(19)国家知识产权局

(12)发明专利

(10)授权公告号 CN 112189022 B
(45)授权公告日 2025.04.15

(21)申请号 201980034952.6
(22)申请日 2019.05.21
(65)同一申请的已公布的文献号
申请公布号 CN 112189022 A
(43)申请公布日 2021.01.05
(30)优先权数据
62/676123 2018.05.24 US
62/825846 2019.03.29 US
(85)PCT国际申请进入国家阶段日
2020.11.24
(86)PCT国际申请的申请数据
PCT/IB2019/054182 2019.05.21
(87)PCT国际申请的公布数据
WO2019/224711 EN 2019.11.28

(73)专利权人 詹森生物科技公司
地址 美国宾夕法尼亚州
(72)发明人 M·迭姆 F·高德特
R·麦克戴德 P·奈尔-古普塔
(74)专利代理机构 中国专利代理(香港)有限公司 72001
专利代理师 初明明 黄希贵

(51)Int.Cl.
C07K 16/28(2006.01)
A61K 39/395(2006.01)
A61P 35/02(2006.01)
(56)对比文件
WO 2016201389 A2,2016.12.15
审查员 陈昂

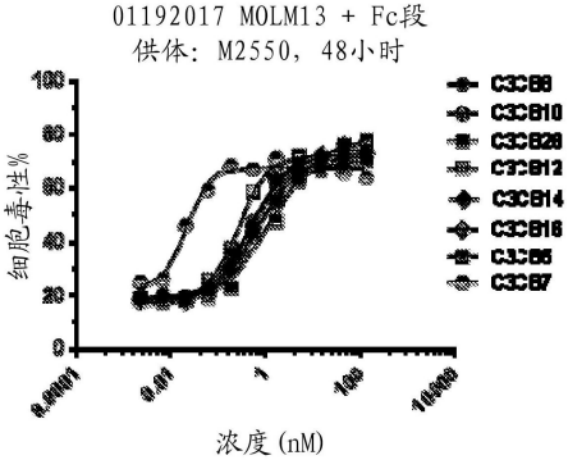
权利要求书3页 说明书92页
序列表316页 附图25页

(54)发明名称

抗CD33抗体、抗CD33/抗CD3双特异性抗体及其用途

(57)摘要

本发明描述了抗CD33抗体及其抗原结合片段以及抗CD33/抗CD3双特异性抗体或其抗原结合片段。本发明还描述了编码所述抗体的核酸、包含所述抗体的组合物、产生所述抗体的方法以及使用所述抗体治疗或预防疾病诸如癌症的方法。



CN 112189022 B

1.一种分离的单克隆抗体或其抗原结合片段,所述分离的单克隆抗体或其抗原结合片段特异性地结合CD33的C2结构域,其中所述抗体或其抗原结合片段包含分别如SEQ ID NO: 447、448、449、567、568和569的多肽序列所示的重链互补决定区(HCDR) 1、HCDR2、HCDR3、轻链互补决定区(LCDR) 1、LCDR2和LCDR3。

2.根据权利要求1所述的分离的单克隆抗体或其抗原结合片段,所述分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO: 292有至少95%同一性的多肽序列的重链可变区或者具有与SEQ ID NO: 332有至少95%同一性的多肽序列的轻链可变区。

3.根据权利要求1或2所述的分离的单克隆抗体或其抗原结合片段,所述分离的单克隆抗体或其抗原结合片段包含:具有SEQ ID NO: 292的多肽序列的重链可变区和具有SEQ ID NO: 332的多肽序列的轻链可变区。

4.根据权利要求1或2所述的分离的单克隆抗体或其抗原结合片段,其中所述单克隆抗体或其抗原结合片段在体外以小于2nM的EC_{50}诱导抗体依赖性细胞介导的细胞毒性(ADCC)。

5.根据权利要求4所述的分离的单克隆抗体或其抗原结合片段,其中所述抗体或其抗原结合片段包含IgG1低岩藻糖主链。

6.根据权利要求1或2所述的分离的单克隆抗体或其抗原结合片段,其中所述抗体或其抗原结合片段以小于5×10^{-9}M的解离常数(KD)结合CD33。

7.根据权利要求1或2所述的分离的单克隆抗体或其抗原结合片段,其中所述抗体或其抗原结合片段结合CD33并且以小于2nM的EC_{50}诱导内化。

8.根据权利要求1或2所述的分离的单克隆抗体或其抗原结合片段,其中所述抗体或其抗原结合片段是嵌合的。

9.根据权利要求1或2所述的分离的单克隆抗体或其抗原结合片段,其中所述抗体或其抗原结合片段是人或人源化的。

10.根据权利要求1或2所述的分离的单克隆抗体或其抗原结合片段,其中将所述抗体或其抗原结合片段缀合至治疗剂。

11.一种分离的核酸,所述分离的核酸编码根据权利要求1至10中任一项所述的单克隆抗体或其抗原结合片段。

12.一种载体,所述载体包含根据权利要求11所述的分离的核酸。

13.一种宿主细胞,所述宿主细胞包含根据权利要求12所述的载体。

14.一种药物组合物,所述药物组合物包含根据权利要求1至10中任一项所述的分离的单克隆抗体或其抗原结合片段,以及药学上可接受的载体。

15.根据权利要求14所述的药物组合物在制备用于在对其有需要的受试者中治疗急性髓性白血病(AML)的药物中的用途。

16.一种产生根据权利要求1至10中任一项所述的单克隆抗体或其抗原结合片段的方法,所述方法包括:在产生所述单克隆抗体或其抗原结合片段的条件下培养包含编码所述单克隆抗体或其抗原结合片段的核酸的细胞,以及从所述细胞或培养物中回收所述抗体或其抗原结合片段。

17.一种产生包含根据权利要求1至10中任一项所述的单克隆抗体或抗原结合片段的药物组合物的方法,所述方法包括将所述单克隆抗体或其抗原结合片段与药学上可接受的载体组合以获得所述药物组合物。

18.一种抗CD33/抗CD3双特异性抗体,所述抗CD33/抗CD3双特异性抗体包含抗CD33抗体或其抗原结合片段以及抗CD3抗体或其抗原结合片段,

其中所述抗CD33抗体或其抗原结合片段包含分别如SEQ ID NO: 447、448、449、567、568和569的多肽序列所示的重链互补决定区(HCDR) 1、HCDR2、HCDR3、轻链互补决定区(LCDR) 1、LCDR2和LCDR3,

并且所述抗CD3抗体或其抗原结合片段包含如以下多肽序列所示的重链互补决定区(HCDR) 1、HCDR2、HCDR3、轻链互补决定区(LCDR) 1、LCDR2和LCDR3:

1) 分别为SEQ ID NO: 342、343、344、465、466和467;或者

2)分别为SEQ ID NO: 345、346、347、468、469和470。

19.根据权利要求18所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段,其中所述抗CD33抗体或其抗原结合片段包含具有与SEQ ID NO: 292有至少95%同一性的多肽序列的重链可变区或者具有与SEQ ID NO: 332有至少95%同一性的多肽序列的轻链可变区;并且所述抗CD3抗体或其抗原结合片段包含具有与SEQ ID NO: 257或258有至少95%同一性的多肽序列的重链可变区或者具有与SEQ ID NO: 298或299有至少95%同一性的多肽序列的轻链可变区。

20.根据权利要求18或19所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段,所述抗CD33/抗CD3双特异性抗体或其抗原结合片段包含:

a. 具有SEQ ID NO: 292的多肽序列的重链可变区和具有SEQ ID NO: 332的多肽序列的轻链可变区;以及具有SEQ ID NO: 257的多肽序列的重链可变区和具有SEQ ID NO: 298的多肽序列的轻链可变区;或

b.具有SEQ ID NO: 292的多肽序列的重链可变区和具有SEQ ID NO: 332的多肽序列的轻链可变区;以及具有SEQ ID NO: 258的多肽序列的重链可变区和具有SEQ ID NO: 299的多肽序列的轻链可变区。

21.根据权利要求18或19所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段,其中所述抗CD33抗体或其抗原结合片段特异性地结合CD33的C2结构域。

22.根据权利要求18或19所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段,其中所述抗CD33/抗CD3双特异性抗体或其抗原结合片段在体外以小于1nM的EC_{50}值诱导表达CD33的细胞的T细胞依赖性细胞毒性。

23.根据权利要求18或19所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段,其中所述双特异性抗体或其抗原结合片段是嵌合的。

24.根据权利要求18或19所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段,其中所述双特异性抗体或其抗原结合片段是人或人源化的。

25.一种分离的核酸,所述分离的核酸编码根据权利要求18至24中任一项所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段。

26.一种载体,所述载体包含根据权利要求25所述的分离的核酸。

27.一种宿主细胞,所述宿主细胞包含根据权利要求26所述的载体。

28.一种药物组合物,所述药物组合物包含根据权利要求18至24中任一项所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段,以及药学上可接受的载体。

29.根据权利要求28所述的药物组合物在制备用于在对其有需要的受试者中治疗急性

髓性白血病(AML)的药物中的用途。

30.一种产生根据权利要求18至24中任一项所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段的方法,所述方法包括:在产生所述抗CD33/抗CD3双特异性抗体或抗原结合片段的条件下培养包含编码所述抗CD33/抗CD3双特异性抗体或抗原结合片段的核酸的细胞,以及从所述细胞或培养物中回收所述抗CD33/抗CD3双特异性抗体或抗原结合片段。

31.一种产生包含根据权利要求18至24中任一项所述的抗CD33/抗CD3双特异性抗体或抗原结合片段的药物组合物的方法,所述方法包括将所述抗CD33/抗CD3双特异性抗体或其抗原结合片段与药学上可接受的载体组合以获得所述药物组合物。

抗CD33抗体、抗CD33/抗CD3双特异性抗体及其用途

技术领域

[0001] 本发明涉及单克隆抗CD33抗体、双特异性抗CD33抗CD3抗体、编码抗体的核酸和表达载体、含有载体的重组细胞以及包含抗体的组合物。还提供了制备这些抗体的方法,以及使用这些抗体治疗包括癌症的疾病的方法。

背景技术

[0002] 急性髓性白血病(AML)是以白血病细胞的克隆扩增为特征的遗传异质性疾病。尽管对AML中潜在的疾病生物学的了解越来越多,但在过去几十年中,细胞毒性化学疗法的标准治疗在很大程度上不变,并且总体五年存活率仍然很差,不到30%(Burnett、Wetzler和Lowenberg,2011年;Cancer Genome Atlas Research等,2013年)。因此,迫切需要具有增加的功效和降低的毒性、理想地靶向AML干细胞的新型疗法,因为据信这些细胞在AML的发病机制中至关重要,并且被标准疗法根除不充分被认为是导致复发的高发因素(Hope、Jin和Dick,2004年;Ishikawa等人,2007年)。虽然已证明针对细胞表面分子的治疗性抗体对于治疗恶性疾病诸如淋巴瘤和急性淋巴母细胞白血病以及实体瘤是有效的(Hoelzer,2013年;Jackson和Chester,2015年),但是目前仅批准了一种基于抗体的疗法用于AML(Godwin、Gale和Walter,2017年)。

[0003] CD33是67kD的单通跨膜糖蛋白并且是唾液酸结合免疫球蛋白样凝集素(Siglecs)家族的成员。虽然其确切的生物学功能尚不清楚,但在正常个体中,其主要被认为是髓细胞样分化抗原,在髓细胞样祖细胞、中性粒细胞和巨噬细胞中表达较低,而在循环的单核细胞和树突状细胞中高度表达。重要的是,已在85%至90%的患有AML的患者的母细胞和白血病干细胞中检测到CD33。有趣的是,CD33的表达仅限于造血细胞(Paul、Taylor、Stansbury和McVicar,2000年;Ulyanova、Blasioli、Woodford-Thomas和Thomas,1999年),但是在正常造血干细胞上却不存在(Andrews、Torok-Storb和Bernstein,1983年;Griffin、Linch、Sabbath、Larcom和Schlossman,1984;Jilani等人,2002年)。这些发现表明CD33是AML中基于抗体的疗法的合适靶标。

[0004] CD33的结构由介导唾液酸结合的氨基末端V-set Ig样结构域(由CD33的外显子2编码)和其细胞外部分中的C2-set Ig样结构域(由外显子3和4编码)组成(Laszlo等人,2016年)。CD33 RNA的另选剪接可导致在细胞表面表达的较短同种型,该较短同种型缺少V-set但保留C2-set Ig样结构域(Laszlo、Estey和Walter,2014年;Laszlo等人,2016年)。该剪接过程的生物相关性在很大程度上是未知的,直至最近的研究显示,单核苷酸多态性(SNP)rs12459419存在于约50%的AML群体中并导致CD33的外显子2的跳越缺失导致了CD33的V结构域的缺失(Lamba等人,2017年)。有趣的是,几种基于CD33抗体的疗法(包括唯一批准的用于AML的抗体Mylotarg)结合并识别CD33的V结构域。上述研究事实上显示,Mylotarg对表达SNP的患者无效,因此仅对约50%的AML群体有效(Lamba等人,2017年)。鉴于Mylotarg的数据,合理的是假设其他V结合CD33抗体也将仅对有限的AML患者池(具体地不具有SNP rs12459419突变的那些患者)有效。

[0005] 实际上,当研究CD33临床领域时,另外的抗CD33抗体包括Amgen公司的AMG330和AMG673、Amphivena公司的AMV564、Immunogen公司的IMGN779、Boehringer Ingelheim公司的BI836858、Actinium Pharma公司的Actimab和Seattle Genetic公司的SGN33A。Amgen公司的AMG330是CD33×CD3 BiTE,并且据报道其"识别位于CD33的V-set结构域中具有核心序列IPYYDKN的线性表位"(Friedrich等人,2014年)。鉴于AMG673是CD33 BiTE的半衰期延长型式,据信其结合与BiTE相同的表位。Amphivena公司的AMV564是四价双特异性CD33/CD3抗体,并且根据US9803029,该抗体与CD33的V结构域结合。Immunogen公司的IMGN779是缀合至DNA烷基化剂的CD33抗体(My9-6),并且根据US9359442专利中的图1,^{125}I-标记的My9-6抗体和My9抗体竞争与CD33-阳性U-937细胞的结合。My9抗体与CD33的V结构域结合(Perez-Oliva等人,2011年)。证据一起表明,IMGN779与CD33的V结构域结合。Boehringer Ingelheim公司的BI 836858是Fc工程化的抗CD33抗体,其介导NK细胞介导的ADCC并与CD33的V结构域结合(Vasu等人,2016年)。另外,Vasu等人以及Malik等人和Perez-Oliva等人一起示出了用于将利妥珠单抗(HuM195)映射至CD33的V结构域的证据(Malik等人,2015年;Perez-Oliva等人,2011年)。HuM195抗体目前处于临床试验中,其由Actinium pharma公司缀合至钢以制备Actimab。HuM195抗体也已由Seattle Genetics公司缀合至DNA结合剂以制备SGN33A;然而,由于毒性问题,该药物目前被搁置。因此,本领域已知的抗CD33抗体与CD33的V结构域结合。

[0006] 鉴于这些数据,当涉及AML中基于CD33的抗体疗法时存在严重未满足的医疗需求,并且需要具有结合CD33的C2结构域的抗体用于治疗表达CD33的癌症。

发明内容

[0007] 在一个总的方面,本发明涉及结合CD33的分离的单克隆抗体或其抗原结合片段。在某些实施方案中,所述分离的单克隆抗体或其抗原结合片段结合所述CD33的C2结构域。在某些实施方案中,所述分离的单克隆抗体或其抗原结合片段结合所述CD33的V结构域。

[0008] 在另一个总的方面,本发明涉及与CD33和CD3结合的分离的双特异性抗体或其抗原结合片段。在某些实施方案中,所述双特异性抗体或其抗原结合片段结合所述CD33的C2结构域。在某些实施方案中,所述双特异性抗体或其抗原结合片段结合所述CD33的V区。

[0009] 本发明提供了分离的单克隆抗体或其抗原结合片段,该分离的单克隆抗体或其抗原结合片段特异性地结合所述CD33的C2结构域。在某些实施方案中,所述分离的单克隆抗体或其抗原结合片段包含具有以下多肽序列的重链互补决定区1(HCDR1)、HCDR2、HCDR3以及轻链互补决定区1(LCDR1)、LCDR2和LCDR3:

[0010] a.分别为SEQ ID NO:447、448、449、567、568和569;

[0011] b.分别为SEQ ID NO:444、445、446、564、565和566;

[0012] c.分别为SEQ ID NO:354、355、356、477、478和479;

[0013] d.分别为SEQ ID NO:378、379、380、501、502和503;

[0014] e.分别为SEQ ID NO:411、412、413、531、532和533;

[0015] f.分别为SEQ ID NO:348、349、350、471、472和473;

[0016] g.分别为SEQ ID NO:360、361、362、483、484和485;

[0017] h.分别为SEQ ID NO:363、364、365、486、487和488;

[0018] i.分别为SEQ ID NO:366、367、368、489、490和491;

[0019] j.分别为SEQ ID NO:369、370、371、492、493和494;

[0020] k.分别为SEQ ID NO:387、388、389、492、493和494;

[0021] l.分别为SEQ ID NO:402、403、404、522、523和524;

[0022] m.分别为SEQ ID NO:408、409、410、528、529和530;

[0023] n.分别为SEQ ID NO:423、424、425、543、544和545;或者

[0024] o.分别为SEQ ID NO:426、427、428、546、547和548。

[0025] 所述抗体或其抗原结合片段可例如特异性与CD33结合,优选人CD33。

[0026] 在某些实施方案中,所述分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:292、291、261、269、280、259、263、264、265、266、272、277、279、284或285有至少95%同一性的多肽序列的重链可变区或者与SEQ ID NO:332、331、302、310、320、300、304、305、306、307、317、319、324或325有至少95%同一性的多肽序列的轻链可变区。

[0027] 在某些实施方案中,所述分离的单克隆抗体或其抗原结合片段包含:

[0028] a.具有SEQ ID NO:292的多肽序列的重链可变区和具有SEQ ID NO:332的多肽序列的轻链可变区;

[0029] b.具有SEQ ID NO:291的多肽序列的重链可变区和具有SEQ ID NO:331的多肽序列的轻链可变区;

[0030] c.具有SEQ ID NO:261的多肽序列的重链可变区和具有SEQ ID NO:302的多肽序列的轻链可变区;

[0031] d.具有SEQ ID NO:269的多肽序列的重链可变区和具有SEQ ID NO:310的多肽序列的轻链可变区;

[0032] e.具有SEQ ID NO:280的多肽序列的重链可变区和具有SEQ ID NO:322的多肽序列的轻链可变区;

[0033] f.具有SEQ ID NO:259的多肽序列的重链可变区和具有SEQ ID NO:300的多肽序列的轻链可变区;

[0034] g.具有SEQ ID NO:263的多肽序列的重链可变区和具有SEQ ID NO:304的多肽序列的轻链可变区;

[0035] h.具有SEQ ID NO:264的多肽序列的重链可变区和具有SEQ ID NO:305的多肽序列的轻链可变区;

[0036] i.具有SEQ ID NO:265的多肽序列的重链可变区和具有SEQ ID NO:306的多肽序列的轻链可变区;

[0037] j.具有SEQ ID NO:266的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序列的轻链可变区;

[0038] k.具有SEQ ID NO:272的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序列的轻链可变区;

[0039] l.具有SEQ ID NO:277的多肽序列的重链可变区和具有SEQ ID NO:317的多肽序列的轻链可变区;

[0040] m.具有SEQ ID NO:279的多肽序列的重链可变区和具有SEQ ID NO:319的多肽序列的轻链可变区;

[0041] n.具有SEQ ID NO:284的多肽序列的重链可变区和具有SEQ ID NO:324的多肽序列的轻链可变区;或

[0042] o.具有SEQ ID NO:285的多肽序列的重链可变区和具有SEQ ID NO:325的多肽序列的轻链可变区。

[0043] 在某些实施方案中,所述分离的单克隆抗体或其抗原结合片段在体外以小于约2nM的EC_{50}诱导抗体依赖性细胞毒性(ADCC)。所述抗体或其抗原结合片段可例如包含IgG1低岩藻糖主链。

[0044] 在某些实施方案中,所述分离的单克隆抗体或其抗原结合片段以小于约5×10^{-9}M的解离常数(KD)结合CD33。

[0045] 在某些实施方案中,所述分离的单克隆抗体或其抗原结合片段结合CD33并且以小于约2nM的EC_{50}诱导内化。

[0046] 在某些实施方案中,将所述分离的单克隆抗体或其抗原结合片段缀合至治疗剂。

[0047] 在某些实施方案中,所述分离的单克隆抗体或其抗原结合片段是嵌合的、部分人源化的或完全人源化的。

[0048] 本文还提供了抗CD33/抗CD3双特异性抗体或其抗原结合片段,包含抗CD33抗体或其抗原结合片段以及抗CD3抗体或其抗原结合片段,其中所述抗CD33抗体或其抗原结合片段包含具有以下多肽序列的重链互补决定区1(HCDR1)、HCDR2、HCDR3以及轻链互补决定区1(LCDR1)、LCDR2和LCDR3:

[0049] a.分别为SEQ ID NO:447、448、449、567、568和569;

[0050] b.分别为SEQ ID NO:444、445、446、564、565和566;

[0051] c.分别为SEQ ID NO:354、355、356、477、478和479;

[0052] d.分别为SEQ ID NO:378、379、380、501、502和503;

[0053] e.分别为SEQ ID NO:411、412、413、531、532和533;

[0054] f.分别为SEQ ID NO:348、349、350、471、472和473;

[0055] g.分别为SEQ ID NO:360、361、362、483、484和485;

[0056] h.分别为SEQ ID NO:363、364、365、486、487和488;

[0057] i.分别为SEQ ID NO:366、367、368、489、490和491;

[0058] j.分别为SEQ ID NO:369、370、371、492、493和494;

[0059] k.分别为SEQ ID NO:387、388、389、492、493和494;

[0060] l.分别为SEQ ID NO:402、403、404、522、523和524;

[0061] m.分别为SEQ ID NO:408、409、410、528、529和530;

[0062] n.分别为SEQ ID NO:423、424、425、543、544和545;或者

[0063] o.分别为SEQ ID NO:426、427、428、546、547和548;

[0064] 并且所述抗CD3抗体或其抗原结合片段包含具有以下多肽序列的重链互补决定区1(HCDR1)、HCDR2、HCDR3以及轻链互补决定区1(LCDR1)、LCDR2和LCDR3:

[0065] 1)分别为SEQ ID NO:342、343、344、465、466和467;或者

[0066] 2)分别为SEQ ID NO:345、346、347、468、469和470。

[0067] 在某些实施方案中,所述抗CD33抗体或其抗原结合片段包含具有与SEQ ID NO:292、291、261、269、280、259、263、264、265、266、272、277、279、284或285有至少95%同一性

的多肽序列的重链可变区或者与SEQ ID NO:332、331、302、310、320、300、304、305、306、307、317、319、324或325有至少95％同一性的多肽序列的轻链可变区;并且所述抗CD3抗体或其抗原结合片段包含具有与SEQ ID NO:257或258有至少95％同一性的多肽序列的重链可变区或者具有与SEQ ID NO:298或299有至少95％同一性的多肽序列的轻链可变区。

[0068] 在某些实施方案中,所述抗CD33/抗CD3双特异性抗体或其抗原结合片段包含:

[0069] a.具有SEQ ID NO:292的多肽序列的重链可变区和具有SEQ ID NO:332的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0070] b.具有SEQ ID NO:291的多肽序列的重链可变区和具有SEQ ID NO:331的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0071] c.具有SEQ ID NO:261的多肽序列的重链可变区和具有SEQ ID NO:302的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0072] d.具有SEQ ID NO:269的多肽序列的重链可变区和具有SEQ ID NO:310的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0073] e.具有SEQ ID NO:280的多肽序列的重链可变区和具有SEQ ID NO:322的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0074] f.具有SEQ ID NO:259的多肽序列的重链可变区和具有SEQ ID NO:300的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0075] g.具有SEQ ID NO:263的多肽序列的重链可变区和具有SEQ ID NO:304的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0076] h.具有SEQ ID NO:264的多肽序列的重链可变区和具有SEQ ID NO:305的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0077] i.具有SEQ ID NO:265的多肽序列的重链可变区和具有SEQ ID NO:306的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0078] j.具有SEQ ID NO:266的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0079] k.具有SEQ ID NO:272的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0080] l.具有SEQ ID NO:277的多肽序列的重链可变区和具有SEQ ID NO:317的多肽序

列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0081] m.具有SEQ ID NO:279的多肽序列的重链可变区和具有SEQ ID NO:319的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0082] n.具有SEQ ID NO:284的多肽序列的重链可变区和具有SEQ ID NO:324的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0083] o.具有SEQ ID NO:285的多肽序列的重链可变区和具有SEQ ID NO:325的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0084] p.具有SEQ ID NO:292的多肽序列的重链可变区和具有SEQ ID NO:332的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0085] q.具有SEQ ID NO:291的多肽序列的重链可变区和具有SEQ ID NO:331的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0086] r.具有SEQ ID NO:261的多肽序列的重链可变区和具有SEQ ID NO:302的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0087] s.具有SEQ ID NO:269的多肽序列的重链可变区和具有SEQ ID NO:310的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0088] t.具有SEQ ID NO:280的多肽序列的重链可变区和具有SEQ ID NO:322的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0089] u.具有SEQ ID NO:259的多肽序列的重链可变区和具有SEQ ID NO:300的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0090] v.具有SEQ ID NO:263的多肽序列的重链可变区和具有SEQ ID NO:304的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0091] w.具有SEQ ID NO:264的多肽序列的重链可变区和具有SEQ ID NO:305的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0092] x.具有SEQ ID NO:265的多肽序列的重链可变区和具有SEQ ID NO:306的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0093] y.具有SEQ ID NO:266的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序

列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0094] z.具有SEQ ID NO:272的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0095] aa.具有SEQ ID NO:277的多肽序列的重链可变区和具有SEQ ID NO:317的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0096] bb.具有SEQ ID NO:279的多肽序列的重链可变区和具有SEQ ID NO:319的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0097] cc.具有SEQ ID NO:284的多肽序列的重链可变区和具有SEQ ID NO:324的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;或

[0098] dd.具有SEQ ID NO:285的多肽序列的重链可变区和具有SEQ ID NO:325的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区。

[0099] 在某些实施方案中,所述抗CD33/抗CD3双特异性抗体或其抗原结合片段在体外在表达CD33的细胞中以小于约1nM的EC_{50}值诱导T细胞依赖性细胞毒性。

[0100] 在某些实施方案中,抗CD33/抗CD3双特异性抗体或其抗原结合片段是嵌合的、部分人源化的或完全人源化的。

[0101] 还提供了编码本发明的所述单克隆和/或双特异性抗体或其抗原结合片段的分离的核酸。

[0102] 还提供了包含编码本发明的所述单克隆和/或双特异性抗体或其抗原结合片段的所述分离的核酸的载体。

[0103] 还提供了包含载体的宿主细胞,所述载体包含编码本发明的所述单克隆和/或双特异性抗体或其抗原结合片段的所述分离的核酸。

[0104] 在某些实施方案中,提供了药物组合物,所述药物组合物包含本发明的所述分离的单克隆抗体或其抗原结合片段和药学上可接受的载体。在某些实施方案中,提供了药物组合物,所述药物组合物包含本发明的所述分离的双特异性抗体或其抗原结合片段和药学上可接受的载体。

[0105] 还提供了在对其有需要的受试者中治疗癌症的方法,所述方法包括向所述受试者施用本发明的所述药物组合物。在某些实施方案中,所述癌症是血液学癌症。所述血液学癌症可例如选自但不限于白血病、淋巴瘤或多发性骨髓瘤。在某些实施方案中,所述血液学癌症可以是急性髓性白血病(AML)、骨髓增生异常综合征(MDS,低风险或高风险)、急性淋巴细胞白血病(ALL,包括所有亚型)、弥漫性大B细胞淋巴瘤(DLBCL)、慢性髓性白血病(CML)或母细胞性浆细胞样树突状细胞瘤(DPDCN)。

[0106] 还提供了制备本发明的所述单克隆或双特异性抗体或其抗原结合片段的方法。所述方法包括在制备所述单克隆或双特异性抗体或抗原结合片段的条件下培养包含编码所

述单克隆或双特异性抗体或抗原结合片段的核酸的细胞,以及从所述细胞或培养物回收所述单克隆或双特异性抗体或抗原结合片段。

[0107] 还提供了制备包含本发明的所述单克隆和/或双特异性抗体或抗原结合片段的药物组合物的方法。所述方法包括将所述单克隆和/或双特异性抗体或其抗原结合片段与药学上可接受的载体组合以获得所述药物组合物。

附图说明

[0108] 结合附图进行阅读时,能够更好地理解前述发明内容和以下对本专利申请的优选实施方案的详细说明。但是,应当理解,本专利申请不限于附图中示出的精确实施方案。

[0109] 图1A至图1B示出了CD33×CD3 T-细胞介导的细胞毒性测定法。将使用抗CD3臂CD3B219的CD33×CD3双特异性抗体与人pan T细胞和$CD33^+$AML细胞系一起温育。在37℃、5%的CO_2下温育48小时之后,通过流式细胞术测量总肿瘤细胞的细胞毒性。图1A示出了通过OMNIRat鉴定的抗体候选,并且图1B示出了通过OMNIMouse鉴定的抗体候选。

[0110] 图2A至图2B示出了使用抗CD3臂CD3B219和CD3B376的CD33×CD3双特异性抗体对新鲜AML患者全血中的母细胞的细胞毒性和T细胞活化进行的体外评估。图2A示出了使用CD33双特异性抗体或CD3×空白对照的AML细胞的总细胞毒性百分比。图2B示出了由CD33双特异性抗体或CD3×空白对照诱导的T细胞活化。未添加Fc阻断剂。

[0111] 图3A至图3C示出了CD33×CD3 T-细胞介导的细胞毒性测定法。将使用抗CD3臂CD3B219和抗CD3B376的CD33×CD3双特异性抗体与人pan T细胞和对于CD33 SNP rs12459419突变是野生型(KG1,图3A)、杂合型(SH2,图3B)或纯合型(OCIAML3,图3C)的AML细胞系一起温育。在37℃、5%的CO_2下温育48小时之后,通过流式细胞术测量总肿瘤细胞的细胞毒性。

[0112] 图4A至图4B示出了与CD3B219或CD3B376配对的C33B904抗体对外源添加到正常健康人全血(N=6个供体)的MOLM-13细胞的细胞毒性的体外评估:使用CD33×CD3双特异性抗体和相应空白×CD3对照在48小时后,MOLM-13细胞(图4A)和$CD33^+CD14^+$单核细胞(图4B)的细胞毒性百分比。

[0113] 图5A至图5B示出了使用抗CD3臂CD3B219和CD3B376的CD33×CD3双特异性抗体对来自六个正常食蟹猕猴供体的新鲜全血中的单核细胞的细胞毒性和T细胞活化进行的体外评估。图5A示出了使用CD33双特异性抗体或其CD3×空白对照的$CD33^+CD14^+$食蟹猕猴单核细胞的总细胞毒性百分比。图5B示出了由CD33双特异性抗体或其CD3×空白对照诱导的T细胞活化。未添加Fc阻断剂。

[0114] 图6示出了C3CB189在T细胞人源化NSG小鼠中的MOLM-13人AML异种移植物中的抗肿瘤功效。每周对弥散的MOLM-13肿瘤进行生物发光(BLI)成像两次,并且结果以平均光亮度(p/s/cm^2/sr)±SEM(n=8-10/组)表示。*处理与对照的$p \leq 0.0001$,通过双因素方差分析与Bonferroni检验进行计算。

[0115] 图7示出了用C3CB189处理的动物在T细胞人源化NSG小鼠中的MOLM-13人AML异种移植物中的存活率。使用Kaplan-Meier曲线以图形表示携带MOLM-13的小鼠的存活率,并通过对数秩(Mantel-Cox)检验进行评估。*处理与对照组的$p \leq 0.0001$。

[0116] 图8示出了C3CB88在T细胞人源化NSG小鼠中的MOLM-13人AML异种移植物中的抗肿

瘤功效。每周对弥散的MOLM-13肿瘤进行生物发光(BLI)成像两次,并且结果以平均光亮度(p/s/cm^2/sr)±SEM(n=8-10/组)表示。*处理与对照的p≤0.0001,通过双因素方差分析与Bonferroni检验进行计算。

[0117] 图9示出了用C3CB88处理的动物在T细胞人源化NSG小鼠的MOLM-13人AML异种移植物中的存活率。使用Kaplan-Meier曲线以图形表示携带MOLM-13的小鼠的存活率,并通过对数秩(Mantel-Cox)检验进行评估。*处理与对照组的p≤0.05。

[0118] 图10示出了用于检测MOLM13细胞中的五种抗CD33抗体内化的体外蛋白质A药物缀合细胞活力测定。全部五种抗CD33抗体以剂量依赖性方式示出细胞毒性。

[0119] 图11A至图11B示出了低岩藻糖IgG1抗CD33 mAb介导ADCC活性。响应于IgG1抗CD33 mAb浓度的增加,人NK细胞针对MOLM-13(图11A)和MV4-11(图11B)靶细胞的ADCC。

[0120] 图12示出了CD33阳性细胞系和CD33阴性细胞系用各种浓度的C3CB189染色4h以表征双特异性抗体的表面结合曲线。

[0121] 图13示出了在T细胞重定向测定中用指定细胞系测试来自六个健康供体的T细胞,并且通过FACS测定细胞毒性百分比。绘制平均值±SD。

[0122] 图14A和图14B。C3CB189与C2结构域结合并介导原代样本的细胞毒性,无论其SNP 12459419基因型状态如何。图14A)在CD33$^+$KG-1细胞系和CD33$^-$KG1ΔCD33细胞系中使用CD33×CD3或CD123×CD3双特异性抗体进行的T细胞介导的细胞毒性和活化测定。图14B)将单独的T细胞与浓度渐增的C3CB189一起温育48小时,并通过流式细胞术测量T细胞活化。绘制平均值±SD。

[0123] 图15A至图15C。图15A示出了显示从六个健康供体中读出的细胞毒性的EC_{20}、EC_{50}和EC_{90}的中值。图15B类似于图13,但此处测量了T细胞活化。图15C类似于图15A,但此处示出了从六个健康供体读出的T细胞活化的中值EC_{20}、EC_{50}和EC_{90}的值。

[0124] 图16A至图16E:在体内C3CB189在两个已建立的鼠AML模型中介导强效的肿瘤活性。图16A示出了对携带已建立的KG-1肿瘤的T细胞人源化NSG小鼠腹膜内注射0.1mg/kg、0.5mg/kg和1mg/kg的C3CB189。每周测量两次肿瘤体积,并且结果表示为每组的平均肿瘤体积±SEM。图16B示出了对携带弥散的MOLM-13Luc细胞的T细胞人源化NSG小鼠腹膜内注射0.005mg/kg、0.05mg/kg和0.5mg/kg的C3CB189。利用Kaplan Meier生存分析来确定生存率。图16C与图16B相同,但此处每周测量两次生物发光,并且示出第9天、第13天和第16天生物发光的活动物成像的代表性图像(n=3-5只动物的腹视图和背视图)(由于死亡,对照组在第16天n=3)。图16D类似于图16B,但此处小鼠以0.005mg/kg和0.05mg/kg施用C3CB189,共三剂。通过流式细胞术分析测量骨髓中的T细胞浸润,并且结果以肿瘤细胞百分比(上图)或CD3$^+$T细胞百分比(下图)表示。图16E与图16D相同,但此处骨髓中的T细胞浸润通过IHC染色测量,并且结果以CD33$^+$肿瘤细胞(上图)或CD8$^+$T细胞(下图)表示。

[0125] 图17示出了C3CB189在弥散的鼠AML模型中介导抗肿瘤应答。在第0天植入肿瘤细胞,在第5天植入T细胞,并且如X轴下方的柱所示进行给药。将组生物发光绘制为平均值±SEM。*表示在第13天用C3CB189处理与空白×CD3对照之间的显著差异(p≤0.05)(在第13天n=9-10/组)。

[0126] 图18A和图18B示出了C3CB189诱导的全血中CD33$^+$细胞系的T细胞依赖性细胞毒性。图18A示出了在T细胞重定向测定中用指定细胞系测试来自十个健康供体(每个供体一

个点)的T细胞。绘制平均值±SD。图18B与图18A相同,但此处示出了细胞毒性和T细胞活化EC_{20}、EC_{50}和EC_{90}的值。ND表示无法确定,即,Prism要么提供近似值,要么曲线不明确。值是来自10个健康供体的中值。

[0127] 图19A和图19B示出了C3CB189介导原代患者样本中AML母细胞的细胞毒性。图19A示出了48小时之后C3CB189介导的新鲜AML患者全血中$CD33^+$母细胞的细胞毒性的体外评估。示出每个患者样本的各个EC_{50}值。图19B与图19A相同,但此处测量了T细胞活化。

[0128] 图20示出了CD33在食蟹猕猴免疫亚群中表达。将六名正常健康食蟹猕猴供体的全血用CD33的单克隆抗体染色,并通过流式细胞术进行分析。绘制平均值±SD。

[0129] 图21示出了C3CB189介导MOLM-13细胞、正常$CD33^+$食蟹猕猴单核细胞和中性粒细胞的细胞毒性以及活化食蟹猕猴T细胞。在外源添加到正常健康食蟹猕猴全血(n=6)中的AML细胞系MOLM-13细胞中C3CB189介导的细胞毒性的体外评估。示出了使用C3CB189和空白×CD3双特异性抗体的MOLM-13细胞的细胞毒性百分比、T细胞活化以及$CD33^+$单核细胞和中性粒细胞的细胞毒性。绘制平均值±SEM。

[0130] 图22A至图22D示出了C3CB189介导食蟹猕猴中$CD33^+$白细胞的降低。用单次静脉注射对照(载体)、0.05mg/kg、0.2mg/kg或1mg/kg的C3CB189处理食蟹猕猴。图22A示出了C3CB189浓度随时间曲线的变化。图22B示出了外周血中的T细胞活化($CD8^+$中的%$CD25^+$)。图22C示出了C3CB189对粒细胞(中性粒细胞)的影响。图22D示出了C3CB189对单核细胞的影响。

[0131] 图23示出了给食蟹猕猴施用C3CB189后的细胞因子释放。单次静脉注射C3CB189后食蟹猕猴的平均(SD)细胞因子水平。(A)IFNγ、(B)IL-10、(C)IL-2、(D)IL-6、(E)MCP、(F)TNFα。将所有以下LLOQ值视为LLOQ的一半,以用于绘图和平均的计算目的。

[0132] 图24A至图24C示出了C3CB189与C2结构域结合并介导原代样本的细胞毒性,无论其SNP 12459419基因型状态如何。图24A示出了对于V和C2结合剂mAb的CD33 ECD蛋白质的IgC和IgV结构域中的表位区的HDX作图和后续图解。V表位区以蓝色着色,并且C2表位区以红色着色。图24B示出了在27nM双特异性抗体浓度下进行新鲜AML患者全血中$CD33^+$母细胞的细胞毒性的体外评估。绘制平均值±SD。图24C示出了在0.27nM双特异性抗体浓度下评估C3CB189介导的来自25个正常供体的冷冻纯化单核细胞的细胞毒性。绘制平均值±SD。

[0133] 图25A至图25C示出了SNP rs12459419的基因分型结果。图25A示出了来自Taqman测定法的细胞系中SNP rs12459419的基因分型结果。图25B与图25A相同,但此处对原代患者样本进行了基因分型。图25C与图25A相同,但此处使用Taqman测定法以及Sanger测序对来自健康供体的冷冻单核细胞进行了基因分型。

具体实施方式

[0134] 背景以及说明书全篇中引用或描述了各种出版物、文章和专利;这些参考文献中的每一者全文均以引用方式并入本文。本说明书中包括的对文件、行为、材料、装置、文章等的讨论旨在为本发明提供上下文。此类讨论并不是承认这些事项中的任一事项或全部事项均相对于所公开或受权利要求书保护的任何发明形成现有技术的一部分。

[0135] 除非另有定义,否则本文使用的所有技术和科学术语的含义与本发明所属领域的普通技术人员通常所理解的含义相同。否则,本文所用的某些术语具有本说明书中所述的

含义。

[0136] 应该注意的是,除非上下文清楚地指明,否则如本文和所附权利要求中所用的单数形式“一个/一种”和“所述/该”包括复数引用物。

[0137] 除非另有说明,否则任何数值,例如本文所述的浓度或浓度范围,应理解为在所有情况下均由术语“约”修饰。因此,数值通常包括所述值±10%。例如,1mg/mL的浓度包括0.9mg/mL至1.1mg/mL。同样,1%至10%(w/v)的浓度范围包括0.9%(w/v)至11%(w/v)。除非上下文另有明确指示,否则如本文所用,使用的数值范围明确地包括所有可能的子范围、该范围之内的所有单个数值,包括此类范围之内的整数和该范围之内的分数。

[0138] 除非另有说明,否则在一系列元素之前的术语“至少”应理解为指代系列中的每个元素。本领域的技术人员将会认识到、或仅使用常规实验就能够确定本文所述发明的具体实施方案的多种等同物。此类等同物旨在由本发明所涵盖。

[0139] 如本文所用,术语“包含”、“包括”、“具有”或“含有”或其任何其他变型应被理解为是指包括指定的整数或整数组,但不排除任何其他整数或整数组,并且是非排他性的或开放式的。例如,包含元素列表的组合物、混合物、过程、方法、制品或设备不一定仅限于那些元素,而是可以包括这些组合物、混合物、过程、方法、制品或设备未明确列出或固有的其他元素。此外,除非明确地指明相反,否则“或”是指包括性的“或”而不是排他性的“或”。例如,条件A或B由以下任一项满足:A为真(或存在)而B为假(或不存在),A为假(或不存在)而B为真(或存在),以及A和B均为真(或存在)。

[0140] 如本文所用,多个列举的要素之间的连接术语“和/或”被理解为包含单个选项和组合选项两者。例如,在两个要素由“和/或”连接的情况下,第一种选项是指在没有第二个要素的情况下适用第一个要素。第二种选项是指在没有第一个要素的情况下适用第二个要素。第三种选项是指适合一起使用第一要素和第二要素。这些选项中的任一种均被理解为落在含义内,并且因此满足如本文所用的术语“和/或”的要求。多于一种选项的并行适用性也被理解为落在含义内,并且因此满足术语“和/或”的要求。

[0141] 如本文所用,在说明书和权利要求书中通篇使用的术语“由……组成”表示包括任何列举的整数或整数组,但不能将附加的整数或整数组添加到指定的方法、结构或组成中。

[0142] 如本文所用,在说明书和权利要求书中通篇使用的术语“基本上由……组成”表示包括任何列举的整数或整数组,并且任选地包括不会实质上改变指定方法、结构或组成的基本或新型特性的任何列举的整数或整数组。参见M.P.E.P.§2111.03。

[0143] 如本文所用,“受试者”是指任何动物,优选哺乳动物,最优选人。如本文所用,术语“哺乳动物”涵盖任何哺乳动物。哺乳动物的示例包括但不限于奶牛、马、绵羊、猪、猫、狗、小鼠、大鼠、兔子、豚鼠、猴子、人等,更优选地包括人。

[0144] 还应当理解,当提及优选发明的部件的尺寸或特性时,本文使用的“约”、“大约”、“大致”、“基本上”和类似的术语表示所描述的尺寸/特性不是严格的边界或参数,并且不排除在功能上相同或相似的微小变化,如本领域普通技术人员所理解的。至少,包括数值参数的这种参考将包括使用本领域已接受的数学和工业原理(例如,舍入、测量或其他系统误差、制造公差等)的变化,不会改变最低有效数字。

[0145] 在两条或更多条核酸或多肽序列(例如,抗CD33抗体和编码其的多核苷酸、抗CD33抗CD3双特异性抗体和编码其的多核苷酸、CD33多肽和编码其的CD33多核苷酸)的上下文

中,术语“相同”或百分比“同一性”是指当进行比较和比对以获得最大对应时,相同的或具有相同的氨基酸残基或核苷酸的指定百分比的两条或更多条序列或子序列,如使用以下序列比较算法之一或通过目视检查所测量的。

[0146] 对于序列比对,通常将一个序列作为参考序列,将测试序列与其进行对比。当使用序列比对算法时,将测试序列和参考序列输入计算机中,指定子序列坐标(如果必要的话),并指定序列算法的程序参数。然后,序列比较算法基于指定的程序参数来计算对于测试序列相对于参考序列的序列同一性百分比。

[0147] 用于比较的序列的最佳比对可例如通过Smith&Waterman的局部同源性算法进行(Adv.Appl.Math.第2卷:第482页(1981年)),通过使用Needleman&Wunsch的同源比对算法进行(J.Mol.Biol.第48卷:第443页(1970年)),通过搜索Pearson&Lipman的相似性方法进行(Proc.Nat'l.Acad.Sci.USA第85卷:第2444页(1988年)),通过这些算法(GAP,BESTFIT,FASTA和TFASTA,在威斯康星州遗传学软件包,遗传学计算小组,威斯康辛州,麦迪逊,科学街区575号(575Science Dr.,Madison,WI)计算机化实施,或通过目测(大体参见Current Protocols in Molecular Biology,F.M.Ausubel等人编辑,《实验室指南》,格林尼出版协会和约翰威利父子公司的合资企业(1995年增补版)(Ausubel))。

[0148] 适用于确定序列同一性百分比和序列相似性的算法的示例是BLAST和BLAST 2.0算法,其分别描述于Altschul等人1990年的J.Mol.Biol.第215卷,第403至第410页和Altschul等人1997年的Nucleic Acids Res.第25卷:第3389-3402页。用于执行BLAST分析的软件可通过美国国家生物技术信息中心公开获得。该算法涉及首先通过识别查询序列中长度为W的短字词来识别高评分序列对(HSP),当与数据库序列中相同长度的字词比对时,该短字词匹配或满足一些正值阈值分数T。T被称为邻近字词分数阈值(Altschul等人,出处同上)。这些初始邻近字词命中充当用于发起搜索以找到包含它们的较长HSP的种子。然后将字词命中沿每个序列在两个方向上延伸,只要可增加累积的比对分数。

[0149] 对于核苷酸序列,使用参数M(一对匹配残基的奖励分数;始终>0)和N(错配残基的处罚分数;始终<0)来计算累积分数。对于氨基酸序列,评分矩阵用于计算累积分数。字词命中在每个方向上的延伸在以下情况下停止:累积比对分数从其最大实现值下降数量X;累积分数由于一个或多个负分数残基比对的累积而变为零或更低;或到达任一序列的末端。BLAST算法参数W、T和X确定比对的灵敏度和速度。BLASTN程序(用于核苷酸序列)默认使用字长(W)11、期望值(E)10、M=5、N=-4以及两条链的比较。对于氨基酸序列,BLASTP程序默认使用字长(W)3、期望值(E)10以及BLOSUM62评分矩阵(参见Henikoff和Henikoff的Proc.Natl.Acad.Sci.USA第89卷:第10915页(1989年))。

[0150] 除了计算序列同一性百分比之外,BLAST算法还对两条序列之间的相似性进行统计分析(参见例如Karlin和Altschul的Proc.Nat'l.Acad.Sci.USA第90卷:第5873页至5787页(1993年))。BLAST算法提供的一种相似性量度是最小总和概率(P(N)),其提供了两条核苷酸或氨基酸序列之间偶然发生匹配的概率的指示。例如,如果在测试核酸与参考核酸的比较中最小总和概率小于约0.1,更优选地小于约0.01,并且最优选地小于约0.001,则认为核酸类似于参考序列。

[0151] 两个核酸序列或多肽基本上相同的另一个指示是通过第一核酸编码的多肽与通过第二核酸编码的多肽免疫地交叉反应,如下所述。因此,多肽通常与第二多肽基本上相

同,例如,其中两个肽仅通过保守置换而不同。两个核酸序列基本上相同的另一个指示是,两个分子在严格条件下彼此杂交,如下所述。

[0152] 抗体

[0153] 本发明一般涉及分离的抗CD33抗体或其抗原结合片段、编码抗体的核酸和表达载体、含有载体的重组细胞以及包含抗体的组合物。本发明另外涉及分离的抗CD33/抗CD3双特异性抗体或其抗原结合片段、编码抗体的核酸和表达载体、含有载体的重组细胞以及包含双特异性抗体的组合物。还提供了制备这些抗体的方法,以及使用这些抗体治疗包括癌症的疾病的方法。本发明的抗体具有一种或多种期望的功能特性,包括但不限于与CD33和/或CD3的高亲和力结合,与CD33和/或CD3的高特异性以及当单独施用或与其他抗癌疗法联合施用时治疗癌症或预防癌症的能力。

[0154] 在一个总的方面,本发明涉及分离的单克隆抗体或其抗原结合片段,该分离的单克隆抗体或其抗原结合片段特异性地结合CD33。在某些实施方案中,分离的单克隆抗体或其抗原结合片段结合CD33的C2结构域。在某些实施方案中,分离的单克隆抗体或其抗原结合片段结合CD33的V结构域。

[0155] 如本文所用,术语“抗体”广义地使用,并且包括免疫球蛋白或抗体分子,包括人抗体、人源化抗体、复合抗体和嵌合抗体以及单克隆或多克隆抗体片段。一般来讲,抗体是蛋白质或肽链,其对于特定抗原表现出结合特异性。抗体结构是众所周知的。根据重链恒定结构域氨基酸序列,可将免疫球蛋白指定为五大类(即IgA、IgD、IgE、IgG和IgM)。IgA和IgG进一步亚分类为同种型IgA1、IgA2、IgG1、IgG2、IgG3和IgG4。因此,本发明的抗体可为五种主要种类或对应的亚类中的任一种。优选地,本发明的抗体为IgG1、IgG2、IgG3或IgG4。基于其恒定结构域的氨基酸序列,可将脊椎物种的抗体轻链指定为两种完全不同的类型即κ和λ中的一种。因此,本发明的抗体可含有κ或λ轻链恒定域。根据具体实施方案,本发明的抗体包括来自大鼠或人抗体的重链和/或轻链恒定区。除重链和轻链恒定域之外,抗体还包含由轻链可变区和重链可变区组成的抗原结合区,每个可变区包含三个域(即,互补决定区1-3;CDR1、CDR2和CDR3)。轻链可变区另选地被称为LCDR1、LCDR2和LCRD3,并且重链可变区另选地被称为HCDR1、HCRD2和HCDR3。

[0156] 如本文所用,术语“分离的抗体”是指基本上不含具有不同抗原特异性的其他抗体的抗体(例如,与CD33特异性地结合的分离的抗体基本上不含不与CD33结合的抗体)。另外,分离的抗体可基本上不含其他细胞物质和/或化学物质。

[0157] 如本文所用,术语“单克隆抗体”是指从一组基本上均质的抗体获得的抗体,即,除了可能以少量存在的可能天然存在的突变之外,构成该组的各个抗体是相同的。本发明单克隆抗体可以通过杂交瘤方法、噬菌体展示技术、单淋巴细胞基因克隆技术或通过重组DNA方法制备。例如,单克隆抗体可以由包括获自转基因非人动物诸如转基因小鼠或大鼠的B细胞的杂交瘤产生,转基因非人动物具有包含人重链转基因和轻链转基因的基因组。

[0158] 如本文所用,术语“抗原结合片段”是指抗体片段,诸如像,双抗体、Fab、Fab’、F(ab’)2、Fv片段、二硫键稳定Fv片段(dsFv)、$(dsFv)_2$、双特异性dsFv(dsFv-dsFv’)、二硫键稳定双抗体(ds双抗体)、单链抗体分子(scFv)、单结构域抗体(sdab)、scFv二聚体(二价双抗体)、由包含一个或多个CDR的抗体的一部分形成的多特异性抗体、骆驼化单结构域抗体、纳米抗体、结构域抗体、二价结构域抗体或结合抗原但不包含完整抗体结构的任何其它抗

体片段。抗原结合片段能够结合至与亲本抗体或亲本抗体片段结合的抗原相同的抗原。根据具体实施方案,抗原结合片段包含轻链可变区、轻链恒定区和重链的Fd区段。根据其他具体实施方案,抗原结合片段包含Fab和F(ab')。

[0159] 如本文所用,术语"单链抗体"是指本领域中的常规单链抗体,这种单链抗体包含通过约15至约20个氨基酸的短肽连接的重链可变区和轻链可变区。如本文所用,术语"单域抗体"是指本领域中的常规单域抗体,这种单域抗体包含重链可变区和重链恒定区或者仅包含重链可变区。

[0160] 如本文所用,术语"人抗体"是指由人产生的抗体或具有与使用本领域已知的任何技术制备的人产生的抗体对应的氨基酸序列的抗体。人抗体的该定义包括完整或全长抗体、其片段以及/或者包含至少一种人重链多肽和/或轻链多肽的抗体。

[0161] 如本文所用,术语"人源化抗体"是指被修饰成提高与人抗体的序列同源性的非人抗体,使得抗体的抗原结合特性得以保留,但其在人体内的抗原性下降。

[0162] 如本文所用,术语"嵌合抗体"是指免疫球蛋白分子的氨基酸序列来源于两个或更多个物种的抗体。轻链和重链两者的可变区经常对应于来源于一个哺乳动物物种(例如,小鼠、大鼠、兔等)的具有期望的特异性、亲和力和能力的抗体的可变区,而恒定区对应于来源于另一个哺乳动物物种(例如,人)的抗体中的序列,以便避免在那个物种中引出免疫反应。

[0163] 如本文所用,术语"多特异性抗体"是指包含多个免疫球蛋白可变结构域序列的抗体,其中该多个免疫球蛋白可变结构域序列中的第一免疫球蛋白可变结构域序列对第一表位具有结合特异性,并且该多个免疫球蛋白可变结构域序列中的第二免疫球蛋白可变结构域序列对第二表位具有结合特异性。在一个实施方案中,第一表位和第二表位在相同的抗原,例如相同的蛋白质(或多聚蛋白质的亚基)上。在一个实施方案中,第一表位和第二表位重叠或基本上重叠。在一个实施方案中,第一表位和第二表位不重叠或基本上不重叠。在一个实施方案中,第一表位和第二表位在不同的抗原,例如不同的蛋白质(或多聚蛋白质的不同亚基)上。在一个实施方案中,多特异性抗体包含第三、第四或第五免疫球蛋白可变域。在一个实施方案中,多特异性抗体是双特异性抗体分子、三特异性抗体分子或四特异性抗体分子。

[0164] 如本文所用,术语"双特异性抗体"是指结合不超过两个表位或两个抗原的多特异性抗体。双特异性抗体的特征在于对第一表位具有结合特异性的第一免疫球蛋白可变结构域序列和对第二表位具有结合特异性的第二免疫球蛋白可变结构域序列。在一个实施方案中,第一表位和第二表位在相同的抗原,例如相同的蛋白质(或多聚蛋白质的亚基)上。在一个实施方案中,第一表位和第二表位重叠或基本上重叠。在一个实施方案中,第一表位和第二表位在不同的抗原,例如不同的蛋白质(或多聚蛋白质的不同亚基)上。在一个实施方案中,双特异性抗体包含对第一表位具有结合特异性的重链可变结构域序列和轻链可变结构域序列以及对第二表位具有结合特异性的重链可变结构域序列和轻链可变结构域序列。在一个实施方案中,双特异性抗体包含对第一表位具有结合特异性的半抗体或其片段以及对第二表位具有结合特异性的半抗体或其片段。在一个实施方案中,双特异性抗体包含对第一表位具有结合特异性的scFv或其片段以及对第二表位具有结合特异性的scFv或其片段。在一个实施方案中,第一表位位于CD33上,并且第二表位位于CD3上。在一个实施方案中,第一表位位于CD33上,并且第二表位位于PD-1、PD-L1、LAG-3、TIM-3、CTLA-4、EGFR、HER-2、

CD19、CD20、CD3和/或其他肿瘤相关的免疫抑制因子或表面抗原上。

[0165] 如本文所用,术语“CD33”是指67kD的单通跨膜糖蛋白,其是唾液酸结合免疫球蛋白样凝集素(Siglecs)家族的成员。CD33也称为Siglec-3、gp67、或p67。CD33的结构由介导唾液酸结合的氨基末端V-set Ig样结构域(由CD33的外显子2编码)和其细胞外部分中的C2-set IG样结构域(由外显子4编码)组成(Laszlo等人,2016年)。CD33 RNA的另选剪接可导致在细胞表面表达的较短同种型,该较短同种型缺少V-set但保留C2-set Ig样结构域(Laszlo、Estey和Walter,2014年;Laszlo等人,2016年)。该剪接过程的生物相关性在很大程度上是未知的,直至最近的研究显示,单核苷酸多态性(SNP)rs12459419存在于约50%的AML群体中并导致CD33的外显子2的跳越缺失导致了CD33的V结构域的缺失(Lamba等人,2017年)。全长人CD33由Uniprot P20138(SEQ ID NO:1)提供。

[0166] 如本文所用,“与CD33特异性地结合”的抗体是指以1×10^{-7}M或更小、优选地1×10^{-8}M或更小、更优选地5×10^{-9}M或更小、1×10^{-9}M或更小、5×10^{-10}M或更小或1×10^{-10}M或更小的KD与CD33结合、优选地与人CD33结合、优选地与CD33的C2结构域结合的抗体。术语“KD”是指从Kd对Ka的比(即Kd/Ka)获得并且表示为摩尔浓度(M)的解离常数。根据本公开,抗体的KD值可以使用本领域中的方法确定。例如,抗体的KD可通过使用表面等离振子共振,诸如通过使用生物传感器系统(例如Biacore®系统),或者通过使用生物层干涉测量技术(诸如Octet RED96系统)来确定。

[0167] 抗体KD的值越小,抗体与靶抗原结合的亲和力越高。

[0168] 根据一个具体方面,本发明涉及分离的单克隆抗体或其抗原结合片段,所述分离的单克隆抗体或其抗原结合片段包含具有以下多肽序列的重链互补决定区1(HCDR1)、HCDR2、HCDR3以及轻链互补决定区1(LCDR1)、LCDR2和LCDR3:

[0169] a.分别为SEQ ID NO:447、448、449、567、568和569;

[0170] b.分别为SEQ ID NO:444、445、446、564、565和566;

[0171] c.分别为SEQ ID NO:354、355、356、477、478和479;

[0172] d.分别为SEQ ID NO:378、379、380、501、502和503;

[0173] e.分别为SEQ ID NO:411、412、413、531、532和533;

[0174] f.分别为SEQ ID NO:348、349、350、471、472和473;

[0175] g.分别为SEQ ID NO:360、361、362、483、484和485;

[0176] h.分别为SEQ ID NO:363、364、365、486、487和488;

[0177] i.分别为SEQ ID NO:366、367、368、489、490和491;

[0178] j.分别为SEQ ID NO:369、370、371、492、493和494;

[0179] k.分别为SEQ ID NO:387、388、389、492、493和494;

[0180] l.分别为SEQ ID NO:402、403、404、522、523和524;

[0181] m.分别为SEQ ID NO:408、409、410、528、529和530;

[0182] n.分别为SEQ ID NO:423、424、425、543、544和545;

[0183] o.分别为SEQ ID NO:426、427、428、546、547和548;

[0184] p.分别为SEQ ID NO:351、352、353、474、475和476;

[0185] q.分别为SEQ ID NO:357、358、359、480、481和482;

[0186] r.分别为SEQ ID NO:372、373、374、495、496和497;

[0187] s.分别为SEQ ID NO:375、376、377、498、499和500;

[0188] t.分别为SEQ ID NO:381、382、383、504、505和506;

[0189] u.分别为SEQ ID NO:384、385、386、507、508和509;

[0190] v.分别为SEQ ID NO:390、391、392、510、511和512;

[0191] w.分别为SEQ ID NO:393、394、395、513、514和515;

[0192] x.分别为SEQ ID NO:396、397、398、516、517和518;

[0193] y.分别为SEQ ID NO:399、400、401、519、520和521;

[0194] z.分别为SEQ ID NO:405、406、407、525、526和527;

[0195] aa.分别为SEQ ID NO:414、415、416、534、535和536;

[0196] bb.分别为SEQ ID NO:417、418、419、537、538和539;

[0197] cc.分别为SEQ ID NO:420、421、422、540、541和542;

[0198] dd.分别为SEQ ID NO:429、430、431、549、550和551;

[0199] ee.分别为SEQ ID NO:432、433、434、552、553和554;

[0200] ff.分别为SEQ ID NO:435、436、437、555、556和557;

[0201] gg.分别为SEQ ID NO:438、439、440、558、559和560;

[0202] hh.分别为SEQ ID NO:441、442、443、561、562和563;

[0203] ii.分别为SEQ ID NO:450、451、452、570、571和572;

[0204] jj.分别为SEQ ID NO:453、454、455、573、574和575;

[0205] kk.分别为SEQ ID NO:456、457、458、576、577和578;

[0206] ll.分别为SEQ ID NO:459、460、461、579、580和581;

[0207] mm.分别为SEQ ID NO:378、379、380、582、583和584;

[0208] nn.分别为SEQ ID NO:414、415、416、585、586和587;或者

[0209] oo.分别为SEQ ID NO:429、430、431、480、481和482;

[0210] 其中抗体或其抗原结合片段特异性地结合CD33,优选人CD33。

[0211] 根据另一个具体方面,本发明涉及包含具有与SEQ ID NO:259-296中的一者有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区或者具有与SEQ ID NO:300-338中的一者有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区的分离的单克隆抗体或其抗原结合片段。根据一个优选的实施方案,本发明的分离的单克隆抗体或其抗原结合片段包含分别具有与SEQ ID NO:259-296中的一者有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:300-338中的一者有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。

[0212] 根据另一个具体方面,本发明涉及本发明的分离的单克隆抗体或其抗原结合片段,所述分离的单克隆抗体或其抗原结合片段包含:

[0213] a.具有SEQ ID NO:292的多肽序列的重链可变区和具有SEQ ID NO:332的多肽序列的轻链可变区;

[0214] b.具有SEQ ID NO:291的多肽序列的重链可变区和具有SEQ ID NO:331的多肽序列的轻链可变区;

[0215] c.具有SEQ ID NO:261的多肽序列的重链可变区和具有SEQ ID NO:302的多肽序列的轻链可变区；

[0216] d.具有SEQ ID NO:269的多肽序列的重链可变区和具有SEQ ID NO:310的多肽序列的轻链可变区；

[0217] e.具有SEQ ID NO:280的多肽序列的重链可变区和具有SEQ ID NO:322的多肽序列的轻链可变区；

[0218] f.具有SEQ ID NO:259的多肽序列的重链可变区和具有SEQ ID NO:300的多肽序列的轻链可变区；

[0219] g.具有SEQ ID NO:263的多肽序列的重链可变区和具有SEQ ID NO:304的多肽序列的轻链可变区；

[0220] h.具有SEQ ID NO:264的多肽序列的重链可变区和具有SEQ ID NO:305的多肽序列的轻链可变区；

[0221] i.具有SEQ ID NO:265的多肽序列的重链可变区和具有SEQ ID NO:306的多肽序列的轻链可变区；

[0222] j.具有SEQ ID NO:266的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序列的轻链可变区；

[0223] k.具有SEQ ID NO:272的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序列的轻链可变区；

[0224] l.具有SEQ ID NO:277的多肽序列的重链可变区和具有SEQ ID NO:317的多肽序列的轻链可变区；

[0225] m.具有SEQ ID NO:279的多肽序列的重链可变区和具有SEQ ID NO:319的多肽序列的轻链可变区；

[0226] n.具有SEQ ID NO:284的多肽序列的重链可变区和具有SEQ ID NO:324的多肽序列的轻链可变区；

[0227] o.具有SEQ ID NO:285的多肽序列的重链可变区和具有SEQ ID NO:325的多肽序列的轻链可变区；

[0228] p.具有SEQ ID NO:260的多肽序列的重链可变区和具有SEQ ID NO:301的多肽序列的轻链可变区；

[0229] q.具有SEQ ID NO:262的多肽序列的重链可变区和具有SEQ ID NO:303的多肽序列的轻链可变区；

[0230] r.具有SEQ ID NO:267的多肽序列的重链可变区和具有SEQ ID NO:308的多肽序列的轻链可变区；

[0231] s.具有SEQ ID NO:268的多肽序列的重链可变区和具有SEQ ID NO:309的多肽序列的轻链可变区；

[0232] t.具有SEQ ID NO:270的多肽序列的重链可变区和具有SEQ ID NO:311的多肽序列的轻链可变区；

[0233] u.具有SEQ ID NO:271的多肽序列的重链可变区和具有SEQ ID NO:312的多肽序列的轻链可变区；

[0234] v.具有SEQ ID NO:273的多肽序列的重链可变区和具有SEQ ID NO:313的多肽序

列的轻链可变区；

[0235] w.具有SEQ ID NO:274的多肽序列的重链可变区和具有SEQ ID NO:314的多肽序列的轻链可变区；

[0236] x.具有SEQ ID NO:275的多肽序列的重链可变区和具有SEQ ID NO:315的多肽序列的轻链可变区；

[0237] y.具有SEQ ID NO:276的多肽序列的重链可变区和具有SEQ ID NO:316的多肽序列的轻链可变区；

[0238] z.具有SEQ ID NO:278的多肽序列的重链可变区和具有SEQ ID NO:318的多肽序列的轻链可变区；

[0239] aa.具有SEQ ID NO:281的多肽序列的重链可变区和具有SEQ ID NO:321的多肽序列的轻链可变区；

[0240] bb.具有SEQ ID NO:282的多肽序列的重链可变区和具有SEQ ID NO:322的多肽序列的轻链可变区；

[0241] cc.具有SEQ ID NO:283的多肽序列的重链可变区和具有SEQ ID NO:323的多肽序列的轻链可变区；

[0242] dd.具有SEQ ID NO:286的多肽序列的重链可变区和具有SEQ ID NO:326的多肽序列的轻链可变区；

[0243] ee.具有SEQ ID NO:287的多肽序列的重链可变区和具有SEQ ID NO:327的多肽序列的轻链可变区；

[0244] ff.具有SEQ ID NO:288的多肽序列的重链可变区和具有SEQ ID NO:328的多肽序列的轻链可变区；

[0245] gg.具有SEQ ID NO:289的多肽序列的重链可变区和具有SEQ ID NO:329的多肽序列的轻链可变区；

[0246] hh.具有SEQ ID NO:290的多肽序列的重链可变区和具有SEQ ID NO:330的多肽序列的轻链可变区；

[0247] ii.具有SEQ ID NO:293的多肽序列的重链可变区和具有SEQ ID NO:333的多肽序列的轻链可变区；

[0248] jj.具有SEQ ID NO:294的多肽序列的重链可变区和具有SEQ ID NO:334的多肽序列的轻链可变区；

[0249] kk.具有SEQ ID NO:295的多肽序列的重链可变区和具有SEQ ID NO:335的多肽序列的轻链可变区；

[0250] ll.具有SEQ ID NO:296的多肽序列的重链可变区和具有SEQ ID NO:336的多肽序列的轻链可变区；

[0251] mm.具有SEQ ID NO:269的多肽序列的重链可变区和具有SEQ ID NO:337的多肽序列的轻链可变区；

[0252] nn.具有SEQ ID NO:281的多肽序列的重链可变区和具有SEQ ID NO:338的多肽序列的轻链可变区；或

[0253] oo.具有SEQ ID NO:286的多肽序列的重链可变区和具有SEQ ID NO:303的多肽序列的轻链可变区。

[0254] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:348、349、350、471、472和473的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:259有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:300有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:259的多肽序列的重链可变区;以及具有SEQ ID NO:300的多肽序列的轻链可变区。

[0255] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:351、352、353、474、475和476的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:260有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:301有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:260的多肽序列的重链可变区;以及具有SEQ ID NO:301的多肽序列的轻链可变区。

[0256] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:354、355、356、477、478和479的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:261有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:302有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:261的多肽序列的重链可变区;以及具有SEQ ID NO:301的多肽序列的轻链可变区。

[0257] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:357、358、359、480、481和482的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:262有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:303有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:262的多肽序列的重链可变区;以及具有SEQ ID NO:303的多肽序列的轻链可变区。

[0258] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:360、361、362、483、484和485的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:263有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:304有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:263的多肽序列的重链可变区;

以及具有SEQ ID NO:304的多肽序列的轻链可变区。

[0259] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:363、364、365、486、487和488的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:264有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:305有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:264的多肽序列的重链可变区;以及具有SEQ ID NO:305的多肽序列的轻链可变区。

[0260] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:366、367、368、489、490和491的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:265有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:306有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:265的多肽序列的重链可变区;以及具有SEQ ID NO:306的多肽序列的轻链可变区。

[0261] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:369、370、371、492、493和494的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:266有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:307有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:266的多肽序列的重链可变区;以及具有SEQ ID NO:307的多肽序列的轻链可变区。

[0262] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:372、373、374、495、496和497的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:267有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:308有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:267的多肽序列的重链可变区;以及具有SEQ ID NO:308的多肽序列的轻链可变区。

[0263] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:375、376、377、498、499和500的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:268有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:309有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,

分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:268的多肽序列的重链可变区;以及具有SEQ ID NO:309的多肽序列的轻链可变区。

[0264] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:378、379、380、501、502和503的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:269有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:310有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:269的多肽序列的重链可变区;以及具有SEQ ID NO:310的多肽序列的轻链可变区。

[0265] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:381、382、383、504、505和506的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:270有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:311有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:270的多肽序列的重链可变区;以及具有SEQ ID NO:311的多肽序列的轻链可变区。

[0266] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:384、385、386、507、508和509的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:271有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:312有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:271的多肽序列的重链可变区;以及具有SEQ ID NO:312的多肽序列的轻链可变区。

[0267] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:387、388、389、492、493和494的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:272有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:307有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:272的多肽序列的重链可变区;以及具有SEQ ID NO:307的多肽序列的轻链可变区。

[0268] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:390、391、392、510、511和512的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:273有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:313有至少85%、优选90%、更优选

95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的轻链可变区。优选地，分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:273的多肽序列的重链可变区；以及具有SEQ ID NO:313的多肽序列的轻链可变区。

[0269] 在一个实施方案中，本发明涉及分离的单克隆抗体或其抗原结合片段，其包含分别具有SEQ ID NO:393、394、395、513、54和515的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中，分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:274有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:314有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的轻链可变区。优选地，分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:274的多肽序列的重链可变区；以及具有SEQ ID NO:314的多肽序列的轻链可变区。

[0270] 在一个实施方案中，本发明涉及分离的单克隆抗体或其抗原结合片段，其包含分别具有SEQ ID NO:396、397、398、516、517和518的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中，分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:275有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:315有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的轻链可变区。优选地，分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:275的多肽序列的重链可变区；以及具有SEQ ID NO:315的多肽序列的轻链可变区。

[0271] 在一个实施方案中，本发明涉及分离的单克隆抗体或其抗原结合片段，其包含分别具有SEQ ID NO:399、400、401、519、520和521的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中，分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:276有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:316有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的轻链可变区。优选地，分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:276的多肽序列的重链可变区；以及具有SEQ ID NO:316的多肽序列的轻链可变区。

[0272] 在一个实施方案中，本发明涉及分离的单克隆抗体或其抗原结合片段，其包含分别具有SEQ ID NO:402、403、404、522、523和524的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中，分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:277有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:317有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的轻链可变区。优选地，分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:277的多肽序列的重链可变区；以及具有SEQ ID NO:317的多肽序列的轻链可变区。

[0273] 在一个实施方案中，本发明涉及分离的单克隆抗体或其抗原结合片段，其包含分别具有SEQ ID NO:405、406、407、525、526和527的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中，分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:278有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)

同一性的多肽序列的重链可变区以及具有与SEQ ID NO:318有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的轻链可变区。优选地，分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:278的多肽序列的重链可变区；以及具有SEQ ID NO:318的多肽序列的轻链可变区。

[0274] 在一个实施方案中，本发明涉及分离的单克隆抗体或其抗原结合片段，其包含分别具有SEQ ID NO:408、409、410、528、529和530的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中，分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:279有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:319有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的轻链可变区。优选地，分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:279的多肽序列的重链可变区；以及具有SEQ ID NO:319的多肽序列的轻链可变区。

[0275] 在一个实施方案中，本发明涉及分离的单克隆抗体或其抗原结合片段，其包含分别具有SEQ ID NO:411、412、413、531、532和533的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中，分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:280有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:320有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的轻链可变区。优选地，分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:280的多肽序列的重链可变区；以及具有SEQ ID NO:320的多肽序列的轻链可变区。

[0276] 在一个实施方案中，本发明涉及分离的单克隆抗体或其抗原结合片段，其包含分别具有SEQ ID NO:414、415、416、534、535和536的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中，分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:281有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:321有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的轻链可变区。优选地，分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:281的多肽序列的重链可变区；以及具有SEQ ID NO:321的多肽序列的轻链可变区。

[0277] 在一个实施方案中，本发明涉及分离的单克隆抗体或其抗原结合片段，其包含分别具有SEQ ID NO:417、418、419、537、538和539的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中，分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:282有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:322有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的轻链可变区。优选地，分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:282的多肽序列的重链可变区；以及具有SEQ ID NO:322的多肽序列的轻链可变区。

[0278] 在一个实施方案中，本发明涉及分离的单克隆抗体或其抗原结合片段，其包含分别具有SEQ ID NO:420、421、422、540、541和542的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中，分离的单克隆抗体或其抗原结合片段包含具有与SEQ

ID NO:283有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:323有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:283的多肽序列的重链可变区;以及具有SEQ ID NO:323的多肽序列的轻链可变区。

[0279] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:423、424、425、543、544和545的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:284有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:324有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:284的多肽序列的重链可变区;以及具有SEQ ID NO:324的多肽序列的轻链可变区。

[0280] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:426、427、428、546、547和548的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:285有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:325有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:285的多肽序列的重链可变区;以及具有SEQ ID NO:325的多肽序列的轻链可变区。

[0281] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:429、430、431、549、550和551的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:286有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:326有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:286的多肽序列的重链可变区;以及具有SEQ ID NO:326的多肽序列的轻链可变区。

[0282] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:432、433、434、552、553和554的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:287有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:327有至少85％、优选90％、更优选95％或更高(诸如95％、96％、97％、98％或99％)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:287的多肽序列的重链可变区;以及具有SEQ ID NO:327的多肽序列的轻链可变区。

[0283] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:435、436、437、555、556和557的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、

LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:288有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:328有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:288的多肽序列的重链可变区;以及具有SEQ ID NO:328的多肽序列的轻链可变区。

[0284] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:438、439、440、558、559和560的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:289有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:329有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:289的多肽序列的重链可变区;以及具有SEQ ID NO:329的多肽序列的轻链可变区。

[0285] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:441、442、443、561、562和563的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:290有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:330有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:290的多肽序列的重链可变区;以及具有SEQ ID NO:330的多肽序列的轻链可变区。

[0286] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:444、445、446、564、565和566的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:291有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:331有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:291的多肽序列的重链可变区;以及具有SEQ ID NO:331的多肽序列的轻链可变区。

[0287] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:447、448、449、567、568和569的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:292有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:332有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:292的多肽序列的重链可变区;以及具有SEQ ID NO:332的多肽序列的轻链可变区。

[0288] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分

别具有SEQ ID NO:450、451、452、570、571和572的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:293有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:333有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:293的多肽序列的重链可变区;以及具有SEQ ID NO:333的多肽序列的轻链可变区。

[0289] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:453、454、455、573、574和575的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:294有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:334有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:294的多肽序列的重链可变区;以及具有SEQ ID NO:334的多肽序列的轻链可变区。

[0290] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:456、457、458、576、577和578的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:295有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:335有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:295的多肽序列的重链可变区;以及具有SEQ ID NO:335的多肽序列的轻链可变区。

[0291] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:459、460、461、579、580和581的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:296有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:336有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:296的多肽序列的重链可变区;以及具有SEQ ID NO:336的多肽序列的轻链可变区。

[0292] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:378、379、380、582、583和584的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:269有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:337有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:269的多肽序列的重链可变区;以及具有SEQ ID NO:337的多肽序列的轻链可变区。

[0293] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:414、415、416、585、586和587的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:281有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:338有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:281的多肽序列的重链可变区;以及具有SEQ ID NO:338的多肽序列的轻链可变区。

[0294] 在一个实施方案中,本发明涉及分离的单克隆抗体或其抗原结合片段,其包含分别具有SEQ ID NO:429、430、431、480、481和482的多肽序列的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3。在另一个实施方案中,分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:286有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区以及具有与SEQ ID NO:303有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。优选地,分离的单克隆抗体或其抗原结合片段包含具有SEQ ID NO:286的多肽序列的重链可变区;以及具有SEQ ID NO:303的多肽序列的轻链可变区。

[0295] 本文还提供了抗CD33/抗CD3双特异性抗体或其抗原结合片段,包含抗CD33抗体或其抗原结合片段以及抗CD3抗体或其抗原结合片段。在某些实施方案中,抗CD33抗体或其抗原结合片段是本发明的抗CD33单克隆抗体或其抗原结合片段,并且抗CD3抗体或其抗原结合片段包含具有以下多肽序列的重链互补决定区1(HCDR1)、HCDR2、HCDR3、轻链互补决定区1(LCDR1)、LCDR2和LCDR3,(1)分别为SEQ ID NO:342、343、344、465、466和467或(2)分别为SEQ ID NO:345、346、347、468、469和470。

[0296] 术语“CD3”是指CD3蛋白质多亚基复合体。CD3也可称为“分化簇3”。CD3蛋白质多亚基复合体由六(6)条不同的多肽链组成,其包括CD3γ链(SwissProt P09693)(SEQ ID NO:588)、CD3δ链(SwissProt P04234)(SEQ ID NO:589)、两条CD3ε链(SwissProt P07766)(SEQ ID NO:590)和一条CD3链同源二聚体(SwissProt 20963)(SEQ ID NO:591),其与T细胞受体α和β链相关联。CD3是同时用于激活细胞毒性T细胞(CD8+初始T细胞)和T辅助细胞(CD4+初始T细胞)的T细胞共受体。CD3多亚基复合体的CD3γ、CD3δ和CD3ε多肽链与T细胞受体(TCR)和CD3链相关联以在T淋巴细胞中产生激活信号,并且CD3和T细胞受体之间的相互作用构成TCR复合体。除非另有说明,否则术语“CD3”包括由细胞(包括T细胞)天然表达或者能够在用编码那些多肽的基因或cDNA转染的细胞上表达的任何CD3变体、同种型和物种同源物,优选地“CD3”是人CD3蛋白质多亚基复合体。

[0297] 经由TCR/CD3复合体将T淋巴细胞重定向至表达CD33的癌症细胞代表了一种有吸引力的另选处理方法。T淋巴细胞的TCR/CD3复合体由在细胞表面共表达的TCRα/β或TCRγ/δ异二聚体与CD3标记的γ、δ、ε、ζ和η的不变亚基组成。人CD3ε以UniProt P07766描述(CD3E_HUMAN)。现有技术中所述的抗CD3ε抗体是SP34(Yang SJ,The Journal of Immunology,(1986)137;1097-1100),其与灵长类和人CD3两者反应并且可从Pharmingen公司商购获得。现有技术中所述的其他抗CD3抗体包括UCHT-1(参见WO2000041474)和BC-3(弗雷德哈钦森癌症研究中心(Fred Hutchinson Cancer Research Institute);用于GvHD的

I/II期试验,Anasetti等人,Transplantation,54:844(1992))。SP34与UCHT-1和BC-3的不同之处在于,SP-34识别仅存在于CD3的ε链上的表位(参见Salmeron等人,1991年,J.Immunol.,第147卷,第3047页),而UCHT-1和BC-3识别由ε链和γ链二者贡献的表位。具有与SP34相同的序列的抗体序列至少在WO2008119565、WO2008119566、WO2008119567、WO2010037836、WO2010037837和WO2010037838中有所描述。与SP34VH有96%同一性的抗体序列在US8236308(WO2007042261)中有所描述。

[0298] 不同形式的双特异性抗体已有所描述,并且最近由Chames和Baty在Curr Opin Drug Disc Dev,2009年,第12卷,第276页中进行了综述。

[0299] 在一些实施方案中,本发明的双特异性抗体是通过受控Fab臂交换得到的双体抗体、交叉体或双特异性抗体,如本发明所述的那些。

[0300] 在一些实施方案中,双特异性抗体包括具有互补CH3结构域以强制发生异源二聚体化的IgG样分子;重组IgG样双靶向分子,其中该分子的两侧各自含有至少两种不同抗体的Fab片段的一部分或Fab片段;IgG融合分子,其中全长IgG抗体与额外的Fab片段或Fab片段的部分融合;Fc融合分子,其中单链Fv分子或稳定的双体抗体与重链恒定域、Fc区或其部分融合;Fab融合分子,其中不同的Fab片段融合在一起;基于ScFv和双体抗体的重链抗体(例如域抗体、纳米抗体),其中不同的单链Fv分子或不同的双体抗体或不同的重链抗体(例如域抗体、纳米抗体)彼此融合或与另一蛋白或载体分子融合。

[0301] 在一些实施方案中,具有互补CH3结构域分子的IgG样分子包括Triomab/Quadroma(Trion Pharma/Fresenius Biotech)、纽扣结构(Knobs-into-Holes)(Genentech)、CrossMAbs(Roche)和静电配对体(electrostatically-matched)(Amgen)、LUZ-Y(Genentech)、链交换工程结构域体(Strand Exchange Engineered Domain body)(SEEDbody)(EMD Serono)、Biclonic(Merus)和DuoBody(Genmab A/S)。

[0302] 在一些实施方案中,重组IgG样双靶向分子包括双重靶向(DT)-Ig(GSK/Domantis)、二合一抗体(Genentech)、交联Mabs(Karmanos Cancer Center)、mAb2(F-Star)和CovX体(CovX/Pfizer)。

[0303] 在一些实施方案中,IgG融合分子包括双重可变结构域(DVD)-Ig(Abbott)、IgG样双特异性抗体(InnClone/Eli Lilly)、Ts2Ab(MedImmune/AZ)和BsAb(Zymogenetics)、HERCULES(Biogen Idec)以及TvAb(Roche)。

[0304] 在一些实施方案中,Fc融合分子包括ScFv/Fc融合体(Academic Institution)、SCORPION(Emergent BioSolutions/Trubion,Zymogenetics/BMS)、双亲和性再靶向技术(Fc-DART)(MacroGenics)以及Dual(ScFv).sub.2-Fab(中国国家抗体医药研究中心(National Research Center forAntibodyMedicine--China))。

[0305] 在一些实施方案中,Fab融合双特异性抗体包括F(ab)2(Medarex/AMGEN)、Dual-Action或Bis-Fab(Genentech)、Dock-and-Lock(DNL)(ImmunoMedics)、二价双特异性抗体(Biotecnol)和Fab-Fv(UCB-Celltech)。基于ScFv的、基于双体抗体的结构域抗体包括但不限于双特异性T细胞衔接器(BiTE)(Micromet)、串联双体抗体(Tandab)(Affimed)、双亲和性再靶向分子(DART)(MacroGenics)、单链双体抗体(Academic)、TCR样抗体(AIT,ReceptorLogics)、人血清白蛋白ScFv融合体(Merrimack)和COMBODY(Epigen Biotech)、双靶向纳米抗体(Ablynx)、仅双重靶向重链结构域抗体。

[0306] 本发明的全长双特异性抗体可例如使用两个单特异性二价抗体之间的Fab臂交换(或半分子交换)通过下列方式产生:在每个半分子中的重链CH3交界处引入置换以促成两个在体外无细胞环境中或使用共表达而具有不同特异性的抗体半分子的异源二聚体形成。Fab臂交换反应是二硫键异构化反应和CH3域解离-缔合的结果。亲本单特异性抗体的铰链区中的重链二硫键减少。亲本单特异性抗体之一的所得游离半胱氨酸与第二亲本单特异性抗体分子的半胱氨酸残基形成重链间二硫键,同时亲本抗体的CH3结构域通过解离-缔合而释放和重新形成。可将Fab臂的CH3域改造成促成异源二聚化而非同源二聚化。所得产物是具有两个Fab臂或半分子的双特异性抗体,这两个Fab臂或半分子各自结合不同的表位,即CD33上的表位和CD3上的表位。

[0307] 如本文所用,“同源二聚化”是指具有相同CH3氨基酸序列的两条重链的相互作用。如本文所用,“同源二聚体”是指具有含有相同CH3氨基酸序列的两条重链的抗体。

[0308] 如本文所用,“异源二聚化”是指具有不同CH3氨基酸序列的两条重链的相互作用。如本文所用,“异源二聚体”是指具有含有不同CH3氨基酸序列的两条重链的抗体。

[0309] “钮扣”技术(参见,例如PCT国际二聚抗体WO 2006/028936)可用于产生全长双特异性抗体。简而言之,在人IgG中形成CH3域的交界的选定氨基酸可在影响CH3域相互作用的位置处突变,从而促进异源二聚体形成。将具有小侧链(扣)的氨基酸引入特异性地结合第一抗原的抗体的重链中,并将具有大侧链(钮)的氨基酸引入特异性地结合第二抗原的抗体的重链中。在两种抗体共表达后,由于具有“扣”的重链与具有“钮”的重链的优先相互作用而形成异源二聚体。形成钮和扣的示例性CH3置换对(表示为第一重链的第一CH3结构域中的修饰位置/第二重链的第二CH3结构域中的修饰位置)是:T366Y/F405A、T366W/F405W、F405W/Y407A、T394W/Y407T、T394S/Y407A、T366W/T394S、F405W/T394S和T366W/T366S_L368A_Y407V。

[0310] 还可使用其他策略,诸如通过在一个CH3表面置换带正电荷的残基并在第二CH3表面置换带负电荷的残基使用静电相互作用促进重链异源二聚化,如美国专利公布US2010/0015133;美国专利公布US2009/0182127;美国专利公布US2010/028637或美国专利公布US2011/0123532中所述。在其它技术中,可通过下面的置换(表示为第一重链的第一CH3结构域中的修饰位置/第二重链的第二CH3结构域中的修饰位置)促进异源二聚化:L351Y_F405AY407V/T394W、T366I_K392M_T394W/F405A_Y407V、T366L_K392M_T394W/F405A_Y407V、L351Y_Y407A/T366A_K409F、L351Y_Y407A/T366V K409F Y407A/T366A_K409F或T350V_L351Y_F405A Y407V/T350V_T366L_K392L_T394W,如美国专利公布US2012/0149876或美国专利公布US2013/0195849中所述。

[0311] 除上述方法之外,本发明的双特异性抗体还可在体外无细胞环境中通过下列方式产生:在两种单特异性同源二聚抗体的CH3区中引入不对称突变,并且在还原条件下由两种亲本单特异性同源二聚抗体形成双特异性异源二聚抗体,从而根据国际专利公布号WO2011/131746所述的方法使得二硫键异构化。在所述方法中,将第一单特异性二价抗体(例如,抗CD33抗体)和第二单特异性二价抗体(例如,抗CD3抗体)改造为在CH3结构域处具有促进异源二聚体稳定性的某些置换;将这些抗体在足以使铰链区中的半胱氨酸发生二硫键异构化的还原条件下一起温育;从而通过Fab臂交换产生双特异性抗体。温育条件最佳可恢复到非还原条件。可使用的示例性还原剂为2-巯基乙胺(2-MEA)、二硫苏糖醇(DTT)、二硫

赤藓糖醇(DTE)、谷胱甘肽、三(2-羧乙基)膦(TCEP)、L-半胱氨酸和β-巯基乙醇,优选为选自2-巯基乙胺、二硫苏糖醇和三(2-羧乙基)膦的还原剂。例如,可使用如下条件:在至少25mM 2-MEA的存在下或至少0.5mM二硫苏糖醇的存在下,在5-8的pH例如pH7.0或pH7.4,至少20℃的温度下,温育至少90分钟。

[0312] 在某些实施方案中,抗CD33抗体或其抗原结合片段包含具有以下多肽序列的重链互补决定区1(HCDR1)、HCDR2、HCDR3以及轻链互补决定区1(LCDR1)、LCDR2和LCDR3:

[0313] a.分别为SEQ ID NO:447、448、449、567、568和569;

[0314] b.分别为SEQ ID NO:444、445、446、564、565和566;

[0315] c.分别为SEQ ID NO:354、355、356、477、478和479;

[0316] d.分别为SEQ ID NO:378、379、380、501、502和503;

[0317] e.分别为SEQ ID NO:411、412、413、531、532和533;

[0318] f.分别为SEQ ID NO:348、349、350、471、472和473;

[0319] g.分别为SEQ ID NO:360、361、362、483、484和485;

[0320] h.分别为SEQ ID NO:363、364、365、486、487和488;

[0321] i.分别为SEQ ID NO:366、367、368、489、490和491;

[0322] j.分别为SEQ ID NO:369、370、371、492、493和494;

[0323] k.分别为SEQ ID NO:387、388、389、492、493和494;

[0324] l.分别为SEQ ID NO:402、403、404、522、523和524;

[0325] m.分别为SEQ ID NO:408、409、410、528、529和530;

[0326] n.分别为SEQ ID NO:423、424、425、543、544和545;

[0327] o.分别为SEQ ID NO:426、427、428、546、547和548;

[0328] p.分别为SEQ ID NO:357、358、359、480、481和482;

[0329] q.分别为SEQ ID NO:372、373、374、495、496和497;

[0330] r.分别为SEQ ID NO:375、376、377、498、499和500;

[0331] s.分别为SEQ ID NO:381、382、383、504、505和506;

[0332] t.分别为SEQ ID NO:384、385、386、507、508和509;

[0333] u.分别为SEQ ID NO:390、391、392、510、511和512;

[0334] v.分别为SEQ ID NO:393、394、395、513、514和515;

[0335] w.分别为SEQ ID NO:396、397、398、516、517和518;

[0336] x.分别为SEQ ID NO:399、400、401、519、520和521;

[0337] y.分别为SEQ ID NO:405、406、407、525、526和527;

[0338] z.分别为SEQ ID NO:414、415、416、534、535和536;

[0339] aa.分别为SEQ ID NO:417、418、419、537、538和539;

[0340] bb.分别为SEQ ID NO:420、421、422、540、541和542;

[0341] cc.分别为SEQ ID NO:429、430、431、549、550和551;

[0342] dd.分别为SEQ ID NO:432、433、434、552、553和554;

[0343] ee.分别为SEQ ID NO:435、436、437、555、556和557;

[0344] ff.分别为SEQ ID NO:438、439、440、558、559和560;

[0345] gg.分别为SEQ ID NO:441、442、443、561、562和563;

[0346] hh.分别为SEQ ID NO:450、451、452、570、571和572;

[0347] ii.分别为SEQ ID NO:453、454、455、573、574和575;

[0348] jj.分别为SEQ ID NO:456、457、458、576、577和578;

[0349] kk.分别为SEQ ID NO:459、460、461、579、580和581;

[0350] ll.分别为SEQ ID NO:378、379、380、582、583和584;

[0351] mm.分别为SEQ ID NO:414、415、416、585、586和587;或者

[0352] nn.分别为SEQ ID NO:429、430、431、480、481和482;

[0353] 并且抗CD3抗体或其抗原结合片段包含具有以下多肽序列的重链互补决定区1(HCDR1)、HCDR2、HCDR3以及轻链互补决定区1(LCDR1)、LCDR2和LCDR3:

[0354] 1)分别为SEQ ID NO:342、343、344、465、466和467;或者

[0355] 2)分别为SEQ ID NO:345、346、347、468、469和470。

[0356] 在某些实施方案中,抗CD33抗体或其抗原结合片段包含具有与SEQ ID NO:259-296中的一者有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区或者具有与SEQ ID NO:300-338中的一者有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区;并且抗CD3抗体或其抗原结合片段包含具有与SEQ ID NO:257或258有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的重链可变区或者具有与SEQ ID NO:298或299有至少85%、优选90%、更优选95%或更高(诸如95%、96%、97%、98%或99%)同一性的多肽序列的轻链可变区。

[0357] 在某些实施方案中,抗CD33/抗CD3双特异性抗体或其抗原结合片段包含:

[0358] a.具有SEQ ID NO:292的多肽序列的重链可变区和具有SEQ ID NO:332的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0359] b.具有SEQ ID NO:291的多肽序列的重链可变区和具有SEQ ID NO:331的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0360] c.具有SEQ ID NO:261的多肽序列的重链可变区和具有SEQ ID NO:302的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0361] d.具有SEQ ID NO:269的多肽序列的重链可变区和具有SEQ ID NO:310的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0362] e.具有SEQ ID NO:280的多肽序列的重链可变区和具有SEQ ID NO:322的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0363] f.具有SEQ ID NO:259的多肽序列的重链可变区和具有SEQ ID NO:300的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0364] g.具有SEQ ID NO:263的多肽序列的重链可变区和具有SEQ ID NO:304的多肽序

列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0365] h.具有SEQ ID NO:264的多肽序列的重链可变区和具有SEQ ID NO:305的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0366] i.具有SEQ ID NO:265的多肽序列的重链可变区和具有SEQ ID NO:306的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0367] j.具有SEQ ID NO:266的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0368] k.具有SEQ ID NO:272的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0369] l.具有SEQ ID NO:277的多肽序列的重链可变区和具有SEQ ID NO:317的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0370] m.具有SEQ ID NO:279的多肽序列的重链可变区和具有SEQ ID NO:319的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0371] n.具有SEQ ID NO:284的多肽序列的重链可变区和具有SEQ ID NO:324的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0372] o.具有SEQ ID NO:285的多肽序列的重链可变区和具有SEQ ID NO:325的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0373] p.具有SEQ ID NO:260的多肽序列的重链可变区和具有SEQ ID NO:301的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0374] q.具有SEQ ID NO:262的多肽序列的重链可变区和具有SEQ ID NO:303的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0375] r.具有SEQ ID NO:267的多肽序列的重链可变区和具有SEQ ID NO:308的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0376] s.具有SEQ ID NO:268的多肽序列的重链可变区和具有SEQ ID NO:309的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0377] t.具有SEQ ID NO:270的多肽序列的重链可变区和具有SEQ ID NO:311的多肽序

列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0378] u.具有SEQ ID NO:271的多肽序列的重链可变区和具有SEQ ID NO:312的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0379] v.具有SEQ ID NO:273的多肽序列的重链可变区和具有SEQ ID NO:313的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0380] w.具有SEQ ID NO:274的多肽序列的重链可变区和具有SEQ ID NO:314的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0381] x.具有SEQ ID NO:275的多肽序列的重链可变区和具有SEQ ID NO:315的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0382] y.具有SEQ ID NO:276的多肽序列的重链可变区和具有SEQ ID NO:316的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0383] z.具有SEQ ID NO:278的多肽序列的重链可变区和具有SEQ ID NO:318的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0384] aa.具有SEQ ID NO:281的多肽序列的重链可变区和具有SEQ ID NO:321的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0385] bb.具有SEQ ID NO:282的多肽序列的重链可变区和具有SEQ ID NO:322的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0386] cc.具有SEQ ID NO:283的多肽序列的重链可变区和具有SEQ ID NO:323的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0387] dd.具有SEQ ID NO:286的多肽序列的重链可变区和具有SEQ ID NO:326的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0388] ee.具有SEQ ID NO:287的多肽序列的重链可变区和具有SEQ ID NO:327的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0389] ff.具有SEQ ID NO:288的多肽序列的重链可变区和具有SEQ ID NO:328的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0390] gg.具有SEQ ID NO:289的多肽序列的重链可变区和具有SEQ ID NO:329的多肽序

列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0391] hh.具有SEQ ID NO:290的多肽序列的重链可变区和具有SEQ ID NO:330的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0392] ii.具有SEQ ID NO:293的多肽序列的重链可变区和具有SEQ ID NO:333的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0393] jj.具有SEQ ID NO:294的多肽序列的重链可变区和具有SEQ ID NO:334的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0394] kk.具有SEQ ID NO:295的多肽序列的重链可变区和具有SEQ ID NO:335的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0395] ll.具有SEQ ID NO:296的多肽序列的重链可变区和具有SEQ ID NO:336的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0396] mm.具有SEQ ID NO:269的多肽序列的重链可变区和具有SEQ ID NO:337的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0397] nn.具有SEQ ID NO:281的多肽序列的重链可变区和具有SEQ ID NO:338的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0398] oo.具有SEQ ID NO:286的多肽序列的重链可变区和具有SEQ ID NO:303的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0399] pp.具有SEQ ID NO:292的多肽序列的重链可变区和具有SEQ ID NO:332的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0400] qq.具有SEQ ID NO:291的多肽序列的重链可变区和具有SEQ ID NO:331的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0401] rr.具有SEQ ID NO:261的多肽序列的重链可变区和具有SEQ ID NO:302的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0402] ss.具有SEQ ID NO:269的多肽序列的重链可变区和具有SEQ ID NO:310的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0403] tt.具有SEQ ID NO:280的多肽序列的重链可变区和具有SEQ ID NO:322的多肽序

列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0404] uu.具有SEQ ID NO:259的多肽序列的重链可变区和具有SEQ ID NO:300的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0405] vv.具有SEQ ID NO:263的多肽序列的重链可变区和具有SEQ ID NO:304的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0406] ww.具有SEQ ID NO:264的多肽序列的重链可变区和具有SEQ ID NO:305的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0407] xx.具有SEQ ID NO:265的多肽序列的重链可变区和具有SEQ ID NO:306的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0408] yy.具有SEQ ID NO:266的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0409] zz.具有SEQ ID NO:272的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0410] aaa.具有SEQ ID NO:277的多肽序列的重链可变区和具有SEQ ID NO:317的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0411] bbb.具有SEQ ID NO:279的多肽序列的重链可变区和具有SEQ ID NO:319的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0412] ccc.具有SEQ ID NO:284的多肽序列的重链可变区和具有SEQ ID NO:324的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;或

[0413] ddd.具有SEQ ID NO:285的多肽序列的重链可变区和具有SEQ ID NO:325的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0414] eee.具有SEQ ID NO:260的多肽序列的重链可变区和具有SEQ ID NO:301的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0415] fff.具有SEQ ID NO:262的多肽序列的重链可变区和具有SEQ ID NO:303的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0416] ggg.具有SEQ ID NO:267的多肽序列的重链可变区和具有SEQ ID NO:308的多肽

序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0417] hhh.具有SEQ ID NO:268的多肽序列的重链可变区和具有SEQ ID NO:309的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0418] iii.具有SEQ ID NO:270的多肽序列的重链可变区和具有SEQ ID NO:311的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0419] jjj.具有SEQ ID NO:271的多肽序列的重链可变区和具有SEQ ID NO:312的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0420] kkk.具有SEQ ID NO:273的多肽序列的重链可变区和具有SEQ ID NO:313的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0421] lll.具有SEQ ID NO:274的多肽序列的重链可变区和具有SEQ ID NO:314的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0422] mmm.具有SEQ ID NO:275的多肽序列的重链可变区和具有SEQ ID NO:315的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0423] nnn.具有SEQ ID NO:276的多肽序列的重链可变区和具有SEQ ID NO:316的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0424] ooo.具有SEQ ID NO:278的多肽序列的重链可变区和具有SEQ ID NO:318的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0425] ppp.具有SEQ ID NO:281的多肽序列的重链可变区和具有SEQ ID NO:321的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0426] qqq.具有SEQ ID NO:282的多肽序列的重链可变区和具有SEQ ID NO:322的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0427] rrr.具有SEQ ID NO:283的多肽序列的重链可变区和具有SEQ ID NO:323的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0428] sss.具有SEQ ID NO:286的多肽序列的重链可变区和具有SEQ ID NO:326的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0429] ttt.具有SEQ ID NO:287的多肽序列的重链可变区和具有SEQ ID NO:327的多肽

序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0430] uuu.具有SEQ ID NO:288的多肽序列的重链可变区和具有SEQ ID NO:328的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0431] vvv.具有SEQ ID NO:289的多肽序列的重链可变区和具有SEQ ID NO:329的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0432] www.具有SEQ ID NO:290的多肽序列的重链可变区和具有SEQ ID NO:330的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0433] xxx.具有SEQ ID NO:293的多肽序列的重链可变区和具有SEQ ID NO:333的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0434] yyy.具有SEQ ID NO:294的多肽序列的重链可变区和具有SEQ ID NO:334的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0435] zzz.具有SEQ ID NO:295的多肽序列的重链可变区和具有SEQ ID NO:335的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0436] aaaa.具有SEQ ID NO:296的多肽序列的重链可变区和具有SEQ ID NO:336的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0437] bbbb.具有SEQ ID NO:269的多肽序列的重链可变区和具有SEQ ID NO:337的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0438] cccc.具有SEQ ID NO:281的多肽序列的重链可变区和具有SEQ ID NO:338的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;或

[0439] dddd.具有SEQ ID NO:286的多肽序列的重链可变区和具有SEQ ID NO:303的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区。

[0440] 根据另一个具体方面,本发明涉及诱导抗体依赖性细胞介导的细胞毒性(ADCC)的分离的抗CD33单克隆抗体或其抗原结合片段。单克隆抗体或其抗原结合片段可例如在体外诱导ADCC。单克隆抗体或其抗原结合片段可以小于约2nM的EC_{50}诱导ADCC。在某些实施方案中,EC_{50}小于约2.0nM、小于约1.9nM、小于约1.8nM、小于约1.7nM、小于约1.6nM、小于约1.5nM、小于约1.4nM、小于约1.3nM、小于约1.2nM,小于约1.1nM、小于约1.0nM、小于约0.9nM、小于约0.8nM、小于约0.7nM、小于约0.6nM、小于约0.5nM、小于约0.4nM、小于约0.3nM、小于约0.2nM或小于约0.1nM。在某些实施方案中,CD33单克隆抗体或其抗原结合片

段包含IgG1低岩藻糖主链。

[0441] 在本文所述的一些实施方案中,CD33特异性抗体的免疫效应子特性可通过本领域技术人员已知的技术经由Fc修饰得到增强或沉默。例如,Fc效应子功能诸如C1q结合、补体依赖性细胞毒性(CDC)、抗体依赖性细胞介导的细胞毒性(ADCC)、抗体依赖性细胞介导的吞噬作用(ADCP)、细胞表面受体(例如B细胞受体;BCR)的下调等,可通过修饰促成这些活性的Fc中的残基来提供和/或控制。

[0442] "抗体依赖性细胞介导的细胞毒性"或"ADCC"是指细胞介导的反应,在这个反应过程中,表达Fc受体(FcR)的非特异性细胞毒性细胞(例如自然杀伤(NK)细胞、嗜中性粒细胞和巨噬细胞)识别靶细胞上的结合抗体并随后致使靶细胞裂解。

[0443] 单克隆抗体诱导ADCC的能力可通过改造其寡糖组分来增强。人IgG1或IgG3在Asn297处被熟知的双分枝G0、G0F、G1、G1F、G2或G2F形式的大多数聚糖N-糖基化。未工程化的CHO细胞所产生的抗体通常具有约至少85%的聚糖岩藻糖含量。从连接到Fc区的双分枝复合物型低聚糖去除核心岩藻糖,可经由改善的Fc.γ.RIIIa结合来增强抗体的ADCC,而不会改变抗原结合或CDC活性。此类mAb可使用所报告的能引起具有双分枝复合物型Fc低聚糖的相对较高去岩藻糖基化抗体的成功表达的不同方法实现,诸如控制培养物渗透压(Konno等人,Cytotechnology,64:249-65,2012),应用变体CHO细胞系Lec13作为宿主细胞系(Shields等人,J Biol Chem,277:26733-26740,2002),应用变体CHO细胞系EB66作为宿主细胞系(Olivier等人,MAbs,2(4),2010;Epub ahead of print;PMID:20562582),应用大鼠杂交瘤细胞系YB2/0作为宿主细胞系(Shinkawa等人,J Biol Chem,第278卷,第3466至第3473页,2003年),引入特异性针对α-1,6-岩藻糖基转移酶(FUT8)基因的小干扰RNA(Mori等人,Biotechnol Bioeng,第88卷,第901页至第908页,2004年),或共表达β-1,4-N-乙酰葡糖胺基转移酶III和高尔基体α-甘露糖苷酶II或有效的α-甘露糖苷酶I抑制剂、几夫碱(Ferrara等人,J Biol Chem,第281卷,第5032页至第5036页,2006年;Ferrara等人,Biotechnol Bioeng,第93卷,第851页至第861页,2006年;Xhou等人,Biotechnol Bioeng,99:652-65,2008)。

[0444] 在本文所述的一些实施方案中,也可通过抗体Fc中的某些置换来增强由CD33抗体引发的ADCC。示例性置换为例如在氨基酸位置256、290、298、312、356、330、333、334、360、378或430(根据EU索引对残基进行编号)处的置换,如美国专利6,737,056中有所描述。

[0445] 根据另一个具体方面,本发明涉及分离的抗CD33单克隆抗体或其抗原结合片段,其能够以小于约5×10^{-8}M的解离常数(KD)结合CD33。在某些实施方案中,解离常数小于约5×10^{-8}M、小于1×10^{-8}M、小于5×10^{-9}M、小于1×10^{-9}M、小于5×10^{-10}M、小于1×10^{-10}M、小于5×10^{-11}M或小于1×10^{-11}M。

[0446] 根据另一个具体方面,本发明涉及分离的抗CD33单克隆抗体或其抗原结合片段,其能够以小于约2nM的EC_{50}结合CD33并诱导CD33的内化。在某些实施方案中,EC_{50}小于约2.0nM、小于约1.9nM、小于约1.8nM、小于约1.7nM、小于约1.6nM、小于约1.5nM、小于约1.4nM、小于约1.3nM、小于约1.2nM,小于约1.1nM、小于约1.0nM、小于约0.9nM、小于约0.8nM、小于约0.7nM、小于约0.6nM、小于约0.5nM、小于约0.4nM、小于约0.3nM、小于约0.2nM以及小于约0.1nM。

[0447] 根据另一个具体方面,本发明涉及分离的抗CD33/抗CD3双特异性抗体或其抗原结

合片段,其能够在表达CD33的细胞中诱导T细胞依赖性细胞毒性。双特异性抗体或其抗原结合片段可例如在体外在表达CD33的细胞中以小于约2nM的EC_{50}值诱导T细胞依赖性细胞毒性。在某些实施方案中,EC_{50}小于约2.0nM、小于约1.9nM、小于约1.8nM、小于约1.7nM、小于约1.6nM、小于约1.5nM、小于约1.4nM、小于约1.3nM、小于约1.2nM,小于约1.1nM、小于约1.0nM、小于约0.9nM、小于约0.8nM、小于约0.7nM、小于约0.6nM、小于约0.5nM、小于约0.4nM、小于约0.3nM、小于约0.2nM以及小于约0.1nM。

[0448] 根据另一个具体方面,本发明涉及分离的抗CD33单克隆抗体和/或分离的抗CD33/抗CD3双特异性抗体或其抗原结合片段,其中抗CD33单克隆抗体或抗CD33/抗CD3双特异性抗体或其抗原结合片段是嵌合的。

[0449] 根据另一个具体方面,本发明涉及分离的抗CD33单克隆抗体和/或分离的抗CD33/抗CD3双特异性抗体或其抗原结合片段,其中抗CD33单克隆抗体或抗CD33/抗CD3双特异性抗体或其抗原结合片段是人或人源化的。

[0450] 在另一个总的方面,本发明涉及编码本发明的单克隆抗体或其抗原结合片段的分离的核酸。在另一个总的方面,本发明涉及编码本发明的双特异性抗体或其抗原结合片段的分离的核酸。本领域的技术人员将理解,可以改变(例如置换、缺失、插入等)蛋白质的编码序列而不改变蛋白质的氨基酸序列。因此,本领域的技术人员将理解,可变更编码本发明的单克隆抗体和/或双特异性抗体的核酸序列而不改变蛋白质的氨基酸序列。

[0451] 在另一个总的方面,本发明涉及包含编码本发明的单克隆抗体或其抗原结合片段的分离的核酸的载体。在另一个总的方面,本发明涉及包含编码本发明的双特异性抗体或其抗原结合片段的分离的核酸的载体。根据本公开,可使用本领域的技术人员已知的任何载体,诸如质粒、粘端质粒、噬菌体载体或病毒载体。在一些实施方案中,载体是重组表达载体,诸如质粒。载体可包括建立表达载体的常规功能的任何元件,例如启动子、核糖体结合元件、终止子、增强子、选择标记和复制起点。启动子可为组成型、诱导型或阻抑型启动子。能够向细胞递送核酸的多种表达载体在本领域中是已知的,并且在本文可用于在细胞中产生抗体或其抗原结合片段。常规克隆技术或人工基因合成可用于根据本发明的实施方案生成重组表达载体。根据本公开,此类技术是本领域技术人员所熟知的。

[0452] 在另一个总的方面,本发明涉及包含编码本发明的单克隆抗体和/或双特异性抗体或其抗原结合片段的分离的核酸的宿主细胞。鉴于本公开,本领域的技术人员已知的任何宿主细胞可用于重组表达本发明的抗体或其抗原结合片段。在一些实施方案中,宿主细胞是大肠杆菌TG1或BL21细胞(用于表达例如scFv或Fab抗体)、CHO-DG44或CHO-K1细胞或HEK293细胞(用于表达例如全长IgG抗体)。根据具体实施方案,通过常规方法诸如化学转染、热休克或电穿孔将重组表达载体转化到宿主细胞中,其中将该重组表达载体稳定整合到宿主细胞基因组中,使得重组核酸有效表达。

[0453] 在另一个总的方面,本发明涉及产生本发明的单克隆抗体或其抗原结合片段的方法,该方法包括在产生本发明的单克隆抗体或其抗原结合片段的条件下培养包含编码单克隆抗体或其抗原结合片段的苷酸的细胞,以及从该细胞或细胞培养物(例如,从上清液)回收该抗体或其抗原结合片段。在另一个总的方面,本发明涉及产生本发明的双特异性抗体或其抗原结合片段的方法,该方法包括在产生本发明的双特异性抗体或其抗原结合片段的条件下培养包含编码双特异性抗体或其抗原结合片段的苷酸的细胞,以及从该细胞或细胞

培养物(例如,从上清液)回收该抗体或其抗原结合片段。可从细胞收获表达的抗体或其抗原结合片段并且根据本领域已知以及如本文所述的常规技术进行纯化。

[0454] 药物组合物

[0455] 在另一个总的方面,本发明涉及药物组合物,该药物组合物包含本发明的分离的单克隆抗体或其抗原结合片段和药学上可接受的载体。在另一个总的方面,本发明涉及药物组合物,该药物组合物包含本发明的双特异性抗体或其抗原结合片段和药学上可接受的载体。如本文所用,术语"药物组合物"意指包含本发明的抗体和药学上可接受的载体的产品。本发明的抗体和包含其的组合物也可用于制造本文提及的治疗应用的药物。

[0456] 如本文所用,术语"载体"是指任何赋形剂、稀释剂、填充剂、盐、缓冲剂、稳定剂、增溶剂、油、类脂、含脂质囊泡、微球体、脂质体包囊、或本领域公知的用于药物制剂中的其他材料。应当理解,载体、赋形剂或稀释剂的特征将取决于具体应用的施用途径。如本文所用,术语"药学上可接受的载体"是指不干扰根据本发明的组合物的效果或根据本发明的组合物的生物活性的非毒性材料。根据本公开,根据具体实施方案,适用于抗体药物组合物的任何药学上可接受的载体均可用于本发明。

[0457] 药物活性成分与药学上可接受的载体的制剂为本领域中已知的,例如Remington: The Science and Practice of Pharmacy(例如第21版(2005)以及任何后续版本)。附加成分的非限制性示例包括:缓冲剂、稀释剂、溶剂、张度调节剂、防腐剂、稳定剂和螯合剂。一种或多种药学上可接受的载体可用于配制本发明的药物组合物。

[0458] 在本发明的一个实施方案中,药物组合物为液体制剂。液体制剂的一个优选示例为水性制剂,即包含水的制剂。液体制剂可包含溶液、悬浮液、乳液、微乳液、凝胶等等。水性制剂通常包含至少50%w/w的水,或至少60%w/w、70%w/w、75%w/w、80%w/w、85%w/w、90%w/w或至少95%w/w的水。

[0459] 在一个实施方案中,可将药物组合物配制为可注射的,其可例如经由注射装置(例如,注射器或输液泵)注射。注射可例如皮下、肌内、腹膜内、玻璃体腔内或静脉内递送。

[0460] 在另一个实施方案中,药物组合物为固体制剂,例如冷冻干燥或喷雾干燥的组合物,其可按原样使用,或在使用前由医师或患者添加溶剂和/或稀释剂。固体剂型可包括片剂,诸如压片和/或包衣片,以及胶囊剂(例如硬明胶胶囊或软明胶胶囊)。药物组合物也可为例如用于重构的小药囊、糖衣丸、粉末、颗粒剂、锭剂或粉末的形式。

[0461] 剂型可以是速释型,在这种情况下它们可包含水可溶或水可分散的载体,或者它们可被延迟释放、缓释或改变释放,在这种情况下它们可包含在胃肠道中或在皮下调节剂型的溶解速率的水不溶的聚合物。

[0462] 在其他实施方案中,药物组合物可在鼻内、颊内或舌下递送。

[0463] 水性制剂中的pH可介于pH 3和pH 10之间。在本发明的一个实施方案中,制剂的pH为约7.0至约9.5。在本发明的另一个实施方案中,制剂的pH为约3.0至约7.0。

[0464] 在本发明的另一个实施方案中,药物组合物包含缓冲剂。缓冲剂的非限制性示例包括:精氨酸、天冬氨酸、二羟乙基甘氨酸、柠檬酸盐、磷酸氢二钠、富马酸、甘氨酸、双甘氨肽、组氨酸、赖氨酸、马来酸、苹果酸、乙酸钠、碳酸钠、磷酸二氢钠、磷酸钠、琥珀酸盐、酒石酸、三嗪和三(羟甲基)氨基甲烷、以及它们的混合物。缓冲剂可单独存在或在聚集体中以约0.01mg/ml至约50mg/ml,例如约0.1mg/ml至约20mg/ml的浓度存在。包含这些特定缓冲剂中

的每一种的药物组合物构成本发明的可供选择的实施方案。

[0465] 在本发明的另一个实施方案中,药物组合物包含防腐剂。缓冲剂的非限制性示例包括:苄索氯铵、苯甲酸、苄醇、溴代硝基丙二醇、4-羟基苯甲酸丁酯、氯丁醇、氯甲酚、氯己啶、氯苯甘油醚、邻甲酚、间甲酚、对甲酚、4-羟基苯甲酸乙酯、咪脲、4-羟基苯甲酸甲酯、苯酚、2-苯氧基乙醇、2-苯基乙醇、4-羟基苯甲酸丙酯、脱氢乙酸钠、硫柳汞以及它们的混合物。防腐剂可单独存在或在聚集体中以约0.01mg/ml至约50mg/ml,例如约0.1mg/ml至约20mg/ml的浓度存在。包含这些特定防腐剂中的每一种的药物组合物构成本发明可供选择的实施方案。

[0466] 在本发明的另一个实施方案中,药物组合物包含等渗剂。该实施方案的非限制性示例包括盐(诸如氯化钠)、氨基酸(诸如甘氨酸、组氨酸、精氨酸、赖氨酸、异亮氨酸、天冬氨酸、色氨酸和苏氨酸)、糖醇(诸如甘油、1,2-丙二醇、丙二醇)、1,3-丙二醇和1,3-丁二醇)、聚乙二醇(例如,PEG400)以及它们的混合物。等渗剂的另一个示例包括糖。糖的非限制性示例可以是单糖、二糖或多糖,或水溶性葡聚糖,包括例如果糖、葡萄糖、甘露糖、山梨糖、木糖、麦芽糖、乳糖、蔗糖、海藻糖、葡聚糖、支链淀粉、糊精、环糊精、α和β-HPCD、可溶性淀粉、羟乙基淀粉和羧甲基纤维素钠。等渗剂的另一个示例是糖醇,其中术语“糖醇”被定义为具有至少一个-OH基团的C(4-8)烃。糖醇的非限制性示例包括甘露糖醇、山梨醇、肌醇、半乳糖醇、己六醇、木糖醇和阿拉伯糖醇。包含本段中列出的每种等渗剂的药物组合物构成本发明的可供选择的实施方案。等渗剂可单独存在或在聚集体中以约0.01mg/ml至约50mg/ml,例如约0.1mg/ml至约20mg/ml的浓度存在。包含这些特定等渗剂中的每一种的药物组合物构成本发明的可供选择的实施方案。

[0467] 在本发明的另一个实施方案中,药物组合物包含螯合剂。螯合剂的非限制性示例包括柠檬酸、天冬氨酸、乙二胺四乙酸(EDTA)的盐、以及它们的混合物。螯合剂可单独存在或在聚集体中以约0.01mg/ml至约50mg/ml,例如约0.1mg/ml至约20mg/ml的浓度存在。包含这些特定螯合剂中的每一种的药物组合物构成本发明的可供选择的实施方案。

[0468] 在本发明的另一个实施方案中,药物组合物包含稳定剂。稳定剂的非限制性示例包括一种或多种聚集抑制剂、一种或多种氧化抑制剂、一种或多种表面活性剂和/或一种或多种蛋白酶抑制剂。

[0469] 在本发明的另一个实施方案中,药物组合物包含稳定剂,其中所述稳定剂为羧基-/羟基纤维素及其衍生物(诸如HPC、HPC-SL、HPC-L和HPMC)、环糊精、2-甲基硫基乙醇、聚乙二醇(诸如PEG 3350)、聚乙烯醇(PVA)、聚乙烯基吡咯烷酮、盐(诸如氯化钠)、含硫的物质,诸如硫代甘油或巯基乙酸。稳定剂可单独存在或在聚集体中以约0.01mg/ml至约50mg/ml,例如约0.1mg/ml至约20mg/ml的浓度存在。包含这些特定稳定剂中的每一种的药物组合物构成本发明的可供选择的实施方案。

[0470] 在本发明的另一个实施方案中,药物组合物包含一种或多种表面活性剂,优选一种表面活性剂、至少一种表面活性剂或两种不同的表面活性剂。术语“表面活性剂”是指任何由水溶性部分(亲水性)和脂溶性和部分(亲脂性)组成的分子或离子。例如,表面活性剂选自:阴离子表面活性剂、阳离子表面活性剂、非离子表面活性剂和/或两性离子表面活性剂。表面活性剂可单独存在或在聚集体中以约0.1mg/ml至约20mg/ml的浓度存在。包含这些特定表面活性剂中的每一种的药物组合物构成本发明的可供选择的实施方案。

[0471] 在本发明的另一个实施方案中,药物组合物包含一种或多种蛋白酶抑制剂,诸如例如EDTA和/或苯甲脒盐酸盐(HCl)。蛋白酶抑制剂可单独存在或在聚集体中以约0.1mg/ml至约20mg/ml的浓度存在。包含这些特定蛋白酶抑制剂中的每一种的药物组合物构成本发明的可供选择的实施方案。

[0472] 在另一个总的方面,本发明涉及产生包含本发明的单克隆抗体或其抗原结合片段的药物组合物的方法,包括将单克隆抗体或其抗原结合片段与药学上可接受的载体组合,以获得药物组合物。在另一个总的方面,本发明涉及产生包含本发明的双特异性抗体或其抗原结合片段的药物组合物的方法,该方法包括将双特异性抗体或其抗原结合片段与药学上可接受的载体组合,以获得药物组合物。

[0473] 使用方法

[0474] 在另一个总的方面,本发明涉及在受试者的癌细胞表面上靶向CD33的方法,该方法包括向受试者施用特异性地结合CD33的分离的单克隆抗体或其抗原结合片段、或抗CD33/抗CD3双特异性抗体或其抗原结合片段、或本发明的药物组合物。

[0475] 本文还设想了一种治疗性抗CD33抗体免疫缀合物,包含选自放射性核素、硼、钆或铀原子,免疫调节剂诸如细胞因子、干细胞生长因子、淋巴毒素诸如肿瘤坏死因子(TNF)、造血因子诸如白介素(IL)、集落刺激因子(CSF)诸如粒细胞集落刺激因子(G-CSF)或粒细胞巨噬细胞集落刺激因子(GM-CSF)、干扰素(IFN)诸如干扰素-α、-β或-γ和干细胞生长因子诸如命名为"S1因子"、造血因子、促红细胞生成素、促血小板生成素、抗体、激素、激素拮抗剂、酶、酶抑制剂、光敏治疗剂,细胞毒性药物诸如抗有丝分裂剂、烷基化剂、抗代谢物、血管生成抑制剂、凋亡剂、生物碱剂、COX-2抑制剂和抗生素,细胞毒素诸如植物毒素、微生物毒素和动物毒素及其合成变体、血管生成抑制剂、不同抗体以及它们的组合的治疗剂。在一个优选的实施方案中,细胞因子选自IL-1、IL-2、IL-3、IL-6、IL-10、IL-12、IL-18、IL-21、干扰素-γ、TNF-α以及它们的组合,放射性核素选自Auger发射器、β-发射器和α-发射器,诸如P-32、P-33、Sc-47、Fe-59、Cu-64、Cu-67、Se-75、As-77、Sr-89、Y-90、Mo-99、Rh-105、Pd-109、Ag-111、I-125、I-131、Pr-142、Pr-143、Pm-149、Sm-153、Tb-161、Ho-166、Er-169、Lu-177、Re-186、Re-188、Re-189、Ir-194、Au-198、Au-199、Pb-211、Pb-212和Bi-213、Co-58、Ga-67、Br-80m、Tc-99m、Rh-103m、Pt-109、In-111、Sb-119、I-125、Ho-161、Os-189m、Ir-192、Dy-152、At-211、Bi-212、Ra-223、Rn-219、Po-215、Bi-211、Ac-225、Fr-221、At-217、Bi-213、Fm-255、B-10、Gd-157、U-235以及它们的组合。优选地,放射性核素的能量介于20keV和10,000keV之间。

[0476] 结合CD33的抗体及其抗原结合片段的功能活性可通过本领域已知及如本文所述的方法进行表征。用于表征结合CD33的抗体及其抗原结合片段的方法包括但不限于亲和力和特异性测定,包括Biacore、ELISA和OctetRed分析;通过FACS检测抗体与癌细胞上的CD33结合的结合测定。根据具体的实施方案,用于表征结合CD33的抗体及其抗原结合片段的方法包括以下所述的那些。

[0477] 在另一个总体方面,本发明涉及治疗对有需要的受试者中的癌症的方法,该方法包括向该受试者施用特异性地结合CD33或本发明的药物组合物的分离的单克隆抗体或其抗原结合片段。癌症可以是例如表达CD33的癌症。癌症可例如选自但不限于肺癌、胃癌、结肠癌、肝细胞癌、肾细胞癌、膀胱尿道上皮癌、转移性黑素瘤、乳腺癌、卵巢癌、宫颈癌、头颈

癌、胰腺癌、胶质瘤、胶质母细胞瘤和其他实体瘤,以及非霍奇金淋巴瘤(NHL)、急性淋巴细胞白血病(ALL)、慢性淋巴细胞白血病(CLL)、慢性粒细胞白血病(CML)、多发性骨髓瘤(MM)、急性髓性白血病(AML)和其他液体肿瘤。癌症可以是例如血液学癌症。血液学癌症可以是例如白血病、淋巴瘤和骨髓瘤。。在某些实施方案中,所述血液学癌症可以是急性髓性白血病(AML)、骨髓增生异常综合征(MDS,低风险或高风险)、急性淋巴细胞白血病(ALL,包括所有亚型)、弥漫性大B细胞淋巴瘤(DLBCL)、慢性髓性白血病(CML)或母细胞性浆细胞样树突状细胞瘤(DPDCN)。

[0478] 根据本发明的实施方案,药物组合物包含治疗有效量的抗CD33抗体或其抗原结合片段。如本文所用,术语“治疗有效量”是指在受治疗者中引起期望的生物学或药物学响应的活性成分或组分的量。治疗有效量可相对于指定目的根据经验并以常规方式进行确定。

[0479] 如本文所用,提及到抗CD33抗体或其抗原结合片段,治疗有效量意指在对其有需要的受试者中调节免疫应答的抗CD33抗体或其抗原结合片段的量。

[0480] 根据具体实施方案,治疗有效量是指足以实现以下作用中的一者、两者、三者、四者、或更多者的治疗量:(i)减小或改善所治疗疾病、障碍或病症或与之相关联的症状的严重性;(ii)减少所治疗疾病、障碍或病症或与之相关联的症状的持续时间;(iii)预防所治疗疾病、障碍或病症或与之相关联的症状发展;(iv)引起所治疗疾病、障碍或病症或与之相关联的症状消退;(v)预防所治疗疾病、障碍或病症或与之相关联的症状发展或发作;(vi)预防所治疗疾病、障碍或病症或与之相关联的症状复发;(vii)减少患有所治疗疾病、障碍或病症或与之相关联的症状的受试者的住院治疗;(viii)减少患有所治疗疾病、障碍或病症或与之相关联的症状的受试者的住院时间;(ix)提高患有所治疗疾病、障碍或病症或与之相关联的症状的受试者的存活;(xi)抑制或减少受试者中所治疗疾病、障碍或病症或与之相关联的症状;和/或(xii)增强或改善另一种疗法的预防或治疗效果。

[0481] 治疗有效量或剂量可根据各种因素,诸如欲被治疗的疾病、障碍或病症、施用方式、目标部位、受试者的生理状态(包括例如年龄、体重、健康)而变化,不论受试者是人或动物、施用的其他药物,以及是否为预防性或治疗性治疗。最佳地滴定治疗剂量以优化安全性和功效。

[0482] 根据特定实施方案,本文所述的组合物被配制成适于施用于受治疗者的预期途径。例如,本文所述组合物可被配制成适于静脉内、皮下或肌内注射施用。

[0483] 如本文所用,术语“处理”和“治疗”(“treat”、“treating”和“treatment”)均旨在是指与癌症有关的至少一种可测量物理参数的改善或逆转,其不一定是受治疗者中可识别的,但能够在受治疗者中识别。术语“处理”和“治疗”也可指导致消退,预防发展,或至少延缓疾病、障碍或病症的发展。在特定实施方案中,“处理”和“治疗”是指减轻、预防发展或发作,或缩短与疾病、障碍或病症(诸如肿瘤或更优选癌症)相关的一种或多种症状的持续时间。在特定实施方案中,“处理”和“治疗”是指预防疾病、障碍或病症的复发。在特定实施方案中,“处理”和“治疗”是指患有疾病、障碍或病症的受试者的存活提高。在特定实施方案中,“处理”和“治疗”是指受试者中疾病、障碍或病症的消除。

[0484] 根据具体实施方案,提供了用于治疗癌症的组合物。对于癌症治疗,组合物可与另一种治疗联合使用,包括但不限于化学疗法、抗CD20mAb、抗TIM-3mAb、抗-CTLA-4抗体、抗PD-L1抗体、抗PD-1抗体、PD-1/PD-L1疗法、其他免疫肿瘤学药物、抗血管生成剂、放射疗法、

抗体-药物缀合物(ADC)、靶向疗法或其他抗癌药物。

[0485] 如本文所用,在将两种或更多种疗法施用于受试者的上下文中,术语“联合”是指使用多于一种疗法。术语“联合”的使用并不限制疗法施用于受试者的次序。例如,第一疗法(例如,本文所述的组合物)可在第二疗法施用于受试者之前(例如5分钟、15分钟、30分钟、45分钟、1小时、2小时、4小时、6小时、12小时、16小时、24小时、48小时、72小时、96小时、1周、2周、3周、4周、5周、6周、8周、或12周以前),与此同时,或之后(例如5分钟、15分钟、30分钟、45分钟、1小时、2小时、4小时、6小时、12小时、16小时、24小时、48小时、72小时、96小时、1周、2周、3周、4周、5周、6周、8周、或12周以后)施用。

[0486] 实施方案

[0487] 本发明提供了以下非限制性实施方案。

[0488] 实施方案1是一种分离的单克隆抗体或其抗原结合片段,该分离的单克隆抗体或其抗原结合片段特异性地结合CD33的C2结构域。

[0489] 实施方案2是根据实施方案1所述的分离的单克隆抗体或其抗原结合片段,其中所述分离的单克隆抗体或其抗原结合片段包含具有以下多肽序列的重链互补决定区1(HCDR1)、HCDR2、HCDR3以及轻链互补决定区1(LCDR1)、LCDR2和LCDR3:

[0490] a.分别为SEQ ID NO:447、448、449、567、568和569;

[0491] b.分别为SEQ ID NO:444、445、446、564、565和566;

[0492] c.分别为SEQ ID NO:354、355、356、477、478和479;

[0493] d.分别为SEQ ID NO:378、379、380、501、502和503;

[0494] e.分别为SEQ ID NO:411、412、413、531、532和533;

[0495] f.分别为SEQ ID NO:348、349、350、471、472和473;

[0496] g.分别为SEQ ID NO:360、361、362、483、484和485;

[0497] h.分别为SEQ ID NO:363、364、365、486、487和488;

[0498] i.分别为SEQ ID NO:366、367、368、489、490和491;

[0499] j.分别为SEQ ID NO:369、370、371、492、493和494;

[0500] k.分别为SEQ ID NO:387、388、389、492、493和494;

[0501] l.分别为SEQ ID NO:402、403、404、522、523和524;

[0502] m.分别为SEQ ID NO:408、409、410、528、529和530;

[0503] n.分别为SEQ ID NO:423、424、425、543、544和545;或者

[0504] o.分别为SEQ ID NO:426、427、428、546、547和548;

[0505] 其中所述抗体或其抗原结合片段特异性地结合CD33,优选人CD33。

[0506] 实施方案3是根据实施方案1或2所述的分离的单克隆抗体或其抗原结合片段,所述分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:292、291、261、269、280、259、263、264、265、266、272、277、279、284或285有至少95%同一性的多肽序列的重链可变区或者与SEQ ID NO:332、331、302、310、320、300、304、305、306、307、317、319、324或325有至少95%同一性的多肽序列的轻链可变区。

[0507] 实施方案4是根据实施方案1至3中任一项所述的分离的单克隆抗体或其抗原结合片段,所述分离的单克隆抗体或其抗原结合片段包含:

[0508] a.具有SEQ ID NO:292的多肽序列的重链可变区和具有SEQ ID NO:332的多肽序

列的轻链可变区；

[0509] b.具有SEQ ID NO:291的多肽序列的重链可变区和具有SEQ ID NO:331的多肽序列的轻链可变区；

[0510] c.具有SEQ ID NO:261的多肽序列的重链可变区和具有SEQ ID NO:302的多肽序列的轻链可变区；

[0511] d.具有SEQ ID NO:269的多肽序列的重链可变区和具有SEQ ID NO:310的多肽序列的轻链可变区；

[0512] e.具有SEQ ID NO:280的多肽序列的重链可变区和具有SEQ ID NO:322的多肽序列的轻链可变区；

[0513] f.具有SEQ ID NO:259的多肽序列的重链可变区和具有SEQ ID NO:300的多肽序列的轻链可变区；

[0514] g.具有SEQ ID NO:263的多肽序列的重链可变区和具有SEQ ID NO:304的多肽序列的轻链可变区；

[0515] h.具有SEQ ID NO:264的多肽序列的重链可变区和具有SEQ ID NO:305的多肽序列的轻链可变区；

[0516] i.具有SEQ ID NO:265的多肽序列的重链可变区和具有SEQ ID NO:306的多肽序列的轻链可变区；

[0517] j.具有SEQ ID NO:266的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序列的轻链可变区；

[0518] k.具有SEQ ID NO:272的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序列的轻链可变区；

[0519] l.具有SEQ ID NO:277的多肽序列的重链可变区和具有SEQ ID NO:317的多肽序列的轻链可变区；

[0520] m.具有SEQ ID NO:279的多肽序列的重链可变区和具有SEQ ID NO:319的多肽序列的轻链可变区；

[0521] n.具有SEQ ID NO:284的多肽序列的重链可变区和具有SEQ ID NO:324的多肽序列的轻链可变区;或

[0522] o.具有SEQ ID NO:285的多肽序列的重链可变区和具有SEQ ID NO:325的多肽序列的轻链可变区。

[0523] 实施方案5是一种分离的单克隆抗体或其抗原结合片段,所述分离的单克隆抗体或其抗原结合片段包含具有以下多肽序列的重链互补决定区1(HCDR1)、HCDR2、HCDR3以及轻链互补决定区1(LCDR1)、LCDR2和LCDR3：

[0524] a.分别为SEQ ID NO:357、358、359、480、481和482；

[0525] b.分别为SEQ ID NO:372、373、374、495、496和497；

[0526] c.分别为SEQ ID NO:375、376、377、498、499和500；

[0527] d.分别为SEQ ID NO:381、382、383、504、505和506；

[0528] e.分别为SEQ ID NO:384、385、386、507、508和509；

[0529] f.分别为SEQ ID NO:390、391、392、510、511和512；

[0530] g.分别为SEQ ID NO:393、394、395、513、514和515；

[0531] h.分别为SEQ ID NO:396、397、398、516、517和518;

[0532] i.分别为SEQ ID NO:399、400、401、519、520和521;

[0533] j.分别为SEQ ID NO:405、406、407、525、526和527;

[0534] k.分别为SEQ ID NO:414、415、416、534、535和536;

[0535] l.分别为SEQ ID NO:417、418、419、537、538和539;

[0536] m.分别为SEQ ID NO:420、421、422、540、541和542;

[0537] n.分别为SEQ ID NO:429、430、431、549、550和551;

[0538] o.分别为SEQ ID NO:432、433、434、552、553和554;

[0539] p.分别为SEQ ID NO:435、436、437、555、556和557;

[0540] q.分别为SEQ ID NO:438、439、440、558、559和560;

[0541] r.分别为SEQ ID NO:441、442、443、561、562和563;

[0542] s.分别为SEQ ID NO:450、451、452、570、571和572;

[0543] t.分别为SEQ ID NO:453、454、455、573、574和575;

[0544] u.分别为SEQ ID NO:456、457、458、576、577和578;

[0545] v.分别为SEQ ID NO:459、460、461、579、580和581;

[0546] w.分别为SEQ ID NO:378、379、380、582、583和584;

[0547] x.分别为SEQ ID NO:414、415、416、585、586和587;或者

[0548] y.分别为SEQ ID NO:429、430、431、480、481和482;

[0549] 其中所述抗体或其抗原结合片段特异性地结合CD33,优选人CD33。

[0550] 实施方案6是根据实施方案5所述的分离的单克隆抗体或其抗原结合片段,所述分离的单克隆抗体或其抗原结合片段包含具有与SEQ ID NO:260、262、267、268、270、271、273、274、275、276、278、281、282、283、286、287、288、289、290、293、294、295或296中的一者有至少95%同一性的多肽序列的重链可变区或者与SEQ ID NO:301、303、308、309、311、312、313、314、315、316、318、321、322、323、326、327、328、329、330、333、334、335、336、337或338中的一者有至少95%同一性的多肽序列的轻链可变区。

[0551] 实施方案7是根据实施方案5或6所述的分离的单克隆抗体或其抗原结合片段,所述分离的单克隆抗体或其抗原结合片段包含:

[0552] a.具有SEQ ID NO:260的多肽序列的重链可变区和具有SEQ ID NO:301的多肽序列的轻链可变区;

[0553] b.具有SEQ ID NO:262的多肽序列的重链可变区和具有SEQ ID NO:303的多肽序列的轻链可变区;

[0554] c.具有SEQ ID NO:267的多肽序列的重链可变区和具有SEQ ID NO:308的多肽序列的轻链可变区;

[0555] d.具有SEQ ID NO:268的多肽序列的重链可变区和具有SEQ ID NO:309的多肽序列的轻链可变区;

[0556] e.具有SEQ ID NO:270的多肽序列的重链可变区和具有SEQ ID NO:311的多肽序列的轻链可变区;

[0557] f.具有SEQ ID NO:271的多肽序列的重链可变区和具有SEQ ID NO:312的多肽序列的轻链可变区;

[0558] g.具有SEQ ID NO:273的多肽序列的重链可变区和具有SEQ ID NO:313的多肽序列的轻链可变区;

[0559] h.具有SEQ ID NO:274的多肽序列的重链可变区和具有SEQ ID NO:314的多肽序列的轻链可变区;

[0560] i.具有SEQ ID NO:275的多肽序列的重链可变区和具有SEQ ID NO:315的多肽序列的轻链可变区;

[0561] j.具有SEQ ID NO:276的多肽序列的重链可变区和具有SEQ ID NO:316的多肽序列的轻链可变区;

[0562] k.具有SEQ ID NO:278的多肽序列的重链可变区和具有SEQ ID NO:318的多肽序列的轻链可变区;

[0563] l.具有SEQ ID NO:281的多肽序列的重链可变区和具有SEQ ID NO:321的多肽序列的轻链可变区;

[0564] m.具有SEQ ID NO:282的多肽序列的重链可变区和具有SEQ ID NO:322的多肽序列的轻链可变区;

[0565] n.具有SEQ ID NO:283的多肽序列的重链可变区和具有SEQ ID NO:323的多肽序列的轻链可变区;

[0566] o.具有SEQ ID NO:286的多肽序列的重链可变区和具有SEQ ID NO:326的多肽序列的轻链可变区;

[0567] p.具有SEQ ID NO:287的多肽序列的重链可变区和具有SEQ ID NO:327的多肽序列的轻链可变区;

[0568] q.具有SEQ ID NO:288的多肽序列的重链可变区和具有SEQ ID NO:328的多肽序列的轻链可变区;

[0569] r.具有SEQ ID NO:289的多肽序列的重链可变区和具有SEQ ID NO:329的多肽序列的轻链可变区;

[0570] s.具有SEQ ID NO:290的多肽序列的重链可变区和具有SEQ ID NO:330的多肽序列的轻链可变区;

[0571] t.具有SEQ ID NO:293的多肽序列的重链可变区和具有SEQ ID NO:333的多肽序列的轻链可变区;

[0572] u.具有SEQ ID NO:294的多肽序列的重链可变区和具有SEQ ID NO:334的多肽序列的轻链可变区;

[0573] v.具有SEQ ID NO:295的多肽序列的重链可变区和具有SEQ ID NO:335的多肽序列的轻链可变区;

[0574] w.具有SEQ ID NO:296的多肽序列的重链可变区和具有SEQ ID NO:336的多肽序列的轻链可变区;

[0575] x.具有SEQ ID NO:269的多肽序列的重链可变区和具有SEQ ID NO:337的多肽序列的轻链可变区;

[0576] y.具有SEQ ID NO:281的多肽序列的重链可变区和具有SEQ ID NO:338的多肽序列的轻链可变区;或

[0577] z.具有SEQ ID NO:286的多肽序列的重链可变区和具有SEQ ID NO:303的多肽序

列的轻链可变区。

[0578] 实施方案8是根据实施方案1至4中任一项所述的分离的单克隆抗体或其抗原结合片段,其中所述单克隆抗体或其抗原结合片段在体外以小于约2nM的EC_{50}诱导抗体依赖性细胞介导的细胞毒性(ADCC)。

[0579] 实施方案9是根据实施方案8所述的分离的单克隆抗体或其抗原结合片段,其中所述单克隆抗体或其抗原结合片段包含IgG1低岩藻糖主链。

[0580] 实施方案10是根据实施方案1至7中任一项所述的分离的单克隆抗体或其抗原结合片段,其中所述单克隆抗体或其抗原结合片段以小于约5×10^{-9}M的解离常数(KD)结合CD33。

[0581] 实施方案11是根据实施方案1至7中任一项所述的分离的单克隆抗体或其抗原结合片段,其中所述单克隆抗体或其抗原结合片段结合CD33并且以小于约2nM的EC_{50}诱导内化。

[0582] 实施方案12是根据实施方案1至11中任一项所述的分离的单克隆抗体或其抗原结合片段,其中所述单克隆抗体或其抗原结合片段抑制CD33的活性。

[0583] 实施方案13是根据实施方案1至12中任一项所述的分离的单克隆抗体或其抗原结合片段,其中所述抗体或其抗原结合片段是嵌合的。

[0584] 实施方案14是根据实施方案1至13中任一项所述的分离的单克隆抗体或其抗原结合片段,其中所述抗体或其抗原结合片段是人或人源化的。

[0585] 实施方案15是根据实施方案1至13中任一项所述的分离的单克隆抗体或其抗原结合片段,其中将所述抗体或其抗原结合片段缀合至治疗剂。

[0586] 实施方案16是一种分离的核酸,编码根据实施方案1至14中任一项所述的单克隆抗体或其抗原结合片段。

[0587] 实施方案17是一种载体,包含根据实施方案16所述的分离的核酸。

[0588] 实施方案18是一种宿主细胞,包含根据实施方案17所述的载体。

[0589] 实施方案19是一种药物组合物,包含根据实施方案1至14中任一项所述的分离的单克隆抗体或其抗原结合片段以及药学上可接受的载体。

[0590] 实施方案20是一种在对其有需要的受试者中治疗癌症的方法,包括向所述受试者施用根据实施方案19所述的药物组合物。

[0591] 实施方案21是根据实施方案20所述的方法,其中所述癌症是血液学癌症。

[0592] 实施方案22是根据实施方案21所述的方法,其中所述血液学癌症选自白血病、淋巴瘤或多发性骨髓瘤。

[0593] 实施方案23是根据实施方案22所述的方法,其中所述血液学癌症是急性髓性白血病(AML)、骨髓增生异常综合征(MDS)、急性淋巴细胞白血病(ALL)、弥漫性大B细胞淋巴瘤(DLBCL)、慢性髓性白血病(CML)或母细胞性浆细胞样树突状细胞瘤(DPDCN)。

[0594] 实施方案24是一种产生根据实施方案1至14中任一项所述的单克隆抗体或其抗原结合片段的方法,包括在产生所述单克隆抗体或抗原结合片段的条件下培养包含编码所述单克隆抗体或抗原结合片段的核酸的细胞,以及从所述细胞或培养物回收所述抗体或抗原结合片段。

[0595] 实施方案25是一种产生包含根据实施方案1至14中任一项所述的单克隆抗体或抗

原结合片段的药物组合物的方法,包括将所述单克隆抗体或其抗原结合片段与药学上可接受的载体组合以获得所述药物组合物。

[0596] 实施方案26是一种抗CD33/抗CD3双特异性抗体,包含抗CD33抗体或其抗原结合片段以及抗CD3抗体或其抗原结合片段,

[0597] 其中所述抗CD33抗体或其抗原结合片段包含具有以下多肽序列的重链互补决定区1(HCDR1)、HCDR2、HCDR3以及轻链互补决定区1(LCDR1)、LCDR2和LCDR3:

[0598] a.分别为SEQ ID NO:447、448、449、567、568和569;

[0599] b.分别为SEQ ID NO:444、445、446、564、565和566;

[0600] c.分别为SEQ ID NO:354、355、356、477、478和479;

[0601] d.分别为SEQ ID NO:378、379、380、501、502和503;

[0602] e.分别为SEQ ID NO:411、412、413、531、532和533;

[0603] f.分别为SEQ ID NO:348、349、350、471、472和473;

[0604] g.分别为SEQ ID NO:360、361、362、483、484和485;

[0605] h.分别为SEQ ID NO:363、364、365、486、487和488;

[0606] i.分别为SEQ ID NO:366、367、368、489、490和491;

[0607] j.分别为SEQ ID NO:369、370、371、492、493和494;

[0608] k.分别为SEQ ID NO:387、388、389、492、493和494;

[0609] l.分别为SEQ ID NO:402、403、404、522、523和524;

[0610] m.分别为SEQ ID NO:408、409、410、528、529和530;

[0611] n.分别为SEQ ID NO:423、424、425、543、544和545;或者

[0612] o.分别为SEQ ID NO:426、427、428、546、547和548;

[0613] 并且所述抗CD3抗体或其抗原结合片段包含具有以下多肽序列的重链互补决定区1(HCDR1)、HCDR2、HCDR3以及轻链互补决定区1(LCDR1)、LCDR2和LCDR3:

[0614] 1)分别为SEQ ID NO:342、343、344、465、466和467;或者

[0615] 2)分别为SEQ ID NO:345、346、347、468、469和470。

[0616] 实施方案27是根据实施方案25所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段,其中所述抗CD33抗体或其抗原结合片段包含具有与SEQ ID NO:292、291、261、269、280、259、263、264、265、266、272、277、279、284或285有至少95%同一性的多肽序列的重链可变区或者与SEQ ID NO:332、331、302、310、320、300、304、305、306、307、317、319、324或325有至少95%同一性的多肽序列的轻链可变区;并且所述抗CD3抗体或其抗原结合片段包含具有与SEQ ID NO:257或258有至少95%同一性的多肽序列的重链可变区或者具有与SEQ ID NO:298或299有至少95%同一性的多肽序列的轻链可变区。

[0617] 实施方案28是根据实施方案25或26所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段,包含:

[0618] a.具有SEQ ID NO:292的多肽序列的重链可变区和具有SEQ ID NO:332的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0619] b.具有SEQ ID NO:291的多肽序列的重链可变区和具有SEQ ID NO:331的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298

的多肽序列的轻链可变区；

[0620] c.具有SEQ ID NO:261的多肽序列的重链可变区和具有SEQ ID NO:302的多肽序列的轻链可变区；以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区；

[0621] d.具有SEQ ID NO:269的多肽序列的重链可变区和具有SEQ ID NO:310的多肽序列的轻链可变区；以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区；

[0622] e.具有SEQ ID NO:280的多肽序列的重链可变区和具有SEQ ID NO:322的多肽序列的轻链可变区；以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区；

[0623] f.具有SEQ ID NO:259的多肽序列的重链可变区和具有SEQ ID NO:300的多肽序列的轻链可变区；以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区；

[0624] g.具有SEQ ID NO:263的多肽序列的重链可变区和具有SEQ ID NO:304的多肽序列的轻链可变区；以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区；

[0625] h.具有SEQ ID NO:264的多肽序列的重链可变区和具有SEQ ID NO:305的多肽序列的轻链可变区；以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区；

[0626] i.具有SEQ ID NO:265的多肽序列的重链可变区和具有SEQ ID NO:306的多肽序列的轻链可变区；以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区；

[0627] j.具有SEQ ID NO:266的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序列的轻链可变区；以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区；

[0628] k.具有SEQ ID NO:272的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序列的轻链可变区；以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区；

[0629] l.具有SEQ ID NO:277的多肽序列的重链可变区和具有SEQ ID NO:317的多肽序列的轻链可变区；以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区；

[0630] m.具有SEQ ID NO:279的多肽序列的重链可变区和具有SEQ ID NO:319的多肽序列的轻链可变区；以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区；

[0631] n.具有SEQ ID NO:284的多肽序列的重链可变区和具有SEQ ID NO:324的多肽序列的轻链可变区；以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区；

[0632] o.具有SEQ ID NO:285的多肽序列的重链可变区和具有SEQ ID NO:325的多肽序列的轻链可变区；以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298

的多肽序列的轻链可变区；

[0633] p.具有SEQ ID NO:292的多肽序列的重链可变区和具有SEQ ID NO:332的多肽序列的轻链可变区；以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区；

[0634] q.具有SEQ ID NO:291的多肽序列的重链可变区和具有SEQ ID NO:331的多肽序列的轻链可变区；以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区；

[0635] r.具有SEQ ID NO:261的多肽序列的重链可变区和具有SEQ ID NO:302的多肽序列的轻链可变区；以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区；

[0636] s.具有SEQ ID NO:269的多肽序列的重链可变区和具有SEQ ID NO:310的多肽序列的轻链可变区；以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区；

[0637] t.具有SEQ ID NO:280的多肽序列的重链可变区和具有SEQ ID NO:322的多肽序列的轻链可变区；以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区；

[0638] u.具有SEQ ID NO:259的多肽序列的重链可变区和具有SEQ ID NO:300的多肽序列的轻链可变区；以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区；

[0639] v.具有SEQ ID NO:263的多肽序列的重链可变区和具有SEQ ID NO:304的多肽序列的轻链可变区；以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区；

[0640] w.具有SEQ ID NO:264的多肽序列的重链可变区和具有SEQ ID NO:305的多肽序列的轻链可变区；以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区；

[0641] x.具有SEQ ID NO:265的多肽序列的重链可变区和具有SEQ ID NO:306的多肽序列的轻链可变区；以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区；

[0642] y.具有SEQ ID NO:266的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序列的轻链可变区；以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区；

[0643] z.具有SEQ ID NO:272的多肽序列的重链可变区和具有SEQ ID NO:307的多肽序列的轻链可变区；以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区；

[0644] aa.具有SEQ ID NO:277的多肽序列的重链可变区和具有SEQ ID NO:317的多肽序列的轻链可变区；以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区；

[0645] bb.具有SEQ ID NO:279的多肽序列的重链可变区和具有SEQ ID NO:319的多肽序列的轻链可变区；以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299

的多肽序列的轻链可变区;

[0646] cc.具有SEQ ID NO:284的多肽序列的重链可变区和具有SEQ ID NO:324的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;或

[0647] dd.具有SEQ ID NO:285的多肽序列的重链可变区和具有SEQ ID NO:325的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区。

[0648] 实施方案29是根据实施方案26至28中任一项所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段,其中所述抗CD33抗体或其抗原结合片段特异性地结合所述CD33的C2结构域。

[0649] 实施方案30是一种抗CD33/抗CD3双特异性抗体,包含抗CD33抗体或其抗原结合片段以及抗CD3抗体或其抗原结合片段,

[0650] 其中所述抗CD33抗体或其抗原结合片段包含具有以下多肽序列的重链互补决定区1(HCDR1)、HCDR2、HCDR3以及轻链互补决定区1(LCDR1)、LCDR2和LCDR3:

[0651] a.分别为SEQ ID NO:357、358、359、480、481和482;

[0652] b.分别为SEQ ID NO:372、373、374、495、496和497;

[0653] c.分别为SEQ ID NO:375、376、377、498、499和500;

[0654] d.分别为SEQ ID NO:381、382、383、504、505和506;

[0655] e.分别为SEQ ID NO:384、385、386、507、508和509;

[0656] f.分别为SEQ ID NO:390、391、392、510、511和512;

[0657] g.分别为SEQ ID NO:393、394、395、513、514和515;

[0658] h.分别为SEQ ID NO:396、397、398、516、517和518;

[0659] i.分别为SEQ ID NO:399、400、401、519、520和521;

[0660] j.分别为SEQ ID NO:405、406、407、525、526和527;

[0661] k.分别为SEQ ID NO:414、415、416、534、535和536;

[0662] l.分别为SEQ ID NO:417、418、419、537、538和539;

[0663] m.分别为SEQ ID NO:420、421、422、540、541和542;

[0664] n.分别为SEQ ID NO:429、430、431、549、550和551;

[0665] o.分别为SEQ ID NO:432、433、434、552、553和554;

[0666] p.分别为SEQ ID NO:435、436、437、555、556和557;

[0667] q.分别为SEQ ID NO:438、439、440、558、559和560;

[0668] r.分别为SEQ ID NO:441、442、443、561、562和563;

[0669] s.分别为SEQ ID NO:450、451、452、570、571和572;

[0670] t.分别为SEQ ID NO:453、454、455、573、574和575;

[0671] u.分别为SEQ ID NO:456、457、458、576、577和578;

[0672] v.分别为SEQ ID NO:459、460、461、579、580和581;

[0673] w.分别为SEQ ID NO:378、379、380、582、583和584;

[0674] x.分别为SEQ ID NO:414、415、416、585、586和587;或者

[0675] y.分别为SEQ ID NO:429、430、431、480、481和482;

[0676] 并且所述抗CD3抗体或其抗原结合片段包含具有以下多肽序列的重链互补决定区1(HCDR1)、HCDR2、HCDR3以及轻链互补决定区1(LCDR1)、LCDR2和LCDR3：

[0677] 1)分别为SEQ ID NO:342、343、344、465、466和467;或者

[0678] 2)分别为SEQ ID NO:345、346、347、468、469和470。

[0679] 实施方案31是根据实施方案29所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段,其中所述抗CD33抗体或其抗原结合片段包含具有与SEQ ID NO:260、262、267、268、270、271、273、274、275、276、278、281、282、283、286、287、288、289、290、293、294、295或296中的一者有至少95％同一性的多肽序列的重链可变区或者与SEQ ID NO:301、303、308、309、311、312、313、314、315、316、318、321、322、323、326、327、328、329、330、333、334、335、336、337或338中的一者有至少95％同一性的多肽序列的轻链可变区;并且所述抗CD3抗体或其抗原结合片段包含具有与SEQ ID NO:257或258有至少95％同一性的多肽序列的重链可变区或者具有与SEQ ID NO:298或299有至少95％同一性的多肽序列的轻链可变区。

[0680] 实施方案32是根据实施方案29或30所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段,包含：

[0681] a.具有SEQ ID NO:260的多肽序列的重链可变区和具有SEQ ID NO:301的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0682] b.具有SEQ ID NO:262的多肽序列的重链可变区和具有SEQ ID NO:303的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0683] c.具有SEQ ID NO:267的多肽序列的重链可变区和具有SEQ ID NO:308的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0684] d.具有SEQ ID NO:268的多肽序列的重链可变区和具有SEQ ID NO:309的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0685] e.具有SEQ ID NO:270的多肽序列的重链可变区和具有SEQ ID NO:311的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0686] f.具有SEQ ID NO:271的多肽序列的重链可变区和具有SEQ ID NO:312的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0687] g.具有SEQ ID NO:273的多肽序列的重链可变区和具有SEQ ID NO:313的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0688] h.具有SEQ ID NO:274的多肽序列的重链可变区和具有SEQ ID NO:314的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0689] i.具有SEQ ID NO:275的多肽序列的重链可变区和具有SEQ ID NO:315的多肽序

列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0690] j.具有SEQ ID NO:276的多肽序列的重链可变区和具有SEQ ID NO:316的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0691] k.具有SEQ ID NO:278的多肽序列的重链可变区和具有SEQ ID NO:318的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0692] l.具有SEQ ID NO:281的多肽序列的重链可变区和具有SEQ ID NO:321的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0693] m.具有SEQ ID NO:282的多肽序列的重链可变区和具有SEQ ID NO:322的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0694] n.具有SEQ ID NO:283的多肽序列的重链可变区和具有SEQ ID NO:323的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0695] o.具有SEQ ID NO:286的多肽序列的重链可变区和具有SEQ ID NO:326的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0696] p.具有SEQ ID NO:287的多肽序列的重链可变区和具有SEQ ID NO:327的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0697] q.具有SEQ ID NO:288的多肽序列的重链可变区和具有SEQ ID NO:328的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0698] r.具有SEQ ID NO:289的多肽序列的重链可变区和具有SEQ ID NO:329的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0699] s.具有SEQ ID NO:290的多肽序列的重链可变区和具有SEQ ID NO:330的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0700] t.具有SEQ ID NO:293的多肽序列的重链可变区和具有SEQ ID NO:333的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0701] u.具有SEQ ID NO:294的多肽序列的重链可变区和具有SEQ ID NO:334的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0702] v.具有SEQ ID NO:295的多肽序列的重链可变区和具有SEQ ID NO:335的多肽序

列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0703] w.具有SEQ ID NO:296的多肽序列的重链可变区和具有SEQ ID NO:336的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0704] x.具有SEQ ID NO:269的多肽序列的重链可变区和具有SEQ ID NO:337的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0705] y.具有SEQ ID NO:281的多肽序列的重链可变区和具有SEQ ID NO:338的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0706] z.具有SEQ ID NO:286的多肽序列的重链可变区和具有SEQ ID NO:303的多肽序列的轻链可变区;以及具有SEQ ID NO:257的多肽序列的重链可变区和具有SEQ ID NO:298的多肽序列的轻链可变区;

[0707] aa.具有SEQ ID NO:260的多肽序列的重链可变区和具有SEQ ID NO:301的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0708] bb.具有SEQ ID NO:262的多肽序列的重链可变区和具有SEQ ID NO:303的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0709] cc.具有SEQ ID NO:267的多肽序列的重链可变区和具有SEQ ID NO:308的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0710] dd.具有SEQ ID NO:268的多肽序列的重链可变区和具有SEQ ID NO:309的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0711] ee.具有SEQ ID NO:270的多肽序列的重链可变区和具有SEQ ID NO:311的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0712] ff.具有SEQ ID NO:271的多肽序列的重链可变区和具有SEQ ID NO:312的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0713] gg.具有SEQ ID NO:273的多肽序列的重链可变区和具有SEQ ID NO:313的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0714] hh.具有SEQ ID NO:274的多肽序列的重链可变区和具有SEQ ID NO:314的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0715] ii.具有SEQ ID NO:275的多肽序列的重链可变区和具有SEQ ID NO:315的多肽序

列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0716] jj.具有SEQ ID NO:276的多肽序列的重链可变区和具有SEQ ID NO:316的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0717] kk.具有SEQ ID NO:278的多肽序列的重链可变区和具有SEQ ID NO:318的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0718] ll.具有SEQ ID NO:281的多肽序列的重链可变区和具有SEQ ID NO:321的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0719] mm.具有SEQ ID NO:282的多肽序列的重链可变区和具有SEQ ID NO:322的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0720] nn.具有SEQ ID NO:283的多肽序列的重链可变区和具有SEQ ID NO:323的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0721] oo.具有SEQ ID NO:286的多肽序列的重链可变区和具有SEQ ID NO:326的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0722] pp.具有SEQ ID NO:287的多肽序列的重链可变区和具有SEQ ID NO:327的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0723] qq.具有SEQ ID NO:288的多肽序列的重链可变区和具有SEQ ID NO:328的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0724] rr.具有SEQ ID NO:289的多肽序列的重链可变区和具有SEQ ID NO:329的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0725] ss.具有SEQ ID NO:290的多肽序列的重链可变区和具有SEQ ID NO:330的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0726] tt.具有SEQ ID NO:293的多肽序列的重链可变区和具有SEQ ID NO:333的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0727] uu.具有SEQ ID NO:294的多肽序列的重链可变区和具有SEQ ID NO:334的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0728] vv.具有SEQ ID NO:295的多肽序列的重链可变区和具有SEQ ID NO:335的多肽序

列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0729] ww.具有SEQ ID NO:296的多肽序列的重链可变区和具有SEQ ID NO:336的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0730] xx.具有SEQ ID NO:269的多肽序列的重链可变区和具有SEQ ID NO:337的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;

[0731] yy.具有SEQ ID NO:281的多肽序列的重链可变区和具有SEQ ID NO:338的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区;或

[0732] zz.具有SEQ ID NO:286的多肽序列的重链可变区和具有SEQ ID NO:303的多肽序列的轻链可变区;以及具有SEQ ID NO:258的多肽序列的重链可变区和具有SEQ ID NO:299的多肽序列的轻链可变区。

[0733] 实施方案33是根据实施方案26至32中任一项所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段,其中所述抗CD33/抗CD3双特异性抗体或其抗原结合片段在体外在表达CD33的细胞中以小于约1nM的EC_{50}值诱导T细胞依赖性细胞毒性。

[0734] 实施方案34是根据实施方案26至33中任一项所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段,其中所述双特异性抗体或其抗原结合片段是嵌合的。

[0735] 实施方案35是根据实施方案26至34中任一项所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段,其中所述双特异性抗体或其抗原结合片段是人或人源化的。

[0736] 实施方案36是一种分离的核酸,所述分离的核酸编码根据实施方案26至35中任一项所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段。

[0737] 实施方案37是一种载体,包含根据实施方案36所述的分离的核酸。

[0738] 实施方案38是一种宿主细胞,包含根据实施方案37所述的载体。

[0739] 实施方案39是一种药物组合物,包含根据实施方案26至35中任一项所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段以及药学上可接受的载体。

[0740] 实施方案40是一种在对其有需要的受试者中治疗癌症的方法,包括向所述受试者施用根据实施方案39所述的药物组合物。

[0741] 实施方案41是根据实施方案40所述的方法,其中所述癌症是血液学癌症。

[0742] 实施方案42是根据实施方案41所述的方法,其中所述血液学癌症选自白血病、淋巴瘤或多发性骨髓瘤。

[0743] 实施方案43是根据实施方案42所述的方法,其中所述血液学癌症是急性髓性白血病(AML)、骨髓增生异常综合征(MDS)、急性淋巴细胞白血病(ALL)、弥漫性大B细胞淋巴瘤(DLBCL)、慢性髓性白血病(CML)或母细胞性浆细胞样树突状细胞瘤(DPDCN)。

[0744] 实施方案44是一种产生根据实施方案26至35中任一项所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段的方法,包括在产生所述抗CD33/抗CD3双特异性抗体或其抗原结合片段的条件下培养包含编码所述抗CD33/抗CD3双特异性抗体或其抗原结合片段的核酸的细胞,以及从所述细胞或培养物回收所述抗CD33/抗CD3双特异性抗体或抗原结合片

段。

[0745] 实施方案45是一种产生包含根据实施方案26至35中任一项所述的抗CD33/抗CD3双特异性抗体或其抗原结合片段的药物组合物的方法,包括将所述抗CD33/抗CD3双特异性抗体或其抗原结合片段与药学上可接受的载体组合以获得所述药物组合物。

[0746] 实施例

[0747] 试剂

[0748] 抗原生成

[0749] 在具有或不具有突变的单体形式的人血清白蛋白(HSA)(具有C58S突变的Uniprot P02768)的情况下产生人和食蟹猕猴CD33蛋白,在C-末端融合以用于免疫和测定。合成具有六个组氨酸标签的编码CD33蛋白质抗原的cDNA并使用标准分子生物学技术将其克隆到肌动蛋白启动子下的哺乳动物分泌表达载体中。

[0750] 将来源于Uniprot P20138(SEQ ID NO:1)的全长人CD33胞外域(ECD)(人CD33 ECD)在N末端与信号序列融合,并且具有或不具有HSA,随后在C末端与六个组氨酸标签融合,hCD33 ECD仅具有HSA并且仅具有hCD33 ECD。根据制造商规程使用Expifectamine将人CD33 ECD表达构建体瞬时转染到HEK293衍生细胞Expi293(美国马萨诸塞州沃尔瑟姆的Gibco/Thermo Fisher Scientific公司(Gibco/Thermo Fisher Scientific;Waltham,MA))中。在收获之前,将细胞在37℃下在轨道式摇动器上与8%的CO_2温育5天。通过离心移除所表达的细胞,并且使用固定化的金属亲和色谱法(使用Ni Sepharose 6 Fast Flow树脂(英国Little Chalfont的通用电气医疗集团(GE Healthcare;Little Chalfont,United Kingdom)),然后在Dubelcco的磷酸盐盐水缓冲液pH 7.2(1×DPBS)中进行Superdex 200制备尺寸排阻色谱法(SEC)(通用电气医疗集团(GE Healthcare)),从培养基中纯化可溶性CD33。将排除任何二硫化物聚集体的SEC洗脱级分合并并无菌过滤以产生用于免疫和CD33测定的最终蛋白质。通过A280测定蛋白质浓度,并且通过SDS-PAGE和分析型SEC(美国加利福尼亚州托伦斯的Phenomenex公司(Phenomenex;Torrance,CA))评估纯化蛋白质的质量。内毒素的测量是使用EndoSafe-PTS色谱柱进行的,一种发色的LAL测定(美国马萨诸塞州威尔明顿Charles River公司(Charles River;Wilmington,MA))。

[0751] 类似地将人CD33 ECD亚结构域蛋白质、hCD33 V结构域-HSA、hCD33 V结构域-his、hCD33 C2结构域-HSA和hCD33 C2结构域-His构建、表达和纯化为全长人CD33 ECD。

[0752] 基于Genbank序列XP_005590138.1,还产生了用于免疫和交叉选择性测定的食蟹猕猴CD33构建体食蟹猕猴CD33 ECD-HSA、食蟹猕猴CD33-His。食蟹猕猴CD33蛋白质的表达和纯化与人CD33蛋白质相同。

[0753] 根据制造商的条件,使用SureLink Chromagenic Biotin Labeling试剂盒(SeraCare KPL公司)将用于筛选的CD33抗原在50mM磷酸钠(pH 7.2)中生物素酰化。简而言之,以生物素与蛋白质的4:1摩尔比将25mM的生物素原液添加到CD33蛋白质中,并且在室温下轻轻旋转温育30分钟,然后切换到4℃再持续2小时。通过将缓冲液交换到1×DPBS中来移除未掺入的生物素。通过使用NanoDrop在A280nm和A354nm下测量来测定蛋白质浓度和生物素掺入。上述抗原中的每一者的序列参见表1。

[0754] 表1:抗原序列

[0755]

蛋白质名称	蛋白ID	SEQ ID NO

食蟹猕猴CD33 ECD-HSA	C33W1	2
人CD33 ECD-HSA	C33W2	3
人CD33-V-HSA	C33W3	4
人CD33-C2-HSA	C33W4	5
人CD33-V-His	C33W8	6
人CD33 C2-His	C33W9	7
人CD33 ECD-His	C33W49	8
食蟹猕猴CD33 ECD-His	C33W50	9
人CD33全长		10
食蟹猕猴CD33全长		11

[0756] 表达CD33同基因细胞系的生成

[0757] 使用包含全长人CD33或食蟹猕猴CD33和嘌呤霉素的慢病毒(美国马里兰州罗克维尔Genecopoeia公司(Genecopoeia;Rockville,MD))产生表达人和食蟹猕猴CD33的细胞系以用于选择CD33阳性细胞。用慢病毒颗粒转导对CD33呈阴性的HEK293F细胞(ATCC)以过表达人CD33和食蟹猕猴CD33。在转导后,通过处理合并的细胞选择阳性表达CD33和抗性标志物的细胞,使其在DMEM+10％的HI FBS(美国加利福尼亚州卡尔斯巴德的美国生命科技公司)中生长并补充不同浓度的嘌呤霉素(美国生命科技公司)。

[0758] 除了HEK产生的细胞系之外,还使用了几个商业细胞系进行结合和细胞毒性测定。这些包括MOLM13、KG1、SH2、OCIAML3和MV411,并且可购自美国典型培养物保藏中心(American Type Culture Collection)或德国微生物菌种保藏中心(Deutsche Sammlung von Mikrooranismen und Zellkulturen),并且在37℃、5％的CO_2下在具有10％的FBS的完全RPMI培养基中培养。

[0759] 实施例1:免疫活动

[0760] OmniRat

[0761] 人免疫球蛋白转基因大鼠品系(OmniRat®;Ligand Pharmaceuticals;San Diego,CA)用于培养表达人CD33单克隆抗体的杂交瘤细胞。OmniRat®含有嵌合人/大鼠IgH基因座(包含22个人V_H,全部的人D和J_H片段以天然构型连接至大鼠C_H基因座)连同完整人IgL基因座(连接至Jκ-Cκ的12个Vκ和连接至Jλ-Cλ的16个Vλ)。(参见例如,Osborn等人,2013年,J Immunol,第190卷,第4期,第1481-1490页)。因此,大鼠表现出大鼠免疫球蛋白的表达降低,并且响应于免疫,所引入的人重链和轻链转基因经历类别转换和体细胞突变以产生具有全人类可变区的高亲和力嵌合的人/鼠IgG单克隆抗体。授予Bruggemann等人的PCT公布WO 2014/093908中描述了OmniRat®的制备和用途以及由此类大鼠携带的基因组修饰。

[0762] 当用重组人和食蟹猕猴CD33(分别为人CD33 ECD-HSA和食蟹猕猴CD33 ECD-HSA)免疫时,该转基因大鼠产生针对人CD33的嵌合人-大鼠IgG抗体,其中一些也与食蟹猕猴CD33结合。

[0763] 用人CD33 ECD-HSA和食蟹猕猴CD33 ECD-HSA交替免疫八只OmniRats。在46天免疫方案后,从所有八只OmniRats收获淋巴结并用于产生杂交瘤。使用标准技术经由结合ELISA

和AlphaLISA筛选八十一个96孔杂交瘤上清液板,其中选择128个杂交瘤上清液用于与人CD33 ECD-HSA和食蟹猕猴CD33 ECD-HSA特异性地结合。128个上清液中的大多数也对过表达人CD33或食蟹猕猴CD33的细胞的结合是阳性的。

[0764] 仅用rhuCD33免疫六只另外的OmniRats。在31天免疫方案后,从所有六只OmniRats收获淋巴结并用于产生杂交瘤。使用标准技术经由结合ELISA筛选三十个96孔杂交瘤上清液板,其中选择94个杂交瘤上清液用于与人CD33 ECD-HSA和食蟹猕猴CD33 ECD-HSA特异性地结合。从阳性克隆制备杂交瘤裂解物并进行到下述v区克隆。

[0765] OmniMouse

[0766] 人免疫球蛋白转基因小鼠品系(OmniMouse®;Ligand Pharmaceuticals公司)用于培养表达人CD33单克隆抗体的杂交瘤细胞。OmniMouse®包含嵌合人/大鼠IgH基因座以及完全人IgL基因座。小鼠表现出小鼠免疫球蛋白的表达降低,并且响应于免疫,所引入的人重链和轻链转基因经历类别转换和体细胞突变以产生具有全人类可变区的高亲和力嵌合的人/鼠IgG单克隆抗体。

[0767] 当用重组人和食蟹猕猴CD33(分别为人CD33 ECD-HSA和食蟹猕猴CD33 ECD-HAS)免疫时,该转基因小鼠产生针对人CD33的嵌合人-大鼠IgG抗体,其中一些也与食蟹猕猴CD33结合。

[0768] 用人CD33 ECD-HSA和食蟹猕猴CD33 ECD-HSA交替免疫四只OmniMice。在53天免疫方案后,从所有四只OmniMice收获脾脏和淋巴结并用于产生杂交瘤。经由结合ELISA和AlphaLISA筛选四十八个96孔杂交瘤上清液板,其中选择8个杂交瘤上清液用于与人CD33 ECD-HSA和食蟹猕猴CD33 ECD-HSA特异性地结合。从阳性克隆制备杂交瘤裂解物并进行到下述v区克隆。

[0769] V区克隆

[0770] 根据制造商规程使用RNeasy 96试剂盒(德国希尔登Qiagen公司(Qiagen;Hilden,Germany))纯化杂交瘤细胞裂解物中的总RNA,并且使用Drop Sense定量所得RNA并保存于-80℃或使用用于RT-PCR的Invitrogen SuperScript III First-Strand Synthesis System(美国加利福尼亚州卡尔斯巴德的Invitrogen公司(Invitrogen;Carlsbad,CA))合成cDNA。使用分别退火至重链、k链和λ链恒定区的基因特异性引物进行第一链cDNA合成。RT-PCR反应混合物由至多3gμ纯化的RNA、基因特异性引物、dNTP混合物、反应缓冲液、25mM的$MgCl_2$、DTT、RNaseOUT™(40U/μl,Invitrogen公司)和SuperScript™ III RT(200U/μl,Invitrogen目录号18080-051)组成,并在50℃下温育50分钟并在85℃下温育5分钟。将所得单链cDNA保存在-20℃下,或者对单链DNA进行PCR扩增。使用Platinum Pfx聚合酶(Invitrogen公司)进行PCR反应。使用优化的PCR条件,通过分别退火至先导序列和重链、k链和λ链恒定区的正向引物和反向引物来扩增v区片段。将所得的PCR片段在凝胶上运行并使用预先设计的引物在GENEWIZ上测序以获得V区序列。收集V区序列的所得.abi文件,并通过Janssen Biologics Discovery创建的Sanger V区序列分析程序进行分析。将回收的V区的AA序列记录在内部数据库中,优化密码子并克隆到携带所需人抗体同种型IgG1 F405L和IgG4 PAA的适当恒定区的基于pUnder的表达载体中。成功克隆了总共76种OMNIRat抗体和8种OMNIMouse抗体,并继续进一步表征。下表汇总了来自OMNIRat活动中鉴定的前42条序列

(参见表2)和来自OMNIMouse活动中鉴定的前16条序列(参见表3),其中将几种OMNIRat抗体克隆到IgG1以及IgG4 PAA中,全部来自OMNIMouse活动的抗体都克隆到IgG1和IgG4 PAA两者中。

[0771] 表2:在OMNIRat中经由CD33免疫鉴定的抗体序列

mAb	HC ID	HC 同种型	蛋白质 SEQ ID	核苷酸 SEQ ID	LC ID	蛋白质 SEQ ID	核苷酸 SEQ ID
C33B46	C33H108	hulgG1F405L	12	54	C33L74	96	138
C33B48	C33H80	hulgG1F405L	13	55	C33L73	97	139
C33B52	C33H42	hulgG1F405L	14	56	C33L8	98	140
C33B54	C33H44	hulgG1F405L	15	57	C33L10	99	141
C33B55	C33H45	hulgG1F405L	16	58	C33L11	100	142
C33B56	C33H46	hulgG1F405L	17	59	IAPL24	101	143
C33B61	C33H48	hulgG1F405L	18	60	C33L58	102	144
C33B62	C33H49	hulgG1F405L	19	61	C33L59	103	145
C33B63	C33H51	hulgG1F405L	20	62	C33L34	104	146
C33B64	C33H52	hulgG1F405L	21	63	N46L109	105	147
C33B66	C33H55	hulgG1F405L	22	64	C33L42	106	148
C33B72	C33H65	hulgG1F405L	23	65	C33L47	107	149
C33B73	C33H66	hulgG1F405L	24	66	C33L60	108	150
C33B75	C33H70	hulgG1F405L	25	67	N46L109	109	151
C33B77	C33H72	hulgG1F405L	26	68	C33L40	110	152
C33B79	C33H74	hulgG1F405L	27	69	C33L38	111	153
C33B80	C33H76	hulgG1F405L	28	70	C33L39	112	154
C33B82	C33H78	hulgG1F405L	29	71	C33L57	113	155
C33B83	C33H81	hulgG1F405L	30	72	C33L53	114	156
C33B87	C33H87	hulgG1F405L	31	73	C33L35	115	157
C33B88	C33H88	hulgG1F405L	32	74	C33L61	116	158
C33B89	C33H90	hulgG1F405L	33	75	C33L51	117	159
C33B94	C33H98	hulgG1F405L	34	76	C33L69	118	160
C33B95	C33H98	hulgG1F405L	35	77	IAPL24	119	161
C33B96	C33H99	hulgG1F405L	36	78	C33L37	120	162
C33B101	C33H69	hulgG1F405L	37	79	C4LL152	121	163
C33B107	C33H68	hulgG1F405L	38	80	C33L17	122	164
C33B120	C33H87	hulgG1F405L	39	81	C33L41	123	165
C33B122	C33H92	hulgG1F405L	40	82	C33L30	124	166
C33B123	C33H91	hulgG1F405L	41	83	C33L44	125	167
C33B124	C33H73	hulgG1F405L	42	84	C33L32	126	168
C33B125	C33H84	hulgG1F405L	43	85	C33L66	127	169
C33B760	C33H45	huIgG4 PAA	44	86	C33L11	128	170
C33B777	C33H65	huIgG4 PAA	45	87	C33L47	129	171
C33B778	C33H66	huIgG4 PAA	46	88	C33L60	130	172
C33B782	C33H72	huIgG4 PAA	47	89	C33L40	131	173
C33B792	C33H87	huIgG4 PAA	48	90	C33L35	132	174
C33B799	C33H98	huIgG4 PAA	49	91	C33L69	133	175
C33B806	C33H69	huIgG4 PAA	50	92	C4LL152	134	176
C33B830	C33H84	huIgG4 PAA	51	93	C33L66	135	177
C33B836	C33H80	huIgG4 PAA	52	94	C33L73	136	178
C33B937	C33H66	huIGG4 PAA	53	95	C33L132	137	179

[0772]

[0773]

[0774] HC:重链;LC:轻链

[0775] 表3:在OMNIMouse中经由CD33免疫鉴定的抗体序列

[0776]

mAb	HC ID	蛋白质 SEQ ID NO	核苷酸 SEQ ID NO	LC ID	蛋白质 SEQ ID NO	核苷酸 SEQ ID NO
C33B901	C33H249	180	196	C33L115	212	228
C33B902	C33H250	181	197	C33L116	213	229
C33B903	C33H251	182	198	C33L117	214	230
C33B904	C33H252	183	199	C33L118	215	231
C33B905	C33H253	184	200	C33L119	216	232
C33B906	C33H254	185	201	C33L120	217	233
C33B907	C33H255	186	202	C33L121	218	234
C33B908	C33H256	187	203	C33L122	219	235
C33B909	C33H249	188	204	C33L115	220	236
C33B910	C33H250	189	205	C33L116	221	237
C33B911	C33H251	190	206	C33L117	222	238
C33B912	C33H252	191	207	C33L118	223	239
C33B913	C33H253	192	208	C33L119	224	240
C33B914	C33H254	193	209	C33L120	225	241
C33B915	C33H255	194	210	C33L121	226	242
C33B916	C33H256	195	211	C33L122	227	243

[0777] HC:重链;LC:轻链

[0778] Expi293小规模转染和纯化

[0779] 经由小2ml规模表达和纯化在免疫活动和后续v区克隆(到IgG1 F405L和IgG4 PAA)中鉴定的抗体。将Expi293™细胞(来自赛默飞世尔科技公司(ThermoFisher Scientific))以1.25×10^5至2.25×10^5个活细胞/mL的密度接种到Expi293™ Expression Medium中,并在37℃、7%的CO_2摇动培养箱(INFORS HT Multitron Pro)中的聚碳酸酯、一次性、无菌、通风、无挡板的锥形摇动烧瓶中培养。对于125mL至2L摇瓶中的常规细胞生长,对于具有19mm摇动直径的摇动器,将摇动速度设定为130rpm。当密度达到具有98%至99%活力的3×^{6}10至5×10^6个活细胞/mL的对数生长期时,对细胞进行继代培养。

[0780] 在转染当天,测定活细胞密度和活力百分比。以3×10^6个活细胞/mL的密度转染细胞。为了最佳转染,使用TE缓冲液(10mM的Tris-HCl,1mM EDTA,pH 8.0)中0.1mg/mL浓度的无菌重链和轻链质粒DNA。

[0781] 根据制造商的转染方案(赛默飞世尔公布号MAN0007814)转染Expi293™细胞。在24孔深孔板(通用电气医疗集团(GE Healthcare))中进行转染。简而言之,用0.1mL的OptiMEM™培养基(赛默飞世尔科技公司(ThermoFisher Scientific))以下列比率稀释质粒DNA:0.250μg重链DNA:0.750μg轻链DNA:0.5μg pAdvantage。稀释5μL的ExpiFectamine™293转染试剂,并且将其与95μL的OptiMEM™培养基轻轻混合并温育1分钟。将所稀释的ExpiFectamine™ 293试剂添加到所稀释的DNA中,轻轻混合,并将ExpiFectamine™ 293/质粒DNA复合物在室温下温育40分钟。在温育后,将1.8mL的Expi293™细胞添加到复合物中,在37℃、7%的CO_2摇动培养箱中温育过夜。

[0782] 在转染后第1天,添加10μL的ExpiFectamine™ 293增强剂1和100Lμ的Expifectamine 293™增强剂2,并且将板放回培养箱中再温育5天。在转染后第6天通过以850×G离心15分钟来收获培养物,然后进行纯化。

[0783] 将上文制备的1.7ml的澄清表达上清液转移到新的962ml的深孔板。通过将800μl的mAb Select Sure树脂(通用电气医疗集团(GE Healthcare))和DPBS-/-浆液的1:4混合

物移到96孔Acroprep Advance 1μM玻璃滤板(颇尔公司(Pall))的每个孔中来制备纯化板。向该板施加200mbar的真空压力以去除过量的PBS,随后用800μl的新鲜PBS洗涤。施加200mbar的真空压力以去除洗涤缓冲液。然后将澄清的上清液转移到PBS洗涤过的树脂,轻轻混合并温育15分钟。在温育后,施加200mbar的真空压力以去除上清液。用PBS将mAb Select Sure树脂洗涤三次,并用25mM的乙酸钠(pH 5)(美国加利福尼亚州霍利斯特的天惠华公司(TEKNOVA;Hollister,CA))洗涤一次,在洗涤之间施加200mbar的真空压力以去除过量的缓冲液。使用0.1M的乙酸钠(pH 3.5)洗脱与树脂结合的mAb,并温育10分钟以进行有效解离。将滤板置于96深孔板的顶部,并且经由在1000g下离心2分钟将所洗脱的mAb收集在底板中。添加80μl的2.5M的Tris-乙酸盐(pH 7.2)以中和mAb。将mAb在96孔DispoDIALYZER板(美国马萨诸塞州霍利斯顿的哈佛仪器公司(Harvard Apparatus;Holliston,MA))中渗入PBS中过夜,转移至96孔Acroprep Advance 0.2μm Supor滤板(美国纽约州华盛顿港的颇尔公司(Pall;Port Washington,NY))中,置于96深孔板的顶部,并经由台式离心机以1,500g离心15分钟过滤蛋白质溶液。使用DropSense Instrument(Trinean公司)通过在滤液上进行A280测量来确定蛋白质浓度。

[0784] 实施例2:抗CD33 mAb的特征

[0785] 经由免疫鉴定、克隆的v区并随后表达和纯化的OMNIRat抗体进一步表征与表达CD33的细胞结合以及与重组抗原结合。评估所纯化的抗体与稳定转染的表达人CD33或食蟹猕猴CD33(上述产生)的HEK293F细胞以及作为阴性对照的亲本HEK293F的结合。使用非酶解离缓冲液(赛默科技公司(Thermo Scientific))从组织培养瓶收获细胞。将该瓶用PBS冲洗两次,并将解离缓冲液添加到该瓶中,并将该瓶在37℃下温育10分钟,直到细胞变为非粘连的。将细胞以300g离心5分钟,然后以1.0×10^{6}细胞/ml重悬在染色缓冲液(美国新泽西州富兰克林湖的贝迪医疗公司(Becton Dickinson;Franklin Lakes,NJ))中。将50,000个细胞/孔的每种细胞类型置于圆底板(贝迪医疗公司(Becton Dickinson))中的50μl染色缓冲液中。以3种稀释度和零(120nM、12nM以及1.2nM和0nM)添加50μl的2X浓度的测试mAb或同种型对照,并且将所得的溶液在4℃下温育30分钟。将100μl的染色缓冲液添加到每个板的所有孔,将板以300g离心5分钟,去除缓冲液,将200μl的染色缓冲液添加到每个板的所有孔,将板以300g离心5分钟,并去除缓冲液。将50μl的2μg/ml的山羊抗人Fc AF647二抗(美国宾夕法尼亚州西格罗夫的Jackson Immunoresearch公司(Jackson Immunoresearch;West Grove,PA))添加到板的所有孔中,并将该板在4℃下温育30分钟。将100μl的染色缓冲液添加到板的所有孔,将该板以300g离心5分钟,并去除缓冲液。将200μl的运行缓冲液(运行缓冲液是染色缓冲液、1mM EDTA、0.1%的古洛糖醛酸)添加到板的所有孔中,将该板以300g离心5分钟,并去除缓冲液。将含有Sytox Green活/死染料的30μl运行缓冲液(赛默飞世尔公司(ThermoFisher))添加到具有细胞的所有孔中,并且在iQue IntelliCyt流式细胞仪上读取板。在前向与侧向散射中对细胞进行门控以消除碎片,然后对单峰进行门控,然后对排除了Sytox染色的活细胞进行门控。通过AF647通道中的平均荧光强度来评估抗体结合。

[0786] 为了开始评估所纯化的mAb的生物物理结合特性,进行解离速率筛选。测试76种OMNIRat抗CD33 mAb与重组人CD33 ECD-HSA(C33W2)和食蟹猕猴CD33 ECD-HSA(C33W1)蛋白(Janssen生产)的结合,并且通过IBIS MX96 SPRi阵列平台(美国宾夕法尼亚州牛顿市的Carterra公司(Carterra;Newton,PA))测量解离速率。在IBIS仪器中使用缔合时间为10分

钟的CMD50m传感器芯片(Xantec公司,lot CMD50m0415.a),经由100μg/mL的胺偶联将山羊抗人Fc IgG(Jackson Immunoresearch目录号109-005-098)直接固定在乙酸盐缓冲液(pH 4.5)中。达到约9000Rus的平均GAH-Fc固定水平。将传感器芯片转移到连续流微点滴器(CFM)单元以10μg/ml捕集每种抗CD33 mAb 10分钟。通过单循环动力学在不再生的情况下测量对IBIS SPRi的结合。使用PBST(具有0.005%Tween的PBS)作为运行缓冲液,按顺序从低浓度(0.46nM)到高浓度(μ3M)注射每个抗原浓度系列(3μM,3倍稀释系列)以5分钟的缔合时间和15分钟的解离时间结合所捕获的mAb。引用原始结合数据(.trix文件格式)并用SprintX软件(Wasatch,1.9.3.2版本)进行比对,然后导出(.ibmx文件格式)到Scrubber软件(2.0版本)进行1:1结合动力学分析(Wasatch,2.0.0.33版本)以提取k_{off}结果。

[0787] 下表4汇总了通过与表达人和食蟹猕猴CD33的细胞系以及与重组抗原(其中抗原中的一种抗原的解离速率至少>10e-3)的结合而评估的前32个克隆。在这32个克隆中,除4种之外的所有克隆均显示出可测量的与表达人或食蟹猕猴的细胞的结合。经由表位分箱和完全动力学分析进一步表征所有32个克隆。

[0788] 表4.来源于OMNIRat的抗CD33抗体的细胞结合和解离速率分析

[0789]

蛋白质 AA ID	Mon %	60nM CD33	6nM CD33	0.6nM CD33	0nM CD33	kD
C33B48	91.96	400995.84	428948.75	391157.69	91.12	5.47E-05
C33B73	100.00	201493.02	33443.28	4034.64	93.98	9.12E-05
C33B125	98.48	258779.13	79728.78	9203.75	78.26	1.54E-04
C33B55	96.39	188278.42	59155.10	7625.56	105.39	2.15E-04
C33B96	98.75	476040.28	475653.41	187925.80	55.23	2.28E-04
C33B124	100.00	798.33	126.37	90.26	172.03	2.38E-04
C33B72	96.94	328194.72	105474.59	12506.85	93.32	2.84E-04
C33B79	100.00	236644.03	41925.89	4988.81	77.78	3.28E-04
C33B77	92.11	241787.16	88691.05	11484.97	69.46	3.37E-04
C33B82	96.21	188508.56	41264.92	5033.60	73.44	3.41E-04
C33B87	100.00	242185.48	79532.87	12547.05	73.65	3.52E-04
C33B80	98.33	5799.64	409.97	114.93	88.88	3.84E-04
C33B101	96.91	268805.28	204984.16	35513.63	70.07	3.98E-04
C33B83	98.07	92956.55	7856.70	1020.48	87.37	4.61E-04
C33B46	95.81	509865.97	447627.97	418017.22	134.53	4.67E-04
C33B94	98.31	200142.00	93852.22	13274.87	89.59	5.38E-04
C33B88	98.36	393148.13	481100.91	274293.53	94.81	8.25E-04
C33B66	98.71	444680.31	313288.41	56628.04	129.73	8.59E-04
C33B120	97.63	190036.14	60357.11	7054.28	92.94	1.40E-03
C33B64	98.13	200158.36	54138.77	7556.04	114.85	1.71E-03
C33B52	96.76	196557.09	46286.13	6751.01	82.46	3.13E-03
C33B56	95.59	143.73	79.73	111.95	138.04	4.02E-03
C33B75	98.68	163795.25	29603.57	4517.81	95.94	4.16E-03
C33B107	96.90	375388.25	339798.53	161369.64	86.54	4.44E-03
C33B63	98.79	247758.77	62221.71	9671.48	86.34	4.57E-03
C33B95	97.77	154556.58	44354.07	6402.00	87.38	5.99E-03
C33B61	98.87	198777.34	38699.10	5308.45	79.84	6.71E-03
C33B89	100.00	315.38	119.12	65.61	70.94	8.11E-03
C33B122	98.49	259183.69	84281.03	14291.17	65.01	8.74E-03
C33B62	99.05	157786.36	37359.44	6092.03	75.00	1.00E-02
C33B123	95.08	224078.95	88155.99	8864.39	71.05	1.03E-02
C33B54	100.00	147753.30	27461.06	3766.69	61.26	2.48E-02

[0790]

蛋白质 AA ID	60nM 食蟹猕猴 CD33	6nM 食蟹猕猴 CD33	0.6nM 食蟹猕猴 CD33	0nM 食蟹猕猴 CD33	结合 kD 的食蟹猕猴 CD33
C33B48	56491.32	47326.85	43351.12	94.01	1.20E-04
C33B73	14799.14	6987.92	795.57	72.51	4.08E-04
C33B125	15603.45	11526.47	3458.27	70.22	3.51E-04
C33B55	16020.78	9994.42	2433.94	69.38	1.16E-04
C33B96	37273.19	20087.29	11574.59	86.31	8.19E-04

[0791]

C33B124	593.00	132.19	77.26	98.41	4.77E-04
C33B72	19422.07	13975.14	3894.84	90.81	7.63E-04
C33B79	15538.97	6427.73	1082.85	63.59	6.82E-03
C33B77	17516.20	11665.49	3601.76	85.23	4.18E-04
C33B82	14269.38	6622.07	1540.09	84.24	6.70E-04
C33B87	19597.18	12652.44	3266.36	103.07	2.28E-04
C33B80	4612.58	248.60	108.93	82.38	2.66E-04
C33B101	48016.75	46115.96	17989.37	79.69	1.06E-04
C33B83	5304.40	687.44	159.37	87.35	2.17E-03
C33B46	49840.14	49816.36	49729.78	92.05	1.48E-04
C33B94	16126.84	10782.54	3183.70	87.82	5.37E-04
C33B88	50388.18	43928.95	43940.23	90.13	3.89E-04
C33B66	48905.04	49076.39	42160.22	77.96	9.33E-05
C33B120	13211.32	7865.37	2726.18	75.77	8.54E-04
C33B64	21109.59	9685.04	3102.56	99.82	1.21E-03
C33B52	12582.90	8444.39	2063.44	75.24	1.20E-03
C33B56	104.27	85.94	78.56	83.31	8.46E-04
C33B75	12194.41	5577.80	1709.40	124.32	1.20E-03
C33B107	50325.07	47810.05	36786.69	55.11	1.35E-04
C33B63	18322.71	11642.38	2879.89	87.94	9.47E-04
C33B95	14774.34	9594.12	1637.99	80.81	6.98E-03
C33B61	13552.71	8211.09	1595.90	106.84	1.83E-03
C33B89	47301.14	34193.78	23334.20	112.80	4.65E-05
C33B122	19740.29	13907.32	5838.25	82.53	1.45E-03
C33B62	12737.71	5620.17	1922.97	934.44	1.32E-03
C33B123	10665.93	10404.03	3232.18	61.08	2.74E-03
C33B54	50466.68	43011.75	38091.89	28785.80	1.35E-04

[0792] 然后进一步表征这批mAb以用于完全亲和力分析以及表位分箱。通过ProteOn SPR(Bio-Rad)测量抗CD33 mAb与重组人CD33 ECD-HSA(C33W2)和食蟹猕猴CD33 ECD-HSA(C33W1)的结合。经由30μg/mL的胺偶联将山羊抗人Fc IgG(Jackson Immunoresearch,目录号109-005-098)直接固定在乙酸盐缓冲液(pH 5.0)中,在GLC传感器芯片(Bio-Rad,目录号176-5011)上垂直取向的所有6个配体通道上,流速为30μL/min,在含0.005％Tween-20的PBS中。固定密度平均为约5000应答单位(RU),在不同通道之间具有小于5％的变化。在垂直的配体取向上不同的mAb以0.25μg/ml或0.5μg/ml(160RU至300RU)捕获在抗人Fc IgG表面上,其中第6配体通道作为无配体表面对照。在5倍浓度的3倍稀释系列中,0.3μM浓度的人和食蟹猕猴CD33-HSA蛋白质作为被分析物飞入,从而在水平取向上与捕获的mAb结合。还在第6通道中注入缓冲液样品以监测捕获的mAb的解离和基线稳定性。以100μL/min的流速监测所有浓度的人和食蟹猕猴CD33-HSA的解离阶段,持续15分钟以与C33B782结合,持续60分钟以与C33B912结合(与具有hIgG4的C33B904相同),然后使用0.85％磷酸的18秒脉冲再生以

去除抗原和所结合的mAb。在从以下减去应答数据之后,通过双重参考处理原始结合数据:1)校正Ag和空芯片表面之间的非特异性相互作用的中间点;2)校正由于捕获mAb表面随时间的解离所致的基线漂移的缓冲液通道。将每种mAb在所有抗原浓度下的处理数据全局拟合到1:1简单的朗缪尔结合模型,以提取动力学(k_{on},k_{off})和亲和力(KD)常数的估计值。

[0793] 为了确定这批mAb是否全部结合1个不同的表位或是否存在广泛的表位覆盖率,进行表位分箱实验。使用CMD-200M传感器棱镜芯片,在IBIS SPRi仪器(Carterra公司)上进行CD33 mAb的竞争性抗原表位分箱。使用单独的连续流微点滴器(CFM),经由胺偶联将每种抗CD33抗体以10μg/ml直接固定在芯片上的乙酸盐缓冲液(pH 4.5)中。然后将印刷的传感器芯片转移到IBIS仪器,使用经典或"夹置"分箱格式进行分箱分析。通过依次注射50nM的人CD33 ECD-HSA(C33W2),然后在133nM的溶液中作为竞争性分析物注射单次抗CD33mAb以在抗原和抗体的每个顺序注射循环之后使固定的抗CD33 mAb与表面再生结合来进行分箱。

[0794] 为了监测再生前后固定化mAb的活性,在实验开始和结束时进行无任何竞争mAb的缓冲液注射以测量抗原单独的结合活性。竞争mAb结合相对于缓冲液(单独的抗原)结合的应答指示溶液中的抗体是阻断还是将抗原夹置结合在固定的mAb。引用原始分箱数据(.trix文件格式)并使用SprintX软件(Wasatch,1.9.3.2版本)归零,然后将其导出(.ibmx文件格式)到分箱软件HtTools.exe(Wasatch,2.0.0.33版本)用于分析。通过移除抗原应答低于20RU的抗体和不自身阻断的抗体来处理数据。竞争mAb应答相对于单独的抗原结合应答进行归一化。归一化应答<0.25的抗体表示阻断剂,归一化应答≥0.25的抗体表示非阻断剂/夹置剂。在组合树状图上使用高度2.5处的切口来预测不同的箱。

[0795] 下表汇总了32种所选mAb的完全动力学分析和表位分箱。总共有8个抗CD33 mAb对人和食蟹猕猴CD33均具有亚纳摩尔亲和力,并且这些mAb对应于3个不同的表位箱,而较大的一批具有一系列亲和力和7个不同的表位箱。

[0796] 表5.来源于OMNIRat的mAb的全动力学分析和表位分箱

[0797]

人 CD33 ECD-HSA					
蛋白质 AA ID	V 区 ID	ka（1/Ms）	kd（1/s）	KD (M)	表位箱
C33B48	C33F53	1.62E+06	1.82E-05	1.12E-11	1
C33B46	C33F51	1.45E+06	1.99E-03	1.38E-09	1
C33B66	C33F71	3.85E+04	2.03E-03	5.29E-08	1
C33B107	C33F112	结合/无拟合	结合/无拟合	结合/无拟合	1
C33B88	C33F93	结合/无拟合	结合/无拟合	结合/无拟合	1
C33B96	C33F101	2.26E+05	4.36E-04	1.92E-09	3
C33B101	C33F106	1.62E+05	1.08E-03	6.64E-09	3
C33B73	C33F78	5.59E+05	5.59E-05	1.00E-10	4
C33B125	C33F130	9.92E+05	1.34E-04	1.40E-10	4
C33B55	C33F60	9.85E+05	2.53E-04	2.60E-10	4
C33B82	C33F87	4.45E+05	2.70E-04	6.10E-10	4
C33B83	C33F88	2.70E+05	5.21E-04	1.93E-09	4
C33B75	C33F80	3.85E+05	4.41E-03	1.14E-08	4
C33B123	C33F128	1.02E+06	1.52E-02	1.48E-08	4
C33B52	C33F57	2.06E+05	3.96E-03	1.92E-08	4
C33B61	C33F66	4.89E+05	1.05E-02	2.14E-08	4
C33B62	C33F67	5.07E+05	1.26E-02	2.49E-08	4
C33B64	C33F69	4.33E+05	2.21E-03	5.10E-09	4
C33B63	C33F68	5.33E+05	3.74E-03	7.01E-09	4
C33B122	C33F127	7.47E+05	7.12E-03	9.53E-09	4
C33B72	C33F77	8.71E+05	2.00E-04	2.30E-10	5
C33B79	C33F84	5.15E+05	3.90E-04	7.60E-10	5
C33B77	C33F82	8.28E+05	2.62E-04	3.20E-10	6
C33B87	C33F92	7.20E+05	4.32E-04	6.00E-10	6
C33B94	C33F99	9.22E+05	5.85E-04	6.30E-10	6
C33B95	C33F100	4.82E+05	7.40E-03	1.54E-08	6
C33B120	C33F125	5.75E+05	1.68E-03	2.93E-09	6
C33B89	C33F94	低结合	低结合	低结合	8
C33B54	C33F59	低结合	低结合	低结合	9
C33B124	C33F129	3.57E+05	1.24E-04	3.50E-10	NB
C33B80	C33F85	3.23E+05	4.25E-04	1.32E-09	NB
C33B56	C33F61	低结合	低结合	低结合	NB

[0798]

食蟹猕猴 CD33 ECD-HSA					
蛋白质 AA ID	V 区 ID	ka（1/Ms）	kd（1/s）	KD (M)	表位箱
C33B48	C33F53	4.31E+06	1.58E-04	3.66E-11	1
C33B46	C33F51	2.97E+06	3.75E-04	1.26E-10	1
C33B66	C33F71	1.22E+06	2.66E-04	2.17E-10	1

[0799]

C33B107	C33F112	3.31E+05	7.01E-05	2.12E-10	1
C33B88	C33F93	结合/无拟合	结合/无拟合	结合/无拟合	1
C33B96	C33F101	结合/无拟合	结合/无拟合	结合/无拟合	3
C33B101	C33F106	2.25E+05	2.69E-04	1.20E-09	3
C33B73	C33F78	6.00E+05	5.08E-04	8.46E-10	4
C33B125	C33F130	1.12E+06	3.39E-04	3.04E-10	4
C33B55	C33F60	1.16E+06	8.37E-05	7.23E-11	4
C33B82	C33F87	5.45E+05	7.51E-04	1.38E-09	4
C33B83	C33F88	2.47E+05	2.88E-03	1.17E-08	4
C33B75	C33F80	6.16E+05	1.32E-03	2.15E-09	4
C33B123	C33F128	1.26E+06	3.39E-03	2.69E-09	4
C33B52	C33F57	3.13E+05	1.48E-03	4.74E-09	4
C33B61	C33F66	7.34E+05	1.62E-03	2.21E-09	4
C33B62	C33F67	8.05E+05	1.49E-03	1.85E-09	4
C33B64	C33F69	5.90E+05	1.01E-03	1.71E-09	4
C33B63	C33F68	7.23E+05	8.80E-04	1.22E-09	4
C33B122	C33F127	结合/无拟合	结合/无拟合	结合/无拟合	4
C33B72	C33F77	9.19E+05	5.40E-04	5.87E-10	5
C33B79	C33F84	5.48E+05	2.20E-03	4.01E-09	5
C33B77	C33F82	1.08E+06	2.66E-04	2.47E-10	6
C33B87	C33F92	1.12E+06	2.64E-04	2.36E-10	6
C33B94	C33F99	1.10E+06	5.20E-04	4.73E-10	6
C33B95	C33F100	8.44E+05	8.06E-03	9.56E-09	6
C33B120	C33F125	8.76E+05	9.02E-04	1.03E-09	6
C33B89	C33F94	2.65E+05	2.01E-04	7.60E-10	8
C33B54	C33F59	1.32E+06	6.37E-04	4.84E-10	9
C33B124	C33F129	4.67E+05	4.72E-04	1.01E-09	NB
C33B80	C33F85	4.92E+05	2.59E-04	5.27E-10	NB
C33B56	C33F61	低结合	低结合	低结合	NB

[0800] OmniMouse批次(总计8种mAb)是单独生成的并进一步表征了与细胞的结合。如上所述进行细胞结合并汇总于下表中。在所测试的8种mAb中,6种直接与表达CD33的细胞结合,而2种不与表达CD33的细胞结合。

[0801] 表6.来源于OMNIMouse的mAb与表达人和食蟹猕猴的细胞系的细胞结合

[0802]

	亲本				人 CD33			
mAb	60nM	6nM	0.6nM	0nM	60nM	6nM	0.6nM	0nM
C33B909	253.50	206.04	169.77	119.51	176.49	170.25	154.00	191.28
C33B910	193.52	176.14	108.46	190.17	213.55	183.33	151.25	155.29
C33B911	1466.02	389.41	186.22	113.30	237954.27	100333.48	13501.02	114.07
C33B912	977.91	273.07	140.62	124.53	237140.86	101295.70	15726.96	149.54
C33B913	174.49	118.08	123.26	129.07	518952.00	409071.06	204694.14	127.82
C33B914	181.37	142.74	139.10	113.48	304350.88	315129.56	153252.58	185.45
C33B915	101.28	147.65	143.51	100.00	390477.25	362902.66	138398.56	112.22
C33B916	416.08	145.16	115.70	91.75	447815.47	404033.19	192941.55	167.07

[0803]

	食蟹猕猴 CD33			
mAb	60nM	6nM	0.6nM	0nM
C33B909	180.33	135.33	115.73	124.03
C33B910	202.42	135.18	116.71	175.97
C33B911	17036.56	7729.14	1935.16	97.94
C33B912	15070.88	7271.38	1726.03	124.69
C33B913	40661.90	36920.95	35224.10	106.19
C33B914	44964.85	33368.26	22086.01	86.76
C33B915	37495.34	35692.21	36165.59	113.92
C33B916	41004.43	33294.78	22790.61	104.43

[0804] 使用上述和下表中汇总的方法,经由对重组抗原的完全动力学分析,对细胞上结合CD33的6种mAb进行进一步生物物理表征。在测试的6种mAb中,1种与人CD33结合为皮摩尔亲和力(C33B912),对食蟹猕猴CD33具有亚摩尔亲和力,而1种对人CD33具有非常强的亲和力,但对食蟹猕猴CD33(C33B911)仅具有纳摩尔亲和力。对于人和食蟹猕猴CD33(C33B913和C33B916),另外两种克隆是亚纳摩尔亲和力,但亲和力均不在C33B912的范围内。

[0805] 表7.来源于OMNIMouse的mAb的完全动力学分析

[0806]

	人 CD33 ECD-HSA			食蟹猕猴 CD33 ECD-HSA		
mAb	ka(1/Ms)	kd(1/s)	KD (M)	ka(1/Ms)	kd(1/s)	KD (M)
C33B911	1.10E+06	4.14E-05	3.78E-11	1.15E+06	1.15E-03	1.00E-09
C33B912	1.42E+06	4.29E-05	3.02E-11	1.50E+06	6.50E-04	4.33E-10
C33B913	6.60E+05	6.40E-04	9.69E-10	2.56E+06	3.08E-04	1.20E-10
C33B914	4.44E+05	9.80E-03	2.21E-08	5.29E+05	2.33E-04	4.40E-10
C33B915	2.18E+05	9.89E-04	4.53E-09	3.81E+06	8.93E-05	2.34E-11
C33B916	6.27E+05	4.11E-04	6.55E-10	4.73E+05	4.03E-04	8.52E-10

[0807] 对来源于OMNIMouse的6细胞结合mAb以及先前在早期OMNIRat活动中鉴定的几个对照mAb进行表位分箱实验。基于对人CD33的亚纳摩尔亲和力和不同表位箱的数量来选择对照mAb。分箱软件HtTools在每个实验的基础上分配表位箱编号,因此对已经定义的表位箱具有几个对照对于交叉比较至关重要。两种来源于OMNIMouse的人CD33高亲和力克隆(C33B911和C33B912)均与来自上文箱4的克隆(本实验中箱4)分箱,而亚纳摩尔克隆(C33B916)与C33B836(上述实验中箱1)一起分箱成2。

[0808] 表8:OMNIMouse抗CD33 mAb的表位箱

[0809]

mAb	V区ID	表位箱
C33B915	C33F553	1
C33B916	C33F554	2
C33B836	C33F53	2
C33B914	C33F552	2
C33B913	C33F551	3
C33B806	C33F106	3
C33B911	C33F549	4
C33B912	C33F550	4
C33B778	C33F78	4
C33B830	C33F130	4

C33B782	C33F82	5
C33B792	C33F92	5
C33B799	C33F99	5
C33B760	C33F60	6
C33B777	C33F77	7

[0810] CD33由2个IgG结构域、膜远侧V结构域和膜近侧C2结构域构成。SNP rs12459419可导致CD33前mRNA转录物的选择性另选剪接,以产生在细胞上表达的仅C2形式,因此靶向该结构域可提供临床益处。为了确定mAb能够结合两个结构域中哪一个结构域,使用人CD33 ECD-HSA、人CD33 V-HSA和人CD33 C2-HSA作为结合抗原,根据上述方案对覆盖4个不同表位箱的具有最高结合能力的6种mAb进行解离速率筛选。如下表所示,先前分组于箱4中的两个克隆均与人CD33 C2结构域结合而非人CD33 V结构域,而箱2和箱3中的克隆结合V结构域而非C2结构域。分组到箱5中的两个克隆不结合任一结构域,因此它们的确切结合位置可跨越两个结构域。本实验包括三(3)种市售的mAb(WM53(德国达姆施塔特的EMD Millipore公司(EMD Millipore;Darmstadt,Germany))、P67.7(美国加利福尼亚州圣地亚哥的Biolegend公司(Biolegend,San Diego,CA))和LSBio克隆906(美国华盛顿州西雅图的LifeSpan Biosciences公司(LifeSpan Biosciences,Seattle,WA)))并全部显示与V结构域结合,但不与C2结构域结合。相对于表9中的C2结构域结合数据查看表5和表8中的表位箱,总共有15种mAb能够潜在地结合人全长蛋白上约25nM至约30pM范围内的C2结构域。

[0811] 表9.解离速率结构域结合

[0812]

	人 CD33 ECD-HSA	人 CD33-V-HSA	人 CD33-C2-HSA	表位箱
蛋白 ID	kd (1/s)	kd (1/s)	kd (1/s)	
C33B912	1.29E-05	无/低结合应答	6.68E-05	4
C33B778	4.72E-05	无/低结合应答	2.57E-03	4
C33B782	2.58E-04	无/低结合应答	无/低结合应答	5
C33B792	4.27E-04	无/低结合应答	无/低结合应答	5
C33B836	5.52E-05	3.71E-05	无/低结合应答	2
C33B806	1.36E-03	3.18E-03	无/低结合应答	3
WM53	2.37E-03	3.78E-02	无/低结合应答	
P67.7	1.05E-03	2.43E-03	无/低结合应答	
LSBio 克隆 906	2.45E-03	4.34E-02	无/低结合应答	

[0813] 为了支持进一步的体内和体外研究,选择选择选择克隆体(C33B836、C33B782、C33B778、C33B904、C33B806、C33B830、C33B937、C33B792、C33B760和C33B777)进行放大和fab臂交换以产生具有抗CD3抗体的双特异性DuoBody分子。将ExpiCHO-S™细胞(来自赛默飞世尔科技公司(ThermoFisher Scientific))以1.25×10^5至2.25×10^5个活细胞/mL接种到ExpiCHO™ Expression Medium中,并在37℃、7%的CO_2摇动培养箱(INFORS HT Multitron Pro)中的聚碳酸酯、一次性、无菌、通风、无挡板的锥形摇动烧瓶中培养。对于125mL至2L摇瓶中的常规细胞生长,对于具有19mm摇动直径的摇动器,将摇动速度设定为130rpm。当密度达到具有98%至99%活力的$4\times^{6}10$至6×10^6个活细胞/mL的对数生长期时,对细胞进行继代培养。

[0814] 在转染前两天,将ExpiCHO-S™细胞以1.5×10^6个活细胞/mL接种到所需的培养物

体积。在转染当天,测定活细胞密度和活力百分比。以6×10^{6}个活细胞/mL的密度转染细胞。为了最佳转染,使用TE缓冲液(10mM的Tris-HCl,1mM EDTA,pH 8.0)中≥1mg/mL浓度的无菌重链和轻链质粒DNA。

[0815] 根据制造商的Max Titer转染方案(赛默飞世尔公布号MAN0014337)转染ExpiCHO-S™细胞。下文所示的所有量和体积均为每mL最终转染培养物体积。简而言之,用0.04mL的冷的OptiPRO™培养基(赛默飞世尔科技公司(ThermoFisher Scientific))以下列比率稀释质粒DNA:0.125μg重链DNA:0.375μg轻链DNA:0.5μg pAdvantage。稀释6.4μL的ExpiFectamine™ CHO转染试剂,并且将其与0.04mL的OptiPRO™培养基轻轻混合并温育1分钟。将所稀释的ExpiFectamine™ CHO试剂添加到所稀释的DNA中,轻轻混合,并将ExpiFectamine™ CHO/质粒DNA复合物在室温下温育5分钟。在温育后,将复合物添加到摇动烧瓶中的ExpiCHO-S™细胞中,并在37℃、7%的CO_2摇动培养箱中温育过夜。

[0816] 对于Max Titer方案,在转染后第1天,添加6μL的ExpiFectamine™ CHO增强剂和160μL的ExpiCHO™ Feed,并且将烧瓶转移到32℃、7%的CO_2摇动培养箱。在转染后第5天,再次向烧瓶中添加160μL的ExpiCHO™ Feed,并将其摇动放回32℃培养箱中。在转染后第12天收获培养物,以5000rpm离心15分钟并通过0.2um的Acropak 1500过滤器胶囊(颇尔公司(Pall))澄清。

[0817] 使用mAbSelect Sure树脂(通用电气医疗集团(GE Healthcare))从所澄清的上清液中纯化表达的抗体。在上样各个培养上清液之前,用1×D-PBS(pH 7.2)平衡MabSelect SuRe Protein A柱。通过用1×D-PBS(pH 7.2)充分洗涤来去除未结合的蛋白质。用0.1M的乙酸钠(pH 3.5)洗脱结合的蛋白质。将峰级分用2.5M的Tris(pH 7.2)中和并合并。将所中和的级分池透析到1×dPBS中用于测定和生物物理表征,或者用于双特异性DuoBody组装。

[0818] 通过测量OD280nm处的吸光度来确定每个洗脱池的蛋白质浓度,并使用基于氨基酸序列的吸光度消光系数进行计算。

[0819] 实施例3:使用纯化的亲本mAb的Fab臂交换

[0820] CD33×CD3双特异性抗体的形成需要两种亲本mAb,一种是对靶标臂具有特异性的(例如CD33),一种是对效应臂具有特异性的(例如CD3)。将CD33 mAb与高亲和力(CD3B219)或低亲和力CD3臂(CD3B376)臂重组。这些亲本mAb是IgG4 PAA形式(Labrijn等人,2013年),其中靶标亲本(CD33)包含K409R突变(IgG4的天然氨基酸),而杀伤亲本(CD3)包含F405L突变和R409K。单特异性抗CD3抗体表达为IgG4,在其Fc区中具有Fc置换S228P、F234A、L235A、F405L和R409K(CD3臂)(根据EU索引进行编号)。如上所述表达和纯化单特异性抗体。在纯化后,将亲本CD33抗体与所需亲本CD3抗体在75mM的半胱胺-HCl中在还原条件下混合,并在31℃下温育5小时。重组反应基于摩尔比,其中将设定量的CD33抗体(例如,10mg或约74.6纳摩尔)与CD3抗体(例如,约67.8纳摩尔)组合,其中CD33抗体的添加量比CD3抗体高6%。CD33抗体原液的浓度在0.8mg/mL至6mg/mL之间变化,并且重组反应的体积在每个配对中都不同。重组反应随后用PBS透析过夜以去除还原剂。用过量的CD33抗体(比率)进行CD33×CD3双特异性抗体反应,以使重组后剩余的未反应CD3亲本抗体的量最小化。

[0821] 产生的最终CD33×CD3双特异性抗体以及用于重组反应的亲本mAb(即CD33、CD3或空白)一起列于表10中。

[0822] 选择的CD33命中也与非杀伤臂(空白)配对以产生用于测试目的阴性对照。对于对

照双特异性抗体,生成、纯化B2M1(IgG4 PAA形式的RSV抗体),并将其分别与CD3臂CD3B219和CD3B376-F405L、R409K组合以生成CD3B288(CD3×空白)和CD3B510(CD3B376×空白)或与CD33臂C33B836、C33B806、C33B782、C33B792、C33B760、C33B830、C33B799、C33B778、C33B777组合以生成C33B941、C33B943、C33B946、C33B945、C33B949、C33B942、C33B944、C33B947、C33B948(CD33×空白)。

[0823] 表10:CD33×CD3双特异性抗体

[0824]

双特异性抗体	亲本	HC Pep ID	HC Pep SEQ ID	HC Nuc SEQ ID	LC Pep ID	LC Pep SEQ ID	LC Nuc SEQ ID
C3CB7	C33B836	C33H80	52	94	C33L73	136	178
	CD3B219	CD3H141	244	247	CD3L66	250	253
C3CB5	C33B830	C33H84	51	93	C33L66	135	177
	CD3B219	CD3H141	244	147	CD3L66	250	253
C3CB4	C33B806	C33H69	50	92	C4LL152	134	176
	CD3B219	CD3H141	244	247	CD3L66	250	253
C3CB16	C33B799	C33H98	49	91	C33L69	133	175
	CD3B219	CD3H141	244	247	CD3L66	250	253
C3CB14	C33B792	C33H87	48	90	C33L35	132	174
	CD3B219	CD3H141	244	247	CD3L66	250	253
C3CB12	C33B782	C33H72	47	89	C33L40	131	173
	CD3B219	CD3H141	244	247	CD3L66	250	253
C3CB11	C33B778	C33H66	46	88	C33L60	130	172
	CD3B219	CD3H141	244	247	CD3L66	250	253
C3CB10	C33B777	C33H65	45	86	C33L47	129	171
	CD3B219	CD3H141	244	247	CD3L66	250	253
C3CB8	C33B760	C33H45	44	85	C33L11	128	170
	CD3B219	CD3H141	244	247	CD3L66	250	253
C3CB97	C33B836	C33H80	52	94	C33L73	136	178
	CD3B376	CD3H219	245	248	CD3L150	251	254
C3CB98	C33B830	C33H84	51	93	C33L66	135	177
	CD3B376	CD3H219	245	248	CD3L150	251	254
C3CB99	C33B806	C33H69	50	92	C4LL152	134	176
	CD3B376	CD3H219	245	248	CD3L150	251	254
C3CB100	C33B799	C33H98	49	91	C33L69	133	175
	CD3B376	CD3H219	245	248	CD3L150	251	254
C3CB101	C33B792	C33H87	48	90	C33L35	132	174
	CD3B376	CD3H219	245	248	CD3L150	251	254
C3CB102	C33B782	C33H72	47	89	C33L40	131	173
	CD3B376	CD3H219	245	248	CD3L150	251	254
C3CB103	C33B778	C33H66	46	88	C33L60	130	172
	CD3B376	CD3H219	245	248	CD3L150	251	254
C3CB104	C33B777	C33H65	45	86	C33L47	129	171
	CD3B376	CD3H219	245	248	CD3L150	251	254

[0825]

C3CB105	C33B760	C33H45	44	85	C33L11	128	170
	CD3B376	CD3H219	245	248	CD3L150	251	254
C33B941	C33B836	C33H80	52	94	C33L73	136	178
	B23B49	B23H1	246	249	B23L3	252	255
C33B942	C33B830	C33H84	51	93	C33L66	135	177
	B23B49	B23H1	246	249	B23L3	252	255
C33B943	C33B806	C33H69	50	92	C4LL152	134	176
	B23B49	B23H1	246	249	B23L3	252	255
C33B944	C33B799	C33H98	49	91	C33L69	133	175
	B23B49	B23H1	246	249	B23L3	252	255
C33B945	C33B792	C33H87	48	90	C33L35	132	174
	B23B49	B23H1	246	249	B23L3	252	255
C33B946	C33B782	C33H72	47	89	C33L40	131	173
	B23B49	B23H1	246	249	B23L3	252	255
C33B947	C33B778	C33H66	46	88	C33L60	130	172
	B23B49	B23H1	246	249	B23L3	252	255
C33B948	C33B777	C33H65	45	86	C33L47	129	171
	B23B49	B23H1	246	249	B23L3	252	255
C33B949	C33B760	C33H45	44	85	C33L11	128	170
	B23B49	B23H1	246	249	B23L3	252	255
CD3B288	B23B39	B23H1	246	249	B23L3	252	255
	CD3B219	CD3H141	244	247	CD3L66	250	253
CD3B510	B23B39	B23H1	246	249	B23L3	252	255
	CD3B376	CD3H219	245	248	CD3L150	251	254
C3CB87	C33B903	C33H251	182	198	C33L117	214	230
	CD3B219	CD3H141	244	247	CD3L66	250	253
C3CB88	C33B904	C33H252	183	199	C33L118	215	231
	CD3B219	CD3H141	244	247	CD3L66	250	253
C3CB89	C33B905	C33H253	184	200	C33L119	216	232
	CD3B219	CD3H141	244	247	CD3L66	250	253
C3CB90	C33B907	C33H255	186	202	C33L121	218	234
	CD3B219	CD3H141	244	247	CD3L66	250	253
C3CB91	C33B908	C33H256	187	203	C33L122	219	235
	CD3B219	CD3H141	244	247	CD3L66	250	253
C3CB189	C33B904	C33H252	183	199	C33L118	215	231
	CD3B376	CD3H219	245	248	CD3L150	251	254

[0826] Pep:肽;Nuc:核苷酸;SEQ ID:SEQ ID NO

[0827] 实施例4:用CD33×CD3双特异性抗体的体外T细胞介导的细胞毒性测定

[0828] 进行体外T细胞介导的细胞毒性测定以评估CD33命中与CD3臂(CD3B219)配对是否介导杀伤表达AML细胞系OCI-AML5的CD33。简而言之,收获效应细胞(pan T细胞,购自Biological Speciality公司),对其计数、洗涤并将其重悬于含10%的FBS(Invitrogen公司)细胞培养基的RPMI(Invitrogen公司)中至1×10^6个细胞/ml。用CFSE(Invitrogen公司)标记靶细胞(MOLM13)并将其重悬于具有10%的FBS的RPMI中至2×10^5个细胞/mL。效应细胞和CFSE标记的靶细胞在无菌96孔圆底板中以效应细胞:CFSE标记的靶细胞(E:T)=5:1混合。将10μL的Fc阻断剂(ReoPro Fc片段)以及5μL双特异性抗体等分试样一起添加到含有各种浓度的每个孔中。将培养物在5%的CO_2下于37℃温育48小时。在48小时之后,向样本中添加LIVE/DEAD® Fixable Near-IR Dead Cell Stain缓冲液(Life Technologies公司),并且室温下,将培养物在暗处温育20分钟,然后将其洗涤并重悬于100μL至200μL的FAC缓冲

液中。使用CANTO II流式细胞仪(美国新泽西州富兰克林湖的BD生物科学公司(BD Biosciences;Franklin Lakes,NJ))测定药物诱导的细胞毒性,并使用FlowJo软件或Dive软件(BD生物科学公司(BD Biosciences))进行分析。感兴趣的群体是双阳性CFSE+/活/死+细胞。如图1所示,所有CD33×CD3多特异性抗体在48小时后诱导$CD33^+$MOLM-13细胞的T细胞重定向细胞毒性。表11汇总了用CD33×CD3多特异性抗体产生的EC_{50}值。将前4种抗体C3CB10、C3CB12、C3CB7和C3CB88用于进一步表征。

[0829] 表11:CD33×CD3 T-细胞介导的细胞毒性测定。13种CD33×CD3双特异性抗体的EC_{50}值的汇总

[0830]

先导	C3CB8	C3CB10	C3CB28	C3CB12	C3CB14	C3CB16	C3CB5	C3CB7
细胞毒性 EC_{50} (nM)	0.513	0.4728	0.6041	0.2677	0.538	0.6669	1.262	0.02129
先导	C3CB87	C3CB88	C3CB89	C3CB90	C3CB91			
细胞毒性 EC_{50} (nM)	0.067	0.11	0.41	10.56	0.35			

[0831] 实施例5:体外CD33×CD3介导的AML原代样本中AML母细胞的降低和T细胞活化

[0832] 为了进一步评估CD33×CD3双特异性抗体的细胞毒性潜力,使用前四种抗体使用AML患者全血进行离体细胞毒性测定(图2)。在该测定中,将各种双特异性抗体(与CD3臂CD3B219和CD3B376配对的CD33抗体)添加到来自AML患者的稀释全血中48小时的时间段而不提供另外的T细胞,因为该测定依赖于患者血液中自体同源T细胞的存在。在48小时后,将样本用CD3 PerCPCy5.5、CD25 PE、CD33 FITC和CD38 APC(所有抗体均购自美国加利福尼亚州圣地亚哥的Biolegend公司(Biolegend,San Diego,CA))染色。然后将样本在1X Lyse RBC Lysis Buffer(eBioscience公司)中至少洗涤3次。然后用LIVE/DEAD® Fixable Near-IR Dead Cell Stain缓冲液(Life Technologies公司)对样本进行染色。通过首先在双特异性抗体存在下定量AML患者癌细胞级分(定义为$CD3^-CD38^+$细胞)中的活$CD33^+$细胞来确定肿瘤细胞毒性的程度。细胞毒性使用以下公式计算为相对于PBS/未处理的对照的百分比:(PBS/未处理的对照中的$CD33^+$%-处理的样本中的$CD33^+$%)/(PBS/未处理的对照中的$CD33^+$%)。将T细胞活化计算为$CD3^+$级分中$CD25^+$事件的百分比。

[0833] 如图2所示,与任一CD3臂(CD3B376和CD3B219)配对的所有CD33先导抗体促进了48小时后与T细胞活化相关的总细胞毒性的剂量依赖性降低。空白臂对照抗体(空白×CD3B219和空白×CD3B376)未能显示出肿瘤细胞毒性或T细胞活化。该结果还表明CD33×CD3双特异性抗体在自体同源环境中起作用。这些结果代表了4个其他AML供体样本(数据未示出)。表12汇总了用CD33×CD3多特异性抗体产生的EC_{50}值。从EC_{50}值可以看出,与CD3臂(C3CB88、C3CB189)配对的C33B904以及与CD3臂(C3CB7、C3CB97)配对的C33B836是最有效的抗体。因此,这4种抗体是进一步表征的焦点。

[0834] 表12:CD33×CD3 T-细胞介导的体外细胞毒性测定。8种CD33×CD3双特异性抗体的EC_{50}值的汇总

[0835]

双特异性AbID	原代AML细胞杀伤EC_{50}(nM)
C3CB11	3.958
C3CB12	2.635
C3CB7	0.3315
C3CB88	0.6722
C3CB103	4.186
C3CB102	4.973
C3CB97	~0.2316
C3CB189	0.5782

[0836] 实施例6:CD33×CD3双特异性抗体与CD33的C2结构域结合并诱导表达CD33单核苷酸多态性(SNP)的细胞系的细胞毒性的证实

[0837] 用CD33×CD3双特异性抗体的体外T细胞介导的细胞毒性测定

[0838] 最近的研究显示,单核苷酸多态性(SNP)rs12459419存在于约50%的AML群体中并导致CD33的外显子2的跳越缺失导致了CD33的V结构域的缺失。该研究还显示,与CD33的V结构域结合的Mylotarg在表达SNP的患者中无效,并且因此降低了约50%AML群体的复发风险并改善了存活率(Lamba等人,2017,JCO,CD33 Splicing Polymorphism Determines Gemtuzumab Ozogamicin Response in De Novo Acute Myeloid Leukemia:Report From Randomized Phase III Children's Oncology Group Trial AAML0531)。鉴于上述研究中Mylotarg的数据,进行体外T细胞介导的细胞毒性测定以评估CD33命中(V结合C33B836与C2结合C33B904)是否与CD3臂(CD3B219或CD3B376)配对介导了表达SNP rs12459419细胞系的杀伤。简而言之,收获效应细胞(pan T细胞,购自Biological Speciality公司),对其计数、洗涤并将其重悬于含10%的FBS(Invitrogen公司)细胞培养基的RPMI(Invitrogen公司)中至1×10^6个细胞/ml。用CFSE(Invitrogen公司)标记靶细胞(KG1、SH2和OCIAML3)并将其重悬于具有10%的FBS的RPMI中至2×10^5个细胞/mL。选择KG1、SH2和OCIAML3以分别表示对于CD33 SNP rs12459419突变的野生型、杂合型和纯合型。将效应细胞和CFSE标记的靶细胞在无菌96孔圆底板中以效应细胞:CFSE标记的靶细胞比率(E:T)=5:1混合。将10μl的Fc阻断剂(ReoPro Fc片段)以及5μμL双特异性抗体等分试样一起添加到含有各种浓度的每个孔中。将培养物在5%的CO_2下于37℃温育48小时。在48小时之后,向样本中添加LIVE/DEAD® Fixable Near-IR Dead Cell Stain缓冲液(Life Technologies公司),并且室温下,将培养物在暗处温育20分钟,然后将其洗涤并重悬于100μL至200μL的FAC缓冲液中。使用CANTO II流式细胞仪(BD Biosciences)测定药物诱导的细胞毒性,并使用FlowJo软件或Dive软件(BD Biosciences)进行分析。感兴趣的群体是双阳性CFSE+/活/死+细胞。如图3所示,与空白组对照(空白组×CD3B219和空白组×CD3B376)不同,V结合和C2结合CD33×CD3多特异性抗体在48小时后诱导SNP rs12459419突变细胞系KG1的CD33+WT的T细胞重定向细胞毒性。相比之下,与V结合剂C33B836(C3CB97、C3CB7)不同,仅C2结合C33B904配对的双特异性抗体(C3CB189、C3CB88)介导了分别对rs12459419 SNP突变为杂合型或纯合型的SH2和OCIAML3细胞系的细胞毒性。为此,对C33B904配对的双特异性抗体(C3CB189、C3CB88)进行进一步分析和表征。总之,这些数据表明,与V结合竞争抗CD33抗体相比,CD33 C2结合双特异性抗体(诸如C33B904配对的双特异性抗体)在更广泛的AML患者中具有显示

疗效的潜力。

[0839] 实施例7:在体外全血MOLM-13细胞毒性测定中,体外CD33×CD3介导的MOLM-13和单核细胞中加标的降低

[0840] 为了评估CD33×CD3双特异性抗体在消除MOLM-13细胞和正常人单核细胞中加标时的细胞毒性潜力,利用使用具有外源添加的$CD33^+$ AML细胞系MOLM-13的正常健康人全血的体外细胞毒性测定。类似于上述实验,将各种双特异性抗体(与CD3臂CD3B219和CD3B376配对的CD33抗体)添加到来自6个不同正常人供体的稀释全血中48小时的时间段而不提供另外的T细胞,因为该测定依赖于供体血液中自体同源T细胞的存在。在稀释之前,对每个供体的血液中的T细胞的浓度进行计数。然后将血液用CFSE(Invitrogen)标记的MOLM-13细胞稀释,使得效应细胞:靶细胞比率(E:T)为1:5以模拟AML患者样本中的效应细胞:靶细胞。在48小后,将样本用CD3 PerCPCy5.5、CD25 PE、CD33 FITC和CD14 Pacific Blue(所有抗体购自均Biolegend公司)染色。然后将样本在1X Lyse RBC Lysis Buffer(eBioscience公司)中至少洗涤3次。然后用LIVE/DEAD®Fixable Near-IR Dead Cell Stain缓冲液(Life Technologies公司)对样本进行染色。通过首先在双特异性抗体存在下定量$CD14^+$单核细胞级分中的活$CD33^+$细胞来确定肿瘤细胞毒性的程度。通过对死$CFSE^+$细胞的百分比进行计数来确定MOLM-13细胞的细胞毒性。单核细胞的细胞毒性使用以下公式计算为相对于PBS/未处理的对照的百分比:(PBS/未处理的对照中的$CD33^+CD14^+$%-处理的样本中的$CD33^+CD14^+$%)/(PBS/未处理的对照中的$CD33^+CD14^+$%)。图4中的数据表明,两种CD33×CD3双特异性抗体(与CD3臂CD3B376和CD3B219配对的相同CD33先导C33B904)在48小时后特异性诱导MOLM-13细胞和$CD33^+$单核细胞的细胞毒性。将空白臂对照用作阴性双特异性抗体对照。空白臂对照显示MOLM-13和$CD33^+$单核细胞几乎没有细胞毒性活性。这些数据显示了6个不同正常供体的平均值。MOLM-13和$CD14^+$单核细胞的细胞毒性的平均EC_{50}值示于表13中。

[0841] 表13:CD33×CD3 T-细胞介导的体外细胞毒性测定。2种CD33×CD3双特异性抗体的EC_{50}值的汇总。

[0842]

双特异性Ab ID	MOLM13杀伤EC_{50}(nM)	$CD33^+CD14^+$杀伤EC_{50}(nM)
C3CB189	0.1677	1.156
C3CB88	0.671	0.506

[0843] 实施例8:CD33×CD3双特异性抗体与食蟹猕猴的物种交叉反应性的证实

[0844] 在用食蟹猕猴全血进行的体外细胞毒性测定中,体外CD33×CD3介导的单核细胞的降低

[0845] 为了证实功能交叉反应性并评估CD33×CD3双特异性抗体在消除正常食蟹猕猴单核细胞时的细胞毒性的潜力,利用使用健康食蟹猕猴全血的体外细胞毒性测定。类似于上述实验,将各种双特异性抗体(与CD3臂CD3B219和CD3B376配对的CD33抗体)添加到来自6个不同正常食蟹猕猴供体的稀释全血中48小时的时间段而不提供另外的T细胞,因为该测定依赖于供体血液中自体同源T细胞的存在。在48小后,将样本用CD3 PerCPCy5.5、CD25 PE、CD33 FITC和CD14 Pacific Blue(除了购自德国贝尔吉施格拉德巴赫的美天旎公司(Miltenyi;Bergisch Gladbach,Germany)的CD33抗体之外,所有抗体均购自Biolegend公司)染色。然后将样本在1×Lyse RBC Lysis Buffer(eBioscience公司)中至少洗涤3次,之

后用LIVE/DEAD®Fixable Near-IR Dead Cell Stain缓冲液(Life Technologies公司)染色。通过首先在双特异性抗体存在下定量$CD14^+$单核细胞级分中的活$CD33^+$细胞来确定单核细胞细胞毒性的程度。细胞毒性使用以下公式计算为相对于PBS/未处理的对照的百分比:(PBS/未处理的对照中的$CD33^+CD14^+$%-处理的样本中的$CD33^+CD14^+$%)/(PBS/未处理的对照中的$CD33^+CD14^+$%)。将T细胞活化计算为$CD3^+$级分中$CD25^+$事件的百分比。图5中的数据表明,CD33×CD3双特异性抗体(与CD3臂CD3B376和CD3B219配对的相同CD33先导C33B904)在48小时后特异性诱导$CD33^+$单核细胞的细胞毒性以及T细胞活化。将空白臂对照用作阴性双特异性抗体对照,并且显示几乎没有细胞毒性或T细胞活性。表14示出了6个不同的食蟹猕猴供体的平均值。

[0846] 表14:CD33×CD3 T-细胞介导的体外细胞毒性测定。2种CD33×CD3双特异性抗体的EC_{50}值的汇总。

[0847]

蛋白质AA ID	$CD33^+CD14^+$杀伤EC_{50}(nM)	T细胞活化EC_{50}(nM)
C3CB189	3.60	0.02
C3CB88	0.89	0.02

[0848] 实施例9:C3CB189和C3CB88在T细胞人源化NSG小鼠的MOLM-13人AML异种移植物中的功效

[0849] 在用2千万个T细胞人源化的雌性NOD.Cg-Prkdc^{sci} I12rg^{tm1Wjl}1/SzJ(NSG)小鼠中在已建立荧光素酶转染的弥散的MOLM-13人急性髓性白血病(AML)异种移植物中评估C3CB189和C3CB88的功效。在静脉注射肿瘤植入后的第5天,通过活生物发光成像(BLI)将动物随机分成n=10/组。以0.005mg/kg、0.05mg/kg和0.5mg/kg施用C3CB189和C3CB88或以0.5mg/kg施用空白×CD3抗体对照,每3至4天施用一次,持续6周。

[0850] 在肿瘤植入后的第13天,当每组保留至少八只动物时,计算通过生物发光测定的肿瘤生长抑制(TGI%)。与空白×CD3对照相比,在所有浓度下C3CB189(图6)和C3CB88(图8)均观察到统计意义上显著的肿瘤生长抑制。与用空白×CD3治疗的对照相比,0.005mg/kg、0.05mg/kg和0.5mg/kg的C3CB189分别引发76%、100%和82%的肿瘤生长抑制,并且0.005mg/kg、0.05mg/kg和0.5mg/kg的C3CB88分别引发100%、100%和91%的肿瘤生长抑制。

[0851] 用C3CB189和C3CB88处理导致肿瘤负荷降低和寿命增加(ILS)大于空白×CD3对照组的16天中位生存期。在不同剂量下,用C3CB189处理的动物的中位生存期为19天至27.5天(图7),而用C3CB88处理的动物的中位生存期为26至28.5天(图9)。与对照组相比,0.005mg/kg、0.05mg/kg和0.5mg/kg的C3CB189分别导致19%、72%和50%的寿命增加,并且C3CB88分别导致63%、78%和72%的寿命增加。

[0852] 实施例10:CD33抗体在体外蛋白质A药物缀合物细胞活力测定中的内化的证实

[0853] 使用预上样的蛋白质A药物缀合物A-MMAF进行体外细胞活力测定,以检测配体结合的靶抗体的内化。用一批抗CD33抗体、C33B782、C33B806、C33B836、C33B904、C33B937和同种型对照抗体CNTO9412在AML细胞系MOLM13中进行该基于细胞的功能测定。在该测定法中,仅测试了靶抗体作为对照,以区分由于抗体内化而引起的细胞毒性和由于测试抗体自身的活性而引起的细胞毒性。图10示出了在37℃、5%的CO_2下温育72小时之后MOLM13中蛋白质A-MMAF结合的抗体的细胞毒性。在MOLM13细胞中观察到所有五种CD33抗体的浓度依赖性细

胞毒性,这表明在该细胞系中所有五种抗体均内化。同种型对照抗体CNTO9412不显示显著的浓度依赖性细胞毒性,这表明这些CD33抗体在MOLM13细胞中的靶特异性内化。表15示出了五(5)种CD33×CD3双特异性抗体的EC_{50}值。

[0854] 结果还表明抗体C33B836在MOLM13细胞中具有比其他更好的内化。

[0855] 表14:CD33内化测定。五种抗CD33抗体的EC_{50}值的汇总。

[0856]

	C33B782	C33B806	C33B836	C33B904	C33B937	CNTO9412
EC_{50}(nM)	0.88	0.22	0.04	0.96	1.92	

[0857] 实施例11:证实CD33抗体可介导ADCC活性

[0858] 为了表征抗CD33 mAb的抗体依赖性细胞介导的细胞毒性(ADCC)活性,利用健康供体NK效应细胞和MOLM-13和MV4-11 AML靶细胞进行体外ADCC测定。在发起ADCC测定之前,将健康供体NK细胞(美国宾夕法尼亚州科尔马的Biological Specialty公司(Biological Specialty Corporation;Colmar,PA)的供体CC00061和M7015))接种在补充有1×10^{-6}M的氢化可的松(干细胞)、7.5ng/ml的重组人IL-2(美国明尼苏达州明尼阿波里斯市的安迪生物公司(R&D Systems;Minneapolis,MN))、1%的丙酮酸钠(Life Technologies公司)、1%的非必需氨基酸(Life Technologies公司)、1%青霉素链霉素(Life Technologies公司)的MyeloCult H5100生长培养基(美国加利福尼亚州温哥华市Stem Cell Technologies公司(Stem Cell Technologies;Vancouver,CA))中16小时至24小时。在测定当天,将1×10^{6}个细胞/ml的MOLM-13和MV4-11细胞在37℃下用10μM钙黄绿素AM标记30分钟。在标记之后,将细胞洗涤三次以去除过量的钙黄绿素AM。随后,在不同浓度的抗CD33抗体的存在下,将1×10^{5}钙黄绿素AM标记的MOLM-13或MV4-11靶细胞与健康供体NK细胞(3×10^{5})在37℃下温育1.5小时。通过将Triton X100以0.5%的最终浓度添加到指定的对照样本孔中来产生最大裂解对照样本。用SpectraMax® M5多模读板机(美国加利福尼亚州森尼维尔市的Molecular Devices有限公司(Molecular Devices,LLC;Sunnyvale,CA,USA))通过485nm至535nm处的荧光测量钙黄绿素AM的释放。使用以下公式,通过将数据归一化为最大(Triton X100介导的)和最小(单独的效应细胞)裂解来确定细胞裂解百分比:裂解%=[(实验裂解-自发裂解)/(最大裂解-自发裂解)]*100。

[0859] IgG1低岩藻糖抗CD33抗体以浓度依赖性方式诱导ADCC(图11)。与C33B912.CLF相比,C33B48.CLF展示出更有效的针对MOLM-13和MV4-11细胞的ADCC活性,其最大有效浓度值的一半高出12至23倍(EC_{50},表16)。MOLM-13和MV4-11细胞响应于C33B48.CLF和C33B912.CLF的最大裂解是相似的。

[0860] 表16:CD33的ADCC测定。2种抗CD33抗体和2种细胞系的EC_{50}值的汇总

[0861]

	EC_{50} ADCC C33B48.CLF(nM)	EC_{50} ADCC C33B912.CLF(nM)
MOLM-13	0.023	0.292
MV4-11	0.113	2.008

[0862] 实施例12:靶向CD33的C3CB189抗体的结合特性,CD33是白血病母细胞丰富表达的抗原。

[0863] C3CB189是完全人免疫球蛋白G(IgG)4-PAA双特异性抗体,其靶向T细胞上的CD3受体复合物和髓细胞样细胞上的CD33。C3CB189以0.89pM的亲和力(K_d)与人重组(r)CD33结

合,并且以363pM的亲和力(K_d)与食蟹猕猴(cyno)rCD33结合。C3CB189还分别以151.32nM和43.83nM的亲和力($_{Kd}$)与人和食蟹猕猴rCD3e结合。C3CB189与表达CD33的AML细胞系KG-1、MOLM-13、Kasumi-1和OCI-AML3特异性地结合(图12)。如预期的,用阴性对照CD33×空白抗体观察到类似的结合模式,因为其包含单个抗CD33 Fab臂。阴性对照双特异性抗体空白×CD3以及空白×空白显示出对这些细胞无显著结合。所测试的双特异性抗体均不与CD33阴性细胞系CARNAVAL和KG-1ΔCD33(即,使用CRISPR遗传缺失CD33的KG 1细胞)结合(图12)。另外,与亲本HEK-293T细胞相反,C3CB189与表达食蟹猕猴CD33的HEK 293T细胞结合,这证实食蟹猕猴的交叉反应性(图12)。

[0864] 实施例13:C3CB189在体外杀伤$CD33^+$AML细胞系并活化T细胞

[0865] 接下来使用T细胞介导的细胞毒性测定来评估C3CB189在各种细胞系中的体外活性,这些细胞系包括$CD33^+$细胞系,诸如MOLM-13、KG-1、SKNO-1、Kasumi-1和OCI-AML3以及$CD33^{no/low}$细胞系诸如CARNAVAL和KG1ΔCD33。用来自六个健康供体和片段可结晶区域(Fc)阻断剂的分离的pan人$CD3^+$T细胞建立测定。添加Fc阻断剂以防止Fc介导的C3CB189增长,因为IgG4 Fc区中的PAA突变不会使其完全沉默(Vafa等人,2014年),并且因为Fcγ受体(FcγR)通常在AML细胞上表达(Ball等人,1989年)。

[0866] 如图13中所见,在48小时后当与纯化的T细胞组合时C3CB189展示出$CD33^+$AML细胞系的T细胞介导的细胞毒性(图13)。MOLM-13、KG-1、Kasumi-1和OCI-AML3的中值半最大有效浓度(EC_{50})[以及EC_{20}值]分别是0.1307[0.0283]、0.1677[0.0525]、0.05[0.0366]和0.1826[0.0844]nM(图2B)。对于CD33阴性细胞系CARNAVAL和KG-1ΔCD33或对照双特异性抗体(空白×CD3或CD33×空白;参见图13)未观察到细胞毒性。我们证实,通过用CD123×CD3双特异性抗体进行细胞毒性测定,KG1ΔCD33细胞确实可被T细胞靶向(图14A)。

[0867] 在细胞毒性测定中还体外评估了在$CD33^+$肿瘤细胞系的存在下由C3CB189诱导的T细胞活化程度,其中CD25表达被测量为活化的指标。如图2C所示,当用$CD33^+$肿瘤细胞系和健康供体pan T细胞温育时C3CB189诱导T细胞活化,而用$CD33^-$CARNAVAL和KG-1ΔCD33细胞观察到极少的T细胞活化或未观察到T细胞活化。MOLM-13、KG-1、Kasumi-1和OCI-AML3的中值EC_{50}[EC_{20}]值分别是0.0283[0.0077]、0.0664[0.0256]、0.0432[0.0267]和0.0500[0.0178]nM(图15C)。C3CB189在不存在靶细胞的情况下不引起T细胞的活化,这证实T细胞活化的特异性(图14B)。CD33×空白对照抗体在任何细胞系中不诱导T细胞活化。在$CD33^+$和$CD33^-$细胞系的存在下,空白×CD3对照抗体在最高浓度533nM和53nM下诱导T细胞活化,但在任何其他剂量下不能介导活化。重要的是,仅在存在$CD33^+$细胞系的情况下而不在存在$CD33^-$细胞系的情况下(图15A)或当T细胞在不存在靶细胞的情况下温育时(图14B),C3CB189显示出T细胞活化的特异性诱导。

[0868] 最后,还在上述用Kasumi-1细胞系进行的体外T细胞重定向测定中评估细胞因子应答。C3CB189导致分泌了几种细胞因子,包括干扰素γ(IFN-γ)、肿瘤坏死因子α(TNF-α)、白介素(IL)-2和IL-8(补充图3)。这些数据与图13和图15A至图15C中所示的细胞毒性和T细胞活化数据一致。细胞因子应答的中值EC_{50}和产生最大可能效应(EC_{20})值的20%的浓度的汇总报告于表17中。

[0869] 表17.在用纯化的T细胞和Kasumi-1靶细胞的T细胞重定向测定中C3CB189介导的细胞因子释放的有效浓度值。EC值以nM为单位。n表示6个供体中可以确定EC值的数量。

[0870]

细胞因子	n	中值 EC_{20}	中值 EC_{50}	中值 EC_{90}
IFN-γ	6	0.048	0.16	1.409
IL-1β	6	0.013	0.045	0.226
IL-2	4	0.090	0.346	5.282
IL-4	4	0.054	0.078	0.153
IL-8	6	0.015	0.042	0.246
IL-10	6	0.052	0.123	1.271
IL-13	5	0.008	0.034	0.103
TNF-α	6	0.049	0.208	3.530

[0871] 实施例14:C3CB189示出体内有效的抗肿瘤活性

[0872] 评估了C3CB189在T细胞人源化NSG小鼠中的两种已建立异种移植肿瘤模型中的功能。在已建立的皮下KG-1¯荷瘤小鼠中,与空白×CD3处理的对照动物相比,以0.1mg/kg、0.5mg/kg和1mg/kg施用C3CB189进行处理分别引发41%、92%和87%的肿瘤生长抑制(对于0.5mg/kg和1mg/kg,P<0.0001,图16A)。0.5mg/kg和1mg/kg的C3CB189在第55天也分别导致6种和7种完全应答。

[0873] 在已建立的弥散的荧光素酶表达的MOLM-13模型(MOLM-13-luc)中,在静脉内注射后确认AML细胞归巢到骨髓(BM)后开始C3CB189处理。与空白×CD3对照处理小鼠相比,每隔3天至4天施用0.005mg/kg、0.05mg/kg和0.5mg/kg的C3CB189显著抑制肿瘤生长,如通过生物发光所评估的(分别为76%、100%和82%)(图17)。0.005mg/kg、0.05mg/kg和0.5mg/kg的C3CB189分别导致19%、72%和50%的统计意义上显著增加的寿命(P<0.0001,图16B),这与生物发光所观察到的BM、脊柱和后肢的肿瘤负荷降低相关(图16C)。在研究结束时,在第55天,通过BLI评估,用0.05mg/kg的C3CB189处理的三只动物显示出完全应答。

[0874] 此外,通过流式细胞术测量(图16D),用0.05mg/kg和0.005mg/kg较小程度的C3CB189处理的MOLM-13-Luc荷瘤小鼠在第11天在骨髓中显示出肿瘤细胞减少和$CD3^+$T细胞浸润增加,并且通过IHC $CD8^+$T细胞浸润增加(图3E)。这些数据是相关的,因为BM通常是AML中对白血病干细胞(LSC)的抗性位点并且残留的疾病最少。这些数据一起证实C3CB189通过募集T细胞到T细胞人源化小鼠中的肿瘤位点来抑制两种AML肿瘤模型的肿瘤生长。

[0875] 实施例15:C3CB189介导在健康全血中加标的AML细胞以及来自原代患者样本的AML母细胞的细胞毒性

[0876] 据报道,CD33的胞外域(ECD)从细胞中脱落;因此,正常样本和患者样本可包含可溶性CD33(sCD33)。研究显示,在AML患者血浆中检测到大约4ng/mL至30ng/mL的sCD33(Biedermann,B.、Gil,D.、Bowen,D.T.和Crocker,P.R.(2007年),Leuk Res,第31卷,第211页至第220页)。该值高于在健康人血清中测定的0.6ng/mL至5.8ng/mL的浓度(Biedermann,B.、Gil,D.、Bowen,D.T.和Crocker,P.R.(2007年),Leuk Res,第31卷,第211页至第220页)。

[0877] 为了确定正常供体和AML供体中的生理sCD33水平,开发了免疫捕获偶联质谱(MS)测定。正常血清样本和AML血清样本的分析显示相似的平均sCD33水平分别为53.03ng/mL(1.91nM)和52.90ng/mL(1.90nM)(表18)。

[0878] 表18:对正常样本和AML患者样本中的sCD33水平的评估。使用质谱分析健康人和AML血清样本(n=20/每个)的sCD33水平。

[0879]

	样本	浓度(nM)	浓度（ng/ml）
正常人血清（NHS）	个体 1	0.23	6.15
	个体 2	NR	NR
	个体 3	NR	NR
	个体 4	0.21	5.59
	个体 5	NR	NR
	个体 6	0.25	6.73
	个体 7	0.24	6.39
	个体 8	NR	NR
	个体 9	0.23	6.14
	个体 10	0.21	5.69
	平均 NHS（可报告）	0.23	6.12
AML 供体血清（AML）	AML 供体 1	0.14	3.76
	AML 供体 2	0.14	3.71
	AML 供体 3	NR	NR
	AML 供体 4	0.15	3.92
	AML 供体 5	0.16	4.32

[0880]

AML 供体 6	0.13	3.61
AML 供体 7	NR	NR
AML 供体 8	0.17	4.44
AML 供体 9	0.14	3.81
AML 供体 10	NR	NR
平均 AML（可报告）	0.15	3.94

[0881] 为了在生理上更相关的环境中评估C3CB189的活性,我们使用人外周全血作为效应T细胞的来源,添加各种$CD33^+$肿瘤细胞作为靶标并温育48小时来进行T细胞介导的细胞毒性测定。C3CB189诱导$CD33^+$MOLM-13和Kasumi-1细胞的T细胞介导的细胞毒性,中值EC_{50}[EC_{20}]值分别为0.111[0.054]nM和0.124[0.06]nM(图17)。类似地,C3CB189导致T细胞(如CD25所示)、MOLM-13和Kasumi-1细胞的活化,中值EC_{50}[EC_{20}]值分别为0.037[0.017]nM和0.085[0.039]nM(图18A和图18B)。所测量的C3CB189介导的T细胞活化代表血液中的总T细胞活化,并且其反映了与杀伤外源$CD33^+$肿瘤细胞和可能的内源$CD33^+$外周血白细胞(诸如中性粒细胞和单核细胞,在该测定中未对细胞毒性进行测量)两者相关的活化。另外,这些数据表明尽管全血中存在基线水平的sCD33和其他$CD33^+$白细胞,C3CB189介导了肿瘤细胞杀伤。

[0882] 接下来使用来自AML供体的全血在离体细胞毒性测定中评估C3CB189在更临床相关的环境中诱导细胞毒性的能力。该系统依赖于患者自身血液中自体同源T细胞的存在来杀伤AML细胞。测量T细胞介导的$CD33^+$细胞的细胞毒性和T细胞活化的程度。诱导$CD33^+$母细胞的浓度依赖性细胞毒性(图19A)的C3CB189也与所有6个患者样本中增加的T细胞活化相关(图19B)。C3CB189诱导的最大细胞毒性为大约60％的$CD33^+$母细胞。空白臂对照抗体诱导有限的细胞毒性和T细胞活化。诱导细胞毒性和T细胞活化的C3CB189分别导致EC_{50}值在

0.052nM至9.52nM(中值:0.365nM)和0.03nM至5.109nM(中值:0.355nM)的范围内(图19A和图19B)。这些数据表明C3CB189在更生理的体外环境中和在基线sCD33水平的存在下有效杀伤$CD33^+$AML细胞。

[0883] 实施例16:C3CB189的食蟹猕猴交叉反应性的评估

[0884] 为了评估食蟹猕猴(cyno)是否是评估C3CB189活性的合适模型,我们首先通过FACS分析研究从6个健康食蟹猕猴获得的白细胞上的CD33表达。结果发现食蟹猕猴外周血中的T细胞和B细胞具有低至零水平的CD33表达(图20)。大约75%至96%的食蟹猕猴中性粒细胞以7,545分子/细胞的平均抗原密度表达CD33(图20)。另一方面,$CD33^+$食蟹猕猴单核细胞的百分比在6个供体中是可变的,范围为0%至84%,其中平均抗原密度为2,146个分子/细胞(图20)。

[0885] 接下来,为了证实食蟹猕猴交叉反应性并评估C3CB189消除正常食蟹猕猴单核细胞和中性粒细胞的细胞毒性潜力,我们使用健康食蟹猕猴全血以及外源添加的$CD33^+$MOLM-13细胞进行了体外细胞毒性测定。在该系统中,还监测了$CD33^+$正常食蟹猕猴单核细胞和正常食蟹猕猴中性粒细胞的耗尽以及T细胞的活化。实际上,在体外温育48小时之后,C3CB189在体外介导了$CD33^+$MOLM-13细胞(EC_{50}:0.013nM至0.452nM)以及$CD33^+$正常食蟹猕猴单核细胞(EC_{50}:0.625nM至5.636nM)和正常食蟹猕猴中性粒细胞(EC_{50}:0.013nM至0.714nM)的杀伤(图21)。空白×CD3对照显示出所有$CD33^+$靶细胞的有限细胞毒性,并且仅在533nM的最高剂量下显示出T细胞活化。这些数据一起显示出C3CB189的功能性食蟹猕猴的交叉反应性,并且建立$CD33^+$食蟹猕猴和中性粒细胞作为在非人灵长类研究中的潜在的药效动力学(PD)标志物。这些数据还显示出C3CB189可介导食蟹猕猴T细胞对人AML细胞系的耗尽。重要的是,这些结果验证食蟹猕猴作为C3CB189的适当功效模型。

[0886] 实施例17:C3CB189介导食蟹猕猴中CD33+白细胞的降低

[0887] 为了评估体内C3CB189的药代动力学(PK)和药效动力学(PD),将C3CB189作为单一静脉注射剂量施用给食蟹猕猴。PK曲线示于图22A中。C3CB189在0.05mg/kg至1mg/kg剂量范围内表现出具有近似线性PK的典型单克隆抗体(mAb)的PK特性。C3CB189的所估计的平均总清除率是13.03mL/d/kg至21.39mL/d/kg,分布体积是89.14mL/kg至154.91mL/kg,并且终末半衰期为4.20天至5.06天。观察到在1mg/kg剂量组动物中在第10天之后C3CB189的消除明显加速。这最可能与抗药物抗体(ADA)的发展相关,但在该研究中未测试ADA。

[0888] 与预期的作用机制一致,在单次静脉注射C3CB189后观察到T细胞活化的剂量依赖性增加($CD25^+$%),在给药后24小时的第一时间点观察到T细胞毒性淋巴细胞($CD8^+/CD4^-$)上的峰值$CD25^+$%(图22B)。T辅助淋巴细胞($CD4^+/CD8^-$)在C3CB189给药后也表现出类似的活化($CD25^+$%)曲线(数据未示出)。C3CB189施用还导致在给药后2小时被分析的细胞因子(IFNγ、IL-10、IL-2、IL-6、MCP-1和TNFα)的血浆浓度的剂量依赖性增加(图23)。除IL-10和MCP-1之外,细胞因子在给药后24小时回到低于定量下限(LLOQ)水平。

[0889] C3CB189相关剂量导致$CD33^+$粒细胞(中性粒细胞)持续降低。与单核细胞上较低的CD33表达水平一致,还观察到$CD33^+$单核细胞的更瞬时的降低。粒细胞和单核细胞的浓度-时间曲线分别在图22C和图22D中示出。虽然粒细胞和单核细胞从外周血的初始快速消失可与和T细胞活化相关联的瞬时白细胞边缘化相关,但$CD33^+$粒细胞/单核细胞群的减低却更持久。具体地讲,粒细胞群体的降低到第8天一直处于接近最大水平,之后逐渐恢复。单核细

胞的回弹较早发生并且更显著。

[0890] 在以0.01mg/kg至30mg/kg范围内的剂量水平多次静脉施用后,在另外两项食蟹猕猴研究中也研究了C3CB189。C3CB189相关变化通常与单剂量后观察到的变化一致,并且C3CB189在这些剂量水平下耐受性良好(数据未示出)。这些数据一起提供C3CB189介导活性的证据,同时保持对食蟹猕猴的耐受性。

[0891] 实施例18:不考虑rs12459419 SNP的基因型,C3CB189介导的$CD33^+$细胞系和患者样本的细胞毒性

[0892] SNP rs12459419(C>T;外显子2中的Ala14Val)存在于CD33的调控剪接位点内,其中T等位基因导致预测编码缺乏V set结构域的CD33蛋白质同种型的转录物的表达增加。最近的数据进一步证实,具有SNP rs12459419 CC基因型(约50%的参与者)的受试者在GO治疗之后复发风险显著降低并且无事件存活率(EFS)和无疾病存活率更高,而在具有CT或TT基因型的患者中看不到这种有益效果(Lamba,J.K.、Chauhan,L.、Shin,M.、Loken,M.R.、Pollard,J.A.、Wang,Y.C.、Ries,R.E.、Aplenc,R.、Hirsch,B.A.、Raimondi,S.C.等人,(2017年)J Clin Oncol,第35卷,第2674页至2682页)。鉴于上述研究中的GO数据,我们评估了SNP-rs12459419基因型对C3CB189活性的影响。我们首先经由氢氘交换(HDX)作图确认,C33B904(C3CB189的CD33亲本臂的IgG_4型式)与CD33的C2结构域(图24A中的IgC)中的不同区域结合并且在V区(图24A中的IgV)中不具有结合。相比之下,C33B836(C3CB97的CD33亲本臂的IgG_4型式)与CD33的V结构域结合并且在CD33的C2区中不具有结合。接下来,我们使用体外T细胞介导的细胞毒性测定来比较由C3CB97(V结合剂)介导的应答与由C3CB189(C2结合剂)介导的应答。基于基因分型数据(图25A),选择KG-1、SH2和OCI-AML3分别表示对于CD33 SNP rs12459419突变的野生型CC、杂合型CT和纯合型TT。与空白×CD3对照不同,V结合和C2结合CD33×CD3双特异性抗体在48小时诱导$CD33^+$KG-1“CC”细胞系的T细胞重定向细胞毒性(图6B)。相比之下,与V结合剂C3CB97不同,仅C2结合剂C3CB189介导SH2“CT”细胞系和OCI-AML3“TT”细胞系的细胞毒性,而对于V结合剂C3CB97未观察到活性。

[0893] 然后我们使用AML患者全血进行体外细胞毒性测定以延长并确认我们的上述观察结果。基于基因分型数据,患者样本6095、6116和6152被鉴定为CC基因型,而患者样本6129和USAML0078分别被鉴定为CD33 SNP rs12459419的杂合型CT(图25B)。没有样本被鉴定为CD33 SNP rs12459419的纯合型TT。V结合和C2结合CD33×CD3双特异性抗体的确诱导相当的被鉴定为CC基因型的AML样本的T细胞重定向细胞毒性;相比之下,与V结合C3CB97相比,C2结合C3CB189显示出对于SNP rs12459419突变为杂合型(CT)的AML样本的细胞毒性增强(图24B)。接下来,鉴于SNP rs12459419是种系突变,我们用来自25个不同健康供体的经纯化的单核细胞和匹配的自体同源T细胞进行类似的体外实验。所有25个供体的基因分型数据在图25C中示出。与C3CB189结合CD33的C2结构域的事实一致,C3CB189介导了原代人单核细胞的细胞毒性,无论它们的SNP基因型状态如何(参见图24C)。相比之下,当样本对于SNP rs12459419为CT或TT时,V结合C3CB97介导的细胞毒性有限至无细胞毒性。这三条证据一起表明C3CB189可通过靶向保守的C2表位来证明在更广泛的AML患者群组中的功效。

[0894] 本领域的技术人员应当理解,在不脱离本发明的广义的发明构思的情况下,可对上述实施方案作出修改。因此,应当理解,本发明不局限于所公开的特定实施方案,但本发明旨在涵盖在本发明实质和范围内的修改,如本说明书所定义。

[0895] 表19:重链可变区序列

HC ID	ID	氨基酸序列
B23H1	256	QITLKESGPTLVKPTQTLTLTCTFSGFSLSTSGMGVSWIRQPPGKALE WLAHIYWDDDKRYNPSLKSRLTITKDTSKNQVVLTMTNMDPVDT ATYYCARLYGFTYGFAYWGQGTLVTVSS
CD3H141	257	EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGL EWVARIRSKYNNYATYYAASVKGRFTISRDDSKNSLYLQMNSLKT EDTAVYYCARHGNFGNSYVSWFAYWGQGTLVTVSS
CD3H219	258	QVQLQQSGPRLVRPSQTLSLTCAISGDSVFNNNAAWSWIRQSPSRG LEWLGRTYYRSKWLYDYAVSVKSRITVNPDTSRNQFTLQLNSVTPE DTALYYCARGYSSSFDYWGQGTLVTVSS
C33H442	259	QLQLQESGPGLVNPSETLSHTCTVSGGSISSSSHYWGWIRQPPGKGL EWIGKIYYSGNTYYNPSLKSRVTISIDTSKNQFSLKMSSVTAADTAV YYCARLADVVVVPAARYFDSWGQGTLVTVSS
C33H444	260	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRG LEWLGRTYYRSKWYNDYAVSVRSRITINPDTSKNQFSLQLNSVTPE DTAVYHCARETMFRGLMDYWGQGTLVTVSS
C33H445	261	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQSPGKGL EWVAVISYDGSNKYCADSVKGRFTISRDNSKSTLYLQMNSLRAEDT AVYYCAKDFRSLDWLPPDSTSYDGMDVWGQGTTVTVSS
C33H446	262	QVQLVQSGSELKKPGASVKVSCKASGYTFTNYAMNWVRQAPGQG LEWMGWINTNTGNPTYAQAFTGRFVFSLDTSVSTAYLQISSLKAED TAVYYCARDREVRDYWGQGTLVTVSS
C33H448	263	QLQLQESGPGLVKPSETLSLTCTVSGGSIRSTNYYWGWIRQPPGKG LEWIGTIYYSGNTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTA VYYCARLADVVVVPAARYFDYWGQGILVTVSS
C33H449	264	QLQLQESGPGLVKPSETLSLTCTVSGGSIRSSGFYWGWIRQPPRKGL EWIGTIYYSGNTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAV YFCARLADVVVVPAARYFDNWGQGTLVTVSS
C33H551	265	QLQLQESGPGLVKPSETLSLTCTVSGGSISTGRYYWGWIRQPPGKG VIWIGNIYYSGNTYYNPSLKSRVTISVDTSKNQFSLKLNSVTAADTA VYYCARLGSLVVVPAAMSFDYWGQGTLVTVSS
C33H552	266	QLQLQESGPGLVKPSETLSLTCTVSGGSIRGSSYYWGWVRQPPGKG LEWIGSIYSSGNTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTA LYYCARLGSLVVVPAAMSFDYWGQGTLVTVSS
C33H555	267	QVQLQESGPGLVKPSGTLSLTCAVSGGSISSSNWWSWVRQPPGRGL EWIGEIYHSGNTNNSPSLKSRVTISADKSKNQFSLKLSSVTAADTAV YFCARIIAVARYFDSWGQGTLVTVSS
C33H665	268	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGL EWVVVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAED

[0896]

[0897]

		TAVYYCAKDFRDFDWLPPDSTSYHGMDVWGQGTTVTVSS
C33H66	269	QVQLVESGGGVVQPGRSLRLSCVASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEGTAVYYCAKDFRSFDWLPPDSASYHGMDVWGQGTTVTVSS
C33H68	270	EVQLLESGGGLVQPGGSLGLSCAASGFTFSGYAMSWVRQAPGKGLNWVSAIDYSGNDTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKESQLLHGLFEHWGQGILVTVSS
C33H69	271	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLDWIGSINYSGSTYYNPSLKSRVTISVDTSKIQFSLKLRSVTAADTAVYYCARLDGYESPFDYWGQGTLVTVSS
C33H70	272	QLQLQESGPGLVKPSETLSLTCTVSGGSIRGSSYYWGWIRQPPGKGLEWIGSIYSSGNTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARLGSLVVVPAAMSFDYWGQGTLVTVSS
C33H72	273	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKQHGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDRDLGYFDYWGQGTLVTVSS
C33H73	274	EVQLLESGGGLVQPGGSLRLSCAASRFTFSSYAMTWVRQAPGKGLEWVSTINISGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTKGGYSSGPFDYWGQGTLVSVSS
C33H74	275	QVQLVESGGGVVQPGRSLRLSCAASRFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVHYCAKDFRSFDWLPPDSASYHGMDVWGQGTTVTVSS
C33H76	276	EVQLLESGGGLVQPGGSLRLSCAASGFTFNYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDISKNTLYLQMNSLRAEDTAVYYCARTYNSGYYDGDFDYWGQGTLVTVSS
C33H78	277	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCAKDFRYFDWLPPDSSSYYGMDVWGQGTTVTVSS
C33H80	278	QVQLVQSGSELRKPGASVKVSCKASGYTFTNYAMNWVRQAPGQGLEWMGWINTNTGNPTYAQGFTGRFVFSLDTSVSSAYLQISSLKAEDTAMYYCATDRDRGTDYWGQGTLVTVSS
C33H81	279	QVQLVESGGGVVQPGRSLRLSCAASGFTFSAYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEGTAVYYCAKDFRSFDWLPPDSASYHGMDVWGQGTTVTVSS
C33H84	280	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDFRSFDWLPPDSTSYYGMDVWGQGTTVTVSS
C33H87	281	EVQLVESGGGFVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKQHGSEKYYVDSVKGRFTISRDNVKNSLYLQMNSLRTEDTAVYYCARDRDLGYFDYWGQGTLVTVSS
C33H88	282	QVQLVQSGSELKKPGASVKVSCKASGYTLTRSAMNWVRQAPGQGLEWMGWINTNTGNPTYAQGFTGRFVFSLDTSVNTAYLLISSLKTEDTAVYYCASDILPGYHEDYWGQGTLVTVSS
C33H90	283	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRTYYRSKWYNDYALSVQSRITINPDTSKNQFSLQLNSVTPEDTAVYYCAREVAVAASFDYWGQGTLVTVSS
C33H91	284	QLQLQESGPGLVKPSETLSLTCTVSGGSISSRSHYWGWIRQPPGVGLEWIGSIYYTGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAV

[0898]

		YYCARLADIVVVPAARYFDYWGQGTLVTVSS
C33H92	285	QLQLQESGPGLVKPSETLSLTCTVSGGSIRSSSYYWGWIRQPPGKGPEWIGSIYSSGNTYYNPSLKSRVTISVDTSKNQFSLKLISMTAADTAVFYCARLAATIVVPAARYFDCWGQGTLVTVSS
C33H98	286	EVQLVESGGGFVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKQHGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDRDLGYFDYWGQGTLVTVSS
C33H99	287	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMTWVRPAPGKGLEWVANIKRDGGEKYYVDSVKGRFTISRDNAANSLYLQMNSLRVEDTAVYYCARPFYDHFDYWGQGTLVTVSS
C33H108	288	QVQLVQSGSELKKPGASVKVSCKASGYTFSTYAMNWVRQAPGQGLEWMGWINTNTGNPTYAQGFTGRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARDRDRGTDYWGQGTLVTVSS
C33H249	289	EVQLVESGGGLVQPGRSLRLSCVASGFTFDDYAIHWVRQAPGKGLEWVSGLSWNGGNIGYADSVKGRFTISRDNAKNSLYLQMNSLKTEDTAFYYCTKDTPYGDYFDYWGQGTLVTVSS
C33H250	290	EVQLVESGGGLVQPGRSLRLSCAGSGFTFDDYAIHWVRQAPGKGLEWVSGLSWNGGNIGYADSVKGRFTISRDNAKNSLYLQLNSLKTEDTAFYYCAKDSPYGDYFDYWGQGTLVTVSS
C33H251	291	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGIGWSGGSIVYADSVKGRFKISRDNAKNSLYLQMNSLRAEDTALYYCAKDSPYGDFFDYWGQGTLVTVSS
C33H252	292	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGIGWSGGSIVYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDSPYGDFFDYWGQGTLVTVSS
C33H253	293	EVQLLESGGGLVQPGGSLKLSCTASGFTFRSYAMSWVRQAPGKGLEWVSAINGYGDGRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYSCAKDQGFGELFFDYWGQGTLVTVSS
C33H254	294	QVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMHWVRQAPDKGLEWVAVIWFDGNNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRELLFDYWGQGTLVTVSS
C33H255	295	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQVPGEGLEWVSGISWNGGDMVYADSVKGRFTISRDNAKNSLYLQMNSLRPEDTALYYCVKDMPYFDFLTGSDYYYYGMDVWGQGTTVTVSS
C33H256	296	QVQLVESGGGVVQPGRSLRLSCATSGFTFSNYGMHWVRQAPGKGLEWVAVIWYVGSHKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDGSLCFDYWGQGTLVTVSS

[0899] 表20:轻链可变区

[0900]

LC ID	ID	氨基酸序列
B23L3	297	DIVMTQSPDSLAVSLGERATINCRASQSVDYNGISYMHWYQQKPGQPPKLLIYAASNPESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQIIEDPWTFGQGTKVEIK
CD3L66	298	QTVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQAPRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNLWVFGGGTKLTVL
CD3L150	299	QSALTQPASVSGSPGQSITISCTGTSSNIGTYKFVSWYQQHPDKAPKVLLYEVSKRPSGVSSRFSGSKSGNTASLTISGLQAEDQADYHCVSYAGSGTLLFGGGTKLTVL
C33L8	300	SYELTQPPSVSVSPGQTASIICSGDKLGNKYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQAVDEADYYCQAWDSSTYVFGTGTKVTVL
C33L10	301	SYVLTQPPSVSVAPGQTARITCGGSNIGSKSVHWYQQKPGQAPVMVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDVVFGGGTKLTVL
C33L11	302	SYELTQPPSVSVSPGQTASITCSGHKLGDKYACWYQQKPGQSPVVVIYKDSKRPSGIPERFSGSNFGNTATLTISGTQAMDEADYYCQAWDSSTVVFGGGTKLTVL
IAPL24	303	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTVVFGGGTKLTVL
C33L58	304	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDYKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTYVFGTGTKVTVL
C33L59	305	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDYKRPSGIPERFSGSNSGNTATLTISGTQTMDEADYYCQAWDISTYVFGTGTKVTVL
C33L34	306	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQLRPGQSPILVIYQDSNRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTWVFGGGTKLTVL
N46L109	307	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTWVFGGGTKLTVL
C33L42	308	SYVLTQPPSVSVAPGQTARITCGGNNIGIKSVHWYQQKPGQAPVLVVYDDSDRPPGIPERFSGSNSGNTATLTITRVEAGDEADYYCQVWDSSSDHVVFGGGTKLTVL
C33L47	309	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVVVIYQDRKRPSGIPERFSGSNFGNTATLTISGTQAMDEADYYCQAWDSSTVVFGGGTKLTVL
C33L60	310	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDGKRPSGIPERFSGSNFGNKATLTISGTQAMDEADYYCQAWDRNTVVFGGGTKLTVL
C33L17	311	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKAGQPPKLLIYWASTRESGVPDRFSGSGSGTDFILIISSLQAEDVAVYYC

[0901]

		QQYYGTPWTFGQGTKVEIK
C4LL152	312	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPFTFGPGTKVDIK
C33L40	313	SYELTQPPSVSVSPGQTASITCSGNKLGAKFASWYQQKPGQSPVLVIYQDNKRPSGIPERFSGSNSGNTATLTISGTQAVDEADYYCQAWDSSTVVFGGGTKLTVL
C33L32	314	SYELTQPPSVSVSPGQTASITCSGDKLGDKYVRWYQQKTGQSPVLVMYQDSKRPSGIRERFYGSNSGNTATPTISGTQAVDEAEYYCQAWDSSTGVVFGGGTKLTVL
C33L38	315	SYELTQPPSVSVPPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDNKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWGRNTVVFGGGTKLTVL
C33L39	316	QSALTQPASVSGSPGQSIPISSTGTSSDDGKNNIVSWYQQHPGKAPKLMIYKDSKRPSGVSNRFSGSKSGNTASLTISGLQADDEADYHCCSYAGASNHVVFGGGTKLTVL
C33L57	317	SYELTQPPSVSVSPGQTASITCSGDELGNKYACWYQQKPGQSPVVVVYQDRKRPSGIPERFSGSNFGNTATLTISGTQAMDEADYYCQAWDSSTVVFGGGTKLTVL
C33L73	318	QSALTQPASVSGSPGQSITISCTGTSSDVGDYNYVSWYQQHPGKVPKLMIYDVSNRPSGVSNRFSGSMSGNTASLTISGLQAEDEADYYCSSYSSSSALEVFGGGTKLTVL
C33L53	319	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDNKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSNTVVFGGGTKLTVL
C33L66	320	SYELTQPPSVSVSPGQTASITCSGDKLGDKYVCWYQQKPGQSPVVVIHQDRKRPSGIPERFSGSNFGNTATLTISGTQAMDEADYYCQAWDSSTVVFGGGTKLTVL
C33L35	321	SYELTQPPSVSVSPGQTASITCSGDKLGNKYASWYQQKPGQSPVLVIYQDTKRPSGIPERVSGSNSGNTATLTISGTQAMDEADYHCQAWDSSTVVFGGGTKLTVL
C33L61	322	QSALTQPASVSGSPGQSITISCTGINSDVGSYDLVSWYQQHPGKAPKLLIYDGSERPSGVFGRFSGSKSDNTTSLTISGLQAEDEAAYYCCSYEVTTTYVVFGGGTKLTVL
C33L51	323	SYVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWSQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSNSDHVVFGGGTKLTVL
C33L44	324	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDSNRPSGIPERFSGSNSGNTATLTISETQAMDEADYYCQAWDSSTYVFGTGTKVTVL
C33L30	325	SYELTQPPSVSVSPGQTVSISCSGDRLGDKYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSSYVFGTGTKVTVL
C33L69	326	SYELTQPPSVSVSPGQTASITCSGDKLGSKFACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTVVFGGGTKLTVL
C33L37	327	SYVLTQPPSVAVAPGQTARITCGGSNIGKISVHWYQQKAGQAPVLVVHDDRARPSGIPERLSGSNSGTTATLTISRVEVGDEADYYCQVWNSS

[0902]

		SVHPVFGGGTKLTVL
C33L74	328	QSALTQPASVSGSPGQSITISCTGTSSDVGDDNYVSWYQQHPGKAPKLMIYDVSNRPSGVSNRFSGSKSGNTASLTISGLQSEDEADYYCSSYSSSTTLEVFGGGTKLTVL
C33L115	329	DIQMTQSPSSVWASVGDRVTITCRASQGISSWLAWYQQQPGKAPNLLIYRSSSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQDNSFPYTFGQGTKLEIK
C33L116	330	DIQMTQSPSSEWASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYGASSWQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQDNSFPYTFGQGTKLEIK
C33L117	331	DIVMTQSPDSLAVSLGERATINCKSSQTVLYSSNNKNYLAWYQQKPGQPPKLLISWASTRKSGVPDRFSGSGSGTDFTLTVSSLQAEDVAVYYCQHYYSTPYTFGQGTKLEIK
C33L118	332	DIVMTQSPDSLAVSLGERATINCKSSQTVFYSSNNKNYLAWYQQKPGQPPKLLISWASTRKSGVPDRFSGSGSGTDFTLTVSSLQAEDVAVYYCQHYYSTPYTFGQGTKLEIK
C33L119	333	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYCCQQYNSYPWTFGQGTKVEIK
C33L120	334	SYELTQPPSVSVSPGQTASITCSGDELGDMYACWYQQKPGQSPLVVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQAMDEAAYYCQTWDTRIAVFGGGTNLTVL
C33L121	335	SYELTQPPSVSVSPGQTASITCSGDNLGNEHVCWYHQKPGQSPVLVIYQNNKRPSGIPERFSGSNSGNTATLSISGTQATDEADYYCQAWDSTTAVFGGGTKLTVL
C33L122	336	SYELTQPPSVSVSPGQTANISCSGVTLGYNYAYWYQQKPGQSPILVISQDTQRPSGIPERFSGSNSGNTATLTISGTQAMDEAAYYCQAWDITTVLFGGGTKLTVL
C33L132	337	SYELTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQKPGQSPVLVIYQDGKRPSGIPERFSGSNFGNKATLTISGTQAMDEADYYCQAWDRNTVVFGGGTKLTVL
C33L41	338	SYELTQPPSVSVSPGQTASITCSGDKLGNKYASWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTVVFGGGTKLTVL

[0903] 表21:重链CDR1-3序列

[0904]

HC ID	ID	CDR1	ID	CDR2	ID	CDR3	ID
B23H1	256	GFSLSTSGM	339	YWDDD	340	LYGFTYGFA	341
CD3H141	257	GFTFNTY	342	RSKYNNYA	343	HGNFGNSYVSWFA	344
CD3H219	258	GDSVFNNNA	345	YYRSKWL	346	GYSSSFD	347
C33H42	259	GGSISSSSH	348	YYSGN	349	LADVVVVPAARYFD	350
C33H44	260	GDSVSSNSA	351	YYRSKWY	352	ETMFRGLMD	353
C33H45	261	GFTFSSY	354	SYDGSN	355	DFRSLDWLPPDSTSYDGMD	356
C33H46	262	GYTFTNY	357	NTNTGN	358	DREVRD	359
C33H48	263	GGSIRSTNY	360	YYSGN	361	LADVVVVPAARYFD	362
C33H49	264	GGSIRSSGF	363	YYSGN	364	LADVVVVPAARYFD	365
C33H51	265	GGSISTGRY	366	YYSGN	367	LGSLVVVPAAMSFD	368
C33H52	266	GGSIRGSSY	369	YSSGN	370	LGSLVVVPAAMSFD	371
C33H55	267	GGSISSSN	372	YHSGN	373	IIAVARYFD	374
C33H65	268	GFTFSSY	375	SYDGSN	376	DFRDFDWLPPDSTSYHGMD	377
C33H66	269	GFTFSSY	378	SYDGSN	379	DFRSFDWLPPDSASYHGMD	380
C33H68	270	GFTFSGY	381	DYSGND	382	ESQLLHGLFE	383
C33H69	271	GGSISSSSY	384	NYSGS	385	LDGYESPFD	386
C33H70	272	GGSIRGSSY	387	YSSGN	388	LGSLVVVPAAMSFD	389
C33H72	273	GFTFSSY	390	KQHGSE	391	DRDLGYFD	392
C33H73	274	RFTFSSY	393	NISGGS	394	GGYSSGPFD	395
C33H74	275	RFTFSSY	396	SYDGSN	397	DFRSFDWLPPDSASYHGMD	398
C33H76	276	GFTFNY	399	SGSGGS	400	TYNSGYYDGDFD	401
C33H78	277	GFTFSSY	402	SYDGSN	403	DFRYFDWLPPDSSSYYGMD	404

C33H80	278	GYTFTNY	405	NTNTGN	406	DRDRGTD	407
C33H81	279	GFTFSAY	408	SYDGSN	409	DFRSFDWLPPDSASYHGMD	410
C33H84	280	GFTFSSY	411	SYDGSN	412	DFRSFDWLPPDSTSYYGMD	413
C33H87	281	GFTFSSY	414	KQHGSE	415	DRDLGYFD	416
C33H88	282	GYTLTRS	417	NTNTGN	418	DILPGYHED	419
C33H90	283	GDSVSSNSA	420	YYRSKWY	421	EVAVAASFD	422
C33H91	284	GGSISSRSH	423	YYTGS	424	LADIVVVPAARYFD	425
C33H92	285	GGSIRSSSY	426	YSSGN	427	LAATIVVPAARYFD	428
C33H98	286	GFTFSSY	429	KQHGSE	430	DRDLGYFD	431
C33H99	287	GFTFSSY	432	KRDGGE	433	PFYDHFD	434
C33H108	288	GYTFSTY	435	NTNTGN	436	DRDRGTD	437
C33H249	289	GFTFDDY	438	SWNGGN	439	DTPYGDYFD	440
C33H250	290	GFTFDDY	441	SWNGGN	442	DSPYGDYFD	443
C33H251	291	GFTFDDY	444	GWSGGS	445	DSPYGDFFD	446
C33H252	292	GFTFDDY	447	GWSGGS	448	DSPYGDFFD	449
C33H253	293	GFTFRSY	450	NGYGDG	451	DQGFGELFFD	452
C33H254	294	GFTFSYY	453	WFDGNN	454	DRELLFD	455
C33H255	295	GFTFDDY	456	SWNGGD	457	DMPYFDFLTGSDYYYYGMD	458
C33H256	296	GFTFSNY	459	WYVGSH	460	DGSLCFD	461

[0905]

[0906] 表22:轻链CDR1-3序列

LC ID	ID	CDR1	ID	CDR2	ID	CDR3	ID
B23L3	297	SQSVDYNGISY	462	AAS	463	IIEDPW	464
CD3L66	298	STGAVTTSNY	465	GTN	466	WYSNLW	467
CD3L150	299	TSSNIGTYKF	468	EVS	469	YAGSGTL	470
C33L8	300	DKLGNKY	471	QDS	472	WDSSTY	473

[0907]

[0908]

C33L10	301	SNIGSKS	474	DDS	475	WDSSSDV	476
C33L11	302	HKLGDKY	477	KDS	478	WDSSTV	479
IAPL24	303	DKLGDKY	480	QDS	481	WDSSTV	482
C33L58	304	DKLGDKY	483	QDY	484	WDSSTY	485
C33L59	305	DKLGDKY	486	QDY	487	WDISTY	488
C33L34	306	DKLGDKY	489	QDS	490	WDSSTW	491
N46L109	307	DKLGDKY	492	QDS	493	WDSSTW	494
C33L42	308	NNIGIKS	495	DDS	496	WDSSSDHV	497
C33L47	309	DKLGDKY	498	QDR	499	WDSSTV	500
C33L60	310	DKLGDKY	501	QDG	502	WDRNTV	503
C33L17	311	SQSVLYSSNNKNY	504	WAS	505	YYGTPW	506
C4LL152	312	SQGISSW	507	AAS	508	ANSFPF	509
C33L40	313	NKLGAKF	510	QDN	511	WDSSTV	512
C33L32	314	DKLGDKY	513	QDS	514	WDSSTGV	515
C33L38	315	DKLGDKY	516	QDN	517	WGRNTV	518
C33L39	316	TSSDDGKNNI	519	KDS	520	YAGASNHV	521
C33L57	317	DELGNKY	522	QDR	523	WDSSTV	524
C33L73	318	TSSDVGDYNY	525	DVS	526	YSSSSALE	527
C33L53	319	DKLGDKY	528	QDN	529	WDSNTV	530
C33L66	320	DKLGDKY	531	QDR	532	WDSSTV	533
C33L35	321	DKLGNKY	534	QDT	535	WDSSTV	536
C33L61	322	INSDVGSYDL	537	DGS	538	YEVTTTYV	539
C33L51	323	NNIGSKS	540	DDS	541	WDSNSDHV	542
C33L44	324	DKLGDKY	543	QDS	544	WDSSTY	545
C33L30	325	DRLGDKY	546	QDS	547	WDSSSY	548
C33L69	326	DKLGSKF	549	QDS	550	WDSSTV	551
C33L37	327	SNIGKIS	552	DDR	553	WNSSSVHP	554
C33L74	328	TSSDVGDDNY	555	DVS	556	YSSSTTLE	557
C33L115	329	SQGISSW	558	RSS	559	DNSFPY	560
C33L116	330	SQGISSW	561	GAS	562	DNSFPY	563
C33L117	331	SQTVLYSSNNKNY	564	WAS	565	YYSTPY	566
C33L118	332	SQTVFYSSNNKNY	567	WAS	568	YYSTPY	569
C33L119	333	SQSISSW	570	KAS	571	YNSYPW	572
C33L120	334	DELGDMY	573	QDS	574	WDTRIA	575
C33L121	335	DNLGNEH	576	QNN	577	WDSTTA	578
C33L122	336	VTLGYNY	579	QDT	580	WDITTV	581
C33L132	337	DKLGDKY	582	QDG	583	WDRNTV	584
C33L41	338	DKLGNKY	585	QDS	586	WDSSTV	587

序列表

<110> Janssen Biotech, INC.

<120> 抗 CD33 抗体、抗 CD33/抗 CD3 双特异性抗体及其用途

<130> 688097.455US

<160> 591

<170> PatentIn 版本 3.5

<210> 1

<211> 364

<212> PRT

<213> 智人(Homo sapiens)

<400> 1

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

[0001]

Glu Val Gln Glu Glu Thr Gln Gly Arg Phe Arg Leu Leu Gly Asp Pro
85 90 95
Ser Arg Asn Asn Cys Ser Leu Ser Ile Val Asp Ala Arg Arg Arg Asp
100 105 110
Asn Gly Ser Tyr Phe Phe Arg Met Glu Arg Gly Ser Thr Lys Tyr Ser
115 120 125
Tyr Lys Ser Pro Gln Leu Ser Val His Val Thr Asp Leu Thr His Arg
130 135 140
Pro Lys Ile Leu Ile Pro Gly Thr Leu Glu Pro Gly His Ser Lys Asn
145 150 155 160
Leu Thr Cys Ser Val Ser Trp Ala Cys Glu Gln Gly Thr Pro Pro Ile
165 170 175
Phe Ser Trp Leu Ser Ala Ala Pro Thr Ser Leu Gly Pro Arg Thr Thr
180 185 190
His Ser Ser Val Leu Ile Ile Thr Pro Arg Pro Gln Asp His Gly Thr
195 200 205
Asn Leu Thr Cys Gln Val Lys Phe Ala Gly Ala Gly Val Thr Thr Glu
210 215 220
Arg Thr Ile Gln Leu Asn Val Thr Tyr Val Pro Gln Asn Pro Thr Thr
225 230 235 240
Gly Ile Phe Pro Gly Asp Gly Ser Gly Lys Gln Glu Thr Arg Ala Gly
245 250 255
Val Val His Gly Ala Ile Gly Gly Ala Gly Val Thr Ala Leu Leu Ala
260 265 270

Leu Cys Leu Cys Leu Ile Phe Phe Ile Val Lys Thr His Arg Arg Lys
275 280 285
Ala Ala Arg Thr Ala Val Gly Arg Asn Asp Thr His Pro Thr Thr Gly
290 295 300
Ser Ala Ser Pro Lys His Gln Lys Lys Ser Lys Leu His Gly Pro Thr
305 310 315 320
Glu Thr Ser Ser Cys Ser Gly Ala Ala Pro Thr Val Glu Met Asp Glu
325 330 335
Glu Leu His Tyr Ala Ser Leu Asn Phe His Gly Met Asn Pro Ser Lys
340 345 350
Asp Thr Ser Thr Glu Tyr Ser Glu Val Arg Thr Gln
355 360

<210> 2
<211> 851
<212> PRT
<213> 人工序列
<220>
<223> 食蟹猕猴 CD33 ECD-HSA
<400> 2
Asp Pro Arg Val Arg Leu Glu Val Gln Glu Ser Val Thr Val Gln Glu
1 5 10 15
Gly Leu Cys Val Leu Val Pro Cys Thr Phe Phe His Pro Val Pro Tyr
20 25 30

[0002] His Thr Arg Asn Ser Pro Val His Gly Tyr Trp Phe Arg Glu Gly Ala
35 40 45
Ile Val Ser Leu Asp Ser Pro Val Ala Thr Asn Lys Leu Asp Gln Glu
50 55 60
Val Gln Glu Glu Thr Gln Gly Arg Phe Arg Leu Leu Gly Asp Pro Ser
65 70 75 80
Arg Asn Asn Cys Ser Leu Ser Ile Val Asp Ala Arg Arg Arg Asp Asn
85 90 95
Gly Ser Tyr Phe Phe Arg Met Glu Lys Gly Ser Thr Lys Tyr Ser Tyr
100 105 110
Lys Ser Thr Gln Leu Ser Val His Val Thr Asp Leu Thr His Arg Pro
115 120 125
Gln Ile Leu Ile Pro Gly Ala Leu Asp Pro Asp His Ser Lys Asn Leu
130 135 140
Thr Cys Ser Val Pro Trp Ala Cys Glu Gln Gly Thr Pro Pro Ile Phe
145 150 155 160
Ser Trp Met Ser Ala Ala Pro Thr Ser Leu Gly Leu Arg Thr Thr His
165 170 175
Ser Ser Val Leu Ile Ile Thr Pro Arg Pro Gln Asp His Gly Thr Asn
180 185 190
Leu Thr Cys Gln Val Lys Phe Pro Gly Ala Gly Val Thr Thr Glu Arg
195 200 205
Thr Ile Gln Leu Asn Val Ser Tyr Ala Ser Gln Asn Pro Arg Thr Asp
210 215 220

Ile Phe Leu Gly Asp Gly Ser Gly Lys Gln Gly Val Val Gln Gly Ser
225 230 235 240
Gly Ser Gly Ser Glu Asn Leu Tyr Phe Gln Gly Val Arg Ser Ser Ser
245 250 255
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
260 265 270
Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
275 280 285
Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
290 295 300
Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
305 310 315 320
Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
325 330 335
Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
340 345 350
Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
355 360 365
Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
370 375 380
Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
385 390 395 400
Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
[0003] 405 410 415
Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
420 425 430
Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
435 440 445
Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
450 455 460
Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
465 470 475 480
Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
485 490 495
Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
500 505 510
Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
515 520 525
Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
530 535 540
Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
545 550 555 560
Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
565 570 575
Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
580 585 590
Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr

595 600 605
Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
610 615 620
Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
625 630 635 640
Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
645 650 655
Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
660 665 670
Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
675 680 685
Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
690 695 700
Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
705 710 715 720
Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
725 730 735
Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
740 745 750
Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
755 760 765
Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
770 775 780

[0004] Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
785 790 795 800
Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
805 810 815
Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
820 825 830
Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Gly Gly Ser His His His
835 840 845
His His His
850

<210> 3
<211> 0
<212> PRT
<213> 人工序列
<220>
<223> 人CD33 ECD-HSA
<400> 3
000
<210> 4
<211> 718
<212> PRT
<213> 人工序列
<220>
<223> 人CD33-V-HSA

<400> 4

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

[0005] Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser
180 185 190
Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg
195 200 205
Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu
210 215 220
Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro
225 230 235 240
Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp
245 250 255
Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg
260 265 270
His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr
275 280 285
Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys
290 295 300
Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser
305 310 315 320
Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg
325 330 335
Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys
340 345 350
Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val
355 360 365

His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg
370 375 380
Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser
385 390 395 400
Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys
405 410 415
Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu
420 425 430
Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu
435 440 445
Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg
450 455 460
His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr
465 470 475 480
Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys
485 490 495
Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln
500 505 510
Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr
515 520 525
Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln
530 535 540
Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val
[0006] 545 550 555 560
Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala
565 570 575
Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu
580 585 590
Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu
595 600 605
Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr
610 615 620
Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile
625 630 635 640
Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu
645 650 655
Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys
660 665 670
Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala
675 680 685
Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala
690 695 700
Ala Ser Gln Ala Ala Leu Gly Leu His His His His His His
705 710 715

<210> 5
<211> 715
<212> PRT

<213> 人工序列
<220>
<223> 人CD33-C2-HSA
<400> 5

Val His Val Thr Asp Leu Thr His Arg Pro Lys Ile Leu Ile Pro Gly
1 5 10 15
Thr Leu Glu Pro Gly His Ser Lys Asn Leu Thr Cys Ser Val Ser Trp
20 25 30
Ala Cys Glu Gln Gly Thr Pro Pro Ile Phe Ser Trp Leu Ser Ala Ala
35 40 45
Pro Thr Ser Leu Gly Pro Arg Thr Thr His Ser Ser Val Leu Ile Ile
50 55 60
Thr Pro Arg Pro Gln Asp His Gly Thr Asn Leu Thr Cys Gln Val Lys
65 70 75 80
Phe Ala Gly Ala Gly Val Thr Thr Glu Arg Thr Ile Gln Leu Asn Val
85 90 95
Thr Tyr Val Pro Gln Asn Pro Thr Thr Gly Ile Phe Pro Gly Asp Gly
100 105 110
Ser Gly Lys Gln Glu Thr Arg Ala Gly Val Val His Asp Ala His Lys
115 120 125
Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
130 135 140
Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Ser Pro Phe
[0007] 145 150 155 160
Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
165 170 175
Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
180 185 190
Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
195 200 205
Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
210 215 220
Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
225 230 235 240
Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
245 250 255
Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
260 265 270
Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
275 280 285
Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
290 295 300
Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
305 310 315 320
Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
325 330 335
Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe

340 345 350
Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
355 360 365
Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
370 375 380
Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
385 390 395 400
Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
405 410 415
Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
420 425 430
Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
435 440 445
Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
450 455 460
Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
465 470 475 480
Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
485 490 495
Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
500 505 510
Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
515 520 525

[0008]
Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
530 535 540
Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
545 550 555 560
Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
565 570 575
Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
580 585 590
Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
595 600 605
Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
610 615 620
Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
625 630 635 640
Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
645 650 655
Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
660 665 670
Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
675 680 685
Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
690 695 700
Ala Ala Leu Gly Leu His His His His His His
705 710 715

<210> 6
<211> 135
<212> PRT
<213> 人工序列
<220>
<223> 人CD33-V-His
<400> 6

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

[0009] Ser His His His His His His
130 135

<210> 7
<211> 132
<212> PRT
<213> 人工序列
<220>
<223> 人CD33 C2-His
<400> 7

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

115 120 125

His His His His
130

<210> 8
<211> 250
<212> PRT
<213> 人工序列
<220>
<223> 人CD33 ECD-His
<400> 8

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

[0010]

Lys Ser Pro Gln Leu Ser Val His Val Thr Asp Leu Thr His Arg Pro
115 120 125
Lys Ile Leu Ile Pro Gly Thr Leu Glu Pro Gly His Ser Lys Asn Leu
130 135 140
Thr Cys Ser Val Ser Trp Ala Cys Glu Gln Gly Thr Pro Pro Ile Phe
145 150 155 160
Ser Trp Leu Ser Ala Ala Pro Thr Ser Leu Gly Pro Arg Thr Thr His
165 170 175
Ser Ser Val Leu Ile Ile Thr Pro Arg Pro Gln Asp His Gly Thr Asn
180 185 190
Leu Thr Cys Gln Val Lys Phe Ala Gly Ala Gly Val Thr Thr Glu Arg
195 200 205
Thr Ile Gln Leu Asn Val Thr Tyr Val Pro Gln Asn Pro Thr Thr Gly
210 215 220
Ile Phe Pro Gly Asp Gly Ser Gly Lys Gln Glu Thr Arg Ala Gly Val
225 230 235 240
Val His Gly Ser His His His His His His
245 250

<210> 9
<211> 0
<212> PRT
<213> 人工序列
<220>

<223> 食蟹猕猴 CD33 ECD-His
<400> 9
000
<210> 10
<211> 364
<212> PRT
<213> 人工序列
<220>
<223> 人 CD33 全长
<400> 10

Met Pro Leu Leu Leu Leu Leu Pro Leu Leu Trp Ala Gly Ala Leu Ala
1 5 10 15
Met Asp Pro Asn Phe Trp Leu Gln Val Gln Glu Ser Val Thr Val Gln
20 25 30
Glu Gly Leu Cys Val Leu Val Pro Cys Thr Phe Phe His Pro Ile Pro
35 40 45
Tyr Tyr Asp Lys Asn Ser Pro Val His Gly Tyr Trp Phe Arg Glu Gly
50 55 60
Ala Ile Ile Ser Arg Asp Ser Pro Val Ala Thr Asn Lys Leu Asp Gln
65 70 75 80
Glu Val Gln Glu Glu Thr Gln Gly Arg Phe Arg Leu Leu Gly Asp Pro
85 90 95
Ser Arg Asn Asn Cys Ser Leu Ser Ile Val Asp Ala Arg Arg Arg Asp
[0011] 100 105 110
Asn Gly Ser Tyr Phe Phe Arg Met Glu Arg Gly Ser Thr Lys Tyr Ser
115 120 125
Tyr Lys Ser Pro Gln Leu Ser Val His Val Thr Asp Leu Thr His Arg
130 135 140
Pro Lys Ile Leu Ile Pro Gly Thr Leu Glu Pro Gly His Ser Lys Asn
145 150 155 160
Leu Thr Cys Ser Val Ser Trp Ala Cys Glu Gln Gly Thr Pro Pro Ile
165 170 175
Phe Ser Trp Leu Ser Ala Ala Pro Thr Ser Leu Gly Pro Arg Thr Thr
180 185 190
His Ser Ser Val Leu Ile Ile Thr Pro Arg Pro Gln Asp His Gly Thr
195 200 205
Asn Leu Thr Cys Gln Val Lys Phe Ala Gly Ala Gly Val Thr Thr Glu
210 215 220
Arg Thr Ile Gln Leu Asn Val Thr Tyr Val Pro Gln Asn Pro Thr Thr
225 230 235 240
Gly Ile Phe Pro Gly Asp Gly Ser Gly Lys Gln Glu Thr Arg Ala Gly
245 250 255
Val Val His Gly Ala Ile Gly Gly Ala Gly Val Thr Ala Leu Leu Ala
260 265 270
Leu Cys Leu Cys Leu Ile Phe Phe Ile Val Lys Thr His Arg Arg Lys
275 280 285
Ala Ala Arg Thr Ala Val Gly Arg Asn Asp Thr His Pro Thr Thr Gly

290 295 300
Ser Ala Ser Pro Lys His Gln Lys Lys Ser Lys Leu His Gly Pro Thr
305 310 315 320
Glu Thr Ser Ser Cys Ser Gly Ala Ala Pro Thr Val Glu Met Asp Glu
325 330 335
Glu Leu His Tyr Ala Ser Leu Asn Phe His Gly Met Asn Pro Ser Lys
340 345 350
Asp Thr Ser Thr Glu Tyr Ser Glu Val Arg Thr Gln
355 360

<210> 11
<211> 363
<212> PRT
<213> 人工序列
<220>
<223> 食蟹猕猴 CD33 全长
<400> 11

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

[0012]

50 55 60
Ile Val Ser Leu Asp Ser Pro Val Ala Thr Asn Lys Leu Asp Gln Glu
65 70 75 80
Val Gln Glu Glu Thr Gln Gly Arg Phe Arg Leu Leu Gly Asp Pro Ser
85 90 95
Arg Asn Asn Cys Ser Leu Ser Ile Val Asp Ala Arg Arg Arg Asp Asn
100 105 110
Gly Ser Tyr Phe Phe Arg Met Glu Lys Gly Ser Thr Lys Tyr Ser Tyr
115 120 125
Lys Ser Thr Gln Leu Ser Val His Val Thr Asp Leu Thr His Arg Pro
130 135 140
Gln Ile Leu Ile Pro Gly Ala Leu Asp Pro Asp His Ser Lys Asn Leu
145 150 155 160
Thr Cys Ser Val Pro Trp Ala Cys Glu Gln Gly Thr Pro Pro Ile Phe
165 170 175
Ser Trp Met Ser Ala Ala Pro Thr Ser Leu Gly Leu Arg Thr Thr His
180 185 190
Ser Ser Val Leu Ile Ile Thr Pro Arg Pro Gln Asp His Gly Thr Asn
195 200 205
Leu Thr Cys Gln Val Lys Phe Pro Gly Ala Gly Val Thr Thr Glu Arg
210 215 220
Thr Ile Gln Leu Asn Val Ser Tyr Ala Ser Gln Asn Pro Arg Thr Asp
225 230 235 240
Ile Phe Leu Gly Asp Gly Ser Gly Arg Lys Ala Arg Lys Gln Gly Val

245 250 255
Val Gln Gly Ala Ile Gly Gly Ala Gly Val Thr Val Leu Leu Ala Leu
260 265 270
Cys Leu Cys Leu Ile Phe Phe Thr Val Lys Thr His Arg Arg Lys Ala
275 280 285
Ala Arg Thr Ala Val Gly Arg Ile Asp Thr His Pro Ala Thr Gly Pro
290 295 300
Thr Ser Ser Lys His Gln Lys Lys Ser Lys Leu His Gly Ala Thr Glu
305 310 315 320
Thr Ser Gly Cys Ser Gly Thr Thr Leu Thr Val Glu Met Asp Glu Glu
325 330 335
Leu His Tyr Ala Ser Leu Asn Phe His Gly Met Asn Pro Ser Glu Asp
340 345 350
Thr Ser Thr Glu Tyr Ser Glu Val Arg Thr Gln
355 360

<210> 12
<211> 447
<212> PRT
<213> 人工序列
<220>
<223> C33B46 重链
<400> 12

[0013]
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Thr Tyr
20 25 30
Ala Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Thr Asn Thr Gly Asn Pro Thr Tyr Ala Gln Gly Phe
50 55 60
Thr Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65 70 75 80
Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Arg Asp Arg Gly Thr Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn

195 200 205
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220
Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

[0014]
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 13
<211> 447
<212> PRT
<213> 人工序列
<220>
<223> C33B48 重链
<400> 13
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Arg Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Ala Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Thr Asn Thr Gly Asn Pro Thr Tyr Ala Gln Gly Phe
50 55 60
Thr Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Ser Ala Tyr

65 70 75 80
Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Thr Asp Arg Asp Arg Gly Thr Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220
Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

[0015]

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 14
<211> 455
<212> PRT
<213> 人工序列
<220>
<223> C33B52 重链
<400> 14

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

[0016]

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
130 135 140
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145 150 155 160
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
165 170 175
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
180 185 190
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
195 200 205
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
210 215 220
Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
275 280 285
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
290 295 300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
355 360 365
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385 390 395 400
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser
405 410 415
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
420 425 430
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445
Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 15
<211> 452
<212> PRT
<213> 人工序列
<220>

[0017] <223> C33B54 重链
<400> 15

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

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190
Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
195 200 205
His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
210 215 220
Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225 230 235 240
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
260 265 270
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
290 295 300
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305 310 315 320
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
325 330 335
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
340 345 350
Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[0018] 355 360 365
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
370 375 380
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385 390 395 400
Pro Val Leu Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr
405 410 415
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445
Ser Pro Gly Lys
450

<210> 16
<211> 459
<212> PRT
<213> 人工序列
<220>
<223> C33B55 重链
<400> 16
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Cys Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Ser Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Phe Arg Ser Leu Asp Trp Leu Pro Pro Asp Ser Thr Ser
100 105 110
Tyr Asp Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
130 135 140
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
145 150 155 160
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
165 170 175
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
180 185 190
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
195 200 205
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
[0019] 210 215 220
Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
225 230 235 240
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
245 250 255
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
260 265 270
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
275 280 285
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
290 295 300
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
305 310 315 320
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
325 330 335
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
340 345 350
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
355 360 365
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
370 375 380
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
385 390 395 400
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe

405 410 415
Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
420 425 430
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
435 440 445
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 17
<211> 446
<212> PRT
<213> 人工序列
<220>
<223> C33B57 重链
<400> 17

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Ala Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Thr Asn Thr Gly Asn Pro Thr Tyr Ala Gln Ala Phe
50 55 60
Thr Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
[0020] 65 70 75 80
Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Arg Glu Val Arg Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205
Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220
Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val

260 265 270
Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320
Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350
Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400
Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415
Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

[0021] <210> 18
<211> 455
<212> PRT
<213> 人工序列
<220>
<223> C33B61 重链
<400> 18
Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Arg Ser Thr
20 25 30
Asn Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45
Trp Ile Gly Thr Ile Tyr Tyr Ser Gly Asn Thr Tyr Tyr Asn Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Leu Ala Asp Val Val Val Val Pro Ala Ala Arg Tyr Phe
100 105 110
Asp Tyr Trp Gly Gln Gly Ile Leu Val Thr Val Ser Ser Ala Ser Thr
115 120 125
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser

130 135 140
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145 150 155 160
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
165 170 175
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
180 185 190
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
195 200 205
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
210 215 220
Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
275 280 285
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
290 295 300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320
[0022] Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
355 360 365
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385 390 395 400
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser
405 410 415
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
420 425 430
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445
Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 19
<211> 455
<212> PRT
<213> 人工序列
<220>
<223> C33B62 重链

<400> 19

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

[0023]

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
180 185 190
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
195 200 205
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
210 215 220
Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
275 280 285
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
290 295 300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
355 360 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385 390 395 400
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser
405 410 415
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
420 425 430
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445
Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 20
<211> 455
<212> PRT
<213> 人工序列
<220>
<223> C33B63 重链
<400> 20
Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Thr Gly
20 25 30

[0024] Arg Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Val Ile
35 40 45
Trp Ile Gly Asn Ile Tyr Tyr Ser Gly Asn Thr Tyr Tyr Asn Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Leu Gly Ser Leu Val Val Val Pro Ala Ala Met Ser Phe
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
115 120 125
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
130 135 140
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145 150 155 160
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
165 170 175
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
180 185 190
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
195 200 205
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
210 215 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
275 280 285
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
290 295 300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
355 360 365
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385 390 395 400
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser
[0025] 405 410 415
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
420 425 430
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445
Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 21
<211> 455
<212> PRT
<213> 人工序列
<220>
<223> C33B64 重链
<400> 21

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Leu Tyr Tyr
85 90 95
Cys Ala Arg Leu Gly Ser Leu Val Val Val Pro Ala Ala Met Ser Phe
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
115 120 125
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
130 135 140
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145 150 155 160
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
165 170 175
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
180 185 190
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
195 200 205
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
210 215 220
Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
[0026] 260 265 270
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
275 280 285
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
290 295 300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
355 360 365
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385 390 395 400
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser
405 410 415
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
420 425 430
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445
Leu Ser Leu Ser Pro Gly Lys

450 455

<210> 22
<211> 449
<212> PRT
<213> 人工序列
<220>
<223> C33B66 重链
<400> 22

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp
35 40 45
Ile Gly Glu Ile Tyr His Ser Gly Asn Thr Asn Asn Ser Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Ala Asp Lys Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys
85 90 95
Ala Arg Ile Ile Ala Val Ala Arg Tyr Phe Asp Ser Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[0027] 115 120 125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu

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

<210> 23
<211> 459
<212> PRT
<213> 人工序列
[0028] <220>
<223> C33B72 重链
<400> 23
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Val Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Phe Arg Asp Phe Asp Trp Leu Pro Pro Asp Ser Thr Ser
100 105 110
Tyr His Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
130 135 140
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
145 150 155 160
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr

165 170 175
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
180 185 190
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
195 200 205
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
210 215 220
Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
225 230 235 240
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
245 250 255
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
260 265 270
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
275 280 285
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
290 295 300
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
305 310 315 320
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
325 330 335
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
340 345 350

[0029] Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
355 360 365
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
370 375 380
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
385 390 395 400
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
405 410 415
Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
420 425 430
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
435 440 445
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 24
<211> 459
<212> PRT
<213> 人工序列
<220>
<223> C33B73 重链
<400> 24
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Tyr

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

[0030]

```
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
    210                 215                 220
Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
225                 230                 235                 240
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
                245                 250                 255
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
            260                 265                 270
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
        275                 280                 285
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
    290                 295                 300
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
305                 310                 315                 320
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
                325                 330                 335
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
            340                 345                 350
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
        355                 360                 365
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
    370                 375                 380
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
385                 390                 395                 400
```

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
405 410 415
Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
420 425 430
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
435 440 445
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 25
<211> 455
<212> PRT
<213> 人工序列
<220>
<223> C33B75 重链
<400> 25

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

[0031]

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Leu Gly Ser Leu Val Val Val Pro Ala Ala Met Ser Phe
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
115 120 125
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
130 135 140
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145 150 155 160
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
165 170 175
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
180 185 190
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
195 200 205
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
210 215 220
Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
275 280 285
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
290 295 300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
355 360 365
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385 390 395 400
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser
405 410 415
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
420 425 430
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
[0032] 435 440 445
Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 26
<211> 448
<212> PRT
<213> 人工序列
<220>
<223> C33B77 重链
<400> 26

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

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220
His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240
Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255
Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270
Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285
Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
[0033] 290 295 300
Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320
Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335
Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350
Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365
Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380
Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400
Ser Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415
Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430
Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 27
<211> 459
<212> PRT
<213> 人工序列
<220>

<223> C33B79 重链

<400> 27

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val His Tyr Cys
85 90 95
Ala Lys Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Ala Ser
100 105 110
Tyr His Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
130 135 140
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
145 150 155 160
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
[0034] 165 170 175
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
180 185 190
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
195 200 205
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
210 215 220
Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
225 230 235 240
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
245 250 255
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
260 265 270
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
275 280 285
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
290 295 300
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
305 310 315 320
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
325 330 335
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
340 345 350
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu

355 360 365
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
370 375 380
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
385 390 395 400
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
405 410 415
Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
420 425 430
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
435 440 445
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 28
<211> 451
<212> PRT
<213> 人工序列
<220>
<223> C33B80 重链
<400> 28
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Tyr Ala
[0035] 20 25 30
Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
35 40 45
Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp Ile Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Thr Tyr Asn Ser Gly Tyr Tyr Asp Gly Asp Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys

210 215 220
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225 230 235 240
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
290 295 300
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
325 330 335
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

[0036] Val Leu Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val
405 410 415
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445
Pro Gly Lys
450

<210> 29
<211> 459
<212> PRT
<213> 人工序列
<220>
<223> C33B82 重链
<400> 29
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe

65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Phe Arg Tyr Phe Asp Trp Leu Pro Pro Asp Ser Ser Ser
100 105 110
Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
130 135 140
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
145 150 155 160
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
165 170 175
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
180 185 190
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
195 200 205
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
210 215 220
Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
225 230 235 240
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
245 250 255

[0037] Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
260 265 270
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
275 280 285
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
290 295 300
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
305 310 315 320
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
325 330 335
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
340 345 350
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
355 360 365
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
370 375 380
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
385 390 395 400
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
405 410 415
Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
420 425 430
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
435 440 445

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 30
<211> 459
<212> PRT
<213> 人工序列
<220>
<223> C33B83 重链
<400> 30

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

[0038] Tyr His Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
130 135 140
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
145 150 155 160
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
165 170 175
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
180 185 190
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
195 200 205
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
210 215 220
Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
225 230 235 240
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
245 250 255
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
260 265 270
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
275 280 285
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
290 295 300

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
305 310 315 320
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
325 330 335
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
340 345 350
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
355 360 365
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
370 375 380
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
385 390 395 400
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
405 410 415
Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
420 425 430
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
435 440 445
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 31
<211> 448
<212> PRT

[0039] <213> 人工序列

<220>
<223> C33B87 重链
<400> 31

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

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220
His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240
Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255
Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270
Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285
Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
290 295 300
Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320
Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335
Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[0040] 340 345 350
Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365
Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380
Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400
Ser Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415
Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430
Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 32
<211> 449
<212> PRT
<213> 人工序列
<220>
<223> C33B88 重链
<400> 32

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Thr Asn Thr Gly Asn Pro Thr Tyr Ala Gln Gly Phe
50 55 60
Thr Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Asn Thr Ala Tyr
65 70 75 80
Leu Leu Ile Ser Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ser Asp Ile Leu Pro Gly Tyr His Glu Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
[0041] 210 215 220
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350
Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400
Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

Lys

<210> 33
<211> 452
<212> PRT
<213> 人工序列
<220>
<223> C33B89 重链
<400> 33

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

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

Leu Ser Val Gln Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
[0042] 65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Glu Val Ala Val Ala Ala Ser Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
210 215 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

260 265 270
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
290 295 300
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305 310 315 320
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
325 330 335
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
340 345 350
Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
355 360 365
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
370 375 380
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385 390 395 400
Pro Val Leu Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr
405 410 415
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

[0043] Ser Pro Gly Lys
450

<210> 34
<211> 448
<212> PRT
<213> 人工序列
<220>
<223> C33B94 重链
<400> 34
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Asn Ile Lys Gln His Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Arg Asp Leu Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro

115 120 125
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220
His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240
Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255
Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270
Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285
Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
290 295 300

[0044]
Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320
Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335
Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350
Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365
Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380
Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400
Ser Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415
Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430
Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 35
<211> 448
<212> PRT
<213> 人工序列
<220>
<223> C33B95 重链

<400> 35

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

[0045] Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220
His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240
Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255
Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270
Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285
Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
290 295 300
Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320
Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335
Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350
Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380
Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400
Ser Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415
Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430
Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 36
<211> 447
<212> PRT
<213> 人工序列
<220>
<223> C33B96 重链
<400> 36

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

[0046]
Ala Asn Ile Lys Arg Asp Gly Gly Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Ala Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Pro Phe Tyr Asp His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220
Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
[0047] 420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 37
<211> 450
<212> PRT
<213> 人工序列
<220>
<223> C33B101 重链
<400> 37

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[0048] 290 295 300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400
Leu Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445
Gly Lys
450

<210> 38
<211> 450
<212> PRT

<213> 人工序列
<220>
<223> C33B107 重链
<400> 38

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Gly Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gly Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Asn Trp Val
35 40 45
Ser Ala Ile Asp Tyr Ser Gly Asn Asp Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Glu Ser Gln Leu Leu His Gly Leu Phe Glu His Trp Gly Gln
100 105 110
Gly Ile Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
[0049] 145 150 155 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr

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

<210> 39
<211> 448
<212> PRT
<213> 人工序列
<220>
<223> C33B120 重链
<400> 39

[0050]
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Asn Ile Lys Gln His Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Arg Asp Leu Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser

195 200 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
290 295 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

[0051] Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 40
<211> 455
<212> PRT
<213> 人工序列
<220>
<223> C33B122 重链
<400> 40

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Arg Ser Ser
20 25 30

Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Pro Glu
35 40 45

Trp Ile Gly Ser Ile Tyr Ser Ser Gly Asn Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe

65 70 75 80
Ser Leu Lys Leu Ile Ser Met Thr Ala Ala Asp Thr Ala Val Phe Tyr
85 90 95
Cys Ala Arg Leu Ala Ala Thr Ile Val Val Pro Ala Ala Arg Tyr Phe
100 105 110
Asp Cys Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
115 120 125
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
130 135 140
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145 150 155 160
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
165 170 175
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
180 185 190
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
195 200 205
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
210 215 220
Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255

[0052]
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
275 280 285
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
290 295 300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
355 360 365
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385 390 395 400
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser
405 410 415
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
420 425 430
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445

Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 41
<211> 455
<212> PRT
<213> 人工序列
<220>
<223> C33B123 重链
<400> 41

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

[0053]
Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
115 120 125
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
130 135 140
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145 150 155 160
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
165 170 175
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
180 185 190
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
195 200 205
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
210 215 220
Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
275 280 285
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
290 295 300

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
355 360 365
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385 390 395 400
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser
405 410 415
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
420 425 430
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445
Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 42
<211> 449
<212> PRT
[0054] <213> 人工序列
<220>
<223> C33B124 重链
<400> 42

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

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[0055] 340 345 350
Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400
Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445
Lys

<210> 43
<211> 459
<212> PRT
<213> 人工序列
<220>
<223> C33B125 重链
<400> 43
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Thr Ser
100 105 110
Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
130 135 140
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
145 150 155 160
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
165 170 175
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
180 185 190
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
[0056] 195 200 205
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
210 215 220
Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
225 230 235 240
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
245 250 255
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
260 265 270
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
275 280 285
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
290 295 300
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
305 310 315 320
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
325 330 335
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
340 345 350
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
355 360 365
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
370 375 380
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu

385 390 395 400
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
405 410 415
Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
420 425 430
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
435 440 445
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 44
<211> 456
<212> PRT
<213> 人工序列
<220>
<223> C33B760 重链
<400> 44

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Cys Ala Asp Ser Val
[0057] 50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Ser Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Phe Arg Ser Leu Asp Trp Leu Pro Pro Asp Ser Thr Ser
100 105 110
Tyr Asp Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
130 135 140
Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
145 150 155 160
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
165 170 175
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
180 185 190
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
195 200 205
Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
210 215 220
Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
225 230 235 240
Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro

245 250 255
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
260 265 270
Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
275 280 285
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
290 295 300
Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
305 310 315 320
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
325 330 335
Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
340 345 350
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
355 360 365
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
370 375 380
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
385 390 395 400
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
405 410 415
Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
420 425 430

[0058] Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
435 440 445
Ser Leu Ser Leu Ser Leu Gly Lys
450 455

<210> 45
<211> 456
<212> PRT
<213> 人工序列
<220>
<223> C33B777 重链
<400> 45
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Val Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Phe Arg Asp Phe Asp Trp Leu Pro Pro Asp Ser Thr Ser

100 105 110

Tyr His Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
130 135 140

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
145 150 155 160

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
165 170 175

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
180 185 190

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
195 200 205

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
210 215 220

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
225 230 235 240

Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
245 250 255

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
260 265 270

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
275 280 285

[0059] Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
290 295 300

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
305 310 315 320

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
325 330 335

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
340 345 350

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
355 360 365

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
370 375 380

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
385 390 395 400

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
405 410 415

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
420 425 430

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
435 440 445

Ser Leu Ser Leu Ser Leu Gly Lys
450 455

<210> 46

<211> 456

<212> PRT
<213> 人工序列
<220>
<223> C33B778 重链
<400> 46

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

[0060]

```
Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
145                 150                 155                 160
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
                165                 170                 175
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
            180                 185                 190
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
        195                 200                 205
Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
    210                 215                 220
Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
225                 230                 235                 240
Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
                245                 250                 255
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
            260                 265                 270
Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
        275                 280                 285
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
    290                 295                 300
Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
305                 310                 315                 320
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
                325                 330                 335
```

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
340 345 350
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
355 360 365
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
370 375 380
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
385 390 395 400
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
405 410 415
Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
420 425 430
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
435 440 445
Ser Leu Ser Leu Ser Leu Gly Lys
450 455

<210> 47
<211> 445
<212> PRT
<213> 人工序列
<220>
<223> C33B782 重链
<400> 47

[0061] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Asn Ile Lys Gln His Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Arg Asp Leu Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125
Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
130 135 140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
195 200 205
Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys
210 215 220
Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu
225 230 235 240
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
245 250 255
Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln
260 265 270
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
275 280 285
Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu
290 295 300
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
305 310 315 320
Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys
325 330 335
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
340 345 350
Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
355 360 365
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
[0062] 370 375 380
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
385 390 395 400
Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln
405 410 415
Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
420 425 430
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 48
<211> 445
<212> PRT
<213> 人工序列
<220>
<223> C33B792 重链
<400> 48

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Arg Asp Leu Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125
Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
130 135 140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190
Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
195 200 205
Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys
210 215 220
Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu
225 230 235 240
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
[0063] 245 250 255
Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln
260 265 270
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
275 280 285
Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu
290 295 300
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
305 310 315 320
Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys
325 330 335
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
340 345 350
Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
355 360 365
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
370 375 380
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
385 390 395 400
Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln
405 410 415
Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
420 425 430
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys

435 440 445

<210> 49
<211> 445
<212> PRT
<213> 人工序列
<220>
<223> C33B799 重链
<400> 49

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Asn Ile Lys Gln His Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Arg Asp Leu Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
[0064] 115 120 125
Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
130 135 140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190
Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
195 200 205
Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys
210 215 220
Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu
225 230 235 240
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
245 250 255
Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln
260 265 270
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
275 280 285
Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu
290 295 300
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys

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

<210> 50
<211> 447
<212> PRT
<213> 人工序列
<220>
<223> C33B806 重链

[0065] <400> 50
Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30
Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Asp
35 40 45
Trp Ile Gly Ser Ile Asn Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Ile Gln Phe
65 70 75 80
Ser Leu Lys Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Leu Asp Gly Tyr Glu Ser Pro Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125
Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro

180 185 190
Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220
Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255
Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270
Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285
Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320
Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

[0066]
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 51
<211> 456
<212> PRT
<213> 人工序列
<220>
<223> C33B830 重链
<400> 51
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Thr Ser
100 105 110

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
130 135 140

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
145 150 155 160

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
165 170 175

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
180 185 190

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
195 200 205

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
210 215 220

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
225 230 235 240

[0067] Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
245 250 255

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
260 265 270

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
275 280 285

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
290 295 300

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
305 310 315 320

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
325 330 335

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
340 345 350

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
355 360 365

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
370 375 380

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
385 390 395 400

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
405 410 415

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
420 425 430

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
435 440 445
Ser Leu Ser Leu Ser Leu Gly Lys
450 455

<210> 52
<211> 444
<212> PRT
<213> 人工序列
<220>
<223> C33B836 重链
<400> 52

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

[0068] Ala Thr Asp Arg Asp Arg Gly Thr Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn
195 200 205
Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro
210 215 220
Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
225 230 235 240
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
245 250 255
Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
260 265 270
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
275 280 285

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

<210> 53
<211> 456
<212> PRT

[0069] <213> 人工序列

<220>
<223> C33B937 重链
<400> 53

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

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
165 170 175
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
180 185 190
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
195 200 205
Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
210 215 220
Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
225 230 235 240
Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
245 250 255
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
260 265 270
Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
275 280 285
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
290 295 300
Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
305 310 315 320
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
325 330 335
Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
[0070] 340 345 350
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
355 360 365
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
370 375 380
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
385 390 395 400
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
405 410 415
Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
420 425 430
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
435 440 445
Ser Leu Ser Leu Ser Leu Gly Lys
450 455

<210> 54
<211> 1801
<212> DNA
<213> 人工序列
<220>
<223> C33B46 重链
<400> 54
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120

gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgg tgcagagcgg cagcgagctg aagaagcccg 300
gagccagcgt gaaggtgagc tgcaaggcct ccggctacac cttcagcacc tacgccatga 360
actgggtgag gcaagccccc ggacagggcc tggagtggat gggctggatc aacaccaaca 420
ccggcaaccc cacctacgcc cagggcttca caggcaggtt cgtgttcagc ctggacacca 480
gcgtgagcac cgcctacctg cagatcagca gcctgaaagc cgaggacacc gccgtgtact 540
actgcgccag ggacagggac aggggcacag actactgggg ccagggcaca ctggtgaccg 600
tgagcagcgc ctccaccaag ggcccatcgg tcttcccccc ggcaccctcc tccaagagca 660
cctctggggg cacagcggcc ctgggctgcc tggtcaagga ctacttcccc gaaccggtga 720
cggtgtcgtg gaactcaggc gccctgacca gcggcgtgca caccttcccg gctgtcctac 780
agtcctcagg actctactcc ctcagcagcg tggtgaccgt gccctccagc agcttgggca 840
cccagaccta catctgcaac gtgaatcaca agcccagcaa caccaaggtg gacaagaaag 900
ttgagcccaa atcttgtgac aaaactcaca catgcccacc gtgcccagca cctgaactcc 960
tgggggacc gtcagtcttc ctcttccccc caaaacccaa ggacaccctc atgatctccc 1020
ggaccccctga ggtcacatgc gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt 1080
tcaactggta cgtggacggc gtggaggtgc ataatgccaa gacaaagccg cgggaggagc 1140
agtacaacag cacgtaccgt gtggtcagcg tcctcaccgt cctgcaccag gactggctga 1200
atggcaagga gtacaagtgc aaggtctcca acaaagccct cccagccccc atcgagaaaa 1260
ccatctccaa agccaaaggg cagccccgag aaccacaggt gtacaccctg cccccatccc 1320
gggaggagat gaccaagaac caggtcagcc tgacctgcct ggtcaaaggc ttctatccca 1380
gcgacatcgc cgtggagtgg gagagcaatg ggcagccgga gaacaactac aagaccacgc 1440
ctcccgtgct ggactccgac ggctccttcc tgctctacag caagctcacc gtggacaaga 1500
[0071] gcaggtggca gcaggggaac gtcttctcat gctccgtgat gcatgaggct ctgcacaacc 1560
actacacgca gaagagcctc tccctgtctc cgggtaaatg atagttcgaa ttcctagaag 1620
acatgataag atacattgat gagtttggac aaaccacaac tagaatgcag tgaaaaaaat 1680
gctttatttg tgaaatttgt gatgctattg ctttatttgt aaccattata agctgcaata 1740
aacaagttaa caacaacaat tgcattcatt ttatgtttca ggttcagggg gaggtgtggg 1800
a 1801

<210> 55
<211> 1801
<212> DNA
<213> 人工序列
<220>
<223> C33B48 重链
<400> 55

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgg tgcagagcgg aagcgagctg agaaagcccg 300
gcgccagcgt gaaggtgagc tgcaaggcca gcggctacac cttcaccaac tacgccatga 360
actgggtgag gcaggccccc ggacaaggcc tggagtggat gggctggatc aacaccaaca 420
ccggcaaccc cacctacgcc cagggcttta ccggcaggtt cgtgttcagc ctggacacca 480
gcgtgagcag cgcctacctg cagatcagca gcctgaaggc cgaggacacc gccatgtact 540
actgcgccac cgacagggac aggggaaccg actactgggg ccagggcaca ctggtgaccg 600
tgagcagcgc ctccaccaag ggcccatcgg tcttcccccc ggcaccctcc tccaagagca 660

cctctggggg cacagcggcc ctgggctgcc tggtcaagga ctacttcccc gaaccggtga 720
cggtgtcgtg gaactcaggc gccctgacca gcggcgtgca caccttcccg gctgtcctac 780
agtcctcagg actctactcc ctcagcagcg tggtgaccgt gccctccagc agcttgggca 840
cccagaccta catctgcaac gtgaatcaca agcccagcaa caccaaggtg gacaagaaag 900
ttgagcccaa atcttgtgac aaaactcaca catgcccacc gtgcccagca cctgaactcc 960
tgggggacc gtcagtcttc ctcttccccc caaaacccaa ggacaccctc atgatctccc 1020
ggacccctga ggtcacatgc gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt 1080
tcaactggta cgtggacggc gtggaggtgc ataatgccaa gacaaagccg cgggaggagc 1140
agtacaacag cacgtaccgt gtggtcagcg tcctcaccgt cctgcaccag gactggctga 1200
atggcaagga gtacaagtgc aaggtctcca acaaagccct cccagccccc atcgagaaaa 1260
ccatctccaa agccaaaggg cagccccgag aaccacaggt gtacaccctg cccccatccc 1320
gggaggagat gaccaagaac caggtcagcc tgacctgcct ggtcaaaggc ttctatccca 1380
gcgacatcgc cgtggagtgg gagagcaatg ggcagccgga gaacaactac aagaccacgc 1440
ctcccgtgct ggactccgac ggctccttcc tgctctacag caagctcacc gtggacaaga 1500
gcaggtggca gcaggggaac gtcttctcat gctccgtgat gcatgaggct ctgcacaacc 1560
actacacgca gaagagcctc tccctgtctc cgggtaaatg atagttcgaa ttcctagaag 1620
acatgataag atacattgat gagtttggac aaaccacaac tagaatgcag tgaaaaaaat 1680
gctttatttg tgaaatttgt gatgctattg ctttatttgt aaccattata agctgcaata 1740
aacaagttaa caacaacaat tgcattcatt ttatgtttca ggttcagggg gaggtgtggg 1800
a 1801

<210> 56
<211> 1825
<212> DNA
[0072] <213> 人工序列
<220>
<223> C33B52 重链
<400> 56

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag ctgcagctgc aggagagcgg ccctggactg gtgaacccca 300
gcgagaccct gagccacacc tgtaccgtga gcggcggcag catctccagc agcagccact 360
actggggctg gatcagacag ccccctggca agggcctgga gtggatcggc aagatctact 420
acagcggcaa cacctactac aaccccagcc tgaagtccag ggtgaccatc agcatcgaca 480
cctccaagaa ccagttctcc ctgaagatga gctccgtgac cgccgccgat acagccgtgt 540
actactgcgc caggctggct gatgtggtgg tggtgcctgc cgccaggtac ttcgacagct 600
ggggccaggg cacactggtg accgtgagct ccgcctccac caagggccca tcggtcttcc 660
ccctggcacc ctcctccaag agcacctctg ggggcacagc ggccctgggc tgcctggtca 720
aggactactt ccccgaaccg gtgacggtgt cgtggaactc aggcgccctg accagcggcg 780
tgcacacctt cccggctgtc ctacagtcct caggactcta ctccctcagc agcgtggtga 840
ccgtgccctc cagcagcttg ggcacccaga cctacatctg caacgtgaat cacaagccca 900
gcaacaccaa ggtggacaag aaagttgagc ccaaatcttg tgacaaaact cacacatgcc 960
caccgtgccc agcacctgaa ctcctggggg gaccgtcagt cttcctcttc cccccaaaac 1020
ccaaggacac cctcatgatc tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga 1080
gccacgaaga ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg 1140
ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca 1200

ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag 1260
ccctcccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc cgagaaccac 1320
aggtgtacac cctgccccca tcccgggagg agatgaccaa gaaccaggtc agcctgacct 1380
gcctggtcaa aggcttctat cccagcgaca tcgccgtgga gtgggagagc aatgggcagc 1440
cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggctcc ttcctgctct 1500
acagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg 1560
tgatgcatga ggctctgcac aaccactaca cgcagaagag cctctccctg tctccgggta 1620
aatgatagtt cgaattccta gaagacatga taagatacat tgatgagttt ggacaaacca 1680
caactagaat gcagtgaaaa aaatgcttta tttgtgaaat ttgtgatgct attgctttat 1740
ttgtaaccat tataagctgc aataaacaag ttaacaacaa caattgcatt cattttatgt 1800
ttcaggttca gggggaggtg tggga 1825

<210> 57
<211> 1816
<212> DNA
<213> 人工序列
<220>
<223> C33B54 重链
<400> 57

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgc agcagagcgg acccggactg gtgaagccca 300
[0073] gccagaccct gagcctcacc tgcgccatca gcggcgactc cgtgagcagc aatagcgccg 360
cctggaactg gatcaggcag agccctagca ggggactgga gtggctgggc aggacctact 420
acaggagcaa gtggtacaac gactacgccg tgagcgtgag gagcaggatc accatcaacc 480
ccgacaccag caagaaccag ttcagcctgc agctgaactc cgtgaccccc gaggataccg 540
ccgtgtacca ctgcgccagg gagaccatgt tcaggggcct gatggactac tggggccagg 600
gaaccctggt gaccgtgagc agcgcctcca ccaagggccc atcggtcttc cccctggcac 660
cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc aaggactact 720
tccccgaacc ggtgacggtg tcgtggaact caggcgccct gaccagcggc gtgcacacct 780
tcccggctgt cctacagtcc tcaggactct actccctcag cagcgtggtg accgtgccct 840
ccagcagctt gggcacccag acctacatct gcaacgtgaa tcacaagccc agcaacacca 900
aggtggacaa gaaagttgag cccaaatctt gtgacaaaac tcacacatgc ccaccgtgcc 960
cagcacctga actcctgggg ggaccgtcag tcttcctctt ccccccaaaa cccaaggaca 1020
ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg agccacgaag 1080
accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat gccaagacaa 1140
agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc accgtcctgc 1200
accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa gccctcccag 1260
cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca caggtgtaca 1320
ccctgccccc atcccgggag gagatgacca agaaccaggt cagcctgacc tgcctggtca 1380
aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag ccggagaaca 1440
actacaagac cacgcctccc gtgctggact ccgacggctc cttcctgctc tacagcaagc 1500
tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg 1560
aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt aaatgatagt 1620
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 1680
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1740

ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1800
aggggggaggt gtggga 1816
<210> 58
<211> 1837
<212> DNA
<213> 人工序列
<220>
<223> C33B55 重链
<400> 58
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgg tggagagcgg aggcggagtg gtgcagcctg 300
gcagaagcct gagactgagc tgcgccgcca gcggcttcac cttcagcagc tacggcatgc 360
actgggtgag gcagagccct ggcaaaggcc tggagtgggt ggccgtgatc agctacgacg 420
gcagcaacaa gtactgcgcc gacagcgtga agggcaggtt caccatcagc agggacaaca 480
gcaagagcac cctgtacctg cagatgaaca gcctgagggc cgaggacacc gccgtgtact 540
actgcgccaa ggacttcagg agcctggact ggctgccccc cgatagcacc agctatgacg 600
gcatggacgt gtggggacag ggcaccaccg tgaccgtgag cagcgcctcc accaagggcc 660
catcggtctt ccccctggca ccctcctcca agagcacctc tgggggcaca gcggccctgg 720
gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc 780
tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca 840
[0074] gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc tgcaacgtga 900
atcacaagcc cagcaacacc aaggtggaca agaaagttga gcccaaatct tgtgacaaaa 960
ctcacacatg cccaccgtgc ccagcacctg aactcctggg gggaccgtca gtcttcctct 1020
tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc acatgcgtgg 1080
tggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg 1140
aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg taccgtgtgg 1200
tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac aagtgcaagg 1260
tctccaacaa agccctccca gccccccatcg agaaaaccat ctccaaagcc aaagggcagc 1320
cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc aagaaccagg 1380
tcagcctgac ctgcctggtc aaaggcttct atcccagcga catcgccgtg gagtgggaga 1440
gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac tccgacggct 1500
ccttcctgct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag gggaacgtct 1560
tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag agcctctccc 1620
tgtctccggg taaatgatag ttcgaattcc tagaagacat gataagatac attgatgagt 1680
ttggacaaac cacaactaga atgcagtgaa aaaaatgctt tatttgtgaa atttgtgatg 1740
ctattgcttt atttgtaacc attataagct gcaataaaca agttaacaac aacaattgca 1800
ttcattttat gtttcaggtt caggggggagg tgtggga 1837
<210> 59
<211> 1798
<212> DNA
<213> 人工序列
<220>
<223> C33B56 重链
<400> 59

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgg tgcagagcgg cagcgagctg aagaaacccg 300
gcgccagcgt gaaggtgagc tgcaaggcct ccggctacac cttcaccaac tacgccatga 360
actgggtgag acaggctcct ggccagggcc tggagtggat gggctggatc aacacaaaca 420
ccggcaaccc tacctacgcc caggccttca ccggcaggtt cgtgttcagc ctggacacca 480
gcgtgagcac cgcctacctg cagatcagca gcctgaaggc cgaggacacc gccgtgtact 540
actgcgccag ggacagagag gtgagggact actggggcca gggcaccctc gtgacagtga 600
gcagcgcctc caccaagggc ccatcggtct tccccctggc accctcctcc aagagcacct 660
ctgggggcac agcggccctg ggctgcctgg tcaaggacta cttccccgaa ccggtgacgg 720
tgtcgtggaa ctcaggcgcc ctgaccagcg gcgtgcacac cttcccggct gtcctacagt 780
cctcaggact ctactccctc agcagcgtgg tgaccgtgcc ctccagcagc ttgggcaccc 840
agacctacat ctgcaacgtg aatcacaagc ccagcaacac caaggtggac aagaaagttg 900
agcccaaatc ttgtgacaaa actcacacat gcccaccgtg cccagcacct gaactcctgg 960
ggggaccgtc agtcttcctc ttccccccaa aacccaagga caccctcatg atctcccgga 1020
cccctgaggt cacatgcgtg gtggtggacg tgagccacga agaccctgag gtcaagttca 1080
actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg gaggagcagt 1140
acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac tggctgaatg 1200
gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc gagaaaacca 1260
tctccaaagc caaagggcag ccccgagaac cacaggtgta caccctgccc ccatcccggg 1320
aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc tatcccagcg 1380
[0075] acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag accacgcctc 1440
ccgtgctgga ctccgacggc tccttcctgc tctacagcaa gctcaccgtg gacaagagca 1500
ggtggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg cacaaccact 1560
acacgcagaa gagcctctcc ctgtctccgg gtaaatgata gttcgaattc ctagaagaca 1620
tgataagata cattgatgag tttggacaaa ccacaactag aatgcagtga aaaaaatgct 1680
ttatttgtga aatttgtgat gctattgctt tatttgtaac cattataagc tgcaataaac 1740
aagttaacaa caacaattgc attcatttta tgtttcaggt tcaggggggag gtgtggga 1798

<210> 60
<211> 1825
<212> DNA
<213> 人工序列
<220>
<223> C33B61 重链
<400> 60

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag ctgcagctgc aggagagcgg acctggcctg gtgaagccca 300
gcgagacact gagcctgaca tgcaccgtga gcggcggcag catcaggagc accaactact 360
actggggctg gatcaggcag cctcccggaa agggcctgga gtggatcggc accatctact 420
acagcggcaa cacctactac aaccccagcc tgaagagcag ggtgaccatc agcgtggaca 480
cctccaagaa ccagttcagc ctgaagctgt ccagcgtgac agccgccgac acagccgtgt 540
actactgcgc tagactggcc gacgtggtgg tggtgcctgc cgccaggtac ttcgactact 600

ggggccaggg catcctggtg accgtgagca gcgcctccac caagggccca tcggtcttcc 660
ccctggcacc ctcctccaag agcacctctg ggggcacagc ggccctgggc tgcctggtca 720
aggactactt ccccgaaccg gtgacggtgt cgtggaactc aggcgccctg accagcggcg 780
tgcacacctt cccggctgtc ctacagtcct caggactcta ctccctcagc agcgtggtga 840
ccgtgccctc cagcagcttg ggcacccaga cctacatctg caacgtgaat cacaagccca 900
gcaacaccaa ggtggacaag aaagttgagc ccaaatcttg tgacaaaact cacacatgcc 960
caccgtgccc agcacctgaa ctcctggggg gaccgtcagt cttcctcttc cccccaaaac 1020
ccaaggacac cctcatgatc tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga 1080
gccacgaaga ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg 1140
ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca 1200
ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag 1260
ccctcccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc cgagaaccac 1320
aggtgtacac cctgccccca tcccgggagg agatgaccaa gaaccaggtc agcctgacct 1380
gcctggtcaa aggcttctat cccagcgaca tcgccgtgga gtgggagagc aatgggcagc 1440
cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggctcc ttcctgctct 1500
acagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg 1560
tgatgcatga ggctctgcac aaccactaca cgcagaagag cctctccctg tctccgggta 1620
aatgatagtt cgaattccta gaagacatga taagatacat tgatgagttt ggacaaacca 1680
caactagaat gcagtgaaaa aaatgcttta tttgtgaaat ttgtgatgct attgctttat 1740
ttgtaaccat tataagctgc aataaacaag ttaacaacaa caattgcatt cattttatgt 1800
ttcaggttca gggggaggtg tggga 1825

<210> 61
<211> 1825
[0076] <212> DNA
<213> 人工序列
<220>
<223> C33B62 重链
<400> 61

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag ctgcagctgc aggagagcgg acctggcctg gtgaagccca 300
gcgagaccct gagcctgacc tgcacagtga gcggcggcag catcaggtcc tccggcttct 360
actggggctg gatcaggcag cctcccagga agggcctgga gtggatcggc accatctact 420
acagcggcaa cacctactac aaccccagcc tgaagagcag ggtgaccatc agcgtggaca 480
ccagcaagaa ccagttcagc ctgaagctga gcagcgtgac agccgccgat accgccgtgt 540
acttctgcgc cagactggcc gatgtggtgg tggtgcctgc cgccaggtac ttcgacaact 600
ggggccaggg caccctggtg acagtgagca gcgcctccac caagggccca tcggtcttcc 660
ccctggcacc ctcctccaag agcacctctg ggggcacagc ggccctgggc tgcctggtca 720
aggactactt ccccgaaccg gtgacggtgt cgtggaactc aggcgccctg accagcggcg 780
tgcacacctt cccggctgtc ctacagtcct caggactcta ctccctcagc agcgtggtga 840
ccgtgccctc cagcagcttg ggcacccaga cctacatctg caacgtgaat cacaagccca 900
gcaacaccaa ggtggacaag aaagttgagc ccaaatcttg tgacaaaact cacacatgcc 960
caccgtgccc agcacctgaa ctcctggggg gaccgtcagt cttcctcttc cccccaaaac 1020
ccaaggacac cctcatgatc tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga 1080
gccacgaaga ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg 1140

ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca 1200
ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag 1260
ccctcccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc cgagaaccac 1320
aggtgtacac cctgccccca tcccgggagg agatgaccaa gaaccaggtc agcctgacct 1380
gcctggtcaa aggcttctat cccagcgaca tcgccgtgga gtgggagagc aatgggcagc 1440
cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggctcc ttcctgctct 1500
acagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg 1560
tgatgcatga ggctctgcac aaccactaca cgcagaagag cctctccctg tctccgggta 1620
aatgatagtt cgaattccta gaagacatga taagatacat tgatgagttt ggacaaacca 1680
caactagaat gcagtgaaaa aaatgcttta tttgtgaaat ttgtgatgct attgctttat 1740
ttgtaaccat tataagctgc aataaacaag ttaacaacaa caattgcatt cattttatgt 1800
ttcaggttca gggggaggtg tggga 1825

<210> 62
<211> 1825
<212> DNA
<213> 人工序列
<220>
<223> C33B63 重链
<400> 62

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
[0077] cccaaagtat acaggcccag ctgcagctgc aggaaagcgg ccctggcctg gtgaagccct 300
ccgaaaccct gagcctgaca tgcaccgtga gcggcggcag catcagcaca ggcaggtact 360
actggggctg gatcaggcag cctcctggca agggcgtgat ctggatcggc aacatctact 420
atagcggcaa cacctactac aaccctagcc tgaagagcag ggtgaccatc agcgtggaca 480
ccagcaagaa ccagttctcc ctgaagctga acagcgtgac cgccgccgac acagccgtgt 540
actactgcgc cagactggga agcctggtgg tggtgcctgc cgccatgagc ttcgactact 600
ggggacaggg caccctggtg accgtgagca gcgcctccac caagggccca tcggtcttcc 660
ccctggcacc ctcctccaag agcacctctg ggggcacagc ggccctgggc tgcctggtca 720
aggactactt ccccgaaccg gtgacggtgt cgtggaactc aggcgccctg accagcggcg 780
tgcacacctt cccggctgtc ctacagtcct caggactcta ctccctcagc agcgtggtga 840
ccgtgccctc cagcagcttg ggcacccaga cctacatctg caacgtgaat cacaagccca 900
gcaacaccaa ggtggacaag aaagttgagc ccaaatcttg tgacaaaact cacacatgcc 960
caccgtgccc agcacctgaa ctcctggggg gaccgtcagt cttcctcttc cccccaaaac 1020
ccaaggacac cctcatgatc tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga 1080
gccacgaaga ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg 1140
ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca 1200
ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag 1260
ccctcccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc cgagaaccac 1320
aggtgtacac cctgccccca tcccgggagg agatgaccaa gaaccaggtc agcctgacct 1380
gcctggtcaa aggcttctat cccagcgaca tcgccgtgga gtgggagagc aatgggcagc 1440
cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggctcc ttcctgctct 1500
acagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg 1560
tgatgcatga ggctctgcac aaccactaca cgcagaagag cctctccctg tctccgggta 1620
aatgatagtt cgaattccta gaagacatga taagatacat tgatgagttt ggacaaacca 1680

caactagaat gcagtgaaaa aaatgcttta tttgtgaaat ttgtgatgct attgctttat 1740
ttgtaaccat tataagctgc aataaacaag ttaacaacaa caattgcatt cattttatgt 1800
ttcaggttca gggggaggtg tggga 1825

<210> 63
<211> 1825
<212> DNA
<213> 人工序列
<220>
<223> C33B64 重链
<400> 63

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag ctgcagctgc aggaaagcgg ccctggcctg gtgaagccta 300
gcgagaccct gagcctgacc tgtaccgtga gcggcggcag catcagaggc agcagctact 360
actggggctg ggtgagacag ccccctggaa agggcctgga gtggatcggc agcatctaca 420
gcagcggcaa cacctactac aacccctccc tcaagtccag ggtgaccatc agcgtggaca 480
ccagcaagaa ccagttcagc ctgaagctga gcagcgtgac cgctgccgat accgccctgt 540
actactgcgc cagactggga agcctggtgg tggtgcctgc cgccatgagc ttcgactact 600
ggggccaggg cacactggtg accgtgtcca gcgcctccac caagggccca tcggtcttcc 660
ccctggcacc ctcctccaag agcacctctg ggggcacagc ggccctgggc tgcctggtca 720
aggactactt ccccgaaccg gtgacggtgt cgtggaactc aggcgccctg accagcggcg 780
[0078] tgcacacctt cccggctgtc ctacagtcct caggactcta ctccctcagc agcgtggtga 840
ccgtgccctc cagcagcttg ggcacccaga cctacatctg caacgtgaat cacaagccca 900
gcaacaccaa ggtggacaag aaagttgagc ccaaatcttg tgacaaaact cacacatgcc 960
caccgtgccc agcacctgaa ctcctggggg gaccgtcagt cttcctcttc cccccaaaac 1020
ccaaggacac cctcatgatc tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga 1080
gccacgaaga ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg 1140
ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca 1200
ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag 1260
ccctcccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc cgagaaccac 1320
aggtgtacac cctgccccca tcccgggagg agatgaccaa gaaccaggtc agcctgacct 1380
gcctggtcaa aggcttctat cccagcgaca tcgccgtgga gtgggagagc aatgggcagc 1440
cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggctcc ttcctgctct 1500
acagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg 1560
tgatgcatga ggctctgcac aaccactaca cgcagaagag cctctccctg tctccgggta 1620
aatgatagtt cgaattccta gaagacatga taagatacat tgatgagttt ggacaaacca 1680
caactagaat gcagtgaaaa aaatgcttta tttgtgaaat ttgtgatgct attgctttat 1740
ttgtaaccat tataagctgc aataaacaag ttaacaacaa caattgcatt cattttatgt 1800
ttcaggttca gggggaggtg tggga 1825

<210> 64
<211> 1807
<212> DNA
<213> 人工序列
<220>
<223> C33B66 重链

<400> 64

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtccagctgc aggagagcgg acctggcctg gtgaagccta 300
gcggcaccct gagcctgacc tgtgccgtga gcggaggcag catcagcagc agcaactggt 360
ggagctgggt gagacagcct cctggcagag gcctggagtg gatcggcgag atctaccaca 420
gcggcaacac caacaacagc cccagcctga agagcagggt gaccatcagc gccgacaaga 480
gcaagaacca gttcagcctg aagctgagca gcgtgaccgc tgccgatacc gccgtgtact 540
tctgcgccag gatcatcgcc gtggccaggt acttcgacag ctggggacag ggcaccctgg 600
tgaccgtgag cagcgcctcc accaagggcc catcggtctt ccccctggca ccctcctcca 660
agagcacctc tgggggcaca gcggccctgg gctgcctggt caaggactac ttccccgaac 720
cggtgacggt gtcgtggaac tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg 780
tcctacagtc ctcaggactc tactccctca gcagcgtggt gaccgtgccc tccagcagct 840
tgggcaccca gacctacatc tgcaacgtga atcacaagcc cagcaacacc aaggtggaca 900
agaaagttga gcccaaatct tgtgacaaaa ctcacacatg cccaccgtgc ccagcacctg 960
aactcctggg gggaccgtca gtcttcctct tccccccaaa acccaaggac accctcatga 1020
tctcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa gaccctgagg 1080
tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca aagccgcggg 1140
aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg caccaggact 1200
ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca gccccatcg 1260
agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac accctgcccc 1320
[0079] catcccggga ggagatgacc aagaaccagg tcagcctgac ctgcctggtc aaaggcttct 1380
atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac aactacaaga 1440
ccacgcctcc cgtgctggac tccgacggct ccttcctgct ctacagcaag ctcaccgtgg 1500
acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat gaggctctgc 1560
acaaccacta cacgcagaag agcctctccc tgtctccggg taaatgatag ttcgaattcc 1620
tagaagacat gataagatac attgatgagt ttggacaaac cacaactaga atgcagtgaa 1680
aaaaatgctt tatttgtgaa atttgtgatg ctattgcttt atttgtaacc attataagct 1740
gcaataaaca agttaacaac aacaattgca ttcattttat gtttcaggtt caggggggagg 1800
tgtggga 1807

<210> 65
<211> 1837
<212> DNA
<213> 人工序列
<220>
<223> C33B72 重链

<400> 65

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgg tggagagcgg cggaggagtg gtgcagcctg 300
gaaggagcct gagactgtcc tgcgccgcta gcggcttcac cttcagcagc tacggcatgc 360
actgggtgag acaggctccc ggcaagggac tggagtgggt ggtggtgatc agctacgacg 420
gcagcaacaa gtactacgcc gacagcgtga agggcaggtt caccatcagc agggacaaca 480

gcaagaacac cctgtacctg cagatgaaca gcctgagggc cgaggacacc gccgtgtact 540
actgcgccaa ggacttcagg gacttcgact ggctgcctcc tgatagcacc agctaccacg 600
gcatggacgt gtggggccag ggaaccaccg tgaccgtgag cagcgcctcc accaagggcc 660
catcggtctt ccccctggca ccctcctcca agagcacctc tgggggcaca gcggccctgg 720
gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc 780
tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca 840
gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc tgcaacgtga 900
atcacaagcc cagcaacacc aaggtggaca agaaagttga gcccaaatct tgtgacaaaa 960
ctcacacatg cccaccgtgc ccagcacctg aactcctggg gggaccgtca gtcttcctct 1020
tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc acatgcgtgg 1080
tggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg 1140
aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg taccgtgtgg 1200
tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac aagtgcaagg 1260
tctccaacaa agccctccca gccccatcg agaaaaccat ctccaaagcc aaagggcagc 1320
cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc aagaaccagg 1380
tcagcctgac ctgcctggtc aaaggcttct atcccagcga catcgccgtg gagtgggaga 1440
gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac tccgacggct 1500
ccttcctgct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag gggaacgtct 1560
tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag agcctctccc 1620
tgtctccggg taaatgatag ttcgaattcc tagaagacat gataagatac attgatgagt 1680
ttggacaaac cacaactaga atgcagtgaa aaaaatgctt tatttgtgaa atttgtgatg 1740
ctattgcttt atttgtaacc attataagct gcaataaaca agttaacaac aacaattgca 1800
ttcattttat gtttcaggtt cagggggagg tgtggga 1837

[0080] <210> 66
<211> 1837
<212> DNA
<213> 人工序列
<220>
<223> C33B73 重链
<400> 66
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgg tggaaagcgg cggaggcgtg gtgcagcctg 300
gaagaagcct gagactgagc tgcgtggcca gcggcttcac ctttagcagc tacggcatgc 360
actgggtgag gcaggctcct ggcaagggac tggagtgggt ggccgtgatc agctacgacg 420
gcagcaacaa gtactacgcc gacagcgtga agggcaggtt caccatcagc agggacaaca 480
gcaagaacac cctgtacctg cagatgaaca gcctgagagc cgagggcacc gccgtgtact 540
actgcgccaa ggacttcagg agctttgatt ggctgccccc tgatagcgcc agctaccacg 600
gcatggacgt gtggggccag ggcacaaccg tgaccgtgag cagcgcctcc accaagggcc 660
catcggtctt ccccctggca ccctcctcca agagcacctc tgggggcaca gcggccctgg 720
gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc 780
tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca 840
gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc tgcaacgtga 900
atcacaagcc cagcaacacc aaggtggaca agaaagttga gcccaaatct tgtgacaaaa 960
ctcacacatg cccaccgtgc ccagcacctg aactcctggg gggaccgtca gtcttcctct 1020

tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc acatgcgtgg 1080
tggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg 1140
aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg taccgtgtgg 1200
tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac aagtgcaagg 1260
tctccaacaa agccctccca gcccccatcg agaaaaccat ctccaaagcc aaagggcagc 1320
cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc aagaaccagg 1380
tcagcctgac ctgcctggtc aaaggcttct atcccagcga catcgccgtg gagtgggaga 1440
gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac tccgacggct 1500
ccttcctgct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag gggaacgtct 1560
tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag agcctctccc 1620
tgtctccggg taaatgatag ttcgaattcc tagaagacat gataagatac attgatgagt 1680
ttggacaaac cacaactaga atgcagtgaa aaaaatgctt tatttgtgaa atttgtgatg 1740
ctattgcttt atttgtaacc attataagct gcaataaaca agttaacaac aacaattgca 1800
ttcattttat gtttcaggtt cagggggagg tgtggga 1837

<210> 67
<211> 1825
<212> DNA
<213> 人工序列
<220>
<223> C33B75 重链
<400> 67

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
[0081] gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag ctgcagctgc aggaaagcgg ccctggcctg gtgaagccca 300
gcgaaaccct gagcctgacc tgcacagtga gcggcggcag catcaggggc agcagctact 360
actggggctg gatcagacag ccccctggca agggcctgga gtggatcggc agcatctaca 420
gcagcggcaa cacctactac aaccccagcc tgaagagcag agtgaccatc agcgtggaca 480
ccagcaagaa ccagttcagc ctgaagctga gcagcgtgac cgccgctgat accgccgtgt 540
actactgcgc cagactggga agcctggtgg tggtgcctgc cgccatgtcc tttgactact 600
ggggccaggg aaccctggtg accgtgagca gcgcctccac caagggccca tcggtcttcc 660
ccctggcacc ctcctccaag agcacctctg ggggcacagc ggccctgggc tgcctggtca 720
aggactactt ccccgaaccg gtgacggtgt cgtggaactc aggcgccctg accagcggcg 780
tgcacacctt cccggctgtc ctacagtcct caggactcta ctccctcagc agcgtggtga 840
ccgtgccctc cagcagcttg ggcacccaga cctacatctg caacgtgaat cacaagccca 900
gcaacaccaa ggtggacaag aaagttgagc ccaaatcttg tgacaaaact cacacatgcc 960
caccgtgccc agcacctgaa ctcctggggg gaccgtcagt cttcctcttc cccccaaaac 1020
ccaaggacac cctcatgatc tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga 1080
gccacgaaga ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg 1140
ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca 1200
ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag 1260
ccctcccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc cgagaaccac 1320
aggtgtacac cctgccccca tcccgggagg agatgaccaa gaaccaggtc agcctgacct 1380
gcctggtcaa aggcttctat cccagcgaca tcgccgtgga gtgggagagc aatgggcagc 1440
cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggctcc ttcctgctct 1500
acagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg 1560

tgatgcatga ggctctgcac aaccactaca cgcagaagag cctctccctg tctccgggta 1620
aatgatagtt cgaattccta gaagacatga taagatacat tgatgagttt ggacaaacca 1680
caactagaat gcagtgaaaa aaatgcttta tttgtgaaat ttgtgatgct attgctttat 1740
ttgtaaccat tataagctgc aataaacaag ttaacaacaa caattgcatt cattttatgt 1800
ttcaggttca gggggaggtg tggga 1825

<210> 68
<211> 1804
<212> DNA
<213> 人工序列
<220>
<223> C33B77 重链
<400> 68

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggagagcgg aggaggactg gtgcagcctg 300
gaggcagcct gagactgagc tgcgccgcta gcggcttcac cttcagcagc tactggatga 360
gctgggtgag acaggcccct ggcaagggac tggagtgggt ggccaacatc aagcagcacg 420
gcagcgagaa gtactacgtg gatagcgtga agggcaggtt caccatcagc agggacaacg 480
ccaaaaacag cctgtacctg cagatgaaca gcctgagggc cgaggacacc gccgtgtatt 540
actgcgccag ggacagggac ctgggctact tcgactactg gggccagggc accctggtga 600
cagtgagcag cgcctccacc aagggcccat cggtcttccc cctggcaccc tcctccaaga 660
[0082] gcacctctgg gggcacagcg gccctgggct gcctggtcaa ggactacttc cccgaaccgg 720
tgacggtgtc gtggaactca ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc 780
tacagtcctc aggactctac tccctcagca gcgtggtgac cgtgccctcc agcagcttgg 840
gcacccagac ctacatctgc aacgtgaatc acaagcccag caacaccaag gtggacaaga 900
aagttgagcc caaatcttgt gacaaaactc acacatgccc accgtgccca gcacctgaac 960
tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc ctcatgatct 1020
cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca 1080
agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag ccgcgggagg 1140
agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac caggactggc 1200
tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga 1260
aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc ctgccccccat 1320
cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa ggcttctatc 1380
ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac tacaagacca 1440
cgcctcccgt gctggactcc gacggctcct tcctgctcta cagcaagctc accgtggaca 1500
agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag gctctgcaca 1560
accactacac gcagaagagc ctctccctgt ctccgggtaa atgatagttc gaattcctag 1620
aagacatgat aagatacatt gatgagtttg gacaaaccac aactagaatg cagtgaaaaa 1680
aatgctttat ttgtgaaatt tgtgatgcta ttgctttatt tgtaaccatt ataagctgca 1740
ataaacaagt taacaacaac aattgcattc attttatgtt tcaggttcag ggggaggtgt 1800
ggga 1804

<210> 69
<211> 1837
<212> DNA
<213> 人工序列

<220>
<223> C33B79 重链
<400> 69
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgg tggagagcgg aggaggagtg gtgcagcctg 300
gcaggagcct gagactgagc tgcgccgcct ccagattcac cttcagcagc tacggcatgc 360
actgggtgag acaggccccc ggcaaaggcc tggagtgggt ggccgtgatc agctacgacg 420
gcagcaacaa gtactacgcc gacagcgtga agggcaggtt caccatcagc agggacaaca 480
gcaagaacac cctgtacctg cagatgaaca gcctgagagc cgaggacacc gccgtgcact 540
actgcgccaa ggactttagg agcttcgact ggctgccccc tgatagcgcc agctaccacg 600
gcatggacgt gtggggccag ggcaccacag tgaccgtgtc cagcgcctcc accaagggcc 660
catcggtctt ccccctggca ccctcctcca agagcacctc tgggggcaca gcggccctgg 720
gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc 780
tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca 840
gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc tgcaacgtga 900
atcacaagcc cagcaacacc aaggtggaca agaaagttga gcccaaatct tgtgacaaaa 960
ctcacacatg cccaccgtgc ccagcacctg aactcctggg gggaccgtca gtcttcctct 1020
tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc acatgcgtgg 1080
tggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg 1140
aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg taccgtgtgg 1200
[0083] tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac aagtgcaagg 1260
tctccaacaa agccctccca gccccccatcg agaaaaccat ctccaaagcc aaagggcagc 1320
cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc aagaaccagg 1380
tcagcctgac ctgcctggtc aaaggcttct atcccagcga catcgccgtg gagtgggaga 1440
gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac tccgacggct 1500
ccttcctgct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag gggaacgtct 1560
tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag agcctctccc 1620
tgtctccggg taaatgatag ttcgaattcc tagaagacat gataagatac attgatgagt 1680
ttggacaaac cacaactaga atgcagtgaa aaaaatgctt tatttgtgaa atttgtgatg 1740
ctattgcttt atttgtaacc attataagct gcaataaaca agttaacaac aacaattgca 1800
ttcattttat gtttcaggtt cagggggagg tgtggga 1837
<210> 70
<211> 1813
<212> DNA
<213> 人工序列
<220>
<223> C33B80 重链
<400> 70
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgc tggagagcgg aggaggcctg gtgcaacctg 300
gcggaagcct gagactgagc tgcgccgcca gcggcttcac cttcaactac gccatgagct 360

gggtgaggca ggcccctgga aagggcctgg agtgggtgtc cgccattagc ggaagcggcg 420
gcagcaccta ctacgccgac agcgtgaagg gcaggttcac catcagcagg gacatctcca 480
agaacaccct gtacctgcag atgaacagcc tgagggccga ggacaccgcc gtgtactact 540
gcgccaggac ctacaacagc ggctactacg acggcgactt cgactactgg ggccagggca 600
ccctggtgac agtgagcagc gcctccacca agggcccatc ggtcttcccc ctggcaccct 660
cctccaagag cacctctggg ggcacagcgg ccctgggctg cctggtcaag gactacttcc 720
ccgaaccggt gacggtgtcg tggaactcag gcgccctgac cagcggcgtg cacaccttcc 780
cggctgtcct acagtcctca ggactctact ccctcagcag cgtggtgacc gtgccctcca 840
gcagcttggg cacccagacc tacatctgca acgtgaatca caagcccagc aacaccaagg 900
tggacaagaa agttgagccc aaatcttgtg acaaaactca cacatgccca ccgtgcccag 960
cacctgaact cctgggggga ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc 1020
tcatgatctc ccggacccct gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc 1080
ctgaggtcaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc aagacaaagc 1140
cgcgggagga gcagtacaac agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc 1200
aggactggct gaatggcaag gagtacaagt gcaaggtctc caacaaagcc ctcccagccc 1260
ccatcgagaa aaccatctcc aaagccaaag ggcagccccg agaaccacag gtgtacaccc 1320
tgcccccatc ccgggaggag atgaccaaga accaggtcag cctgacctgc ctggtcaaag 1380
gcttctatcc cagcgacatc gccgtggagt gggagagcaa tgggcagccg gagaacaact 1440
acaagaccac gcctcccgtg ctggactccg acggctcctt cctgctctac agcaagctca 1500
ccgtggacaa gagcaggtgg cagcagggga acgtcttctc atgctccgtg atgcatgagg 1560
ctctgcacaa ccactacacg cagaagagcc tctccctgtc tccgggtaaa tgatagttcg 1620
aattcctaga agacatgata agatacattg atgagtttgg acaaaccaca actagaatgc 1680
agtgaaaaaa atgctttatt tgtgaaattt gtgatgctat tgctttattt gtaaccatta 1740
[0084] taagctgcaa taaacaagtt aacaacaaca attgcattca ttttatgttt caggttcagg 1800
gggaggtgtg gga 1813

<210> 71
<211> 1837
<212> DNA
<213> 人工序列
<220>
<223> C33B82 重链
<400> 71

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgg tggagagcgg cggaggagtg gtgcagcctg 300
gcagaagcct gaggctgagc tgcgctgcct ccggcttcac cttcagcagc tacggcatgc 360
actgggtgag acaggcccct ggcaagggac tggagtgggt ggccgtgatc agctacgacg 420
gctccaacaa gtactacgcc gacagcgtga agggcaggtt caccatcagc agggacaaca 480
gcaagaacac cctgttcctg cagatgaaca gcctgagggc cgaggacacc gccgtgtact 540
actgcgccaa ggacttcagg tacttcgact ggctgccccc cgacagcagc agctactacg 600
gcatggacgt gtggggacag ggcaccaccg tgaccgtgag cagcgcctcc accaagggcc 660
catcggtctt ccccctggca ccctcctcca agagcacctc tgggggcaca gcggccctgg 720
gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc 780
tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca 840
gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc tgcaacgtga 900

atcacaagcc cagcaacacc aaggtggaca agaaagttga gcccaaatct tgtgacaaaa 960
ctcacacatg cccaccgtgc ccagcacctg aactcctggg gggaccgtca gtcttcctct 1020
tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc acatgcgtgg 1080
tggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg 1140
aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg taccgtgtgg 1200
tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac aagtgcaagg 1260
tctccaacaa agccctccca gccccccatcg agaaaaccat ctccaaagcc aaagggcagc 1320
cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc aagaaccagg 1380
tcagcctgac ctgcctggtc aaaggcttct atcccagcga catcgccgtg gagtgggaga 1440
gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac tccgacggct 1500
ccttcctgct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag gggaacgtct 1560
tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag agcctctccc 1620
tgtctccggg taaatgatag ttcgaattcc tagaagacat gataagatac attgatgagt 1680
ttggacaaac cacaactaga atgcagtgaa aaaaatgctt tatttgtgaa atttgtgatg 1740
ctattgcttt atttgtaacc attataagct gcaataaaca agttaacaac aacaattgca 1800
ttcattttat gtttcaggtt cagggggagg tgtggga 1837

<210> 72
<211> 1837
<212> DNA
<213> 人工序列
<220>
<223> C33B83 重链
<400> 72

[0085] tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgg tggagagcgg aggaggcgtg gtgcagcctg 300
gaaggtccct gagactgagc tgcgctgcca gcggcttcac cttcagcgcc tacggcatgc 360
actgggtgag acaggccccct ggcaaaggcc tggaatgggt ggccgtgatc agctacgacg 420
gcagcaacaa gtactacgcc gacagcgtga agggcaggtt caccatcagc agggacaaca 480
gcaagaacac cctgtacctg cagatgaaca gcctgagggc cgagggcacc gctgtgtact 540
actgcgccaa ggacttcagg agcttcgact ggctgccccc cgatagcgcc agctaccacg 600
gcatggacgt gtggggccag ggaaccaccg tgaccgtgag ctccgcctcc accaagggcc 660
catcggtctt ccccctggca ccctcctcca agagcacctc tgggggcaca gcggccctgg 720
gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc 780
tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca 840
gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc tgcaacgtga 900
atcacaagcc cagcaacacc aaggtggaca agaaagttga gcccaaatct tgtgacaaaa 960
ctcacacatg cccaccgtgc ccagcacctg aactcctggg gggaccgtca gtcttcctct 1020
tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc acatgcgtgg 1080
tggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg 1140
aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg taccgtgtgg 1200
tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac aagtgcaagg 1260
tctccaacaa agccctccca gccccccatcg agaaaaccat ctccaaagcc aaagggcagc 1320
cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc aagaaccagg 1380
tcagcctgac ctgcctggtc aaaggcttct atcccagcga catcgccgtg gagtgggaga 1440

gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac tccgacggct 1500
ccttcctgct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag gggaacgtct 1560
tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag agcctctccc 1620
tgtctccggg taaatgatag ttcgaattcc tagaagacat gataagatac attgatgagt 1680
ttggacaaac cacaactaga atgcagtgaa aaaaatgctt tatttgtgaa atttgtgatg 1740
ctattgcttt atttgtaacc attataagct gcaataaaca agttaacaac aacaattgca 1800
ttcattttat gtttcaggtt caggggggagg tgtggga 1837

<210> 73
<211> 1804
<212> DNA
<213> 人工序列
<220>
<223> C33B87 重链
<400> 73

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggagagcgg cggaggattc gtgcagcccg 300
gaggaagcct gagactgagc tgcgccgcca gcggcttcac cttcagctcc tactggatga 360
gctgggtgag acaggctccc ggcaagggac tggagtgggt ggccaacatc aagcagcacg 420
gcagcgagaa gtactacgtg gacagcgtga agggcaggtt caccatcagc agggacaacg 480
tgaagaacag cctgtacctg cagatgaaca gcctgaggac cgaggacacc gccgtgtact 540
[0086] actgcgccag ggacagggac ctgggctact tcgactactg gggccaggga accctggtga 600
ccgtgagcag cgcctccacc aagggcccat cggtcttccc cctggcaccc tcctccaaga 660
gcacctctgg gggcacagcg gccctgggct gcctggtcaa ggactacttc cccgaaccgg 720
tgacggtgtc gtggaactca ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc 780
tacagtcctc aggactctac tccctcagca gcgtggtgac cgtgccctcc agcagcttgg 840
gcacccagac ctacatctgc aacgtgaatc acaagcccag caacaccaag gtggacaaga 900
aagttgagcc caaatcttgt gacaaaactc acacatgccc accgtgccca gcacctgaac 960
tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc ctcatgatct 1020
cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca 1080
agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag ccgcgggagg 1140
agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac caggactggc 1200
tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga 1260
aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc ctgccccccat 1320
cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa ggcttctatc 1380
ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac tacaagacca 1440
cgcctcccgt gctggactcc gacggctcct tcctgctcta cagcaagctc accgtggaca 1500
agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag gctctgcaca 1560
accactacac gcagaagagc ctctccctgt ctccgggtaa atgatagttc gaattcctag 1620
aagacatgat aagatacatt gatgagtttg gacaaaccac aactagaatg cagtgaaaaa 1680
aatgctttat ttgtgaaatt tgtgatgcta ttgctttatt tgtaaccatt ataagctgca 1740
ataaacaagt taacaacaac aattgcattc attttatgtt tcaggttcag ggggaggtgt 1800
ggga 1804

<210> 74
<211> 1807

<212> DNA
<213> 人工序列
<220>
<223> C33B88 重链
<400> 74
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgg tgcagagcgg aagcgagctg aagaagcccg 300
gcgcctccgt gaaggtgagc tgcaaggcca gcggctacac cctgaccaga agcgccatga 360
actgggtgag acaggctcct ggccagggcc tggagtggat gggctggatc aacaccaaca 420
ccggcaaccc cacctacgcc cagggcttta ccggcaggtt cgtgttcagc ctggacacca 480
gcgtgaacac cgcctacctg ctgatcagca gcctgaagac cgaggacacc gccgtgtact 540
actgcgcctc cgacatcctg cccggctacc acgaggacta ctggggccag ggcacactgg 600
tgaccgtgag ctccgcctcc accaagggcc catcggtctt ccccctggca ccctcctcca 660
agagcacctc tgggggcaca gcggccctgg gctgcctggt caaggactac ttccccgaac 720
cggtgacggt gtcgtggaac tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg 780
tcctacagtc ctcaggactc tactccctca gcagcgtggt gaccgtgccc tccagcagct 840
tgggcaccca gacctacatc tgcaacgtga atcacaagcc cagcaacacc aaggtggaca 900
agaaagttga gcccaaatct tgtgacaaaa ctcacacatg cccaccgtgc ccagcacctg 960
aactcctggg gggaccgtca gtcttcctct tccccccaaa acccaaggac accctcatga 1020
tctcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa gaccctgagg 1080
[0087] tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca aagccgcggg 1140
aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg caccaggact 1200
ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca gccccccatcg 1260
agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac accctgcccc 1320
catcccggga ggagatgacc aagaaccagg tcagcctgac ctgcctggtc aaaggcttct 1380
atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac aactacaaga 1440
ccacgcctcc cgtgctggac tccgacggct ccttcctgct ctacagcaag ctcaccgtgg 1500
acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat gaggctctgc 1560
acaaccacta cacgcagaag agcctctccc tgtctccggg taaatgatag ttcgaattcc 1620
tagaagacat gataagatac attgatgagt ttggacaaac cacaactaga atgcagtgaa 1680
aaaaatgctt tatttgtgaa atttgtgatg ctattgcttt atttgtaacc attataagct 1740
gcaataaaca agttaacaac aacaattgca ttcattttat gtttcaggtt caggggggag 1800
tgtggga 1807
<210> 75
<211> 1816
<212> DNA
<213> 人工序列
<220>
<223> C33B89 重链
<400> 75
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240

cccaaagtat acaggcccag gtgcagctgc agcagagcgg ccctggcctg gtgaagccta 300
gccagaccct gagcctgacc tgcgccatca gcggcgatag cgtgtccagc aactccgccg 360
cctggaactg gatcaggcag agccctagca gaggcctgga gtggctgggc aggacctact 420
acaggagcaa gtggtacaac gactacgccc tgagcgtgca gtccaggatc accatcaacc 480
ccgacaccag caagaaccag ttctccctgc agctgaactc cgtgaccccc gaggacaccg 540
ccgtgtacta ctgcgctaga gaggtggccg tggccgccag cttcgattac tggggccagg 600
gcacactggt gaccgtgagc agcgcctcca ccaagggccc atcggtcttc cccctggcac 660
cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc aaggactact 720
tccccgaacc ggtgacggtg tcgtggaact caggcgccct gaccagcggc gtgcacacct 780
tcccggctgt cctacagtcc tcaggactct actccctcag cagcgtggtg accgtgccct 840
ccagcagctt gggcacccag acctacatct gcaacgtgaa tcacaagccc agcaacacca 900
aggtggacaa gaaagttgag cccaaatctt gtgacaaaac tcacacatgc ccaccgtgcc 960
cagcacctga actcctgggg ggaccgtcag tcttcctctt ccccccaaaa cccaaggaca 1020
ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg agccacgaag 1080
accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat gccaagacaa 1140
agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc accgtcctgc 1200
accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa gccctcccag 1260
ccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca caggtgtaca 1320
ccctgccccc atcccgggag gagatgacca agaaccaggt cagcctgacc tgcctggtca 1380
aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag ccggagaaca 1440
actacaagac cacgcctccc gtgctggact ccgacggctc cttcctgctc tacagcaagc 1500
tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg 1560
aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt aaatgatagt 1620
[0088] tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 1680
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1740
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1800
aggggggaggt gtggga 1816

<210> 76
<211> 1804
<212> DNA
<213> 人工序列
<220>
<223> C33B94 重链
<400> 76

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggagagcgg aggcggattt gtgcagcctg 300
gcggcagcct gagactgagc tgtgccgcca gcggcttcac cttcagcagc tactggatga 360
gctgggtgag gcaggcccct ggaaagggac tggagtgggt ggccaacatc aagcagcacg 420
gaagcgagaa gtactacgtg gacagcgtga agggaaggtt cacaatcagc agggacaacg 480
ccaagaacag cctgtacctg cagatgaaca gcctgagggc cgaggacacc gccgtgtact 540
actgcgccag ggacagggac ctgggctact tcgactactg gggccagggc accctggtga 600
cagtgagcag cgcctccacc aagggcccat cggtcttccc cctggcaccc tcctccaaga 660
gcacctctgg gggcacagcg gccctgggct gcctggtcaa ggactacttc cccgaaccgg 720
tgacggtgtc gtggaactca ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc 780

tacagtcctc aggactctac tccctcagca gcgtggtgac cgtgccctcc agcagcttgg 840
gcacccagac ctacatctgc aacgtgaatc acaagcccag caacaccaag gtggacaaga 900
aagttgagcc caaatcttgt gacaaaactc acacatgccc accgtgccca gcacctgaac 960
tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc ctcatgatct 1020
cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca 1080
agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag ccgcgggagg 1140
agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac caggactggc 1200
tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga 1260
aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc ctgccccccat 1320
cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa ggcttctatc 1380
ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac tacaagacca 1440
cgcctcccgt gctggactcc gacggctcct tcctgctcta cagcaagctc accgtggaca 1500
agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag gctctgcaca 1560
accactacac gcagaagagc ctctccctgt ctccgggtaa atgatagttc gaattcctag 1620
aagacatgat aagatacatt gatgagtttg gacaaaccac aactagaatg cagtgaaaaa 1680
aatgctttat ttgtgaaatt tgtgatgcta ttgctttatt tgtaaccatt ataagctgca 1740
ataaacaagt taacaacaac aattgcattc attttatgtt tcaggttcag ggggaggtgt 1800
ggga 1804

<210> 77
<211> 1804
<212> DNA
<213> 人工序列
<220>

[0089] <223> C33B95 重链
<400> 77

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggagagcgg aggcggattt gtgcagcctg 300
gcggcagcct gagactgagc tgtgccgcca gcggcttcac cttcagcagc tactggatga 360
gctgggtgag gcaggcccct ggaaagggac tggagtgggt ggccaacatc aagcagcacg 420
gaagcgagaa gtactacgtg gacagcgtga agggaaggtt cacaatcagc agggacaacg 480
ccaagaacag cctgtacctg cagatgaaca gcctgagggc cgaggacacc gccgtgtact 540
actgcgccag ggacagggac ctgggctact tcgactactg gggccagggc accctggtga 600
cagtgagcag cgcctccacc aagggcccat cggtcttccc cctggcaccc tcctccaaga 660
gcacctctgg gggcacagcg gccctgggct gcctggtcaa ggactacttc cccgaaccgg 720
tgacggtgtc gtggaactca ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc 780
tacagtcctc aggactctac tccctcagca gcgtggtgac cgtgccctcc agcagcttgg 840
gcacccagac ctacatctgc aacgtgaatc acaagcccag caacaccaag gtggacaaga 900
aagttgagcc caaatcttgt gacaaaactc acacatgccc accgtgccca gcacctgaac 960
tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc ctcatgatct 1020
cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca 1080
agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag ccgcgggagg 1140
agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac caggactggc 1200
tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga 1260
aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc ctgccccccat 1320

cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa ggcttctatc 1380
ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac tacaagacca 1440
cgcctcccgt gctggactcc gacggctcct tcctgctcta cagcaagctc accgtggaca 1500
agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag gctctgcaca 1560
accactacac gcagaagagc ctctccctgt ctccgggtaa atgatagttc gaattcctag 1620
aagacatgat aagatacatt gatgagtttg gacaaaccac aactagaatg cagtgaaaaa 1680
aatgctttat ttgtgaaatt tgtgatgcta ttgctttatt tgtaaccatt ataagctgca 1740
ataaacaagt taacaacaac aattgcattc attttatgtt tcaggttcag ggggaggtgt 1800
ggga 1804

<210> 78
<211> 1801
<212> DNA
<213> 人工序列
<220>
<223> C33B96 重链
<400> 78

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggagagcgg aggaggcctg gtgcagcctg 300
gaggaagcct gagactgagc tgcgccgcct ccggcttcac cttcagcagc tactggatga 360
cctgggtgag acctgccccc ggaaagggcc tggagtgggt ggccaacatc aagagggacg 420
[0090] gcggcgagaa gtactacgtg gactccgtga agggcaggtt caccatcagc agggacaacg 480
ccgccaactc cctgtacctg cagatgaaca gcctgagggt ggaggacacc gccgtgtact 540
actgcgccag gcccttctac gaccacttcg actactgggg ccagggcaca ctggtgaccg 600
tgagcagcgc ctccaccaag ggcccatcgg tcttcccccc ggcaccctcc tccaagagca 660
cctctggggg cacagcggcc ctgggctgcc tggtcaagga ctacttcccc gaaccggtga 720
cggtgtcgtg gaactcaggc gccctgacca gcggcgtgca caccttcccg gctgtcctac 780
agtcctcagg actctactcc ctcagcagcg tggtgaccgt gccctccagc agcttgggca 840
cccagaccta catctgcaac gtgaatcaca agcccagcaa caccaaggtg gacaagaaag 900
ttgagcccaa atcttgtgac aaaactcaca catgcccacc gtgcccagca cctgaactcc 960
tgggggggacc gtcagtcttc ctcttccccc caaaacccaa ggacaccctc atgatctccc 1020
ggaccccctga ggtcacatgc gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt 1080
tcaactggta cgtggacggc gtggaggtgc ataatgccaa gacaaagccg cgggaggagc 1140
agtacaacag cacgtaccgt gtggtcagcg tcctcaccgt cctgcaccag gactggctga 1200
atggcaagga gtacaagtgc aaggtctcca acaaagccct cccagccccc atcgagaaaa 1260
ccatctccaa agccaaaggg cagccccgag aaccacaggt gtacaccctg cccccatccc 1320
gggaggagat gaccaagaac caggtcagcc tgacctgcct ggtcaaaggc ttctatccca 1380
gcgacatcgc cgtggagtgg gagagcaatg ggcagccgga gaacaactac aagaccacgc 1440
ctcccgtgct ggactccgac ggctccttcc tgctctacag caagctcacc gtggacaaga 1500
gcaggtggca gcaggggaac gtcttctcat gctccgtgat gcatgaggct ctgcacaacc 1560
actacacgca gaagagcctc tccctgtctc cgggtaaatg atagttcgaa ttcctagaag 1620
acatgataag atacattgat gagtttggac aaaccacaac tagaatgcag tgaaaaaaat 1680
gctttatttg tgaaatttgt gatgctattg ctttatttgt aaccattata agctgcaata 1740
aacaagttaa caacaacaat tgcattcatt ttatgtttca ggttcagggg gaggtgtggg 1800
a 1801

<210> 79
<211> 1810
<212> DNA
<213> 人工序列
<220>
<223> C33B101 重链
<400> 79

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag ctgcagctgc aggagagcgg acctggcctg gtgaagccca 300
gcgagaccct gagcctgacc tgcacagtga gcggcggcag catcagcagc agcagctact 360
actggggctg gatcaggcag cctcctggca agggcctgga ctggatcggc agcatcaact 420
acagcggcag cacctactac aaccccagcc tgaagagcag ggtgaccatc agcgtggaca 480
ccagcaagat ccagttcagc ctgaagctca gaagcgtgac cgccgccgac acagccgtgt 540
actactgcgc cagactggac ggctacgaga gcccccttcga ctactggggc cagggcaccc 600
tggtgacagt gagcagcgcc tccaccaagg gcccatcggt cttccccctg gcaccctcct 660
ccaagagcac ctctgggggc acagcggccc tgggctgcct ggtcaaggac tacttccccg 720
aaccggtgac ggtgtcgtgg aactcaggcg ccctgaccag cggcgtgcac accttcccgg 780
ctgtcctaca gtcctcagga ctctactccc tcagcagcgt ggtgaccgtg ccctccagca 840
gcttgggcac ccagacctac atctgcaacg tgaatcacaa gcccagcaac accaaggtgg 900
acaagaaagt tgagcccaaa tcttgtgaca aaactcacac atgcccaccg tgcccagcac 960
[0091] ctgaactcct ggggggaccg tcagtcttcc tcttcccccc aaaacccaag gacaccctca 1020
tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac gaagaccctg 1080
aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag acaaagccgc 1140
gggaggagca gtacaacagc acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg 1200
actggctgaa tggcaaggag tacaagtgca aggtctccaa caaagccctc ccagccccca 1260
tcgagaaaac catctccaaa gccaaagggc agccccgaga accacaggtg tacaccctgc 1320
ccccatcccg ggaggagatg accaagaacc aggtcagcct gacctgcctg gtcaaaggct 1380
tctatcccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag aacaactaca 1440
agaccacgcc tcccgtgctg gactccgacg gctccttcct gctctacagc aagctcaccg 1500
tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg catgaggctc 1560
tgcacaacca ctacacgcag aagagcctct ccctgtctcc gggtaaatga tagttcgaat 1620
tcctagaaga catgataaga tacattgatg agtttggaca aaccacaact agaatgcagt 1680
gaaaaaaatg ctttatttgt gaaatttgtg atgctattgc tttatttgta accattataa 1740
gctgcaataa acaagttaac aacaacaatt gcattcattt tatgtttcag gttcaggggg 1800
aggtgtggga 1810

<210> 80
<211> 1810
<212> DNA
<213> 人工序列
<220>
<223> C33B107 重链
<400> 80

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120

gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgc tggagagcgg cggaggactg gtgcagcctg 300
gaggaagcct gggcctgagc tgtgctgcca gcggctttac cttcagcggc tacgccatga 360
gctgggtgag acaggcccct ggcaagggcc tgaactgggt gagcgccatc gactacagcg 420
gcaacgacac ctactacgcc gacagcgtga agggaaggtt caccatcagc agggacaaca 480
gcaagaacac cctgtacctg cagatgaaca gcctgagggc cgaggacacc gctgtgtact 540
actgcgccaa ggagagccag ctgctgcacg gcctgttcga gcactggggc cagggcatcc 600
tggtgaccgt gagcagcgcc tccaccaagg gcccatcggt cttccccctg gcaccctcct 660
ccaagagcac ctctgggggc acagcggccc tgggctgcct ggtcaaggac tacttccccg 720
aaccggtgac ggtgtcgtgg aactcaggcg ccctgaccag cggcgtgcac accttcccgg 780
ctgtcctaca gtcctcagga ctctactccc tcagcagcgt ggtgaccgtg ccctccagca 840
gcttgggcac ccagacctac atctgcaacg tgaatcacaa gcccagcaac accaaggtgg 900
acaagaaagt tgagcccaaa tcttgtgaca aaactcacac atgcccaccg tgcccagcac 960
ctgaactcct gggggggaccg tcagtcttcc tcttcccccc aaaacccaag gacaccctca 1020
tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac gaagaccctg 1080
aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag acaaagccgc 1140
gggaggagca gtacaacagc acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg 1200
actggctgaa tggcaaggag tacaagtgca aggtctccaa caaagccctc ccagccccca 1260
tcgagaaaac catctccaaa gccaaagggc agccccgaga accacaggtg tacaccctgc 1320
ccccatcccg ggaggagatg accaagaacc aggtcagcct gacctgcctg gtcaaaggct 1380
tctatcccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag aacaactaca 1440
agaccacgcc tcccgtgctg gactccgacg gctccttcct gctctacagc aagctcaccg 1500
[0092] tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg catgaggctc 1560
tgcacaacca ctacacgcag aagagcctct ccctgtctcc gggtaaatga tagttcgaat 1620
tcctagaaga catgataaga tacattgatg agtttggaca aaccacaact agaatgcagt 1680
gaaaaaaatg ctttatttgt gaaatttgtg atgctattgc tttatttgta accattataa 1740
gctgcaataa acaagttaac aacaacaatt gcattcattt tatgtttcag gttcaggggg 1800
aggtgtggga 1810

<210> 81
<211> 1804
<212> DNA
<213> 人工序列
<220>
<223> C33B120 重链
<400> 81

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggagagcgg cggaggattc gtgcagcccg 300
gaggaagcct gagactgagc tgcgccgcca gcggcttcac cttcagctcc tactggatga 360
gctgggtgag acaggctccc ggcaagggac tggagtgggt ggccaacatc aagcagcacg 420
gcagcgagaa gtactacgtg gacagcgtga agggcaggtt caccatcagc agggacaacg 480
tgaagaacag cctgtacctg cagatgaaca gcctgaggac cgaggacacc gccgtgtact 540
actgcgccag ggacagggac ctgggctact tcgactactg gggccaggga accctggtga 600
ccgtgagcag cgcctccacc aagggcccat cggtcttccc cctggcaccc tcctccaaga 660

gcacctctgg gggcacagcg gccctgggct gcctggtcaa ggactacttc cccgaaccgg 720
tgacggtgtc gtggaactca ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc 780
tacagtcctc aggactctac tccctcagca gcgtggtgac cgtgccctcc agcagcttgg 840
gcacccagac ctacatctgc aacgtgaatc acaagcccag caacaccaag gtggacaaga 900
aagttgagcc caaatcttgt gacaaaactc acacatgccc accgtgccca gcacctgaac 960
tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc ctcatgatct 1020
cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca 1080
agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag ccgcgggagg 1140
agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac caggactggc 1200
tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga 1260
aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc ctgccccat 1320
cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa ggcttctatc 1380
ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac tacaagacca 1440
cgcctcccgt gctggactcc gacggctcct tcctgctcta cagcaagctc accgtggaca 1500
agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag gctctgcaca 1560
accactacac gcagaagagc ctctccctgt ctccgggtaa atgatagttc gaattcctag 1620
aagacatgat aagatacatt gatgagtttg gacaaaccac aactagaatg cagtgaaaaa 1680
aatgctttat ttgtgaaatt tgtgatgcta ttgctttatt tgtaaccatt ataagctgca 1740
ataaacaagt taacaacaac aattgcattc attttatgtt tcaggttcag ggggaggtgt 1800
ggga 1804

<210> 82
<211> 1825
<212> DNA
[0093] <213> 人工序列
<220>
<223> C33B122 重链
<400> 82

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag ctgcagctgc aggagagcgg acctggcctg gtgaagccca 300
gcgagaccct gagcctcaca tgcaccgtga gcggcggctc catcaggagc agcagctact 360
actggggctg gatcaggcag cctcccggaa aaggccccga gtggatcggc agcatctaca 420
gcagcggcaa cacctactac aacccctccc tcaagagcag ggtcaccatc agcgtggaca 480
ccagcaagaa ccagttcagc ctgaagctca tcagcatgac cgccgccgac accgccgtgt 540
tttactgcgc cagactggct gccaccatcg tggtgcctgc cgccaggtac ttcgactgct 600
ggggccaggg cacactggtg accgtgagca gcgcctccac caagggccca tcggtcttcc 660
ccctggcacc ctcctccaag agcacctctg ggggcacagc ggccctgggc tgcctggtca 720
aggactactt ccccgaaccg gtgacggtgt cgtggaactc aggcgccctg accagcggcg 780
tgcacacctt cccggctgtc ctacagtcct caggactcta ctccctcagc agcgtggtga 840
ccgtgccctc cagcagcttg ggcacccaga cctacatctg caacgtgaat cacaagccca 900
gcaacaccaa ggtggacaag aaagttgagc ccaaatcttg tgacaaaact cacacatgcc 960
caccgtgccc agcacctgaa ctcctggggg gaccgtcagt cttcctcttc cccccaaaac 1020
ccaaggacac cctcatgatc tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga 1080
gccacgaaga ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg 1140
ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca 1200

ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag 1260
ccctcccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc cgagaaccac 1320
aggtgtacac cctgccccca tcccgggagg agatgaccaa gaaccaggtc agcctgacct 1380
gcctggtcaa aggcttctat cccagcgaca tcgccgtgga gtgggagagc aatgggcagc 1440
cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggctcc ttcctgctct 1500
acagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg 1560
tgatgcatga ggctctgcac aaccactaca cgcagaagag cctctccctg tctccgggta 1620
aatgatagtt cgaattccta gaagacatga taagatacat tgatgagttt ggacaaacca 1680
caactagaat gcagtgaaaa aaatgcttta tttgtgaaat ttgtgatgct attgctttat 1740
ttgtaaccat tataagctgc aataaacaag ttaacaacaa caattgcatt cattttatgt 1800
ttcaggttca gggggaggtg tggga 1825

<210> 83
<211> 1825
<212> DNA
<213> 人工序列
<220>
<223> C33B123 重链
<400> 83

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag ctgcagctgc aggagagcgg acctggcctg gtgaagccca 300
[0094] gcgagacact gagcctgacc tgtaccgtga gcggcggcag catcagcagc aggagccact 360
actggggctg gattaggcag cctcctggag tgggcctgga gtggatcggc agcatctact 420
acaccggcag cacctactac aaccccagcc tgaagagcag ggtgaccatc agcgtggaca 480
ccagcaagaa ccagttcagc ctgaagctga gcagcgtgac agccgccgac acagccgtgt 540
actactgcgc caggctggcc gatatcgtgg tggtgcctgc cgccaggtac ttcgattact 600
ggggacaggg caccctggtg accgtgagca gcgcctccac caagggccca tcggtcttcc 660
ccctggcacc ctcctccaag agcacctctg ggggcacagc ggccctgggc tgcctggtca 720
aggactactt ccccgaaccg gtgacggtgt cgtggaactc aggcgccctg accagcggcg 780
tgcacacctt cccggctgtc ctacagtcct caggactcta ctccctcagc agcgtggtga 840
ccgtgccctc cagcagcttg ggcacccaga cctacatctg caacgtgaat cacaagccca 900
gcaacaccaa ggtggacaag aaagttgagc ccaaatcttg tgacaaaact cacacatgcc 960
caccgtgccc agcacctgaa ctcctggggg gaccgtcagt cttcctcttc cccccaaaac 1020
ccaaggacac cctcatgatc tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga 1080
gccacgaaga ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg 1140
ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca 1200
ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag 1260
ccctcccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc cgagaaccac 1320
aggtgtacac cctgccccca tcccgggagg agatgaccaa gaaccaggtc agcctgacct 1380
gcctggtcaa aggcttctat cccagcgaca tcgccgtgga gtgggagagc aatgggcagc 1440
cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggctcc ttcctgctct 1500
acagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg 1560
tgatgcatga ggctctgcac aaccactaca cgcagaagag cctctccctg tctccgggta 1620
aatgatagtt cgaattccta gaagacatga taagatacat tgatgagttt ggacaaacca 1680
caactagaat gcagtgaaaa aaatgcttta tttgtgaaat ttgtgatgct attgctttat 1740

ttgtaaccat tataagctgc aataaacaag ttaacaacaa caattgcatt cattttatgt 1800
ttcaggttca gggggaggtg tggga 1825

<210> 84
<211> 1807
<212> DNA
<213> 人工序列
<220>
<223> C33B124 重链
<400> 84

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgc tggagagcgg aggaggactg gtgcagcctg 300
gcggaagcct gaggctgagc tgtgccgcca gcagattcac cttcagcagc tacgccatga 360
cctgggtgag acaggcccct ggcaagggac tggagtgggt gagcaccatc aacatcagcg 420
gcggcagcac ctactacgcc gacagcgtga agggcaggtt caccatcagc agggacaaca 480
gcaagaacac cctgtacctg cagatgaaca gcctgagggc cgaggacacc gccgtgtact 540
actgcaccaa gggaggctac agcagcggcc ccttcgacta ctggggacag ggcaccctgg 600
tgagcgtgag cagcgcctcc accaagggcc catcggtctt ccccctggca ccctcctcca 660
agagcacctc tgggggcaca gcggccctgg gctgcctggt caaggactac ttccccgaac 720
cggtgacggt gtcgtggaac tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg 780
tcctacagtc ctcaggactc tactccctca gcagcgtggt gaccgtgccc tccagcagct 840
[0095] tgggcaccca gacctacatc tgcaacgtga atcacaagcc cagcaacacc aaggtggaca 900
agaaagttga gcccaaatct tgtgacaaaa ctcacacatg cccaccgtgc ccagcacctg 960
aactcctggg gggaccgtca gtcttcctct tccccccaaa acccaaggac accctcatga 1020
tctcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa gaccctgagg 1080
tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca aagccgcggg 1140
aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg caccaggact 1200
ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca gccccatcg 1260
agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac accctgcccc 1320
catcccggga ggagatgacc aagaaccagg tcagcctgac ctgcctggtc aaaggcttct 1380
atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac aactacaaga 1440
ccacgcctcc cgtgctggac tccgacggct ccttcctgct ctacagcaag ctcaccgtgg 1500
acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat gaggctctgc 1560
acaaccacta cacgcagaag agcctctccc tgtctccggg taaatgatag ttcgaattcc 1620
tagaagacat gataagatac attgatgagt ttggacaaac cacaactaga atgcagtgaa 1680
aaaaatgctt tatttgtgaa atttgtgatg ctattgcttt atttgtaacc attataagct 1740
gcaataaaca agttaacaac aacaattgca ttcattttat gtttcaggtt cagggggagg 1800
tgtggga 1807

<210> 85
<211> 1837
<212> DNA
<213> 人工序列
<220>
<223> C33B125 重链
<400> 85

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcaactgg tggagagcgg cggcggagtg gtgcaacctg 300
gcagaagcct gagactgagc tgcgccgcca gcggcttcac cttcagcagc tacggcatgc 360
actgggtgag acaggcccct ggcaaaggcc tggaatgggt ggccgtgatc agctacgacg 420
gcagcaacaa gtactacgcc gacagcgtga agggcaggtt caccatcagc agggacaaca 480
gcaagaacac cctgtacctg cagatgaaca gcctgagggc cgaggacacc gccgtgtact 540
actgcgccaa ggacttcagg agcttcgact ggctgccccc cgacagcacc tcctactacg 600
gcatggacgt gtggggccag ggaaccaccg tgaccgtgag cagcgcctcc accaagggcc 660
catcggtctt ccccctggca ccctcctcca agagcacctc tgggggcaca gcggccctgg 720
gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc 780
tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca 840
gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc tgcaacgtga 900
atcacaagcc cagcaacacc aaggtggaca agaaagttga gcccaaatct tgtgacaaaa 960
ctcacacatg cccaccgtgc ccagcacctg aactcctggg gggaccgtca gtcttcctct 1020
tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc acatgcgtgg 1080
tggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg 1140
aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg taccgtgtgg 1200
tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac aagtgcaagg 1260
tctccaacaa agccctccca gccccccatcg agaaaaccat ctccaaagcc aaagggcagc 1320
cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc aagaaccagg 1380
[0096] tcagcctgac ctgcctggtc aaaggcttct atcccagcga catcgccgtg gagtgggaga 1440
gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac tccgacggct 1500
ccttcctgct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag gggaacgtct 1560
tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag agcctctccc 1620
tgtctccggg taaatgatag ttcgaattcc tagaagacat gataagatac attgatgagt 1680
ttggacaaac cacaactaga atgcagtgaa aaaaatgctt tatttgtgaa atttgtgatg 1740
ctattgcttt atttgtaacc attataagct gcaataaaca agttaacaac aacaattgca 1800
ttcattttat gtttcaggtt cagggggagg tgtggga 1837

<210> 86
<211> 1828
<212> DNA
<213> 人工序列
<220>
<223> C33B760 重链
<400> 86

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgg tggagagcgg aggcggagtg gtgcagcctg 300
gcagaagcct gagactgagc tgcgccgcca gcggcttcac cttcagcagc tacggcatgc 360
actgggtgag gcagagccct ggcaaaggcc tggagtgggt ggccgtgatc agctacgacg 420
gcagcaacaa gtactgcgcc gacagcgtga agggcaggtt caccatcagc agggacaaca 480
gcaagagcac cctgtacctg cagatgaaca gcctgagggc cgaggacacc gccgtgtact 540

actgcgccaa ggacttcagg agcctggact ggctgccccc cgatagcacc agctatgacg 600
gcatggacgt gtggggacag ggcaccaccg tgaccgtgag cagcgcttcc accaagggcc 660
catccgtctt ccccctggcg ccctgctcca ggagcacctc cgagagcaca gccgccctgg 720
gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc 780
tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca 840
gcagcgtggt gaccgtgccc tccagcagct tgggcacgaa aacctacacc tgcaacgtag 900
atcacaagcc cagcaacacc aaggtggaca agagagttga gtccaaatat ggtcccccat 960
gcccaccatg cccagcacct gaggccgccg ggggaccatc agtcttcctg ttcccccaa 1020
aacccaagga cactctcatg atctcccgga cccctgaggt cacgtgcgtg gtggtggacg 1080
tgagccagga agaccccgag gtccagttca actggtacgt ggatggcgtg gaggtgcata 1140
atgccaagac aaagccgcgg gaggagcagt tcaacagcac gtaccgtgtg gtcagcgtcc 1200
tcaccgtcct gcaccaggac tggctgaacg gcaaggagta caagtgcaag gtctccaaca 1260
aaggcctccc gtcctccatc gagaaaacca tctccaaagc caaagggcag ccccgagagc 1320
cacaggtgta caccctgccc ccatcccagg aggagatgac caagaaccag gtcagcctga 1380
cctgcctggt caaaggcttc taccccagcg acatcgccgt ggagtgggag agcaatgggc 1440
agccggagaa caactacaag accacgcctc ccgtgctgga ctccgacggc tccttcttcc 1500
tctacagcag gctaaccgtg gacaagagca ggtggcagga ggggaatgtc ttctcatgct 1560
ccgtgatgca tgaggctctg cacaaccact acacacagaa gagcctctcc ctgtctctgg 1620
gtaaatgata gttcgaattc ctagaagaca tgataagata cattgatgag tttggacaaa 1680
ccacaactag aatgcagtga aaaaaatgct ttatttgtga aatttgtgat gctattgctt 1740
tatttgtaac cattataagc tgcaataaac aagttaacaa caacaattgc attcatttta 1800
tgtttcaggt tcaggggggag gtgtggga 1828

<210> 87

[0097] <211> 1828

<212> DNA

<213> 人工序列

<220>

<223> C33B777 重链

<400> 87

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgg tggagagcgg cggaggagtg gtgcagcctg 300
gaaggagcct gagactgtcc tgcgccgcta gcggcttcac cttcagcagc tacggcatgc 360
actgggtgag acaggctccc ggcaagggac tggagtgggt ggtggtgatc agctacgacg 420
gcagcaacaa gtactacgcc gacagcgtga agggcaggtt caccatcagc agggacaaca 480
gcaagaacac cctgtacctg cagatgaaca gcctgagggc cgaggacacc gccgtgtact 540
actgcgccaa ggacttcagg gacttcgact ggctgcctcc tgatagcacc agctaccacg 600
gcatggacgt gtggggccag ggaaccaccg tgaccgtgag cagcgcttcc accaagggcc 660
catccgtctt ccccctggcg ccctgctcca ggagcacctc cgagagcaca gccgccctgg 720
gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc 780
tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca 840
gcagcgtggt gaccgtgccc tccagcagct tgggcacgaa aacctacacc tgcaacgtag 900
atcacaagcc cagcaacacc aaggtggaca agagagttga gtccaaatat ggtcccccat 960
gcccaccatg cccagcacct gaggccgccg ggggaccatc agtcttcctg ttcccccaa 1020
aacccaagga cactctcatg atctcccgga cccctgaggt cacgtgcgtg gtggtggacg 1080

tgagccagga agaccccgag gtccagttca actggtacgt ggatggcgtg gaggtgcata 1140
atgccaagac aaagccgcgg gaggagcagt tcaacagcac gtaccgtgtg gtcagcgtcc 1200
tcaccgtcct gcaccaggac tggctgaacg gcaaggagta caagtgcaag gtctccaaca 1260
aaggcctccc gtcctccatc gagaaaacca tctccaaagc caaagggcag ccccgagagc 1320
cacaggtgta caccctgccc ccatcccagg aggagatgac caagaaccag gtcagcctga 1380
cctgcctggt caaaggcttc taccccagcg acatcgccgt ggagtgggag agcaatgggc 1440
agccggagaa caactacaag accacgcctc ccgtgctgga ctccgacggc tccttcttcc 1500
tctacagcag gctaaccgtg gacaagagca ggtggcagga ggggaatgtc ttctcatgct 1560
ccgtgatgca tgaggctctg cacaaccact acacacagaa gagcctctcc ctgtctctgg 1620
gtaaatgata gttcgaattc ctagaagaca tgataagata cattgatgag tttggacaaa 1680
ccacaactag aatgcagtga aaaaaatgct ttatttgtga aatttgtgat gctattgctt 1740
tatttgtaac cattataagc tgcaataaac aagttaacaa caacaattgc attcatttta 1800
tgtttcaggt tcaggggggag gtgtggga 1828

<210> 88
<211> 1828
<212> DNA
<213> 人工序列
<220>
<223> C33B778 重链
<400> 88

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
[0098] tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgg tggaaagcgg cggaggcgtg gtgcagcctg 300
gaagaagcct gagactgagc tgcgtggcca gcggcttcac ctttagcagc tacggcatgc 360
actgggtgag gcaggctcct ggcaagggac tggagtgggt ggccgtgatc agctacgacg 420
gcagcaacaa gtactacgcc gacagcgtga agggcaggtt caccatcagc agggacaaca 480
gcaagaacac cctgtacctg cagatgaaca gcctgagagc cgagggcacc gccgtgtact 540
actgcgccaa ggacttcagg agctttgatt ggctgccccc tgatagcgcc agctaccacg 600
gcatggacgt gtggggccag ggcacaaccg tgaccgtgag cagcgcttcc accaagggcc 660
catccgtctt ccccctggcg ccctgctcca ggagcacctc cgagagcaca gccgccctgg 720
gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc 780
tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca 840
gcagcgtggt gaccgtgccc tccagcagct tgggcacgaa aacctacacc tgcaacgtag 900
atcacaagcc cagcaacacc aaggtggaca agagagttga gtccaaatat ggtccccccat 960
gcccaccatg cccagcacct gaggccgccg ggggaccatc agtcttcctg ttcccccccaa 1020
aacccaagga cactctcatg atctcccgga cccctgaggt cacgtgcgtg gtggtggacg 1080
tgagccagga agaccccgag gtccagttca actggtacgt ggatggcgtg gaggtgcata 1140
atgccaagac aaagccgcgg gaggagcagt tcaacagcac gtaccgtgtg gtcagcgtcc 1200
tcaccgtcct gcaccaggac tggctgaacg gcaaggagta caagtgcaag gtctccaaca 1260
aaggcctccc gtcctccatc gagaaaacca tctccaaagc caaagggcag ccccgagagc 1320
cacaggtgta caccctgccc ccatcccagg aggagatgac caagaaccag gtcagcctga 1380
cctgcctggt caaaggcttc taccccagcg acatcgccgt ggagtgggag agcaatgggc 1440
agccggagaa caactacaag accacgcctc ccgtgctgga ctccgacggc tccttcttcc 1500
tctacagcag gctaaccgtg gacaagagca ggtggcagga ggggaatgtc ttctcatgct 1560
ccgtgatgca tgaggctctg cacaaccact acacacagaa gagcctctcc ctgtctctgg 1620

gtaaatgata gttcgaattc ctagaagaca tgataagata cattgatgag tttggacaaa 1680
ccacaactag aatgcagtga aaaaaatgct ttatttgtga aatttgtgat gctattgctt 1740
tatttgtaac cattataagc tgcaataaac aagttaacaa caacaattgc attcatttta 1800
tgtttcaggt tcagggggag gtgtggga 1828

<210> 89
<211> 1795
<212> DNA
<213> 人工序列
<220>
<223> C33B782 重链
<400> 89

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggagagcgg aggaggactg gtgcagcctg 300
gaggcagcct gagactgagc tgcgccgcta gcggcttcac cttcagcagc tactggatga 360
gctgggtgag acaggcccct ggcaagggac tggagtgggt ggccaacatc aagcagcacg 420
gcagcgagaa gtactacgtg gatagcgtga agggcaggtt caccatcagc agggacaacg 480
ccaaaaacag cctgtacctg cagatgaaca gcctgagggc cgaggacacc gccgtgtatt 540
actgcgccag ggacagggac ctgggctact tcgactactg gggccagggc accctggtga 600
cagtgagcag cgcttccacc aagggcccat ccgtcttccc cctggcgccc tgctccagga 660
gcacctccga gagcacagcc gccctgggct gcctggtcaa ggactacttc cccgaaccgg 720
[0099] tgacggtgtc gtggaactca ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc 780
tacagtcctc aggactctac tccctcagca gcgtggtgac cgtgccctcc agcagcttgg 840
gcacgaaaac ctacacctgc aacgtagatc acaagcccag caacaccaag gtggacaaga 900
gagttgagtc caaatatggt cccccatgcc caccatgccc agcacctgag gccgccgggg 960
gaccatcagt cttcctgttc cccccaaaac ccaaggacac tctcatgatc tcccggaccc 1020
ctgaggtcac gtgcgtggtg gtggacgtga gccaggaaga ccccgaggtc cagttcaact 1080
ggtacgtgga tggcgtggag gtgcataatg ccaagacaaa gccgcgggag gagcagttca 1140
acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca ccaggactgg ctgaacggca 1200
aggagtacaa gtgcaaggtc tccaacaaag gcctcccgtc ctccatcgag aaaaccatct 1260
ccaaagccaa agggcagccc cgagagccac aggtgtacac cctgccccca tcccaggagg 1320
agatgaccaa gaaccaggtc agcctgacct gcctggtcaa aggcttctac cccagcgaca 1380
tcgccgtgga gtgggagagc aatgggcagc cggagaacaa ctacaagacc acgcctcccg 1440
tgctggactc cgacggctcc ttcttcctct acagcaggct aaccgtggac aagagcaggt 1500
ggcaggaggg gaatgtcttc tcatgctccg tgatgcatga ggctctgcac aaccactaca 1560
cacagaagag cctctccctg tctctgggta aatgatagtt cgaattccta gaagacatga 1620
taagatacat tgatgagttt ggacaaacca caactagaat gcagtgaaaa aaatgcttta 1680
tttgtgaaat ttgtgatgct attgctttat ttgtaaccat tataagctgc aataaacaag 1740
ttaacaacaa caattgcatt cattttatgt ttcaggttca gggggaggtg tggga 1795

<210> 90
<211> 1795
<212> DNA
<213> 人工序列
<220>
<223> C33B792 重链

<400> 90

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggagagcgg cggaggattc gtgcagcccg 300
gaggaagcct gagactgagc tgcgccgcca gcggcttcac cttcagctcc tactggatga 360
gctgggtgag acaggctccc ggcaagggac tggagtgggt ggccaacatc aagcagcacg 420
gcagcgagaa gtactacgtg gacagcgtga agggcaggtt caccatcagc agggacaacg 480
tgaagaacag cctgtacctg cagatgaaca gcctgaggac cgaggacacc gccgtgtact 540
actgcgccag ggacagggac ctgggctact tcgactactg gggccaggga accctggtga 600
ccgtgagcag cgcttccacc aagggcccat ccgtcttccc cctggcgccc tgctccagga 660
gcacctccga gagcacagcc gccctgggct gcctggtcaa ggactacttc cccgaaccgg 720
tgacggtgtc gtggaactca ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc 780
tacagtcctc aggactctac tccctcagca gcgtggtgac cgtgccctcc agcagcttgg 840
gcacgaaaac ctacacctgc aacgtagatc acaagcccag caacaccaag gtggacaaga 900
gagttgagtc caaatatggt cccccatgcc caccatgccc agcacctgag gccgccgggg 960
gaccatcagt cttcctgttc cccccaaaac ccaaggacac tctcatgatc tcccggaccc 1020
ctgaggtcac gtgcgtggtg gtggacgtga gccaggaaga ccccgaggtc cagttcaact 1080
ggtacgtgga tggcgtggag gtgcataatg ccaagacaaa gccgcgggag gagcagttca 1140
acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca ccaggactgg ctgaacggca 1200
aggagtacaa gtgcaaggtc tccaacaaag gcctcccgtc ctccatcgag aaaaccatct 1260
ccaaagccaa agggcagccc cgagagccac aggtgtacac cctgccccca tcccaggagg 1320
[0100] agatgaccaa gaaccaggtc agcctgacct gcctggtcaa aggcttctac cccagcgaca 1380
tcgccgtgga gtgggagagc aatgggcagc cggagaacaa ctacaagacc acgcctcccg 1440
tgctggactc cgacggctcc ttcttcctct acagcaggct aaccgtggac aagagcaggt 1500
ggcaggaggg gaatgtcttc tcatgctccg tgatgcatga ggctctgcac aaccactaca 1560
cacagaagag cctctccctg tctctgggta aatgatagtt cgaattccta gaagacatga 1620
taagatacat tgatgagttt ggacaaacca caactagaat gcagtgaaaa aaatgcttta 1680
tttgtgaaat ttgtgatgct attgctttat ttgtaaccat tataagctgc aataaacaag 1740
ttaacaacaa caattgcatt cattttatgt ttcaggttca gggggaggtg tggga 1795

<210> 91
<211> 1795
<212> DNA
<213> 人工序列
<220>
<223> C33B799 重链
<400> 91

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggagagcgg aggcggattt gtgcagcctg 300
gcggcagcct gagactgagc tgtgccgcca gcggcttcac cttcagcagc tactggatga 360
gctgggtgag gcaggccgct ggaaagggac tggagtgggt ggccaacatc aagcagcacg 420
gaagcgagaa gtactacgtg gacagcgtga agggaaggtt cacaatcagc agggacaacg 480
ccaagaacag cctgtacctg cagatgaaca gcctgagggc cgaggacacc gccgtgtact 540

actgcgccag ggacagggac ctgggctact tcgactactg gggccagggc accctggtga 600
cagtgagcag cgcttccacc aagggcccat ccgtcttccc cctggcgccc tgctccagga 660
gcacctccga gagcacagcc gccctgggct gcctggtcaa ggactacttc cccgaaccgg 720
tgacggtgtc gtggaactca ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc 780
tacagtcctc aggactctac tccctcagca gcgtggtgac cgtgccctcc agcagcttgg 840
gcacgaaaac ctacacctgc aacgtagatc acaagcccag caacaccaag gtggacaaga 900
gagttgagtc caaatatggt cccccatgcc caccatgccc agcacctgag gccgccgggg 960
gaccatcagt cttcctgttc cccccaaaac ccaaggacac tctcatgatc tcccggaccc 1020
ctgaggtcac gtgcgtggtg gtggacgtga gccaggaaga ccccgaggtc cagttcaact 1080
ggtacgtgga tggcgtggag gtgcataatg ccaagacaaa gccgcgggag gagcagttca 1140
acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca ccaggactgg ctgaacggca 1200
aggagtacaa gtgcaaggtc tccaacaaag gcctcccgtc ctccatcgag aaaaccatct 1260
ccaaagccaa agggcagccc cgagagccac aggtgtacac cctgccccca tcccaggagg 1320
agatgaccaa gaaccaggtc agcctgacct gcctggtcaa aggcttctac cccagcgaca 1380
tcgccgtgga gtgggagagc aatgggcagc cggagaacaa ctacaagacc acgcctcccg 1440
tgctggactc cgacggctcc ttcttcctct acagcaggct aaccgtggac aagagcaggt 1500
ggcaggaggg gaatgtcttc tcatgctccg tgatgcatga ggctctgcac aaccactaca 1560
cacagaagag cctctccctg tctctgggta aatgatagtt cgaattccta gaagacatga 1620
taagatacat tgatgagttt ggacaaacca caactagaat gcagtgaaaa aaatgcttta 1680
tttgtgaaat ttgtgatgct attgctttat ttgtaaccat tataagctgc aataaacaag 1740
ttaacaacaa caattgcatt cattttatgt ttcaggttca gggggaggtg tggga 1795

<210> 92
<211> 1801
[0101] <212> DNA
<213> 人工序列
<220>
<223> C33B806 重链
<400> 92

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag ctgcagctgc aggagagcgg acctggcctg gtgaagccca 300
gcgagaccct gagcctgacc tgcacagtga gcggcggcag catcagcagc agcagctact 360
actggggctg gatcaggcag cctcctggca agggcctgga ctggatcggc agcatcaact 420
acagcggcag cacctactac aaccccagcc tgaagagcag ggtgaccatc agcgtggaca 480
ccagcaagat ccagttcagc ctgaagctca gaagcgtgac cgccgccgac acagccgtgt 540
actactgcgc cagactggac ggctacgaga gccccttcga ctactggggc cagggcaccc 600
tggtgacagt gagcagcgct tccaccaagg gcccatccgt cttccccctg gcgccctgct 660
ccaggagcac ctccgagagc acagccgccc tgggctgcct ggtcaaggac tacttccccg 720
aaccggtgac ggtgtcgtgg aactcaggcg ccctgaccag cggcgtgcac accttcccgg 780
ctgtcctaca gtcctcagga ctctactccc tcagcagcgt ggtgaccgtg ccctccagca 840
gcttgggcac gaaaacctac acctgcaacg tagatcacaa gcccagcaac accaaggtgg 900
acaagagagt tgagtccaaa tatggtcccc catgcccacc atgcccagca cctgaggccg 960
ccgggggacc atcagtcttc ctgttccccc caaaacccaa ggacactctc atgatctccc 1020
ggaccccctga ggtcacgtgc gtggtggtgg acgtgagcca ggaagacccc gaggtccagt 1080
tcaactggta cgtggatggc gtggaggtgc ataatgccaa gacaaagccg cgggaggagc 1140

agttcaacag cacgtaccgt gtggtcagcg tcctcaccgt cctgcaccag gactggctga 1200
acggcaagga gtacaagtgc aaggtctcca acaaaggcct cccgtcctcc atcgagaaaa 1260
ccatctccaa agccaaaggg cagccccgag agccacaggt gtacaccctg cccccatccc 1320
aggaggagat gaccaagaac caggtcagcc tgacctgcct ggtcaaaggc ttctacccca 1380
gcgacatcgc cgtggagtgg gagagcaatg ggcagccgga gaacaactac aagaccacgc 1440
ctcccgtgct ggactccgac ggctccttct tcctctacag caggctaacc gtggacaaga 1500
gcaggtggca ggaggggaat gtcttctcat gctccgtgat gcatgaggct ctgcacaacc 1560
actacacaca gaagagcctc tccctgtctc tgggtaaatg atagttcgaa ttcctagaag 1620
acatgataag atacattgat gagtttggac aaaccacaac tagaatgcag tgaaaaaaat 1680
gctttatttg tgaaatttgt gatgctattg ctttatttgt aaccattata agctgcaata 1740
aacaagttaa caacaacaat tgcattcatt ttatgtttca ggttcagggg gaggtgtggg 1800
a 1801

<210> 93
<211> 1828
<212> DNA
<213> 人工序列
<220>
<223> C33B830 重链
<400> 93

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
[0102] cccaaagtat acaggcccag gtgcaactgg tggagagcgg cggcggagtg gtgcaacctg 300
gcagaagcct gagactgagc tgcgccgcca gcggcttcac cttcagcagc tacggcatgc 360
actgggtgag acaggccgct ggcaaaggcc tggaatgggt ggccgtgatc agctacgacg 420
gcagcaacaa gtactacgcc gacagcgtga agggcaggtt caccatcagc agggacaaca 480
gcaagaacac cctgtacctg cagatgaaca gcctgagggc cgaggacacc gccgtgtact 540
actgcgccaa ggacttcagg agcttcgact ggctgccccc cgacagcacc tcctactacg 600
gcatggacgt gtggggccag ggaaccaccg tgaccgtgag cagcgcttcc accaagggcc 660
catccgtctt ccccctggcg ccctgctcca ggagcacctc cgagagcaca gccgccctgg 720
gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc 780
tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca 840
gcagcgtggt gaccgtgccc tccagcagct tgggcacgaa aacctacacc tgcaacgtag 900
atcacaagcc cagcaacacc aaggtggaca agagagttga gtccaaatat ggtccccccat 960
gcccaccatg cccagcacct gaggccgccg ggggaccatc agtcttcctg ttcccccccaa 1020
aacccaagga cactctcatg atctcccgga cccctgaggt cacgtgcgtg gtggtggacg 1080
tgagccagga agaccccgag gtccagttca actggtacgt ggatggcgtg gaggtgcata 1140
atgccaagac aaagccgcgg gaggagcagt tcaacagcac gtaccgtgtg gtcagcgtcc 1200
tcaccgtcct gcaccaggac tggctgaacg gcaaggagta caagtgcaag gtctccaaca 1260
aaggcctccc gtcctccatc gagaaaacca tctccaaagc caaagggcag ccccgagagc 1320
cacaggtgta caccctgccc ccatcccagg aggagatgac caagaaccag gtcagcctga 1380
cctgcctggt caaaggcttc taccccagcg acatcgccgt ggagtgggag agcaatgggc 1440
agccggagaa caactacaag accacgcctc ccgtgctgga ctccgacggc tccttcttcc 1500
tctacagcag gctaaccgtg gacaagagca ggtggcagga ggggaatgtc ttctcatgct 1560
ccgtgatgca tgaggctctg cacaaccact acacacagaa gagcctctcc ctgtctctgg 1620
gtaaatgata gttcgaattc ctagaagaca tgataagata cattgatgag tttggacaaa 1680

ccacaactag aatgcagtga aaaaaatgct ttatttgtga aatttgtgat gctattgctt 1740
tatttgtaac cattataagc tgcaataaac aagttaacaa caacaattgc attcatttta 1800
tgtttcaggt tcagggggag gtgtggga 1828

<210> 94
<211> 1792
<212> DNA
<213> 人工序列
<220>
<223> C33B836 重链
<400> 94

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgg tgcagagcgg aagcgagctg agaaagcccg 300
gcgccagcgt gaaggtgagc tgcaaggcca gcggctacac cttcaccaac tacgccatga 360
actgggtgag gcaggccctt ggacaaggcc tggagtggat gggctggatc aacaccaaca 420
ccggcaaccc cacctacgcc cagggcttta ccggcaggtt cgtgttcagc ctggacacca 480
gcgtgagcag cgcctacctg cagatcagca gcctgaaggc cgaggacacc gccatgtact 540
actgcgccac cgacagggac aggggaaccg actactgggg ccagggcaca ctggtgaccg 600
tgagcagcgc ttccaccaag ggcccatccg tcttccccct ggcgccctgc tccaggagca 660
cctccgagag cacagccgcc ctgggctgcc tggtcaagga ctacttcccc gaaccggtga 720
cggtgtcgtg gaactcaggc gccctgacca gcggcgtgca caccttcccg gctgtcctac 780
[0103] agtcctcagg actctactcc ctcagcagcg tggtgaccgt gccctccagc agcttgggca 840
cgaaaaccta cacctgcaac gtagatcaca agcccagcaa caccaaggtg gacaagagag 900
ttgagtccaa atatggtccc ccatgcccac catgcccagc acctgaggcc gccgggggac 960
catcagtctt cctgttcccc ccaaaaccca aggacactct catgatctcc cggacccctg 1020
aggtcacgtg cgtggtggtg gacgtgagcc aggaagaccc cgaggtccag ttcaactggt 1080
acgtggatgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag cagttcaaca 1140
gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg aacggcaagg 1200
agtacaagtg caaggtctcc aacaaaggcc tcccgtcctc catcgagaaa accatctcca 1260
aagccaaagg gcagccccga gagccacagg tgtacaccct gccccccatcc caggaggaga 1320
tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctacccc agcgacatcg 1380
ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg cctcccgtgc 1440
tggactccga cggctccttc ttcctctaca gcaggctaac cgtggacaag agcaggtggc 1500
aggaggggaa tgtcttctca tgctccgtga tgcatgaggc tctgcacaac cactacacac 1560
agaagagcct ctccctgtct ctgggtaaat gatagttcga attcctagaa gacatgataa 1620
gatacattga tgagtttgga caaaccacaa ctagaatgca gtgaaaaaaa tgctttattt 1680
gtgaaatttg tgatgctatt gctttatttg taaccattat aagctgcaat aaacaagtta 1740
acaacaacaa ttgcattcat tttatgtttc aggttcaggg ggaggtgtgg ga 1792

<210> 95
<211> 1828
<212> DNA
<213> 人工序列
<220>
<223> C33B937 重链
<400> 95

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgg tggaaagcgg cggaggcgtg gtgcagcctg 300
gaagaagcct gagactgagc tgcgtggcca gcggcttcac ctttagcagc tacggcatgc 360
actgggtgag gcaggctcct ggcaagggac tggagtgggt ggccgtgatc agctacgacg 420
gcagcaacaa gtactacgcc gacagcgtga agggcaggtt caccatcagc agggacaaca 480
gcaagaacac cctgtacctg cagatgaaca gcctgagagc cgagggcacc gccgtgtact 540
actgcgccaa ggacttcagg agctttgatt ggctgccccc tgatagcgcc agctaccacg 600
gcatggacgt gtggggccag ggcacaaccg tgaccgtgag cagcgcttcc accaagggcc 660
catccgtctt ccccctggcg ccctgctcca ggagcacctc cgagagcaca gccgccctgg 720
gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc 780
tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca 840
gcagcgtggt gaccgtgccc tccagcagct tgggcacgaa aacctacacc tgcaacgtag 900
atcacaagcc cagcaacacc aaggtggaca agagagttga gtccaaatat ggtccccccat 960
gcccaccatg cccagcacct gaggccgccg ggggaccatc agtcttcctg ttcccccccaa 1020
aacccaagga cactctcatg atctcccgga cccctgaggt cacgtgcgtg gtggtggacg 1080
tgagccagga agaccccgag gtccagttca actggtacgt ggatggcgtg gaggtgcata 1140
atgccaagac aaagccgcgg gaggagcagt tcaacagcac gtaccgtgtg gtcagcgtcc 1200
tcaccgtcct gcaccaggac tggctgaacg gcaaggagta caagtgcaag gtctccaaca 1260
aaggcctccc gtcctccatc gagaaaacca tctccaaagc caaagggcag ccccgagagc 1320
cacaggtgta caccctgccc ccatcccagg aggagatgac caagaaccag gtcagcctga 1380
[0104] cctgcctggt caaaggcttc taccccagcg acatcgccgt ggagtgggag agcaatgggc 1440
agccggagaa caactacaag accacgcctc ccgtgctgga ctccgacggc tccttcttcc 1500
tctacagcag gctaaccgtg gacaagagca ggtggcagga ggggaatgtc ttctcatgct 1560
ccgtgatgca tgaggctctg cacaaccact acacacagaa gagcctctcc ctgtctctgg 1620
gtaaatgata gttcgaattc ctagaagaca tgataagata cattgatgag tttggacaaa 1680
ccacaactag aatgcagtga aaaaaatgct ttatttgtga aatttgtgat gctattgctt 1740
tatttgtaac cattataagc tgcaataaac aagttaacaa caacaattgc attcatttta 1800
tgtttcaggt tcaggggggag gtgtggga 1828

<210> 96
<211> 217
<212> PRT
<213> 人工序列
<220>
<223> C33B46 轻链
<400> 96

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

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

<210> 97
<211> 217
<212> PRT
<213> 人工序列

[0105] <220>
<223> C33B48 轻链
<400> 97

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

165 170 175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
180 185 190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
195 200 205
Lys Thr Val Ala Pro Thr Glu Cys Ser
210 215
<210> 98
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B52 轻链
<400> 98
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Ile Cys Ser Gly Asp Lys Leu Gly Asn Lys Tyr Ala
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Val
[0106] 65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Tyr Val
85 90 95
Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210
<210> 99
<211> 213
<212> PRT
<213> 人工序列
<220>

<223> C33B54 轻链
<400> 99
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Thr Cys Gly Gly Ser Asn Ile Gly Ser Lys Ser Val
20 25 30
His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Met Val Val Tyr
35 40 45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp Val
85 90 95
Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
100 105 110
Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
115 120 125
Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
130 135 140
Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150 155 160
Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
[0107] 165 170 175
Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
180 185 190
Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
195 200 205
Pro Thr Glu Cys Ser
210
<210> 100
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B55 轻链
<400> 100
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly His Lys Leu Gly Asp Lys Tyr Ala
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Val Val Ile Tyr
35 40 45
Lys Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Phe Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

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

<210> 101
<211> 212
<212> PRT
<213> 人工序列
<220>

[0108] <223> C33B56 轻链
<400> 101

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

Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 102
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B61 轻链
<400> 102

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

[0109]

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

<210> 103
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B62 轻链

<400> 103

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

[0110] Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 104
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B63 轻链

<400> 104

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

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

<210> 105
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B64 轻链

[0111] <400> 105
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Trp Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser

180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210
<210> 106
<211> 214
<212> PRT
<213> 人工序列
<220>
<223> C33B66 轻链
<400> 106
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ile Lys Ser Val
20 25 30
His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
35 40 45
Asp Asp Ser Asp Arg Pro Pro Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Thr Arg Val Glu Ala Gly
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
[0112] 85 90 95
Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205
Ala Pro Thr Glu Cys Ser
210
<210> 107
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B72 轻链
<400> 107

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Val Val Ile Tyr
35 40 45
Gln Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Phe Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
[0113] 180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 108
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B73 轻链
<400> 108

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

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 109
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B75 轻链
<400> 109

[0114]
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Trp Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190

Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 110
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B77 轻链
<400> 110

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

[0115] Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 111
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B79 轻链
<400> 111

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Pro Pro Gly Gln

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

[0116]
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 112
<211> 217
<212> PRT
<213> 人工序列
<220>
<223> C33B80 轻链
<400> 112

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

100 105 110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
115 120 125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
130 135 140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145 150 155 160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
165 170 175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
180 185 190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
195 200 205
Lys Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 113
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B82 轻链
<400> 113

[0117]
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Glu Leu Gly Asn Lys Tyr Ala
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Val Val Val Tyr
35 40 45
Gln Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Phe Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro

195 200 205

Thr Glu Cys Ser
210

<210> 114
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B83 轻链
<400> 114

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asp Asn Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Asn Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
[0118] 100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205

Thr Glu Cys Ser
210

<210> 115
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B87 轻链
<400> 115

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asn Lys Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asp Thr Lys Arg Pro Ser Gly Ile Pro Glu Arg Val Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr His Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
[0119] 195 200 205
Thr Glu Cys Ser
210

<210> 116
<211> 217
<212> PRT
<213> 人工序列
<220>
<223> C33B88 轻链
<400> 116

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

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
115 120 125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
130 135 140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145 150 155 160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
165 170 175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
180 185 190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
195 200 205
Lys Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 117
<211> 214
<212> PRT
<213> 人工序列
<220>
<223> C33B89 轻链
<400> 117

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

[0120]

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

Ala Pro Thr Glu Cys Ser
210

<210> 118
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B94 轻链
<400> 118

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

[0121]

Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 119
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B95 轻链
<400> 119

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

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

[0122] Thr Glu Cys Ser
210

<210> 120
<211> 214
<212> PRT
<213> 人工序列
<220>
<223> C33B96 轻链
<400> 120
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ala Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Thr Cys Gly Gly Ser Asn Ile Gly Lys Ile Ser Val
20 25 30
His Trp Tyr Gln Gln Lys Ala Gly Gln Ala Pro Val Leu Val Val His
35 40 45
Asp Asp Arg Ala Arg Pro Ser Gly Ile Pro Glu Arg Leu Ser Gly Ser
50 55 60
Asn Ser Gly Thr Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Val Gly
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asn Ser Ser Ser Val His
85 90 95
Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln

115 120 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205
Ala Pro Thr Glu Cys Ser
210

<210> 121
<211> 214
<212> PRT
<213> 人工序列
<220>
<223> C33B101 轻链
<400> 121
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
[0123] 20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Phe
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala
100 105 110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205
Phe Asn Arg Gly Glu Cys

210

<210> 122
<211> 220
<212> PRT
<213> 人工序列
<220>
<223> C33B107 轻链
<400> 122

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30
Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Ala Gly Gln
35 40 45
Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ile Leu Ile
65 70 75 80
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95
Tyr Tyr Gly Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110
Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
[0124] 115 120 125
Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
130 135 140
Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
145 150 155 160
Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
165 170 175
Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
180 185 190
Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
195 200 205
Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215 220

<210> 123
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B120 轻链
<400> 123

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

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

[0125]

<210> 124
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B122 轻链
<400> 124
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Val Ser Ile Ser Cys Ser Gly Asp Arg Leu Gly Asp Lys Tyr Ala
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Ser Tyr Val
85 90 95
Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125

Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 125
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B123 轻链
<400> 125
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

[0126] Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Glu Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Tyr Val
85 90 95
Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 126
<211> 213
<212> PRT
<213> 人工序列
<220>
<223> C33B124 轻链
<400> 126

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

[0127]

Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
130 135 140
Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150 155 160
Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
165 170 175
Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
180 185 190
Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
195 200 205
Pro Thr Glu Cys Ser
210

<210> 127
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B125 轻链
<400> 127

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

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

[0128] <210> 128
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B760 轻链
<400> 128
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly His Lys Leu Gly Asp Lys Tyr Ala
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Val Val Ile Tyr
35 40 45
Lys Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Phe Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val

130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 129
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B777 轻链
<400> 129
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Val Val Ile Tyr
[0129] 35 40 45
Gln Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Phe Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 130

<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B778 轻链
<400> 130

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asp Gly Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Phe Gly Asn Lys Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Arg Asn Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
[0130] 130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 131
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B782 轻链
<400> 131

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

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

<210> 132

[0131]

<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B792 轻链
<400> 132
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asn Lys Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asp Thr Lys Arg Pro Ser Gly Ile Pro Glu Arg Val Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr His Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140

Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 133
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B799 轻链
<400> 133

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

[0132]

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

<210> 134
<211> 214

<212> PRT
<213> 人工序列
<220>
<223> C33B806 轻链
<400> 134

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

[0133]

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205
Phe Asn Arg Gly Glu Cys
210

<210> 135
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B830 轻链
<400> 135

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

50 55 60

Asn Phe Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110

Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125

Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140

Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160

Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175

Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190

Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205

Thr Glu Cys Ser
210

<210> 136
<211> 217
[0134] <212> PRT
<213> 人工序列
<220>
<223> C33B836 轻链
<400> 136

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Asp Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Val Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Met Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ser Ser Ser
85 90 95

Ser Ala Leu Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
115 120 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
130 135 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val

145 150 155 160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
165 170 175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
180 185 190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
195 200 205
Lys Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 137
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B937 轻链
<400> 137

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asp Gly Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
[0135] 50 55 60
Asn Phe Gly Asn Lys Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Arg Asn Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 138
<211> 1111
<212> DNA

<213> 人工序列
<220>
<223> C33B46 轻链
<400> 138
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag agcgccctga cacaacctgc cagcgtgagc ggctcccctg 300
gacagagcat caccatcagc tgcaccggca ccagcagcga tgtgggcgac gacaactacg 360
tgagctggta ccagcagcac cctggcaagg cccccaagct gatgatctac gatgtgagca 420
acaggcccag cggcgtgagc aataggttca gcggcagcaa gagcggcaac accgcttccc 480
tgaccatcag cggcctgcag agcgaggatg aggccgacta ctactgctcc tcctacagca 540
gcagcaccac cctggaggtg tttggcggcg gcaccaagct gaccgtgctg ggtcagccca 600
aggctgcacc cagtgtcact ctgttcccgc cctcctctga ggagcttcaa gccaacaagg 660
ccacactggt gtgtctcata agtgacttct acccgggagc cgtgacagtg gcctggaagg 720
ccgatagcag ccccgtcaag gcgggagtgg agaccaccac accctccaaa caaagcaaca 780
acaagtacgc ggccagcagc tatctgagcc tgacgcctga gcagtggaag tcccacagaa 840
gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg gcccctacag 900
aatgttcata gtgattcgaa ttcctagaag acatgataag atacattgat gagtttggac 960
aaaccacaac tagaatgcag tgaaaaaaat gctttatttg tgaaatttgt gatgctattg 1020
ctttatttgt aaccattata agctgcaata aacaagttaa caacaacaat tgcattcatt 1080
ttatgtttca ggttcagggg gaggtgtggg a 1111

[0136] <210> 139
<211> 1111
<212> DNA
<213> 人工序列
<220>
<223> C33B48 轻链
<400> 139
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag agcgccctga cacagcctgc tagcgtgagc ggcagccctg 300
gacagtccat caccatcagc tgcaccggca ccagcagcga tgtgggcgac tacaactacg 360
tgagctggta ccagcagcac cccggcaagg tgcccaagct gatgatctac gatgtgagca 420
acaggcccag cggcgtgagc aataggttca gcggcagcat gagcggcaac accgccagcc 480
tgaccatttc cggcctgcag gccgaggacg aagccgacta ctactgctcc agctacagca 540
gcagcagcgc cctggaagtg tttggcggcg gcaccaagct gaccgtgctg ggtcagccca 600
aggctgcacc cagtgtcact ctgttcccgc cctcctctga ggagcttcaa gccaacaagg 660
ccacactggt gtgtctcata agtgacttct acccgggagc cgtgacagtg gcctggaagg 720
ccgatagcag ccccgtcaag gcgggagtgg agaccaccac accctccaaa caaagcaaca 780
acaagtacgc ggccagcagc tatctgagcc tgacgcctga gcagtggaag tcccacagaa 840
gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg gcccctacag 900
aatgttcata gtgattcgaa ttcctagaag acatgataag atacattgat gagtttggac 960
aaaccacaac tagaatgcag tgaaaaaaat gctttatttg tgaaatttgt gatgctattg 1020

ctttatttgt aaccattata agctgcaata aacaagttaa caacaacaat tgcattcatt 1080
ttatgtttca ggttcagggg gaggtgtggg a 1111
<210> 140
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B52 轻链
<400> 140
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc ttccgtgagc gtgagccctg 300
gccagacagc cagcatcatc tgcagcggcg ataagctggg caacaagtac gcctgctggt 360
accagcagaa gcccggccaa agccccgtgc tggtgatcta ccaggacagc aagagaccca 420
gcggcatccc cgagaggttc agcggctcca atagcggcaa caccgccacc ctgaccatta 480
gcggcaccca ggccgtggat gaggccgact actactgcca ggcctgggac agcagcacct 540
acgtgttcgg caccggcacc aaggtgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
[0137] tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggggaggt gtggga 1096
<210> 141
<211> 1099
<212> DNA
<213> 人工序列
<220>
<223> C33B54 轻链
<400> 141
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgtgctga cccagcctcc tagcgtgagc gtggctcctg 300
gacagaccgc caggatcaca tgcggcggct ccaacatcgg cagcaagagc gtgcactggt 360
accagcagaa gcccggacag gcccccgtga tggtggtgta cgacgactcc gacaggccct 420
ccggcattcc cgagagattc agcggcagca acagcggcaa caccgccacc ctgaccatca 480
gcagagtgga ggccggcgat gaggccgact actactgcca ggtgtgggat agcagcagcg 540
acgtggtgtt tggcggcggc acaaaactga ccgtgctggg tcagcccaag gctgcaccca 600
gtgtcactct gttcccgccc tcctctgagg agcttcaagc caacaaggcc acactggtgt 660
gtctcataag tgacttctac ccgggagccg tgacagtggc ctggaaggcc gatagcagcc 720

ccgtcaaggc gggagtggag accaccacac cctccaaaca aagcaacaac aagtacgcgg 780
ccagcagcta tctgagcctg acgcctgagc agtggaagtc ccacagaagc tacagctgcc 840
aggtcacgca tgaagggagc accgtggaga agacagtggc ccctacagaa tgttcatagt 900
gattcgaatt cctagaagac atgataagat acattgatga gtttggacaa accacaacta 960
gaatgcagtg aaaaaaatgc tttatttgtg aaatttgtga tgctattgct ttatttgtaa 1020
ccattataag ctgcaataaa caagttaaca acaacaattg cattcatttt atgtttcagg 1080
ttcaggggga ggtgtggga 1099

<210> 142
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B55 轻链
<400> 142

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccagaccgc tagcatcacc tgcagcggcc acaagctggg cgacaagtac gcctgctggt 360
accagcagaa acccggccag agccccgtgg tggtgatcta caaggacagc aagagaccca 420
gcggcatccc cgagaggttc agcggcagca acttcggcaa caccgccacc ctgaccatca 480
gcggcacaca ggccatggac gaggccgact actactgcca ggcctgggac agcagcacag 540
[0138] tggtgttcgg cggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
agggggaggt gtggga 1096

<210> 143
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B56 轻链
<400> 143

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccagacagc cagcatcacc tgcagcggcg acaagctggg cgacaagtac gcctgctggt 360
accagcagaa acccggccag agccccgtgc tggtgatcta ccaggacagc aagagaccca 420

gcggcatccc cgagaggttc agcggcagca acagcggcaa caccgccacc ctgacaatca 480
gcggcacaca ggccatggac gaggccgact actactgcca ggcctgggac agcagcaccg 540
tggtgttcgg cggaggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggaggt gtggga 1096

<210> 144
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B61 轻链
<400> 144

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
[0139] cccaaagtat acaggcctcc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gacagaccgc cagcatcacc tgcagcggcg acaagctggg cgacaagtac gcctgctggt 360
accagcagaa acccggccag agccccgtgc tggtgatcta ccaggactac aagaggccca 420
gcggcatccc tgagaggttc agcggcagca actccggcaa caccgccacc ctgaccatct 480
ccggcacaca ggccatggac gaggccgact actactgcca ggcctgggac agcagcacct 540
acgtgttcgg caccggcacc aaggtgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggaggt gtggga 1096

<210> 145
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B62 轻链
<400> 145

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120

gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccagacagc cagcatcacc tgcagcggcg acaagctggg cgacaagtat gcctgctggt 360
accagcagaa acccggccag agccccgtgc tggtgatcta ccaggactac aaaaggccca 420
gcggcatccc cgagagattc agcggcagca acagcggcaa caccgccacc ctgaccatca 480
gcggcaccca gaccatggac gaggccgact actactgcca ggcctgggac atcagcacct 540
acgtgttcgg caccggcacc aaggtgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggaggt gtggga 1096

<210> 146
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B63 轻链

[0140] <400> 146

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccagacagc cagcatcacc tgcagcggcg acaagctggg cgacaagtac gcctgctggt 360
accagctgag acccggccag agccccatcc tggtgatcta ccaggacagc aacaggccca 420
gcggcatccc cgagagattc agcggcagca acagcggcaa caccgccacc ctgaccatca 480
gcggaaccca ggccatggac gaggccgact actactgcca ggcctgggac agcagcacct 540
gggtgttcgg aggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggaggt gtggga 1096

<210> 147
<211> 1096
<212> DNA
<213> 人工序列

<220>
<223> C33B64 轻链
<400> 147
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gacagaccgc cagcatcacc tgcagcggcg acaagctggg cgacaagtac gcctgctggt 360
accagcagaa gcccggacag agccccgtgc tggtgatcta ccaggacagc aagagaccca 420
gcggcatccc cgagaggttc agcggcagca acagcggcaa caccgccaca ctgaccatca 480
gcggcaccca ggccatggat gaggccgact actactgcca ggcctgggac agcagcacct 540
gggtgtttgg cggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
agggggaggt gtggga 1096
<210> 148
[0141] <211> 1102
<212> DNA
<213> 人工序列
<220>
<223> C33B66 轻链
<400> 148
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgtcctga cacagcctcc cagcgtgagc gtggctcctg 300
gacagaccgc caggatcacc tgcggcggca acaacatcgg catcaagagc gtgcactggt 360
accagcagaa gcccggccag gctcctgtgc tggtggtgta cgacgacagc gacagacccc 420
ccggcatccc tgagaggttc agcggcagca acagcggcaa caccgccacc ctgaccatca 480
caagagtgga ggccggcgac gaggccgact actactgcca ggtgtgggac agcagcagcg 540
atcacgtggt gttcggcggc ggcaccaagc tgaccgtgct gggtcagccc aaggctgcac 600
ccagtgtcac tctgttcccg ccctcctctg aggagcttca agccaacaag gccacactgg 660
tgtgtctcat aagtgacttc tacccgggag ccgtgacagt ggcctggaag gccgatagca 720
gccccgtcaa ggcgggagtg gagaccacca caccctccaa acaaagcaac aacaagtacg 780
cggccagcag ctatctgagc ctgacgcctg agcagtggaa gtcccacaga agctacagct 840
gccaggtcac gcatgaaggg agcaccgtgg agaagacagt ggcccctaca gaatgttcat 900
agtgattcga attcctagaa gacatgataa gatacattga tgagtttgga caaaccacaa 960
ctagaatgca gtgaaaaaaa tgctttattt gtgaaatttg tgatgctatt gctttatttg 1020
taaccattat aagctgcaat aaacaagtta acaacaacaa ttgcattcat tttatgtttc 1080

aggttcaggg ggaggtgtgg ga 1102

<210> 149

<211> 1096

<212> DNA

<213> 人工序列

<220>

<223> C33B72 轻链

<400> 149

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60

tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120

gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180

tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240

cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300

gccagaccgc tagcatcacc tgcagcggcg acaagctggg cgacaagtac gcctgctggt 360

accagcagaa gcccggccag agccctgtgg tggtgatcta ccaggacagg aagaggccca 420

gcggcatccc cgagagattc agcggcagca acttcggcaa caccgccacc ctgaccatca 480

gcggcacaca ggccatggac gaggccgact actactgcca ggcctgggac agcagcaccg 540

tggtgtttgg cggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600

tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660

tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720

tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780

gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840

tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900

[0142] tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960

tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020

ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080

aggggggaggt gtggga 1096

<210> 150

<211> 1096

<212> DNA

<213> 人工序列

<220>

<223> C33B73 轻链

<400> 150

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60

tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120

gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180

tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240

cccaaagtat acaggcctcc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300

gacagaccgc cagcatcacc tgcagcggcg acaagctggg cgacaagtac gcctgctggt 360

accagcagaa gcccggacag agccccgtgc tggtgatcta ccaggacggc aaaaggccca 420

gcggcatccc cgagaggttt agcggcagca acttcggcaa caaggccacc ctgaccatta 480

gcggcaccca ggccatggac gaggccgact actactgcca ggcctgggat aggaacaccg 540

tggtgttcgg cggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600

tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660

tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720

tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780

gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggaggt gtggga 1096

<210> 151
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B75 轻链
<400> 151

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gacagaccgc cagcatcacc tgcagcggcg acaagctggg cgacaagtac gcctgctggt 360
accagcagaa gcccggacag agccccgtgc tggtgatcta ccaggacagc aagagaccca 420
gcggcatccc cgagaggttc agcggcagca acagcggcaa caccgccaca ctgaccatca 480
gcggcaccca ggccatggat gaggccgact actactgcca ggcctgggac agcagcacct 540
gggtgtttgg cggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
[0143] tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggaggt gtggga 1096

<210> 152
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B77 轻链
<400> 152

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccagacagc cagcatcacc tgcagcggca acaagctggg cgccaagttc gccagctggt 360
accagcagaa gcctggccag agccccgtgc tggtgatcta ccaggacaac aagaggccca 420
gcggcatccc cgagagattc agcggcagca acagcggcaa caccgccacc ctgaccatta 480

gcggcaccca ggccgtggat gaggccgact actactgcca ggcctgggac tccagcaccg 540
tggtgtttgg cggcggcacc aagctcaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggaggt gtggga 1096

<210> 153
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B79 轻链
<400> 153

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc ttccgtgagc gtgcctcctg 300
[0144] gacagacagc cagcatcacc tgcagcggcg ataagctggg cgacaagtac gcctgctggt 360
accagcagaa gcccggccag agccctgtgc tggtgatcta ccaggacaac aagaggccca 420
gcggcatccc cgagagattc agcggcagca acagcggcaa caccgccacc ctgacaatca 480
gcggcacaca ggccatggac gaggccgact actactgcca ggcctggggc aggaataccg 540
tggtgttcgg cggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggaggt gtggga 1096

<210> 154
<211> 1111
<212> DNA
<213> 人工序列
<220>
<223> C33B80 轻链
<400> 154

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180

tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag agcgccctga cacagcctgc tagcgtgagc ggaagccccg 300
gacagagcat ccccatcagc agcaccggca caagcagcga cgacggcaag aacaacatcg 360
tgtcctggta ccagcagcac cctggcaagg cccccaagct gatgatctac aaggacagca 420
agaggcccag cggcgtgagc aacaggttca gcggcagcaa gagcggcaac accgccagcc 480
tgaccattag cggcctgcag gccgacgatg aggccgacta ccactgctgc agctacgccg 540
gcgctagcaa ccacgtggtg ttcggcggcg gcaccaagct gaccgtgctg ggtcagccca 600
aggctgcacc cagtgtcact ctgttcccgc cctcctctga ggagcttcaa gccaacaagg 660
ccacactggt gtgtctcata agtgacttct acccgggagc cgtgacagtg gcctggaagg 720
ccgatagcag ccccgtcaag gcgggagtgg agaccaccac accctccaaa caaagcaaca 780
acaagtacgc ggccagcagc tatctgagcc tgacgcctga gcagtggaag tcccacagaa 840
gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg gcccctacag 900
aatgttcata gtgattcgaa ttcctagaag acatgataag atacattgat gagtttggac 960
aaaccacaac tagaatgcag tgaaaaaaat gctttatttg tgaaatttgt gatgctattg 1020
ctttatttgt aaccattata agctgcaata aacaagttaa caacaacaat tgcattcatt 1080
ttatgtttca ggttcagggg gaggtgtggg a 1111

<210> 155
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B82 轻链
<400> 155

[0145] tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccagaccgc tagcatcacc tgcagcggcg acgagctggg caacaagtac gcctgctggt 360
accagcagaa gcccggacag tcccccgtgg tggtggtgta ccaggacaga aagagaccca 420
gcggcatccc cgagaggttc agcggcagca acttcggcaa caccgccacc ctgaccatct 480
ccggcacaca ggccatggac gaggccgact actactgcca ggcctgggac agctccaccg 540
tggtgtttgg cggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggggaggt gtggga 1096

<210> 156
<211> 1096
<212> DNA
<213> 人工序列
<220>

<223> C33B83 轻链

<400> 156

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc ttccgtgtcc gtgagccctg 300
gacagaccgc cagcatcacc tgcagcggcg acaagctggg cgacaagtac gcctgctggt 360
accagcagaa gcctggccag agccccgtgc tggtgatcta ccaggacaac aagaggccca 420
gcggcatccc cgagaggttt agcggcagca acagcggcaa caccgccaca ctgaccatca 480
gcggcaccca ggccatggat gaggccgact actactgcca ggcctgggac agcaacaccg 540
tggtgttcgg cggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
agggggaggt gtggga 1096

<210> 157

<211> 1096

[0146] <212> DNA

<213> 人工序列

<220>

<223> C33B87 轻链

<400> 157

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccaaaccgc cagcatcacc tgcagcggcg acaagctggg caacaagtac gccagctggt 360
accagcagaa gcccggccag agccctgtgc tggtgatcta ccaggacacc aagagaccca 420
gcggcatccc cgagagagtg agcggcagca acagcggcaa caccgccacc ctgaccatta 480
gcggcaccca ggccatggac gaggccgact accactgcca ggcctgggac agcagcaccg 540
tggtgtttgg cggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
agggggaggt gtggga 1096

<210> 158
<211> 1111
<212> DNA
<213> 人工序列
<220>
<223> C33B88 轻链
<400> 158

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag agcgccctga cccagcctgc tagcgtgagc ggaagccctg 300
gccagagcat caccatctcc tgcaccggca tcaacagcga cgtgggcagc tacgacctgg 360
tgagctggta ccagcagcac cctggcaagg cccccaagct gctgatctac gacggcagcg 420
agagacccag cggcgtgttt ggcaggttca gcggcagcaa gagcgacaac accaccagcc 480
tgacaatcag cggcctgcag gccgaggacg aggccgccta ctactgctgc tcctacgagg 540
tgaccaccac ctacgtggtg ttcggcggcg gcaccaagct gaccgtgctg ggtcagccca 600
aggctgcacc cagtgtcact ctgttcccgc cctcctctga ggagcttcaa gccaacaagg 660
ccacactggt gtgtctcata agtgacttct acccgggagc cgtgacagtg gcctggaagg 720
ccgatagcag ccccgtcaag gcgggagtgg agaccaccac accctccaaa caaagcaaca 780
acaagtacgc ggccagcagc tatctgagcc tgacgcctga gcagtggaag tcccacagaa 840
gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg gcccctacag 900
aatgttcata gtgattcgaa ttcctagaag acatgataag atacattgat gagtttggac 960
[0147] aaaccacaac tagaatgcag tgaaaaaaat gctttatttg tgaaatttgt gatgctattg 1020
ctttatttgt aaccattata agctgcaata aacaagttaa caacaacaat tgcattcatt 1080
ttatgtttca ggttcagggg gaggtgtggg a 1111

<210> 159
<211> 1102
<212> DNA
<213> 人工序列
<220>
<223> C33B89 轻链
<400> 159

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgtgctga cccagcctcc tagcgtgagc gtggcccctg 300
gacagacagc caggatcacc tgtggcggca acaacatcgg cagcaaaagc gtgcactgga 360
gccagcagaa gcctggccag gcccctgtgc tggtggtgta cgacgacagc gacaggccca 420
gcggcatccc tgagaggttc agcggctcca acagcggcaa caccgccacc ctgaccatca 480
gcagagtgga ggccggcgac gaggccgact actactgcca ggtgtgggac agcaacagcg 540
accacgtggt gttcggcggc ggcaccaagc tgaccgtgct gggtcagccc aaggctgcac 600
ccagtgtcac tctgttcccg ccctcctctg aggagcttca agccaacaag gccacactgg 660
tgtgtctcat aagtgacttc tacccgggag ccgtgacagt ggcctggaag gccgatagca 720
gccccgtcaa ggcgggagtg gagaccacca caccctccaa acaaagcaac aacaagtacg 780
cggccagcag ctatctgagc ctgacgcctg agcagtggaa gtcccacaga agctacagct 840

gccaggtcac gcatgaaggg agcaccgtgg agaagacagt ggcccctaca gaatgttcat 900
agtgattcga attcctagaa gacatgataa gatacattga tgagtttgga caaaccacaa 960
ctagaatgca gtgaaaaaaa tgctttattt gtgaaatttg tgatgctatt gctttatttg 1020
taaccattat aagctgcaat aaacaagtta acaacaacaa ttgcattcat tttatgtttc 1080
aggttcaggg ggaggtgtgg ga 1102

<210> 160
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B94 轻链
<400> 160

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccagacagc cagcatcacc tgcagcggcg acaagctggg ctccaagttc gcctgctggt 360
accagcagaa acccggccag tcccccgtgc tggtgatcta ccaggacagc aagaggccca 420
gcggcatccc tgagaggttc agcggcagca acagcggcaa caccgctacc ctgaccatca 480
gcggcaccca ggccatggat gaggccgact actactgcca ggcctgggac agcagcaccg 540
tggtgttcgg aggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
[0148] tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
agggggaggt gtggga 1096

<210> 161
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B95 轻链
<400> 161

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccagacagc cagcatcacc tgcagcggcg acaagctggg cgacaagtac gcctgctggt 360
accagcagaa acccggccag agccccgtgc tggtgatcta ccaggacagc aagagaccca 420
gcggcatccc cgagaggttc agcggcagca acagcggcaa caccgccacc ctgacaatca 480
gcggcacaca ggccatggac gaggccgact actactgcca ggcctgggac agcagcaccg 540

tggtgttcgg cggaggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggggaggt gtggga 1096

<210> 162
<211> 1102
<212> DNA
<213> 人工序列
<220>
<223> C33B96 轻链
<400> 162

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgtgctga cacagccccc ttccgtggcc gtggcccctg 300
gccagacagc cagaatcacc tgcggcggca gcaacatcgg caagatcagc gtgcactggt 360
[0149] accagcagaa agccggccag gcccctgtgc tggtggtgca cgatgacaga gccaggccca 420
gcggaatccc cgagagactg agcggcagca atagcggcac aaccgccacc ctgaccatca 480
gcagagtgga ggtgggcgac gaggccgact actactgcca ggtgtggaac tccagcagcg 540
tgcaccctgt gttcggcgga ggcaccaagc tgaccgtgct gggtcagccc aaggctgcac 600
ccagtgtcac tctgttcccg ccctcctctg aggagcttca agccaacaag gccacactgg 660
tgtgtctcat aagtgacttc tacccgggag ccgtgacagt ggcctggaag gccgatagca 720
gccccgtcaa ggcgggagtg gagaccacca caccctccaa acaaagcaac aacaagtacg 780
cggccagcag ctatctgagc ctgacgcctg agcagtggaa gtcccacaga agctacagct 840
gccaggtcac gcatgaaggg agcaccgtgg agaagacagt ggcccctaca gaatgttcat 900
agtgattcga attcctagaa gacatgataa gatacattga tgagtttgga caaaccacaa 960
ctagaatgca gtgaaaaaaa tgctttattt gtgaaatttg tgatgctatt gctttatttg 1020
taaccattat aagctgcaat aaacaagtta acaacaacaa ttgcattcat tttatgtttc 1080
aggttcaggg ggaggtgtgg ga 1102

<210> 163
<211> 1102
<212> DNA
<213> 人工序列
<220>
<223> C33B101 轻链
<400> 163

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240

cccaaagtat acaggccgac atccagatga cccagagccc tagcagcgtg agcgccagcg 300
tgggcgatag ggtgaccatc acctgcaggg ccagccaggg cattagcagc tggctggcct 360
ggtaccagca gaagccccggc aaggccccca agctgctgat ctacgccgcc agcagcctgc 420
agagcggcgt gcctagcagg ttctccggat ccggcagcgg caccgacttc accctgacca 480
tcagcagcct gcagccccgag gacttcgcca cctactactg ccagcaggcc aacagcttcc 540
ccttcacctt cggccccggc accaaggtgg acatcaagcg tacggtggct gcaccatctg 600
tcttcatctt cccgccatct gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc 660
tgctgaataa cttctatccc agagaggcca aagtacagtg gaaggtggat aacgccctcc 720
aatcgggtaa ctcccaggag agtgtcacag agcaggacag caaggacagc acctacagcc 780
tcagcagcac cctgacgctg agcaaagcag actacgagaa acacaaagtc tacgcctgcg 840
aagtcaccca tcagggcctg agctcgcccg tcacaaagag cttcaacagg ggagagtgtt 900
agtgattcga attcctagaa gacatgataa gatacattga tgagtttgga caaaccacaa 960
ctagaatgca gtgaaaaaaa tgctttattt gtgaaatttg tgatgctatt gctttatttg 1020
taaccattat aagctgcaat aaacaagtta acaacaacaa ttgcattcat tttatgtttc 1080
aggttcaggg ggaggtgtgg ga 1102

<210> 164
<211> 1120
<212> DNA
<213> 人工序列
<220>
<223> C33B107 轻链
<400> 164

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
[0150] tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgac atcgtgatga cccagagccc tgattccctg gccgtgagcc 300
tgggagagag agccaccatc aactgcaaga gcagccagag cgtgctgtac agcagcaata 360
acaagaacta cctggcctgg taccagcaga aggccggcca gcctcccaag ctgctgatct 420
actgggccag caccagagag agcggcgtgc ctgacaggtt tagcggcagc ggcagcggca 480
ccgacttcat cctgatcatc agcagcctgc aggccgagga tgtggccgtg tactactgcc 540
agcagtacta cggcaccccc tggaccttcg gccagggcac caaggtggag atcaagcgta 600
cggtggctgc accatctgtc ttcatcttcc cgccatctga tgagcagttg aaatctggaa 660
ctgcctctgt tgtgtgcctg ctgaataact tctatcccag agaggccaaa gtacagtgga 720
aggtggataa cgccctccaa tcgggtaact cccaggagag tgtcacagag caggacagca 780
aggacagcac ctacagcctc agcagcaccc tgacgctgag caaagcagac tacgagaaac 840
acaaagtcta cgcctgcgaa gtcacccatc agggcctgag ctcgcccgtc acaaagagct 900
tcaacagggg agagtgttag tgattcgaat tcctagaaga catgataaga tacattgatg 960
agtttggaca aaccacaact agaatgcagt gaaaaaaatg ctttatttgt gaaatttgtg 1020
atgctattgc tttatttgta accattataa gctgcaataa acaagttaac aacaacaatt 1080
gcattcattt tatgtttcag gttcaggggg aggtgtggga 1120

<210> 165
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B120 轻链

<400> 165

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gacagaccgc cagcatcacc tgcagcggcg acaagctggg caacaagtac gccagctggt 360
accagcagaa gcccggccag agccctgtgc tggtgatcta ccaggacagc aagaggccca 420
gcggcatccc cgagagattc agcggcagca acagcggcaa caccgccaca ctgaccatca 480
gcggcaccca ggccatggat gaggccgact actactgcca ggcctgggac agcagcaccg 540
tggtgtttgg cggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggaggt gtggga 1096

<210> 166
<211> 1096
<212> DNA

[0151] <213> 人工序列

<220>
<223> C33B122 轻链

<400> 166

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccagaccgt gagcatcagc tgcagcggcg acaggctggg cgacaagtat gcctgctggt 360
accagcagaa gcccggccag agccctgtgc tggtgatcta ccaggacagc aagaggccca 420
gcggcatccc tgagaggttc agcggcagca acagcggcaa caccgccacc ctgaccatca 480
gcggcacaca ggccatggac gaggccgact actactgcca ggcctgggac agcagcagct 540
acgtgttcgg caccggcacc aaggtgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggaggt gtggga 1096

<210> 167

<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B123 轻链
<400> 167

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagccccc tagcgtgagc gtgagccctg 300
gacagaccgc cagcatcacc tgcagcggcg acaagctggg cgacaagtac gcctgctggt 360
accagcagaa gcccggacag agccccgtgc tggtgatcta ccaggacagc aacaggccca 420
gcggcatccc tgagaggttc agcggcagca acagcggcaa caccgccaca ctgaccatca 480
gcgagaccca ggccatggac gaggccgact actactgcca ggcctgggac agcagcacct 540
acgtgttcgg caccggcacc aaggtgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
[0152] ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggaggt gtggga 1096

<210> 168
<211> 1099
<212> DNA
<213> 人工序列
<220>
<223> C33B124 轻链
<400> 168

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc ttccgtgagc gtgagccctg 300
gccagacagc cagcatcacc tgcagcggcg acaagctggg cgacaagtac gtgaggtggt 360
accagcagaa gaccggccag agccccgtgc tggtgatgta ccaggacagc aagaggccca 420
gcggcatcag ggagaggttt tacggctcca acagcggcaa caccgccaca cccaccatca 480
gcggaaccca ggccgtggat gaggccgagt actactgcca ggcctgggac agcagcacag 540
gcgtggtgtt tggcggcggc accaagctga ccgtgctggg tcagcccaag gctgcaccca 600
gtgtcactct gttcccgccc tcctctgagg agcttcaagc caacaaggcc acactggtgt 660
gtctcataag tgacttctac ccgggagccg tgacagtggc ctggaaggcc gatagcagcc 720
ccgtcaaggc gggagtggag accaccacac cctccaaaca aagcaacaac aagtacgcgg 780
ccagcagcta tctgagcctg acgcctgagc agtggaagtc ccacagaagc tacagctgcc 840
aggtcacgca tgaagggagc accgtggaga agacagtggc ccctacagaa tgttcatagt 900

gattcgaatt cctagaagac atgataagat acattgatga gtttggacaa accacaacta 960
gaatgcagtg aaaaaaatgc tttatttgtg aaatttgtga tgctattgct ttatttgtaa 1020
ccattataag ctgcaataaa caagttaaca acaacaattg cattcatttt atgtttcagg 1080
ttcaggggga ggtgtggga 1099

<210> 169
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B125 轻链
<400> 169

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccccg 300
gacagacagc cagcatcacc tgcagcggcg acaagctggg cgacaagtac gtgtgctggt 360
accagcagaa gcccggacag agccccgtgg tggtgatcca ccaggacagg aagaggccca 420
gcggcatccc cgagagattc agcggcagca acttcggcaa caccgccacc ctgaccatca 480
gcggcaccca ggccatggat gaggccgact actactgcca ggcctgggac agcagcaccg 540
tggtgttcgg aggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
[0153] tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
agggggaggt gtggga 1096

<210> 170
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B760 轻链
<400> 170

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccagaccgc tagcatcacc tgcagcggcc acaagctggg cgacaagtac gcctgctggt 360
accagcagaa acccggccag agccccgtgg tggtgatcta caaggacagc aagagaccca 420
gcggcatccc cgagaggttc agcggcagca acttcggcaa caccgccacc ctgaccatca 480
gcggcacaca ggccatggac gaggccgact actactgcca ggcctgggac agcagcacag 540
tggtgttcgg cggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600

tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
agggggaggt gtggga 1096

<210> 171
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B777 轻链
<400> 171

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccagaccgc tagcatcacc tgcagcggcg acaagctggg cgacaagtac gcctgctggt 360
accagcagaa gcccggccag agccctgtgg tggtgatcta ccaggacagg aagaggccca 420
[0154] gcggcatccc cgagagattc agcggcagca acttcggcaa caccgccacc ctgaccatca 480
gcggcacaca ggccatggac gaggccgact actactgcca ggcctgggac agcagcaccg 540
tggtgtttgg cggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
agggggaggt gtggga 1096

<210> 172
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B778 轻链
<400> 172

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcctcc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300

gacagaccgc cagcatcacc tgcagcggcg acaagctggg cgacaagtac gcctgctggt 360
accagcagaa gcccggacag agccccgtgc tggtgatcta ccaggacggc aaaaggccca 420
gcggcatccc cgagaggttt agcggcagca acttcggcaa caaggccacc ctgaccatta 480
gcggcaccca ggccatggac gaggccgact actactgcca ggcctgggat aggaacaccg 540
tggtgttcgg cggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggaggt gtggga 1096

<210> 173
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B782 轻链
<400> 173

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
[0155] gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccagacagc cagcatcacc tgcagcggca acaagctggg cgccaagttc gccagctggt 360
accagcagaa gcctggccag agccccgtgc tggtgatcta ccaggacaac aagaggccca 420
gcggcatccc cgagagattc agcggcagca acagcggcaa caccgccacc ctgaccatta 480
gcggcaccca ggccgtggat gaggccgact actactgcca ggcctgggac tccagcaccg 540
tggtgtttgg cggcggcacc aagctcaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggaggt gtggga 1096

<210> 174
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B792 轻链
<400> 174

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccaaaccgc cagcatcacc tgcagcggcg acaagctggg caacaagtac gccagctggt 360
accagcagaa gcccggccag agccctgtgc tggtgatcta ccaggacacc aagagaccca 420
gcggcatccc cgagagagtg agcggcagca acagcggcaa caccgccacc ctgaccatta 480
gcggcaccca ggccatggac gaggccgact accactgcca ggcctgggac agcagcaccg 540
tggtgtttgg cggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggaggt gtggga 1096

<210> 175
<211> 1096
<212> DNA
<213> 人工序列

[0156] <220>
<223> C33B799 轻链
<400> 175

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccagacagc cagcatcacc tgcagcggcg acaagctggg ctccaagttc gcctgctggt 360
accagcagaa acccggccag tcccccgtgc tggtgatcta ccaggacagc aagaggccca 420
gcggcatccc tgagaggttc agcggcagca acagcggcaa caccgctacc ctgaccatca 480
gcggcaccca ggccatggat gaggccgact actactgcca ggcctgggac agcagcaccg 540
tggtgttcgg aggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggaggt gtggga 1096

<210> 176
<211> 1102

<212> DNA
<213> 人工序列
<220>
<223> C33B806 轻链
<400> 176

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgac atccagatga cccagagccc tagcagcgtg agcgccagcg 300
tgggcgatag ggtgaccatc acctgcaggg ccagccaggg cattagcagc tggctggcct 360
ggtaccagca gaagccccggc aaggccccca agctgctgat ctacgccgcc agcagcctgc 420
agagcggcgt gcctagcagg ttctccggat ccggcagcgg caccgacttc accctgacca 480
tcagcagcct gcagcccgag gacttcgcca cctactactg ccagcaggcc aacagcttcc 540
ccttcacctt cggccccggc accaaggtgg acatcaagcg tacggtggct gcaccatctg 600
tcttcatctt cccgccatct gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc 660
tgctgaataa cttctatccc agagaggcca aagtacagtg gaaggtggat aacgccctcc 720
aatcgggtaa ctcccaggag agtgtcacag agcaggacag caaggacagc acctacagcc 780
tcagcagcac cctgacgctg agcaaagcag actacgagaa acacaaagtc tacgcctgcg 840
aagtcaccca tcagggcctg agctcgcccg tcacaaagag cttcaacagg ggagagtgtt 900
agtgattcga attcctagaa gacatgataa gatacattga tgagtttgga caaaccacaa 960
ctagaatgca gtgaaaaaaa tgctttattt gtgaaatttg tgatgctatt gctttatttg 1020
taaccattat aagctgcaat aaacaagtta acaacaacaa ttgcattcat tttatgtttc 1080
[0157] aggttcaggg ggaggtgtgg ga 1102

<210> 177
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B830 轻链
<400> 177

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccccg 300
gacagacagc cagcatcacc tgcagcggcg acaagctggg cgacaagtac gtgtgctggt 360
accagcagaa gccccggacag agccccgtgg tggtgatcca ccaggacagg aagaggccca 420
gcggcatccc cgagagattc agcggcagca acttcggcaa caccgccacc ctgaccatca 480
gcggcaccca ggccatggat gaggccgact actactgcca ggcctgggac agcagcaccg 540
tggtgttcgg aggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960

tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggggaggt gtggga 1096

<210> 178
<211> 1111
<212> DNA
<213> 人工序列
<220>
<223> C33B836 轻链
<400> 178

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag agcgccctga cacagcctgc tagcgtgagc ggcagccctg 300
gacagtccat caccatcagc tgcaccggca ccagcagcga tgtgggcgac tacaactacg 360
tgagctggta ccagcagcac cccggcaagg tgcccaagct gatgatctac gatgtgagca 420
acaggcccag cggcgtgagc aataggttca gcggcagcat gagcggcaac accgccagcc 480
tgaccatttc cggcctgcag gccgaggacg aagccgacta ctactgctcc agctacagca 540
gcagcagcgc cctggaagtg tttggcggcg gcaccaagct gaccgtgctg ggtcagccca 600
aggctgcacc cagtgtcact ctgttcccgc cctcctctga ggagcttcaa gccaacaagg 660
ccacactggt gtgtctcata agtgacttct acccgggagc cgtgacagtg gcctggaagg 720
ccgatagcag ccccgtcaag gcgggagtgg agaccaccac accctccaaa caaagcaaca 780
[0158] acaagtacgc ggccagcagc tatctgagcc tgacgcctga gcagtggaag tcccacagaa 840
gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg gcccctacag 900
aatgttcata gtgattcgaa ttcctagaag acatgataag atacattgat gagtttggac 960
aaaccacaac tagaatgcag tgaaaaaaat gctttatttg tgaaatttgt gatgctattg 1020
ctttatttgt aaccattata agctgcaata aacaagttaa caacaacaat tgcattcatt 1080
ttatgtttca ggttcagggg gaggtgtggg a 1111

<210> 179
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B937 轻链
<400> 179

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagccccc tagcgtgagc gtgagccctg 300
gacagaccgc cagcatcacc tgcagcggcg acaagctggg cgacaagtac gccagctggt 360
accagcagaa gcccggccag agccctgtgc tggtgatcta ccaggacggc aagaggccca 420
gcggcattcc cgagaggttc agcggcagca acttcggcaa caaggccacc ctgaccatca 480
gcggcaccca ggccatggat gaggccgact actactgcca ggcctgggac aggaacaccg 540
tggtcttcgg cggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660

tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggggaggt gtggga 1096

<210> 180
<211> 446
<212> PRT
<213> 人工序列
<220>
<223> C33B901 重链
<400> 180

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

[0159]

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Phe Tyr Tyr Cys
85 90 95
Thr Lys Asp Thr Pro Tyr Gly Asp Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125
Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
130 135 140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190
Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
195 200 205
Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
210 215 220
Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
260 265 270
Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285
Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320
Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
325 330 335
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350
Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400
Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
405 410 415
Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

[0160]

<210> 181
<211> 446
<212> PRT
<213> 人工序列
<220>
<223> C33B902 重链
<400> 181
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30
Ala Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Leu Ser Trp Asn Gly Gly Asn Ile Gly Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Leu Asn Ser Leu Lys Thr Glu Asp Thr Ala Phe Tyr Tyr Cys
85 90 95
Ala Lys Asp Ser Pro Tyr Gly Asp Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
130 135 140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190
Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
195 200 205
Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
210 215 220
Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255
Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
260 265 270
Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285
Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
[0161] 305 310 315 320
Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
325 330 335
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350
Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400
Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
405 410 415
Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 182
<211> 446
<212> PRT
<213> 人工序列
<220>
<223> C33B903 重链
<400> 182

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Gly Trp Ser Gly Gly Ser Ile Val Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Lys Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95
Ala Lys Asp Ser Pro Tyr Gly Asp Phe Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125
Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
    130                 135                 140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190
Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
        195                 200                 205
Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
    210                 215                 220
Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225                 230                 235                 240
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255
Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
            260                 265                 270
Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285
Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320
Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
                325                 330                 335
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340                 345                 350
Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
```

[0162]

370 375 380
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400
Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
405 410 415
Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 183
<211> 446
<212> PRT
<213> 人工序列
<220>
<223> C33B904 重链
<400> 183
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Gly Trp Ser Gly Gly Ser Ile Val Tyr Ala Asp Ser Val
[0163] 50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Ala Lys Asp Ser Pro Tyr Gly Asp Phe Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125
Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
130 135 140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190
Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
195 200 205
Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
210 215 220
Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

245 250 255
Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
260 265 270
Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285
Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320
Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
325 330 335
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350
Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400
Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
405 410 415
Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

[0164] Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 184
<211> 446
<212> PRT
<213> 人工序列
<220>
<223> C33B905 重链
<400> 184
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Gly Trp Ser Gly Gly Ser Ile Val Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Ala Lys Asp Ser Pro Tyr Gly Asp Phe Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe

115 120 125
Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
130 135 140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190
Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
195 200 205
Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
210 215 220
Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255
Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
260 265 270
Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285
Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

[0165] Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320
Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
325 330 335
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350
Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400
Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
405 410 415
Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 185
<211> 447
<212> PRT
<213> 人工序列
<220>
<223> C33B906 重链

<400> 185

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

[0166]

```
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
        195                 200                 205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
    210                 215                 220
Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225                 230                 235                 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255
Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
            260                 265                 270
Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285
Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320
Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
                325                 330                 335
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350
Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365
```

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 186
<211> 444
<212> PRT
<213> 人工序列
<220>
<223> C33B907 重链
<400> 186

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

[0167]

Ala Val Ile Trp Phe Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Arg Glu Leu Leu Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn
195 200 205
Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro
210 215 220
Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
225 230 235 240

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
245 250 255
Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
260 265 270
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
275 280 285
Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
290 295 300
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305 310 315 320
Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
325 330 335
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln
340 345 350
Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
355 360 365
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
370 375 380
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
385 390 395 400
Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
405 410 415
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[0168] 420 425 430
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440

<210> 187
<211> 456
<212> PRT
<213> 人工序列
<220>
<223> C33B908 重链
<400> 187

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

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
130 135 140
Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
145 150 155 160
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
165 170 175
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
180 185 190
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
195 200 205
Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
210 215 220
Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
225 230 235 240
Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
245 250 255
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
260 265 270
Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
275 280 285
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
[0169] 290 295 300
Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
305 310 315 320
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
325 330 335
Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
340 345 350
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
355 360 365
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
370 375 380
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
385 390 395 400
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
405 410 415
Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
420 425 430
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
435 440 445
Ser Leu Ser Leu Ser Leu Gly Lys
450 455

<210> 188
<211> 444
<212> PRT

<213> 人工序列
<220>
<223> C33B909 重链
<400> 188

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Val Gly Ser His Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Gly Ser Leu Cys Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
[0170] 145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn
195 200 205
Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro
210 215 220
Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
225 230 235 240
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
245 250 255
Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
260 265 270
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
275 280 285
Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
290 295 300
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305 310 315 320
Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
325 330 335
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln

340 345 350
Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
355 360 365
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
370 375 380
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
385 390 395 400
Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
405 410 415
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
420 425 430
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440

<210> 189
<211> 449
<212> PRT
<213> 人工序列
<220>
<223> C33B910 重链
<400> 189

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Asp Asp Tyr
[0171] 20 25 30
Ala Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Leu Ser Trp Asn Gly Gly Asn Ile Gly Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Phe Tyr Tyr Cys
85 90 95
Thr Lys Asp Thr Pro Tyr Gly Asp Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350
Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

[0172]
Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445
Lys

<210> 190
<211> 449
<212> PRT
<213> 人工序列
<220>
<223> C33B911 重链
<400> 190
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30
Ala Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Leu Ser Trp Asn Gly Gly Asn Ile Gly Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

65 70 75 80
Leu Gln Leu Asn Ser Leu Lys Thr Glu Asp Thr Ala Phe Tyr Tyr Cys
85 90 95
Ala Lys Asp Ser Pro Tyr Gly Asp Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

[0173] Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350
Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400
Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

Lys

<210> 191
<211> 449
<212> PRT
<213> 人工序列
<220>
<223> C33B912 重链
<400> 191

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

[0174]

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

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

<210> 192
<211> 449
<212> PRT
[0175] <213> 人工序列
<220>
<223> C33B913 重链
<400> 192
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Gly Trp Ser Gly Gly Ser Ile Val Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Ala Lys Asp Ser Pro Tyr Gly Asp Phe Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[0176] 340 345 350
Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400
Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445
Lys

<210> 193
<211> 450
<212> PRT
<213> 人工序列
<220>
<223> C33B914 重链
<400> 193
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Arg Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Asn Gly Tyr Gly Asp Gly Arg Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Ser Cys
85 90 95
Ala Lys Asp Gln Gly Phe Gly Glu Leu Phe Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
[0177] 195 200 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val

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

<210> 194
<211> 447
<212> PRT
<213> 人工序列
<220>
<223> C33B915 重链
<400> 194

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Tyr Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Asp Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Phe Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
[0178] 50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Arg Glu Leu Leu Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220
Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr

245 250 255
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

[0179] His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 195
<211> 459
<212> PRT
<213> 人工序列
<220>
<223> C33B916 重链
<400> 195
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30
Ala Met His Trp Val Arg Gln Val Pro Gly Glu Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Trp Asn Gly Gly Asp Met Val Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Val Lys Asp Met Pro Tyr Phe Asp Phe Leu Thr Gly Ser Asp Tyr Tyr
100 105 110
Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser

115 120 125

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
130 135 140

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
145 150 155 160

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
165 170 175

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
180 185 190

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
195 200 205

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
210 215 220

Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
225 230 235 240

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
245 250 255

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
260 265 270

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
275 280 285

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
290 295 300

[0180] Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
305 310 315 320

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
325 330 335

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
340 345 350

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
355 360 365

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
370 375 380

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
385 390 395 400

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
405 410 415

Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
420 425 430

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
435 440 445

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 196
<211> 1798
<212> DNA
<213> 人工序列

<220>
<223> C33B901 重链
<400> 196
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggagtccgg aggaggcctg gtgcagcctg 300
gaaggtccct gagactgtcc tgcgtggcca gcggcttcac cttcgacgac tacgccatcc 360
actgggtgag acaggcccct ggcaaaggcc tggagtgggt gagcggcctg agctggaatg 420
gcggcaacat cggctacgcc gacagcgtga agggcaggtt caccatcagc agggacaacg 480
ccaagaacag cctgtacctc cagatgaaca gcctgaagac cgaggacacc gccttctact 540
actgcaccaa ggatacccca tacggcgact acttcgacta ctggggccag ggcaccctgg 600
tgacagtgag cagcgcttcc accaagggcc catccgtctt ccccctggcg ccctgctcca 660
ggagcacctc cgagagcaca gccgccctgg gctgcctggt caaggactac ttccccgaac 720
cggtgacggt gtcgtggaac tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg 780
tcctacagtc ctcaggactc tactccctca gcagcgtggt gaccgtgccc tccagcagct 840
tgggcacgaa gacctacacc tgcaacgtag atcacaagcc cagcaacacc aaggtggaca 900
agagagttga gtccaaatat ggtccccat gcccaccatg cccagcacct gaggccgccg 960
ggggaccatc agtcttcctg ttcccccaa aacccaagga cactctcatg atctcccgga 1020
cccctgaggt cacgtgcgtg gtggtggacg tgagccagga agaccccgag gtccagttca 1080
actggtacgt ggatggcgtg gaggtgcata atgccaagac aaagccgcgg gaggagcagt 1140
tcaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac tggctgaacg 1200
[0181] gcaaggagta caagtgcaag gtctccaaca aaggcctccc gtcctccatc gagaaaacca 1260
tctccaaagc caaagggcag ccccgagagc cacaggtgta caccctgccc ccatcccagg 1320
aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc taccccagcg 1380
acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag accacgcctc 1440
ccgtgctgga ctccgacggc tccttcttcc tctacagcag gctaaccgtg gacaagagca 1500
ggtggcagga ggggaatgtc ttctcatgct ccgtgatgca tgaggctctg cacaaccact 1560
acacacagaa gagcctctcc ctgtctctgg gtaaatgata gttcgaattc ctagaagaca 1620
tgataagata cattgatgag tttggacaaa ccacaactag aatgcagtga aaaaaatgct 1680
ttatttgtga aatttgtgat gctattgctt tatttgtaac cattataagc tgcaataaac 1740
aagttaacaa caacaattgc attcatttta tgtttcaggt tcaggggggag gtgtggga 1798
<210> 197
<211> 1798
<212> DNA
<213> 人工序列
<220>
<223> C33B902 重链
<400> 197
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggagagcgg aggcggactg gtgcagcctg 300
gaaggagcct gagactgagc tgcgccggaa gcggcttcac cttcgacgac tacgccatcc 360
actgggtcag acaggctcct ggcaagggcc tggagtgggt gagcggactg agctggaacg 420

gcggcaacat cggctacgcc gacagcgtga agggcaggtt caccatcagc agggacaacg 480
ccaagaacag cctgtacctg cagctgaaca gcctgaagac cgaggacacc gccttctact 540
actgcgccaa ggacagcccc tacggcgact acttcgacta ctggggccag ggcacactgg 600
tgaccgtgag cagcgcttcc accaagggcc catccgtctt ccccctggcg ccctgctcca 660
ggagcacctc cgagagcaca gccgccctgg gctgcctggt caaggactac ttccccgaac 720
cggtgacggt gtcgtggaac tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg 780
tcctacagtc ctcaggactc tactccctca gcagcgtggt gaccgtgccc tccagcagct 840
tgggcacgaa aacctacacc tgcaacgtag atcacaagcc cagcaacacc aaggtggaca 900
agagagttga gtccaaatat ggtcccccat gcccaccatg cccagcacct gaggccgccg 960
ggggaccatc agtcttcctg ttcccccaa aacccaagga cactctcatg atctcccgga 1020
cccctgaggt cacgtgcgtg gtggtggacg tgagccagga agaccccgag gtccagttca 1080
actggtacgt ggatggcgtg gaggtgcata atgccaagac aaagccgcgg gaggagcagt 1140
tcaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac tggctgaacg 1200
gcaaggagta caagtgcaag gtctccaaca aaggcctccc gtcctccatc gagaaaacca 1260
tctccaaagc caaagggcag ccccgagagc cacaggtgta caccctgccc ccatcccagg 1320
aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc taccccagcg 1380
acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag accacgcctc 1440
ccgtgctgga ctccgacggc tccttcttcc tctacagcag gctaaccgtg gacaagagca 1500
ggtggcagga ggggaatgtc ttctcatgct ccgtgatgca tgaggctctg cacaaccact 1560
acacacagaa gagcctctcc ctgtctctgg gtaaatgata gttcgaattc ctagaagaca 1620
tgataagata cattgatgag tttggacaaa ccacaactag aatgcagtga aaaaaatgct 1680
ttatttgtga aatttgtgat gctattgctt tatttgtaac cattataagc tgcaataaac 1740
aagttaacaa caacaattgc attcatttta tgtttcaggt tcaggggggag gtgtggga 1798

[0182] <210> 198
<211> 1798
<212> DNA
<213> 人工序列
<220>
<223> C33B903 重链
<400> 198

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggaaagcgg cggcggactg gtgcaacctg 300
gcagaagcct gagactgagc tgcgccgcca gcggcttcac cttcgacgac tacgccatgc 360
actgggtgag acaggccctt ggaaagggcc tggagtgggt gagcggcatt ggctggtccg 420
gaggcagcat cgtgtacgcc gacagcgtga agggcaggtt caagatcagc agggacaacg 480
ccaagaacag cctgtacctg cagatgaaca gcctgagagc cgaggacacc gccctgtact 540
actgcgccaa ggacagcccc tacggcgact tcttcgacta ctggggccag ggcacactgg 600
tgaccgtgag cagcgcttcc accaagggcc catccgtctt ccccctggcg ccctgctcca 660
ggagcacctc cgagagcaca gccgccctgg gctgcctggt caaggactac ttccccgaac 720
cggtgacggt gtcgtggaac tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg 780
tcctacagtc ctcaggactc tactccctca gcagcgtggt gaccgtgccc tccagcagct 840
tgggcacgaa aacctacacc tgcaacgtag atcacaagcc cagcaacacc aaggtggaca 900
agagagttga gtccaaatat ggtcccccat gcccaccatg cccagcacct gaggccgccg 960
ggggaccatc agtcttcctg ttcccccaa aacccaagga cactctcatg atctcccgga 1020

ccctgaggt cacgtgcgtg gtggtggacg tgagccagga agaccccgag gtccagttca 1080
actggtacgt ggatggcgtg gaggtgcata atgccaagac aaagccgcgg gaggagcagt 1140
tcaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac tggctgaacg 1200
gcaaggagta caagtgcaag gtctccaaca aaggcctccc gtcctccatc gagaaaacca 1260
tctccaaagc caaagggcag ccccgagagc cacaggtgta caccctgccc ccatcccagg 1320
aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc taccccagcg 1380
acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag accacgcctc 1440
ccgtgctgga ctccgacggc tccttcttcc tctacagcag gctaaccgtg gacaagagca 1500
ggtggcagga ggggaatgtc ttctcatgct ccgtgatgca tgaggctctg cacaaccact 1560
acacacagaa gagcctctcc ctgtctctgg gtaaatgata gttcgaattc ctagaagaca 1620
tgataagata cattgatgag tttggacaaa ccacaactag aatgcagtga aaaaaatgct 1680
ttatttgtga aatttgtgat gctattgctt tatttgtaac cattataagc tgcaataaac 1740
aagttaacaa caacaattgc attcatttta tgtttcaggt tcaggggggag gtgtggga 1798

<210> 199
<211> 1798
<212> DNA
<213> 人工序列
<220>
<223> C33B904 重链
<400> 199

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
[0183] tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggagagcgg cggaggactg gtgcagcctg 300
gcagaagcct gagactgagc tgtgccgcca gcggcttcac ctttgacgac tacgccatgc 360
actgggtgag acaggctcct ggcaagggcc tggagtgggt gagcggcatt ggatggagcg 420
gcggcagcat cgtgtacgcc gacagcgtga agggcaggtt caccattagc agggacaacg 480
ccaagaacag cctgtacctg cagatgaaca gcctgagggc cgaggacacc gccctgtact 540
actgcgccaa ggacagcccc tacggcgact tcttcgacta ctggggccag ggcaccctgg 600
tgacagtgag cagcgcttcc accaagggcc catccgtctt ccccctggcg ccctgctcca 660
ggagcacctc cgagagcaca gccgccctgg gctgcctggt caaggactac ttccccgaac 720
cggtgacggt gtcgtggaac tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg 780
tcctacagtc ctcaggactc tactccctca gcagcgtggt gaccgtgccc tccagcagct 840
tgggcacgaa aacctacacc tgcaacgtag atcacaagcc cagcaacacc aaggtggaca 900
agagagttga gtccaaatat ggtcccccat gcccaccatg cccagcacct gaggccgccg 960
ggggaccatc agtcttcctg ttcccccaa aacccaagga cactctcatg atctcccgga 1020
ccctgaggt cacgtgcgtg gtggtggacg tgagccagga agaccccgag gtccagttca 1080
actggtacgt ggatggcgtg gaggtgcata atgccaagac aaagccgcgg gaggagcagt 1140
tcaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac tggctgaacg 1200
gcaaggagta caagtgcaag gtctccaaca aaggcctccc gtcctccatc gagaaaacca 1260
tctccaaagc caaagggcag ccccgagagc cacaggtgta caccctgccc ccatcccagg 1320
aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc taccccagcg 1380
acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag accacgcctc 1440
ccgtgctgga ctccgacggc tccttcttcc tctacagcag gctaaccgtg gacaagagca 1500
ggtggcagga ggggaatgtc ttctcatgct ccgtgatgca tgaggctctg cacaaccact 1560
acacacagaa gagcctctcc ctgtctctgg gtaaatgata gttcgaattc ctagaagaca 1620

tgataagata cattgatgag tttggacaaa ccacaactag aatgcagtga aaaaaatgct 1680
ttatttgtga aatttgtgat gctattgctt tatttgtaac cattataagc tgcaataaac 1740
aagttaacaa caacaattgc attcatttta tgtttcaggt tcaggggggag gtgtggga 1798

<210> 200
<211> 1798
<212> DNA
<213> 人工序列
<220>
<223> C33B905 重链
<400> 200

cagctgagtt gttgtgttct gataagagtc agaggtaact cccgttgcgg tgctgttaac 60
ggtggagggc agtgtagtct gagcagtact cgttgctgcc gcgcgcgcca ccagacataa 120
tagctgacag actaacagac tgttcctttc catgggtctt ttctgcagtc accgtccttg 180
acacgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgaa gtgcagctgg tggaatctgg cggaggactg gttcagcctg 300
gcagatctct gagactgtct tgtgccgcct ctggcttcac cttcgacgat tacgctatgc 360
actgggtccg acaggccccc ggaaaaggat tggagtgggt gtccggaatt ggttggagcg 420
gcggctctat cgtgtacgcc gattctgtga agggcagatt caccatcagc cgggacaacg 480
ccaagaactc cctgtacctg cagatgaaca gcctgagagc cgaggacacc gctctgtact 540
actgcgccaa ggactctccc tacggcgact tctttgatta ctggggccag ggcacactgg 600
tcaccgtttc ttctgcttcc accaagggcc catccgtctt ccccctggcg ccctgctcca 660
ggagcacctc cgagagcaca gccgccctgg gctgcctggt caaggactac ttccccgaac 720
cggtgacggt gtcgtggaac tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg 780
[0184] tcctacagtc ctcaggactc tactccctca gcagcgtggt gaccgtgccc tccagcagct 840
tgggcacgaa aacctacacc tgcaacgtag atcacaagcc cagcaacacc aaggtggaca 900
agagagttga gtccaaatat ggtcccccat gcccaccatg cccagcacct gaggccgccg 960
ggggaccatc agtcttcctg ttcccccaa aacccaagga cactctcatg atctcccgga 1020
cccctgaggt cacgtgcgtg gtggtggacg tgagccagga agaccccgag gtccagttca 1080
actggtacgt ggatggcgtg gaggtgcata atgccaagac aaagccgcgg gaggagcagt 1140
tcaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac tggctgaacg 1200
gcaaggagta caagtgcaag gtctccaaca aaggcctccc gtcctccatc gagaaaacca 1260
tctccaaagc caaagggcag ccccgagagc cacaggtgta caccctgccc ccatcccagg 1320
aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc taccccagcg 1380
acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag accacgcctc 1440
ccgtgctgga ctccgacggc tccttcttcc tctacagcag gctaaccgtg gacaagagca 1500
ggtggcagga ggggaatgtc ttctcatgct ccgtgatgca tgaggctctg cacaaccact 1560
acacacagaa gagcctctcc ctgtctctgg gtaaatgatg attcgaaccc gggcacgtgc 1620
ggaccgaatt cattgatcat aatcagccat accacatttg tagaggtttt acttgcttta 1680
aaaaacctcc cacacctccc cctgaacctg aaacataaaa tgaatgcaat tgttgttgtt 1740
aacttgttta ttgcagctta taatggttac aaataaagca atagcatcac aaatttca 1798

<210> 201
<211> 1801
<212> DNA
<213> 人工序列
<220>
<223> C33B906 重链
<400> 201

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgc tggagagcgg aggaggactg gtgcagcccg 300
gaggaagcct gaagctgtcc tgcaccgcca gcggcttcac cttcaggagc tacgccatga 360
gctgggtgag acaggcccct ggcaagggcc tggaatgggt gagcgccatc aacggctacg 420
gcgacggcag gtactacgcc gacagcgtga agggcaggtt caccatcagc agggacaaca 480
gcaagaacac cctgtacctg cagatgaaca gcctgagagc cgaggacacc gccgtgtaca 540
gctgcgccaa ggaccagggc ttcggcgagc tgttcttcga ctactggggc cagggcacac 600
tggtgaccgt gagcagcgct tccaccaagg gcccatccgt cttccccctg gcgccctgct 660
ccaggagcac ctccgagagc acagccgccc tgggctgcct ggtcaaggac tacttccccg 720
aaccggtgac ggtgtcgtgg aactcaggcg ccctgaccag cggcgtgcac accttcccgg 780
ctgtcctaca gtcctcagga ctctactccc tcagcagcgt ggtgaccgtg ccctccagca 840
gcttgggcac gaaaacctac acctgcaacg tagatcacaa gcccagcaac accaaggtgg 900
acaagagagt tgagtccaaa tatggtcccc catgcccacc atgcccagca cctgaggccg 960
ccgggggacc atcagtcttc ctgttccccc caaaacccaa ggacactctc atgatctccc 1020
ggaccccctga ggtcacgtgc gtggtggtgg acgtgagcca ggaagacccc gaggtccagt 1080
tcaactggta cgtggatggc gtggaggtgc ataatgccaa gacaaagccg cgggaggagc 1140
agttcaacag cacgtaccgt gtggtcagcg tcctcaccgt cctgcaccag gactggctga 1200
acggcaagga gtacaagtgc aaggtctcca acaaaggcct cccgtcctcc atcgagaaaa 1260
ccatctccaa agccaaaggg cagccccgag agccacaggt gtacaccctg cccccatccc 1320
aggaggagat gaccaagaac caggtcagcc tgacctgcct ggtcaaaggc ttctacccca 1380
[0185] gcgacatcgc cgtggagtgg gagagcaatg ggcagccgga gaacaactac aagaccacgc 1440
ctcccgtgct ggactccgac ggctccttct tcctctacag caggctaacc gtggacaaga 1500
gcaggtggca ggaggggaat gtcttctcat gctccgtgat gcatgaggct ctgcacaacc 1560
actacacaca gaagagcctc tccctgtctc tgggtaaatg atagttcgaa ttcctagaag 1620
acatgataag atacattgat gagtttggac aaaccacaac tagaatgcag tgaaaaaaat 1680
gctttatttg tgaaatttgt gatgctattg ctttatttgt aaccattata agctgcaata 1740
aacaagttaa caacaacaat tgcattcatt ttatgtttca ggttcagggg gaggtgtggg 1800
a 1801

<210> 202
<211> 1792
<212> DNA
<213> 人工序列
<220>
<223> C33B907 重链
<400> 202

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgg tggaaagcgg aggcggagtg gtgcagcccg 300
gaagaagcct gagactgtcc tgcgccgcca gcggcttcac cttcagctac tacggcatgc 360
actgggtgag gcaggcccct gacaagggac tggagtgggt ggccgtgatc tggttcgacg 420
gcaacaacaa gtactacgcc gacagcgtga agggcaggtt caccatcagc agggacaact 480
ccaagaacac cctgtacctg cagatgaaca gcctgagggc cgaggacacc gccgtgtact 540

actgcgccag ggacagggag ctgctgttcg actactgggg ccagggaacc ctggtgaccg 600
tgagcagcgc ttccaccaag ggcccatccg tcttcccccc ggcgccctgc tccaggagca 660
cctccgagag cacagccgcc ctgggctgcc tggtcaagga ctacttcccc gaaccggtga 720
cggtgtcgtg gaactcaggc gccctgacca gcggcgtgca caccttcccg gctgtcctac 780
agtcctcagg actctactcc ctcagcagcg tggtgaccgt gccctccagc agcttgggca 840
cgaaaaccta cacctgcaac gtagatcaca agcccagcaa caccaaggtg gacaagagag 900
ttgagtccaa atatggtccc ccatgcccac catgcccagc acctgaggcc gccgggggac 960
catcagtctt cctgttcccc ccaaaaccca aggacactct catgatctcc cggacccctg 1020
aggtcacgtg cgtggtggtg gacgtgagcc aggaagaccc cgaggtccag ttcaactggt 1080
acgtggatgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag cagttcaaca 1140
gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg aacggcaagg 1200
agtacaagtg caaggtctcc aacaaaggcc tcccgtcctc catcgagaaa accatctcca 1260
aagccaaagg gcagccccga gagccacagg tgtacaccct gccccccatcc caggaggaga 1320
tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctacccc agcgacatcg 1380
ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg cctcccgtgc 1440
tggactccga cggctccttc ttcctctaca gcaggctaac cgtggacaag agcaggtggc 1500
aggaggggaa tgtcttctca tgctccgtga tgcatgaggc tctgcacaac cactacacac 1560
agaagagcct ctccctgtct ctgggtaaat gatagttcga attcctagaa gacatgataa 1620
gatacattga tgagtttgga caaaccacaa ctagaatgca gtgaaaaaaa tgctttattt 1680
gtgaaatttg tgatgctatt gctttatttg taaccattat aagctgcaat aaacaagtta 1740
acaacaacaa ttgcattcat tttatgtttc aggttcaggg ggaggtgtgg ga 1792

<210> 203
<211> 1828
[0186] <212> DNA
<213> 人工序列
<220>
<223> C33B908 重链
<400> 203

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtccagctgg tggaatccgg cggaggactg gtgcagcctg 300
gcagaagcct gagactgagc tgcgccgcca gcggcttcac cttcgacgac tacgccatgc 360
actgggtgag acaggtgcct ggcgagggac tggagtgggt gagcggaatc agctggaacg 420
gcggcgacat ggtgtacgcc gacagcgtga agggcaggtt caccatcagc agggacaacg 480
ccaagaacag cctgtacctg cagatgaaca gcctgaggcc tgaggacacc gccctgtact 540
actgcgtgaa ggacatgccc tacttcgact tcctgaccgg cagcgactac tactactacg 600
gcatggacgt gtggggccag ggcacaaccg tgaccgtgag cagcgcttcc accaagggcc 660
catccgtctt ccccctggcg ccctgctcca ggagcacctc cgagagcaca gccgccctgg 720
gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc 780
tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca 840
gcagcgtggt gaccgtgccc tccagcagct tgggcacgaa aacctacacc tgcaacgtag 900
atcacaagcc cagcaacacc aaggtggaca agagagttga gtccaaatat ggtcccccat 960
gcccaccatg cccagcacct gaggccgccg ggggaccatc agtcttcctg ttcccccaa 1020
aacccaagga cactctcatg atctcccgga cccctgaggt cacgtgcgtg gtggtggacg 1080
tgagccagga agaccccgag gtccagttca actggtacgt ggatggcgtg gaggtgcata 1140

atgccaagac aaagccgcgg gaggagcagt tcaacagcac gtaccgtgtg gtcagcgtcc 1200
tcaccgtcct gcaccaggac tggctgaacg gcaaggagta caagtgcaag gtctccaaca 1260
aaggcctccc gtcctccatc gagaaaacca tctccaaagc caaagggcag ccccgagagc 1320
cacaggtgta caccctgccc ccatcccagg aggagatgac caagaaccag gtcagcctga 1380
cctgcctggt caaaggcttc taccccagcg acatcgccgt ggagtgggag agcaatgggc 1440
agccggagaa caactacaag accacgcctc ccgtgctgga ctccgacggc tccttcttcc 1500
tctacagcag gctaaccgtg gacaagagca ggtggcagga ggggaatgtc ttctcatgct 1560
ccgtgatgca tgaggctctg cacaaccact acacacagaa gagcctctcc ctgtctctgg 1620
gtaaatgata gttcgaattc ctagaagaca tgataagata cattgatgag tttggacaaa 1680
ccacaactag aatgcagtga aaaaaatgct ttatttgtga aatttgtgat gctattgctt 1740
tatttgtaac cattataagc tgcaataaac aagttaacaa caacaattgc attcatttta 1800
tgtttcaggt tcaggggggag gtgtggga 1828

<210> 204
<211> 1792
<212> DNA
<213> 人工序列
<220>
<223> C33B909 重链
<400> 204

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
[0187] cccaaagtat acaggcccag gtgcagctgg tggaaagcgg aggaggagtg gtgcagcctg 300
gcaggagcct gaggctgagc tgtgccacca gcggcttcac cttcagcaat tacggcatgc 360
actgggtgag acaggctcct ggcaagggcc tggagtgggt ggccgtgatc tggtacgtgg 420
gcagccacaa gtactacgcc gacagcgtga agggcaggtt caccatcagc agggacaaca 480
gcaagaacac cctgtacctg cagatgaaca gcctgagggc cgaggacacc gccgtgtact 540
actgcgccag ggacggcagc ctgtgcttcg actactgggg ccagggaacc ctggtgaccg 600
tgagcagcgc ttccaccaag ggcccatccg tcttccccct ggcgccctgc tccaggagca 660
cctccgagag cacagccgcc ctgggctgcc tggtcaagga ctacttcccc gaaccggtga 720
cggtgtcgtg gaactcaggc gccctgacca gcggcgtgca caccttcccg gctgtcctac 780
agtcctcagg actctactcc ctcagcagcg tggtgaccgt gccctccagc agcttgggca 840
cgaaaaccta cacctgcaac gtagatcaca agcccagcaa caccaaggtg gacaagagag 900
ttgagtccaa atatggtccc ccatgcccac catgcccagc acctgaggcc gccgggggac 960
catcagtctt cctgttcccc ccaaaaccca aggacactct catgatctcc cggacccctg 1020
aggtcacgtg cgtggtggtg gacgtgagcc aggaagaccc cgaggtccag ttcaactggt 1080
acgtggatgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag cagttcaaca 1140
gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg aacggcaagg 1200
agtacaagtg caaggtctcc aacaaaggcc tcccgtcctc catcgagaaa accatctcca 1260
aagccaaagg gcagccccga gagccacagg tgtacaccct gcccccatcc caggaggaga 1320
tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctacccc agcgacatcg 1380
ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg cctcccgtgc 1440
tggactccga cggctccttc ttcctctaca gcaggctaac cgtggacaag agcaggtggc 1500
aggaggggaa tgtcttctca tgctccgtga tgcatgaggc tctgcacaac cactacacac 1560
agaagagcct ctccctgtct ctgggtaaat gatagttcga attcctagaa gacatgataa 1620
gatacattga tgagtttgga caaaccacaa ctagaatgca gtgaaaaaaa tgctttattt 1680

gtgaaatttg tgatgctatt gctttatttg taaccattat aagctgcaat aaacaagtta 1740
acaacaacaa ttgcattcat tttatgtttc aggttcaggg ggaggtgtgg ga 1792
<210> 205
<211> 1807
<212> DNA
<213> 人工序列
<220>
<223> C33B910 重链
<400> 205
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggagtccgg cggaggactg gtgcaacctg 300
gcaggagcct gagactgagc tgcgtggcca gcggcttcac cttcgacgac tacgccatcc 360
actgggtgag gcaggcccct ggcaaaggcc tggagtgggt gagcggcctg agctggaatg 420
gcggcaacat cggctacgcc gacagcgtga agggcaggtt caccatcagc agggacaacg 480
ccaagaacag cctgtacctg cagatgaaca gcctgaaaac cgaggacacc gccttctact 540
actgcaccaa ggacaccccc tacggcgact acttcgacta ctggggccag ggaaccctgg 600
tgaccgtgag ctccgcctcc accaagggcc catcggtctt ccccctggca ccctcctcca 660
agagcacctc tgggggcaca gcggccctgg gctgcctggt caaggactac ttccccgaac 720
cggtgacggt gtcgtggaac tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg 780
tcctacagtc ctcaggactc tactccctca gcagcgtggt gaccgtgccc tccagcagct 840
[0188] tgggcaccca gacctacatc tgcaacgtga atcacaagcc cagcaacacc aaggtggaca 900
agaaagttga gcccaaatct tgtgacaaaa ctcacacatg cccaccgtgc ccagcacctg 960
aactcctggg gggaccgtca gtcttcctct tccccccaaa acccaaggac accctcatga 1020
tctcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa gaccctgagg 1080
tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca aagccgcggg 1140
aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg caccaggact 1200
ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca gccccatcg 1260
agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac accctgcccc 1320
catcccggga ggagatgacc aagaaccagg tcagcctgac ctgcctggtc aaaggcttct 1380
atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac aactacaaga 1440
ccacgcctcc cgtgctggac tccgacggct ccttcctgct ctacagcaag ctcaccgtgg 1500
acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat gaggctctgc 1560
acaaccacta cacgcagaag agcctctccc tgtctccggg taaatgatag ttcgaattcc 1620
tagaagacat gataagatac attgatgagt ttggacaaac cacaactaga atgcagtgaa 1680
aaaaatgctt tatttgtgaa atttgtgatg ctattgcttt atttgtaacc attataagct 1740
gcaataaaca agttaacaac aacaattgca ttcattttat gtttcaggtt cagggggagg 1800
tgtggga 1807
<210> 206
<211> 1807
<212> DNA
<213> 人工序列
<220>
<223> C33B911 重链
<400> 206

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggaaagcgg cggaggactg gtgcagcccg 300
gcaggagcct gagactgagc tgtgccggca gcggcttcac cttcgacgac tacgccatcc 360
actgggtgag acaggcccct ggaaagggcc tggagtgggt gagcggactg agctggaacg 420
gcggcaacat cggctacgcc gacagcgtga aaggcaggtt caccatcagc agggacaacg 480
ccaagaacag cctgtacctg cagctgaaca gcctgaagac cgaggatacc gccttctact 540
actgcgccaa ggacagcccc tatggcgact acttcgacta ctggggccag ggcacactgg 600
tgaccgtgag cagcgcctcc accaagggcc catcggtctt ccccctggca ccctcctcca 660
agagcacctc tgggggcaca gcggccctgg gctgcctggt caaggactac ttccccgaac 720
cggtgacggt gtcgtggaac tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg 780
tcctacagtc ctcaggactc tactccctca gcagcgtggt gaccgtgccc tccagcagct 840
tgggcaccca gacctacatc tgcaacgtga atcacaagcc cagcaacacc aaggtggaca 900
agaaagttga gcccaaatct tgtgacaaaa ctcacacatg cccaccgtgc ccagcacctg 960
aactcctggg gggaccgtca gtcttcctct tccccccaaa acccaaggac accctcatga 1020
tctcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa gaccctgagg 1080
tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca aagccgcggg 1140
aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg caccaggact 1200
ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca gccccccatcg 1260
agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac accctgcccc 1320
catcccggga ggagatgacc aagaaccagg tcagcctgac ctgcctggtc aaaggcttct 1380
[0189] atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac aactacaaga 1440
ccacgcctcc cgtgctggac tccgacggct ccttcctgct ctacagcaag ctcaccgtgg 1500
acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat gaggctctgc 1560
acaaccacta cacgcagaag agcctctccc tgtctccggg taaatgatag ttcgaattcc 1620
tagaagacat gataagatac attgatgagt ttggacaaac cacaactaga atgcagtgaa 1680
aaaaatgctt tatttgtgaa atttgtgatg ctattgcttt atttgtaacc attataagct 1740
gcaataaaca agttaacaac aacaattgca ttcattttat gtttcaggtt cagggggagg 1800
tgtggga 1807

<210> 207
<211> 1807
<212> DNA
<213> 人工序列
<220>
<223> C33B912 重链
<400> 207

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggagagcgg cggaggactg gtgcagcctg 300
gcagaagcct gagactgagc tgcgccgcca gcggcttcac cttcgacgac tacgccatgc 360
actgggtcag acaggccccc ggaaagggac tggagtgggt gagcggaatc ggctggagcg 420
gaggcagcat cgtgtacgcc gacagcgtga agggcaggtt caagatcagc agggacaacg 480
ccaagaacag cctgtacctg cagatgaact ccctgagagc cgaggacacc gccctgtact 540

actgcgccaa ggacagcccc tacggcgact tcttcgacta ctggggccag ggaaccctgg 600
tgaccgtgag cagcgcctcc accaagggcc catcggtctt ccccctggca ccctcctcca 660
agagcacctc tgggggcaca gcggccctgg gctgcctggt caaggactac ttccccgaac 720
cggtgacggt gtcgtggaac tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg 780
tcctacagtc ctcaggactc tactccctca gcagcgtggt gaccgtgccc tccagcagct 840
tgggcaccca gacctacatc tgcaacgtga atcacaagcc cagcaacacc aaggtggaca 900
agaaagttga gcccaaatct tgtgacaaaa ctcacacatg cccaccgtgc ccagcacctg 960
aactcctggg gggaccgtca gtcttcctct tccccccaaa acccaaggac accctcatga 1020
tctcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa gaccctgagg 1080
tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca aagccgcggg 1140
aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg caccaggact 1200
ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca gccccccatcg 1260
agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac accctgcccc 1320
catcccggga ggagatgacc aagaaccagg tcagcctgac ctgcctggtc aaaggcttct 1380
atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac aactacaaga 1440
ccacgcctcc cgtgctggac tccgacggct ccttcctgct ctacagcaag ctcaccgtgg 1500
acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat gaggctctgc 1560
acaaccacta cacgcagaag agcctctccc tgtctccggg taaatgatag ttcgaattcc 1620
tagaagacat gataagatac attgatgagt ttggacaaac cacaactaga atgcagtgaa 1680
aaaaatgctt tatttgtgaa atttgtgatg ctattgcttt atttgtaacc attataagct 1740
gcaataaaca agttaacaac aacaattgca ttcattttat gtttcaggtt cagggggagg 1800
tgtggga 1807

<210> 208

[0190] <211> 1807

<212> DNA

<213> 人工序列

<220>

<223> C33B913 重链

<400> 208

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggagagcgg cggaggactg gtgcagcctg 300
gcagaagcct gaggctgagc tgtgccgcca gcggcttcac cttcgacgac tacgccatgc 360
actgggtgag acaggctcct ggcaagggcc tggagtgggt gagcggcatc ggatggagcg 420
gaggcagcat cgtgtacgcc gacagcgtga agggcaggtt caccatcagc agggacaacg 480
ccaagaacag cctgtacctg cagatgaact ccctgagggc cgaggacacc gccctgtact 540
actgcgccaa ggacagcccc tacggcgact tcttcgacta ctggggccag ggcaccctgg 600
tgacagtgag cagcgcctcc accaagggcc catcggtctt ccccctggca ccctcctcca 660
agagcacctc tgggggcaca gcggccctgg gctgcctggt caaggactac ttccccgaac 720
cggtgacggt gtcgtggaac tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg 780
tcctacagtc ctcaggactc tactccctca gcagcgtggt gaccgtgccc tccagcagct 840
tgggcaccca gacctacatc tgcaacgtga atcacaagcc cagcaacacc aaggtggaca 900
agaaagttga gcccaaatct tgtgacaaaa ctcacacatg cccaccgtgc ccagcacctg 960
aactcctggg gggaccgtca gtcttcctct tccccccaaa acccaaggac accctcatga 1020
tctcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa gaccctgagg 1080

tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca aagccgcggg 1140
aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg caccaggact 1200
ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca gcccccatcg 1260
agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac accctgcccc 1320
catcccggga ggagatgacc aagaaccagg tcagcctgac ctgcctggtc aaaggcttct 1380
atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac aactacaaga 1440
ccacgcctcc cgtgctggac tccgacggct ccttcctgct ctacagcaag ctcaccgtgg 1500
acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat gaggctctgc 1560
acaaccacta cacgcagaag agcctctccc tgtctccggg taaatgatag ttcgaattcc 1620
tagaagacat gataagatac attgatgagt ttggacaaac cacaactaga atgcagtgaa 1680
aaaaatgctt tatttgtgaa atttgtgatg ctattgcttt atttgtaacc attataagct 1740
gcaataaaca agttaacaac aacaattgca ttcattttat gtttcaggtt cagggggagg 1800
tgtggga 1807

<210> 209
<211> 1810
<212> DNA
<213> 人工序列
<220>
<223> C33B914 重链
<400> 209

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
[0191] tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgc tggagagcgg cggaggactg gtgcagcctg 300
gaggcagcct gaagctgagc tgcaccgcca gcggcttcac cttcaggagc tacgccatga 360
gctgggtgag acaggctccc ggaaagggcc tggagtgggt gtccgccatc aacggctacg 420
gcgacggcag gtactacgcc gacagcgtga agggcaggtt caccatcagc agggacaact 480
ccaagaacac cctgtacctg cagatgaaca gcctgagggc cgaggatacc gccgtgtaca 540
gctgcgccaa ggaccagggc ttcggcgagc tgttcttcga ctactggggc cagggaaccc 600
tggtgaccgt gagcagcgcc tccaccaagg gcccatcggt cttccccctg gcaccctcct 660
ccaagagcac ctctgggggc acagcggccc tgggctgcct ggtcaaggac tacttccccg 720
aaccggtgac ggtgtcgtgg aactcaggcg ccctgaccag cggcgtgcac accttcccgg 780
ctgtcctaca gtcctcagga ctctactccc tcagcagcgt ggtgaccgtg ccctccagca 840
gcttgggcac ccagacctac atctgcaacg tgaatcacaa gcccagcaac accaaggtgg 900
acaagaaagt tgagcccaaa tcttgtgaca aaactcacac atgcccaccg tgcccagcac 960
ctgaactcct gggggggaccg tcagtcttcc tcttcccccc aaaacccaag gacaccctca 1020
tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac gaagaccctg 1080
aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag acaaagccgc 1140
gggaggagca gtacaacagc acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg 1200
actggctgaa tggcaaggag tacaagtgca aggtctccaa caaagccctc ccagccccca 1260
tcgagaaaac catctccaaa gccaaagggc agccccgaga accacaggtg tacaccctgc 1320
ccccatcccg ggaggagatg accaagaacc aggtcagcct gacctgcctg gtcaaaggct 1380
tctatcccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag aacaactaca 1440
agaccacgcc tcccgtgctg gactccgacg gctccttcct gctctacagc aagctcaccg 1500
tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg catgaggctc 1560
tgcacaacca ctacacgcag aagagcctct ccctgtctcc gggtaaatga tagttcgaat 1620

tcctagaaga catgataaga tacattgatg agtttggaca aaccacaact agaatgcagt 1680
gaaaaaaatg ctttatttgt gaaatttgtg atgctattgc tttatttgta accattataa 1740
gctgcaataa acaagttaac aacaacaatt gcattcattt tatgtttcag gttcaggggg 1800
aggtgtggga 1810

<210> 210
<211> 1801
<212> DNA
<213> 人工序列
<220>
<223> C33B915 重链
<400> 210

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag gtgcagctgg tggagtccgg aggaggagtg gtgcagcccg 300
gcagaagcct gagactgagc tgcgccgcca gcggcttcac cttcagctac tacggcatgc 360
actgggtgag gcaggccccc gataagggcc tggagtgggt ggccgtgatc tggttcgacg 420
gcaacaacaa gtactacgcc gacagcgtga agggcaggtt caccatcagc agggacaaca 480
gcaagaacac cctgtacctg cagatgaaca gcctgagggc cgaggacacc gccgtgtact 540
actgcgccag ggacagggag ctgctgttcg actactgggg ccagggcaca ctggtcaccg 600
tgagctccgc ctccaccaag ggcccatcgg tcttcccccc ggcaccctcc tccaagagca 660
cctctggggg cacagcggcc ctgggctgcc tggtcaagga ctacttcccc gaaccggtga 720
[0192] cggtgtcgtg gaactcaggc gccctgacca gcggcgtgca caccttcccg gctgtcctac 780
agtcctcagg actctactcc ctcagcagcg tggtgaccgt gccctccagc agcttgggca 840
cccagaccta catctgcaac gtgaatcaca agcccagcaa caccaaggtg gacaagaaag 900
ttgagcccaa atcttgtgac aaaactcaca catgcccacc gtgcccagca cctgaactcc 960
tgggggggacc gtcagtcttc ctcttccccc caaaacccaa ggacaccctc atgatctccc 1020
ggaccccctga ggtcacatgc gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt 1080
tcaactggta cgtggacggc gtggaggtgc ataatgccaa gacaaagccg cgggaggagc 1140
agtacaacag cacgtaccgt gtggtcagcg tcctcaccgt cctgcaccag gactggctga 1200
atggcaagga gtacaagtgc aaggtctcca acaaagccct cccagccccc atcgagaaaa 1260
ccatctccaa agccaaaggg cagccccgag aaccacaggt gtacaccctg cccccatccc 1320
gggaggagat gaccaagaac caggtcagcc tgacctgcct ggtcaaaggc ttctatccca 1380
gcgacatcgc cgtggagtgg gagagcaatg ggcagccgga gaacaactac aagaccacgc 1440
ctcccgtgct ggactccgac ggctccttcc tgctctacag caagctcacc gtggacaaga 1500
gcaggtggca gcaggggaac gtcttctcat gctccgtgat gcatgaggct ctgcacaacc 1560
actacacgca gaagagcctc tccctgtctc cgggtaaatg atagttcgaa ttcctagaag 1620
acatgataag atacattgat gagtttggac aaaccacaac tagaatgcag tgaaaaaaat 1680
gctttatttg tgaaatttgt gatgctattg ctttatttgt aaccattata agctgcaata 1740
aacaagttaa caacaacaat tgcattcatt ttatgtttca ggttcagggg gaggtgtggg 1800
a 1801

<210> 211
<211> 1837
<212> DNA
<213> 人工序列
<220>

<223> C33B916 重链
<400> 211
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgag gtgcagctgg tggagagcgg aggcggactg gtgcagcctg 300
gaaggagcct gaggctgagc tgtgccgcca gcggcttcac cttcgacgac tacgccatgc 360
actgggtgag acaggtgcct ggcgagggac tggagtgggt gagcggcatc agctggaacg 420
gcggcgacat ggtgtacgcc gacagcgtga agggcaggtt caccatcagc agggacaacg 480
ccaagaacag cctgtacctg cagatgaaca gcctgaggcc cgaggacacc gccctgtact 540
actgcgtgaa ggatatgccc tacttcgact tcctgaccgg cagcgactac tactactacg 600
gcatggatgt gtggggccag ggcaccaccg tgacagtgag cagcgcctcc accaagggcc 660
catcggtctt ccccctggca ccctcctcca agagcacctc tgggggcaca gcggccctgg 720
gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc 780
tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca 840
gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc tgcaacgtga 900
atcacaagcc cagcaacacc aaggtggaca agaaagttga gcccaaatct tgtgacaaaa 960
ctcacacatg cccaccgtgc ccagcacctg aactcctggg gggaccgtca gtcttcctct 1020
tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc acatgcgtgg 1080
tggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg 1140
aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg taccgtgtgg 1200
tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac aagtgcaagg 1260
[0193] tctccaacaa agccctccca gcccccatcg agaaaaccat ctccaaagcc aaagggcagc 1320
cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc aagaaccagg 1380
tcagcctgac ctgcctggtc aaaggcttct atcccagcga catcgccgtg gagtgggaga 1440
gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac tccgacggct 1500
ccttcctgct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag gggaacgtct 1560
tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag agcctctccc 1620
tgtctccggg taaatgatag ttcgaattcc tagaagacat gataagatac attgatgagt 1680
ttggacaaac cacaactaga atgcagtgaa aaaaatgctt tatttgtgaa atttgtgatg 1740
ctattgcttt atttgtaacc attataagct gcaataaaca agttaacaac aacaattgca 1800
ttcattttat gtttcaggtt cagggggagg tgtggga 1837
<210> 212
<211> 214
<212> PRT
<213> 人工序列
<220>
<223> C33B901 轻链
<400> 212
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Trp Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Gln Pro Gly Lys Ala Pro Asn Leu Leu Ile
35 40 45
Tyr Arg Ser Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Asp Asn Ser Phe Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 213
<211> 214
[0194] <212> PRT
<213> 人工序列
<220>
<223> C33B902 轻链
<400> 213

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

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

Tyr Gly Ala Ser Ser Trp Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Asp Asn Ser Phe Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln

145 150 155 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205
Phe Asn Arg Gly Glu Cys
210

<210> 214
<211> 220
<212> PRT
<213> 人工序列
<220>
<223> C33B903 轻链
<400> 214

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Thr Val Leu Tyr Ser
20 25 30
Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45
Pro Pro Lys Leu Leu Ile Ser Trp Ala Ser Thr Arg Lys Ser Gly Val
[0195] 50 55 60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80
Val Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln His
85 90 95
Tyr Tyr Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105 110
Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
115 120 125
Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
130 135 140
Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
145 150 155 160
Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
165 170 175
Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
180 185 190
Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
195 200 205
Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215 220

<210> 215
<211> 220
<212> PRT

<213> 人工序列
<220>
<223> C33B904 轻链
<400> 215

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Thr Val Phe Tyr Ser
20 25 30
Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45
Pro Pro Lys Leu Leu Ile Ser Trp Ala Ser Thr Arg Lys Ser Gly Val
50 55 60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80
Val Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln His
85 90 95
Tyr Tyr Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105 110
Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
115 120 125
Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
130 135 140
Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
[0196] 145 150 155 160
Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
165 170 175
Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
180 185 190
Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
195 200 205
Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215 220

<210> 216
<211> 220
<212> PRT
<213> 人工序列
<220>
<223> C33B905 轻链
<400> 216

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

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

<210> 217
<211> 214
<212> PRT
[0197] <213> 人工序列
<220>
<223> C33B906 轻链
<400> 217

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

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205
Phe Asn Arg Gly Glu Cys
210

<210> 218
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B907 轻链
<400> 218

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

[0198]
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Ala Tyr Tyr Cys Gln Thr Trp Asp Thr Arg Ile Ala Val
85 90 95
Phe Gly Gly Gly Thr Asn Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 219
<211> 212
<212> PRT
<213> 人工序列

<220>
<223> C33B908 轻链
<400> 219
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Asn Leu Gly Asn Glu His Val
20 25 30
Cys Trp Tyr His Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asn Asn Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Ser Ile Ser Gly Thr Gln Ala Thr
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Thr Thr Ala Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
[0199] Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210
<210> 220
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B909 轻链
<400> 220
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Asn Ile Ser Cys Ser Gly Val Thr Leu Gly Tyr Asn Tyr Ala
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Ile Leu Val Ile Ser
35 40 45
Gln Asp Thr Gln Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met

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

<210> 221
<211> 214
<212> PRT
<213> 人工序列

[0200] <220>
<223> C33B910 轻链
<400> 221

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

165 170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205
Phe Asn Arg Gly Glu Cys
210
<210> 222
<211> 214
<212> PRT
<213> 人工序列
<220>
<223> C33B911 轻链
<400> 222
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Glu Trp Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Ser Trp Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
[0201] 65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Asp Asn Ser Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205
Phe Asn Arg Gly Glu Cys
210
<210> 223
<211> 220
<212> PRT
<213> 人工序列
<220>

<223> C33B912 轻链
<400> 223

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Thr Val Leu Tyr Ser
20 25 30
Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45
Pro Pro Lys Leu Leu Ile Ser Trp Ala Ser Thr Arg Lys Ser Gly Val
50 55 60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80
Val Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln His
85 90 95
Tyr Tyr Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105 110
Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
115 120 125
Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
130 135 140
Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
145 150 155 160
Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
[0202] 165 170 175
Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
180 185 190
Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
195 200 205
Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215 220

<210> 224
<211> 220
<212> PRT
<213> 人工序列
<220>
<223> C33B913 轻链
<400> 224

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

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

<210> 225
<211> 214
<212> PRT
<213> 人工序列
<220>

[0203] <223> C33B914 轻链
<400> 225

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

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205
Phe Asn Arg Gly Glu Cys
210

<210> 226
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B915 轻链
<400> 226

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

[0204] Asp Glu Ala Ala Tyr Tyr Cys Gln Thr Trp Asp Thr Arg Ile Ala Val
85 90 95
Phe Gly Gly Gly Thr Asn Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 227
<211> 212
<212> PRT
<213> 人工序列
<220>
<223> C33B916 轻链

<400> 227

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Asn Leu Gly Asn Glu His Val
20 25 30
Cys Trp Tyr His Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asn Asn Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Ser Ile Ser Gly Thr Gln Ala Thr
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Thr Thr Ala Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
[0205] Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Cys Ser
210

<210> 228
<211> 1102
<212> DNA
<213> 人工序列
<220>
<223> C33B901 轻链
<400> 228

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgac atccagatga cccagagccc tagcagcgtg tgggctagcg 300
tgggcgacag ggtgaccatc acctgcaggg ccagccaggg catcagcagc tggctggcct 360
ggtaccaaca gcagcctggc aaggccccca acctgctgat ctacagaagc agcagcctgc 420
agagcggagt gcccagcagg tttagcggaa gcggcagcgg caccgacttc accctgacca 480
tcagcagcct gcagcccgag gacttcgcca cctactactg ccagcaggac aacagcttcc 540
cctacacctt cggccagggc accaagctgg agatcaagcg tacggtggct gcaccatctg 600
tcttcatctt cccgccatct gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc 660

tgctgaataa cttctatccc agagaggcca aagtacagtg gaaggtggat aacgccctcc 720
aatcgggtaa ctcccaggag agtgtcacag agcaggacag caaggacagc acctacagcc 780
tcagcagcac cctgacgctg agcaaagcag actacgagaa acacaaagtc tacgcctgcg 840
aagtcaccca tcagggcctg agctcgcccg tcacaaagag cttcaacagg ggagagtgtt 900
agtgattcga attcctagaa gacatgataa gatacattga tgagtttgga caaaccacaa 960
ctagaatgca gtgaaaaaaa tgctttattt gtgaaatttg tgatgctatt gctttatttg 1020
taaccattat aagctgcaat aaacaagtta acaacaacaa ttgcattcat tttatgtttc 1080
aggttcaggg ggaggtgtgg ga 1102

<210> 229
<211> 1102
<212> DNA
<213> 人工序列
<220>
<223> C33B902 轻链
<400> 229

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgac atccagatga cccagagccc tagcagcgag tgggctagcg 300
tgggcgacag ggtgaccatc acctgcagag ccagccaggg catcagcagc tggctggcct 360
ggtaccagca gaagcccggc aaggccccca agctgctgat ctacggcgcc agcagctggc 420
agagcggagt gcctagcagg ttcagcggca gcggaagcgg caccgacttc accctgacca 480
[0206] tcagcagcct gcagcccgag gacttcgcca cctactactg ccagcaggac aacagcttcc 540
cctacacctt cggccagggc accaagctgg agatcaagcg tacggtggct gcaccatctg 600
tcttcatctt cccgccatct gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc 660
tgctgaataa cttctatccc agagaggcca aagtacagtg gaaggtggat aacgccctcc 720
aatcgggtaa ctcccaggag agtgtcacag agcaggacag caaggacagc acctacagcc 780
tcagcagcac cctgacgctg agcaaagcag actacgagaa acacaaagtc tacgcctgcg 840
aagtcaccca tcagggcctg agctcgcccg tcacaaagag cttcaacagg ggagagtgtt 900
agtgattcga attcctagaa gacatgataa gatacattga tgagtttgga caaaccacaa 960
ctagaatgca gtgaaaaaaa tgctttattt gtgaaatttg tgatgctatt gctttatttg 1020
taaccattat aagctgcaat aaacaagtta acaacaacaa ttgcattcat tttatgtttc 1080
aggttcaggg ggaggtgtgg ga 1102

<210> 230
<211> 1120
<212> DNA
<213> 人工序列
<220>
<223> C33B903 轻链
<400> 230

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgac atcgtgatga cccagagccc tgatagcctg gccgtgagcc 300
tgggagagag agccaccatc aactgcaaga gcagccagac cgtgctgtac agcagcaaca 360

acaagaacta cctggcctgg taccagcaga agcctggcca gccccccaag ctgctgatca 420
gctgggccag caccagaaag agcggcgtgc ctgacagatt tagcggcagc ggcagcggca 480
ccgatttcac cctgaccgtg agcagcctgc aggccgagga tgtggccgtg tactactgcc 540
agcactacta cagcaccccc tacaccttcg gccagggcac caagctggag atcaagcgta 600
cggtggctgc accatctgtc ttcatcttcc cgccatctga tgagcagttg aaatctggaa 660
ctgcctctgt tgtgtgcctg ctgaataact tctatcccag agaggccaaa gtacagtgga 720
aggtggataa cgccctccaa tcgggtaact cccaggagag tgtcacagag caggacagca 780
aggacagcac ctacagcctc agcagcaccc tgacgctgag caaagcagac tacgagaaac 840
acaaagtcta cgcctgcgaa gtcacccatc agggcctgag ctcgcccgtc acaaagagct 900
tcaacagggg agagtgttag tgattcgaat tcctagaaga catgataaga tacattgatg 960
agtttggaca aaccacaact agaatgcagt gaaaaaaatg ctttatttgt gaaatttgtg 1020
atgctattgc tttatttgta accattataa gctgcaataa acaagttaac aacaacaatt 1080
gcattcattt tatgtttcag gttcaggggg aggtgtggga 1120

<210> 231
<211> 1120
<212> DNA
<213> 人工序列
<220>
<223> C33B904 轻链
<400> 231

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
[0207] tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgac attgtgatga cccagagccc tgatagcctg gccgtgagcc 300
tgggcgagag agccaccatc aactgcaaga gcagccagac cgtgttctac agcagcaaca 360
acaagaacta cctggcctgg taccagcaga agcctggcca gccccccaag ctgctgatca 420
gctgggccag caccagaaag agcggcgtgc ctgataggtt tagcggcagc ggcagcggca 480
ccgatttcac cctgaccgtg agctccctgc aggctgagga cgtggccgtg tactactgcc 540
agcactacta cagcaccccc tacaccttcg gccagggcac caagctggag atcaagcgta 600
cggtggctgc accatctgtc ttcatcttcc cgccatctga tgagcagttg aaatctggaa 660
ctgcctctgt tgtgtgcctg ctgaataact tctatcccag agaggccaaa gtacagtgga 720
aggtggataa cgccctccaa tcgggtaact cccaggagag tgtcacagag caggacagca 780
aggacagcac ctacagcctc agcagcaccc tgacgctgag caaagcagac tacgagaaac 840
acaaagtcta cgcctgcgaa gtcacccatc agggcctgag ctcgcccgtc acaaagagct 900
tcaacagggg agagtgttag tgattcgaat tcctagaaga catgataaga tacattgatg 960
agtttggaca aaccacaact agaatgcagt gaaaaaaatg ctttatttgt gaaatttgtg 1020
atgctattgc tttatttgta accattataa gctgcaataa acaagttaac aacaacaatt 1080
gcattcattt tatgtttcag gttcaggggg aggtgtggga 1120

<210> 232
<211> 1129
<212> DNA
<213> 人工序列
<220>
<223> C33B905 轻链
<400> 232

cagctgagtt gttgtgttct gataagagtc agaggtaact cccgttgcgg tgctgttaac 60

ggtggagggc agtgtagtct gagcagtact cgttgctgcc gcgcgcgcca ccagacataa 120
tagctgacag actaacagac tgttcctttc catgggtctt ttctgcagtc accgtccttg 180
acacgaagct tgccgccacc atggcccgga agagcgccct gctggccctg gccctgctgc 240
tgctgggctt cggccccgcc tgggccgaca tcgtgatgac ccagtctcca gacagcctgg 300
ctgtgtctct gggcgagaga gccaccatca actgcaagtc cagccagacc gtgttctact 360
cctccaacaa caagaactac ctggcctggt atcagcagaa gcccggacag cctcctaagc 420
tgctgatctc ttgggcctcc accagaaagt ctggcgtgcc cgatagattc tccggctctg 480
gctctggcac cgatttcaca ctgaccgttt ctagcctgca agccgaggac gtggccgtgt 540
actactgcca gcactactac agcacccctt acacctttgg ccagggcacc aagctggaaa 600
tcaagcgtac ggtggctgca ccatctgtct tcatcttccc gccatctgat gagcagttga 660
aatctggaac tgcctctgtt gtgtgcctgc tgaataactt ctatcccaga gaggccaaag 720
tacagtggaa ggtggataac gccctccaat cgggtaactc ccaggagagt gtcacagagc 780
aggacagcaa ggacagcacc tacagcctca gcagcaccct gacgctgagc aaagcagact 840
acgagaaaca caaagtctac gcctgcgaag tcacccatca gggcctgagc tcgcccgtca 900
caaagagctt caacagggga gagtgttagt gagaattcat tgatcataat cagccatacc 960
acatttgtag aggttttact tgctttaaaa aacctcccac acctcccccc gaacctgaaa 1020
cataaaatga atgcaattgt tgttgttaac ttgtttattg cagcttataa tggttacaaa 1080
taaagcaata gcatcacaaa tttcacaaat aaagcatttt tttcactgc 1129

<210> 233
<211> 1102
<212> DNA
<213> 人工序列
<220>

[0208] <223> C33B906 轻链
<400> 233

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgac atccagatga cccagtcccc tagcacactg agcgccagcg 300
tgggcgacag ggtgaccatc acctgcaggg ccagccagag catcagcagc tggctggcct 360
ggtaccagca gaagcccggc aaggccccca agctgctgat ctacaaggcc agcagcctgg 420
agagcggcgt gcctagcaga ttcagcggca gcggaagcgg caccgagttc accctgacca 480
tcagcagcct gcagcccgac gacttcgcca cctactgctg ccagcagtac aacagctacc 540
cctggacctt cggccagggc accaaggtgg agatcaagcg tacggtggct gcaccatctg 600
tcttcatctt cccgccatct gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc 660
tgctgaataa cttctatccc agagaggcca aagtacagtg gaaggtggat aacgccctcc 720
aatcgggtaa ctcccaggag agtgtcacag agcaggacag caaggacagc acctacagcc 780
tcagcagcac cctgacgctg agcaaagcag actacgagaa acacaaagtc tacgcctgcg 840
aagtcaccca tcagggcctg agctcgcccg tcacaaagag cttcaacagg ggagagtgtt 900
agtgattcga attcctagaa gacatgataa gatacattga tgagtttgga caaaccacaa 960
ctagaatgca gtgaaaaaaa tgctttattt gtgaaatttg tgatgctatt gctttatttg 1020
taaccattat aagctgcaat aaacaagtta acaacaacaa ttgcattcat tttatgtttc 1080
aggttcaggg ggaggtgtgg ga 1102

<210> 234
<211> 1096
<212> DNA

<213> 人工序列
<220>
<223> C33B907 轻链
<400> 234
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccagacagc cagcatcacc tgctccggcg acgagctggg cgacatgtac gcctgctggt 360
accagcagaa gcccggacag tccccctgg tggtgatcta ccaggacagc aagaggccca 420
gcggcatccc cgagagattc agcggcagca actccggcaa caccgccacc ctgaccatca 480
gcggaaccca ggccatggat gaggccgcct actactgcca gacctgggac accaggatcg 540
ccgtgttcgg aggcggcacc aacctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggggaggt gtggga 1096

[0209] <210> 235
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B908 轻链
<400> 235
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagccccc tagcgtgagc gtgagccctg 300
gacagaccgc ctccatcacc tgcagcggcg acaacctggg caatgagcac gtgtgctggt 360
accaccagaa acccggccag agccccgtgc tggtgatcta ccagaacaac aagaggccct 420
ccggcatccc cgagaggttt agcggcagca acagcggcaa caccgccacc ctgagcatct 480
ccggcacaca ggccaccgat gaggccgact actactgtca ggcctgggac agcaccaccg 540
ccgtgtttgg cggcggaacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020

ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggggaggt gtggga 1096
<210> 236
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B909 轻链
<400> 236
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccagaccgc caacatcagc tgcagcggcg tgaccctggg ctacaactac gcctactggt 360
accagcagaa gcccggccag agccccatcc tggtgatcag ccaggacacc cagagaccca 420
gcggcatccc cgagaggttc agcggctcca acagcggcaa caccgccacc ctgaccatca 480
gcggcacaca ggccatggat gaggccgcct actactgcca ggcctgggac atcaccaccg 540
tgctgttcgg cggcggcacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
[0210] tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggggaggt gtggga 1096
<210> 237
<211> 1102
<212> DNA
<213> 人工序列
<220>
<223> C33B910 轻链
<400> 237
tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgac atccagatga cccagagccc tagcagcgtg tgggctagcg 300
tgggcgacag ggtgaccatc acctgcaggg ccagccaggg catcagcagc tggctggcct 360
ggtaccaaca gcagcctggc aaggccccca acctgctgat ctacagaagc agcagcctgc 420
agagcggagt gcccagcagg tttagcggaa gcggcagcgg caccgacttc accctgacca 480
tcagcagcct gcagcccgag gacttcgcca cctactactg ccagcaggac aacagcttcc 540
cctacacctt cggccagggc accaagctgg agatcaagcg tacggtggct gcaccatctg 600
tcttcatctt cccgccatct gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc 660
tgctgaataa cttctatccc agagaggcca aagtacagtg gaaggtggat aacgccctcc 720

aatcgggtaa ctcccaggag agtgtcacag agcaggacag caaggacagc acctacagcc 780
tcagcagcac cctgacgctg agcaaagcag actacgagaa acacaaagtc tacgcctgcg 840
aagtcaccca tcagggcctg agctcgcccg tcacaaagag cttcaacagg ggagagtgtt 900
agtgattcga attcctagaa gacatgataa gatacattga tgagtttgga caaaccacaa 960
ctagaatgca gtgaaaaaaa tgctttattt gtgaaatttg tgatgctatt gctttatttg 1020
taaccattat aagctgcaat aaacaagtta acaacaacaa ttgcattcat tttatgtttc 1080
aggttcaggg ggaggtgtgg ga 1102

<210> 238
<211> 1102
<212> DNA
<213> 人工序列
<220>
<223> C33B911 轻链
<400> 238

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgac atccagatga cccagagccc tagcagcgag tgggctagcg 300
tgggcgacag ggtgaccatc acctgcagag ccagccaggg catcagcagc tggctggcct 360
ggtaccagca gaagccccgg aaggccccca agctgctgat ctacggcgcc agcagctggc 420
agagcggagt gcctagcagg ttcagcggca gcggaagcgg caccgacttc accctgacca 480
tcagcagcct gcagcccgag gacttcgcca cctactactg ccagcaggac aacagcttcc 540
[0211] cctacacctt cggccagggc accaagctgg agatcaagcg tacggtggct gcaccatctg 600
tcttcatctt cccgccatct gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc 660
tgctgaataa cttctatccc agagaggcca aagtacagtg gaaggtggat aacgccctcc 720
aatcgggtaa ctcccaggag agtgtcacag agcaggacag caaggacagc acctacagcc 780
tcagcagcac cctgacgctg agcaaagcag actacgagaa acacaaagtc tacgcctgcg 840
aagtcaccca tcagggcctg agctcgcccg tcacaaagag cttcaacagg ggagagtgtt 900
agtgattcga attcctagaa gacatgataa gatacattga tgagtttgga caaaccacaa 960
ctagaatgca gtgaaaaaaa tgctttattt gtgaaatttg tgatgctatt gctttatttg 1020
taaccattat aagctgcaat aaacaagtta acaacaacaa ttgcattcat tttatgtttc 1080
aggttcaggg ggaggtgtgg ga 1102

<210> 239
<211> 1120
<212> PRT
<213> 人工序列
<220>
<223> C33B912 轻链
<400> 239

Thr Cys Thr Gly Ala Thr Ala Ala Gly Ala Gly Thr Cys Ala Gly Ala
1 5 10 15
Gly Gly Thr Ala Ala Cys Thr Cys Cys Cys Gly Thr Thr Gly Cys Gly
20 25 30
Gly Thr Gly Cys Thr Gly Thr Thr Ala Ala Cys Gly Gly Thr Gly Gly
35 40 45
Ala Gly Gly Gly Cys Ala Gly Thr Gly Thr Ala Gly Thr Cys Thr Gly

50 55 60

Ala Gly Cys Ala Gly Thr Ala Cys Thr Cys Gly Thr Thr Gly Cys Thr
65 70 75 80
Gly Cys Cys Gly Cys Gly Cys Gly Cys Gly Cys Cys Ala Cys Cys Ala
85 90 95
Gly Ala Cys Ala Thr Ala Ala Thr Ala Gly Cys Thr Gly Ala Cys Ala
100 105 110
Gly Ala Cys Thr Ala Ala Cys Ala Gly Ala Cys Thr Gly Thr Thr Cys
115 120 125
Cys Thr Thr Thr Cys Cys Ala Thr Gly Gly Gly Thr Cys Thr Thr Thr
130 135 140
Thr Cys Thr Gly Cys Ala Gly Thr Cys Ala Cys Cys Gly Thr Cys Cys
145 150 155 160
Thr Thr Ala Gly Ala Thr Cys Cys Ala Cys Thr Ala Gly Thr Cys Cys
165 170 175
Ala Gly Thr Gly Thr Gly Gly Thr Gly Ala Ala Gly Cys Thr Thr Gly
180 185 190
Cys Cys Gly Cys Cys Ala Cys Cys Ala Thr Gly Gly Cys Thr Thr Gly
195 200 205
Gly Gly Thr Gly Thr Gly Gly Ala Cys Cys Thr Thr Gly Cys Thr Ala
210 215 220
Thr Thr Cys Cys Thr Gly Ala Thr Gly Gly Cys Ala Gly Cys Thr Gly
225 230 235 240

[0212]

Cys Cys Cys Ala Ala Ala Gly Thr Ala Thr Ala Cys Ala Gly Gly Cys
245 250 255
Cys Gly Ala Cys Ala Thr Cys Gly Thr Gly Ala Thr Gly Ala Cys Cys
260 265 270
Cys Ala Gly Ala Gly Cys Cys Cys Thr Gly Ala Thr Ala Gly Cys Cys
275 280 285
Thr Gly Gly Cys Cys Gly Thr Gly Ala Gly Cys Cys Thr Gly Gly Gly
290 295 300
Ala Gly Ala Gly Ala Gly Ala Gly Cys Cys Ala Cys Cys Ala Thr Cys
305 310 315 320
Ala Ala Cys Thr Gly Cys Ala Ala Gly Ala Gly Cys Ala Gly Cys Cys
325 330 335
Ala Gly Ala Cys Cys Gly Thr Gly Cys Thr Gly Thr Ala Cys Ala Gly
340 345 350
Cys Ala Gly Cys Ala Ala Cys Ala Ala Cys Ala Ala Gly Ala Ala Cys
355 360 365
Thr Ala Cys Cys Thr Gly Gly Cys Cys Thr Gly Gly Thr Ala Cys Cys
370 375 380
Ala Gly Cys Ala Gly Ala Ala Gly Cys Cys Thr Gly Gly Cys Cys Ala
385 390 395 400
Gly Cys Cys Cys Cys Cys Cys Ala Ala Gly Cys Thr Gly Cys Thr Gly
405 410 415
Ala Thr Cys Ala Gly Cys Thr Gly Gly Gly Cys Cys Ala Gly Cys Ala
420 425 430

Cys Cys Ala Gly Ala Ala Ala Gly Ala Gly Cys Gly Gly Cys Gly Thr
435 440 445
Gly Cys Cys Thr Gly Ala Cys Ala Gly Ala Thr Thr Thr Ala Gly Cys
450 455 460
Gly Gly Cys Ala Gly Cys Gly Gly Cys Ala Gly Cys Gly Gly Cys Ala
465 470 475 480
Cys Cys Gly Ala Thr Thr Thr Cys Ala Cys Cys Cys Thr Gly Ala Cys
485 490 495
Cys Gly Thr Gly Ala Gly Cys Ala Gly Cys Cys Thr Gly Cys Ala Gly
500 505 510
Gly Cys Cys Gly Ala Gly Gly Ala Thr Gly Thr Gly Gly Cys Cys Gly
515 520 525
Thr Gly Thr Ala Cys Thr Ala Cys Thr Gly Cys Cys Ala Gly Cys Ala
530 535 540
Cys Thr Ala Cys Thr Ala Cys Ala Gly Cys Ala Cys Cys Cys Cys Cys
545 550 555 560
Thr Ala Cys Ala Cys Cys Thr Thr Cys Gly Gly Cys Cys Ala Gly Gly
565 570 575
Gly Cys Ala Cys Cys Ala Ala Gly Cys Thr Gly Gly Ala Gly Ala Thr
580 585 590
Cys Ala Ala Gly Cys Gly Thr Ala Cys Gly Gly Thr Gly Gly Cys Thr
595 600 605
Gly Cys Ala Cys Cys Ala Thr Cys Thr Gly Thr Cys Thr Thr Cys Ala
[0213] 610 615 620
Thr Cys Thr Thr Cys Cys Cys Gly Cys Cys Ala Thr Cys Thr Gly Ala
625 630 635 640
Thr Gly Ala Gly Cys Ala Gly Thr Thr Gly Ala Ala Ala Thr Cys Thr
645 650 655
Gly Gly Ala Ala Cys Thr Gly Cys Cys Thr Cys Thr Gly Thr Thr Gly
660 665 670
Thr Gly Thr Gly Cys Cys Thr Gly Cys Thr Gly Ala Ala Thr Ala Ala
675 680 685
Cys Thr Thr Cys Thr Ala Thr Cys Cys Cys Ala Gly Ala Gly Ala Gly
690 695 700
Gly Cys Cys Ala Ala Ala Gly Thr Ala Cys Ala Gly Thr Gly Gly Ala
705 710 715 720
Ala Gly Gly Thr Gly Gly Ala Thr Ala Ala Cys Gly Cys Cys Cys Thr
725 730 735
Cys Cys Ala Ala Thr Cys Gly Gly Gly Thr Ala Ala Cys Thr Cys Cys
740 745 750
Cys Ala Gly Gly Ala Gly Ala Gly Thr Gly Thr Cys Ala Cys Ala Gly
755 760 765
Ala Gly Cys Ala Gly Gly Ala Cys Ala Gly Cys Ala Ala Gly Gly Ala
770 775 780
Cys Ala Gly Cys Ala Cys Cys Thr Ala Cys Ala Gly Cys Cys Thr Cys
785 790 795 800
Ala Gly Cys Ala Gly Cys Ala Cys Cys Cys Thr Gly Ala Cys Gly Cys

805 810 815
Thr Gly Ala Gly Cys Ala Ala Ala Gly Cys Ala Gly Ala Cys Thr Ala
820 825 830
Cys Gly Ala Gly Ala Ala Ala Cys Ala Cys Ala Ala Ala Gly Thr Cys
835 840 845
Thr Ala Cys Gly Cys Cys Thr Gly Cys Gly Ala Ala Gly Thr Cys Ala
850 855 860
Cys Cys Cys Ala Thr Cys Ala Gly Gly Gly Cys Cys Thr Gly Ala Gly
865 870 875 880
Cys Thr Cys Gly Cys Cys Cys Gly Thr Cys Ala Cys Ala Ala Ala Gly
885 890 895
Ala Gly Cys Thr Thr Cys Ala Ala Cys Ala Gly Gly Gly Gly Ala Gly
900 905 910
Ala Gly Thr Gly Thr Thr Ala Gly Thr Gly Ala Thr Thr Cys Gly Ala
915 920 925
Ala Thr Thr Cys Cys Thr Ala Gly Ala Ala Gly Ala Cys Ala Thr Gly
930 935 940
Ala Thr Ala Ala Gly Ala Thr Ala Cys Ala Thr Thr Gly Ala Thr Gly
945 950 955 960
Ala Gly Thr Thr Thr Gly Gly Ala Cys Ala Ala Ala Cys Cys Ala Cys
965 970 975
Ala Ala Cys Thr Ala Gly Ala Ala Thr Gly Cys Ala Gly Thr Gly Ala
980 985 990

[0214] Ala Ala Ala Ala Ala Ala Thr Gly Cys Thr Thr Thr Ala Thr Thr Thr
995 1000 1005
Gly Thr Gly Ala Ala Ala Thr Thr Thr Gly Thr Gly Ala Thr Gly
1010 1015 1020
Cys Thr Ala Thr Thr Gly Cys Thr Thr Thr Ala Thr Thr Thr Gly
1025 1030 1035
Thr Ala Ala Cys Cys Ala Thr Thr Ala Thr Ala Ala Gly Cys Thr
1040 1045 1050
Gly Cys Ala Ala Thr Ala Ala Ala Cys Ala Ala Gly Thr Thr Ala
1055 1060 1065
Ala Cys Ala Ala Cys Ala Ala Cys Ala Ala Thr Thr Gly Cys Ala
1070 1075 1080
Thr Thr Cys Ala Thr Thr Thr Thr Ala Thr Gly Thr Thr Thr Cys
1085 1090 1095
Ala Gly Gly Thr Thr Cys Ala Gly Gly Gly Gly Gly Ala Gly Gly
1100 1105 1110
Thr Gly Thr Gly Gly Gly Ala
1115 1120

<210> 240
<211> 1120
<212> DNA
<213> 人工序列
<220>
<223> C33B913 轻链

<400> 240

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgac attgtgatga cccagagccc tgatagcctg gccgtgagcc 300
tgggcgagag agccaccatc aactgcaaga gcagccagac cgtgttctac agcagcaaca 360
acaagaacta cctggcctgg taccagcaga agcctggcca gccccccaag ctgctgatca 420
gctgggccag caccagaaag agcggcgtgc ctgataggtt tagcggcagc ggcagcggca 480
ccgatttcac cctgaccgtg agctccctgc aggctgagga cgtggccgtg tactactgcc 540
agcactacta cagcaccccc tacaccttcg gccagggcac caagctggag atcaagcgta 600
cggtggctgc accatctgtc ttcatcttcc cgccatctga tgagcagttg aaatctggaa 660
ctgcctctgt tgtgtgcctg ctgaataact tctatcccag agaggccaaa gtacagtgga 720
aggtggataa cgccctccaa tcgggtaact cccaggagag tgtcacagag caggacagca 780
aggacagcac ctacagcctc agcagcaccc tgacgctgag caaagcagac tacgagaaac 840
acaaagtcta cgcctgcgaa gtcacccatc agggcctgag ctcgcccgtc acaaagagct 900
tcaacagggg agagtgttag tgattcgaat tcctagaaga catgataaga tacattgatg 960
agtttggaca aaccacaact agaatgcagt gaaaaaaatg ctttatttgt gaaatttgtg 1020
atgctattgc tttatttgta accattataa gctgcaataa acaagttaac aacaacaatt 1080
gcattcattt tatgtttcag gttcaggggg aggtgtggga 1120

<210> 241
<211> 1102
<212> DNA

[0215] <213> 人工序列

<220>
<223> C33B914 轻链

<400> 241

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccgac atccagatga cccagtcccc tagcacactg agcgccagcg 300
tgggcgacag ggtgaccatc acctgcaggg ccagccagag catcagcagc tggctggcct 360
ggtaccagca gaagccccggc aaggccccca agctgctgat ctacaaggcc agcagcctgg 420
agagcggcgt gcctagcaga ttcagcggca gcggaagcgg caccgagttc accctgacca 480
tcagcagcct gcagcccgac gacttcgcca cctactgctg ccagcagtac aacagctacc 540
cctggacctt cggccagggc accaaggtgg agatcaagcg tacggtggct gcaccatctg 600
tcttcatctt cccgccatct gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc 660
tgctgaataa cttctatccc agagaggcca aagtacagtg gaaggtggat aacgccctcc 720
aatcgggtaa ctcccaggag agtgtcacag agcaggacag caaggacagc acctacagcc 780
tcagcagcac cctgacgctg agcaaagcag actacgagaa acacaaagtc tacgcctgcg 840
aagtcaccca tcagggcctg agctcgcccg tcacaaagag cttcaacagg ggagagtgtt 900
agtgattcga attcctagaa gacatgataa gatacattga tgagtttgga caaaccacaa 960
ctagaatgca gtgaaaaaaa tgctttattt gtgaaatttg tgatgctatt gctttatttg 1020
taaccattat aagctgcaat aaacaagtta acaacaacaa ttgcattcat tttatgtttc 1080
aggttcaggg ggaggtgtgg ga 1102

<210> 242

<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B915 轻链
<400> 242

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagcctcc tagcgtgagc gtgagccctg 300
gccagacagc cagcatcacc tgctccggcg acgagctggg cgacatgtac gcctgctggt 360
accagcagaa gcccggacag tccccctgg tggtgatcta ccaggacagc aagaggccca 420
gcggcatccc cgagagattc agcggcagca actccggcaa caccgccacc ctgaccatca 480
gcggaaccca ggccatggat gaggccgcct actactgcca gacctgggac accaggatcg 540
ccgtgttcgg aggcggcacc aacctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900
tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
[0216] ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
aggggaggt gtggga 1096

<210> 243
<211> 1096
<212> DNA
<213> 人工序列
<220>
<223> C33B916 轻链
<400> 243

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggccagc tacgagctga cccagccccc tagcgtgagc gtgagccctg 300
gacagaccgc ctccatcacc tgcagcggcg acaacctggg caatgagcac gtgtgctggt 360
accaccagaa acccggccag agccccgtgc tggtgatcta ccagaacaac aagaggccct 420
ccggcatccc cgagaggttt agcggcagca acagcggcaa caccgccacc ctgagcatct 480
ccggcacaca ggccaccgat gaggccgact actactgtca ggcctgggac agcaccaccg 540
ccgtgtttgg cggcggaacc aagctgaccg tgctgggtca gcccaaggct gcacccagtg 600
tcactctgtt cccgccctcc tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc 660
tcataagtga cttctacccg ggagccgtga cagtggcctg gaaggccgat agcagccccg 720
tcaaggcggg agtggagacc accacaccct ccaaacaaag caacaacaag tacgcggcca 780
gcagctatct gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg 840
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcatagtgat 900

tcgaattcct agaagacatg ataagataca ttgatgagtt tggacaaacc acaactagaa 960
tgcagtgaaa aaaatgcttt atttgtgaaa tttgtgatgc tattgcttta tttgtaacca 1020
ttataagctg caataaacaa gttaacaaca acaattgcat tcattttatg tttcaggttc 1080
agggggaggt gtggga 1096

<210> 244
<211> 452
<212> PRT
<213> 人工序列
<220>
<223> CD3B219 重链
<400> 244

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
20 25 30
Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Ala
50 55 60
Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95
[0217] Tyr Cys Ala Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
100 105 110
Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
115 120 125
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser
130 135 140
Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145 150 155 160
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
165 170 175
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
180 185 190
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys
195 200 205
Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
210 215 220
Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
225 230 235 240
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
260 265 270
Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

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

<210> 245

[0218] <211> 447
<212> PRT
<213> 人工序列
<220>
<223> CD3B376 重链
<400> 245
Gln Val Gln Leu Gln Gln Ser Gly Pro Arg Leu Val Arg Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Phe Asn Asn
20 25 30
Asn Ala Ala Trp Ser Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45
Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Leu Tyr Asp Tyr Ala
50 55 60
Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80
Gln Phe Thr Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95
Tyr Tyr Cys Ala Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125
Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190
Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220
Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255
Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270
Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285
Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320
Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
[0219] 325 330 335
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 246
<211> 447
<212> PRT
<213> 人工序列
<220>
<223> B23B49 重链
<400> 246

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

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30
Gly Met Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
35 40 45
Trp Leu Ala His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser
50 55 60
Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65 70 75 80
Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95
Cys Ala Arg Leu Tyr Gly Phe Thr Tyr Gly Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125
Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190
Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
[0220] 195 200 205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220
Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255
Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270
Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285
Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320
Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser

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

<210> 247
<211> 1356
<212> DNA
<213> 人工序列
<220>
<223> CD3B219 重链
<400> 247

gaagtgcagc tggtggaatc tggcggcgga ctggtgcagc ctggcggatc tctgagactg 60
agctgtgccg ccagcggctt caccttcaac acctacgcca tgaactgggt gcgccaggcc 120
cctggcaaag gcctggaatg ggtggcccgg atcagaagca agtacaacaa ttacgccacc 180
tactacgccg cctccgtgaa gggcagattc accatcagcc gggacgacag caagaacagc 240
ctgtacctgc agatgaactc cctgaaaacc gaggacaccg ccgtgtacta ctgcgccaga 300
cacggcaact tcggcaacag ctatgtgtct tggtttgcct actggggcca gggcaccctc 360
gtgaccgtgt catctgcttc caccaagggc ccatccgtct tccccctggc gccctgctcc 420
aggagcacct ccgagagcac agccgccctg ggctgcctgg tcaaggacta cttccccgaa 480
ccggtgacgg tgtcgtggaa ctcaggcgcc ctgaccagcg gcgtgcacac cttcccggct 540
[0221] gtcctacagt cctcaggact ctactccctc agcagcgtgg tgaccgtgcc ctccagcagc 600
ttgggcacga aaacctacac ctgcaacgta gatcacaagc ccagcaacac caaggtggac 660
aagagagttg agtccaaata tggtccccca tgcccaccat gcccagcacc tgaggccgcc 720
gggggaccat cagtcttcct gttcccccca aaacccaagg acactctcat gatctcccgg 780
acccctgagg tcacgtgcgt ggtggtggac gtgagccagg aagaccccga ggtccagttc 840
aactggtacg tggatggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 900
ttcaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaac 960
ggcaaggagt acaagtgcaa ggtctccaac aaaggcctcc cgtcctccat cgagaaaacc 1020
atctccaaag ccaaagggca gccccgagag ccacaggtgt acaccctgcc cccatcccag 1080
gaggagatga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctaccccagc 1140
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1200
cccgtgctgg actccgacgg ctccttcctc ctctacagca agctaaccgt ggacaagagc 1260
aggtggcagg aggggaatgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 1320
tacacacaga agagcctctc cctgtctctg ggtaaa 1356

<210> 248
<211> 1341
<212> DNA
<213> 人工序列
<220>
<223> CD3B376 重链
<400> 248

caggtgcagc tgcagcagtc tggccctaga ctcgtgcggc cttcccagac cctgtctctg 60
acctgtgcca tctccggcga ctccgtgttc aacaacaacg ccgcctggtc ctggatccgg 120
cagagccctt ctagaggcct ggaatggctg ggccggacct actaccggtc caagtggctg 180

tacgactacg ccgtgtccgt gaagtcccgg atcaccgtga accctgacac ctcccggaac 240
cagttcaccc tgcagctgaa ctccgtgacc cctgaggaca ccgccctgta ctactgcgcc 300
agaggctact cctcctcctt cgactattgg ggccagggca ccctcgtgac cgtgtcctct 360
gcttccacca agggcccatc cgtcttcccc ctggcgccct gctccaggag cacctccgag 420
agcacagccg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 480
tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca 540
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacgaaaacc 600
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagag agttgagtcc 660
aaatatggtc ccccatgccc accatgccca gcacctgagg ccgccggggg accatcagtc 720
ttcctgttcc ccccaaaacc caaggacact ctcatgatct cccggacccc tgaggtcacg 780
tgcgtggtgg tggacgtgag ccaggaagac cccgaggtcc agttcaactg gtacgtggat 840
ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagttcaa cagcacgtac 900
cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaacggcaa ggagtacaag 960
tgcaaggtct ccaacaaagg cctcccgtcc tccatcgaga aaaccatctc caaagccaaa 1020
gggcagcccc gagagccaca ggtgtacacc ctgcccccat cccaggagga gatgaccaag 1080
aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1200
gacggctcct tcctcctcta cagcaagcta accgtggaca agagcaggtg gcaggagggg 1260
aatgtcttct catgctccgt gatgcatgag gctctgcaca accactacac acagaagagc 1320
ctctccctgt ctctgggtaa a 1341

<210> 249
<211> 1801
<212> DNA
[0222] <213> 人工序列
<220>
<223> B23B49 重链
<400> 249

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggcttggg tgtggacctt gctattcctg atggcagctg 240
cccaaagtat acaggcccag attaccctga aggaatccgg accaactctc gtcaaaccca 300
cacagacact cacactcacc tgtaccttta gcggcttttc cctgtccact tctggaatgg 360
gcgtgtcatg gattagacag ccccctggga aggccctcga atggctggct cacatctact 420
gggacgacga caaacgctac aatcctagcc tcaaatcacg actcactatc actaaggaca 480
cctccaaaaa tcaggtggtg ctcacaatga ccaacatgga ccccgtggat actgccacat 540
actactgtgc taggctgtac ggcttcactt acggatttgc ttactggggc cagggcacac 600
tggtgaccgt gtctagtgct tccaccaagg gcccatccgt cttccccctg gcgccctgct 660
ccaggagcac ctccgagagc acagccgccc tgggctgcct ggtcaaggac tacttccccg 720
aaccggtgac ggtgtcgtgg aactcaggcg ccctgaccag cggcgtgcac accttcccgg 780
ctgtcctaca gtcctcagga ctctactccc tcagcagcgt ggtgaccgtg ccctccagca 840
gcttgggcac gaaaacctac acctgcaacg tagatcacaa gcccagcaac accaaggtgg 900
acaagagagt tgagtccaaa tatggtcccc catgcccacc atgcccagca cctgaggccg 960
ccgggggacc atcagtcttc ctgttccccc caaaacccaa ggacactctc atgatctccc 1020
ggaccctga ggtcacgtgc gtggtggtgg acgtgagcca ggaagacccc gaggtccagt 1080
tcaactggta cgtggatggc gtggaggtgc ataatgccaa gacaaagccg cgggaggagc 1140
agttcaacag cacgtaccgt gtggtcagcg tcctcaccgt cctgcaccag gactggctga 1200

acggcaagga gtacaagtgc aaggtctcca acaaaggcct cccgtcctcc atcgagaaaa 1260
ccatctccaa agccaaaggg cagccccgag agccacaggt gtacaccctg cccccatccc 1320
aggaggagat gaccaagaac caggtcagcc tgacctgcct ggtcaaaggc ttctacccca 1380
gcgacatcgc cgtggagtgg gagagcaatg ggcagccgga gaacaactac aagaccacgc 1440
ctcccgtgct ggactccgac ggctccttcc tcctctacag caagctaacc gtggacaaga 1500
gcaggtggca ggaggggaat gtcttctcat gctccgtgat gcatgaggct ctgcacaacc 1560
actacacaca gaagagcctc tccctgtctc tgggtaaatg atagttcgaa ttcctagaag 1620
acatgataag atacattgat gagtttggac aaaccacaac tagaatgcag tgaaaaaaat 1680
gctttatttg tgaaatttgt gatgctattg ctttatttgt aaccattata agctgcaata 1740
aacaagttaa caacaacaat tgcattcatt ttatgtttca ggttcagggg gaggtgtggg 1800
a 1801

<210> 250
<211> 215
<212> PRT
<213> 人工序列
<220>
<223> CD3B219 轻链
<400> 250

Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30
Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
[0223] 35 40 45
Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe
50 55 60
Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65 70 75 80
Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
85 90 95
Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
100 105 110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
115 120 125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
130 135 140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145 150 155 160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
165 170 175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
180 185 190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
195 200 205
Val Ala Pro Thr Glu Cys Ser
210 215

<210> 251

<211> 216
<212> PRT
<213> 人工序列
<220>
<223> CD3B376 轻链
<400> 251

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asn Ile Gly Thr Tyr
20 25 30
Lys Phe Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Val
35 40 45
Leu Leu Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Ser Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Gln Ala Asp Tyr His Cys Val Ser Tyr Ala Gly Ser
85 90 95
Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
[0224] 130 135 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205
Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 252
<211> 218
<212> PRT
<213> 人工序列
<220>
<223> B23B49 轻链
<400> 252

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

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80
Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Ile Ile
85 90 95
Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110
Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
115 120 125
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160
Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205
Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 253

[0225] <211> 645

<212> DNA

<213> 人工序列

<220>

<223> CD3B219 轻链

<400> 253

cagaccgtcg tgacccagga acctagcctg accgtgtctc ctggcggcac cgtgaccctg 60
acctgcagat cttctacagg cgccgtgacc accagcaact acgccaactg ggtgcagcag 120
aagccaggcc aggctcccag aggactgatc ggcggcacca acaagagagc ccctggcacc 180
cctgccagat tcagcggatc tctgctggga ggaaaggccg ccctgacact gtctggcgtg 240
cagcctgaag atgaggccga gtactactgc gccctgtggt acagcaacct gtgggtgttc 300
ggcggaggca ccaagctgac agtgctgggt cagcccaagg ctgcacccag tgtcactctg 360
ttcccgccct cctctgagga gcttcaagcc aacaaggcca cactggtgtg tctcataagt 420
gacttctacc cgggagccgt gacagtggcc tggaaggccg atagcagccc cgtcaaggcg 480
ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat 540
ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat 600
gaagggagca ccgtggagaa gacagtggcc cctacagaat gttca 645

<210> 254

<211> 648

<212> DNA

<213> 人工序列

<220>

<223> CD3B376 轻链

<400> 254

cagtctgctc tgacccagcc tgcctccgtg tctggctctc ccggccagtc catcaccatc 60
agctgtaccg gcacctcctc caacatcggc acctacaagt tcgtgtcctg gtatcagcag 120
caccccgaca aggcccccaa agtgctgctg tacgaggtgt ccaagcggcc ctctggcgtg 180
tcctccagat tctccggctc caagtctggc aacaccgcct ccctgaccat cagcggactg 240
caggctgagg accaggccga ctaccactgt gtgtcctacg ctggctctgg caccctgctg 300
tttggcggag gcaccaagct gaccgtgctg ggtcagccca aggctgcacc cagtgtcact 360
ctgttcccgc cctcctctga ggagcttcaa gccaacaagg ccacactggt gtgtctcata 420
agtgacttct acccgggagc cgtgacagtg gcctggaagg ccgatagcag ccccgtcaag 480
gcgggagtgg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc 540
tatctgagcc tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg 600
catgaaggga gcaccgtgga gaagacagtg gcccctacag aatgttca 648

<210> 255
<211> 1117
<212> DNA
<213> 人工序列
<220>
<223> B23B49 轻链
<400> 255

tctgataaga gtcagaggta actcccgttg cggtgctgtt aacggtggag ggcagtgtag 60
tctgagcagt actcgttgct gccgcgcgcg ccaccagaca taatagctga cagactaaca 120
gactgttcct ttccatgggt cttttctgca gtcaccgtcc ttagatccac tagtccagtg 180
tggtgaagct tgccgccacc atggagacac attctcaggt ctttgtatac atgttgctgt 240
ggttgtctgg tgtcgagggc gatattgtga tgacccagtc ccccgattct ctcgctgtct 300
[0226] ctctgggcga acgggctaca atcaactgta gggcttcaca gtctgtcgac tacaacggca 360
tctcttacat gcattggtac cagcagaaac ctggacagcc accaaaactc ctcatctacg 420
ccgcttccaa tcctgaatct ggcgtgcccg accgattttc cggatccggc tctggcaccg 480
actttacact cactattagt agcctccagg ccgaggatgt ggccgtgtac tactgtcagc 540
agatcatcga ggatccttgg acatttggac agggaaccaa agtggagatc aaacgtacgg 600
tggctgcacc atctgtcttc atcttcccgc catctgatga gcagttgaaa tctggaactg 660
cctctgttgt gtgcctgctg aataacttct atcccagaga ggccaaagta cagtggaagg 720
tggataacgc cctccaatcg ggtaactccc aggagagtgt cacagagcag gacagcaagg 780
acagcaccta cagcctcagc agcaccctga cgctgagcaa agcagactac gagaaacaca 840
aagtctacgc ctgcgaagtc acccatcagg gcctgagctc gcccgtcaca aagagcttca 900
acaggggaga gtgttagtga ttcgaattcc tagaagacat gataagatac attgatgagt 960
ttggacaaac cacaactaga atgcagtgaa aaaaatgctt tatttgtgaa atttgtgatg 1020
ctattgcttt atttgtaacc attataagct gcaataaaca agttaacaac aacaattgca 1080
ttcattttat gtttcaggtt caggggggagg tgtggga 1117

<210> 256
<211> 120
<212> PRT
<213> 人工序列
<220>
<223> B23H1（重链可变区）
<400> 256

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

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

<210> 257
<211> 125
<212> PRT
<213> 人工序列
<220>
<223> CD3H141（重链可变区）
<400> 257

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
20 25 30
[0227]
Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Ala
50 55 60
Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95
Tyr Cys Ala Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
100 105 110
Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 258
<211> 120
<212> PRT
<213> 人工序列
<220>
<223> CD3H219（重链可变区）
<400> 258

Gln Val Gln Leu Gln Gln Ser Gly Pro Arg Leu Val Arg Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Phe Asn Asn
20 25 30

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

<210> 259
<211> 125
<212> PRT
<213> 人工序列
<220>
<223> C33H42（重链可变区）
<400> 259

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Asn Pro Ser Glu
1 5 10 15
Thr Leu Ser His Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

[0228]

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

<210> 260
<211> 122
<212> PRT
<213> 人工序列
<220>
<223> C33H44（重链可变区）
<400> 260

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

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

<210> 261
<211> 129
<212> PRT
<213> 人工序列
<220>
<223> C33H45（重链可变区）
<400> 261
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Val
[0229] 35 40 45
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Cys Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Ser Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Phe Arg Ser Leu Asp Trp Leu Pro Pro Asp Ser Thr Ser
100 105 110
Tyr Asp Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125
Ser

<210> 262
<211> 116
<212> PRT
<213> 人工序列
<220>
<223> C33H46（重链可变区）
<400> 262
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

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

<210> 263
<211> 125
<212> PRT
<213> 人工序列
<220>
<223> C33H48（重链可变区）
<400> 263

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Arg Ser Thr
20 25 30

[0230] Asn Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45
Trp Ile Gly Thr Ile Tyr Tyr Ser Gly Asn Thr Tyr Tyr Asn Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Leu Ala Asp Val Val Val Val Pro Ala Ala Arg Tyr Phe
100 105 110
Asp Tyr Trp Gly Gln Gly Ile Leu Val Thr Val Ser Ser
115 120 125

<210> 264
<211> 125
<212> PRT
<213> 人工序列
<220>
<223> C33H49（重链可变区）
<400> 264

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

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

<210> 265
<211> 125
<212> PRT
<213> 人工序列
<220>
<223> C33H51（重链可变区）
<400> 265

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

[0231]

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

<210> 266
<211> 125
<212> PRT
<213> 人工序列
<220>
<223> C33H52（重链可变区）
<400> 266

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

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

<210> 267
<211> 119
<212> PRT
<213> 人工序列
<220>
<223> C33H55（重链可变区）
<400> 267

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

[0232] Ile Gly Glu Ile Tyr His Ser Gly Asn Thr Asn Asn Ser Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Ala Asp Lys Ser Lys Asn Gln Phe Ser
65 70 75 80
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys
85 90 95
Ala Arg Ile Ile Ala Val Ala Arg Tyr Phe Asp Ser Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 268
<211> 129
<212> PRT
<213> 人工序列
<220>
<223> C33H65（重链可变区）
<400> 268

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

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

<210> 269
<211> 129
<212> PRT
<213> 人工序列
<220>
<223> C33H66（重链可变区）
<400> 269
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[0233] 35 40 45
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Gly Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Ala Ser
100 105 110
Tyr His Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125
Ser

<210> 270
<211> 120
<212> PRT
<213> 人工序列
<220>
<223> C33H68（重链可变区）
<400> 270
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Gly Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gly Tyr
20 25 30

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

<210> 271
<211> 120
<212> PRT
<213> 人工序列
<220>
<223> C33H69（重链可变区）
<400> 271

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

[0234] Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Asp
35 40 45
Trp Ile Gly Ser Ile Asn Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Ile Gln Phe
65 70 75 80
Ser Leu Lys Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Leu Asp Gly Tyr Glu Ser Pro Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 272
<211> 125
<212> PRT
<213> 人工序列
<220>
<223> C33H70（重链可变区）
<400> 272

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

35 40 45

Trp Ile Gly Ser Ile Tyr Ser Ser Gly Asn Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Leu Gly Ser Leu Val Val Val Pro Ala Ala Met Ser Phe
100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 273
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> C33H72（重链可变区）
<400> 273

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[0235] 35 40 45

Ala Asn Ile Lys Gln His Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Asp Leu Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 274
<211> 119
<212> PRT
<213> 人工序列
<220>
<223> C33H73（重链可变区）
<400> 274

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Phe Thr Phe Ser Ser Tyr
20 25 30

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

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

<210> 275
<211> 129
<212> PRT
<213> 人工序列
<220>
<223> C33H74（重链可变区）
<400> 275

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

[0236] Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val His Tyr Cys
85 90 95
Ala Lys Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Ala Ser
100 105 110
Tyr His Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125
Ser

<210> 276
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> C33H76（重链可变区）
<400> 276

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

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

<210> 277
<211> 129
<212> PRT
<213> 人工序列
<220>
<223> C33H77（重链可变区）
<400> 277
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[0237] 35 40 45
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Phe Arg Tyr Phe Asp Trp Leu Pro Pro Asp Ser Ser Ser
100 105 110
Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125
Ser

<210> 278
<211> 117
<212> PRT
<213> 人工序列
<220>
<223> C33H80（重链可变区）
<400> 278
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Arg Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

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

<210> 279
<211> 129
<212> PRT
<213> 人工序列
<220>
<223> C33H81（重链可变区）
<400> 279
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ala Tyr
20 25 30

[0238]
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Gly Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Ala Ser
100 105 110
Tyr His Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125
Ser

<210> 280
<211> 129
<212> PRT
<213> 人工序列
<220>
<223> C33H84（重链可变区）
<400> 280
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr

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

<210> 281
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> C33H87（重链可变区）
<400> 281
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
[0239] 1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Asn Ile Lys Gln His Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Arg Asp Leu Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115
<210> 282
<211> 119
<212> PRT
<213> 人工序列
<220>
<223> C33H88（重链可变区）
<400> 282
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

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

<210> 283
<211> 122
<212> PRT
<213> 人工序列
<220>
<223> C33H90（重链可变区）
<400> 283

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

[0240]

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

<210> 284
<211> 125
<212> PRT
<213> 人工序列
<220>
<223> C33H91（重链可变区）
<400> 284

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Arg

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

<210> 285
<211> 125
<212> PRT
<213> 人工序列
<220>
<223> C33H92（重链可变区）
<400> 285

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Arg Ser Ser
20 25 30
[0241]
Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Pro Glu
35 40 45
Trp Ile Gly Ser Ile Tyr Ser Ser Gly Asn Thr Tyr Tyr Asn Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ile Ser Met Thr Ala Ala Asp Thr Ala Val Phe Tyr
85 90 95
Cys Ala Arg Leu Ala Ala Thr Ile Val Val Pro Ala Ala Arg Tyr Phe
100 105 110
Asp Cys Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 286
<211> 118
<212> PRT
<213> 人工序列
<220>
<223> C33H98（重链可变区）
<400> 286

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

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

<210> 287
<211> 117
<212> PRT
<213> 人工序列
<220>
<223> C33H99（重链可变区）
<400> 287

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

[0242] Trp Met Thr Trp Val Arg Pro Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Asn Ile Lys Arg Asp Gly Gly Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Ala Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Pro Phe Tyr Asp His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 288
<211> 117
<212> PRT
<213> 人工序列
<220>
<223> C33H108（重链可变区）
<400> 288

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

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

<210> 289
<211> 119
<212> PRT
<213> 人工序列
<220>
<223> C33H249（重链可变区）
<400> 289
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30
Ala Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[0243] 35 40 45
Ser Gly Leu Ser Trp Asn Gly Gly Asn Ile Gly Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Phe Tyr Tyr Cys
85 90 95
Thr Lys Asp Thr Pro Tyr Gly Asp Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 290
<211> 119
<212> PRT
<213> 人工序列
<220>
<223> C33H250（重链可变区）
<400> 290
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30
Ala Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

<210> 291
<211> 119
<212> PRT
<213> 人工序列
<220>
<223> C33H251（重链可变区）
<400> 291

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

[0244]

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

<210> 292
<211> 119
<212> PRT
<213> 人工序列
<220>
<223> C33H252（重链可变区）
<400> 292

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

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

<210> 293
<211> 120
<212> PRT
<213> 人工序列
<220>
<223> C33H253（重链可变区）
<400> 293

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

[0245]

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

<210> 294
<211> 117
<212> PRT
<213> 人工序列
<220>
<223> C33H254（重链可变区）
<400> 294

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

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

<210> 295
<211> 129
<212> PRT
<213> 人工序列
<220>
<223> C33H255（重链可变区）
<400> 295

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

[0246] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Val Lys Asp Met Pro Tyr Phe Asp Phe Leu Thr Gly Ser Asp Tyr Tyr
100 105 110
Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125
Ser

<210> 296
<211> 117
<212> PRT
<213> 人工序列
<220>
<223> C33H256（重链可变区）
<400> 296

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

50 55 60

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

<210> 297
<211> 111
<212> PRT
<213> 人工序列
<220>
<223> B23L3（轻链可变区）
<400> 297

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

[0247]

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

<210> 298
<211> 109
<212> PRT
<213> 人工序列
<220>
<223> CD3L66（轻链可变区）
<400> 298

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

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
85 90 95
Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 299
<211> 110
<212> PRT
<213> 人工序列
<220>
<223> CD3L150（轻链可变区）
<400> 299
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asn Ile Gly Thr Tyr
20 25 30
Lys Phe Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Val
35 40 45
Leu Leu Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Ser Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Gln Ala Asp Tyr His Cys Val Ser Tyr Ala Gly Ser
85 90 95

[0248] Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 300
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L8（轻链可变区）
<400> 300
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Ile Cys Ser Gly Asp Lys Leu Gly Asn Lys Tyr Ala
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Val
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Tyr Val
85 90 95
Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105

<210> 301

<211> 107
<212> PRT
<213> 人工序列
<220>
<223> C33L10（轻链可变区）
<400> 301

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

<210> 302
<211> 106
<212> PRT
[0249] <213> 人工序列
<220>
<223> C33L11（轻链可变区）
<400> 302

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

<210> 303
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> IAPL24（轻链可变区）

<400> 303
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 304
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L58（轻链可变区）

[0250]
<400> 304
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asp Tyr Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Tyr Val
85 90 95
Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105

<210> 305
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L59（轻链可变区）
<400> 305
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

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

<210> 306
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L34（轻链可变区）
<400> 306

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

[0251]

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

<210> 307
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> N46L109（轻链可变区）
<400> 307

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

65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Trp Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 308
<211> 108
<212> PRT
<213> 人工序列
<220>
<223> C33L42（轻链可变区）
<400> 308
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ile Lys Ser Val
20 25 30
His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
35 40 45
Asp Asp Ser Asp Arg Pro Pro Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Thr Arg Val Glu Ala Gly
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
[0252] 85 90 95
Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 309
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L47（轻链可变区）
<400> 309
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Val Val Ile Tyr
35 40 45
Gln Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Phe Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 310
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L60（轻链可变区）
<400> 310

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

<210> 311
<211> 113
[0253] <212> PRT
<213> 人工序列
<220>
<223> C33L17（轻链可变区）
<400> 311

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

<210> 312
<211> 107
<212> PRT

<213> 人工序列
<220>
<223> C4LL152（轻链可变区）
<400> 312

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

<210> 313
<211> 106
<212> PRT
<213> 人工序列
<220>
[0254] <223> C33L40（轻链可变区）
<400> 313

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

<210> 314
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> C33L32（轻链可变区）
<400> 314

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln

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

<210> 315
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L38（轻链可变区）
<400> 315
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Pro Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala

[0255]

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

<210> 316
<211> 111
<212> PRT
<213> 人工序列
<220>
<223> C33L39（轻链可变区）
<400> 316
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Pro Ile Ser Ser Thr Gly Thr Ser Ser Asp Asp Gly Lys Asn
20 25 30
Asn Ile Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

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

<210> 317
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L57（轻链可变区）
<400> 317

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

[0256] Asn Phe Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 318
<211> 111
<212> PRT
<213> 人工序列
<220>
<223> C33L73（轻链可变区）
<400> 318

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

85 90 95
Ser Ala Leu Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110
<210> 319
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L53（轻链可变区）
<400> 319
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asp Asn Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Asn Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
[0257] 100 105
<210> 320
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L66（轻链可变区）
<400> 320
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Val
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Val Val Ile His
35 40 45
Gln Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Phe Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105
<210> 321
<211> 106

<212> PRT
<213> 人工序列
<220>
<223> C33L35（轻链可变区）
<400> 321

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

<210> 322
<211> 111
<212> PRT
<213> 人工序列
[0258] <220>
<223> C33L61（轻链可变区）
<400> 322

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

<210> 323
<211> 108
<212> PRT
<213> 人工序列
<220>
<223> C33L51（轻链可变区）
<400> 323

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

<210> 324
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L44（轻链可变区）
<400> 324

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

[0259]

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

<210> 325
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L30（轻链可变区）
<400> 325

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

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

<210> 326
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L69（轻链可变区）
<400> 326
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Ser Lys Phe Ala
20 25 30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
[0260] 50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 327
<211> 108
<212> PRT
<213> 人工序列
<220>
<223> C33L37（轻链可变区）
<400> 327
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ala Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Thr Cys Gly Gly Ser Asn Ile Gly Lys Ile Ser Val
20 25 30
His Trp Tyr Gln Gln Lys Ala Gly Gln Ala Pro Val Leu Val Val His
35 40 45
Asp Asp Arg Ala Arg Pro Ser Gly Ile Pro Glu Arg Leu Ser Gly Ser
50 55 60
Asn Ser Gly Thr Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asn Ser Ser Ser Val His
85 90 95
Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 328
<211> 111
<212> PRT
<213> 人工序列
<220>
<223> C33L74（轻链可变区）
<400> 328
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Asp Asp
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ser Ser Ser
85 90 95
[0261] Thr Thr Leu Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 329
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> C33L115（轻链可变区）
<400> 329
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Trp Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Gln Pro Gly Lys Ala Pro Asn Leu Leu Ile
35 40 45
Tyr Arg Ser Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Asp Asn Ser Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 330

<211> 107
<212> PRT
<213> 人工序列
<220>
<223> C33L116（轻链可变区）
<400> 330

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

<210> 331
<211> 113
<212> PRT
[0262] <213> 人工序列
<220>
<223> C33L117（轻链可变区）
<400> 331

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

<210> 332
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> C33L118（轻链可变区）
<400> 332
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Thr Val Phe Tyr Ser
20 25 30
Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45
Pro Pro Lys Leu Leu Ile Ser Trp Ala Ser Thr Arg Lys Ser Gly Val
50 55 60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80
Val Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln His
85 90 95
Tyr Tyr Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105 110
Lys

<210> 333
<211> 107
<212> PRT
<213> 人工序列
[0263] <220>
<223> C33L119（轻链可变区）
<400> 333
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Asp Asp Phe Ala Thr Tyr Cys Cys Gln Gln Tyr Asn Ser Tyr Pro Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105
<210> 334
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L120（轻链可变区）
<400> 334

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

<210> 335
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L121（轻链可变区）
<400> 335

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

[0264]

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

<210> 336
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L122（轻链可变区）
<400> 336

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

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

<210> 337
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L132（轻链可变区）
<400> 337
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asp Gly Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
[0265] 50 55 60
Asn Phe Gly Asn Lys Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Arg Asn Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 338
<211> 106
<212> PRT
<213> 人工序列
<220>
<223> C33L41（轻链可变区）
<400> 338
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asn Lys Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45
Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105
<210> 339
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> B23H1 HC CDR1
<400> 339
Gly Phe Ser Leu Ser Thr Ser Gly Met
1 5
<210> 340
<211> 5
<212> PRT
<213> 人工序列
<220>
<223> B23H1 HC CDR2
<400> 340
Tyr Trp Asp Asp Asp
1 5
<210> 341
[0266] <211> 9
<212> PRT
<213> 人工序列
<220>
<223> B23H1 HC CDR3
<400> 341
Leu Tyr Gly Phe Thr Tyr Gly Phe Ala
1 5
<210> 342
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> CD3H141 HC CDR1
<400> 342
Gly Phe Thr Phe Asn Thr Tyr
1 5
<210> 343
<211> 8
<212> PRT
<213> 人工序列
<220>
<223> CD3H141 HC CDR2
<400> 343

Arg Ser Lys Tyr Asn Asn Tyr Ala
1 5
<210> 344
<211> 13
<212> PRT
<213> 人工序列
<220>
<223> CD3H141 HC CDR3
<400> 344
His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala
1 5 10
<210> 345
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> CD3H219 HC CDR1
<400> 345
Gly Asp Ser Val Phe Asn Asn Asn Ala
1 5
<210> 346
<211> 7
<212> PRT
[0267] <213> 人工序列
<220>
<223> CD3H219 HC CDR2
<400> 346
Tyr Tyr Arg Ser Lys Trp Leu
1 5
<210> 347
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> CD3H219 HC CDR3
<400> 347
Gly Tyr Ser Ser Ser Phe Asp
1 5
<210> 348
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> C33H42 HC CDR1
<400> 348
Gly Gly Ser Ile Ser Ser Ser Ser His
1 5

<210> 349
<211> 5
<212> PRT
<213> 人工序列
<220>
<223> C33H42 HC CDR2
<400> 349
Tyr Tyr Ser Gly Asn
1 5
<210> 350
<211> 14
<212> PRT
<213> 人工序列
<220>
<223> C33H42 HC CDR3
<400> 350
Leu Ala Asp Val Val Val Val Pro Ala Ala Arg Tyr Phe Asp
1 5 10
<210> 351
<211> 9
<212> PRT
<213> 人工序列
<220>
[0268] <223> C33H44 HC CDR1
<400> 351
Gly Asp Ser Val Ser Ser Asn Ser Ala
1 5
<210> 352
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H44 HC CDR2
<400> 352
Tyr Tyr Arg Ser Lys Trp Tyr
1 5
<210> 353
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> C33H44 HC CDR3
<400> 353
Glu Thr Met Phe Arg Gly Leu Met Asp
1 5
<210> 354
<211> 7

<212> PRT
<213> 人工序列
<220>
<223> C33H45 HC CDR1
<400> 354
Gly Phe Thr Phe Ser Ser Tyr
1 5
<210> 355
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H45 HC CDR2
<400> 355
Ser Tyr Asp Gly Ser Asn
1 5
<210> 356
<211> 19
<212> PRT
<213> 人工序列
<220>
<223> C33H45 HC CDR3
<400> 356

[0269] Asp Phe Arg Ser Leu Asp Trp Leu Pro Pro Asp Ser Thr Ser Tyr Asp
1 5 10 15
Gly Met Asp

<210> 357
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H46 HC CDR1
<400> 357
Gly Tyr Thr Phe Thr Asn Tyr
1 5
<210> 358
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H46 HC CDR2
<400> 358
Asn Thr Asn Thr Gly Asn
1 5
<210> 359
<211> 6

<212> PRT
<213> 人工序列
<220>
<223> C33H46 HC CDR3
<400> 359
Asp Arg Glu Val Arg Asp
1 5
<210> 360
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> C33H48 HC CDR1
<400> 360
Gly Gly Ser Ile Arg Ser Thr Asn Tyr
1 5
<210> 361
<211> 5
<212> PRT
<213> 人工序列
<220>
<223> C33H48 HC CDR2
<400> 361

[0270] Tyr Tyr Ser Gly Asn
1 5
<210> 362
<211> 14
<212> PRT
<213> 人工序列
<220>
<223> C33H48 HC CDR3
<400> 362
Leu Ala Asp Val Val Val Val Pro Ala Ala Arg Tyr Phe Asp
1 5 10
<210> 363
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> C33H49 HC CDR1
<400> 363
Gly Gly Ser Ile Arg Ser Ser Gly Phe
1 5
<210> 364
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> C33H49 HC CDR2
<400> 364
Tyr Tyr Ser Gly Asn
1 5
<210> 365
<211> 14
<212> PRT
<213> 人工序列
<220>
<223> C33H49 HC CDR3
<400> 365
Leu Ala Asp Val Val Val Val Pro Ala Ala Arg Tyr Phe Asp
1 5 10
<210> 366
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> C33H51 HC CDR1
<400> 366
Gly Gly Ser Ile Ser Thr Gly Arg Tyr
1 5

[0271]
<210> 367
<211> 5
<212> PRT
<213> 人工序列
<220>
<223> C33H51 HC CDR2
<400> 367
Tyr Tyr Ser Gly Asn
1 5
<210> 368
<211> 14
<212> PRT
<213> 人工序列
<220>
<223> C33H51 HC CDR3
<400> 368
Leu Gly Ser Leu Val Val Val Pro Ala Ala Met Ser Phe Asp
1 5 10
<210> 369
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> C33H52 HC CDR1

<400> 369
Gly Gly Ser Ile Arg Gly Ser Ser Tyr
1 5
<210> 370
<211> 5
<212> PRT
<213> 人工序列
<220>
<223> C33H52 HC CDR2
<400> 370
Tyr Ser Ser Gly Asn
1 5
<210> 371
<211> 14
<212> PRT
<213> 人工序列
<220>
<223> C33H52 HC CDR3
<400> 371
Leu Gly Ser Leu Val Val Val Pro Ala Ala Met Ser Phe Asp
1 5 10
<210> 372
<211> 8
[0272] <212> PRT
<213> 人工序列
<220>
<223> C33H55 HC CDR1
<400> 372
Gly Gly Ser Ile Ser Ser Ser Asn
1 5
<210> 373
<211> 5
<212> PRT
<213> 人工序列
<220>
<223> C33H55 HC CDR2
<400> 373
Tyr His Ser Gly Asn
1 5
<210> 374
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> C33H55 HC CDR3
<400> 374
Ile Ile Ala Val Ala Arg Tyr Phe Asp

1 5

<210> 375

<211> 7

<212> PRT

<213> 人工序列

<220>

<223> C33H65 HC CDR1

<400> 375

Gly Phe Thr Phe Ser Ser Tyr

1 5

<210> 376

<211> 6

<212> PRT

<213> 人工序列

<220>

<223> C33H65 HC CDR2

<400> 376

Ser Tyr Asp Gly Ser Asn

1 5

<210> 377

<211> 19

<212> PRT

<213> 人工序列

[0273] <220>

<223> C33H65 HC CDR3

<400> 377

Asp Phe Arg Asp Phe Asp Trp Leu Pro Pro Asp Ser Thr Ser Tyr His

1 5 10 15

Gly Met Asp

<210> 378

<211> 7

<212> PRT

<213> 人工序列

<220>

<223> C33H66 HC CDR1

<400> 378

Gly Phe Thr Phe Ser Ser Tyr

1 5

<210> 379

<211> 6

<212> PRT

<213> 人工序列

<220>

<223> C33H66 HC CDR2

<400> 379

Ser Tyr Asp Gly Ser Asn

1 5

<210> 380
<211> 19
<212> PRT
<213> 人工序列
<220>
<223> C33H66 HC CDR3
<400> 380
Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Ala Ser Tyr His
1 5 10 15
Gly Met Asp

<210> 381
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H68 HC CDR1
<400> 381
Gly Phe Thr Phe Ser Gly Tyr
1 5
<210> 382
<211> 6
[0274] <212> PRT
<213> 人工序列
<220>
<223> C33H68 HC CDR2
<400> 382
Asp Tyr Ser Gly Asn Asp
1 5
<210> 383
<211> 10
<212> PRT
<213> 人工序列
<220>
<223> C33H68 HC CDR3
<400> 383
Glu Ser Gln Leu Leu His Gly Leu Phe Glu
1 5 10
<210> 384
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> C33H69 HC CDR1
<400> 384
Gly Gly Ser Ile Ser Ser Ser Ser Tyr

1 5
<210> 385
<211> 5
<212> PRT
<213> 人工序列
<220>
<223> C33H69 HC CDR2
<400> 385
Asn Tyr Ser Gly Ser
1 5
<210> 386
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> C33H69 HC CDR3
<400> 386
Leu Asp Gly Tyr Glu Ser Pro Phe Asp
1 5
<210> 387
<211> 9
<212> PRT
<213> 人工序列
[0275] <220>
<223> C33H70 HC CDR1
<400> 387
Gly Gly Ser Ile Arg Gly Ser Ser Tyr
1 5
<210> 388
<211> 5
<212> PRT
<213> 人工序列
<220>
<223> C33H70 HC CDR2
<400> 388
Tyr Ser Ser Gly Asn
1 5
<210> 389
<211> 14
<212> PRT
<213> 人工序列
<220>
<223> C33H70 HC CDR3
<400> 389
Leu Gly Ser Leu Val Val Val Pro Ala Ala Met Ser Phe Asp
1 5 10
<210> 390

<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H72 HC CDR1
<400> 390
Gly Phe Thr Phe Ser Ser Tyr
1 5
<210> 391
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H72 HC CDR2
<400> 391
Lys Gln His Gly Ser Glu
1 5
<210> 392
<211> 8
<212> PRT
<213> 人工序列
<220>
<223> C33H72 HC CDR3
[0276] <400> 392
Asp Arg Asp Leu Gly Tyr Phe Asp
1 5
<210> 393
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H73 HC CDR1
<400> 393
Arg Phe Thr Phe Ser Ser Tyr
1 5
<210> 394
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H73 HC CDR2
<400> 394
Asn Ile Ser Gly Gly Ser
1 5
<210> 395
<211> 9
<212> PRT

<213> 人工序列
<220>
<223> C33H73 HC CDR3
<400> 395
Gly Gly Tyr Ser Ser Gly Pro Phe Asp
1 5
<210> 396
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H74 HC CDR1
<400> 396
Arg Phe Thr Phe Ser Ser Tyr
1 5
<210> 397
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H74 HC CDR2
<400> 397
Ser Tyr Asp Gly Ser Asn

[0277]

1 5
<210> 398
<211> 19
<212> PRT
<213> 人工序列
<220>
<223> C33H74 HC CDR3
<400> 398
Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Ala Ser Tyr His
1 5 10 15
Gly Met Asp

<210> 399
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H76 HC CDR1
<400> 399
Gly Phe Thr Phe Asn Tyr
1 5
<210> 400
<211> 6
<212> PRT

<213> 人工序列
<220>
<223> C33H76 HC CDR2
<400> 400
Ser Gly Ser Gly Gly Ser
1 5
<210> 401
<211> 12
<212> PRT
<213> 人工序列
<220>
<223> C33H76 HC CDR3
<400> 401
Thr Tyr Asn Ser Gly Tyr Tyr Asp Gly Asp Phe Asp
1 5 10
<210> 402
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H78 HC CDR1
<400> 402
Gly Phe Thr Phe Ser Ser Tyr
[0278] 1 5
<210> 403
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H78 HC CDR2
<400> 403
Ser Tyr Asp Gly Ser Asn
1 5
<210> 404
<211> 19
<212> PRT
<213> 人工序列
<220>
<223> C33H78 HC CDR3
<400> 404
Asp Phe Arg Tyr Phe Asp Trp Leu Pro Pro Asp Ser Ser Ser Tyr Tyr
1 5 10 15
Gly Met Asp

<210> 405
<211> 7
<212> PRT

<213> 人工序列
<220>
<223> C33H80 HC CDR1
<400> 405
Gly Tyr Thr Phe Thr Asn Tyr
1 5
<210> 406
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H80 HC CDR2
<400> 406
Asn Thr Asn Thr Gly Asn
1 5
<210> 407
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H80 HC CDR3
<400> 407
Asp Arg Asp Arg Gly Thr Asp
[0279] 1 5
<210> 408
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H81 HC CDR1
<400> 408
Gly Phe Thr Phe Ser Ala Tyr
1 5
<210> 409
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H81 HC CDR2
<400> 409
Ser Tyr Asp Gly Ser Asn
1 5
<210> 410
<211> 19
<212> PRT
<213> 人工序列
<220>

<223> C33H81 HC CDR3
<400> 410
Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Ala Ser Tyr His
1 5 10 15
Gly Met Asp

<210> 411
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H84 HC CDR1
<400> 411
Gly Phe Thr Phe Ser Ser Tyr
1 5
<210> 412
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H84 HC CDR2
<400> 412
Ser Tyr Asp Gly Ser Asn
[0280] 1 5
<210> 413
<211> 19
<212> PRT
<213> 人工序列
<220>
<223> C33H84 HC CDR3
<400> 413
Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Thr Ser Tyr Tyr
1 5 10 15
Gly Met Asp

<210> 414
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H87 HC CDR1
<400> 414
Gly Phe Thr Phe Ser Ser Tyr
1 5
<210> 415
<211> 6
<212> PRT

<213> 人工序列
<220>
<223> C33H87 HC CDR2
<400> 415
Lys Gln His Gly Ser Glu
1 5
<210> 416
<211> 8
<212> PRT
<213> 人工序列
<220>
<223> C33H87 HC CDR3
<400> 416
Asp Arg Asp Leu Gly Tyr Phe Asp
1 5
<210> 417
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H88 HC CDR1
<400> 417
Gly Tyr Thr Leu Thr Arg Ser
[0281] 1 5
<210> 418
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H88 HC CDR2
<400> 418
Asn Thr Asn Thr Gly Asn
1 5
<210> 419
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> C33H88 HC CDR3
<400> 419
Asp Ile Leu Pro Gly Tyr His Glu Asp
1 5
<210> 420
<211> 9
<212> PRT
<213> 人工序列
<220>

<223> C33H90 HC CDR1
<400> 420
Gly Asp Ser Val Ser Ser Asn Ser Ala
1 5
<210> 421
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H90 HC CDR2
<400> 421
Tyr Tyr Arg Ser Lys Trp Tyr
1 5
<210> 422
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> C33H90 HC CDR3
<400> 422
Glu Val Ala Val Ala Ala Ser Phe Asp
1 5
<210> 423
[0282] <211> 9
<212> PRT
<213> 人工序列
<220>
<223> C33H91 HC CDR1
<400> 423
Gly Gly Ser Ile Ser Ser Arg Ser His
1 5
<210> 424
<211> 5
<212> PRT
<213> 人工序列
<220>
<223> C33H91 HC CDR2
<400> 424
Tyr Tyr Thr Gly Ser
1 5
<210> 425
<211> 14
<212> PRT
<213> 人工序列
<220>
<223> C33H91 HC CDR3
<400> 425

Leu Ala Asp Ile Val Val Val Pro Ala Ala Arg Tyr Phe Asp
1 5 10
<210> 426
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> C33H92 HC CDR1
<400> 426
Gly Gly Ser Ile Arg Ser Ser Ser Tyr
1 5
<210> 427
<211> 5
<212> PRT
<213> 人工序列
<220>
<223> C33H92 HC CDR2
<400> 427
Tyr Ser Ser Gly Asn
1 5
<210> 428
<211> 14
<212> PRT
[0283] <213> 人工序列
<220>
<223> C33H92 HC CDR3
<400> 428
Leu Ala Ala Thr Ile Val Val Pro Ala Ala Arg Tyr Phe Asp
1 5 10
<210> 429
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H98 HC CDR1
<400> 429
Gly Phe Thr Phe Ser Ser Tyr
1 5
<210> 430
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H98 HC CDR2
<400> 430
Lys Gln His Gly Ser Glu
1 5

<210> 431
<211> 8
<212> PRT
<213> 人工序列
<220>
<223> C33H98 HC CDR3
<400> 431
Asp Arg Asp Leu Gly Tyr Phe Asp
1 5
<210> 432
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H99 HC CDR1
<400> 432
Gly Phe Thr Phe Ser Ser Tyr
1 5
<210> 433
<211> 6
<212> PRT
<213> 人工序列
<220>

[0284]

<223> C33H99 HC CDR2
<400> 433
Lys Arg Asp Gly Gly Glu
1 5
<210> 434
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H99 HC CDR3
<400> 434
Pro Phe Tyr Asp His Phe Asp
1 5
<210> 435
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H108 HC CDR1
<400> 435
Gly Tyr Thr Phe Ser Thr Tyr
1 5
<210> 436
<211> 6

<212> PRT
<213> 人工序列
<220>
<223> C33H108 HC CDR2
<400> 436
Asn Thr Asn Thr Gly Asn
1 5
<210> 437
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H108 HC CDR3
<400> 437
Asp Arg Asp Arg Gly Thr Asp
1 5
<210> 438
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H249 HC CDR1
<400> 438

[0285] Gly Phe Thr Phe Asp Asp Tyr
1 5
<210> 439
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H249 HC CDR2
<400> 439
Ser Trp Asn Gly Gly Asn
1 5
<210> 440
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> C33H249 HC CDR3
<400> 440
Asp Thr Pro Tyr Gly Asp Tyr Phe Asp
1 5
<210> 441
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> C33H250 HC CDR1
<400> 441
Gly Phe Thr Phe Asp Asp Tyr
1 5
<210> 442
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H250 HC CDR2
<400> 442
Ser Trp Asn Gly Gly Asn
1 5
<210> 443
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> C33H250 HC CDR3
<400> 443
Asp Ser Pro Tyr Gly Asp Tyr Phe Asp
1 5

[0286]

<210> 444
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H251 HC CDR1
<400> 444
Gly Phe Thr Phe Asp Asp Tyr
1 5
<210> 445
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H251 HC CDR2
<400> 445
Gly Trp Ser Gly Gly Ser
1 5
<210> 446
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> C33H251 HC CDR3

<400> 446
Asp Ser Pro Tyr Gly Asp Phe Phe Asp
1 5
<210> 447
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H252 HC CDR1
<400> 447
Gly Phe Thr Phe Asp Asp Tyr
1 5
<210> 448
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H252 HC CDR2
<400> 448
Gly Trp Ser Gly Gly Ser
1 5
<210> 449
<211> 9
[0287] <212> PRT
<213> 人工序列
<220>
<223> C33H252 HC CDR3
<400> 449
Asp Ser Pro Tyr Gly Asp Phe Phe Asp
1 5
<210> 450
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H253 HC CDR1
<400> 450
Gly Phe Thr Phe Arg Ser Tyr
1 5
<210> 451
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H253 HC CDR2
<400> 451
Asn Gly Tyr Gly Asp Gly

1 5

<210> 452

<211> 10

<212> PRT

<213> 人工序列

<220>

<223> C33H253 HC CDR3

<400> 452

Asp Gln Gly Phe Gly Glu Leu Phe Phe Asp

1 5 10

<210> 453

<211> 7

<212> PRT

<213> 人工序列

<220>

<223> C33H254 HC CDR1

<400> 453

Gly Phe Thr Phe Ser Tyr Tyr

1 5

<210> 454

<211> 6

<212> PRT

<213> 人工序列

[0288] <220>

<223> C33H254 HC CDR2

<400> 454

Trp Phe Asp Gly Asn Asn

1 5

<210> 455

<211> 7

<212> PRT

<213> 人工序列

<220>

<223> C33H254 HC CDR3

<400> 455

Asp Arg Glu Leu Leu Phe Asp

1 5

<210> 456

<211> 7

<212> PRT

<213> 人工序列

<220>

<223> C33H255 HC CDR1

<400> 456

Gly Phe Thr Phe Asp Asp Tyr

1 5

<210> 457

<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H255 HC CDR2
<400> 457
Ser Trp Asn Gly Gly Asp
1 5
<210> 458
<211> 19
<212> PRT
<213> 人工序列
<220>
<223> C33H255 HC CDR3
<400> 458
Asp Met Pro Tyr Phe Asp Phe Leu Thr Gly Ser Asp Tyr Tyr Tyr Tyr
1 5 10 15
Gly Met Asp

<210> 459
<211> 7
<212> PRT
<213> 人工序列
[0289] <220>
<223> C33H256 HC CDR1
<400> 459
Gly Phe Thr Phe Ser Asn Tyr
1 5
<210> 460
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33H256 HC CDR2
<400> 460
Trp Tyr Val Gly Ser His
1 5
<210> 461
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33H256 HC CDR3
<400> 461
Asp Gly Ser Leu Cys Phe Asp
1 5
<210> 462

<211> 11
<212> PRT
<213> 人工序列
<220>
<223> B23L3 LC CDR1
<400> 462
Ser Gln Ser Val Asp Tyr Asn Gly Ile Ser Tyr
1 5 10
<210> 463
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> B23L3 LC CDR2
<400> 463
Ala Ala Ser
1
<210> 464
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> B23L3 LC CDR3
[0290] <400> 464
Ile Ile Glu Asp Pro Trp
1 5
<210> 465
<211> 10
<212> PRT
<213> 人工序列
<220>
<223> CD3L66 LC CDR1
<400> 465
Ser Thr Gly Ala Val Thr Thr Ser Asn Tyr
1 5 10
<210> 466
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> CD3L66 LC CDR2
<400> 466
Gly Thr Asn
1
<210> 467
<211> 6
<212> PRT

<213> 人工序列
<220>
<223> CD3L66 LC CDR3
<400> 467
Trp Tyr Ser Asn Leu Trp
1 5
<210> 468
<211> 10
<212> PRT
<213> 人工序列
<220>
<223> CD3L150 LC CDR1
<400> 468
Thr Ser Ser Asn Ile Gly Thr Tyr Lys Phe
1 5 10
<210> 469
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> CD3L150 LC CDR2
<400> 469
Glu Val Ser
[0291] 1
<210> 470
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> CD3L150 LC CDR3
<400> 470
Tyr Ala Gly Ser Gly Thr Leu
1 5
<210> 471
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L8 LC CDR1
<400> 471
Asp Lys Leu Gly Asn Lys Tyr
1 5
<210> 472
<211> 3
<212> PRT
<213> 人工序列
<220>

<223> C33L8 LC CDR2
<400> 472
Gln Asp Ser
1
<210> 473
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L8 LC CDR3
<400> 473
Trp Asp Ser Ser Thr Tyr
1 5
<210> 474
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L10 LC CDR1
<400> 474
Ser Asn Ile Gly Ser Lys Ser
1 5
<210> 475
[0292] <211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L10 LC CDR2
<400> 475
Asp Asp Ser
1
<210> 476
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L10 LC CDR3
<400> 476
Trp Asp Ser Ser Ser Asp Val
1 5
<210> 477
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L11 LC CDR1
<400> 477

His Lys Leu Gly Asp Lys Tyr
1 5
<210> 478
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L11 LC CDR2
<400> 478
Lys Asp Ser
1
<210> 479
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L11 LC CDR3
<400> 479
Trp Asp Ser Ser Thr Val
1 5
<210> 480
<211> 7
<212> PRT
[0293] <213> 人工序列
<220>
<223> IAPL24 LC CDR1
<400> 480
Asp Lys Leu Gly Asp Lys Tyr
1 5
<210> 481
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> IAPL24 LC CDR2
<400> 481
Gln Asp Ser
1
<210> 482
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> IAPL24 LC CDR3
<400> 482
Trp Asp Ser Ser Thr Val
1 5

<210> 483
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L58 LC CDR1
<400> 483
Asp Lys Leu Gly Asp Lys Tyr
1 5
<210> 484
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L58 LC CDR2
<400> 484
Gln Asp Tyr
1
<210> 485
<211> 6
<212> PRT
<213> 人工序列
<220>
[0294] <223> C33L58 LC CDR3
<400> 485
Trp Asp Ser Ser Thr Tyr
1 5
<210> 486
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L59 LC CDR1
<400> 486
Asp Lys Leu Gly Asp Lys Tyr
1 5
<210> 487
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L59 LC CDR2
<400> 487
Gln Asp Tyr
1
<210> 488
<211> 6

<212> PRT
<213> 人工序列
<220>
<223> C33L59 LC CDR3
<400> 488
Trp Asp Ile Ser Thr Tyr
1 5
<210> 489
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L34 LC CDR1
<400> 489
Asp Lys Leu Gly Asp Lys Tyr
1 5
<210> 490
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L34 LC CDR2
<400> 490

[0295] Gln Asp Ser
1
<210> 491
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L34 LC CDR3
<400> 491
Trp Asp Ser Ser Thr Trp
1 5
<210> 492
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> N46L109 LC CDR1
<400> 492
Asp Lys Leu Gly Asp Lys Tyr
1 5
<210> 493
<211> 3
<212> PRT
<213> 人工序列

<220>
<223> N46L109 LC CDR2
<400> 493
Gln Asp Ser
1
<210> 494
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> N46L109 LC CDR3
<400> 494
Trp Asp Ser Ser Thr Trp
1 5
<210> 495
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L42 LC CDR1
<400> 495
Asn Asn Ile Gly Ile Lys Ser
1 5

[0296]

<210> 496
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L42 LC CDR2
<400> 496
Asp Asp Ser
1
<210> 497
<211> 8
<212> PRT
<213> 人工序列
<220>
<223> C33L42 LC CDR3
<400> 497
Trp Asp Ser Ser Ser Asp His Val
1 5
<210> 498
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L47 LC CDR1

<400> 498
Asp Lys Leu Gly Asp Lys Tyr
1 5
<210> 499
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L47 LC CDR2
<400> 499
Gln Asp Arg
1
<210> 500
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L47 LC CDR3
<400> 500
Trp Asp Ser Ser Thr Val
1 5
<210> 501
<211> 7
[0297] <212> PRT
<213> 人工序列
<220>
<223> C33L60 LC CDR1
<400> 501
Asp Lys Leu Gly Asp Lys Tyr
1 5
<210> 502
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L60 LC CDR2
<400> 502
Gln Asp Gly
1
<210> 503
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L60 LC CDR3
<400> 503
Trp Asp Arg Asn Thr Val

1 5

<210> 504

<211> 13

<212> PRT

<213> 人工序列

<220>

<223> C33L17 LC CDR1

<400> 504

Ser Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr

1 5 10

<210> 505

<211> 3

<212> PRT

<213> 人工序列

<220>

<223> C33L17 LC CDR2

<400> 505

Trp Ala Ser

1

<210> 506

<211> 6

<212> PRT

<213> 人工序列

[0298] <220>

<223> C33L17 LC CDR3

<400> 506

Tyr Tyr Gly Thr Pro Trp

1 5

<210> 507

<211> 7

<212> PRT

<213> 人工序列

<220>

<223> C4LL152 LC CDR1

<400> 507

Ser Gln Gly Ile Ser Ser Trp

1 5

<210> 508

<211> 3

<212> PRT

<213> 人工序列

<220>

<223> C4LL152 LC CDR2

<400> 508

Ala Ala Ser

1

<210> 509

<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C4LL152 LC CDR3
<400> 509
Ala Asn Ser Phe Pro Phe
1 5
<210> 510
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L40 LC CDR1
<400> 510
Asn Lys Leu Gly Ala Lys Phe
1 5
<210> 511
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L40 LC CDR2
[0299] <400> 511
Gln Asp Asn
1
<210> 512
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L40 LC CDR3
<400> 512
Trp Asp Ser Ser Thr Val
1 5
<210> 513
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L32 LC CDR1
<400> 513
Asp Lys Leu Gly Asp Lys Tyr
1 5
<210> 514
<211> 3
<212> PRT

<213> 人工序列
<220>
<223> C33L32 LC CDR2
<400> 514
Gln Asp Ser
1
<210> 515
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L32 LC CDR3
<400> 515
Trp Asp Ser Ser Thr Gly Val
1 5
<210> 516
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L38 LC CDR1
<400> 516
Asp Lys Leu Gly Asp Lys Tyr
[0300] 1 5
<210> 517
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L38 LC CDR2
<400> 517
Gln Asp Asn
1
<210> 518
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L38 LC CDR3
<400> 518
Trp Gly Arg Asn Thr Val
1 5
<210> 519
<211> 10
<212> PRT
<213> 人工序列
<220>

<223> C33L39 LC CDR1
<400> 519
Thr Ser Ser Asp Asp Gly Lys Asn Asn Ile
1 5 10
<210> 520
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L39 LC CDR2
<400> 520
Lys Asp Ser
1
<210> 521
<211> 8
<212> PRT
<213> 人工序列
<220>
<223> C33L39 LC CDR3
<400> 521
Tyr Ala Gly Ala Ser Asn His Val
1 5
<210> 522
[0301] <211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L57 LC CDR1
<400> 522
Asp Glu Leu Gly Asn Lys Tyr
1 5
<210> 523
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L57 LC CDR2
<400> 523
Gln Asp Arg
1
<210> 524
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L57 LC CDR3
<400> 524

Trp Asp Ser Ser Thr Val
1 5
<210> 525
<211> 10
<212> PRT
<213> 人工序列
<220>
<223> C33L73 LC CDR1
<400> 525
Thr Ser Ser Asp Val Gly Asp Tyr Asn Tyr
1 5 10
<210> 526
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L73 LC CDR2
<400> 526
Asp Val Ser
1
<210> 527
<211> 8
<212> PRT
[0302] <213> 人工序列
<220>
<223> C33L73 LC CDR3
<400> 527
Tyr Ser Ser Ser Ser Ala Leu Glu
1 5
<210> 528
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L53 LC CDR1
<400> 528
Asp Lys Leu Gly Asp Lys Tyr
1 5
<210> 529
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L53 LC CDR2
<400> 529
Gln Asp Asn
1

<210> 530
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L53 LC CDR3
<400> 530
Trp Asp Ser Asn Thr Val
1 5
<210> 531
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L66 LC CDR1
<400> 531
Asp Lys Leu Gly Asp Lys Tyr
1 5
<210> 532
<211> 3
<212> PRT
<213> 人工序列
<220>

[0303]

<223> C33L66 LC CDR2
<400> 532
Gln Asp Arg
1
<210> 533
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L66 LC CDR3
<400> 533
Trp Asp Ser Ser Thr Val
1 5
<210> 534
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L35 LC CDR1
<400> 534
Asp Lys Leu Gly Asn Lys Tyr
1 5
<210> 535
<211> 3

<212> PRT
<213> 人工序列
<220>
<223> C33L35 LC CDR2
<400> 535
Gln Asp Thr
1
<210> 536
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L35 LC CDR3
<400> 536
Trp Asp Ser Ser Thr Val
1 5
<210> 537
<211> 10
<212> PRT
<213> 人工序列
<220>
<223> C33L61 LC CDR1
<400> 537

[0304] Ile Asn Ser Asp Val Gly Ser Tyr Asp Leu
1 5 10
<210> 538
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L61 LC CDR2
<400> 538
Asp Gly Ser
1
<210> 539
<211> 8
<212> PRT
<213> 人工序列
<220>
<223> C33L61 LC CDR3
<400> 539
Tyr Glu Val Thr Thr Thr Tyr Val
1 5
<210> 540
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> C33L51 LC CDR1
<400> 540
Asn Asn Ile Gly Ser Lys Ser
1 5
<210> 541
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L51 LC CDR2
<400> 541
Asp Asp Ser
1
<210> 542
<211> 8
<212> PRT
<213> 人工序列
<220>
<223> C33L51 LC CDR3
<400> 542
Trp Asp Ser Asn Ser Asp His Val
1 5

[0305]

<210> 543
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L44 LC CDR1
<400> 543
Asp Lys Leu Gly Asp Lys Tyr
1 5
<210> 544
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L44 LC CDR2
<400> 544
Gln Asp Ser
1
<210> 545
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L44 LC CDR3

<400> 545
Trp Asp Ser Ser Thr Tyr
1 5
<210> 546
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L30 LC CDR1
<400> 546
Asp Arg Leu Gly Asp Lys Tyr
1 5
<210> 547
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L30 LC CDR2
<400> 547
Gln Asp Ser
1
<210> 548
<211> 6
[0306] <212> PRT
<213> 人工序列
<220>
<223> C33L30 LC CDR3
<400> 548
Trp Asp Ser Ser Ser Tyr
1 5
<210> 549
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L69 LC CDR1
<400> 549
Asp Lys Leu Gly Ser Lys Phe
1 5
<210> 550
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L69 LC CDR2
<400> 550
Gln Asp Ser

1

<210> 551

<211> 6

<212> PRT

<213> 人工序列

<220>

<223> C33L69 LC CDR3

<400> 551

Trp Asp Ser Ser Thr Val

1 5

<210> 552

<211> 7

<212> PRT

<213> 人工序列

<220>

<223> C33L37 LC CDR1

<400> 552

Ser Asn Ile Gly Lys Ile Ser

1 5

<210> 553

<211> 3

<212> PRT

<213> 人工序列

[0307] <220>

<223> C33L37 LC CDR2

<400> 553

Asp Asp Arg

1

<210> 554

<211> 8

<212> PRT

<213> 人工序列

<220>

<223> C33L37 LC CDR3

<400> 554

Trp Asn Ser Ser Ser Val His Pro

1 5

<210> 555

<211> 10

<212> PRT

<213> 人工序列

<220>

<223> C33L74 LC CDR1

<400> 555

Thr Ser Ser Asp Val Gly Asp Asp Asn Tyr

1 5 10

<210> 556

<210> 3
<211> PRT
<212> 人工序列
<213>
<220>
<223> C33L74 LC CDR2
<400> 556
Asp Val Ser
1
<210> 557
<211> 8
<212> PRT
<213> 人工序列
<220>
<223> C33L74 LC CDR3
<400> 557
Tyr Ser Ser Ser Thr Thr Leu Glu
1 5
<210> 558
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L115 LC CDR1
[0308] <400> 558
Ser Gln Gly Ile Ser Ser Trp
1 5
<210> 559
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L115 LC CDR2
<400> 559
Arg Ser Ser
1
<210> 560
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L115 LC CDR3
<400> 560
Asp Asn Ser Phe Pro Tyr
1 5
<210> 561
<211> 7
<212> PRT

<213> 人工序列
<220>
<223> C33L116 LC CDR1
<400> 561
Ser Gln Gly Ile Ser Ser Trp
1 5
<210> 562
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L116 LC CDR2
<400> 562
Gly Ala Ser
1
<210> 563
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L116 LC CDR3
<400> 563
Asp Asn Ser Phe Pro Tyr
[0309] 1 5
<210> 564
<211> 13
<212> PRT
<213> 人工序列
<220>
<223> C33L117 LC CDR1
<400> 564
Ser Gln Thr Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr
1 5 10
<210> 565
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L117 LC CDR2
<400> 565
Trp Ala Ser
1
<210> 566
<211> 6
<212> PRT
<213> 人工序列
<220>

<223> C33L117 LC CDR3
<400> 566
Tyr Tyr Ser Thr Pro Tyr
1 5
<210> 567
<211> 13
<212> PRT
<213> 人工序列
<220>
<223> C33L118 LC CDR1
<400> 567
Ser Gln Thr Val Phe Tyr Ser Ser Asn Asn Lys Asn Tyr
1 5 10
<210> 568
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L118 LC CDR2
<400> 568
Trp Ala Ser
1
<210> 569
[0310] <211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L118 LC CDR3
<400> 569
Tyr Tyr Ser Thr Pro Tyr
1 5
<210> 570
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L119 LC CDR1
<400> 570
Ser Gln Ser Ile Ser Ser Trp
1 5
<210> 571
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L119 LC CDR2
<400> 571

Lys Ala Ser
1
<210> 572
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L119 LC CDR3
<400> 572
Tyr Asn Ser Tyr Pro Trp
1 5
<210> 573
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L120 LC CDR1
<400> 573
Asp Glu Leu Gly Asp Met Tyr
1 5
<210> 574
<211> 3
<212> PRT
[0311] <213> 人工序列
<220>
<223> C33L120 LC CDR2
<400> 574
Gln Asp Ser
1
<210> 575
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L120 LC CDR3
<400> 575
Trp Asp Thr Arg Ile Ala
1 5
<210> 576
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L121 LC CDR1
<400> 576
Asp Asn Leu Gly Asn Glu His
1 5

<210> 577
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L121 LC CDR2
<400> 577
Gln Asn Asn
1
<210> 578
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L121 LC CDR3
<400> 578
Trp Asp Ser Thr Thr Ala
1 5
<210> 579
<211> 7
<212> PRT
<213> 人工序列
<220>
[0312] <223> C33L122 LC CDR1
<400> 579
Val Thr Leu Gly Tyr Asn Tyr
1 5
<210> 580
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L122 LC CDR2
<400> 580
Gln Asp Thr
1
<210> 581
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L122 LC CDR3
<400> 581
Trp Asp Ile Thr Thr Val
1 5
<210> 582
<211> 7

<212> PRT
<213> 人工序列
<220>
<223> C33L132 LC CDR1
<400> 582
Asp Lys Leu Gly Asp Lys Tyr
1 5
<210> 583
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L132 LC CDR2
<400> 583
Gln Asp Gly
1
<210> 584
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> C33L132 LC CDR3
<400> 584

[0313] Trp Asp Arg Asn Thr Val
1 5
<210> 585
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> C33L41 LC CDR1
<400> 585
Asp Lys Leu Gly Asn Lys Tyr
1 5
<210> 586
<211> 3
<212> PRT
<213> 人工序列
<220>
<223> C33L41 LC CDR2
<400> 586
Gln Asp Ser
1
<210> 587
<211> 6
<212> PRT
<213> 人工序列

<220>
<223> C33L41 LC CDR3
<400> 587
Trp Asp Ser Ser Thr Val
1 5
<210> 588
<211> 182
<212> PRT
<213> 智人(Homo sapiens)
<400> 588
Met Glu Gln Gly Lys Gly Leu Ala Val Leu Ile Leu Ala Ile Ile Leu
1 5 10 15
Leu Gln Gly Thr Leu Ala Gln Ser Ile Lys Gly Asn His Leu Val Lys
20 25 30
Val Tyr Asp Tyr Gln Glu Asp Gly Ser Val Leu Leu Thr Cys Asp Ala
35 40 45
Glu Ala Lys Asn Ile Thr Trp Phe Lys Asp Gly Lys Met Ile Gly Phe
50 55 60
Leu Thr Glu Asp Lys Lys Lys Trp Asn Leu Gly Ser Asn Ala Lys Asp
65 70 75 80
Pro Arg Gly Met Tyr Gln Cys Lys Gly Ser Gln Asn Lys Ser Lys Pro
85 90 95
Leu Gln Val Tyr Tyr Arg Met Cys Gln Asn Cys Ile Glu Leu Asn Ala
[0314] 100 105 110
Ala Thr Ile Ser Gly Phe Leu Phe Ala Glu Ile Val Ser Ile Phe Val
115 120 125
Leu Ala Val Gly Val Tyr Phe Ile Ala Gly Gln Asp Gly Val Arg Gln
130 135 140
Ser Arg Ala Ser Asp Lys Gln Thr Leu Leu Pro Asn Asp Gln Leu Tyr
145 150 155 160
Gln Pro Leu Lys Asp Arg Glu Asp Asp Gln Tyr Ser His Leu Gln Gly
165 170 175
Asn Gln Leu Arg Arg Asn
180
<210> 589
<211> 171
<212> PRT
<213> 智人(Homo sapiens)
<400> 589
Met Glu His Ser Thr Phe Leu Ser Gly Leu Val Leu Ala Thr Leu Leu
1 5 10 15
Ser Gln Val Ser Pro Phe Lys Ile Pro Ile Glu Glu Leu Glu Asp Arg
20 25 30
Val Phe Val Asn Cys Asn Thr Ser Ile Thr Trp Val Glu Gly Thr Val
35 40 45
Gly Thr Leu Leu Ser Asp Ile Thr Arg Leu Asp Leu Gly Lys Arg Ile
50 55 60

Leu Asp Pro Arg Gly Ile Tyr Arg Cys Asn Gly Thr Asp Ile Tyr Lys
65 70 75 80
Asp Lys Glu Ser Thr Val Gln Val His Tyr Arg Met Cys Gln Ser Cys
85 90 95
Val Glu Leu Asp Pro Ala Thr Val Ala Gly Ile Ile Val Thr Asp Val
100 105 110
Ile Ala Thr Leu Leu Leu Ala Leu Gly Val Phe Cys Phe Ala Gly His
115 120 125
Glu Thr Gly Arg Leu Ser Gly Ala Ala Asp Thr Gln Ala Leu Leu Arg
130 135 140
Asn Asp Gln Val Tyr Gln Pro Leu Arg Asp Arg Asp Asp Ala Gln Tyr
145 150 155 160
Ser His Leu Gly Gly Asn Trp Ala Arg Asn Lys
165 170

<210> 590
<211> 207
<212> PRT
<213> 智人(Homo sapiens)
<400> 590

Met Gln Ser Gly Thr His Trp Arg Val Leu Gly Leu Cys Leu Leu Ser
1 5 10 15
Val Gly Val Trp Gly Gln Asp Gly Asn Glu Glu Met Gly Gly Ile Thr
20 25 30

[0315]

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

<210> 591
<211> 164

[0316]

<212> PRT
<213> 智人(Homo sapiens)
<400> 591

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

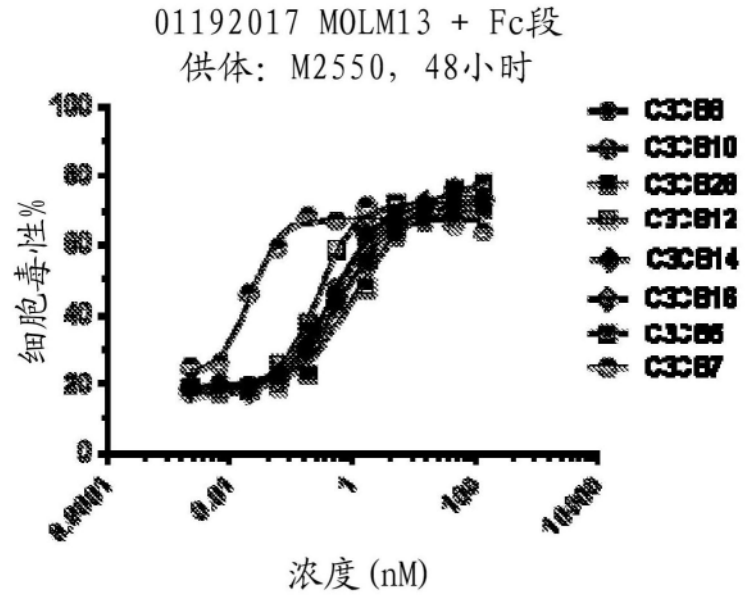

01192017 MOLM13 + Fc段
供体: M2550, 48小时
细胞毒性%
浓度(nM)
C3C88
C3C810
C3C828
C3C812
C3C814
C3C816
C3C85
C3C87

图1A

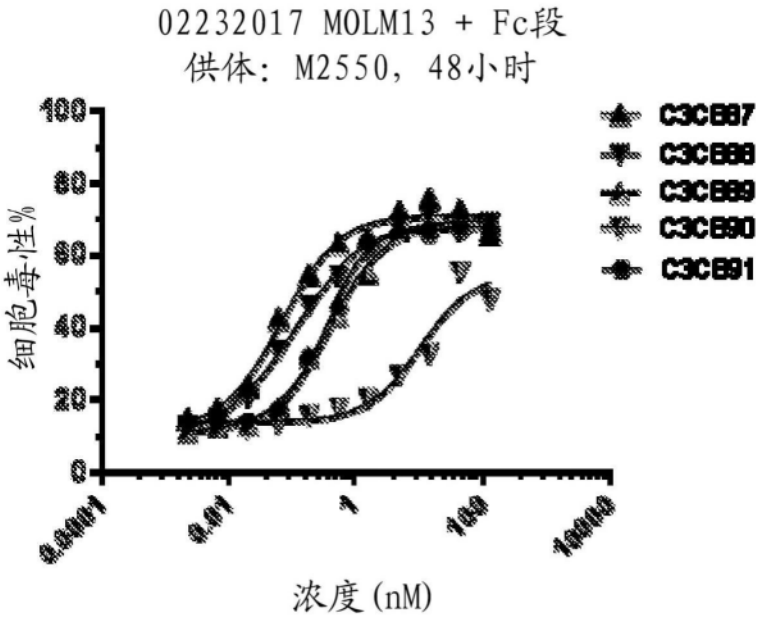

02232017 MOLM13 + Fc段
供体: M2550, 48小时
细胞毒性%
浓度(nM)
C3C887
C3C888
C3C889
C3C890
C3C891

图1B

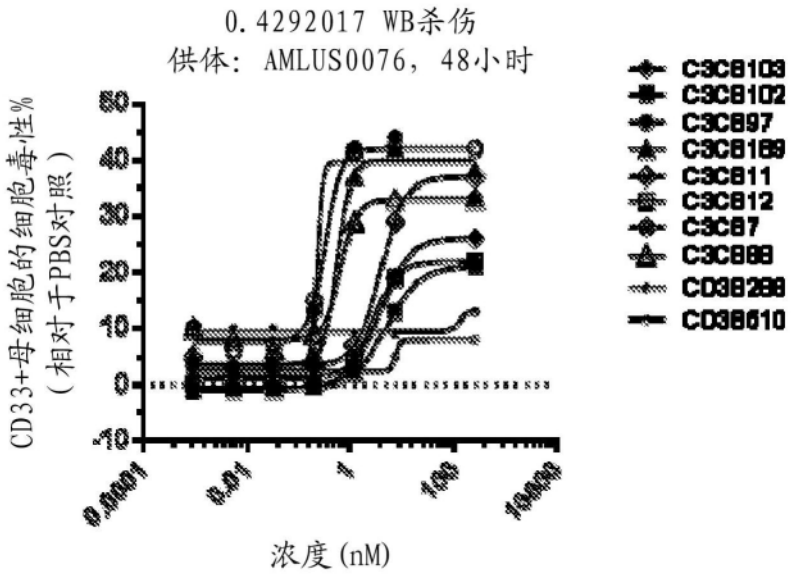

0.4292017 WB杀伤
供体: AMLUS0076, 48小时
CD33+母细胞的细胞毒性%
(相对于PBS对照)
浓度(nM)
C3C8103
C3C8102
C3C897
C3C8189
C3C811
C3C812
C3C87
C3C888
CD38288
CD38610

图2A

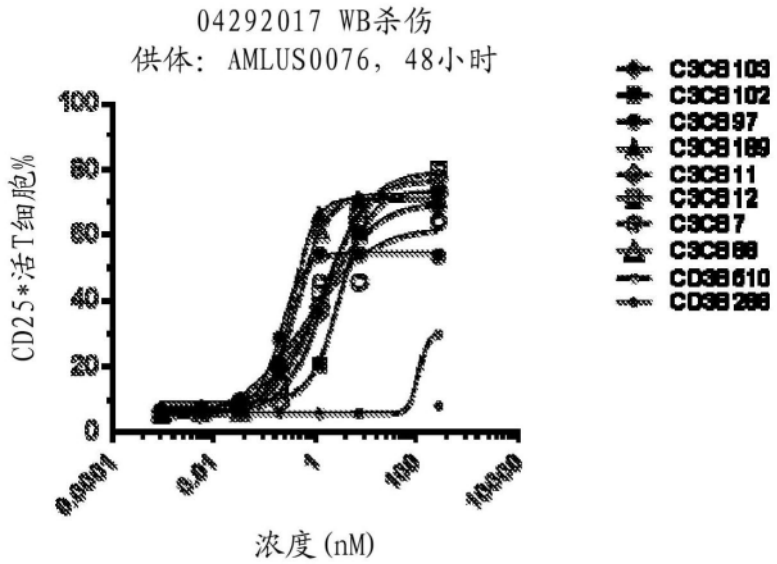

04292017 WB杀伤
供体: AMLUS0076, 48小时
CD25*活T细胞%
浓度(nM)
C3C8103
C3C8102
C3C897
C3C8189
C3C811
C3C812
C3C87
C3C888
CD38610
CD38288

图2B

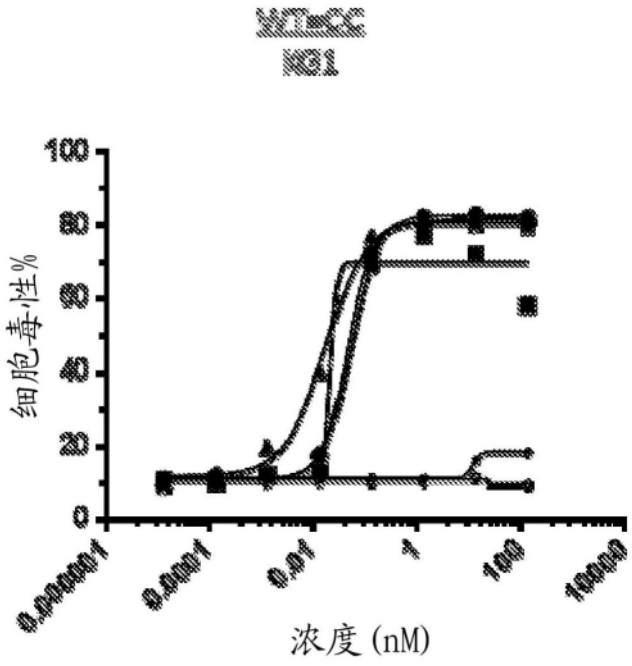


图3A

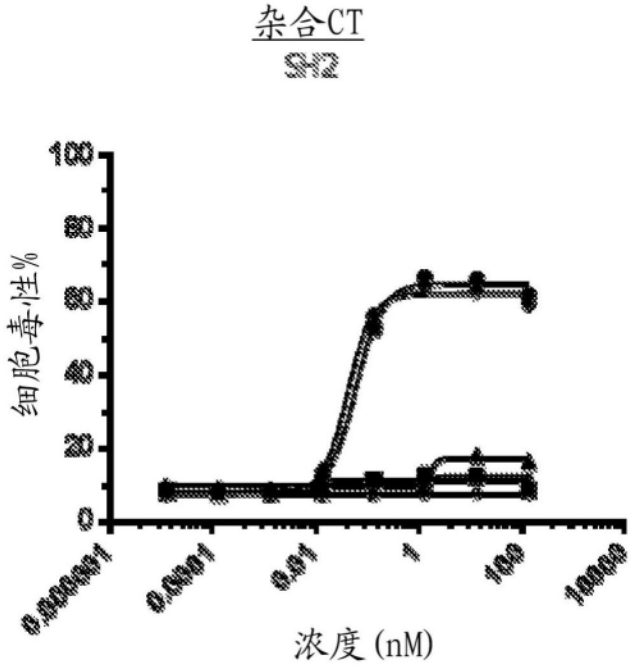


图3B

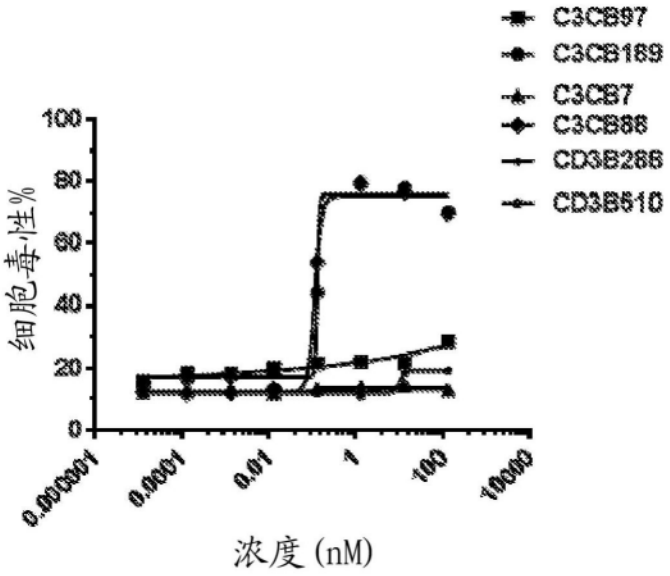

C3CB97
C3CB189
C3CB7
C3CB88
CD3B286
CD3B510
细胞毒性%
100
80
60
40
20
0
0.000001
0.0001
0.01
1
100
10000
浓度(nM)

图3C

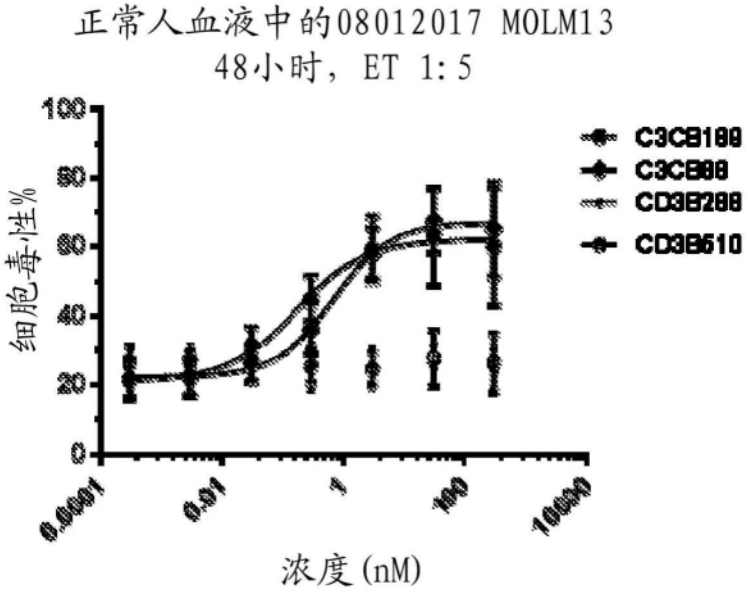

正常人血液中的08012017 MOLM13
48小时, ET 1:5
C3CB189
C3CB88
CD3B286
CD3B510
细胞毒性%
100
80
60
40
20
0
0.0001
0.01
1
100
10000
浓度(nM)

图4A

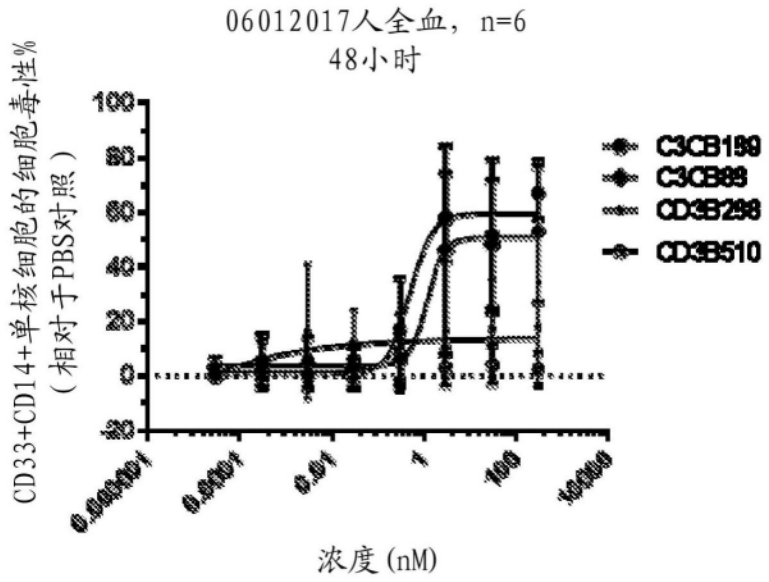

06012017人全血，n=6
48小时
CD33+CD14+单核细胞的细胞毒性%
（相对于PBS对照）
C3CB189
C3CB88
CD3B288
CD3B510
浓度(nM)

图4B

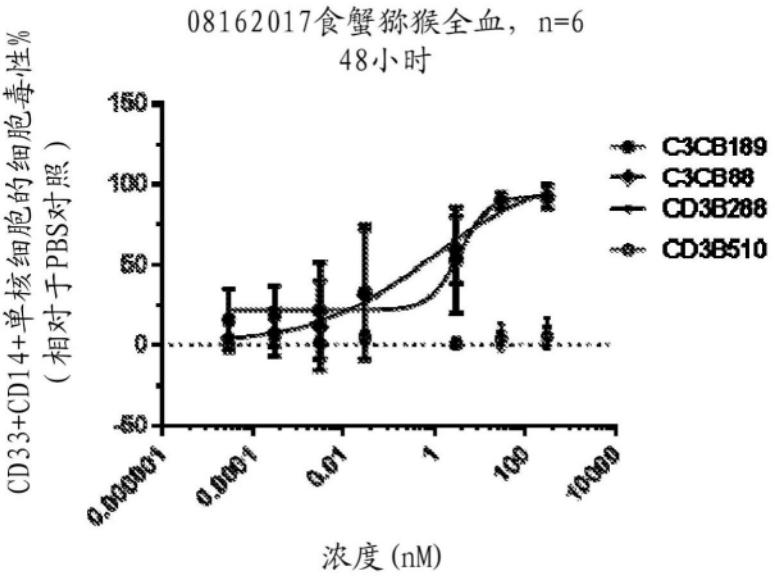

08162017食蟹猕猴全血，n=6
48小时
CD33+CD14+单核细胞的细胞毒性%
（相对于PBS对照）
C3CB189
C3CB88
CD3B288
CD3B510
浓度(nM)

图5A

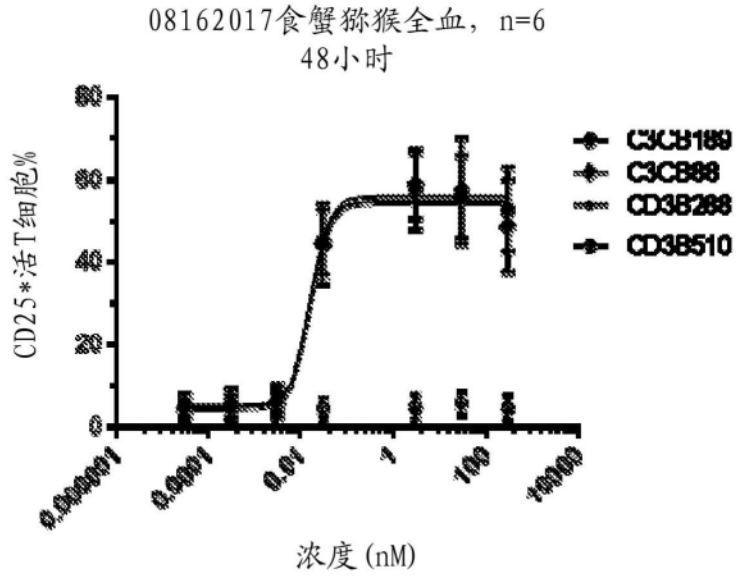

08162017食蟹猕猴全血，n=6
48小时
CD25*活T细胞%
浓度(nM)
C3CB189
C3CB88
CD3B288
CD3B510

图5B

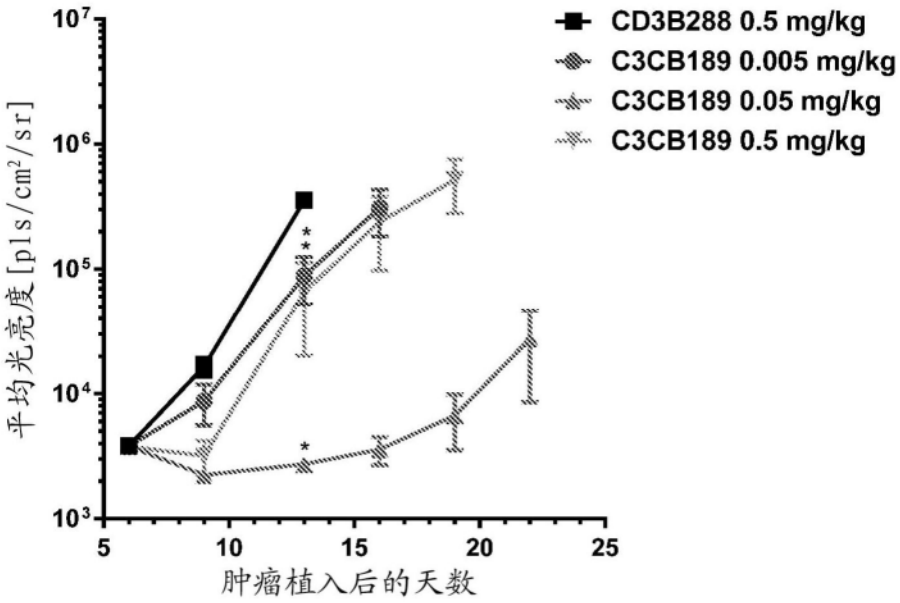

CD3B288 0.5 mg/kg
C3CB189 0.005 mg/kg
C3CB189 0.05 mg/kg
C3CB189 0.5 mg/kg
平均光亮度[p1s/cm²/sr]
肿瘤植入后的天数

图6

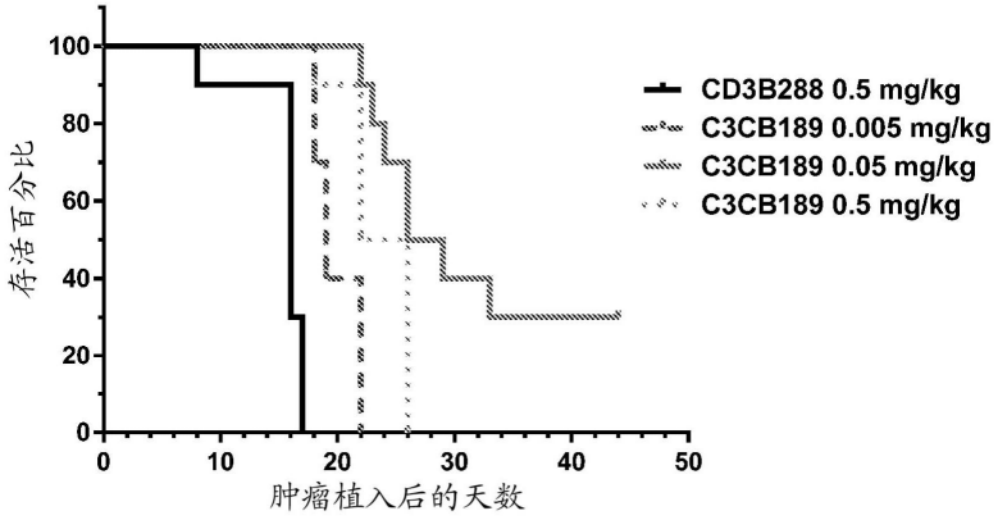

存活百分比
100
80
60
40
20
0
0
10
20
30
40
50
肿瘤植入后的天数
CD3B288 0.5 mg/kg
C3CB189 0.005 mg/kg
C3CB189 0.05 mg/kg
C3CB189 0.5 mg/kg

图7

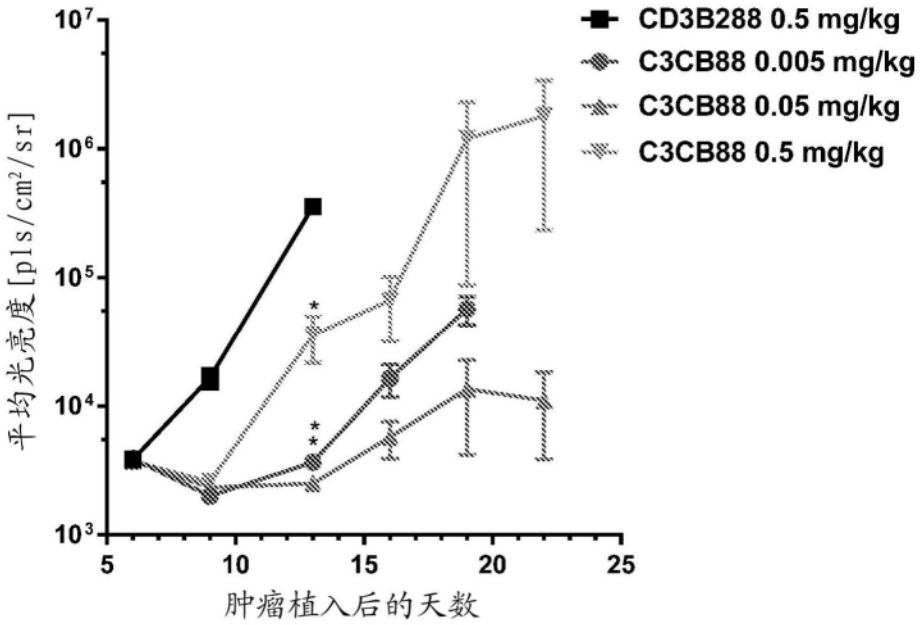

平均光亮度[pls/cm²/sr]
10⁷
10⁶
10⁵
10⁴
10³
5
10
15
20
25
肿瘤植入后的天数
CD3B288 0.5 mg/kg
C3CB88 0.005 mg/kg
C3CB88 0.05 mg/kg
C3CB88 0.5 mg/kg
*
**

图8

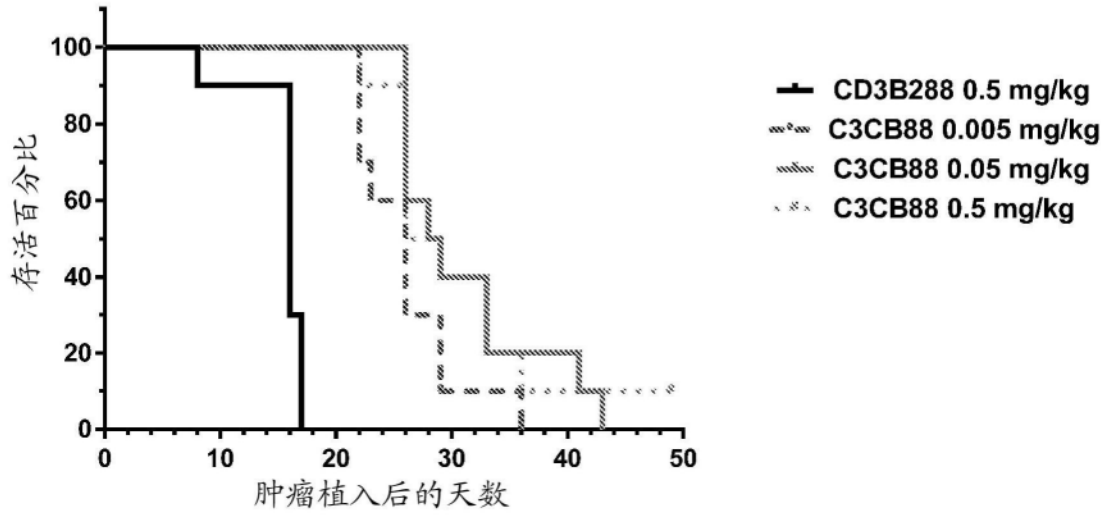

100
80
60
40
20
0
存活百分比
0
10
20
30
40
50
肿瘤植入后的天数
CD3B288 0.5 mg/kg
C3CB88 0.005 mg/kg
C3CB88 0.05 mg/kg
C3CB88 0.5 mg/kg

图9

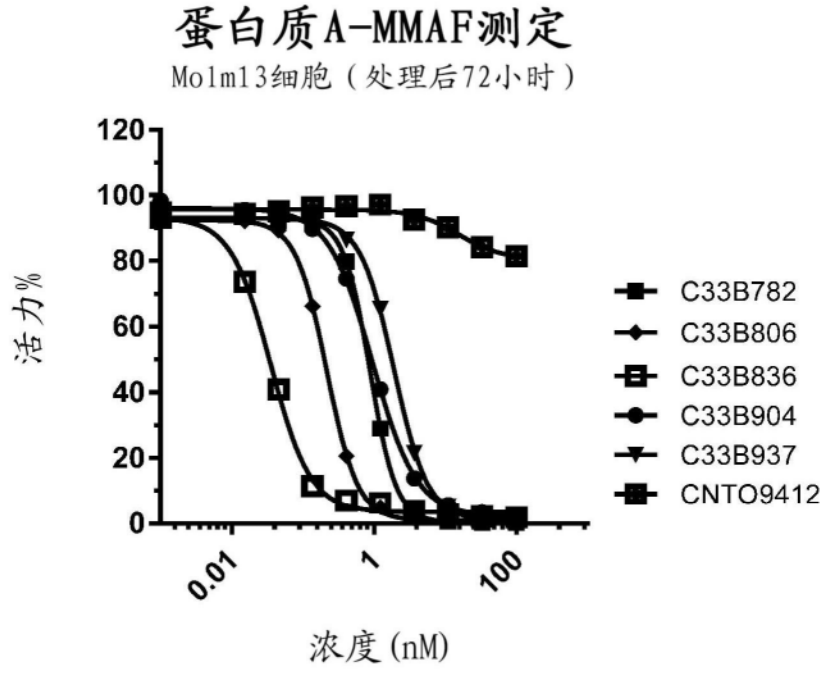

蛋白质A-MMAF测定
Molm13细胞（处理后72小时）
120
100
80
60
40
20
0
活力%
0.01
1
100
浓度(nM)
C33B782
C33B806
C33B836
C33B904
C33B937
CNTO9412

图10

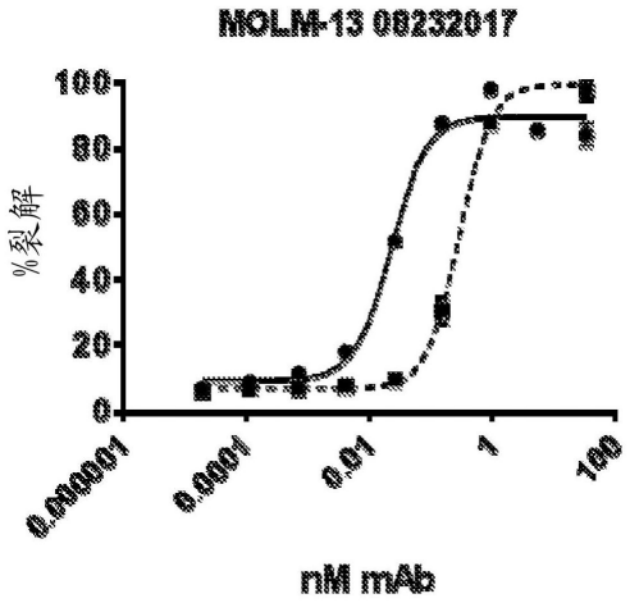

MOLM-13 08232017
%裂解
100
80
60
40
20
0
0.000001
0.0001
0.01
1
100
nM mAb

图11A

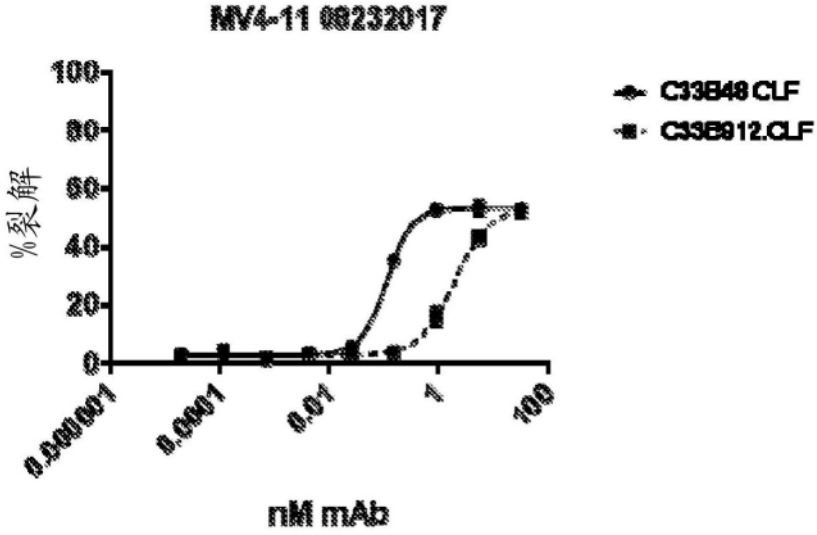

MV4-11 08232017
C33B48.CLF
C33B912.CLF
%裂解
100
80
60
40
20
0
0.000001
0.0001
0.01
1
100
nM mAb

图11B

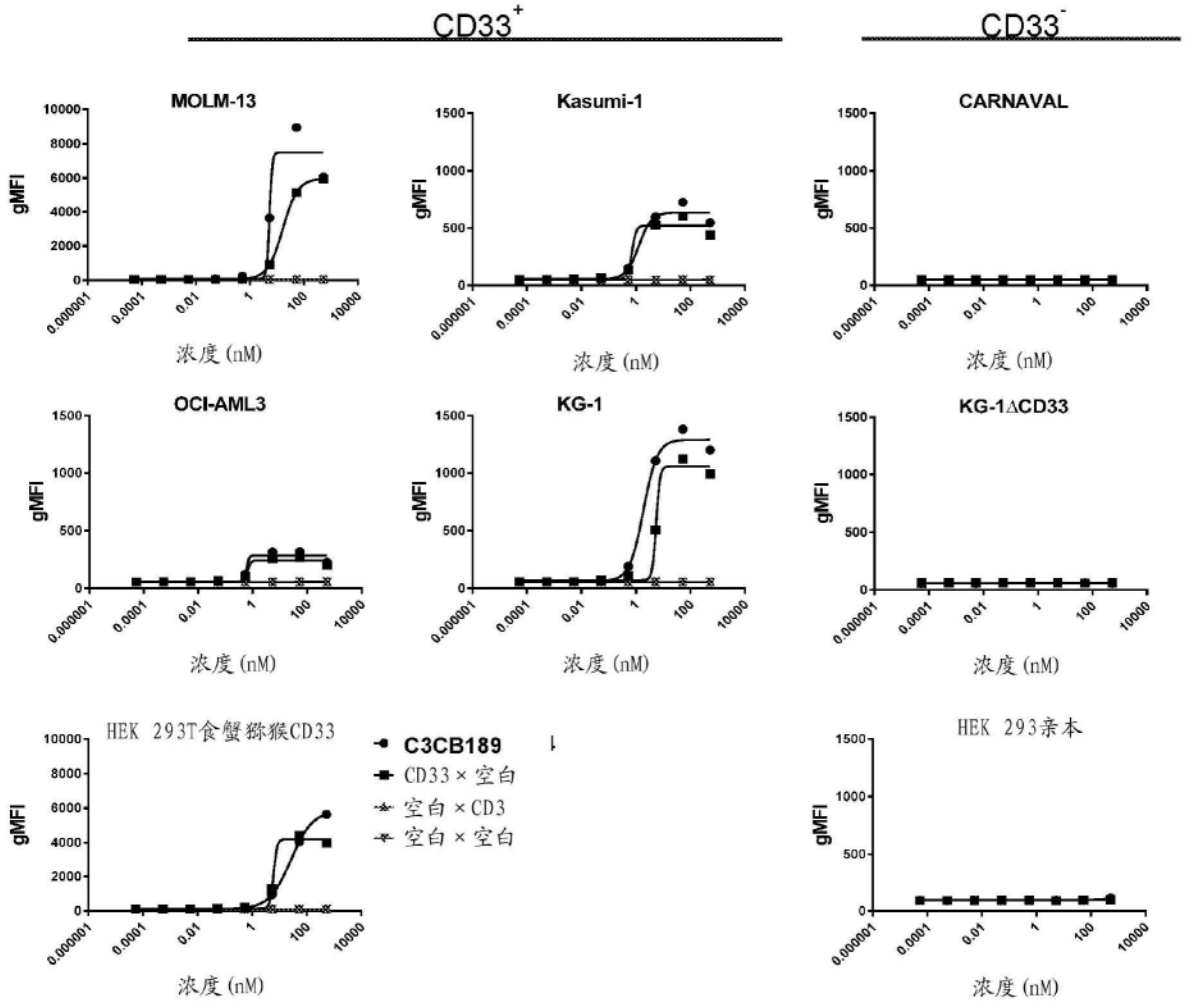

CD33+
CD33-
MOLM-13
Kasumi-1
CARNAVAL
OCI-AML3
KG-1
KG-1ΔCD33
HEK 293T食蟹猕猴CD33
HEK 293亲本
gMFI
浓度(nM)
C3CB189
CD33×空白
空白×CD3
空白×空白

图12

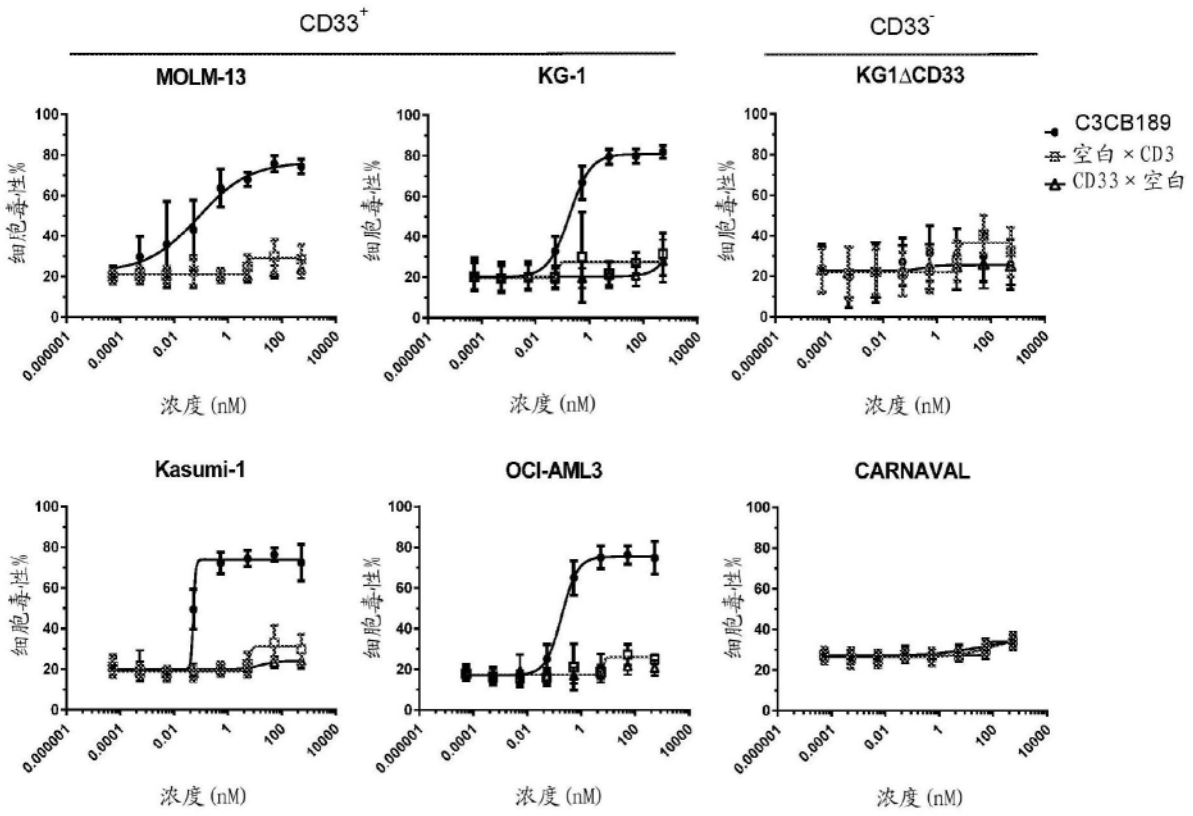

CD33+
CD33-
MOLM-13
KG-1
KG1ΔCD33
C3CB189
空白×CD3
CD33×空白
细胞毒性%
浓度(nM)
Kasumi-1
OCI-AML3
CARNAVAL

图13

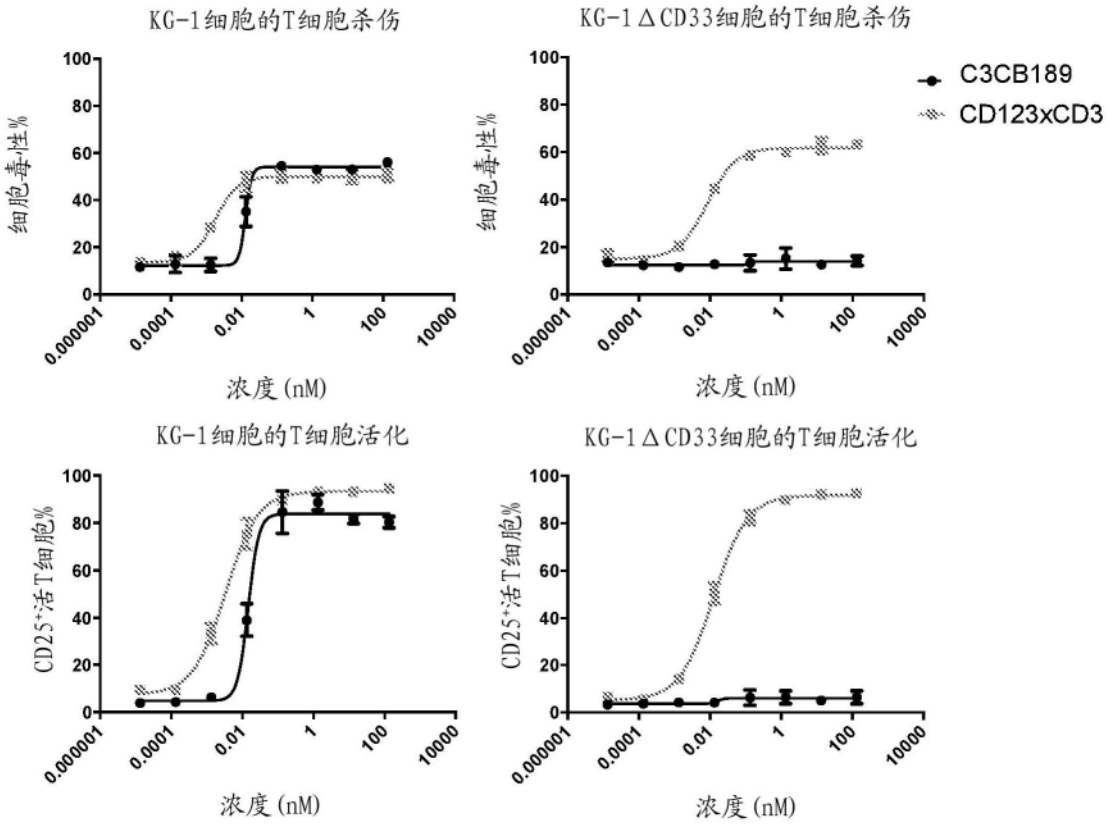

KG-1细胞的T细胞杀伤
KG-1ΔCD33细胞的T细胞杀伤
C3CB189
CD123xCD3
细胞毒性%
浓度(nM)
KG-1细胞的T细胞活化
KG-1ΔCD33细胞的T细胞活化
CD25+活T细胞%
浓度(nM)

图14A

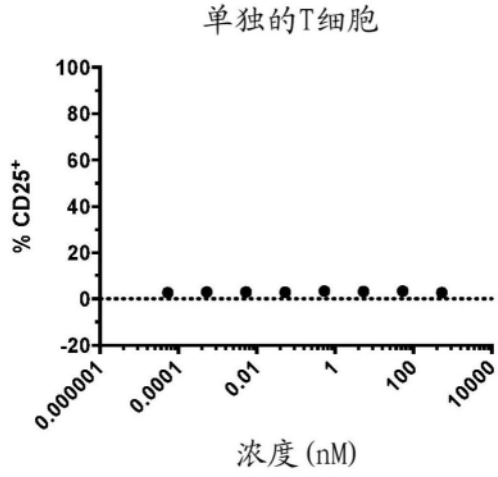

单独的T细胞
% CD25+
浓度(nM)

图14B

有效浓度 (nM)	MOLM-13	KG-1	Kasumi-1	OCI-AML3
EC_{25}	0.0283	0.0525	0.0366	0.0844
EC_{50}	0.1307	0.1677	0.0500	0.1826
EC_{90}	2.2865	1.6978	0.0842	0.6220

图15A

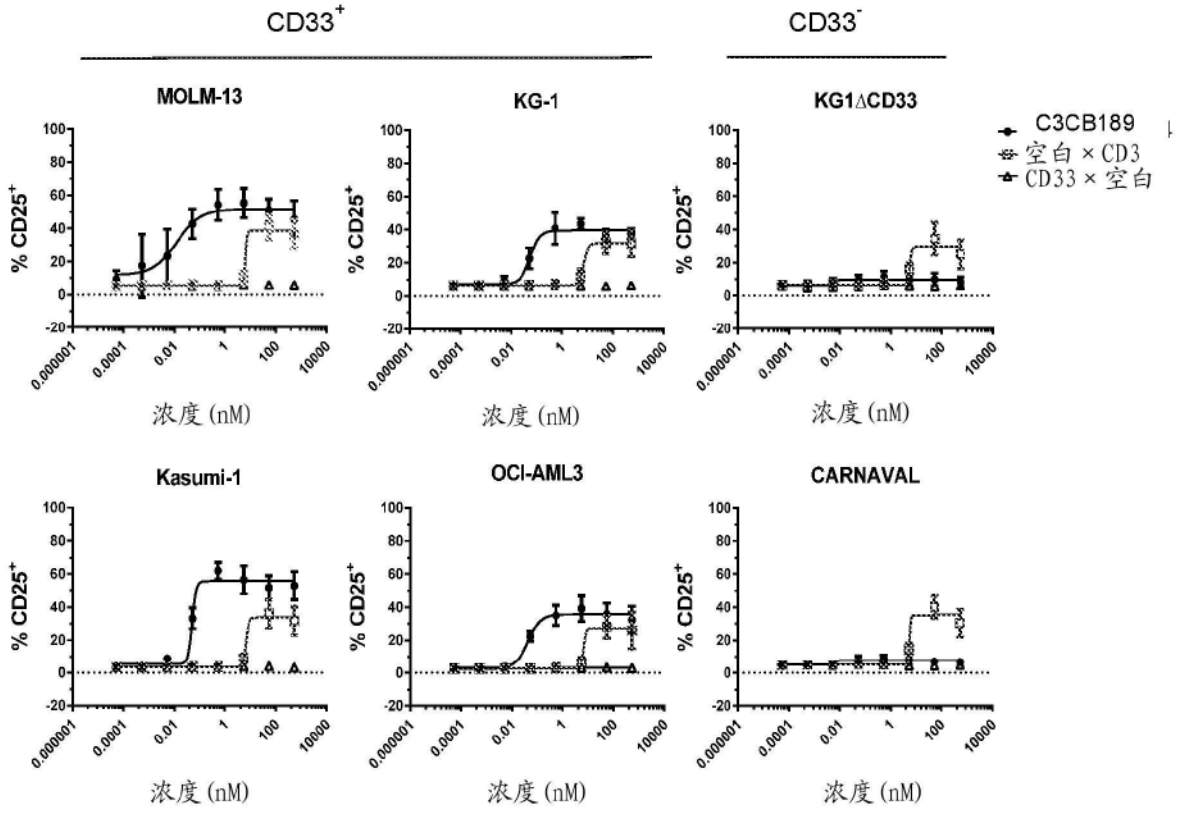


图15B

有效浓度 (nM)	MOLM-13	KG-1	Kasumi-1	OCI-AML3
EC_{25}	0.0077	0.0256	0.0267	0.0178
EC_{50}	0.0283	0.0664	0.0432	0.0500
EC_{90}	0.1677	0.4236	0.1126	0.2585

图15C

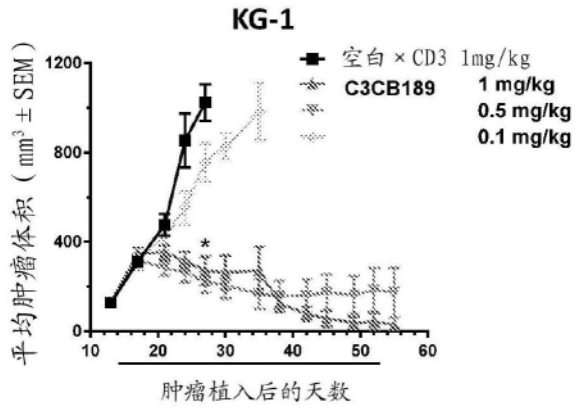


图16A

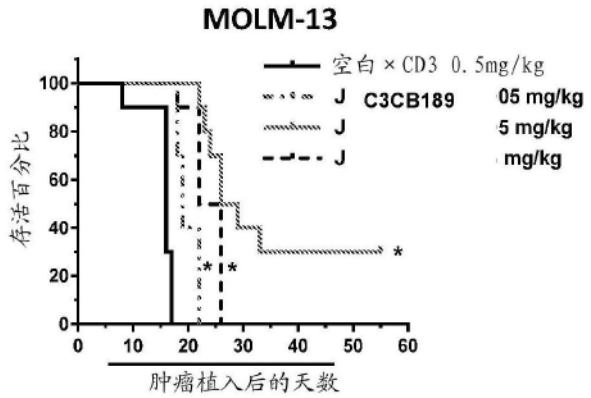


图16B

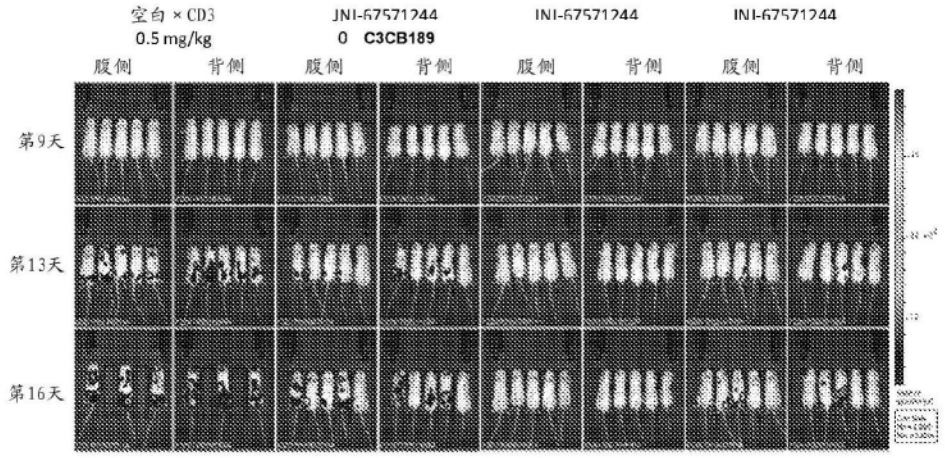


图16C

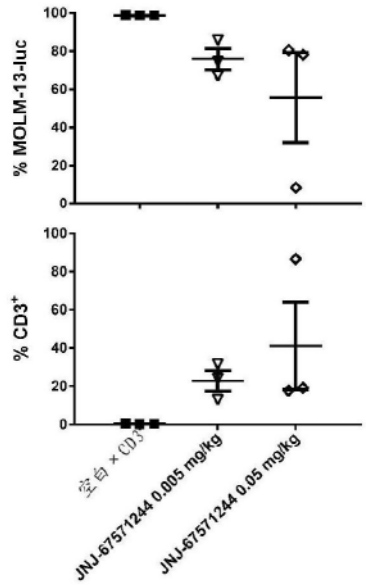

% MOLM-13-luc
100
80
60
40
20
0
% CD3+
100
80
60
40
20
0
空白 × CD3
JNJ-67571244 0.005 mg/kg
JNJ-67571244 0.05 mg/kg

图16D

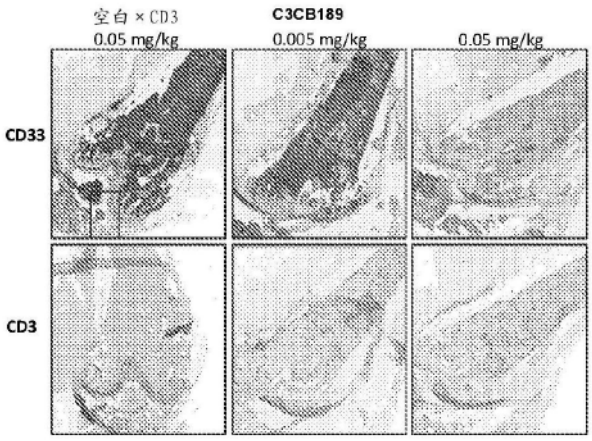

空白 × CD3
0.05 mg/kg
C3CB189
0.005 mg/kg
0.05 mg/kg
CD33
CD3

图16E

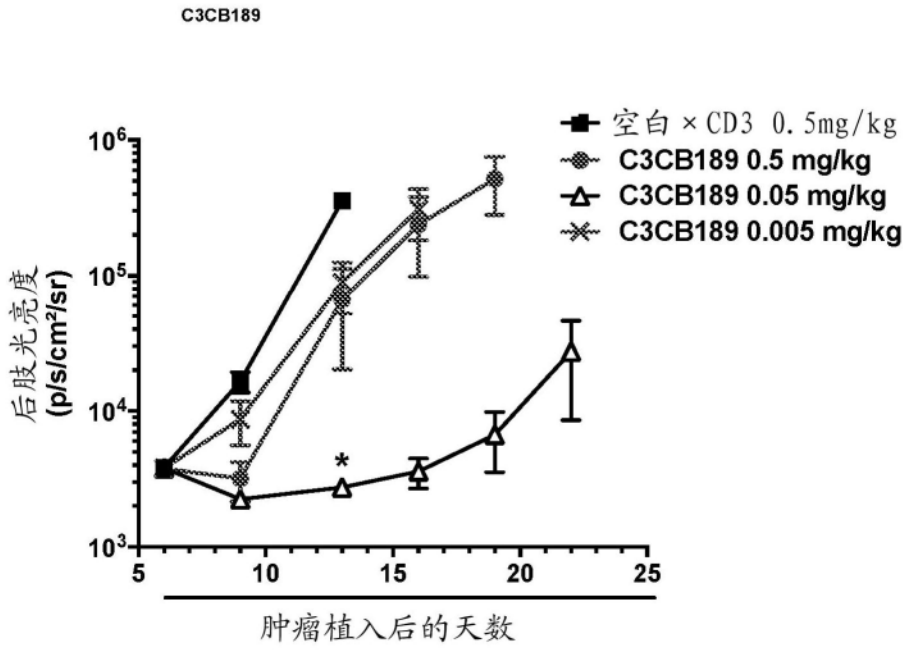

C3CB189
空白 × CD3 0.5mg/kg
C3CB189 0.5 mg/kg
C3CB189 0.05 mg/kg
C3CB189 0.005 mg/kg
后肢光亮度
(p/s/cm²/sr)
10⁶
10⁵
10⁴
10³
5
10
15
20
25
*
肿瘤植入后的天数

图17

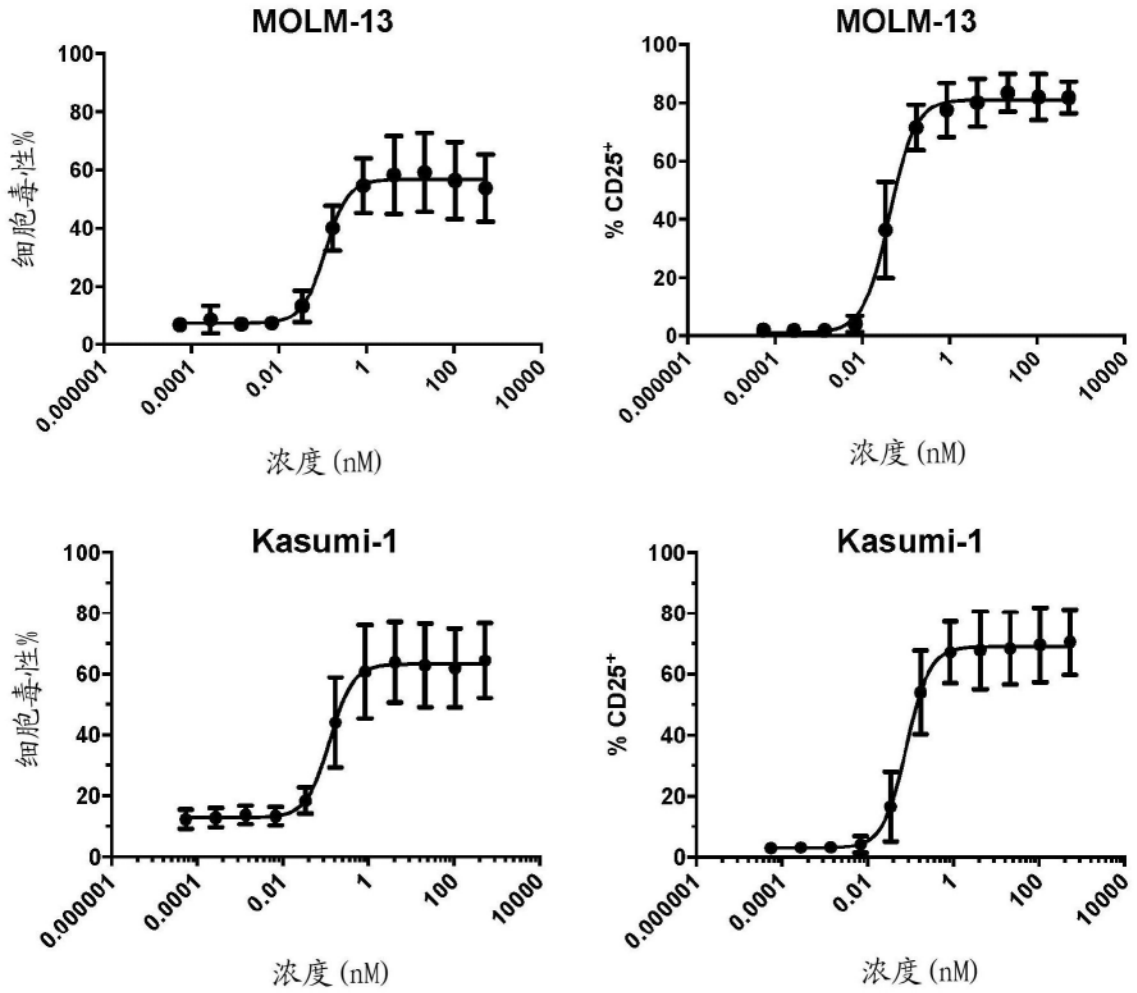


图18A

有效浓度 (nM)	中值细胞毒性: MOLM-13	中值T细胞活化: MOLM-13	中值细胞毒性: Kasumi-1	中值T细胞活化: Kasumi-1
EC_{20}	0.017	0.054	0.039	0.060
EC_{50}	0.037	0.111	0.085	0.124
EC_{90}	0.132	0.420	0.281	0.496

图18B

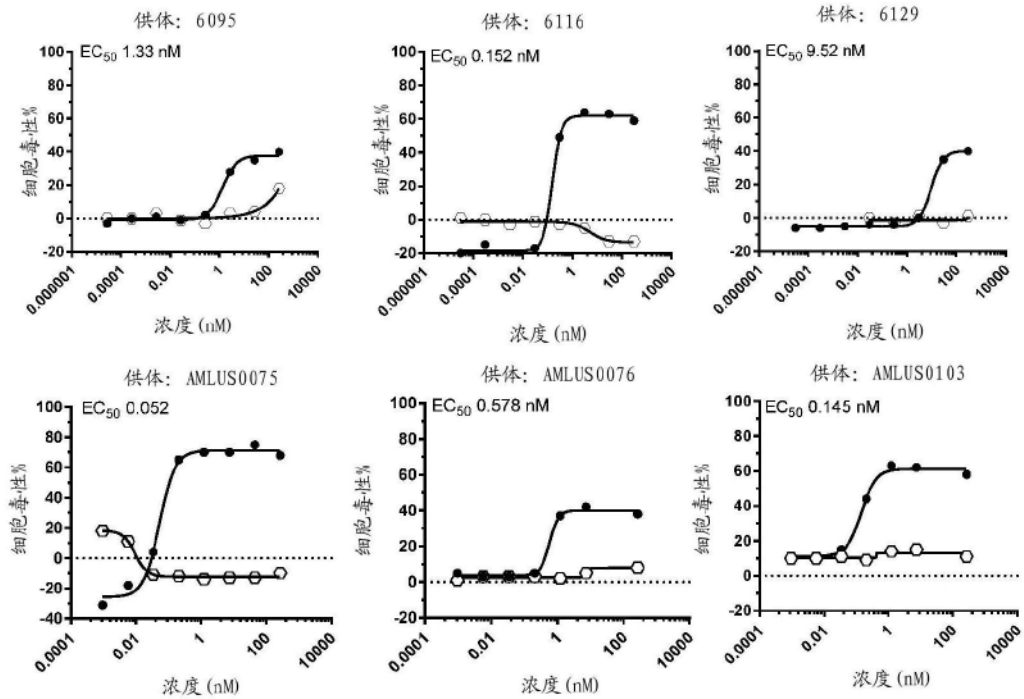

供体：6095
EC50 1.33 nM
供体：6116
EC50 0.152 nM
供体：6129
EC50 9.52 nM
供体：AMLUS0075
EC50 0.052
供体：AMLUS0076
EC50 0.578 nM
供体：AMLUS0103
EC50 0.145 nM
细胞毒性%
浓度(nM)

图19A

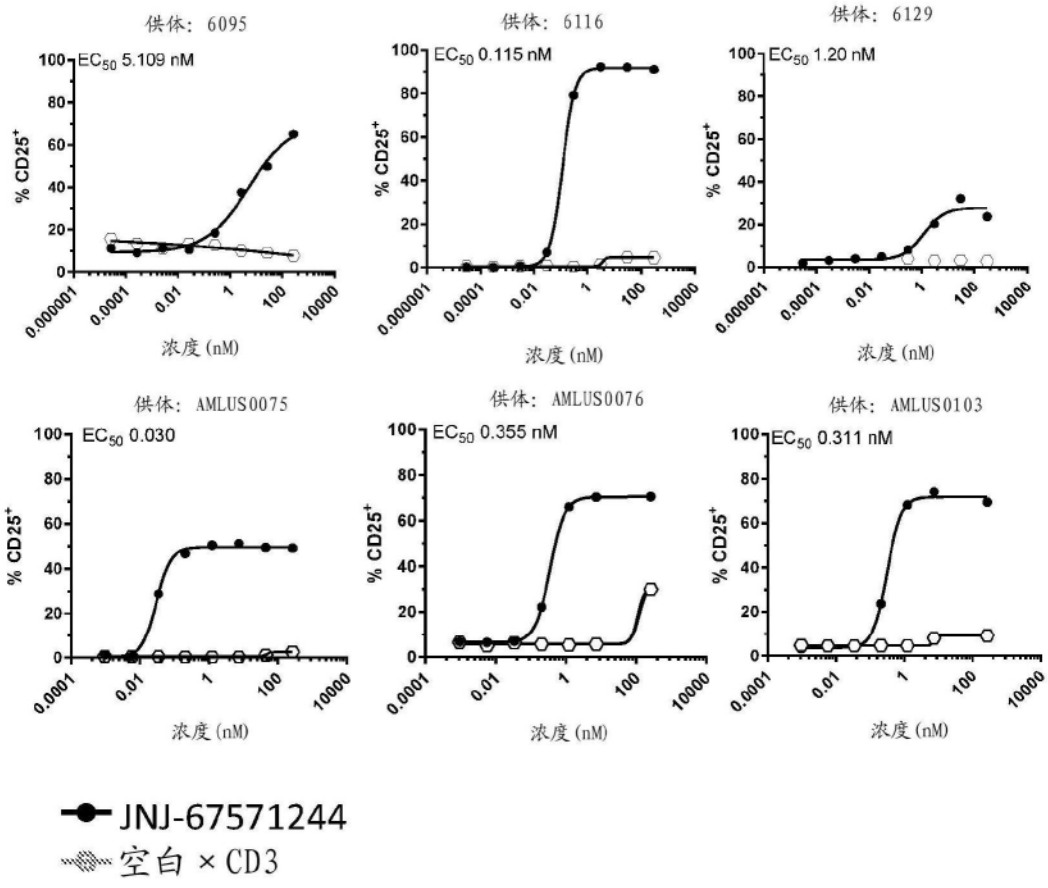

供体：6095
EC50 5.109 nM
供体：6116
EC50 0.115 nM
供体：6129
EC50 1.20 nM
供体：AMLUS0075
EC50 0.030
供体：AMLUS0076
EC50 0.355 nM
供体：AMLUS0103
EC50 0.311 nM
% CD25+
浓度(nM)
JNJ-67571244
空白 × CD3

图19B

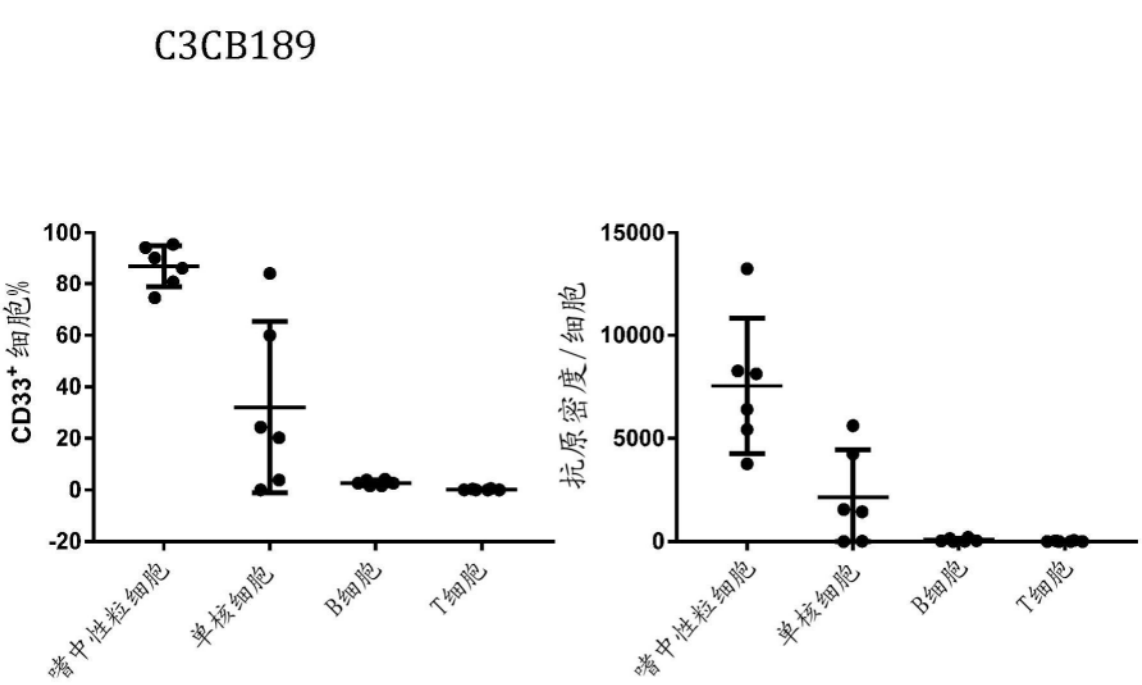

C3CB189
CD33+细胞%
抗原密度/细胞
嗜中性粒细胞
单核细胞
B细胞
T细胞

图20

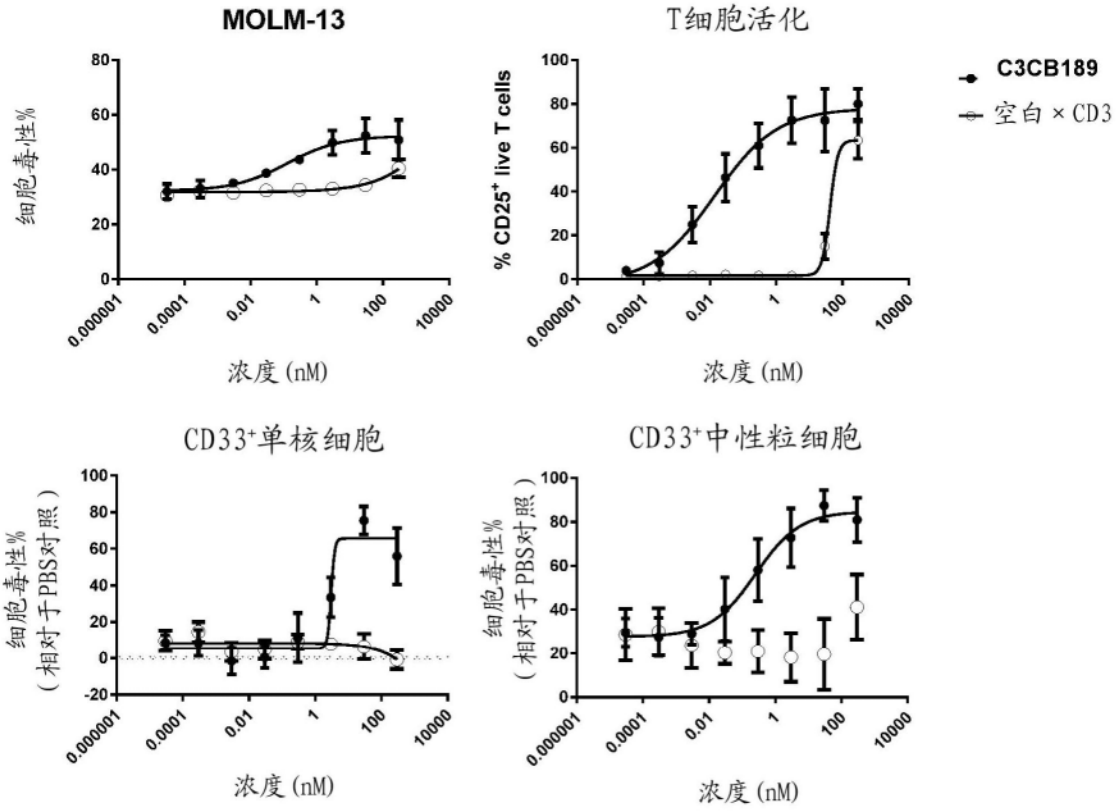

MOLM-13
T细胞活化
C3CB189
空白×CD3
细胞毒性%
% CD25+ live T cells
浓度(nM)
CD33+单核细胞
CD33+中性粒细胞
细胞毒性%（相对于PBS对照）

图21

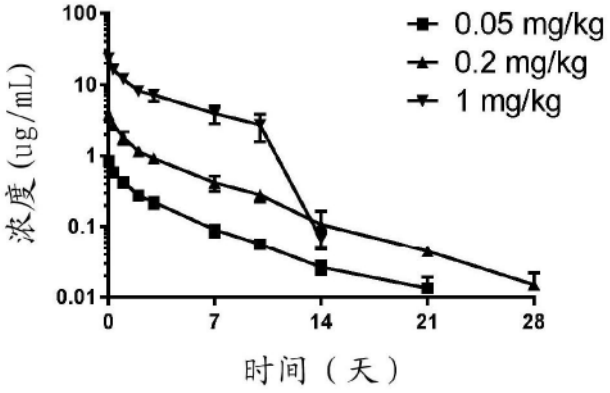


图22A

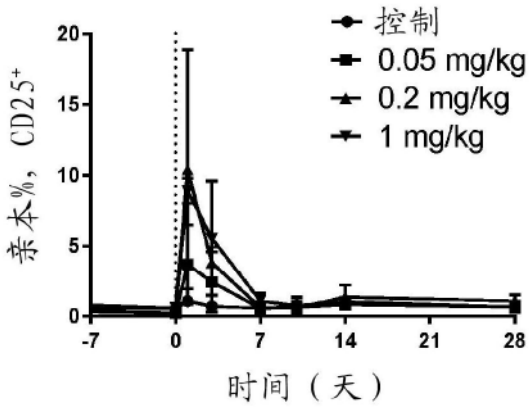


图22B

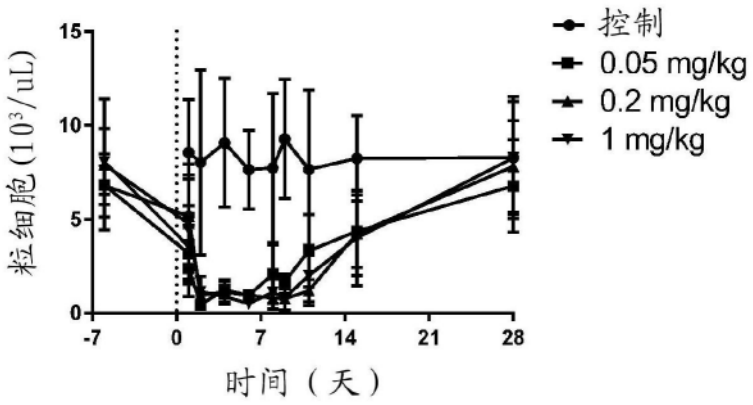


图22C

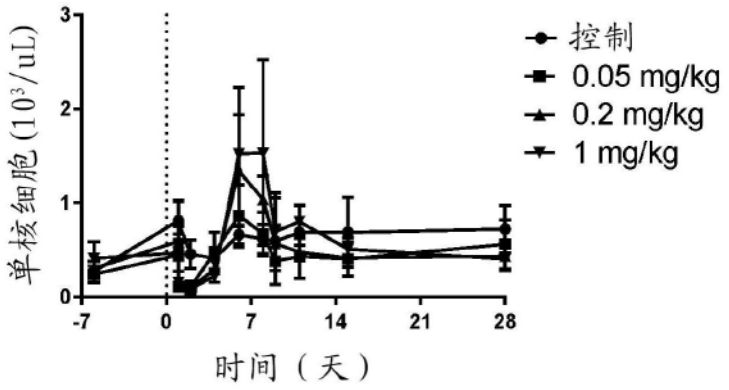


图22D

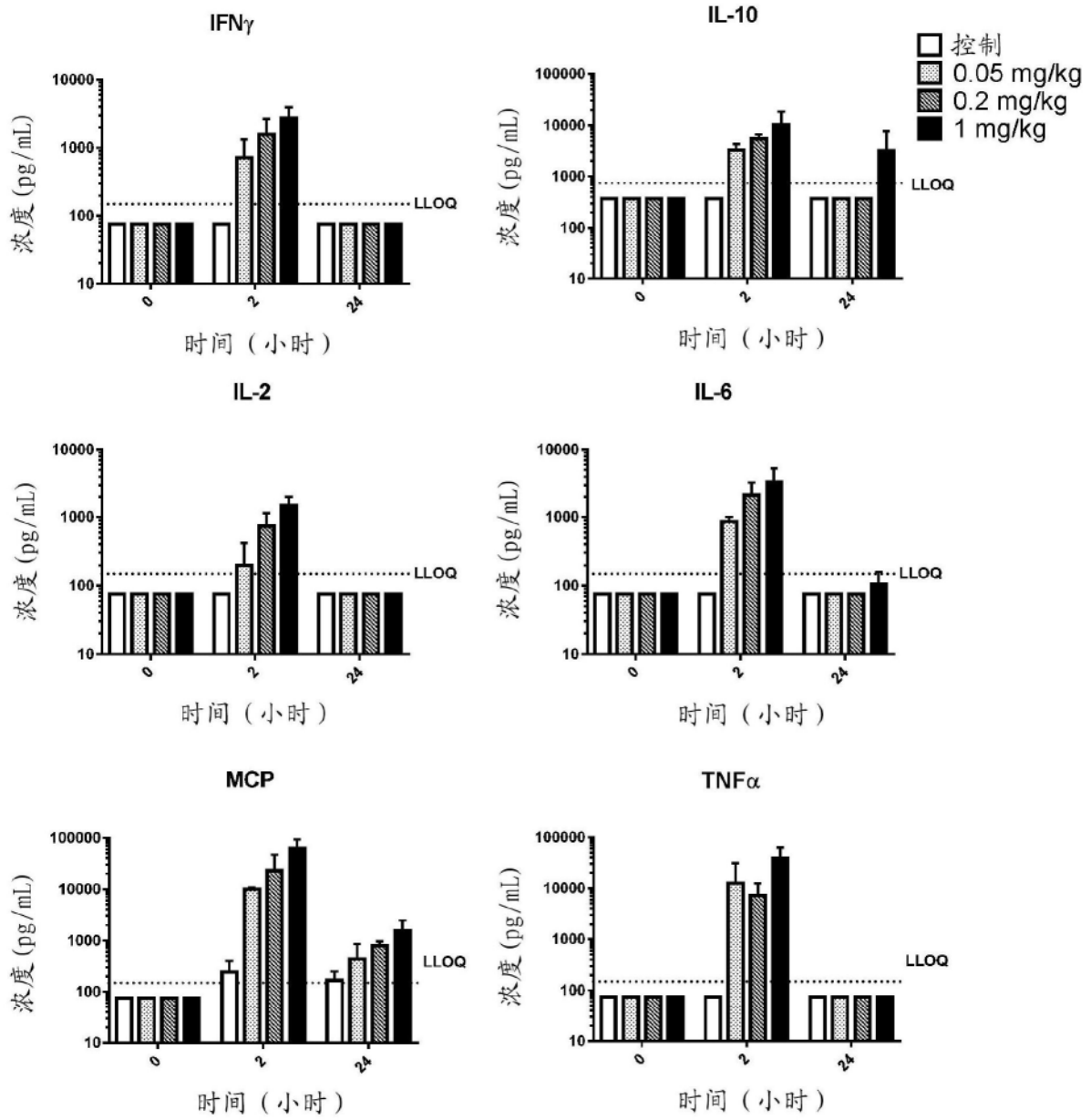

IFNγ
IL-10
IL-2
IL-6
MCP
TNFα
浓度 (pg/mL)
时间（小时）
LLOQ
控制
0.05 mg/kg
0.2 mg/kg
1 mg/kg

图23

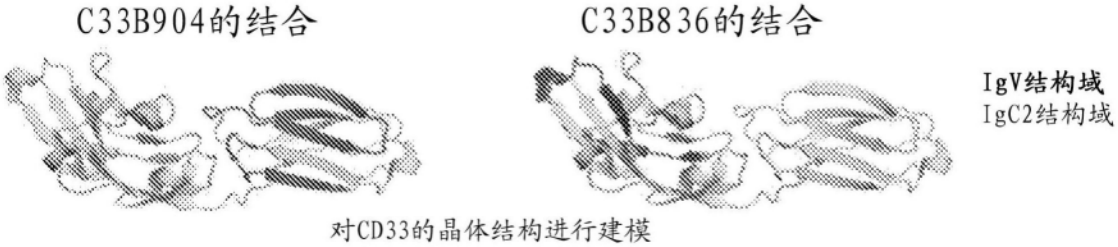

C33B904的结合
C33B836的结合
IgV结构域
IgC2结构域
对CD33的晶体结构进行建模

图24A

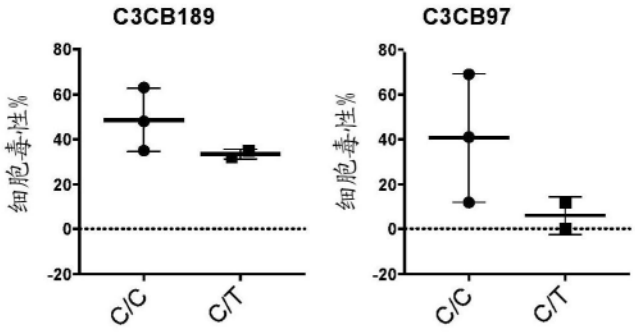


图24B

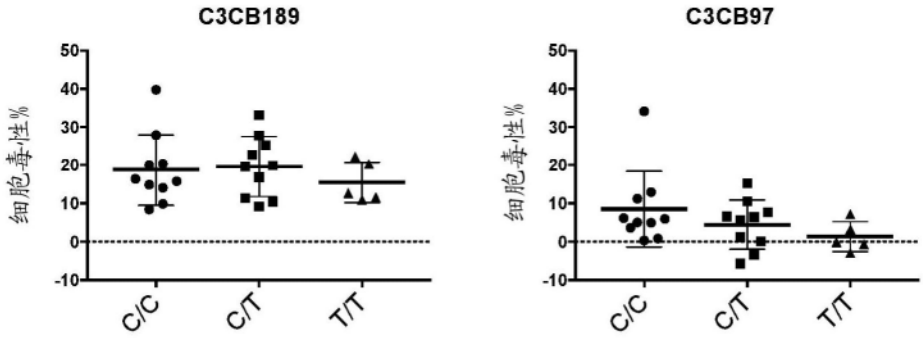


图24C

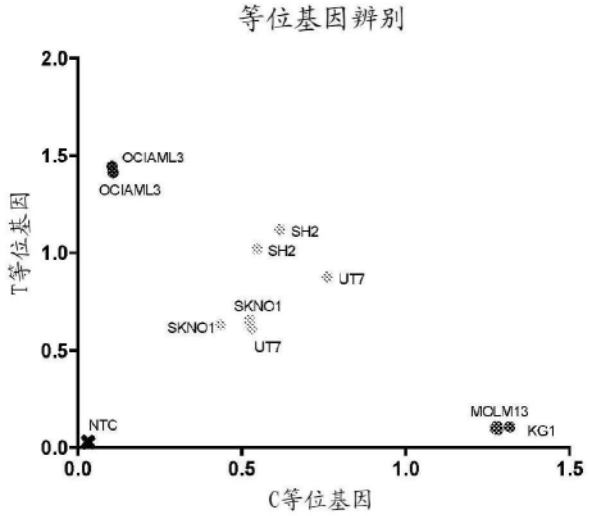


图25A

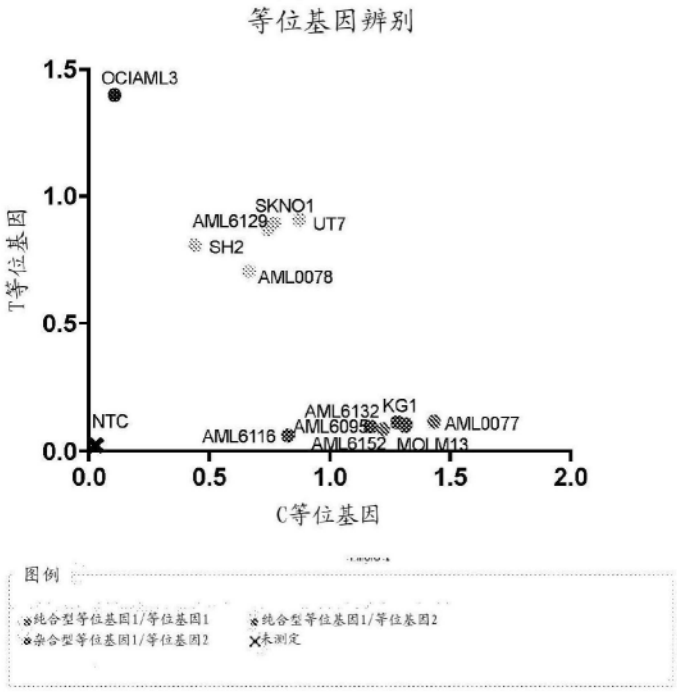

等位基因辨别
1.5
1.0
0.5
0.0
T等位基因
OCIAML3
SKNO1
AML6129
UT7
SH2
AML0078
NTC
AML6132
KG1
AML6095
AML0077
AML6116
AML6152
MOLM13
0.0
0.5
1.0
1.5
2.0
C等位基因
图例
纯合型等位基因1/等位基因1
纯合型等位基因1/等位基因2
杂合型等位基因1/等位基因2
未测定

图25B

样本ID	Rs12459419（taqman法）	Rs12459419（sanger法）
D1	C/C	C|C
D2	C/T	C|T
D3	T/T	T|T
D4	C/C	C|C
D5	C/C	C|C
D6	C/C	C|C
D7	C/T	C|T
D8	T/T	T|T
D9	C/C	C|C
D11	C/T	C|T
D12	C/T	C|T
D13	C/T	C|T
D14	C/T	C|T
D17	C/T	C|T
D18	C/C	C|C
D20	T/T	T|T
D21	C/T	C|T
D22	T/T	T|T
D23	C/C	C|C
D24	C/T	C|T
D25	C/C	C|C
D26	C/C	C|C
D28	T/T	T|T
D29	C/T	C|T
D30	C/C	C|C
总计:	C|C; 10	C|C ;10
	C|T; 10	C|T; 10
	T|T; 5	T|T; 5

图25C