存在于某些细胞上的硫酸乙酰肝素蛋白多糖。

[0084] 可以通过在抗体的存在和不存在下测量VISTA(或VISTA ECD或VISTA IgV结构域或VISTA阳性细胞)与VISTA所结合的细胞(例如T细胞(例如激活或未激活的CD4+T细胞、CD8+T细胞)、NK细胞或VISTA所结合的其他细胞)的结合的抑制来测定与VISTA结合配偶体结合

的抑制。可以用于确定抗体是否抑制VISTA与其结合配偶体或表达结合配偶体的T细胞的结合的示例性实验是流式细胞术测定,例如包含以下内容的测定:将来自供体血液、血沉棕黄层或leukopak的人外周血单核细胞重悬于由HBSS+1％BSA组成的、调节至所需pH(例如用MES调节至pH 6.0或用HEPES调节至pH 7.4)的缓冲液中。然后将细胞在4℃下与由融合至人IgG1 Fc的hVISTA ECD(VISTA-Fc)组成的20μg/mL重组嵌合蛋白和不同浓度的候选VISTA阻断抗体或对照抗体孵育30分钟。然后将细胞在相同的缓冲液中洗涤两次以保持所需的pH(例如pH为6.0或7.4),并在4℃下与识别VISTA-Fc的荧光团缀合的二抗而非候选阻断抗体或对照抗体孵育另外30分钟,并且在降低的pH值下稳定。然后像以前一样洗涤细胞,并立即将其获取在BD Fortessa或其他流式细胞仪上,但不固定。可以例如如实施例中所述来测定结合的抑制。

[0085] 在特定实施方案中,本文所述的Ab可以触发或增强免疫应答,例如抗原特异性免疫应答。在某些实施方案中,Ab刺激T细胞活性,特别是在酸性pH(如在肿瘤微环境中发现的)下。可以例如在混合的淋巴细胞反应(MLR)中或在用抗原呈递细胞(天然或人工)和T细胞的体外测定中测量T细胞活性的刺激。也可以使用例如实施例中所述的Jurkat测定来测量T细胞活性的刺激。

[0086] 在特定实施方案中,本文所述的Ab抑制细胞粘附,其可以如实施例中所述进行测量。

[0087] 抗VISTA Ab的活性也可以在单核细胞测定、ADCC测定和ADCP测定中,特别是在酸性pH(如在肿瘤微环境中发现的)下显示。

[0088] 在某些实施方案中,抗VISTAAb在肿瘤模型例如人VISTA敲入的肿瘤模型中抑制肿瘤生长。

[0089] 如本文的实施例中所示,抗VISTAAb在内体中再循环以增强抗体的药代动力学(PK)特性即半衰期,需要抗VISTA抗体在酸性条件下与VISTA结合。因此,如本文进一步所述,相对于在酸性pH下不与VISTA结合的VISTA抗体,在低pH(例如pH为6.5或更低)下与VISTA结合的抗VISTA Ab也预期具有更长的可接受的半衰期。

[0090] 示例性结合hVISTA-ECD的Ab

[0091] 本文提供了相对于生理pH或中性pH,优先在酸性pH下(例如在酸性条件下)与hVISTA(ECD)结合的Ab。

[0092] 在某些实施方案中,抗hVISTA Ab包含含有本文提供的任何抗hVISTA抗体的VH CDR1、CDR2和/或CDR3的重链可变区(“VH”)。在某些实施方案中,抗hVISTA Ab包含含有本文提供的任何抗hVISTA Ab的VH CDR1、CDR2和CDR3的VH。在某些实施方案中,抗hVISTA Ab包含含有P1-061029或P1-061015或其后代如P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_

E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF的VH CDR1、CDR2和/或CDR3的VH。这些种类的每一种的VH CDR1、CDR2和CDR3包含以下序列表中提供的上述抗体种类的每一种的VH序列的氨基酸位置26-35(VH CDR1)、50-66(VH CDR2)和99-110(VH CDR3)。CDR也在以下序列表中提供的上述抗体种类的每个VH序列上加下划线并呈粗体。

[0093] 在某些实施方案中,抗hVISTA Ab包含含有本文提供的任何抗hVISTAAb的VH CDR1、CDR2和CDR3的VH。在某些实施方案中,抗hVISTA Ab包含含有P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF中一种的VH CDR1、CDR2和CDR3的VH。这些种类的每一种的VL CDR1、CDR2和CDR3包含以下序列表中提供的上述抗体种类的每一种的VL序列的氨基酸位置24-35(VL CDR1)、51-57(VL CDR2)和90-98(VL CDR3)。CDR也在那些序列的每一个上加下划线并呈粗体。

[0094] 在某些实施方案中,抗hVISTA Ab包含含有本文提供的任何抗hVISTAAb的VH CDR1、CDR2和/或CDR3的VH和含有本文提供的任何抗hVISTAAb的CDR1、CDR2和/或CDR3的VL。在某些实施方案中,抗hVISTAAb包含含有本文提供的任何抗hVISTAAb的VH CDR1、CDR2和CDR3的VH和含有本文提供的任何抗hVISTAAb的CDR1、CDR2和CDR3的VL。在某些实施方案中,抗hVISTAAb包含含有P1-061029或P1-061015或其后代如P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-

068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF的VH CDR1、CDR2和/或CDR3的VH和含有P1-061029或P1-061015或其后代如P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF的VL CDR1、CDR2和CDR3的VL。

[0095] 在一些实施方案中,抗hVISTAAb可以包含:

[0096] (a)含有P1-061029的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-061029的VL CDR1、CDR2和CDR3的VL;

[0097] (b)含有P1-061015的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-061015的VL CDR1、CDR2和CDR3的VL;

[0098] (c)含有P1-068757的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068757的VL CDR1、CDR2和CDR3的VL;

[0099] (d)含有P1-068759的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068759的VL CDR1、CDR2和CDR3的VL;

[0100] (e)含有P1-068761的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761的VL CDR1、CDR2和CDR3的VL;

[0101] (f)含有P1-068763的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068763的VL CDR1、CDR2和CDR3的VL;

[0102] (g)含有P1-068765的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068765的VL CDR1、CDR2和CDR3的VL;

[0103] (h)含有P1-068767的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068767的VL CDR1、CDR2和CDR3的VL;

[0104] (i)含有P1-068769的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068769的

VL CDR1、CDR2和CDR3的VL；

[0105] (j)含有P1-068771的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068771的VL CDR1、CDR2和CDR3的VL；

[0106] (k)含有P1-068773的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068773的VL CDR1、CDR2和CDR3的VL；

[0107] (l)含有P1-068775的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068775的VL CDR1、CDR2和CDR3的VL；

[0108] (m)含有P1-069059的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-069059的VL CDR1、CDR2和CDR3的VL；

[0109] (n)含有P1-069061的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-069061的VL CDR1、CDR2和CDR3的VL；

[0110] (o)含有P1-069063的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-069063的VL CDR1、CDR2和CDR3的VL；

[0111] (p)含有P1-069065的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-069065的VL CDR1、CDR2和CDR3的VL；

[0112] (q)含有P1-069067的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-069067的VL CDR1、CDR2和CDR3的VL；

[0113] (r)含有P1-069069的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-069069的VL CDR1、CDR2和CDR3的VL；

[0114] (s)含有P1-069071的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-069071的VL CDR1、CDR2和CDR3的VL；

[0115] (t)含有P1-069073的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-069073的VL CDR1、CDR2和CDR3的VL；

[0116] (u)含有P1-069075的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-069075的VL CDR1、CDR2和CDR3的VL；

[0117] (v)含有P1-069077的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-069077的VL CDR1、CDR2和CDR3的VL；

[0118] (w)含有P1-068736的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068736的VL CDR1、CDR2和CDR3的VL；

[0119] (x)含有P1-068738的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068738的VL CDR1、CDR2和CDR3的VL；

[0120] (y)含有P1-068740的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068740的VL CDR1、CDR2和CDR3的VL；

[0121] (z)含有P1-068742的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068742的VL CDR1、CDR2和CDR3的VL；

[0122] (aa)含有P1-068744的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068744的VL CDR1、CDR2和CDR3的VL；

[0123] (bb)含有P1-068746的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068746的VL CDR1、CDR2和CDR3的VL；

[0124] (cc)含有P1-068748的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068748的VL CDR1、CDR2和CDR3的VL；

[0125] (dd)含有P1-068750的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068750的VL CDR1、CDR2和CDR3的VL；

[0126] (ee)含有P1-068752的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068752的VL CDR1、CDR2和CDR3的VL；

[0127] (ff)含有P1-068754的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068754的VL CDR1、CDR2和CDR3的VL；

[0128] (gg)含有P1-068761_E55A的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_E55A的VL CDR1、CDR2和CDR3的VL；

[0129] (hh)含有P1-068761_H100G的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_H100G的VL CDR1、CDR2和CDR3的VL；

[0130] (ii)含有P1-068761_E56N的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_E56N的VL CDR1、CDR2和CDR3的VL；

[0131] (jj)含有P1-068761_E55A_E56N的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_E55A_E56N的VL CDR1、CDR2和CDR3的VL；

[0132] (kk)含有P1-068761_E30D的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_E30D的VL CDR1、CDR2和CDR3的VL；

[0133] (ll)含有P1-068761_E30D_E55A的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_E30D_E55A的VL CDR1、CDR2和CDR3的VL；

[0134] (mm)含有P1-068761_E56N_H100G的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_E56N_H100G的VL CDR1、CDR2和CDR3的VL；

[0135] (nn)含有P1-068761_E30D_H100G的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_E30D_H100G的VL CDR1、CDR2和CDR3的VL；

[0136] (oo)含有P1-068761_E30D_E56N的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_E30D_E56N的VL CDR1、CDR2和CDR3的VL；

[0137] (pp)含有P1-068761_E100fF的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_E100fF的VL CDR1、CDR2和CDR3的VL；

[0138] (qq)含有P1-068761_E55A_E100fF的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_E55A_E100fF的VL CDR1、CDR2和CDR3的VL；

[0139] (rr)含有P1-068761_H100G_E100fF的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_H100G_E100fF的VL CDR1、CDR2和CDR3的VL；

[0140] (ss)含有P1-068761_E30D_E100fF的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_E30D_E100fF的VL CDR1、CDR2和CDR3的VL；

[0141] (tt)含有P1-068761_E56N_E100fF的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_E56N_E100fF的VL CDR1、CDR2和CDR3的VL；

[0142] (uu)含有P1-068761_E32Y的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_E32Y的VL CDR1、CDR2和CDR3的VL；

[0143] (vv)含有P1-068761_E32Y_E55A的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有

P1-068761_E32Y_E55A的VL CDR1、CDR2和CDR3的VL；

[0144] (ww)含有P1-068761_E32Y_E56N的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_E32Y_E56N的VL CDR1、CDR2和CDR3的VL；

[0145] (xx)含有P1-068761_E30D_E32Y的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_E30D_E32Y的VL CDR1、CDR2和CDR3的VL；

[0146] (yy)含有P1-068761_E32Y_H100G的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_E32Y_H100G的VL CDR1、CDR2和CDR3的VL；

[0147] (zz)含有P1-068761_E32Y_E100fF的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068761_E32Y_E100fF的VL CDR1、CDR2和CDR3的VL；

[0148] (aaa)含有P1-068767_D52N_D102V的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068767_D52N_D102V的VL CDR1、CDR2和CDR3的VL；

[0149] (bbb)含有P1-068767_D52N的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068767_D52N的VL CDR1、CDR2和CDR3的VL；

[0150] (ccc)含有P1-068767_D52N_E55A的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068767_D52N_E55A的VL CDR1、CDR2和CDR3的VL；

[0151] (ddd)含有P1-068767_E55A_D102V的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068767_E55A_D102V的VL CDR1、CDR2和CDR3的VL；

[0152] (eee)含有P1-068767_D102V的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068767_D102V的VL CDR1、CDR2和CDR3的VL；

[0153] (fff)含有P1-068767_E55A的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068767_E55A的VL CDR1、CDR2和CDR3的VL；

[0154] (ggg)含有P1-068767_E30D_D52N的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068767_E30D_D52N的VL CDR1、CDR2和CDR3的VL；

[0155] (hhh)含有P1-068767_E30D_D102V的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068767_E30D_D102V的VL CDR1、CDR2和CDR3的VL；

[0156] (iii)含有P1-068767_E30D的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068767_E30D的VL CDR1、CDR2和CDR3的VL；

[0157] (jjj)含有P1-068767_E30D_E55A的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068767_E30D_E55A的VL CDR1、CDR2和CDR3的VL；

[0158] (kkk)含有P1-068767_E100fF_D102V的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068767_E100fF_D102V的VL CDR1、CDR2和CDR3的VL；

[0159] (lll)含有P1-068767_E55A_E100fF的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068767_E55A_E100fF的VL CDR1、CDR2和CDR3的VL；

[0160] (mmm)含有P1-068767_D52N_E100fF的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068767_D52N_E100fF的VL CDR1、CDR2和CDR3的VL；

[0161] (nnn)含有P1-068767_E100fF的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068767_E100fF的VL CDR1、CDR2和CDR3的VL；

[0162] (ooo)含有P1-068767_E30D_E100fF的VH CDR1、CDR2和CDR3的氨基酸序列的VH和含有P1-068767_E30D_E100fF的VL CDR1、CDR2和CDR3的VL。

[0163] 同样,以下序列表提供了具有IgG1.3重链恒定区(除非在表中指出了不同的HC恒定区)的以上所列抗体的重链和轻链可变区序列以及全长重链和轻链序列,并且通过氨基酸残基和在每个VH和VL序列中对CDR使用粗体和加下划线来指出其VH CDR1、CDR2和CDR3以及VL CDR1、CDR2和CDR3的位置。因此,例如P1-061029的VH CDR1包含SEQ ID NO:67的氨基酸26-35,而VH CDR2包含SEQ ID NO:67的氨基酸50-66,并且VH CDR3包含SEQ ID NO:67的氨基酸99-110,等等,如通过序列表中所示SEQ ID NO:67的粗体和加下划线的氨基酸所指出的。

[0164] 在某些实施方案中,抗hVISTAAb包含含有本文提供的任何抗hVISTAAb的VH的氨基酸序列的VH。序列表中列出了本文提供的特定抗体种类的单独VH序列。在某些实施方案中,抗hVISTAAb包含含有P1-061029或P1-061015或其后代如P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF的VH的氨基酸序列的VH。在某些实施方案中,抗hVISTAAb包含含有本文提供的任何抗hVISTA Ab的VH CDR的氨基酸序列的VH CDR1、CDR2和CDR3,并且包含与本文提供的任何抗hVISTAAb的VH至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%或至少99%相同的VH。在某些实施方案中,抗hVISTAAb包含含有如下氨基酸序列的VH,所述氨基酸序列与P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-

068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF的VH的氨基酸序列是至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的。在某些实施方案中,抗hVISTAAb包含由本文提供的任何抗hVISTAAb的VH的氨基酸序列组成的VH。在某些实施方案中,抗hVISTAAb包含由P1-061029或P1-061015或其后代如P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF的VH的氨基酸序列组成的VH。

[0165] 在某些实施方案中,抗hVISTAAb包含含有本文提供的任何抗hVISTAAb的VL的氨基酸序列的VL。在某些实施方案中,抗hVISTAAb包含含有P1-061029或P1-061015或其后代如P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF的VL的氨基酸序列的VL。在某些实施方案中,抗hVISTAAb包含含有本文提供的任何抗hVISTAAb的VL CDR的氨基酸序列的VL CDR1、CDR2和CDR3,并且包含与本文提供的任何抗hVISTA Ab的VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VL。在某些实施方案中,抗hVISTA Ab包含含有如下氨基酸序列的VL,所述氨基酸序列与P1-061029、P1-068757、P1-

068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF的VL的氨基酸序列是至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的。在某些实施方案中,抗hVISTA Ab包含由本文提供的任何抗hVISTA Ab的VL的氨基酸序列组成的VL。在某些实施方案中,抗hVISTA Ab包含由P1-061029或P1-061015或其后代如P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF的VL的氨基酸序列组成的VL。

[0166] 在某些实施方案中,抗hVISTA Ab包含含有本文提供的任何抗hVISTA Ab的VH的氨基酸序列的VH,并且包含含有本文提供的任何抗hVISTA Ab的VL的氨基酸序列的VL。在这些实施方案中的某些实施方案中,抗hVISTA Ab包含含有P1-061029或P1-061015或其后代如P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_

E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF的VH的氨基酸序列的VH;和含有P1-061029或P1-061015的VL的氨基酸序列。在某些实施方案中,抗hVISTAAb包含含有P1-061029或P1-061015或其后代如P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF的VH和VL的氨基酸序列的VH和VL。

[0167] 在某些实施方案中,抗hVISTAAb包含含有本文提供的任何抗hVISTA Ab的VH CDR的氨基酸序列的VH CDR1、CDR2和CDR3以及含有本文提供的任何抗hVISTAAb的VL CDR的氨基酸序列的VL CDR1、CDR2和CDR3,并且还包含各自与本文提供的任何抗hVISTA Ab的相应VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL。在某些实施方案中,抗hVISTA Ab包含本文提供的抗hVISTA Ab的所有6个CDR,并且还包含各自与抗hVISTA Ab的相应VH和VL,如P1-061029或P1-061015或其后代如P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-

068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列。在某些实施方案中,抗hVISTA Ab包含由本文提供的任何抗hVISTA Ab的VH和VL的氨基酸序列组成的VH和VL。在某些实施方案中,抗hVISTA Ab包含各自由P1-061029或P1-061015或其后代如P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF的VH和VL的氨基酸序列组成的VH和VL。

[0168] 抗hVISTA Ab可以包含:

[0169] (a)含有P1-061029的VH的氨基酸序列的VH和含有P1-061029的VL的氨基酸序列的VL;

[0170] (b)含有P1-061015的VH的氨基酸序列的VH和含有P1-061015的VL的氨基酸序列的VL;

[0171] (c)含有P1-068757的VH的氨基酸序列的VH和含有P1-068757的VL的氨基酸序列的VL;

[0172] (d)含有P1-068759的VH的氨基酸序列的VH和含有P1-068759的VL的氨基酸序列的VL;

[0173] (e)含有P1-068761的VH的氨基酸序列的VH和含有P1-068761的VL的氨基酸序列的VL;

[0174] (f)含有P1-068763的VH的氨基酸序列的VH和含有P1-068763的VL的氨基酸序列的VL;

[0175] (g)含有P1-068765的VH的氨基酸序列的VH和含有P1-068765的VL的氨基酸序列的VL;

[0176] (h)含有P1-068767的VH的氨基酸序列的VH和含有P1-068767的VL的氨基酸序列的VL;

[0177] (i)含有P1-068769的VH的氨基酸序列的VH和含有P1-068769的VL的氨基酸序列的VL;

[0178] (j)含有P1-068771的VH的氨基酸序列的VH和含有P1-068771的VL的氨基酸序列的VL;

[0179] (k)含有P1-068773的VH的氨基酸序列的VH和含有-068773的VL的氨基酸序列的VL;

[0180] (l)含有P1-068775的VH的氨基酸序列的VH和含有P1-068775的VL的氨基酸序列的VL;

[0181] (m)含有P1-069059的VH的氨基酸序列的VH和含有P1-069059的VL的氨基酸序列的VL;

[0182] (n)含有P1-069061的VH的氨基酸序列的VH和含有P1-069061的VL的氨基酸序列的VL;

[0183] (o)含有P1-069063的VH的氨基酸序列的VH和含有P1-069063的VL的氨基酸序列的VL;

[0184] (p)含有P1-069065的VH的氨基酸序列的VH和含有P1-069065的VL的氨基酸序列的VL;

[0185] (q)含有P1-069067的VH的氨基酸序列的VH和含有P1-069067的VL的氨基酸序列的VL;

[0186] (r)含有P1-069069的VH的氨基酸序列的VH和含有P1-069069的VL的氨基酸序列的VL;

[0187] (s)含有P1-069071的VH的氨基酸序列的VH和含有P1-069071的VL的氨基酸序列的VL;

[0188] (t)含有P1-069073的VH的氨基酸序列的VH和含有P1-069073的VL的氨基酸序列的VL;

[0189] (u)含有P1-069075的VH的氨基酸序列的VH和含有P1-069075的VL的氨基酸序列的VL;

[0190] (v)含有P1-069077的VH的氨基酸序列的VH和含有P1-069077的VL的氨基酸序列的VL;

[0191] (w)含有P1-068736的VH的氨基酸序列的VH和含有P1-068736的VL的氨基酸序列的VL;

[0192] (x)含有P1-068738的VH的氨基酸序列的VH和含有P1-068738的VL的氨基酸序列的VL;

[0193] (y)含有P1-068740的VH的氨基酸序列的VH和含有P1-068740的VL的氨基酸序列的VL;

[0194] (z)含有P1-068742的VH的氨基酸序列的VH和含有P1-068742的VL的氨基酸序列的VL;

[0195] (aa)含有P1-068744的VH的氨基酸序列的VH和含有P1-068744的VL的氨基酸序列的VL;

[0196] (bb)含有P1-068746的VH的氨基酸序列的VH和含有P1-068746的VL的氨基酸序列

的VL；

[0197] (cc)含有P1-068748的VH的氨基酸序列的VH和含有P1-068748的VL的氨基酸序列的VL；

[0198] (dd)含有P1-068750的VH的氨基酸序列的VH和含有P1-068750的VL的氨基酸序列的VL；

[0199] (ee)含有P1-068752的VH的氨基酸序列的VH和含有P1-068752的VL的氨基酸序列的VL；

[0200] (ff)含有P1-068754的VH的氨基酸序列的VH和含有P1-068754的VL的氨基酸序列的VL；

[0201] (gg)含有P1-068761_E55A的VH的氨基酸序列的VH和含有P1-068761_E55A的VL的氨基酸序列的VL；

[0202] (hh)含有P1-068761_H100G的VH的氨基酸序列的VH和含有P1-068761_H100G的VL的氨基酸序列的VL；

[0203] (ii)含有P1-068761_E56N的VH的氨基酸序列的VH和含有P1-068761_E56N的VL的氨基酸序列的VL；

[0204] (jj)含有P1-068761_E55A_E56N的VH的氨基酸序列的VH和含有P1-068761_E55A_E56N的VL的氨基酸序列的VL；

[0205] (kk)含有P1-068761_E30D的VH的氨基酸序列的VH和含有P1-068761_E30D的VL的氨基酸序列的VL；

[0206] (ll)含有P1-068761_E30D_E55A的VH的氨基酸序列的VH和含有P1-068761_E30D_E55A的VL的氨基酸序列的VL；

[0207] (mm)含有P1-068761_E56N_H100G的VH的氨基酸序列的VH和含有P1-068761_E56N_H100G的VL的氨基酸序列的VL；

[0208] (nn)含有P1-068761_E30D_H100G的VH的氨基酸序列的VH和含有P1-068761_E30D_H100G的VL的氨基酸序列的VL；

[0209] (oo)含有P1-068761_E30D_E56N的VH的氨基酸序列的VH和含有P1-068761_E30D_E56N的VL的氨基酸序列的VL；

[0210] (pp)含有P1-068761_E100fF的VH的氨基酸序列的VH和含有P1-068761_E100fF的VL的氨基酸序列的VL；

[0211] (qq)含有P1-068761_E55A_E100fF的VH的氨基酸序列的VH和含有P1-068761_E55A_E100fF的VL的氨基酸序列的VL；

[0212] (rr)含有P1-068761_H100G_E100fF的VH的氨基酸序列的VH和含有P1-068761_H100G_E100fF的VL的氨基酸序列的VL；

[0213] (ss)含有P1-068761_E30D_E100fF的VH的氨基酸序列的VH和含有P1-068761_E30D_E100fF的VL的氨基酸序列的VL；

[0214] (tt)含有P1-068761_E56N_E100fF的VH的氨基酸序列的VH和含有P1-068761_E56N_E100fF的VL的氨基酸序列的VL；

[0215] (uu)含有P1-068761_E32Y的VH的氨基酸序列的VH和含有P1-068761_E32Y的VL的氨基酸序列的VL；

[0216] (vv)含有P1-068761_E32Y_E55A的VH的氨基酸序列的VH和含有P1-068761_E32Y_E55A的VL的氨基酸序列的VL;

[0217] (ww)含有P1-068761_E32Y_E56N的VH的氨基酸序列的VH和含有P1-068761_E32Y_E56N的VL的氨基酸序列的VL;

[0218] (xx)含有P1-068761_E30D_E32Y的VH的氨基酸序列的VH和含有P1-068761_E30D_E32Y的VL的氨基酸序列的VL;

[0219] (yy)含有P1-068761_E32Y_H100G的VH的氨基酸序列的VH和含有P1-068761_E32Y_H100G的VL的氨基酸序列的VL;

[0220] (zz)含有P1-068761_E32Y_E100fF的VH的氨基酸序列的VH和含有P1-068761_E32Y_E100fF的VL的氨基酸序列的VL;

[0221] (aaa)含有P1-068767_D52N_D102V的VH的氨基酸序列的VH和含有P1-068767_D52N_D102V的VL的氨基酸序列的VL;

[0222] (bbb)含有P1-068767_D52N的VH的氨基酸序列的VH和含有P1-068767_D52N的VL的氨基酸序列的VL;

[0223] (ccc)含有P1-068767_D52N_E55A的VH的氨基酸序列的VH和含有P1-068767_D52N_E55A的VL的氨基酸序列的VL;

[0224] (ddd)含有P1-068767_E55A_D102V的VH的氨基酸序列的VH和含有P1-068767_E55A_D102V的VL的氨基酸序列的VL;

[0225] (eee)含有P1-068767_D102V的VH的氨基酸序列的VH和含有P1-068767_D102V的VL的氨基酸序列的VL;

[0226] (fff)含有P1-068767_E55A的VH的氨基酸序列的VH和含有P1-068767_E55A的VL的氨基酸序列的VL;

[0227] (ggg)含有P1-068767_E30D_D52N的VH的氨基酸序列的VH和含有P1-068767_E30D_D52N的VL的氨基酸序列的VL;

[0228] (hhh)含有P1-068767_E30D_D102V的VH的氨基酸序列的VH和含有P1-068767_E30D_D102V的VL的氨基酸序列的VL;

[0229] (iii)含有P1-068767_E30D的VH的氨基酸序列的VH和含有P1-068767_E30D的VL的氨基酸序列的VL;

[0230] (jjj)含有P1-068767_E30D_E55A的VH的氨基酸序列的VH和含有P1-068767_E30D_E55A的VL的氨基酸序列的VL;

[0231] (kkk)含有P1-068767_E100fF_D102V的VH的氨基酸序列的VH和含有P1-068767_E100fF_D102V的VL的氨基酸序列的VL;

[0232] (lll)含有P1-068767_E55A_E100fF的VH的氨基酸序列的VH和含有P1-068767_E55A_E100fF的VL的氨基酸序列的VL;

[0233] (mmm)含有P1-068767_D52N_E100fF的VH的氨基酸序列的VH和含有P1-068767_D52N_E100fF的VL的氨基酸序列的VL;

[0234] (nnn)含有P1-068767_E100fF的VH的氨基酸序列的VH和含有P1-068767_E100fF的VL的氨基酸序列的VL;或

[0235] (ooo)含有P1-068767_E30D_E100fF的VH的氨基酸序列的VH和含有P1-068767_

E30D_E100fF的VL的氨基酸序列的VL。抗hVISTA Ab可以包含：

[0236] (a)含有P1-061029的VH的VH CDR的VH和含有P1-061029的VL CDR的VL以及与P1-061029的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0237] (b)含有P1-061015的VH的VH CDR的VH和含有P1-061015的VL CDR的VL以及与P1-061015的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0238] (c)含有P1-068757的VH的VH CDR的VH和含有P1-068757的VL CDR的VL以及与P1-068757的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0239] (d)含有P1-068759的VH的VH CDR的VH和含有P1-068759的VL CDR的VL以及与P1-068759的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0240] (e)含有P1-068761的VH的VH CDR的VH和含有P1-068761的VL CDR的VL以及与P1-068761的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0241] (f)含有P1-068763的VH的VH CDR的VH和含有P1-068763的VL CDR的VL以及与P1-068763的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0242] (g)含有P1-068765的VH的VH CDR的VH和含有P1-068765的VL CDR的VL以及与P1-068765的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0243] (h)含有P1-068767的VH的VH CDR的VH和含有P1-068767的VL CDR的VL以及与P1-068767的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0244] (i)含有P1-068769的VH的VH CDR的VH和含有P1-068769的VL CDR的VL以及与P1-068769的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0245] (j)含有P1-068771的VH的VH CDR的VH和含有P1-068771的VL CDR的VL以及与P1-068771的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0246] (k)含有P1-068773的VH的VH CDR的VH和含有P1-068773的VL CDR的VL以及与P1-068773的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0247] (l)含有P1-068775的VH的VH CDR的VH和含有P1-068775的VL CDR的VL以及与P1-068775的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0248] (m)含有P1-069059的VH的VH CDR的VH和含有P1-069059的VL CDR的VL以及与P1-069059的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、

至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0249] (n)含有P1-069061的VH的VH CDR的VH和含有P1-069061的VL CDR的VL以及与P1-069061的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0250] (o)含有P1-069063的VH的VH CDR的VH和含有P1-069063的VL CDR的VL以及与P1-069063的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0251] (p)含有P1-069065的VH的VH CDR的VH和含有P1-069065的VL CDR的VL以及与P1-069065的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0252] (q)含有P1-069067的VH的VH CDR的VH和含有P1-069067的VL CDR的VL以及与P1-069067的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0253] (r)含有P1-069069的VH的VH CDR的VH和含有P1-069069的VL CDR的VL以及与P1-069069的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0254] (s)含有P1-069071的VH的VH CDR的VH和含有P1-069071的VL CDR的VL以及与P1-069071的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0255] (t)含有P1-069073的VH的VH CDR的VH和含有P1-069073的VL CDR的VL以及与P1-069073的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0256] (u)含有P1-069075的VH的VH CDR的VH和含有P1-069075的VL CDR的VL以及与P1-069075的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0257] (v)含有P1-069077的VH的VH CDR的VH和含有P1-069077的VL CDR的VL以及与P1-069077的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0258] (w)含有P1-068736的VH的VH CDR的VH和含有P1-068736的VL CDR的VL以及与P1-068736的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0259] (x)含有P1-068738的VH的VH CDR的VH和含有P1-068738的VL CDR的VL以及与P1-068738的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0260] (y)含有P1-068740的VH的VH CDR的VH和含有P1-068740的VL CDR的VL以及与P1-068740的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0261] (z)含有P1-068742的VH的VH CDR的VH和含有P1-068742的VL CDR的VL以及与P1-068742的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、

至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0262] (aa)含有P1-068744的VH的VH CDR的VH和含有P1-068744的VL CDR的VL以及与P1-068744的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0263] (bb)含有P1-068746的VH的VH CDR的VH和含有P1-068746的VL CDR的VL以及与P1-068746的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0264] (cc)含有P1-068748的VH的VH CDR的VH和含有P1-068748的VL CDR的VL以及与P1-068748的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0265] (dd)含有P1-068750的VH的VH CDR的VH和含有P1-068750的VL CDR的VL以及与P1-068750的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0266] (ee)含有P1-068752的VH的VH CDR的VH和含有P1-068752的VL CDR的VL以及与P1-068752的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0267] (ff)含有P1-068754的VH的VH CDR的VH和含有P1-068754的VL CDR的VL以及与P1-068754的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0268] (gg)含有P1-068761_E55A的VH的VH CDR的VH和含有P1-068761_E55A的VL CDR的VL以及与P1-068761_E55A的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0269] (hh)含有P1-068761_H100G的VH的VH CDR的VH和含有P1-068761_H100G的VL CDR的VL以及与P1-068761_H100G的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0270] (ii)含有P1-068761_E56N的VH的VH CDR的VH和含有P1-068761_E56N的VL CDR的VL以及与P1-068761_E56N的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0271] (jj)含有P1-068761_E55A_E56N的VH的VH CDR的VH和含有P1-068761_E55A_E56N的VL CDR的VL以及与P1-068761_E55A_E56N的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0272] (kk)含有P1-068761_E30D的VH的VH CDR的VH和含有P1-068761_E30D的VL CDR的VL以及与P1-068761_E30D的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0273] (ll)含有P1-068761_E30D_E55A的VH的VH CDR的VH和含有P1-068761_E30D_E55A的VL CDR的VL以及与P1-068761_E30D_E55A的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0274] (mm)含有P1-068761_E56N_H100G的VH的VH CDR的VH和含有P1-068761_E56N_H100G的VL CDR的VL以及与P1-068761_E56N_H100G的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0275] (nn)含有P1-068761_E30D_H100G的VH的VH CDR的VH和含有P1-068761_E30D_H100G的VL CDR的VL以及与P1-068761_E30D_H100G的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0276] (oo)含有P1-068761_E30D_E56N的VH的VH CDR的VH和含有P1-068761_E30D_E56N的VL CDR的VL以及与P1-068761_E30D_E56N的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0277] (pp)含有P1-068761_E100fF的VH的VH CDR的VH和含有P1-068761_E100fF的VL CDR的VL以及与P1-068761_E100fF的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0278] (qq)含有P1-068761_E55A_E100fF的VH的VH CDR的VH和含有P1-068761_E55A_E100fF的VL CDR的VL以及与P1-068761_E55A_E100fF的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0279] (rr)含有P1-068761_H100G_E100fF的VH的VH CDR的VH和含有P1-068761_H100G_E100fF的VL CDR的VL以及与P1-068761_H100G_E100fF的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0280] (ss)含有P1-068761_E30D_E100fF的VH的VH CDR的VH和含有P1-068761_E30D_E100fF的VL CDR的VL以及与P1-068761_E30D_E100fF的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0281] (tt)含有P1-068761_E56N_E100fF的VH的VH CDR的VH和含有P1-068761_E56N_E100fF的VL CDR的VL以及与P1-068761_E56N_E100fF的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0282] (uu)含有P1-068761_E32Y的VH的VH CDR的VH和含有P1-068761_E32Y的VL CDR的VL以及与P1-068761_E32Y的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0283] (vv)含有P1-068761_E32Y_E55A的VH的VH CDR的VH和含有P1-068761_E32Y_E55A的VL CDR的VL以及与P1-068761_E32Y_E55A的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0284] (ww)含有P1-068761_E32Y_E56N的VH的VH CDR的VH和含有P1-068761_E32Y_E56N

的VL CDR的VL以及与P1-068761_E32Y_E56N的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0285] (xx)含有P1-068761_E30D_E32Y的VH的VH CDR的VH和含有P1-068761_E30D_E32Y的VL CDR的VL以及与P1-068761_E30D_E32Y的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0286] (yy)含有P1-068761_E32Y_H100G的VH的VH CDR的VH和含有P1-068761_E32Y_H100G的VL CDR的VL以及与P1-068761_E32Y_H100G的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0287] (zz)含有P1-068761_E32Y_E100fF的VH的VH CDR的VH和含有P1-068761_E32Y_E100fF的VL CDR的VL以及与P1-068761_E32Y_E100fF的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0288] (aaa)含有P1-068767_D52N_D102V的VH的VH CDR的VH和含有P1-068767_D52N_D102V的VL CDR的VL以及与P1-068767_D52N_D102V的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0289] (bbb)含有P1-068767_D52N的VH的VH CDR的VH和含有P1-068767_D52N的VL CDR的VL以及与P1-068767_D52N的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0290] (ccc)含有P1-068767_D52N_E55A的VH的VH CDR的VH和含有P1-068767_D52N_E55A的VL CDR的VL以及与P1-068767_D52N_E55A的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0291] (ddd)含有P1-068767_E55A_D102V的VH的VH CDR的VH和含有P1-068767_E55A_D102V的VL CDR的VL以及与P1-068767_E55A_D102V的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0292] (eee)含有P1-068767_D102V的VH的VH CDR的VH和含有P1-068767_D102V的VL CDR的VL以及与P1-068767_D102V的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0293] (fff)含有P1-068767_E55A的VH的VH CDR的VH和含有P1-068767_E55A的VL CDR的VL以及与P1-068767_E55A的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0294] (ggg)含有P1-068767_E30D_D52N的VH的VH CDR的VH和含有P1-068767_E30D_D52N的VL CDR的VL以及与P1-068767_E30D_D52N的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸

序列；

[0295] (hhh)含有P1-068767_E30D_D102V的VH的VH CDR的VH和含有P1-068767_E30D_D102V的VL CDR的VL以及与P1-068767_E30D_D102V的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0296] (iii)含有P1-068767_E30D的VH的VH CDR的VH和含有P1-068767_E30D的VL CDR的VL以及与P1-068767_E30D的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0297] (jjj)含有P1-068767_E30D_E55A的VH的VH CDR的VH和含有P1-068767_E30D_E55A的VL CDR的VL以及与P1-068767_E30D_E55A的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0298] (kkk)含有P1-068767_E100fF_D102V的VH的VH CDR的VH和含有P1-068767_E100fF_D102V的VL CDR的VL以及与P1-068767_E100fF_D102V的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0299] (lll)含有P1-068767_E55A_E100fF的VH的VH CDR的VH和含有P1-068767_E55A_E100fF的VL CDR的VL以及与P1-068767_E55A_E100fF的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0300] (mmm)含有P1-068767_D52N_E100fF的VH的VH CDR的VH和含有P1-068767_D52N_E100fF的VL CDR的VL以及与P1-068767_D52N_E100fF的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；

[0301] (nnn)含有P1-068767_E100fF的VH的VH CDR的VH和含有P1-068767_E100fF的VL CDR的VL以及与P1-068767_E100fF的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列；或

[0302] (ooo)含有P1-068767_E30D_E100fF的VH的VH CDR的VH和含有P1-068767_E30D_E100fF的VL CDR的VL以及与P1-068767_E30D_E100fF的VH和VL至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的VH和VL氨基酸序列。抗hVISTA Ab可以包含：

[0303] (a)由P1-061029的VH的氨基酸序列组成的VH和由P1-061029的VL组成的VL；

[0304] (b)由P1-061015的VH的氨基酸序列组成的VH和由P1-061015的VL组成的VL；

[0305] (c)由P1-068757的VH的氨基酸序列组成的VH和由P1-068757的VL组成的VL；

[0306] (d)由P1-068759的VH的氨基酸序列组成的VH和由P1-068759的VL组成的VL；

[0307] (e)由P1-068761的VH的氨基酸序列组成的VH和由P1-068761的VL组成的VL；

[0308] (f)由P1-068763的VH的氨基酸序列组成的VH和由P1-068763的VL组成的VL；

[0309] (g)由P1-068765的VH的氨基酸序列组成的VH和由P1-068765的VL组成的VL；

[0310] (h)由P1-068767的VH的氨基酸序列组成的VH和由P1-068767的VL组成的VL；

[0311] (i)由P1-068769的VH的氨基酸序列组成的VH和由P1-068769的VL组成的VL;

[0312] (j)由P1-068771的VH的氨基酸序列组成的VH和由P1-068771的VL组成的VL;

[0313] (k)由P1-068773的VH的氨基酸序列组成的VH和由P1-068773的VL组成的VL;

[0314] (l)由P1-068775的VH的氨基酸序列组成的VH和由P1-068775的VL组成的VL;

[0315] (m)由P1-069059的VH的氨基酸序列组成的VH和由P1-069059的VL组成的VL;

[0316] (n)由P1-069061的VH的氨基酸序列组成的VH和由P1-069061的VL组成的VL;

[0317] (o)由P1-069063的VH的氨基酸序列组成的VH和由P1-069063的VL组成的VL;

[0318] (p)由P1-069065的VH的氨基酸序列组成的VH和由P1-069065的VL组成的VL;

[0319] (q)由P1-069067的VH的氨基酸序列组成的VH和由P1-069067的VL组成的VL;

[0320] (r)由P1-069069的VH的氨基酸序列组成的VH和由P1-069069的VL组成的VL;

[0321] (s)由P1-069071的VH的氨基酸序列组成的VH和由P1-069071的VL组成的VL;

[0322] (t)由P1-069073的VH的氨基酸序列组成的VH和由P1-069073的VL组成的VL;

[0323] (u)由P1-069075的VH的氨基酸序列组成的VH和由P1-069075的VL组成的VL;

[0324] (v)由P1-069077的VH的氨基酸序列组成的VH和由P1-069077的VL组成的VL;

[0325] (w)由P1-068736的VH的氨基酸序列组成的VH和由P1-068736的VL组成的VL;

[0326] (x)由P1-068738的VH的氨基酸序列组成的VH和由P1-068738的VL组成的VL;

[0327] (y)由P1-068740的VH的氨基酸序列组成的VH和由P1-068740的VL组成的VL;

[0328] (z)由P1-068742的VH的氨基酸序列组成的VH和由P1-068742的VL组成的VL;

[0329] (aa)由P1-068744的VH的氨基酸序列组成的VH和由P1-068744的VL组成的VL;

[0330] (bb)由P1-068746的VH的氨基酸序列组成的VH和由P1-068746的VL组成的VL;

[0331] (cc)由P1-068748的VH的氨基酸序列组成的VH和由P1-068748的VL组成的VL;

[0332] (dd)由P1-068750的VH的氨基酸序列组成的VH和由P1-068750的VL组成的VL;

[0333] (ee)由P1-068752的VH的氨基酸序列组成的VH和由P1-068752的VL组成的VL;

[0334] (ff)由P1-068754的VH的氨基酸序列组成的VH和由P1-068754的VL组成的VL;

[0335] (gg)由P1-068761_E55A的VH的氨基酸序列组成的VH和由P1-068761_E55A的VL的氨基酸序列组成的VL;

[0336] (hh)由P1-068761_H100G的VH的氨基酸序列组成的VH和由P1-068761_H100G的VL的氨基酸序列组成的VL;

[0337] (ii)由P1-068761_E56N的VH的氨基酸序列组成的VH和由P1-068761_E56N的VL的氨基酸序列组成的VL;

[0338] (jj)由P1-068761_E55A_E56N的VH的氨基酸序列组成的VH和由P1-068761_E55A_E56N的VL的氨基酸序列组成的VL;

[0339] (kk)由P1-068761_E30D的VH的氨基酸序列组成的VH和由P1-068761_E30D的VL的氨基酸序列组成的VL;

[0340] (ll)由P1-068761_E30D_E55A的VH的氨基酸序列组成的VH和由P1-068761_E30D_E55A的VL的氨基酸序列组成的VL;

[0341] (mm)由P1-068761_E56N_H100G的VH的氨基酸序列组成的VH和由P1-068761_E56N_H100G的VL的氨基酸序列组成的VL;

[0342] (nn)由P1-068761_E30D_H100G的VH的氨基酸序列组成的VH和由P1-068761_E30D_

H100G的VL的氨基酸序列组成的VL；

[0343] (oo)由P1-068761_E30D_E56N的VH的氨基酸序列组成的VH和由P1-068761_E30D_E56N的VL的氨基酸序列组成的VL；

[0344] (pp)由P1-068761_E100fF的VH的氨基酸序列组成的VH和由P1-068761_E100fF的VL的氨基酸序列组成的VL；

[0345] (qq)由P1-068761_E55A_E100fF的VH的氨基酸序列组成的VH和由P1-068761_E55A_E100fF的VL的氨基酸序列组成的VL；

[0346] (rr)由P1-068761_H100G_E100fF的VH的氨基酸序列组成的VH和由P1-068761_H100G_E100fF的VL的氨基酸序列组成的VL；

[0347] (ss)由P1-068761_E30D_E100fF的VH的氨基酸序列组成的VH和由P1-068761_E30D_E100fF的VL的氨基酸序列组成的VL；

[0348] (tt)由P1-068761_E56N_E100fF的VH的氨基酸序列组成的VH和由P1-068761_E56N_E100fF的VL的氨基酸序列组成的VL；

[0349] (uu)由P1-068761_E32Y的VH的氨基酸序列组成的VH和由P1-068761_E32Y的VL的氨基酸序列组成的VL；

[0350] (vv)由P1-068761_E32Y_E55A的VH的氨基酸序列组成的VH和由P1-068761_E32Y_E55A的VL的氨基酸序列组成的VL；

[0351] (ww)由P1-068761_E32Y_E56N的VH的氨基酸序列组成的VH和由P1-068761_E32Y_E56N的VL的氨基酸序列组成的VL；

[0352] (xx)由P1-068761_E30D_E32Y的VH的氨基酸序列组成的VH和由P1-068761_E30D_E32Y的VL的氨基酸序列组成的VL；

[0353] (yy)由P1-068761_E32Y_H100G的VH的氨基酸序列组成的VH和由P1-068761_E32Y_H100G的VL的氨基酸序列组成的VL；

[0354] (zz)由P1-068761_E32Y_E100fF的VH的氨基酸序列组成的VH和由P1-068761_E32Y_E100fF的VL的氨基酸序列组成的VL；

[0355] (aaa)由P1-068767_D52N_D102V的VH的氨基酸序列组成的VH和由P1-068767_D52N_D102V的VL的氨基酸序列组成的VL；

[0356] (bbb)由P1-068767_D52N的VH的氨基酸序列组成的VH和由P1-068767_D52N的VL的氨基酸序列组成的VL；

[0357] (ccc)由P1-068767_D52N_E55A的VH的氨基酸序列组成的VH和由P1-068767_D52N_E55A的VL的氨基酸序列组成的VL；

[0358] (ddd)由P1-068767_E55A_D102V的VH的氨基酸序列组成的VH和由P1-068767_E55A_D102V的VL的氨基酸序列组成的VL；

[0359] (eee)由P1-068767_D102V的VH的氨基酸序列组成的VH和由P1-068767_D102V的VL的氨基酸序列组成的VL；

[0360] (fff)由P1-068767_E55A的VH的氨基酸序列组成的VH和由P1-068767_E55A的VL的氨基酸序列组成的VL；

[0361] (ggg)由P1-068767_E30D_D52N的VH的氨基酸序列组成的VH和由P1-068767_E30D_D52N的VL的氨基酸序列组成的VL；

[0362] (hhh)由P1-068767_E30D_D102V的VH的氨基酸序列组成的VH和由P1-068767_E30D_D102V的VL的氨基酸序列组成的VL;

[0363] (iii)由P1-068767_E30D的VH的氨基酸序列组成的VH和由P1-068767_E30D的VL的氨基酸序列组成的VL;

[0364] (jjj)由P1-068767_E30D_E55A的VH的氨基酸序列组成的VH和由P1-068767_E30D_E55A的VL的氨基酸序列组成的VL;

[0365] (kkk)由P1-068767_E100fF_D102V的VH的氨基酸序列组成的VH和由P1-068767_E100fF_D102V的VL的氨基酸序列组成的VL;

[0366] (lll)由P1-068767_E55A_E100fF的VH的氨基酸序列组成的VH和由P1-068767_E55A_E100fF的VL的氨基酸序列组成的VL;

[0367] (mmm)由P1-068767_D52N_E100fF的VH的氨基酸序列组成的VH和由P1-068767_D52N_E100fF的VL的氨基酸序列组成的VL;

[0368] (nnn)由P1-068767_E100fF的VH的氨基酸序列组成的VH和由P1-068767_E100fF的VL的氨基酸序列组成的VL;或

[0369] (ooo)由P1-068767_E30D_E100fF的VH的氨基酸序列组成的VH和由P1-068767_E30D_E100fF的VL的氨基酸序列组成的VL。在某些实施方案中,抗VISTAAb包含上文和本文其他地方所述的以下抗体的任何可变区和/或可变区CDR 1-3,如:

[0370] (1)以下抗体的VH CDR1、CDR2和CDR3中的一个或多个:

[0371] (2)以下抗体的VH CDR1、CDR2和CDR3:

[0372] (3)以下抗体的VH:

[0373] (4)以下抗体的VH CDR1、CDR2和CDR3以及VL CDR1、CDR2和CDR3:

[0374] (5)以下抗体的VH CDR1、CDR2和CDR3以及VL CDR1、CDR2和CDR3:或

[0375] (6)以下抗体的VH和VL:

[0376] P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF;并且抗VISTAAb

[0377] 也是IgG抗体(如IgG1、IgG2、IgG3或IgG4抗体)或如以下部分中所述的其修饰形式。在一些实施方案中,恒定区具有效应子功能,并且在一些实施方案中,恒定区无效应子。

在某些实施方案中,恒定区是IgG1.3的恒定区。

[0378] 在某些实施方案中,抗VISTAAb包含上文和本文其他地方所述的以下抗体的任何可变区和/或可变区CDR 1-3,如:

[0379] (1)以下抗体的VH CDR1、CDR2和CDR3中的一个或多个:

[0380] (2)以下抗体的VH CDR1、CDR2和CDR3:

[0381] (3)以下抗体的VH:

[0382] (4)以下抗体的VH CDR1、CDR2和CDR3以及VL CDR1、CDR2和CDR3:

[0383] (5)以下抗体的VH CDR1、CDR2和CDR3以及VL CDR1、CDR2和CDR3:或

[0384] (6)以下抗体的VH和VL:

[0385] P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF,

[0386] 并进一步包含以下特征中的一个或多个:

[0387] -在酸性pH(例如pH 6.0或pH 6.5)下与hVISTA(例如ECD或包含SEQ ID NO:2的氨基酸残基35-127的多肽的富组氨酸区域)特异性地结合;

[0388] -在生理pH或中性pH(例如pH 7.4或pH 7.0)下缺乏与hVISTA(例如ECD或包含SEQ ID NO:2的氨基酸残基35-127的多肽的富组氨酸区域)的显著结合;

[0389] -在酸性pH(例如pH 6.0或pH 6.5)下与cyno VISTA(例如ECD的富组氨酸区域)特异性地结合;

[0390] -在生理pH或中性pH(例如pH 7.4或pH 7.0)下缺乏与cyno VISTA(例如ECD的富组氨酸区域)的显著结合;

[0391] -与相对于具有SEQ ID NO:2的hVISTAECD,在以下氨基酸的一个或多个处具有取代的hVISTA-ECD具有降低的结合:T35、Y37、K38、T39、Y41、R54、T61、F62、Q63、L65、H66、L67、H68、H69、F97、L115、V117、I119、H121、H122、S124、E125、R127;

[0392] -与P1-061029、P1-068761、P1-068767和/或P1-061015交叉竞争与hVISTA的结合;

[0393] -在酸性pH(例如pH 6.0或pH 6.5)下抑制hVISTA与人T细胞的结合;

[0394] -在酸性pH(例如pH 6.0或pH 6.5)下抑制hVISTA与PSGL-1的结合;

[0395] -在食蟹猴中的平均停留时间为至少350小时;

[0396] -刺激T细胞激活;

[0397] -抑制VISTA介导的细胞:细胞粘附;以及

[0398] -与人肿瘤细胞的样品或发炎的人组织的样品中的hVISTA特异性地结合。

[0399] 在某些实施方案中,抗hVISTA Ab包含含有本文提供的任何抗hVISTA Ab的重链的氨基酸序列的重链(HC)。在某些实施方案中,抗hVISTA Ab包含含有如以下序列表中所示包含IgG1.3重链恒定区的P1-061029或P1-061015或其后代如P1-061029.IgG1.3(SEQ ID NO:69)、P1-068757.IgG1.3、P1-068759.IgG1.3、P1-068761.IgG1.3、P1-068763.IgG1.3、P1-068765.IgG1.3、P1-068767.IgG1.3、P1-068769.IgG1.3、P1-068771.IgG1.3、P1-068773.IgG1.3、P1-068775.IgG1.3、P1-069059.IgG1.3、P1-069061.IgG1.3、P1-069063.IgG1.3、P1-069065.IgG1.3、P1-069067.IgG1.3、P1-069069.IgG1.3、P1-069071.IgG1.3、P1-069073.IgG1.3、P1-069075.IgG1.3、P1-069077.IgG1.3、P1-061015.IgG1.3、P1-068736.IgG1.3、P1-068738.IgG1.3、P1-068740.IgG1.3、P1-068742.IgG1.3、P1-068744.IgG1.3、P1-068766.IgG1.3、P1-068748.IgG1.3、P1-068750.IgG1.3、P1-068752.IgG1.3、P1-068754.IgG1.3、P1-068761_E55A.IgG1.3、P1-068761_H100G.IgG1.3、P1-068761_E56N.IgG1.3、P1-068761_E55A_E56N.IgG1.3、P1-068761_E30D.IgG1.3、P1-068761_E30D_E55A.IgG1.3、P1-068761_E56N_H100G.IgG1.3、P1-068761_E30D_H100G.IgG1.3、P1-068761_E30D_E56N.IgG1.3、P1-068761_E100fF.IgG1.3、P1-068761_E55A_E100fF.IgG1.3、P1-068761_H100G_E100fF.IgG1.3、P1-068761_E30D_E100fF.IgG1.3、P1-068761_E56N_E100fF.IgG1.3、P1-068761_E32Y.IgG1.3、P1-068761_E32Y_E55A.IgG1.3、P1-068761_E32Y_E56N.IgG1.3、P1-068761_E30D_E32Y.IgG1.3、P1-068761_E32Y_H100G.IgG1.3、P1-068761_E32Y_E100fF.IgG1.3、P1-068767_D52N_D102V.IgG1.3、P1-068767_D52N.IgG1.3、P1-068767_D52N_E55A.IgG1.3、P1-068767_E55A_D102V.IgG1.3、P1-068767_D102V.IgG1.3、P1-068767_E55A.IgG1.3、P1-068767_E30D_D52N.IgG1.3、P1-068767_E30D_D102V.IgG1.3、P1-068767_E30D.IgG1.3、P1-068767_E30D_E55A.IgG1.3、P1-068767_E100fF_D102V.IgG1.3、P1-068767_E55A_E100fF.IgG1.3、P1-068767_D52N_E100fF.IgG1.3、P1-068767_E100fF.IgG1.3或P1-068767_E30D_E100fF.IgG1.3的重链的氨基酸序列的重链。

[0400] 在某些实施方案中,抗hVISTA Ab包含含有本文提供的任何抗hVISTAAb(其包含IgG1.3重链恒定区)的重链的氨基酸序列的重链和本文提供的任何抗hVISTA Ab的轻链的氨基酸序列。在某些实施方案中,抗hVISTA Ab包含含有P1-061029或P1-061015或其后代(它们包含IgG1.3 HC恒定区)如P1-061029.IgG1.3(SEQ ID NO:69)、P1-068757.IgG1.3、P1-068759.IgG1.3、P1-068761.IgG1.3、P1-068763.IgG1.3、P1-068765.IgG1.3、P1-068767.IgG1.3、P1-068769.IgG1.3、P1-068771.IgG1.3、P1-068773.IgG1.3、P1-068775.IgG1.3、P1-069059.IgG1.3、P1-069061.IgG1.3、P1-069063.IgG1.3、P1-069065.IgG1.3、P1-069067.IgG1.3、P1-069069.IgG1.3、P1-069071.IgG1.3、P1-069073.IgG1.3、P1-069075.IgG1.3、P1-069077.IgG1.3、P1-061015.IgG1.3、P1-068736.IgG1.3、P1-068738.IgG1.3、P1-068740.IgG1.3、P1-068742.IgG1.3、P1-068744.IgG1.3、P1-068766.IgG1.3、P1-068748.IgG1.3、P1-068750.IgG1.3、P1-068752.IgG1.3、P1-068754.IgG1.3、P1-068761_E55A.IgG1.3、P1-068761_H100G.IgG1.3、

P1-068761_E56N.IgG1.3、P1-068761_E55A_E56N.IgG1.3、P1-068761_E30D.IgG1.3、P1-068761_E30D_E55A.IgG1.3、P1-068761_E56N_H100G.IgG1.3、P1-068761_E30D_H100G.IgG1.3、P1-068761_E30D_E56N.IgG1.3、P1-068761_E100fF.IgG1.3、P1-068761_E55A_E100fF.IgG1.3、P1-068761_H100G_E100fF.IgG1.3、P1-068761_E30D_E100fF.IgG1.3、P1-068761_E56N_E100fF.IgG1.3、P1-068761_E32Y.IgG1.3、P1-068761_E32Y_E55A.IgG1.3、P1-068761_E32Y_E56N.IgG1.3、P1-068761_E30D_E32Y.IgG1.3、P1-068761_E32Y_H100G.IgG1.3、P1-068761_E32Y_E100fF.IgG1.3、P1-068767_D52N_D102V.IgG1.3、P1-068767_D52N.IgG1.3、P1-068767_D52N_E55A.IgG1.3、P1-068767_E55A_D102V.IgG1.3、P1-068767_D102V.IgG1.3、P1-068767_E55A.IgG1.3、P1-068767_E30D_D52N.IgG1.3、P1-068767_E30D_D102V.IgG1.3、P1-068767_E30D.IgG1.3、P1-068767_E30D_E55A.IgG1.3、P1-068767_E100fF_D102V.IgG1.3、P1-068767_E55A_E100fF.IgG1.3、P1-068767_D52N_E100fF.IgG1.3、P1-068767_E100fF.IgG1.3或P1-068767_E30D_E100fF.IgG1.3的VH的氨基酸序列的重链;和含有P1-061029或P1-061015的轻链的氨基酸序列的轻链。

[0401] 抗hVISTA Ab可以包含:

[0402] (a)含有P1-061029.IgG1.3(SEQ ID NO:69)的重链的氨基酸序列的重链和含有P1-061029(SEQ ID NO:70)的轻链氨基酸序列的轻链;

[0403] (b)含有P1-061015.IgG1.3的重链的氨基酸序列的重链和含有P1-061015的轻链氨基酸序列的轻链;

[0404] (c)含有P1-068757.IgG1.3的重链的氨基酸序列的重链和含有P1-068757的轻链氨基酸序列的轻链;

[0405] (d)含有P1-068759.IgG1.3的重链的氨基酸序列的重链和含有P1-068759的轻链氨基酸序列的轻链;

[0406] (e)含有P1-068761.IgG1.3的重链的氨基酸序列的重链和含有P1-068761的轻链氨基酸序列的轻链;

[0407] (f)含有P1-068763.IgG1.3的重链的氨基酸序列的重链和含有P1-068763的轻链氨基酸序列的轻链;

[0408] (g)含有P1-068765.IgG1.3的重链的氨基酸序列的重链和含有P1-068765的轻链氨基酸序列的轻链;

[0409] (h)含有P1-068767.IgG1.3的重链的氨基酸序列的重链和含有P1-068767的轻链氨基酸序列的轻链;

[0410] (i)含有P1-068769.IgG1.3的重链的氨基酸序列的重链和含有P1-068769的轻链氨基酸序列的轻链;

[0411] (j)含有P1-068771.IgG1.3的重链的氨基酸序列的重链和含有P1-068771的轻链氨基酸序列的轻链;

[0412] (k)含有P1-068773.IgG1.3的重链的氨基酸序列的重链和含有P1-068773的轻链氨基酸序列的轻链;

[0413] (l)含有P1-068775.IgG1.3的重链的氨基酸序列的重链和含有P1-068775的轻链氨基酸序列的轻链;

[0414] (m)含有P1-069059.IgG1.3的重链的氨基酸序列的重链和含有P1-069059的轻链氨基酸序列的轻链;

[0415] (n)含有P1-069061.IgG1.3的重链的氨基酸序列的重链和含有P1-069061的轻链氨基酸序列的轻链;

[0416] (o)含有P1-069063.IgG1.3的重链的氨基酸序列的重链和含有P1-069063的轻链氨基酸序列的轻链;

[0417] (p)含有P1-069065.IgG1.3的重链的氨基酸序列的重链和含有P1-069065的轻链氨基酸序列的轻链;

[0418] (q)含有P1-069067.IgG1.3的重链的氨基酸序列的重链和含有P1-069067的轻链氨基酸序列的轻链;

[0419] (r)含有P1-069069.IgG1.3的重链的氨基酸序列的重链和含有P1-069069的轻链氨基酸序列的轻链;

[0420] (s)含有P1-069071.IgG1.3的重链的氨基酸序列的重链和含有P1-069071的轻链氨基酸序列的轻链;

[0421] (t)含有P1-069073.IgG1.3的重链的氨基酸序列的重链和含有P1-069073的轻链氨基酸序列的轻链;

[0422] (u)含有P1-069075.IgG1.3的重链的氨基酸序列的重链和含有P1-069075的轻链氨基酸序列的轻链;

[0423] (v)含有P1-069077.IgG1.3的重链的氨基酸序列的重链和含有P1-069077的轻链氨基酸序列的轻链;

[0424] (w)含有P1-068736.IgG1.3的重链的氨基酸序列的重链和含有P1-068736的轻链氨基酸序列的轻链;

[0425] (x)含有P1-068738.IgG1.3的重链的氨基酸序列的重链和含有P1-068738的轻链氨基酸序列的轻链;

[0426] (y)含有P1-068740.IgG1.3的重链的氨基酸序列的重链和含有P1-068740的轻链氨基酸序列的轻链;

[0427] (z)含有P1-068742.IgG1.3的重链的氨基酸序列的重链和含有P1-068742的轻链氨基酸序列的轻链;

[0428] (aa)含有P1-068744.IgG1.3的重链的氨基酸序列的重链和含有P1-068744的轻链氨基酸序列的轻链;

[0429] (bb)含有P1-068746.IgG1.3的重链的氨基酸序列的重链和含有P1-068746的轻链氨基酸序列的轻链;

[0430] (cc)含有P1-068748.IgG1.3的重链的氨基酸序列的重链和含有P1-068748的轻链氨基酸序列的轻链;

[0431] (dd)含有P1-068750.IgG1.3的重链的氨基酸序列的重链和含有P1-068750的轻链氨基酸序列的轻链;

[0432] (ee)含有P1-068752.IgG1.3的重链的氨基酸序列的重链和含有P1-068752的轻链氨基酸序列的轻链;

[0433] (ff)含有P1-068754.IgG1.3的重链的氨基酸序列的重链和含有P1-068754的轻链

氨基酸序列的轻链；

[0434] (gg)含有P1-068761_E55A.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E55A的轻链氨基酸序列的轻链；

[0435] (hh)含有P1-068761_H100G.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_H100G的轻链氨基酸序列的轻链；

[0436] (ii)含有P1-068761_E56N.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E56N的轻链氨基酸序列的轻链；

[0437] (jj)含有P1-068761_E55A_E56N.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E55A_E56N的轻链氨基酸序列的轻链；

[0438] (kk)含有P1-068761_E30D.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E30D的轻链氨基酸序列的轻链；

[0439] (ll)含有P1-068761_E30D_E55A.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E30D_E55A的轻链氨基酸序列的轻链；

[0440] (mm)含有P1-068761_E56N_H100G.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E56N_H100G的轻链氨基酸序列的轻链；

[0441] (nn)含有P1-068761_E30D_H100G.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E30D_H100G的轻链氨基酸序列的轻链；

[0442] (oo)含有P1-068761_E30D_E56N.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E30D_E56N的轻链氨基酸序列的轻链；

[0443] (pp)含有P1-068761_E100fF.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E100fF的轻链氨基酸序列的轻链；

[0444] (qq)含有P1-068761_E55A_E100fF.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E55A_E100fF的轻链氨基酸序列的轻链；

[0445] (rr)含有P1-068761_H100G_E100fF.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_H100G_E100fF的轻链氨基酸序列的轻链；

[0446] (ss)含有P1-068761_E30D_E100fF.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E30D_E100fF的轻链氨基酸序列的轻链；

[0447] (tt)含有P1-068761_E56N_E100fF.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E56N_E100fF的轻链氨基酸序列的轻链；

[0448] (uu)含有P1-068761_E32Y.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E32Y的轻链氨基酸序列的轻链；

[0449] (vv)含有P1-068761_E32Y_E55A.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E32Y_E55A的轻链氨基酸序列的轻链；

[0450] (ww)含有P1-068761_E32Y_E56N.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E32Y_E56N的轻链氨基酸序列的轻链；

[0451] (xx)含有P1-068761_E30D_E32Y.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E30D_E32Y的轻链氨基酸序列的轻链；

[0452] (yy)含有P1-068761_E32Y_H100G.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E32Y_H100G的轻链氨基酸序列的轻链；

[0453] (zz)含有P1-068761_E32Y_E100fF.IgG1.3的重链的氨基酸序列的重链和含有P1-068761_E32Y_E100fF的轻链氨基酸序列的轻链;

[0454] (aaa)含有P1-068767_D52N_D102V.IgG1.3的重链的氨基酸序列的重链和含有P1-068767_D52N_D102V的轻链氨基酸序列的轻链;

[0455] (bbb)含有P1-068767_D52N.IgG1.3的重链的氨基酸序列的重链和含有P1-068767_D52N的轻链氨基酸序列的轻链;

[0456] (ccc)含有P1-068767_D52N_E55A.IgG1.3的重链的氨基酸序列的重链和含有P1-068767_D52N_E55A的轻链氨基酸序列的轻链;

[0457] (ddd)含有P1-068767_E55A_D102V.IgG1.3的重链的氨基酸序列的重链和含有P1-068767_E55A_D102V的轻链氨基酸序列的轻链;

[0458] (eee)含有P1-068767_D102V.IgG1.3的重链的氨基酸序列的重链和含有P1-068767_D102V的轻链氨基酸序列的轻链;

[0459] (fff)含有P1-068767_E55A.IgG1.3的重链的氨基酸序列的重链和含有P1-068767_E55A的轻链氨基酸序列的轻链;

[0460] (ggg)含有P1-068767_E30D_D52N.IgG1.3的重链的氨基酸序列的重链和含有P1-068767_E30D_D52N的轻链氨基酸序列的轻链;

[0461] (hhh)含有P1-068767_E30D_D102V.IgG1.3的重链的氨基酸序列的重链和含有P1-068767_E30D_D102V的轻链氨基酸序列的轻链;

[0462] (iii)含有P1-068767_E30D.IgG1.3的重链的氨基酸序列的重链和含有P1-068767_E30D的轻链氨基酸序列的轻链;

[0463] (jjj)含有P1-068767_E30D_E55A.IgG1.3的重链的氨基酸序列的重链和含有P1-068767_E30D_E55A的轻链氨基酸序列的轻链;

[0464] (kkk)含有P1-068767_E100fF_D102V.IgG1.3的重链的氨基酸序列的重链和含有P1-068767_E100fF_D102V的轻链氨基酸序列的轻链;

[0465] (lll)含有P1-068767_E55A_E100fF.IgG1.3的重链的氨基酸序列的重链和含有P1-068767_E55A_E100fF的轻链氨基酸序列的轻链;

[0466] (mmm)含有P1-068767_D52N_E100fF.IgG1.3的重链的氨基酸序列的重链和含有P1-068767_D52N_E100fF的轻链氨基酸序列的轻链;

[0467] (nnn)含有P1-068767_E100fF.IgG1.3的重链的氨基酸序列的重链和含有P1-068767_E100fF的轻链氨基酸序列的轻链;或

[0468] (ooo)含有P1-068767_E30D_E100fF.IgG1.3的重链的氨基酸序列的重链和含有P1-068767_E30D_E100fF的轻链氨基酸序列的轻链。抗hVISTA Ab可以包含:

[0469] (a)含有P1-061029的HC的HC CDR的重链(HC)和含有P1-061029的LCCDR的轻链(LC)以及分别与P1-061029.IgG1.3的HC和LC至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%或至少99%相同的HC和LC氨基酸序列;

[0470] (b)含有P1-061015的HC的HC CDR的HC和含有P1-061015的LC CDR的LC以及分别与P1-061015.IgG1.3的HC和LC至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%或至少99%相同的HC和LC氨基酸序列;

[0471] (c)含有P1-068757的HC的HC CDR的HC和含有P1-068757的LC CDR的LC以及分别与

P1-068757.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0472] (d)含有P1-068759的HC的HC CDR的HC和含有P1-068759的LC CDR的LC以及分别与P1-068759.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0473] (e)含有P1-068761的HC的HC CDR的HC和含有P1-068761的LC CDR的LC以及分别与P1-068761.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0474] (f)含有P1-068763的HC的HC CDR的HC和含有P1-068763的LC CDR的LC以及分别与P1-068763.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0475] (g)含有P1-068765的HC的HC CDR的HC和含有P1-068765的LC CDR的LC以及分别与P1-068765.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0476] (h)含有P1-068767的HC的HC CDR的HC和含有P1-068767的LC CDR的LC以及分别与P1-068767.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0477] (i)含有P1-068769的HC的HC CDR的HC和含有P1-068769的LC CDR的LC以及分别与P1-068769.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0478] (j)含有P1-068771的HC的HC CDR的HC和含有P1-068771的LC CDR的LC以及分别与P1-068771.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0479] (k)含有P1-068773的HC的HC CDR的HC和含有P1-068773的LC CDR的LC以及分别与P1-068773.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0480] (l)含有P1-068775的HC的HC CDR的HC和含有P1-068775的LC CDR的LC以及分别与P1-068775.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0481] (m)含有P1-069059的HC的HC CDR的HC和含有P1-069059的LC CDR的LC以及分别与P1-069059.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0482] (n)含有P1-069061的HC的HC CDR的HC和含有P1-069061的LC CDR的LC以及分别与P1-069061.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0483] (o)含有P1-069063的HC的HC CDR的HC和含有P1-069063的LC CDR的LC以及分别与P1-069063.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0484] (p)含有P1-069065的HC的HC CDR的HC和含有P1-069065的LC CDR的LC以及分别与

P1-069065.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0485] (q)含有P1-069067的HC的HC CDR的HC和含有P1-069067的LC CDR的LC以及分别与P1-069067.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0486] (r)含有P1-069069的HC的HC CDR的HC和含有P1-069069的LC CDR的LC以及分别与P1-069069.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0487] (s)含有P1-069071的HC的HC CDR的HC和含有P1-069071的LC CDR的LC以及分别与P1-069071.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0488] (t)含有P1-069073的HC的HC CDR的HC和含有P1-069073的LC CDR的LC以及分别与P1-069073.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0489] (u)含有P1-069075的HC的HC CDR的HC和含有P1-069075的LC CDR的LC以及分别与P1-069075.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0490] (v)含有P1-069077的HC的HC CDR的HC和含有P1-069077的LC CDR的LC以及分别与P1-069077.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0491] (w)含有P1-068736的HC的HC CDR的HC和含有P1-068736的LC CDR的LC以及分别与P1-068736.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0492] (x)含有P1-068738的HC的HC CDR的HC和含有P1-068738的LC CDR的LC以及分别与P1-068738.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0493] (y)含有P1-068740的HC的HC CDR的HC和含有P1-068740的LC CDR的LC以及分别与P1-068740.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0494] (z)含有P1-068742的HC的HC CDR的HC和含有P1-068742的LC CDR的LC以及分别与P1-068742.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0495] (aa)含有P1-068744的HC的HC CDR的HC和含有P1-068744的LC CDR的LC以及分别与P1-068744.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0496] (bb)含有P1-068746的HC的HC CDR的HC和含有P1-068746的LC CDR的LC以及分别与P1-068746.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0497] (cc)含有P1-068748的HC的HC CDR的HC和含有P1-068748的LC CDR的LC以及分别

与P1-068748.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0498] (dd)含有P1-068750的HC的HC CDR的HC和含有P1-068750的LC CDR的LC以及分别与P1-068750.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0499] (ee)含有P1-068752的HC的HC CDR的HC和含有P1-068752的LC CDR的LC以及分别与P1-068752.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0500] (ff)含有P1-068754的HC的HC CDR的HC和含有P1-068754的LC CDR的LC以及分别与P1-068754.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0501] (gg)含有P1-068761_E55A.IgG1.3的HC的HC CDR的HC和含有P1-068761_E55A的LC CDR的LC以及分别与P1-068761_E55A.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0502] (hh)含有P1-068761_H100G.IgG1.3的HC的HC CDR的HC和含有P1-068761_H100G的LC CDR的LC以及分别与P1-068761_H100G.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0503] (ii)含有P1-068761_E56N.IgG1.3的HC的HC CDR的HC和含有P1-068761_E56N的LC CDR的LC以及分别与P1-068761_E56N.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0504] (jj)含有P1-068761_E55A_E56N.IgG1.3的HC的HC CDR的HC和含有P1-068761_E55A_E56N的LC CDR的LC以及分别与P1-068761_E55A_E56N.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0505] (kk)含有P1-068761_E30D.IgG1.3的HC的HC CDR的HC和含有P1-068761_E30D的LC CDR的LC以及分别与P1-068761_E30D.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0506] (ll)含有P1-068761_E30D_E55A.IgG1.3的HC的HC CDR的HC和含有P1-068761_E30D_E55A的LC CDR的LC以及分别与P1-068761_E30D_E55A.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0507] (mm)含有P1-068761_E56N_H100G.IgG1.3的HC的HC CDR的HC和含有P1-068761_E56N_H100G的LC CDR的LC以及分别与P1-068761_E56N_H100G.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0508] (nn)含有P1-068761_E30D_H100G.IgG1.3的HC的HC CDR的HC和含有P1-068761_E30D_H100G的LC CDR的LC以及分别与P1-068761_E30D_H100G.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0509] (oo)含有P1-068761_E30D_E56N.IgG1.3的HC的HC CDR的HC和含有P1-068761_E30D_E56N的LC CDR的LC以及分别与P1-068761_E30D_E56N.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0510] (pp)含有P1-068761_E100fF.IgG1.3的HC的HC CDR的HC和含有P1-068761_E100fF的LC CDR的LC以及分别与P1-068761_E100fF.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0511] (qq)含有P1-068761_E55A_E100fF.IgG1.3的HC的HC CDR的HC和含有P1-068761_E55A_E100fF的LC CDR的LC以及分别与P1-068761_E55A_E100fF.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0512] (rr)含有P1-068761_H100G_E100fF.IgG1.3的HC的HC CDR的HC和含有P1-068761_H100G_E100fF的LC CDR的LC以及分别与P1-068761_H100G_E100fF.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0513] (ss)含有P1-068761_E30D_E100fF.IgG1.3的HC的HC CDR的HC和含有P1-068761_E30D_E100fF的LC CDR的LC以及分别与P1-068761_E30D_E100fF.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0514] (tt)含有P1-068761_E56N_E100fF.IgG1.3的HC的HC CDR的HC和含有P1-068761_E56N_E100fF的LC CDR的LC以及分别与P1-068761_E56N_E100fF.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0515] (uu)含有P1-068761_E32Y.IgG1.3的HC的HC CDR的HC和含有P1-068761_E32Y的LC CDR的LC以及分别与P1-068761_E32Y.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0516] (vv)含有P1-068761_E32Y_E55A.IgG1.3的HC的HC CDR的HC和含有P1-068761_E32Y_E55A的LC CDR的LC以及分别与P1-068761_E32Y_E55A.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0517] (ww)含有P1-068761_E32Y_E56N.IgG1.3的HC的HC CDR的HC和含有P1-068761_E32Y_E56N的LC CDR的LC以及分别与P1-068761_E32Y_E56N.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少

99％相同的HC和LC氨基酸序列；

[0518] (xx)含有P1-068761_E30D_E32Y.IgG1.3的HC的HC CDR的HC和含有P1-068761_E30D_E32Y的LC CDR的LC以及分别与P1-068761_E30D_E32Y.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0519] (yy)含有P1-068761_E32Y_H100G.IgG1.3的HC的HC CDR的HC和含有P1-068761_E32Y_H100G的LC CDR的LC以及分别与P1-068761_E32Y_H100G.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0520] (zz)含有P1-068761_E32Y_E100fF.IgG1.3的HC的HC CDR的HC和含有P1-068761_E32Y_E100fF的LC CDR的LC以及分别与P1-068761_E32Y_E100fF.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0521] (aaa)含有P1-068767_D52N_D102V.IgG1.3的HC的HC CDR的HC和含有P1-068767_D52N_D102V的LC CDR的LC以及分别与P1-068767_D52N_D102V.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0522] (bbb)含有P1-068767_D52N.IgG1.3的HC的HC CDR的HC和含有P1-068767_D52N的LC CDR的LC以及分别与P1-068767_D52N.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0523] (ccc)含有P1-068767_D52N_E55A.IgG1.3的HC的HC CDR的HC和含有P1-068767_D52N_E55A的LC CDR的LC以及分别与P1-068767_D52N_E55A.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0524] (ddd)含有P1-068767_E55A_D102V.IgG1.3的HC的HC CDR的HC和含有P1-068767_E55A_D102V的LC CDR的LC以及分别与P1-068767_E55A_D102V.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0525] (eee)含有P1-068767_D102V.IgG1.3的HC的HC CDR的HC和含有P1-068767_D102V的LC CDR的LC以及分别与P1-068767_D102V.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0526] (fff)含有P1-068767_E55A.IgG1.3的HC的HC CDR的HC和含有P1-068767_E55A的LC CDR的LC以及分别与P1-068767_E55A.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0527] (ggg)含有P1-068767_E30D_D52N.IgG1.3的HC的HC CDR的HC和含有P1-068767_E30D_D52N的LC CDR的LC以及分别与P1-068767_E30D_D52N.IgG1.3的HC和LC至少90％、至

少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0528] (hhh)含有P1-068767_E30D_D102V.IgG1.3的HC的HC CDR的HC和含有P1-068767_E30D_D102V的LC CDR的LC以及分别与P1-068767_E30D_D102V.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0529] (iii)含有P1-068767_E30D.IgG1.3的HC的HC CDR的HC和含有P1-068767_E30D的LC CDR的LC以及分别与P1-068767_E30D.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0530] (jjj)含有P1-068767_E30D_E55A.IgG1.3的HC的HC CDR的HC和含有P1-068767_E30D_E55A的LC CDR的LC以及分别与P1-068767_E30D_E55A.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0531] (kkk)含有P1-068767_E100fF_D102V.IgG1.3的HC的HC CDR的HC和含有P1-068767_E100fF_D102V的LC CDR的LC以及分别与P1-068767_E100fF_D102V.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0532] (lll)含有P1-068767_E55A_E100fF.IgG1.3的HC的HC CDR的HC和含有P1-068767_E55A_E100fF的LC CDR的LC以及分别与P1-068767_E55A_E100fF.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0533] (mmm)含有P1-068767_D52N_E100fF.IgG1.3的HC的HC CDR的HC和含有P1-068767_D52N_E100fF的LC CDR的LC以及分别与P1-068767_D52N_E100fF.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；

[0534] (nnn)含有P1-068767_E100fF.IgG1.3的HC的HC CDR的HC和含有P1-068767_E100fF的LC CDR的LC以及分别与P1-068767_E100fF.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列；或

[0535] (ooo)含有P1-068767_E30D_E100fF.IgG1.3的HC的HC CDR的HC和含有P1-068767_E30D_E100fF的LC CDR的LC以及分别与P1-068767_E30D_E100fF.IgG1.3的HC和LC至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的HC和LC氨基酸序列。在一些实施方案中，抗hVISTA Ab可以包含：

[0536] (a)由P1-061029.IgG1.3的重链的氨基酸序列组成的重链和由P1-061029的轻链的氨基酸序列组成的轻链；

[0537] (b)由P1-061015.IgG1.3的重链的氨基酸序列组成的重链和由P1-061015的轻链的氨基酸序列组成的轻链；

[0538] (c)由P1-068757.IgG1.3的重链的氨基酸序列组成的重链和由P1-068757的轻链

的氨基酸序列组成的轻链；

[0539] (d)由P1-068759.IgG1.3的重链的氨基酸序列组成的重链和由P1-068759的轻链的氨基酸序列组成的轻链；

[0540] (e)由P1-068761.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761的轻链的氨基酸序列组成的轻链；

[0541] (f)由P1-068763.IgG1.3的重链的氨基酸序列组成的重链和由P1-068763的轻链的氨基酸序列组成的轻链；

[0542] (g)由P1-068765.IgG1.3的重链的氨基酸序列组成的重链和由P1-068765的轻链的氨基酸序列组成的轻链；

[0543] (h)由P1-068767.IgG1.3的重链的氨基酸序列组成的重链和由P1-068767的轻链的氨基酸序列组成的轻链；

[0544] (i)由P1-068769.IgG1.3的重链的氨基酸序列组成的重链和由P1-068769的轻链的氨基酸序列组成的轻链；

[0545] (j)由P1-068771.IgG1.3的重链的氨基酸序列组成的重链和由P1-068771的轻链的氨基酸序列组成的轻链；

[0546] (k)由P1-068773.IgG1.3的重链的氨基酸序列组成的重链和由P1-068773的轻链的氨基酸序列组成的轻链；

[0547] (l)由P1-068775.IgG1.3的重链的氨基酸序列组成的重链和由P1-068775的轻链的氨基酸序列组成的轻链；

[0548] (m)由P1-069059.IgG1.3的重链的氨基酸序列组成的重链和由P1-069059的轻链的氨基酸序列组成的轻链；

[0549] (n)由P1-069061.IgG1.3的重链的氨基酸序列组成的重链和由P1-069061的轻链的氨基酸序列组成的轻链；

[0550] (o)由P1-069063.IgG1.3的重链的氨基酸序列组成的重链和由P1-069063的轻链的氨基酸序列组成的轻链；

[0551] (p)由P1-069065.IgG1.3的重链的氨基酸序列组成的重链和由P1-069065的轻链的氨基酸序列组成的轻链；

[0552] (q)由P1-069067.IgG1.3的重链的氨基酸序列组成的重链和由P1-069067的轻链的氨基酸序列组成的轻链；

[0553] (r)由P1-069069.IgG1.3的重链的氨基酸序列组成的重链和由P1-069069的轻链的氨基酸序列组成的轻链；

[0554] (s)由P1-069071.IgG1.3的重链的氨基酸序列组成的重链和由P1-069071的轻链的氨基酸序列组成的轻链；

[0555] (t)由P1-069073.IgG1.3的重链的氨基酸序列组成的重链和由P1-069073的轻链的氨基酸序列组成的轻链；

[0556] (u)由P1-069075.IgG1.3的重链的氨基酸序列组成的重链和由P1-069075的轻链的氨基酸序列组成的轻链；

[0557] (v)由P1-069077.IgG1.3的重链的氨基酸序列组成的重链和由P1-069077的轻链的氨基酸序列组成的轻链；

[0558] (w)由P1-068736的重链的氨基酸序列组成的重链和由P1-068736的轻链的氨基酸序列组成的轻链;

[0559] (x)由P1-068738.IgG1.3的重链的氨基酸序列组成的重链和由P1-068738的轻链的氨基酸序列组成的轻链;

[0560] (y)由P1-068740.IgG1.3的重链的氨基酸序列组成的重链和由P1-068740的轻链的氨基酸序列组成的轻链;

[0561] (z)由P1-068742.IgG1.3的重链的氨基酸序列组成的重链和由P1-068742的轻链的氨基酸序列组成的轻链;

[0562] (aa)由P1-068744.IgG1.3的重链的氨基酸序列组成的重链和由P1-068744的轻链的氨基酸序列组成的轻链;

[0563] (bb)由P1-068746.IgG1.3的重链的氨基酸序列组成的重链和由P1-068746的轻链的氨基酸序列组成的轻链;

[0564] (cc)由P1-068748.IgG1.3的重链的氨基酸序列组成的重链和由P1-068748的轻链的氨基酸序列组成的轻链;

[0565] (dd)由P1-068750.IgG1.3的重链的氨基酸序列组成的重链和由P1-068750的轻链的氨基酸序列组成的轻链;

[0566] (ee)由P1-068752.IgG1.3的重链的氨基酸序列组成的重链和由P1-068752的轻链的氨基酸序列组成的轻链;

[0567] (ff)由P1-068754的重链的氨基酸序列组成的重链和由P1-068754的轻链的氨基酸序列组成的轻链;

[0568] (gg)由P1-068761_E55A.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_E55A的轻链的氨基酸序列组成的轻链;

[0569] (hh)由P1-068761_H100G.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_H100G的轻链的氨基酸序列组成的轻链;

[0570] (ii)由P1-068761_E56N.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_E56N的轻链的氨基酸序列组成的轻链;

[0571] (jj)由P1-068761_E55A_E56N.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_E55A_E56N的轻链的氨基酸序列组成的轻链;

[0572] (kk)由P1-068761_E30D.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_E30D的轻链的氨基酸序列组成的轻链;

[0573] (ll)由P1-068761_E30D_E55A.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_E30D_E55A的轻链的氨基酸序列组成的轻链;

[0574] (mm)由P1-068761_E56N_H100G.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_E56N_H100G的轻链的氨基酸序列组成的轻链;

[0575] (nn)由P1-068761_E30D_H100G.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_E30D_H100G的轻链的氨基酸序列组成的轻链;

[0576] (oo)由P1-068761_E30D_E56N.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_E30D_E56N的轻链的氨基酸序列组成的轻链;

[0577] (pp)由P1-068761_E100fF.IgG1.3的重链的氨基酸序列组成的重链和由P1-

068761_E100fF的轻链的氨基酸序列组成的轻链；

[0578] (qq)由P1-068761_E55A_E100fF.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_E55A_E100fF的轻链的氨基酸序列组成的轻链；

[0579] (rr)由P1-068761_H100G_E100fF.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_H100G_E100fF的轻链的氨基酸序列组成的轻链；

[0580] (ss)由P1-068761_E30D_E100fF.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_E30D_E100fF的轻链的氨基酸序列组成的轻链；

[0581] (tt)由P1-068761_E56N_E100fF.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_E56N_E100fF的轻链的氨基酸序列组成的轻链；

[0582] (uu)由P1-068761_E32Y.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_E32Y的轻链的氨基酸序列组成的轻链；

[0583] (vv)由P1-068761_E32Y_E55A.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_E32Y_E55A的轻链的氨基酸序列组成的轻链；

[0584] (ww)由P1-068761_E32Y_E56N.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_E32Y_E56N的轻链的氨基酸序列组成的轻链；

[0585] (xx)由P1-068761_E30D_E32Y.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_E30D_E32Y的轻链的氨基酸序列组成的轻链；

[0586] (yy)由P1-068761_E32Y_H100G.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_E32Y_H100G的轻链的氨基酸序列组成的轻链；

[0587] (zz)由P1-068761_E32Y_E100fF.IgG1.3的重链的氨基酸序列组成的重链和由P1-068761_E32Y_E100fF的轻链的氨基酸序列组成的轻链；

[0588] (aaa)由P1-068767_D52N_D102V.IgG1.3的重链的氨基酸序列组成的重链和由P1-068767_D52N_D102V的轻链的氨基酸序列组成的轻链；

[0589] (bbb)由P1-068767_D52N.IgG1.3的重链的氨基酸序列组成的重链和由P1-068767_D52N的轻链的氨基酸序列组成的轻链；

[0590] (ccc)由P1-068767_D52N_E55A.IgG1.3的重链的氨基酸序列组成的重链和由P1-068767_D52N_E55A的轻链的氨基酸序列组成的轻链；

[0591] (ddd)由P1-068767_E55A_D102V.IgG1.3的重链的氨基酸序列组成的重链和由P1-068767_E55A_D102V的轻链的氨基酸序列组成的轻链；

[0592] (eee)由P1-068767_D102V.IgG1.3的重链的氨基酸序列组成的重链和由P1-068767_D102V的轻链的氨基酸序列组成的轻链；

[0593] (fff)由P1-068767_E55A.IgG1.3的重链的氨基酸序列组成的重链和由P1-068767_E55A的轻链的氨基酸序列组成的轻链；

[0594] (ggg)由P1-068767_E30D_D52N.IgG1.3的重链的氨基酸序列组成的重链和由P1-068767_E30D_D52N的轻链的氨基酸序列组成的轻链；

[0595] (hhh)由P1-068767_E30D_D102V.IgG1.3的重链的氨基酸序列组成的重链和由P1-068767_E30D_D102V的轻链的氨基酸序列组成的轻链；

[0596] (iii)由P1-068767_E30D.IgG1.3的重链的氨基酸序列组成的重链和由P1-068767_E30D的轻链的氨基酸序列组成的轻链；

[0597] (jjj)由P1-068767_E30D_E55A.IgG1.3的重链的氨基酸序列组成的重链和由P1-068767_E30D_E55A的轻链的氨基酸序列组成的轻链;

[0598] (kkk)由P1-068767_E100fF_D102V.IgG1.3的重链的氨基酸序列组成的重链和由P1-068767_E100fF_D102V的轻链的氨基酸序列组成的轻链;

[0599] (lll)由P1-068767_E55A_E100fF.IgG1.3的重链的氨基酸序列组成的重链和由P1-068767_E55A_E100fF的轻链的氨基酸序列组成的轻链;

[0600] (mmm)由P1-068767_D52N_E100fF.IgG1.3的重链的氨基酸序列组成的重链和由P1-068767_D52N_E100fF的轻链的氨基酸序列组成的轻链;

[0601] (nnn)由P1-068767_E100fF.IgG1.3的重链的氨基酸序列组成的重链和由P1-068767_E100fF的轻链的氨基酸序列组成的轻链;或

[0602] (ooo)由P1-068767_E30D_E100fF.IgG1.3的重链的氨基酸序列组成的重链和由P1-068767_E30D_E100fF的轻链的氨基酸序列组成的轻链。

[0603] 在一些实施方案中,本公开文本考虑了抗VISTA mAb,其包含:

[0604] 由以上所列的(a)至(ooo)的重链的氨基酸序列和随后的Lys残基组成的重链;和

[0605] 由以上所列的(a)至(ooo)的轻链氨基酸序列组成的轻链;

[0606] 其中所述重链和轻链氨基酸序列选自来自以上所列的(a)至(ooo)的相同抗体种类。

[0607] 在一些实施方案中,抗hVISTA Ab可以包含含有本文的抗体种类的VH氨基酸序列而非IgG1.3重链恒定区的重链氨基酸序列,如本文的序列表中的HC序列中所提供的(并且参见SEQ ID NO:163),所述抗体可以包含不同的重链恒定区序列,如人野生型IgG1恒定区(如人IgG1同种异型f(IgG1f)(SEQID NO:182))或修饰的人IgG1恒定区(如IgG1.1f(SEQ ID NO:183))或修饰的人IgG1恒定区(如IgG1.P238K(SEQ ID NO:184))。因此,本公开文本的实施方案包括抗VISTA Ab,其包含:

[0608] (a)含有(i)P1-061029(SEQ ID NO:67)的VH的氨基酸序列和(ii)SEQ IDNO:182的氨基酸序列的重链和含有P1-061029(SEQ ID NO:70)的轻链氨基酸序列的轻链;

[0609] (b)含有(i)P1-061015的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-061015的轻链氨基酸序列的轻链;

[0610] (c)含有(i)P1-068757的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068757的轻链氨基酸序列的轻链;

[0611] (d)含有(i)P1-068759的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068759的轻链氨基酸序列的轻链;

[0612] (e)含有(i)P1-068761的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761的轻链氨基酸序列的轻链;

[0613] (f)含有(i)P1-068763的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068763的轻链氨基酸序列的轻链;

[0614] (g)含有(i)P1-068765的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068765的轻链氨基酸序列的轻链;

[0615] (h)含有(i)P1-068767的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068767的轻链氨基酸序列的轻链;

[0616] (i)含有(i)P1-068769的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068769的轻链氨基酸序列的轻链；

[0617] (j)含有(i)P1-068771的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068771的轻链氨基酸序列的轻链；

[0618] (k)含有(i)P1-068773的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068773的轻链氨基酸序列的轻链；

[0619] (l)含有(i)P1-068775的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068775的轻链氨基酸序列的轻链；

[0620] (m)含有(i)P1-069059的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-069059的轻链氨基酸序列的轻链；

[0621] (n)含有(i)P1-069061的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-069061的轻链氨基酸序列的轻链；

[0622] (o)含有(i)P1-069063的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-069063的轻链氨基酸序列的轻链；

[0623] (p)含有(i)P1-069065的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-069065的轻链氨基酸序列的轻链；

[0624] (q)含有(i)P1-069067的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-069067的轻链氨基酸序列的轻链；

[0625] (r)含有(i)P1-069069的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-069069的轻链氨基酸序列的轻链；

[0626] (s)含有(i)P1-069071的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-069071的轻链氨基酸序列的轻链；

[0627] (t)含有(i)P1-069073的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-069073的轻链氨基酸序列的轻链；

[0628] (u)含有(i)P1-069075的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-069075的轻链氨基酸序列的轻链；

[0629] (v)含有(i)P1-069077的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-069077的轻链氨基酸序列的轻链；

[0630] (w)含有(i)P1-068736的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068736的轻链氨基酸序列的轻链；

[0631] (x)含有(i)P1-068738的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068738的轻链氨基酸序列的轻链；

[0632] (y)含有(i)P1-068740的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068740的轻链氨基酸序列的轻链；

[0633] (z)含有(i)P1-068742的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068742的轻链氨基酸序列的轻链；

[0634] (aa)含有(i)P1-068744的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068744的轻链氨基酸序列的轻链；

[0635] (bb)含有P1-068746的重链的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的

重链和含有P1-068746的轻链氨基酸序列的轻链；

[0636] (cc)含有(i)P1-068748的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068748的轻链氨基酸序列的轻链；

[0637] (dd)含有(i)P1-068750的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068750的轻链氨基酸序列的轻链；

[0638] (ee)含有(i)P1-068752的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068752的轻链氨基酸序列的轻链；

[0639] (ff)含有(i)P1-068754的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068754的轻链氨基酸序列的轻链；

[0640] (gg)含有(i)P1-068761_E55A的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E55A的轻链氨基酸序列的轻链；

[0641] (hh)含有(i)P1-068761_H100G的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_H100G的轻链氨基酸序列的轻链；

[0642] (ii)含有(i)P1-068761_E56N的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E56N的轻链氨基酸序列的轻链；

[0643] (jj)含有(i)P1-068761_E55A_E56N的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E55A_E56N的轻链氨基酸序列的轻链；

[0644] (kk)含有(i)P1-068761_E30D的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E30D的轻链氨基酸序列的轻链；

[0645] (ll)含有(i)P1-068761_E30D_E55A的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E30D_E55A的轻链氨基酸序列的轻链；

[0646] (mm)含有(i)P1-068761_E56N_H100G的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E56N_H100G的轻链氨基酸序列的轻链；

[0647] (nn)含有(i)P1-068761_E30D_H100G的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E30D_H100G的轻链氨基酸序列的轻链；

[0648] (oo)含有(i)P1-068761_E30D_E56N的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E30D_E56N的轻链氨基酸序列的轻链；

[0649] (pp)含有(i)P1-068761_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E100fF的轻链氨基酸序列的轻链；

[0650] (qq)含有(i)P1-068761_E55A_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E55A_E100fF的轻链氨基酸序列的轻链；

[0651] (rr)含有(i)P1-068761_H100G_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_H100G_E100fF的轻链氨基酸序列的轻链；

[0652] (ss)含有(i)P1-068761_E30D_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E30D_E100fF的轻链氨基酸序列的轻链；

[0653] (tt)含有(i)P1-068761_E56N_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E56N_E100fF的轻链氨基酸序列的轻链；

[0654] (uu)含有(i)P1-068761_E32Y的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E32Y的轻链氨基酸序列的轻链；

[0655] (vv)含有(i)P1-068761_E32Y_E55A的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E32Y_E55A的轻链氨基酸序列的轻链;

[0656] (ww)含有(i)P1-068761_E32Y_E56N的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E32Y_E56N的轻链氨基酸序列的轻链;

[0657] (xx)含有(i)P1-068761_E30D_E32Y的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E30D_E32Y的轻链氨基酸序列的轻链;

[0658] (yy)含有(i)P1-068761_E32Y_H100G的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E32Y_H100G的轻链氨基酸序列的轻链;

[0659] (zz)含有(i)P1-068761_E32Y_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068761_E32Y_E100fF的轻链氨基酸序列的轻链;

[0660] (aaa)含有(i)P1-068767_D52N_D102V的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068767_D52N_D102V的轻链氨基酸序列的轻链;

[0661] (bbb)含有(i)P1-068767_D52N的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068767_D52N的轻链氨基酸序列的轻链;

[0662] (ccc)含有(i)P1-068767_D52N_E55A的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068767_D52N_E55A的轻链氨基酸序列的轻链;

[0663] (ddd)含有(i)P1-068767_E55A_D102V的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068767_E55A_D102V的轻链氨基酸序列的轻链;

[0664] (eee)含有(i)P1-068767_D102V的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068767_D102V的轻链氨基酸序列的轻链;

[0665] (fff)含有(i)P1-068767_E55A的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068767_E55A的轻链氨基酸序列的轻链;

[0666] (ggg)含有(i)P1-068767_E30D_D52N的VH的氨基酸序列和(ii)SEQ IDNO:182的氨基酸序列的重链和含有P1-068767_E30D_D52N的轻链氨基酸序列的轻链;

[0667] (hhh)含有(i)P1-068767_E30D_D102V的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068767_E30D_D102V的轻链氨基酸序列的轻链;

[0668] (iii)含有(i)P1-068767_E30D的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068767_E30D的轻链氨基酸序列的轻链;

[0669] (jjj)含有(i)P1-068767_E30D_E55A的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068767_E30D_E55A的轻链氨基酸序列的轻链;

[0670] (kkk)含有(i)P1-068767_E100fF_D102V的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068767_E100fF_D102V的轻链氨基酸序列的轻链;

[0671] (lll)含有(i)P1-068767_E55A_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068767_E55A_E100fF的轻链氨基酸序列的轻链;

[0672] (mmm)含有(i)P1-068767_D52N_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068767_D52N_E100fF的轻链氨基酸序列的轻链;

[0673] (nnn)含有(i)P1-068767_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列的重链和含有P1-068767_E100fF的轻链氨基酸序列的轻链;或

[0674] (ooo)含有(i)P1-068767_E30D_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182

的氨基酸序列的重链和含有P1-068767_E30D_E100fF的轻链氨基酸序列的轻链。

[0675] 本公开文本的某些实施方案包括抗VISTA Ab,其包含:

[0676] (a)由(i)P1-061029(SEQ ID NO:67)的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-061029(SEQ ID NO:70)的轻链氨基酸序列组成的轻链;

[0677] (b)由(i)P1-061015的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-061015的轻链氨基酸序列组成的轻链;

[0678] (c)由(i)P1-068757的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068757的轻链氨基酸序列组成的轻链;

[0679] (d)由(i)P1-068759的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068759的轻链氨基酸序列组成的轻链;

[0680] (e)由(i)P1-068761的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761的轻链氨基酸序列组成的轻链;

[0681] (f)由(i)P1-068763的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068763的轻链氨基酸序列组成的轻链;

[0682] (g)由(i)P1-068765的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068765的轻链氨基酸序列组成的轻链;

[0683] (h)由(i)P1-068767的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068767的轻链氨基酸序列组成的轻链;

[0684] (i)由(i)P1-068769的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068769的轻链氨基酸序列组成的轻链;

[0685] (j)由(i)P1-068771的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068771的轻链氨基酸序列组成的轻链;

[0686] (k)由(i)P1-068773的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068773的轻链氨基酸序列组成的轻链;

[0687] (l)由(i)P1-068775的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068775的轻链氨基酸序列组成的轻链;

[0688] (m)由(i)P1-069059的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-069059的轻链氨基酸序列组成的轻链;

[0689] (n)由(i)P1-069061的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-069061的轻链氨基酸序列组成的轻链;

[0690] (o)由(i)P1-069063的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-069063的轻链氨基酸序列组成的轻链;

[0691] (p)由(i)P1-069065的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-069065的轻链氨基酸序列组成的轻链;

[0692] (q)由(i)P1-069067的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-069067的轻链氨基酸序列组成的轻链;

[0693] (r)由(i)P1-069069的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-069069的轻链氨基酸序列组成的轻链;

[0694] (s)由(i)P1-069071的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成

的重链和由P1-069071的轻链氨基酸序列组成的轻链；

[0695] (t)由(i)P1-069073的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-069073的轻链氨基酸序列组成的轻链；

[0696] (u)由(i)P1-069075的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-069075的轻链氨基酸序列组成的轻链；

[0697] (v)由(i)P1-069077的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-069077的轻链氨基酸序列组成的轻链；

[0698] (w)由(i)P1-068736的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068736的轻链氨基酸序列组成的轻链；

[0699] (x)由(i)P1-068738的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068738的轻链氨基酸序列组成的轻链；

[0700] (y)由(i)P1-068740的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068740的轻链氨基酸序列组成的轻链；

[0701] (z)由(i)P1-068742的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068742的轻链氨基酸序列组成的轻链；

[0702] (aa)由(i)P1-068744的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068744的轻链氨基酸序列组成的轻链；

[0703] (bb)由P1-068746的重链的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068746的轻链氨基酸序列组成的轻链；

[0704] (cc)由(i)P1-068748的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068748的轻链氨基酸序列组成的轻链；

[0705] (dd)由(i)P1-068750的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068750的轻链氨基酸序列组成的轻链；

[0706] (ee)由(i)P1-068752的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068752的轻链氨基酸序列组成的轻链；

[0707] (ff)由(i)P1-068754的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068754的轻链氨基酸序列组成的轻链；

[0708] (gg)由(i)P1-068761_E55A的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_E55A的轻链氨基酸序列组成的轻链；

[0709] (hh)由(i)P1-068761_H100G的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_H100G的轻链氨基酸序列组成的轻链；

[0710] (ii)由(i)P1-068761_E56N的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_E56N的轻链氨基酸序列组成的轻链；

[0711] (jj)由(i)P1-068761_E55A_E56N的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_E55A_E56N的轻链氨基酸序列组成的轻链；

[0712] (kk)由(i)P1-068761_E30D的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_E30D的轻链氨基酸序列组成的轻链；

[0713] (ll)由(i)P1-068761_E30D_E55A的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_E30D_E55A的轻链氨基酸序列组成的轻链；

[0714] (mm)由(i)P1-068761_E56N_H100G的VH的氨基酸序列和(ii)SEQ IDNO:182的氨基酸序列组成的重链和由P1-068761_E56N_H100G的轻链氨基酸序列组成的轻链;

[0715] (nn)由(i)P1-068761_E30D_H100G的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_E30D_H100G的轻链氨基酸序列组成的轻链;

[0716] (oo)由(i)P1-068761_E30D_E56N的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_E30D_E56N的轻链氨基酸序列组成的轻链;

[0717] (pp)由(i)P1-068761_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_E100fF的轻链氨基酸序列组成的轻链;

[0718] (qq)由(i)P1-068761_E55A_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_E55A_E100fF的轻链氨基酸序列组成的轻链;

[0719] (rr)由(i)P1-068761_H100G_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_H100G_E100fF的轻链氨基酸序列组成的轻链;

[0720] (ss)由(i)P1-068761_E30D_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_E30D_E100fF的轻链氨基酸序列组成的轻链;

[0721] (tt)由(i)P1-068761_E56N_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_E56N_E100fF的轻链氨基酸序列组成的轻链;

[0722] (uu)由(i)P1-068761_E32Y的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_E32Y的轻链氨基酸序列组成的轻链;

[0723] (vv)由(i)P1-068761_E32Y_E55A的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_E32Y_E55A的轻链氨基酸序列组成的轻链;

[0724] (ww)由(i)P1-068761_E32Y_E56N的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_E32Y_E56N的轻链氨基酸序列组成的轻链;

[0725] (xx)由(i)P1-068761_E30D_E32Y的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_E30D_E32Y的轻链氨基酸序列组成的轻链;

[0726] (yy)由(i)P1-068761_E32Y_H100G的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_E32Y_H100G的轻链氨基酸序列组成的轻链;

[0727] (zz)由(i)P1-068761_E32Y_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068761_E32Y_E100fF的轻链氨基酸序列组成的轻链;

[0728] (aaa)由(i)P1-068767_D52N_D102V的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068767_D52N_D102V的轻链氨基酸序列组成的轻链;

[0729] (bbb)由(i)P1-068767_D52N的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068767_D52N的轻链氨基酸序列组成的轻链;

[0730] (ccc)由(i)P1-068767_D52N_E55A的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068767_D52N_E55A的轻链氨基酸序列组成的轻链;

[0731] (ddd)由(i)P1-068767_E55A_D102V的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068767_E55A_D102V的轻链氨基酸序列组成的轻链;

[0732] (eee)由(i)P1-068767_D102V的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068767_D102V的轻链氨基酸序列组成的轻链;

[0733] (fff)由(i)P1-068767_E55A的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序

列组成的重链和由P1-068767_E55A的轻链氨基酸序列组成的轻链;

[0734] (ggg)由(i)P1-068767_E30D_D52N的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068767_E30D_D52N的轻链氨基酸序列组成的轻链;

[0735] (hhh)由(i)P1-068767_E30D_D102V的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068767_E30D_D102V的轻链氨基酸序列组成的轻链;

[0736] (iii)由(i)P1-068767_E30D的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068767_E30D的轻链氨基酸序列组成的轻链;

[0737] (jjj)由(i)P1-068767_E30D_E55A的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068767_E30D_E55A的轻链氨基酸序列组成的轻链;

[0738] (kkk)由(i)P1-068767_E100fF_D102V的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068767_E100fF_D102V的轻链氨基酸序列组成的轻链;

[0739] (lll)由(i)P1-068767_E55A_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068767_E55A_E100fF的轻链氨基酸序列组成的轻链;

[0740] (mmm)由(i)P1-068767_D52N_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068767_D52N_E100fF的轻链氨基酸序列组成的轻链;

[0741] (nnn)由(i)P1-068767_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068767_E100fF的轻链氨基酸序列组成的轻链;或

[0742] (ooo)由(i)P1-068767_E30D_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:182的氨基酸序列组成的重链和由P1-068767_E30D_E100fF的轻链氨基酸序列组成的轻链,

[0743] 其中VH的C末端氨基酸和SEQ ID NO:182的N末端氨基酸形成肽键。在一些实施方案中,本公开文本考虑了抗VISTA mAb,其包含:

[0744] 由(i)以上所列的(a)至(ooo)的VH、(ii)SEQ ID NO:182和(iii)Lys残基的氨基酸序列组成的重链,其中VH的C末端氨基酸和SEQ ID NO:182的N末端氨基酸形成肽键,并且SEQ ID NO:182的C末端氨基酸与Lys的N末端连接;和

[0745] 由以上所列的(a)至(ooo)的轻链氨基酸序列组成的轻链;

[0746] 其中所述VH和轻链氨基酸序列选自来自以上所列的(a)至(ooo)的相同抗体种类。

[0747] 本公开文本的某些实施方案包括抗VISTA Ab,其包含:

[0748] (a)含有(i)P1-061029(SEQ ID NO:67)的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-061029(SEQ ID NO:70)的轻链氨基酸序列的轻链;

[0749] (b)含有(i)P1-061015的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-061015的轻链氨基酸序列的轻链;

[0750] (c)含有(i)P1-068757的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068757的轻链氨基酸序列的轻链;

[0751] (d)含有(i)P1-068759的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068759的轻链氨基酸序列的轻链;

[0752] (e)含有(i)P1-068761的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761的轻链氨基酸序列的轻链;

[0753] (f)含有(i)P1-068763的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068763的轻链氨基酸序列的轻链;

[0754] (g)含有(i)P1-068765的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068765的轻链氨基酸序列的轻链；

[0755] (h)含有(i)P1-068767的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068767的轻链氨基酸序列的轻链；

[0756] (i)含有(i)P1-068769的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068769的轻链氨基酸序列的轻链；

[0757] (j)含有(i)P1-068771的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068771的轻链氨基酸序列的轻链；

[0758] (k)含有(i)P1-068773的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068773的轻链氨基酸序列的轻链；

[0759] (l)含有(i)P1-068775的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068775的轻链氨基酸序列的轻链；

[0760] (m)含有(i)P1-069059的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-069059的轻链氨基酸序列的轻链；

[0761] (n)含有(i)P1-069061的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-069061的轻链氨基酸序列的轻链；

[0762] (o)含有(i)P1-069063的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-069063的轻链氨基酸序列的轻链；

[0763] (p)含有(i)P1-069065的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-069065的轻链氨基酸序列的轻链；

[0764] (q)含有(i)P1-069067的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-069067的轻链氨基酸序列的轻链；

[0765] (r)含有(i)P1-069069的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-069069的轻链氨基酸序列的轻链；

[0766] (s)含有(i)P1-069071的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-069071的轻链氨基酸序列的轻链；

[0767] (t)含有(i)P1-069073的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-069073的轻链氨基酸序列的轻链；

[0768] (u)含有(i)P1-069075的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-069075的轻链氨基酸序列的轻链；

[0769] (v)含有(i)P1-069077的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-069077的轻链氨基酸序列的轻链；

[0770] (w)含有(i)P1-068736的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068736的轻链氨基酸序列的轻链；

[0771] (x)含有(i)P1-068738的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068738的轻链氨基酸序列的轻链；

[0772] (y)含有(i)P1-068740的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068740的轻链氨基酸序列的轻链；

[0773] (z)含有(i)P1-068742的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的

重链和含有P1-068742的轻链氨基酸序列的轻链；

[0774] (aa)含有(i)P1-068744的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068744的轻链氨基酸序列的轻链；

[0775] (bb)含有P1-068746的重链的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068746的轻链氨基酸序列的轻链；

[0776] (cc)含有(i)P1-068748的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068748的轻链氨基酸序列的轻链；

[0777] (dd)含有(i)P1-068750的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068750的轻链氨基酸序列的轻链；

[0778] (ee)含有(i)P1-068752的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068752的轻链氨基酸序列的轻链；

[0779] (ff)含有(i)P1-068754的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068754的轻链氨基酸序列的轻链；

[0780] (gg)含有(i)P1-068761_E55A的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E55A的轻链氨基酸序列的轻链；

[0781] (hh)含有(i)P1-068761_H100G的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_H100G的轻链氨基酸序列的轻链；

[0782] (ii)含有(i)P1-068761_E56N的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E56N的轻链氨基酸序列的轻链；

[0783] (jj)含有(i)P1-068761_E55A_E56N的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E55A_E56N的轻链氨基酸序列的轻链；

[0784] (kk)含有(i)P1-068761_E30D的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E30D的轻链氨基酸序列的轻链；

[0785] (ll)含有(i)P1-068761_E30D_E55A的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E30D_E55A的轻链氨基酸序列的轻链；

[0786] (mm)含有(i)P1-068761_E56N_H100G的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E56N_H100G的轻链氨基酸序列的轻链；

[0787] (nn)含有(i)P1-068761_E30D_H100G的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E30D_H100G的轻链氨基酸序列的轻链；

[0788] (oo)含有(i)P1-068761_E30D_E56N的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E30D_E56N的轻链氨基酸序列的轻链；

[0789] (pp)含有(i)P1-068761_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E100fF的轻链氨基酸序列的轻链；

[0790] (qq)含有(i)P1-068761_E55A_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E55A_E100fF的轻链氨基酸序列的轻链；

[0791] (rr)含有(i)P1-068761_H100G_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_H100G_E100fF的轻链氨基酸序列的轻链；

[0792] (ss)含有(i)P1-068761_E30D_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E30D_E100fF的轻链氨基酸序列的轻链；

[0793] (tt)含有(i)P1-068761_E56N_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E56N_E100fF的轻链氨基酸序列的轻链;

[0794] (uu)含有(i)P1-068761_E32Y的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E32Y的轻链氨基酸序列的轻链;

[0795] (vv)含有(i)P1-068761_E32Y_E55A的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E32Y_E55A的轻链氨基酸序列的轻链;

[0796] (ww)含有(i)P1-068761_E32Y_E56N的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E32Y_E56N的轻链氨基酸序列的轻链;

[0797] (xx)含有(i)P1-068761_E30D_E32Y的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E30D_E32Y的轻链氨基酸序列的轻链;

[0798] (yy)含有(i)P1-068761_E32Y_H100G的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E32Y_H100G的轻链氨基酸序列的轻链;

[0799] (zz)含有(i)P1-068761_E32Y_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068761_E32Y_E100fF的轻链氨基酸序列的轻链;

[0800] (aaa)含有(i)P1-068767_D52N_D102V的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068767_D52N_D102V的轻链氨基酸序列的轻链;

[0801] (bbb)含有(i)P1-068767_D52N的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068767_D52N的轻链氨基酸序列的轻链;

[0802] (ccc)含有(i)P1-068767_D52N_E55A的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068767_D52N_E55A的轻链氨基酸序列的轻链;

[0803] (ddd)含有(i)P1-068767_E55A_D102V的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068767_E55A_D102V的轻链氨基酸序列的轻链;

[0804] (eee)含有(i)P1-068767_D102V的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068767_D102V的轻链氨基酸序列的轻链;

[0805] (fff)含有(i)P1-068767_E55A的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068767_E55A的轻链氨基酸序列的轻链;

[0806] (ggg)含有(i)P1-068767_E30D_D52N的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068767_E30D_D52N的轻链氨基酸序列的轻链;

[0807] (hhh)含有(i)P1-068767_E30D_D102V的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068767_E30D_D102V的轻链氨基酸序列的轻链;

[0808] (iii)含有(i)P1-068767_E30D的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068767_E30D的轻链氨基酸序列的轻链;

[0809] (jjj)含有(i)P1-068767_E30D_E55A的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068767_E30D_E55A的轻链氨基酸序列的轻链;

[0810] (kkk)含有(i)P1-068767_E100fF_D102V的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068767_E100fF_D102V的轻链氨基酸序列的轻链;

[0811] (lll)含有(i)P1-068767_E55A_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068767_E55A_E100fF的轻链氨基酸序列的轻链;

[0812] (mmm)含有(i)P1-068767_D52N_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183

的氨基酸序列的重链和含有P1-068767_D52N_E100fF的轻链氨基酸序列的轻链;

[0813] (nnn)含有(i)P1-068767_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068767_E100fF的轻链氨基酸序列的轻链;或

[0814] (ooo)含有(i)P1-068767_E30D_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列的重链和含有P1-068767_E30D_E100fF的轻链氨基酸序列的轻链。本公开文本的某些实施方案包括抗VISTA Ab,其包含:

[0815] (a)由(i)P1-061029(SEQ ID NO:67)的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-061029(SEQ ID NO:70)的轻链氨基酸序列组成的轻链;

[0816] (b)由(i)P1-061015的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-061015的轻链氨基酸序列组成的轻链;

[0817] (c)由(i)P1-068757的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068757的轻链氨基酸序列组成的轻链;

[0818] (d)由(i)P1-068759的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068759的轻链氨基酸序列组成的轻链;

[0819] (e)由(i)P1-068761的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761的轻链氨基酸序列组成的轻链;

[0820] (f)由(i)P1-068763的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068763的轻链氨基酸序列组成的轻链;

[0821] (g)由(i)P1-068765的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068765的轻链氨基酸序列组成的轻链;

[0822] (h)由(i)P1-068767的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068767的轻链氨基酸序列组成的轻链;

[0823] (i)由(i)P1-068769的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068769的轻链氨基酸序列组成的轻链;

[0824] (j)由(i)P1-068771的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068771的轻链氨基酸序列组成的轻链;

[0825] (k)由(i)P1-068773的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068773的轻链氨基酸序列组成的轻链;

[0826] (l)由(i)P1-068775的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068775的轻链氨基酸序列组成的轻链;

[0827] (m)由(i)P1-069059的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-069059的轻链氨基酸序列组成的轻链;

[0828] (n)由(i)P1-069061的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-069061的轻链氨基酸序列组成的轻链;

[0829] (o)由(i)P1-069063的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-069063的轻链氨基酸序列组成的轻链;

[0830] (p)由(i)P1-069065的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-069065的轻链氨基酸序列组成的轻链;

[0831] (q)由(i)P1-069067的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成

的重链和由P1-069067的轻链氨基酸序列组成的轻链；

[0832] (r)由(i)P1-069069的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-069069的轻链氨基酸序列组成的轻链；

[0833] (s)由(i)P1-069071的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-069071的轻链氨基酸序列组成的轻链；

[0834] (t)由(i)P1-069073的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-069073的轻链氨基酸序列组成的轻链；

[0835] (u)由(i)P1-069075的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-069075的轻链氨基酸序列组成的轻链；

[0836] (v)由(i)P1-069077的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-069077的轻链氨基酸序列组成的轻链；

[0837] (w)由(i)P1-068736的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068736的轻链氨基酸序列组成的轻链；

[0838] (x)由(i)P1-068738的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068738的轻链氨基酸序列组成的轻链；

[0839] (y)由(i)P1-068740的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068740的轻链氨基酸序列组成的轻链；

[0840] (z)由(i)P1-068742的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068742的轻链氨基酸序列组成的轻链；

[0841] (aa)由(i)P1-068744的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068744的轻链氨基酸序列组成的轻链；

[0842] (bb)由P1-068746的重链的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068746的轻链氨基酸序列组成的轻链；

[0843] (cc)由(i)P1-068748的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068748的轻链氨基酸序列组成的轻链；

[0844] (dd)由(i)P1-068750的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068750的轻链氨基酸序列组成的轻链；

[0845] (ee)由(i)P1-068752的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068752的轻链氨基酸序列组成的轻链；

[0846] (ff)由(i)P1-068754的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068754的轻链氨基酸序列组成的轻链；

[0847] (gg)由(i)P1-068761_E55A的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E55A的轻链氨基酸序列组成的轻链；

[0848] (hh)由(i)P1-068761_H100G的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_H100G的轻链氨基酸序列组成的轻链；

[0849] (ii)由(i)P1-068761_E56N的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E56N的轻链氨基酸序列组成的轻链；

[0850] (jj)由(i)P1-068761_E55A_E56N的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E55A_E56N的轻链氨基酸序列组成的轻链；

[0851] (kk)由(i)P1-068761_E30D的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E30D的轻链氨基酸序列组成的轻链;

[0852] (ll)由(i)P1-068761_E30D_E55A的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E30D_E55A的轻链氨基酸序列组成的轻链;

[0853] (mm)由(i)P1-068761_E56N_H100G的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E56N_H100G的轻链氨基酸序列组成的轻链;

[0854] (nn)由(i)P1-068761_E30D_H100G的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E30D_H100G的轻链氨基酸序列组成的轻链;

[0855] (oo)由(i)P1-068761_E30D_E56N的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E30D_E56N的轻链氨基酸序列组成的轻链;

[0856] (pp)由(i)P1-068761_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E100fF的轻链氨基酸序列组成的轻链;

[0857] (qq)由(i)P1-068761_E55A_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E55A_E100fF的轻链氨基酸序列组成的轻链;

[0858] (rr)由(i)P1-068761_H100G_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_H100G_E100fF的轻链氨基酸序列组成的轻链;

[0859] (ss)由(i)P1-068761_E30D_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E30D_E100fF的轻链氨基酸序列组成的轻链;

[0860] (tt)由(i)P1-068761_E56N_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E56N_E100fF的轻链氨基酸序列组成的轻链;

[0861] (uu)由(i)P1-068761_E32Y的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E32Y的轻链氨基酸序列组成的轻链;

[0862] (vv)由(i)P1-068761_E32Y_E55A的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E32Y_E55A的轻链氨基酸序列组成的轻链;

[0863] (ww)由(i)P1-068761_E32Y_E56N的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E32Y_E56N的轻链氨基酸序列组成的轻链;

[0864] (xx)由(i)P1-068761_E30D_E32Y的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E30D_E32Y的轻链氨基酸序列组成的轻链;

[0865] (yy)由(i)P1-068761_E32Y_H100G的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E32Y_H100G的轻链氨基酸序列组成的轻链;

[0866] (zz)由(i)P1-068761_E32Y_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068761_E32Y_E100fF的轻链氨基酸序列组成的轻链;

[0867] (aaa)由(i)P1-068767_D52N_D102V的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068767_D52N_D102V的轻链氨基酸序列组成的轻链;

[0868] (bbb)由(i)P1-068767_D52N的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068767_D52N的轻链氨基酸序列组成的轻链;

[0869] (ccc)由(i)P1-068767_D52N_E55A的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068767_D52N_E55A的轻链氨基酸序列组成的轻链;

[0870] (ddd)由(i)P1-068767_E55A_D102V的VH的氨基酸序列和(ii)SEQ ID NO:183的氨

基酸序列组成的重链和由P1-068767_E55A_D102V的轻链氨基酸序列组成的轻链;

[0871] (eee)由(i)P1-068767_D102V的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068767_D102V的轻链氨基酸序列组成的轻链;

[0872] (fff)由(i)P1-068767_E55A的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068767_E55A的轻链氨基酸序列组成的轻链;

[0873] (ggg)由(i)P1-068767_E30D_D52N的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068767_E30D_D52N的轻链氨基酸序列组成的轻链;

[0874] (hhh)由(i)P1-068767_E30D_D102V的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068767_E30D_D102V的轻链氨基酸序列组成的轻链;

[0875] (iii)由(i)P1-068767_E30D的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068767_E30D的轻链氨基酸序列组成的轻链;

[0876] (jjj)由(i)P1-068767_E30D_E55A的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068767_E30D_E55A的轻链氨基酸序列组成的轻链;

[0877] (kkk)由(i)P1-068767_E100fF_D102V的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068767_E100fF_D102V的轻链氨基酸序列组成的轻链;

[0878] (lll)由(i)P1-068767_E55A_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068767_E55A_E100fF的轻链氨基酸序列组成的轻链;

[0879] (mmm)由(i)P1-068767_D52N_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068767_D52N_E100fF的轻链氨基酸序列组成的轻链;

[0880] (nnn)由(i)P1-068767_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068767_E100fF的轻链氨基酸序列组成的轻链;或

[0881] (ooo)由(i)P1-068767_E30D_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:183的氨基酸序列组成的重链和由P1-068767_E30D_E100fF的轻链氨基酸序列组成的轻链,

[0882] 其中VH的C末端氨基酸和SEQ ID NO:183的N末端氨基酸形成肽键。在一些实施方案中,本公开文本考虑了抗VISTA mAb,其包含:

[0883] 由(i)以上所列的(a)至(ooo)的VH、(ii)SEQ ID NO:183和(iii)Lys残基的氨基酸序列组成的重链,其中VH的C末端氨基酸和SEQ ID NO:183的N末端氨基酸形成肽键,并且SEQ ID NO:183的C末端氨基酸与Lys的N末端连接;和

[0884] 由以上所列的(a)至(ooo)的轻链氨基酸序列组成的轻链;

[0885] 其中所述VH和轻链氨基酸序列选自来自以上所列的(a)至(ooo)的相同抗体种类。

[0886] 本公开文本的其他实施方案包括抗VISTA Ab,其包含:

[0887] (a)含有(i)P1-061029(SEQ ID NO:67)的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-061029(SEQ ID NO:70)的轻链氨基酸序列的轻链;

[0888] (b)含有(i)P1-061015的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-061015的轻链氨基酸序列的轻链;

[0889] (c)含有(i)P1-068757的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068757的轻链氨基酸序列的轻链;

[0890] (d)含有(i)P1-068759的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068759的轻链氨基酸序列的轻链;

[0891] (e)含有(i)P1-068761的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761的轻链氨基酸序列的轻链；

[0892] (f)含有(i)P1-068763的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068763的轻链氨基酸序列的轻链；

[0893] (g)含有(i)P1-068765的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068765的轻链氨基酸序列的轻链；

[0894] (h)含有(i)P1-068767的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068767的轻链氨基酸序列的轻链；

[0895] (i)含有(i)P1-068769的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068769的轻链氨基酸序列的轻链；

[0896] (j)含有(i)P1-068771的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068771的轻链氨基酸序列的轻链；

[0897] (k)含有(i)P1-068773的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068773的轻链氨基酸序列的轻链；

[0898] (l)含有(i)P1-068775的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068775的轻链氨基酸序列的轻链；

[0899] (m)含有(i)P1-069059的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-069059的轻链氨基酸序列的轻链；

[0900] (n)含有(i)P1-069061的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-069061的轻链氨基酸序列的轻链；

[0901] (o)含有(i)P1-069063的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-069063的轻链氨基酸序列的轻链；

[0902] (p)含有(i)P1-069065的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-069065的轻链氨基酸序列的轻链；

[0903] (q)含有(i)P1-069067的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-069067的轻链氨基酸序列的轻链；

[0904] (r)含有(i)P1-069069的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-069069的轻链氨基酸序列的轻链；

[0905] (s)含有(i)P1-069071的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-069071的轻链氨基酸序列的轻链；

[0906] (t)含有(i)P1-069073的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-069073的轻链氨基酸序列的轻链；

[0907] (u)含有(i)P1-069075的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-069075的轻链氨基酸序列的轻链；

[0908] (v)含有(i)P1-069077的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-069077的轻链氨基酸序列的轻链；

[0909] (w)含有(i)P1-068736的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068736的轻链氨基酸序列的轻链；

[0910] (x)含有(i)P1-068738的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的

重链和含有P1-068738的轻链氨基酸序列的轻链；

[0911] (y)含有(i)P1-068740的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068740的轻链氨基酸序列的轻链；

[0912] (z)含有(i)P1-068742的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068742的轻链氨基酸序列的轻链；

[0913] (aa)含有(i)P1-068744的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068744的轻链氨基酸序列的轻链；

[0914] (bb)含有P1-068746的重链的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068746的轻链氨基酸序列的轻链；

[0915] (cc)含有(i)P1-068748的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068748的轻链氨基酸序列的轻链；

[0916] (dd)含有(i)P1-068750的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068750的轻链氨基酸序列的轻链；

[0917] (ee)含有(i)P1-068752的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068752的轻链氨基酸序列的轻链；

[0918] (ff)含有(i)P1-068754的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068754的轻链氨基酸序列的轻链；

[0919] (gg)含有(i)P1-068761_E55A的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E55A的轻链氨基酸序列的轻链；

[0920] (hh)含有(i)P1-068761_H100G的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_H100G的轻链氨基酸序列的轻链；

[0921] (ii)含有(i)P1-068761_E56N的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E56N的轻链氨基酸序列的轻链；

[0922] (jj)含有(i)P1-068761_E55A_E56N的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E55A_E56N的轻链氨基酸序列的轻链；

[0923] (kk)含有(i)P1-068761_E30D的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E30D的轻链氨基酸序列的轻链；

[0924] (ll)含有(i)P1-068761_E30D_E55A的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E30D_E55A的轻链氨基酸序列的轻链；

[0925] (mm)含有(i)P1-068761_E56N_H100G的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E56N_H100G的轻链氨基酸序列的轻链；

[0926] (nn)含有(i)P1-068761_E30D_H100G的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E30D_H100G的轻链氨基酸序列的轻链；

[0927] (oo)含有(i)P1-068761_E30D_E56N的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E30D_E56N的轻链氨基酸序列的轻链；

[0928] (pp)含有(i)P1-068761_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E100fF的轻链氨基酸序列的轻链；

[0929] (qq)含有(i)P1-068761_E55A_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E55A_E100fF的轻链氨基酸序列的轻链；

[0930] (rr)含有(i)P1-068761_H100G_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_H100G_E100fF的轻链氨基酸序列的轻链;

[0931] (ss)含有(i)P1-068761_E30D_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E30D_E100fF的轻链氨基酸序列的轻链;

[0932] (tt)含有(i)P1-068761_E56N_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E56N_E100fF的轻链氨基酸序列的轻链;

[0933] (uu)含有(i)P1-068761_E32Y的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E32Y的轻链氨基酸序列的轻链;

[0934] (vv)含有(i)P1-068761_E32Y_E55A的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E32Y_E55A的轻链氨基酸序列的轻链;

[0935] (ww)含有(i)P1-068761_E32Y_E56N的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E32Y_E56N的轻链氨基酸序列的轻链;

[0936] (xx)含有(i)P1-068761_E30D_E32Y的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E30D_E32Y的轻链氨基酸序列的轻链;

[0937] (yy)含有(i)P1-068761_E32Y_H100G的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E32Y_H100G的轻链氨基酸序列的轻链;

[0938] (zz)含有(i)P1-068761_E32Y_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068761_E32Y_E100fF的轻链氨基酸序列的轻链;

[0939] (aaa)含有(i)P1-068767_D52N_D102V的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068767_D52N_D102V的轻链氨基酸序列的轻链;

[0940] (bbb)含有(i)P1-068767_D52N的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068767_D52N的轻链氨基酸序列的轻链;

[0941] (ccc)含有(i)P1-068767_D52N_E55A的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068767_D52N_E55A的轻链氨基酸序列的轻链;

[0942] (ddd)含有(i)P1-068767_E55A_D102V的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068767_E55A_D102V的轻链氨基酸序列的轻链;

[0943] (eee)含有(i)P1-068767_D102V的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068767_D102V的轻链氨基酸序列的轻链;

[0944] (fff)含有(i)P1-068767_E55A的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068767_E55A的轻链氨基酸序列的轻链;

[0945] (ggg)含有(i)P1-068767_E30D_D52N的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068767_E30D_D52N的轻链氨基酸序列的轻链;

[0946] (hhh)含有(i)P1-068767_E30D_D102V的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068767_E30D_D102V的轻链氨基酸序列的轻链;

[0947] (iii)含有(i)P1-068767_E30D的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068767_E30D的轻链氨基酸序列的轻链;

[0948] (jjj)含有(i)P1-068767_E30D_E55A的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068767_E30D_E55A的轻链氨基酸序列的轻链;

[0949] (kkk)含有(i)P1-068767_E100fF_D102V的VH的氨基酸序列和(ii)SEQ ID NO:184

的氨基酸序列的重链和含有P1-068767_E100fF_D102V的轻链氨基酸序列的轻链;

[0950] (lll)含有(i)P1-068767_E55A_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068767_E55A_E100fF的轻链氨基酸序列的轻链;

[0951] (mmm)含有(i)P1-068767_D52N_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068767_D52N_E100fF的轻链氨基酸序列的轻链;

[0952] (nnn)含有(i)P1-068767_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068767_E100fF的轻链氨基酸序列的轻链;或

[0953] (ooo)含有(i)P1-068767_E30D_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列的重链和含有P1-068767_E30D_E100fF的轻链氨基酸序列的轻链。本公开文本的又其他实施方案包括抗VISTA Ab,其包含:

[0954] (a)由(i)P1-061029(SEQ ID NO:67)的VH的氨基酸序列和(ii)SEQ IDNO:184的氨基酸序列组成的重链和由P1-061029(SEQ ID NO:70)的轻链氨基酸序列组成的轻链;

[0955] (b)由(i)P1-061015的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-061015的轻链氨基酸序列组成的轻链;

[0956] (c)由(i)P1-068757的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068757的轻链氨基酸序列组成的轻链;

[0957] (d)由(i)P1-068759的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068759的轻链氨基酸序列组成的轻链;

[0958] (e)由(i)P1-068761的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761的轻链氨基酸序列组成的轻链;

[0959] (f)由(i)P1-068763的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068763的轻链氨基酸序列组成的轻链;

[0960] (g)由(i)P1-068765的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068765的轻链氨基酸序列组成的轻链;

[0961] (h)由(i)P1-068767的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068767的轻链氨基酸序列组成的轻链;

[0962] (i)由(i)P1-068769的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068769的轻链氨基酸序列组成的轻链;

[0963] (j)由(i)P1-068771的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068771的轻链氨基酸序列组成的轻链;

[0964] (k)由(i)P1-068773的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068773的轻链氨基酸序列组成的轻链;

[0965] (l)由(i)P1-068775的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068775的轻链氨基酸序列组成的轻链;

[0966] (m)由(i)P1-069059的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-069059的轻链氨基酸序列组成的轻链;

[0967] (n)由(i)P1-069061的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-069061的轻链氨基酸序列组成的轻链;

[0968] (o)由(i)P1-069063的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成

的重链和由P1-069063的轻链氨基酸序列组成的轻链；

[0969] (p)由(i)P1-069065的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-069065的轻链氨基酸序列组成的轻链；

[0970] (q)由(i)P1-069067的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-069067的轻链氨基酸序列组成的轻链；

[0971] (r)由(i)P1-069069的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-069069的轻链氨基酸序列组成的轻链；

[0972] (s)由(i)P1-069071的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-069071的轻链氨基酸序列组成的轻链；

[0973] (t)由(i)P1-069073的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-069073的轻链氨基酸序列组成的轻链；

[0974] (u)由(i)P1-069075的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-069075的轻链氨基酸序列组成的轻链；

[0975] (v)由(i)P1-069077的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-069077的轻链氨基酸序列组成的轻链；

[0976] (w)由(i)P1-068736的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068736的轻链氨基酸序列组成的轻链；

[0977] (x)由(i)P1-068738的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068738的轻链氨基酸序列组成的轻链；

[0978] (y)由(i)P1-068740的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068740的轻链氨基酸序列组成的轻链；

[0979] (z)由(i)P1-068742的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068742的轻链氨基酸序列组成的轻链；

[0980] (aa)由(i)P1-068744的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068744的轻链氨基酸序列组成的轻链；

[0981] (bb)由P1-068746的重链的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068746的轻链氨基酸序列组成的轻链；

[0982] (cc)由(i)P1-068748的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068748的轻链氨基酸序列组成的轻链；

[0983] (dd)由(i)P1-068750的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068750的轻链氨基酸序列组成的轻链；

[0984] (ee)由(i)P1-068752的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068752的轻链氨基酸序列组成的轻链；

[0985] (ff)由(i)P1-068754的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068754的轻链氨基酸序列组成的轻链；

[0986] (gg)由(i)P1-068761_E55A的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E55A的轻链氨基酸序列组成的轻链；

[0987] (hh)由(i)P1-068761_H100G的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_H100G的轻链氨基酸序列组成的轻链；

[0988] (ii)由(i)P1-068761_E56N的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E56N的轻链氨基酸序列组成的轻链;

[0989] (jj)由(i)P1-068761_E55A_E56N的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E55A_E56N的轻链氨基酸序列组成的轻链;

[0990] (kk)由(i)P1-068761_E30D的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E30D的轻链氨基酸序列组成的轻链;

[0991] (ll)由(i)P1-068761_E30D_E55A的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E30D_E55A的轻链氨基酸序列组成的轻链;

[0992] (mm)由(i)P1-068761_E56N_H100G的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E56N_H100G的轻链氨基酸序列组成的轻链;

[0993] (nn)由(i)P1-068761_E30D_H100G的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E30D_H100G的轻链氨基酸序列组成的轻链;

[0994] (oo)由(i)P1-068761_E30D_E56N的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E30D_E56N的轻链氨基酸序列组成的轻链;

[0995] (pp)由(i)P1-068761_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E100fF的轻链氨基酸序列组成的轻链;

[0996] (qq)由(i)P1-068761_E55A_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E55A_E100fF的轻链氨基酸序列组成的轻链;

[0997] (rr)由(i)P1-068761_H100G_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_H100G_E100fF的轻链氨基酸序列组成的轻链;

[0998] (ss)由(i)P1-068761_E30D_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E30D_E100fF的轻链氨基酸序列组成的轻链;

[0999] (tt)由(i)P1-068761_E56N_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E56N_E100fF的轻链氨基酸序列组成的轻链;

[1000] (uu)由(i)P1-068761_E32Y的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E32Y的轻链氨基酸序列组成的轻链;

[1001] (vv)由(i)P1-068761_E32Y_E55A的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E32Y_E55A的轻链氨基酸序列组成的轻链;

[1002] (ww)由(i)P1-068761_E32Y_E56N的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E32Y_E56N的轻链氨基酸序列组成的轻链;

[1003] (xx)由(i)P1-068761_E30D_E32Y的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E30D_E32Y的轻链氨基酸序列组成的轻链;

[1004] (yy)由(i)P1-068761_E32Y_H100G的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E32Y_H100G的轻链氨基酸序列组成的轻链;

[1005] (zz)由(i)P1-068761_E32Y_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068761_E32Y_E100fF的轻链氨基酸序列组成的轻链;

[1006] (aaa)由(i)P1-068767_D52N_D102V的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068767_D52N_D102V的轻链氨基酸序列组成的轻链;

[1007] (bbb)由(i)P1-068767_D52N的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序

列组成的重链和由P1-068767_D52N的轻链氨基酸序列组成的轻链;

[1008] (ccc)由(i)P1-068767_D52N_E55A的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068767_D52N_E55A的轻链氨基酸序列组成的轻链;

[1009] (ddd)由(i)P1-068767_E55A_D102V的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068767_E55A_D102V的轻链氨基酸序列组成的轻链;

[1010] (eee)由(i)P1-068767_D102V的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068767_D102V的轻链氨基酸序列组成的轻链;

[1011] (fff)由(i)P1-068767_E55A的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068767_E55A的轻链氨基酸序列组成的轻链;

[1012] (ggg)由(i)P1-068767_E30D_D52N的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068767_E30D_D52N的轻链氨基酸序列组成的轻链;

[1013] (hhh)由(i)P1-068767_E30D_D102V的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068767_E30D_D102V的轻链氨基酸序列组成的轻链;

[1014] (iii)由(i)P1-068767_E30D的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068767_E30D的轻链氨基酸序列组成的轻链;

[1015] (jjj)由(i)P1-068767_E30D_E55A的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068767_E30D_E55A的轻链氨基酸序列组成的轻链;

[1016] (kkk)由(i)P1-068767_E100fF_D102V的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068767_E100fF_D102V的轻链氨基酸序列组成的轻链;

[1017] (lll)由(i)P1-068767_E55A_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068767_E55A_E100fF的轻链氨基酸序列组成的轻链;

[1018] (mmm)由(i)P1-068767_D52N_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068767_D52N_E100fF的轻链氨基酸序列组成的轻链;

[1019] (nnn)由(i)P1-068767_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068767_E100fF的轻链氨基酸序列组成的轻链;或

[1020] (ooo)由(i)P1-068767_E30D_E100fF的VH的氨基酸序列和(ii)SEQ ID NO:184的氨基酸序列组成的重链和由P1-068767_E30D_E100fF的轻链氨基酸序列组成的轻链,

[1021] 其中VH的C末端氨基酸和SEQ ID NO:184的N末端氨基酸形成肽键。在一些实施方案中,本公开文本考虑了抗VISTA mAb,其包含:

[1022] 由(i)以上所列的(a)至(ooo)的VH、(ii)SEQ ID NO:184和(iii)Lys残基的氨基酸序列组成的重链,其中VH的C末端氨基酸和SEQ ID NO:184的N末端氨基酸形成肽键,并且SEQ ID NO:184的C末端氨基酸与Lys的N末端连接;和

[1023] 由以上所列的(a)至(ooo)的轻链氨基酸序列组成的轻链;

[1024] 其中所述VH和轻链氨基酸序列选自来自以上所列的(a)至(ooo)的相同抗体种类。

[1025] 在一些实施方案中,抗hVISTA Ab可以包含与P1-061029的相应序列至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%或至少99%相同的氨基酸VH序列,其中所述抗体包含至少一个残基已经被D、E或H取代的P1-061029的VH CDR1、CDR2和/或CDR3。在一些实施方案中,P1-061029的VH CDR1、CDR2和CDR3中的每一个含有被D、E或H取代的一个、两个或三个残基。在一些实施方案中,抗hVISTA Ab

可以包含与P1-061029的相应序列至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的氨基酸VH序列,其中所述抗体包含在CDR1的氨基酸位置4、5或7含有一个或两个D或E残基的VH CDR1,和/或包含在CDR2的位置3、5、6或7处具有一个、两个或三个D、E或H残基的VH CDR2,和/或在CDR 3的位置6、12或14处具有一个、两个或三个D、E或H残基的VH CDR3。(关于落入这些实施方案中的抗体的例子参见下文表5。)在此类情况下,轻链可变区可以包含P1-061029或P1-061015或其后代如P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF的CDR1、CDR2和/或CDR3,和/或轻链可变区可以与P1-061029或P1-061015或其后代如P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF的CDR1、CDR2和/或CDR3是至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的。

[1026] 在一些实施方案中,抗hVISTA Ab可以包含与P1-061015的相应序列至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的氨基酸VH序列,其中所述抗体包含至少一个残基已经被D、E或H取代的P1-

061015的VH CDR1、CDR2和/或CDR3。在一些实施方案中,P1-061015的VH CDR1、CDR2和CDR3中的每一个含有被D、E或H取代的一个、两个或三个残基。在一些实施方案中,抗hVISTA Ab可以包含与P1-061015的相应序列至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的氨基酸VH序列,其中所述抗体包含在CDR1的氨基酸位置6、7、8和9处含有一个或两个D、E或H残基的VH CDR1,和/或包含在CDR2的位置1、2、4或8-11处具有一个、两个或三个D、E或H残基的VH CDR2,和/或在CDR 3的位置2、3、6、7或12处具有一个、两个或三个D、E或H残基的VH CDR3。(关于落入这些实施方案中的抗体的例子参见下文表6。)在此类情况下,轻链可变区可以包含P1-061029或P1-061015或其后代如P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF的CDR1、CDR2和/或CDR3,和/或轻链可变区可以与P1-061029或P1-061015或其后代如P1-061029、P1-068757、P1-068759、P1-068761、P1-068763、P1-068765、P1-068767、P1-068769、P1-068771、P1-068773、P1-068775、P1-069059、P1-069061、P1-069063、P1-069065、P1-069067、P1-069069、P1-069071、P1-069073、P1-069075、P1-069077、P1-061015、P1-068736、P1-068738、P1-068740、P1-068742、P1-068744、P1-068766、P1-068748、P1-068750、P1-068752、P1-068754、P1-068761_E55A、P1-068761_H100G、P1-068761_E56N、P1-068761_E55A_E56N、P1-068761_E30D、P1-068761_E30D_E55A、P1-068761_E56N_H100G、P1-068761_E30D_H100G、P1-068761_E30D_E56N、P1-068761_E100fF、P1-068761_E55A_E100fF、P1-068761_H100G_E100fF、P1-068761_E30D_E100fF、P1-068761_E56N_E100fF、P1-068761_E32Y、P1-068761_E32Y_E55A、P1-068761_E32Y_E56N、P1-068761_E30D_E32Y、P1-068761_E32Y_H100G、P1-068761_E32Y_E100fF、P1-068767_D52N_D102V、P1-068767_D52N、P1-068767_D52N_E55A、P1-068767_E55A_D102V、P1-068767_D102V、P1-068767_E55A、P1-068767_E30D_D52N、P1-068767_E30D_D102V、P1-068767_E30D、P1-068767_E30D_E55A、P1-068767_E100fF_D102V、P1-068767_E55A_E100fF、P1-068767_D52N_E100fF、P1-068767_E100fF或P1-068767_E30D_E100fF的CDR1、CDR2和/或CDR3是至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％或至少99％相同的。

[1027] 在一些实施方案中,此类修饰的抗hVISTA P1-061029或P1-061015后代具有以下

特征中的一个或多个：

[1028] -在酸性pH(例如pH 6.0或pH 6.5)下与hVISTA(例如ECD或包含SEQ ID NO:2的氨基酸残基35-127的多肽的富组氨酸区域)特异性地结合；

[1029] -在生理pH或中性pH(例如pH 7.4或pH 7.0)下缺乏与hVISTA(例如ECD或包含SEQ ID NO:2的氨基酸残基35-127的多肽的富组氨酸区域)的显著结合；

[1030] -在酸性pH(例如pH 6.0或pH 6.5)下与cyno VISTA(例如ECD的富组氨酸区域)特异性地结合；

[1031] -在生理pH或中性pH(例如pH 7.4或pH 7.0)下缺乏与cyno VISTA(例如ECD的富组氨酸区域)的显著结合；

[1032] -与相对于具有SEQ ID NO:2的hVISTA ECD,在以下氨基酸的一个或多个处具有取代的hVISTA-ECD具有降低的结合:T35、Y37、K38、T39、Y41、R54、T61、F62、Q63、L65、H66、L67、H68、H69、F97、L115、V117、I119、H121、H122、S124、E125、R127；

[1033] -与P1-061029、P1-068761、P1-068767和/或P1-061015交叉竞争与hVISTA的结合；

[1034] -在酸性pH(例如pH 6.0或pH 6.5)下抑制hVISTA与人T细胞的结合；

[1035] -在酸性pH(例如pH 6.0或pH 6.5)下抑制hVISTA与PSGL-1的结合；

[1036] -在食蟹猴中的平均停留时间为至少350小时；

[1037] -刺激T细胞激活；

[1038] -抑制VISTA介导的细胞:细胞粘附;以及

[1039] -与人肿瘤细胞的样品或发炎的人组织的样品中的hVISTA特异性地结合。

[1040] 示例性抗体恒定区

[1041] 在一些实施方案中,本文所述的抗体包含一个或多个人恒定区。在一些实施方案中,人重链恒定区具有选自IgA、IgG和IgD的同种型。在一些实施方案中,人轻链恒定区具有选自κ和λ的同种型。在一些实施方案中,本文所述的抗体包含人IgG恒定区,如IgG1、IgG2、IgG3或IgG4。在一些实施方案中,本文所述的抗体包含人IgG4重链恒定区。在一些此类实施方案中,本文所述的抗体在人IgG4恒定区中包含S241P突变。在一些实施方案中,本文所述的抗体包含人IgG4恒定区和人κ轻链。

[1042] 重链恒定区的选择可以决定抗体在体内是否具有效应子功能。在一些实施方案中,此类效应子功能包括抗体依赖性细胞介导的细胞毒性(ADCC)和/或补体依赖性细胞毒性(CDC),并且可以导致与抗体结合的细胞被杀死。在一些治疗方法(包括治疗一些癌症的方法)中,例如当抗体与支持肿瘤维持或生长的细胞结合时,可能需要细胞杀死。可以支持肿瘤维持或生长的示例性细胞包括但不限于肿瘤细胞本身、帮助血管募集至肿瘤的细胞以及提供支持或促进肿瘤生长或肿瘤存活的配体、生长因子或反受体的细胞。在一些实施方案中,当需要效应子功能时,选择包含人IgG1重链或人IgG3重链的抗体。

[1043] 在某些实施方案中,改变本文提供的抗体以增加或减少抗体被糖基化的程度。通过改变氨基酸序列可以方便地完成糖基化位点在抗体中的添加或缺失,使得产生或去除一个或多个糖基化位点。

[1044] 当抗体包含F区域时,与其附接的碳水化合物可以被改变。哺乳动物细胞产生的天然抗体通常包含支链、双角寡糖,其通常通过N键附接至Fc区域的CH2结构域的Asn297。参见例如Wright等人TIBTECH 15:26-32(1997)。寡糖可以包括各种碳水化合物,例如甘露糖、N-

乙酰基葡糖胺(GlcNAc)、半乳糖和唾液酸以及附接至双角寡糖结构的“茎”中GlcNAc的岩藻糖。在一些实施方案中,可以对本发明的抗体中的寡糖进行修饰以产生具有某些改善的特性的抗体。例如,在一些实施方案中,可以例如通过使通常用含岩藻糖的糖基化作用进行糖基化的残基如Asn297突变,或通过其他方式来对抗体进行去岩藻糖基化。在一些实施方案中,本文的抗体可以包含去岩藻糖基化的人IgG1恒定区。

[1045] 抗体进一步提供有二等分的寡糖,例如其中附接至抗体的Fc区域的双角寡糖被GlcNAc二等分。此类抗体可以具有降低的岩藻糖基化和/或改善的ADCC功能。此类抗体的例子描述在例如WO 2003/011878(Jean-Mairet等人)、美国专利号6,602,684(Umana等人)和US 2005/0123546(Umana等人)中。还提供了寡糖中至少一个半乳糖残基附接至Fc区域的抗体。此类抗体可以具有改善的CDC功能。此类抗体描述在例如WO 1997/30087(Patel等人)、WO1998/58964(Raju,S.)和WO 1999/22764(Raju,S.)中。

[1046] 还提供了具有氨基末端前导序列延伸的抗体。例如,氨基末端前导序列的一个或多个氨基酸残基存在于抗体的任何一个或多个重链或轻链的氨基末端。示例性的氨基末端前导序列延伸包含存在于抗体的一个或两个轻链上的三个氨基酸残基VHS或由其组成。

[1047] 人FcRn高亲和力结合多肽的体内或血清半衰期可以例如在被给予了具有变体Fc区域的多肽的转基因小鼠、人或非人灵长类动物中进行测定。还参见例如Petkova等人International Immunology 18(12):1759-1769(2006)。

[1048] 在本发明的一些实施方案中,去岩藻糖基化抗体在人效应细胞的存在下比包含岩藻糖的亲本抗体更有效地介导ADCC。通常,ADCC活性可以使用本文公开的体外ADCC测定来测定,但是考虑了用于例如在动物模型等中测定ADCC活性的其他测定或方法。

[1049] 在某些实施方案中,通过用不同的氨基酸残基替代至少一个氨基酸残基来改变Fc区域,以改变抗体的一个或多个效应子功能。例如,可以用不同的氨基酸残基替代选自氨基酸残基234、235、236、237、297、318、320、322、330和/或331的一个或多个氨基酸,使得抗体对效应配体具有改变的亲和力,但保留亲本抗体的抗原结合能力。改变对其亲和力的效应配体可以是例如Fc受体或补体的C1组分。此方法的进一步细节描述在美国专利号5,624,821和5,648,260中,二者均出自Winter等人。

[1050] 在一些例子中,可以用不同的氨基酸残基替代选自氨基酸残基329、331和322的一个或多个氨基酸,使得抗体具有改变的C1q结合和/或降低或消除的补体依赖性细胞毒性(CDC)。此方法的进一步细节描述在Idusogie等人的美国专利号6,194,551中。

[1051] 在一些例子中,改变氨基酸位置231和239内的一个或多个氨基酸残基,从而改变抗体固定补体的能力。此方法进一步描述在Bodmer等人的PCT公开案WO 94/29351中。在一些例子中,可以修饰以下位置处的一个或多个氨基酸来修饰Fc区域以减小抗体依赖性细胞毒性(ADCC)和/或减小对Fcγ受体的亲和力:234、235、236、238、239、240、241、243、244、245、247、248、249、252、254、255、256、258、262、263、264、265、267、268、269、270、272、276、278、280、283、285、286、289、290、292、293、294、295、296、298、299、301、303、305、307、309、312、313、315、320、322、324、325、326、327、329、330、331、332、333、334、335、337、338、340、360、373、376、378、382、388、389、398、414、416、419、430、433、434、435、436、437、438或439。示例性取代包括236A、239D、239E、268D、267E、268E、268F、324T、332D和332E。示例性变体包括239D/332E、236A/332E、236A/239D/332E、268F/324T、267E/268F、267E/324T和267E/

268F7324T。可以对Fc进行的其他Fc修饰是用于降低或消除与Fcγ R和/或补体蛋白的结合，从而降低或消除Fc介导的效应子功能(如ADCC、ADCP和CDC)的那些修饰。示例性修饰包括但不限于在位置234、235、236、237、267、269、325、328、330和/或331(例如330和331)处的取代、插入和缺失，其中编号是根据EU索引。示例性取代包括但不限于234A、235E、236R、237A、267R、269R、325L、328R、330S和331S(例如330S和331S)，其中编号是根据EU索引。Fc变体可以包含236R/328R。用于降低Fcγ R和补体相互作用的其他修饰包括取代297A、234A、235A、237A、318A、228P、236E、268Q、309L、330S、331S、220S、226S、229S、238S、233P和234V，以及通过突变或酶促方式或通过在不对蛋白质进行糖基化的生物(如细菌)中生产来去除位置297处的糖基化。这些和其他修饰综述于Strohl，2009，Current Opinion in Biotechnology 20:685-691中。例如，人IgG1.3 Fc恒定区含有L234A、L235E和G237A取代。IgG1fa.P238K(或IgG1.P238K)含有P238K取代。IgG1.1f包含L234A、L235E、G237A、A330S和P331S取代。

[1052] 也可以使用能增强对抑制性受体Fcγ RIIb的亲和力的Fc变体。此类变体可以提供具有与Fcγ RIIb细胞(包括例如B细胞和单核细胞)有关的免疫调节活性的Fc融合蛋白。在一个实施方案中，相对于一种或多种激活受体，Fc变体提供对Fcγ RIIb的选择性增强的亲和力。用于改变与Fcγ RIIb的结合的修饰包括在选自234、235、236、237、239、266、267、268、325、326、327、328、330、331和332(根据EU索引)的位置处的一个或多个修饰。用于增强Fcγ Rllb亲和力的示例性取代包括但不限于234A、234D、234E、234F、234W、235D、235E、235F、235R、235Y、236D、236N、237A、237D、237N、239D、239E、266M、267D、267E、268D、268E、327D、327E、328F、328W、328Y、330S、331S和332E。示例性取代包括235Y、236D、239D、266M、267E、268D、268E、328F、328W和328Y。用于增强与Fcγ RIIb结合的其他Fc变体包括235Y/267E、236D/267E、239D/268D、239D/267E、267E/268D、267E/268E和267E/328F。

[1053] 用于增强Fcγ R与补体相互作用的其他修饰包括但不限于取代298A、333A、334A、326A、2471、339D、339Q、280H、290S、298D、298V、243L、292P、300L、396L、3051和396L。这些和其他修饰综述于Strohl，2009，Current Opinion in Biotechnology 20:685-691中。增加与Fcγ 受体结合的Fc修饰包括氨基酸位置238、239、248、249、252、254、255、256、258、265、267、268、269、270、272、279、280、283、285、298、289、290、292、293、294、295、296、298、301、303、305、307、312、315、324、327、329、330、335、337、338、340、360、373、376、379、382、388、389、398、414、416、419、430、434、435、437、438或439中的任何一个或多个处的氨基酸修饰，其中Fc区域中的残基编号是如专利公开号WO 00/42072中的EU索引的编号。

[1054] 任选地，Fc区域可以包含本领域技术人员已知的另外和/或替代位置处的非天然存在的氨基酸残基(参见例如美国专利号5,624,821;6,277,375;6,737,056;6,194,551;7,317,091;8,101,720;PCX专利公开WO 00/42072;WO 01/58957;WO 02/06919;WO 04/016750;WO 04/029207;WO 04/035752;WO 04/074455;WO 04/099249;WO 04/063351;WO 05/070963;WO05/040217、WO 05/092925和WO 06/0201 14)。

[1055] Fc区域与其配体的亲和力和结合特性可以通过本领域已知的多种体外测定方法(基于生物化学或免疫学的测定)来测定，所述体外测定方法包括但不限于平衡方法(例如，酶联免疫吸附测定(ELISA)或放射免疫测定(RIA))或动力学(例如BIACORE分析)以及其他方法，如间接结合测定、竞争抑制测定、荧光共振能量转移(FRET)、凝胶电泳和色谱法(例如凝胶过滤)。这些和其他方法可以在一种或多种被检查的组分上使用标记和/或采用多种检

测方法,包括但不限于发色、荧光、发光或同位素标记。结合亲和力和动力学的具体描述可以发现于Paul,W.E.编,Fundamental immunology,第4版,Lippincott-Raven,Philadelphia(1999)中,其聚焦于抗体-免疫原相互作用。

[1056] 在某些实施方案中,修饰抗体以增加其生物半衰期。可进行多种方法。例如,这可以通过增加Fc区域对FcRn的结合亲和力来完成。例如,可以使以下残基中的一个或多个突变:252、254、256、433、435、436,如美国专利号6,277,375中所述。特定的示例性取代包括以下中的一个或多个:T252L、T254S和/或T256F。可替代地,为了增加生物半衰期,可以在CH1或CL区域内改变抗体以含有取自IgG的Fc区域的CH2结构域的两个环的救助受体结合表位,如在Presta等人的美国专利号5,869,046和6,121,022中所述的。增加与FcRn的结合和/或改善药代动力学特性的其他示例性变体包括在位置259、308、428和434处的取代,包括例如2591、308F、428L、428M、434S、43411、434F、434Y和434X1。增加Fc与FcRn结合的其他变体包括:250E、250Q、428L、428F、250Q/428L(Hinton等人2004,J.Biol.Chem.279(8):6213-6216,Hinton等人2006Journal of Immunology 176:346-356)、256A、272A、286A、305A、307A、307Q、31 1A、312A、376A、378Q、380A、382A、434A(Shields等人,Journal of Biological Chemistry,2001,276(9):6591-6604)、252F、252T、252Y、252W、254T、256S、256R、256Q、256E、256D、256T、309P、31 1S、433R、433S、4331、433P、433Q、434H、434F、434Y、252Y/254T/256E、433K/434F/436H、308T/309P/311S(Dall Acqua等人Journal of Immunology,2002,169:5171-5180,Dall'Acqua等人,2006,Journal of Biological Chemistry281:23514-23524)。用于调节FcRn结合的其他修饰描述于Yeung等人,2010,J Immunol,182:7663-7671中。

[1057] 在某些实施方案中,可以使用具有特定生物学特征的杂交IgG同种型。例如,可以通过用两个同种型不同的位置处的来自IgG3的氨基酸取代CH2和/或CH3区域中的IgG1位置来构建IgG1/IgG3杂交变体。因此,可以构建包含一个或多个取代(例如274Q、276K、300F、339T、356E、358M、384S、392N、397M、4221、435R和436F)的杂交变体IgG抗体。在本文所述的一些实施方案中,可以通过用两个同种型不同的位置处的来自IgG1的氨基酸取代CH2和/或CH3区域中的IgG2位置来构建IgG1/IgG2杂交变体。因此,可以构建包含一个或多个取代,例如以下氨基酸取代中的一个或多个的杂交变体IgG抗体:233E、234L、235L、-236G(指在位置236处插入甘氨酸)和327A。

[1058] 此外,已经在人IgG1上绘制了Fcγ RI、Fcγ RII、Fcγ RIII和FcRn的结合位点,并且已经描述了具有改善的结合的变体(参见Shields,R.L.等人(2001)J.Biol.Chem.276:6591-6604)。显示了位置256、290、298、333、334和339处的特定突变以改善与Fcγ RIII的结合。另外,显示了以下组合突变体以改善Fcγ RIII结合:T256A/S298A、S298A/E333A、S298A/K224A和S298A/E333A/K334A,所述组合突变体已显示出展现增强的Fcγ RIIIa结合和ADCC活性(Shields等人,2001)。已鉴定了与Fcγ RIIIa的结合增强的其他IgG1变体,包括具有S239D/I332E和S239D/I332E/A330L突变的变体,所述变体在食蟹猴中显示出对Fcγ RIIIa的亲和力的最大增加、Fcγ RIIb结合的减少和强细胞毒性活性(Lazar等人,2006)。将三重突变引入抗体,如阿仑单抗(CD52特异性)、曲妥珠单抗(HER2/neu特异性)、利妥昔单抗(CD20特异性)和西妥昔单抗(EGFR特异性)中转化为极大增强的体外ADCC活性,并且S239D/I332E变体显示出增强的耗减猴的B细胞的能力(Lazar等人,2006)。此外,已鉴定了含有

L235V、F243L、R292P、Y300L和P396L突变的IgG1突变体,其在B细胞恶性肿瘤和乳腺癌的模型中的表达人Fc γ RIIIa的转基因小鼠中展现出与Fc γ RIIIa增强的结合和随之增强的ADCC活性(Stavenhagen等人,2007;Nordstrom等人,2011)。可使用的其他Fc突变体包括:S298A/E333A/L334A、S239D/I332E、S239D/I332E/A330L、L235V/F243L/R292P/Y300L/P396L和M428L/N434S。

[1059] 在某些实施方案中,选择具有与Fc γ R的降低的结合的Fc。具有降低的Fc γ R结合的示例性Fc(例如IgG1 Fc)包含以下三个氨基酸取代:L234A、L235E和G237A。

[1060] 在某些实施方案中,选择具有降低的补体结合的Fc。具有降低的补体结合的示例性Fc(例如IgG1 Fc)具有以下两个氨基酸取代:A330S和P331S。

[1061] 在某些实施方案中,选择具有基本无效应子功能的Fc,即其具有与Fc γ R的降低的结合和降低的补体固定。无效应子的示例性Fc(例如IgG1 Fc)包含以下五个突变:L234A、L235E、G237A、A330S和P331S。

[1062] 当使用IgG4恒定结构域时,它可以包含取代S228P,其模仿IgG1中的铰链序列,从而稳定IgG4分子。

[1063] 也可以使用在WO 2017/087678或WO 2016081746中描述的Fc修饰。

[1064] 在某些实施方案中,修饰抗体的糖基化。例如,可以制备去糖基化的抗体(即,抗体缺乏糖基化)。可以改变糖基化以例如增加抗体对抗原的亲和力。此类碳水化合物修饰可以通过例如改变抗体序列内的糖基化的一个或多个位点来实现。例如,可以进行一个或多个氨基酸取代,其导致消除一个或多个可变区框架糖基化位点,从而消除该位点的糖基化。此类去糖基化可以增加抗体对抗原的亲和力。这种方法的进一步细节描述于Co等人的美国专利号5,714,350和6,350,861中。

[1065] 通过将N297残基突变为另一个残基(例如N297A)和/或通过使相邻氨基酸(例如298)突变从而降低N297上的糖基化,可以防止恒定区在N297上的糖基化。

[1066] 另外地或可替代地,可以制备具有改变的糖基化类型的抗体,如具有减少量的岩藻糖基残基的低岩藻糖基化抗体或具有增加的二等分GlcNac结构的抗体。已经证明此类改变的糖基化模式增加抗体的ADCC能力。此类碳水化合物修饰可以通过例如在具有改变的糖基化机制的宿主细胞中表达抗体来实现。本领域已经描述了具有改变的糖基化机制的细胞,并且可以将其用作表达本文所述重组抗体的宿主细胞,从而产生具有改变的糖基化的抗体。例如,Hanai等人的EP 1,176,195描述了具有功能上破坏的编码岩藻糖基转移酶的FUT8基因的细胞系,使得在这种细胞系中表达的抗体展现出低岩藻糖基化。Presta的PCT公开案WO 03/035835描述了变体CHO细胞系Led 3细胞,其具有降低的将岩藻糖附接至Asn(297)连接的碳水化合物的能力,还导致了在该宿主细胞中表达的抗体的低岩藻糖基化(还参见Shields,R.L.等人(2002)J.Biol.Chem.277:26733-26740)。Umana等人的PCT公开案WO99/54342描述了如下细胞系,其被工程化为表达修饰糖蛋白的糖基转移酶(例如,β(1,4)-N乙酰基葡糖胺转移酶III(GnTIII)),使得在工程化细胞系中表达的抗体展现出增加的二等分GlcNac结构,这导致抗体的ADCC活性增加(还参见Umana等人(1999)Nat.Biotech.17:176-180)。

[1067] 本文所述抗体的另一种修饰是聚乙二醇化。可以将抗体聚乙二醇化以例如增加抗体的生物(例如血清)半衰期。为了将抗体聚乙二醇化,通常在一个或多个PEG基团附接至抗

体或抗体片段的条件下,使抗体或其片段与聚乙二醇(PEG)(如PEG的反应性酯或醛衍生物)反应。在一些实施方案中,经由与反应性PEG分子(或类似的反应性水溶性聚合物)的酰化反应或烷基化反应进行聚乙二醇化。如本文所用,术语"聚乙二醇"旨在涵盖已经用于衍生化其他蛋白质的任何形式的PEG,如单(C1-C10)烷氧基-或芳氧基-聚乙二醇或聚乙二醇-马来酰亚胺。在某些实施方案中,待聚乙二醇化的抗体是去糖基化的抗体。聚乙二醇化蛋白质的方法是本领域已知的,并且可以应用于本文所述的抗体。参见例如Nishimura等人的EP 0 154 316和Ishikawa等人的EP 0 401 384。

[1068] 核酸和宿主细胞

[1069] 还提供了编码抗体或其重链或轻链或其一部分的核酸。序列表中提供了示例性核酸。本文涵盖了与序列表中的核酸至少80%、85%、90%、95%、97%、98%或99%相同的任何核酸。还涵盖了包含编码本文提供的抗体的核酸的组合物,以及包含这些的细胞和用于制备抗体的方法,其包括培养用编码抗VISTA抗体的核酸转化的细胞和从培养基或细胞分离抗体。

[1070] 使用结合VISTA-ECD的Ab和相关药物组合物的治疗方法

[1071] 在某些实施方案中,在低pH下与VISTA结合并且例如在中性或生理pH下缺乏显著结合的抗VISTA抗体可以是VISTA拮抗剂抗体,即抑制VISTA的作用从而刺激免疫应答的抗体。此类抗体可以用于治疗需要刺激免疫系统或免疫应答的疾病,例如增殖性疾病(良性或恶性)、癌症和感染性疾病(例如病毒感染)。

[1072] 在某些实施方案中,在低pH下与VISTA结合并且例如在中性或生理pH下缺乏显著结合的抗VISTA抗体可以是VISTA激动剂抗体,即增加VISTA的作用从而抑制免疫应答的抗体。此类抗体可以用于治疗需要抑制免疫系统或免疫应答的疾病,如自身免疫病和炎性疾病,如类风湿性关节炎、系统性红斑狼疮、乳糜泻、舍格伦综合征(Sjoigren's syndrome)、格雷夫斯病(Grave's disease)、炎性肠病、银屑病、强直性脊柱炎、移植物抗宿主病、过敏和哮喘。

[1073] 本文所述的抗体可以用于例如治疗癌症。在一些实施方案中,提供了治疗癌症的方法,其包括向患者给予有效量的本文所述的抗体。在一些实施方案中,Ab可以触发或增强患者的免疫应答,如抗原特异性免疫应答。在一些实施方案中,Ab可以刺激T细胞活性。在一些实施方案中,Ab可以抑制患者中至少一种肿瘤的生长。

[1074] 本文提供了治疗患有癌症的受试者的方法,其包括向所述受试者给予治疗有效量的本文所述的抗VISTA抗体,从而治疗所述受试者。抗VISTA抗体可以单独使用。可替代地,抗VISTA抗体可以与另一种药剂一起使用,如下文进一步所述。

[1075] 可以使用如本文所述在酸性条件下与VISTA-ECD蛋白特异性地结合的Ab治疗的癌症的例子包括但不限于癌、淋巴瘤、母细胞瘤、肉瘤和白血病。可以使用本文所述的Ab治疗的癌症还包括通常对免疫疗法有反应的癌症和通常对免疫疗法无反应的那些癌症。可以治疗的癌症还包括VISTA阳性癌症,例如具有VISTA阳性肿瘤浸润细胞(例如淋巴细胞、骨髓或单核细胞)的癌症。癌症可以是具有实体瘤或血液恶性肿瘤(液体肿瘤)的癌症。

[1076] 用于治疗的癌症的非限制性例子包括鳞状细胞癌、小细胞肺癌、非小细胞肺癌、鳞状非小细胞肺癌(NSCLC)、非鳞状NSCLC、神经胶质瘤、胃肠道癌、肾癌(例如透明细胞癌)、卵巢癌、肝癌、结直肠癌、子宫内膜癌、肾癌(例如肾细胞癌(RCC))、前列腺癌(例如激素难治性

前列腺腺癌)、甲状腺癌、神经母细胞瘤、胰腺癌、胶质母细胞瘤(多形性胶质母细胞瘤)、宫颈癌、胃癌、膀胱癌、肝细胞瘤、乳腺癌、结肠癌和头颈癌(或癌)、胃癌、生殖细胞瘤、小儿肉瘤、鼻窦自然杀伤、黑色素瘤(例如转移性恶性黑色素瘤,如皮肤或眼内恶性黑色素瘤)、骨癌、皮肤癌、子宫癌、肛门区域癌、睾丸癌、输卵管癌、子宫内膜癌、子宫颈癌、阴道癌、外阴癌、食道癌、小肠癌、内分泌系统癌、甲状旁腺癌、肾上腺癌、软组织肉瘤、尿道癌、阴茎癌、儿童实体瘤、输尿管癌、肾盂癌、中枢神经系统(CNS)肿瘤、原发性中枢神经系统淋巴瘤、肿瘤血管生成、脊柱肿瘤、脑癌、脑干神经胶质瘤、垂体腺瘤、卡波西肉瘤(Kaposi's sarcoma)、表皮样癌、鳞状细胞癌、T细胞淋巴瘤、环境诱导的癌症(包括石棉诱导的那些癌症)、病毒相关的癌症或病毒起源的癌症(例如人乳头瘤病毒(HPV相关或起源的肿瘤))以及源自两种主要血细胞系(即髓样细胞系(其产生粒细胞、红细胞、血小板、巨噬细胞和肥大细胞)或淋巴细胞系(其产生B、T、NK和浆细胞))中任一种的恶性血液病(例如所有类型的白血病、淋巴瘤和骨髓瘤,例如急性、慢性、淋巴细胞性和/或骨髓性白血病,如急性白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞性白血病(CLL)和慢性骨髓性白血病(CML)、未分化AML(MO)、粒细胞性白血病(M1)、粒细胞性白血病(M2;伴随细胞成熟)、早幼粒细胞白血病(M3或M3变体[M3V])、骨髓单核细胞性白血病(M4或M4变体伴随嗜酸性粒细胞增多症[M4E])、单核细胞性白血病(M5)、红白血病(M6)、巨核细胞白血病(M7)、孤立的粒细胞肉瘤和绿色瘤);淋巴瘤,如霍奇金淋巴瘤(HL)、非霍奇金淋巴瘤(NHL)、B细胞血液恶性肿瘤(例如B细胞淋巴瘤)、T细胞淋巴瘤、淋巴浆细胞样淋巴瘤、单核细胞B细胞淋巴瘤、粘膜相关淋巴组织(MALT)淋巴瘤、间变性(例如Ki 1+)大细胞淋巴瘤、成人T细胞淋巴瘤/白血病、套细胞淋巴瘤、血管免疫原性T细胞淋巴瘤、血管中心性淋巴瘤、肠T细胞淋巴瘤、原发性纵隔B细胞淋巴瘤、前体T淋巴细胞淋巴瘤、T淋巴细胞;和淋巴瘤/白血病(T-Lbly/T-ALL)、外周T细胞淋巴瘤、淋巴母细胞淋巴瘤、移植后淋巴细胞增殖性疾病、真性组织细胞淋巴瘤、原发中枢性系统淋巴瘤、原发渗出性淋巴瘤、B细胞淋巴瘤、淋巴母细胞淋巴瘤LBL)、造血淋巴系肿瘤、急性淋巴细胞白血病、弥漫性大B细胞淋巴瘤、伯基特淋巴瘤(Burkitt's lymphoma)、滤泡性淋巴瘤、弥散组织细胞淋巴瘤(DHL)、免疫母细胞性大细胞淋巴瘤、前体B淋巴细胞性淋巴瘤、皮肤T细胞淋巴瘤(CTLC)(也称为蕈样真菌病或塞扎综合征(Sezary syndrome))以及伴随沃尔登斯特伦巨球蛋白血症(Waldenstrom's macroglobulinemia)的淋巴浆细胞样淋巴瘤(LPL);骨髓瘤,如IgG骨髓瘤、轻链骨髓瘤、非分泌性骨髓瘤、阴燃骨髓瘤(也称为惰性骨髓瘤)、孤立性浆细胞瘤和多发性骨髓瘤、慢性淋巴细胞性白血病(CLL)、毛细胞淋巴瘤;骨髓系造血肿瘤、间质性起源的肿瘤(包括纤维肉瘤和横纹肌肉瘤);精原细胞瘤、畸胎瘤、中枢神经和外周神经肿瘤(包括星形细胞瘤、神经鞘瘤);间质起源的肿瘤(包括纤维肉瘤、横纹肌瘤和骨肉瘤);以及其他肿瘤,包括黑色素瘤、着色性干皮病、角化棘皮瘤、精原细胞瘤、甲状腺滤泡癌和畸胎癌、淋巴系造血肿瘤(例如T细胞和B细胞肿瘤,包括但不限于T细胞障碍,如T前淋巴细胞性白血病(T-PLL)(包括小细胞和脑细胞类型的));T细胞类型的大颗粒淋巴细胞白血病(LGL);a/d T-NHL肝脾淋巴瘤;外周/胸腺后T细胞淋巴瘤(多形和免疫母细胞亚型);血管中心(鼻)T细胞淋巴瘤;头或颈癌、肾癌、直肠癌、甲状腺癌;急性骨髓淋巴瘤以及所述癌症的任何组合。本文所述的方法还可以用于治疗转移性癌症、不可切除的、难治性癌症(例如免疫疗法(例如使用阻断性CTLA-4或PD-1抗体)难治的癌症)和/或复发性癌症。

[1077] 在一些实施方案中,提供了治疗癌症的方法,其中所述方法包括向患有癌症的受

试者给予如本文所述的在酸性条件下与huVISTA特异性地结合的分离的抗体。在一些实施方案中,提供了本文所述的抗体用于治疗癌症的用途。

[1078] 在某些实施方案中,将本文所述的抗体给予至患有已经展现出对先前治疗(例如使用免疫肿瘤学或免疫疗法药物的先前治疗)不充分反应或在先前治疗的基础上进展的癌症的患者。在一些实施方案中,癌症对先前治疗是难治性的或耐药性的,即内在难治性或耐药性的(例如,对PD-1途径拮抗剂的难治性的)或者获得的耐药性或难治性状态。例如,本文所述的抗体可以单独或与另一种疗法(例如与抗PD-1途径的拮抗剂治疗)组合给予至对第一疗法没有反应或没有充分反应的受试者或在治疗(例如抗PD-1途径拮抗剂治疗)后具有疾病进展的受试者。在其他实施方案中,将本文所述的抗体给予至先前未接受(即未用其治疗)免疫肿瘤学药剂(例如PD-1途径拮抗剂)的患者。

[1079] 在某些实施方案中,治疗受试者中的癌症的方法包括首先测定受试者中肿瘤的肿瘤突变负荷(TMB),并基于结果向例如发现患有高TMB的受试者给予抗VISTA抗体。

[1080] 与免疫刺激剂组合

[1081] 在一些实施方案中,将本文所述的抗体(例如本文所述的拮抗剂VISTA抗体)与至少一种免疫刺激剂组合给予。例如,所述治疗剂可以一起输注或大致同时输注。在一些实施方案中,所述抗体和所述至少一种免疫刺激剂是顺序地给予。例如,在一些实施方案中,所述抗体在至少一种免疫刺激剂之前或之后顺序地给予,使得这两种治疗剂的给予相隔30分钟、60分钟、90分钟、120分钟、3小时、6小时、12小时、24小时、36小时、48小时、3天、5天、7天或两周。

[1082] 在一些实施方案中,在给予至少一种免疫刺激剂之前给予至少一个、至少两个、至少三个剂量、至少五个剂量或至少十个剂量的所述抗体。在一些实施方案中,在给予所述抗体之前给予至少一个、至少两个、至少三个剂量、至少五个剂量或至少十个剂量的至少一种免疫刺激剂。在一些实施方案中,在所述抗体的第一剂量之前至少一天、两天、三天、五天或十天,或一周、两周、三周、五周、十二周或二十四周时给予免疫刺激剂的最后一个剂量。在一些实施方案中,在至少一种免疫刺激剂的第一剂量之前至少一天、两天、三天、五天或十天,或一周、两周、三周、五周、十二周或二十四周时给予所述抗体的最后一个剂量。在一些实施方案中,受试者已经接受或正在接受至少一种免疫刺激剂的疗法,并且将结合VISTA-ECD的抗体添加到治疗方案中。

[1083] 在一些实施方案中,所述至少一种免疫刺激剂包含T细胞激活的抑制剂的拮抗剂,而在一些实施方案中,所述至少一种免疫刺激剂包含T细胞激活的刺激剂的激动剂。在一些实施方案中,所述至少一种免疫刺激剂包含CTLA4、LAG-3、PD-1、PD-L1、半乳糖凝集素1、半乳糖凝集素9、CEACAM-1、BTLA、CD25、CD69、TIGIT、CD113、GPR56、VISTA、B7-H3、B7-H4、2B4、CD48、GARP、PD1H、LAIR1、TIM1、TIM3、TIM4、ILT4、IL-6、IL-10、TGFβ、VEGF、KIR、LAG-3、腺苷A2A受体、PI3Kδ或IDO的拮抗剂。在一些实施方案中,所述至少一种免疫刺激剂包含B7-1、B7-2、CD28、4-1BB(CD137)、4-1BBL、ICOS、ICOS-L、OX40、OX40L、GITR、GITRL、CD27、CD40、CD40L、DR3、CD28H、IL-2、IL-7、IL-12、IL-15、IL-21、IFNα、STING的激动剂或Toll样受体激动剂(如TLR2/4激动剂)。在一些实施方案中,所述至少一种免疫刺激剂包含与膜结合的蛋白的B7家族的另一个成员(如B7-1、B7-2、B7-H2(ICOS-L)、B7-H3、B7-H4和B7-H6)结合的药剂。在一些实施方案中,所述至少一种免疫刺激剂包含如下药剂,所述药剂与TNF受体家族

的成员或与TNF受体家族的成员(如CD40、CD40L、OX40、OX40L、GITR、GITRL、CD70、CD27L、CD30、CD30L、4-1BBL、CD137(4-1BB)、TRAIL/Apo2-L、TRAILR1/DR4、TRAILR2/DR5、TRAILR3、TRAILR4、OPG、RANK、RANKL、TWEAKR/Fn14、TWEAK、BAFFR、EDAR、XEDAR、EDA1、EDA2、TACI、APRIL、BCMA、LTβR、LIGHT、DeR3、HVEM、VEGL/TL1A、TRAMP/DR3、TNFR1、TNFβ、TNFR2、TNFα、1β2、FAS、FASL、RELT、DR6、TROY或NGFβ)结合的共刺激或共抑制分子结合。在一些实施方案中,所述至少一种免疫刺激剂包含拮抗或抑制细胞因子(如IL-6、IL-10、TGFβ、VEGF)的药剂,所述细胞因子抑制T细胞激活。在一些实施方案中,所述至少一种免疫刺激剂包含刺激T细胞激活的细胞因子(如IL-2、IL-7、IL-12、IL-15、IL-21和IFNα)的激动剂。在一些实施方案中,所述至少一种免疫刺激剂包含趋化因子(如CXCR2、CXCR4、CCR2或CCR4)的拮抗剂。在一些实施方案中,所述至少一种免疫刺激剂包含抗体。在一些实施方案中,所述至少一种免疫刺激剂可以包含疫苗,如靶向间皮素的疫苗或减毒的李斯特菌属癌症疫苗(如CRS-207)。

[1084] 例如,本文所述的抗VISTA抗体可以与以下药剂中的一种或多种一起给予:

[1085] (1)抑制T细胞激活的蛋白质(例如免疫检查点抑制剂)如CTLA-4、PD-1、PD-L1、PD-L2和LAG-3、半乳糖凝集素9、CEACAM-1、BTLA、CD69、半乳糖凝集素1、TIGIT、CD113、GPR56、B7-H3、B7-H4、2B4、CD48、GARP、PD1H、LAIR1、TIM-1、TIM-3和TIM-4的拮抗剂(抑制剂或阻断剂);和/或(2)刺激T细胞激活的蛋白质如B7-1、B7-2、CD28、4-1BB(CD137)、4-1BBL、GITR、ICOS、ICOS-L、OX40、OX40L、CD70、CD27、CD40、DR3和CD28H的激动剂。

[1086] 可以与本文所述的抗VISTA抗体组合用于治疗癌症的示例性药剂包括:Yervoy®(伊匹木单抗)或曲美利木单抗(抗CTLA-4)、加利昔单抗(抗B7.1)、BMS-936558(抗PD-1)、MK-3475(抗PD-1)、阿特珠单抗(TECENTRIQ®)、阿维鲁单抗、度伐单抗、AMP224(抗B7DC)、BMS-936559(抗B7-H1)、MPDL3280A(抗B7-H1)、MEDI-570(抗ICOS)、AMG557(抗B7H2)、MGA271(抗B7H3)、IMP321(抗LAG-3)、BMS-663513(抗CD137)、PF-05082566(抗CD137)、CDX-1127(抗CD27)、抗OX40(Providence Health Services)、huMAbOX40L(抗OX40L)、阿塞西普(抗TACI)、CP-870893(抗CD40)、鲁卡妥木单抗(抗CD40)、达塞妥珠单抗(抗CD40)、莫罗单抗-CD3(抗CD3);抗GITR抗体MK4166、TRX518、Medi1873、INBRX-110、LK2-145、GWN-323、GITRL-Fc或其任何组合。

[1087] 可以与抗VISTA抗体组合用于治疗癌症的其他分子包括NK细胞上抑制性受体的拮抗剂或NK细胞上激活受体的激动剂,例如KIR的拮抗剂(例如利瑞鲁单抗)。

[1088] T细胞激活也可以通过可溶性细胞因子来调节。在一些实施方案中,抗VISTA抗体可以与旨在抑制T细胞激活的细胞因子拮抗剂或刺激T细胞激活的细胞因子激动剂组合给予。例如,抗VISTA抗体可与(i)抑制T细胞激活的IgSF家族或B7家族或TNF家族的蛋白质的拮抗剂(或抑制剂或阻断剂)或抑制T细胞激活的细胞因子(例如IL-6、IL-10、TGF-β、VEGF;“免疫抑制性细胞因子”)的拮抗剂和/或(ii)刺激T细胞激活的IgSF家族、B7家族或TNF家族的刺激受体或细胞因子的激动剂。

[1089] 用于组合疗法的又其他药剂包括抑制或耗减巨噬细胞或单核细胞的药剂,其包括但不限于CSF-1R拮抗剂,如CSF-1R拮抗剂抗体,其包括RG7155(WO 11/70024、WO11/107553、WO 11/131407、WO 13/87699、WO 13/119716、WO 13/132044)或FPA-008(WO 11/140249;WO 13169264;WO 14/036357)。

[1090] 也可以将抗VISTA抗体与抑制TGF-β信号传导的药剂一起给予。

[1091] 可以与抗VISTA抗体组合的另外的药剂包括增强肿瘤抗原呈递的药剂(例如树突细胞疫苗,分泌GM-CSF的细胞疫苗,CpG寡核苷酸和咪喹莫特)或增强肿瘤细胞的免疫原性的疗法(例如蒽环类药物)。

[1092] 可以与抗VISTA抗体组合的又其他疗法包括耗减或阻断Treg细胞的疗法,例如与CD25特异性地结合的药剂。

[1093] 可以与抗VISTA抗体组合的另一种疗法是抑制代谢酶(如吲哚胺二氧合酶(IDO)、二氧合酶、精氨酸酶或一氧化氮合成酶)的疗法。

[1094] 可以与抗VISTA抗体一起使用的另一类药剂包括抑制腺苷形成(例如CD73抑制剂)或抑制腺苷A2A受体的药剂。

[1095] 可以与抗VISTA抗体组合用于治疗癌症的其他疗法包括逆转/预防T细胞无能或衰竭的疗法和在肿瘤部位触发先天性免疫激活和/或炎症的疗法。

[1096] 可以与抗VISTA抗体组合用于治疗癌症的其他疗法包括阻断IL-8的疗法,例如使用HuMax®-IL8。

[1097] 抗VISTA抗体可以与多于一种免疫肿瘤学药剂组合,并且可以例如与旨在靶向免疫途径的多种元件的组合方法结合,所述组合方法如以下的一种或多种:增强肿瘤抗原呈递的疗法(例如树突细胞疫苗、分泌GM-CSF的细胞疫苗、CpG寡核苷酸、咪喹莫特);抑制负免疫调节的疗法,例如通过抑制CTLA-4和/或PD1/PD-L1/PD-L2途径和/或耗减或阻断Treg或其他免疫抑制细胞;刺激阳性免疫调节的疗法,例如使用刺激CD-137、OX-40和/或CD40或GITR途径和/或刺激T细胞效应子功能的激动剂;全身性地增加抗肿瘤T细胞频率的疗法;耗减或抑制Treg(如肿瘤中的Treg)的疗法,例如使用CD25的拮抗剂(例如达克珠单抗)或通过离体抗CD25珠粒耗减;影响肿瘤中抑制性髓样细胞功能的疗法;增强肿瘤细胞的免疫原性的疗法(例如蒽环类抗生素);过继性T细胞或NK细胞转移,所述细胞包括基因修饰的细胞,例如通过嵌合抗原受体修饰的细胞(CAR-T疗法);抑制代谢酶(如吲哚胺二氧合酶(IDO)、二氧合酶、精氨酸酶或一氧化氮合成酶)的疗法;逆转/预防T细胞无能或衰竭的疗法;在肿瘤部位触发先天性免疫激活和/或炎症的疗法;给予免疫刺激细胞因子;或阻断免疫抑制细胞因子。

[1098] 本文所述的抗VISTA抗体可以与一种或多种连接阳性共刺激受体的激动剂、通过抑制性受体减弱信号传导的阻断剂、拮抗剂以及一种或多种全身性地增加抗肿瘤T细胞频率的药剂、克服肿瘤微环境中的不同免疫抑制途径(例如,阻断抑制性受体结合(例如,PD-L1/PD-1相互作用)、耗减或抑制Treg(例如,使用抗CD25单克隆抗体(例如达克珠单抗)或通过离体抗CD25珠粒耗减)、抑制代谢酶(如IDO)或逆转/预防T细胞无能或衰竭)的药剂和在肿瘤部位触发先天性免疫激活和/或炎症的药剂一起使用。

[1099] 在某些实施方案中,如果受试者为BRAF V600突变阳性,则将抗VISTA抗体与BRAF抑制剂一起给予至受试者。

[1100] 用于本文所述的组合疗法的PD-1拮抗剂包括但不限于配体、抗体(例如单克隆抗体和双特异性抗体)和多价药剂。在一个实施方案中,PD-1拮抗剂是融合蛋白,例如Fc融合蛋白(如AMP-244)。在一个实施方案中,PD-1拮抗剂是抗PD-1或抗PD-L1抗体。

[1101] 示例性的抗PD-1抗体是纳武单抗(BMS-936558)或包含WO 2006/121168中所述的

抗体17D8、2D3、4H1、5C4、7D3、5F4和4A11之一的CDR或可变区的抗体。在某些实施方案中,抗PD-1抗体是在WO 2012/145493中所述的MK-3475(Lambrolizumab);在WO 2012/145493中所述的AMP-514;或PDR001。其他已知的PD-1抗体和其他PD-1抑制剂包括WO 2009/014708、WO 03/099196、WO 2009/114335、WO 2011/066389、WO 2011/161699、WO2012/145493、美国专利号7,635,757和8,217,149以及美国专利公开号2009/0317368中所述的那些。也可以使用WO 2013/173223中披露的任何抗PD-1抗体。与这些抗体中的一种竞争结合和/或在PD-1上的与这些抗体中的一种相同的表位结合的抗PD-1抗体也可以用于组合治疗。

[1102] 在一些实施方案中,可用于组合治疗的抗PD-L1抗体是BMS-936559(在WO 2007/005874和美国专利号7,943,743中称为12A4)或包含描述于PCT公开案WO 07/005874和美国专利号7,943,743中的3G10、12A4、10A5、5F8、10H10、1B12、7H1、11E6、12B7和13G4的CDR或可变区的抗体。在某些实施方案中,抗PD-L1抗体是MEDI4736(也称为度伐单抗和抗B7-H1)、MPDL3280A(也称为阿特珠单抗和RG7446)、MSB0010718C(也称为阿维鲁单抗;WO2013/79174)或rHigM12B7。也可以使用在WO 2013/173223、WO2011/066389、WO 2012/145493、美国专利号7,635,757和8,217,149以及美国公开号2009/145493中披露的任何抗PD-L1抗体。与这些抗体中的任何一种竞争和/或与这些抗体中的任何一种的表位相同的表位结合的抗PD-L1抗体也可以用于组合治疗。

[1103] 在某些实施方案中,本公开文本的抗VISTA抗体可以与CTLA-4拮抗剂(例如抗CTLA-4抗体)一起使用。在一个实施方案中,抗CTLA-4抗体是选自以下的抗体:Yervoy® (伊匹木单抗或抗体10D1,描述在PCT公开案WO01/14424中)、曲美利木单抗(以前为替西木单抗(ticilimumab),CP-675,206)、单克隆抗体或在以下任何出版物中描述的抗CTLA-4抗体:WO 98/42752;WO 00/37504;美国专利号6,207,156;Hurwitz等人(1998)Pro.Natl.Acad.Sci.USA 95(17):10067-10071;Camacho等人(2004)J.Clin.Oncology 22(145):Abstract No.2505(antibody CP-675206);和Mokyr等人(1998)Cancer Res.58:5301-5304。也可以使用WO 2013/173223中披露的任何抗CTLA-4抗体。

[1104] 在一些实施方案中,本公开文本的抗VISTA抗体与LAG3拮抗剂组合使用。抗LAG3抗体的例子包括包含在美国专利公开号US 2011/0150892、WO10/19570和WO 2014/008218中描述的抗体25F7、26H10、25E3、8B7、11F2或17E5的CDR或可变区的抗体。在一个实施方案中,抗LAG-3抗体是BMS-986016。可以使用的其他本领域公认的抗LAG-3抗体包括US2011/007023、WO 08/132601和WO 09/44273中描述的IMP731和IMP-321。与这些抗体中的任何一种竞争和/或与这些抗体中的任何一种的表位相同的表位结合的抗LAG-3抗体也可以用于组合治疗。

[1105] 在一些实施方案中,本公开文本的抗VISTA抗体可以与CD137(4-1BB)激动剂(如激动性CD137抗体)组合给予。合适的CD137抗体包括例如乌瑞鲁单抗或PF-05082566(WO 12/32433)。

[1106] 在一些实施方案中,抗VISTA抗体可以与OX40激动剂(如激动性OX40抗体)组合给予。合适的OX40抗体包括例如MEDI-6383、MEDI-6469或MOXR0916(RG7888;WO 06/029879)。

[1107] 在一个实施方案中,将抗VISTA抗体与CD40激动剂(如激动性CD40抗体)组合给予。在某些实施方案中,免疫肿瘤学药剂是CD40拮抗剂(如拮抗性CD40抗体)。合适的CD40抗体包括例如鲁卡妥木单抗(HCD122)、达塞妥珠单抗(SGN-40)、CP-870,893或Chi Lob 7/4。

[1108] 在一个实施方案中,将抗VISTA抗体与CD27激动剂(如激动性CD27抗体)组合给予。合适的CD27抗体包括例如伐立鲁单抗(CDX-1127)。

[1109] 在某些实施方案中,将抗VISTA抗体与如例如WO 2006/105021中所述的抗GITR抗体(例如具有6C8的CDR序列的抗体,例如具有6C8的CDR的人源化抗体);包含WO2011/028683中所述的抗GITR抗体的CDR的抗体;包含JP2008278814中所述的抗GITR抗体的CDR的抗体、包含WO 2015/031667、WO 2015/187835、WO 2015/184099、WO 2016/054638、WO 2016/057841或WO 2016/057846中所述的抗GITR抗体或本文所述或提及的其他抗GITR抗体的CDR的抗体一起给予。

[1110] 在一些实施方案中,将抗VISTA抗体与MGA271(抗B7H3)(WO11/109400)组合给予。

[1111] 在一些实施方案中,将抗VISTA抗体与KIR拮抗剂(如利瑞鲁单抗)组合给予。

[1112] 在一些实施方案中,将抗VISTA抗体与IDO拮抗剂组合给予。合适的IDO拮抗剂包括例如INCB-024360(WO 2006/122150、WO 07/75598、WO08/36653、WO08/36642)、英多莫德(indoximod)、NLG-919(WO 09/73620、WO 09/1156652、WO 11/56652、WO 12/142237)或F001287。

[1113] 在一些实施方案中,将抗VISTA抗体与Toll样受体激动剂,例如TLR2/4激动剂(例如卡介苗);TLR7激动剂(例如Hiltonol或咪喹莫特);TLR7/8激动剂(例如雷西莫特);或TLR9激动剂(例如CpG7909)组合给予。

[1114] 在一个实施方案中,将抗VISTA与TGF-β抑制剂,例如GC1008、LY2157299、TEW7197或IMC-TR1组合给予。

[1115] 另外的组合疗法

[1116] 还可以在其他治疗方式之前、基本上同时或之后提供本文的Ab,所述其他治疗方式是例如外科手术、化学疗法、放射疗法或生物制剂如另一种治疗性抗体的给予。在一些实施方案中,癌症在选自手术、化学疗法和放射疗法或其组合的疗法之后复发或进展。例如,当存在微小转移的风险和/或为了降低复发风险时,本文所述的抗VISTA抗体可以作为辅助疗法给予。

[1117] 为了治疗癌症,可以将所述组合与一种或多种其他抗癌剂(如化学治疗剂、生长抑制剂、抗癌疫苗如基因疗法疫苗、抗血管生成剂和/或抗肿瘤组合物)一起给予。本文在“定义”下提供了可与本发明的抗体组合使用的化学治疗剂、生长抑制剂、抗癌疫苗、抗血管生成剂和抗肿瘤组合物的非限制性例子。

[1118] 在一些实施方案中,抗炎药(如类固醇或非类固醇抗炎药(NSAID))可以与所述组合一起给予。在需要与用本文所述的抗VISTA抗体治疗一起或在其之前使异常增殖细胞休眠的情况下,还可以向受试者给予激素和类固醇(包括合成类似物),如17a-乙炔雌二醇、己烯雌酚、睾酮、泼尼松、氟甲睾酮、丙酸甲雄烷酮、睾内酯、甲地孕酮、甲基泼尼松龙、甲基-睾酮、泼尼松龙、去炎松、氯烯雌醚、羟孕酮、氨鲁米特、雌莫司汀、甲孕酮、亮丙瑞林、氟他胺、托瑞米芬、ZOLADEX®。当采用本文所述的方法或组合物时,还可以根据需要给予在临床环境中用于调节肿瘤生长或转移的其他药剂,如抗模拟药。

[1119] 本文所述的抗体也可以与免疫原性剂组合,所述免疫原性剂是如癌性细胞、纯化的肿瘤抗原(包括重组蛋白、肽和碳水化合物分子)、细胞和用编码免疫刺激细胞因子的基因转染的细胞(He等人,(2004)J.Immunol.173:4919-28)。可以使用的肿瘤疫苗的非限制性

例子包括黑色素瘤抗原的肽(如gp100、MAGE抗原、Trp-2、MART1和/或酪氨酸酶的肽)或转染以表达细胞因子GM-CSF(下文进一步所讨论)的肿瘤细胞。

[1120] 在人中,已经显示一些肿瘤(如黑色素瘤)具有免疫原性。通过经由VISTA抑制降低T细胞激活的阈值,可以激活宿主中的肿瘤应答,从而允许治疗非免疫原性肿瘤或具有有限免疫原性的那些肿瘤。

[1121] 本文所述的抗VISTA抗体也可以与疫苗接种方案组合。已经设计了许多用于针对肿瘤的疫苗接种的实验策略(参见Rosenberg,S.,2000,Development of Cancer Vaccines,ASCO Educational Book Spring:60-62;Logothetis,C,2000,ASCO Educational Book Spring:300-302;Khayat,D.2000,ASCO Educational Book Spring:414-428;Foon,K.2000,ASCO Educational Book Spring:730-738;还参见Restifo,N.和Sznol,M.,Cancer Vaccines,第61章,第3023-3043页,在DeVita等人(编),1997,Cancer:Principles and Practice of Oncology,第五版)。在这些策略之一中,使用自体或同种异体肿瘤细胞制备疫苗。已经显示,当肿瘤细胞被转导以表达GM-CSF时,这些细胞疫苗是最有效的。已经显示GM-CSF是用于肿瘤疫苗接种的抗原呈递的有效力的激活剂(Dranoff等人(1993)Proc.Natl.Acad.Sci U.S.A.90:3539-43)。

[1122] 对各种肿瘤中的基因表达和大规模基因表达模式的研究已经产生了所谓的肿瘤特异性抗原的定义(Rosenberg,S A(1999)Immunity 10:281-7)。在许多情况下,这些肿瘤特异性抗原是在肿瘤和肿瘤产生的细胞中表达的分化抗原,例如黑素细胞抗原gp100、MAGE抗原和Trp-2。更重要的是,许多这些抗原可以显示为宿主中发现的肿瘤特异性T细胞的靶标。VISTA抑制可以与肿瘤中表达的重组蛋白和/或肽的集合结合使用,以产生针对这些蛋白质的免疫应答。这些蛋白质通常被免疫系统视为自身抗原,并且因此对它们具有耐受性。肿瘤抗原可以包括蛋白质端粒酶,其是合成染色体端粒所需的并且在超过85%的人类癌症和仅有限数量的体细胞组织中表达(Kim等人(1994)Science 266:2011-2013)。肿瘤抗原也可以是因以下原因在癌细胞中表达的"新抗原":改变蛋白质序列或在两个不相关序列之间产生融合蛋白(即费城染色体中的bcr-abl)的体细胞突变,或者来自B细胞肿瘤的独特型。

[1123] 其他肿瘤疫苗可以包括来自牵涉在人类癌症中的病毒的蛋白质,所述病毒是如人乳头瘤病毒(HPV)、肝炎病毒(HBV和HCV)和卡波西疱疹肉瘤病毒(KHSV)。可以与VISTA抑制一起使用的另一种形式的肿瘤特异性抗原是从肿瘤组织本身分离的纯化的热休克蛋白(HSP)。这些热休克蛋白含有来自肿瘤细胞的蛋白质片段,并且这些HSP在递送至抗原呈递细胞时高效引发肿瘤免疫(Suot&Srivastava(1995)Science 269:1585-1588;Tamura等人(1997)Science 278:117-120)。

[1124] 树突细胞(DC)是有效力的抗原呈递细胞,其可以用于引发抗原特异性应答。DC可以离体产生并加载各种蛋白质和肽抗原以及肿瘤细胞提取物(Nestle等人(1998)Nature Medicine 4:328-332)。DC还可以通过遗传手段转导以也表达这些肿瘤抗原。出于免疫目的,DC还已经直接与肿瘤细胞融合(Kugler等人(2000)Nature Medicine 6:332-336)。作为一种疫苗接种方法,DC免疫可以与VISTA抑制有效地组合以激活更有效力的抗肿瘤应答。

[1125] 感染性疾病治疗

[1126] 本文所述的方法还可以用于治疗已经暴露于特定毒素或病原体中的患者。因此,本公开文本还考虑了治疗受试者中感染性疾病的方法,所述方法包括向受试者给予本文所

述的抗体(例如拮抗剂VISTA抗体),从而治疗受试者的感染性疾病。类似于如上文讨论的其对肿瘤的应用,抗体介导的VISTA抑制可以单独使用,或作为佐剂与疫苗组合使用,以刺激针对病原体、毒素和自身抗原的免疫应答。这种治疗方法可能特别有用的病原体的例子包括目前没有有效疫苗的病原体或常规疫苗不完全有效的病原体。这些包括但不限于HIV、肝炎病毒(甲型、乙型和丙型)、流感病毒、疱疹病毒、贾第虫(Giardia)、疟原虫(Malaria)、利什曼原虫(Leishmania)、金黄色葡萄球菌(Staphylococcus aureus)、铜绿假单胞菌(Pseudomonas aeruginosa)。VISTA抑制可对于在感染过程中呈现改变的抗原的诸如HIV等剂的确定感染特别有用。

[1127] 引起可通过本文所述方法可治疗的感染的致病病毒的一些例子包括HIV、肝炎(甲型、乙型或丙型)、疱疹病毒(例如,VZV、HSV-1、HAV-6、HSV-II和CMV、爱泼斯坦-巴尔病毒(Epstein Barr virus))、腺病毒、流感病毒、黄病毒、埃可病毒、鼻病毒、柯萨奇病毒、冠状病毒、呼吸道合胞病毒、腮腺炎病毒、轮状病毒、麻疹病毒、风疹病毒、细小病毒、痘苗病毒、HTLV病毒、登革热病毒、乳头瘤病毒、软疣病毒、脊髓灰质炎病毒、狂犬病病毒、JC病毒和虫媒病毒性脑炎病毒。

[1128] 引起可通过本文所述方法可治疗的感染的致病细菌的一些例子包括衣原体属(chlamydia)、立克次体细菌(rickettsial bacteria)、分枝杆菌属(mycobacteria)、葡萄球菌属(staphylococci)、链球菌属(streptococci)、肺炎球菌属(pneumonococci)、脑膜炎球菌(meningococci)和淋球菌(gonococci)、克雷伯氏菌属(klebsiella)、变形杆菌属(proteus)、沙雷氏菌属(serratia)、假单胞菌属(pseudomonas)、军团菌属(legionella)、白喉、沙门氏菌属(salmonella)、芽孢杆菌属、霍乱、破伤风、肉毒杆菌、炭疽、鼠疫、钩端螺旋体病和莱姆病细菌。

[1129] 引起可通过本文所述方法可治疗的感染的致病真菌的一些例子包括念珠菌(Candida)(白色念珠菌(albicans)、克柔念珠菌(krusei)、光滑念珠菌(glabrata)、热带念珠菌(tropicalis)等)、新型隐球菌(Cryptococcus neoformans)、曲霉(Aspergillus)(烟曲霉(fumigatus)、黑曲霉(niger)等)、属毛霉目(Genus Mucorales)(毛霉菌属(mucor)、犁头霉属(absidia)、根霉属(rhizopus))、申克孢子丝菌(Sporothrix schenkii)、皮炎芽生菌(Blastomyces dermatitidis)、巴西副球孢子菌(Paracoccidioides brasiliensis)、粗球孢子菌(Coccidioides immitis)和荚膜组织胞浆菌(Histoplasma capsulatum)。

[1130] 引起可通过本文所述方法可治疗的感染的致病寄生虫的一些例子包括溶组织内阿米巴(Entamoeba histolytica)、结肠小袋纤毛虫(Balantidium coli)、福氏耐格里阿米巴(Naegleriafowleri)、棘阿米巴属物种(Acanthamoeba sp.)、蓝氏贾第虫(Giardia lambia)、隐孢子虫属物种(Cryptosporidium sp.)、卡氏肺孢子虫(Pneumocystis carinii)、间日疟原虫(Plasmodium vivax)、微小巴贝虫(Babesia microti)、布氏锥虫(Trypanosoma brucei)、克氏锥虫(Trypanosoma cruzi)、杜氏利什曼原虫(Leishmania donovani)、刚地弓形虫(Toxoplasma gondii)和巴西日圆线虫(Nippostrongylus brasiliensis)。

[1131] 在所有上述方法中,可以将VISTA抑制与其他形式的免疫疗法(例如本文所述的那些免疫疗法)结合,如细胞因子治疗(例如,干扰素、GM-CSF、G-CSF、IL-2)或双特异性抗体疗法,其可以提供增强的肿瘤抗原呈递(参见例如Holliger(1993)Proc.Natl.Acad.Sci.USA

90:6444-6448;Poljak(1994)Structure 2:1121-1123)。

[1132] 给予途径和载体

[1133] 在各个实施方案中,抗体可以通过各种途径在体内给予,所述途径包括但不限于口服、动脉内、肠胃外、鼻内、肌内、心内、心室内、气管内、颊、直肠、腹膜内、皮内、局部、透皮以及鞘内,或否则通过植入或吸入。可以将主题组合物配制成固体、半固体、液体或气体形式的制剂,包括但不限于片剂、胶囊、粉末、颗粒剂、软膏、溶液、栓剂、灌肠剂、注射剂、吸入剂和气雾剂。如文献中所述,可以将编码抗体的核酸分子包被在金色微粒上并通过粒子轰击装置或"基因枪"皮内递送(参见例如Tang等人,Nature356:152-154(1992))。可以根据预期的应用选择适当的配制品和给予途径。

[1134] 在各个实施方案中,在包含多种药学上可接受的载体的配制品中提供了包含抗体的组合物(参见例如Gennaro,Remington:The Science and Practice of Pharmacy with Facts and Comparisons:Drugfacts Plus,第20版(2003);Ansel等人,Pharmaceutical Dosage Forms and Drug Delivery Systems,第7版,Lippencott Williams和Wilkins(2004);Kibbe等人,Handbook of Pharmaceutical Excipients,第3版,Pharmaceutical Press(2000))。可以使用各种药学上可接受的载体,包括媒介物、佐剂和稀释剂。此外,还可以使用各种药学上可接受的辅助物质,如pH调节剂和缓冲剂、张力调节剂、稳定剂、湿润剂等。非限制性示例性载体包括盐水、缓冲盐水、右旋糖、水、甘油、乙醇及其组合。

[1135] 在各个实施方案中,可以通过以下方式配制包含抗体的组合物用于注射(包括皮下给予):将所述组合物溶解、悬浮或乳化在水性或非水性溶剂(如植物油或其他油、合成脂肪酸甘油酯、高级脂肪酸酯或丙二醇)中;并且如果需要,与常规添加剂(如增溶剂、等渗剂、助悬剂、乳化剂、稳定剂和防腐剂)一起配制。在各个实施方案中,可以例如使用加压的可接受的推进剂如二氯二氟甲烷、丙烷、氮气等来配制组合物用于吸入。也可以在各个实施方案中将组合物配制成缓释微胶囊,如使用可生物降解或不可生物降解的聚合物。非限制性示例性可生物降解配制品包括聚乳酸-乙醇酸聚合物。非限制性示例性不可生物降解的配制品包括聚甘油脂肪酸酯。制备此类配制品的某些方法描述于例如EP 1 125 584A1中。

[1136] 还提供了包含一个或多个容器的药物包装和药剂盒,每个容器包含一个或多个剂量的抗体或抗体的组合。在一些实施方案中,提供了单位剂量,其中所述单位剂量含有预定量的包含抗体或抗体组合、具有或不具有一种或多种另外的药剂的组合物。在一些实施方案中,这种单位剂量以一次性使用的预填充注射器形式提供用于注射。在各个实施方案中,单位剂量中所含的组合物可以包含盐水、蔗糖等;缓冲剂,如磷酸盐等;和/或在稳定有效的Ph范围内配制。可替代地,在一些实施方案中,组合物可以以冻干粉末的形式提供,其可以通过添加适当的液体例如无菌水来重构。在一些实施方案中,组合物包含一种或多种抑制蛋白质聚集的物质,包括但不限于蔗糖和精氨酸。在一些实施方案中,本发明的组合物包含肝素和/或蛋白聚糖。

[1137] 以有效治疗或预防特定适应症的量给予药物组合物。治疗有效量通常取决于被治疗的受试者的体重、他或她的身体或健康状况、待治疗的病症的广泛性或被治疗的受试者的年龄。一般而言,可以以每剂量约10μg/kg体重至约100mg/kg体重范围内的量给予抗体。在一些实施方案中,可以以每剂量约50μg/kg体重至约5mg/kg体重的量给予抗体。在一些实施方案中,可以以每剂量约100μg/kg体重至约10mg/kg体重的量给予抗体。在一些实施方案

中,可以以每剂量约100μg/kg体重至约20mg/kg体重的量给予抗体。在一些实施方案中,可以以每剂量约0.5mg/kg体重至约20mg/kg体重的量给予抗体。

[1138] 可以根据需要将抗体组合物给予至受试者。给予频率的确定可以由本领域技术人员(如主治医生)根据对被治疗的病症、被治疗的受试者的年龄、被治疗的病症的严重程度、被治疗的受试者的一般健康状况的考虑来进行。在一些实施方案中,将有效剂量的抗体一次或多次给予至受试者。在各个实施方案中,将有效剂量的抗体每月一次、每月少于一次(例如每两个月或每三个月一次)给予至受试者。在其他实施方案中,将有效剂量的抗体每月给予多于一次,例如每三周、每两周或每周一次。在一些实施方案中,将有效剂量的抗体每1、2、3、4或5周给予一次。在一些实施方案中,将有效剂量的抗体每周给予两次或三次。将有效剂量的抗体至少一次给予至受试者。在一些实施方案中,将有效剂量的抗体可以多次给予,包括持续至少一个月、至少六个月或至少一年的时间段。

[1139] 在某些实施方案中,可以将本文所讨论的抗VISTA抗体和第二药剂的组合在药学上可接受的载体中作为单一组合物同时给予,或作为单独的组合物同时给予,其中抗VISTA抗体和第二药剂在药学上可接受的载体中。在一个实施方案中,可以顺序地给予抗VISTA抗体和第二药剂的组合。两种药剂的给予可以在相隔例如30分钟、60分钟、90分钟、120分钟、3小时、6小时、12小时、24小时、36小时、48小时、3天、5天、7天或一周或多周的时间开始,或者第二药剂的给予可以在已经给予第一药剂后例如30分钟、60分钟、90分钟、120分钟、3小时、6小时、12小时、24小时、36小时、48小时、3天、5天、7天或一周或多周时开始。

[1140] 鉴定低pH结合hVISTA-ECD Ab的方法

[1141] 本文还提供了用于鉴定在酸性(或低pH)条件下与VISTA-ECD蛋白特异性地结合的Ab的方法。在某些实施方案中,用于鉴定在pH 6.5下或更低时与VISTA-ECD蛋白特异性地结合的Ab的方法包括在pH 6.5下或更低时使一个测试Ab或多个测试Ab与VISTA-ECD蛋白接触,并选择以10^{-7}M、10^{-8}M、10^{-9}M或更低的K_D与VISTA蛋白的ECD结合的测试Ab。在一些实施方案中,所述方法在pH 6.5下进行,而在其他情况下,其在pH 6.0或pH 5.5或pH 5.0下进行。在一些实施方案中,VISTA-ECD蛋白是hVISTA-ECD蛋白或包含hVISTA IgV结构域,或者是包含SEQ ID NO:2的氨基酸20-95或SEQ ID NO:2的氨基酸20-70、35-95或35-70的多肽。在一些实施方案中,多肽还包含SEQ ID NO:2的氨基酸95-105。在一些实施方案中,多肽包含SEQ ID NO:2的氨基酸35-127或37-125。

[1142] 在一些实施方案中,所述方法进一步包括测试一个测试Ab或多个测试Ab在中性、生理或碱性pH下(如在pH 7.0或pH 7.4下)的结合。在一些实施方案中,所述方法进一步包括选择如下抗体,其不仅在pH 6.5下或更低时以10^{-7}M、10^{-8}M、10^{-9}M或更小的K_D与VISTA-ECD蛋白结合,而且在pH 7.0或pH 7.4下与多肽特异性地结合。在一些实施方案中,选择如下测试Ab,其在酸性条件下(例如在pH 6.5下或更低)与VISTA-ECD蛋白特异性地结合,在中性和/或碱性pH下还以相似的亲和力特异性地结合VISTA-ECD蛋白(即它们是“泛结合剂”)。例如,一些此类Ab可以在pH 6.5和pH 7.0或pH 7.4下以10^{-7}M、10^{-8}M、10^{-9}M或更小的K_D与VISTA-ECD蛋白结合(在例如25℃或37℃的恒定温度下),使得pH 6.5下的K_D在pH 7.0下的K_D的1.5倍内。

[1143] 选择如下的某些Ab,其在酸性条件下(例如,在pH 6.5下或更低)以比在中性或碱性pH下更高的亲和力与VISTA-ECD蛋白(“pH敏感性结合剂”或“pH敏感性Ab”)特异性地结

合。例如,在一些实施方案中,Ab可以在pH 6.5下以10^{-8}M或更小的K_D并且在pH 7.0或pH 7.4下以大于10^{-8}M的K_D与VISTA-ECD蛋白结合。在一些此类实施方案中,Ab可以在pH 6.5下以10^{-8}M或更小的K_D和在pH 7.0或pH 7.4下以比在pH 6.5下高大于1.5倍的K_D与VISTA-ECD蛋白结合。在某些实施方案中,选择与VISTA-ECD蛋白特异性地结合的pH敏感性Ab,其中K_D在pH 6.5下比在pH 7.0或pH 7.4下低至少1.5倍、2倍、5倍、10倍、20倍、50倍、100倍、300倍、500倍、1000倍或5000倍(在例如25℃或37℃的恒定温度下)。例如,在一些情况下选择与VISTA-ECD蛋白结合的Ab,其中相对于pH 7.0或pH 7.4或更高,K_D在pH 6.0下至少小1.5倍、2倍、5倍、10倍、20倍、50倍、100倍、300倍、500倍、1000倍或5000倍(在例如25℃或37℃的恒定温度下)。

[1144] 在某些实施方案中,选择与VISTA-ECD蛋白特异性地结合的Ab,其中k_{off}在酸性条件下低于在中性、生理或碱性条件下的k_{off}。在某些实施方案中,选择在酸性条件下与VISTA-ECD蛋白结合的Ab,其中在pH 6.5下的k_{off}比在pH 7.0和/或pH 7.4下的k_{off}低至少1.5倍、2倍、5倍、10倍、20倍、50倍或100倍,如例如在25℃或37℃下所测量的。例如,在一些实施方案中,选择与VISTA-ECD蛋白结合的Ab,其中相对于pH 7.0或pH 7.4,k_{off}速率在pH 6.0下低至少1.5倍、2倍、5倍、10倍、20倍、50倍或100倍,如例如在25℃或37℃下所测量的。

[1145] 在某些实施方案中,选择与VISTA-ECD蛋白结合的Ab,其中相对于中性或碱性条件,k_{on}在酸性条件下较高。在某些实施方案中,选择在酸性条件下与VISTA-ECD蛋白结合的Ab,其中在pH 6.5下的k_{on}比在pH 7.0或pH 7.4下的k_{on}高至少2倍、5倍、10倍、20倍、50倍或100倍,如例如在25℃或37℃下所测量的。例如,在一些实施方案中,选择与VISTA-ECD蛋白结合的Ab,其中k_{on}在pH 6.0下比在pH 7.0或pH 7.4下高至少2倍、5倍、10倍、20倍、50倍或100倍,如例如在25℃或37℃下所测量的。

[1146] 对结合VISTA-ECD的Ab的pH敏感性进行修饰的方法

[1147] 与VISTA-ECD蛋白结合但在pH 6.5或更低时不结合或在pH 6.5下或更低时不以高亲和力结合的Ab可以被工程化以增加其在pH 6.5下或更低时的结合亲和力。例如,Ab的补位可以例如通过一个或多个氨基酸残基的取代而突变。例如,在一些实施方案中,Ab的重链或轻链中的1至8个(例如1至6个、1至4个、1至3个、1至2个或1个)氨基酸残基作为与VISTA-ECD接触的残基(例如一个或多个CDR中的残基)可以被不同的氨基酸残基替代。然后,可以测试突变的Ab在pH 6.5下或更低时与VISTA-ECD蛋白的结合,并且可以选择与亲本抗体相比以更高亲和力结合的Ab种类。如果需要,可以重复上述步骤,使得对Ab进行两轮或更多轮诱变和选择,并选择在酸性pH下具有最高亲和力的结合剂。在一些实施方案中,此类选择可以改善所得抗体相对于其亲本的抗肿瘤功效。

[1148] 还可以将上述选择方法设计为遵循先前对特异性地结合VISTA-ECD蛋白的抗体的一般选择。即,在某些实施方案中,选择在pH 6.5下以10^{-8}M或更小的K_D与VISTA蛋白的ECD结合的改善的Ab。在一些实施方案中,选择是在pH 6.0或pH 5.5或pH 5.0下而不是在pH 6.5进行。在一些实施方案中,用于选择过程的VISTA-ECD蛋白是完整的hVISTA-ECD蛋白,或者是包含hVISTA IgV结构域的多肽,或者是包含SEQ ID NO:2氨基酸20-95或SEQ ID NO:2的氨基酸20-70、35-95或35-70的多肽。在一些实施方案中,多肽还包含SEQ ID NO:2的氨基酸95-105。在一些实施方案中,使用了包含SEQ ID NO:2的氨基酸残基35-127的多肽。

[1149] 在一些实施方案中,用于改善在酸性pH下VISTA抗体与VISTA ECD结合的方法包括

增加一个或多个VH CDR(例如VH CDR1、CDR2和CDR3)中谷氨酸、天冬氨酸和组氨酸残基的数目。

[1150] 在一些实施方案中,所述方法进一步包括测试在中性、碱性或生理pH下(如在pH 7.0或7.4下)选择的Ab的结合。在一些实施方案中,所述方法进一步包括选择如下抗体,其不仅在pH 6.5下或更低以10^{-8}M或更小的K_D与VISTA-ECD蛋白结合,而且在pH 7.0或7.4下与多肽特异性地结合。在一些此类实施方案中,选择如下测试Ab,其在酸性条件下(例如在pH 6.5下或更低)与VISTA-ECD蛋白特异性地结合,并且在中性和/或碱性或生理pH下还以相似的亲和力特异性地结合VISTA-ECD蛋白(即它们是"泛结合剂")。例如,一些此类Ab可以在pH 6.5和pH 7.0下以10^{-8}M或更小的K_D与VISTA-ECD蛋白结合(在例如25℃或37℃的恒定温度下),使得pH 6.5下的K_D在pH 7.0或pH7.4下的K_D的1.5倍内。

[1151] 选择如下的某些Ab,其在酸性条件下(例如,在pH 6.5下或更低)以比在中性、生理或碱性pH下更高的亲和力与VISTA-ECD蛋白("pH敏感性结合剂"或"pH敏感性Ab")特异性地结合。例如,在一些实施方案中,Ab可以在pH 6.5下以10^{-8}M或更小的K_D并且在pH 7.0下以大于10^{-8}M的K_D与VISTA-ECD蛋白结合。在一些此类实施方案中,Ab可以在pH 6.5下以10^{-8}M或更小的K_D并且在pH 7.0下以大于pH 6.5下K_D的1.5倍的K_D与VISTA-ECD蛋白结合。在某些实施方案中,选择与VISTA-ECD蛋白特异性地结合的pH敏感性Ab,其中在pH 6.5下的K_D比在pH 7.0或pH 7.4下低至少1.5倍、2倍、5倍、10倍、20倍、50倍、100倍、300倍、500倍、1000倍或5000倍(在例如25℃或37℃的恒定温度下)。例如,在一些情况下选择与VISTA-ECD蛋白结合的Ab,其中相对于pH 7.0或pH 7.4或更高,K_D在pH 6.0下至少小1.5倍、2倍、5倍、10倍、20倍、50倍、100倍、300倍、500倍、1000倍或5000倍(在例如25℃或37℃的恒定温度下)。

[1152] 在某些实施方案中,所述方法进一步包括测定在两个pH值下的k_{off}。在一些此类实施方案中,选择与VISTA-ECD蛋白特异性地结合的Ab,其中k_{off}在酸性条件下低于在中性、生理或碱性条件下的k_{off}。在某些实施方案中,选择在酸性条件下与VISTA-ECD蛋白结合的Ab,其中在pH 6.5下的k_{off}比在pH7.0和/或pH 7.4下的k_{off}低至少1.5倍、2倍、5倍、10倍、20倍、50倍或100倍,如例如在25℃或37℃下所测量的。例如,在一些实施方案中,选择与VISTA-ECD蛋白结合的Ab,其中相对于pH 7.0,k_{off}速率在pH 6.0下低至少1.5倍、2倍、5倍、10倍、20倍、50倍或100倍,如例如在25℃或37℃下所测量的。

[1153] 在某些实施方案中,所述方法进一步包括测定在两个pH值下的k_{on}。在一些此类实施方案中,选择与VISTA-ECD蛋白结合的Ab,其中相对于中性、生理或碱性条件,k_{on}在酸性条件下较高。在某些实施方案中,选择在酸性条件下与VISTA-ECD蛋白结合的Ab,其中在pH 6.5下的k_{on}比在pH 7.0或pH 7.4下的k_{on}高至少2倍、5倍、10倍、20倍、50倍或100倍,如例如在25℃或37℃下所测量的。例如,在一些实施方案中,选择与VISTA-ECD蛋白结合的Ab,其中k_{on}在pH 6.0下比在pH 7.0或pH 7.4下高至少2倍、5倍、10倍、20倍、50倍或100倍,如例如在25℃或37℃下所测量的。

[1154] 通过针对在酸性pH(例如pH 6.0或6.5)下的结合来阳性地筛选VISTA抗体或Fab或scFv的文库,和通过针对在中性pH(例如pH 7.0或生理pH,例如pH 7.4)下缺乏结合来阴性地筛选文库,可以鉴定相对于中性或生理pH,在酸性pH下与huVISTA优先结合的抗体。文库可以富集谷氨酸、天冬氨酸和组氨酸残基,如以便选择带正电荷且更可能在酸性pH下与VISTA结合的结合结构域。筛选可以包括在酸性pH下的阳性选择和在中性或生理pH下的阴

性选择。阳性选择和阴性选择可以交替进行。

[1155] 可替代地,在中性pH下结合和/或在酸性pH下缺乏与VISTA的结合可以被工程化为在中性pH下缺乏结合而在酸性pH下结合。

[1156] 特定实施方案

[1157] 本公开文本的另外的实施方案包括以下内容:

[1158] 1.一种分离的抗体(Ab),其与含人V结构域免疫球蛋白的T细胞激活抑制剂(hVISTA)细胞外结构域(ECD)特异性地结合,其中所述Ab:

[1159] a.在pH 6.5下或更低时以10^{-7}M或更小的亲和力常数(K_D)与hVISTA-ECD结合;

[1160] b.在pH 6.5下或更低时以$10^{-3}sec^{-1}$或更小的解离速率常数(k_{off})与hVISTA-ECD结合;或

[1161] c.在pH 6.5下或更低时以10^{-7}M或更小的K_D和$10^{-3}sec^{-1}$或更小的k_{off}与hVISTA-ECD结合。

[1162] 2.根据实施方案1的分离的Ab,其中所述Ab在pH 6.5下或更低时以10^{-8}M或更小的K_D与hVISTA-ECD结合。

[1163] 3.根据实施方案2的分离的Ab,其中所述Ab在pH 6.5下或更低时以10^{-9}M或更小的K_D与hVISTA-ECD结合。

[1164] 4.根据实施方案1-3中任一项的分离的Ab,其中所述Ab在pH 6.5下或更低时以$10^{-4}sec^{-1}$或更小的k_{off}与hVISTA-ECD结合。

[1165] 5.根据实施方案1-4中任一项的分离的Ab,其中所述Ab在pH 7.0下或更高时与hVISTA-ECD结合,其中:

[1166] a.K_D为10^{-7}M或更小;

[1167] b.k_{off}为$10^{-3}sec^{-1}$或更小;或

[1168] c.K_D为10^{-7}M或更小并且k_{off}为$10^{-3}sec^{-1}$或更小。

[1169] 6.根据实施方案5的分离的Ab,其中所述Ab在pH 7.0下或更高时以10^{-8}M或更小的K_D与hVISTA-ECD结合。

[1170] 7.根据实施方案6的分离的Ab,其中所述Ab在pH 7.0下或更高时以10^{-9}M或更小的K_D与hVISTA-ECD结合。

[1171] 8.根据实施方案5-7中任一项的分离的Ab,其中所述Ab在pH 7.0下或更高时以$10^{-4}sec^{-1}$或更小的k_{off}与hVISTA-ECD结合。

[1172] 9.根据实施方案5-8中任一项的分离的Ab,其中所述Ab在pH 6.5下以与pH 7.0下相似的亲和力与hVISTA-ECD结合。

[1173] 10.根据实施方案9的分离的Ab,其中所述Ab在pH 6.5下以比在pH 7.0下更高的亲和力与hVISTA-ECD结合。

[1174] 11.根据实施方案10的分离的Ab,其中所述Ab在pH 6.5下以比在pH 7.0下低至少1.5倍的K_D与hVISTA-ECD结合。

[1175] 12.根据实施方案11的分离的Ab,其中所述Ab在pH 6.5下以比在pH 7.0下低至少2倍的K_D与hVISTA-ECD结合。

[1176] 13.根据实施方案11的分离的Ab,其中所述Ab在pH 6.5下以比在pH 7.0下低至少5倍的K_D与hVISTA-ECD结合。

[1177] 14.根据实施方案10-13中任一项的分离的Ab,其中所述Ab在pH 6.5下以低于在pH 7.0下的k_{off}与hVISTA-ECD结合。

[1178] 15.根据实施方案14的分离的Ab,其中所述Ab在pH 6.5下以比在pH 7.0下低至少1.5倍的k_{off}与hVISTA-ECD结合。

[1179] 16.根据实施方案15的分离的Ab,其中所述Ab在pH 6.5下以比在pH 7.0下低至少2倍的k_{off}与hVISTA-ECD结合。

[1180] 17.根据实施方案16的分离的Ab,其中所述Ab在pH 6.5下以比在pH 7.0下低至少5倍的k_{off}与hVISTA-ECD结合。

[1181] 18.根据实施方案1-17中任一项的分离的Ab,其中在hVISTA-ECD的至少一个组氨酸残基被质子化的条件下,所述Ab与hVISTA-ECD特异性地结合。

[1182] 19.根据实施方案18的分离的Ab,其中所述Ab与hVISTA-ECD的IgV结构域结合。

[1183] 20.根据实施方案19的分离的Ab,其中所述Ab与位于SEQ ID NO:2的氨基酸20和95内的区域结合。

[1184] 21.根据实施方案20的分离的Ab,其中所述Ab与位于SEQ ID NO:2的氨基酸20和70内的区域结合。

[1185] 22.根据实施方案21的分离的Ab,其中所述Ab与位于SEQ ID NO:2的氨基酸35和70内的区域结合。

[1186] 23.根据实施方案20-22中任一项的分离的Ab,其中所述Ab进一步与hVISTA的ECD的另一个区域结合。

[1187] 24.根据实施方案23的分离的Ab,其中另一个区域位于SEQ ID NO:2的氨基酸95和105内。

[1188] 25.根据实施方案18-24中任一项的分离的Ab,其中结合是通过氢-氘交换质谱法(HDX-MS)来测定。

[1189] 26.根据实施方案1-25中任一项的分离的Ab,其中所述Ab抑制hVISTA与原本将与hVISTA结合的细胞结合。

[1190] 27.根据实施方案1-26中任一项的分离的Ab,其中所述Ab触发或增强肿瘤模型中的免疫应答。

[1191] 28.根据实施方案27的分离的Ab,其中所述Ab在肿瘤模型中触发或增强T细胞活性。

[1192] 29.根据实施方案1-28中任一项的分离的Ab,其中所述Ab抑制肿瘤模型中的肿瘤生长。

[1193] 30.根据实施方案1-29中任一项的分离的Ab,其中所述Ab抑制hVISTA与T细胞的结合。

[1194] 31.根据实施方案30的Ab,其中与在pH 7.0下或更高时相比,所述Ab在pH 6.5下更强烈地抑制hVISTA与T细胞的结合,如其中与在pH7.0下相比,所述抗体在pH 6.5下更强烈地抑制hVISTA与T细胞的结合。

[1195] 32.一种包含实施方案1-31中任一项的分离的Ab和药学上可接受的载体的组合物。

[1196] 33.一种治疗患有癌症的受试者的方法,其包括向所述受试者给予实施方案32的

组合物。

[1197] 34.一种用于鉴定在pH 6.5下或更低时以10^{-7}M或更小的K_D与hVISTA-ECD结合的Ab的方法,其包括在pH 6.5下或更低时使一个测试Ab或多个测试Ab与包含hVISTA-ECD或其片段的多肽接触,所述片段包含hVISTA-ECD的IgV结构域或包含SEQ ID NO:2的氨基酸20-95、20-70或35-70,并且选择以10^{-7}M或更小的K_D与所述多肽结合的一个测试Ab或多个测试Ab。

[1198] 35.一种用于鉴定在pH 6.5下或更低时以$10^{-3}sec^{-1}$或更小的k_{off}与hVISTA-ECD结合的Ab的方法,其包括在pH 6.5下或更低时使一个测试Ab或多个测试Ab与包含hVISTA-ECD或其片段的多肽接触,所述片段包含hVISTA-ECD的IgV结构域或包含SEQ ID NO:2的氨基酸20-95、20-70或35-70,并且选择以$10^{-3}sec^{-1}$或更小的k_{off}与所述多肽结合的一个测试Ab或多个测试Ab。

[1199] 36.一种用于鉴定在pH 6.5下以与在pH 7.0下相似的亲和力与hVISTA-ECD特异性地结合的Ab的方法,其包括:

[1200] a.在pH 6.5下使一个测试Ab或多个测试Ab与包含hVISTA-ECD或其片段的多肽接触,所述片段包含hVISTA-ECD的IgV结构域或包含SEQ ID NO:2的氨基酸20-95、20-70或35-70;

[1201] b.在pH 7.0下使一个测试Ab或多个测试Ab与(a)的多肽接触;和

[1202] c.选择在pH 6.5和pH 7.0下以10^{-7}M或更小的K_D与多肽结合的测试Ab。

[1203] 37.一种用于鉴定在pH 6.5下以比在pH 7.0下更高的亲和力与hVISTA-ECD结合的Ab的方法,其包括:

[1204] a.在pH 6.5下使一个测试Ab或多个测试Ab与包含hVISTA-ECD或其片段的多肽接触,所述片段包含hVISTA-ECD的IgV结构域或包含SEQ ID NO:2的氨基酸20-95、20-70或35-70;

[1205] b.在pH 7.0下使一个测试Ab或多个测试Ab与(a)的多肽接触;和

[1206] c.选择在pH 6.5下以比在pH 7.0下低至少2倍的K_D与多肽结合的测试Ab。

[1207] 38.一种用于鉴定与hVISTA-ECD特异性地结合以用于治疗癌症的Ab的方法,其包括

[1208] a.如根据实施方案32-35的方法,鉴定在pH 6.5下或更低时与hVISTA-ECD特异性地结合的Ab;和

[1209] b.选择(a)在pH 6.5下或更低时触发或增强肿瘤模型中的免疫应答或抑制肿瘤生长的Ab。

[1210] 39.根据实施方案38的方法,其中步骤(b)包括测量T细胞活性。

[1211] 40.根据实施方案38或39的方法,其进一步包括测量Ab的抗肿瘤作用。

[1212] 41.一种用于改善与hVISTA-ECD结合的Ab的抗肿瘤功效的方法,其包括

[1213] a.提供在pH 6.5下或更低时以低于所需值的亲和力与hVISTA-ECD结合的Ab;

[1214] b.用不同的氨基酸残基替代Ab的重链或轻链中的1至5个氨基酸残基,其中所述1至5个氨基酸残基是与hVISTA-ECD接触的残基;

[1215] c.确定相对于(a)中的Ab,在(b)中获得的Ab是否在pH 6.5下或更低时具有对hVISTA-ECD的更高亲和力;和

[1216] d.重复步骤(a)-(c)足够的若干轮,以获得在pH 6.5下或更低时以10^{-7}M或更小的

K_D与hVISTA-ECD结合的Ab。

[1217] 42.一种用于改善与hVISTA-ECD结合的Ab的抗肿瘤功效的方法,其包括:

[1218] a.提供在pH 6.5下或更低时以低于所需值的亲和力与hVISTA-ECD结合的Ab;

[1219] b.制备(a)的Ab的变体的文库,其中每个变体包含用不同的氨基酸残基对Ab的重链或轻链中的1至5个氨基酸残基进行的取代,其中所述1至5个氨基酸残基是与hVISTA-ECD接触的残基;

[1220] c.选择在pH 6.5下或更低时以10^{-7}M或更小的K_D与hVISTA-ECD结合的(b)的变体的文库的Ab;和

[1221] d.测试肿瘤模型中(c)的Ab的抗肿瘤功效。

[1222] 43.一种用于改善与人VISTA ECD结合的抗体的药代动力学的方法,其包括增强抗体在酸性条件(例如等于或低于pH 6.5)下与人VISTA结合的能力。

[1223] 44.一种用于选择与人VISTA结合并且具有延长的半衰期(良好的药代动力学特性)的抗体的方法,其中所述方法包括选择在酸性条件例如等于或低于pH 6.5下与人VISTA结合的抗体。

[1224] 实施例

[1225] 以下所讨论的实施例仅旨在举例说明本发明,并且因此不应视为以任何方式限制本发明。实施例并不旨在表示以下实验是进行的全部或仅有的实验。已经努力确保关于所使用的数字(例如,量、温度等)的准确性,但是应考虑到一些实验误差和偏差。除非另有指示,否则份数是重量份,分子量是重均分子量,温度是按摄氏度计,并且压力是大气压或接近大气压。

[1226] 实施例1:VISTA的细胞外结构域异常富含组氨酸

[1227] 此实施例表明,VISTA的细胞外结构域异常富含组氨酸残基,这些组氨酸残基在进化上是保守的,并且它们可能有助于涉及VISTA的受体-配体相互作用。

[1228] 从uniprot和swiss-prot数据库中提取含免疫球蛋白结构域的蛋白质的细胞外结构域(ECD)的氨基酸序列,并分析组氨酸含量。图1A以图描绘了此分析的结果。对于每种蛋白质,组氨酸残基的频率以所有细胞外结构域氨基酸残基的百分比的形式绘制在y轴上,而细胞外结构域氨基酸残基的总数绘制在x轴上。每个数据点的直径对应于每种蛋白质的细胞外结构域中组氨酸残基的总数。VISTA(标记的)在其细胞外结构域中含有异常高频率的组氨酸残基。

[1229] 然后评估了VISTA中组氨酸残基的进化保守性。图1B显示了比对人、食蟹猴和小鼠VISTA的氨基酸参考序列,不包括信号肽(“Sig”)、跨膜结构域(“TMD”)和细胞内结构域。在所有三个物种中保守的组氨酸残基是粗体加下划线的。在人和cyno VISTA中保守的组氨酸残基是未加下划线的粗体。许多VISTA的细胞外结构域组氨酸残基在进化上是保守的,这表明VISTA的高组氨酸含量具有重要的生物学作用。

[1230] 基于对PDB数据库中可用的已求解的结构序列的同源性分析,建立了hVISTA IgV结构域的三维模型。所述模型如图1C中所示,表明VISTA的ECD中的许多组氨酸都暴露在分子表面,其中它们可能在配体结合以及抗体识别中发挥作用。组氨酸残基描绘为球形和棒状。

[1231] 实施例2:组氨酸质子化可以调节肿瘤和其他酸性微环境中的VISTA受体-配体结

合和免疫抑制活性

[1232] 此实施例描述了响应于生理学相关的酸性pH的组氨酸质子化,以及其中VISTA细胞外结构域组氨酸赋予反受体或配体对于酸性pH而不是生理pH的选择性的模型。

[1233] 图2A显示了在组氨酸残基中吡咯铵基团(NH)的质子化的缺乏与存在之间的平衡。溶液中组氨酸的pK_a为6.5,这表明组氨酸残基在pH 6.5或更低时与更高的pH相比更可能被质子化,因此带正电。质子化导致的VISTA ECD表面正电荷的增加可能影响受体或配体结合以及VISTA结构和/或功能。因此,pH的变化也可以修饰抗体结合表位和/或导致变化的抗体亲和力。

[1234] 图2B显示了如下模型,其中VISTA在酸性pH下选择性地接合PSGL-1或其他反受体和配体("VISTA-R")。在生理pH下(如血液中),预计VISTA ECD上的组氨酸残基是非质子化的。因此,VISTA与PSGL-1或其他反受体和配体的结合在生理pH下可忽略不计。相反,在倾向于具有酸性细胞外pH的位置中,如肿瘤微环境或炎症部位,酸性pH可以部分或完全驱动VISTA ECD组氨酸质子化,从而使VISTA与PSGL-1或其他反受体和配体结合。因此,在酸性pH范围内与VISTA-ECD蛋白强烈结合的抗体可以更有效地抑制肿瘤中的VISTA活性。

[1235] 实施例3:VISTA由肿瘤中的骨髓单核细胞表达

[1236] 此实施例显示VISTA通常由肿瘤中的骨髓单核细胞(包括巨噬细胞、树突细胞和粒细胞)表达。

[1237] 将手术切除的非小细胞肺癌、肾透明细胞癌、黑色素瘤、结直肠癌和其他肿瘤样品在冰冷PBS中洗涤,切成约15mm^3大小的碎片,并悬浮在补充有2%热灭活的FBS和2mM EDTA(Fisher Scientific 15575020)的冰冷RPMI-1640培养基(Fisher Scientific目录号11875093)中。将每个样品转移到一个大的净空玻璃杜恩斯(dounce)(Tenbroeck组织研磨机)中并研磨,直到从视觉上分离出组织块为止。将悬浮液通过70μM尼龙网过滤并离心。弃去上清液,在室温下将细胞沉淀重悬于补充有0.1%牛血清白蛋白和250mg/mL无菌过滤的DNase 1(II级,来自牛胰腺,Roche目录号10104159001)的室温PBS中,持续3分钟。然后将细胞在冰冷的补充RPMI中洗涤,并重悬于冰冷的PBS中。添加细胞活力染料,并将细胞在黑暗中在冰上孵育。20分钟后,通过添加4%正常大鼠血清、4%正常小鼠血清、20%来自AB血浆的人血清和1:125稀释的Human TruStain FcX™(Biolegend目录号422302)来封闭非特异性抗体染色。将细胞用悬浮在Brilliant Stain Buffer(BD Biosciences目录号562794)中的抗HLA-DR(BD Biosciences目录号564040)、CD8(Fisher Scientific目录号46-0087-42)、CD14(Biolegend目录号325620)、CD45(Biolegend目录号304017)、CD4(BD Biosciences目录号563875)、CD11c(BD Biosciences目录号744439)、CD15(BD Biosciences目录号563142)、PD-1(BD Biosciences目录号565299)、CD3(BD Biosciences目录号565515)、CD56(Fisher科学目录号61-0567-42)、CD19(BD Biosciences目录号564977)和VISTA(与AlexaFluor™647缀合的VISTA抗体3,Fisher Scientific目录号A20186)的荧光团缀合的抗体在黑暗中冰上染色30分钟。将染色的细胞在冰冷的PBS中洗涤,固定(Fisher Scientific目录号00-5523-00),并获取在流式细胞仪上。使用FlowJo™软件(BD Biosciences)分析数据。如图3所示,VISTA细胞表面表达在巨噬细胞和粒细胞上最高,在树突细胞上中等,并且在T细胞、自然杀伤细胞和B细胞上低。

[1238] 实施例4:VISTA细胞结合展现出酸性pH选择性

[1239] 此实施例显示,在酸性pH下比在中性或生理pH下,多聚化人VISTA ECD与刺激的人CD4+T细胞和人外周血单核细胞更有效地结合,并且这种结合可以被抗人VISTA锁定抗体阻断。还显示了酸性pH选择性二聚化小鼠VISTA ECD与小鼠脾细胞的结合。

[1240] 通过RosetteSep™(Stemcell目录号15062)从健康供体血液中富集人CD4+T细胞,并用在补充有10%热灭活的FBS、Glutamax™(Fisher Scientific目录号35050061)、非必需氨基酸(Fisher Scientific 11140050)、丙酮酸钠(Fisher Scientific目录号11360070)和2-巯基乙醇(Fisher Scientific 21985023)的RPMI-1640中的人T激活剂CD3/CD28 Dynabeads™(Fisher Scientific目录号111.32D)和重组人IL-2(Peprotech目录号200-02)在体外刺激约4天。在室温下将激活的CD4+T细胞用单生物素化hVISTA ECD分子(Phe 33-Ala 194(登录号AAH20568)-多组氨酸;AcroBiosystems,Inc.B75-H82F3)染色30分钟,二者以28:1摩尔比加载到稀释至用mM MES(Sigma,1317-100ML)酸化为多种pH的汉克缓冲盐溶液(HBSS,Fisher Scientific目录号14025134)中的藻红蛋白(PE)缀合的链霉亲和素dextramer(目录号DX01-PE)上。作为对照,将激活的CD4+T细胞用未加载hVISTA的PE缀合的链霉亲和素dextramer染色。用HBSS+MES洗涤染色的细胞,并获取在流式细胞仪上。使用FlowJo™软件(BD Biosciences)分析数据。在图4A中描绘的结果显示,在pH>6.5时,hVISTA没有比对照更好地结合CD4+T细胞。相比之下,在pH<6.5时,hVISTA展现出与CD4+T细胞的结合逐渐增强。左图,从深灰色到浅灰色,填充的直方图描绘了在pH 7.0、6.5、6.4、6.3、6.1和6.0下的结合。一些直方图用其相应的pH标记。在pH 6.0下的非VISTA对照多聚体结合显示为未填充的直方图。右图表示在不同pH下用hVISTA加载的dextramer(蓝色圆圈)或用未加载的dextramer(三角形)染色的CD4+T细胞的PE平均荧光强度(MFI)。

[1241] 通过聚蔗糖梯度离心(Ficoll-Paque Plus,GE Life Sciences目录号17144003)从健康供体血液中富集外周血单核细胞(PBMC),并用hVISTA加载的dextramer(也称为多聚体)染色,并在如上所述的HBSS+MES缓冲液中稀释荧光团缀合。图4B显示了填充的直方图,其从深灰色到较浅描绘了在pH 6.0下与CD19+B细胞、CD4+T细胞、CD8+T细胞、CD56+NK细胞和CD14+单核细胞的结合。未填充的实线边界和虚线边界直方图分别描绘了在pH 7.4下与总PBMC淋巴细胞和单核细胞的结合。结果显示,hVISTA可以在酸性pH下结合许多白细胞,但在生理pH下并非显著结合。

[1242] 在滴定的抗人VISTA抗体或同种型匹配的非VISTA特异性抗体的存在下,在pH 6下用hVISTA多聚体对激活的人CD4+T细胞进行染色。如图4C所示的结果显示相对于抗体浓度的VISTA多聚体MFI。抗hVISTA抗体(VISTA抗体3;方形)而不是非VISTA特异性对照抗体(圆形),以浓度依赖性方式阻断hVISTA与激活的CD4+T细胞的结合。包含未用hVISTA加载的多聚体染色的CD4+T细胞的PE MFI作为对照(单个三角形)。

[1243] 图4D显示了在pH 6.0下对硫酸乙酰肝素突变体中国仓鼠卵巢(CHO)细胞(细胞系pGSD-677,美国典型培养物保藏中心)的VISTA多聚体染色的代表性二维流式细胞术图,所述细胞被转染以表达全长人PSGL-1(SEQ ID NO:3;核酸NM_003006.4)。在存在或不存在滴定的抗VISTA阻断抗体(mAb 3)的情况下进行染色。VISTA多聚体未染色的细胞显示为对照。将PSGL-1抗体(BD Biosciences目录号562758)染色绘制在y轴上,将VISTA多聚体染色绘制在x轴上。

[1244] 从C57BL6/J小鼠(杰克逊实验室目录号000664)收集脾细胞,并在pH 6.0或7.4下

用mVISTA ECD/人IgG Fc(片段,可结晶)嵌合融合蛋白染色,接着用荧光团缀合的抗人IgG Fc二抗(杰克逊免疫研究目录号109-065-098)染色。由图4E中的直方图描绘的结果显示,mVISTA在pH 6.0下比在生理pH(约pH7.4)下更有效地结合鼠脾细胞。从深灰色到浅灰色,填充的直方图描绘了在pH 6.0下与CD8+T细胞、CD11b+髓样细胞和CD4+T细胞的结合。未填充的直方图描绘了在pH 7.4下与总脾细胞的结合。

[1245] 实施例5:VISTA在酸性pH下选择性地介导细胞:细胞粘附和免疫抑制

[1246] 此实施例显示,VISTA在酸性pH下比在中性或生理pH下更有效地介导细胞:细胞粘附和抑制T细胞激活。

[1247] 建立了酸性pH相容的基于流式细胞术的细胞/细胞缀合物测定。将异位表达全长人VISTA的293T细胞(永生化的人胚胎肾细胞系,ATCC目录号CRL-3216)或载体用CFSE(羧基荧光素琥珀酰亚胺酯;Fisher Scientific目录号C34554)标记。将CHO细胞用CellTrace™Far Red(Fisher Scientific目录号C34564)标记。然后将Vector或VISTA 293T细胞与CHO细胞在pH 7.0或pH 6.0缓冲液中以1:1的比率混合,并在室温下孵育1小时。通过流式细胞术评估CHO和293T细胞/细胞缀合物的形成。图5A至图5B中所示的结果表明,表达VISTA的293T细胞在酸性pH下优先粘附至CHO细胞,并且包含抗VISTA阻断抗体(VISTA mAb 3;红色条)抑制了VISTA介导的细胞/细胞粘附。

[1248] 建立了酸性pH相容的T细胞抑制测定。将表达NFkB启动子驱动的萤光素酶报告基因的Jurkat细胞(永生化的人T细胞系,ATCC目录号TIB-152)与异位表达全长人VISTA和抗人T细胞受体激动剂抗体克隆OKT3的单链可变片段的293T细胞(永生化的人胚胎肾细胞系,ATCC目录号CRL-3216)在各种pH的HBSS+MES缓冲液中以10:1的Jurkat:293T细胞比率共培养。将抗VISTA阻断抗体(VISTA mAb 3)或同种型匹配的非VISTA特异性对照抗体以10μg/mL添加到共培养物中。孵育后,通过测量萤光素酶活性(1秒间隔,Promega目录号G7940)对Jurkat T细胞激活进行定量。结果显示在图5C至图5D中。图5C显示了在不同pH下用抗VISTA(红色方形)或对照抗体(蓝色圆形)处理的Jurkats中萤光素酶单位的图。图5D显示了在每个测试的pH下,抗VISTA抗体处理的共培养物中的萤光素酶信号除以对照抗体处理的共培养物中的萤光素酶信号的图。结果显示,VISTA介导的T细胞抑制在酸性pH下最有效。

[1249] 实施例6:VISTA通过细胞内再循环内体运输

[1250] 此实施例显示VISTA可以发现于细胞内的内体、特别是Rab11+再循环内体中,并且可以经由内体运输再循环至细胞表面和从细胞表面再循环。抗VISTA抗体在酸性pH下结合VISTA的强度影响其在内体运输过程中保持与VISTA结合的能力。

[1251] 通过磁性激活的细胞分选从PBMC分离出单核细胞。然后将单核细胞和293T细胞均固定在4%多聚甲醛中,并在细胞内用抗VISTA或对照抗体针对Rab5、Rab7或Rab11进行染色。对照抗体(“cAb”)作为与抗VISTA抗体相同的同种型的非VISTA结合抗体,未检测其结合表达人VISTA的单核细胞或293T细胞。抗VISTA和对照抗体用Alexa488直接标记。使用Alexa594抗兔Ig二抗检测Rab抗体。进行Hoescht 33342染色以鉴定细胞核。使用旋转盘共聚焦显微镜捕获图像。图6A显示了在表达人VISTA的293T细胞内VISTA、Rab5(早期内体标记物)、Rab7(晚期内体标记物)和Rab11(再循环内体标记物)的共定位。图6B显示了VISTA和Rab11在人单核细胞内的共定位。细胞内VISTA与Rab11+再循环内体共定位。

[1252] 为了评估VISTA通过内体再循环的能力,使用在生理和酸性pH下具有不同的VISTA

结合特性的三种抗hVISTA抗体(VISTA mAb 1、2和3)进行了内溶酶体依赖性抗体药物缀合物杀伤测定。首先进行SPR测定,以比较pH 7.4、6.7和6.0下所有三种VISTA抗体的hVISTA结合谱。在含有固定化蛋白A的Biacore®T100(GE Healthcare)CM5生物传感器上捕获VISTA抗体,然后使100nM hVISTA-ECD(具有7xHis尾部的SEQ ID NO:1的氨基酸32-193,即AFKVATPYSL YVCPEGQNVT LTCRLLGPVD KGHDVTFYKT WYRSSRGEVQ TCSERRPIRN LTFQDLHLHH GGHQAANTSH DLAQRHGLES ASDHHGNFSI TMRNLTLLDS GLYCCLVVEI RHHHSEHRVH GAMELQVQTG KDAPSNCVVY PSSSQESENI TAHHHHHHH;SEQ ID NO:325)在37℃下在指定的pH下的PBST运行缓冲液中流动。将减去参考的传感器图针对"结合"报告点进行归一化并绘制。VISTA抗体3"mAb 3"(图6C,顶部)在酸性pH下展现出最大程度的VISTA结合损伤,接着是VISTA抗体2"mAb 2"(图6C,中间),其仅中度受损。VISTA抗体1("mAb 1")在酸性和生理pH条件下均保持强大的VISTA结合(图6C,底部)。

[1253] 如下进行溶酶体依赖性抗体药物缀合物杀伤测定。将内源表达人VISTA的AML3细胞(永生化的人单核细胞细胞系,ATCC CRL-9589)与滴定的抗VISTA抗体或非VISTA特异性对照抗体和与组织蛋白酶B敏感性接头和细胞毒性微管溶素有效载荷缀合的抗人IgG二抗一起培养。由于组织蛋白酶B主要在晚期内体和溶酶体中具有活性,因此与VISTA通过早期内体和再循环内体循环的抗VISTA抗体将经历低水平的接头裂解,并且结果是低水平的细胞毒性有效载荷释放和细胞死亡。在酸性内体中与VISTA分离并被分为晚期内体和溶酶体的抗VISTA抗体将经历更高水平的接头裂解。培养五天后,通过CellTiter(Promega目录号G7573)测量细胞活力。图6D显示了此测定的结果,AML3活力(Cell Titer Glo)绘制在y轴上,并且一抗浓度绘制在x轴上。一抗的EC50计算值:VISTA抗体1,倒三角形,0.485μg/mL;VISTA抗体2,圆形,0.092μg/mL;VISTA抗体3,方形,0.006μg/mL;对照,三角形,1.085μg/mL。在酸性pH下,抗体效价与抗VISTA抗体结合呈负相关。

[1254] 为了确认在酸性pH下的结合是效价差异的原因,对VISTA抗体3进行了亲和力优化,从而提高了其在酸性pH下结合VISTA的能力。图6E显示了使用针对图6C描述的测定条件,比较VISTA抗体3与此变体VISTA抗体3c的hVISTA抗体结合谱的SPR测定。VISTA抗体3在酸性pH下再次展现出VISTA结合受损,而变体VISTA抗体3c在酸性和生理pH下展现出可比较的VISTA结合。图6F示出了在针对图6D描述的杀伤测定中的VISTA抗体3c(菱形)的活性。酸性pH优化的VISTA抗体3的变体展现出比原始抗体的效价低31倍的效价,这表明在酸性pH下抗VISTA抗体结合能力受损导致VISTA再循环过程中抗体结合的损失。

[1255] 基于这些发现,提出了一种再循环模型,其中VISTA经由早期内体和再循环内体再循环至细胞表面和从细胞表面再循环。在图6G中描绘了此模型。抗VISTA抗体可以通过这些内体与VISTA一起再循环使用,从而保持靶标结合。但是,在酸性pH下具有受损的VISTA结合的VISTA抗体、特别是在酸性pH下具有较快解离速率的VISTA抗体在再循环过程中可能会与VISTA分离,并在细胞内被捕获或降解,从而导致不良的靶标结合和循环抗体的持续消耗。相比之下,在酸性pH下、特别是在酸性微环境(如肿瘤)中结合并保持与VISTA结合的抗体可以维持较高水平的靶标结合,并且在体内展现更长的平均停留时间。

[1256] 实施例7:在生理pH下缺乏结合的VISTA抗体的优越性

[1257] 诸位发明人已证明VISTA是酸性pH选择性免疫受体,这表明在酸性pH下能良好结合的抗体靶向VISTA的重要性和实用性。此外,由于多种原因,在生理pH下不结合或可忽略

地结合VISTA的抗体是有利的。首先,由于VISTA在循环的骨髓单核细胞、特别是单核细胞和嗜中性粒细胞上的表达相对丰富,因此在生理pH下结合VISTA的抗体在血液中会经历高水平的靶标介导的药物处置(TMDD)。VISTA通过细胞内体再循环的倾向加剧了这种作用,从而导致抗VISTA抗体的内化和降解。对于在酸性pH下结合受损的抗体来说,这种次要作用特别成问题,正如对于结合VISTA的富组氨酸配体界面的抗体所观察到的那样。两种作用都将减少循环中抗VISTA抗体的量,减少到达肿瘤的抗体的量,从而减少抗体的预期生物学活性。其次,在生理pH下结合VISTA并具有效应子功能的抗体(如诱导抗体依赖性细胞的细胞毒性(ADCC)、抗体依赖性细胞的吞噬作用(ADCP)或免疫调节有效载荷的递送)将使循环的骨髓单核细胞受到这些效应子功能的影响,从而可能导致不期望的作用,如循环的嗜中性粒细胞耗减或激活。因此,诸位发明人发现在酸性pH下与huVISTA结合但在生理pH下可忽略不计地结合的抗体具有双重优势:(1)在相关部位(如肿瘤)的更好暴露和(2)在具有效应子功能(如ADCC、ADCP或免疫调节性有效载荷的递送)的抗体的情况下降低毒性。此外,由于VISTA本身是酸性pH选择性免疫受体,因此在生理pH下阻断VISTA的配体界面对于调节VISTA受体-配体的活性可能是不必要的。因此,如下所述产生了在酸性pH下与huVISTA结合但在生理pH下并非显著结合的抗体。

[1258] 实施例8:在酸性pH比生理pH下与人VISTA优先结合的抗VISTA抗体的分离

[1259] 此实施例描述了相对于中性或生理pH,在低(酸性)pH下与人VISTA优先结合的抗体的产生。

[1260] 如下构建和筛选抗体的抗VISTA抗原结合片段的文库。使用从用全长人VISTA(hVISTA)免疫的HuMab小鼠分离的遗传物质创建抗体文库。这些抗体被格式化为scFv,并经由mRNA展示针对在低pH(pH 6.0)下全长hVISTA结合进行选择(Xu L等人(2002)Chemistry& Biology 9:933;Roberts RW和JW Szostak(1997)Proc.Natl.Acad.Sci.USA 94:12297;Kurz等人(2000)Nucleic Acids Res.28(18):E83)。经由下一代测序(NGS)分析选择输出,并鉴定在低pH下富集VISTA结合的文库成员,将其重新格式化为IgG 1.3(由具有氨基酸突变L234A、L235E和G237A的IgG1 Fc组成的无效应子IgG1恒定区),并通过SPR筛选与VISTA的结合。

[1261] 使用Biacore®T200仪器(GE Healthcare)进行表面等离子体共振(SPR)分析以测量VISTA Ab在酸性和生理pH下的缔合速率(定义为ka或k_{on},1/M单位)、解离速率(定义为kd或k_{off},s^{-1})和亲和力常数(定义为K_D,M单位)。将蛋白A(Fisher Scientific目录号21181)在pH 4.5的10mM乙酸钠中稀释至20ug/ml,并按照制造商的胺偶联方案(GE Healthcare)固定在CM5生物传感器的流动池上,从而靶向每个流动池的6,000RU固定化密度的蛋白A。在37℃下使用pH 7.4和6.0下的PBST(137mM氯化钠、2.7mM氯化钾、10mM磷酸盐缓冲液、0.05%吐温20)运行缓冲液进行SPR实验。将抗体在PBST pH7.4中稀释至20nM,并以5ul/min的速度跨活性生物传感器流动池捕获50秒。在pH 7.4和6.0运行缓冲液中制备了浓度为50-0.2nM单价hVISTA-ECD(SEQ ID NO:325)的浓度系列,并以40ul/min的速度注射至捕获的抗体上,以测量缔合和解离。在两次测定周期之间,两次15秒注射pH 1.5的10mM甘氨酸,以再生A蛋白捕获表面。速率常数k_a(k_{on})和k_d(k_{off})源自参考流动池和减去0nM空白的传感器图,并在Biacore® T200评估软件v.2.0中拟合为1:1结合模型。对于每种VISTA抗体,计算在pH 6下的k_{off}/在pH 7.4下的k_{off}的比率,以鉴定在酸性pH下展现出缓慢解离速率而在生理pH下展

现出快速解离速率的抗体。

[1262] 重新格式化为IgG1.3抗体的六种抗体在pH 6和pH 7.4下均表现出接近相等的亲和力。特别地,两种抗体在pH 6.0下的解离速率比在pH 7.4下慢(即,k_{off}在pH 7.4下比在pH 6.0下更快)。这两种huVISTA抗体的可变区称为P1-061015和P1-061029,并且包含这些可变区并格式化为IgG1.3抗体的抗体分别称为P1-061015.IgG1.3和P1-061029.IgG1.3。表1中提供了P1-061015.IgG1.3和P1-061029.IgG1.3的k_{off}速率。

[1263] 表1:在pH 6.0和pH 7.0下选择的抗体的k_{off}

[1264]

抗体名称	pH 6k_{off}(s^{-1})	pH 7k_{off}(s^{-1})	pH 6/pH 7k_{off}
P1-061015.IgG1.3	$1.4x10^{-3}$	$2.3x10^{-3}$	0.6
P1-061029.IgG1.3	$4.8x10^{-3}$	$9.1x10^{-3}$	0.5

[1265] P1-061015和P1-061029的重链和轻链CDR1、CDR2和CDR3序列在下面的表2中提供,并且也显示在本公开文本的实施例部分后面的序列表中。

[1266] 表2:在pH 6.0下比在pH 7.4下与huVISTA优先结合的huVISTA抗体的氨基酸序列

[1267]

P1 ID	VH基因	VH CDR1	VH CDR2	VH CDR3
P1-061015.IgG1.3	3-33	GFTFSSYAMH (SEQ ID NO: 95残基26-35)	IIWYDGSNK YYADSVKG (SEQ ID NO: 95残基50-66)	DSGFYSSYYFDY (SEQ ID NO: 95残基99-110)
P1-061029.IgG1.3	3-09	GFTLDDYAMH (SEQ ID NO: 67残基26-35)	GINWNSANI GYADSVKG (SEQ ID NO: 67残基50-66)	VPGYSGGWIDAFDV (SEQ ID NO: 67残基99-112)
	VL基因	VL CDR1	VL CDR2	VL CDR3
P1-061015.IgG1.3	L6	RASQSVSSSYLA (SEQ ID NO: 96残基24-35)	DASNRAT (SEQ ID NO: 96残基51-57)	QQYNSYPYT (SEQ ID NO: 96残基90-98)
P1-061029.IgG1.3	A27	RASQSVSSSYLA (SEQ ID NO: 68残基24-35)	GASSRAT (SEQ ID NO: 68残基51-57)	QQYGSSPFT (SEQ ID NO: 68残基90-98)

[1268] 实施例9:进一步工程化P1-061015和P1-061029抗VISTA抗体以开发酸性pH选择性抗体

[1269] 此实施例描述了进一步工程化在实施例2中鉴定的可变区P1-061015和P1-061029的以获得抗huVISTA可变区,相对于pH 7.4,其在pH 6.0下的结合之间具有较高的k_{off}比率。

[1270] 通过分别在P1-061015和P1-061029的VH CDR中引入特异性突变来构建两个文库。文库仅允许最可能改善在低pH下的结合的氨基酸取代,即天冬氨酸、谷氨酸和组氨酸。文库

还允许在每个CDR中进行单氨基酸和双氨基酸取代,并允许跨CDR重组(每条链最多6个氨基酸取代)。图7A显示了引入P1-061029的重链CDR3氨基酸序列中以形成P1-061029文库的突变。所述图指示排除了特定序列以避免引入负值(例如DG)。

[1271] 经由酵母表面展示,通过在pH 6.0下与全长hVISTA的几轮结合来筛选‘029和’015文库。通过在阳性(pH 6.0下与huVISTA结合)与阴性(pH 7.4下与huVISTA结合)(图7B中所示)选择之间进行切换,进行更多轮的选择,其中在阴性选择轮中收集了在pH 7.4下不与VISTA结合的文库成员。通过NGS分析选择输出。在第9轮选择后,针对在pH 6.0和pH 7.4下与人VISTA的结合经由流式细胞术分析了在pH 6.0下与huVISTA结合的’029文库成员。图7C显示了代表性二维流式细胞术图,其显示了9轮选择之后的变体池。VISTA结合绘制在y轴上,并且变体抗体表达绘制在x轴上。显示了在各种抗体浓度和pH下的结合数据。结果表明,与人VISTA、特别是在20nM下的pH 6选择性结合非常强烈。

[1272] 使用另一种方法从‘029文库分离出‘029的其他后代克隆。一些克隆与通过第一种方法鉴定的克隆相同,并分离了九个另外的克隆。

[1273] 将选择用于进一步分析的从’029文库分离出的19个克隆重新格式化为IgG1.3抗体。这些克隆的重链CDR中的氨基酸相对于‘029VH CDR的那些的差异如表5所示。

[1274] 表5:衍生自‘029亲本抗体的抗体的VH CDR1、CDR2和CDR3氨基酸序列(用下划线分隔)

[1275]

名称	CDR1 (pos 26-35)	CDR2 (pos 50-66)	CDR3 (pos 99-110)	SEQ ID NO
P1-061029	GFT**LD**D**Y**AMH	GI**N**WNS**AN**IGYADSVKG	VPGYS**G**GWIDA**F**D**V**	67
P1-068757	----E-E---	------EE---------	----------E-D	71
P1-068759	----E-E---	--D---E----------	----------E-D	87
P1-068761	----E-E---	------EE---------	-----H-----E--	51
P1-068763	----E-----	--D---E----------	-----H-----E--	91
P1-068765	---DE-----	------EE---------	----------E-D	63
P1-068767	----E-----	--D---E----------	----------E-D	55
P1-068769	----E-E---	------DH---------	----------E-D	83
P1-068771	----E-E---	------HE---------	----------E-D	75
P1-068773	----E-----	--D---D----------	----------E-D	59
P1-068775	----E-E---	--D---EE---------	-----H-----E-D	79
P1-069059	----E-----	------DH---------	----------E-D	11
P1-069061	----E-----	-------E---------	----------E-D	15
P1-069063	----E-----	-------E---------	----------D-E	19
P1-069065	----E-E---	------DD---------	----------	23
P1-069067	----------	------EE---------	----------D-E	27
P1-069069	----------	------EE---------	----------D--	31
P1-069071	----E-E---	-------D---------	-----E--------	35

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P1-069073   ----E-----_--D---D----------_----------E-D    39
P1-069075   ----E-----_----D--E---------_-----H-----E--    43
P1-069077   ----E-E---_------DE---------_--------------    47
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[1276]

[1277] 通过表面等离子体共振(SPR)测量格式化为IgG1.3抗体的‘029后代克隆和亲本‘029抗体中的每一个的几种制剂在pH 6.0和7.4下与人VISTA的结合。使用Biacore®T100仪器(GE Healthcare)进行SPR分析以测量在酸性和中性pH下VISTA Ab的koff和K_D结合亲和力测量结果。将蛋白A(ThermoFisher Scientific目录号21181)在pH 4.5的10mM乙酸钠中稀释至20ug/ml,并按照制造商的胺偶联方案(GE Healthcare)固定在CM5生物传感器的流动池上,从而靶向每个流动池的2,000RU固定化密度的蛋白A。在37℃下使用pH 7.4和6.0下的PBST(137mM氯化钠、2.7mM氯化钾、10mM磷酸盐缓冲液、0.05％ Tween®20)运行缓冲液进行SPR实验。将抗体在PBST pH 7.4中稀释至25nM,并以5ul/min的速度跨活性生物传感器流动池捕获60秒。在pH 7.4和6.0运行缓冲液中制备了浓度为50-5nM单价hVISTA-ECD(SEQ ID NO:325)的浓度系列,并以40ul/min的速度注射至捕获的抗体上,以测量缔合和解离。在两次测定周期之间,两次15秒注射pH 1.5的10mM甘氨酸,以再生A蛋白捕获表面。速率常数k_a(k_{on})和kd(k_{off})源自参考流动池和0nM减去空白的传感器图,并在Biacore®T200评估软件v.2.0中拟合为1:1结合模型。将亲和力常数K_D计算为每种VISTA抗体的速率常数k_{off}/k_{on}的比率。

[1278] 将最大(或量级)人VISTA结合响应定义为每种抗体在50nM VISTA注射结束时减去参考的“结合”报告点响应,并以响应单位(RU)报告。在图7D中绘制了对每种抗体的最大人VISTA结合响应(RU)。绘制了平均结合响应(两至四个重复抗体之间),并且误差条代表标准差。结果指示,选择的‘029后代克隆在pH 6.0下与hVISTA结合,但在pH 7.4下不结合(除了在亲本‘029克隆以外,所有代表pH 7.4下结合的空心圆都位于图的底部)。

[1279] 使用上述方法,通过SPR测定了‘029及其后代在pH 6.0下的k_{off}速率,并且表示在图7E中。图中的虚线表示‘029的k_{off}速率,虚线左侧的克隆在pH 6.0下的k_{off}速率相对于亲本‘029抗体的k_{off}速率较慢,而在右侧的克隆在pH 6.0下的k_{off}速率相对于亲代‘029抗体的k_{off}速率较快。

[1280] 图7F显示了在中性和酸性pH下与‘029、‘761和‘767抗体的代表性hVISTA SPR结合传感器图。绘制了减去参考的50nM和5nM huVISTA传感器图。在中性pH值下,对于‘761和‘767,观察到<10RU VISTA结合信号,因此为了充分测量和比较‘761和‘767与‘029的k_{off}和K_D,需要利用在生理pH下μM VISTA浓度的SPR动力学测定。

[1281] 对于此测定,将‘029、‘761和‘767重新格式化为hIgG1f同种型,并分别表示为标准hIgG1f和hIgG1f去岩藻糖基化格式,以与hIgG1.3f Fc进行比较。使用Biacore®T100仪器(GE Healthcare)进行SPR动力学测定以测量在酸性和生理pH下VISTA Ab的koff和K_D结合亲和力测量结果。将蛋白A(ThermoFisher Scientific目录号21181)在pH 4.5的10mM乙酸钠中稀释至20μg/ml,并按照制造商的胺偶联方案(GE Healthcare)固定在CM5生物传感器的流动池上,从而靶向每个流动池的2,000RU固定化密度的蛋白A。在37℃下使用pH 7.4和6.0下的PBST(137mM氯化钠、2.7mM氯化钾、10mM磷酸盐缓冲液、0.05％吐温20)运行缓冲液进行SPR实验。将抗体在PBST pH 7.4中稀释至25nM,并以5ul/min的速度跨活性生物传感器

流动池捕获45秒。运行缓冲液中制备了1600-0.78nM(pH 7.4)和100-0.78nM(pH 6.0)单价hVISTA-ECD(SEQ ID NO:325)的浓度系列,并以40ul/min的速度注射到捕获的抗体上度量关联和分裂。在两次测定周期之间,两次15秒注射pH 1.5的10mM甘氨酸,以再生A蛋白捕获表面。速率常数k_a(k_{on})和kd(k_{off})源自参考流动池和0nM减去空白的传感器图,并在Biacore® T200评估软件v.2.0中拟合为1:1结合模型。将亲和力常数K_D计算为每种VISTA抗体的速率常数k_{off}/k_{on}的比率。计算在pH 7.4/pH 6.0下k_{off}和K_D的比率以比较酸性pH相对于生理pH的解离速率和亲和力改善。尽管先前使用50nM hVISTA无法测定‘761和‘767的中性pH结合速率常数(图7D和图7F),但将中性pH VISTA浓度范围增加至1.6μM会导致对于那些克隆的结合响应(>10RU)以拟合为1:1结合模型。这些酸性选择性VISTA抗体的动力学数据如表6所示。‘029亲本在两个pH下均展现出相同的k_{off}值,而‘761和‘767展现出在k_{off}方面pH 6相对于pH7.4的超过10倍的选择性和在K_D方面pH 6相对于pH 7.4的超过2000倍的选择性。人VISTA结合速率常数在hIgG1.3f、hIgG1f和去岩藻糖基化的hIgG1f同种型变体中是保守的。

[1282] 表6:通过SPR测定的VISTA抗体的结合特征

[1283]

抗体	同种型	pH 7.4			pH 6.0			Kd 比率 (7.4/6)	KD 比率 (7.4/6)
		ka (1/Ms)	kd (1/s)	KD (M)	ka (1/Ms)	kd (1/s)	KD (M)		

[1284]

P1-061029	hIgG1.3f	1.6E+05	6.8E-03	4.2E-08	1.1E+06	7.9E-03	7.2E-09	0.9	5.8
	hIgG1f	1.7E+05	7.4E-03	4.2E-08	1.1E+06	8.0E-03	7.1E-09	0.9	5.9
	hIgG1f 去岩藻糖基化	1.7E+05	7.2E-03	4.1E-08	1.1E+06	7.8E-03	6.9E-09	0.9	5.9
P1-068761	hIgG1.3f	3.8E+03	4.2E-02	1.1E-05	3.7E+05	1.6E-03	4.3E-09	26.3	2558.1
	hIgG1f	1.2E+03	4.2E-02	3.5E-05	3.6E+05	1.5E-03	4.2E-09	28.0	8333.3
	hIgG1f 去岩藻糖基化	5.1E+03	4.2E-02	8.2E-06	3.7E+05	1.5E-03	4.1E-09	28.0	2000.0
P1-068767	hIgG1.3f	1.9E+03	3.6E-02	1.9E-05	3.3E+05	2.6E-03	7.8E-09	13.8	2435.9
	hIgG1f	1.5E+03	3.2E-02	2.2E-05	3.2E+05	2.6E-03	8.0E-09	12.3	2750.0
	hIgG1f 去岩藻糖基化	1.3E+03	3.3E-02	2.4E-05	3.3E+05	2.6E-03	7.9E-09	12.7	3038.0
α-VISTA 酸性pH敏感性	hIgG1.3f	2.2E+05	7.8E-04	3.6E-09	2.8E+06	9.0E-02	3.2E-08	0.01	0.1

[1285] 使用Biacore® T100仪器(GE Healthcare)在pH 7.4与pH 6.0之间的pH值下(即在pH 6.9和pH 6.45下)测量了‘029、‘761和‘767(作为IgG1.3抗体)的人VISTA结合动力学。将蛋白A(ThermoFisher Scientific目录号21181)在pH4.5的10mM乙酸钠中稀释至20ug/ml,并按照制造商的胺偶联方案(GE Healthcare)固定在CM5生物传感器的流动池上,从而靶向每个流动池的2,000RU固定化密度的蛋白A。在37℃下使用pH 7.4、6.9、6.45和6.0下的PBST(137mM氯化钠、2.7mM氯化钾、10mM磷酸盐缓冲液、0.05%吐温20)运行缓冲液进行测定。将抗体在PBST pH 7.4中稀释至25nM,并以5ul/min的速度跨活性生物传感器流动池捕获45秒。在pH 7.4、6.9、6.45和6.0运行缓冲液中制备了浓度为100-0.78nM单价hVISTA-ECD(SEQ ID NO:325)的浓度系列,并以40ul/min的速度注射至捕获的抗体上,以测量缔合和解离。在两次测定周期之间,两次15秒注射pH 1.5的10mM甘氨酸,以再生A蛋白捕获表面。速率常数k_a(k_{on})和kd(k_{off})源自参考流动池和0nM减去空白的传感器图,并在Biacore® T200评估软件v.2.0中拟合为1:1结合模型。将亲和力常数K_D计算为每种VISTA抗体的速率常数k_{off}/k_{on}的比率。计算每个pH相对于pH6.0的k_{off}和K_D之比,以评价VISTA k_{off}和K_D如何随着缓冲液pH转变为生理性而变化,并且显示在表7中。与pH 6.0相比,在各个测试的pH下,‘029亲本展现出一致的k_{off},而‘761和’767后代在pH 6.9下展现出至少快10倍的VISTA k_{off}和弱100倍的

VISTA K_D。随着缓冲液pH从酸性转变为生理性,针对761和767的VISTA k_{off}和K_D二者均会减弱。‘761和‘767的生理pH数据的比较参考表7,并且标有星号(*)。

[1286] 表7:不同pH值下‘029、‘761和‘767抗体的动力学结合特征

[1287]

抗体	pH	ka(1/Ms)	kd (1/s)	KD (M)	与pH 6.0的koff比率	与pH 6.0的KD比率
P1-061029（亲本）	6.0	2.9E+06	5.7E-03	2.0E-09	1.0	1.0
	6.45	7.4E+05	4.0E-03	5.3E-09	0.7	2.7
	6.9	4.1E+05	5.7E-03	1.4E-08	1.0	7.1
	7.4	2.5E+05	6.4E-03	2.6E-08	1.1	13.2
P1-068761	6.0	6.0E+05	6.6E-04	1.1E-09	1.0	1.0
	6.45	1.1E+05	2.1E-03	2.0E-08	3.2	18.4
	6.9	4.8E+04	8.9E-03	1.9E-07	13.4	170
	7.4 *	3.8E+03	4.2E-02	1.1E-05	~63.6	~10000
P1-068768	6.0	5.6E+05	1.9E-03	3.4E-09	1.0	1.0
	6.45	1.3E+05	4.8E-03	3.8E-08	2.5	11.0
	6.9	7.4E+04	2.9E-02	4.0E-07	15.3	115.1
	7.4 *	1.9E+03	3.6E-02	1.9E-05	~19.0	~5000

[1288] 表7中的数据指示,与pH 6.0下相比,在pH 6.45下‘761和‘767与hVISTA的结合亲和力低至少低10倍;与pH 6.0下相比,在pH 6.9下‘761和‘767与hVISTA的结合亲和力低至少100倍;与pH 6.0下相比,在pH 7.4下‘761和‘767与hVISTA的结合亲和力低至少1000倍。

[1289] ‘015文库还显示出对与VISTA的pH 6选择性结合的轻微偏爱。表8中显示了后代克隆相对于‘015VH CDR的氨基酸差异。使用上述‘029分析中所述的相同方法,经由SPR测量了‘015后代克隆和亲本‘015(全部作为IgG1.3抗体)中的每一个的几种制剂在pH 6.0和7.4下与人VISTA的结合,并且显示在表8中。

[1290] 表8:衍生自‘015亲本抗体的抗体的VH CDR1、CDR2和CDR3氨基酸序列(用下划线分隔)

[1291]

名称	CDR1 (pos 26-35)	CDR2 (pos 50-66)	CDR3 (pos 99-110)	SEQ ID NO
P1-061015	GFTFS**S**YA**M**H	IIW**Y**DGS**NKYY**ADSVKG	DSGFY**SS**YYFDY	95
P1-068736	-----E-----	-D-------	D-------	-----D-----D	107
P1-068738	-----E--H-	---D----H--------	-----ED-----	131
P1-068740	-----D----	-------D-D-------	-----D-----D	115
P1-068742	-----D----	-------D-D-------	-----ED-----	119
P1-068744	-----E-----	H---------E------	-----E-----E	103
P1-068746	----------	--------HH-------	-----D------	123
P1-068748	-----HH---	--------DD-------	-----D------	99
P1-068750	-----D-D--	E--D-----------	-EE---------	127
P1-068752	----------	E--------D-------	-----D-----E	111
P1-068754	-----D-D--	E--D----------	----H-D-----	135

[1292] 表9和表10中显示了‘029和’015及其后代克隆在pH 6.0和7.4下与huVISTA结合的动力学(如通过SPR所测定的)的总结。

[1293]

表 9: '029 克隆及其后代的 huVISTA 动力学总结和 VH CDR 序列

ID	Avg 7.4 ka (1/Ms)	Avg 7.4 kd (1/s)	Avg 7.4 KD (M)	Avg 6.0 ka (1/Ms)	Avg 6.0 kd (1/s)	Avg 6.0 KD (M)	VH CDR 1 (pos 26-35)	VH CDR 2 (pos 50-66)	VH CDR 3 (pos 99-110)	SEQ ID NO
P1-069077	6.0E+04	1.9E-03	3.1E-08	6.3E+05	1.2E-04	1.9E-10	....E.E...	.......DE.....	.....	47
P1-069065	5.9E+04	2.3E-03	3.9E-08	5.7E+05	2.2E-04	3.8E-10	....E.E...	.......DD.....	.....	23
P1-069075	1.3E+05	2.3E-03	1.8E-08	1.3E+06	2.9E-04	2.2E-10	....E.....	....D..E.....	.....H.....E..	43
P1-069071	4.3E+04	4.0E-03	9.3E-08	7.0E+05	5.1E-04	7.3E-10	....E.E...	.......D.....	....E.....	35
P1-069061		弱，快 kd		4.3E+05	1.1E-03	2.5E-09	....E.....	.......E.....	.....E.D	15
P1-069069	9.0E+04	7.5E-03	8.4E-08	1.4E+06	1.2E-03	8.6E-10	.....	.......EE.....	.....D..	31
P1-068761		弱，快 kd		3.8E+05	1.4E-03	3.8E-09	....E.E...	.......EE.....	....H.....E..	51
P1-069059		弱，快 kd		3.4E+05	1.6E-03	4.8E-09	....E.....	.......DH.....	.....E.D	11
P1-068767		弱，快 kd		3.4E+05	2.6E-03	7.6E-09	....E.....	..D...E.....	.....E.D	55
P1-068773		弱，快 kd		3.0E+05	2.9E-03	9.4E-09	....E.....	..D...D.....	.....E.D	59
P1-069063	1.2E+05	2.7E-02	2.3E-07	1.9E+06	4.4E-03	2.4E-09	....E.....	.......E.....	.....D.E	19
P1-069067	1.0E+05	2.7E-02	2.9E-07	1.7E+06	4.5E-03	2.7E-09	.....	.......EE.....	.....D.E	27
P1-069073		弱，快 kd		6.1E+05	5.8E-03	9.4E-09	....E.E...	.......E.....	.....E..	39
P1-061029	2.9E+05	5.6E-03	1.9E-08	1.6E+06	5.8E-03	3.6E-09	GFTLDDYAMH	GINWNSANIGYADSVKG	VPGYSGGWIDAFDV	67
P1-068765		无结合		3.7E+05	7.0E-03	1.9E-08	...DE.....	.......EE.....	.....E.D	63
P1-068757		无结合		8.9E+05	1.7E-02	1.9E-08	....E.E...	.......EE.....	.....E.D	71
P1-068771		无结合		7.6E+05	1.8E-02	2.5E-08	....E.E...	.......HE.....	.....E.D	75
P1-068769		无结合		8.1E+05	4.0E-02	5.5E-08	....E.E...	.......DH.....	.....E.D	83
P1-068775		无结合		1.8E+06	4.7E-02	2.3E-08	....E.E...	..D...EE.....	.....H.....E.D	79
P1-068759		无结合		1.3E+06	8.0E-02	6.0E-08	....E.E...	..D...E.....	.....E.D	87

[1294]

表 10: '015 克隆及其后代的 huVISTA 动力学总结和 VH CDR 序列

克隆	Avg 7.4 ka (1/Ms)	Avg 7.4 kd (1/s)	Avg 7.4 KD (M)	Avg 6.0 ka (1/Ms)	Avg 6.0 kd (1/s)	Avg 6.0 KD (M)	HCDR序列 (pos 26-35) (pos 50-66) (pos 99-110)	SEQ ID NO
P1-061015	2.3E+05	2.0E-03	8.8E-09	1.8E+06	9.5E-04	5.4E-10	GFTFSSYAMH_IIWYDGSNKYYADSVKG_DSGFYSSYYFDY	95
P1-068748	无结合			1.4E+06	1.5E-03	1.0E-09	.....HH...._.....DD....._.....D.....	99
P1-068744				1.3E+06	1.8E-03	1.3E-09	.....E.....H....._.....E....._.....E.....E	103
P1-068736				8.4E+06	9.5E-03	1.1E-09	.....E....._D....._D....._.....D.....D	107
P1-068752				6.1E+06	3.4E-02	5.6E-09	....._.....E....._D....._.....D.....E	111
P1-068740				太快	4.7E-02	ND	.....D....._.....D.D....._.....D.....D	115
P1-068742				太快	>1E-02	ND	.....D....._.....D.D....._.....ED.....	119
P1-068746				太快	>1E-02	ND	....._.....HH....._.....D.....	123
P1-068750				弱			.....D.D._E..D....._.....EE.....	127

[1295] 因此,鉴定了若干'029后代克隆,它们与'029亲本相比在pH 6.0下维持或改善了与VISTA-ECD的k_{off},并且还证明了在生理pH下的弱k_{off}或与VISTA结合的损失。'015后代展

现出与VISTA-ECD的酸性pH选择性结合,其中在中性pH下未检测到与VISTA的结合,但是与‘015亲本相比,所有测定的‘015后代在pH 6.0下产生更快的k_{off}。

[1296] 实施例10:酸性pH选择性‘029后代显示出酸性pH依赖性细胞结合和效应子功能,同时保持VISTA阻断活性

[1297] 测量了克隆‘761和‘767与工程化为异位表达全长人VISTA(具有D187E取代的SEQ ID NO:1)的Raji细胞的pH依赖性结合。对于本实验,将‘761和‘767格式化为IgG1.3抗体,并通过抗人IgG二抗(Jackson Immunoresearch目录编号109-065-098)测量结合。图8A至图8B中所示的结果指示,‘761(图8A)和‘767克隆(图8B)在pH 7.2和8.1下结合不良,但在酸性pH下、特别是在pH 6.0、6.1、6.2和6.4下结合较好。将结合的MFI绘制在y轴上,并且将一抗浓度以对数刻度绘制在x轴上绘制。还显示了非线性回归。

[1298] 图8C显示了来自图8A至图8B中描述的实验的数据,所述实验测量了在不同pH下P1-068767(圆形)和同种型匹配的非特异性对照抗体(三角形)以3125ng/mL与表达人VISTA的Raji细胞的结合。“pH50”即失去50%的P1-068767结合的pH值为约6.6。结合MFI绘制在y轴上,并且缓冲液pH绘制在x轴上。还显示了非线性回归。

[1299] 图8D显示了同种型匹配的非特异性对照抗体(填充和未填充圆形分别为pH 7.0和6.0)、抗VISTA mAb 2(“对照”,参见图6C,填充和未填充方形分别为pH 7.0和6.0)、P1-068761(填充和未填充三角形分别为pH 7.0和6.0)和P1-068767(填充和未填充倒三角形分别为pH 7.0和6.0)与人单核细胞结合的MFI。如图8A至图8B所述检测结合。非pH选择性VISTA对照抗体(mAb 2)在两个pH下均结合单核细胞。两种工程化酸性pH选择性抗体在pH 6.0下均能很好地结合单核细胞,但在pH 7.0下没有比非特异性同种型匹配的对照更好地结合。因此,克隆‘761和‘767在中性pH下与VISTA的结合较弱或不结合,而在酸性pH下选择性地结合细胞上的VISTA。

[1300] 图8E显示了通过‘029(方形)、‘761(三角形)和‘767(倒三角形)对在pH 6.0下重组VISTA多聚体与激活的人CD4+T细胞的结合的可比较的阻断,而非VISTA特异性对照抗体(圆形)不阻断VISTA结合。如实施例4中所述进行此阻断测定。这些数据显示,工程化酸性pH选择性VISTA抗体仍然能够在酸性pH下阻断VISTA受体-配体结合。

[1301] 对于P1-061029.IgG1f、P1-068761.IgG1f、P1-068767.IgG1f抗体、非VISTA特异性抗体和非VISTA特异性阴性对照抗体(均表示为去岩藻糖基化IgG1抗体)测量了在生理pH下经由抗体依赖性细胞的细胞毒性(ADCC)对靶细胞(图8A至图8B中所述的表达人VISTA的相同Raji细胞)的NK细胞特异性裂解。NK细胞经由阴性珠粒选择(StemCell Technologies目录号19055)从PBMC中富集,并在补充有1μM氢化可的松(StemCell Technologies目录号07904)和500U/mL重组人IL-2(Peprotech目录号200-02)的Myelocult™培养基(StemCell Technologies目录号05150)中培养过夜。在测定的当天,将异位表达人VISTA的Raji细胞(图8A至图8B中所述)用钙黄绿素AM(Life Technologies目录号C3100MP)标记,并在生理pH下与培养的NK细胞以10:1的NK:靶细胞比率以及与P1-061029.IgG1f、P1-068761.IgG1f、P1-068767.IgG1f抗体、非VISTA特异性抗体和非VISTA特异性阴性对照抗体共培养2小时。根据上清液荧光信号(EnVision™读板器)对特异性裂解进行内插值计算。从没有抗体的共培养物获得的自发裂解信号以及最大裂解信号是通过用Delfia®裂解缓冲液(PerkinElmer目录号4005-0010)裂解靶细胞来测定的。抗体特异性裂解计算为观察到的裂

解百分比除以(最大裂解信号减去自发裂解信号)。

[1302] 图8F中提供的结果显示,相对于P1-061029和阳性对照,P1-068761.IgG1f和P1-068767.IgG1f在生理pH下介导抗体依赖性细胞毒性(ADCC)中降低的效价。

[1303] 实施例11:VISTA抗体的Cyno PK

[1304] 向人抗体幼稚食蟹猴静脉注射单次5mpk剂量的在酸性和中性pH下可比较地结合的VISTA抗体("对照";mAb2)、在酸性pH下具有受损的结合的VISTA抗体("酸性pH敏感性",mAb3)或酸性pH选择性抗体'767,以测定这些抗体的cyno PK。

[1305] 此实施例中使用的抗体的SPR结合动力学提供在表11中,并如下进行测定。评估了在酸性和中性pH下针对酸性pH选择性和对照抗VISTA抗体的Cyno VISTA交叉反应性。使用Biacore® T100仪器(GE Healthcare)对VISTA Ab进行结合亲和力测量。将蛋白A(ThermoFisher Scientific目录号21181)在pH 4.5的10mM乙酸钠中稀释至20ug/ml,并按照制造商的胺偶联方案(GE Healthcare)固定在CM5生物传感器的流动池上,从而靶向每个流动池的2,000RU固定化密度的蛋白A。在37℃下使用pH 7.4和6.0下的PBST(137mM氯化钠、2.7mM氯化钾、10mM磷酸盐缓冲液、0.05%吐温20)运行缓冲液进行测定。将抗体(格式化为IgG1.3抗体)在PBST pH 7.4中稀释至25nM,并以5ul/min的速度跨活性生物传感器流动池捕获45秒。在运行缓冲液中制备1600-0.78nM(pH 7.4)和100-0.78nM(pH 6.0)单价hVISTA-ECD(SEQ ID NO:325)和cyno VISTA-ECD(AFKVATLYSL YVCPEGQNVT LTCRVFGPVD KGHDVTFYKT WYRSSRGEVQ TCSERRPIRNLTFQDLHLHH GGHQAANTSH DLAQRHGLES ASDHHGNFSI TMRNLTLLDS GLYCCLVVEIRHHHSEHRVH GAMELQVQTGKDAPSSCVAY PSSSQESENI TAHHHHHHH;SEQ ID NO:326)的浓度系列,并将其以40ul/min注射到捕获的抗体上以测量缔合和解离。在两次测定周期之间,两次15秒注射pH 1.5的10mM甘氨酸,以再生A蛋白捕获表面。速率常数k_a(k_{on})和kd(k_{off})源自参考流动池和0nM减去空白的传感器图,并在Biacore® T200评估软件v.2.0中拟合为1:1结合模型。将亲和力常数K_D计算为每种VISTA抗体的速率常数koff/kon的比率。计算在pH 7.4/pH 6.0下k_{off}和K_D的比率以比较酸性pH相对于中性pH的解离速率和亲和力差异,并显示在表11中。所有测试的抗VISTA抗体在两个测试的pH值下均展现出可比较的(在2倍之内)人和cyno VISTA动力学结合参数,从而证实了与cyno VISTA的交叉反应性。与酸性pH相比,两种抗VISTA对照抗体在生理pH下均展现出改善的kd和更强的K_D,而酸性pH敏感性对照与对照抗体相比在酸性pH下展现出更快的VISTA kd。

[1306] 表11:VISTA抗体与cyno VISTA的SPR结合动力学

[1307]

抗体	VISTA	pH 7.4			pH 6.0			Kd 比率 (7.4/6)	KD 比率 (7.4/6)
		ka (1/Ms)	kd (1/s)	KD (M)	ka (1/Ms)	kd (1/s)	KD (M)		
P1-061029	人	1.2E+05	7.5E-03	6.2E-08	9.8E+05	6.6E-03	6.8E-09	1.1	9.1

[1308]

	cyno	1.4E+05	6.7E-03	4.7E-08	6.2E+05	6.2E-03	1.0E-08	1.1	4.7
P1-068761	人	4.3E+03	3.7E-02	8.7E-06	3.5E+05	1.4E-03	4.1E-09	26.4	2122.0
	cyno	6.5E+03	3.6E-02	5.5E-06	2.1E+05	1.7E-03	7.9E-09	21.2	696.2
P1-068767	人	1.6E+03	3.5E-02	2.3E-05	3.2E+05	2.4E-03	7.5E-09	14.6	3066.7
	cyno	1.3E+03	3.4E-02	2.6E-05	1.9E+05	2.5E-03	1.3E-08	13.6	2000.0
α-VISTA对照（mAb 3）	人	4.4E+05	1.3E-03	3.0E-09	9.6E+05	6.0E-03	6.2E-09	0.2	0.5
	cyno	4.9E+05	1.7E-03	3.4E-09	5.5E+05	7.1E-03	1.3E-08	0.2	0.3
α-VISTA酸性pH敏感性（mAb 2）	人	1.8E+05	7.8E-04	4.3E-09	1.8E+06	5.0E-02	2.8E-08	0.02	0.2
	cyno	1.9E+05	6.8E-04	3.5E-09	1.2E+06	5.2E-02	4.4E-08	0.01	0.08

[1309] 对人抗体幼稚食蟹猴静脉注射单次5mpk剂量的VISTA mAb2(“对照”)、VISTA mAb3(“酸性pH敏感性”)或P1-068767.IgG1.3。注射后每种抗体的血清浓度显示在图9中。P1-068767.IgG1.3和对照抗VISTA抗体的平均停留时间分别为717和22小时,表明酸性pH选择性极大地降低了VISTA抗体TMDD。尽管对照抗体(mAb 2)和酸性pH敏感性抗体(mAb 3)在生理pH下可比较地结合VISTA,但酸性pH敏感性抗体的平均停留时间较低,为7.6小时,这证明了酸性pH下与如实施例6和7中所述再循环的VISTA抗体结合的重要性。结果显示,酸性pH选择性抗体具有优异的PK,因此将更容易实现在肿瘤或其他微环境中的靶标结合。

[1310] 实施例12:pH选择性‘029后代不与高pI蛋白非特异性地结合

[1311] 使用Biacore®T100仪器(GE Healthcare),通过SPR评估‘029、‘761和‘767克隆在中性和酸性pH下与VISTA和其他高pI蛋白的结合特异性。将蛋白A(ThermoFisher Scientific目录号21181)在pH 4.5的10mM乙酸钠中稀释至20ug/ml,并按照制造商的胺偶联方案(GE Healthcare)固定在CM3生物传感器的流动池上,从而靶向每个流动池的800RU固定化密度的蛋白A。在25℃下使用pH 7.4和6.0下的PBST(137mM氯化钠、2.7mM氯化钾、10mM磷酸盐缓冲液、0.05％吐温20)运行缓冲液进行SPR实验。将抗体(格式化为IgG1.3抗体)在PBST pH 7.4中稀释至50nM,并以5ul/min的速度跨活性生物传感器流动池捕获60秒。在pH 7.4和6.0运行缓冲液中制备100-10nM单价hVISTA-ECD(SEQ ID NO:325)、抗生物素蛋白(ThermoFisher Scientific目录号21128)、细胞色素C(Sigma目录号C2867)、BSA(Calbiochem目录号126593)和单价对照抗原(“Ag”),并将其以50ul/min注射到捕获抗体上以评价结合特异性。在两次测定周期之间,两次15秒注射pH 1.5的10mM甘氨酸,以再生A蛋白捕获表面。使用Biacore®T200评估软件v.2.0检查参考流动池和减去0nM空白的传感器

图。结果显示在表12中。

[1312] 表12:VISTA克隆与具有高pI的蛋白质的结合

[1313]

样品	Isoel. pt (pI)	‘029		‘761		‘767		抗Ag		PBS（无Ab）	
		pH 6	pH 7.4	pH 6	pH 7.4	pH 6	pH 7.4	pH 6	pH 7.4	pH 6	pH 7.4
huVISTA-His	6.9										
抗生物素蛋白	10										
Cyto-铬C	10.7										
BSA	4.7										
Ag-His	6.5										

[1314] 在表12中,特异性结合被定义为在样品注射结束时>10RU SPR结合响应,用填充的灰色框指示。“抗Ag”是VISTA结合对照Ab。‘029克隆在酸性和中性pH下对VISTA具有特异性。‘029后代克隆‘761和‘767在酸性pH下对VISTA具有特异性,而对照抗体也保持了抗原特异性。在此测定中未观察到pI对照蛋白与蛋白A参考表面的非特异性结合(“NSB”)。

[1315] 因此,被引入‘761和‘767的VH CDR中的带电氨基酸不会导致这些抗体与其他高pI蛋白(如抗生物素蛋白和细胞色素C)或低pI蛋白(如BSA)静电地结合。

[1316] 实施例13:通过抗体‘761和‘767抑制T细胞激活

[1317] 此实施例描述了如下测定,其可以进行以测定抗体‘761和‘767阻断Jurkat T细胞激活的hVISTA抑制的能力。

[1318] 使用与实施例5中描述的相同的测定。简而言之,在不同pH下将表达NFkB萤光素酶报告基因的Jurkat(人T细胞系)细胞与表达人VISTA和抗人T细胞受体激动剂抗体OKT3的单链可变片段的293T细胞共培养。将抗VISTA抗体‘761和‘767或同种型匹配的非VISTA特异性对照抗体添加到共培养的细胞中。Jurkat激活显示为萤光素酶单位,和相对于对照,抗VISTA处理下的萤光素酶信号增加倍数。

[1319] 实施例14:突变分析鉴定了赋予与VISTA抗体的pH依赖性结合特性的关键残基

[1320] 抗体P1-068761.IgG1.3和P1-068767.IgG1.3含有来自P1-061029的5-6个突变(表7)。进行了突变分析,以鉴定对于赋予VISTA抗体pH依赖性特性重要的关键残基。因此,合成了P1-068761和P1-068767的一组N-1(1个氨基酸回复至P1-061029)和N-2(2个氨基酸回复至P1-061029)变体,表示为IgG1.3,并分析了它们在pH 6、pH 6.7和pH 7.4下与huVISTA的结合。

[1321] 使用Biacore® T100仪器(GE Healthcare)测量结合动力学。将蛋白A(ThermoFisher Scientific目录号21181)在pH 4.5的10mM乙酸钠中稀释至20ug/ml,并按照制造商的胺偶联方案(GE Healthcare)固定在CM5生物传感器的流动池上,从而靶向每个流动池的2,000RU固定化密度的蛋白A。在37℃下使用pH 7.4、6.7和6.0下的PBST(137mM氯化钠、2.7mM氯化钾、10mM磷酸盐缓冲液、0.05％吐温20)运行缓冲液进行测定。将抗体在

PBST pH 7.4中稀释至25nM,并以5ul/min的速度跨活性生物传感器流动池捕获40秒。在pH 7.4、6.7和6.0运行缓冲液中制备了浓度为100-10nM单价hVISTA-ECD(SEQ ID NO:325)的浓度系列,并以40ul/min的速度注射至捕获的抗体上,以测量缔合和解离。在两次测定周期之间,两次15秒注射pH 1.5的10mM甘氨酸,以再生A蛋白捕获表面。速率常数ka(kon)和kd(koff)源自参考流动池和0nM减去空白的传感器图,并在Biacore® T200评估软件v.2.0中拟合为1:1结合模型。

[1322] 将亲和力常数K_D计算为每种VISTA抗体的速率常数k_{off}/k_{on}的比率。计算Rmax%以比较pH如何影响抗体对VISTA的结合能力,并表示所测量的最大VISTA结合响应相对于预期的最大VISTA结合响应。将Rmax%定义为每种抗体(Rmax)在100nM VISTA注射结束时减去参考的"结合"报告点响应相对于预期的VISTA结合响应(Rexp)的比率。Rexp计算为:Rexp=[(VISTA-ECD分子量/mAb分子量)x(mAb"捕获"报告点响应(RUs)]x每个mAb的2个结合位点。

[1323] 对于P1-068761回复变体获得的SPR结果显示在图10A中,将其按pH 6.0koff从最慢到最快进行排序。在所述表中,展现出与100nM hVISTA的弱或无结合响应(<10RU)的抗体被归类为非结合(NB)。结果指示,位置32(即,'761的VH CDR1中的氨基酸残基7)和100f('761的VH CDR3中的氨基酸残基12)的E都是保持酸性pH选择性所必需的,因为这些至P1-061029亲本序列的回复允许在生理pH(Rmax%>10)下显著的hVISTA结合。进一步的分析揭示,具有E55A('761的VH CDR2中的氨基酸残基6)回复的变体保持了酸性pH选择性,并展现出在P1-068761的2倍内的可比较的结合动力学。相比之下,虽然具有H100G、E56N和E30D(分别为'761的VH CDR3的氨基酸残基12、VH CDR2的氨基酸残基7和VH CDR1的氨基酸残基4)回复的变体保持了酸性pH选择性,但这些mAb也展现出在酸性pH下与P1-068761相比快约3倍的k_{off},使得这些突变体在酸性pH下的解离速率更接近P1-061029亲本。因此,在原始P1-061029克隆中添加G100H、N56E和/或D30E突变有助于在酸性选择性P1-068761克隆中观察到酸性pH VISTA亲和力的提高。

[1324] 对于P1-068767回复变体获得的SPR结果显示在图10B中,将其按pH 6.0k_{off}从最慢到最快进行排序。结果指示,保持酸性pH选择性需要位置102处的D('767的VH CDR3中的氨基酸残基14),并且D102V回复至P1-061029亲本序列允许在中性pH下显著的hVISTA结合(Rmax%>10)。进一步的分析揭示,具有E30D、D52N和E55A(分别为'767的VH CDR1的氨基酸残基4、VH CDR2的氨基酸残基3和VH CDR3的氨基酸残基6)回复的变体保持酸性pH选择性,并展现出在P1-068767的2倍内的可比较的pH 6.0结合动力学。相反,具有E100fF('767的VH CDR3的氨基酸残基12)回复的变体保持了酸性pH选择性,尽管在酸性pH下的k_{off}与P1-068767相比快>3倍。值得注意的是,与亲本单抗P1-061029相比,具有E100fF回复的变体在酸性pH下展现出更快的k_{off}。

[1325] 因此,相对于P1-061029(pH耐受性)的P1-068761和P1-068767(酸性pH选择性)的回复突变体的总结如下表13所示(HCDR1、HCDR2和HCDR3用下划线分隔)。

[1326] 表13:Seq Id.

[1327]

P1-061029	GFTLDDYAMH_GINWNSANIGYADSVKG_VPGYSGGWIDAFDV	67
P1-068761	....E.E..._.....EE.........._.....H.....E..	51
P1-068767	....E....._..D...E.........._..........E.D	55
aa pos.	26-35 50-66 99-110	

[1328] 表13中的P1-061029、P1-068761和P1-068767的上述VH CDR序列分别在SEQ ID NO:67、51、55的氨基酸(“aa pos.”)26-35、50-66和99-110处。酸性pH选择性所需的关键突变以粗体指示,并且与P1-068761和P1-068767相比,对pH 6.0k_d具有超过3倍影响的突变用是加下划线的。

[1329] 实施例15:VISTA抗体表位的定位

[1330] 通过两种不同的方法(分别是BLI(生物层干涉测量法)竞争和酵母表面展示)确定了格式化为IgG1.3抗体的‘015、‘029、‘761和‘767的hVISTA表位。

[1331] 进行了竞争性BLI表位分组测定,以评估与P1-061029亲本、P1-061015和相关的VISTA对照抗体1、2和3相比,酸性pH选择性VISTA抗体P1-068761和P1-068767是否在VISTA上保留相似或重叠的表位。在OctetRed384 BLI仪器(PALL/ForteBio)上进行夹心和串联形式的分组测定。所有测定步骤均在30℃,1000rpm摇动速度下进行,并且所用缓冲液为酸性(pH 6.0)或中性(pH 7.4)PBST(137mM氯化钠、2.7mM氯化钾、10mM磷酸盐缓冲液、0.05%吐温20)。对于夹心形式,抗人IgG-Fc传感器(AHC,PALL/ForteBio)首先捕获pH 7.4下的VISTA抗体组,然后将抗人捕获传感器用总人IgG(Jackson编号009-000-002)阻断。接下来在pH 6.0下捕获人VISTA-ECD,最后在pH 6.0下评估所有可能的抗体组合的竞争。在串联形式测定中,链霉亲和素包被的生物传感器(SAX,PALL/ForteBio)首先在pH 7.4下捕获生物素化的hVISTA-ECD,然后在pH 6.0下捕获完整的VISTA抗体组,从而确保在评估在pH 6.0下与所有可能的抗体组合的竞争之前每种抗体在VISTA上的完全结合饱和。

[1332] 竞争性BLI表位分组测定的结果通过竞争矩阵总结,图11A。在此图中,捕获的第一抗体按行列出,其与(第二)竞争抗体的结合或阻断活性在每列中显示。两种测定形式的竞争矩阵相同。对于夹心测定,竞争抗体的结合(浅灰色)由在0.4-1.2nm之间范围内的信号定义,并且阻断的抗体(黑色)展现出<0.1nm的非结合信号。对于串联测定,竞争抗体的结合由在0.3-0.8nm之间范围内的信号定义,并且阻断的抗体展现出<0.2nm的非结合信号。“VISTA mAb 3”在37℃下通过SPR展现出从hVISTA-ECD的快速酸性pH解离(图6C),但在任一种BLI测定形式(在30℃下进行)中均未迅速解离。这些竞争性测定指示,P1-061015、P1-061029、酸性pH选择性抗体P1-068761和P1-068767以及VISTA抗体2和3全部彼此竞争VISTA上相似或重叠的表位。但是VISTA抗体1与单独且不同的表位结合。因此,被引入P1-061029的VH CDR中以产生酸性选择性克隆P1-068761和P1-068767的带电氨基酸突变并非显著改变VISTA结合表位。

[1333] 抗体‘029、‘015、‘761和‘767的表位也根据Chao等人(2004)J.Mol.Biol.342:539-550,Oliphant等人(2006)J.Virol.80:12149-12159和Kowalsky等人(2015)J.Biol.Chem.290:26457-26470的方法使用酵母表面展示和NGS进行定位。简而言之,生成了VISTA ECD单点突变体的饱和诱变文库,并将其展示在酵母表面上。对VISTA突变体进行分选和测序,所述突变体损失与被定位的抗体的结合,但保留与非阻断抗体(mAb1)的结合。由于它们保留了与mAb1的结合,因此这些突变体可能正确折叠,并且与被定位的抗体的结

合损失可能是由于损失了能量上重要的接触残基。这些突变的位置被指定为抗体表位中能量上重要的残基,并且显示在表14中。

[1334]

表14：huVISTA的被鉴定为抗VISTA mAb的表位残基的残基

mAb	T 35	Y 37	K 38	T 39	Y 41	R 54	T 61	F 62	Q 63	L 65	H 66	L 67	H 68	H 69	F 97	L 115	V 117	I 119	H 121	H 122	S 124	E 125	R 127
P1-061015		x	x	x		x		x	x	x	x				x	x	x	x			x	x	
P1-061029		x		x	x	x	x	x	x	x	x		x	x		x	x	x			x	x	x
P1-068761	x	x		x		x	x	x	x		x	x	x	x		x	x	x			x	x	x
P1-068767		x		x	x	x	x	x	x	x	x					x	x	x	x	x	x	x	x

[1335] 表15包括表14的详细数据,并列出了hVISTA的氨基酸残基,所述hVISTA的氨基酸残基基于酵母表面展示/NGS方法中观察到的残基频率可能降低所列每种抗体的结合。

[1336] 表15:可能降低所列抗体的结合的VISTA氨基酸取代

[1337]

	P1-061015 pH 6	P1-061015 pH 7	P1-061029 pH 6	P1-061029 pH 7	P1-068761 pH 6	P1-068767 pH 6
T35					P, Y, W	
Y37	P, G, A, S, T, K, R, H, N, D, E, Q	P, G, S, N, D, E Q	Y, S, T, V, L, I, M, K, R, N, D, Q	P, G, S, T, V, L, I, M, K, R, N, D, E, Q	P, G, A, S, T, V, L, I, M, K, R, N, D, E, Q	G, T, V, L, I, M, K, R, N, Q
K38	P, G, A, S, V					
T39	G, M, R, H, F, Y, W, N, D, E, Q	M, K, R, H, F, Y, W, D, E, Q	G, A, S, M, Y, W, N, D, E, Q	G, A, S, V, L, M, R, H, F, Y, W, N, D, E, Q	G, Y, D, E	G, A, S, H, Y, W, N, D, E, Q
Y41				A, S, T, I, M		P, I, M, H
R54	L, M, F, Y, E	M, E	P, A, T, V, I, M, F, Y, N, D, E, Q	P, G, A, S, T, V, L, I, M, H, F, Y, W, N, D, E, Q	A, T, V, L, I, M, K, F, Y, E, Q	P, A, S, T, V, L, I, M, F, Y, W, D, E, Q
T61			G, L, R, H, F, Y, D, E, Q	V, L, K, R, H, F, Y	G, V, H, Y, D	L, R, H, F, Y, D, E
F62	G, A, S, M, K, R, N, D, E, Q	G, K, R, D, E, Q	P, G, A, S, T, V, I, M, H, Y, W, D, E, Q	P, G, A, S, T, V, L, I, M, K, R, H, Y, W, N, D, E, Q	P, G, A, S, T, V, M, H, Y, W, D, E, Q	P, G, A, S, T, V, L, M, H, Y, W, N, D, E, Q
Q63	G, R, W, D, E	W, D, E	G, A, S, T, V, K, R, H, Y, W, N, D, E	P, G, S, T, L, M, K, R, H, F, Y, W, N, D, E	G, S, T, K, H, Y, N, D, E	P, G, A, S, T, V, L, I, M, K, H, F, Y, W, N, D, E
L65	P, G, A,	P, G, S,	G, T, Y,	P, G, A,		P, G, S,

[1338]

	P1-061015 pH 6	P1-061015 pH 7	P1-061029 pH 6	P1-061029 pH 7	P1-068761 pH 6	P1-068767 pH 6
	S, T, K, R, H, W, N, D, E, Q	K, W, D, E, Q	D, E, Q	S, T, H, Y, W, N, D, E, Q,		H, D, E, Q
H66	P, T, V, L, I, M, K, R, F, Y, W	P, T, V, L, I, M, K, R, F, Y, W	T, V, L, I, Y, D, E, Q	G, S, T, V, L, I, M, K, R, W, N, D, E, Q	T, I, K, W, D	T, V, I, K, W, D, E
L67					G, A	
H68			L, I, M, F, E	L, I, E	G, T, V, L, I, Y, W, D, E, Q	
F97	G, D, E					
L115	R, W		A, T, K, N, Q	A, T, K, F, N, Q	A, T, M, K, F, N	A, T, K, F, N, Q
V117	M, K, N, D	M, K, R, W, E	T, M, K, R, W, E	T, L, I, M, K, R, W, E	T, I, M, K, W	T, L, I, M, K, R, W, E
I119	F, P	P, N	P, M, E	P, M, E	M, H	P, M, H, F, N, E
H121						V, E, Q
H122						P, Y, N, D
S124	P, V, L, I, K, F, D, E	L, I, M, H, W, Q	L, I, M, H, W, Q		L, I, M, Q	L, I, M
E125	A, S, T, L, M, K, H, Y, D	A, T, V, I, M, K, H, F, Y, W, N, D	T, V, I, M, H, F, Y, W	G, T, K, H, Y, W, N, D	V, I, H, N	T, V, I, F, Y, W, N
R127			S, V, M, H	P, S, V, M, K, H, N	P, V, M, N	P, S, V, M, H, N

[1339] 图11B和图11C显示了与非阻断hVISTA抗体(mAb1;图11C)的表位相比,包含如表14中列出的用于阻断hVISTA抗体的所有残基的表位(图11B)的表示。指示了氨基酸残基66(H)和162(A)以表示分子的取向。组氨酸残基呈灰色,并且表位残基呈黑色。值得注意的是,与八位位组(octet)分组数据(显示它们彼此竞争)一致,所有阻断的抗VISTA mAb占据相同的表位区域,其中所查询的抗体之间存在细微的残基差异。相比之下,非阻断hVISTA抗体(mAb1)在hVISTA分子上占据独特的表位区域,并且八位位组分组数据进一步支持了这一点,其显示没有一种阻断mAb与mAb1竞争。

[1340] 实施例16:'761和'767的生物物理特性

[1341] 通过以下分析和生物物理技术,将P1-068761和P1-068767与亲本P1-061029(全部都具有IgG1.3恒定区)的物理和化学特性进行了比较。

[1342] 使用Agilent 1260HPLC仪器(使用Shodex™KW403-4F柱(4.6mmID X300mmL))在以0.30mL/min的流速运行的含有100mM磷酸钠、150mM氯化钠、pH 7.3(0.2um过滤)的缓冲液中获取分析性SEC数据。通过设置为在280nm处收集的Agilent 1260无限二极管阵列检测器收集数据,并通过Agilent Chemstation软件(Agilent,圣克拉拉,加利福尼亚州)进行分析。

[1343] 在配备Alcott 720NV自动进样器的ProteinSimple iCE3仪器上获取成像的毛细管等电聚焦(icIEF)数据。将抗体样品与分离混合物混合以产生0.2mg/ml抗体、0.35%甲基纤维素、2.0M脲、1%v/v pharmalyte pI 5-8和3%v/vpharmalyte pI 8-10.5的终浓度。在ProteinSimple cIEF柱带FC涂层(产品编号101701)中,使用1500V下1min的预聚焦时间和3000V下10min的聚焦时间来分析这些样品。使用iCE CFR软件V4.3.1.5352分析数据。

[1344] 通过动态光散射(DLS)测定抗体流体动力学大小,通过荧光光谱和静态光散射(SLS)使用UNcle分子表征仪器(Unchained Labs)表征热稳定性。在1X PBS缓冲液中以2mg/ml的浓度制备抗体P1-061029、P1-068761和P1-068767,然后在不同的pH下用在1X PBS中的40mM Tris或1X PBS中的40mM柠檬酸盐1:1稀释以在pH 3.0、4.0、5.0、6.0、7.0、8.0或9.0下在20mM Tris/1X PBS或20mM柠檬酸盐/1X PBS中产生1mg/ml抗体的最终样品。将这些样品加载到UNi比色杯中,并在稀释到不同pH配制品中的1小时内进行分析。DLS数据是在25℃下收集的,使用每回获取4次,每次5s。使用UNcle分析软件V2.0版安装强度自相关函数。通过以0.5°/min的扫描速率从25℃到90℃扫描样品获得热变性数据,其中在266nm和473nm处激发。在250nm-720nm范围内获取荧光数据。使用UNcle分析软件V2.0版分析荧光和SLS数据。

[1345] 抗体P1-061029、P1-068761和P1-068767的表观粘度使用基于珠粒的DLS方法在UNcle分子表征仪器(Unchained Labs)上进行测量,所述方法按照Unchained Labs推荐的方案在配制的抗体浓度的存在下测量聚苯乙烯珠粒的扩散速率。简而言之,在含有0.5%吐温80的配制缓冲液中制备10%的100nm聚苯乙烯珠粒溶液(Thermo Scientific目录号3100A)。将3ul的这种聚苯乙烯珠粒混合物添加到30ul配制的抗体(20mM组氨酸、pH 6.0的260mM蔗糖中的各种Ab浓度)中,并将所得的蛋白质/珠粒混合物加载到UNi比色杯的3个独立道中(每道9ul)以进行一式三份地分析。使用UNcle分析软件V2.0版和1.3cP的参考粘度对数据进行分析。

[1346] 通过在20mM组氨酸、pH 6.0的260mM蔗糖中制备50mg/ml抗体样品并在40℃热应力中暴露4周,在加速应激条件下研究了抗体P1-061029、P1-068761和P1-068767的物理稳定性。在40℃孵育之前(时间零=t0)以及热应力1周(1w)和4周(4w)之后立即取出等分试样,并使用配制缓冲液将样品稀释至2mg/ml,并将其通过aSEC分析。使用Agilent 1260HPLC仪器(使用Shodex KW403-4F柱(4.6mmID X 300mmL))在以0.30mL/min的流速运行的含有100mM磷酸钠、150mM氯化钠、pH 7.3(0.2um过滤)的缓冲液中获取aSEC数据。通过设置为在280nm处收集的Agilent 1260无限二极管阵列检测器收集数据,并通过Agilent Chemstation软件(Agilent,圣克拉拉,加利福尼亚州)进行分析。

[1347] 结果如下。分析尺寸排阻色谱(aSEC)数据显示,所有三种抗体均可纯化至高纯度,其中每种抗体样品均由超过99.3%的单体(主峰)、少于0.7%的高分子量(HMW)种类和不可

检测水平的低分子量(LMW)种类组成,表16。

[1348] 表16:抗VISTA抗体的分析SEC数据,显示了高分子量种类的百分比(HMW%)、单体/主要种类的百分比(Main%)和低分子量种类的百分比(LMW%)。

[1349]

样品名称	HMW%	Main%	LMW%
P1-061029	0.4	99.6	0.0
P1-068761	0.6	99.4	0.0
P1-068767	0.5	99.5	0.0

[1350] 通过成像的毛细管等电聚焦(icIEF)测得的抗体P1-061029的电荷变体谱显示了等电点(pI)为8.56的主要种类(69.4%)和30.6%酸性种类的存在。(图12A至图12C)P1-068761显示出pI为6.69的主要种类(66.4%)和33.6%酸性种类。P1-068767显示出pI为6.63的主要种类(61.4%)和38.6%酸性种类。因此,这三种抗体的酸性、碱性和主要种类的分布相似,但工程化抗体P1-068761和P1-068767的等电点明显低于亲本P1-061029抗体。

[1351] 使用动态光散射(DLS)在不同pH的缓冲液中测定了在3-9的pH范围内P1-061029、P1-068761和P1-068767的低聚状态。每种抗体的所有流体动力学半径(Rh)值都在4.8-5.7nM的范围内,这是单体抗体样品的典型值,表17。这表明这些抗体在稀释成pH为3-9的配制品后的第一个小时内,在1mg/ml的浓度下不会形成可检测水平的高分子量聚集种类。

[1352] 表17:通过DLS在pH 3-pH 9的pH范围内测定的抗VISTA抗体的1mg/ml样品的流体动力学半径。

[1353]

pH	缓冲液	Rh (nm) P1-061029	Rh (nm) P1-068761	Rh (nm) P1-068767
9	20 mM Tris/1 X PBS	5.2	4.8	5.2
8	20 mM Tris/1 X PBS	5.2	5.2	5.2
7	20 mM Tris/1 X PBS	4.8	5.2	5.2
7	20 mM柠檬酸盐/1 X PBS	4.8	5.2	5.7
6	20 mM柠檬酸盐/1 X PBS	5.2	5.2	4.8
5	20 mM柠檬酸盐/1 X PBS	5.2	4.8	5.2
4	20 mM柠檬酸盐/1 X PBS	4.8	4.8	5.2
3	20 mM柠檬酸盐/1 X PBS	5.2	5.2	5.2

[1354] 通过监测在不同pH的缓冲液中随温度变化的荧光和静态光散射,可以测量在3-9的pH范围内P1-061029、P1-068761和P1-068767的热稳定性。通过荧光确定通常代表IgG1抗体的CH2结构域变性的第一个热变性转变(Tm1),并显示在表18中,并且通常代表IgG1抗体的FAB结构域变性的聚集的起始(Tagg)是通过静态光散射来测量,并显示在表19中。在中性pH(pH 7.0)下,在Tris/PBS配制品中三种抗体的Tm1值分别为P1-061029(67.4℃),P1-

068761(67.0℃)和P1-068767(65.3℃),其中Tagg值为P1-061029(67.8℃),P1-068761(67.5℃)和P1-068767(65.8℃)。在相同的中性pH 7.0或6.0的略微酸性的pH下,在柠檬酸盐/PBS配制品中每种抗体的Tm1都在Tris/PBS pH7.0值的0.7°之内。但是对于每种抗体,在更高的8-9碱性pH下Tm1值略低(在0.3°-1.1°之间或更低),而在3-5的更酸性的pH下则显著更低。与中性pH相比,P1-061029的Tagg在更碱性的pH 8.0-9.0下是在pH 7.0值的0.1°之内,在pH5.0下低1.0°,并且在pH 3.0-4.0的最酸性pH条件下低得多(低6.1°-19.6°)。在pH 3.0-4.0下,P1-068761和P1-068767的Tagg也显著更低。但是在pH 5.0下,P1-068761的Tagg仅比在pH 6.0下的Tagg低0.2°,而在pH 5.0下P1-068767的Tagg比在pH 6.0下低2.2°,这表明每种抗体的Tagg有一些差异,表19。

[1355] 表18:通过荧光光谱测定的在pH 3-pH 9的pH范围内,P1-061029、P1-068761、P1-068767的热稳定性(Tm1值)

[1356]

pH	缓冲液	Tm1 (°C) P1-061029	Tm1 (°C) P1-068761	Tm1 (°C) P1-068767
9	20 mM Tris/1 X PBS	66.6	65.9	65.0
8	20 mM Tris/1 X PBS	67.0	66.5	64.8
7	20 mM Tris/1 X PBS	67.4	67.0	65.3
7	20 mM柠檬酸盐/1 X PBS	67.2	66.9	64.8
6	20 mM柠檬酸盐/1 X PBS	67.6	67.5	65.0
5	20 mM柠檬酸盐/1 X PBS	64.4	64.7	62.1
4	20 mM柠檬酸盐/1 X PBS	51.8	52.0	50.8
3	20 mM柠檬酸盐/1 X PBS	30.7	28.1	28.7

[1357] 表19:通过静态光散射测定的在pH 3-pH 9的pH范围内,P1-061029、P1-068761、P1-068767的热稳定性(Tagg值)

[1358]

pH	缓冲液	Tagg (°C) P1-061029	Tagg (°C) P1-068761	Tagg (°C) P1-068767
9	20 mM Tris/1 X PBS	67.7	67.1	66.0
8	20 mM Tris/1 X PBS	67.8	67.5	65.8
7	20 mM Tris/1 X PBS	67.8	68.2	65.9
7	20 mM柠檬酸盐/1 X PBS	67.8	68.1	65.7
6	20 mM柠檬酸盐/1 X PBS	68.1	68.9	65.6
5	20 mM柠檬酸盐/1 X PBS	66.8	68.7	63.7

[1359]

4	20 mM柠檬酸盐/1 X PBS	61.7	63.6	56.9
3	20 mM柠檬酸盐/1 X PBS	48.2	48.8	41.0

[1360] 使用基于珠粒的DLS方法测量P1-061029、P1-068761和P1-068767的表观粘度,所述方法在配制的抗体溶液的存在下测量聚苯乙烯珠粒的扩散速率。所有这三种抗体在44mg/ml下的比较显示,在这些条件下两种工程化抗体的粘度与亲本抗体相似,表20。在第二项研究中,将P1-068761和P1-068767的另外的蛋白质物质浓缩至更高的浓度,以在136mg/ml、100mg/ml和50mg/ml下分析粘度。这些数据显示,在较高的抗体浓度下,表观粘度升高,其中在136mg/ml下,P1-068761的最大表观粘度为5.7±0.7且P1-068767的最大表观粘度为5.3±0.6。

[1361] 表20:通过基于珠粒的DLS方法测定的25℃下20mM组氨酸、260mM蔗糖(pH 6.0)中抗体的表观粘度(以cP计)。值代表来自三个UNi道的数据的平均值和标准差

[1362]

抗体	在136 mg/ml下的表观粘度(cP)	在100 mg/ml下的表观粘度(cP)	在50 mg/ml下的表观粘度(cP)	在44 mg/ml下的表观粘度(cP)
P1-061029				1.6 ± 0.1
P1-068761	5.7 ± 0.7	3.1 ± 0.0	1.4 ± 0.2	1.5 ± 0.4
P1-068767	5.3 ± 0.6	3.0 ± 0.3	1.7 ± 0.2	1.6 ± 0.2

[1363] 在40℃持续4周的加速应力条件下研究了P1-061029、P1-068761和P1-068767的50mg/ml样品在20mM组氨酸、pH 6.0的260mM蔗糖中的物理稳定性。在40℃孵育即将开始之前(时间零=t0),以及在40℃应力1周(1w)和4周(4w)之后,通过aSEC监测样品的抗体低聚状态。这些数据表明,在40℃下4周后,所有三种抗体的单体含量均保持在96%以上,其中HMW物种含量较低(<1.6%HMW)并且LMW物种含量较低(<2.0%LMW),表21。

[1364] 表21:抗VISTA抗体加速的稳定性样品的aSEC数据,显示了对于t0、1w、4w样品的高分子量种类的百分比(HMW%)、单体/主要种类的百分比(Main%)和低分子量种类的百分比(LMW%)。

[1365]

抗体	样品	HMW%	Main%	LMW%
P1-061029	t0	0.4	99.7	0.0
	1w	0.5	99.4	0.2
	4w	0.8	97.2	2.0
P1-068761	t0	0.6	99.4	0.0
	1w	0.9	98.8	0.3
	4w	1.6	96.4	2.0
P1-068767	t0	0.5	99.5	0.0
	1w	0.8	98.9	0.3
	4w	1.6	96.4	2.0

[1366] 序列表

[1367] 下表是本申请中提及的某些序列的表。在SEQ ID NO:2中,氨基酸位置187可以是D或E。

[1368] 在以下抗体序列中,VH CDR1、CDR2和CDR3序列分别位于包含氨基酸26-35、50-66和99-110的氨基酸位置处,而VL CDR1、CDR2和CDR3序列分别位于包含氨基酸24-35、51-57和90-98的氨基酸位置处。VH CDR1根据AbM进行编号(AA 26-35;Abhinandan和Martin(2008)Mol.Immunol.45:3832-3839;Swindells等人(2017)J.Mol.Biol.429:356-364),并且所有其他CDR(VH CDR2、VH CDR3、VL CDR1-3)均按Kabat进行编号。特定抗体种类的CDR序列在其VH和VL序列下方用粗体和下划线标出。

[1369]

SEQ ID NO	名称	序列
1	hVISTA（具有前导序列）	MGVPTALEAG SWRWGSLLFA LFLAASLGPV AAFKVATPYS LYVCPEGQNV TLTCRLLGPV DKGHDVTFYK TWYRSSRGEV QTCSERRPIR NLTFQDLHLH HGGHQAANTS HDLAQRHGLE SASDHHGNFS ITMRNLTLLD SGLYCCLVVE IRHHHSEHRV HGAMELQVQT GKDAPSNCVV YPSSSQDSEN ITAAALATGA CIVGILCLPL ILLLVYKQRQ AASNRRAQEL VRMDSNIQGI ENPGFEASPP AQGIPEAKVR HPLSYVAQRQ PSESGRHLLS EPSTPLSPPG PGDVFFPSLD PVPDSPNFEV I
2	hVISTA(无前导序列)	FKVATPYSLY VCPEGQNVTL TCRLLGPVDK GHDVTFYKTW YRSSRGEVQT CSERRPIRNL TFQDLHLHHG GHQAANTSHD LAQRHGLESA SDHHGNFSIT MRNLTLLDSG LYCCLVVEIR HHHSEHRVHG AMELQVQTGK DAPSNCVVYP SSSQ[D/E]SENIT AAALATGACI VGILCLPLIL LLVYKQRQAA SNRRAQELVR MDSNIQGIEN PGFEASPPAQ GIPEAKVRHP LSYVAQRQPS ESGRHLLSEP STPLSPPGPG DVFFPSLDPV PDSPNFEVI
3	人PSGL-1同种型2前体，具有信号肽	MPLQLLLLLI LLGPGNSLQL WDTWADEAEK ALGPLLARDR RQATEYEYLD YDFLPETEPP EMLRNSTDTT PLTGPGTPES TTVEPAARRS TGLDAGGAVT ELTTELANMG NLSTDSAAME IQTTQPAATE AQTTQPVPTE AQTTPLAATE AQTTRLTATE AQTTPLAATE AQTTPPAATE AQTTQPTGLE AQTTAPAAME AQTTAPAAME AQTTPPAAME AQTTQTTAME AQTTAPEATE AQTTQPTATE AQTTPLAAME ALSTEPSATE ALSMEPTTKR GLFIPFSVSS VTHKGIPMAA SNLSVNYPVG APDHISVKQC LLAILILALV ATIFFVCTVV LAVRLSRKGH MYPVRNYSPT EMVCISSLLP DGGEGPSATA NGGLSKAKSP GLTPEPREDR EGDDLTLHSF LP
4	人PSGL-1同种型2,无信号肽	LQL WDTWADEAEK ALGPLLARDR RQATEYEYLD YDFLPETEPP EMLRNSTDTT PLTGPGTPES TTVEPAARRS TGLDAGGAVT ELTTELANMG NLSTDSAAME IQTTQPAATE AQTTQPVPTE AQTTPLAATE AQTTRLTATE AQTTPLAATE AQTTPPAATE AQTTQPTGLE AQTTAPAAME AQTTAPAAME AQTTPPAAME AQTTQTTAME AQTTAPEATE AQTTQPTATE AQTTPLAAME ALSTEPSATE ALSMEPTTKR

[1370]

SEQ ID NO	名称	序列
		GLFIPFSVSS VTHKGIPMAA SNLSVNYPVG APDHISVKQC LLAILILALV ATIFFVCTVV LAVRLSRKGH MYPVRNYSPT EMVCISSLLP DGGEGPSATA NGGLSKAKSP GLTPEPREDR EGDDLTLHSF LP
5	人 PSGL-1 同种型 2 ECD，具有信号肽	MPLQLLLLLI LLGPGNSLQL WDTWADEAEK ALGPLLARDR RQATEYEYLD YDFLPETEPP EMLRNSTDTT PLTGPGTPES TTVEPAARRS TGLDAGGAVT ELTTELANMG NLSTDSAAME IQTTQPAATE AQTTQPVPTE AQTTPLAATE AQTTRLTATE AQTTPLAATE AQTTPPAATE AQTTQPTGLE AQTTAPAAME AQTTAPAAME AQTTPPAAME AQTTQT
6	人 PSGL-1 同种型 2 ECD，无信号肽	LQL WDTWADEAEK ALGPLLARDR RQATEYEYLD YDFLPETEPP EMLRNSTDTT PLTGPGTPES TTVEPAARRS TGLDAGGAVT ELTTELANMG NLSTDSAAME IQTTQPAATE AQTTQPVPTE AQTTPLAATE AQTTRLTATE AQTTPLAATE AQTTPPAATE AQTTQPTGLE AQTTAPAAME AQTTAPAAME AQTTPPAAME AQTTQT
7	人PSGL-1 ECD（全长人 PSGL-1 登录号 AAC50061的N末端位置42至295）	QATEYEYLD YDFLPETEPP EMLRNSTDTT PLTGPGTPES TTVEPAARRS TGLDAGGAVT ELTTELANMG NLSTDSAAME IQTTQPAATE AQTTPLAATE AQTTRLTATE AQTTPLAATE AQTTPPAATE AQTTQPTGLE AQTTAPAAME AQTTAPAAME AQTTPPAAME AQTTQTTAME AQTTAPEATE AQTTQPTATE AQTTPLAAME ALSTEPSATE ALSMEPTTKR GLFIPFSVSS VTHKGIPMAA SNLSV
8	HumPSGL-1 同种型 1 前体，具有信号肽 NP_001193538	MAVGASGLEG DKMAGAMPLQ LLLLLILLGP GNSLQLWDTW ADEAEKALGP LLARDRRQAT EYEYLDYDFL PETEPPEMLR NSTDTTPLTG PGTPESTTVE PAARRSTGLD AGGAVTELTT ELANMGNLST DSAAMEIQTT QPAATEAQTT QPVPTEAQTT PLAATEAQTT RLTATEAQTT PLAATEAQTT PPAATEAQTT QPTGLEAQTT APAAMEAQTT APAAMEAQTT PPAAMEAQTT QTTAMEAQTT APEATEAQTT QPTATEAQTT PLAAMEALST EPSATEALSM EPTTKRGLFI PFSVSSVTHK GIPMAASNLS VNYPVGAPDH ISVKQCLLAI LILALVATIF FVCTVVLAVR LSRKGHMYPV RNYSPTEMVC ISSLLPDGGE GPSATANGGL SKAKSPGLTP EPREDREGDD LTLHSFLP
9	人PSGL-1，无信号肽	LQLWDTW ADEAEKALGP LLARDRRQAT EYEYLDYDFL PETEPPEMLR NSTDTTPLTG PGTPESTTVE PAARRSTGLD AGGAVTELTT ELANMGNLST DSAAMEIQTT QPAATEAQTT QPVPTEAQTT PLAATEAQTT RLTATEAQTT PLAATEAQTT PPAATEAQTT QPTGLEAQTT APAAMEAQTT APAAMEAQTT PPAAMEAQTT QTTAMEAQTT APEATEAQTT QPTATEAQTT PLAAMEALST EPSATEALSM EPTTKRGLFI PFSVSSVTHK GIPMAASNLS VNYPVGAPDH ISVKQCLLAI LILALVATIF FVCTVVLAVR LSRKGHMYPV RNYSPTEMVC ISSLLPDGGE GPSATANGGL SKAKSPGLTP EPREDREGDD LTLHSFLP
10	人PSGL-1 ECD，具有信号肽	MAVGASGLEG DKMAGAMPLQ LLLLLILLGP GNSLQLWDTW ADEAEKALGP LLARDRRQAT EYEYLDYDFL PETEPPEMLR NSTDTTPLTG PGTPESTTVE PAARRSTGLD AGGAVTELTT ELANMGNLST DSAAMEIQTT QPAATEAQTT QPVPTEAQTT PLAATEAQTT RLTATEAQTT PLAATEAQTT PPAATEAQTT QPTGLEAQTT APAAMEAQTT APAAMEAQTT PPAAMEAQTT QT
11	P1-069059 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GINWNSDHIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDD**WGQGTMVTVSS
12	P1-069059 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP

[1371]

SEQ ID NO	名称	序列
		RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
13	P1-069059 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGINWNSDHIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
14	P1-069059 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
15	P1-069061 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GINWNSAEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDD**WGQGTMVTVSS
16	P1-069061 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
17	P1-069061 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGINWNSAEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
18	P1-069061 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
19	P1-069063 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GINWNSAEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDADDE**WGQGTMVTVSS
20	P1-069063 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
21	P1-069063 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGINWNSAEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDADDEWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS

[1372]

SEQ ID NO	名称	序列
		REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
22	P1-069063 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
23	P1-069065 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSDDIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAFDV**WGQGTMVTVSS
24	P1-069065 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
25	P1-069065 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSDDIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAFDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
26	P1-069065 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
27	P1-069067 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLDDYAMH**WVRQAPGKGL EWVS**GINWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDADDE**WGQGTMVTVSS
28	P1-069067 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
29	P1-069067 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLDDYAMHWVRQAPGKGL EWVSGINWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDADDEWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
30	P1-069067 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
31	P1-069069 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLDDYAMH**WVRQAPGKGL

[1373]

SEQ ID NO	名称	序列
		EWVS**GINWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDADDV**WGQGTMVTVSS
32	P1-069069 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
33	P1-069069 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLDDYAMHWVRQAPGKGL EWVSGINWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDADDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
34	P1-069069 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
35	P1-069071 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSADIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSEGWIDAFDV**WGQGTMVTVSS
36	P1-069071 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
37	P1-069071 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSADIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSEGWIDAFDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
38	P1-069071 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
39	P1-069073 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSAEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDV**WGQGTMVTVSS
40	P1-069073 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
41	P1-069073 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSAEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL

[1374]

SEQ ID NO	名称	序列
		QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
42	P1-069073 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
43	P1-069075 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GINWDSAEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAEDV**WGQGTMVTVSS
44	P1-069075 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
45	P1-069075 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGINWDSAEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
46	P1-069075 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
47	P1-069077 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSDEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAFDV**WGQGTMVTVSS
48	P1-069077 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
49	P1-069077 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSDEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAFDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
50	P1-069077 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC

[1375]

SEQ ID NO	名称	序列
		LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
51	P1-068761 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAEDV**WGQGTMVTVSS
52	P1-068761 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
53	P1-068761 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
54	P1-068761 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
55	P1-068767 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GIDWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDD**WGQGTMVTVSS
56	P1-068767 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
57	P1-068767 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGIDWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
58	P1-068767 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
59	P1-068773 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GIDWNSDNIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDD**WGQGTMVTVSS
60	P1-068773 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
61	P1-068773 IgG1.3	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL

[1376]

SEQ ID NO	名称	序列
	HC	EWVSGIDWNSDNIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
62	P1-068773 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
63	P1-068765 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTDEDYAMH**WVRQAPGKGL EWVS**GINWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDD**WGQGTMVTVSS
64	P1-068765 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
65	P1-068765 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTDEDYAMHWVRQAPGKGL EWVSGINWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
66	P1-068765 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
67	P1-061029 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLDDYAMH**WVRQAPGKGL EWVS**GINWNSANIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAFDV**WGQGTMVTVSS
68	P1-061029 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
69	P1-061029 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLDDYAMHWVRQAPGKGL EWVSGINWNSANIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAFDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG

[1377]

SEQ ID NO	名称	序列
70	P1-061029 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
71	P1-068757 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDD**WGQGTMVTVSS
72	P1-068757 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
73	P1-068757 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
74	P1-068757 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
75	P1-068771 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSHEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDD**WGQGTMVTVSS
76	P1-068771 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
77	P1-068771 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSHEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
78	P1-068771 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
79	P1-068775 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GIDWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAEDD**WGQGTMVTVSS
80	P1-068775 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP

[1378]

SEQ ID NO	名称	序列
		RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
81	P1-068775 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGIDWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
82	P1-068775 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
83	P1-068769 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSDHIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDD**WGQGTMVTVSS
84	P1-068769 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
85	P1-068769 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSDHIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
86	P1-068769 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
87	P1-068759 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GIDWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDD**WGQGTMVTVSS
88	P1-068759 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
89	P1-068759 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGIDWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS

SEQ ID NO	名称	序列
		REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
90	P1-068759 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
91	P1-068763 VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GIDWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAEDV**WGQGTMVTVSS
92	P1-068763 VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
93	P1-068763 IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGIDWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
[1379] 94	P1-068763 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
95	P1-061015 VH	QVQLVESGGGVVQPGRSLRLSCAAS**GFTFSSYAMH**WVRQAPGKGL EWVA**IIWYDGSNKYYADSVKG**RFTISRDNSKNTLYLQMNSLRAED TAVYYCAR**DSGFYSSYYFDY**WGQGTLVTVSS
96	P1-061015 VL	EIVLTQSPATLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**DASNRAT**GIPARFSGSGSGTDFTLTISSLEPEDFATYYC**Q QYNSYPYT**FGQGTKLEIK
97	P1-061015 IgG1.3 HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGL EWVAIIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAED TAVYYCARDSGFYSSYYFDYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD KTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
98	P1-061015 LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFATYYCQ QYNSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
99	P1-068748 VH	QVQLVESGGGVVQPGRSLRLSCAAS**GFTFSHHAMH**WVRQAPGKGL EWVA**IIWYDGSNDDYADSVKG**RFTISRDNSKNTLYLQMNSLRAED

[1380]

SEQ ID NO	名称	序列
		TAVYYCAR**DSGFYDSYYFDY**WGQGTLVTVSS
100	P1-068748 VL	EIVLTQSPATLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**DASNRAT**GIPARFSGSGSGTDFTLTISSLEPEDFATYYC**Q QYNSYPYT**FGQGTKLEIK
101	P1-068748 IgG1.3 HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSHHAMHWVRQAPGKGL EWVAIIWYDGSNDDYADSVKGRFTISRDNSKNTLYLQMNSLRAED TAVYYCARDSGFYDSYYFDYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD KTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
102	P1-068748 LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFATYYCQ QYNSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
103	P1-068744 VH	QVQLVESGGGVVQPGRSLRLSCAAS**GFTFSEYAMH**WVRQAPGKGL EWVA**HIWYDGSNKYEADSVKG**RFTISRDNSKNTLYLQMNSLRAED TAVYYCAR**DSGFYESYYFDE**WGQGTLVTVSS
104	P1-068744 VL	EIVLTQSPATLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**DASNRAT**GIPARFSGSGSGTDFTLTISSLEPEDFATYYC**Q QYNSYPYT**FGQGTKLEIK
105	P1-068744 IgG1.3 HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSEYAMHWVRQAPGKGL EWVAHIWYDGSNKYEADSVKGRFTISRDNSKNTLYLQMNSLRAED TAVYYCARDSGFYESYYFDEWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD KTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
106	P1-068744 LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFATYYCQ QYNSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
107	P1-068736 VH	QVQLVESGGGVVQPGRSLRLSCAAS**GFTFSEYAMH**WVRQAPGKGL EWVA**IDWYDGSNKDYADSVKG**RFTISRDNSKNTLYLQMNSLRAED TAVYYCAR**DSGFYDSYYFDD**WGQGTLVTVSS
108	P1-068736 VL	EIVLTQSPATLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**DASNRAT**GIPARFSGSGSGTDFTLTISSLEPEDFATYYC**Q QYNSYPYT**FGQGTKLEIK
109	P1-068736 IgG1.3 HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSEYAMHWVRQAPGKGL EWVAIDWYDGSNKDYADSVKGRFTISRDNSKNTLYLQMNSLRAED TAVYYCARDSGFYDSYYFDDWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD KTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ

[1381]

SEQ ID NO	名称	序列
		DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
110	P1-068736 LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFATYYCQ QYNSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
111	P1-068752 VH	QVQLVESGGGVVQPGRSLRLSCAAS**GFTFSSYAMH**WVRQAPGKGL EWVA**EIWYDGSNKDYADSVKG**RFTISRDNSKNTLYLQMNSLRAED TAVYYCAR**DSGFYDSYYFDE**WGQGTLVTVSS
112	P1-068752 VL	EIVLTQSPATLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**DASNRAT**GIPARFSGSGSGTDFTLTISSLEPEDFATYYC**Q QYNSYPYT**FGQGTKLEIK
113	P1-068752 IgG1.3 HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGL EWVAEIWYDGSNKDYADSVKGRFTISRDNSKNTLYLQMNSLRAED TAVYYCARDSGFYDSYYFDEWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD KTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
114	P1-068752 LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFATYYCQ QYNSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
115	P1-068740 VH	QVQLVESGGGVVQPGRSLRLSCAAS**GFTFSDYAMH**WVRQAPGKGL EWVA**IIWYDGSDKDYADSVKG**RFTISRDNSKNTLYLQMNSLRAED TAVYYCAR**DSGFYDSYYFDD**WGQGTLVTVSS
116	P1-068740 VL	EIVLTQSPATLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**DASNRAT**GIPARFSGSGSGTDFTLTISSLEPEDFATYYC**Q QYNSYPYT**FGQGTKLEIK
117	P1-068740 IgG1.3 HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSDYAMHWVRQAPGKGL EWVAIIWYDGSDKDYADSVKGRFTISRDNSKNTLYLQMNSLRAED TAVYYCARDSGFYDSYYFDDWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD KTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
118	P1-068740 LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFATYYCQ QYNSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
119	P1-068742 VH	QVQLVESGGGVVQPGRSLRLSCAAS**GFTFSDYAMH**WVRQAPGKGL EWVA**IIWYDGSDKDYADSVKG**RFTISRDNSKNTLYLQMNSLRAED TAVYYCAR**DSGFYEDYYFDY**WGQGTLVTVSS

SEQ ID NO	名称	序列
120	P1-068742 VL	EIVLTQSPATLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**DASNRAT**GIPARFSGSGSGTDFTLTISSLEPEDFATYYC**Q QYNSYPYT**FGQGTKLEIK
121	P1-068742 IgG1.3 HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSDYAMHWVRQAPGKGL EWVAIIWYDGSDKDYADSVKGRFTISRDNSKNTLYLQMNSLRAED TAVYYCARDSGFYEDYYFDYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD KTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
122	P1-068742 LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFATYYCQ QYNSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
123	P1-068746 VH	QVQLVESGGGVVQPGRSLRLSCAAS**GFTFSSYAMH**WVRQAPGKGL EWVA**IIWYDGSNHHYADSVKG**RFTISRDNSKNTLYLQMNSLRAED TAVYYCAR**DSGFYDSYYFDY**WGQGTLVTVSS
124	P1-068746 VL	EIVLTQSPATLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**DASNRAT**GIPARFSGSGSGTDFTLTISSLEPEDFATYYC**Q QYNSYPYT**FGQGTKLEIK
125	P1-068746 IgG1.3 HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGL EWVAIIWYDGSNHHYADSVKGRFTISRDNSKNTLYLQMNSLRAED TAVYYCARDSGFYDSYYFDYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD KTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
126	P1-068746 LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFATYYCQ QYNSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
127	P1-068750 VH	QVQLVESGGGVVQPGRSLRLSCAAS**GFTFSDYDMH**WVRQAPGKGL EWVA**EIWDDGSNKYYADSVKG**RFTISRDNSKNTLYLQMNSLRAED TAVYYCAR**DEEFYSSYYFDY**WGQGTLVTVSS
128	P1-068750 VL	EIVLTQSPATLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**DASNRAT**GIPARFSGSGSGTDFTLTISSLEPEDFATYYC**Q QYNSYPYT**FGQGTKLEIK
129	P1-068750 IgG1.3 HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSDYDMHWVRQAPGKGL EWVAEIWDDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAED TAVYYCARDEEFYSSYYFDYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD KTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE

[1382]

[1383]

SEQ ID NO	名称	序列
		EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
130	P1-068750 LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFATYYCQ QYNSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
131	P1-068738 VH	QVQLVESGGGVVQPGRSLRLSCAAS**GFTFSEYAHH**WVRQAPGKGL EWVA**IIWDDGSNHYYADSVKG**RFTISRDNSKNTLYLQMNSLRAED TAVYYCAR**DSGFYEDYYFDY**WGQGTLVTVSS
132	P1-068738 VL	EIVLTQSPATLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**DASNRAT**GIPARFSGSGSGTDFTLTISSLEPEDFATYYC**Q QYNSYPYT**FGQGTKLEIK
133	P1-068738 IgG1.3 HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSEYAHHWVRQAPGKGL EWVAIIWDDGSNHYYADSVKGRFTISRDNSKNTLYLQMNSLRAED TAVYYCARDSGFYEDYYFDYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD KTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
134	P1-068738 LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFATYYCQ QYNSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
135	P1-068754 VH	QVQLVESGGGVVQPGRSLRLSCAAS**GFTFSDYDMH**WVRQAPGKGL EWVA**EIWDDGSNKYYADSVKG**RFTISRDNSKNTLYLQMNSLRAED TAVYYCAR**DSGFHSDYYFDY**WGQGTLVTVSS
136	P1-068754 VL	EIVLTQSPATLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**DASNRAT**GIPARFSGSGSGTDFTLTISSLEPEDFATYYC**Q QYNSYPYT**FGQGTKLEIK
137	P1-068754 IgG1.3 HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSDYDMHWVRQAPGKGL EWVAEIWDDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAED TAVYYCARDSGFHSDYYFDYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD KTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
138	P1-068754 LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFATYYCQ QYNSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
139	P1-069293 VH (P1-068761.IgG1f)	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAEDV**WGQGTMVTVSS

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SEQ ID NO	名称	序列
140	P1-069293 VL (P1-068761.IgG1f)	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
141	P1-069293 HC (P1-068761.IgG1f)	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
142	P1-069293 LC (P1-068761.IgG1f)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
143	P1-069298 VH (P1-068767.IgG1f)	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GIDWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDD**WGQGTMVTVSS
144	P1-069298 VL (P1-068767.IgG1f)	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
145	P1-069298 HC (P1-068767.IgG1f)	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGIDWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
146	P1-069298 LC (P1-068767.IgG1f)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
147	P1-069302 VH (P1-061029.IgG1f)	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLDDYAMH**WVRQAPGKGL EWVS**GINWNSANIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAFDV**WGQGTMVTVSS
148	P1-069302 VL (P1-061029.IgG1f)	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
149	P1-069302 HC (P1-061029.IgG1f)	EVQLVESGGGLVQPGKSLRLSCAASGFTLDDYAMHWVRQAPGKGL EWVSGINWNSANIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAFDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL

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SEQ ID NO	名称	序列
		QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
150	P1-069302 LC (P1-061029.IgG1f)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
151	P1-069312 VH （P1-068761.IgG1f去岩藻糖基化）	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAEDV**WGQGTMVTVSS
152	P1-069312 VL （P1-068761.IgG1f去岩藻糖基化）	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
153	P1-069312 HC （P1-068761.IgG1f去岩藻糖基化）	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
154	P1-069312 LC （P1-068761.IgG1f去岩藻糖基化）	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
155	P1-069309 VH （P1-068767.IgG1f去岩藻糖基化）	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GIDWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDD**WGQGTMVTVSS
156	P1-069309 VL （P1-068767.IgG1f去岩藻糖基化）	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
157	P1-069309 HC （P1-068767.IgG1f去岩藻糖基化）	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGIDWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS

[1386]

SEQ ID NO	名称	序列
		CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
158	P1-069309 LC （P1-068767.IgG1f去岩藻糖基化）	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
159	P1-069307 VH （P1-061029.IgG1f去岩藻糖基化）	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLDDYAMH**WVRQAPGKGL EWVS**GINWNSANIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAFDV**WGQGTMVTVSS
160	P1-069307 VL （P1-061029.IgG1f去岩藻糖基化）	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
161	P1-069307 HC （P1-061029.IgG1f去岩藻糖基化）	EVQLVESGGGLVQPGKSLRLSCAASGFTLDDYAMHWVRQAPGKGL EWVSGINWNSANIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAFDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
162	P1-069307 LC （P1-061029.IgG1f去岩藻糖基化）	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
163	IgG1.3（或IgG1.3f)重链恒定区 （L234A、L235E、G237A）	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKRVEPKSCDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPG
164	示例性轻链恒定区	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC
165	人VISTA NP_071436.1 （图1B）	参见图1B
166	Cyno VISTA XP_005565644.1 （图1B）	参见图1B

[1387]

SEQ ID NO	名称	序列
167	小 鼠 VISTA NP_083008.1 （图1B）	参见图1B
168	P1-061029 HDR3芯片寡聚物 （图7A）	XPGYSGGWIDAFDV
169	P1-061029 HDR3芯片寡聚物 （图7A）	XXGYSGGWIDAFDV
170	P1-061029 HDR3芯片寡聚物 （图7A）	XPXYSGGWIDAFDV
171	P1-061029 HDR3芯片寡聚物 （图7A）	XPGXSGGWIDAFDV
172	P1-061029 HDR3芯片寡聚物 （图7A）	XPGYXGGWIDAFDV
173	P1-061029 HDR3芯片寡聚物 （图7A）	XPGYSXGWIDAFDV
174	P1-061029 HDR3芯片寡聚物 （图7A）	XPGYSGXWIDAFDV
175	P1-061029 HDR3芯片寡聚物 （图7A）	XPGYSGGXIDAFDV
176	P1-061029 HDR3芯片寡聚物 （图7A）	XPGYSGGWXDAFDV
177	P1-061029 HDR3芯片寡聚物 （图7A）	XPGYSGGWIXAFDV
178	P1-061029 HDR3芯片寡聚物 （图7A）	XPGYSGGWIDXFDV
179	P1-061029 HDR3芯片寡聚物 （图7A）	XPGYSGGWIDAXDV

[1388]

SEQ ID NO	名称	序列
180	P1-061029 HDR3芯片寡聚物（图7A）	**X**PGYSGGWIDAF**X**V
181	P1-061029 HDR3芯片寡聚物（图7A）	**X**PGYSGGWIDAFD**X**
182	IgG1f（人野生型同种异型f）重链恒定区	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	
183	IgG1.1f重链恒定区（L234A、L235E、G237A、A330S、P331S）	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPSSIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	
184	IgG1fa.P238K（或IgG1.P238K）重链恒定区	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	
185	P1-070864 P1-068761_E30D VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLDDEAMH**WVRQAPGKGLEWVS**GINWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTEDTALYYCAK**VPGYSHGWIDAEDV**WGQGTMVTVSS	
186	P1-070864 P1-068761_E30D VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAPRLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYGSSPFT**FGPGTKVDIK	
187	P1-070864 P1-068761_E30D IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLDDEAMHWVRQAPGKGLEWVSGINWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTEDTALYYCAKVPGYSHGWIDAEDVWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	
188	P1-070864 P1-068761_E30D	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC	

[1389]

SEQ ID NO	名称	序列
	LC	LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
189	P1-070866 P1-068761_E32Y VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GINWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAEDV**WGQGTMVTVSS
190	P1-070866 P1-068761_E32Y VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
191	P1-070866 P1-068761_E32Y IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGINWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
192	P1-070866 P1-068761_E32Y LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
193	P1-070868 P1-068761_E55A VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSAEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAEDV**WGQGTMVTVSS
194	P1-070868 P1-068761_E55A VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
195	P1-070868 P1-068761_E55A IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSAEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
196	P1-070868 P1-068761_E55A LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
197	P1-070870 P1-068761_E56N VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAEDV**WGQGTMVTVSS

[1390]

SEQ ID NO	名称	序列
198	P1-070870 P1-068761_E56N VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q** **QYGSSPFT**FGPGTKVDIK
199	P1-070870 P1-068761_E56N IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
200	P1-070870 P1-068761_E56N LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
201	P1-070872 P1-068761_H100G VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDV**WGQGTMVTVSS
202	P1-070872 P1-068761_H100G VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q** **QYGSSPFT**FGPGTKVDIK
203	P1-070872 P1-068761_H100G IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
204	P1-070872 P1-068761_H100G LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
205	P1-070874 P1-068761_E100fF VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAFDV**WGQGTMVTVSS
206	P1-070874 P1-068761_E100fF VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q** **QYGSSPFT**FGPGTKVDIK
207	P1-070874	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL

[1391]

SEQ ID NO	名称	序列
	P1-068761_E100fF IgG1.3 HC	EWVSGINWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAFDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
208	P1-070874 P1-068761_E100fF LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
209	P1-070876 P1-068761_E30D_E32Y VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLDDYAMH**WVRQAPGKGL EWVS**GINWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAEDV**WGQGTMVTVSS
210	P1-070876 P1-068761_E30D_E32Y VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
211	P1-070876 P1-068761_E30D_E32Y IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLDDYAMHWVRQAPGKGL EWVSGINWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
212	P1-070876 P1-068761_E30D_E32Y LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
213	P1-070878 P1-068761_E55A_E56N VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSANIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAEDV**WGQGTMVTVSS
214	P1-070878 P1-068761_E55A_E56N VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
215	P1-070878 P1-068761_E55A_E56N	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSANIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA

[1392]

SEQ ID NO	名称	序列
	IgG1.3 HC	PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
216	P1-070878 P1-068761_E55A_E56N LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
217	P1-070880 P1-068761_H100G_E100fF VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAFDV**WGQGTMVTVSS
218	P1-070880 P1-068761_H100G_E100fF VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
219	P1-070880 P1-068761_H100G_E100fF IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAFDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
220	P1-070880 P1-068761_H100G_E100fF LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
221	P1-070882 P1-068761_E32Y_E55A VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GINWNSAEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAEDV**WGQGTMVTVSS
222	P1-070882 P1-068761_E32Y_E55A VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
223	P1-070882 P1-068761_E32Y_E55A IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGINWNSAEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS

[1393]

SEQ ID NO	名称	序列
		CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
224	P1-070882 P1-068761_E32Y_E55A LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
225	P1-070884 P1-068761_E32Y_E56N VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GINWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAEDV**WGQGTMVTVSS
226	P1-070884 P1-068761_E32Y_E56N VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
227	P1-070884 P1-068761_E32Y_E56N IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGINWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
228	P1-070884 P1-068761_E32Y_E56N LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
229	P1-070886 P1-068761_E32Y_H100G VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GINWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDV**WGQGTMVTVSS
230	P1-070886 P1-068761_E32Y_H100G VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
231	P1-070886 P1-068761_E32Y_H100G IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGINWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL

[1394]

SEQ ID NO	名称	序列
		HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
232	P1-070886 P1-068761_E32Y_H100G LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
233	P1-070888 P1-068761_E32Y_E100fF VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GINWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAFDV**WGQGTMVTVSS
234	P1-070888 P1-068761_E32Y_E100fF VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
235	P1-070888 P1-068761_E32Y_E100fF IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGINWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAFDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
236	P1-070888 P1-068761_E32Y_E100fF LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
237	P1-070890 P1-068761_E30D_E55A VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLDDEAMH**WVRQAPGKGL EWVS**GINWNSAEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAEDV**WGQGTMVTVSS
238	P1-070890 P1-068761_E30D_E55A VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
239	P1-070890 P1-068761_E30D_E55A IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLDDEAMHWVRQAPGKGL EWVSGINWNSAEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD

[1395]

SEQ ID NO	名称	序列
		SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
240	P1-070890 P1-068761_E30D_E 55A LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
241	P1-070892 P1-068761_E30D_E 56N VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLDDEAMH**WVRQAPGKGL EWVS**GINWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAEDV**WGQGTMVTVSS
242	P1-070892 P1-068761_E30D_E 56N VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
243	P1-070892 P1-068761_E30D_E 56N IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLDDEAMHWVRQAPGKGL EWVSGINWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
244	P1-070892 P1-068761_E30D_E 56N LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
245	P1-070894 P1-068761_E30D_H 100G VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLDDEAMH**WVRQAPGKGL EWVS**GINWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDV**WGQGTMVTVSS
246	P1-070894 P1-068761_E30D_H 100G VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
247	P1-070894 P1-068761_E30D_H 100G IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLDDEAMHWVRQAPGKGL EWVSGINWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG

[1396]

SEQ ID NO	名称	序列
248	P1-070894 P1-068761_E30D_H100G LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
249	P1-070896 P1-068761_E30D_E100fF VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLDDEAMH**WVRQAPGKGL EWVS**GINWNSEEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAFDV**WGQGTMVTVSS
250	P1-070896 P1-068761_E30D_E100fF VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
251	P1-070896 P1-068761_E30D_E100fF IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLDDEAMHWVRQAPGKGL EWVSGINWNSEEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAFDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
252	P1-070896 P1-068761_E30D_E100fF LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
253	P1-070898 P1-068761_E55A_E100fF VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSAEIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAFDV**WGQGTMVTVSS
254	P1-070898 P1-068761_E55A_E100fF VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
255	P1-070898 P1-068761_E55A_E100fF IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSAEIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAFDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
256	P1-070898	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ

[1397]

SEQ ID NO	名称	序列
	P1-068761_E55A_E100fF LC	QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
257	P1-070900 P1-068761_E56N_H100G VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDV**WGQGTMVTVSS
258	P1-070900 P1-068761_E56N_H100G VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q** **QYGSSPFT**FGPGTKVDIK
259	P1-070900 P1-068761_E56N_H100G IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
260	P1-070900 P1-068761_E56N_H100G LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
261	P1-070902 P1-068761_E56N_E100fF VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDEAMH**WVRQAPGKGL EWVS**GINWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSHGWIDAFDV**WGQGTMVTVSS
262	P1-070902 P1-068761_E56N_E100fF VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q** **QYGSSPFT**FGPGTKVDIK
263	P1-070902 P1-068761_E56N_E100fF IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDEAMHWVRQAPGKGL EWVSGINWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSHGWIDAFDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
264	P1-070902 P1-068761_E56N_E100fF	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC

[1398]

SEQ ID NO	名称	序列
	LC	LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
265	P1-070904 P1-068767_E30D VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLDDYAMH**WVRQAPGKGL EWVS**GIDWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDD**WGQGTMVTVSS
266	P1-070904 P1-068767_E30D VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
267	P1-070904 P1-068767_E30D IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLDDYAMHWVRQAPGKGL EWVSGIDWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
268	P1-070904 P1-068767_E30D LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
269	P1-070906 P1-068767_D52N VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GINWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDD**WGQGTMVTVSS
270	P1-070906 P1-068767_D52N VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
271	P1-070906 P1-068767_D52N IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGINWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
272	P1-070906 P1-068767_D52N LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
273	P1-070908 P1-068767_E55A VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GIDWNSANIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDD**WGQGTMVTVSS

[1399]

SEQ ID NO	名称	序列
274	P1-070908 P1-068767_E55A VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q** **QYGSSPFT**FGPGTKVDIK
275	P1-070908 P1-068767_E55A IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGIDWNSANIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
276	P1-070908 P1-068767_E55A LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
277	P1-070910 P1-068767_E100fF VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GIDWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAFDD**WGQGTMVTVSS
278	P1-070910 P1-068767_E100fF VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q** **QYGSSPFT**FGPGTKVDIK
279	P1-070910 P1-068767_E100fF IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGIDWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAFDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
280	P1-070910 P1-068767_E100fF LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
281	P1-070912 P1-068767_D102V VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GIDWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDV**WGQGTMVTVSS
282	P1-070912 P1-068767_D102V VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q** **QYGSSPFT**FGPGTKVDIK
283	P1-070912	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL

[1400]

SEQ ID NO	名称	序列
	P1-068767_D102V IgG1.3 HC	EWVSGIDWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
284	P1-070912 P1-068767_D102V LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
285	P1-070914 P1-068767_E30D_D52N VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLDDYAMH**WVRQAPGKGL EWVS**GINWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDD**WGQGTMVTVSS
286	P1-070914 P1-068767_E30D_D52N VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
287	P1-070914 P1-068767_E30D_D52N IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLDDYAMHWVRQAPGKGL EWVSGINWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
288	P1-070914 P1-068767_E30D_D52N LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
289	P1-070916 P1-068767_D52N_E55A VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GINWNSANIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDD**WGQGTMVTVSS
290	P1-070916 P1-068767_D52N_E55A VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
291	P1-070916 P1-068767_D52N_E55A	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGINWNSANIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA

[1401]

SEQ ID NO	名称	序列
	IgG1.3 HC	PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
292	P1-070916 P1-068767_D52N_E55A LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
293	P1-070918 P1-068767_E55A_E100fF VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GIDWNSANIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAFDD**WGQGTMVTVSS
294	P1-070918 P1-068767_E55A_E100fF VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
295	P1-070918 P1-068767_E55A_E100fF IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGIDWNSANIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAFDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
296	P1-070918 P1-068767_E55A_E100fF LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
297	P1-070920 P1-068767_E100fF_D102V VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMHW**VRQAPGKGL EWVS**GIDWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAFDV**WGQGTMVTVSS
298	P1-070920 P1-068767_E100fF_D102V VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
299	P1-070920 P1-068767_E100fF_D102V IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGIDWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAFDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS

[1402]

SEQ ID NO	名称	序列
		CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
300	P1-070920 P1-068767_E100fF_D102V LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
301	P1-070922 P1-068767_E30D_E55A VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLDDYAMH**WVRQAPGKGL EWVS**GIDWNSANIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDD**WGQGTMVTVSS
302	P1-070922 P1-068767_E30D_E55A VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
303	P1-070922 P1-068767_E30D_E55A IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLDDYAMHWVRQAPGKGL EWVSGIDWNSANIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
304	P1-070922 P1-068767_E30D_E55A LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
305	P1-070924 P1-068767_E30D_E100fF VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLDDYAMH**WVRQAPGKGL EWVS**GIDWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAFDD**WGQGTMVTVSS
306	P1-070924 P1-068767_E30D_E100fF VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYL**AWYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
307	P1-070924 P1-068767_E30D_E100fF IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLDDYAMHWVRQAPGKGL EWVSGIDWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAFDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL

[1403]

SEQ ID NO	名称	序列
		HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
308	P1-070924 P1-068767_E30D_E100fF LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
309	P1-070926 P1-068767_E30D_D102V VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLDDYAMH**WVRQAPGKGL EWVS**GIDWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAEDV**WGQGTMVTVSS
310	P1-070926 P1-068767_E30D_D102V VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
311	P1-070926 P1-068767_E30D_D102V IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLDDYAMHWVRQAPGKGL EWVSGIDWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
312	P1-070926 P1-068767_E30D_D102V LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
313	P1-070928 P1-068767_D52N_E100fF VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GINWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAFDD**WGQGTMVTVSS
314	P1-070928 P1-068767_D52N_E100fF VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
315	P1-070928 P1-068767_D52N_E100fF IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGINWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAFDDWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD

[1404]

SEQ ID NO	名称	序列
		SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
316	P1-070928 P1-068767_D52N_E 100fF LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
317	P1-070930 P1-068767_D52N_D 102V VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GINWNSENIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAED**VWGQGTMVTVSS
318	P1-070930 P1-068767_D52N_D 102V VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
319	P1-070930 P1-068767_D52N_D 102V IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGINWNSENIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
320	P1-070930 P1-068767_D52N_D 102V LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
321	P1-070932 P1-068767_E55A_D 102V VH	EVQLVESGGGLVQPGKSLRLSCAAS**GFTLEDYAMH**WVRQAPGKGL EWVS**GIDWNSANIGYADSVKG**RFTISRDNAKNSLYLQMNSLRTED TALYYCAK**VPGYSGGWIDAED**VWGQGTMVTVSS
322	P1-070932 P1-068767_E55A_D 102V VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**Q QYGSSPFT**FGPGTKVDIK
323	P1-070932 P1-068767_E55A_D 102V IgG1.3 HC	EVQLVESGGGLVQPGKSLRLSCAASGFTLEDYAMHWVRQAPGKGL EWVSGIDWNSANIGYADSVKGRFTISRDNAKNSLYLQMNSLRTED TALYYCAKVPGYSGGWIDAEDVWGQGTMVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG

[1405]

SEQ ID NO	名称	序列
324	P1-070932 P1-068767_E55A_D102V LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAP RLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQ QYGSSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
325	hVISTA-ECD 6-His标签	AFKVATPYSL YVCPEGQNVT LTCRLLGPVD KGHDVTFYKT WYRSSRGEVQ TCSERRPIRN LTFQDLHLHH GGHQAANTSH DLAQRHGLES ASDHHGNFSI TMRNLTLLDS GLYCCLVVEI RHHHSEHRVH GAMELQVQTG KDAPSNCVVY PSSSQESENI TAHHHHHHH
326	Cyno VISTA-ECD 6-His标签	AFKVATLYSL YVCPEGQNVT LTCRVFGPVD KGHDVTFYKT WYRSSRGEVQ TCSERRPIRN LTFQDLHLHH GGHQAANTSH DLAQRHGLES ASDHHGNFSI TMRNLTLLDS GLYCCLVVEI RHHHSEHRVH GAMELQVQTG KDAPSSCVAY PSSSQESENI TAHHHHHHH
327	P1-069059 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAA GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGACCATATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
328	P1-069059 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
329	P1-069061 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAA GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGCTGAAATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
330	P1-069061 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
331	P1-069063 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAA GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGCTGAAATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC

[1406]

SEQ ID NO	名称	序列
		AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGACGATGAATGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
332	P1-069063 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
333	P1-069065 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAA GATGAAGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGACGACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTTTTGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
334	P1-069065 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
335	P1-069067 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAT GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAGAAATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGACGATGAATGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
336	P1-069067 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
337	P1-069069 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAT GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAGAAATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGACGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA

[1407]

SEQ ID NO	名称	序列
338	P1-069069 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
339	P1-069071 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAA GATGAAGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGCTGACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGAAGGC TGGATTGACGCTTTTGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
340	P1-069071 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
341	P1-069073 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAA GATGAAGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGCTGAAATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
342	P1-069073 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
343	P1-069075 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAA GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGGACAGTGCTGAAATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
344	P1-069075 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA

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SEQ ID NO	名称	序列
		GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
345	P1-069077 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAA GATGAAGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGACGAAATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTTTTGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
346	P1-069077 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
347	P1-068761 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
348	P1-068761 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
349	P1-068767 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTGATTGGAACAGTGAAAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
350	P1-068767 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA

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SEQ ID NO	名称	序列
351	P1-068773 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTGATTGGAACAGTGATAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
352	P1-068773 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
353	P1-068765 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCGATGAG GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
354	P1-068765 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
355	P1-061029 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAT GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGCTAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTTTTGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
356	P1-061029 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
357	P1-068757 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAGAGATAGGCTAT

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SEQ ID NO	名称	序列
		GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
358	P1-068757 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
359	P1-068771 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTCATGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
360	P1-068771 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
361	P1-068775 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTGATTGGAACAGTGAAGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTGAAGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
362	P1-068775 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
363	P1-068769 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGATCACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGACTGGGGCCAAGGGACAATGGTCACC

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		GTCTCTTCA
364	P1-068769 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
365	P1-068759 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTGATTGGAACAGTGAAAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
366	P1-068759 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
367	P1-068763 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTGATTGGAACAGTGAAAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
368	P1-068763 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
369	P1-061015 VH DNA	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGG AGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGT AGCTATGCCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTG GAGTGGGTGGCAATTATATGGTATGATGGAAGTAATAAATACTAT GCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGAC ACGGCTGTGTATTACTGTGCGAGAGATAGTGGTTTTTACTCCTCG TACTACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCC TCA
370	P1-061015 VL DNA	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC

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		AGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCA GCCAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACC ATCAGCAGCCTGGAGCCTGAAGATTTTGCAACTTATTACTGCCAA CAGTATAATAGTTACCCGTACACTTTTGGCCAGGGGACCAAGCTG GAGATCAAA
371	P1-068748 VH DNA	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGG AGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGT CACCATGCCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTG GAGTGGGTGGCAATTATATGGTATGATGGAAGTAATGACGACTAT GCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGAC ACGGCTGTGTATTACTGTGCGAGAGATAGTGGTTTTTACGACTCG TACTACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCC TCA
372	P1-068748 VL DNA	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCA GCCAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACC ATCAGCAGCCTGGAGCCTGAAGATTTTGCAACTTATTACTGCCAA CAGTATAATAGTTACCCGTACACTTTTGGCCAGGGGACCAAGCTG GAGATCAAA
373	P1-068744 VH DNA	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGG AGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGT GAGTATGCCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTG GAGTGGGTGGCACATATATGGTATGATGGAAGTAATAAATACGAG GCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGAC ACGGCTGTGTATTACTGTGCGAGAGATAGTGGTTTTTACGAATCG TACTACTTTGACGAGTGGGGCCAGGGAACCCTGGTCACCGTCTCC TCA
374	P1-068744 VL DNA	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCA GCCAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACC ATCAGCAGCCTGGAGCCTGAAGATTTTGCAACTTATTACTGCCAA CAGTATAATAGTTACCCGTACACTTTTGGCCAGGGGACCAAGCTG GAGATCAAA
375	P1-068736 VH DNA	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGG AGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGT GAGTATGCCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTG GAGTGGGTGGCAATTGATTGGTATGATGGAAGTAATAAAGACTAT GCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGAC ACGGCTGTGTATTACTGTGCGAGAGATAGTGGTTTTTACGACTCG TACTACTTTGACGACTGGGGCCAGGGAACCCTGGTCACCGTCTCC TCA
376	P1-068736 VL DNA	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCA GCCAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACC ATCAGCAGCCTGGAGCCTGAAGATTTTGCAACTTATTACTGCCAA CAGTATAATAGTTACCCGTACACTTTTGGCCAGGGGACCAAGCTG

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		GAGATCAAA
377	P1-068752 VH DNA	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGG AGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGT AGCTATGCCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTG GAGTGGGTGGCAGAGATATGGTATGATGGAAGTAATAAAGACTAT GCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGAC ACGGCTGTGTATTACTGTGCGAGAGATAGTGGTTTTTACGACTCG TACTACTTTGACGAGTGGGGCCAGGGAACCCTGGTCACCGTCTCC TCA
378	P1-068752 VL DNA	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCA GCCAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACC ATCAGCAGCCTGGAGCCTGAAGATTTTGCAACTTATTACTGCCAA CAGTATAATAGTTACCCGTACACTTTTGGCCAGGGGACCAAGCTG GAGATCAAA
379	P1-068740 VH DNA	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGG AGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGT GACTATGCCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTG GAGTGGGTGGCAATTATATGGTATGATGGAAGTGATAAAGACTAT GCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGAC ACGGCTGTGTATTACTGTGCGAGAGATAGTGGTTTTTACGACTCG TACTACTTTGACGACTGGGGCCAGGGAACCCTGGTCACCGTCTCC TCA
380	P1-068740 VL DNA	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCA GCCAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACC ATCAGCAGCCTGGAGCCTGAAGATTTTGCAACTTATTACTGCCAA CAGTATAATAGTTACCCGTACACTTTTGGCCAGGGGACCAAGCTG GAGATCAAA
381	P1-068742 VH DNA	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGG AGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGT GACTATGCCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTG GAGTGGGTGGCAATTATATGGTATGATGGAAGTGATAAAGACTAT GCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGAC ACGGCTGTGTATTACTGTGCGAGAGATAGTGGTTTTTACGAAGAT TACTACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCC TCA
382	P1-068742 VL DNA	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCA GCCAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACC ATCAGCAGCCTGGAGCCTGAAGATTTTGCAACTTATTACTGCCAA CAGTATAATAGTTACCCGTACACTTTTGGCCAGGGGACCAAGCTG GAGATCAAA
383	P1-068746 VH DNA	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGG AGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGT AGCTATGCCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTG

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		GAGTGGGTGGCAATTATATGGTATGATGGAAGTAATCACCACTAT GCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGAC ACGGCTGTGTATTACTGTGCGAGAGATAGTGGTTTTTACGACTCG TACTACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCC TCA
384	P1-068746 VL DNA	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCA GCCAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACC ATCAGCAGCCTGGAGCCTGAAGATTTTGCAACTTATTACTGCCAA CAGTATAATAGTTACCCGTACACTTTTGGCCAGGGGACCAAGCTG GAGATCAAA
385	P1-068750 VH DNA	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGG AGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGT GACTATGACATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTG GAGTGGGTGGCAGAGATATGGGATGATGGAAGTAATAAATACTAT GCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGAC ACGGCTGTGTATTACTGTGCGAGAGATGAGGAATTTTACTCCTCG TACTACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCC TCA
386	P1-068750 VL DNA	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCA GCCAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACC ATCAGCAGCCTGGAGCCTGAAGATTTTGCAACTTATTACTGCCAA CAGTATAATAGTTACCCGTACACTTTTGGCCAGGGGACCAAGCTG GAGATCAAA
387	P1-068738 VH DNA	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGG AGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGT GAGTATGCCCATCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTG GAGTGGGTGGCAATTATATGGGATGATGGAAGTAATCACTACTAT GCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGAC ACGGCTGTGTATTACTGTGCGAGAGATAGTGGTTTTTACGAAGAT TACTACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCC TCA
388	P1-068738 VL DNA	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCA GCCAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACC ATCAGCAGCCTGGAGCCTGAAGATTTTGCAACTTATTACTGCCAA CAGTATAATAGTTACCCGTACACTTTTGGCCAGGGGACCAAGCTG GAGATCAAA
389	P1-068754 VH DNA	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGG AGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGT GACTATGACATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTG GAGTGGGTGGCAGAGATATGGGATGATGGAAGTAATAAATACTAT GCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGAC ACGGCTGTGTATTACTGTGCGAGAGATAGTGGTTTTCACTCCGAT

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		TACTACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCC TCA
390	P1-068754 VL DNA	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCA GCCAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACC ATCAGCAGCCTGGAGCCTGAAGATTTTGCAACTTATTACTGCCAA CAGTATAATAGTTACCCGTACACTTTTGGCCAGGGGACCAAGCTG GAGATCAAA
391	P1-070864 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAT GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
392	P1-070864 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
393	P1-070866 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
394	P1-070866 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
395	P1-070868 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGCTGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
396	P1-070868 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC

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		AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
397	P1-070870 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
398	P1-070870 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
399	P1-070872 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
400	P1-070872 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
401	P1-070874 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTTTTGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
402	P1-070874 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG

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		CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
403	P1-070876 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAT GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
404	P1-070876 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
405	P1-070878 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGCTAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
406	P1-070878 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
407	P1-070880 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTTTTGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
408	P1-070880 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
409	P1-070882 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG

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		GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGCTGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
410	P1-070882 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
411	P1-070884 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
412	P1-070884 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
413	P1-070886 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
414	P1-070886 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
415	P1-070888 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC

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SEQ ID NO	名称	序列
		ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTTTTGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
416	P1-070888 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
417	P1-070890 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAT GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGCTGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
418	P1-070890 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
419	P1-070892 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAT GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
420	P1-070892 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
421	P1-070894 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAT GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
422	P1-070894 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA

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		GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
423	P1-070896 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAT GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTTTTGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
424	P1-070896 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
425	P1-070898 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGCTGAGATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTTTTGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
426	P1-070898 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
427	P1-070900 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
428	P1-070900 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC

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		ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
429	P1-070902 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATGAGGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCCATGGC TGGATTGACGCTTTTGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
430	P1-070902 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
431	P1-070904 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAT GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTGATTGGAACAGTGAAAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
432	P1-070904 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
433	P1-070906 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
434	P1-070906 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
435	P1-070908 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC

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		AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTGATTGGAACAGTGCTAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
436	P1-070908 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
437	P1-070910 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTGATTGGAACAGTGAAAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTTTTGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
438	P1-070910 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
439	P1-070912 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTGATTGGAACAGTGAAAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
440	P1-070912 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
441	P1-070914 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAT GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGAAAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC

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		AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
442	P1-070914 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
443	P1-070916 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTAATTGGAACAGTGCTAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
444	P1-070916 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
445	P1-070918 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTGATTGGAACAGTGCTAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTTTTGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
446	P1-070918 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
447	P1-070920 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAG GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTGATTGGAACAGTGAAAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTTTTGATGTCTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA

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448	P1-070920 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
449	P1-070922 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAT GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTGATTGGAACAGTGCTAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTGAAGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
450	P1-070922 VL DNA	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAA
451	P1-070924 VH DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGC AAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCCTTGAT GATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTG GAGTGGGTCTCAGGTATTGATTGGAACAGTGAAAACATAGGCTAT GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGAC ACGGCCTTGTATTACTGTGCAAAAGTTCCTGGGTATAGCGGTGGC TGGATTGACGCTTTTGATGACTGGGGCCAAGGGACAATGGTCACC GTCTCTTCA
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[2626] Ser Phe Asn Arg Gly Glu Cys
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[2809] 50 55 60
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[2815] 100 105
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[2928] 35 40 45
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[3039] 50 55 60

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[3045] 100 105 110

[3046] Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser

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[3050] Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser

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[3052] Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu

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[3055] 180 185 190

[3056] Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys

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[3058] Ser Phe Asn Arg Gly Glu Cys

[3059] 210 215

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[3062] <212> PRT

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[3080] 100 105 110
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[3125] Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly

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[3146] 275 280 285

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[3241] 50 55 60
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[3327] 50 55 60
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[3346] Ser Phe Asn Arg Gly Glu Cys
[3347] 210 215
[3348] <210> 91
[3349] <211> 123
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[3817] 50 55 60
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[4053] 100 105 110

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[4063] 180 185 190

[4064] Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys

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[4335] 50 55 60
[4336] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
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[4354] Ser Phe Asn Arg Gly Glu Cys
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[4398] Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
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[4512] 35 40 45
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[4514] 50 55 60
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[4519] Ala Arg Asp Ser Gly Phe Tyr Asp Ser Tyr Tyr Phe Asp Tyr Trp Gly
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[4535] 35 40 45

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[4556] 35 40 45
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[4582] 245 250 255
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[4623] 50 55 60
[4624] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
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[4626] Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro
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[4628] Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala
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[4639] 180 185 190
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[4642] Ser Phe Asn Arg Gly Glu Cys
[4643] 210 215
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[4823] 35 40 45
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[4825] 50 55 60
[4826] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
[4827] 65 70 75 80
[4828] Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro
[4829] 85 90 95

[4830] Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
[4831] 100 105
[4832] <210> 133
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[4879] Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
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[4891] Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
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[4910] Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser
[4911] 50 55 60
[4912] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
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[4914] Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro
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[4916] Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala
[4917] 100 105 110
[4918] Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
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[4920] Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
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[4924] Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
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[4927] 180 185 190
[4928] Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
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[4930] Ser Phe Asn Arg Gly Glu Cys
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[4944] 35 40 45
[4945] Ala Glu Ile Trp Asp Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
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[4947] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[4948] 65 70 75 80
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[4954] 115 120
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[4969] 50 55 60
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[4974] Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
[4975] 100 105
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[4988] 35 40 45
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[4992] 65 70 75 80
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[4994] 85 90 95
[4995] Ala Arg Asp Ser Gly Phe His Ser Asp Tyr Tyr Phe Asp Tyr Trp Gly
[4996] 100 105 110
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[4998] 115 120 125
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[5003] Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
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[5005] Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
[5006] 180 185 190
[5007] Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
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[5010] 210 215 220
[5011] Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Glu Gly
[5012] 225 230 235 240
[5013] Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
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[5018] 275 280 285
[5019] His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
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[5021] Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
[5022] 305 310 315 320
[5023] Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
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[5025] Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
[5026] 340 345 350
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[5028] 355 360 365
[5029] Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
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[5034] 405 410 415
[5035] Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
[5036] 420 425 430
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[5040] 450

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[5050] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser

[5051] 20 25 30

[5052] Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu

[5053] 35 40 45

[5054] Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser

[5055] 50 55 60

[5056] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu

[5057] 65 70 75 80

[5058] Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro

[5059] 85 90 95

[5060] Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala

[5061] 100 105 110

[5062] Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser

[5063] 115 120 125

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[5065] 130 135 140

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[5067] 145 150 155 160

[5068] Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu

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[5070] Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val

[5071] 180 185 190

[5072] Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys

[5073] 195 200 205

[5074] Ser Phe Asn Arg Gly Glu Cys

[5075] 210 215

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[5084] 1 5 10 15

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[5086] 20 25 30

[5087] Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[5088] 35 40 45

[5089] Ser Gly Ile Asn Trp Asn Ser Glu Glu Ile Gly Tyr Ala Asp Ser Val

[5090] 50 55 60

[5091] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

[5092] 65 70 75 80

[5093] Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Leu Tyr Tyr Cys

[5094] 85 90 95

[5095] Ala Lys Val Pro Gly Tyr Ser His Gly Trp Ile Asp Ala Glu Asp Val

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[5097] Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser

[5098] 115 120

[5099] <210> 140

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[5104] <223> P1-069293 VL (P1-068761.IgG1f)

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[5107] 1 5 10 15

[5108] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser

[5109] 20 25 30

[5110] Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu

[5111] 35 40 45

[5112] Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser

[5113] 50 55 60

[5114] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu

[5115] 65 70 75 80

[5116] Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro

[5117] 85 90 95

[5118] Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys

[5119] 100 105

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[5125] <223> P1-069293 HC (P1-068761.IgG1f)

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[5130] 20 25 30
[5131] Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[5132] 35 40 45
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[5134] 50 55 60
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[5136] 65 70 75 80
[5137] Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Leu Tyr Tyr Cys
[5138] 85 90 95
[5139] Ala Lys Val Pro Gly Tyr Ser His Gly Trp Ile Asp Ala Glu Asp Val
[5140] 100 105 110
[5141] Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly
[5142] 115 120 125
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[5144] 130 135 140
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[5150] 180 185 190
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[5160] 260 265 270
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[5165] Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu

[5166] 305 310 315 320
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[5168] 325 330 335
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[5170] 340 345 350
[5171] Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
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[5173] Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
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[5176] 385 390 395 400
[5177] Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
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[5180] 420 425 430
[5181] Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
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[5183] Leu Ser Pro Gly
[5184] 450
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[5195] 20 25 30
[5196] Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
[5197] 35 40 45
[5198] Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
[5199] 50 55 60
[5200] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
[5201] 65 70 75 80
[5202] Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
[5203] 85 90 95
[5204] Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala
[5205] 100 105 110
[5206] Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
[5207] 115 120 125

[5208] Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
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[5211] 145 150 155 160
[5212] Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
[5213] 165 170 175
[5214] Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
[5215] 180 185 190
[5216] Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
[5217] 195 200 205
[5218] Ser Phe Asn Arg Gly Glu Cys
[5219] 210 215
[5220] <210> 143
[5221] <211> 123
[5222] <212> PRT
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[5231] Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[5232] 35 40 45
[5233] Ser Gly Ile Asp Trp Asn Ser Glu Asn Ile Gly Tyr Ala Asp Ser Val
[5234] 50 55 60
[5235] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[5236] 65 70 75 80
[5237] Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Leu Tyr Tyr Cys
[5238] 85 90 95
[5239] Ala Lys Val Pro Gly Tyr Ser Gly Gly Trp Ile Asp Ala Glu Asp Asp
[5240] 100 105 110
[5241] Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
[5242] 115 120
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[5252] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
[5253] 20 25 30
[5254] Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
[5255] 35 40 45
[5256] Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
[5257] 50 55 60
[5258] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
[5259] 65 70 75 80
[5260] Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
[5261] 85 90 95
[5262] Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
[5263] 100 105
[5264] <210> 145
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[5274] 20 25 30
[5275] Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[5276] 35 40 45
[5277] Ser Gly Ile Asp Trp Asn Ser Glu Asn Ile Gly Tyr Ala Asp Ser Val
[5278] 50 55 60
[5279] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[5280] 65 70 75 80
[5281] Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Leu Tyr Tyr Cys
[5282] 85 90 95
[5283] Ala Lys Val Pro Gly Tyr Ser Gly Gly Trp Ile Asp Ala Glu Asp Asp
[5284] 100 105 110
[5285] Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly
[5286] 115 120 125
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[5288] 130 135 140
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[5292] 165 170 175
[5293] Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
[5294] 180 185 190
[5295] Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
[5296] 195 200 205
[5297] Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys
[5298] 210 215 220
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[5302] 245 250 255
[5303] Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
[5304] 260 265 270
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[5308] 290 295 300
[5309] Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
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[5319] Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
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[5323] Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
[5324] 420 425 430
[5325] Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
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[5327] Leu Ser Pro Gly
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[5343] 50 55 60
[5344] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
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[5347] 85 90 95
[5348] Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala
[5349] 100 105 110
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[5354] Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
[5355] 145 150 155 160
[5356] Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
[5357] 165 170 175
[5358] Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
[5359] 180 185 190
[5360] Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
[5361] 195 200 205
[5362] Ser Phe Asn Arg Gly Glu Cys
[5363] 210 215
[5364] <210> 147
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[5375] Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[5376] 35 40 45
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[5378] 50 55 60
[5379] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[5380] 65 70 75 80
[5381] Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Leu Tyr Tyr Cys
[5382] 85 90 95
[5383] Ala Lys Val Pro Gly Tyr Ser Gly Gly Trp Ile Asp Ala Phe Asp Val
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[5385] Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
[5386] 115 120
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[5398] Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
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[5401] 50 55 60
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[5404] Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
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[5406] Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
[5407] 100 105
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[5420] 35 40 45
[5421] Ser Gly Ile Asn Trp Asn Ser Ala Asn Ile Gly Tyr Ala Asp Ser Val
[5422] 50 55 60
[5423] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[5424] 65 70 75 80
[5425] Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Leu Tyr Tyr Cys
[5426] 85 90 95
[5427] Ala Lys Val Pro Gly Tyr Ser Gly Gly Trp Ile Asp Ala Phe Asp Val
[5428] 100 105 110
[5429] Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly
[5430] 115 120 125
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[5432] 130 135 140
[5433] Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
[5434] 145 150 155 160
[5435] Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
[5436] 165 170 175
[5437] Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
[5438] 180 185 190
[5439] Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
[5440] 195 200 205
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[5442] 210 215 220
[5443] Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
[5444] 225 230 235 240
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[5446] 245 250 255
[5447] Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
[5448] 260 265 270
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[5450] 275 280 285
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[5452] 290 295 300
[5453] Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
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[5455] Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
[5456] 325 330 335
[5457] Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
[5458] 340 345 350
[5459] Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln

[5460] 355 360 365
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[5462] 370 375 380
[5463] Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
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[5465] Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
[5466] 405 410 415
[5467] Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
[5468] 420 425 430
[5469] Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
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[5472] 450
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[5484] Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
[5485] 35 40 45
[5486] Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
[5487] 50 55 60
[5488] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
[5489] 65 70 75 80
[5490] Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
[5491] 85 90 95
[5492] Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala
[5493] 100 105 110
[5494] Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
[5495] 115 120 125
[5496] Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
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[5498] Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
[5499] 145 150 155 160
[5500] Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
[5501] 165 170 175

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[5503] 180 185 190
[5504] Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
[5505] 195 200 205
[5506] Ser Phe Asn Arg Gly Glu Cys
[5507] 210 215
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[5510] <212> PRT
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[5517] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Glu Asp Glu
[5518] 20 25 30
[5519] Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[5520] 35 40 45
[5521] Ser Gly Ile Asn Trp Asn Ser Glu Glu Ile Gly Tyr Ala Asp Ser Val
[5522] 50 55 60
[5523] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[5524] 65 70 75 80
[5525] Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Leu Tyr Tyr Cys
[5526] 85 90 95
[5527] Ala Lys Val Pro Gly Tyr Ser His Gly Trp Ile Asp Ala Glu Asp Val
[5528] 100 105 110
[5529] Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
[5530] 115 120
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[5532] <211> 108
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[5536] <223> P1-069312 VL (P1-068761.IgG1f afucosylated)
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[5540] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
[5541] 20 25 30
[5542] Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
[5543] 35 40 45

[5544] Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
[5545] 50 55 60
[5546] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
[5547] 65 70 75 80
[5548] Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
[5549] 85 90 95
[5550] Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
[5551] 100 105
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[5562] 20 25 30
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[5564] 35 40 45
[5565] Ser Gly Ile Asn Trp Asn Ser Glu Glu Ile Gly Tyr Ala Asp Ser Val
[5566] 50 55 60
[5567] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[5568] 65 70 75 80
[5569] Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Leu Tyr Tyr Cys
[5570] 85 90 95
[5571] Ala Lys Val Pro Gly Tyr Ser His Gly Trp Ile Asp Ala Glu Asp Val
[5572] 100 105 110
[5573] Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly
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[5580] 165 170 175
[5581] Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
[5582] 180 185 190
[5583] Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
[5584] 195 200 205
[5585] Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys

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[5590] 245 250 255
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[5592] 260 265 270
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[5611] Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
[5612] 420 425 430
[5613] Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
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[5616] 450
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[5626] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
[5627] 20 25 30

[5628] Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
[5629] 35 40 45
[5630] Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
[5631] 50 55 60
[5632] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
[5633] 65 70 75 80
[5634] Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
[5635] 85 90 95
[5636] Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala
[5637] 100 105 110
[5638] Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
[5639] 115 120 125
[5640] Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
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[5642] Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
[5643] 145 150 155 160
[5644] Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
[5645] 165 170 175
[5646] Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
[5647] 180 185 190
[5648] Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
[5649] 195 200 205
[5650] Ser Phe Asn Arg Gly Glu Cys
[5651] 210 215
[5652] <210> 155
[5653] <211> 123
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[5664] 35 40 45
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[5666] 50 55 60
[5667] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[5668] 65 70 75 80
[5669] Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Leu Tyr Tyr Cys

[5670] 85 90 95
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[5672] 100 105 110
[5673] Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
[5674] 115 120
[5675] <210> 156
[5676] <211> 108
[5677] <212> PRT
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[5684] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
[5685] 20 25 30
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[5687] 35 40 45
[5688] Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
[5689] 50 55 60
[5690] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
[5691] 65 70 75 80
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[5693] 85 90 95
[5694] Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
[5695] 100 105
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[5708] 35 40 45
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[5710] 50 55 60
[5711] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

[5712] 65 70 75 80
[5713] Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Leu Tyr Tyr Cys
[5714] 85 90 95
[5715] Ala Lys Val Pro Gly Tyr Ser Gly Gly Trp Ile Asp Ala Glu Asp Asp
[5716] 100 105 110
[5717] Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly
[5718] 115 120 125
[5719] Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
[5720] 130 135 140
[5721] Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
[5722] 145 150 155 160
[5723] Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
[5724] 165 170 175
[5725] Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
[5726] 180 185 190
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[5730] 210 215 220
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[5734] 245 250 255
[5735] Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
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[5741] Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
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[5747] Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
[5748] 355 360 365
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[5753] Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu

[5754] 405 410 415
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[5756] 420 425 430
[5757] Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
[5758] 435 440 445
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[5760] 450
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[5788] Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
[5789] 165 170 175
[5790] Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
[5791] 180 185 190
[5792] Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
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[5795] 210 215

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[5807] Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[5808] 35 40 45
[5809] Ser Gly Ile Asn Trp Asn Ser Ala Asn Ile Gly Tyr Ala Asp Ser Val
[5810] 50 55 60
[5811] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[5812] 65 70 75 80
[5813] Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Leu Tyr Tyr Cys
[5814] 85 90 95
[5815] Ala Lys Val Pro Gly Tyr Ser Gly Gly Trp Ile Asp Ala Phe Asp Val
[5816] 100 105 110
[5817] Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
[5818] 115 120
[5819] <210> 160
[5820] <211> 108
[5821] <212> PRT
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[5828] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
[5829] 20 25 30
[5830] Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
[5831] 35 40 45
[5832] Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
[5833] 50 55 60
[5834] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
[5835] 65 70 75 80
[5836] Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
[5837] 85 90 95

[5838] Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
[5839] 100 105
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[5854] 50 55 60
[5855] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
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[5866] 145 150 155 160
[5867] Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
[5868] 165 170 175
[5869] Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
[5870] 180 185 190
[5871] Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
[5872] 195 200 205
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[5874] 210 215 220
[5875] Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
[5876] 225 230 235 240
[5877] Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
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[5885] Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
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[5887] Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
[5888] 325 330 335
[5889] Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
[5890] 340 345 350
[5891] Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
[5892] 355 360 365
[5893] Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
[5894] 370 375 380
[5895] Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
[5896] 385 390 395 400
[5897] Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
[5898] 405 410 415
[5899] Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
[5900] 420 425 430
[5901] Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
[5902] 435 440 445
[5903] Leu Ser Pro Gly
[5904] 450
[5905] <210> 162
[5906] <211> 215
[5907] <212> PRT
[5908] <213> 人工序列
[5909] <220>
[5910] <223> P1-069307 LC (P1-061029.IgG1f afucosylated)
[5911] <400> 162
[5912] Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
[5913] 1 5 10 15
[5914] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
[5915] 20 25 30
[5916] Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
[5917] 35 40 45
[5918] Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
[5919] 50 55 60
[5920] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
[5921] 65 70 75 80

[5922] Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
[5923] 85 90 95
[5924] Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala
[5925] 100 105 110
[5926] Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
[5927] 115 120 125
[5928] Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
[5929] 130 135 140
[5930] Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
[5931] 145 150 155 160
[5932] Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
[5933] 165 170 175
[5934] Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
[5935] 180 185 190
[5936] Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
[5937] 195 200 205
[5938] Ser Phe Asn Arg Gly Glu Cys
[5939] 210 215
[5940] <210> 163
[5941] <211> 329
[5942] <212> PRT
[5943] <213> 人工序列
[5944] <220>
[5945] <223> IgG1.3 (or IgG1.3f) heavy chain constant region (L234A, L235E,
[5946] G237A)
[5947] <400> 163
[5948] Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
[5949] 1 5 10 15
[5950] Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
[5951] 20 25 30
[5952] Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
[5953] 35 40 45
[5954] Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
[5955] 50 55 60
[5956] Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
[5957] 65 70 75 80
[5958] Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
[5959] 85 90 95
[5960] Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
[5961] 100 105 110
[5962] Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
[5963] 115 120 125

[5964] Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
[5965] 130 135 140
[5966] Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
[5967] 145 150 155 160
[5968] Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
[5969] 165 170 175
[5970] Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
[5971] 180 185 190
[5972] His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
[5973] 195 200 205
[5974] Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
[5975] 210 215 220
[5976] Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
[5977] 225 230 235 240
[5978] Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
[5979] 245 250 255
[5980] Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
[5981] 260 265 270
[5982] Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
[5983] 275 280 285
[5984] Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
[5985] 290 295 300
[5986] Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
[5987] 305 310 315 320
[5988] Gln Lys Ser Leu Ser Leu Ser Pro Gly
[5989] 325
[5990] <210> 164
[5991] <211> 107
[5992] <212> PRT
[5993] <213> 人工序列
[5994] <220>
[5995] <223> 示例性轻链恒定区
[5996] <400> 164
[5997] Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
[5998] 1 5 10 15
[5999] Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
[6000] 20 25 30
[6001] Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
[6002] 35 40 45
[6003] Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
[6004] 50 55 60
[6005] Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu

[6006] 65 70 75 80
[6007] Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
[6008] 85 90 95
[6009] Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
[6010] 100 105
[6011] <210> 165
[6012] <211> 162
[6013] <212> PRT
[6014] <213> 智人
[6015] <400> 165
[6016] Phe Lys Val Ala Thr Pro Tyr Ser Leu Tyr Val Cys Pro Glu Gly Gln
[6017] 1 5 10 15
[6018] Asn Val Thr Leu Thr Cys Arg Leu Leu Gly Pro Val Asp Lys Gly His
[6019] 20 25 30
[6020] Asp Val Thr Phe Tyr Lys Thr Trp Tyr Arg Ser Ser Arg Gly Glu Val
[6021] 35 40 45
[6022] Gln Thr Cys Ser Glu Arg Arg Pro Ile Arg Asn Leu Thr Phe Gln Asp
[6023] 50 55 60
[6024] Leu His Leu His His Gly Gly His Gln Ala Ala Asn Thr Ser His Asp
[6025] 65 70 75 80
[6026] Leu Ala Gln Arg His Gly Leu Glu Ser Ala Ser Asp His His Gly Asn
[6027] 85 90 95
[6028] Phe Ser Ile Thr Met Arg Asn Leu Thr Leu Leu Asp Ser Gly Leu Tyr
[6029] 100 105 110
[6030] Cys Cys Leu Val Val Glu Ile Arg His His His Ser Glu His Arg Val
[6031] 115 120 125
[6032] His Gly Ala Met Glu Leu Gln Val Gln Thr Gly Lys Asp Ala Pro Ser
[6033] 130 135 140
[6034] Asn Cys Val Val Tyr Pro Ser Ser Ser Gln Asp Ser Glu Asn Ile Thr
[6035] 145 150 155 160
[6036] Ala Ala
[6037] <210> 166
[6038] <211> 162
[6039] <212> PRT
[6040] <213> Macaca fascicularis
[6041] <400> 166
[6042] Phe Lys Val Ala Thr Leu Tyr Ser Leu Tyr Val Cys Pro Glu Gly Gln
[6043] 1 5 10 15
[6044] Asn Val Thr Leu Thr Cys Arg Val Phe Gly Pro Val Asp Lys Gly His
[6045] 20 25 30
[6046] Asp Val Thr Phe Tyr Lys Thr Trp Tyr Arg Ser Ser Arg Gly Glu Val
[6047] 35 40 45

[6048] Gln Thr Cys Ser Glu Arg Arg Pro Ile Arg Asn Leu Thr Phe Gln Asp
[6049] 50 55 60
[6050] Leu His Leu His His Gly Gly His Gln Ala Ala Asn Thr Ser His Asp
[6051] 65 70 75 80
[6052] Leu Ala Gln Arg His Gly Leu Glu Ser Ala Ser Asp His His Gly Asn
[6053] 85 90 95
[6054] Phe Ser Ile Thr Met Arg Asn Leu Thr Leu Leu Asp Ser Gly Leu Tyr
[6055] 100 105 110
[6056] Cys Cys Leu Val Val Glu Ile Arg His His His Ser Glu His Arg Val
[6057] 115 120 125
[6058] His Gly Ala Met Glu Leu Gln Val Gln Thr Gly Lys Asp Ala Pro Ser
[6059] 130 135 140
[6060] Ser Cys Val Ala Tyr Pro Ser Ser Ser Gln Glu Ser Glu Asn Ile Thr
[6061] 145 150 155 160
[6062] Ala Ala
[6063] <210> 167
[6064] <211> 159
[6065] <212> PRT
[6066] <213> Mus musculus
[6067] <400> 167
[6068] Phe Lys Val Thr Thr Pro Tyr Ser Leu Tyr Val Cys Pro Glu Gly Gln
[6069] 1 5 10 15
[6070] Asn Ala Thr Leu Thr Cys Arg Ile Leu Gly Pro Val Ser Lys Gly His
[6071] 20 25 30
[6072] Asp Val Thr Ile Tyr Lys Thr Trp Tyr Leu Ser Ser Arg Gly Glu Val
[6073] 35 40 45
[6074] Gln Met Cys Lys Glu His Arg Pro Ile Arg Asn Phe Thr Leu Gln His
[6075] 50 55 60
[6076] Leu Gln His His Gly Ser His Leu Lys Ala Asn Ala Ser His Asp Gln
[6077] 65 70 75 80
[6078] Pro Gln Lys His Gly Leu Glu Leu Ala Ser Asp His His Gly Asn Phe
[6079] 85 90 95
[6080] Ser Ile Thr Leu Arg Asn Val Thr Pro Arg Asp Ser Gly Leu Tyr Cys
[6081] 100 105 110
[6082] Cys Leu Val Ile Glu Leu Lys Asn His His Pro Glu Gln Arg Phe Tyr
[6083] 115 120 125
[6084] Gly Ser Met Glu Leu Gln Val Gln Ala Gly Lys Gly Ser Gly Ser Thr
[6085] 130 135 140
[6086] Cys Met Ala Ser Asn Glu Gln Asp Ser Asp Ser Ile Thr Ala Ala
[6087] 145 150 155
[6088] <210> 168
[6089] <211> 14

[6090] <212> PRT
[6091] <213> 人工序列
[6092] <220>
[6093] <223> P1-061029 HDR3 chip oligo (Fig. 7A)
[6094] <220>
[6095] <221> MISC_FEATURE
[6096] <222> (1)..(14)
[6097] <223> X = H, D, or E
[6098] <400> 168
[6099] Xaa Pro Gly Tyr Ser Gly Gly Trp Ile Asp Ala Phe Asp Val
[6100] 1 5 10
[6101] <210> 169
[6102] <211> 14
[6103] <212> PRT
[6104] <213> 人工序列
[6105] <220>
[6106] <223> P1-061029 HDR3 chip oligo (Fig. 7A)
[6107] <220>
[6108] <221> MISC_FEATURE
[6109] <222> (1)..(14)
[6110] <223> X = H, D, or E
[6111] <400> 169
[6112] Xaa Xaa Gly Tyr Ser Gly Gly Trp Ile Asp Ala Phe Asp Val
[6113] 1 5 10
[6114] <210> 170
[6115] <211> 14
[6116] <212> PRT
[6117] <213> 人工序列
[6118] <220>
[6119] <223> P1-061029 HDR3 chip oligo (Fig. 7A)
[6120] <220>
[6121] <221> MISC_FEATURE
[6122] <222> (1)..(14)
[6123] <223> X = H, D, or E
[6124] <400> 170
[6125] Xaa Pro Xaa Tyr Ser Gly Gly Trp Ile Asp Ala Phe Asp Val
[6126] 1 5 10
[6127] <210> 171
[6128] <211> 14
[6129] <212> PRT
[6130] <213> 人工序列
[6131] <220>

[6132] <223> P1-061029 HDR3 chip oligo (Fig. 7A)
[6133] <220>
[6134] <221> MISC_FEATURE
[6135] <222> (1)..(14)
[6136] <223> X = H, D, or E
[6137] <400> 171
[6138] Xaa Pro Gly Xaa Ser Gly Gly Trp Ile Asp Ala Phe Asp Val
[6139] 1 5 10
[6140] <210> 172
[6141] <211> 14
[6142] <212> PRT
[6143] <213> 人工序列
[6144] <220>
[6145] <223> P1-061029 HDR3 chip oligo (Fig. 7A)
[6146] <220>
[6147] <221> MISC_FEATURE
[6148] <222> (1)..(14)
[6149] <223> X = H, D, or E
[6150] <400> 172
[6151] Xaa Pro Gly Tyr Xaa Gly Gly Trp Ile Asp Ala Phe Asp Val
[6152] 1 5 10
[6153] <210> 173
[6154] <211> 14
[6155] <212> PRT
[6156] <213> 人工序列
[6157] <220>
[6158] <223> P1-061029 HDR3 chip oligo (Fig. 7A)
[6159] <220>
[6160] <221> MISC_FEATURE
[6161] <222> (1)..(14)
[6162] <223> X = H, D, or E
[6163] <400> 173
[6164] Xaa Pro Gly Tyr Ser Xaa Gly Trp Ile Asp Ala Phe Asp Val
[6165] 1 5 10
[6166] <210> 174
[6167] <211> 14
[6168] <212> PRT
[6169] <213> 人工序列
[6170] <220>
[6171] <223> P1-061029 HDR3 chip oligo (Fig. 7A)
[6172] <220>
[6173] <221> MISC_FEATURE

[6174] <222> (1)..(14)
[6175] <223> X = H, D, or E
[6176] <400> 174
[6177] Xaa Pro Gly Tyr Ser Gly Xaa Trp Ile Asp Ala Phe Asp Val
[6178] 1 5 10
[6179] <210> 175
[6180] <211> 14
[6181] <212> PRT
[6182] <213> 人工序列
[6183] <220>
[6184] <223> P1-061029 HDR3 chip oligo (Fig. 7A)
[6185] <220>
[6186] <221> MISC_FEATURE
[6187] <222> (1)..(14)
[6188] <223> X = H, D, or E
[6189] <400> 175
[6190] Xaa Pro Gly Tyr Ser Gly Gly Xaa Ile Asp Ala Phe Asp Val
[6191] 1 5 10
[6192] <210> 176
[6193] <211> 14
[6194] <212> PRT
[6195] <213> 人工序列
[6196] <220>
[6197] <223> P1-061029 HDR3 chip oligo (Fig. 7A)
[6198] <220>
[6199] <221> MISC_FEATURE
[6200] <222> (1)..(14)
[6201] <223> X = H, D, or E
[6202] <400> 176
[6203] Xaa Pro Gly Tyr Ser Gly Gly Trp Xaa Asp Ala Phe Asp Val
[6204] 1 5 10
[6205] <210> 177
[6206] <211> 14
[6207] <212> PRT
[6208] <213> 人工序列
[6209] <220>
[6210] <223> P1-061029 HDR3 chip oligo (Fig. 7A)
[6211] <220>
[6212] <221> MISC_FEATURE
[6213] <222> (1)..(14)
[6214] <223> X = H, D, or E
[6215] <400> 177

[6216] Xaa Pro Gly Tyr Ser Gly Gly Trp Ile Xaa Ala Phe Asp Val
[6217] 1 5 10
[6218] <210> 178
[6219] <211> 14
[6220] <212> PRT
[6221] <213> 人工序列
[6222] <220>
[6223] <223> P1-061029 HDR3 chip oligo (Fig. 7A)
[6224] <220>
[6225] <221> MISC_FEATURE
[6226] <222> (1)..(14)
[6227] <223> X = H, D, or E
[6228] <400> 178
[6229] Xaa Pro Gly Tyr Ser Gly Gly Trp Ile Asp Xaa Phe Asp Val
[6230] 1 5 10
[6231] <210> 179
[6232] <211> 14
[6233] <212> PRT
[6234] <213> 人工序列
[6235] <220>
[6236] <223> P1-061029 HDR3 chip oligo (Fig. 7A)
[6237] <220>
[6238] <221> MISC_FEATURE
[6239] <222> (1)..(14)
[6240] <223> X = H, D, or E
[6241] <400> 179
[6242] Xaa Pro Gly Tyr Ser Gly Gly Trp Ile Asp Ala Xaa Asp Val
[6243] 1 5 10
[6244] <210> 180
[6245] <211> 14
[6246] <212> PRT
[6247] <213> 人工序列
[6248] <220>
[6249] <223> P1-061029 HDR3 chip oligo (Fig. 7A)
[6250] <220>
[6251] <221> MISC_FEATURE
[6252] <222> (1)..(14)
[6253] <223> X = H, D, or E
[6254] <400> 180
[6255] Xaa Pro Gly Tyr Ser Gly Gly Trp Ile Asp Ala Phe Xaa Val
[6256] 1 5 10
[6257] <210> 181

[6258] <211> 14
[6259] <212> PRT
[6260] <213> 人工序列
[6261] <220>
[6262] <223> P1-061029 HDR3 chip oligo (Fig. 7A)
[6263] <220>
[6264] <221> MISC_FEATURE
[6265] <222> (1)..(14)
[6266] <223> X = H, D, or E
[6267] <400> 181
[6268] Xaa Pro Gly Tyr Ser Gly Gly Trp Ile Asp Ala Phe Asp Xaa
[6269] 1 5 10
[6270] <210> 182
[6271] <211> 329
[6272] <212> PRT
[6273] <213> 人工序列
[6274] <220>
[6275] <223> IgG1f (human wild-type allotype f) heavy chain constant region
[6276] <400> 182
[6277] Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
[6278] 1 5 10 15
[6279] Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
[6280] 20 25 30
[6281] Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
[6282] 35 40 45
[6283] Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
[6284] 50 55 60
[6285] Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
[6286] 65 70 75 80
[6287] Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
[6288] 85 90 95
[6289] Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
[6290] 100 105 110
[6291] Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
[6292] 115 120 125
[6293] Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
[6294] 130 135 140
[6295] Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
[6296] 145 150 155 160
[6297] Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
[6298] 165 170 175
[6299] Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu

[6300] 180 185 190
[6301] His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
[6302] 195 200 205
[6303] Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
[6304] 210 215 220
[6305] Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
[6306] 225 230 235 240
[6307] Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
[6308] 245 250 255
[6309] Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
[6310] 260 265 270
[6311] Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
[6312] 275 280 285
[6313] Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
[6314] 290 295 300
[6315] Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
[6316] 305 310 315 320
[6317] Gln Lys Ser Leu Ser Leu Ser Pro Gly
[6318] 325
[6319] <210> 183
[6320] <211> 329
[6321] <212> PRT
[6322] <213> 人工序列
[6323] <220>
[6324] <223> IgG1.1f Heavy chain constant region (L234A, L235E, G237A, A330S,
[6325] P331S)
[6326] <400> 183
[6327] Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
[6328] 1 5 10 15
[6329] Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
[6330] 20 25 30
[6331] Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
[6332] 35 40 45
[6333] Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
[6334] 50 55 60
[6335] Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
[6336] 65 70 75 80
[6337] Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
[6338] 85 90 95
[6339] Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
[6340] 100 105 110
[6341] Pro Ala Pro Glu Ala Glu Gly Ala Pro Ser Val Phe Leu Phe Pro Pro

[6342] 115 120 125
[6343] Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
[6344] 130 135 140
[6345] Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
[6346] 145 150 155 160
[6347] Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
[6348] 165 170 175
[6349] Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
[6350] 180 185 190
[6351] His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
[6352] 195 200 205
[6353] Lys Ala Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
[6354] 210 215 220
[6355] Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
[6356] 225 230 235 240
[6357] Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
[6358] 245 250 255
[6359] Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
[6360] 260 265 270
[6361] Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
[6362] 275 280 285
[6363] Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
[6364] 290 295 300
[6365] Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
[6366] 305 310 315 320
[6367] Gln Lys Ser Leu Ser Leu Ser Pro Gly
[6368] 325
[6369] <210> 184
[6370] <211> 329
[6371] <212> PRT
[6372] <213> 人工序列
[6373] <220>
[6374] <223> IgG1fa.P238K (or IgG1.P238K) heavy chain constant region
[6375] <400> 184
[6376] Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
[6377] 1 5 10 15
[6378] Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
[6379] 20 25 30
[6380] Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
[6381] 35 40 45
[6382] Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
[6383] 50 55 60

[6384] Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
[6385] 65 70 75 80
[6386] Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
[6387] 85 90 95
[6388] Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
[6389] 100 105 110
[6390] Pro Ala Pro Glu Leu Leu Gly Gly Lys Ser Val Phe Leu Phe Pro Pro
[6391] 115 120 125
[6392] Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
[6393] 130 135 140
[6394] Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
[6395] 145 150 155 160
[6396] Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
[6397] 165 170 175
[6398] Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
[6399] 180 185 190
[6400] His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
[6401] 195 200 205
[6402] Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
[6403] 210 215 220
[6404] Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
[6405] 225 230 235 240
[6406] Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
[6407] 245 250 255
[6408] Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
[6409] 260 265 270
[6410] Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
[6411] 275 280 285
[6412] Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
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[6414] Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
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260 265 270
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
275 280 285
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
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Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
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Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
340 345 350
Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
355 360 365
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370 375 380
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385 390 395 400
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
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Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
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[7319] 50 55 60
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[7354] 165 170 175

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[7356] 180 185 190

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[13216] cctgggacca aagtggatat caaa 324
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[13222] <223> P1-070926 VH DNA
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[13225] tcctgtgcag cctctggatt cacccttgat gattatgcca tgcactgggt ccggcaagct 120
[13226] ccagggaagg gcctggagtg ggtctcaggt attgattgga acagtgaaaa cataggctat 180
[13227] gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
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[13230] gtctcttca 369
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[13423] Gly
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[13526] <220>

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[13530] <400> 468

[13531] Asp Xaa Xaa Phe Tyr Xaa Xaa Tyr Tyr Asp Phe Xaa

[13532] 1 5 10

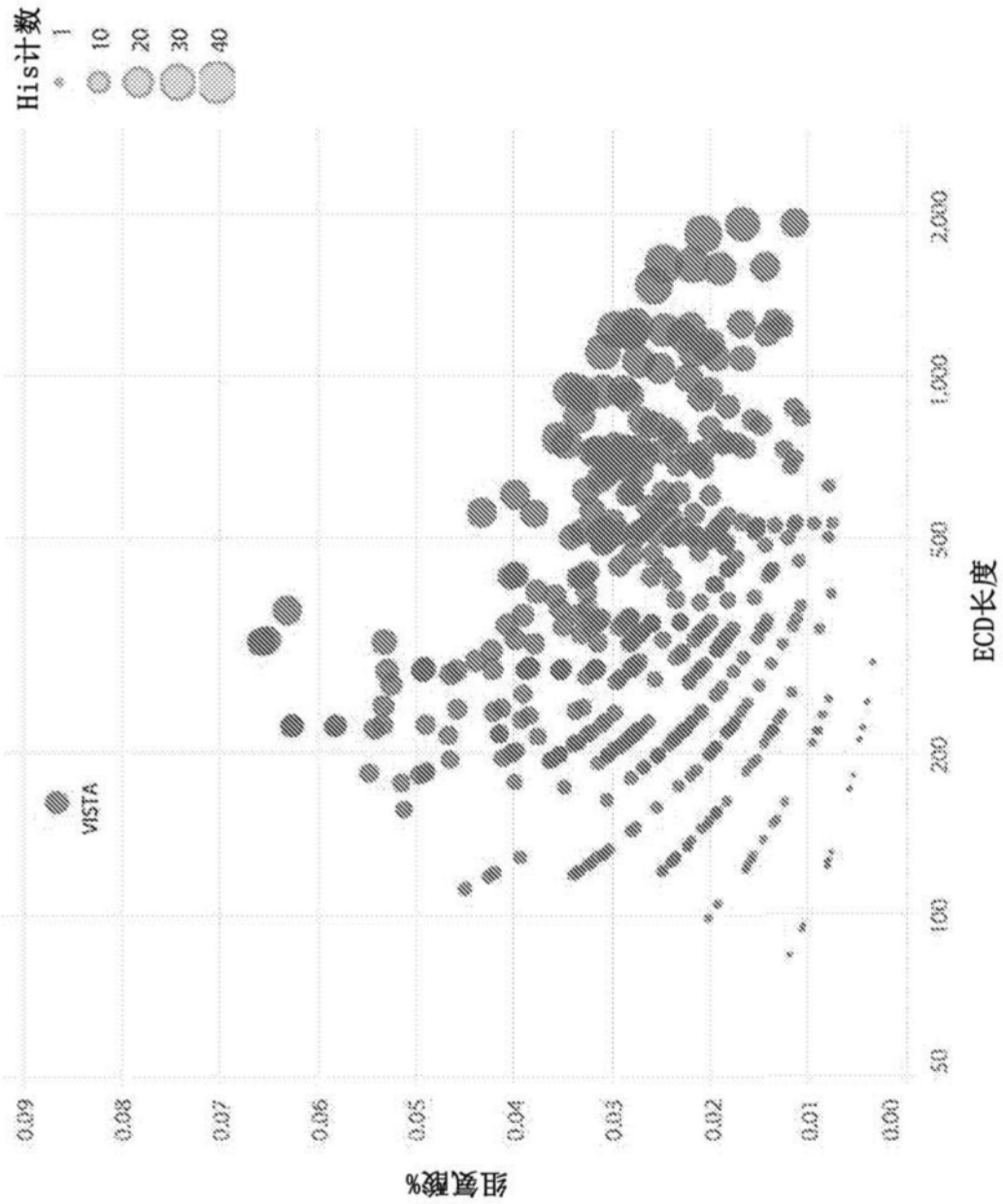
His计数
1
10
20
30
40
VISTA
ECD长度
2,000
1,000
500
200
100
50
组氨酸%
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00

图1A

Hu/Cy/Ms 保守的组氨酸（粗体，加下划线）
Hu/Cy-保守的组氨酸（粗体）

```
人  NP_071436.1      Sig-  FKVATPYSLYVCPEGQNVTLTCRLLGPVDKGHDVTFYKTWYR
Cyno XP_005565644.1  Sig-  FKVATLYSLYVCPEGQNVTLTCRVFGPVDKGHDVTFYKTWYR
小鼠 NP_083008.1     Sig-  FKVTTPYSLYVCPEGQNATLTCRILGPVSKGHDVTIYKTWYL

人  NP_071436.1      SSRGEVQTCSERRPIRNLTFQDLHLHHGGHQAANTSHDLAQRHGLES
Cyno XP_005565644.1  SSRGEVQTCSERRPIRNLTFQDLHLHHGGHQAANTSHDLAQRHGLES
小鼠 NP_083008.1     SSRGEVQMCKEHRPIRNFTLQHLQ-HHGSHLKANASHDQPQKHGLEL

人  NP_071436.1      ASDHHGNFSITMRNLTLLDSGLYCCLVVEIRHHHSEHRVHGAMELQV
Cyno XP_005565644.1  ASDHHGNFSITMRNLTLLDSGLYCCLVVEIRHHHSEHRVHGAMELQV
小鼠 NP_083008.1     ASDHHGNFSITLRNVTPRDSGLYCCLVIELKNHHPEQRFYGSMELQV

人  NP_071436.1      QTGKDAPSNCVVYPSSSQDSENITAA -TMD
Cyno XP_005565644.1  QTGKDAPSSCVAYPSSSQESENITAA -TMD
小鼠 NP_083008.1     QAGKGSGSTCMA--SNEQDSDSITAA -TMD
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图1B

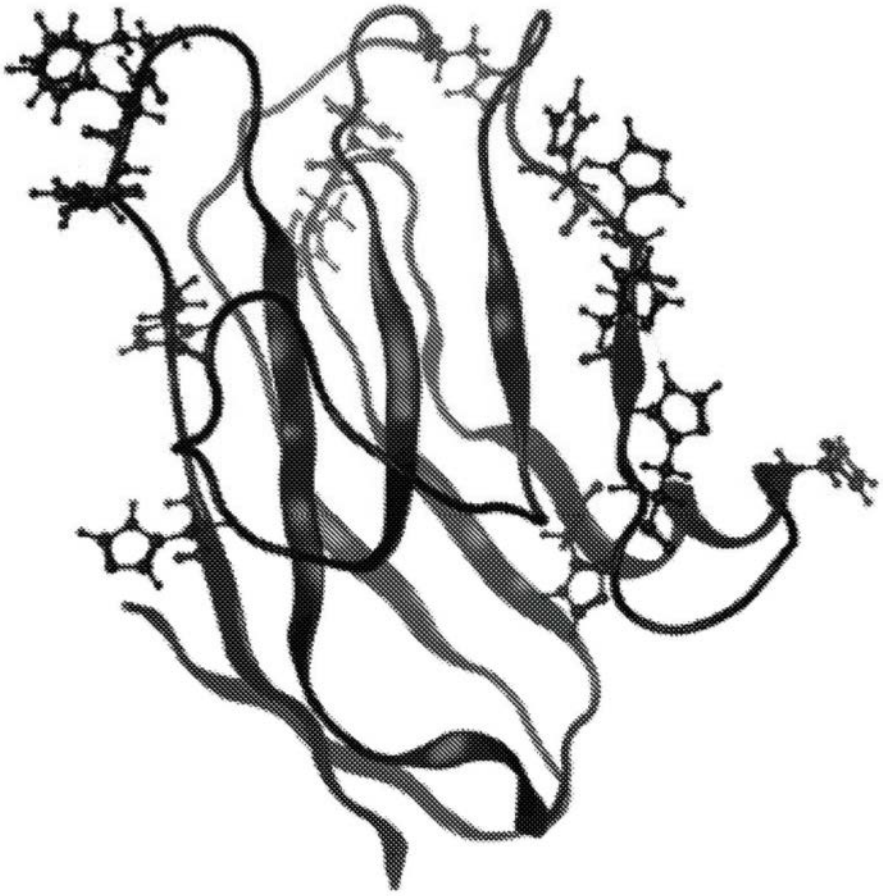


图1C

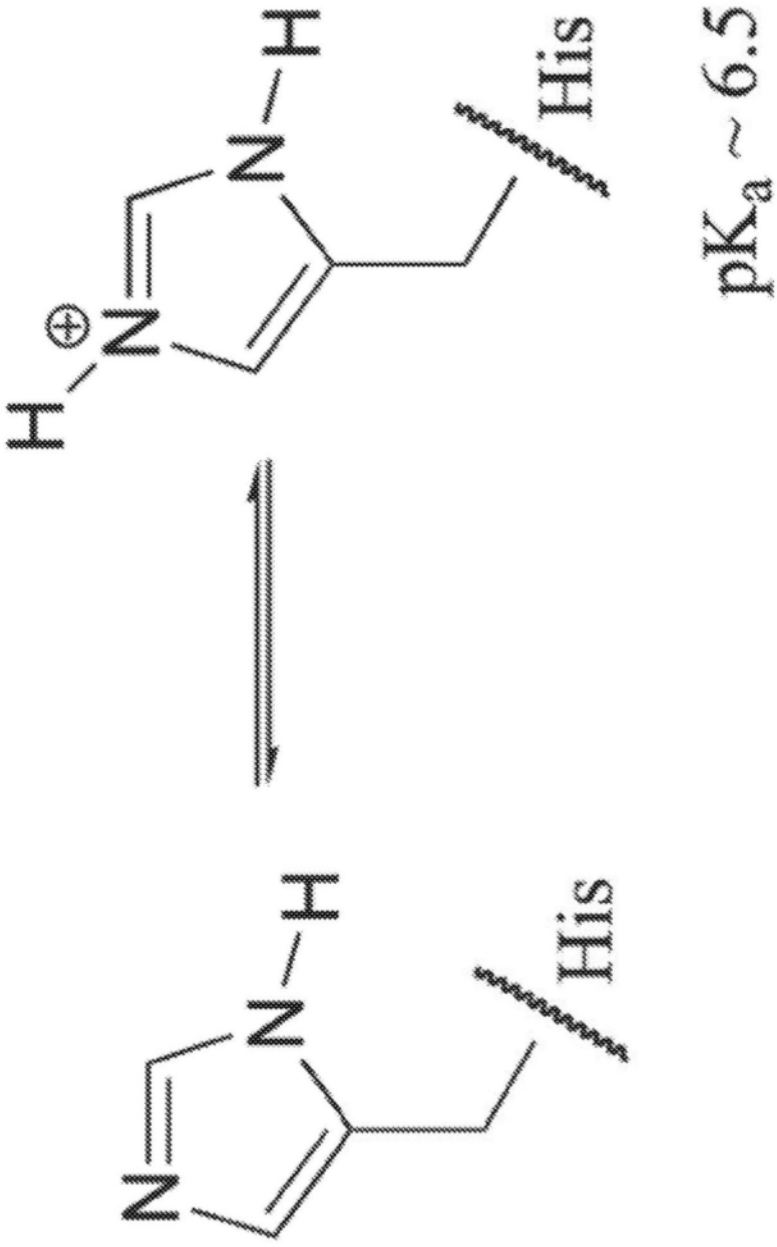


图2A

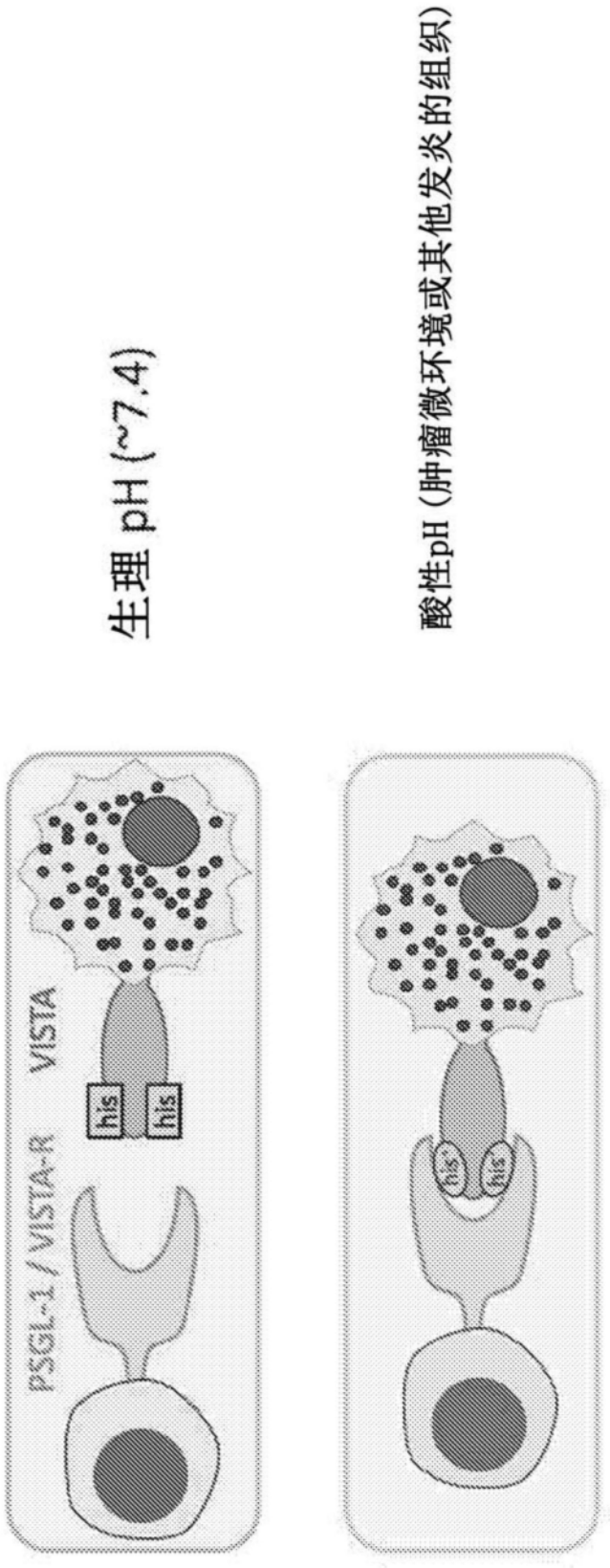

生理 pH (~7.4)
酸性pH (肿瘤微环境或其他发炎的组织)
PSGL-1 / VISTA-R
VISTA
his
his
his
his

图2B

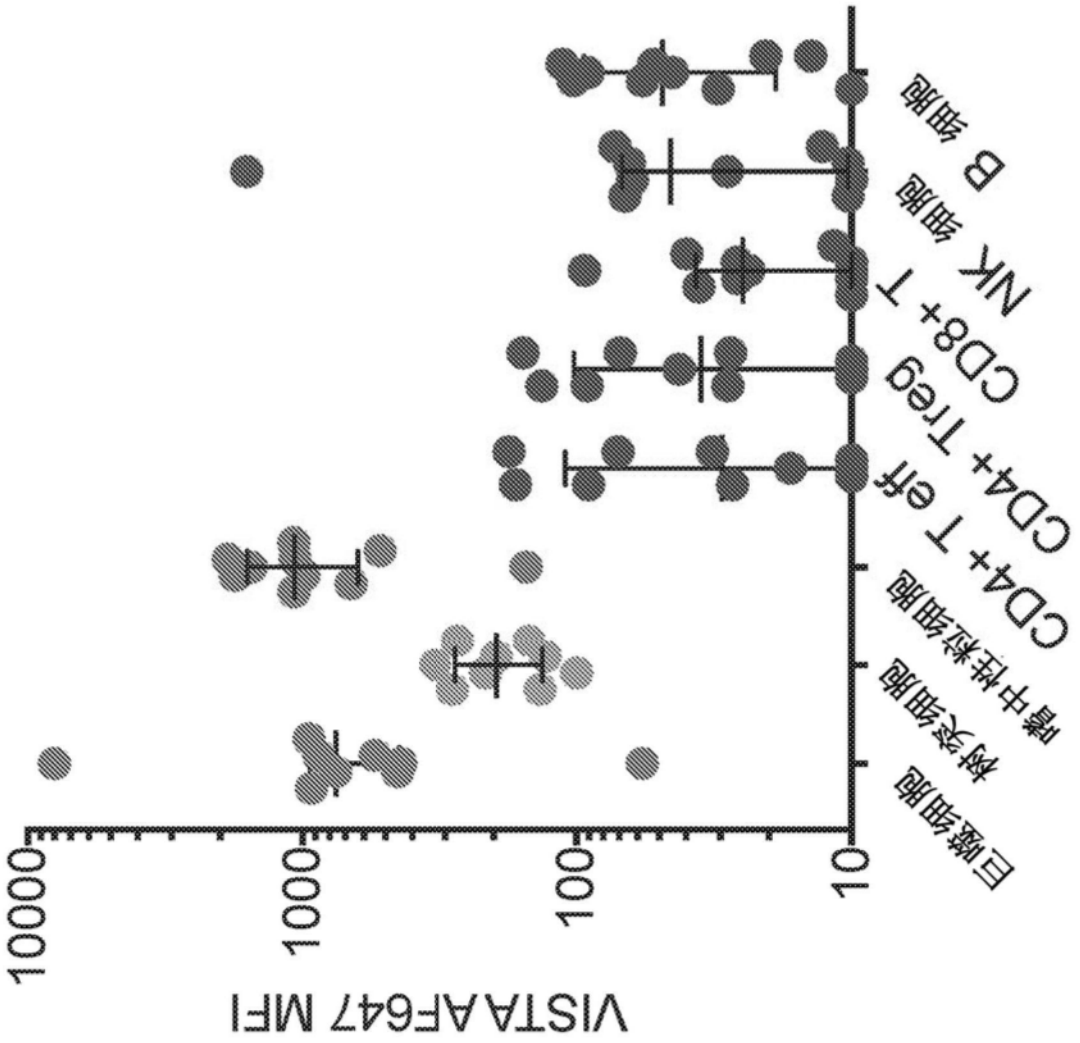

VISTA AF647 MFI
10000
1000
100
10
巨噬细胞
树突细胞
嗜中性粒细胞
CD4+ T eff
CD4+ Treg
CD8+ T
NK 细胞
B 细胞

图3

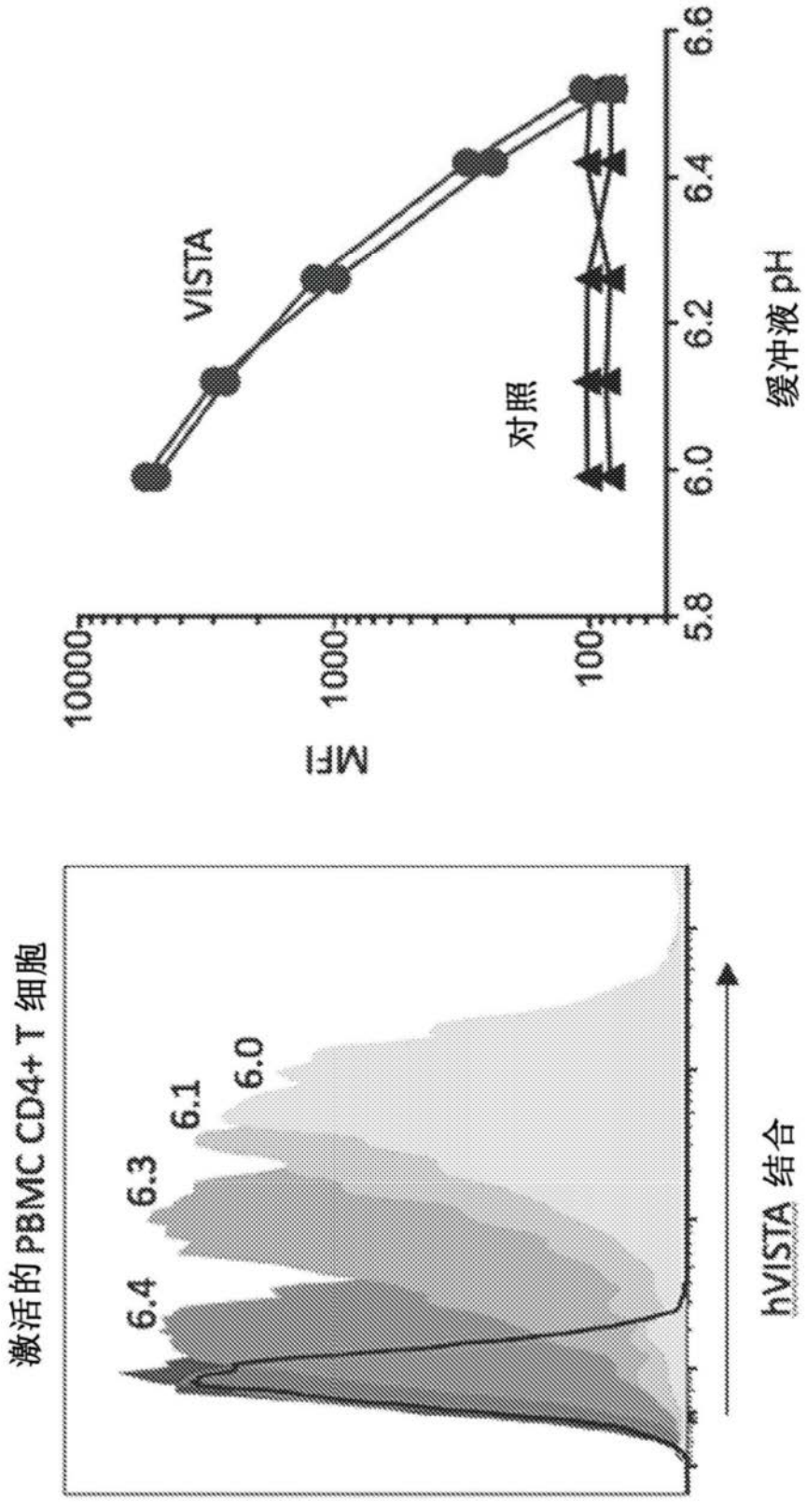

VISTA
对照
MFI
10000
1000
100
5.8
6.0
6.2
6.4
6.6
缓冲液 pH
激活的 PBMC CD4+ T 细胞
6.4
6.3
6.1
6.0
hVISTA 结合

图4A

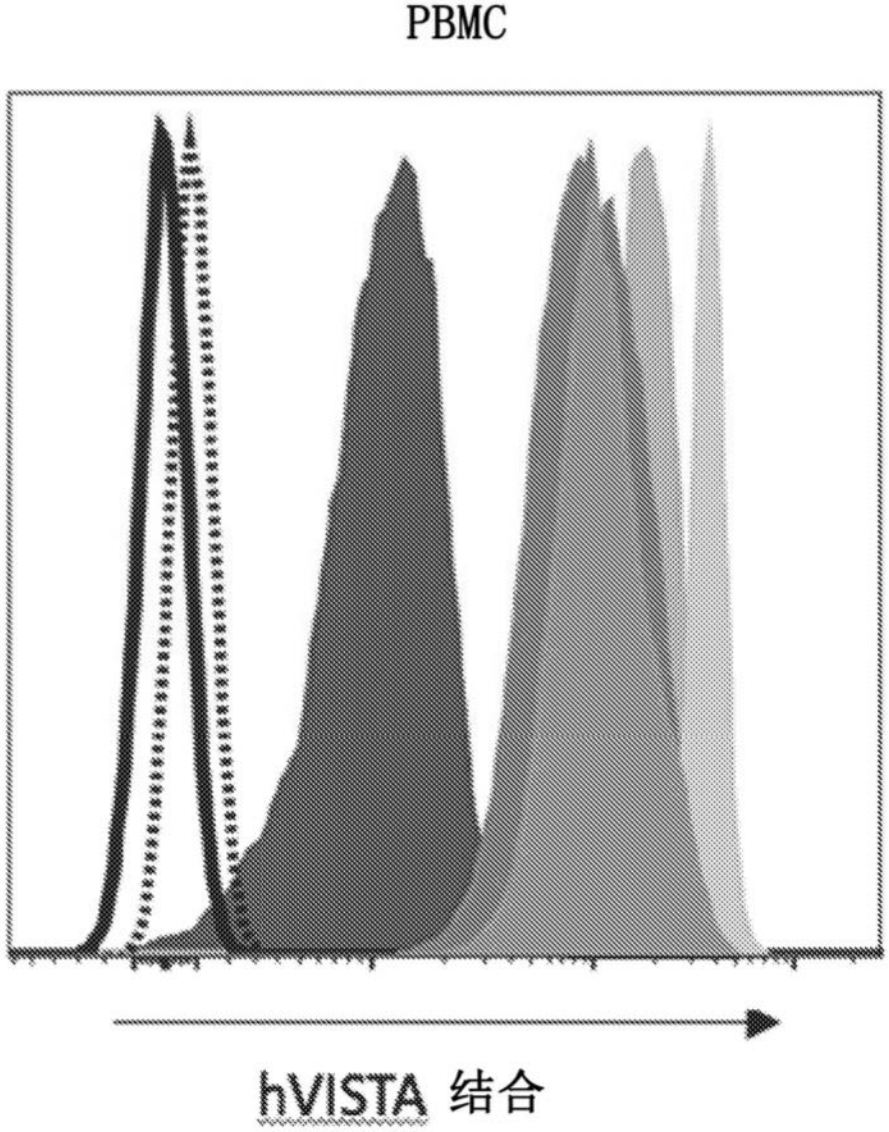


图4B

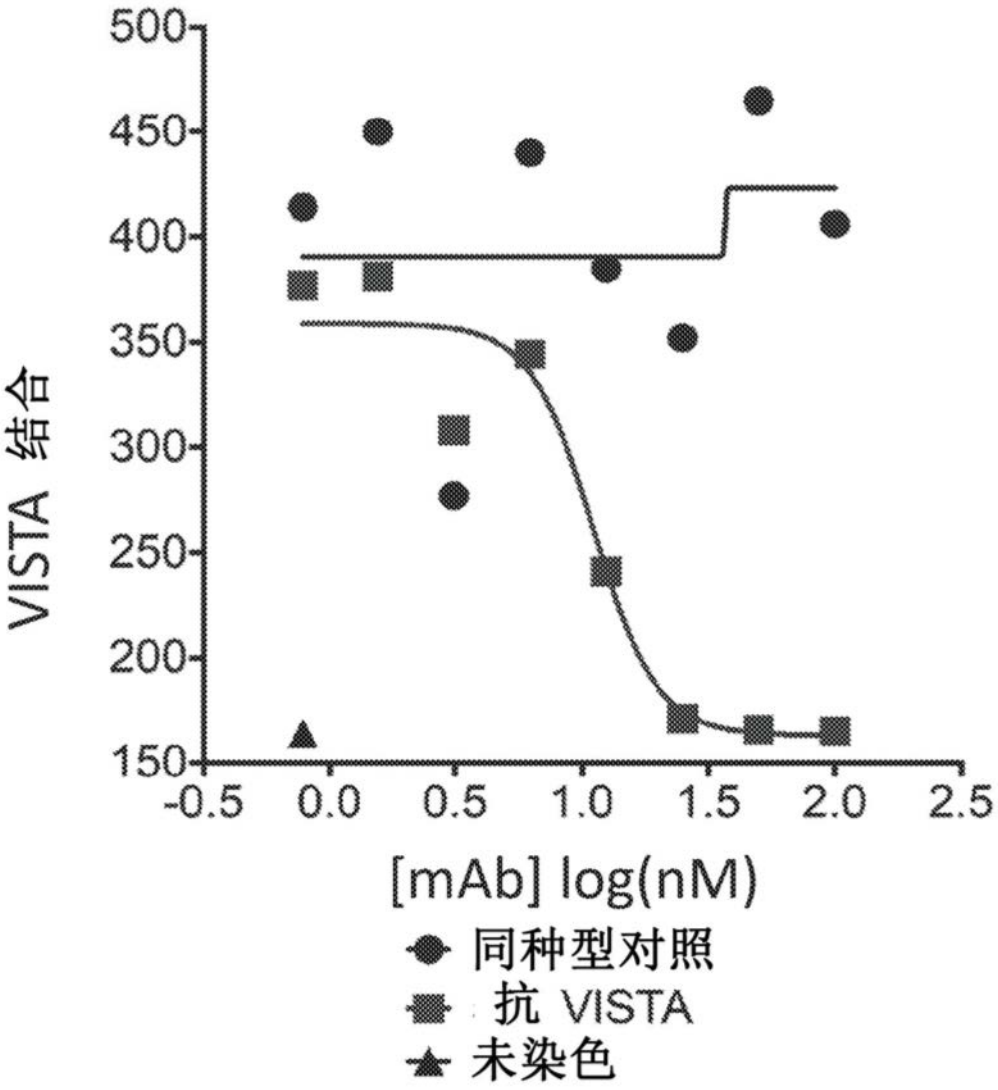

500
450
400
350
300
250
200
150
VISTA 结合
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
[mAb] log(nM)
同种型对照
抗 VISTA
未染色

图4C

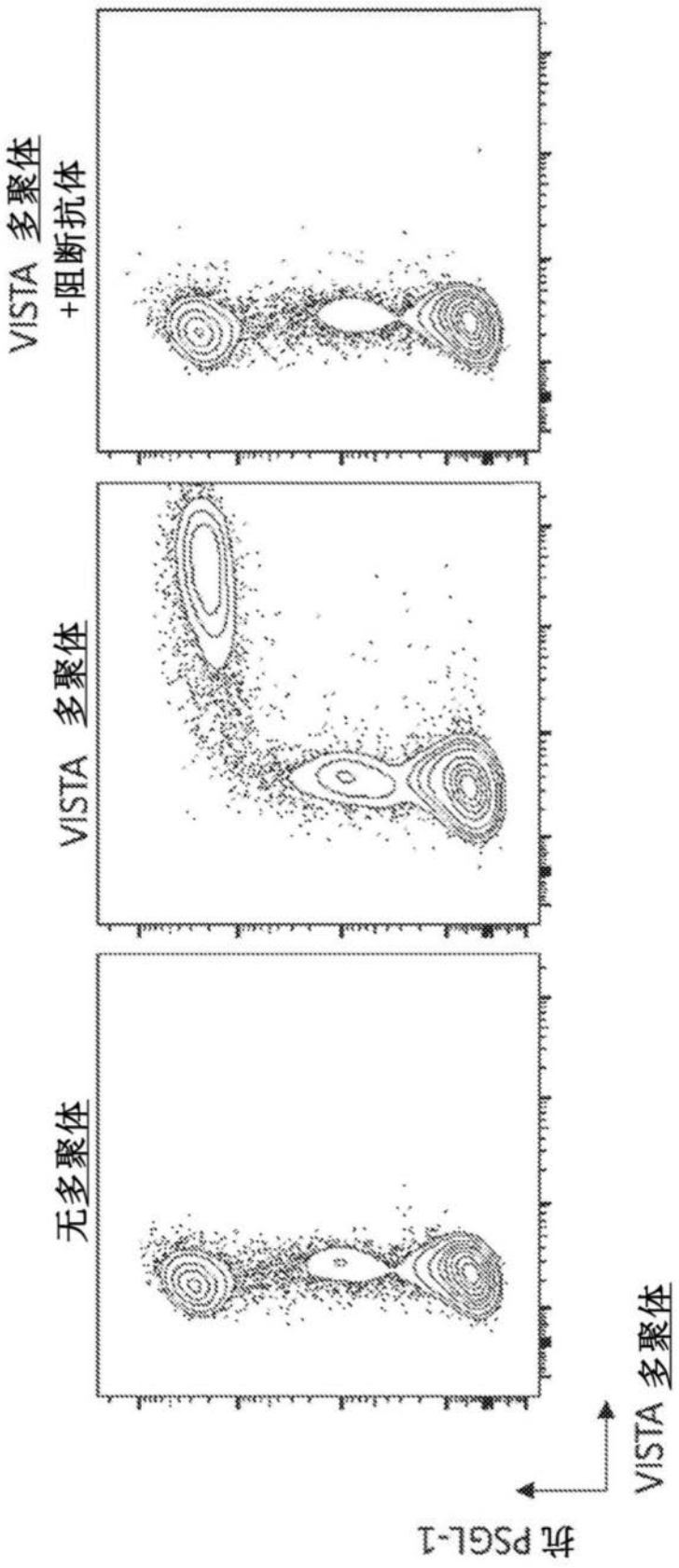


图4D

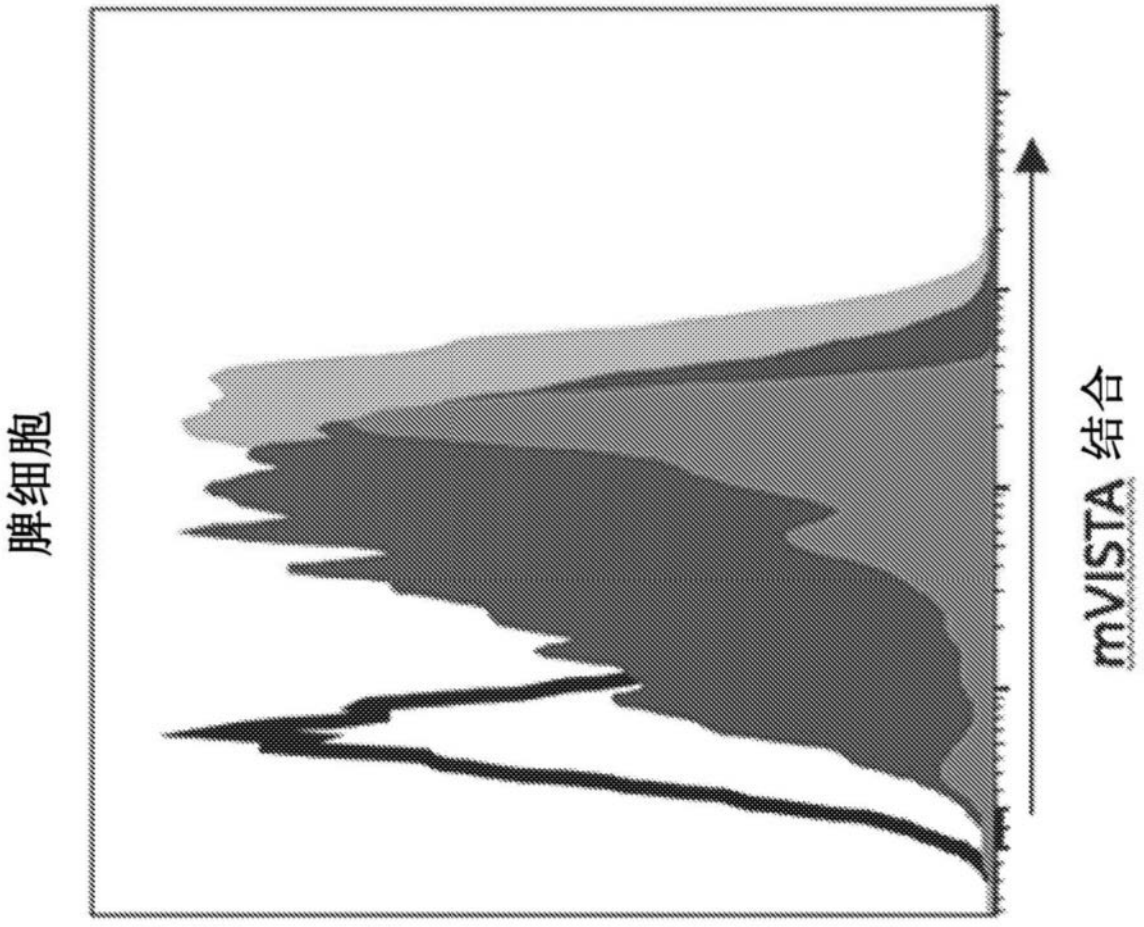


图4E

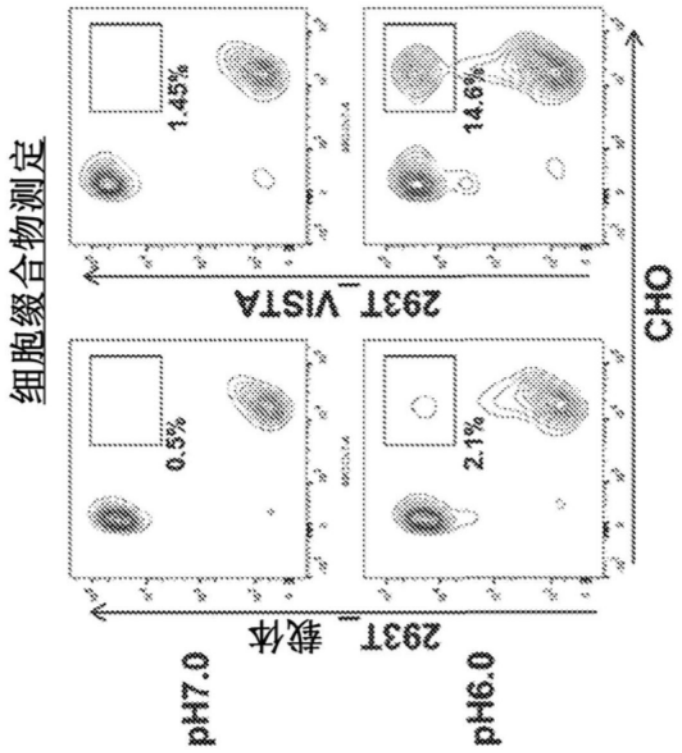

细胞缀合物测定
293T_载体
293T_VISTA
CHO
pH7.0
pH6.0
0.5%
1.45%
2.1%
14.6%

图5A

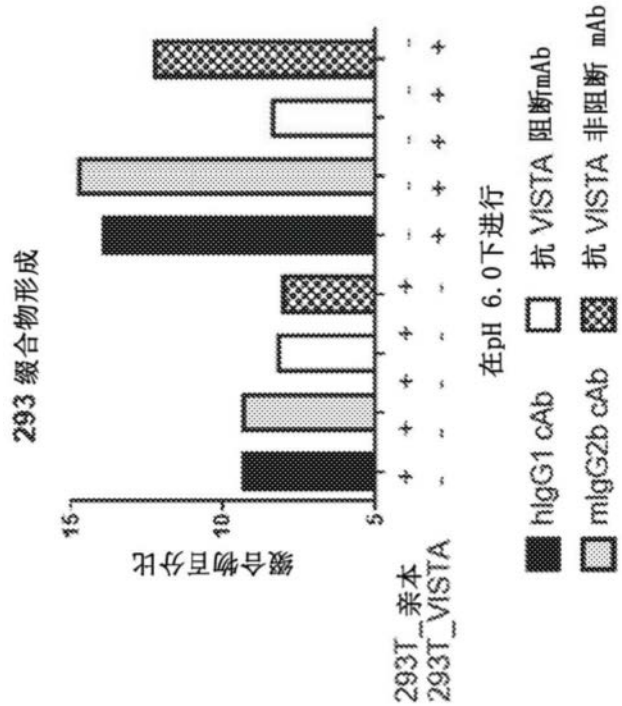

293 缀合物形成
缀合物百分比
293T_亲本
293T_VISTA
在pH 6.0下进行
hIgG1 cAb
抗 VISTA 阻断mAb
mIgG2b cAb
抗 VISTA 非阻断 mAb

图5B

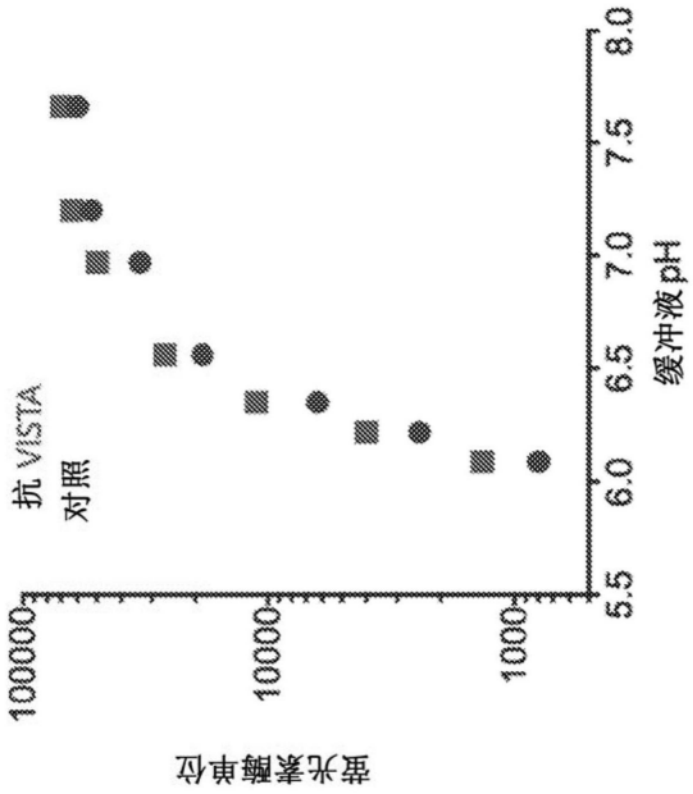

萤光素酶单位
100000
10000
1000
抗 VISTA
对照
5.5
6.0
6.5
7.0
7.5
8.0
缓冲液 pH

图5C

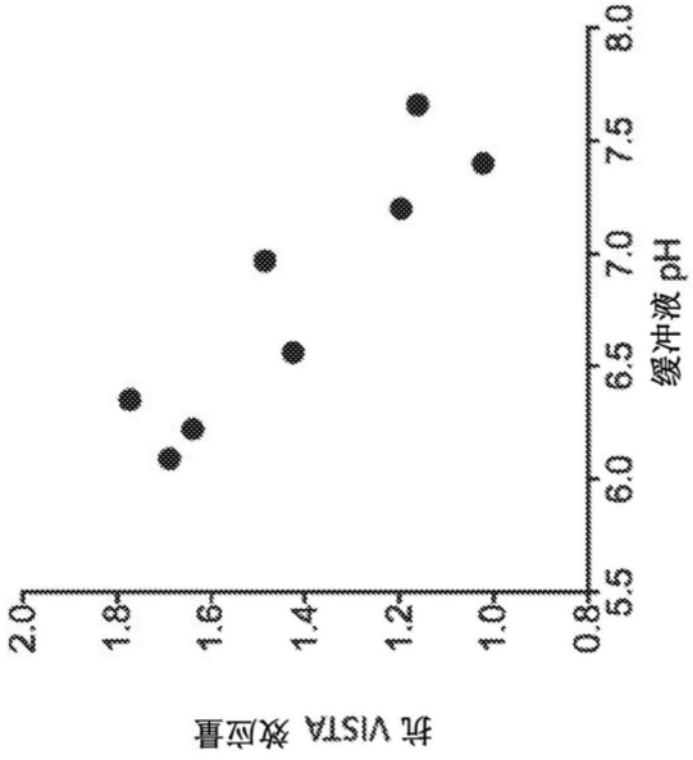

抗 VISTA 效应量
2.0
1.8
1.6
1.4
1.2
1.0
0.8
5.5
6.0
6.5
7.0
7.5
8.0
缓冲液 pH

图5D

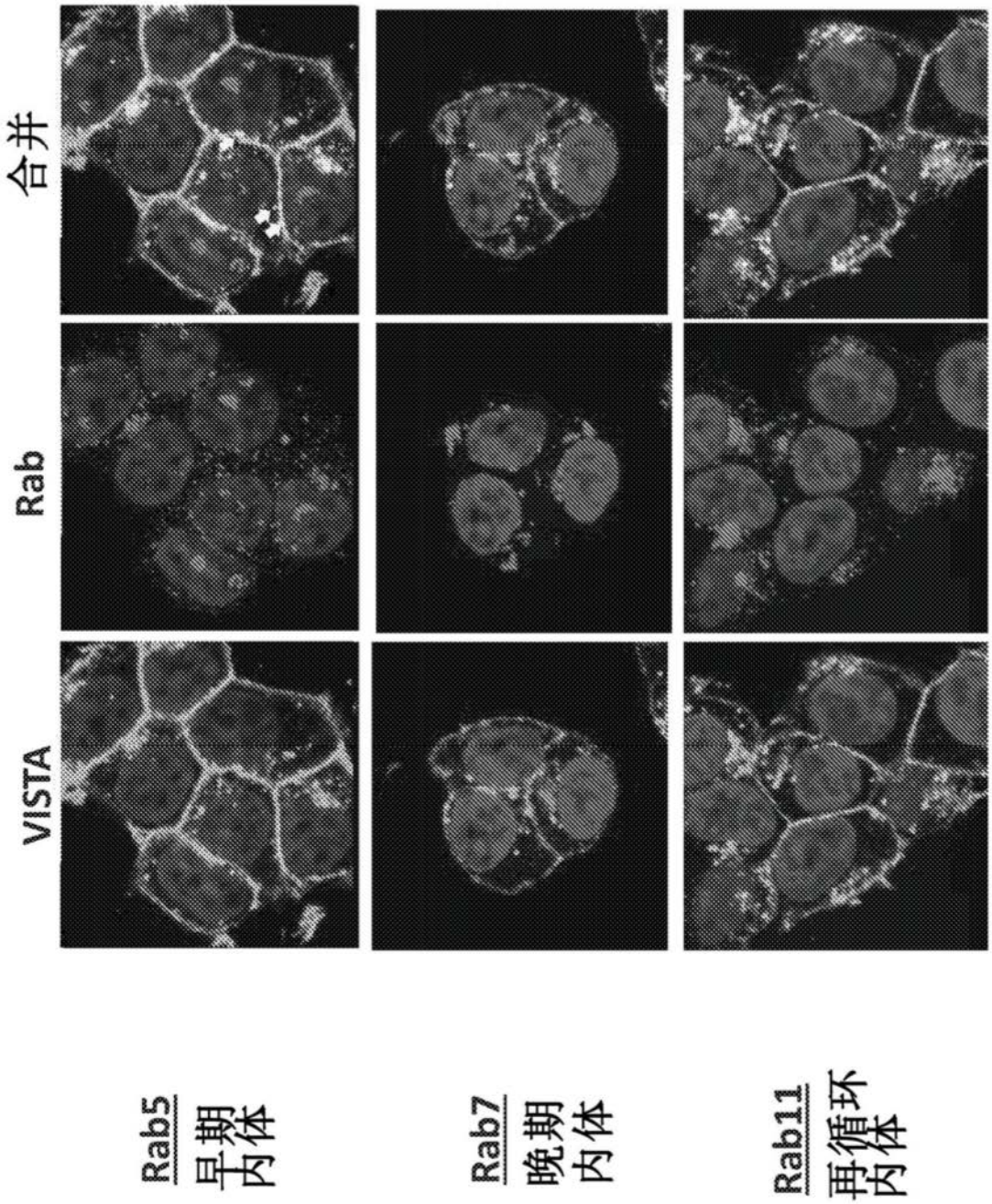


图6A

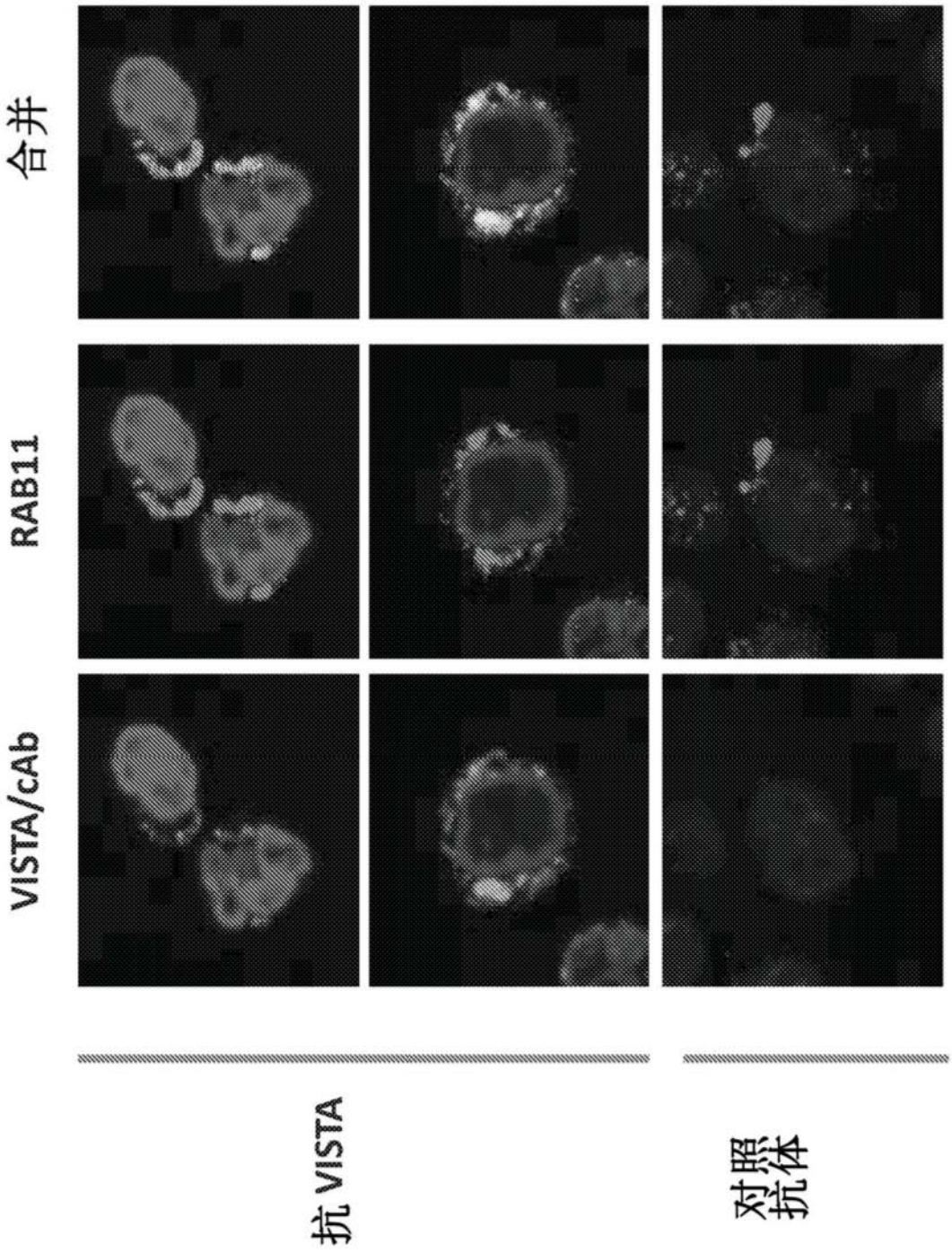


图6B

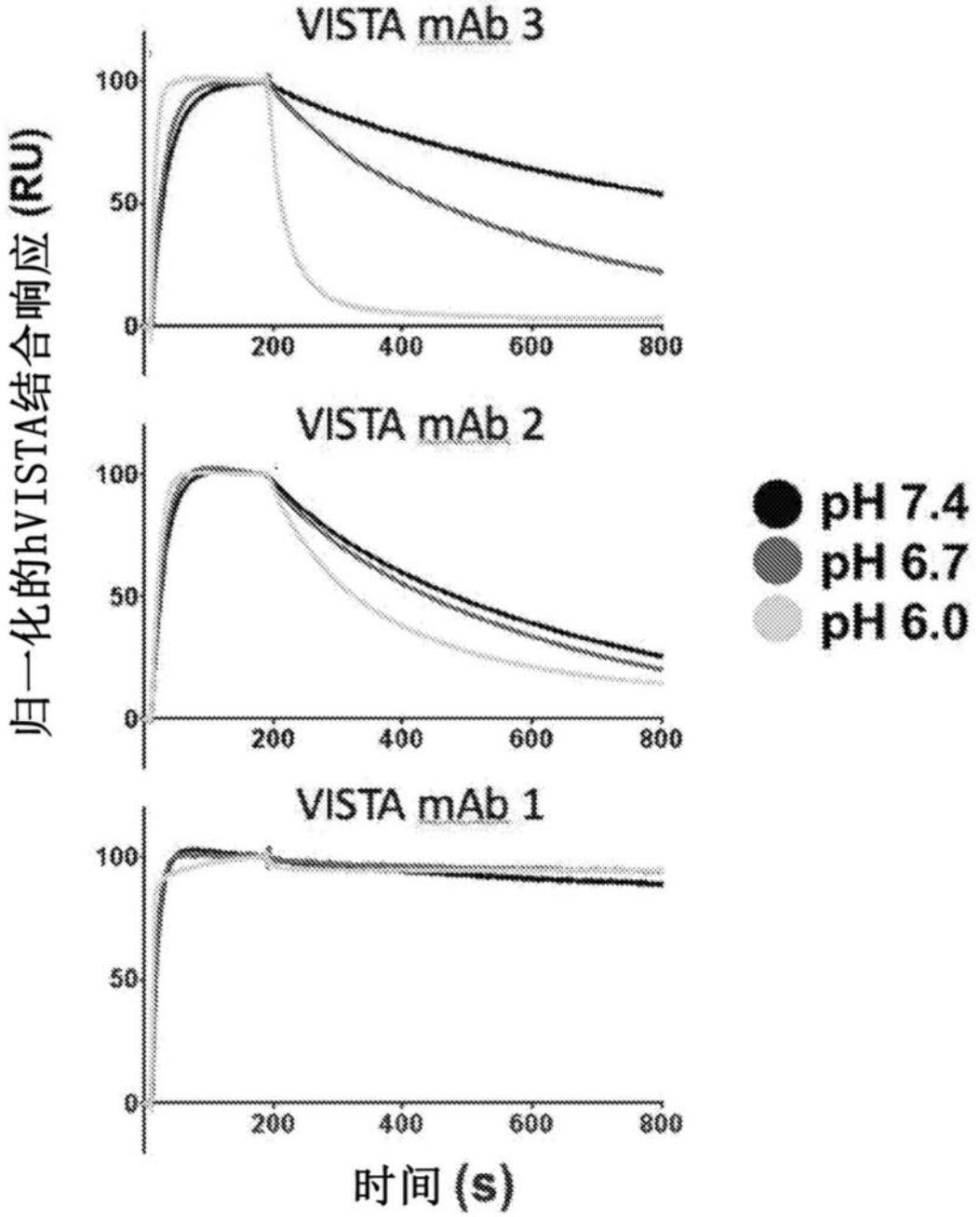

VISTA mAb 3
VISTA mAb 2
VISTA mAb 1
归一化的hVISTA结合响应 (RU)
100
50
0
200
400
600
800
时间 (s)
pH 7.4
pH 6.7
pH 6.0

图6C

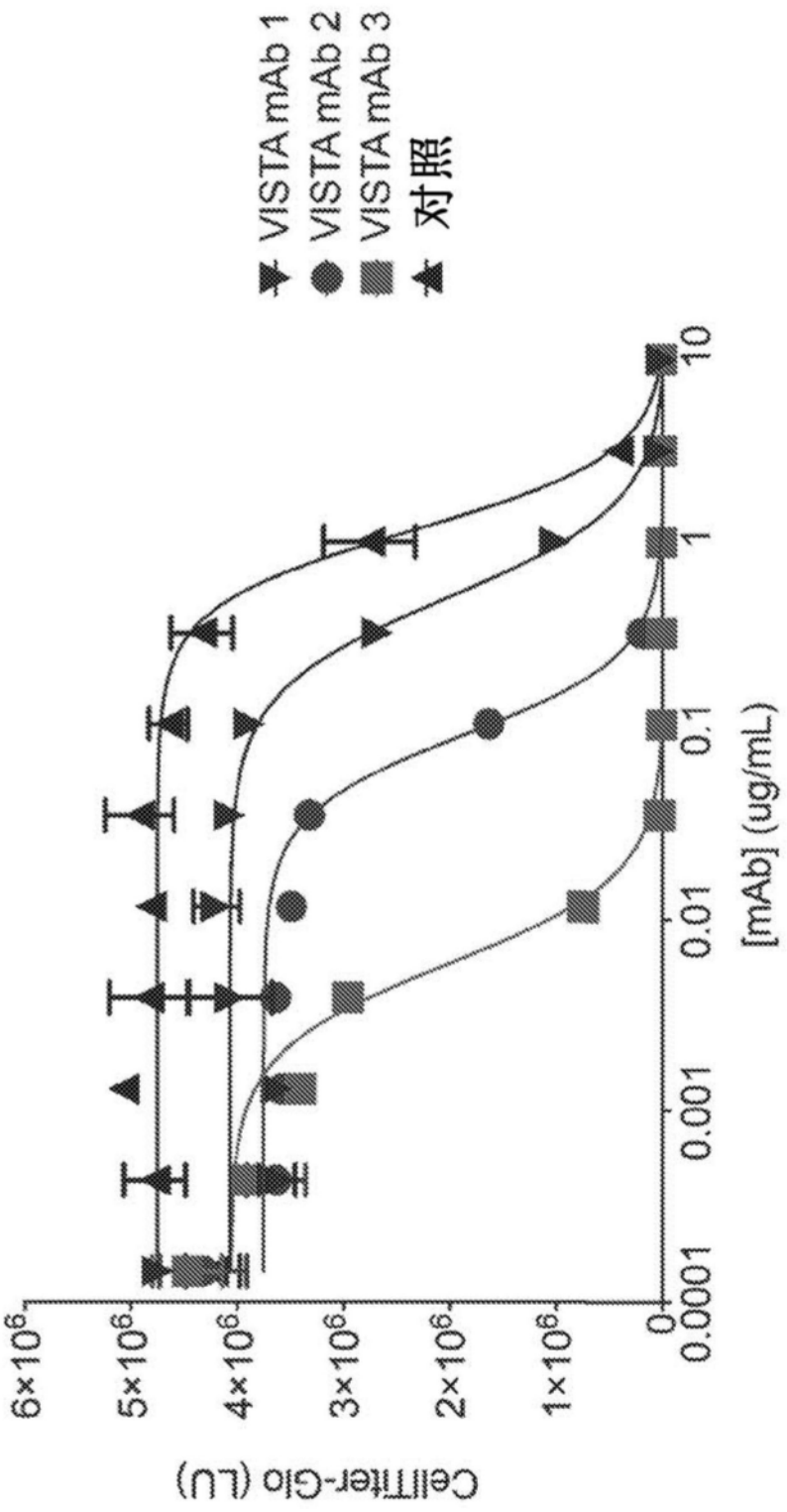

VISTA mAb 1
VISTA mAb 2
VISTA mAb 3
对照
CellTiter-Glo (LU)
6×10^6
5×10^6
4×10^6
3×10^6
2×10^6
1×10^6
0
0.0001
0.001
0.01
0.1
1
10
[mAb] (ug/mL)

图6D

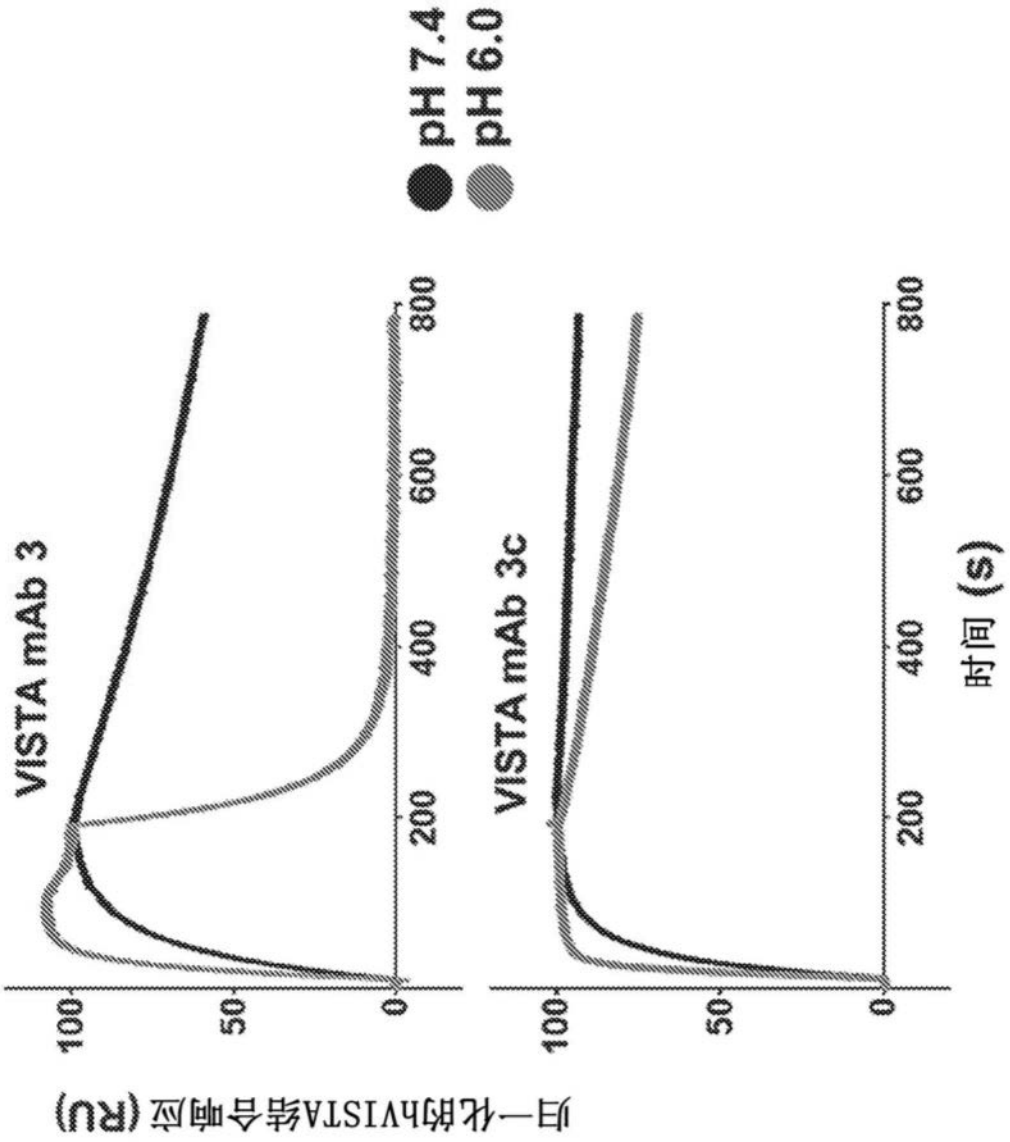

pH 7.4
pH 6.0
VISTA mAb 3
VISTA mAb 3c
0
50
100
200
400
600
800
时间 (s)
归一化的hVISTA结合响应 (RU)

图6E

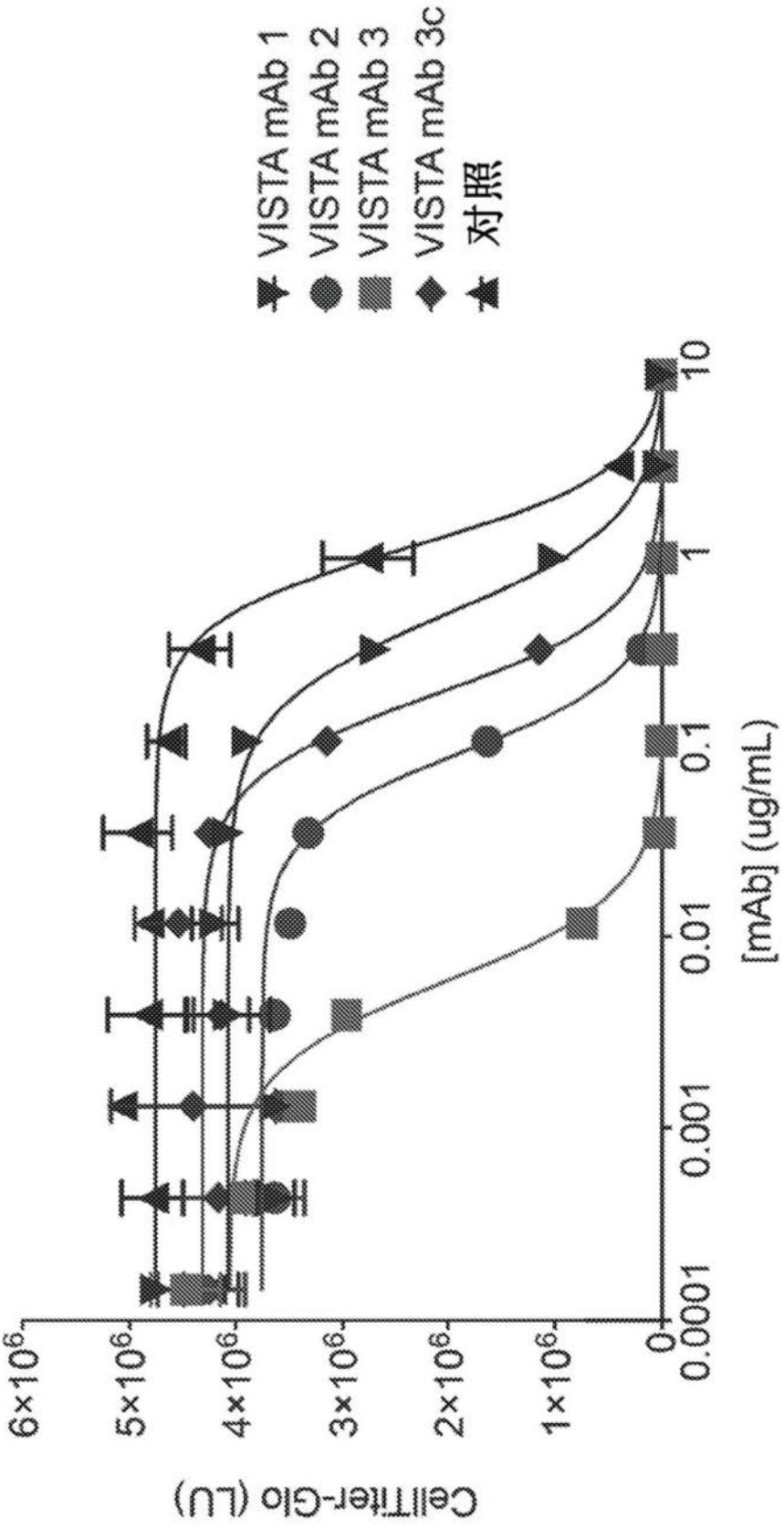

VISTA mAb 1
VISTA mAb 2
VISTA mAb 3
VISTA mAb 3c
对照
CellTiter-Glo (LU)
6×10^6
5×10^6
4×10^6
3×10^6
2×10^6
1×10^6
0
0.0001
0.001
0.01
0.1
1
10
[mAb] (ug/mL)

图6F

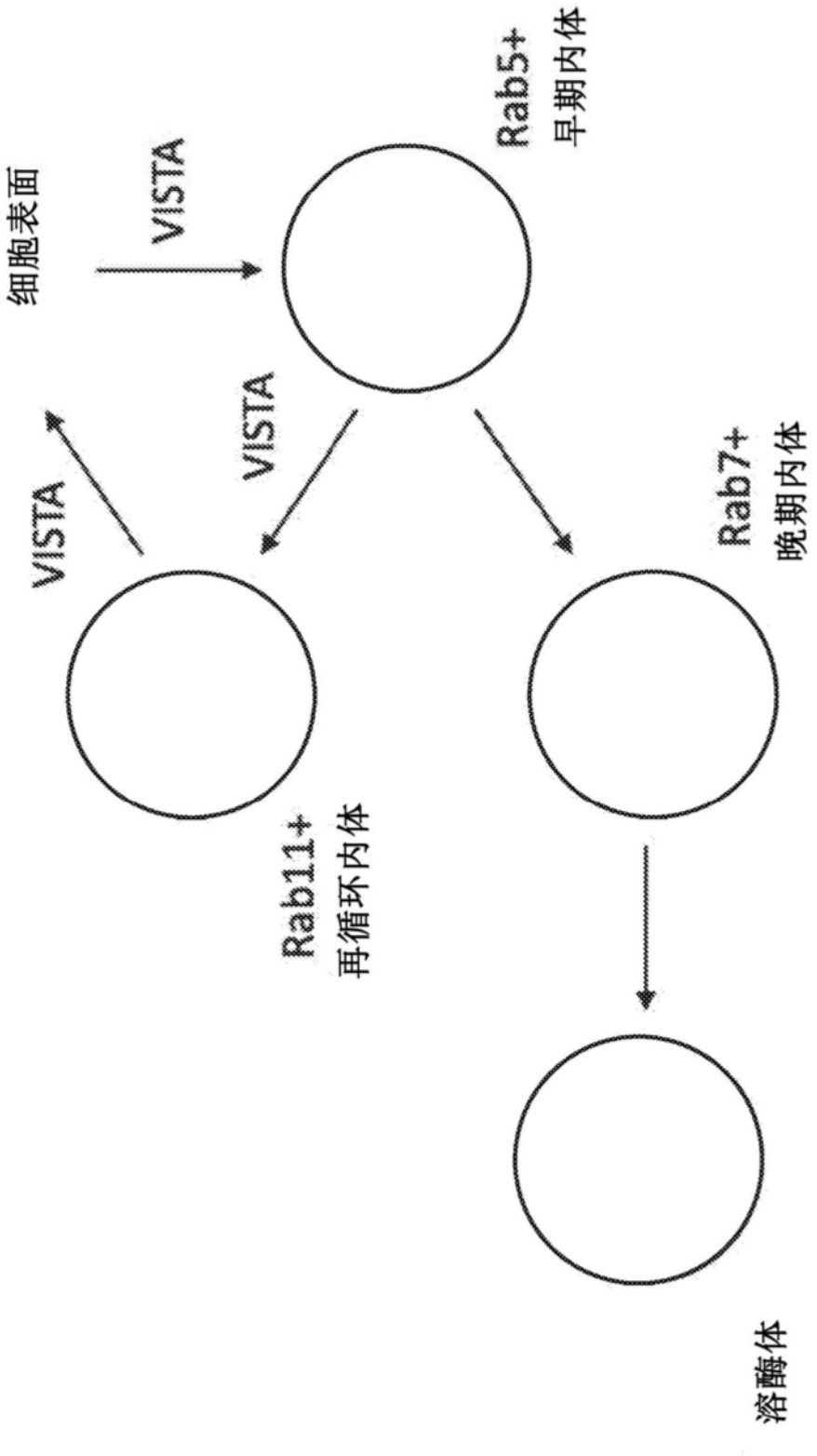

细胞表面
VISTA
Rab5+
早期内体
VISTA
VISTA
VISTA
Rab7+
晚期内体
Rab11+
再循环内体
溶酶体

图6G

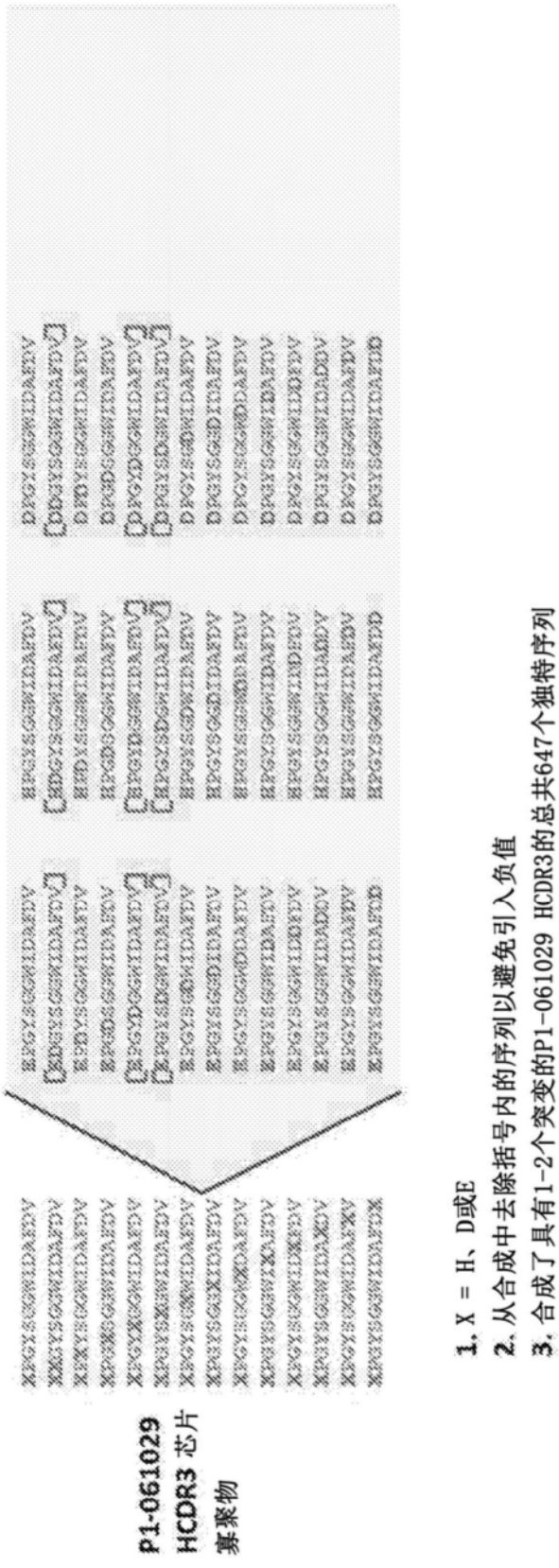

P1-061029
HCDR3 芯片
簇聚物
1. X = H、D或E
2. 从合成中去除括号内的序列以避免引入负值
3. 合成了具有1-2个突变的P1-061029 HCDR3的总共647个独特序列

图7A

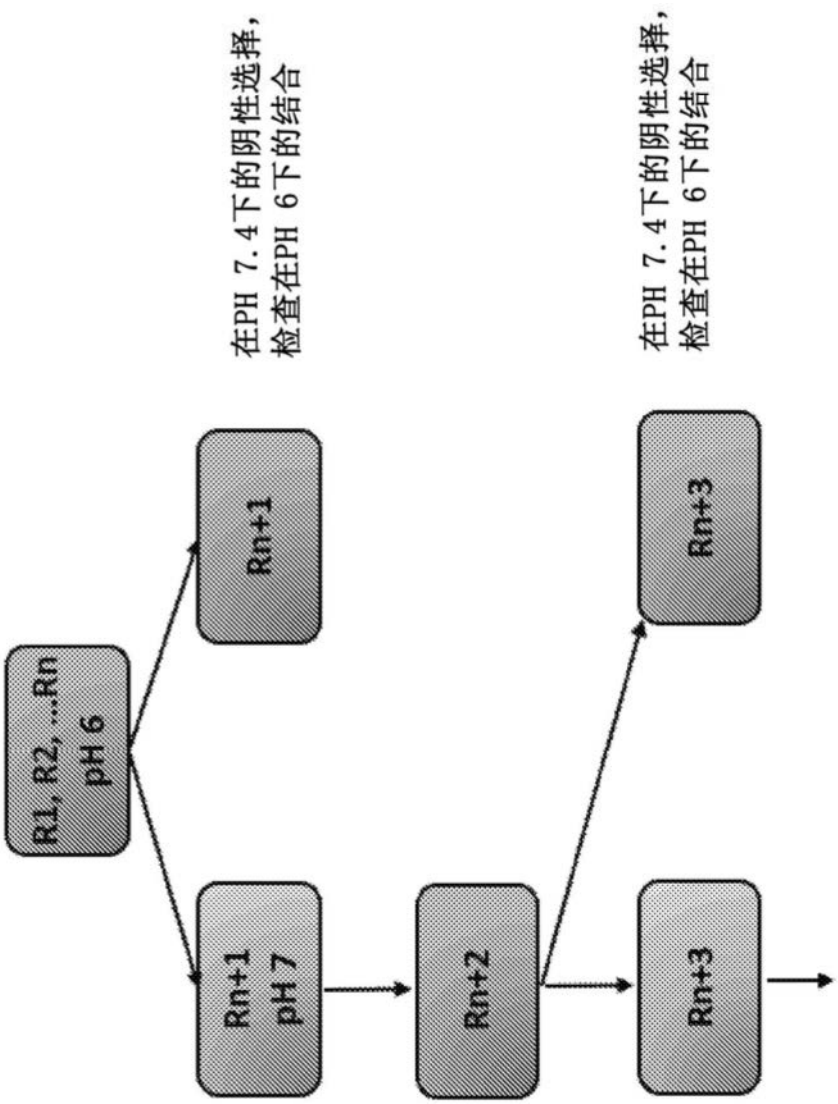

在PH 7.4下的阴性选择，
检查在PH 6下的结合
在PH 7.4下的阴性选择，
检查在PH 6下的结合
R1, R2, ...Rn
pH 6
Rn+1
Rn+1
pH 7
Rn+2
Rn+3
Rn+3

图7B

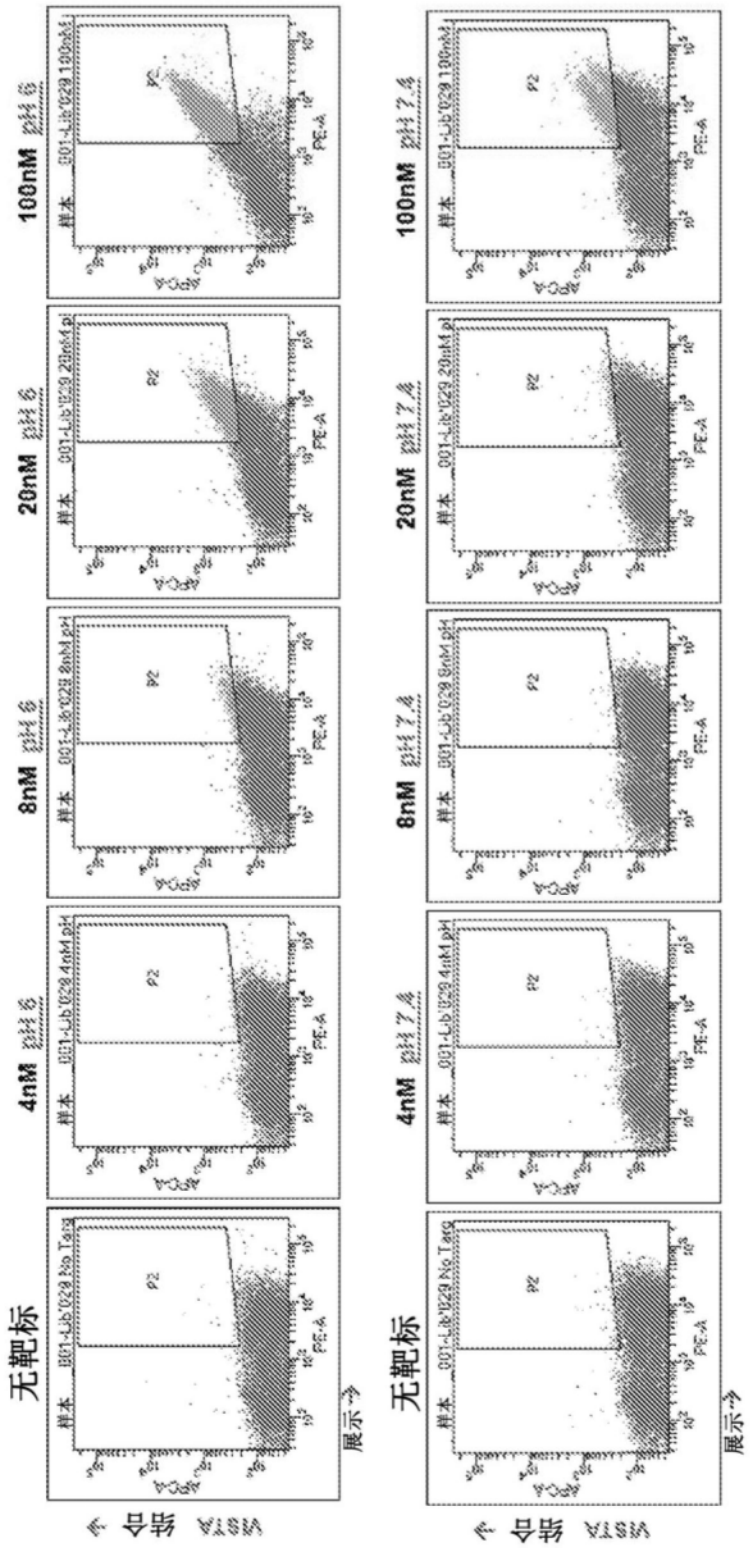


图7C

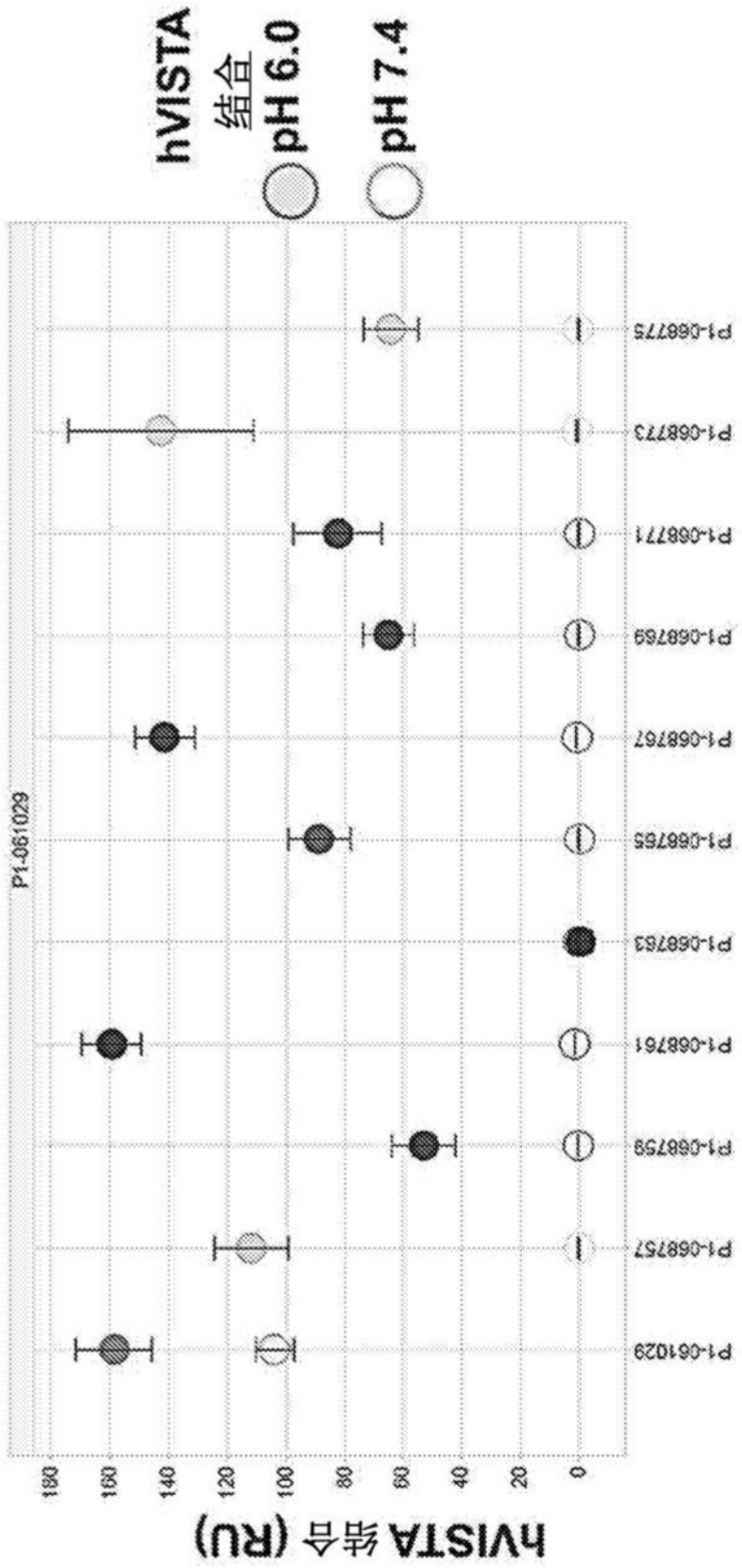

hVISTA
结合
pH 6.0
pH 7.4
P1-061029
P1-068775
P1-068773
P1-068771
P1-068769
P1-068767
P1-068765
P1-068763
P1-068761
P1-068759
P1-068757
P1-061029
hVISTA 结合 (RU)
180
160
140
120
100
80
60
40
20
0

图7D

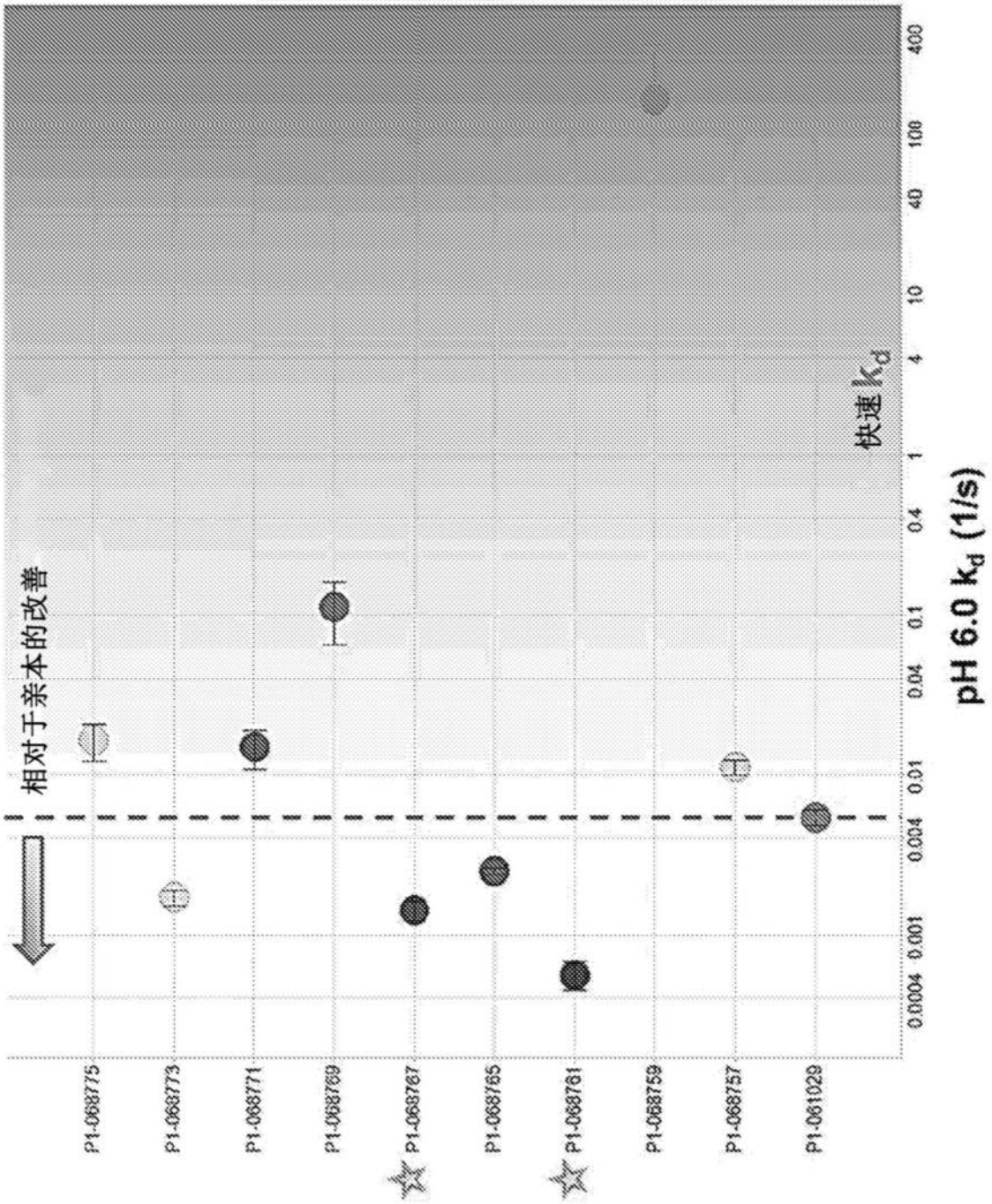

相对于亲本的改善
快速 k_d
pH 6.0 k_d (1/s)
0.0004
0.001
0.004
0.01
0.04
0.1
0.4
1
4
10
40
100
400
P1-068775
P1-068773
P1-068771
P1-068769
P1-068767
P1-068765
P1-068761
P1-068759
P1-068757
P1-061029

图7E

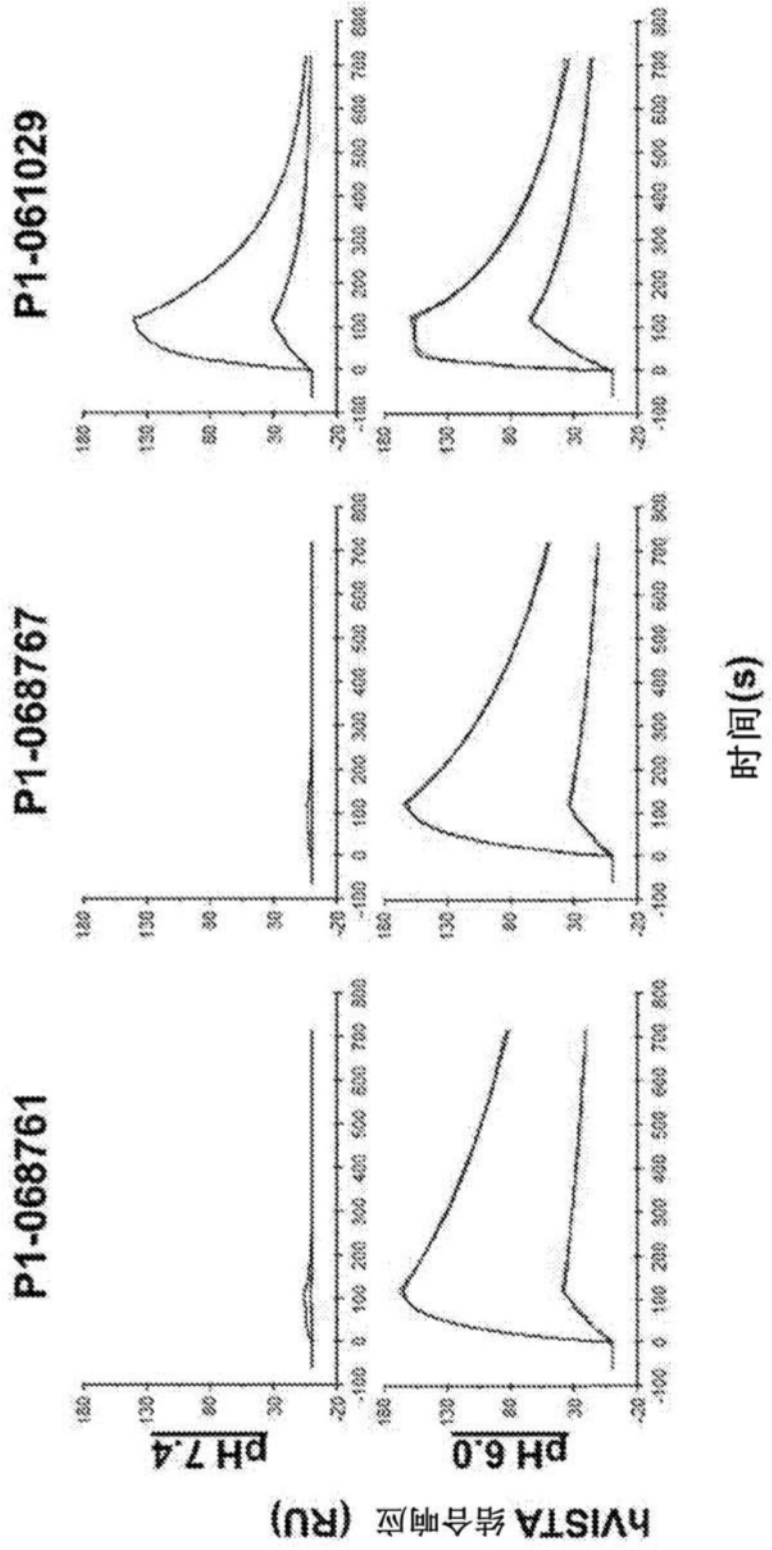


图7F

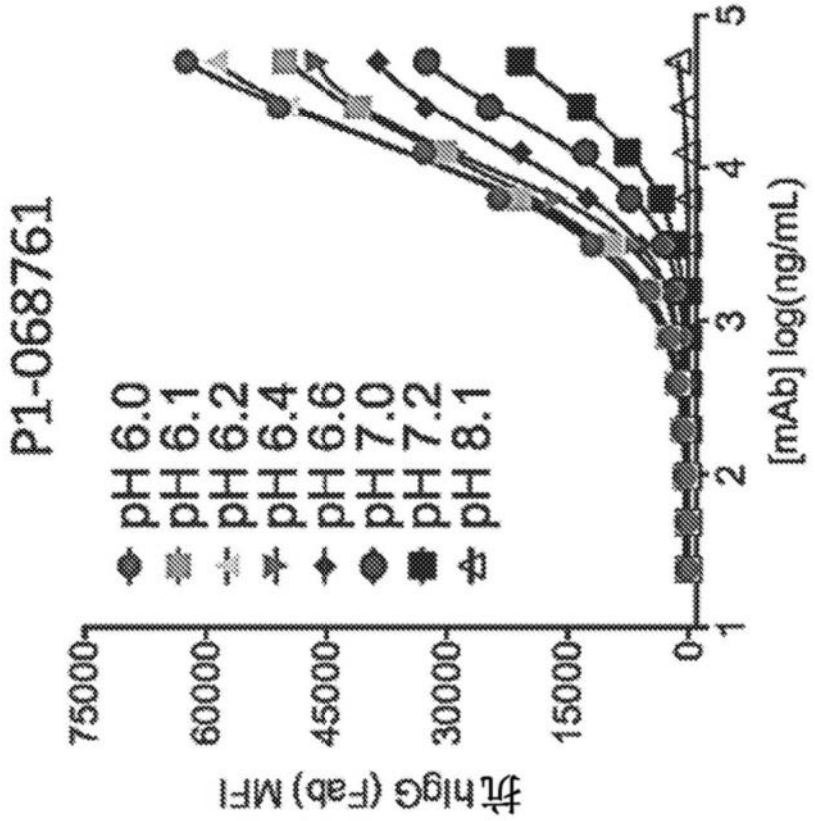

P1-068761
pH 6.0
pH 6.1
pH 6.2
pH 6.4
pH 6.6
pH 7.0
pH 7.2
pH 8.1
抗hIgG (Fab) MFI
75000
60000
45000
30000
15000
0
1
2
3
4
5
[mAb] log(ng/mL)

图8A

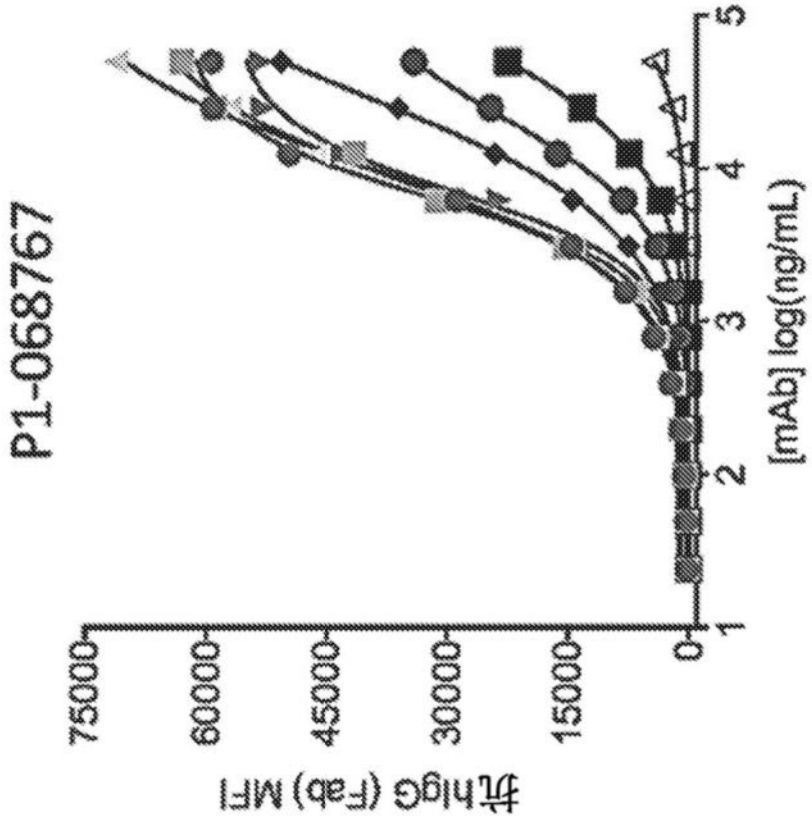

P1-068767
抗hIgG (Fab) MFI
75000
60000
45000
30000
15000
0
1
2
3
4
5
[mAb] log(ng/mL)

图8B

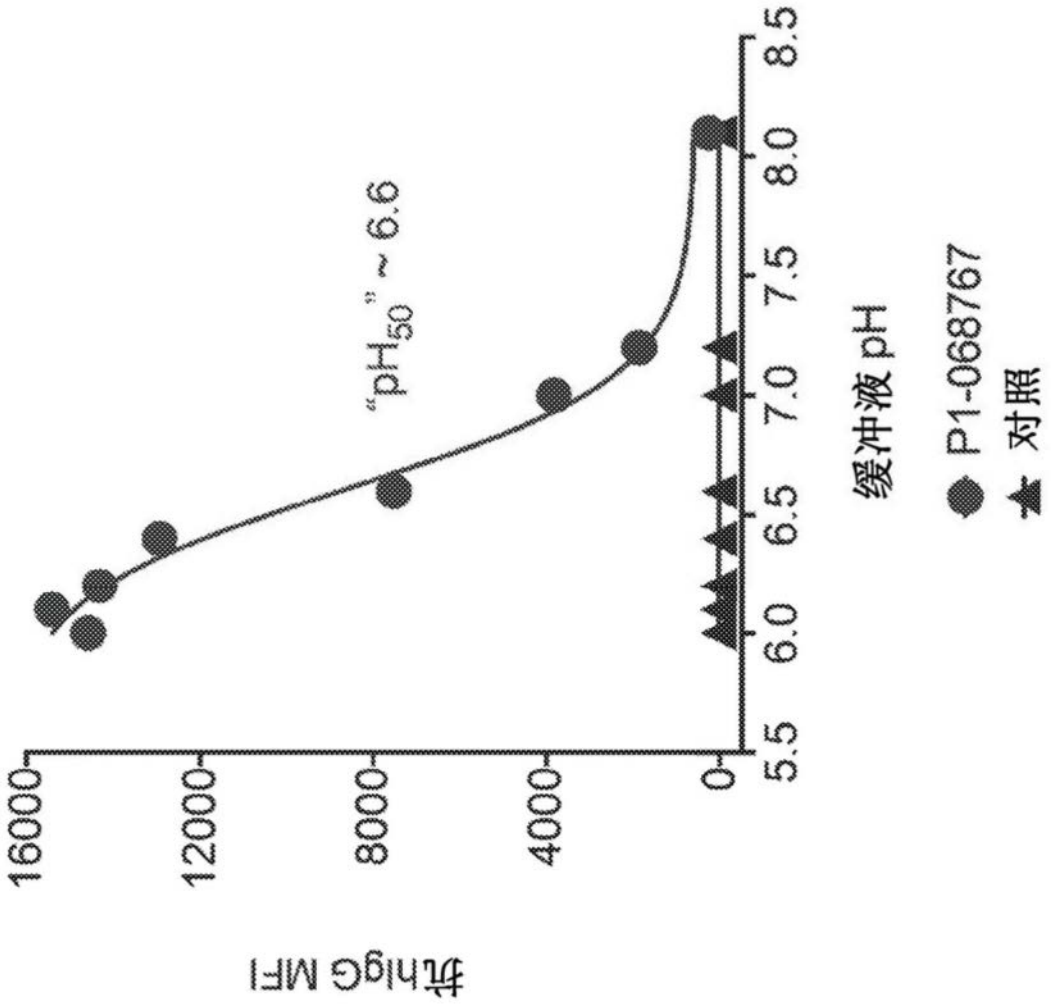

抗hIgG MFI
16000
12000
8000
4000
0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
缓冲液 pH
"pH50" ~ 6.6
P1-0687767
对照

图8C

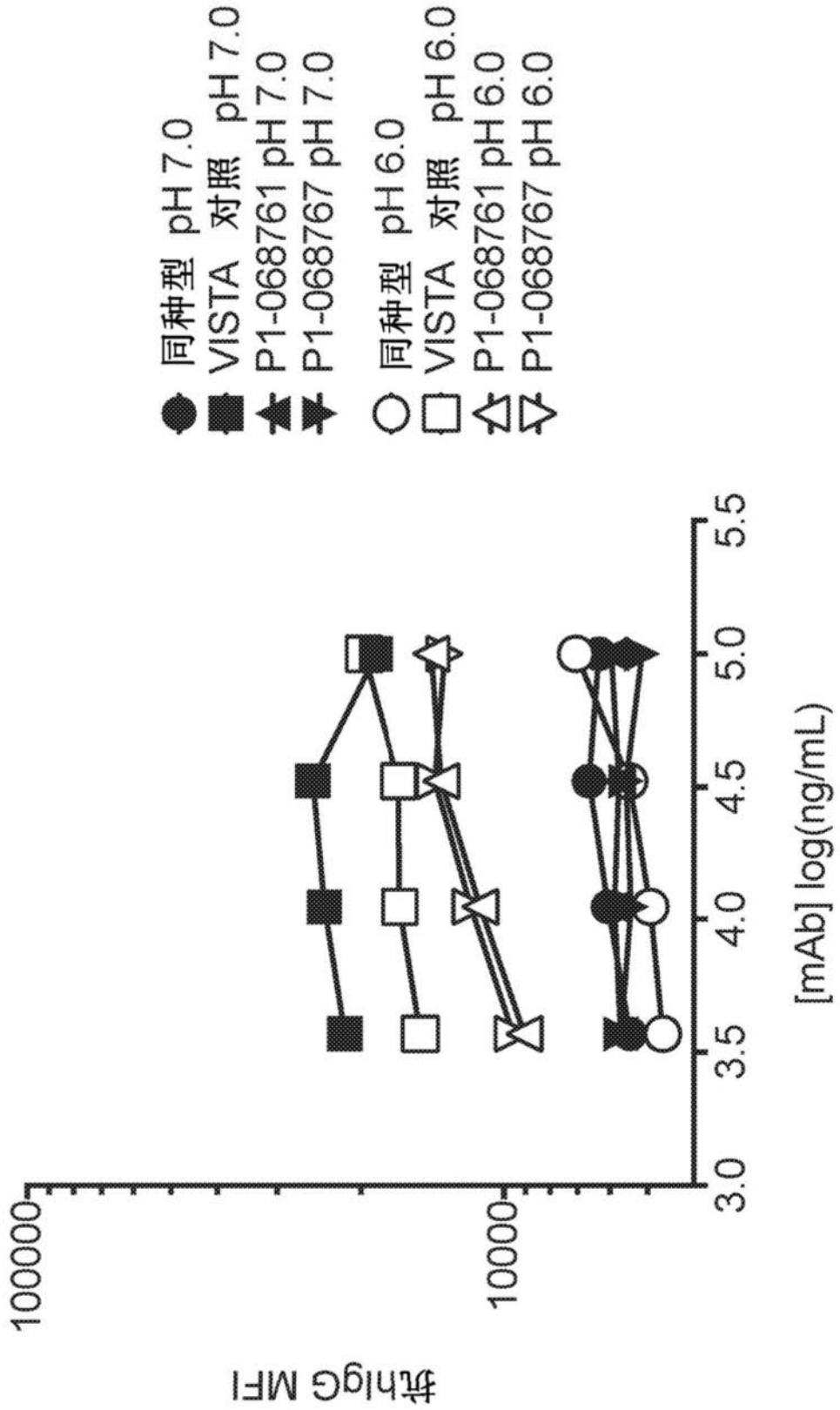

同种型 pH 7.0
VISTA 对照 pH 7.0
P1-0687761 pH 7.0
P1-0687767 pH 7.0
同种型 pH 6.0
VISTA 对照 pH 6.0
P1-0687761 pH 6.0
P1-0687767 pH 6.0
100000
10000
抗hIgG MFI
3.0
3.5
4.0
4.5
5.0
5.5
[mAb] log(ng/mL)

图8D

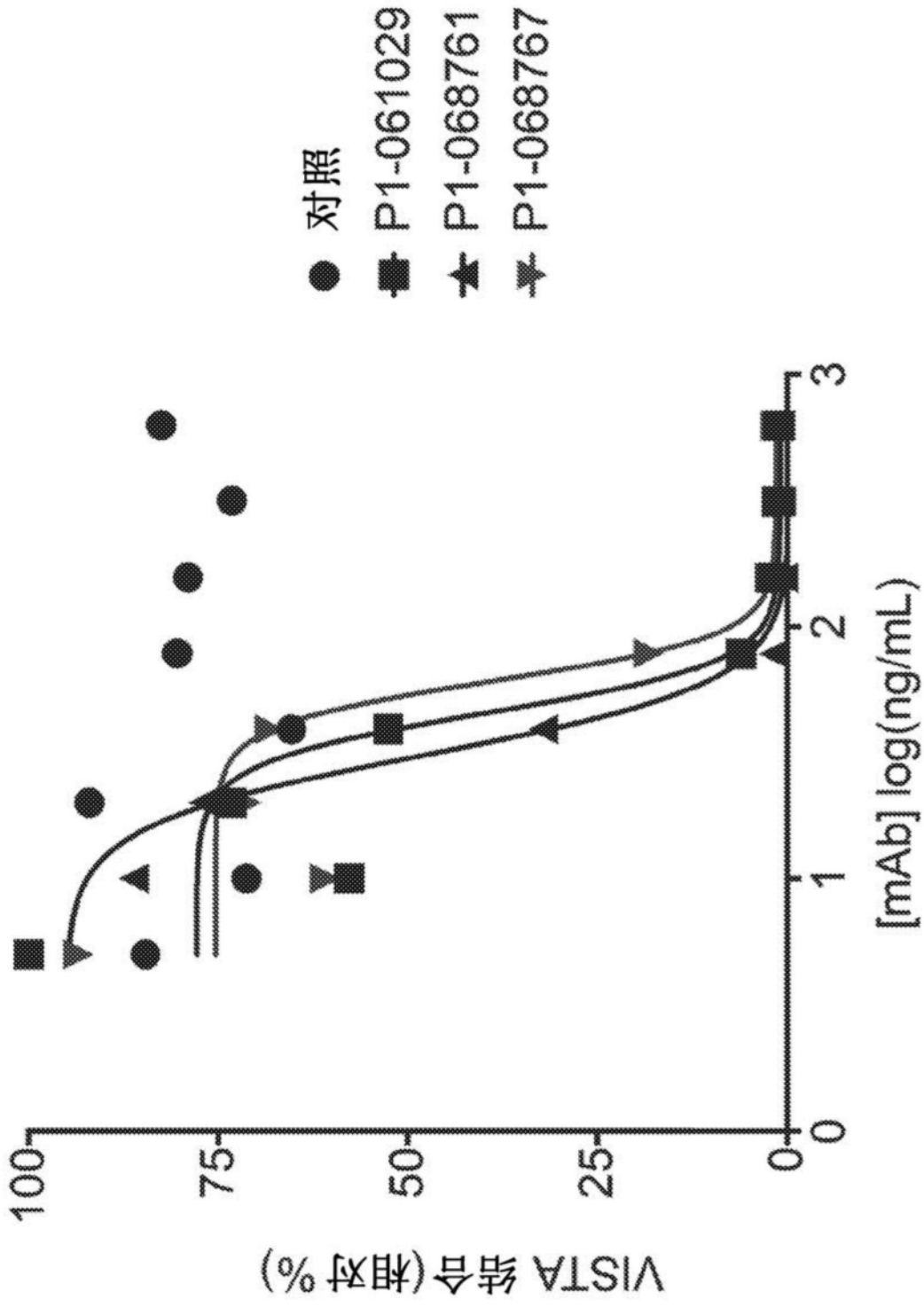

对照
P1-0610029
P1-0687761
P1-0687767
VISTA 结合(相对 %)
100
75
50
25
0
0
1
2
3
[mAb] log(ng/mL)

图8E

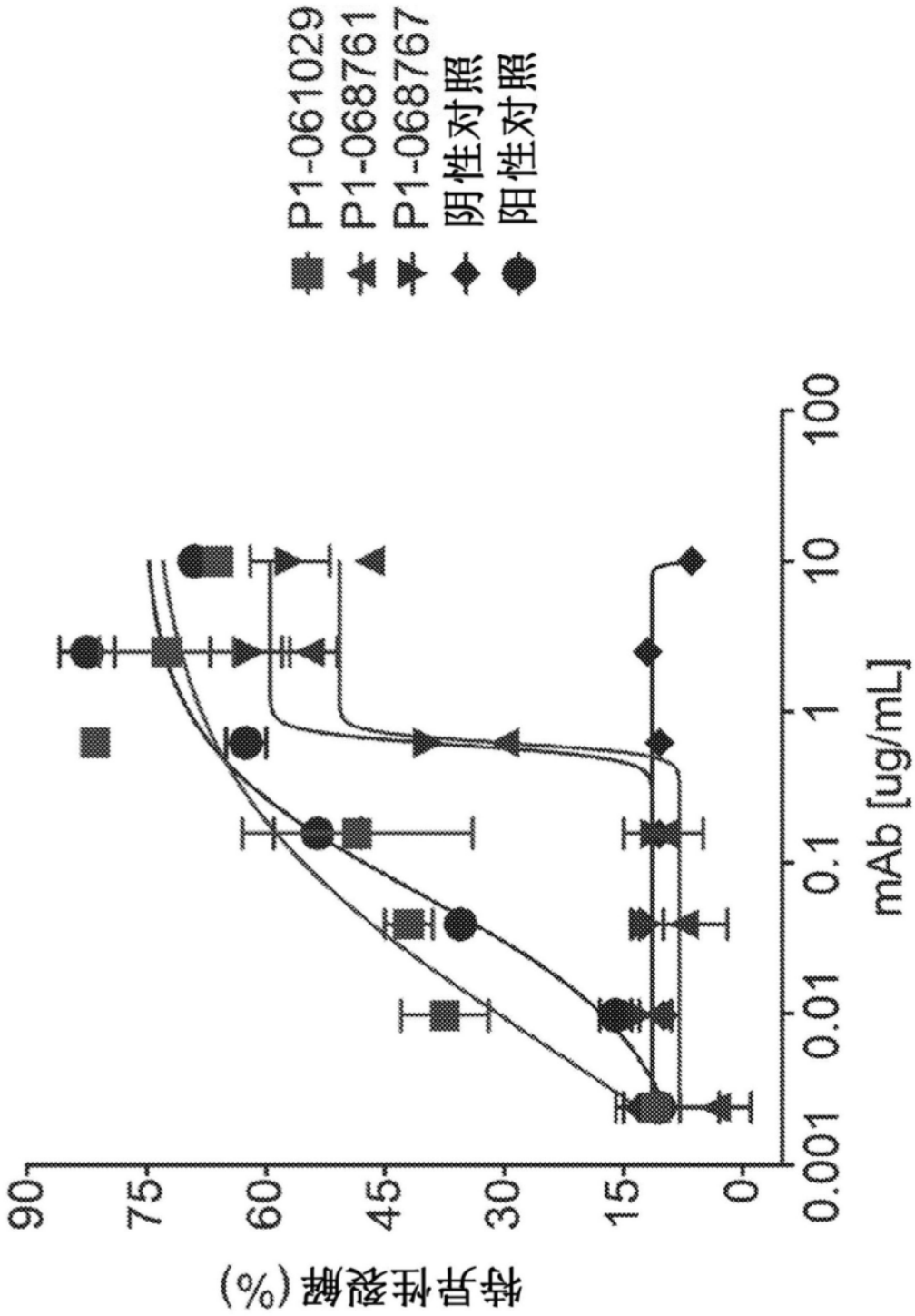

P1-061029
P1-068761
P1-068767
阴性对照
阳性对照
特异性裂解(%)
90
75
60
45
30
15
0
0.001
0.01
0.1
1
10
100
mAb [ug/mL]

图8F

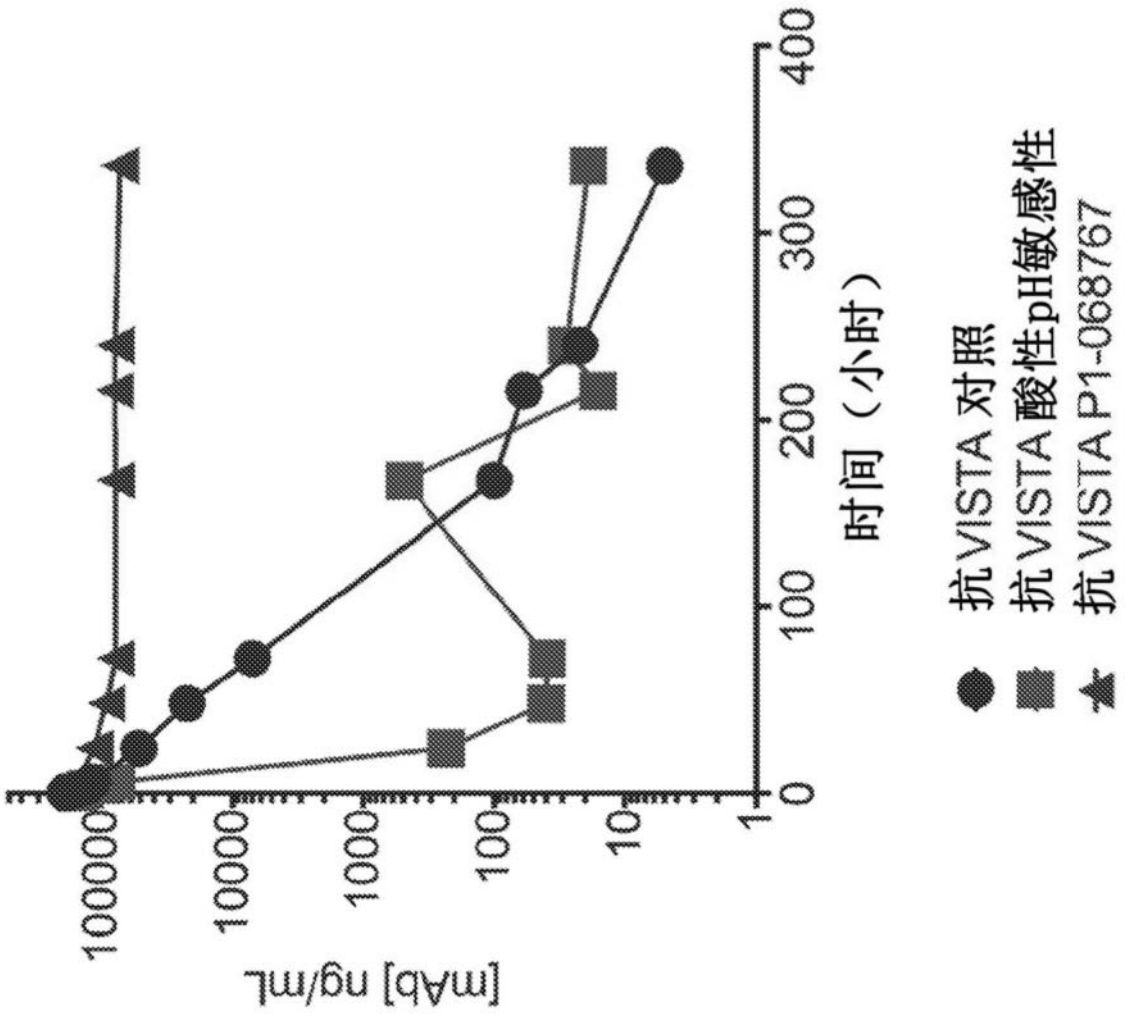
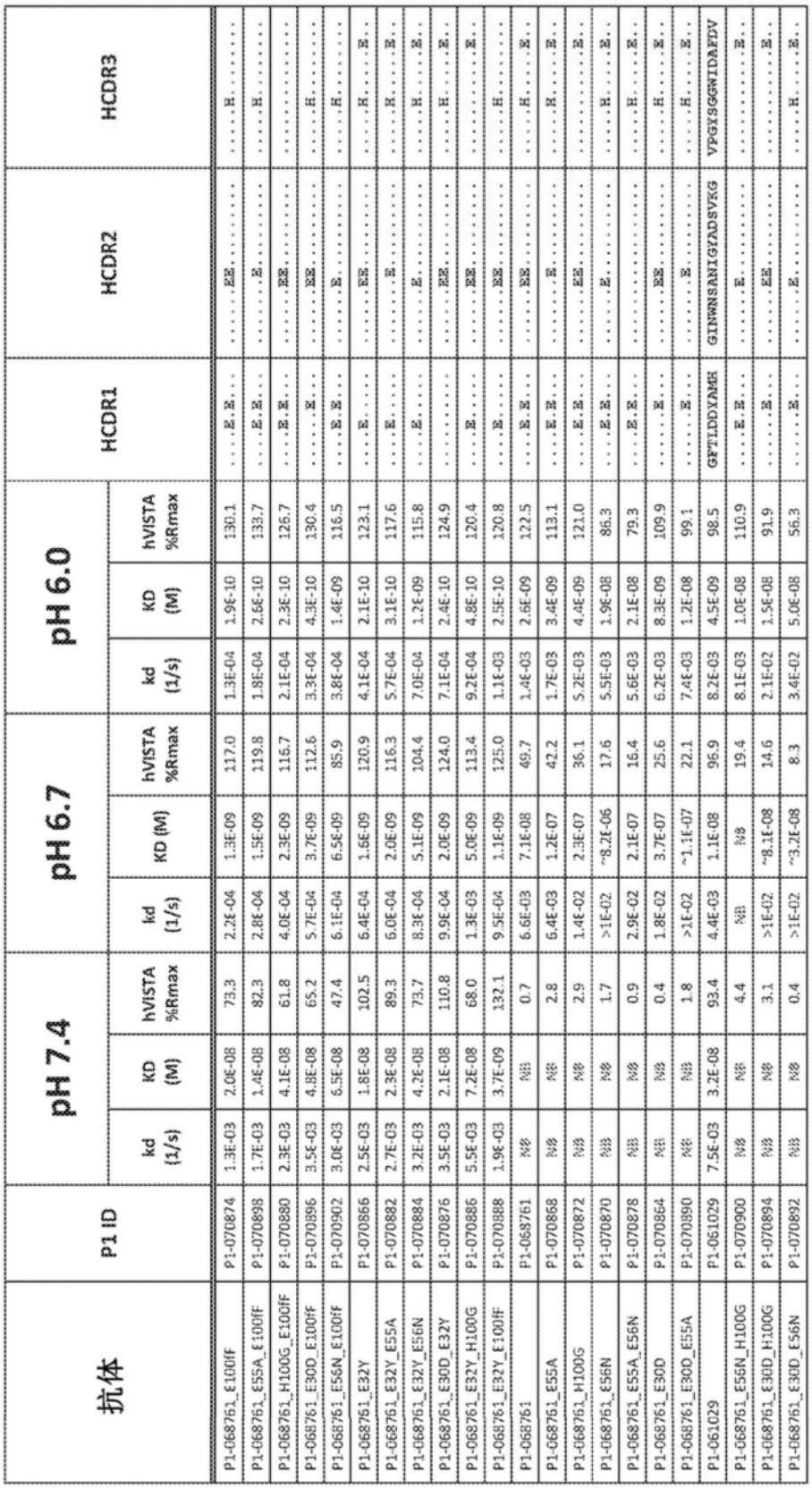
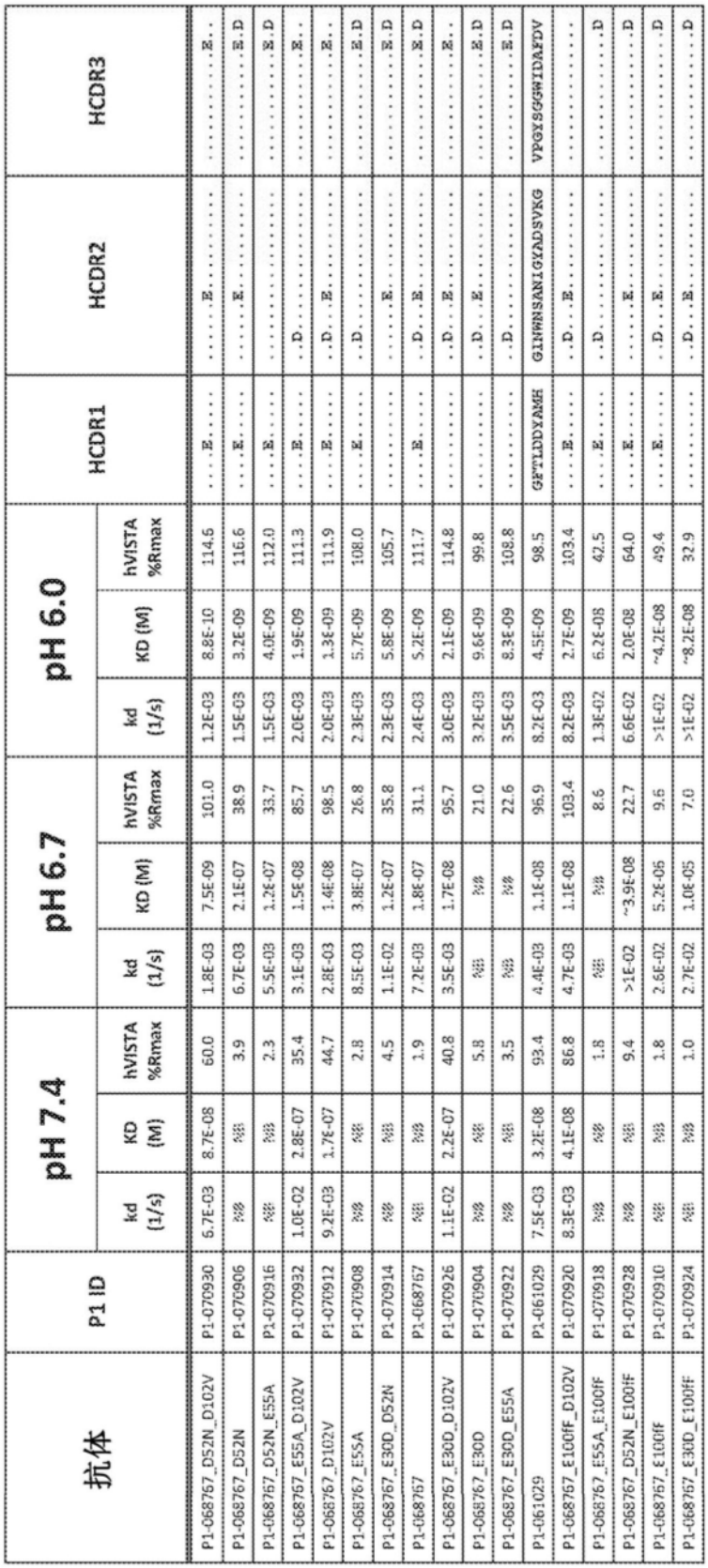

[mAb] ng/mL
100000
10000
1000
100
10
1
0
100
200
300
400
时间（小时）
抗VISTA 对照
抗VISTA 酸性pH敏感性
抗VISTA P1-068767

图9



抗体	P1 ID	pH 7.4			pH 6.7			pH 6.0			HCDR1	HCDR2	HCDR3
		kd (1/s)	KD (M)	hVISTA %Rmax	kd (1/s)	KD (M)	hVISTA %Rmax	kd (1/s)	KD (M)	hVISTA %Rmax			
P1-068761_E100fF	P1-070874	1.3E-03	2.0E-08	73.3	2.2E-04	1.3E-09	117.0	1.3E-04	1.9E-10	130.1	....E.E..	.....EE.....	.....H.....
P1-068761_E55A_E100fF	P1-070898	1.7E-03	1.4E-08	82.3	2.8E-04	1.5E-09	119.8	1.8E-04	2.6E-10	133.7	....E.E..	.....E.....	.....H.....
P1-068761_H100G_E100fF	P1-070880	2.3E-03	4.1E-08	61.8	4.0E-04	2.3E-09	116.7	2.1E-04	2.3E-10	126.7	....E.E..	.....EE.....	.....
P1-068761_E30D_E100fF	P1-070896	3.5E-03	4.8E-08	65.2	5.7E-04	3.7E-09	112.6	3.3E-04	4.3E-10	130.4	....E.E..	.....EE.....	.....H.....
P1-068761_E56N_E100fF	P1-070902	3.0E-03	6.5E-08	47.4	6.1E-04	6.5E-09	85.9	3.8E-04	1.4E-09	116.5	....E.E..	.....E.....	.....H.....
P1-068761_E32Y	P1-070866	2.5E-03	1.8E-08	102.5	6.4E-04	1.6E-09	120.9	4.1E-04	2.1E-10	123.1	....E.....	.....EE.....	.....H.....E..
P1-068761_E32Y_E55A	P1-070882	2.7E-03	2.3E-08	89.3	6.0E-04	2.0E-09	116.3	5.7E-04	3.1E-10	117.6	....E.....	.....E.....	.....H.....E..
P1-068761_E32Y_E56N	P1-070884	3.2E-03	4.2E-08	73.7	8.3E-04	5.1E-09	104.4	7.0E-04	1.2E-09	115.8	....E.....	.....E.....	.....H.....E..
P1-068761_E30D_E32Y	P1-070876	3.5E-03	2.1E-08	110.8	9.9E-04	2.0E-09	124.0	7.1E-04	2.4E-10	124.9	.....	.....EE.....	.....H.....E..
P1-068761_E32Y_H100G	P1-070886	5.5E-03	7.2E-08	68.0	1.3E-03	5.0E-09	113.4	9.2E-04	4.8E-10	120.4	....E.....	.....EE.....	.....E.....
P1-068761_E32Y_E100fF	P1-070888	1.9E-03	3.7E-09	132.1	9.5E-04	1.1E-09	125.0	1.1E-03	2.5E-10	120.8	....E.....	.....EE.....	.....H.....
P1-068761	P1-068761	NB	NB	0.7	6.6E-03	7.1E-08	49.7	1.4E-03	2.6E-09	122.5	....E.E..	.....EE.....	.....H.....E..
P1-068761_E55A	P1-070868	NB	NB	2.8	6.4E-03	1.2E-07	42.2	1.7E-03	3.4E-09	113.1	....E.E..	.....E.....	.....H.....E..
P1-068761_H100G	P1-070872	NB	NB	2.9	1.4E-02	2.3E-07	36.1	5.2E-03	4.4E-09	121.0	....E.E..	.....EE.....	.....E.....
P1-068761_E56N	P1-070870	NB	NB	1.7	>1E-02	~8.2E-06	17.6	5.5E-03	1.9E-08	86.3	....E.E..	.....E.....	.....H.....E..
P1-068761_E55A_E56N	P1-070878	NB	NB	0.9	2.9E-02	2.1E-07	16.4	5.6E-03	2.1E-08	79.3	....E.E..	.....	.....H.....E..
P1-068761_E30D	P1-070864	NB	NB	0.4	1.8E-02	3.7E-07	25.6	6.2E-03	8.3E-09	109.9	.....E..	.....EE.....	.....H.....E..
P1-068761_E30D_E55A	P1-070890	NB	NB	1.8	>1E-02	~1.1E-07	22.1	7.4E-03	1.2E-08	99.1	.....E..	.....E.....	.....H.....E..
P1-061029	P1-061029	7.5E-03	3.2E-08	93.4	4.4E-03	1.1E-08	96.9	8.2E-03	4.5E-09	98.5	GFTLDDYAMH	G1NWNSAN1GYADSVKG	VPGYSGGW1DAFDV
P1-068761_E56N_H100G	P1-070900	NB	NB	4.4	NB	NB	19.4	8.1E-03	1.0E-08	110.9	....E.E..	.....E.....	.....E.....
P1-068761_E30D_H100G	P1-070894	NB	NB	3.1	>1E-02	~8.1E-08	14.6	2.1E-02	1.5E-08	91.9	.....E..	.....EE.....	.....E.....
P1-068761_E30D_E56N	P1-070892	NB	NB	0.4	>1E-02	~3.2E-08	8.3	3.4E-02	5.0E-08	56.3	.....E..	.....E.....	.....H.....E..

图10A



抗体	P1 ID	pH 7.4			pH 6.7			pH 6.0			HCDR1	HCDR2	HCDR3
		kd (1/s)	KD (M)	hVISTA %Rmax	kd (1/s)	KD (M)	hVISTA %Rmax	kd (1/s)	KD (M)	hVISTA %Rmax			
P1-068767_D52N_D102V	P1-070930	6.7E-03	8.7E-08	60.0	1.8E-03	7.5E-09	101.0	1.2E-03	8.8E-10	114.5	....E.....	.....E.....	.....E..
P1-068767_D52N	P1-070906	##	##	3.9	6.7E-03	2.1E-07	38.9	1.5E-03	3.2E-09	116.6	....E.....	.....E.....	.....E.D
P1-068767_D52N_E55A	P1-070916	##	##	2.3	5.5E-03	1.2E-07	33.7	1.5E-03	4.0E-09	112.0	....E.....	....	.....E.D
P1-068767_E55A_D102V	P1-070932	1.0E-02	2.8E-07	35.4	3.1E-03	1.5E-08	85.7	2.0E-03	1.9E-09	111.3	....E.....	..D.....	.....E..
P1-068767_D102V	P1-070912	9.2E-03	1.7E-07	44.7	2.8E-03	1.4E-08	98.5	2.0E-03	1.3E-09	111.9	....E.....	..D...E.	.....E..
P1-068767_E55A	P1-070908	##	##	2.8	8.5E-03	3.8E-07	26.8	2.3E-03	5.7E-09	108.0	....E.....	..D.....	.....E.D
P1-068767_E30D_D52N	P1-070914	##	##	4.5	1.1E-02	1.2E-07	35.8	2.3E-03	5.8E-09	105.7	....	.....E.....	.....E.D
P1-068767	P1-068767	##	##	1.9	7.2E-03	1.8E-07	31.1	2.4E-03	5.2E-09	111.7	....E.....	..D...E.	.....E.D
P1-068767_E30D_D102V	P1-070926	1.1E-02	2.2E-07	40.8	3.5E-03	1.7E-08	95.7	3.0E-03	2.1E-09	114.8	....	..D...E.	.....E..
P1-068767_E30D	P1-070904	##	##	5.8	##	##	21.0	3.2E-03	9.6E-09	99.8	....	..D...E.	.....E.D
P1-068767_E30D_E55A	P1-070922	##	##	3.5	##	##	22.6	3.5E-03	8.3E-09	108.8	....	..D.....	.....E.D
P1-061029	P1-061029	7.5E-03	3.2E-08	93.4	4.4E-03	1.1E-08	96.9	8.2E-03	4.5E-09	98.5	GFTLDDYAMH	GINWNSANIGYADSVKG	VPGYSGGWIDAFDV
P1-068767_E100fF_D102V	P1-070920	8.3E-03	4.1E-08	86.8	4.7E-03	1.1E-08	103.4	8.2E-03	2.7E-09	103.4	....E.....	..D...E.	.....
P1-068767_E55A_E100fF	P1-070918	##	##	1.8	##	##	8.6	1.3E-02	6.2E-08	42.5	....E.....	..D.....	.....D
P1-068767_D52N_E100fF	P1-070928	##	##	9.4	>1E-02	~3.9E-08	22.7	6.6E-02	2.0E-08	64.0	....E.....	.....E.	.....D
P1-068767_E100fF	P1-070910	##	##	1.8	2.6E-02	5.2E-05	9.6	>1E-02	~4.2E-08	49.4	....E.....	..D...E.	.....D
P1-068767_E30D_E100fF	P1-070924	##	##	1.0	2.7E-02	1.0E-05	7.0	>1E-02	~8.2E-08	32.9	....	..D...E.	.....D

图10B

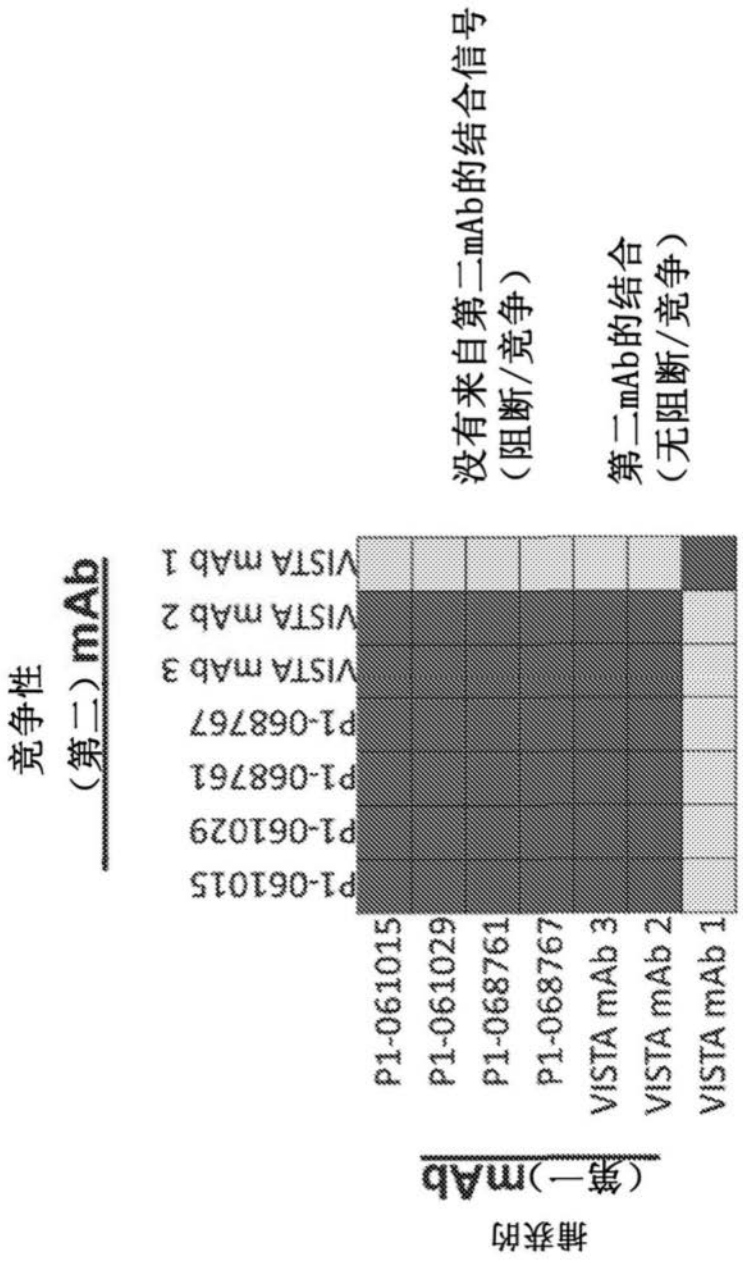

捕获的
(第一)mAb
P1-061015
P1-061029
P1-068761
P1-068767
VISTA mAb 3
VISTA mAb 2
VISTA mAb 1
没有来自第二mAb的结合信号
(阻断/竞争)
第二mAb的结合
(无阻断/竞争)
竞争性
(第二)mAb
P1-061015
P1-061029
P1-068761
P1-068767
VISTA mAb 3
VISTA mAb 2
VISTA mAb 1

图11A

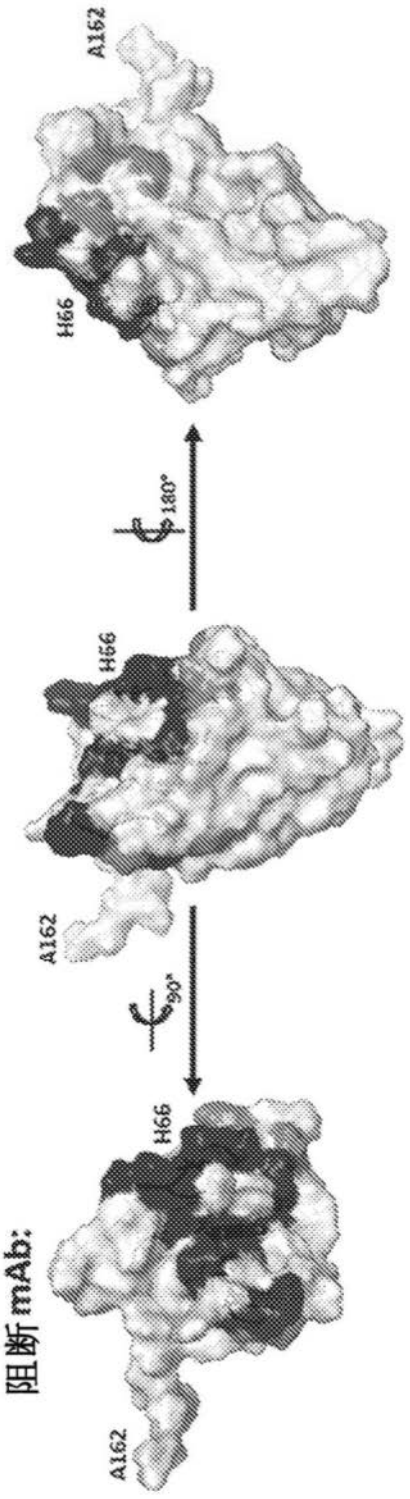


图11B

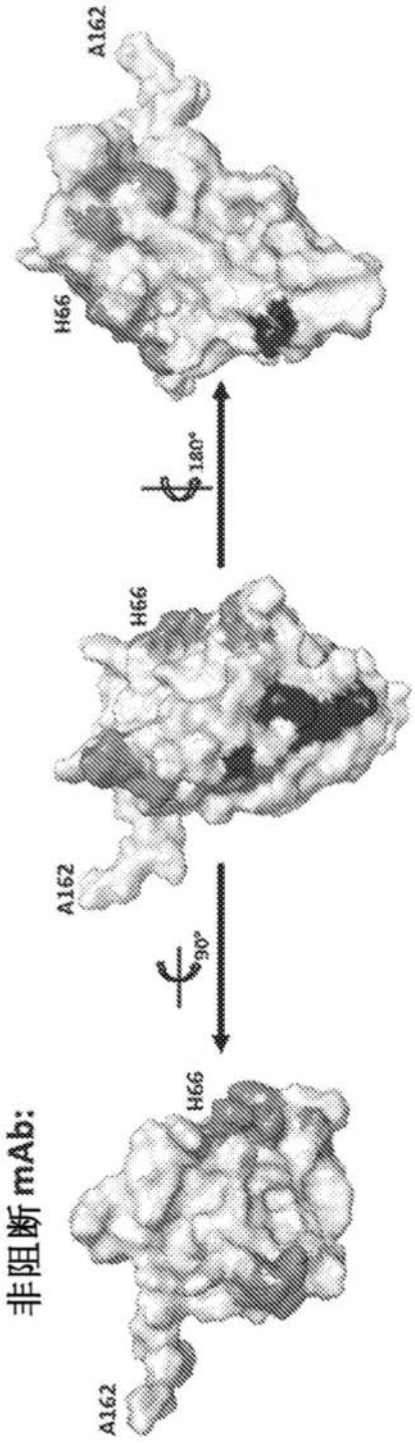


图11C

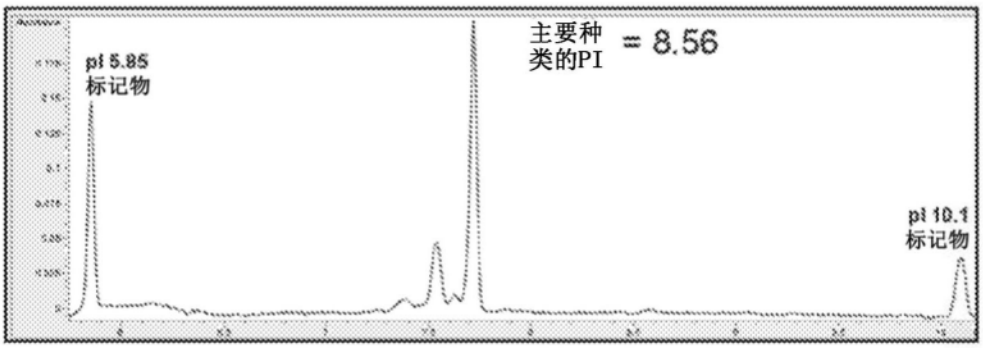


图12A

图12B

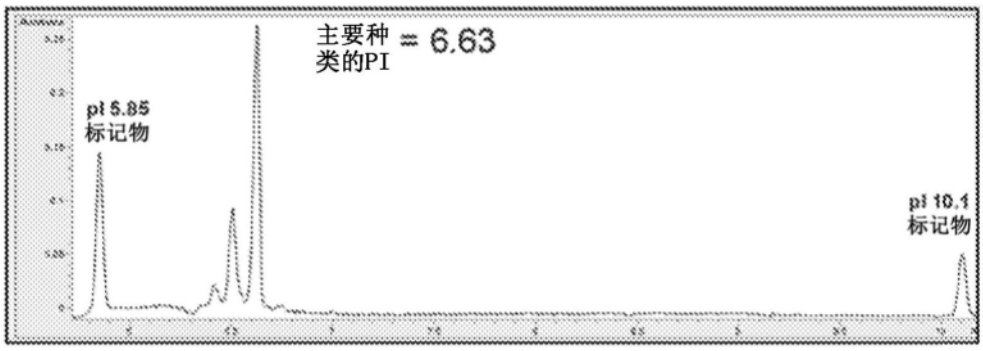


图12C

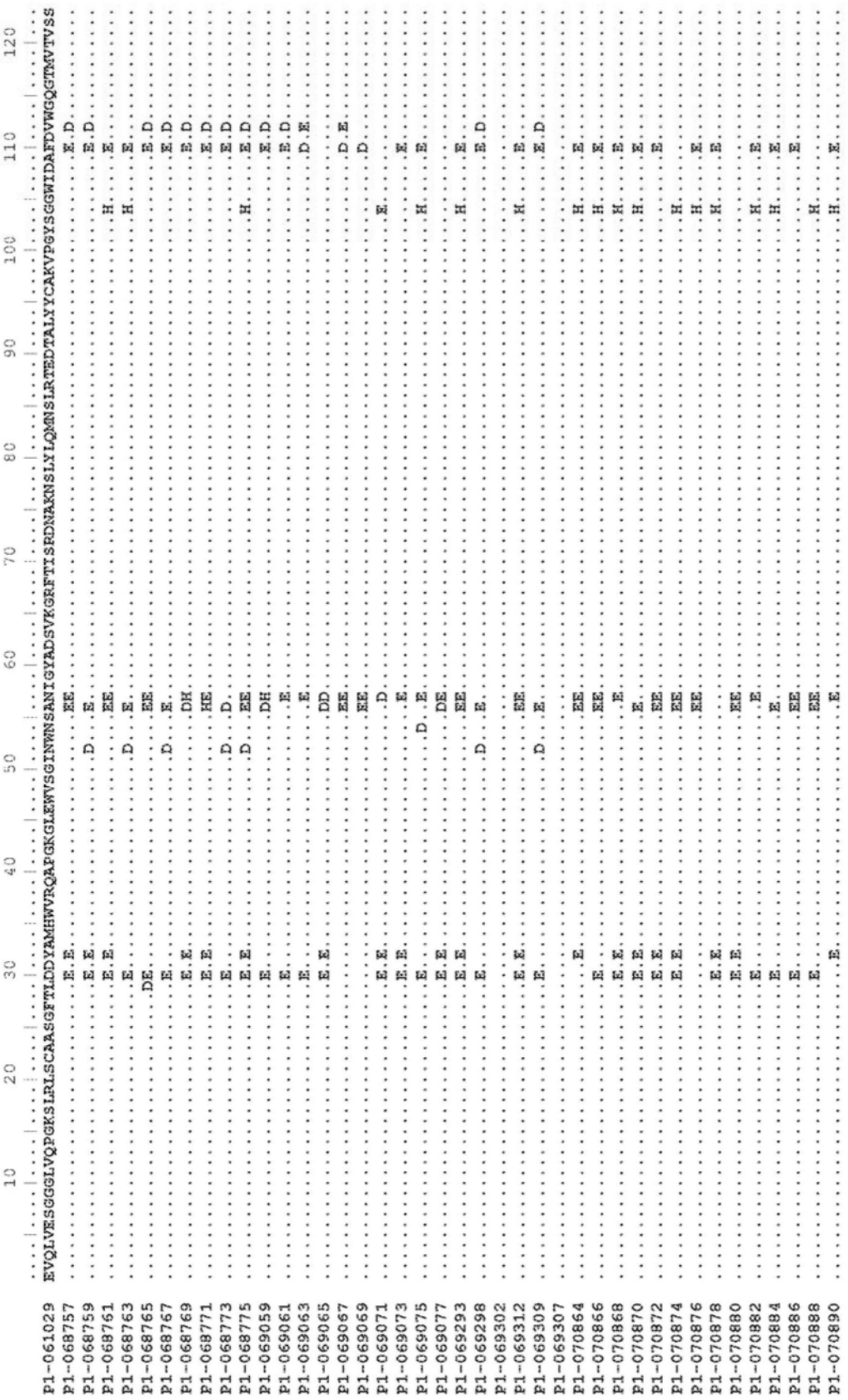


图13A

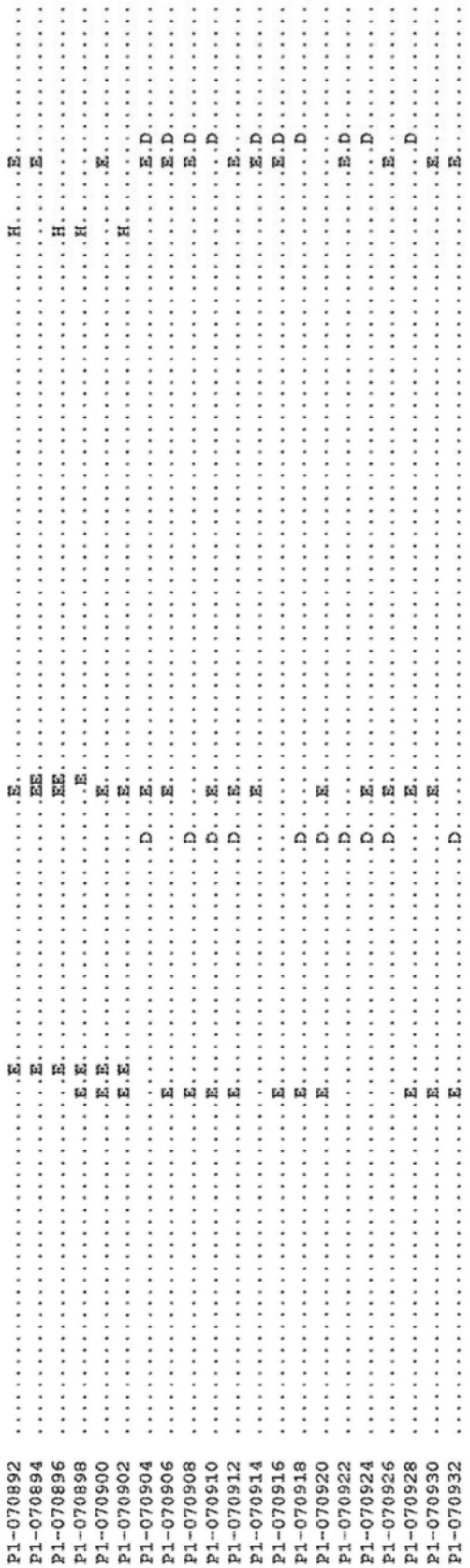

P1-070892
P1-070894
P1-070896
P1-070898
P1-070900
P1-070902
P1-070904
P1-070906
P1-070908
P1-070910
P1-070912
P1-070914
P1-070916
P1-070918
P1-070920
P1-070922
P1-070924
P1-070926
P1-070928
P1-070930
P1-070932

图13A(续)

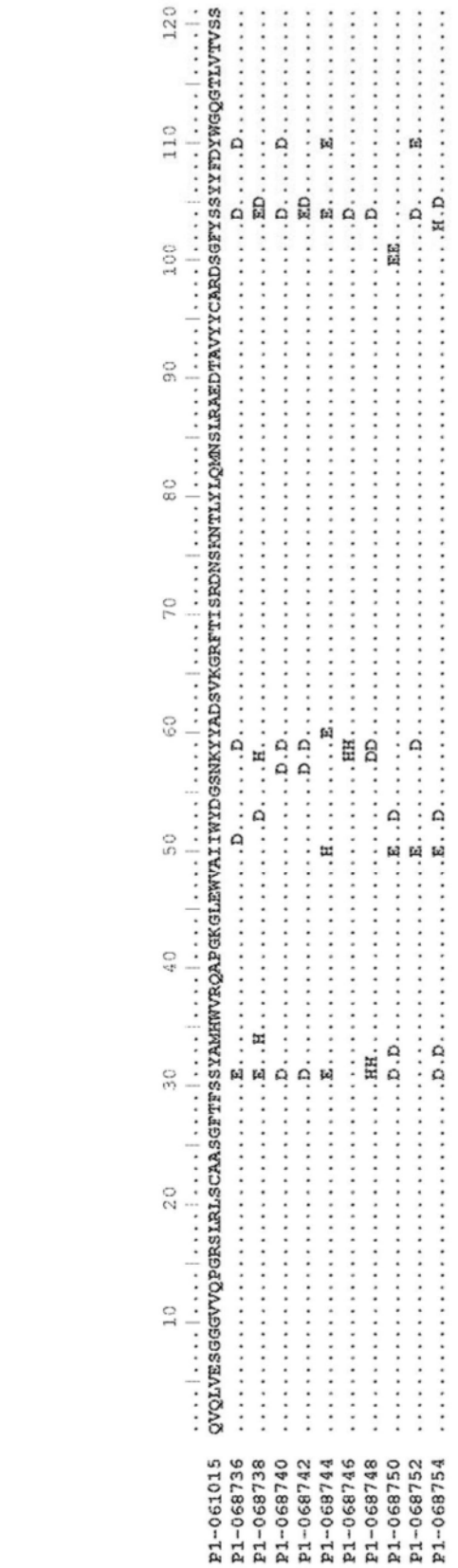

10 20 30 40 50 60 70 80 90 100 110 120
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAIIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDSGFYSSYYFDYWGQGTLVTVSS
P1-061015
P1-068736
P1-068738
P1-068740
P1-068742
P1-068744
P1-068746
P1-068748
P1-068750
P1-068752
P1-068754

图13B