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US 2013058962 A1,2013.03.07
Yang ZY等.A Novel Multivalent, Single-Domain Antibody Targeting TcdA and TcdB Prevents Fulminant Clostridium difficile Infection in Mice.《JOURNAL OF INFECTIOUS DISEASES》.2014,第210卷(第6期),第964-972页. (续)

审查员 润顺琪

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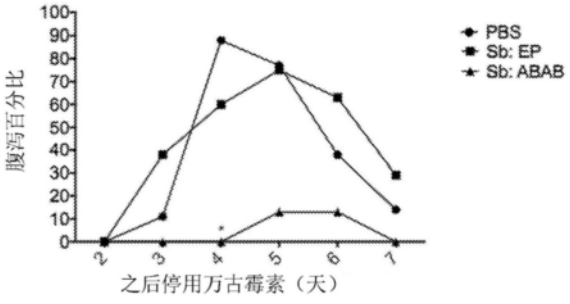
(54)发明名称

针对艰难梭菌感染的基于酵母的免疫疗法

(57)摘要

描述了衍生自人类和骆驼科动物免疫球蛋白的基于抗体的结合剂,以及工程化以分泌结合剂的酵母菌株,以及使用工程化酵母菌株治疗和预防艰难梭菌感染的方法。这些结合剂识别并特异性结合艰难梭菌毒素A和/或毒素B,并且在一些情况下显示出毒素中和活性。结合剂包括骆驼科V_HH肽单体、V_HH肽单体的连接基团、连接到抗体Fc结构域的VHH肽单体和连接到IgG抗体的V_HH肽单体。



CN 108495685 B

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(56)对比文件

Diane J Schmidt等.A Tetraspecific VHH-Based Neutralizing Antibody Modifies Disease Outcome in Three Animal Models of Clostridium difficile Infection.《Clin Vaccine Immunol》.2016,第23卷(第9期),第774-784页.

Yang ZY等.A Novel Multivalent, Single-Domain Antibody Targeting TcdA and TcdB Prevents Fulminant Clostridium difficile Infection in Mice.《JOURNAL OF INFECTIOUS DISEASES》.2014,第210卷(第6期),第964-972页.

Spiess C等.Alternative molecular formats and therapeutic applications for bispecific antibodies.《MOLECULAR IMMUNOLOGY》.2015,第67卷(第2期),第95-106页.

Liu JL等.Single domain antibody-alkaline phosphatase fusion proteins for antigen detection - Analysis of affinity and thermal stability of single domain antibody.《JOURNAL OF IMMUNOLOGICAL METHODS》.2013,第393卷(第1-2期),第1-7页.

冯汉平.多特异性单结构域抗体治疗艰难梭状芽孢杆菌感染.《抗体研发与人类健康——2013第五届国际抗体大会论文集》.2013,第186页.

VONHEIJNE G等.SPECIES-SPECIFIC VARIATION IN SIGNAL PEPTIDE DESIGN - IMPLICATIONS FOR PROTEIN SECRETION IN FOREIGN HOSTS.《FEBS LETTERS》.1989,第244卷(第2期),第439-446页.

1.一种布拉酵母工程菌株,其包含产生四特异性四聚体ABAB结合剂的基因,所述基因整合到至少两个染色体位点,所述ABAB结合剂的氨基酸序列由SEQ ID NO:109组成,其中所述ABAB结合剂包括连接的第一、第二、第三和第四V_HH肽单体,并且其中所述V_HH肽各自单体独立地对艰难梭菌毒素A(TcdA)或毒素B(TcdB)的表位具有结合特异性。

2.根据权利要求1所述的布拉酵母工程菌株,其中所述第一、第二、第三和第四V_HH肽单体各自具有针对不同表位的结合特异性。

3.根据权利要求1所述的布拉酵母工程菌株,其中两个V_HH肽单体对TcdA的表位具有结合特异性,并且两个V_HH肽单体对TcdB的表位具有结合特异性。

4.根据权利要求1所述的布拉酵母工程菌株,其中所述V_HH肽单体各自独立地对TcdA或TcdB的葡糖基转移酶结构域、半胱氨酸蛋白酶结构域、易位结构域或受体结合结构域中的表位具有结合特异性。

5.根据权利要求1所述的布拉酵母工程菌株,其中所述第一和第三单体对TcdA的表位具有结合特异性,并且所述第一和第三单体分别是SEQ ID NO:7所示的V_HH肽单体AH3和SEQ ID NO:5所示的AA6,以及

所述第二和第四单体对TcdB表位具有结合特异性,并且所述第二和第四单体分别是SEQ ID NO:1所示的V_HH肽单体5D和SEQ ID NO:3所示的E3。

6.一种药物制剂,其包含权利要求1-5中任一项所述的布拉酵母工程菌株和药学上可接受的载剂或稀释剂。

7.一种制备权利要求1-5中任一项所述的布拉酵母工程菌株的方法,包括(a)用编码所述ABAB结合剂的表达载体转化布拉酵母菌株,和(b)筛选(a)的酵母以产生所述ABAB结合剂。

8.根据权利要求7所述的方法,其中所述表达载体是SEQ ID NO:88所示的质粒pCEV-URA3-TEF-AT-yABAB-cMyc。

9.一种制备权利要求5所述的布拉酵母工程菌株的方法,包括(a)将编码所述ABAB结合剂的多核苷酸序列染色体整合到布拉酵母菌株的基因组中,和(b)筛选(a)的酵母以产生所述ABAB结合剂。

10.根据权利要求9所述的方法,其中使用免疫测定进行所述筛选。

11.根据权利要求9所述的方法,其中通过以下方法进行染色体整合:

a)使用引物从质粒SEQ ID NO:90所示的pCEV-G4-Km-TEF-AT-yABAB hAA6T83N-tagless扩增编码ABAB结合剂的多核苷酸序列以产生整合盒,所述引物含有(i)与选择的酵母染色体整合位点同源的核酸序列和(ii)与所述质粒的ABAB结合剂编码序列的5'和3'区域同源的核酸序列,

(b)在促进所述整合盒自发整合到双链断裂位点的条件下,将(a)中产生的所述整合盒用SEQ ID NO:91所示的pCRI-Sb-δ1或SEQ ID NO:92所示的pCRI-Sb-δ2转化酵母以诱导相应酵母染色体δ位点内的双链断裂,

(c)筛选(b)中的转化酵母以产生ABAB结合剂。

12.根据权利要求11所述的方法,其中使用免疫测定进行所述筛选。

13.治疗有效量的一种或多种根据权利要求1-5中任一项所述的布拉酵母工程菌株在制备用于治疗或预防受试者中由艰难梭菌诱发的疾病症状的药物中的用途。

14.根据权利要求13所述的用途,其中由艰难梭菌诱发的所述疾病症状是腹泻。

15.治疗有效量的一种或多种根据权利要求1-5中任一项所述的布拉酵母工程菌株在制备用于在艰难梭菌感染的受试者中中和艰难梭菌毒素TcdA和/或TcdB的药物中的用途。

16.根据权利要求15所述的用途,其中所述中和是部分或完全中和。

17.治疗有效量的一种或多种根据权利要求1-5中任一项所述的布拉酵母工程菌株在制备用于在受试者中治疗或预防艰难梭菌感染的药物中的用途。

18.根据权利要求17所述的用途,还包括向所述受试者施用治疗有效量的抗生素。

19.治疗有效量的一种或多种根据权利要求1-5中任一项所述的布拉酵母工程菌株在制备用于在患有艰难梭菌感染的受试者中维持正常肠功能的药物中的用途。

20.根据权利要求13、15、17或19所述的用途,其中所述布拉酵母工程菌株处于包括所述布拉酵母工程菌株和药学上可接受的载剂或稀释剂的药物制剂中。

21.根据权利要求13、15、17或19所述的用途,其中所述布拉酵母工程菌株的治疗有效量在所述每个受试者体重的10ug/kg和100mg/kg之间。

22.根据权利要求13、15、17或19所述的用途,其中所述布拉酵母工程菌株经口、鼻或直肠给予所述受试者。

23.一种布拉酵母工程菌株,其包含产生V_HH肽ABAB结合剂的基因,所述基因整合到至少两个染色体位点,所述V_HH肽ABAB结合剂的氨基酸序列由SEQ ID NO:109组成,其中所述V_HH肽ABAB结合剂包括至少一个V_HH肽单体,其中每个V_HH肽单体独立地对艰难梭菌毒素A(TcdA)或毒素B(TcdB)的独特表位具有结合特异性。

24.根据权利要求23所述的布拉酵母工程菌株,其中所述V_HH肽ABAB结合剂包括两个连接的V_HH肽单体。

25.根据权利要求23所述的布拉酵母工程菌株,其中所述V_HH肽ABAB结合剂包括三个连接的V_HH肽单体。

26.根据权利要求23所述的布拉酵母工程菌株,其中所述V_HH肽ABAB结合剂包括四个连接的V_HH肽单体。

27.根据权利要求26所述的布拉酵母工程菌株,其中两个所述V_HH肽单体对TcdA的表位具有结合特异性,并且两个所述V_HH肽单体对TcdB的表位具有结合特异性。

28.根据权利要求23-27中任一项所述的布拉酵母工程菌株,其中所述V_HH肽单体选自由SEQ ID NO:1所示的5D、SEQ ID NO:3所示的E3、SEQ ID NO:5所示的AA6和SEQ ID NO:7所示的AH3V_HH肽单体组成的组。

29.根据权利要求24-27中任一项所述的布拉酵母工程菌株,其中所述V_HH肽单体使用选自SEQ ID NO:9所示的接头-1、SEQ ID NO:11所示的接头-2和SEQ ID NO:13所示的接头-3的接头连接。

30.治疗有效量的一种或多种根据权利要求23-29中任一项所述的布拉酵母工程菌株在制备用于治疗或预防受试者中由艰难梭菌诱发的疾病症状的药物中的用途。

31.根据权利要求30所述的用途,其中由艰难梭菌诱发的所述疾病症状是腹泻。

32.治疗有效量的一种或多种根据权利要求23-29中任一项所述的布拉酵母工程菌株在制备用于在艰难梭菌感染的受试者中中和艰难梭菌毒素TcdA和/或TcdB的药物中的用途。

33.根据权利要求32所述的用途，其中所述中和是部分或完全中和。

34.治疗有效量的一种或多种根据权利要求23-29中任一项所述的布拉酵母工程菌株在制备用于在受试者中治疗或预防艰难梭菌感染的药物中的用途。

35.根据权利要求34所述的用途，还包括向所述受试者施用治疗有效量的抗生素。

36.治疗有效量的一种或多种根据权利要求23-29中任一项所述的布拉酵母工程菌株在制备用于在患有艰难梭菌感染的受试者中维持正常肠功能的药物中的用途。

37.根据权利要求30、32、34或36所述的用途，其中所述布拉酵母工程菌株处于包括所述布拉酵母工程菌株和药学上可接受的载剂或稀释剂的药物制剂中。

38.根据权利要求30、32、34或36所述的用途，其中所述布拉酵母工程菌株的治疗有效量在所述每个受试者体重的10ug/kg和100mg/kg之间。

39.根据权利要求30、32、34或36所述的用途，其中所述布拉酵母工程菌株经口、鼻或直肠给予所述受试者。

40.一种布拉酵母工程菌株，其包含产生对艰难梭菌毒素A(TcdA)或毒素B(TcdB)或两者的独特表位具有结合特异性的治疗性ABAB蛋白质的基因，所述基因整合到至少两个染色体位点，所述治疗性ABAB蛋白质的氨基酸序列由SEQ ID NO:109组成。

41.根据权利要求40所述的布拉酵母工程菌株，其中所述治疗性ABAB蛋白质是抗体。

42.根据权利要求40所述的布拉酵母工程菌株，其中通过(a)用编码所述治疗性ABAB蛋白质的表达载体转化布拉酵母菌株，和(b)筛选(a)的酵母以产生所述治疗性ABAB蛋白质来工程化所述布拉酵母菌株。

43.根据权利要求40所述的布拉酵母工程菌株，其中通过(a)将编码所述治疗性ABAB蛋白质的多核苷酸序列染色体整合到所述布拉酵母菌株基因组中，和(b)筛选(a)的酵母以产生所述治疗性ABAB蛋白质来工程化所述布拉酵母菌株。

44.根据权利要求43所述的布拉酵母工程菌株，其中使用免疫测定进行所述筛选。

45.治疗有效量的根据权利要求40所述的布拉酵母工程菌株在制备用于治疗或预防受试者中由艰难梭菌诱发的疾病症状的药物中的用途。

46.根据权利要求45所述的用途，其中由艰难梭菌诱发的所述疾病症状是腹泻。

47.治疗有效量的根据权利要求40所述的布拉酵母工程菌株在制备用于在艰难梭菌感染的受试者中中和艰难梭菌毒素TcdA和/或TcdB的药物中的用途。

48.根据权利要求47所述的用途，其中所述中和是部分或完全中和。

49.治疗有效量的根据权利要求40所述的布拉酵母工程菌株在制备用于在受试者中治疗或预防艰难梭菌感染的药物中的用途。

50.根据权利要求49所述的用途，还包括向所述受试者施用治疗有效量的抗生素。

51.治疗有效量的根据权利要求40所述的布拉酵母工程菌株在制备用于在患有艰难梭菌感染的受试者中维持正常肠功能的药物中的用途。

52.根据权利要求45、47、49或51所述的用途，其中所述布拉酵母工程菌株处于包括所述布拉酵母工程菌株和药学上可接受的载剂或稀释剂的药物制剂中。

53.根据权利要求45、47、49或51所述的用途，其中所述布拉酵母工程菌株的治疗有效量在所述每个受试者体重的10ug/kg和100mg/kg之间。

54.根据权利要求45、47、49或51所述的用途，其中所述布拉酵母工程菌株经口、鼻或直

肠给予所述受试者。

针对艰难梭菌感染的基于酵母的免疫疗法

[0001] 联邦政府赞助研究与发展的声明

[0002] 本发明是在国立卫生研究院授予的基金号DK084509和AI109776的政府支持下完成的。政府对本发明享有一定的权利。

[0003] 序列表

[0004] 电子(ASCII文本文件)格式的序列表与本申请一起提交,并且通过引用并入本文。ASCII文件的名称是“2016_1343A_ST25.txt”;该文件于2016年10月13日创建;该文件的大小是407KB。

背景技术

[0005] 细菌艰难梭菌(Clostridium difficile)是医院内抗生素相关性腹泻的最常见原因以及假膜性结肠炎(pseudomembranous colitis)的病原体[1]。据估计,美国每年有超过500,000例艰难梭菌相关性疾病(CDI)发生,取决于菌株,每年的死亡率约为3-17%。随着高毒性和抗生素耐药菌株的出现,CDI患者的死亡率迅速增加[2]。

[0006] CDI主要由两种艰难梭菌外毒素TcdA和TcdB引起(因为TcdA-TcdB-菌株是无毒的)[21,22]。这两种毒素在结构上相似,并且对宿主细胞表现出类似的作用模式。这两种毒素都将宿主Rho GTP酶作为目标,导致它们失活以及细胞骨架破坏。两种毒素在CDI发病机制中的相关作用尚未得到很好的理解,但很明显任一种毒素单独地在动物中可引起CDI[22,23]。

[0007] 治疗CDI患者的选择是有限的,且复发率高(20-35%的患者)。目前使用抗生素治疗CDI的标准治疗会导致微生物群的破坏并导致复发率接近35%[3,13]。尽管已经尝试了其他干预措施(例如益生菌、吸收毒素的聚合物和类毒素疫苗),但预防和治疗策略都没有跟上这种感染的发病率和严重程度的增加。在复发患者中进一步发作CDI的风险可能超过50%[14],并且一部分患者会有多次复发。CDI的复发可能由同一株或新定殖菌株所引起[15-18]。

[0008] 已经表明较新的基于免疫的疗法在临床试验中稍微有效,包括针对严重CDI[4-8]的静脉内免疫球蛋白(IVIG)和针对复发性CDI的人单克隆抗体[9]。非达霉素(Fidaxomicin),一种窄谱大环抗生素,在CDI上显示类似于口服万古霉素的效果,但在降低复发率方面效果更加显著[10]。粪便移植对顽固性和复发性CDI有效,但难以标准化,且与风险相关[11,12]。

[0009] CDI是一种令人沮丧的疾病,难以治疗,可能影响患者数月甚至数年,从而造成巨大的发病率和死亡率[19]。因此,需要针对CDI的新疗法以及用于预防有发展为CDI风险的受试者中的原发性和复发性CDI的手段。

发明内容

[0010] 本文提供选择性结合艰难梭菌毒力因子TcdA和TcdB的基于抗体的融合蛋白结合剂,以及基因工程改造以表达和分泌这些艰难梭菌毒素结合剂的益生酵母酵母属

(Saccharomyces)菌株。酵母和结合剂都显示出治疗和预防受试者中的原发性和复发性CDI的实用性。在宿主肠中分泌结合剂的口服施用酵母属可以减轻进行中的CDI并防止复发。

[0011] 因此,本发明涉及艰难梭菌毒素结合剂,酵母属的菌株,包括但不限于工程化以产生结合剂的布拉酵母(Saccharomyces boulardii),涉及制备酵母的工程菌株的方法,以及使用结合剂和酵母的工程菌株以及其他重要特征来治疗和预防原发性和复发性CDI的方法。

[0012] 结合剂

[0013] 本发明的结合剂包括简单的V_HH肽单体和V_HH肽单体的连接基团(包括2、3、4或更多个单体)以及包括连接至抗体Fc结构域的V_HH肽单体以及连接至部分或完整IgG抗体的V_HH肽单体的更复杂的结合剂。

[0014] 在第一实施例中,本发明涉及包括V_HH肽单体和包括2、3、4或更多个单体的V_HH肽单体的连接基团的结合剂,其中的每一个结合TcdA和/或TcdB,优选具有特异性。因此,本发明涵盖包括至少一个V_HH肽单体的V_HH肽结合剂,其中每个V_HH肽单体对艰难梭菌毒素A(TcdA)或毒素B(TcdB)的表位具有结合特异性。在某些方面,这些结合剂包括2、3、4或更多个连接的V_HH肽单体。V_HH肽单体包括但不限于V_HH肽单体5D(SEQ ID NO:1)、E3(SEQ ID NO:3)、AA6(SEQ ID NO:5)和AH3(SEQ ID NO:7)。

[0015] 在其中两个或更多个单体连接的该实施例的多个方面,单体可以通过柔性肽接头连接,通常包含10-20个氨基酸。合适的接头包括但不限于接头-1(SEQ ID NO:9)、接头-2(SEQ ID NO:11)和接头-3(SEQ ID NO:13)。

[0016] 在该实施例的某些方面,结合剂以特异性结合TcdA和/或TcdB。在该实施例的某些方面,结合剂显示TcdA和/或TcdB中和活性。

[0017] 在该实施例的具体方面,结合剂包含四个连接的V_HH肽单体,其中两个单体对TcdA的表位具有结合特异性,两个单体对TcdB的表位具有结合特异性。TcdA的表位可以相同或不同。TcdB的表位可以相同或不同。

[0018] 在该实施例的具体方面,结合剂包括SEQ ID NO:19所示的氨基酸序列或其与其具有至少95%序列同一性的序列变体,并且其中所述序列变体保留TcdA和/或TcdB的结合特异性,或序列变体保留毒素中和活性,或保留两者。在一些情况下,序列变体的变体氨基酸位于V_HH肽单体的框架区中。

[0019] 在第二实施例中,本发明涉及包括连接至IgG抗体的V_HH肽单体的结合剂,其中所述结合剂结合TcdA和/或TcdB。在这些基于IgG的结合剂中,IgG抗体的轻链和重链的可变区被1、2、3、4个或更多个V_HH肽单体替换。

[0020] 在该实施例的某些方面,这些结合剂包含连接到IgG轻链和重链的氨基末端以代替可变区的2、3、4或更多个连接的V_HH肽单体。V_HH肽单体包括但不限于V_HH肽单体5D(SEQ ID NO:1)、E3(SEQ ID NO:3)、AA6(SEQ ID NO:5)和AH3(SEQ ID NO:7)。

[0021] 在其中两个或更多个单体连接的该实施例的多个方面,单体可以通过柔性肽接头连接,通常包含10-20个氨基酸。合适的接头包括但不限于接头-1(SEQ ID NO:9)、接头-2(SEQ ID NO:11)和接头-3(SEQ ID NO:13)。

[0022] 在第一子实施例中,本发明涉及包括IgG抗体、两组连接的第一和第二V_HH肽单体和两组连接的第三和第四V_HH肽单体的四特异性八聚体结合剂,其中所述IgG抗体包含两个

臂，每个臂包括缺少可变区的轻链和缺少可变区的重链，并且每条链具有氨基末端，其中对于抗体的每个臂，一组连接的第一和第二V_HH肽单体连接到轻链的氨基末端，并且一组连接的第三和第四V_HH肽单体连接到重链的氨基末端，以及其中V_HH肽单体对艰难梭菌毒素A(TcdA)或毒素B(TcdB)的表位具有结合特异性。这种结合剂因其识别四种不同的毒素表位而称为“四特异性”。由于它携带八个V_HH肽单体(第一单体的两个拷贝、第二单体的两个拷贝、第三单体的两个拷贝和第四单体的两个拷贝)，因此它被称为“八聚体”。

[0023] 在该子实施例中，第一、第二、第三和第四V_HH肽单体各自具有对不同表位的结合特异性。

[0024] 在该子实施例的某些方面，两个V_HH肽单体对TcdA的表位具有结合特异性，并且两个V_HH肽单体对TcdB的表位具有结合特异性。

[0025] 在该子实施例的某些方面，V_HH肽单体独立地对TcdA或TcdB的葡糖基转移酶结构域、半胱氨酸蛋白酶结构域、易位结构域或受体结合结构域中的表位具有结合特异性。

[0026] 在该子实施例的具体方面，结合剂的轻(kappa)链包括SEQ ID NO:46(AA6/E3 kappa)所示的氨基酸序列或与其具有至少95％序列同一性的序列变体，以及结合剂的重链包括SEQ ID NO:44(AH3/5D重)所示的氨基酸序列或与其具有至少95％序列同一性的序列变体。由于这种结合剂是基于IgG的结合剂，技术人员清楚，具有所述氨基酸序列的两个重链多肽和两个轻链多肽将通过二硫键组装以提供完整的结合剂。序列变体保留TcdA和/或TcdB结合特异性，或序列变体保留毒素中和活性或保留两者。序列变体的变体氨基酸可以位于V_HH肽单体的框架区中。

[0027] 在第二子实施例中，本发明涉及包括IgG抗体和第一、第二、第三和第四V_HH肽单体的双特异性或四特异性的四聚体结合剂，其中IgG抗体包括两个臂，每个臂包括缺少可变区的重链和缺少可变区的轻链，并且每条链具有氨基末端，其中对于抗体的第一臂，第一V_HH肽单体连接至轻链的氨基末端，并且第二V_HH肽单体连接至重链的氨基末端，其中对于抗体的第二臂，第三V_HH肽单体连接至轻链的氨基末端，并且第四V_HH肽单体连接至重链的氨基末端，以及其中V_HH肽单体对艰难梭菌毒素A(TcdA)或毒素B(TcdB)的表位具有结合特异性。当结合剂是“四特异性”时，它识别四种不同的毒素表位；当“双特异性”时，它识别两种不同的毒素表位。由于它们带有四个V_HH肽单体，结合剂是“四聚的”(当双特异性时，第一和第三单体具有相同的序列并结合相同的表位，并且第二和第四单体具有相同的序列并结合相同的表位；当四特异性时，每个单体具有不同的序列并结合不同的表位)。

[0028] 当结合剂是双特异性时，第一和第二单体对不同表位具有结合特异性，第一和第三单体具有相同的氨基酸序列，并且第二和第四单体可以具有相同的氨基酸序列。V_HH肽单体中的一个可以对TcdA的表位具有结合特异性，并且V_HH肽单体中的一个可以对TcdB的表位具有结合特异性。

[0029] 当结合剂是四特异性时，每个V_HH肽单体对不同表位具有结合特异性。两个V_HH肽单体可以对TcdA的表位具有结合特异性，并且两个V_HH肽单体可以对TcdB的表位具有结合特异性。

[0030] 在该子实施例的某些方面，每个V_HH肽单体对TcdA的表位具有结合特异性。

[0031] 在该子实施例的某些方面，每个V_HH肽单体对TcdB的表位具有结合特异性。

[0032] 在该子实施例的某些方面，V_HH肽单体独立地对TcdA或TcdB的葡糖基转移酶结构

域、半胱氨酸蛋白酶结构域、易位结构域或受体结合结构域中的表位具有结合特异性。

[0033] 在该子实施例的具体方面，结合剂的轻(kappa)链包括SEQ ID NO:40(AA6kappa)所示的氨基酸序列或与其具有至少95％序列同一性的序列变体，以及结合剂的重链包括SEQ ID NO:36(AH3重)所示的氨基酸序列或与其具有至少95％序列同一性的序列变体。由于这种结合剂是基于IgG的结合剂，技术人员清楚，具有所述氨基酸序列的两个重链多肽和两个轻链多肽将通过二硫键组装以提供完整的结合剂。序列变体保留TcdA和/或TcdB结合特异性，或序列变体保留毒素中和活性或保留两者。序列变体的变体氨基酸可以位于V_HH肽单体的框架区中。

[0034] 在该子实施例的另一具体方面，结合剂的轻(kappa)链包括SEQ ID NO:42(E3kappa)所示的氨基酸序列或与其具有至少95％序列同一性的序列变体，以及结合剂的重链包括SEQ ID NO:38(5D重)所示的氨基酸序列或与其具有至少95％序列同一性的序列变体。由于这种结合剂是基于IgG的结合剂，技术人员清楚，具有所述氨基酸序列的两个重链多肽和两个轻链多肽将通过二硫键组装以提供完整的结合剂。序列变体保留TcdA和/或TcdB结合特异性，或序列变体保留毒素中和活性或保留两者。序列变体的变体氨基酸可以位于V_HH肽单体的框架区中。

[0035] 在该实施例和子实施例的某些方面，结合剂以特异性结合TcdA和/或TcdB。在该实施例的某些方面，结合剂显示TcdA和/或TcdB中和活性。

[0036] 在第三实施例中，本发明涉及包含连接至抗体Fc结构域的V_HH肽单体的结合剂，其中结合剂结合TcdA和/或TcdB。在这些基于Fc结构域的结合剂中，1、2、3、4或更多个V_HH肽单体连接至抗体重链的Fc结构域的每个臂的铰链、C_H2和C_H3区。因此，肽单体取代抗体的Fab区域。

[0037] 在该实施例的某些方面，这些结合剂包含连接至Fc结构域的臂的氨基末端的2、3、4或更多个连接的V_HH肽单体。V_HH肽单体包括但不限于V_HH肽单体5D(SEQ ID NO:1)、E3(SEQ ID NO:3)、AA6(SEQ ID NO:5)和AH3(SEQ ID NO:7)。

[0038] 在其中两个或更多个单体连接的该实施例的方面，单体可以通过柔性肽接头连接，通常包括10-20个氨基酸。合适的接头包括但不限于接头-1(SEQ ID NO:9)、接头-2(SEQ ID NO:11)和接头-3(SEQ ID NO:13)。

[0039] 在第一子实施例中，本发明涉及包含抗体Fc结构域和两组连接的第一、第二、第三和第四V_HH肽单体的四特异性八聚体结合剂，其中抗体Fc结构域包括两个臂，每个臂包括抗体重链的铰链、C_H2和C_H3区，以及每个臂具有氨基末端，其中对于Fc结构域的每个臂，将一组连接的第一、第二、第三和第四V_HH肽单体连接至臂的氨基末端，并且其中V_HH肽单体对艰难梭菌毒素A(TcdA)或毒素B(TcdB)的表位具有结合特异性。这种结合剂因其识别四种不同的毒素表位而称为“四特异性”。由于它携带八个V_HH肽单体(第一单体的两个拷贝、第二单体的两个拷贝、第三单体的两个拷贝以及第四单体的两个拷贝)，因此它被称为“八聚体”。

[0040] 在该子实施例的某些方面，第一、第二、第三和第四V_HH肽单体各自具有针对不同表位的结合特异性。

[0041] 在该子实施例的某些方面，两个V_HH肽单体对TcdA的表位具有结合特异性，并且两个V_HH肽单体对TcdB的表位具有结合特异性。

[0042] 在该子实施例的某些方面，V_HH肽单体独立地对TcdA或TcdB的葡糖基转移酶结构

域、半胱氨酸蛋白酶结构域、易位结构域或受体结合结构域中的表位具有结合特异性。

[0043] 在该子实施例的具体方面，结合剂包括SEQ ID NO:22(ABAB-Fc)中所示的氨基酸序列或与其具有至少95％序列同一性的序列变体，其中序列变体保留TcdA和/或TcdB结合特异性，或序列变体保留毒素中和活性，或保留两者。由于这种结合剂是基于Fc结构域的结合剂，技术人员将清楚，具有所述氨基酸序列的两个相同多肽充当结合剂的臂，并且臂将通过二硫键组装以提供完整的结合剂。序列变体的变体氨基酸可以位于V_HH肽单体的框架区中。

[0044] 在第二子实施例中，本发明涉及包含抗体Fc结构域和两组连接的第一和第二V_HH肽单体的双特异性四聚体结合剂，其中抗体Fc结构域包括两个臂，每个臂包括抗体重链的铰链、C_H2和C_H3区，以及每个臂具有氨基末端，其中对于Fc结构域的每个臂，将一组连接的第一和第二V_HH肽单体连接至臂的氨基末端，并且其中V_HH肽单体对艰难梭菌毒素A(TcdA)或毒素B(TcdB)的表位具有结合特异性。这种结合剂因其识别两种不同的毒素表位而称为“双特异性”。由于它携带四个V_HH肽单体(第一单体的两个拷贝以及第二单体的两个拷贝)，因此它被称为“四聚体”。

[0045] 在该子实施例的某些方面，第一和第二V_HH肽单体对相同或不同的表位具有结合特异性。

[0046] 在该子实施例的某些方面，V_HH肽单体独立地对TcdA或TcdB的葡糖基转移酶结构域、半胱氨酸蛋白酶结构域、易位结构域或受体结合结构域中的表位具有结合特异性。

[0047] 在该子实施例的具体方面，结合剂包括SEQ ID NO:32(AH3/5D-Fc)中所示的氨基酸序列或与其具有至少95％序列同一性的序列变体，其中序列变体保留TcdA和/或TcdB结合特异性，或序列变体保留毒素中和活性，或保留两者。由于这种结合剂是基于Fc结构域的结合剂，技术人员将清楚，具有所述氨基酸序列的两个相同多肽充当结合剂的臂，并且臂将通过二硫键组装以提供完整的结合剂。序列变体的变体氨基酸可以位于V_HH肽单体的框架区中。

[0048] 在该子实施例的另一具体方面，结合剂包括SEQ ID NO:34(AA6/E3-Fc)中所示的氨基酸序列或与其具有至少95％序列同一性的序列变体，其中序列变体保留TcdA和/或TcdB结合特异性，或序列变体保留毒素中和活性，或保留两者。由于这种结合剂是基于Fc结构域的结合剂，技术人员将清楚，具有所述氨基酸序列的两个相同多肽充当结合剂的臂，并且臂将通过二硫键组装以提供完整的结合剂。序列变体的变体氨基酸可以位于V_HH肽单体的框架区中。

[0049] 在该实施例和子实施例的某些方面，结合剂以特异性结合TcdA和/或TcdB。在该实施例的某些方面，结合剂显示TcdA和/或TcdB中和活性。

[0050] 本发明包括在本文定义的各种实施例和方面提供的每种结合剂的人源化变体。同样，本发明包括本文定义的各种实施例和方面提供的每种结合剂的表位结合片段。

[0051] 多核苷酸、表达载体和宿主细胞

[0052] 本发明包括包含编码本文定义的各种实施例和方面提供的每种结合剂的核苷酸序列的多核苷酸及其互补链。本发明还包括包含所述多核苷酸的表达载体(例如细菌和酵母)以及包含所述表达载体的宿主细胞(例如细菌、酵母、哺乳动物、昆虫)。本发明进一步包括产生本文定义的结合剂的方法，包括在促进由表达载体编码的结合剂表达的条件下培养

宿主细胞，并从细胞培养物中回收结合剂。

[0053] 布拉酵母(S.boulardii)的工程菌株

[0054] 在第四实施例中，本发明涉及酵母属(Saccharomyces)酵母菌株，例如酿酒酵母(S.cerevisiae)和布拉酵母(S.boulardii)，其经工程改造以产生一种或多种本文所定义的结合剂。在优选的方面，酵母属酵母的工程菌株分泌结合剂。

[0055] 酵母属酵母菌株的身份仅限于其可工程化以产生并优选分泌一种或多种本发明的结合剂。在本发明的优选方面，工程化以产生一种或多种结合剂的酵母属酵母的菌株是酿酒酵母或布拉酵母。因此，本发明包括产生一种或多种本文定义的结合剂的酿酒酵母的工程菌株，以及分泌一种或多种本文定义的结合剂的酿酒酵母的工程菌株。本发明还包括产生一种或多种本文定义的结合剂的布拉酵母的工程菌株，以及分泌一种或多种本文定义的结合剂的布拉酵母的工程菌株。

[0056] 在该实施例的示例中，本发明涉及产生结合剂的酿酒酵母的工程菌株，所述结合剂V_HH肽单体或包括2、3、4或更多个单体的V_HH肽单体的连接基团，每个单体优选地以特异性结合TcdA和/或TcdB。因此，本发明包括产生V_HH肽结合剂的酿酒酵母工程菌株，所述V_HH肽结合剂包括至少一个V_HH肽单体，其中每个V_HH肽单体对艰难梭菌毒素A(TcdA)或毒素B(TcdB)的表位具有结合特异性。在某些方面，这些结合剂包括2、3、4或更多个连接的V_HH肽单体。V_HH肽单体包括但不限于V_HH肽单体5D(SEQ ID NO:1)、E3(SEQ ID NO:3)、AA6(SEQ ID NO:5)和AH3(SEQ ID NO:7)。

[0057] 在该实施例的另一示例中，本发明涉及产生结合剂的酿酒酵母工程菌株，所述结合剂包括连接至IgG抗体的V_HH肽单体，其中所述结合剂结合本文定义的TcdA和/或TcdB。在这些基于IgG的结合剂中，IgG抗体的轻链和重链的可变区被1、2、3、4个或更多个V_HH肽单体替换。

[0058] 在该实施例的另一示例中，本发明涉及产生结合剂的酿酒酵母工程菌株，所述结合剂包含连接至抗体Fc结构域的V_HH肽单体，其中所述结合剂结合如本文所定义的TcdA和/或TcdB。在这些基于Fc结构域的结合剂中，1、2、3、4个或更多个V_HH肽单体连接至抗体重链的Fc结构域的每个臂的铰链区、C_H2和C_H3区。因此，肽单体取代抗体的Fab区域。

[0059] 在该实施例的又一示例中，本发明涉及产生四特异性四聚体结合剂的酿酒酵母工程菌株，其中所述结合剂包含连接的第一、第二、第三和第四V_HH肽单体，并且其中V_HH肽单体独立地对艰难梭菌毒素A(TcdA)或毒素B(TcdB)的表位具有结合特异性。在某些方面，第一、第二、第三和第四V_HH肽单体各自对不同表位具有结合特异性。在某些方面，两个V_HH肽单体对TcdA的表位具有结合特异性，并且两个V_HH肽单体对TcdB的表位具有结合特异性。在某些方面，V_HH肽单体独立地对TcdA或TcdB的葡糖基转移酶结构域、半胱氨酸蛋白酶结构域、易位结构域或受体结合结构域中的表位具有结合特异性。

[0060] 在该实施例的优选示例中，本发明涉及工程酵母菌株，其中结合剂是ABAB，其中第一和第三单体对TcdA的表位具有结合特异性以及第一和第三单体分别是V_HH肽单体AH3(SEQ ID NO:7)和AA6(SEQ ID NO:5)，并且其中第二和第四单体对TcdB表位具有结合特异性以及第二和第四单体分别是V_HH肽单体5D(SEQ ID NO:1)和E3(SEQ ID NO:3)。在某些方面，ABAB结合剂包括SEQ ID NO:19所示的氨基酸序列或与其具有至少95％序列同一性的序列变体，其中所述序列变体保留TcdA和/或TcdB结合特异性，或所述序列变体保留毒素中和

活性或保留两者。在某些方面，ABAB结合剂还包括选自AT分泌信号(MRFPSIFTAVLFAASSALA(SEQ ID NO:99))和IVS分泌信号(MLLQAFLFLLAGFAAKISA(SEQ ID NO:103))的N端分泌信号。

[0061] 在某些方面，ABAB结合剂由酵母内的质粒表达，其中ABAB结合剂包括SEQ ID NO:107所示的氨基酸序列或与其具有至少95％序列同一性的序列变体，并且其中所述序列变体保留TcdA和/或TcdB结合特异性，或所述序列变体保留毒素中和活性或保留两者。质粒可以是但不限于pCEV-URA3-TEF-AT-yABAB-cMyc(SEQ ID NO:88)。

[0062] 在某些方面，将ABAB结合剂编码序列整合到酵母菌株的染色体中，其中ABAB结合剂包含SEQ ID NO:109所示的氨基酸序列或与其具有至少95％序列同一性的序列变体，并且其中所述序列变体保留TcdA和/或TcdB结合特异性，或所述序列变体保留毒素中和活性或保留两者。

[0063] 该实施例的方面包括产生对艰难梭菌毒素A(TcdA)或毒素B(TcdB)或两者的独特表位具有结合特异性的治疗性蛋白质的酵母属酵母的工程菌株。优选地，酵母属的工程菌株是酿酒酵母或布拉酵母。治疗性蛋白质是可以在受试者的医学状况中带来改善或治愈，或者可以抑制或预防受试者中医学状况发展的任何蛋白质。合适的治疗性蛋白质包括但不限于能够(a)代替缺陷或异常的蛋白质；(b)增加现有途径；(c)提供新颖的功能或活动；(d)干扰分子或生物体；和(e)传递其他化合物或蛋白质，如放射性核素、细胞毒性药物或效应蛋白质的蛋白质。治疗性蛋白质还包括抗体和基于抗体的药物、Fc融合蛋白质、抗凝血剂、血液因子、骨形态发生蛋白质、工程蛋白质支架、酶、生长因子、激素、干扰素、白细胞介素和溶栓剂。治疗性蛋白质进一步包括双特异性单克隆抗体(mAb)和多特异性融合蛋白质，与小分子药物缀合的mAb以及具有优化药代动力学的蛋白质。

[0064] 制备布拉酵母(S.boulardii)工程菌株的方法

[0065] 本发明还涉及制备经工程化以产生一种或多种本文所定义的结合剂的酵母属酵母菌株的方法。

[0066] 因此，本发明包括制备工程化以产生一种或多种本文定义的结合剂的酵母属酵母菌株的方法，包括(a)用编码结合剂的表达载体转化酵母属酵母菌株，和(b)筛选(a)的酵母以产生结合剂。在某一方面，表达载体是质粒pCEV-URA3-TEF-AT-yABAB-cMyc(SEQ ID NO:88)。

[0067] 因此，本发明包括制备工程化产生一种或多种本文定义的结合剂的酵母属酵母菌株的方法，其包括(a)将编码结合剂的多核苷酸序列染色体整合到酵母属酵母菌株的基因组中，和(b)筛选(a)的酵母以产生结合剂。在某些方面，染色体整合通过以下方式进行：

[0068] (a)使用引物从质粒pCEV-G4-Km-TEF-AT-yABAB hAA6T83N-tagless(SEQ ID NO:90)扩增编码ABAB结合剂的多核苷酸序列以产生整合盒，所述引物含有(i)与选择的酵母染色体整合位点同源的核酸序列和(ii)与质粒的ABAB结合剂编码序列的5'和3'区域同源的核酸序列，

[0069] (b)在促进整合盒自发整合到双链断裂位点的条件下，将(a)中产生的整合盒用pCRI-Sb-δ1(SEQ ID NO:91)或pCRI-Sb-δ2(SEQ ID NO:92)转化酵母以诱导相应酵母染色体δ位点内的双链断裂，

[0070] (c)筛选(b)中的转化酵母以产生ABAB结合剂。

[0071] 在这些方法的某些方面，工程化以产生结合剂的酵母属酵母菌株是酵母属酵母的营养缺陷型菌株，例如酵母的ura3-菌株。可以在ura3选择下使用酵母的ura3-菌株。

[0072] 在这些方法的某些方面，工程化以产生结合剂的酵母属酵母的菌株是酿酒酵母或布拉酵母。

[0073] 在这些方法的某些方面，筛选使用免疫测定如ELISA进行。

[0074] 药物制剂

[0075] 本发明包括含有一种或多种本文定义的结合剂和药学上可接受的载体或稀释剂的药物制剂。本发明还包括药物制剂，其包含一种或多种本文定义的酵母属酵母的工程菌株和药学上可接受的载体或稀释剂。在某些方面，酵母属酵母是酿酒酵母或布拉酵母。

[0076] 治疗和预防的方法

[0077] 在第六实施例中，本发明涉及在受试者中治疗或预防由艰难梭菌诱导的疾病症状的方法，其包括向患有艰难梭菌感染或发展成艰难梭菌感染的受试者施用治疗有效量的如本文所定义的一种或多种结合剂和/或一种或多种酵母属酵母的工程菌株。在优选的方面，酵母属酵母是酿酒酵母或布拉酵母。

[0078] 在该实施例的某些方面，由艰难梭菌诱发的疾病症状是腹泻。

[0079] 在第七实施例中，本发明涉及在由艰难梭菌感染的受试者中中和艰难梭菌毒素TcdA和/或TcdB的方法，其包括向患有艰难梭菌感染的受试者施用治疗有效量的如本文所定义的一种或多种结合剂和/或一种或多种酵母属酵母的工程菌株。在优选的方面，酵母属酵母是酿酒酵母或布拉酵母。

[0080] 在第八实施例中，本发明涉及在受试者中治疗或预防艰难梭菌感染的方法，其包括向患有艰难梭菌感染或发展成艰难梭菌感染的受试者施用治疗有效量的如本文所定义的一种或多种结合剂和/或一种或多种酵母属酵母的工程菌株。在优选的方面，酵母属酵母是酿酒酵母或布拉酵母。在第八实施例的某些方面，该方法进一步包括向受试者施用治疗有效量的抗生素。

[0081] 在第九实施例中，本发明涉及在患有艰难梭菌感染的受试者中维持正常肠功能的方法，其包括向患有艰难梭菌感染或发展成艰难梭菌感染的受试者施用治疗有效量的如本文所定义的一种或多种结合剂和/或一种或多种酵母属酵母的工程菌株。在优选的方面，酵母属酵母是酿酒酵母或布拉酵母。在第九实施例的某些方面，该方法进一步包括向受试者施用治疗有效量的抗生素。

[0082] 在该方法的某些方面，结合剂处于包括结合剂和药学上可接受的载体或稀释剂的药物制剂中。

[0083] 在该方法的某些方面，结合剂的治疗有效量为每个受试者体重10μg/kg至100mg/kg的药剂。

[0084] 在该方法的某些方面，将药剂经口服、胃肠外或直肠施用于受试者。

[0085] 在该方法的某些方面，酵母属酵母的工程菌株处于包括工程菌株和药学上可接受的载体或稀释剂的药物制剂中。在优选的方面种，酵母属酵母是酿酒酵母或布拉酵母。

[0086] 在该方法的某些方面，酵母属酵母的工程菌株的治疗有效量为每个受试者体重10ug/kg至100mg/kg工程菌株。在优选的方面，酵母属酵母是酿酒酵母或布拉酵母。

[0087] 在该方法的某些方面，将酵母菌酵母的工程菌株经口服、经鼻或直肠施用于受试

者。在优选的方面，酵母属酵母是酿酒酵母或布拉酵母。

[0088] 前面已经相当广泛地概述了本发明的特征和技术优点，以便可以更好地理解随后的本发明的详细描述。本文将描述本发明的附加特征和优点，其形成本发明权利要求的主题。本领域技术人员应该理解，本文公开的任何概念和具体实施例可以容易地用作修改或设计用于实现本发明的相同目的的其他结构的基础。本领域技术人员还应该认识到，这样的等同构造不脱离如所附权利要求书中阐述的本发明的精神和范围。结合附图考虑下面的描述，将更好地理解被认为是本发明的特征的新颖特征(无论是其组织和操作方法)以及其他目的和优点。然而，要明确理解的是，仅出于说明和描述的目的而提供任何描述、附图、示例等，而绝非意在限定本发明的限制。

附图说明

[0089] 图1.用于制备本发明的结合剂的策略的说明。

[0090] 图2.艰难梭菌毒素TcdA和TcdB的图示，示出每种毒素的葡糖基转移酶结构域(GT)、半胱氨酸蛋白酶结构域(CPD)、易位结构域(TD)和受体结合结构域(RBD)。示出了识别和结合不同毒素结构域的V_HH。有下划线的是具有毒素中和活性的V_HH。

[0091] 图3A-3F.单体或二聚体V_HH具有有效的中和活性。在nM浓度下，V_HH阻断由TcdA(图3A)或TcdB(图3B)诱导的细胞变圆。(图3C)针对TcdA或TcdB两个异二聚体的图示。在N端的$His_{(6)}$标签便于纯化；柔性间隔区(FS)将两个V_HH分开。(图3D)二聚体5D/E3比两个V_HH的简单混合物增加至少10倍的中和活性。异二聚体完全保护小鼠免受TcdB(图3E)或TcdA(图3F)的致死性ip攻击。

[0092] 图4.ABAB的图示。His-标签和E-标签分别是用于纯化和检测的表位标签。FS:柔性接头；ABP:白蛋白结合肽。

[0093] 图5A-5B.ABAB在保护小鼠免受艰难梭菌孢子(图5A)和毒素(图5B)攻击方面非常有效。MK HuMabs:正在进行临床试验的Merck抗-TcdA(actoxumab)和抗TcdB(bezlotoxumab)人单克隆抗体的混合物。

[0094] 图6A-6B.针对这两种毒素的抗毒素血清保护小鼠免受CDI的伤害。在艰难梭菌孢子(UK1菌株，10^6孢子/小鼠)接种之前，向小鼠腹膜内注射50ul针对TcdA(“抗-A”)、TcdB(“抗-B”)、TcdA+TcdB(“抗-A+抗-B”)的羊驼抗血清或100ul presera或PBS(“CTR”)4小时。举例说明了小鼠存活(图6A；抗-A+抗-B vs.PBS，$p=0.006$)和体重减轻(图6B)(*，在抗-A+抗-B vs.对照组之间$p<0.05$)

[0095] 图7.ABAB和ABAB-IgG分子的图示。

[0096] 图8A-8B.与各个V_HH与各毒素的结合相比，ABAB-IgG与TcdA(图8A)和TcdB(图8B)的结合的ELISA分析。

[0097] 图9A-9B.同时结合四特异性抗体IgG-ABAB和TcdA和TcdB的夹心ELISA分析。图9A示出了添加到用TcdA(TxA)涂布，然后是TcdB(TxB)涂布的ELISA板中连续稀释的ABAB-IgG。图9B示出了添加到用TcdB(TxB)涂布，然后是TcdA(TxA)涂布的ELISA板中连续稀释的ABAB-IgG。

[0098] 图10A-10B.针对TcdA(图10A)和TcdB(图10B)的ABAB-IgG中和活性。

[0099] 图11.该图示出了小鼠中针对艰难梭菌感染的ABAB-IgG和针对TcdA和TcdB

(actoxumab和bezlotoxumab)的Merck抗体的体内中和活性的比较。

[0100] 图12.针对艰难梭菌感染的预防性ABAB-IgG影响的研究设计。

[0101] 图13A-13B.双特异性夹心ELISA。(图13A)ELISA中建立的毒素和抗体的图示。(图13B)不同TcdA浓度的O.D.读数;选择125ng/ml的TcdA用于亚序列ELISA。

[0102] 图14A-14B.由Sc-ABAB分泌的ABAB的活性。(图14A)分泌的ABAB在酿酒酵母培养物上清液中的中和作用。Sc:酿酒酵母(BY4741);Sc-ABAB:酿酒酵母(BY4741)-pD1214-FAKS-ABAB;r-ABAB:重组ABAB。Sc-ABAB上清中的ABAB能够充分保护细胞免于中毒。来自单个Sc-ABAB克隆的上清液的ELISA O.D.读数(图14B)。

[0103] 图15A-15B.带有各种分泌信号的ABAB分泌水平。(图15A)通过ELISA测量ABAB分泌并基于在酿酒酵母中O.D.600归一化细胞密度。统计显著性通过Kruskal-Walls检验然后进行Dunn's多重比较检验来确定。*p<0.05**p<0.01(图15B)通过ELISA测量ABAB分泌并基于在布拉酵母中O.D.600归一化细胞密度。统计显著性由Mann Whitney检验确定。****p<0.0001。

[0104] 图16.布拉酵母中通过同源重组靶向缺失染色体编码基因的图示。

[0105] 图17A-17D.表达ABAB的布拉酵母URA3Δ/Δ。(图17A)在含有万古霉素(1mg/ml)和不含的情况下YPD的生长比较。(图17B)通过ELISA确定培养2小时后布拉酵母培养物上清液中ABAB的稳定性。(图17C)来自表达ABAB的布拉酵母URA3Δ/Δ培养物上清液中ABAB的中和活性。(图17D)通过蛋白质印迹在表达ABAB培养物上清液的布拉酵母URA3Δ/Δ中的ABAB检测。富集:ABAB在C-末端包含c-Myc标签,并使用α-c-Myc标签抗体进一步浓缩。

[0106] 图18A-18C.在小鼠CDI预防中表达ABAB的布拉酵母的保护作用。(图18A)存活率,(图18B)体重减轻,(图18C)记录并呈现整个感染过程中的腹泻事件。具有双尾和95%置信区间的Fisher精确检验确定显著性*;对于图18A,p值是0.0108,以及对于图18B和图18C,使用常规双向方差分析(ANOVA)(不重复测量),然后使用Dunnett的多重比较检验,*P≤0.05。"Sb:EP"是具有空质粒的布拉酵母;"Sb:ABAB"是表达ABAB的布拉酵母。

[0107] 图19A-19C.在治疗CDI小鼠中表达ABAB的布拉酵母的保护。(图19A)存活率,(图19B)体重减轻,(图19C)记录并呈现整个感染过程中的腹泻事件。具有双尾和95%置信区间的Fisher精确检验确定显著性*;对于图19A,p值是0.0256;对于图19B和图19C,使用常规双向方差分析(不重复测量),然后使用Dunnett的多重比较检验。对于图19B和图19C,*P≤0.05**P≤0.01****P≤0.0001。"Sb:EP"是具有空质粒的布拉酵母;"Sb:ABAB"是表达ABAB的布拉酵母。

[0108] 图20A-20C.在CDI复发小鼠中表达ABAB的布拉酵母的保护作用。(图20A)存活率,(图20B)体重减轻,(图20C)记录并呈现整个感染过程中的腹泻事件。具有双尾和95%置信区间的Fisher精确检验确定显著性*;对于图20A,p值是0.017;对于图20B和图20C,使用常规双向方差分析(不重复测量),然后使用Dunnett的多重比较检验。对于图20B和图20C,*P≤0.05***P≤0.001****P≤0.0001。"Sb:EP"是具有空质粒的布拉酵母;"Sb:ABAB"是表达ABAB的布拉酵母。

[0109] 图21.使用CRISPR的δ位点靶向染色体整合的图示。使用Ty1-H3(Genbank登录号M18706)针对MYA796的草图基因组进行blast以获得δ位点序列。编译序列用于鉴定共同的原型间隔子邻接基序(PAM)位点和原型间隔子。基于对位于原型间隔子和PAM位点上游和下

游的多个位点和常见同源序列的最佳覆盖范围选择两个PAM位点序列，以便简单整合ABAB表达盒。PAM位点“I”在SEQ ID NO:93中提供;PAM位点“II”在SEQ ID NO:94中提供。下划线标出了用于通过PCR产生ABAB表达盒的引物中使用的同源重组序列。

[0110] 图22A-22B.利用基于CRISPR的靶向δ位点染色体整合的布拉酵母的ABAB分泌。(图22A)通过ELISA测量ABAB分泌。ITG:ABAB整合盒。低:CRISPR质粒与ITG比率为2;高:CRISPR质粒与ITG比率为0.25。(图22B)ABAB分泌量比较。M-/-^{Cir0}:pKC、M-/-$^{Cir+}$:ABAB、M-/-^{Cir0}:ABAB是基于质粒的。Ch^{Ins}:通过常规同源重组将单个位点靶向ABAB盒的染色体整合。C^{RISPR}1-2:在位点I处的ABAB盒整合。C^{RISPR}3-4:在位点II处的ABAB盒整合。

[0111] 图23A-23C.在治疗CDI小鼠中表达ABAB的布拉酵母的保护作用。(图23A)存活率，(图23B)体重减轻，(图23C)记录并呈现整个感染过程中的腹泻事件。具有双尾和95％置信区间的Fisher精确检验确定显著性*;对于图23A,p值是0.0325;对于图23B和图23C,使用常规双向方差分析(不重复测量)，然后使用Dunnett的多重比较检验。对于图23B和图23C,*P≤0.05**P≤0.01。

具体实施方式

[0112] I.定义

[0113] 除非另有说明，否则根据常规用法使用技术术语。分子生物学中常用术语的定义可见于例如由牛津大学出版社于2000年出版的Benjamin Lewin,Genes VII(ISBN 019879276X);Kendrew et al.(编辑);由Blackwell Publishers于1994年出版的The Encyclopedia of Molecular Biology(ISBN 0632021829)以及由Wiley,John&Sons,Inc.于1995出版的Robert A.Meyers(编辑),Molecular Biology and Biotechnology:a Comprehensive Desk Reference(ISBN 0471186341);和其他类似的技术参考文献。

[0114] 如本文所使用的，“一”或“一个”可以表示一个或多个。如本文所使用的，当与单词“包括”一起使用时，单词“一”或“一个”可以表示一个或多于一个。如本文所使用的，“另一个”可以表示至少第二个或更多个。此外，除非上下文另有要求，否则单数术语包括复数，复数术语包括单数。

[0115] 如本文所使用的，“约”是指数值，包括例如整数、分数和百分比，无论是否明确指出。术语“约”通常是指本领域普通技术人员认为等同于所述值(例如，具有相同的功能或结果)的数值范围(例如，所述值的+/-5-10％)。在一些情况下，术语“约”可以包括四舍五入到最接近的有效数字的数值。

[0116] II.本发明

[0117] 艰难梭菌相关性疾病(CDI)主要由两种大的外毒素引起，即由细菌产生的毒素A(TcdA)和毒素B(TcdB)。这些毒素是结构上相似的大单链蛋白(TcdA约为300kD;TcdB约为270kD)，其对宿主细胞表现出类似的作用模式。这两种毒素都靶向宿主Rho GTP酶，导致酶失活，接着细胞骨架解体和细胞凋亡。在肠上皮细胞中，TcdA催化Rho GTP酶的葡糖基化，从而导致肌动蛋白细胞骨架的重组，伴随形态变化，例如细胞完全变圆和破坏肠屏障功能。毒素可以在动物中单独引起CDI，并且TcdA-TcdB-菌株是无毒的。

[0118] 许多独立研究已经证明中和抗毒素的抗体赋予针对CDI的保护作用[24-33]。因为TcdA和TcdB是艰难梭菌的基本毒力因子，所以针对这两种毒素产生的中和抗体在动物模型

中防止产生毒素的艰难梭菌感染[30-33]。在人体中，高血清抗毒素抗体水平与疾病严重程度和复发率降低有关[9,25,29]。

[0119] 因此，存在全身和口服施用的抗毒素抗体的预防性理由。然而，靶向单个表位的单克隆抗体通常是低亲和力的，并且使用这样的抗体具有在毒素表位内诱导突变的风险，从而产生额外的毒株。因此，中和靶向多个、关键和保守毒素表位的抗毒素是非常需要的。

[0120] 本发明基于关于用于治疗和预防CDI以及CDI症状的抗-TcdA和抗-TcdB抗体的现有知识。本文提供了衍生自人和骆驼科动物免疫球蛋白的基于抗体的融合蛋白结合剂，其任选由受试者中的益生酵母酵母属菌株表达。这些结合剂识别并特异性结合艰难梭菌TcdA和/或TcdB。这些结合剂中的一些显示出毒素中和活性。这些基于酵母的免疫治疗剂可用于治疗或预防原发CDI和复发性CDI，以及原发性和复发性CDI的症状。在优选的方面，酵母属酵母是酿酒酵母或布拉酵母。

[0121] 如下面详细讨论的，骆驼科动物(单峰骆驼、双峰骆驼、野生双峰骆驼、美洲驼、羊驼、骆马骆驼和栗色羊驼)产生一类缺乏轻链的功能性免疫球蛋白，因此是仅有重链的抗体(HCAbs)[34]，其结合特性与常规IgG所达到的结合特性相当[35]。HCAbs的V_H结构域称为V_HH，与传统的人V_H结构域相似，但具有独特的序列和结构特征[36]。编码该结构域的DNA可以容易地克隆并在微生物中表达以产生保留亲本HCAb的抗原结合性质的可溶性蛋白质单体。这些V_HH肽单体结合剂很小(～15kDa)，易于生产，并且通常比常规抗体片段更稳定[37-39]。正在探索V_HH治疗肠道疾病，因为它们对蛋白酶具有相对抗性，并且可以进一步工程化以提高这些性质[40]。它们也可以作为具有人抗体如IgG的融合蛋白和人抗体的片段如Fc结构域产生。

[0122] 本发明利用HCAb在制备可用于治疗和预防CDI的结合剂的有利特征。如本文所公开的，筛选V_HH肽单体，用于TcdA和TcdB表位识别和结合。显示表位结合并具有毒素中和活性的那些单体被连接以产生本发明的结合剂。结合剂包括简单V_HH肽单体和V_HH肽单体的连接基团(包括2、3、4或更多个单体)以及更复杂的结合剂，其包括连接至抗体Fc结构域的V_HH肽单体以及连接到IgG抗体的V_HH肽单体(参见图1)。

[0123] 此外，FDA通常认为安全(GRAS)生物的布拉酵母(Saccharomyces boulardii)通常在非处方可用于促进肠道健康和由于腹泻疾病引起的胃肠疾病的改善。这种酵母菌株已经在多项随机双盲安慰剂对照临床试验中进行了研究，以确定其针对包括CDI在内的肠道疾病的安全性和有效性[42-46]。布拉酵母治疗可显着减少CDI复发[44-46]，而那些复发患者粪便中布拉酵母明显少于非复发患者[43]。已经描述了布拉酵母对抗艰难梭菌毒素诱导的炎症提供保护的免疫调节作用[47-49]。此外，布拉酵母可能有助于维持正常的微生物群[50]；最近的一项临床试验(NCT01473368)发现布拉酵母的治疗可以预防一些抗生素诱导的微生物组的变化，同时可以减少抗生素相关的腹泻。

[0124] 酿酒酵母(通常称为“啤酒酵母”)，其与布拉酵母遗传上有关，已成功用于以高产率表达V_HH[51]。布拉酵母在生理学上与酿酒酵母不同，尽管基因组分析显示两种基因组在核苷酸水平上都非常相似[52,53]。因此，之前开发用于酿酒酵母的分子遗传工具现在已经与布拉酵母一起使用[54-56]，使得该益生菌成为CDI治疗剂的候选工程。

[0125] 有几个额外的代谢特征使布拉酵母理想地用作口服治疗剂。与酿酒酵母相反，布拉酵母在37℃时生长良好，对酸性环境条件更具抗性[57]，使得该菌株特别适用于口服后

更好的存活和持续存在于人体肠道中。此外，一个带有酵母属的实验性的鼠类口腔定殖模型已被很好地表征[58]；使用该模型，已经报道了在用布拉酵母口服治疗的常规小鼠中用肠道病原体例如鼠伤寒沙门氏菌(Salmonella Typhimurium)[58,59]和肠炎沙门氏菌[60]口服攻击的保护作用，以及在预处理的无菌动物中防止CDI攻击[58,61]。通过基因工程化以分泌能够中和艰难梭菌TcdA和TcdB两者的V_HH结合剂的益生菌布拉酵母可以显着提高该益生菌治疗正在进行的和复发性CDI的能力。

[0126] 鉴于布拉酵母的特殊特征，表达本文所定义的结合剂(其中产生和测试的)的布拉酵母菌株。如示例中所述，这些基于酵母的免疫治疗剂可用于治疗或预防原发性和复发性CDI以及原发性和复发性CDI的症状。

[0127] V_HH单体&V_HH异型二聚体

[0128] 如WO 16/127104中最初报道的，本发明人建立了筛选针对艰难梭菌毒素的特定结构域的V_HH单体的有效平台。使用高度免疫原性的无毒全毒素用于免疫，和生物活性嵌合毒素(具有正常的功能域功能)用于筛选，制备与TcdA或TcdB的不同结构域结合的V_HH单体组。这些V_HH单体中的大多数具有有效的中和活性，并确定了它们与TcdA和TcdB的特定结构域的结合(图2)。

[0129] 几种V_HH单体结合高度保守的TcdA/TcdB表位。例如，E3 V_HH单体结合Rho GTP酶结合位点并阻断葡糖基化；AH3 V_HH单体结合毒素的GT结构域；7F V_HH单体结合半胱氨酸蛋白酶切割位点并阻断GT结构域切割和释放。一些V_HH单体具有有效的毒素中和活性，能够在nM浓度下阻断毒素细胞毒性活性(图2中加下划线的单体；也参见图3A和3B)。表1对于这些V_HH肽单体中的一些，包括野生型和密码子优化版本，都参考序列表中的氨基酸和核酸序列。虽然优化和未优化的版本均可用于生产本发明的各种结合剂，但密码子优化版本优选用于在哺乳动物细胞中表达。

[0130] 本发明包括表1中提及的每个V_HH肽单体及其序列变体，其在肽序列的整个长度上具有至少85％、86％、87％、88％、89％、90％、91％、92％、93％、94％、95％、96％、97％、98％或99％的序列同一性并保留野生型肽的毒素结合和/或中和活性。本发明还包括编码表1中每个V_HH肽单体及其序列变体以及其互补链的多核苷酸序列。

[0131] 表1

[0132]

名称	优化的密码子?	表位的位置	氨基酸序列的 SEQ ID NO	核酸序列的 SEQ ID NO
5D	是	TcdB 葡糖基转移酶结构域	1	2
E3	是	TcdB 葡糖基转移酶结构域	3	4
AA6	是	TcdA 半胱氨酸蛋白酶结构域	5	6
AH3	是	TcdA 葡糖基转移酶结构域	7	8
5D	否	TcdB 葡糖基转移酶结构域	48	49
E3	否	TcdB 葡糖基转移酶结构域	50	51
AA6	否	TcdA 半胱氨酸蛋白酶结构域	52	53
AH3	否	TcdA 葡糖基转移酶结构域	54	55

[0133] 为了增强肽单体的结合活性，产生了V_HH肽同型和异型二聚体结合剂，其中连接了两个V_HH肽单体(图3C)。同型二聚体结合剂包括两个相同的单体，其结合两个不同毒素上的相同表位。异型二聚体结合剂包含两个不同的单体，其结合相同毒素的两个不同表位或两个不同毒素上的不同表位。与包括异型二聚体的单个V_HH肽单体的等摩尔混合物相比，发现V_HH异型二聚体具有显着增强的中和活性(图3D)。实际上，发现异型二聚体5D/E3和AH3/AA6分别完全保护小鼠免受致死性全身TcdB或TcdA攻击，而混合的5D和E3或AA6单独仅部分保护(图3E和3F)。

[0134] 使用10至20个氨基酸的短的柔性接头连接同型和异型二聚体中的V_HH单体。适合的接头包括表2中提供的那些。表2还包括三个接头的密码子优化版本。虽然优化和未优化的版本均可用于生产本发明的各种结合剂，但密码子优化版本优选用于在哺乳动物细胞中表达。

[0135] 表2

[0136]

名称	优化的密码子?	氨基酸序列的 SEQ ID NO	核酸序列的 SEQ ID NO

[0137]

接头 -1	是	9	10
接头 -2	是	11	12
接头 -3	是	13	14
接头 -1	否	56	57
接头 -2	否	58	59
接头 -3	否	60	61

[0138] 本领域技术人员将理解，可以在不脱离肽的性质的情况下对柔性接头的序列进行微小改变。因此可以使用它们所基于的接头的在肽序列的整个长度上具有至少85％、86％、87％、88％、89％、90％、91％、92％、93％、94％、95％、96％、97％、98％或99％的序列同一性的和保留特性的柔性接头序列变体。

[0139] 本发明包括V_HH肽同型二聚体结合剂，其包括通过如上所定义的柔性接头连接的表1中所列的任何单体对。本发明还包括V_HH肽异型二聚体结合剂，其包含通过如上定义的柔性接头连接的表1中所列的两种单体的任何组合。示例性的异型二聚体在表3中提供。

[0140] 表3

[0141]

名称	氨基酸序列的SEQ ID NO	核酸序列的SEQ ID NO
AH3-5D	15	16
AA6-E3	17	18
5D-E3	62	63
AH3-AA6	64	65

[0142] 本发明还包括在蛋白质序列的整个长度上具有至少85％、86％、87％、88％、89％、90％、91％、92％、93％、94％、95％、96％、97％、98％或99％的序列同一性并保留野生型蛋白质的毒素结合和/或中和活性的V_HH肽同型二聚体和异型二聚体的序列变体。本发明还包括编码每个V_HH肽同型和异型二聚体及其序列变体及其互补链的多核苷酸序列。

[0143] 本发明还包括V_HH肽同型和异型三聚体结合剂，其中三个单体使用上面表2中定义

的柔性接头连接。可以使用表1的单体的任何组合，包括包含相同单体的三个拷贝的三聚体，包含一个单体的两个拷贝和另一个单体的三个拷贝的三聚体，以及包含三个不同单体的三聚体。本发明包括V_HH肽同型和异型三聚体的序列变体，其在蛋白质序列的整个长度上具有至少85％、86％、87％、88％、89％、90％、91％、92％、93％、94％、95％、96％、97％、98％或99％的序列同一性并保留野生型蛋白质的毒素结合和/或中和活性。本发明进一步包括编码每个V_HH肽同型和异型三聚体及其序列变体以及其互补链的多核苷酸序列。

[0144] ABAB

[0145] 肽单体和异型二聚体的成功允许发明人开发包含四个连接的V_HH肽单体的结合剂。这是该研究的一个目标，因为早期的研究表明，在治疗和预防CDI中最有用的药剂将是单一抗体，其可同时中和TcdA和TcdB两者，因为这是传递针对大多数致病性艰难梭菌菌株的完全保护所必需的。通过产生识别和结合每个毒素上的两个表位的四特异性结合剂，可以加强蛋白质的结合和中和活性。因此，产生了四种结构域(四特异性)V_HH结合剂。

[0146] 四特异性四聚体结合剂可由表1的单体的任何组合制备，其中单体使用表2的柔性接头连接。这些结合剂包括具有相同单体的四个拷贝的那些，具有相同单体的三个拷贝的那些，具有相同单体的两个拷贝的那些，具有四个独特单体的那些以及其中的变体。本发明包括四聚体的序列变体，其在蛋白质序列的整个长度上具有至少85％、86％、87％、88％、89％、90％、91％、92％、93％、94％、95％、96％、97％、98％或99％的序列同一性并保留野生型蛋白质的毒素结合和/或中和活性。本发明进一步包括编码每个四聚体及其序列变体以及其互补链的多核苷酸序列。

[0147] ABBA是本发明的特定结合剂，其包括四个连接的V_HH单体AH3-E3-E3-AA6。因此ABBA具有两个相同的单体(E3)和两个另外的不同单体(AH3和AA6)(参见表1)。

[0148] ABAB是本发明的另一特定结合剂，其包括四个连接的V_HH单体，每个单体对TcdA或TcdB的不同表位具有结合特异性。ABAB因此是四特异性四聚体结合剂，其由四个不同的中和V_HH单体组成，两个针对TcdA而两个针对TcdB。该结构特征允许ABAB同时结合每个毒素上的两个不同的中和表位。如下所述，ABAB的亲和力/亲合力和中和活性比目前正在接受治疗CDI的临床试验的人单克隆抗体(HuMabs)高3个数量级以上。

[0149] 通过使用柔性接头(表2)连接V_HH单体AH3、5D、AA6和E3(表1)来制备ABAB结合剂。这种结合剂靶向保守的非重叠表位并具有优异的毒素中和活性。在ABAB的设计中(图4)，由于AH3和AA6分别与GT和TD结合(图2)，因此V_HH肽单体AH3和AA6通过放置它们之间的5D进行分离(图2)，其在空间上彼此相距很远。这种设计允许AH3和AA6同时结合TcdA。

[0150] 包括ABAB的完整氨基酸序列在SEQ ID NO:19中提供；编码蛋白质的核酸序列在SEQ ID NO:20中提供。因此，本发明包括SEQ ID NO:19中提供的ABAB结合剂，以及ABAB结合剂的序列变体，其在蛋白质序列的整个长度上具有至少85％、86％、87％、88％、89％、90％、91％、92％、93％、94％、95％、96％、97％、98％或99％的序列同一性并保留野生型蛋白质的毒素结合和/或中和活性。序列变体包括其中变体是人源化的变体和/或其中将氨基酸优化用于酵母的生产和分泌。

[0151] 本发明进一步包括编码ABAB结合剂(例如，SEQ ID NO:20)及其序列变体以及其互补链的多核苷酸序列。

[0152] 本发明所涵盖的ABAB结合剂的修饰版本包括具有以下一种或多种的修饰版本：

(i)位于蛋白质氨基末端处的$His_{(6)}$标签(HHHHHH;SEQ ID NO:66)以帮助纯化,(ii)位于蛋白质的羧基末端处的E标签(GAPVPYPDPLEPR;SEQ ID NO:67)以帮助检测;(iii)位于构建体的羧基末端处的白蛋白结合肽(ABP)(DICLPRWGCLWD;SEQ ID NO:21)以增加蛋白质的血清半衰期,因为V_HH单体具有2-3小时的半衰期并且包含ABP可将血清半衰期增加至10小时(参见图4);和位于蛋白质的羧基末端的D7标签(SSAPTKAKRRVVQREKT;SEQ ID NO:112)。本发明包括具有这些标签和肽中的1、2、3、4个的ABAB结合剂的版本。包含His标签和D7标签的示例性修饰的ABAB结合剂包括SEQ ID NO:113所示的氨基酸序列(编码序列如SEQ ID NO:114所示)。

[0153] 当酵母菌株工程化以产生ABAB时,也可以修饰蛋白质以在蛋白质的氨基末端包含分泌信号。分泌信号可以是但不限于表4所示的序列之一。

[0154] 表4-酵母中蛋白质分泌的分泌序列

[0155]

分泌信号	氨基酸序列	缩写
α-因子_full(酿酒酵母)	MRFPSIFTAVLFAASSALAAPVNTTTEDETAQIPAEAVIGYSDLEGDFDVAVLPFSNSTNNGLLFINTTIASIAAKEEGVSLEKREAEA (SEQ ID NO:96)	FAKS
α-因子_T_kex_ste(酿酒酵母)	MRFPSIFTAVLFAASSALAAPVNTTTEDELEGDFDVAVLPFSASIAAKEEGVSLEKREAEA (SEQ ID NO:97)	AKS
α-因子_T_kex(酿酒酵母)	MRFPSIFTAVLFAASSALAAPVNTTTEDELEGDFDVAVLPFSASIAAKEEGVSLEKR (SEQ ID NO:98)	AK
α-因子_T(酿酒酵母)	MRFPSIFTAVLFAASSALA (SEQ ID NO:99)	AT
Alpha-淀粉酶(黑曲霉)	MVAWWSLFLYGLQVAAPALA (SEQ ID NO:100)	AA
糖化酶(泡盛曲霉)	MSFRSLLALSGLVCSGLA (SEQ ID NO:101)	GA
菊粉酶(克鲁维酵母)	MKLAYSLLLPLAGVSA (SEQ ID NO:102)	IN
蔗糖酶(酿酒酵母)	MLLQAFLFLLAGFAAKISA (SEQ ID NO:103)	IVS
杀伤蛋白(酿酒酵母)	MTKPTQVLVRSVSILFFITLLHLVVA (SEQ ID NO:104)	KP
溶菌酶(原鸡)	MLGKNDPMCLVLVLLGLTALLGICQG (SEQ ID NO:105)	LZ
血清蛋白(智人)	MKWVTFISLLFLFSSAYS (SEQ ID NO:106)	SA

[0156] 包括氨基末端分泌信号的示例性修饰的ABAB结合剂包括AT-ABAB和IVS-ABAB。

[0157] 从酵母或细菌中的质粒表达的示例性修饰的ABAB结合剂包括SEQ ID NO:107所示的ABAB结合剂,其由SEQ ID NO:108中所示的多核苷酸序列编码。

[0158] 在染色体整合后在酵母中表达的示例性修饰的ABAB结合剂包括SEQ ID NO:109所示的ABAB结合剂,其由SEQ ID NO:110所示的多核苷酸序列编码。

[0159] 本发明的每种结合剂以特异性结合TcdA和/或TcdB。在本发明的某些方面,结合剂表现出TcdA和/或TcdB中和活性。

[0160] 为了清楚起见,可以注意到,如本文所使用的,“单特异性”、“双特异性”、“三特异性”,“四特异性”等意指特定的结合剂分别与1、2、3、4等不同的表位结合。如本文所使用的,“单体”、“二聚体”、“三聚体”、“四聚体”等意指特定结合剂具有分别与表位结合的1、2、3、4等单独的V_HH肽单体。因此,单特异性二聚体结合剂将显示结合相同表位的两个V_HH肽单体(例如同型二聚体),并且双特异性二聚体结合剂将具有结合两个不同表位的两个V_HH肽单体(例如,异型二聚体)。四特异性八聚体结合剂具有识别四个不同表位的八个V_HH肽单体。

[0161] V_HH-FC

[0162] 众所周知嵌合Fc融合蛋白具有增加蛋白体内半衰期的潜力。这种策略已经应用于几种FDA批准的药物，如依那西普。原理研究的证据表明，单链抗体可以被携带编码单峰驼V_HH的mini-Ig构建体和人IgG的Fc结构域的转基因小鼠的B细胞正确组装和表达。EG2-Fc，一种嵌合抗-EGFR/EGFRvIII V_HH，在体内表现出优异的肿瘤积累并具有可改善成胶质细胞瘤靶向的药代动力学性质。

[0163] 本发明包括包含连接至抗体Fc结构域(V_HH-Fc)的V_HH肽单体的结合剂，其中结合剂结合TcdA和/或TcdB。在这些基于Fc结构域的结合剂中，1、2、3、4或更多个V_HH肽单体连接至抗体重链的Fc结构域的铰链区、C_H2和C_H3区。因此，肽单体取代抗体的Fab区域。

[0164] V_HH肽单体可以是上表1中提供的那些中的任一种，并且包括5D(SEQ ID NO:1)、E3(SEQ ID NO:3)、AA6(SEQ ID NO:5)和AH3(SEQ ID NO:7)V_HH肽单体。当两个或更多个单体连接时，单体可以通过柔性肽接头连接，通常包含10-20个氨基酸。合适的接头包括表2中提供的接头，例如接头-1(SEQ ID NO:9)、接头-2(SEQ ID NO:11)和接头-3(SEQ ID NO:13)。

[0165] 尽管V_HH-Fc通常由两个在产生后在细胞内自组装的相同链组成，但本发明还包括包含两个不同Fc链的V_HH-Fc结合剂。在这种情况下，单独的V_HH单体的序列可以在两条Fc链之间不同，或者Fc链本身可以在序列上不同，或者V_HH单体和Fc链两者可以在序列上不同。

[0166] 一种类型的V_HH-Fc结合剂是包括抗体Fc结构域和第一、第二、第三和第四V_HH肽单体的八聚体结合剂，其中V_HH肽单体对TcdA或毒素B TcdB的表位具有结合特异性，其中第一、第二、第三和第四V_HH肽单体连接在一起并连接到两个抗体Fc结构域的氨基末端，并且其中抗体Fc结构域包含抗体重链的铰链区、C_H2和C_H3区。因为这种结合剂具有四个V_HH肽单体，所以它可以是单特异性的(其中所有单体结合相同的表位)、双特异性(其中单体结合两个不同的表位)、三特异性(其中单体结合三个不同的表位)或四特异性(其中单体结合四个不同的表位)。

[0167] 四特异性V_HH-Fc结合剂的具体示例是ABAB-Fc结合剂，包括抗体Fc结构域和两组连接的第一、第二、第三和第四V_HH肽单体的四特异性八聚体结合剂，其中抗体Fc结构域包括两个臂，每个臂包括抗体重链的铰链区、C_H2和C_H3区，并且每个臂具有氨基末端，其中对于Fc结构域的每个臂，一组连接的第一、第二、第三和第四V_HH肽单体连接到臂的氨基末端，并且其中V_HH肽单体对TcdA或TcdB的表位具有结合特异性(参见图1)。这种结合剂因其识别四个不同的毒素表位而称为“四特异性”。由于它携带八个V_HH肽单体(第一单体的两个拷贝、第二单体的两个拷贝、第三单体的两个拷贝以及第四单体的两个拷贝)，因此它被称为“八聚体”。发现ABAB-Fc表现出特异性结合和中和活性。

[0168] 通过产生编码与人IgG1Fc结构域连接的V_HH肽单体AH3/5D/AA6/E3(以所示顺序连接)的表达载体来制备ABAB-Fc结合剂。V_HH肽单体通过表2的柔性接头分离。编码每条链的核酸序列在SEQ ID NO:23中提供。每条链的氨基酸序列在SEQ ID NO:22中提供。在表达后自我组装成对链时，产生四特异性八聚体结合剂。本发明包括SEQ ID NO:22的ABAB-Fc结合剂，如上定义的ABAB结合剂的修饰版本及其在蛋白质序列的整个长度上具有至少85％、86％、87％、88％、89％、90％、91％、92％、93％、94％、95％、96％、97％、98％或99％的序列同一性并保留野生型蛋白质的毒素结合和/或中和活性的序列变体。本发明进一步包括编码这些序列变体及其互补链的多核苷酸序列。

[0169] 单特异性V_HH-Fc结合剂(AH3-Fc、5D-Fc、E3-Fc、AA6-Fc)和双特异性V_HH-Fc结合剂

(例如AH3/5D-Fc和AA6/E3-Fc)也使用该Fc融合系统制备。关于单特异性结合剂,将单个V_HH肽单体连接至人IgG1Fc结构域。在表达和组装时,成对的链产生单特异性二聚体结合剂(当链相同时)或双特异性二聚体结合剂(当链不同时)。关于双特异性结合剂,将两个连接的V_HH肽单体(V_HH同型或异型二聚体)连接至人IgG1Fc结构域。在表达和组装时,成对的链产生双特异性四聚体结合剂(当链相同时)或四特异性四聚体结合剂(当链不同时)。表5提供了一些这些结合剂的序列。

[0170] 表5

[0171]

名称	氨基酸序列的SEQ ID NO	核酸序列的SEQ ID NO
5D-Fc	24	25
E3-Fc	26	27
AA6-Fc	28	29
AH3-Fc	30	31
AH3-5D-Fc	32	33
AA6-E3-Fc	34	35

[0172] 与一种单体的特异性配对包括:5D-Fc+5D-Fc;E3-Fc+E3-Fc;AA6-Fc+AA6-Fc;AH3-Fc+AH3-Fc;5D-Fc+E3-Fc;5D-Fc+AA6-Fc;5D-Fc+AH3-Fc;E3-Fc+AA6-Fc;E3-Fc+AH3-Fc和AA6-Fc+AH3-Fc。与两种单体的特异性配对包括:AH3-5D-Fc+AH3-5D-Fc;AA6-E3-Fc+AA6-E3-Fc和AH3-5D-Fc+AA6-E3-Fc。

[0173] 产生包括抗体Fc结构域和两组连接的第一和第二V_HH肽单体的双特异性四聚体V_HH-Fc结合剂,其中抗体Fc结构域包括两个臂,每个臂包括抗体重链的铰链区、C_H2和C_H3区,并且每个臂具有氨基末端,其中对于Fc结构域的每个臂,一组连接的第一和第二V_HH肽单体连接到臂的氨基末端,并且其中V_HH肽单体对TcdA或TcdB的表位具有结合特异性。这种结合剂因其识别两种不同的毒素表位而称为“双特异性”。因为它携带四个V_HH肽单体(第一单体的两个拷贝和第二单体的两个拷贝),所以它被称为“四聚体”。第一和第二V_HH肽单体可以对相同或不同表位具有结合特异性。V_HH肽单体可独立地对TcdA或TcdB的葡糖基转移酶结构域、半胱氨酸蛋白酶结构域、易位结构域或受体结合结构域中的表位具有结合特异性。

[0174] 双特异性四聚体V_HH-Fc结合剂的具体示例包括SEQ ID NO:32(AH3/5D-Fc)所示的氨基酸序列。本发明还包括具有至少95%序列同一性的序列变体,其中序列变体保持毒素中和活性。序列变体的变体氨基酸可以位于V_HH肽单体的框架区中。

[0175] 双特异性四聚体V_HH-Fc结合剂的具体示例包括SEQ ID NO:34(AA6/E3-Fc)所示的氨基酸序列。本发明还包括具有至少95%序列同一性的序列变体,其中序列变体保持毒素中和活性。序列变体的变体氨基酸可以位于V_HH肽单体的框架区中。

[0176] V_HH-Fc结合剂以特异性结合TcdA和/或TcdB。在本发明的某些方面,结合剂表现出TcdA和/或TcdB中和活性。

[0177] V_HH-IgG

[0178] 本发明还包括包含V_HH肽单体的结合剂,所述V_HH肽单体连接至更多的单独Fc结构域的抗体。包括1、2、3、4或更多个V_HH肽单体的V_HH-IgG结合剂与缺少抗体可变区的IgG抗体的轻链(kappa或lambda)和重链连接。因此,肽单体取代抗体的可变区。

[0179] V_HH肽单体可以是上表1中提供的那些中的任一种,并且包括5D(SEQ ID NO:1)、E3

(SEQ ID NO:3)、AA6(SEQ ID NO:5)和AH3(SEQ ID NO:7)V_HH肽单体。当两个或更多个单体连接时,单体可以通过柔性肽接头连接,通常包括10至20个氨基酸。合适的接头包括表2中提供的接头,例如接头-1(SEQ ID NO:9)、接头-2(SEQ ID NO:11)和接头-3(SEQ ID NO:13)。

[0180] V_HH-IgG结合剂包括包含IgG抗体和第一、第二、第三和第四V_HH肽单体的八聚体结合剂,其中V_HH肽单体对TcdA或TcdB的表位具有结合特异性,其中第一和第二V_HH肽单体连接在一起并连接至抗体两条轻链的氨基末端,其中轻链缺少抗体可变区,并且其中第三和第四V_HH肽单体连接在一起并连接至抗体两条重链的氨基末端,其中重链缺少抗体可变区。因为这种结合剂具有四个V_HH肽单体,所以它可以是单特异性的(其中所有单体结合相同的表位)、双特异性(其中单体结合两个不同的表位)、三特异性(其中单体结合三个不同的表位)或四特异性(其中单体结合四个不同的表位)。

[0181] 四特异性V_HH-IgG结合剂的具体示例是ABAB-IgG结合剂,包括IgG抗体、两组连接的第一和第二V_HH肽单体和两组连接的第三和第四V_HH肽单体的四特异性八聚体结合剂,其中IgG抗体包括两个臂,每个臂包含缺乏可变区的轻链和缺少可变区的重链,并且每条链具有氨基末端,其中对于抗体的每个臂,将一组连接的第一和第二V_HH肽单体连接至轻链的氨基末端,并将一组连接的第三和第四V_HH肽单体连接至重链的氨基末端,并且其中V_HH肽单体对TcdA或TcdB的表位具有结合特异性(参见图1)。这种结合剂因其识别四个不同的毒素表位而称为“四特异性”。由于它携带八个V_HH肽单体(第一单体的两个拷贝、第二单体的两个拷贝、第三单体的两个拷贝以及第四单体的两个拷贝),因此被称为“八聚体”。在某些方面,第一、第二、第三和第四V_HH肽单体可各自具有针对不同表位的结合特异性。在某些方面,两个V_HH肽单体可以对TcdA的表位具有结合特异性,并且两个V_HH肽单体可以对TcdB的表位具有结合特异性。在某些方面,V_HH肽单体独立地针对TcdA或TcdB的葡糖基转移酶结构域、半胱氨酸蛋白酶结构域、易位结构域或受体结合结构域中的表位具有结合特异性。

[0182] 四特异性八聚体ABAB-IgG结合剂的具体示例包括具有SEQ ID NO:46所示氨基酸序列(AA6/E3 kappa)的轻(kappa)链或与其具有至少95%序列同一性的序列变体,以及具有SEQ ID NO:44所示氨基酸序列(AH3/5D重)的重链或与其具有至少95%序列同一性的序列变体。在这方面,序列变体保留毒素中和活性。序列变体的变体氨基酸可以位于V_HH肽单体的框架区中。这种结合剂通过制备两种分开的表达载体来制备,第一种编码V_HH肽单体AH3/5D(按照所述顺序连接)与缺乏可变区的人IgG1抗体重链连接,第二种编码V_HH肽单体AA6/E3(按照所述顺序连接)与缺乏可变区的人IgG1抗体轻(kappa)链连接。编码AA6/E3-IgG1轻(kappa)链的核苷酸序列在SEQ ID NO:47中提供。编码AH3/5D-IgG1重链的核苷酸序列在SEQ ID NO:45中提供。本发明包括在蛋白质序列的整个长度上具有至少85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%、98%或99%的序列同一性并保留野生型蛋白质的毒素结合和/或中和活性的ABAB-IgG的序列变体。本发明进一步包括编码这些序列变体及其互补链的多核苷酸序列。

[0183] 双特异性或四特异性四聚体IgG结合剂包括在本发明中。这样的结合剂包括IgG抗体和第一、第二、第三和第四V_HH肽单体,其中IgG抗体包含两个臂,每个臂包含缺乏可变区的重链和缺少可变区的轻链,并且每条链具有氨基末端,其中对于抗体的第一臂,第一V_HH肽单体连接至轻链的氨基末端,并且第二V_HH肽单体连接至重链的氨基末端,其中对于抗体

的第二臂，第三V_HH肽单体连接至轻链的氨基末端，并且第四V_HH肽单体连接至重链的氨基末端，并且其中V_HH肽单体对TcdA或TcdB的表位具有结合特异性。当结合剂是“四特异性”时，它识别四个不同的毒素表位；当是“双特异性”时，它识别两个不同的毒素表位。由于结合剂具有四个V_HH肽单体，结合剂是“四聚体”(当双特异性时，第一和第二单体具有相同的序列并结合相同的表位，并且第三和第四单体具有相同的序列并结合相同的表位；当四特异性时，每个单体具有不同的序列并结合不同的表位)。

[0184] 当结合剂是双特异性时，第一和第三单体对不同表位具有结合特异性，第一和第二单体具有相同的氨基酸序列，并且第三和第四单体具有相同的氨基酸序列。在某些方面，V_HH肽单体中的一个对TcdA的表位具有结合特异性，并且V_HH肽单体中的一个对TcdB的表位具有结合特异性。

[0185] 当结合剂是四特异性时，每个V_HH肽单体对不同表位具有结合特异性。在某些方面，两个VHH肽单体对TcdA的表位具有结合特异性和两个V_HH肽单体对TcdB的表位具有结合特异性。

[0186] 在某些方面，每个V_HH肽单体对TcdA的表位具有结合特异性。在其他方面，每个V_HH肽单体对TcdB的表位具有结合特异性。

[0187] 在某些方面，V_HH肽单体独立地针对TcdA或TcdB的葡糖基转移酶结构域、半胱氨酸蛋白酶结构域、易位结构域或受体结合结构域中的表位具有结合特异性。

[0188] 双特异性四聚体IgG结合剂的具体示例包括具有SEQ ID NO:40(AA6kappa)所示氨基酸序列的轻(kappa)链和具有SEQ ID NO:36(AH3重)所示的氨基酸序列的重链。本发明还包括具有至少95％序列同一性的序列变体，其中序列变体保持毒素中和活性。序列变体的变体氨基酸可以位于V_HH肽单体的框架区中。

[0189] 双特异性四聚体IgG结合剂的另一个具体示例包括具有SEQ ID NO:42(E3 kappa)所示氨基酸序列的轻(kappa)链和具有SEQ ID NO:38(5D重)所示的氨基酸序列的重链。本发明还包括具有至少95％序列同一性的序列变体，其中序列变体保持毒素中和活性。序列变体的变体氨基酸可以位于V_HH肽单体的框架区中。

[0190] 表6提供了用于产生双特异性和四特异性V_HH-IgG结合剂的序列。其他合适的配对包括(i)5D-IgG1-重链+AA6-轻(kappa或lambda)链，和(ii)AH3-IgG1-重链+E3-轻(kappa或lambda)链。

[0191] 表6

[0192]

名称	氨基酸序列的 SEQ ID NO	核酸序列的 SEQ ID NO
AH3-IgG1 重链	36	37
5D-IgG1 重链	38	39
AA6-IgG1 轻 (kappa) 链	40	41
E3-IgG1 轻 (kappa) 链	42	43

[0193]

AH3/5D-IgG1 重链	44	45
AA6/E3-IgG 轻 (kappa) 链	46	47

[0194] 然而，本发明包括与AH3、5D、AA6和E3中的任何一个连接的IgG1重链，以及与AH3、5D、AA6和E3中的任何一个连接的IgG1轻(kappa或lambda)链。此外，本文涵盖重链和轻(kappa或lambda)链的所有可能的组合。

[0195] 人源化结合剂

[0196] 由于它们的框架尺寸小并且它们与家族III的人V_H框架具有高度的同一性，因此预期V_HH肽单体在施用于人时表现出低免疫原性。尽管小单价V_HH单体的系统应用看起来几乎不引起中和抗体应答，但蛋白质免疫原性通常随着尺寸和复杂性而增加。重复和/或长期体内使用V_HH单体的两个主要障碍是它们可能很短的半衰期和潜在的免疫原性。为了增加效价和循环半衰期，可以将V_HH单体与本文讨论的人IgG和Fc结构域融合。为了解决可能的免疫原性，可以根据需要将V_HH单体人源化而不损害它们的表达水平、亲和力、溶解度和稳定性。这些策略应导致人源化V_HH单体(hV_HH单体)的良好表达、稳定性和溶解性，同时保持环供体V_HH的抗原特异性和亲和力。

[0197] 选择与人V_H基因具有最高同一性并具有最高结合/中和活性的hV_HH单体，然后将它们转移到V_HH多聚体(例如ABAB)、V_HH-Fc和V_HH-IgG构建体中以产生完全人源化的结合剂，例如完全人源化的ABAB、ABAB-IgG和ABAB-Fc结合剂。这些人源化结合剂的蛋白质序列可以与人类抗体变体的蛋白质序列基本上相同，尽管其负责抗体结合其靶抗原的能力的一些CDR区段的非人来源。因此，这种策略降低了体内潜在的免疫原性的机会，从而增加了它们在体内的安全性和半衰期。

[0198] 因此，本发明的结合剂涵盖包括hV_HH肽单体的本文定义的每种结合剂的人源化版本。

[0199] 表位结合片段

[0200] 本发明的结合剂包括本文定义的每个V_HH-Fc和V_HH-IgG结合剂的表位结合片段。由于V_HH-Fc和V_HH-IgG结合剂在结构上与人IgG抗体相当，其中可变区被V_HH单体取代，所以人抗体片段的术语也适用于这样的结合剂。片段包括但不限于Fab片段、F(ab')$_2$片段，单链Fv(scFv)抗体和由Fab表达文库产生的片段以及双特异性抗体和三特异性抗体。

[0201] 本发明的V_HH-Fc和V_HH-IgG结合剂包括完全人源化的、人源化的和嵌合的结合剂。结合剂可以是单克隆或多克隆的。此外，结合剂可以是重组结合剂。

[0202] 虽然优选来自哺乳动物如人、猿、小鼠、大鼠、兔、豚鼠、马、牛、绵羊、山羊、猪、狗或猫，但可以在任何动物物种中产生结合剂。例如，结合剂可以是人的或人源化的，或适合于施用于人的任何结合剂制剂。

[0203] 多核苷酸、表达载体、宿主细胞和制备方法

[0204] 本发明包括含有编码本文提供的每种结合剂的核苷酸序列的多核苷酸以及其互补链。

[0205] 本发明还包括包括多核苷酸的表达载体和包含表达载体的宿主细胞。合适的表达载体包括例如pcDNA3.1和pSec-His，以及用于将酵母细胞转化为本发明结合剂的生产者和分泌者的质粒。合适的宿主细胞包括例如中国仓鼠卵巢细胞(CHO细胞)、人胚肾细胞293(HEK 293细胞)、酵母细胞和昆虫细胞。

[0206] 本发明进一步包括产生本文定义的结合剂的方法，包括在促进由表达载体编码的结合剂表达的条件下培养宿主细胞，并从细胞培养物中回收结合剂。

[0207] 酵母的工程菌株

[0208] 本发明的每种结合剂也可以通过酵母属酵母的工程菌株生产。因此，本发明还涉及酿酒酵母属酵母的菌株(例如酿酒酵母和布拉酵母)，其工程化以产生一种或多种本文所

定义的结合剂，包括但不限于V_HH单体结合剂(参见表1)、V_HH同型二聚体结合剂、V_HH异型二聚体结合剂(参见表3)、ABAB结合剂、V_HH-Fc结合剂(参见表5)、V_HH-IgG结合剂(参见表6)及其表位结合片段。在优选的方面，酵母属酵母的工程菌株分泌结合剂。

[0209] 酵母属酵母菌株的身份仅限于其可工程化以产生并优选分泌一种或多种本发明的结合剂。在本发明的优选方面，工程化以产生一种或多种结合剂的酵母属酵母的菌株是酿酒酵母或布拉酵母。因此，本发明包括产生一种或多种本文定义的结合剂的酿酒酵母的工程菌株，以及分泌一种或多种本文定义的结合剂的酿酒酵母的工程菌株。本发明还包括产生一种或多种本文定义的结合剂的布拉酵母的工程菌株，以及分泌一种或多种本文定义的结合剂的布拉酵母的工程菌株。酵母的合适菌株还包括粟酒裂殖酵母(Schizosaccharomyces pombe)、奇异酿酒酵母(Saccharomyces paradoxus)和单孢酵母(Saccharomyces unisporus)。

[0210] 布拉酵母是FDA指定的通常被视为安全(GRAS)的生物体，并且其通常可在非处方用于促进肠道健康和改善由于腹泻疾病引起的胃肠疾病。已对这种酵母菌种进行了多项随机双盲安慰剂对照临床试验，以对包括CDI在内的肠道疾病的安全性和有效性进行研究[42-46]。布拉酵母的合适菌株为布拉酵母菌株MYA796(ATCC，Manassas，VA)。

[0211] 本发明的酵母属酵母工程菌株的具体示例是酵母属酵母的工程菌株，其产生包括V_HH肽单链连接的包括2、3、4或更多个单体的V_HH肽单体基团的结合剂，它们中的每一个优选地以特异性结合TcdA和/或TcdB。因此，本发明包括产生V_HH肽结合剂的酵母属酵母工程菌株，所述V_HH肽结合剂包括至少一种V_HH肽单体，其中每个V_HH肽单体对艰难梭菌毒素A(TcdA)或毒素B(TcdB)的表位具有结合特异性。在某些方面，这些结合剂包括2、3、4或更多个连接的V_HH肽单体。V_HH肽单体包括但不限于V_HH肽单体5D(SEQ ID NO:1)、E3(SEQ ID NO:3)、AA6(SEQ ID NO:5)和AH3(SEQ ID NO:7)。

[0212] 本发明的酵母属酵母的工程菌株的另一个具体示例是酵母属酵母的工程菌株，其产生包括与IgG抗体连接的V_HH肽单体的结合剂，其中所述结合剂结合如本文所定义的TcdA和/或TcdB。在这些基于IgG的结合剂中，IgG抗体的轻链和重链的可变区被1、2、3、4或更多个V_HH肽单体替换。

[0213] 本发明的酵母属酵母的工程菌株的另一个具体示例是酵母属酵母的工程菌株，其产生包括连接至抗体Fc结构域的V_HH肽单体的结合剂，其中所述结合剂结合如本文所定义的TcdA和/或TcdB。在这些基于Fc结构域的结合剂中，1、2、3、4或更多个V_HH肽单体连接至抗体重链的Fc结构域的每个臂的铰链区、C_H2和C_H3区。因此，肽单体取代抗体的Fab区域。

[0214] 本发明的酵母属酵母的工程菌株的另一个具体示例是产生四特异性四聚体结合剂的酵母属酵母的工程菌株，其中所述结合剂包括连接的第一、第二、第三和第四V_HH肽单体，并且其中所述V_HH肽单体独立地对艰难梭菌毒素A(TcdA)或毒素B(TcdB)的表位具有结合特异性。在某些方面，第一、第二、第三和第四V_HH肽单体各自对不同表位具有结合特异性。在某些方面，两个V_HH肽单体对TcdA的表位具有结合特异性，并且两个V_HH肽单体对TcdB的表位具有结合特异性。在某些方面，V_HH肽单体独立地针对TcdA或TcdB的葡糖基转移酶结构域、半胱氨酸蛋白酶结构域、易位结构域或受体结合结构域中的表位具有结合特异性。合适的V_HH肽单体包括AH3单体(SEQ ID NO:7)、AA6单体(SEQ ID NO:5)、5D单体(SEQ ID NO:1)和E3单体(SEQ ID NO:3)。其他单体包括但不限于表1中提供的那些单体。

[0215] 在优选的示例中，本发明涉及酵母的工程菌株，其中结合剂是ABAB，其中第一和第三单体对TcdA的表位具有结合特异性，第一和第三单体分别是V_HH肽单体AH3(SEQ ID NO:7)和AA6(SEQ ID NO:5)，并且其中第二和第四单体对TcdB的表位具有结合特异性，第二和第四单体分别是V_HH肽单体5D(SEQ ID NO:1)和E3(SEQ ID NO:3)。

[0216] ABAB结合剂可以包括SEQ ID NO:19所示的氨基酸序列或与其具有至少95％序列同一性的序列变体，其中所述序列变体保留TcdA和/或TcdB结合特异性，或序列变体保留毒素中和活性或保留两者。

[0217] ABAB结合剂还可以包含选自表4中提供的分泌信号的N端分泌信号。在优选的方面，N端分泌信号是AT分泌信号(MRFPSIFTAVLFAASSALA(SEQ ID NO:99))或IVS分泌信号(MLLQAFLFLLAGFAAKISA(SEQ ID NO:103))。

[0218] ABAB结合剂可以从酵母内的质粒表达。质粒可以是但不限于pCEV-URA3-TEF-AT-yABAB-cMyc(SEQ ID NO:88)。由质粒编码的ABAB结合剂可以包括SEQ ID NO:107所示的氨基酸序列或与其具有至少95％序列同一性的序列变体，并且其中所述序列变体保留TcdA和/或TcdB结合特异性，或序列变体保留毒素中和活性，或保留两者。

[0219] ABAB结合剂也可以从整合到酵母染色体中的编码序列表达。从整合到酵母染色体中的编码序列表达的ABAB结合剂可以包括SEQ ID NO:109所示的氨基酸序列或与其具有至少95％序列同一性的序列变体，并且其中所述序列变体保留TcdA和/或TcdB结合特异性，或序列变体保留毒素中和活性，或保留两者。

[0220] 本发明还涉及产生对艰难梭菌毒素A(TcdA)或毒素B(TcdB)或两者的独特表位具有结合特异性的治疗性蛋白的酵母属酵母的工程菌株。优选地，酵母属酵母的工程菌株是酿酒酵母或布拉酵母。治疗性蛋白质是可以在受试者的医学状况中带来改善或治愈，或者可以抑制或预防受试者的医学状况发展的任何蛋白质。合适的治疗性蛋白质包括但不限于能够(a)代替缺陷或异常的蛋白质；(b)增加现有途径；(c)提供新颖的功能或活动；(d)干扰分子或生物体；和(e)传递其他化合物或蛋白质，如放射性核素、细胞毒性药物或效应蛋白质。治疗性蛋白质还包括抗体和基于抗体的药物、Fc融合蛋白质、抗凝血剂、血液因子、骨形态发生蛋白质、工程蛋白质支架、酶、生长因子、激素、干扰素、白细胞介素和溶栓剂。治疗性蛋白质进一步包括双特异性单克隆抗体(mAb)和多特异性融合蛋白质，与小分子药物缀合的mAb以及具有优化药代动力学的蛋白质。

[0221] 制备工程化酵母菌株的方法

[0222] 本发明还涉及工程化酵母属酵母的菌株以产生本文定义的一种或多种结合剂的方法。用于生产酵母的工程菌株的手段没有特别限制，并且存在许多用于工程化酵母以产生本领域技术人员已知的同源和异源蛋白质的已知技术。在这些方法的某些方面，酿酒酵母或布拉酵母菌经工程化以产生结合剂。

[0223] 作为示例，可以通过(a)用编码结合剂的表达载体转化酵母属酵母菌株，和(b)筛选产生的酵母，将酵母属酵母工程化以产生本文定义的一种或多种结合剂用于生产结合剂。在某一方面，表达载体是质粒pCEV-URA3-TEF-AT-yABAB-cMyc(SEQ ID NO:88)。虽然该质粒编码特定的ABAB结合剂，但这种结合剂的编码区可被本文定义的任何结合剂的编码区取代。

[0224] 作为进一步的示例，可以通过(a)将编码结合剂的多核苷酸序列染色体整合到酵

母属酵母菌株的基因组中，和(b)筛选(a)中的酵母将酵母属酵母工程化以产生本文定义的一种或多种结合剂用于生产结合剂。在某些方面，使用CRISPR技术进行染色体整合[85-88]。作为示例，这样的方法可以包括以下步骤：(a)使用引物从质粒pCEV-G4-Km-TEF-AT-yABAB hAA6T83N-tagless(SEQ ID NO:90)扩增编码ABAB结合剂的多核苷酸序列，所述引物包含(i)与选择的酵母染色体整合位点同源的核酸序列和(ii)与质粒的ABAB结合剂编码序列的5'和3'区域同源的核酸序列，以产生整合盒，(b)在促进整合盒自发整合到双链断裂位点的条件下，将(a)中产生的整合盒用pCRI-Sb-δ1(SEQ ID NO:91)或pCRI-Sb-δ2(SEQ ID NO:92)转化酵母以诱导相应酵母染色体δ位点内的双链断裂，(c)筛选(b)中的转化酵母以产生ABAB结合剂。

[0225] 虽然质粒pCEV-G4-Km-TEF-AT-yABAB hAA6T83N-tagless编码特定的ABAB结合剂，但这种结合剂的编码区可由本文定义的任何结合剂的编码区取代。

[0226] 筛选用于产生结合剂的酵母的合适手段对于本领域技术人员将是显而易见的，并且包括但不限于免疫测定法，例如ELISA或蛋白质印迹。

[0227] 治疗和预防的方法

[0228] 本发明的结合剂和酵母属酵母的工程菌株可以用于治疗或预防受试者中由艰难梭菌诱导的疾病症状的方法。这些方法通常包括向患有艰难梭菌感染或发展艰难梭菌感染风险的受试者施用治疗有效量的如本文定义的一种或多种结合剂和/或一种或多种酵母属酵母的工程菌株。在该实施例的某些方面，由艰难梭菌诱发的疾病症状是腹泻。

[0229] 本发明的结合剂和酵母属酵母的工程菌株也可用于在艰难梭菌感染的受试者中中和艰难梭菌毒素TcdA和/或TcdB。这些方法通常包括向患有艰难梭菌感染的受试者施用治疗有效量的如本文定义的一种或多种结合剂和/或一种或多种酵母属酵母的工程菌株。

[0230] 本发明的结合剂和酵母属酵母的工程菌株可以进一步用于治疗受试者的艰难梭菌感染的方法中。这些方法通常包括向患有艰难梭菌感染的受试者施用治疗有效量的如本文所定义的一种或多种结合剂和/或一种或多种酵母属酵母的工程菌株。如本文所定义的，这些相同的方法可以用于治疗CDI。

[0231] 本发明的结合剂和酵母属酵母的工程菌株也可用于在患有艰难梭菌感染的受试者中维持正常肠功能的方法中。这些方法通常包括向患有艰难梭菌感染或患有发生艰难梭菌感染的风险的受试者施用治疗有效量的如本文所定义的一种或多种结合剂和/或一种或多种酵母属酵母的工程菌株。

[0232] 结合剂和酵母属酵母的工程菌株也可以用于免疫预防以防止立即的CDI威胁。另外，被动免疫预防可以用来预防直接和长期的CDI威胁。每种方法都有其特殊的优势，适合针对特定的高风险人群。这些方法通常包括向患有艰难梭菌感染风险的受试者施用治疗有效量的如本文所定义的一种或多种结合剂和/或一种或多种酵母属酵母的工程菌株。

[0233] 在本发明方法的优选方面，酵母属酵母是酿酒酵母或布拉酵母。

[0234] 本发明的每种方法可以包括在一种或多种药物制剂中施用一种或多种结合剂和/或一种或多种酵母属酵母的工程菌株，所述药物制剂包括结合剂和/或酵母属酵母的工程菌株和药学上可接受的载体或稀释剂。在优选的方面，酵母属酵母是酿酒酵母或布拉酵母。

[0235] 如本文所使用的，术语“治疗”(treat、treating和treatment)具有其普通和习惯的含义，并且包括以下的一种或多种：在受试者中阻断、改善或降低艰难梭菌感染或艰难梭

菌相关性疾病(CDI)的症状的严重程度和/或频率;和/或在感染艰难梭菌的受试者中部分或完全抑制生物活性和/或促进艰难梭菌TcdA和/或TcdB的免疫清除;和/或在受试者中艰难梭菌细胞或艰难梭菌感染的生长、分裂、扩散或增殖。治疗意指相对于尚未实施本发明的方法的受试者阻断、改善、降低或抑制约为1%至约100%。优选地,与其中尚未实施本发明的方法的受试者相比较,阻断、改善、降低或抑制约为100%、99%、98%、97%、96%、95%、90%、80%、70%、60%、50%、40%、30%、20%、10%、5%或1%。

[0236] 如本文所使用的,术语"预防"(prevent、preventing和prevention)具有其普通和习惯的含义,并且包括以下的一种或多种:在受试者中阻止、防止、避免,缓解或阻断艰难梭菌定殖化、发展或进展;和/或部分或完全抑制感染艰难梭菌的受试者中TcdA和/或TcdB的生物学活性和/或毒性作用;和/或阻止、防止、避免、缓解或阻断受试者中细菌细胞或细菌感染的生长、分裂、扩散或增殖。预防意味着相对未预防给药的受试者阻止至少约95%。优选地,阻止为约100%、约99%、约98%、约97%、约96%或约95%。预防的结果可以持续数天(例如1、2、3、4、5、6或7天),数周(例如1、2、3或4周)或数月(例如1、2、3、4、5、6或更多个月)。

[0237] 本文提供的治疗和预防方法可通过还向受试者施用治疗有效量的抗生素来补充。优选地,抗生素将具有针对艰难梭菌的抗菌活性。

[0238] 药物制剂

[0239] 尽管结合剂和酵母属酵母的工程菌株可以直接施用于受试者,但本发明的方法优选基于施用包含一种或多种结合剂和/或一种或多种酵母属酵母的工程菌株,以及药学上可接受的载体或稀释剂。因此,本发明包括药物制剂,其包含本文定义的一种或多种结合剂和/或一种或多种酵母属酵母的工程菌株以及药学上可接受的载体或稀释剂。

[0240] 药学上可接受的载体和稀释剂通常是已知的,并且将根据施用的特定的结合剂或酵母属酵母的工程菌株和施用模式而变化。通常使用的载体和稀释剂的示例包括但不限于盐水、缓冲盐水、右旋糖、注射用水、甘油、乙醇及其组合,稳定剂、增溶剂和表面活性剂,缓冲剂和防腐剂,张力剂、填充剂和润滑剂。包括结合剂和/或酵母属酵母的工程菌株的制剂通常将在没有任何非人组分,诸如动物血清(例如牛血清白蛋白)的情况下制备和培养。

[0241] 可以使用本领域技术人员已知的模式和技术将包含一种或多种结合剂和/或一种或多种酵母属酵母的工程菌株的药物制剂给予受试者。CDI疾病的特征可使其更适合于使用治疗剂的结肠递送(即将结合剂靶向递送至下胃肠道,例如大肠或结肠)进行治疗和预防。其他递送模式包括但不限于口服、鼻腔、肛门和通过静脉注射或气雾剂给药。其他模式包括但不限于皮内、皮下(s.c.、s.q.、sub-Q、Hypo)、肌内(i.m.)、腹膜内(i.p.)、动脉内、髓内、心内、关节内(关节)、滑膜内(关节流体区域)、颅内、脊柱内和鞘内(脊髓液)。

[0242] 取决于给药方式,剂量可一次全部给药,例如在胶囊或液体中的口服制剂,或缓慢地通过一段时间给药,例如肌内或静脉内给药。

[0243] 给受试者单独或在药物制剂中的结合剂的量是有效治疗或预防感染的量。因此,当实施本发明的方法时,将治疗有效量施用于受试者。通常,每个受试者体重施用约1ug/kg至约1000mg/kg的结合剂。合适的范围还包括约50ug/kg至约500mg/kg之间,以及约10ug/kg至约100mg/kg之间。然而,根据感染的部位、来源、程度和严重程度,待治疗的受试者的年龄和状况、给药方式等,给予受试者的结合剂的量将在宽的范围内变化。医师将最终确定使用的适当剂量。

[0244] 给受试者单独或在药物制剂中的酵母属酵母的工程菌株的量是有效治疗或预防感染的量。因此，当实施本发明的方法时，将治疗有效量施用于受试者。通常，每个受试者体重施用约1ug/kg至约1000mg/kg的酵母属酵母的工程菌株。合适的范围还包括约50ug/kg至约500mg/kg之间，以及约10ug/kg至约100mg/kg之间。然而，根据感染的部位、来源、程度和严重程度，待治疗的受试者的年龄和状况、给药方式等，给予受试者的酵母属酵母的工程菌株的量将在宽的范围内变化。医师将最终确定使用的适当剂量。

[0245] 结合剂、酵母属酵母的工程菌株和包括结合剂和/或酵母属酵母的工程菌株的药物制剂的施用频率将根据包括细菌感染的位置，待治疗或预防的感染的细节以及施用模式的因素而变化。每种制剂可以每天4、3、2或一次、隔日一次、每三天一次、每四天一次、每五天一次、每六天一次、每周一次、每八天一次、每九天一次、每十天一次、双周、每月和双月独立施用。

[0246] 治疗或预防的持续时间将基于所治疗感染的位置和严重程度或感染的相对风险，并由主治医师最好地确定。但是，继续治疗预计会持续数天、数周或数月。

[0247] 在本发明的每个实施例和方面中，受试者是人、非人灵长类动物、鸟、马、牛、山羊、绵羊、伴侣动物，例如狗、猫或啮齿动物或其他哺乳动物。可以应用本发明方法的受试者包括具有使其更容易感染艰难梭菌的潜在疾病或病症的受试者。

[0248] 本发明还提供了一种试剂盒，其包括一个或多个装有一种或多种结合剂、一种或多种酵母属酵母的工程菌株或一种或多种包括结合剂和/或酵母属酵母的工程菌株的药物制剂的容器。该试剂盒还可能包含使用说明。与试剂盒相关的进一步信息可能是政府机构规定的关于制造、使用或销售药品或生物制品的规定的通知，该通知反映了制造、使用或销售机构对人类管理的批准。

[0249] III.示例

[0250] V_HH单体和异型二聚体结合剂

[0251] 建立了筛选针对毒素TcdA和TcdB的特定结构域的单结构域(单体)，单特异性V_HH肽单体的有效平台。使用高度免疫原性的无毒全毒素用于免疫，和生物活性嵌合毒素(具有正常的功能域功能)用于筛选，制备与TcdA或TcdB的不同结构域结合的V_HH单体组。这些V_HH单体中的大多数具有有效的中和活性，并确定了它们与特定结构域的结合(图2)。如前所述，无毒全毒素在其酶促葡糖基转移酶结构域处有点突变[33]。生物活性嵌合毒素是通过在TcdA和TcdB之间转换功能域而产生的，这在之前也有介绍[33]。

[0252] 几种V_HH单体结合高度保守的TcdA/TcdB表位。例如，V_HH E3结合到Rho GTP酶结合位点并阻断葡糖基化；V_HH AH3结合毒素的GT结构域；V_HH 7F结合半胱氨酸蛋白酶切割位点并阻断GT结构域切割和释放。一些V_HH单体具有有效的中和活性，能够在nM浓度下阻断毒素细胞毒活性(参见表1；图3A和3B)。

[0253] 为了增强结合活性，产生了两个结构域(二聚体)，双特异性V_HH异型二聚体(表3；图3C)，允许单一蛋白质靶向毒素的两个不同表位。与相同的两个V_HH单体的等摩尔混合物相比，这些双特异性V_HH异型二聚体具有显着增强的中和活性(图3D)。发现异型二聚体5D/E3和AH3/AA6分别完全保护小鼠免受致死性全身TcdB或TcdA攻击，而混合的5D和E3或AA6单独仅部分保护(图3E和3F)。

[0254] 通过遗传融合具有靶向保守、非重叠表位(AH3/E3/E3/AA6)的最高中和活性的

V_HH,产生四价三特异性V_HH结合剂(ABA)[41]。这种合理设计的毒素结合剂实现了对各单体的显着增强的结合亲和力和中和活性以及对暴发性CDI的有效治疗效力。ABA能够广泛地中和来自11种不同$TcdA^+TcdB^+$艰难梭菌临床分离株的毒素,但不能中和来源于两个$TcdA^-TcdB^+$菌株的TcdB。ABA的氨基酸序列示于SEQ ID NO:111。

[0255] 使用选自SEQ ID NO:9-13(表2)的柔性接头连接包括异型二聚体的V_HH单体。

[0256] ABAB结合剂

[0257] 通过连接V_HH单体AH3、5D、E3和AA6,即ABBA(AH3/5D/E3/AA6)和ABAB(AH3/5D/AA6/E3),产生四个结构域(四聚体)四特异性V_HH结合剂。这些四特异性四聚体结合剂靶向保守的非重叠表位并具有优异的毒素中和活性。在ABAB的设计中(图4),通过将5D单体置于它们之间来分离V_HH肽单体AH3和AA6,因为AH3和AA6分别结合GT和TD(图2),它们在空间上彼此相距很远。这种设计允许AH3和AA6同时结合TcdA。

[0258] 在ABAB结合剂的构建中,柔性接头置于V_HH单体之间(参见图4)。编码ABAB的完整核酸序列在SEQ ID NO:20中提供;该蛋白质的氨基酸序列在SEQ ID NO:19中提供。

[0259] 在某些变体中,在蛋白质的氨基末端提供$His_{(6)}$标签以帮助纯化,在蛋白质的羧基末端提供E标签以帮助检测,和/或白蛋白结合肽(ABP,DICLPRWGCLWD;SEQ ID NO:21)置于构建体的羧基末端以增加蛋白质的血清半衰期(参见图4)。

[0260] 发现ABAB对单个单体和ABA表现出显着提高的结合亲和力(表7)和中和活性(表8)。在表8中,在连续稀释的AA6、AH3、ABAB或Merck抗-TcdA HuMab存在下,将Vero细胞暴露于5ng/ml的TcdA [9]。显示了保护细胞免受TcdA诱导的细胞变圆破坏的抗体的最小剂量。

[0261] 表7

[0262]

	V_HH	K_{on} (Ms^{-1})	K_{off} (s^{-1})	K_D (nM)
TcdA	AH3	2.20×10^4	7.10×10^{-4}	32.0
	AA6	3.52×10^4	6.92×10^{-4}	19.7
	ABAB	***6.96×10^5***	***1.21×10^{-6}***	***0.002***
TcdB	5D	1.52×10^6	9.94×10^{-4}	0.65
	E3	2.95×10^6	9.4×10^{-5}	0.03
	ABAB	***1.79×10^6***	***3.57×10^{-6}***	***0.002***

[0263] 表8

[0264]

AA6	AH3	ABAB	Merck抗-TcdA HuMab
8nM	8nM	0.25nM	>10nM

[0265] 还发现ABAB在竞争性ELISA中与全部四种单独的V_HH肽单体竞争,并且可以同时结合TcdA和TcdB,如通过夹心ELISA所测定的。此外,ABAB具有广泛的反应性,能够中和来自代表大多数当前流行毒株的13种不同艰难梭菌菌株的毒素(表9)。

[0266] 表9

[0267]

菌株	核糖核酸型	REA 型	PFGE 型	毒素	分离的地点/日期	ABAB 中和
R20291	27	Bl	NAP1	TcdA/TcdB	伦敦/2006	Yes
CD196	27	Bl	NAP1	TcdA/TcdB	法国/1985	Yes
630	12	R		TcdA/TcdB	苏黎世/1982	Yes
M120	78	BK	NAP7,8,9	TcdA/TcdB	英国/2007	Yes
BI-9	1	J	NAP2	TcdA/TcdB	Gerding 集合	Yes
Liv024	1	J	NAP2	TcdA/TcdB	利物浦/2009	Yes
Liv022	106	DH	NAP11	TcdA/TcdB	利物浦/2009	Yes
TL178	2	G	NAP6	TcdA/TcdB	贝尔法斯特/2009	Yes
TL176	14	Y	NAP4	TcdA/TcdB	剑桥，英国/2009	Yes
TL174	15			TcdA/TcdB	剑桥，英国/2009	Yes
CD305	23			TcdA/TcdB	伦敦/2008	Yes
CFS	17			TcdB	比利时/1995/人	Yes
M68	17			TcdB	都柏林/2006/人	Yes

[0268] 由于ABAB在结合和中和两种毒素方面表现出高效力，因此评估了其治疗暴发性CDI的功效。在小鼠中，艰难梭菌芽孢攻击后一天低至40μg/kg的ABAB单次注射可以使暴发性CDI逆转。感染后3天，ABAB处理的小鼠没有一只死亡，而50％的对照小鼠濒死(图5A)。TcdA和TcdB系统攻击后ABAB的预防死亡率比Merck HuMabs高4个数量级(图5B)[9]。因此，ABAB对艰难梭菌毒素和孢子攻击具有非凡的体内效力。

[0269] 动物和人体研究表明，被动施用的抗毒素抗体提供针对CDI的保护。这里的初步研究还显示抗毒素polysera保护小鼠免于原发性CDI(图6A和6B)和复发性/再发性CDI。图5A和5B的这些发现和结果支持该假设并提供了开发用于预防CDI的肠胃外ABAB免疫策略的基本原理。为了实现优化ABAB用于全身递送的目标，如图1所示生成嵌合和人源化ABAB，即V_HH-Fc和V_HH-IgG结合剂以及人源化蛋白hV_HH-Fc和hV_HH-IgG，之后评估主要蛋白质在动物模型中的体内中和活性和保护作用。在以下段落中提供了关于附加结合剂的制备和测试的细节。

[0270] ABAB-Fc

[0271] 通过产生编码与人IgG1Fc结构域连接的V_HH肽单体AH3/5D/AA6/E3(以所述顺序连接)的表达载体来制备ABAB-Fc结合剂。V_HH肽单体通过表2的柔性接头分离。编码蛋白质的核酸序列提供于SEQ ID NO:23中。在允许二硫键形成和二价分子产生的条件下，使用蛋白质A珠从稳定转染的HEK293细胞系培养物上清液中表达和纯化ABAB-Fc。表达水平为约20mg/L培养物上清液。ABAB-Fc在结合和中和TcdA和TcdB方面具有完全功能(数据未显示)。ABAB-Fc的氨基酸序列在SEQ ID NO:22中提供。

[0272] 单特异性V_HH-Fc结合剂(AH3-Fc、5D-Fc、E3-Fc和AA6-Fc)和双特异性V_HH-Fc结合剂(AH3/5D-Fc)和AA6/E3-Fc)也使用该Fc-融合系统制成。上表5提供了这些额外的结合剂的序列。

[0273] ABAB-IgG

[0274] 如图1中所示，双特异性V_HH-IgG(AH3/5D-IgG和E3/AA6-IgG)可通过将单体分别与人IgG重链和轻(kappa或lambda)链融合而产生。四聚体特异性V_HH-IgG(ABAB-IgG)结合剂可通过将二聚体分别与人IgG重链和轻链融合来产生。共转染重链和轻链构建体产生AH3/

5D-IgG、E3/AA6-IgG和ABAB-IgG嵌合蛋白。将两个V_HH分离成重链和轻链可能会提高双特异性和四特异性V_HH嵌合蛋白的产量和稳定性。这可以确定V_HH-人IgG嵌合抗体是否有助于体内ABAB的稳定性和功效。类似地,ABAB-IgG的体内半衰期的进一步改善也可以在对FcRn受体具有增强的结合亲和力的ABAB-IgG变体中测试。

[0275] 通过共转染编码每种结合剂的重链和轻(kappa)链的表达载体来制备双特异性(AH3/5D-IgG1和E3/AA6-IgG1)和四特异性(ABAB-IgG1)IgG1结合剂。V_HH肽单体通过表2的柔性接头分离。

[0276] 双特异性四聚体V_HH-IgG1结合剂通过制备两种分开的表达载体来产生,第一种编码与缺少重链可变区的人IgG1抗体重链(CH1-铰链-CH2-CH3)连接的V_HH肽单体,并且第二种编码与缺少轻链可变区的人IgG1抗体轻(kappa)链(CK)连接的V_HH肽单体。这些结合剂是双特异性和四聚体的,因为所得结合剂的每条轻链连接至第一V_HH单体,并且所得结合剂的每条重链连接至第二V_HH单体。上表6提供了这些另外的结合剂的序列。合适的配对包括(i)AH3-IgG1-重链+AA6-轻(kappa或lambda)链,(ii)5D-IgG1-重链+E3-轻(kappa或lambda)链,(iii)5D-IgG1-重链+AA6-轻(kappa或lambda)链,和(iv)AH3-IgG1-重链+E3-轻(kappa或lambda)链。

[0277] 制备了四特异性八聚体ABAB-IgG结合剂。这些结合剂是四特异性和八聚体的,因为所得结合剂的每个轻(kappa或lambda)链连接到两个(第一和第二)连接的V_HH单体,并且所得结合剂的每条重链连接至两个(第三和第四)连接的V_HH单体,其中第一、第二、第三和第四单体结合不同的表位。

[0278] 通过制备两种分开的表达载体来产生特定的四特异性八聚体ABAB-IgG(图7)结合剂,第一种编码与缺少重链可变区的人IgG1抗体重链(CH1-铰链-CH2-CH3)连接的V_HH肽单体AH3/5D(按上述顺序连接),并且第二种编码与缺少轻链可变区的人IgG1抗体轻(kappa)链(CK)连接的V_HH肽单体AA6/E3(按上述顺序连接)。编码AH3/5D-IgG1重链的核苷酸序列在SEQ ID NO:45中提供;氨基酸序列在SEQ ID NO:44中提供。编码AA6/E3-IgG1 kappa链的核苷酸序列在SEQ ID NO:47中提供;氨基酸序列在SEQ ID NO:46中提供。

[0279] 在允许二硫键形成和二价分子生产的条件下,使用蛋白A珠在稳定转染的HEK293细胞系培养物上清液中表达和纯化双特异性(AH3/5D-IgG1和E3/AA6-IgG1)和四特异性(ABAB-IgG1)IgG1结合剂。SDS-PAGE显示纯化的ABAB-IgG1的纯度在非还原凝胶上在218KDa附近具有总分子量(轻链和重链一起)的超过90%的纯度(数据未显示)。在还原的凝胶上显示重链的分子量为68KDa,轻链为41KDa。

[0280] 测定了ABAB-IgG1与TcdA和TcdB的结合。图8A-8B示出了ABAB-IgG1与两种毒素的结合与单独组分(AH3、AA6、E3和5D)的比较。图8A显示了其中平板用1ug/ml TcdA(TxA)涂布的实验结果。以0、0.64、3.2、16、80、400和2,000ng/ml的浓度添加连续稀释的ABAB-IgG。洗涤平板并以指定量(ng/ml)加入Merck Ab(抗TcdA)、Fc-ABBA(ABAB-Fc)、Habab(ABAB-IgG)和V_HH抗TcdB单体AA6和AH3。使用适当的标记抗体用于检测。图8B显示了其中平板用1ug/ml TcdB(TxB)涂布的实验结果。以0、0.64、3.2、16、80和400ng/ml的浓度添加连续稀释的ABAB-IgG。洗涤平板并以指定量(ng/ml)加入Merck Ab(抗TcdA)、Fc-abba(ABAB-Fc)、Habab(ABAB-IgG)和V_HH抗TcdB单体E3和5D。使用适当的标记抗体用于检测。

[0281] 如所预期的,如通过夹心ELISA(图9A-9B)所确定的,四特异性抗体可以同时结合

TcdA和TcdB。在第一组实验中，用1ug/ml TcdA(TxA)涂布平板。以0、1.6、8、40、200和1000ng/ml的浓度添加连续稀释的ABAB-IgG(Habab)。洗涤平板并加入下列量的TcdB:1.6、8、40、200和1000ng/ml。使用小鼠抗TxB抗体(500x)和山羊抗小鼠IgG-HRP(3000x)抗体用于检测。图9A中提供的结果显示通过涂布TxA检测TxB，表明IgG-ABAB同时结合TxA/B。在第二组实验中，用1ug/ml TcdB(TxB)涂布平板。以0、1.6、8、40、200和1000ng/ml的浓度添加连续稀释的ABAB-IgG(Habab)。洗涤平板并加入下列量的TcdA:1.6、8、40、200和1000ng/ml。使用小鼠抗TxA抗体(500x)和山羊抗小鼠IgG-HRP(3000x)抗体进行检测。图9B中提供的结果显示通过涂布TxB检测TxA，再次表明IgG-ABAB同时结合TxA/B。

[0282] 还检测了ABAB-IgG1对于毒素对培养细胞的致细胞病变作用的中和活性。在加入100ul培养基中的Vero细胞单层之前，将TcdA(100ng/ml，图10A)与连续稀释的Merck抗-TcdA人单克隆抗体ABAB-IgG1(Hababa)和V_HH抗-TcdA单体AA6和AH3混合，并在37℃温育24小时。图10A中提供的结果显示ABAB-IgG1在中和TcdA方面比Merck抗体有效至少1000倍。在类似的实验中，在加入100ul培养基中的Vero细胞单层之前，将TcdB(10pg/ml，图10B)与连续稀释的Merck抗-TcdB人单克隆抗体ABAB-IgG1(Hababa)和V_HH抗-TcdB单体E3和5D混合，并在37℃温育24小时。图10B中提供的结果显示ABAB-IgG1在中和TcdB方面比Merck抗体有效至少1000倍。

[0283] 在小鼠CDI模型中研究了ABAB-IgG1的体内中和活性，其结果显示在图11中。用致死剂量的混合TcdA和TcdB(每只小鼠每种毒素25ng)和4小时后将ABAB-IgG(10、30或100ug/kg)，Merck抗毒素A和抗毒素B抗体(10mg/kg)的混合物或PBS施用给小鼠。结果表明ABAB-IgG的中和活性比Merck抗体大得多，并且在较低的浓度下。

[0284] ABAB-IgG的动物测试

[0285] 在预防性治疗和再次攻击存活测定中都测试了ABAB-IgG结合剂。图12提供了这两项研究的实验设计。使用6-8周龄的雌性C57小鼠，条件包括PBS:10ml/kg，i.p.，n＝14；ABAB-IgG:200ug/kg，i.p.，n＝10；ABAB-IgG:1mg/kg，i.p.，n＝10；ABAB-IgG:5mg/kg，i.p.，n＝10。

[0286] 表10提供了针对艰难梭菌芽孢预防性治疗小鼠(UK1，027/BI/NAP1流行菌株)所见结果的总结。在施用艰难梭菌孢子之前一天施用ABAB-IgG或PBS。可以看出，ABAB-IgG显示剂量相关的抗CDI预防性保护，其中5mg/kg显示对所有检查参数的完全保护，并且发现200ug/kg比200ug/kg双特异性V_HH融合抗体ABA更有效[41]。

[0287] 表10

[0288]

	腹泻			体重变化				存活
	发生	第一天得分	第二天得分	全部	第二天	第三天	第四天	
200 ug/kg		–	–	–	√	–	√	√
1 mg/kg	√	–	√	–	√	√	–	√
5 mg/kg	√	√	√	√	√	√	√	√

[0289] 表11提供了小鼠针对艰难梭菌孢子的再次攻击所见的结果的总结。在施用艰难梭菌孢子之前15天施用ABAB-IgG或PBS。可以看出，一次剂量的ABAB-IgG显示出一些针对由孢子再次攻击引起的CDI的保护作用，但与初次攻击相比，保护效率低得多。这可能是由于随着时间的推移，抗体水平的下降以及初次攻击后PBS组中抗体的产生。

[0290] 表11

[0291]

	腹泻			体重变化				存活
	发生	第一天得分	第二天得分	全部	第二天	第三天	第四天	
200 ug/kg	√	√	-	-	-	-	-	-
1 mg/kg	√	-	-	-	-	-	√	-
5 mg/kg	-	-	-	√	-	-	-	-

[0292] 还测试了IgG-ABAB的肠道递送保护小鼠免受暴发性CDI的影响。在剖腹术后将单个IgG-ABAB注射入小鼠ceca后，完全保护小鼠免受死亡结果的暴发性CDI，而50％的对照小鼠死亡(数据未显示)。疾病的进展和严重程度每天使用从先前的出版物修改的临床评分系统评估[62]，其包括四个标准(活动水平、姿势、毛发(coat)和腹泻)，每个标准以0-4的等级进行分级并且加在一起以产生最高值为16的分数。一只正常小鼠得分为0，一只发现死亡的小鼠得分为16。得分等于或高于11的小鼠应该安乐死。在IgG-ABAB治疗组中只有一只小鼠出现短暂性腹泻，而用PBS注射的小鼠产生严重的CDI疾病症状(数据未显示)。因此，通过注射手动递送到小鼠肠中的Ig-ABAB显示出有效的治疗效果。

[0293] 结合剂的表达、纯化和评估

[0294] 使用多种选择标准来选择在本文方法中描述的实验中产生的结合剂。首先，本文定义的每种构建体可用于瞬时转染293T细胞以通过蛋白A亲和层析来制备小规模重组蛋白质。每种构建体的产量可以通过定量ELISA确定。其次，可以使用ELISA和表面等离子体共振(SPR)来筛选重组蛋白质的结合活性，以选择保留其对毒素的原始结合活性的构建体。第三，在体外测定中评估蛋白质的中和活性(图3)。

[0295] 积累的观察表明体内重组结合剂的多反应性和/或自体反应性是与它们的体内安全性和半衰期有关的潜在问题。选择的ABAB结合剂作为全身性结合剂预防原发性急性CDI的应用可能需要嵌合和人源化ABAB蛋白限制多反应性和/或自体反应性。蛋白质蛋白组学的进展使得可以在体外筛选重组抗体的多反应性和自体反应性，这是用来替代治疗性抗体的很好工具。因此，使用自身抗原微阵列测试和ProtoArray蛋白质微阵列(Invitrogen)，可以进一步测试具有良好收率、高结合亲和力和有效中和活性的所选人源化结合剂的潜在多反应性和自体反应性。

[0296] 从以上体外测定中，可评估候选ABAB-Fc和ABAB-IgG结合剂的体内毒性、血清半衰期和免疫原性。

[0297] 分泌ABAB的酿酒酵母的产生(Sc-ABAB)

[0298] 开发了用于体内生产和递送结合剂至患有CDI或有发展为CDI风险的受试者的肠道的手段。由于酿酒酵母与布拉酵母在遗传上相似[52,53]，并且遗传工具容易用于酿酒酵母，酿酒酵母首先用于ABAB分泌验证。

[0299] 首先开发了新的双特异性夹心ELISA方法来评估ABAB分泌。该设置利用纯化的TcdA和TcdB作为用于ABAB双特异性的结合抗原和用于检测的α-TcdA抗体(图13A)。为了标准化，将平板用TcdB(1ug/ml)涂布，向其中加入连续稀释的ABBA((AH3-E3-E3-AA6))标准品。然后加入连续稀释的rTcdA(1ug/ml至7.8ng/ml)。然后通过加入针对TcdA的单克隆抗体，然后加入HRP缀合的第二抗体来测量TcdA的捕获。标准曲线的结果显示在图13B中。基于这些结果，选择使用125ng/ml rTcdA得到的标准曲线来确定酵母培养物上清液中ABAB的分

泌水平,并用于所有随后的ELISA。

[0300] 含有来自大肠杆菌(pUC)和酵母(2微米环)两者的复制起点的穿梭质粒(pD1214-FAKS)以及酵母营养缺陷型选择标记URA3(赋予合成尿嘧啶的能力)从DNA 2.0(Newark,CA)获得。将分别在ABAB的N端和C端编码ABAB(SEQ ID NO:20)和His标签(SEQ ID NO:66)和D7标签(SEQ ID NO:112)的序列插入到该质粒主链,其中转录受强组成型酵母翻译延伸因子启动子(P_{TEF})控制,并通过与α交配因子分泌信号前导序列(FAKS)融合而提供细胞外分泌。所得质粒(pD1214-FAKS-His-hABAB-D7)的序列在SEQ ID NO:68中提供。

[0301] 将质粒pD1214-FAKS-His-hABAB-D7转化进入酿酒酵母菌株BY4741(MATahis3Δ1leu2Δ0Met15Δ0ura3Δ0)、URA3敲除S288C衍生物实验室菌株。然后将酵母转化体在无尿嘧啶的含脱落混合物的YNB培养基中(在1L无菌ddH_2O中,6.8g YNB,20g葡萄糖,2g脱落混合物)在摇床中在30℃以250rpm过夜培养以达到O.D.1。然后将细胞离心并在1X SDS上样缓冲液中超声裂解。超声处理后,将总细胞裂解物在98℃下处理5分钟,然后加载到SDS凝胶上。除了对照细胞在没有尿嘧啶的YNB培养基中不存活,因此在与尿嘧啶相配的YNB中培养外,将等量的酵母对照细胞裂解物加载到每个孔中。

[0302] 将来自25个酵母转化体以及3个酵母对照菌落的培养物上清液离心以分离细胞,然后将无细胞上清液用含有0.05%吐温20的PBS中的2.5%牛奶以1:3的比例稀释并在摇床中以250rpm和30℃温育24小时后通过如上所述的ELISA筛选。图14B显示与来自酵母对照菌落的培养物上清液相比,所有酵母转化体在培养物上清液中分泌ABAB。

[0303] 使用基于细胞的中和测定来评估培养物上清液中分泌的ABAB的生物学活性。在该测定中,向在4小时内引起100%细胞变圆的足够量的毒素A或毒素B添加来自BY4741对照菌落或BY4741-ABAB菌落的无细胞培养物上清液。重组ABAB用作阳性对照。通过中和活性以防止细胞变圆的水平确定培养物上清液中分泌的ABAB的生物学活性。与纯化的重组ABAB相比,从酿酒酵母分泌的全长ABAB确实保持其中和活性(图14A)。这些综合结果意味着布拉酵母ABAB分泌的合理性。

[0304] 在进一步的实验中,证明了在剂量为10^{10}CFU下的Sc-ABAB对小鼠进行口服灌胃对小鼠没有副作用,并且通过在Sabouraud CAF琼脂上涂覆粪便确定小鼠脱落的活Sc-ABAB(数据未显示)。使用上述测定法从小鼠回收的分离物保留了其产生功能性ABAB的能力。

[0305] ABAB分泌优化

[0306] ABAB分泌水平与体内治疗功效紧密相关。因此,探索了通过用许多市售的分泌信号代替现有的FAKS分泌信号来进一步优化ABAB分泌的可能性。在细胞外输出之前,分泌序列促进异源蛋白质的共翻译或翻译后易位进入内质网和高尔基隔室。尽管α-交配因子是异源蛋白质分泌的常用信号序列,通常在酿酒酵母中产生高分泌蛋白质的产量[69,70],但研究表明来自其他蛋白质的其他分泌序列如菊粉酶或转化酶可能更适合分泌某些异源蛋白质[71,72]。

[0307] 在同一pD1214质粒主链中,在TEF启动子的控制下,11种不同的可商购的分泌信号(表4;DNA 2.0,Newark,CA)分别与ABAB在基因上融合。编码具有可选分泌信号的ABAB的质粒包括以下质粒,其中FAKS分泌信号被来自表4的所述新分泌信号所取代,并且其中去除了his标签和D7标签:

[0308] 质粒pD1214-AKS-hABAB(SEQ ID NO:70)

[0309] 质粒pD1214-AK-hABAB(SEQ ID NO:71)

[0310] 质粒pD1214-AT-hABAB(SEQ ID NO:72)

[0311] 质粒pD1214-AA-hABAB(SEQ ID NO:73)

[0312] 质粒pD1214-GA-hABAB(SEQ ID NO:74)

[0313] 质粒pD1214-IN-hABAB(SEQ ID NO:75)

[0314] 质粒pD1214-IVS-hABAB(SEQ ID NO:76)

[0315] 质粒pD1214-KP-hABAB(SEQ ID NO:77)

[0316] 质粒pD1214-LZ-hABAB(SEQ ID NO:78)

[0317] 质粒pD1214-SA-hABAB(SEQ ID NO:79)

[0318] 此外,除去原始ABAB构建体(pD1214-FAKS-His-hABAB-D7)中的his标签和D7标签以产生质粒pD1214-FAKS-hABAB(SEQ ID NO:69)并将培养温育温度升高至37℃以便更好地适应体内和临床测试相关情况。然后将所有11个质粒转化进BY4741中,选择来自每个选择平板的5个独立菌落以产生培养物上清液。如上所述通过相同的ELISA测定分泌的ABAB的量。此外,E/O值用于提供所有组的公平比较。E/O值由ELISA O.D.值针对培养O.D.值进行标准化而定义。发现ABAB的两种最佳分泌信号是AT和IVS(表4;图15A)。

[0319] 由于布拉酵母营养缺陷型突变菌株的缺乏,使用另一种携带编码对G418的抗性的aphA1基因(PCEV-G4-Km;SEQ ID NO:80;来自Lars Nielsen&Claudia Vickers的礼物(Addgene质粒#46819))的基于2um的质粒代替pD1214质粒以确认布拉氏酵母中的ABAB分泌。将酿酒酵母的最佳两种分泌信号(AT和IVS)与ABAB基因上融合并插入pCEV-G4-Km质粒主链中以产生质粒pCEV-G4-Km-TEF-AT-hABAB*(SEQ ID NO:81)和pCEV-G4-Km-TEF-IVS-hABAB*(SEQ ID NO:82)。通过ELISA确定,两种质粒都用于转化布拉酵母(菌株MYA796)并且布拉酵母中的AT和IVS的ABAB分泌与酿酒酵母相当(图15B)。制备与pCEV-G4-Km-TEF-AT-hABAB*不同的另一构建体(pCEV-G4-Km-TEF-AT-hABAB(SEQ ID NO:83)),因为它含有AT和hABAB序列之间的分子克隆位点。

[0320] 然后通过在具有AT分泌信号的构建体中的核苷酸水平上的酵母密码子优化(yABAB)进一步优化ABAB分泌,产生质粒pCEV-G4-Km-TEF-AT-yABAB(SEQ ID NO:84)。还发现在P_{TEF}和ABAB编码序列之间含有40个核苷酸的序列对于ABAB分泌是不必要的并且被去除,从而产生质粒pCEV-G4-Km-TEF-X40-AT-yABAB(SEQ ID NO:85)。发现在AT和ABAB序列之间含有两个限制性克隆位点的进一步序列负面影响ABAB分泌,因此该序列也被省略(质粒pCEV-G4-Km-TEF-AT-^{RS}yABAB;SEQ ID NO:115)用于随后的研究以最大化ABAB分泌。

[0321] 接下来,测量单个单体的分泌量,发现AA6分泌最少。为了改善AA6分泌,并由此进一步优化ABAB分泌,使用了一组关键氨基酸残基。发现T83N突变可改善AA6分泌。另外,发现携带hAA6序列的布拉酵母比携带酵母优化的yAA6序列的菌株分泌更多的AA6。因此,在携带AA6中的T83N突变的ABAB(AT-yABAB T83N;质粒pCEV-G4-Km-TEF-AT-yABAB AA6T83N;SEQ ID NO:116)和其中yAA6序列被hAA6T83N序列替换的ABAB(AT-yABAB hAA6 T83N;质粒pCEV-G4-Km-TEF-AT-yABAB hAA6T83N,其具有SEQ ID NO:90的序列,但缺少c-Myc的编码序列)之间进行比较,以确定哪个序列表现出更好的分泌。发现这些构建体与AT-yABAB hAA6T83N之间没有显着性差异,作为最终序列前进的结论。在质粒pCEV-G4-Km-TEF-AT-yABAB hAA6T83N-tagless(SEQ ID NO:90)中提供编码AT-yABAB hAA6 T83N的核苷酸序列。AT-

yABAB hAA6T83N的氨基酸序列在SEQ ID NO:117中提供。

[0322] 营养缺陷型布拉酵母菌株的产生

[0323] 编码ABAB的表达质粒可以克隆到布拉酵母菌株中。布拉酵母菌株可以比酿酒酵母更好地耐受正常体温和酸性条件,这可以提高作为基于口服酵母的新型治疗策略的功效。可以对野生型布拉酵母菌株进行两种修饰以保持由酵母URA3代谢选择标记赋予的表达质粒的体内稳定性:1)可以在URA3的两个染色体等位基因中构建携带缺失的二倍体营养缺陷型突变体,并且2)可以从布拉酵母中治愈内源性2微米环以防止意外重组干扰ABAB表达。

[0324] 用于在野生型酵母属菌株中构建营养缺陷型突变体的最直接且有效的方法包括通过同源重组靶向缺失染色体编码的基因,其在酵母属中以非常高的频率发生。靶向基因的完全缺失优于选择可恢复为野生型的自发突变。因此,对于酿酒酵母中的单倍体状态优选基因缺失,其通常通过使用营养差的生长培养基并在低温(30℃)下温育通过孢子形成从野生型二倍体诱导。然而,布拉酵母孢子形成不足并且在正常产孢条件下难以形成单倍体细胞[64,65]。使用缺失染色体基因等位基因(例如URA3)的两步法,其中可以选择每个缺失步骤。该过程在图16中示意性地概述。

[0325] 通过线性DNA缺失盒的乙酸锂促进的遗传转化[73]进行所有染色体缺失。基于乙酸锂的转化起源于酿酒酵母协议,并发现它与布拉氏菌相容,尽管发现布拉酵母很难转化[55,56]。差距约为100倍。通过调整葡萄糖浓度和热休克时间可以提高酿酒酵母的转化效率[74]。因此,各种葡萄糖浓度和热休克时间引入布拉酵母转化用于优化。布拉酵母测试的最佳条件是预培养时葡萄糖含量为2%,42℃时为20分钟热休克时间,这些条件用于所有研究中的所有转化过程。

[0326] 使用pCEV-G4-Km(SEQ ID NO:80)和pCEV-G4-Ph(SEQ ID NO:86)(来自Lars Nielsen&Claudia Vickers的礼物(Addgene质粒#46820))作为模板,通过PCR产生了含有分别对G418和酵母中腐草霉素赋予抗性的基因aphA1和ble的两个缺失盒。两个缺失盒都在相同方向上侧接两个X超过P1(loxP)的基因座,从而允许使用Cre重组酶去除抗生素抗性基因。将URA3启动子上游(P_{URA3})和URA3终止密码子下游的40个碱基对的同源序列整合到PCR引物中以产生用于布拉酵母中用于位点特异性基因缺失的两个最终缺失盒(参见图16)。使用来自酵母属基因组数据库(SGD)的在线发表的序列的URA3基因注释来映射布拉酵母的V染色体上的URA3基因的确切序列和位置。选择用aphA1缺失盒取代第一URA3等位基因的交叉(crossover)1的选择用于使用对G418的抗性[66];选择用ble缺失盒取代第二URA3等位基因的第二交叉用于使用对腐草霉素的抗性[75](图16)。用aphA1和ble缺失盒取代两个URA3等位基因由两种抗生素的抗性(数据未显示)以及在缺少尿嘧啶的最小合成培养基平板上缺乏生长证明(数据未显示)。用氯霉素(100ug/ml)在Sabouraud平板上生长也证实了酵母表型(数据未显示)。此外,设计了三组靶向URA3染色体区域中的URA3、aphA1或ble基因的独特引物,并使用野生型(WT)、URA3Δ::aphA/URA3(第一交叉)和URA3Δ::aphA1/Δ::ble(第二交叉)基因组DNA作为模板进行PCR。靶向URA3染色体区域中的URA3、aphA1或ble基因的预期PCR产物大小分别为766bp、1183bp和662bp。使用这三组独特引物,来自WT、第一交叉和第二交叉克隆的PCR产物的DNA电泳证实了URA3等位基因的缺失以及第二交叉株的aphA1和ble缺失盒的整合。

[0327] 然后用pPL5071_TEF1-Cre_URA3(pPL5071;SEQ ID NO:95)[76]转化第二交叉菌株

以去除aphA1和ble缺失盒。在P_{TEF} Cre重组酶下菌株携带pPL5071组成型表达Cre重组酶，然后靶向aphA1和ble缺失盒侧翼的loxp序列；这导致aphA1和ble删除盒的切除，在URA3染色体区域仅留下一个loxp位点。经历成功切除aphA1和ble缺失盒的菌株不能在G418或腐草霉素存在下生长；但仍保留两个URA3等位基因的损失，因此只能在尿嘧啶存在下在最小合成培养基平板上生长，并且在没有尿嘧啶补充物的最小合成培养基平板上不显示生长。

[0328] 通过在YPD中生长并选择稍后在含有尿嘧啶和嘧啶类似物5-氟-乳清酸(5-FOA)的最小合成培养基上生长的菌落来实现pPL5071的去除[77]。拥有pPL5071的菌株携带URA3基因，该基因可以合成有毒的中间体5-氟脱氧尿苷，这是一种胸苷酸合成酶的有效抑制剂，其中断DNA合成并导致细胞死亡并允许选择已经失去pPL5071的菌株。pPL5071的缺失也通过PCR和PCR产物的DNA电泳由pPL5071特异性引物证实。

[0329] 2um质粒是在酵母属菌株中无处不在的非常稳定的6.1kb质粒。该质粒对酵母宿主生物体没有选择性优势，并且由于存在有效的REP1-REP2-STB质粒分配系统而显着稳定[68]。使用的布拉酵母菌株也含有通过PCR确认的该质粒。为除去2um质粒，用pBIS-GALkFLP-URA3(SEQ ID NO:87)[67]固化2um质粒，随后用尿嘧啶和5-FOA去除。使用对复制起点特异性的引物通过PCR证实2um质粒的丢失。

[0330] 由这些操作产生的布拉酵母的营养缺陷型菌株命名为布拉酵母URA3Δ/Δ。

[0331] 用于原位ABAB递送的营养缺陷型布拉酵母菌株

[0332] 为了构建用于原位ABAB递送的营养缺陷型布拉酵母菌株，用来自pD质粒的URA3盒取代质粒pCEV-G4-Km-TEF-X40-AT-yABAB(SEQ ID NO:85)的aphA1盒以产生质粒pCEV-URA3-TEF-AT-yABAB-cMyc(SEQ ID NO:88)。该质粒然后用来转化为布拉酵母URA3Δ/Δ。在细胞毒性测定中，与纯化的ABAB相比，所得菌株分泌完全功能的ABAB(图17C)。蛋白质印迹使用缀合有HRP的α-Llama抗体，显示来自布拉酵母培养物上清液的相应ABAB条带(图17D)。ABAB的C-末端含有c-Myc标签，并且可以被α-c-Myc抗体进一步拉下(图17D)。

[0333] 对于空质粒(EP)对照，稍后从pCEV-URA3-TEF-AT-yABAB-cMyc(SEQ ID NO:88)中除去AT-yABAB序列以产生pCEV-URA3-TEF-cMyc(SEQ ID NO:89)。用该质粒转化的布拉酵母URA3Δ/Δ菌株产生与URA3互补的菌株，但不分泌ABAB。分泌ABAB的布拉酵母URA3Δ/Δ菌株当在含有万古霉素(1mg/ml)的YPD中培养时也显示没有生长抑制(图17A)。这表明布拉酵母可以与通常用于治疗CDI患者的万古霉素共同施用并分泌ABAB以治疗正在进行的CDI。另外，在O.D.为10的超过2小时从布拉酵母收集的培养物上清液中纯化的ABAB稳定表明分泌的ABAB可能从布拉酵母扩散出来而不降解。

[0334] 布拉酵母对抗生素治疗小鼠的口服安全性评估

[0335] 在评估表达ABAB的布拉酵母URA3Δ/Δ是否可以保护CDI模型中的小鼠之前[20,33,62,78]，进行安全评估以确定抗生素处理的小鼠中布拉酵母的安全剂量。在该安全评估中，首先小鼠在其日常饮用水中被给予抗生素混合物三天，然后转换为普通水。口服布拉酵母前一天，小鼠腹腔注射克林霉素。这完成了对小鼠的抗生素治疗，然后将布拉酵母经口服递送给小鼠进行安全评估，其包括监测这些抗生素处理的小鼠的每日重量的变化和粪便样品布拉酵母的持久性。小鼠在监测6天期间没有表现出疾病迹象和稳定的体重增加，其中口服布拉酵母的10^{10}个细胞符合布拉酵母作为GRAS生物体的想法。然而，对于随后的CDI小鼠研究，由于颗粒再悬浮的容易性和对小鼠的给药量变化较小，只有10^{9}个布拉酵母细胞被给

予,这可能在再悬浮中存在高粘度时发生。布拉酵母在这些抗生素处理的小鼠胃肠道中也显示有限的定殖;最后一次灌胃后三天,从Sabouroud平板上未检测到布拉酵母(数据未显示)。

[0336] 表达ABAB的布拉酵母针对小鼠中原发性CDI的保护作用

[0337] 使用建立的原发性小鼠CDI模型评估表达ABAB的布拉酵母的保护作用。递送表达ABAB的布拉酵母作为针对小鼠中原发性CDI的预防或治疗。简而言之,通过将抗生素混合物补充到其饮用水中三天,然后在艰难梭菌孢子攻击前24小时腹膜内注射克林霉素,在小鼠中建立了原发性CDI。将10^5艰难梭菌孢子(UK1,027/BI/NAP1流行株)灌胃给小鼠以诱导CDI。对于预防性评估,在转换为常规饮用水后的第二天,小鼠开始接受口服剂量的布拉酵母,其每天进行持续7天。对于治疗性评估,小鼠在孢子攻击后6、24、48和72小时接受口服剂量的布拉酵母。对照包括PBS和用空质粒转化的布拉酵母。在两种方法中,接收表达ABAB的布拉酵母的小鼠显着受保护免于CDI诱导的死亡(图18A和19A;PBS;阴性对照;Sb:EP:用空质粒转化的布拉酵母;Sb:BAB:分泌ABAB的布拉酵母)。CDI小鼠典型地遭受体重减轻,由于腹泻而在第2天至第3天大部分体重下降并且逐渐恢复。接受表达ABAB的布拉酵母的小鼠体重迅速恢复(图18B和19B),攻击后第2天腹泻事件的百分比显着降低(图18C和19C)。

[0338] 表达ABAB的布拉酵母针对小鼠中复发性CDI的保护作用

[0339] 针对小鼠中的复发性CDI评估表达ABAB的布拉酵母的保护作用。为了诱发复发性CDI,小鼠在其日常饮用水中被给予抗生素混合物三天。经过三天的抗生素水后,小鼠然后被转回饮用普通水。在口服10^5艰难梭菌孢子(UK1,027/BI/NAP1流行株)前一天,小鼠腹腔注射克林霉素。孢子攻击后6小时,将普通水换成含有0.5mg/ml万古霉素的水6天,并在剩余的研究中再转回到普通水。万古霉素停用4天后,小鼠典型地发生CDI征象,而没有另外的艰难梭菌孢子攻击。在复发模型过程中,布拉酵母每天一次与万古霉素水一起口服,持续12天。该模型用于评估表达ABAB的布拉酵母防止小鼠CDI复发的保护效力。每天监测这些小鼠的存活率、体重减轻和腹泻事件。对照包括PBS和用空质粒转化的布拉酵母。接受表达ABAB的布拉酵母的小鼠显著受保护以防止复发诱导的CDI死亡(图20A;PBS;阴性对照;Sb:EP:用空质粒转化的布拉酵母;Sb:BAB:分泌ABAB的布拉酵母)。与原发性CDI小鼠类似,复发性CDI小鼠也通常在万古霉素水停用后大约第4天至第5天大部分体重下降时体重下降。接受表达ABAB的布拉酵母的小鼠显著受到保护免于体重减轻(图20B)并且具有显著降低的腹泻复发事件百分比(图20C)。

[0340] 通过染色体整合ABAB盒的稳定性优化

[0341] 最近在酿酒酵母和布拉酵母中都证明了使用基于CRISPR-Cas9的系统的基因组编辑[79-81]。此外,通过同时靶向两个指导序列可以实现大片段缺失[82]。当没有选择压力时,与通过质粒引入相比,整合到染色体中时,外源基因通常更稳定地维持。然而,染色体整合通常需要多轮整合来获得高拷贝。最近发表的一项方案克服了这一障碍,通过CRISPR诱导的双染色破坏靶向酿酒酵母基因组中常见序列的多个拷贝,例如δ位点,实现了在这些位点大片段的同时整合[83]。DNA双链断裂可以通过非同源末端连接或同源重组来修复;然而,当存在内源同源序列时,宿主优先使用同源序列通过同源重组修复DNA双链断裂[83]。

[0342] δ位点是长末端重复序列(LTR)属于Ty元件I和II,并且是酿酒酵母中最丰富的LTR。有以II型转座子(逆转录转座子)为代表的五种类型的Ty元件(1-5),这在酿酒酵母中

更常见。据估计，酿酒酵母基因组中约有51个反转录转座子(Ty1-5)和251个δ位点[84]。这些δ位点是吸引ABAB表达盒整合到布拉酵母染色体中的靶序列。然而，关于布拉酵母中δ位点的知识要少得多。因此，Ty1-H3(Genbank登录号M18706)[84]首先用作调查布拉酵母菌株MYA796(ATCC，Manassas，VA)(来自NCBI的基因组草图)中Ty1-2元件的探针，以鉴定布拉酵母基因组中可能的Ty1-2元件及其δ位点。令人惊讶的是，在MYA796中没有发现完整的Ty1-2元件。共发现57个δ站点；这包括44个完整δ位点和12个部分位点以及在所有16个染色体中鉴定的含有1个完整δ位点的部分Ty元件(表12)。

[0343] 表12-在MYA796染色体上δ位点的数目及其分布

[0344]

	完整 δ 位点	完整 Ty1、2 元件	部分 δ 位点 60< X <200 bp	具有完整 δ 位点的部分 Ty1、2 元件
Ch I	0	0	1	0
Ch II	0	0	0	0
Ch III	1	0	0	0
Ch IV	5	0	1	1
Ch V	2	0	1	0

[0345]

Ch VI	2	0	0	0
Ch VII	8	0	1	0
Ch VIII	2	0	0	0
Ch IX	3	0	0	0
Ch X	3	0	1	0
Ch XI	0	0	0	0
Ch XII	8	0	1	0
Ch XIII	2	0	1	0
Ch XIV	1	0	0	0
Ch XV	2	0	4	0
Ch XVI	5	0	1	0
总计	**44**	**0**	**12**	**1**

[0346] 由于布拉酵母二倍体状态；布拉酵母基因组中有大约114个δ位点。为了允许通过CRISPR进行简单的多重δ位点靶向，使用MUSCLE将所有57个δ位点序列编译成多序列比对以鉴定在57个δ序列中存在大数目的原型间隔子邻接基序(PAM)位点。根据原型间隔子中具有均匀性的最高数量的δ序列作为上游和下游序列而选择两个PAM位点。这些PAM位点的序列如图21所示，具体序列如下：

[0347] PAM位点I

[0348] TGTTGGAATAAAAATCAACTATCATCTACTAACTAGTATTTACGTTACTAGTATATTATCATATACGGTGTTAGAAGATGACGCAAATGATGAGAAATAGTCATCTAAATTAGTGGAAGCTGAAAC（SEQ ID NO：93）

[0349] PAM位点II

[0350] AATATTTATAGAATTGTGTAGAATTGCAGATTCCCTTTTATGGATTCCTAAATCCTCGAGGAGAACTTCTAGTATATCTACATACCTAATATTATAGCCTTAATC（SEQ ID NO：94）。

[0351] 在Pam位点I和Pam位点II中，由虚线所下划的序列对应于上游同源序列；由一条线所下划的序列对应于20bp的原型间隔子；由双线所下划的序列对应于PAM序列；由波浪线所下划的序列对应于下游同源序列。

[0352] 这两个PAM位点伴随着它们在δ位点内的共同的上游和下游同源序列，允许将ABAB表达盒中简单的染色体整合到布拉酵母基因组中。使用引物通过PCR产生含有同源重组序列的ABAB整合盒，所述引物包含在3'末端去除最后三个核苷酸的上游同源序列和在5'末端去除前两个核苷酸的下游同源序列和使用质粒pCEV-G4-Km-TEF-AT-yABAB hAA6T83N-tagless作为模板(SEQ ID NO:90)进行PCR所需的相应退火序列。

[0353] 具有CRISPR质粒的ABAB整合盒的PCR产物含有相应的引导序列(pCRI-Sb-δ1(SEQ ID NO:91)和pCRI-Sb-δ2(SEQ ID NO:92))，然后与布拉酵母共转化用于ABAB整合到染色体中，独立并顺序地靶向PAM位点I和PAM位点II。发现PCR产物与CRISPR质粒的比例对于产生成功的整合克隆是重要的(图22A;$ITG^{低}$对$ITG^{高}$)。另外，来自具有相同整合盒和CRISPR质粒的$ITG^{高}$组的最高ABAB分泌克隆的重复转化不会进一步改善独立克隆的整体ABAB分泌(图22A;2^{nd} $ITG^{高}$)。通过在CRISPR质粒靶向位点II中共转化含有同源重组序列及其相应引导序列的第二套ABAB整合盒(图22A)，进一步提高来自$ITG^{高}$组的最高ABAB分泌克隆(C^{RISPR}-2)的ABAB分泌。选择两个最高的ABAB分泌克隆C^{RISP}-3和C^{RISPR}-4。图22B中显示了这四个代表性克隆的ABAB分泌量和随时间的稳定性。进行初步的小鼠CDI研究。然而，发现C^{RISPR}-4并不比先前的M-/-:ABAB克隆好，它在许多小鼠CDI模型中显示出保护作用(图23)。

[0354] 虽然已经参照本发明的某些特定实施例描述了本发明，但是本领域技术人员将会理解，可以在不脱离本发明的精神和范围的情况下进行各种修改。所附权利要求的范围不限于所描述的具体实施例。

[0355] 参考文献

[0356] 本说明书中提及的所有专利和出版物指示了本发明所属领域的技术人员的技术水平。每个引用的专利和出版物都通过引用整体并入本文。本申请中引用了以下所有参考文献：

[0357] 1.Cloud,J.&Kelly,C.P.Update on Clostridium difficile associated disease.Curr Opin Gastroenterol 23,4-9(2007).

[0358] 2.Kelly,C.P.&LaMont,J.T.Clostridium difficile--more difficult than ever.N Engl J Med 359,1932-1940(2008).

[0359] 3.Barbut,F.,et al.Epidemiology of recurrences or reinfections of Clostridium difficile-associated diarrhea.J Clin Microbiol 38,2386-2388(2000).

[0360] 4.Hassoun,A.&Ibrahim,F.Use of intravenous immunoglobulin for the treatment of severe Clostridium difficile colitis.Am J Geriatr Pharmacother 5,48-51(2007).

[0361] 5.Shahani,L.&Koirala,J.Intravenous immunoglobulin in treatment of Clostridium difficile colitis.BMJ Case Rep 2012(2012).

[0362] 6.Saito,T.,et al.Evidence of intravenous immunoglobulin as a critical supportive therapy against Clostridium difficile toxin-mediated lethality in mice.J Antimicrob Chemother 66,1096-1099(2011).

[0363] 7.Abougergi,M.S.&Kwon,J.H.Intravenous immunoglobulin for the treatment of Clostridium difficile infection:a review.Dig Dis Sci 56,19-26

(2011).

[0364] 8.Sokol,H.,Maury,E.,Seksik,P.,Cosnes,J.&Beaugerie,L.Single immunoglobulin infusion can reverse hemodynamic failure associated with severe Clostridium difficile colitis.Am J Gastroenterol 104,2649-2650(2009).

[0365] 9.Lowy,I.,et al.Treatment with monoclonal antibodies against Clostridium difficile toxins.N Engl J Med 362,197-205(2010).

[0366] 10.Louie,T.J.,et al.Fidaxomicin versus vancomycin for Clostridium difficile infection.The New England journal of medicine 364,422-431(2011).

[0367] 11.Rao,K.&Young,V.B.Fecal Microbiota Transplantation for the Management of Clostridium difficile Infection.Infectious disease clinics of North America 29,109-122(2015).

[0368] 12.Vyas,D.,Aekka,A.&Vyas,A.Fecal transplant policy and legislation.World journal of gastroenterology:WJG 21,6-11(2015).

[0369] 13.Tonna,I.&Welsby,P.D.Pathogenesis and treatment of Clostridium difficile infection.Postgrad Med J 81,367-369(2005).

[0370] 14.McFarland,L.V.,Elmer,G.W.&Surawicz,C.M.Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease.The American journal of gastroenterology 97,1769-1775(2002).

[0371] 15.O'Neill,G.L.,Beaman,M.H.&Riley,T.V.Relapse versus reinfection with Clostridium difficile.Epidemiol Infect 107,627-635(1991).

[0372] 16.Wilcox,M.H.,Fawley,W.N.,Settle,C.D.&Davidson,A.Recurrence of symptoms in Clostridium difficile infection--relapse or reinfection?J Hosp Infect 38,93-100(1998).

[0373] 17.Johnson,S.,Adelmann,A.,Clabots,C.R.,Peterson,L.R.&Gerding, D.N.Recurrences of Clostridium difficile diarrhea not caused by the original infecting organism.J Infect Dis 159,340-343(1989).

[0374] 18.Tang-Feldman,Y.,Mayo,S.,Silva Jr,J.,Jr.&Cohen,S.H.Molecular analysis of Clostridium difficile strains isolated from 18 cases of recurrent clostridium difficile-associated diarrhea.J Clin Microbiol 41,3413-3414 (2003).

[0375] 19.Johnson,S.Recurrent Clostridium difficile infection:causality and therapeutic approaches.Int J Antimicrob Agents 33 Suppl 1,S33-36(2009).

[0376] 20.Sun,X.,et al.Mouse relapse model of Clostridium difficile infection.Infection and immunity 79,2856-2864(2011).

[0377] 21.Seal,D.,et al.Treatment of relapsing Clostridium difficile diarrhoea by administration of a non-toxigenic strain.Eur J Clin Microbiol 6, 51-53(1987).

[0378] 22.Kuehne,S.A.,et al.The role of toxin A and toxin B in Clostridium difficile infection.Nature(2010).

[0379] 23.Lyras,D.,et al.Toxin B is essential for virulence of Clostridium difficile.Nature 458,1176-1179(2009).

[0380] 24.Libby,J.M.&Wilkins,T.D.Production of antitoxins to two toxins of Clostridium difficile and immunological comparison of the toxins by cross-neutralization studies.Infection and immunity 35,374-376(1982).

[0381] 25.Katchar,K.,et al.Association between IgG2 and IgG3 subclass responses to toxin A and recurrent Clostridium difficile-associated disease.Clinical gastroenterology and hepatology:the official clinical practice journal of the American Gastroenterological Association 5,707-713(2007).

[0382] 26.Ghose,C.,et al.Transcutaneous immunization with Clostridium difficile toxoid A induces systemic and mucosal immune responses and toxin A-neutralizing antibodies in mice.Infection and immunity 75,2826-2832(2007).

[0383] 27.Sougioultzis,S.,et al.Clostridium difficile toxoid vaccine in recurrent C.difficile-associated diarrhea.Gastroenterology 128,764-770(2005).

[0384] 28.Kyne,L.,Warny,M.,Qamar,A.&Kelly,C.P.Association between antibody response to toxin A and protection against recurrent Clostridium difficile diarrhoea.Lancet 357,189-193(2001).

[0385] 29.Leav,B.A.,et al.Serum anti-toxin B antibody correlates with protection from recurrent Clostridium difficile infection(CDI).Vaccine 28,965-969(2010).

[0386] 30.Fernie,D.S.,Thomson,R.O.,Batty,I.&Walker,P.D.Active and passive immunization to protect against antibiotic associated caecitis in hamsters.Dev Biol Stand 53,325-332(1983).

[0387] 31.Kim,P.H.,Iaconis,J.P.&Rolfe,R.D.Immunization of adult hamsters against Clostridium difficile-associated ileocecitis and transfer of protection to infant hamsters.Infection and immunity 55,2984-2992(1987).

[0388] 32.Lyerly,D.M.,Bostwick,E.F.,Binion,S.B.&Wilkins,T.D.Passive immunization of hamsters against disease caused by Clostridium difficile by use of bovine immunoglobulin G concentrate.Infection and immunity 59,2215-2218(1991).

[0389] 33.Wang,H.,et al.A chimeric toxin vaccine protects against primary and recurrent Clostridium difficile infection.Infection and immunity 80,2678-2688(2012).

[0390] 34.Hamers-Casterman,C.,et al.Naturally occurring antibodies devoid of light chains.Nature 363,446-448(1993).

[0391] 35.van der Linden,R.,et al.Induction of immune responses and molecular cloning of the heavy chain antibody repertoire of Lama glama.J Immunol Methods 240,185-195(2000).

[0392] 36.Harmsen,M.M.&De Haard,H.J.Properties,production,and applications of camelid single-domain antibody fragments.Appl Microbiol Biotechnol 77,13-22(2007).

[0393] 37.Arbabi Ghahroudi,M.,Desmyter,A.,Wyns,L.,Hamers,R.&Muyldermans,S.Selection and identification of single domain antibody fragments from camel heavy-chain antibodies.FEBS Lett 414,521-526(1997).

[0394] 38.van der Linden,R.H.,et al.Comparison of physical chemical properties of llama VHH antibody fragments and mouse monoclonal antibodies.Biochim Biophys Acta 1431,37-46(1999).

[0395] 39.Dumoulin,M.,et al.Single-domain antibody fragments with high conformational stability.Protein Sci 11,500-515(2002).

[0396] 40.Hussack,G.,Hirama,T.,Ding,W.,Mackenzie,R.&Tanha,J.Engineered single-domain antibodies with high protease resistance and thermal stability.PloS one 6,e28218(2011).

[0397] 41.Yang,Z.,et al.A novel multivalent,single-domain antibody targeting TcdA and TcdB prevents fulminant Clostridium difficile infection in mice.The Journal of infectious diseases 210,964-972(2014).

[0398] 42.McFarland,L.V.Systematic review and meta-analysis of Saccharomyces boulardii in adult patients.World J.Gastroenterol.16,2202-2222(2010).

[0399] 43.Elmer,G.W.,McFarland,L.V.,Surawicz,C.M.,Danko,L.&Greenberg,R.N.Behaviour of Saccharomyces boulardii in recurrent Clostridium difficile disease patients.Aliment.Pharmacol.Ther.13,1663-1668(1999).

[0400] 44.Surawicz,C.M.,et al.The search for a better treatment for recurrent Clostridium difficile disease:use of high-dose vancomycin combined with Saccharomyces boulardii.Clin.Infect.Dis.31,1012-1017(2000).

[0401] 45.McFarland,L.V.,et al.A randomized placebo-controlled trial of Saccharomyces boulardii in combination with standard antibiotics for Clostridium difficile disease.Jama 271,1913-1918(1994).

[0402] 46.Czerucka,D.,Piche,T.&Rampal,P.Review article:yeast as probiotics--Saccharomyces boulardii.Alimentary pharmacology&therapeutics 26,767-778(2007).

[0403] 47.Sougioultzis,S.,et al.Saccharomyces boulardii produces a soluble anti-inflammatory factor that inhibits NF-kappaB-mediated IL-8 gene expression.Biochemical and biophysical research communications 343,69-76(2006).

[0404] 48.Qamar,A.,et al.Saccharomyces boulardii stimulates intestinal immunoglobulin A immune response to Clostridium difficile toxin A in mice.Infection and immunity 69,2762-2765(2001).

[0405] 49.Chen,X.,et al.Saccharomyces boulardii inhibits ERK1/2 mitogen-

activated protein kinase activation both in vitro and in vivo and protects against Clostridium difficile toxin A-induced enteritis.The Journal of biological chemistry281,24449-24454(2006).

[0406] 50.Barc,M.C.,et al.Molecular analysis of the digestive microbiota in a gnotobiotic mouse model during antibiotic treatment:Influence of Saccharomyces boulardii.Anaerobe 14,229-233(2008).

[0407] 51.Gorlani,A.,de Haard,H.&Verrips,T.Expression of VHHs in Saccharomyces cerevisiae.Methods in molecular biology 911,277-286(2012).

[0408] 52.Khatri,I.,et al.Gleaning evolutionary insights from the genome sequence of a probiotic yeast Saccharomyces boulardii.Gut Pathog.5,30(2013).

[0409] 53.Batista,T.M.,Marques,E.T.,Jr.,Franco,G.R.&Douradinha,B.Draft Genome Sequence of the Probiotic Yeast Saccharomyces cerevisiae var.boulardii Strain ATCC MYA-796.Genome announcements 2,578-579(2014).

[0410] 54.Hamedi,H.,et al.Generation of a uracil auxotroph strain of the probiotic yeast Saccharomyces boulardii as a host for the recombinant protein production.Avicenna journal of medical biotechnology 5,29-34(2013).

[0411] 55.Hudson,L.E.,et al.Functional heterologous protein expression by genetically engineered probiotic yeast Saccharomyces boulardii.PLoS One 9, e112660(2014).

[0412] 56.Douradinha,B.,et al.Novel insights in genetic transformation of the probiotic yeast Saccharomyces boulardii.Bioengineered 5,21-29(2014).

[0413] 57.Fietto,J.L.,et al.Molecular and physiological comparisons between Saccharomyces cerevisiae and Saccharomyces boulardii.Canadian journal of microbiology 50,615-621(2004).

[0414] 58.Martins,F.S.,et al.Screening of yeasts as probiotic based on capacities to colonize the gastrointestinal tract and to protect against enteropathogen challenge in mice.The Journal of general and applied microbiology 51,83-92(2005).

[0415] 59.Martins,F.S.,Veloso,L.C.,Arantes,R.M.&Nicoli,J.R.Effects of yeast probiotic formulation on viability,revival and protection against infection with Salmonella enterica ssp.enterica serovar Typhimurium in mice.Lett.Appl.Microbiol.49,738-744(2009).

[0416] 60.Wu,D.,Teng,D.,Wang,X.,Dai,C.&Wang,J.Saccharomyces boulardii prevention of the hepatic injury induced by Salmonella Enteritidis infection.Can.J.Microbiol.60,681-686(2014).

[0417] 61.Elmer,G.W.&Corthier,G.Modulation of Clostridium difficile induced mortality as a function of the dose and the viability of the Saccharomyces boulardii used as a preventative agent in gnotobiotic mice.Can.J.Microbiol.37,315-317(1991).

[0418] 62.Chen,X.,et al.A mouse model of Clostridium difficile-associated disease.Gastroenterology 135,1984-1992(2008).

[0419] 63.Pawlowski,S.W.,et al.Murine model of Clostridium difficile infection with agedgnotobiotic C57BL/6 mice and a BI/NAP1 strain.The Journal of infectious diseases 202,1708-1712(2010).

[0420] 64.McFarland,L.V.Saccharomyces boulardii is not Saccharomyces cerevisiae.Clin.Infect.Dis.22,200-201(1996).

[0421] 65.Edwards-Ingram,L.,et al.Genotypic and physiological characterization of Saccharomyces boulardii,the probiotic strain of Saccharomyces cerevisiae.Appl.Environ.Microbiol.73,2458-2467(2007).

[0422] 66.Panchal,C.J.,Whitney,G.K.&Stewart,G.G.Susceptibility of Saccharomyces spp.and Schwanniomyces spp.to the aminoglycoside antibiotic G418.Appl.Environ.Microbiol.47,1164-1166(1984).

[0423] 67.Tsalik,E.L.&Gartenberg,M.R.Curing Saccharomyces cerevisiae of the 2 micron plasmid by targeted DNA damage.Yeast 14,847-852(1998).

[0424] 68.Chan,K.M.,Liu,Y.T.,Ma,C.H.,Jayaram,M.&Sau,S.The 2 micron plasmid of Saccharomyces cerevisiae:a miniaturized selfish genome with optimized functional competence.Plasmid 70,2-17(2013).

[0425] 69.Brake,A.J.,et al.Alpha-factor-directed synthesis and secretion of mature foreign proteins in Saccharomyces cerevisiae.Proceedings of the National Academy of Sciences of the United States of America 81,4642-4646(1984).

[0426] 70.Porro,D.,Sauer,M.,Branduardi,P.&Mattanovich,D.Recombinant protein production in yeasts.Molecular biotechnology 31,245-259(2005).

[0427] 71.Chung,B.H.,Nam,S.W.,Kim,B.M.&Park,Y.H.Highly efficient secretion of heterologous proteins from Saccharomyces cerevisiae using inulinase signal peptides.Biotechnology and bioengineering 49,473-479(1996).

[0428] 72.Hahm,M.S.&Chung,B.H.Secretory expression of human growth hormone in Saccharomyces cerevisiae using three different leader sequences.Biotechnology and Bioprocess Engineering 6,306-309(2001).

[0429] 73.Gietz,R.D.&Schiestl,R.H.High-efficiency yeast transformation using the LiAc/SS carrier DNA/PEG method.Nat.Protoc.2,31-4(2007).

[0430] 74.Konishi,T.&Harata,M.Improvement of the transformation efficiency of Sacchaaromyces cerevisiae by altering carbon sources in pre-culture.Biosci.Biotechnol.Biochem.78,1090-1093(2014).

[0431] 75.Gatignol,A.,Baron,M.&Tiraby,G.Phleomycin resistance encoded by the ble gene from transposon Tn 5 as a dominant selectable marker in Saccharomyces cerevisiae.MGG Mol.Gen.Genet.207,342-348(1987).

[0432] 76.Macdonald,C.&Piper,R.C.Puromycin-and methotrexate-resistance

cassettes and optimized Cre-recombinase expression plasmids for use in yeast.Yeast 32,423-438(2015).

[0433] 77.Boeke,J.D.,LaCroute,F.&Fink,G.R.A positive selection for mutants lacking orotidine-5'-phosphate decarboxylase activity in yeast:5-fluoro-orotic acid resistance.Mol Gen Genet 197,345-346(1984).

[0434] 78.Yang,Z.et al.Intravenous adenovirus expressing a multi-specific, single-domain antibody neutralizing TcdA and TcdB protects mice from Clostridium difficile infection.Pathog.Dis.74,ftw078(2016).

[0435] 79.DiCarlo,J.E.et al.Genome engineering in Saccharomyces cerevisiae using CRISPR-Cas systems.Nucleic Acids Res.41,4336-43(2013).

[0436] 80.Bao,Z.et al.Homology-Integrated CRISPR-Cas(HI-CRISPR)System for One-Step Multigene Disruption in Saccharomyces cerevisiae.ACS Synth.Biol.4, 585-594(2015).

[0437] 81.Liu,J.-J.et al.Metabolic engineering of a probiotic Saccharomyces boulardii.Appl.Environ.Microbiol.AEM.00057-16(2016).doi:10.1128/AEM.00057-16

[0438] 82.Hao,H.et al.Large fragment deletion using a CRISPR/Cas9 system in Saccharomyces cerevisiae.(2016).doi:10.1016/j.ab.2016.07.008.This

[0439] 83.Shi,S.,Liang,Y.,Zhang,M.M.,Ang,E.L.&Zhao,H.A highly efficient single-step,markerless strategy for multi-copy chromosomal integration of large biochemical pathways in Saccharomyces cerevisiae.Metab.Eng.33,19-27 (2016).

[0440] 84.Kim,J.M.et al.Transposable Elements and Genome Organization:A Comprehensive Survey of Retrotransposons Revealed by the Complete Saccharomyces cerevisiae.Genome Research.8(5):464-478(1998).

[0441] 85.Bao Z,Xiao H,Liang J,Zhang L,Xiong X,Sun N,Si T,Zhao H.Homology-Integrated CRISPR-Cas(HI-CRISPR)System for One-Step Multigene Disruption in Saccharomyces cerevisiae.ACS Synth Biol.4(5):585-94(2015).

[0442] 86.DiCarlo JE,Norville JE,Mali P,Rios X,Aach J,Church GM.Genome engineering in Saccharomyces cerevisiae using CRISPR-Cas systems.Nucleic Acids Res 41:4336-43(2013).

[0443] 87.Liu J-J,Kong II,Zhang G-C,Jayakody LN,Kim H,Xia P-F,Kwak S,Sung BH,Sohn J-H,Walukiewicz HE,Rao C V.,Jin Y-S.Metabolic engineering of a probiotic Saccharomyces boulardii.Appl Environ Microbiol.82(8):2280-7(2016).

[0444] 88.Shi S,Liang Y,Zhang MM,Ang EL,Zhao H.A highly efficient single-step,markerless strategy for multi-copy chromosomal integration of large biochemical pathways in Saccharomyces cerevisiae.Metab Eng 33:19-27(2016).

[0001] 序列表(SEQUENCE LISTING)

[0002] <110> 冯汉平(FENG, Hanping)

[0003] J•盖伦(GALEN, James)

[0004] J•A•卡拉斯科洛佩兹(CARRASCO LOPEZ, Jose Antonio)

[0005] K•陈(CHEN, Kevin)

[0006] <120> 针对艰难梭菌感染的基于酵母的免疫疗法(YEAST-BASED IMMUNOTHERAPY AGAINST CLOSTRIDIUM DIFFICILE INFECTION)

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[0362] Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ala Val Tyr Leu Gln

[0363] 210 215 220

[0364] Met Asn Ser Leu Lys Arg Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg

[0365] 225 230 235 240

[0366] Arg Arg Phe Ser Ala Ser Ser Val Asn Arg Trp Leu Ala Asp Asp Tyr

[0367] 245 250 255

[0368] Asp Val Trp Gly Arg Gly Thr Gln Val Ala Val Ser Ser Gly Gly Gly

[0369] 260 265 270

[0370] Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gln Leu Gln

[0371] 275 280 285

[0372] Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg

[0373] 290 295 300

[0374] Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr Val Met Thr

[0375] 305 310 315 320

[0376] Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Ile Ala Thr Ile

[0377] 325 330 335

[0378] Asn Thr Asp Gly Ser Thr Met Arg Asp Asp Ser Thr Lys Gly Arg Phe

[0379] 340 345 350

[0380] Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Thr

[0381] 355 360 365

[0382] Ser Leu Lys Pro Glu Asp Thr Ala Leu Tyr Tyr Cys Ala Arg Gly Arg

[0383] 370 375 380

[0384] Val Ile Ser Ala Ser Ala Ile Arg Gly Ala Val Arg Gly Pro Gly Thr

[0385] 385 390 395 400

[0386] Gln Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser

[0387] 405 410 415

[0388] Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu

[0389] 420 425 430

[0390] Val Gln Thr Gly Gly Ser Leu Arg Leu Ser Cys Ala Ser Ser Gly Ser

[0391] 435 440 445

[0392] Ile Ala Gly Phe Glu Thr Val Thr Trp Ser Arg Gln Ala Pro Gly Lys

[0393] 450 455 460

[0394] Ser Leu Gln Trp Val Ala Ser Met Thr Lys Thr Asn Asn Glu Ile Tyr

[0395] 465 470 475 480

[0396] Ser Asp Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys

[0397] 485 490 495

[0398] Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Gly

[0399] 500 505 510

[0400] Val Tyr Phe Cys Lys Gly Pro Glu Leu Arg Gly Gln Gly Ile Gln Val

[0401] 515 520 525

[0402] Thr Val Ser Ser

[0403] 530

[0404] <210> 20

[0405] <211> 1596

[0406] <212> DNA

[0407] <213> 人工序列(Artificial Sequence)

[0408] <220>

[0409] <223> ABAB结合剂(ABAB binding agent)

[0410] <400> 20

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[0412] tcctgtgccg catctgggtt cacactggat tattcgtcca tagggtggtt tcggcaggct 120

[0413] cctggcaaag agcgtgaggg ggtctcatgt attagtagta gtggtgatag cacaaagtac 180

[0414] gccgattccg taaagggccg gtttacaacc tccagggata atgctaagaa caccgtatat 240

[0415] ctccagatga actctctgaa gcccgacgat acggccgtat attactgtgc ggctttcagg 300

[0416] gcgactatgt gcggcgtgtt ccctctgagc ccttacggca aggacgactg gggcaagggg 360

[0417] accctggtga ccgtatcctc aggcggtgga gggtctggtg ggggaggctc agggggtgga 420

[0418] ggcagccagg tgcaactggt tgaatctggg ggaggcttgg tacaacctgg gggatccctg 480

[0419] agactctctt gcgaggcctc cggattcacc ttggactact atggcatcgg ctggttccgc 540
[0420] cagcccccag ggaaggagcg ggaggccgtt tcatacatta gtgccagtgc ccggaccata 600
[0421] ctgtacgcag actctgtgaa gggacgcttt accatctcta gggacaatgc caaaaatgct 660
[0422] gtgtacctgc aaatgaacag cctcaagcgg gaggataccg cagtgtacta ctgcgcgaga 720
[0423] cggcgcttct ccgcttctag cgtgaataga tggctggccg acgactacga cgtgtgggga 780
[0424] cggggcacac aggtggctgt gtcttccggt ggcggaagcg gaggggggcag cgggggtggg 840
[0425] agcggtgggg gcagccaact gcagctggta gagacagggg gcggcttagt tcagcctgga 900
[0426] gggtctctca gactgtcatg cgctgcctct ggctttacct tcagtgacta cgtgatgaca 960
[0427] tgggtccgcc aagctccagg gaaggggcct gagtggatcg ctactattaa tacagatggc 1020
[0428] agcacaatgc gggacgactc cacaaagggg cggttcacca tttccagaga caacgccaag 1080
[0429] aatactctgt accttcagat gaccagtctg aaacccgagg acactgctct gtactattgt 1140
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[0431] caggtaaccg tttcatccgg gggaggcggt tcaggcggtg ggggatctgg cgggggtgga 1260
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[0435] tctgactcag tgaaaggccg cttcatcatt tctagagata acgctaaaaa cacagtgtat 1500
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[0437] ctgaggggcc agggcatcca ggtaacagtc tcgagt 1596
[0438] <210> 21
[0439] <211> 12
[0440] <212> PRT
[0441] <213> 人工序列(Artificial Sequence)
[0442] <220>
[0443] <223> 白蛋白结合肽(Albumin-binding peptide)
[0444] <400> 21
[0445] Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp Asp
[0446] 1 5 10
[0447] <210> 22
[0448] <211> 761
[0449] <212> PRT
[0450] <213> 人工序列(Artificial Sequence)
[0451] <220>
[0452] <223> ABAB-Fc结合剂(ABAB-Fc binding agent)
[0453] <400> 22
[0454] Gln Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
[0455] 1 5 10 15
[0456] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Ser
[0457] 20 25 30
[0458] Ser Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
[0459] 35 40 45
[0460] Ser Cys Ile Ser Ser Ser Gly Asp Ser Thr Lys Tyr Ala Asp Ser Val

[0461] 50 55 60

[0462] Lys Gly Arg Phe Thr Thr Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr

[0463] 65 70 75 80

[0464] Leu Gln Met Asn Ser Leu Lys Pro Asp Asp Thr Ala Val Tyr Tyr Cys

[0465] 85 90 95

[0466] Ala Ala Phe Arg Ala Thr Met Cys Gly Val Phe Pro Leu Ser Pro Tyr

[0467] 100 105 110

[0468] Gly Lys Asp Asp Trp Gly Lys Gly Thr Leu Val Thr Val Ser Ser Gly

[0469] 115 120 125

[0470] Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val

[0471] 130 135 140

[0472] Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu

[0473] 145 150 155 160

[0474] Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Leu Asp Tyr Tyr Gly Ile

[0475] 165 170 175

[0476] Gly Trp Phe Arg Gln Pro Pro Gly Lys Glu Arg Glu Ala Val Ser Tyr

[0477] 180 185 190

[0478] Ile Ser Ala Ser Ala Arg Thr Ile Leu Tyr Ala Asp Ser Val Lys Gly

[0479] 195 200 205

[0480] Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ala Val Tyr Leu Gln

[0481] 210 215 220

[0482] Met Asn Ser Leu Lys Arg Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg

[0483] 225 230 235 240

[0484] Arg Arg Phe Ser Ala Ser Ser Val Asn Arg Trp Leu Ala Asp Asp Tyr

[0485] 245 250 255

[0486] Asp Val Trp Gly Arg Gly Thr Gln Val Ala Val Ser Ser Gly Gly Gly

[0487] 260 265 270

[0488] Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gln Leu Gln

[0489] 275 280 285

[0490] Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg

[0491] 290 295 300

[0492] Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr Val Met Thr

[0493] 305 310 315 320

[0494] Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Ile Ala Thr Ile

[0495] 325 330 335

[0496] Asn Thr Asp Gly Ser Thr Met Arg Asp Asp Ser Thr Lys Gly Arg Phe

[0497] 340 345 350

[0498] Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Thr

[0499] 355 360 365

[0500] Ser Leu Lys Pro Glu Asp Thr Ala Leu Tyr Tyr Cys Ala Arg Gly Arg

[0501] 370 375 380

[0502] Val Ile Ser Ala Ser Ala Ile Arg Gly Ala Val Arg Gly Pro Gly Thr

[0503] 385 390 395 400

[0504] Gln Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser

[0505] 405 410 415

[0506] Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu

[0507] 420 425 430

[0508] Val Gln Thr Gly Gly Ser Leu Arg Leu Ser Cys Ala Ser Ser Gly Ser

[0509] 435 440 445

[0510] Ile Ala Gly Phe Glu Thr Val Thr Trp Ser Arg Gln Ala Pro Gly Lys

[0511] 450 455 460

[0512] Ser Leu Gln Trp Val Ala Ser Met Thr Lys Thr Asn Asn Glu Ile Tyr

[0513] 465 470 475 480

[0514] Ser Asp Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys

[0515] 485 490 495

[0516] Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Gly

[0517] 500 505 510

[0518] Val Tyr Phe Cys Lys Gly Pro Glu Leu Arg Gly Gln Gly Ile Gln Val

[0519] 515 520 525

[0520] Thr Val Ser Ser Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro

[0521] 530 535 540

[0522] Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys

[0523] 545 550 555 560

[0524] Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val

[0525] 565 570 575

[0526] Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr

[0527] 580 585 590

[0528] Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu

[0529] 595 600 605

[0530] Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His

[0531] 610 615 620

[0532] Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys

[0533] 625 630 635 640

[0534] Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln

[0535] 645 650 655

[0536] Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met

[0537] 660 665 670

[0538] Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro

[0539] 675 680 685

[0540] Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn

[0541] 690 695 700

[0542] Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu

[0543] 705 710 715 720

[0544] Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val

[0545] 725 730 735

[0546] Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln

[0547] 740 745 750

[0548] Lys Ser Leu Ser Leu Ser Pro Gly Lys

[0549] 755 760

[0550] <210> 23

[0551] <211> 2286

[0552] <212> DNA

[0553] <213> 人工序列(Artificial Sequence)

[0554] <220>

[0555] <223> ABAB-Fc结合剂(ABAB-Fc binding agent)

[0556] <400> 23

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[0558] tcctgtgccg catctgggtt cacactggat tattcgtcca tagggtggtt tcggcaggct 120

[0559] cctggcaaag agcgtgaggg ggtctcatgt attagtagta gtggtgatag cacaaagtac 180

[0560] gccgattccg taaagggccg gtttacaacc tccagggata atgctaagaa caccgtatat 240

[0561] ctccagatga actctctgaa gcccgacgat acggccgtat attactgtgc ggctttcagg 300

[0562] gcgactatgt gcggcgtgtt ccctctgagc ccttacggca aggacgactg gggcaagggg 360

[0563] accctggtga ccgtatcctc aggcggtgga gggtctggtg ggggaggctc agggggtgga 420

[0564] ggcagccagg tgcaactggt tgaatctggg ggaggcttgg tacaacctgg gggatccctg 480

[0565] agactctctt gcgaggcctc cggattcacc ttggactact atggcatcgg ctggttccgc 540

[0566] cagcccccag ggaaggagcg ggaggccgtt tcatacatta gtgccagtgc ccggaccata 600

[0567] ctgtacgcag actctgtgaa gggacgcttt accatctcta gggacaatgc caaaaatgct 660

[0568] gtgtacctgc aaatgaacag cctcaagcgg gaggataccg cagtgtacta ctgcgcgaga 720

[0569] cggcgcttct ccgcttctag cgtgaataga tggctggccg acgactacga cgtgtgggga 780

[0570] cggggcacac aggtggctgt gtcttccggt ggcggaagcg gaggggcag cgggggtggg 840

[0571] agcggtgggg gcagccaact gcagctggta gagacagggg gcggcttagt tcagcctgga 900

[0572] gggtctctca gactgtcatg cgctgcctct ggctttacct tcagtgacta cgtgatgaca 960

[0573] tgggtccgcc aagctccagg gaaggggcct gagtggatcg ctactattaa tacagatggc 1020

[0574] agcacaatgc gggacgactc cacaaagggg cggttcacca tttccagaga caacgccaag 1080

[0575] aatactctgt accttcagat gaccagtctg aaacccgagg acactgctct gtactattgt 1140

[0576] gcaagaggcc gggtgatctc tgcttccgct atcagaggcg cagtaagggg ccctggaaca 1200

[0577] caggtaaccg tttcatccgg gggaggcggt tcaggcggtg ggggatctgg cgggggtgga 1260

[0578] tcccaagttc agctggtcga atccgggggc ggactggtcc agacaggggg ctccctgagg 1320

[0579] ctctcctgtg catcttccgg aagcatcgcc ggcttcgaga ccgtgacctg gtctcgccag 1380

[0580] gctcccggga agtctctgca gtgggtcgct tccatgacta agactaacaa cgagatctac 1440

[0581] tctgactcag tgaaaggccg cttcatcatt tctagagata acgctaaaaa cacagtgtat 1500

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[0587] gccaagacaa agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc 1860
[0588] accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa 1920
[0589] gccctcccag cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 1980
[0590] caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt cagcctgacc 2040
[0591] tgcctggtca aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag 2100
[0592] ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc 2160
[0593] tatagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc 2220
[0594] gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 2280
[0595] aaatga 2286
[0596] <210> 24
[0597] <211> 356
[0598] <212> PRT
[0599] <213> 人工序列(Artificial Sequence)
[0600] <220>
[0601] <223> 5D-Fc结合剂(5D-Fc binding agent)
[0602] <400> 24
[0603] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[0604] 1 5 10 15
[0605] Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Leu Asp Tyr Tyr
[0606] 20 25 30
[0607] Gly Ile Gly Trp Phe Arg Gln Pro Pro Gly Lys Glu Arg Glu Ala Val
[0608] 35 40 45
[0609] Ser Tyr Ile Ser Ala Ser Ala Arg Thr Ile Leu Tyr Ala Asp Ser Val
[0610] 50 55 60
[0611] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ala Val Tyr
[0612] 65 70 75 80
[0613] Leu Gln Met Asn Ser Leu Lys Arg Glu Asp Thr Ala Val Tyr Tyr Cys
[0614] 85 90 95
[0615] Ala Arg Arg Arg Phe Ser Ala Ser Ser Val Asn Arg Trp Leu Ala Asp
[0616] 100 105 110
[0617] Asp Tyr Asp Val Trp Gly Arg Gly Thr Gln Val Ala Val Ser Ser Gly
[0618] 115 120 125
[0619] Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[0620] 130 135 140
[0621] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[0622] 145 150 155 160
[0623] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[0624] 165 170 175
[0625] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[0626] 180 185 190
[0627] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[0628] 195 200 205

[0629] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[0630] 210 215 220
[0631] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[0632] 225 230 235 240
[0633] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[0634] 245 250 255
[0635] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[0636] 260 265 270
[0637] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[0638] 275 280 285
[0639] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[0640] 290 295 300
[0641] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[0642] 305 310 315 320
[0643] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[0644] 325 330 335
[0645] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[0646] 340 345 350
[0647] Ser Pro Gly Lys
[0648] 355
[0649] <210> 25
[0650] <211> 1071
[0651] <212> DNA
[0652] <213> 人工序列(Artificial Sequence)
[0653] <220>
[0654] <223> 5D-Fc结合剂(5D-Fc binding agent)
[0655] <400> 25
[0656] caggtgcaac tggttgaatc tgggggaggc ttggtacaac ctgggggatc cctgagactc 60
[0657] tcttgcgagg cctccggatt caccttggac tactatggca tcggctggtt ccgccagccc 120
[0658] ccagggaagg agcgggaggc cgtttcatac attagtgcca gtgcccggac catactgtac 180
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[0660] ctgcaaatga acagcctcaa gcgggaggat accgcagtgt actactgcgc gagacggcgc 300
[0661] ttctccgctt ctagcgtgaa tagatggctg gccgacgact acgacgtgtg gggacggggc 360
[0662] acacaggtgg ctgtctcgag cggatccgac aaaactcaca catgcccacc gtgcccagca 420
[0663] cctgaactcc tgggggggacc gtcagtcttc ctcttccccc caaaacccaa ggacaccctc 480
[0664] atgatctccc ggacccctga ggtcacatgc gtggtggtgg acgtgagcca cgaagaccct 540
[0665] gaggtcaagt tcaactggta cgtggacggc gtggaggtgc ataatgccaa gacaaagccg 600
[0666] cgggaggagc agtacaacag cacgtaccgt gtggtcagcg tcctcaccgt cctgcaccag 660
[0667] gactggctga atggcaagga gtacaagtgc aaggtctcca acaaagccct cccagccccc 720
[0668] atcgagaaaa ccatctccaa agccaaaggg cagccccgag aaccacaggt gtacaccctg 780
[0669] cccccatccc gggaggagat gaccaagaac caggtcagcc tgacctgcct ggtcaaaggc 840
[0670] ttctatccca gcgacatcgc cgtggagtgg gagagcaatg ggcagccgga gaacaactac 900

[0671] aagaccacgc ctcccgtgct ggactccgac ggctccttct tcctctatag caagctcacc 960

[0672] gtggacaaga gcaggtggca gcaggggaac gtcttctcat gctccgtgat gcatgaggct 1020

[0673] ctgcacaacc actacacgca gaagagcctc tccctgtctc cgggtaaatg a 1071

[0674] <210> 26

[0675] <211> 340

[0676] <212> PRT

[0677] <213> 人工序列(Artificial Sequence)

[0678] <220>

[0679] <223> E3-Fc结合剂(E3-Fc binding agent)

[0680] <400> 26

[0681] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Thr Gly Gly

[0682] 1 5 10 15

[0683] Ser Leu Arg Leu Ser Cys Ala Ser Ser Gly Ser Ile Ala Gly Phe Glu

[0684] 20 25 30

[0685] Thr Val Thr Trp Ser Arg Gln Ala Pro Gly Lys Ser Leu Gln Trp Val

[0686] 35 40 45

[0687] Ala Ser Met Thr Lys Thr Asn Asn Glu Ile Tyr Ser Asp Ser Val Lys

[0688] 50 55 60

[0689] Gly Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu

[0690] 65 70 75 80

[0691] Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Gly Val Tyr Phe Cys Lys

[0692] 85 90 95

[0693] Gly Pro Glu Leu Arg Gly Gln Gly Ile Gln Val Thr Val Ser Ser Gly

[0694] 100 105 110

[0695] Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

[0696] 115 120 125

[0697] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu

[0698] 130 135 140

[0699] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

[0700] 145 150 155 160

[0701] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

[0702] 165 170 175

[0703] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

[0704] 180 185 190

[0705] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

[0706] 195 200 205

[0707] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

[0708] 210 215 220

[0709] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln

[0710] 225 230 235 240

[0711] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val

[0712] 245 250 255

[0713] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[0714] 260 265 270
[0715] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[0716] 275 280 285
[0717] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[0718] 290 295 300
[0719] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[0720] 305 310 315 320
[0721] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[0722] 325 330 335
[0723] Ser Pro Gly Lys
[0724] 340
[0725] <210> 27
[0726] <211> 1023
[0727] <212> DNA
[0728] <213> 人工序列(Artificial Sequence)
[0729] <220>
[0730] <223> E3-Fc结合剂(E3-Fc binding agent)
[0731] <400> 27
[0732] caagttcagc tggtcgaatc cgggggcgga ctggtccaga cagggggctc cctgaggctc 60
[0733] tcctgtgcat cttccggaag catcgccggc ttcgagaccg tgacctggtc tcgccaggct 120
[0734] cccgggaagt ctctgcagtg ggtcgcttcc atgactaaga ctaacaacga gatctactct 180
[0735] gactcagtga aaggccgctt catcatttct agagataacg ctaaaaacac agtgtatctg 240
[0736] cagatgaata gtctcaaacc tgaagacaca ggcgtgtatt tctgtaaggg tcctgagctg 300
[0737] aggggccagg gcatccaggt aacagtctcg agcggatccg acaaaactca cacatgccca 360
[0738] ccgtgcccag cacctgaact cctgggggga ccgtcagtct tcctcttccc cccaaaaccc 420
[0739] aaggacaccc tcatgatctc ccggacccct gaggtcacat gcgtggtggt ggacgtgagc 480
[0740] cacgaagacc ctgaggtcaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc 540
[0741] aagacaaagc cgcgggagga gcagtacaac agcacgtacc gtgtggtcag cgtcctcacc 600
[0742] gtcctgcacc aggactggct gaatggcaag gagtacaagt gcaaggtctc caacaaagcc 660
[0743] ctcccagccc ccatcgagaa aaccatctcc aaagccaaag ggcagccccg agaaccacag 720
[0744] gtgtacaccc tgcccccatc ccgggaggag atgaccaaga accaggtcag cctgacctgc 780
[0745] ctggtcaaag gcttctatcc cagcgacatc gccgtggagt gggagagcaa tgggcagccg 840
[0746] gagaacaact acaagaccac gcctcccgtg ctggactccg acggctcctt cttcctctat 900
[0747] agcaagctca ccgtggacaa gagcaggtgg cagcagggga acgtcttctc atgctccgtg 960
[0748] atgcatgagg ctctgcacaa ccactacacg cagaagagcc tctccctgtc tccgggtaaa 1020
[0749] tga 1023
[0750] <210> 28
[0751] <211> 350
[0752] <212> PRT
[0753] <213> 人工序列(Artificial Sequence)
[0754] <220>

[0755] <223> AA6-Fc结合剂(AA6-Fc binding agent)

[0756] <400> 28

[0757] Gln Leu Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly

[0758] 1 5 10 15

[0759] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr

[0760] 20 25 30

[0761] Val Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Ile

[0762] 35 40 45

[0763] Ala Thr Ile Asn Thr Asp Gly Ser Thr Met Arg Asp Asp Ser Thr Lys

[0764] 50 55 60

[0765] Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu

[0766] 65 70 75 80

[0767] Gln Met Thr Ser Leu Lys Pro Glu Asp Thr Ala Leu Tyr Tyr Cys Ala

[0768] 85 90 95

[0769] Arg Gly Arg Val Ile Ser Ala Ser Ala Ile Arg Gly Ala Val Arg Gly

[0770] 100 105 110

[0771] Pro Gly Thr Gln Val Thr Val Ser Ser Gly Ser Asp Lys Thr His Thr

[0772] 115 120 125

[0773] Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe

[0774] 130 135 140

[0775] Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

[0776] 145 150 155 160

[0777] Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val

[0778] 165 170 175

[0779] Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr

[0780] 180 185 190

[0781] Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val

[0782] 195 200 205

[0783] Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys

[0784] 210 215 220

[0785] Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser

[0786] 225 230 235 240

[0787] Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

[0788] 245 250 255

[0789] Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val

[0790] 260 265 270

[0791] Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly

[0792] 275 280 285

[0793] Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp

[0794] 290 295 300

[0795] Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp

[0796] 305 310 315 320

[0797] Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
[0798] 325 330 335
[0799] Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[0800] 340 345 350
[0801] <210> 29
[0802] <211> 1053
[0803] <212> DNA
[0804] <213> 人工序列(Artificial Sequence)
[0805] <220>
[0806] <223> AA6-Fc结合剂(AA6-Fc binding agent)
[0807] <400> 29
[0808] caactgcagc tggtagagac agggggcggc ttagttcagc ctggagggtc tctcagactg 60
[0809] tcatgcgctg cctctggctt taccttcagt gactacgtga tgacatgggt ccgccaagct 120
[0810] ccagggaagg ggcctgagtg gatcgctact attaatacag atggcagcac aatgcgggac 180
[0811] gactccacaa aggggcggtt caccatttcc agagacaacg ccaagaatac tctgtacctt 240
[0812] cagatgacca gtctgaaacc cgaggacact gctctgtact attgtgcaag aggccgggtg 300
[0813] atctctgctt ccgctatcag aggcgcagta aggggccctg gaacacaagt aactgtctcg 360
[0814] agcggatccg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga 420
[0815] ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct 480
[0816] gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg 540
[0817] tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac 600
[0818] agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag 660
[0819] gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 720
[0820] aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag 780
[0821] atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 840
[0822] gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg 900
[0823] ctggactccg acggctcctt cttcctctat agcaagctca ccgtggacaa gagcaggtgg 960
[0824] cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 1020
[0825] cagaagagcc tctccctgtc tccgggtaaa tga 1053
[0826] <210> 30
[0827] <211> 356
[0828] <212> PRT
[0829] <213> 人工序列(Artificial Sequence)
[0830] <220>
[0831] <223> AH3-Fc结合剂(AH3-Fc binding agent)
[0832] <400> 30
[0833] Gln Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
[0834] 1 5 10 15
[0835] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Ser
[0836] 20 25 30
[0837] Ser Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
[0838] 35 40 45

[0839] Ser Cys Ile Ser Ser Ser Gly Asp Ser Thr Lys Tyr Ala Asp Ser Val
[0840] 50 55 60
[0841] Lys Gly Arg Phe Thr Thr Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
[0842] 65 70 75 80
[0843] Leu Gln Met Asn Ser Leu Lys Pro Asp Asp Thr Ala Val Tyr Tyr Cys
[0844] 85 90 95
[0845] Ala Ala Phe Arg Ala Thr Met Cys Gly Val Phe Pro Leu Ser Pro Tyr
[0846] 100 105 110
[0847] Gly Lys Asp Asp Trp Gly Lys Gly Thr Leu Val Thr Val Ser Ser Gly
[0848] 115 120 125
[0849] Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[0850] 130 135 140
[0851] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[0852] 145 150 155 160
[0853] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[0854] 165 170 175
[0855] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[0856] 180 185 190
[0857] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[0858] 195 200 205
[0859] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[0860] 210 215 220
[0861] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[0862] 225 230 235 240
[0863] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[0864] 245 250 255
[0865] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[0866] 260 265 270
[0867] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[0868] 275 280 285
[0869] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[0870] 290 295 300
[0871] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[0872] 305 310 315 320
[0873] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[0874] 325 330 335
[0875] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[0876] 340 345 350
[0877] Ser Pro Gly Lys
[0878] 355
[0879] <210> 31
[0880] <211> 1071

[0881] <212> DNA

[0882] <213> 人工序列(Artificial Sequence)

[0883] <220>

[0884] <223> AH3-Fc结合剂(AH3-Fc binding agent)

[0885] <400> 31

[0886] caggtacagc tggtggagac gggggggaggg ctggtacaac caggcgggtc actgaggctt 60

[0887] tcctgtgccg catctgggtt cacactggat tattcgtcca tagggtggtt tcggcaggct 120

[0888] cctggcaaag agcgtgaggg ggtctcatgt attagtagta gtggtgatag cacaaagtac 180

[0889] gccgattccg taaagggccg gtttacaacc tccagggata atgctaagaa caccgtatat 240

[0890] ctccagatga actctctgaa gcccgacgat acggccgtat attactgtgc ggctttcagg 300

[0891] gcgactatgt gcggcgtgtt ccctctgagc ccttacggca aggacgactg gggcaagggg 360

[0892] accctggtga ccgtctcgag cggatccgac aaaactcaca catgcccacc gtgcccagca 420

[0893] cctgaactcc tgggggggacc gtcagtcttc ctcttccccc caaaacccaa ggacaccctc 480

[0894] atgatctccc ggacccctga ggtcacatgc gtggtggtgg acgtgagcca cgaagaccct 540

[0895] gaggtcaagt tcaactggta cgtggacggc gtggaggtgc ataatgccaa gacaaagccg 600

[0896] cgggaggagc agtacaacag cacgtaccgt gtggtcagcg tcctcaccgt cctgcaccag 660

[0897] gactggctga atggcaagga gtacaagtgc aaggtctcca acaaagccct cccagccccc 720

[0898] atcgagaaaa ccatctccaa agccaaaggg cagccccgag aaccacaggt gtacaccctg 780

[0899] cccccatccc gggaggagat gaccaagaac caggtcagcc tgacctgcct ggtcaaaggc 840

[0900] ttctatccca gcgacatcgc cgtggagtgg gagagcaatg ggcagccgga gaacaactac 900

[0901] aagaccacgc ctcccgtgct ggactccgac ggctccttct tcctctatag caagctcacc 960

[0902] gtggacaaga gcaggtggca gcaggggaac gtcttctcat gctccgtgat gcatgaggct 1020

[0903] ctgcacaacc actacacgca gaagagcctc tccctgtctc cgggtaaatg a 1071

[0904] <210> 32

[0905] <211> 498

[0906] <212> PRT

[0907] <213> 人工序列(Artificial Sequence)

[0908] <220>

[0909] <223> AH3-5D-Fc结合剂(AH3-5D-Fc binding agent)

[0910] <400> 32

[0911] Gln Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly

[0912] 1 5 10 15

[0913] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Ser

[0914] 20 25 30

[0915] Ser Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val

[0916] 35 40 45

[0917] Ser Cys Ile Ser Ser Ser Gly Asp Ser Thr Lys Tyr Ala Asp Ser Val

[0918] 50 55 60

[0919] Lys Gly Arg Phe Thr Thr Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr

[0920] 65 70 75 80

[0921] Leu Gln Met Asn Ser Leu Lys Pro Asp Asp Thr Ala Val Tyr Tyr Cys

[0922] 85 90 95

[0923] Ala Ala Phe Arg Ala Thr Met Cys Gly Val Phe Pro Leu Ser Pro Tyr
[0924] 100 105 110
[0925] Gly Lys Asp Asp Trp Gly Lys Gly Thr Leu Val Thr Val Ser Ser Gly
[0926] 115 120 125
[0927] Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val
[0928] 130 135 140
[0929] Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
[0930] 145 150 155 160
[0931] Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Leu Asp Tyr Tyr Gly Ile
[0932] 165 170 175
[0933] Gly Trp Phe Arg Gln Pro Pro Gly Lys Glu Arg Glu Ala Val Ser Tyr
[0934] 180 185 190
[0935] Ile Ser Ala Ser Ala Arg Thr Ile Leu Tyr Ala Asp Ser Val Lys Gly
[0936] 195 200 205
[0937] Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ala Val Tyr Leu Gln
[0938] 210 215 220
[0939] Met Asn Ser Leu Lys Arg Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
[0940] 225 230 235 240
[0941] Arg Arg Phe Ser Ala Ser Ser Val Asn Arg Trp Leu Ala Asp Asp Tyr
[0942] 245 250 255
[0943] Asp Val Trp Gly Arg Gly Thr Gln Val Ala Val Ser Ser Gly Ser Asp
[0944] 260 265 270
[0945] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
[0946] 275 280 285
[0947] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[0948] 290 295 300
[0949] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[0950] 305 310 315 320
[0951] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[0952] 325 330 335
[0953] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[0954] 340 345 350
[0955] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[0956] 355 360 365
[0957] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
[0958] 370 375 380
[0959] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[0960] 385 390 395 400
[0961] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[0962] 405 410 415
[0963] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[0964] 420 425 430

[0965] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[0966] 435 440 445
[0967] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[0968] 450 455 460
[0969] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[0970] 465 470 475 480
[0971] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[0972] 485 490 495
[0973] Gly Lys
[0974] <210> 33
[0975] <211> 1497
[0976] <212> DNA
[0977] <213> 人工序列(Artificial Sequence)
[0978] <220>
[0979] <223> AH3-5D-Fc结合剂(AH3-5D-Fc binding agent)
[0980] <400> 33
[0981] caggtacagc tggtggagac gggggggaggg ctggtacaac caggcgggtc actgaggctt 60
[0982] tcctgtgccg catctgggtt cacactggat tattcgtcca tagggtggtt tcggcaggct 120
[0983] cctggcaaag agcgtgaggg ggtctcatgt attagtagta gtggtgatag cacaaagtac 180
[0984] gccgattccg taaagggccg gtttacaacc tccagggata atgctaagaa caccgtatat 240
[0985] ctccagatga actctctgaa gcccgacgat acggccgtat attactgtgc ggctttcagg 300
[0986] gcgactatgt gcggcgtgtt ccctctgagc ccttacggca aggacgactg gggcaagggg 360
[0987] accctggtga ccgtatcctc aggcggtgga gggtctggtg ggggaggctc agggggtgga 420
[0988] ggcagccagg tgcaactggt tgaatctggg ggaggcttgg tacaacctgg gggatccctg 480
[0989] agactctctt gcgaggcctc cggattcacc ttggactact atggcatcgg ctggttccgc 540
[0990] cagcccccag ggaaggagcg ggaggccgtt tcatacatta gtgccagtgc ccggaccata 600
[0991] ctgtacgcag actctgtgaa gggacgcttt accatctcta gggacaatgc caaaaatgct 660
[0992] gtgtacctgc aaatgaacag cctcaagcgg gaggataccg cagtgtacta ctgcgcgaga 720
[0993] cggcgcttct ccgcttctag cgtgaataga tggctggccg acgactacga cgtgtgggga 780
[0994] cggggcacac aggtggctgt ctcgagcgga tccgacaaaa ctcacacatg cccaccgtgc 840
[0995] ccagcacctg aactcctggg gggaccgtca gtcttcctct tccccccaaa acccaaggac 900
[0996] accctcatga tctcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa 960
[0997] gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca 1020
[0998] aagccgcggg aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg 1080
[0999] caccaggact ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca 1140
[1000] gcccccatcg agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac 1200
[1001] accctgcccc catcccggga ggagatgacc aagaaccagg tcagcctgac ctgcctggtc 1260
[1002] aaaggcttct atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac 1320
[1003] aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctatagcaag 1380
[1004] ctcaccgtgg acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat 1440
[1005] gaggctctgc acaaccacta cacgcagaag agcctctccc tgtctccggg taaatga 1497
[1006] <210> 34

[1007] <211> 476

[1008] <212> PRT

[1009] <213> 人工序列(Artificial Sequence)

[1010] <220>

[1011] <223> AA6-E3-Fc结合剂(AA6-E3-Fc binding agent)

[1012] <400> 34

[1013] Gln Leu Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly

[1014] 1 5 10 15

[1015] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr

[1016] 20 25 30

[1017] Val Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Ile

[1018] 35 40 45

[1019] Ala Thr Ile Asn Thr Asp Gly Ser Thr Met Arg Asp Asp Ser Thr Lys

[1020] 50 55 60

[1021] Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu

[1022] 65 70 75 80

[1023] Gln Met Thr Ser Leu Lys Pro Glu Asp Thr Ala Leu Tyr Tyr Cys Ala

[1024] 85 90 95

[1025] Arg Gly Arg Val Ile Ser Ala Ser Ala Ile Arg Gly Ala Val Arg Gly

[1026] 100 105 110

[1027] Pro Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly

[1028] 115 120 125

[1029] Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly

[1030] 130 135 140

[1031] Gly Gly Leu Val Gln Thr Gly Gly Ser Leu Arg Leu Ser Cys Ala Ser

[1032] 145 150 155 160

[1033] Ser Gly Ser Ile Ala Gly Phe Glu Thr Val Thr Trp Ser Arg Gln Ala

[1034] 165 170 175

[1035] Pro Gly Lys Ser Leu Gln Trp Val Ala Ser Met Thr Lys Thr Asn Asn

[1036] 180 185 190

[1037] Glu Ile Tyr Ser Asp Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp

[1038] 195 200 205

[1039] Asn Ala Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu

[1040] 210 215 220

[1041] Asp Thr Gly Val Tyr Phe Cys Lys Gly Pro Glu Leu Arg Gly Gln Gly

[1042] 225 230 235 240

[1043] Ile Gln Val Thr Val Ser Ser Gly Ser Asp Lys Thr His Thr Cys Pro

[1044] 245 250 255

[1045] Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe

[1046] 260 265 270

[1047] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val

[1048] 275 280 285

[1049] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[1050] 290 295 300
[1051] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[1052] 305 310 315 320
[1053] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[1054] 325 330 335
[1055] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[1056] 340 345 350
[1057] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[1058] 355 360 365
[1059] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[1060] 370 375 380
[1061] Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[1062] 385 390 395 400
[1063] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
[1064] 405 410 415
[1065] Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[1066] 420 425 430
[1067] Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
[1068] 435 440 445
[1069] Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[1070] 450 455 460
[1071] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[1072] 465 470 475
[1073] <210> 35
[1074] <211> 1431
[1075] <212> DNA
[1076] <213> 人工序列(Artificial Sequence)
[1077] <220>
[1078] <223> AA6-E3-Fc结合剂(AA6-E3-Fc binding agent)
[1079] <400> 35
[1080] caactgcagc tggtagagac aggggcggc ttagttcagc ctggagggtc tctcagactg 60
[1081] tcatgcgctg cctctggctt taccttcagt gactacgtga tgacatgggt ccgccaagct 120
[1082] ccagggaagg ggcctgagtg gatcgctact attaatacag atggcagcac aatgcgggac 180
[1083] gactccacaa aggggcggtt caccatttcc agagacaacg ccaagaatac tctgtacctt 240
[1084] cagatgacca gtctgaaacc cgaggacact gctctgtact attgtgcaag aggccgggtg 300
[1085] atctctgctt ccgctatcag aggcgcagta aggggccctg gaacacaggt aaccgtttca 360
[1086] tccgggggag gcggttcagg cggtggggga tctggcgggg gtggatccca agttcagctg 420
[1087] gtcgaatccg ggggcggact ggtccagaca gggggctccc tgaggctctc ctgtgcatct 480
[1088] tccggaagca tcgccggctt cgagaccgtg acctggtctc gccaggctcc cgggaagtct 540
[1089] ctgcagtggg tcgcttccat gactaagact aacaacgaga tctactctga ctcagtgaaa 600
[1090] ggccgcttca tcatttctag agataacgct aaaaacacag tgtatctgca gatgaatagt 660

[1091] ctcaaacctg aagacacagg cgtgtatttc tgtaagggtc ctgagctgag gggccagggc 720
[1092] atccaggtaa cagtctcgag cggatccgac aaaactcaca catgcccacc gtgcccagca 780
[1093] cctgaactcc tgggggacc gtcagtcttc ctcttccccc caaaacccaa ggacaccctc 840
[1094] atgatctccc ggacccctga ggtcacatgc gtggtggtgg acgtgagcca cgaagaccct 900
[1095] gaggtcaagt tcaactggta cgtggacggc gtggaggtgc ataatgccaa gacaaagccg 960
[1096] cgggaggagc agtacaacag cacgtaccgt gtggtcagcg tcctcaccgt cctgcaccag 1020
[1097] gactggctga atggcaagga gtacaagtgc aaggtctcca acaaagccct cccagccccc 1080
[1098] atcgagaaaa ccatctccaa agccaaaggg cagccccgag aaccacaggt gtacaccctg 1140
[1099] cccccatccc gggaggagat gaccaagaac caggtcagcc tgacctgcct ggtcaaaggc 1200
[1100] ttctatccca gcgacatcgc cgtggagtgg gagagcaatg ggcagccgga gaacaactac 1260
[1101] aagaccacgc ctcccgtgct ggactccgac ggctccttct tcctctatag caagctcacc 1320
[1102] gtggacaaga gcaggtggca gcaggggaac gtcttctcat gctccgtgat gcatgaggct 1380
[1103] ctgcacaacc actacacgca gaagagcctc tccctgtctc cgggtaaatg a 1431
[1104] <210> 36
[1105] <211> 457
[1106] <212> PRT
[1107] <213> 人工序列(Artificial Sequence)
[1108] <220>
[1109] <223> AH3-IgG1-重链(AH3-IgG1-heavy chain)
[1110] <400> 36

[1111] Gln Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
[1112] 1 5 10 15
[1113] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Ser
[1114] 20 25 30
[1115] Ser Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
[1116] 35 40 45
[1117] Ser Cys Ile Ser Ser Ser Gly Asp Ser Thr Lys Tyr Ala Asp Ser Val
[1118] 50 55 60
[1119] Lys Gly Arg Phe Thr Thr Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
[1120] 65 70 75 80
[1121] Leu Gln Met Asn Ser Leu Lys Pro Asp Asp Thr Ala Val Tyr Tyr Cys
[1122] 85 90 95
[1123] Ala Ala Phe Arg Ala Thr Met Cys Gly Val Phe Pro Leu Ser Pro Tyr
[1124] 100 105 110
[1125] Gly Lys Asp Asp Trp Gly Lys Gly Thr Leu Val Thr Val Ser Ser Ala
[1126] 115 120 125
[1127] Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
[1128] 130 135 140
[1129] Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
[1130] 145 150 155 160
[1131] Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
[1132] 165 170 175

[1133] Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
[1134] 180 185 190
[1135] Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
[1136] 195 200 205
[1137] Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
[1138] 210 215 220
[1139] Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
[1140] 225 230 235 240
[1141] Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
[1142] 245 250 255
[1143] Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
[1144] 260 265 270
[1145] Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
[1146] 275 280 285
[1147] Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
[1148] 290 295 300
[1149] Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
[1150] 305 310 315 320
[1151] Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
[1152] 325 330 335
[1153] Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
[1154] 340 345 350
[1155] Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
[1156] 355 360 365
[1157] Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
[1158] 370 375 380
[1159] Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
[1160] 385 390 395 400
[1161] Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
[1162] 405 410 415
[1163] Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
[1164] 420 425 430
[1165] Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
[1166] 435 440 445
[1167] Lys Ser Leu Ser Leu Ser Pro Gly Lys
[1168] 450 455
[1169] <210> 37
[1170] <211> 1374
[1171] <212> DNA
[1172] <213> 人工序列(Artificial Sequence)
[1173] <220>
[1174] <223> AH3-IgG1-重链(AH3-IgG1-heavy chain)

[1175] <400> 37

[1176] caggtacagc tggtggagac gggggggaggg ctggtacaac caggcgggtc actgaggctt 60

[1177] tcctgtgccg catctgggtt cacactggat tattcgtcca tagggtggtt tcggcaggct 120

[1178] cctggcaaag agcgtgaggg ggtctcatgt attagtagta gtggtgatag cacaaagtac 180

[1179] gccgattccg taaagggccg gtttacaacc tccagggata atgctaagaa caccgtatat 240

[1180] ctccagatga actctctgaa gcccgacgat acggccgtat attactgtgc ggctttcagg 300

[1181] gcgactatgt gcggcgtgtt ccctctgagc ccttacggca aggacgactg gggcaagggg 360

[1182] accctggtga ccgtctcgag tgcgtcgacc aagggcccat cggtcttccc gctagcaccc 420

[1183] tcctccaaga gcacctctgg gggcacagcg gccctgggct gcctggtcaa ggactacttc 480

[1184] cccgaacctg tgacggtctc gtggaactca ggcgccctga ccagcggcgt gcacaccttc 540

[1185] ccggctgtcc tacagtcctc aggactctac tccctcagca gcgtggtgac cgtgccctcc 600

[1186] agcagcttgg gcacccagac ctacatctgc aacgtgaatc acaagcccag caacaccaag 660

[1187] gtggacaaga gagttgagcc caaatcttgt gacaaaactc acacatgccc accgtgccca 720

[1188] gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 780

[1189] ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 840

[1190] cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 900

[1191] ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 960

[1192] caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 1020

[1193] cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 1080

[1194] ctgcccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 1140

[1195] ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 1200

[1196] tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcaagctc 1260

[1197] accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1320

[1198] gctctgcaca accactacac gcagaagagc ctctccctgt ccccgggtaa atga 1374

[1199] <210> 38

[1200] <211> 457

[1201] <212> PRT

[1202] <213> 人工序列(Artificial Sequence)

[1203] <220>

[1204] <223> 5D-IgG1-重链(5D-IgG1-heavy chain)

[1205] <400> 38

[1206] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

[1207] 1 5 10 15

[1208] Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Leu Asp Tyr Tyr

[1209] 20 25 30

[1210] Gly Ile Gly Trp Phe Arg Gln Pro Pro Gly Lys Glu Arg Glu Ala Val

[1211] 35 40 45

[1212] Ser Tyr Ile Ser Ala Ser Ala Arg Thr Ile Leu Tyr Ala Asp Ser Val

[1213] 50 55 60

[1214] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ala Val Tyr

[1215] 65 70 75 80

[1216] Leu Gln Met Asn Ser Leu Lys Arg Glu Asp Thr Ala Val Tyr Tyr Cys

[1217] 85 90 95
[1218] Ala Arg Arg Arg Phe Ser Ala Ser Ser Val Asn Arg Trp Leu Ala Asp
[1219] 100 105 110
[1220] Asp Tyr Asp Val Trp Gly Arg Gly Thr Gln Val Ala Val Ser Ser Ala
[1221] 115 120 125
[1222] Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
[1223] 130 135 140
[1224] Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
[1225] 145 150 155 160
[1226] Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
[1227] 165 170 175
[1228] Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
[1229] 180 185 190
[1230] Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
[1231] 195 200 205
[1232] Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
[1233] 210 215 220
[1234] Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
[1235] 225 230 235 240
[1236] Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
[1237] 245 250 255
[1238] Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
[1239] 260 265 270
[1240] Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
[1241] 275 280 285
[1242] Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
[1243] 290 295 300
[1244] Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
[1245] 305 310 315 320
[1246] Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
[1247] 325 330 335
[1248] Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
[1249] 340 345 350
[1250] Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
[1251] 355 360 365
[1252] Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
[1253] 370 375 380
[1254] Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
[1255] 385 390 395 400
[1256] Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
[1257] 405 410 415
[1258] Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val

[1259] 420 425 430

[1260] Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln

[1261] 435 440 445

[1262] Lys Ser Leu Ser Leu Ser Pro Gly Lys

[1263] 450 455

[1264] <210> 39

[1265] <211> 1374

[1266] <212> DNA

[1267] <213> 人工序列(Artificial Sequence)

[1268] <220>

[1269] <223> 5D-IgG1-重链(5D-IgG1-heavy chain)

[1270] <400> 39

[1271] caggtgcaac tggttgaatc tgggggaggc ttggtacaac ctgggggatc cctgagactc 60

[1272] tcttgcgagg cctccggatt caccttggac tactatggca tcggctggtt ccgccagccc 120

[1273] ccagggaagg agcgggaggc cgtttcatac attagtgcca gtgcccggac catactgtac 180

[1274] gcagactctg tgaagggacg ctttaccatc tctagggaca atgccaaaaa tgctgtgtac 240

[1275] ctgcaaatga acagcctcaa gcgggaggat accgcagtgt actactgcgc gagacggcgc 300

[1276] ttctccgctt ctagcgtgaa tagatggctg gccgacgact acgacgtgtg gggacggggc 360

[1277] acacaggtgg ctgtctcgag cgcgtcgacc aagggcccat cggtcttccc gctagcaccc 420

[1278] tcctccaaga gcacctctgg gggcacagcg gccctgggct gcctggtcaa ggactacttc 480

[1279] cccgaacctg tgacggtctc gtggaactca ggcgccctga ccagcggcgt gcacaccttc 540

[1280] ccggctgtcc tacagtcctc aggactctac tccctcagca gcgtggtgac cgtgccctcc 600

[1281] agcagcttgg gcacccagac ctacatctgc aacgtgaatc acaagcccag caacaccaag 660

[1282] gtggacaaga gagttgagcc caaatcttgt gacaaaactc acacatgccc accgtgccca 720

[1283] gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 780

[1284] ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 840

[1285] cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 900

[1286] ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 960

[1287] caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 1020

[1288] cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 1080

[1289] ctgcccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 1140

[1290] ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 1200

[1291] tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcaagctc 1260

[1292] accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1320

[1293] gctctgcaca accactacac gcagaagagc ctctccctgt ccccgggtaa atga 1374

[1294] <210> 40

[1295] <211> 228

[1296] <212> PRT

[1297] <213> 人工序列(Artificial Sequence)

[1298] <220>

[1299] <223> AA6-IgG1-kappa链(AA6-IgG1-kappa chain)

[1300] <400> 40

[1301] Gln Leu Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
[1302] 1 5 10 15
[1303] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[1304] 20 25 30
[1305] Val Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Ile
[1306] 35 40 45
[1307] Ala Thr Ile Asn Thr Asp Gly Ser Thr Met Arg Asp Asp Ser Thr Lys
[1308] 50 55 60
[1309] Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu
[1310] 65 70 75 80
[1311] Gln Met Thr Ser Leu Lys Pro Glu Asp Thr Ala Leu Tyr Tyr Cys Ala
[1312] 85 90 95
[1313] Arg Gly Arg Val Ile Ser Ala Ser Ala Ile Arg Gly Ala Val Arg Gly
[1314] 100 105 110
[1315] Pro Gly Thr Gln Val Thr Val Ser Ser Arg Thr Val Ala Ala Pro Ser
[1316] 115 120 125
[1317] Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala
[1318] 130 135 140
[1319] Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val
[1320] 145 150 155 160
[1321] Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser
[1322] 165 170 175
[1323] Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr
[1324] 180 185 190
[1325] Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys
[1326] 195 200 205
[1327] Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn
[1328] 210 215 220
[1329] Arg Gly Glu Cys
[1330] 225
[1331] <210> 41
[1332] <211> 687
[1333] <212> DNA
[1334] <213> 人工序列(Artificial Sequence)
[1335] <220>
[1336] <223> AA6-IgG1-kappa链(AA6-IgG1-kappa chain)
[1337] <400> 41
[1338] caactgcagc tggtagagac aggggcggc ttagttcagc ctggagggtc tctcagactg 60
[1339] tcatgcgctg cctctggctt taccttcagt gactacgtga tgacatgggt ccgccaagct 120
[1340] ccagggaagg ggcctgagtg gatcgctact attaatacag atggcagcac aatgcgggac 180
[1341] gactccacaa aggggcggtt caccatttcc agagacaacg ccaagaatac tctgtacctt 240
[1342] cagatgacca gtctgaaacc cgaggacact gctctgtact attgtgcaag aggccgggtg 300

[1343] atctctgctt ccgctatcag aggcgcagta aggggccctg gaacacaagt aactgtctcg 360
[1344] agccgtacgg tggctgcacc atctgtcttc atcttcccgc catctgatga gcagttgaaa 420
[1345] tctggaactg cctctgttgt gtgcctgctg aataacttct atcccagaga ggccaaagta 480
[1346] cagtggaagg tggataacgc cctccaatcg ggtaactccc aggagagtgt cacagagcag 540
[1347] gacagcaagg acagcaccta cagcctcagc agcaccctga cgctgagcaa agcagactac 600
[1348] gagaaacaca aagtctacgc ctgcgaagtc acccatcagg gcctgagctc gcccgtcaca 660
[1349] aagagcttca acaggggaga gtgttga 687
[1350] <210> 42
[1351] <211> 218
[1352] <212> PRT
[1353] <213> 人工序列(Artificial Sequence)
[1354] <220>
[1355] <223> E3-IgG1-kappa链(E3-IgG1-kappa chain)
[1356] <400> 42
[1357] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Thr Gly Gly
[1358] 1 5 10 15
[1359] Ser Leu Arg Leu Ser Cys Ala Ser Ser Gly Ser Ile Ala Gly Phe Glu
[1360] 20 25 30
[1361] Thr Val Thr Trp Ser Arg Gln Ala Pro Gly Lys Ser Leu Gln Trp Val
[1362] 35 40 45
[1363] Ala Ser Met Thr Lys Thr Asn Asn Glu Ile Tyr Ser Asp Ser Val Lys
[1364] 50 55 60
[1365] Gly Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
[1366] 65 70 75 80
[1367] Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Gly Val Tyr Phe Cys Lys
[1368] 85 90 95
[1369] Gly Pro Glu Leu Arg Gly Gln Gly Ile Gln Val Thr Val Ser Ser Arg
[1370] 100 105 110
[1371] Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
[1372] 115 120 125
[1373] Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
[1374] 130 135 140
[1375] Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
[1376] 145 150 155 160
[1377] Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
[1378] 165 170 175
[1379] Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
[1380] 180 185 190
[1381] His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
[1382] 195 200 205
[1383] Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
[1384] 210 215

[1385] <210> 43
[1386] <211> 657
[1387] <212> DNA
[1388] <213> 人工序列(Artificial Sequence)
[1389] <220>
[1390] <223> E3-IgG1-kappa链(E3-IgG1-kappa chain)
[1391] <400> 43
[1392] caagttcagc tggtcgaatc cgggggcgga ctggtccaga caggggctc cctgaggctc 60
[1393] tcctgtgcat cttccggaag catcgccggc ttcgagaccg tgacctggtc tcgccaggct 120
[1394] cccgggaagt ctctgcagtg ggtcgcttcc atgactaaga ctaacaacga gatctactct 180
[1395] gactcagtga aaggccgctt catcatttct agagataacg ctaaaaacac agtgtatctg 240
[1396] cagatgaata gtctcaaacc tgaagacaca ggcgtgtatt tctgtaaggg tcctgagctg 300
[1397] aggggccagg gcatccaggt aacagtctcg agccgtacgg tggctgcacc atctgtcttc 360
[1398] atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg 420
[1399] aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg 480
[1400] ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc 540
[1401] agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc 600
[1402] acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgttga 657
[1403] <210> 44
[1404] <211> 599
[1405] <212> PRT
[1406] <213> 人工序列(Artificial Sequence)
[1407] <220>
[1408] <223> AH3-5D-IgG1重链(AH3-5D-IgG1 heavy chain)
[1409] <400> 44
[1410] Gln Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
[1411] 1 5 10 15
[1412] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Ser
[1413] 20 25 30
[1414] Ser Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
[1415] 35 40 45
[1416] Ser Cys Ile Ser Ser Ser Gly Asp Ser Thr Lys Tyr Ala Asp Ser Val
[1417] 50 55 60
[1418] Lys Gly Arg Phe Thr Thr Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
[1419] 65 70 75 80
[1420] Leu Gln Met Asn Ser Leu Lys Pro Asp Asp Thr Ala Val Tyr Tyr Cys
[1421] 85 90 95
[1422] Ala Ala Phe Arg Ala Thr Met Cys Gly Val Phe Pro Leu Ser Pro Tyr
[1423] 100 105 110
[1424] Gly Lys Asp Asp Trp Gly Lys Gly Thr Leu Val Thr Val Ser Ser Gly
[1425] 115 120 125
[1426] Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val

[1427] 130 135 140

[1428] Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu

[1429] 145 150 155 160

[1430] Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Leu Asp Tyr Tyr Gly Ile

[1431] 165 170 175

[1432] Gly Trp Phe Arg Gln Pro Pro Gly Lys Glu Arg Glu Ala Val Ser Tyr

[1433] 180 185 190

[1434] Ile Ser Ala Ser Ala Arg Thr Ile Leu Tyr Ala Asp Ser Val Lys Gly

[1435] 195 200 205

[1436] Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ala Val Tyr Leu Gln

[1437] 210 215 220

[1438] Met Asn Ser Leu Lys Arg Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg

[1439] 225 230 235 240

[1440] Arg Arg Phe Ser Ala Ser Ser Val Asn Arg Trp Leu Ala Asp Asp Tyr

[1441] 245 250 255

[1442] Asp Val Trp Gly Arg Gly Thr Gln Val Ala Val Ser Ser Ala Ser Thr

[1443] 260 265 270

[1444] Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser

[1445] 275 280 285

[1446] Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu

[1447] 290 295 300

[1448] Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His

[1449] 305 310 315 320

[1450] Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser

[1451] 325 330 335

[1452] Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys

[1453] 340 345 350

[1454] Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu

[1455] 355 360 365

[1456] Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro

[1457] 370 375 380

[1458] Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys

[1459] 385 390 395 400

[1460] Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val

[1461] 405 410 415

[1462] Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp

[1463] 420 425 430

[1464] Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr

[1465] 435 440 445

[1466] Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp

[1467] 450 455 460

[1468] Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu

[1469] 465 470 475 480
[1470] Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
[1471] 485 490 495
[1472] Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
[1473] 500 505 510
[1474] Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
[1475] 515 520 525
[1476] Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
[1477] 530 535 540
[1478] Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
[1479] 545 550 555 560
[1480] Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
[1481] 565 570 575
[1482] Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
[1483] 580 585 590
[1484] Leu Ser Leu Ser Pro Gly Lys
[1485] 595
[1486] <210> 45
[1487] <211> 1800
[1488] <212> DNA
[1489] <213> 人工序列(Artificial Sequence)
[1490] <220>
[1491] <223> AH3-5D-IgG1重链(AH3-5D-IgG1 heavy chain)
[1492] <400> 45
[1493] caggtacagc tggtggagac ggggggaggg ctggtacaac caggcgggtc actgaggctt 60
[1494] tcctgtgccg catctgggtt cacactggat tattcgtcca tagggtggtt tcggcaggct 120
[1495] cctggcaaag agcgtgaggg ggtctcatgt attagtagta gtggtgatag cacaaagtac 180
[1496] gccgattccg taaagggccg gtttacaacc tccagggata atgctaagaa caccgtatat 240
[1497] ctccagatga actctctgaa gcccgacgat acggccgtat attactgtgc ggctttcagg 300
[1498] gcgactatgt gcggcgtgtt ccctctgagc ccttacggca aggacgactg gggcaagggg 360
[1499] accctggtga ccgtatcctc aggcggtgga gggtctggtg ggggaggctc agggggtgga 420
[1500] ggcagccagg tgcaactggt tgaatctggg ggaggcttgg tacaacctgg gggatccctg 480
[1501] agactctctt gcgaggcctc cggattcacc ttggactact atggcatcgg ctggttccgc 540
[1502] cagcccccag ggaaggagcg ggaggccgtt tcatacatta gtgccagtgc ccggaccata 600
[1503] ctgtacgcag actctgtgaa gggacgcttt accatctcta gggacaatgc caaaaatgct 660
[1504] gtgtacctgc aaatgaacag cctcaagcgg gaggataccg cagtgtacta ctgcgcgaga 720
[1505] cggcgcttct ccgcttctag cgtgaataga tggctggccg acgactacga cgtgtgggga 780
[1506] cggggcacac aggtggctgt ctcgagcgcg tcgaccaagg gcccatcggt cttcccgcta 840
[1507] gcaccctcct ccaagagcac ctctgggggc acagcggccc tgggctgcct ggtcaaggac 900
[1508] tacttccccg aacctgtgac ggtctcgtgg aactcaggcg ccctgaccag cggcgtgcac 960
[1509] accttcccgg ctgtcctaca gtcctcagga ctctactccc tcagcagcgt ggtgaccgtg 1020
[1510] ccctccagca gcttgggcac ccagacctac atctgcaacg tgaatcacaa gcccagcaac 1080

[1511] accaaggtgg acaagagagt tgagcccaaa tcttgtgaca aaactcacac atgcccaccg 1140
[1512] tgcccagcac ctgaactcct gggggggaccg tcagtcttcc tcttcccccc aaaacccaag 1200
[1513] gacaccctca tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac 1260
[1514] gaagaccctg aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag 1320
[1515] acaaagccgc gggaggagca gtacaacagc acgtaccgtg tggtcagcgt cctcaccgtc 1380
[1516] ctgcaccagg actggctgaa tggcaaggag tacaagtgca aggtctccaa caaagccctc 1440
[1517] ccagccccca tcgagaaaac catctccaaa gccaaagggc agccccgaga accacaggtg 1500
[1518] tacaccctgc ccccatcccg ggaggagatg accaagaacc aggtcagcct gacctgcctg 1560
[1519] gtcaaaggct tctatcccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag 1620
[1520] aacaactaca agaccacgcc tcccgtgctg gactccgacg gctccttctt cctctatagc 1680
[1521] aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg 1740
[1522] catgaggctc tgcacaacca ctacacgcag aagagcctct ccctgtcccc gggtaaatga 1800
[1523] <210> 46
[1524] <211> 354
[1525] <212> PRT
[1526] <213> 人工序列(Artificial Sequence)
[1527] <220>
[1528] <223> AA6-E3-IgG1轻链(AA6-E3-IgG1 light chain)
[1529] <400> 46
[1530] Gln Leu Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
[1531] 1 5 10 15
[1532] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[1533] 20 25 30
[1534] Val Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Ile
[1535] 35 40 45
[1536] Ala Thr Ile Asn Thr Asp Gly Ser Thr Met Arg Asp Asp Ser Thr Lys
[1537] 50 55 60
[1538] Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu
[1539] 65 70 75 80
[1540] Gln Met Thr Ser Leu Lys Pro Glu Asp Thr Ala Leu Tyr Tyr Cys Ala
[1541] 85 90 95
[1542] Arg Gly Arg Val Ile Ser Ala Ser Ala Ile Arg Gly Ala Val Arg Gly
[1543] 100 105 110
[1544] Pro Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
[1545] 115 120 125
[1546] Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly
[1547] 130 135 140
[1548] Gly Gly Leu Val Gln Thr Gly Gly Ser Leu Arg Leu Ser Cys Ala Ser
[1549] 145 150 155 160
[1550] Ser Gly Ser Ile Ala Gly Phe Glu Thr Val Thr Trp Ser Arg Gln Ala
[1551] 165 170 175
[1552] Pro Gly Lys Ser Leu Gln Trp Val Ala Ser Met Thr Lys Thr Asn Asn

[1553] 180 185 190
[1554] Glu Ile Tyr Ser Asp Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp
[1555] 195 200 205
[1556] Asn Ala Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu
[1557] 210 215 220
[1558] Asp Thr Gly Val Tyr Phe Cys Lys Gly Pro Glu Leu Arg Gly Gln Gly
[1559] 225 230 235 240
[1560] Ile Gln Val Thr Val Ser Ser Arg Thr Val Ala Ala Pro Ser Val Phe
[1561] 245 250 255
[1562] Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val
[1563] 260 265 270
[1564] Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
[1565] 275 280 285
[1566] Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr
[1567] 290 295 300
[1568] Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr
[1569] 305 310 315 320
[1570] Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
[1571] 325 330 335
[1572] Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
[1573] 340 345 350
[1574] Glu Cys
[1575] <210> 47
[1576] <211> 1065
[1577] <212> DNA
[1578] <213> 人工序列(Artificial Sequence)
[1579] <220>
[1580] <223> AA6-E3-IgG1轻链(AA6-E3-IgG1 light chain)
[1581] <400> 47
[1582] caactgcagc tggtagagac agggggcggc ttagttcagc ctggagggtc tctcagactg 60
[1583] tcatgcgctg cctctggctt taccttcagt gactacgtga tgacatgggt ccgccaagct 120
[1584] ccagggaagg ggcctgagtg gatcgctact attaatacag atggcagcac aatgcgggac 180
[1585] gactccacaa aggggcggtt caccatttcc agagacaacg ccaagaatac tctgtacctt 240
[1586] cagatgacca gtctgaaacc cgaggacact gctctgtact attgtgcaag aggccgggtg 300
[1587] atctctgctt ccgctatcag aggcgcagta aggggccctg gaacacaggt aaccgtttca 360
[1588] tccgggggag gcggttcagg cggtggggga tctggcgggg gtggatccca agttcagctg 420
[1589] gtcgaatccg ggggcggact ggtccagaca gggggctccc tgaggctctc ctgtgcatct 480
[1590] tccggaagca tcgccggctt cgagaccgtg acctggtctc gccaggctcc cgggaagtct 540
[1591] ctgcagtggg tcgcttccat gactaagact aacaacgaga tctactctga ctcagtgaaa 600
[1592] ggccgcttca tcatttctag agataacgct aaaaacacag tgtatctgca gatgaatagt 660
[1593] ctcaaacctg aagacacagg cgtgtatttc tgtaagggtc ctgagctgag gggccagggc 720
[1594] atccaggtaa cagtctcgag ccgtacggtg gctgcaccat ctgtcttcat cttcccgcca 780

[1595] tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 840
[1596] cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 900
[1597] gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 960
[1598] ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 1020
[1599] ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gttga 1065
[1600] <210> 48
[1601] <211> 127
[1602] <212> PRT
[1603] <213> 人工序列(Artificial Sequence)
[1604] <220>
[1605] <223> VHH肽单体5D(VHH peptide monomer 5D)
[1606] <400> 48
[1607] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[1608] 1 5 10 15
[1609] Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Leu Asp Tyr Tyr
[1610] 20 25 30
[1611] Gly Ile Gly Trp Phe Arg Gln Pro Pro Gly Lys Glu Arg Glu Ala Val
[1612] 35 40 45
[1613] Ser Tyr Ile Ser Ala Ser Ala Arg Thr Ile Leu Tyr Ala Asp Ser Val
[1614] 50 55 60
[1615] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ala Val Tyr
[1616] 65 70 75 80
[1617] Leu Gln Met Asn Ser Leu Lys Arg Glu Asp Thr Ala Val Tyr Tyr Cys
[1618] 85 90 95
[1619] Ala Arg Arg Arg Phe Ser Ala Ser Ser Val Asn Arg Trp Leu Ala Asp
[1620] 100 105 110
[1621] Asp Tyr Asp Val Trp Gly Arg Gly Thr Gln Val Ala Val Ser Ser
[1622] 115 120 125
[1623] <210> 49
[1624] <211> 381
[1625] <212> DNA
[1626] <213> 人工序列(Artificial Sequence)
[1627] <220>
[1628] <223> VHH肽单体5D(VHH peptide monomer 5D)
[1629] <400> 49
[1630] caggtgcagc tcgtggagtc aggtggaggc ttggtgcagc ctgggggggtc tctgagactc 60
[1631] tcctgtgaag cctctggatt cactttggat tattatggta taggctggtt ccgccagccc 120
[1632] ccagggaagg agcgcgaggc ggtctcatat attagtgcca gtgcccgtac gatattgtat 180
[1633] gcagattccg tgaagggccg atttaccatc tccagagaca atgccaagaa cgcggtgtat 240
[1634] ctacaaatga acagcctgaa acgtgaggac acggctgtct attactgtgc gaggcggcga 300
[1635] ttctccgcgt ctagtgttaa tagatggctt gccgacgact atgacgtctg gggtcggggg 360
[1636] acccaggtcg cggtgtcctc a 381

[1637] <210> 50
[1638] <211> 111
[1639] <212> PRT
[1640] <213> 人工序列(Artificial Sequence)
[1641] <220>
[1642] <223> VHH肽单体E3(VHH peptide monomer E3)
[1643] <400> 50
[1644] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Thr Gly Gly
[1645] 1 5 10 15
[1646] Ser Leu Arg Leu Ser Cys Ala Ser Ser Gly Ser Ile Ala Gly Phe Glu
[1647] 20 25 30
[1648] Thr Val Thr Trp Ser Arg Gln Ala Pro Gly Lys Ser Leu Gln Trp Val
[1649] 35 40 45
[1650] Ala Ser Met Thr Lys Thr Asn Asn Glu Ile Tyr Ser Asp Ser Val Lys
[1651] 50 55 60
[1652] Gly Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
[1653] 65 70 75 80
[1654] Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Gly Val Tyr Phe Cys Lys
[1655] 85 90 95
[1656] Gly Pro Glu Leu Arg Gly Gln Gly Ile Gln Val Thr Val Ser Ser
[1657] 100 105 110
[1658] <210> 51
[1659] <211> 333
[1660] <212> DNA
[1661] <213> 人工序列(Artificial Sequence)
[1662] <220>
[1663] <223> VHH肽单体E3(VHH peptide monomer E3)
[1664] <400> 51
[1665] caggtgcagc tcgtggagtc gggcggaggc ttggtgcaga ctgggggtc tctgagactc 60
[1666] tcctgtgcat cctctggaag tatcgccggt ttcgaaaccg tgacctggtc ccgccaggct 120
[1667] cctggaaagt cgctccagtg ggtcgcatcg atgactaaaa ctaataacga gatctattca 180
[1668] gactccgtga agggccgatt catcatctcc agagacaacg ccaagaatac ggtgtatcta 240
[1669] caaatgaaca gcctgaaacc tgaggacaca ggcgtctatt tttgtaaagg tcctgagttg 300
[1670] aggggccagg ggatccaggt caccgtctcc tcg 333
[1671] <210> 52
[1672] <211> 121
[1673] <212> PRT
[1674] <213> 人工序列(Artificial Sequence)
[1675] <220>
[1676] <223> VHH肽单体AA6(VHH peptide monomer AA6)
[1677] <400> 52
[1678] Gln Leu Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly

[1679] 1 5 10 15
[1680] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[1681] 20 25 30
[1682] Val Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Ile
[1683] 35 40 45
[1684] Ala Thr Ile Asn Thr Asp Gly Ser Thr Met Arg Asp Asp Ser Thr Lys
[1685] 50 55 60
[1686] Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu
[1687] 65 70 75 80
[1688] Gln Met Thr Ser Leu Lys Pro Glu Asp Thr Ala Leu Tyr Tyr Cys Ala
[1689] 85 90 95
[1690] Arg Gly Arg Val Ile Ser Ala Ser Ala Ile Arg Gly Ala Val Arg Gly
[1691] 100 105 110
[1692] Pro Gly Thr Gln Val Thr Val Ser Ser
[1693] 115 120
[1694] <210> 53
[1695] <211> 363
[1696] <212> DNA
[1697] <213> 人工序列(Artificial Sequence)
[1698] <220>
[1699] <223> VHH肽单体AA6(VHH peptide monomer AA6)
[1700] <400> 53
[1701] cagttgcagc tcgtggagac aggggaggc ttggtgcagc ctgggggtc tctgagactc 60
[1702] tcctgtgcag cctctggatt cacgttcagt gactacgtca tgacctgggt ccgccaggct 120
[1703] ccaggaaagg ggcccgaatg gatcgcaact attaatacgg acggtagcac gatgcgtgat 180
[1704] gactccacaa aaggccgatt caccatctcc agagacaacg ccaagaacac actgtatctg 240
[1705] caaatgacca gcctgaaacc ggaggacacg gccctgtatt actgtgcgag aggccgcgtg 300
[1706] atctccgcct ccgcgataag aggggcggtt aggggcccgg ggacccaggt caccgtctcc 360
[1707] tca 363
[1708] <210> 54
[1709] <211> 126
[1710] <212> PRT
[1711] <213> 人工序列(Artificial Sequence)
[1712] <220>
[1713] <223> VHH肽单体AH3(VHH peptide monomer AH3)
[1714] <400> 54
[1715] Gln Val Gln Leu Val Glu Thr Gly Gly Leu Val Gln Pro Gly Gly Ser
[1716] 1 5 10 15
[1717] Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Ser Ser
[1718] 20 25 30
[1719] Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val Ser
[1720] 35 40 45

[1721] Cys Ile Ser Ser Ser Gly Asp Ser Thr Lys Tyr Ala Asp Ser Val Lys
[1722] 50 55 60
[1723] Gly Arg Phe Thr Thr Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
[1724] 65 70 75 80
[1725] Gln Met Asn Ser Leu Lys Pro Asp Asp Thr Ala Val Tyr Tyr Cys Ala
[1726] 85 90 95
[1727] Ala Phe Arg Ala Thr Met Cys Gly Val Phe Pro Leu Ser Pro Tyr Gly
[1728] 100 105 110
[1729] Lys Asp Asp Trp Gly Lys Gly Thr Leu Val Thr Val Ser Ser
[1730] 115 120 125
[1731] <210> 55
[1732] <211> 378
[1733] <212> DNA
[1734] <213> 人工序列(Artificial Sequence)
[1735] <220>
[1736] <223> VHH肽单体AH3(VHH peptide monomer AH3)
[1737] <400> 55
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[1739] tgtgcagcct ctggattcac tttggattat tcgtccatag gctggttccg ccaggcccca 120
[1740] gggaaggagc gtgaggggggt ctcatgtatt agtagtagtg gtgatagcac aaagtatgca 180
[1741] gactccgtga agggccgatt caccacctcc agagacaacg ccaagaacac ggtgtatctg 240
[1742] caaatgaaca gcctgaaacc tgacgacaca gccgtttatt actgtgcagc ttttagggcg 300
[1743] actatgtgcg gcgtgttccc ccttagcccc tacggcaagg acgactgggg caaagggacc 360
[1744] ctggtcaccg tctcctca 378
[1745] <210> 56
[1746] <211> 15
[1747] <212> PRT
[1748] <213> 人工序列(Artificial Sequence)
[1749] <220>
[1750] <223> 柔性接头1(Flexible linker 1)
[1751] <400> 56
[1752] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[1753] 1 5 10 15
[1754] <210> 57
[1755] <211> 45
[1756] <212> DNA
[1757] <213> 人工序列(Artificial Sequence)
[1758] <220>
[1759] <223> 柔性接头1(Flexible linker 1)
[1760] <400> 57
[1761] ggcggtggtg gctctggtgg cggcggttcc ggtggcggtg gcagc 45
[1762] <210> 58

[1763] <211> 15
[1764] <212> PRT
[1765] <213> 人工序列(Artificial Sequence)
[1766] <220>
[1767] <223> 柔性接头2(Flexible linker 2)
[1768] <400> 58
[1769] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[1770] 1 5 10 15
[1771] <210> 59
[1772] <211> 45
[1773] <212> DNA
[1774] <213> 人工序列(Artificial Sequence)
[1775] <220>
[1776] <223> 柔性接头2(Flexible linker 2)
[1777] <400> 59
[1778] ggtggaggcg gttcaggcgg aggtggctct ggcggtggcg gttcc 45
[1779] <210> 60
[1780] <211> 15
[1781] <212> PRT
[1782] <213> 人工序列(Artificial Sequence)
[1783] <220>
[1784] <223> 柔性接头3(Flexible linker 3)
[1785] <400> 60
[1786] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[1787] 1 5 10 15
[1788] <210> 61
[1789] <211> 45
[1790] <212> DNA
[1791] <213> 人工序列(Artificial Sequence)
[1792] <220>
[1793] <223> 柔性接头3(Flexible linker 3)
[1794] <400> 61
[1795] ggcggtggtg gctctggtgg cggcggttcc ggtggcggtg gcagc 45
[1796] <210> 62
[1797] <211> 259
[1798] <212> PRT
[1799] <213> 人工序列(Artificial Sequence)
[1800] <220>
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[1802] <400> 62
[1803] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[1804] 1 5 10 15

[1805] Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Leu Asp Tyr Tyr
[1806] 20 25 30
[1807] Gly Ile Gly Trp Phe Arg Gln Pro Pro Gly Lys Glu Arg Glu Ala Val
[1808] 35 40 45
[1809] Ser Tyr Ile Ser Ala Ser Ala Arg Thr Ile Leu Tyr Ala Asp Ser Val
[1810] 50 55 60
[1811] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ala Val Tyr
[1812] 65 70 75 80
[1813] Leu Gln Met Glu Thr Asn Ser Leu Lys Arg Glu Asp Thr Ala Val Tyr
[1814] 85 90 95
[1815] Tyr Cys Ala Arg Arg Arg Phe Ser Ala Ser Ser Val Asn Arg Trp Leu
[1816] 100 105 110
[1817] Ala Asp Asp Tyr Asp Val Trp Gly Arg Gly Thr Gln Val Ala Val Ser
[1818] 115 120 125
[1819] Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[1820] 130 135 140
[1821] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Thr Gly Gly
[1822] 145 150 155 160
[1823] Ser Leu Arg Leu Ser Cys Ala Ser Ser Gly Ser Ile Ala Gly Phe Glu
[1824] 165 170 175
[1825] Thr Val Thr Trp Ser Arg Gln Ala Pro Gly Lys Ser Leu Gln Trp Val
[1826] 180 185 190
[1827] Ala Ser Met Glu Thr Thr Lys Thr Asn Asn Glu Ile Tyr Ser Asp Ser
[1828] 195 200 205
[1829] Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
[1830] 210 215 220
[1831] Tyr Leu Gln Met Glu Thr Asn Ser Leu Lys Pro Glu Asp Thr Gly Val
[1832] 225 230 235 240
[1833] Tyr Phe Cys Lys Gly Pro Glu Leu Arg Gly Gln Gly Ile Gln Val Thr
[1834] 245 250 255
[1835] Val Ser Ser
[1836] <210> 63
[1837] <211> 759
[1838] <212> DNA
[1839] <213> 人工序列(Artificial Sequence)
[1840] <220>
[1841] <223> 5D-E3异型二聚体(5D-E3 heterodimer)
[1842] <400> 63
[1843] caggtgcagc tcgtggagtc aggtggaggc ttggtgcagc ctgggggtc tctgagactc 60
[1844] tcctgtgaag cctctggatt cactttggat tattatggta taggctggtt ccgccagccc 120
[1845] ccagggaagg agcgcgaggc ggtctcatat attagtgcca gtgcccgtac gatattgtat 180
[1846] gcagattccg tgaagggccg atttaccatc tccagagaca atgccaagaa cgcggtgtat 240

[1847] ctacaaatga acagcctgaa acgtgaggac acggctgtct attactgtgc gaggcggcga 300
[1848] ttctccgcgt ctagtgttaa tagatggctt gccgacgact atgacgtctg gggtcggggg 360
[1849] acccaggtcg cggtgtcctc aggcggtggt ggctctggtg gcggcggttc cggtggcggt 420
[1850] ggcagccagg tgcagctcgt ggagtcgggc ggaggcttgg tgcagactgg ggggtctctg 480
[1851] agactctcct gtgcatcctc tggaagtatc gccggtttcg aaaccgtgac ctggtcccgc 540
[1852] caggctcctg gaaagtcgct ccagtgggtc gcatcgatga ctaaaactaa taacgagatc 600
[1853] tattcagact ccgtgaaggg ccgattcatc atctccagag acaacgccaa gaatacggtg 660
[1854] tatctacaaa tgaacagcct gaaacctgag gacacaggcg tctatttttg taaaggtcct 720
[1855] gagttgaggg gccaggggat ccaggtcacc gtctcctcg 759
[1856] <210> 64
[1857] <211> 272
[1858] <212> PRT
[1859] <213> 人工序列(Artificial Sequence)
[1860] <220>
[1861] <223> AH3-AA6异型二聚体(AH3-AA6 heterodimer)
[1862] <400> 64
[1863] Gln Val Gln Leu Val Glu Thr Gly Gly Leu Val Gln Pro Gly Gly Ser
[1864] 1 5 10 15
[1865] Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Ser Ser
[1866] 20 25 30
[1867] Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val Ser
[1868] 35 40 45
[1869] Cys Ile Ser Ser Ser Gly Asp Ser Thr Lys Tyr Ala Asp Ser Val Lys
[1870] 50 55 60
[1871] Gly Arg Phe Thr Thr Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
[1872] 65 70 75 80
[1873] Gln Met Glu Thr Asn Ser Leu Lys Pro Asp Asp Thr Ala Val Tyr Tyr
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[5284] aggggttccg cgcacatttc cccgaaaagt gccacctggg tccttttcat cacgtgctat 6420
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[5286] aaaagaaatt aaagaaaaaa tagtttttgt tttccgaaga tgtaaaagac tctaggggga 6540
[5287] tcgccaacaa atactacctt ttatcttgct cttcctgctc tcaggtatta atgccgaatt 6600
[5288] gtttcatctt gtctgtgtag aagaccacac acgaaaatcc tgtgatttta cattttactt 6660
[5289] atcgttaatc gaatgtatat ctatttaatc tgcttttctt gtctaataaa tatatatgta 6720

[5290] aagtacgctt tttgttgaaa ttttttaaac ctttgtttat ttttttttct tcattccgta 6780
[5291] actcttctac cttctttatt tactttctaa aatccaaata caaaacataa aaataaataa 6840
[5292] acacagagta aattcccaaa ttattccatc attaaaagat acgaggcgcg tgtaagttac 6900
[5293] aggcaagcga tccgtccta 6919
[5294] <210> 96
[5295] <211> 89
[5296] <212> PRT
[5297] <213> 酿酒酵母(Saccharomyces cerevisiae)
[5298] <400> 96
[5299] Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
[5300] 1 5 10 15
[5301] Ala Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
[5302] 20 25 30
[5303] Ile Pro Ala Glu Ala Val Ile Gly Tyr Ser Asp Leu Glu Gly Asp Phe
[5304] 35 40 45
[5305] Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
[5306] 50 55 60
[5307] Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val
[5308] 65 70 75 80
[5309] Ser Leu Glu Lys Arg Glu Ala Glu Ala
[5310] 85
[5311] <210> 97
[5312] <211> 61
[5313] <212> PRT
[5314] <213> 酿酒酵母(Saccharomyces cerevisiae)
[5315] <400> 97
[5316] Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
[5317] 1 5 10 15
[5318] Ala Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Leu Glu Gly
[5319] 20 25 30
[5320] Asp Phe Asp Val Ala Val Leu Pro Phe Ser Ala Ser Ile Ala Ala Lys
[5321] 35 40 45
[5322] Glu Glu Gly Val Ser Leu Glu Lys Arg Glu Ala Glu Ala
[5323] 50 55 60
[5324] <210> 98
[5325] <211> 57
[5326] <212> PRT
[5327] <213> 酿酒酵母(Saccharomyces cerevisiae)
[5328] <400> 98
[5329] Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
[5330] 1 5 10 15
[5331] Ala Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Leu Glu Gly

[5332] 20 25 30
[5333] Asp Phe Asp Val Ala Val Leu Pro Phe Ser Ala Ser Ile Ala Ala Lys
[5334] 35 40 45
[5335] Glu Glu Gly Val Ser Leu Glu Lys Arg
[5336] 50 55
[5337] <210> 99
[5338] <211> 19
[5339] <212> PRT
[5340] <213> 酿酒酵母(Saccharomyces cerevisiae)
[5341] <400> 99
[5342] Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
[5343] 1 5 10 15
[5344] Ala Leu Ala
[5345] <210> 100
[5346] <211> 20
[5347] <212> PRT
[5348] <213> 黑曲霉(Aspergillus niger)
[5349] <400> 100
[5350] Met Val Ala Trp Trp Ser Leu Phe Leu Tyr Gly Leu Gln Val Ala Ala
[5351] 1 5 10 15
[5352] Pro Ala Leu Ala
[5353] 20
[5354] <210> 101
[5355] <211> 18
[5356] <212> PRT
[5357] <213> 泡盛曲霉(Aspergillus awamori)
[5358] <400> 101
[5359] Met Ser Phe Arg Ser Leu Leu Ala Leu Ser Gly Leu Val Cys Ser Gly
[5360] 1 5 10 15
[5361] Leu Ala
[5362] <210> 102
[5363] <211> 16
[5364] <212> PRT
[5365] <213> 克鲁维酵母(Kluyveromyces marxianus)
[5366] <400> 102
[5367] Met Lys Leu Ala Tyr Ser Leu Leu Leu Pro Leu Ala Gly Val Ser Ala
[5368] 1 5 10 15
[5369] <210> 103
[5370] <211> 19
[5371] <212> PRT
[5372] <213> 酿酒酵母(Saccharomyces cerevisiae)
[5373] <400> 103

[5374] Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
[5375] 1 5 10 15
[5376] Ile Ser Ala
[5377] <210> 104
[5378] <211> 26
[5379] <212> PRT
[5380] <213> 酿酒酵母(Saccharomyces cerevisiae)
[5381] <400> 104
[5382] Met Thr Lys Pro Thr Gln Val Leu Val Arg Ser Val Ser Ile Leu Phe
[5383] 1 5 10 15
[5384] Phe Ile Thr Leu Leu His Leu Val Val Ala
[5385] 20 25
[5386] <210> 105
[5387] <211> 26
[5388] <212> PRT
[5389] <213> 原鸡(Gallus gallus)
[5390] <400> 105
[5391] Met Leu Gly Lys Asn Asp Pro Met Cys Leu Val Leu Val Leu Leu Gly
[5392] 1 5 10 15
[5393] Leu Thr Ala Leu Leu Gly Ile Cys Gln Gly
[5394] 20 25
[5395] <210> 106
[5396] <211> 18
[5397] <212> PRT
[5398] <213> 智人(Homo sapiens)
[5399] <400> 106
[5400] Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
[5401] 1 5 10 15
[5402] Tyr Ser
[5403] <210> 107
[5404] <211> 566
[5405] <212> PRT
[5406] <213> 人工序列(Artificial Sequence)
[5407] <220>
[5408] <223> 从质粒表达的ABAB结合蛋白质(ABAB binding protein expressed from plasmid)
[5409] <400> 107
[5410] Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
[5411] 1 5 10 15
[5412] Ala Leu Ala Met Gln Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val
[5413] 20 25 30
[5414] Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr

[5415] 35 40 45

[5416] Leu Asp Tyr Ser Ser Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu

[5417] 50 55 60

[5418] Arg Glu Gly Val Ser Cys Ile Ser Ser Ser Gly Asp Ser Thr Lys Tyr

[5419] 65 70 75 80

[5420] Ala Asp Ser Val Lys Gly Arg Phe Thr Thr Ser Arg Asp Asn Ala Lys

[5421] 85 90 95

[5422] Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Asp Asp Thr Ala

[5423] 100 105 110

[5424] Val Tyr Tyr Cys Ala Ala Phe Arg Ala Thr Met Cys Gly Val Phe Pro

[5425] 115 120 125

[5426] Leu Ser Pro Tyr Gly Lys Asp Asp Trp Gly Lys Gly Thr Leu Val Thr

[5427] 130 135 140

[5428] Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly

[5429] 145 150 155 160

[5430] Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro

[5431] 165 170 175

[5432] Gly Gly Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Leu Asp

[5433] 180 185 190

[5434] Tyr Tyr Gly Ile Gly Trp Phe Arg Gln Pro Pro Gly Lys Glu Arg Glu

[5435] 195 200 205

[5436] Ala Val Ser Tyr Ile Ser Ala Ser Ala Arg Thr Ile Leu Tyr Ala Asp

[5437] 210 215 220

[5438] Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ala

[5439] 225 230 235 240

[5440] Val Tyr Leu Gln Met Asn Ser Leu Lys Arg Glu Asp Thr Ala Val Tyr

[5441] 245 250 255

[5442] Tyr Cys Ala Arg Arg Arg Phe Ser Ala Ser Ser Val Asn Arg Trp Leu

[5443] 260 265 270

[5444] Ala Asp Asp Tyr Asp Val Trp Gly Arg Gly Thr Gln Val Ala Val Ser

[5445] 275 280 285

[5446] Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly

[5447] 290 295 300

[5448] Ser Gln Leu Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly

[5449] 305 310 315 320

[5450] Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp

[5451] 325 330 335

[5452] Tyr Val Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp

[5453] 340 345 350

[5454] Ile Ala Thr Ile Asn Thr Asp Gly Ser Thr Met Arg Asp Asp Ser Thr

[5455] 355 360 365

[5456] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr

[5457] 370 375 380

[5458] Leu Gln Met Thr Ser Leu Lys Pro Glu Asp Thr Ala Leu Tyr Tyr Cys

[5459] 385 390 395 400

[5460] Ala Arg Gly Arg Val Ile Ser Ala Ser Ala Ile Arg Gly Ala Val Arg

[5461] 405 410 415

[5462] Gly Pro Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly

[5463] 420 425 430

[5464] Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser

[5465] 435 440 445

[5466] Gly Gly Gly Leu Val Gln Thr Gly Gly Ser Leu Arg Leu Ser Cys Ala

[5467] 450 455 460

[5468] Ser Ser Gly Ser Ile Ala Gly Phe Glu Thr Val Thr Trp Ser Arg Gln

[5469] 465 470 475 480

[5470] Ala Pro Gly Lys Ser Leu Gln Trp Val Ala Ser Met Thr Lys Thr Asn

[5471] 485 490 495

[5472] Asn Glu Ile Tyr Ser Asp Ser Val Lys Gly Arg Phe Ile Ile Ser Arg

[5473] 500 505 510

[5474] Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro

[5475] 515 520 525

[5476] Glu Asp Thr Gly Val Tyr Phe Cys Lys Gly Pro Glu Leu Arg Gly Gln

[5477] 530 535 540

[5478] Gly Ile Gln Val Thr Val Ser Ser Val Asp Met Glu Gln Lys Leu Ile

[5479] 545 550 555 560

[5480] Ser Glu Glu Asp Leu Glu

[5481] 565

[5482] <210> 108

[5483] <211> 1701

[5484] <212> DNA

[5485] <213> 人工序列(Artificial Sequence)

[5486] <220>

[5487] <223> 从质粒表达的编码ABAB结合蛋白质的多核苷酸序列(Polynucleotide sequence encoding ABAB binding protein expressed from plasmid)

[5488] <400> 108

[5489] atgagatttc cttcaatttt tactgctgtt ttattcgcag catcctccgc attagctatg 60

[5490] caagtacaat tggttgaaac cggtggtggt ttagttcaac caggtggtag tttgagatta 120

[5491] tcttgtgctg catcaggttt tacattggat tattcttcaa taggttggtt cagacaagct 180

[5492] cctggtaaag aaagagaagg tgtttcttgc atatccagtt ctggtgactc aactaaatat 240

[5493] gctgactccg ttaagggtag attcactact tcaagagata acgctaaaaa tacagtctac 300

[5494] ttgcaaatga actcattaaa gccagatgac acagcagtct attactgtgc cgcttttaga 360

[5495] gccaccatgt gcggtgtatt cccattgtct ccttacggta aagatgactg gggtaaaggt 420

[5496] actttagtta ctgtctcatc cggtggtggt ggttccggtg gtggtggtag tggtggtggt 480

[5497] ggttctcaag ttcaattagt agaatccggt ggtggtttag tccaacctgg tggtagttta 540

[5498] agattatcct gcgaagcaag tggttttaca ttagattatt acggtatcgg ttggtttaga 600
[5499] caaccacctg gtaaagaaag agaagctgtc tcttatattt ccgctagtgc aagaactata 660
[5500] ttgtacgcag attctgtaaa gggtagattc acaatttcaa gagacaatgc caagaacgct 720
[5501] gtttatttgc aaatgaactc tttgaagaga gaagacaccg cagtttatta ctgtgccaga 780
[5502] agaagatttt ctgcttcttc agtcaacaga tggttagcag acgattatga tgtttggggt 840
[5503] agaggtacac aagtcgccgt aagttctggt ggtggttccg gtggtggtag tggtggtggt 900
[5504] tctggtggtg gttcacaatt gcaattagta gaaactggtg gtggtttggt tcaaccaggt 960
[5505] ggttccttga gattaagttg tgctgcatct ggttttactt tctctgatta cgttatgaca 1020
[5506] tgggtcagac aagctccagg taaaggtcct gaatggatcg ctacaattaa taccgacggt 1080
[5507] tccacaatga gagatgacag taccaagggt agattcacta tttcaagaga taacgctaag 1140
[5508] aacacattgt acttacaaat gacctctttg aaaccagaag acaccgcatt atattactgt 1200
[5509] gccagaggta gagtcatatc cgccagtgct atcagaggtg cagtaagagg tcctggtact 1260
[5510] caagttacag tctcttcagg tggcggcggt agtggcggcg gcggttctgg cggtggtggt 1320
[5511] tcacaagtcc aattggtaga atctggtggt ggtttagttc aaactggtgg ttcattgaga 1380
[5512] ttatcctgcg cttccagtgg ttccattgca ggtttcgaaa ctgttacatg gtcaagacaa 1440
[5513] gctccaggta aatctttgca atgggtcgcc tcaatgacca agactaacaa cgaaatctat 1500
[5514] tctgattcag ttaagggtag attcattatt tcaagagata atgctaaaaa caccgtttat 1560
[5515] ttgcaaatga actcattgaa gccagaagat actggtgttt acttctgcaa gggtcctgaa 1620
[5516] ttaagaggtc aaggtattca agtaacagtt tcttcagtcg acatggaaca gaagttgatt 1680
[5517] tccgaagaag acctcgagta a 1701
[5518] <210> 109
[5519] <211> 557
[5520] <212> PRT
[5521] <213> 人工序列(Artificial Sequence)
[5522] <220>
[5523] <223> 从染色体整合表达的ABAB结合蛋白质序列(ABAB binding protein expressed from chromosomal integration)
[5524] <400> 109
[5525] Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
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[5527] Ala Leu Ala Met Gln Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val
[5528] 20 25 30
[5529] Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr
[5530] 35 40 45
[5531] Leu Asp Tyr Ser Ser Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu
[5532] 50 55 60
[5533] Arg Glu Gly Val Ser Cys Ile Ser Ser Ser Gly Asp Ser Thr Lys Tyr
[5534] 65 70 75 80
[5535] Ala Asp Ser Val Lys Gly Arg Phe Thr Thr Ser Arg Asp Asn Ala Lys
[5536] 85 90 95
[5537] Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Asp Asp Thr Ala
[5538] 100 105 110

[5539] Val Tyr Tyr Cys Ala Ala Phe Arg Ala Thr Met Cys Gly Val Phe Pro
[5540] 115 120 125
[5541] Leu Ser Pro Tyr Gly Lys Asp Asp Trp Gly Lys Gly Thr Leu Val Thr
[5542] 130 135 140
[5543] Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
[5544] 145 150 155 160
[5545] Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
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[5547] Gly Gly Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Leu Asp
[5548] 180 185 190
[5549] Tyr Tyr Gly Ile Gly Trp Phe Arg Gln Pro Pro Gly Lys Glu Arg Glu
[5550] 195 200 205
[5551] Ala Val Ser Tyr Ile Ser Ala Ser Ala Arg Thr Ile Leu Tyr Ala Asp
[5552] 210 215 220
[5553] Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ala
[5554] 225 230 235 240
[5555] Val Tyr Leu Gln Met Asn Ser Leu Lys Arg Glu Asp Thr Ala Val Tyr
[5556] 245 250 255
[5557] Tyr Cys Ala Arg Arg Arg Phe Ser Ala Ser Ser Val Asn Arg Trp Leu
[5558] 260 265 270
[5559] Ala Asp Asp Tyr Asp Val Trp Gly Arg Gly Thr Gln Val Ala Val Ser
[5560] 275 280 285
[5561] Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
[5562] 290 295 300
[5563] Ser Gln Leu Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly
[5564] 305 310 315 320
[5565] Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp
[5566] 325 330 335
[5567] Tyr Val Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp
[5568] 340 345 350
[5569] Ile Ala Thr Ile Asn Thr Asp Gly Ser Thr Met Arg Asp Asp Ser Thr
[5570] 355 360 365
[5571] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
[5572] 370 375 380
[5573] Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Leu Tyr Tyr Cys
[5574] 385 390 395 400
[5575] Ala Arg Gly Arg Val Ile Ser Ala Ser Ala Ile Arg Gly Ala Val Arg
[5576] 405 410 415
[5577] Gly Pro Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
[5578] 420 425 430
[5579] Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser
[5580] 435 440 445

[5581] Gly Gly Gly Leu Val Gln Thr Gly Gly Ser Leu Arg Leu Ser Cys Ala
[5582] 450 455 460
[5583] Ser Ser Gly Ser Ile Ala Gly Phe Glu Thr Val Thr Trp Ser Arg Gln
[5584] 465 470 475 480
[5585] Ala Pro Gly Lys Ser Leu Gln Trp Val Ala Ser Met Thr Lys Thr Asn
[5586] 485 490 495
[5587] Asn Glu Ile Tyr Ser Asp Ser Val Lys Gly Arg Phe Ile Ile Ser Arg
[5588] 500 505 510
[5589] Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro
[5590] 515 520 525
[5591] Glu Asp Thr Gly Val Tyr Phe Cys Lys Gly Pro Glu Leu Arg Gly Gln
[5592] 530 535 540
[5593] Gly Ile Gln Val Thr Val Ser Ser Val Asp Ala Ala Ser
[5594] 545 550 555
[5595] <210> 110
[5596] <211> 1674
[5597] <212> DNA
[5598] <213> 人工序列(Artificial Sequence)
[5599] <220>
[5600] <223> 从染色体整合表达的编码ABAB结合蛋白质的多核苷酸序列(Polynucleotide sequence encoding ABAB binding protein expressed from chromosomal integration)
[5601] <400> 110
[5602] atgagatttc cttcaatttt tactgctgtt ttattcgcag catcctccgc attagctatg 60
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[5604] tcttgtgctg catcaggttt tacattggat tattcttcaa taggttggtt cagacaagct 180
[5605] cctggtaaag aaagagaagg tgtttcttgc atatccagtt ctggtgactc aactaaatat 240
[5606] gctgactccg ttaagggtag attcactact tcaagagata acgctaaaaa tacagtctac 300
[5607] ttgcaaatga actcattaaa gccagatgac acagcagtct attactgtgc cgcttttaga 360
[5608] gccaccatgt gcggtgtatt cccattgtct ccttacggta aagatgactg gggtaaaggt 420
[5609] actttagtta ctgtctcatc cggtggtggt ggttccggtg gtggtggtag tggtggtggt 480
[5610] ggttctcaag ttcaattagt agaatccggt ggtggtttag tccaacctgg tggtagttta 540
[5611] agattatcct gcgaagcaag tggttttaca ttagattatt acggtatcgg ttggtttaga 600
[5612] caaccacctg gtaaagaaag agaagctgtc tcttatattt ccgctagtgc aagaactata 660
[5613] ttgtacgcag attctgtaaa gggtagattc acaatttcaa gagacaatgc caagaacgct 720
[5614] gtttatttgc aaatgaactc tttgaagaga gaagacaccg cagtttatta ctgtgccaga 780
[5615] agaagatttt ctgcttcttc agtcaacaga tggttagcag acgattatga tgtttggggt 840
[5616] agaggtacac aagtcgccgt aagttctggt ggtggttccg gtggtggtag tggtggtggt 900
[5617] tctggtggtg gttcacagct gcagctggtg gagaccgggg gaggcttagt tcagcctggg 960
[5618] gggtccctga gactctcctg tgcagcctct ggattcacct tcagtgacta cgtgatgacc 1020
[5619] tgggtccgcc aagctccagg gaaggggcct gagtggatcg caactattaa tactgatggg 1080
[5620] agcacaatgc gcgacgactc cacaaagggc cggttcacca tctccagaga caacgccaag 1140
[5621] aacactctgt atctgcaaat gaacagtctg aaacccgagg acactgctct gtattactgt 1200

[5622] gcaagaggcc gggtgatctc tgcttccgct atcagaggcg cagtcagagg ccctggaacc 1260
[5623] caggtcaccg tctcgagcgg tggcggcggt agtggcggcg gcggttctgg cggtggtggt 1320
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[5625] ttatcctgcg cttccagtgg ttccattgca ggtttcgaaa ctgttacatg gtcaagacaa 1440
[5626] gctccaggta aatctttgca atgggtcgcc tcaatgacca agactaacaa cgaaatctat 1500
[5627] tctgattcag ttaagggtag attcattatt tcaagagata atgctaaaaa caccgtttat 1560
[5628] ttgcaaatga actcattgaa gccagaagat actggtgttt acttctgcaa gggtcctgaa 1620
[5629] ttaagaggtc aaggtattca agtaacagtt tcttcagtcg acgcggctag ctaa 1674
[5630] <210> 111
[5631] <211> 549
[5632] <212> PRT
[5633] <213> 人工序列(Artificial Sequence)
[5634] <220>
[5635] <223> ABA结合剂(ABA binding agent)
[5636] <400> 111
[5637] Gln Val Gln Leu Val Glu Thr Gly Gly Leu Val Gln Pro Gly Gly Ser
[5638] 1 5 10 15
[5639] Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Ser Ser
[5640] 20 25 30
[5641] Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val Ser
[5642] 35 40 45
[5643] Cys Ile Ser Ser Ser Gly Asp Ser Thr Lys Tyr Ala Asp Ser Val Lys
[5644] 50 55 60
[5645] Gly Arg Phe Thr Thr Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
[5646] 65 70 75 80
[5647] Gln Met Asn Ser Leu Lys Pro Asp Asp Thr Ala Val Tyr Tyr Cys Ala
[5648] 85 90 95
[5649] Ala Phe Arg Ala Thr Met Cys Gly Val Phe Pro Leu Ser Pro Tyr Gly
[5650] 100 105 110
[5651] Lys Asp Asp Trp Gly Lys Gly Thr Leu Val Thr Val Ser Ser Glu Pro
[5652] 115 120 125
[5653] Lys Thr Pro Lys Pro Gln Pro Thr Ser Gly Gly Gly Gly Ser Gly Gly
[5654] 130 135 140
[5655] Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly
[5656] 145 150 155 160
[5657] Gly Gly Leu Val Gln Thr Gly Gly Ser Leu Arg Leu Ser Cys Ala Ser
[5658] 165 170 175
[5659] Ser Gly Ser Ile Ala Gly Phe Glu Thr Val Thr Trp Ser Arg Gln Ala
[5660] 180 185 190
[5661] Pro Gly Lys Ser Leu Gln Trp Val Ala Ser Met Thr Lys Thr Asn Asn
[5662] 195 200 205
[5663] Glu Ile Tyr Ser Asp Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp

[5664] 210 215 220

[5665] Asn Ala Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu

[5666] 225 230 235 240

[5667] Asp Thr Gly Val Tyr Phe Cys Lys Gly Pro Glu Leu Arg Gly Gln Gly

[5668] 245 250 255

[5669] Ile Gln Val Thr Val Ser Ser Glu Pro Lys Thr Pro Lys Pro Gln Thr

[5670] 260 265 270

[5671] Ser Ala Ile Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly

[5672] 275 280 285

[5673] Gly Gly Ser Leu Gln Ala Met Ala Ala Ala Ser Gln Val Gln Leu Val

[5674] 290 295 300

[5675] Glu Ser Gly Gly Gly Leu Val Gln Thr Gly Gly Ser Leu Arg Leu Ser

[5676] 305 310 315 320

[5677] Cys Ala Ser Ser Gly Ser Ile Ala Gly Phe Glu Thr Val Thr Trp Ser

[5678] 325 330 335

[5679] Arg Gln Ala Pro Gly Lys Ser Leu Gln Trp Val Ala Ser Met Thr Lys

[5680] 340 345 350

[5681] Thr Asn Asn Glu Ile Tyr Ser Asp Ser Val Lys Gly Arg Phe Ile Ile

[5682] 355 360 365

[5683] Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu

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[5711] <220>

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[5713] <400> 112

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[5716] <210> 113

[5717] <211> 553

[5718] <212> PRT

[5719] <213> 人工序列(Artificial Sequence)

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[5957] <211> 8202

[5958] <212> DNA

[5959] <213> 人工序列(Artificial Sequence)

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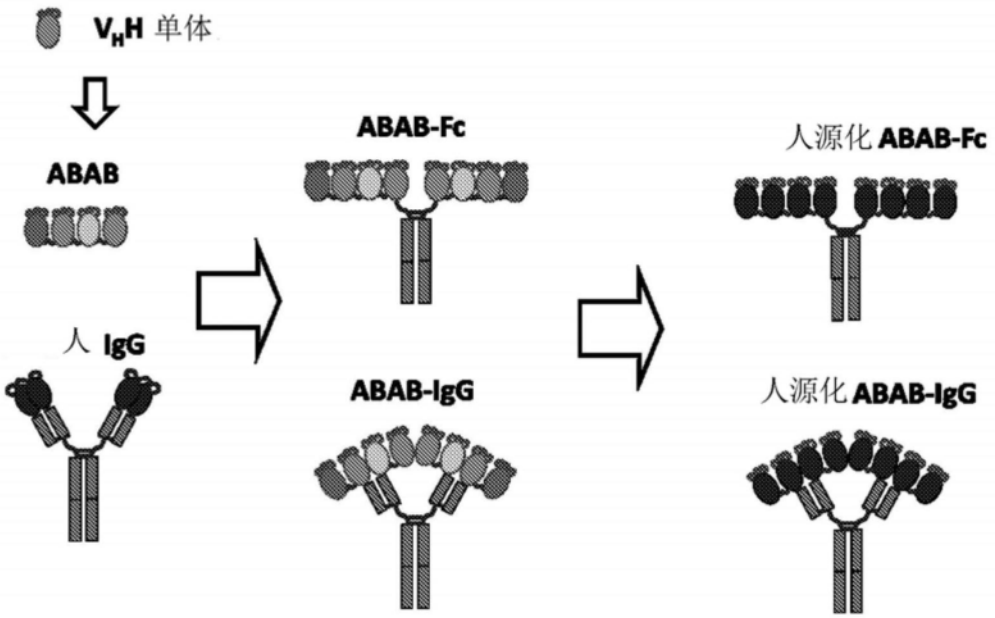
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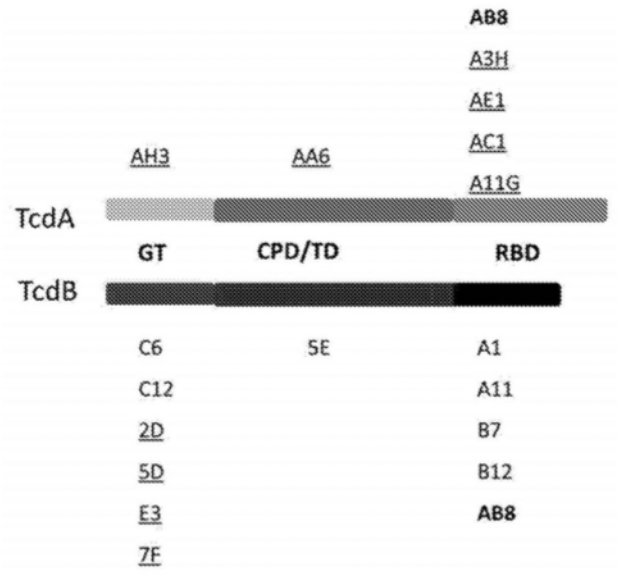
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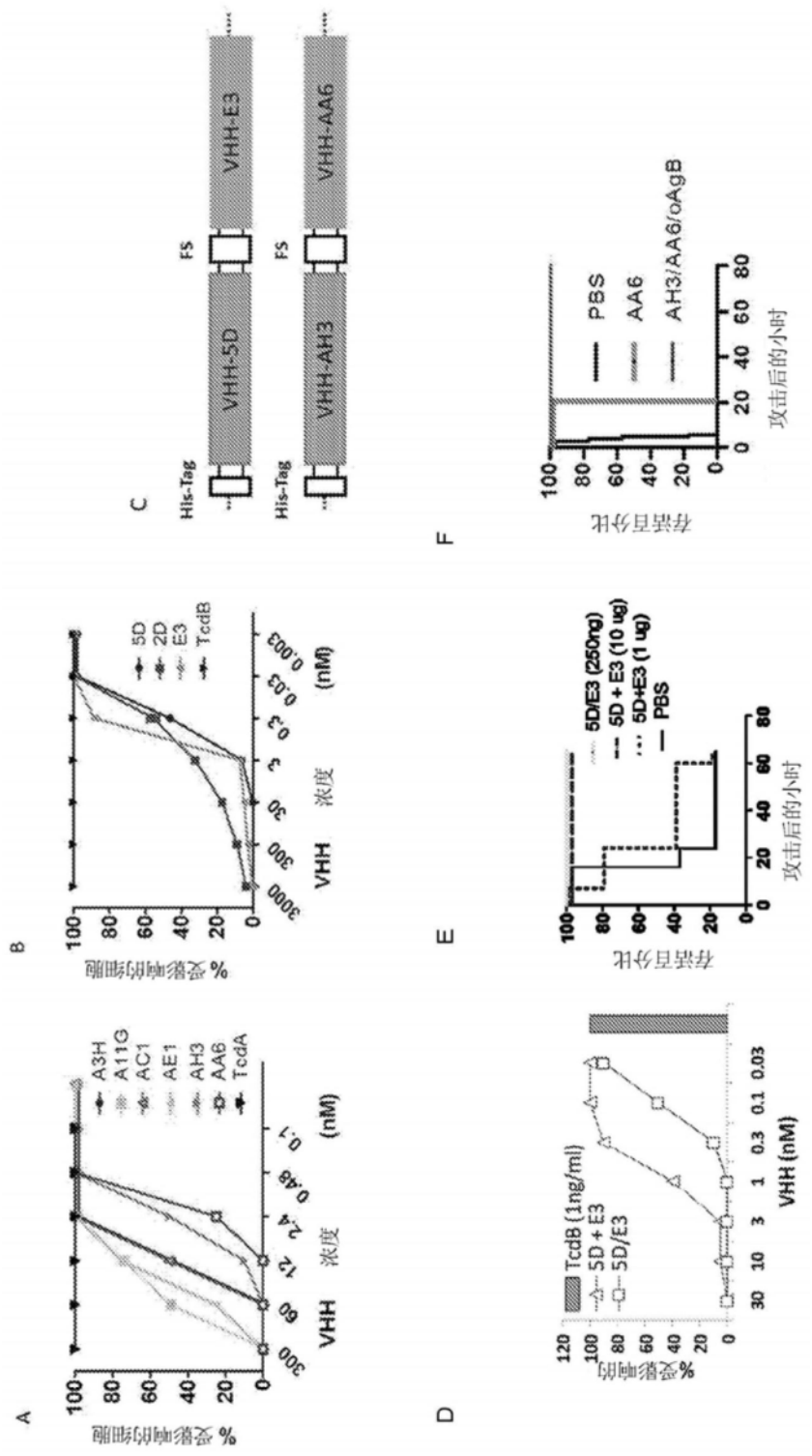
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VHH 浓度 (nM)
B
% 受影响的细胞
5D
2D
E3
TcdB
VHH 浓度 (nM)
C
His-Tag
VHH-5D
FS
VHH-E3
His-Tag
VHH-AH3
FS
VHH-AA6
D
TcdB (1ng/ml)
5D + E3
5D/E3
% 受影响的
VHH (nM)
E
存活百分比
5D/E3 (250ng)
5D + E3 (10 ug)
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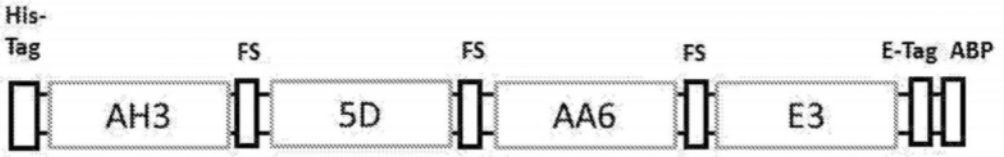
图3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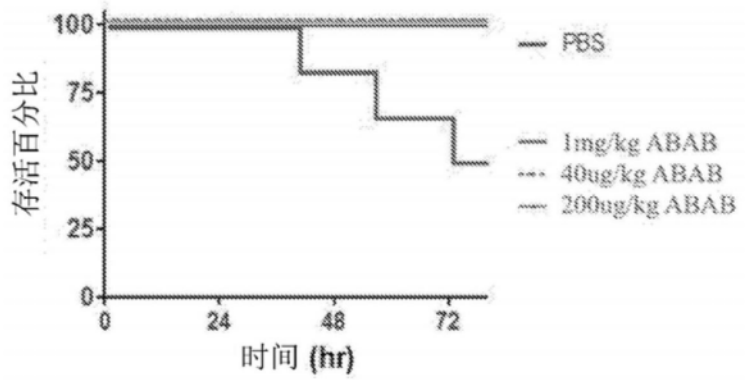
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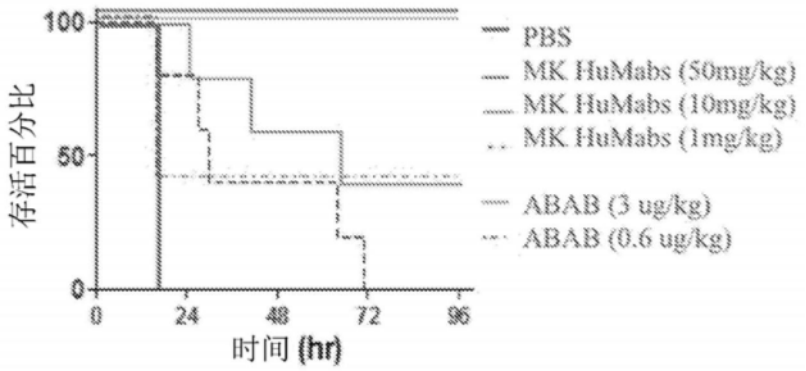
图5A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MK HuMabs (1mg/kg)
ABAB (3 ug/kg)
ABAB (0.6 ug/kg)

图5B

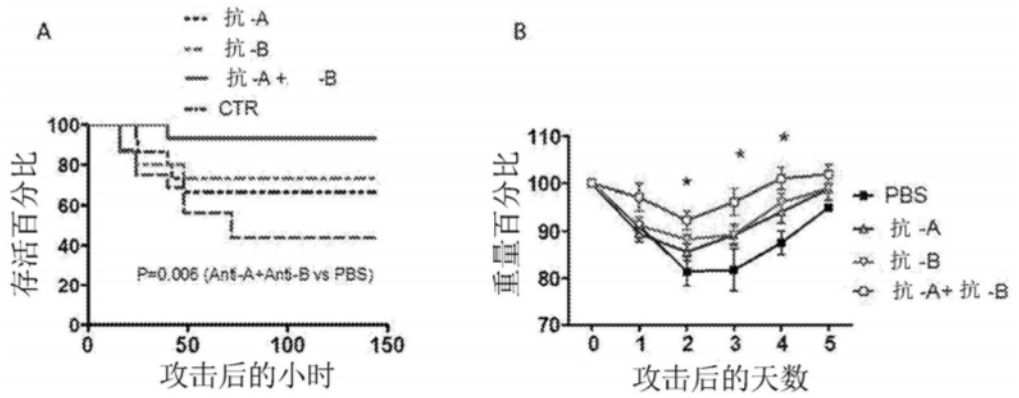
A
抗-A
抗-B
抗-A+ -B
CTR
存活百分比
P=0.006 (Anti-A+Anti-B vs PBS)
攻击后的小时
B
重量百分比
PBS
抗-A
抗-B
抗-A+抗-B
攻击后的天数

图6

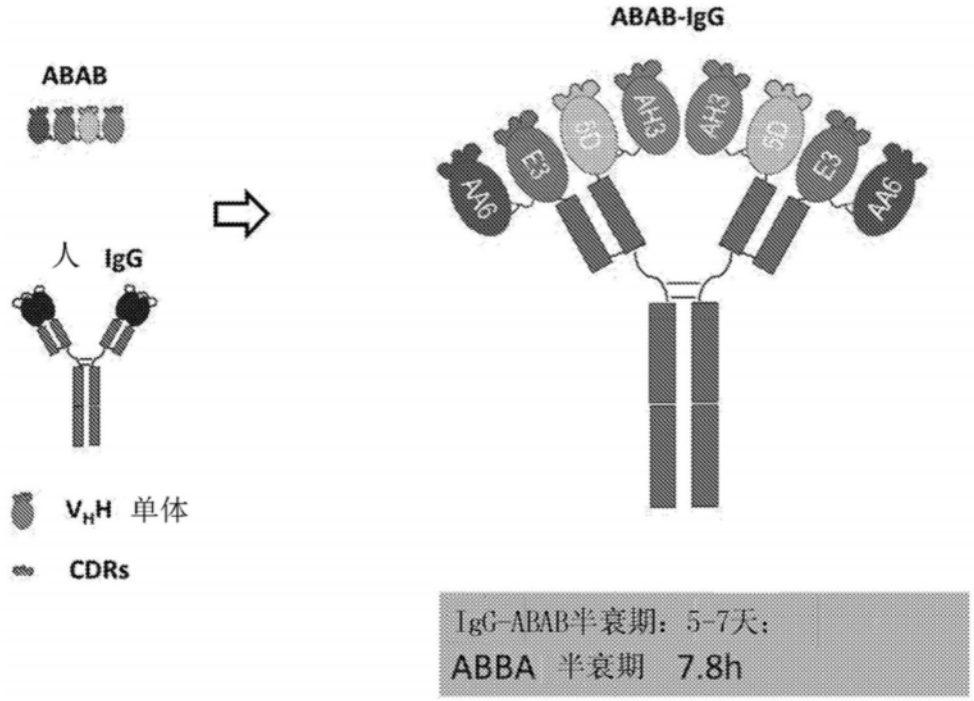
ABAB
人 IgG
VHH 单体
CDRs
ABAB-IgG
AA6
E3
6D
AH3
AH3
6D
E3
AA6
IgG-ABAB半衰期：5-7天；
ABBA 半衰期 7.8h

图7

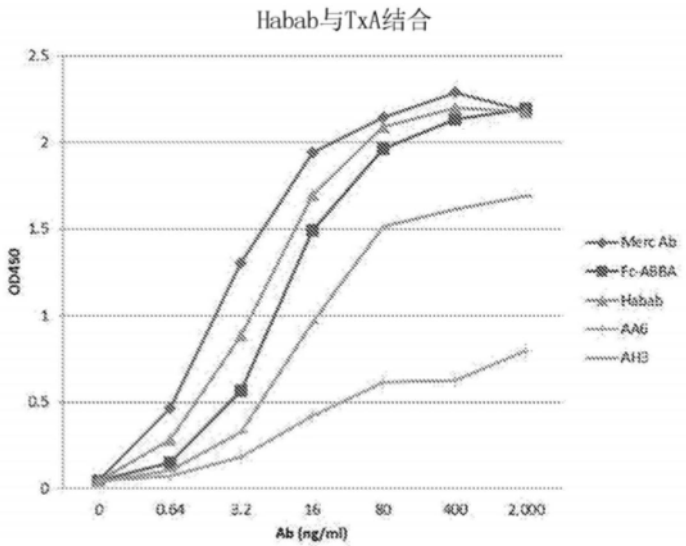
Habab与TxA结合
OD450
2.5
2
1.5
1
0.5
0
0
0.64
3.2
16
80
400
2,000
Ab (ng/ml)
Merc Ab
Fc-ABBA
Habab
AA6
AH3

图8A

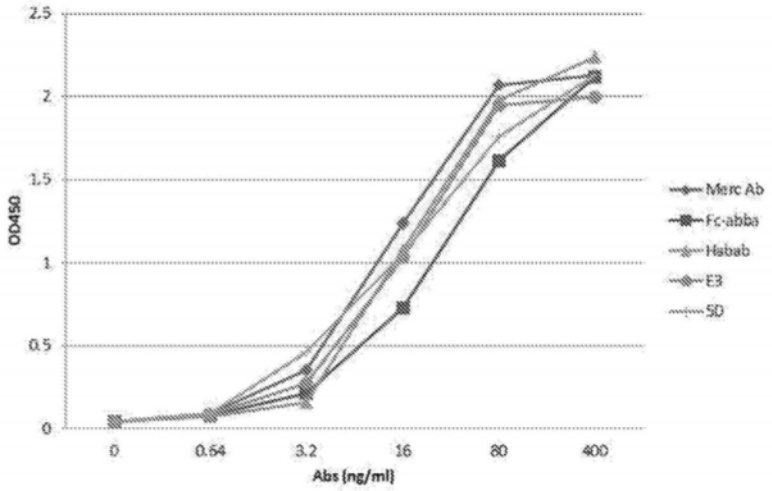
OD450
2.5
2
1.5
1
0.5
0
0
0.64
3.2
16
80
400
Abs (ng/ml)
Merc Ab
Fc-abba
Habab
E3
5D

图8B

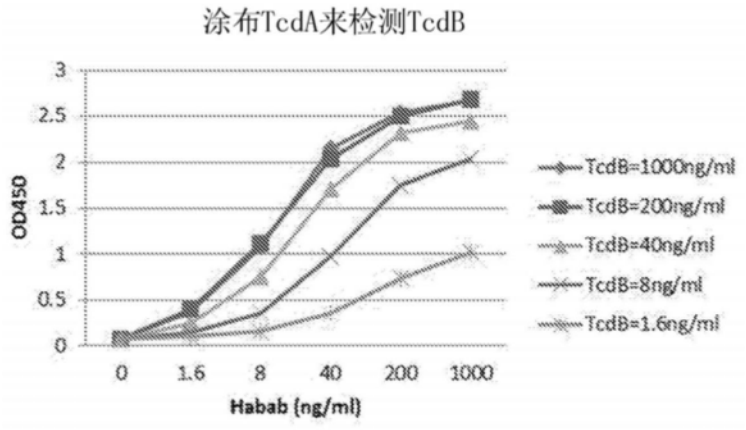
涂布TcdA来检测TcdB
OD450
3
2.5
2
1.5
1
0.5
0
0
1.6
8
40
200
1000
Habab (ng/ml)
TcdB=1000ng/ml
TcdB=200ng/ml
TcdB=40ng/ml
TcdB=8ng/ml
TcdB=1.6ng/ml

图9A

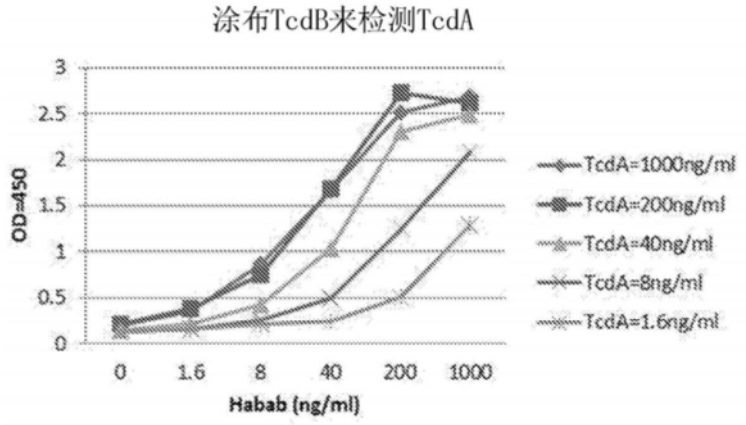
涂布TcdB来检测TcdA
OD=450
3
2.5
2
1.5
1
0.5
0
0
1.6
8
40
200
1000
Habab (ng/ml)
TcdA=1000ng/ml
TcdA=200ng/ml
TcdA=40ng/ml
TcdA=8ng/ml
TcdA=1.6ng/ml

图9B

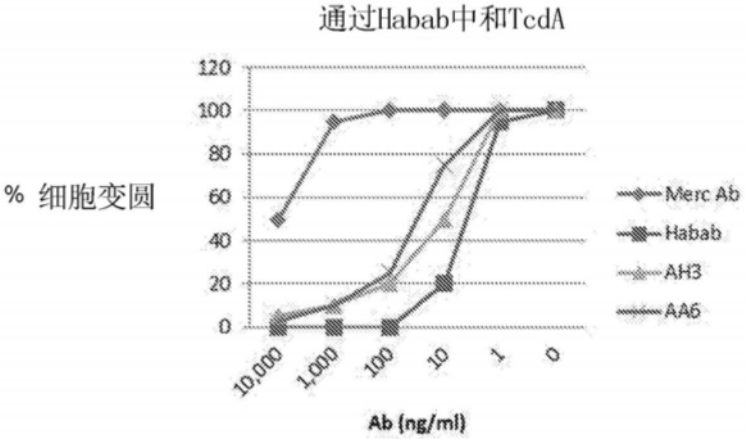
通过Habab中和TcdA
% 细胞变圆
120
100
80
60
40
20
0
10,000
1,000
100
10
1
0
Ab (ng/ml)
Merc Ab
Habab
AH3
AA6

图10A

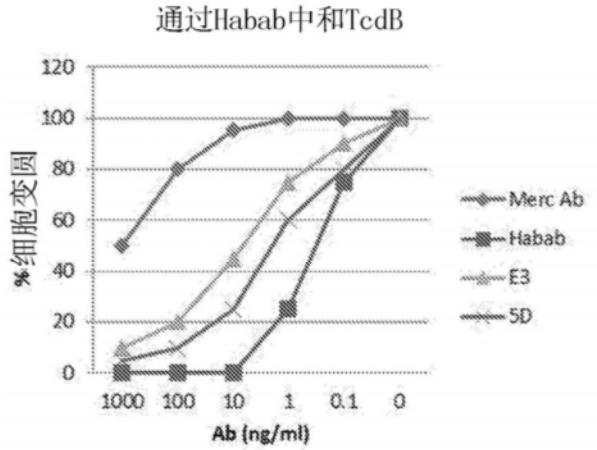
通过Habab中和TcdB
%细胞变圆
120
100
80
60
40
20
0
1000 100 10 1 0.1 0
Ab (ng/ml)
Merc Ab
Habab
E3
5D

图10B

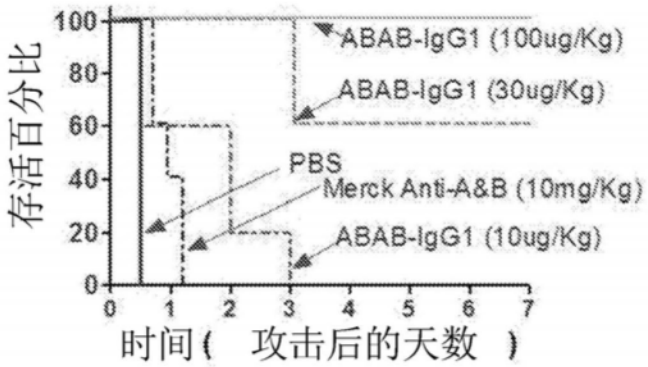
存活百分比
100
80
60
40
20
0
0 1 2 3 4 5 6 7
时间(攻击后的天数)
ABAB-IgG1 (100ug/Kg)
ABAB-IgG1 (30ug/Kg)
PBS
Merck Anti-A&B (10mg/Kg)
ABAB-IgG1 (10ug/Kg)

图11

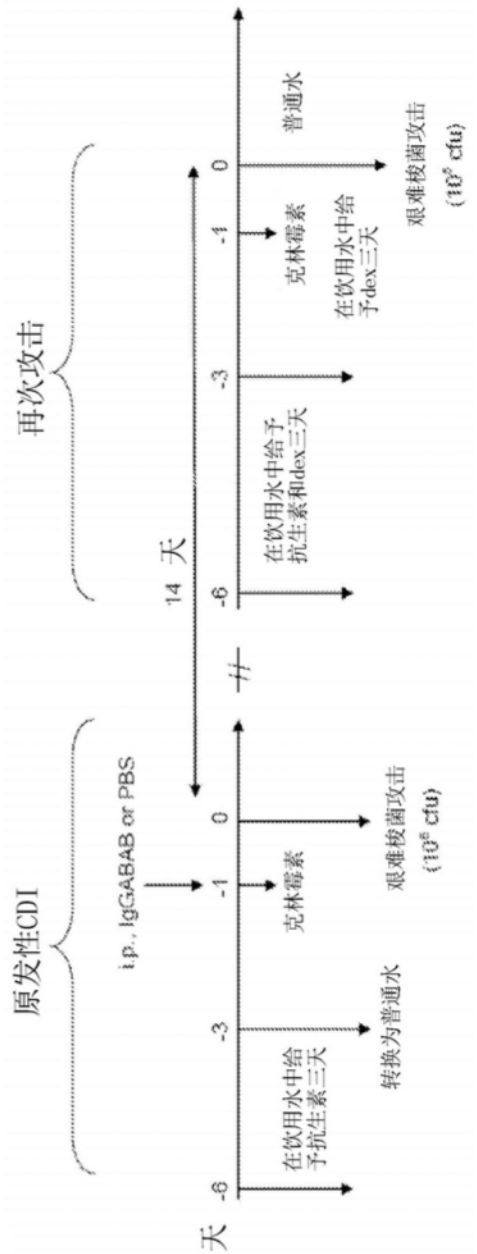
原发性CDI
再次攻击
i.p., IgGA8AB or PBS
克林霉素
在饮用水中给予抗生素三天
转换为普通水
艰难梭菌攻击
(10^5 cfu)
14 天
在饮用水中给予抗生素和dex三天
克林霉素
在饮用水中给予dex三天
普通水
艰难梭菌攻击
(10^5 cfu)
天
-6
-3
-1
0
-6
-3
-1
0

图12

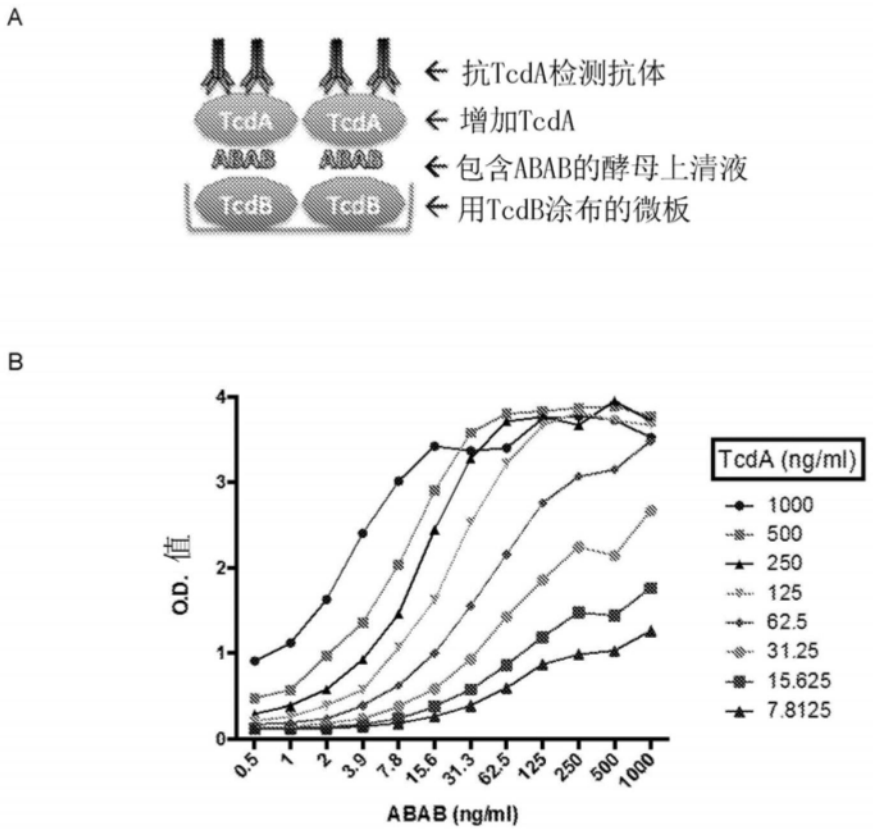
A
抗TcdA检测抗体
增加TcdA
包含ABAB的酵母上清液
用TcdB涂布的微板
TcdA
TcdA
ABAB
ABAB
TcdB
TcdB
B
O.D. 值
ABAB (ng/ml)
0.5
1
2
3.9
7.8
15.6
31.3
62.5
125
250
500
1000
TcdA (ng/ml)
1000
500
250
125
62.5
31.25
15.625
7.8125

图13

A

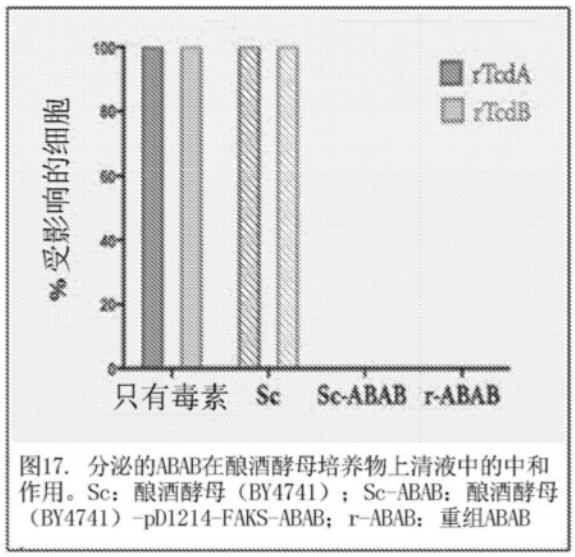

图17. 分泌的ABAB在酿酒酵母培养物上清液中的中和作用。Sc：酿酒酵母（BY4741）；Sc-ABAB：酿酒酵母（BY4741）-pD1214-FAKS-ABAB；r-ABAB：重组ABAB

B

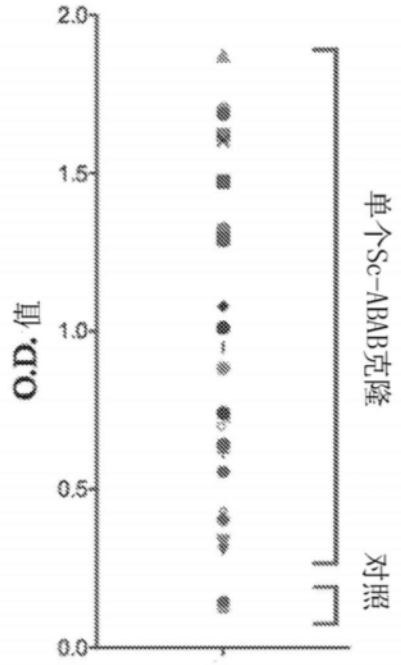

图14

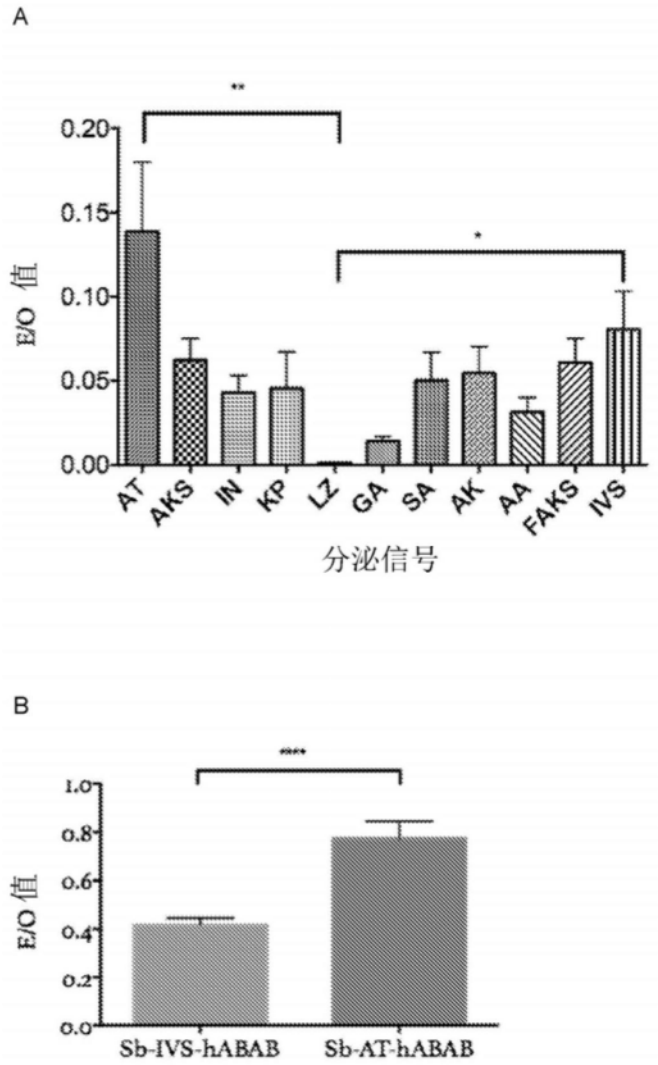
A
**
*
0.20
0.15
0.10
0.05
0.00
E/O 值
AT
AKS
IN
KP
LZ
GA
SA
AK
AA
FAKS
IVS
分泌信号
B
****
1.0
0.8
0.6
0.4
0.2
0.0
E/O 值
Sb-IVS-hABAB
Sb-AT-hABAB

图15

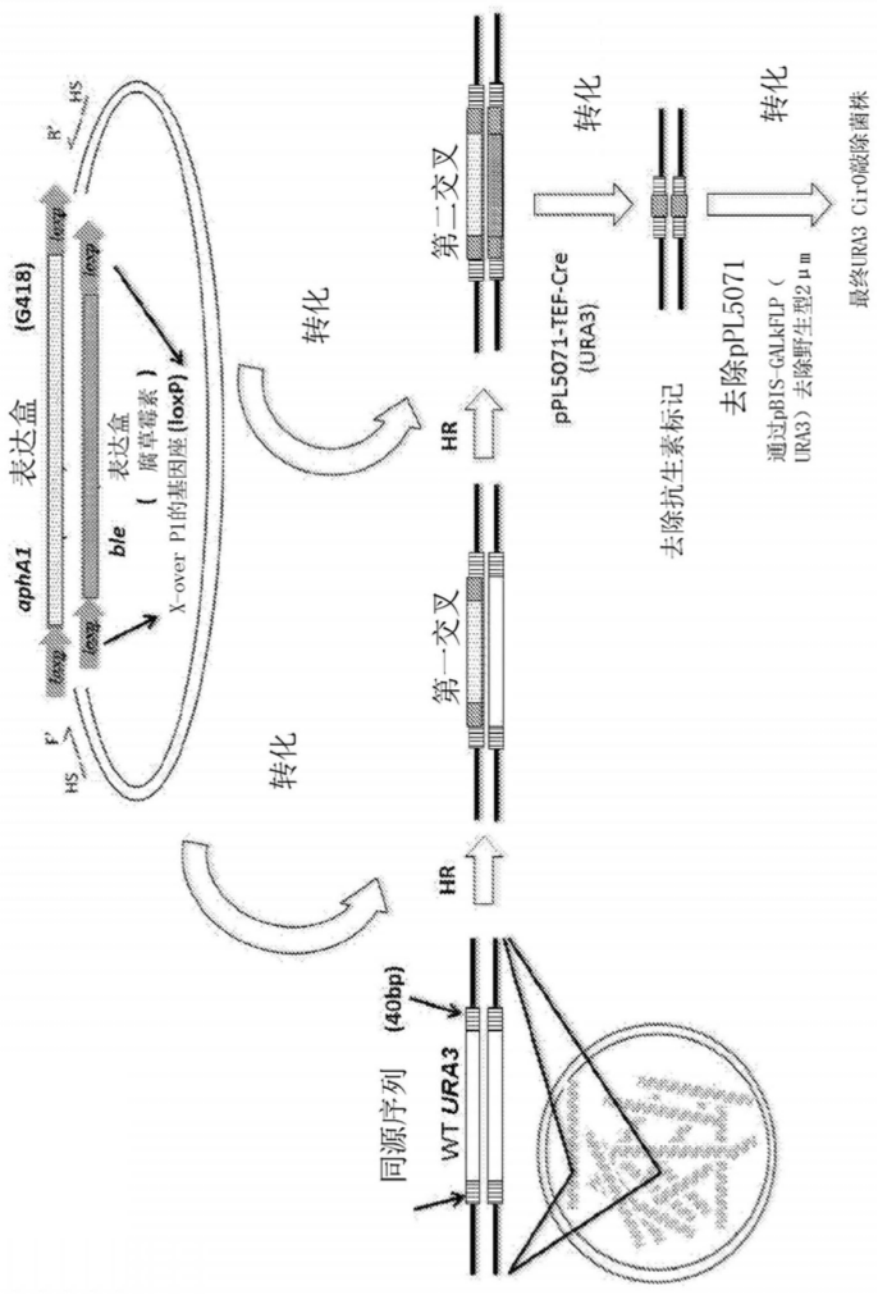
表达盒
(G418)
aphA1
ble
表达盒
(腐草霉素)
X-over P1的基因座(loxP)
loxp
F'
HS
R'
HS
转化
第一交叉
HR
同源序列
(40bp)
WT URA3
转化
第二交叉
HR
pPL5071-TEF-Cre
(URA3)
转化
去除抗生素标记
去除pPL5071
通过pBIS-GALKFLP(
URA3)去除野生型2μm
转化
最终URA3 Cir0敲除菌株

图16

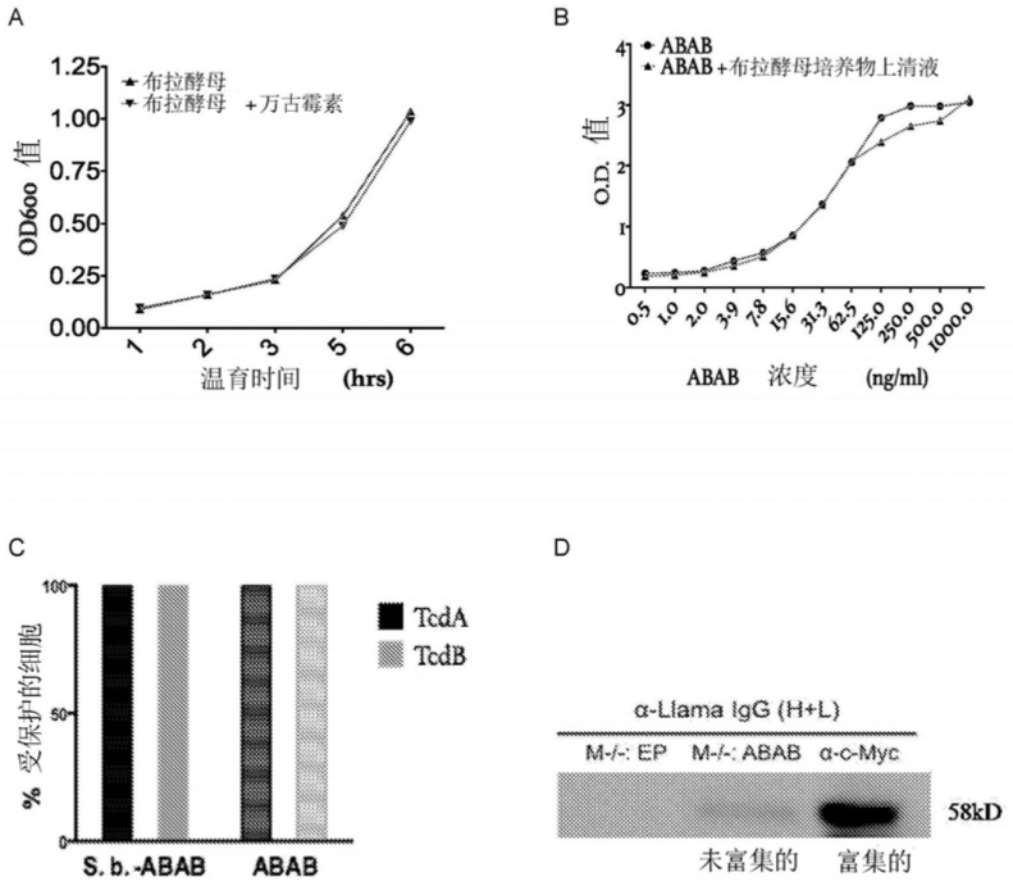
A
布拉酵母
布拉酵母 +万古霉素
OD600 值
温育时间 (hrs)
B
ABAB
ABAB+布拉酵母培养物上清液
O.D. 值
ABAB 浓度 (ng/ml)
C
TcdA
TcdB
% 受保护的细胞
S. b. -ABAB
ABAB
D
α-Llama IgG (H+L)
M-/-: EP
M-/-: ABAB
α-c-Myc
58kD
未富集的
富集的

图17

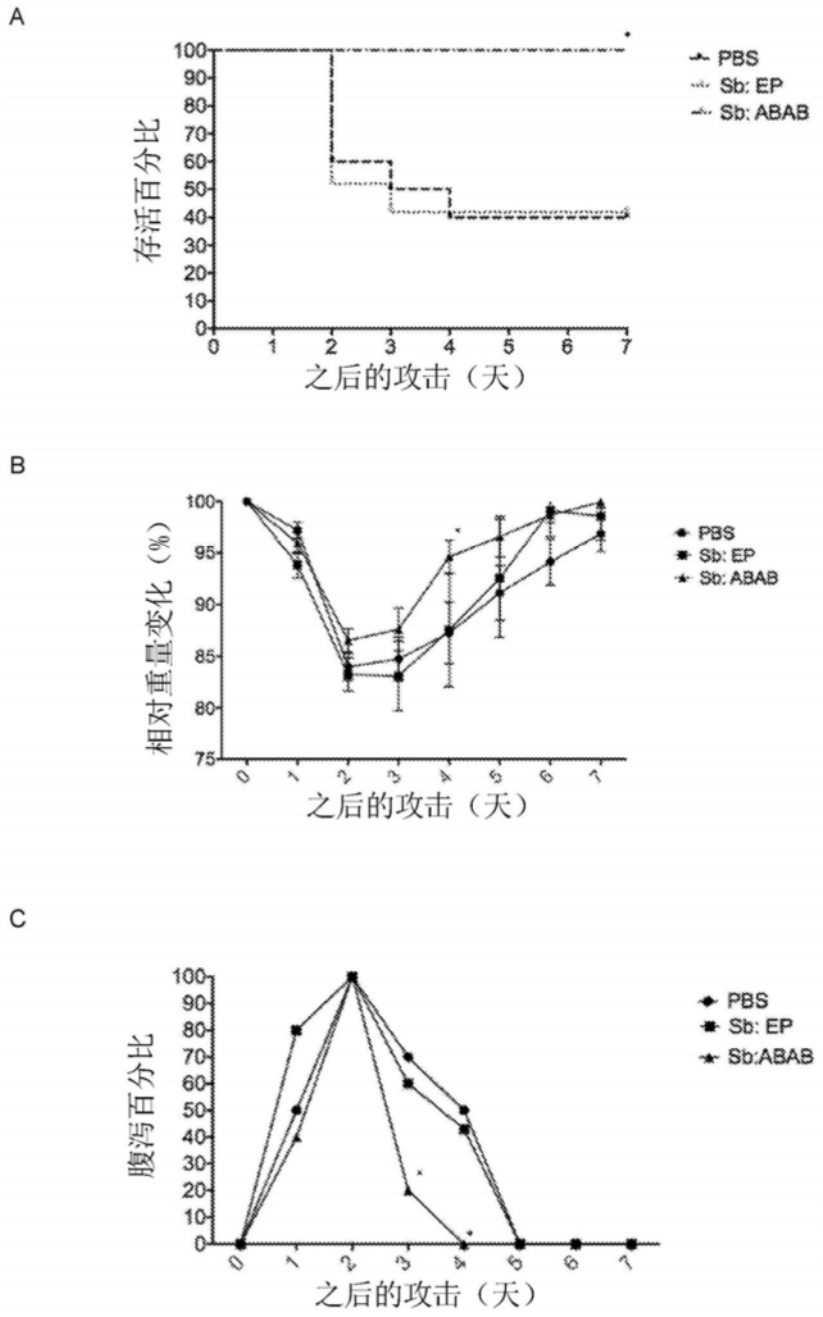
A
存活百分比
之后的攻击（天）
PBS
Sb: EP
Sb: ABAB
B
相对重量变化（%）
之后的攻击（天）
PBS
Sb: EP
Sb: ABAB
C
腹泻百分比
之后的攻击（天）
PBS
Sb: EP
Sb:ABAB

图18

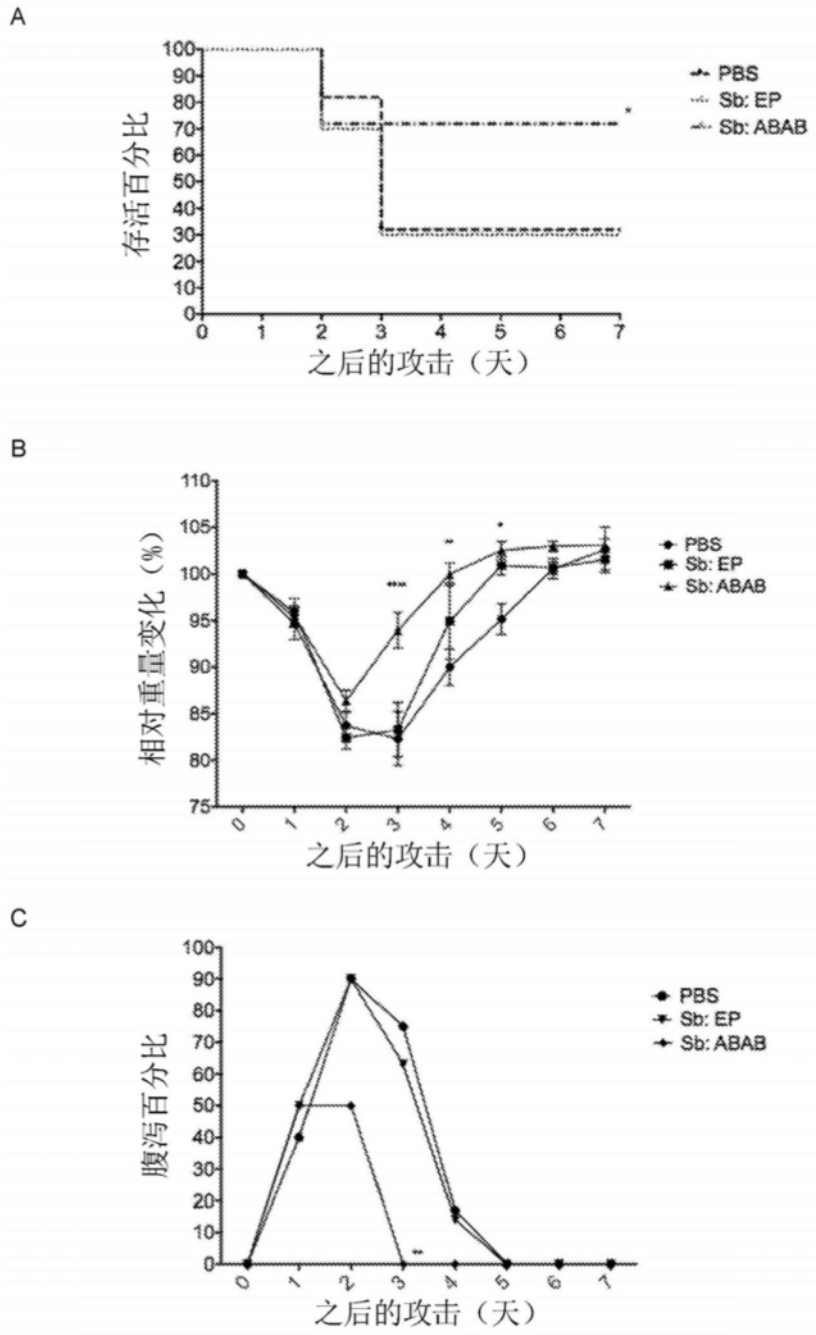
A
存活百分比
之后的攻击（天）
PBS
Sb: EP
Sb: ABAB
B
相对重量变化（%）
之后的攻击（天）
PBS
Sb: EP
Sb: ABAB
C
腹泻百分比
之后的攻击（天）
PBS
Sb: EP
Sb: ABAB

图19

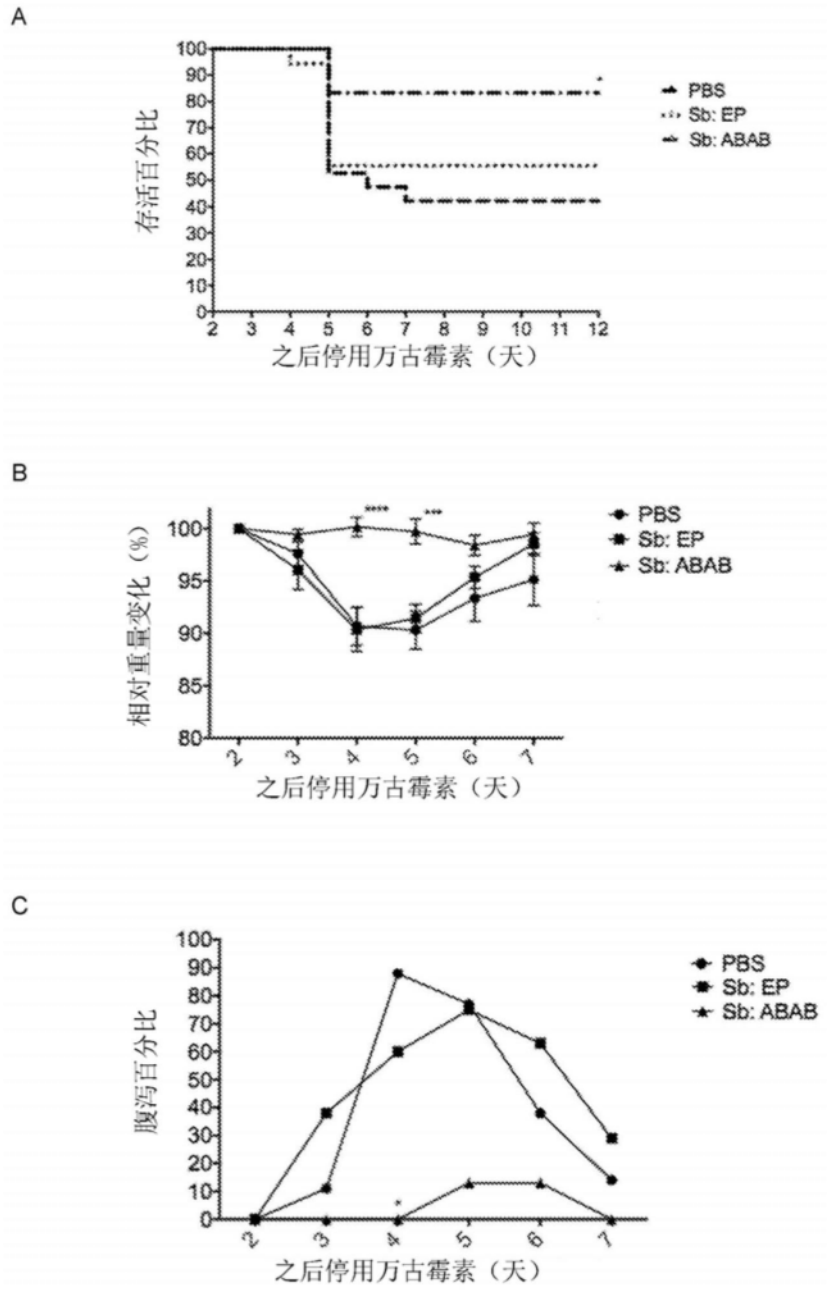
A
存活百分比
之后停用万古霉素（天）
PBS
Sb: EP
Sb: ABAB
B
相对重量变化（%）
之后停用万古霉素（天）
PBS
Sb: EP
Sb: ABAB
C
腹泻百分比
之后停用万古霉素（天）
PBS
Sb: EP
Sb: ABAB

图20

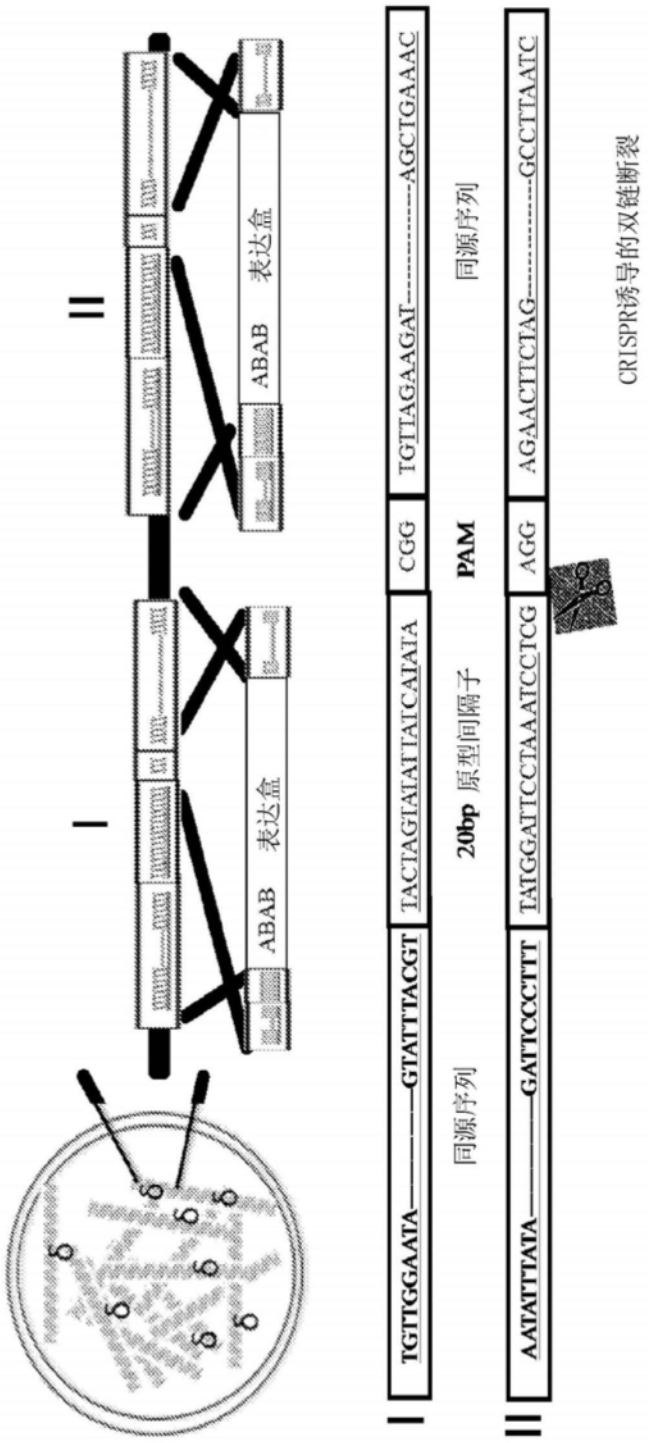
ABAB 表达盒
ABAB 表达盒
I
II
TGTTGGAATA——GTATTTACGT
TACTAGTATATTATCATATA
CGG
TGTTAGAAGAT——AGCTGAAAC
同源序列
20bp 原型间隔子
PAM
同源序列
AATATTTATA——GATTCCCTTT
TATGGATTCCTAAATCCTCG
AGG
AGAACTTCTAG——GCCTTAATC
CRISPR诱导的双链断裂

图21

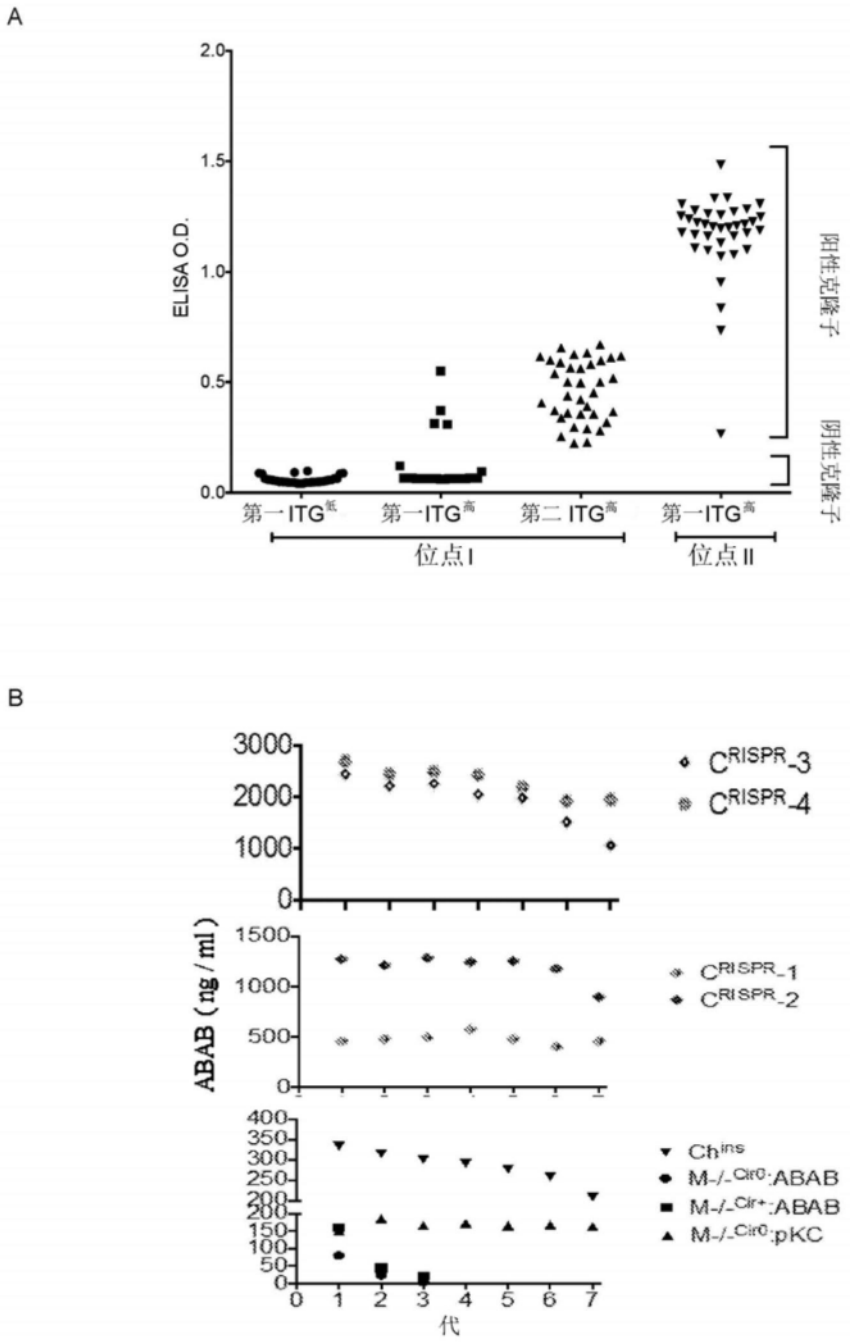
A
ELISA O.D.
2.0
1.5
1.0
0.5
0.0
阳性克隆子
阴性克隆子
第一ITG低
第一ITG高
第二ITG高
第一ITG高
位点I
位点II
B
ABAB (ng/ml)
3000
2000
1000
0
1500
1000
500
0
400
350
300
250
200
200
150
100
50
0
0 1 2 3 4 5 6 7
代
CRISPR-3
CRISPR-4
CRISPR-1
CRISPR-2
Chins
M-/-Cir0:ABAB
M-/-Cir+:ABAB
M-/-Cir0:pKC

图22

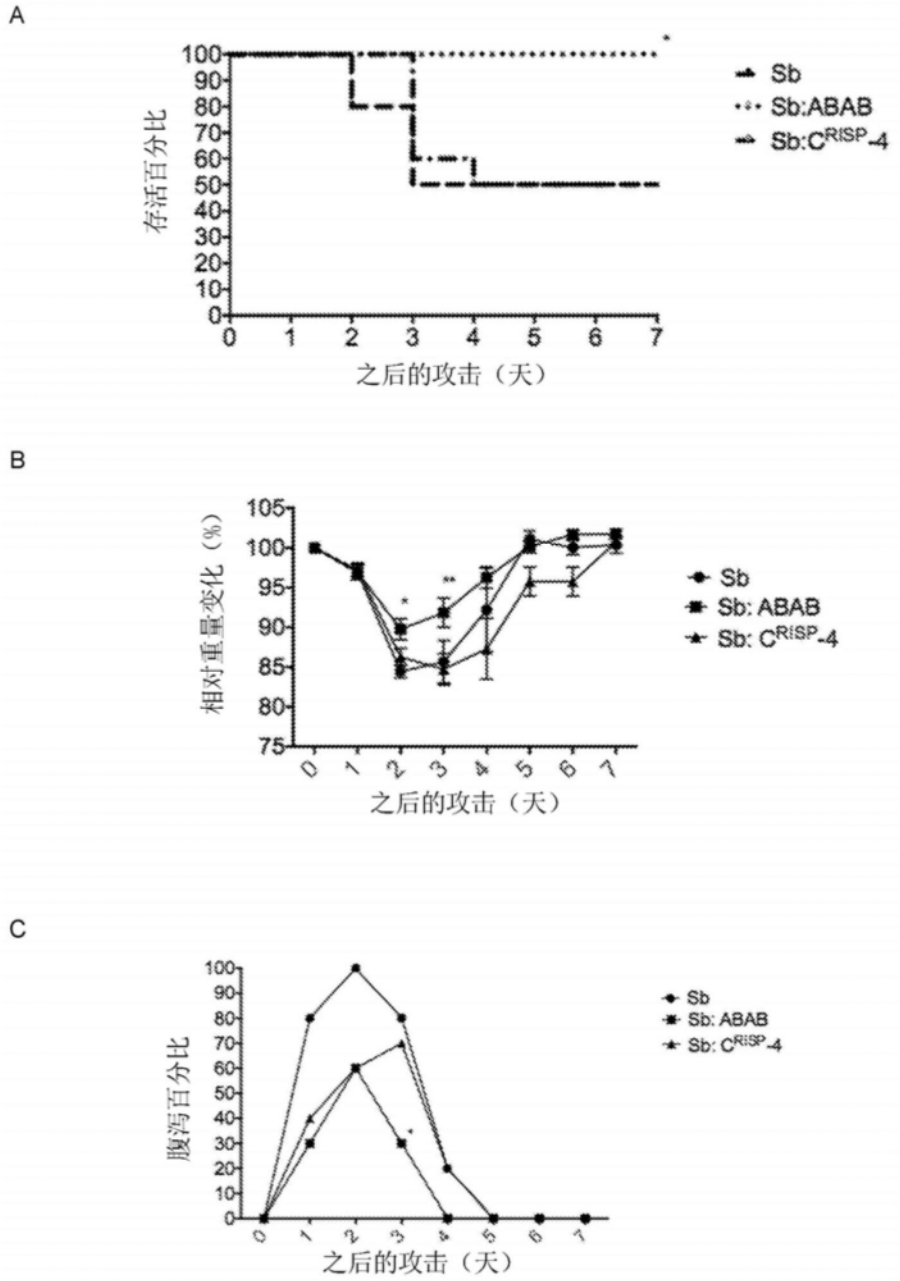
A
存活百分比
之后的攻击（天）
Sb
Sb:ABAB
Sb:C^RISP-4
B
相对重量变化（%）
之后的攻击（天）
Sb
Sb: ABAB
Sb: C^RISP-4
C
腹泻百分比
之后的攻击（天）
Sb
Sb: ABAB
Sb: C^RISP-4

图23