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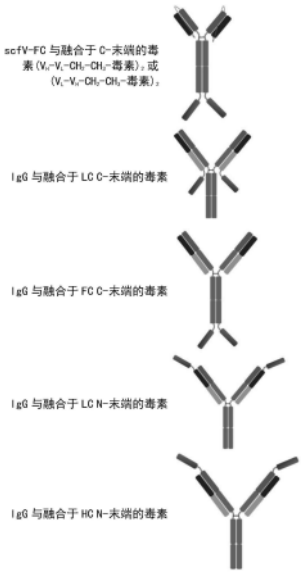
权利要求书3页 说明书49页
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(54)发明名称

包含核糖体毒素或RNAse的重组免疫毒素

(57)摘要

本发明涉及结合剂-毒素融合蛋白，其包含选自由以下组成的组的至少一种蛋白质结合剂：·抗体·保留靶结合能力的抗体片段或衍生物，或·抗体模拟物，核糖体毒素或原毒素，以及任选地连接a)和b)的肽接头和/或包含在原毒素中的可裂解结构域。



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1.结合剂-毒素融合蛋白,其包含anisoplin或其活性片段,优选地包含根据SEQ ID NO:48或49的序列,或与其具有至少66%序列相同性的其同源物。

2.根据权利要求1的结合剂-毒素融合蛋白,其中所述蛋白质结合剂选自由以下组成的组:

• 抗体,

• 保留靶结合能力的抗体片段或衍生物,或

• 抗体模拟物。

3.根据权利要求1或2的结合剂-毒素融合蛋白,其中所述融合蛋白包含连接结合剂或其结构域与毒素或毒素中包含的可裂解结构域的肽接头。

3.根据权利要求1至3任一项的结合剂-毒素融合蛋白,其中

• 所述肽接头或可裂解结构域是能被哺乳动物细胞表达的酶或哺乳动物宿主产生的酶特异性或非特异性裂解的,和/或

• 所述肽接头或可裂解结构域是不能被植物细胞表达的酶或植物宿主产生的酶裂解的,和/或

• 所述结合剂-毒素融合蛋白在转染的植物细胞或转染的整株植物中表达。

4.根据权利要求1至3任一项的结合剂-毒素融合蛋白,其中所述蛋白质结合剂结合人CD20或人CD79B。

5.一种结合剂-毒素融合蛋白,其至少包含:

a)一种选自由以下组成的组的蛋白质结合剂:

• 抗体,

• 保留靶结合能力的抗体片段或衍生物,或

• 抗体模拟物,

b)RNAse、核糖体毒素或相应的原毒素,和

c)任选地,连接所述结合剂或其结构域与毒素或包含在所述原毒素中的可裂解结构域的肽接头,

其中所述结合剂-毒素融合蛋白是选自由以下组成的组的形式之一:

• (scFv-FC)-(接头)-毒素(二聚体),

• 两个HC和两个LC-(接头)-毒素的四聚体,

• 两个LC和两个HC-(接头)-毒素的四聚体,或

• 两个LC-(接头)-毒素和两个HC-(接头)-毒素的四聚体,

其中所述接头是任选地。

6.结合剂-毒素融合蛋白,其至少包含:

a)一种选自由以下组成的组的蛋白质结合剂:

• 抗体,

• 保留靶结合能力的抗体片段或衍生物,或

• 抗体模拟物,

b)RNAse、核糖体毒素或相应的原毒素,和

c)任选地,连接所述结合剂或其结构域与毒素或包含在所述原毒素中的可裂解结构域的肽接头,

其中以下至少之一：

• 所述肽接头或所述原毒素中的可裂解结构域是能被哺乳动物细胞表达的酶或哺乳动物宿主产生的酶特异性或非特异性裂解的，和/或

• 所述肽接头或所述原毒素中的可裂解结构域是不能被植物细胞表达的酶或植物宿主产生的酶裂解的。

7.结合剂-毒素融合蛋白，其至少包含：

a)一种选自由以下组成的组的蛋白质结合剂：

• 抗体，

• 保留靶结合能力的抗体片段或衍生物，或

• 抗体模拟物，

b)RNAse、核糖体毒素或相应的原毒素，和

c)任选地，连接所述结合剂或其结构域与毒素或包含在所述原毒素中的可裂解结构域的肽接头，

其中所述结合剂-毒素融合蛋白在转染的植物细胞或转染的整株植物中表达。

8.结合剂-毒素融合蛋白，其至少包含：

a)一种选自由以下组成的组的蛋白质结合剂：

• 抗体，

• 保留靶结合能力的抗体片段或衍生物，或

• 抗体模拟物，

b)RNAse、核糖体毒素或相应的原毒素，和

c)任选地，连接所述结合剂或其结构域与毒素或包含在所述原毒素中的可裂解结构域的肽接头，

其中所述蛋白质结合剂结合人CD20或人CD79b。

9.根据权利要求5至8任一项的结合剂-毒素融合蛋白，其中所述核糖体毒素是选自由以下组成的组的毒素或其活性片段：

• 八叠球菌素(sarcin)，

• 局限曲菌素(restrictocin)，

• anisoplin，

• hirsutellin，

• clavin，

• 丝裂菌褶素(mitogillin)，

• ageritin，及

• 大曲菌素(gigantin)。

10.根据权利要求5至8任一项的结合剂-毒素融合蛋白，其中所述RNase是选自由以下组成的组的毒素或其活性片段：

• Onconase:rampirinase，frog rnase

• RNase 1:胰腺核糖核酸酶(SEQ ID NO:57)

• RNase 2:非分泌性核糖核酸酶

• RNase 3:嗜酸性粒细胞阳离子蛋白质

• RNase 4:核糖核酸酶4

• RNase 5:血管生成素(SEQ ID NO:50)

• RNase 6:核糖核酸酶K6/核糖核酸酶T2/核糖核酸酶K3

• RNase 7:核糖核酸酶7/核糖核酸酶A E1,以及

• RNase 8:核糖核酸酶8。

11.根据前述权利要求任一项的结合剂-毒素融合蛋白,所述结合剂-毒素融合蛋白在植物宿主或植物细胞中产生。

12.根据前述权利要求任一项的结合剂-毒素融合蛋白,其中所述植物宿主或植物细胞来自烟草属(Nicotiana)。

13.根据前述权利要求任一项的结合剂-毒素融合蛋白,其中所述可裂解接头或所述原毒素中的可裂解结构域包含选自由以下组成的组的至少一个裂解位点:

a)内体和/或溶酶体蛋白酶裂解位点,

b)细胞溶质蛋白酶裂解位点,和/或

c)细胞表面蛋白酶裂解位点。

14.根据前述权利要求任一项的结合剂-毒素融合蛋白,所述蛋白质包含至少一种植物特异性N-聚糖。

15.一种药物组合物,其至少包含前述权利要求任一项的结合剂-毒素融合蛋白,以及任选地一种或多种药学上可接受的赋形剂。

16.一种组合,其包含(i)根据权利要求1至14任一项的结合剂-毒素融合蛋白或根据权利要求15的药物组合物,和(ii)一种或多种另外的治疗活性化合物。

17.根据权利要求1至14任一项的结合剂-毒素融合蛋白,或权利要求15的组合物,或权利要求16的组合,(用于制备药物,所述药物)用于治疗人或动物对象或用于预防人或动物对象以下病况,所述对象

• 患有

• 处于发生风险中,和/或

• 被诊断为,

发生赘生性疾病。

18.一种治疗人或动物对象或预防人或动物对象以下病况的方法,所述对象

• 患有

• 处于发生风险中,和/或

• 被诊断为,

发生赘生性疾病,所述方法包括施用治疗有效量的根据权利要求1至4任一项的结合剂-毒素融合蛋白、或权利要求15的组合物、或权利要求16的其组合。

包含核糖体毒素或RNAse的重组免疫毒素

发明领域

[0001] 本申请涉及结合剂-毒素融合蛋白的领域。

[0002] 发明背景

[0003] 组合靶结合剂和毒素的缀合物已在40年前开发出来，现在代表着抗癌的主要希望。这些缀合物主要以抗体-药物-缀合物(ADC)类为代表，由通过接头化学缀合于化学细胞毒性剂的单克隆抗体组成。这些药物组合单克隆抗体靶向癌细胞的特异性和有效载荷的高毒力，以杀死靶细胞，同时保护健康组织。

[0004] 仍然需要新的这种实体来为不同的肿瘤类型提供更好的治疗选择。因此，本发明的一个目的是提供这样的新实体。

[0005] 本发明的另一个目的是为癌症患者提供替代的或甚至更好的治疗选择。

[0006] 这些和进一步的目的与根据本发明的独立权利要求的方法和方式一致。从属权利要求涉及具体实施方案。

发明内容

[0007] 在PCT申请PCT/EP2020/054263中公开了用于本发明的构思和付诸实施的方法，其内容通过引用整体并入本文。其中公开的定义和实施方案构成本公开的一部分。为清楚起见，PCT申请PCT/EP2020/054263的文本附于本申请并构成其公开内容的一部分。

[0008] 发明的实施方案

[0009] 在详细描述本发明之前，应当理解本发明不限于所描述的装置的特定组成部分或所描述的方法的处理步骤，因为这样的装置和方法可以变化。还应理解，本文使用的术语仅用于描述特定实施方案的目的，而不旨在限制。必须注意，如在说明书和所附权利要求中所使用的，单数形式“一个”、“一种”和“所述”包括单数和/或复数指示物，除非上下文另有明确规定。此外应当理解，在给出由数值界定的参数范围的情况下，该范围被认为包括这些限制值。

[0010] 还应理解，本文公开的实施方案并不意味着被理解为不相互关联的单独实施方案。一个实施方案讨论的特征也意在结合本文所示的其它实施方案来公开。如果在一种情况下，某特定特征未与一个实施方案一起公开，但与另一实施方案一起公开，则本领域技术人员将理解这并不一定意味着所述特征不打算与所述另一实施方案一起公开。本领域技术人员将理解，本申请的主旨是也针对其它实施方案公开所述特征，但是仅仅为了清楚的目的并且为了将说明书保持在可控篇幅内而没有这样做。

[0011] 此外，本文引用的现有技术文献的内容通过引用并入。这尤其适用于公开标准或常规方法的现有技术文件。在这种情况下，通过引用并入的主要目的是提供充分的公开信息，并避免冗长的重复。

[0012] 本发明的实施方案在权利要求中示出。

[0013] 根据一个实施方案，提供了一种结合剂-毒素融合蛋白，其包含anisoplin或其活性片段。优选地，所述结合剂-毒素融合蛋白包含根据SEQ ID NO:48或49的毒素序列，或其

与SEQ ID NO:48或49具有至少66％序列相同性的同源物。

[0014] 根据一个实施方案,提供了一种结合剂-毒素融合蛋白,其包含anisoplin同源物或其活性片段。优选地,所述结合剂-毒素融合蛋白包含根据SEQ ID NO:51、52或53的毒素序列,或其与SEQ ID NO:51、52或53具有至少66％序列相同性的同源物。

[0015] Anisoplin是一种真菌核糖体毒素,在自然界中由昆虫病原性真菌绿僵菌(Metarhizium anisopliae)产生。绿僵菌(M.anisopliae)在1800年代后期首次被用于小麦谷物甲虫的生物防治。从那时起,基于这种真菌的生物农药得到了极大的发展。最近,绿僵菌(M.anisopliae)也成为一种感兴趣且有前途的替代品,用于控制如冈比亚按蚊(Anopheles gambiae mosquito)等成年疟疾载体,因为对杀虫剂的抗药性的出现阻碍了控制该疾病的努力。

[0016] 迄今为止,Anioplin尚未在抗肿瘤治疗的背景下进行描述,也未作为结合剂-毒素融合蛋白中的毒素成分进行描述。本发明人首先探索了anisoplin在这些情况下的潜力,并令人惊讶地发现该毒素具有使其适合这些应用的优异特性。

[0017] 在一些实施方案中,所述毒素序列与SEQ ID NO:48或49具有≥67％、≥68％、≥69％、≥70％、≥71％、≥72％、≥73％、≥74％、≥75％、≥76％、≥77％、≥78％、≥79％、≥80％、≥81％、≥82％、≥83％、≥84％、≥85％、≥86％、≥87％、≥88％、≥89％、≥90％、≥91％、≥92％、≥93％、≥94％、≥95％、≥96％、≥97％、≥98％、≥99％及最优选100％的序列相同性。

[0018] 根据一个实施方案,所述蛋白质结合剂选自由以下组成的组:

[0019] •抗体,

[0020] •保留靶结合能力的抗体片段或衍生物,或

[0021] •抗体模拟物。

[0022] 根据一个实施方案,所述结合剂-毒素融合蛋白包含将结合剂或其结构域与毒素或与毒素中包含的可裂解结构域连接的肽接头。

[0023] 根据所述结合剂-毒素融合蛋白的一些实施方案:

[0024] •所述肽接头或可裂解结构域可被哺乳动物细胞表达的酶或哺乳动物宿主产生的酶特异性或非特异性裂解,和/或

[0025] •所述肽接头或可裂解结构域不能被植物细胞表达的酶或植物宿主产生的酶裂解,和/或

[0026] •所述结合剂-毒素融合蛋白在转染的植物细胞或转染的整株植物中表达。

[0027] 本领域技术人员手头有一堆常规方法来检查所述肽接头或原毒素中的可裂解结构域不可被植物细胞表达的酶或植物宿主产生的酶裂解的条件是否符合。见例如Wilbers等人(2016)。此外,本领域技术人员可以用常规方法检查所述肽接头或可裂解结构域是否可被哺乳动物细胞表达的酶或哺乳动物宿主产生的酶特异性或非特异性裂解。

[0028] 根据一个实施方案,所述蛋白质结合剂结合人CD20或人CD79B。

[0029] 根据本发明的进一步方面,结合剂-毒素融合蛋白至少包含:

[0030] a)一种选自由以下组成的组的蛋白质结合剂:

[0031] •抗体,

[0032] •保留靶结合能力的抗体片段或衍生物,或

[0033] • 抗体模拟物，

[0034] b)RNAse、核糖体毒素或相应的原毒素，和

[0035] c)任选地，将所述结合剂或其结构域与毒素或包含在原毒素中的可裂解结构域连接的肽接头。

[0036] 根据一个方面，这种结合剂-毒素融合蛋白是选自由以下组成的组的形式之一：

[0037] • (scFv-FC)-(接头)-毒素(二聚体)

[0038] • 两个HC和两个LC-(接头)-毒素的四聚体

[0039] • 两个LC和两个HC-(接头)-毒素的四聚体，或

[0040] • 两个LC-(接头)-毒素和两个HC-(接头)-毒素的四聚体

[0041] 其中所述接头是任选地。

[0042] 图1显示了可能的结合剂-毒素融合蛋白形式的选择。

[0043] CH_3＝重链恒定域3

[0044] CH_2＝重链恒定域2

[0045] V_L＝轻链可变域

[0046] V_H＝重链可变域

[0047] FC＝抗体FC结构域

[0048] LC＝轻链

[0049] HC＝重链

[0050] 根据进一步的方面，

[0051] • 所述肽接头或原毒素中的可裂解结构域可被哺乳动物细胞表达的酶或哺乳动物宿主产生的酶特异性或非特异性裂解，和/或

[0052] • 所述肽接头或原毒素中的可裂解结构域不能被植物细胞表达的酶或植物宿主产生的酶裂解。

[0053] 根据一方面，这种结合剂-毒素融合蛋白在转染的植物细胞或转染的整株植物中表达。

[0054] 根据一方面，这种结合剂-毒素融合蛋白中的蛋白质结合剂结合人CD20或人CD79B。

[0055] CD79b(B细胞抗原受体复合物相关蛋白β链)是一种表面蛋白，参与体液免疫应答。CD79b由B细胞产生。它与CD79a结合并通过二硫键与之相连。这些异二聚体的两个与mIgM或mIgD亚型的膜结合抗体结合，形成抗原结合的B细胞受体(BCR)。CD79b增强CD79a的磷酸化。抗原结合后，抗原-抗体BCR被内吞。CD79b被糖基化。其具有一个细胞内ITAM基序，在BCR激活后结合蛋白激酶Syk或Lyn并被蛋白激酶Syk或Lyn磷酸化。

[0056] Hashimoto et al.Immunogenetics.1994;40(2):145-149首次公开了CD79b的全序列。CD79B的蛋白质结合剂在本领域中已有描述。针对CD79b的第一个抗体(鼠)称为SN8，并已由Okazaki et al.,Blood,81:84-94(1993))公开。Polson et al.,Blood.2007;110(2):616-623讨论了制备针对CD79b的抗体药物缀合物(ADC)或重组免疫毒素的可能性。第一个人源化抗CD79b抗体(Polatuzumab)在US8545850中公开。在这个专利中，还公开了一种包含与泊洛妥珠单抗(Polatuzumab)连接的MMAE的ADC。

[0057] B淋巴细胞抗原CD20或表达于所有B细胞的表面，从pro-B期开始。在人类中，CD20

由MS4A1基因编码。该蛋白没有已知的天然配体,其功能是实现最佳B细胞免疫应答,特别是针对T非依赖性抗原。其疑似充当细胞膜中的钙通道。CD20在微环境相互作用的背景下由CXCR4/SDF1(CXCL12)趋化因子信号传导诱导,以及在此背景下CD20的分子功能与B细胞受体(BCR)的信号传导倾向相关联。

[0058] CD20是单克隆抗体利妥昔单抗(rituximab)、奥瑞珠单抗(ocrelizumab)、奥比妥珠单抗(obinutuzumab)、奥法木单抗(ofatumumab)、替伊莫单抗(ibritumomabtiuxetan)、托西莫单抗(tositumomab)和乌妥昔单抗(ublituximab)的靶标,它们都是治疗所有B细胞淋巴瘤、白血病和B细胞介导的自我免疫性疾病的活性药物。所有这些抗体在现有文献中都有很充分的描述,包括其序列,并且应被视为在本发明的上下文中公开。

[0059] 如本文所用,术语“核糖体毒素”涉及一组由真菌分泌的胞外核糖核酸酶(RNases)。其最显著的特征是其非凡的特异性。它们通过裂解在普遍保守序列中发现的rRNA的单个磷酸二酯键来失活核糖体。这种裂解通过细胞凋亡导致细胞死亡。然而,由于它们是细胞外蛋白,其必须首先进入构成其靶标的细胞才能发挥细胞毒性作用。这个进入构成其作用的决定速率的步骤。

[0060] 所有已知的核糖体毒素都是由130至150个氨基酸组成的蛋白质,其共享至少两个不同的有序二级结构元件:一个β-折叠(活性中心所在的位置)和一个短α-螺旋。结构排列与其它无毒的细胞外真菌RNase非常相似,并构成了一个家族,其最著名的代表是米曲霉(Aspergillus oryzae)的RNase T1。这解释了为什么核糖体毒素被认为是该组的毒性代表。对其三维结构的观察揭示了其在毒性方面的功能差异,因为核糖体毒素呈现无序、带正电的长环,而在其无毒的“亲属”中,这些环更短且带负电。这些核糖体毒素键负责识别促进其进入细胞的带负电荷的酸性磷脂,以及使其造成失活的核糖体特异性特征。

[0061] 核糖体毒素根据迄今为止表征的所有细胞外真菌RNase共有的一般酸碱机制裂解RNA,而不管其毒性如何。使用二核苷,例如GpA,已经证明底物的磷酸二酯键3’-5’的断裂是通过形成环状中间体发生的,环状中间体变成相应的衍生物3’-单磷酸酯,这是所述反应的最终产物。这是一个转磷酸化反应,随后是这个环状中间体的水解。因此,这些蛋白质被称为周期核糖核酸酶。

[0062] 根据不同的实施方案,所述核糖体毒素是选自由以下组成的组的毒素或其活性片段:

[0063] • 八叠球菌素(sarcin),

[0064] • 局限曲菌素(restrictocin),

[0065] • anisoplin,

[0066] • hirsutellin,

[0067] • clavin,

[0068] • 丝裂菌褶素(mitogillin),

[0069] • ageritin,及

[0070] • 大曲菌素(gigantin)。

[0071] 已在许多不同的真菌中检测到核糖体毒素,包括昆虫病原体和可食用物种,但仅解析了其中三种的三维结构:α-八叠球菌素、局限曲菌素和hirsutellin A(HtA)。前两种(分别由巨曲霉(Aspergillus giganteus)和局限曲霉(Aspergillus restrictus)产生)几

乎完全相同。

[0072] 在一个实施方案中,所述核糖体毒素是α-八叠球菌素或其活性片段。

[0073] 存在不同的α-八叠球菌素变体,其实例以UniProt标识符P00655、Q7LVR0、O14446、O13323、O13324、O13322、O13325、A0A0G2DUB2发表。虽然本申请中的一些实施例使用P00655,但同样可以使用其它八叠球菌素变体。技术人员可以通过例行的工作在各自的数据库中找到这样的变体。八叠球菌素的一个示例性序列在SEQ ID NO:56中给出,示出其去免疫化的变体。SEQ ID NO:55示出野生型。

[0074] 在一个实施方案中,所述核糖体毒素是hirsutellin A(HtA)或其活性片段。HtA由昆虫病原性真菌汤普森多毛菌(Hrsutella thompsonii)产生,其较小,与其它较大的核糖体毒素仅显示25%的序列相同性。尽管如此,其仍保留了家族的所有功能特征。存在不同的hirsutellin A变体,其实例在UniProt标识符下发表:N4VY63,P78696,A0A0B4HUA1,A0A0B4FSP6,T5AB58,A0A0B4EQU3,E9FCV0,A0A014PJJ6,A0A0B4GG41,L2G0X6,A0A063C0Y4,A0A179FJ94,A0A166WTA3,A1CDH8,I8AC84,A0A364MLV5,A0A4Q7JNA6,Q8NJP2,Q8NJP0,Q8NJP3,Q8NJP1,Q8NJN9,Q8NIC7,E9E2C8。虽然本申请中的一些实施例使用N4VY63,但同样可以使用其它hirsutellin A变体。本领域技术人员可以通过常规工作在各自的数据库中找到这样的变体。SEQ ID NO:47给出一种示例性的hirsutellin A序列。

[0075] 在一个实施方案中,所述核糖体毒素是局限曲菌素(有时也称为丝裂菌褶素(mitogillin))或其活性片段(UniProt标识符:P67876)。SEQ ID NO:27给出局限曲菌素的一个示例性序列。

[0076] 同样可以使用其它变体。本领域技术人员可以通过常规工作在各自的数据库中找到这样的变体。

[0077] 在一个实施方案中,所述核糖体毒素是clavin或其活性片段。存在不同的clavin变体,其示例以UniProt标识符P0CL70、P0CL71、E0YUC8、A0A4R8PRX1、A0A4R8T0U3、U4KU86、A0A4R8R208、U4KUQ3发表。同样可以使用其它变体。本领域技术人员可以通过常规工作在各自的数据库中找到这样的变体。

[0078] 在一个实施例中,核糖体毒素是大曲菌素(gigantin)或其活性片段(UniProt标识符:P87063)。同样可以使用其它变体。本领域技术人员可以通过常规工作在各自的数据库中找到这样的变体。

[0079] 在一个实施方案中,所述核糖体毒素是anisoplin或其活性片段(见例如SEQ ID NO:48,和SEQ ID NO:49中的修饰变体)。其由另一种昆虫病原体绿僵菌(Metarhizium anisopliae)产生。

[0080] 如本文所用,术语“核糖核酸酶(RNase)”涉及一组催化RNA降解成更小组分的核酸酶(“核糖核酸酶”)。核糖核酸酶可分为核糖核酸内切酶和核糖核酸外切酶,并包含EC 2.7(磷酸解酶)和3.1(水解酶)酶类别中的几个亚类。

[0081] 本文公开的核糖核酸内切酶的主要类型如下:

[0082] EC 3.1.27.5:RNase A是一种常用于研究的RNase。RNase A(例如,牛胰腺核糖核酸酶A:PDB:2AAS)是实验室常用的最坚固的酶之一;分离其的一种方法是将细胞粗制提取物煮沸,直到除RNase A之外的所有酶都变性。其特异于单链RNA。其裂解未配对的C和U残基的3’-末端,最终通过2’,3’-环状单磷酸中间体形成3’-磷酸化产物。其活性不需要任何辅

因子。

[0083] EC3.1.26.4:RNase H是一种核糖核酸酶,其裂解DNA/RNA双链体中的RNA以产生ssDNA。Rnase H是一种非特异性核酸内切酶,在酶结合的二价金属离子的帮助下,通过水解机制催化RNA的裂解。Rnase H留下5'-磷酸化产物。

[0084] EC 3.1.26.3:RNaseIII是一种核糖核酸酶,其从在原核生物中转录的多顺反子RNA操纵子中裂解rRNA(16s rRNA和23s rRNA)。其还消化Rnase的双链RNA(dsRNA)-Dicer家族的,在特定位点裂解pre-miRNA(长度60-70bp)并将其转化为miRNA(22-30bp),miRNA积极参与转录调控和mRNA寿命。

[0085] EC编号3.1.26:RNase L是一种干扰素诱导的核酸酶,激活后会破坏细胞内的所有RNA。

[0086] EC 3.1.26.5:Rnase P是一种核糖核酸酶,其独特之处在于其是一种核酶-一种以与酶相同的方式充当催化剂的核糖核酸。其功能之一是从一条链的pre-tRNA的5'端切下前导序列。Rnase P是自然界中两种已知的多周转核酶之一(另一种是核糖体)。在细菌中,Rnase P还负责全酶的催化活性,全酶由脱辅基酶组成,脱辅基酶通过与辅酶结合形成活性酶系统,并决定这个系统对底物的特异性。最近发现一种是蛋白质且不含有RNA的RNaseP形式。

[0087] EC编号3.1.:Rnase PhyM是特异于单链RNA的序列。其裂解未配对的A和U残基的3'端。

[0088] EC 3.1.27.3:Rnase T1是特异于单链RNA的序列。其裂解未配对的G残基的3'端。

[0089] EC 3.1.27.1:Rnase T2是特异于单链RNA的序列。其裂解所有4个残基的3'端,但优先裂解A的3'端。

[0090] EC 3.1.27.4:Rnase U2是特异于单链RNA的序列。其裂解未配对的A残基的3'端。

[0091] EC 3.1.27.8:Rnase V特异于聚腺嘌呤和聚尿苷RNA。

[0092] EC 3.1.26.12:RNase E是一种植物来源的核糖核酸酶,其调节细菌的SOS应答,通过转录性抑制多种基因的RecA/LexA依赖的信号转导途径激活SOS机制,导致细胞分裂的转运停止以及启动DNA修复,从而应答DNA损伤的应激。

[0093] EC 3.1.26.-:Rnase G参与加工5s rRNA的16'-末端。其与染色体分离和细胞分裂有关。其被认为是细胞质轴丝束的组成部分之一。其还被认为可以调节这种结构的形成。

[0094] 核糖核酸外切酶的主要类型:

[0095] EC编号EC 2.7.7.8:多核苷酸磷酸化酶(PNPase)具有核酸外切酶和核苷酸基转移酶的功能。

[0096] EC编号EC 2.7.7.56:RnasePH具有核酸外切酶和核苷酸基转移酶的功能。

[0097] EC编号3.1.??:Rnase R是Rnase II的密切同系物,但与Rnase II不同,其可以在没有辅助因子帮助下降解具有二级结构的RNA。

[0098] EC编号EC3.1.13.5:Rnase D参与pre-tRNA的3'-至-5'的加工。

[0099] EC编号3.1.??:Rnase T是许多稳定RNA从3'至5'成熟的主要贡献者。

[0100] EC 3.1.13.3:寡核糖核酸酶将短寡核苷酸降解为单核苷酸。

[0101] EC 3.1.11.1:核糖核酸外切酶I将单链RNA从5'至3'降解,仅存在于真核生物中。

[0102] EC 3.1.13.1:核糖核酸外切酶II是核糖核酸外切酶I的密切同系物。

[0103] 在一些实施方案中,RNase选自由以下组成的组:

[0104] • Onconase:(rampirinase,frog rnase):Onconase的不同变体:存在,其实例以Uni Prot标识符Q8UVX5、Q9I8V8、Q6EUW9、Q6EUW8、Q6EUW7或P22069发表。

[0105] • RNase 1:胰腺核糖核酸酶(例如RNAse1,例如Uniprot标识符P07998;见例如SEQ ID NO:57)

[0106] • RNase 2:非分泌性核糖核酸酶(例如RNAse2,例如Uniprot标识符P10153)

[0107] • RNase 3:嗜酸性粒细胞阳离子蛋白(例如RNAse3/Drosha,例如Uniprot标识符Q9NRR4或P12724)

[0108] • RNase 4:核糖核酸酶4(例如RNAse4,例如Uniprot标识符P34096)

[0109] • RNase 5:血管生成素(例如RNAse 5,例如Uniprot标识符P03950),见例如SEQ ID NO:50)

[0110] • RNase 6:核糖核酸酶K6/核糖核酸酶T2/核糖核酸酶K3(例如RNAse6,例如Uniprot标识符Q93091)

[0111] • RNase 7:核糖核酸酶7/核糖核酸酶AE1(例如RNAse7,例如Uniprot标识符Q9H1E1)

[0112] • RNase 8:核糖核酸酶8(例如RNAse8,例如Uniprot标识符Q8TDE3)

[0113] 上述Uniprot标识符仅用于示例目的。同样可以使用其它变体。本领域技术人员可以通过常规工作在各自的数据库中找到这样的变体。

[0114] 在一些实施方案中,所述肽接头或原毒素中的可裂解结构域可被哺乳动物细胞表达的酶或哺乳动物宿主产生的酶特异性或非特异性裂解,或不可被植物细胞表达的酶或植物宿主产生的酶裂解。

[0115] 在一个实施方案中,所述结合剂-毒素融合蛋白在植物宿主或植物细胞中产生。正如其它地方所讨论的,这提供创建具有接头的构建体的选项,所述接头可被植物宿主中不存在的哺乳动物酶裂解。在这种情况下,避免生产系统的自我中毒,同时所述可裂解接头允许毒素在体内快速释放。

[0116] 在一个实施方案中,所述结合剂-毒素融合蛋白在哺乳动物细胞例如CHO中产生。

[0117] 在一个实施方案中,植物宿主或植物细胞通过编码尤其是所述结合剂-毒素融合蛋白的载体被瞬时修饰。

[0118] 在一个实施方案中,植物宿主或植物细胞通过编码尤其是所述结合剂-毒素融合蛋白的载体被永久修饰。

[0119] 在WO2020169620中提供关于在植物宿主或植物细胞中瞬时或永久表达结合剂-毒素融合蛋白的方法的背景,为了实现目的将其内容并入本文。

[0120] 在一个实施方案中,所述植物宿主或植物细胞来自烟草属(Nicotiana)。在本文中,再次提及在一个实施方案中,所述肽接头或原毒素的可裂解结构域不能被植物细胞表达的酶或植物宿主产生的酶裂解。以这种方式,生产的植物细胞或植物宿主被保护免于由于结合剂-毒素融合蛋白的不需要的裂解而导致的自我中毒。

[0121] 在一个实施方案中,与所述核酸构建体接触的所述植物或植物细胞不是叶绿体,或不是藻类的叶绿体,尤其不是莱茵衣藻(Chlamydomonas reinhardtii)的叶绿体。在另一个实施方案中,与所述核酸构建体接触的所述植物或植物细胞中的结构不是叶绿体,或不

是藻类的叶绿体,尤其不是莱茵衣藻(Chlamydomonas reinhardtii)的叶绿体。

[0122] 在所述蛋白质结合剂包含两条或更多条链的另一个实施方案中,可以规定提供两个核酸构建体,第一个包含编码所述蛋白质结合剂的第一链、接头和毒素的三个多核苷酸,而第二个包含编码所述蛋白质结合剂第二链的多核苷酸。

[0123] "诱导型启动子"可诱导瞬时和稳定表达。这些启动子在存在内源或外源刺激后或应答化学、环境、激素和/或发育信号时选择性表达可操作地连接的DNA序列。这些调节元件对乙醇、热、光、应力、茉莉酮、水杨酸、植物激素、盐、洪水或干旱敏感,但不限于此,正如Abdel-Ghany等人(2015年)所回顾和在US 10344290 B2中所讨论的那样,这两者均通过引用并入本文。诱导型启动子包括但不限于Ali等人(2019)中讨论的合成组分,其内容通过引用并入本文。

[0124] 烟草属(Nicotiana)涵盖烟草植物。已经对烟草植物或植物细胞进行了测试,以产生重组免疫治疗性结合剂-毒素融合蛋白,所述融合蛋白包含通过稳定接头连接于蛋白质毒素的小sFv片段(Francisco et al.(1997),及US6140075A。

[0125] 根据本发明的另一个实施方案,所述植物细胞是选自由以下组成的组的至少一种植物细胞:

[0126] • 普通烟草(Nicotiana tabacum)cv.BY2,

[0127] • 普通烟草(Nicotiana tabacum)NT-1,

[0128] • 拟南芥(Arabidopsis thaliana)

[0129] • 胡萝卜(Daucus carota),和/或

[0130] • 水稻(Oyrza sativa)。

[0131] 普通烟草(Nicotiana tabacum)cv.BY2又名烟草BY-2细胞和cv.普通烟草(Nicotiana tabacum)1(NT-1,BY-2的姊妹株)是非绿色、快速生长的植物细胞,在充足的培养基和良好的培养条件下,其数量可在一周内增加100倍。这种烟草栽培品种作为细胞培养物保存,以及更特别是作为细胞悬浮培养物保存(在液体培养基中生长的特化细胞群,科学家培养它们以研究植物细胞的特定生物学特性)。在细胞悬浮培养物中,每个细胞独立漂浮或至多仅以短链漂浮在培养基中。每个细胞都具有与其它细胞相似的特性。

[0132] 所述模型植物系统堪比用于人类研究的HeLa细胞。由于生物体相对简单且可预测,这使生物过程的研究更加容易,并且可以成为理解更复杂生物体的中间步骤。其被植物生理学家和分子生物学家用作模式生物体,并且由于其具有相对高的同质性和高生长速率,还被用作高等植物的模型系统,仍然具有植物细胞的一般行为特征。自然生长的植物(体内)的任何部分内的细胞类型的多样性使得研究和理解活植物细胞的一些一般生化现象变得非常困难。例如,溶质进出细胞的转运很难研究,因为多细胞生物体中的特化细胞表现不同。烟草BY-2等细胞悬浮培养物在单个细胞及其区室水平上为这些研究提供良好的模型系统,因为烟草BY-2细胞彼此之间的行为非常相似。相邻细胞行为的影响在悬浮液中并不像在完整植物中那么重要。因此,在应用刺激后观察到的任何变化都可以在统计上相关,并且可以确定这些变化是对刺激的反应还是仅仅是巧合。BY-2和NT-1细胞相对得以充分理解并经常用于研究,包括异源蛋白质特别是抗体的表达(Hellwig等人(2004年)。此类方法在Häkkinen等人(2018年)中公开,其内容通过引用并入本文。

[0133] Torres(1989)讨论建立胡萝卜细胞悬浮培养物(Daucus carota)的方法。

Shaaltiel等人(2007)讨论使用基于胡萝卜细胞的表达系统生产酶。这些文章的内容通过引用并入本文。Santos等人(2016)也将胡萝卜(Daucus carota)和水稻(Oryza sativa)作为合适的基于植物细胞的表达系统进行讨论,其内容通过引用并入本文。在Plasson等人(2009)中公开普通烟草(Nicotiana tabacum)、拟南芥(Arabidopsis thaliana)、水稻(Oryza sativa)中重组蛋白质的生产,其内容通过引用并入本文。

[0134] 通常,本发明可用于任何植物品种,其中植物细胞可用适于表达外来多肽的DNA构建体转化并在标准植物细胞培养条件下培养。植物细胞悬浮液或植物组织培养是优选的,尽管可以使用愈伤组织培养或其它常规植物细胞培养方法。

[0135] 根据本发明的另一个实施方案,所述植物是本氏烟草(Nicotiana benthamiana)。烟草属植物中抗体的产生例如在Daniell等人(2001)中公开,其内容通过引用并入本文。

[0136] 可以在本发明的上下文中使用的其它植物或植物细胞包括但不限于生菜(Lactuca spp.)、菠菜(Spinacia oleracea)和拟南芥(Arabidopsis spp.)。

[0137] 在一些实施方案中,所述裂解位点选自由以下组成的组:

[0138] a)内体和/或溶酶体蛋白酶裂解位点,

[0139] b)细胞溶质蛋白酶裂解位点,和/或

[0140] c)细胞表面蛋白酶裂解位点。

[0141] 这种酶及其裂解位点的实例示于下表中(另见Choi等人(2012),其内容通过引用并入本文。在这个表中,参考"Merops"数据库以获取更多有关各种酶的使能信息。https://www.ebi.ac.uk/merops/index.shtml。

[0142]

类别	酶类别	实例	裂解序列(一个字母代码) 一般基序(仅示例) X 可以是任何天然蛋白原氨基酸	参考
"接头类别1"内体和/或溶酶体裂解位点	前蛋白转化酶枯草杆菌蛋白酶/kexin家族	弗林蛋白酶	RXR/KR↓S/A/G/Nxxx	merops S08.071
	组织蛋白酶	组织蛋白酶B	xxF/xV/R/G/L/S/A↓A/F/Lxxx	merops C01.060
		组织蛋白酶E	xxxL/F↓Vxxx	merops A01.010
		组织蛋白酶D	xxxL/F↓xxxx	merops A01.009
		组织蛋白酶L	xxL/V/F/IR/K↓S/A/Gxxx	merops C01.032
		组织蛋白酶K	xK/R/GF/L/I/V/Px↓xxxx	merops C01.036
		组织蛋白酶C	xSxE/S↓xxxG/R	merops C01.070

[0143]

“接头类别2”胞质裂解位点	半胱天冬酶	半胱天冬酶3	DxxD↓A/G/S/Txxx 或 xxxx↓GGFV	merops C14.003
		半胱天冬酶8	D/LxxD↓G/S/Axxx	merops C14.009
	激肽释放酶(hK)	hK 1	xxF/IR/Y↓R/SxGx	merops S01.160
		hK 2	G/K/AxxR↓xxxG/S/T	merops S01.161
		hK3	S/IS/QxY/Q/R↓SSxx	
		hK10	未确定	
“接头类别3”细胞表面裂解位点	基质金属蛋白酶	MMP2	xP/Axx↓L/Ixxx	merops M10.003
		MMP1	xP/Axx↓L/Ixx	merops M10.001
		MMP3	xxxR/N/G↓L/Kxx	merops S01.072
		MMP7	xPA/G/Lx↓Lxxx	merops M10.005
		MMP8	GP/A/Sxx↓Lxxx	merops M10.002
		MMP9	GP/Axx↓Lxxx P2优选是L P1优选是G	merops M10.004
		MMP12	GP/A/GL/A/Gx↓Lxxx	merops M10.009
		MMP14	xPxx↓Lxxx	merops M10.014
	蛋白裂解酶	蛋白裂解酶2	xxxR↓k/G/Rxxx	merops S01.308
		蛋白裂解酶1	xxxR↓K/V/A/RVxx	merops S01.302
	组织型纤溶酶原激活物	尿激酶型纤溶酶原激活物(uPA)	xSG/SR/K↓xR/Vxx	merops S01.231

[0144] 裂解位点是从裂解位点点(由↓表示)描述。字母x代表所有氨基酸。在有几个优选的氨基酸的地方,用斜线(/)隔开。

[0145] 这种酶优选是蛋白酶。在一个实施方案中,所述肽接头不可被植物酶裂解。

[0146] 弗林蛋白酶是一种属于枯草杆菌蛋白酶样前蛋白转化酶家族的酶,并且裂解经典碱性氨基酸序列基序Arg-X-Arg/Lys-Arg(RX(R/K)R)的C端蛋白质,其中X可以是任何天然的蛋白原氨基酸。所述基序在本文中称为弗林蛋白酶裂解位点。

[0147] ###

[0148] 优选地,其序列是HRRRKRSLDTS(SEQ ID NO:46,在本文中也称为Liop或FCS I(“弗林蛋白酶裂解位点1”))。可以在本发明的上下文中使用的其它可裂解接头是TRHRQPRGWEQL(SEQ ID NO:44,本文也称为Fpe或FCS II)和AGNRVRRSVG(SEQ ID NO:45,本文也称为Fdt或FCS III)。

[0149] 组织蛋白酶是存在于所有动物以及其它生物体中的蛋白酶。大多数成员在溶酶体中发现的低pH值下被激活。组织蛋白酶B能够裂解包含二肽基序Val-Ala(VA)的肽序列。所述基序在本文中称为组织蛋白酶B裂解位点。本领域技术人员在Turk等人(2012)中找到关

于组织蛋白酶及其裂解位点的足够使能信息,其内容通过引用并入本文。

[0150] 半胱天冬酶(半胱氨酸-天冬氨酸蛋白酶、半胱氨酸天冬氨酸酶或半胱氨酸依赖性天冬氨酸定向蛋白酶)是一个蛋白酶家族,在程序性细胞死亡中起着重要作用。在人类蛋白质组中已发现超过1500种半胱天冬酶底物。一般裂解基序是DXXD-A/G/S/T,其中X可以是任何天然的蛋白原氨基酸。本领域技术人员在Kumar等人(2014)中找到关于半胱天冬酶及其裂解位点的足够使能信息,其内容通过引用并入本文。

[0151] 基质金属蛋白酶(MMP),也称为matrixin,是钙依赖性含锌内肽酶;其它家族成员是去整合素(adamalysins)、沙雷氏蛋白酶(serralysin)和虾红素(astacins)。总的来说,这些酶能够降解各种各样的细胞外基质蛋白,但也能加工许多生物活性分子。本领域技术人员在Eckard等人(2016)中找到关于基质金属蛋白酶及其裂解位点的足够使能信息,其内容通过引用并入本文。

[0152] 通常,本领域技术人员能够通过常规考虑和参考文献,选择与相应哺乳动物酶匹配的特定裂解位点,以控制蛋白质毒素或原毒素的靶特异性释放。发现这些裂解位点的一般指南是例如在Rawlings(2016)中公开。

[0153] 根据本发明的一个实施方案,所述蛋白质毒素或原毒素是天然蛋白质毒素的去免疫化变体。通过序列修饰使蛋白质毒素去免疫化的重组方法在例如Schmohl等人(2015)或Grinberg和Benhar(2017)中公开,其内容通过引用并入本文。

[0154] 在一个实施方案中,所述蛋白质毒素或原毒素对植物或植物细胞无毒性。本领域技术人员手头有一堆常规方法来检查是否满足这个条件。见例如Klaine和Lewis(1995)的概述,其内容通过引用并入本文。

[0155] 根据本发明的一个实施方案,所述蛋白质包含至少一种植物特异性N-聚糖。N-聚糖是与蛋白质中天冬酰胺(Asn)残基的酰胺基团连接的聚糖,主要是Asn-X-Thr或Asn-X-Ser(NXT或NXS)基序,其中X是除脯氨酸之外的任何氨基酸。Gomord等人(2010)公开典型的植物特异性N-聚糖,并且与哺乳动物N-聚糖模式有显著差异。

[0156] 在这方面,重要的是要强调由植物产生的N-聚糖与例如哺乳动物等产生的N-聚糖明显不同。特别是,烟草植物产生的N-聚糖具有:

[0157] • 岩藻糖残基通过α3糖苷键(而不是哺乳动物中的α6)与近端N-乙酰氨基葡萄糖残基缀合,

[0158] • 木糖残基通过β2糖苷键与近端甘露糖残基缀合,

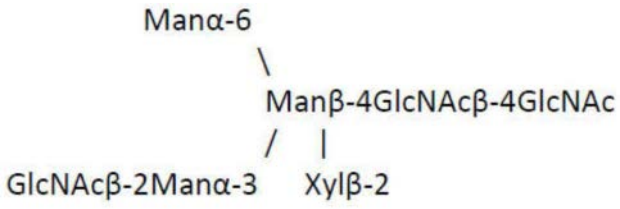
[0159] • 两个远端N-乙酰氨基葡萄糖残基,每个残基通过α3糖苷键携带岩藻糖残基,以及通过β3糖苷键携带半乳糖残基(而不是哺乳动物中的神经氨酸)。

[0160] 另一方面,在例如藻类中重组表达的蛋白质通常缺乏任何一种糖基化。然而,藻类能够表达IgG型抗体,或具有一个或多个二硫键桥的抗体片段。

[0161] 经鉴定的主要的基于植物的糖型是复合型聚糖(GnGn/GnGnXF)。也可以检测其它糖型(Man5-Man9、GnGnF、GnGnX、MMXF、Man5Gn和GnM(X)(F))。

[0162] 根据这一命名法,MGnX意味着例如:

[0163]



[0164] WO2020169620中提供分析肽糖型的方法的背景，为了实现目的将其内容并入本文。

[0165] 根据本发明的另一个方面，提供至少包含根据上文描述的结合剂-毒素融合蛋白的药物组合物，其任选地包含一种或多种药学上可接受的赋形剂。

[0166] 根据本发明的另一个方面，提供一种组合，其包含(i)根据上文描述的结合剂-毒素融合蛋白或药物组合物，和(ii)一种或多种另外的治疗活性化合物。

[0167] 根据本发明的另一个方面，提供根据上文描述的结合剂-毒素融合蛋白、组合物或组合，(用于制备药物，所述药物)用于治疗人或动物对象或用于预防人或动物对象以下病况，所述对象：

[0168] • 患有，

[0169] • 处于发生危险，和/或

[0170] • 经诊断为

[0171] 发生赘生性疾病。

[0172] 根据本发明的另一个方面，提供了一种治疗人类或动物对象或预防人类或动物对象以下病况的方法，所述对象：

[0173] • 患有，

[0174] • 处于发生危险，和/或

[0175] • 经诊断为

[0176] 发生赘生性疾病，所述方法包括施用治疗有效量的根据上文描述的结合剂-毒素融合蛋白、组合物或组合。

实施例

[0177] 虽然本发明已在附图和前面的描述中详细进行了示例说明和描述，但这种示例说明和描述应被视为说明性或示例性而非限制性的；本发明不限于所公开的实施方案。通过对附图、公开内容和所附权利要求的研究，本领域技术人员在实践要求保护的发明时可以理解和实现对所公开的实施方案的其它变型。在权利要求中，“包含”一词不除外其它元件或步骤，不定冠词“一”或“一个”不除外复数。某些措施在相互不同的从属权利要求中叙述的事实并不表明这些措施的组合不能被有利地使用。权利要求中的任何参考标记不应被解释为限制范围。

[0178] 本文公开的所有氨基酸序列均是从N-末端至C-末端显示；本文公开的所有核酸序列均显示为5'->3'序列。

[0179] 所述实施例基于使用HPRNAse和Anisoplin以及其它一些毒素进行的实验。然而，所述实验方案也适用于属于或接近那些家族的其它毒素。

[0180] 所述实施例基于使用弗林蛋白酶可裂解接头进行的实验。但是，所述实验方案适

用于对哺乳动物酶敏感的其它序列。

[0181] 材料和方法

[0182] 遗传构建体结合剂-毒素融合体

[0183] 全长利妥昔单抗(Rituximab)HC和LC序列已用于开发基于mAb的结合剂-毒素融合蛋白。利妥昔单抗序列的重链和轻链的可变部分序列已组装成单链scFv并与人IgG1Fc部分序列融合。然后使用人弗林蛋白酶裂解序列在全长利妥昔单抗的LC或HC的C端部分融合α八叠球菌素(Sarcin)序列与scFv-Fc的C端部分以获得HC+LC-FCS-α八叠球菌素、HC-FCS-α八叠球菌素+LC和scFv-c-FCS-α八叠球菌素融合蛋白序列。另一种结合剂-毒素融合蛋白实现scFv-Fc部分与α八叠球菌素连接而不用裂解位点,以获得scFv-Fc-α八叠球菌素。这些序列是通过两侧带有XbaI和IsceI的基因合成法产生的。

[0184] 包含抗体的遗传构建体

[0185] 全长HC和LC抗体序列已用于开发基于抗体的结合剂-毒素融合蛋白。未公开序列的重链和轻链的可变部分序列已组装在单链scFv中并与人IgG1 Fc部分序列融合。然后分别用人弗林蛋白酶裂解序列将人Anisoplin序列融合到全长未公开抗体的LC或HC或两者的C端部分或scFv-Fc的C端部分,以获得HC+LC-FCS-Anisoplin、HC-FCS-Anisoplin+LC和scFv-Fc-FCS-Anisoplin或scFv-Fc-Anisoplin融合蛋白序列。另一种结合剂-毒素融合蛋白是用scFv-Fc、HC、LC部分与Anisoplin连接而不用裂解位点实现的,以获得scFv-Fc-Anisoplin、HC+LC-Anisoplin、HC-Anisoplin+LC、LC-Anisoplin+HC-Anisoplin。这些序列是通过两侧带有XbaI和IsceI的基因合成法产生的。

[0186] 在本氏烟草(Nicotiana benthamiana)植物叶中瞬时表达

[0187] 将本氏烟草(Nicotiana benthaminana)在16小时光照/8小时黑暗的光循环、22+/-3℃下生长。将7至8周龄的植物叶子通过渗入注射器进行瞬时转化。通过以3500g离心10分钟收集根癌农杆菌(Agrobacterium tumefaciens)GV3101(pMP90RK),所述根癌农杆菌携带未公开的质粒,该质粒含有在600nm光密度(OD_{600})达到约0.8-1.0的遗传构建体。最后,在渗入缓冲液(10mM $MgCl_2$、10mM MES、100μM乙酰丁香酮,pH 5.6)中将细菌调整至OD_{600}为0.5,并使用无针注射器渗入所述混合物。在农杆菌渗入后4天和6天收获渗入区域。在农杆菌渗入后4天收获的整片叶子用于蛋白质A纯化。

[0188] 在普通烟草(N.tabacum)细胞中表达

[0189] 如Nagata等人(1992)所述,将普通烟草(Nicotiana tabacum)植物悬浮细胞在植物培养基中以130rpm、25℃生长5天,所述文章内容并入本文。通过以2000g离心5分钟收集根癌农杆菌(Agrobacterium tumefaciens)LBA4404(pBBR1MCS-5.virGN54D),所述根癌农杆菌携带在600nm光密度(OD_{600})达到约0.8-1.0的pPZP-ATB双元质粒。然后将植物细胞和细菌细胞在共培养培养基中共培养30分钟,然后以2000g离心5分钟。去除上清液后,将细胞铺板在固体共培养培养基上两天。在瞬时转化的情况下,然后收集细胞并洗涤3次,并在收获用于进一步分析之前在含有头孢噻肟和羧苄青霉素的植物培养基中培养。在稳定转化的情况下,在固体共培养2天后,洗涤细胞并铺板在含有选择性卡那霉素及头孢噻肟和羧苄青霉素抗生素的植物培养基上。4周后选择愈伤组织并在固体培养基或液体悬浮培养物中传代培养用于后续分析。

[0190] 蛋白质分析:ELISA、SDS-PAGE和Western印迹

[0191] 收集的叶组织(120mg)在400μL提取缓冲液(250mM山梨糖醇,60mM Tris Na_2EDTA,0.6% Polyclar AT,pH8.0)中研磨。将匀浆组织在4℃以18200g离心40分钟。然后回收上清液,在液氮中冷冻并储存在-20℃。

[0192] 通过Western印迹分析提取的组织。将蛋白质在还原或非还原SDS加样缓冲液(80mM Tris-HCl,pH 6.8,2% SDS,10%甘油,0.005%溴酚蓝)中煮沸5分钟,以13 000rpm离心5分钟并通过SDS-PAGE分离(4-20%聚丙烯酰胺)。对于Western印迹,使用半干电泳装置(Biorad Trans-Blot Turbo)将蛋白质电转移到PVDF膜(Biorad)上;然后将膜在室温下用在TBST缓冲液(50mM Tris-HCl,150mM NaCl,0.5% Tween 20,pH 7.5)中的3%(w/v)脱脂奶粉封闭1小时,然后与1:10.000稀释的HRP缀合的抗人IgG Fc特异性区域的抗体(A0170;Sigma-Aldrich)或与1:10.000稀释的抗Alpha Sarcin一抗(内部试剂,抗八叠球菌素兔血清,用来自Santa Cruz CAS 86243-64-3的α-八叠球菌素免疫的兔)在室温下温育(TBS-Tween 0.1%+0.5%脱脂奶粉)1小时。抗α-八叠球菌素/HPRnase抗体之后是稀释度为1:10000的HRP缀合的抗兔抗体(0545;Sigma)。通过增强化学发光(Amersham Imager 600/GE;GE Healthcare)检测蛋白质。

[0193] 抗CD79b ELISA

[0194] 对于特异于CD79b的缀合物的特异性分析,通过96孔微孔板(Greiner)分析包含针对CD79b的结合剂的纯化的结合剂-毒素融合蛋白。将所述孔用50μl抗原CD79b(2.5μg/mL)在37℃下包被1小时,然后用250μL洗涤缓冲液(PBS Tween 0.1%)洗涤5次。然后用150μL氢化酪蛋白(hydrocasein)(3.6%)在PBST中在室温下封闭30分钟,然后洗涤5次。加样50μL抗抗原对照抗体以获得在5和0μg/mL之间的校准曲线,并将50μL样品加样到相同的96孔板上在室温下封闭1小时、然后洗涤5次以进行比较。加样50μL的1/200.000稀释的检测抗体(山羊抗人HRPO,Bethyl)并在室温下温育1小时。然后用50μL TMB反应缓冲液(Zentech)进行显示15分钟,最后用1M H_3PO_4停止。然后在450nm通过光谱法分析酶活性。结果如图4B所示。

[0195] 蛋白质A纯化

[0196] 在农杆菌渗入后四天,收集叶子、称重,并在混料器中使用2mL提取缓冲液(250mM山梨糖醇,60mM Tris Na_2EDTA,0.6% Polyclar AT,pH8.0)/克新鲜农杆菌渗入叶子研磨。然后通过双层Miracloth(Millipore)层过滤所述混合物。然后将滤液在4℃以20.000g离心30分钟。然后将上清液加样到用提取缓冲液预平衡的蛋白质A树脂上。然后用10柱体积的60mM Tris pH8.0洗涤树脂,并使用直接用10% Tris 1M pH8.0缓冲的100mM甘氨酸pH3.0进行洗脱。然后收集富集的蛋白质级分并在液氮中冷冻。

[0197] 体外细胞毒性测定

[0198] 使用Cell Titer Glo Assay(Promega,G9241)评估结合剂-毒素融合蛋白对表达CD20或CD79b的细胞系活力的影响。在这个测定中,在Mg^{2+}和ATP存在下,通过荧光素酶催化荧光素的单氧化。这个反应产生与活细胞数量成正比的发光信号。

[0199] 根据测试的细胞系,将细胞以2000或5000个细胞/孔的密度接种在96孔板的空腔中的50μl生长培养基(RPMI1640)中。通过将10μl结合剂-毒素融合体或缓冲液(PBS,Tween 0.02%)加入40μl生长培养基中,制备结合剂-毒素融合体的系列稀释液。将所述混合物加入细胞中并在37℃和5% CO_2条件下温育72小时。一式两份测试结合剂-毒素融合体。缓冲液作为阴性对照,培养基和细胞分别仅作为空白和未处理的对照。

[0200] 72小时后,将板在室温下平衡30分钟,并向每个孔中加入100μl CellTiter Glo试剂。随后将板置于摇动平台上2分钟,然后使信号在室温在黑暗中稳定10分钟。然后记录发光。

[0201] 为确定存活力百分比,从每个孔中减去空白(仅生长培养基)的平均发光信号,并将未处理细胞的平均发光信号设为100%存活率。然后将处理的细胞的平均信号标准化并绘制与ATB浓度成函数的图。

[0202] 在靶细胞WSU-NHL(CD20+)和非靶细胞K562(CD20-)上评估基于抗CD20的结合剂-毒素融合蛋白。

[0203] 在靶细胞JEKO、OCY-LY3、BJAB和WSU-DLCL2(CD79+)及非靶细胞K-562(CD79-)上评估基于抗CD79b的结合剂-毒素融合蛋白。

[0204] 体内测定:急性毒性

[0205] 为了证实结合剂-毒素融合体在动物中的安全性,对20g雌性NOG小鼠(Taconic)进行急性毒性研究。将未公开的抗体sc-Fv-Fc-α八叠球菌素(125)、单独的α八叠球菌素和sc-Fv-Fc(86,作为对照)分别以20mg/kg、4.9mg/kg和15mg/kg经静脉注射。注射后连续8天每天测量体重。所述研究由EPO Experimentelle Pharmakologie&Onkologie Berlin-Buch GmbH使用ATB Therapeutics提供的材料进行。

[0206] 肽糖型分析

[0207] WO2020169620中提供了用于分析肽糖型的方法的背景,为了实现目的将其内容并入本文。

[0208] 裂解测定

[0209] 在纯化的scFv-Fc-FCS-α八叠球菌素、scFv-Fc-α八叠球菌素或HPRNAse(结合剂-毒素融合蛋白)上加入重组弗林蛋白酶后,已在体外证明使毒素释放的可裂解性。在将1μl的25单位/ml弗林蛋白酶(NEB P8077S)与微克的结合剂-毒素融合蛋白加入15μl裂解缓冲液(醋酸钠1M pH 5.5+10mM $CaCl_2$)中后,在37℃进行反应4小时。通过SDS Page考马斯蓝凝胶(4-20%聚丙烯酰胺)观察到裂解。

[0210] CHO瞬时表达

[0211] 为了对照目的,在CHO细胞中也表达一些构建体414、301、452、221和125。这是在Evitria使用常规(非基于PCR的)克隆技术开发的载体系统中完成的。evitria载体质粒是基因合成的。基于阴离子交换层析,在低内毒素条件下制备质粒DNA。通过测量260nm波长处的吸光度来确定DNA浓度。使用Sanger测序验证序列的正确性(每个质粒最多有两个测序反应,具体取决于cDNA的大小。)

[0212] 使用悬浮适应的CHO K1细胞(最初从ATCC获得并使其适应在Evitria的悬浮培养中无血清生长)用于生产。将种子在eviGrow养基中生长,eviGrow培养基是一种化学成分确定、不含动物组分、无血清的培养基。用Evitria定制的专有转染试剂eviFect转染细胞,并在转染后将细胞在不含动物组分、无血清的eviMake2培养基中生长。

[0213] 通过离心和随后的过滤(0.2pm过滤器)收获上清液。

[0214] 使用MabSelect SuRe(Cytivia)纯化抗体。

[0215] 结果

[0216] 已经构建了几种基于scFv-Fc形式的重组结合剂-毒素融合蛋白:scFv-Fc-FCS-

Anisoplin,scFv-Fc-Anisopin,scFv-Fc-FCS-HPRNAse,scFv-Fc-HPRNAse,scFv-Fc-FCS-α八叠球菌素,scFv-Fc-α八叠球菌素,scFv-Fc-FCS-α八叠球菌素同系物,scFv-Fc-α八叠球菌素同源物,scFv-Fc-FCS-HPRNAse同源物,及scFv-Fc-HPRNAse同源物。基于全长mAb的结合剂-毒素融合蛋白已用Anisoplin、HPRNAse和α八叠球菌素构建:HC+LC--Anisoplin、HC-Anisoplin或LC、HC-Anisoplin+LC Anisoplin、LC+HC-FCS-Anisoplin或HPRNAse或α八叠球菌素。还构建单独未缀合的mAb作为对照。

[0217] 细胞活力测定

[0218] 已在癌细胞系上评估纯化的结合剂-毒素融合体的细胞毒性。所有结合剂-毒素融合体均已显示损伤阳性细胞系的活力。此外,我们证实优于靶向相同抗原的市售ADC(Polivy®,包含与MMAE连接的第一人源化抗CD79b抗体(泊洛妥珠单抗(Polatuzumab)),如US8545850中所公开)的优越性(见425和507)。此外,上述结合剂-毒素融合蛋白对阴性细胞系的影响非常低(见425和125)。

[0219] 结合剂-毒素融合蛋白对靶阴性原代细胞HUVEC和HEP2无害,对癌细胞确定具有高效作用。

[0220] 急性毒性

[0221] 当以较高剂量(4.91mg/kg)注射时,核糖体毒素α八叠球菌素在小鼠中表现出良好的耐受性。基于核糖体毒素的结合剂-毒素融合体,与单独的核糖体毒素相比,对癌细胞具有很高的活性,动物模型耐受性良好,因为IV注射20mg/kg的结合剂α八叠球菌素不会引发任何急性毒性迹象。

[0222] CHO瞬时表达

[0223] 结果表明,构建体414、301、452、221和125实际上也可以在CHO细胞中产生,尽管产量要显著更低。

[0224] 例如,相对于烟草属实验,构建体452的产量在CHO实验中低14-15倍。构建体452在抗体和毒素之间有一个G4S接头,其不能被哺乳动物蛋白酶裂解。然而,不受理论的束缚,CHO中较低产量的一个原因可能是CHO中发生的自发裂解和部分自我中毒,但在植物如烟草属中没有发生。

[0225] 构建体22具有弗林蛋白酶可裂解接头(Fpe),并且在CHO中的表达相对于烟草属同样减少。

[0226]

构建体	哺乳动物细胞可裂解的接头?	CHO vs 烟草属中产量的相对降低
221 (Fpe-SA)	是(Fpe)	7-8 倍
301 (G4S-ANI)	否	8.5-9.5 倍
452 (全长-G4S-ANI)	否	14-15 倍

[0227] 仍然可以证明,在CHO中产生的构建体221(具有弗林蛋白酶可裂解接头,Fpe)以IC_{50}为0.2595nM对阳性细胞系以剂量依赖性方式降低细胞活力。具有不可裂解的G4S接头的构建体125,以IC_{50}为0.7792nM对阳性细胞系以剂量依赖性方式降低细胞活力。

[0228] 实验结果概述

[0229] 实验结果在下表中概述。

[0230]

图	实验类型	抗体靶位	抗体形式	接头	毒素	生产系统	细胞	构建体编号	发现
2	存活力测定	CD20	sc-Fv-FC	G4S	八叠球菌素	烟草属	WSU-NHL	206	ATB 206 以剂量依赖的方式降低细胞活力，IC_{50} 为 0.03669 nM。
3		CD79b	sc-Fv-FC	G4S	八叠球菌素	烟草属	CD79b + (JEKO) 和 - (K-562)	86 和 125	ATB 125 对阳性细胞系以剂量依赖的方式降低细胞活力，其 IC_{50} 为 0.3669 nM，而单独的 α-八叠球菌素只在较高的剂量下有活性，其 IC_{50} 为 565 nM。对于阴性细胞系，ATB 125 没有活性，而我们观察到单独 α-八叠球菌素在较高剂量下对阳性细胞系有作用。
4		CD79b	sc-Fv-FC	Liop	八叠球菌素	烟草属	CD79b + (BJAB) 和 - (K-562)	222	ATB 222 对阳性细胞系以剂量依赖的方式降低细胞活力，其 IC_{50} 为 0.000058 nM，而单独的 α-八叠球菌素仅在较高剂量下具有活性，IC_{50} 为 1.143 nM。对于阴性细胞系，ATB 222 没有活性，而我们观察到单独的 α-八叠球菌素在较高剂量下有活性，IC_{50} 为 205.3 nM。
5		CD79b	sc-Fv-FC	Fpe	八叠球菌素	烟草属	CD79b + (JEKO)	221	ATB 221 对阳性细胞系以剂量依赖的方式降低细胞活力，IC_{50} 为 0.1405 nM。
6		CD79b	sc-Fv-FC	Fdt	八叠球菌素	烟草属	CD79b + (JEKO)	229	ATB 229 对阳性细胞系以剂量依赖的方式降低细胞活力，IC_{50} 为 0.06368 nM。

[0231]

7	CD79b	全长IgG	G4S 2x RRKR	八叠球菌素	烟草属	CD79b + (JEKO)	323	ATB 323 对阳性细胞系以剂量依赖的方式降低细胞活力，IC_{50}为 0.1601 nM。
8	CD79b	sc-Fv-FC	G4S	Ageritin	烟草属	CD79b + (JEKO)	304	ATB 304 对阳性细胞系以剂量依赖的方式降低细胞活力，IC_{50}为 0.2807 nM。
9	CD79b	sc-Fv-FC	G4S	Hirsutelin A	烟草属	CD79b + (JEKO)	302	ATB 304 对阳性细胞系以剂量依赖的方式降低细胞活力，IC_{50}为 1.107 nM。
10	CD79b	sc-Fv-FC	G4S	Anisoplin	烟草属	CD79b + (JEKO)	301	ATB 301 对阳性细胞系以剂量依赖的方式降低细胞活力，IC_{50}为 0.1032 nM。
11	CD79b	sc-Fv-FC	Liop	Anisoplin	烟草属	CD79b + (JEKO)	466	ATB 466 对阳性细胞系以剂量依赖的方式降低细胞活力，IC_{50}为 0.0005326 nM。
12	CD79b	sc-Fv-FC	Fpe	Anisoplin	烟草属	CD79b + (JEKO)	467	ATB 467 对阳性细胞系以剂量依赖的方式降低细胞活力，IC_{50}为 0.08602 nM。
13	CD20	全长IgG	G4S	Anisoplin	烟草属	WSU-NHL	676	ATB 676 对阳性细胞系以剂量依赖的方式降低细胞活力，IC_{50}为 0.03760 nM。
14	CD20	全长IgG	Liop	Anisoplin	烟草属	WSU-NHL	680	ATB 680 对阳性细胞系 WSU-NHL 以剂量依赖的方式降低细胞活力，IC_{50}为 0.01906 nM。
15	CD79b	全长	G4S	Anisoplin	烟草属	CD79b +	452	ATB 452 对阳性细胞系以剂量依赖的方式降低细胞活

[0232]

		IgG	oplin		(BJAB) 和 -(K-562)		力，IC_{50} 为 0.00003325 nM，与市售的识别相同抗原的抗体药物缀合物(泊洛妥珠单抗(Polatuzumab))相比，效力好 3000 倍。ATB 452 和基准抗体药物缀合物不降低阴性细胞系的存活力。
16	CD79b	全长 IgG	G4S Anisoplin	烟草属	CD79b + (JEKO) 和 -(K-562)	452	ATB 452 对阳性细胞系以剂量依赖的方式降低细胞活力，其 IC_{50} 为 0.01507 nM，与识别相同抗原的市售抗体药物缀合物相比，效力提高了 4.5 倍。单独使用 anisoplin 不会引起阳性细胞系的任何活力下降。ATB 452、单独 anisoplin 和基准抗体药物缀合物不降低阴性细胞的存活力。
17	CD79b	全长 IgG	G4S Anisoplin	烟草属	CD79b + (BJAB) 和 -(K-562)	452	ATB 452 对阳性细胞系以剂量依赖的方式降低细胞活力，IC_{50} 为 0.00003325 nM，而对阴性细胞系不产生细胞毒性。
18	CD79b	全长 IgG	G4S Anisoplin	烟草属	CD79b + (OCY-LY3) 和 -(K-562)	452	ATB 452 对阳性细胞系以剂量依赖的方式降低细胞活力，IC_{50} 为 0.05866 nM，而对阴性细胞系不产生细胞毒性。
19	CD79b	全长 IgG	G4S Anisoplin	烟草属	Huvec/HepG2	452	ATB 452，用不可裂解接头与核糖体毒素的全长 mab 融合体，被人内皮细胞(HUVEC)和人肝脏细胞(HEP-G2)良好耐受。

[0233]

20		CD79b	全长IgG	Liop	Anisoplin	烟草属	CD79b + (JEKO)	507	ATB 507 对阳性细胞系以剂量依赖的方式降低细胞活力，IC_{50}为0.02582 nM。
21		CD79b	全长IgG	Liop	Anisoplin	烟草属	Huvec/Hepg2	507	ATB 507，用可裂解接头与核糖体毒素的全长 mab 融合体，被人内皮细胞(HUVEC)和人肝脏细胞(HEP-G2)良好耐受。
22		CD79b	全长IgG	Fpe	Anisoplin	烟草属	CD79b + (JEKO)	508	ATB 508 对阳性细胞系以剂量依赖的方式降低细胞活力，其IC_{50}为0.1573 nM。
23		CD79b	全长IgG	G4S	Anisoplin	烟草属	CD79b + (JEKO)	509	ATB 509 对阳性细胞系以剂量依赖的方式降低细胞活力，IC_{50}为0.02870 nM。
24		CD79b	全长IgG	G4S	Anisoplin	烟草属	CD79b + (JEKO)	536	ATB 536 对阳性细胞系以剂量依赖的方式降低细胞活力，IC_{50}为0.03743 nM。
25	凝胶	CD79b	sc-Fv-FC	G4S	Anisoplin同源物ONC2	烟草属	n/a		
26	存活力测定	CD79b	sc-Fv-FC	G4S	Anisoplin同源	烟草属	CD79b + (JEKO)	495	ATB 495 对阳性细胞系以剂量依赖的方式降低细胞活力，其IC_{50}为0.3263 nM。

[0234]

27		CD79b	sc-Fv-FC	G4S	Anis oplin 同源物 2	烟草属	CD79b + (JEKO)	496	ATB 496 对阳性细胞系以剂量依赖的方式降低细胞活力，其 IC_{50} 为 0.5317 nM。
28		CD79b	sc-Fv-FC	G4S	Anis oplin 同源物 3	烟草属	CD79b + (JEKO)	497	ATB 497 对阳性细胞系以剂量依赖的方式降低细胞活力，IC_{50} 为 0.1377 nM。
29	裂解测定	CD79b (八叠球菌素) n/d (hPRNase)	sc-Fv-FC	G4S (任选地 RRK RAS)	八叠球菌素或 hpRNase 1	烟草属	n/a	125, 222 和 48	弗林蛋白酶裂解实验表明，当接头是可裂解的(222 和 48)时，有效载荷，无论是 α-八叠球菌素还是 HPRNAse，在加入弗林蛋白酶(+)后都会从抗体中释放出来，而不可裂解的接头(125)即使暴露在弗林蛋白酶中也会阻止有效载荷释放。
30	毒性研究	CD79b	sc-Fv-FC	G4S	八叠球菌素	烟草属	n/a	125 (86 w/o 毒素)	静脉注射单独的 α 八叠球菌素(绿色)、未公开的 sc-Fv-Fc(蓝色)、未公开的 sc-Fv-Fc-α 八叠球菌素(红色)后 8 天的平均体重变化百分比。平均体重变化不超过 6%，说明基于核糖体毒素的结合剂-毒素融合具有良好的耐受性。

[0235]

31	Elisa	CD79b	sc-Fv-FC	G4S	八叠球菌素	烟草属	n/a	125 (86 w/o 毒素)	有效载荷的存在并不改变抗体对同一包被抗原的结合。
32	存活力测定	CD79b	sc-Fv-FC	G4S	hpRNase 1	烟草属	CD79b + (WSU-DLCL2)	96	ATB 96 对阳性细胞系以剂量依赖的方式降低细胞活力，IC_{50}为 9.044 nM。
33	凝胶	CD79b	sc-Fv-FC	G4S	hpRNase 1	烟草属		92 和 63	
34	存活力测定	CD79b	sc-Fv-FC	G4S	Angiogenin	烟草属	CD79b + (JEKO)	228	ATB 228 对阳性细胞系以剂量依赖的方式降低细胞活力，IC_{50}为 0.160 nM。
35	凝胶	CD79b	sc-Fv-FC or 全长 IgG	G4S	八叠球菌素或 Anisoplin	CHO	n/a	414, 301, 452	
36	存活	CD79b	sc-Fv-	Fpe	八叠	CHO	CD79b +	221 和 125	ATB 221 对阳性细胞系以剂量依赖的方式降低细胞活

[0236]

	力测定		FC		球菌素		(JEKO)	力，其 IC_{50} 为 0.2595 nM。ATB 125 对阳性细胞系以剂量依赖的方式降低细胞活力，其 IC_{50} 为 0.7792 nM。在 CHO 中的生产产量非常小，可能是由于宿主酶对 Fpe 接头的部分裂解和导致自我中毒所致。
37	凝胶	n/d	IgG		hpR Nase 1	烟草属	n/a	

[0237] 定义

[0238] 如本文所用，“序列相同性百分比”是通过在比较窗口中比较两个最佳比对的生物

序列(氨基酸序列或多核苷酸序列)来确定的,其中比较窗口中相应序列的部分与不包含添加或缺失的参考序列相比可以包含添加或缺失(即,缺口),以实现两个序列的最佳比对。百分比计算是通过确定两个序列中出现相同核酸碱基或氨基酸残基的位置数以产生匹配位置数,将匹配位置数除以比较窗口中的位置总数,并将结果乘以100得到序列相同性的百分比。

[0239] 在两个或更多个核酸或多肽序列的上下文中,术语"相同的"或百分比"相同性"是指两个或更多个序列或子序列是相同的序列。如果在比较窗口或指定区域内进行最大限度的对应比较和比对时,使用下列序列比较算法之一或通过手动比对和目视检查测得两个序列的氨基酸残基或核苷酸有一定百分比的相同(即在指定区域内或者当没有指定时在参考序列的整个序列上至少有85%、90%、95%、96%、97%、98%或99%的序列相同性),则两个序列是"基本相同的"。本公开提供与本文示例的多肽基本相同的多肽。关于氨基酸序列,相同性或基本相同性可存在于长度为至少5、10、15或20个氨基酸、任选地长度为至少约25、30、35、40、50、75或100个氨基酸、任选地长度为至少约150、200或250个氨基酸、或参考序列全长的区域。对于较短的氨基酸序列,例如20个或更少氨基酸的氨基酸序列,根据本文定义的保守取代,当一个或两个氨基酸残基被保守取代时存在基本相同性。

[0240] 术语"蛋白质毒素"或"蛋白质原毒素(protoxin)"指的是但不限于根据其化学性质属于蛋白质(即长度≥50个氨基酸残基的肽)或多肽(即长度为≥10个至≤50个氨基酸残基)的毒素。在本发明的意义上,原毒素是毒素的前体,也称为潜毒素,其需要被激活,例如,通过裂解抑制性氨基酸序列或通过经历构象变化而激活。术语"原毒素"和"蛋白质原毒素"在本文可互换使用,是指相同的主题。

[0241] 如本文所用,术语"融合蛋白"是指具有可操作地连接至至少一种额外组分的肽组分并且在其结构域的组成和/或组织方面不同于天然蛋白质的蛋白质。

[0242] 本文所用的术语"可操作地连接"当指两个或更多个多核苷酸时,是指不同的多核苷酸彼此处于功能关系中的情况。例如,如果启动子实现编码序列的转录,则启动子与编码序列可操作地连接。同样,如果信号肽实现多肽的细胞外分泌,则信号肽的编码序列与多肽编码序列可操作地连接。根据本发明的一个实施方案,当各多核苷酸编码不同的肽时,"可操作地连接"是指各多核苷酸是连续的,并且在需要连接两个蛋白质编码区时,开放阅读框是对齐的。

[0243] 本文所用的术语"可裂解肽接头"是指融合蛋白内的内部氨基酸序列,其含有连接结合部分和毒素蛋白的残基,以使毒素蛋白不能在靶细胞外发挥其毒性作用或限制毒素蛋白抑制细胞生长(细胞停滞)或导致细胞死亡(细胞毒性)的能力。通过这种方式,只要蛋白质毒素在血浆中,它就会保持无活性,直到它到达靶细胞,在靶细胞细胞毒性有效载荷将被选择性释放和/或激活(Grawunder&Stein,2017)。在靶细胞内,可裂解接头序列被裂解,毒素蛋白变成活性或毒性的。本发明的融合蛋白包含细胞特异性结合部分和蛋白质毒素部分,这两部分通过特定氨基酸残基或氨基酸序列连接,所述氨基酸残基或氨基酸序列具有特定蛋白酶特别是但不限于癌症特异性蛋白酶的裂解识别位点,和/或在特定条件下是可裂解的,例如但不限于酸和/或还原条件。编码特定蛋白酶的裂解识别位点的序列可以在已知的遍在人蛋白酶中和/或通过测试癌症相关蛋白酶的表达来鉴别。此外,接头序列不应干扰结合部分在细胞结合和内化到溶酶体中的作用。

[0244] 术语原毒素的“可裂解结构域”涉及这样的序列，一旦被水解或酶促裂解而裂解，则激活原毒素的毒素部分。许多原毒素具有被酶特异性裂解或通过pH依赖性水解(例如在内体中的内吞作用后)特异性裂解的氨基酸结构域，以便将活性毒素部分释放到胞质溶胶中。这种可裂解结构域兼作“天然存在的”可裂解肽接头(或“固有裂解位点”)，这与在毒素不包含用于激活的可裂解结构域的情况下必须使用的可裂解肽接头相反，例如，因为它不是原毒素。

[0245] 因此，虽然可裂解接头在活性谱方面比稳定接头具有明显优势，但其使用使得在哺乳动物、昆虫和酵母细胞中相应的结合蛋白-毒素缀合物的生产复杂化，因为接头的裂解会导致生产系统自我中毒。然而，这不适用于以植物为基础的生产系统，因为

[0246] (i)其不裂解接头(由于缺乏相应的蛋白酶或还原/水解条件)和/或

[0247] (ii)对哺乳动物或哺乳动物细胞有毒的相应蛋白质毒素对植物或植物细胞无毒。

[0248] 如本文所用，术语抗体应指具有同质抗体群体的抗体组合物，即，包含完整免疫球蛋白或其保留靶结合能力的片段或衍生物的同质群体。

[0249] 特别优选地，此类抗体是IgG抗体，或其保留靶结合能力的片段或衍生物。免疫球蛋白G(IgG)是一种抗体类型。IgG约占人类血清抗体的75％，是血液循环中最常见的抗体类型。IgG分子由浆B细胞产生和释放。每个IgG都有两个抗原结合位点。

[0250] IgG抗体是包含4条肽链的分子量约为150kDa的大分子。它包含两条相同的约50kDa的γ类重链和两条相同的约25kDa的轻链，因此是四聚体四级结构。两条重链通过二硫键相互连接并各自连接至一条轻链。由此产生的四聚体有两个相同的一半，它们一起形成Y形。Y形的每一端都包含一个相同的抗原结合位点。IgG的Fc区带有一个高度保守的N-糖基化位点。连接到该位点的N-聚糖主要是复杂类型的核心-岩藻糖基化双触角结构。此外，少量这些N-聚糖也带有二等分GlcNAc和α-2,6-连接的唾液酸残基。

[0251] 人类有四种IgG亚类(IgG1、2、3和4)，按其在血清中的丰度顺序命名(IgG1是丰度最大的)。

[0252] 如本文所用，术语“抗体片段”应指此类抗体的保留靶结合能力的片段，例如

[0253] • CDR(互补决定区)，

[0254] • 高变区，

[0255] • 可变结构域(Fv)，

[0256] • IgG重链(由VH、CH1、铰链、CH2和CH3区域组成)，

[0257] • IgG轻链(由VL和CL区组成)，和/或

[0258] • Fab和/或F(ab)2。

[0259] 如本文所用，术语“衍生物”应指在结构上不同于常见抗体概念但仍具有一些结构关系的蛋白质构建体，例如scFv、scFv-FC、Fab和/或F(ab)2，以及双、三或更高特异性抗体构建体或单价抗体，并进一步保留靶结合能力。所有这些项目解释如下。

[0260] 本领域技术人员已知的其它抗体衍生物是双抗体、骆驼抗体、纳米抗体、结构域抗体、具有由scFv组成的两条链的二价同源二聚体、IgA(两个IgG结构通过J链和分泌组分连接)、鲨鱼抗体、由新世界灵长类动物构架加非新世界灵长类动物CDR组成的抗体、包含CH3+VL+VH的二聚化构建体以及抗体缀合物(例如连接到毒素、细胞因子、放射性同位素或标记的抗体或片段或衍生物)。这些类型在文献中有很好的描述，本领域技术人员可以在本公开

的基础上使用,并增加进一步的创造性活动。

[0261] 先前已经描述用于产生杂交瘤细胞的方法(参见Köhler和Milstein 1975,通过引用并入本文)。基本上,例如,用人可溶性鸟苷酸环化酶(sGC)蛋白免疫小鼠,然后从所述小鼠分离B细胞并将分离的B细胞与骨髓瘤细胞融合。

[0262] 用于生产和/或选择嵌合或人源化mAb的方法是本领域已知的。基本上,例如来自鼠抗sGC抗体的不参与靶结合的蛋白质序列被相应的人序列替换。例如,Genentech的US6331415描述嵌合抗体的生产,而Medical Research Council的US6548640描述CDR移植技术,Celltech的US5859205描述人源化抗体的生产。所有这些公开内容均通过引用并入本文。

[0263] 用于产生和/或选择全人mAb的方法是本领域已知的。这些可能涉及使用用人sGC免疫的转基因动物,或使用合适的展示技术,如酵母展示、噬菌体展示、B细胞展示或核糖体展示,其中针对处于稳定阶段的人sGC筛选文库中的抗体。

[0264] 在MorphoSys的US6300064和MRC/Scripps/Stratagene的US6248516等文献中公开体外抗体文库。噬菌体展示技术例如在Dyax的US5223409中公开。转基因哺乳动物平台例如在TaconicArtemis的EP1480515A2中描述。所有这些公开内容均通过引用并入本文。

[0265] IgG、scFv、scFv-FC、Fab和/或F(ab)2是本领域技术人员熟知的抗体形式。相关的实现技术可从相应教科书中获得。

[0266] 如本文所用,术语“Fab”涉及包含抗原结合区的IgG片段,所述片段包含来自抗体的每条重链和轻链的一个恒定域和一个可变域。

[0267] 如本文所用,术语“F(ab)2”涉及包含通过一个或多个二硫键彼此连接的两个Fab片段的IgG片段。

[0268] 如本文所用,术语“scFv”涉及单链可变片段,其是通过短接头连接在一起的免疫球蛋白重链和轻链的可变区的融合体,接头通常是丝氨酸(S)或甘氨酸(G)。这种嵌合分子保留原始免疫球蛋白的特异性,尽管去除恒定区并引入接头肽。

[0269] 如本文所用,术语“scFv-FC”涉及特异性抗体形式。这种形式特别稳定,并可以在植物细胞和植物中以高产量表达。scFv-FC构建体例如公开于Buja等人(2014),其内容通过引用并入本文。scFv-Fc构建体是二聚体构建体,包含例如通过一个或多个二硫键彼此缔合的两条链,其中每条链由如下结构组成(从N到C方向):

[0270] VL-接头-VH-接头-FC,或

[0271] VH-接头-VL-接头-FC,

[0272] 其中VL为抗体轻链可变结构域,VH为抗体重链可变结构域,以及FC为抗体恒定结构域。

[0273] 使用全长IgG形抗体或scFv-Fc结合结构域赋予缀合物更长的半衰期。此外,当需要激活CDC(补体依赖性细胞毒性)或ADCC(抗体依赖性细胞毒性)时,抗体的Fc部分可能最为重要。

[0274] 修饰的抗体形式例如是双特异性或三特异性抗体构建体、基于抗体的融合蛋白、免疫缀合物等。这些类型在文献中有很好的描述,以及本领域技术人员可以在本公开的基础上使用,并增加进一步的创造性活动。此外,单价抗体先前也已描述于US 2004/0033561A1(在其中称为monobodies)或WO2007048037;两者均通过引用并入本文。

[0275] 抗体模拟物是有机化合物-在大多数情况下是重组蛋白或肽-它们与抗体一样,可以特异性结合抗原,但在结构上与抗体无关。与抗体相比的常见优势是更好的溶解性、组织渗透性、对热和酶的稳定性以及相对较低的生产成本。抗体模拟物正在开发为治疗剂和诊断剂,尤其包括Affibody分子、Affilins、泛素、Affimers、Affitins、Alphabodies、Anticalins、Avimers、DARPins、Fynomers、Kunitz结构域肽、Monobodies和nanoCLAMP。抗体模拟物尤其在Gebauer and Skerra(2009)中进行了非常详细的讨论,该文献通过引用并入本文。

[0276] 通常,蛋白质结合剂(binder)可以由单链组成。例如,当蛋白质结合剂是scFv抗体或scFv-FC时就是这种情况。在这种情况下,整个蛋白质结合剂可以编码在单个多核苷酸上。

[0277] 在另一个实施方案中,蛋白质结合剂可包含两条或更多条链,例如在全长IgG或F(ab)2片段中。在这种情况下,可以规定核酸构建体可以包含两个或更多个编码蛋白质结合剂的不同链或结构域的多核苷酸。

[0278] 如本文所用,术语“植物”(包括源自其的细胞)涉及藻类(包括绿藻门(Chlorophyta)和轮藻门/链藻门(Charophyta/Streptophyta),以及中斑藻纲(Mesostigmatophyceae)、绿方藻纲(Chlorokybophyceae)和螺旋藻(Spirotaenia),并且还涉及陆生植物(有胚植物门(Embryophytes)),包括裸子植物和被子植物,包括单子叶植物和双子叶植物。

[0279] 如本文所用,术语“瞬时表达”是指在核酸(最常见的是编码表达盒的质粒DNA)被引入宿主细胞或植物后,基因在短时间内的临时表达。

[0280] 如本文所用,术语“稳定表达”涉及在核酸(最常见的是编码表达盒的质粒DNA)被引入宿主细胞的基因组(核或质体整合)后在时间上连续表达的基因表达。在稳定转染的细胞中,外源基因成为基因组的一部分,并因此被复制。

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[0307] 序列

[0308] 以下序列构成本申请的公开内容的一部分。这个申请也提供了WIPO ST 25兼容的电子序列表。为免生疑问,如果下表中的序列与电子序列表之间存在差异,则应认为本表中的序列是正确的。

[0309] 还要注意,在一些实施方案中,相应的氨基酸序列具有或不具有信号肽/前导肽。所有实施方案应被视为具有信号肽/前导肽以及没有信号肽/前导肽一起公开。

[0310] 还应注意,在一些实施方案中,所述毒素的相应氨基酸序列显示其去免疫化版本。所有实施方案都应被视为公开了野生型毒素序列或去免疫化变体。

[0311]

SEQ ID NO	抗体形式	构建体编号	序列
1	sc-Fv-FC	206	QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSS PKPWIYATSNLASGVPVRFSGSGSGTSYSLTISRVEAEDAAT YYCQQWTSNPPTFGGGTKLEIK ***GGGGSGGGGSGGGGS*** QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVK QTPGRGLEWIGAIYPGNGDTSYNQKFKGKATLTADKSSST AYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTT VTVSA ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSP ***GGGGS*** AVTWTCLNDQKNPKTNKYETKRLLYNQNKAESNSHHAPL SDGKTGSSYPHWFTNGYDGDGKLPKGRTPIKFGKSDCDRP PKHSKDGNGKTDHYLLEFPTFPDGHDYKFDSKKPKENPGP

[0312]

			ARVIYTYPNKVFCGIIAHTKENQGELKLCSH
2	sc-Fv-FC	125	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLT**C**LVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSP ***GGGGS*** AVTWTCLNDQKNPKTNKYETKRLLYNQNKAESNSHHAPL SDGKTGSSYPHWFTNGYDGDGKLPKGRTPIKFGKSDCDRP PKHSKDGNGKTDHYLLEFPTFPDGHDYKFDSKKPKENPGP ARVIYTYPNKVFCGIIAHTKENQGELKLCSH
3	sc-Fv-FC	222	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLT**C**LVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSPG ***HRRRKRSLDTS***

[0313]

			AVTWTCLNDQKNPKTNKYETKRLLYNQNKAESNSHHAPL SDGKTGSSYPHWFTNGYDGDGKLPKGRTPIKFGKSDCDRP PKHSKDGNGKTDHYLLEFPTFPDGHDYKFDSKKPKENPGP ARVIYTYPNKVFCGIIAHTKENQGELKLCSH
4	sc-Fv-FC	221	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLT**C**LVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSPG ***TRHRQPRGWEQL*** AVTWTCLNDQKNPKTNKYETKRLLYNQNKAESNSHHAPL SDGKTGSSYPHWFTNGYDGDGKLPKGRTPIKFGKSDCDRP PKHSKDGNGKTDHYLLEFPTFPDGHDYKFDSKKPKENPGP ARVIYTYPNKVFCGIIAHTKENQGELKLCSH
5	sc-Fv-FC	229	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLT**C**LVKGFYPSDIAVEW

[0314]

			ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSPG ***AGNRVRRSVG*** AVTWTCLNDQKNPKTNKYETKRLLYNQNKAESNSHHAPL SDGKTGSSYPHWFTNGYDGDGKLPKGRTPIKFGKSDCDRP PKHSKDGNGKTDHYLLEFPTFPDGHDYKFDSKKPKENPGP ARVIYTYPNKVFCGIIAHTKENQGELKLCSH
6	全 长 IgG	323, HC	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLT**C**LVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSP ***GGGGSGGGGS*** ***RRKR*** AVTWTCLNDQKNPKTNKYETKRLLYNQNKAESNSHHAPL SDGKTGSSYPHWFTNGYDGDGKLPKGRTPIKFGKSDCDRP PKHSKDGNGKTDHYLLEFPTFPDGHDYKFDSKKPKENPGP ARVIYTYPNKVFCGIIAHTKENQGELKLCSH
7		323, LC	QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSS PKPWIYATSNLASGVPVRFSGSGSGTSYSLTISRVEAEDAAT YYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
8	sc-Fv-FC	304	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL

			QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLT**C**LVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSP GGGGS AETVQYYNSYSDASIASCAFVDSGKDKIDKTKLVTYTSRL AASPAYQKVVGVGLKTAAGSIVPYVRLDMDNTGKGIHFN ATKLSDSSAKLAAVLKTTVSMTEAQRTQLYMEYIKGIENRS AQFIWDWWRTGKAPA
[0315]	9	sc-Fv-FC	302	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLT**C**LVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSP GGGGS APIVTCRPKLDGREKPFKVDVATAQAQARKAGLTTGKSGD PHRYFAGDHIRWGVNNCDKADAILWEYPIYWVGKNAEWA KDVKTSQQKGGPTPIRVVYANSRGAVQYCGVMTHSKVDK

[0316]

			NNQGKEFFEKCD
10	sc-Fv-FC	301	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLT**C**LVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSP ***GGGGS*** ADTVICEPHQDTETGKIKKFKVDVGVAEDQAKKAGLTTGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
11	sc-Fv-FC	466	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPG ***HRRRKRSLDTS***

[0317]

			ADTVICEPHQDTETGKIKKFKVDVGVAEDQAKKAGLTTGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
12	sc-Fv-FC	467	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPG ***TRHRQPRGWEQL*** ADTVICEPHQDTETGKIKKFKVDVGVAEDQAKKAGLTTGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
13	全长 IgG	676, HC	QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVK QTPGRGLEWIGAIYPGNGDTSYNQKFKGKATLTADKSSST AYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTT VTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSP

[0318]

			GGGGS ADTVICEPHQDTETGKIKKFKVDVGVAEDQAKKAGLTTGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
	14		676, LC	QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSS PKPWIYATSNLASGVPVRFSGSGSGTSYSLTISRVEAEDAAT YYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
	15	全长 IgG	680, HC	QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVK QTPGRGLEWIGAIYPGNGDTSYNQKFKGKATLTADKSSST AYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTT VTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPG ***HRRRKRSLDTS*** ADTVICEPHQDTETGKIKKFKVDVGVAEDQAKKAGLTTGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
	16		680, LC	QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSS PKPWIYATSNLASGVPVRFSGSGSGTSYSLTISRVEAEDAAT YYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
	17	全长	452, HC	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA

[0319]

	IgG		PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSP GGGGS ADTVICEPHQDTETGKIKKFKVDVGVAEDQAKKAGLTTGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
18		452, LC	DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIKRTVAAPSVFIFPPS DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
19	全长 IgG	507, HC	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPG ***HRRRKRSLDTS***

[0320]

			ADTVICEPHQDTETGKIKKFKVDVGVAEDQAKKAGLTTGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
20		507, LC	DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIKRTVAAPSVFIFPPS DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
21	全长 IgG	508, HC	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPG ***TRHRQPRGWEQL*** ADTVICEPHQDTETGKIKKFKVDVGVAEDQAKKAGLTTGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
22		508, LC	DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIKRTVAAPSVFIFPPS DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
23	全长 IgG	509, LC	DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ

[0321]

			PEDFATYYCQQSNEDPLTFGQGTKVEIKRTVAAPSVFIFPPS DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC ***GGGGS*** ADTVICEPHQDTETGKIKKFKVDVGVAEDQAKKAGLTTGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
	24		509, HC	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPG
	25	全长IgG	536, LC	DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIKRTVAAPSVFIFPPS DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC ***GGGGS*** ADTVICEPHQDTETGKIKKFKVDVGVAEDQAKKAGLTTGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
	26		536, HC	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSSASTK

[0322]

			GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSP ***GGGGS*** ADTVICEPHQDTETGKIKKFKVDVGVAEDQAKKAGLTTGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
27	丝裂菌褶素		APSPLDARATWTCINQQLNPKTNKWEDKRLLYNQAKAES NSHHAPLSDGKTGSSYPHWFTNGYDGNGKLIKGRTPIKFG KADCDRPPKHSQNGMGKDDHYLLEFPTFPDGHDYKFDSK KPKEDPGPARVIYTYPNKVFCGIVAHQRGNQGDLRLCSH
28	sc-Fv-FC	495	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLT**C**LVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSP ***GGGGS*** ADTVICEPHQDTETGKIKKFKVDVGVAEDQAKKAGLITGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA

[0323]

			EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
29	sc-Fv-FC	496	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLT**C**LVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSP ***GGGGS*** ADTVICEPRQDTETGKIKKFKVDVGVAEDQAKKAGLITGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
30	sc-Fv-FC	497	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLT**C**LVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSP

[0324]

			GGGGS ADTVICEPHQDTETGKIKKFTVDVGVAEDQAKKAGLTTGK SGDPHRYMNGDNINFGIHNCDKEGAILWEYPIYWVGKKA EWKKDEKTDRQPGGPTPLRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
31	sc-Fv-FC	48	EVQLVESGGGLVKPGGSLKLS**C**AASGFAFSIYDMSWVRQT PEKRLEWVAYISSGGGTTYYPDTVKGRFTISRDNAKNTLYL QMSSLKSEDTAMYY**C**ARHSGYGTHWGVLFAYWGQGTLV TVSA ***GGGGSGGGGSGGGGS*** DIQMTQTTSSLSASLGDRVTIS**C**RASQDIHGYLNWYQQKP DGTVKLLIYYTSILHSGVPSRFSGSGSGTDYSLTISNLEQED FATYF**C**QQGNTLPWTFGGGTKLEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLT**C**LVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSP ***GGGGS*** ***RRKR*AS** KESRAKKFQRQHMDSDSSPSSSSTY**C**NQMMRRR**SMTQGD** **C**KPVNTFVHEPLVDVQNV**C**FQEKVT**C**K**D**GQGN**C**YKS**NS**A MHITD**C**RLT**AD**S**D**YPN**C**AYRTSPKERHIIVA**C**EGSPYVPVH FDASV
32	sc-Fv-FC	125	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP

[0325]

			EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLT**C**LVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSP ***GGGGS*** AVTWTCLNDQKNPKTNKYETKRLLYNQNKAESNSHHAPL SDGKTGSSYPHWFTNGYDGDGKLPKGRTPIKFGKSDCDRP PKHSKDGNGKTDHYLLEFPTFPDGHDYKFDSKKPKENPGP ARVIYTYPNKVFCGIIAHTKENQGELKLCSH
	33	sc-Fv-FC	86	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLT**C**LVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSPGK
	34	sc-Fv-FC	96	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK

[0326]

			GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK
35	sc-Fv-FC	92	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIKR ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSP ***GGGGS*** ***RRKR*AS** KESRAKKFQRQHMDSDSSPSSSSTYCNQMMRRRSMTQGD CKPVNTFVHEPLVDVQNVCFQEKVTCKDGQGNCYKSNSA MHITDCRLTADSDYPNCAYRTSPKERHIIVACEGSPYVPVH FDASV
36	sc-Fv-FC	228	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW

[0327]

			ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSP ***GGGGS*** QDNSRYTHFLTQHYDAKPQGRDDRYCESIMRRRGLTSPCK DINTFIHGNKRSIKAICENKNGNPHRENLRISKSSFQVTTCK LHRRSPWPPCQYRATAGFRNVVVACENGLPVHLDQSIFRR P
37	sc-Fv-FC	125	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLT**C**LVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSP ***GGGGS*** AVTWTCLNDQKNPKTNKYETKRLLYNQNKAESNSHHAPL SDGKTGSSYPHWFTNGYDGDGKLPKGRTPIKFGKSDCDRP PKHSKDGNGKTDHYLLEFPTFPDGHDYKFDSKKPKENPGP ARVIYTYPNKVFCGIIAHTKENQGELKLCSH
38	sc-Fv-FC	221	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP

[0328]

			EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLT**C**LVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSPG***TRHRQPRGWEQL*** AVTWTCLNDQKNPKTNKYETKRLLYNQNKAESNSHHAPL SDGKTGSSYPHWFTNGYDGDGKLPKGRTPIKFGKSDCDRP PKHSKDGNGKTDHYLLEFPTFPDGHDYKFDSKKPKENPGP ARVIYTYPNKVFCGIIAHTKENQGELKLCSH
	39	sc-Fv-FC	301	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ***GGGGSGGGGSGGGGS*** DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK ***ASTKTHTCPPCP*** APELLGGPSVFLFPPKPKDTLMISRTPEVT**C**VVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLH QDWLNGKEYK**C**KVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLT**C**LVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFS**C**SVMHEALHNHYTQKSLSLSP GGGGS ADTVICEPHQDTETGKIKKFKVDVGVAEDQAKKAGLTTGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
	40	全长 IgG	414, HC	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD

			GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSP ***GGGGS*** AVTWTCLNDQKNPKTNKYETKRLLYNQNKAESNSHHAPL SDGKTGSSYPHWFTNGYDGDGKLPKGRTPIKFGKSDCDRP PKHSKDGNGKTDHYLLEFPTFPDGHDYKFDSKKPKENPGP ARVIYTYPNKVFCGIIAHTKENQGELKLCSH
	41		414, LC	DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSNEDPLTFGQGTKVEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC
[0329]	42	全长IgG	452, HC	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQA PGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTSKNTAYL QMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKAEPKSCDKTHTCPPCP APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSP ***GGGGS*** ADTVICEPHQDTETGKIKKFKVDVGVAEDQAKKAGLTTGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
	43		452, LC	DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQ QKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISSLQ

[0330]

		PEDFATYYCQQSNEDPLTFGQGTKVEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC
44	Fpe 接头	*TRHRQPRGWEQL*
45	Fdt 接头	*AGNRVRRSVG*
46	弗林蛋白酶裂解位点 (FCS)/Liop	*HRRRKRSLDTS*
47	hirsutelin A	APIVTCRPKLDGREKPFKVDVATAQAQARKAGLTTGKSGD PHRYFAGDHIRWGVNNCDKADAILWEYPIYWVGKNAEWA KDVKTSQQKGGPTPIRVVYANSRGAVQYCGVMTHSKVDK NNQGKEFFEKCD
48	Anisoplin	ADTVICEPHQDTETGKIKKFKVDVGVAEDQAKKAGLTTGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
49	Anisoplin (D43Y 版本)	ADTVICEPHQDTETGKIKKFKVDVGVAEDQAKKAGLTTGK SGYPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
50	血管生成素	QDNSRYTHFLTQHYDAKPQGRDDRYCESIMRRRGLTSPCK DINTFIHGNKRSIKAICENKNGNPHRENLRISKSSFQVTTCK LHRRSPWPPCQYRATAGFRNVVVACENGLPVHLDQSIFRR P
51	Anisoplin 同源物 1	ADTVICEPHQDTETGKIKKFKVDVGVAEDQAKKAGLITGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
52	Anisoplin 同源物 2	ADTVICEPRQDTETGKIKKFKVDVGVAEDQAKKAGLITGK SGDPHRYMNGDKINFGIHNCDKEGAILWEYPIYWVGKKA EWMKDEKTDRQPGGPTPIRVVYANNNGNIVYCGVMTHAV VKSNNQGEKFFLKCT
53	Anisoplin 同源物 3	ADTVICEPHQDTETGKIKKFTVDVGVAEDQAKKAGLTTGK SGDPHRYMNGDNINFGIHNCDKEGAILWEYPIYWVGKKA EWKKDEKTDRQPGGPTPLRVVYANNNGNIVYCGVMTHAV

[0331]

		VKSNNQGEKFFLKCT
54	Ageritin	AETVQYYNSYSDASIASCAFVDSGKDKIDKTKLVTYTSRL AASPAYQKVVGVGLKTAAGSIVPYVRLDMDNTGKGIHFN ATKLSDSSAKLAAVLKTTVSMTEAQRTQLYMEYIKGIENRS AQFIWDWWRTGKAPA
55	α-八叠球菌素	AVTWTCLNDQKNPKTNKYETKRLLYNQNKAESNSHHAPL SDGKTGSSYPHWFTNGYDGDGKLPKGRTPIKFGKSDCDRP PKHSKDGNGKTDHYLLEFPTFPDGHDYKFDSKKPKENPGP ARVIYTYPNKVFCGIIAHTKENQGELKLCSH
56	α-八叠球菌素(去免疫化版本D9T/Q142T)	AVTWTCLNTQKNPKTNKYETKRLLYNQNKAESNSHHAPL SDGKTGSSYPHWFTNGYDGDGKLPKGRTPIKFGKSDCDRP PKHSKDGNGKTDHYLLEFPTFPDGHDYKFDSKKPKENPGP ARVIYTYPNKVFCGIIAHTKENTGELKLCSH
57	hpRNase1	KESRAKKFQRQHMDSDSSPSSSSTYCNQMMRRRNMTQGR CKPVNTFVHEPLVDVQNVCFQEKVTCKNGQGNCYKSNSS MHITDCRLTNGSRYPNCAYRTSPKERHIIVACEGSPYVPVHF DASVEDST
58	抗 CD79B HCDR1	GYTFSSYWIE
59	抗 CD79B HCDR2	GEILPGGGDTNYNEIFKG
60	抗 CD79B HCDR3	TRRVPIRLDY
61	抗 CD79B LCDR1	KASQSVDYEGDSFLN
62	抗 CD79B LCDR2	AASNLES
63	抗 CD79B LCDR3	CQQSNEDPLT
64	抗 CD20 HCDR1	YTFTSYNMH
65	抗 CD20 HCDR2	WIGAIYPGNGDTSY
66	抗 CD20 HCDR3	RSTYYGGDWYFNV
67	抗 CD20 LCDR1	SSVSYIH
68	抗 CD20 LCDR2	PWIYATSNLAS
69	抗 CD20 LCDR3	QQWTSNPP

[0332] 波浪下划线＝毒素

[0333] EVQL…＝V_H结构域，下划线＝HCDR 1-3

[0334] DIQL…＝V_L结构域，下划线＝LCDR 1-3

[0335] QIVL…＝V_L结构域，下划线＝LCDR 1-3APELL…＝CH_2结构域GQPRE…＝CH_3结构域RTVAAP…＝CL_1结构域斜体字＝接头或裂解位点

序列表

<110> ATB 治疗公司

<120> 包含核糖体毒素或RNAse的重组免疫毒素

<130> AD42605

<160> 69

<170> PatentIn version 3.5

<210> 1
<211> 624
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 1

[0001]

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35 40 45

Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly
100 105 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Pro
115 120 125

Gly Ala Glu Leu Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys
130 135 140

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Asn Met His Trp Val Lys Gln
145 150 155 160

Thr Pro Gly Arg Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn
165 170 175

[0002]

Gly Asp Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr
180 185 190

Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr
195 200 205

Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Ser Thr Tyr Tyr Gly
210 215 220

Gly Asp Trp Tyr Phe Asn Val Trp Gly Ala Gly Thr Thr Val Thr Val
225 230 235 240

Ser Ala Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
245 250 255

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
260 265 270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
275 280 285

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
290 295 300

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
305 310 315 320

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
325 330 335

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
340 345 350

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
355 360 365

[0003]

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
370 375 380

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
385 390 395 400

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
405 410 415

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
420 425 430

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
435 440 445

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

450 455 460

Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Ala Val Thr Trp Thr Cys
465 470 475 480

Leu Asn Asp Gln Lys Asn Pro Lys Thr Asn Lys Tyr Glu Thr Lys Arg
485 490 495

Leu Leu Tyr Asn Gln Asn Lys Ala Glu Ser Asn Ser His His Ala Pro
500 505 510

Leu Ser Asp Gly Lys Thr Gly Ser Ser Tyr Pro His Trp Phe Thr Asn
515 520 525

Gly Tyr Asp Gly Asp Gly Lys Leu Pro Lys Gly Arg Thr Pro Ile Lys
530 535 540

[0004]

Phe Gly Lys Ser Asp Cys Asp Arg Pro Pro Lys His Ser Lys Asp Gly
545 550 555 560

Asn Gly Lys Thr Asp His Tyr Leu Leu Glu Phe Pro Thr Phe Pro Asp
565 570 575

Gly His Asp Tyr Lys Phe Asp Ser Lys Lys Pro Lys Glu Asn Pro Gly
580 585 590

Pro Ala Arg Val Ile Tyr Thr Tyr Pro Asn Lys Val Phe Cys Gly Ile
595 600 605

Ile Ala His Thr Lys Glu Asn Gln Gly Glu Leu Lys Leu Cys Ser His
610 615 620

<210> 2
<211> 625

<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 2

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

[0005]

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser

145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

[0006]

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

[0007] Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Ala Val Thr Trp Thr
465 470 475 480

Cys Leu Asn Asp Gln Lys Asn Pro Lys Thr Asn Lys Tyr Glu Thr Lys
485 490 495

Arg Leu Leu Tyr Asn Gln Asn Lys Ala Glu Ser Asn Ser His His Ala
500 505 510

Pro Leu Ser Asp Gly Lys Thr Gly Ser Ser Tyr Pro His Trp Phe Thr
515 520 525

Asn Gly Tyr Asp Gly Asp Gly Lys Leu Pro Lys Gly Arg Thr Pro Ile
530 535 540

Lys Phe Gly Lys Ser Asp Cys Asp Arg Pro Pro Lys His Ser Lys Asp
545 550 555 560

Gly Asn Gly Lys Thr Asp His Tyr Leu Leu Glu Phe Pro Thr Phe Pro
565 570 575

Asp Gly His Asp Tyr Lys Phe Asp Ser Lys Lys Pro Lys Glu Asn Pro
580 585 590

Gly Pro Ala Arg Val Ile Tyr Thr Tyr Pro Asn Lys Val Phe Cys Gly
595 600 605

[0008]

Ile Ile Ala His Thr Lys Glu Asn Gln Gly Glu Leu Lys Leu Cys Ser
610 615 620

His
625

<210> 3
<211> 632
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 3

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

[0009]

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

[0010] Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

[0011]

Ser Leu Ser Leu Ser Pro Gly His Arg Arg Arg Lys Arg Ser Leu Asp
465 470 475 480

Thr Ser Ala Val Thr Trp Thr Cys Leu Asn Asp Gln Lys Asn Pro Lys
485 490 495

Thr Asn Lys Tyr Glu Thr Lys Arg Leu Leu Tyr Asn Gln Asn Lys Ala
500 505 510

Glu Ser Asn Ser His His Ala Pro Leu Ser Asp Gly Lys Thr Gly Ser
515 520 525

Ser Tyr Pro His Trp Phe Thr Asn Gly Tyr Asp Gly Asp Gly Lys Leu
530 535 540

Pro Lys Gly Arg Thr Pro Ile Lys Phe Gly Lys Ser Asp Cys Asp Arg

545 550 555 560

Pro Pro Lys His Ser Lys Asp Gly Asn Gly Lys Thr Asp His Tyr Leu
565 570 575

Leu Glu Phe Pro Thr Phe Pro Asp Gly His Asp Tyr Lys Phe Asp Ser
580 585 590

Lys Lys Pro Lys Glu Asn Pro Gly Pro Ala Arg Val Ile Tyr Thr Tyr
595 600 605

Pro Asn Lys Val Phe Cys Gly Ile Ile Ala His Thr Lys Glu Asn Gln
610 615 620

Gly Glu Leu Lys Leu Cys Ser His
625 630

[0012]

<210> 4
<211> 633
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 4

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

[0013]

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val

225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

[0014]

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Thr Arg His Arg Gln Pro Arg Gly Trp
465 470 475 480

Glu Gln Leu Ala Val Thr Trp Thr Cys Leu Asn Asp Gln Lys Asn Pro
485 490 495

[0015]

Lys Thr Asn Lys Tyr Glu Thr Lys Arg Leu Leu Tyr Asn Gln Asn Lys
500 505 510

Ala Glu Ser Asn Ser His His Ala Pro Leu Ser Asp Gly Lys Thr Gly
515 520 525

Ser Ser Tyr Pro His Trp Phe Thr Asn Gly Tyr Asp Gly Asp Gly Lys
530 535 540

Leu Pro Lys Gly Arg Thr Pro Ile Lys Phe Gly Lys Ser Asp Cys Asp
545 550 555 560

Arg Pro Pro Lys His Ser Lys Asp Gly Asn Gly Lys Thr Asp His Tyr
565 570 575

Leu Leu Glu Phe Pro Thr Phe Pro Asp Gly His Asp Tyr Lys Phe Asp
580 585 590

Ser Lys Lys Pro Lys Glu Asn Pro Gly Pro Ala Arg Val Ile Tyr Thr
595 600 605

Tyr Pro Asn Lys Val Phe Cys Gly Ile Ile Ala His Thr Lys Glu Asn
610 615 620

Gln Gly Glu Leu Lys Leu Cys Ser His
625 630

<210> 5
<211> 631
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 5

[0016]

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

[0017] Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

[0018] Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Ala Gly Asn Arg Val Arg Arg Ser Val
465 470 475 480

Gly Ala Val Thr Trp Thr Cys Leu Asn Asp Gln Lys Asn Pro Lys Thr
485 490 495

Asn Lys Tyr Glu Thr Lys Arg Leu Leu Tyr Asn Gln Asn Lys Ala Glu
500 505 510

Ser Asn Ser His His Ala Pro Leu Ser Asp Gly Lys Thr Gly Ser Ser
515 520 525

Tyr Pro His Trp Phe Thr Asn Gly Tyr Asp Gly Asp Gly Lys Leu Pro
530 535 540

[0019]

Lys Gly Arg Thr Pro Ile Lys Phe Gly Lys Ser Asp Cys Asp Arg Pro
545 550 555 560

Pro Lys His Ser Lys Asp Gly Asn Gly Lys Thr Asp His Tyr Leu Leu
565 570 575

Glu Phe Pro Thr Phe Pro Asp Gly His Asp Tyr Lys Phe Asp Ser Lys
580 585 590

Lys Pro Lys Glu Asn Pro Gly Pro Ala Arg Val Ile Tyr Thr Tyr Pro
595 600 605

Asn Lys Val Phe Cys Gly Ile Ile Ala His Thr Lys Glu Asn Gln Gly
610 615 620

Glu Leu Lys Leu Cys Ser His

625 630

<210> 6
<211> 634
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 6

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

[0020] Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

[0021]

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln

305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

[0022]

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
465 470 475 480

Arg Arg Lys Arg Ala Val Thr Trp Thr Cys Leu Asn Asp Gln Lys Asn
485 490 495

Pro Lys Thr Asn Lys Tyr Glu Thr Lys Arg Leu Leu Tyr Asn Gln Asn
500 505 510

Lys Ala Glu Ser Asn Ser His His Ala Pro Leu Ser Asp Gly Lys Thr
515 520 525

Gly Ser Ser Tyr Pro His Trp Phe Thr Asn Gly Tyr Asp Gly Asp Gly
530 535 540

Lys Leu Pro Lys Gly Arg Thr Pro Ile Lys Phe Gly Lys Ser Asp Cys
545 550 555 560

Asp Arg Pro Pro Lys His Ser Lys Asp Gly Asn Gly Lys Thr Asp His
565 570 575

Tyr Leu Leu Glu Phe Pro Thr Phe Pro Asp Gly His Asp Tyr Lys Phe
[0023] 580 585 590

Asp Ser Lys Lys Pro Lys Glu Asn Pro Gly Pro Ala Arg Val Ile Tyr
595 600 605

Thr Tyr Pro Asn Lys Val Phe Cys Gly Ile Ile Ala His Thr Lys Glu
610 615 620

Asn Gln Gly Glu Leu Lys Leu Cys Ser His
625 630

<210> 7
<211> 213
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 7

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35 40 45

Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65 70 75 80

[0024]

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> 8
<211> 610
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 8

[0025]

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

[0026]

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

[0027] Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Ala Glu Thr Val Gln
465 470 475 480

Tyr Tyr Asn Ser Tyr Ser Asp Ala Ser Ile Ala Ser Cys Ala Phe Val
485 490 495

Asp Ser Gly Lys Asp Lys Ile Asp Lys Thr Lys Leu Val Thr Tyr Thr
500 505 510

Ser Arg Leu Ala Ala Ser Pro Ala Tyr Gln Lys Val Val Gly Val Gly
515 520 525

[0028] Leu Lys Thr Ala Ala Gly Ser Ile Val Pro Tyr Val Arg Leu Asp Met
530 535 540

Asp Asn Thr Gly Lys Gly Ile His Phe Asn Ala Thr Lys Leu Ser Asp
545 550 555 560

Ser Ser Ala Lys Leu Ala Ala Val Leu Lys Thr Thr Val Ser Met Thr
565 570 575

Glu Ala Gln Arg Thr Gln Leu Tyr Met Glu Tyr Ile Lys Gly Ile Glu
580 585 590

Asn Arg Ser Ala Gln Phe Ile Trp Asp Trp Trp Arg Thr Gly Lys Ala
595 600 605

Pro Ala
610

<210> 9
<211> 605
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 9

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

[0029]

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

[0030]

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

[0031]

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Ala Pro Ile Val Thr
465 470 475 480

Cys Arg Pro Lys Leu Asp Gly Arg Glu Lys Pro Phe Lys Val Asp Val
485 490 495

Ala Thr Ala Gln Ala Gln Ala Arg Lys Ala Gly Leu Thr Thr Gly Lys

500 505 510

Ser Gly Asp Pro His Arg Tyr Phe Ala Gly Asp His Ile Arg Trp Gly
515 520 525

Val Asn Asn Cys Asp Lys Ala Asp Ala Ile Leu Trp Glu Tyr Pro Ile
530 535 540

Tyr Trp Val Gly Lys Asn Ala Glu Trp Ala Lys Asp Val Lys Thr Ser
545 550 555 560

Gln Gln Lys Gly Gly Pro Thr Pro Ile Arg Val Val Tyr Ala Asn Ser
565 570 575

Arg Gly Ala Val Gln Tyr Cys Gly Val Met Thr His Ser Lys Val Asp
580 585 590

[0032]

Lys Asn Asn Gln Gly Lys Glu Phe Phe Glu Lys Cys Asp
595 600 605

<210> 10
<211> 608
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 10

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

[0033]

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys

210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

[0034]

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Ala Asp Thr Val Ile
465 470 475 480

[0035] Cys Glu Pro His Gln Asp Thr Glu Thr Gly Lys Ile Lys Lys Phe Lys
485 490 495

Val Asp Val Gly Val Ala Glu Asp Gln Ala Lys Lys Ala Gly Leu Thr
500 505 510

Thr Gly Lys Ser Gly Asp Pro His Arg Tyr Met Asn Gly Asp Lys Ile
515 520 525

Asn Phe Gly Ile His Asn Cys Asp Lys Glu Gly Ala Ile Leu Trp Glu
530 535 540

Tyr Pro Ile Tyr Trp Val Gly Lys Lys Ala Glu Trp Met Lys Asp Glu
545 550 555 560

Lys Thr Asp Arg Gln Pro Gly Gly Pro Thr Pro Ile Arg Val Val Tyr
565 570 575

Ala Asn Asn Asn Gly Asn Ile Val Tyr Cys Gly Val Met Thr His Ala
580 585 590

Val Val Lys Ser Asn Asn Gln Gly Glu Lys Phe Phe Leu Lys Cys Thr
595 600 605

<210> 11
<211> 615
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 11

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

[0036]

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

[0037]

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

[0038] Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly His Arg Arg Arg Lys Arg Ser Leu Asp
465 470 475 480

Thr Ser Ala Asp Thr Val Ile Cys Glu Pro His Gln Asp Thr Glu Thr
485 490 495

Gly Lys Ile Lys Lys Phe Lys Val Asp Val Gly Val Ala Glu Asp Gln
500 505 510

Ala Lys Lys Ala Gly Leu Thr Thr Gly Lys Ser Gly Asp Pro His Arg
515 520 525

Tyr Met Asn Gly Asp Lys Ile Asn Phe Gly Ile His Asn Cys Asp Lys
530 535 540

Glu Gly Ala Ile Leu Trp Glu Tyr Pro Ile Tyr Trp Val Gly Lys Lys
545 550 555 560

[0039]

Ala Glu Trp Met Lys Asp Glu Lys Thr Asp Arg Gln Pro Gly Gly Pro
565 570 575

Thr Pro Ile Arg Val Val Tyr Ala Asn Asn Asn Gly Asn Ile Val Tyr
580 585 590

Cys Gly Val Met Thr His Ala Val Val Lys Ser Asn Asn Gln Gly Glu
595 600 605

Lys Phe Phe Leu Lys Cys Thr
610 615

<210> 12
<211> 616
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 12

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

[0040] Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

[0041]

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala

340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

[0042]

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Thr Arg His Arg Gln Pro Arg Gly Trp
465 470 475 480

Glu Gln Leu Ala Asp Thr Val Ile Cys Glu Pro His Gln Asp Thr Glu
485 490 495

Thr Gly Lys Ile Lys Lys Phe Lys Val Asp Val Gly Val Ala Glu Asp
500 505 510

Gln Ala Lys Lys Ala Gly Leu Thr Thr Gly Lys Ser Gly Asp Pro His
515 520 525

Arg Tyr Met Asn Gly Asp Lys Ile Asn Phe Gly Ile His Asn Cys Asp
530 535 540

Lys Glu Gly Ala Ile Leu Trp Glu Tyr Pro Ile Tyr Trp Val Gly Lys
545 550 555 560

Lys Ala Glu Trp Met Lys Asp Glu Lys Thr Asp Arg Gln Pro Gly Gly
565 570 575

Pro Thr Pro Ile Arg Val Val Tyr Ala Asn Asn Asn Gly Asn Ile Val
580 585 590

Tyr Cys Gly Val Met Thr His Ala Val Val Lys Ser Asn Asn Gln Gly
595 600 605

Glu Lys Phe Phe Leu Lys Cys Thr
[0043] 610 615

<210> 13
<211> 587
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 13

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile

35 40 45

Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly
100 105 110

Ala Gly Thr Thr Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser
115 120 125

[0044]

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Ala Glu Pro Lys Ser Cys
210 215 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
290 295 300

[0045] Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly Gly Gly Gly Ser Ala Asp Thr Val Ile Cys Glu Pro His Gln
450 455 460

Asp Thr Glu Thr Gly Lys Ile Lys Lys Phe Lys Val Asp Val Gly Val
465 470 475 480

[0046] Ala Glu Asp Gln Ala Lys Lys Ala Gly Leu Thr Thr Gly Lys Ser Gly
485 490 495

Asp Pro His Arg Tyr Met Asn Gly Asp Lys Ile Asn Phe Gly Ile His
500 505 510

Asn Cys Asp Lys Glu Gly Ala Ile Leu Trp Glu Tyr Pro Ile Tyr Trp
515 520 525

Val Gly Lys Lys Ala Glu Trp Met Lys Asp Glu Lys Thr Asp Arg Gln
530 535 540

Pro Gly Gly Pro Thr Pro Ile Arg Val Val Tyr Ala Asn Asn Asn Gly
545 550 555 560

Asn Ile Val Tyr Cys Gly Val Met Thr His Ala Val Val Lys Ser Asn
565 570 575

Asn Gln Gly Glu Lys Phe Phe Leu Lys Cys Thr
580 585

<210> 14
<211> 213
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 14

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
20 25 30

[0047]

His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35 40 45

Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

[0048]

<210> 15
<211> 594
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 15

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly
100 105 110

Ala Gly Thr Thr Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser
115 120 125

[0049] Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Ala Glu Pro Lys Ser Cys
210 215 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
290 295 300

[0050] Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly His Arg Arg Arg Lys Arg Ser Leu Asp Thr Ser Ala Asp Thr
450 455 460

Val Ile Cys Glu Pro His Gln Asp Thr Glu Thr Gly Lys Ile Lys Lys
465 470 475 480

Phe Lys Val Asp Val Gly Val Ala Glu Asp Gln Ala Lys Lys Ala Gly
485 490 495

[0051]

Leu Thr Thr Gly Lys Ser Gly Asp Pro His Arg Tyr Met Asn Gly Asp
500 505 510

Lys Ile Asn Phe Gly Ile His Asn Cys Asp Lys Glu Gly Ala Ile Leu
515 520 525

Trp Glu Tyr Pro Ile Tyr Trp Val Gly Lys Lys Ala Glu Trp Met Lys
530 535 540

Asp Glu Lys Thr Asp Arg Gln Pro Gly Gly Pro Thr Pro Ile Arg Val
545 550 555 560

Val Tyr Ala Asn Asn Asn Gly Asn Ile Val Tyr Cys Gly Val Met Thr
565 570 575

His Ala Val Val Lys Ser Asn Asn Gln Gly Glu Lys Phe Phe Leu Lys

580 585 590

Cys Thr

<210> 16
<211> 213
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 16

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1 5 10 15

[0052] Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35 40 45

Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

[0053]

Asn Arg Gly Glu Cys
210

<210> 17
<211> 583
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 17

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

[0054]

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Ala Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

[0055]

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser

385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly
435 440 445

Gly Ser Ala Asp Thr Val Ile Cys Glu Pro His Gln Asp Thr Glu Thr
450 455 460

Gly Lys Ile Lys Lys Phe Lys Val Asp Val Gly Val Ala Glu Asp Gln
465 470 475 480

[0056]

Ala Lys Lys Ala Gly Leu Thr Thr Gly Lys Ser Gly Asp Pro His Arg
485 490 495

Tyr Met Asn Gly Asp Lys Ile Asn Phe Gly Ile His Asn Cys Asp Lys
500 505 510

Glu Gly Ala Ile Leu Trp Glu Tyr Pro Ile Tyr Trp Val Gly Lys Lys
515 520 525

Ala Glu Trp Met Lys Asp Glu Lys Thr Asp Arg Gln Pro Gly Gly Pro
530 535 540

Thr Pro Ile Arg Val Val Tyr Ala Asn Asn Asn Gly Asn Ile Val Tyr
545 550 555 560

Cys Gly Val Met Thr His Ala Val Val Lys Ser Asn Asn Gln Gly Glu
565 570 575

Lys Phe Phe Leu Lys Cys Thr
580

<210> 18
<211> 218
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 18

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Asp Tyr Glu
20 25 30

[0057]

Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
85 90 95

Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln

115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

[0058]

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 19
<211> 590
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 19

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

[0059]

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Ala Glu Pro Lys Ser Cys Asp Lys Thr His

210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

[0060]

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly His Arg
435 440 445

Arg Arg Lys Arg Ser Leu Asp Thr Ser Ala Asp Thr Val Ile Cys Glu
450 455 460

Pro His Gln Asp Thr Glu Thr Gly Lys Ile Lys Lys Phe Lys Val Asp
465 470 475 480

[0061] Val Gly Val Ala Glu Asp Gln Ala Lys Lys Ala Gly Leu Thr Thr Gly
485 490 495

Lys Ser Gly Asp Pro His Arg Tyr Met Asn Gly Asp Lys Ile Asn Phe
500 505 510

Gly Ile His Asn Cys Asp Lys Glu Gly Ala Ile Leu Trp Glu Tyr Pro
515 520 525

Ile Tyr Trp Val Gly Lys Lys Ala Glu Trp Met Lys Asp Glu Lys Thr
530 535 540

Asp Arg Gln Pro Gly Gly Pro Thr Pro Ile Arg Val Val Tyr Ala Asn
545 550 555 560

Asn Asn Gly Asn Ile Val Tyr Cys Gly Val Met Thr His Ala Val Val
565 570 575

Lys Ser Asn Asn Gln Gly Glu Lys Phe Phe Leu Lys Cys Thr
580 585 590

<210> 20
<211> 218
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 20

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Asp Tyr Glu
20 25 30

[0062]

Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
85 90 95

Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
[0063] 210 215

<210> 21
<211> 591
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 21

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile

35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

[0064]

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Ala Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

[0065]

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Thr Arg
435 440 445

His Arg Gln Pro Arg Gly Trp Glu Gln Leu Ala Asp Thr Val Ile Cys
450 455 460

Glu Pro His Gln Asp Thr Glu Thr Gly Lys Ile Lys Lys Phe Lys Val
465 470 475 480

[0066] Asp Val Gly Val Ala Glu Asp Gln Ala Lys Lys Ala Gly Leu Thr Thr
485 490 495

Gly Lys Ser Gly Asp Pro His Arg Tyr Met Asn Gly Asp Lys Ile Asn
500 505 510

Phe Gly Ile His Asn Cys Asp Lys Glu Gly Ala Ile Leu Trp Glu Tyr
515 520 525

Pro Ile Tyr Trp Val Gly Lys Lys Ala Glu Trp Met Lys Asp Glu Lys
530 535 540

Thr Asp Arg Gln Pro Gly Gly Pro Thr Pro Ile Arg Val Val Tyr Ala
545 550 555 560

Asn Asn Asn Gly Asn Ile Val Tyr Cys Gly Val Met Thr His Ala Val
565 570 575

Val Lys Ser Asn Asn Gln Gly Glu Lys Phe Phe Leu Lys Cys Thr
580 585 590

<210> 22
<211> 218
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 22

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Asp Tyr Glu
20 25 30

[0067]

Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
85 90 95

Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

[0068]

<210> 23
<211> 356
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 23

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Asp Tyr Glu
20 25 30

Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
85 90 95

Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
115 120 125

[0069] Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser Ala
210 215 220

Asp Thr Val Ile Cys Glu Pro His Gln Asp Thr Glu Thr Gly Lys Ile
225 230 235 240

Lys Lys Phe Lys Val Asp Val Gly Val Ala Glu Asp Gln Ala Lys Lys
245 250 255

Ala Gly Leu Thr Thr Gly Lys Ser Gly Asp Pro His Arg Tyr Met Asn
260 265 270

Gly Asp Lys Ile Asn Phe Gly Ile His Asn Cys Asp Lys Glu Gly Ala
275 280 285

Ile Leu Trp Glu Tyr Pro Ile Tyr Trp Val Gly Lys Lys Ala Glu Trp
290 295 300

Met Lys Asp Glu Lys Thr Asp Arg Gln Pro Gly Gly Pro Thr Pro Ile
[0070] 305 310 315 320

Arg Val Val Tyr Ala Asn Asn Asn Gly Asn Ile Val Tyr Cys Gly Val
325 330 335

Met Thr His Ala Val Val Lys Ser Asn Asn Gln Gly Glu Lys Phe Phe
340 345 350

Leu Lys Cys Thr
355

<210> 24
<211> 446
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 24

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

[0071]

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Ala Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

[0072] Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

[0073]

<210> 25
<211> 356
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 25

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Asp Tyr Glu
20 25 30

Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
85 90 95

Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
115 120 125

[0074] Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser Ala
210 215 220

Asp Thr Val Ile Cys Glu Pro His Gln Asp Thr Glu Thr Gly Lys Ile
225 230 235 240

Lys Lys Phe Lys Val Asp Val Gly Val Ala Glu Asp Gln Ala Lys Lys
245 250 255

Ala Gly Leu Thr Thr Gly Lys Ser Gly Asp Pro His Arg Tyr Met Asn
260 265 270

Gly Asp Lys Ile Asn Phe Gly Ile His Asn Cys Asp Lys Glu Gly Ala
275 280 285

Ile Leu Trp Glu Tyr Pro Ile Tyr Trp Val Gly Lys Lys Ala Glu Trp
290 295 300

Met Lys Asp Glu Lys Thr Asp Arg Gln Pro Gly Gly Pro Thr Pro Ile
305 310 315 320

[0075]

Arg Val Val Tyr Ala Asn Asn Asn Gly Asn Ile Val Tyr Cys Gly Val
325 330 335

Met Thr His Ala Val Val Lys Ser Asn Asn Gln Gly Glu Lys Phe Phe
340 345 350

Leu Lys Cys Thr
355

<210> 26
<211> 583
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 26

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

[0076] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Ala Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

[0077]

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu

355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly
435 440 445

[0078]

Gly Ser Ala Asp Thr Val Ile Cys Glu Pro His Gln Asp Thr Glu Thr
450 455 460

Gly Lys Ile Lys Lys Phe Lys Val Asp Val Gly Val Ala Glu Asp Gln
465 470 475 480

Ala Lys Lys Ala Gly Leu Thr Thr Gly Lys Ser Gly Asp Pro His Arg
485 490 495

Tyr Met Asn Gly Asp Lys Ile Asn Phe Gly Ile His Asn Cys Asp Lys
500 505 510

Glu Gly Ala Ile Leu Trp Glu Tyr Pro Ile Tyr Trp Val Gly Lys Lys
515 520 525

Ala Glu Trp Met Lys Asp Glu Lys Thr Asp Arg Gln Pro Gly Gly Pro
530 535 540

Thr Pro Ile Arg Val Val Tyr Ala Asn Asn Asn Gly Asn Ile Val Tyr
545 550 555 560

Cys Gly Val Met Thr His Ala Val Val Lys Ser Asn Asn Gln Gly Glu
565 570 575

Lys Phe Phe Leu Lys Cys Thr
580

<210> 27
<211> 157
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 27

[0079]

Ala Pro Ser Pro Leu Asp Ala Arg Ala Thr Trp Thr Cys Ile Asn Gln
1 5 10 15

Gln Leu Asn Pro Lys Thr Asn Lys Trp Glu Asp Lys Arg Leu Leu Tyr
20 25 30

Asn Gln Ala Lys Ala Glu Ser Asn Ser His His Ala Pro Leu Ser Asp
35 40 45

Gly Lys Thr Gly Ser Ser Tyr Pro His Trp Phe Thr Asn Gly Tyr Asp
50 55 60

Gly Asn Gly Lys Leu Ile Lys Gly Arg Thr Pro Ile Lys Phe Gly Lys
65 70 75 80

Ala Asp Cys Asp Arg Pro Pro Lys His Ser Gln Asn Gly Met Gly Lys

85 90 95

Asp Asp His Tyr Leu Leu Glu Phe Pro Thr Phe Pro Asp Gly His Asp
100 105 110

Tyr Lys Phe Asp Ser Lys Lys Pro Lys Glu Asp Pro Gly Pro Ala Arg
115 120 125

Val Ile Tyr Thr Tyr Pro Asn Lys Val Phe Cys Gly Ile Val Ala His
130 135 140

Gln Arg Gly Asn Gln Gly Asp Leu Arg Leu Cys Ser His
145 150 155

[0080]

<210> 28
<211> 608
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 28

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

[0081]

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala

245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

[0082]

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Ala Asp Thr Val Ile
465 470 475 480

Cys Glu Pro His Gln Asp Thr Glu Thr Gly Lys Ile Lys Lys Phe Lys
485 490 495

Val Asp Val Gly Val Ala Glu Asp Gln Ala Lys Lys Ala Gly Leu Ile
500 505 510

[0083] Thr Gly Lys Ser Gly Asp Pro His Arg Tyr Met Asn Gly Asp Lys Ile
515 520 525

Asn Phe Gly Ile His Asn Cys Asp Lys Glu Gly Ala Ile Leu Trp Glu
530 535 540

Tyr Pro Ile Tyr Trp Val Gly Lys Lys Ala Glu Trp Met Lys Asp Glu
545 550 555 560

Lys Thr Asp Arg Gln Pro Gly Gly Pro Thr Pro Ile Arg Val Val Tyr
565 570 575

Ala Asn Asn Asn Gly Asn Ile Val Tyr Cys Gly Val Met Thr His Ala
580 585 590

Val Val Lys Ser Asn Asn Gln Gly Glu Lys Phe Phe Leu Lys Cys Thr
595 600 605

<210> 29
<211> 608
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 29

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

[0084]

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

[0085]

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

[0086] Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Ala Asp Thr Val Ile
465 470 475 480

Cys Glu Pro Arg Gln Asp Thr Glu Thr Gly Lys Ile Lys Lys Phe Lys
485 490 495

Val Asp Val Gly Val Ala Glu Asp Gln Ala Lys Lys Ala Gly Leu Ile
500 505 510

Thr Gly Lys Ser Gly Asp Pro His Arg Tyr Met Asn Gly Asp Lys Ile
515 520 525

Asn Phe Gly Ile His Asn Cys Asp Lys Glu Gly Ala Ile Leu Trp Glu
530 535 540

Tyr Pro Ile Tyr Trp Val Gly Lys Lys Ala Glu Trp Met Lys Asp Glu
545 550 555 560

Lys Thr Asp Arg Gln Pro Gly Gly Pro Thr Pro Ile Arg Val Val Tyr
565 570 575

Ala Asn Asn Asn Gly Asn Ile Val Tyr Cys Gly Val Met Thr His Ala
580 585 590

[0087]

Val Val Lys Ser Asn Asn Gln Gly Glu Lys Phe Phe Leu Lys Cys Thr
595 600 605

<210> 30
<211> 608
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 30

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

[0088] Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

[0089]

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

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

385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Ala Asp Thr Val Ile
465 470 475 480

[0090]

Cys Glu Pro His Gln Asp Thr Glu Thr Gly Lys Ile Lys Lys Phe Thr
485 490 495

Val Asp Val Gly Val Ala Glu Asp Gln Ala Lys Lys Ala Gly Leu Thr
500 505 510

Thr Gly Lys Ser Gly Asp Pro His Arg Tyr Met Asn Gly Asp Asn Ile
515 520 525

Asn Phe Gly Ile His Asn Cys Asp Lys Glu Gly Ala Ile Leu Trp Glu
530 535 540

Tyr Pro Ile Tyr Trp Val Gly Lys Lys Ala Glu Trp Lys Lys Asp Glu
545 550 555 560

Lys Thr Asp Arg Gln Pro Gly Gly Pro Thr Pro Leu Arg Val Val Tyr
565 570 575

Ala Asn Asn Asn Gly Asn Ile Val Tyr Cys Gly Val Met Thr His Ala
580 585 590

Val Val Lys Ser Asn Asn Gln Gly Glu Lys Phe Phe Leu Lys Cys Thr
595 600 605

<210> 31
<211> 607
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 31

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

[0091]

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Ile Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Tyr Ile Ser Ser Gly Gly Gly Thr Thr Tyr Tyr Pro Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg His Ser Gly Tyr Gly Thr His Trp Gly Val Leu Phe Ala Tyr

100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Gly Gly Gly Gly Ser
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln
130 135 140

Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser
145 150 155 160

Cys Arg Ala Ser Gln Asp Ile His Gly Tyr Leu Asn Trp Tyr Gln Gln
165 170 175

Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr Ser Ile Leu
180 185 190

[0092]

His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
195 200 205

Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu Asp Phe Ala Thr Tyr
210 215 220

Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp Thr Phe Gly Gly Gly Thr
225 230 235 240

Lys Leu Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys
245 250 255

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
260 265 270

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
275 280 285

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
290 295 300

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
305 310 315 320

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
325 330 335

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
340 345 350

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
355 360 365

[0093] Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
370 375 380

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
385 390 395 400

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
405 410 415

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
420 425 430

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
435 440 445

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
450 455 460

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Arg Arg Lys
465 470 475 480

Arg Ala Ser Lys Glu Ser Arg Ala Lys Lys Phe Gln Arg Gln His Met
485 490 495

Asp Ser Asp Ser Ser Pro Ser Ser Ser Ser Thr Tyr Cys Asn Gln Met
500 505 510

Met Arg Arg Arg Ser Met Thr Gln Gly Asp Cys Lys Pro Val Asn Thr
515 520 525

Phe Val His Glu Pro Leu Val Asp Val Gln Asn Val Cys Phe Gln Glu
530 535 540

Lys Val Thr Cys Lys Asp Gly Gln Gly Asn Cys Tyr Lys Ser Asn Ser
[0094] 545 550 555 560

Ala Met His Ile Thr Asp Cys Arg Leu Thr Ala Asp Ser Asp Tyr Pro
565 570 575

Asn Cys Ala Tyr Arg Thr Ser Pro Lys Glu Arg His Ile Ile Val Ala
580 585 590

Cys Glu Gly Ser Pro Tyr Val Pro Val His Phe Asp Ala Ser Val
595 600 605

<210> 32
<211> 625
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 32

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

[0095]

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

[0096] Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

[0097]

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Ala Val Thr Trp Thr
465 470 475 480

Cys Leu Asn Asp Gln Lys Asn Pro Lys Thr Asn Lys Tyr Glu Thr Lys
485 490 495

Arg Leu Leu Tyr Asn Gln Asn Lys Ala Glu Ser Asn Ser His His Ala
500 505 510

Pro Leu Ser Asp Gly Lys Thr Gly Ser Ser Tyr Pro His Trp Phe Thr
515 520 525

Asn Gly Tyr Asp Gly Asp Gly Lys Leu Pro Lys Gly Arg Thr Pro Ile

530 535 540

Lys Phe Gly Lys Ser Asp Cys Asp Arg Pro Pro Lys His Ser Lys Asp
545 550 555 560

Gly Asn Gly Lys Thr Asp His Tyr Leu Leu Glu Phe Pro Thr Phe Pro
565 570 575

Asp Gly His Asp Tyr Lys Phe Asp Ser Lys Lys Pro Lys Glu Asn Pro
580 585 590

Gly Pro Ala Arg Val Ile Tyr Thr Tyr Pro Asn Lys Val Phe Cys Gly
595 600 605

Ile Ile Ala His Thr Lys Glu Asn Gln Gly Glu Leu Lys Leu Cys Ser
610 615 620

[0098]

His
625

<210> 33
<211> 472
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 33

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

[0099]

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys

210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

[0100]

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Lys
465 470

[0101]

<210> 34
<211> 472
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 34

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe

50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

[0102]

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

[0103] Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 35
<211> 606
<212> PRT
<213> artificial sequence

[0104]
<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 35

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

[0105] Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Arg Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro
245 250 255

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
260 265 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
275 280 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
290 295 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305 310 315 320

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
325 330 335

[0106]

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
340 345 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
355 360 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
370 375 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385 390 395 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450 455 460

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Arg Arg Lys Arg
465 470 475 480

Ala Ser Lys Glu Ser Arg Ala Lys Lys Phe Gln Arg Gln His Met Asp
485 490 495

Ser Asp Ser Ser Pro Ser Ser Ser Ser Thr Tyr Cys Asn Gln Met Met
500 505 510

Arg Arg Arg Ser Met Thr Gln Gly Asp Cys Lys Pro Val Asn Thr Phe
515 520 525

[0107]

Val His Glu Pro Leu Val Asp Val Gln Asn Val Cys Phe Gln Glu Lys
530 535 540

Val Thr Cys Lys Asp Gly Gln Gly Asn Cys Tyr Lys Ser Asn Ser Ala
545 550 555 560

Met His Ile Thr Asp Cys Arg Leu Thr Ala Asp Ser Asp Tyr Pro Asn
565 570 575

Cys Ala Tyr Arg Thr Ser Pro Lys Glu Arg His Ile Ile Val Ala Cys
580 585 590

Glu Gly Ser Pro Tyr Val Pro Val His Phe Asp Ala Ser Val
595 600 605

<210> 36

<211> 598
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 36

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

[0108] Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

[0109]

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln

325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

[0110]

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Gln Asp Asn Ser Arg
465 470 475 480

Tyr Thr His Phe Leu Thr Gln His Tyr Asp Ala Lys Pro Gln Gly Arg
485 490 495

Asp Asp Arg Tyr Cys Glu Ser Ile Met Arg Arg Arg Gly Leu Thr Ser
500 505 510

Pro Cys Lys Asp Ile Asn Thr Phe Ile His Gly Asn Lys Arg Ser Ile
515 520 525

Lys Ala Ile Cys Glu Asn Lys Asn Gly Asn Pro His Arg Glu Asn Leu
530 535 540

Arg Ile Ser Lys Ser Ser Phe Gln Val Thr Thr Cys Lys Leu His Arg
545 550 555 560

Arg Ser Pro Trp Pro Pro Cys Gln Tyr Arg Ala Thr Ala Gly Phe Arg
565 570 575

Asn Val Val Val Ala Cys Glu Asn Gly Leu Pro Val His Leu Asp Gln
580 585 590

Ser Ile Phe Arg Arg Pro
[0111] 595

<210> 37
<211> 625
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 37

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile

35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

[0112]

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

[0113] Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Ala Val Thr Trp Thr
465 470 475 480

[0114] Cys Leu Asn Asp Gln Lys Asn Pro Lys Thr Asn Lys Tyr Glu Thr Lys
485 490 495

Arg Leu Leu Tyr Asn Gln Asn Lys Ala Glu Ser Asn Ser His His Ala
500 505 510

Pro Leu Ser Asp Gly Lys Thr Gly Ser Ser Tyr Pro His Trp Phe Thr
515 520 525

Asn Gly Tyr Asp Gly Asp Gly Lys Leu Pro Lys Gly Arg Thr Pro Ile
530 535 540

Lys Phe Gly Lys Ser Asp Cys Asp Arg Pro Pro Lys His Ser Lys Asp
545 550 555 560

Gly Asn Gly Lys Thr Asp His Tyr Leu Leu Glu Phe Pro Thr Phe Pro
565 570 575

Asp Gly His Asp Tyr Lys Phe Asp Ser Lys Lys Pro Lys Glu Asn Pro
580 585 590

Gly Pro Ala Arg Val Ile Tyr Thr Tyr Pro Asn Lys Val Phe Cys Gly
595 600 605

Ile Ile Ala His Thr Lys Glu Asn Gln Gly Glu Leu Lys Leu Cys Ser
610 615 620

His
625

<210> 38
<211> 633
<212> PRT
<213> artificial sequence

[0115]
<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 38

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

[0116] Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

[0117]

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe

435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Thr Arg His Arg Gln Pro Arg Gly Trp
465 470 475 480

Glu Gln Leu Ala Val Thr Trp Thr Cys Leu Asn Asp Gln Lys Asn Pro
485 490 495

Lys Thr Asn Lys Tyr Glu Thr Lys Arg Leu Leu Tyr Asn Gln Asn Lys
500 505 510

Ala Glu Ser Asn Ser His His Ala Pro Leu Ser Asp Gly Lys Thr Gly
515 520 525

[0118]

Ser Ser Tyr Pro His Trp Phe Thr Asn Gly Tyr Asp Gly Asp Gly Lys
530 535 540

Leu Pro Lys Gly Arg Thr Pro Ile Lys Phe Gly Lys Ser Asp Cys Asp
545 550 555 560

Arg Pro Pro Lys His Ser Lys Asp Gly Asn Gly Lys Thr Asp His Tyr
565 570 575

Leu Leu Glu Phe Pro Thr Phe Pro Asp Gly His Asp Tyr Lys Phe Asp
580 585 590

Ser Lys Lys Pro Lys Glu Asn Pro Gly Pro Ala Arg Val Ile Tyr Thr
595 600 605

Tyr Pro Asn Lys Val Phe Cys Gly Ile Ile Ala His Thr Lys Glu Asn
610 615 620

Gln Gly Glu Leu Lys Leu Cys Ser His
625 630

<210> 39
<211> 608
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 39

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

[0119]

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly

115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser
145 150 155 160

Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

[0120]

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Ser Asn Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Ala Ser Thr Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

[0121] Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Ala Asp Thr Val Ile
465 470 475 480

Cys Glu Pro His Gln Asp Thr Glu Thr Gly Lys Ile Lys Lys Phe Lys
485 490 495

Val Asp Val Gly Val Ala Glu Asp Gln Ala Lys Lys Ala Gly Leu Thr
500 505 510

Thr Gly Lys Ser Gly Asp Pro His Arg Tyr Met Asn Gly Asp Lys Ile
515 520 525

Asn Phe Gly Ile His Asn Cys Asp Lys Glu Gly Ala Ile Leu Trp Glu
530 535 540

Tyr Pro Ile Tyr Trp Val Gly Lys Lys Ala Glu Trp Met Lys Asp Glu
545 550 555 560

Lys Thr Asp Arg Gln Pro Gly Gly Pro Thr Pro Ile Arg Val Val Tyr
565 570 575

[0122]

Ala Asn Asn Asn Gly Asn Ile Val Tyr Cys Gly Val Met Thr His Ala
580 585 590

Val Val Lys Ser Asn Asn Gln Gly Glu Lys Phe Phe Leu Lys Cys Thr
595 600 605

<210> 40
<211> 600
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 40

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

[0123] Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Ala Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

[0124] Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly
435 440 445

Gly Ser Ala Val Thr Trp Thr Cys Leu Asn Asp Gln Lys Asn Pro Lys
450 455 460

[0125]

Thr Asn Lys Tyr Glu Thr Lys Arg Leu Leu Tyr Asn Gln Asn Lys Ala
465 470 475 480

Glu Ser Asn Ser His His Ala Pro Leu Ser Asp Gly Lys Thr Gly Ser
485 490 495

Ser Tyr Pro His Trp Phe Thr Asn Gly Tyr Asp Gly Asp Gly Lys Leu
500 505 510

Pro Lys Gly Arg Thr Pro Ile Lys Phe Gly Lys Ser Asp Cys Asp Arg
515 520 525

Pro Pro Lys His Ser Lys Asp Gly Asn Gly Lys Thr Asp His Tyr Leu
530 535 540

Leu Glu Phe Pro Thr Phe Pro Asp Gly His Asp Tyr Lys Phe Asp Ser

545 550 555 560

Lys Lys Pro Lys Glu Asn Pro Gly Pro Ala Arg Val Ile Tyr Thr Tyr
565 570 575

Pro Asn Lys Val Phe Cys Gly Ile Ile Ala His Thr Lys Glu Asn Gln
580 585 590

Gly Glu Leu Lys Leu Cys Ser His
595 600

<210> 41
<211> 218
<212> PRT
<213> artificial sequence

<220>
[0126] <223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 41

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Asp Tyr Glu
20 25 30

Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
85 90 95

Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

[0127]

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 42
<211> 583
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 42

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
50 55 60

Lys Gly Arg Ala Thr Phe Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

[0128] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Ala Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

[0129]

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu

355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly
435 440 445

[0130]

Gly Ser Ala Asp Thr Val Ile Cys Glu Pro His Gln Asp Thr Glu Thr
450 455 460

Gly Lys Ile Lys Lys Phe Lys Val Asp Val Gly Val Ala Glu Asp Gln
465 470 475 480

Ala Lys Lys Ala Gly Leu Thr Thr Gly Lys Ser Gly Asp Pro His Arg
485 490 495

Tyr Met Asn Gly Asp Lys Ile Asn Phe Gly Ile His Asn Cys Asp Lys
500 505 510

Glu Gly Ala Ile Leu Trp Glu Tyr Pro Ile Tyr Trp Val Gly Lys Lys
515 520 525

Ala Glu Trp Met Lys Asp Glu Lys Thr Asp Arg Gln Pro Gly Gly Pro
530 535 540

Thr Pro Ile Arg Val Val Tyr Ala Asn Asn Asn Gly Asn Ile Val Tyr
545 550 555 560

Cys Gly Val Met Thr His Ala Val Val Lys Ser Asn Asn Gln Gly Glu
565 570 575

Lys Phe Phe Leu Lys Cys Thr
580

<210> 43
<211> 218
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 43

[0131]

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Asp Tyr Glu
20 25 30

Gly Asp Ser Phe Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn

85 90 95

Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

[0132]

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 44
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 44

Thr Arg His Arg Gln Pro Arg Gly Trp Glu Gln Leu
1 5 10

<210> 45
<211> 10
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 45

Ala Gly Asn Arg Val Arg Arg Ser Val Gly
1 5 10

<210> 46
<211> 11
<212> PRT
<213> artificial sequence

[0133]

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 46

His Arg Arg Arg Lys Arg Ser Leu Asp Thr Ser
1 5 10

<210> 47
<211> 130
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 47

Ala Pro Ile Val Thr Cys Arg Pro Lys Leu Asp Gly Arg Glu Lys Pro
1 5 10 15

Phe Lys Val Asp Val Ala Thr Ala Gln Ala Gln Ala Arg Lys Ala Gly
20 25 30

Leu Thr Thr Gly Lys Ser Gly Asp Pro His Arg Tyr Phe Ala Gly Asp
35 40 45

His Ile Arg Trp Gly Val Asn Asn Cys Asp Lys Ala Asp Ala Ile Leu
50 55 60

Trp Glu Tyr Pro Ile Tyr Trp Val Gly Lys Asn Ala Glu Trp Ala Lys
65 70 75 80

Asp Val Lys Thr Ser Gln Gln Lys Gly Gly Pro Thr Pro Ile Arg Val
85 90 95

Val Tyr Ala Asn Ser Arg Gly Ala Val Gln Tyr Cys Gly Val Met Thr
100 105 110

[0134]

His Ser Lys Val Asp Lys Asn Asn Gln Gly Lys Glu Phe Phe Glu Lys
115 120 125

Cys Asp
130

<210> 48
<211> 133
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 48

Ala Asp Thr Val Ile Cys Glu Pro His Gln Asp Thr Glu Thr Gly Lys
1 5 10 15

Ile Lys Lys Phe Lys Val Asp Val Gly Val Ala Glu Asp Gln Ala Lys
20 25 30

Lys Ala Gly Leu Thr Thr Gly Lys Ser Gly Asp Pro His Arg Tyr Met
35 40 45

Asn Gly Asp Lys Ile Asn Phe Gly Ile His Asn Cys Asp Lys Glu Gly
50 55 60

Ala Ile Leu Trp Glu Tyr Pro Ile Tyr Trp Val Gly Lys Lys Ala Glu
65 70 75 80

Trp Met Lys Asp Glu Lys Thr Asp Arg Gln Pro Gly Gly Pro Thr Pro
85 90 95

Ile Arg Val Val Tyr Ala Asn Asn Asn Gly Asn Ile Val Tyr Cys Gly
[0135] 100 105 110

Val Met Thr His Ala Val Val Lys Ser Asn Asn Gln Gly Glu Lys Phe
115 120 125

Phe Leu Lys Cys Thr
130

<210> 49
<211> 133
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 49

Ala Asp Thr Val Ile Cys Glu Pro His Gln Asp Thr Glu Thr Gly Lys

1 5 10 15

Ile Lys Lys Phe Lys Val Asp Val Gly Val Ala Glu Asp Gln Ala Lys
20 25 30

Lys Ala Gly Leu Thr Thr Gly Lys Ser Gly Tyr Pro His Arg Tyr Met
35 40 45

Asn Gly Asp Lys Ile Asn Phe Gly Ile His Asn Cys Asp Lys Glu Gly
50 55 60

Ala Ile Leu Trp Glu Tyr Pro Ile Tyr Trp Val Gly Lys Lys Ala Glu
65 70 75 80

Trp Met Lys Asp Glu Lys Thr Asp Arg Gln Pro Gly Gly Pro Thr Pro
85 90 95

[0136]

Ile Arg Val Val Tyr Ala Asn Asn Asn Gly Asn Ile Val Tyr Cys Gly
100 105 110

Val Met Thr His Ala Val Val Lys Ser Asn Asn Gln Gly Glu Lys Phe
115 120 125

Phe Leu Lys Cys Thr
130

<210> 50
<211> 123
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 50

Gln Asp Asn Ser Arg Tyr Thr His Phe Leu Thr Gln His Tyr Asp Ala
1 5 10 15

Lys Pro Gln Gly Arg Asp Asp Arg Tyr Cys Glu Ser Ile Met Arg Arg
20 25 30

Arg Gly Leu Thr Ser Pro Cys Lys Asp Ile Asn Thr Phe Ile His Gly
35 40 45

Asn Lys Arg Ser Ile Lys Ala Ile Cys Glu Asn Lys Asn Gly Asn Pro
50 55 60

His Arg Glu Asn Leu Arg Ile Ser Lys Ser Ser Phe Gln Val Thr Thr
65 70 75 80

Cys Lys Leu His Arg Arg Ser Pro Trp Pro Pro Cys Gln Tyr Arg Ala
85 90 95

[0137]

Thr Ala Gly Phe Arg Asn Val Val Val Ala Cys Glu Asn Gly Leu Pro
100 105 110

Val His Leu Asp Gln Ser Ile Phe Arg Arg Pro
115 120

<210> 51
<211> 133
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 51

Ala Asp Thr Val Ile Cys Glu Pro His Gln Asp Thr Glu Thr Gly Lys
1 5 10 15

Ile Lys Lys Phe Lys Val Asp Val Gly Val Ala Glu Asp Gln Ala Lys
20 25 30

Lys Ala Gly Leu Ile Thr Gly Lys Ser Gly Asp Pro His Arg Tyr Met
35 40 45

Asn Gly Asp Lys Ile Asn Phe Gly Ile His Asn Cys Asp Lys Glu Gly
50 55 60

Ala Ile Leu Trp Glu Tyr Pro Ile Tyr Trp Val Gly Lys Lys Ala Glu
65 70 75 80

Trp Met Lys Asp Glu Lys Thr Asp Arg Gln Pro Gly Gly Pro Thr Pro
85 90 95

Ile Arg Val Val Tyr Ala Asn Asn Asn Gly Asn Ile Val Tyr Cys Gly
100 105 110

[0138]

Val Met Thr His Ala Val Val Lys Ser Asn Asn Gln Gly Glu Lys Phe
115 120 125

Phe Leu Lys Cys Thr
130

<210> 52
<211> 133
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 52

Ala Asp Thr Val Ile Cys Glu Pro Arg Gln Asp Thr Glu Thr Gly Lys
1 5 10 15

Ile Lys Lys Phe Lys Val Asp Val Gly Val Ala Glu Asp Gln Ala Lys
20 25 30

Lys Ala Gly Leu Ile Thr Gly Lys Ser Gly Asp Pro His Arg Tyr Met
35 40 45

Asn Gly Asp Lys Ile Asn Phe Gly Ile His Asn Cys Asp Lys Glu Gly
50 55 60

Ala Ile Leu Trp Glu Tyr Pro Ile Tyr Trp Val Gly Lys Lys Ala Glu
65 70 75 80

Trp Met Lys Asp Glu Lys Thr Asp Arg Gln Pro Gly Gly Pro Thr Pro
85 90 95

Ile Arg Val Val Tyr Ala Asn Asn Asn Gly Asn Ile Val Tyr Cys Gly
[0139] 100 105 110

Val Met Thr His Ala Val Val Lys Ser Asn Asn Gln Gly Glu Lys Phe
115 120 125

Phe Leu Lys Cys Thr
130

<210> 53
<211> 133
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 53

Ala Asp Thr Val Ile Cys Glu Pro His Gln Asp Thr Glu Thr Gly Lys

1 5 10 15

Ile Lys Lys Phe Thr Val Asp Val Gly Val Ala Glu Asp Gln Ala Lys
20 25 30

Lys Ala Gly Leu Thr Thr Gly Lys Ser Gly Asp Pro His Arg Tyr Met
35 40 45

Asn Gly Asp Asn Ile Asn Phe Gly Ile His Asn Cys Asp Lys Glu Gly
50 55 60

Ala Ile Leu Trp Glu Tyr Pro Ile Tyr Trp Val Gly Lys Lys Ala Glu
65 70 75 80

Trp Lys Lys Asp Glu Lys Thr Asp Arg Gln Pro Gly Gly Pro Thr Pro
85 90 95

[0140]

Leu Arg Val Val Tyr Ala Asn Asn Asn Gly Asn Ile Val Tyr Cys Gly
100 105 110

Val Met Thr His Ala Val Val Lys Ser Asn Asn Gln Gly Glu Lys Phe
115 120 125

Phe Leu Lys Cys Thr
130

<210> 54
<211> 135
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 54

Ala Glu Thr Val Gln Tyr Tyr Asn Ser Tyr Ser Asp Ala Ser Ile Ala
1 5 10 15

Ser Cys Ala Phe Val Asp Ser Gly Lys Asp Lys Ile Asp Lys Thr Lys
20 25 30

Leu Val Thr Tyr Thr Ser Arg Leu Ala Ala Ser Pro Ala Tyr Gln Lys
35 40 45

Val Val Gly Val Gly Leu Lys Thr Ala Ala Gly Ser Ile Val Pro Tyr
50 55 60

Val Arg Leu Asp Met Asp Asn Thr Gly Lys Gly Ile His Phe Asn Ala
65 70 75 80

Thr Lys Leu Ser Asp Ser Ser Ala Lys Leu Ala Ala Val Leu Lys Thr
85 90 95

[0141]

Thr Val Ser Met Thr Glu Ala Gln Arg Thr Gln Leu Tyr Met Glu Tyr
100 105 110

Ile Lys Gly Ile Glu Asn Arg Ser Ala Gln Phe Ile Trp Asp Trp Trp
115 120 125

Arg Thr Gly Lys Ala Pro Ala
130 135

<210> 55
<211> 150
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 55

Ala Val Thr Trp Thr Cys Leu Asn Asp Gln Lys Asn Pro Lys Thr Asn
1 5 10 15

Lys Tyr Glu Thr Lys Arg Leu Leu Tyr Asn Gln Asn Lys Ala Glu Ser
20 25 30

Asn Ser His His Ala Pro Leu Ser Asp Gly Lys Thr Gly Ser Ser Tyr
35 40 45

Pro His Trp Phe Thr Asn Gly Tyr Asp Gly Asp Gly Lys Leu Pro Lys
50 55 60

Gly Arg Thr Pro Ile Lys Phe Gly Lys Ser Asp Cys Asp Arg Pro Pro
65 70 75 80

Lys His Ser Lys Asp Gly Asn Gly Lys Thr Asp His Tyr Leu Leu Glu
85 90 95

[0142]

Phe Pro Thr Phe Pro Asp Gly His Asp Tyr Lys Phe Asp Ser Lys Lys
100 105 110

Pro Lys Glu Asn Pro Gly Pro Ala Arg Val Ile Tyr Thr Tyr Pro Asn
115 120 125

Lys Val Phe Cys Gly Ile Ile Ala His Thr Lys Glu Asn Gln Gly Glu
130 135 140

Leu Lys Leu Cys Ser His
145 150

<210> 56
<211> 150
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 56

Ala Val Thr Trp Thr Cys Leu Asn Thr Gln Lys Asn Pro Lys Thr Asn
1 5 10 15

Lys Tyr Glu Thr Lys Arg Leu Leu Tyr Asn Gln Asn Lys Ala Glu Ser
20 25 30

Asn Ser His His Ala Pro Leu Ser Asp Gly Lys Thr Gly Ser Ser Tyr
35 40 45

Pro His Trp Phe Thr Asn Gly Tyr Asp Gly Asp Gly Lys Leu Pro Lys
50 55 60

[0143] Gly Arg Thr Pro Ile Lys Phe Gly Lys Ser Asp Cys Asp Arg Pro Pro
65 70 75 80

Lys His Ser Lys Asp Gly Asn Gly Lys Thr Asp His Tyr Leu Leu Glu
85 90 95

Phe Pro Thr Phe Pro Asp Gly His Asp Tyr Lys Phe Asp Ser Lys Lys
100 105 110

Pro Lys Glu Asn Pro Gly Pro Ala Arg Val Ile Tyr Thr Tyr Pro Asn
115 120 125

Lys Val Phe Cys Gly Ile Ile Ala His Thr Lys Glu Asn Thr Gly Glu
130 135 140

Leu Lys Leu Cys Ser His
145 150

<210> 57
<211> 128
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 57

Lys Glu Ser Arg Ala Lys Lys Phe Gln Arg Gln His Met Asp Ser Asp
1 5 10 15

Ser Ser Pro Ser Ser Ser Ser Thr Tyr Cys Asn Gln Met Met Arg Arg
20 25 30

Arg Asn Met Thr Gln Gly Arg Cys Lys Pro Val Asn Thr Phe Val His
35 40 45

[0144]

Glu Pro Leu Val Asp Val Gln Asn Val Cys Phe Gln Glu Lys Val Thr
50 55 60

Cys Lys Asn Gly Gln Gly Asn Cys Tyr Lys Ser Asn Ser Ser Met His
65 70 75 80

Ile Thr Asp Cys Arg Leu Thr Asn Gly Ser Arg Tyr Pro Asn Cys Ala
85 90 95

Tyr Arg Thr Ser Pro Lys Glu Arg His Ile Ile Val Ala Cys Glu Gly
100 105 110

Ser Pro Tyr Val Pro Val His Phe Asp Ala Ser Val Glu Asp Ser Thr
115 120 125

<210> 58
<211> 10

<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 58

Gly Tyr Thr Phe Ser Ser Tyr Trp Ile Glu
1 5 10

<210> 59
<211> 18
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 59

[0145] Gly Glu Ile Leu Pro Gly Gly Gly Asp Thr Asn Tyr Asn Glu Ile Phe
1 5 10 15

Lys Gly

<210> 60
<211> 10
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 60

Thr Arg Arg Val Pro Ile Arg Leu Asp Tyr
1 5 10

<210> 61

<211> 15
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 61

Lys Ala Ser Gln Ser Val Asp Tyr Glu Gly Asp Ser Phe Leu Asn
1 5 10 15

<210> 62
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 62

[0146]

Ala Ala Ser Asn Leu Glu Ser
1 5

<210> 63
<211> 10
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 63

Cys Gln Gln Ser Asn Glu Asp Pro Leu Thr
1 5 10

<210> 64
<211> 9
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 64

Tyr Thr Phe Thr Ser Tyr Asn Met His
1 5

<210> 65
<211> 14
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 65

Trp Ile Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr
1 5 10

[0147]

<210> 66
<211> 13
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 66

Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val
1 5 10

<210> 67
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 67

Ser Ser Val Ser Tyr Ile His
1 5

<210> 68
<211> 11
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 68

[0148]

Pro Trp Ile Tyr Ala Thr Ser Asn Leu Ala Ser
1 5 10

<210> 69
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> Recombinant immunotoxin, antibody CDR, linker or toxin

<400> 69

Gln Gln Trp Thr Ser Asn Pro Pro
1 5

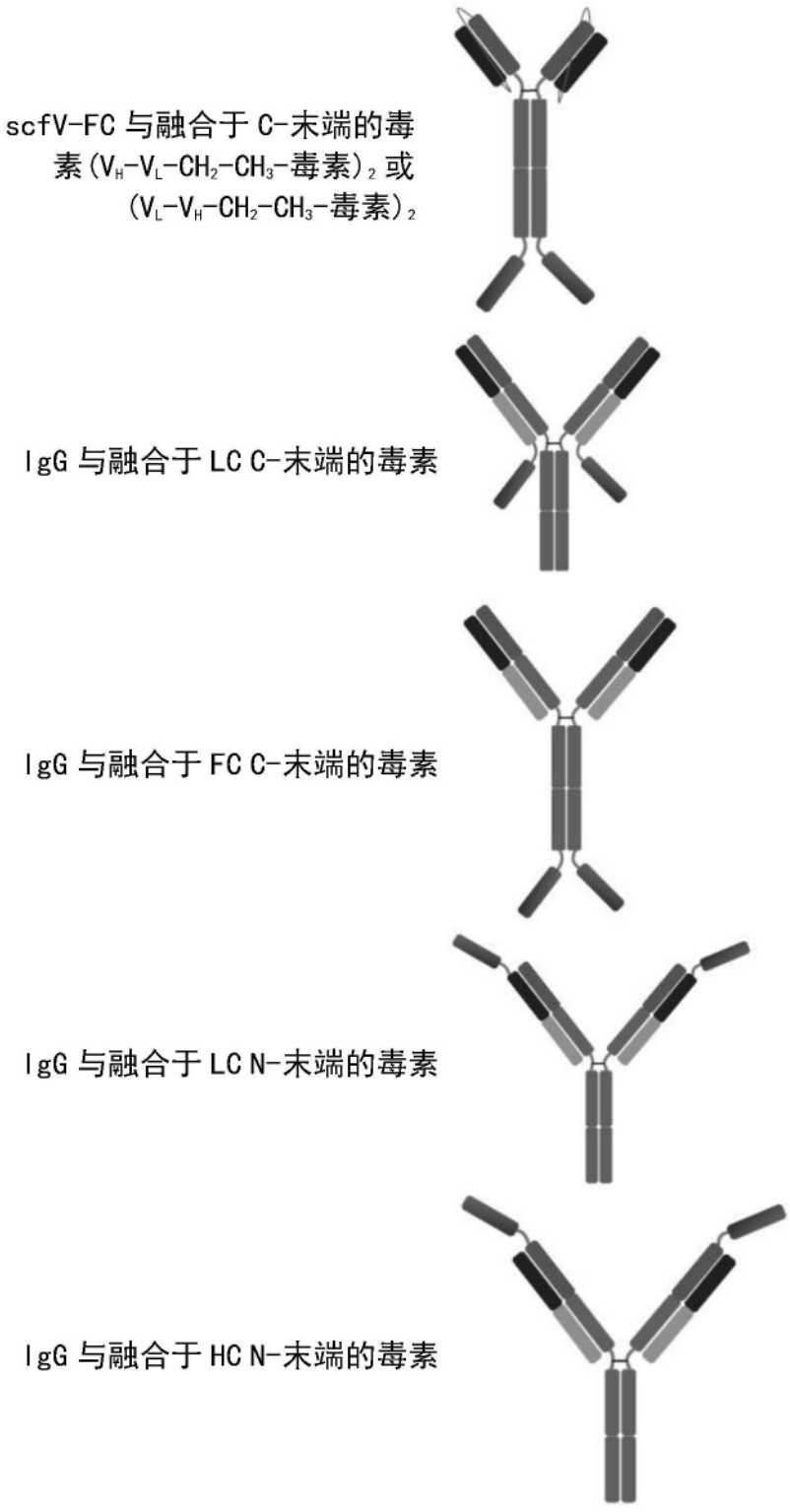

scfV-FC 与融合于 C-末端的毒素(V_H-V_L-CH_2-CH_3-毒素)$_2$ 或 (V_L-V_H-CH_2-CH_3-毒素)$_2$
IgG 与融合于 LC C-末端的毒素
IgG 与融合于 FC C-末端的毒素
IgG 与融合于 LC N-末端的毒素
IgG 与融合于 HC N-末端的毒素

图1

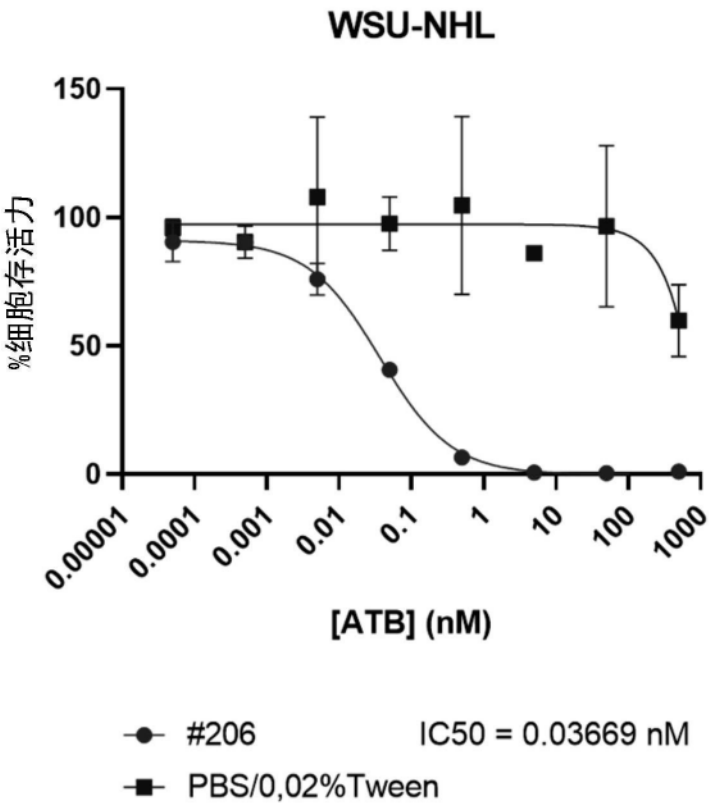

WSU-NHL
%细胞存活力
150
100
50
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[ATB] (nM)
#206
IC50 = 0.03669 nM
PBS/0,02%Tween

图2

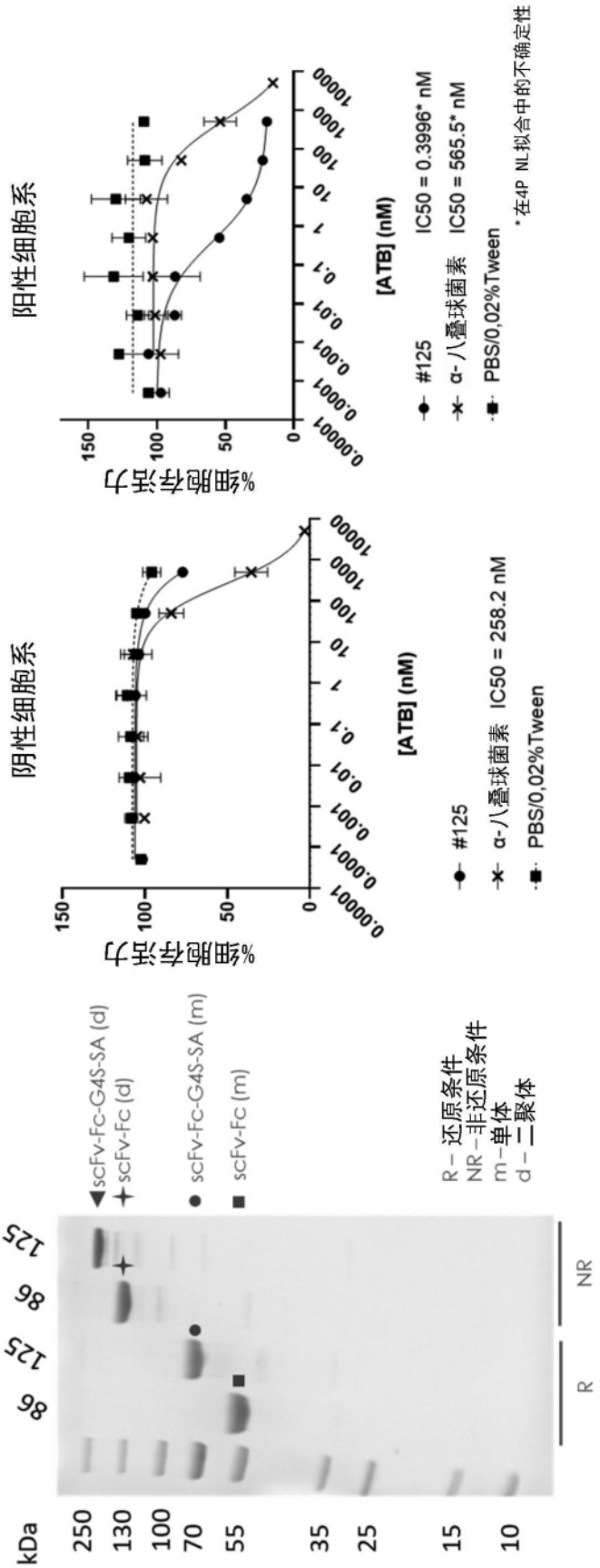

阳性细胞系
%细胞存活力
[ATB] (nM)
#125 IC50 = 0.3996* nM
α-八叠球菌素 IC50 = 565.5* nM
PBS/0,02%Tween
*在4P NL拟合中的不确定性
阴性细胞系
%细胞存活力
[ATB] (nM)
#125
α-八叠球菌素 IC50 = 258.2 nM
PBS/0,02%Tween
kDa
250
130
100
70
55
35
25
15
10
86
125
86
125
R
NR
scFv-Fc-G4S-SA (d)
scFv-Fc (d)
scFv-Fc-G4S-SA (m)
scFv-Fc (m)
R – 还原条件
NR – 非还原条件
m – 单体
d – 二聚体

图3

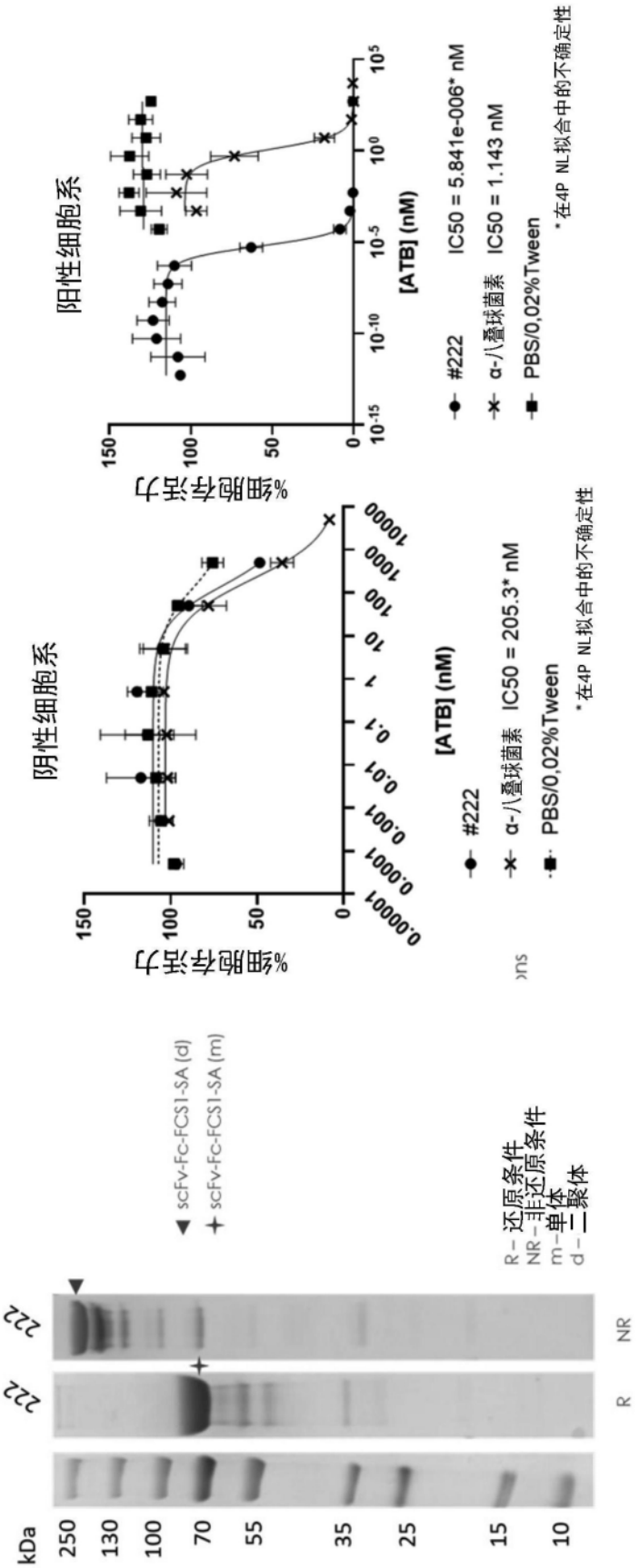
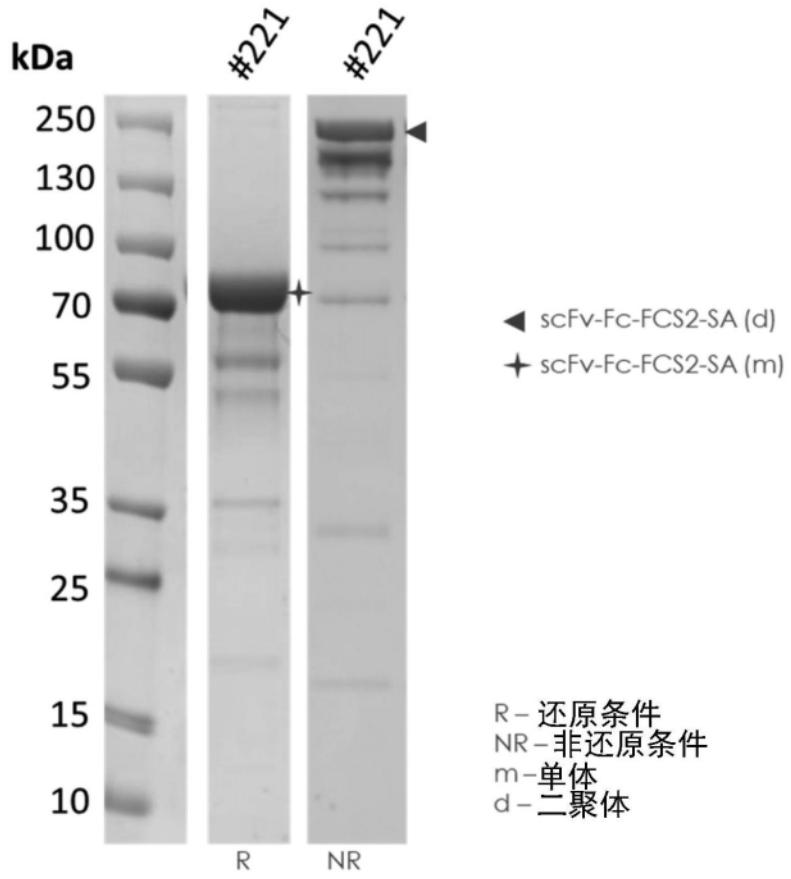

阳性细胞系
%细胞存活力
[ATB] (nM)
#222 IC50 = 5.841e-006* nM
α-八叠球菌素 IC50 = 1.143 nM
PBS/0,02%Tween
*在4P NL拟合中的不确定性
阴性细胞系
%细胞存活力
[ATB] (nM)
#222
α-八叠球菌素 IC50 = 205.3* nM
PBS/0,02%Tween
*在4P NL拟合中的不确定性
scFv-Fc-FCS1-SA (d)
scFv-Fc-FCS1-SA (m)
R – 还原条件
NR – 非还原条件
m – 单体
d – 二聚体
kDa
250
130
100
70
55
35
25
15
10
R
NR

图4


kDa
#221
#221
250
130
100
70
55
35
25
15
10
R
NR
scFv-Fc-FCS2-SA (d)
scFv-Fc-FCS2-SA (m)
R – 还原条件
NR – 非还原条件
m – 单体
d – 二聚体

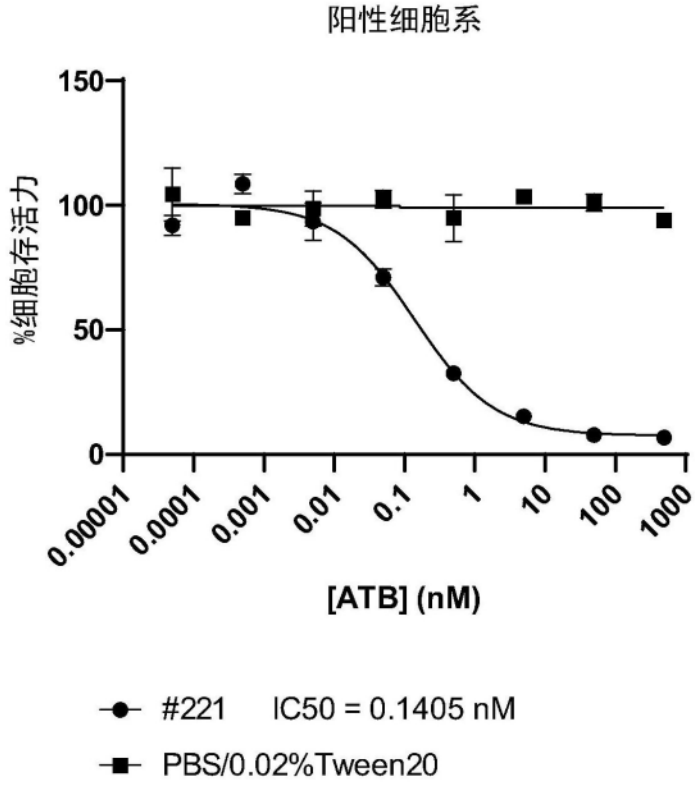
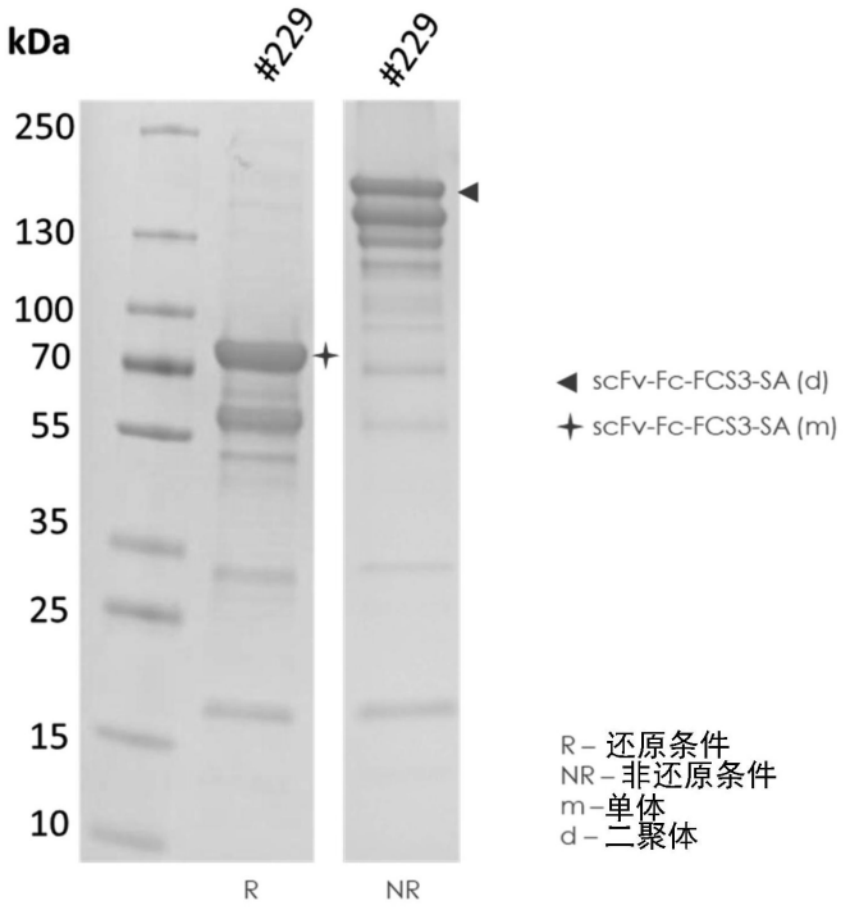

阳性细胞系
%细胞存活力
150
100
50
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[ATB] (nM)
#221 IC50 = 0.1405 nM
PBS/0.02%Tween20

图5


kDa
#229
#229
250
130
100
70
55
35
25
15
10
R
NR
scFv-Fc-FCS3-SA (d)
scFv-Fc-FCS3-SA (m)
R – 还原条件
NR – 非还原条件
m – 单体
d – 二聚体

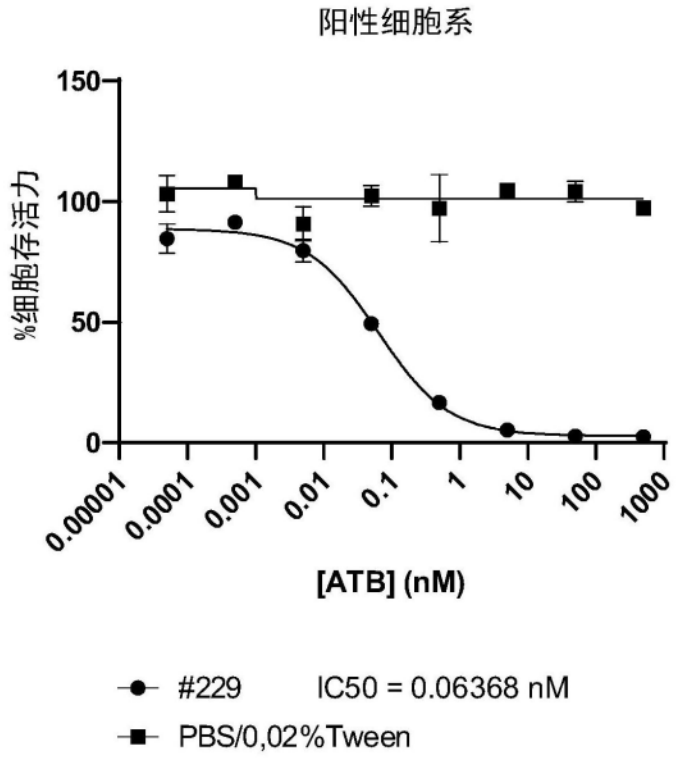
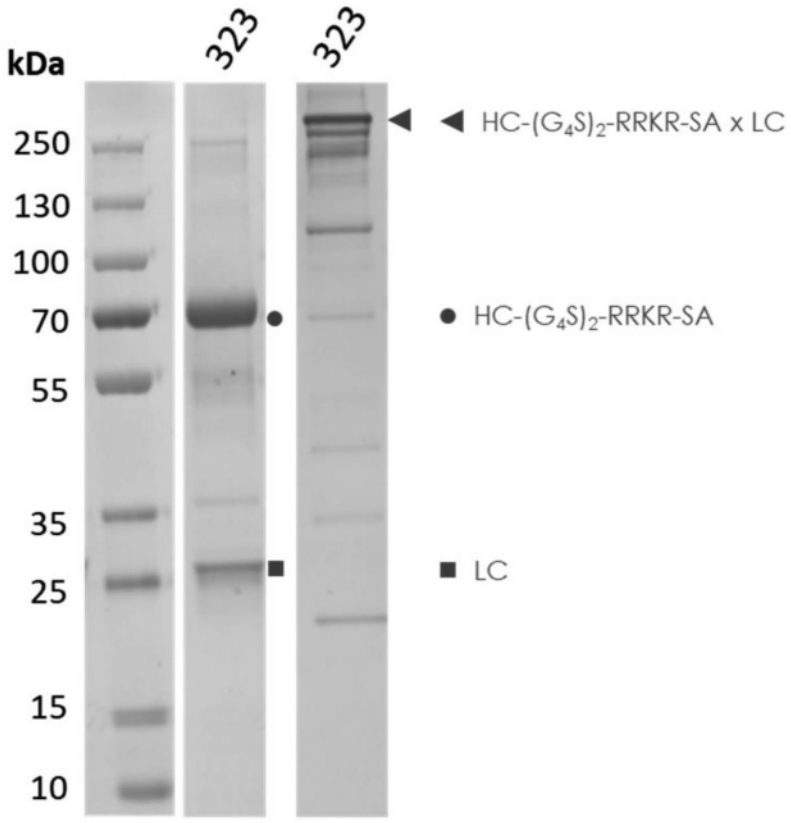

阳性细胞系
%细胞存活力
150
100
50
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[ATB] (nM)
#229 IC50 = 0.06368 nM
PBS/0,02%Tween

图6


kDa
323
323
250
130
100
70
55
35
25
15
10
HC-(G4S)2-RRKR-SA x LC
HC-(G4S)2-RRKR-SA
LC

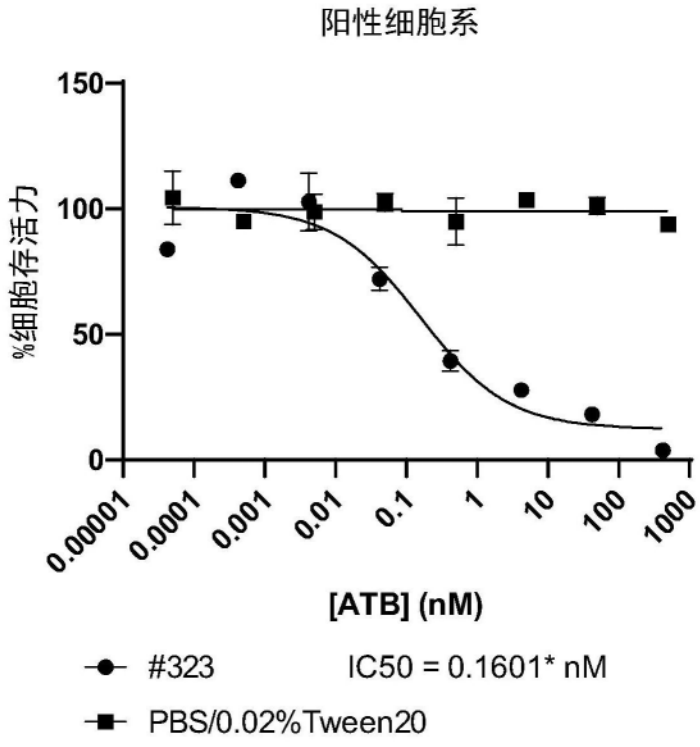
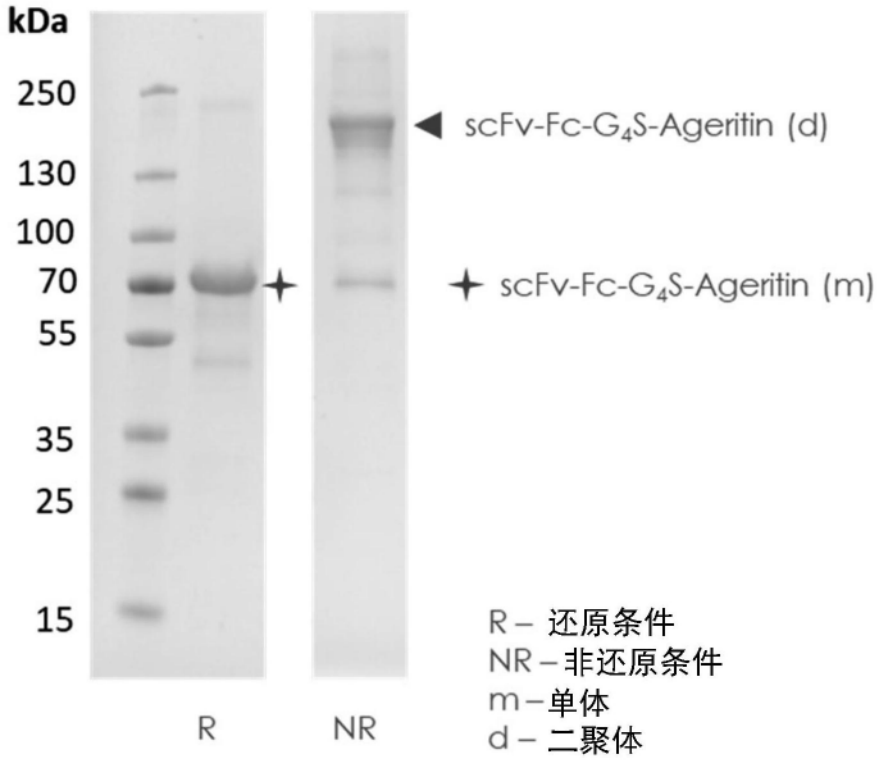

阳性细胞系
%细胞存活力
150
100
50
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[ATB] (nM)
#323
IC50 = 0.1601* nM
PBS/0.02%Tween20

图7


kDa
250
130
100
70
55
35
25
15
scFv-Fc-G4S-Ageritin (d)
scFv-Fc-G4S-Ageritin (m)
R
NR
R – 还原条件
NR – 非还原条件
m – 单体
d – 二聚体

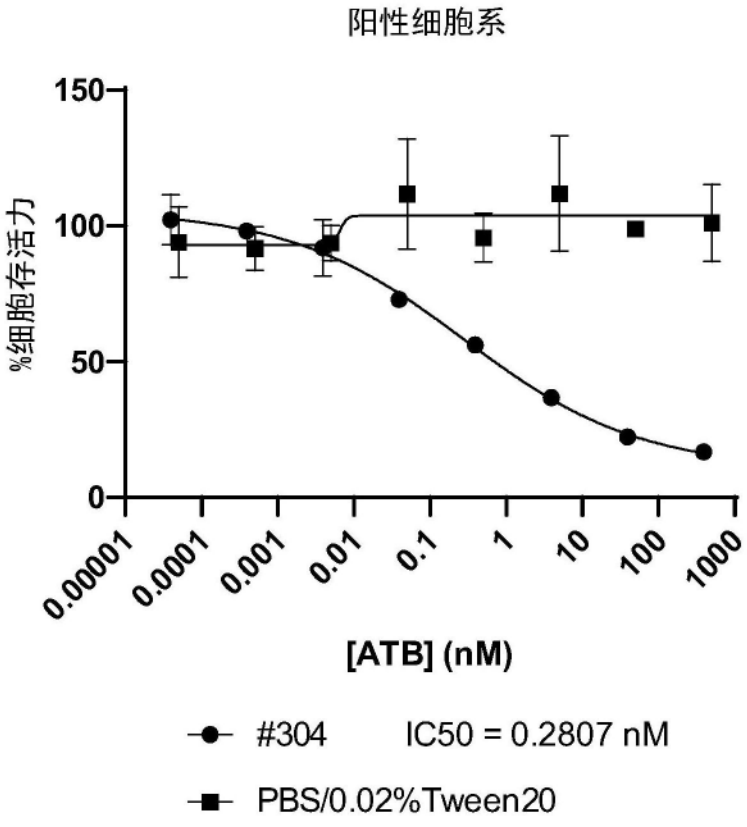
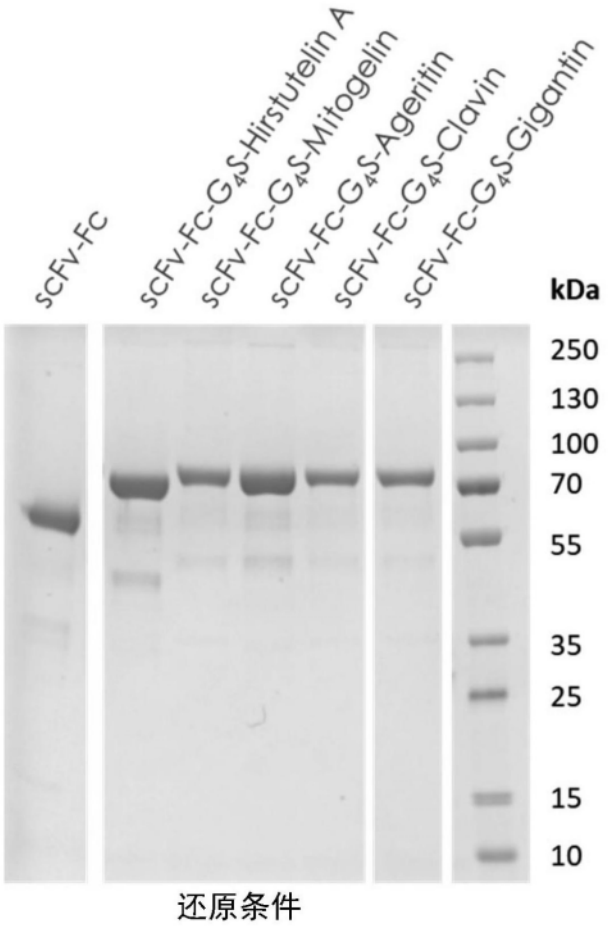

阳性细胞系
%细胞存活力
150
100
50
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[ATB] (nM)
#304 IC50 = 0.2807 nM
PBS/0.02%Tween20

图8


scFv-Fc
scFv-Fc-G4S-Hirstutelin A
scFv-Fc-G4S-Mitogelin
scFv-Fc-G4S-Ageritin
scFv-Fc-G4S-Clavin
scFv-Fc-G4S-Gigantin
kDa
250
130
100
70
55
35
25
15
10
还原条件

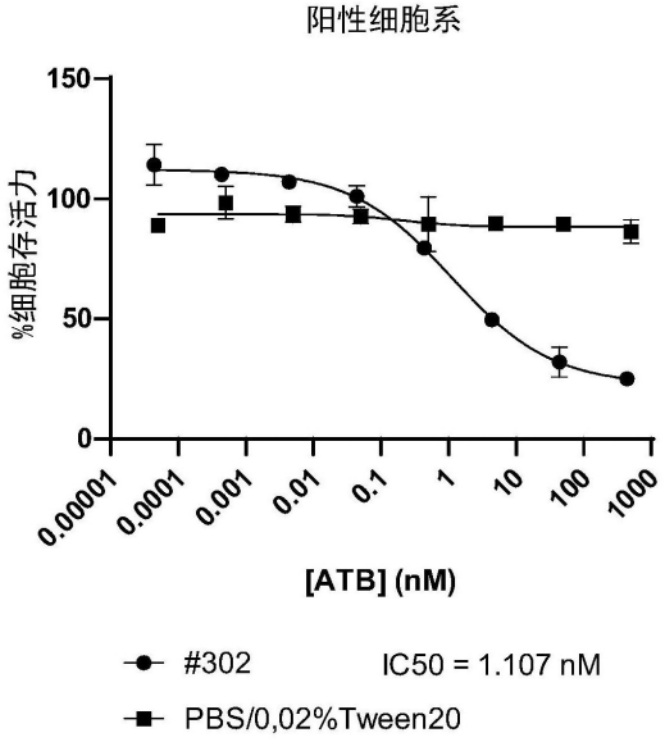
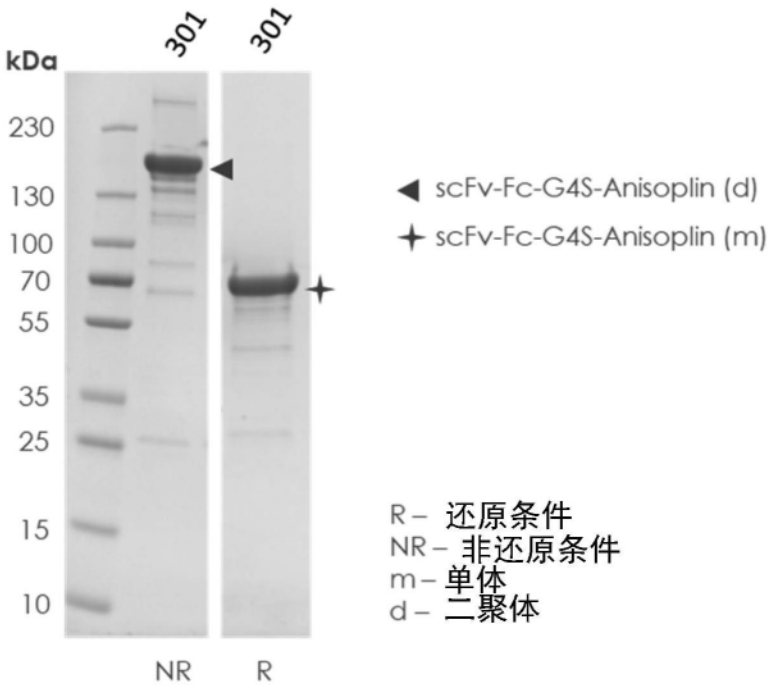

阳性细胞系
%细胞存活力
150
100
50
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[ATB] (nM)
#302
IC50 = 1.107 nM
PBS/0,02%Tween20

图9


kDa
301
301
230
130
100
70
55
35
25
15
10
NR
R
scFv-Fc-G4S-Anisoplin (d)
scFv-Fc-G4S-Anisoplin (m)
R – 还原条件
NR – 非还原条件
m – 单体
d – 二聚体

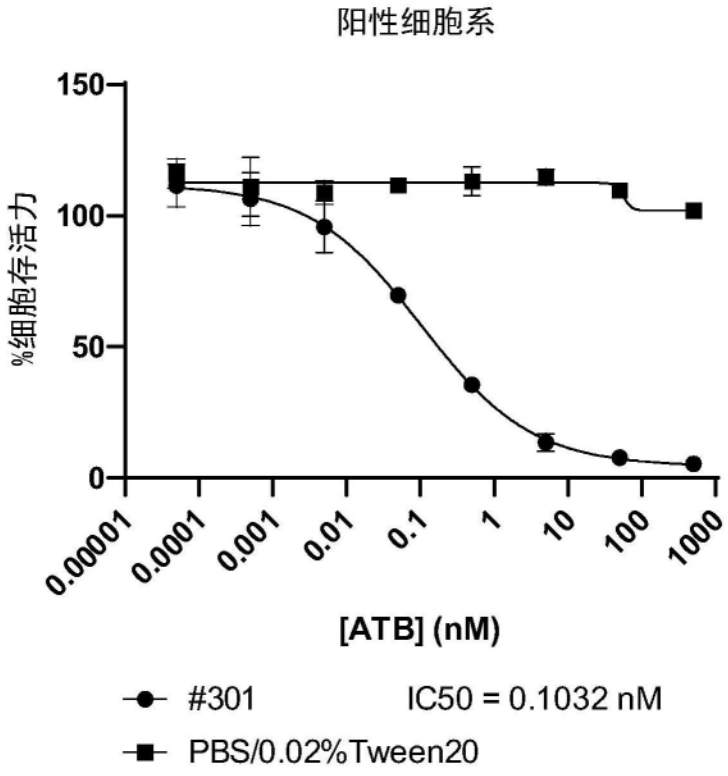
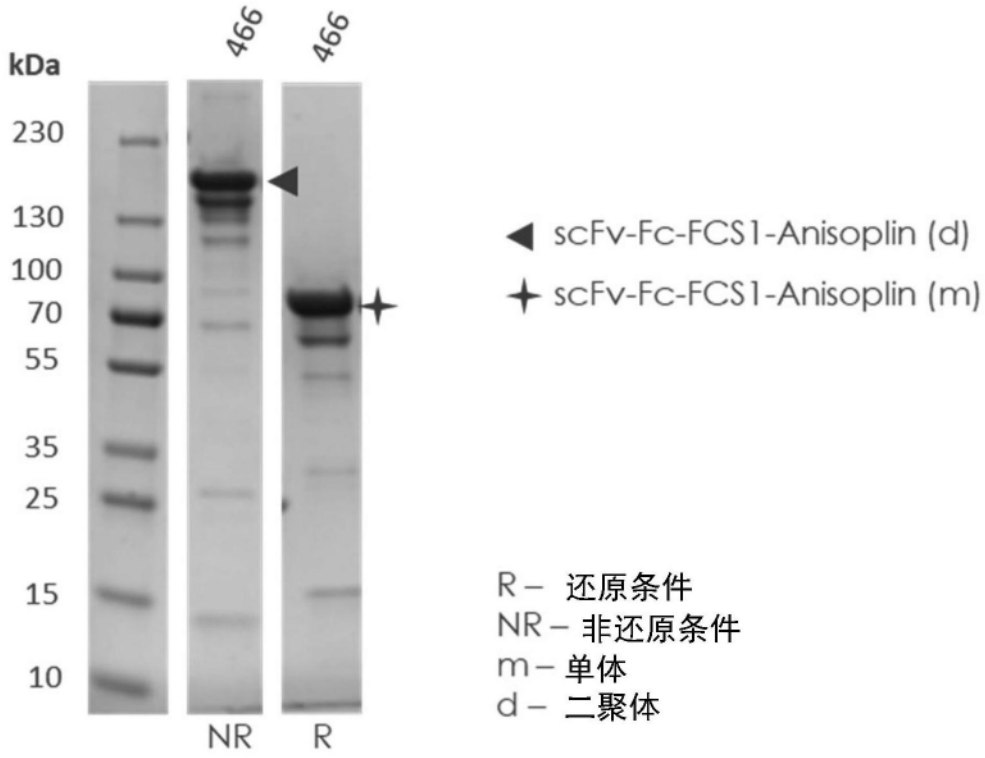

阳性细胞系
%细胞存活力
150
100
50
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[ATB] (nM)
#301
IC50 = 0.1032 nM
PBS/0.02%Tween20

图10


466
466
kDa
230
130
100
70
55
35
25
15
10
NR
R
scFv-Fc-FCS1-Anisoplin (d)
scFv-Fc-FCS1-Anisoplin (m)
R – 还原条件
NR – 非还原条件
m – 单体
d – 二聚体

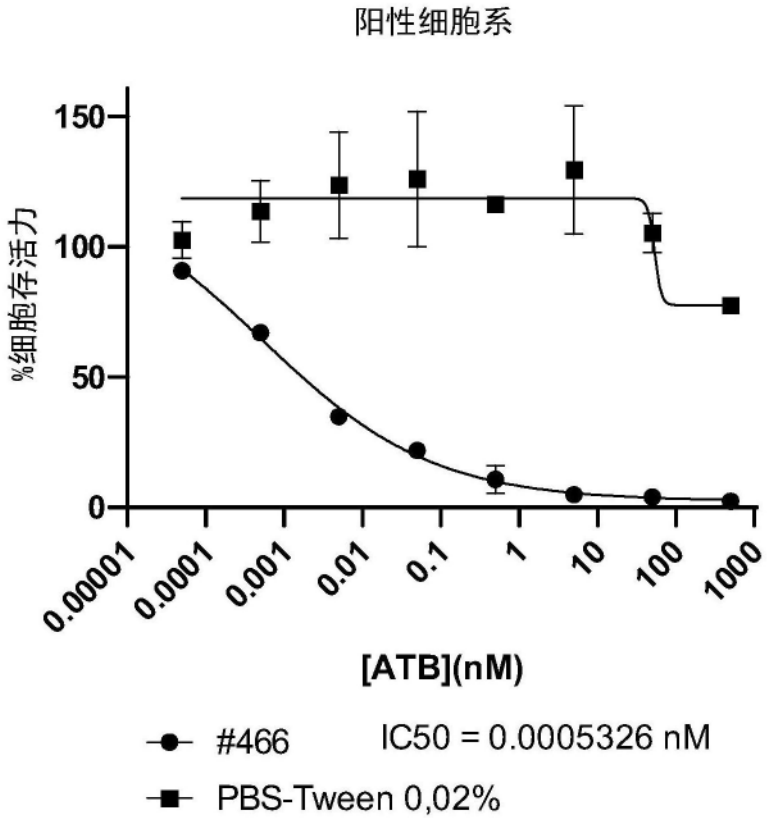
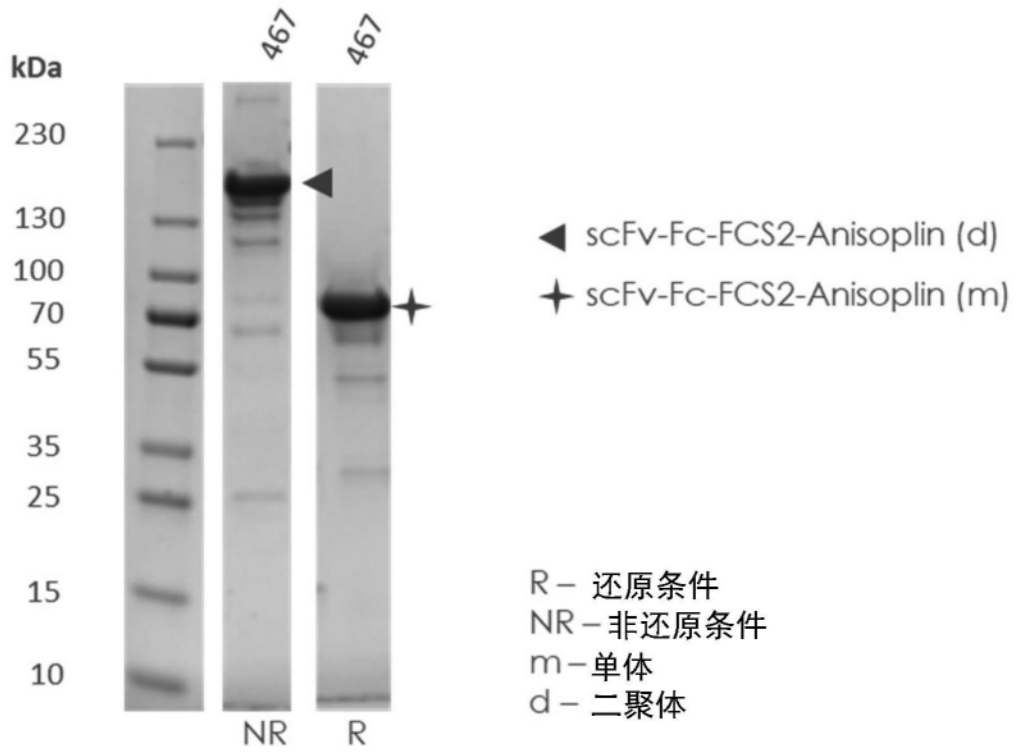

阳性细胞系
%细胞存活力
150
100
50
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[ATB](nM)
#466 IC50 = 0.0005326 nM
PBS-Tween 0,02%

图11


kDa
230
130
100
70
55
35
25
15
10
467
467
NR
R
scFv-Fc-FCS2-Anisoplin (d)
scFv-Fc-FCS2-Anisoplin (m)
R – 还原条件
NR – 非还原条件
m – 单体
d – 二聚体

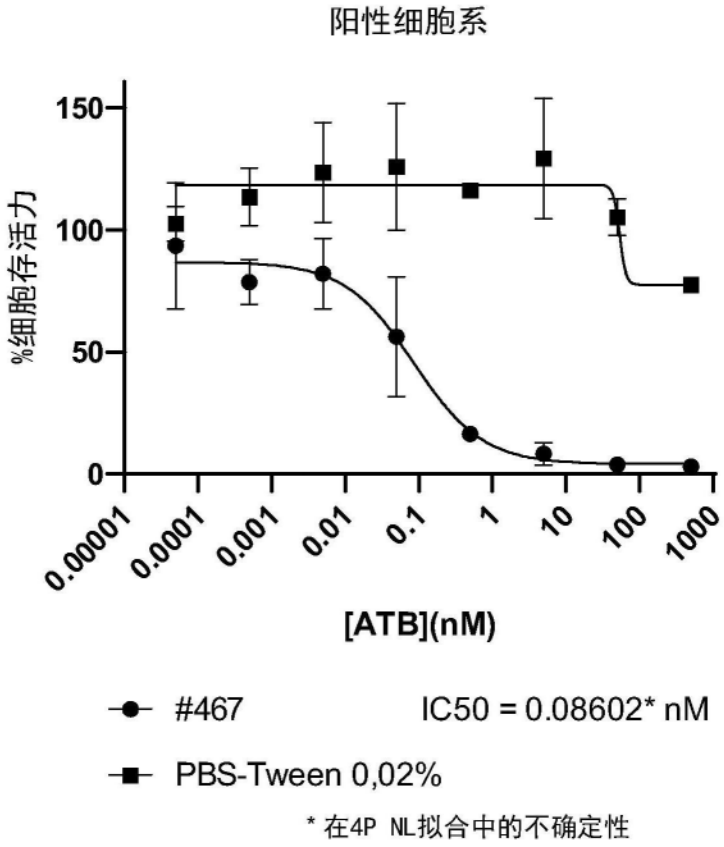
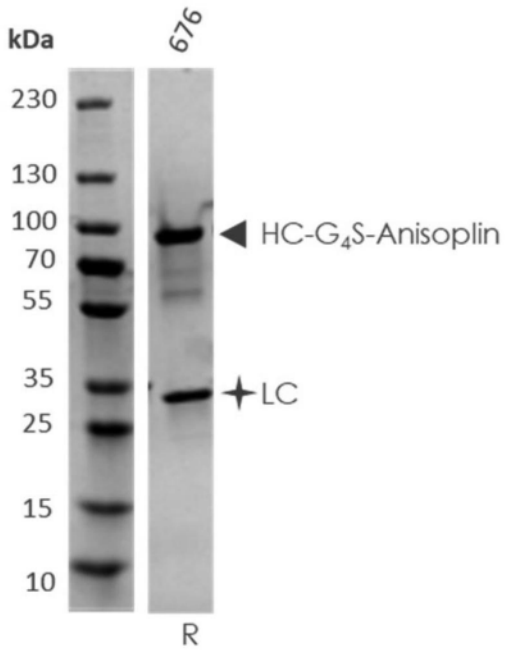

阳性细胞系
%细胞存活力
150
100
50
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[ATB](nM)
#467
IC50 = 0.08602* nM
PBS-Tween 0,02%
* 在4P NL拟合中的不确定性

图12


kDa
676
230
130
100
70
55
35
25
15
10
HC-G4S-Anisoplin
LC
R

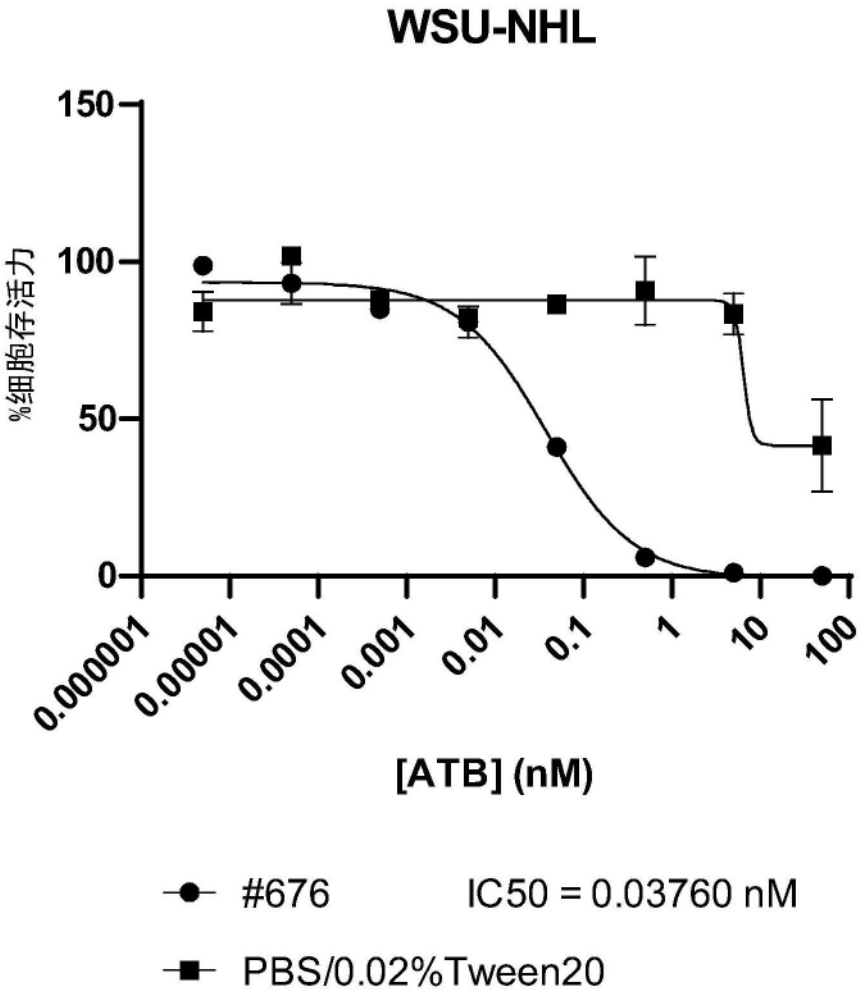
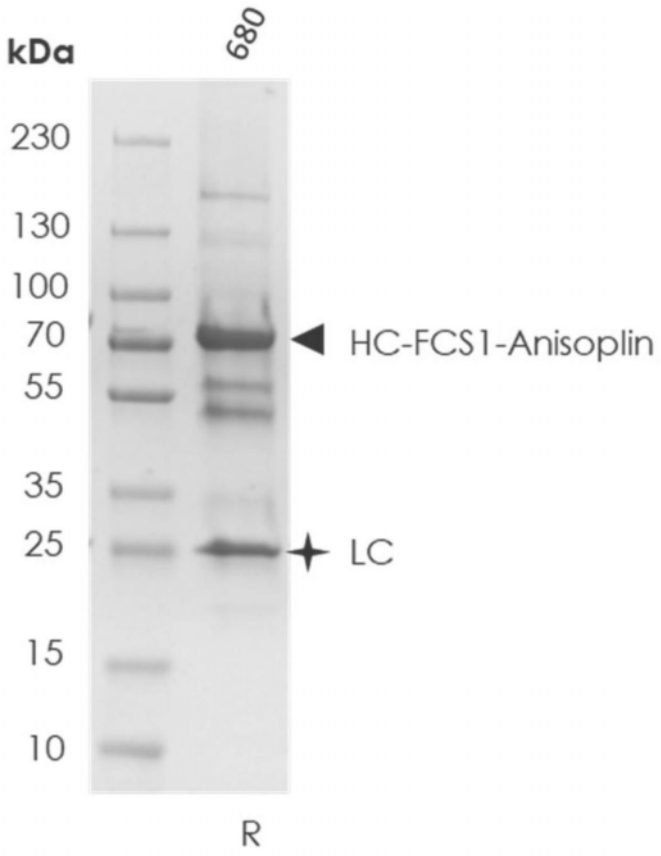

WSU-NHL
%细胞存活力
150
100
50
0
0.000001
0.00001
0.0001
0.001
0.01
0.1
1
10
100
[ATB] (nM)
#676 IC50 = 0.03760 nM
PBS/0.02%Tween20

图13


kDa
680
230
130
100
70
55
35
25
15
10
HC-FCS1-Anisoplin
LC
R

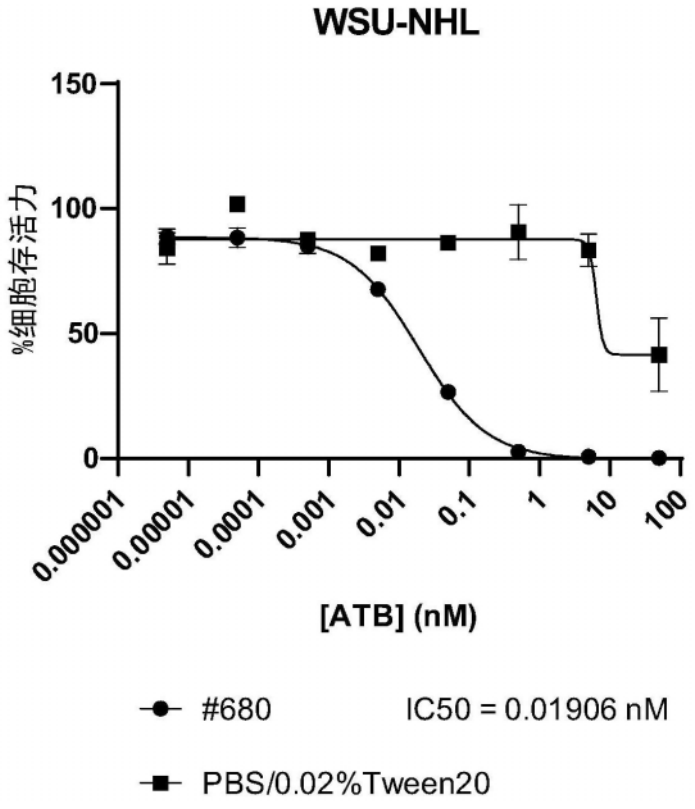

WSU-NHL
%细胞存活力
150
100
50
0
0.000001
0.00001
0.0001
0.001
0.01
0.1
1
10
100
[ATB] (nM)
#680
IC50 = 0.01906 nM
PBS/0.02%Tween20

图14

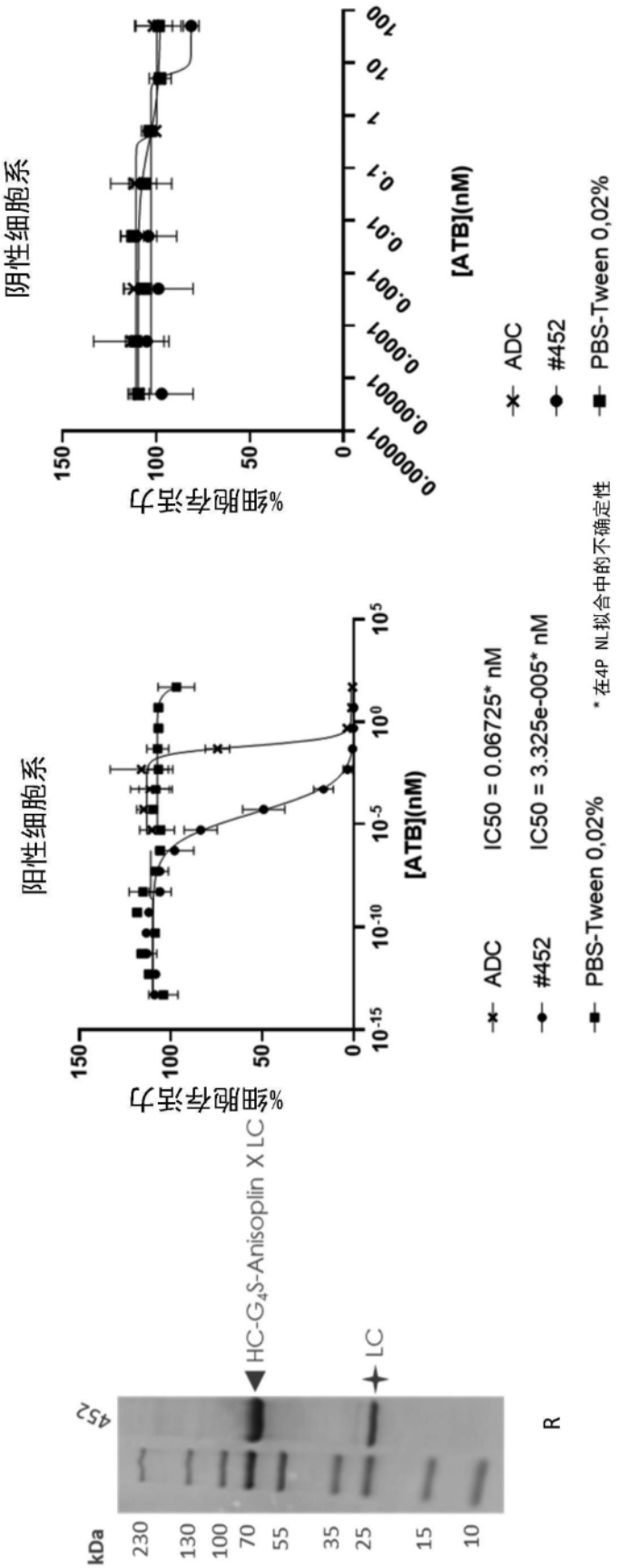

阴性细胞系
%细胞存活力
[ATB](nM)
ADC
#452
PBS-Tween 0,02%
阳性细胞系
%细胞存活力
[ATB](nM)
ADC IC50 = 0.06725* nM
#452 IC50 = 3.325e-005* nM
PBS-Tween 0,02%
* 在4P NL拟合中的不确定性
HC-G4S-Anisoplin X LC
LC
452
kDa
230
130
100
70
55
35
25
15
10
R

图15

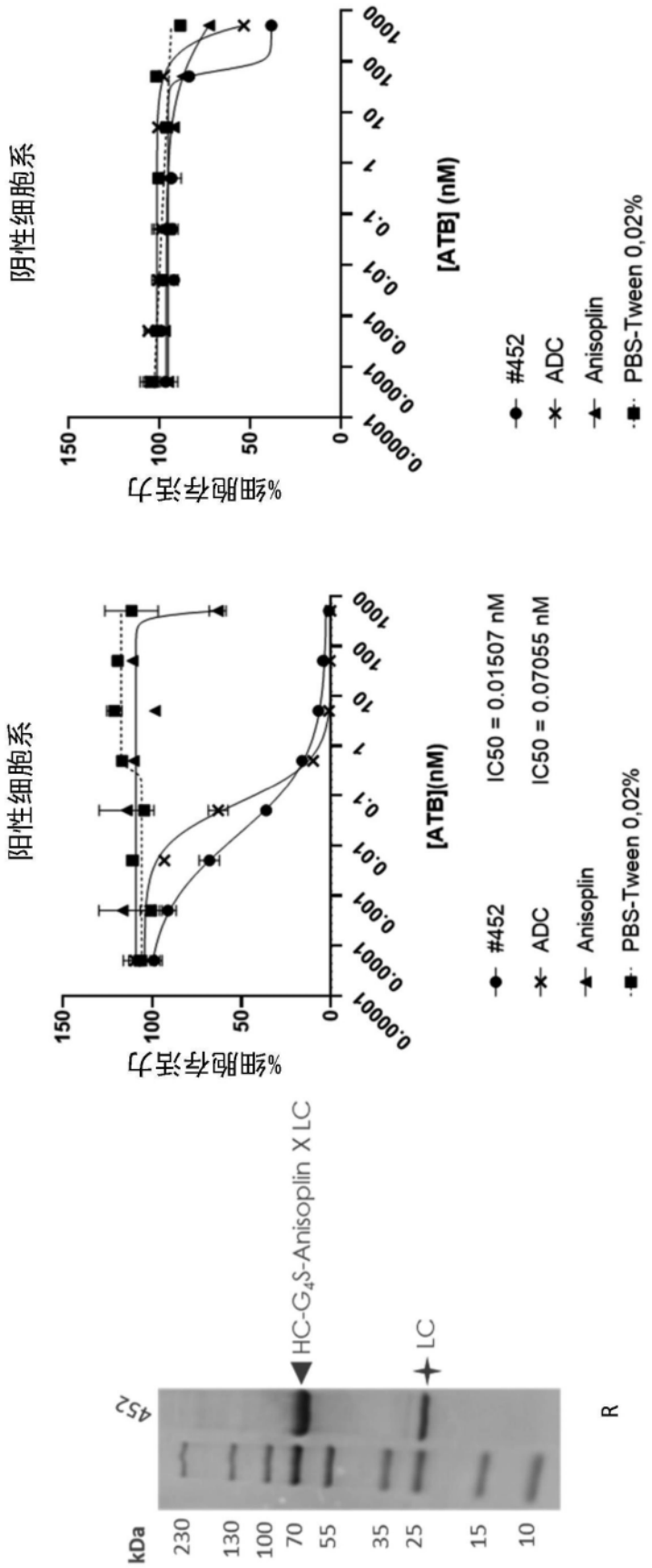

阴性细胞系
%细胞存活力
150
100
50
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[ATB] (nM)
#452
ADC
Anisoplin
PBS-Tween 0,02%
阳性细胞系
%细胞存活力
[ATB](nM)
IC50 = 0.01507 nM
IC50 = 0.07055 nM
#452
ADC
Anisoplin
PBS-Tween 0,02%
HC-G4S-Anisoplin X LC
LC
452
R
kDa
230
130
100
70
55
35
25
15
10

图16

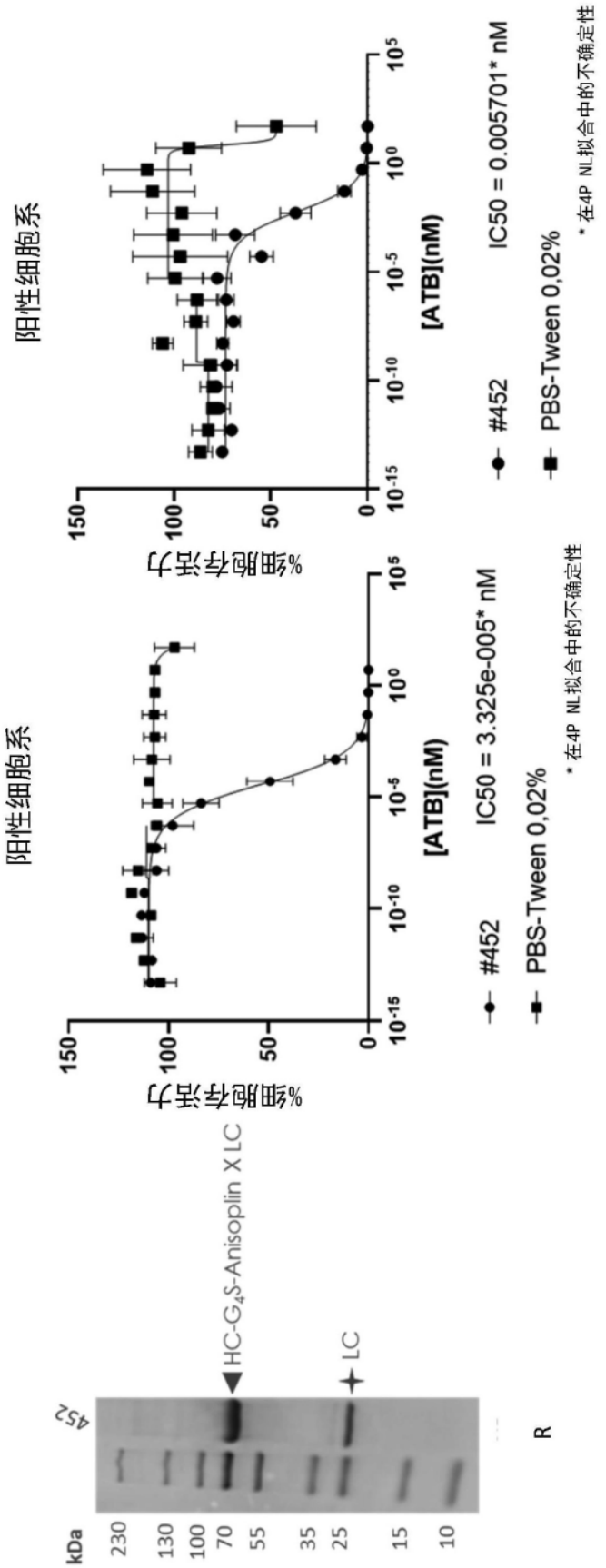

阳性细胞系
%细胞存活力
[ATB](nM)
IC50 = 3.325e-005* nM
#452
PBS-Tween 0,02%
* 在4P NL拟合中的不确定性
阳性细胞系
%细胞存活力
[ATB](nM)
IC50 = 0.005701* nM
#452
PBS-Tween 0,02%
* 在4P NL拟合中的不确定性
HC-G4S-Anisoplin X LC
LC
452
R
kDa
230
130
100
70
55
35
25
15
10

图17

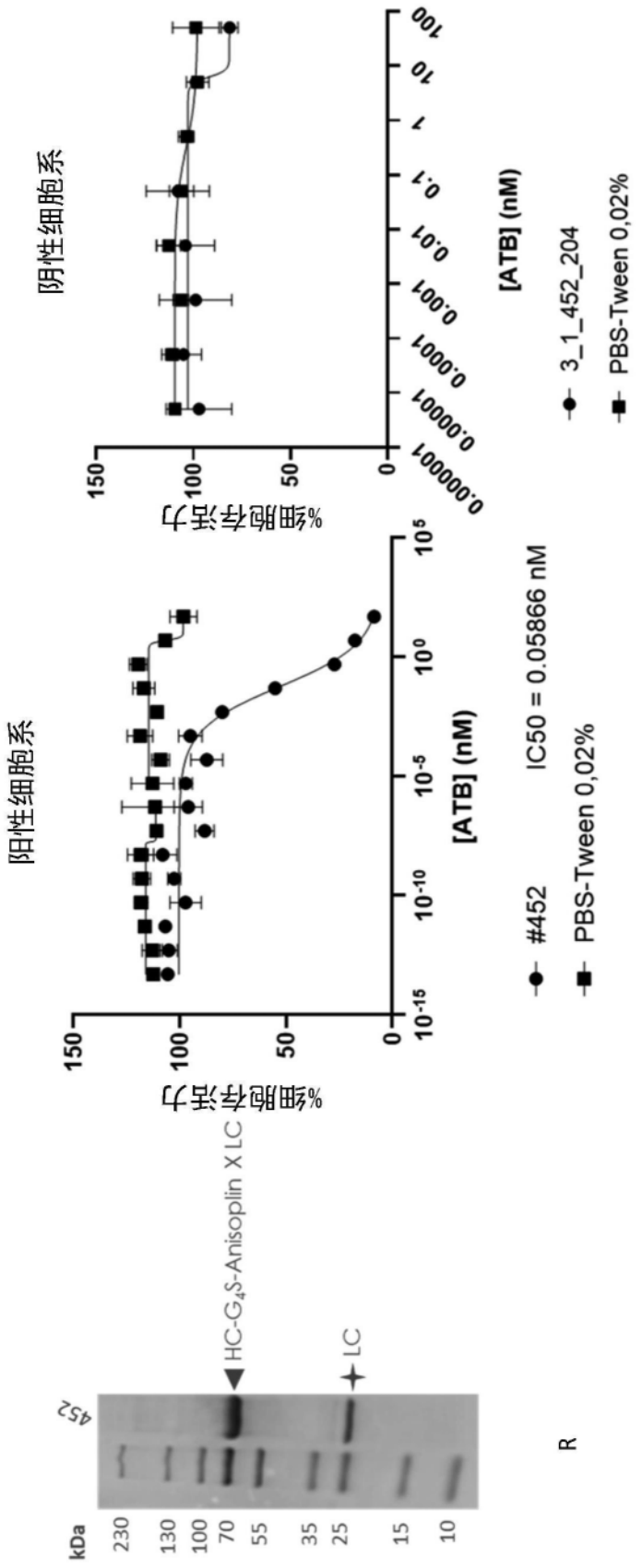

阴性细胞系
%细胞存活力
[ATB] (nM)
3_1_452_204
PBS-Tween 0,02%
阳性细胞系
%细胞存活力
[ATB] (nM)
#452
IC50 = 0.05866 nM
PBS-Tween 0,02%
HC-G4S-Anisoplin X LC
LC
452
kDa
230
130
100
70
55
35
25
15
10
R

图18

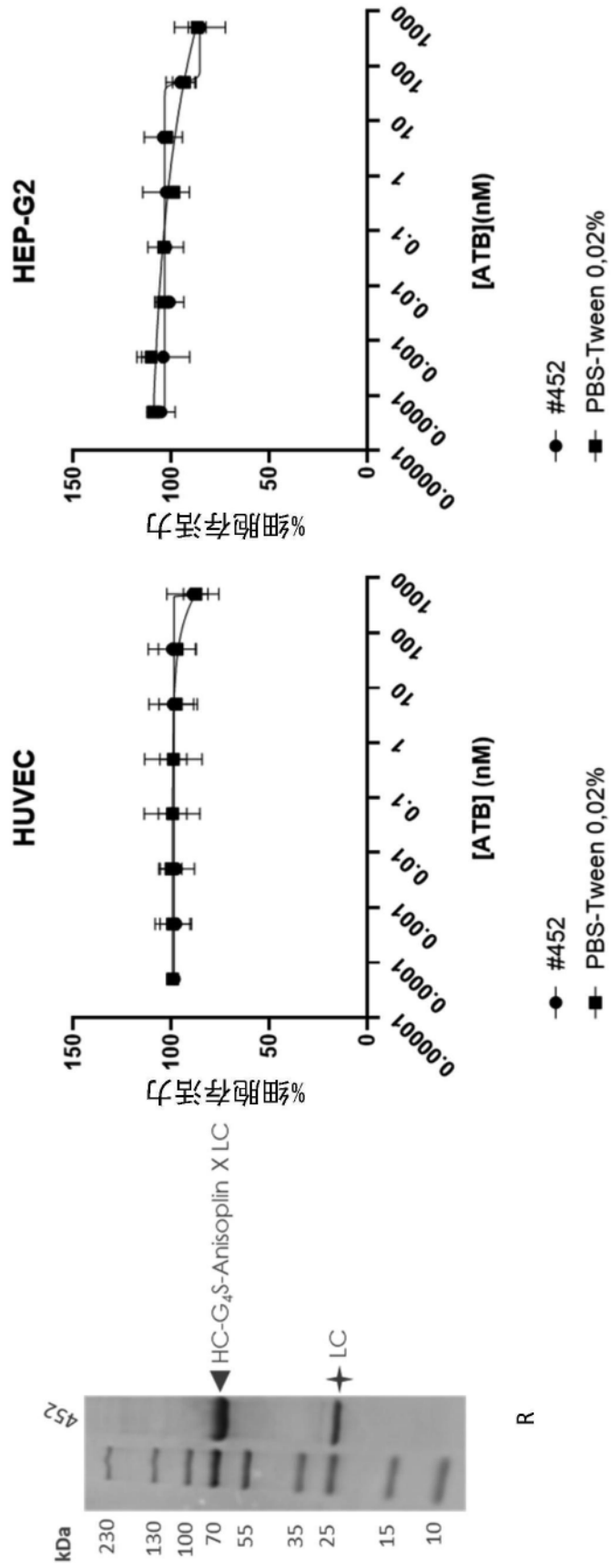
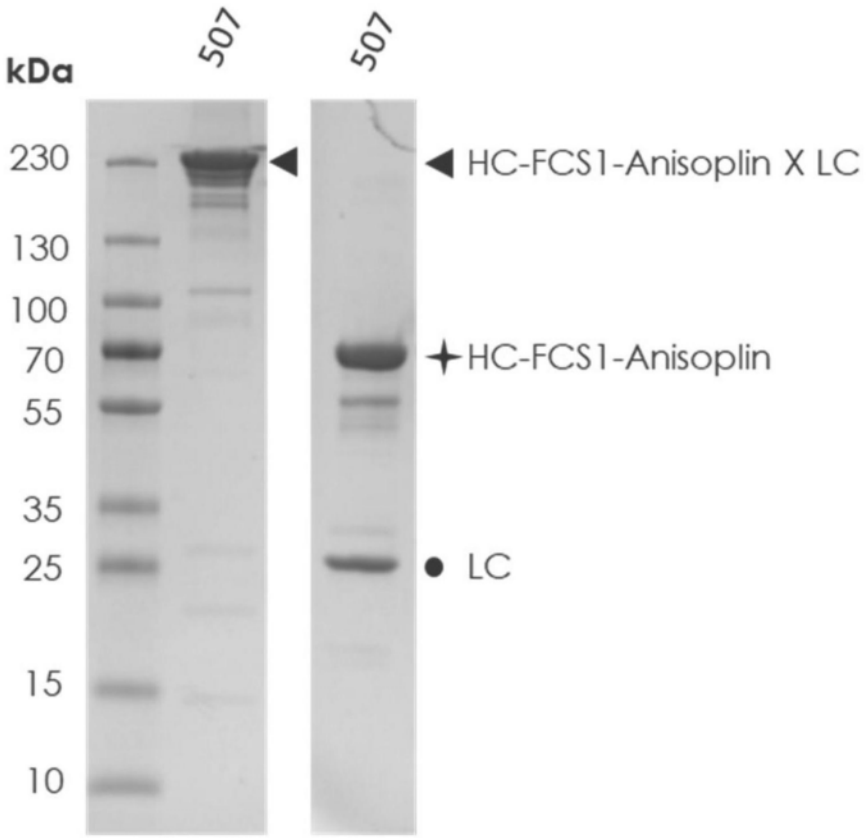

HEP-G2
%细胞存活力
150
100
50
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[ATB](nM)
#452
PBS-Tween 0,02%
HUVEC
%细胞存活力
150
100
50
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[ATB] (nM)
#452
PBS-Tween 0,02%
HC-G4S-Anisoplin X LC
LC
452
R
kDa
230
130
100
70
55
35
25
15
10

图19


kDa
507
507
230
130
100
70
55
35
25
15
10
HC-FCS1-Anisoplin X LC
HC-FCS1-Anisoplin
LC

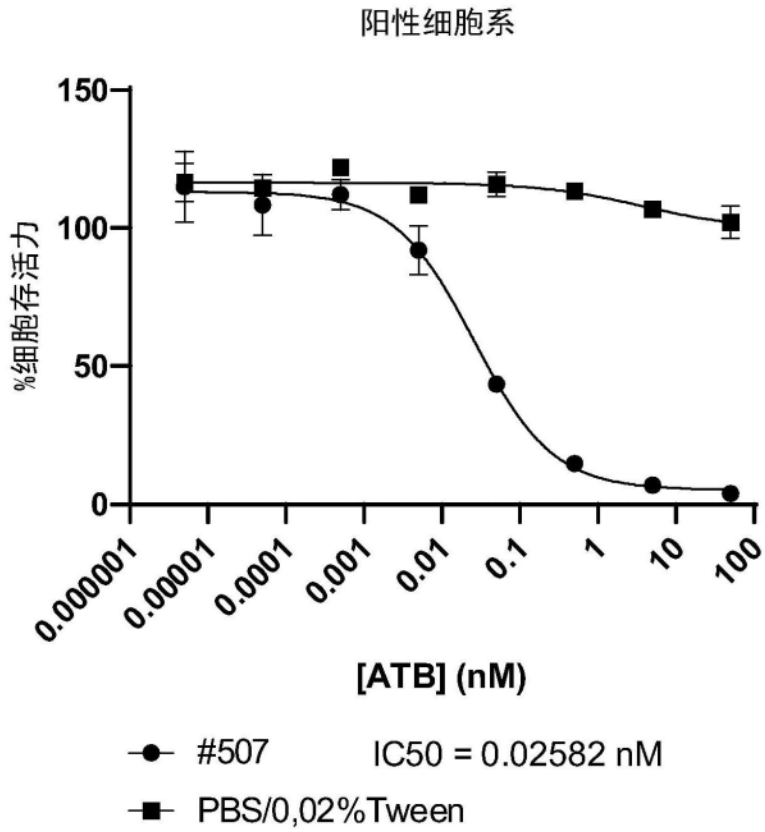

阳性细胞系
%细胞存活力
150
100
50
0
0.000001
0.00001
0.0001
0.001
0.01
0.1
1
10
100
[ATB] (nM)
#507 IC50 = 0.02582 nM
PBS/0,02%Tween

图20

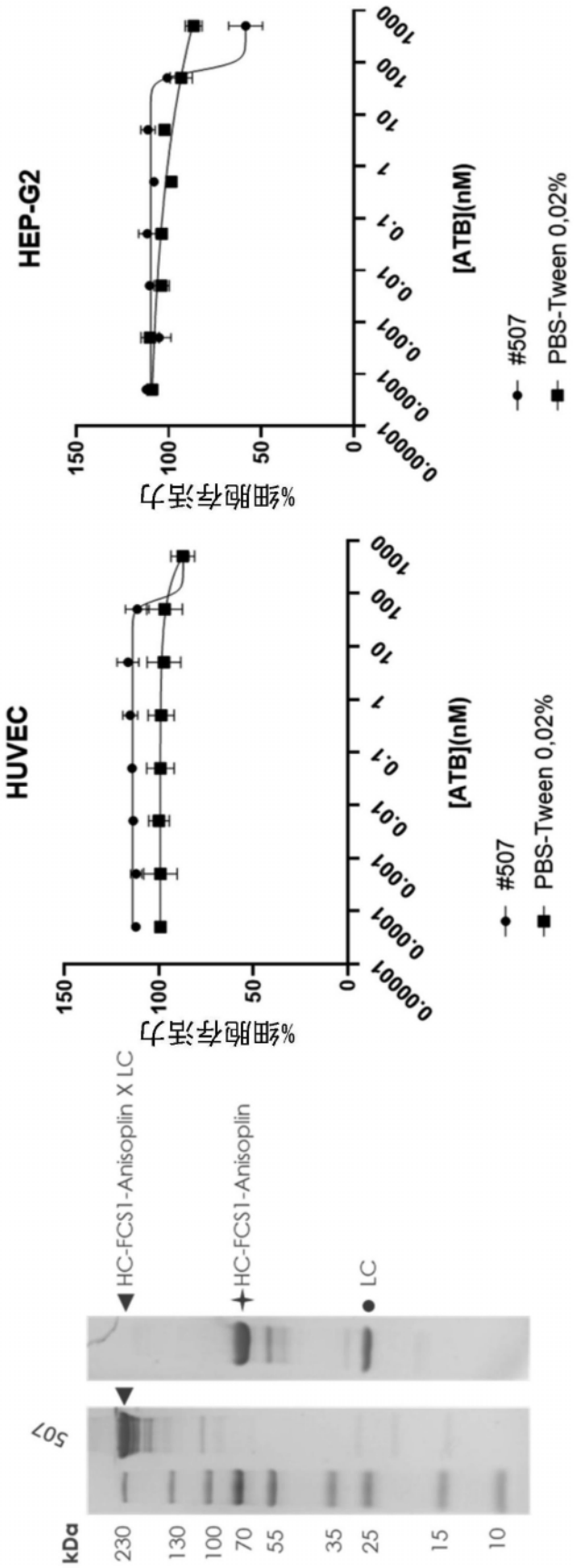
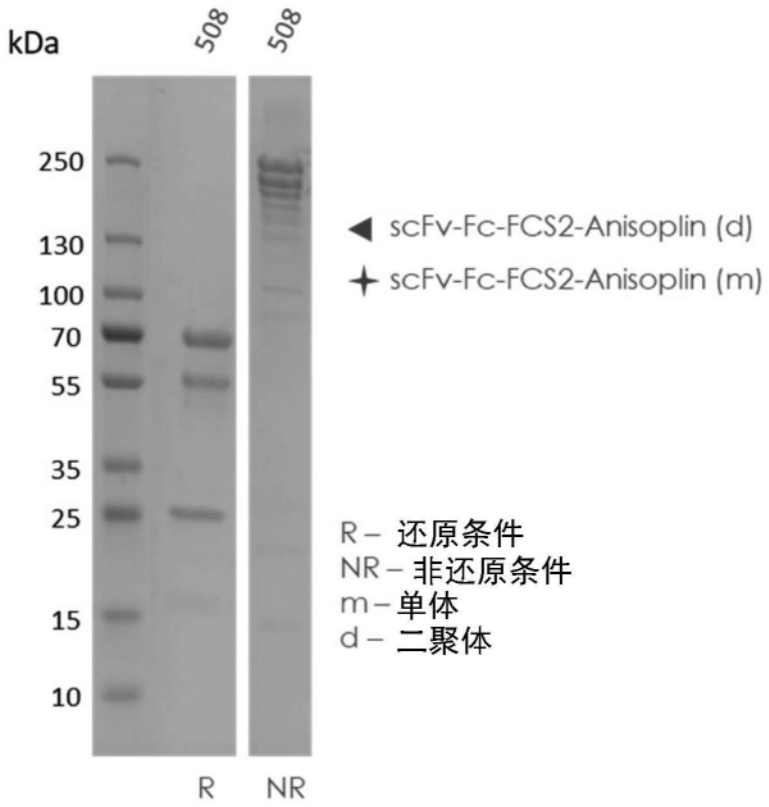

HEP-G2
%细胞存活力
150
100
50
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[ATB](nM)
#507
PBS-Tween 0,02%
HUVEC
%细胞存活力
150
100
50
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[ATB](nM)
#507
PBS-Tween 0,02%
HC-FCS1-Anisoplin X LC
HC-FCS1-Anisoplin
LC
507
kDa
230
130
100
70
55
35
25
15
10

图21


kDa
508
508
250
130
100
70
55
35
25
15
10
R
NR
scFv-Fc-FCS2-Anisoplin (d)
scFv-Fc-FCS2-Anisoplin (m)
R – 还原条件
NR – 非还原条件
m – 单体
d – 二聚体

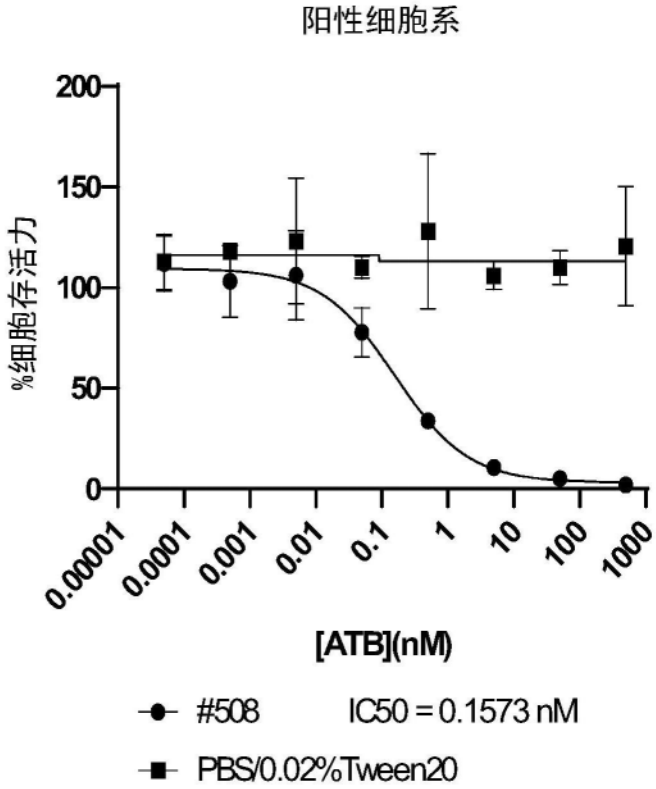
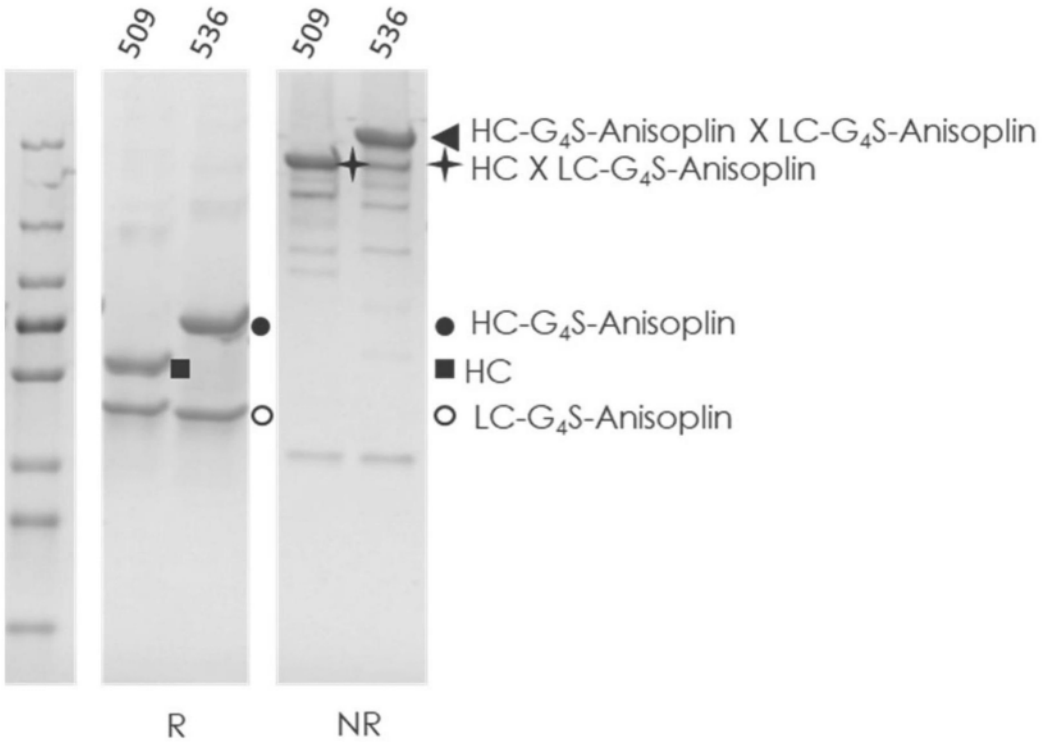

阳性细胞系
%细胞存活力
200
150
100
50
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[ATB](nM)
#508 IC50 = 0.1573 nM
PBS/0.02%Tween20

图22


509
536
509
536
HC-G4S-Anisoplin X LC-G4S-Anisoplin
HC X LC-G4S-Anisoplin
HC-G4S-Anisoplin
HC
LC-G4S-Anisoplin
R
NR

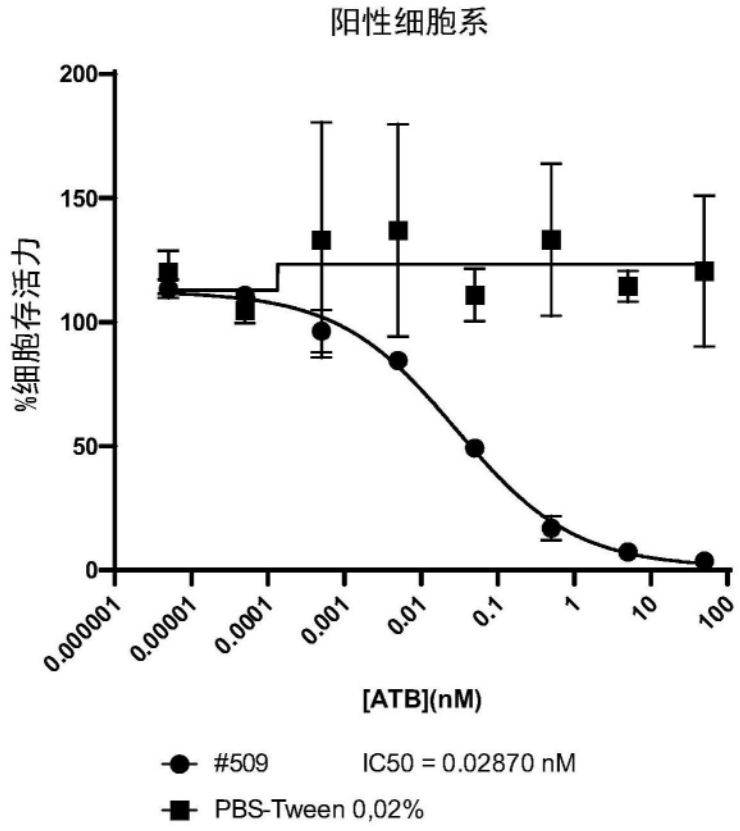
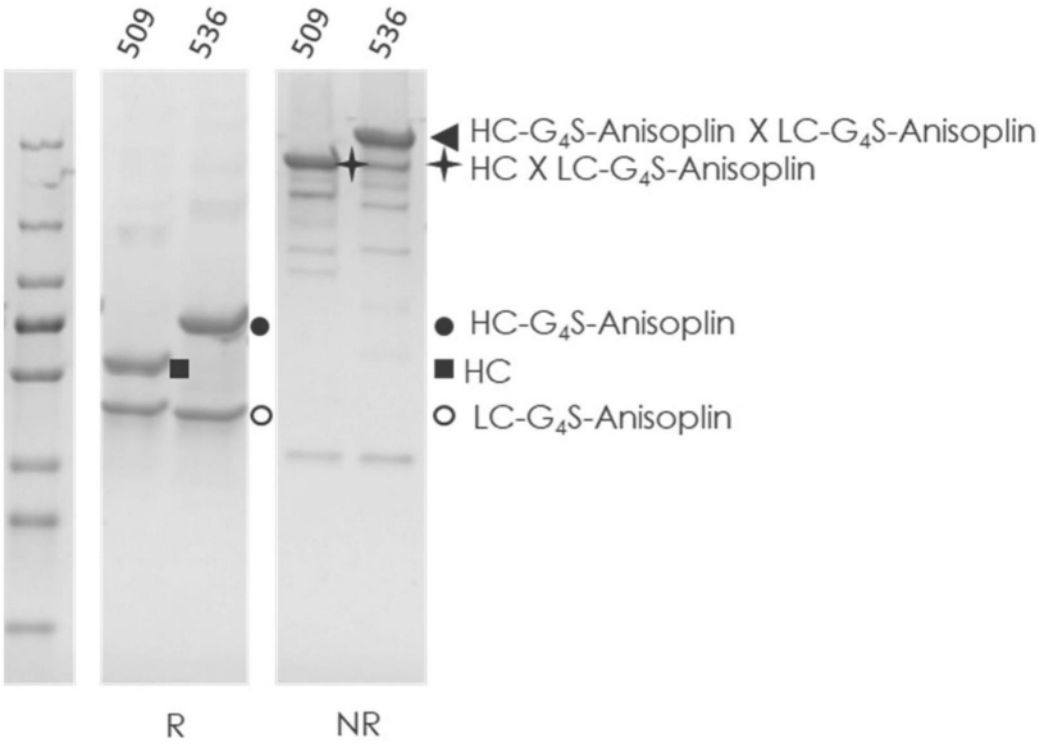

阳性细胞系
%细胞存活力
200
150
100
50
0
0.00001
0.00001
0.0001
0.001
0.01
0.1
1
10
100
[ATB](nM)
#509
IC50 = 0.02870 nM
PBS-Tween 0,02%

图23


509
536
509
536
HC-G4S-Anisoplin X LC-G4S-Anisoplin
HC X LC-G4S-Anisoplin
HC-G4S-Anisoplin
HC
LC-G4S-Anisoplin
R
NR

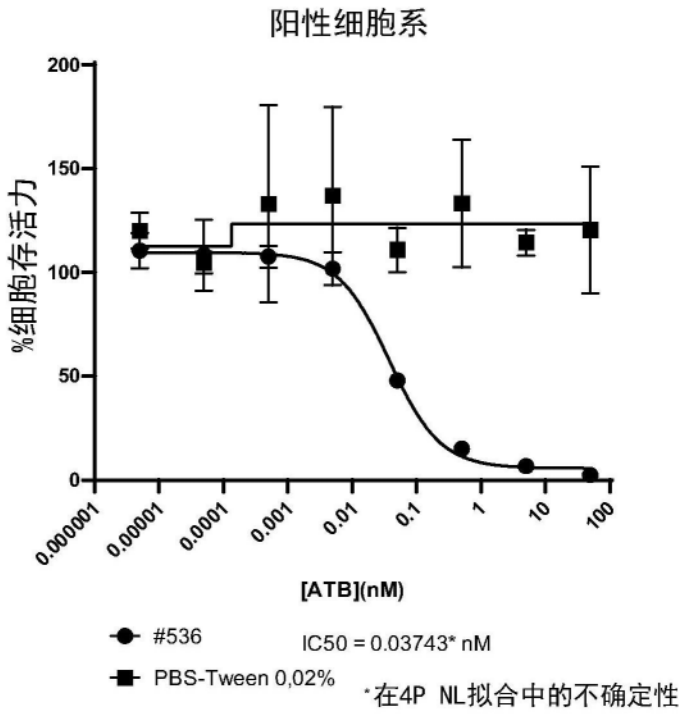

阳性细胞系
%细胞存活力
200
150
100
50
0
0.000001
0.00001
0.0001
0.001
0.01
0.1
1
10
100
[ATB](nM)
#536
IC50 = 0.03743* nM
PBS-Tween 0,02%
*在4P NL拟合中的不确定性

图24

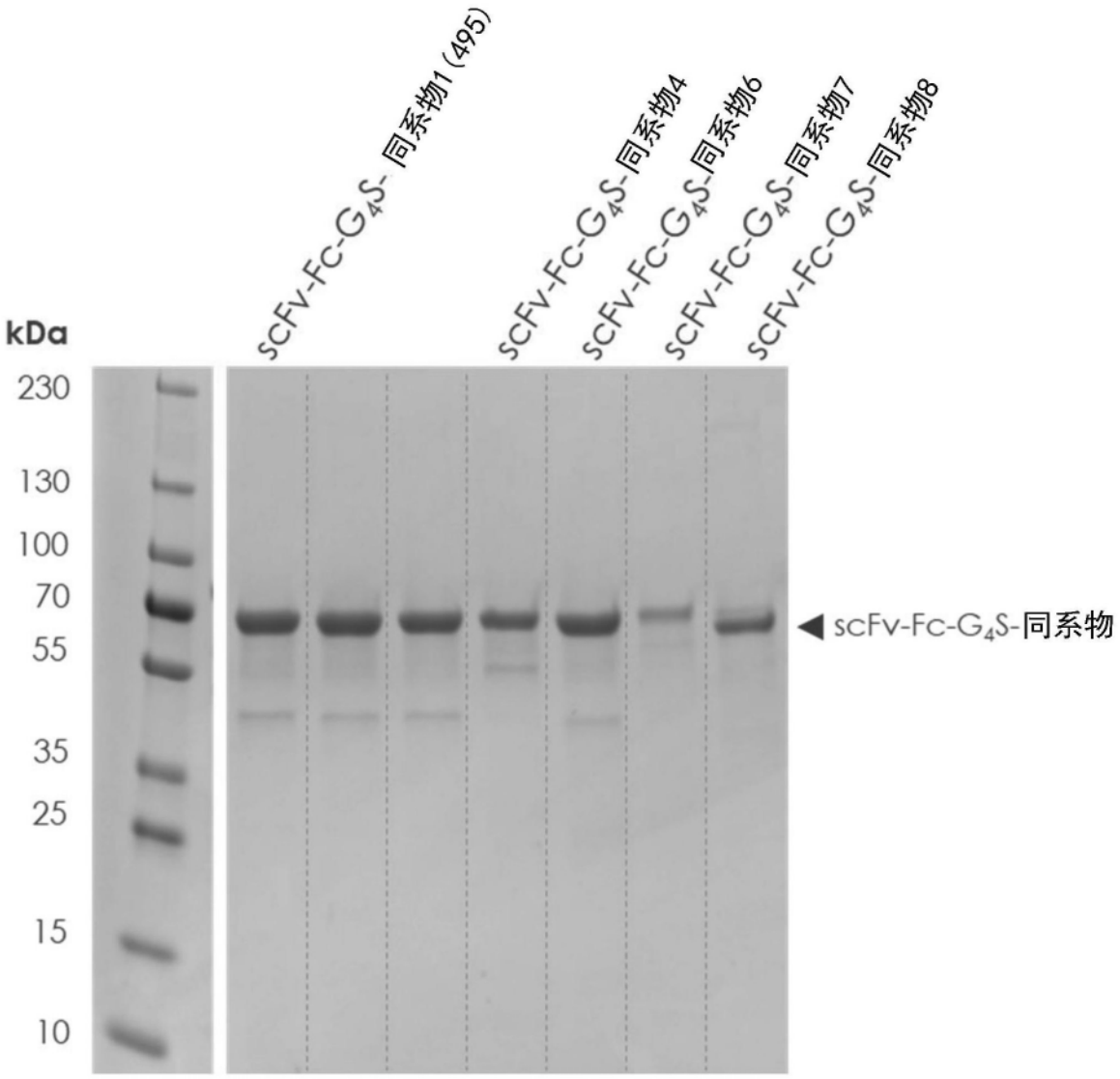

scFv-Fc-G4S-同系物1(495)
scFv-Fc-G4S-同系物4
scFv-Fc-G4S-同系物6
scFv-Fc-G4S-同系物7
scFv-Fc-G4S-同系物8
kDa
230
130
100
70
55
35
25
15
10
scFv-Fc-G4S-同系物

图25

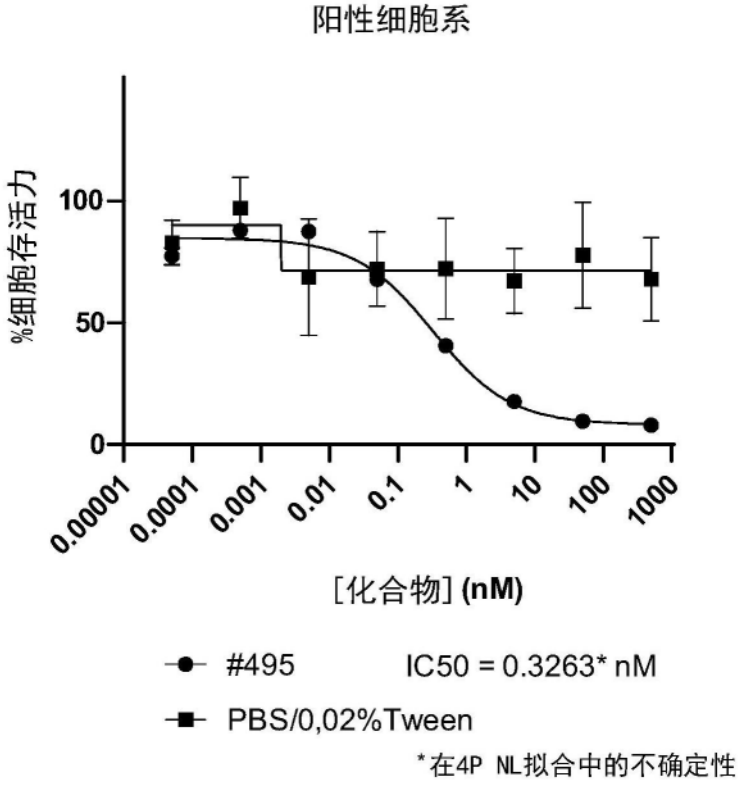

阳性细胞系
%细胞存活力
100
50
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[化合物] (nM)
#495 IC50 = 0.3263* nM
PBS/0,02%Tween
*在4P NL拟合中的不确定性

图26

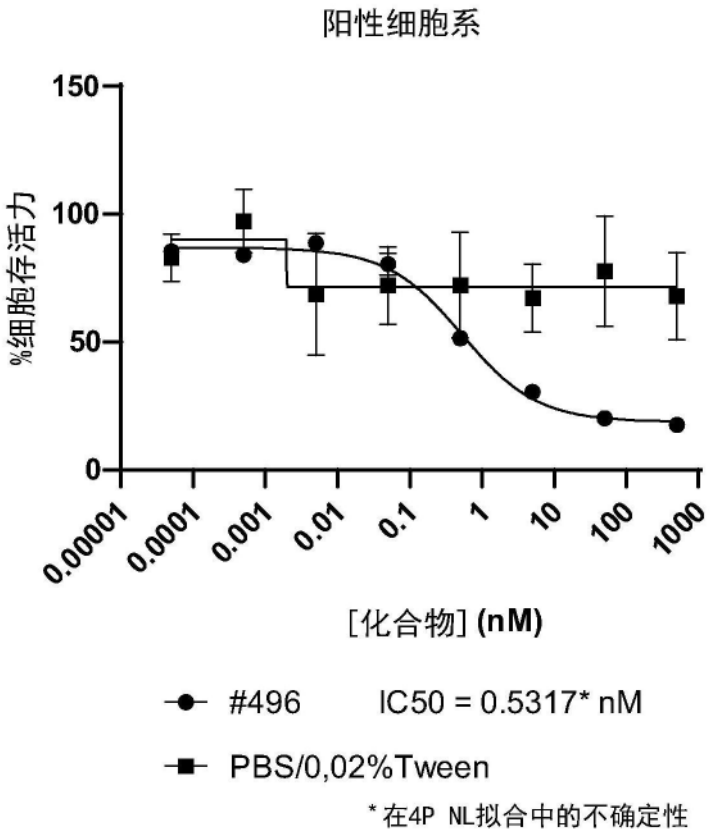

阳性细胞系
150
100
50
0
%细胞存活力
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[化合物] (nM)
#496 IC50 = 0.5317* nM
PBS/0,02%Tween
*在4P NL拟合中的不确定性

图27

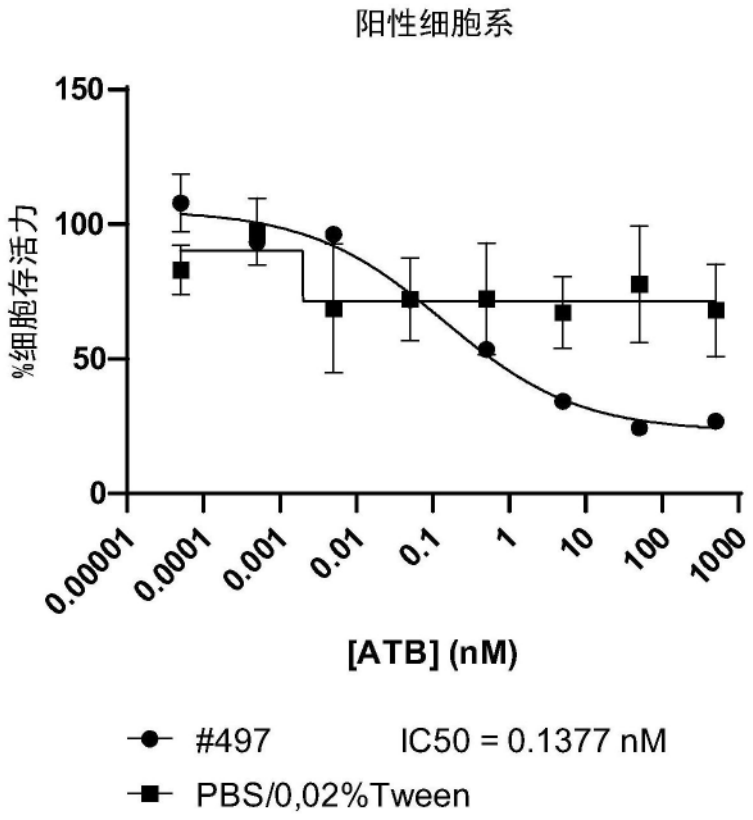

阳性细胞系
150
100
50
0
%细胞存活力
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[ATB] (nM)
#497 IC50 = 0.1377 nM
PBS/0,02%Tween

图28

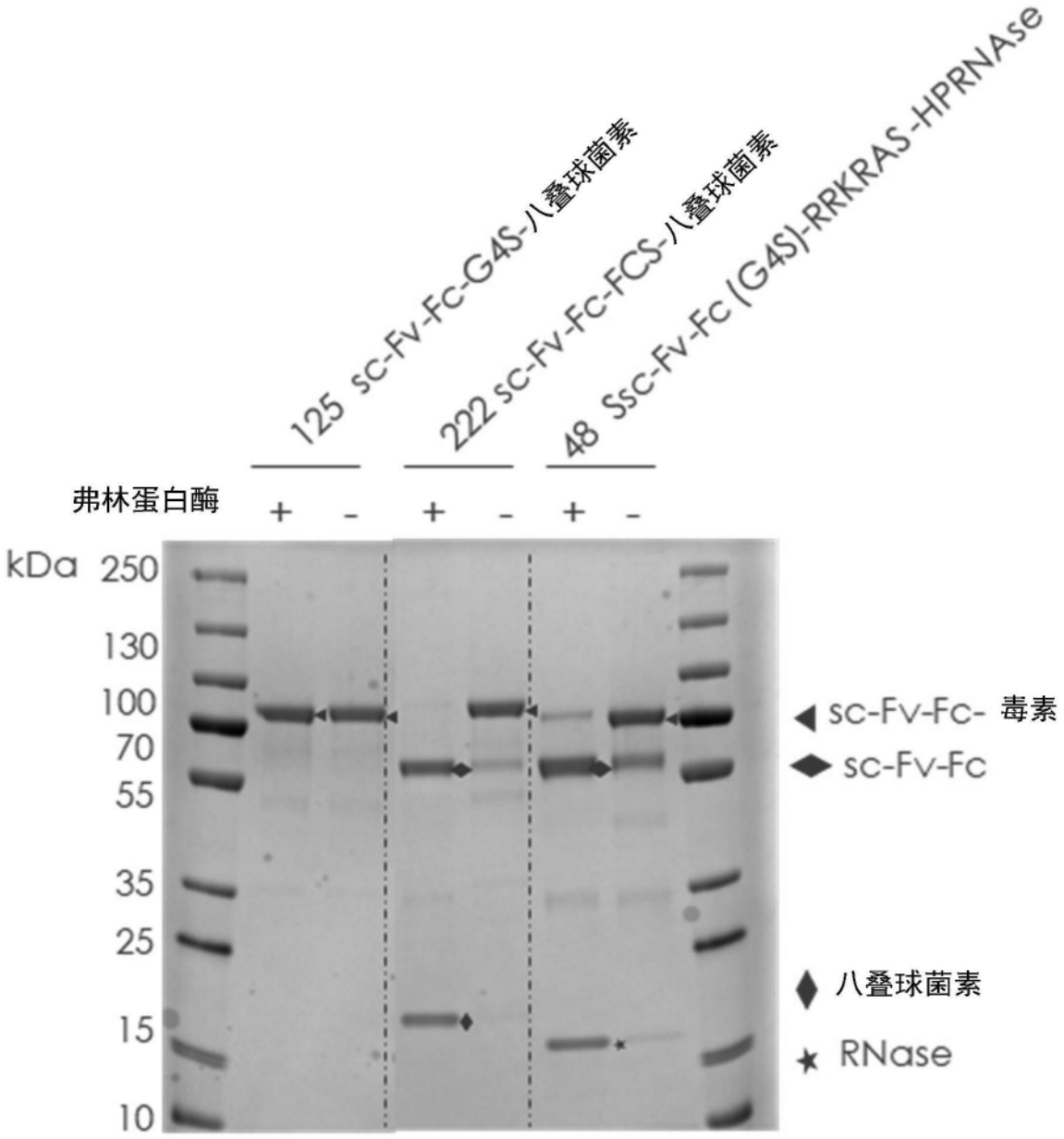

125 sc-Fv-Fc-G4S-八叠球菌素
222 sc-Fv-Fc-FCS-八叠球菌素
48 Ssc-Fv-Fc (G4S)-RRKRAS-HPRNAse
弗林蛋白酶
+ - + - + -
kDa
250
130
100
70
55
35
25
15
10
sc-Fv-Fc- 毒素
sc-Fv-Fc
八叠球菌素
RNase

图29

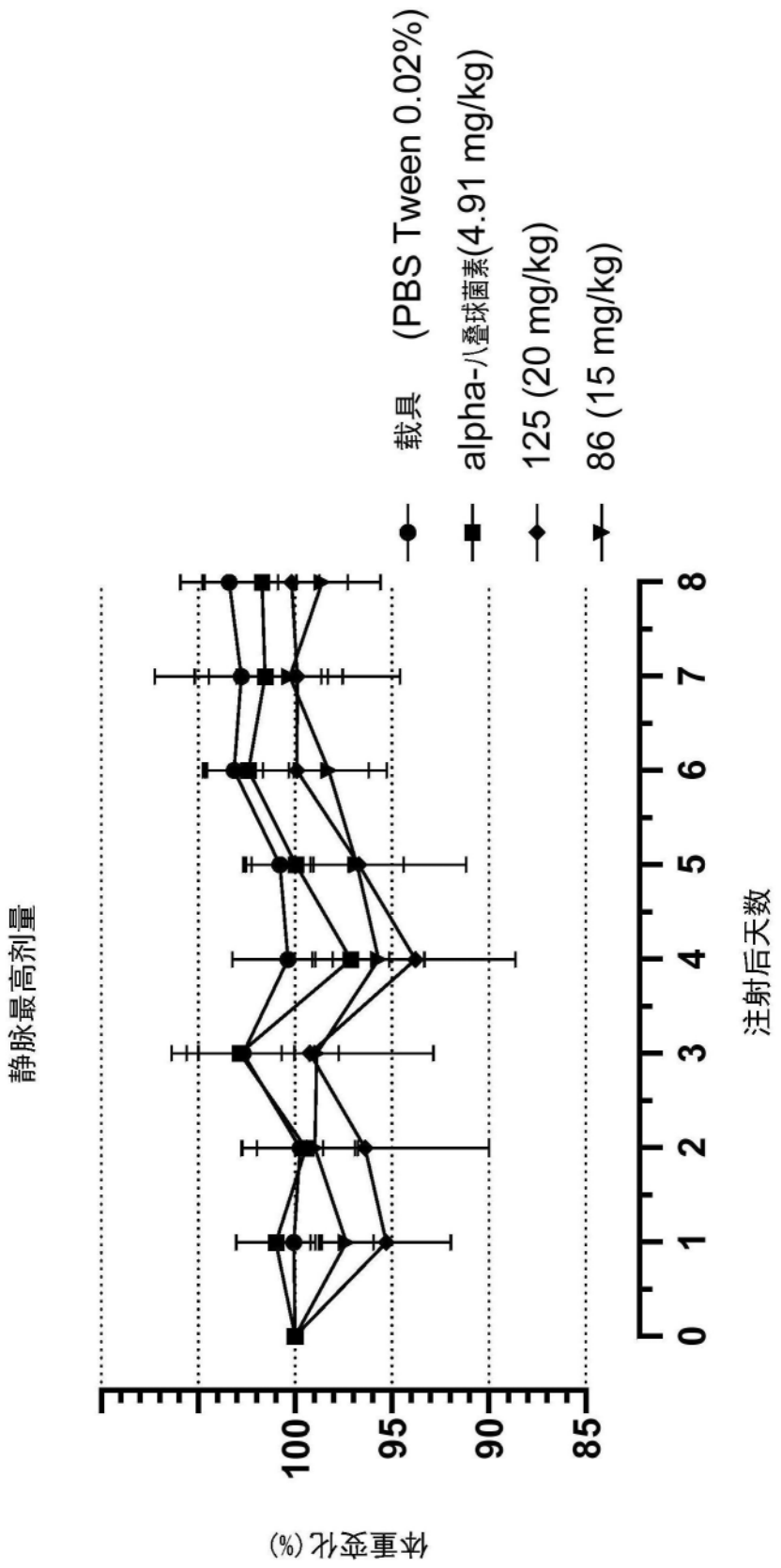

静脉最高剂量
载具 (PBS Tween 0.02%)
alpha-八叠球菌素(4.91 mg/kg)
125 (20 mg/kg)
86 (15 mg/kg)
100
95
90
85
0
1
2
3
4
5
6
7
8
注射后天数
体重变化(%)

图30

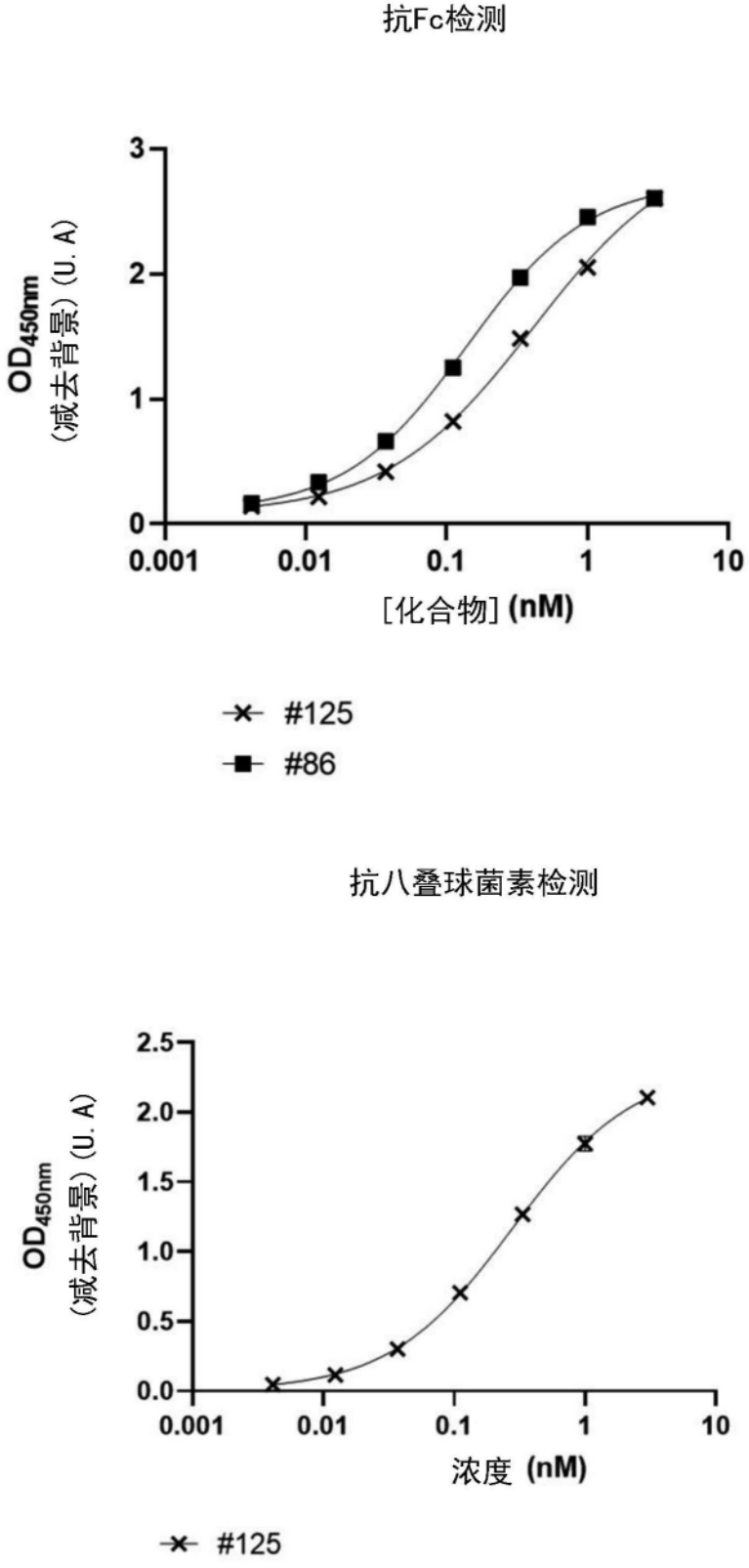
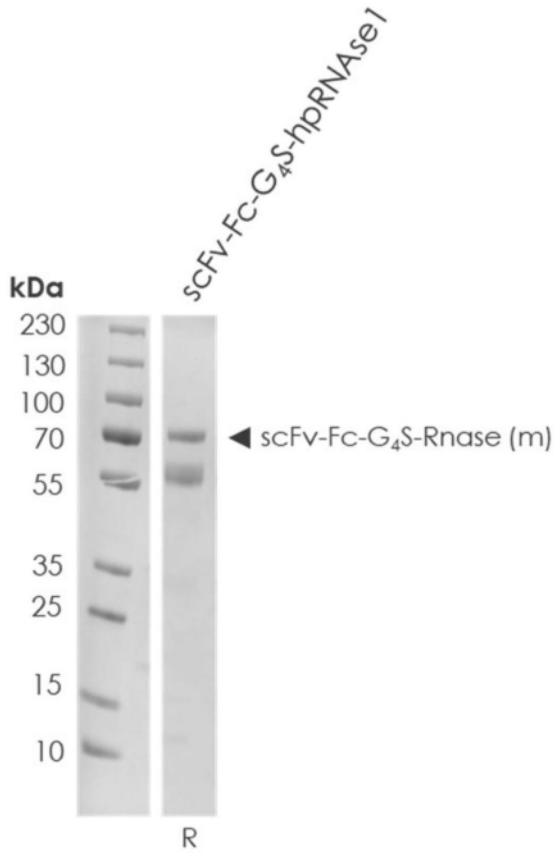

抗Fc检测
OD450nm
(减去背景) (U. A)
3
2
1
0
0.001
0.01
0.1
1
10
[化合物] (nM)
#125
#86
抗八叠球菌素检测
OD450nm
(减去背景) (U. A)
2.5
2.0
1.5
1.0
0.5
0.0
0.001
0.01
0.1
1
10
浓度 (nM)
#125

图31


scFv-Fc-G4S-hpRNAse1
kDa
230
130
100
70
55
35
25
15
10
scFv-Fc-G4S-Rnase (m)
R

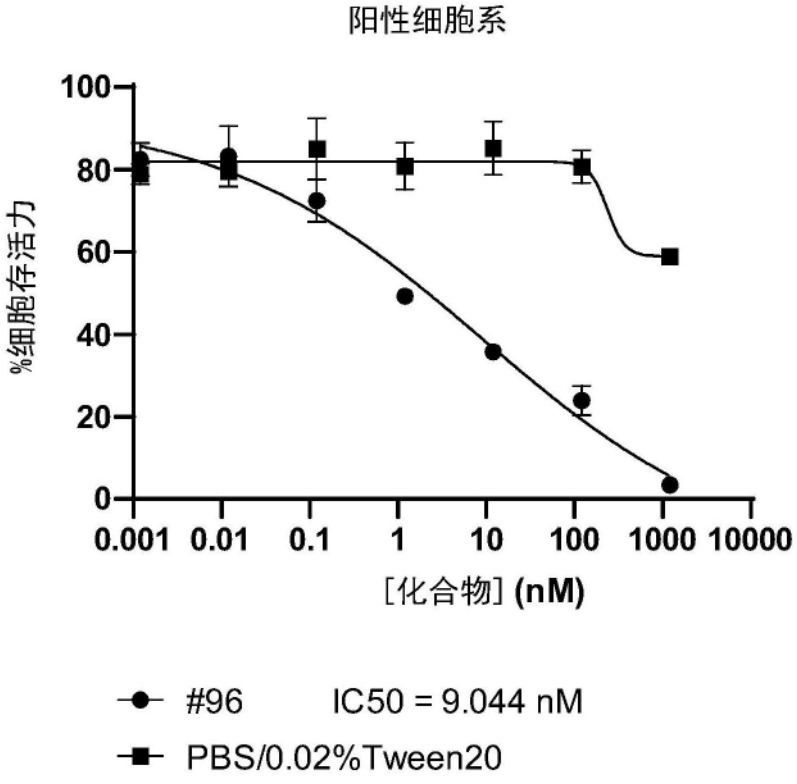

阳性细胞系
%细胞存活力
100
80
60
40
20
0
0.001
0.01
0.1
1
10
100
1000
10000
[化合物] (nM)
#96 IC50 = 9.044 nM
PBS/0.02%Tween20

图32

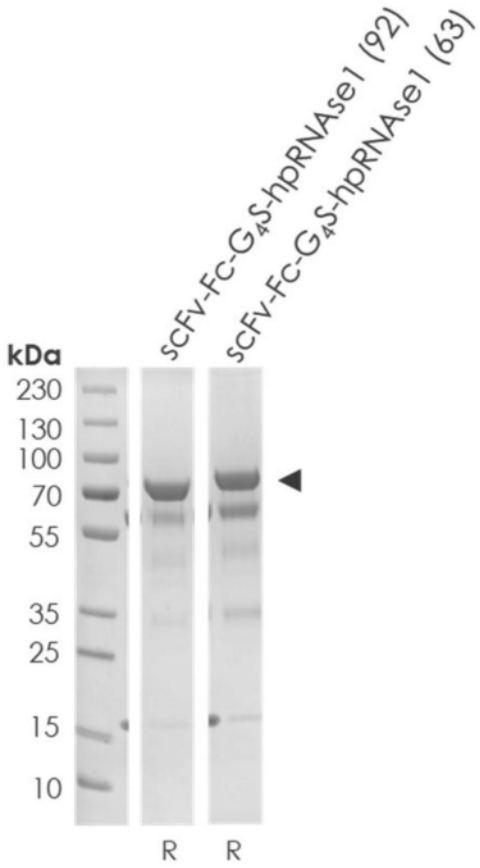
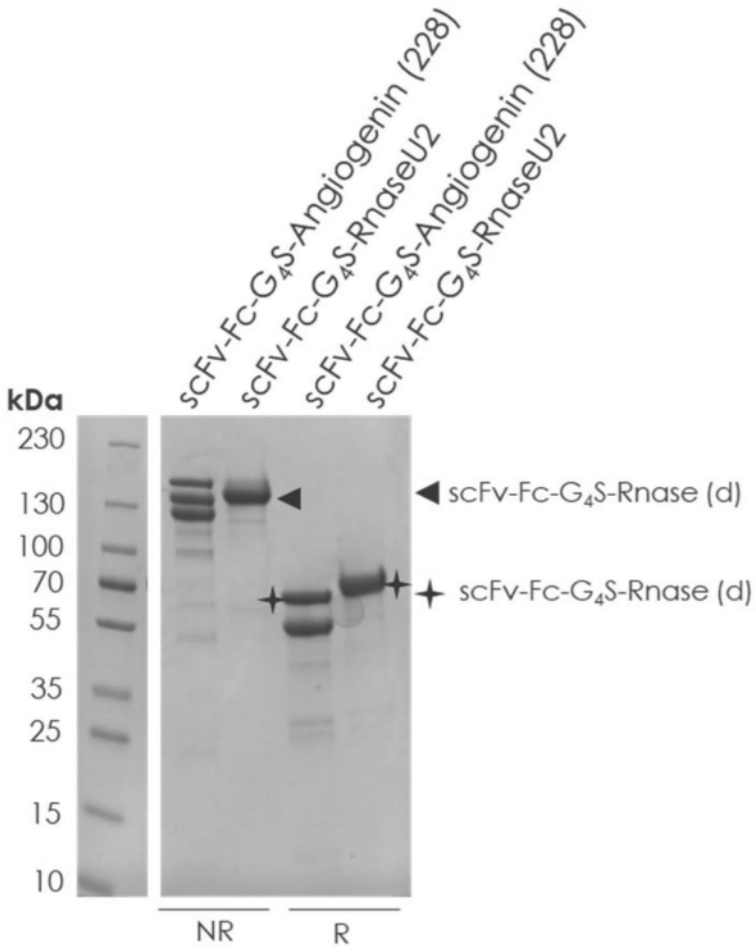

scFv-Fc-G4S-hpRNAse1 (92)
scFv-Fc-G4S-hpRNAse1 (63)
kDa
230
130
100
70
55
35
25
15
10
R
R

图33


scFv-Fc-G4S-Angiogenin (228)
scFv-Fc-G4S-RnaseU2
scFv-Fc-G4S-Angiogenin (228)
scFv-Fc-G4S-RnaseU2
kDa
230
130
100
70
55
35
25
15
10
scFv-Fc-G4S-Rnase (d)
scFv-Fc-G4S-Rnase (d)
NR
R

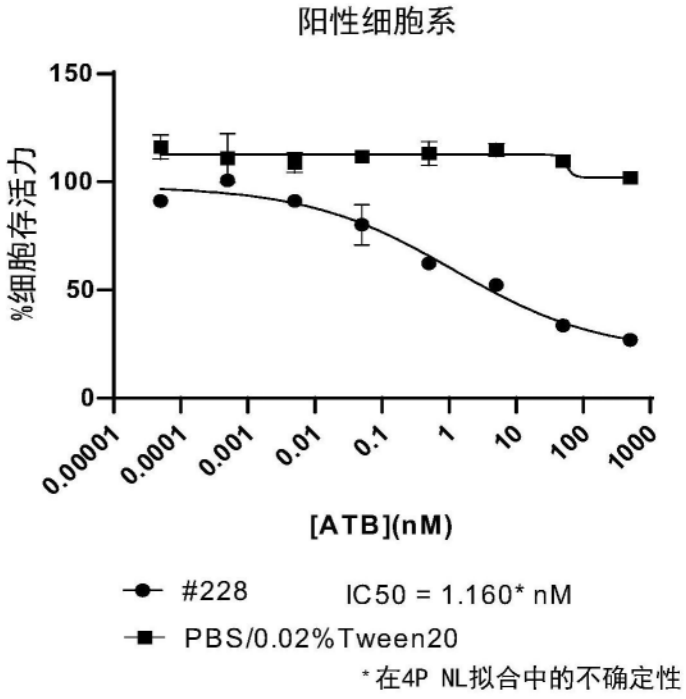

阳性细胞系
%细胞存活力
150
100
50
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[ATB](nM)
#228
IC50 = 1.160* nM
PBS/0.02%Tween20
*在4P NL拟合中的不确定性

图34

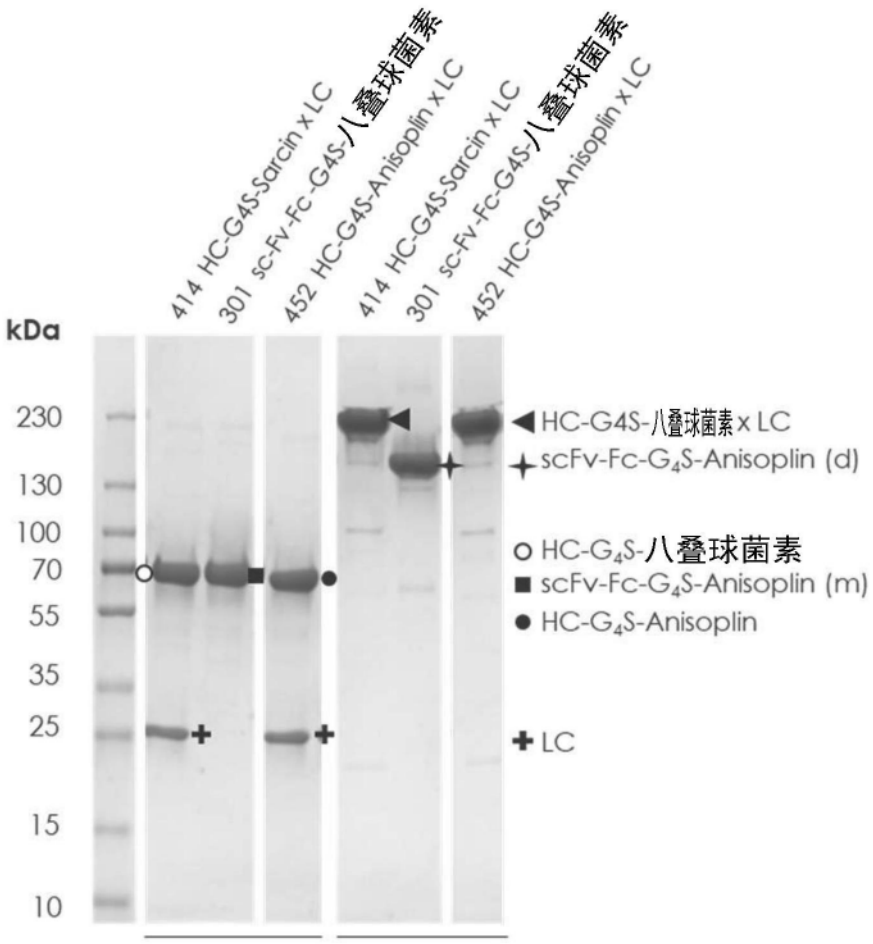

414 HC-G4S-Sarcin x LC
301 scFv-Fc-G4S-八叠球菌素
452 HC-G4S-Anisoplin x LC
414 HC-G4S-Sarcin x LC
301 scFv-Fc-G4S-八叠球菌素
452 HC-G4S-Anisoplin x LC
kDa
230
130
100
70
55
35
25
15
10
HC-G4S-八叠球菌素 x LC
scFv-Fc-G4S-Anisoplin (d)
HC-G4S-八叠球菌素
scFv-Fc-G4S-Anisoplin (m)
HC-G4S-Anisoplin
LC

图35

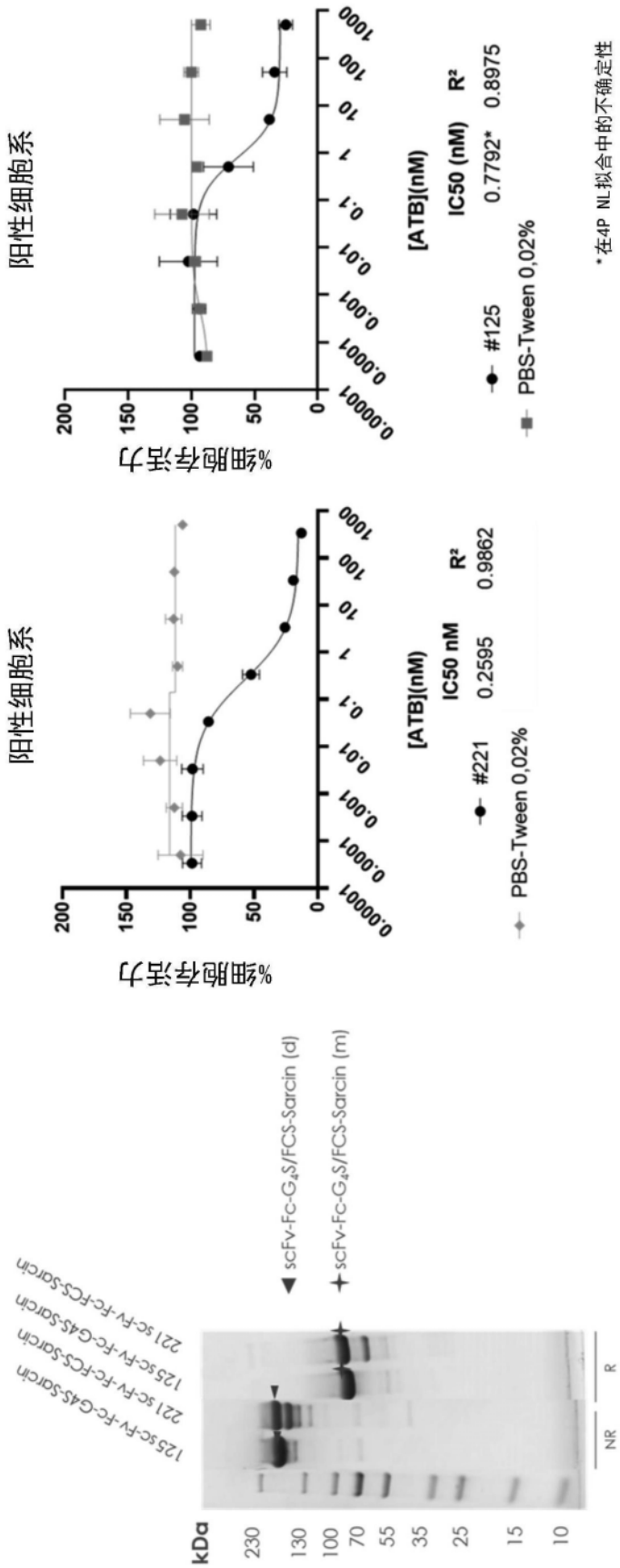

阳性细胞系
%细胞存活力
[ATB](nM)
IC50 (nM) R²
#125 0.7792* 0.8975
PBS-Tween 0,02%
*在4P NL拟合中的不确定性
阳性细胞系
%细胞存活力
[ATB](nM)
IC50 nM R²
#221 0.2595 0.9862
PBS-Tween 0,02%
scFv-Fc-G4S/FCS-Sarcin (d)
scFv-Fc-G4S/FCS-Sarcin (m)
125 sc-Fv-Fc-G4S-Sarcin
221 sc-Fv-Fc-FCS-Sarcin
125 sc-Fv-Fc-G4S-Sarcin
221 sc-Fv-Fc-FCS-Sarcin
kDa
230
130
100
70
55
35
25
15
10
NR
R

图36

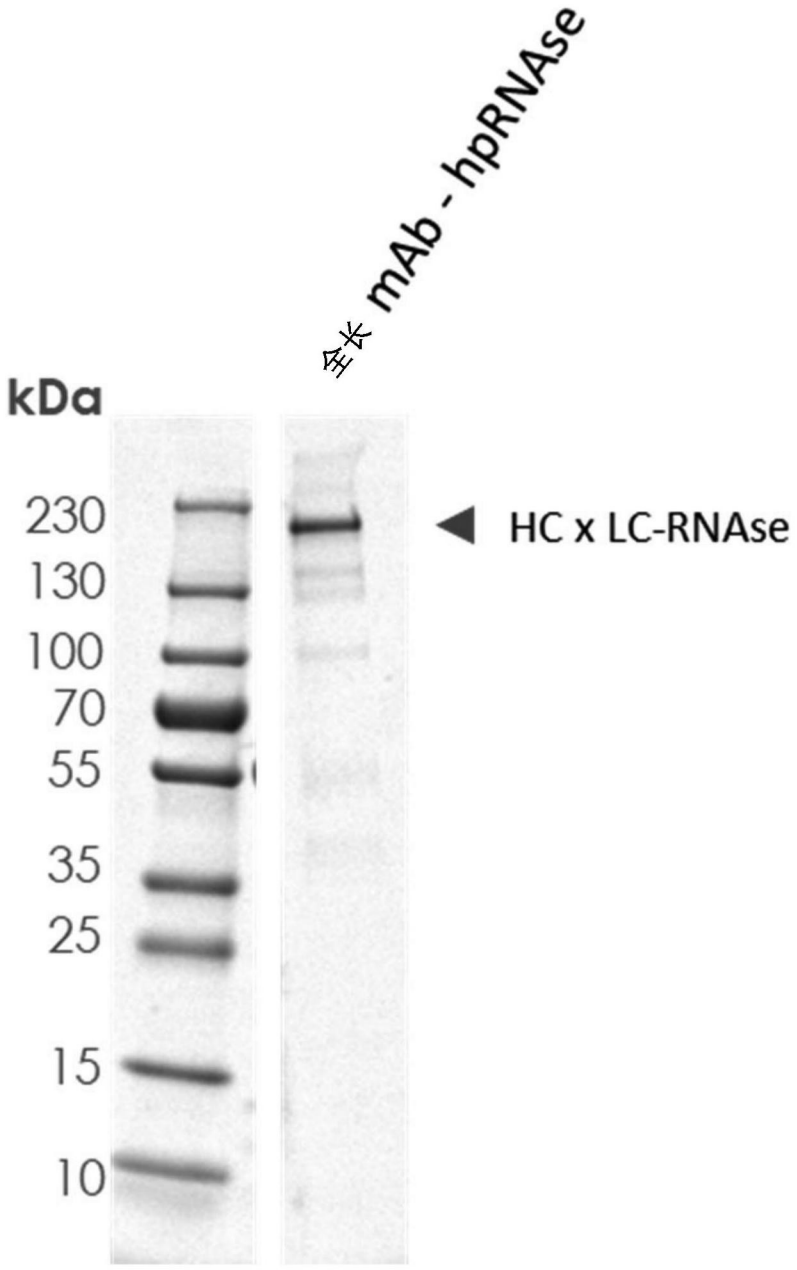


图37