(19)中华人民共和国国家知识产权局

(12)发明专利

(10)授权公告号 CN 112010978 B
(45)授权公告日 2022.04.08

(21)申请号 202010465851.9

(22)申请日 2020.05.28

(65)同一申请的已公布的文献号
申请公布号 CN 112010978 A

(43)申请公布日 2020.12.01

(66)本国优先权数据
201910464016.0 2019.05.30 CN

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(51)Int.Cl.
C07K 16/28(2006.01)
C12N 15/13(2006.01)
G01N 33/573(2006.01)
C12N 5/10(2006.01)
A61K 39/395(2006.01)
A61P 29/00(2006.01)
A61P 35/00(2006.01)
A61P 25/28(2006.01)
A61P 15/00(2006.01)
A61P 25/02(2006.01)
A61P 3/10(2006.01)
A61P 13/08(2006.01)
A61P 19/08(2006.01)
A61P 37/02(2006.01)
A61P 11/00(2006.01)
A61P 13/10(2006.01)
A61P 1/00(2006.01)
A61P 17/00(2006.01)
A61P 17/02(2006.01)
A61P 9/00(2006.01)
A61P 13/12(2006.01)
A61P 19/02(2006.01)
A61P 27/02(2006.01)
A61P 35/02(2006.01)

审查员 田园

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(54)发明名称

TrkA的抗体及其应用

(57)摘要

本发明提出了一种能够特异性识别TrkA的抗体或其抗原结合片段及其用途。该抗体含有选自下列至少之一的CDR序列或与其具有至少95%同一性的氨基酸序列:重链可变区CDR序列:SEQ ID NO:1～27,轻链可变区CDR序列:SEQ IN NO:28～54。根据本发明实施例的上述抗体能够特异性的靶向结合TrkA受体,阻断NGF和TrkA结合。

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1.一种能够特异性识别TrkA的抗体或其抗原结合片段,其特征在于,所述抗体包括:

分别如SEQ ID NO: 4、5和6的氨基酸序列所示的重链可变区CDR1、CDR2、CDR3序列;和

分别如SEQ ID NO: 31、32和33的氨基酸序列所示的轻链可变区CDR1、CDR2、CDR3序列。

2.根据权利要求1所述的抗体或其抗原结合片段,其特征在于,所述抗体或其抗原结合片段特异性识别TrkA的胞外区。

3.根据权利要求1所述的抗体或其抗原结合片段,其特征在于,所述抗体含有重链框架区序列和轻链框架区序列的至少之一,所述重链框架区序列和轻链框架区序列的至少之一的至少一部分来自于鼠源抗体、灵长目源抗体或其突变体的至少之一。

4.根据权利要求3所述的抗体或其抗原结合片段,其特征在于,所述灵长目源抗体包括人源抗体。

5.根据权利要求1所述的抗体或其抗原结合片段,其特征在于,所述抗体具有如SEQ ID NO:56所示氨基酸序列的重链可变区。

6.根据权利要求1所述的抗体或其抗原结合片段,其特征在于,所述抗体具有如SEQ ID NO:65所示氨基酸序列的轻链可变区。

7.根据权利要求1所述的抗体或其抗原结合片段,其特征在于,所述抗体含有重链恒定区和轻链恒定区的至少之一,所述重链恒定区和轻链恒定区的至少之一的至少一部分来自于鼠源抗体、灵长目源抗体或其突变体的至少之一。

8.根据权利要求7所述的抗体或其抗原结合片段,其特征在于,所述灵长目源抗体包括人源抗体。

9.根据权利要求1所述的抗体或其抗原结合片段,其特征在于,所述抗体的轻链恒定区和重链恒定区均来自于人源IgG抗体或其突变体。

10.根据权利要求1所述的抗体或其抗原结合片段,其特征在于,所述抗体的轻链恒定区和重链恒定区均来自于人源IgG4。

11.根据权利要求9所述的抗体或其抗原结合片段,其特征在于,所述抗体的Fc区域与野生型相比具有S10P,F16A,L17A,R191K突变以及229 K缺失突变。

12.根据权利要求9所述的抗体或其抗原结合片段,其特征在于,所述抗体恒定区的全长序列如SEQ ID NO:74或75所示。

13.根据权利要求9所述的抗体或其抗原结合片段,其特征在于,所述抗体具有SEQ ID NO:77所示氨基酸序列的重链和具有SEQ ID NO:86所示氨基酸序列的轻链。

14.根据权利要求1所述的抗体或其抗原结合片段,其特征在于,所述抗体为单链抗体、多聚体抗体、CDR移植抗体或小分子抗体。

15.根据权利要求14 所述的抗体或其抗原结合片段,其特征在于,所述抗体为单链抗体,所述抗体具有SEQ ID NO:96或97所示的氨基酸序列。

16.根据权利要求14 所述的抗体或其抗原结合片段,其特征在于,所述小分子抗体包括Fab抗体、Fv抗体、单域抗体以及最小识别单位的至少之一。

17.一种核酸分子,其特征在于,所述核酸分子编码权利要求1~16任一项所述的抗体或其抗原结合片段。

18.根据权利要求17所述的核酸分子,其特征在于,所述核酸分子为DNA。

19.根据权利要求18所述的核酸分子,其特征在于,所述核酸分子具有如SEQ ID NO:

113所示核苷酸序列和具有SEQ ID NO:122所示核苷酸序列；

或所述核酸分子具有SEQ ID NO:132或133所示核苷酸序列。

20.一种表达载体，其特征在于，携带权利要求17~19任一项所述的核酸分子。

21.根据权利要求20所述的表达载体，其特征在于，所述表达载体为真核表达载体。

22.一种重组细胞，其特征在于，所述重组细胞携带权利要求17~19任一项所述的核酸分子，或者表达权利要求1~14任一项所述的抗体或其抗原结合片段。

23.根据权利要求22所述的重组细胞，其特征在于，所述重组细胞是通过将权利要求20或21所述的表达载体引入至宿主细胞中而获得的。

24.根据权利要求23所述的重组细胞，其特征在于，通过电转导的方法将所述表达载体引入所述宿主细胞中。

25.根据权利要求22所述的重组细胞，其特征在于，所述重组细胞为真核细胞。

26.根据权利要求22所述的重组细胞，其特征在于，所述重组细胞为哺乳动物细胞。

27.一种药物组合物，其特征在于，含有权利要求1~16任一项所述的抗体。

28.权利要求1~16任一项所述的抗体或权利要求27所述的药物组合物在制备药物中的用途，所述药物用于治疗或者预防疼痛、癌症、炎症或炎性疾病、神经变性疾病、舍格伦氏综合征、子宫内膜异位、与骨重塑调节失衡相关的疾病以及由结缔组织生长因子异常信号传导引起的疾病。

29.根据权利要求28所述的用途，其特征在于，所述神经变性疾病包括糖尿病性周围神经病变，所述炎症或炎性疾病包括前列腺炎，所述疼痛包括盆腔疼痛综合征。

30.根据权利要求28所述的用途，其特征在于，所述药物用于治疗或预防神经性疼痛、炎性疼痛、与癌症有关的疼痛、与骨折有关的疼痛、与手术有关的疼痛、炎性肺病、间质性膀胱炎、痛性膀胱综合征、炎性肠疾病、炎性皮肤病、雷诺氏综合征、特发性肺纤维化、瘢痕(肥大型、瘢痕瘤型和其他形式)、硬化、心内膜心肌纤维化、心房纤维化、骨髓纤维化、进行性块状纤维化(肺)、肾源性系统性纤维化、硬皮病、系统性硬化、关节纤维化、眼部纤维化、非小细胞肺癌、乳头状甲状腺癌、多形性成胶质细胞瘤、结肠直肠癌、黑色素瘤、胆管癌或肉瘤、急性骨髓性白血病、大细胞神经内分泌癌、成神经细胞瘤、前列腺癌、成神经细胞瘤、胰腺癌、黑色素瘤、头颈鳞状细胞癌或胃癌。

31.一种检测TrkA的试剂盒，其特征在于，包括权利要求利要求1~16任一项所述的抗体。

32.权利要求1~16任一项所述的抗体在制备试剂盒中的用途，所述试剂盒用于检测TrkA或者诊断TrkA相关的疾病。

TrkA的抗体及其应用

技术领域

[0001] 本发明涉及生物技术领域，具体地，本发明涉及TrkA的抗体及其应用，更具体地，本发明涉及能够特异性识别TrkA的抗体或其抗原结合片段、核酸分子、表达载体、重组细胞、药物组合物、制药用途、检测TrkA的试剂盒以及小鼠B细胞。

背景技术

[0002] 目前临床上对于轻至中度疼痛，主要使用非阿片类镇痛药，如非甾体类抗炎药(NSAIDs)；对于中至重度疼痛，主要使用阿片类镇痛药。然而，NSAIDs存在“封顶效应”，阿片仅能使不到30％的非肿瘤性慢性疼痛得到有效缓解，20％的癌痛患者存在阿片类药物耐药。此外，NSAIDs存在胃肠道和心血管安全性隐患，长期用药过程中尤其明显。对于阿片类镇痛药，多年的药物改进实验未能有效的降低其成瘾性和其它诸多副作用，患者期许新的更安全有效的药物。

[0003] 神经生长因子(NGF，nerve growth factor)参与疼痛的病理生理过程，主要通过结合高亲和力的酪氨酸激酶(tyrosine-nase，TrkA)受体激活NGF/TrKA信号通路，影响炎症介质的释放、离子通道的开放以及促进神经纤维的生长，从而参与疼痛的发生，传导以及增敏过程。研究表明，阻断NGF-TrkA信号通路可以有效的缓解疼痛和痛觉过敏，NGF-TrkA信号通路是开发新型镇痛药物的有效靶点。对于NGF-TrkA靶点镇痛药物，目前在研的药物主要分为两大类：大分子抗NGF单克隆抗体和小分子TrkA激酶抑制剂。由于TrKA受体并不是NGF的唯一受体，NGF还存在一种低亲和力的受体P75，而NGF与P75的结合对于神经系统的功能以及损伤修复是有重要作用的，大分子抗NGF单克隆抗体作为一种新型的镇痛药物存在很大的安全性隐患。从目前的临床数据来看，最常见毒副作用包括骨组织坏死(潜在)、感官异常等。而小分子TrkA激酶抑制剂存在着更多的问题。首先，小分子药物的半衰期一般较短，给药频繁，病人的依从性差。其次，小分子Trka激酶抑制剂是受体酪氨酸激酶抑制剂，机体内存在多种受体酪氨酸激酶，因此，药物对于特定靶点的特异性和选择性很难保证，药物的不良反应多，毒副作用大。

[0004] 因此，针对NGF-TrkA靶点的镇痛药物，仍然需要科研工作者不断的开发和改进。

发明内容

[0005] 本申请是基于发明人对下列问题和事实的发现而提出的：

[0006] NGF-TrkA信号通路作为开发新型镇痛药物的有效靶点，如果通过TrkA单克隆抗体选择性的靶向结合TrkA受体，不仅可以阻断NGF对TrkA信号通路的激活，有效的抑制疼痛信号的传递，又不会发生像抑制NGF受体所造成的诸多神经毒性，以及使用抗NGF抗体过度中和NGF所带来的骨关节坏死等不可预测的毒副作用。但由于TrkA分子是受体膜蛋白，筛选阻断型抗TrkA单克隆抗体的难度比较大，其次，设计阻断TrkA受体抗体存在由于抗体介导免疫反应导致的安全性风险，因此，设计开发针对TrkA的单克隆抗体难度比较大。

[0007] 然而本申请的发明人却成功地筛选到了一种新型的具有长效镇痛作用的抗TrkA

单克隆抗体，同时，发明人通过选取特定的Fc亚型并对其进行改造有效避免了免疫毒性的风险。具体地，本研究通过杂交瘤技术筛选出一系列阻断NGF和TrkA结合的高亲和力抗TrkA单克隆抗体，并将鼠源抗TrkA单克隆抗体的恒定区人源化，保留鼠源抗TrkA单克隆抗体的可变区，得到一系列的抗TrkA嵌合单克隆抗体。发明人发现，本申请所获得的这些嵌合抗体候选物，不仅能够特异性的靶向结合TrkA受体，阻断NGF和TrkA结合，有效的抑制疼痛，而且具有免疫毒性低，基本没有抗体依赖的细胞介导的细胞毒性作用(ADCC)的特点。

[0008] 在本发明的的第一方面，本发明提出了一种能够特异性识别TrkA的抗体或其抗原结合片段。根据本发明的实施例，所述抗体含有选自下列至少之一的CDR序列或与其具有至少95％同一性的氨基酸序列：重链可变区CDR序列：SEQ ID NO:1～27，轻链可变区CDR序列：SEQ IN NO:28～54。

[0009] VYSFTAYT(SEQ ID NO:1)。

[0010] INPHNGGT(SEQ ID NO:2)。

[0011] AISRYGSSSFYFDV(SEQ ID NO:3)。

[0012] GYAFTNYW(SEQ ID NO:4)。

[0013] FYPRTGNT(SEQ ID NO:5)。

[0014] ARAGTGFDY(SEQ ID NO:6)。

[0015] GYRFSSYW(SEQ ID NO:7)。

[0016] ILPGRGII(SEQ ID NO:8)。

[0017] ARTDPPYFGV(SEQ ID NO:9)。

[0018] GYTFSTYW(SEQ ID NO:10)。

[0019] NLPGRHIT(SEQ ID NO:11)。

[0020] ARGRGTYYFDY(SEQ ID NO:12)。

[0021] GYSFTGYT(SEQ ID NO:13)。

[0022] INPYNGGT(SEQ ID NO:14)。

[0023] AFSYYGSRGFYFDY(SEQ ID NO:15)。

[0024] GYSFTGYT(SEQ ID NO:16)。

[0025] INPYNGGT(SEQ ID NO:17)。

[0026] ASSSYRNDGNWYFDV(SEQ ID NO:18)。

[0027] GYSITGYT(SEQ ID NO:19)。

[0028] VNPYNGGT(SEQ ID NO:20)。

[0029] AISRYGSESWYFDV(SEQ ID NO:21)。

[0030] GYTFNIYW(SEQ ID NO:22)。

[0031] ILPGSGNT(SEQ ID NO:23)。

[0032] ARTDGRGYFDY(SEQ ID NO:24)。

[0033] GYTFSSYW(SEQ ID NO:25)。

[0034] FLPRSGKT(SEQ ID NO:26)。

[0035] ARTDPPYFGV(SEQ ID NO:27)。

[0036] SSISY(SEQ ID NO:28)。

[0037] ATS(SEQ ID NO:29)。

[0038] QQWSSNPPT(SEQ ID NO:30)。

[0039] ENVGGY(SEQ ID NO:31)。

[0040] GAS(SEQ ID NO:32)。

[0041] GQNYIYPFT(SEQ ID NO:33)。

[0042] TGAVTISNY(SEQ ID NO:34)。

[0043] GTN(SEQ ID NO:35)。

[0044] VLWYSNHWV(SEQ ID NO:36)。

[0045] QSLLHSNGITY(SEQ ID NO:37)。

[0046] QMS(SEQ ID NO:38)。

[0047] AQNLEFPFT(SEQ ID NO:39)。

[0048] SSVSY(SEQ ID NO:40)。

[0049] LTS(SEQ ID NO:41)。

[0050] QQWSSNPPT(SEQ ID NO:42)。

[0051] SSVSY(SEQ ID NO:43)。

[0052] DTS(SEQ ID NO:44)。

[0053] QQWSSNPPT(SEQ ID NO:45)。

[0054] SSVSY(SEQ ID NO:46)。

[0055] ATS(SEQ ID NO:47)。

[0056] QQWSSNPPT(SEQ ID NO:48)。

[0057] KSVSSSAYSY(SEQ ID NO:49)。

[0058] LAS(SEQ ID NO:50)。

[0059] QHSRELPFT(SEQ ID NO:51)。

[0060] SNISY(SEQ ID NO:52)。

[0061] DTS(SEQ ID NO:53)。

[0062] QQWSSVPLT(SEQ ID NO:54)。

[0063] 根据本发明实施例的上述抗体能够特异性的靶向结合TrkA受体,阻断NGF和TrkA结合。

[0064] 根据本发明的实施例,上述抗体或抗原结合片段还可以进一步包括如下附加技术特征至少之一:

[0065] 根据本发明的实施例,所述抗体包括:

[0066] 分别如SEQ ID NO:1、2和3或者与SEQ ID NO:1、2和3具有至少95%同一性的氨基酸序列所示的重链可变区CDR1、CDR2、CDR3序列;或者

[0067] 分别如SEQ ID NO:4、5和6或者与SEQ ID NO:4、5和6具有至少95%同一性的氨基酸序列所示的重链可变区CDR1、CDR2、CDR3序列;或者

[0068] 分别如SEQ ID NO:7、8和9或者与SEQ ID NO:7、8和9具有至少95%同一性的氨基酸序列所示的重链可变区CDR1、CDR2、CDR3序列;或者

[0069] 分别如SEQ ID NO:10、11和12或者与SEQ ID NO:10、11和12具有至少95%同一性的氨基酸序列所示的重链可变区CDR1、CDR2、CDR3序列;或者

[0070] 分别如SEQ ID NO:13、14和15或者与SEQ ID NO:13、14和15具有至少95%同一性

的氨基酸序列所示的重链可变区CDR1、CDR2、CDR3序列;或者

[0071] 分别如SEQ ID NO:16、17和18或者与SEQ ID NO:16、17和18具有至少95%同一性的氨基酸序列所示的重链可变区CDR1、CDR2、CDR3序列;或者

[0072] 分别如SEQ ID NO19、20和21或者与SEQ ID NO:19、20和21具有至少95%同一性的氨基酸序列所示的重链可变区CDR1、CDR2、CDR3序列;或者

[0073] 分别如SEQ ID NO:22、23和24或者与SEQ ID NO:22、23和24具有至少95%同一性的氨基酸序列所示的重链可变区CDR1、CDR2、CDR3序列;或者

[0074] 分别如SEQ ID NO:25、26和27或者与SEQ ID NO:25、26和27具有至少95%同一性的氨基酸序列所示的重链可变区CDR1、CDR2、CDR3序列。

[0075] 根据本发明的实施例,所述抗体包括:

[0076] 分别如SEQ ID NO:28、29和30或者与SEQ ID NO:28、39和30具有至少95%同一性的氨基酸序列所示的轻链可变区CDR1、CDR2、CDR3序列;或者

[0077] 分别如SEQ ID NO:31、32和33或者与SEQ ID NO:31、32和33具有至少95%同一性的氨基酸序列所示的轻链可变区CDR1、CDR2、CDR3序列;或者

[0078] 分别如SEQ ID NO:34、35和36或者与SEQ ID NO:34、35和36具有至少95%同一性的氨基酸序列所示的轻链可变区CDR1、CDR2、CDR3序列;或者

[0079] 分别如SEQ ID NO:37、38和39或者与SEQ ID NO:37、38和39具有至少95%同一性的氨基酸序列所示的轻链可变区CDR1、CDR2、CDR3序列;或者

[0080] 分别如SEQ ID NO:40、41和42或者与SEQ ID NO:40、41和42具有至少95%同一性的氨基酸序列所示的轻链可变区CDR1、CDR2、CDR3序列;或者

[0081] 分别如SEQ ID NO:43、44和45或者与SEQ ID NO:43、44和45具有至少95%同一性的氨基酸序列所示的轻链可变区CDR1、CDR2、CDR3序列;或者

[0082] 分别如SEQ ID NO:46、47和48或者与SEQ ID NO:46、47和48具有至少95%同一性的氨基酸序列所示的轻链可变区CDR1、CDR2、CDR3序列;或者

[0083] 分别如SEQ ID NO:49、50和51或者与SEQ ID NO:49、50和51具有至少95%同一性的氨基酸序列所示的轻链可变区CDR1、CDR2、CDR3序列;或者

[0084] 分别如SEQ ID NO:52、53和54或者与SEQ ID NO:52、53和54具有至少95%同一性的氨基酸序列所示的轻链可变区CDR1、CDR2、CDR3序列。

[0085] 根据本发明的实施例,所述抗体或其抗原结合片段特异性识别TrkA的胞外区。

[0086] 根据本发明的实施例,所述抗体含有重链框架区序列和轻链框架区序列的至少之一,所述重链框架区序列和轻链框架区序列的至少之一的至少一部分来自于鼠源抗体、人源抗体、灵长目源抗体或其突变体的至少之一。

[0087] 根据本发明的实施例,所述抗体具有如SEQ ID NO:55～63任一项所示氨基酸序列的重链可变区。

[0088] EVLLQQSGPELVKPGASMKISCKASVYSFTAYTMNWVKQSHGKNLEWIGLINPHNGGTRYNQKFKGKATLTLDKSSSTAYMDLLSLTSEDSAVYYCAISRYGSSSFYFDVWGAGTTVAVSS(SEQ ID NO:55)。

[0089] QVQLQQSGAELVRPGTSVKISCKASGYAFTNYWLGWMKQRPGHGLEWIGDFYPRTGNTFYNENFKGKVTLTADKSSNTAYMQLSSLTSEDSAVYLCARAGTGFDYWGQGTTLTVSS(SEQ ID NO:56)。

[0090] QVQLQQSGAELMKPGASVKISCKTTGYRFSSYWIEWVKQRPGHGLEWLGEILPGRGIINYNENFRGKA

TFTADTSSNTAYVQLSSLTSEDSAVYFCARTDPPYFGVWGAGTTVTVSS(SEQ ID NO:57)。

[0091] QVQLQQSGAELMKPGASMKISCKATGYTFSTYWIEWVKQRPGHGLEWIGENLPGRHITNYNEKFKGKATFTADTSSNTAYMQLSSLTSEDSAVYYCARGRGTYYFDYWGQGTPLTVSS(SEQ ID NO:58)。

[0092] EVQLQQSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKNLEWIGLINPYNGGTNYNQKFKGKATLTVDKSSSTAYMELLSLTSEDSAVYYCAFSYYGSRGFYFDYWGQGTTLTVSS(SEQ ID NO:59)。

[0093] EVQLQQSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKNLEWIGLINPYNGGTRYNQKFKGKATLTVDKSSSTAYMELLSLTSEDSAVYYCASSSYRNDGNWYFDVWGAGTTVTVSS(SEQ ID NO:60)。

[0094] EVQLQQSGPELVKPGASMKISCKASGYSITGYTMNWVKQSHGKNLEWIGLVNPYNGGTSYNQKFKGKATLTVDKSSSTAYMELLSLKSEDSAVYYCAISRYGSESWYFDVWGAGTTVTVSS(SEQ ID NO:61)。

[0095] QVHLQQSGAELMKPGASVKISCKATGYTFNIYWIDWVKQRPGHGLEWIGEILPGSGNTHYNENFKGKATMTADTSSNTAYMQLTSLTSEDSAVYYCARTDGRGYFDYWGQGTTLTVSS(SEQ ID NO:62)。

[0096] QVQLQQSGAELMKPGASVKISCKATGYTFSSYWIEWVKQRPGHGLEWLGEFLPRSGKTNYNEEFRGKATFTADTSSNTAYMQLSSLTSEDSAVYYCARTDPPYFGVWGAGTMVAVSS(SEQ ID NO:63)。

[0097] 根据本发明的实施例,所述抗体具有如SEQ ID NO:64～72任一项所示氨基酸序列的轻链可变区。

[0098] QIVLSQSPAILSASPGEKVTMTCRASSSISYMHWYQQKPGSSPKPWISATSNLASGVPARFSGSGSGTSYSLTISGVEAEDAATYYCQQWSSNPPTFGGGTNLEIK(SEQ ID NO:64)。

[0099] SIVMTQSPKSMSMSVGERVTLSCKASENVGGYVSWYQQKPDQSPKLLIYGASSRHTGVPDRFTGSGSETDFTLTISSVQAEDLAAYHCGQNYIYPFTFGGGTKLEIK(SEQ ID NO:65)。

[0100] QAVVTQESALTTSPGETVTLTCRSSTGAVTISNYANWVQEKPDHLFTGLIGGTNNRPPGVPARFSGSLIGDKAALTITGAQTEDEAIYFCVLWYSNHWVFGGGTKLTVL(SEQ ID NO:66)。

[0101] DIVMTQAAFSTPVTLGTSASISCRSSQSLLHSNGITYLYWYLQKPGQSPQLLIYQMSNLASGVPDRFSSSGSGTDFTLRISRVEAEDVGVYYCAQNLEFPFTFGSGTKLEIK(SEQ ID NO:67)。

[0102] QIVLTQSPALMSASPGEKVTMTCSATSSVSYIYWYQQKPRSSPKPWIYLTSNLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQQWSSNPPTFGGGTKLEIK(SEQ ID NO:68)。

[0103] DIVMTQSPAIMSASPGEKVTMTCSASSSVSYMHWYQQKSGTSPKRWIYDTSKLASGVPARFSGSGSGTSYSLTISSMETEDAATYYCQQWSSNPPTFGGGTKLELK(SEQ ID NO:69)。

[0104] QIVLSQSPAILSASPGEKVTMTCRATSSVSYMYWYQQKPGSSPKPWIYATSNLASGVPARFSGSGSGTSYSLTISRVEAEDAATYYCQQWSSNPPTFGGGTKLEKK(SEQ ID NO:70)。

[0105] DIVLTQSPASLVVSLGQRATISCRTSKSVSSSAYSYMHWYQQKPGQPPKVLIYLASNLESGVPARFSGSGSGTDFTLNIHPVEEEDAATYYCQHSRELPFTFGSGTKLEIK(SEQ ID NO:71)。

[0106] QIVLTQSPPIMSASPGEKVTMTCSASSNISYMHWYQQKSGTSPKRWIYDTSKLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQQWSSVPLTFGAGTKLEIK(SEQ ID NO:72)。

[0107] 根据本发明的实施例,所述抗体含有重链恒定区和轻链恒定区的至少之一,所述重链恒定区和轻链恒定区的至少之一的至少一部分来自于鼠源抗体、人源抗体、灵长目源抗体或其突变体的至少之一。

[0108] 根据本发明的实施例,所述抗体的轻链恒定区和重链恒定区均来自于人源IgG抗体或其突变体。进而所述抗体的免疫原性可以得到有效降低。

[0109] 根据本发明的实施例,所述抗体的轻链恒定区和重链恒定区均来自于人源IgG4。

[0110] 根据本发明的实施例，所述抗体的Fc区域与人源IgG4野生型的Fc相比具有S10P，F16A，L17A，R191K突变以及229K缺失突变。其中，上述氨基酸位置的定位是以人源IgG4野生型Fc序列SEQ ID NO:73所示氨基酸序列进行定位的，如S10P，是指SEQ ID NO:75所示氨基酸序列的第10位S突变为P，依次类推。发明人发现，所述抗体的Fc区域具有上述突变以及缺失后，抗体的安全性、稳定性可以得到显著提高，抗体在体内的半衰期也显著延长。

[0111] ESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK(SEQ ID NO:73)。

[0112] 根据本发明的实施例，所述抗体恒定区的全长序列如SEQ ID NO:74或75所示。

[0113] ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG(SEQ ID NO:74)。

[0114] RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:75)。

[0115] 其中，上述SEQ ID NO:74所示的抗体恒定区的全长序列包括IgG4重链恒定区和Fc区，其中，IgG4重链恒定区序列为ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV，Fc区序列为ESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG。上述SEQ ID NO:75所示的抗体恒定区的全长序列为IgG4轻链恒定区。

[0116] 根据本发明的实施例，所述抗体具有SEQ ID NO:76～84任一项所示氨基酸序列的重链和具有SEQ ID NO:85～93任一项所示氨基酸序列的轻链。

[0117] EVLLQQSGPELVKPGASMKISCKASVYSFTAYTMNWVKQSHGKNLEWIGLINPHNGGTRYNQKFKGKATLTLDKSSSTAYMDLLSLTSEDSAVYYCAISRYGSSSFYFDVWGAGTTVAVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG(SEQ ID NO:76)。

[0118] QIVLSQSPAILSASPGEKVTMTCRASSSISYMHWYQQKPGSSPKPWISATSNLASGVPARFSGSGSGTSYSLTISGVEAEDAATYYCQQWSSNPPTFGGGTNLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:85)。

[0119] QVQLQQSGAELVRPGTSVKISCKASGYAFTNYWLGWMKQRPGHGLEWIGDFYPRTGNTFYNENFKGKVTLTADKSSNTAYMQLSSLTSEDSAVYLCARAGTGFDYWGQGTTLTVSSASTKGPSVFPLAPCSRSTSESTAALGCL

VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGP PCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG(SEQ ID NO:77)。

[0120] SIVMTQSPKSMSMSVGERVTLSCKASENVGGYVSWYQQKPDQSPKLLIYGASSRHTGVPDRFTGSGSE TDFTLTISSVQAEDLAAYHCGQNYIYPFTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:86)。

[0121] QVQLQQSGAELMKPGASVKISCKTTGYRFSSYWIEWVKQRPGHGLEWLGEILPGRGIINYNENFRGKA TFTADTSSNTAYVQLSSLTSEDSAVYFCARTDPPYFGVWGAGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYG PPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG(SEQ ID NO:78)。

[0122] QAVVTQESALTTSPGETVTLTCRSSTGAVTISNYANWVQEKPDHLFTGLIGGTNNRPPGVPARFSGSL IGDKAALTITGAQTEDEAIYFCVLWYSNHWVFGGGTKLTVLRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:87)。

[0123] QVQLQQSGAELMKPGASMKISCKATGYTFSTYWIEWVKQRPGHGLEWIGENLPGRHITNYNEKFKGKA TFTADTSSNTAYMQLSSLTSEDSAVYYCARGRGTYYFDYWGQGTPLTVSSASTKGPSVFPLAPCSRSTSESTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG(SEQ ID NO:79)。

[0124] DIVMTQAAFSTPVTLGTSASISCRSSQSLLHSNGITYLYWYLQKPGQSPQLLIYQMSNLASGVPDRFS SSGSGTDFTLRISRVEAEDVGVYYCAQNLEFPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:88)。

[0125] EVQLQQSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKNLEWIGLINPYNGGTNYNQKFKGKA TLTVDKSSSTAYMELLSLTSEDSAVYYCAFSYYGSRGFYFDYWGQGTTLTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVE SKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQ FNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG (SEQ ID NO:80)。

[0126] QIVLTQSPALMSASPGEKVTMTCSATSSVSYIYWYQQKPRSSPKPWIYLTSNLASGVPARFSGSGSGT

SYSLTISSMEAEDAATYYCQQWSSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:89)。

[0127] EVQLQQSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKNLEWIGLINPYNGGTRYNQKFKGKA TLTVDKSSSTAYMELLSLTSEDSAVYYCASSSYRNDGNWYFDVWGAGTTVTVSSASTKGPSVFPLAPCSRSTSEST AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV ESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG (SEQ ID NO:81)。

[0128] DIVMTQSPAIMSASPGEKVTMTCSASSSVSYMHWYQQKSGTSPKRWIYDTSKLASGVPARFSGSGSGT SYSLTISSMETEDAATYYCQQWSSNPPTFGGGTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:90)。

[0129] EVQLQQSGPELVKPGASMKISCKASGYSITGYTMNWVKQSHGKNLEWIGLVNPYNGGTSYNQKFKGKA TLTVDKSSSTAYMELLSLKSEDSAVYYCAISRYGSESWYFDVWGAGTTVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVE SKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQ FNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG (SEQ ID NO:82)。

[0130] QIVLSQSPAILSASPGEKVTMTCRATSSVSYMYWYQQKPGSSPKPWIYATSNLASGVPARFSGSGSGT SYSLTISRVEAEDAATYYCQQWSSNPPTFGGGTKLEKKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:91)。

[0131] QVHLQQSGAELMKPGASVKISCKATGYTFNIYWIDWVKQRPGHGLEWIGEILPGSGNTHYNENFKGKA TMTADTSSNTAYMQLTSLTSEDSAVYYCARTDGRGYFDYWGQGTTLTVSSASTKGPSVFPLAPCSRSTSESTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG(SEQ ID NO:83)。

[0132] DIVLTQSPASLVVSLGQRATISCRTSKSVSSSAYSYMHWYQQKPGQPPKVLIYLASNLESGVPARFSG SGSGTDFTLNIHPVEEEDAATYYCQHSRELPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:92)。

[0133] QVQLQQSGAELMKPGASVKISCKATGYTFSSYWIEWVKQRPGHGLEWLGEFLPRSGKTNYNEEFRGKA TFTADTSSNTAYMQLSSLTSEDSAVYYCARTDPPYFGVWGAGTMVAVSSASTKGPSVFPLAPCSRSTSESTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYG

PPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG(SEQ ID NO:84)。

[0134] QIVLTQSPPIMSASPGEKVTMTCSASSNISYMHWYQQKSGTSPKRWIYDTSKLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQQWSSVPLTFGAGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:93)。

[0135] 其中,在本申请中,上述SEQ ID NO:76和85所组成的抗体被称为20C8嵌合抗体,上述SEQ ID NO:77和86所组成的抗体被称为23E12嵌合抗体,上述SEQ ID NO:78和87所组成的抗体被称为27H3嵌合抗体,上述SEQ ID NO:79和88所组成的抗体被称为21E5嵌合抗体,上述SEQ ID NO:80和89所组成的抗体被称为2A5嵌合抗体,上述SEQ ID NO:81和SEQ ID NO:90所组成的抗体被称为4H4嵌合抗体,上述SEQ ID NO:82和SEQ ID NO:91所组成的抗体被称为22D12嵌合抗体,上述SEQ ID NO:83和SEQ ID NO:92所组成的抗体被称为1B9嵌合抗体,上述SEQ ID NO:84和SEQ ID NO:93所组成的抗体被称为15D4嵌合抗体。

[0136] 根据本发明的实施例,所述抗体为单链抗体、多聚体抗体、CDR移植抗体或小分子抗体。

[0137] 根据本发明的实施例,所述抗体为单链抗体,所述抗体具有SEQ ID NO:94～111所示的氨基酸序列。

[0138] QIVLSQSPAILSASPGEKVTMTCRASSSISYMHWYQQKPGSSPKPWISATSNLASGVPARFSGSGSGTSYSLTISGVEAEDAATYYCQQWSSNPPTFGGGTNLEIKGGGGSGGGGSGGGGSEVLLQQSGPELVKPGASMKISCKASVYSFTAYTMNWVKQSHGKNLEWIGLINPHNGGTRYNQKFKGKATLTLDKSSSTAYMDLLSLTSEDSAVYYCAISRYGSSSFYFDVWGAGTTVAVSS(SEQ ID NO:94)。

[0139] EVLLQQSGPELVKPGASMKISCKASVYSFTAYTMNWVKQSHGKNLEWIGLINPHNGGTRYNQKFKGKATLTLDKSSSTAYMDLLSLTSEDSAVYYCAISRYGSSSFYFDVWGAGTTVAVSSGGGGSGGGGSGGGGSQIVLSQSPAILSASPGEKVTMTCRASSSISYMHWYQQKPGSSPKPWISATSNLASGVPARFSGSGSGTSYSLTISGVEAEDAATYYCQQWSSNPPTFGGGTNLEIK(SEQ ID NO:95)。

[0140] SIVMTQSPKSMSMSVGERVTLSCKASENVGGYVSWYQQKPDQSPKLLIYGASSRHTGVPDRFTGSGSETDFTLTISSVQAEDLAAYHCGQNYIYPFTFGGGTKLEIKGGGGSGGGGSGGGGSQVQLQQSGAELVRPGTSVKISCKASGYAFTNYWLGWMKQRPGHGLEWIGDFYPRTGNTFYNENFKGKVTLTADKSSNTAYMQLSSLTSEDSAVYLCARAGTGFDYWGQGTTLTVSS(SEQ ID NO:96)。

[0141] QVQLQQSGAELVRPGTSVKISCKASGYAFTNYWLGWMKQRPGHGLEWIGDFYPRTGNTFYNENFKGKVTLTADKSSNTAYMQLSSLTSEDSAVYLCARAGTGFDYWGQGTTLTVSSGGGGSGGGGSGGGGSSIVMTQSPKSMSMSVGERVTLSCKASENVGGYVSWYQQKPDQSPKLLIYGASSRHTGVPDRFTGSGSETDFTLTISSVQAEDLAAYHCGQNYIYPFTFGGGTKLEIK(SEQ ID NO:97)。

[0142] QAVVTQESALTTSPGETVTLTCRSSTGAVTISNYANWVQEKPDHLFTGLIGGTNNRPPGVPARFSGSLIGDKAALTITGAQTEDEAIYFCVLWYSNHWVFGGGTKLTVLGGGGSGGGGSGGGGSQVQLQQSGAELMKPGASVKISCKTTGYRFSSYWIEWVKQRPGHGLEWLGEILPGRGIINYNENFRGKATFTADTSSNTAYVQLSSLTSEDSAVYFCARTDPPYFGVWGAGTTVTVSS(SEQ ID NO:98)。

[0143] QVQLQQSGAELMKPGASVKISCKTTGYRFSSYWIEWVKQRPGHGLEWLGEILPGRGIINYNENFRGKA TFTADTSSNTAYVQLSSLTSEDSAVYFCARTDPPYFGVWGAGTTVTVSSGGGGSGGGGSGGGGSQAVVTQESALTT SPGETVTLTCRSSTGAVTISNYANWVQEKPDHLFTGLIGGTNNRPPGVPARFSGSLIGDKAALTITGAQTEDEAIY FCVLWYSNHWVFGGGTKLTVL(SEQ ID NO:99)。

[0144] DIVMTQAAFSTPVTLGTSASISCRSSQSLLHSNGITYLYWYLQKPGQSPQLLIYQMSNLASGVPDRFS SSGSGTDFTLRISRVEAEDVGVYYCAQNLEFPFTFGSGTKLEIKGGGGSGGGGSGGGGSQVQLQQSGAELMKPGAS MKISCKATGYTFSTYWIEWVKQRPGHGLEWIGENLPGRHITNYNEKFKGKATFTADTSSNTAYMQLSSLTSEDSAV YYCARGRGTYYFDYWGQGTPLTVSS(SEQ ID NO:100)。

[0145] QVQLQQSGAELMKPGASMKISCKATGYTFSTYWIEWVKQRPGHGLEWIGENLPGRHITNYNEKFKGKA TFTADTSSNTAYMQLSSLTSEDSAVYYCARGRGTYYFDYWGQGTPLTVSSGGGGSGGGGSGGGGSDIVMTQAAFST PVTLGTSASISCRSSQSLLHSNGITYLYWYLQKPGQSPQLLIYQMSNLASGVPDRFSSSGSGTDFTLRISRVEAED VGVYYCAQNLEFPFTFGSGTKLEIK(SEQ ID NO:101)。

[0146] QIVLTQSPALMSASPGEKVTMTCSATSSVSYIYWYQQKPRSSPKPWIYLTSNLASGVPARFSGSGSGT SYSLTISSMEAEDAATYYCQQWSSNPPTFGGGTKLEIKGGGGSGGGGSGGGGSEVQLQQSGPELVKPGASMKISCK ASGYSFTGYTMNWVKQSHGKNLEWIGLINPYNGGTNYNQKFKGKATLTVDKSSSTAYMELLSLTSEDSAVYYCAFS YYGSRGFYFDYWGQGTTLTVSS(SEQ ID NO:102)。

[0147] EVQLQQSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKNLEWIGLINPYNGGTNYNQKFKGKA TLTVDKSSSTAYMELLSLTSEDSAVYYCAFSYYGSRGFYFDYWGQGTTLTVSSGGGGSGGGGSGGGGSQIVLTQSP ALMSASPGEKVTMTCSATSSVSYIYWYQQKPRSSPKPWIYLTSNLASGVPARFSGSGSGTSYSLTISSMEAEDAAT YYCQQWSSNPPTFGGGTKLEIK(SEQ ID NO:103)。

[0148] DIVMTQSPAIMSASPGEKVTMTCSASSSVSYMHWYQQKSGTSPKRWIYDTSKLASGVPARFSGSGSGT SYSLTISSMETEDAATYYCQQWSSNPPTFGGGTKLELKGGGGSGGGGSGGGGSEVQLQQSGPELVKPGASMKISCK ASGYSFTGYTMNWVKQSHGKNLEWIGLINPYNGGTRYNQKFKGKATLTVDKSSSTAYMELLSLTSEDSAVYYCASS SYRNDGNWYFDVWGAGTTVTVSS(SEQ ID NO:104)。

[0149] EVQLQQSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKNLEWIGLINPYNGGTRYNQKFKGKA TLTVDKSSSTAYMELLSLTSEDSAVYYCASSSYRNDGNWYFDVWGAGTTVTVSSGGGGSGGGGSGGGGSDIVMTQS PAIMSASPGEKVTMTCSASSSVSYMHWYQQKSGTSPKRWIYDTSKLASGVPARFSGSGSGTSYSLTISSMETEDAA TYYCQQWSSNPPTFGGGTKLELK(SEQ ID NO:105)。

[0150] QIVLSQSPAILSASPGEKVTMTCRATSSVSYMYWYQQKPGSSPKPWIYATSNLASGVPARFSGSGSGT SYSLTISRVEAEDAATYYCQQWSSNPPTFGGGTKLEKKGGGGSGGGGSGGGGSEVQLQQSGPELVKPGASMKISCK ASGYSITGYTMNWVKQSHGKNLEWIGLVNPYNGGTSYNQKFKGKATLTVDKSSSTAYMELLSLKSEDSAVYYCAIS RYGSESWYFDVWGAGTTVTVSS(SEQ ID NO:106)。

[0151] EVQLQQSGPELVKPGASMKISCKASGYSITGYTMNWVKQSHGKNLEWIGLVNPYNGGTSYNQKFKGKA TLTVDKSSSTAYMELLSLKSEDSAVYYCAISRYGSESWYFDVWGAGTTVTVSSGGGGSGGGGSGGGGSQIVLSQSP AILSASPGEKVTMTCRATSSVSYMYWYQQKPGSSPKPWIYATSNLASGVPARFSGSGSGTSYSLTISRVEAEDAAT YYCQQWSSNPPTFGGGTKLEKK(SEQ ID NO:107)。

[0152] DIVLTQSPASLVVSLGQRATISCRTSKSVSSSAYSYMHWYQQKPGQPPKVLIYLASNLESGVPARFSG SGSGTDFTLNIHPVEEEDAATYYCQHSRELPFTFGSGTKLEIKGGGGSGGGGSGGGGSQVHLQQSGAELMKPGASV KISCKATGYTFNIYWIDWVKQRPGHGLEWIGEILPGSGNTHYNENFKGKATMTADTSSNTAYMQLTSLTSEDSAVY

YCARTDGRGYFDYWGQGTTLTVSS(SEQ ID NO:108)。

[0153] QVHLQQSGAELMKPGASVKISCKATGYTFNIYWIDWVKQRPGHGLEWIGEILPGSGNTHYNENFKGKATMTADTSSNTAYMQLTSLTSEDSAVYYCARTDGRGYFDYWGQGTTLTVSSGGGGSGGGGSGGGGSDIVLTQSPASLVVSLGQRATISCRTSKSVSSSAYSYMHWYQQKPGQPPKVLIYLASNLESGVPARFSGSGSGTDFTLNIHPVEEEDAATYYCQHSRELPFTFGSGTKLEIK(SEQ ID NO:109)。

[0154] QIVLTQSPPIMSASPGEKVTMTCSASSNISYMHWYQQKSGTSPKRWIYDTSKLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQQWSSVPLTFGAGTKLEIKGGGGSGGGGSGGGGSQVQLQQSGAELMKPGASVKISCKATGYTFSSYWIEWVKQRPGHGLEWLGEFLPRSGKTNYNEEFRGKATFTADTSSNTAYMQLSSLTSEDSAVYYCARTDPPYFGVWGAGTMVAVSS(SEQ ID NO:110)。

[0155] QVQLQQSGAELMKPGASVKISCKATGYTFSSYWIEWVKQRPGHGLEWLGEFLPRSGKTNYNEEFRGKATFTADTSSNTAYMQLSSLTSEDSAVYYCARTDPPYFGVWGAGTMVAVSSGGGGSGGGGSGGGGSQIVLTQSPPIMSASPGEKVTMTCSASSNISYMHWYQQKSGTSPKRWIYDTSKLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQQWSSVPLTFGAGTKLEIK(SEQ ID NO:111)。

[0156] 其中,在本申请中,上述SEQ ID NO:94或95所示氨基酸序列的抗体被称为20C8单链抗体,上述SEQ ID NO:96或97所示氨基酸序列的抗体被称为23E12单链抗体,上述SEQ ID NO:98或99所示氨基酸序列的抗体被称为27H3单链抗体,上述SEQ ID NO:100或101所示氨基酸序列的抗体被称为21E5单链抗体,上述SEQ ID NO:102和103所示氨基酸序列的抗体被称为2A5单链抗体,上述SEQ ID NO:104和SEQ ID NO:105所示氨基酸序列的抗体被称为4H4单链抗体,上述SEQ ID NO:106和SEQ ID NO:107所示氨基酸序列的抗体被称为22D12单链抗体,上述SEQ ID NO:108和SEQ ID NO:109所示氨基酸序列的抗体被称为1B9单链抗体,上述SEQ ID NO:110和SEQ ID NO:111所示氨基酸序列的抗体被称为15D4单链抗体。其中,SEQ ID NO:94、96、98、100、102、104、106、108、110所示氨基酸序列的抗体从N端到C端可表示为VL-Link-VH(VL表示轻链可变区,VH表示重链可变区,Link表示连接VL和VH的连接链),SEQ ID NO:95、97、99、101、103、105、107、109、111所示氨基酸序列的抗体从N端到C端可表示为VH-Link-VL(VL表示轻链可变区,VH表示重链可变区,Link表示连接VL和VH的连接链)。

[0157] 根据本发明的实施例,所述小分子抗体包括Fab抗体、Fv抗体、单域抗体以及最小识别单位的至少之一。

[0158] 在本发明的第二方面,本发明提出了一种核酸分子。根据本发明的实施例,所述核酸分子编码前面所述的抗体或其抗原结合片段。根据本发明实施例的核酸分子所编码的抗体或抗原结合片段可特异性靶向结合TrkA受体,阻断NGF和TrkA结合,且具有免疫原性低,ADCC低的优势。

[0159] 根据本发明的实施例,上述核酸分子还可以进一步包括如下附加技术特征至少之一:

[0160] 根据本发明的实施例,所述核酸分子为DNA。

[0161] 根据本发明的实施例,所述核酸分子具有如SEQ ID NO:112～120任一项所示核苷酸序列或具有SEQ ID NO:121～129任一项所示核苷酸序列或具有SEQ ID NO:130～147所示的核苷酸序列。

[0162] GAAGTGCTGCTGCAGCAGAGCGGACCAGAGCTGGTCAAGCCCGGCGCCTCCATGAAGATCAGCTGTAAGGCCTCCGTGTACAGCTTCACAGCCTACACAATGAACTGGGTGAAGCAGAGCCACGGCAAGAATCTGGAGTGGATC

GGACTGATCAACCCACACAATGGCGGCACTAGGTACAACCAGAAGTTCAAGGGCAAGGCCACACTGACTCTGGATA
AGTCCAGCAGCACTGCCTACATGGATCTGCTGTCTCTGACAAGCGAGGACAGCGCCGTCTACTATTGCGCCATCTC
TAGGTACGGCAGCAGCAGCTTCTACTTCGATGTGTGGGGCGCCGGCACAACAGTGGCTGTGAGCAGCGCCAGCACC
AAGGGCCCCAGCGTGTTCCCTCTGGCTCCTTGTAGCCGGTCCACCTCCGAGTCCACAGCTGCTCTGGGCTGCCTCG
TGAAGGACTACTTTCCCGAACCCGTTACCGTGAGCTGGAATAGCGGCGCTTTAACCTCCGGAGTGCACACCTTCCC
CGCTGTGCTCCAGTCCTCCGGTTTATACTCTTTATCCTCCGTGGTGACCGTGCCTTCCTCCAGCCTCGGCACCAAG
ACCTACACTTGTAACGTGGACCACAAGCCCAGCAACACCAAGGTGGACAAGAGGGTGGAGTCCAAGTACGGACCTC
CTTGTCCCCCTTGCCCCGCCCCCGAGGCCGCTGGCGGACCCTCCGTGTTCCTCTTCCCCCCCAAACCCAAGGACAC
TTTAATGATCTCCCGGACCCCCGAAGTGACTTGTGTGGTGGTGGACGTGTCCCAAGAAGACCCCGAGGTGCAGTTT
AACTGGTACGTGGATGGCGTGGAGGTGCACAACGCCAAGACCAAGCCTAGGGAGGAACAGTTCAACTCCACCTACC
GGGTGGTGTCCGTGCTCACCGTGCTGCATCAAGATTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAA
GGGACTGCCCAGCTCCATCGAGAAGACCATCAGCAAGGCCAAAGGCCAGCCCCGGGAACCTCAAGTTTATACACTG
CCCCCCAGCCAAGAAGAGATGACCAAGAACCAAGTTTCTTTAACTTGTTTAGTGAAGGGCTTCTACCCTAGCGACA
TCGCTGTGGAGTGGGAGTCCAATGGCCAGCCCGAAAACAATTATAAGACCACCCCCCCCGTGCTGGACTCCGATGG
TTCTTTTTTTTTATACTCCAAGCTGACAGTGGACAAGTCTCGTTGGCAAGAAGGCAACGTGTTCTCTTGTAGCGTG
ATGCACGAGGCTTTACACAACCACTACACCCAGAAGTCTTTATCTCTGTCTTTAGGCTGATGAGAATTC(SEQ ID NO:112)。

[0163] CAAGTGCAGCTCCAGCAGAGCGGAGCTGAGCTGGTGAGACCCGGCACTAGCGTGAAGATCAGCTGTAA
GGCCAGCGGCTACGCCTTCACTAATTACTGGCTGGGCTGGATGAAGCAGAGACCCGGCCATGGACTGGAGTGGATC
GGCGACTTCTACCCAAGGACTGGCAACACTTTCTACAACGAGAACTTTAAGGGCAAGGTGACTCTGACTGCCGATA
AGTCCAGCAACACTGCCTACATGCAGCTGTCCTCTCTGACTAGCGAAGATAGCGCCGTGTATCTGTGTGCTAGGGC
TGGCACTGGCTTCGATTACTGGGGCCAAGGCACAACACTGACAGTGAGCAGCGCCAGCACCAAGGGCCCCAGCGTG
TTCCCTCTGGCTCCTTGTAGCCGGTCCACCTCCGAGTCCACAGCTGCTCTGGGCTGCCTCGTGAAGGACTACTTTC
CCGAACCCGTTACCGTGAGCTGGAATAGCGGCGCTTTAACCTCCGGAGTGCACACCTTCCCCGCTGTGCTCCAGTC
CTCCGGTTTATACTCTTTATCCTCCGTGGTGACCGTGCCTTCCTCCAGCCTCGGCACCAAGACCTACACTTGTAAC
GTGGACCACAAGCCCAGCAACACCAAGGTGGACAAGAGGGTGGAGTCCAAGTACGGACCTCCTTGTCCCCCTTGCC
CCGCCCCCGAGGCCGCTGGCGGACCCTCCGTGTTCCTCTTCCCCCCCAAACCCAAGGACACTTTAATGATCTCCCG
GACCCCCGAAGTGACTTGTGTGGTGGTGGACGTGTCCCAAGAAGACCCCGAGGTGCAGTTTAACTGGTACGTGGAT
GGCGTGGAGGTGCACAACGCCAAGACCAAGCCTAGGGAGGAACAGTTCAACTCCACCTACCGGGTGGTGTCCGTGC
TCACCGTGCTGCATCAAGATTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGGACTGCCCAGCTC
CATCGAGAAGACCATCAGCAAGGCCAAAGGCCAGCCCCGGGAACCTCAAGTTTATACACTGCCCCCCAGCCAAGAA
GAGATGACCAAGAACCAAGTTTCTTTAACTTGTTTAGTGAAGGGCTTCTACCCTAGCGACATCGCTGTGGAGTGGG
AGTCCAATGGCCAGCCCGAAAACAATTATAAGACCACCCCCCCCGTGCTGGACTCCGATGGTTCTTTTTTTTTATA
CTCCAAGCTGACAGTGGACAAGTCTCGTTGGCAAGAAGGCAACGTGTTCTCTTGTAGCGTGATGCACGAGGCTTTA
CACAACCACTACACCCAGAAGTCTTTATCTCTGTCTTTAGGCTGATGAGAATTC(SEQ ID NO:113)。

[0164] CAAGTGCAGCTGCAGCAGAGCGGCGCTGAGCTGATGAAGCCCGGCGCTTCCGTCAAGATCAGCTGCAA
GACTACTGGCTATAGGTTCAGCAGCTACTGGATCGAGTGGGTGAAGCAGAGACCCGGCCACGGACTGGAATGGCTG
GGCGAAATCCTCCCCGGAAGGGGCATCATCAACTACAATGAGAACTTTAGGGGCAAGGCCACATTCACAGCCGACA
CAAGCAGCAACACTGCCTACGTGCAGCTGAGCTCTCTGACTTCCGAGGACAGCGCCGTGTACTTCTGCGCCAGAAC

AGACCCTCCTTATTTCGGCGTGTGGGGCGCCGGAACTACTGTGACTGTGTCCAGCGCCAGCACCAAGGGCCCCAGC
GTGTTCCCTCTGGCTCCTTGTAGCCGGTCCACCTCCGAGTCCACAGCTGCTCTGGGCTGCCTCGTGAAGGACTACT
TTCCCGAACCCGTTACCGTGAGCTGGAATAGCGGCGCTTTAACCTCCGGAGTGCACACCTTCCCCGCTGTGCTCCA
GTCCTCCGGTTTATACTCTTTATCCTCCGTGGTGACCGTGCCTTCCTCCAGCCTCGGCACCAAGACCTACACTTGT
AACGTGGACCACAAGCCCAGCAACACCAAGGTGGACAAGAGGGTGGAGTCCAAGTACGGACCTCCTTGTCCCCCTT
GCCCCGCCCCCGAGGCCGCTGGCGGACCCTCCGTGTTCCTCTTCCCCCCCAAACCCAAGGACACTTTAATGATCTC
CCGGACCCCCGAAGTGACTTGTGTGGTGGTGGACGTGTCCCAAGAAGACCCCGAGGTGCAGTTTAACTGGTACGTG
GATGGCGTGGAGGTGCACAACGCCAAGACCAAGCCTAGGGAGGAACAGTTCAACTCCACCTACCGGGTGGTGTCCG
TGCTCACCGTGCTGCATCAAGATTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGGACTGCCCAG
CTCCATCGAGAAGACCATCAGCAAGGCCAAAGGCCAGCCCCGGGAACCTCAAGTTTATACACTGCCCCCCAGCCAA
GAAGAGATGACCAAGAACCAAGTTTCTTTAACTTGTTTAGTGAAGGGCTTCTACCCTAGCGACATCGCTGTGGAGT
GGGAGTCCAATGGCCAGCCCGAAAACAATTATAAGACCACCCCCCCCGTGCTGGACTCCGATGGTTCTTTTTTTTT
ATACTCCAAGCTGACAGTGGACAAGTCTCGTTGGCAAGAAGGCAACGTGTTCTCTTGTAGCGTGATGCACGAGGCT
TTACACAACCACTACACCCAGAAGTCTTTATCTCTGTCTTTAGGCTGATGAGAATTC(SEQ ID NO:114)。

[0165] CAAGTGCAGCTGCAGCAGAGCGGAGCCGAGCTGATGAAGCCCGGCGCCTCCATGAAGATCAGCTGCAA
GGCCACTGGCTACACATTCAGCACATACTGGATCGAGTGGGTCAAGCAGAGACCCGGCCACGGACTGGAGTGGATC
GGAGAGAATCTGCCCGGAAGGCACATCACTAACTACAACGAGAAGTTCAAGGGCAAGGCCACTTTCACAGCCGACA
CTAGCAGCAACACTGCCTACATGCAGCTCAGCTCTCTGACAAGCGAAGATAGCGCCGTGTACTACTGTGCTAGGGG
AAGGGGCACTTACTACTTCGATTACTGGGGCCAAGGCACTCCACTGACTGTGTCCAGCGCCAGCACCAAGGGCCCC
AGCGTGTTCCCTCTGGCTCCTTGTAGCCGGTCCACCTCCGAGTCCACAGCTGCTCTGGGCTGCCTCGTGAAGGACT
ACTTTCCCGAACCCGTTACCGTGAGCTGGAATAGCGGCGCTTTAACCTCCGGAGTGCACACCTTCCCCGCTGTGCT
CCAGTCCTCCGGTTTATACTCTTTATCCTCCGTGGTGACCGTGCCTTCCTCCAGCCTCGGCACCAAGACCTACACT
TGTAACGTGGACCACAAGCCCAGCAACACCAAGGTGGACAAGAGGGTGGAGTCCAAGTACGGACCTCCTTGTCCCC
CTTGCCCCGCCCCCGAGGCCGCTGGCGGACCCTCCGTGTTCCTCTTCCCCCCCAAACCCAAGGACACTTTAATGAT
CTCCCGGACCCCCGAAGTGACTTGTGTGGTGGTGGACGTGTCCCAAGAAGACCCCGAGGTGCAGTTTAACTGGTAC
GTGGATGGCGTGGAGGTGCACAACGCCAAGACCAAGCCTAGGGAGGAACAGTTCAACTCCACCTACCGGGTGGTGT
CCGTGCTCACCGTGCTGCATCAAGATTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGGACTGCC
CAGCTCCATCGAGAAGACCATCAGCAAGGCCAAAGGCCAGCCCCGGGAACCTCAAGTTTATACACTGCCCCCCAGC
CAAGAAGAGATGACCAAGAACCAAGTTTCTTTAACTTGTTTAGTGAAGGGCTTCTACCCTAGCGACATCGCTGTGG
AGTGGGAGTCCAATGGCCAGCCCGAAAACAATTATAAGACCACCCCCCCCGTGCTGGACTCCGATGGTTCTTTTTT
TTTATACTCCAAGCTGACAGTGGACAAGTCTCGTTGGCAAGAAGGCAACGTGTTCTCTTGTAGCGTGATGCACGAG
GCTTTACACAACCACTACACCCAGAAGTCTTTATCTCTGTCTTTAGGCTGATGAGAATTC(SEQ ID NO:115)。

[0166] GAGGTGCAGCTCCAACAGAGCGGACCAGAGCTGGTGAAACCCGGCGCCAGCATGAAGATCAGCTGTAA
GGCCTCCGGCTACAGCTTCACTGGCTACACTATGAACTGGGTGAAGCAGTCCCACGGCAAGAATCTGGAGTGGATC
GGACTGATCAACCCATACAACGGCGGCACAAACTACAACCAGAAGTTCAAGGGCAAGGCCACTCTGACAGTCGATA
AGAGCTCCAGCACTGCCTACATGGAGCTGCTGAGCCTCACTAGCGAGGACAGCGCTGTGTACTACTGTGCCTTCTC
CTACTACGGCTCTAGGGGCTTCTACTTCGATTACTGGGGCCAAGGCACAACACTGACAGTGTCCAGCGCCAGCACC
AAGGGCCCCAGCGTGTTCCCTCTGGCTCCTTGTAGCCGGTCCACCTCCGAGTCCACAGCTGCTCTGGGCTGCCTCG
TGAAGGACTACTTTCCCGAACCCGTTACCGTGAGCTGGAATAGCGGCGCTTTAACCTCCGGAGTGCACACCTTCCC

CGCTGTGCTCCAGTCCTCCGGTTTATACTCTTTATCCTCCGTGGTGACCGTGCCTTCCTCCAGCCTCGGCACCAAG
ACCTACACTTGTAACGTGGACCACAAGCCCAGCAACACCAAGGTGGACAAGAGGGTGGAGTCCAAGTACGGACCTC
CTTGTCCCCCTTGCCCCGCCCCCGAGGCCGCTGGCGGACCCTCCGTGTTCCTCTTCCCCCCCAAACCCAAGGACAC
TTTAATGATCTCCCGGACCCCCGAAGTGACTTGTGTGGTGGTGGACGTGTCCCAAGAAGACCCCGAGGTGCAGTTT
AACTGGTACGTGGATGGCGTGGAGGTGCACAACGCCAAGACCAAGCCTAGGGAGGAACAGTTCAACTCCACCTACC
GGGTGGTGTCCGTGCTCACCGTGCTGCATCAAGATTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAA
GGGACTGCCCAGCTCCATCGAGAAGACCATCAGCAAGGCCAAAGGCCAGCCCCGGGAACCTCAAGTTTATACACTG
CCCCCCAGCCAAGAAGAGATGACCAAGAACCAAGTTTCTTTAACTTGTTTAGTGAAGGGCTTCTACCCTAGCGACA
TCGCTGTGGAGTGGGAGTCCAATGGCCAGCCCGAAAACAATTATAAGACCACCCCCCCCGTGCTGGACTCCGATGG
TTCTTTTTTTTTATACTCCAAGCTGACAGTGGACAAGTCTCGTTGGCAAGAAGGCAACGTGTTCTCTTGTAGCGTG
ATGCACGAGGCTTTACACAACCACTACACCCAGAAGTCTTTATCTCTGTCTTTAGGCTGATGAGAATTC(SEQ ID
NO:116)。

[0167] GAAGTGCAGCTGCAACAGAGCGGCCCAGAGCTCGTGAAGCCCGGCGCCAGCATGAAGATCAGCTGCAA
GGCCAGCGGCTACAGCTTCACTGGCTACACAATGAACTGGGTCAAGCAGAGCCACGGAAAAAATCTGGAGTGGATC
GGACTGATCAACCCTTACAACGGCGGCACAAGGTACAATCAGAAGTTCAAGGGCAAGGCCACTCTCACTGTGGATA
AGAGCAGCAGCACTGCCTACATGGAGCTGCTGTCTCTGACAAGCGAGGATAGCGCCGTGTACTACTGCGCCAGCTC
CTCCTATAGGAACGACGGCAACTGGTACTTCGATGTGTGGGGCGCCGGCACTACTGTGACAGTGAGCTCCGCCAGC
ACCAAGGGCCCCAGCGTGTTCCCTCTGGCTCCTTGTAGCCGGTCCACCTCCGAGTCCACAGCTGCTCTGGGCTGCC
TCGTGAAGGACTACTTTCCCGAACCCGTTACCGTGAGCTGGAATAGCGGCGCTTTAACCTCCGGAGTGCACACCTT
CCCCGCTGTGCTCCAGTCCTCCGGTTTATACTCTTTATCCTCCGTGGTGACCGTGCCTTCCTCCAGCCTCGGCACC
AAGACCTACACTTGTAACGTGGACCACAAGCCCAGCAACACCAAGGTGGACAAGAGGGTGGAGTCCAAGTACGGAC
CTCCTTGTCCCCCTTGCCCCGCCCCCGAGGCCGCTGGCGGACCCTCCGTGTTCCTCTTCCCCCCCAAACCCAAGGA
CACTTTAATGATCTCCCGGACCCCCGAAGTGACTTGTGTGGTGGTGGACGTGTCCCAAGAAGACCCCGAGGTGCAG
TTTAACTGGTACGTGGATGGCGTGGAGGTGCACAACGCCAAGACCAAGCCTAGGGAGGAACAGTTCAACTCCACCT
ACCGGGTGGTGTCCGTGCTCACCGTGCTGCATCAAGATTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAA
CAAGGGACTGCCCAGCTCCATCGAGAAGACCATCAGCAAGGCCAAAGGCCAGCCCCGGGAACCTCAAGTTTATACA
CTGCCCCCCAGCCAAGAAGAGATGACCAAGAACCAAGTTTCTTTAACTTGTTTAGTGAAGGGCTTCTACCCTAGCG
ACATCGCTGTGGAGTGGGAGTCCAATGGCCAGCCCGAAAACAATTATAAGACCACCCCCCCCGTGCTGGACTCCGA
TGGTTCTTTTTTTTTTATACTCCAAGCTGACAGTGGACAAGTCTCGTTGGCAAGAAGGCAACGTGTTCTCTTGTAGC
GTGATGCACGAGGCTTTACACAACCACTACACCCAGAAGTCTTTATCTCTGTCTTTAGGCTGATGAGAATTC(SEQ
ID NO:117)。

[0168] GAAGTGCAGCTGCAGCAGAGCGGACCAGAGCTGGTCAAGCCCGGCGCCAGCATGAAGATCAGCTGTAA
GGCCAGCGGCTACAGCATCACTGGCTACACTATGAACTGGGTGAAGCAGAGCCACGGCAAGAACCTCGAGTGGATT
GGCCTCGTGAACCCATACAACGGCGGCACTTCCTACAACCAGAAGTTCAAAGGCAAGGCCACACTCACAGTCGATA
AGTCCAGCTCCACAGCCTACATGGAGCTGCTGTCTCTGAAGAGCGAGGATAGCGCTGTCTACTACTGTGCCATCAG
CAGATACGGCAGCGAGAGCTGGTACTTCGACGTGTGGGGCGCCGGCACAACAGTGACAGTGAGCAGCGCCAGCACA
AAGGGCCCCAGCGTGTTCCCTCTGGCTCCTTGTAGCCGGTCCACCTCCGAGTCCACAGCTGCTCTGGGCTGCCTCG
TGAAGGACTACTTTCCCGAACCCGTTACCGTGAGCTGGAATAGCGGCGCTTTAACCTCCGGAGTGCACACCTTCCC
CGCTGTGCTCCAGTCCTCCGGTTTATACTCTTTATCCTCCGTGGTGACCGTGCCTTCCTCCAGCCTCGGCACCAAG

ACCTACACTTGTAACGTGGACCACAAGCCCAGCAACACCAAGGTGGACAAGAGGGTGGAGTCCAAGTACGGACCTC
CTTGTCCCCCTTGCCCCGCCCCCGAGGCCGCTGGCGGACCCTCCGTGTTCCTCTTCCCCCCCAAACCCAAGGACAC
TTTAATGATCTCCCGGACCCCCGAAGTGACTTGTGTGGTGGTGGACGTGTCCCAAGAAGACCCCGAGGTGCAGTTT
AACTGGTACGTGGATGGCGTGGAGGTGCACAACGCCAAGACCAAGCCTAGGGAGGAACAGTTCAACTCCACCTACC
GGGTGGTGTCCGTGCTCACCGTGCTGCATCAAGATTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAA
GGGACTGCCCAGCTCCATCGAGAAGACCATCAGCAAGGCCAAAGGCCAGCCCCGGGAACCTCAAGTTTATACACTG
CCCCCCAGCCAAGAAGAGATGACCAAGAACCAAGTTTCTTTAACTTGTTTAGTGAAGGGCTTCTACCCTAGCGACA
TCGCTGTGGAGTGGGAGTCCAATGGCCAGCCCGAAAACAATTATAAGACCACCCCCCCCGTGCTGGACTCCGATGG
TTCTTTTTTTTTATACTCCAAGCTGACAGTGGACAAGTCTCGTTGGCAAGAAGGCAACGTGTTCTCTTGTAGCGTG
ATGCACGAGGCTTTACACAACCACTACACCCAGAAGTCTTTATCTCTGTCTTTAGGCTGATGAGAATTC(SEQ ID
NO:118)。

[0169] CAAGTGCATCTGCAGCAGAGCGGCGCTGAGCTGATGAAGCCCGGCGCCAGCGTGAAGATTAGCTGCAA
GGCCACTGGCTACACATTCAACATCTACTGGATCGACTGGGTGAAGCAGAGGCCCGGCCACGGACTGGAATGGATC
GGCGAAATTCTGCCCGGCAGCGGCAACACTCACTACAACGAGAACTTCAAGGGCAAGGCCACAATGACAGCCGACA
CAAGCTCCAACACTGCTTACATGCAGCTGACTTCTCTGACTAGCGAGGACAGCGCCGTGTACTATTGCGCTAGGAC
AGACGGAAGGGGCTACTTCGATTACTGGGGCCAAGGCACTACACTCACAGTGAGCAGCGCCAGCACTAAGGGCCCC
AGCGTGTTCCCTCTGGCTCCTTGTAGCCGGTCCACCTCCGAGTCCACAGCTGCTCTGGGCTGCCTCGTGAAGGACT
ACTTTCCCGAACCCGTTACCGTGAGCTGGAATAGCGGCGCTTTAACCTCCGGAGTGCACACCTTCCCCGCTGTGCT
CCAGTCCTCCGGTTTATACTCTTTATCCTCCGTGGTGACCGTGCCTTCCTCCAGCCTCGGCACCAAGACCTACACT
TGTAACGTGGACCACAAGCCCAGCAACACCAAGGTGGACAAGAGGGTGGAGTCCAAGTACGGACCTCCTTGTCCCC
CTTGCCCCGCCCCCGAGGCCGCTGGCGGACCCTCCGTGTTCCTCTTCCCCCCCAAACCCAAGGACACTTTAATGAT
CTCCCGGACCCCCGAAGTGACTTGTGTGGTGGTGGACGTGTCCCAAGAAGACCCCGAGGTGCAGTTTAACTGGTAC
GTGGATGGCGTGGAGGTGCACAACGCCAAGACCAAGCCTAGGGAGGAACAGTTCAACTCCACCTACCGGGTGGTGT
CCGTGCTCACCGTGCTGCATCAAGATTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGGACTGCC
CAGCTCCATCGAGAAGACCATCAGCAAGGCCAAAGGCCAGCCCCGGGAACCTCAAGTTTATACACTGCCCCCCAGC
CAAGAAGAGATGACCAAGAACCAAGTTTCTTTAACTTGTTTAGTGAAGGGCTTCTACCCTAGCGACATCGCTGTGG
AGTGGGAGTCCAATGGCCAGCCCGAAAACAATTATAAGACCACCCCCCCCGTGCTGGACTCCGATGGTTCTTTTTT
TTTATACTCCAAGCTGACAGTGGACAAGTCTCGTTGGCAAGAAGGCAACGTGTTCTCTTGTAGCGTGATGCACGAG
GCTTTACACAACCACTACACCCAGAAGTCTTTATCTCTGTCTTTAGGCTGATGAGAATTC(SEQ ID NO:119)。

[0170] CAGGTGCAGCTGCAGCAGTCCGGCGCTGAGCTCATGAAGCCCGGCGCCAGCGTGAAGATCAGCTGCAA
GGCCACTGGCTACACATTCAGCAGCTACTGGATCGAGTGGGTGAAGCAGAGACCCGGCCACGGACTGGAATGGCTG
GGAGAGTTTCTGCCTAGAAGCGGCAAGACAAACTACAACGAGGAGTTTAGGGGCAAGGCTACATTCACTGCCGACA
CATCCAGCAACACTGCCTACATGCAGCTGAGCAGCCTCACAAGCGAGGATTCCGCCGTCTACTACTGTGCTAGGAC
TGATCCTCCTTACTTCGGAGTGTGGGGCGCTGGCACAATGGTGGCTGTGAGCAGCGCCTCCACTAAGGGCCCCAGC
GTGTTCCCTCTGGCTCCTTGTAGCCGGTCCACCTCCGAGTCCACAGCTGCTCTGGGCTGCCTCGTGAAGGACTACT
TTCCCGAACCCGTTACCGTGAGCTGGAATAGCGGCGCTTTAACCTCCGGAGTGCACACCTTCCCCGCTGTGCTCCA
GTCCTCCGGTTTATACTCTTTATCCTCCGTGGTGACCGTGCCTTCCTCCAGCCTCGGCACCAAGACCTACACTTGT
AACGTGGACCACAAGCCCAGCAACACCAAGGTGGACAAGAGGGTGGAGTCCAAGTACGGACCTCCTTGTCCCCCTT
GCCCCGCCCCCGAGGCCGCTGGCGGACCCTCCGTGTTCCTCTTCCCCCCCAAACCCAAGGACACTTTAATGATCTC

CCGGACCCCCGAAGTGACTTGTGTGGTGGTGGACGTGTCCCAAGAAGACCCCGAGGTGCAGTTTAACTGGTACGTG
GATGGCGTGGAGGTGCACAACGCCAAGACCAAGCCTAGGGAGGAACAGTTCAACTCCACCTACCGGGTGGTGTCCG
TGCTCACCGTGCTGCATCAAGATTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGGACTGCCCAG
CTCCATCGAGAAGACCATCAGCAAGGCCAAAGGCCAGCCCCGGGAACCTCAAGTTTATACACTGCCCCCCAGCCAA
GAAGAGATGACCAAGAACCAAGTTTCTTTAACTTGTTTAGTGAAGGGCTTCTACCCTAGCGACATCGCTGTGGAGT
GGGAGTCCAATGGCCAGCCCGAAAACAATTATAAGACCACCCCCCCCGTGCTGGACTCCGATGGTTCTTTTTTTTT
ATACTCCAAGCTGACAGTGGACAAGTCTCGTTGGCAAGAAGGCAACGTGTTCTCTTGTAGCGTGATGCACGAGGCT
TTACACAACCACTACACCCAGAAGTCTTTATCTCTGTCTTTAGGCTGATGAGAATTC(SEQ ID NO:120)。

[0171] CAGATCGTGCTGAGCCAGAGCCCAGCTATTCTGTCCGCCAGCCCCGGCGAGAAGGTGACTATGACTTG
TAGGGCCAGCTCCAGCATCAGCTACATGCACTGGTACCAGCAGAAGCCCGGCTCCTCCCCAAAGCCTTGGATCAGC
GCCACTAGCAATCTGGCCAGCGGCGTGCCAGCCAGATTCAGCGGAAGCGGCAGCGGCACTAGCTACTCTCTGACTA
TCTCCGGCGTGGAAGCTGAGGATGCCGCCACTTACTACTGCCAGCAGTGGTCCAGCAACCCTCCTACTTTCGGCGG
CGGCACAAATCTGGAGATCAAGCGGACCGTGGCTGCCCCCTCCGTGTTCATCTTCCCCCCTTCCGACGAGCAGCTG
AAGTCCGGCACCGCTAGCGTGGTGTGTTTACTGAACAACTTCTACCCTCGTGAGGCCAAGGTGCAGTGGAAGGTGG
ACAACGCTTTACAGTCCGGCAACTCCCAAGAATCCGTGACCGAGCAAGATTCCAAGGACTCCACCTACTCTTTATC
CTCCACTTTAACTTTATCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTTGTGAGGTGACCCATCAAGGTTTA
TCCTCCCCCGTGACCAAGTCCTTCAATCGTGGCGAGTGCTGATGAGAATTC(SEQ ID NO:121)。

[0172] AGCATCGTCATGACACAAAGCCCTAAGAGCATGAGCATGAGCGTGGGCGAGAGAGTGACTCTGAGCTG
TAAGGCCAGCGAGAATGTGGGCGGCTACGTGAGCTGGTATCAGCAGAAGCCAGATCAGAGCCCAAAGCTGCTGATC
TACGGCGCCAGCAGCAGACACACTGGCGTGCCAGATAGGTTCACTGGCAGCGGCTCCGAGACAGACTTCACTCTGA
CTATCAGCAGCGTCCAAGCCGAAGATCTGGCCGCCTATCACTGCGGCCAGAACTACATCTACCCATTCACATTCGG
CGGCGGCACAAAGCTGGAGATCAAGCGGACCGTGGCTGCCCCCTCCGTGTTCATCTTCCCCCCTTCCGACGAGCAG
CTGAAGTCCGGCACCGCTAGCGTGGTGTGTTTACTGAACAACTTCTACCCTCGTGAGGCCAAGGTGCAGTGGAAGG
TGGACAACGCTTTACAGTCCGGCAACTCCCAAGAATCCGTGACCGAGCAAGATTCCAAGGACTCCACCTACTCTTT
ATCCTCCACTTTAACTTTATCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTTGTGAGGTGACCCATCAAGGT
TTATCCTCCCCCGTGACCAAGTCCTTCAATCGTGGCGAGTGCTGATGAGAATTC(SEQ ID NO:122)。

[0173] CAAGCCGTCGTGACACAAGAGTCCGCTCTGACAACTTCCCCCGGCGAGACTGTGACACTGACTTGTAG
GAGCAGCACTGGCGCCGTGACTATCAGCAACTACGCCAACTGGGTCCAAGAGAAGCCAGATCATCTGTTCACTGGA
CTGATCGGCGGCACAAATAATAGGCCTCCCGGCGTGCCAGCCAGATTTAGCGGCTCTCTGATTGGCGATAAGGCTG
CTCTGACAATCACTGGCGCCCAGACTGAGGACGAGGCCATCTACTTCTGCGTCCTCTGGTACAGCAACCACTGGGT
GTTCGGCGGCGGCACTAAGCTGACTGTGCTGCGGACCGTGGCTGCCCCCTCCGTGTTCATCTTCCCCCCTTCCGAC
GAGCAGCTGAAGTCCGGCACCGCTAGCGTGGTGTGTTTACTGAACAACTTCTACCCTCGTGAGGCCAAGGTGCAGT
GGAAGGTGGACAACGCTTTACAGTCCGGCAACTCCCAAGAATCCGTGACCGAGCAAGATTCCAAGGACTCCACCTA
CTCTTTATCCTCCACTTTAACTTTATCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTTGTGAGGTGACCCAT
CAAGGTTTATCCTCCCCCGTGACCAAGTCCTTCAATCGTGGCGAGTGCTGATGAGAATTC(SEQ ID NO:123)。

[0174] GATATCGTCATGACTCAAGCCGCCTTCAGCACTCCAGTCACTCTCGGCACAAGCGCCAGCATCAGCTG
TAGGTCCAGCCAGTCTCTGCTGCACAGCAACGGCATCACTTATCTGTACTGGTATCTGCAGAAGCCCGGCCAAAGC
CCACAGCTGCTGATCTACCAGATGAGCAATCTGGCCAGCGGCGTGCCAGATAGATTCAGCAGCAGCGGAAGCGGAA
CAGACTTCACACTGAGGATCTCTAGGGTGGAAGCCGAAGATGTGGGCGTCTATTACTGCGCCCAGAACCTCGAGTT

CCCTTTCACATTCGGCAGCGGCACTAAGCTGGAGATCAAGCGGACCGTGGCTGCCCCCTCCGTGTTCATCTTCCCC
CCTTCCGACGAGCAGCTGAAGTCCGGCACCGCTAGCGTGGTGTGTTTACTGAACAACTTCTACCCTCGTGAGGCCA
AGGTGCAGTGGAAGGTGGACAACGCTTTACAGTCCGGCAACTCCCAAGAATCCGTGACCGAGCAAGATTCCAAGGA
CTCCACCTACTCTTTATCCTCCACTTTAACTTTATCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTTGTGAG
GTGACCCATCAAGGTTTATCCTCCCCCGTGACCAAGTCCTTCAATCGTGGCGAGTGCTGATGAGAATTC(SEQ ID
NO:124)。

[0175] CAGATCGTGCTGACACAGAGCCCAGCTCTGATGAGCGCCAGCCCCGGCGAGAAGGTCACAATGACTTG
CAGCGCCACATCCAGCGTGAGCTACATCTACTGGTACCAGCAGAAGCCTAGGAGCAGCCCTAAGCCTTGGATCTAC
CTCACAAGCAATCTGGCCAGCGGAGTGCCAGCTAGGTTCAGCGGAAGCGGCAGCGGCACAAGCTACTCTCTGACAA
TCTCCAGCATGGAAGCCGAAGATGCCGCCACTTACTACTGCCAGCAGTGGAGCAGCAATCCACCTACATTCGGAGG
CGGCACTAAGCTGGAGATCAAGCGGACCGTGGCTGCCCCCTCCGTGTTCATCTTCCCCCCTTCCGACGAGCAGCTG
AAGTCCGGCACCGCTAGCGTGGTGTGTTTACTGAACAACTTCTACCCTCGTGAGGCCAAGGTGCAGTGGAAGGTGG
ACAACGCTTTACAGTCCGGCAACTCCCAAGAATCCGTGACCGAGCAAGATTCCAAGGACTCCACCTACTCTTTATC
CTCCACTTTAACTTTATCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTTGTGAGGTGACCCATCAAGGTTTA
TCCTCCCCCGTGACCAAGTCCTTCAATCGTGGCGAGTGCTGATGAGAATTC(SEQ ID NO:125)。

[0176] GATATCGTGATGACTCAGTCCCCAGCCATCATGTCCGCCAGCCCCGGCGAGAAGGTGACTATGACTTG
CTCCGCCAGCAGCAGCGTGAGCTACATGCACTGGTACCAGCAGAAGAGCGGCACATCCCCAAAGAGGTGGATCTAC
GACACAAGCAAGCTGGCCAGCGGCGTGCCAGCCAGATTCAGCGGCTCCGGCAGCGGAACAAGCTACTCTCTGACTA
TCAGCAGCATGGAGACAGAGGACGCTGCCACTTACTACTGCCAGCAGTGGAGCAGCAATCCTCCAACTTTCGGCGG
AGGCACTAAGCTGGAGCTGAAGCGGACCGTGGCTGCCCCCTCCGTGTTCATCTTCCCCCCTTCCGACGAGCAGCTG
AAGTCCGGCACCGCTAGCGTGGTGTGTTTACTGAACAACTTCTACCCTCGTGAGGCCAAGGTGCAGTGGAAGGTGG
ACAACGCTTTACAGTCCGGCAACTCCCAAGAATCCGTGACCGAGCAAGATTCCAAGGACTCCACCTACTCTTTATC
CTCCACTTTAACTTTATCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTTGTGAGGTGACCCATCAAGGTTTA
TCCTCCCCCGTGACCAAGTCCTTCAATCGTGGCGAGTGCTGATGAGAATTC(SEQ ID NO:126)。

[0177] CAGATTGTGCTGTCCCAGTCCCCAGCCATTCTGAGCGCCAGCCCCGGCGAGAAGGTGACTATGACTTG
TAGGGCCACAAGCAGCGTGAGCTACATGTACTGGTACCAGCAGAAGCCCGGCAGCAGCCCTAAGCCTTGGATCTAC
GCCACAAGCAATCTGGCCAGCGGCGTCCCAGCTAGATTTAGCGGCAGCGGATCCGGCACTAGCTATTCTCTGACTA
TCTCTAGGGTCGAGGCCGAAGATGCCGCCACATACTACTGCCAGCAGTGGTCCTCCAATCCTCCAACATTCGGCGG
CGGAACTAAGCTGGAGAAGAAGAGGACAGTGGCTGCCCCTTCCGTGTTCATCTTCCCTCCAAGCGACGAGCAGCTG
AAGTCCGGCACTGCTAGCGTGGTGTGTTTACTGAACAACTTCTACCCTCGTGAGGCCAAGGTGCAGTGGAAGGTGG
ACAACGCTTTACAGTCCGGCAACTCCCAAGAATCCGTGACCGAGCAAGATTCCAAGGACTCCACCTACTCTTTATC
CTCCACTTTAACTTTATCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTTGTGAGGTGACCCATCAAGGTTTA
TCCTCCCCCGTGACCAAGTCCTTCAATCGTGGCGAGTGCTGATGAGAATTC(SEQ ID NO:127)。

[0178] GATATCGTGCTGACTCAGAGCCCAGCCTCTCTGGTGGTGTCTCTGGGACAGAGGGCCACAATCAGCTG
TAGGACTTCCAAGAGCGTGAGCAGCTCCGCCTACAGCTACATGCACTGGTACCAGCAGAAGCCCGGCCAGCCTCCT
AAGGTGCTGATCTATCTGGCCAGCAATCTGGAGAGCGGCGTCCCAGCTAGATTCAGCGGCTCCGGAAGCGGCACTG
ACTTCACTCTGAACATCCACCCAGTGGAAGAGGAGGATGCCGCCACATACTACTGCCAGCACTCTAGGGAGCTGCC
TTTCACATTTGGCAGCGGAACTAAGCTGGAGATCAAGAGGACTGTCGCCGCCCCTAGCGTGTTCATCTTCCCTCCA
AGCGATGAGCAGCTGAAGAGCGGCACTGCTAGCGTGGTGTGTTTACTGAACAACTTCTACCCTCGTGAGGCCAAGG

TGCAGTGGAAGGTGGACAACGCTTTACAGTCCGGCAACTCCCAAGAATCCGTGACCGAGCAAGATTCCAAGGACTC
CACCTACTCTTTATCCTCCACTTTAACTTTATCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTTGTGAGGTG
ACCCATCAAGGTTTATCCTCCCCCGTGACCAAGTCCTTCAATCGTGGCGAGTGCTGATGAGAATTC(SEQ ID NO:
128)。

[0179] CAAATTGTTCTCACACAGAGCCCTCCTATCATGAGCGCCAGCCCCGGCGAGAAGGTGACTATGACTTG
TTCCGCCAGCAGCAACATCAGCTACATGCACTGGTACCAGCAGAAGTCCGGCACAAGCCCAAAGAGGTGGATCTAC
GACACAAGCAAGCTGGCCAGCGGCGTGCCAGCCAGATTTAGCGGCTCCGGAAGCGGCACTAGCTACTCTCTGACAA
TCAGCAGCATGGAAGCCGAGGACGCCGCTACATACTACTGCCAGCAGTGGAGCTCCGTCCCACTGACTTTCGGCGC
TGGCACTAAGCTGGAGATCAAGAGGACTGTGGCCGCCCCTTCCGTGTTCATCTTCCCTCCTAGCGACGAACAGCTC
AAGAGCGGCACTGCTAGCGTGGTGTGTTTACTGAACAACTTCTACCCTCGTGAGGCCAAGGTGCAGTGGAAGGTGG
ACAACGCTTTACAGTCCGGCAACTCCCAAGAATCCGTGACCGAGCAAGATTCCAAGGACTCCACCTACTCTTTATC
CTCCACTTTAACTTTATCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTTGTGAGGTGACCCATCAAGGTTTA
TCCTCCCCCGTGACCAAGTCCTTCAATCGTGGCGAGTGCTGATGAGAATTC(SEQ ID NO:129)。

[0180] CAGATCGTGCTGAGCCAGAGCCCAGCTATTCTGTCCGCCAGCCCCGGCGAGAAGGTGACTATGACTTG
TAGGGCCAGCTCCAGCATCAGCTACATGCACTGGTACCAGCAGAAGCCCGGCTCCTCCCCAAAGCCTTGGATCAGC
GCCACTAGCAATCTGGCCAGCGGCGTGCCAGCCAGATTCAGCGGAAGCGGCAGCGGCACTAGCTACTCTCTGACTA
TCTCCGGCGTGGAAGCTGAGGATGCCGCCACTTACTACTGCCAGCAGTGGTCCAGCAACCCTCCTACTTTCGGCGG
CGGCACAAATCTGGAGATCAAGGGTGGCGGTGGCTCGGGCGGTGGTGGGTCGGGTGGCGGCGGATCTGAAGTGCTG
CTGCAGCAGAGCGGACCAGAGCTGGTCAAGCCCGGCGCCTCCATGAAGATCAGCTGTAAGGCCTCCGTGTACAGCT
TCACAGCCTACACAATGAACTGGGTGAAGCAGAGCCACGGCAAGAATCTGGAGTGGATCGGACTGATCAACCCACA
CAATGGCGGCACTAGGTACAACCAGAAGTTCAAGGGCAAGGCCACACTGACTCTGGATAAGTCCAGCAGCACTGCC
TACATGGATCTGCTGTCTCTGACAAGCGAGGACAGCGCCGTCTACTATTGCGCCATCTCTAGGTACGGCAGCAGCA
GCTTCTACTTCGATGTGTGGGGCGCCGGCACAACAGTGGCTGTGAGCAGC(SEQ ID NO:130)。

[0181] GAAGTGCTGCTGCAGCAGAGCGGACCAGAGCTGGTCAAGCCCGGCGCCTCCATGAAGATCAGCTGTAA
GGCCTCCGTGTACAGCTTCACAGCCTACACAATGAACTGGGTGAAGCAGAGCCACGGCAAGAATCTGGAGTGGATC
GGACTGATCAACCCACACAATGGCGGCACTAGGTACAACCAGAAGTTCAAGGGCAAGGCCACACTGACTCTGGATA
AGTCCAGCAGCACTGCCTACATGGATCTGCTGTCTCTGACAAGCGAGGACAGCGCCGTCTACTATTGCGCCATCTC
TAGGTACGGCAGCAGCAGCTTCTACTTCGATGTGTGGGGCGCCGGCACAACAGTGGCTGTGAGCAGCGGTGGCGGT
GGCTCGGGCGGTGGTGGGTCGGGTGGCGGCGGATCTCAGATCGTGCTGAGCCAGAGCCCAGCTATTCTGTCCGCCA
GCCCCGGCGAGAAGGTGACTATGACTTGTAGGGCCAGCTCCAGCATCAGCTACATGCACTGGTACCAGCAGAAGCC
CGGCTCCTCCCCAAAGCCTTGGATCAGCGCCACTAGCAATCTGGCCAGCGGCGTGCCAGCCAGATTCAGCGGAAGC
GGCAGCGGCACTAGCTACTCTCTGACTATCTCCGGCGTGGAAGCTGAGGATGCCGCCACTTACTACTGCCAGCAGT
GGTCCAGCAACCCTCCTACTTTCGGCGGCGGCACAAATCTGGAGATCAAG(SEQ ID NO:131)。

[0182] AGCATCGTCATGACACAAAGCCCTAAGAGCATGAGCATGAGCGTGGGCGAGAGAGTGACTCTGAGCTG
TAAGGCCAGCGAGAATGTGGGCGGCTACGTGAGCTGGTATCAGCAGAAGCCAGATCAGAGCCCAAAGCTGCTGATC
TACGGCGCCAGCAGCAGACACACTGGCGTGCCAGATAGGTTCACTGGCAGCGGCTCCGAGACAGACTTCACTCTGA
CTATCAGCAGCGTCCAAGCCGAAGATCTGGCCGCCTATCACTGCGGCCAGAACTACATCTACCCATTCACATTCGG
CGGCGGCACAAAGCTGGAGATCAAGGGTGGCGGTGGCTCGGGCGGTGGTGGGTCGGGTGGCGGCGGATCTCAAGTG
CAGCTCCAGCAGAGCGGAGCTGAGCTGGTGAGACCCGGCACTAGCGTGAAGATCAGCTGTAAGGCCAGCGGCTACG

CCTTCACTAATTACTGGCTGGGCTGGATGAAGCAGAGACCCGGCCATGGACTGGAGTGGATCGGCGACTTCTACCC
AAGGACTGGCAACACTTTCTACAACGAGAACTTTAAGGGCAAGGTGACTCTGACTGCCGATAAGTCCAGCAACACT
GCCTACATGCAGCTGTCCTCTCTGACTAGCGAAGATAGCGCCGTGTATCTGTGTGCTAGGGCTGGCACTGGCTTCG
ATTACTGGGGCCAAGGCACAACACTGACAGTGAGCAGC(SEQ ID NO:132)。

[0183] CAAGTGCAGCTCCAGCAGAGCGGAGCTGAGCTGGTGAGACCCGGCACTAGCGTGAAGATCAGCTGTAA
GGCCAGCGGCTACGCCTTCACTAATTACTGGCTGGGCTGGATGAAGCAGAGACCCGGCCATGGACTGGAGTGGATC
GGCGACTTCTACCCAAGGACTGGCAACACTTTCTACAACGAGAACTTTAAGGGCAAGGTGACTCTGACTGCCGATA
AGTCCAGCAACACTGCCTACATGCAGCTGTCCTCTCTGACTAGCGAAGATAGCGCCGTGTATCTGTGTGCTAGGGC
TGGCACTGGCTTCGATTACTGGGGCCAAGGCACAACACTGACAGTGAGCAGCGGTGGCGGTGGCTCGGGCGGTGGT
GGGTCGGGTGGCGGCGGATCTAGCATCGTCATGACACAAAGCCCTAAGAGCATGAGCATGAGCGTGGGCGAGAGAG
TGACTCTGAGCTGTAAGGCCAGCGAGAATGTGGGCGGCTACGTGAGCTGGTATCAGCAGAAGCCAGATCAGAGCCC
AAAGCTGCTGATCTACGGCGCCAGCAGCAGACACACTGGCGTGCCAGATAGGTTCACTGGCAGCGGCTCCGAGACA
GACTTCACTCTGACTATCAGCAGCGTCCAAGCCGAAGATCTGGCCGCCTATCACTGCGGCCAGAACTACATCTACC
CATTCACATTCGGCGGCGGCACAAAGCTGGAGATCAAG(SEQ ID NO:133)。

[0184] CAAGCCGTCGTGACACAAGAGTCCGCTCTGACAACTTCCCCCGGCGAGACTGTGACACTGACTTGTAG
GAGCAGCACTGGCGCCGTGACTATCAGCAACTACGCCAACTGGGTCCAAGAGAAGCCAGATCATCTGTTCACTGGA
CTGATCGGCGGCACAAATAATAGGCCTCCCGGCGTGCCAGCCAGATTTAGCGGCTCTCTGATTGGCGATAAGGCTG
CTCTGACAATCACTGGCGCCCAGACTGAGGACGAGGCCATCTACTTCTGCGTCCTCTGGTACAGCAACCACTGGGT
GTTCGGCGGCGGCACTAAGCTGACTGTGCTGGGTGGCGGTGGCTCGGGCGGTGGTGGGTCGGGTGGCGGCGGATCT
CAAGTGCAGCTGCAGCAGAGCGGCGCTGAGCTGATGAAGCCCGGCGCTTCCGTCAAGATCAGCTGCAAGACTACTG
GCTATAGGTTCAGCAGCTACTGGATCGAGTGGGTGAAGCAGAGACCCGGCCACGGACTGGAATGGCTGGGCGAAAT
CCTCCCCGGAAGGGGCATCATCAACTACAATGAGAACTTTAGGGGCAAGGCCACATTCACAGCCGACACAAGCAGC
AACACTGCCTACGTGCAGCTGAGCTCTCTGACTTCCGAGGACAGCGCCGTGTACTTCTGCGCCAGAACAGACCCTC
CTTATTTCGGCGTGTGGGGCGCCGGAACTACTGTGACTGTGTCCAGC(SEQ ID NO:134)。

[0185] CAAGTGCAGCTGCAGCAGAGCGGCGCTGAGCTGATGAAGCCCGGCGCTTCCGTCAAGATCAGCTGCAA
GACTACTGGCTATAGGTTCAGCAGCTACTGGATCGAGTGGGTGAAGCAGAGACCCGGCCACGGACTGGAATGGCTG
GGCGAAATCCTCCCCGGAAGGGGCATCATCAACTACAATGAGAACTTTAGGGGCAAGGCCACATTCACAGCCGACA
CAAGCAGCAACACTGCCTACGTGCAGCTGAGCTCTCTGACTTCCGAGGACAGCGCCGTGTACTTCTGCGCCAGAAC
AGACCCTCCTTATTTCGGCGTGTGGGGCGCCGGAACTACTGTGACTGTGTCCAGCGGTGGCGGTGGCTCGGGCGGT
GGTGGGTCGGGTGGCGGCGGATCTCAAGCCGTCGTGACACAAGAGTCCGCTCTGACAACTTCCCCCGGCGAGACTG
TGACACTGACTTGTAGGAGCAGCACTGGCGCCGTGACTATCAGCAACTACGCCAACTGGGTCCAAGAGAAGCCAGA
TCATCTGTTCACTGGACTGATCGGCGGCACAAATAATAGGCCTCCCGGCGTGCCAGCCAGATTTAGCGGCTCTCTG
ATTGGCGATAAGGCTGCTCTGACAATCACTGGCGCCCAGACTGAGGACGAGGCCATCTACTTCTGCGTCCTCTGGT
ACAGCAACCACTGGGTGTTCGGCGGCGGCACTAAGCTGACTGTGCTG(SEQ ID NO:135)。

[0186] GATATCGTCATGACTCAAGCCGCCTTCAGCACTCCAGTCACTCTCGGCACAAGCGCCAGCATCAGCTG
TAGGTCCAGCCAGTCTCTGCTGCACAGCAACGGCATCACTTATCTGTACTGGTATCTGCAGAAGCCCGGCCAAAGC
CCACAGCTGCTGATCTACCAGATGAGCAATCTGGCCAGCGGCGTGCCAGATAGATTCAGCAGCAGCGGAAGCGGAA
CAGACTTCACACTGAGGATCTCTAGGGTGGAAGCCGAAGATGTGGGCGTCTATTACTGCGCCCAGAACCTCGAGTT
CCCTTTCACATTCGGCAGCGGCACTAAGCTGGAGATCAAGGGTGGCGGTGGCTCGGGCGGTGGTGGGTCGGGTGGC

GGCGGATCTCAAGTGCAGCTGCAGCAGAGCGGAGCCGAGCTGATGAAGCCCGGCGCCTCCATGAAGATCAGCTGCA
AGGCCACTGGCTACACATTCAGCACATACTGGATCGAGTGGGTCAAGCAGAGACCCGGCCACGGACTGGAGTGGAT
CGGAGAGAATCTGCCCGGAAGGCACATCACTAACTACAACGAGAAGTTCAAGGGCAAGGCCACTTTCACAGCCGAC
ACTAGCAGCAACACTGCCTACATGCAGCTCAGCTCTCTGACAAGCGAAGATAGCGCCGTGTACTACTGTGCTAGGG
GAAGGGGCACTTACTACTTCGATTACTGGGGCCAAGGCACTCCACTGACTGTGTCCAGC(SEQ IDNO:136)。

[0187] CAAGTGCAGCTGCAGCAGAGCGGAGCCGAGCTGATGAAGCCCGGCGCCTCCATGAAGATCAGCTGCAA
GGCCACTGGCTACACATTCAGCACATACTGGATCGAGTGGGTCAAGCAGAGACCCGGCCACGGACTGGAGTGGATC
GGAGAGAATCTGCCCGGAAGGCACATCACTAACTACAACGAGAAGTTCAAGGGCAAGGCCACTTTCACAGCCGACA
CTAGCAGCAACACTGCCTACATGCAGCTCAGCTCTCTGACAAGCGAAGATAGCGCCGTGTACTACTGTGCTAGGGG
AAGGGGCACTTACTACTTCGATTACTGGGGCCAAGGCACTCCACTGACTGTGTCCAGCGGTGGCGGTGGCTCGGGC
GGTGGTGGGTCGGGTGGCGGCGGATCTGATATCGTCATGACTCAAGCCGCCTTCAGCACTCCAGTCACTCTCGGCA
CAAGCGCCAGCATCAGCTGTAGGTCCAGCCAGTCTCTGCTGCACAGCAACGGCATCACTTATCTGTACTGGTATCT
GCAGAAGCCCGGCCAAAGCCCACAGCTGCTGATCTACCAGATGAGCAATCTGGCCAGCGGCGTGCCAGATAGATTC
AGCAGCAGCGGAAGCGGAACAGACTTCACACTGAGGATCTCTAGGGTGGAAGCCGAAGATGTGGGCGTCTATTACT
GCGCCCAGAACCTCGAGTTCCCTTTCACATTCGGCAGCGGCACTAAGCTGGAGATCAAG(SEQ IDNO:137)。

[0188] CAGATCGTGCTGACACAGAGCCCAGCTCTGATGAGCGCCAGCCCCGGCGAGAAGGTCACAATGACTTG
CAGCGCCACATCCAGCGTGAGCTACATCTACTGGTACCAGCAGAAGCCTAGGAGCAGCCCTAAGCCTTGGATCTAC
CTCACAAGCAATCTGGCCAGCGGAGTGCCAGCTAGGTTCAGCGGAAGCGGCAGCGGCACAAGCTACTCTCTGACAA
TCTCCAGCATGGAAGCCGAAGATGCCGCCACTTACTACTGCCAGCAGTGGAGCAGCAATCCACCTACATTCGGAGG
CGGCACTAAGCTGGAGATCAAGGGTGGCGGTGGCTCGGGCGGTGGTGGGTCGGGTGGCGGCGGATCTGAGGTGCAG
CTCCAACAGAGCGGACCAGAGCTGGTGAAACCCGGCGCCAGCATGAAGATCAGCTGTAAGGCCTCCGGCTACAGCT
TCACTGGCTACACTATGAACTGGGTGAAGCAGTCCCACGGCAAGAATCTGGAGTGGATCGGACTGATCAACCCATA
CAACGGCGGCACAAACTACAACCAGAAGTTCAAGGGCAAGGCCACTCTGACAGTCGATAAGAGCTCCAGCACTGCC
TACATGGAGCTGCTGAGCCTCACTAGCGAGGACAGCGCTGTGTACTACTGTGCCTTCTCCTACTACGGCTCTAGGG
GCTTCTACTTCGATTACTGGGGCCAAGGCACAACACTGACAGTGTCCAGC(SEQ ID NO:138)。

[0189] GAGGTGCAGCTCCAACAGAGCGGACCAGAGCTGGTGAAACCCGGCGCCAGCATGAAGATCAGCTGTAA
GGCCTCCGGCTACAGCTTCACTGGCTACACTATGAACTGGGTGAAGCAGTCCCACGGCAAGAATCTGGAGTGGATC
GGACTGATCAACCCATACAACGGCGGCACAAACTACAACCAGAAGTTCAAGGGCAAGGCCACTCTGACAGTCGATA
AGAGCTCCAGCACTGCCTACATGGAGCTGCTGAGCCTCACTAGCGAGGACAGCGCTGTGTACTACTGTGCCTTCTC
CTACTACGGCTCTAGGGGCTTCTACTTCGATTACTGGGGCCAAGGCACAACACTGACAGTGTCCAGCGGTGGCGGT
GGCTCGGGCGGTGGTGGGTCGGGTGGCGGCGGATCTCAGATCGTGCTGACACAGAGCCCAGCTCTGATGAGCGCCA
GCCCCGGCGAGAAGGTCACAATGACTTGCAGCGCCACATCCAGCGTGAGCTACATCTACTGGTACCAGCAGAAGCC
TAGGAGCAGCCCTAAGCCTTGGATCTACCTCACAAGCAATCTGGCCAGCGGAGTGCCAGCTAGGTTCAGCGGAAGC
GGCAGCGGCACAAGCTACTCTCTGACAATCTCCAGCATGGAAGCCGAAGATGCCGCCACTTACTACTGCCAGCAGT
GGAGCAGCAATCCACCTACATTCGGAGGCGGCACTAAGCTGGAGATCAAG(SEQ ID NO:139)。

[0190] GATATCGTGATGACTCAGTCCCCAGCCATCATGTCCGCCAGCCCCGGCGAGAAGGTGACTATGACTTG
CTCCGCCAGCAGCAGCGTGAGCTACATGCACTGGTACCAGCAGAAGAGCGGCACATCCCCAAAGAGGTGGATCTAC
GACACAAGCAAGCTGGCCAGCGGCGTGCCAGCCAGATTCAGCGGCTCCGGCAGCGGAACAAGCTACTCTCTGACTA
TCAGCAGCATGGAGACAGAGGACGCTGCCACTTACTACTGCCAGCAGTGGAGCAGCAATCCTCCAACTTTCGGCGG

AGGCACTAAGCTGGAGCTGAAGGGTGGCGGTGGCTCGGGCGGTGGTGGGTCGGGTGGCGGCGGATCTGAAGTGCAG
CTGCAACAGAGCGGCCCAGAGCTCGTGAAGCCCGGCGCCAGCATGAAGATCAGCTGCAAGGCCAGCGGCTACAGCT
TCACTGGCTACACAATGAACTGGGTCAAGCAGAGCCACGGAAAAAATCTGGAGTGGATCGGACTGATCAACCCTTA
CAACGGCGGCACAAGGTACAATCAGAAGTTCAAGGGCAAGGCCACTCTCACTGTGGATAAGAGCAGCAGCACTGCC
TACATGGAGCTGCTGTCTCTGACAAGCGAGGATAGCGCCGTGTACTACTGCGCCAGCTCCTCCTATAGGAACGACG
GCAACTGGTACTTCGATGTGTGGGGCGCCGGCACTACTGTGACAGTGAGCTCC(SEQ ID NO:140)。

[0191] GAAGTGCAGCTGCAACAGAGCGGCCCAGAGCTCGTGAAGCCCGGCGCCAGCATGAAGATCAGCTGCAA
GGCCAGCGGCTACAGCTTCACTGGCTACACAATGAACTGGGTCAAGCAGAGCCACGGAAAAAATCTGGAGTGGATC
GGACTGATCAACCCTTACAACGGCGGCACAAGGTACAATCAGAAGTTCAAGGGCAAGGCCACTCTCACTGTGGATA
AGAGCAGCAGCACTGCCTACATGGAGCTGCTGTCTCTGACAAGCGAGGATAGCGCCGTGTACTACTGCGCCAGCTC
CTCCTATAGGAACGACGGCAACTGGTACTTCGATGTGTGGGGCGCCGGCACTACTGTGACAGTGAGCTCCGGTGGC
GGTGGCTCGGGCGGTGGTGGGTCGGGTGGCGGCGGATCTGATATCGTGATGACTCAGTCCCCAGCCATCATGTCCG
CCAGCCCCGGCGAGAAGGTGACTATGACTTGCTCCGCCAGCAGCAGCGTGAGCTACATGCACTGGTACCAGCAGAA
GAGCGGCACATCCCCAAAGAGGTGGATCTACGACACAAGCAAGCTGGCCAGCGGCGTGCCAGCCAGATTCAGCGGC
TCCGGCAGCGGAACAAGCTACTCTCTGACTATCAGCAGCATGGAGACAGAGGACGCTGCCACTTACTACTGCCAGC
AGTGGAGCAGCAATCCTCCAACTTTCGGCGGAGGCACTAAGCTGGAGCTGAAG(SEQ ID NO:141)。

[0192] CAGATTGTGCTGTCCCAGTCCCCAGCCATTCTGAGCGCCAGCCCCGGCGAGAAGGTGACTATGACTTG
TAGGGCCACAAGCAGCGTGAGCTACATGTACTGGTACCAGCAGAAGCCCGGCAGCAGCCCTAAGCCTTGGATCTAC
GCCACAAGCAATCTGGCCAGCGGCGTCCCAGCTAGATTTAGCGGCAGCGGATCCGGCACTAGCTATTCTCTGACTA
TCTCTAGGGTCGAGGCCGAAGATGCCGCCACATACTACTGCCAGCAGTGGTCCTCCAATCCTCCAACATTCGGCGG
CGGAACTAAGCTGGAGAAGAAGGGTGGCGGTGGCTCGGGCGGTGGTGGGTCGGGTGGCGGCGGATCTGAAGTGCAG
CTGCAGCAGAGCGGACCAGAGCTGGTCAAGCCCGGCGCCAGCATGAAGATCAGCTGTAAGGCCAGCGGCTACAGCA
TCACTGGCTACACTATGAACTGGGTGAAGCAGAGCCACGGCAAGAACCTCGAGTGGATTGGCCTCGTGAACCCATA
CAACGGCGGCACTTCCTACAACCAGAAGTTCAAAGGCAAGGCCACACTCACAGTCGATAAGTCCAGCTCCACAGCC
TACATGGAGCTGCTGTCTCTGAAGAGCGAGGATAGCGCTGTCTACTACTGTGCCATCAGCAGATACGGCAGCGAGA
GCTGGTACTTCGACGTGTGGGGCGCCGGCACAACAGTGACAGTGAGCAGC(SEQ ID NO:142)。

[0193] GAAGTGCAGCTGCAGCAGAGCGGACCAGAGCTGGTCAAGCCCGGCGCCAGCATGAAGATCAGCTGTAA
GGCCAGCGGCTACAGCATCACTGGCTACACTATGAACTGGGTGAAGCAGAGCCACGGCAAGAACCTCGAGTGGATT
GGCCTCGTGAACCCATACAACGGCGGCACTTCCTACAACCAGAAGTTCAAAGGCAAGGCCACACTCACAGTCGATA
AGTCCAGCTCCACAGCCTACATGGAGCTGCTGTCTCTGAAGAGCGAGGATAGCGCTGTCTACTACTGTGCCATCAG
CAGATACGGCAGCGAGAGCTGGTACTTCGACGTGTGGGGCGCCGGCACAACAGTGACAGTGAGCAGCGGTGGCGGT
GGCTCGGGCGGTGGTGGGTCGGGTGGCGGCGGATCTCAGATTGTGCTGTCCCAGTCCCCAGCCATTCTGAGCGCCA
GCCCCGGCGAGAAGGTGACTATGACTTGTAGGGCCACAAGCAGCGTGAGCTACATGTACTGGTACCAGCAGAAGCC
CGGCAGCAGCCCTAAGCCTTGGATCTACGCCACAAGCAATCTGGCCAGCGGCGTCCCAGCTAGATTTAGCGGCAGC
GGATCCGGCACTAGCTATTCTCTGACTATCTCTAGGGTCGAGGCCGAAGATGCCGCCACATACTACTGCCAGCAGT
GGTCCTCCAATCCTCCAACATTCGGCGGCGGAACTAAGCTGGAGAAGAAG(SEQ ID NO:143)。

[0194] GATATCGTGCTGACTCAGAGCCCAGCCTCTCTGGTGGTGTCTCTGGGACAGAGGGCCACAATCAGCTG
TAGGACTTCCAAGAGCGTGAGCAGCTCCGCCTACAGCTACATGCACTGGTACCAGCAGAAGCCCGGCCAGCCTCCT
AAGGTGCTGATCTATCTGGCCAGCAATCTGGAGAGCGGCGTCCCAGCTAGATTCAGCGGCTCCGGAAGCGGCACTG

ACTTCACTCTGAACATCCACCCAGTGGAAGAGGAGGATGCCGCCACATACTACTGCCAGCACTCTAGGGAGCTGCC
TTTCACATTTGGCAGCGGAACTAAGCTGGAGATCAAGGGTGGCGGTGGCTCGGGCGGTGGTGGGTCGGGTGGCGGC
GGATCTCAAGTGCATCTGCAGCAGAGCGGCGCTGAGCTGATGAAGCCCGGCGCCAGCGTGAAGATTAGCTGCAAGG
CCACTGGCTACACATTCAACATCTACTGGATCGACTGGGTGAAGCAGAGGCCCGGCCACGGACTGGAATGGATCGG
CGAAATTCTGCCCGGCAGCGGCAACACTCACTACAACGAGAACTTCAAGGGCAAGGCCACAATGACAGCCGACACA
AGCTCCAACACTGCTTACATGCAGCTGACTTCTCTGACTAGCGAGGACAGCGCCGTGTACTATTGCGCTAGGACAG
ACGGAAGGGGCTACTTCGATTACTGGGGCCAAGGCACTACACTCACAGTGAGCAGC(SEQ ID NO:144)。

[0195] CAAGTGCATCTGCAGCAGAGCGGCGCTGAGCTGATGAAGCCCGGCGCCAGCGTGAAGATTAGCTGCAA
GGCCACTGGCTACACATTCAACATCTACTGGATCGACTGGGTGAAGCAGAGGCCCGGCCACGGACTGGAATGGATC
GGCGAAATTCTGCCCGGCAGCGGCAACACTCACTACAACGAGAACTTCAAGGGCAAGGCCACAATGACAGCCGACA
CAAGCTCCAACACTGCTTACATGCAGCTGACTTCTCTGACTAGCGAGGACAGCGCCGTGTACTATTGCGCTAGGAC
AGACGGAAGGGGCTACTTCGATTACTGGGGCCAAGGCACTACACTCACAGTGAGCAGCGGTGGCGGTGGCTCGGGC
GGTGGTGGGTCGGGTGGCGGCGGATCTGATATCGTGCTGACTCAGAGCCCAGCCTCTCTGGTGGTGTCTCTGGGAC
AGAGGGCCACAATCAGCTGTAGGACTTCCAAGAGCGTGAGCAGCTCCGCCTACAGCTACATGCACTGGTACCAGCA
GAAGCCCGGCCAGCCTCCTAAGGTGCTGATCTATCTGGCCAGCAATCTGGAGAGCGGCGTCCCAGCTAGATTCAGC
GGCTCCGGAAGCGGCACTGACTTCACTCTGAACATCCACCCAGTGGAAGAGGAGGATGCCGCCACATACTACTGCC
AGCACTCTAGGGAGCTGCCTTTCACATTTGGCAGCGGAACTAAGCTGGAGATCAAG(SEQ ID NO:145)。

[0196] CAAATTGTTCTCACACAGAGCCCTCCTATCATGAGCGCCAGCCCCGGCGAGAAGGTGACTATGACTTG
TTCCGCCAGCAGCAACATCAGCTACATGCACTGGTACCAGCAGAAGTCCGGCACAAGCCCAAAGAGGTGGATCTAC
GACACAAGCAAGCTGGCCAGCGGCGTGCCAGCCAGATTTAGCGGCTCCGGAAGCGGCACTAGCTACTCTCTGACAA
TCAGCAGCATGGAAGCCGAGGACGCCGCTACATACTACTGCCAGCAGTGGAGCTCCGTCCCACTGACTTTCGGCGC
TGGCACTAAGCTGGAGATCAAGGGTGGCGGTGGCTCGGGCGGTGGTGGGTCGGGTGGCGGCGGATCTCAGGTTCAG
CTGCAGCAGTCCGGCGCTGAGCTCATGAAGCCCGGCGCCAGCGTGAAGATCAGCTGCAAGGCCACTGGCTACACAT
TCAGCAGCTACTGGATCGAGTGGGTGAAGCAGAGACCCGGCCACGGACTGGAATGGCTGGGAGAGTTTCTGCCTAG
AAGCGGCAAGACAAACTACAACGAGGAGTTTAGGGGCAAGGCTACATTCACTGCCGACACATCCAGCAACACTGCC
TACATGCAGCTGAGCAGCCTCACAAGCGAGGATTCCGCCGTCTACTACTGTGCTAGGACTGATCCTCCTTACTTCG
GAGTGTGGGGCGCTGGCACAATGGTGGCTGTGAGCAGC(SEQ ID NO:146)。

[0197] CAGGTTCAGCTGCAGCAGTCCGGCGCTGAGCTCATGAAGCCCGGCGCCAGCGTGAAGATCAGCTGCAA
GGCCACTGGCTACACATTCAGCAGCTACTGGATCGAGTGGGTGAAGCAGAGACCCGGCCACGGACTGGAATGGCTG
GGAGAGTTTCTGCCTAGAAGCGGCAAGACAAACTACAACGAGGAGTTTAGGGGCAAGGCTACATTCACTGCCGACA
CATCCAGCAACACTGCCTACATGCAGCTGAGCAGCCTCACAAGCGAGGATTCCGCCGTCTACTACTGTGCTAGGAC
TGATCCTCCTTACTTCGGAGTGTGGGGCGCTGGCACAATGGTGGCTGTGAGCAGCGGTGGCGGTGGCTCGGGCGGT
GGTGGGTCGGGTGGCGGCGGATCTCAAATTGTTCTCACACAGAGCCCTCCTATCATGAGCGCCAGCCCCGGCGAGA
AGGTGACTATGACTTGTTCCGCCAGCAGCAACATCAGCTACATGCACTGGTACCAGCAGAAGTCCGGCACAAGCCC
AAAGAGGTGGATCTACGACACAAGCAAGCTGGCCAGCGGCGTGCCAGCCAGATTTAGCGGCTCCGGAAGCGGCACT
AGCTACTCTCTGACAATCAGCAGCATGGAAGCCGAGGACGCCGCTACATACTACTGCCAGCAGTGGAGCTCCGTCC
CACTGACTTTCGGCGCTGGCACTAAGCTGGAGATCAAG(SEQ ID NO:147)。

[0198] 其中,在本申请中,上述SEQ ID NO:112和121所示核苷酸序列分别编码20C8嵌合抗体的重链和轻链,上述SEQ ID NO:113和122所示核苷酸序列分别编码23E12嵌合抗体的

重链和轻链，上述SEQ ID NO:114和123所示核苷酸序列分别编码27H3嵌合抗体的重链和轻链，上述SEQ ID NO:115和124所示核苷酸序列分别编码21E5嵌合抗体的重链和轻链，上述SEQ ID NO:116和125所示核苷酸序列分别编码2A5嵌合抗体的重链和轻链，上述SEQ ID NO:117和SEQ ID NO:126所示核苷酸序列分别编码4H4嵌合抗体的重链和轻链，上述SEQ ID NO:118和SEQ ID NO:127所示核苷酸序列分别编码22D12嵌合抗体的重链和轻链，上述SEQ ID NO:119和SEQ ID NO:128所示核苷酸序列分别编码1B9嵌合抗体的重链和轻链，上述SEQ ID NO:120和SEQ ID NO:129所示核苷酸序列分别编码15D4嵌合抗体的重链和轻链。SEQ ID NO:130、132、134、136、138、140、142、144、146所示核苷酸序列分别编码SEQ ID NO:94、96、98、100、102、104、106、108、110所示氨基酸序列的单链抗体，SEQ ID NO:131、133、135、137、139、141、143、145、147所示核苷酸序列分别编码SEQ ID NO:95、97、99、101、103、105、107、109、111所示氨基酸序列的单链抗体。

[0199] 在本发明的第三方面，本发明提出了一种表达载体。根据本发明的实施例，所述表达载体携带前面所述的核酸分子。根据本发明实施例的表达载体导入合适的受体细胞后，可在调控系统的介导下，有效实现前面所述的特异性识别TrkA的抗体或其抗原结合片段表达，进而实现所述抗体或抗原结合片段的体外大量获得。

[0200] 根据本发明的实施例，上述表达载体还可以进一步包括如下附加技术特征至少之一：

[0201] 根据本发明的实施例，所述表达载体为真核表达载体。进而实现前面所述的特异性识别TrkA的抗体或其抗原结合片段在真核细胞中的表达，如CHO细胞。

[0202] 在本发明的第四方面，本发明提出了一种重组细胞。根据本发明的实施例，所述重组细胞携带前面所述的核酸分子，或者表达前面所述的抗体或其抗原结合片段。根据本发明实施例的重组细胞可用于前面所述的特异性识别TrkA的抗体或其抗原结合片段体外表达和大量获得。

[0203] 根据本发明的实施例，上述重组细胞还可以进一步包括如下附加技术特征至少之一：

[0204] 根据本发明的实施例，所述重组细胞是通过将前面所述的表达载体引入至宿主细胞中而获得的。

[0205] 根据本发明的实施例，通过电转导的方法将所述表达载体引入所述宿主细胞中。

[0206] 根据本发明的实施例，所述重组细胞为真核细胞。

[0207] 根据本发明的实施例，所述重组细胞为哺乳动物细胞。

[0208] 在本发明的第五方面，本发明提出了一种药物组合物。根据本发明的实施例，所述药物组合物含有前面所述的抗体，前面所述的核酸分子，前面所述的表达载体或前面所述的重组细胞。根据本发明实施例的药物组合物中所包含的抗体或表达的抗体不仅能够特异性的靶向结合TrkA受体，阻断NGF和TrkA结合，有效的抑制疼痛，而且具有免疫原性低，基本没有抗体依赖的细胞介导的细胞毒性作用(ADCC)的特点。

[0209] 在本发明的第六方面，本发明提出了前面所述的抗体、前面所述的核酸分子、前面所述的表达载体或前面所述的重组细胞、前面所述的药物组合物在制备药物中的用途，所述药物用于治疗或者预防疼痛、癌症、炎症或炎性疾病、神经变性疾病、舍格伦氏综合征、子宫内膜异位、糖尿病性周围神经病变、前列腺炎、盆腔疼痛综合征、与骨重塑调节失衡相关

的疾病以及由结缔组织生长因子异常信号传导引起的疾病。

[0210] 根据本发明的实施例，上述用途还可以进一步包括如下附加技术特征至少之一：

[0211] 根据本发明的实施例，所述药物用于治疗或预防神经性疼痛、炎性疼痛、与癌症有关的疼痛、与骨折有关的疼痛、与手术有关的疼痛、炎性肺病、间质性膀胱炎、痛性膀胱综合征、炎性肠疾病、炎性皮肤病、雷诺氏综合征、特发性肺纤维化、瘢痕(肥大型、瘢痕瘤型和其他形式)、硬化、心内膜心肌纤维化、心房纤维化、骨髓纤维化、进行性块状纤维化(肺)、肾源性系统性纤维化、硬皮病、系统性硬化、关节纤维化、眼部纤维化、非小细胞肺癌、乳头状甲状腺癌、多形性成胶质细胞瘤、结肠直肠癌、黑色素瘤、胆管癌或肉瘤、急性骨髓性白血病、大细胞神经内分泌癌、成神经细胞瘤、前列腺癌、成神经细胞瘤、胰腺癌、黑色素瘤、头颈鳞状细胞癌或胃癌。

[0212] 在本发明的第七方面，本发明提出了一种检测TrkA的试剂盒。根据本发明的实施例，所述试剂盒包括前面任一所述的抗体。前面所述的TrkA抗体能够特异性靶向结合TrkA，根据本发明实施例的试剂盒可以实现TrkA的特异性检测，如当抗体结合有荧光基团时，可以采用荧光检测装置实现对TrkA的定位或实时检测。

[0213] 在本发明的第八方面，本发明提出了前面所述的抗体、前面所述的核酸分子、前面所述的表达载体或前面所述的重组细胞在制备试剂盒中的用途，所述试剂盒用于检测TrkA或者诊断TrkA相关的疾病。

[0214] 在本发明的第九方面，本发明提出了一种小鼠B细胞。根据本发明的实施例，所述B细胞的基因组中携带编码恒定区的序列，所述恒定区序列与人IgG4的恒定区相比，存在S108P,F114A,L115A,R289K突变以及327K缺失突变。其中，人IgG4的恒定区具有SEQ ID NO:148所示的氨基酸序列。

[0215] ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK(SEQ ID NO:148)。

[0216] 根据本发明实施例的小鼠B细胞可用于分泌鼠源抗体，所分泌的鼠源抗体在人体内的免疫原性进一步降低，稳定性得到显著提高，在体内的半衰期显著延长。

[0217] 在本发明的第十方面，本发明提出了前面所述的小鼠B细胞在制备单克隆抗体中的用途。

附图说明

[0218] 图1是根据本发明实施例的通过ELISA方法筛选得到的9株能产生分子水平阻断NGF和TrkA结合的抗TrkA单克隆抗体的单克隆杂交瘤细胞株的实验结果图；

[0219] 图2是根据本发明实施例的流式筛选得到的9株能产生细胞水平阻断NGF和TrkA结合的抗TrkA单克隆抗体的单克隆杂交瘤细胞株的实验结果图，%parent(百分比)；

[0220] 图3是根据本发明实施例的ELISA方法检测各阳性克隆上清产生的单克隆抗体与Mouse-TrKA受体的结合情况的实验结果图；

[0221] 图4是根据本发明实施例的应用HEK-293T-TrkA细胞模型评价受试抗体的阻断活

性的结果图，%parent(百分比)；

[0222] 图5是根据本发明实施例的Tanezumab验证NIH-3T3-TrkA细胞模型是否可以用于评价抑制NGF-TrkA通路药物(受试药物)的体外活性的结果图；

[0223] 图6是根据本发明实施例的通过AlphaLISA的方法检测受试抗体及阳性抗体MNAC13作用下，TrkA蛋白的酪氨酸磷酸化水平的实验结果图，p-TrkA level(TrkA蛋白的酪氨酸磷酸化水平)；

[0224] 图7是根据本发明实施例的通过流式细胞术检测受试抗体亲和力EC_{50}的结果图；

[0225] 图8A～8G是根据本发明实施例的ELISA方法评价受试抗体与靶标TrKA结合的特异性的结果图；

[0226] 图9是根据本发明实施例的应用ELISA方法检测受试抗体对Mouse-TrKA蛋白的结合能力的结果图；

[0227] 图10是根据本发明实施例的应用流式细胞术检测受试抗体与Mouse-TrKA蛋白的结合能力的结果图；

[0228] 图11是根据本发明实施例的应用ELISA方法检测受试抗体对Mouse-NGF和Mouse-TrKA结合的抑制作用的结果图；

[0229] 图12是根据本发明实施例的应用流式细胞术检测受试抗体对Mouse-NGF和Mouse-TrKA结合的抑制作用的结果图；

[0230] 图13是根据本发明实施例的应用ELISA方法检测受试抗体对Human-NGF和Human-TrKA结合的抑制作用的结果图；

[0231] 图14是根据本发明实施例的应用福尔马林致痛模型评价受试抗体的体内镇痛活性的结果图；以及

[0232] 图15是根据本发明实施例的应用完全弗氏佐剂诱导炎疼痛模型评价受试抗体的体内镇痛活性的结果图。

具体实施方式

[0233] 下面详细描述本发明的实施例，所述实施例的示例在附图中示出，其中自始至终相同或类似的标号表示相同或类似的元件或具有相同或类似功能的元件。下面通过参考附图描述的实施例是示例性的，旨在用于解释本发明，而不能理解为对本发明的限制。

[0234] 在对本发明描述的过程中，对于本文中有关的术语进行了解释和说明，这些解释和说明仅仅是为了方便对于方案的理解，并不能看做是对本发明保护方案的限制。

[0235] 抗体

[0236] 本文中，术语“抗体”是能够与特异性抗原结合的免疫球蛋白分子。包括两条分子量较轻的轻链和两条分子量较重的重链，重链(H链)和轻链(L链)由二硫键连接形成一个四肽链分子。其中，肽链的氨基端(N端)氨基酸序列变化很大，称为可变区(V区)，羧基端(C端)相对稳定，变化很小，称为恒定区(C区)。L链和H链的V区分别称为VL和VH。

[0237] 在可变区中某些区域氨基酸组成和排列顺序具有更高的变化程度，称为高变区(Hypervariable region，HVR)，高变区为抗原和抗体结合的位置，因此也称为决定簇互补区(complementarity-determining region，CDR)。重链可变区和轻链可变区上均有三个CDR区。

[0238] 本发明利用TrkA胞外段，通过免疫获得了高特异性的高亲和力的抗TrkA的Fab(antigen-binding fragment)抗体片段。利用该抗体片段能够与TrkA抗原特异性结合，从而可以靶向性治疗疼痛或肿瘤等疾病。

[0239] 在一些实施方案中，本发明提供了一种能够特异性识别TrkA的抗体或者抗原结合片段，所述抗体含有选自下列至少之一的CDR序列或与其具有至少95％同一性的氨基酸序列：重链可变区CDR序列：SEQ ID NO:1～27，轻链可变区CDR序列：SEQ IN NO:28～54。在另一些实施方案中，本发明所提供的抗体或者抗原结合片段与上述重链和轻链相比，具有保守氨基酸取代。“抗原结合片段”是指保持特异性结合抗原(ROR2)能力的抗体片段。“保守氨基酸取代”指的是氨基酸被另一氨基酸发生生物学上、化学上或者结构上相似的残基所取代。生物学上相似的指的是该取代不破坏TrkA抗体或者与TrkA抗原的生物学活性。结构上相似指的是氨基酸具有相似长度的侧链，如丙氨酸、甘氨酸或丝氨酸，或具有相似大小的侧链。化学相似性指的是氨基酸具有相同的荷电或者都是亲水或者疏水的。例如疏水残基异亮氨酸、缬氨酸、亮氨酸或者甲硫氨酸相互取代。或者极性氨基酸相互取代，例如用精氨酸取代赖氨酸、谷氨酸取代天冬氨酸、谷氨酰胺取代天冬酰胺，丝氨酸取代苏氨酸等等。

[0240] 在一些实施方案中，本发明提供了一种抗体或抗原结合片段，所述抗体或抗原结合片段具有SEQ ID NO:55～63任一项所示氨基酸序列的重链可变区和具有如SEQ ID NO:64～72任一项所示氨基酸序列的轻链可变区。发明人通过抗体序列比对数据库(NCBI、IMGT)可得到上述抗重链可变区序列的CDR区(如SEQ ID NO:1～27所示)和轻链可变区序列的CDR区(如SEQ ID NO:28～54所示)。在另一些实施方案中，所述抗体或抗原结合片段的重链可变区序列与SEQ ID NO:55～63所示氨基酸序列相比，具有保守氨基酸取代。在一些实施方案中，所述抗体或抗原结合片段的轻链可变区序列与SEQ ID NO:64～72任一项所示氨基酸序列相比，具有保守氨基酸取代。当然，这些保守氨基酸取代不会对抗体或者抗原结合片段的生物学功能带来改变。在一些具体方式中，这些保守氨基酸取代可以发生在重链可变区和轻链可变区中除了CDR区之外的氨基酸上。

[0241] 在一些优选方案中，本发明提供了一种抗TrkA抗体，该抗体具有SEQ ID NO:76～84任一项所示氨基酸序列的重链和具有SEQ ID NO:85～93任一项所示氨基酸序列的轻链。

[0242] 在一些优选方案中，本发明提供了一种抗TrkA单链抗体，该抗体具有SEQ ID NO:94～111所示的氨基酸序列。

[0243] 核酸分子、表达载体、重组细胞

[0244] 在制备或者获取这些抗体的过程中，可以利用表达这些抗体的核酸分子，与不同的载体连接，然后在不同细胞中表达，来获得相应抗体。

[0245] 为此，本发明还提供了一种分离的核酸分子，所述核酸分子编码上述所述的抗体或抗原结合片段。

[0246] 在一些实施方案中，所述分离核酸分子具有如SEQ ID NO:112～120任一项所示核苷酸序列或具有SEQ ID NO:121～129任一项所示核苷酸序列或具有SEQ ID NO:130～147所示的核苷酸序列.

[0247] 在一些实施方案中，所述分离的核酸分子与上述SEQ ID NO:112～120所示的核苷酸序列至少具有90％以上的同源性，优选具有95％以上的同源性，更优选具有98％、99％以上的同源性。在至少一些实施方案中，所述分离的多核苷酸与所述SEQ ID NO:121～129所

示的核苷酸序列至少具有90％以上的同源性，优选具有95％以上的同源性，更优选具有98％、99％以上的同源性。在至少一些实施方案中，所述分离的多核苷酸与所述SEQ ID NO:130～147所示的核苷酸序列至少具有90％以上的同源性，优选具有95％以上的同源性，更优选具有98％、99％以上的同源性。这些与SEQ ID NO:112～120或者SEQ ID NO:121～129或SEQ ID NO:130～147所示核苷酸序列具有同源性的序列，能够表达与SEQ ID NO:76～84和SEQ ID NO:85～93相似的氨基酸或与SEQ ID NO:94～111相似的氨基酸序列，从而能够与TrkA抗原特异性结合，实现抗体的靶向性功能。

[0248] 在一些优选实施方式中，所述分离的核酸分子具有SEQ ID NO:112～120所示的重链核苷酸序列和SEQ ID NO:121～129所示的轻链核苷酸序列。这些核苷酸序列经过种属优化，更易在哺乳动物细胞中表达。

[0249] 本发明还提供了一种表达载体，所述表达载体包含上述分离的核酸分子。在将上述分离的多核苷酸连接到载体上时，可以将多核苷酸与载体上的控制元件直接或者间接相连，只要这些控制元件能够控制多核苷酸的翻译和表达等即可。当然这些控制元件可以直接来自于载体本身，也可以是外源性的，即并非来自于载体本身。当然，多核苷酸与控制元件进行可操作地连接即可。本文中“可操作地连接”是指将外源基因连接到载体上，使得载体内的控制元件，例如转录控制序列和翻译控制序列等等，能够发挥其预期的调节外源基因的转录和翻译的功能。当然用来编码抗体重链和轻链的多核苷酸，可以分别独立的插入到不同的载体上，常见的是插入到同一载体上。常用的载体例如可以为质粒、噬菌体等等。例如Plasmid-X质粒。

[0250] 本发明还提供了一种重组细胞，该重组细胞中包含有该表达载体。可以将表达载体导入到哺乳动物细胞中，构建获得重组细胞，然后利用这些重组细胞表达本发明提供的抗体或者抗原结合片段。通过该重组细胞进行培养，即可以获得相应抗体。这些可用的哺乳动物细胞例如可以为CHO细胞等。

[0251] 药物组合物、试剂盒及制药用途和在制备试剂盒中的用途。

[0252] 本发明还提供了一种药物组合物，所述药物组合物包括上述所述的抗体或者抗原结合片段和药学可接受的载体。

[0253] 本文提供的抗TrkA抗体可以掺入适合受试者施用的药物组合物中。通常，这些药物组合物包括本文提供的抗TrkA抗体以及药学上可接受的载体。“药学上可接受的载体”可以包括生理学上相容的任何和所有溶剂、分散介质、包衣、抗细菌剂和抗真菌剂、等渗剂和延迟吸收剂等等。具体实例可以是水、盐水、磷酸盐缓冲盐水、葡萄糖、甘油、乙醇等以及它们的组合物中的一种或多种。有许多情况下，药物组合物中包括等渗剂，例如糖类、多元醇(如甘露醇、山梨醇)或氯化钠等。当然药学上可接受的载体还可包括微量的辅助物质，例如润湿剂或乳化剂、防腐剂或缓冲剂，用来延长抗体的保存限期或效力。

[0254] 例如，本发明的抗体可掺入适用于胃肠外施用(例如静脉内、皮下、腹膜内、肌肉内)的药物组合物中。这些药物组合物可以被制备成各种形式。例如液体、半固体和固体剂型等，包括但不限于液体溶液(例如，注射溶液和输注溶液)、分散剂或悬浮剂、片剂、丸剂、粉末、脂质体和栓剂。典型的药物组合物为注射溶液或输注溶液形式。所述抗体可通过静脉输注或注射或肌肉内或皮下注射来施用。

[0255] 当然，本文中的抗TrkA抗体还可以根据需要被制成试剂盒或者其他诊断性试剂的

一部分。根据本发明的实施例，本发明还提供了一种试剂盒，所述试剂盒包括上述TrkA抗体。应用本发明提供的试剂盒，例如可以用于免疫印迹、免疫沉淀等涉及到利用TrkA抗原和抗体特异性结合性能，来检测的试剂盒等。这些试剂盒可包含下列中的任意一种或多种：拮抗剂、抗TrkA抗体或者药物参照材料；蛋白纯化柱；免疫球蛋白亲和纯化缓冲剂；细胞的测定稀释剂；说明书或者文献等。抗TrkA抗体可被用于不同类型的诊断测试，例如可以在体外或者体内检测各种各样的疾病或者药物、毒素或者其他蛋白等的存在。例如可以通过对受试者的血清或者血液进行检测，用来测试相关疾病。这种相关疾病可包括TrkA相关疾病，例如疼痛、癌症、炎症或炎性疾病、神经变性疾病、舍格伦氏综合征、子宫内膜异位、糖尿病性周围神经病变、前列腺炎、盆腔疼痛综合征、与骨重塑调节失衡相关的疾病以及由结缔组织生长因子异常信号传导引起的疾病等等。当然本文提供的抗体也可以用于上述疾病的放射免疫检测和放射免疫治疗等等。

[0256] 具体地，上述疼痛、炎症或炎性疾病、神经变性疾病、舍格伦氏综合征、子宫内膜异位、糖尿病性周围神经病变、前列腺炎、盆腔疼痛综合征、与骨重塑调节失衡相关的疾病以及由结缔组织生长因子异常信号传导引起的疾病包括神经性疼痛、炎性疼痛、与癌症有关的疼痛、与骨折有关的疼痛、与手术有关的疼痛、炎性肺病、间质性膀胱炎、痛性膀胱综合征、炎性肠疾病、炎性皮肤病、雷诺氏综合征、特发性肺纤维化、瘢痕(肥大型、瘢痕瘤型和其他形式)、硬化、心内膜心肌纤维化、心房纤维化、骨髓纤维化、进行性块状纤维化(肺)、肾源性系统性纤维化、硬皮病、系统性硬化、关节纤维化、眼部纤维化。

[0257] 这些癌症或者肿瘤可以是任何不受调控的细胞生长。具体地，可以是非小细胞肺癌、乳头状甲状腺癌、多形性成胶质细胞瘤、结肠直肠癌、黑色素瘤、胆管癌或肉瘤、急性骨髓性白血病、大细胞神经内分泌癌、前列腺癌、成神经细胞瘤、胰腺癌、黑色素瘤、头颈鳞状细胞癌或胃癌等等。

[0258] 在利用本发明所提供的抗TrkA抗体治疗上述疾病时，可以将本发明提供的抗TrkA抗体提供给受试者即可。为此，本发明提供了一种用于治疗上述疾病的方法，包括向有需要的受试者施用本发明所提供的的抗体或其抗原结合片段。

[0259] 下面将结合实施例对本发明的方案进行解释。本领域技术人员将会理解，下面的实施例仅用于说明本发明，而不应视为限定本发明的范围。实施例中未注明具体技术或条件的，按照本领域内的文献所描述的技术或条件或者按照产品说明书进行。所用试剂或仪器未注明生产厂商者，均为可以通过市购获得的常规产品。

[0260] 实施例1杂交瘤技术筛选抗TrkA单克隆抗体

[0261] 通过杂交瘤技术和ELISA方法筛选可以产生分子水平阻断NGF和TrkA结合的抗TrkA单克隆抗体的杂交瘤细胞株。采用NCBI数据库设计出TrkA蛋白胞外区编码基因，构建到哺乳动物真核表达系统中，表达得到TrkA蛋白胞外区，用于抗TrkA单克隆抗体筛选。免疫原TrkA蛋白胞外区来源于北京义翘神州生物科技有限公司，Balb/C小鼠三次腹腔注射免疫后，ELISA方法测定免疫小鼠血清抗体滴度，达到10^5级。脾脏注射加强免疫后，与骨髓瘤细胞融合。采用HAT选择培养基和HT选择培养基选择性培养筛选融合的杂交瘤细胞株，采用ELISA方法筛选能产生抗TrkA抗体的阳性杂交瘤细胞株，采用有限稀释法进行阳性杂交瘤细胞的克隆化培养，筛选稳定的能产生抗TrkA单克隆抗体的杂交瘤细胞株。经三次克隆化培养，四次ELISA检测后，共筛选得到147株阳性单克隆杂交瘤细胞株。将NGF生物素化，利用

NGF可以结合TrkA蛋白胞外区，抗TrkA单克隆抗体也可以结合TrkA蛋白胞外区，设计竞争性实验，通过ELISA方法，检测抗TrkA单克隆抗体作用下，NGF与TrkA蛋白胞外区结合情况，筛选分子水平阻断NGF和TrkA结合的抗TrkA单克隆抗体。图1是147株阳性单克隆杂交瘤细胞株中能产生分子水平阻断NGF和TrkA结合的抗TrkA单克隆抗体的9株杂交瘤细胞株的阻断实验结果，即经筛选共得到9株能产生分子水平阻断NGF和TrkA结合的抗TrkA单克隆抗体的单克隆杂交瘤细胞株，实验结果见图1。图中，OD450反映了与TrkA蛋白胞外区结合的NGF信号，读值越高，表明与TrkA蛋白胞外区结合的NGF信号越强，抗体阻断NGF与TrkA结合的效果越差；如图所示，与阴性克隆组相比，9个阳性克隆组的ELISA读值显著性的降低，与TrkA蛋白胞外区结合的NGF信号显著性降低；可见，这9个阳性克隆能通过产生抗TrkA单克隆抗体阻断NGF与TrkA蛋白胞外区结合，降低与TrkA蛋白胞外区结合的NGF信号。

[0262] 实施例2 HEK-293T-TrkA细胞模型筛选抗TrkA单克隆抗体

[0263] 利用慢病毒技术构建HEK-293T-TrkA细胞模型，通过流式细胞术，筛选可以产生细胞水平阻断NGF和TrkA结合的抗TrkA单克隆抗体的杂交瘤细胞株。将NGF生物素化，利用NGF可以结合HEK-293T-TrkA细胞上的TrkA蛋白胞外区，抗TrkA单克隆抗体也可以结合HEK-293T-TrkA细胞上的TrkA蛋白胞外区，设计竞争性实验，通过流式细胞术，检测抗TrkA单克隆抗体作用下，NGF与HEK-293T-TrkA细胞上TrkA蛋白胞外区结合情况，筛选细胞水平阻断NGF和TrkA结合的抗TrkA单克隆抗体。经筛选共得到9株能产生细胞水平阻断NGF和TrkA结合的抗TrkA单克隆抗体的单克隆杂交瘤细胞株，与分子水平阻断实验结果一致，实验结果见图2，图中，%parent值反映了与HEK-293T-TrKA细胞上TrkA蛋白胞外区结合的NGF信号，读值越高，表明与HEK-293T-TrKA细胞上TrkA蛋白胞外区结合的NGF信号越强，抗体阻断NGF与TrkA结合的效果越差；如图所示，与阴性克隆组相比，9个阳性克隆组的%parent值显著性的降低，与TrkA蛋白胞外区结合的NGF信号显著性降低；可见，这9个阳性克隆能通过产生抗TrkA单克隆抗体阻断NGF与HEK-293T-TrkA细胞上TrkA蛋白胞外区结合，降低与HEK-293T-TrkA细胞上TrkA蛋白胞外区结合的NGF信号。

[0264] 实施例3应用ELISA方法检测阳性克隆产生单克隆抗体的人鼠交叉反应

[0265] 通过ELISA方法检测各阳性克隆上清产生的单克隆抗体与Mouse-TrKA受体的结合情况，检测阳性克隆产生单克隆抗体的人鼠交叉反应，结果见图3，图中，OD_{450}值反映抗体与蛋白的结合强弱，读值越大表示抗体与蛋白的结合越强。如图所示，23E12、21E5、15D4、27H3组的OD_{450}值在3.5左右，与阴性对照组相比有显著性差异；20C8、1B9、4H4、3A5、22D12组的OD_{450}值几乎接近于0，与阴性克隆组相比没有显著性差异。可见，克隆23E12、21E5、15D4、27H3能产生与Human-TrKA和Mouse-TrKA都结合的单克隆抗体，存在人鼠交叉反应。

[0266] 实施例4载体的构建

[0267] 采用分子克隆的方法构建一系列(20C8、23E12、27H3、21E5、2A5、4H4、1B9、22D12、15D4)嵌合抗体表达载体，在CHO表达系统中，重组表达嵌合抗体。编码一系列(20C8、23E12、27H3、21E5、2A5、4H4、1B9、22D12、15D4)嵌合单克隆抗体轻重链的核苷酸序列是委托金唯智生物科技有限公司通过化学合成获得的，所获得的序列经双酶切后，插入到真核表达载体的相同酶切位点间，构建一系列(20C8、23E12、27H3、21E5、2A5、4H4、1B9、22D12、15D4)嵌合抗体表达载体。然后采用Invitrogen质粒提取试剂盒提取一系列经验证正确的表达载体，并用限制性内切酶进行线性化后纯化回收，-20℃保藏。

[0268] 实施例5编码一系列嵌合抗体载体转染并在细胞中表达

[0269] 将CHO宿主细胞用CD CHO培养基复苏培养后，当细胞密度约8*10^5cell/mL时收集细胞进行转染。转染细胞约1*10^7cell，载体约40μg，通过电击方法转染(Bio-Rad，Gene pulser Xcell)。电击后细胞于20mL CD CHO培养基中培养。培养第二天，离心收集细胞，并在加入MSX至终浓度50μM的20mL CD CHO培养基中重悬培养。当细胞密度约0.6*10^6cell/mL时，对获得的混合克隆株用CD CHO培养基进行传代，传代细胞密度约0.2*10^6cell/mL。当细胞存活率约90％时，收集细胞培养液。

[0270] 实施例6收集细胞发酵培养液纯化嵌合抗体

[0271] 对一系列的嵌合抗体进行翻译水平上的检测。采用Protein A层析柱对收集的细胞培养液进行纯化，并收集吸收峰，进行质谱检测，质谱检测一系列嵌合抗体分子量150KD左右，与理论分子量一致。同时对收集的样品经还原与非还原后通过10％SDS-PAGE电泳检测，还原型SDS-PAGE电泳图谱显示二条带，分别在25KD和50KD左右，非还原型SDS-PAGE电泳图谱显示单一条带，在150KD左右，电泳图谱条带大小与理论一致。纯化后样品采用pH7.4的0.02M PBS缓冲液在4℃透析过夜。

[0272] 在以下实施例7～16中，发明人评价了所构建纯化获得的嵌合抗体20C8、23E12、27H3、21E5、2A5、4H4、1B9、22D12、15D4的与TrkA的亲和力和结合TrkA、阻断NGF与TrkA蛋白胞外区结合的活性。

[0273] 实施例7应用HEK-293T-TrkA细胞模型评价受试抗体的阻断活性

[0274] 将NGF生物素化，利用NGF可以结合HEK-293T-TrkA细胞上的TrkA蛋白胞外区，抗TrkA单克隆抗体也可以结合HEK-293T-TrkA细胞上的TrkA蛋白胞外区，设计竞争性实验，通过流式细胞术，检测不同浓度(20μg/mL，10μg/mL，5μg/mL，2.5μg/mL，1.25μg/mL，0.625μg/mL，0.313μg/mL，0.156μg/mL，0.078μg/mL，0.039μg/mL，0.019μg/mL)受试抗体作用下，NGF与HEK-293T-TrkA细胞上TrkA蛋白胞外区结合情况，研究受试抗体对NGF和TrKA结合的抑制作用。实验结果见图4。图中，parent％值反映了与HEK-293T-TrkA细胞上TrKA蛋白胞外区结合的NGF信号，读值越低，与HEK-293T-TrkA细胞上TrkA蛋白胞外区结合的NGF信号越弱，抗体抑制NGF与TrKA结合的作用越大；如图所示，随着受试抗体浓度的增加，parent％值逐渐降低，直到趋近于零，即与TrkA蛋白胞外区结合的NGF信号逐渐降低，直到没有NGF结合TrkA蛋白胞外区，NGF与TrkA的结合全部抑制。可见，一定的浓度范围内，各受试抗体在细胞水平上能够剂量依赖性的抑制NGF与TrkA的结合。

[0275] 实施例8应用NIH-3T3-TrkA细胞模型评价受试抗体的体外活性

[0276] 在NGF刺激下，NIH-3T3-TrkA细胞膜上的TrkA蛋白酪氨酸磷酸化水平上调，TrkA下游信号通路激活。受试抗体可以结合NIH-3T3-TrkA细胞膜表面的TrkA蛋白，抑制NGF的刺激，下调TrkA蛋白酪氨酸磷酸化水平。试验中，以IgG4为阴性对照(该抗体不结合NGF及TrkA)，tanezumab(抗NGF单克隆抗体，轻链氨基酸序列如SEQ ID NO:149所示，重链氨基酸序列如SEQID NO:150所示，抑制NGF-TrkA通路药物)、MNAC13(抗TrKA单克隆抗体，轻链氨基酸序列如SEQ ID NO:151所示，重链氨基酸序列如SEQID NO:152所示，抑制NGF-TrkA通路药物)为阳性对照，其中，Tanezumab用于验证NIH-3T3-TrkA细胞模型是否可以用于评价抑制NGF-TrkA通路药物(受试药物)的体外活性，实验数据如图5所示。通过AlphaLISA的方法检测不同浓度受试抗体及阳性抗体MNAC13作用下，TrkA蛋白的酪氨酸磷酸化水平下调情况，

衡量受试抗体的体外活性，p-TrkA检测结果见图6，实验结果显示，受试抗体及阳性抗体MNAC13均能抑制NGF-TrKA通路，剂量依赖性地下调TrkA蛋白酪氨酸磷酸化水平，其中，受试抗体23E12、20C8、27H3、21E5、1B9、4H4的半数抑制浓度IC_{50}小于阳性抗体MNAC13。可见，受试抗体23E12、20C8、27H3、21E5、1B9、4H4的体外活性优于阳性抗体MNAC13。

[0277] DIQMTQSPSSLSASVGDRVTITCRASQSISNNLNWYQQKPGKAPKLLIYYTSRFHSGVPSRFSGSGSGTDFTFTISSLQPEDIATYYCQQEHTLPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:149)。

[0278] QVQLQESGPGLVKPSETLSLTCTVSGFSLIGYDLNWIRQPPGKGLEWIGIIWGDGTTDYNSAVKSRVTISKDTSKNQFSLKLSSVTAADTAVYYCARGGYWYATSYYFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:150)。

[0279] DIVLTQSPSSLSASVGDRVTITCSASSSVSYMHWYQQKPGQAPKLLIYTTSNLASGVPSRFSGSGSGTDYTLTISSLQPEDVATYYCHQWSSYPWTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:151)。

[0280] EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYTMSWARQAPGKGLEWVAYISKGGGSTYYPDTVKGRFTISRDNSKNTLYLQMNSLRAEDSAVYYCARGAMFGNDFFFPMDRWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG(SEQ ID NO:152)。

[0281] 实施例9应用Fortebio方法评价受试抗体与TrkA的亲和力

[0282] 将受试抗体(23E12、20C8、21E5、27H3、1B9、4H4、2A5)样品分别用缓冲液(PBS缓冲液100ml，加入0.1gBSA搅拌至充分溶解，再加入20μL的吐温20，混合均匀)稀释至4个浓度梯度(80nM、26.67nM、8.89nM、2.93nM)，分别加入到样品板的各孔中，通过亲和力检测系统(OCTET RED 96 SYSTEM)，用带有Ni-NTA传感器(厂家:PALL，货号:18-5101)结合带有组氨酸标签的TRKA(50μg/ml，75kDa，HEC实验室提供)蛋白后，自动检测其与各受试抗体的结合情况，结果见表1。K_D值是抗体与其抗原之间的平衡解离常数，K_D值与亲和力成反比。K_D值与抗体的浓度(特定实验所需的抗体量)有关，K_D值越低(浓度越低)，抗体的亲和力越高。通常认为，高亲和力抗体处于低纳摩尔范围内(10^{-9})。表1结果显示，受试抗体(23E12、20C8、21E5、27H3、1B9、4H4、2A5)的K_D值处于低纳摩尔范围内(10^{-9})，表明，受试抗体都具有很高的亲和力。

[0283] 表1：

[0284]

Sample ID	K_D (M)	kon(1/Ms)	kon Error	kdis(1/s)	kdis Error	Full R^2
23E12	5.70E-11	1.90E+06	6.33E+04	1.09E-04	7.47E-06	0.944
4H4	1.68E-09	1.39E+05	6.01E+03	2.34E-04	1.55E-05	0.961
20C8	1.15E-10	5.51E+05	2.34E+04	6.33E-05	1.17E-05	0.949

[0285]

27H3	1.78E-10	1.57E+06	4.53E+04	2.79E-04	7.91E-06	0.929
21E5	1.73E-10	1.01E+06	2.08E+04	1.75E-04	5.60E-06	0.977
1B9	8.99E-10	1.01E+06	6.65E+04	9.04E-04	6.29E-05	0.910
2A5	1.62E-11	2.22E+05	1.42E+04	3.60E-06	1.96E-05	0.944

[0286] 实施例10应用流式细胞术评价受试抗体的亲和力

[0287] 将受试抗体(23E12、20C8、21E5、27H3、1B9、4H4、2A5)样品分别用PBS缓冲液稀释至11个浓度梯度(20μg/mL,10μg/mL,5μg/mL,2.5μg/mL,1.25μg/mL,0.625μg/mL,0.313μg/mL,0.156μg/mL,0.078μg/mL,0.039μg/mL,0.019μg/mL),通过流式细胞术检测各浓度梯度受试抗体与HEK-293T-TrKA细胞表面TrKA受体的结合情况,从细胞水平评价受试抗体的亲和力,结果见图7。图中,EC_{50}(半数结合浓度)值反映抗体的亲和力高低,EC_{50}值越小,抗体的亲和力越高,通常认为,高亲和力抗体的EC_{50}值低于1.5μg/mL。图中结果显示,受试抗体23E12、20C8、21E5、27H3、1B9、4H4、2A5的EC_{50}值均低于1.5μg/mL,表明,受试抗体都具有很高的亲和力。

[0288] 实施例11应用ELISA方法评价受试抗体与靶标TrKA结合的特异性

[0289] TrkA受体家族属于受体酪氨酸激酶(RTKs),包括TrkA、TrkB和TrkC,它们具有很高的同源性。TrkA是神经生长因子(NGF)的受体酪氨酸激酶,选择性结合NGF,是NGF的功能性受体。除高亲和力受体TrkA外,NGF还可与其低亲和力受体p75结合。试验中,通过ELISA方法检测不同浓度(20μg/mL,10μg/mL,5μg/mL,2.5μg/mL,1.25μg/mL,0.625μg/mL,0.313μg/mL,0.156μg/mL,0.078μg/mL,0.039μg/mL,0.019μg/mL)受试抗体分别与TrKA、TrKB、TrKC、P75的结合情况,评价受试抗体与靶标TrKA结合的特异性,结果如图8A～8G所示。图中,一定的抗体浓度下,OD_{450}值反映抗体与蛋白的结合强弱,读值越大抗体与蛋白的结合越强。实验结果显示,受试抗体23E12、20C8、27H3、21E5、1B9、4H4、2A5与TrKA受体都有很好的结合(受试抗体浓度由0μg/mL增加到20μg/mL,OD_{450}值逐渐增加直至趋近稳定,接近3左右),与TrKB、TrKC、P75基本不结合(各受试抗体浓度由0μg/mL增加到20μg/mL,OD_{450}值基本没有变化,接近于0)。可见,受试抗体与靶标TrKA结合的特异性都很好。

[0290] 实施例12应用ELISA方法检测受试抗体与Mouse-TrKA蛋白的结合能力

[0291] 将受试抗体(23E12、21E5)样品分别用PBS缓冲液稀释至11个浓度梯度(20μg/mL,10μg/mL,5μg/mL,2.5μg/mL,1.25μg/mL,0.625μg/mL,0.313μg/mL,0.156μg/mL,0.078μg/mL,0.039μg/mL,0.019μg/mL),通过ELISA方法检测各浓度梯度受试抗体与Mouse-TrKA受体的结合情况,检测受试抗体与Mouse-TrKA蛋白的结合能力,结果见图9,图中,一定的抗体浓度下,OD_{450}值反映抗体与蛋白的结合强弱,读值越大抗体与蛋白的结合越强。实验结果显示,受试抗体的浓度由0μg/mL增加到20μg/mL,OD_{450}值逐渐增加直至趋近稳定,接近3.5左右。可见,受试抗体23E12、21E5和Mouse-TrKA蛋白都有很好的结合能力。

[0292] 实施例13应用流式细胞术检测受试抗体与Mouse-TrKA蛋白的结合能力

[0293] 将受试抗体23E12样品分别用PBS缓冲液稀释至11个浓度梯度(20μg/mL,10μg/mL,5μg/mL,2.5μg/mL,1.25μg/mL,0.625μg/mL,0.313μg/mL,0.156μg/mL,0.078μg/mL,0.039μg/mL,0.019μg/mL),通过流式细胞术检测各浓度梯度受试抗体与HEK293T-Mouse-TrKA细胞表面Mouse-TrKA受体的结合情况,检测受试抗体与Mouse-TrKA蛋白的结合能力,结果见图10。图中,EC_{50}(半数结合浓度)值反映抗体的结合能力,EC_{50}值越小,抗体的结合能力越强,实验结果显示,受试抗体的浓度由0μg/mL增加到20μg/mL,%Parent值逐渐增加直至趋近稳定,EC_{50}值=0.08012μg/mL。可见,受试抗体23E12与HEK293T-Mouse-TrKA细胞表面Mouse-TrKA受体有很好的结合能力。

[0294] 实施例14应用ELISA方法检测受试抗体对Mouse-NGF和Mouse-TrKA结合的抑制作用

[0295] 试验中,以IgG4为阴性对照(该抗体不结合Mouse-NGF及Mouse-TrkA),将Mouse-NGF生物素化,利用Mouse-NGF可以结合Mouse-TrkA蛋白,抗Mouse-TrkA单克隆抗体也可以结合Mouse-TrkA蛋白,设计竞争性实验,通过ELISA方法,检测不同浓度(2.5μg/mL,0.25μg/mL)受试抗体(23E12,21E5)作用下,Mouse-NGF与Mouse-TrkA蛋白结合情况,研究受试抗体对Mouse-NGF和Mouse-TrKA结合的抑制作用。实验结果见图11。图中,OD_{450}值反映了与Mouse-TrkA结合的Mouse-NGF信号。读值越低,与Mouse-TrkA结合的Mouse-NGF信号越弱,抗体抑制Mouse-NGF与Mouse-TrKA结合的作用越大;如图所示,与阴性对照组相比,不同浓度(2.5μg/mL,0.25μg/mL)受试抗体(23E12,21E5)作用下,与Mouse-TrkA结合的Mouse-NGF信号显著性降低。可见,受试抗体23E12、21E5能够抑制Mouse-NGF和Mouse-TrKA结合。

[0296] 实施例15应用流式细胞术检测受试抗体对Mouse-NGF和Mouse-TrKA结合的抑制作用

[0297] 将Mouse-NGF生物素化,利用Mouse-NGF可以结合HEK293T-Mouse-TrkA细胞上的Mouse-TrkA蛋白胞外区,抗Mouse-TrkA单克隆抗体也可以结合HEK293T-Mouse-TrkA细胞上的Mouse-TrkA蛋白胞外区,设计竞争性实验,通过流式细胞术,检测不同浓度(20μg/mL,10μg/mL,5μg/mL,2.5μg/mL,1.25μg/mL,0.625μg/mL,0.313μg/mL,0.156μg/mL,0.078μg/mL,0.039μg/mL,0.019μg/mL)受试抗体作用下,Mouse-NGF与HEK-293T-Mouse-TrkA细胞上Mouse-TrkA蛋白胞外区结合情况,研究受试抗体对Mouse-NGF和Mouse-TrKA结合的抑制作用。实验结果见图12。图中,parent%值反映了与HEK293T-Mouse-TrkA细胞上Mouse-TrKA蛋白胞外区结合的Mouse-NGF信号,读值越低,与HEK293T-Mouse-TrkA细胞上Mouse-TrkA蛋白胞外区结合的Mouse-NGF信号越弱,抗体抑制Mouse-NGF与Mouse-TrKA结合的作用越大;如图所示,随着受试抗体浓度的增加,%parent值逐渐降低,直到趋近于零,即与Mouse-TrkA蛋白胞外区结合的Mouse-NGF信号逐渐降低,直到没有Mouse-NGF结合Mouse-TrkA蛋白胞外区,Mouse-NGF与Mouse-TrkA的结合全部抑制,IC50=0.05147μg/mL。可见,一定的浓度范围内,受试抗体23E12在细胞水平上能够剂量依赖性的抑制Mouse-NGF与Mouse-TrkA的结合。

[0298] 实施例16应用ELISA方法检测受试抗体对Human-NGF和Human-TrKA结合的抑制作用

[0299] 将Mouse-NGF生物素化,利用Mouse-NGF可以结合Mouse-TrkA蛋白,抗Mouse-TrkA单克隆抗体也可以结合Mouse-TrkA蛋白,设计竞争性实验,通过Elisa方法,检测不同浓度(20μg/mL,10μg/mL,5μg/mL,2.5μg/mL,1.25μg/mL,0.625μg/mL,0.313μg/mL,0.156μg/mL,

0.078μg/mL,0.039μg/mL,0.019μg/mL)受试抗体作用下,Mouse-NGF与Mouse-TrkA蛋白结合情况,研究受试抗体对Mouse-NGF和Mouse-TrKA结合的抑制作用。实验结果见图13。图中,OD_{450}值反映了与Mouse-TrkA结合的Mouse-NGF信号。读值越低,与Mouse-TrkA结合的Mouse-NGF信号越弱,抗体抑制Mouse-NGF与Mouse-TrKA结合的作用越大;如图所示,随着受试抗体浓度的增加,OD450值逐渐降低,直到趋近于零,即与Mouse-TrkA蛋白胞外区结合的Mouse-NGF信号逐渐降低,直到几乎没有Mouse-NGF结合Mouse-TrkA蛋白胞外区,Mouse-NGF与Mouse-TrkA的结合几乎完全抑制。可见,一定的浓度范围内,受试抗体23E12、20C8、21E5、27H3、4H4、2A5在分子水平上能够剂量依赖性的抑制NGF与TrkA的结合。

[0300] 实施例17应用福尔马林致痛模型评价受试抗体的体内镇痛活性

[0301] 福尔马林炎症痛模型是通过注射福尔马林来产生持续而非短暂的疼痛刺激及应答的验证痛模型。该模型产生两相疼痛,分别是第I相化学刺激疼痛和第II相炎症疼痛,造成的疼痛应答具有可重复性、可计量性,是临床前疼痛研究最佳的模型之一,且被广泛应用于评估不同药物的镇痛效果。试验中,选用6-8周雄性ICR小鼠,造模前根据体重随机分为6组:模型组(皮下注射生理盐水)、Tanezumab 60μg/mouse剂量组、20C8 60μg/mouse剂量组、21E5 60μg/mouse剂量组、23E12 15μg/mouse剂量组、23E12 60μg/mouse剂量组,每组10只。药物经皮下给药,18个小时后于小鼠右后爪足背皮下注射2.5%福尔马林溶液15μL,观察其后45分钟内小鼠抬脚次数,记1-15min为第I相疼痛,16-45min为第II相疼痛,一般而言,第I相疼痛反映的是急性疼痛,第II相疼痛反映的是慢性疼痛。结果见图14(图中数据展示为Mean±SEM,n=10/组,*p<0.05与溶剂模型组比较,使用单因素方差分析附加LSD多重比较检验),图中抬脚次数反映小鼠造模后的疼痛强度,抬脚次数越少,疼痛越弱。结果显示,与模型组相比,23E12 60μg/mouse剂量组能显著减少小鼠第II相疼痛的抬脚次数,其它剂量组未能降低小鼠造模后的抬脚次数。结论:在福尔马林致痛模型中,皮下注射60μg/mouse的受试抗体23E12对于慢性疼痛有效,而阳性药Tanezumab未体现镇痛效果,可能对福尔马林致痛模型不敏感。

[0302] 实施例18应用完全弗氏佐剂诱导炎症疼痛模型评价受试抗体的体内镇痛活性

[0303] 完全弗氏佐剂诱导炎症痛模型通过在小鼠掌心注射完全弗氏佐剂来产生类似骨关节炎症的慢性炎症疼痛刺激及应答的疼痛模型,通过机械痛测试对疼痛测量,机械刺激力度越大,说明动物对疼痛的耐受性越强。试验中,选用8周龄雄性ICR小鼠,在造模前根据疼痛敏感随机分为6组(15只/组):对照组(小鼠左后肢足底注射生理盐水25μl+皮下注射生理盐水),模型组(小鼠左后肢足底注射25μl CFA诱导炎性痛+皮下注射生理盐水)、Tanezumab 60μg/mouse剂量组,23E12 60μg/mouse剂量组,在造模后第4天皮下注射药物,给药后36hr进行机械痛测试。结果见图15(图中数据展示为Mean±SEM,n=15/组,#p<0.05,##p<0.01与空白对照组比较,*p<0.05,**p<0.01与模型组比较,使用非参数统计分析附加独立样本T检验),纵坐标表示机械刺激力度,小鼠爪子撤离的压力阈值越大,镇痛效果越好。结果显示:与模型组比较,皮下注射60μg/mouse 23E12、60μg/mouse tanezumab能够显著增加小鼠爪子撤离的压力阈值(P<0.01;P<0.05),呈现镇痛作用,两者镇痛效果作用效果相当。结论:皮下注射60μg/mouse的受试抗体23E12,在完全弗氏佐剂诱导的炎症痛模型中呈现镇痛作用。

[0304] 实施例19受试抗体毒理实验

[0305] 在本实施例中,发明人所要进行的毒性测试如下表2所示。

[0306] 表2:

[0307]

研究项目	给药方式	种属 or 探究系统	主要研究	结果
单次给药毒性	i.v.	SD 大鼠 食蟹猴	观察是否出现靶器官毒性。观察相关的症状，对体重、摄食、检眼镜检查、心电图、血液学、临床生化、尿液、脏器重量的影响，提供最大耐受剂量 MTD，足够的安全系数，	无动物死亡，在器官和组织上观察到弥散型炎症浸润，但是无论临床病理还是组织学分析，都没有显示出靶器官毒性。对体重、摄食、检眼镜检查、心电图、血液学、临床生化、尿液、脏器重量无显著影响。大体解剖无显著异常。
重复给药毒性	i.v. /（一周一	SD 大鼠 食蟹猴	观察临床病理学和组织学确定是否存在靶器官毒性 NOAEL，	无动物死亡，在器官和组织上观察到弥散型炎症浸润，但是无论临床病理还是组织学分析，都没有显示

研究项目	给药方式	种属 or 探究系统	主要研究	结果
	次，4周）		观察对体重、摄食、检眼镜检查、心电图、血液学、临床生化、尿液、脏器重量的影响，免疫原性（ADA（抗药抗体）分析方法），免疫毒性研究（评价内容包括：血液学白细胞分类计数（包括巨噬细胞）、临床化学（球蛋白和白蛋白：球蛋白比值）），器官质量（胸腺、脾脏、淋巴结）和组织病理学（淋巴器官和组织）计算安全窗	出靶器官毒性。没有出现纳武单抗相关的症状，对体重、摄食、检眼镜检查、心电图、血液学、临床生化、尿液、脏器重量无显著影响。大体解剖无显著异常。
一般安全药理学	i.v. / 单次给药	中枢神经系统 呼吸系统 心血管系统	主要研究药物在治疗范围内或治疗范围以上的剂量时，潜在的不期望出现的对生理功能的不良影响，即观察药物对中枢神经系统、心血管系统和呼吸系统的影响。	药物对中枢神经系统、心血管系统和呼吸系统的无影响。
局部给药安全性实验	血管刺激性实验和体外溶血实验	兔	检验药物对血管和血液是否有影响	无影响
高致敏性试验	豚鼠全身主动过敏实验	豚鼠	判断是否有致敏作用	无致敏作用

[0308]

[0309] 其中，上述实验过程和实验结论如下所述：

[0310] 毒理实验：

[0311] 单次给药毒性

[0312] SD大鼠、食蟹猴，观察是否出现靶器官毒性。观察相关的症状，对体重、摄食、检眼镜检查、心电图、血液学、临床生化、尿液、脏器重量的影响，提供最大耐受剂量MTD，足够的安全系数。结果显示：无动物死亡，在器官和组织上观察到弥散型炎症浸润，但是无论临床病理还是组织学分析，都没有显示出靶器官毒性。对体重、摄食、检眼镜检查、心电图、血液学、临床生化、尿液、脏器重量无显著影响。大体解剖无显著异常。

[0313] 重复给药毒性:SD大鼠、食蟹猴,一周一次静脉注射药物,连续4周,观察临床病理学和组织学确定是否存在靶器官毒性NOAEL,观察对体重、摄食、检眼镜检查、心电图、血液学、临床生化、尿液、脏器重量的影响,免疫原性(ADA(抗药抗体)分析方法),免疫毒性研究(评价内容包括:血液学白细胞分类计数(包括巨噬细胞)、临床化学(球蛋白和白蛋白:球蛋白比值)),器官质量(胸腺、脾脏、淋巴结)和组织病理学(淋巴器官和组织)计算安全窗。结果显示:无动物死亡,在器官和组织上观察到弥散型炎症浸润,但是无论临床病理还是组织学分析,都没有显示出靶器官毒性。没有出现纳武单抗相关的症状,对体重、摄食、检眼镜检查、心电图、血液学、临床生化、尿液、脏器重量无显著影响。大体解剖无显著异常。

[0314] 一般安全药理学:SD大鼠单次静脉注射药物,观察药物对中枢神经系统、心血管系统和呼吸系统的影响。结果显示:药物对中枢神经系统、心血管系统和呼吸系统的无影响。

[0315] 局部给药安全性实验(血管刺激性实验和体外溶血实验):新西兰大白兔静脉注射药物,检验药物对血管和血液是否有影响。结果显示:无影响。

[0316] 高致敏性试验(豚鼠全身主动过敏实验):豚鼠单次静脉注射药物,观察其是否有致敏作用。结果显示:无致敏作用。

[0317] 在本说明书的描述中,参考术语“一个实施例”、“一些实施例”、“示例”、“具体示例”、或“一些示例”等的描述意指结合该实施例或示例描述的具体特征、结构、材料或者特点包含于本发明的至少一个实施例或示例中。在本说明书中,对上述术语的示意性表述不必须针对的是相同的实施例或示例。而且,描述的具体特征、结构、材料或者特点可以在任一个或多个实施例或示例中以合适的方式结合。此外,在不相互矛盾的情况下,本领域的技术人员可以将本说明书中描述的不同实施例或示例以及不同实施例或示例的特征进行结合和组合。

[0318] 尽管上面已经示出和描述了本发明的实施例,可以理解的是,上述实施例是示例性的,不能理解为对本发明的限制,本领域的普通技术人员在本发明的范围内可以对上述实施例进行变化、修改、替换和变型。

[0001] SEQUENCE LISTING
[0002] <110> 广东东阳光药业有限公司
[0003] <120> TrkA的抗体及其应用
[0004] <130> PIDC4200110
[0005] <160> 152
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[0222] 1 5 10

[0223] <210> 25

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[0242] <211> 10

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[0248] Ala Arg Thr Asp Pro Pro Tyr Phe Gly Val

[0249] 1 5 10

[0250] <210> 28

[0251] <211> 5

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[0366] 1 5

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[0446] Lys Ser Val Ser Ser Ser Ala Tyr Ser Tyr

[0447] 1 5 10

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[0465] 1 5

[0466] <210> 52

[0467] <211> 5

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[0474] 1 5

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[0482] Asp Thr Ser

[0483] 1

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[0492] 1 5

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[0498] <223> 重链可变区

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[0501] 1 5 10 15

[0502] Ser Met Lys Ile Ser Cys Lys Ala Ser Val Tyr Ser Phe Thr Ala Tyr

[0503] 20 25 30

[0504] Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
[0505] 35 40 45
[0506] Gly Leu Ile Asn Pro His Asn Gly Gly Thr Arg Tyr Asn Gln Lys Phe
[0507] 50 55 60
[0508] Lys Gly Lys Ala Thr Leu Thr Leu Asp Lys Ser Ser Ser Thr Ala Tyr
[0509] 65 70 75 80
[0510] Met Asp Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[0511] 85 90 95
[0512] Ala Ile Ser Arg Tyr Gly Ser Ser Ser Phe Tyr Phe Asp Val Trp Gly
[0513] 100 105 110
[0514] Ala Gly Thr Thr Val Ala Val Ser Ser
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[0524] 1 5 10 15
[0525] Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Tyr
[0526] 20 25 30
[0527] Trp Leu Gly Trp Met Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
[0528] 35 40 45
[0529] Gly Asp Phe Tyr Pro Arg Thr Gly Asn Thr Phe Tyr Asn Glu Asn Phe
[0530] 50 55 60
[0531] Lys Gly Lys Val Thr Leu Thr Ala Asp Lys Ser Ser Asn Thr Ala Tyr
[0532] 65 70 75 80
[0533] Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Leu Cys
[0534] 85 90 95
[0535] Ala Arg Ala Gly Thr Gly Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu
[0536] 100 105 110
[0537] Thr Val Ser Ser
[0538] 115
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[0547] 1 5 10 15
[0548] Ser Val Lys Ile Ser Cys Lys Thr Thr Gly Tyr Arg Phe Ser Ser Tyr
[0549] 20 25 30
[0550] Trp Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Leu
[0551] 35 40 45
[0552] Gly Glu Ile Leu Pro Gly Arg Gly Ile Ile Asn Tyr Asn Glu Asn Phe
[0553] 50 55 60
[0554] Arg Gly Lys Ala Thr Phe Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
[0555] 65 70 75 80
[0556] Val Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
[0557] 85 90 95
[0558] Ala Arg Thr Asp Pro Pro Tyr Phe Gly Val Trp Gly Ala Gly Thr Thr
[0559] 100 105 110
[0560] Val Thr Val Ser Ser
[0561] 115
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[0570] 1 5 10 15
[0571] Ser Met Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Thr Tyr
[0572] 20 25 30
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[0574] 35 40 45
[0575] Gly Glu Asn Leu Pro Gly Arg His Ile Thr Asn Tyr Asn Glu Lys Phe
[0576] 50 55 60
[0577] Lys Gly Lys Ala Thr Phe Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
[0578] 65 70 75 80
[0579] Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[0580] 85 90 95
[0581] Ala Arg Gly Arg Gly Thr Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
[0582] 100 105 110
[0583] Pro Leu Thr Val Ser Ser
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[0595] 20 25 30
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[0597] 35 40 45
[0598] Gly Leu Ile Asn Pro Tyr Asn Gly Gly Thr Asn Tyr Asn Gln Lys Phe
[0599] 50 55 60
[0600] Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
[0601] 65 70 75 80
[0602] Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[0603] 85 90 95
[0604] Ala Phe Ser Tyr Tyr Gly Ser Arg Gly Phe Tyr Phe Asp Tyr Trp Gly
[0605] 100 105 110
[0606] Gln Gly Thr Thr Leu Thr Val Ser Ser
[0607] 115 120
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[0616] 1 5 10 15
[0617] Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
[0618] 20 25 30
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[0620] 35 40 45
[0621] Gly Leu Ile Asn Pro Tyr Asn Gly Gly Thr Arg Tyr Asn Gln Lys Phe
[0622] 50 55 60
[0623] Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
[0624] 65 70 75 80
[0625] Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[0626] 85 90 95
[0627] Ala Ser Ser Ser Tyr Arg Asn Asp Gly Asn Trp Tyr Phe Asp Val Trp
[0628] 100 105 110
[0629] Gly Ala Gly Thr Thr Val Thr Val Ser Ser

[0630] 115 120

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[0633] <212> PRT

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[0639] 1 5 10 15

[0640] Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Ile Thr Gly Tyr

[0641] 20 25 30

[0642] Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile

[0643] 35 40 45

[0644] Gly Leu Val Asn Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe

[0645] 50 55 60

[0646] Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr

[0647] 65 70 75 80

[0648] Met Glu Leu Leu Ser Leu Lys Ser Glu Asp Ser Ala Val Tyr Tyr Cys

[0649] 85 90 95

[0650] Ala Ile Ser Arg Tyr Gly Ser Glu Ser Trp Tyr Phe Asp Val Trp Gly

[0651] 100 105 110

[0652] Ala Gly Thr Thr Val Thr Val Ser Ser

[0653] 115 120

[0654] <210> 62

[0655] <211> 118

[0656] <212> PRT

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[0663] Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Asn Ile Tyr

[0664] 20 25 30

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[0666] 35 40 45

[0667] Gly Glu Ile Leu Pro Gly Ser Gly Asn Thr His Tyr Asn Glu Asn Phe

[0668] 50 55 60

[0669] Lys Gly Lys Ala Thr Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr

[0670] 65 70 75 80

[0671] Met Gln Leu Thr Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys

[0672] 85 90 95

[0673] Ala Arg Thr Asp Gly Arg Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr

[0674] 100 105 110

[0675] Thr Leu Thr Val Ser Ser

[0676] 115

[0677] <210> 63

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[0685] 1 5 10 15

[0686] Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Ser Tyr

[0687] 20 25 30

[0688] Trp Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Leu

[0689] 35 40 45

[0690] Gly Glu Phe Leu Pro Arg Ser Gly Lys Thr Asn Tyr Asn Glu Glu Phe

[0691] 50 55 60

[0692] Arg Gly Lys Ala Thr Phe Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr

[0693] 65 70 75 80

[0694] Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys

[0695] 85 90 95

[0696] Ala Arg Thr Asp Pro Pro Tyr Phe Gly Val Trp Gly Ala Gly Thr Met

[0697] 100 105 110

[0698] Val Ala Val Ser Ser

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[0709] Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Ile Ser Tyr Met

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[0711] His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Ser

[0712] 35 40 45

[0713] Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser

[0714] 50 55 60

[0715] Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Gly Val Glu Ala Glu

[0716] 65 70 75 80

[0717] Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Pro Thr

[0718] 85 90 95

[0719] Phe Gly Gly Gly Thr Asn Leu Glu Ile Lys

[0720] 100 105

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[0730] Glu Arg Val Thr Leu Ser Cys Lys Ala Ser Glu Asn Val Gly Gly Tyr

[0731] 20 25 30

[0732] Val Ser Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Leu Ile

[0733] 35 40 45

[0734] Tyr Gly Ala Ser Ser Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly

[0735] 50 55 60

[0736] Ser Gly Ser Glu Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala

[0737] 65 70 75 80

[0738] Glu Asp Leu Ala Ala Tyr His Cys Gly Gln Asn Tyr Ile Tyr Pro Phe

[0739] 85 90 95

[0740] Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys

[0741] 100 105

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[0751] Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Ile Ser

[0752] 20 25 30

[0753] Asn Tyr Ala Asn Trp Val Gln Glu Lys Pro Asp His Leu Phe Thr Gly

[0754] 35 40 45

[0755] Leu Ile Gly Gly Thr Asn Asn Arg Pro Pro Gly Val Pro Ala Arg Phe

[0756] 50 55 60

[0757] Ser Gly Ser Leu Ile Gly Asp Lys Ala Ala Leu Thr Ile Thr Gly Ala

[0758] 65 70 75 80

[0759] Gln Thr Glu Asp Glu Ala Ile Tyr Phe Cys Val Leu Trp Tyr Ser Asn

[0760] 85 90 95

[0761] His Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu

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[0772] Thr Ser Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser

[0773] 20 25 30

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[0775] 35 40 45

[0776] Pro Gln Leu Leu Ile Tyr Gln Met Ser Asn Leu Ala Ser Gly Val Pro

[0777] 50 55 60

[0778] Asp Arg Phe Ser Ser Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile

[0779] 65 70 75 80

[0780] Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ala Gln Asn

[0781] 85 90 95

[0782] Leu Glu Phe Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys

[0783] 100 105 110

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[0793] Glu Lys Val Thr Met Thr Cys Ser Ala Thr Ser Ser Val Ser Tyr Ile

[0794] 20 25 30

[0795] Tyr Trp Tyr Gln Gln Lys Pro Arg Ser Ser Pro Lys Pro Trp Ile Tyr

[0796] 35 40 45

[0797] Leu Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser

[0798] 50 55 60

[0799] Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu

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[0801] Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Pro Thr

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[0803] Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys

[0804] 100 105

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[0814] Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met

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[0817] 35 40 45

[0818] Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser

[0819] 50 55 60

[0820] Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Thr Glu

[0821] 65 70 75 80

[0822] Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Pro Thr

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[0824] Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys

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[0835] Glu Lys Val Thr Met Thr Cys Arg Ala Thr Ser Ser Val Ser Tyr Met

[0836] 20 25 30

[0837] Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr

[0838] 35 40 45

[0839] Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser

[0840] 50 55 60

[0841] Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu

[0842] 65 70 75 80

[0843] Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Pro Thr

[0844] 85 90 95

[0845] Phe Gly Gly Gly Thr Lys Leu Glu Lys Lys

[0846] 100 105

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[0852] <223> 轻链可变区

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[0856] Gln Arg Ala Thr Ile Ser Cys Arg Thr Ser Lys Ser Val Ser Ser Ser

[0857] 20 25 30

[0858] Ala Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro

[0859] 35 40 45

[0860] Lys Val Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser Gly Val Pro Ala

[0861] 50 55 60

[0862] Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His

[0863] 65 70 75 80

[0864] Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ser Arg

[0865] 85 90 95

[0866] Glu Leu Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys

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[0874] <400> 72

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[0876] 1 5 10 15

[0877] Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Asn Ile Ser Tyr Met

[0878] 20 25 30

[0879] His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr

[0880] 35 40 45

[0881] Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser

[0882] 50 55 60

[0883] Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu

[0884] 65 70 75 80

[0885] Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Val Pro Leu Thr

[0886] 85 90 95

[0887] Phe Gly Ala Gly Thr Lys Leu Glu Ile Lys

[0888] 100 105

[0889] <210> 73

[0890] <211> 229

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[0898] Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr

[0899] 20 25 30

[0900] Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val

[0901] 35 40 45

[0902] Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val

[0903] 50 55 60

[0904] Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser

[0905] 65 70 75 80

[0906] Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu

[0907] 85 90 95

[0908] Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser

[0909] 100 105 110

[0910] Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro

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[0912] Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln

[0913] 130 135 140

[0914] Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala

[0915] 145 150 155 160

[0916] Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr

[0917] 165 170 175

[0918] Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu

[0919] 180 185 190

[0920] Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser

[0921] 195 200 205

[0922] Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser

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[0924] Leu Ser Leu Gly Lys

[0925] 225

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[0927] <211> 326

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[0930] <220>

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[0936] 20 25 30

[0937] Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser

[0938] 35 40 45

[0939] Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser

[0940] 50 55 60

[0941] Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr

[0942] 65 70 75 80

[0943] Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys

[0944] 85 90 95

[0945] Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro

[0946] 100 105 110

[0947] Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys

[0948] 115 120 125

[0949] Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val

[0950] 130 135 140

[0951] Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp

[0952] 145 150 155 160

[0953] Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe

[0954] 165 170 175

[0955] Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp

[0956] 180 185 190

[0957] Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu

[0958] 195 200 205

[0959] Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg

[0960] 210 215 220

[0961] Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys

[0962] 225 230 235 240

[0963] Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp

[0964] 245 250 255

[0965] Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys

[0966] 260 265 270

[0967] Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser

[0968] 275 280 285

[0969] Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser

[0970] 290 295 300

[0971] Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser

[0972] 305 310 315 320

[0973] Leu Ser Leu Ser Leu Gly

[0974] 325

[0975] <210> 75

[0976] <211> 107

[0977] <212> PRT

[0978] <213> Artificial Sequence

[0979] <220>

[0980] <223> 抗体恒定区的全长序列

[0981] <400> 75

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[0983] 1 5 10 15

[0984] Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe

[0985] 20 25 30

[0986] Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln

[0987] 35 40 45

[0988] Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser

[0989] 50 55 60

[0990] Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu

[0991] 65 70 75 80

[0992] Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser

[0993] 85 90 95

[0994] Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

[0995] 100 105

[0996] <210> 76

[0997] <211> 447

[0998] <212> PRT

[0999] <213> Artificial Sequence

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[1006] 20 25 30

[1007] Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile

[1008] 35 40 45
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[1010] 50 55 60
[1011] Lys Gly Lys Ala Thr Leu Thr Leu Asp Lys Ser Ser Ser Thr Ala Tyr
[1012] 65 70 75 80
[1013] Met Asp Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[1014] 85 90 95
[1015] Ala Ile Ser Arg Tyr Gly Ser Ser Ser Phe Tyr Phe Asp Val Trp Gly
[1016] 100 105 110
[1017] Ala Gly Thr Thr Val Ala Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
[1018] 115 120 125
[1019] Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
[1020] 130 135 140
[1021] Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
[1022] 145 150 155 160
[1023] Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
[1024] 165 170 175
[1025] Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
[1026] 180 185 190
[1027] Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His
[1028] 195 200 205
[1029] Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly
[1030] 210 215 220
[1031] Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
[1032] 225 230 235 240
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[1036] 260 265 270
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[1042] 305 310 315 320
[1043] Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
[1044] 325 330 335
[1045] Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[1046] 340 345 350
[1047] Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
[1048] 355 360 365
[1049] Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser

[1050] 370 375 380
[1051] Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
[1052] 385 390 395 400
[1053] Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
[1054] 405 410 415
[1055] Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
[1056] 420 425 430
[1057] Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
[1058] 435 440 445
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[1060] <211> 442
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[1069] 20 25 30
[1070] Trp Leu Gly Trp Met Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
[1071] 35 40 45
[1072] Gly Asp Phe Tyr Pro Arg Thr Gly Asn Thr Phe Tyr Asn Glu Asn Phe
[1073] 50 55 60
[1074] Lys Gly Lys Val Thr Leu Thr Ala Asp Lys Ser Ser Asn Thr Ala Tyr
[1075] 65 70 75 80
[1076] Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Leu Cys
[1077] 85 90 95
[1078] Ala Arg Ala Gly Thr Gly Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu
[1079] 100 105 110
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[1081] 115 120 125
[1082] Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu
[1083] 130 135 140
[1084] Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
[1085] 145 150 155 160
[1086] Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
[1087] 165 170 175
[1088] Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
[1089] 180 185 190
[1090] Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr
[1091] 195 200 205

[1092] Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
[1093] 210 215 220
[1094] Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
[1095] 225 230 235 240
[1096] Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
[1097] 245 250 255
[1098] Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
[1099] 260 265 270
[1100] Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
[1101] 275 280 285
[1102] Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
[1103] 290 295 300
[1104] Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
[1105] 305 310 315 320
[1106] Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
[1107] 325 330 335
[1108] Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
[1109] 340 345 350
[1110] Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
[1111] 355 360 365
[1112] Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
[1113] 370 375 380
[1114] Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
[1115] 385 390 395 400
[1116] Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
[1117] 405 410 415
[1118] Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
[1119] 420 425 430
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[1121] 435 440
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[1123] <211> 443
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[1132] 20 25 30
[1133] Trp Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Leu

[1134] 35 40 45
[1135] Gly Glu Ile Leu Pro Gly Arg Gly Ile Ile Asn Tyr Asn Glu Asn Phe
[1136] 50 55 60
[1137] Arg Gly Lys Ala Thr Phe Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
[1138] 65 70 75 80
[1139] Val Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
[1140] 85 90 95
[1141] Ala Arg Thr Asp Pro Pro Tyr Phe Gly Val Trp Gly Ala Gly Thr Thr
[1142] 100 105 110
[1143] Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
[1144] 115 120 125
[1145] Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
[1146] 130 135 140
[1147] Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
[1148] 145 150 155 160
[1149] Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
[1150] 165 170 175
[1151] Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
[1152] 180 185 190
[1153] Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn
[1154] 195 200 205
[1155] Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro
[1156] 210 215 220
[1157] Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
[1158] 225 230 235 240
[1159] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[1160] 245 250 255
[1161] Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
[1162] 260 265 270
[1163] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[1164] 275 280 285
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[1166] 290 295 300
[1167] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[1168] 305 310 315 320
[1169] Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
[1170] 325 330 335
[1171] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln
[1172] 340 345 350
[1173] Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[1174] 355 360 365
[1175] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro

[1176] 370 375 380
[1177] Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[1178] 385 390 395 400
[1179] Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
[1180] 405 410 415
[1181] Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[1182] 420 425 430
[1183] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
[1184] 435 440
[1185] <210> 79
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[1188] <213> Artificial Sequence
[1189] <220>
[1190] <223> 重链
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[1194] Ser Met Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Thr Tyr
[1195] 20 25 30
[1196] Trp Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
[1197] 35 40 45
[1198] Gly Glu Asn Leu Pro Gly Arg His Ile Thr Asn Tyr Asn Glu Lys Phe
[1199] 50 55 60
[1200] Lys Gly Lys Ala Thr Phe Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
[1201] 65 70 75 80
[1202] Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[1203] 85 90 95
[1204] Ala Arg Gly Arg Gly Thr Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
[1205] 100 105 110
[1206] Pro Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
[1207] 115 120 125
[1208] Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
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[1210] Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
[1211] 145 150 155 160
[1212] Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
[1213] 165 170 175
[1214] Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
[1215] 180 185 190
[1216] Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
[1217] 195 200 205

[1218] Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys
[1219] 210 215 220
[1220] Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu
[1221] 225 230 235 240
[1222] Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
[1223] 245 250 255
[1224] Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln
[1225] 260 265 270
[1226] Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
[1227] 275 280 285
[1228] Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu
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[1230] Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
[1231] 305 310 315 320
[1232] Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys
[1233] 325 330 335
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[1235] 340 345 350
[1236] Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
[1237] 355 360 365
[1238] Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
[1239] 370 375 380
[1240] Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
[1241] 385 390 395 400
[1242] Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
[1243] 405 410 415
[1244] Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
[1245] 420 425 430
[1246] His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
[1247] 435 440
[1248] <210> 80
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[1253] <223> 重链
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[1260] 35 40 45
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[1262] 50 55 60
[1263] Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
[1264] 65 70 75 80
[1265] Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[1266] 85 90 95
[1267] Ala Phe Ser Tyr Tyr Gly Ser Arg Gly Phe Tyr Phe Asp Tyr Trp Gly
[1268] 100 105 110
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[1270] 115 120 125
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[1272] 130 135 140
[1273] Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
[1274] 145 150 155 160
[1275] Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
[1276] 165 170 175
[1277] Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
[1278] 180 185 190
[1279] Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His
[1280] 195 200 205
[1281] Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly
[1282] 210 215 220
[1283] Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
[1284] 225 230 235 240
[1285] Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
[1286] 245 250 255
[1287] Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
[1288] 260 265 270
[1289] Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
[1290] 275 280 285
[1291] Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val
[1292] 290 295 300
[1293] Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
[1294] 305 310 315 320
[1295] Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
[1296] 325 330 335
[1297] Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[1298] 340 345 350
[1299] Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
[1300] 355 360 365
[1301] Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser

[1302] 370 375 380
[1303] Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
[1304] 385 390 395 400
[1305] Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
[1306] 405 410 415
[1307] Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
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[1309] Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
[1310] 435 440 445
[1311] <210> 81
[1312] <211> 448
[1313] <212> PRT
[1314] <213> Artificial Sequence
[1315] <220>
[1316] <223> 重链
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[1320] Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
[1321] 20 25 30
[1322] Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
[1323] 35 40 45
[1324] Gly Leu Ile Asn Pro Tyr Asn Gly Gly Thr Arg Tyr Asn Gln Lys Phe
[1325] 50 55 60
[1326] Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
[1327] 65 70 75 80
[1328] Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[1329] 85 90 95
[1330] Ala Ser Ser Ser Tyr Arg Asn Asp Gly Asn Trp Tyr Phe Asp Val Trp
[1331] 100 105 110
[1332] Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
[1333] 115 120 125
[1334] Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
[1335] 130 135 140
[1336] Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
[1337] 145 150 155 160
[1338] Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
[1339] 165 170 175
[1340] Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
[1341] 180 185 190
[1342] Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
[1343] 195 200 205

[1344] His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
[1345] 210 215 220
[1346] Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
[1347] 225 230 235 240
[1348] Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[1349] 245 250 255
[1350] Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
[1351] 260 265 270
[1352] Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[1353] 275 280 285
[1354] Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
[1355] 290 295 300
[1356] Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[1357] 305 310 315 320
[1358] Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
[1359] 325 330 335
[1360] Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[1361] 340 345 350
[1362] Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
[1363] 355 360 365
[1364] Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[1365] 370 375 380
[1366] Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[1367] 385 390 395 400
[1368] Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[1369] 405 410 415
[1370] Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[1371] 420 425 430
[1372] Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
[1373] 435 440 445
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[1375] <211> 447
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[1380] <400> 82
[1381] Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
[1382] 1 5 10 15
[1383] Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Ile Thr Gly Tyr
[1384] 20 25 30
[1385] Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile

[1386] 35 40 45
[1387] Gly Leu Val Asn Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe
[1388] 50 55 60
[1389] Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
[1390] 65 70 75 80
[1391] Met Glu Leu Leu Ser Leu Lys Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[1392] 85 90 95
[1393] Ala Ile Ser Arg Tyr Gly Ser Glu Ser Trp Tyr Phe Asp Val Trp Gly
[1394] 100 105 110
[1395] Ala Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
[1396] 115 120 125
[1397] Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
[1398] 130 135 140
[1399] Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
[1400] 145 150 155 160
[1401] Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
[1402] 165 170 175
[1403] Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
[1404] 180 185 190
[1405] Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His
[1406] 195 200 205
[1407] Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly
[1408] 210 215 220
[1409] Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
[1410] 225 230 235 240
[1411] Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
[1412] 245 250 255
[1413] Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
[1414] 260 265 270
[1415] Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
[1416] 275 280 285
[1417] Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val
[1418] 290 295 300
[1419] Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
[1420] 305 310 315 320
[1421] Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
[1422] 325 330 335
[1423] Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[1424] 340 345 350
[1425] Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
[1426] 355 360 365
[1427] Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser

[1428] 370 375 380
[1429] Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
[1430] 385 390 395 400
[1431] Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
[1432] 405 410 415
[1433] Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
[1434] 420 425 430
[1435] Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
[1436] 435 440 445
[1437] <210> 83
[1438] <211> 444
[1439] <212> PRT
[1440] <213> Artificial Sequence
[1441] <220>
[1442] <223> 重链
[1443] <400> 83
[1444] Gln Val His Leu Gln Gln Ser Gly Ala Glu Leu Met Lys Pro Gly Ala
[1445] 1 5 10 15
[1446] Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Asn Ile Tyr
[1447] 20 25 30
[1448] Trp Ile Asp Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
[1449] 35 40 45
[1450] Gly Glu Ile Leu Pro Gly Ser Gly Asn Thr His Tyr Asn Glu Asn Phe
[1451] 50 55 60
[1452] Lys Gly Lys Ala Thr Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
[1453] 65 70 75 80
[1454] Met Gln Leu Thr Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[1455] 85 90 95
[1456] Ala Arg Thr Asp Gly Arg Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
[1457] 100 105 110
[1458] Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
[1459] 115 120 125
[1460] Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
[1461] 130 135 140
[1462] Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
[1463] 145 150 155 160
[1464] Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
[1465] 165 170 175
[1466] Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
[1467] 180 185 190
[1468] Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
[1469] 195 200 205

[1470] Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys
[1471] 210 215 220
[1472] Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu
[1473] 225 230 235 240
[1474] Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
[1475] 245 250 255
[1476] Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln
[1477] 260 265 270
[1478] Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
[1479] 275 280 285
[1480] Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu
[1481] 290 295 300
[1482] Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
[1483] 305 310 315 320
[1484] Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys
[1485] 325 330 335
[1486] Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
[1487] 340 345 350
[1488] Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
[1489] 355 360 365
[1490] Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
[1491] 370 375 380
[1492] Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
[1493] 385 390 395 400
[1494] Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
[1495] 405 410 415
[1496] Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
[1497] 420 425 430
[1498] His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
[1499] 435 440
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[1501] <211> 443
[1502] <212> PRT
[1503] <213> Artificial Sequence
[1504] <220>
[1505] <223> 重链
[1506] <400> 84
[1507] Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Met Lys Pro Gly Ala
[1508] 1 5 10 15
[1509] Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Ser Tyr
[1510] 20 25 30
[1511] Trp Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Leu

[1512] 35 40 45
[1513] Gly Glu Phe Leu Pro Arg Ser Gly Lys Thr Asn Tyr Asn Glu Glu Phe
[1514] 50 55 60
[1515] Arg Gly Lys Ala Thr Phe Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
[1516] 65 70 75 80
[1517] Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[1518] 85 90 95
[1519] Ala Arg Thr Asp Pro Pro Tyr Phe Gly Val Trp Gly Ala Gly Thr Met
[1520] 100 105 110
[1521] Val Ala Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
[1522] 115 120 125
[1523] Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
[1524] 130 135 140
[1525] Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
[1526] 145 150 155 160
[1527] Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
[1528] 165 170 175
[1529] Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
[1530] 180 185 190
[1531] Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn
[1532] 195 200 205
[1533] Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro
[1534] 210 215 220
[1535] Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
[1536] 225 230 235 240
[1537] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[1538] 245 250 255
[1539] Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
[1540] 260 265 270
[1541] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[1542] 275 280 285
[1543] Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[1544] 290 295 300
[1545] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[1546] 305 310 315 320
[1547] Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
[1548] 325 330 335
[1549] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln
[1550] 340 345 350
[1551] Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[1552] 355 360 365
[1553] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro

[1554] 370 375 380
[1555] Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[1556] 385 390 395 400
[1557] Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
[1558] 405 410 415
[1559] Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[1560] 420 425 430
[1561] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
[1562] 435 440
[1563] <210> 85
[1564] <211> 213
[1565] <212> PRT
[1566] <213> Artificial Sequence
[1567] <220>
[1568] <223> 轻链
[1569] <400> 85
[1570] Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
[1571] 1 5 10 15
[1572] Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Ile Ser Tyr Met
[1573] 20 25 30
[1574] His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Ser
[1575] 35 40 45
[1576] Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
[1577] 50 55 60
[1578] Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Gly Val Glu Ala Glu
[1579] 65 70 75 80
[1580] Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Pro Thr
[1581] 85 90 95
[1582] Phe Gly Gly Gly Thr Asn Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
[1583] 100 105 110
[1584] Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
[1585] 115 120 125
[1586] Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
[1587] 130 135 140
[1588] Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
[1589] 145 150 155 160
[1590] Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
[1591] 165 170 175
[1592] Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
[1593] 180 185 190
[1594] Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
[1595] 195 200 205

[1596] Asn Arg Gly Glu Cys
[1597] 210
[1598] <210> 86
[1599] <211> 214
[1600] <212> PRT
[1601] <213> Artificial Sequence
[1602] <220>
[1603] <223> 轻链
[1604] <400> 86
[1605] Ser Ile Val Met Thr Gln Ser Pro Lys Ser Met Ser Met Ser Val Gly
[1606] 1 5 10 15
[1607] Glu Arg Val Thr Leu Ser Cys Lys Ala Ser Glu Asn Val Gly Gly Tyr
[1608] 20 25 30
[1609] Val Ser Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Leu Ile
[1610] 35 40 45
[1611] Tyr Gly Ala Ser Ser Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
[1612] 50 55 60
[1613] Ser Gly Ser Glu Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
[1614] 65 70 75 80
[1615] Glu Asp Leu Ala Ala Tyr His Cys Gly Gln Asn Tyr Ile Tyr Pro Phe
[1616] 85 90 95
[1617] Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
[1618] 100 105 110
[1619] Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
[1620] 115 120 125
[1621] Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
[1622] 130 135 140
[1623] Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
[1624] 145 150 155 160
[1625] Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
[1626] 165 170 175
[1627] Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
[1628] 180 185 190
[1629] Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
[1630] 195 200 205
[1631] Phe Asn Arg Gly Glu Cys
[1632] 210
[1633] <210> 87
[1634] <211> 216
[1635] <212> PRT
[1636] <213> Artificial Sequence
[1637] <220>

[1638] <223> 轻链
[1639] <400> 87
[1640] Gln Ala Val Val Thr Gln Glu Ser Ala Leu Thr Thr Ser Pro Gly Glu
[1641] 1 5 10 15
[1642] Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Ile Ser
[1643] 20 25 30
[1644] Asn Tyr Ala Asn Trp Val Gln Glu Lys Pro Asp His Leu Phe Thr Gly
[1645] 35 40 45
[1646] Leu Ile Gly Gly Thr Asn Asn Arg Pro Pro Gly Val Pro Ala Arg Phe
[1647] 50 55 60
[1648] Ser Gly Ser Leu Ile Gly Asp Lys Ala Ala Leu Thr Ile Thr Gly Ala
[1649] 65 70 75 80
[1650] Gln Thr Glu Asp Glu Ala Ile Tyr Phe Cys Val Leu Trp Tyr Ser Asn
[1651] 85 90 95
[1652] His Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Arg Thr Val
[1653] 100 105 110
[1654] Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
[1655] 115 120 125
[1656] Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
[1657] 130 135 140
[1658] Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
[1659] 145 150 155 160
[1660] Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
[1661] 165 170 175
[1662] Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
[1663] 180 185 190
[1664] Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
[1665] 195 200 205
[1666] Lys Ser Phe Asn Arg Gly Glu Cys
[1667] 210 215
[1668] <210> 88
[1669] <211> 219
[1670] <212> PRT
[1671] <213> Artificial Sequence
[1672] <220>
[1673] <223> 轻链
[1674] <400> 88
[1675] Asp Ile Val Met Thr Gln Ala Ala Phe Ser Thr Pro Val Thr Leu Gly
[1676] 1 5 10 15
[1677] Thr Ser Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
[1678] 20 25 30
[1679] Asn Gly Ile Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Ser

[1680] 35 40 45
[1681] Pro Gln Leu Leu Ile Tyr Gln Met Ser Asn Leu Ala Ser Gly Val Pro
[1682] 50 55 60
[1683] Asp Arg Phe Ser Ser Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile
[1684] 65 70 75 80
[1685] Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ala Gln Asn
[1686] 85 90 95
[1687] Leu Glu Phe Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
[1688] 100 105 110
[1689] Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
[1690] 115 120 125
[1691] Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
[1692] 130 135 140
[1693] Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
[1694] 145 150 155 160
[1695] Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
[1696] 165 170 175
[1697] Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
[1698] 180 185 190
[1699] Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
[1700] 195 200 205
[1701] Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
[1702] 210 215
[1703] <210> 89
[1704] <211> 213
[1705] <212> PRT
[1706] <213> Artificial Sequence
[1707] <220>
[1708] <223> 轻链
[1709] <400> 89
[1710] Gln Ile Val Leu Thr Gln Ser Pro Ala Leu Met Ser Ala Ser Pro Gly
[1711] 1 5 10 15
[1712] Glu Lys Val Thr Met Thr Cys Ser Ala Thr Ser Ser Val Ser Tyr Ile
[1713] 20 25 30
[1714] Tyr Trp Tyr Gln Gln Lys Pro Arg Ser Ser Pro Lys Pro Trp Ile Tyr
[1715] 35 40 45
[1716] Leu Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
[1717] 50 55 60
[1718] Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
[1719] 65 70 75 80
[1720] Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Pro Thr
[1721] 85 90 95

[1722] Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
[1723] 100 105 110
[1724] Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
[1725] 115 120 125
[1726] Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
[1727] 130 135 140
[1728] Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
[1729] 145 150 155 160
[1730] Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
[1731] 165 170 175
[1732] Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
[1733] 180 185 190
[1734] Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
[1735] 195 200 205
[1736] Asn Arg Gly Glu Cys
[1737] 210
[1738] <210> 90
[1739] <211> 213
[1740] <212> PRT
[1741] <213> Artificial Sequence
[1742] <220>
[1743] <223> 轻链
[1744] <400> 90
[1745] Asp Ile Val Met Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
[1746] 1 5 10 15
[1747] Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
[1748] 20 25 30
[1749] His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
[1750] 35 40 45
[1751] Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
[1752] 50 55 60
[1753] Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Thr Glu
[1754] 65 70 75 80
[1755] Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Pro Thr
[1756] 85 90 95
[1757] Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro
[1758] 100 105 110
[1759] Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
[1760] 115 120 125
[1761] Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
[1762] 130 135 140
[1763] Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu

[1764] 145 150 155 160
[1765] Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
[1766] 165 170 175
[1767] Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
[1768] 180 185 190
[1769] Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
[1770] 195 200 205
[1771] Asn Arg Gly Glu Cys
[1772] 210
[1773] <210> 91
[1774] <211> 213
[1775] <212> PRT
[1776] <213> Artificial Sequence
[1777] <220>
[1778] <223> 轻链
[1779] <400> 91
[1780] Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
[1781] 1 5 10 15
[1782] Glu Lys Val Thr Met Thr Cys Arg Ala Thr Ser Ser Val Ser Tyr Met
[1783] 20 25 30
[1784] Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
[1785] 35 40 45
[1786] Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
[1787] 50 55 60
[1788] Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
[1789] 65 70 75 80
[1790] Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Pro Thr
[1791] 85 90 95
[1792] Phe Gly Gly Gly Thr Lys Leu Glu Lys Lys Arg Thr Val Ala Ala Pro
[1793] 100 105 110
[1794] Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
[1795] 115 120 125
[1796] Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
[1797] 130 135 140
[1798] Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
[1799] 145 150 155 160
[1800] Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
[1801] 165 170 175
[1802] Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
[1803] 180 185 190
[1804] Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
[1805] 195 200 205

[1806] Asn Arg Gly Glu Cys
[1807] 210
[1808] <210> 92
[1809] <211> 218
[1810] <212> PRT
[1811] <213> Artificial Sequence
[1812] <220>
[1813] <223> 轻链
[1814] <400> 92
[1815] Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Val Val Ser Leu Gly
[1816] 1 5 10 15
[1817] Gln Arg Ala Thr Ile Ser Cys Arg Thr Ser Lys Ser Val Ser Ser Ser
[1818] 20 25 30
[1819] Ala Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
[1820] 35 40 45
[1821] Lys Val Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
[1822] 50 55 60
[1823] Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
[1824] 65 70 75 80
[1825] Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ser Arg
[1826] 85 90 95
[1827] Glu Leu Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg
[1828] 100 105 110
[1829] Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
[1830] 115 120 125
[1831] Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
[1832] 130 135 140
[1833] Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
[1834] 145 150 155 160
[1835] Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
[1836] 165 170 175
[1837] Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
[1838] 180 185 190
[1839] His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
[1840] 195 200 205
[1841] Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
[1842] 210 215
[1843] <210> 93
[1844] <211> 213
[1845] <212> PRT
[1846] <213> Artificial Sequence
[1847] <220>

[1848] <223> 轻链

[1849] <400> 93

[1850] Gln Ile Val Leu Thr Gln Ser Pro Pro Ile Met Ser Ala Ser Pro Gly

[1851] 1 5 10 15

[1852] Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Asn Ile Ser Tyr Met

[1853] 20 25 30

[1854] His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr

[1855] 35 40 45

[1856] Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser

[1857] 50 55 60

[1858] Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu

[1859] 65 70 75 80

[1860] Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Val Pro Leu Thr

[1861] 85 90 95

[1862] Phe Gly Ala Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro

[1863] 100 105 110

[1864] Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr

[1865] 115 120 125

[1866] Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys

[1867] 130 135 140

[1868] Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu

[1869] 145 150 155 160

[1870] Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser

[1871] 165 170 175

[1872] Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala

[1873] 180 185 190

[1874] Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe

[1875] 195 200 205

[1876] Asn Arg Gly Glu Cys

[1877] 210

[1878] <210> 94

[1879] <211> 242

[1880] <212> PRT

[1881] <213> Artificial Sequence

[1882] <220>

[1883] <223> 单链抗体

[1884] <400> 94

[1885] Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly

[1886] 1 5 10 15

[1887] Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Ile Ser Tyr Met

[1888] 20 25 30

[1889] His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Ser

[1890] 35 40 45
[1891] Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
[1892] 50 55 60
[1893] Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Gly Val Glu Ala Glu
[1894] 65 70 75 80
[1895] Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Pro Thr
[1896] 85 90 95
[1897] Phe Gly Gly Gly Thr Asn Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly
[1898] 100 105 110
[1899] Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Leu Leu Gln Gln Ser
[1900] 115 120 125
[1901] Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Met Lys Ile Ser Cys Lys
[1902] 130 135 140
[1903] Ala Ser Val Tyr Ser Phe Thr Ala Tyr Thr Met Asn Trp Val Lys Gln
[1904] 145 150 155 160
[1905] Ser His Gly Lys Asn Leu Glu Trp Ile Gly Leu Ile Asn Pro His Asn
[1906] 165 170 175
[1907] Gly Gly Thr Arg Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr
[1908] 180 185 190
[1909] Leu Asp Lys Ser Ser Ser Thr Ala Tyr Met Asp Leu Leu Ser Leu Thr
[1910] 195 200 205
[1911] Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Ile Ser Arg Tyr Gly Ser
[1912] 210 215 220
[1913] Ser Ser Phe Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Val Ala Val
[1914] 225 230 235 240
[1915] Ser Ser
[1916] <210> 95
[1917] <211> 242
[1918] <212> PRT
[1919] <213> Artificial Sequence
[1920] <220>
[1921] <223> 单链抗体
[1922] <400> 95
[1923] Glu Val Leu Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
[1924] 1 5 10 15
[1925] Ser Met Lys Ile Ser Cys Lys Ala Ser Val Tyr Ser Phe Thr Ala Tyr
[1926] 20 25 30
[1927] Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
[1928] 35 40 45
[1929] Gly Leu Ile Asn Pro His Asn Gly Gly Thr Arg Tyr Asn Gln Lys Phe
[1930] 50 55 60
[1931] Lys Gly Lys Ala Thr Leu Thr Leu Asp Lys Ser Ser Ser Thr Ala Tyr

[1932] 65 70 75 80
[1933] Met Asp Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[1934] 85 90 95
[1935] Ala Ile Ser Arg Tyr Gly Ser Ser Ser Phe Tyr Phe Asp Val Trp Gly
[1936] 100 105 110
[1937] Ala Gly Thr Thr Val Ala Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
[1938] 115 120 125
[1939] Gly Gly Ser Gly Gly Gly Gly Ser Gln Ile Val Leu Ser Gln Ser Pro
[1940] 130 135 140
[1941] Ala Ile Leu Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Arg
[1942] 145 150 155 160
[1943] Ala Ser Ser Ser Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly
[1944] 165 170 175
[1945] Ser Ser Pro Lys Pro Trp Ile Ser Ala Thr Ser Asn Leu Ala Ser Gly
[1946] 180 185 190
[1947] Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu
[1948] 195 200 205
[1949] Thr Ile Ser Gly Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln
[1950] 210 215 220
[1951] Gln Trp Ser Ser Asn Pro Pro Thr Phe Gly Gly Gly Thr Asn Leu Glu
[1952] 225 230 235 240
[1953] Ile Lys
[1954] <210> 96
[1955] <211> 238
[1956] <212> PRT
[1957] <213> Artificial Sequence
[1958] <220>
[1959] <223> 单链抗体
[1960] <400> 96
[1961] Ser Ile Val Met Thr Gln Ser Pro Lys Ser Met Ser Met Ser Val Gly
[1962] 1 5 10 15
[1963] Glu Arg Val Thr Leu Ser Cys Lys Ala Ser Glu Asn Val Gly Gly Tyr
[1964] 20 25 30
[1965] Val Ser Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Leu Ile
[1966] 35 40 45
[1967] Tyr Gly Ala Ser Ser Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
[1968] 50 55 60
[1969] Ser Gly Ser Glu Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
[1970] 65 70 75 80
[1971] Glu Asp Leu Ala Ala Tyr His Cys Gly Gln Asn Tyr Ile Tyr Pro Phe
[1972] 85 90 95
[1973] Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser

[1974] 100 105 110
[1975] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln
[1976] 115 120 125
[1977] Ser Gly Ala Glu Leu Val Arg Pro Gly Thr Ser Val Lys Ile Ser Cys
[1978] 130 135 140
[1979] Lys Ala Ser Gly Tyr Ala Phe Thr Asn Tyr Trp Leu Gly Trp Met Lys
[1980] 145 150 155 160
[1981] Gln Arg Pro Gly His Gly Leu Glu Trp Ile Gly Asp Phe Tyr Pro Arg
[1982] 165 170 175
[1983] Thr Gly Asn Thr Phe Tyr Asn Glu Asn Phe Lys Gly Lys Val Thr Leu
[1984] 180 185 190
[1985] Thr Ala Asp Lys Ser Ser Asn Thr Ala Tyr Met Gln Leu Ser Ser Leu
[1986] 195 200 205
[1987] Thr Ser Glu Asp Ser Ala Val Tyr Leu Cys Ala Arg Ala Gly Thr Gly
[1988] 210 215 220
[1989] Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
[1990] 225 230 235
[1991] <210> 97
[1992] <211> 238
[1993] <212> PRT
[1994] <213> Artificial Sequence
[1995] <220>
[1996] <223> 单链抗体
[1997] <400> 97
[1998] Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Thr
[1999] 1 5 10 15
[2000] Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Tyr
[2001] 20 25 30
[2002] Trp Leu Gly Trp Met Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
[2003] 35 40 45
[2004] Gly Asp Phe Tyr Pro Arg Thr Gly Asn Thr Phe Tyr Asn Glu Asn Phe
[2005] 50 55 60
[2006] Lys Gly Lys Val Thr Leu Thr Ala Asp Lys Ser Ser Asn Thr Ala Tyr
[2007] 65 70 75 80
[2008] Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Leu Cys
[2009] 85 90 95
[2010] Ala Arg Ala Gly Thr Gly Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu
[2011] 100 105 110
[2012] Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
[2013] 115 120 125
[2014] Gly Gly Ser Ser Ile Val Met Thr Gln Ser Pro Lys Ser Met Ser Met
[2015] 130 135 140

[2016] Ser Val Gly Glu Arg Val Thr Leu Ser Cys Lys Ala Ser Glu Asn Val
[2017] 145 150 155 160
[2018] Gly Gly Tyr Val Ser Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys
[2019] 165 170 175
[2020] Leu Leu Ile Tyr Gly Ala Ser Ser Arg His Thr Gly Val Pro Asp Arg
[2021] 180 185 190
[2022] Phe Thr Gly Ser Gly Ser Glu Thr Asp Phe Thr Leu Thr Ile Ser Ser
[2023] 195 200 205
[2024] Val Gln Ala Glu Asp Leu Ala Ala Tyr His Cys Gly Gln Asn Tyr Ile
[2025] 210 215 220
[2026] Tyr Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
[2027] 225 230 235
[2028] <210> 98
[2029] <211> 241
[2030] <212> PRT
[2031] <213> Artificial Sequence
[2032] <220>
[2033] <223> 单链抗体
[2034] <400> 98
[2035] Gln Ala Val Val Thr Gln Glu Ser Ala Leu Thr Thr Ser Pro Gly Glu
[2036] 1 5 10 15
[2037] Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Ile Ser
[2038] 20 25 30
[2039] Asn Tyr Ala Asn Trp Val Gln Glu Lys Pro Asp His Leu Phe Thr Gly
[2040] 35 40 45
[2041] Leu Ile Gly Gly Thr Asn Asn Arg Pro Pro Gly Val Pro Ala Arg Phe
[2042] 50 55 60
[2043] Ser Gly Ser Leu Ile Gly Asp Lys Ala Ala Leu Thr Ile Thr Gly Ala
[2044] 65 70 75 80
[2045] Gln Thr Glu Asp Glu Ala Ile Tyr Phe Cys Val Leu Trp Tyr Ser Asn
[2046] 85 90 95
[2047] His Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
[2048] 100 105 110
[2049] Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu
[2050] 115 120 125
[2051] Gln Gln Ser Gly Ala Glu Leu Met Lys Pro Gly Ala Ser Val Lys Ile
[2052] 130 135 140
[2053] Ser Cys Lys Thr Thr Gly Tyr Arg Phe Ser Ser Tyr Trp Ile Glu Trp
[2054] 145 150 155 160
[2055] Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Leu Gly Glu Ile Leu
[2056] 165 170 175
[2057] Pro Gly Arg Gly Ile Ile Asn Tyr Asn Glu Asn Phe Arg Gly Lys Ala

[2058] 180 185 190
[2059] Thr Phe Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr Val Gln Leu Ser
[2060] 195 200 205
[2061] Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Thr Asp
[2062] 210 215 220
[2063] Pro Pro Tyr Phe Gly Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser
[2064] 225 230 235 240
[2065] Ser
[2066] <210> 99
[2067] <211> 241
[2068] <212> PRT
[2069] <213> Artificial Sequence
[2070] <220>
[2071] <223> 单链抗体
[2072] <400> 99
[2073] Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Met Lys Pro Gly Ala
[2074] 1 5 10 15
[2075] Ser Val Lys Ile Ser Cys Lys Thr Thr Gly Tyr Arg Phe Ser Ser Tyr
[2076] 20 25 30
[2077] Trp Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Leu
[2078] 35 40 45
[2079] Gly Glu Ile Leu Pro Gly Arg Gly Ile Ile Asn Tyr Asn Glu Asn Phe
[2080] 50 55 60
[2081] Arg Gly Lys Ala Thr Phe Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
[2082] 65 70 75 80
[2083] Val Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
[2084] 85 90 95
[2085] Ala Arg Thr Asp Pro Pro Tyr Phe Gly Val Trp Gly Ala Gly Thr Thr
[2086] 100 105 110
[2087] Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
[2088] 115 120 125
[2089] Gly Gly Gly Ser Gln Ala Val Val Thr Gln Glu Ser Ala Leu Thr Thr
[2090] 130 135 140
[2091] Ser Pro Gly Glu Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala
[2092] 145 150 155 160
[2093] Val Thr Ile Ser Asn Tyr Ala Asn Trp Val Gln Glu Lys Pro Asp His
[2094] 165 170 175
[2095] Leu Phe Thr Gly Leu Ile Gly Gly Thr Asn Asn Arg Pro Pro Gly Val
[2096] 180 185 190
[2097] Pro Ala Arg Phe Ser Gly Ser Leu Ile Gly Asp Lys Ala Ala Leu Thr
[2098] 195 200 205
[2099] Ile Thr Gly Ala Gln Thr Glu Asp Glu Ala Ile Tyr Phe Cys Val Leu

[2100] 210 215 220
[2101] Trp Tyr Ser Asn His Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
[2102] 225 230 235 240
[2103] Leu
[2104] <210> 100
[2105] <211> 245
[2106] <212> PRT
[2107] <213> Artificial Sequence
[2108] <220>
[2109] <223> 单链抗体
[2110] <400> 100
[2111] Asp Ile Val Met Thr Gln Ala Ala Phe Ser Thr Pro Val Thr Leu Gly
[2112] 1 5 10 15
[2113] Thr Ser Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
[2114] 20 25 30
[2115] Asn Gly Ile Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Ser
[2116] 35 40 45
[2117] Pro Gln Leu Leu Ile Tyr Gln Met Ser Asn Leu Ala Ser Gly Val Pro
[2118] 50 55 60
[2119] Asp Arg Phe Ser Ser Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile
[2120] 65 70 75 80
[2121] Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ala Gln Asn
[2122] 85 90 95
[2123] Leu Glu Phe Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
[2124] 100 105 110
[2125] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
[2126] 115 120 125
[2127] Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Met Lys Pro Gly Ala Ser
[2128] 130 135 140
[2129] Met Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Thr Tyr Trp
[2130] 145 150 155 160
[2131] Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile Gly
[2132] 165 170 175
[2133] Glu Asn Leu Pro Gly Arg His Ile Thr Asn Tyr Asn Glu Lys Phe Lys
[2134] 180 185 190
[2135] Gly Lys Ala Thr Phe Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr Met
[2136] 195 200 205
[2137] Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala
[2138] 210 215 220
[2139] Arg Gly Arg Gly Thr Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Pro
[2140] 225 230 235 240
[2141] Leu Thr Val Ser Ser

[2142] 245

[2143] <210> 101

[2144] <211> 245

[2145] <212> PRT

[2146] <213> Artificial Sequence

[2147] <220>

[2148] <223> 单链抗体

[2149] <400> 101

[2150] Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Met Lys Pro Gly Ala

[2151] 1 5 10 15

[2152] Ser Met Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Thr Tyr

[2153] 20 25 30

[2154] Trp Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile

[2155] 35 40 45

[2156] Gly Glu Asn Leu Pro Gly Arg His Ile Thr Asn Tyr Asn Glu Lys Phe

[2157] 50 55 60

[2158] Lys Gly Lys Ala Thr Phe Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr

[2159] 65 70 75 80

[2160] Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys

[2161] 85 90 95

[2162] Ala Arg Gly Arg Gly Thr Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr

[2163] 100 105 110

[2164] Pro Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser

[2165] 115 120 125

[2166] Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ala Ala Phe Ser Thr

[2167] 130 135 140

[2168] Pro Val Thr Leu Gly Thr Ser Ala Ser Ile Ser Cys Arg Ser Ser Gln

[2169] 145 150 155 160

[2170] Ser Leu Leu His Ser Asn Gly Ile Thr Tyr Leu Tyr Trp Tyr Leu Gln

[2171] 165 170 175

[2172] Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Gln Met Ser Asn Leu

[2173] 180 185 190

[2174] Ala Ser Gly Val Pro Asp Arg Phe Ser Ser Ser Gly Ser Gly Thr Asp

[2175] 195 200 205

[2176] Phe Thr Leu Arg Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr

[2177] 210 215 220

[2178] Tyr Cys Ala Gln Asn Leu Glu Phe Pro Phe Thr Phe Gly Ser Gly Thr

[2179] 225 230 235 240

[2180] Lys Leu Glu Ile Lys

[2181] 245

[2182] <210> 102

[2183] <211> 242

[2184] <212> PRT
[2185] <213> Artificial Sequence
[2186] <220>
[2187] <223> 单链抗体
[2188] <400> 102
[2189] Gln Ile Val Leu Thr Gln Ser Pro Ala Leu Met Ser Ala Ser Pro Gly
[2190] 1 5 10 15
[2191] Glu Lys Val Thr Met Thr Cys Ser Ala Thr Ser Ser Val Ser Tyr Ile
[2192] 20 25 30
[2193] Tyr Trp Tyr Gln Gln Lys Pro Arg Ser Ser Pro Lys Pro Trp Ile Tyr
[2194] 35 40 45
[2195] Leu Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
[2196] 50 55 60
[2197] Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
[2198] 65 70 75 80
[2199] Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Pro Thr
[2200] 85 90 95
[2201] Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly
[2202] 100 105 110
[2203] Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Gln Gln Ser
[2204] 115 120 125
[2205] Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Met Lys Ile Ser Cys Lys
[2206] 130 135 140
[2207] Ala Ser Gly Tyr Ser Phe Thr Gly Tyr Thr Met Asn Trp Val Lys Gln
[2208] 145 150 155 160
[2209] Ser His Gly Lys Asn Leu Glu Trp Ile Gly Leu Ile Asn Pro Tyr Asn
[2210] 165 170 175
[2211] Gly Gly Thr Asn Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr
[2212] 180 185 190
[2213] Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Leu Ser Leu Thr
[2214] 195 200 205
[2215] Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Phe Ser Tyr Tyr Gly Ser
[2216] 210 215 220
[2217] Arg Gly Phe Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
[2218] 225 230 235 240
[2219] Ser Ser
[2220] <210> 103
[2221] <211> 242
[2222] <212> PRT
[2223] <213> Artificial Sequence
[2224] <220>
[2225] <223> 单链抗体

[2226] <400> 103
[2227] Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
[2228] 1 5 10 15
[2229] Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
[2230] 20 25 30
[2231] Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
[2232] 35 40 45
[2233] Gly Leu Ile Asn Pro Tyr Asn Gly Gly Thr Asn Tyr Asn Gln Lys Phe
[2234] 50 55 60
[2235] Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
[2236] 65 70 75 80
[2237] Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[2238] 85 90 95
[2239] Ala Phe Ser Tyr Tyr Gly Ser Arg Gly Phe Tyr Phe Asp Tyr Trp Gly
[2240] 100 105 110
[2241] Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
[2242] 115 120 125
[2243] Gly Gly Ser Gly Gly Gly Gly Ser Gln Ile Val Leu Thr Gln Ser Pro
[2244] 130 135 140
[2245] Ala Leu Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Ser
[2246] 145 150 155 160
[2247] Ala Thr Ser Ser Val Ser Tyr Ile Tyr Trp Tyr Gln Gln Lys Pro Arg
[2248] 165 170 175
[2249] Ser Ser Pro Lys Pro Trp Ile Tyr Leu Thr Ser Asn Leu Ala Ser Gly
[2250] 180 185 190
[2251] Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu
[2252] 195 200 205
[2253] Thr Ile Ser Ser Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln
[2254] 210 215 220
[2255] Gln Trp Ser Ser Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu
[2256] 225 230 235 240
[2257] Ile Lys
[2258] <210> 104
[2259] <211> 243
[2260] <212> PRT
[2261] <213> Artificial Sequence
[2262] <220>
[2263] <223> 单链抗体
[2264] <400> 104
[2265] Asp Ile Val Met Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
[2266] 1 5 10 15
[2267] Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met

[2268] 20 25 30
[2269] His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
[2270] 35 40 45
[2271] Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
[2272] 50 55 60
[2273] Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Thr Glu
[2274] 65 70 75 80
[2275] Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Pro Thr
[2276] 85 90 95
[2277] Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Gly Gly Gly Gly Ser Gly
[2278] 100 105 110
[2279] Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Gln Gln Ser
[2280] 115 120 125
[2281] Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Met Lys Ile Ser Cys Lys
[2282] 130 135 140
[2283] Ala Ser Gly Tyr Ser Phe Thr Gly Tyr Thr Met Asn Trp Val Lys Gln
[2284] 145 150 155 160
[2285] Ser His Gly Lys Asn Leu Glu Trp Ile Gly Leu Ile Asn Pro Tyr Asn
[2286] 165 170 175
[2287] Gly Gly Thr Arg Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr
[2288] 180 185 190
[2289] Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Leu Ser Leu Thr
[2290] 195 200 205
[2291] Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Ser Ser Ser Tyr Arg Asn
[2292] 210 215 220
[2293] Asp Gly Asn Trp Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr
[2294] 225 230 235 240
[2295] Val Ser Ser
[2296] <210> 105
[2297] <211> 243
[2298] <212> PRT
[2299] <213> Artificial Sequence
[2300] <220>
[2301] <223> 单链抗体
[2302] <400> 105
[2303] Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
[2304] 1 5 10 15
[2305] Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
[2306] 20 25 30
[2307] Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
[2308] 35 40 45
[2309] Gly Leu Ile Asn Pro Tyr Asn Gly Gly Thr Arg Tyr Asn Gln Lys Phe

[2310] 50 55 60
[2311] Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
[2312] 65 70 75 80
[2313] Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[2314] 85 90 95
[2315] Ala Ser Ser Ser Tyr Arg Asn Asp Gly Asn Trp Tyr Phe Asp Val Trp
[2316] 100 105 110
[2317] Gly Ala Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
[2318] 115 120 125
[2319] Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
[2320] 130 135 140
[2321] Pro Ala Ile Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys
[2322] 145 150 155 160
[2323] Ser Ala Ser Ser Ser Val Ser Tyr Met His Trp Tyr Gln Gln Lys Ser
[2324] 165 170 175
[2325] Gly Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala Ser
[2326] 180 185 190
[2327] Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser
[2328] 195 200 205
[2329] Leu Thr Ile Ser Ser Met Glu Thr Glu Asp Ala Ala Thr Tyr Tyr Cys
[2330] 210 215 220
[2331] Gln Gln Trp Ser Ser Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu
[2332] 225 230 235 240
[2333] Glu Leu Lys
[2334] <210> 106
[2335] <211> 242
[2336] <212> PRT
[2337] <213> Artificial Sequence
[2338] <220>
[2339] <223> 单链抗体
[2340] <400> 106
[2341] Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
[2342] 1 5 10 15
[2343] Glu Lys Val Thr Met Thr Cys Arg Ala Thr Ser Ser Val Ser Tyr Met
[2344] 20 25 30
[2345] Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
[2346] 35 40 45
[2347] Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
[2348] 50 55 60
[2349] Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
[2350] 65 70 75 80
[2351] Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Pro Thr

[2352] 85 90 95
[2353] Phe Gly Gly Gly Thr Lys Leu Glu Lys Lys Gly Gly Gly Gly Ser Gly
[2354] 100 105 110
[2355] Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Gln Gln Ser
[2356] 115 120 125
[2357] Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Met Lys Ile Ser Cys Lys
[2358] 130 135 140
[2359] Ala Ser Gly Tyr Ser Ile Thr Gly Tyr Thr Met Asn Trp Val Lys Gln
[2360] 145 150 155 160
[2361] Ser His Gly Lys Asn Leu Glu Trp Ile Gly Leu Val Asn Pro Tyr Asn
[2362] 165 170 175
[2363] Gly Gly Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr
[2364] 180 185 190
[2365] Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Leu Ser Leu Lys
[2366] 195 200 205
[2367] Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Ile Ser Arg Tyr Gly Ser
[2368] 210 215 220
[2369] Glu Ser Trp Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val
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[2382] 20 25 30
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[2384] 35 40 45
[2385] Gly Leu Val Asn Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe
[2386] 50 55 60
[2387] Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
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[2394] 115 120 125
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[2396] 130 135 140
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[2398] 145 150 155 160
[2399] Ala Thr Ser Ser Val Ser Tyr Met Tyr Trp Tyr Gln Gln Lys Pro Gly
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[2402] 180 185 190
[2403] Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu
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[2405] Thr Ile Ser Arg Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln
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[2423] Lys Val Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
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[2425] Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
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[2432] 115 120 125
[2433] His Leu Gln Gln Ser Gly Ala Glu Leu Met Lys Pro Gly Ala Ser Val
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[2439] Ile Leu Pro Gly Ser Gly Asn Thr His Tyr Asn Glu Asn Phe Lys Gly
[2440] 180 185 190
[2441] Lys Ala Thr Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr Met Gln
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[2444] 210 215 220
[2445] Thr Asp Gly Arg Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu
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[2458] 20 25 30
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[2460] 35 40 45
[2461] Gly Glu Ile Leu Pro Gly Ser Gly Asn Thr His Tyr Asn Glu Asn Phe
[2462] 50 55 60
[2463] Lys Gly Lys Ala Thr Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
[2464] 65 70 75 80
[2465] Met Gln Leu Thr Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[2466] 85 90 95
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[2469] Thr Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[2470] 115 120 125
[2471] Gly Gly Gly Gly Ser Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu
[2472] 130 135 140
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[2474] 145 150 155 160
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[2476] 165 170 175
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[2480] 195 200 205
[2481] Thr Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr
[2482] 210 215 220
[2483] Cys Gln His Ser Arg Glu Leu Pro Phe Thr Phe Gly Ser Gly Thr Lys
[2484] 225 230 235 240
[2485] Leu Glu Ile Lys
[2486] <210> 110
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[2496] 20 25 30
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[2498] 35 40 45
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[2502] 65 70 75 80
[2503] Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Val Pro Leu Thr
[2504] 85 90 95
[2505] Phe Gly Ala Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly
[2506] 100 105 110
[2507] Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser
[2508] 115 120 125
[2509] Gly Ala Glu Leu Met Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys
[2510] 130 135 140
[2511] Ala Thr Gly Tyr Thr Phe Ser Ser Tyr Trp Ile Glu Trp Val Lys Gln
[2512] 145 150 155 160
[2513] Arg Pro Gly His Gly Leu Glu Trp Leu Gly Glu Phe Leu Pro Arg Ser
[2514] 165 170 175
[2515] Gly Lys Thr Asn Tyr Asn Glu Glu Phe Arg Gly Lys Ala Thr Phe Thr
[2516] 180 185 190
[2517] Ala Asp Thr Ser Ser Asn Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr
[2518] 195 200 205
[2519] Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Thr Asp Pro Pro Tyr

[2520] 210 215 220
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[2522] 225 230 235
[2523] <210> 111
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[2532] Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Ser Tyr
[2533] 20 25 30
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[2535] 35 40 45
[2536] Gly Glu Phe Leu Pro Arg Ser Gly Lys Thr Asn Tyr Asn Glu Glu Phe
[2537] 50 55 60
[2538] Arg Gly Lys Ala Thr Phe Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
[2539] 65 70 75 80
[2540] Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[2541] 85 90 95
[2542] Ala Arg Thr Asp Pro Pro Tyr Phe Gly Val Trp Gly Ala Gly Thr Met
[2543] 100 105 110
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[2545] 115 120 125
[2546] Gly Gly Gly Ser Gln Ile Val Leu Thr Gln Ser Pro Pro Ile Met Ser
[2547] 130 135 140
[2548] Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Asn
[2549] 145 150 155 160
[2550] Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys
[2551] 165 170 175
[2552] Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala Arg
[2553] 180 185 190
[2554] Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser
[2555] 195 200 205
[2556] Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser
[2557] 210 215 220
[2558] Val Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile Lys
[2559] 225 230 235
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[2569] cacggcaaga atctggagtg gatcggactg atcaacccac acaatggcgg cactaggtac 180
[2570] aaccagaagt tcaagggcaa ggccacactg actctggata agtccagcag cactgcctac 240
[2571] atggatctgc tgtctctgac aagcgaggac agcgccgtct actattgcgc catctctagg 300
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[2573] agcgccagca ccaagggccc cagcgtgttc cctctggctc cttgtagccg gtccacctcc 420
[2574] gagtccacag ctgctctggg ctgcctcgtg aaggactact ttcccgaacc cgttaccgtg 480
[2575] agctggaata gcggcgcttt aacctccgga gtgcacacct tccccgctgt gctccagtcc 540
[2576] tccggtttat actctttatc ctccgtggtg accgtgcctt cctccagcct cggcaccaag 600
[2577] acctacactt gtaacgtgga ccacaagccc agcaacacca aggtggacaa gagggtggag 660
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[2579] gtgttcctct tccccccccaa acccaaggac actttaatga tctcccggac ccccgaagtg 780
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[2598] agctgtaagg ccagcggcta cgccttcact aattactggc tgggctggat gaagcagaga 120
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[2600] aacgagaact ttaagggcaa ggtgactctg actgccgata agtccagcaa cactgcctac 240
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[2602] actggcttcg attactgggg ccaaggcaca acactgacag tgagcagcgc cagcaccaag 360
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[2606] ttatcctccg tggtgaccgt gccttcctcc agcctcggca ccaagaccta cacttgtaac 600
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[2654] <220>
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[2670] gtggtggacg tgtcccaaga agaccccgag gtgcagttta actggtacgt ggatggcgtg 840
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[2672] gtgtccgtgc tcaccgtgct gcatcaagat tggctgaacg gcaaggagta caagtgcaag 960
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[2711] <211> 1356
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[2713] <213> Artificial Sequence
[2714] <220>
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[2718] agctgcaagg ccagcggcta cagcttcact ggctacacaa tgaactgggt caagcagagc 120
[2719] cacggaaaaa atctggagtg gatcggactg atcaaccctt acaacggcgg cacaaggtac 180
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[3282] ggcgtcccag ctagattcag cggctccgga agcggcactg acttcactct gaacatccac 240

[3283] ccagtggaag aggaggatgc cgccacatac tactgccagc actctaggga gctgcctttc 300

[3284] acatttggca gcggaactaa gctggagatc aagggtggcg gtggctcggg cggtggtggg 360

[3285] tcgggtggcg gcggatctca agtgcatctg cagcagagcg gcgctgagct gatgaagccc 420

[3286] ggcgccagcg tgaagattag ctgcaaggcc actggctaca cattcaacat ctactggatc 480

[3287] gactgggtga agcagaggcc cggccacgga ctggaatgga tcggcgaaat tctgcccggc 540

[3288] agcggcaaca ctcactacaa cgagaacttc aagggcaagg ccacaatgac agccgacaca 600

[3289] agctccaaca ctgcttacat gcagctgact tctctgacta gcgaggacag cgccgtgtac 660

[3290] tattgcgcta ggacagacgg aaggggctac ttcgattact ggggccaagg cactacactc 720

[3291] acagtgagca gc 732

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[3293] <211> 732

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[3296] <220>

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[3301] cccggccacg gactggaatg gatcggcgaa attctgcccg gcagcggcaa cactcactac 180

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[3304] ggaaggggct acttcgatta ctggggccaa ggcactacac tcacagtgag cagcggtggc 360

[3305] ggtggctcgg gcggtggtgg gtcgggtggc ggcggatctg atatcgtgct gactcagagc 420

[3306] ccagcctctc tggtggtgtc tctgggacag agggccacaa tcagctgtag gacttccaag 480

[3307] agcgtgagca gctccgccta cagctacatg cactggtacc agcagaagcc cggccagcct 540

[3308] cctaaggtgc tgatctatct ggccagcaat ctggagagcg gcgtcccagc tagattcagc 600

[3309] ggctccggaa gcggcactga cttcactctg aacatccacc cagtggaaga ggaggatgcc 660

[3310] gccacatact actgccagca ctctagggag ctgcctttca catttggcag cggaactaag 720

[3311] ctggagatca ag 732

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[3313] <211> 714

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[3321] acaagcccaa agaggtggat ctacgacaca agcaagctgg ccagcggcgt gccagccaga 180

[3322] tttagcggct ccggaagcgg cactagctac tctctgacaa tcagcagcat ggaagccgag 240

[3323] gacgccgcta catactactg ccagcagtgg agctccgtcc cactgacttt cggcgctggc 300

[3324] actaagctgg agatcaaggg tggcggtggc tcgggcggtg gtgggtcggg tggcggcgga 360

[3325] tctcaggttc agctgcagca gtccggcgct gagctcatga agcccggcgc cagcgtgaag 420

[3326] atcagctgca aggccactgg ctacacattc agcagctact ggatcgagtg ggtgaagcag 480

[3327] agacccggcc acggactgga atggctggga gagtttctgc ctagaagcgg caagacaaac 540

[3328] tacaacgagg agtttagggg caaggctaca ttcactgccg acacatccag caacactgcc 600

[3329] tacatgcagc tgagcagcct cacaagcgag gattccgccg tctactactg tgctaggact 660

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[3331] <210> 147

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[3334] <213> Artificial Sequence

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[3340] cccggccacg gactggaatg gctgggagag tttctgccta gaagcggcaa gacaaactac 180

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[3395] Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
[3396] 305 310 315 320
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[3398] 325
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[3411] 35 40 45
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[3416] Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Glu His Thr Leu Pro Tyr
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[3420] Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
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[3453] Arg Gly Gly Tyr Trp Tyr Ala Thr Ser Tyr Tyr Phe Asp Tyr Trp Gly
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[3492] 405 410 415
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[3509] 35 40 45
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[3572] 260 265 270
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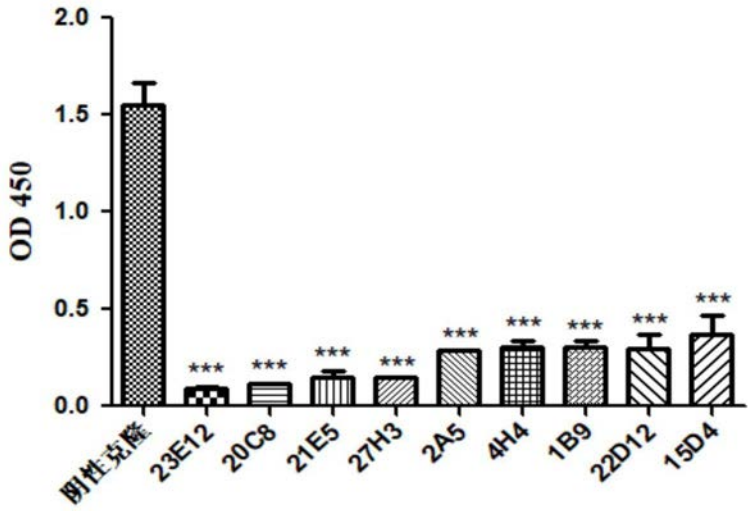

OD 450
2.0
1.5
1.0
0.5
0.0
***
阴性克隆
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20C8
21E5
27H3
2A5
4H4
1B9
22D12
15D4

图1

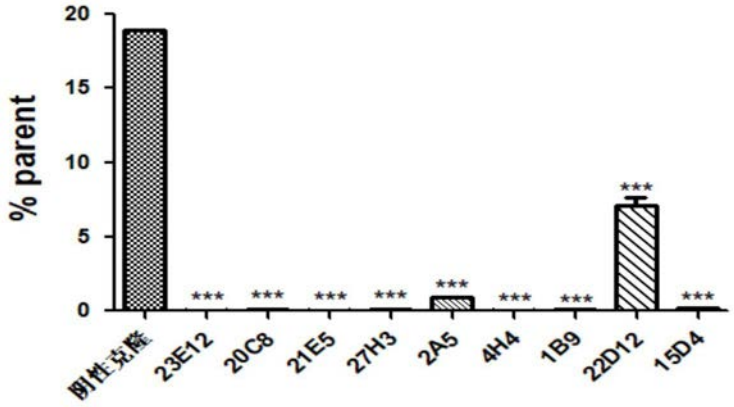

% parent
20
15
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阴性克隆
23E12
20C8
21E5
27H3
2A5
4H4
1B9
22D12
15D4

图2

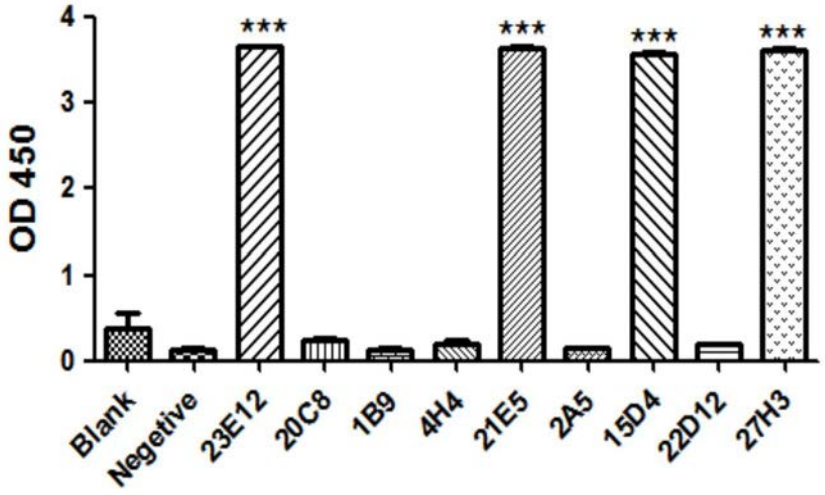
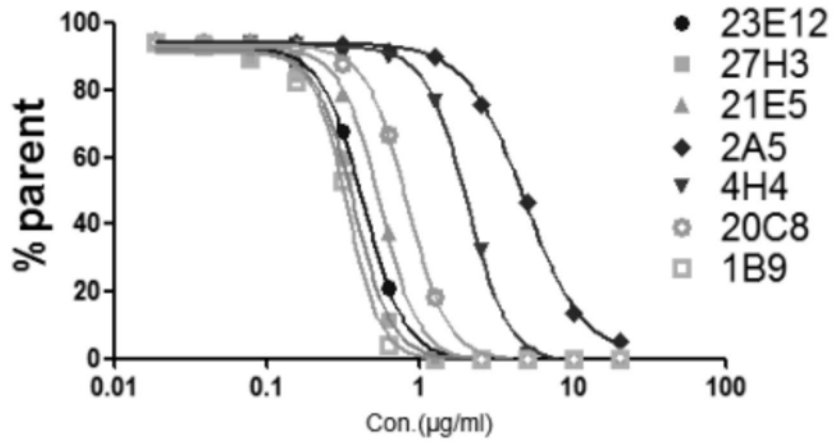

OD 450
4
3
2
1
0
***
Blank
Negetive
23E12
20C8
1B9
4H4
21E5
2A5
15D4
22D12
27H3

图3



McAb	23E12	27H3	21E5	4H4	2A5	20C8	1B9
IC50	0.4258	0.3695	0.5472	2.041	4.800	0.8218	0.3342

图4

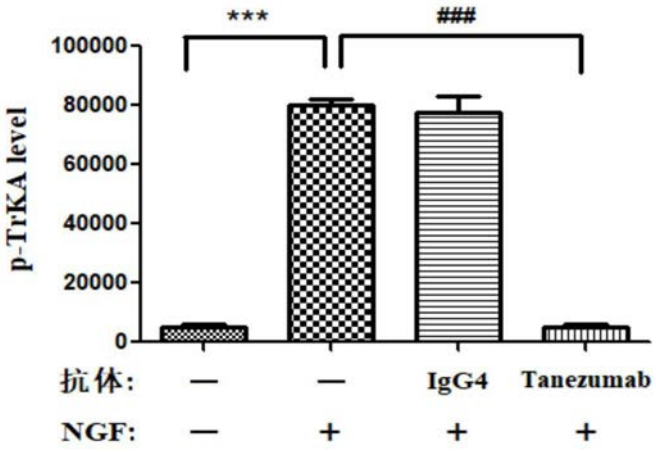
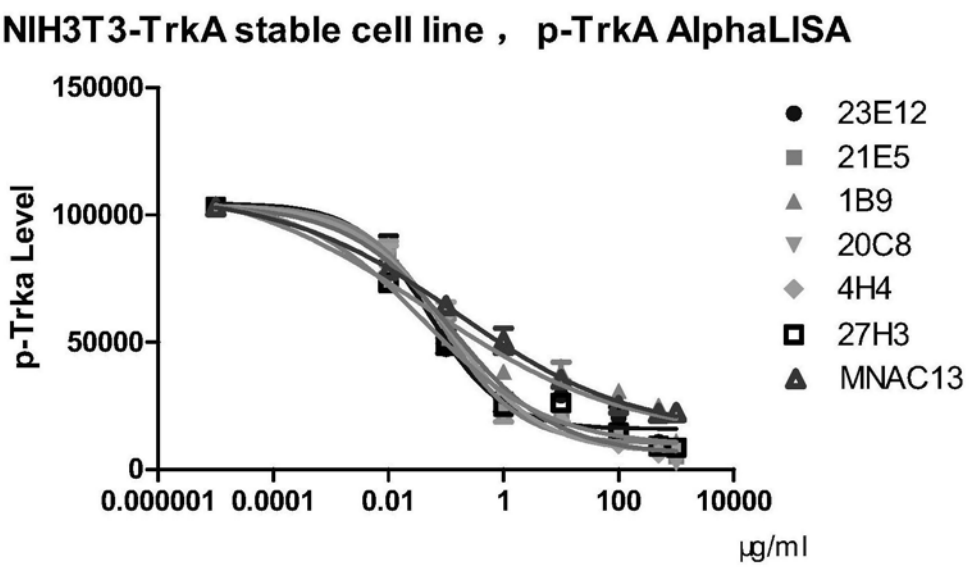
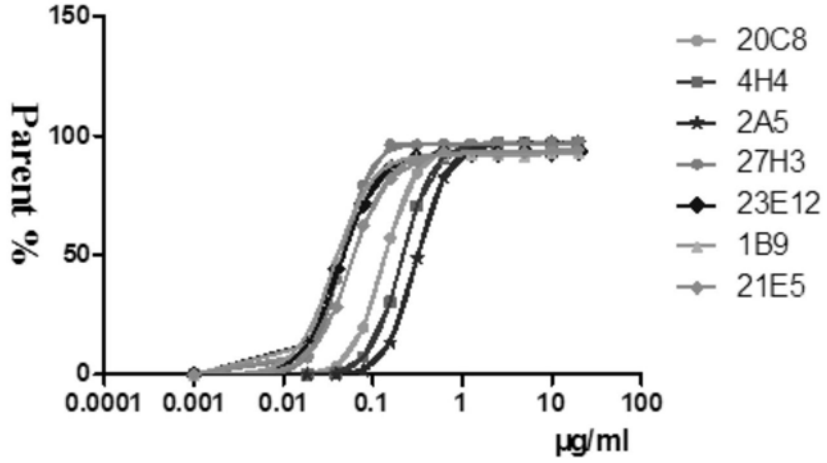


图5



IC50						
23E12	21E5	1B9	20C8	4H4	27H3	MNAC13
0.05372	0.08564	0.04727	0.1099	0.1288	0.04374	0.16

图6



McAb	20C8	4H4	2A5	27H3	23E12	1B9	21E5
EC50	0.1357	0.2113	0.3116	0.04465	0.04429	0.03724	0.05752

图7

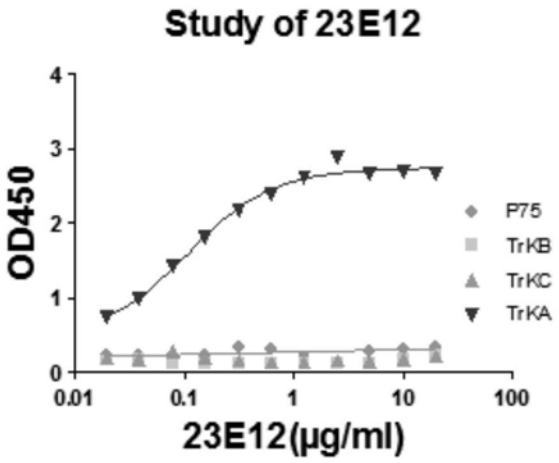

Study of 23E12
OD450
23E12(μg/ml)
P75
TrKB
TrKC
TrKA

图8A

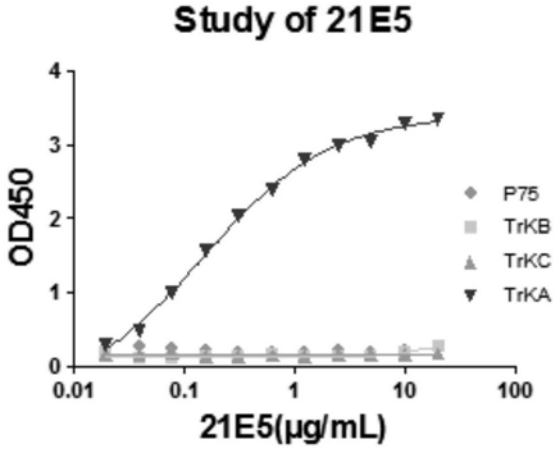

Study of 21E5
OD450
21E5(μg/mL)
P75
TrKB
TrKC
TrKA

图8B

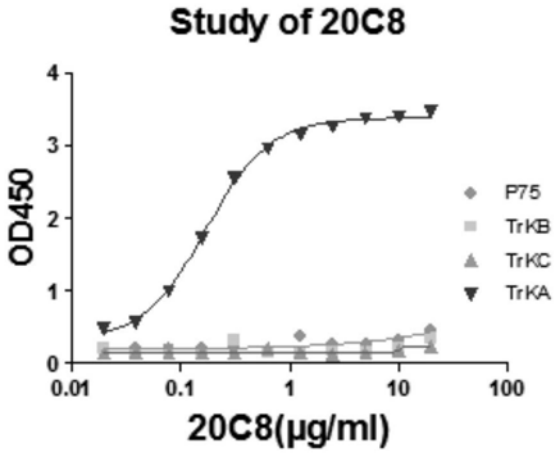

Study of 20C8
OD450
20C8(μg/ml)
P75
TrKB
TrKC
TrKA

图8C

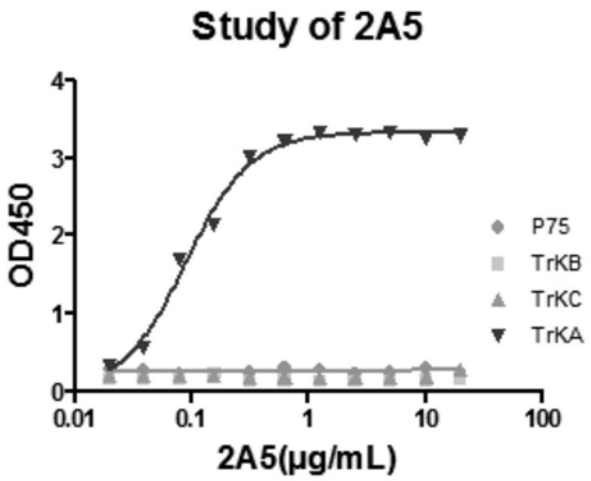

Study of 2A5
OD450
4
3
2
1
0
0.01
0.1
1
10
100
2A5(μg/mL)
P75
TrKB
TrKC
TrKA

图8D

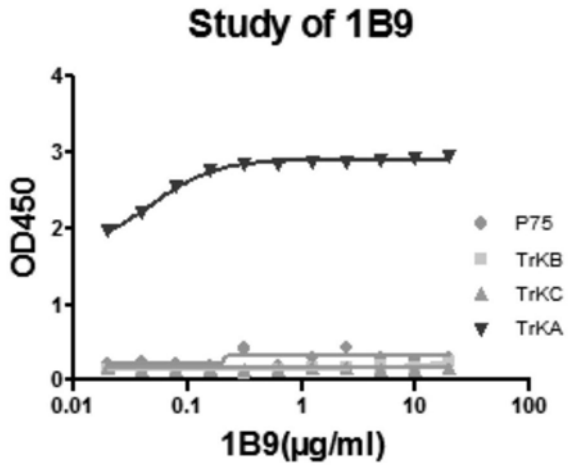

Study of 1B9
OD450
4
3
2
1
0
0.01
0.1
1
10
100
1B9(μg/ml)
P75
TrKB
TrKC
TrKA

图8E

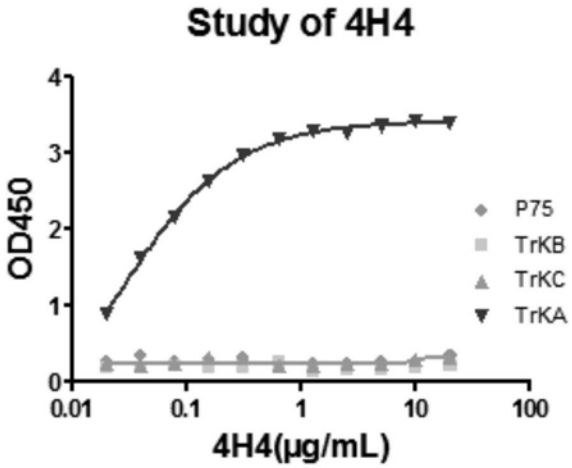

Study of 4H4
OD450
4
3
2
1
0
0.01
0.1
1
10
100
4H4(μg/mL)
P75
TrKB
TrKC
TrKA

图8F

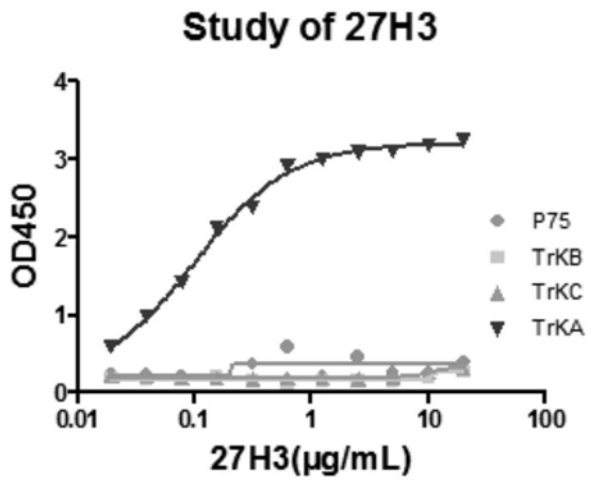
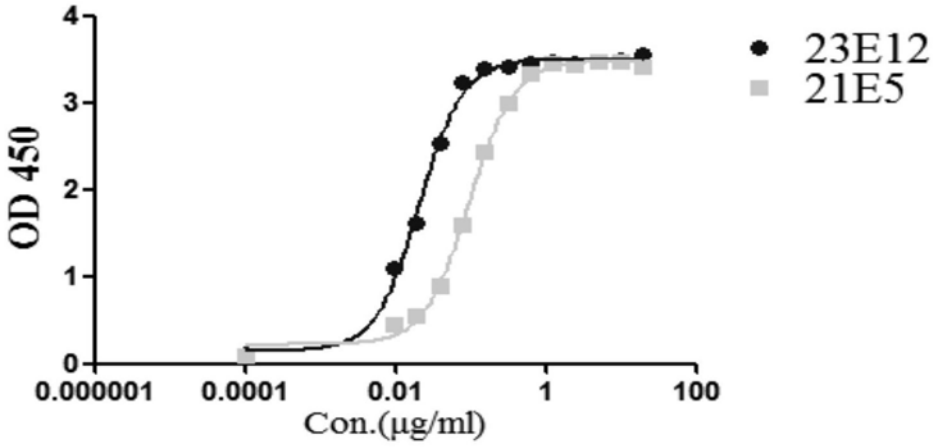


图8G



McAb	23E12	21E5
EC50	0.02076	0.09543

图9

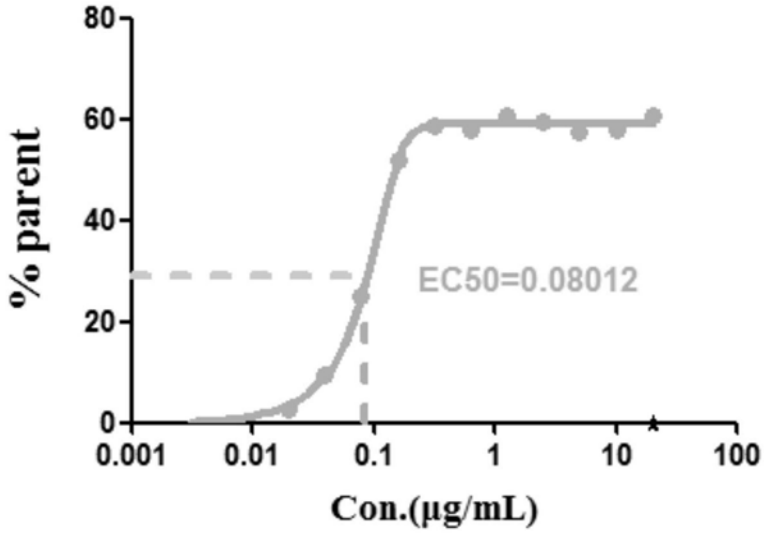

80
60
40
20
0
% parent
EC50=0.08012
0.001
0.01
0.1
1
10
100
Con.(μg/mL)

图10

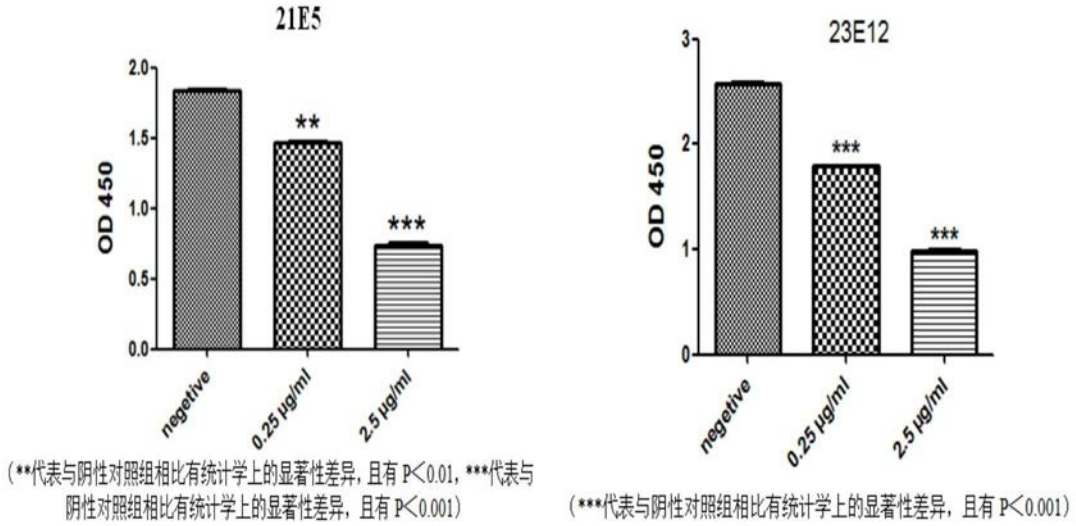

21E5
OD 450
2.0
1.5
1.0
0.5
0.0
**
***
negetive
0.25 μg/ml
2.5 μg/ml
(**代表与阴性对照组相比有统计学上的显著性差异，且有 P<0.01，***代表与阴性对照组相比有统计学上的显著性差异，且有 P<0.001)
23E12
OD 450
3
2
1
0
***
***
negetive
0.25 μg/ml
2.5 μg/ml
(***代表与阴性对照组相比有统计学上的显著性差异，且有 P<0.001)

图11

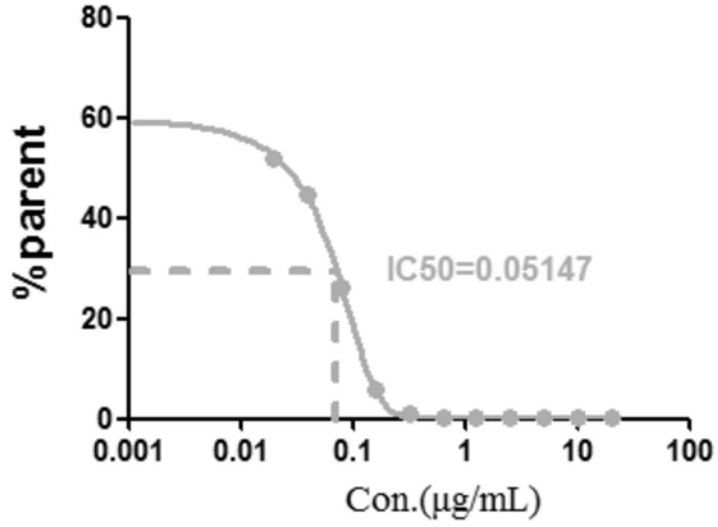
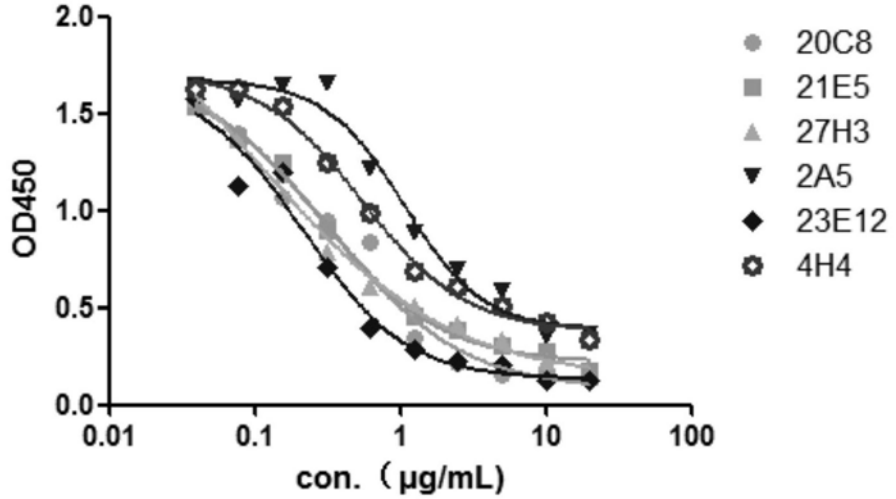


图12



McAb	20C8	21E5	27H3	2A5	23E12	4H4
IC50	0.3100	0.2940	0.1097	1.059	0.2126	0.5508

图13

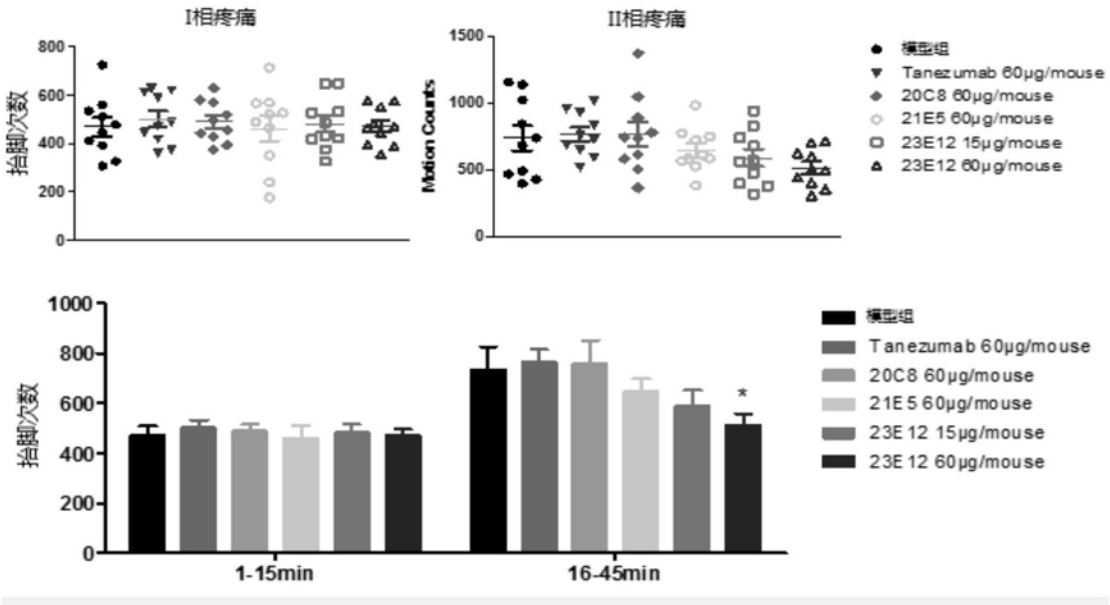

I相疼痛
II相疼痛
抬脚次数
Motion Counts
模型组
Tanezumab 60μg/mouse
20C8 60μg/mouse
21E5 60μg/mouse
23E12 15μg/mouse
23E12 60μg/mouse
1-15min
16-45min

图14

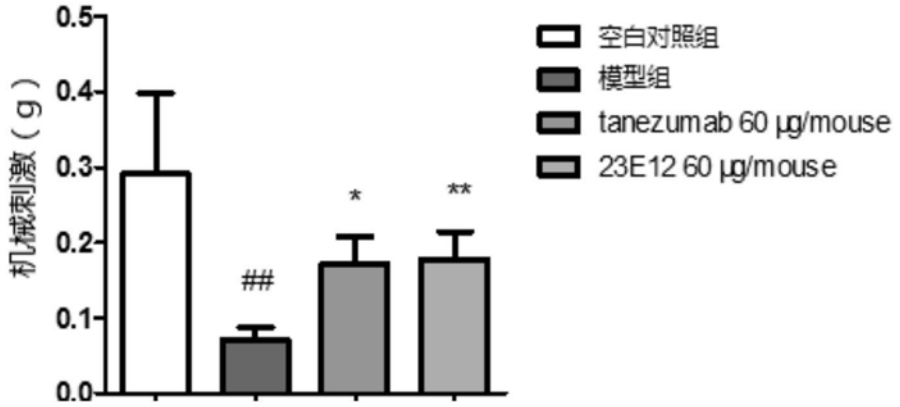

机械刺激（g）
空白对照组
模型组
tanezumab 60 μg/mouse
23E12 60 μg/mouse
##
*
**

图15