



(12) 发明专利



(10) 授权公告号 CN 111542543 B

(45) 授权公告日 2023. 12. 22

(21) 申请号 201880084814.4

(22) 申请日 2018.12.28

(65) 同一申请的已公布的文献号
申请公布号 CN 111542543 A

(43) 申请公布日 2020.08.14

(66) 本国优先权数据
PCT/CN2017/119505 2017.12.28 CN

(85) PCT国际申请进入国家阶段日
2020.06.29

(86) PCT国际申请的申请数据
PCT/CN2018/124925 2018.12.28

(87) PCT国际申请的公布数据
W02019/129211 EN 2019.07.04

(73) 专利权人 南京传奇生物科技有限公司
地址 211100 江苏省南京市江宁区龙眼大道568号南京生命科技小镇6号楼

(72) 发明人 杨帅 周传初 武术 殷刘松
林峰

(74) 专利代理机构 中国贸促会专利商标事务所
有限公司 11038
专利代理师 孔熹 崔锡强

(51) Int.Cl.
C07K 16/28 (2006.01)
A61K 39/395 (2006.01)
C12N 15/13 (2006.01)
A61P 35/00 (2006.01)

(56) 对比文件
CN 108239149 A, 2018.07.03
CN 104072613 A, 2014.10.01
WO 2017181031 A2, 2017.10.19
CN 107151269 A, 2017.09.12
CN 105968200 A, 2016.09.28
WO 2017084495 A1, 2017.05.26
Brant A Inman等. Atezolizumab: A PD-L1-Blocking Antibody for Bladder Cancer. 《Clinical Cancer Research》. 2017, 第23卷 (第8期), 1886-1890页.

审查员 武雪梅

权利要求书4页 说明书85页
序列表267页 附图26页

(54) 发明名称

针对PD-L1的抗体及其变体

(57) 摘要

提供一种特异性识别PD-L1的抗体诸如单克隆抗体 (mAb) 或其抗原结合片段。还提供药物组合物、或制备及使用所述抗体或其抗原结合片段的方法。

1. 一种分离的抗体或其抗原结合片段,所述抗体或其抗原结合片段包含重链可变结构域VH和轻链可变结构域VL,其特征在于:

(1) 重链可变结构域包含氨基酸序列如SEQ ID NO:75所示的重链CDR1,氨基酸序列如SEQ ID NO:87所示的重链CDR2,及氨基酸序列如SEQ ID NO:102所示的重链CDR3;且轻链可变结构域包含氨基酸序列如SEQ ID NO:123所示的轻链CDR1,氨基酸序列如SEQ ID NO:128所示的轻链CDR2,及氨基酸序列如SEQ ID NO:140所示的轻链CDR3;或

(2) 重链可变结构域包含氨基酸序列如SEQ ID NO:75所示的重链CDR1,氨基酸序列如SEQ ID NO:95所示的重链CDR2,及氨基酸序列如SEQ ID NO:102所示的重链CDR3;且轻链可变结构域包含氨基酸序列如SEQ ID NO:123所示的轻链CDR1,氨基酸序列如SEQ ID NO:128所示的轻链CDR2,及氨基酸序列如SEQ ID NO:140所示的轻链CDR3;或

(3) 重链可变结构域包含氨基酸序列如SEQ ID NO:75所示的重链CDR1,氨基酸序列如SEQ ID NO:96所示的重链CDR2,及氨基酸序列如SEQ ID NO:102所示的重链CDR3;且轻链可变结构域包含氨基酸序列如SEQ ID NO:123所示的轻链CDR1,氨基酸序列如SEQ ID NO:128所示的轻链CDR2,及氨基酸序列如SEQ ID NO:140所示的轻链CDR3;或

(4) 重链可变结构域包含氨基酸序列如SEQ ID NO:75所示的重链CDR1,氨基酸序列如SEQ ID NO:97所示的重链CDR2,及氨基酸序列如SEQ ID NO:102所示的重链CDR3;且轻链可变结构域包含氨基酸序列如SEQ ID NO:123所示的轻链CDR1,氨基酸序列如SEQ ID NO:128所示的轻链CDR2,及氨基酸序列如SEQ ID NO:140所示的轻链CDR3;或

(5) 重链可变结构域包含氨基酸序列如SEQ ID NO:75所示的重链CDR1,氨基酸序列如SEQ ID NO:95所示的重链CDR2,及氨基酸序列如SEQ ID NO:102所示的重链CDR3;且轻链可变结构域包含氨基酸序列如SEQ ID NO:114所示的轻链CDR1,氨基酸序列如SEQ ID NO:128所示的轻链CDR2,及氨基酸序列如SEQ ID NO:140所示的轻链CDR3;或

(6) 重链可变结构域包含氨基酸序列如SEQ ID NO:75所示的重链CDR1,氨基酸序列如SEQ ID NO:96所示的重链CDR2,及氨基酸序列如SEQ ID NO:102所示的重链CDR3;且轻链可变结构域包含氨基酸序列如SEQ ID NO:114所示的轻链CDR1,氨基酸序列如SEQ ID NO:128所示的轻链CDR2,及氨基酸序列如SEQ ID NO:140所示的轻链CDR3;或

(7) 重链可变结构域包含氨基酸序列如SEQ ID NO:75所示的重链CDR1,氨基酸序列如SEQ ID NO:97所示的重链CDR2,及氨基酸序列如SEQ ID NO:102所示的重链CDR3;且轻链可变结构域包含氨基酸序列如SEQ ID NO:114所示的轻链CDR1,氨基酸序列如SEQ ID NO:128所示的轻链CDR2,及氨基酸序列如SEQ ID NO:140所示的轻链CDR3;

所述的抗体或抗原结合片段能够与PD-L1特异性结合。

2. 如权利要求1所述的分离的抗体或其抗原结合片段,其中所述VH选自SEQ ID NO:13、14、15之一,且所述VL为SEQ ID NO:58。

3. 如权利要求1所述的分离的抗体或其抗原结合片段,其中所述VH选自SEQ ID NO:21、22、23之一,且所述VL选自SEQ ID NO:68-70之一。

4. 如权利要求1所述的分离的抗体或其抗原结合片段,其中所述VH选自SEQ ID NO:24-27、29-32之一,且所述VL为SEQ ID NO:68。

5. 如权利要求1至4中任一项所述的分离的抗体或其抗原结合片段,其中所述VH融合至免疫球蛋白的重链恒定区。

6. 如权利要求1至4中任一项所述的分离的抗体或其抗原结合片段,其中所述VL融合至免疫球蛋白的轻链恒定区。

7. 如权利要求1至4中任一项所述的分离的抗体或其抗原结合片段,其中所述抗体或其抗原结合片段与所述PD-L1之间的结合的 K_D 为 10^{-7} M至 10^{-12} M。

8. 如权利要求7所述的分离的抗体或其抗原结合片段,其中所述抗体或其抗原结合片段与所述PD-L1之间的结合的 K_D 为 10^{-8} M至 10^{-12} M。

9. 如权利要求7所述的分离的抗体或其抗原结合片段,其中所述抗体或其抗原结合片段与所述PD-L1之间的结合的 K_D 为 10^{-9} M至 10^{-12} M。

10. 如权利要求1至4中任一项所述的分离的抗体或其抗原结合片段,其为嵌合的、人的、部分人源化的或完全人源化的。

11. 如权利要求10所述的分离的抗体,其还包含人IgG1的恒定结构域。

12. 如权利要求11所述的分离的抗体,其重链氨基酸序列为SEQ ID NO:282、290-292之一,且轻链氨基酸序列为SEQ ID NO:335。

13. 如权利要求11所述的分离的抗体,其重链氨基酸序列为SEQ ID NO:290-292之一,且轻链氨基酸序列为SEQ ID NO:326。

14. 如权利要求11所述的分离的抗体,其重链氨基酸序列为SEQ ID NO:298-300之一,且轻链氨基酸序列为SEQ ID NO:345-347之一。

15. 如权利要求11所述的分离的抗体,其重链氨基酸序列为SEQ ID NO:301-304、306-309之一,且轻链氨基酸序列为SEQ ID NO:345。

16. 如权利要求1至4中任一项所述的分离的抗体或其抗原结合片段,其还包含第二抗体部分,其中所述第二抗体部分能够与第二抗原特异性结合。

17. 如权利要求16所述的分离的抗体或其抗原结合片段,其中所述第二抗体部分为Fab、Fab'、(Fab')₂、Fv、单链Fv(scFv)、scFv-scFv、双抗体或sdAb。

18. 如权利要求16所述的分离的抗体或其抗原结合片段,其中所述第二抗体部分为sdAb。

19. 如权利要求17所述的分离的抗体或其抗原结合片段,其中所述第二抗体部分能够与CTLA-4特异性结合。

20. 如权利要求19所述的分离的抗体或其抗原结合片段,其中,所述第二抗体部分为能够与CTLA-4特异性结合的sdAb。

21. 如权利要求17所述的分离的抗体或其抗原结合片段,其中所述第二抗体部分能够与TIGIT特异性结合。

22. 如权利要求21所述的分离的抗体或其抗原结合片段,其中,所述第二抗体部分为能够与TIGIT特异性结合的sdAb。

23. 如权利要求17所述的分离的抗体或其抗原结合片段,其中所述第二抗体部分能够与TIM-3特异性结合。

24. 如权利要求23所述的分离的抗体或其抗原结合片段,其中,所述第二抗体部分为能够与TIM-3特异性结合的sdAb。

25. 如权利要求17所述的分离的抗体或其抗原结合片段,其中所述第二抗体部分能够与LAG-3特异性结合。

26. 如权利要求25所述的分离的抗体或其抗原结合片段,其中,所述第二抗体部分为能够与LAG-3特异性结合的sdAb。

27. 如权利要求20、22、24或26中任一项所述的分离的抗体或其抗原结合片段,其中能够特异性识别PD-L1的全长IgG的重链或轻链的氨基末端任选地经由肽接头融合至能够与CTLA-4、TIGIT、TIM-3或LAG-3特异性结合的所述sdAb的羧基末端。

28. 如权利要求20、22、24或26中任一项所述的分离的抗体或其抗原结合片段,其中能够特异性识别PD-L1的全长IgG的重链或轻链的羧基末端任选地经由肽接头融合至能够与CTLA-4、TIGIT、TIM-3或LAG-3特异性结合的所述sdAb的氨基末端。

29. 如权利要求27所述的分离的抗体或其抗原结合片段,其中能够特异性识别PD-L1的所述全长IgG经由SEQ ID NO:397-399之一的肽接头融合至能够与CTLA-4、TIGIT、TIM-3或LAG-3特异性结合的所述sdAb。

30. 一种药物组合物,其包含如权利要求1至29中任一项所述的分离的抗体或其抗原结合片段及药学上可接受的载剂。

31. 如权利要求1至29中任一项所述的分离的抗体或其抗原结合片段或如权利要求30所述的药物组合物在制备治疗PD-L1相关疾病的药物中的应用。

32. 如权利要求31所述的分离的抗体或其抗原结合片段或药物组合物的应用,其中所述PD-L1相关疾病为癌症。

33. 如权利要求32所述的分离的抗体或其抗原结合片段或药物组合物的应用,其中所述癌症为实体肿瘤。

34. 如权利要求32所述的分离的抗体或其抗原结合片段或药物组合物的应用,其中所述癌症为结肠癌。

35. 如权利要求31所述的分离的抗体或其抗原结合片段或药物组合物的应用,其与另外的癌症疗法组合。

36. 如权利要求35所述的分离的抗体或其抗原结合片段或药物组合物的应用,其中所述另外的癌症疗法为手术、放射、化学疗法、免疫疗法、激素疗法或其组合。

37. 如权利要求31所述的分离的抗体或其抗原结合片段或药物组合物的应用,其中所述PD-L1相关疾病为病原性感染。

38. 如权利要求31至37中任一项所述的分离的抗体或其抗原结合片段或药物组合物的应用,其中所述分离的抗体或抗原结合片段或药物组合物用于全身或局部施用。

39. 如权利要求31至37中任一项所述的分离的抗体或其抗原结合片段或药物组合物的应用,其中所述分离的抗体或抗原结合片段或药物组合物用于静脉内施用。

40. 如权利要求31至37中任一项所述的分离的抗体或其抗原结合片段或药物组合物的应用,其中所述分离的抗体或抗原结合片段或药物组合物用于肿瘤内施用。

41. 如权利要求31至37中任一项所述的分离的抗体或其抗原结合片段或药物组合物的应用,其中所述受试者为人。

42. 一种编码如权利要求1-29中任一项所述的分离的抗体或其抗原结合片段的核酸分子。

43. 一种载体,所述载体包含如权利要求42所述的核酸分子。

44. 一种宿主细胞,所述宿主细胞包含如权利要求42所述的核酸或如权利要求43所述

的载体。

针对PD-L1的抗体及其变体

[0001] 对以电子方式提交的序列表的引用

[0002] 本申请含有序列表,其作为ASCII格式序列表经由EFS-Web以电子方式提交,文件名为“688096.119序列表”,创建日期为2017年12月26日,且大小为约546KB。经由EFS-Web提交的序列表为本发明的一部分且以全文引用的方式并入本文。

技术领域

[0003] 本申请涉及能够与PD-L1蛋白特异性结合的抗体或其抗原结合片段以及此类药剂的用途。在一些实施方案中,本申请涉及针对PD-L1的小鼠及人源化单克隆抗体以及这些抗体的用途。所述抗体或其抗原结合片段可用作诊断剂且可用于治疗与PD-L1的活性和/或表达相关联的疾病。

背景技术

[0004] 体液免疫(经B细胞介导)及细胞免疫(经T细胞介导)是人获得性免疫系统对抗体外感染及体内病理变化的两种武器。T细胞作为免疫系统中的重要成员,在肿瘤免疫疗法中起到必不可少的作用。T细胞活化是传统细胞因子药物及新提出的免疫检查点药物二者消除癌细胞的重要机制(Esther等人,physiol,25(2):85-101,2010;Drew,Nature Reviews Cancer 12:252-264,2012)。

[0005] T细胞活化有两个信号步骤。第一步为通过TCR识别MHC所呈递的抗原来活化的主要刺激。此信号为抗原特异性的。T细胞活化的第二类信号也称为共刺激信号(Jennifer等人,Annu Rev Immunol,27:591-619,2009)。相比之下,T细胞还接收一些共抑制信号。这些刺激或抑制T细胞功能的生物分子被称为免疫检查点分子。免疫检查点疗法的目的为通过免疫检查点控制T细胞的刺激或抑制信号来杀死肿瘤细胞并最终治愈癌症(Suzanne等人,Cancer Cell 27(4):450-461,2015)。

[0006] 程序性细胞死亡蛋白1(PD-1)为一种细胞表面受体,其通过抑制T细胞发炎活性在下调免疫系统及促进自身耐受性中起到重要作用。PD-1为免疫检查点且通过促进淋巴结中抗原特异性T细胞的细胞凋亡(程序性细胞死亡)同时减少调节性T细胞(消炎、抑制性T细胞)的细胞凋亡的双重机制来预防自身免疫(Francisco等人,Immunological Reviews.236:219-42,2010;Fife等人,Annals of the New York Academy of Sciences.1217:45-59,2011)。通过这些机制,PD-1抑制免疫系统。此举预防自身免疫疾病,但其也可妨碍免疫系统杀死癌细胞。一类新的阻断PD-1的药物(即PD-1抑制剂)激活免疫系统以攻击肿瘤且因此在用于治疗一些类型的癌症中取得不同程度的成功。

[0007] 已开发出许多靶向PD-1受体的癌症免疫疗法药剂。一种此类抗PD-1抗体药物纳武单抗(nivolumab)(Opdivo-Bristol Myers Squibb)于2014年7月被日本且于2014年12月被US FDA批准治疗转移性黑素瘤。另一抗PD-1抗体药物为派姆单抗(Pembrolizumab)(Keytruda,MK-3475,Merck),其于2014年9月被FDA批准治疗转移性黑素瘤。英国晚期黑素瘤患者可经由2015年3月的英国早期获得药物计划(Early Access to Medicines Scheme;

EAMS) 获得派姆单抗。其在美国正用于肺癌、淋巴瘤及间皮瘤的临床试验中。其已获得一定的成功,副作用小。2015年10月2日,派姆单抗被FDA批准用于在其他治疗之后疾病进展的晚期(转移性)非小细胞肺癌(NSCLC)患者。

[0008] PD-1结合两种配体,程序性死亡配体1(PD-L1)及程序性死亡配体2(PD-L2)。PD-L1为大小约53kDa的单跨膜蛋白且同样为非常重要的免疫检查点分子。PD-1与PD-L1结合将激活减少T细胞活性及增殖的共抑制信号。在人体中,PD-L1表达于许多免疫细胞类型包括活化的及免疫无能的/耗竭的T细胞上,于天然及活化B细胞上,以及于脊髓树突状细胞(DC)、单核细胞及肥大细胞上。其也表达于非免疫细胞上,包括胰岛、肝枯否(Kupffer)细胞、血管内皮及经选择的上皮细胞例如气道上皮细胞及肾小管上皮细胞,在所述细胞中其表达在发炎事件期间增强。PD-L1表达也以增加的水平存在于许多肿瘤上,包括但不限于乳腺癌、结肠癌、结肠直肠癌、肺癌、肾癌(包括肾细胞癌)、胃癌、膀胱癌、非小细胞肺癌(NSCLC)、肝细胞癌(HCC)及胰脏癌以及黑素瘤。过度表达的PD-L1将大大抑制T细胞对肿瘤细胞的毒性并帮助肿瘤细胞避开T细胞监视及消除(Dong等人,Nat Med;8:793-800,2002)。

[0009] 抑制PD-1与PD-L1之间的结合的PD-L1单克隆抗体减弱或阻断PD-L1对T细胞施加的下调信号传导,且因此恢复T细胞对免疫原的活性。目前,PD-L1单克隆抗体用于对抗许多人癌症的临床研究,包括非小细胞肺癌、黑素瘤、结肠直肠癌、肾细胞癌、卵巢癌、前列腺癌、胃癌及乳腺癌(Julie等人,N Engl Med 366:2455-2465,2012)。

[0010] FDA于2016年批准第一种抗PD-L1抗体药物。此药物由Genentech开发且名为阿特珠单抗(atezolizumab)(商标名Tecentriq)以治疗晚期膀胱癌。所述药物证明,此特别的分子可成功地用于临床阶段的免疫检查点疗法中。临床前研究已证明,针对不同免疫检查点分子的抗体可协同地作用以治愈癌症(Mace等人,Journal for Immuno Therapy of cancer 3:366,2015;Lussier等人,Journalfor Immuno Therapy of Cancer 3:21,2015)。有临床研究测试PD-L1抗体与其他免疫检查点抑制单克隆抗体或小分子的组合疗法以治疗不同癌症。

[0011] 度伐鲁单抗(durvalumab)为另一种FDA批准的抗PD-L1抗体药物,其由Medimmune/AstraZeneca开发。度伐鲁单抗被批准用于治疗具有局部晚期或转移性泌尿上皮癌的患者,所述患者在含铂化疗期间或之后具有疾病进展或在以含铂化疗进行的新辅助或辅助治疗的12个月内具有疾病进展。

发明内容

[0012] 本申请涉及针对PD-L1蛋白的靶向结合剂以及其制备和使用方法。

[0013] 在一般方面中,本申请涉及一种分离的抗体或其抗原结合片段,其包含:

[0014] (a) 重链可变结构域(VH),其包含

[0015] i. 重链CDR1,其包含选自由SEQ ID NO:71-82组成的组的氨基酸序列;

[0016] ii. 重链CDR2,其包含分别选自由SEQ ID NO:83-94组成的组的氨基酸序列,其中SEQ ID NO:87任选地由SEQ ID NO:95-97中的任一者置换;及

[0017] iii. 重链CDR3,其包含分别选自由SEQ ID NO:98-109组成的组的氨基酸序列;及

[0018] (b) 轻链可变结构域(VL),其分别包含,

[0019] i. 轻链CDR1,其包含选自由SEQ ID NO:110-121组成的组的氨基酸序列,其中SEQ

ID NO:111任选地由SEQ ID NO:122置换,且SEQ ID NO:114任选地由SEQ ID NO:123置换;

[0020] ii.轻链CDR2,其包含分别选自SEQ ID NO:124-135组成的组的氨基酸序列;及

[0021] iii.轻链CDR3,其包含分别选自SEQ ID NO:136-147组成的组的氨基酸序列,

[0022] 其中所述抗体或抗原结合片段能够与PD-L1优选人PD-L1特异性结合。

[0023] 优选地,本申请的抗体或其抗原结合片段与PD-L1(优选地,人PD-L1)之间的结合的 K_D 为 10^{-7} M至约 10^{-12} M、优选约 10^{-8} M至约 10^{-12} M、更优选约 10^{-9} M至约 10^{-12} M或更小。

[0024] 本申请的抗体或其抗原结合片段可为啮齿动物的、嵌合的、人的、部分人源化的或完全人源化的。其也可作为双特异性的,还包含能够与第二抗原诸如CTLA-4、TIGIT、TIM-3或LAG-3特异性结合的第二抗体部分。优选地,第二抗体部分为单结构域抗体(sdAb)。

[0025] 进一步提供一种药物组合物,其包含本申请的任一分离的抗PD-L1抗体或其抗原结合片段及药学上可接受的载剂。

[0026] 本申请的另一方面提供一种治疗患有PD-L1相关疾病的个体的方法,其包括向所述个体施用有效量的上文所述的任一药物组合物。在一些实施方案中,PD-L1相关疾病为癌症。在一些实施方案中,癌症为实体肿瘤,诸如结肠癌。在一些实施方案中,所述方法进一步包括向所述个体施用另外的癌症疗法,诸如手术、放射、化学疗法、免疫疗法、激素疗法或其组合。在一些实施方案中,PD-L1相关疾病为病原性感染。在一些实施方案中,药物组合物是全身施用,例如静脉内(i.v.)施用。在一些实施方案中,药物组合物是局部施用,例如肿瘤内施用。在一些实施方案中,所述个体为人。

[0027] 本发明的其他方面、特征及优点将从以下公开内容(包括具体实施方式及其优选实施方案以及随附权利要求)显而易见。

附图说明

[0028] 前述发明内容以及以下具体实施方式当结合随附图式阅读时将更好理解。出于说明本发明的目的,在附图中示出目前优选的实施方案。然而应理解,本发明不限于所示的精确布置和手段。在附图中:

[0029] 图1描绘以重组PD-L1 ECD蛋白第4次免疫之后经免疫的小鼠的免疫反应。

[0030] 图2A-2L描绘PD-L1过表达稳定细胞系与根据本申请的实施方案的小鼠单克隆抗体(mAb)之间的结合亲和力,更具体地,图2A:1H1G4D9;图2B:18B7G2;图2C:21D1F4D4;图2D:25B6E5D8;图2E:25G1F9F8;图2F:27D3D3G2;图2G:29A8H8C7;图2H:30A6B2D9;图2I:30A7B5D9;图2J:42G2D7C3;图2K:51F3D2G4;且图2L:53C1F3D4。

[0031] 图3A-3J描绘根据本申请的实施方案的小鼠mAb对PD-L1细胞系与其受体PD-1ECD蛋白之间的相互作用的阻断作用,更具体地,图3A:1H1G4D9;图3B:21D1F4D4;图3C:25G1F9F8;图3D:27D3D3G2;图3E:29A8H8C7;图3F:30A6B2D9;图3G:30A7B5D9;图3H:42G2D7C3;图3I:51F3D2G4;且图3J:53C1F3D4。

[0032] 图4A-4H描绘通过基于PD-L1细胞的报告基因测定的根据本申请的实施方案的小鼠mAb的功能活性评估,更具体地,图4A:18B7F4G8;图4B:27D3D3G2;图4C:29A8H8C7;图4D:42G2D7C3;图4E:51F3D2G4;且图4F:53C1F3D4,以及度伐鲁单抗(阳性抗PD-L1抗体对照)(图4G)及人IgG1同型对照mAb(图4H)。

[0033] 图5A-5F描绘通过混合淋巴细胞反应(MLR)测定的根据本申请的实施方案的小鼠

mAb的功能活性评估,更具体地,图5B:29A8H8C7;图5C:53C1F3D4;FIG. 5E:27D7G3D4;且图5F:18B7F4G8,以及阿特殊单抗(阳性抗PD-L1抗体对照)(图5A及5D)。

[0034] 图6A-6D描绘根据本申请的实施方案的两种小鼠mAb29A8H8C7(图6A)及53C1F3D4(图6B)的单价结合亲和力测定。也测定阿特殊单抗(图6C)及度伐鲁单抗(图6D)的结合亲和力以供比较。

[0035] 图7A-7J描绘根据本申请的实施方案的嵌合抗体29A8H8C7(图7A)及嵌合53C1F3D4(图7B)、3种人源化29A8H8C7(图7C-7E)及5种人源化53C1F3D4(图7F-7J)与带His标签的人PD-L1的单价结合亲和力测定。

[0036] 图8A-8L描绘根据本申请的实施方案的嵌合抗体29A8H8C7(图8A)及53C1F3D4(图8B)、3种人源化29A8H8C7(图8C-8E)、5种人源化53C1F3D4(图8F-8J)以及阳性对照抗体阿特殊单抗(图8K)及度伐鲁单抗(图8L)与食蟹猴PD-L1 Fc-融合蛋白的单价结合亲和力测定。

[0037] 图9A-9L描绘人PD-L1过表达稳定细胞系与根据本申请的实施方案的嵌合(图9A及图9E)或人源化抗体(图9B-9D及图9F-9J)之间的结合亲和力。度伐鲁单抗(图9K)及阿特殊单抗(图9L)用作抗PD-L1阳性对照。

[0038] 图10A-10L描绘食蟹猴PD-L1过表达稳定细胞系与根据本申请的实施方案的嵌合抗体(图10A及图10E)及人源化抗体(图10B-10D及图10F-10J)之间的结合亲和力。度伐鲁单抗(图10K)及阿特殊单抗(图10L)用作抗PD-L1阳性对照。

[0039] 图11A-11L描绘根据本申请的实施方案的嵌合mAb(图11A及图11E)及人源化mAb(图11B-11D及图11F-11J)对PD-L1细胞系及其受体PD-1ECD蛋白之间的相互作用的阻断作用。度伐鲁单抗(图11K)及阿特殊单抗(图11L)用作抗PD-L1阳性对照。

[0040] 图12A-12L描绘通过基于PD-L1细胞的报告基因测定的根据本申请的实施方案的嵌合mAb(图12A及图12E)及人源化mAb(图12B-12D及图12F-12J)的功能活性评估。度伐鲁单抗(图12K)及阿特殊单抗(图12L)用作抗PD-L1阳性对照。

[0041] 图13A-13I描绘通过混合淋巴细胞反应(MLR)测定的根据本申请的实施方案的6种人源化mAb(图13B-13C、图13E-13F及图13H-13I)及度伐鲁单抗(阳性抗PD-L1抗体对照)(图13A、图13D及图13G)的功能活性评估。

[0042] 图14A-14G描绘以根据本申请的实施方案的人源化抗体及基准抗体度伐鲁单抗治疗之后的肿瘤生长。图14A-14E描绘治疗之后个别携带肿瘤的小鼠的肿瘤体积。图14F描绘治疗之后五组携带肿瘤的小鼠的平均肿瘤体积。图14G描绘在研究结束时五组携带肿瘤的小鼠的平均体重。

具体实施方式

[0043] 先前技术中及本说明书通篇引用或描述各种出版物、文章及专利;这些引用各自以全文引用的方式并入本文。已包括在本说明书中的文件、法令、材料、装置、物品或诸如此类的讨论是出于为本发明提供情境的目的。此类讨论并非承认任一或所有这些事项形成关于所公开或主张的任何发明的先前技术的一部分。

[0044] 除非另外定义,否则本文所用的所有技术及科学术语均具有与本发明所属领域的技术人员通常所理解相同的含义。否则,本文所用的某些术语具有如本说明书中所阐述的含义。本文所引用的所有专利、公开的专利申请及公布如同在本文中充分陈述一般以引用

的方式并入。

[0045] 所属领域技术人员应理解,描述具有广泛应用且涵盖可考虑的各种章节、段落及句子的所有组合。任一实施方案的讨论仅意指示例性且并不旨在表明本公开(包括权利要求)的范围限于这些实例。

[0046] 本申请提供与PD-L1特异性结合的抗体(尤其单克隆抗体(mAb))或其抗原结合片段(下文也称为“抗PD-L1 mAb”)及其作为治疗PD-L1相关疾病诸如癌症的新策略的用途。

[0047] 据此,本申请的一个方面提供一种能够特异性识别PD-L1(优选人PD-L1)的分离的抗体(优选单克隆抗体)或其抗原结合片段。分离的抗PD-L1抗体可为全长抗PD-L1 mAb(例如,鼠类或人源化)、包含融合至另一抗体(诸如单结构域抗体(sdAb))或另一抗体的抗原结合片段的抗PD-L1 mAb或其抗原结合片段的蛋白或多肽。抗PD-L1抗体可为单特异性的或多特异性的、单价的或多价的。

[0048] 还提供包含本申请的分离的抗体(优选单克隆抗体)或其抗原结合片段的组合物(诸如药物组合物)、试剂盒及制品,以及制备所述分离的抗体或其抗原结合片段、所述组合物、试剂盒及制品的方法,及使用本申请的所述组合物、试剂盒及制品治疗PD-L1相关疾病(诸如癌症)的方法。

[0049] I. 定义

[0050] 必须注意的是,除非上下文另外明确规定,否则如本文及随附权利要求中所用,单数形式“一(a/an)”及“所述(the)”包括多个指示物。

[0051] 除非另外说明,否则处于一系列要素之前的术语“至少”应理解为表示所述系列中的每一要素。所属领域技术人员将仅使用常规实验即会认识到或能够确定本文所述的本发明的特定实施方案的许多等效物。此类等效物旨在由本发明涵盖。

[0052] 除非上下文另外要求,否则在整个本说明书及随附权利要求中,用语“包含(comprise)”及变型(诸如包含“comprises”及包含“comprising”)应理解为意指包括所述整数或步骤或者整数或步骤的群组,而不排除任何其他整数或步骤或者整数或步骤的群组。当在本文中使用时,术语“包含”可替代为术语“含有”或“包括”,或者有时在本文中使用时可替代为术语“具有”。

[0053] 当在本文中使用时,“由……组成”排除在所主张要素中未指明的任何要素、步骤或成分。当在本文中使用时,“基本上由……组成”不排除对所主张的基本及新颖特征不产生实质性影响的材料或步骤。每当在本文用于本申请的方面或实施方案的上下文中使用时,任何前述术语“包含”、“含有”、“包括”及“具有”可由术语“由……组成”或“基本上由……组成”置换以改变本公开的范围。

[0054] 如本文所用,多个所述要素之间的连接术语“和/或”应理解为涵盖个体及组合选项两者。例如,当两个要素通过“和/或”结合时,第一选项是指第一要素在无第二要素的情况下的适用性。第二选项是指第二要素在无第一要素的情况下的适用性。第三选项是指第一要素及第二要素一起的适用性。这些选项的任一者均理解为落在所述含义内,且因此满足如本文所用的术语“和/或”的要求。多于一个选项的同时适用性也理解为落在所述含义内,因此满足术语“和/或”的要求。

[0055] 除非以其他方式说明,在本文中描述的任何数值诸如浓度或浓度范围应理解为在所有情况下均受到用语“约(about)”的修饰。因此,数值通常包括所述值的 $\pm 10\%$ 。例如,浓

度1mg/mL包括0.9mg/mL至1.1mg/mL。同样,浓度范围1mg/mL至10mg/mL包括0.9mg/mL至11mg/mL。除非上下文另有明确指出,否则如本文所用,数值范围的使用明确地包括所述范围内的所有可能的子范围、所有单独数值,包括这些范围内的整数及所述值的分数。

[0056] 术语“程序性细胞死亡1配体1”、“PD-L1”、“B7同源物1 (B7-H1)”、“PD-L1抗原”、“PDCD1配体1”及“CD274”(参见例如Chemnitz (2004) *J. Immunol.* 173:945-954)可互换使用,且包括人PD-L1的变体、同功型、物种同源物,及具有至少一个与PD-L1共有的表位的类似物(参见例如Butte (2008) *Mol Immunol.* 45:3567-3572)。因此,在某些实施方案中,本申请的抗PD-L1构建体可与来自除人之外的物种的PD-L1或在结构上与人PD-L1相关的其他蛋白(例如,人PD-L1同源物)交叉反应。在其他实施方案中,本申请的抗PD-L1构建体可对人PD-L1具有完全特异性,且不表达出物种或其他类型的交叉反应性。

[0057] 术语“人PD-L1”是指人序列PD-L1或其衍生物。例如,人PD-L1可具有GenBank登录号Q9NZQ7的氨基酸序列。人PD-L1也可通过具有例如保守突变或在非保守区中的突变而具有与Genbank登录号Q9NZQ7的人PD-L1不同的氨基酸序列,且所述PD-L1具有与Genbank登录号Q9NZQ7的人PD-L1实质上相同的生物学功能。例如,人PD-L1的生物学功能是PD-L1的细胞外结构域中具有表位,其特异性地由本发明的抗PD-L1构建体来结合或人PD-L1的生物学功能是T细胞活性的调节。

[0058] 术语“表位”意指能够与抗体特异性结合的蛋白决定子。表位通常由分子的化学活性表面分组诸如氨基酸或糖侧链组成且通常具有具体的三维结构特征以及具体的电荷特征。构象表位与非构象表位的区别在于:在变性溶剂存在下,丧失与前者的结合而未丧失与后者的结合。

[0059] 如本文所用的术语“程序性细胞死亡1 (PD-1)”旨在指代属于免疫球蛋白超家族且在T细胞及前B细胞上表达的细胞表面受体。人PD-1的示例性氨基酸序列在Genbank登录号NP_005009.2中公开。

[0060] 如本文所用,“治疗(treatment)”或“治疗(treating)”用于获得有利或所需结果(包括临床结果)的方法。出于本发明的目的,有益或期望的临床结果包括但不限于以下一种或多种:缓解由疾病引起的一种或多种症状,减少疾病的程度,稳定疾病(例如,预防或延迟疾病的恶化),预防或延迟疾病的传播(例如,转移),预防或延迟疾病的复发,延迟或减缓疾病的进展,改善疾病状态,提供疾病的缓解(部分或全部),减少治疗疾病所需的一种或多种其他药物的剂量,延迟疾病的进展,提高生活品质和/或延长生存期。“治疗”也涵盖降低癌症的病理后果。本发明的方法考虑这些治疗方面中的任何一种或多种。

[0061] 本文所用的术语“有效量”是指足以治疗特定病症、病状或疾病诸如改善、缓和、减轻和/或延迟其症状中的一种或多种的药剂或药剂组合的量。关于癌症,有效量包括足以引起肿瘤缩小和/或降低肿瘤生长速率(诸如抑制肿瘤生长)或预防或延迟其他不需要的细胞增殖的量。在一些实施方案中,有效量是足以延缓发展的量。在一些实施方案中,有效量是足以预防或延缓复发的量。有效量可以一次或多次施用的形式施用。有效量的药物或组合物可:(i)减少癌细胞的数量;(ii)减小肿瘤大小;(iii)在一定程度上抑制、延缓、减缓并优选阻止癌细胞浸润到外周器官中;(iv)抑制(即,在某种程度上减缓并且优选地停止)肿瘤转移;(v)抑制肿瘤生长;(vi)预防或延迟肿瘤的发生和/或复发;和/或(vii)在一定程度上缓解与癌症相关的一种或多种症状。

[0062] 术语“抗体”、“抗体部分”或“抗体构建体”以其最广泛意义使用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)、全长抗体及其抗原结合片段,只要其展现所要抗原结合活性即可。

[0063] 基本的4链抗体单元为由两个相同轻(L)链及两个相同重(H)链组成的异四聚糖蛋白。IgM抗体由5个基本的异四聚体单元连同称为J链的另外的肽组成,且含有10个抗原结合位点,而IgA抗体包含2-5个基本的4链单元,所述单元可聚合以与J链组合而形成多价集合体。在IgG的情况下,4链单元一般为约150,000道耳顿。各L链通过共价二硫键连接至H链,而两个H链取决于H链同型而通过一个或多个二硫键彼此连接。各H链及L链也具有规则隔开的链内二硫桥。各H链在N末端具有可变结构域(V_H),接着对于 α 及 γ 链的各者而言为三个恒定结构域(C_H),且对于 μ 及 ϵ 同型而言为四个 C_H 结构域。各L链在N末端具有可变结构域(V_L),接着在其另一端为恒定结构域。 V_L 与 V_H 对齐,且 C_L 与重链的第一恒定结构域(C_H1)对齐。据信特定氨基酸残基形成轻链可变结构域与重链可变结构域之间的界面。将 V_H 及 V_L 配对在一起形成单一抗原结合位点。不同类别抗体的结构及性质参见例如Basic and Clinical Immunology,第8版,Daniel P.Sties,Abba I.Terr及Tristram G.Parslow(编),Appleton& Lange,Norwalk,Conn.,1994,第71页及第6章。任何脊椎动物物种的L链可基于其恒定结构域的氨基酸序列归于两种截然不同类型(称为 κ 及 λ)之一。取决于其重链恒定结构域(C_H)的氨基酸序列,免疫球蛋白可归于不同类别或同型。有五类免疫球蛋白:IgA、IgD、IgE、IgG及IgM,其具有分别称为 α 、 δ 、 ϵ 、 γ 及 μ 的重链。 γ 及 α 类基于 C_H 序列及功能的相对较小的差异被进一步分成亚类,例如,人表达以下亚类:IgG1、IgG2A、IgG2B、IgG3、IgG4、IgA1及IgA2。

[0064] 术语“仅有重链的抗体”或“HCAb”是指功能性抗体,其包含重链,但缺少通常在4-链抗体中发现的轻链。已知骆驼科动物(例如骆驼、美洲驼或羊驼)产生HCAb。

[0065] 术语“单结构域抗体”或“sdAb”是指具有三个互补决定区(CDR)的单一抗原结合多肽。单独sdAb能够在不与相应含CDR多肽配对的情况下结合至抗原。在一些情况下,单结构域抗体由骆驼科HCAb改造,并且其重链可变结构域在本文中称为“ V_HH ”(重链抗体重链的可变结构域)。一些 V_HH 也可称为纳米抗体。骆驼科动物sdAb是已知最小的抗原结合抗体片段之一(参见,例如,Hamers-Casterman等人,Nature 363:446-8(1993);Greenberg等人,Nature 374:168-73(1995);Hassanzadeh-Ghassabeh等人,Nanomedicine(Lond),8:1013-26(2013))。基本 V_HH 具有从N末端到C末端的以下结构:FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4,其中FR1至FR4分别指框架区1至4,并且其中CDR1至CDR3是指互补决定区1至3。

[0066] “分离”抗体是已经从其生产环境(例如天然或重组)的组分中鉴定、分离和/或回收的抗体。优选地,分离的多肽不与来自其产生环境的所有其他组分缔合。来自其产生环境的污染物组分(诸如由重组转染细胞导致的那些组分)是通常干扰抗体的研究、诊断或治疗用途的物质,并且可包括酶、激素及其他蛋白质或非蛋白质溶质。在优选实施方案中,将多肽被纯化至:(1)如例如通过劳里法(Lowry method)所确定的大于95重量%抗体,并且在一些实施方案中大于99重量%;(2)足以通过使用旋杯式测序仪获得N末端或内部氨基酸序列的至少15个残基的程度,或者(3)均质,通过使用考马斯蓝(Coomassie Blue)或优选地银染色法,在非还原或还原条件下进行SDS-PAGE。分离的抗体包括重组细胞内的原位抗体,因为抗体的天然环境的至少一种组分将不存在。然而,分离的多肽、抗体或构建体通常将通过至少一个纯化步骤来制备。

[0067] 抗体的“可变区”或“可变结构域”是指抗体重链或轻链的氨基末端结构域。重链及轻链的可变结构域可分别称为“ V_H ”及“ V_L ”。这些结构域通常是抗体的最易变部分(相对于相同类别的其他抗体)并且包含抗原结合位点。来自骆驼科物种的仅有重链的抗体具有单个重链可变区,其被称为“ V_HH ”。因此 V_HH 是一种特殊类型的 V_H 。

[0068] 术语“可变”是指如下实情,即在各抗体之间可变结构域的某些区段在序列上有很大差异。 V 结构域介导抗原结合且限定具体抗体对其具体抗原的特异性。然而,可变性未在可变结构域的整体跨度内均匀地分布。而是,其集中于轻链及重链可变结构域中的称为互补决定区(CDR)或超变区(HVR)的三个区段中。可变结构域的更高度保守部分称为框架区(FR)。天然重链及轻链的可变结构域各自包含四个FR区,其主要采用 β -折叠构型,由三个CDR连接,所述CDR形成连接 β -折叠结构的环且在一些情况下形成 β -折叠结构的一部分。各链中的CDR通过FR区紧密地保持在一起,且与来自另一链的CDR一起促进形成抗体的抗原结合位点(参见Kabat等人,Sequences of Immunological Interest,第五版,National Institute of Health,Bethesda,Md.(1991))。恒定结构域不直接参与抗体与抗原的结合,但表达出多种效应子功能,诸如抗体参与抗体依赖性细胞毒性。

[0069] 如本文所用的术语“单克隆抗体”是指从实质上均质的抗体群体获得的抗体,即构成所述群体的个别抗体是相同的,除了可以微量存在的可能天然存在的突变和/或翻译后修饰(例如,异构化,脱酰胺)之外。单克隆抗体具有高度特异性,其针对单一抗原位点。相较于通常包括针对不同决定子(表位)的不同抗体的多克隆抗体制剂,各单克隆抗体是针对抗原上的单一决定子。除了其特异性,单克隆抗体的优势在于,其通过融合瘤培养来合成,不受其他免疫球蛋白污染。修饰语“单克隆”指示抗体的特性为获自实质上均质的抗体群体,且不应理解为需要通过任何具体方法来产生抗体。例如,待根据本申请使用的单克隆抗体可通过多种技术制成,包括例如融合瘤方法(例如,Kohler及Milstein.,Nature,256:495-97(1975);Hongo等人,Hybridoma,14(3):253-260(1995);Harlow等人,Antibodies:A Laboratory Manual,(Cold Spring Harbor Laboratory Press,第2版1988);Hammerling等人,Monoclonal Antibodies and T-Cell Hybridomas 563-681(Elsevier,N.Y.,1981));重组DNA方法(参见例如美国专利第4,816,567号);噬菌体呈现技术(参见例如Clackson等人,Nature,352:624-628(1991);Marks等人,J.Mol.Biol.222:581-597(1992);Sidhu等人,J.Mol.Biol.338(2):299-310(2004);Lee等人,J.Mol.Biol.340(5):1073-1093(2004);Fellouse,Proc.Nat'l.Acad.Sci.USA 101(34):12467-12472(2004);及Lee等人,J.Immunol.Methods 284(1-2):119-132(2004));及用于在具有部分或全部编码人免疫球蛋白序列的人免疫球蛋白基因座或基因的动物中产生人或人样抗体的技术(参见例如W0 1998/24893;W0 1996/34096;W0 1996/33735;W0 1991/10741;Jakobovits等人,Proc.Nat'l.Acad.Sci.USA 90:2551(1993);Jakobovits等人,Nature 362:255-258(1993);Bruggemann等人,Year in Immunol.7:33(1993);美国专利第5,545,807号、第5,545,806号、第5,569,825号、第5,625,126号、第5,633,425号及第5,661,016号;Marks等人,Bio/Technology 10:779-783(1992);Lonberg等人,Nature 368:856-859(1994);Morrison,Nature368:812-813(1994);Fishwild等人,Nature Biotechnol.14:845-851(1996);Neuberger,Nature Biotechnol.14:826(1996);及Lonberg及Huszar,Intern.Rev.Immunol.13:65-93(1995))。

[0070] 术语“全长抗体”、“完整抗体”或“完全抗体”可互换使用,表示呈大致上完整形式的抗体,与抗体片段不同。具体地说,全长4链抗体包括具有重链及轻链(包括Fc区)的抗体。全长仅重链抗体包括重链(例如 V_H H)及Fc区。恒定结构域可为天然序列恒定结构域(例如人天然序列恒定结构域)或其氨基酸序列变体。在一些情况下,完整抗体可具有一种或多种效应子功能。

[0071] “抗体片段”包括完整抗体的一部分,优选地所述完整抗体的抗原结合区和/或可变区。抗体片段的实例包括但不限于Fab、Fab'、 $F(ab')_2$ 以及Fv片段;双抗体(diabody);线性抗体(参见美国专利第5,641,870号,实例2;Zapata等人,Protein Eng.8(10):1057-1062[1995]);单链抗体分子;单结构域抗体(诸如 V_H H)及由抗体片段形成的多特异性抗体。木瓜蛋白酶消化抗体产生两个的相同抗原结合片段,称为“Fab”片段,及残留“Fc”片段,所述名称反映了容易结晶的能力。Fab片段由整条L链连同H链的可变区结构域(V_H)及一条重链的第一恒定结构域(C_H1)组成。每个Fab片段关于抗原结合是单价的,即,它具有单一抗原结合位点。抗体经木瓜蛋白酶处理产生单个大 $F(ab')_2$ 片段,所述片段大致对应于具有不同抗原结合活性的两个二硫键连接的Fab片段并且仍然能够交联抗原。Fab'片段因在 C_H1 结构域的羧基末端处具有少量额外的残基(包括来自抗体铰链区的一个或多个半胱氨酸)而不同于Fab片段。Fab'-SH为本文中恒定结构域的半胱氨酸残基携带自由硫醇基的Fab'的名称。 $F(ab')_2$ 抗体片段最初以Fab'片段对的形式产生,所述片段之间具有铰链半胱氨酸。抗体片段的其他化学偶联也是已知的。

[0072] Fc片段包含通过二硫键保持在一起的两条H链的羧基末端部分。抗体的效应子功能由Fc区中的序列决定,所述区也由存在于某些细胞型上的Fc受体(FcR)识别。

[0073] 术语“恒定结构域”是指免疫球蛋白分子的相对于免疫球蛋白的其他部分,即含有抗原结合位点的可变结构域,具有更保守的氨基酸序列的部分。恒定结构域含有重链的 C_H1 、 C_H2 及 C_H3 结构域(统称为CH)及轻链的CHL(或CL)结构域。

[0074] 来自任何哺乳动物物种的抗体(免疫球蛋白)的“轻链”可基于其恒定结构域的氨基酸序列指定为两种明显不同类型(称为卡帕(κ)及拉姆达(λ))中的一者。

[0075] “Fv”是含有完全抗原识别及结合位点的最小抗体片段。此片段由处于紧密、非共价缔合的一个重链可变区结构域及一个轻链可变区结构域的二聚体组成。从此两个结构域的折叠产生六个高变环(从H链及L链各自产生3个环),所述高变环促成用于抗原结合的氨基酸残基并且赋予抗体抗原结合特性。然而,甚至单个可变结构域(或仅包含三个对抗原具有特异性的CDR的Fv中的一半)具有识别及结合抗原的能力,但与整个结合位点相比,处于较低的亲和力下。

[0076] “单链Fv”(也缩写为“sFv”或“scFv”)是包含连接到单一多肽链中的 V_H 及 V_L 抗体结构域的抗体片段。优选地,sFv多肽也包含 V_H 结构域与 V_L 结构域之间的多肽接头,所述接头能够使sFv形成用于抗原结合的所需结构。关于sFv的评述,参见Pluckthun, The Pharmacology of Monoclonal Antibodies,第113卷,Rosenburg及Moore编,Springer-Verlag,New York,第269-315页(1994)。

[0077] 本文所述的抗体的“功能片段”构成完整抗体的一部分,通常包括完整抗体的抗原结合区或可变区或保留或具有经修饰的FcR结合能力的抗体的Fc区。抗体片段的实例包括线性抗体、单链抗体分子及由抗体片段形成的多特异性抗体。

[0078] 术语“双抗体”是指通过在 V_H 与 V_L 结构域之间以短接头(约5-10个残基)构建sFv片段(参见前一段落)来制备的小抗体片段,使得达成V结构域的链内而不是链间配对,从而得到二价片段,即具有两个抗原结合位点的片段。双特异性抗体为两种抗体的 V_H 及 V_L 结构域存在于不同多肽链上的两个“交叉”sFv片段的异二聚体。双抗体更详细地描述于例如EP 404,097;WO 93/11161;Hollinger等人,Proc.Nat'l.Acad.Sci.USA 90:6444-6448(1993)中。

[0079] 本文中的单克隆抗体特定地包括“嵌合”抗体(免疫球蛋白),其中重链和/或轻链的一部分与源于特定物种或属特定抗体类别或亚类的抗体中的相应序列具有同一性或同源,而所述链的剩余部分与源于另一物种或属另一抗体类别或亚类的抗体中的相应序列具有同一性或同源,以及所述抗体的片段,只要其展现所需生物活性即可(美国专利第4,816,567号;Morrison等人,Proc.Nat'l.Acad.Sci.USA 81:6851-6855(1984))。“人源化抗体”用作“嵌合抗体”的亚组。

[0080] 非人(例如,美洲驼或骆驼科)抗体的“人源化”形式为含有来源于非人免疫球蛋白的最小序列的抗体。在一些实施方案中,人源化抗体为其中来自受者的CDR(在下文定义)的残基被来自诸如小鼠、大鼠、兔、骆驼科、美洲驼、羊驼或非人灵长类动物的非人物种(供体抗体)的CDR的具有所需特异性、亲和力和/或能力的残基置换的人免疫球蛋白(受者抗体)。在一些情况下,人免疫球蛋白的框架区(“FR”)残基由对应的非人残基置换。此外,人源化抗体可包含不存在于受者抗体或供体抗体中的残基。可进行这些修饰以进一步改良抗体性能,诸如结合亲和力。一般而言,人源化抗体将包含至少一个且通常两个可变结构域的实质上全部,其中全部或实质上全部高变环对应于非人免疫球蛋白序列的那些,且全部或实质上全部FR区为人免疫球蛋白序列的那些,但是FR区可包括一或多处个别FR残基取代,所述一或多处取代改良抗体性能,诸如结合亲和力、异构化、免疫原性等。FR中这些氨基酸取代的数目通常在H链中不多于6,且在L链中不多于3。人源化抗体任选地也将包含至少一部分免疫球蛋白恒定区(Fc),通常为人免疫球蛋白的恒定区。关于其他细节,参见例如Jones等人,Nature 321:522-525(1986);Riechmann等人,Nature 332:323-329(1988);及Presta,Curr.Op.Struct.Biol.2:593-596(1992)。也参见例如Vaswani及Hamilton,Ann.Allergy,Asthma&Immunol.1:105-115(1998);Harris,Biochem.Soc.Transactions 23:1035-1038(1995);Hurle及Gross,Curr.Op.Biotech.5:428-433(1994);及美国专利第6,982,321号与第7,087,409号。

[0081] “人抗体”为具有对应于人所产生的抗体的氨基酸序列的氨基酸序列和/或已使用如本文所公开的制备人抗体的任一技术制成的抗体。人抗体的此定义特定地排除包含非人抗原结合残基的人源化抗体。人抗体可使用所属领域中已知的各种技术,包括噬菌体呈现文库产生。Hoogenboom及Winter,J.Mol.Biol.,227:381(1991);Marks等人,J.Mol.Biol.,222:581(1991)。Cole等人,Monoclonal Antibodies and Cancer Therapy,Alan R.Liss,第77页(1985);Boerner等人,J.Immunol.,147(1):86-95(1991)中所述的方法也可用于制备人单克隆抗体。也参见van Dijk及van de Winkel,Curr.Opin.Pharmacol.,5:368-74(2001)。人抗体可通过向转基因动物施用抗原来制备,所述转基因动物已经修饰以响应于抗原攻击产生所述抗体,但其内源基因座已失能,例如经免疫的异种小鼠(关于XENOMOUSE™技术,参见例如美国专利第6,075,181号及第6,150,584号)。关于经由人B细胞融合瘤技术产生的人抗体,也参见例如Li等人,Proc.Nat'l.Acad.Sci.USA,103:3557-3562(2006)。

[0082] 当在本文中使用时,术语“高变区”、“HVR”或“HV”是指抗体可变结构域的序列高度可变和/或形成结构确定环的各区。通常,单结构域抗体包含三个HVR(或CDR):HVR1(或CDR1)、HVR2(或CDR2)及HVR3(或CDR3)。在三种HVR中,HVR3(或CDR3)显示最大多样性,并且被认为在赋予抗体的精细特异性方面发挥独特作用。参见,例如Hamers-Casterman等人,Nature 363:446-448(1993);Sheriff等人,Nature Struct.Biol.3:733-736(1996)。

[0083] 术语“互补决定区”或“CDR”用于指由Kabat系统定义的高变区。参见Kabat等人,Sequences of Proteins of Immunological Interest,第5版Public Health Service,National Institutes of Health,Bethesda,Md(1991)。

[0084] 多个HVR描述在使用中并且涵盖在本文中。Kabat互补决定区(CDR)基于序列可变性并且是最常用的(Kabat等人,Sequences of Proteins of Immunological Interest,第5版Public Health Service,National Institutes of Health,Bethesda,Md.(1991))。Chothia替代地提及结构环的位置(Chothia及Lesk,J.Mol.Biol.196:901-917(1987))。AbM HVR表示Kabat HVR与Chothia结构化环之间的折衷,并且通过Oxford Molecular的AbM抗体建模软件来使用。“接触”HVR基于可用复合物晶体结构的分析。来自这些HVR中每个残基在以下表1中指出。

[0085] 表1.HVR描述。

环	Kabat	AbM	Chothia	接触
L1	L24-L34	L24-L34	L26-L32	L30-L36
L2	L50-L56	L50-L56	L50-L52	L46-L55
L3	L89-L97	L89-L97	L91-L96	L89-L96
[0086]	H1 H31-H35B	H26-H35B	H26-H32	H30-H35B
	(Kabat 编号)			
	H1 H31-H35	H26-H35	H26-H32	H30-H35
	(Chothia 编号)			
	H2 H50-H65	H50-H58	H53-H55	H47-H58
	H3 H95-H102	H95-H102	H96-H101	H93-H101

[0087] HVR可包括如下的“延长HVR”:在 V_L 中,24-36或24-34(L1)、46-56或50-56(L2)、以及89-97或89-96(L3),且在 V_H 中,26-35(H1)、50-65或49-65(H2)、以及93-102、94-102或95-102(H3)。对于这些定义中的每个,可变结构域残基是根据Kabat等人(出处同上)进行编号。

[0088] 单结构域抗体(诸如 V_H H)的氨基酸残基是根据Kabat等人给出的VH结构域的一般编号进行编号(“Sequence of proteins of immunological interest”,US Public Health Services,NIH Bethesda,Md.,出版号91),如同在Riechmann及Muyldermans,J.Immunol.Methods2000年6月23日;240(1-2):185-195的文章中应用于来自骆驼科动物的 V_H H结构域。根据所述编号, V_H H的FR1包含1-30位的氨基酸残基, V_H H的CDR1包含31-35位的氨基酸残基, V_H H的FR2包含36-49位的氨基酸, V_H H的CDR2包含50-65位的氨基酸残基, V_H H的FR3包含66-94位的氨基酸残基, V_H H的CDR3包含95-102位的氨基酸残基, V_H H的FR4包含103-113位的氨基酸残基。在所述方面中,应注意,如业内对于 V_H 结构域及 V_H H结构域所周知,每个CDR

中氨基酸残基的总数可以不同,并且可以不对应于由Kabat编号指示的氨基酸残基的总数(即,根据Kabat编号的一个或多个位置在实际序列中可能未被占据,或者实际序列可能含有比Kabat编号允许的数量更多的氨基酸残基)。

[0089] 表述“如Kabat中的可变结构域残基编号”或“如Kabat中的氨基酸位置编号”及其变型是指用于Kabat等人(出处同上)中的抗体编译的重链可变结构域或轻链可变结构域的编号系统。使用此编号系统,实际线性氨基酸序列可含有更少的或额外的氨基酸,所述氨基酸对应于可变结构域的FR或HVR的缩短或对其进行的插入。例如,重链可变结构域可包括H2的残基52之后的单个氨基酸插入(根据Kabat的残基52a)及重链FR残基82之后的插入残基(例如,根据Kabat的残基82a、82b及82c等)。可通过在抗体序列的同源区处与“标准”Kabat编号序列比对来确定给定抗体的残基的Kabat编号。

[0090] 除非本文另有说明,否则免疫球蛋白重链中残基的编号是如Kabat等人(出处同上)的EU索引的编号。“如Kabat中的EU索引”是指人IgG1 EU抗体的残基编号。

[0091] “框架”或“FR”残基是除了如本文所定义的HVR残基以外的那些可变结构域残基。

[0092] “人共有框架”或“受体人框架”为表示人免疫球蛋白V_L或V_H框架序列的选择中最常出现的氨基酸残基的框架。一般而言,人免疫球蛋白V_L或V_H序列选自可变结构域序列的亚组。一般而言,序列的亚组为如Kabat等人,Sequences of Proteins of Immunological Interest,第5版.Public Health Service,National Institutes of Health,Bethesda,Md.(1991)中的亚组。实例包括对于V_L,亚组可为如Kabat等人(出处同上)中的亚组κI、κII、κIII或κIV。另外,对于V_H,亚组可为如Kabat等人中的亚组I、亚组II或亚组III。可替代地,人共有框架可来源于上述者,其中具体残基,诸如当人框架残基基于其与供体框架的同源性通过将供体框架序列与各种人框架序列的集合进行比对来选择时。“来源于”人免疫球蛋白框架或人共有框架的受体人框架可包含人免疫球蛋白框架或人共有框架的相同氨基酸序列,或其可含有预先存在的氨基酸序列变化。在一些实施方案中,预先存在的氨基酸变化的数目为10个或更少、9个或更少、8个或更少、7个或更少、6个或更少、5个或更少、4个或更少、3个或更少、或2个或更少。

[0093] “亲和力成熟”抗体是在其一个或多个CDR中具有一个或多个改变而导致抗体对抗原的亲和力相较于不具有那些改变的亲本抗体改良的抗体。在一些实施方案中,亲和力成熟抗体对靶抗原具有纳摩尔或甚至皮摩尔的亲和力。亲和力成熟抗体是通过所属领域中已知的程序产生。例如,Marks等人,Bio/Technology 10:779-783(1992)描述通过V_H结构域及V_L结构域改组的亲和力成熟。CDR和/或框架残基的随机诱变描述于例如:Barbas等人Proc Nat'l Acad.Sci.USA 91:3809-3813(1994);Schier等人Gene 169:147-155(1995);Yelton等人J.Immunol.155:1994-2004(1995);Jackson等人,J.Immunol.154(7):3310-9(1995);及Hawkins等人,J.Mol.Biol.226:889-896(1992)。

[0094] 如本文所用,术语“特异性结合”、“特异性识别”或“对...具有特异性”是指可测量的及可再现的相互作用,诸如靶标与抗原结合蛋白质(诸如mAb)的结合,所述结合在存在包括生物分子在内的分子的异种群体的情况下确定靶标的存在。例如,特异性结合靶标(其可以为表位)的抗原结合蛋白(诸如mAb)是与结合其他靶标相比,以更大亲和力、亲合力、更容易地和/或以更长持续时间结合所述靶标的抗原结合蛋白(诸如mAb)。在一些实施方案中,抗原结合蛋白(诸如mAb)与不相关靶标的结合程度不到抗原结合蛋白(诸如mAb)与靶标的

结合的约10%，如例如通过放射免疫分析(RIA)所测量。在一些实施方案中，特异性结合靶标的抗原结合蛋白(诸如mAb)具有 $\leq 10^{-5}\text{M}$ 、 $\leq 10^{-6}\text{M}$ 、 $\leq 10^{-7}\text{M}$ 、 $\leq 10^{-8}\text{M}$ 、 $\leq 10^{-9}\text{M}$ 、 $\leq 10^{-10}\text{M}$ 、 $\leq 10^{-11}\text{M}$ 或 $\leq 10^{-12}\text{M}$ 的解离常数(K_D)。在一些实施方案中，抗原结合蛋白特异性地结合在来自不同物种的蛋白间保守的蛋白上的表位。在一些实施方案中，特异性结合可包括但不限于专一性结合。

[0095] 术语“特异性”是指抗原结合蛋白(诸如mAb)针对抗原的特定表位的选择性识别。例如，天然抗体为单特异性的。如本文所用的术语“多特异性”表示抗原结合蛋白具有多表位特异性(即，能够特异性结合一个生物分子上的两个、三个或更多个不同的表位或能够特异性结合两个、三个或更多个不同的生物分子上的表位)。如本文所用的“双特异性”表示抗原结合蛋白具有两种不同的抗原结合特异性。除非另有说明，否则所列出的双特异性抗体结合的抗原的顺序是任意的。即，例如，术语“抗PD-L1/PD-1”、“抗PD-1/PD-L1”、“PD-L1 $\times$ PD-1”、“PD-1 $\times$ PD-L1”、“PD-1-PD-L1”及“PD-L1-PD-1”可互换地用来指特异性结合PD-L1及PD-1的双特异性抗体。如本文所用的术语“单特异性”表示具有一个或多个结合位点的抗原结合蛋白(诸如mAb)，每个结合位点结合相同抗原的相同表位。

[0096] 如本文所用的术语“价”表示抗原结合蛋白质中存在特定数目的结合位点。例如天然抗体或全长抗体具有两个结合位点并且是二价的。因此，术语“三价”、“四价”、“五价”及“六价”分别表示抗原结合蛋白中存在两个结合位点、三个结合位点、四个结合位点、五个结合位点及六个结合位点。

[0097] “抗体效应子功能”是指可归因于抗体的Fc区(天然序列Fc区或氨基酸序列变体Fc区)的那些生物活性，且随抗体同型而有所不同。抗体效应子功能的实例包括：C1q结合及补体依赖性细胞毒性；Fc受体结合；抗体依赖性细胞介导的细胞毒性(ADCC)；吞噬作用；细胞表面受体(例如B细胞受体)的下调；及B细胞活化。“减少或最小化的”抗体效应子功能意指其自野生型或未经修饰的抗体减少至少50%(可替代地60%、65%、70%、75%、80%、85%、90%、95%、96%、97%、98%、99%)。所属领域技术人员可易于确定及衡量抗体效应子功能的测定。在优选实施方案中，补体结合、补体依赖性细胞毒性及抗体依赖性细胞毒性的抗体效应子功能受到影响。在一些实施方案中，效应子功能通过恒定区中消除糖基化的突变(例如“无效应子突变”)来消除。在一个方面中，无效应子突变包含 C_H2 区中的N297A或DANA突变(D265A和/或N297A)。Shields等人, J. Biol. Chem. 276(9):6591-6604(2001)。可替代地，导致减少或消除效应子功能的另外的突变包括：K322A及L234A/L235A(LALA)。可替代地，效应子功能可通过生产技术来减少或消除，诸如在未经糖基化的宿主细胞(例如，大肠杆菌(E. coli.))中的表达或以导致糖基化模式改变成在促进效应子功能时无效或不太有效的方式(例如Shinkawa等人, J. Biol. Chem. 278(5):3466-3473(2003))。

[0098] “抗体依赖性细胞介导的细胞毒性”或ADCC是指一种细胞毒性形式，其中结合至某些细胞毒性细胞(例如，自然杀伤(NK)细胞、中性粒细胞及巨噬细胞)上存在的Fc受体(FcR)上的分泌Ig使得这些细胞毒性效应细胞能够与携带抗原的靶细胞特异性结合并随后以细胞毒素杀伤靶细胞。抗体“武装”细胞毒性细胞且为通过此机制杀伤靶细胞所需。用于介导ADCC的原代细胞NK细胞仅表达Fc γ RIII，而单核细胞表达Fc γ RI、Fc γ RII及Fc γ RIII。造血细胞上的Fc表达概述于Ravetch及Kinet, Annu. Rev. Immunol. 9:457-92(1991)第464页中的表3中。为了评估所关注的分子的ADCC活性，可执行体外ADCC测定，诸如美国专利第5，

500,362号或第5,821,337号中所述者。用于此类测定的有效效应细胞包括外周血单核细胞(PBMC)及自然杀伤(NK)细胞。可替代地或另外,所关注的分子的ADCC活性可例如在动物模型(诸如Clynes等人Proc.Nat'l Acad.Sci.USA 95:652-656(1998)中公开的动物模型)中进行体内评估。

[0099] 本文术语“Fc区”用于定义免疫球蛋白重链的C末端区,包括天然序列Fc区及变体Fc区。虽然免疫球蛋白重链的Fc区的边界可变化,但人IgG重链Fc区通常限定为从在位置Cys226处的氨基酸残基或从Pro230延伸至其羧基末端。Fc区的C末端赖氨酸(根据EU编号系统的残基447)可例如在抗体产生或纯化期间或通过编码抗体的重链的核酸进行重组工程化来去除。因此,完整抗体的组合物可包括K447残基全部去除的抗体群体、无K447残基去除的抗体群体、以及具有拥有或没有K447残基的抗体的混合物的抗体群体。用于本文描述的抗体中的合适的天然序列Fc区包括人IgG1、IgG2(IgG2A、IgG2B)、IgG3及IgG4。

[0100] “Fc受体”或“FcR”描述结合抗体Fc区的受体。优选FcR为天然序列人FcR。此外,优选FcR为结合IgG抗体(γ 受体)且包括Fc γ RI、Fc γ RII及Fc γ RIII亚类的受体(包括这些受体的等位基因变体及替代地剪接形式)的FcR,Fc γ RII受体包括Fc γ RIIA(“活化受体”)及Fc γ RIIB(“抑制受体”),其具有主要在其细胞质结构域中不同的相似氨基酸序列。活化受体Fc γ RIIA在其细胞质结构域中含有基于免疫受体酪氨酸的活化基序(ITAM)。抑制受体Fc γ RIIB在其细胞质结构域中含有基于免疫受体酪氨酸的抑制基序(ITIM)。(参见M.Daëron,Annu.Rev.Immunol.15:203-234(1997))。FcR综述于Ravetch及Kinet,Annu.Rev.Immunol.9:457-92(1991);Capel等人,Immunomethods 4:25-34(1994);及de Haas等人,J.Lab.Clin.Med.126:330-41(1995)中。本文中术语“FcR”涵盖其他FcR(包括将来待鉴别的FcR)。

[0101] 术语“Fc受体”或“FcR”也包括新生儿受体FcRn,其负责将母体IgG转移至胎儿。Guyer等人,J.Immunol.117:587(1976)及Kim等人,J.Immunol.24:249(1994)。测量与FcRn结合的方法为已知的(参见例如Ghetie及Ward,Immunol.Today 18:(12):592-8(1997);Ghetie等人,Nature Biotechnology 15(7):637-40(1997);Hinton等人,J.Biol.Chem.279(8):6213-6(2004);WO 2004/92219(Hinton等人))。可以例如在表达人FcRn的转基因小鼠或转染人细胞系中或者在施用具有变体Fc区的多肽的灵长类动物中测定体内与FcRn的结合及人FcRn高亲和力结合多肽的血清半衰期。WO 2004/42072(Presta)描述改良或减弱与FcR的结合的抗体变体。也参见例如Shields等人,J.Biol.Chem.9(2):6591-6604(2001)。

[0102] “补体依赖性细胞毒性”或“CDC”是指靶细胞在补体存在下溶解的能力。经典补体途径的活化是通过补体系统的第一组分(C1q)与结合其同源抗原的(适当亚类的)抗体的结合来起始。为了评估补体活化,可执行CDC测定,例如,如Gazzano-Santoro等人,J.Immunol.Methods202:163(1996)中所述。具有改变的Fc区氨基酸序列及增加或减少的C1q结合能力的抗体变体描述于美国专利第6,194,551B1号及W099/51642中。那些专利公布的内容明确地以引用的方式并入本文。也参见Idusogie等人J.Immunol.164:4178-4184(2000)。

[0103] “结合亲和力”总体上是指分子(例如,抗体)的单一结合位点与它的结合配偶体(例如,抗原)之间的非共价相互作用的总和的强度。除非另外指示,否则如本文所用,“结合亲和力”是指反映结合对的成员之间的1:1相互作用的内在结合亲和力。结合亲和力可以由

K_D 、 K_{off} 、 K_{on} 或 K_a 表示。如本文所用,术语“ K_{off} ”意指抗体(或抗原结合结构域)从抗体/抗原复合物中解离的解离速率常数,如从动力学选择设置确定,以 s^{-1} 为单位表示。如本文所用,术语“ K_{on} ”意指抗体(或抗原结合结构域)与抗原结合形成抗体/抗原复合物的缔合速率常数,以 $M^{-1}s^{-1}$ 为单位表示。如本文所用,术语平衡解离常数“ K_D ”是指特定抗体-抗原相互作用的解离常数,并且描述占据存在于平衡的抗体分子溶液中的所有抗体结合结构域的一半所需的抗原浓度,并且等于 K_{off}/K_{on} ,以 M 为单位表示。 K_D 的测量预先假定所有结合剂都在溶液中。在抗体与细胞壁连接的情况下,例如在酵母表达系统中,相应平衡速率常数表示为 EC_{50} ,此给出了 K_D 的良好近似值。亲和常数 K_a 是解离常数 K_D 的倒数,以 M^{-1} 为单位表示。

[0104] 解离常数(K_D)用作显示抗体对抗原的亲合力的指标。例如,通过使用标记有多种标记物试剂的抗体的Scatchard方法,以及通过使用BiacoreX(Amersham Biosciences制造)(其是柜枱买卖测量试剂盒)或类似试剂盒,根据用户手册及试剂盒附带的实验操作方法,可以易于进行分析。可以使用这些方法导出的 K_D 值以 M (摩尔每升)为单位表示。特异性结合靶标的抗体或其抗原结合片段可具有例如 $\leq 10^{-5}M$ 、 $\leq 10^{-6}M$ 、 $\leq 10^{-7}M$ 、 $\leq 10^{-8}M$ 、 $\leq 10^{-9}M$ 、 $\leq 10^{-10}M$ 、 $\leq 10^{-11}M$ 或 $\leq 10^{-12}M$ 的解离常数(K_D)。

[0105] 抗体或抗原结合结构域的结合特异性可以通过所属领域中已知的方法经实验确定。此类方法包括但不限于Western印迹、ELISA印迹、RIA印迹、ECL印迹、IRMA印迹、EIA印迹、BIAcore测试及肽扫描。

[0106] 半数最大抑制浓度(IC_{50})是物质(诸如抗体)抑制特定生物或生物化学功能的有效性的量度。它表明需要多少特定药物或其他物质(抑制剂,诸如抗体)来抑制特定的生物过程(例如,PD-L1与B7-1,或过程的组分,即酶、细胞、细胞受体或微生物之间的结合)达一半。所述值通常表示为摩尔浓度。对于激动剂药物或其他物质(例如抗体), IC_{50} 与“ EC_{50} ”相当。 EC_{50} 也表示在体内获得最大作用的50%所需的血浆浓度。如本文所用,“ IC_{50} ”用于指示在体外中和50%的抗原生物活性(诸如PD-L1生物活性)所需的抗体(诸如抗PD-L1 mAb)的有效浓度。 IC_{50} 或 EC_{50} 可以通过生物测定来测量,诸如通过FACS分析(竞争结合测定)的配体结合的抑制,基于细胞的细胞因子释放测定或扩增的发光邻近均相测定(AlphaLISA)。

[0107] 相对于肽、多肽或抗体序列的“氨基酸序列同一性百分比(%)”及“同源性”定义为,在比对序列并且引入缺口(若需要)以获得最大序列同一性百分比之后,候选序列中与特定肽或多肽序列中氨基酸残基相同的氨基酸残基的百分比,而不考虑任何保守取代作为序列同一性的一部分。出于确定氨基酸序列同一性百分比的目的所进行的比对可以本领域技术范围内的各种方式实现,例如使用公众可获得的计算机软件,诸如BLAST、BLAST-2、ALIGN或MEGALIGN™(DNASTAR)软件。所属领域技术人员可确定测量比对的适当参数,包括对所比较的序列的全长获得最大比对所需的任何算法。

[0108] 编码构建体、抗体或其抗原结合片段的“分离的”核酸分子是经鉴定并且与至少一种污染物核酸分子分开的核酸分子,所述核酸分子在其产生的环境中通常与污染物核酸分子缔合。优选地,分离的核酸分子不与产生环境相关联的所有组分缔合。编码本文所述多肽及抗体的分离的核酸分子呈其在自然界中存在的形式或状态以外的形式。因此分离的核酸分子有别于天然存在于细胞中的编码本文所述多肽及抗体的核酸。分离的核酸包括通常含有核酸分子的细胞中所含有的核酸分子,但核酸分子存在于染色体外或存在于不同于其天然染色体位置的染色体位置处。

[0109] 如本文所用,术语“载体”是指一种核酸分子,其能够传播其所连接的另一种核酸分子。所述术语包括呈自主复制核酸结构的载体以及并入其中已引入其的宿主细胞的基因组中的载体。某些载体能够指导其可操作性连接的核酸的表达。此类载体在本文中称为“表达载体”。

[0110] 如本文所用的术语“转染”或“转化”或“转导”是指将外源性核酸转移或引入至宿主细胞中的过程。“转染”或“转化”或“转导”细胞为已经以外源性核酸转染、转化或转导的细胞。细胞包括原代受试者细胞及其后代。

[0111] 术语“宿主细胞”、“宿主细胞系”及“宿主细胞培养物”可互换使用且是指已引入有外源性核酸的细胞,包括此类细胞的子代。宿主细胞包括“转化体”及“转化细胞”,其包括原代转化细胞及由其衍生的子代而不考虑继代数。后代可能在核酸含量方面未与亲本细胞完全一致,但可含有突变。本文包括具有与针对原始转化细胞所筛选或选择相同的功能或生物活性的突变后代。

[0112] “辅助环境”是指个体已具有癌症病史且一般(但不必要)对疗法有反应的临床环境,疗法包括但不限于手术(例如,手术切除)、放疗及化学疗法。然而,这些个体因其癌症病史而被认为处于产生疾病的风险。“辅助环境”中的治疗或施用是指随后的治疗模式。风险程度(例如,当辅助环境中的个体被认为“高风险”或“低风险”时)取决于若干因素,最通常为首次治疗时的疾病程度。

[0113] “新辅助环境”是指在初步/确定性疗法之前进行方法的临床环境。

[0114] 术语“药物组合物”的“药物调配物”是指以下制剂,其呈允许活性成分的生物活性有效的形式,且不含对调配物所将施用的受试者有不可接受毒性的额外组分。此类调配物是无菌的。“无菌”调配物是灭菌的或不含所有活的微生物及其孢子。

[0115] 应理解,本文中描述的本发明的实施方案包括“由实施方案组成”和/或“基本上由实施方案组成”。

[0116] 本文中对“约”某一个值或参数的提及包括(以及描述)针对所述值或参数本身的变量。例如,关于“约X”的描述包括“X”的描述。

[0117] 如本文所使用,提及“并非”某一值或参数通常意指并描述“不同于”某一值或参数。例如,所述方法不用于治疗X型癌症,意味着所述方法用于治疗不同于X的类型的癌症。

[0118] 本文使用的术语“约X-Y”具有与“约X至约Y”相同的含义。

[0119] II. 抗PD-L1构建体

[0120] 抗PD-L1单克隆抗体

[0121] 本文所述的分离的抗PD-L1构建体包含特异性识别PD-L1或与PD-L1结合的单克隆抗体(mAb)部分(或“抗PD-L1 mAb”)。在本发明的一些实施方案中,分离的抗PD-L1构建体为全长IgG。

[0122] PD-L1

[0123] 结构与相关B7家族成员类似,PD-L1蛋白含有细胞外IgV及IgC结构域以及短的细胞质区。PD-L1具有与CD28类似的细胞内结构域,其缺乏内在催化活性且含有一个能够结合PI3K、PP2A及SHP-2的YVKM基序以及一个能够结合含SH3蛋白的富脯氨酸基序。

[0124] 人PD-L1的示例性氨基酸序列公开于Genbank登录号Q9NZQ7,在其中,氨基酸1-18的区为前导肽;氨基酸19-238的区为细胞外结构域;氨基酸239-259的区为跨膜结构域;且

氨基酸260-290的区为细胞质结构域。

[0125] 根据本发明的实施方案,人PD-L1序列的氨基酸序列与Genbank登录号Q9NZQ7的人PD-L1具有至少90%同一性,并且含有与其他物种(例如,鼠类)的PD-L1氨基酸序列相比,将氨基酸序列鉴定为人的氨基酸残基。在一些实施方案中,人PD-L1的氨基酸序列可以与Genbank登录号Q9NZQ7的PD-L1具有至少约95%、96%、97%、98%或99%同一性。在一些实施方案中,人PD-L1序列将展示与Genbank登录号Q9NZQ7的PD-L1不多于10个氨基酸差异。在一些实施方案中,人PD-L1可以展示与Genbank登录号Q9NZQ7的PD-L1不多于5个、4个、3个、2个或1个氨基酸差异。可以如本文所述确定同一性百分比。在一些实施方案中,本文所述的抗PD-L1 mAb特异性结合与Genbank登录号Q9NZQ7的PD-L1具有100%氨基酸序列同一性的PD-L1多肽。在一些实施方案中,本申请的抗PD-L1mAb特异性结合包含SEQ ID NO:395的氨基酸序列的PD-L1多肽。

[0126] 在一些实施方案中,本申请的抗PD-L1 mAb可与来自除人之外的物种的PD-L1或在结构上与人PD-L1相关的其他蛋白(例如,人PD-L1同源物)交叉反应。在一些实施方案中,本申请的抗PD-L1 mAb对人PD-L1具有完全特异性,且不表达出物种或其他类型的交叉反应性。在一些实施方案中,本申请的抗PD-L1 mAb特异性结合人PD-L1的可溶性同功型。在一些实施方案中,本申请的抗PD-L1 mAb特异性识别人PD-L1的膜结合同功型(SEQ ID NO:395)。

[0127] 在一些实施方案中,本文所述的抗PD-L1 mAb特异性识别或结合PD-L1的细胞外结构域(ECD)。在一些实施方案中,抗PD-L1 mAb特异性结合PD-L1细胞外结构域(ECD)的N末端部分。在一些实施方案中,抗PD-L1 mAb特异性识别PD-L1实施方案细胞外结构域(ECD)的C末端部分。在一些实施方案中,抗PD-L1 mAb特异性识别PD-L1细胞外结构域(ECD)的中间部分。在一些实施方案中,抗PD-L1mAb所特异性识别的PD-L1细胞外结构域的氨基酸序列与Genbank登录号Q9NZQ7的PD-L1细胞外结构域具有至少约95%、96%、97%、98%或99%同一性。在一些实施方案中,抗PD-L1 mAb所特异性识别的PD-L1细胞外结构域的氨基酸序列与Genbank登录号Q9NZQ7的PD-L1细胞外结构域具有100%同一性。在一些实施方案中,抗PD-L1 mAb特异性识别具有SEQ ID NO:396的氨基酸序列的PD-L1 ECD多肽。

[0128] 抗体亲和力

[0129] 抗体或抗原结合结构域的结合特异性可以通过所属领域中已知的方法经实验确定。此类方法包括但不限于Western印迹、ELISA测试、RIA测试、ECL测试、IRMA测试、EIA测试、BIAcore测试及肽扫描。

[0130] 在一些实施方案中,抗PD-L1 mAb与PD-L1之间的结合的 K_D 为约 $10^{-5}M$ 至约 $10^{-6}M$ 、约 $10^{-6}M$ 至约 $10^{-7}M$ 、约 $10^{-7}M$ 至约 $10^{-8}M$ 、约 $10^{-8}M$ 至约 $10^{-9}M$ 、约 $10^{-9}M$ 至约 $10^{-10}M$ 、约 $10^{-10}M$ 至约 $10^{-11}M$ 、约 $10^{-11}M$ 至约 $10^{-12}M$ 、约 $10^{-5}M$ 至约 $10^{-12}M$ 、约 $10^{-6}M$ 至约 $10^{-12}M$ 、约 $10^{-7}M$ 至约 $10^{-12}M$ 、约 $10^{-8}M$ 至约 $10^{-12}M$ 、约 $10^{-9}M$ 至约 $10^{-12}M$ 、约 $10^{-10}M$ 至约 $10^{-12}M$ 、约 $10^{-5}M$ 至约 $10^{-11}M$ 、约 $10^{-7}M$ 至约 $10^{-11}M$ 、约 $10^{-8}M$ 至约 $10^{-11}M$ 、约 $10^{-9}M$ 至约 $10^{-11}M$ 、约 $10^{-5}M$ 至约 $10^{-10}M$ 、约 $10^{-7}M$ 至约 $10^{-10}M$ 、约 $10^{-8}M$ 至约 $10^{-10}M$ 、约 $10^{-5}M$ 至约 $10^{-9}M$ 、约 $10^{-7}M$ 至约 $10^{-9}M$ 、约 $10^{-5}M$ 至约 $10^{-8}M$ 或约 $10^{-6}M$ 至约 $10^{-8}M$ 。

[0131] 在一些实施方案中,抗PD-L1 mAb与PD-L1之间的结合的 K_{on} 为约 $10^2M^{-1}s^{-1}$ 至约 $10^4M^{-1}s^{-1}$ 、约 $10^4M^{-1}s^{-1}$ 至约 $10^6M^{-1}s^{-1}$ 、约 $10^6M^{-1}s^{-1}$ 至约 $10^7M^{-1}s^{-1}$ 、约 $10^2M^{-1}s^{-1}$ 至约 $10^7M^{-1}s^{-1}$ 、约 $10^3M^{-1}s^{-1}$ 至约 $10^7M^{-1}s^{-1}$ 、约 $10^4M^{-1}s^{-1}$ 至约 $10^7M^{-1}s^{-1}$ 、约 $10^5M^{-1}s^{-1}$ 至约 $10^7M^{-1}s^{-1}$ 、约 $10^3M^{-1}s^{-1}$ 至约 $10^6M^{-1}s^{-1}$ 或约 $10^4M^{-1}s^{-1}$ 至约 $10^6M^{-1}s^{-1}$ 。

[0132] 在一些实施方案中,抗PD-L1 mAb与PD-L1之间的结合的 K_{off} 为约 1s^{-1} 至约 10^{-2}s^{-1} 、约 10^{-2}s^{-1} 至约 10^{-4}s^{-1} 、约 10^{-4}s^{-1} 至约 10^{-5}s^{-1} 、约 10^{-5}s^{-1} 至约 10^{-6}s^{-1} 、约 1s^{-1} 至约 10^{-6}s^{-1} 、约 10^{-2}s^{-1} 至约 10^{-6}s^{-1} 、约 10^{-3}s^{-1} 至约 10^{-6}s^{-1} 、约 10^{-4}s^{-1} 至约 10^{-6}s^{-1} 、约 10^{-2}s^{-1} 至约 10^{-5}s^{-1} 或约 10^{-3}s^{-1} 至约 10^{-5}s^{-1} 。

[0133] 在一些实施方案中,在以0.12nM PD-1及0.2nM PD-L1进行的扩增的发光邻近均相测定(AlphaLISA)中,抗PD-L1 mAb的 IC_{50} 小于10nM。在一些实施方案中,通过FACS分析(竞争结合测定)或基于细胞的细胞因子释放测定,在配体结合的抑制中,抗PD-L1 mAb的 IC_{50} 小于500nM。在一些实施方案中,抗PD-L1 mAb的 IC_{50} 小于1nM、约1nM至约10nM、约10nM至约50nM、约50nM至约100nM、约100nM至约200nM、约200nM至约300nM、约300nM至约400nM或约400nM至约500nM。

[0134] 嵌合或人源化抗体

[0135] 在一些实施方案中,本文所提供的抗PD-L1抗体为嵌合抗体。某些嵌合抗体描述于例如美国专利第4,816,567号以及Morrison等人,Proc.Nat'l.Acad.Sci.USA,81:6851-6855(1984))中。在一个实例中,嵌合抗体包含非人可变区(例如,来源于骆驼科物种,例如美洲驼的可变区)及人恒定区。在又一个实例中,嵌合抗体为“类别转换”抗体,其中类别或亚类与亲本抗体的类别或亚类相比已经改变。嵌合抗体包括其抗原结合片段。

[0136] 在一些实施方案中,嵌合抗体为人源化抗体。通常,非人抗体被人源化以降低对人的免疫原性,同时保留亲本非人抗体的特异性及亲和力。一般说来,人源化抗体包含一个或多个可变结构域,其中HVR,例如CDR(或其部分)来源于非人抗体,并且FR(或其部分)来源于人抗体序列。人源化抗体任选地也将包含至少一部分人恒定区。在一些实施方案中,人源化抗体中的一些FR残基被来自非人抗体(例如HVR残基所来源的抗体)的相应残基取代,例如以恢复或改善抗体特异性或亲和力。

[0137] 人源化抗体及其制备方法综述于例如Almagro及Fransson,Front.Biosci.13:1619-1633(2008),且进一步描述于例如Riechmann等人,Nature 332:323-329(1988);Queen等人,Proc.Nat'l.Acad.Sci.USA 86:10029-10033(1989);美国专利第5,821,337号、第7,527,791号、第6,982,321号及第7,087,409号;Kashmiri等人,Methods 36:25-34(2005)(描述SDR(α -CDR)移植);Padlan,Mol.Immunol.28:489-498(1991)(描述“表面重塑”);Dall'Acqua等人,Methods 36:43-60(2005)(描述“FR改组”);以及Osborn等人,Methods 36:61-68(2005)及Klimka等人,Br.J.Cancer,83:252-260(2000)(描述达成FR改组的“导向选择”方法)。

[0138] 可用于人源化的人框架区包括但不限于:使用“最佳拟合”方法选择的框架区(参见例如Sims等人,J.Immunol.151:2296(1993));源于轻链或重链可变区的特定亚组的人抗体的共有序列的框架区(参见例如Carter等人,Proc.Nat'l.Acad.Sci.USA,89:4285(1992);及Presta等人,J.Immunol.,151:2623(1993));人成熟(体细胞突变)框架区或人种系框架区(参见例如Almagro及Fransson,Front.Biosci.13:1619-1633(2008));及由筛选FR文库获得的框架区(参见例如Baca等人,J.Biol.Chem.272:10678-10684(1997)及Rosok等人,J.Biol.Chem.271:22611-22618(1996))。

[0139] 在一些实施方案中,mAb被修饰,例如经人源化,而不降低所述结构域对抗原的天然亲和力,同时降低其对异源物种的免疫原性。例如,可以确定抗体重链及轻链可变结构域

(VH及VL)的氨基酸残基,并且例如在框架区中的一个或多个小鼠氨基酸被如在人共有序列中发现的其人对应物置换,所述多肽不失去其典型特征,即人源化不会显著影响所产生多肽的抗原结合能力。小鼠单克隆抗体的人源化需要在两条链(重链及轻链)中引入并诱变有限量的氨基酸且保存两条链的组装。

[0140] 人抗体

[0141] 在一些实施方案中,本文所提供的抗PD-L1抗体(尤其mAb)为人抗体。可以使用所属领域中已知的各种技术产生人抗体。人抗体概述于van Dijk及van de Winkel, Curr.Opin.Pharmacol.5:368-74(2001)以及Lonberg, Curr.Opin.Immunol.20:450-459(2008)中。能够产生完全人单结构域抗体的转基因小鼠或大鼠是所属领域中已知的。参见,例如,US20090307787A1、美国专利第8,754,287号、US20150289489A1、US20100122358A1及W02004049794。

[0142] 可以通过向转基因动物施用免疫原来制备人抗体,所述转基因动物已经被修饰以响应抗原性攻击产生完整人抗体或具有人可变区的完整抗体。此类动物通常含有全部或一部分人免疫球蛋白基因座,其替换内源免疫球蛋白基因座,或者存在于染色体外或随机整合到动物染色体中。在此类转基因小鼠中,内源免疫球蛋白基因座通常已经失活。关于从转基因动物获得人抗体的方法的综述参见Lonberg, Nat. Biotech. 23:1117-1125(2005)。也参见例如描述XENOMOUSE™技术的美国专利第6,075,181号及第6,150,584号;描述HUMAB®技术的美国专利第5,770,429号;描述K-MOUSE®技术的美国专利第7,041,870号;及描述VELOCIMOUSE®技术的美国专利申请公布第US 2007/0061900号。可以例如通过与不同的人恒定区组合来进一步修饰来自此类动物产生的完整抗体的人可变区。

[0143] 也可以通过基于融合瘤的方法制备人抗体。用于产生人单克隆抗体的人骨髓瘤及小鼠-人异源骨髓瘤(heteromyeloma)细胞系已有描述。(参见例如Kozbor J. Immunol., 133:3001(1984); Brodeur等人, Monoclonal Antibody Production Techniques and Applications, 第51-63页(Marcel Dekker公司, New York, 1987); 及Boerner等人, J. Immunol., 147:86(1991))。经由人B细胞融合瘤技术产生的人抗体也描述于Li等人, Proc. Nat'l. Acad. Sci. USA, 103:3557-3562(2006)中。其他方法包括例如美国专利第7,189,826号(描述自融合瘤细胞系产生单克隆人IgM抗体)及Ni, Xiandai Mianyixue, 26(4):265-268(2006)(描述人-人融合瘤)中所描述的那些方法。人融合瘤技术(三源融合瘤技术(Trioma technology))也描述于Vollmers及Brandlein, Histology and Histopathology, 20(3):927-937(2005)以及Vollmers及Brandlein, Methods and Findings in Experimental and Clinical Pharmacology, 27(3):185-91(2005)中。

[0144] 也可以通过分离选自人来源的噬菌体展示文库的Fv克隆可变结构域序列来产生人抗体。然后可将此类可变结构域序列与所需人恒定结构域组合。下文描述了从抗体文库中选择人抗体的技术。

[0145] 文库衍生的抗体

[0146] 可以通过对组合文库筛选具有期望的一种或多种活性的抗体来分离本发明抗体。例如,本领域中已知用于产生噬菌体展示文库并对此类文库筛选具有期望的结合特性的抗体的多种方法。这些方法例如综述于Hoogenboom等人, Methods in Molecular Biology

178:1-37 (O'Brien等人编, Human Press, Totowa, NJ, 2001), 且进一步描述于例如 McCafferty等人, Nature 348:552-554; Clackson等人, Nature 352:624-628 (1991); Marks等人, J. Mol. Biol. 222:581-597 (1992); Marks及Bradbury, Methods in Molecular Biology 248:161-175 (Lo编, Human Press, Totowa, NJ, 2003); Sidhu等人, J. Mol. Biol. 338 (2):299-310 (2004); Lee等人, J. Mol. Biol. 340 (5):1073-1093 (2004); Fellouse, Proc. Nat'l. Acad. Sci. USA 101 (34):12467-12472 (2004); 及Lee等人, J. Immunol. Methods 284 (1-2):119-132 (2004)。已经描述了构建单结构域抗体文库的方法, 例如, 参见美国专利第7371849号。

[0147] 在某些噬菌体展示方法中, 通过聚合酶链式反应 (PCR) 分别克隆 VH 及 VL 基因的组库, 并随机重组在噬菌体文库中, 然后可以对其筛选抗原结合噬菌体, 如 Winter 等人, Ann. Rev. Immunol., 12:433-455 (1994) 中描述。噬菌体通常展示作为单链 Fv (scFv) 片段或作为 Fab 片段的抗体片段。来自经免疫来源的文库提供对免疫原的高亲和力抗体, 而不需要构建融合瘤。可替代地, 可以在没有任何免疫的情况下 (例如, 从人) 克隆天然组库以提供针对各种各样的非自身抗原以及自身抗原的抗体的单一来源, 如由 Griffiths 等人, EMBO J, 12:725-734 (1993) 描述。最后, 也可以通过从干细胞克隆未重排的 V 基因区段, 并使用含有随机序列的 PCR 引物来合成制备天然文库, 以编码高度可变的 CDR3 区并在体外实现重排, 如由 Hoogenboom 及 Winter, J. Mol. Biol., 227:381-388 (1992) 描述。描述人抗体噬菌体文库的专利公布包括例如美国专利第 5,750,373 号以及美国专利公布第 2005/0079574 号、第 2005/0119455 号、第 2005/0266000 号、第 2007/0117126 号、第 2007/0160598 号、第 2007/0237764 号、第 2007/0292936 号及第 2009/0002360 号。

[0148] 认为从人抗体文库分离的抗体或抗体片段是本文中的人抗体或人抗体片段。

[0149] 生物活性

[0150] 本文所述的抗 PD-L1 mAb 的生物活性可以通过测量其半数最大抑制浓度 (IC_{50}) 来确定, IC_{50} 是抗体抑制特定生物或生物化学功能 (例如抑制 PD-L1 与其受体 PD-1 之间的结合) 的有效性的量度。例如, 此处 IC_{50} 可用于指示体外中和 50% PD-L1 生物活性所需的抗 PD-L1 sAb 的有效浓度。对于激动剂药物或其他物质 (诸如抗体), IC_{50} 与 " EC_{50} " 相当。 EC_{50} 也表示在体内获得最大作用的 50% 所需的血浆浓度。 IC_{50} 或 EC_{50} 可以通过所属领域中已知的测定来测量, 例如生物测定, 诸如通过 FACS 分析 (竞争结合测定) 的配体结合的抑制, 基于细胞的细胞因子释放测定或扩增的发光邻近均相测定 (AlphaLISA)。

[0151] 例如, 可以使用流式细胞术研究配体结合的阻断 (也参见实施例 1)。表达人 PD-L1 的 CHO 细胞可以从贴壁培养瓶中解离, 并与用于测试的不同浓度的抗 PD-L1 mAb, 及恒定浓度的经标记的 PD-1 蛋白 (例如生物素标记的 hPD-1/Fc 蛋白) 混合。可采用抗 PD-L1 抗体阳性对照, 诸如阿特殊单抗。将混合物在室温下平衡 30 分钟, 用 FACS 缓冲液 (含有 1% BSA 的 PBS) 洗涤三次。然后, 加入特异性识别恒定浓度的经标记 PD-1 蛋白的抗体 (如 PE/Cy5 链霉抗生物素蛋白二级抗体), 并在室温下温育 15 分钟。用 FACS 缓冲液洗涤细胞并通过流式细胞术分析。可以使用 Prism (GraphPad Software, San Diego, CA) 使用非线性回归分析数据以计算 IC_{50} 。竞争测定的结果将证明抗 PD-L1 mAb 抑制经标记的 PD-1 与 PD-L1 之间相互作用的能力。

[0152] 也可通过基于 PD-L1 的细胞因子释放的阻断测定来测试抗 PD-L1 mAb 的生物活性。与对细胞增殖相比, PD-1 信号传导通常对细胞因子产生具有较大作用, 其中对 IFN- γ 、TNF-

α 及IL-2产生的作用显著。PD-1介导的抑制信号传导也取决于TCR信号传导的强度,其中在低水平TCR刺激下实现较大抑制。此减少可通过通过CD28的共刺激(Freeman等人, J. Exp. Med. 192:1027-34 (2000))或IL-2的存在(Carter等人, Eur. J. Immunol. 32:634-43 (2002))来克服。此外,若干研究显示独立于PD-1的PD-L1或PD-L2的受体。B7.1已被鉴定为PD-L1的结合配偶体(Butte等人, Immunity 27:111-22 (2007))。化学交联研究表明,PD-L1及B7.1可通过其IgV样结构域相互作用。B7.1:PD-L1相互作用可将抑制信号引入至T细胞中。因此,通过对PD-L1的信号传导的拮抗作用,包括阻断PD-L1与PD-1、B7.1或两者相互作用,从而防止PD-L1将阴性共刺激信号发送至T细胞及其他抗原呈递细胞有可能回应于对感染(例如,急性及慢性)及肿瘤免疫而增强免疫。此外,本申请的抗PD-L1抗体可与PD-1:PD-L1信号传导的其他组分的拮抗剂(例如拮抗剂抗PD-1及抗PD-L2抗体)组合。因此,通过抗PD-L1抗体的PD-L1路径的阻断可使用多种监测T细胞增殖、IFN- γ 释放或IL-2分泌的生物测定进行研究。

[0153] 例如,将PD-1效应细胞(以人PD-1蛋白及NFAT荧光素酶稳定转染的Jurkat细胞)及CHO-K1/人CD274(稳定表达人CD274的CHO-K1)混合于孔中。在不同的浓度下将抗PD-L1 mAb添加至各孔中。没有抗体可用作背景对照。可采用阴性对照(诸如人IgG1)及阳性对照(诸如阿特珠单抗)。在37°C/5% CO₂温育箱中温育24小时之后,自各测试孔取出培养基以供IL-2分泌测量(Cisbio)。测量各测试抗体的EC₅₀值,所述值将反映测试抗PD-L1 mAb阻断Jurkat细胞上PD-1与PD-L1之间的相互作用因此活化T细胞IL-2产生的能力。

[0154] 在一些实施方案中,本申请的抗PD-L1抗体(尤其抗PD-L1 mAb)阻断或拮抗PD-L1配体所转导的信号。在一些实施方案中,抗PD-L1mAb可结合PD-L1上的表位,以便抑制PD-L1与PD-1相互作用。在一些实施方案中,在抗体组合位点与PD-L1配体结合位点的比例大于1:1且抗体浓度大于10⁻⁸M的条件下,抗PD-L1 mAb可以将PD-L1与其受体PD-1的结合降低至少约5%、10%、20%、25%、30%、40%、50%、60%、70%、75%、80%、90%、95%、99%或99.9%中的任一者。

[0155] 在一些实施方案中,提供一种抗PD-L1 mAb,其包含:重链可变结构域(VH),其具有包含SEQ ID NO:71-82中任一者的氨基酸序列的重链CDR1或其包含至多约3个(诸如约1个、2个或3个中的任一者)氨基酸取代的变体,包含SEQ ID NO:83-97中任一者的氨基酸序列的重链CDR2或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,及包含SEQ ID NO:98-109中任一者的氨基酸序列的重链CDR3或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体;及轻链可变结构域(VL),其具有包含SEQ ID NO:110-123中任一者的氨基酸序列的轻链CDR1或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,包含SEQ ID NO:124-135中任一者的氨基酸序列的轻链CDR2或其包含至多约3个(诸如约1个、2个或3个)氨基酸取代的变体,及包含SEQ ID NO:136-147中任一者的氨基酸序列的轻链CDR3或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体。在一些实施方案中,抗PD-L1 mAb与PD-L1之间的结合的K_D为约10⁻⁵M至约10⁻¹²M(诸如约10⁻⁷M至约10⁻¹²M或约10⁻⁸M至约10⁻¹²M)。在一些实施方案中,抗PD-L1抗体是啮齿动物的、嵌合的、人的、部分人源化的或完全人源化的。

[0156] 在一些实施方案中,抗PD-L1 mAb包含有包含SEQ ID NO:98-109中任一者的氨基酸序列的VH CDR3及包含SEQ ID NO:136-147中任一者的氨基酸序列的VL CDR3,且氨基酸

取代位于VH及VL结构域的CDR1和/或CDR2。

[0157] 因此,在一些实施方案中,提供一种抗PD-L1 mAb,其包含:重链可变结构域(VH),其具有包含SEQ ID NO:71-82中任一者的氨基酸序列的CDR1或其包含至多约3个(诸如约1个、2个或3个中的任一者)氨基酸取代的变体,包含SEQ ID NO:83-97中任一者的氨基酸序列的CDR2或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,及包含SEQ ID NO:98-109中任一者的氨基酸序列的CDR3;及轻链可变结构域(VL),其具有包含SEQ ID NO:110-123中任一者的氨基酸序列的CDR1或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,包含SEQ ID NO:124-135中任一者的氨基酸序列的CDR2或其包含至多约3个(诸如约1个、2个或3个)氨基酸取代的变体,及包含SEQ ID NO:136-147中任一者的氨基酸序列的CDR3。在一些实施方案中,抗PD-L1 mAb与PD-L1之间的结合的 K_D 为约 10^{-5} M至约 10^{-12} M(诸如约 10^{-7} M至约 10^{-12} M或约 10^{-8} M至约 10^{-12} M)或更小。在一些实施方案中,抗PD-L1 mAb是啮齿动物的、嵌合的、人的、部分人源化的或完全人源化的。

[0158] 在一些实施方案中,提供一种抗PD-L1 mAb,其包含:重链可变结构域(VH),其具有包含SEQ ID NO:71-82中任一者的氨基酸序列的CDR1,包含SEQ ID NO:83-97中任一者的氨基酸序列的CDR2,及包含SEQ ID NO:98-109中任一者的氨基酸序列的CDR3;及轻链可变结构域(VL),其具有包含SEQ ID NO:110-123中任一者的氨基酸序列的CDR1,包含SEQ ID NO:124-135中任一者的氨基酸序列的CDR2,及包含SEQ ID NO:136-147中任一者的氨基酸序列的CDR3。在一些实施方案中,抗PD-L1 mAb与PD-L1之间的结合的 K_D 为约 10^{-5} M至约 10^{-12} M(诸如约 10^{-7} M至约 10^{-12} M或约 10^{-8} M至约 10^{-12} M)。在一些实施方案中,抗PD-L1 mAb是啮齿动物的、嵌合的、人的、部分人源化的或完全人源化的。

[0159] 在一些实施方案中,本申请的抗体或抗原结合片段包含表20及21中提供的CDR的序列。

[0160] CDR可以以各种成对组合进行组合以产生许多人源化抗PD-L1抗体。人源化取代对于所属领域技术人员来说是清楚的。例如,可以通过比较天然存在的VH或VL的FR序列与一个或多个密切相关的人VH或VL的对应FR序列,然后使用所属领域中已知(也如本文所述)的方法将一个或多个这些潜在有用的人源化取代引入所述VH或VL中来确定潜在有用的人源化取代。将人源化重链及轻链配对。可以测试所产生的人源化抗体的PD-L1结合亲和力、稳定性、表达的容易程度及水平,和/或其他所需性质。本文所述的抗PD-L1 mAb可以为部分或完全人源化的。优选地,所产生的人源化抗体(诸如人源化mAb)或其抗原结合片段在本文所述的 K_D 、 K_{on} 、 K_{off} 的情况下结合PD-L1。

[0161] 在一些实施方案中,提供一种抗PD-L1人源化mAb或其抗原结合片段,其包含:包含SEQ ID NO:1-44中任一者的氨基酸序列的VH结构域或其与SEQ ID NO:1-44中任一者具有至少约80%(诸如至少约80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%或99%中任一者)序列同一性的变体;及包含SEQ ID NO:45-70中任一者的氨基酸序列的VL结构域或其与SEQ ID NO:45-70中任一者具有至少约80%(诸如至少约80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%或99%)序列同一性的变体。在一些实施方案中,提供一种抗PD-L1 mAb,其包含:包含SEQ ID NO:1-44中任一者的氨基酸序列的VH结构域或其包含在VH结构域中包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体;及包含SEQ ID NO:45-70中任一者的氨基酸序列的VL结构域或其包含在VL结构域中包含至多约

3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体。在一些实施方案中,抗PD-L1 mAb或其抗原结合片段包含:具有SEQ ID NO:1-44中任一者的氨基酸序列的VH结构域的变体,其中所述变体在CDR中包含氨基酸取代,诸如VH的CDR1、和/或CDR2、和/或CDR3;及具有SEQ ID NO:45-70中任一者的氨基酸序列的VL结构域的变体,其中所述变体在CDR中包含氨基酸取代,诸如VL中任一者的CDR1、和/或CDR2、和/或CDR3。在一些实施方案中,抗PD-L1 mAb或其抗原结合片段包含:具有SEQ ID NO:1-44中任一者的氨基酸序列的VH结构域的变体,其中所述变体在FR中包含氨基酸取代,诸如VH中任一者的FR1、和/或FR2、和/或FR3、和/或FR4;及具有SEQ ID NO:45-70中任一者的氨基酸序列的VL结构域的变体,其中所述变体在FR中包含氨基酸取代,诸如SEQ ID NO:45-70中任一者的FR1、和/或FR2、和/或FR3、和/或FR4。

[0162] 在一些实施方案中,提供一种抗PD-L1抗体,诸如mAb(后文称为“竞争性抗PD-L1抗体或竞争性抗PD-L1 mAb”)或其抗原结合片段,其与本文所述的抗PD-L1 mAb竞争地特异性结合PD-L1。在一些实施方案中,可以使用ELISA测定来确定竞争性结合。例如,在一些实施方案中,提供一种抗PD-L1 mAb,其与包含分别以下的抗PD-L1mAb竞争地特异性结合PD-L1: SEQ ID NO:1-44中任一者的VH氨基酸序列及SEQ ID NO:45-70中任一者的VL氨基酸序列。又例如,在一些实施方案中,提供一种抗PD-L1 mAb,其与包含以下的抗PD-L1 mAb竞争地特异性结合PD-L1:重链可变结构域(VH),其具有包含SEQ ID NO:71-82中任一者的氨基酸序列的CDR1,包含SEQ ID NO:83-97中任一者的氨基酸序列的CDR2,及包含SEQ ID NO:98-109中任一者的氨基酸序列的CDR3;及轻链可变结构域(VL),其具有包含SEQ ID NO:110-123中任一者的氨基酸序列的CDR1,包含SEQ ID NO:124-135中任一者的氨基酸序列的CDR2,及包含SEQ ID NO:136-147中任一者的氨基酸序列的CDR3。又例如,在一些实施方案中,提供一种抗PD-L1 mAb,其与表20及21中所述的任何抗PD-L1 mAb竞争地特异性结合PD-L1。在一些实施方案中,竞争性抗PD-L1 mAb与PD-L1之间的结合的 K_D 为约 10^{-5} M至约 10^{-12} M(诸如约 10^{-7} M至约 10^{-12} M或约 10^{-8} M至约 10^{-12} M)或更小。在一些实施方案中,竞争性抗PD-L1 mAb是啮齿动物的、嵌合的、人的、部分人源化的或完全人源化的。

[0163] 包含抗PD-L1 mAb的构建体

[0164] 包含抗PD-L1 mAb的抗PD-L1构建体可以为任何可能的形式。

[0165] 在一些实施方案中,包含抗PD-L1 mAb的抗PD-L1构建体可以还包含另外的多肽序列,例如一个或多个抗体部分。此类另外的多肽序列可以或不改变或以其他方式影响抗PD-L1 mAb的(生物学)性质,并且可以或不向本文所述的抗PD-L1 mAb添加其他功能。在一些实施方案中,另外的多肽序列赋予本申请的抗PD-L1 mAb一种或多种所需的性质或功能。在一些实施方案中,抗PD-L1构建体为嵌合抗原受体(CAR),其包含有包含本文所述的一个或多个抗PD-L1结合部分的细胞外抗原结合结构域。

[0166] 在一些实施方案中,另外的多肽序列可为特异性识别第二抗原的第二抗体部分(诸如sdAb、scFv)。在一些实施方案中,第二抗原决定不为PD-L1。在一些实施方案中,第二抗体部分特异性识别PD-L1上与本文所述的抗PD-L1 mAb相同的表位。在一些实施方案中,第二抗体部分特异性识别PD-L1上与本文所述的抗PD-L1 mAb不同的表位。

[0167] 在一些实施方案中,额外的多肽序列可以增加分子的稳定性、溶解度或吸收,降低免疫原性或毒性,消除或减弱不期望的副作用,和/或与本文所述的抗PD-L1 mAb本身相比,

赋予本发明的抗PD-L1构建体其他有利性质和/或降低其不希望的性质。

[0168] 全长IgG

[0169] 在一些实施方案中,抗PD-L1 mAb为全长IgG。在一些实施方案中,抗PD-L1 mAb包含IgG(诸如IgG1、IgG2、IgG3或IgG4中任一者)的恒定区。在一些实施方案中,恒定区为人恒定区。在一些实施方案中,恒定区为人IgG1恒定区。

[0170] 因此在一些实施方案中,提供一种抗PD-L1全长IgG,其包含:重链,其中所述可变区(VH)包含有包含SEQ ID NO:71-82中任一者的氨基酸序列的CDR1或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,包含SEQ ID NO:83-97中任一者的氨基酸序列的CDR2或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,及包含SEQ ID NO:98-109中任一者的氨基酸序列的CDR3或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,且其中所述VH融合至免疫球蛋白的重链恒定区(铰链、 C_H1 、 C_H2 及 C_H3);及轻链,其中所述可变区(VL)包含有包含SEQ ID NO:110-123中任一者的氨基酸序列的CDR1或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,包含SEQ ID NO:124-135中任一者的氨基酸序列的CDR2或其包含约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,及包含SEQ ID NO:136-147中任一者的氨基酸序列的CDR3或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,且其中所述VL融合至免疫球蛋白的轻链恒定区(CL)。在一些实施方案中,提供一种抗PD-L1全长IgG,其包含:重链,其中所述可变区(VH)包含有包含SEQ ID NO:71-82中任一者的氨基酸序列的CDR1,包含SEQ ID NO:83-97中任一者的氨基酸序列的CDR2,及包含SEQ ID NO:98-109中任一者的氨基酸序列的CDR3,或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,且其中所述VH融合至免疫球蛋白的重链恒定区(铰链、 C_H1 、 C_H2 及 C_H3);及轻链,其中所述可变区(VL)包含有包含SEQ ID NO:110-123中任一者的氨基酸序列的CDR1,包含SEQ ID NO:124-135中任一者的氨基酸序列的CDR2,及包含SEQ ID NO:136-147中任一者的氨基酸序列的CDR3或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,且其中所述VL融合至免疫球蛋白的轻链恒定区(CL)。在一些实施方案中,恒定区为人IgG1恒定区。在一些实施方案中,全长抗PD-L1 IgG与PD-L1之间的结合的 K_D 为约 10^{-5} M至约 10^{-12} M(诸如约 10^{-7} M至约 10^{-12} M或约 10^{-8} M至约 10^{-12} M)或更小。在一些实施方案中,全长抗PD-L1 IgG是啮齿动物的、嵌合的、人的、部分人源化的或完全人源化的。

[0171] 在一些实施方案中,提供一种全长抗PD-L1 mAb,其包含SEQ ID NO:1-44中任一者的重链氨基酸序列及SEQ ID NO:45-70中任一者的轻链氨基酸序列。

[0172] 在一些实施方案中,提供一种全长抗PD-L1 IgG(后文称为“竞争性抗PD-L1 IgG”),其与本文所述的任一全长抗PD-L1 IgG竞争地特异性结合PD-L1。可以使用ELISA测定来确定竞争性结合。例如,在一些实施方案中,提供一种抗PD-L1 IgG,其与包含以下的抗PD-L1 IgG竞争地特异性结合PD-L1:SEQ ID NO:1-44中任一者的重链氨基酸序列及SEQ ID NO:45-70中任一者的轻链氨基酸序列。又例如,在一些实施方案中,提供一种抗PD-L1 IgG,其与包含以下的抗PD-L1 IgG竞争地特异性结合PD-L1:重链,其中可变区(VH)包含有包含SEQ ID NO:71-82中任一者的氨基酸序列的CDR1,包含SEQ ID NO:83-97中任一者的氨基酸序列的CDR2,及包含SEQ ID NO:98-109中任一者的氨基酸序列的CDR3;及轻链,其中可变区(VL)包含有包含SEQ ID NO:110-123中任一者的氨基酸序列的CDR1,包含SEQ ID NO:124-

135中任一者的氨基酸序列的CDR2,及包含SEQ ID NO:136-147中任一者的氨基酸序列的CDR3。在一些实施方案中,竞争性抗PD-L1 IgG与PD-L1之间的结合的 K_D 为约 10^{-5} M至约 10^{-12} M(诸如约 10^{-7} M至约 10^{-12} M或约 10^{-8} M至约 10^{-12} M)或更小。在一些实施方案中,竞争性抗PD-L1 IgG是啮齿动物的、嵌合的、人的、部分人源化的或完全人源化的。

[0173] 多价和/或多特异性抗体

[0174] 在一些实施方案中,抗PD-L1构建体包含与一种或多种其他抗体部分(例如特异性识别另一抗原的抗体部分)融合的本文所述的抗PD-L1 mAb。所述一种或多种其他抗体部分可以为任何抗体或抗体片段形式,例如sdAb、全长抗体、Fab、Fab'、(Fab')₂、Fv、单链Fv(scFv)、scFv-scFv、微抗体或双抗体。对于某些抗体片段的综述,参见Hudson等人,Nat.Med.9:129-134(2003)。对于scFv片段的综述,参见例如Pluckthün,The Pharmacology of Monoclonal Antibodies,第113卷,Rosenburg及Moore编,(Springer-Verlag,New York),第269-315页(1994);也参见WO 93/16185;及美国专利第5,571,894号及第5,587,458号。对于包含补救受体结合表位残基且具有延长的体内半衰期的Fab及F(ab')₂片段的讨论,参见美国专利第5,869,046号。对于多特异性抗体的综述,参见Weidle等人,Cancer Genomics Proteomics,10(1):1-18,2013;Geering及Fussenegger,Trends Biotechnol.,33(2):65-79,2015;Stamova等人,Antibodies,1(2):172-198,2012。双抗体为可为二价或双特异性的具有两个抗原结合位点的抗体片段。参见例如EP 404,097;WO 1993/01161;Hudson等人,Nat.Med.9:129-134(2003);及Hollinger等人,Proc.Nat'l.Acad.Sci.USA 90:6444-6448(1993)。三抗体及四抗体也描述于Hudson等人,Nat.Med.9:129-134(2003)中。抗体片段可通过各种技术制备,包括但不限于蛋白水解消化完整抗体以及通过重组宿主细胞(例如大肠杆菌或噬菌体)产生,如本文所述。在一些实施方案中,所述一种或多种其他抗体部分是抗体模拟物,其是包含令人联想到抗体的抗原结合结构域的小工程化蛋白质(Geering及Fussenegger,Trends Biotechnol.,33(2):65-79,2015)。这些分子衍生自现有人支架蛋白并包含单一多肽。可包含在本文所述的抗PD-L1构建体内的示例性抗体模拟物可以为,但不限于,设计的锚蛋白重复蛋白(DARPin;包含3-5个完全合成的锚蛋白重复序列,其侧翼为N-及C末端Cap结构域),一种亲和力多聚体(avimer;高亲和力蛋白质,其包含多个A结构域,每个结构域对靶标具有低亲和力),或Anticalin(基于脂质运载蛋白的支架,具有四个可接近的环,每个环的序列可以为随机的)。

[0175] 用于制造多特异性抗体的技术包括但不限于具有不同特异性的两个免疫球蛋白重链-轻链对的重组共表达(参见Milstein及Cuellar,Nature 305:537(1983),WO 93/08829,及Traunecker等人,EMBO J.10:3655(1991)),及“隆突(knob-in-hole)”工程改造(参见例如美国专利第5,731,168号)。多特异性抗体也可通过以下方式制得:工程改造针对制造抗体Fc-杂二聚分子的静电转向效应(WO 2009/089004A1);使两种或更多种抗体或片段交联(参见例如美国专利第4,676,980号,及Brennan等人,Science,229:81(1985));使用亮氨酸拉链来生产双特异性抗体(参见例如Kostelny等人,J.Immunol.,148(5):1547-1553(1992));使用用于制造双特异性抗体片段的“双抗体”技术(参见例如Hollinger等人,Proc.Nat'l.Acad.Sci.USA,90:6444-6448(1993));及使用单链Fv(scFv)二聚体(参见例如Gruber等人,J.Immunol.,152:5368(1994));及如例如Tutt等人,J.Immunol.147:60(1991)中所述制备三特异性抗体;以及产生包含串联单结构域抗体的多肽(参见例如美国专利申

请第20110028695号;及Conrath等人,J.Biol.Chem.,2001;276(10):7346-50)。本文也包括具有三个或更多个功能性抗原结合位点的经改造抗体,包括“章鱼抗体(Octopus antibody)”(参见例如US 2006/0025576A1)。

[0176] 肽接头

[0177] 在一些实施方案中,抗PD-L1构建体内的两种或更多个抗体部分可任选地通过肽接头连接。抗PD-L1构建体中使用的肽接头的长度、可挠性和/或其他性质可能对性质具有一些影响,所述性质包括但不限于对于一种或多种特定抗原或表位的亲和力、特异性或亲合力。例如,可以选择较长的肽接头以确保两个相邻的结构域不在空间上相互干扰。在一些实施方案中,肽接头包含挠性残基(例如甘氨酸及丝氨酸),使得相邻的结构域相对于彼此自由移动。例如,甘氨酸-丝氨酸双联体可以为合适的肽接头。

[0178] 肽接头可具有任何合适的长度。在一些实施方案中,肽接头为至少约1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、25、30、35、40、50、75、100或更多个氨基酸长度中的任一者。在一些实施方案中,肽接头为不超过约100、75、50、40、35、30、25、20、19、18、17、16、15、14、13、12、11、10、9、8、7、6、5或更少个氨基酸长度中的任一者。在一些实施方案中,肽接头的长度为约1个氨基酸至约10个氨基酸,约1个氨基酸至约20个氨基酸,约1个氨基酸至约30个氨基酸,约5个氨基酸至约15个氨基酸,约10个氨基酸至约25个氨基酸,约5个氨基酸至约30个氨基酸,约10个氨基酸至约30个氨基酸长,约30个氨基酸至约50个氨基酸,约50个氨基酸至约100个氨基酸,或约1个氨基酸至约100个氨基酸中的任一者。

[0179] 肽接头可具有天然存在的序列或非天然存在的序列。例如,衍生自仅重链抗体的铰链区的序列可用作接头。参见,例如,W01996/34103。在一些实施方案中,肽接头为突变人IgG1铰链(EPKSSDKTHTSPSP,SEQ ID NO:399)。在一些实施方案中,肽接头是柔性接头。示例性柔性接头包括甘氨酸聚合物(G_n),甘氨酸-丝氨酸聚合物(包括,例如, $(GS)_n$ 、 $(GSGGS)_n$ 、 $(GGGS)_n$ 及 $(GGGG)_n$,其中n至少为1的整数),甘氨酸-丙氨酸聚合物,丙氨酸-丝氨酸聚合物,及在所属领域中已知的其他柔性接头。在一些实施方案中,肽接头包含GGGGSGGGG(SEQ ID NO:397)的氨基酸序列。在一些实施方案中,肽接头包含SEQ ID NO:398(GGGSGGGSGGGG)的氨基酸序列。

[0180] 双特异性抗体

[0181] 在一些实施方案中,本申请的分离的抗体或抗原结合片段为双特异性或多特异性抗体,其包含本文所述的融合至第二抗体部分的抗PD-L1 IgG,其中所述第二抗体部分特异性结合另一抗原,优选另一抑制性免疫检查点分子。

[0182] 在一实施方案中,另一抗原为CTLA-4且所述第二抗体部分包含特异性结合CTLA-4的抗体或抗原结合片段,诸如抗CTLA-4mAb,优选抗CTLA-4sdAb。包含针对PD-L1及CTLA-4的双特异性的分离的抗体或抗原结合部分可在后文称为“抗PD-L1/CTLA-4抗体”、“抗PD-L1/CTLA-4构建体”或“PD-L1×CTLA-4抗体”。

[0183] 在一实施方案中,另一抗原为TIGIT且所述第二抗体部分包含特异性结合TIGIT的抗体或抗原结合片段,诸如抗TIGIT mAb,优选抗TIGIT sdAb。包含针对PD-L1及TIGIT的双特异性的分离的抗体或抗原结合部分可在后文称为“抗PD-L1/TIGIT抗体”、“抗PD-L1/TIGIT构建体”或“PD-L1×TIGIT抗体”。

[0184] 在一实施方案中,另一抗原为TIM-3且所述第二抗体部分包含特异性结TIM-3的抗

体或抗原结合片段,诸如抗TIM-3mAb,优选抗TIM3 sdAb。包含针对PD-L1及TIM-3的双特异性的分离的抗体或抗原结合部分可在后文称为“抗PD-L1/TIM-3抗体”、“抗PD-L1/TIM-3构建体”或“PD-L1×TIM-3抗体”。

[0185] 在一实施方案中,另一抗原为LAG-3且所述第二抗体部分包含特异性结合LAG-3的抗体或抗原结合片段,诸如抗LAG-3mAb,优选抗LAG-3sdAb。包含针对PD-L1及LAG-3的双特异性的分离的抗体或抗原结合部分可在后文称为“抗PD-L1/LAG-3抗体”、“抗PD-L1/LAG-3构建体”或“PD-L1×LAG-3抗体”。

[0186] 与PD-L1类似,CTLA-4、TIGIT、TIM-3及LAG-3是抑制性免疫检查点分子。

[0187] 因此在一些实施方案中,提供一种抗PD-L1构建体,其包含特异性识别PD-L1的全长IgG及选自由抗CTLA-4sdAb、抗TIGIT sdAb、抗TIM-3sdAb及抗LAG-3sdAb组成的组的sdAb,其中所述抗PD-L1 IgG包含:重链,其中所述可变区(VH)包含有包含SEQ ID NO:71-82中任一者的氨基酸序列的CDR1或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,包含SEQ ID NO:83-97中任一者的氨基酸序列的CDR2或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,及包含SEQ ID NO:98-109中任一者的氨基酸序列的CDR3或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,且其中所述VH融合至免疫球蛋白的重链恒定区(铰链、 C_H1 、 C_H2 及 C_H3);及轻链,其中所述可变区(VL)包含有包含SEQ ID NO:110-123中任一者的氨基酸序列的CDR1或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,包含SEQ ID NO:124-135中任一者的氨基酸序列的CDR2或其包含约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,及包含SEQ ID NO:136-147中任一者的氨基酸序列的CDR3或其包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,且其中所述VL融合至免疫球蛋白的轻链恒定区(CL)。在一些实施方案中,sdAb的N末端融合至特异性识别PD-L1的全长抗体的重链的至少一者的C末端。在一些实施方案中,sdAb的C末端融合至特异性识别PD-L1的全长抗体的重链的至少一者的N末端。在一些实施方案中,sdAb的N末端融合至特异性识别PD-L1的全长抗体的轻链的至少一者的C末端。在一些实施方案中,sdAb的C末端融合至特异性识别PD-L1的全长抗体的轻链的至少一者的N末端。在一些实施方案中,特异性识别PD-L1的全长IgG及第二结合部分sdAb任选地通过肽接头连接。在一些实施方案中,肽接头包含SEQ ID NO:397-399的氨基酸序列。在一些实施方案中,抗PD-L1 mAb与PD-L1之间的结合的 K_D 为约 10^{-5} M至约 10^{-12} M(诸如约 10^{-7} M至约 10^{-12} M或约 10^{-8} M至约 10^{-12} M)或更小。在一些实施方案中,抗PD-L1 IgG是啮齿动物的、嵌合的、人的、部分人源化的或完全人源化的。

[0188] 在一些实施方案中,提供一种抗PD-L1构建体,其包含特异性识别PD-L1的全长IgG及选自由抗CTLA-4sdAb、抗TIGIT sdAb、抗TIM-3sdAb及抗LAG-3sdAb组成的组的sdAb,其中所述全长IgG包含:包含SEQ ID NO:1-44中任一者的氨基酸序列的VH结构域或其与SEQ ID NO:1-44中任一者具有至少约80%(诸如至少约80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%或99%中任一者)序列同一性的变体,且其中所述VH融合至免疫球蛋白的重链恒定区(铰链、 C_H1 、 C_H2 及 C_H3);及包含SEQ ID NO:45-70中任一者的氨基酸序列的VL结构域或其与SEQ ID NO:45-70中任一者具有至少约80%(诸如至少约80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%或99%中任一者)序列同一性的变体,且其中所述VL融合至免疫球蛋白的轻链恒定区(CL)。在一些实施方案中,提供一种分离的抗PD-L1

构建体,其包含特异性识别PD-L1的全长IgG及选自由抗CTLA-4sdAb、抗TIGIT sdAb、抗TIM-3sdAb及抗LAG-3sdAb组成的组的sdAb,其中所述全长IgG包含:包含SEQ ID NO:1-44中任一者的氨基酸序列的VH结构域或其在VH结构域中包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,且其中所述VH融合至免疫球蛋白的重链恒定区(铰链、C_H1、C_H2及C_H3);及包含SEQ ID NO:45-70中任一者的氨基酸序列的VL结构域或其在VL结构域中包含至多约3个(诸如约1个、2个或3个中任一者)氨基酸取代的变体,且其中所述VL融合至免疫球蛋白的轻链恒定区(CL)。

[0189] 在一些实施方案中,包含有包含SEQ ID NO:1-44的氨基酸序列的VH结构域或其变体的抗PD-L1全长IgG在CDR诸如SEQ ID NO:1-44中任一者的CDR1、和/或CDR2、和/或CDR3中包含氨基酸取代,且其中所述VH融合至免疫球蛋白的重链恒定区(铰链、C_H1、C_H2及C_H3);且包含SEQ ID NO:45-70中任一者的氨基酸序列的VL结构域或其变体在CDR诸如SEQ ID NO:45-70中任一者的CDR1、和/或CDR2、和/或CDR3中包含氨基酸取代,且其中所述VH融合至免疫球蛋白的轻链恒定区(CL)。在一些实施方案中,包含有包含SEQ ID NO:1-44的氨基酸序列的VH结构域或其变体的抗PD-L1全长IgG包含SEQ ID NO:1-44中任一者的CDR1、CDR2及CDR3,且氨基酸取代处于FR中,诸如SEQ ID NO:1-44中任一者的FR1、和/或FR2、和/或FR3、和/或FR4,且其中所述VH融合至免疫球蛋白的重链恒定区(铰链、C_H1、C_H2及C_H3);且包含SEQ ID NO:45-70中任一者的氨基酸序列的VL结构域或其变体包含SEQ ID NO:45-70中任一者的CDR1、CDR2及CDR3,且氨基酸取代处于FR中,诸如SEQ ID NO:45-70中任一者的FR1、和/或FR2、和/或FR3、和/或FR4,且其中所述VL融合至免疫球蛋白的轻链恒定区(CL)。在一些实施方案中,包含有包含SEQ ID NO:1-44的氨基酸序列的VH结构域或其变体的抗PD-L1全长IgG在CDR及FR中包含氨基酸取代,且其中所述VH融合至免疫球蛋白的重链恒定区(铰链、C_H1、C_H2及C_H3);且包含SEQ ID NO:45-70中任一者的氨基酸序列的VL结构域或其变体在CDR及FR中包含氨基酸取代,且其中所述VL融合至免疫球蛋白的轻链恒定区(CL)。在一些实施方案中,提供一种分离的抗PD-L1构建体,其包含特异性识别PD-L1的全长IgG及选自由抗CTLA-4sdAb、抗TIGIT sdAb、抗TIM-3sdAb及抗LAG-3sdAb组成的组的sdAb,其中所述全长IgG包含:包含SEQ ID NO:1-44中任一者的氨基酸序列的VH结构域,其融合至免疫球蛋白的重链恒定区(铰链、C_H1、C_H2及C_H3);及包含SEQ ID NO:45-70中任一者的氨基酸序列的VL结构域,其融合至免疫球蛋白的轻链恒定区(CL)。在一些实施方案中,sdAb的N末端融合至特异性识别PD-L1的全长抗体的重链的至少一者的C末端。在一些实施方案中,sdAb的C末端融合至特异性识别PD-L1的全长抗体的重链的至少一者的N末端。在一些实施方案中,sdAb的N末端融合至特异性识别PD-L1的全长抗体的轻链的至少一者的C末端。在一些实施方案中,sdAb的C末端融合至特异性识别PD-L1的全长抗体的轻链的至少一者的N末端。在一些实施方案中,特异性识别PD-L1的全长IgG及第二结合部分sdAb任选地通过肽接头连接。在一些实施方案中,肽接头包含SEQ ID NO:397-399的氨基酸序列。在一些实施方案中,抗PD-L1 mAb与PD-L1之间的结合的K_D为约10⁻⁵M至约10⁻¹²M(诸如约10⁻⁷M至约10⁻¹²M或约10⁻⁸M至约10⁻¹²M)。在一些实施方案中,抗PD-L1 mAb是啮齿动物的、嵌合的、人的、部分人源化的或完全人源化的。

[0190] 在一些实施方案中,还提供一种包含特异性识别PD-L1的全长IgG的抗PD-L1构建体(后文称为“竞争性抗PD-L1构建体”),其与本文所述的抗PD-L1/CTLA-4构建体、抗PD-L1/TIGIT构建体、抗PD-L1/TIM-3构建体或抗PD-L1/LAG-3构建体竞争地特异性结合PD-L1。

[0191] 抗PD-L1抗体变体

[0192] 在一些实施方案中,涵盖本文所提供的抗体的氨基酸序列变体。例如,可能需要改善抗体的结合亲和力和/或其他生物特性。抗体的氨基酸序列变体可通过将适当修饰引入编码所述抗体的核苷酸序列中或通过肽合成来制备。此类修饰包括例如抗体的氨基酸序列内的残基的缺失和/或插入和/或取代。可对缺失、插入及取代进行任何组合以获得最终构建体,其限制条件为最终构建体具有所需特征,例如抗原结合性。

[0193] a) 取代、插入及缺失变体

[0194] 在一些实施方案中,提供具有一个或多个氨基酸取代的抗体变体。用于取代突变诱发的所关注位点包括HVR及FR。保守性取代展示于表2中的标题“优选取代”下。更实质性变化提供于表2中的标题“示例性取代”下,且如以下关于氨基酸侧链类别进一步所述。氨基酸取代可引入所关注抗体及经筛选所需活性(例如,保留的/改善的抗原结合性、降低的免疫原性或改善的ADCC或CDC)的产物中。

[0195] 表2. 氨基酸取代

原始残基	示例性取代	优选取代
Ala (A)	Val;Leu;Ile	Val
Arg (R)	Lys;Gln;Asn	Lys
Asn (N)	Gln;His;Asp;Lys;Arg	Gln
Asp (D)	Glu;Asn	Glu
Cys (C)	Ser;Ala	Ser
Gln (Q)	Asn;Glu	Asn
Glu (E)	Asp;Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn;Gln;Lys;Arg	Arg
Ile (I)	Leu;Val;Met;Ala;Phe;正亮氨酸	Leu
Leu (L)	正亮氨酸;Ile;Val;Met;Ala;Phe	Ile
Lys (K)	Arg;Gln;Asn	Arg
Met (M)	Leu;Phe;Ile	Leu
Phe (F)	Trp;Leu;Val;Ile;Ala;Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Val;Ser	Ser
Trp (W)	Tyr;Phe	Tyr
Tyr (Y)	Trp;Phe;Thr;Ser	Phe
Val (V)	Ile;Leu;Met;Phe;Ala;正亮氨酸	Leu

[0197] 可基于共同侧链性质将氨基酸分成以下类别:

[0198] (1) 疏水性:正亮氨酸、Met、Ala、Val、Leu、Ile;

[0199] (2) 中性亲水性:Cys、Ser、Thr、Asn、Gln;

[0200] (3) 酸性:Asp、Glu;

[0201] (4) 碱性:His、Lys、Arg;

[0202] (5) 影响链取向的残基: Gly、Pro;

[0203] (6) 芳香性: Trp、Tyr、Phe。

[0204] 非保守性取代将需要将这些类别之一的成员更换成另一类别。

[0205] 一种类型的取代变体涉及取代亲本抗体 (例如, 人源化抗体或人抗体) 的一个或多个高变区残基。一般说来, 选择用于进一步研究的所产生变体相对于亲本抗体将在某些生物特性方面具有改变 (例如改善) (例如亲和力增加、免疫原性降低) 和/或将基本上保留亲本抗体的某些生物特性。一个示例性取代变体为亲和力成熟抗体, 其可例如使用基于噬菌体展示的亲和力成熟技术 (诸如本文描述的那些技术) 便利地产生。简而言之, 使一个或多个HVR残基突变, 并且使变体抗体展示在噬菌体上并筛选特定生物活性 (例如结合亲和力)。

[0206] 可在HVR中进行改变 (例如取代) 以例如改善抗体亲和力。可在HVR“热点” (即由在体细胞成熟过程期间以高频率经受突变的密码子编码的残基) (参见例如Chowdhury, *Methods Mol. Biol.* 207:179-196 (2008)) 和/或SDR (a-CDR) 中进行这些改变, 且测试所得变体VH或VL的结合亲和力。通过构建及从二级文库中重新选择的亲和力成熟已经例如在Hoogenboom等人的*Methods in Molecular Biology* 178:1-37 (O'Brien等人编, Human Press, Totowa, NJ, (2001)) 中描述。在亲和力成熟的一些实施方案中, 通过多种方法 (例如易错PCR、链改组或寡核苷酸定向诱变) 中的任一种将多样性引入选用于成熟的可变基因中。然后产生二级文库。然后筛选文库以鉴别具有所需亲和力的任何抗体变体。引入多样性的另一方法涉及HVR定向方法, 其中使若干HVR残基 (例如一次4-6个残基) 随机化。可例如使用丙氨酸扫描诱变或模型化来特异性地鉴别抗原结合中涉及的HVR残基。特别地, 经常靶向CDR-H3及CDR-L3。

[0207] 在一些实施方案中, 取代、插入或缺失可发生在一个或多个HVR内, 只要此类改变基本上不降低抗体结合抗原的能力即可。例如, 可在HVR中进行基本上不降低结合亲和力的保守性改变 (例如如本文所提供的保守性取代)。此类改变可处于HVR“热点”或CDR以外。在以上提供的变体V_HH序列的一些实施方案中, 各HVR未被改变或含有不超过一个、两个或三个氨基酸取代。

[0208] 一种可用于鉴定抗体中可以作为诱变靶位的残基或区域的方法称作“丙氨酸扫描诱变”, 如由Cunningham及Wells (1989) *Science*, 244:1081-1085所描述。在此方法中, 鉴别某一残基或一组目标残基 (例如带电荷残基, 诸如Arg、Asp、His、Lys及Glu) 且置换为中性或带负电荷氨基酸 (例如丙氨酸或聚丙氨酸) 以确定抗体与抗原的相互作用是否受到影响。可在对初始取代显示功能敏感性的氨基酸位置上引入其他取代。可替代地或另外, 抗原-抗体复合物的晶体结构用来鉴别抗体与抗原之间的接触点。此类接触残基及相邻残基可作为取代的候选物而被靶向或消除。可筛选变体以确定其是否含有所需特性。

[0209] 氨基酸序列插入包括长度在一个残基至含有一百个或更多个残基的多肽的范围内的氨基末端和/或羧基末端融合, 以及具有单个或多个氨基酸残基的序列内插入。末端插入的实例包括具有N端甲硫胺酰基残基的抗体。抗体分子的其他插入变体包括抗体的N端或C端与增加抗体的血清半衰期的酶 (例如用于ADEPT) 或多肽的融合。

[0210] b) 糖基化变体

[0211] 在一些实施方案中, 改变本文提供的抗PD-L1抗体以提高或降低抗体糖基化的程度。对抗体添加糖基化位点或使抗体缺失糖基化位点可通过改变氨基酸序列以使得产生或

除去一个或多个糖基化位点来便利地实现。

[0212] 当抗PD-L1构建体包含Fc区时,可以改变与其连接的碳水化合物。由哺乳动物细胞产生的天然抗体通常包含一般通过N-键连接到Fc区的CH2结构域的Asn297的分支二天线低聚糖。参见例如Wright等人TIBTECH 15:26-32(1997)。低聚糖可包括各种碳水化合物,例如甘露糖、N-乙酰基葡萄糖胺(GlcNAc)、半乳糖及唾液酸,以及连接到二天线低聚糖结构的“主干”中的GlcNAc的岩藻糖。在一些实施方案中,可对本发明的抗PD-L1抗体中的低聚糖进行修饰以产生具有某些改善特性的抗体变体。

[0213] 在一些实施方案中,提供具有缺乏(直接或间接)连接到Fc区上的岩藻糖的碳水化合物结构的抗体变体。例如,此类抗体中的岩藻糖量可以是1%至80%、1%至65%、5%至65%或20%至40%。如通过MALDI-TOF质谱法所测量,通过相对于连接到Asn297的所有糖结构(例如复合、杂合及高甘露糖结构)的总和计算Asn297上的糖链内岩藻糖的平均量来测定岩藻糖的量,如例如WO 2008/077546中所述。Asn297是指位于Fc区中大致位置297(Fc区残基的EU编号)上的天冬酰胺残基;然而,Asn297也可由于抗体中的微小序列变型而位于位置297的上游或下游约±3个氨基酸处,即在位置294与300之间。此类岩藻糖基化变体可具有改善的ADCC功能。参见,例如,美国专利公开第US 2003/0157108号(Presta,L.);第US 2004/0093621号(Kyowa Hakko Kogyo公司)。涉及“脱岩藻糖基化的”或“岩藻糖缺乏的”抗体变体的出版物的实例包括:US 2003/0157108;WO 2000/61739;WO 2001/29246;US 2003/0115614;US 2002/0164328;US 2004/0093621;US 2004/0132140;US 2004/0110704;US 2004/0110282;US 2004/0109865;WO 2003/085119;WO 2003/084570;WO 2005/035586;WO 2005/035778;WO2005/053742;WO2002/031140;Okazaki等人J.Mol.Biol.336:1239-1249(2004);Yamane-Ohnuki等人Biotech.Bioeng.87:614(2004)。能够产生去海藻糖基化抗体的细胞系的实例包括缺乏蛋白质海藻糖基化作用的Lec13 CHO细胞(Ripka等人Arch.Biochem.Biophys.249:533-545(1986);美国专利申请第US 2003/0157108A1号,Presta,L;及WO 2004/056312 A1,Adams等人,尤其在实施例11中)及基因剔除细胞系,诸如 α -1,6-海藻糖基转移酶基因FUT8基因剔除CHO细胞(参见例如Yamane-Ohnuki等人Biotech.Bioeng.87:614(2004);Kanda,Y.等人,Biotechnol.Bioeng.,94(4):680-688(2006);及WO2003/085107)。

[0214] 进一步提供具有二等分低聚糖的抗PD-L1抗体变体,例如其中连接到抗体的Fc区的二天线低聚糖是由GlcNAc二等分。此类抗体变体可具有降低的岩藻糖基化和/或改善的ADCC功能。此类抗体变体的实例描述于例如WO 2003/011878(Jean-Mairet等人);美国专利第6,602,684号(Umana等人);及US 2005/0123546(Umana等人)。还提供在连接到Fc区的低聚糖中具有至少一个半乳糖残基的抗体变体。此类抗体变体可具有改善的CDC功能。此类抗体变体描述于例如WO 1997/30087(Patel等人);WO 1998/58964(Raju,S.);及WO 1999/22764(Raju,S.)中。

[0215] c)Fc区变体

[0216] 在一些实施方案中,可以将一个或多个氨基酸修饰引入本文所提供的抗PD-L1构建体的Fc区,从而产生Fc区变体。Fc区变体可以包含在一个或多个氨基酸位置处包含氨基酸修饰(例如,取代)的人Fc区序列(例如,人IgG1、IgG2、IgG3或IgG4 Fc区)。

[0217] 在一些实施方案中,本申请涵盖具有一些而非所有效应子功能的抗PD-L1构建体

变体,所述效应子功能使其成为抗PD-L1构建体的体内半衰期较为重要但某些效应子功能(诸如补体及ADCC)不必要或有害的应用所需要的候选物。可进行体外和/或体内细胞毒性测定以确认CDC和/或ADCC活性的降低/减少。例如,可以进行Fc受体(FcR)结合测定以确保抗体缺乏Fc γ R结合(因此有可能缺乏ADCC活性),但保留FcRn结合能力。用于介导ADCC的原代细胞NK细胞仅表达Fc γ RIII,而单核细胞表达Fc γ RI、Fc γ RII及Fc γ RIII。在Ravetch及Kinet,Annu.Rev.Immunol.9:457-492(1991)第464页上的表3中汇总了造血细胞上的FcR表达。用于评估所关注分子的ADCC活性的体外测定的非限制性实例描述于美国专利第5,500,362(参见例如Hellstrom,I.等人Proc.Nat'l Acad.Sci.USA 83:7059-7063(1986))及Hellstrom,I等人Proc.Nat'l Acad.Sci.USA 82:1499-1502(1985);第5,821,337号(参见Bruggemann,M.等人,J.Exp.Med.166:1351-1361(1987))中。可替代地,可采用非放射性测定方法(参见例如用于流式细胞术的ACTITM非放射性细胞毒性测定(Cell Technology公司Mountain View,CA);以及CytoTox⁹⁶[®]非放射性细胞毒性测定(Promega, Madison, WI)。用于此类测定的有用效应细胞包括外周血单核细胞(PBMC)及自然杀伤(NK)细胞。可替代地或另外,所关注的分子的ADCC活性可例如在动物模型中进行体内评估,诸如Clynes等人Proc.Nat'l Acad.Sci.USA 95:652-656(1998)中公开的动物模型。也可进行C1q结合测定以确认抗体不能结合C1q并且因此缺乏CDC活性。参见,例如WO 2006/029879及WO 2005/100402中的C1q及C3c结合ELISA。为了评估补体活化,可进行CDC测定(参见例如Gazzano-Santoro等人,J.Immunol.Methods 202:163(1996);Cragg,M.S.等人,Blood 101:1045-1052(2003);及Cragg,M.S.及M.J.Glennie,Blood103:2738-2743(2004))。也可以使用本领域中已知的方法来实施FcRn结合及体内清除/半衰期测定(参见例如Petkova,S.B.等人,Int'l.Immunol.18(12):1759-1769(2006))。

[0218] 具有降低的效应功能的抗体包括具有Fc区残基238、265、269、270、297、327及329中的一个或多个的取代的那些(美国专利第6,737,056号)。此类Fc突变体包括在氨基酸位置265、269、270、297及327中的两处或更多处具有取代的Fc突变体,包括残基265及297取代成丙氨酸的所谓的“DANA”Fc突变体(美国专利第7,332,581号)。

[0219] 与FcR的结合改善或削弱的某些抗体变体已有描述。(参见例如美国专利第6,737,056号;WO 2004/056312及Shields等人,J.Biol.Chem.9(2):6591-6604(2001)。)

[0220] 在一些实施方案中,抗PD-L1构建体变体包含具有一个或多个改善的ADCC的氨基酸取代(例如在Fc区的的位置298、333和/或334(EU残基编号)处的取代)的Fc区。

[0221] 在一些实施方案中,对Fc区做出改变,其导致改变的(即,改善的或降低的)C1q结合和/或补体依赖性细胞毒性(CDC),例如,如描述于美国专利第6,194,551号、WO 99/51642及Idusogie等人J.Immunol.164:4178-4184(2000)中。

[0222] 在一些实施方案中,提供一种抗PD-L1构建体(例如,HCAb)变体,其包含有包含一或多处氨基酸取代的变体Fc区,所述取代增加半衰期和/或改善与新生儿Fc受体(FcRn)的结合。具有延长的半衰期及改善的与新生儿Fc受体(FcRn)的结合的抗体描述于US2005/0014934A1(Hinton等人)中,新生儿Fc受体(FcRn)负责将母体IgG转移至胎儿(Guyer等人,J.Immunol.117:587(1976)及Kim等人,J.Immunol.24:249(1994))。那些抗体包含其中具有改善Fc区与FcRn的结合的一个或多个取代的Fc区。此类Fc变体包括在Fc区残基238、256、265、272、286、303、305、307、311、312、317、340、356、360、362、376、378、380、382、413、424或

434中的一或多者处具有取代的Fc变体,例如具有Fc区残基434的取代的Fc变体(美国专利第7,371,826号)。

[0223] 关于Fc区变体的其他实例也可见Duncan及Winter,Nature322:738-40(1988);美国专利第5,648,260号;美国专利第5,624,821号;及W0 94/29351。

[0224] 也涵盖包含本文所述的Fc变体的抗PD-L1构建体(诸如融合至sdAb的全长IgG或抗PD-L1 IgG)或其组合。

[0225] d) 半胱氨酸工程化抗体变体

[0226] 在一些实施方案中,可能需要产生半胱氨酸改造抗PD-L1抗体,例如“巯基MAb”,其中抗体的一个或多个残基由半胱氨酸残基取代。在特定实施方案中,经取代的残基存在于抗体的可及位点处。通过用半胱氨酸取代那些残基,反应性硫醇基由此定位在抗体的可及位点处且可用于使抗体缀合至其他部分(诸如药物部分或接头-药物部分)以产生如本文进一步所述的免疫缀合物。在一些实施方案中,以下残基中的任一者或多个可以由半胱氨酸取代:重链的A118(EU编号);及重链Fc区的S400(EU编号)。可如例如美国专利第7,521,541号中所述来生成半胱氨酸改造抗PD-L1抗体。

[0227] e) 抗体衍生物

[0228] 在一些实施方案中,可以进一步修饰本文中提供的抗PD-L1抗体以含有本领域已知的且易于获得的额外非蛋白质部分。适于抗体的衍生化的部分包括但不限于水溶性聚合物。水溶性聚合物的非限制性实例包括但不限于聚乙二醇(PEG)、乙二醇/丙二醇共聚物、羧甲基纤维素、葡聚糖、聚乙烯醇、聚乙烯吡咯烷酮、聚-1,3-二氧戊环、聚-1,3,6-三噁烷、乙烯/马来酸酐共聚物、聚氨基酸(均聚物或无规共聚物)及葡聚糖或聚(n-乙烯吡咯烷酮)聚乙二醇、丙二醇均聚物、环氧丙烷/环氧乙烷共聚物、聚氧乙烯化多元醇(例如甘油)、聚乙烯醇及其混合物。聚乙二醇丙醛由于其在水中的稳定性可具有制造优势。所述聚合物可具有任何分子量,并且可为分支或未分支的。连接到抗体上的聚合物数目可以变化,而且若连接了超过一个聚合物,那么它们可以是相同或不同的分子。通常,用于衍生化的聚合物的数量和/或类型可基于包括但不限于有待改善的抗体的具体特性或功能、抗体衍生物是否在限定条件下用于疗法中等考虑因素来确定。

[0229] 在一些实施方案中,提供抗PD-L1抗体与可通过暴露于辐射而选择性加热的非蛋白质部分的缀合物。在一些实施方案中,非蛋白质部分是碳纳米管(Kam等人,Proc.Nat'l.Acad.Sci.USA 102:11600-11605(2005))。辐射可具有任何波长,并且包括但不限于不损害普通细胞但会将非蛋白质部分加热至杀死邻近于抗体-非蛋白质部分的细胞的温度的波长。

[0230] 在一些实施方案中,本文所提供的抗PD-L1构建体(诸如抗PD-L1 IgG、抗PD-L1/CTLA-4双特异性抗体、抗PD-L1/TIGIT双特异性抗体、抗PD-L1/TIM-3双特异性抗体或抗PD-L1/LAG-3双特异性抗体)可以进一步经修饰以含有一种或多种具生物学上活性的蛋白、多肽或其片段。如本文所用的“生物活性”或“生物学上活性”是指在体内显示生物活性以实现特定功能。例如,它可以指与特定生物分子(例如蛋白质,DNA等)的组合,然后促进或抑制此生物分子的活性。在一些实施方案中,生物活性蛋白质或其片段具有免疫刺激/免疫调节、膜转运或酶活性。

[0231] 在一些实施方案中,可与在本文所述的抗PD-L1构建体融合的生物活性蛋白质或

其片段是配体,例如与特定细胞受体相互作用的淋巴因子及细胞因子。淋巴因子是低分子量蛋白质,当抗原或凝集素刺激T细胞生长时,T细胞分泌这些蛋白质。淋巴因子的实例包括但不限于干扰素- α 、干扰素- γ 、白细胞介素-1(IL-1)、白细胞介素-2(IL-2)、白细胞介素-3(IL-3)、肿瘤坏死因子(TNF)、集落刺激因子(例如CSF-1、G-CSF或GM-CSF)、趋化因子、巨噬细胞迁移抑制因子(MIF)、巨噬细胞活化因子(MAF)、NK细胞活化因子、T细胞置换因子、白血病抑制因子(LIF)、淋巴毒素、蚀骨细胞活化因子(OAF)、可溶免疫反应抑制因子(SIRS)、生长刺激因子、单核细胞生长因子等。可并入至本发明的抗PD-L1融合蛋白的细胞因子包括但不限于肿瘤坏死因子 α (TNF α)、干扰素(IFN)及神经生长因子(NGF)等。

[0232] III. 药物组合物

[0233] 本申请进一步提供药物组合物,其包含如本文所述的包含特异性识别PD-L1的全长IgG的抗PD-L1构建体中的任一种(诸如抗PD-L1 IgG、抗PD-L1/CTLA-4双特异性抗体、抗PD-L1/TIGIT双特异性抗体、抗PD-L1/TIM-3双特异性抗体或抗PD-L1/LAG-3双特异性抗体)及任选地药学上可接受的载剂。可通过混合具有期望纯度的本文所述抗PD-L1构建体与可选药学上可接受的载剂、赋形剂或稳定剂(Remington's Pharmaceutical Sciences第16版,Osol, A. 编(1980))以冻干调配物或水性溶液形式制备药物组合物。

[0234] 药物组合物优选是稳定的,其中包含本文所述的抗PD-L1 mAb的抗PD-L1构建体在储存时基本上保持其物理及化学稳定性及完整性。用于测量蛋白质稳定性的各种分析技术是所属领域中可用的且综述于Peptide and Protein Drug Delivery,247-301,Vincent Lee编,Marcel Dekker公司,New York, N.Y., Pubs. (1991)及Jones, A. Adv. Drug Delivery Rev. 10:29-90(1993)。可在选定温度下持续选定时期测量稳定性。为了快速筛选,可以将调配物在40℃下保持2周至1个月,届时测量稳定性。当调配物在2-8℃下储存时,通常调配物应在30℃或40℃下稳定至少1个月,和/或在2-8℃下稳定至少2年。当调配物在30℃下储存时,调配物通常应在30℃下稳定至少2年,和/或在40℃下稳定至少6个月。例如,储存期间的聚集程度可用作蛋白质稳定性的指标。在一些实施方案中,本文所述的抗PD-L1构建体的稳定调配物可包含少于约10%(优选少于约5%)的作为调配物中聚集体存在的抗PD-L1构建体。

[0235] 可接受的载剂、赋形剂或稳定剂在所用剂量及浓度下对接受者无毒,且包括缓冲剂;抗氧化剂,包括抗坏血酸、甲硫氨酸、维生素E、偏亚硫酸氢钠;防腐剂,等渗剂(例如氯化钠),稳定剂,金属复合物(如锌-蛋白质复合物);螯合剂诸如EDTA和/或非离子表面活性剂。

[0236] 可接受的载剂的实例包括缓冲剂,诸如磷酸盐、柠檬酸盐及其他有机酸;抗氧化剂,包括抗坏血酸及甲硫氨酸;防腐剂(诸如十八烷基二甲基苄基氯化铵、六甲基氯化铵、苯扎氯铵、苄索氯铵;苯酚、丁醇或苄醇;对羟基苯甲酸烷基酯,诸如对羟基苯甲酸甲酯或对羟基苯甲酸丙酯;邻苯二酚;间苯二酚;环己醇;3-戊醇;以及间-甲酚);低分子量(小于约10个残基)多肽;蛋白质,诸如血清白蛋白、明胶或免疫球蛋白;亲水性聚合物,诸如聚乙烯基吡咯烷酮;氨基酸,诸如甘氨酸、谷氨酰胺、天冬酰胺、精氨酸或赖氨酸;单糖、二糖以及其他碳水化合物,包括葡萄糖、甘露糖或糊精;螯合剂,诸如EDTA;糖,诸如蔗糖、甘露醇、海藻糖或山梨醇;成盐相对离子,诸如钠离子;金属复合物(例如Zn-蛋白质复合物);和/或非离子表面活性剂,诸如TWEENTM、聚乙二醇(PEG)、以及PLURONICSTM或聚乙二醇(PEG)。

[0237] 缓冲剂用于将pH控制在优化治疗效果的范围,特别是在稳定性取决于pH的情况

下。缓冲剂优选以约50mM至约250mM的浓度存在。适用于本申请的缓冲剂包括有机酸及无机酸及其盐。例如,柠檬酸盐、磷酸盐、琥珀酸盐、酒石酸盐、富马酸盐、葡萄糖酸盐、草酸盐、乳酸盐、乙酸盐。另外,缓冲剂可包含组氨酸及三甲胺盐,诸如Tris。

[0238] 添加防腐剂以阻止微生物生长,并且通常以0.2% - 1.0% (w/v) 的范围存在。添加防腐剂可以例如促进多用途(多剂量)调配物的生产。适用于本申请的防腐剂包括十八烷基二甲基苄基氯化铵;六甲基氯化铵;苯二甲羟铵卤化物(例如氯化物、溴化物、碘化物),苄索氯铵;硫柳汞,苯酚,丁醇或苄醇;对羟基苯甲酸烷基酯诸如对羟基苯甲酸甲酯或对羟基苯甲酸丙酯;邻苯二酚;间苯二酚;环己醇、3-戊醇及间甲酚。

[0239] 存在有时称为“稳定剂”的张力剂以调节或维持组合物中液体的张力。当与大的带电生物分子诸如蛋白质及抗体一起使用时,它们通常被称为“稳定剂”,因为它们可以与氨基酸侧链的带电基团相互作用,从而减少分子间及分子内相互作用的可能性。考虑到其他成分的相对量,张力剂可以以0.1重量%至25重量%,优选1重量%至5重量%的任何量存在。优选的张力剂包括多元糖醇,优选三元或更高级糖醇,诸如甘油、赤藓糖醇、阿拉伯糖醇、木糖醇、山梨糖醇及甘露糖醇。

[0240] 另外的赋形剂包括可以作为以下一者或多者的试剂:(1)填充剂,(2)溶解度增强剂,(3)稳定剂及(4)防止变性或粘附到容器壁上的试剂。这些赋形剂包括:多元糖醇(上面列举的);氨基酸诸如丙氨酸、甘氨酸、谷氨酰胺、天冬酰胺、组氨酸、精氨酸、赖氨酸、鸟氨酸、亮氨酸、2-苯丙氨酸、谷氨酸、苏氨酸等;有机糖或糖醇,诸如蔗糖、乳糖、乳糖醇、海藻糖、水苏糖、甘露糖、山梨糖、木糖、核糖、核糖醇、肌糖(myoinisitol)、肌醇(myoinisitol)、半乳糖、半乳糖醇、甘油、环醇(例如肌醇)、聚乙二醇;含硫还原剂,诸如尿素、谷胱甘肽、硫辛酸、硫代乙醇酸钠、硫代甘油、 α -硫代甘油及硫代硫酸钠;低分子量蛋白质,诸如人血清白蛋白、牛血清白蛋白、明胶或其他免疫球蛋白;亲水性聚合物,诸如聚乙烯吡咯烷酮;单糖(例如,木糖、甘露糖、果糖、葡萄糖;二糖(例如乳糖、麦芽糖、蔗糖);三糖诸如棉子糖;及多糖例如糊精或葡聚糖。

[0241] 存在非离子表面活性剂或清洁剂(也称为“润湿剂”)以帮助溶解治疗剂以及保护治疗性蛋白免于搅动诱导的聚集,从而也允许调配物暴露于剪切表面应力而不会引起活性治疗蛋白质或抗体的变性。非离子表面活性剂的存在量为约0.05mg/ml至约1.0mg/ml,优选约0.07mg/ml至约0.2mg/ml。

[0242] 合适的非离子表面活性剂包括聚山梨醇酯(20、40、60、65、80等),聚氧乙烯醚(184、188等)、PLURONIC®多元醇、TRITON®、聚氧乙烯脱水山梨糖醇单醚(TWEEN®-20、TWEEN®-80等)、聚桂醇400、聚乙二醇40硬脂酸酯、聚氧乙烯氢化蓖麻油10、50及60、单硬脂酸甘油酯、蔗糖脂肪酸酯、甲基纤维素及羧甲基纤维素。可以使用的阴离子清洁剂包括十二烷基硫酸钠、二辛基磺基琥珀酸钠及二辛基磺酸钠。阳离子清洁剂包括苯扎氯铵或苄索氯铵。

[0243] 为了使药物组合物用于体内施用,它们必须是无菌的。可通过无菌过滤膜过滤使药物组合物无菌。通常将本文中的药物组合物放到具有无菌进入端口的容器中,例如具有通过皮下注射针可刺穿的塞子的静脉内溶液袋或小瓶。

[0244] 施用途径根据已知及可接受的方法,诸如通过单次或多次推注或以合适的方式长时间输注,例如通过皮下、静脉内、腹膜内、肌肉内、动脉内、病灶内或关节内途径来注射或

输注、局部施用、吸入或通过持续释放或延长释放方式。在一些实施方案中,药物组合物是局部施用,例如肿瘤内施用。

[0245] 可制备持续释放制剂。持续释放制剂的合适实例包括含有拮抗剂的固体疏水性聚合物半透性基质,半透性基质呈成形制品的形式,例如膜或微胶囊。所述持续释放基质的实例包括聚酯、水凝胶(例如,聚(甲基丙烯酸2-羟乙基酯)或聚(乙烯醇))、聚交酯(美国专利第3,773,919号)、L-谷氨酸与L-谷氨酸乙基酯的共聚物、不可降解的乙烯-乙酸乙烯酯、可降解的乳酸-乙醇酸共聚物诸如LUPRON DEPOT™(由乳酸-乙醇酸共聚物及乙酸亮丙瑞林(leuprolide acetate)组成的可注射微球),以及聚-D-(-)-3-羟基丁酸。

[0246] 本文中的药物组合物也可含有所治疗的特定适应症所需要的一种以上活性化合物,优选为具有互补活性并且不会对彼此有不利影响的化合物。或者/另外,组合物可包含细胞毒剂、化学治疗剂、细胞因子、免疫抑制剂或生长抑制剂。此类分子适合于以对于预期用途有效的量组合存在。

[0247] 所述活性成分也可截留在例如通过凝聚技术或界面聚合作用制备的微胶囊(例如分别为羟甲基纤维素或明胶微胶囊及聚(甲基丙酸甲酯)微胶囊)中、胶状药物递送系统(例如,脂质体、白蛋白微球、微乳液、纳米粒子及纳米胶囊)中或粗乳液中。此类技术公开于Remington's Pharmaceutical Sciences,第18版中。

[0248] 在一些实施方案中,药物组合物包含在一次性小瓶(诸如一次性密封小瓶)中。在一些实施方案中,药物组合物包含在多用途小瓶中。在一些实施方案中,药物组合物以散装形式包含在容器中。在一些实施方案中,药物组合物为冷冻保存的。

[0249] IV. 使用方法或应用

[0250] 如本文所述的包含特异性识别PD-L1的mAb的抗PD-L1构建体(诸如抗PD-L1全长IgG、抗PD-L1/CTLA-4双特异性抗体、抗PD-L1/TIGIT双特异性抗体、抗PD-L1/TIM-3双特异性抗体或抗PD-L1/LAG-3双特异性抗体)及其组合物(诸如药物组合物)可用于多种应用,诸如诊断、分子测定及治疗。

[0251] 本发明的一个方面提供了治疗有需要的个体中的PD-L1相关疾病或病症的方法,其包括向所述个体施用有效量的包含本文所述的抗PD-L1构建体的药物组合物。在一些实施方案中,PD-L1相关疾病为癌症。在一些实施方案中,PD-L1相关疾病是病原性感染,诸如病毒感染。

[0252] 本申请部分涵盖蛋白质构建体(诸如抗PD-L1全长IgG、抗PD-L1/CTLA-4双特异性抗体、抗PD-L1/TIGIT双特异性抗体、抗PD-L1/TIM-3双特异性抗体或抗PD-L1/LAG-3双特异性抗体)、编码其的核酸分子和/或载体、包含编码其的核酸分子和/或载体的宿主细胞,其可以单独或以任何方式与另一种疗法组合施用,并且在至少一些方面,与药学上可接受的载剂或赋形剂一起组合施用。在一些实施方案中,在施用抗PD-L1构建体之前,它们可以与所属领域中熟知的合适的药物载剂及赋形剂组合。根据本公开制备的组合物可用于治疗癌症或延迟癌症的恶化。

[0253] 在一些实施方案中,提供一种治疗癌症的方法,其包括向个体施用有效量的包含有包含特异性识别PD-L1的mAb的分离的抗PD-L1构建体(诸如抗PD-L1全长IgG、抗PD-L1/CTLA-4双特异性抗体、抗PD-L1/TIGIT双特异性抗体、抗PD-L1/TIM-3双特异性抗体或抗PD-L1/LAG-3双特异性抗体)的药物组合物。在一些实施方案中,癌症是实体肿瘤(诸如结肠

癌)。在一些实施方案中,药物组合物是全身(例如静脉内)施用。在一些实施方案中,药物组合物是局部(例如肿瘤内)施用。在一些实施方案中,所述方法也包括向个体施用另外的癌症疗法(诸如手术、放射、化学疗法、免疫疗法、激素疗法或其组合)。在一些实施方案中,所述个体为人。在一些实施方案中,治疗癌症的方法具有以下一种或多种生物活性:(1)杀死癌细胞(包括旁观者杀死);(2)抑制癌细胞的增殖;(3)在肿瘤中诱导免疫反应;(4)减小肿瘤大小;(5)缓解患有癌症的个体的一种或多种症状;(6)抑制肿瘤转移;(7)延长生存期;(8)延长癌症进展时间;以及(9)预防、抑制或降低癌症复发的可能性。在一些实施方案中,通过本文所述的药物组合物介导的杀伤癌细胞的方法可达成至少约40%、50%、60%、70%、80%、90%、95%或更大中任一者的肿瘤细胞死亡率。在一些实施方案中,通过本文所述的药物组合物介导的杀伤癌细胞的方法可达成至少约10%、20%、30%、40%、50%、60%、70%、80%、90%、95%或更大中任一者的旁观肿瘤细胞(未受溶瘤VV感染)死亡率。在一些实施方案中,通过本文所述的药物组合物介导的减小肿瘤大小的方法可减小至少约10%(包括例如至少约20%、30%、40%、60%、70%、80%、90%或100%中任一者)肿瘤大小。在一些实施方案中,通过本文所述的药物组合物介导的抑制肿瘤转移的方法可抑制至少约10%(包括例如至少约20%、30%、40%、60%、70%、80%、90%或100%中任一者)转移。在一些实施方案中,通过本文所述的药物组合物介导的延长个体(诸如人)存活的方法可延长个体的存活至少1个月、2个月、3个月、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、12个月、18个月或24个月中任一者。在一些实施方案中,通过本文所述的药物组合物介导的延长癌症进展时间的方法可延长癌症进展时间至少1周、2周、3周、4周、5周、6周、7周、8周、9周、10周、11周或12周中任一者。

[0254] 本文描述的方法适用于治疗多种癌症,包括实体癌症及液体癌症。所述方法适用于所有阶段的癌症,包括早期癌症、非转移性癌症、原发性癌症、晚期癌症、局部晚期癌症、转移性癌症或缓解期癌症。本文描述的方法可以用作第一疗法、第二疗法、第三疗法或与所属领域中已知的其他类型的癌症疗法的组合疗法,诸如化疗、手术、激素疗法、放射、基因疗法、免疫疗法(诸如T细胞疗法)、骨髓移植、干细胞移植、靶向疗法、冷冻疗法、超声疗法、光动力疗法、射频消融等,在辅助环境或新辅助环境中(即,所述方法可以在初步/确定性治疗之前进行)。在一些实施方案中,所述方法用于治疗先前已经治疗的个体。在一些实施方案中,癌症对于先前疗法是难以治愈的。在一些实施方案中,所述方法用于治疗先前未接受过治疗的个体。

[0255] 在一些实施方案中,所述方法合适于治疗PD-L1表达、活性和/或信号传导异常的癌症,所述癌症包括(作为非限制性实例)黑素瘤、前列腺癌、肺癌、结肠癌、胃癌、卵巢癌、乳腺癌及胶质母细胞瘤。

[0256] 因此,在一些实施方案中,提供一种治疗免疫疗法反应性实体瘤(诸如癌或腺癌,诸如具有异常PD-L1表达、活性和/或信号传导的癌症)的方法,其包括向个体施用有效量的包含有包含特异性识别PD-L1的单克隆抗体的分离的抗PD-L1构建体(诸如抗PD-L1全长IgG、抗PD-L1/CTLA-4双特异性抗体、抗PD-L1/TIGIT双特异性抗体、抗PD-L1/TIM-3双特异性抗体或抗PD-L1/LAG-3双特异性抗体)的药物组合物。在一些实施方案中,癌症是实体肿瘤(诸如结肠癌)。在一些实施方案中,药物组合物是全身(例如静脉内)施用。在一些实施方案中,药物组合物是局部(例如肿瘤内)施用。在一些实施方案中,所述方法也包括向个体施用另

外的癌症疗法(例如手术、放射、化学疗法、免疫疗法、激素疗法或其组合)。在一些实施方案中,所述个体为人。在一些实施方案中,治疗癌症的方法具有以下一种或多种生物活性:(1)杀死癌细胞(包括旁观者杀死);(2)抑制癌细胞的增殖;(3)在肿瘤中诱导免疫反应;(4)减小肿瘤大小;(5)缓解患有癌症的个体的一种或多种症状;(6)抑制肿瘤转移;(7)延长生存期;(8)延长癌症进展时间;以及(9)预防、抑制或降低癌症复发的可能性。在一些实施方案中,通过本文所述的药物组合物介导的杀伤癌细胞的方法可达成至少约40%、50%、60%、70%、80%、90%、95%或更大中任一者的肿瘤细胞死亡率。在一些实施方案中,通过本文所述的药物组合物介导的杀伤癌细胞的方法可达成至少约10%、20%、30%、40%、50%、60%、70%、80%、90%、95%或更大中任一者的旁观肿瘤细胞(未受溶瘤VV感染)死亡率。在一些实施方案中,通过本文所述的药物组合物介导的减小肿瘤大小的方法可减小至少约10%(包括例如至少约20%、30%、40%、60%、70%、80%、90%或100%中任一者)肿瘤大小。在一些实施方案中,通过本文所述的药物组合物介导的抑制肿瘤转移的方法可抑制至少约10%(包括例如至少约20%、30%、40%、60%、70%、80%、90%或100%中任一者)转移。在一些实施方案中,通过本文所述的药物组合物介导的延长个体(诸如人)存活的方法可延长个体的存活至少1个月、2个月、3个月、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、12个月、18个月或24个月中任一者。在一些实施方案中,通过本文所述的药物组合物介导的延长癌症进展时间的方法可延长癌症进展时间至少1周、2周、3周、4周、5周、6周、7周、8周、9周、10周、11周或12周中任一者。

[0257] 在一些实施方案中,所述方法适用于治疗具有异常PD-1或PD-L1/PD-L2表达、活性和/或信号传导的癌症,作为非限制性实例,所述癌症包括血液癌症和/或实体瘤。可以使用本发明的抗体抑制其生长的一些癌症包括通常对免疫疗法有反应的癌症。用于治疗的其他癌症的非限制性实例包括黑素瘤(例如,转移性恶性黑素瘤)、肾癌(例如透明细胞癌)、前列腺癌(例如激素难治性前列腺腺癌)、乳腺癌、结肠癌及肺癌(例如非小细胞肺癌)。另外,本发明包括其生长可以使用本发明的抗体抑制的难治性或复发性恶性肿瘤。可以使用本发明的抗体治疗的其他癌症的实例包括骨癌、胰脏癌、皮肤癌、头颈癌、皮肤或眼内恶性黑素瘤、子宫癌、卵巢癌、直肠癌、肛区癌症、胃癌、睾丸癌、子宫癌、输卵管癌、子宫内膜癌、子宫颈癌、阴道癌、外阴癌、霍奇金氏病(Hodgkin's Disease)、非霍奇金氏淋巴瘤、食道癌、小肠癌、内分泌系统癌、甲状腺癌、甲状旁腺癌、肾上腺癌、软组织肉瘤、尿道癌、阴茎癌、慢性或急性白血病(包括急性髓性白血病、慢性髓性白血病、急性淋巴细胞性白血病、慢性淋巴细胞性白血病)、儿童实体瘤、淋巴细胞性淋巴瘤、膀胱癌、肾癌或输尿管癌、肾盂癌、中枢神经系统(CNS)赘瘤、原发性CNS淋巴瘤、肿瘤血管生成、脊髓轴肿瘤、脑干胶质瘤、垂体腺瘤、卡波西氏肉瘤(Kaposi's sarcoma)、表皮样癌、鳞状细胞癌、T-细胞淋巴瘤、环境诱发的癌症(包括由石棉诱导的癌症)以及所述癌症的组合。本申请也可用于治疗转移性癌症,尤其是表达PD-L1的转移性癌症(Iwai等人(2005)Int.Immunol.17:133-144)。

[0258] 因此,在一些实施方案中,提供一种治疗免疫疗法反应性实体瘤(诸如癌或腺癌,诸如具有异常PD-L1表达、活性和/或信号传导和/或异常CTLA-4、TIGIT、TIM-3及LAG-3表达、活性和/或信号传导的癌症)的方法,其包括向个体施用有效量的包含有包含融合至CTLA-4、TIGIT、TIM-3或LAG-3sAb的特异性识别PD-L1的全长IgG的分离的抗PD-L1构建体的药物组合物。在一些实施方案中,提供一种治疗免疫疗法反应性实体瘤(诸如癌或腺癌,

诸如具有异常PD-L1表达、活性和/或信号传导和/或异常CTLA-4、TIGIT、TIM-3、LAG-3表达、活性和/或信号传导的癌症)的方法,其包括向个体施用有效量的包含有包含融合至CTLA-4、TIGIT、TIM-3或LAG-3sAb的特异性识别PD-L1的全长IgG的分离的抗PD-L1构建体的药物组合物。

[0259] 在一些实施方案中,本文所述的方法适用于治疗结肠直肠癌,诸如腺癌、胃肠道类癌瘤、胃肠道间质瘤、平滑肌肉瘤、黑素瘤或鳞状细胞癌。

[0260] 本申请的药物组合物的剂量及所需药物浓度可根据设想的特定用途而变化。确定施用的适当剂量或途径完全在普通技术人员的技能的内。动物实验为人疗法的有效剂量的确定提供了可靠的指导。有效剂量的物种间类推可以遵循Mordenti, J. 及Chappell, W. "The Use of Interspecies Scaling in Toxicokinetics," In Toxicokinetics and New Drug Development, Yacobi等人编, Pergamon Press, New York 1989, 第42-46页来进行。

[0261] 当使用包含本文所述的抗PD-L1 mAb的抗PD-L1构建体的体内施用,正常剂量可以从每天约10ng/kg至约100mg/kg哺乳动物体重或更多变化,优选约1mg/kg/天至10mg/kg/天,诸如约1-3mg/kg/天、约2-4mg/kg/天、约3-5mg/kg/天、约4-6mg/kg/天、约5-7mg/kg/天、约6-8mg/kg/天、约6-6.5mg/kg/天、约6.5-7mg/kg/天、约7-9mg/kg/天或约8-10mg/kg/天,此取决于施用途。在申请范围内的是,不同的调配物将对于不同的治疗及不同的病症是有效的,并且旨在治疗特定器官或组织的施用可需要不同于对另一种器官或组织的递送方式的递送。此外,剂量可通过一次或多次单独的施用来施用,或通过连续输注来施用。对于经若干天或更长时间的重复施用,根据病状,持续进行治疗,直至发生期望的疾病症状阻抑为止。然而,其他剂量方案可以是有用的。此疗法的进展通过常规技术及测定容易地监测。

[0262] 在一些实施方案中,药物组合物是施用单次(例如推注)。在一些实施方案中,药物组合物是施用多次(例如2次、3次、4次、5次、6次或更多次中的任一者)。若为多次施用,则可以通过相同或不同的途径执行,并且可以在同一部位或在可替代的部位进行。药物组合物可以每周施用两次,每周施用3次,每周施用4次,每周施用5次,不中断地每日施用,每周施用一次,不中断地每周施用,每2周施用一次,每3周施用一次,每月施用一次,每2个月施用一次,每3个月施用一次,每4个月施用一次,每5个月施用一次,每6个月施用一次,每7个月施用一次,每8个月施用一次,每9个月施用一次,每10个月施用一次,每11个月施用一次,或每年施用一次。施用间隔可以为24h至48h、2天至3天、3天至5天、5天至1周、1周至2周、2周至1个月、1个月至2个月、2个月至3个月、3个月至6个月或6个月至一年中的任一者。间隔也可以为不规则的(例如在肿瘤进展后)。在一些实施方案中,施用方案没有中断。在一些实施方案中,每4天施用组合物达4次。通过监测患者的疾病迹象并相应地调整治疗,医学技术所属领域的技术人员可以容易地确定特定患者的最佳剂量及治疗方案。

[0263] 根据已知方法,诸如静脉内推注施用,或通过在规定时间内连续输注,通过肌肉内、腹膜内、脑脊髓内、皮下、静脉内(i.v.)、关节内、滑膜内、鞘内、经口、局部或吸入途径将本申请的药物组合物(包括但不限于复溶调配物及液体调配物)施用需要用本文所述的抗PD-L1构建体治疗的个体,优选人。可通过将冻干的本文所述的抗PD-L1构建体溶解在稀释剂中以使蛋白质分散在各处来制备复溶的调配物。适用于本申请的示例性药学上可接受的(对人施用是安全且无毒的)稀释剂包括但不限于无菌水、抑菌性注射用水(BWFI)、pH缓冲溶液(例如磷酸盐缓冲盐水)、无菌盐水溶液、林格氏溶液(Ringer's solution)或右旋糖溶

液,或盐和/或缓冲剂的水溶液。

[0264] 在一些实施方案中,通过皮下(即在皮肤下)施用来向个体施用药物组合物。出于此种目的,可以使用注射器来注射药物组合物。然而,其他用于施用药物组合物的装置为可用的,诸如注射装置;注射笔;自动注射器装置,无针装置;及皮下贴片递送系统。

[0265] 在一些实施方案中,将药物组合物静脉内施用给个体。在一些实施方案中,通过输注(例如静脉内输注)将药物组合物施用给个体。免疫疗法的输注技术为所属领域中已知的(参见例如Rosenberg等人,New Eng.J.of Med.319:1676(1988))。

[0266] 如本文所述的包含特异性识别PD-L1的mAb的抗PD-L1构建体(诸如抗PD-L1全长IgG、抗PD-L1/CTLA-4双特异性抗体、抗PD-L1/TIGIT双特异性抗体、抗PD-L1/TIM-3双特异性抗体或抗PD-L1/LAG-3双特异性抗体)及其组合物(诸如药物组合物)也可用于诊断或分子测定。例如,所述抗体或抗原结合片段可用于检测或定量生物样品中的PD-L1,从而检测或监测与PD-L1有关的疾病(诸如上文所述的疾病)的进展或治疗。

[0267] V. 制备方法

[0268] 本文所述的抗PD-L1构建体(诸如抗PD-L1单克隆抗体)可使用所属领域中已知或如本文所述的任何方法制备。也参见实施例1-2。

[0269] 啮齿动物单克隆抗体可以使用所属领域中已知的方法获得,诸如通过对啮齿动物物种(诸如小鼠或大鼠)进行免疫并从中获得融合瘤,或通过使用所属领域中已知的分子生物学技术克隆Fab片段或单链Fc(scFv)的文库并且随后利用未选择的文库的单个克隆通过ELISA进行选择或通过使用噬菌体展示。

[0270] 为了重组产生单克隆抗体,将编码单克隆抗体的核酸分离或合成并插入可复制的载体中以进一步克隆(扩增DNA)或用于表达。编码单克隆抗体的DNA容易分离并且使用常规程序(例如,通过使用能够与编码所述抗体的重链及轻链的基因特异性结合的寡核苷酸探针)进行测序。很多载体是可用的。载体的选择部分取决于要使用的宿主细胞。通常,优选的宿主细胞是原核或真核(通常是哺乳动物)来源的宿主细胞。

[0271] 实施方案

[0272] 本发明还提供以下非限制性实施方案。

[0273] 实施方案1包含一种分离的抗体,优选mAb,或其抗原结合片段,其包含:

[0274] (a) 重链可变结构域(VH),其包含:

[0275] i. 重链CDR1,其包含SEQ ID NO:71-82中任一者的氨基酸序列,或其包含至多约3个(诸如约1个、2个或3个中的任一者)氨基酸取代的变体;

[0276] ii. 重链CDR2,其包含SEQ ID NO:83-97中任一者的氨基酸序列,或其包含至多约3个(诸如约1个、2个或3个中的任一者)氨基酸取代的变体;及

[0277] iii. 重链CDR3,其包含SEQ ID NO:98-109中任一者的氨基酸序列,或其包含至多约3个(诸如约1个、2个或3个中的任一者)氨基酸取代的变体;及

[0278] (b) 轻链可变结构域(VL),其包含:

[0279] i. 轻链CDR1,其包含SEQ ID NO:110-123中任一者的氨基酸序列,或其包含至多约3个(诸如约1个、2个或3个中的任一者)氨基酸取代的变体;

[0280] ii. 轻链CDR2,其包含SEQ ID NO:124-135中任一者的氨基酸序列,或其包含至多约3个(诸如约1个、2个或3个中的任一者)氨基酸取代的变体;及

[0281] iii.轻链CDR3,其包含SEQ ID NO:136-147中任一者的氨基酸序列,或其包含至多约3个(诸如约1个、2个或3个中的任一者)氨基酸取代的变体,

[0282] 其中所述抗体或抗原结合片段能够与PD-L1、优选人PD-L1特异性结合。

[0283] 实施方案2为一种分离的抗体,优选mAb,或其抗原结合片段,其包含:

[0284] (a)重链可变结构域(VH),其包含:

[0285] i.重链CDR1,其包含选自由SEQ ID NO:71-82组成的组的氨基酸序列;

[0286] ii.重链CDR2,其包含分别选自由SEQ ID NO:83-94组成的组的氨基酸序列,其中SEQ ID NO:87任选地由SEQ ID NO:95-97中的任一者置换;及

[0287] iii.重链CDR3,其包含分别选自由SEQ ID NO:98-109组成的组的氨基酸序列;及

[0288] (b)轻链可变结构域(VL),其分别包含,

[0289] i.轻链CDR1,其包含选自由SEQ ID NO:110-121组成的组的氨基酸序列,其中SEQ ID NO:111任选地由SEQ ID NO:122置换,且SEQ ID NO:114任选地由SEQ ID NO:123置换;

[0290] ii.轻链CDR2,其包含分别选自由SEQ ID NO:124-135组成的组的氨基酸序列;及

[0291] iii.轻链CDR3,其包含分别选自由SEQ ID NO:136-147组成的组的氨基酸序列,

[0292] 其中所述抗体或抗原结合片段能够与PD-L1、优选人PD-L1特异性结合。

[0293] 实施方案3为如实施方案1或2的分离的抗体,优选mAb,或其抗原结合片段,其包含表20的重链CDR及表21的相应轻链CDR。

[0294] 实施方案4为如实施方案1至3中任一项的分离的抗体,优选mAb,或其抗原结合片段,其包含:VH结构域,其包含SEQ ID NO:1-44中任一者的氨基酸序列,或其与SEQ ID NO:1-44中任一者具有至少约80%、至少约90%或至少约95%序列同一性的变体;及VL结构域,其包含SEQ ID NO:45-70中任一者的氨基酸序列,或其与SEQ ID NO:45-70中任一者具有至少约80%、至少约90%或至少约95%序列同一性的变体。

[0295] 实施方案5为如实施方案1至4中任一项的分离的抗体,优选mAb,或其抗原结合片段,其包含:VH结构域,其包含SEQ ID NO:1-44中任一者的氨基酸序列,或其所述VH结构域中包含至多约3个氨基酸取代的变体;及VL结构域,其包含SEQ ID NO:45-70中任一者的氨基酸序列,或其所述VL结构域中包含至多约3个氨基酸取代的变体。

[0296] 实施方案6为如实施方案5的分离的抗体,优选mAb,或其抗原结合片段,其中分别地,所述VH结构域包含选自由SEQ ID NO:1-44组成的组的氨基酸序列;且所述VL结构域包含选自由SEQ ID NO:45-70组成的组的氨基酸序列。

[0297] 实施方案7包含一种分离的抗体,优选mAb,或抗原结合片段,其包含:

[0298] (1)包含分别具有SEQ ID NO:75、87及102的氨基酸序列的重链CDR1、CDR2及CDR3序列的VH,以及包含分别具有SEQ ID NO:114、128及140的氨基酸序列的轻链CDR1、CDR2及CDR3序列的VL,其中SEQ ID NO:87任选地由SEQ ID NO:95-97中的任一者置换,且SEQ ID NO:114任选地由SEQ ID NO:123置换;或

[0299] (2)包含分别具有SEQ ID NO:72、84及99的氨基酸序列的重链CDR1、CDR2及CDR3序列的VH,以及包含分别具有SEQ ID NO:111、125及137的氨基酸序列的轻链CDR1、CDR2及CDR3序列的VL,其中SEQ ID NO:111任选地由SEQ ID NO:122置换。

[0300] 实施方案8为如实施方案7的分离的抗体,优选mAb,或其抗原结合片段,其中所述VH包含分别具有SEQ ID NO:72、84及99的氨基酸序列的重链CDR1、CDR2及CDR3序列,且所述

VL包含分别具有SEQ ID NO:122、125及137的氨基酸序列的轻链CDR1、CDR2及CDR3序列。

[0301] 实施方案9为如实施方案7或8的分离的抗体,优选mAb,或其抗原结合片段,其中:所述VH包含分别具有SEQ ID NO:75、97及102的氨基酸序列的重链CDR1、CDR2及CDR3序列,且所述VL包含分别具有SEQ ID NO:123、128及140的氨基酸序列的轻链CDR1、CDR2及CDR3。

[0302] 实施方案10为如实施方案1至9中任一项的分离的抗体,优选mAb,或其抗原结合片段,其中所述抗体或抗原结合片段与PD-L1之间的结合的 K_D 为约 10^{-5} M至约 10^{-12} M、约 10^{-7} M至约 10^{-12} M或约 10^{-8} M至约 10^{-12} M或更小。

[0303] 实施方案11为如实施方案1至10中任一项的分离的抗体,优选mAb,或其抗原结合片段,其为啮齿动物的、嵌合的、人的、部分人源化的或完全人源化的。

[0304] 实施方案12为如实施方案11的分离的抗体,优选mAb,或其抗原结合片段,其中所述VH融合至免疫球蛋白的重链恒定区(C_H1 、 C_H2 及 C_H3)。

[0305] 实施方案13为如实施方案11或12的分离的抗体,优选mAb,或其抗原结合片段,其中所述VL融合至免疫球蛋白的轻链恒定区(CL)。

[0306] 实施方案14为如实施方案13的分离的抗体,优选mAb,其包含人IgG1的恒定结构域。

[0307] 实施方案15为如实施方案13或14的分离的抗体,优选mAb,其为包含SEQ ID NO:278-321或348-391中任一者的重链氨基酸序列及SEQ ID NO:322-347中任一者的轻链氨基酸序列的全长IgG。

[0308] 实施方案16为如实施方案1至15中任一项的分离的抗体,优选mAb,或其抗原结合片段,其还包含特异性识别第二抗原的第二抗体部分。

[0309] 实施方案17为如实施方案16的分离的抗体,优选mAb,或其抗原结合片段,其中所述第二抗体部分为Fab、Fab'、(Fab')₂、Fv、单链Fv(scFv)、scFv-scFv、微抗体、双抗体、sdAb或抗体模拟物。

[0310] 实施方案18为如实施方案16或17的分离的抗体,优选mAb,或其抗原结合片段,其中所述第二抗体部分为sdAb。

[0311] 实施方案19为如实施方案16至18中任一项的分离的抗体,优选mAb,或其抗原结合片段,其中所述第二抗体部分能够与CTLA-4特异性结合,优选地,所述第二抗体部分为能够与CTLA-4特异性结合的sdAb。

[0312] 实施方案20为如实施方案16至18中任一项的分离的抗体,优选mAb,或其抗原结合片段,其中所述第二抗体部分能够与TIGIT特异性结合,优选地,所述第二抗体部分为能够与TIGIT特异性结合的sdAb。

[0313] 实施方案21为如实施方案16至18中任一项的分离的抗体,优选mAb,或其抗原结合片段,其中所述第二抗体部分能够与TIM-3特异性结合,优选地,所述第二抗体部分为能够与TIM-3特异性结合的sdAb。

[0314] 实施方案22为如实施方案16至18中任一项的分离的抗体,优选mAb,或其抗原结合片段,其中所述第二抗体部分能够与LAG-3特异性结合,优选地,所述第二抗体部分为能够与LAG-3特异性结合的sdAb。

[0315] 实施方案23为如实施方案19至22中任一项的分离的抗体,优选mAb,或其抗原结合片段,其中能够特异性识别PD-L1的全长IgG的重链或轻链的氨基末端任选地经由肽接头融

合至能够与CTLA-4、TIGIT、TIM-3或LAG-3特异性结合的所述sdAb的羧基末端。

[0316] 实施方案24为如实施方案19至22中任一项的分离的抗体,优选mAb,或其抗原结合片段,其中能够特异性识别PD-L1的全长IgG的重链或轻链的羧基末端任选地经由肽接头融合至能够与CTLA-4、TIGIT、TIM-3或LAG-3特异性结合的所述sdAb的氨基末端。

[0317] 实施方案25为如实施方案23或24的分离的抗体或其抗原结合片段,其中能够特异性识别PD-L1的所述全长IgG经由具有SEQ ID NO:397-399之一的氨基酸序列的肽接头融合至能够与CTLA-4、TIGIT、TIM-3或LAG-3特异性结合的所述sdAb。

[0318] 实施方案26包含一种第二分离的抗体或其抗原结合片段,其能够与实施方案1至25中任一项的分离的抗体或其抗原结合片段竞争地与PD-L1特异性结合。

[0319] 实施方案27包含一种药物组合物,其包含如实施方案1至25中任一项的分离的抗体或其抗原结合片段或如实施方案26的第二分离的抗体或其抗原结合片段及药学上可接受的载剂。

[0320] 实施方案28为如实施方案1至25中任一项的分离的抗体或其抗原结合片段,如实施方案26的第二分离的抗体或其抗原结合片段、如实施方案27的药物组合物,其用于治疗有需要的受试者的PD-L1相关疾病。

[0321] 实施方案29为如实施方案28的供使用的分离的抗体或其抗原结合片段或药物组合物,其中所述PD-L1相关疾病为癌症。

[0322] 实施方案30为如实施方案29的供使用的分离的抗体或其抗原结合片段或药物组合物,其中所述癌症为实体肿瘤。

[0323] 实施方案31为如实施方案29的供使用的分离的抗体或其抗原结合片段或药物组合物,其中所述癌症为结肠癌。

[0324] 实施方案32为如实施方案28至31中任一项的供使用的分离的抗体或其抗原结合片段或药物组合物,其与另外的癌症疗法组合。

[0325] 实施方案33为如实施方案32的供使用的分离的抗体或其抗原结合片段或药物组合物,其中所述另外的癌症疗法为手术、放射、化学疗法、免疫疗法、激素疗法或其组合。

[0326] 实施方案34为如实施方案28的供使用的分离的抗体或其抗原结合片段或药物组合物,其中所述PD-L1相关疾病为病原性感染。

[0327] 实施方案35为如实施方案28至34中任一项的供使用的分离的抗体或其抗原结合片段或药物组合物,其中所述分离的抗体或抗原结合片段或药物组合物用于全身或局部施用。

[0328] 实施方案36为如实施方案28至34中任一项的供使用的分离的抗体或其抗原结合片段或药物组合物,其中所述分离的抗体或抗原结合片段或药物组合物用于静脉内施用。

[0329] 实施方案37为如实施方案28至34中任一项的供使用的分离的抗体或其抗原结合片段或药物组合物,其中所述分离的抗体或抗原结合片段或药物组合物用于肿瘤内施用。

[0330] 实施方案38为如实施方案28至37中任一项的供使用的分离的抗体或其抗原结合片段或药物组合物,其中所述受试者为人。

[0331] 实施方案39为一种治疗有需要的受试者的PD-L1相关疾病的方法,其包括向所述受试者施用有效量的如实施方案27的药物组合物。

[0332] 实施方案40为如实施方案39的方法,其中所述PD-L1相关疾病为癌症。

- [0333] 实施方案41为如实施方案40的方法,其中所述癌症为实体肿瘤。
- [0334] 实施方案42为如实施方案40或41的方法,其中所述癌症为结肠癌。
- [0335] 实施方案43为如实施方案40至42中任一项的方法,其进一步包括向所述个体施用另外的癌症疗法。
- [0336] 实施方案44为如实施方案43的方法,其中所述另外的癌症疗法为手术、放射、化学疗法、免疫疗法、激素疗法或其组合。
- [0337] 实施方案45为如实施方案39的方法,其中所述PD-L1相关疾病为病原性感染。
- [0338] 实施方案46为如实施方案39至45中任一项的方法,其中所述药物组合物是全身或局部施用。
- [0339] 实施方案47为如实施方案39至45中任一项的方法,其中所述药物组合物是静脉内施用。
- [0340] 实施方案48为如实施方案39至45中任一项的方法,其中所述药物组合物是肿瘤内施用。
- [0341] 实施方案49为如实施方案39至48中任一项的方法,其中所述个体为人。
- [0342] 实施例
- [0343] 以下实施例仅旨在例示本发明,并且因此不应视为以任何方式限制本发明。提供以下实施例及详细说明是用以说明而非用以限制。
- [0344] 实施例1:抗PD-L1 mAb的产生
- [0345] 免疫
- [0346] 将人PD-L1细胞外结构域Fc融合蛋白(PD-L1-Fc)(GenScript,目录号:Z03371,SEQ ID NO:396)用作免疫原。为了进行免疫,将抗原蛋白调配成具有CFA(初次免疫)或IFA(加强免疫)、或不具有佐剂(最终加强)的乳液。将约50 μ g蛋白以1:1比率与弗氏完全佐剂(Sigma-Aldrich)混合且用于使雌性Balb/c及C57b1/6小鼠免疫。然后,将小鼠每两周腹膜内用以1:1比率与弗氏不完全佐剂(Sigma-Aldrich)混合的25 μ g PD-L1-Fc免疫,多达3次。全部10只免疫小鼠的滴度均达到高于 10^5 (图1)。对两只小鼠(#848及#853)腹膜内使用25 μ g PD-L1-Fc(无佐剂)进行最终加强,所述两只小鼠显示针对抗原蛋白的最高滴度。最终加强之后四天,进行细胞融合。
- [0347] 融合瘤融合及筛选
- [0348] 将两只选择的小鼠的分离的脾及与融合配偶体骨髓瘤细胞(SP 2/0)制成均质化单细胞悬浮液。通过电融合法融合约 8.9×10^7 个脾细胞及 4.1×10^7 个SP 2/0细胞。将融合细胞再悬浮于100ml含有胸腺核苷嘧啶、次黄嘌呤及氨基蝶呤融合瘤选择试剂的DMEM/10% FBS培养基中。将细胞悬浮液分配至多于50个96孔板中,每孔100 μ l。将细胞于具有6% CO₂的37 $^{\circ}$ C温育箱中培养7天。收集融合瘤上清液并通过酶联免疫吸附测定(ELISA)进行PD-L1结合测定及PD-1竞争测定,通过荧光活化细胞分选(FACS)进行PD-1过表达细胞系结合,以使用以下方法鉴别PD-L1特异性抗体。
- [0349] 通过ELISA的PD-L1蛋白结合测定
- [0350] 采用间接ELISA评估融合瘤上清液中抗体与PD-L1 ECD(Acrobiosystems,目录号:PD1-H5229)的结合能力。将重组PD-L1-Fc或人IgG1(阴性对照)通过磷酸盐缓冲盐水(PBS)稀释至0.5 μ g/ml,并在4 $^{\circ}$ C下涂布于96孔ELISA板(每孔100 μ l)上隔夜。使用PBST(补充有

0.05% Tween-20的PBS)洗涤各板。在37℃下使用补充有1% BSA的PBST将板(每孔200μl)阻断0.5小时,然后丢弃。将融合瘤上清液添加于各孔中(每孔100μl),并在室温下温育1小时。将板用PBST洗涤3次。添加山羊抗小鼠IgG (Fab特异性)HRP (GenScript) 二级抗体(每孔100μl)并在37℃下温育0.5小时。然后将板用PBST洗涤5次。将四甲基联苯胺(TMB, GenScript)添加至孔中,并在室温下温育15分钟。添加盐酸盐(HCl, Sigma)终止缓冲液(1M, 每孔50μl)以终止反应,并使用光谱仪在450nm下读板。

[0351] 通过ELISA的PD-1竞争测定

[0352] 采用竞争ELISA评估融合瘤上清液中抗体阻断PD-L1与其受体PD-1结合的能力。通过PBS将重组PD-1ECD蛋白(GenScript目录号:Z03424)稀释至0.5μg/ml,并在4℃下涂布于ELISA板(每孔100μl)上隔夜。使用PBST洗涤各板。在37℃下使用补充有1% BSA的PBST将板(每孔200μl)阻断0.5小时,然后丢弃。将融合瘤上清液添加于各孔中(每孔50μl),并将添加至其他经涂布孔(每孔50μl)的非相关上清液用作对照。然后将经生物素化的PD-L1-Fc(0.15μg/ml, 每孔50μl)添加至孔中。将板在37℃下温育1小时,并用PBST洗涤3次。将山葵过氧化物酶(HRP)标记的链霉抗生物素蛋白(SA-HRP, GenScript)添加至孔中(每孔100μl),并在37℃下将板温育0.5小时。将板用PBST洗涤5次。将TMB (GenScript)添加至孔中,并在室温下温育15分钟。添加HCl (Sigma)终止缓冲液(1M, 每孔50μl)以终止反应,并使用光谱仪在450nm下读板。

[0353] 通过FACS的PD-L1稳定细胞系结合

[0354] 采用FACS评估融合瘤上清液中抗体与CHO细胞表面上表达的PD-L1蛋白的结合能力。收集过表达PD-L1的CHO细胞及亲本CHO细胞,并用PBS洗涤3次。将约 2.5×10^5 个细胞及100μl融合瘤上清液添加至96孔板的各孔中,并在4℃下温育1小时。将板使用PBS洗涤3次。将山羊抗小鼠IgG (H+L) iFluor647 (GenScript)添加至孔中(每孔100μl)并在4℃下温育45分钟。将细胞用PBS洗涤3次,且通过FACS BD Calibur读取信号。

[0355] 单克隆抗体可变结构域测序

[0356] 通过上文所述的筛选程序,鉴别十二种PD-L1特异性单克隆抗体,即1H1G4D9、18B7F4G8、21D1F4D4、25B6E5D8、25G1F9F8、27D3D3G2、29A8H8C7、30A6B2D9、30A7B5D9、42G2D7C3、51F3D2G4及53C1F3D4。为了得到单克隆抗体的可变结构域序列,使用TRIzol (Ambion)从 3×10^6 至 5×10^6 个融合瘤细胞中提取单克隆的总RNA。使用表达小鼠同型ELISA试剂盒(Clontyping System-HRP, Southern Biotech)测定单克隆抗体的同型。使用同型特异性引物及通用引物(PrimeScript™第1股cDNA合成试剂盒, Takara)将RNA逆转录成cDNA。使用cDNA末端的快速扩增(RACE)聚合酶链反应(PCR)扩增抗体重链及轻链的可变区DNA,并将其亚克隆至pMD18-T载体系统(Takara)中。使用载体特异性引物对插入的可变结构域DNA进行测序。可变结构域的氨基酸序列显示于表18及19中。

[0357] 实施例2:小鼠单克隆抗体表征

[0358] 由融合瘤培养物产生小鼠单克隆抗体。使用SPR、FACS、报告基因测定及混合淋巴细胞反应(MLR)测定来表征诸如抗原结合、受体阻断、小鼠mAb的功能活性的性质。

[0359] 融合瘤细胞培养及小鼠mAb产生

[0360] 将冷冻的融合瘤细胞快速解冻并转移至含有10% FBS的温热RPMI 1640培养基中并扩增。将扩增的细胞培养物转移至含有融合瘤细胞培养基的滚瓶中,使最终细胞密度为

1-2×10⁵个细胞/ml。将滚瓶立即置于37℃温育箱中的滚筒装置上。然后将融合瘤细胞在2-3rpm转速下培养两周。通过在3,000-4,000rpm下离心15min使融合瘤细胞离心沉降。将培养上清液通过1.0μm过滤器过滤,然后浓缩至原始体积的1/10。可以按照制造商的手册,使用1ml HiTrap蛋白A HP柱(GE healthcare)立即纯化浓缩的上清液。

[0361] 通过FACS的PD-L1稳定细胞系结合

[0362] 使用FACS进行12种小鼠mAb的PD-L1稳定细胞系结合活性评估。将表达人PD-L1的CHO-K1细胞(Genscript,目录号M00543)从贴壁培养瓶中解离,并与不同浓度的抗体混合。将抗体及细胞在室温下温育30分钟,用FACS缓冲液(含有1% BSA的PBS)洗涤三次。添加PE标记的山羊抗小鼠IgG(最小x-反应性)二级抗体(BioLegend,目录号405307)并在室温下温育15分钟。用FACS缓冲液再次洗涤细胞,并通过FACSCalibur(BD Bioscience, San Jose, CA)及Flowjo软件分析。使用Prism 6(GraphPad软件, San Diego, CA)使用非线性回归分析数据,并计算EC₅₀值(图2A-2L及表3)。一些小鼠mAb,即18B7F4G8、29A8H8C7、42G2D7C3、51F3D2G4及53C1F3D4对细胞上表达的PD-L1蛋白显示出非常高的亲和力。

[0363] 表3. PD-L1过表达细胞系与小鼠mAb之间的结合亲和力

样品	最佳拟合值				
	底部	顶部	LogEC ₅₀	Hill 斜率	EC ₅₀ (nM)
1H1G4D9	12.85	1760	1.089	2.266	12.28
18B7F4G8	12.75	398.6	-0.2089	2.578	0.62
21D1F4D4	24.13	1959	0.9715	2.055	9.37
25B6E5D8	29.44	1411	0.6535	2.654	4.50
25G1F9F8	8.399	1752	1.257	2.138	18.08
27D3D3G2	29.58	1773	0.6223	1.868	4.19
29A8H8C7	45.55	2444	0.4852	1.811	3.06
30A6B2D9	23.76	1639	1.046	3.256	11.12
30A7B5D9	22.88	1719	0.7868	2.551	6.12
42G2D7C3	11.98	1776	0.5176	2.235	3.29
51F3D2G4	21.09	1724	0.328	2.786	2.13
53C1F3D4	38.87	2023	0.5717	1.922	3.73

[0366] 通过FACS的PD-L1与PD-1相互作用阻断

[0367] 将表达人PD-L1的CHO-K1细胞(Genscript,目录号M00543)从贴壁培养瓶解离,用洗涤缓冲液(补充有0.2% BSA的1×PBS)洗涤两次并与生物素化PD-1Fc融合蛋白(28μg/ml,每孔50μl)混合(2×10⁵个细胞/孔,100μl)。然后添加一系列稀释的小鼠mAb(浓度从900nM开始,3倍稀释,每孔50μl)。将混合物在4℃下温育30分钟,用洗涤缓冲液洗涤两次,然后添加PEcy5/链霉抗生物素蛋白(1μg/ml,150μl/孔)。将板再次在4℃下温育30分钟,然后通过FACSCalibur(BD Bioscience, San Jose, CA)及Flowjo软件分析各孔中的细胞。使用Prism(GraphPad软件, San Diego, CA)使用非线性回归分析数据,并计算EC₅₀值(图3A-3J及表4)。一些小鼠mAb,即18B7F4G8、25B6E5D8对PD-L1细胞系与PD-1蛋白之间的结合没有阻断作用,而一些小鼠mAb,即27D3D3G2、29A8H8C7、51F3D2G4及53C1F3D4可以最有效地阻断相互作用。

[0368] 表4.小鼠mAb对PD-L1细胞系及PD-1ECD的阻断作用。

样品	最佳拟合值					
	底部	顶部	LogIC ₅₀	Hill 斜率	IC ₅₀ (nM)	
[0369]	1H1G4D9	-4.207	469.5	1.074	-2.52	11.85
	18B7F4G8	无阻断作用				
	21D1F4D4	-3.712	480.4	0.579	-2.409	3.794
[0370]	25B6E5D8	无阻断作用				
	25G1F9F8	-11.67	482.5	1.139	-2.088	13.76
	27D3D3G2	-0.8319	481	0.1074	-2.228	1.281
	29A8H8C7	3.803	482.8	0.1499	-2.939	1.412
	30A6B2D9	-3.543	488.6	0.9218	-2.379	8.352
	30A7B5D9	-1.139	486.1	0.6466	-3.302	4.432
	42G2D7C3	19.73	464.3	0.4614	-2.591	2.894
	51F3D2G4	0.08551	484.8	0.08928	-2.476	1.228
	53C1F3D4	-2.682	483.2	0.1048	-2.127	1.273

[0371] 基于PD-L1细胞的报告基因测定

[0372] 使用基于PD-L1细胞的报告基因测定评估显示高结合活性和/或高阻断活性的六种小鼠mAb,即18B7F4G8、27D3D3G2、29A8H8C7、42G2D7C3、51F3D2G4及53C1F3D4。效应细胞含有荧光素酶构建体,其在破坏PD-1/PD-L1受体-配体相互作用时经诱导,例如当PD-L1细胞与表达PD-1的效应细胞混合时。因此,可以通过测量荧光素酶报告基因活性来评估抗PD-L1 mAb抑制CHO-K1稳定细胞上PD-L1的功效。如下进行测定。

[0373] 在第一天,将PD-L1细胞于37℃水浴中解冻,直至细胞刚好解冻(约3-4分钟),并将0.5mL解冻的细胞转移至14.5mL细胞回收培养基(10% FBS/F-12)中。通过轻轻颠倒管1-2次将细胞悬浮液充分混合。然后将细胞悬浮液转移至无菌试剂储存器,并以每孔25μL细胞悬浮液分配至测定板中。添加每孔100μL测定培养基作为空白对照。对作为空白对照的各孔添加每孔100μL细胞回收培养基。然后将板盖上盖子并在CO₂温育箱中在37℃下温育隔夜。

[0374] 在测定当天,制备新鲜测定缓冲液(RPMI 1640+1% FBS)。对于对照抗PD-L1抗体(例如度伐鲁单抗)及小鼠mAb中的各者,在测定缓冲液中进行八点连续稀释。对起始浓度及稀释方案进行优化以达成全剂量反应曲线。自CO₂温育箱回收含有PD-L1细胞的测定板。自全部孔移除每孔95μL培养基。向含有PD-L1细胞的孔中添加每孔40μL对照抗PD-L1抗体或抗原结合蛋白的连续稀释液。向各板的空白对照孔中添加每孔80μL测定缓冲液。

[0375] 接着,将PD-1效应细胞于37℃水浴中解冻,直至细胞刚好解冻(约3-4分钟)。通过上下吸取将小瓶中的细胞悬浮液轻轻混合,且将0.5mL细胞添加至5.9mL测定缓冲液中。通过轻轻颠倒管1-2次将细胞悬浮液充分混合。然后将细胞悬浮液转移至无菌试剂储存器中,且将40μL细胞悬浮液分散至含有PD-1细胞及对照抗体或双特异性抗原结合蛋白的各孔中。将板盖上盖子并在CO₂温育箱中在37℃下温育六小时。

[0376] 通过将一瓶缓冲液转移至含有受质的瓶中来重构荧光素酶测定系统。将系统在室温下储存且避光保存以供某天使用。6小时温育之后,将测定板自CO₂温育箱移除并在周围

温度下平衡5-10min。向各孔中添加80 μ L试剂。将板在周围温度下温育5-10min。于GloMax®发现系统(Promega, Madison, WI)或具有辉光型(glow-type)发光读取能力的板读取器中测量发光。

[0377] 发光表示为相对光单位(RLU)。将具有稀释抗体或双特异性抗原结合蛋白的孔的RLU值正规化至无抗体或双特异性抗原结合蛋白对照的RLU以得到荧光素酶诱导倍数。将数据绘制为RLU对抗体或双特异性抗原结合蛋白浓度的Log10,及诱导倍数对抗体或双特异性抗原结合蛋白浓度的Log10。使用Prism 6(GraphPad软件, San Diego, CA)使用非线性回归分析数据,并计算EC₅₀值(图4A-4H及表5)。三种抗体,即27D3D3G2、29A8H8C7及53C1F3D4显示高功能活性。小鼠mAb 18B7F4G8具有较低EC₅₀值,然而相较于其他抗体的活化百分比为低的,相较于其他三种抗体,最大20%活化。

[0378] 表5.通过基于细胞的报告基因测定的小鼠mAb的功能活性

[0379]	样品	最佳拟合值				
		底部	顶部	LogEC ₅₀	Hill 斜率	EC ₅₀ (nM)
	18B7F4G8	-0.3657	20.56	0.3565	1.52	2.272
	27D3D3G2	0.8835	97.2	0.5585	2.581	3.618
	29A8H8C7	0.5048	95.38	0.5572	2.419	3.607
[0380]	42G2D7C3	未确定				
	51F3D2G4	1.672	100	0.939	1.798	8.69
	53C1F3D4	1.495	98.58	0.6483	3.358	4.449
	度伐鲁单抗	2.458	100.1	0.2329	2.919	1.71

[0381] 混合淋巴细胞反应 (MLR) 测定

[0382] 使用MLR测定,评估四种小鼠mAb,即18B7F4G8、27D3D3G2、29A8H8C7及53C1F3D4的功能活性。从人外周血单核细胞(PBMC)分离树突细胞(DC)及CD4+T细胞。于FACS测定中分析DC的共刺激分子及MHC II类的表达。验证表面标记物即CD1a、CD83、CD86及HLA-DR的表达。将合适比率的CD4+T细胞及DC接种至96孔板的各孔中,并用上文所提及的抗体处理。将测定板在37℃/5% CO₂温育箱中温育72小时,并使用人IL-2HTRF试剂盒(Cisbio, 目录号64IL2PEB)测量由细胞释放的IL-2。使用Prism 6(GraphPad软件, San Diego, CA)使用非线性回归分析数据,并计算EC₅₀值(图5A-5F及表6)。根据测定结果,29A8H8C7、53C1F3D4及18B7F4G8的功能活性显示与抗PD-L1阳性对照抗体阿特殊单抗的功能活性相当的功能活性。

表 6. 通过 MLR 测定的小鼠 mAb 的功能活性

样品	最佳拟合值				
	底部	顶部	LogEC ₅₀	Hill 斜率	EC ₅₀ (nM)
阿特殊单抗(板 1)	54.16	81.27	-0.1644	3.5	0.6848
[0383] 29A8H8C7 (板 1)	48.62	75.02	-0.2784	2.727	0.5268
53C1F3D4 (板 1)	41.65	67.63	-0.1309	3.5	0.7397
阿特殊单抗(板 2)	48.04	76.64	-0.05928	3.048	0.8724
27D7G3D4 (板 2)	43.47	66.23	0.399	1.062	2.506
18B7F4G8 (板 2)	43.36	68.13	-0.01998	1.654	0.955

[0384] 通过SPR的亲和力确定

[0385] 于Biacore™ T200仪器上通过表面等离子体共振 (SPR) 确定小鼠mAb 29A8H8C7及53C1F3D4的平衡解离常数 (K_D)。简而言之,使用EDC活化的胺偶联化学,将捕获抗体 (用于小鼠mAb的亲和力测量的抗小鼠Fc抗体,或用于嵌合及人源化mAb的亲和力测量的抗人Fc抗体,GE healthcare) 固定于Biacore™ CM5芯片上达约7,000RU。将所关注的抗体 (5 μ g/ml) 捕获60秒至感测芯片表面上。使带His标签的PD-L1 ECD蛋白 (ACROBiosystems) 在一系列浓度下流过感测芯片表面。在所有实验中流速为30 μ l/min。缔合期及解离期分别为5及15min。使用Glycine/HCl pH 1.5使芯片再生。各循环之间使用50mM HCl移除捕获的抗体及抗原,以确保各浓度抗原的新鲜结合表面。使用1:1结合模型全面拟合所得感测图,以计算缔合速率及解离速率 (分别为 k_a 及 k_d) 以及亲和力 (K_D)。根据结果 (图6A-6D及表7), 29A8H8C7及53C1F3D4显示比阿特殊单抗及度伐鲁单抗高的与PD-L1 ECD蛋白的结合亲和力。

[0386] 表7. 小鼠IgG及抗PD-L1对照抗体的亲和力确定。

[0387]	配体	分析物	k_a (1/Ms)	k_d (1/s)	K_D (M)	Rmax (RU)	Chi ² (RU ²)	U-值
	29A8H8C7	PD-L1-His	6.20E+05	1.70E-04	2.80E-10	77.11	0.328	1
	53C1F3D4		3.20E+05	1.90E-04	6.10E-10	56.83	0.097	1
	度伐鲁单抗		3.04E+05	2.99E-04	9.84E-10	134.2	0.717	1
	阿特殊单抗		2.92E+05	3.19E-04	1.10E-09	47.97	0.374	1

[0388] 实施例3: 小鼠mAb的人源化

[0389] 使用CDR移植技术,选择两种小鼠抗PD-L1 mAb,即29A8H8C7及53C1F3D4用于人源化 (参见例如美国专利第5,225,539号)。在执行CDR移植之前,使这些抗体的若干CDR残基突变以增加CDR的人性或减少潜在的翻译后修饰 (PTM) 的可能性。这些突变为: 1. 将小鼠29A8H8C7及53C1F3D4的轻链可变结构域 (VL) 的CDR1中的赖氨酸24突变成精氨酸 (K24R) 以增加人性,得到29A8VL.M1及53C1VL.M1的VL序列; 2. 将小鼠53C1F3D4的重链可变结构域 (VH) 的CDR2中的天冬酰胺57突变成丝氨酸 (N57S)、丙氨酸 (N57A) 及谷氨酰胺 (N57Q), 得到分别53C1VH.M1、53C1VH.M2及53C1VH.M3的VH序列,以减少潜在去酰胺的可能性。

[0390] 使用哺乳动物细胞产生嵌合IgG及其突变体。简而言之,合成编码重链可变区 (VH) 的DNA片段并插入至经修饰的pTT5载体中,所述载体含有编码具有无效应子突变的人IgG1重链恒定区 (铰链、 C_H1 、 C_H2 及 C_H3) 的DNA (恒定区氨基酸序列参见SEQ ID NO:392), 得到重链表达质粒; 类似地,合成编码轻链可变区 (VL) 的DNA片段并插入至经修饰的pTT5载体,所述载体含有编码人IgG1 κ 链恒定区 (CL) 的DNA,得到轻链表达质粒。制备Maxiprep质粒。

[0391] 将野生型及突变体重链及轻链合并,得到野生型嵌合IgG及一系列突变体IgG。例如,29A8_嵌合为29A8H8C7嵌合抗体,且使用连接至具有无效应子Fc突变的重链恒定区的编码29A8VH的野生型重链质粒及连接至轻链恒定区的编码29A8VL的轻链质粒产生; 53C1_VH.M3-VL.M1为嵌合53C1F3D4的突变体,且使用连接至具有无效应子Fc突变的重链恒定区的编码53C1VH.M3的突变体重链质粒及连接至轻链恒定区的编码53C1VL.M1的突变体轻链质粒产生。使用合并的质粒来转染HEK293-6E细胞。将转染的细胞在37°C下培养2天。收集上清液,过滤; 且对分泌的嵌合及突变体抗体进行SPR亲和力评估。

[0392] 根据SPR亲和力测量,没有突变显著影响人PD-L1与抗PD-L1抗体之间的结合亲和

力(表8),因此两种抗体的VL-CDR1中的K24R以及53C1F3D4的VH-CDR2中的N57Q、N57S及N57A可引入至人源化抗体中。

[0393] 表8.嵌合及突变体IgG的亲和力确定。

[0394]	配体	分析物	k_a (1/Ms)	k_d (1/s)	K_D (M)	Rmax (RU)	Chi ² (RU ²)	U - 值
	29A8_嵌合	PD-L1/His	5.30E+05	1.70E-04	3.20E-10	83.75	0.243	1
	29A8_VH-VL.M1		5.30E+05	1.50E-04	2.90E-10	96.63	0.394	1
	53C1_嵌合		2.60E+05	1.90E-04	7.50E-10	45.85	0.056	1
[0395]	53C1_VH.M1-VL		2.40E+05	2.10E-04	8.70E-10	51.26	0.078	1
	53C1_VH.M2-VL		2.00E+05	1.60E-04	8.10E-10	50.07	0.05	1
	53C1_VH.M3-VL		2.60E+05	1.40E-04	5.30E-10	40.06	0.043	1
	53C1_VH-VL.M1		2.60E+05	2.00E-04	7.60E-10	54.59	0.089	1
	53C1_VH.M1-VL.M1		2.40E+05	2.00E-04	8.60E-10	51.42	0.074	1
	53C1_VH.M2-VL.M1		2.00E+05	1.80E-04	9.40E-10	36.73	0.042	1
	53C1_VH.M3-VL.M1		2.60E+05	1.40E-04	5.60E-10	54.65	0.052	1

[0396] 使用CDR移植技术将小鼠抗体人源化(参见例如美国专利第5,225,539号)。简而言之,将鼠类抗体29A8H8C7及53C1F3D4的可变链序列与结构生物信息学合作研究协会(Research Collaboratory for Structural Bioinformatics;RCSB)蛋白数据库可获得的序列相比较。基于最接近的VH及VK结构生成29A8H8C7及53C1F3D4的同源模型。鉴别并分析与29A8H8C7及53C1F3D4具有最高同一性的人序列(Foote及Winter,J.Mol.Biol.224:487-499(1992);Morea V.等人,Methods 20:267-279(2000);Chothia C.等人,J.Mol.Biol.186:651-663(1985))。鉴别其上建立CDR移植重链及轻链的最适当的人框架。对于重链,通过Genbank登录号CAB51716及BAC02193编码的框架(其序列以引用方式并入本文)经确定分别最适于29A8H8C7及53C1F3D4。对于轻链,通过Genbank登录号ABA70776及CAG27369编码的框架(其序列以引用方式并入本文)经确定分别最适于29A8H8C7及53C1F3D4。

[0397] 对各链执行直接移植以生成表达构建体。直接移植的29A8VH1、29A8VL1、53C1VH1及53C1VL1的氨基酸序列公开于序列表中(SEQ ID NO:293、336、298及339)。构建直接移植的重链(SEQ ID NO:298)及其N57Q突变体即53C1VH1.M3(SEQ ID NO:304)以及具有上文提

及的K24R突变的直接移植的轻链变体即29A8VL1.M1及53C1VL1.M1 (SEQ ID NO:342及345)。

[0398] 在人源化抗体的亲和力丧失的情况下,使若干框架残基突变回其鼠类对应物以恢复抗体的结合亲和力。对于29A8H8C7的人源化,构建人源化VH变体29A8VH2、29A8VH3、29A8VH4及29A8VH5 (SEQ ID NO:294-297) 及人源化VL变体29A8VL2.M1及29A8VL3.M1 (SEQ ID NO:343及344)。对于53C1F3D4的人源化,也构建人源化VH变体53C1VH2、53C1VH3、53C1VH4、53C1VH5及53C1VH6 (SEQ ID NO:299-303) 及其N57Q突变体即53C1VH2.M3、53C1VH3.M3、53C1VH4.M3、53C1VH5.M3及53C1VH6.M3 (SEQ ID NO:305-309) 以及人源化VL变体53C1VL2.M1及53C1VL3.M1 (SEQ ID NO:346及347)。

[0399] 将人源化重链及轻链合并,且用于产生一系列人源化抗体。使用HEK293细胞短暂地产生这些抗体,且对上清液中的抗体进行SPR亲和力评估。人源化变体的结合亲和力显示于表9及10中。根据亲和力评估,人源化29A8H8C7具有一定程度的亲和力丧失,而53C1F3D4的结合亲和力在人源化之后被保留。选择29A8H8C7的3种人源化变体即29A8_VH1-VL1.M1、29A8_VH4-VL1.M1及29A8_VH5-VL1.M1以及53C1F3D4的5种人源化变体即53C1_VH1-VL1.M1、53C1_VH3-VL1.M1、53C1_VH5-VL1.M1、53C1_VH1.M3-VL1.M1及53C1_VH5.M3-VL1.M1连同嵌合抗体一起用于抗体产生、表征及功能剖析。这些人源化变体具有最高人性例如较少的回复突变,或最高的与人PD-L1蛋白的亲和力。

[0400] 表9.人源化29A8H8C7的亲和力评估。

配体		分析物	k_a (1/Ms)	k_d (1/s)	K_D (M)	Rmax (RU)	Chi ² (RU ²)
[0401]	29A8_嵌合	PD-L1-His	5.8E+05	1.5E-04	2.5E-10	43.02	0.136
	29A8_VH1-VL1.M1		4.7E+05	7.1E-04	1.5E-09	70.10	0.161
	29A8_VH1-VL2.M1		4.7E+05	6.0E-04	1.3E-09	64.79	0.120
	29A8_VH1-VL3.M1		4.6E+05	6.2E-04	1.3E-09	67.91	0.136
	29A8_VH2-VL1.M1		4.7E+05	6.1E-04	1.3E-09	64.97	0.096
	29A8_VH2-VL2.M1		4.9E+05	5.7E-04	1.2E-09	58.63	0.086
[0402]	29A8_VH2-VL3.M1		4.7E+05	6.0E-04	1.3E-09	60.45	0.087
	29A8_VH3-VL1.M1		4.8E+05	5.1E-04	1.1E-09	62.72	0.141
	29A8_VH3-VL2.M1		4.8E+05	4.4E-04	9.0E-10	61.22	0.099
	29A8_VH3-VL3.M1		5.4E+05	4.5E-04	8.3E-10	43.53	0.230
	29A8_VH4-VL1.M1		5.6E+05	6.3E-04	1.1E-09	58.32	0.083
	29A8_VH5-VL1.M1		5.5E+05	4.2E-04	7.6E-10	81.41	0.23

[0403] 表10.人源化53C1F3D4的亲和力评估。

配体	分析物	k_a (1/Ms)	k_d (1/s)	K_D (M)	Rmax (RU)	Chi ² (RU ²)
53C1_嵌合	PD-L1- His	2.5E+05	1.8E-04	7.2E-10	28.39	0.063
53C1_VH1-VL1.M1		2.4E+05	2.6E-04	1.1E-09	29.46	0.124
53C1_VH1-VL2.M1		2.1E+05	2.6E-04	1.2E-09	59.58	0.188
53C1_VH1-VL3.M1		2.0E+05	3.1E-04	1.5E-09	62.91	0.140
53C1_VH2-VL1.M1		2.4E+05	2.5E-04	1.0E-09	32.49	0.101
53C1_VH2-VL2.M1		2.2E+05	2.7E-04	1.2E-09	56.03	0.135
53C1_VH2-VL3.M1		2.0E+05	3.0E-04	1.5E-09	65.37	0.126
53C1_VH3-VL1.M1		3.0E+05	1.5E-04	4.9E-10	37.51	0.204
53C1_VH3-VL2.M1		2.9E+05	1.6E-04	5.7E-10	64.90	0.241
53C1_VH3-VL3.M1		2.6E+05	1.8E-04	6.8E-10	55.70	0.155
53C1_VH4-VL1.M1		2.6E+05	2.0E-04	7.5E-10	43.52	0.012
53C1_VH5-VL1.M1		3.8E+05	1.2E-04	3.1E-10	50.03	0.042
53C1_VH6-VL1.M1		3.7E+05	1.0E-04	2.7E-10	42.4	0.038
53C1_VH1.M3-VL1.M1		3.2E+05	1.0E-04	3.2E-10	47.76	0.025
53C1_VH3.M3-VL1.M1		3.5E+05	7.3E-05	2.1E-10	58.38	0.042
53C1_VH4.M3-VL1.M1		3.1E+05	9.8E-05	3.2E-10	48.86	0.028
53C1_VH5.M3-VL1.M1		3.8E+05	6.1E-05	1.6E-10	50.47	0.047
53C1_VH6.M3-VL1.M1		3.7E+05	6.3E-05	1.7E-10	59.18	0.050

[0405] 实施例4：人源化mAb的产生、表征及功能剖析

[0406] 人源化抗体产生

[0407] 将编码2种嵌合抗体及上文提及的8种人源化抗体的合并的重链及轻链质粒用于转染HEK293-6E细胞。将转染的细胞在37℃下于摇瓶中培养6天。收集上清液，过滤并加载至蛋白A亲和柱上。将柱用1xPBS, pH 7.4彻底洗涤，之后用无菌0.1M柠檬酸钠, pH 3.5洗脱剩余抗体。使用1/9体积的1M Tris-HCl, pH 9.0缓冲液中和洗脱的抗体溶液。将抗体的缓冲液改变成1xPBS, pH 7.4或50mM组氨酸pH 6.0。然后通过280nm下的吸光度 (OD280) 确定浓度。使用十二烷基硫酸钠聚丙烯酰胺凝胶电泳 (SDS-PAGE) 及尺寸排阻色谱法 (SEC) 确定纯

度。嵌合抗体及人源化抗体的恒定区可为野生型人IgG1的恒定区或具有无效应子Fc突变的人IgG1的恒定区。为简洁起见,使用具有带有无效应子Fc突变的人IgG1的恒定区的嵌合及人源化抗PD-L1进行以下特征测定。

[0408] 通过SPR的亲和力确定

[0409] 于Biacore™ T200仪器上通过表面等离子体共振 (SPR) 确定人源化29A8H8C7及53C1F3D4与人及食蟹猴PD-L1的平衡解离常数 (K_D)。对于单价人PD-L1结合亲和力确定,所述方法类似于之前所述的方法,除了所用的捕获抗体为抗人Fc抗体。对于食蟹猴PD-L1结合亲和力确定,通过胺偶联将食蟹猴PD-L1 Fc融合蛋白固定于感测芯片上,且将嵌合及人源化PD-L1抗体及基准抗体阿特殊单抗及度伐鲁单抗用作分析物。根据结果(图7A-7J及图8以及表11及12),29A8H8C7与带His标签的人PD-L1及食蟹猴PD-L1 Fc融合蛋白的结合亲和力略微减小,而53C1F3D4的结合亲和力在人源化之后被完全保留。

[0410] 表11. 嵌合及人源化抗PD-L1抗体与带His标签的人PD-L1的单价结合亲和力

	配体	分析物	k_a (1/Ms)	k_d (1/s)	K_D (M)	Rmax (RU)	Chi ² (RU ²)	U-值
[0411]	29A8_嵌合	人 PD-L1	6.40E+05	1.90E-04	3.00E-10	47.85	0.057	1
	29A8_VH1-VL1M1		5.90E+05	8.00E-04	1.40E-09	35.08	0.039	1
	29A8_VH4-VL1M1		6.30E+05	7.10E-04	1.10E-09	28.79	0.026	1
	29A8_VH5-VL1M1		6.20E+05	4.60E-04	7.40E-10	33.61	0.049	1
	53C1_嵌合		2.40E+05	1.90E-04	7.80E-10	46.99	0.093	1
	53C1_VH1-VL1M		2.00E+05	2.70E-04	1.30E-09	56.61	0.101	1
	53C1_VH3-VL1M		2.90E+05	1.60E-04	5.50E-10	38.93	0.081	2
	53C1_VH5-VL1M		3.10E+05	1.50E-04	4.70E-10	39.51	0.079	2
	53C1_VH1M3-VL1M		2.50E+05	1.40E-04	5.70E-10	43.84	0.083	2
	53C1_VH5M3-VL1M		2.90E+05	1.10E-04	4.00E-10	69.01	0.21	2

[0412] 表12. 嵌合及人源化抗PD-L1抗体与食蟹猴PD-L1 Fc融合蛋白的结合亲和力。

[0413]

配体	分析物	k_a (1/Ms)	k_d (1/s)	K_D (M)	Rmax (RU)	Chi ² (RU ²)	U-值
食蟹猴 PD-L1 Fc 融合蛋白	29A8_嵌合	1.50E+05	7.30E-05	4.80E-10	23.02	0.131	9
	29A8_VH1-VL1.M1	1.10E+05	4.30E-04	4.00E-09	19.66	0.044	1
	29A8_VH4-VL1.M1	1.30E+05	4.40E-04	3.30E-09	20.71	0.111	1
	29A8_VH5-VL1.M1	2.00E+05	2.00E-04	9.80E-10	23.17	0.248	4
	53C1_嵌合	8.70E+04	9.50E-05	1.10E-09	31.18	0.15	5
	53C1_VH1-VL1.M1	7.50E+04	6.40E-05	8.60E-10	32.26	0.072	5
	53C1_VH3-VL1.M1	9.50E+04	6.80E-05	7.10E-10	32.72	0.123	7
	53C1_VH5-VL1.M1	1.00E+05	8.40E-05	8.30E-10	31.62	0.153	5
	53C1_VH1.M3-VL1.M1	9.80E+04	9.40E-05	9.50E-10	32.03	0.16	5
	53C1_VH5.M3-VL1.M1	1.40E+05	<1.0E-05*	<6.9E-11*	34.28	0.363	95
	阿特殊单抗	3.60E+04	9.90E-04	2.80E-08	35.79	0.241	1
	度伐鲁单抗	1.90E+05	2.10E-04	1.10E-09	38.08	0.982	9
*解离太慢, k_d 在 SPR 范围之外, 且不可准确确定。							

[0414] 通过FACS的PD-L1稳定细胞系结合

[0415] 如上文所述,使用FACS进行嵌合及人源化mAb的人及食蟹猴PD-L1稳定细胞系结合活性评估(图9A-9L及图10A-10L以及表13及14)。根据结果,人源化抗体具有与其嵌合对应物类似的结合EC₅₀值,且与人及食蟹猴PD-L1细胞系的结合亲和力与抗PD-L1基准抗体度伐鲁单抗及阿特殊单抗的结合亲和力相当。

[0416] 表13. 人PD-L1过表达细胞系与嵌合及人源化mAb之间的结合亲和力

[0417]

样品	最佳拟合值				
	底部	顶部	LogEC ₅₀	Hill 斜率	EC ₅₀ (nM)
29A8_嵌合	188. 3	640 7	0.03364	1.726	1.081
29A8_VH1-VL1.M1	151. 1	639 9	0.2442	1.611	1.755
29A8_VH4-VL1.M1	167. 1	518 2	0.02287	1.562	1.054
29A8_VH5-VL1.M1	188. 7	510 1	0.1173	1.716	1.31
53C1_嵌合	238. 7	623 4	0.2538	1.36	1.794
53C1_VH1-VL1.M1	273. 3	637 0	0.05041	1.675	1.123
53C1_VH3-VL1.M1	216. 1	641 3	0.3	1.652	1.995
53C1_VH5-VL1.M1	189. 4	644 7	0.2925	1.641	1.961
53C1_VH1.M3-VL1.M1	273. 1	643 4	0.01313	1.954	1.031
53C1_VH5.M3-VL1.M1	264. 7	638 3	0.02358	1.754	1.056
度伐鲁单抗	289. 4	536 1	0.1474	1.713	1.404
阿特殊单抗	173. 1	535 1	0.5011	1.843	3.171

[0418] 表14. 食蟹猴PD-L1过表达细胞系与嵌合及人源化mAb之间的结合亲和力

[0419]

样品	最佳拟合值

[0420]

	底部	顶部	LogEC ₅₀	Hill 斜率	EC ₅₀ (nM)
29A8_嵌合	152.2	8669	0.4433	1.503	2.775
29A8_VH1-VL1.M1	154.6	7466	0.5483	1.578	3.534
29A8_VH4-VL1.M1	77.01	7824	0.1731	1.323	1.490
29A8_VH5-VL1.M1	148.2	7951	0.4871	1.411	3.070
53C1_嵌合	283	8490	0.4599	1.765	2.884
53C1_VH1-VL1.M1	242.1	8432	0.4407	1.619	2.759
53C1_VH3-VL1.M1	222.6	8308	0.6683	2.037	4.659
53C1_VH5-VL1.M1	249.5	8389	0.6789	2.059	4.774
53C1_VH1.M3-VL1.M1	204.2	8419	0.42	1.726	2.630
53C1_VH5.M3-VL1.M1	236.3	8571	0.4359	1.824	2.729
度伐鲁单抗	255.8	8221	0.4869	1.589	3.069
阿特殊单抗	71.42	7863	0.8319	1.223	6.791

[0421] 通过FACS的PD-L1与PD-1相互作用阻断

[0422] 如上文所述,评估嵌合及人源化抗PD-L1抗体及基准对人PD-1蛋白及人PD-L1过表达细胞系之间的相互作用的阻断(图11A-11L及表15)。根据结果,人源化抗体具有与其嵌合对应物类似的阻断IC₅₀值,且阻断IC₅₀值与抗PD-L1基准抗体度伐鲁单抗相当且低于阿特殊单抗。

[0423] 表15.嵌合及人源化mAb对PD-L1细胞系及PD-1ECD结合的阻断作用。

[0424]

样品	最佳拟合值

[0425]

	底部	顶部	LogIC ₅₀	Hill 斜率	IC ₅₀ (nM)
29A8_嵌合	1.271	56.8	-0.5227	-2.333	0.3001
29A8_VH1-VL1.M1	1.009	53.67	-0.3349	-1.851	0.4625
29A8_VH4-VL1.M1	1.306	59.59	-0.4146	-2.677	0.385
29A8_VH5-VL1.M1	1.137	59.5	-0.2636	-2.076	0.5449
53C1_嵌合	1.169	26.24	-0.2288	-2.715	0.5904
53C1_VH1-VL1.M1	0.9265	49.62	-0.04501	-2.111	0.9016
53C1_VH3-VL1.M1	0.8081	47.88	-0.3173	-1.567	0.4816
53C1_VH5-VL1.M1	0.1624	51.8	-0.3677	-1.146	0.4288
53C1_VH1.M3-VL1.M1	0.6388	54.4	-0.5526	-1.454	0.2802
53C1_VH5.M3-VL1.M1	-0.08543	152.6	-0.525	-1.804	0.2985
度伐鲁单抗	1.236	60.08	-0.2767	-2.332	0.5288
阿特殊单抗	0.9048	68.85	0.09979	-2.005	1.258

[0426] 基于PD-L1细胞的报告基因测定

[0427] 评估嵌合及人源化抗体的功能活性并使用基于PD-L1细胞的报告基因测定如之前所述进行比较(图12A-12L及表16)。根据结果,人源化抗体具有与嵌合对应物类似的功能活性,且功能活性与抗PD-L1基准抗体度伐鲁单抗及阿特殊单抗相当。

[0428] 表16.通过基于细胞的报告基因测定的mAb的功能活性。

[0429]

样品	最佳拟合值				
	底部	顶部	LogEC ₅₀	Hill 斜率	EC ₅₀ (nM)
29A8_嵌合	0.9063	87.24	0.1285	4.753	1.344
29A8_VH1-VL1.M1	0.6272	92.19	0.3034	3.518	2.011
29A8_VH4-VL1.M1	0.2767	103	0.09214	3.336	1.236
29A8_VH5-VL1.M1	0.0779	99.1	0.2573	3.132	1.808
53C1_嵌合	-0.3672	86.27	0.2959	3.225	1.977
53C1_VH1-VL1.M1	-1.953	95.39	0.4009	1.961	2.517
53C1_VH3-VL1.M1	-0.6545	87.26	0.3538	2.192	2.258
53C1_VH5-VL1.M1	-0.09158	80.9	0.3674	3.968	2.33
53C1_VH1.M3-VL1.M1	-0.7789	92.12	0.1671	3.272	1.469
53C1_VH5.M3-VL1.M1	0.06753	100	0.1163	3.036	1.307
度伐鲁单抗	2.029	91.15	0.2847	3.379	1.926
阿特殊单抗	1.498	87.61	0.4246	3.5	2.658

[0430] 混合淋巴细胞反应 (MLR) 测定

[0431] 使用MLR测定评估6种人源化mAb即29A8_VH1-VL1.M1、29A8_VH4-VL1.M1、53C1_VH1-VL1.M1、53C1_VH5-VL1.M1、53C1_VH1.M3-VL1.M1及53C1_VH5.M3-VL1.M1的功能活性(图13A-13I及表17)。除了29A8_VH1-VL1.M1,全部六种人源化抗体显示与基准抗体度伐鲁单抗类似的功能活性。

表 17. 通过 MLR 测定的人源化 mAb 的功能活性。

样品	最佳拟合值				
	底部	顶部	LogEC ₅₀	Hill 斜率	EC ₅₀ (nM)
度伐鲁单抗(板 1)	107.3	159.7	-0.6445	2.034	0.2267
53C1_VH1.M3-VL1.M1 (板 1)	79.24	163.5	-0.8825	3.500	0.1311
[0432] 53C1_VH5.M3-VL1.M1 (板 1)	91.67	163.1	-0.7945	1.94	0.1605
度伐鲁单抗(板 2)	74.58	152	-0.8079	2.691	0.1556
29A8_VH1-VL1.M1 (板 2)	96.35	146.9	0.5013	0.7035	3.171
29A8_VH4-VL1.M1 (板 2)	82.94	122	-0.955	2.029	0.1109
度伐鲁单抗(板 3)	84.34	156.3	-0.4893	0.8964	0.3241
53C1_VH1-VL1.M1 (板 3)	81.25	146.8	-0.3687	2.602	0.4278
53C1_VH5-VL1.M1 (板 3)	73.79	140.9	-0.5169	2.173	0.3041

[0433] 通过异种移植模型的体内功效研究

[0434] 使用异种移植模型评估3种人源化mAb即29A8_VH4-VL1.M1、53C1_VH1.M3-VL1.M1及53C1_VH5.M3-VL1.M1的体内功效(图14A-14G及表18)。将基准抗体度伐鲁单抗用作阳性对照。简而言之,通过胰酶消化收集实验生长期的MC38-A29-hPDL1 D13-1细胞且在细胞数计数之后再悬浮于HBSS-/-溶液中。将五十四(54)只hPD-1敲入小鼠(C57BL/6品系)(制造及目录号)在右下侧腹处(接近股背面区域)皮下接种单一体积的100 μ l细胞悬浮液(1×10^6 个细胞,细胞体积:基质胶体积=1:0.8)。最终,将40只携带肿瘤的小鼠纳入研究中。自肿瘤植入之后,使用卡尺二维地每周两次测量动物的肿瘤大小。如下计算肿瘤体积、肿瘤体积的抑制速率及肿瘤生长的抑制速率:

[0435] a. 肿瘤体积: $V(\text{mm}^3) = (a \cdot b^2) / 2$, 其中“a”及“b”分别为肿瘤的长径及短径。

[0436] b. 肿瘤体积的抑制速率(IRTV): $\text{IRTV} = (\text{CRTV} - \text{TRTV}) / \text{CRTV} \cdot 100\%$ 。(TRTV:治疗组RTV;CRTV:阴性对照组RTV)。

[0437] c. 肿瘤生长的抑制速率(IRTW): $\text{IRTW} = (\text{对照组的平均肿瘤重量} - \text{治疗组的平均肿瘤重量}) / \text{对照组的平均肿瘤重量} \cdot 100\%$

[0438] 肿瘤接种之后五(5)天,根据肿瘤大小及动物体重,将动物随机成6组,每组8只。每周三次腹膜内(i.p.)施用测试或对照制品达2周。出于伦理原因,对病状恶化和/或肿瘤大小 $>3,000\text{mm}^3$ 和/或体重损失超过基础值的30%的动物进行CO₂人道安乐死。在研究期间,小鼠体重略微增加 $<30\%$ 。阴性PBS对照组中6只小鼠及53C1_VH5.M3-VL1.M1治疗组中1只小鼠的肿瘤大小达到 $3,000\text{mm}^3$,因此在研究结束之前进行安乐死。所以,不包括第18天的肿瘤大小,其可能为甚至度伐鲁单抗治疗组的肿瘤生长抑制不显著的原因。尽管如此,两种人源化抗体即53C1_VH1.M3-VL1.M1及53C1_VH5.M3-VL1.M1显示优于基准度伐鲁单抗的肿瘤生长抑制活性。

[0439] 表18. 小鼠抗PD-L1抗体的重链可变区(VH)序列。

[0440]

Ab	mAb	SEQ ID NO:	序列
小鼠	18B7F4G8	1	DVQLQESGPDLVKPSQSLSLTCTVTGYSITSGYTHWIRQFPNGKLEWMGYIH YSGSTKYNPSLKSRSFISITRDTSKNQFFLQLNSMTAEDTATYYCARNSLFASWG HGLLTVSA
	29A8H8C7	2	DVQLQSGGPGLVKPSQSLSLTCTVTGYSITSDFAWDWIRQFPNGKLEWMGHIR FSGTTSYNPSLKSRSISITRDTSKNQFFLQLNSVTSEDATYYCARSTLITKGF FDYWGQGTTTLTVSS
	51F3D2G4	3	QVQLQQSGAELARPGASVRLSCKASGYIFTGYGISWVKQRTGQGLEWIGEIFP RTANTYFNEKFKGKATLTADKSSSTAYMELRSLTSEDSAVYFCARDYDPYYAL DYWGQGISVTIVSS
	42G2D7D3	4	DVQLLESGLVLPKPSQSLSLTCSVTGYSITSGYYWNWIRQFPNGNLEWMGSIN YDGSNDYNPSLQDRISITRDTSKNQFFLKLNSVTETDATTYYCARRLDYWGQG TTLIVSS
	53C1F3D4	5	QVQLQQSGNELARPGASVRLSCKASGYIFTGYGITWVRQRPQGLEWIGEIFP RRVNTYYSEKFKGRATLTADISSSTAYMELRSLTSEDSAVYFCARDYDPYFAL DYWGQGISVTIVSS
	21D1F4D4	6	QVQLQQPGAEEVVRPGASVRLSCKASGYTFTNYWISWVKQRPQGLEWIGNIYP SDSYTNYNQNFQDKATLTVDKSSSTAYMQLSSPTSEDSAVYCYCTGIIITVIAT RDYWGQGTTTLTVSS
	30A6B2D9	7	EGQLQQSGAGLVKPGASVNLSTASGFNIKDTYIHWKQRPQGLEWIGRIAP TNGNTKYDPTFQGGKATITADSSSNTAYLQVSSLTSEDATVYYCSRGGIYYYS HWYFDVWGAGTTIVTVSS
	25G1F9F8	8	EGQLQQSGAELVLPKPGASVNLSTASGFNIKDTYIHWKQRPDQGLEWIGRIAP TNGNAKFPHTFQGGKATITADTSSNTAYLQLSSLTSEDATVYYCTRGGIYYYS HWYFDVWGAGTTIVTVSS
	27D3D3G2	9	QVLLQQSGPELVKPGASVRLSCKASGYTFTSYMHVWVKQRPQGLEWIGWIYP GNVNTKYNEKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYFCASYGNYGGWY FDVWGAGTTIVTVSS
	30A7B5D9	10	KVQLQQSGAELVPGTSLVLSCKASGYTFTYIYWIQKRSQGLEWIGWFYF GTGSIKYNEKFKKATLTADKSSSTVFMELRSLTSEDSAVYFCARHEEGNLWF AYWGQGTLLTVSA
	1H1G4D9	11	EGQLQQSGAELVLPKPGASVILSTASGFNIKDTYIHWLNQRPQGLEWIGRIEP ANGNTKYDPTFQGGKATITADTSSNTAYLQLSLTSEDATVYYCSRGGIYYYS HWYFDVWGAGTLTVSS
	25B6E5D8	12	QFQLQQSGAELVPPGSSVKISCKASGYEFSSNWNWVKQRPQGSLEWIGQIWP GDGDTNYNGKFRGKATLTSDKSSSTAYMQLNSLTSEDSAVYFCARGRASFPYD YWGQGTALTIVSS
小鼠， 具有CDR2 突变	53C1VH.M1	13	QVQLQQSGNELARPGASVRLSCKASGYIFTGYGITWVRQRPQGLEWIGEIFP RRVSTYYSEKFKGRATLTADISSSTAYMELRSLTSEDSAVYFCARDYDPYFAL DYWGQGISVTIVSS
	53C1VH.M2	14	QVQLQQSGNELARPGASVRLSCKASGYIFTGYGITWVRQRPQGLEWIGEIFP RRVATYYSEKFKGRATLTADISSSTAYMELRSLTSEDSAVYFCARDYDPYFAL DYWGQGISVTIVSS
	53C1VH.M3	15	QVQLQQSGNELARPGASVRLSCKASGYIFTGYGITWVRQRPQGLEWIGEIFP RRVQTYSEKFKGRATLTADISSSTAYMELRSLTSEDSAVYFCARDYDPYFAL DYWGQGISVTIVSS
人源化	29A8VH1	16	EVQLQESGPGLVKPSSETLSLTCTVSGYSITSDFAWDWIRQPPGKLEWIGHIR FSGTTSYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARSTLITKGF FDYWGQGTLTVSS
	29A8VH2	17	EVQLQESGPGLVKPSSETLSLTCTVSGYSITSDFAWDWIRQPPGKLEWIGHIR FSGTTSYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARSTLITKGF FDYWGQGTLTVSS
	29A8VH3	18	EVQLQESGPGLVKPSSETLSLTCTVSGYSITSDFAWDWIRQPPGKLEWIGHIR FSGTTSYNPSLKSRTISVDTSKNQFSLKLSSVTAADTATYYCARSTLITKGF FDYWGQGTLTVSS
	29A8VH4	19	EVQLQESGPGLVKPSSETLSLTCTVSGYSITSDFAWDWIRQPPGKLEWIGHIR FSGTTSYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARSTLITKGF FDYWGQGTLTVSS

[0441]

	29A8VH5	20	EVQLQESGPGLVKPSSETLSLTCTVSGYSITSDFAWDWIRQPPGKLEWIGHIR FSGITTSYNFSLKSRVTISRDTISKNQFSLKLSVIAADTAVYYCARSTLTITKGF FDYWGQGTLTIVTSS
	53C1VH1	21	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGGGLEWMGEIFF RRVNTYYSEKFKGRVIMTTDTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH2	22	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGGGLEWIGEIFF RRVNTYYSEKFKGRATLTDTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH3	23	EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGGGLEWIGEIFF RRVNTYYSEKFKGRATLTADTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH4	24	EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGGGLEWMGEIFF RRVNTYYSEKFKGRVIMTTDTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH5	25	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGGGLEWMGEIFF RRVNTYYSEKFKGRVIMTADTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH6	26	EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGGGLEWMGEIFF RRVNTYYSEKFKGRVIMTADTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTLTIVTSS
人源化, 具有CDR2 突变	53C1VH1.M3	27	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGGGLEWMGEIFF RRVQTYSEKFKGRVIMTTDTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH2.M3	28	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGGGLEWIGEIFF RRVQTYSEKFKGRATLTDTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH3.M3	29	EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGGGLEWIGEIFF RRVQTYSEKFKGRATLTADTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH4.M3	30	EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGGGLEWMGEIFF RRVQTYSEKFKGRVIMTTDTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH5.M3	31	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGGGLEWMGEIFF RRVQTYSEKFKGRVIMTADTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH6.M3	32	EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGGGLEWMGEIFF RRVQTYSEKFKGRVIMTADTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH1.M1	33	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGGGLEWMGEIFF RRVSTYYSEKFKGRVIMTTDTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH2.M1	34	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGGGLEWIGEIFF RRVSTYYSEKFKGRATLTDTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH3.M1	35	EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGGGLEWIGEIFF RRVSTYYSEKFKGRATLTADTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH4.M1	36	EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGGGLEWMGEIFF RRVSTYYSEKFKGRVIMTTDTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH5.M1	37	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGGGLEWMGEIFF RRVSTYYSEKFKGRVIMTADTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH6.M1	38	EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGGGLEWMGEIFF RRVSTYYSEKFKGRVIMTADTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH1.M2	39	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGGGLEWMGEIFF RRVATYYSEKFKGRVIMTTDTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH2.M2	40	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGGGLEWIGEIFF RRVATYYSEKFKGRATLTDTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTLTIVTSS

[0442]

	53C1VH3.M2	41	DYWGQGTLTIVTSS EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGGGLEWIGEIFF RRVATYYSEKFKGRATLTADTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH4.M2	42	EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGGGLEWMGEIFF RRVATYYSEKFKGRVIMTTDTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH5.M2	43	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGGGLEWMGEIFF RRVATYYSEKFKGRVIMTADTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTLTIVTSS
	53C1VH6.M2	44	EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGGGLEWMGEIFF RRVATYYSEKFKGRVIMTADTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTLTIVTSS

[0443] 表19.小鼠抗PD-L1抗体的轻链可变区(VL)序列。

[0444]

Ab	mAb	SEQ ID NO:	序列
小鼠	18B7F4G8	45	DIVLTQSPASLAVSLGQRATISCRASESVDTYGDSFMHWFQQKPGQPPKLLIY RASNLESGIPARFSGSGSRTDFTLTINPVEADDVATYYCQQSNEAPYTFGGGT KLEIK
	29A8H8C7	46	DIVMTQSHKFMSTSVGGRVSIITCKASQDVSPAVAWYQQKPGQSPKLLIYWAST RHTGVPDRFTGSGSGTDFTLTISVQTEDLALYYCQQHYSTPWTFGGGTKLEI K
	51F3D2G4	47	DIVMTQSHKFMSTSVGDRVTITCKASQDVSTAVDWYQQKPGQSPKLLIYSASY RYTGVPDRFTGSGSGTAFTFTISSEQAEDLAVYYCQQHYSPVPTFGGGTKLEI K
	42G2D7D3	48	QIVLTQSPAIMASASPGEKVTISCSASSFINMYWYQQKPGSSPKPWILRTSTL ASGVPARFSGSGSGTSYSLTISSEAEADAATYYCQQYHSYPLTFGAGTKLELK
	53C1F3D4	49	DIVMTQSHKFMSTSVGDRVSIITCKASQDVSTAVDWYQQKPGQSPKLLIYSASY RYTGVPDRFTGSGSGTAFTFTISGEQAEDLAVYYCQQHYSIPPTFGGGTKLEI K
	21D1F4D4	50	QIVLTQSPAIMASASPGEKVTITCSASSSVSSSYLYWYQQKPGSSPKLWIYSTS NLASGVPARFSGSGSGTSYSLTVSSMEAEADAASYFCHQWSSYPPTFGSGTKLE IK
	30A6B2D9	51	SVLMTQTPLSLPVSLGDQASISCRSSQNIVYSDGDTYLEWYLQKPGQSPKLLI FKVSNRFFGVDPDRFSGSGSGTDFTLKINRVEAEDLGVIYCFQGSHPVPTFGSG TKLEIK
	25G1F9F8	52	DVLNQQTPLSLPVSLGDQASISCRSSQNIVYSDGNTYLEWYLQKPGQSPKLLI FQVSNRFGVDPDRFSGSGSGTDFTLKISRVEAEDLGFYYCFQGSHPVPTFGSG TKLEIK
	27D3D3G2	53	DIQMTQTSSLSASLGDRVTISCRASQDIGNYLNWYQQKPDGTVKLLIYYTSR LHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGDTFPWTFGGGTKLEI K
	30A7B5D9	54	QIVLTQSPALMASPGERVTMTCSASSDVSYMYWYQQKPRSSPKWIYLTSLNL ASGVPARFSGSGSGTSYSLTISSEAEADAATYYCQQWTGNPLTFGAGTKLELK
	1H1G4D9	55	DVLMTQTPLSLPVSLGDQASISCRSSQNIVYSDGDTYLEWYLQKPGQSPKLLI FKVSNRFGVDPDRFSGSGSGTDFTLKISRVEAEDLGVIYCFQGSHPVPTFGSG TKLEIK
小鼠， 具有 CDR1 突变	25B6E5D8	56	DIVLTQSPASLAVSLGQRATISCRASESVDDYGNFMHWFQQKPGQPPKLLIY RASNLESGIPVRFSGSGSRTDFTLTINPVEADDVATYYCQQSNEDPHTFGGGT KLEIK
	29A8VL.M1	57	DIVMTQSHKFMSTSVGGRVSIITCRASQDVSPAVAWYQQKPGQSPKLLIYWAST RHTGVPDRFTGSGSGTDFTLTISVQTEDLALYYCQQHYSTPWTFGGGTKLEI K
	53C1VL.M1	58	DIVMTQSHKFMSTSVGDRVSIITCRASQDVSTAVDWYQQKPGQSPKLLIYSASY

[0445]

			RYTGVPPDRFTGSGSGTAFTFTISGEQAEDLAVYYCQQHYSIPFTFGGGTKLEIK
人源化	29A8VL1	59	DIQMTQSPSSLSASVGDRVTITCKASQDVSPAVAWYQQKPGKAPKLLIYWAST RHTGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQHYSTPWTFGQGTKVEIK
	29A8VL2	60	DIQMTQSPSSLSASVGDRVTITCKASQDVSPAVAWYQQKPGKAPKLLIYWAST RHTGVPSRFSGSGSGTDFTLTISLQPEDLALYYCQQHYSTPWTFGQGTKVEIK
	29A8VL3	61	DIQMTQSPSSLSASVGDRVTITCKASQDVSPAVAWYQQKPGKAPKLLIYWAST RHTGVPSRFSGSGSGTDFTLTISSVQPEDLALYYCQQHYSTPWTFGQGTKLEIK
	53C1VL1	62	DIQMTQSPSSLSASVGDRVTITCKASQDVSTAVDWYQQKPGKAPKLLIYSASY RYTGVPPDRFSGSGSGTDFTFTISLQPEDLATYYCQQHYSIPFTFGGGTKLEIK
	53C1VL2	63	DIQMTQSPSSMSASVGDRVTITCKASQDVSTAVDWYQQKPGKAPKLLIYSASY RYTGVPPDRFSGSGSGTDFTFTISLQPEDLATYYCQQHYSIPFTFGGGTKLEIK
	53C1VL3	64	DIQMTQSPSSMSTSVGDRVTITCKASQDVSTAVDWYQQKPGKAPKLLIYSASY RYTGVPPDRFSGSGSGTDFTFTISSEQPEDLATYYCQQHYSIPFTFGGGTKLEIK
人源化， 具有 CDR1 突变	29A8VL1.M1	65	DIQMTQSPSSLSASVGDRVTITCRASQDVSPAVAWYQQKPGKAPKLLIYWAST RHTGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQHYSTPWTFGQGTKVEIK
	29A8VL2.M1	66	DIQMTQSPSSLSASVGDRVTITCRASQDVSPAVAWYQQKPGKAPKLLIYWAST RHTGVPSRFSGSGSGTDFTLTISLQPEDLALYYCQQHYSTPWTFGQGTKVEIK
	29A8VL3.M1	67	DIQMTQSPSSLSASVGDRVTITCRASQDVSPAVAWYQQKPGKAPKLLIYWAST RHTGVPSRFSGSGSGTDFTLTISSVQPEDLALYYCQQHYSTPWTFGQGTKLEIK
	53C1VL1.M1	68	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVDWYQQKPGKAPKLLIYSASY RYTGVPPDRFSGSGSGTDFTFTISLQPEDLATYYCQQHYSIPFTFGGGTKLEIK
	53C1VL2.M1	69	DIQMTQSPSSMSASVGDRVTITCRASQDVSTAVDWYQQKPGKAPKLLIYSASY RYTGVPPDRFSGSGSGTDFTFTISLQPEDLATYYCQQHYSIPFTFGGGTKLEIK
	53C1VL3.M1	70	DIQMTQSPSSMSTSVGDRVTITCRASQDVSTAVDWYQQKPGKAPKLLIYSASY RYTGVPPDRFSGSGSGTDFTFTISSEQPEDLATYYCQQHYSIPFTFGGGTKLEIK

[0446] 表20. 重链可变区 (VH) CDR序列。

[0447]

Ab	mAb	ID	CDR1	ID	CDR2	ID	CDR3
小鼠	18B7F4G8	71	GYSITSGYIWH	83	YIHYSGSTKYNPS LKS	98	NSLFAS
	29A8H8C7	72	GYSITSDFAWD	84	HIRFSGTTSYNPS LKS	99	STLITKGFFDY
	51F3D2G4	73	GYIFTGYGIS	85	EIFPRTANTYFNE KFKG	100	DYDPYYALDY
	42G2D7D3	74	GYSITSGYYWN	86	SINYDGSNDYNPS LQD	101	RLDY
	53C1F3D4	75	GYIFTGYGIT	87	EIFPRRVNTYYSE KFKG	102	DYDPYFALDY
	21D1F4D4	76	GYIFTNYWIS	88	NIYPSDSYTNYNQ NFKD	103	GIITVIATRDDY
	30A6B2D9	77	GFNIKDTYIH	89	RIAPTINGNTKYDP TFQG	104	GGIYYYGSHWYFDV
	25G1F9F8	78	GFNIKDTYIH	90	RIAPTINGNAKFHP TFQG	105	GGIYYYGTHWYFDV
	27D3D3G2	79	GYIFTSYYMH	91	WIYPGNVNTKYNE KFKG	106	YGNYGGWYFDV
	30A7B5D9	80	GYIFTEYIIY	92	WFYPGTGSIKYNE KFKD	107	HEEGNLWFAY
	1H1G4D9	81	GFNIKDTYIH	93	RIEPANGNTKYDP	108	GGIYYYGSHWYFDV

[0448]

	25B6E5D8	82	GYEFSSNWMN	94	TFQG		
					QIWPBGDTNYNG KFRG	109	GRASFYFDY
小鼠, 具有CDR2 突变	53C1VH.M1	75	GYIFTGYGIT	95	EIFPRRVSTYYSE KFKG	102	DYDPYFALDY
	53C1VH.M2	75	GYIFTGYGIT	96	EIFPRRVATYYSE KFKG	102	DYDPYFALDY
	53C1VH.M3	75	GYIFTGYGIT	97	EIFPRRVQTYYYSE KFKG	102	DYDPYFALDY
人源化	29A8VH1	72	GYSITSDFAWD	84	HIRFSGTTSYNPS LKS	99	STLITKGFFDY
	29A8VH2	72	GYSITSDFAWD	84	HIRFSGTTSYNPS LKS	99	STLITKGFFDY
	29A8VH3	72	GYSITSDFAWD	84	HIRFSGTTSYNPS LKS	99	STLITKGFFDY
	29A8VH4	72	GYSITSDFAWD	84	HIRFSGTTSYNPS LKS	99	STLITKGFFDY
	29A8VH5	72	GYSITSDFAWD	84	HIRFSGTTSYNPS LKS	99	STLITKGFFDY
	53C1VH1	75	GYIFTGYGIT	87	EIFPRRVNTYYSE KFKG	102	DYDPYFALDY
	53C1VH2	75	GYIFTGYGIT	87	EIFPRRVNTYYSE KFKG	102	DYDPYFALDY
	53C1VH3	75	GYIFTGYGIT	87	EIFPRRVNTYYSE KFKG	102	DYDPYFALDY
	53C1VH4	75	GYIFTGYGIT	87	EIFPRRVNTYYSE KFKG	102	DYDPYFALDY
	53C1VH5	75	GYIFTGYGIT	87	EIFPRRVNTYYSE KFKG	102	DYDPYFALDY
	53C1VH6	75	GYIFTGYGIT	87	EIFPRRVNTYYSE KFKG	102	DYDPYFALDY
人源化, 具有CDR2 突变	53C1VH1.M3	75	GYIFTGYGIT	97	EIFPRRVQTYYYSE KFKG	102	DYDPYFALDY
	53C1VH2.M3	75	GYIFTGYGIT	97	EIFPRRVQTYYYSE KFKG	102	DYDPYFALDY
	53C1VH3.M3	75	GYIFTGYGIT	97	EIFPRRVQTYYYSE KFKG	102	DYDPYFALDY
	53C1VH4.M3	75	GYIFTGYGIT	97	EIFPRRVQTYYYSE KFKG	102	DYDPYFALDY
	53C1VH5.M3	75	GYIFTGYGIT	97	EIFPRRVQTYYYSE KFKG	102	DYDPYFALDY
	53C1VH6.M3	75	GYIFTGYGIT	97	EIFPRRVQTYYYSE KFKG	102	DYDPYFALDY
	53C1VH1.M1	75	GYIFTGYGIT	95	EIFPRRVSTYYSE KFKG	102	DYDPYFALDY
	53C1VH2.M1	75	GYIFTGYGIT	95	EIFPRRVSTYYSE KFKG	102	DYDPYFALDY
	53C1VH3.M1	75	GYIFTGYGIT	95	EIFPRRVSTYYSE KFKG	102	DYDPYFALDY
	53C1VH4.M1	75	GYIFTGYGIT	95	EIFPRRVSTYYSE KFKG	102	DYDPYFALDY
	53C1VH5.M1	75	GYIFTGYGIT	95	EIFPRRVSTYYSE KFKG	102	DYDPYFALDY
	53C1VH6.M1	75	GYIFTGYGIT	95	EIFPRRVSTYYSE KFKG	102	DYDPYFALDY
	53C1VH1.M2	75	GYIFTGYGIT	96	EIFPRRVATYYSE KFKG	102	DYDPYFALDY
	53C1VH2.M2	75	GYIFTGYGIT	96	EIFPRRVATYYSE KFKG	102	DYDPYFALDY
	53C1VH3.M2	75	GYIFTGYGIT	96	EIFPRRVATYYSE KFKG	102	DYDPYFALDY
[0449]	53C1VH4.M2	75	GYIFTGYGIT	96	EIFPRRVATYYSE KFKG	102	DYDPYFALDY
	53C1VH5.M2	75	GYIFTGYGIT	96	EIFPRRVATYYSE KFKG	102	DYDPYFALDY
	53C1VH6.M2	75	GYIFTGYGIT	96	EIFPRRVATYYSE KFKG	102	DYDPYFALDY

[0450] 表21.轻链可变区(VL)CDR序列。

[0451]

Ab	mAb	ID	CDR1	ID	CDR2	ID	CDR3
小鼠	18B7F4G8VL	110	RASESVDTYGDSFMH	124	RASNLES	136	QQSNEAPYT
	29A8H8C7VL	111	KASQDVSPAVA	125	WASTRHT	137	QQHYSTPWT
	51F3D2G4VL	112	KASQDVSTAVD	126	SASYRYT	138	QQHYSVPFT
	42G2D7D3VL	113	SASSFINYMY	127	RTSTLAS	139	QQYHSYPLT
	53C1F3D4VL	114	KASQDVSTAVD	128	SASYRYT	140	QQHYSIPFT
	21D1F4D4VL	115	SASSSVSSSYLY	129	STSNLAS	141	HQWSSYPFT
	30A6B2D9VL	116	RSSQNIVYSDGDTYLE	130	KVSNRFF	142	FQGSHPVFT
	25G1F9F8VL	117	RSSQNIVYSDGNTYLE	131	QVSNRFS	143	FQGSHPVFT
	27D3D3G2VL	118	RASQDIGNYLN	132	YTSRLHS	144	QQGDTFPWT
	30A7B5D9VL	119	SASSDVSYMY	133	LTSNLAS	145	QQWTGNPLT
	1H1G4D9VL	120	RSSQNIVYSDGDTYLE	134	KVSNRFS	146	FQGSHPVFT
	25B6E5D8VL	121	RASESVDYDGNFSFMH	135	RASNLES	147	QQSNEDPHT
突变体 嵌合	29A8VL.M1	122	RASQDVSPAVA	125	WASTRHT	137	QQHYSTPWT
	53C1VL.M1	123	RASQDVSTAVD	128	SASYRYT	140	QQHYSIPFT
人源化	29A8VL1	111	KASQDVSPAVA	125	WASTRHT	137	QQHYSTPWT
	29A8VL2	111	KASQDVSPAVA	125	WASTRHT	137	QQHYSTPWT
	29A8VL3	111	KASQDVSPAVA	125	WASTRHT	137	QQHYSTPWT
	53C1VL1	114	KASQDVSTAVD	128	SASYRYT	140	QQHYSIPFT
	53C1VL2	114	KASQDVSTAVD	128	SASYRYT	140	QQHYSIPFT
	53C1VL3	114	KASQDVSTAVD	128	SASYRYT	140	QQHYSIPFT
人源 化, 具 有CDR1 突变	29A8VL1.M1	122	RASQDVSPAVA	125	WASTRHT	137	QQHYSTPWT
	29A8VL2.M1	122	RASQDVSPAVA	125	WASTRHT	137	QQHYSTPWT
	29A8VL3.M1	122	RASQDVSPAVA	125	WASTRHT	137	QQHYSTPWT
	53C1VL1.M1	123	RASQDVSTAVD	128	SASYRYT	140	QQHYSIPFT
	53C1VL2.M1	123	RASQDVSTAVD	128	SASYRYT	140	QQHYSIPFT
	53C1VL3.M1	123	RASQDVSTAVD	128	SASYRYT	140	QQHYSIPFT

[0452] 表22. 重链可变区 (VH) 框架 (FR) 序列。

[0453]

Ab	mAb	ID	FR1	ID	FR2
小鼠	18B7F4G8	148	DVQLQESGPDLVKPSQSLSLTCTVT	163	WIRQFPGNKLEWMG
	29A8H8C7	149	DVQLQSGGPGLVKPSQSLSLTCTVT	164	WIRQFPGNKLEWMG
	51F3D2G4	150	QVQLQQSGAELARPGASVRLSCKAS	165	WVKQRTGGGLEWIG
	42G2D7D3	151	DVQLLESFGPLVKPSQSLSLTCSVT	166	WIRQFPGNKLEWMG
	53C1F3D4	152	QVQLQQSGNELARPGASVRLSCKAS	167	WVRQRPQGGLWIG
	21D1F4D4	153	QVQLQQPGAELVVRPGASVKLSCKAS	168	WVKQRPQGGLWIG
	30A6B2D9	154	EGQLQQSGAGLVKPGASVNLSCITAS	169	WMKORPEQGGLWIG
	25G1F9F8	155	EGQLQQSGAELVKPGASVNLSCITAS	170	WVKQRPDQGLWIG
	27D3D3G2	156	QVLLQQSGPELVKPGASVRLSCKAS	171	WVKQRPQGGLWIG
	30A7B5D9	157	KVQLQQSGAELVKPGTSVKLSCKAS	172	WIKQSGQGGLWIG
	1H1G4D9	158	EGQLQQSGAELVKPGASVILSCTAS	173	WLNQRPQGGLWIG
	25B6E5D8	159	QFQLQQSGAELVRPGSSVKLSCKAS	174	WVKQRPQGSLEWIG
小鼠, 具 有CDR2 突变	53C1VH.M1	152	QVQLQQSGNELARPGASVRLSCKAS	167	WVRQRPQGGLWIG
	53C1VH.M2	152	QVQLQQSGNELARPGASVRLSCKAS	167	WVRQRPQGGLWIG
	53C1VH.M3	152	QVQLQQSGNELARPGASVRLSCKAS	167	WVRQRPQGGLWIG

[0454]

人源化	29A8VH1	160	EVQLQESGPGGLVLPKSETLSLTCTVS	175	WIRQPPGKGLEWIG
	29A8VH2	160	EVQLQESGPGGLVLPKSETLSLTCTVS	176	WIRQPPGKGLEWMG
	29A8VH3	160	EVQLQESGPGGLVLPKSETLSLTCTVS	176	WIRQPPGKGLEWMG
	29A8VH4	160	EVQLQESGPGGLVLPKSETLSLTCTVS	175	WIRQPPGKGLEWIG
	29A8VH5	160	EVQLQESGPGGLVLPKSETLSLTCTVS	175	WIRQPPGKGLEWIG
	53C1VH1	161	EVQLVQSGAEVKKPGASVKVSCKAS	177	WVRQAPGQGLEWMG
	53C1VH2	161	EVQLVQSGAEVKKPGASVKVSCKAS	178	WVRQAPGQGLEWIG
	53C1VH3	162	EVQLVQSGAEVKKPGASVKLSCKAS	178	WVRQAPGQGLEWIG
	53C1VH4	162	EVQLVQSGAEVKKPGASVKLSCKAS	177	WVRQAPGQGLEWMG
	53C1VH5	161	EVQLVQSGAEVKKPGASVKVSCKAS	177	WVRQAPGQGLEWMG
人源化， 具有CDR2 突变	53C1VH6	162	EVQLVQSGAEVKKPGASVKLSCKAS	177	WVRQAPGQGLEWMG
	53C1VH1.M3	161	EVQLVQSGAEVKKPGASVKVSCKAS	177	WVRQAPGQGLEWMG
	53C1VH2.M3	161	EVQLVQSGAEVKKPGASVKVSCKAS	178	WVRQAPGQGLEWIG
	53C1VH3.M3	162	EVQLVQSGAEVKKPGASVKLSCKAS	178	WVRQAPGQGLEWIG
	53C1VH4.M3	162	EVQLVQSGAEVKKPGASVKLSCKAS	177	WVRQAPGQGLEWMG
	53C1VH5.M3	161	EVQLVQSGAEVKKPGASVKVSCKAS	177	WVRQAPGQGLEWMG
	53C1VH6.M3	162	EVQLVQSGAEVKKPGASVKLSCKAS	177	WVRQAPGQGLEWMG
	53C1VH1.M1	161	EVQLVQSGAEVKKPGASVKVSCKAS	177	WVRQAPGQGLEWMG
	53C1VH2.M1	161	EVQLVQSGAEVKKPGASVKVSCKAS	178	WVRQAPGQGLEWIG
	53C1VH3.M1	162	EVQLVQSGAEVKKPGASVKLSCKAS	178	WVRQAPGQGLEWIG
	53C1VH4.M1	162	EVQLVQSGAEVKKPGASVKLSCKAS	177	WVRQAPGQGLEWMG
	53C1VH5.M1	161	EVQLVQSGAEVKKPGASVKVSCKAS	177	WVRQAPGQGLEWMG
	53C1VH6.M1	162	EVQLVQSGAEVKKPGASVKLSCKAS	177	WVRQAPGQGLEWMG
	53C1VH1.M2	161	EVQLVQSGAEVKKPGASVKVSCKAS	177	WVRQAPGQGLEWMG
	53C1VH2.M2	161	EVQLVQSGAEVKKPGASVKVSCKAS	178	WVRQAPGQGLEWIG
	53C1VH3.M2	162	EVQLVQSGAEVKKPGASVKLSCKAS	178	WVRQAPGQGLEWIG
	53C1VH4.M2	162	EVQLVQSGAEVKKPGASVKLSCKAS	177	WVRQAPGQGLEWMG
	53C1VH5.M2	161	EVQLVQSGAEVKKPGASVKVSCKAS	177	WVRQAPGQGLEWMG
	53C1VH6.M2	162	EVQLVQSGAEVKKPGASVKLSCKAS	177	WVRQAPGQGLEWMG

[0455]

Ab	mAb	ID	FR3	ID	FR4
小鼠	18B7F4G8	179	RFSITRDTSKNQFFLQLNSMTAEDTATYYCAR	199	WGHTGLTVTSA
	29A8H8C7	180	RISITRDTSKNQFFLQLNSVTSEDATYYCAR	200	WGQGTTLTVSS
	51F3D2G4	181	KATLTADKSSSTAYMELRSLTSEDSAVYFCAR	201	WGQGTSTVTSS
	42G2D7D3	182	RISITRDTSKNQFFLQLNSVTEDTATYYCAR	202	WGQGTTLTVSS
	53C1F3D4	183	RATLTADISSSTAYMELRSLTSEDSAVYFCAR	203	WGQGTSTVTSS
	21D1F4D4	184	KATLTVDKSSSTAYMQLSSPTSEDSAVYYCTT	204	WGQGTTLTVSS
	30A6B2D9	185	KATITADSSSNTAYLQVSSLTSEDTAVYYCSR	205	WGAGTTVTSS
	25G1F9F8	186	KATITADTSSNTAYLQLSSLTSEDTAVYYCTR	206	WGAGTTVTSS
	27D3D3G2	187	KATLTADKSSSTAYMQLSSLTSEDSAVYFCAS	207	WGAGTTVTSS
	30A7B5D9	188	KATLTADKSSSTVFMELRSLTSEDSAVYFCAR	208	WGQGTTLTVTSA
	1H1G4D9	189	KATITADTSSNTAYLQLTSLTSEDTAVYYCSR	209	WGAGTLTVTSS
	25B6E5D8	190	KATLTSDKSSSTAYMQLNSLTSEDSAVYFCAR	210	WGQGTALTVSS
小鼠， 具有CDR2 突变	53C1VH.M1	183	RATLTADISSSTAYMELRSLTSEDSAVYFCAR	203	WGQGTSTVTSS
	53C1VH.M2	183	RATLTADISSSTAYMELRSLTSEDSAVYFCAR	203	WGQGTSTVTSS
	53C1VH.M3	183	RATLTADISSSTAYMELRSLTSEDSAVYFCAR	203	WGQGTSTVTSS
人源化	29A8VH1	191	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR	211	WGQGTTLTVTSS
	29A8VH2	192	RITISVDTSKNQFSLKLSSVTAADTAVYYCAR	211	WGQGTTLTVTSS
	29A8VH3	193	RITISVDTSKNQFSLKLSSVTAADTATYYCAR	212	WGQGTLLTVSS
	29A8VH4	191	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR	212	WGQGTLLTVSS
	29A8VH5	194	RVTISRDTSKNQFSLKLSSVTAADTAVYYCAR	212	WGQGTTLTVTSS
	53C1VH1	195	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR	213	WGQGTTVTVSS
	53C1VH2	196	RATLTADTSTSTAYMELRSLRSDDTAVYFCAR	213	WGQGTTVTVSS
	53C1VH3	197	RATLTADTSTSTAYMELRSLRSDDTAVYFCAR	213	WGQGTTVTVSS
	53C1VH4	195	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR	213	WGQGTTVTVSS
	53C1VH5	198	RVTMTADTSTSTAYMELRSLRSDDTAVYYCAR	213	WGQGTTVTVSS
	53C1VH6	198	RVTMTADTSTSTAYMELRSLRSDDTAVYYCAR	213	WGQGTTVTVSS
	53C1VH1.M3	195	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR	213	WGQGTTVTVSS

[0456]

人源化, 具有CDR2 突变	53C1VH2.M3	196	RATLTDTSTSTAYMELRSLRSDDTAVYFCAR	213	WGQGTITVTVSS
	53C1VH3.M3	197	RATLTADTSTSTAYMELRSLRSDDTAVYFCAR	213	WGQGTITVTVSS
	53C1VH4.M3	195	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR	213	WGQGTITVTVSS
	53C1VH5.M3	198	RVTMTADTSTSTAYMELRSLRSDDTAVYYCAR	213	WGQGTITVTVSS
	53C1VH6.M3	198	RVTMTADTSTSTAYMELRSLRSDDTAVYYCAR	213	WGQGTITVTVSS
	53C1VH1.M1	195	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR	213	WGQGTITVTVSS
	53C1VH2.M1	196	RATLTDTSTSTAYMELRSLRSDDTAVYFCAR	213	WGQGTITVTVSS
	53C1VH3.M1	197	RATLTADTSTSTAYMELRSLRSDDTAVYFCAR	213	WGQGTITVTVSS
	53C1VH4.M1	195	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR	213	WGQGTITVTVSS
	53C1VH5.M1	198	RVTMTADTSTSTAYMELRSLRSDDTAVYYCAR	213	WGQGTITVTVSS
	53C1VH6.M1	198	RVTMTADTSTSTAYMELRSLRSDDTAVYYCAR	213	WGQGTITVTVSS
	53C1VH1.M2	195	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR	213	WGQGTITVTVSS
	53C1VH2.M2	196	RATLTDTSTSTAYMELRSLRSDDTAVYFCAR	213	WGQGTITVTVSS
	53C1VH3.M2	197	RATLTADTSTSTAYMELRSLRSDDTAVYFCAR	213	WGQGTITVTVSS
	53C1VH4.M2	195	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR	213	WGQGTITVTVSS
	53C1VH5.M2	198	RVTMTADTSTSTAYMELRSLRSDDTAVYYCAR	213	WGQGTITVTVSS
	53C1VH6.M2	198	RVTMTADTSTSTAYMELRSLRSDDTAVYYCAR	213	WGQGTITVTVSS

[0457] 表23.轻链可变区 (VL) 框架 (FR) 序列。

[0458]

Ab	mAb	ID	FR1	ID	FR2
小鼠	18B7F4G8VL	214	DIVLTQSPASLAVSLGQRATISC	231	WFQQKPGQSPKLLIY
	29A8H8C7VL	215	DIVMTQSHKFMSTSVGGRVSITC	232	WYQQKPGQSPKLLIY
	51F3D2G4VL	216	DIVMTQSHKFMSTSVGDRVTITC	233	WYQQKPGQSPKLLIY
	42G2D7D3VL	217	QIVLTQSPAIMASAPGEKVTISC	234	WYQQKPGSSPKPWIL
	53C1F3D4VL	218	DIVMTQSHKFMSTSVGDRVSITC	235	WYQQKPGQSPKLLIY
	21D1F4D4VL	219	QIVLTQSPAIMASAPGEKVTITC	236	WYQQKPGSSPKWIIY
	30A6B2D9VL	220	SVLMTQTPLSLPVSLGDAQSISC	237	WYLQKPGQSPKLLIF
	25G1F9F8VL	221	DVLMNQTPSLPVSLGDAQSISC	238	WYLQKPGQSPKLLIF
	27D3D3G2VL	222	DIQMTQTSSSLASLGDRVTISC	239	WYQQKPDGTVKLLIY
	30A7B5D9VL	223	QIVLTQSPAIMASAPGERVTIMC	240	WYQQKPRSSPKFWIY
	1H1G4D9VL	224	DVLMQTPLSLPVSLGDAQSISC	241	WYLQKPGQSPKLLIF
	25B6E5D8VL	225	DIVLTQSPASLAVSLGQRATISC	242	WYQQKPGQSPKLLIY
突变体 嵌合	29A8VL.M1	215	DIVMTQSHKFMSTSVGGRVSITC	232	WYQQKPGQSPKLLIY
	53C1VL.M1	218	DIVMTQSHKFMSTSVGDRVSITC	235	WYQQKPGQSPKLLIY
人源化	29A8VL1	226	DIQMTQSPSSLSASVGRVTITC	243	WYQQKPGKAPKLLIY
	29A8VL2	226	DIQMTQSPSSLSASVGRVTITC	243	WYQQKPGKAPKLLIY
	29A8VL3	227	DIQMTQSPSSLSASVGRVTITC	243	WYQQKPGKAPKLLIY
	53C1VL1	228	DIQMTQSPSSLSASVGRVTITC	244	WYQQKPGKAPKLLIY
	53C1VL2	229	DIQMTQSPSSMSASVGRVTITC	244	WYQQKPGKAPKLLIY
人源化, 具有CDR1 突变	53C1VL3	230	DIQMTQSPSSMSTSVGDRVTITC	244	WYQQKPGKAPKLLIY
	29A8VL1.M1	226	DIQMTQSPSSLSASVGRVTITC	243	WYQQKPGKAPKLLIY
	29A8VL2.M1	226	DIQMTQSPSSLSASVGRVTITC	243	WYQQKPGKAPKLLIY
	29A8VL3.M1	227	DIQMTQSPSSLSASVGRVTITC	243	WYQQKPGKAPKLLIY
	53C1VL1.M1	228	DIQMTQSPSSLSASVGRVTITC	244	WYQQKPGKAPKLLIY
	53C1VL2.M1	229	DIQMTQSPSSMSASVGRVTITC	244	WYQQKPGKAPKLLIY
	53C1VL3.M1	230	DIQMTQSPSSMSTSVGDRVTITC	244	WYQQKPGKAPKLLIY

[0459]

Ab	mAb	ID	FR3	ID	FR4
小鼠	18B7F4G8VL	245	GIPARFSGSGSRTDFTLTINPVEADDVATYYC	263	FGGGTKLEIK
	29A8H8C7VL	246	GVPDRFTGSGSGTFTLTISVQTEDLALYYC	264	FGGGTKLEIK
	51F3D2G4VL	247	GVPDRFTGSGSGTFTLTISSEQAEDLAVYYC	265	FGGGTKLEIK
	42G2D7D3VL	248	GVPARFSGSGSGTISYSLTISSEAEADAATYYC	266	FGAGTKLEIK
	53C1F3D4VL	249	GVPDRFTGSGSGTFTLTISGEQAEDLAVYYC	267	FGGGTKLEIK
	21D1F4D4VL	250	GVPARFSGSGSGTISYSLTVSSMEAEADAASYFC	268	FGSGTKLEIK
	30A6B2D9VL	251	GVPDRFSGSGSGTFTLTINRVEAEDLGYYC	269	FGSGTKLEIK

[0460]

	25G1F9F8VL	252	GVPDRFSGSGSGTDFTLKISRVEAEDLGFYYC	270	FGSGTKLEIK
	27D3D3G2VL	253	GVPSRFSGSGSGTDYSLTISNLEQEDIAITYFC	271	FGGGTKLEIK
	30A7B5D9VL	254	GVPARFSGSGSGTSYSLTISSEAEADAITYYC	272	FGAGTKLELK
	1H1G4D9VL	255	GVDRFSGSGSGTDFTLKISRVEAEDLGVYYC	273	FGSGTKLEIK
	25B6E5D8VL	256	GIPVRFSGSGSGTDFTLTINPVEADDAITYYC	274	FGGGTKLEIK
突变体嵌合	29A8VL.M1	246	GVDRFTGSGSGTDFTLTISVQTEDLALYYC	264	FGGGTKLEIK
	53C1VL.M1	249	GVDRFTGSGSGTAFTFTISGEQAEDLAVYYC	267	FGGGTKLEIK
人源化	29A8VL1	257	GVPSRFSGSGSGTDFTLTISLQPEDFATYYC	275	FGQGTKVEIK
	29A8VL2	258	GVPSRFSGSGSGTDFTLTISLQPEDLALYYC	275	FGQGTKVEIK
	29A8VL3	259	GVPSRFSGSGSGTDFTLTISVQPEDLALYYC	276	FGQGTKLEIK
	53C1VL1	260	GVDRFSGSGSGTDFTFTISLQPEDIAITYYC	277	FGQGTKLEIK
	53C1VL2	261	GVDRFSGSGSGTDFTFTISLQPEDLALYYC	277	FGQGTKLEIK
	53C1VL3	262	GVDRFSGSGSGTDFTFTISSEQPEDLALYYC	277	FGQGTKLEIK
人源化, 具有CDR1突变	29A8VL1.M1	257	GVPSRFSGSGSGTDFTLTISLQPEDFATYYC	275	FGQGTKVEIK
	29A8VL2.M1	258	GVPSRFSGSGSGTDFTLTISLQPEDLALYYC	275	FGQGTKVEIK
	29A8VL3.M1	259	GVPSRFSGSGSGTDFTLTISVQPEDLALYYC	276	FGQGTKLEIK
	53C1VL1.M1	260	GVDRFSGSGSGTDFTFTISLQPEDIAITYYC	277	FGQGTKLEIK
	53C1VL2.M1	261	GVDRFSGSGSGTDFTFTISLQPEDLALYYC	277	FGQGTKLEIK
	53C1VL3.M1	262	GVDRFSGSGSGTDFTFTISSEQPEDLALYYC	277	FGQGTKLEIK

[0461] 表24. 具有无效应子Fc突变的全长IgG1重链序列。

[0462]

Ab	mAb	SEQ ID NO:	序列
嵌合	18B7F4G8	278	DVQLQESGPDLVKPSQSLSTCTVTIGYSITSGYITWHIRQFPGNKLEWMGYIH YSGSTKYNPSLKSRSFISITRDTSKNQFFLQLNSMTAEDTATYYCARNSLFASWG HGTLVITVSAASTKGPSVFPLAPSSKSTISGGTAALGCLVKDYFPEPTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKK VEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDS HEDPEVKFNWYVDGVEVHNATKPREEQYASTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKITPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSS VMHEALHNHYTQKSLSLSPGK
	29A8H8C7	279	DVQLQSGGPGLVKPSQSLSTCTVTIGYSITSDFAWDWIRQFPGNKLEWMGHIR FSGTTSYNPSLKSRSISITRDTSKNQFFLQLNSVTSEDTATYYCARSLITLTKGF FDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTISGGTAALGCLVKDYFPEPTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNATKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKITPPVLDSDGSFFLYSKLTVDKSRWQQGN VFCSSVMHEALHNHYTQKSLSLSPGK
	51F3D2G4	280	QVQLQQSGAELARPGASVRLSCKASGYIFTGYGISWVKQRTGQGLEWIGEIFP RTANTYFNEKFKGKATLTADKSSSTAYMELRSLTSEDSAVYFCARDYDPPYAL DYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTISGGTAALGCLVKDYFPEPTV WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VDVSHEDPEVKFNWYVDGVEVHNATKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKITPPVLDSDGSFFLYSKLTVDKSRWQQGN VFCSSVMHEALHNHYTQKSLSLSPGK
	42G2D7D3	281	DVQLLESGPGLVKPSQSLSTCTVTIGYSITSGYYWNWIRQFPGNNLEWMGSIN YDGSNDYNPSLQDRISITRDTSKNQFFLKLNSVTTEDTATYYCARRLDYWGQ TTLIVSSASTKGPSVFPLAPSSKSTISGGTAALGCLVKDYFPEPTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSH EDPEVKFNWYVDGVEVHNATKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS

[0463]

			DI AVEWESNGQ PENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK
53C1F3D4	282		QVQLQQSGNELARPGASVRLSCKASGYIFTGYGITWVRQRPQGGLIEWIGEIFP RRVNTYYSEKFKGRATLTADISSSTAYMELRSLTSEDSAVYFCARDYDPYFAL DYWGQGTSTVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDI AVEWESNGQ PENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
21D1F4D4	283		QVQLQQPGA EVVRPGASVRLSCKASGYFTNYWISWVKQRPQGGLIEWIGNIYP SDSYTNYNQNFKDKATLTVDKSSSTAYMQLSSPTSEDSAVYYCTGTGIITVIAT RDDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDI AVEWESNGQ PENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
30A6B2D9	284		EGQLQQSGAGLVKPGASVNLSCASGFNI KDYIHWKQRPQGGLIEWIGRIAP TNGNTKYDPTFGGKATITADSSNTAYLQVSLTSEDTAVYYCSRGGIYYGGS HWYFDVWGAGTTVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTC TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDI AVEWESNGQ PENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK
25G1F9F8	285		EGQLQQSGAELVKPGASVNLSCASGFNI KDYIHWKQRPDQGGLIEWIGRIAP TNGNAKTHPTFGGKATITADTSSNTAYLQSLTSEDTAVYYCTRGGIYYGGS HWYFDVWGAGTTVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDI AVEWESNGQ PENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK
27D3D3G2	286		QVLLQQSGPELVKPGASVRLSCKASGYFTTSYMHVWKQRPQGGLIEWIGWIYP GNVNTKYNEKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYFCAS YGNYGGWY FDVWGAGTTVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDI AVEWESNGQ PENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK
30A7B5D9	287		KVQLQQSGAELVKPGTSVRLSCKASGYTFTEYIIYWKQRSGQGLEWIGWFYF GTGSIKYNEKFKDKATLTADKSSSTVFMELSRLTSEDSAVYFCARHEEGLNLF AYWGQGTTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDI AVEWESNGQ PENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
1H1G4D9	288		EGQLQQSGAELVKPGASVILSCTASGFNI KDYIHWLNQRPEQGGLIEWIGRIEP ANGNTKYDPTFGGKATITADTSSNTAYLQSLTSEDTAVYYCSRGGIYYGGS HWYFDVWGAGTLVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSL

[0464]

	25B6E5D8	289	TCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK QFQLQQSGAEIVRPGSSVKISCKASGYEFSSNMMNVKQRFQGSLEWIGQIWP GDGDTNNGKFRGKATLTSDKSSSTAYMQLNSLTSEDSAVYFCARGRASFYFD YWGQGTALTIVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFC SCVMHEALHNHYTQKSLSLSPGK
嵌合, 具有 CDR2突变	53C1VH.M1	290	QVQLQQSGNELARPGASVRLSCKASGYIFTGYGITWVRQRFQGLEWIGEIFP RRVSTYYSEKFKGRATLTADISSSTAYMELRSLTSEDSAVYFCARDYDPYFAL DYWGQGTISVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFC SCVMHEALHNHYTQKSLSLSPGK
	53C1VH.M2	291	QVQLQQSGNELARPGASVRLSCKASGYIFTGYGITWVRQRFQGLEWIGEIFP RRVATYYSEKFKGRATLTADISSSTAYMELRSLTSEDSAVYFCARDYDPYFAL DYWGQGTISVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFC SCVMHEALHNHYTQKSLSLSPGK
	53C1VH.M3	292	QVQLQQSGNELARPGASVRLSCKASGYIFTGYGITWVRQRFQGLEWIGEIFP RRVQTYSEKFKGRATLTADISSSTAYMELRSLTSEDSAVYFCARDYDPYFAL DYWGQGTISVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFC SCVMHEALHNHYTQKSLSLSPGK
人源化	29A8VH1	293	EVQLQESGGPLVKPSETLSLTCTVSGYSITSDFAWDWIRQFPFGKLEWIGHIR FSGTTSYNPFLKSRITISVDTSKNQFSLKLSVTAADTAVYYCARSTLIITKGF FDYWGQGTILTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPDTLMISRTPEVTCV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFC SCVMHEALHNHYTQKSLSLSPGK
	29A8VH2	294	EVQLQESGGPLVKPSETLSLTCTVSGYSITSDFAWDWIRQFPFGKLEWIGHIR FSGTTSYNPFLKSRITISVDTSKNQFSLKLSVTAADTAVYYCARSTLIITKGF FDYWGQGTILTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPDTLMISRTPEVTCV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFC SCVMHEALHNHYTQKSLSLSPGK
	29A8VH3	295	EVQLQESGGPLVKPSETLSLTCTVSGYSITSDFAWDWIRQFPFGKLEWIGHIR FSGTTSYNPFLKSRITISVDTSKNQFSLKLSVTAADTAVYYCARSTLIITKGF FDYWGQGTILTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPDTLMISRTPEVTCV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL

[0465]

			VKGFPSPDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCVMHEALHNHYTQKSLSLSPGK
29A8VH4	296		EVQLQESGPGGLVKPSETLSLTCTVSGYSITSDFAWDWIRQPPGKLEWIGHIR FSGTTSYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARSLITKGF FDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFPSPDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCVMHEALHNHYTQKSLSLSPGK
29A8VH5	297		EVQLQESGPGGLVKPSETLSLTCTVSGYSITSDFAWDWIRQPPGKLEWIGHIR FSGTTSYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCARSLITKGF FDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFPSPDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCVMHEALHNHYTQKSLSLSPGK
53C1VH1	298		EVQLVQSGAEVKKPGASVKVSCKASGYFTGYGITWVRQAPGQGLEWMGEIFP RRVNTYYSEKPKGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCVMHEALHNHYTQKSLSLSPGK
53C1VH2	299		EVQLVQSGAEVKKPGASVKVSCKASGYFTGYGITWVRQAPGQGLEWMGEIFP RRVNTYYSEKPKGRATLTADTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCVMHEALHNHYTQKSLSLSPGK
53C1VH3	300		EVQLVQSGAEVKKPGASVKLSCKASGYFTGYGITWVRQAPGQGLEWMGEIFP RRVNTYYSEKPKGRATLTADTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCVMHEALHNHYTQKSLSLSPGK
53C1VH4	301		EVQLVQSGAEVKKPGASVKLSCKASGYFTGYGITWVRQAPGQGLEWMGEIFP RRVNTYYSEKPKGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCVMHEALHNHYTQKSLSLSPGK
53C1VH5	302		EVQLVQSGAEVKKPGASVKVSCKASGYFTGYGITWVRQAPGQGLEWMGEIFP RRVNTYYSEKPKGRVTMTADTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV

[0466]

人源化, 具有CDR2突变	53C1VH6	303	KGFPSPDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWMGEIFP RRVNTYYSEKFKGRVIMTADISTSTAYMELRSLRSDTAVYYCARDYDPYFAL DYWGQGITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHPKSNK VDKKVEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPPKPDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFPSPDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
	53C1VH1.M3	304	EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWMGEIFP RRVNTYYSEKFKGRVIMTADISTSTAYMELRSLRSDTAVYYCARDYDPYFAL DYWGQGITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHPKSNK VDKKVEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPPKPDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFPSPDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
	53C1VH2.M3	305	EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVNTYYSEKFKGRATLTADISTSTAYMELRSLRSDTAVYFCARDYDPYFAL DYWGQGITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHPKSNK VDKKVEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPPKPDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFPSPDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
	53C1VH3.M3	306	EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVNTYYSEKFKGRATLTADISTSTAYMELRSLRSDTAVYFCARDYDPYFAL DYWGQGITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHPKSNK VDKKVEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPPKPDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFPSPDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
	53C1VH4.M3	307	EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWMGEIFP RRVNTYYSEKFKGRVIMTADISTSTAYMELRSLRSDTAVYYCARDYDPYFAL DYWGQGITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHPKSNK VDKKVEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPPKPDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFPSPDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
	53C1VH5.M3	308	EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWMGEIFP RRVNTYYSEKFKGRVIMTADISTSTAYMELRSLRSDTAVYYCARDYDPYFAL DYWGQGITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHPKSNK VDKKVEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPPKPDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFPSPDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
	53C1VH6.M3	309	EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWMGEIFP RRVNTYYSEKFKGRVIMTADISTSTAYMELRSLRSDTAVYYCARDYDPYFAL DYWGQGITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHPKSNK VDKKVEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPPKPDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV

[0467]

			KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
53C1VH1.M1	310		EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGQGLEWMGEIFP RRVSTYYSEKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
53C1VH2.M1	311		EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVSTYYSEKFKGRATLTDTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
53C1VH3.M1	312		EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVSTYYSEKFKGRATLTADTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
53C1VH4.M1	313		EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWMGEIFP RRVSTYYSEKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
53C1VH5.M1	314		EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGQGLEWMGEIFP RRVSTYYSEKFKGRVTMTADTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
53C1VH6.M1	315		EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWMGEIFP RRVSTYYSEKFKGRVTMTADTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
53C1VH1.M2	316		EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGQGLEWMGEIFP RRVATYYSEKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV

[0468]

			KGFPSPDI AVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
	53C1VH2.M2	317	EVQLVQSGAEVKKPGASVKVCKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVATYYSEKFKGRATLTDTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFPSPDI AVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
	53C1VH3.M2	318	EVQLVQSGAEVKKPGASVKVCKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVATYYSEKFKGRATLTADTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFPSPDI AVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
	53C1VH4.M2	319	EVQLVQSGAEVKKPGASVKVCKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVATYYSEKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFPSPDI AVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
	53C1VH5.M2	320	EVQLVQSGAEVKKPGASVKVCKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVATYYSEKFKGRVTMTADTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFPSPDI AVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
	53C1VH6.M2	321	EVQLVQSGAEVKKPGASVKVCKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVATYYSEKFKGRVTMTADTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFPSPDI AVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK

[0469] 表25. 全长κ轻链序列。

[0470]

Ab	mAb	SEQ ID NO:	序列
嵌合	18B7F4G8	322	DIVLTQSPASLAVSLGQRATISCRASESDTYGDSFMHWFQQKPGQPPKLLIY RASNLESGIPARFSGSGSRTDFTLTINPVEADAVTYCCQQSNEAPYTFGGGT KLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC
	29A8H8C7	323	DIVMTQSHKFMSTSVGGRVSI TCKASQDVSPAVAWYQQKPGQSPKLLIYWAST RHTGVPDRFTGSGSGTDFTLTISVQTEDLALYYCQQHYSTPWTFGGGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
	51F3D2G4	324	DIVMTQSHKFMSTSVGDRVTITCKASQDVSTAVDWYQQKPGQSPKLLIYSASY RYTGVPDRFTGSGSGTAFTFTISSEQAEDLAVYYCQQHYSVPFTFGGGTKLEI

[0471]

			KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
42G2D7D3	325		QIVLTQSPAISASPGKVTITSCASSFINMYWYQQKPGSSPKWILRTSTL ASGVPARFSGSGSGTSYSLTISSEAEADAATYYCQQYHSYPLTFGAGTKLELK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C
53C1F3D4	326		DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVDWYQQKPGQSPKLLIYSASY RYTGVPDRFTGSGSGTAFTFTISGEQAEDLAVYYCQQYHSYPLTFGAGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
21D1F4D4	327		QIVLTQSPAISASPGKVTITCSASSSVSSSYLYWYQQKPGSSPKLWIYSTS NLASGVPARFSGSGSGTSYSLTVSSMEAEADAASYFCHQWSSYPFTFGSGTKLE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR GEC
30A6B2D9	328		SVLMTQTPLSLPVSLGDQASISCRSSQNIVYSDGDTYLEWYLQKPGQSPKLLI FKVSNRFFGVPDRFSGSGSGTDFTLKISRVEAEDLGVYCFQGSHVPFTFGSG TKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC
25G1F9F8	329		DVLMTQTPLSLPVSLGDQASISCRSSQNIVYSDGNTYLEWYLQKPGQSPKLLI FQVSNRFFGVPDRFSGSGSGTDFTLKISRVEAEDLGVYCFQGSHVPFTFGSG TKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC
27D3D3G2	330		DIQMTQTSSLSASLGDRVTISCRASQDIGNYLNWYQQKPDGTVKLLIYYTSR LHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGDTFPWTFGGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
30A7B5D9	331		QIVLTQSPALMSASPGERVMTTCSASSDVSIMYWYQQKPRSSPKWIIYLTSLN ASGVPARFSGSGSGTSYSLTISSEAEADAATYYCQQWTGNPLTFGAGTKLELK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C
1H1G4D9	332		DVLMTQTPLSLPVSLGDQASISCRSSQNIVYSDGDTYLEWYLQKPGQSPKLLI FKVSNRFFGVPDRFSGSGSGTDFTLKISRVEAEDLGVYCFQGSHVPFTFGSG TKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC
25B6E5D8	333		DIVLTQSPASLAVSLGQRATISCRASESVDDYGNFMHWYQQKPGQPPKLLIY

[0472]

			RASNLESGIPVRFSGSGSRTDFTLTINPVEADDVATYYCQQSNEDPHTFGGGT KLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC
嵌合，具 有 CDR1 突变	29A8VL.M1	334	DIVMTQSHKFMSTSVGGRVSTICRASQDVSPAVAWYQQKPGQSPKLLIYWAST RHTGVPDRFTGSGSGTDFTLTISVQTEDLALYYCQQHYSTPWTFGGGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
	53C1VL.M1	335	DIVMTQSHKFMSTSVGDRVSTICRASQDVSTAVDWYQQKPGQSPKLLIYSASY RYTGVPDRFTGSGSGTAFTFTISGEQAEDLAVYYCQQHYSIPFTFGGGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
人源化	29A8VL1	336	DIQMTQSPSSLSASVGRVTITCKASQDVSPAVAWYQQKPGKAPKLLIYWAST RHTGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQHYSTPWTFGGQTKVEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
	29A8VL2	337	DIQMTQSPSSLSASVGRVTITCKASQDVSPAVAWYQQKPGKAPKLLIYWAST RHTGVPSRFSGSGSGTDFTLTISLQPEDLALYYCQQHYSTPWTFGGQTKVEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
	29A8VL3	338	DIQMTQSPSSLSASVGRVTITCKASQDVSPAVAWYQQKPGKAPKLLIYWAST RHTGVPSRFSGSGSGTDFTLTISVQPEDLALYYCQQHYSTPWTFGGQTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
	53C1VL1	339	DIQMTQSPSSLSASVGRVTITCKASQDVSTAVDWYQQKPGKAPKLLIYSASY RYTGVPDRFSGSGSGTDFTFTISLQPEDLATYYCQQHYSIPFTFGGQTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
	53C1VL2	340	DIQMTQSPSSMSASVGRVTITCKASQDVSTAVDWYQQKPGKAPKLLIYSASY RYTGVPDRFSGSGSGTDFTFTISLQPEDLATYYCQQHYSIPFTFGGQTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
	53C1VL3	341	DIQMTQSPSSMSTSVGDRVTITCKASQDVSTAVDWYQQKPGKAPKLLIYSASY RYTGVPDRFSGSGSGTDFTFTISSEQPEDLATYYCQQHYSIPFTFGGQTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC

[0473]

人源化, 具 有 CDR1 突 变	29A8VL1.M1	342	DIQMTQSPSSLSASVGDRTITCRASQDVSPAVAWYQQKPGKAPKLLIYWAST RHTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQHYSTPWTFGQGTKVEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
	29A8VL2.M1	343	DIQMTQSPSSLSASVGDRTITCRASQDVSPAVAWYQQKPGKAPKLLIYWAST RHTGVPSRFSGSGSGTDFTLTISSLQPEDLALYYCQQHYSTPWTFGQGTKVEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
	29A8VL3.M1	344	DIQMTQSPSSLSASVGDRTITCRASQDVSPAVAWYQQKPGKAPKLLIYWAST RHTGVPSRFSGSGSGTDFTLTISSVQPEDLALYYCQQHYSTPWTFGQGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
	53C1VL1.M1	345	DIQMTQSPSSLSASVGDRTITCRASQDVSTAVDWYQQKPGKAPKLLIYSASY RYTGVPSRFSGSGSGTDFTFTISSLQPEDLATYYCQQHYSIPFTFGQGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
	53C1VL2.M1	346	DIQMTQSPSSMSASVGDRTITCRASQDVSTAVDWYQQKPGKAPKLLIYSASY RYTGVPSRFSGSGSGTDFTFTISSLQPEDLATYYCQQHYSIPFTFGQGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
	53C1VL3.M1	347	DIQMTQSPSSMSTSVGDRTITCRASQDVSTAVDWYQQKPGKAPKLLIYSASY RYTGVPSRFSGSGSGTDFTFTISSEQPEDLATYYCQQHYSIPFTFGQGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC

[0474] 表26. 具有野生型恒定区序列的全长IgG1重链序列。

[0475]

Ab	mAb	SEQ ID NO:	序列
嵌合	18B7F4G8	348	DVQLQESGPDLVKPSQSLSLTCTVTGYISITSGYTWHWIRQFPNGKLEWGMGYIH YSGSTKYNPSLKSRSITRDTSKNQFFLQNSMTAEDTATYYCARNSLPASWG HGTILVTVAASIKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSQVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHPKPSNTKVDKR VEPKSCDKHTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCS VMHEALHNHYTQKSLSLSPGK
	29A8H8C7	349	DVQLQSGGPGLVKPSQSLSLTCTVTGYISITSDFAWDWIRQFPNGKLEWGMHIR FSGTTSYNPSLKSRSITRDTSKNQFFLQNSVTSEDATATYYCARSLITKGF FDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHPKPSNT KVDKRVEPKSCDKHTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMEALHNHYTQKSLSLSPGK
	51F3D2G4	350	QVQLQQSGAELARPGASVRLSCKASGYIFTGYGISNVKQRTQGQGLEWIGEIFP RTANTYFNEKFKGKATLTADKSSSTAYMELRSLTSEDSAVYFCARDYDYPYAL DYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHPKPSNTK VDKRVEPKSCDKHTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
	42G2D7D3	351	DVQLLESGLVGVKPSQSLSLTCTSVTGYISITSGYWNWIRQFPNGNLEWNGSIN YDGSNDYNPSLQDRISITRDTSKNQFFLKLNSVTTEDATATYYCARRLDYWGQG TTLIVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHPKPSNTKVDKRVE PKSCDKHTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSH DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCSV MEALHNHYTQKSLSLSPGK
	53C1F3D4	352	QVQLQQSGNELARPGASVRLSCKASGYIFTGYGITWVRQRPQGQGLEWIGEIFP RRVNTYYSEKFKGRATLTADISSSTAYMELRSLTSEDSAVYFCARDYDYPYAL DYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHPKPSNTK VDKRVEPKSCDKHTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
	21D1F4D4	353	QVQLQQSGAEVVRPGASVRLSCKASGYFTNYWISNVKQRPQGQGLEWIGNIYP SDSYTNYNQNFKDKATLTVDKSSSTAYMQLSSPTSEDSAVYYCTIGIITVIAT RDDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHPKPSN TKVDKRVEPKSCDKHTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMEALHNHYTQKSLSLSPGK
	30A6B2D9	354	EGQLQQSGAGLVKPGASVNLSTASGFNIKDTYIHNMQRPEQGLEWIGRIAP TNGNTKYDPTFGKATITADSSSNATYLVSSLTSEDATAVYYCSRGGIYYGGS HWYFDVWGAGITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP

[0476]

			VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
25G1F9F8	355		EGQLQQSGAELVKPGASVNLSCASGFNIKDTYIHWVKQRPDQGLEWIGRIAPTNGNAKFHPTFQGGKATITADTSSNTAYLQLSSLTSEDYAVYCYTRGGIYYGT HWYFDVWGAGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
27D3D3G2	356		QVLLQQSGPELVKPGASVRLSCKASGYFTFTSYMHVVKQRPGQGLEWIGWIYPGNVNTKYNEKFKGKATLTADKSSSTAYMQLSSLTSEDYAVYFCASYGNYGGWYFDVWGAGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
30A7B5D9	357		KVQLQQSGAELVKPGTSVLSCKASGYFTTEYIIYWIKQRSGQGLEWIGWFYPTGGSIKYNEKFKDKATLTADKSSSTVFMELSLTSEDYAVYFCARHEEGNLWFAYWGQGTSLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
1H1G4D9	358		EGQLQQSGAELVKPGASVILSCTASGFNIKDTYIHWLNQRPEQGLEWIGRIEPANGNTKYDPTFQGGKATITADTSSNTAYLQLSLTSEDYAVYICSRGGIYYGSHWYFDVWGAGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
25B6E5D8	359		QFQLQQSGAELVRPGSSVKISCKASGYEFSSNWMNVKQRPGQGLEWIGQIWP GDGDTNYNGKFRGKATLTSDKSSSTAYMQLNSLTSEDYAVYFCARGRASFYFDYWGQGTALTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
嵌合, 具有 CDR2突变	53C1VH.M1	360	QVQLQQSGNELARPGASVRLSCKASGYIFTGYGITVVRQRPGQGLEWIGEIPFRVSTYYSEKFKGRATLTADISSSTAYMELSLTSEDYAVYFCARDYDPYFALDYWGQGTSLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
	53C1VH.M2	361	QVQLQQSGNELARPGASVRLSCKASGYIFTGYGITVVRQRPGQGLEWIGEIPFRVATYYSEKFKGRATLTADISSSTAYMELSLTSEDYAVYFCARDYDPYFALDYWGQGTSLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[0477]

			WNSGALTSQVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKRVKPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
	53C1VH.M3	362	QVQLQESGNEELARPASVRLSCKASGYIFTGYGITWVRQRPQGQLEWIGEIFP RRVQTYIYSEKPKGRATLTADISSSTAYMELRSLTSEDNAVYFCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV WNSGALTSQVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKRVKPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
人源化	29A8VH1	363	EVQLQESGPGLVKPSSETLSLTCTVSGYSITSDFAWDWIRQPPGKLEWIGHIR FSGTTSYNPSLKSRVTISVDTSKNQFSLKLSVTAADTAVYYCARSTLIITKGF FDYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSQVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVKPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQDWLNG GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMEALHNHYTQKSLSLSPGK
	29A8VH2	364	EVQLQESGPGLVKPSSETLSLTCTVSGYSITSDFAWDWIRQPPGKLEWIGHIR FSGTTSYNPSLKSRVTISVDTSKNQFSLKLSVTAADTAVYYCARSTLIITKGF FDYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSQVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVKPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQDWLNG GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMEALHNHYTQKSLSLSPGK
	29A8VH3	365	EVQLQESGPGLVKPSSETLSLTCTVSGYSITSDFAWDWIRQPPGKLEWIGHIR FSGTTSYNPSLKSRVTISVDTSKNQFSLKLSVTAADTAVYYCARSTLIITKGF FDYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSQVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVKPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQDWLNG GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMEALHNHYTQKSLSLSPGK
	29A8VH4	366	EVQLQESGPGLVKPSSETLSLTCTVSGYSITSDFAWDWIRQPPGKLEWIGHIR FSGTTSYNPSLKSRVTISVDTSKNQFSLKLSVTAADTAVYYCARSTLIITKGF FDYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSQVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVKPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQDWLNG GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMEALHNHYTQKSLSLSPGK
	29A8VH5	367	EVQLQESGPGLVKPSSETLSLTCTVSGYSITSDFAWDWIRQPPGKLEWIGHIR FSGTTSYNPSLKSRVTISVDTSKNQFSLKLSVTAADTAVYYCARSTLIITKGF FDYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSQVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVKPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQDWLNG GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMEALHNHYTQKSLSLSPGK
	53C1VH1	368	EVQLVQSGAEVKKPGASVKVSCKASGYIFTGYGITWVRQAPQGQLEWMEIFP RRVNTYYSEKPKGRVTMTITDSTSTAYMELRSLRSDTAVYYCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV

[0478]

			WNSGALTSQVHTFFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKDITLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTIISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
	53C1VH2	369	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVNTYYSEKFKGRATLTDTSTAYMELRSLRSDDTAVYFCARDYDYPFAL DYWGQGITVTVSSASTKGPSVFPLAPSSKSTISGGTAALGCLVKDYFPEPVTVS WNSGALTSQVHTFFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKDITLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTIISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
	53C1VH3	370	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVNTYYSEKFKGRATLTDTSTAYMELRSLRSDDTAVYFCARDYDYPFAL DYWGQGITVTVSSASTKGPSVFPLAPSSKSTISGGTAALGCLVKDYFPEPVTVS WNSGALTSQVHTFFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKDITLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTIISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
	53C1VH4	371	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVNTYYSEKFKGRVIMTDTSTAYMELRSLRSDDTAVYFCARDYDYPFAL DYWGQGITVTVSSASTKGPSVFPLAPSSKSTISGGTAALGCLVKDYFPEPVTVS WNSGALTSQVHTFFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKDITLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTIISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
	53C1VH5	372	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVNTYYSEKFKGRVIMTDTSTAYMELRSLRSDDTAVYFCARDYDYPFAL DYWGQGITVTVSSASTKGPSVFPLAPSSKSTISGGTAALGCLVKDYFPEPVTVS WNSGALTSQVHTFFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKDITLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTIISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
	53C1VH6	373	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVNTYYSEKFKGRVIMTDTSTAYMELRSLRSDDTAVYFCARDYDYPFAL DYWGQGITVTVSSASTKGPSVFPLAPSSKSTISGGTAALGCLVKDYFPEPVTVS WNSGALTSQVHTFFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKDITLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTIISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
人源化，具有CDR2突变	53C1VH1.M3	374	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVQTYSEKFKGRVIMTDTSTAYMELRSLRSDDTAVYFCARDYDYPFAL DYWGQGITVTVSSASTKGPSVFPLAPSSKSTISGGTAALGCLVKDYFPEPVTVS WNSGALTSQVHTFFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKDITLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTIISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
	53C1VH2.M3	375	EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVQTYSEKFKGRATLTDTSTAYMELRSLRSDDTAVYFCARDYDYPFAL DYWGQGITVTVSSASTKGPSVFPLAPSSKSTISGGTAALGCLVKDYFPEPVTVS

[0479]

			WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
53C1VH3.M3	376		EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVQTYIYSEKFKGRATLTADTSTSTAYMELRSLRSDTAVYFCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
53C1VH4.M3	377		EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWMGEIFP RRVQTYIYSEKFKGRVTMTTDTSTSTAYMELRSLRSDTAVYFCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
53C1VH5.M3	378		EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGQGLEWMGEIFP RRVQTYIYSEKFKGRVTMTADTSTSTAYMELRSLRSDTAVYFCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
53C1VH6.M3	379		EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWMGEIFP RRVQTYIYSEKFKGRVTMTADTSTSTAYMELRSLRSDTAVYFCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
53C1VH1.M1	380		EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGQGLEWMGEIFP RRVSTYIYSEKFKGRVTMTTDTSTSTAYMELRSLRSDTAVYFCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
53C1VH2.M1	381		EVQLVQSGAEVKKPGASVKVSKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVSTYIYSEKFKGRATLTDTSTSTAYMELRSLRSDTAVYFCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
53C1VH3.M1	382		EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWIGEIFP RRVSTYIYSEKFKGRATLTADTSTSTAYMELRSLRSDTAVYFCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS

[0480]

			WNSGALTSQVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
53C1VH4.M1	383		EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWMGEI FFP RRVSTYYSEKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSQVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
53C1VH5.M1	384		EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWMGEI FFP RRVSTYYSEKFKGRVTMTADTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSQVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
53C1VH6.M1	385		EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWMGEI FFP RRVSTYYSEKFKGRVTMTADTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSQVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
53C1VH1.M2	386		EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWMGEI FFP RRVATYYSEKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSQVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
53C1VH2.M2	387		EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWIGE I FFP RRVATYYSEKFKGRATLTDTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSQVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
53C1VH3.M2	388		EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWIGE I FFP RRVATYYSEKFKGRATLTADTSTSTAYMELRSLRSDDTAVYFCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSQVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
53C1VH4.M2	389		EVQLVQSGAEVKKPGASVKLSCKASGYIFTGYGITWVRQAPGQGLEWMGEI FFP RRVATYYSEKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDYDPYFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS

[0481]

			WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPDKTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
	53C1VH5.M2	390	EVQLVQSGAEVKKPGASVKVCKASGYIFTGYGITWVRQAPGQGLEWMGEIFP RRVATYYSEKFKGRVTMTADTSTSTAYMELRSLRSDTAVYYCARDYDYPFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPDKTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
	53C1VH6.M2	391	EVQLVQSGAEVKKPGASVKVCKASGYIFTGYGITWVRQAPGQGLEWMGEIFP RRVATYYSEKFKGRVTMTADTSTSTAYMELRSLRSDTAVYYCARDYDYPFAL DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPDKTLMI SRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK

[0482] 表27:恒定区序列

[0483]

恒定区	ID	序列
具有无效应子Fc突变的IgG1的重链恒定区	392	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPDKTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
IgG1的轻链恒定区	393	RTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
野生型IgG1的重链恒定区	394	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPDKTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK

[0484] 表28.抗原序列

[0485]

抗原蛋白	ID	序列
全长人PD-L1	395	FTVTVPKDLVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDK NIIQFVHGEEDLKVQHSSYRQARLLKDQLSLGNAALQITDVKL QDAGVYRCMISYGGADYKRITVKVNAPYKNINQRILVDPVTSE HELTCQAEGYPKAEVIWTSDDHQVLSGKTTTNSKREEKLFNVT STLRINTTTNEIFYCTFRRLDPEENHTAELVPELPLAHPNER THLVILGAILLCLGVALTFIFRLRKGRMMDVKKCGIQDTSKKQ SDTHLEET
人PD-L1 ECD	396	FTVTVPKDLVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDK NIIQFVHGEEDLKVQHSSYRQARLLKDQLSLGNAALQITDVKL QDAGVYRCMISYGGADYKRITVKVNAPYKNINQRILVDPVTSE HELTCQAEGYPKAEVIWTSDDHQVLSGKTTTNSKREEKLFNVT STLRINTTTNEIFYCTFRRLDPEENHTAELVPELPLAHPNER
人PD-1 ECD	400	LDSPDRPWNPTTFSPALLVVTEDGNATFTCSFSNTSESFVLNWI RMSPSNQTDKLAAPEDRSQPGQDCRFRTQLPNGRDHFMSVVR ARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHP SPSPRPAGQFQ

[0486] 表29.接头序列

[0487]

接头	ID	序列
G4SG3S	397	GGGSGGGG

(G4S) 3	398	GGGGS GGGGS GGGGS
突变体hIgG1铰链	399	EPKSSDKTHTSPPSP

[0001] 序列表
 [0002] <110> 南京传奇生物技术公司(Nanjing Legend Biotech Co., Ltd.)
 [0003] <120> 针对PD-L1的抗体及其变体
 [0004] <130> 688096.0119
 [0005] <160> 400
 [0006] <170> PatentIn version 3.5
 [0007] <210> 1
 [0008] <211> 115
 [0009] <212> PRT
 [0010] <213> 人工序列(Artificial Sequence)
 [0011] <220>
 [0012] <223> 小鼠VH
 [0013] <400> 1
 [0014] Asp Val Gln Leu Gln Glu Ser Gly Pro Asp Leu Val Lys Pro Ser Gln
 [0015] 1 5 10 15
 [0016] Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Gly
 [0017] 20 25 30
 [0018] Tyr Thr Trp His Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
 [0019] 35 40 45
 [0020] Met Gly Tyr Ile His Tyr Ser Gly Ser Thr Lys Tyr Asn Pro Ser Leu
 [0021] 50 55 60
 [0022] Lys Ser Arg Phe Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
 [0023] 65 70 75 80
 [0024] Leu Gln Leu Asn Ser Met Thr Ala Glu Asp Thr Ala Thr Tyr Tyr Cys
 [0025] 85 90 95
 [0026] Ala Arg Asn Ser Leu Phe Ala Ser Trp Gly His Gly Thr Leu Val Thr
 [0027] 100 105 110
 [0028] Val Ser Ala
 [0029] 115
 [0030] <210> 2
 [0031] <211> 120
 [0032] <212> PRT
 [0033] <213> 人工序列(Artificial Sequence)
 [0034] <220>
 [0035] <223> 小鼠VH
 [0036] <400> 2
 [0037] Asp Val Gln Leu Gln Gly Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 [0038] 1 5 10 15

[0039]	Ser	Leu	Ser	Leu	Thr	Cys	Thr	Val	Thr	Gly	Tyr	Ser	Ile	Thr	Ser	Asp
[0040]				20						25					30	
[0041]	Phe	Ala	Trp	Asp	Trp	Ile	Arg	Gln	Phe	Pro	Gly	Asn	Lys	Leu	Glu	Trp
[0042]				35						40					45	
[0043]	Met	Gly	His	Ile	Arg	Phe	Ser	Gly	Thr	Thr	Ser	Tyr	Asn	Pro	Ser	Leu
[0044]			50							55					60	
[0045]	Lys	Ser	Arg	Ile	Ser	Ile	Thr	Arg	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Phe
[0046]	65						70					75				80
[0047]	Leu	Gln	Leu	Asn	Ser	Val	Thr	Ser	Glu	Asp	Thr	Ala	Thr	Tyr	Tyr	Cys
[0048]						85					90				95	
[0049]	Ala	Arg	Ser	Thr	Leu	Ile	Thr	Lys	Gly	Phe	Phe	Asp	Tyr	Trp	Gly	Gln
[0050]					100					105					110	
[0051]	Gly	Thr	Thr	Leu	Thr	Val	Ser	Ser								
[0052]					115					120						
[0053]	<210> 3															
[0054]	<211> 119															
[0055]	<212> PRT															
[0056]	<213> 人工序列(Artificial Sequence)															
[0057]	<220>															
[0058]	<223> 小鼠VH															
[0059]	<400> 3															
[0060]	Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Ala	Glu	Leu	Ala	Arg	Pro	Gly	Ala
[0061]	1				5					10					15	
[0062]	Ser	Val	Arg	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Gly	Tyr
[0063]				20						25					30	
[0064]	Gly	Ile	Ser	Trp	Val	Lys	Gln	Arg	Thr	Gly	Gln	Gly	Leu	Glu	Trp	Ile
[0065]				35						40					45	
[0066]	Gly	Glu	Ile	Phe	Pro	Arg	Thr	Ala	Asn	Thr	Tyr	Phe	Asn	Glu	Lys	Phe
[0067]			50							55					60	
[0068]	Lys	Gly	Lys	Ala	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Ser	Ser	Thr	Ala	Tyr
[0069]	65						70					75				80
[0070]	Met	Glu	Leu	Arg	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Phe	Cys
[0071]						85						90				95
[0072]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Tyr	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[0073]					100					105					110	
[0074]	Thr	Ser	Val	Thr	Val	Ser	Ser									
[0075]					115											
[0076]	<210> 4															
[0077]	<211> 113															

[0078]	<212>	PRT
[0079]	<213>	人工序列(Artificial Sequence)
[0080]	<220>	
[0081]	<223>	小鼠VH
[0082]	<400>	4
[0083]	Asp Val Gln Leu Leu Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln	
[0084]	1 5 10 15	
[0085]	Ser Leu Ser Leu Thr Cys Ser Val Thr Gly Tyr Ser Ile Thr Ser Gly	
[0086]	20 25 30	
[0087]	Tyr Tyr Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Asn Leu Glu Trp	
[0088]	35 40 45	
[0089]	Met Gly Ser Ile Asn Tyr Asp Gly Ser Asn Asp Tyr Asn Pro Ser Leu	
[0090]	50 55 60	
[0091]	Gln Asp Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe	
[0092]	65 70 75 80	
[0093]	Leu Lys Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys	
[0094]	85 90 95	
[0095]	Ala Arg Arg Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Ile Val Ser	
[0096]	100 105 110	
[0097]	Ser	
[0098]	<210>	5
[0099]	<211>	119
[0100]	<212>	PRT
[0101]	<213>	人工序列(Artificial Sequence)
[0102]	<220>	
[0103]	<223>	小鼠VH
[0104]	<400>	5
[0105]	Gln Val Gln Leu Gln Gln Ser Gly Asn Glu Leu Ala Arg Pro Gly Ala	
[0106]	1 5 10 15	
[0107]	Ser Val Arg Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr	
[0108]	20 25 30	
[0109]	Gly Ile Thr Trp Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile	
[0110]	35 40 45	
[0111]	Gly Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe	
[0112]	50 55 60	
[0113]	Lys Gly Arg Ala Thr Leu Thr Ala Asp Ile Ser Ser Ser Thr Ala Tyr	
[0114]	65 70 75 80	
[0115]	Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys	
[0116]	85 90 95	

[0117]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[0118]	100 105 110
[0119]	Thr Ser Val Thr Val Ser Ser
[0120]	115
[0121]	<210> 6
[0122]	<211> 121
[0123]	<212> PRT
[0124]	<213> 人工序列(Artificial Sequence)
[0125]	<220>
[0126]	<223> 小鼠VH
[0127]	<400> 6
[0128]	Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Val Val Arg Pro Gly Ala
[0129]	1 5 10 15
[0130]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
[0131]	20 25 30
[0132]	Trp Ile Ser Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
[0133]	35 40 45
[0134]	Gly Asn Ile Tyr Pro Ser Asp Ser Tyr Thr Asn Tyr Asn Gln Asn Phe
[0135]	50 55 60
[0136]	Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
[0137]	65 70 75 80
[0138]	Met Gln Leu Ser Ser Pro Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[0139]	85 90 95
[0140]	Thr Thr Gly Ile Ile Thr Val Ile Ala Thr Arg Asp Asp Tyr Trp Gly
[0141]	100 105 110
[0142]	Gln Gly Thr Thr Leu Thr Val Ser Ser
[0143]	115 120
[0144]	<210> 7
[0145]	<211> 123
[0146]	<212> PRT
[0147]	<213> 人工序列(Artificial Sequence)
[0148]	<220>
[0149]	<223> 小鼠VH
[0150]	<400> 7
[0151]	Glu Gly Gln Leu Gln Gln Ser Gly Ala Gly Leu Val Lys Pro Gly Ala
[0152]	1 5 10 15
[0153]	Ser Val Asn Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Thr
[0154]	20 25 30
[0155]	Tyr Ile His Trp Met Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile

[0156]	35	40	45
[0157]	Gly Arg Ile Ala Pro Thr Asn Gly Asn Thr Lys Tyr Asp Pro Thr Phe		
[0158]	50	55	60
[0159]	Gln Gly Lys Ala Thr Ile Thr Ala Asp Ser Ser Ser Asn Thr Ala Tyr		
[0160]	65	70	75
[0161]	Leu Gln Val Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys		
[0162]	85	90	95
[0163]	Ser Arg Gly Gly Ile Tyr Tyr Tyr Gly Ser His Trp Tyr Phe Asp Val		
[0164]	100	105	110
[0165]	Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser		
[0166]	115	120	
[0167]	<210> 8		
[0168]	<211> 123		
[0169]	<212> PRT		
[0170]	<213> 人工序列(Artificial Sequence)		
[0171]	<220>		
[0172]	<223> 小鼠VH		
[0173]	<400> 8		
[0174]	Glu Gly Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala		
[0175]	1	5	10
[0176]	Ser Val Asn Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Thr		
[0177]	20	25	30
[0178]	Tyr Ile His Trp Val Lys Gln Arg Pro Asp Gln Gly Leu Glu Trp Ile		
[0179]	35	40	45
[0180]	Gly Arg Ile Ala Pro Thr Asn Gly Asn Ala Lys Phe His Pro Thr Phe		
[0181]	50	55	60
[0182]	Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr		
[0183]	65	70	75
[0184]	Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys		
[0185]	85	90	95
[0186]	Thr Arg Gly Gly Ile Tyr Tyr Tyr Gly Thr His Trp Tyr Phe Asp Val		
[0187]	100	105	110
[0188]	Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser		
[0189]	115	120	
[0190]	<210> 9		
[0191]	<211> 120		
[0192]	<212> PRT		
[0193]	<213> 人工序列(Artificial Sequence)		
[0194]	<220>		

[0195]	<223>	小鼠VH
[0196]	<400>	9
[0197]	Gln Val Leu Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala	
[0198]	1	5 10 15
[0199]	Ser Val Arg Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr	
[0200]		20 25 30
[0201]	Tyr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile	
[0202]		35 40 45
[0203]	Gly Trp Ile Tyr Pro Gly Asn Val Asn Thr Lys Tyr Asn Glu Lys Phe	
[0204]		50 55 60
[0205]	Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr	
[0206]	65	70 75 80
[0207]	Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys	
[0208]		85 90 95
[0209]	Ala Ser Tyr Gly Asn Tyr Gly Gly Trp Tyr Phe Asp Val Trp Gly Ala	
[0210]		100 105 110
[0211]	Gly Thr Thr Val Thr Val Ser Ser	
[0212]		115 120
[0213]	<210>	10
[0214]	<211>	119
[0215]	<212>	PRT
[0216]	<213>	人工序列(Artificial Sequence)
[0217]	<220>	
[0218]	<223>	小鼠VH
[0219]	<400>	10
[0220]	Lys Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Thr	
[0221]	1	5 10 15
[0222]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Glu Tyr	
[0223]		20 25 30
[0224]	Ile Ile Tyr Trp Ile Lys Gln Arg Ser Gly Gln Gly Leu Glu Trp Ile	
[0225]		35 40 45
[0226]	Gly Trp Phe Tyr Pro Gly Thr Gly Ser Ile Lys Tyr Asn Glu Lys Phe	
[0227]		50 55 60
[0228]	Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Val Phe	
[0229]	65	70 75 80
[0230]	Met Glu Leu Ser Arg Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys	
[0231]		85 90 95
[0232]	Ala Arg His Glu Glu Gly Asn Leu Trp Phe Ala Tyr Trp Gly Gln Gly	
[0233]		100 105 110

[0234]	Thr Leu Val Thr Val Ser Ala
[0235]	115
[0236]	<210> 11
[0237]	<211> 123
[0238]	<212> PRT
[0239]	<213> 人工序列(Artificial Sequence)
[0240]	<220>
[0241]	<223> 小鼠VH
[0242]	<400> 11
[0243]	Glu Gly Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
[0244]	1 5 10 15
[0245]	Ser Val Ile Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Thr
[0246]	20 25 30
[0247]	Tyr Ile His Trp Leu Asn Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
[0248]	35 40 45
[0249]	Gly Arg Ile Glu Pro Ala Asn Gly Asn Thr Lys Tyr Asp Pro Thr Phe
[0250]	50 55 60
[0251]	Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
[0252]	65 70 75 80
[0253]	Leu Gln Leu Thr Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
[0254]	85 90 95
[0255]	Ser Arg Gly Gly Ile Tyr Tyr Tyr Gly Ser His Trp Tyr Phe Asp Val
[0256]	100 105 110
[0257]	Trp Gly Ala Gly Thr Leu Val Thr Val Ser Ser
[0258]	115 120
[0259]	<210> 12
[0260]	<211> 118
[0261]	<212> PRT
[0262]	<213> 人工序列(Artificial Sequence)
[0263]	<220>
[0264]	<223> 小鼠VH
[0265]	<400> 12
[0266]	Gln Phe Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser
[0267]	1 5 10 15
[0268]	Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Glu Phe Ser Ser Asn
[0269]	20 25 30
[0270]	Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Ser Leu Glu Trp Ile
[0271]	35 40 45
[0272]	Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe

[0273]	50	55	60
[0274]	Arg Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr		
[0275]	65	70	75
[0276]	Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys		80
[0277]		85	90
[0278]	Ala Arg Gly Arg Ala Ser Phe Tyr Phe Asp Tyr Trp Gly Gln Gly Thr		95
[0279]		100	105
[0280]	Ala Leu Thr Val Ser Ser		110
[0281]	115		
[0282]	<210> 13		
[0283]	<211> 119		
[0284]	<212> PRT		
[0285]	<213> 人工序列(Artificial Sequence)		
[0286]	<220>		
[0287]	<223> 具有CDR突变的小鼠VH		
[0288]	<400> 13		
[0289]	Gln Val Gln Leu Gln Gln Ser Gly Asn Glu Leu Ala Arg Pro Gly Ala		
[0290]	1	5	10
[0291]	Ser Val Arg Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		15
[0292]		20	25
[0293]	Gly Ile Thr Trp Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile		30
[0294]		35	40
[0295]	Gly Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe		45
[0296]	50	55	60
[0297]	Lys Gly Arg Ala Thr Leu Thr Ala Asp Ile Ser Ser Ser Thr Ala Tyr		
[0298]	65	70	75
[0299]	Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys		80
[0300]		85	90
[0301]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly		95
[0302]		100	105
[0303]	Thr Ser Val Thr Val Ser Ser		110
[0304]	115		
[0305]	<210> 14		
[0306]	<211> 119		
[0307]	<212> PRT		
[0308]	<213> 人工序列(Artificial Sequence)		
[0309]	<220>		
[0310]	<223> 具有CDR突变的小鼠VH		
[0311]	<400> 14		

[0312]	Gln Val Gln Leu Gln Gln Ser Gly Asn Glu Leu Ala Arg Pro Gly Ala
[0313]	1 5 10 15
[0314]	Ser Val Arg Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[0315]	20 25 30
[0316]	Gly Ile Thr Trp Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
[0317]	35 40 45
[0318]	Gly Glu Ile Phe Pro Arg Arg Val Ala Thr Tyr Tyr Ser Glu Lys Phe
[0319]	50 55 60
[0320]	Lys Gly Arg Ala Thr Leu Thr Ala Asp Ile Ser Ser Ser Thr Ala Tyr
[0321]	65 70 75 80
[0322]	Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
[0323]	85 90 95
[0324]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[0325]	100 105 110
[0326]	Thr Ser Val Thr Val Ser Ser
[0327]	115
[0328]	<210> 15
[0329]	<211> 119
[0330]	<212> PRT
[0331]	<213> 人工序列(Artificial Sequence)
[0332]	<220>
[0333]	<223> 具有CDR突变的小鼠VH
[0334]	<400> 15
[0335]	Gln Val Gln Leu Gln Gln Ser Gly Asn Glu Leu Ala Arg Pro Gly Ala
[0336]	1 5 10 15
[0337]	Ser Val Arg Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[0338]	20 25 30
[0339]	Gly Ile Thr Trp Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
[0340]	35 40 45
[0341]	Gly Glu Ile Phe Pro Arg Arg Val Gln Thr Tyr Tyr Ser Glu Lys Phe
[0342]	50 55 60
[0343]	Lys Gly Arg Ala Thr Leu Thr Ala Asp Ile Ser Ser Ser Thr Ala Tyr
[0344]	65 70 75 80
[0345]	Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
[0346]	85 90 95
[0347]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[0348]	100 105 110
[0349]	Thr Ser Val Thr Val Ser Ser
[0350]	115

[0351]	<210> 16
[0352]	<211> 120
[0353]	<212> PRT
[0354]	<213> 人工序列(Artificial Sequence)
[0355]	<220>
[0356]	<223> 人源化VH
[0357]	<400> 16
[0358]	Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
[0359]	1 5 10 15
[0360]	Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp
[0361]	20 25 30
[0362]	Phe Ala Trp Asp Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
[0363]	35 40 45
[0364]	Ile Gly His Ile Arg Phe Ser Gly Thr Thr Ser Tyr Asn Pro Ser Leu
[0365]	50 55 60
[0366]	Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
[0367]	65 70 75 80
[0368]	Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
[0369]	85 90 95
[0370]	Ala Arg Ser Thr Leu Ile Thr Lys Gly Phe Phe Asp Tyr Trp Gly Gln
[0371]	100 105 110
[0372]	Gly Thr Leu Val Thr Val Ser Ser
[0373]	115 120
[0374]	<210> 17
[0375]	<211> 120
[0376]	<212> PRT
[0377]	<213> 人工序列(Artificial Sequence)
[0378]	<220>
[0379]	<223> 人源化VH
[0380]	<400> 17
[0381]	Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
[0382]	1 5 10 15
[0383]	Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp
[0384]	20 25 30
[0385]	Phe Ala Trp Asp Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp
[0386]	35 40 45
[0387]	Met Gly His Ile Arg Phe Ser Gly Thr Thr Ser Tyr Asn Pro Ser Leu
[0388]	50 55 60
[0389]	Lys Ser Arg Ile Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser

[0390]	65	70	75	80
[0391]	Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys			
[0392]	85	90	95	
[0393]	Ala Arg Ser Thr Leu Ile Thr Lys Gly Phe Phe Asp Tyr Trp Gly Gln			
[0394]	100	105	110	
[0395]	Gly Thr Leu Val Thr Val Ser Ser			
[0396]	115	120		
[0397]	<210> 18			
[0398]	<211> 120			
[0399]	<212> PRT			
[0400]	<213> 人工序列(Artificial Sequence)			
[0401]	<220>			
[0402]	<223> 人源化VH			
[0403]	<400> 18			
[0404]	Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu			
[0405]	1	5	10	15
[0406]	Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp			
[0407]	20	25	30	
[0408]	Phe Ala Trp Asp Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp			
[0409]	35	40	45	
[0410]	Met Gly His Ile Arg Phe Ser Gly Thr Thr Ser Tyr Asn Pro Ser Leu			
[0411]	50	55	60	
[0412]	Lys Ser Arg Ile Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Phe			
[0413]	65	70	75	80
[0414]	Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Thr Tyr Tyr Cys			
[0415]	85	90	95	
[0416]	Ala Arg Ser Thr Leu Ile Thr Lys Gly Phe Phe Asp Tyr Trp Gly Gln			
[0417]	100	105	110	
[0418]	Gly Thr Leu Leu Thr Val Ser Ser			
[0419]	115	120		
[0420]	<210> 19			
[0421]	<211> 120			
[0422]	<212> PRT			
[0423]	<213> 人工序列(Artificial Sequence)			
[0424]	<220>			
[0425]	<223> 人源化VH			
[0426]	<400> 19			
[0427]	Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu			
[0428]	1	5	10	15

[0429]	Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Tyr	Ser	Ile	Thr	Ser	Asp
[0430]				20					25					30		
[0431]	Phe	Ala	Trp	Asp	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp
[0432]			35					40					45			
[0433]	Ile	Gly	His	Ile	Arg	Phe	Ser	Gly	Thr	Thr	Ser	Tyr	Asn	Pro	Ser	Leu
[0434]		50					55				60					
[0435]	Lys	Ser	Arg	Val	Thr	Ile	Ser	Val	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Ser
[0436]	65					70				75					80	
[0437]	Leu	Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[0438]					85					90				95		
[0439]	Ala	Arg	Ser	Thr	Leu	Ile	Thr	Lys	Gly	Phe	Phe	Asp	Tyr	Trp	Gly	Gln
[0440]				100					105					110		
[0441]	Gly	Thr	Leu	Leu	Thr	Val	Ser	Ser								
[0442]				115					120							
[0443]	<210> 20															
[0444]	<211> 120															
[0445]	<212> PRT															
[0446]	<213> 人工序列(Artificial Sequence)															
[0447]	<220>															
[0448]	<223> 人源化VH															
[0449]	<400> 20															
[0450]	Glu	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu
[0451]	1			5					10					15		
[0452]	Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Tyr	Ser	Ile	Thr	Ser	Asp
[0453]				20					25					30		
[0454]	Phe	Ala	Trp	Asp	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp
[0455]			35					40					45			
[0456]	Ile	Gly	His	Ile	Arg	Phe	Ser	Gly	Thr	Thr	Ser	Tyr	Asn	Pro	Ser	Leu
[0457]		50					55				60					
[0458]	Lys	Ser	Arg	Val	Thr	Ile	Ser	Arg	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Ser
[0459]	65					70					75				80	
[0460]	Leu	Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[0461]					85					90				95		
[0462]	Ala	Arg	Ser	Thr	Leu	Ile	Thr	Lys	Gly	Phe	Phe	Asp	Tyr	Trp	Gly	Gln
[0463]				100					105					110		
[0464]	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser								
[0465]				115					120							
[0466]	<210> 21															
[0467]	<211> 119															

[0468]	<212>	PRT
[0469]	<213>	人工序列(Artificial Sequence)
[0470]	<220>	
[0471]	<223>	人源化VH
[0472]	<400>	21
[0473]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala	
[0474]	1 5 10 15	
[0475]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr	
[0476]	20 25 30	
[0477]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met	
[0478]	35 40 45	
[0479]	Gly Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe	
[0480]	50 55 60	
[0481]	Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr	
[0482]	65 70 75 80	
[0483]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys	
[0484]	85 90 95	
[0485]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly	
[0486]	100 105 110	
[0487]	Thr Thr Val Thr Val Ser Ser	
[0488]	115	
[0489]	<210>	22
[0490]	<211>	119
[0491]	<212>	PRT
[0492]	<213>	人工序列(Artificial Sequence)
[0493]	<220>	
[0494]	<223>	人源化VH
[0495]	<400>	22
[0496]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala	
[0497]	1 5 10 15	
[0498]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr	
[0499]	20 25 30	
[0500]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile	
[0501]	35 40 45	
[0502]	Gly Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe	
[0503]	50 55 60	
[0504]	Lys Gly Arg Ala Thr Leu Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr	
[0505]	65 70 75 80	
[0506]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys	

[0507]	85	90	95
[0508]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly		
[0509]	100	105	110
[0510]	Thr Thr Val Thr Val Ser Ser		
[0511]	115		
[0512]	<210> 23		
[0513]	<211> 119		
[0514]	<212> PRT		
[0515]	<213> 人工序列(Artificial Sequence)		
[0516]	<220>		
[0517]	<223> 人源化VH		
[0518]	<400> 23		
[0519]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[0520]	1 5 10 15		
[0521]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[0522]	20 25 30		
[0523]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile		
[0524]	35 40 45		
[0525]	Gly Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe		
[0526]	50 55 60		
[0527]	Lys Gly Arg Ala Thr Leu Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr		
[0528]	65 70 75 80		
[0529]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys		
[0530]	85 90 95		
[0531]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly		
[0532]	100 105 110		
[0533]	Thr Thr Val Thr Val Ser Ser		
[0534]	115		
[0535]	<210> 24		
[0536]	<211> 119		
[0537]	<212> PRT		
[0538]	<213> 人工序列(Artificial Sequence)		
[0539]	<220>		
[0540]	<223> 人源化VH		
[0541]	<400> 24		
[0542]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[0543]	1 5 10 15		
[0544]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[0545]	20 25 30		

[0546]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
[0547]	35 40 45
[0548]	Gly Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe
[0549]	50 55 60
[0550]	Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
[0551]	65 70 75 80
[0552]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
[0553]	85 90 95
[0554]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[0555]	100 105 110
[0556]	Thr Thr Val Thr Val Ser Ser
[0557]	115
[0558]	<210> 25
[0559]	<211> 119
[0560]	<212> PRT
[0561]	<213> 人工序列(Artificial Sequence)
[0562]	<220>
[0563]	<223> 人源化VH
[0564]	<400> 25
[0565]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[0566]	1 5 10 15
[0567]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[0568]	20 25 30
[0569]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
[0570]	35 40 45
[0571]	Gly Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe
[0572]	50 55 60
[0573]	Lys Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
[0574]	65 70 75 80
[0575]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
[0576]	85 90 95
[0577]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[0578]	100 105 110
[0579]	Thr Thr Val Thr Val Ser Ser
[0580]	115
[0581]	<210> 26
[0582]	<211> 119
[0583]	<212> PRT
[0584]	<213> 人工序列(Artificial Sequence)

[0585] <220>
 [0586] <223> 人源化VH
 [0587] <400> 26
 [0588] Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 [0589] 1 5 10 15
 [0590] Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
 [0591] 20 25 30
 [0592] Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 [0593] 35 40 45
 [0594] Gly Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe
 [0595] 50 55 60
 [0596] Lys Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
 [0597] 65 70 75 80
 [0598] Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 [0599] 85 90 95
 [0600] Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
 [0601] 100 105 110
 [0602] Thr Thr Val Thr Val Ser Ser
 [0603] 115
 [0604] <210> 27
 [0605] <211> 119
 [0606] <212> PRT
 [0607] <213> 人工序列(Artificial Sequence)
 [0608] <220>
 [0609] <223> 具有CDR2突变的人源化VH
 [0610] <400> 27
 [0611] Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 [0612] 1 5 10 15
 [0613] Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
 [0614] 20 25 30
 [0615] Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 [0616] 35 40 45
 [0617] Gly Glu Ile Phe Pro Arg Arg Val Gln Thr Tyr Tyr Ser Glu Lys Phe
 [0618] 50 55 60
 [0619] Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
 [0620] 65 70 75 80
 [0621] Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 [0622] 85 90 95
 [0623] Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly

[0624]	100	105	110
[0625]	Thr Thr Val Thr Val Ser Ser		
[0626]	115		
[0627]	<210> 28		
[0628]	<211> 119		
[0629]	<212> PRT		
[0630]	<213> 人工序列(Artificial Sequence)		
[0631]	<220>		
[0632]	<223> 具有CDR2突变的人源化VH		
[0633]	<400> 28		
[0634]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[0635]	1 5 10 15		
[0636]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[0637]	20 25 30		
[0638]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile		
[0639]	35 40 45		
[0640]	Gly Glu Ile Phe Pro Arg Arg Val Gln Thr Tyr Tyr Ser Glu Lys Phe		
[0641]	50 55 60		
[0642]	Lys Gly Arg Ala Thr Leu Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr		
[0643]	65 70 75 80		
[0644]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys		
[0645]	85 90 95		
[0646]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly		
[0647]	100 105 110		
[0648]	Thr Thr Val Thr Val Ser Ser		
[0649]	115		
[0650]	<210> 29		
[0651]	<211> 119		
[0652]	<212> PRT		
[0653]	<213> 人工序列(Artificial Sequence)		
[0654]	<220>		
[0655]	<223> 具有CDR2突变的人源化VH		
[0656]	<400> 29		
[0657]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[0658]	1 5 10 15		
[0659]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[0660]	20 25 30		
[0661]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile		
[0662]	35 40 45		

[0663]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Gln	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[0664]		50					55					60				
[0665]	Lys	Gly	Arg	Ala	Thr	Leu	Thr	Ala	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
[0666]	65					70				75					80	
[0667]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Phe	Cys
[0668]					85					90					95	
[0669]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[0670]				100					105					110		
[0671]	Thr	Thr	Val	Thr	Val	Ser	Ser									
[0672]				115												
[0673]	<210>	30														
[0674]	<211>	119														
[0675]	<212>	PRT														
[0676]	<213>	人工序列 (Artificial Sequence)														
[0677]	<220>															
[0678]	<223>	具有CDR2突变的人源化VH														
[0679]	<400>	30														
[0680]	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
[0681]	1			5					10					15		
[0682]	Ser	Val	Lys	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Gly	Tyr
[0683]			20					25					30			
[0684]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
[0685]		35				40						45				
[0686]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Gln	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[0687]		50				55						60				
[0688]	Lys	Gly	Arg	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
[0689]	65					70					75				80	
[0690]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[0691]					85					90					95	
[0692]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[0693]				100					105					110		
[0694]	Thr	Thr	Val	Thr	Val	Ser	Ser									
[0695]				115												
[0696]	<210>	31														
[0697]	<211>	119														
[0698]	<212>	PRT														
[0699]	<213>	人工序列 (Artificial Sequence)														
[0700]	<220>															
[0701]	<223>	具有CDR2突变的人源化VH														

109

[0741]	115
[0742]	<210> 33
[0743]	<211> 119
[0744]	<212> PRT
[0745]	<213> 人工序列(Artificial Sequence)
[0746]	<220>
[0747]	<223> 具有CDR2突变的人源化VH
[0748]	<400> 33
[0749]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[0750]	1 5 10 15
[0751]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[0752]	20 25 30
[0753]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
[0754]	35 40 45
[0755]	Gly Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe
[0756]	50 55 60
[0757]	Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
[0758]	65 70 75 80
[0759]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
[0760]	85 90 95
[0761]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[0762]	100 105 110
[0763]	Thr Thr Val Thr Val Ser Ser
[0764]	115
[0765]	<210> 34
[0766]	<211> 119
[0767]	<212> PRT
[0768]	<213> 人工序列(Artificial Sequence)
[0769]	<220>
[0770]	<223> 具有CDR2突变的人源化VH
[0771]	<400> 34
[0772]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[0773]	1 5 10 15
[0774]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[0775]	20 25 30
[0776]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
[0777]	35 40 45
[0778]	Gly Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe
[0779]	50 55 60

[0780]	Lys Gly Arg Ala Thr Leu Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
[0781]	65 70 75 80
[0782]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
[0783]	85 90 95
[0784]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[0785]	100 105 110
[0786]	Thr Thr Val Thr Val Ser Ser
[0787]	115
[0788]	<210> 35
[0789]	<211> 119
[0790]	<212> PRT
[0791]	<213> 人工序列(Artificial Sequence)
[0792]	<220>
[0793]	<223> 具有CDR2突变的人源化VH
[0794]	<400> 35
[0795]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[0796]	1 5 10 15
[0797]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[0798]	20 25 30
[0799]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
[0800]	35 40 45
[0801]	Gly Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe
[0802]	50 55 60
[0803]	Lys Gly Arg Ala Thr Leu Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
[0804]	65 70 75 80
[0805]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
[0806]	85 90 95
[0807]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[0808]	100 105 110
[0809]	Thr Thr Val Thr Val Ser Ser
[0810]	115
[0811]	<210> 36
[0812]	<211> 119
[0813]	<212> PRT
[0814]	<213> 人工序列(Artificial Sequence)
[0815]	<220>
[0816]	<223> 具有CDR2突变的人源化VH
[0817]	<400> 36
[0818]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala

[0819]	1	5	10	15
[0820]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr			
[0821]	20	25	30	
[0822]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met			
[0823]	35	40	45	
[0824]	Gly Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe			
[0825]	50	55	60	
[0826]	Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr			
[0827]	65	70	75	80
[0828]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys			
[0829]	85	90	95	
[0830]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly			
[0831]	100	105	110	
[0832]	Thr Thr Val Thr Val Ser Ser			
[0833]	115			
[0834]	<210> 37			
[0835]	<211> 119			
[0836]	<212> PRT			
[0837]	<213> 人工序列(Artificial Sequence)			
[0838]	<220>			
[0839]	<223> 具有CDR2突变的人源化VH			
[0840]	<400> 37			
[0841]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala			
[0842]	1	5	10	15
[0843]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr			
[0844]	20	25	30	
[0845]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met			
[0846]	35	40	45	
[0847]	Gly Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe			
[0848]	50	55	60	
[0849]	Lys Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr			
[0850]	65	70	75	80
[0851]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys			
[0852]	85	90	95	
[0853]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly			
[0854]	100	105	110	
[0855]	Thr Thr Val Thr Val Ser Ser			
[0856]	115			
[0857]	<210> 38			

[0858] <211> 119
 [0859] <212> PRT
 [0860] <213> 人工序列(Artificial Sequence)
 [0861] <220>
 [0862] <223> 具有CDR2突变的人源化VH
 [0863] <400> 38
 [0864] Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 [0865] 1 5 10 15
 [0866] Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
 [0867] 20 25 30
 [0868] Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 [0869] 35 40 45
 [0870] Gly Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe
 [0871] 50 55 60
 [0872] Lys Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
 [0873] 65 70 75 80
 [0874] Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 [0875] 85 90 95
 [0876] Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
 [0877] 100 105 110
 [0878] Thr Thr Val Thr Val Ser Ser
 [0879] 115
 [0880] <210> 39
 [0881] <211> 119
 [0882] <212> PRT
 [0883] <213> 人工序列(Artificial Sequence)
 [0884] <220>
 [0885] <223> 具有CDR2突变的人源化VH
 [0886] <400> 39
 [0887] Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 [0888] 1 5 10 15
 [0889] Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
 [0890] 20 25 30
 [0891] Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 [0892] 35 40 45
 [0893] Gly Glu Ile Phe Pro Arg Arg Val Ala Thr Tyr Tyr Ser Glu Lys Phe
 [0894] 50 55 60
 [0895] Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
 [0896] 65 70 75 80

[0897]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
[0898]	85 90 95
[0899]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[0900]	100 105 110
[0901]	Thr Thr Val Thr Val Ser Ser
[0902]	115
[0903]	<210> 40
[0904]	<211> 119
[0905]	<212> PRT
[0906]	<213> 人工序列(Artificial Sequence)
[0907]	<220>
[0908]	<223> 具有CDR2突变的人源化VH
[0909]	<400> 40
[0910]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[0911]	1 5 10 15
[0912]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[0913]	20 25 30
[0914]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
[0915]	35 40 45
[0916]	Gly Glu Ile Phe Pro Arg Arg Val Ala Thr Tyr Tyr Ser Glu Lys Phe
[0917]	50 55 60
[0918]	Lys Gly Arg Ala Thr Leu Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
[0919]	65 70 75 80
[0920]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
[0921]	85 90 95
[0922]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[0923]	100 105 110
[0924]	Thr Thr Val Thr Val Ser Ser
[0925]	115
[0926]	<210> 41
[0927]	<211> 119
[0928]	<212> PRT
[0929]	<213> 人工序列(Artificial Sequence)
[0930]	<220>
[0931]	<223> 具有CDR2突变的人源化VH
[0932]	<400> 41
[0933]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[0934]	1 5 10 15
[0935]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr

[0936]	20	25	30
[0937]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile		
[0938]	35	40	45
[0939]	Gly Glu Ile Phe Pro Arg Arg Val Ala Thr Tyr Tyr Ser Glu Lys Phe		
[0940]	50	55	60
[0941]	Lys Gly Arg Ala Thr Leu Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr		
[0942]	65	70	75
[0943]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys		
[0944]	85	90	95
[0945]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly		
[0946]	100	105	110
[0947]	Thr Thr Val Thr Val Ser Ser		
[0948]	115		
[0949]	<210> 42		
[0950]	<211> 119		
[0951]	<212> PRT		
[0952]	<213> 人工序列(Artificial Sequence)		
[0953]	<220>		
[0954]	<223> 具有CDR2突变的人源化VH		
[0955]	<400> 42		
[0956]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[0957]	1	5	10
[0958]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[0959]	20	25	30
[0960]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met		
[0961]	35	40	45
[0962]	Gly Glu Ile Phe Pro Arg Arg Val Ala Thr Tyr Tyr Ser Glu Lys Phe		
[0963]	50	55	60
[0964]	Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr		
[0965]	65	70	75
[0966]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys		
[0967]	85	90	95
[0968]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly		
[0969]	100	105	110
[0970]	Thr Thr Val Thr Val Ser Ser		
[0971]	115		
[0972]	<210> 43		
[0973]	<211> 119		
[0974]	<212> PRT		

[0975] <213> 人工序列(Artificial Sequence)
 [0976] <220>
 [0977] <223> 具有CDR2突变的人源化VH
 [0978] <400> 43
 [0979] Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 [0980] 1 5 10 15
 [0981] Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
 [0982] 20 25 30
 [0983] Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 [0984] 35 40 45
 [0985] Gly Glu Ile Phe Pro Arg Arg Val Ala Thr Tyr Tyr Ser Glu Lys Phe
 [0986] 50 55 60
 [0987] Lys Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
 [0988] 65 70 75 80
 [0989] Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 [0990] 85 90 95
 [0991] Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
 [0992] 100 105 110
 [0993] Thr Thr Val Thr Val Ser Ser
 [0994] 115
 [0995] <210> 44
 [0996] <211> 119
 [0997] <212> PRT
 [0998] <213> 人工序列(Artificial Sequence)
 [0999] <220>
 [1000] <223> 具有CDR2突变的人源化VH
 [1001] <400> 44
 [1002] Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 [1003] 1 5 10 15
 [1004] Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
 [1005] 20 25 30
 [1006] Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 [1007] 35 40 45
 [1008] Gly Glu Ile Phe Pro Arg Arg Val Ala Thr Tyr Tyr Ser Glu Lys Phe
 [1009] 50 55 60
 [1010] Lys Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
 [1011] 65 70 75 80
 [1012] Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 [1013] 85 90 95

[1014]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[1015]	100 105 110
[1016]	Thr Thr Val Thr Val Ser Ser
[1017]	115
[1018]	<210> 45
[1019]	<211> 111
[1020]	<212> PRT
[1021]	<213> 人工序列(Artificial Sequence)
[1022]	<220>
[1023]	<223> 小鼠VL
[1024]	<400> 45
[1025]	Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
[1026]	1 5 10 15
[1027]	Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Thr Tyr
[1028]	20 25 30
[1029]	Gly Asp Ser Phe Met His Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro
[1030]	35 40 45
[1031]	Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
[1032]	50 55 60
[1033]	Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn
[1034]	65 70 75 80
[1035]	Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
[1036]	85 90 95
[1037]	Glu Ala Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
[1038]	100 105 110
[1039]	<210> 46
[1040]	<211> 107
[1041]	<212> PRT
[1042]	<213> 人工序列(Artificial Sequence)
[1043]	<220>
[1044]	<223> 小鼠VL
[1045]	<400> 46
[1046]	Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
[1047]	1 5 10 15
[1048]	Gly Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Pro Ala
[1049]	20 25 30
[1050]	Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
[1051]	35 40 45
[1052]	Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly

[1053]	50	55	60
[1054]	Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Thr		
[1055]	65	70	75
[1056]	Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp		
[1057]	85	90	95
[1058]	Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys		
[1059]	100	105	
[1060]	<210> 47		
[1061]	<211> 107		
[1062]	<212> PRT		
[1063]	<213> 人工序列(Artificial Sequence)		
[1064]	<220>		
[1065]	<223> 小鼠VL		
[1066]	<400> 47		
[1067]	Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly		
[1068]	1	5	10
[1069]	Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala		
[1070]	20	25	30
[1071]	Val Asp Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile		
[1072]	35	40	45
[1073]	Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly		
[1074]	50	55	60
[1075]	Ser Gly Ser Gly Thr Ala Phe Thr Phe Thr Ile Ser Ser Glu Gln Ala		
[1076]	65	70	75
[1077]	Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Val Pro Phe		
[1078]	85	90	95
[1079]	Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys		
[1080]	100	105	
[1081]	<210> 48		
[1082]	<211> 106		
[1083]	<212> PRT		
[1084]	<213> 人工序列(Artificial Sequence)		
[1085]	<220>		
[1086]	<223> 小鼠VL		
[1087]	<400> 48		
[1088]	Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly		
[1089]	1	5	10
[1090]	Glu Lys Val Thr Ile Ser Cys Ser Ala Ser Ser Phe Ile Asn Tyr Met		
[1091]	20	25	30

[1092]	Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Leu
[1093]	35 40 45
[1094]	Arg Thr Ser Thr Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
[1095]	50 55 60
[1096]	Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
[1097]	65 70 75 80
[1098]	Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Tyr His Ser Tyr Pro Leu Thr
[1099]	85 90 95
[1100]	Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
[1101]	100 105
[1102]	<210> 49
[1103]	<211> 107
[1104]	<212> PRT
[1105]	<213> 人工序列(Artificial Sequence)
[1106]	<220>
[1107]	<223> 小鼠VL
[1108]	<400> 49
[1109]	Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
[1110]	1 5 10 15
[1111]	Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala
[1112]	20 25 30
[1113]	Val Asp Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
[1114]	35 40 45
[1115]	Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
[1116]	50 55 60
[1117]	Ser Gly Ser Gly Thr Ala Phe Thr Phe Thr Ile Ser Gly Glu Gln Ala
[1118]	65 70 75 80
[1119]	Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Ile Pro Phe
[1120]	85 90 95
[1121]	Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
[1122]	100 105
[1123]	<210> 50
[1124]	<211> 108
[1125]	<212> PRT
[1126]	<213> 人工序列(Artificial Sequence)
[1127]	<220>
[1128]	<223> 小鼠VL
[1129]	<400> 50
[1130]	Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly

[1131]	1	5	10	15
[1132]	Glu Lys Val Thr Leu Thr Cys Ser Ala Ser Ser Ser Val Ser Ser Ser			
[1133]	20	25	30	
[1134]	Tyr Leu Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Leu Trp			
[1135]	35	40	45	
[1136]	Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser			
[1137]	50	55	60	
[1138]	Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Val Ser Ser Met Glu			
[1139]	65	70	75	80
[1140]	Ala Glu Asp Ala Ala Ser Tyr Phe Cys His Gln Trp Ser Ser Tyr Pro			
[1141]	85	90	95	
[1142]	Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys			
[1143]	100	105		
[1144]	<210> 51			
[1145]	<211> 112			
[1146]	<212> PRT			
[1147]	<213> 人工序列(Artificial Sequence)			
[1148]	<220>			
[1149]	<223> 小鼠VL			
[1150]	<400> 51			
[1151]	Ser Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly			
[1152]	1	5	10	15
[1153]	Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Asn Ile Val Tyr Ser			
[1154]	20	25	30	
[1155]	Asp Gly Asp Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser			
[1156]	35	40	45	
[1157]	Pro Lys Leu Leu Ile Phe Lys Val Ser Asn Arg Phe Phe Gly Val Pro			
[1158]	50	55	60	
[1159]	Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile			
[1160]	65	70	75	80
[1161]	Asn Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly			
[1162]	85	90	95	
[1163]	Ser His Val Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys			
[1164]	100	105	110	
[1165]	<210> 52			
[1166]	<211> 112			
[1167]	<212> PRT			
[1168]	<213> 人工序列(Artificial Sequence)			
[1169]	<220>			

[1170]	<223>	小鼠VL
[1171]	<400>	52
[1172]	Asp Val Leu Met Asn Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly	
[1173]	1	5 10 15
[1174]	Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Asn Ile Val Tyr Ser	
[1175]	20	25 30
[1176]	Asp Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser	
[1177]	35	40 45
[1178]	Pro Lys Leu Leu Ile Phe Gln Val Ser Asn Arg Phe Ser Gly Val Pro	
[1179]	50	55 60
[1180]	Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile	
[1181]	65	70 75 80
[1182]	Ser Arg Val Glu Ala Glu Asp Leu Gly Phe Tyr Tyr Cys Phe Gln Gly	
[1183]	85	90 95
[1184]	Ser His Val Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys	
[1185]	100	105 110
[1186]	<210>	53
[1187]	<211>	107
[1188]	<212>	PRT
[1189]	<213>	人工序列(Artificial Sequence)
[1190]	<220>	
[1191]	<223>	小鼠VL
[1192]	<400>	53
[1193]	Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly	
[1194]	1	5 10 15
[1195]	Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr	
[1196]	20	25 30
[1197]	Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile	
[1198]	35	40 45
[1199]	Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly	
[1200]	50	55 60
[1201]	Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln	
[1202]	65	70 75 80
[1203]	Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Phe Pro Trp	
[1204]	85	90 95
[1205]	Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys	
[1206]	100	105
[1207]	<210>	54
[1208]	<211>	106

[1209]	<212>	PRT
[1210]	<213>	人工序列(Artificial Sequence)
[1211]	<220>	
[1212]	<223>	小鼠VL
[1213]	<400>	54
[1214]	Gln Ile Val Leu Thr Gln Ser Pro Ala Leu Met Ser Ala Ser Pro Gly	
[1215]	1 5 10 15	
[1216]	Glu Arg Val Thr Met Thr Cys Ser Ala Ser Ser Asp Val Ser Tyr Met	
[1217]	20 25 30	
[1218]	Tyr Trp Tyr Gln Gln Lys Pro Arg Ser Ser Pro Lys Pro Trp Ile Tyr	
[1219]	35 40 45	
[1220]	Leu Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser	
[1221]	50 55 60	
[1222]	Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu	
[1223]	65 70 75 80	
[1224]	Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Gly Asn Pro Leu Thr	
[1225]	85 90 95	
[1226]	Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys	
[1227]	100 105	
[1228]	<210>	55
[1229]	<211>	112
[1230]	<212>	PRT
[1231]	<213>	人工序列(Artificial Sequence)
[1232]	<220>	
[1233]	<223>	小鼠VL
[1234]	<400>	55
[1235]	Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly	
[1236]	1 5 10 15	
[1237]	Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Asn Ile Val Tyr Ser	
[1238]	20 25 30	
[1239]	Asp Gly Asp Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser	
[1240]	35 40 45	
[1241]	Pro Lys Leu Leu Ile Phe Lys Val Ser Asn Arg Phe Ser Gly Val Pro	
[1242]	50 55 60	
[1243]	Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile	
[1244]	65 70 75 80	
[1245]	Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly	
[1246]	85 90 95	
[1247]	Ser His Val Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys	

[1248]	100	105	110
[1249]	<210> 56		
[1250]	<211> 111		
[1251]	<212> PRT		
[1252]	<213> 人工序列(Artificial Sequence)		
[1253]	<220>		
[1254]	<223> 小鼠VL		
[1255]	<400> 56		
[1256]	Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly		
[1257]	1 5 10 15		
[1258]	Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asp Tyr		
[1259]	20 25 30		
[1260]	Gly Asn Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro		
[1261]	35 40 45		
[1262]	Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Val		
[1263]	50 55 60		
[1264]	Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn		
[1265]	65 70 75 80		
[1266]	Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Ser Asn		
[1267]	85 90 95		
[1268]	Glu Asp Pro His Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys		
[1269]	100 105 110		
[1270]	<210> 57		
[1271]	<211> 107		
[1272]	<212> PRT		
[1273]	<213> 人工序列(Artificial Sequence)		
[1274]	<220>		
[1275]	<223> 具有CDR突变的小鼠VL		
[1276]	<400> 57		
[1277]	Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly		
[1278]	1 5 10 15		
[1279]	Gly Arg Val Ser Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Pro Ala		
[1280]	20 25 30		
[1281]	Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile		
[1282]	35 40 45		
[1283]	Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly		
[1284]	50 55 60		
[1285]	Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Thr		
[1286]	65 70 75 80		

[1287]	Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp
[1288]	85 90 95
[1289]	Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
[1290]	100 105
[1291]	<210> 58
[1292]	<211> 107
[1293]	<212> PRT
[1294]	<213> 人工序列(Artificial Sequence)
[1295]	<220>
[1296]	<223> 具有CDR突变的小鼠VL
[1297]	<400> 58
[1298]	Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
[1299]	1 5 10 15
[1300]	Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
[1301]	20 25 30
[1302]	Val Asp Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
[1303]	35 40 45
[1304]	Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
[1305]	50 55 60
[1306]	Ser Gly Ser Gly Thr Ala Phe Thr Phe Thr Ile Ser Gly Glu Gln Ala
[1307]	65 70 75 80
[1308]	Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Ile Pro Phe
[1309]	85 90 95
[1310]	Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
[1311]	100 105
[1312]	<210> 59
[1313]	<211> 107
[1314]	<212> PRT
[1315]	<213> 人工序列(Artificial Sequence)
[1316]	<220>
[1317]	<223> 人源化VL
[1318]	<400> 59
[1319]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
[1320]	1 5 10 15
[1321]	Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Pro Ala
[1322]	20 25 30
[1323]	Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
[1324]	35 40 45
[1325]	Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly

[1326]	50	55	60
[1327]	Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro		
[1328]	65	70	75
[1329]	Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp		
[1330]	85	90	95
[1331]	Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys		
[1332]	100	105	
[1333]	<210> 60		
[1334]	<211> 107		
[1335]	<212> PRT		
[1336]	<213> 人工序列(Artificial Sequence)		
[1337]	<220>		
[1338]	<223> 人源化VL		
[1339]	<400> 60		
[1340]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly		
[1341]	1	5	10
[1342]	Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Pro Ala		
[1343]	20	25	30
[1344]	Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile		
[1345]	35	40	45
[1346]	Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly		
[1347]	50	55	60
[1348]	Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro		
[1349]	65	70	75
[1350]	Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp		
[1351]	85	90	95
[1352]	Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys		
[1353]	100	105	
[1354]	<210> 61		
[1355]	<211> 107		
[1356]	<212> PRT		
[1357]	<213> 人工序列(Artificial Sequence)		
[1358]	<220>		
[1359]	<223> 人源化VL		
[1360]	<400> 61		
[1361]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Thr Ser Val Gly		
[1362]	1	5	10
[1363]	Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Pro Ala		
[1364]	20	25	30

[1365]	Val	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
[1366]			35					40					45			
[1367]	Tyr	Trp	Ala	Ser	Thr	Arg	His	Thr	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
[1368]			50					55					60			
[1369]	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Val	Gln	Pro
[1370]	65					70					75					80
[1371]	Glu	Asp	Leu	Ala	Leu	Tyr	Tyr	Cys	Gln	Gln	His	Tyr	Ser	Thr	Pro	Trp
[1372]					85					90					95	
[1373]	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys					
[1374]					100					105						
[1375]	<210> 62															
[1376]	<211> 107															
[1377]	<212> PRT															
[1378]	<213> 人工序列(Artificial Sequence)															
[1379]	<220>															
[1380]	<223> 人源化VL															
[1381]	<400> 62															
[1382]	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
[1383]	1				5					10					15	
[1384]	Asp	Arg	Val	Thr	Ile	Thr	Cys	Lys	Ala	Ser	Gln	Asp	Val	Ser	Thr	Ala
[1385]					20					25					30	
[1386]	Val	Asp	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
[1387]					35					40					45	
[1388]	Tyr	Ser	Ala	Ser	Tyr	Arg	Tyr	Thr	Gly	Val	Pro	Asp	Arg	Phe	Ser	Gly
[1389]					50					55					60	
[1390]	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Phe	Thr	Ile	Ser	Ser	Leu	Gln	Pro
[1391]	65					70					75					80
[1392]	Glu	Asp	Ile	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	His	Tyr	Ser	Ile	Pro	Phe
[1393]					85					90					95	
[1394]	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys					
[1395]					100					105						
[1396]	<210> 63															
[1397]	<211> 107															
[1398]	<212> PRT															
[1399]	<213> 人工序列(Artificial Sequence)															
[1400]	<220>															
[1401]	<223> 人源化VL															
[1402]	<400> 63															
[1403]	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Met	Ser	Ala	Ser	Val	Gly

[1404]	1	5	10	15
[1405]	Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala			
[1406]	20	25	30	
[1407]	Val Asp Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile			
[1408]	35	40	45	
[1409]	Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly			
[1410]	50	55	60	
[1411]	Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro			
[1412]	65	70	75	80
[1413]	Glu Asp Leu Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Ile Pro Phe			
[1414]	85	90	95	
[1415]	Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys			
[1416]	100	105		
[1417]	<210> 64			
[1418]	<211> 107			
[1419]	<212> PRT			
[1420]	<213> 人工序列(Artificial Sequence)			
[1421]	<220>			
[1422]	<223> 人源化VL			
[1423]	<400> 64			
[1424]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Met Ser Thr Ser Val Gly			
[1425]	1	5	10	15
[1426]	Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala			
[1427]	20	25	30	
[1428]	Val Asp Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile			
[1429]	35	40	45	
[1430]	Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly			
[1431]	50	55	60	
[1432]	Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Glu Gln Pro			
[1433]	65	70	75	80
[1434]	Glu Asp Leu Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Ile Pro Phe			
[1435]	85	90	95	
[1436]	Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys			
[1437]	100	105		
[1438]	<210> 65			
[1439]	<211> 107			
[1440]	<212> PRT			
[1441]	<213> 人工序列(Artificial Sequence)			
[1442]	<220>			

[1443] <223> 具有CDR1突变的人源化VL
 [1444] <400> 65
 [1445] Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 [1446] 1 5 10 15
 [1447] Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Pro Ala
 [1448] 20 25 30
 [1449] Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 [1450] 35 40 45
 [1451] Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
 [1452] 50 55 60
 [1453] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 [1454] 65 70 75 80
 [1455] Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp
 [1456] 85 90 95
 [1457] Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 [1458] 100 105
 [1459] <210> 66
 [1460] <211> 107
 [1461] <212> PRT
 [1462] <213> 人工序列(Artificial Sequence)
 [1463] <220>
 [1464] <223> 具有CDR1突变的人源化VL
 [1465] <400> 66
 [1466] Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 [1467] 1 5 10 15
 [1468] Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Pro Ala
 [1469] 20 25 30
 [1470] Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 [1471] 35 40 45
 [1472] Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
 [1473] 50 55 60
 [1474] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 [1475] 65 70 75 80
 [1476] Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp
 [1477] 85 90 95
 [1478] Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 [1479] 100 105
 [1480] <210> 67
 [1481] <211> 107

[1482]	<212>	PRT
[1483]	<213>	人工序列(Artificial Sequence)
[1484]	<220>	
[1485]	<223>	具有CDR1突变的人源化VL
[1486]	<400>	67
[1487]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Thr Ser Val Gly	
[1488]	1 5 10 15	
[1489]	Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Pro Ala	
[1490]	20 25 30	
[1491]	Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile	
[1492]	35 40 45	
[1493]	Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly	
[1494]	50 55 60	
[1495]	Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Pro	
[1496]	65 70 75 80	
[1497]	Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp	
[1498]	85 90 95	
[1499]	Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys	
[1500]	100 105	
[1501]	<210>	68
[1502]	<211>	107
[1503]	<212>	PRT
[1504]	<213>	人工序列(Artificial Sequence)
[1505]	<220>	
[1506]	<223>	具有CDR1突变的人源化VL
[1507]	<400>	68
[1508]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly	
[1509]	1 5 10 15	
[1510]	Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala	
[1511]	20 25 30	
[1512]	Val Asp Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile	
[1513]	35 40 45	
[1514]	Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly	
[1515]	50 55 60	
[1516]	Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro	
[1517]	65 70 75 80	
[1518]	Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Ile Pro Phe	
[1519]	85 90 95	
[1520]	Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys	

[1521]	100	105
[1522]	<210> 69	
[1523]	<211> 107	
[1524]	<212> PRT	
[1525]	<213> 人工序列(Artificial Sequence)	
[1526]	<220>	
[1527]	<223> 具有CDR1突变的人源化VL	
[1528]	<400> 69	
[1529]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Met Ser Ala Ser Val Gly	
[1530]	1	15
[1531]	Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala	
[1532]	20	30
[1533]	Val Asp Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile	
[1534]	35	45
[1535]	Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly	
[1536]	50	60
[1537]	Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro	
[1538]	65	80
[1539]	Glu Asp Leu Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Ile Pro Phe	
[1540]	85	95
[1541]	Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys	
[1542]	100	105
[1543]	<210> 70	
[1544]	<211> 107	
[1545]	<212> PRT	
[1546]	<213> 人工序列(Artificial Sequence)	
[1547]	<220>	
[1548]	<223> 具有CDR1突变的人源化VL	
[1549]	<400> 70	
[1550]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Met Ser Thr Ser Val Gly	
[1551]	1	15
[1552]	Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala	
[1553]	20	30
[1554]	Val Asp Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile	
[1555]	35	45
[1556]	Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly	
[1557]	50	60
[1558]	Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Glu Gln Pro	
[1559]	65	80

[1560]	Glu Asp Leu Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Ile Pro Phe
[1561]	85 90 95
[1562]	Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
[1563]	100 105
[1564]	<210> 71
[1565]	<211> 11
[1566]	<212> PRT
[1567]	<213> 人工序列(Artificial Sequence)
[1568]	<220>
[1569]	<223> 小鼠VH CDR1
[1570]	<400> 71
[1571]	Gly Tyr Ser Ile Thr Ser Gly Tyr Thr Trp His
[1572]	1 5 10
[1573]	<210> 72
[1574]	<211> 11
[1575]	<212> PRT
[1576]	<213> 人工序列(Artificial Sequence)
[1577]	<220>
[1578]	<223> 小鼠VH CDR1
[1579]	<400> 72
[1580]	Gly Tyr Ser Ile Thr Ser Asp Phe Ala Trp Asp
[1581]	1 5 10
[1582]	<210> 73
[1583]	<211> 10
[1584]	<212> PRT
[1585]	<213> 人工序列(Artificial Sequence)
[1586]	<220>
[1587]	<223> 小鼠VH CDR1
[1588]	<400> 73
[1589]	Gly Tyr Ile Phe Thr Gly Tyr Gly Ile Ser
[1590]	1 5 10
[1591]	<210> 74
[1592]	<211> 11
[1593]	<212> PRT
[1594]	<213> 人工序列(Artificial Sequence)
[1595]	<220>
[1596]	<223> 小鼠VH CDR1
[1597]	<400> 74
[1598]	Gly Tyr Ser Ile Thr Ser Gly Tyr Tyr Trp Asn

[1599]	1	5	10
[1600]	<210> 75		
[1601]	<211> 10		
[1602]	<212> PRT		
[1603]	<213> 人工序列(Artificial Sequence)		
[1604]	<220>		
[1605]	<223> 小鼠VH CDR1		
[1606]	<400> 75		
[1607]	Gly Tyr Ile Phe Thr Gly Tyr Gly Ile Thr		
[1608]	1	5	10
[1609]	<210> 76		
[1610]	<211> 10		
[1611]	<212> PRT		
[1612]	<213> 人工序列(Artificial Sequence)		
[1613]	<220>		
[1614]	<223> 小鼠VH CDR1		
[1615]	<400> 76		
[1616]	Gly Tyr Thr Phe Thr Asn Tyr Trp Ile Ser		
[1617]	1	5	10
[1618]	<210> 77		
[1619]	<211> 10		
[1620]	<212> PRT		
[1621]	<213> 人工序列(Artificial Sequence)		
[1622]	<220>		
[1623]	<223> 小鼠VH CDR1		
[1624]	<400> 77		
[1625]	Gly Phe Asn Ile Lys Asp Thr Tyr Ile His		
[1626]	1	5	10
[1627]	<210> 78		
[1628]	<211> 10		
[1629]	<212> PRT		
[1630]	<213> 人工序列(Artificial Sequence)		
[1631]	<220>		
[1632]	<223> 小鼠VH CDR1		
[1633]	<400> 78		
[1634]	Gly Phe Asn Ile Lys Asp Thr Tyr Ile His		
[1635]	1	5	10
[1636]	<210> 79		
[1637]	<211> 10		

[1638] <212> PRT
[1639] <213> 人工序列(Artificial Sequence)
[1640] <220>
[1641] <223> 小鼠VH CDR1
[1642] <400> 79
[1643] Gly Tyr Thr Phe Thr Ser Tyr Tyr Met His
[1644] 1 5 10
[1645] <210> 80
[1646] <211> 10
[1647] <212> PRT
[1648] <213> 人工序列(Artificial Sequence)
[1649] <220>
[1650] <223> 小鼠VH CDR1
[1651] <400> 80
[1652] Gly Tyr Thr Phe Thr Glu Tyr Ile Ile Tyr
[1653] 1 5 10
[1654] <210> 81
[1655] <211> 10
[1656] <212> PRT
[1657] <213> 人工序列(Artificial Sequence)
[1658] <220>
[1659] <223> 小鼠VH CDR1
[1660] <400> 81
[1661] Gly Phe Asn Ile Lys Asp Thr Tyr Ile His
[1662] 1 5 10
[1663] <210> 82
[1664] <211> 10
[1665] <212> PRT
[1666] <213> 人工序列(Artificial Sequence)
[1667] <220>
[1668] <223> 小鼠VH CDR1
[1669] <400> 82
[1670] Gly Tyr Glu Phe Ser Ser Asn Trp Met Asn
[1671] 1 5 10
[1672] <210> 83
[1673] <211> 16
[1674] <212> PRT
[1675] <213> 人工序列(Artificial Sequence)
[1676] <220>

[1677] <223> 小鼠VH CDR2
 [1678] <400> 83
 [1679] Tyr Ile His Tyr Ser Gly Ser Thr Lys Tyr Asn Pro Ser Leu Lys Ser
 [1680] 1 5 10 15
 [1681] <210> 84
 [1682] <211> 16
 [1683] <212> PRT
 [1684] <213> 人工序列(Artificial Sequence)
 [1685] <220>
 [1686] <223> 小鼠VH CDR2
 [1687] <400> 84
 [1688] His Ile Arg Phe Ser Gly Thr Thr Ser Tyr Asn Pro Ser Leu Lys Ser
 [1689] 1 5 10 15
 [1690] <210> 85
 [1691] <211> 17
 [1692] <212> PRT
 [1693] <213> 人工序列(Artificial Sequence)
 [1694] <220>
 [1695] <223> 小鼠VH CDR2
 [1696] <400> 85
 [1697] Glu Ile Phe Pro Arg Thr Ala Asn Thr Tyr Phe Asn Glu Lys Phe Lys
 [1698] 1 5 10 15
 [1699] Gly
 [1700] <210> 86
 [1701] <211> 16
 [1702] <212> PRT
 [1703] <213> 人工序列(Artificial Sequence)
 [1704] <220>
 [1705] <223> 小鼠VH CDR2
 [1706] <400> 86
 [1707] Ser Ile Asn Tyr Asp Gly Ser Asn Asp Tyr Asn Pro Ser Leu Gln Asp
 [1708] 1 5 10 15
 [1709] <210> 87
 [1710] <211> 17
 [1711] <212> PRT
 [1712] <213> 人工序列(Artificial Sequence)
 [1713] <220>
 [1714] <223> 小鼠VH CDR2
 [1715] <400> 87

[1716]	Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe Lys
[1717]	1 5 10 15
[1718]	Gly
[1719]	<210> 88
[1720]	<211> 17
[1721]	<212> PRT
[1722]	<213> 人工序列(Artificial Sequence)
[1723]	<220>
[1724]	<223> 小鼠VH CDR2
[1725]	<400> 88
[1726]	Asn Ile Tyr Pro Ser Asp Ser Tyr Thr Asn Tyr Asn Gln Asn Phe Lys
[1727]	1 5 10 15
[1728]	Asp
[1729]	<210> 89
[1730]	<211> 17
[1731]	<212> PRT
[1732]	<213> 人工序列(Artificial Sequence)
[1733]	<220>
[1734]	<223> 小鼠VH CDR2
[1735]	<400> 89
[1736]	Arg Ile Ala Pro Thr Asn Gly Asn Thr Lys Tyr Asp Pro Thr Phe Gln
[1737]	1 5 10 15
[1738]	Gly
[1739]	<210> 90
[1740]	<211> 17
[1741]	<212> PRT
[1742]	<213> 人工序列(Artificial Sequence)
[1743]	<220>
[1744]	<223> 小鼠VH CDR2
[1745]	<400> 90
[1746]	Arg Ile Ala Pro Thr Asn Gly Asn Ala Lys Phe His Pro Thr Phe Gln
[1747]	1 5 10 15
[1748]	Gly
[1749]	<210> 91
[1750]	<211> 17
[1751]	<212> PRT
[1752]	<213> 人工序列(Artificial Sequence)
[1753]	<220>
[1754]	<223> 小鼠VH CDR2

[1755]	<400> 91
[1756]	Trp Ile Tyr Pro Gly Asn Val Asn Thr Lys Tyr Asn Glu Lys Phe Lys
[1757]	1 5 10 15
[1758]	Gly
[1759]	<210> 92
[1760]	<211> 17
[1761]	<212> PRT
[1762]	<213> 人工序列(Artificial Sequence)
[1763]	<220>
[1764]	<223> 小鼠VH CDR2
[1765]	<400> 92
[1766]	Trp Phe Tyr Pro Gly Thr Gly Ser Ile Lys Tyr Asn Glu Lys Phe Lys
[1767]	1 5 10 15
[1768]	Asp
[1769]	<210> 93
[1770]	<211> 17
[1771]	<212> PRT
[1772]	<213> 人工序列(Artificial Sequence)
[1773]	<220>
[1774]	<223> 小鼠VH CDR2
[1775]	<400> 93
[1776]	Arg Ile Glu Pro Ala Asn Gly Asn Thr Lys Tyr Asp Pro Thr Phe Gln
[1777]	1 5 10 15
[1778]	Gly
[1779]	<210> 94
[1780]	<211> 17
[1781]	<212> PRT
[1782]	<213> 人工序列(Artificial Sequence)
[1783]	<220>
[1784]	<223> 小鼠VH CDR2
[1785]	<400> 94
[1786]	Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Arg
[1787]	1 5 10 15
[1788]	Gly
[1789]	<210> 95
[1790]	<211> 17
[1791]	<212> PRT
[1792]	<213> 人工序列(Artificial Sequence)
[1793]	<220>

[1794] <223> 具有CDR突变的小鼠VH CDR2
[1795] <400> 95
[1796] Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe Lys
[1797] 1 5 10 15
[1798] Gly
[1799] <210> 96
[1800] <211> 17
[1801] <212> PRT
[1802] <213> 人工序列(Artificial Sequence)
[1803] <220>
[1804] <223> 具有CDR突变的小鼠VH CDR2
[1805] <400> 96
[1806] Glu Ile Phe Pro Arg Arg Val Ala Thr Tyr Tyr Ser Glu Lys Phe Lys
[1807] 1 5 10 15
[1808] Gly
[1809] <210> 97
[1810] <211> 17
[1811] <212> PRT
[1812] <213> 人工序列(Artificial Sequence)
[1813] <220>
[1814] <223> 具有CDR突变的小鼠VH CDR2
[1815] <400> 97
[1816] Glu Ile Phe Pro Arg Arg Val Gln Thr Tyr Tyr Ser Glu Lys Phe Lys
[1817] 1 5 10 15
[1818] Gly
[1819] <210> 98
[1820] <211> 6
[1821] <212> PRT
[1822] <213> 人工序列(Artificial Sequence)
[1823] <220>
[1824] <223> 小鼠VH CDR3
[1825] <400> 98
[1826] Asn Ser Leu Phe Ala Ser
[1827] 1 5
[1828] <210> 99
[1829] <211> 11
[1830] <212> PRT
[1831] <213> 人工序列(Artificial Sequence)
[1832] <220>

- [1833] <223> 小鼠VH CDR3
[1834] <400> 99
[1835] Ser Thr Leu Ile Thr Lys Gly Phe Phe Asp Tyr
[1836] 1 5 10
[1837] <210> 100
[1838] <211> 10
[1839] <212> PRT
[1840] <213> 人工序列(Artificial Sequence)
[1841] <220>
[1842] <223> 小鼠VH CDR3
[1843] <400> 100
[1844] Asp Tyr Asp Pro Tyr Tyr Ala Leu Asp Tyr
[1845] 1 5 10
[1846] <210> 101
[1847] <211> 4
[1848] <212> PRT
[1849] <213> 人工序列(Artificial Sequence)
[1850] <220>
[1851] <223> 小鼠VH CDR3
[1852] <400> 101
[1853] Arg Leu Asp Tyr
[1854] 1
[1855] <210> 102
[1856] <211> 10
[1857] <212> PRT
[1858] <213> 人工序列(Artificial Sequence)
[1859] <220>
[1860] <223> 小鼠VH CDR3
[1861] <400> 102
[1862] Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr
[1863] 1 5 10
[1864] <210> 103
[1865] <211> 12
[1866] <212> PRT
[1867] <213> 人工序列(Artificial Sequence)
[1868] <220>
[1869] <223> 小鼠VH CDR3
[1870] <400> 103
[1871] Gly Ile Ile Thr Val Ile Ala Thr Arg Asp Asp Tyr

[1872]	1	5	10
[1873]	<210> 104		
[1874]	<211> 14		
[1875]	<212> PRT		
[1876]	<213> 人工序列(Artificial Sequence)		
[1877]	<220>		
[1878]	<223> 小鼠VH CDR3		
[1879]	<400> 104		
[1880]	Gly Gly Ile Tyr Tyr Tyr Gly Ser His Trp Tyr Phe Asp Val		
[1881]	1	5	10
[1882]	<210> 105		
[1883]	<211> 14		
[1884]	<212> PRT		
[1885]	<213> 人工序列(Artificial Sequence)		
[1886]	<220>		
[1887]	<223> 小鼠VH CDR3		
[1888]	<400> 105		
[1889]	Gly Gly Ile Tyr Tyr Tyr Gly Thr His Trp Tyr Phe Asp Val		
[1890]	1	5	10
[1891]	<210> 106		
[1892]	<211> 11		
[1893]	<212> PRT		
[1894]	<213> 人工序列(Artificial Sequence)		
[1895]	<220>		
[1896]	<223> 小鼠VH CDR3		
[1897]	<400> 106		
[1898]	Tyr Gly Asn Tyr Gly Gly Trp Tyr Phe Asp Val		
[1899]	1	5	10
[1900]	<210> 107		
[1901]	<211> 10		
[1902]	<212> PRT		
[1903]	<213> 人工序列(Artificial Sequence)		
[1904]	<220>		
[1905]	<223> 小鼠VH CDR3		
[1906]	<400> 107		
[1907]	His Glu Glu Gly Asn Leu Trp Phe Ala Tyr		
[1908]	1	5	10
[1909]	<210> 108		
[1910]	<211> 14		

[1911] <212> PRT
[1912] <213> 人工序列(Artificial Sequence)
[1913] <220>
[1914] <223> 小鼠VH CDR3
[1915] <400> 108
[1916] Gly Gly Ile Tyr Tyr Tyr Gly Ser His Trp Tyr Phe Asp Val
[1917] 1 5 10
[1918] <210> 109
[1919] <211> 9
[1920] <212> PRT
[1921] <213> 人工序列(Artificial Sequence)
[1922] <220>
[1923] <223> 小鼠VH CDR3
[1924] <400> 109
[1925] Gly Arg Ala Ser Phe Tyr Phe Asp Tyr
[1926] 1 5
[1927] <210> 110
[1928] <211> 15
[1929] <212> PRT
[1930] <213> 人工序列(Artificial Sequence)
[1931] <220>
[1932] <223> 小鼠VL CDR1
[1933] <400> 110
[1934] Arg Ala Ser Glu Ser Val Asp Thr Tyr Gly Asp Ser Phe Met His
[1935] 1 5 10 15
[1936] <210> 111
[1937] <211> 11
[1938] <212> PRT
[1939] <213> 人工序列(Artificial Sequence)
[1940] <220>
[1941] <223> 小鼠VL CDR1
[1942] <400> 111
[1943] Lys Ala Ser Gln Asp Val Ser Pro Ala Val Ala
[1944] 1 5 10
[1945] <210> 112
[1946] <211> 11
[1947] <212> PRT
[1948] <213> 人工序列(Artificial Sequence)
[1949] <220>

[1950] <223> 小鼠VL CDR1
[1951] <400> 112
[1952] Lys Ala Ser Gln Asp Val Ser Thr Ala Val Asp
[1953] 1 5 10
[1954] <210> 113
[1955] <211> 10
[1956] <212> PRT
[1957] <213> 人工序列(Artificial Sequence)
[1958] <220>
[1959] <223> 小鼠VL CDR1
[1960] <400> 113
[1961] Ser Ala Ser Ser Phe Ile Asn Tyr Met Tyr
[1962] 1 5 10
[1963] <210> 114
[1964] <211> 11
[1965] <212> PRT
[1966] <213> 人工序列(Artificial Sequence)
[1967] <220>
[1968] <223> 小鼠VL CDR1
[1969] <400> 114
[1970] Lys Ala Ser Gln Asp Val Ser Thr Ala Val Asp
[1971] 1 5 10
[1972] <210> 115
[1973] <211> 12
[1974] <212> PRT
[1975] <213> 人工序列(Artificial Sequence)
[1976] <220>
[1977] <223> 小鼠VL CDR1
[1978] <400> 115
[1979] Ser Ala Ser Ser Ser Val Ser Ser Ser Tyr Leu Tyr
[1980] 1 5 10
[1981] <210> 116
[1982] <211> 16
[1983] <212> PRT
[1984] <213> 人工序列(Artificial Sequence)
[1985] <220>
[1986] <223> 小鼠VL CDR1
[1987] <400> 116
[1988] Arg Ser Ser Gln Asn Ile Val Tyr Ser Asp Gly Asp Thr Tyr Leu Glu

[1989]	1	5	10	15
[1990]	<210> 117			
[1991]	<211> 16			
[1992]	<212> PRT			
[1993]	<213> 人工序列(Artificial Sequence)			
[1994]	<220>			
[1995]	<223> 小鼠VL CDR1			
[1996]	<400> 117			
[1997]	Arg Ser Ser Gln Asn Ile Val Tyr Ser Asp Gly Asn Thr Tyr Leu Glu			
[1998]	1	5	10	15
[1999]	<210> 118			
[2000]	<211> 11			
[2001]	<212> PRT			
[2002]	<213> 人工序列(Artificial Sequence)			
[2003]	<220>			
[2004]	<223> 小鼠VL CDR1			
[2005]	<400> 118			
[2006]	Arg Ala Ser Gln Asp Ile Gly Asn Tyr Leu Asn			
[2007]	1	5	10	
[2008]	<210> 119			
[2009]	<211> 10			
[2010]	<212> PRT			
[2011]	<213> 人工序列(Artificial Sequence)			
[2012]	<220>			
[2013]	<223> 小鼠VL CDR1			
[2014]	<400> 119			
[2015]	Ser Ala Ser Ser Asp Val Ser Tyr Met Tyr			
[2016]	1	5	10	
[2017]	<210> 120			
[2018]	<211> 16			
[2019]	<212> PRT			
[2020]	<213> 人工序列(Artificial Sequence)			
[2021]	<220>			
[2022]	<223> 小鼠VL CDR1			
[2023]	<400> 120			
[2024]	Arg Ser Ser Gln Asn Ile Val Tyr Ser Asp Gly Asp Thr Tyr Leu Glu			
[2025]	1	5	10	15
[2026]	<210> 121			
[2027]	<211> 15			

[2028]	<212>	PRT
[2029]	<213>	人工序列(Artificial Sequence)
[2030]	<220>	
[2031]	<223>	小鼠VL CDR1
[2032]	<400>	121
[2033]	Arg Ala Ser Glu Ser Val Asp Asp Tyr Gly Asn Ser Phe Met His	
[2034]	1	5 10 15
[2035]	<210>	122
[2036]	<211>	11
[2037]	<212>	PRT
[2038]	<213>	人工序列(Artificial Sequence)
[2039]	<220>	
[2040]	<223>	小鼠VL CDR1嵌合
[2041]	<400>	122
[2042]	Arg Ala Ser Gln Asp Val Ser Pro Ala Val Ala	
[2043]	1	5 10
[2044]	<210>	123
[2045]	<211>	11
[2046]	<212>	PRT
[2047]	<213>	人工序列(Artificial Sequence)
[2048]	<220>	
[2049]	<223>	小鼠VL CDR1嵌合
[2050]	<400>	123
[2051]	Arg Ala Ser Gln Asp Val Ser Thr Ala Val Asp	
[2052]	1	5 10
[2053]	<210>	124
[2054]	<211>	7
[2055]	<212>	PRT
[2056]	<213>	人工序列(Artificial Sequence)
[2057]	<220>	
[2058]	<223>	小鼠VL CDR2
[2059]	<400>	124
[2060]	Arg Ala Ser Asn Leu Glu Ser	
[2061]	1	5
[2062]	<210>	125
[2063]	<211>	7
[2064]	<212>	PRT
[2065]	<213>	人工序列(Artificial Sequence)
[2066]	<220>	

[2067] <223> 小鼠VL CDR2
[2068] <400> 125
[2069] Trp Ala Ser Thr Arg His Thr
[2070] 1 5
[2071] <210> 126
[2072] <211> 7
[2073] <212> PRT
[2074] <213> 人工序列(Artificial Sequence)
[2075] <220>
[2076] <223> 小鼠VL CDR2
[2077] <400> 126
[2078] Ser Ala Ser Tyr Arg Tyr Thr
[2079] 1 5
[2080] <210> 127
[2081] <211> 7
[2082] <212> PRT
[2083] <213> 人工序列(Artificial Sequence)
[2084] <220>
[2085] <223> 小鼠VL CDR2
[2086] <400> 127
[2087] Arg Thr Ser Thr Leu Ala Ser
[2088] 1 5
[2089] <210> 128
[2090] <211> 7
[2091] <212> PRT
[2092] <213> 人工序列(Artificial Sequence)
[2093] <220>
[2094] <223> 小鼠VL CDR2
[2095] <400> 128
[2096] Ser Ala Ser Tyr Arg Tyr Thr
[2097] 1 5
[2098] <210> 129
[2099] <211> 7
[2100] <212> PRT
[2101] <213> 人工序列(Artificial Sequence)
[2102] <220>
[2103] <223> 小鼠VL CDR2
[2104] <400> 129
[2105] Ser Thr Ser Asn Leu Ala Ser

[2106]	1	5
[2107]	<210>	130
[2108]	<211>	7
[2109]	<212>	PRT
[2110]	<213>	人工序列(Artificial Sequence)
[2111]	<220>	
[2112]	<223>	小鼠VL CDR2
[2113]	<400>	130
[2114]	Lys Val Ser Asn Arg Phe Phe	
[2115]	1	5
[2116]	<210>	131
[2117]	<211>	7
[2118]	<212>	PRT
[2119]	<213>	人工序列(Artificial Sequence)
[2120]	<220>	
[2121]	<223>	小鼠VL CDR2
[2122]	<400>	131
[2123]	Gln Val Ser Asn Arg Phe Ser	
[2124]	1	5
[2125]	<210>	132
[2126]	<211>	7
[2127]	<212>	PRT
[2128]	<213>	人工序列(Artificial Sequence)
[2129]	<220>	
[2130]	<223>	小鼠VL CDR2
[2131]	<400>	132
[2132]	Tyr Thr Ser Arg Leu His Ser	
[2133]	1	5
[2134]	<210>	133
[2135]	<211>	7
[2136]	<212>	PRT
[2137]	<213>	人工序列(Artificial Sequence)
[2138]	<220>	
[2139]	<223>	小鼠VL CDR2
[2140]	<400>	133
[2141]	Leu Thr Ser Asn Leu Ala Ser	
[2142]	1	5
[2143]	<210>	134
[2144]	<211>	7

[2145] <212> PRT
[2146] <213> 人工序列(Artificial Sequence)
[2147] <220>
[2148] <223> 小鼠VL CDR2
[2149] <400> 134
[2150] Lys Val Ser Asn Arg Phe Ser
[2151] 1 5
[2152] <210> 135
[2153] <211> 7
[2154] <212> PRT
[2155] <213> 人工序列(Artificial Sequence)
[2156] <220>
[2157] <223> 小鼠VL CDR2
[2158] <400> 135
[2159] Arg Ala Ser Asn Leu Glu Ser
[2160] 1 5
[2161] <210> 136
[2162] <211> 9
[2163] <212> PRT
[2164] <213> 人工序列(Artificial Sequence)
[2165] <220>
[2166] <223> 小鼠VL CDR3
[2167] <400> 136
[2168] Gln Gln Ser Asn Glu Ala Pro Tyr Thr
[2169] 1 5
[2170] <210> 137
[2171] <211> 9
[2172] <212> PRT
[2173] <213> 人工序列(Artificial Sequence)
[2174] <220>
[2175] <223> 小鼠VL CDR3
[2176] <400> 137
[2177] Gln Gln His Tyr Ser Thr Pro Trp Thr
[2178] 1 5
[2179] <210> 138
[2180] <211> 9
[2181] <212> PRT
[2182] <213> 人工序列(Artificial Sequence)
[2183] <220>

[2184] <223> 小鼠VL CDR3
[2185] <400> 138
[2186] Gln Gln His Tyr Ser Val Pro Phe Thr
[2187] 1 5
[2188] <210> 139
[2189] <211> 9
[2190] <212> PRT
[2191] <213> 人工序列(Artificial Sequence)
[2192] <220>
[2193] <223> 小鼠VL CDR3
[2194] <400> 139
[2195] Gln Gln Tyr His Ser Tyr Pro Leu Thr
[2196] 1 5
[2197] <210> 140
[2198] <211> 9
[2199] <212> PRT
[2200] <213> 人工序列(Artificial Sequence)
[2201] <220>
[2202] <223> 小鼠VL CDR3
[2203] <400> 140
[2204] Gln Gln His Tyr Ser Ile Pro Phe Thr
[2205] 1 5
[2206] <210> 141
[2207] <211> 9
[2208] <212> PRT
[2209] <213> 人工序列(Artificial Sequence)
[2210] <220>
[2211] <223> 小鼠VL CDR3
[2212] <400> 141
[2213] His Gln Trp Ser Ser Tyr Pro Phe Thr
[2214] 1 5
[2215] <210> 142
[2216] <211> 9
[2217] <212> PRT
[2218] <213> 人工序列(Artificial Sequence)
[2219] <220>
[2220] <223> 小鼠VL CDR3
[2221] <400> 142
[2222] Phe Gln Gly Ser His Val Pro Phe Thr

[2223]	1	5
[2224]	<210>	143
[2225]	<211>	9
[2226]	<212>	PRT
[2227]	<213>	人工序列(Artificial Sequence)
[2228]	<220>	
[2229]	<223>	小鼠VL CDR3
[2230]	<400>	143
[2231]	Phe Gln Gly Ser His Val Pro Phe Thr	
[2232]	1	5
[2233]	<210>	144
[2234]	<211>	9
[2235]	<212>	PRT
[2236]	<213>	人工序列(Artificial Sequence)
[2237]	<220>	
[2238]	<223>	小鼠VL CDR3
[2239]	<400>	144
[2240]	Gln Gln Gly Asp Thr Phe Pro Trp Thr	
[2241]	1	5
[2242]	<210>	145
[2243]	<211>	9
[2244]	<212>	PRT
[2245]	<213>	人工序列(Artificial Sequence)
[2246]	<220>	
[2247]	<223>	小鼠VL CDR3
[2248]	<400>	145
[2249]	Gln Gln Trp Thr Gly Asn Pro Leu Thr	
[2250]	1	5
[2251]	<210>	146
[2252]	<211>	9
[2253]	<212>	PRT
[2254]	<213>	人工序列(Artificial Sequence)
[2255]	<220>	
[2256]	<223>	小鼠VL CDR3
[2257]	<400>	146
[2258]	Phe Gln Gly Ser His Val Pro Phe Thr	
[2259]	1	5
[2260]	<210>	147
[2261]	<211>	9

[2262]	<212>	PRT
[2263]	<213>	人工序列(Artificial Sequence)
[2264]	<220>	
[2265]	<223>	小鼠VL CDR3
[2266]	<400>	147
[2267]		Gln Gln Ser Asn Glu Asp Pro His Thr
[2268]	1	5
[2269]	<210>	148
[2270]	<211>	25
[2271]	<212>	PRT
[2272]	<213>	人工序列(Artificial Sequence)
[2273]	<220>	
[2274]	<223>	小鼠VH FR1
[2275]	<400>	148
[2276]		Asp Val Gln Leu Gln Glu Ser Gly Pro Asp Leu Val Lys Pro Ser Gln
[2277]	1	5 10 15
[2278]		Ser Leu Ser Leu Thr Cys Thr Val Thr
[2279]		20 25
[2280]	<210>	149
[2281]	<211>	25
[2282]	<212>	PRT
[2283]	<213>	人工序列(Artificial Sequence)
[2284]	<220>	
[2285]	<223>	小鼠VH FR1
[2286]	<400>	149
[2287]		Asp Val Gln Leu Gln Gly Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
[2288]	1	5 10 15
[2289]		Ser Leu Ser Leu Thr Cys Thr Val Thr
[2290]		20 25
[2291]	<210>	150
[2292]	<211>	25
[2293]	<212>	PRT
[2294]	<213>	人工序列(Artificial Sequence)
[2295]	<220>	
[2296]	<223>	小鼠VH FR1
[2297]	<400>	150
[2298]		Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
[2299]	1	5 10 15
[2300]		Ser Val Arg Leu Ser Cys Lys Ala Ser

[2301]	20	25
[2302]	<210> 151	
[2303]	<211> 25	
[2304]	<212> PRT	
[2305]	<213> 人工序列(Artificial Sequence)	
[2306]	<220>	
[2307]	<223> 小鼠VH FR1	
[2308]	<400> 151	
[2309]	Asp Val Gln Leu Leu Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln	
[2310]	1 5 10 15	
[2311]	Ser Leu Ser Leu Thr Cys Ser Val Thr	
[2312]	20 25	
[2313]	<210> 152	
[2314]	<211> 25	
[2315]	<212> PRT	
[2316]	<213> 人工序列(Artificial Sequence)	
[2317]	<220>	
[2318]	<223> 小鼠VH FR1	
[2319]	<400> 152	
[2320]	Gln Val Gln Leu Gln Gln Ser Gly Asn Glu Leu Ala Arg Pro Gly Ala	
[2321]	1 5 10 15	
[2322]	Ser Val Arg Leu Ser Cys Lys Ala Ser	
[2323]	20 25	
[2324]	<210> 153	
[2325]	<211> 25	
[2326]	<212> PRT	
[2327]	<213> 人工序列(Artificial Sequence)	
[2328]	<220>	
[2329]	<223> 小鼠VH FR1	
[2330]	<400> 153	
[2331]	Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Val Val Arg Pro Gly Ala	
[2332]	1 5 10 15	
[2333]	Ser Val Lys Leu Ser Cys Lys Ala Ser	
[2334]	20 25	
[2335]	<210> 154	
[2336]	<211> 25	
[2337]	<212> PRT	
[2338]	<213> 人工序列(Artificial Sequence)	
[2339]	<220>	

[2340]	<223> 小鼠VH FR1
[2341]	<400> 154
[2342]	Glu Gly Gln Leu Gln Gln Ser Gly Ala Gly Leu Val Lys Pro Gly Ala
[2343]	1 5 10 15
[2344]	Ser Val Asn Leu Ser Cys Thr Ala Ser
[2345]	20 25
[2346]	<210> 155
[2347]	<211> 25
[2348]	<212> PRT
[2349]	<213> 人工序列(Artificial Sequence)
[2350]	<220>
[2351]	<223> 小鼠VH FR1
[2352]	<400> 155
[2353]	Glu Gly Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
[2354]	1 5 10 15
[2355]	Ser Val Asn Leu Ser Cys Thr Ala Ser
[2356]	20 25
[2357]	<210> 156
[2358]	<211> 25
[2359]	<212> PRT
[2360]	<213> 人工序列(Artificial Sequence)
[2361]	<220>
[2362]	<223> 小鼠VH FR1
[2363]	<400> 156
[2364]	Gln Val Leu Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
[2365]	1 5 10 15
[2366]	Ser Val Arg Ile Ser Cys Lys Ala Ser
[2367]	20 25
[2368]	<210> 157
[2369]	<211> 25
[2370]	<212> PRT
[2371]	<213> 人工序列(Artificial Sequence)
[2372]	<220>
[2373]	<223> 小鼠VH FR1
[2374]	<400> 157
[2375]	Lys Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Thr
[2376]	1 5 10 15
[2377]	Ser Val Lys Leu Ser Cys Lys Ala Ser
[2378]	20 25

[2379]	<210>	158
[2380]	<211>	25
[2381]	<212>	PRT
[2382]	<213>	人工序列(Artificial Sequence)
[2383]	<220>	
[2384]	<223>	小鼠VH FR1
[2385]	<400>	158
[2386]	Glu Gly Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala	
[2387]	1 5 10 15	
[2388]	Ser Val Ile Leu Ser Cys Thr Ala Ser	
[2389]	20 25	
[2390]	<210>	159
[2391]	<211>	25
[2392]	<212>	PRT
[2393]	<213>	人工序列(Artificial Sequence)
[2394]	<220>	
[2395]	<223>	小鼠VH FR1
[2396]	<400>	159
[2397]	Gln Phe Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser	
[2398]	1 5 10 15	
[2399]	Ser Val Lys Ile Ser Cys Lys Ala Ser	
[2400]	20 25	
[2401]	<210>	160
[2402]	<211>	25
[2403]	<212>	PRT
[2404]	<213>	人工序列(Artificial Sequence)
[2405]	<220>	
[2406]	<223>	人源化VH FR1
[2407]	<400>	160
[2408]	Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu	
[2409]	1 5 10 15	
[2410]	Thr Leu Ser Leu Thr Cys Thr Val Ser	
[2411]	20 25	
[2412]	<210>	161
[2413]	<211>	25
[2414]	<212>	PRT
[2415]	<213>	人工序列(Artificial Sequence)
[2416]	<220>	
[2417]	<223>	人源化VH FR1

[2418]	<400> 161
[2419]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[2420]	1 5 10 15
[2421]	Ser Val Lys Val Ser Cys Lys Ala Ser
[2422]	20 25
[2423]	<210> 162
[2424]	<211> 25
[2425]	<212> PRT
[2426]	<213> 人工序列(Artificial Sequence)
[2427]	<220>
[2428]	<223> 人源化VH FR1
[2429]	<400> 162
[2430]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[2431]	1 5 10 15
[2432]	Ser Val Lys Leu Ser Cys Lys Ala Ser
[2433]	20 25
[2434]	<210> 163
[2435]	<211> 14
[2436]	<212> PRT
[2437]	<213> 人工序列(Artificial Sequence)
[2438]	<220>
[2439]	<223> 小鼠VH FR2
[2440]	<400> 163
[2441]	Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp Met Gly
[2442]	1 5 10
[2443]	<210> 164
[2444]	<211> 14
[2445]	<212> PRT
[2446]	<213> 人工序列(Artificial Sequence)
[2447]	<220>
[2448]	<223> 小鼠VH FR2
[2449]	<400> 164
[2450]	Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp Met Gly
[2451]	1 5 10
[2452]	<210> 165
[2453]	<211> 14
[2454]	<212> PRT
[2455]	<213> 人工序列(Artificial Sequence)
[2456]	<220>

[2457]	<223>	小鼠VH FR2
[2458]	<400>	165
[2459]	Trp Val Lys Gln Arg Thr Gly Gln Gly Leu Glu Trp Ile Gly	
[2460]	1	5 10
[2461]	<210>	166
[2462]	<211>	14
[2463]	<212>	PRT
[2464]	<213>	人工序列(Artificial Sequence)
[2465]	<220>	
[2466]	<223>	小鼠VH FR2
[2467]	<400>	166
[2468]	Trp Ile Arg Gln Phe Pro Gly Asn Asn Leu Glu Trp Met Gly	
[2469]	1	5 10
[2470]	<210>	167
[2471]	<211>	14
[2472]	<212>	PRT
[2473]	<213>	人工序列(Artificial Sequence)
[2474]	<220>	
[2475]	<223>	小鼠VH FR2
[2476]	<400>	167
[2477]	Trp Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly	
[2478]	1	5 10
[2479]	<210>	168
[2480]	<211>	14
[2481]	<212>	PRT
[2482]	<213>	人工序列(Artificial Sequence)
[2483]	<220>	
[2484]	<223>	小鼠VH FR2
[2485]	<400>	168
[2486]	Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly	
[2487]	1	5 10
[2488]	<210>	169
[2489]	<211>	14
[2490]	<212>	PRT
[2491]	<213>	人工序列(Artificial Sequence)
[2492]	<220>	
[2493]	<223>	小鼠VH FR2
[2494]	<400>	169
[2495]	Trp Met Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile Gly	

[2496]	1	5	10
[2497]	<210> 170		
[2498]	<211> 14		
[2499]	<212> PRT		
[2500]	<213> 人工序列(Artificial Sequence)		
[2501]	<220>		
[2502]	<223> 小鼠VH FR2		
[2503]	<400> 170		
[2504]	Trp Val Lys Gln Arg Pro Asp Gln Gly Leu Glu Trp Ile Gly		
[2505]	1	5	10
[2506]	<210> 171		
[2507]	<211> 14		
[2508]	<212> PRT		
[2509]	<213> 人工序列(Artificial Sequence)		
[2510]	<220>		
[2511]	<223> 小鼠VH FR2		
[2512]	<400> 171		
[2513]	Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly		
[2514]	1	5	10
[2515]	<210> 172		
[2516]	<211> 14		
[2517]	<212> PRT		
[2518]	<213> 人工序列(Artificial Sequence)		
[2519]	<220>		
[2520]	<223> 小鼠VH FR2		
[2521]	<400> 172		
[2522]	Trp Ile Lys Gln Arg Ser Gly Gln Gly Leu Glu Trp Ile Gly		
[2523]	1	5	10
[2524]	<210> 173		
[2525]	<211> 14		
[2526]	<212> PRT		
[2527]	<213> 人工序列(Artificial Sequence)		
[2528]	<220>		
[2529]	<223> 小鼠VH FR2		
[2530]	<400> 173		
[2531]	Trp Leu Asn Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile Gly		
[2532]	1	5	10
[2533]	<210> 174		
[2534]	<211> 14		

[2535]	<212>	PRT
[2536]	<213>	人工序列(Artificial Sequence)
[2537]	<220>	
[2538]	<223>	小鼠VH FR2
[2539]	<400>	174
[2540]	Trp Val Lys Gln Arg Pro Gly Gln Ser Leu Glu Trp Ile Gly	
[2541]	1	5 10
[2542]	<210>	175
[2543]	<211>	14
[2544]	<212>	PRT
[2545]	<213>	人工序列(Artificial Sequence)
[2546]	<220>	
[2547]	<223>	人源化VH FR2
[2548]	<400>	175
[2549]	Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly	
[2550]	1	5 10
[2551]	<210>	176
[2552]	<211>	14
[2553]	<212>	PRT
[2554]	<213>	人工序列(Artificial Sequence)
[2555]	<220>	
[2556]	<223>	人源化VH FR2
[2557]	<400>	176
[2558]	Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp Met Gly	
[2559]	1	5 10
[2560]	<210>	177
[2561]	<211>	14
[2562]	<212>	PRT
[2563]	<213>	人工序列(Artificial Sequence)
[2564]	<220>	
[2565]	<223>	人源化VH FR2
[2566]	<400>	177
[2567]	Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly	
[2568]	1	5 10
[2569]	<210>	178
[2570]	<211>	14
[2571]	<212>	PRT
[2572]	<213>	人工序列(Artificial Sequence)
[2573]	<220>	

[2574]	<223>	人源化VH FR2
[2575]	<400>	178
[2576]	Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly	
[2577]	1	5 10
[2578]	<210>	179
[2579]	<211>	32
[2580]	<212>	PRT
[2581]	<213>	人工序列(Artificial Sequence)
[2582]	<220>	
[2583]	<223>	小鼠VH FR3
[2584]	<400>	179
[2585]	Arg Phe Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe Leu Gln	
[2586]	1	5 10 15
[2587]	Leu Asn Ser Met Thr Ala Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg	
[2588]		20 25 30
[2589]	<210>	180
[2590]	<211>	32
[2591]	<212>	PRT
[2592]	<213>	人工序列(Artificial Sequence)
[2593]	<220>	
[2594]	<223>	小鼠VH FR3
[2595]	<400>	180
[2596]	Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe Leu Gln	
[2597]	1	5 10 15
[2598]	Leu Asn Ser Val Thr Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg	
[2599]		20 25 30
[2600]	<210>	181
[2601]	<211>	32
[2602]	<212>	PRT
[2603]	<213>	人工序列(Artificial Sequence)
[2604]	<220>	
[2605]	<223>	小鼠VH FR3
[2606]	<400>	181
[2607]	Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu	
[2608]	1	5 10 15
[2609]	Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg	
[2610]		20 25 30
[2611]	<210>	182
[2612]	<211>	32

[2613]	<212>	PRT
[2614]	<213>	人工序列(Artificial Sequence)
[2615]	<220>	
[2616]	<223>	小鼠VH FR3
[2617]	<400>	182
[2618]	Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe Leu Lys	
[2619]	1 5 10 15	
[2620]	Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg	
[2621]	20 25 30	
[2622]	<210>	183
[2623]	<211>	32
[2624]	<212>	PRT
[2625]	<213>	人工序列(Artificial Sequence)
[2626]	<220>	
[2627]	<223>	小鼠VH FR3
[2628]	<400>	183
[2629]	Arg Ala Thr Leu Thr Ala Asp Ile Ser Ser Ser Thr Ala Tyr Met Glu	
[2630]	1 5 10 15	
[2631]	Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg	
[2632]	20 25 30	
[2633]	<210>	184
[2634]	<211>	32
[2635]	<212>	PRT
[2636]	<213>	人工序列(Artificial Sequence)
[2637]	<220>	
[2638]	<223>	小鼠VH FR3
[2639]	<400>	184
[2640]	Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln	
[2641]	1 5 10 15	
[2642]	Leu Ser Ser Pro Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Thr Thr	
[2643]	20 25 30	
[2644]	<210>	185
[2645]	<211>	32
[2646]	<212>	PRT
[2647]	<213>	人工序列(Artificial Sequence)
[2648]	<220>	
[2649]	<223>	小鼠VH FR3
[2650]	<400>	185
[2651]	Lys Ala Thr Ile Thr Ala Asp Ser Ser Ser Asn Thr Ala Tyr Leu Gln	

[2652]	1	5	10	15
[2653]	Val Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ser Arg			
[2654]	20	25	30	
[2655]	<210> 186			
[2656]	<211> 32			
[2657]	<212> PRT			
[2658]	<213> 人工序列(Artificial Sequence)			
[2659]	<220>			
[2660]	<223> 小鼠VH FR3			
[2661]	<400> 186			
[2662]	Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr Leu Gln			
[2663]	1	5	10	15
[2664]	Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys Thr Arg			
[2665]	20	25	30	
[2666]	<210> 187			
[2667]	<211> 32			
[2668]	<212> PRT			
[2669]	<213> 人工序列(Artificial Sequence)			
[2670]	<220>			
[2671]	<223> 小鼠VH FR3			
[2672]	<400> 187			
[2673]	Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln			
[2674]	1	5	10	15
[2675]	Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Ser			
[2676]	20	25	30	
[2677]	<210> 188			
[2678]	<211> 32			
[2679]	<212> PRT			
[2680]	<213> 人工序列(Artificial Sequence)			
[2681]	<220>			
[2682]	<223> 小鼠VH FR3			
[2683]	<400> 188			
[2684]	Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Val Phe Met Glu			
[2685]	1	5	10	15
[2686]	Leu Ser Arg Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg			
[2687]	20	25	30	
[2688]	<210> 189			
[2689]	<211> 32			
[2690]	<212> PRT			

[2691]	<213>	人工序列(Artificial Sequence)															
[2692]	<220>																
[2693]	<223>	小鼠VH FR3															
[2694]	<400>	189															
[2695]		Lys	Ala	Thr	Ile	Thr	Ala	Asp	Thr	Ser	Ser	Asn	Thr	Ala	Tyr	Leu	Gln
[2696]		1				5					10					15	
[2697]		Leu	Thr	Ser	Leu	Thr	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ser	Arg
[2698]						20				25					30		
[2699]	<210>	190															
[2700]	<211>	32															
[2701]	<212>	PRT															
[2702]	<213>	人工序列(Artificial Sequence)															
[2703]	<220>																
[2704]	<223>	小鼠VH FR3															
[2705]	<400>	190															
[2706]		Lys	Ala	Thr	Leu	Thr	Ser	Asp	Lys	Ser	Ser	Ser	Thr	Ala	Tyr	Met	Gln
[2707]		1				5					10					15	
[2708]		Leu	Asn	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Phe	Cys	Ala	Arg
[2709]						20				25					30		
[2710]	<210>	191															
[2711]	<211>	32															
[2712]	<212>	PRT															
[2713]	<213>	人工序列(Artificial Sequence)															
[2714]	<220>																
[2715]	<223>	人源化VH FR3															
[2716]	<400>	191															
[2717]		Arg	Val	Thr	Ile	Ser	Val	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Ser	Leu	Lys
[2718]		1				5					10					15	
[2719]		Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Arg
[2720]						20				25					30		
[2721]	<210>	192															
[2722]	<211>	32															
[2723]	<212>	PRT															
[2724]	<213>	人工序列(Artificial Sequence)															
[2725]	<220>																
[2726]	<223>	人源化VH FR3															
[2727]	<400>	192															
[2728]		Arg	Ile	Thr	Ile	Ser	Val	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Ser	Leu	Lys
[2729]		1				5					10					15	

[2730]	Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg
[2731]	20 25 30
[2732]	<210> 193
[2733]	<211> 32
[2734]	<212> PRT
[2735]	<213> 人工序列(Artificial Sequence)
[2736]	<220>
[2737]	<223> 人源化VH FR3
[2738]	<400> 193
[2739]	Arg Ile Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Phe Leu Lys
[2740]	1 5 10 15
[2741]	Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Thr Tyr Tyr Cys Ala Arg
[2742]	20 25 30
[2743]	<210> 194
[2744]	<211> 32
[2745]	<212> PRT
[2746]	<213> 人工序列(Artificial Sequence)
[2747]	<220>
[2748]	<223> 人源化VH FR3
[2749]	<400> 194
[2750]	Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys
[2751]	1 5 10 15
[2752]	Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg
[2753]	20 25 30
[2754]	<210> 195
[2755]	<211> 32
[2756]	<212> PRT
[2757]	<213> 人工序列(Artificial Sequence)
[2758]	<220>
[2759]	<223> 人源化VH FR3
[2760]	<400> 195
[2761]	Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr Met Glu
[2762]	1 5 10 15
[2763]	Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg
[2764]	20 25 30
[2765]	<210> 196
[2766]	<211> 32
[2767]	<212> PRT
[2768]	<213> 人工序列(Artificial Sequence)

[2769]	<220>
[2770]	<223> 人源化VH FR3
[2771]	<400> 196
[2772]	Arg Ala Thr Leu Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr Met Glu
[2773]	1 5 10 15
[2774]	Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys Ala Arg
[2775]	20 25 30
[2776]	<210> 197
[2777]	<211> 32
[2778]	<212> PRT
[2779]	<213> 人工序列(Artificial Sequence)
[2780]	<220>
[2781]	<223> 人源化VH FR3
[2782]	<400> 197
[2783]	Arg Ala Thr Leu Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr Met Glu
[2784]	1 5 10 15
[2785]	Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys Ala Arg
[2786]	20 25 30
[2787]	<210> 198
[2788]	<211> 32
[2789]	<212> PRT
[2790]	<213> 人工序列(Artificial Sequence)
[2791]	<220>
[2792]	<223> 人源化VH FR3
[2793]	<400> 198
[2794]	Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr Met Glu
[2795]	1 5 10 15
[2796]	Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg
[2797]	20 25 30
[2798]	<210> 199
[2799]	<211> 11
[2800]	<212> PRT
[2801]	<213> 人工序列(Artificial Sequence)
[2802]	<220>
[2803]	<223> 小鼠VH FR4
[2804]	<400> 199
[2805]	Trp Gly His Gly Thr Leu Val Thr Val Ser Ala
[2806]	1 5 10
[2807]	<210> 200

[2808]	<211>	11	
[2809]	<212>	PRT	
[2810]	<213>	人工序列(Artificial Sequence)	
[2811]	<220>		
[2812]	<223>	小鼠VH FR4	
[2813]	<400>	200	
[2814]	Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser		
[2815]	1	5	10
[2816]	<210>	201	
[2817]	<211>	11	
[2818]	<212>	PRT	
[2819]	<213>	人工序列(Artificial Sequence)	
[2820]	<220>		
[2821]	<223>	小鼠VH FR4	
[2822]	<400>	201	
[2823]	Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser		
[2824]	1	5	10
[2825]	<210>	202	
[2826]	<211>	11	
[2827]	<212>	PRT	
[2828]	<213>	人工序列(Artificial Sequence)	
[2829]	<220>		
[2830]	<223>	小鼠VH FR4	
[2831]	<400>	202	
[2832]	Trp Gly Gln Gly Thr Thr Leu Ile Val Ser Ser		
[2833]	1	5	10
[2834]	<210>	203	
[2835]	<211>	11	
[2836]	<212>	PRT	
[2837]	<213>	人工序列(Artificial Sequence)	
[2838]	<220>		
[2839]	<223>	小鼠VH FR4	
[2840]	<400>	203	
[2841]	Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser		
[2842]	1	5	10
[2843]	<210>	204	
[2844]	<211>	11	
[2845]	<212>	PRT	
[2846]	<213>	人工序列(Artificial Sequence)	

[2847] <220>
[2848] <223> 小鼠VH FR4
[2849] <400> 204
[2850] Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
[2851] 1 5 10
[2852] <210> 205
[2853] <211> 11
[2854] <212> PRT
[2855] <213> 人工序列(Artificial Sequence)
[2856] <220>
[2857] <223> 小鼠VH FR4
[2858] <400> 205
[2859] Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser
[2860] 1 5 10
[2861] <210> 206
[2862] <211> 11
[2863] <212> PRT
[2864] <213> 人工序列(Artificial Sequence)
[2865] <220>
[2866] <223> 小鼠VH FR4
[2867] <400> 206
[2868] Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser
[2869] 1 5 10
[2870] <210> 207
[2871] <211> 11
[2872] <212> PRT
[2873] <213> 人工序列(Artificial Sequence)
[2874] <220>
[2875] <223> 小鼠VH FR4
[2876] <400> 207
[2877] Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser
[2878] 1 5 10
[2879] <210> 208
[2880] <211> 11
[2881] <212> PRT
[2882] <213> 人工序列(Artificial Sequence)
[2883] <220>
[2884] <223> 小鼠VH FR4
[2885] <400> 208

[2886]	Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala
[2887]	1 5 10
[2888]	<210> 209
[2889]	<211> 11
[2890]	<212> PRT
[2891]	<213> 人工序列(Artificial Sequence)
[2892]	<220>
[2893]	<223> 小鼠VH FR4
[2894]	<400> 209
[2895]	Trp Gly Ala Gly Thr Leu Val Thr Val Ser Ser
[2896]	1 5 10
[2897]	<210> 210
[2898]	<211> 11
[2899]	<212> PRT
[2900]	<213> 人工序列(Artificial Sequence)
[2901]	<220>
[2902]	<223> 小鼠VH FR4
[2903]	<400> 210
[2904]	Trp Gly Gln Gly Thr Ala Leu Thr Val Ser Ser
[2905]	1 5 10
[2906]	<210> 211
[2907]	<211> 11
[2908]	<212> PRT
[2909]	<213> 人工序列(Artificial Sequence)
[2910]	<220>
[2911]	<223> 人源化VH FR4
[2912]	<400> 211
[2913]	Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
[2914]	1 5 10
[2915]	<210> 212
[2916]	<211> 11
[2917]	<212> PRT
[2918]	<213> 人工序列(Artificial Sequence)
[2919]	<220>
[2920]	<223> 人源化VH FR4
[2921]	<400> 212
[2922]	Trp Gly Gln Gly Thr Leu Leu Thr Val Ser Ser
[2923]	1 5 10
[2924]	<210> 213

[2925]	<211>	11
[2926]	<212>	PRT
[2927]	<213>	人工序列(Artificial Sequence)
[2928]	<220>	
[2929]	<223>	人源化VH FR4
[2930]	<400>	213
[2931]	Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser	
[2932]	1	5 10
[2933]	<210>	214
[2934]	<211>	23
[2935]	<212>	PRT
[2936]	<213>	人工序列(Artificial Sequence)
[2937]	<220>	
[2938]	<223>	小鼠VL FR1
[2939]	<400>	214
[2940]	Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly	
[2941]	1	5 10 15
[2942]	Gln Arg Ala Thr Ile Ser Cys	
[2943]		20
[2944]	<210>	215
[2945]	<211>	23
[2946]	<212>	PRT
[2947]	<213>	人工序列(Artificial Sequence)
[2948]	<220>	
[2949]	<223>	小鼠VL FR1
[2950]	<400>	215
[2951]	Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly	
[2952]	1	5 10 15
[2953]	Gly Arg Val Ser Ile Thr Cys	
[2954]		20
[2955]	<210>	216
[2956]	<211>	23
[2957]	<212>	PRT
[2958]	<213>	人工序列(Artificial Sequence)
[2959]	<220>	
[2960]	<223>	小鼠VL FR1
[2961]	<400>	216
[2962]	Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly	
[2963]	1	5 10 15

[2964]	Asp Arg Val Thr Ile Thr Cys
[2965]	20
[2966]	<210> 217
[2967]	<211> 23
[2968]	<212> PRT
[2969]	<213> 人工序列(Artificial Sequence)
[2970]	<220>
[2971]	<223> 小鼠VL FR1
[2972]	<400> 217
[2973]	Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
[2974]	1 5 10 15
[2975]	Glu Lys Val Thr Ile Ser Cys
[2976]	20
[2977]	<210> 218
[2978]	<211> 23
[2979]	<212> PRT
[2980]	<213> 人工序列(Artificial Sequence)
[2981]	<220>
[2982]	<223> 小鼠VL FR1
[2983]	<400> 218
[2984]	Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
[2985]	1 5 10 15
[2986]	Asp Arg Val Ser Ile Thr Cys
[2987]	20
[2988]	<210> 219
[2989]	<211> 23
[2990]	<212> PRT
[2991]	<213> 人工序列(Artificial Sequence)
[2992]	<220>
[2993]	<223> 小鼠VL FR1
[2994]	<400> 219
[2995]	Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
[2996]	1 5 10 15
[2997]	Glu Lys Val Thr Leu Thr Cys
[2998]	20
[2999]	<210> 220
[3000]	<211> 23
[3001]	<212> PRT
[3002]	<213> 人工序列(Artificial Sequence)

168

[3042]	20
[3043]	<210> 224
[3044]	<211> 23
[3045]	<212> PRT
[3046]	<213> 人工序列(Artificial Sequence)
[3047]	<220>
[3048]	<223> 小鼠VL FR1
[3049]	<400> 224
[3050]	Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
[3051]	1 5 10 15
[3052]	Asp Gln Ala Ser Ile Ser Cys
[3053]	20
[3054]	<210> 225
[3055]	<211> 23
[3056]	<212> PRT
[3057]	<213> 人工序列(Artificial Sequence)
[3058]	<220>
[3059]	<223> 小鼠VL FR1
[3060]	<400> 225
[3061]	Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
[3062]	1 5 10 15
[3063]	Gln Arg Ala Thr Ile Ser Cys
[3064]	20
[3065]	<210> 226
[3066]	<211> 23
[3067]	<212> PRT
[3068]	<213> 人工序列(Artificial Sequence)
[3069]	<220>
[3070]	<223> 人源化VL FR1
[3071]	<400> 226
[3072]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
[3073]	1 5 10 15
[3074]	Asp Arg Val Thr Ile Thr Cys
[3075]	20
[3076]	<210> 227
[3077]	<211> 23
[3078]	<212> PRT
[3079]	<213> 人工序列(Artificial Sequence)
[3080]	<220>

[3081]	<223>	人源化VL FR1
[3082]	<400>	227
[3083]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Thr Ser Val Gly	
[3084]	1	5 10 15
[3085]	Asp Arg Val Thr Ile Thr Cys	
[3086]	20	
[3087]	<210>	228
[3088]	<211>	23
[3089]	<212>	PRT
[3090]	<213>	人工序列(Artificial Sequence)
[3091]	<220>	
[3092]	<223>	人源化VL FR1
[3093]	<400>	228
[3094]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly	
[3095]	1	5 10 15
[3096]	Asp Arg Val Thr Ile Thr Cys	
[3097]	20	
[3098]	<210>	229
[3099]	<211>	23
[3100]	<212>	PRT
[3101]	<213>	人工序列(Artificial Sequence)
[3102]	<220>	
[3103]	<223>	人源化VL FR1
[3104]	<400>	229
[3105]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Met Ser Ala Ser Val Gly	
[3106]	1	5 10 15
[3107]	Asp Arg Val Thr Ile Thr Cys	
[3108]	20	
[3109]	<210>	230
[3110]	<211>	23
[3111]	<212>	PRT
[3112]	<213>	人工序列(Artificial Sequence)
[3113]	<220>	
[3114]	<223>	人源化VL FR1
[3115]	<400>	230
[3116]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Met Ser Thr Ser Val Gly	
[3117]	1	5 10 15
[3118]	Asp Arg Val Thr Ile Thr Cys	
[3119]	20	

[3120]	<210>	231
[3121]	<211>	15
[3122]	<212>	PRT
[3123]	<213>	人工序列(Artificial Sequence)
[3124]	<220>	
[3125]	<223>	小鼠VL FR2
[3126]	<400>	231
[3127]	Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr	
[3128]	1	5 10 15
[3129]	<210>	232
[3130]	<211>	15
[3131]	<212>	PRT
[3132]	<213>	人工序列(Artificial Sequence)
[3133]	<220>	
[3134]	<223>	小鼠VL FR2
[3135]	<400>	232
[3136]	Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr	
[3137]	1	5 10 15
[3138]	<210>	233
[3139]	<211>	15
[3140]	<212>	PRT
[3141]	<213>	人工序列(Artificial Sequence)
[3142]	<220>	
[3143]	<223>	小鼠VL FR2
[3144]	<400>	233
[3145]	Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr	
[3146]	1	5 10 15
[3147]	<210>	234
[3148]	<211>	15
[3149]	<212>	PRT
[3150]	<213>	人工序列(Artificial Sequence)
[3151]	<220>	
[3152]	<223>	小鼠VL FR2
[3153]	<400>	234
[3154]	Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Leu	
[3155]	1	5 10 15
[3156]	<210>	235
[3157]	<211>	15
[3158]	<212>	PRT

[3159]	<213>	人工序列(Artificial Sequence)
[3160]	<220>	
[3161]	<223>	小鼠VL FR2
[3162]	<400>	235
[3163]	Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr	
[3164]	1 5 10 15	
[3165]	<210>	236
[3166]	<211>	15
[3167]	<212>	PRT
[3168]	<213>	人工序列(Artificial Sequence)
[3169]	<220>	
[3170]	<223>	小鼠VL FR2
[3171]	<400>	236
[3172]	Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Leu Trp Ile Tyr	
[3173]	1 5 10 15	
[3174]	<210>	237
[3175]	<211>	15
[3176]	<212>	PRT
[3177]	<213>	人工序列(Artificial Sequence)
[3178]	<220>	
[3179]	<223>	小鼠VL FR2
[3180]	<400>	237
[3181]	Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Phe	
[3182]	1 5 10 15	
[3183]	<210>	238
[3184]	<211>	15
[3185]	<212>	PRT
[3186]	<213>	人工序列(Artificial Sequence)
[3187]	<220>	
[3188]	<223>	小鼠VL FR2
[3189]	<400>	238
[3190]	Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Phe	
[3191]	1 5 10 15	
[3192]	<210>	239
[3193]	<211>	15
[3194]	<212>	PRT
[3195]	<213>	人工序列(Artificial Sequence)
[3196]	<220>	
[3197]	<223>	小鼠VL FR2

[3198]	<400> 239
[3199]	Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
[3200]	1 5 10 15
[3201]	<210> 240
[3202]	<211> 15
[3203]	<212> PRT
[3204]	<213> 人工序列(Artificial Sequence)
[3205]	<220>
[3206]	<223> 小鼠VL FR2
[3207]	<400> 240
[3208]	Trp Tyr Gln Gln Lys Pro Arg Ser Ser Pro Lys Pro Trp Ile Tyr
[3209]	1 5 10 15
[3210]	<210> 241
[3211]	<211> 15
[3212]	<212> PRT
[3213]	<213> 人工序列(Artificial Sequence)
[3214]	<220>
[3215]	<223> 小鼠VL FR2
[3216]	<400> 241
[3217]	Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Phe
[3218]	1 5 10 15
[3219]	<210> 242
[3220]	<211> 15
[3221]	<212> PRT
[3222]	<213> 人工序列(Artificial Sequence)
[3223]	<220>
[3224]	<223> 小鼠VL FR2
[3225]	<400> 242
[3226]	Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr
[3227]	1 5 10 15
[3228]	<210> 243
[3229]	<211> 15
[3230]	<212> PRT
[3231]	<213> 人工序列(Artificial Sequence)
[3232]	<220>
[3233]	<223> 人源化VL FR2
[3234]	<400> 243
[3235]	Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
[3236]	1 5 10 15

[3276]	1	5	10	15
[3277]	Phe Thr Ile Ser Ser Glu Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys			
[3278]	20	25	30	
[3279]	<210> 248			
[3280]	<211> 32			
[3281]	<212> PRT			
[3282]	<213> 人工序列(Artificial Sequence)			
[3283]	<220>			
[3284]	<223> 小鼠VL FR3			
[3285]	<400> 248			
[3286]	Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser			
[3287]	1	5	10	15
[3288]	Leu Thr Ile Ser Ser Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys			
[3289]	20	25	30	
[3290]	<210> 249			
[3291]	<211> 32			
[3292]	<212> PRT			
[3293]	<213> 人工序列(Artificial Sequence)			
[3294]	<220>			
[3295]	<223> 小鼠VL FR3			
[3296]	<400> 249			
[3297]	Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Ala Phe Thr			
[3298]	1	5	10	15
[3299]	Phe Thr Ile Ser Gly Glu Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys			
[3300]	20	25	30	
[3301]	<210> 250			
[3302]	<211> 32			
[3303]	<212> PRT			
[3304]	<213> 人工序列(Artificial Sequence)			
[3305]	<220>			
[3306]	<223> 小鼠VL FR3			
[3307]	<400> 250			
[3308]	Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser			
[3309]	1	5	10	15
[3310]	Leu Thr Val Ser Ser Met Glu Ala Glu Asp Ala Ala Ser Tyr Phe Cys			
[3311]	20	25	30	
[3312]	<210> 251			
[3313]	<211> 32			
[3314]	<212> PRT			

[3315]	<213>	人工序列(Artificial Sequence)															
[3316]	<220>																
[3317]	<223>	小鼠VL FR3															
[3318]	<400>	251															
[3319]		Gly	Val	Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr
[3320]		1				5					10					15	
[3321]		Leu	Lys	Ile	Asn	Arg	Val	Glu	Ala	Glu	Asp	Leu	Gly	Val	Tyr	Tyr	Cys
[3322]					20					25					30		
[3323]	<210>	252															
[3324]	<211>	32															
[3325]	<212>	PRT															
[3326]	<213>	人工序列(Artificial Sequence)															
[3327]	<220>																
[3328]	<223>	小鼠VL FR3															
[3329]	<400>	252															
[3330]		Gly	Val	Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr
[3331]		1				5					10					15	
[3332]		Leu	Lys	Ile	Ser	Arg	Val	Glu	Ala	Glu	Asp	Leu	Gly	Phe	Tyr	Tyr	Cys
[3333]					20					25					30		
[3334]	<210>	253															
[3335]	<211>	32															
[3336]	<212>	PRT															
[3337]	<213>	人工序列(Artificial Sequence)															
[3338]	<220>																
[3339]	<223>	小鼠VL FR3															
[3340]	<400>	253															
[3341]		Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Tyr	Ser
[3342]		1				5					10					15	
[3343]		Leu	Thr	Ile	Ser	Asn	Leu	Glu	Gln	Glu	Asp	Ile	Ala	Thr	Tyr	Phe	Cys
[3344]					20					25					30		
[3345]	<210>	254															
[3346]	<211>	32															
[3347]	<212>	PRT															
[3348]	<213>	人工序列(Artificial Sequence)															
[3349]	<220>																
[3350]	<223>	小鼠VL FR3															
[3351]	<400>	254															
[3352]		Gly	Val	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Ser	Tyr	Ser
[3353]		1				5					10					15	

[3354]	Leu Thr Ile Ser Ser Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
[3355]	20 25 30
[3356]	<210> 255
[3357]	<211> 32
[3358]	<212> PRT
[3359]	<213> 人工序列(Artificial Sequence)
[3360]	<220>
[3361]	<223> 小鼠VL FR3
[3362]	<400> 255
[3363]	Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
[3364]	1 5 10 15
[3365]	Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys
[3366]	20 25 30
[3367]	<210> 256
[3368]	<211> 32
[3369]	<212> PRT
[3370]	<213> 人工序列(Artificial Sequence)
[3371]	<220>
[3372]	<223> 小鼠VL FR3
[3373]	<400> 256
[3374]	Gly Ile Pro Val Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr
[3375]	1 5 10 15
[3376]	Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys
[3377]	20 25 30
[3378]	<210> 257
[3379]	<211> 32
[3380]	<212> PRT
[3381]	<213> 人工序列(Artificial Sequence)
[3382]	<220>
[3383]	<223> 人源化VL FR3
[3384]	<400> 257
[3385]	Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
[3386]	1 5 10 15
[3387]	Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
[3388]	20 25 30
[3389]	<210> 258
[3390]	<211> 32
[3391]	<212> PRT
[3392]	<213> 人工序列(Artificial Sequence)

[3393]	<220>
[3394]	<223> 人源化VL FR3
[3395]	<400> 258
[3396]	Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
[3397]	1 5 10 15
[3398]	Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Leu Ala Leu Tyr Tyr Cys
[3399]	20 25 30
[3400]	<210> 259
[3401]	<211> 32
[3402]	<212> PRT
[3403]	<213> 人工序列(Artificial Sequence)
[3404]	<220>
[3405]	<223> 人源化VL FR3
[3406]	<400> 259
[3407]	Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
[3408]	1 5 10 15
[3409]	Leu Thr Ile Ser Ser Val Gln Pro Glu Asp Leu Ala Leu Tyr Tyr Cys
[3410]	20 25 30
[3411]	<210> 260
[3412]	<211> 32
[3413]	<212> PRT
[3414]	<213> 人工序列(Artificial Sequence)
[3415]	<220>
[3416]	<223> 人源化VL FR3
[3417]	<400> 260
[3418]	Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
[3419]	1 5 10 15
[3420]	Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys
[3421]	20 25 30
[3422]	<210> 261
[3423]	<211> 32
[3424]	<212> PRT
[3425]	<213> 人工序列(Artificial Sequence)
[3426]	<220>
[3427]	<223> 人源化VL FR3
[3428]	<400> 261
[3429]	Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
[3430]	1 5 10 15
[3431]	Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Leu Ala Thr Tyr Tyr Cys

[3432]	20	25	30
[3433]	<210> 262		
[3434]	<211> 32		
[3435]	<212> PRT		
[3436]	<213> 人工序列(Artificial Sequence)		
[3437]	<220>		
[3438]	<223> 人源化VL FR3		
[3439]	<400> 262		
[3440]	Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr		
[3441]	1 5 10 15		
[3442]	Phe Thr Ile Ser Ser Glu Gln Pro Glu Asp Leu Ala Thr Tyr Tyr Cys		
[3443]	20 25 30		
[3444]	<210> 263		
[3445]	<211> 10		
[3446]	<212> PRT		
[3447]	<213> 人工序列(Artificial Sequence)		
[3448]	<220>		
[3449]	<223> 小鼠VL FR4		
[3450]	<400> 263		
[3451]	Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys		
[3452]	1 5 10		
[3453]	<210> 264		
[3454]	<211> 10		
[3455]	<212> PRT		
[3456]	<213> 人工序列(Artificial Sequence)		
[3457]	<220>		
[3458]	<223> 小鼠VL FR4		
[3459]	<400> 264		
[3460]	Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys		
[3461]	1 5 10		
[3462]	<210> 265		
[3463]	<211> 10		
[3464]	<212> PRT		
[3465]	<213> 人工序列(Artificial Sequence)		
[3466]	<220>		
[3467]	<223> 小鼠VL FR4		
[3468]	<400> 265		
[3469]	Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys		
[3470]	1 5 10		

[3471]	<210>	266
[3472]	<211>	10
[3473]	<212>	PRT
[3474]	<213>	人工序列(Artificial Sequence)
[3475]	<220>	
[3476]	<223>	小鼠VL FR4
[3477]	<400>	266
[3478]	Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys	
[3479]	1	5 10
[3480]	<210>	267
[3481]	<211>	10
[3482]	<212>	PRT
[3483]	<213>	人工序列(Artificial Sequence)
[3484]	<220>	
[3485]	<223>	小鼠VL FR4
[3486]	<400>	267
[3487]	Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys	
[3488]	1	5 10
[3489]	<210>	268
[3490]	<211>	10
[3491]	<212>	PRT
[3492]	<213>	人工序列(Artificial Sequence)
[3493]	<220>	
[3494]	<223>	小鼠VL FR4
[3495]	<400>	268
[3496]	Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys	
[3497]	1	5 10
[3498]	<210>	269
[3499]	<211>	10
[3500]	<212>	PRT
[3501]	<213>	人工序列(Artificial Sequence)
[3502]	<220>	
[3503]	<223>	小鼠VL FR4
[3504]	<400>	269
[3505]	Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys	
[3506]	1	5 10
[3507]	<210>	270
[3508]	<211>	10
[3509]	<212>	PRT

- [3510] <213> 人工序列(Artificial Sequence)
[3511] <220>
[3512] <223> 小鼠VL FR4
[3513] <400> 270
[3514] Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
[3515] 1 5 10
[3516] <210> 271
[3517] <211> 10
[3518] <212> PRT
[3519] <213> 人工序列(Artificial Sequence)
[3520] <220>
[3521] <223> 小鼠VL FR4
[3522] <400> 271
[3523] Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
[3524] 1 5 10
[3525] <210> 272
[3526] <211> 10
[3527] <212> PRT
[3528] <213> 人工序列(Artificial Sequence)
[3529] <220>
[3530] <223> 小鼠VL FR4
[3531] <400> 272
[3532] Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
[3533] 1 5 10
[3534] <210> 273
[3535] <211> 10
[3536] <212> PRT
[3537] <213> 人工序列(Artificial Sequence)
[3538] <220>
[3539] <223> 小鼠VL FR4
[3540] <400> 273
[3541] Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
[3542] 1 5 10
[3543] <210> 274
[3544] <211> 10
[3545] <212> PRT
[3546] <213> 人工序列(Artificial Sequence)
[3547] <220>
[3548] <223> 小鼠VL FR4

[3549]	<400> 274		
[3550]	Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys		
[3551]	1	5	10
[3552]	<210> 275		
[3553]	<211> 10		
[3554]	<212> PRT		
[3555]	<213> 人工序列(Artificial Sequence)		
[3556]	<220>		
[3557]	<223> 人源化VL FR4		
[3558]	<400> 275		
[3559]	Phe Gly Gln Gly Thr Lys Val Glu Ile Lys		
[3560]	1	5	10
[3561]	<210> 276		
[3562]	<211> 10		
[3563]	<212> PRT		
[3564]	<213> 人工序列(Artificial Sequence)		
[3565]	<220>		
[3566]	<223> 人源化VL FR4		
[3567]	<400> 276		
[3568]	Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys		
[3569]	1	5	10
[3570]	<210> 277		
[3571]	<211> 10		
[3572]	<212> PRT		
[3573]	<213> 人工序列(Artificial Sequence)		
[3574]	<220>		
[3575]	<223> 人源化VL FR4		
[3576]	<400> 277		
[3577]	Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys		
[3578]	1	5	10
[3579]	<210> 278		
[3580]	<211> 445		
[3581]	<212> PRT		
[3582]	<213> 人工序列(Artificial Sequence)		
[3583]	<220>		
[3584]	<223> 具有N297A突变的嵌合IgG1重链		
[3585]	<400> 278		
[3586]	Asp Val Gln Leu Gln Glu Ser Gly Pro Asp Leu Val Lys Pro Ser Gln		
[3587]	1	5	10 15

[3588]	Ser	Leu	Ser	Leu	Thr	Cys	Thr	Val	Thr	Gly	Tyr	Ser	Ile	Thr	Ser	Gly
[3589]				20					25					30		
[3590]	Tyr	Thr	Trp	His	Trp	Ile	Arg	Gln	Phe	Pro	Gly	Asn	Lys	Leu	Glu	Trp
[3591]			35					40					45			
[3592]	Met	Gly	Tyr	Ile	His	Tyr	Ser	Gly	Ser	Thr	Lys	Tyr	Asn	Pro	Ser	Leu
[3593]		50						55					60			
[3594]	Lys	Ser	Arg	Phe	Ser	Ile	Thr	Arg	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Phe
[3595]	65					70					75					80
[3596]	Leu	Gln	Leu	Asn	Ser	Met	Thr	Ala	Glu	Asp	Thr	Ala	Thr	Tyr	Tyr	Cys
[3597]					85					90					95	
[3598]	Ala	Arg	Asn	Ser	Leu	Phe	Ala	Ser	Trp	Gly	His	Gly	Thr	Leu	Val	Thr
[3599]				100					105					110		
[3600]	Val	Ser	Ala	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro
[3601]			115					120					125			
[3602]	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val
[3603]		130					135					140				
[3604]	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala
[3605]	145					150					155					160
[3606]	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly
[3607]					165					170					175	
[3608]	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly
[3609]				180					185					190		
[3610]	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys
[3611]			195					200					205			
[3612]	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys
[3613]		210						215				220				
[3614]	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu
[3615]	225					230					235					240
[3616]	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu
[3617]				245					250					255		
[3618]	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys
[3619]				260					265					270		
[3620]	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys
[3621]			275					280					285			
[3622]	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu
[3623]		290					295					300				
[3624]	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys
[3625]	305					310					315					320
[3626]	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys

[3627]					325					330						335
[3628]	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser
[3629]					340					345					350	
[3630]	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys
[3631]					355					360					365	
[3632]	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln
[3633]					370					375					380	
[3634]	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly
[3635]	385						390					395				400
[3636]	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln
[3637]					405						410					415
[3638]	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn
[3639]					420						425				430	
[3640]	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys			
[3641]					435					440					445	
[3642]	<210> 279															
[3643]	<211> 450															
[3644]	<212> PRT															
[3645]	<213> 人工序列(Artificial Sequence)															
[3646]	<220>															
[3647]	<223> 具有N297A突变的嵌合IgG1重链															
[3648]	<400> 279															
[3649]	Asp	Val	Gln	Leu	Gln	Gly	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
[3650]	1				5					10					15	
[3651]	Ser	Leu	Ser	Leu	Thr	Cys	Thr	Val	Thr	Gly	Tyr	Ser	Ile	Thr	Ser	Asp
[3652]					20					25					30	
[3653]	Phe	Ala	Trp	Asp	Trp	Ile	Arg	Gln	Phe	Pro	Gly	Asn	Lys	Leu	Glu	Trp
[3654]					35					40					45	
[3655]	Met	Gly	His	Ile	Arg	Phe	Ser	Gly	Thr	Thr	Ser	Tyr	Asn	Pro	Ser	Leu
[3656]		50							55				60			
[3657]	Lys	Ser	Arg	Ile	Ser	Ile	Thr	Arg	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Phe
[3658]	65						70					75				80
[3659]	Leu	Gln	Leu	Asn	Ser	Val	Thr	Ser	Glu	Asp	Thr	Ala	Thr	Tyr	Tyr	Cys
[3660]					85						90					95
[3661]	Ala	Arg	Ser	Thr	Leu	Ile	Thr	Lys	Gly	Phe	Phe	Asp	Tyr	Trp	Gly	Gln
[3662]					100						105				110	
[3663]	Gly	Thr	Thr	Leu	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val
[3664]					115						120				125	
[3665]	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala

[3666]	130	135	140
[3667]	Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser		
[3668]	145	150	155
[3669]	Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val		
[3670]	165	170	175
[3671]	Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro		
[3672]	180	185	190
[3673]	Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys		
[3674]	195	200	205
[3675]	Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp		
[3676]	210	215	220
[3677]	Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly		
[3678]	225	230	235
[3679]	Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile		
[3680]	245	250	255
[3681]	Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu		
[3682]	260	265	270
[3683]	Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His		
[3684]	275	280	285
[3685]	Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg		
[3686]	290	295	300
[3687]	Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys		
[3688]	305	310	315
[3689]	Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu		
[3690]	325	330	335
[3691]	Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr		
[3692]	340	345	350
[3693]	Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu		
[3694]	355	360	365
[3695]	Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp		
[3696]	370	375	380
[3697]	Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val		
[3698]	385	390	395
[3699]	Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp		
[3700]	405	410	415
[3701]	Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His		
[3702]	420	425	430
[3703]	Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro		
[3704]	435	440	445

[3705]	Gly Lys
[3706]	450
[3707]	<210> 280
[3708]	<211> 449
[3709]	<212> PRT
[3710]	<213> 人工序列(Artificial Sequence)
[3711]	<220>
[3712]	<223> 具有N297A突变的嵌合IgG1重链
[3713]	<400> 280
[3714]	Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
[3715]	1 5 10 15
[3716]	Ser Val Arg Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[3717]	20 25 30
[3718]	Gly Ile Ser Trp Val Lys Gln Arg Thr Gly Gln Gly Leu Glu Trp Ile
[3719]	35 40 45
[3720]	Gly Glu Ile Phe Pro Arg Thr Ala Asn Thr Tyr Phe Asn Glu Lys Phe
[3721]	50 55 60
[3722]	Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
[3723]	65 70 75 80
[3724]	Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
[3725]	85 90 95
[3726]	Ala Arg Asp Tyr Asp Pro Tyr Tyr Ala Leu Asp Tyr Trp Gly Gln Gly
[3727]	100 105 110
[3728]	Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[3729]	115 120 125
[3730]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
[3731]	130 135 140
[3732]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[3733]	145 150 155 160
[3734]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[3735]	165 170 175
[3736]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[3737]	180 185 190
[3738]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[3739]	195 200 205
[3740]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
[3741]	210 215 220
[3742]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
[3743]	225 230 235 240

[3744]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[3745]	245 250 255
[3746]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
[3747]	260 265 270
[3748]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[3749]	275 280 285
[3750]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val
[3751]	290 295 300
[3752]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[3753]	305 310 315 320
[3754]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[3755]	325 330 335
[3756]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[3757]	340 345 350
[3758]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
[3759]	355 360 365
[3760]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[3761]	370 375 380
[3762]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[3763]	385 390 395 400
[3764]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[3765]	405 410 415
[3766]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[3767]	420 425 430
[3768]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[3769]	435 440 445
[3770]	Lys
[3771]	<210> 281
[3772]	<211> 443
[3773]	<212> PRT
[3774]	<213> 人工序列(Artificial Sequence)
[3775]	<220>
[3776]	<223> 具有N297A突变的嵌合IgG1重链
[3777]	<400> 281
[3778]	Asp Val Gln Leu Leu Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
[3779]	1 5 10 15
[3780]	Ser Leu Ser Leu Thr Cys Ser Val Thr Gly Tyr Ser Ile Thr Ser Gly
[3781]	20 25 30
[3782]	Tyr Tyr Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Asn Leu Glu Trp

[3783]	35	40	45
[3784]	Met Gly Ser Ile Asn Tyr Asp Gly Ser Asn Asp Tyr Asn Pro Ser Leu		
[3785]	50	55	60
[3786]	Gln Asp Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe		
[3787]	65	70	75
[3788]	Leu Lys Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys		
[3789]	85	90	95
[3790]	Ala Arg Arg Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Ile Val Ser		
[3791]	100	105	110
[3792]	Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser		
[3793]	115	120	125
[3794]	Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp		
[3795]	130	135	140
[3796]	Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr		
[3797]	145	150	155
[3798]	Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr		
[3799]	165	170	175
[3800]	Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln		
[3801]	180	185	190
[3802]	Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp		
[3803]	195	200	205
[3804]	Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro		
[3805]	210	215	220
[3806]	Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro		
[3807]	225	230	235
[3808]	Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr		
[3809]	245	250	255
[3810]	Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn		
[3811]	260	265	270
[3812]	Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg		
[3813]	275	280	285
[3814]	Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val		
[3815]	290	295	300
[3816]	Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser		
[3817]	305	310	315
[3818]	Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys		
[3819]	325	330	335
[3820]	Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu		
[3821]	340	345	350

[3822]	Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
[3823]	355 360 365
[3824]	Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
[3825]	370 375 380
[3826]	Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
[3827]	385 390 395 400
[3828]	Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
[3829]	405 410 415
[3830]	Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
[3831]	420 425 430
[3832]	Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3833]	435 440
[3834]	<210> 282
[3835]	<211> 449
[3836]	<212> PRT
[3837]	<213> 人工序列(Artificial Sequence)
[3838]	<220>
[3839]	<223> 具有N297A突变的嵌合IgG1重链
[3840]	<400> 282
[3841]	Gln Val Gln Leu Gln Gln Ser Gly Asn Glu Leu Ala Arg Pro Gly Ala
[3842]	1 5 10 15
[3843]	Ser Val Arg Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[3844]	20 25 30
[3845]	Gly Ile Thr Trp Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
[3846]	35 40 45
[3847]	Gly Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe
[3848]	50 55 60
[3849]	Lys Gly Arg Ala Thr Leu Thr Ala Asp Ile Ser Ser Ser Thr Ala Tyr
[3850]	65 70 75 80
[3851]	Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
[3852]	85 90 95
[3853]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[3854]	100 105 110
[3855]	Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[3856]	115 120 125
[3857]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
[3858]	130 135 140
[3859]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[3860]	145 150 155 160

[3861]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[3862]	165 170 175
[3863]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[3864]	180 185 190
[3865]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[3866]	195 200 205
[3867]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
[3868]	210 215 220
[3869]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
[3870]	225 230 235 240
[3871]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[3872]	245 250 255
[3873]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
[3874]	260 265 270
[3875]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[3876]	275 280 285
[3877]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val
[3878]	290 295 300
[3879]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[3880]	305 310 315 320
[3881]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[3882]	325 330 335
[3883]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[3884]	340 345 350
[3885]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
[3886]	355 360 365
[3887]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[3888]	370 375 380
[3889]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[3890]	385 390 395 400
[3891]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[3892]	405 410 415
[3893]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[3894]	420 425 430
[3895]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[3896]	435 440 445
[3897]	Lys
[3898]	<210> 283
[3899]	<211> 451

[3900]	<212>	PRT
[3901]	<213>	人工序列(Artificial Sequence)
[3902]	<220>	
[3903]	<223>	具有N297A突变的嵌合IgG1重链
[3904]	<400>	283
[3905]	Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Val Val Arg Pro Gly Ala	
[3906]	1	5 10 15
[3907]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr	
[3908]	20	25 30
[3909]	Trp Ile Ser Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile	
[3910]	35	40 45
[3911]	Gly Asn Ile Tyr Pro Ser Asp Ser Tyr Thr Asn Tyr Asn Gln Asn Phe	
[3912]	50	55 60
[3913]	Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr	
[3914]	65	70 75 80
[3915]	Met Gln Leu Ser Ser Pro Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys	
[3916]	85	90 95
[3917]	Thr Thr Gly Ile Ile Thr Val Ile Ala Thr Arg Asp Asp Tyr Trp Gly	
[3918]	100	105 110
[3919]	Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser	
[3920]	115	120 125
[3921]	Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala	
[3922]	130	135 140
[3923]	Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val	
[3924]	145	150 155 160
[3925]	Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala	
[3926]	165	170 175
[3927]	Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val	
[3928]	180	185 190
[3929]	Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His	
[3930]	195	200 205
[3931]	Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys	
[3932]	210	215 220
[3933]	Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly	
[3934]	225	230 235 240
[3935]	Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met	
[3936]	245	250 255
[3937]	Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His	
[3938]	260	265 270

[3939]	Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
[3940]	275 280 285
[3941]	His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr
[3942]	290 295 300
[3943]	Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
[3944]	305 310 315 320
[3945]	Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
[3946]	325 330 335
[3947]	Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
[3948]	340 345 350
[3949]	Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
[3950]	355 360 365
[3951]	Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
[3952]	370 375 380
[3953]	Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
[3954]	385 390 395 400
[3955]	Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
[3956]	405 410 415
[3957]	Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
[3958]	420 425 430
[3959]	His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
[3960]	435 440 445
[3961]	Pro Gly Lys
[3962]	450
[3963]	<210> 284
[3964]	<211> 453
[3965]	<212> PRT
[3966]	<213> 人工序列(Artificial Sequence)
[3967]	<220>
[3968]	<223> 具有N297A突变的嵌合IgG1重链
[3969]	<400> 284
[3970]	Glu Gly Gln Leu Gln Gln Ser Gly Ala Gly Leu Val Lys Pro Gly Ala
[3971]	1 5 10 15
[3972]	Ser Val Asn Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Thr
[3973]	20 25 30
[3974]	Tyr Ile His Trp Met Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
[3975]	35 40 45
[3976]	Gly Arg Ile Ala Pro Thr Asn Gly Asn Thr Lys Tyr Asp Pro Thr Phe
[3977]	50 55 60

[3978]	Gln Gly Lys Ala Thr Ile Thr Ala Asp Ser Ser Ser Asn Thr Ala Tyr
[3979]	65 70 75 80
[3980]	Leu Gln Val Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
[3981]	85 90 95
[3982]	Ser Arg Gly Gly Ile Tyr Tyr Tyr Gly Ser His Trp Tyr Phe Asp Val
[3983]	100 105 110
[3984]	Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
[3985]	115 120 125
[3986]	Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
[3987]	130 135 140
[3988]	Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
[3989]	145 150 155 160
[3990]	Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
[3991]	165 170 175
[3992]	Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
[3993]	180 185 190
[3994]	Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
[3995]	195 200 205
[3996]	Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
[3997]	210 215 220
[3998]	Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
[3999]	225 230 235 240
[4000]	Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
[4001]	245 250 255
[4002]	Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
[4003]	260 265 270
[4004]	Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
[4005]	275 280 285
[4006]	Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser
[4007]	290 295 300
[4008]	Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
[4009]	305 310 315 320
[4010]	Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
[4011]	325 330 335
[4012]	Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
[4013]	340 345 350
[4014]	Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
[4015]	355 360 365
[4016]	Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala

[4017]	370	375	380
[4018]	Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr		
[4019]	385	390	395 400
[4020]	Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu		
[4021]	405	410	415
[4022]	Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser		
[4023]	420	425	430
[4024]	Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser		
[4025]	435	440	445
[4026]	Leu Ser Pro Gly Lys		
[4027]	450		
[4028]	<210> 285		
[4029]	<211> 453		
[4030]	<212> PRT		
[4031]	<213> 人工序列(Artificial Sequence)		
[4032]	<220>		
[4033]	<223> 具有N297A突变的嵌合IgG1重链		
[4034]	<400> 285		
[4035]	Glu Gly Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala		
[4036]	1 5 10 15		
[4037]	Ser Val Asn Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Thr		
[4038]	20 25 30		
[4039]	Tyr Ile His Trp Val Lys Gln Arg Pro Asp Gln Gly Leu Glu Trp Ile		
[4040]	35 40 45		
[4041]	Gly Arg Ile Ala Pro Thr Asn Gly Asn Ala Lys Phe His Pro Thr Phe		
[4042]	50 55 60		
[4043]	Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr		
[4044]	65 70 75 80		
[4045]	Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys		
[4046]	85 90 95		
[4047]	Thr Arg Gly Gly Ile Tyr Tyr Tyr Gly Thr His Trp Tyr Phe Asp Val		
[4048]	100 105 110		
[4049]	Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly		
[4050]	115 120 125		
[4051]	Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly		
[4052]	130 135 140		
[4053]	Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val		
[4054]	145 150 155 160		
[4055]	Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe		

[4056]	165										170					175						
[4057]	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val						
[4058]	180										185					190						
[4059]	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val						
[4060]	195										200					205						
[4061]	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys						
[4062]	210										215					220						
[4063]	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu						
[4064]	225										230					235					240	
[4065]	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr						
[4066]	245										250					255						
[4067]	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val						
[4068]	260										265					270						
[4069]	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val						
[4070]	275										280					285						
[4071]	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser						
[4072]	290										295					300						
[4073]	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu						
[4074]	305										310					315					320	
[4075]	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala						
[4076]	325										330					335						
[4077]	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro						
[4078]	340										345					350						
[4079]	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln						
[4080]	355										360					365						
[4081]	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala						
[4082]	370										375					380						
[4083]	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr						
[4084]	385										390					395					400	
[4085]	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu						
[4086]	405										410					415						
[4087]	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser						
[4088]	420										425					430						
[4089]	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser						
[4090]	435										440					445						
[4091]	Leu	Ser	Pro	Gly	Lys																	
[4092]	450																					
[4093]	<210>	286																				
[4094]	<211>	450																				

[4095]	<212>	PRT
[4096]	<213>	人工序列(Artificial Sequence)
[4097]	<220>	
[4098]	<223>	具有N297A突变的嵌合IgG1重链
[4099]	<400>	286
[4100]	Gln Val Leu Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala	
[4101]	1 5 10 15	
[4102]	Ser Val Arg Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr	
[4103]	20 25 30	
[4104]	Tyr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile	
[4105]	35 40 45	
[4106]	Gly Trp Ile Tyr Pro Gly Asn Val Asn Thr Lys Tyr Asn Glu Lys Phe	
[4107]	50 55 60	
[4108]	Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr	
[4109]	65 70 75 80	
[4110]	Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys	
[4111]	85 90 95	
[4112]	Ala Ser Tyr Gly Asn Tyr Gly Gly Trp Tyr Phe Asp Val Trp Gly Ala	
[4113]	100 105 110	
[4114]	Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val	
[4115]	115 120 125	
[4116]	Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala	
[4117]	130 135 140	
[4118]	Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser	
[4119]	145 150 155 160	
[4120]	Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val	
[4121]	165 170 175	
[4122]	Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro	
[4123]	180 185 190	
[4124]	Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys	
[4125]	195 200 205	
[4126]	Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp	
[4127]	210 215 220	
[4128]	Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly	
[4129]	225 230 235 240	
[4130]	Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile	
[4131]	245 250 255	
[4132]	Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu	
[4133]	260 265 270	

[4134]	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
[4135]					275			280						285		
[4136]	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg
[4137]					290			295						300		
[4138]	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
[4139]	305						310				315					320
[4140]	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu
[4141]						325					330					335
[4142]	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr
[4143]						340					345				350	
[4144]	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu
[4145]						355					360				365	
[4146]	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp
[4147]						370					375				380	
[4148]	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val
[4149]	385						390				395					400
[4150]	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp
[4151]						405					410					415
[4152]	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His
[4153]						420					425				430	
[4154]	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro
[4155]						435					440				445	
[4156]	Gly	Lys														
[4157]						450										
[4158]	<210>	287														
[4159]	<211>	449														
[4160]	<212>	PRT														
[4161]	<213>	人工序列(Artificial Sequence)														
[4162]	<220>															
[4163]	<223>	具有N297A突变的嵌合IgG1重链														
[4164]	<400>	287														
[4165]	Lys	Val	Gln	Leu	Gln	Gln	Ser	Gly	Ala	Glu	Leu	Val	Lys	Pro	Gly	Thr
[4166]	1				5					10					15	
[4167]	Ser	Val	Lys	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Glu	Tyr
[4168]					20					25					30	
[4169]	Ile	Ile	Tyr	Trp	Ile	Lys	Gln	Arg	Ser	Gly	Gln	Gly	Leu	Glu	Trp	Ile
[4170]					35					40					45	
[4171]	Gly	Trp	Phe	Tyr	Pro	Gly	Thr	Gly	Ser	Ile	Lys	Tyr	Asn	Glu	Lys	Phe
[4172]					50					55					60	

[4173]	Lys	Asp	Lys	Ala	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Ser	Ser	Thr	Val	Phe
[4174]	65					70				75						80
[4175]	Met	Glu	Leu	Ser	Arg	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Phe	Cys
[4176]					85					90						95
[4177]	Ala	Arg	His	Glu	Glu	Gly	Asn	Leu	Trp	Phe	Ala	Tyr	Trp	Gly	Gln	Gly
[4178]				100					105					110		
[4179]	Thr	Leu	Val	Thr	Val	Ser	Ala	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[4180]			115					120					125			
[4181]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[4182]		130					135					140				
[4183]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[4184]	145					150				155						160
[4185]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
[4186]					165					170						175
[4187]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[4188]				180						185					190	
[4189]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[4190]			195					200					205			
[4191]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[4192]		210					215					220				
[4193]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[4194]	225					230					235					240
[4195]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[4196]				245						250						255
[4197]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[4198]				260						265					270	
[4199]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
[4200]		275						280					285			
[4201]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg	Val
[4202]		290					295					300				
[4203]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
[4204]	305					310					315					320
[4205]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
[4206]				325						330					335	
[4207]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
[4208]				340						345					350	
[4209]	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
[4210]			355					360					365			
[4211]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu

[4212]	370	375	380
[4213]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[4214]	385	390	395 400
[4215]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[4216]	405	410	415
[4217]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[4218]	420	425	430
[4219]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[4220]	435	440	445
[4221]	Lys		
[4222]	<210> 288		
[4223]	<211> 453		
[4224]	<212> PRT		
[4225]	<213> 人工序列(Artificial Sequence)		
[4226]	<220>		
[4227]	<223> 具有N297A突变的嵌合IgG1重链		
[4228]	<400> 288		
[4229]	Glu Gly Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala		
[4230]	1 5 10 15		
[4231]	Ser Val Ile Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Thr		
[4232]	20 25 30		
[4233]	Tyr Ile His Trp Leu Asn Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile		
[4234]	35 40 45		
[4235]	Gly Arg Ile Glu Pro Ala Asn Gly Asn Thr Lys Tyr Asp Pro Thr Phe		
[4236]	50 55 60		
[4237]	Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr		
[4238]	65 70 75 80		
[4239]	Leu Gln Leu Thr Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys		
[4240]	85 90 95		
[4241]	Ser Arg Gly Gly Ile Tyr Tyr Tyr Gly Ser His Trp Tyr Phe Asp Val		
[4242]	100 105 110		
[4243]	Trp Gly Ala Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly		
[4244]	115 120 125		
[4245]	Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly		
[4246]	130 135 140		
[4247]	Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val		
[4248]	145 150 155 160		
[4249]	Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe		
[4250]	165 170 175		

[4251]	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val
[4252]				180					185						190	
[4253]	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val
[4254]				195					200						205	
[4255]	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys
[4256]				210					215						220	
[4257]	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu
[4258]				225					230						235	
[4259]	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr
[4260]									245						250	
[4261]	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val
[4262]									260						265	
[4263]	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val
[4264]									275						280	
[4265]	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser
[4266]									290						295	
[4267]	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu
[4268]									305						310	
[4269]	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala
[4270]									325						330	
[4271]	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro
[4272]									340						345	
[4273]	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln
[4274]									355						360	
[4275]	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala
[4276]									370						375	
[4277]	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr
[4278]									385						390	
[4279]	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu
[4280]									405						410	
[4281]	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser
[4282]									420						425	
[4283]	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser
[4284]									435						440	
[4285]	Leu	Ser	Pro	Gly	Lys											
[4286]									450							
[4287]	<210>														289	
[4288]	<211>														448	
[4289]	<212>														PRT	

[4290]	<213> 人工序列(Artificial Sequence)															
[4291]	<220>															
[4292]	<223> 具有N297A突变的嵌合IgG1重链															
[4293]	<400> 289															
[4294]	Gln	Phe	Gln	Leu	Gln	Gln	Ser	Gly	Ala	Glu	Leu	Val	Arg	Pro	Gly	Ser
[4295]	1				5					10					15	
[4296]	Ser	Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Glu	Phe	Ser	Ser	Asn
[4297]					20					25					30	
[4298]	Trp	Met	Asn	Trp	Val	Lys	Gln	Arg	Pro	Gly	Gln	Ser	Leu	Glu	Trp	Ile
[4299]					35					40					45	
[4300]	Gly	Gln	Ile	Trp	Pro	Gly	Asp	Gly	Asp	Thr	Asn	Tyr	Asn	Gly	Lys	Phe
[4301]					50					55					60	
[4302]	Arg	Gly	Lys	Ala	Thr	Leu	Thr	Ser	Asp	Lys	Ser	Ser	Ser	Thr	Ala	Tyr
[4303]	65					70					75					80
[4304]	Met	Gln	Leu	Asn	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Phe	Cys
[4305]					85					90						95
[4306]	Ala	Arg	Gly	Arg	Ala	Ser	Phe	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
[4307]					100					105					110	
[4308]	Ala	Leu	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
[4309]					115					120					125	
[4310]	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
[4311]					130					135					140	
[4312]	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
[4313]	145					150					155					160
[4314]	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
[4315]					165					170					175	
[4316]	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
[4317]					180					185					190	
[4318]	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser
[4319]					195					200					205	
[4320]	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr
[4321]					210					215					220	
[4322]	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser
[4323]	225					230					235					240
[4324]	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
[4325]					245					250					255	
[4326]	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
[4327]					260					265					270	
[4328]	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala

[4329]	275	280	285
[4330]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val		
[4331]	290	295	300
[4332]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr		
[4333]	305	310	315
[4334]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr		
[4335]	325	330	335
[4336]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu		
[4337]	340	345	350
[4338]	Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys		
[4339]	355	360	365
[4340]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser		
[4341]	370	375	380
[4342]	Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp		
[4343]	385	390	395
[4344]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser		
[4345]	405	410	415
[4346]	Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala		
[4347]	420	425	430
[4348]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys		
[4349]	435	440	445
[4350]	<210> 290		
[4351]	<211> 449		
[4352]	<212> PRT		
[4353]	<213> 人工序列(Artificial Sequence)		
[4354]	<220>		
[4355]	<223> 具有CDR突变且具有N297A突变的嵌合IgG1重链		
[4356]	<400> 290		
[4357]	Gln Val Gln Leu Gln Gln Ser Gly Asn Glu Leu Ala Arg Pro Gly Ala		
[4358]	1	5	10
[4359]	Ser Val Arg Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[4360]	20	25	30
[4361]	Gly Ile Thr Trp Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile		
[4362]	35	40	45
[4363]	Gly Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe		
[4364]	50	55	60
[4365]	Lys Gly Arg Ala Thr Leu Thr Ala Asp Ile Ser Ser Ser Thr Ala Tyr		
[4366]	65	70	75
[4367]	Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys		

[4368]					85					90						95
[4369]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[4370]					100					105						110
[4371]	Thr	Ser	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[4372]					115					120						125
[4373]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[4374]					130					135						140
[4375]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[4376]	145						150				155					160
[4377]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
[4378]					165					170						175
[4379]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[4380]					180					185						190
[4381]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[4382]					195					200						205
[4383]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[4384]					210					215						220
[4385]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[4386]	225						230				235					240
[4387]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[4388]					245					250						255
[4389]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[4390]					260					265						270
[4391]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
[4392]					275					280						285
[4393]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg	Val
[4394]					290					295						300
[4395]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
[4396]	305						310				315					320
[4397]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
[4398]					325					330						335
[4399]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
[4400]					340					345						350
[4401]	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
[4402]					355					360						365
[4403]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
[4404]					370					375						380
[4405]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
[4406]	385						390				395					400

[4407]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[4408]	405 410 415
[4409]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[4410]	420 425 430
[4411]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[4412]	435 440 445
[4413]	Lys
[4414]	<210> 291
[4415]	<211> 449
[4416]	<212> PRT
[4417]	<213> 人工序列(Artificial Sequence)
[4418]	<220>
[4419]	<223> 具有CDR突变且具有N297A突变的嵌合IgG1重链
[4420]	<400> 291
[4421]	Gln Val Gln Leu Gln Gln Ser Gly Asn Glu Leu Ala Arg Pro Gly Ala
[4422]	1 5 10 15
[4423]	Ser Val Arg Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[4424]	20 25 30
[4425]	Gly Ile Thr Trp Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
[4426]	35 40 45
[4427]	Gly Glu Ile Phe Pro Arg Arg Val Ala Thr Tyr Tyr Ser Glu Lys Phe
[4428]	50 55 60
[4429]	Lys Gly Arg Ala Thr Leu Thr Ala Asp Ile Ser Ser Ser Thr Ala Tyr
[4430]	65 70 75 80
[4431]	Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
[4432]	85 90 95
[4433]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[4434]	100 105 110
[4435]	Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[4436]	115 120 125
[4437]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
[4438]	130 135 140
[4439]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[4440]	145 150 155 160
[4441]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[4442]	165 170 175
[4443]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[4444]	180 185 190
[4445]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

[4446]	195	200	205
[4447]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys		
[4448]	210	215	220
[4449]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro		
[4450]	225	230	235
[4451]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser		
[4452]	245	250	255
[4453]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp		
[4454]	260	265	270
[4455]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn		
[4456]	275	280	285
[4457]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val		
[4458]	290	295	300
[4459]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
[4460]	305	310	315
[4461]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
[4462]	325	330	335
[4463]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
[4464]	340	345	350
[4465]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr		
[4466]	355	360	365
[4467]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
[4468]	370	375	380
[4469]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[4470]	385	390	395
[4471]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[4472]	405	410	415
[4473]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[4474]	420	425	430
[4475]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[4476]	435	440	445
[4477]	Lys		
[4478]	<210> 292		
[4479]	<211> 449		
[4480]	<212> PRT		
[4481]	<213> 人工序列(Artificial Sequence)		
[4482]	<220>		
[4483]	<223> 具有CDR突变且具有N297A突变的嵌合IgG1重链		
[4484]	<400> 292		

[4485]	Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Asn	Glu	Leu	Ala	Arg	Pro	Gly	Ala
[4486]	1				5					10					15	
[4487]	Ser	Val	Arg	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Gly	Tyr
[4488]				20					25						30	
[4489]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Arg	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
[4490]				35					40					45		
[4491]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Gln	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[4492]		50						55					60			
[4493]	Lys	Gly	Arg	Ala	Thr	Leu	Thr	Ala	Asp	Ile	Ser	Ser	Ser	Thr	Ala	Tyr
[4494]	65					70					75					80
[4495]	Met	Glu	Leu	Arg	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Phe	Cys
[4496]					85					90					95	
[4497]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[4498]				100					105					110		
[4499]	Thr	Ser	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[4500]			115					120					125			
[4501]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[4502]		130					135					140				
[4503]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[4504]	145					150				155						160
[4505]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
[4506]					165				170						175	
[4507]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[4508]				180					185					190		
[4509]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[4510]			195					200					205			
[4511]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[4512]		210					215				220					
[4513]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[4514]	225					230					235					240
[4515]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[4516]				245					250					255		
[4517]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[4518]				260					265					270		
[4519]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
[4520]			275					280				285				
[4521]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg	Val
[4522]		290					295					300				
[4523]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu

[4524]	305	310	315	320
[4525]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys			
[4526]		325	330	335
[4527]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr			
[4528]		340	345	350
[4529]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr			
[4530]		355	360	365
[4531]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu			
[4532]		370	375	380
[4533]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu			
[4534]	385	390	395	400
[4535]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys			
[4536]		405	410	415
[4537]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu			
[4538]		420	425	430
[4539]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly			
[4540]		435	440	445
[4541]	Lys			
[4542]	<210> 293			
[4543]	<211> 450			
[4544]	<212> PRT			
[4545]	<213> 人工序列(Artificial Sequence)			
[4546]	<220>			
[4547]	<223> 具有N297A突变的人源化IgG1重链			
[4548]	<400> 293			
[4549]	Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu			
[4550]	1	5	10	15
[4551]	Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp			
[4552]		20	25	30
[4553]	Phe Ala Trp Asp Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp			
[4554]		35	40	45
[4555]	Ile Gly His Ile Arg Phe Ser Gly Thr Thr Ser Tyr Asn Pro Ser Leu			
[4556]		50	55	60
[4557]	Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser			
[4558]	65	70	75	80
[4559]	Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys			
[4560]		85	90	95
[4561]	Ala Arg Ser Thr Leu Ile Thr Lys Gly Phe Phe Asp Tyr Trp Gly Gln			
[4562]		100	105	110

[4563]	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val
[4564]			115						120				125			
[4565]	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala
[4566]			130						135				140			
[4567]	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser
[4568]	145						150				155					160
[4569]	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val
[4570]					165					170					175	
[4571]	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro
[4572]				180					185					190		
[4573]	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys
[4574]			195						200				205			
[4575]	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp
[4576]		210					215				220					
[4577]	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly
[4578]	225					230				235						240
[4579]	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
[4580]				245					250						255	
[4581]	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu
[4582]			260						265					270		
[4583]	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
[4584]		275						280				285				
[4585]	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg
[4586]		290					295				300					
[4587]	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
[4588]	305					310				315						320
[4589]	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu
[4590]				325					330					335		
[4591]	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr
[4592]			340						345					350		
[4593]	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu
[4594]			355						360					365		
[4595]	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp
[4596]		370					375				380					
[4597]	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val
[4598]	385					390				395						400
[4599]	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp
[4600]				405					410					415		
[4601]	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His

[4602]	420	425	430
[4603]	Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro		
[4604]	435	440	445
[4605]	Gly Lys		
[4606]	450		
[4607]	<210> 294		
[4608]	<211> 450		
[4609]	<212> PRT		
[4610]	<213> 人工序列(Artificial Sequence)		
[4611]	<220>		
[4612]	<223> 具有N297A突变的人源化IgG1重链		
[4613]	<400> 294		
[4614]	Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu		
[4615]	1 5 10 15		
[4616]	Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp		
[4617]	20 25 30		
[4618]	Phe Ala Trp Asp Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp		
[4619]	35 40 45		
[4620]	Met Gly His Ile Arg Phe Ser Gly Thr Thr Ser Tyr Asn Pro Ser Leu		
[4621]	50 55 60		
[4622]	Lys Ser Arg Ile Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser		
[4623]	65 70 75 80		
[4624]	Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys		
[4625]	85 90 95		
[4626]	Ala Arg Ser Thr Leu Ile Thr Lys Gly Phe Phe Asp Tyr Trp Gly Gln		
[4627]	100 105 110		
[4628]	Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val		
[4629]	115 120 125		
[4630]	Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala		
[4631]	130 135 140		
[4632]	Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser		
[4633]	145 150 155 160		
[4634]	Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val		
[4635]	165 170 175		
[4636]	Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro		
[4637]	180 185 190		
[4638]	Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys		
[4639]	195 200 205		
[4640]	Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp		

[4641]	210	215	220
[4642]	Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly		
[4643]	225	230	235 240
[4644]	Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile		
[4645]	245	250	255
[4646]	Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu		
[4647]	260	265	270
[4648]	Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His		
[4649]	275	280	285
[4650]	Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg		
[4651]	290	295	300
[4652]	Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys		
[4653]	305	310	315 320
[4654]	Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu		
[4655]	325	330	335
[4656]	Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr		
[4657]	340	345	350
[4658]	Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu		
[4659]	355	360	365
[4660]	Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp		
[4661]	370	375	380
[4662]	Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val		
[4663]	385	390	395 400
[4664]	Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp		
[4665]	405	410	415
[4666]	Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His		
[4667]	420	425	430
[4668]	Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro		
[4669]	435	440	445
[4670]	Gly Lys		
[4671]	450		
[4672]	<210> 295		
[4673]	<211> 450		
[4674]	<212> PRT		
[4675]	<213> 人工序列(Artificial Sequence)		
[4676]	<220>		
[4677]	<223> 具有N297A突变的人源化IgG1重链		
[4678]	<400> 295		
[4679]	Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu		

[4680]	1	5	10	15
[4681]	Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp			
[4682]	20	25	30	
[4683]	Phe Ala Trp Asp Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp			
[4684]	35	40	45	
[4685]	Met Gly His Ile Arg Phe Ser Gly Thr Thr Ser Tyr Asn Pro Ser Leu			
[4686]	50	55	60	
[4687]	Lys Ser Arg Ile Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Phe			
[4688]	65	70	75	80
[4689]	Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Thr Tyr Tyr Cys			
[4690]	85	90	95	
[4691]	Ala Arg Ser Thr Leu Ile Thr Lys Gly Phe Phe Asp Tyr Trp Gly Gln			
[4692]	100	105	110	
[4693]	Gly Thr Leu Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val			
[4694]	115	120	125	
[4695]	Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala			
[4696]	130	135	140	
[4697]	Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser			
[4698]	145	150	155	160
[4699]	Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val			
[4700]	165	170	175	
[4701]	Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro			
[4702]	180	185	190	
[4703]	Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys			
[4704]	195	200	205	
[4705]	Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp			
[4706]	210	215	220	
[4707]	Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly			
[4708]	225	230	235	240
[4709]	Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile			
[4710]	245	250	255	
[4711]	Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu			
[4712]	260	265	270	
[4713]	Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His			
[4714]	275	280	285	
[4715]	Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg			
[4716]	290	295	300	
[4717]	Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys			
[4718]	305	310	315	320

[4719]	Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
[4720]	325 330 335
[4721]	Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[4722]	340 345 350
[4723]	Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[4724]	355 360 365
[4725]	Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[4726]	370 375 380
[4727]	Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[4728]	385 390 395 400
[4729]	Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[4730]	405 410 415
[4731]	Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[4732]	420 425 430
[4733]	Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[4734]	435 440 445
[4735]	Gly Lys
[4736]	450
[4737]	<210> 296
[4738]	<211> 450
[4739]	<212> PRT
[4740]	<213> 人工序列(Artificial Sequence)
[4741]	<220>
[4742]	<223> 具有N297A突变的人源化IgG1重链
[4743]	<400> 296
[4744]	Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
[4745]	1 5 10 15
[4746]	Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp
[4747]	20 25 30
[4748]	Phe Ala Trp Asp Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
[4749]	35 40 45
[4750]	Ile Gly His Ile Arg Phe Ser Gly Thr Thr Ser Tyr Asn Pro Ser Leu
[4751]	50 55 60
[4752]	Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
[4753]	65 70 75 80
[4754]	Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
[4755]	85 90 95
[4756]	Ala Arg Ser Thr Leu Ile Thr Lys Gly Phe Phe Asp Tyr Trp Gly Gln
[4757]	100 105 110

[4758]	Gly	Thr	Leu	Leu	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val
[4759]			115						120				125			
[4760]	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala
[4761]			130						135				140			
[4762]	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser
[4763]	145						150					155				160
[4764]	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val
[4765]					165					170					175	
[4766]	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro
[4767]				180					185					190		
[4768]	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys
[4769]			195					200					205			
[4770]	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp
[4771]		210					215					220				
[4772]	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly
[4773]	225					230					235					240
[4774]	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
[4775]					245					250					255	
[4776]	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu
[4777]			260						265					270		
[4778]	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
[4779]			275					280					285			
[4780]	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg
[4781]		290					295					300				
[4782]	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
[4783]	305					310					315					320
[4784]	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu
[4785]				325						330					335	
[4786]	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr
[4787]			340						345					350		
[4788]	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu
[4789]			355						360				365			
[4790]	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp
[4791]		370					375					380				
[4792]	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val
[4793]	385					390					395					400
[4794]	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp
[4795]					405				410					415		
[4796]	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His

[4797]	420	425	430
[4798]	Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro		
[4799]	435	440	445
[4800]	Gly Lys		
[4801]	450		
[4802]	<210> 297		
[4803]	<211> 450		
[4804]	<212> PRT		
[4805]	<213> 人工序列(Artificial Sequence)		
[4806]	<220>		
[4807]	<223> 具有N297A突变的人源化IgG1重链		
[4808]	<400> 297		
[4809]	Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu		
[4810]	1 5 10 15		
[4811]	Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp		
[4812]	20 25 30		
[4813]	Phe Ala Trp Asp Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp		
[4814]	35 40 45		
[4815]	Ile Gly His Ile Arg Phe Ser Gly Thr Thr Ser Tyr Asn Pro Ser Leu		
[4816]	50 55 60		
[4817]	Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser		
[4818]	65 70 75 80		
[4819]	Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys		
[4820]	85 90 95		
[4821]	Ala Arg Ser Thr Leu Ile Thr Lys Gly Phe Phe Asp Tyr Trp Gly Gln		
[4822]	100 105 110		
[4823]	Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val		
[4824]	115 120 125		
[4825]	Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala		
[4826]	130 135 140		
[4827]	Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser		
[4828]	145 150 155 160		
[4829]	Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val		
[4830]	165 170 175		
[4831]	Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro		
[4832]	180 185 190		
[4833]	Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys		
[4834]	195 200 205		
[4835]	Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp		

[4836]	210	215	220
[4837]	Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly		
[4838]	225	230	235 240
[4839]	Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile		
[4840]	245	250	255
[4841]	Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu		
[4842]	260	265	270
[4843]	Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His		
[4844]	275	280	285
[4845]	Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg		
[4846]	290	295	300
[4847]	Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys		
[4848]	305	310	315 320
[4849]	Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu		
[4850]	325	330	335
[4851]	Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr		
[4852]	340	345	350
[4853]	Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu		
[4854]	355	360	365
[4855]	Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp		
[4856]	370	375	380
[4857]	Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val		
[4858]	385	390	395 400
[4859]	Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp		
[4860]	405	410	415
[4861]	Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His		
[4862]	420	425	430
[4863]	Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro		
[4864]	435	440	445
[4865]	Gly Lys		
[4866]	450		
[4867]	<210> 298		
[4868]	<211> 449		
[4869]	<212> PRT		
[4870]	<213> 人工序列(Artificial Sequence)		
[4871]	<220>		
[4872]	<223> 具有N297A突变的人源化IgG1重链		
[4873]	<400> 298		
[4874]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		

[4875]	1	5	10	15
[4876]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr			
[4877]	20	25	30	
[4878]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met			
[4879]	35	40	45	
[4880]	Gly Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe			
[4881]	50	55	60	
[4882]	Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr			
[4883]	65	70	75	80
[4884]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys			
[4885]	85	90	95	
[4886]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly			
[4887]	100	105	110	
[4888]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe			
[4889]	115	120	125	
[4890]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu			
[4891]	130	135	140	
[4892]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp			
[4893]	145	150	155	160
[4894]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu			
[4895]	165	170	175	
[4896]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser			
[4897]	180	185	190	
[4898]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro			
[4899]	195	200	205	
[4900]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys			
[4901]	210	215	220	
[4902]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro			
[4903]	225	230	235	240
[4904]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser			
[4905]	245	250	255	
[4906]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp			
[4907]	260	265	270	
[4908]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn			
[4909]	275	280	285	
[4910]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val			
[4911]	290	295	300	
[4912]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu			
[4913]	305	310	315	320

[4914]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
[4915]					325					330					335	
[4916]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
[4917]					340					345					350	
[4918]	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
[4919]					355					360					365	
[4920]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
[4921]					370					375					380	
[4922]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
[4923]					385					390					395	
[4924]	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
[4925]					405					410					415	
[4926]	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
[4927]					420					425					430	
[4928]	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
[4929]					435					440					445	
[4930]	Lys															
[4931]	<210>	299														
[4932]	<211>	449														
[4933]	<212>	PRT														
[4934]	<213>	人工序列(Artificial Sequence)														
[4935]	<220>															
[4936]	<223>	具有N297A突变的人源化IgG1重链														
[4937]	<400>	299														
[4938]	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
[4939]	1				5					10					15	
[4940]	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Gly	Tyr
[4941]					20					25					30	
[4942]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
[4943]					35					40					45	
[4944]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Asn	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[4945]					50					55					60	
[4946]	Lys	Gly	Arg	Ala	Thr	Leu	Thr	Thr	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
[4947]					65					70					75	
[4948]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Phe	Cys
[4949]					85					90					95	
[4950]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[4951]					100					105					110	
[4952]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe

[4953]	115	120	125
[4954]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu		
[4955]	130	135	140
[4956]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
[4957]	145	150	155
[4958]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu		
[4959]	165	170	175
[4960]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser		
[4961]	180	185	190
[4962]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro		
[4963]	195	200	205
[4964]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys		
[4965]	210	215	220
[4966]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro		
[4967]	225	230	235
[4968]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser		
[4969]	245	250	255
[4970]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp		
[4971]	260	265	270
[4972]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn		
[4973]	275	280	285
[4974]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val		
[4975]	290	295	300
[4976]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
[4977]	305	310	315
[4978]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
[4979]	325	330	335
[4980]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
[4981]	340	345	350
[4982]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr		
[4983]	355	360	365
[4984]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
[4985]	370	375	380
[4986]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[4987]	385	390	395
[4988]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[4989]	405	410	415
[4990]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[4991]	420	425	430

[4992]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[4993]	435 440 445
[4994]	Lys
[4995]	<210> 300
[4996]	<211> 449
[4997]	<212> PRT
[4998]	<213> 人工序列(Artificial Sequence)
[4999]	<220>
[5000]	<223> 具有N297A突变的人源化IgG1重链
[5001]	<400> 300
[5002]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[5003]	1 5 10 15
[5004]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[5005]	20 25 30
[5006]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
[5007]	35 40 45
[5008]	Gly Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe
[5009]	50 55 60
[5010]	Lys Gly Arg Ala Thr Leu Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
[5011]	65 70 75 80
[5012]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
[5013]	85 90 95
[5014]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[5015]	100 105 110
[5016]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[5017]	115 120 125
[5018]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
[5019]	130 135 140
[5020]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[5021]	145 150 155 160
[5022]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[5023]	165 170 175
[5024]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[5025]	180 185 190
[5026]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[5027]	195 200 205
[5028]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
[5029]	210 215 220
[5030]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro

[5031]	225	230	235	240
[5032]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser			
[5033]		245	250	255
[5034]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp			
[5035]		260	265	270
[5036]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn			
[5037]		275	280	285
[5038]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val			
[5039]		290	295	300
[5040]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu			
[5041]	305	310	315	320
[5042]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys			
[5043]		325	330	335
[5044]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr			
[5045]		340	345	350
[5046]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr			
[5047]		355	360	365
[5048]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu			
[5049]		370	375	380
[5050]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu			
[5051]	385	390	395	400
[5052]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys			
[5053]		405	410	415
[5054]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu			
[5055]		420	425	430
[5056]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly			
[5057]		435	440	445
[5058]	Lys			
[5059]	<210> 301			
[5060]	<211> 449			
[5061]	<212> PRT			
[5062]	<213> 人工序列(Artificial Sequence)			
[5063]	<220>			
[5064]	<223> 具有N297A突变的人源化IgG1重链			
[5065]	<400> 301			
[5066]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala			
[5067]	1	5	10	15
[5068]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr			
[5069]		20	25	30

[5070]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
[5071]			35					40					45			
[5072]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Asn	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[5073]		50					55					60				
[5074]	Lys	Gly	Arg	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
[5075]	65					70					75					80
[5076]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[5077]					85					90					95	
[5078]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[5079]				100					105					110		
[5080]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[5081]			115					120					125			
[5082]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[5083]		130					135					140				
[5084]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[5085]	145					150					155					160
[5086]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
[5087]					165					170					175	
[5088]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[5089]				180						185				190		
[5090]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[5091]			195					200					205			
[5092]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[5093]		210					215					220				
[5094]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[5095]	225					230					235					240
[5096]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[5097]				245						250					255	
[5098]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[5099]				260						265				270		
[5100]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
[5101]			275						280				285			
[5102]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg	Val
[5103]		290					295					300				
[5104]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
[5105]	305					310					315					320
[5106]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
[5107]					325					330				335		
[5108]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr

[5109]	340	345	350
[5110]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr		
[5111]	355	360	365
[5112]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
[5113]	370	375	380
[5114]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[5115]	385	390	395
[5116]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[5117]	405	410	415
[5118]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[5119]	420	425	430
[5120]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[5121]	435	440	445
[5122]	Lys		
[5123]	<210> 302		
[5124]	<211> 449		
[5125]	<212> PRT		
[5126]	<213> 人工序列(Artificial Sequence)		
[5127]	<220>		
[5128]	<223> 具有N297A突变的人源化IgG1重链		
[5129]	<400> 302		
[5130]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[5131]	1	5	10
[5132]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[5133]	20	25	30
[5134]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met		
[5135]	35	40	45
[5136]	Gly Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe		
[5137]	50	55	60
[5138]	Lys Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr		
[5139]	65	70	75
[5140]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys		
[5141]	85	90	95
[5142]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly		
[5143]	100	105	110
[5144]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe		
[5145]	115	120	125
[5146]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu		
[5147]	130	135	140

[5148]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
[5149]	145	150	155 160
[5150]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu		
[5151]		165	170 175
[5152]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser		
[5153]		180	185 190
[5154]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro		
[5155]		195	200 205
[5156]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys		
[5157]		210	215 220
[5158]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro		
[5159]	225	230	235 240
[5160]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser		
[5161]		245	250 255
[5162]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp		
[5163]		260	265 270
[5164]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn		
[5165]		275	280 285
[5166]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val		
[5167]		290	295 300
[5168]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
[5169]	305	310	315 320
[5170]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
[5171]		325	330 335
[5172]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
[5173]		340	345 350
[5174]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr		
[5175]		355	360 365
[5176]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
[5177]		370	375 380
[5178]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[5179]	385	390	395 400
[5180]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[5181]		405	410 415
[5182]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[5183]		420	425 430
[5184]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[5185]		435	440 445
[5186]	Lys		

[5187]	<210>	303
[5188]	<211>	449
[5189]	<212>	PRT
[5190]	<213>	人工序列(Artificial Sequence)
[5191]	<220>	
[5192]	<223>	具有N297A突变的人源化IgG1重链
[5193]	<400>	303
[5194]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala	
[5195]	1	5 10 15
[5196]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr	
[5197]	20	25 30
[5198]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met	
[5199]	35	40 45
[5200]	Gly Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe	
[5201]	50	55 60
[5202]	Lys Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr	
[5203]	65	70 75 80
[5204]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys	
[5205]	85	90 95
[5206]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly	
[5207]	100	105 110
[5208]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe	
[5209]	115	120 125
[5210]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu	
[5211]	130	135 140
[5212]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp	
[5213]	145	150 155 160
[5214]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu	
[5215]	165	170 175
[5216]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser	
[5217]	180	185 190
[5218]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro	
[5219]	195	200 205
[5220]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys	
[5221]	210	215 220
[5222]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro	
[5223]	225	230 235 240
[5224]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser	
[5225]	245	250 255

[5226]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
[5227]	260 265 270
[5228]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[5229]	275 280 285
[5230]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val
[5231]	290 295 300
[5232]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[5233]	305 310 315 320
[5234]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[5235]	325 330 335
[5236]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[5237]	340 345 350
[5238]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
[5239]	355 360 365
[5240]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[5241]	370 375 380
[5242]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[5243]	385 390 395 400
[5244]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[5245]	405 410 415
[5246]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[5247]	420 425 430
[5248]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[5249]	435 440 445
[5250]	Lys
[5251]	<210> 304
[5252]	<211> 449
[5253]	<212> PRT
[5254]	<213> 人工序列(Artificial Sequence)
[5255]	<220>
[5256]	<223> 具有CDR2突变且具有N297A突变的人源化IgG1重链
[5257]	<400> 304
[5258]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[5259]	1 5 10 15
[5260]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[5261]	20 25 30
[5262]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
[5263]	35 40 45
[5264]	Gly Glu Ile Phe Pro Arg Arg Val Gln Thr Tyr Tyr Ser Glu Lys Phe

[5265]	50	55	60
[5266]	Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr		
[5267]	65	70	75
[5268]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys		
[5269]	85	90	95
[5270]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly		
[5271]	100	105	110
[5272]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe		
[5273]	115	120	125
[5274]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu		
[5275]	130	135	140
[5276]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
[5277]	145	150	155
[5278]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu		
[5279]	165	170	175
[5280]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser		
[5281]	180	185	190
[5282]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro		
[5283]	195	200	205
[5284]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys		
[5285]	210	215	220
[5286]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro		
[5287]	225	230	235
[5288]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser		
[5289]	245	250	255
[5290]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp		
[5291]	260	265	270
[5292]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn		
[5293]	275	280	285
[5294]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val		
[5295]	290	295	300
[5296]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
[5297]	305	310	315
[5298]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
[5299]	325	330	335
[5300]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
[5301]	340	345	350
[5302]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr		
[5303]	355	360	365

[5304]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[5305]	370 375 380
[5306]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[5307]	385 390 395 400
[5308]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[5309]	405 410 415
[5310]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[5311]	420 425 430
[5312]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[5313]	435 440 445
[5314]	Lys
[5315]	<210> 305
[5316]	<211> 449
[5317]	<212> PRT
[5318]	<213> 人工序列(Artificial Sequence)
[5319]	<220>
[5320]	<223> 具有CDR2突变且具有N297A突变的人源化IgG1重链
[5321]	<400> 305
[5322]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[5323]	1 5 10 15
[5324]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[5325]	20 25 30
[5326]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
[5327]	35 40 45
[5328]	Gly Glu Ile Phe Pro Arg Arg Val Gln Thr Tyr Tyr Ser Glu Lys Phe
[5329]	50 55 60
[5330]	Lys Gly Arg Ala Thr Leu Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
[5331]	65 70 75 80
[5332]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
[5333]	85 90 95
[5334]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[5335]	100 105 110
[5336]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[5337]	115 120 125
[5338]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
[5339]	130 135 140
[5340]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[5341]	145 150 155 160
[5342]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

[5343]		165		170		175
[5344]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser					
[5345]		180		185		190
[5346]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro					
[5347]		195		200		205
[5348]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys					
[5349]		210		215		220
[5350]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro					
[5351]	225		230		235	240
[5352]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser					
[5353]		245		250		255
[5354]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp					
[5355]		260		265		270
[5356]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn					
[5357]		275		280		285
[5358]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val					
[5359]		290		295		300
[5360]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu					
[5361]	305		310		315	320
[5362]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys					
[5363]		325		330		335
[5364]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr					
[5365]		340		345		350
[5366]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr					
[5367]		355		360		365
[5368]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu					
[5369]		370		375		380
[5370]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu					
[5371]	385		390		395	400
[5372]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys					
[5373]		405		410		415
[5374]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu					
[5375]		420		425		430
[5376]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly					
[5377]		435		440		445
[5378]	Lys					
[5379]	<210> 306					
[5380]	<211> 449					
[5381]	<212> PRT					

[5382]	<213> 人工序列(Artificial Sequence)															
[5383]	<220>															
[5384]	<223> 具有CDR2突变且具有N297A突变的人源化IgG1重链															
[5385]	<400> 306															
[5386]	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
[5387]	1				5					10					15	
[5388]	Ser	Val	Lys	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Gly	Tyr
[5389]					20					25					30	
[5390]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
[5391]					35					40					45	
[5392]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Gln	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[5393]					50					55					60	
[5394]	Lys	Gly	Arg	Ala	Thr	Leu	Thr	Ala	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
[5395]	65					70					75					80
[5396]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Phe	Cys
[5397]						85					90					95
[5398]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[5399]						100					105				110	
[5400]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[5401]						115					120				125	
[5402]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[5403]						130					135				140	
[5404]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[5405]	145					150					155					160
[5406]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
[5407]						165					170					175
[5408]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[5409]						180					185				190	
[5410]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[5411]						195					200				205	
[5412]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[5413]						210					215				220	
[5414]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[5415]	225						230				235					240
[5416]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[5417]						245					250					255
[5418]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[5419]						260					265				270	
[5420]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn

[5421]	275	280	285
[5422]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val		
[5423]	290	295	300
[5424]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
[5425]	305	310	315
[5426]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
[5427]	325	330	335
[5428]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
[5429]	340	345	350
[5430]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr		
[5431]	355	360	365
[5432]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
[5433]	370	375	380
[5434]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[5435]	385	390	395
[5436]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[5437]	405	410	415
[5438]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[5439]	420	425	430
[5440]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[5441]	435	440	445
[5442]	Lys		
[5443]	<210> 307		
[5444]	<211> 449		
[5445]	<212> PRT		
[5446]	<213> 人工序列(Artificial Sequence)		
[5447]	<220>		
[5448]	<223> 具有CDR2突变且具有N297A突变的人源化IgG1重链		
[5449]	<400> 307		
[5450]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[5451]	1	5	10
[5452]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[5453]	20	25	30
[5454]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met		
[5455]	35	40	45
[5456]	Gly Glu Ile Phe Pro Arg Arg Val Gln Thr Tyr Tyr Ser Glu Lys Phe		
[5457]	50	55	60
[5458]	Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr		
[5459]	65	70	75
			80

[5460]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[5461]					85				90					95		
[5462]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[5463]					100				105					110		
[5464]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[5465]					115				120					125		
[5466]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[5467]					130				135					140		
[5468]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[5469]	145					150				155						160
[5470]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
[5471]					165					170						175
[5472]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[5473]					180					185						190
[5474]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[5475]					195				200					205		
[5476]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[5477]					210				215					220		
[5478]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[5479]	225					230					235					240
[5480]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[5481]					245					250						255
[5482]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[5483]					260					265						270
[5484]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
[5485]					275					280						285
[5486]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg	Val
[5487]					290					295				300		
[5488]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
[5489]	305					310					315					320
[5490]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
[5491]					325					330						335
[5492]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
[5493]					340					345						350
[5494]	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
[5495]					355					360						365
[5496]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
[5497]					370					375						380
[5498]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu

[5499]	385	390	395	400
[5500]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys			
[5501]	405	410	415	
[5502]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu			
[5503]	420	425	430	
[5504]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly			
[5505]	435	440	445	
[5506]	Lys			
[5507]	<210> 308			
[5508]	<211> 449			
[5509]	<212> PRT			
[5510]	<213> 人工序列(Artificial Sequence)			
[5511]	<220>			
[5512]	<223> 具有CDR2突变且具有N297A突变的人源化IgG1重链			
[5513]	<400> 308			
[5514]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala			
[5515]	1 5 10 15			
[5516]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr			
[5517]	20 25 30			
[5518]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met			
[5519]	35 40 45			
[5520]	Gly Glu Ile Phe Pro Arg Arg Val Gln Thr Tyr Tyr Ser Glu Lys Phe			
[5521]	50 55 60			
[5522]	Lys Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr			
[5523]	65 70 75 80			
[5524]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys			
[5525]	85 90 95			
[5526]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly			
[5527]	100 105 110			
[5528]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe			
[5529]	115 120 125			
[5530]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu			
[5531]	130 135 140			
[5532]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp			
[5533]	145 150 155 160			
[5534]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu			
[5535]	165 170 175			
[5536]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser			
[5537]	180 185 190			

[5538]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[5539]	195 200 205
[5540]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
[5541]	210 215 220
[5542]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
[5543]	225 230 235 240
[5544]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[5545]	245 250 255
[5546]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
[5547]	260 265 270
[5548]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[5549]	275 280 285
[5550]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val
[5551]	290 295 300
[5552]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[5553]	305 310 315 320
[5554]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[5555]	325 330 335
[5556]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[5557]	340 345 350
[5558]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
[5559]	355 360 365
[5560]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[5561]	370 375 380
[5562]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[5563]	385 390 395 400
[5564]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[5565]	405 410 415
[5566]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[5567]	420 425 430
[5568]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[5569]	435 440 445
[5570]	Lys
[5571]	<210> 309
[5572]	<211> 449
[5573]	<212> PRT
[5574]	<213> 人工序列(Artificial Sequence)
[5575]	<220>
[5576]	<223> 具有CDR2突变且具有N297A突变的人源化IgG1重链

[5577]	<400> 309																
[5578]	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala	
[5579]	1			5			10			15							
[5580]	Ser	Val	Lys	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Gly	Tyr	
[5581]				20			25			30							
[5582]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	
[5583]				35			40			45							
[5584]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Gln	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe	
[5585]	50						55			60							
[5586]	Lys	Gly	Arg	Val	Thr	Met	Thr	Ala	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr	
[5587]	65			70						75			80				
[5588]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
[5589]				85			90			95							
[5590]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	
[5591]				100			105			110							
[5592]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	
[5593]				115			120			125							
[5594]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	
[5595]	130						135			140							
[5596]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	
[5597]	145			150						155			160				
[5598]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	
[5599]				165			170			175							
[5600]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	
[5601]				180			185			190							
[5602]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	
[5603]				195			200			205							
[5604]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	
[5605]	210						215			220							
[5606]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	
[5607]	225			230						235			240				
[5608]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	
[5609]				245			250			255							
[5610]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	
[5611]				260			265			270							
[5612]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	
[5613]	275						280			285							
[5614]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg	Val	
[5615]	290						295			300							

[5616]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[5617]	305 310 315 320
[5618]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[5619]	325 330 335
[5620]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[5621]	340 345 350
[5622]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
[5623]	355 360 365
[5624]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[5625]	370 375 380
[5626]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[5627]	385 390 395 400
[5628]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[5629]	405 410 415
[5630]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[5631]	420 425 430
[5632]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[5633]	435 440 445
[5634]	Lys
[5635]	<210> 310
[5636]	<211> 449
[5637]	<212> PRT
[5638]	<213> 人工序列(Artificial Sequence)
[5639]	<220>
[5640]	<223> 具有CDR2突变且具有N297A突变的人源化IgG1重链
[5641]	<400> 310
[5642]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[5643]	1 5 10 15
[5644]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[5645]	20 25 30
[5646]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
[5647]	35 40 45
[5648]	Gly Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe
[5649]	50 55 60
[5650]	Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
[5651]	65 70 75 80
[5652]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
[5653]	85 90 95
[5654]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly

[5655]				100					105					110			
[5656]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	
[5657]				115					120					125			
[5658]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	
[5659]				130					135					140			
[5660]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	
[5661]	145							150					155			160	
[5662]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	
[5663]					165					170					175		
[5664]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	
[5665]				180					185					190			
[5666]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	
[5667]				195					200					205			
[5668]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	
[5669]				210					215					220			
[5670]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	
[5671]	225							230					235			240	
[5672]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	
[5673]					245					250					255		
[5674]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	
[5675]				260					265					270			
[5676]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	
[5677]				275					280					285			
[5678]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg	Val	
[5679]		290						295					300				
[5680]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	
[5681]	305							310					315			320	
[5682]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	
[5683]					325					330					335		
[5684]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	
[5685]				340					345					350			
[5686]	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	
[5687]				355					360					365			
[5688]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	
[5689]		370						375				380					
[5690]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	
[5691]	385							390				395				400	
[5692]	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	
[5693]					405					410					415		

[5694]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[5695]	420 425 430
[5696]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[5697]	435 440 445
[5698]	Lys
[5699]	<210> 311
[5700]	<211> 449
[5701]	<212> PRT
[5702]	<213> 人工序列(Artificial Sequence)
[5703]	<220>
[5704]	<223> 具有CDR2突变且具有N297A突变的人源化IgG1重链
[5705]	<400> 311
[5706]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[5707]	1 5 10 15
[5708]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[5709]	20 25 30
[5710]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
[5711]	35 40 45
[5712]	Gly Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe
[5713]	50 55 60
[5714]	Lys Gly Arg Ala Thr Leu Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
[5715]	65 70 75 80
[5716]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
[5717]	85 90 95
[5718]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[5719]	100 105 110
[5720]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[5721]	115 120 125
[5722]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
[5723]	130 135 140
[5724]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[5725]	145 150 155 160
[5726]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[5727]	165 170 175
[5728]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[5729]	180 185 190
[5730]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[5731]	195 200 205
[5732]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

[5733]	210	215	220
[5734]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro		
[5735]	225	230	235 240
[5736]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser		
[5737]	245	250	255
[5738]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp		
[5739]	260	265	270
[5740]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn		
[5741]	275	280	285
[5742]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val		
[5743]	290	295	300
[5744]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
[5745]	305	310	315 320
[5746]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
[5747]	325	330	335
[5748]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
[5749]	340	345	350
[5750]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr		
[5751]	355	360	365
[5752]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
[5753]	370	375	380
[5754]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[5755]	385	390	395 400
[5756]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[5757]	405	410	415
[5758]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[5759]	420	425	430
[5760]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[5761]	435	440	445
[5762]	Lys		
[5763]	<210> 312		
[5764]	<211> 449		
[5765]	<212> PRT		
[5766]	<213> 人工序列(Artificial Sequence)		
[5767]	<220>		
[5768]	<223> 具有CDR2突变且具有N297A突变的人源化IgG1重链		
[5769]	<400> 312		
[5770]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[5771]	1	5	10 15

[5772]	Ser	Val	Lys	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Gly	Tyr
[5773]				20					25					30		
[5774]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
[5775]				35				40					45			
[5776]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Ser	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[5777]		50					55				60					
[5778]	Lys	Gly	Arg	Ala	Thr	Leu	Thr	Ala	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
[5779]	65					70				75					80	
[5780]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Phe	Cys
[5781]				85					90					95		
[5782]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[5783]				100					105					110		
[5784]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[5785]				115				120					125			
[5786]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[5787]		130					135				140					
[5788]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[5789]	145					150				155					160	
[5790]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
[5791]				165					170					175		
[5792]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[5793]				180					185					190		
[5794]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[5795]			195				200					205				
[5796]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[5797]		210					215				220					
[5798]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[5799]	225					230				235					240	
[5800]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[5801]				245					250					255		
[5802]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[5803]				260					265					270		
[5804]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
[5805]			275				280				285					
[5806]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg	Val
[5807]		290					295				300					
[5808]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
[5809]	305					310				315				320		
[5810]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys

[5811]		325		330		335
[5812]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr					
[5813]		340		345		350
[5814]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr					
[5815]		355		360		365
[5816]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu					
[5817]		370		375		380
[5818]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu					
[5819]	385		390		395	400
[5820]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys					
[5821]		405		410		415
[5822]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu					
[5823]		420		425		430
[5824]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly					
[5825]		435		440		445
[5826]	Lys					
[5827]	<210> 313					
[5828]	<211> 449					
[5829]	<212> PRT					
[5830]	<213> 人工序列(Artificial Sequence)					
[5831]	<220>					
[5832]	<223> 具有CDR2突变且具有N297A突变的人源化IgG1重链					
[5833]	<400> 313					
[5834]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala					
[5835]	1	5		10		15
[5836]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr					
[5837]		20		25		30
[5838]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met					
[5839]		35		40		45
[5840]	Gly Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe					
[5841]		50		55		60
[5842]	Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr					
[5843]	65		70		75	80
[5844]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys					
[5845]		85		90		95
[5846]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly					
[5847]		100		105		110
[5848]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe					
[5849]		115		120		125

[5850]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[5851]	130						135					140				
[5852]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[5853]	145					150					155					160
[5854]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
[5855]					165					170					175	
[5856]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[5857]				180					185					190		
[5858]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[5859]			195					200					205			
[5860]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[5861]		210					215					220				
[5862]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[5863]	225					230					235					240
[5864]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[5865]				245						250					255	
[5866]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[5867]			260						265					270		
[5868]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
[5869]			275					280					285			
[5870]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg	Val
[5871]		290					295					300				
[5872]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
[5873]	305					310					315					320
[5874]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
[5875]				325						330					335	
[5876]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
[5877]			340						345					350		
[5878]	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
[5879]			355					360					365			
[5880]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
[5881]		370					375					380				
[5882]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
[5883]	385					390					395					400
[5884]	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
[5885]				405						410					415	
[5886]	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
[5887]				420					425					430		
[5888]	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly

[5889]	435	440	445
[5890]	Lys		
[5891]	<210> 314		
[5892]	<211> 449		
[5893]	<212> PRT		
[5894]	<213> 人工序列(Artificial Sequence)		
[5895]	<220>		
[5896]	<223> 具有CDR2突变且具有N297A突变的人源化IgG1重链		
[5897]	<400> 314		
[5898]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[5899]	1 5 10 15		
[5900]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[5901]	20 25 30		
[5902]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met		
[5903]	35 40 45		
[5904]	Gly Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe		
[5905]	50 55 60		
[5906]	Lys Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr		
[5907]	65 70 75 80		
[5908]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys		
[5909]	85 90 95		
[5910]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly		
[5911]	100 105 110		
[5912]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe		
[5913]	115 120 125		
[5914]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu		
[5915]	130 135 140		
[5916]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
[5917]	145 150 155 160		
[5918]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu		
[5919]	165 170 175		
[5920]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser		
[5921]	180 185 190		
[5922]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro		
[5923]	195 200 205		
[5924]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys		
[5925]	210 215 220		
[5926]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro		
[5927]	225 230 235 240		

[5928]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[5929]	245 250 255
[5930]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
[5931]	260 265 270
[5932]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[5933]	275 280 285
[5934]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val
[5935]	290 295 300
[5936]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[5937]	305 310 315 320
[5938]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[5939]	325 330 335
[5940]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[5941]	340 345 350
[5942]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
[5943]	355 360 365
[5944]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[5945]	370 375 380
[5946]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[5947]	385 390 395 400
[5948]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[5949]	405 410 415
[5950]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[5951]	420 425 430
[5952]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[5953]	435 440 445
[5954]	Lys
[5955]	<210> 315
[5956]	<211> 449
[5957]	<212> PRT
[5958]	<213> 人工序列(Artificial Sequence)
[5959]	<220>
[5960]	<223> 具有CDR2突变且具有N297A突变的人源化IgG1重链
[5961]	<400> 315
[5962]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[5963]	1 5 10 15
[5964]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[5965]	20 25 30
[5966]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

[5967]	35	40	45
[5968]	Gly Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe		
[5969]	50	55	60
[5970]	Lys Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr		
[5971]	65	70	75
[5972]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys		
[5973]	85	90	95
[5974]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly		
[5975]	100	105	110
[5976]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe		
[5977]	115	120	125
[5978]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu		
[5979]	130	135	140
[5980]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
[5981]	145	150	155
[5982]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu		
[5983]	165	170	175
[5984]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser		
[5985]	180	185	190
[5986]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro		
[5987]	195	200	205
[5988]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys		
[5989]	210	215	220
[5990]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro		
[5991]	225	230	235
[5992]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser		
[5993]	245	250	255
[5994]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp		
[5995]	260	265	270
[5996]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn		
[5997]	275	280	285
[5998]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val		
[5999]	290	295	300
[6000]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
[6001]	305	310	315
[6002]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
[6003]	325	330	335
[6004]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
[6005]	340	345	350

[6006]	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
[6007]				355				360					365			
[6008]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
[6009]			370					375					380			
[6010]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
[6011]	385					390					395					400
[6012]	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
[6013]					405					410					415	
[6014]	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
[6015]				420					425					430		
[6016]	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
[6017]			435					440						445		
[6018]	Lys															
[6019]	<210>	316														
[6020]	<211>	449														
[6021]	<212>	PRT														
[6022]	<213>	人工序列(Artificial Sequence)														
[6023]	<220>															
[6024]	<223>	具有CDR2突变且具有N297A突变的人源化IgG1重链														
[6025]	<400>	316														
[6026]	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
[6027]	1			5					10					15		
[6028]	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Gly	Tyr
[6029]			20					25					30			
[6030]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
[6031]		35				40							45			
[6032]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Ala	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[6033]		50				55						60				
[6034]	Lys	Gly	Arg	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
[6035]	65					70				75					80	
[6036]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[6037]				85					90					95		
[6038]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[6039]			100					105					110			
[6040]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[6041]			115					120					125			
[6042]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[6043]		130					135					140				
[6044]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp

[6045]	145	150	155	160
[6046]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu			
[6047]		165	170	175
[6048]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser			
[6049]		180	185	190
[6050]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro			
[6051]		195	200	205
[6052]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys			
[6053]		210	215	220
[6054]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro			
[6055]	225	230	235	240
[6056]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser			
[6057]		245	250	255
[6058]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp			
[6059]		260	265	270
[6060]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn			
[6061]		275	280	285
[6062]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val			
[6063]		290	295	300
[6064]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu			
[6065]	305	310	315	320
[6066]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys			
[6067]		325	330	335
[6068]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr			
[6069]		340	345	350
[6070]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr			
[6071]		355	360	365
[6072]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu			
[6073]		370	375	380
[6074]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu			
[6075]	385	390	395	400
[6076]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys			
[6077]		405	410	415
[6078]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu			
[6079]		420	425	430
[6080]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly			
[6081]		435	440	445
[6082]	Lys			
[6083]	<210> 317			

[6084]	<211>	449
[6085]	<212>	PRT
[6086]	<213>	人工序列(Artificial Sequence)
[6087]	<220>	
[6088]	<223>	具有CDR2突变且具有N297A突变的人源化IgG1重链
[6089]	<400>	317
[6090]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala	
[6091]	1	5 10 15
[6092]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr	
[6093]	20	25 30
[6094]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile	
[6095]	35	40 45
[6096]	Gly Glu Ile Phe Pro Arg Arg Val Ala Thr Tyr Tyr Ser Glu Lys Phe	
[6097]	50	55 60
[6098]	Lys Gly Arg Ala Thr Leu Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr	
[6099]	65	70 75 80
[6100]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys	
[6101]	85	90 95
[6102]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly	
[6103]	100	105 110
[6104]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe	
[6105]	115	120 125
[6106]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu	
[6107]	130	135 140
[6108]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp	
[6109]	145	150 155 160
[6110]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu	
[6111]	165	170 175
[6112]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser	
[6113]	180	185 190
[6114]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro	
[6115]	195	200 205
[6116]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys	
[6117]	210	215 220
[6118]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro	
[6119]	225	230 235 240
[6120]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser	
[6121]	245	250 255
[6122]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp	

[6123]	260	265	270
[6124]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn		
[6125]	275	280	285
[6126]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val		
[6127]	290	295	300
[6128]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
[6129]	305	310	315
[6130]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
[6131]	325	330	335
[6132]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
[6133]	340	345	350
[6134]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr		
[6135]	355	360	365
[6136]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
[6137]	370	375	380
[6138]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[6139]	385	390	395
[6140]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[6141]	405	410	415
[6142]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[6143]	420	425	430
[6144]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[6145]	435	440	445
[6146]	Lys		
[6147]	<210> 318		
[6148]	<211> 449		
[6149]	<212> PRT		
[6150]	<213> 人工序列(Artificial Sequence)		
[6151]	<220>		
[6152]	<223> 具有CDR2突变且具有N297A突变的人源化IgG1重链		
[6153]	<400> 318		
[6154]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[6155]	1 5 10 15		
[6156]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[6157]	20 25 30		
[6158]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile		
[6159]	35 40 45		
[6160]	Gly Glu Ile Phe Pro Arg Arg Val Ala Thr Tyr Tyr Ser Glu Lys Phe		
[6161]	50 55 60		

[6162]	Lys Gly Arg Ala Thr Leu Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
[6163]	65 70 75 80
[6164]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
[6165]	85 90 95
[6166]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[6167]	100 105 110
[6168]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[6169]	115 120 125
[6170]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
[6171]	130 135 140
[6172]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[6173]	145 150 155 160
[6174]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[6175]	165 170 175
[6176]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[6177]	180 185 190
[6178]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[6179]	195 200 205
[6180]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
[6181]	210 215 220
[6182]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
[6183]	225 230 235 240
[6184]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[6185]	245 250 255
[6186]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
[6187]	260 265 270
[6188]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[6189]	275 280 285
[6190]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val
[6191]	290 295 300
[6192]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[6193]	305 310 315 320
[6194]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[6195]	325 330 335
[6196]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[6197]	340 345 350
[6198]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
[6199]	355 360 365
[6200]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu

[6201]	370	375	380
[6202]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[6203]	385	390	395 400
[6204]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[6205]	405	410	415
[6206]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[6207]	420	425	430
[6208]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[6209]	435	440	445
[6210]	Lys		
[6211]	<210> 319		
[6212]	<211> 449		
[6213]	<212> PRT		
[6214]	<213> 人工序列(Artificial Sequence)		
[6215]	<220>		
[6216]	<223> 具有CDR2突变且具有N297A突变的人源化IgG1重链		
[6217]	<400> 319		
[6218]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[6219]	1 5 10 15		
[6220]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[6221]	20 25 30		
[6222]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met		
[6223]	35 40 45		
[6224]	Gly Glu Ile Phe Pro Arg Arg Val Ala Thr Tyr Tyr Ser Glu Lys Phe		
[6225]	50 55 60		
[6226]	Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr		
[6227]	65 70 75 80		
[6228]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys		
[6229]	85 90 95		
[6230]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly		
[6231]	100 105 110		
[6232]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe		
[6233]	115 120 125		
[6234]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu		
[6235]	130 135 140		
[6236]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
[6237]	145 150 155 160		
[6238]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu		
[6239]	165 170 175		

[6240]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[6241]	180 185 190
[6242]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[6243]	195 200 205
[6244]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
[6245]	210 215 220
[6246]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
[6247]	225 230 235 240
[6248]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[6249]	245 250 255
[6250]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
[6251]	260 265 270
[6252]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[6253]	275 280 285
[6254]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val
[6255]	290 295 300
[6256]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[6257]	305 310 315 320
[6258]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[6259]	325 330 335
[6260]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[6261]	340 345 350
[6262]	Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
[6263]	355 360 365
[6264]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[6265]	370 375 380
[6266]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[6267]	385 390 395 400
[6268]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[6269]	405 410 415
[6270]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[6271]	420 425 430
[6272]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[6273]	435 440 445
[6274]	Lys
[6275]	<210> 320
[6276]	<211> 449
[6277]	<212> PRT
[6278]	<213> 人工序列(Artificial Sequence)

[6279]	<220>	
[6280]	<223>	具有CDR2突变且具有N297A突变的人源化IgG1重链
[6281]	<400>	320
[6282]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala	
[6283]	1	5 10 15
[6284]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr	
[6285]	20	25 30
[6286]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met	
[6287]	35	40 45
[6288]	Gly Glu Ile Phe Pro Arg Arg Val Ala Thr Tyr Tyr Ser Glu Lys Phe	
[6289]	50	55 60
[6290]	Lys Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr	
[6291]	65	70 75 80
[6292]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys	
[6293]	85	90 95
[6294]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly	
[6295]	100	105 110
[6296]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe	
[6297]	115	120 125
[6298]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu	
[6299]	130	135 140
[6300]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp	
[6301]	145	150 155 160
[6302]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu	
[6303]	165	170 175
[6304]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser	
[6305]	180	185 190
[6306]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro	
[6307]	195	200 205
[6308]	Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys	
[6309]	210	215 220
[6310]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro	
[6311]	225	230 235 240
[6312]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser	
[6313]	245	250 255
[6314]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp	
[6315]	260	265 270
[6316]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn	
[6317]	275	280 285

[6318]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg	Val
[6319]	290						295					300				
[6320]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
[6321]	305						310				315				320	
[6322]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
[6323]					325					330					335	
[6324]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
[6325]				340					345					350		
[6326]	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
[6327]				355				360					365			
[6328]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
[6329]	370						375					380				
[6330]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
[6331]	385					390					395				400	
[6332]	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
[6333]				405						410					415	
[6334]	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
[6335]				420					425					430		
[6336]	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
[6337]		435					440						445			
[6338]	Lys															
[6339]	<210>	321														
[6340]	<211>	449														
[6341]	<212>	PRT														
[6342]	<213>	人工序列(Artificial Sequence)														
[6343]	<220>															
[6344]	<223>	具有CDR2突变且具有N297A突变的人源化IgG1重链														
[6345]	<400>	321														
[6346]	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
[6347]	1			5					10					15		
[6348]	Ser	Val	Lys	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Gly	Tyr
[6349]			20						25					30		
[6350]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
[6351]		35					40						45			
[6352]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Ala	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[6353]		50					55						60			
[6354]	Lys	Gly	Arg	Val	Thr	Met	Thr	Ala	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
[6355]	65					70					75				80	
[6356]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys

[6357]					85					90						95
[6358]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[6359]					100					105						110
[6360]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[6361]					115					120						125
[6362]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[6363]					130					135						140
[6364]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[6365]					145					150						160
[6366]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
[6367]					165					170						175
[6368]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[6369]					180					185						190
[6370]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[6371]					195					200						205
[6372]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[6373]					210					215						220
[6374]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[6375]					225					230						240
[6376]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[6377]					245					250						255
[6378]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[6379]					260					265						270
[6380]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
[6381]					275					280						285
[6382]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg	Val
[6383]					290					295						300
[6384]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
[6385]					305					310						320
[6386]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
[6387]					325					330						335
[6388]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
[6389]					340					345						350
[6390]	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
[6391]					355					360						365
[6392]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
[6393]					370					375						380
[6394]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
[6395]					385					390						400

[6396]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[6397]	405 410 415
[6398]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[6399]	420 425 430
[6400]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[6401]	435 440 445
[6402]	Lys
[6403]	<210> 322
[6404]	<211> 218
[6405]	<212> PRT
[6406]	<213> 人工序列(Artificial Sequence)
[6407]	<220>
[6408]	<223> 嵌合κ轻链
[6409]	<400> 322
[6410]	Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
[6411]	1 5 10 15
[6412]	Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Thr Tyr
[6413]	20 25 30
[6414]	Gly Asp Ser Phe Met His Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro
[6415]	35 40 45
[6416]	Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
[6417]	50 55 60
[6418]	Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn
[6419]	65 70 75 80
[6420]	Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
[6421]	85 90 95
[6422]	Glu Ala Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
[6423]	100 105 110
[6424]	Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
[6425]	115 120 125
[6426]	Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
[6427]	130 135 140
[6428]	Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
[6429]	145 150 155 160
[6430]	Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
[6431]	165 170 175
[6432]	Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
[6433]	180 185 190
[6434]	His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro

[6435]	195	200	205
[6436]	Val Thr Lys Ser Phe Asn Arg Gly Glu Cys		
[6437]	210	215	
[6438]	<210> 323		
[6439]	<211> 214		
[6440]	<212> PRT		
[6441]	<213> 人工序列(Artificial Sequence)		
[6442]	<220>		
[6443]	<223> 嵌合κ轻链		
[6444]	<400> 323		
[6445]	Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly		
[6446]	1 5 10 15		
[6447]	Gly Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Pro Ala		
[6448]	20 25 30		
[6449]	Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile		
[6450]	35 40 45		
[6451]	Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly		
[6452]	50 55 60		
[6453]	Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Thr		
[6454]	65 70 75 80		
[6455]	Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp		
[6456]	85 90 95		
[6457]	Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala		
[6458]	100 105 110		
[6459]	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly		
[6460]	115 120 125		
[6461]	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala		
[6462]	130 135 140		
[6463]	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln		
[6464]	145 150 155 160		
[6465]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser		
[6466]	165 170 175		
[6467]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr		
[6468]	180 185 190		
[6469]	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser		
[6470]	195 200 205		
[6471]	Phe Asn Arg Gly Glu Cys		
[6472]	210		
[6473]	<210> 324		

[6474]	<211>	214
[6475]	<212>	PRT
[6476]	<213>	人工序列(Artificial Sequence)
[6477]	<220>	
[6478]	<223>	嵌合κ轻链
[6479]	<400>	324
[6480]	Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly	
[6481]	1	5 10 15
[6482]	Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala	
[6483]	20	25 30
[6484]	Val Asp Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile	
[6485]	35	40 45
[6486]	Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly	
[6487]	50	55 60
[6488]	Ser Gly Ser Gly Thr Ala Phe Thr Phe Thr Ile Ser Ser Glu Gln Ala	
[6489]	65	70 75 80
[6490]	Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Val Pro Phe	
[6491]	85	90 95
[6492]	Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala	
[6493]	100	105 110
[6494]	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly	
[6495]	115	120 125
[6496]	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala	
[6497]	130	135 140
[6498]	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln	
[6499]	145	150 155 160
[6500]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser	
[6501]	165	170 175
[6502]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr	
[6503]	180	185 190
[6504]	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser	
[6505]	195	200 205
[6506]	Phe Asn Arg Gly Glu Cys	
[6507]	210	
[6508]	<210>	325
[6509]	<211>	213
[6510]	<212>	PRT
[6511]	<213>	人工序列(Artificial Sequence)
[6512]	<220>	

[6513]	<223> 嵌合κ轻链															
[6514]	<400> 325															
[6515]	Gln	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Ile	Met	Ser	Ala	Ser	Pro	Gly
[6516]	1				5					10					15	
[6517]	Glu	Lys	Val	Thr	Ile	Ser	Cys	Ser	Ala	Ser	Ser	Phe	Ile	Asn	Tyr	Met
[6518]					20					25					30	
[6519]	Tyr	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Ser	Ser	Pro	Lys	Pro	Trp	Ile	Leu
[6520]					35					40					45	
[6521]	Arg	Thr	Ser	Thr	Leu	Ala	Ser	Gly	Val	Pro	Ala	Arg	Phe	Ser	Gly	Ser
[6522]					50					55					60	
[6523]	Gly	Ser	Gly	Thr	Ser	Tyr	Ser	Leu	Thr	Ile	Ser	Ser	Met	Glu	Ala	Glu
[6524]	65									70					75	80
[6525]	Asp	Ala	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	His	Ser	Tyr	Pro	Leu	Thr
[6526]										85					90	95
[6527]	Phe	Gly	Ala	Gly	Thr	Lys	Leu	Glu	Leu	Lys	Arg	Thr	Val	Ala	Ala	Pro
[6528]										100					105	110
[6529]	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly	Thr
[6530]										115					120	125
[6531]	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala	Lys
[6532]										130					135	140
[6533]	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln	Glu
[6534]	145									150					155	160
[6535]	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser	Ser
[6536]										165					170	175
[6537]	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr	Ala
[6538]										180					185	190
[6539]	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser	Phe
[6540]										195					200	205
[6541]	Asn	Arg	Gly	Glu	Cys											
[6542]										210						
[6543]	<210> 326															
[6544]	<211> 214															
[6545]	<212> PRT															
[6546]	<213> 人工序列(Artificial Sequence)															
[6547]	<220>															
[6548]	<223> 嵌合κ轻链															
[6549]	<400> 326															
[6550]	Asp	Ile	Val	Met	Thr	Gln	Ser	His	Lys	Phe	Met	Ser	Thr	Ser	Val	Gly
[6551]	1					5					10					15

[6552]	Asp	Arg	Val	Ser	Ile	Thr	Cys	Lys	Ala	Ser	Gln	Asp	Val	Ser	Thr	Ala
[6553]				20					25					30		
[6554]	Val	Asp	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ser	Pro	Lys	Leu	Leu	Ile
[6555]				35				40					45			
[6556]	Tyr	Ser	Ala	Ser	Tyr	Arg	Tyr	Thr	Gly	Val	Pro	Asp	Arg	Phe	Thr	Gly
[6557]		50					55					60				
[6558]	Ser	Gly	Ser	Gly	Thr	Ala	Phe	Thr	Phe	Thr	Ile	Ser	Gly	Glu	Gln	Ala
[6559]	65					70					75				80	
[6560]	Glu	Asp	Leu	Ala	Val	Tyr	Tyr	Cys	Gln	Gln	His	Tyr	Ser	Ile	Pro	Phe
[6561]					85					90				95		
[6562]	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala
[6563]				100					105					110		
[6564]	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly
[6565]			115					120					125			
[6566]	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
[6567]		130					135					140				
[6568]	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
[6569]	145					150					155				160	
[6570]	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
[6571]				165					170					175		
[6572]	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr
[6573]			180						185					190		
[6574]	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser
[6575]			195					200					205			
[6576]	Phe	Asn	Arg	Gly	Glu	Cys										
[6577]		210														
[6578]	<210>	327														
[6579]	<211>	215														
[6580]	<212>	PRT														
[6581]	<213>	人工序列(Artificial Sequence)														
[6582]	<220>															
[6583]	<223>	嵌合κ轻链														
[6584]	<400>	327														
[6585]	Gln	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Ile	Met	Ser	Ala	Ser	Pro	Gly
[6586]	1			5					10					15		
[6587]	Glu	Lys	Val	Thr	Leu	Thr	Cys	Ser	Ala	Ser	Ser	Ser	Val	Ser	Ser	Ser
[6588]				20					25					30		
[6589]	Tyr	Leu	Tyr	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Ser	Ser	Pro	Lys	Leu	Trp
[6590]			35					40						45		

[6591]	Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser
[6592]	50 55 60
[6593]	Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Val Ser Ser Met Glu
[6594]	65 70 75 80
[6595]	Ala Glu Asp Ala Ala Ser Tyr Phe Cys His Gln Trp Ser Ser Tyr Pro
[6596]	85 90 95
[6597]	Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala
[6598]	100 105 110
[6599]	Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
[6600]	115 120 125
[6601]	Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
[6602]	130 135 140
[6603]	Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
[6604]	145 150 155 160
[6605]	Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
[6606]	165 170 175
[6607]	Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
[6608]	180 185 190
[6609]	Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
[6610]	195 200 205
[6611]	Ser Phe Asn Arg Gly Glu Cys
[6612]	210 215
[6613]	<210> 328
[6614]	<211> 219
[6615]	<212> PRT
[6616]	<213> 人工序列(Artificial Sequence)
[6617]	<220>
[6618]	<223> 嵌合κ轻链
[6619]	<400> 328
[6620]	Ser Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
[6621]	1 5 10 15
[6622]	Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Asn Ile Val Tyr Ser
[6623]	20 25 30
[6624]	Asp Gly Asp Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
[6625]	35 40 45
[6626]	Pro Lys Leu Leu Ile Phe Lys Val Ser Asn Arg Phe Phe Gly Val Pro
[6627]	50 55 60
[6628]	Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
[6629]	65 70 75 80

[6630]	Asn Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
[6631]	85 90 95
[6632]	Ser His Val Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
[6633]	100 105 110
[6634]	Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
[6635]	115 120 125
[6636]	Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
[6637]	130 135 140
[6638]	Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
[6639]	145 150 155 160
[6640]	Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
[6641]	165 170 175
[6642]	Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
[6643]	180 185 190
[6644]	Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
[6645]	195 200 205
[6646]	Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
[6647]	210 215
[6648]	<210> 329
[6649]	<211> 219
[6650]	<212> PRT
[6651]	<213> 人工序列(Artificial Sequence)
[6652]	<220>
[6653]	<223> 嵌合κ轻链
[6654]	<400> 329
[6655]	Asp Val Leu Met Asn Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
[6656]	1 5 10 15
[6657]	Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Asn Ile Val Tyr Ser
[6658]	20 25 30
[6659]	Asp Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
[6660]	35 40 45
[6661]	Pro Lys Leu Leu Ile Phe Gln Val Ser Asn Arg Phe Ser Gly Val Pro
[6662]	50 55 60
[6663]	Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
[6664]	65 70 75 80
[6665]	Ser Arg Val Glu Ala Glu Asp Leu Gly Phe Tyr Tyr Cys Phe Gln Gly
[6666]	85 90 95
[6667]	Ser His Val Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
[6668]	100 105 110

[6669]	Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
[6670]	115 120 125
[6671]	Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
[6672]	130 135 140
[6673]	Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
[6674]	145 150 155 160
[6675]	Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
[6676]	165 170 175
[6677]	Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
[6678]	180 185 190
[6679]	Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
[6680]	195 200 205
[6681]	Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
[6682]	210 215
[6683]	<210> 330
[6684]	<211> 214
[6685]	<212> PRT
[6686]	<213> 人工序列(Artificial Sequence)
[6687]	<220>
[6688]	<223> 嵌合κ轻链
[6689]	<400> 330
[6690]	Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
[6691]	1 5 10 15
[6692]	Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr
[6693]	20 25 30
[6694]	Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
[6695]	35 40 45
[6696]	Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
[6697]	50 55 60
[6698]	Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
[6699]	65 70 75 80
[6700]	Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Phe Pro Trp
[6701]	85 90 95
[6702]	Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
[6703]	100 105 110
[6704]	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
[6705]	115 120 125
[6706]	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
[6707]	130 135 140

[6708]	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
[6709]	145 150 155 160
[6710]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
[6711]	165 170 175
[6712]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
[6713]	180 185 190
[6714]	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
[6715]	195 200 205
[6716]	Phe Asn Arg Gly Glu Cys
[6717]	210
[6718]	<210> 331
[6719]	<211> 213
[6720]	<212> PRT
[6721]	<213> 人工序列(Artificial Sequence)
[6722]	<220>
[6723]	<223> 嵌合κ轻链
[6724]	<400> 331
[6725]	Gln Ile Val Leu Thr Gln Ser Pro Ala Leu Met Ser Ala Ser Pro Gly
[6726]	1 5 10 15
[6727]	Glu Arg Val Thr Met Thr Cys Ser Ala Ser Ser Asp Val Ser Tyr Met
[6728]	20 25 30
[6729]	Tyr Trp Tyr Gln Gln Lys Pro Arg Ser Ser Pro Lys Pro Trp Ile Tyr
[6730]	35 40 45
[6731]	Leu Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
[6732]	50 55 60
[6733]	Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
[6734]	65 70 75 80
[6735]	Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Gly Asn Pro Leu Thr
[6736]	85 90 95
[6737]	Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro
[6738]	100 105 110
[6739]	Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
[6740]	115 120 125
[6741]	Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
[6742]	130 135 140
[6743]	Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
[6744]	145 150 155 160
[6745]	Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
[6746]	165 170 175

[6747]	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr	Ala
[6748]				180				185						190		
[6749]	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser	Phe
[6750]				195				200						205		
[6751]	Asn	Arg	Gly	Glu	Cys											
[6752]				210												
[6753]	<210>	332														
[6754]	<211>	219														
[6755]	<212>	PRT														
[6756]	<213>	人工序列(Artificial Sequence)														
[6757]	<220>															
[6758]	<223>	嵌合κ轻链														
[6759]	<400>	332														
[6760]	Asp	Val	Leu	Met	Thr	Gln	Thr	Pro	Leu	Ser	Leu	Pro	Val	Ser	Leu	Gly
[6761]	1			5				10						15		
[6762]	Asp	Gln	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Asn	Ile	Val	Tyr	Ser
[6763]				20				25						30		
[6764]	Asp	Gly	Asp	Thr	Tyr	Leu	Glu	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser
[6765]				35				40						45		
[6766]	Pro	Lys	Leu	Leu	Ile	Phe	Lys	Val	Ser	Asn	Arg	Phe	Ser	Gly	Val	Pro
[6767]				50				55						60		
[6768]	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
[6769]	65				70					75					80	
[6770]	Ser	Arg	Val	Glu	Ala	Glu	Asp	Leu	Gly	Val	Tyr	Tyr	Cys	Phe	Gln	Gly
[6771]					85					90					95	
[6772]	Ser	His	Val	Pro	Phe	Thr	Phe	Gly	Ser	Gly	Thr	Lys	Leu	Glu	Ile	Lys
[6773]				100				105						110		
[6774]	Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu
[6775]				115				120						125		
[6776]	Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe
[6777]				130				135						140		
[6778]	Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln
[6779]	145				150					155					160	
[6780]	Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser
[6781]					165					170					175	
[6782]	Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu
[6783]				180						185					190	
[6784]	Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser
[6785]				195				200							205	

[6786]	Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
[6787]	210 215
[6788]	<210> 333
[6789]	<211> 218
[6790]	<212> PRT
[6791]	<213> 人工序列(Artificial Sequence)
[6792]	<220>
[6793]	<223> 嵌合κ轻链
[6794]	<400> 333
[6795]	Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
[6796]	1 5 10 15
[6797]	Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asp Tyr
[6798]	20 25 30
[6799]	Gly Asn Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
[6800]	35 40 45
[6801]	Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Val
[6802]	50 55 60
[6803]	Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn
[6804]	65 70 75 80
[6805]	Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
[6806]	85 90 95
[6807]	Glu Asp Pro His Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
[6808]	100 105 110
[6809]	Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
[6810]	115 120 125
[6811]	Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
[6812]	130 135 140
[6813]	Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
[6814]	145 150 155 160
[6815]	Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
[6816]	165 170 175
[6817]	Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
[6818]	180 185 190
[6819]	His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
[6820]	195 200 205
[6821]	Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
[6822]	210 215
[6823]	<210> 334
[6824]	<211> 214

[6825]	<212>	PRT
[6826]	<213>	人工序列(Artificial Sequence)
[6827]	<220>	
[6828]	<223>	具有CDR突变的嵌合κ轻链
[6829]	<400>	334
[6830]	Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly	
[6831]	1 5 10 15	
[6832]	Gly Arg Val Ser Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Pro Ala	
[6833]	20 25 30	
[6834]	Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile	
[6835]	35 40 45	
[6836]	Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly	
[6837]	50 55 60	
[6838]	Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Thr	
[6839]	65 70 75 80	
[6840]	Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp	
[6841]	85 90 95	
[6842]	Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala	
[6843]	100 105 110	
[6844]	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly	
[6845]	115 120 125	
[6846]	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala	
[6847]	130 135 140	
[6848]	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln	
[6849]	145 150 155 160	
[6850]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser	
[6851]	165 170 175	
[6852]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr	
[6853]	180 185 190	
[6854]	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser	
[6855]	195 200 205	
[6856]	Phe Asn Arg Gly Glu Cys	
[6857]	210	
[6858]	<210>	335
[6859]	<211>	214
[6860]	<212>	PRT
[6861]	<213>	人工序列(Artificial Sequence)
[6862]	<220>	
[6863]	<223>	具有CDR突变的嵌合κ轻链

[6864]	<400>	335
[6865]	Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly	
[6866]	1 5 10 15	
[6867]	Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala	
[6868]	20 25 30	
[6869]	Val Asp Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile	
[6870]	35 40 45	
[6871]	Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly	
[6872]	50 55 60	
[6873]	Ser Gly Ser Gly Thr Ala Phe Thr Phe Thr Ile Ser Gly Glu Gln Ala	
[6874]	65 70 75 80	
[6875]	Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Ile Pro Phe	
[6876]	85 90 95	
[6877]	Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala	
[6878]	100 105 110	
[6879]	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly	
[6880]	115 120 125	
[6881]	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala	
[6882]	130 135 140	
[6883]	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln	
[6884]	145 150 155 160	
[6885]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser	
[6886]	165 170 175	
[6887]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr	
[6888]	180 185 190	
[6889]	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser	
[6890]	195 200 205	
[6891]	Phe Asn Arg Gly Glu Cys	
[6892]	210	
[6893]	<210>	336
[6894]	<211>	214
[6895]	<212>	PRT
[6896]	<213>	人工序列(Artificial Sequence)
[6897]	<220>	
[6898]	<223>	人源化κ轻链
[6899]	<400>	336
[6900]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly	
[6901]	1 5 10 15	
[6902]	Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Pro Ala	

[6903]	20	25	30
[6904]	Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile		
[6905]	35	40	45
[6906]	Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly		
[6907]	50	55	60
[6908]	Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro		
[6909]	65	70	75
[6910]	Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp		
[6911]	85	90	95
[6912]	Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala		
[6913]	100	105	110
[6914]	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly		
[6915]	115	120	125
[6916]	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala		
[6917]	130	135	140
[6918]	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln		
[6919]	145	150	155
[6920]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser		
[6921]	165	170	175
[6922]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr		
[6923]	180	185	190
[6924]	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser		
[6925]	195	200	205
[6926]	Phe Asn Arg Gly Glu Cys		
[6927]	210		
[6928]	<210> 337		
[6929]	<211> 214		
[6930]	<212> PRT		
[6931]	<213> 人工序列(Artificial Sequence)		
[6932]	<220>		
[6933]	<223> 人源化κ轻链		
[6934]	<400> 337		
[6935]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly		
[6936]	1	5	10
[6937]	Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Pro Ala		
[6938]	20	25	30
[6939]	Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile		
[6940]	35	40	45
[6941]	Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly		

[6942]	50	55	60
[6943]	Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro		
[6944]	65	70	75
[6945]	Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp		
[6946]	85	90	95
[6947]	Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala		
[6948]	100	105	110
[6949]	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly		
[6950]	115	120	125
[6951]	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala		
[6952]	130	135	140
[6953]	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln		
[6954]	145	150	155
[6955]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser		
[6956]	165	170	175
[6957]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr		
[6958]	180	185	190
[6959]	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser		
[6960]	195	200	205
[6961]	Phe Asn Arg Gly Glu Cys		
[6962]	210		
[6963]	<210> 338		
[6964]	<211> 214		
[6965]	<212> PRT		
[6966]	<213> 人工序列(Artificial Sequence)		
[6967]	<220>		
[6968]	<223> 人源化κ轻链		
[6969]	<400> 338		
[6970]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Thr Ser Val Gly		
[6971]	1	5	10
[6972]	Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Pro Ala		
[6973]	20	25	30
[6974]	Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile		
[6975]	35	40	45
[6976]	Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly		
[6977]	50	55	60
[6978]	Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Pro		
[6979]	65	70	75
[6980]	Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp		

[6981]																85			90			95					
[6982]	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala											
[6983]																100			105			110					
[6984]	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly											
[6985]																115			120			125					
[6986]	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala											
[6987]																130			135			140					
[6988]	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln											
[6989]																145			150			155			160		
[6990]	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser											
[6991]																165			170			175					
[6992]	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr											
[6993]																180			185			190					
[6994]	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser											
[6995]																195			200			205					
[6996]	Phe	Asn	Arg	Gly	Glu	Cys																					
[6997]																		210									
[6998]	<210>																	339									
[6999]	<211>																	214									
[7000]	<212>																	PRT									
[7001]	<213>																	人工序列 (Artificial Sequence)									
[7002]	<220>																										
[7003]	<223>																	人源化κ轻链									
[7004]	<400>																	339									
[7005]	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly											
[7006]	1																	5			10			15			
[7007]	Asp	Arg	Val	Thr	Ile	Thr	Cys	Lys	Ala	Ser	Gln	Asp	Val	Ser	Thr	Ala											
[7008]																20			25			30					
[7009]	Val	Asp	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile											
[7010]																35			40			45					
[7011]	Tyr	Ser	Ala	Ser	Tyr	Arg	Tyr	Thr	Gly	Val	Pro	Asp	Arg	Phe	Ser	Gly											
[7012]																50			55			60					
[7013]	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Phe	Thr	Ile	Ser	Ser	Leu	Gln	Pro											
[7014]																65			70			75			80		
[7015]	Glu	Asp	Ile	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	His	Tyr	Ser	Ile	Pro	Phe											
[7016]																85			90			95					
[7017]	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala											
[7018]																100			105			110					
[7019]	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly											

[7020]	115	120	125
[7021]	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala		
[7022]	130	135	140
[7023]	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln		
[7024]	145	150	155
[7025]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser		
[7026]	165	170	175
[7027]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr		
[7028]	180	185	190
[7029]	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser		
[7030]	195	200	205
[7031]	Phe Asn Arg Gly Glu Cys		
[7032]	210		
[7033]	<210> 340		
[7034]	<211> 214		
[7035]	<212> PRT		
[7036]	<213> 人工序列(Artificial Sequence)		
[7037]	<220>		
[7038]	<223> 人源化κ轻链		
[7039]	<400> 340		
[7040]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Met Ser Ala Ser Val Gly		
[7041]	1	5	10
[7042]	Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala		
[7043]	20	25	30
[7044]	Val Asp Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile		
[7045]	35	40	45
[7046]	Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly		
[7047]	50	55	60
[7048]	Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro		
[7049]	65	70	75
[7050]	Glu Asp Leu Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Ile Pro Phe		
[7051]	85	90	95
[7052]	Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala		
[7053]	100	105	110
[7054]	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly		
[7055]	115	120	125
[7056]	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala		
[7057]	130	135	140
[7058]	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln		

[7059]	145	150	155	160
[7060]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser			
[7061]		165	170	175
[7062]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr			
[7063]		180	185	190
[7064]	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser			
[7065]		195	200	205
[7066]	Phe Asn Arg Gly Glu Cys			
[7067]	210			
[7068]	<210> 341			
[7069]	<211> 214			
[7070]	<212> PRT			
[7071]	<213> 人工序列(Artificial Sequence)			
[7072]	<220>			
[7073]	<223> 人源化κ轻链			
[7074]	<400> 341			
[7075]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Met Ser Thr Ser Val Gly			
[7076]	1	5	10	15
[7077]	Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala			
[7078]		20	25	30
[7079]	Val Asp Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile			
[7080]		35	40	45
[7081]	Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly			
[7082]	50	55	60	
[7083]	Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Glu Gln Pro			
[7084]	65	70	75	80
[7085]	Glu Asp Leu Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Ile Pro Phe			
[7086]		85	90	95
[7087]	Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala			
[7088]		100	105	110
[7089]	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly			
[7090]		115	120	125
[7091]	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala			
[7092]	130	135	140	
[7093]	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln			
[7094]	145	150	155	160
[7095]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser			
[7096]		165	170	175
[7097]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr			

[7098]	180	185	190
[7099]	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser		
[7100]	195	200	205
[7101]	Phe Asn Arg Gly Glu Cys		
[7102]	210		
[7103]	<210> 342		
[7104]	<211> 214		
[7105]	<212> PRT		
[7106]	<213> 人工序列(Artificial Sequence)		
[7107]	<220>		
[7108]	<223> 具有CDR1突变的人源化κ轻链		
[7109]	<400> 342		
[7110]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly		
[7111]	1 5 10 15		
[7112]	Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Pro Ala		
[7113]	20 25 30		
[7114]	Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile		
[7115]	35 40 45		
[7116]	Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly		
[7117]	50 55 60		
[7118]	Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro		
[7119]	65 70 75 80		
[7120]	Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp		
[7121]	85 90 95		
[7122]	Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala		
[7123]	100 105 110		
[7124]	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly		
[7125]	115 120 125		
[7126]	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala		
[7127]	130 135 140		
[7128]	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln		
[7129]	145 150 155 160		
[7130]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser		
[7131]	165 170 175		
[7132]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr		
[7133]	180 185 190		
[7134]	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser		
[7135]	195 200 205		
[7136]	Phe Asn Arg Gly Glu Cys		

[7137]	210
[7138]	<210> 343
[7139]	<211> 214
[7140]	<212> PRT
[7141]	<213> 人工序列(Artificial Sequence)
[7142]	<220>
[7143]	<223> 具有CDR1突变的人源化κ轻链
[7144]	<400> 343
[7145]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
[7146]	1 5 10 15
[7147]	Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Pro Ala
[7148]	20 25 30
[7149]	Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
[7150]	35 40 45
[7151]	Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
[7152]	50 55 60
[7153]	Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
[7154]	65 70 75 80
[7155]	Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp
[7156]	85 90 95
[7157]	Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
[7158]	100 105 110
[7159]	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
[7160]	115 120 125
[7161]	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
[7162]	130 135 140
[7163]	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
[7164]	145 150 155 160
[7165]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
[7166]	165 170 175
[7167]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
[7168]	180 185 190
[7169]	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
[7170]	195 200 205
[7171]	Phe Asn Arg Gly Glu Cys
[7172]	210
[7173]	<210> 344
[7174]	<211> 214
[7175]	<212> PRT

[7176]	<213> 人工序列(Artificial Sequence)																		
[7177]	<220>																		
[7178]	<223> 具有CDR1突变的人源化κ轻链																		
[7179]	<400> 344																		
[7180]	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Thr	Ser	Val	Gly			
[7181]	1				5					10					15				
[7182]	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Asp	Val	Ser	Pro	Ala			
[7183]				20					25					30					
[7184]	Val	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile			
[7185]			35					40					45						
[7186]	Tyr	Trp	Ala	Ser	Thr	Arg	His	Thr	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly			
[7187]		50					55					60							
[7188]	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Val	Gln	Pro			
[7189]	65					70					75				80				
[7190]	Glu	Asp	Leu	Ala	Leu	Tyr	Tyr	Cys	Gln	Gln	His	Tyr	Ser	Thr	Pro	Trp			
[7191]					85					90					95				
[7192]	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala			
[7193]				100					105					110					
[7194]	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly			
[7195]			115					120					125						
[7196]	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala			
[7197]		130					135					140							
[7198]	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln			
[7199]	145					150					155				160				
[7200]	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser			
[7201]				165					170					175					
[7202]	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr			
[7203]				180					185					190					
[7204]	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser			
[7205]			195					200					205						
[7206]	Phe	Asn	Arg	Gly	Glu	Cys													
[7207]		210																	
[7208]	<210> 345																		
[7209]	<211> 214																		
[7210]	<212> PRT																		
[7211]	<213> 人工序列(Artificial Sequence)																		
[7212]	<220>																		
[7213]	<223> 具有CDR1突变的人源化κ轻链																		
[7214]	<400> 345																		

[7215]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
[7216]	1 5 10 15
[7217]	Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
[7218]	20 25 30
[7219]	Val Asp Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
[7220]	35 40 45
[7221]	Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly
[7222]	50 55 60
[7223]	Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
[7224]	65 70 75 80
[7225]	Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Ile Pro Phe
[7226]	85 90 95
[7227]	Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
[7228]	100 105 110
[7229]	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
[7230]	115 120 125
[7231]	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
[7232]	130 135 140
[7233]	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
[7234]	145 150 155 160
[7235]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
[7236]	165 170 175
[7237]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
[7238]	180 185 190
[7239]	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
[7240]	195 200 205
[7241]	Phe Asn Arg Gly Glu Cys
[7242]	210
[7243]	<210> 346
[7244]	<211> 214
[7245]	<212> PRT
[7246]	<213> 人工序列(Artificial Sequence)
[7247]	<220>
[7248]	<223> 具有CDR1突变的人源化κ轻链
[7249]	<400> 346
[7250]	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Met Ser Ala Ser Val Gly
[7251]	1 5 10 15
[7252]	Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
[7253]	20 25 30

[7254]	Val	Asp	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
[7255]			35					40						45		
[7256]	Tyr	Ser	Ala	Ser	Tyr	Arg	Tyr	Thr	Gly	Val	Pro	Asp	Arg	Phe	Ser	Gly
[7257]			50					55						60		
[7258]	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Phe	Thr	Ile	Ser	Ser	Leu	Gln	Pro
[7259]	65					70					75				80	
[7260]	Glu	Asp	Leu	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	His	Tyr	Ser	Ile	Pro	Phe
[7261]					85					90					95	
[7262]	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala
[7263]				100					105					110		
[7264]	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly
[7265]			115					120					125			
[7266]	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
[7267]			130					135					140			
[7268]	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
[7269]	145					150					155				160	
[7270]	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
[7271]				165						170					175	
[7272]	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr
[7273]				180						185					190	
[7274]	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser
[7275]			195					200					205			
[7276]	Phe	Asn	Arg	Gly	Glu	Cys										
[7277]			210													
[7278]	<210>	347														
[7279]	<211>	214														
[7280]	<212>	PRT														
[7281]	<213>	人工序列(Artificial Sequence)														
[7282]	<220>															
[7283]	<223>	具有CDR1突变的人源化κ轻链														
[7284]	<400>	347														
[7285]	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Met	Ser	Thr	Ser	Val	Gly
[7286]	1				5					10					15	
[7287]	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Asp	Val	Ser	Thr	Ala
[7288]				20					25					30		
[7289]	Val	Asp	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
[7290]			35					40					45			
[7291]	Tyr	Ser	Ala	Ser	Tyr	Arg	Tyr	Thr	Gly	Val	Pro	Asp	Arg	Phe	Ser	Gly
[7292]			50					55					60			

[7293]	Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Glu Gln Pro
[7294]	65 70 75 80
[7295]	Glu Asp Leu Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Ile Pro Phe
[7296]	85 90 95
[7297]	Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
[7298]	100 105 110
[7299]	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
[7300]	115 120 125
[7301]	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
[7302]	130 135 140
[7303]	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
[7304]	145 150 155 160
[7305]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
[7306]	165 170 175
[7307]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
[7308]	180 185 190
[7309]	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
[7310]	195 200 205
[7311]	Phe Asn Arg Gly Glu Cys
[7312]	210
[7313]	<210> 348
[7314]	<211> 445
[7315]	<212> PRT
[7316]	<213> 人工序列(Artificial Sequence)
[7317]	<220>
[7318]	<223> 具有野生型恒定区的嵌合IgG1重链
[7319]	<400> 348
[7320]	Asp Val Gln Leu Gln Glu Ser Gly Pro Asp Leu Val Lys Pro Ser Gln
[7321]	1 5 10 15
[7322]	Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Gly
[7323]	20 25 30
[7324]	Tyr Thr Trp His Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
[7325]	35 40 45
[7326]	Met Gly Tyr Ile His Tyr Ser Gly Ser Thr Lys Tyr Asn Pro Ser Leu
[7327]	50 55 60
[7328]	Lys Ser Arg Phe Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
[7329]	65 70 75 80
[7330]	Leu Gln Leu Asn Ser Met Thr Ala Glu Asp Thr Ala Thr Tyr Tyr Cys
[7331]	85 90 95

[7332]	Ala	Arg	Asn	Ser	Leu	Phe	Ala	Ser	Trp	Gly	His	Gly	Thr	Leu	Val	Thr
[7333]				100					105					110		
[7334]	Val	Ser	Ala	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro
[7335]				115					120					125		
[7336]	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val
[7337]				130					135					140		
[7338]	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala
[7339]	145						150					155				160
[7340]	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly
[7341]							165					170				175
[7342]	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly
[7343]							180					185				190
[7344]	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys
[7345]							195					200				205
[7346]	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys
[7347]							210					215				220
[7348]	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu
[7349]	225						230					235				240
[7350]	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu
[7351]							245					250				255
[7352]	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys
[7353]							260					265				270
[7354]	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys
[7355]							275					280				285
[7356]	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu
[7357]							290					295				300
[7358]	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys
[7359]	305						310					315				320
[7360]	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys
[7361]							325					330				335
[7362]	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser
[7363]							340					345				350
[7364]	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys
[7365]							355					360				365
[7366]	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln
[7367]							370					375				380
[7368]	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly
[7369]	385						390					395				400
[7370]	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln

[7371]		405		410		415
[7372]	Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn					
[7373]		420		425		430
[7374]	His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys					
[7375]		435		440		445
[7376]	<210> 349					
[7377]	<211> 450					
[7378]	<212> PRT					
[7379]	<213> 人工序列(Artificial Sequence)					
[7380]	<220>					
[7381]	<223> 具有野生型恒定区的嵌合IgG1重链					
[7382]	<400> 349					
[7383]	Asp Val Gln Leu Gln Gly Ser Gly Pro Gly Leu Val Lys Pro Ser Gln					
[7384]	1	5		10		15
[7385]	Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp					
[7386]		20		25		30
[7387]	Phe Ala Trp Asp Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp					
[7388]		35		40		45
[7389]	Met Gly His Ile Arg Phe Ser Gly Thr Thr Ser Tyr Asn Pro Ser Leu					
[7390]	50		55		60	
[7391]	Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe					
[7392]	65		70		75	80
[7393]	Leu Gln Leu Asn Ser Val Thr Ser Glu Asp Thr Ala Thr Tyr Tyr Cys					
[7394]		85		90		95
[7395]	Ala Arg Ser Thr Leu Ile Thr Lys Gly Phe Phe Asp Tyr Trp Gly Gln					
[7396]		100		105		110
[7397]	Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val					
[7398]		115		120		125
[7399]	Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala					
[7400]	130		135		140	
[7401]	Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser					
[7402]	145		150		155	160
[7403]	Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val					
[7404]		165		170		175
[7405]	Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro					
[7406]		180		185		190
[7407]	Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys					
[7408]		195		200		205
[7409]	Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp					

[7410]	210	215	220
[7411]	Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly		
[7412]	225	230	235 240
[7413]	Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile		
[7414]	245	250	255
[7415]	Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu		
[7416]	260	265	270
[7417]	Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His		
[7418]	275	280	285
[7419]	Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg		
[7420]	290	295	300
[7421]	Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys		
[7422]	305	310	315 320
[7423]	Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu		
[7424]	325	330	335
[7425]	Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr		
[7426]	340	345	350
[7427]	Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu		
[7428]	355	360	365
[7429]	Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp		
[7430]	370	375	380
[7431]	Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val		
[7432]	385	390	395 400
[7433]	Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp		
[7434]	405	410	415
[7435]	Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His		
[7436]	420	425	430
[7437]	Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro		
[7438]	435	440	445
[7439]	Gly Lys		
[7440]	450		
[7441]	<210> 350		
[7442]	<211> 449		
[7443]	<212> PRT		
[7444]	<213> 人工序列(Artificial Sequence)		
[7445]	<220>		
[7446]	<223> 具有野生型恒定区的嵌合IgG1重链		
[7447]	<400> 350		
[7448]	Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala		

[7449]	1	5	10	15
[7450]	Ser Val Arg Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr			
[7451]	20	25	30	
[7452]	Gly Ile Ser Trp Val Lys Gln Arg Thr Gly Gln Gly Leu Glu Trp Ile			
[7453]	35	40	45	
[7454]	Gly Glu Ile Phe Pro Arg Thr Ala Asn Thr Tyr Phe Asn Glu Lys Phe			
[7455]	50	55	60	
[7456]	Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr			
[7457]	65	70	75	80
[7458]	Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys			
[7459]	85	90	95	
[7460]	Ala Arg Asp Tyr Asp Pro Tyr Tyr Ala Leu Asp Tyr Trp Gly Gln Gly			
[7461]	100	105	110	
[7462]	Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe			
[7463]	115	120	125	
[7464]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu			
[7465]	130	135	140	
[7466]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp			
[7467]	145	150	155	160
[7468]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu			
[7469]	165	170	175	
[7470]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser			
[7471]	180	185	190	
[7472]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro			
[7473]	195	200	205	
[7474]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys			
[7475]	210	215	220	
[7476]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro			
[7477]	225	230	235	240
[7478]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser			
[7479]	245	250	255	
[7480]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp			
[7481]	260	265	270	
[7482]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn			
[7483]	275	280	285	
[7484]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val			
[7485]	290	295	300	
[7486]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu			
[7487]	305	310	315	320

[7488]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
[7489]					325					330					335	
[7490]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
[7491]					340					345					350	
[7492]	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
[7493]					355					360					365	
[7494]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
[7495]					370					375					380	
[7496]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
[7497]					385					390					395	
[7498]	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
[7499]					405					410					415	
[7500]	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
[7501]					420					425					430	
[7502]	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
[7503]					435					440					445	
[7504]	Lys															
[7505]	<210>	351														
[7506]	<211>	443														
[7507]	<212>	PRT														
[7508]	<213>	人工序列(Artificial Sequence)														
[7509]	<220>															
[7510]	<223>	具有野生型恒定区的嵌合IgG1重链														
[7511]	<400>	351														
[7512]	Asp	Val	Gln	Leu	Leu	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
[7513]	1				5					10					15	
[7514]	Ser	Leu	Ser	Leu	Thr	Cys	Ser	Val	Thr	Gly	Tyr	Ser	Ile	Thr	Ser	Gly
[7515]					20					25					30	
[7516]	Tyr	Tyr	Trp	Asn	Trp	Ile	Arg	Gln	Phe	Pro	Gly	Asn	Asn	Leu	Glu	Trp
[7517]					35					40					45	
[7518]	Met	Gly	Ser	Ile	Asn	Tyr	Asp	Gly	Ser	Asn	Asp	Tyr	Asn	Pro	Ser	Leu
[7519]					50					55					60	
[7520]	Gln	Asp	Arg	Ile	Ser	Ile	Thr	Arg	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Phe
[7521]					65					70					75	
[7522]	Leu	Lys	Leu	Asn	Ser	Val	Thr	Thr	Glu	Asp	Thr	Ala	Thr	Tyr	Tyr	Cys
[7523]					85					90					95	
[7524]	Ala	Arg	Arg	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Thr	Leu	Ile	Val	Ser
[7525]					100					105					110	
[7526]	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser

[7527]	115	120	125
[7528]	Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp		
[7529]	130	135	140
[7530]	Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr		
[7531]	145	150	155
[7532]	Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr		
[7533]	165	170	175
[7534]	Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln		
[7535]	180	185	190
[7536]	Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp		
[7537]	195	200	205
[7538]	Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro		
[7539]	210	215	220
[7540]	Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro		
[7541]	225	230	235
[7542]	Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr		
[7543]	245	250	255
[7544]	Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn		
[7545]	260	265	270
[7546]	Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg		
[7547]	275	280	285
[7548]	Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val		
[7549]	290	295	300
[7550]	Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser		
[7551]	305	310	315
[7552]	Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys		
[7553]	325	330	335
[7554]	Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp		
[7555]	340	345	350
[7556]	Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe		
[7557]	355	360	365
[7558]	Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu		
[7559]	370	375	380
[7560]	Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe		
[7561]	385	390	395
[7562]	Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly		
[7563]	405	410	415
[7564]	Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr		
[7565]	420	425	430

[7566]	Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[7567]	435 440
[7568]	<210> 352
[7569]	<211> 449
[7570]	<212> PRT
[7571]	<213> 人工序列(Artificial Sequence)
[7572]	<220>
[7573]	<223> 具有野生型恒定区的嵌合IgG1重链
[7574]	<400> 352
[7575]	Gln Val Gln Leu Gln Gln Ser Gly Asn Glu Leu Ala Arg Pro Gly Ala
[7576]	1 5 10 15
[7577]	Ser Val Arg Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[7578]	20 25 30
[7579]	Gly Ile Thr Trp Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
[7580]	35 40 45
[7581]	Gly Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe
[7582]	50 55 60
[7583]	Lys Gly Arg Ala Thr Leu Thr Ala Asp Ile Ser Ser Ser Thr Ala Tyr
[7584]	65 70 75 80
[7585]	Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
[7586]	85 90 95
[7587]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[7588]	100 105 110
[7589]	Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[7590]	115 120 125
[7591]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
[7592]	130 135 140
[7593]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[7594]	145 150 155 160
[7595]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[7596]	165 170 175
[7597]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[7598]	180 185 190
[7599]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[7600]	195 200 205
[7601]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
[7602]	210 215 220
[7603]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
[7604]	225 230 235 240

[7605]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[7606]	245 250 255
[7607]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
[7608]	260 265 270
[7609]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[7610]	275 280 285
[7611]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
[7612]	290 295 300
[7613]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[7614]	305 310 315 320
[7615]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[7616]	325 330 335
[7617]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[7618]	340 345 350
[7619]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
[7620]	355 360 365
[7621]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[7622]	370 375 380
[7623]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[7624]	385 390 395 400
[7625]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[7626]	405 410 415
[7627]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[7628]	420 425 430
[7629]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[7630]	435 440 445
[7631]	Lys
[7632]	<210> 353
[7633]	<211> 451
[7634]	<212> PRT
[7635]	<213> 人工序列(Artificial Sequence)
[7636]	<220>
[7637]	<223> 具有野生型恒定区的嵌合IgG1重链
[7638]	<400> 353
[7639]	Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Val Val Arg Pro Gly Ala
[7640]	1 5 10 15
[7641]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
[7642]	20 25 30
[7643]	Trp Ile Ser Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile

[7644]	35	40	45
[7645]	Gly Asn Ile Tyr Pro Ser Asp Ser Tyr Thr Asn Tyr Asn Gln Asn Phe		
[7646]	50	55	60
[7647]	Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr		
[7648]	65	70	75
[7649]	Met Gln Leu Ser Ser Pro Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys		
[7650]	85	90	95
[7651]	Thr Thr Gly Ile Ile Thr Val Ile Ala Thr Arg Asp Asp Tyr Trp Gly		
[7652]	100	105	110
[7653]	Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser		
[7654]	115	120	125
[7655]	Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala		
[7656]	130	135	140
[7657]	Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val		
[7658]	145	150	155
[7659]	Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala		
[7660]	165	170	175
[7661]	Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val		
[7662]	180	185	190
[7663]	Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His		
[7664]	195	200	205
[7665]	Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys		
[7666]	210	215	220
[7667]	Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly		
[7668]	225	230	235
[7669]	Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met		
[7670]	245	250	255
[7671]	Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His		
[7672]	260	265	270
[7673]	Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val		
[7674]	275	280	285
[7675]	His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr		
[7676]	290	295	300
[7677]	Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly		
[7678]	305	310	315
[7679]	Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile		
[7680]	325	330	335
[7681]	Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val		
[7682]	340	345	350

[7683]	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser
[7684]			355					360					365			
[7685]	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu
[7686]			370				375					380				
[7687]	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro
[7688]	385					390					395					400
[7689]	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val
[7690]					405					410					415	
[7691]	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met
[7692]				420					425					430		
[7693]	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser
[7694]			435					440					445			
[7695]	Pro	Gly	Lys													
[7696]			450													
[7697]	<210>	354														
[7698]	<211>	453														
[7699]	<212>	PRT														
[7700]	<213>	人工序列(Artificial Sequence)														
[7701]	<220>															
[7702]	<223>	具有野生型恒定区的嵌合IgG1重链														
[7703]	<400>	354														
[7704]	Glu	Gly	Gln	Leu	Gln	Gln	Ser	Gly	Ala	Gly	Leu	Val	Lys	Pro	Gly	Ala
[7705]	1			5					10					15		
[7706]	Ser	Val	Asn	Leu	Ser	Cys	Thr	Ala	Ser	Gly	Phe	Asn	Ile	Lys	Asp	Thr
[7707]			20					25					30			
[7708]	Tyr	Ile	His	Trp	Met	Lys	Gln	Arg	Pro	Glu	Gln	Gly	Leu	Glu	Trp	Ile
[7709]			35					40					45			
[7710]	Gly	Arg	Ile	Ala	Pro	Thr	Asn	Gly	Asn	Thr	Lys	Tyr	Asp	Pro	Thr	Phe
[7711]		50					55					60				
[7712]	Gln	Gly	Lys	Ala	Thr	Ile	Thr	Ala	Asp	Ser	Ser	Ser	Asn	Thr	Ala	Tyr
[7713]	65					70					75				80	
[7714]	Leu	Gln	Val	Ser	Ser	Leu	Thr	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[7715]				85					90					95		
[7716]	Ser	Arg	Gly	Gly	Ile	Tyr	Tyr	Tyr	Gly	Ser	His	Trp	Tyr	Phe	Asp	Val
[7717]			100						105					110		
[7718]	Trp	Gly	Ala	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly
[7719]			115					120					125			
[7720]	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly
[7721]			130					135					140			

[7722]	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val
[7723]	145					150					155					160
[7724]	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe
[7725]					165					170						175
[7726]	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val
[7727]				180					185						190	
[7728]	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val
[7729]			195					200					205			
[7730]	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys
[7731]		210					215					220				
[7732]	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu
[7733]	225					230					235					240
[7734]	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr
[7735]					245					250						255
[7736]	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val
[7737]				260					265						270	
[7738]	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val
[7739]			275					280					285			
[7740]	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser
[7741]		290					295					300				
[7742]	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu
[7743]	305					310					315					320
[7744]	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala
[7745]				325						330					335	
[7746]	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro
[7747]			340					345					350			
[7748]	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln
[7749]		355					360					365				
[7750]	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala
[7751]		370					375					380				
[7752]	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr
[7753]	385					390					395					400
[7754]	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu
[7755]				405					410						415	
[7756]	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser
[7757]				420					425				430			
[7758]	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser
[7759]			435					440					445			
[7760]	Leu	Ser	Pro	Gly	Lys											

[7761]	450
[7762]	<210> 355
[7763]	<211> 453
[7764]	<212> PRT
[7765]	<213> 人工序列(Artificial Sequence)
[7766]	<220>
[7767]	<223> 具有野生型恒定区的嵌合IgG1重链
[7768]	<400> 355
[7769]	Glu Gly Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
[7770]	1 5 10 15
[7771]	Ser Val Asn Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Thr
[7772]	20 25 30
[7773]	Tyr Ile His Trp Val Lys Gln Arg Pro Asp Gln Gly Leu Glu Trp Ile
[7774]	35 40 45
[7775]	Gly Arg Ile Ala Pro Thr Asn Gly Asn Ala Lys Phe His Pro Thr Phe
[7776]	50 55 60
[7777]	Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
[7778]	65 70 75 80
[7779]	Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
[7780]	85 90 95
[7781]	Thr Arg Gly Gly Ile Tyr Tyr Tyr Gly Thr His Trp Tyr Phe Asp Val
[7782]	100 105 110
[7783]	Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
[7784]	115 120 125
[7785]	Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
[7786]	130 135 140
[7787]	Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
[7788]	145 150 155 160
[7789]	Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
[7790]	165 170 175
[7791]	Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
[7792]	180 185 190
[7793]	Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
[7794]	195 200 205
[7795]	Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys
[7796]	210 215 220
[7797]	Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
[7798]	225 230 235 240
[7799]	Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr

[7800]		245		250		255
[7801]	Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val					
[7802]		260		265		270
[7803]	Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val					
[7804]		275		280		285
[7805]	Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser					
[7806]		290		295		300
[7807]	Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu					
[7808]	305		310		315	320
[7809]	Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala					
[7810]		325		330		335
[7811]	Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro					
[7812]		340		345		350
[7813]	Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln					
[7814]		355		360		365
[7815]	Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala					
[7816]		370		375		380
[7817]	Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr					
[7818]	385		390		395	400
[7819]	Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu					
[7820]		405		410		415
[7821]	Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser					
[7822]		420		425		430
[7823]	Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser					
[7824]		435		440		445
[7825]	Leu Ser Pro Gly Lys					
[7826]		450				
[7827]	<210>	356				
[7828]	<211>	450				
[7829]	<212>	PRT				
[7830]	<213>	人工序列(Artificial Sequence)				
[7831]	<220>					
[7832]	<223>	具有野生型恒定区的嵌合IgG1重链				
[7833]	<400>	356				
[7834]	Gln Val Leu Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala					
[7835]	1	5		10		15
[7836]	Ser Val Arg Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr					
[7837]		20		25		30
[7838]	Tyr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile					

[7839]	35	40	45
[7840]	Gly Trp Ile Tyr Pro Gly Asn Val Asn Thr Lys Tyr Asn Glu Lys Phe		
[7841]	50	55	60
[7842]	Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr		
[7843]	65	70	75
[7844]	Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys		
[7845]	85	90	95
[7846]	Ala Ser Tyr Gly Asn Tyr Gly Gly Trp Tyr Phe Asp Val Trp Gly Ala		
[7847]	100	105	110
[7848]	Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val		
[7849]	115	120	125
[7850]	Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala		
[7851]	130	135	140
[7852]	Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser		
[7853]	145	150	155
[7854]	Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val		
[7855]	165	170	175
[7856]	Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro		
[7857]	180	185	190
[7858]	Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys		
[7859]	195	200	205
[7860]	Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp		
[7861]	210	215	220
[7862]	Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly		
[7863]	225	230	235
[7864]	Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile		
[7865]	245	250	255
[7866]	Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu		
[7867]	260	265	270
[7868]	Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His		
[7869]	275	280	285
[7870]	Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg		
[7871]	290	295	300
[7872]	Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys		
[7873]	305	310	315
[7874]	Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu		
[7875]	325	330	335
[7876]	Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr		
[7877]	340	345	350

[7878]	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu
[7879]				355					360					365		
[7880]	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp
[7881]			370					375						380		
[7882]	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val
[7883]	385					390					395					400
[7884]	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp
[7885]					405					410					415	
[7886]	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His
[7887]				420					425					430		
[7888]	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro
[7889]			435					440						445		
[7890]	Gly	Lys														
[7891]		450														
[7892]	<210>	357														
[7893]	<211>	449														
[7894]	<212>	PRT														
[7895]	<213>	人工序列(Artificial Sequence)														
[7896]	<220>															
[7897]	<223>	具有野生型恒定区的嵌合IgG1重链														
[7898]	<400>	357														
[7899]	Lys	Val	Gln	Leu	Gln	Gln	Ser	Gly	Ala	Glu	Leu	Val	Lys	Pro	Gly	Thr
[7900]	1			5					10					15		
[7901]	Ser	Val	Lys	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Glu	Tyr
[7902]			20						25					30		
[7903]	Ile	Ile	Tyr	Trp	Ile	Lys	Gln	Arg	Ser	Gly	Gln	Gly	Leu	Glu	Trp	Ile
[7904]		35						40					45			
[7905]	Gly	Trp	Phe	Tyr	Pro	Gly	Thr	Gly	Ser	Ile	Lys	Tyr	Asn	Glu	Lys	Phe
[7906]	50						55					60				
[7907]	Lys	Asp	Lys	Ala	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Ser	Ser	Thr	Val	Phe
[7908]	65					70					75				80	
[7909]	Met	Glu	Leu	Ser	Arg	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Phe	Cys
[7910]					85					90					95	
[7911]	Ala	Arg	His	Glu	Glu	Gly	Asn	Leu	Trp	Phe	Ala	Tyr	Trp	Gly	Gln	Gly
[7912]			100						105					110		
[7913]	Thr	Leu	Val	Thr	Val	Ser	Ala	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[7914]			115						120					125		
[7915]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[7916]		130					135					140				

[7917]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[7918]	145 150 155 160
[7919]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[7920]	165 170 175
[7921]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[7922]	180 185 190
[7923]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[7924]	195 200 205
[7925]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
[7926]	210 215 220
[7927]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
[7928]	225 230 235 240
[7929]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[7930]	245 250 255
[7931]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
[7932]	260 265 270
[7933]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[7934]	275 280 285
[7935]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
[7936]	290 295 300
[7937]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[7938]	305 310 315 320
[7939]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[7940]	325 330 335
[7941]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[7942]	340 345 350
[7943]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
[7944]	355 360 365
[7945]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[7946]	370 375 380
[7947]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[7948]	385 390 395 400
[7949]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[7950]	405 410 415
[7951]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[7952]	420 425 430
[7953]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[7954]	435 440 445
[7955]	Lys

[7956]	<210>	358	
[7957]	<211>	453	
[7958]	<212>	PRT	
[7959]	<213>	人工序列(Artificial Sequence)	
[7960]	<220>		
[7961]	<223>	具有野生型恒定区的嵌合IgG1重链	
[7962]	<400>	358	
[7963]	Glu Gly Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala		
[7964]	1	5	10 15
[7965]	Ser Val Ile Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Thr		
[7966]		20	25 30
[7967]	Tyr Ile His Trp Leu Asn Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile		
[7968]		35	40 45
[7969]	Gly Arg Ile Glu Pro Ala Asn Gly Asn Thr Lys Tyr Asp Pro Thr Phe		
[7970]		50	55 60
[7971]	Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr		
[7972]	65	70	75 80
[7973]	Leu Gln Leu Thr Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys		
[7974]		85	90 95
[7975]	Ser Arg Gly Gly Ile Tyr Tyr Tyr Gly Ser His Trp Tyr Phe Asp Val		
[7976]		100	105 110
[7977]	Trp Gly Ala Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly		
[7978]		115	120 125
[7979]	Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly		
[7980]		130	135 140
[7981]	Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val		
[7982]	145	150	155 160
[7983]	Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe		
[7984]		165	170 175
[7985]	Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val		
[7986]		180	185 190
[7987]	Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val		
[7988]		195	200 205
[7989]	Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys		
[7990]		210	215 220
[7991]	Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu		
[7992]	225	230	235 240
[7993]	Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr		
[7994]		245	250 255

[7995]	Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
[7996]	260 265 270
[7997]	Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
[7998]	275 280 285
[7999]	Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
[8000]	290 295 300
[8001]	Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
[8002]	305 310 315 320
[8003]	Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
[8004]	325 330 335
[8005]	Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
[8006]	340 345 350
[8007]	Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
[8008]	355 360 365
[8009]	Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
[8010]	370 375 380
[8011]	Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
[8012]	385 390 395 400
[8013]	Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
[8014]	405 410 415
[8015]	Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
[8016]	420 425 430
[8017]	Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
[8018]	435 440 445
[8019]	Leu Ser Pro Gly Lys
[8020]	450
[8021]	<210> 359
[8022]	<211> 448
[8023]	<212> PRT
[8024]	<213> 人工序列(Artificial Sequence)
[8025]	<220>
[8026]	<223> 具有野生型恒定区的嵌合IgG1重链
[8027]	<400> 359
[8028]	Gln Phe Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser
[8029]	1 5 10 15
[8030]	Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Glu Phe Ser Ser Asn
[8031]	20 25 30
[8032]	Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Ser Leu Glu Trp Ile
[8033]	35 40 45

[8034]	Gly	Gln	Ile	Trp	Pro	Gly	Asp	Gly	Asp	Thr	Asn	Tyr	Asn	Gly	Lys	Phe
[8035]	50					55					60					
[8036]	Arg	Gly	Lys	Ala	Thr	Leu	Thr	Ser	Asp	Lys	Ser	Ser	Ser	Thr	Ala	Tyr
[8037]	65					70					75					80
[8038]	Met	Gln	Leu	Asn	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Phe	Cys
[8039]	85					90					95					
[8040]	Ala	Arg	Gly	Arg	Ala	Ser	Phe	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
[8041]	100					105					110					
[8042]	Ala	Leu	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
[8043]	115					120					125					
[8044]	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
[8045]	130					135					140					
[8046]	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
[8047]	145					150					155					160
[8048]	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
[8049]	165					170					175					
[8050]	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
[8051]	180					185					190					
[8052]	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser
[8053]	195					200					205					
[8054]	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr
[8055]	210					215					220					
[8056]	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser
[8057]	225					230					235					240
[8058]	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
[8059]	245					250					255					
[8060]	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
[8061]	260					265					270					
[8062]	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
[8063]	275					280					285					
[8064]	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val
[8065]	290					295					300					
[8066]	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
[8067]	305					310					315					320
[8068]	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr
[8069]	325					330					335					
[8070]	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
[8071]	340					345					350					
[8072]	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys

[8073]	355	360	365
[8074]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser		
[8075]	370	375	380
[8076]	Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp		
[8077]	385	390	395
[8078]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser		
[8079]	405	410	415
[8080]	Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala		
[8081]	420	425	430
[8082]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys		
[8083]	435	440	445
[8084]	<210> 360		
[8085]	<211> 449		
[8086]	<212> PRT		
[8087]	<213> 人工序列(Artificial Sequence)		
[8088]	<220>		
[8089]	<223> 具有CDR突变和野生型恒定区的嵌合IgG1重链		
[8090]	<400> 360		
[8091]	Gln Val Gln Leu Gln Gln Ser Gly Asn Glu Leu Ala Arg Pro Gly Ala		
[8092]	1	5	10
[8093]	Ser Val Arg Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[8094]	20	25	30
[8095]	Gly Ile Thr Trp Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile		
[8096]	35	40	45
[8097]	Gly Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe		
[8098]	50	55	60
[8099]	Lys Gly Arg Ala Thr Leu Thr Ala Asp Ile Ser Ser Ser Thr Ala Tyr		
[8100]	65	70	75
[8101]	Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys		
[8102]	85	90	95
[8103]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly		
[8104]	100	105	110
[8105]	Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe		
[8106]	115	120	125
[8107]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu		
[8108]	130	135	140
[8109]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
[8110]	145	150	155
[8111]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu		

[8112]					165					170						175
[8113]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[8114]					180					185						190
[8115]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[8116]					195					200						205
[8117]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[8118]					210					215						220
[8119]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[8120]					225					230						240
[8121]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[8122]					245					250						255
[8123]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[8124]					260					265						270
[8125]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
[8126]					275					280						285
[8127]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val
[8128]					290					295						300
[8129]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
[8130]					305					310						320
[8131]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
[8132]					325					330						335
[8133]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
[8134]					340					345						350
[8135]	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
[8136]					355					360						365
[8137]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
[8138]					370					375						380
[8139]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
[8140]					385					390						400
[8141]	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
[8142]					405					410						415
[8143]	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
[8144]					420					425						430
[8145]	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
[8146]					435					440						445
[8147]	Lys															
[8148]	<210>	361														
[8149]	<211>	449														
[8150]	<212>	PRT														

[8151]	<213> 人工序列(Artificial Sequence)															
[8152]	<220>															
[8153]	<223> 具有CDR突变和野生型恒定区的嵌合IgG1重链															
[8154]	<400> 361															
[8155]	Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Asn	Glu	Leu	Ala	Arg	Pro	Gly	Ala
[8156]	1				5					10					15	
[8157]	Ser	Val	Arg	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Gly	Tyr
[8158]				20						25					30	
[8159]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Arg	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
[8160]				35						40					45	
[8161]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Ala	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[8162]		50						55					60			
[8163]	Lys	Gly	Arg	Ala	Thr	Leu	Thr	Ala	Asp	Ile	Ser	Ser	Ser	Thr	Ala	Tyr
[8164]	65					70					75				80	
[8165]	Met	Glu	Leu	Arg	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Phe	Cys
[8166]					85					90					95	
[8167]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[8168]				100						105					110	
[8169]	Thr	Ser	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[8170]			115							120					125	
[8171]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[8172]		130					135						140			
[8173]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[8174]	145					150					155				160	
[8175]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
[8176]				165						170					175	
[8177]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[8178]				180						185					190	
[8179]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[8180]			195					200					205			
[8181]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[8182]		210						215					220			
[8183]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[8184]	225					230					235				240	
[8185]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[8186]				245						250					255	
[8187]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[8188]				260						265					270	
[8189]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn

[8190]	275	280	285
[8191]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val		
[8192]	290	295	300
[8193]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
[8194]	305	310	315
[8195]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
[8196]	325	330	335
[8197]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
[8198]	340	345	350
[8199]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr		
[8200]	355	360	365
[8201]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
[8202]	370	375	380
[8203]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[8204]	385	390	395
[8205]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[8206]	405	410	415
[8207]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[8208]	420	425	430
[8209]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[8210]	435	440	445
[8211]	Lys		
[8212]	<210> 362		
[8213]	<211> 449		
[8214]	<212> PRT		
[8215]	<213> 人工序列(Artificial Sequence)		
[8216]	<220>		
[8217]	<223> 具有CDR突变和野生型恒定区的嵌合IgG1重链		
[8218]	<400> 362		
[8219]	Gln Val Gln Leu Gln Gln Ser Gly Asn Glu Leu Ala Arg Pro Gly Ala		
[8220]	1	5	10
[8221]	Ser Val Arg Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[8222]	20	25	30
[8223]	Gly Ile Thr Trp Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile		
[8224]	35	40	45
[8225]	Gly Glu Ile Phe Pro Arg Arg Val Gln Thr Tyr Tyr Ser Glu Lys Phe		
[8226]	50	55	60
[8227]	Lys Gly Arg Ala Thr Leu Thr Ala Asp Ile Ser Ser Ser Thr Ala Tyr		
[8228]	65	70	75
			80

[8229]	Met	Glu	Leu	Arg	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Phe	Cys
[8230]					85				90						95	
[8231]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[8232]					100				105						110	
[8233]	Thr	Ser	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[8234]					115				120						125	
[8235]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[8236]					130				135						140	
[8237]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[8238]	145					150				155						160
[8239]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
[8240]					165					170						175
[8241]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[8242]					180					185					190	
[8243]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[8244]					195				200						205	
[8245]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[8246]					210				215						220	
[8247]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[8248]	225					230					235					240
[8249]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[8250]					245					250						255
[8251]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[8252]					260					265					270	
[8253]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
[8254]					275					280					285	
[8255]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val
[8256]					290					295					300	
[8257]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
[8258]	305					310					315					320
[8259]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
[8260]					325					330					335	
[8261]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
[8262]					340					345					350	
[8263]	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
[8264]					355					360					365	
[8265]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
[8266]					370					375					380	
[8267]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu

[8268]	385	390	395	400
[8269]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys			
[8270]	405	410	415	
[8271]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu			
[8272]	420	425	430	
[8273]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly			
[8274]	435	440	445	
[8275]	Lys			
[8276]	<210> 363			
[8277]	<211> 450			
[8278]	<212> PRT			
[8279]	<213> 人工序列(Artificial Sequence)			
[8280]	<220>			
[8281]	<223> 具有野生型恒定区的人源化IgG1重链			
[8282]	<400> 363			
[8283]	Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu			
[8284]	1	5	10	15
[8285]	Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp			
[8286]	20	25	30	
[8287]	Phe Ala Trp Asp Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp			
[8288]	35	40	45	
[8289]	Ile Gly His Ile Arg Phe Ser Gly Thr Thr Ser Tyr Asn Pro Ser Leu			
[8290]	50	55	60	
[8291]	Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser			
[8292]	65	70	75	80
[8293]	Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys			
[8294]	85	90	95	
[8295]	Ala Arg Ser Thr Leu Ile Thr Lys Gly Phe Phe Asp Tyr Trp Gly Gln			
[8296]	100	105	110	
[8297]	Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val			
[8298]	115	120	125	
[8299]	Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala			
[8300]	130	135	140	
[8301]	Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser			
[8302]	145	150	155	160
[8303]	Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val			
[8304]	165	170	175	
[8305]	Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro			
[8306]	180	185	190	

[8307]	Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
[8308]	195 200 205
[8309]	Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
[8310]	210 215 220
[8311]	Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
[8312]	225 230 235 240
[8313]	Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[8314]	245 250 255
[8315]	Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[8316]	260 265 270
[8317]	Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[8318]	275 280 285
[8319]	Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[8320]	290 295 300
[8321]	Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[8322]	305 310 315 320
[8323]	Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
[8324]	325 330 335
[8325]	Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[8326]	340 345 350
[8327]	Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
[8328]	355 360 365
[8329]	Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[8330]	370 375 380
[8331]	Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[8332]	385 390 395 400
[8333]	Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[8334]	405 410 415
[8335]	Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[8336]	420 425 430
[8337]	Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[8338]	435 440 445
[8339]	Gly Lys
[8340]	450
[8341]	<210> 364
[8342]	<211> 450
[8343]	<212> PRT
[8344]	<213> 人工序列(Artificial Sequence)
[8345]	<220>

[8346]	<223> 具有野生型恒定区的人源化IgG1重链															
[8347]	<400> 364															
[8348]	Glu	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu
[8349]	1			5					10					15		
[8350]	Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Tyr	Ser	Ile	Thr	Ser	Asp
[8351]				20					25					30		
[8352]	Phe	Ala	Trp	Asp	Trp	Ile	Arg	Gln	Phe	Pro	Gly	Lys	Gly	Leu	Glu	Trp
[8353]				35					40					45		
[8354]	Met	Gly	His	Ile	Arg	Phe	Ser	Gly	Thr	Thr	Ser	Tyr	Asn	Pro	Ser	Leu
[8355]				50					55					60		
[8356]	Lys	Ser	Arg	Ile	Thr	Ile	Ser	Val	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Ser
[8357]	65					70					75					80
[8358]	Leu	Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[8359]						85					90					95
[8360]	Ala	Arg	Ser	Thr	Leu	Ile	Thr	Lys	Gly	Phe	Phe	Asp	Tyr	Trp	Gly	Gln
[8361]				100						105					110	
[8362]	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val
[8363]				115						120					125	
[8364]	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala
[8365]				130						135					140	
[8366]	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser
[8367]	145					150					155					160
[8368]	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val
[8369]						165					170					175
[8370]	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro
[8371]				180						185					190	
[8372]	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys
[8373]				195						200					205	
[8374]	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp
[8375]				210						215					220	
[8376]	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly
[8377]	225					230					235					240
[8378]	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
[8379]						245					250					255
[8380]	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu
[8381]				260						265					270	
[8382]	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
[8383]				275						280					285	
[8384]	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg

[8385]	290	295	300
[8386]	Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys		
[8387]	305	310	315
[8388]	Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu		
[8389]	325	330	335
[8390]	Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr		
[8391]	340	345	350
[8392]	Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu		
[8393]	355	360	365
[8394]	Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp		
[8395]	370	375	380
[8396]	Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val		
[8397]	385	390	395
[8398]	Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp		
[8399]	405	410	415
[8400]	Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His		
[8401]	420	425	430
[8402]	Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro		
[8403]	435	440	445
[8404]	Gly Lys		
[8405]	450		
[8406]	<210> 365		
[8407]	<211> 450		
[8408]	<212> PRT		
[8409]	<213> 人工序列(Artificial Sequence)		
[8410]	<220>		
[8411]	<223> 具有野生型恒定区的人源化IgG1重链		
[8412]	<400> 365		
[8413]	Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu		
[8414]	1	5	10
[8415]	Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp		
[8416]	20	25	30
[8417]	Phe Ala Trp Asp Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp		
[8418]	35	40	45
[8419]	Met Gly His Ile Arg Phe Ser Gly Thr Thr Ser Tyr Asn Pro Ser Leu		
[8420]	50	55	60
[8421]	Lys Ser Arg Ile Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Phe		
[8422]	65	70	75
[8423]	Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Thr Tyr Tyr Cys		

[8424]					85					90						95
[8425]	Ala	Arg	Ser	Thr	Leu	Ile	Thr	Lys	Gly	Phe	Phe	Asp	Tyr	Trp	Gly	Gln
[8426]					100					105						110
[8427]	Gly	Thr	Leu	Leu	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val
[8428]					115					120						125
[8429]	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala
[8430]					130					135						140
[8431]	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser
[8432]	145									150						160
[8433]	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val
[8434]					165					170						175
[8435]	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro
[8436]					180					185						190
[8437]	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys
[8438]					195					200						205
[8439]	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp
[8440]					210					215						220
[8441]	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly
[8442]	225									230						240
[8443]	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
[8444]					245					250						255
[8445]	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu
[8446]					260					265						270
[8447]	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
[8448]					275					280						285
[8449]	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg
[8450]					290					295						300
[8451]	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
[8452]	305									310						320
[8453]	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu
[8454]					325					330						335
[8455]	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr
[8456]					340					345						350
[8457]	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu
[8458]					355					360						365
[8459]	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp
[8460]					370					375						380
[8461]	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val
[8462]	385									390						400

[8463]	Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[8464]	405 410 415
[8465]	Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[8466]	420 425 430
[8467]	Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[8468]	435 440 445
[8469]	Gly Lys
[8470]	450
[8471]	<210> 366
[8472]	<211> 450
[8473]	<212> PRT
[8474]	<213> 人工序列(Artificial Sequence)
[8475]	<220>
[8476]	<223> 具有野生型恒定区的人源化IgG1重链
[8477]	<400> 366
[8478]	Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
[8479]	1 5 10 15
[8480]	Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp
[8481]	20 25 30
[8482]	Phe Ala Trp Asp Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
[8483]	35 40 45
[8484]	Ile Gly His Ile Arg Phe Ser Gly Thr Thr Ser Tyr Asn Pro Ser Leu
[8485]	50 55 60
[8486]	Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
[8487]	65 70 75 80
[8488]	Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
[8489]	85 90 95
[8490]	Ala Arg Ser Thr Leu Ile Thr Lys Gly Phe Phe Asp Tyr Trp Gly Gln
[8491]	100 105 110
[8492]	Gly Thr Leu Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
[8493]	115 120 125
[8494]	Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
[8495]	130 135 140
[8496]	Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
[8497]	145 150 155 160
[8498]	Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
[8499]	165 170 175
[8500]	Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
[8501]	180 185 190

[8502]	Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
[8503]	195 200 205
[8504]	Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
[8505]	210 215 220
[8506]	Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
[8507]	225 230 235 240
[8508]	Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[8509]	245 250 255
[8510]	Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[8511]	260 265 270
[8512]	Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[8513]	275 280 285
[8514]	Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[8515]	290 295 300
[8516]	Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[8517]	305 310 315 320
[8518]	Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
[8519]	325 330 335
[8520]	Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[8521]	340 345 350
[8522]	Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
[8523]	355 360 365
[8524]	Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[8525]	370 375 380
[8526]	Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[8527]	385 390 395 400
[8528]	Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[8529]	405 410 415
[8530]	Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[8531]	420 425 430
[8532]	Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[8533]	435 440 445
[8534]	Gly Lys
[8535]	450
[8536]	<210> 367
[8537]	<211> 450
[8538]	<212> PRT
[8539]	<213> 人工序列(Artificial Sequence)
[8540]	<220>

[8541]	<223> 具有野生型恒定区的人源化IgG1重链															
[8542]	<400> 367															
[8543]	Glu	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu
[8544]	1			5					10					15		
[8545]	Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Tyr	Ser	Ile	Thr	Ser	Asp
[8546]				20					25					30		
[8547]	Phe	Ala	Trp	Asp	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp
[8548]				35					40					45		
[8549]	Ile	Gly	His	Ile	Arg	Phe	Ser	Gly	Thr	Thr	Ser	Tyr	Asn	Pro	Ser	Leu
[8550]		50						55				60				
[8551]	Lys	Ser	Arg	Val	Thr	Ile	Ser	Arg	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Ser
[8552]	65					70					75				80	
[8553]	Leu	Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[8554]					85					90					95	
[8555]	Ala	Arg	Ser	Thr	Leu	Ile	Thr	Lys	Gly	Phe	Phe	Asp	Tyr	Trp	Gly	Gln
[8556]				100					105					110		
[8557]	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val
[8558]				115					120					125		
[8559]	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala
[8560]		130						135					140			
[8561]	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser
[8562]	145					150					155				160	
[8563]	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val
[8564]					165					170					175	
[8565]	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro
[8566]				180					185					190		
[8567]	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys
[8568]				195					200					205		
[8569]	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp
[8570]		210						215					220			
[8571]	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly
[8572]	225					230					235				240	
[8573]	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
[8574]					245					250					255	
[8575]	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu
[8576]				260					265					270		
[8577]	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
[8578]				275					280					285		
[8579]	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg

[8580]	290	295	300
[8581]	Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys		
[8582]	305	310	315
[8583]	Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu		
[8584]	325	330	335
[8585]	Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr		
[8586]	340	345	350
[8587]	Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu		
[8588]	355	360	365
[8589]	Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp		
[8590]	370	375	380
[8591]	Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val		
[8592]	385	390	395
[8593]	Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp		
[8594]	405	410	415
[8595]	Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His		
[8596]	420	425	430
[8597]	Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro		
[8598]	435	440	445
[8599]	Gly Lys		
[8600]	450		
[8601]	<210> 368		
[8602]	<211> 449		
[8603]	<212> PRT		
[8604]	<213> 人工序列(Artificial Sequence)		
[8605]	<220>		
[8606]	<223> 具有野生型恒定区的人源化IgG1重链		
[8607]	<400> 368		
[8608]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[8609]	1	5	10
[8610]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[8611]	20	25	30
[8612]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met		
[8613]	35	40	45
[8614]	Gly Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe		
[8615]	50	55	60
[8616]	Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr		
[8617]	65	70	75
[8618]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys		

[8619]					85					90					95				
[8620]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly			
[8621]					100					105					110				
[8622]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe			
[8623]					115					120					125				
[8624]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu			
[8625]					130					135					140				
[8626]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp			
[8627]	145						150				155					160			
[8628]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu			
[8629]					165					170					175				
[8630]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser			
[8631]					180					185					190				
[8632]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro			
[8633]					195					200					205				
[8634]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys			
[8635]					210					215					220				
[8636]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro			
[8637]	225						230				235					240			
[8638]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser			
[8639]					245					250					255				
[8640]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp			
[8641]					260					265					270				
[8642]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn			
[8643]					275					280					285				
[8644]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val			
[8645]					290					295					300				
[8646]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu			
[8647]	305						310				315					320			
[8648]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys			
[8649]					325					330					335				
[8650]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr			
[8651]					340					345					350				
[8652]	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr			
[8653]					355					360					365				
[8654]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu			
[8655]					370					375					380				
[8656]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu			
[8657]	385						390				395					400			

[8658]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[8659]	405 410 415
[8660]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[8661]	420 425 430
[8662]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[8663]	435 440 445
[8664]	Lys
[8665]	<210> 369
[8666]	<211> 449
[8667]	<212> PRT
[8668]	<213> 人工序列(Artificial Sequence)
[8669]	<220>
[8670]	<223> 具有野生型恒定区的人源化IgG1重链
[8671]	<400> 369
[8672]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[8673]	1 5 10 15
[8674]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[8675]	20 25 30
[8676]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
[8677]	35 40 45
[8678]	Gly Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe
[8679]	50 55 60
[8680]	Lys Gly Arg Ala Thr Leu Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
[8681]	65 70 75 80
[8682]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
[8683]	85 90 95
[8684]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[8685]	100 105 110
[8686]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[8687]	115 120 125
[8688]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
[8689]	130 135 140
[8690]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[8691]	145 150 155 160
[8692]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[8693]	165 170 175
[8694]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[8695]	180 185 190
[8696]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

[8697]	195	200	205
[8698]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys		
[8699]	210	215	220
[8700]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro		
[8701]	225	230	235
[8702]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser		
[8703]	245	250	255
[8704]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp		
[8705]	260	265	270
[8706]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn		
[8707]	275	280	285
[8708]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val		
[8709]	290	295	300
[8710]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
[8711]	305	310	315
[8712]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
[8713]	325	330	335
[8714]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
[8715]	340	345	350
[8716]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr		
[8717]	355	360	365
[8718]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
[8719]	370	375	380
[8720]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[8721]	385	390	395
[8722]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[8723]	405	410	415
[8724]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[8725]	420	425	430
[8726]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[8727]	435	440	445
[8728]	Lys		
[8729]	<210> 370		
[8730]	<211> 449		
[8731]	<212> PRT		
[8732]	<213> 人工序列(Artificial Sequence)		
[8733]	<220>		
[8734]	<223> 具有野生型恒定区的人源化IgG1重链		
[8735]	<400> 370		

[8736]	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
[8737]	1				5					10					15	
[8738]	Ser	Val	Lys	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Gly	Tyr
[8739]				20					25						30	
[8740]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
[8741]				35					40					45		
[8742]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Asn	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[8743]		50						55					60			
[8744]	Lys	Gly	Arg	Ala	Thr	Leu	Thr	Ala	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
[8745]	65					70					75					80
[8746]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Phe	Cys
[8747]					85					90					95	
[8748]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[8749]				100					105						110	
[8750]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[8751]				115					120					125		
[8752]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[8753]		130						135					140			
[8754]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[8755]	145					150					155					160
[8756]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
[8757]					165					170					175	
[8758]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[8759]				180						185					190	
[8760]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[8761]			195					200					205			
[8762]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[8763]		210						215					220			
[8764]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[8765]	225					230					235					240
[8766]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[8767]				245						250					255	
[8768]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[8769]				260						265					270	
[8770]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
[8771]			275						280					285		
[8772]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val
[8773]		290						295						300		
[8774]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu

[8775]	305	310	315	320
[8776]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys			
[8777]	325	330	335	
[8778]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr			
[8779]	340	345	350	
[8780]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr			
[8781]	355	360	365	
[8782]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu			
[8783]	370	375	380	
[8784]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu			
[8785]	385	390	395	400
[8786]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys			
[8787]	405	410	415	
[8788]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu			
[8789]	420	425	430	
[8790]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly			
[8791]	435	440	445	
[8792]	Lys			
[8793]	<210> 371			
[8794]	<211> 449			
[8795]	<212> PRT			
[8796]	<213> 人工序列(Artificial Sequence)			
[8797]	<220>			
[8798]	<223> 具有野生型恒定区的人源化IgG1重链			
[8799]	<400> 371			
[8800]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala			
[8801]	1	5	10	15
[8802]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr			
[8803]	20	25	30	
[8804]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met			
[8805]	35	40	45	
[8806]	Gly Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe			
[8807]	50	55	60	
[8808]	Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr			
[8809]	65	70	75	80
[8810]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys			
[8811]	85	90	95	
[8812]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly			
[8813]	100	105	110	

[8814]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[8815]			115					120					125			
[8816]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[8817]			130					135					140			
[8818]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[8819]	145						150					155				160
[8820]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
[8821]					165					170					175	
[8822]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[8823]				180						185					190	
[8824]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[8825]			195					200					205			
[8826]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[8827]		210					215					220				
[8828]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[8829]	225					230					235					240
[8830]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[8831]				245						250					255	
[8832]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[8833]			260							265					270	
[8834]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
[8835]		275						280					285			
[8836]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val
[8837]		290					295					300				
[8838]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
[8839]	305					310					315					320
[8840]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
[8841]				325						330					335	
[8842]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
[8843]			340							345				350		
[8844]	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
[8845]		355						360					365			
[8846]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
[8847]		370					375					380				
[8848]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
[8849]	385					390					395					400
[8850]	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
[8851]				405						410					415	
[8852]	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu

[8853]	420	425	430
[8854]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[8855]	435	440	445
[8856]	Lys		
[8857]	<210> 372		
[8858]	<211> 449		
[8859]	<212> PRT		
[8860]	<213> 人工序列(Artificial Sequence)		
[8861]	<220>		
[8862]	<223> 具有野生型恒定区的人源化IgG1重链		
[8863]	<400> 372		
[8864]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[8865]	1 5 10 15		
[8866]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[8867]	20 25 30		
[8868]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met		
[8869]	35 40 45		
[8870]	Gly Glu Ile Phe Pro Arg Arg Val Asn Thr Tyr Tyr Ser Glu Lys Phe		
[8871]	50 55 60		
[8872]	Lys Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr		
[8873]	65 70 75 80		
[8874]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys		
[8875]	85 90 95		
[8876]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly		
[8877]	100 105 110		
[8878]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe		
[8879]	115 120 125		
[8880]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu		
[8881]	130 135 140		
[8882]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
[8883]	145 150 155 160		
[8884]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu		
[8885]	165 170 175		
[8886]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser		
[8887]	180 185 190		
[8888]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro		
[8889]	195 200 205		
[8890]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys		
[8891]	210 215 220		

[8892]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro		
[8893]	225	230	235 240
[8894]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser		
[8895]		245	250 255
[8896]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp		
[8897]		260	265 270
[8898]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn		
[8899]		275	280 285
[8900]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val		
[8901]		290	295 300
[8902]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
[8903]	305	310	315 320
[8904]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
[8905]		325	330 335
[8906]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
[8907]		340	345 350
[8908]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr		
[8909]		355	360 365
[8910]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
[8911]		370	375 380
[8912]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[8913]	385	390	395 400
[8914]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[8915]		405	410 415
[8916]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[8917]		420	425 430
[8918]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[8919]		435	440 445
[8920]	Lys		
[8921]	<210>	373	
[8922]	<211>	449	
[8923]	<212>	PRT	
[8924]	<213>	人工序列(Artificial Sequence)	
[8925]	<220>		
[8926]	<223>	具有野生型恒定区的人源化IgG1重链	
[8927]	<400>	373	
[8928]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[8929]	1	5	10 15
[8930]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		

[8931]	20							25					30						
[8932]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met			
[8933]	35							40					45						
[8934]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Asn	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe			
[8935]	50							55					60						
[8936]	Lys	Gly	Arg	Val	Thr	Met	Thr	Ala	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr			
[8937]	65							70					75					80	
[8938]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys			
[8939]	85							90					95						
[8940]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly			
[8941]	100							105					110						
[8942]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe			
[8943]	115							120					125						
[8944]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu			
[8945]	130							135					140						
[8946]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp			
[8947]	145							150					155					160	
[8948]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu			
[8949]	165							170					175						
[8950]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser			
[8951]	180							185					190						
[8952]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro			
[8953]	195							200					205						
[8954]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys			
[8955]	210							215					220						
[8956]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro			
[8957]	225							230					235					240	
[8958]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser			
[8959]	245							250					255						
[8960]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp			
[8961]	260							265					270						
[8962]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn			
[8963]	275							280					285						
[8964]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val			
[8965]	290							295					300						
[8966]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu			
[8967]	305							310					315					320	
[8968]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys			
[8969]	325							330					335						

[8970]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
[8971]				340				345					350			
[8972]	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
[8973]				355				360					365			
[8974]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
[8975]				370				375					380			
[8976]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
[8977]				385				390					395			400
[8978]	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
[8979]					405					410					415	
[8980]	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
[8981]					420					425					430	
[8982]	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
[8983]					435					440					445	
[8984]	Lys															
[8985]	<210>	374														
[8986]	<211>	449														
[8987]	<212>	PRT														
[8988]	<213>	人工序列(Artificial Sequence)														
[8989]	<220>															
[8990]	<223>	具有CDR2突变和野生型恒定区的人源化IgG1重链														
[8991]	<400>	374														
[8992]	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
[8993]	1				5					10					15	
[8994]	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Gly	Tyr
[8995]					20					25					30	
[8996]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
[8997]					35					40					45	
[8998]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Gln	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[8999]					50					55					60	
[9000]	Lys	Gly	Arg	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
[9001]						65				70					75	
[9002]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[9003]						85				90					95	
[9004]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[9005]						100				105					110	
[9006]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[9007]						115				120					125	
[9008]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu

[9009]	130	135	140
[9010]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
[9011]	145	150	155
[9012]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu		
[9013]	165	170	175
[9014]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser		
[9015]	180	185	190
[9016]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro		
[9017]	195	200	205
[9018]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys		
[9019]	210	215	220
[9020]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro		
[9021]	225	230	235
[9022]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser		
[9023]	245	250	255
[9024]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp		
[9025]	260	265	270
[9026]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn		
[9027]	275	280	285
[9028]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val		
[9029]	290	295	300
[9030]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
[9031]	305	310	315
[9032]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
[9033]	325	330	335
[9034]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
[9035]	340	345	350
[9036]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr		
[9037]	355	360	365
[9038]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
[9039]	370	375	380
[9040]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[9041]	385	390	395
[9042]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[9043]	405	410	415
[9044]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[9045]	420	425	430
[9046]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[9047]	435	440	445

[9048]	Lys
[9049]	<210> 375
[9050]	<211> 449
[9051]	<212> PRT
[9052]	<213> 人工序列(Artificial Sequence)
[9053]	<220>
[9054]	<223> 具有CDR2突变和野生型恒定区的人源化IgG1重链
[9055]	<400> 375
[9056]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[9057]	1 5 10 15
[9058]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[9059]	20 25 30
[9060]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
[9061]	35 40 45
[9062]	Gly Glu Ile Phe Pro Arg Arg Val Gln Thr Tyr Tyr Ser Glu Lys Phe
[9063]	50 55 60
[9064]	Lys Gly Arg Ala Thr Leu Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
[9065]	65 70 75 80
[9066]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
[9067]	85 90 95
[9068]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[9069]	100 105 110
[9070]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[9071]	115 120 125
[9072]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
[9073]	130 135 140
[9074]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[9075]	145 150 155 160
[9076]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[9077]	165 170 175
[9078]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[9079]	180 185 190
[9080]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[9081]	195 200 205
[9082]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
[9083]	210 215 220
[9084]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
[9085]	225 230 235 240
[9086]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser

[9087]		245		250		255
[9088]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp					
[9089]		260		265		270
[9090]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn					
[9091]		275		280		285
[9092]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val					
[9093]		290		295		300
[9094]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu					
[9095]		305		310		315
[9096]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys					
[9097]		325		330		335
[9098]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr					
[9099]		340		345		350
[9100]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr					
[9101]		355		360		365
[9102]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu					
[9103]		370		375		380
[9104]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu					
[9105]		385		390		395
[9106]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys					
[9107]		405		410		415
[9108]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu					
[9109]		420		425		430
[9110]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly					
[9111]		435		440		445
[9112]	Lys					
[9113]	<210> 376					
[9114]	<211> 449					
[9115]	<212> PRT					
[9116]	<213> 人工序列(Artificial Sequence)					
[9117]	<220>					
[9118]	<223> 具有CDR2突变和野生型恒定区的人源化IgG1重链					
[9119]	<400> 376					
[9120]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala					
[9121]	1	5		10		15
[9122]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr					
[9123]		20		25		30
[9124]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile					
[9125]		35		40		45

[9126]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Gln	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[9127]	50						55					60				
[9128]	Lys	Gly	Arg	Ala	Thr	Leu	Thr	Ala	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
[9129]	65					70					75					80
[9130]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Phe	Cys
[9131]					85					90					95	
[9132]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[9133]				100					105					110		
[9134]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[9135]			115					120					125			
[9136]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[9137]		130					135					140				
[9138]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[9139]	145					150					155					160
[9140]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
[9141]					165					170						175
[9142]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[9143]				180						185					190	
[9144]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[9145]			195					200					205			
[9146]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[9147]		210					215					220				
[9148]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[9149]	225					230					235					240
[9150]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[9151]				245						250					255	
[9152]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[9153]				260						265					270	
[9154]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
[9155]			275							280				285		
[9156]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val
[9157]		290					295					300				
[9158]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
[9159]	305					310					315					320
[9160]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
[9161]				325						330					335	
[9162]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
[9163]				340						345					350	
[9164]	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr

[9165]	355	360	365
[9166]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
[9167]	370	375	380
[9168]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[9169]	385	390	395
[9170]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[9171]	405	410	415
[9172]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[9173]	420	425	430
[9174]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[9175]	435	440	445
[9176]	Lys		
[9177]	<210> 377		
[9178]	<211> 449		
[9179]	<212> PRT		
[9180]	<213> 人工序列(Artificial Sequence)		
[9181]	<220>		
[9182]	<223> 具有CDR2突变和野生型恒定区的人源化IgG1重链		
[9183]	<400> 377		
[9184]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[9185]	1	5	10
[9186]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[9187]	20	25	30
[9188]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met		
[9189]	35	40	45
[9190]	Gly Glu Ile Phe Pro Arg Arg Val Gln Thr Tyr Tyr Ser Glu Lys Phe		
[9191]	50	55	60
[9192]	Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr		
[9193]	65	70	75
[9194]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys		
[9195]	85	90	95
[9196]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly		
[9197]	100	105	110
[9198]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe		
[9199]	115	120	125
[9200]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu		
[9201]	130	135	140
[9202]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
[9203]	145	150	155
			160

[9204]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[9205]	165 170 175
[9206]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[9207]	180 185 190
[9208]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[9209]	195 200 205
[9210]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
[9211]	210 215 220
[9212]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
[9213]	225 230 235 240
[9214]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[9215]	245 250 255
[9216]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
[9217]	260 265 270
[9218]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[9219]	275 280 285
[9220]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
[9221]	290 295 300
[9222]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[9223]	305 310 315 320
[9224]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[9225]	325 330 335
[9226]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[9227]	340 345 350
[9228]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
[9229]	355 360 365
[9230]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[9231]	370 375 380
[9232]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[9233]	385 390 395 400
[9234]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[9235]	405 410 415
[9236]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[9237]	420 425 430
[9238]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[9239]	435 440 445
[9240]	Lys
[9241]	<210> 378
[9242]	<211> 449

[9243]	<212>	PRT
[9244]	<213>	人工序列(Artificial Sequence)
[9245]	<220>	
[9246]	<223>	具有CDR2突变和野生型恒定区的人源化IgG1重链
[9247]	<400>	378
[9248]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala	
[9249]	1 5 10 15	
[9250]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr	
[9251]	20 25 30	
[9252]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met	
[9253]	35 40 45	
[9254]	Gly Glu Ile Phe Pro Arg Arg Val Gln Thr Tyr Tyr Ser Glu Lys Phe	
[9255]	50 55 60	
[9256]	Lys Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr	
[9257]	65 70 75 80	
[9258]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys	
[9259]	85 90 95	
[9260]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly	
[9261]	100 105 110	
[9262]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe	
[9263]	115 120 125	
[9264]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu	
[9265]	130 135 140	
[9266]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp	
[9267]	145 150 155 160	
[9268]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu	
[9269]	165 170 175	
[9270]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser	
[9271]	180 185 190	
[9272]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro	
[9273]	195 200 205	
[9274]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys	
[9275]	210 215 220	
[9276]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro	
[9277]	225 230 235 240	
[9278]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser	
[9279]	245 250 255	
[9280]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp	
[9281]	260 265 270	

[9282]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
[9283]				275				280					285			
[9284]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val
[9285]				290				295					300			
[9286]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
[9287]	305						310					315				320
[9288]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
[9289]					325						330				335	
[9290]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
[9291]				340						345				350		
[9292]	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
[9293]				355						360				365		
[9294]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
[9295]				370						375				380		
[9296]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
[9297]	385						390					395				400
[9298]	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
[9299]					405						410				415	
[9300]	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
[9301]				420						425				430		
[9302]	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
[9303]				435						440				445		
[9304]	Lys															
[9305]	<210>	379														
[9306]	<211>	449														
[9307]	<212>	PRT														
[9308]	<213>	人工序列(Artificial Sequence)														
[9309]	<220>															
[9310]	<223>	具有CDR2突变和野生型恒定区的人源化IgG1重链														
[9311]	<400>	379														
[9312]	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
[9313]	1				5					10					15	
[9314]	Ser	Val	Lys	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Gly	Tyr
[9315]				20						25				30		
[9316]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
[9317]				35						40				45		
[9318]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Gln	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[9319]				50						55				60		
[9320]	Lys	Gly	Arg	Val	Thr	Met	Thr	Ala	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr

[9321]	65	70	75	80
[9322]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys			
[9323]		85	90	95
[9324]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly			
[9325]		100	105	110
[9326]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe			
[9327]		115	120	125
[9328]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu			
[9329]		130	135	140
[9330]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp			
[9331]	145	150	155	160
[9332]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu			
[9333]		165	170	175
[9334]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser			
[9335]		180	185	190
[9336]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro			
[9337]		195	200	205
[9338]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys			
[9339]		210	215	220
[9340]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro			
[9341]	225	230	235	240
[9342]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser			
[9343]		245	250	255
[9344]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp			
[9345]		260	265	270
[9346]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn			
[9347]		275	280	285
[9348]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val			
[9349]		290	295	300
[9350]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu			
[9351]	305	310	315	320
[9352]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys			
[9353]		325	330	335
[9354]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr			
[9355]		340	345	350
[9356]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr			
[9357]		355	360	365
[9358]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu			
[9359]		370	375	380

[9360]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[9361]	385 390 395 400
[9362]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[9363]	405 410 415
[9364]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[9365]	420 425 430
[9366]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[9367]	435 440 445
[9368]	Lys
[9369]	<210> 380
[9370]	<211> 449
[9371]	<212> PRT
[9372]	<213> 人工序列(Artificial Sequence)
[9373]	<220>
[9374]	<223> 具有CDR2突变和野生型恒定区的人源化IgG1重链
[9375]	<400> 380
[9376]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[9377]	1 5 10 15
[9378]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[9379]	20 25 30
[9380]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
[9381]	35 40 45
[9382]	Gly Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe
[9383]	50 55 60
[9384]	Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
[9385]	65 70 75 80
[9386]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
[9387]	85 90 95
[9388]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[9389]	100 105 110
[9390]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[9391]	115 120 125
[9392]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
[9393]	130 135 140
[9394]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[9395]	145 150 155 160
[9396]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[9397]	165 170 175
[9398]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

[9399]	180	185	190
[9400]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro		
[9401]	195	200	205
[9402]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys		
[9403]	210	215	220
[9404]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro		
[9405]	225	230	235
[9406]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser		
[9407]	245	250	255
[9408]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp		
[9409]	260	265	270
[9410]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn		
[9411]	275	280	285
[9412]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val		
[9413]	290	295	300
[9414]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
[9415]	305	310	315
[9416]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
[9417]	325	330	335
[9418]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
[9419]	340	345	350
[9420]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr		
[9421]	355	360	365
[9422]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
[9423]	370	375	380
[9424]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[9425]	385	390	395
[9426]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[9427]	405	410	415
[9428]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[9429]	420	425	430
[9430]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[9431]	435	440	445
[9432]	Lys		
[9433]	<210> 381		
[9434]	<211> 449		
[9435]	<212> PRT		
[9436]	<213> 人工序列(Artificial Sequence)		
[9437]	<220>		

[9438]	<223> 具有CDR2突变和野生型恒定区的人源化IgG1重链															
[9439]	<400> 381															
[9440]	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
[9441]	1				5					10					15	
[9442]	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Gly	Tyr
[9443]					20					25					30	
[9444]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
[9445]					35					40					45	
[9446]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Ser	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[9447]					50					55					60	
[9448]	Lys	Gly	Arg	Ala	Thr	Leu	Thr	Thr	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
[9449]	65					70					75					80
[9450]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Phe	Cys
[9451]					85					90						95
[9452]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[9453]					100					105					110	
[9454]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[9455]					115					120					125	
[9456]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[9457]					130					135					140	
[9458]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[9459]	145					150					155					160
[9460]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
[9461]					165					170						175
[9462]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[9463]					180					185					190	
[9464]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[9465]					195					200					205	
[9466]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[9467]					210					215					220	
[9468]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[9469]	225					230					235					240
[9470]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[9471]					245					250						255
[9472]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[9473]					260					265					270	
[9474]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
[9475]					275					280					285	
[9476]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val

[9477]	290	295	300
[9478]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
[9479]	305	310	315
[9480]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
[9481]	325	330	335
[9482]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
[9483]	340	345	350
[9484]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr		
[9485]	355	360	365
[9486]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
[9487]	370	375	380
[9488]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[9489]	385	390	395
[9490]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[9491]	405	410	415
[9492]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[9493]	420	425	430
[9494]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[9495]	435	440	445
[9496]	Lys		
[9497]	<210> 382		
[9498]	<211> 449		
[9499]	<212> PRT		
[9500]	<213> 人工序列(Artificial Sequence)		
[9501]	<220>		
[9502]	<223> 具有CDR2突变和野生型恒定区的人源化IgG1重链		
[9503]	<400> 382		
[9504]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[9505]	1	5	10
[9506]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[9507]	20	25	30
[9508]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile		
[9509]	35	40	45
[9510]	Gly Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe		
[9511]	50	55	60
[9512]	Lys Gly Arg Ala Thr Leu Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr		
[9513]	65	70	75
[9514]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys		
[9515]	85	90	95

[9516]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[9517]				100				105					110			
[9518]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[9519]			115					120					125			
[9520]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[9521]		130					135						140			
[9522]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[9523]	145					150					155					160
[9524]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
[9525]					165					170					175	
[9526]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[9527]				180					185						190	
[9528]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[9529]			195					200					205			
[9530]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[9531]		210					215						220			
[9532]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[9533]	225					230					235					240
[9534]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[9535]				245						250					255	
[9536]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[9537]				260						265					270	
[9538]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
[9539]			275					280					285			
[9540]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val
[9541]		290					295					300				
[9542]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
[9543]	305					310					315					320
[9544]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
[9545]				325						330					335	
[9546]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
[9547]				340					345						350	
[9548]	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
[9549]			355					360					365			
[9550]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
[9551]		370					375					380				
[9552]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
[9553]	385					390					395					400
[9554]	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys

[9555]	405								410				415				
[9556]	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	
[9557]	420								425				430				
[9558]	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	
[9559]	435								440				445				
[9560]	Lys																
[9561]	<210> 383																
[9562]	<211> 449																
[9563]	<212> PRT																
[9564]	<213> 人工序列(Artificial Sequence)																
[9565]	<220>																
[9566]	<223> 具有CDR2突变和野生型恒定区的人源化IgG1重链																
[9567]	<400> 383																
[9568]	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala	
[9569]	1	5								10				15			
[9570]	Ser	Val	Lys	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Gly	Tyr	
[9571]	20								25				30				
[9572]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	
[9573]	35								40				45				
[9574]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Ser	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe	
[9575]	50								55				60				
[9576]	Lys	Gly	Arg	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr	
[9577]	65	70								75				80			
[9578]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
[9579]	85								90				95				
[9580]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	
[9581]	100								105				110				
[9582]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	
[9583]	115								120				125				
[9584]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	
[9585]	130								135				140				
[9586]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	
[9587]	145	150								155				160			
[9588]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	
[9589]	165								170				175				
[9590]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	
[9591]	180								185				190				
[9592]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	
[9593]	195								200				205				

[9594]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
[9595]	210 215 220
[9596]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
[9597]	225 230 235 240
[9598]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[9599]	245 250 255
[9600]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
[9601]	260 265 270
[9602]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[9603]	275 280 285
[9604]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
[9605]	290 295 300
[9606]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[9607]	305 310 315 320
[9608]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[9609]	325 330 335
[9610]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[9611]	340 345 350
[9612]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
[9613]	355 360 365
[9614]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[9615]	370 375 380
[9616]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[9617]	385 390 395 400
[9618]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[9619]	405 410 415
[9620]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[9621]	420 425 430
[9622]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[9623]	435 440 445
[9624]	Lys
[9625]	<210> 384
[9626]	<211> 449
[9627]	<212> PRT
[9628]	<213> 人工序列(Artificial Sequence)
[9629]	<220>
[9630]	<223> 具有CDR2突变和野生型恒定区的人源化IgG1重链
[9631]	<400> 384
[9632]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala

[9633]	1	5	10	15
[9634]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr			
[9635]	20	25	30	
[9636]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met			
[9637]	35	40	45	
[9638]	Gly Glu Ile Phe Pro Arg Arg Val Ser Thr Tyr Tyr Ser Glu Lys Phe			
[9639]	50	55	60	
[9640]	Lys Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr			
[9641]	65	70	75	80
[9642]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys			
[9643]	85	90	95	
[9644]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly			
[9645]	100	105	110	
[9646]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe			
[9647]	115	120	125	
[9648]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu			
[9649]	130	135	140	
[9650]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp			
[9651]	145	150	155	160
[9652]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu			
[9653]	165	170	175	
[9654]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser			
[9655]	180	185	190	
[9656]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro			
[9657]	195	200	205	
[9658]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys			
[9659]	210	215	220	
[9660]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro			
[9661]	225	230	235	240
[9662]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser			
[9663]	245	250	255	
[9664]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp			
[9665]	260	265	270	
[9666]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn			
[9667]	275	280	285	
[9668]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val			
[9669]	290	295	300	
[9670]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu			
[9671]	305	310	315	320

[9672]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
[9673]					325					330					335	
[9674]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
[9675]					340					345					350	
[9676]	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
[9677]					355					360					365	
[9678]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
[9679]					370					375					380	
[9680]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
[9681]					385					390					395	
[9682]	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
[9683]					405					410					415	
[9684]	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
[9685]					420					425					430	
[9686]	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
[9687]					435					440					445	
[9688]	Lys															
[9689]	<210>	385														
[9690]	<211>	449														
[9691]	<212>	PRT														
[9692]	<213>	人工序列(Artificial Sequence)														
[9693]	<220>															
[9694]	<223>	具有CDR2突变和野生型恒定区的人源化IgG1重链														
[9695]	<400>	385														
[9696]	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
[9697]	1				5					10					15	
[9698]	Ser	Val	Lys	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Gly	Tyr
[9699]					20					25					30	
[9700]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
[9701]					35					40					45	
[9702]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Ser	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[9703]					50					55					60	
[9704]	Lys	Gly	Arg	Val	Thr	Met	Thr	Ala	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
[9705]					65					70					75	
[9706]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[9707]					85					90					95	
[9708]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[9709]					100					105					110	
[9710]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe

[9711]	115	120	125
[9712]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu		
[9713]	130	135	140
[9714]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
[9715]	145	150	155
[9716]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu		
[9717]	165	170	175
[9718]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser		
[9719]	180	185	190
[9720]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro		
[9721]	195	200	205
[9722]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys		
[9723]	210	215	220
[9724]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro		
[9725]	225	230	235
[9726]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser		
[9727]	245	250	255
[9728]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp		
[9729]	260	265	270
[9730]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn		
[9731]	275	280	285
[9732]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val		
[9733]	290	295	300
[9734]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
[9735]	305	310	315
[9736]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
[9737]	325	330	335
[9738]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
[9739]	340	345	350
[9740]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr		
[9741]	355	360	365
[9742]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
[9743]	370	375	380
[9744]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[9745]	385	390	395
[9746]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[9747]	405	410	415
[9748]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[9749]	420	425	430

[9750]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[9751]	435 440 445
[9752]	Lys
[9753]	<210> 386
[9754]	<211> 449
[9755]	<212> PRT
[9756]	<213> 人工序列(Artificial Sequence)
[9757]	<220>
[9758]	<223> 具有CDR2突变和野生型恒定区的人源化IgG1重链
[9759]	<400> 386
[9760]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[9761]	1 5 10 15
[9762]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[9763]	20 25 30
[9764]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
[9765]	35 40 45
[9766]	Gly Glu Ile Phe Pro Arg Arg Val Ala Thr Tyr Tyr Ser Glu Lys Phe
[9767]	50 55 60
[9768]	Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
[9769]	65 70 75 80
[9770]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
[9771]	85 90 95
[9772]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly
[9773]	100 105 110
[9774]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[9775]	115 120 125
[9776]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
[9777]	130 135 140
[9778]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[9779]	145 150 155 160
[9780]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[9781]	165 170 175
[9782]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[9783]	180 185 190
[9784]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[9785]	195 200 205
[9786]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
[9787]	210 215 220
[9788]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro

[9789]	225	230	235	240
[9790]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser			
[9791]		245	250	255
[9792]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp			
[9793]		260	265	270
[9794]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn			
[9795]		275	280	285
[9796]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val			
[9797]		290	295	300
[9798]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu			
[9799]	305	310	315	320
[9800]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys			
[9801]		325	330	335
[9802]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr			
[9803]		340	345	350
[9804]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr			
[9805]		355	360	365
[9806]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu			
[9807]		370	375	380
[9808]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu			
[9809]	385	390	395	400
[9810]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys			
[9811]		405	410	415
[9812]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu			
[9813]		420	425	430
[9814]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly			
[9815]		435	440	445
[9816]	Lys			
[9817]	<210> 387			
[9818]	<211> 449			
[9819]	<212> PRT			
[9820]	<213> 人工序列(Artificial Sequence)			
[9821]	<220>			
[9822]	<223> 具有CDR2突变和野生型恒定区的人源化IgG1重链			
[9823]	<400> 387			
[9824]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala			
[9825]	1	5	10	15
[9826]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr			
[9827]		20	25	30

[9828]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
[9829]			35					40					45			
[9830]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Ala	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[9831]		50					55					60				
[9832]	Lys	Gly	Arg	Ala	Thr	Leu	Thr	Thr	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
[9833]	65					70					75					80
[9834]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Phe	Cys
[9835]					85					90					95	
[9836]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[9837]				100					105					110		
[9838]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[9839]			115					120					125			
[9840]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[9841]		130					135					140				
[9842]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[9843]	145					150					155					160
[9844]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
[9845]					165					170					175	
[9846]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
[9847]				180					185					190		
[9848]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
[9849]			195					200					205			
[9850]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
[9851]		210					215					220				
[9852]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
[9853]	225					230					235					240
[9854]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
[9855]				245					250						255	
[9856]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
[9857]				260					265					270		
[9858]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
[9859]			275						280				285			
[9860]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val
[9861]		290					295					300				
[9862]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
[9863]	305					310					315					320
[9864]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
[9865]					325					330				335		
[9866]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr

[9867]	340	345	350
[9868]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr		
[9869]	355	360	365
[9870]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
[9871]	370	375	380
[9872]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
[9873]	385	390	395
[9874]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
[9875]	405	410	415
[9876]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
[9877]	420	425	430
[9878]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[9879]	435	440	445
[9880]	Lys		
[9881]	<210> 388		
[9882]	<211> 449		
[9883]	<212> PRT		
[9884]	<213> 人工序列(Artificial Sequence)		
[9885]	<220>		
[9886]	<223> 具有CDR2突变和野生型恒定区的人源化IgG1重链		
[9887]	<400> 388		
[9888]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[9889]	1 5 10 15		
[9890]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[9891]	20 25 30		
[9892]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile		
[9893]	35 40 45		
[9894]	Gly Glu Ile Phe Pro Arg Arg Val Ala Thr Tyr Tyr Ser Glu Lys Phe		
[9895]	50 55 60		
[9896]	Lys Gly Arg Ala Thr Leu Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr		
[9897]	65 70 75 80		
[9898]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys		
[9899]	85 90 95		
[9900]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly		
[9901]	100 105 110		
[9902]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe		
[9903]	115 120 125		
[9904]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu		
[9905]	130 135 140		

[9906]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[9907]	145 150 155 160
[9908]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[9909]	165 170 175
[9910]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[9911]	180 185 190
[9912]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[9913]	195 200 205
[9914]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
[9915]	210 215 220
[9916]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
[9917]	225 230 235 240
[9918]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[9919]	245 250 255
[9920]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
[9921]	260 265 270
[9922]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[9923]	275 280 285
[9924]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
[9925]	290 295 300
[9926]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[9927]	305 310 315 320
[9928]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[9929]	325 330 335
[9930]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[9931]	340 345 350
[9932]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
[9933]	355 360 365
[9934]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[9935]	370 375 380
[9936]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[9937]	385 390 395 400
[9938]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[9939]	405 410 415
[9940]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[9941]	420 425 430
[9942]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[9943]	435 440 445
[9944]	Lys

[9945]	<210>	389	
[9946]	<211>	449	
[9947]	<212>	PRT	
[9948]	<213>	人工序列(Artificial Sequence)	
[9949]	<220>		
[9950]	<223>	具有CDR2突变和野生型恒定区的人源化IgG1重链	
[9951]	<400>	389	
[9952]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala		
[9953]	1	5	10 15
[9954]	Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr		
[9955]		20	25 30
[9956]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met		
[9957]		35	40 45
[9958]	Gly Glu Ile Phe Pro Arg Arg Val Ala Thr Tyr Tyr Ser Glu Lys Phe		
[9959]		50	55 60
[9960]	Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr		
[9961]		65	70 75 80
[9962]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys		
[9963]		85	90 95
[9964]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly		
[9965]		100	105 110
[9966]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe		
[9967]		115	120 125
[9968]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu		
[9969]		130	135 140
[9970]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
[9971]		145	150 155 160
[9972]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu		
[9973]		165	170 175
[9974]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser		
[9975]		180	185 190
[9976]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro		
[9977]		195	200 205
[9978]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys		
[9979]		210	215 220
[9980]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro		
[9981]		225	230 235 240
[9982]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser		
[9983]		245	250 255

[9984]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
[9985]	260 265 270
[9986]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[9987]	275 280 285
[9988]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
[9989]	290 295 300
[9990]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[9991]	305 310 315 320
[9992]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[9993]	325 330 335
[9994]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[9995]	340 345 350
[9996]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
[9997]	355 360 365
[9998]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[9999]	370 375 380
[10000]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[10001]	385 390 395 400
[10002]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[10003]	405 410 415
[10004]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[10005]	420 425 430
[10006]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[10007]	435 440 445
[10008]	Lys
[10009]	<210> 390
[10010]	<211> 449
[10011]	<212> PRT
[10012]	<213> 人工序列(Artificial Sequence)
[10013]	<220>
[10014]	<223> 具有CDR2突变和野生型恒定区的人源化IgG1重链
[10015]	<400> 390
[10016]	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[10017]	1 5 10 15
[10018]	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
[10019]	20 25 30
[10020]	Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
[10021]	35 40 45
[10022]	Gly Glu Ile Phe Pro Arg Arg Val Ala Thr Tyr Tyr Ser Glu Lys Phe

[10023]	50	55	60
[10024]	Lys Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr		
[10025]	65	70	75
[10026]	Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys		
[10027]	85	90	95
[10028]	Ala Arg Asp Tyr Asp Pro Tyr Phe Ala Leu Asp Tyr Trp Gly Gln Gly		
[10029]	100	105	110
[10030]	Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe		
[10031]	115	120	125
[10032]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu		
[10033]	130	135	140
[10034]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
[10035]	145	150	155
[10036]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu		
[10037]	165	170	175
[10038]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser		
[10039]	180	185	190
[10040]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro		
[10041]	195	200	205
[10042]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys		
[10043]	210	215	220
[10044]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro		
[10045]	225	230	235
[10046]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser		
[10047]	245	250	255
[10048]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp		
[10049]	260	265	270
[10050]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn		
[10051]	275	280	285
[10052]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val		
[10053]	290	295	300
[10054]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
[10055]	305	310	315
[10056]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
[10057]	325	330	335
[10058]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
[10059]	340	345	350
[10060]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr		
[10061]	355	360	365

[10062]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
[10063]		370					375					380				
[10064]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
[10065]	385					390					395					400
[10066]	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
[10067]					405					410					415	
[10068]	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
[10069]				420					425					430		
[10070]	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
[10071]			435					440					445			
[10072]	Lys															
[10073]	<210>	391														
[10074]	<211>	449														
[10075]	<212>	PRT														
[10076]	<213>	人工序列(Artificial Sequence)														
[10077]	<220>															
[10078]	<223>	具有CDR2突变和野生型恒定区的人源化IgG1重链														
[10079]	<400>	391														
[10080]	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
[10081]	1			5					10					15		
[10082]	Ser	Val	Lys	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Gly	Tyr
[10083]			20					25					30			
[10084]	Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
[10085]			35				40					45				
[10086]	Gly	Glu	Ile	Phe	Pro	Arg	Arg	Val	Ala	Thr	Tyr	Tyr	Ser	Glu	Lys	Phe
[10087]		50				55				60						
[10088]	Lys	Gly	Arg	Val	Thr	Met	Thr	Ala	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
[10089]	65				70				75					80		
[10090]	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[10091]				85				90					95			
[10092]	Ala	Arg	Asp	Tyr	Asp	Pro	Tyr	Phe	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
[10093]			100					105				110				
[10094]	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
[10095]			115					120				125				
[10096]	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
[10097]		130					135				140					
[10098]	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
[10099]	145					150				155				160		
[10100]	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu

[10101]					165				170				175											
[10102]	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser								
[10103]					180				185				190											
[10104]	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro								
[10105]					195				200				205											
[10106]	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys								
[10107]					210				215				220											
[10108]	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro								
[10109]	225								230								240							
[10110]	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser								
[10111]					245								250				255							
[10112]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp								
[10113]					260								265				270							
[10114]	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn								
[10115]					275								280				285							
[10116]	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val								
[10117]					290								295				300							
[10118]	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu								
[10119]	305								310								315				320			
[10120]	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys								
[10121]					325								330				335							
[10122]	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr								
[10123]					340								345				350							
[10124]	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr								
[10125]					355								360				365							
[10126]	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu								
[10127]					370								375				380							
[10128]	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu								
[10129]	385								390								395				400			
[10130]	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys								
[10131]					405								410				415							
[10132]	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu								
[10133]					420								425				430							
[10134]	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly								
[10135]					435								440				445							
[10136]	Lys																							
[10137]	<210> 392																							
[10138]	<211> 330																							
[10139]	<212> PRT																							

[10140]	<213> 人工序列(Artificial Sequence)																			
[10141]	<220>																			
[10142]	<223> 具有N297A突变的IgG1的重链恒定区																			
[10143]	<400> 392																			
[10144]	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys				
[10145]	1				5					10					15					
[10146]	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr				
[10147]					20					25					30					
[10148]	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser				
[10149]					35					40					45					
[10150]	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser				
[10151]					50					55					60					
[10152]	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr				
[10153]	65									70					75					80
[10154]	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys				
[10155]					85						90					95				
[10156]	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys				
[10157]					100						105					110				
[10158]	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro				
[10159]					115						120					125				
[10160]	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys				
[10161]					130						135					140				
[10162]	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp				
[10163]	145										150					155				160
[10164]	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu				
[10165]					165						170					175				
[10166]	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu				
[10167]					180						185					190				
[10168]	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn				
[10169]					195						200					205				
[10170]	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly				
[10171]					210						215					220				
[10172]	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu				
[10173]	225										230					235				240
[10174]	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr				
[10175]					245						250					255				
[10176]	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn				
[10177]					260						265					270				
[10178]	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe				

[10179]	275	280	285
[10180]	Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn		
[10181]	290	295	300
[10182]	Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr		
[10183]	305	310	315
[10184]	Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys		320
[10185]	325	330	
[10186]	<210> 393		
[10187]	<211> 107		
[10188]	<212> PRT		
[10189]	<213> 人工序列(Artificial Sequence)		
[10190]	<220>		
[10191]	<223> IgG1的轻链恒定区		
[10192]	<400> 393		
[10193]	Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu		
[10194]	1	5	10
[10195]	Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe		15
[10196]	20	25	30
[10197]	Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln		
[10198]	35	40	45
[10199]	Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser		
[10200]	50	55	60
[10201]	Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu		
[10202]	65	70	75
[10203]	Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser		80
[10204]	85	90	95
[10205]	Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys		
[10206]	100	105	
[10207]	<210> 394		
[10208]	<211> 330		
[10209]	<212> PRT		
[10210]	<213> 人工序列(Artificial Sequence)		
[10211]	<220>		
[10212]	<223> 野生型IgG1的重链恒定区		
[10213]	<400> 394		
[10214]	Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys		
[10215]	1	5	10
[10216]	Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr		15
[10217]	20	25	30

[10218]	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
[10219]			35					40					45			
[10220]	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
[10221]			50					55					60			
[10222]	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr
[10223]	65					70					75					80
[10224]	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
[10225]				85						90					95	
[10226]	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys
[10227]				100					105					110		
[10228]	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro
[10229]				115					120				125			
[10230]	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys
[10231]				130				135					140			
[10232]	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp
[10233]	145					150					155					160
[10234]	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu
[10235]				165						170					175	
[10236]	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu
[10237]				180						185					190	
[10238]	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn
[10239]				195					200				205			
[10240]	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly
[10241]				210				215					220			
[10242]	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu
[10243]	225					230					235					240
[10244]	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr
[10245]				245						250					255	
[10246]	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn
[10247]				260						265				270		
[10248]	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe
[10249]				275					280				285			
[10250]	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn
[10251]				290				295				300				
[10252]	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr
[10253]	305					310					315					320
[10254]	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys						
[10255]				325						330						
[10256]	<210>			395												

[10257]	<211>	272
[10258]	<212>	PRT
[10259]	<213>	人工序列(Artificial Sequence)
[10260]	<220>	
[10261]	<223>	PD-L1
[10262]	<400>	395
[10263]	Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr Gly Ser	
[10264]	1 5 10 15	
[10265]	Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu Asp Leu	
[10266]	20 25 30	
[10267]	Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile Ile Gln	
[10268]	35 40 45	
[10269]	Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser Tyr Arg	
[10270]	50 55 60	
[10271]	Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn Ala Ala	
[10272]	65 70 75 80	
[10273]	Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr Arg Cys	
[10274]	85 90 95	
[10275]	Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val Lys Val	
[10276]	100 105 110	
[10277]	Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val Asp Pro	
[10278]	115 120 125	
[10279]	Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr Pro Lys	
[10280]	130 135 140	
[10281]	Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser Gly Lys	
[10282]	145 150 155 160	
[10283]	Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn Val Thr	
[10284]	165 170 175	
[10285]	Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr Cys Thr	
[10286]	180 185 190	
[10287]	Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu Val Ile	
[10288]	195 200 205	
[10289]	Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg Thr His Leu Val	
[10290]	210 215 220	
[10291]	Ile Leu Gly Ala Ile Leu Leu Cys Leu Gly Val Ala Leu Thr Phe Ile	
[10292]	225 230 235 240	
[10293]	Phe Arg Leu Arg Lys Gly Arg Met Met Asp Val Lys Lys Cys Gly Ile	
[10294]	245 250 255	
[10295]	Gln Asp Thr Asn Ser Lys Lys Gln Ser Asp Thr His Leu Glu Glu Thr	

[10296]	260	265	270
[10297]	<210> 396		
[10298]	<211> 220		
[10299]	<212> PRT		
[10300]	<213> 人工序列(Artificial Sequence)		
[10301]	<220>		
[10302]	<223> PD-L1 ECD		
[10303]	<400> 396		
[10304]	Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr Gly Ser		
[10305]	1 5 10 15		
[10306]	Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu Asp Leu		
[10307]	20 25 30		
[10308]	Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile Ile Gln		
[10309]	35 40 45		
[10310]	Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser Tyr Arg		
[10311]	50 55 60		
[10312]	Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn Ala Ala		
[10313]	65 70 75 80		
[10314]	Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr Arg Cys		
[10315]	85 90 95		
[10316]	Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val Lys Val		
[10317]	100 105 110		
[10318]	Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val Asp Pro		
[10319]	115 120 125		
[10320]	Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr Pro Lys		
[10321]	130 135 140		
[10322]	Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser Gly Lys		
[10323]	145 150 155 160		
[10324]	Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn Val Thr		
[10325]	165 170 175		
[10326]	Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr Cys Thr		
[10327]	180 185 190		
[10328]	Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu Val Ile		
[10329]	195 200 205		
[10330]	Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg		
[10331]	210 215 220		
[10332]	<210> 397		
[10333]	<211> 9		
[10334]	<212> PRT		

[10335]	<213>	人工序列(Artificial Sequence)															
[10336]	<220>																
[10337]	<223>	肽接头															
[10338]	<400>	397															
[10339]		Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Ser							
[10340]		1				5											
[10341]	<210>	398															
[10342]	<211>	15															
[10343]	<212>	PRT															
[10344]	<213>	人工序列(Artificial Sequence)															
[10345]	<220>																
[10346]	<223>	肽接头															
[10347]	<400>	398															
[10348]		Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	
[10349]		1				5					10					15	
[10350]	<210>	399															
[10351]	<211>	15															
[10352]	<212>	PRT															
[10353]	<213>	人工序列(Artificial Sequence)															
[10354]	<220>																
[10355]	<223>	肽接头															
[10356]	<400>	399															
[10357]		Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Ser	Pro	
[10358]		1				5					10					15	
[10359]	<210>	400															
[10360]	<211>	143															
[10361]	<212>	PRT															
[10362]	<213>	人工序列(Artificial Sequence)															
[10363]	<220>																
[10364]	<223>	人PD-1 ECD															
[10365]	<400>	400															
[10366]		Leu	Asp	Ser	Pro	Asp	Arg	Pro	Trp	Asn	Pro	Pro	Thr	Phe	Ser	Pro	Ala
[10367]		1				5					10					15	
[10368]		Leu	Leu	Val	Val	Thr	Glu	Gly	Asp	Asn	Ala	Thr	Phe	Thr	Cys	Ser	Phe
[10369]					20					25					30		
[10370]		Ser	Asn	Thr	Ser	Glu	Ser	Phe	Val	Leu	Asn	Trp	Tyr	Arg	Met	Ser	Pro
[10371]				35					40					45			
[10372]		Ser	Asn	Gln	Thr	Asp	Lys	Leu	Ala	Ala	Phe	Pro	Glu	Asp	Arg	Ser	Gln
[10373]				50				55						60			

[10374]	Pro	Gly	Gln	Asp	Cys	Arg	Phe	Arg	Val	Thr	Gln	Leu	Pro	Asn	Gly	Arg
[10375]	65					70					75					80
[10376]	Asp	Phe	His	Met	Ser	Val	Val	Arg	Ala	Arg	Arg	Asn	Asp	Ser	Gly	Thr
[10377]						85					90					95
[10378]	Tyr	Leu	Cys	Gly	Ala	Ile	Ser	Leu	Ala	Pro	Lys	Ala	Gln	Ile	Lys	Glu
[10379]					100					105					110	
[10380]	Ser	Leu	Arg	Ala	Glu	Leu	Arg	Val	Thr	Glu	Arg	Arg	Ala	Glu	Val	Pro
[10381]					115					120				125		
[10382]	Thr	Ala	His	Pro	Ser	Pro	Ser	Pro	Arg	Pro	Ala	Gly	Gln	Phe	Gln	
[10383]					130				135				140			

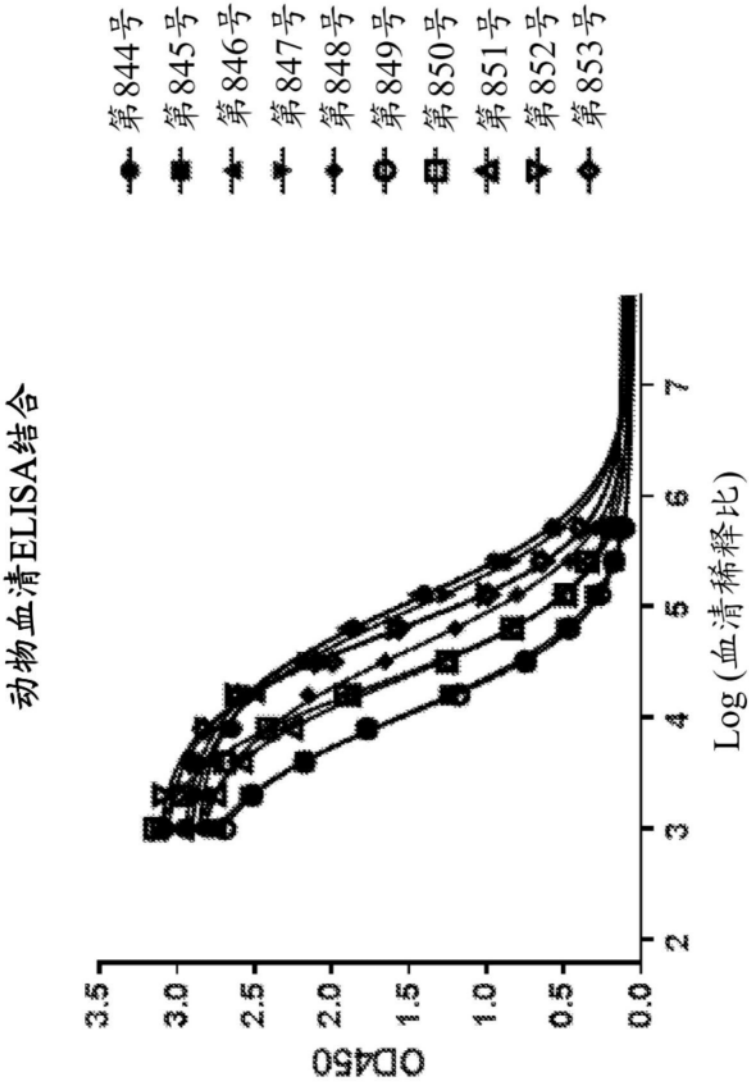


图1

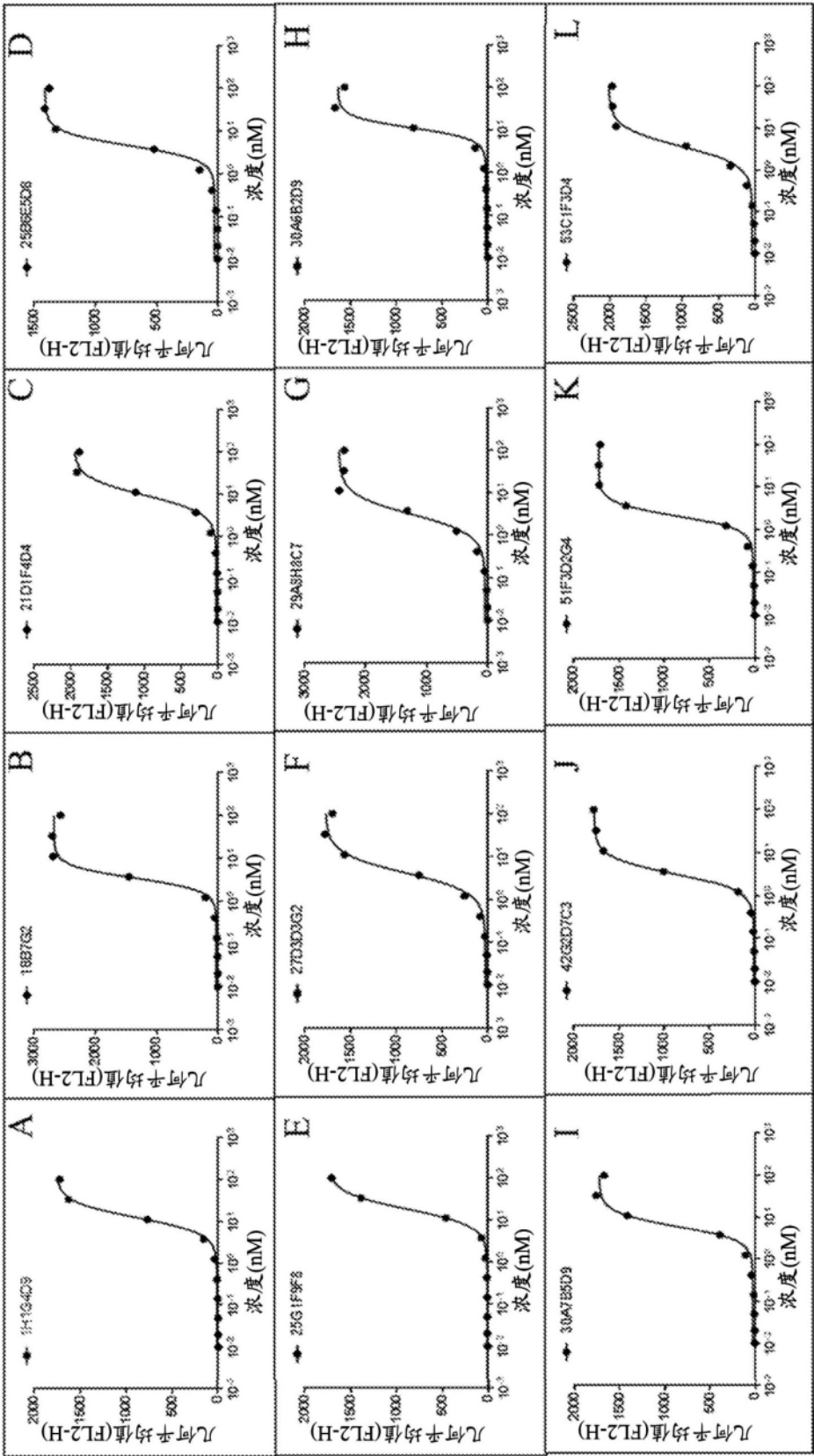


图2A-2L

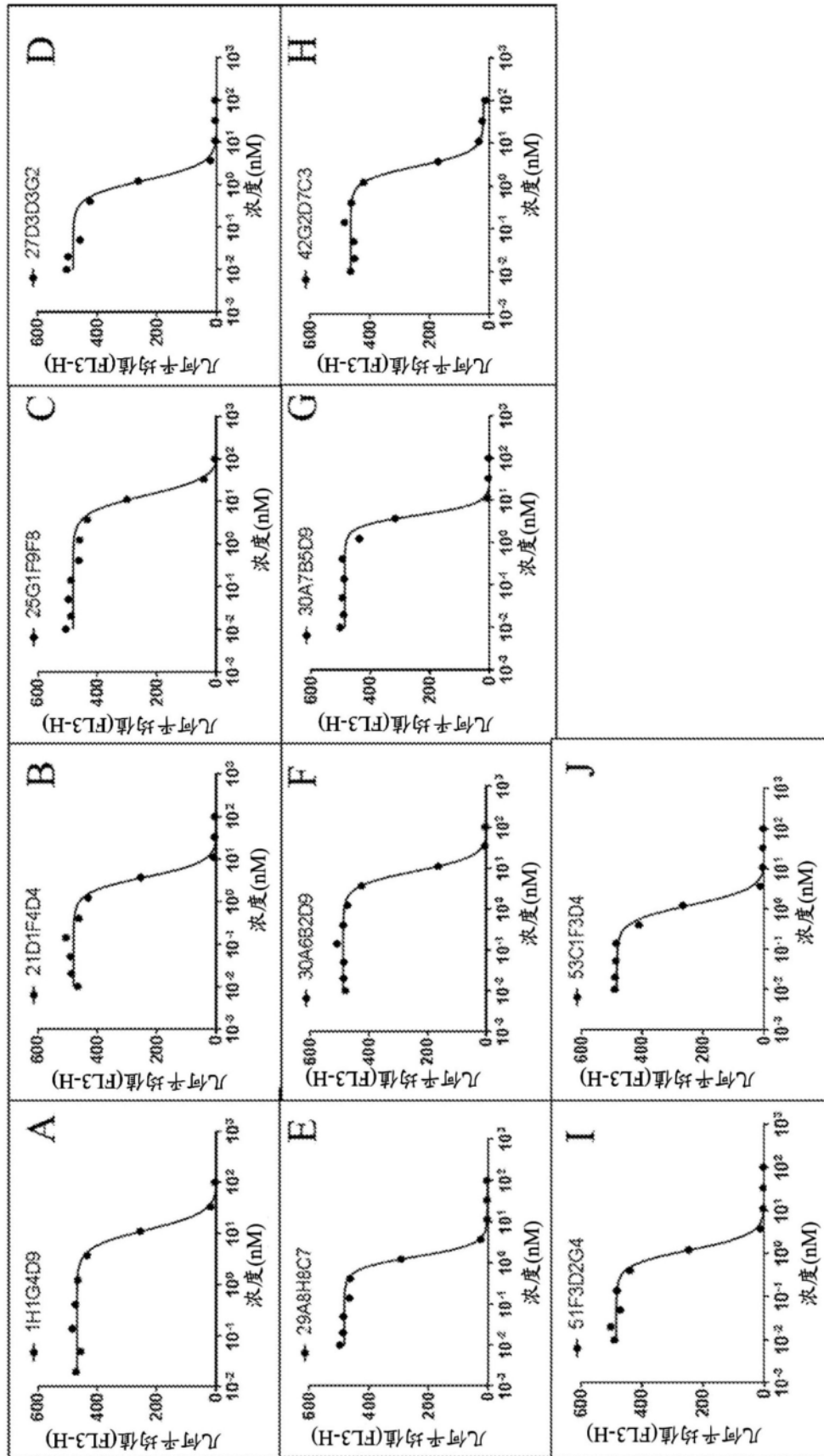


图3A-3J

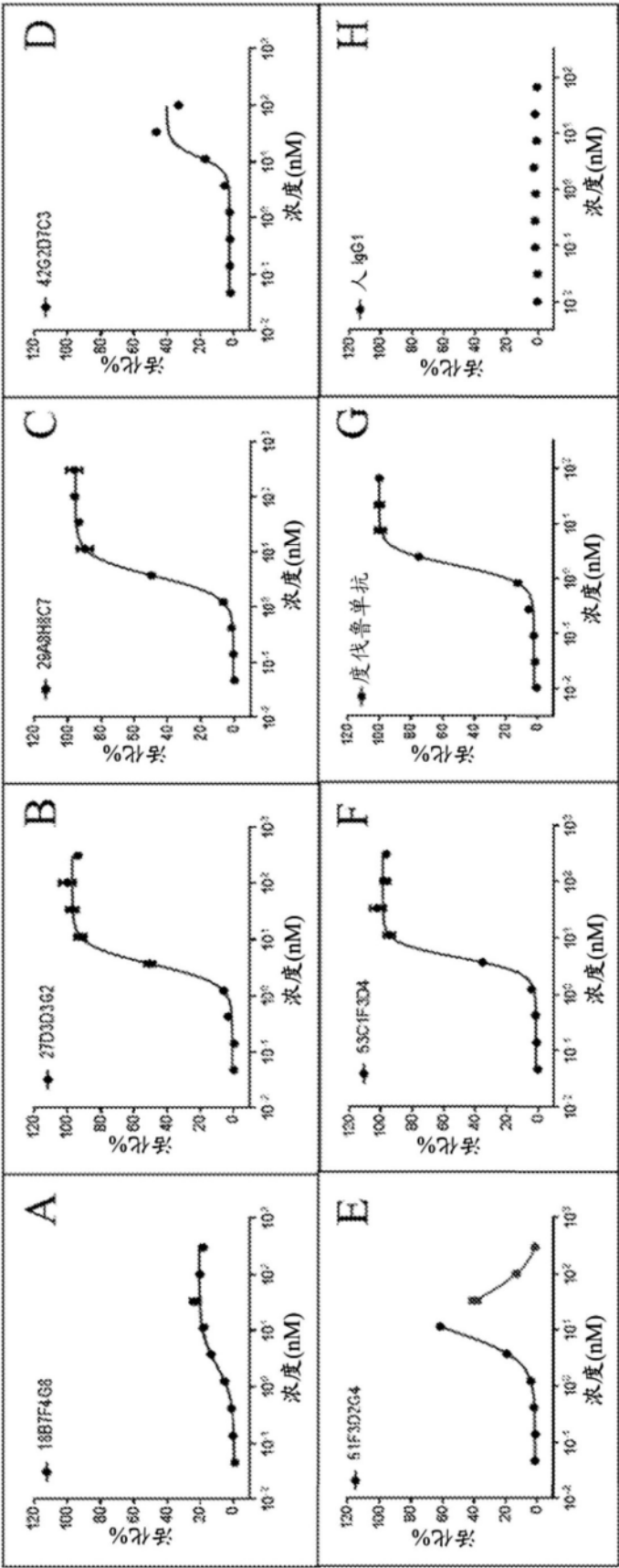


图4A-4H

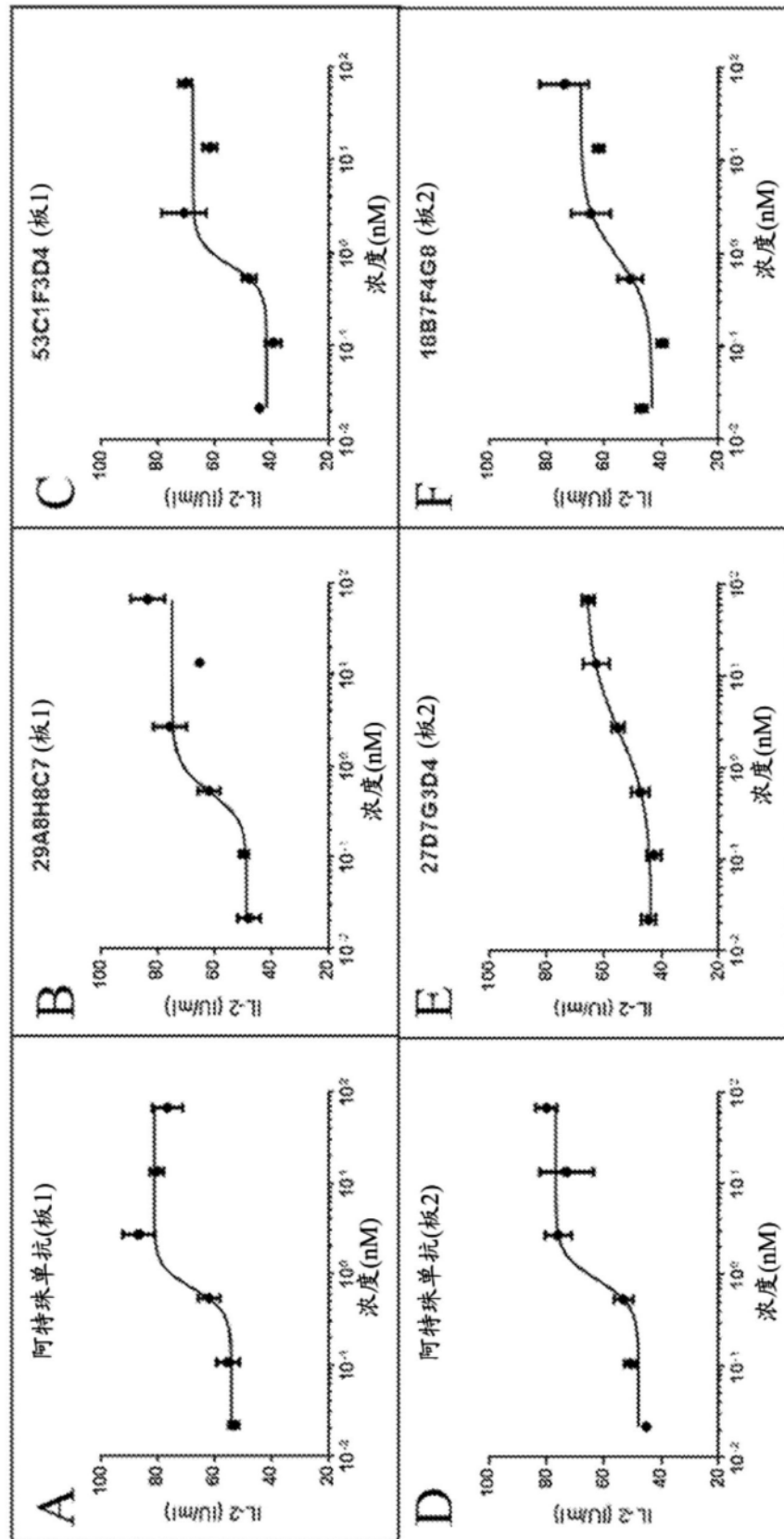


图5A-5F

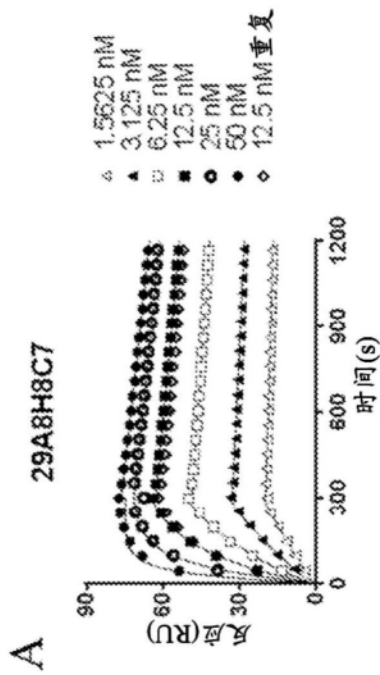


图6A

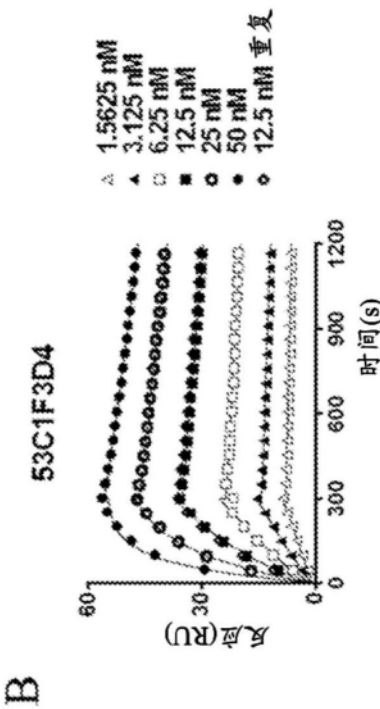


图6B

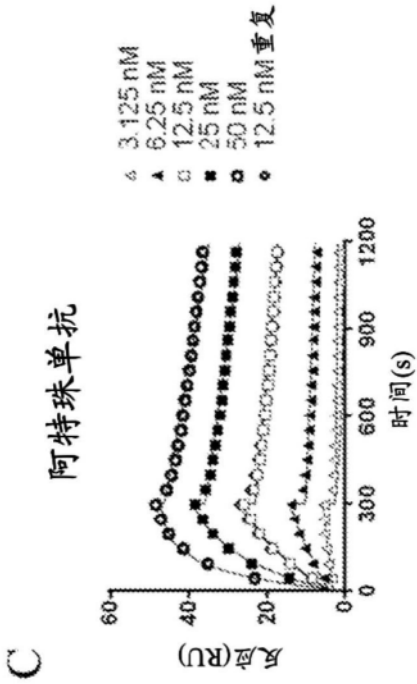


图6C

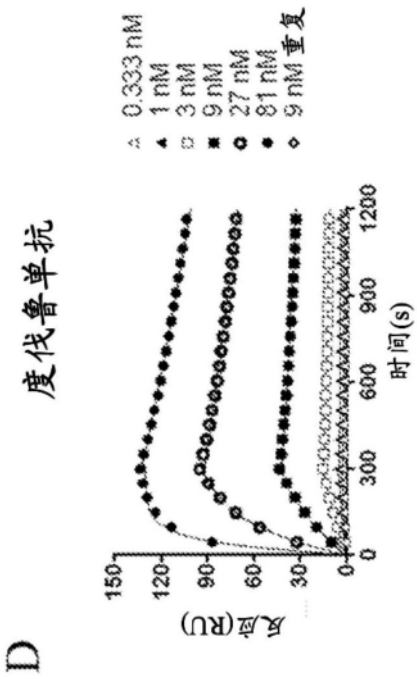


图6D

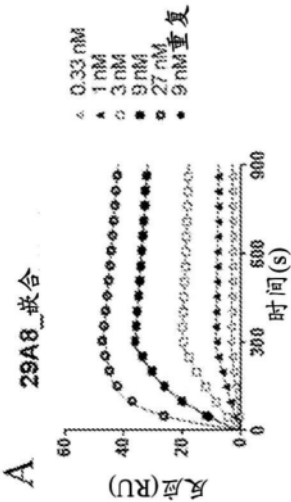


图7A

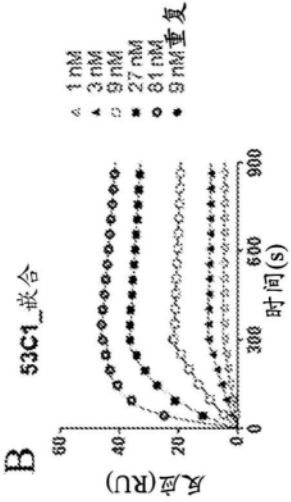


图7B

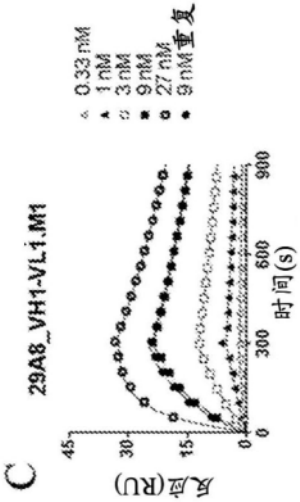


图7C

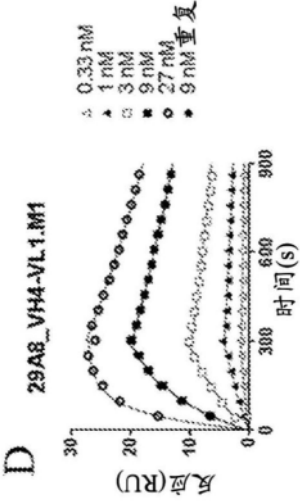


图7D

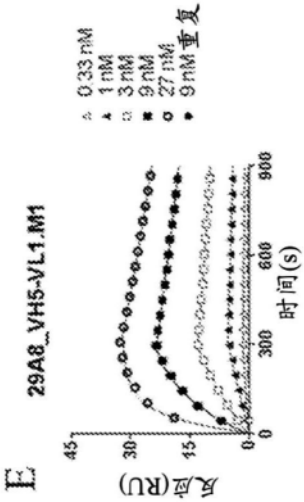


图7E

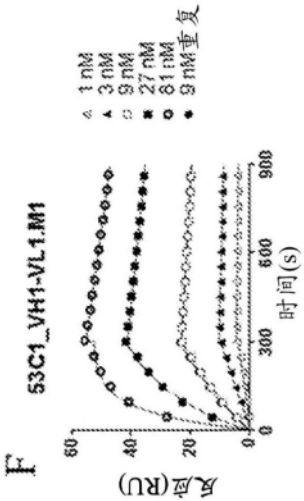


图7F

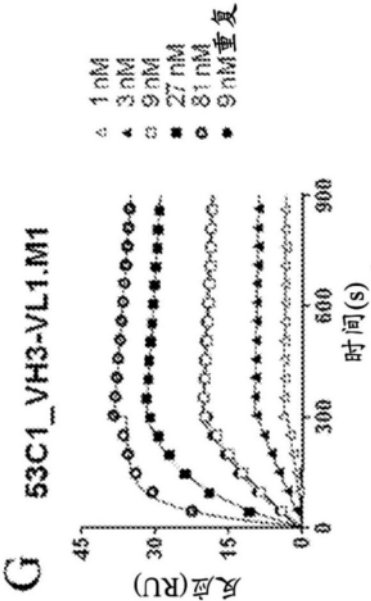


图7G

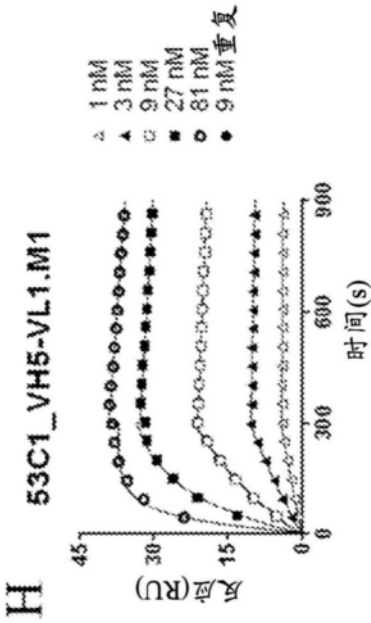


图7H

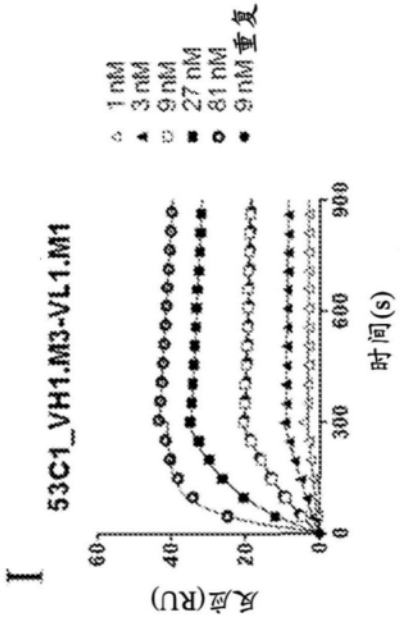


图7I

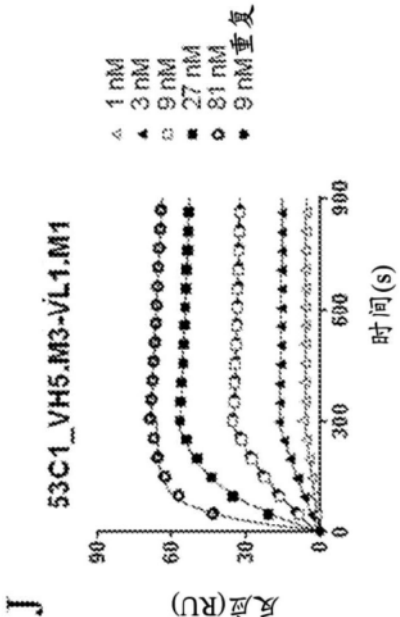


图7J

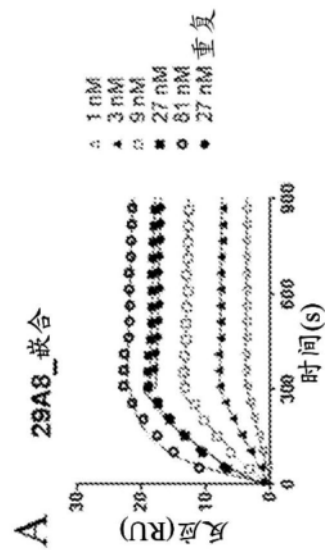


图8A

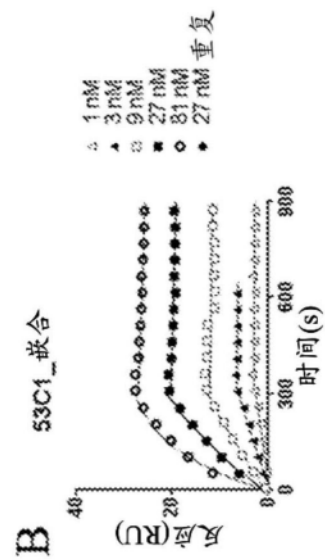


图8B

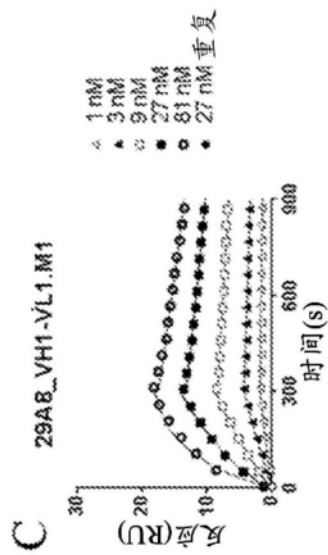


图8C

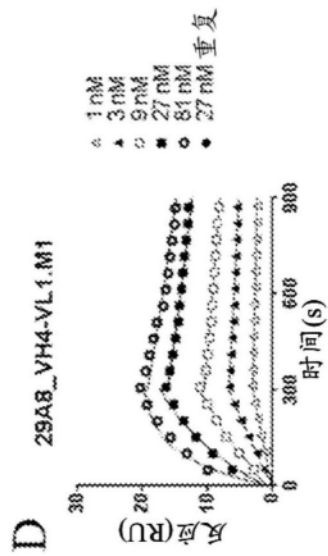


图8D

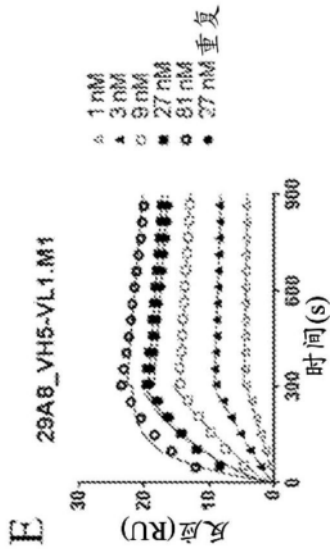


图8E

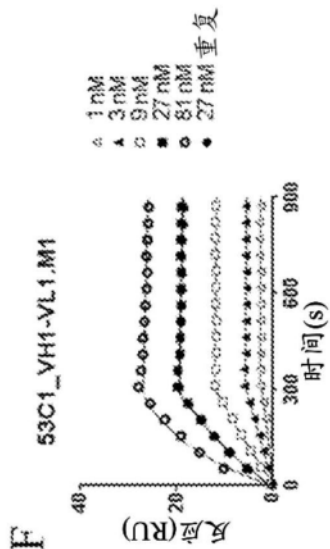


图8F

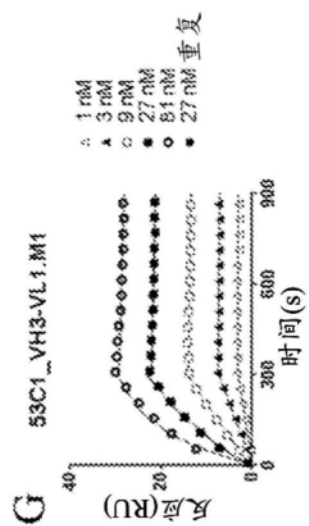


图8G

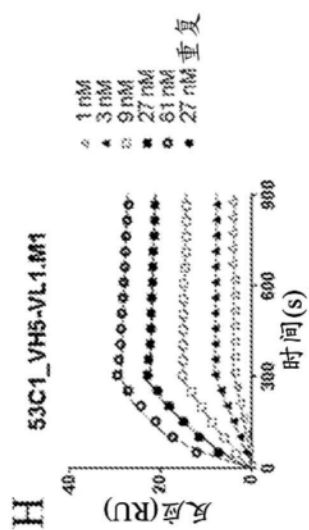


图8H

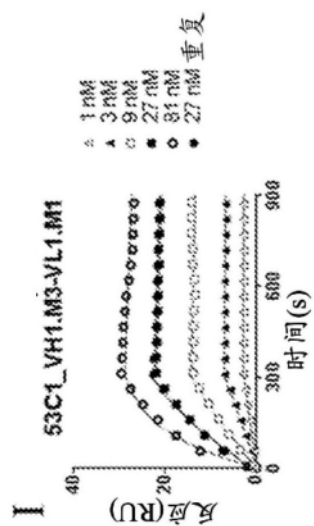


图8I

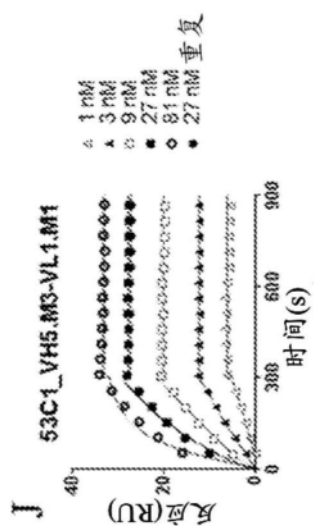


图8J

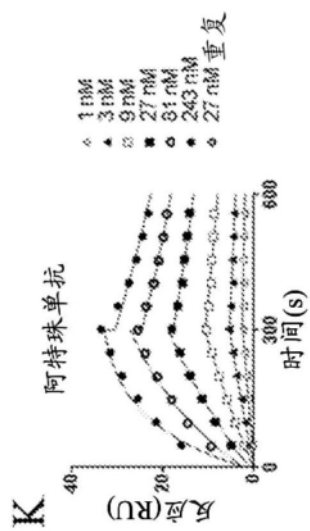


图8K

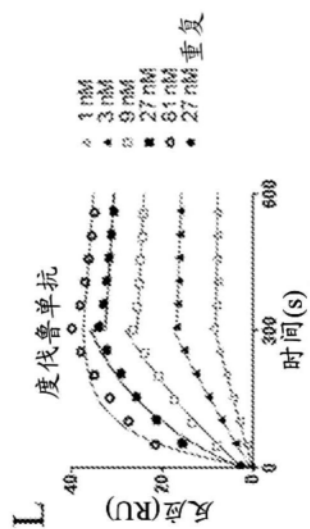


图8L

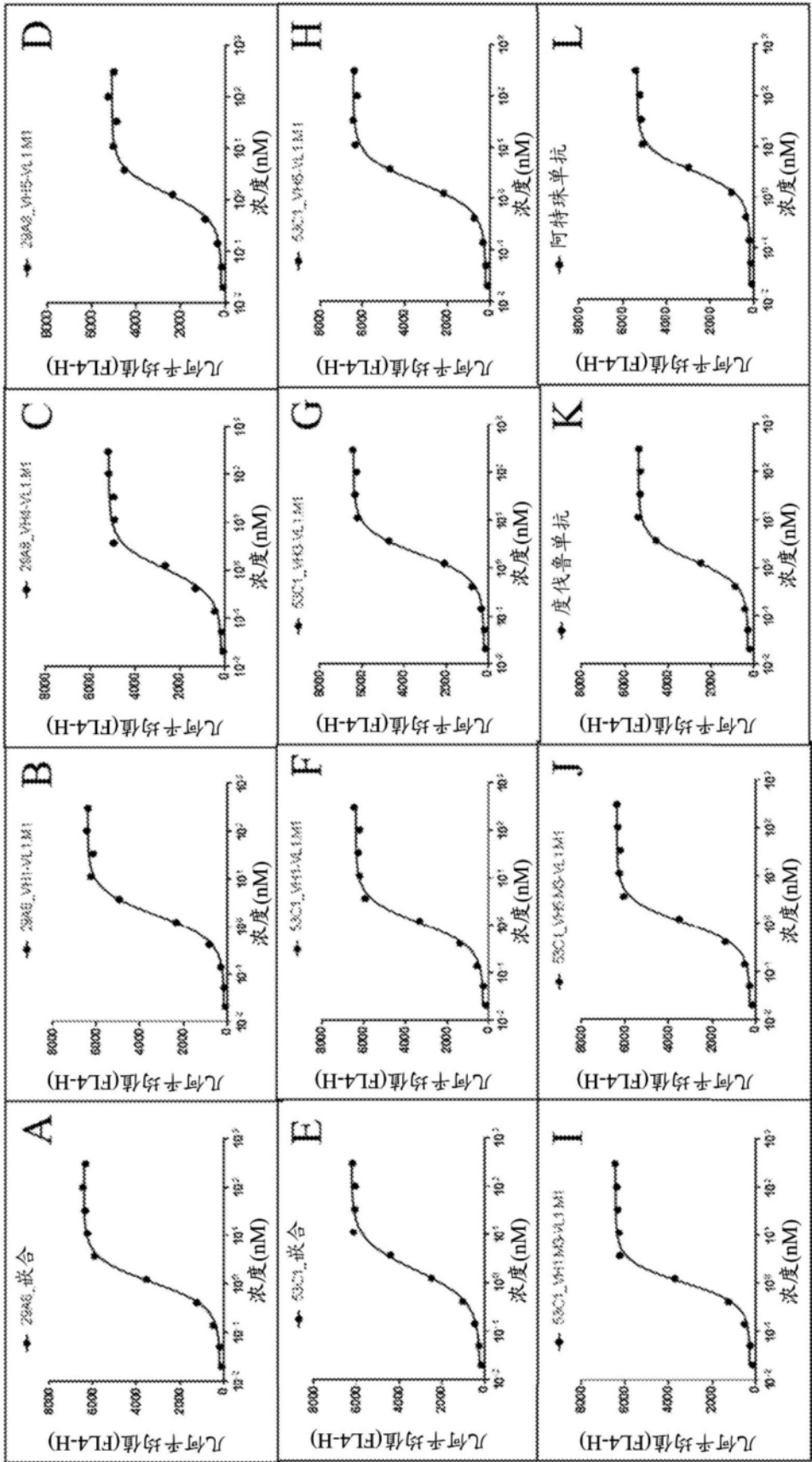


图9A-9L

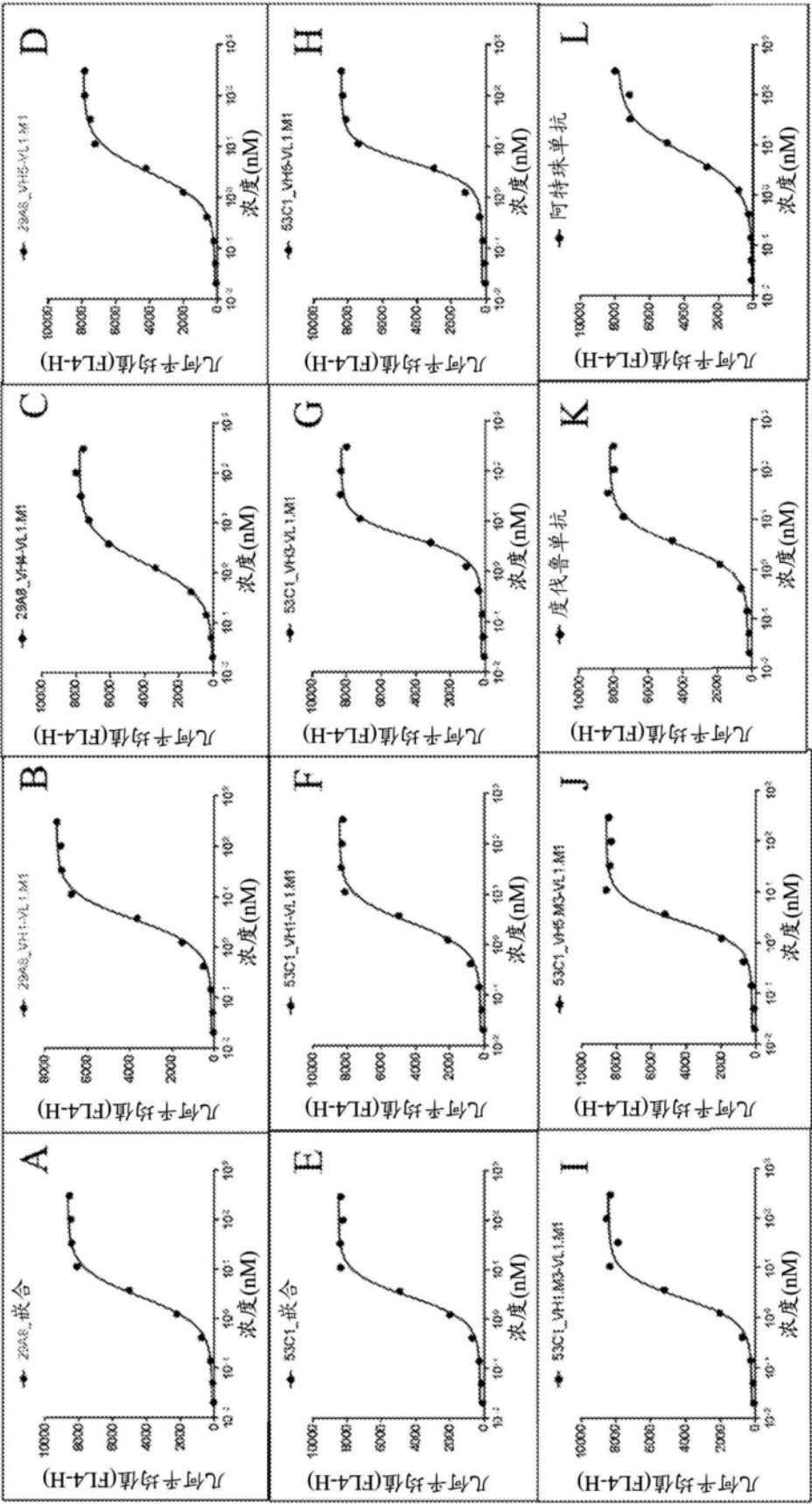


图10A-10L

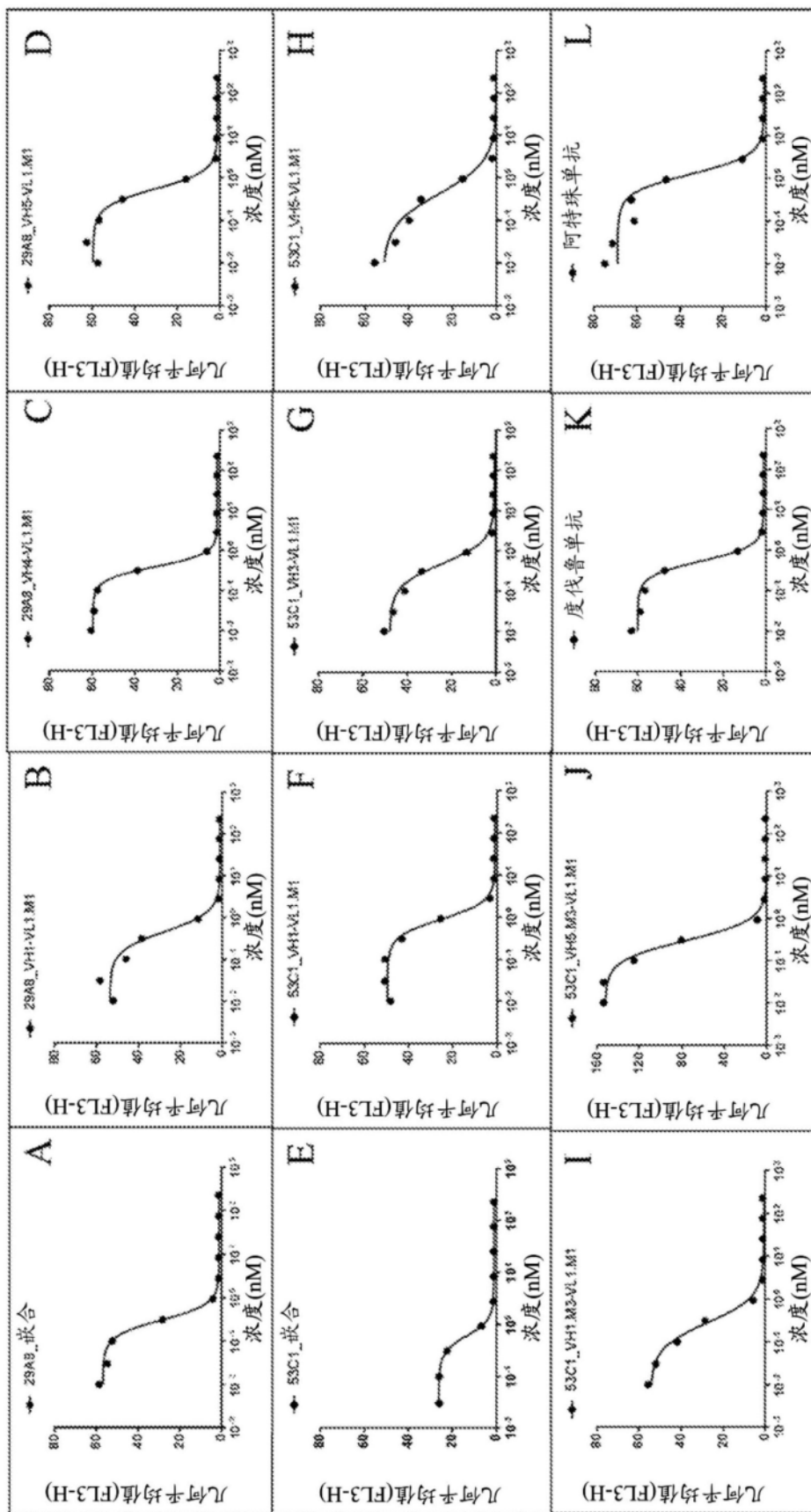


图11A-11L

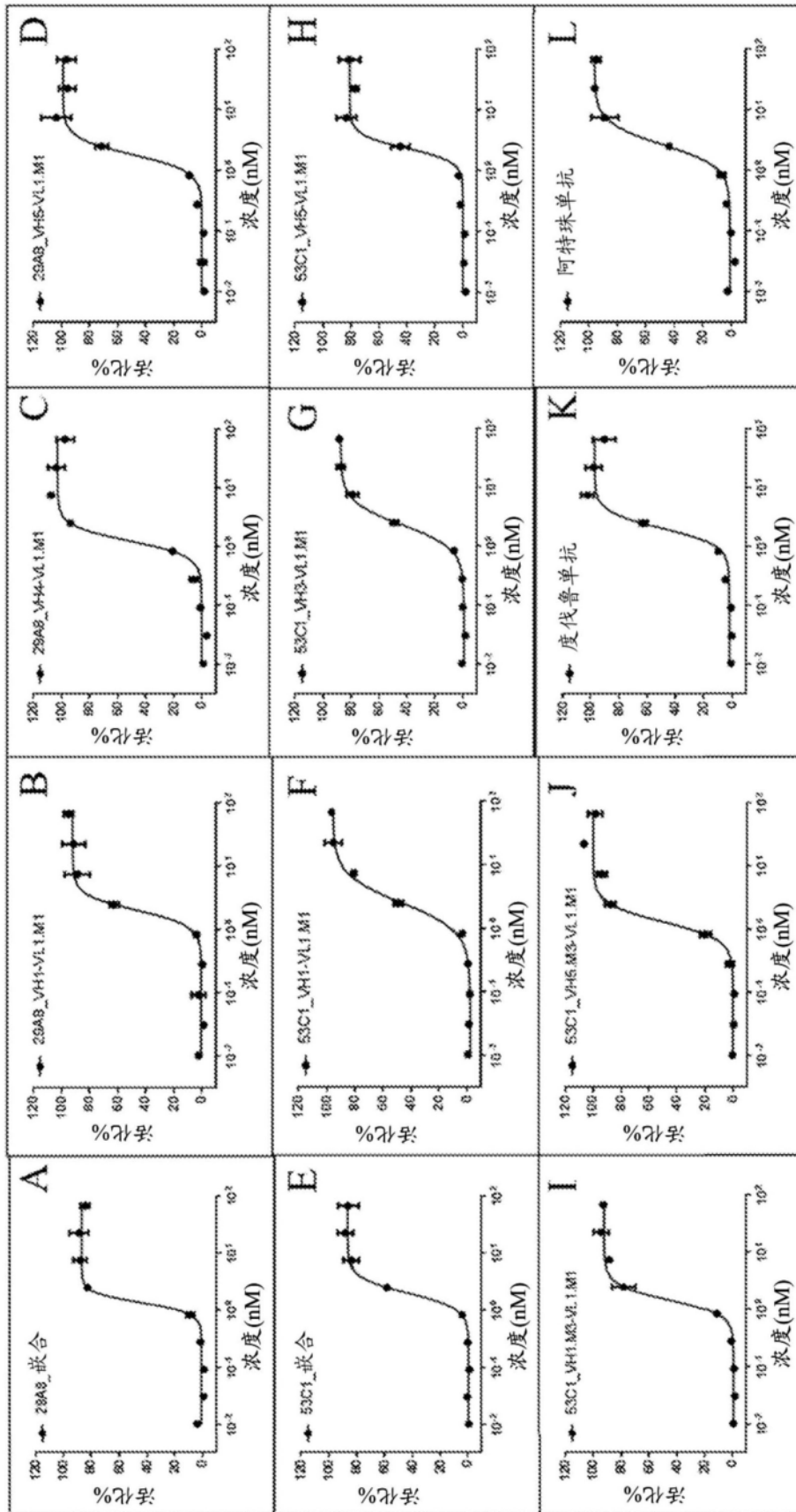


图12A-12L

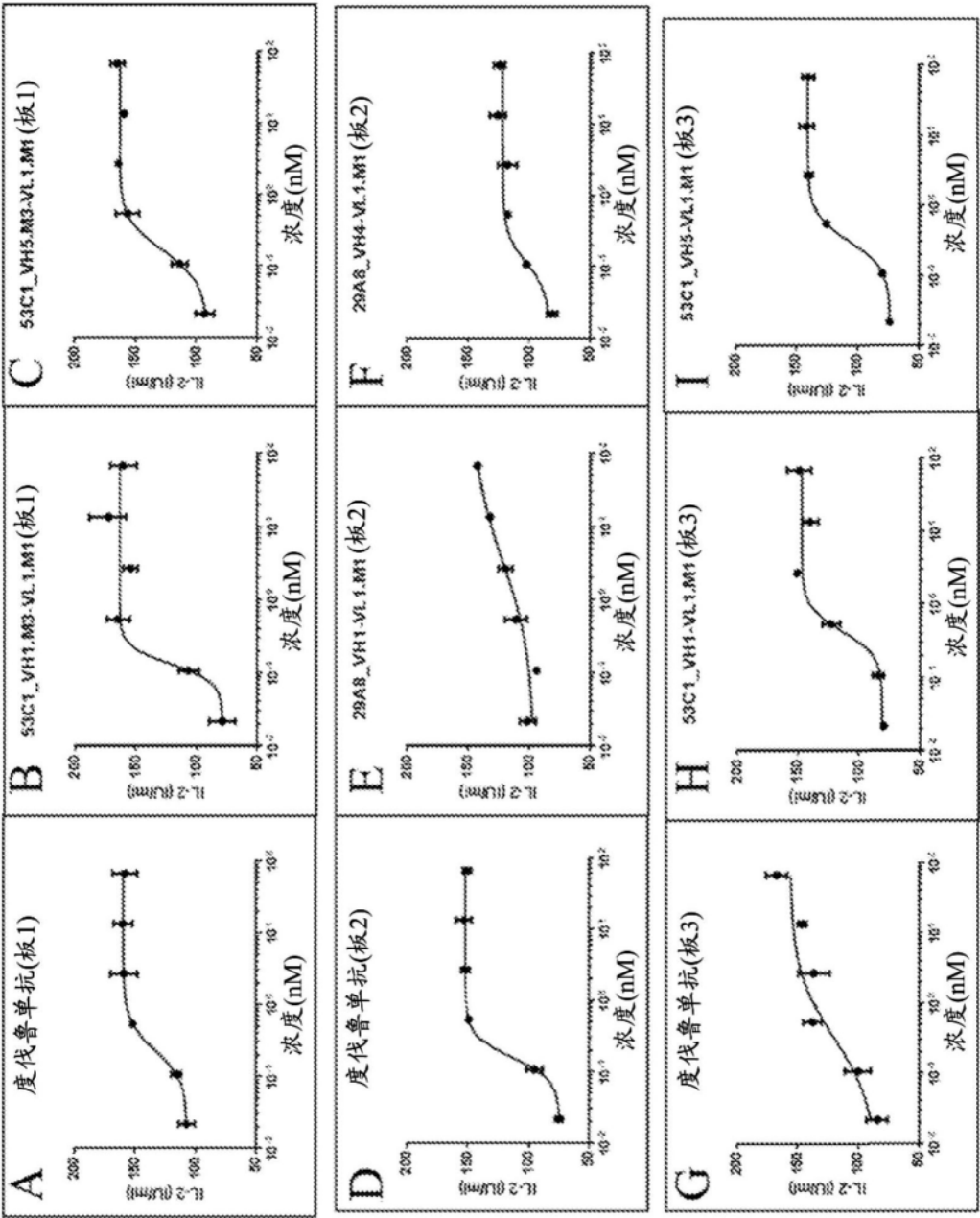


图13A-13I

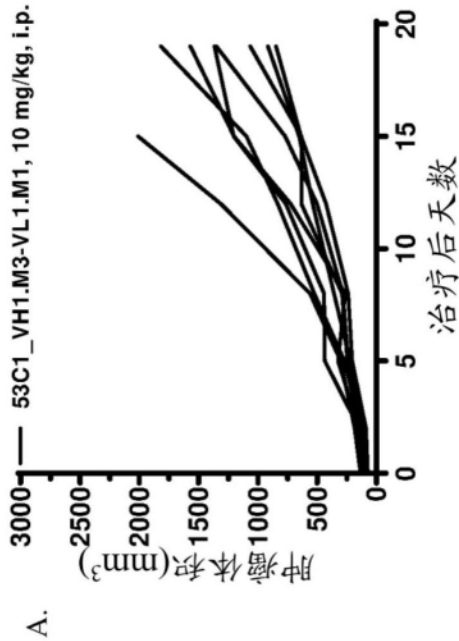


图14A

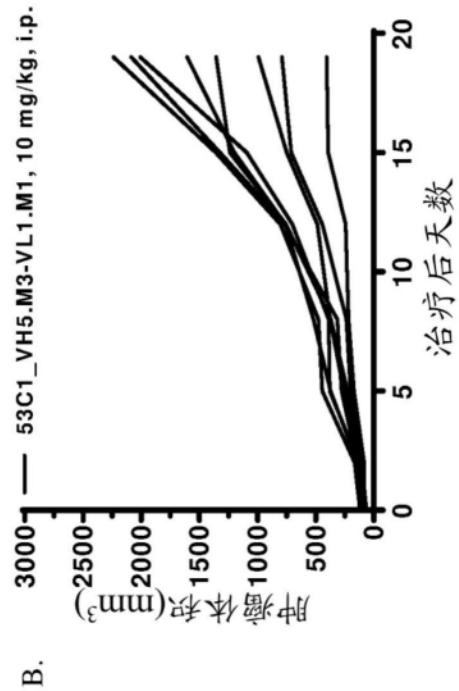


图14B

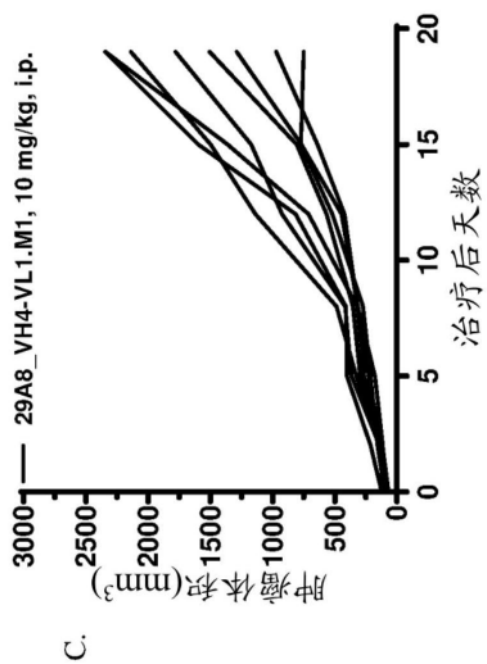


图14C

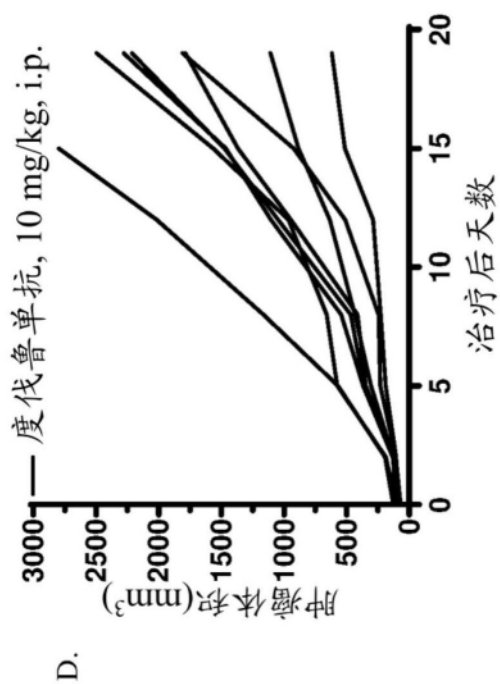


图14D

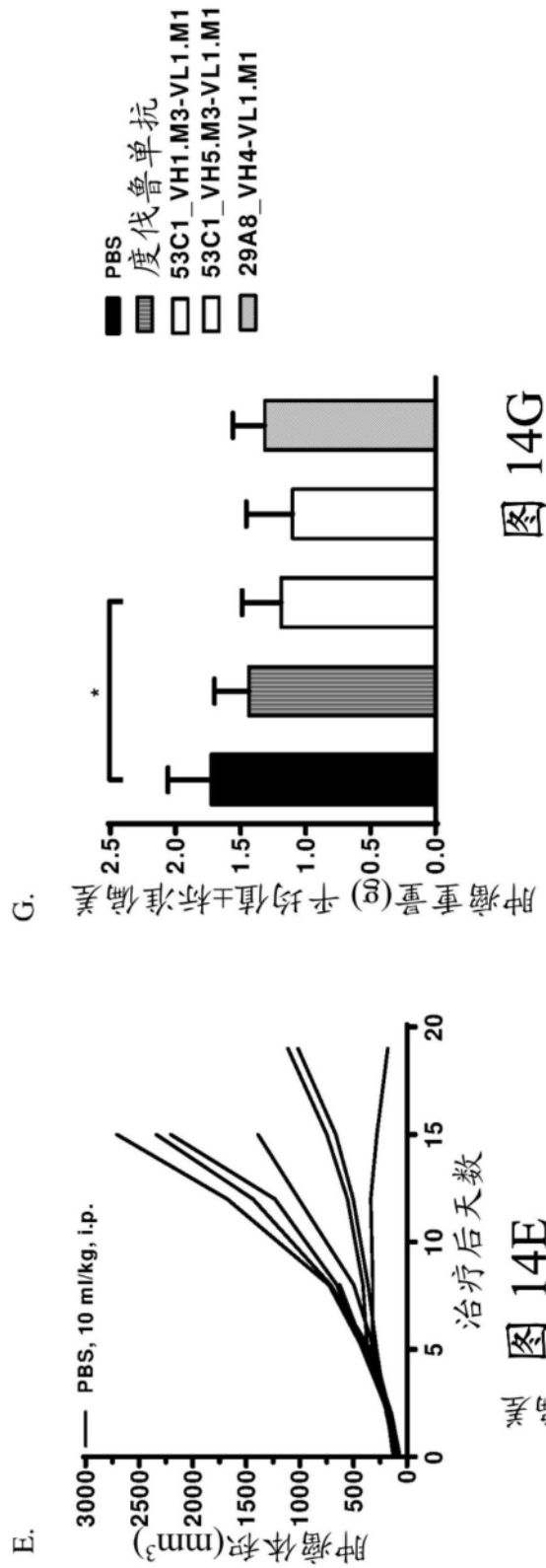


图 14G

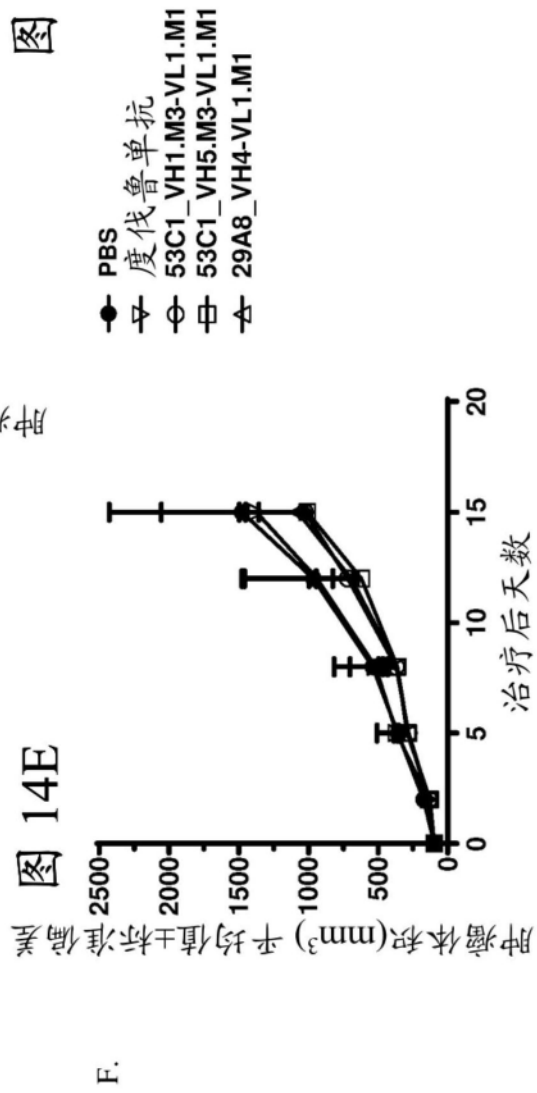


图 14F