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(54)发明名称

全新被掩蔽的细胞因子及其应用

(57)摘要

本发明提供前药、及其制备方法,及在刺激免疫系统、治疗癌症、自身免疫疾病、或感染性疾病中的应用。

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1.一种前药,其特征在于,所述前药包括两条相同轻链和两条重链,轻链氨基酸序列为SEQ ID NO:44,第一重链融合多肽链氨基酸序列为SEQ ID NO:37,第二重链融合多肽链氨基酸序列为SEQ ID NO:75。

2.包括如权利要求1所述前药及药学上可接受的赋形剂的药物组合物。

3.编码如权利要求1所述前药的多核苷酸。

4.包括如权利要求3所述多核苷酸的表达载体。

5.包括如权利要求4所述表达载体的宿主细胞,所述宿主细胞为哺乳动物细胞。

6.制备如权利要求1所述前药的方法,包括:

a)在允许前药表达的条件下培养如权利要求5所述的宿主细胞,所述宿主细胞为哺乳动物细胞,以及

b)从细胞培养物中分离前药。

# 全新被掩蔽的细胞因子及其应用

[0001] 相关申请的交叉引用

[0002] 本申请同时要求于2020年1月11日提交的美国临时申请第62/959,973号、于2020年5月19日提交的美国临时申请第63/027,138号、于2020年5月23日提交的美国临时申请第63/029,473号、以及于2020年12月16日提交的美国临时申请第63/126,393号的优先权,以上美国临时申请的内容以全文引用的方式并入本文中。

[0003] 序列表

[0004] 本申请包含一个已以ASCII格式电子提交的序列清单,序列表在此通过引用全文合并。创建于2021年1月11日的ASCII副本名称为025471_WO008_SL.txt,大小为240,322字节。

## 背景技术

[0005] 白细胞介素(IL)-2,IL-4,IL-7,IL-9,IL-15及IL-21对免疫细胞的增殖、分化、及存活具有重要的影响。上述细胞因子的受体共用γ链(γC),也即CD132,因此这些细胞因子也被叫做γC家族细胞因子。

[0006] IL-2对淋巴细胞的生成、存活及体内稳定性起着重要作用。所述IL-2具有133个氨基酸,由四条反平行的、两亲性的α-螺旋构成,由其构成的四聚体结构是IL-2功能的必要条件(Smith,Science(1988)240:1169-76;Bazan,Science(1992)257:410-13)。IL-2通过和IL-2受体(IL-2R)结合来实现其活性,所述IL-2R由多达三个独立亚基构成:由α(CD25或Tac抗原),β(CD122),和γC亚基构成的三聚体,形成对IL-2具有高亲和力($K_D$～0.01nM)的受体。由β和γ亚基构成的IL-2二聚体受体被称为中间亲和力IL-2受体($K_D$～1nM)。α亚基单体构成低亲和力IL-2受体($K_D$～10nM)(See,e.g.,Kim et al.,Cytokine Growth Factor Rev.(2006)17:349-66)。尽管二聚体中间亲和力IL-2受体结合到IL-2的亲和力相较于三聚体高亲和力受体降低为约1/100,但二聚体和三聚体的IL-2受体结合到IL-2时均能够传到信号(Minami et al.,Annu Rev Immunol.(1993)11:245-68)。

[0007] IL-15是一类和IL-2具有类似结构的细胞因子,IL-15由病毒感染后的吞噬细胞及其他免疫细胞分泌。IL-15能够诱导自然杀伤细胞及免疫系统其他细胞的增殖,并参与杀死病毒感染细胞及肿瘤细胞。和IL-2一样,IL-15和IL-2受体(IL-2R)β/γ复合物,也即中间亲和力受体,以$K_D$约为1nM的亲和力结合(Giri et al.,EMBO J.(1994)13:2822-30)。IL-15以较高的亲和力($K_D$～0.05nM)和IL-15受体(IL-15R)α结合,IL-15Rα可以和IL-2Rβ/γ复合物一起形成对IL-15具有特异性、高亲和力(αβγ)功能性受体(Minami et al.,Annu.Rev.Immunol.(1993)11:245-67;Giri et al.,J Leukoc Biol.(1995)5745:763-6;and Lehours et al.,Eur Cytokine Netw.(2000)11:207-15)。

[0008] IL-21由活化的CD4+T细胞、T-滤泡辅助细胞和自然杀伤细胞(NKT)产生(Spolski和Leonard,Ann Rev Immunol.(2008)26:57008)。IL-21已被证明对各种类型的淋巴细胞的增殖、分化和细胞毒性发挥多效作用。最近,IL-21已被进一步证明在$CD4^+$T细胞分化为辅助性T细胞17($TH_{17}$)中发挥关键作用,其为T细胞的一个亚类与炎症和自身免疫反应有关(Korn

et al.,Nature(2007)448(7152):484-87;Nurieva et al.,Nature(2007)448(7152):480-83)。IL-21受体组合物由私有链IL-21Rα及共有链γC(或Rγ)组成。人IL-21以非常高的亲和力($K_D$～70pM;Zhang et al.,Biochem Biophys Res Commun.(2003)300(2):291-6)和IL-21Rα结合,而以相对低的亲和力($K_D$～160μM)与IL-21Rγ结合。

[0009] 上述细胞因子、其突变体及其融合体在治疗中的潜能正在被研究开发,其中重组IL-2作为首个获批上市的用于癌症治疗的细胞因子。然而,细胞因子药物及候选药物具有明显的副作用,另外,这些药物在体内的半衰期通常较短,甚至以抗体-细胞因子融合蛋白的形式存在,其原因可能是由于免疫细胞上的细胞因子受体而形成的"PK沉降"。

[0010] 因此,有必要进一步研究开发具有更高肿瘤位点选择性,具有改善PK及有效的基于细胞因子的肿瘤治疗方法,以降低副作用。

[0011] 发明概述

[0012] 本发明提供一种前药,包括细胞因子部分、掩蔽部分、载体部分,其中所述掩蔽部分和细胞因子部分结合并抑制所述细胞因子的生物学活性;所述载体部分包括可与靶细胞表面表达的抗原结合的抗原结合部分;且所述掩蔽部分不通过可切割的连接物(如通过不可切割肽连接物和所述载体部分非直接连接,或不通过肽连接物和所述载体部分直接连接)和所述载体部分连接。

[0013] 在一些实施例中,所述前药可被一种细胞活化,所述细胞表面同时表达抗原及细胞因子受体。在一些实施例中,所述前药在含有上述细胞的病灶处的生物活性相比于在不含上述细胞位点处的生物活性提高至少2倍、5倍或10倍。在一些特定实施例中,所述细胞因子部分的受体包括两个或多个亚基。

[0014] 在一些实施例中,所述抗原选自PD-1,PD-L1,CTLA-4,TIGIT,TIM-3,LAG-3,CD25,CD16a,CD16b,NKG2D,NKP44,NKP30,CD19,CD20,CD30,CD38,BCMA,及信号调节蛋白α(SIRPα,命名为CD172a)。

[0015] 在一些实施例中,所述细胞因子部分包括IL-2激动剂多肽,IL-7激动剂多肽,IL-9激动剂多肽,IL-15激动剂多肽、IL-21激动剂多肽,IL-1α激动剂多肽,IL-1β激动剂多肽,IL-4激动剂多肽,IL-5激动剂多肽,IL-6激动剂多肽,IL-8激动剂多肽,IL-10激动剂多肽,IL-12激动剂多肽,IL-17激动剂多肽,IL-18激动剂多肽,IL-22激动剂多肽,IL-23激动剂多肽,IL-31激动剂多肽,IL-33激动剂多肽,IL-36激动剂多肽,干扰素-α激动剂多肽,干扰素γ激动剂多肽,4-1BB配体,OX-40配体或CD-40配体。

[0016] 在一些实施例中,所述细胞因子部分包括IL-2激动剂多肽或IL-15激动剂多肽,所述掩蔽部分包括IL-2受体β胞外域(IL-2RβECD)或其功能性片段。在其他实施例中,所述细胞因子部分包括IL-21激动剂多肽,所述掩蔽部分包括抗IL-21抗体的Fab,单链Fv(scFv),或其单域抗体。在另一些实施例中,所述细胞因子部分包括IL-2激动剂多肽,所述掩蔽部分包括抗IL-2抗体的Fab,scFv,或其单域抗体。在另一些实施例中,所述细胞因子部分包括IL-15激动剂多肽,所述掩蔽部分包括抗IL-15抗体的Fab,scFv,或其单域抗体。在另一些实施例中,所述细胞因子部分包括IL-15激动剂多肽,所述掩蔽部分包括IL-15受体α的Sushi域(IL-15RαSushi域)。

[0017] 在一些实施例中,所述细胞因子部分包括具有SEQ ID NO:1序列的IL-21激动剂多肽,或与其具有至少90%同源性的氨基酸序列。在其他实施例中,所述细胞因子部分包括具

有SEQ ID NO:6或62序列的IL-2激动剂多肽,或与其具有至少95%同源性的氨基酸序列。在其他实施例中,所述细胞因子部分包括具有SEQ ID NO:7序列的IL-15激动剂多肽,或与其具有至少95%同源性的氨基酸序列。

[0018] 在一些实施例中,所述掩蔽部分包括所述细胞因子受体的胞外域(ECD)。在特定实施例中,所述细胞因子包括IL-7激动剂多肽,所述掩蔽部分包括IL-7受体α的胞外域(IL-7RαECD)或其功能类似物。在特定实施例中,所述细胞因子部分为IL-21激动剂多肽,所述掩蔽部分包括IL-21受体α的胞外域(IL-21RαECD)或其功能类似物。在特定实施例中,所述掩蔽部分包括IL-21RαECD或其功能类似物,其氨基酸序列选自SEQ ID NO:12,13及63-73或与其具有至少90%(如至少95%)同源性的氨基酸序列。在一些实施例中,所述掩蔽部分包括IL-2RβECD或其功能类似物,包括SEQ ID NO:11或与其具有至少95%同源性的氨基酸序列。

[0019] 在一些实施例中,所述掩蔽部分包括可与细胞因子部分结合并抑制或干扰所述细胞因子与其受体相互作用的scFv。在特定实施例中,所述掩蔽部分为可与人IL-21结合的scFv,其包括氨基酸序列SEQ ID NO:20或21。在特定实施例中,所述掩蔽部分包括可与IL-2结合的scFv,并通过与IL-2结合抑制IL-2与IL-2Rα的相互作用、IL-2与IL-2Rβ的相互作用,和/或IL-2与IL-2Rγ的相互作用,其中,所述scFv可选择地包括抗体4E12B2D10的轻链和重链的互补决定区(CDR)。在一些实施例中,所述scFv包括抗体4E12B2D10的轻链和重链。在特定实施例中,所述抗体4E12B2D10,其重链和轻链的氨基酸序列分别为SEQ ID NO:60和61。在一些实施例中,所述掩蔽部分为可与IL-2结合的scFv,其包括SEQ ID NO:22或23,或与其具有至少95%同源性的氨基酸序列。在特定实施例中,所述掩蔽部分包括可与IL-15结合的scFv,其通过和scFv结合抑制或干扰IL-15与IL-2Rβ的相互作用,和/或IL-15与IL-2Rγ的相互作用,其中,所述scFv可选择地包括抗体146B7,146H5,或404E4轻链和重链的CDR,或者所述scFv可选择地包括抗IL-15抗体146B7,,146H5,或404E4的轻链和重链,或者所述scFv可选择地包括SEQ ID NO:18或19。在一些实施例中,IL-15激动剂scFv或Fab包括选自146B7,146H5,或404E4的抗IL-15抗体重链的CDR1-3,和轻链CDR1-3,以上内容在WO2003/017935A2中均有描述。

[0020] 在特定实施例中,所述掩蔽部分包括可结合IL-21的scFv,其通过和IL-21的结合抑制或干扰IL-21和IL-21Rα的相互作用,和/或IL-21和IL-2Rγ的相互作用。在特定实施例中,所述掩蔽部分包括scFv,其可和选自IL-2,IL-7,IL-9,IL-15或IL-21的细胞因子结合,并抑制或干扰所述细胞因子和IL-2Rγ的相互作用。

[0021] 在一些实施例中,所述前药相较于相应野生型细胞因子在非人灵长动物或人体内的半衰期增加至少20倍、至少50倍、至少100倍、至少150倍或至少200倍。

[0022] 在特定实施例中,所述前药包括两条轻链,氨基酸序列为SEQ ID NO:44,和两条重链多肽链,氨基酸序列分别包括SEQ ID NO:24和25;SEQ ID NO:35和36;SEQ ID NO:37和36;SEQ ID NO:37和38;SEQ ID NO:39和41,或SEQ ID NO:42和43。

[0023] 在特定实施例中,所述前药包括两条轻链,氨基酸序列为SEQ ID NO:50,和两条重链多肽链,氨基酸序列分别包括SEQ ID NO:51和54;SEQ ID NO:51和55;SEQ ID NO:51和56;SEQ ID NO:52和54;SEQ ID NO:53和58;SEQ ID NO:53和59;或SEQ ID NO:52和57。

[0024] 在一些实施例中,本发明提供一种药物组合物,其包括本发明披露的前药和药学上可接受的赋形剂。

[0025] 另一方面,本发明提供了编码所述前药的多核苷酸、包括所述多核苷酸的表达载体和包括所述表达载体的宿主细胞(如哺乳动物宿主细胞,所述哺乳动物宿主细胞例如CHO、NS0细胞和293T细胞)。本发明亦提供了制备所述前药的方法,包括在允许表达前药的条件下培养哺乳动物宿主细胞,以及分离(纯化)前药。

[0026] 在保证细胞因子部分被掩蔽的前提下,基于Fc的IL-21前药不能和表达IL-21受体(图2)的细胞(如Mino细胞)结合。研究进一步表明以抗体PD-1作为载体的被掩蔽的分子对不表达PD-1的NK92细胞几乎没有活性(图3)。发明人惊喜地发现基于PD-1抗体的IL-21前药分子在活化前对Mino细胞具有明显活性(图4A和图4B)。IL-2前药(图6A和图6B)和IL-15前药(图5A-C)具有类似的现象。虽然不希望受理论的约束,但可以假设当细胞同时表达抗原和细胞因子受体时,PD-1抗体与抗原以及细胞因子与细胞因子受体的顺式结合解除了掩蔽部分的掩蔽效应。因此含有靶向功能部分的前药对表达特定抗原的细胞相较于不含相应抗原的细胞具有明显的选择性,其中所述抗原对前药的载体分子具有靶向性。有基于此,可在无需蛋白酶切割或去除掩蔽部分的前提下构建前药。

[0027] 本发明提供在病灶处无需蛋白酶切割掉或去除掩蔽部分而选择性活化的前药。一方面,本发明提供全新的前药,其包括细胞因子部分(细胞因子激动剂多肽),掩蔽部分,和载体部分,其中所述掩蔽部分通过和细胞因子激动剂多肽结合而抑制细胞因子的生物活性,所述载体部分包括抗原结合部分,所述掩蔽部分通过不可切割肽连接物或不经过肽连接物直接或间接连接到载体部分,其中所述前药在同时表达细胞因子受体以及对载体部分具有靶向性抗原的活化细胞中相较于其在仅表达细胞因子受体而不表达对载体部分有靶向性抗原的活化细胞时具有更高的活性。

[0028] 另一方面,本发明提供的前药包括细胞因子部分(细胞因子激动剂多肽),掩蔽部分和载体部分,其中所述掩蔽部分通过结合到细胞因子激动剂多肽结合而抑制细胞因子的生物活性,所述载体部分包括抗原结合部分,所述掩蔽部分通过不可切割肽连接物或不经过肽连接物直接或间接连接到载体部分,其中所述前药在病灶位点(该部位细胞同时表达细胞因子受体及对载体部分具有靶向性的抗原)被活化,或者所述前药在病灶位点(该部位细胞同时表达细胞因子受体及对载体部分具有靶向性的抗原)被活化,其生物活性在该病灶位点的活性提高至少2倍,至少5倍,或至少10倍。

[0029] 在一些实施例中,所述前药不含有任何可切割肽连接物。

[0030] 在一些实施例中,所述载体部分包括免疫细胞表达抗原的结合部分。在一些实施例中,所述载体部分包括选自PD-1,PD-L1,CTLA-4,TIGIT,TIM-3,LAG-3,CD25,CD16a,及CD16b的抗原的结合部分。

[0031] 在一些实施例中,所述细胞因子部分包括选自IL-2激动剂多肽、IL-17激动剂多肽,IL-9激动剂多肽,IL-15激动剂多肽,IL-21激动剂多肽的细胞因子。在一些实施例中,所述细胞因子选自IL-1α激动剂多肽、IL-1β激动剂多肽,IL-4激动剂多肽,IL-5激动剂多肽,IL-6激动剂多肽,IL-8激动剂多肽,IL-10激动剂多肽,IL-12激动剂多肽,IL-15激动剂多肽,IL-17激动剂多肽,IL-18激动剂多肽,IL-22激动剂多肽,IL-23激动剂多肽,IL-31激动剂多肽,IL-33激动剂多肽,IL-36激动剂多肽,干扰素α激动剂多肽,干扰素γ,4-1BB配体,OX-40配体,CD-40配体。

[0032] 在一些实施例中,所述掩蔽部分为细胞因子受体的胞外域(ECD),所述掩蔽部分包

括抗细胞因子抗体或抗体的结合片段。

[0033] 在一些实施例中,所述细胞因子为IL-21激动剂多肽,其中所述掩蔽部分为IL-21受体胞外域(IL-21RαECD)或其功能类似物。在一些实施例中,所述细胞因子为IL-2激动剂多肽或IL-15激动剂多肽,其中所述掩蔽部分为IL-2受体胞外域(IL-2RβECD)。在一些实施例中,所述细胞因子为IL-21激动剂多肽,其中所述掩蔽部分为抗IL-21的Fab、单链抗体(scFv)或单域抗体。

[0034] 在一些实施例中,所述细胞因子为IL-2激动剂多肽,其中所述掩蔽部分为抗IL-2的Fab,单链抗体(scFv)或单域抗体。

[0035] 在一些实施例中,所述细胞因子为IL-15激动剂多肽,其中所述掩蔽部分为抗IL-15的Fab,单链抗体(scFv)或单域抗体。在一些实施例中,所述细胞因子包括IL-15激动剂多肽,其中的嵌合分子进一步包括IL-15受体的α的sushi域(IL-15Rαsushi域)。

[0036] 在一些实施例中,所述IL-21激动剂多肽包括SEQ ID NO:1或与其具有至少90%同源性的氨基酸序列。在一些实施例中,所述掩蔽部分为IL-21RαECD或其功能类似物,其包括选自SEQ ID NO:12,63-72和73的氨基酸序列,或与SEQ ID NO:12具有至少90%同源性的氨基酸序列。在一些实施例中,所述掩蔽部分为结合人IL-21的scFv,其包括氨基酸序列SEQ ID NO:20或21。

[0037] 在一些实施例中,所述IL-2激动剂多肽包括SEQ ID NO:6或61,或与SEQ ID NO:6或61具有至少95%同源性的氨基酸序列。在一些实施例中,所述掩蔽部分包括IL-2RβECD或其功能类似物,其中所述IL-2RβECD包括SEQ ID NO:11或与其具有至少95%同源性的氨基酸序列。在一些实施例中,所述掩蔽部分为结合IL-2的scFv,所述scFv影响IL-2和IL-2Rα的相互作用。在一些实施例中,所述掩蔽部分为结合IL-2的scFv,所述scFv影响IL-2和IL-2Rβ的相互作用。在一些实施例中,所述掩蔽部分为结合IL-2的scFv,所述scFv影响IL-2和IL-2Rγ的相互作用。在一些实施例中,所述掩蔽部分为结合IL-2的scFv,所述scFv具有和杂交瘤4E12B2D10相同的轻链和重链。在一些实施例中,所述掩蔽部分为结合IL-2的scFv,所述scFv包括SEQ ID NO:22,23,或与其具有至少95%同源性的氨基酸序列。

[0038] 在一些实施例中,所述IL-15激动剂多肽包括SEQ ID NO:7,或与其具有至少95%同源性的氨基酸序列。在一些实施例中,所述IL-15前药进一步包括sushi域,其氨基酸序列为SEQ ID NO:8,或与SEQ ID NO:8具有至少95%同源性的氨基酸序列。在一些实施例中,所述掩蔽部分包括IL-2RβECD或其功能类似物,其中IL-2RβECD包括SEQ ID NO:11或与其具有至少95%同源性的氨基酸序列。在一些实施例中,所述掩蔽部分为结合IL-15的scFv,所述scFv影响IL-15和IL-2Rβ的相互作用。在一些实施例中,所述掩蔽部分为结合IL-15的scFv,所述scFv影响IL-15和IL-2Rγ的相互作用。在一些实施例中,所述掩蔽部分为结合IL-15的scFv,所述scFv具有和IL-15抗体146B7,146H5或404E4相同的轻链和重链。在一些实施例中,所述掩蔽部分为结合IL-15的scFv,所述scFv包括氨基酸序列SEQ ID NO:18或19。

[0039] 在一些实施例中,人IL-21激动剂多肽包括选自D18,Q19,E109及K117(序号和SEQ ID NO:1一致)位点的一个或多个突变。在特定实施例中,人IL-21激动剂多肽包括选自SEQ ID NO:1,2,3,4,和5的氨基酸序列。

[0040] 在所述前药的一些实施例中,细胞因子部分和掩蔽部分通过不可切割肽连接物和载体部分融合,例如,所述不可切割肽连接物选自SEQ ID NO:27-34。

[0041] 在所述前药的一些实施例中,载体部分为包括L234A和L235A("LALA")(EU编号)突变的IgG1抗体或包括S228P/L234A/L235A(PAA)突变的IgG4抗体。当载体部分为Fc结构域或抗体Fc时,也可以包括其他能够降低Fc功能性的其他突变,如参考文献Tam et al., Antibodies(2017)6(12):1-34中描述的突变。

[0042] 在特定实施例中,载体部分为包括球孔突变(knobs-into-holes mutations)的抗体,细胞因子部分和掩蔽部分分别和抗体不同重链融合。在某些实施例中,球孔突变包括抗体重链或Fc结构域其中一条多肽上的T366Y"knob"突变,和抗体重链或Fc结构域另一条多肽上的Y407T"hole"突变(EU编号)。在某些实施例中,球孔突变包括"knob"链CH3结构域的Y349C和/或T366W突变,及"hole"链CH3结构域的E356C,T366S,L368A,和/或Y407V突变(EU编号)。

[0043] 在一些实施例中,载体部分为抗体或抗原结合片段,其特异性结合选自脒基环化酶C(GCC),糖类抗原19-9(CA19-9),糖蛋白A33(gpA33),粘蛋白1(MUC1)、癌胚抗原CEA、胰岛素样生长因子1受体(IGF1-R),人类表皮生长因子受体2(HER2),人类表皮生长因子受体3(HER3),delta-like蛋白3(DLL3),delta-like蛋白4(DLL4)、表皮生长因子受体(EGFR),蛋白多糖-3(GPC3),c-MET,血管内皮生长因子受体1(VEGFR1),血管内皮生长因子受体2(VEGFR2)、Nectin-4、Liv-1、糖蛋白NMB(GPNMB)、前列腺特异性膜抗原(PSMA)、Trop-2、碳酸酐酶IX(CA9),内皮素B受体(ETBR),前列腺1的6个跨膜上皮抗原(STEAP1),叶酸受体α(FR-α),SLIT和NTRK类蛋白6(SLITRK6),碳酸酐酶VI(CA6),磷酸二酯酶家族成员3(ENPP3),间皮素,滋养层糖蛋白(TPBG),CD19,CD20,CD22,CD33,CD40,CD56,CD66e,CD70,CD74,CD79b,CD98,CD123,CD138,CD352,CD47,信号调节蛋白(SIRPα),PD1,Claudin 18.2,Claudin 6,5T4,BCMA、PD-L1、PD-1、成纤维细胞激活蛋白α(FAPα)、黑色素瘤相关硫酸软骨素蛋白聚糖(MCSP)、上皮细胞黏附分子(EPCAM)中的一个或多个抗原。在特定实施例中,载体部分为结合FAPα或5T4的抗体或其片段。

[0044] 另一方面,本发明提供编码所述前药或融合分子的多核苷酸,包含所述多核苷酸的表达载体,和包含所述表达载体的宿主细胞(比如哺乳动物宿主细胞CHO,NS0细胞及293T细胞)。本发明也提供了所述前药或融合分子的制备方法,包括在允许表达前药或融合分子的条件下培养宿主细胞及分离前药或融合分子。

[0045] 本发明也提供了对需要其的患者(如病人)提供了治疗癌症,或感染性疾病,或刺激免疫系统的方法,包括向患者施用治疗有效量的细胞因子前药或本发明提供的药物组合物。患者可能患有,例如,病毒感染(如HIV,HBV,HCV或HPV感染)或选自乳腺癌,肺癌,胰腺癌,食道癌,髓样甲状腺癌,卵巢癌,子宫癌,前列腺癌,睾丸癌,结直肠癌和胃癌中的任一癌症。同时也提供细胞因子前药在治疗癌症、感染性疾病、或刺激免疫系统的应用,细胞因子前药在制备治疗癌症、感染性疾病、或刺激免疫系统药物中的应用,以及包括所述细胞因子前药的一个或多个剂量单位的制品(如试剂盒)。

[0046] 本发明也提供前药在治疗癌症、感染性疾病、或刺激免疫系统的应用,前药在制备治疗癌症、感染性疾病、或刺激免疫系统药物中的应用,以及包括所述前药的一个或多个剂量单位的制品(如试剂盒)。

[0047] 本发明的其他特征,目的和有益效果可显而易见于下述的详细描述中,应当理解,说明本发明的实施例和方面的详细描述仅用来说明,而并非用于限制。本发明范围内的各

种变化和修改对于本领域技术人员来说是显而易见的。

## 附图说明

[0048] 图1A-E列举了以抗体作为载体的异二聚体细胞因子前药。图1A是以具有两条轻链和两条重链的典型抗体作为其载体的前药;图1B是以双特异性抗体作为其载体的前药,每个抗原结合部分都是单体,其中一条抗原结合部分包括Fab结构域,另一条抗原结合部分包括scFv或单域抗体;图1C是以双特异性抗体作为其载体的前药,其中每个抗原结合部分均为二聚体;图1D是二聚体Fc结构域的一条多肽链和Fab结构域融合,另一条多肽链和细胞因子多肽融合的前药,其中所述细胞因子在N末端和掩蔽部分融合;图1E是二聚体Fc结构域的一条多肽链和Fab结构域融合,另一条多肽链和细胞因子多肽融合的前药,其中掩蔽部分N末端和细胞因子融合。

[0049] 图2为通过FACS分析的PD-1抗体和Fc-IL-21融合分子以及对照分子对Mino细胞的结合结果。

[0050] 图3为经MMP2蛋白酶活化前后的IL-21前药和对照分子分别对NK-92细胞生物活性的影响结果。PW04-38αPD1-IL21-a*和PW09-16αPD1-IL21-a*为不同批次的同一分子,其是以IL-21Rα-ECD作为掩蔽部分的PD-1抗体-IL-21前药;PW05-68αPD1-IL21-scFv是以scFv作为掩蔽部分的PD-1抗体-IL-21前药;其中一个对照分子PW04-67αPD1-IL21为不含有掩蔽部分的PD-1抗体-IL-21融合分子,其中IL-21为野生型;另一个对照分子PW09-02αPD1-IL21的R9ER76A突变体为不含掩蔽部分的PD-1抗体-IL-21融合分子,其中IL-21具有R9E及R76A氨基酸突变(序列编号和SEQ ID NO:1一致);活化的PW04-38αPD1-IL21-a*和活化的PW09-16αPD1-IL21-a*为不含突变的PD-1抗体-IL-21融合分子,其掩蔽部分被蛋白酶切割掉。

[0051] 图4A和图4B为经MMP2蛋白酶活化前后的PD-1-IL-21前药和对照分子对Mino细胞生物活性的影响结果。图4A为细胞因子融合分子和Mino细胞一起孵育72小时后的分析结果;图4B为孵育120小时后的分析结果。

[0052] 图5A,图5B和图5C为PBMC中的$CD4^+$T细胞的Ki67活性,其中PBMC用PD-1抗体(PD-1)、scFv掩蔽的Fc-IL-15融合分子(215β)、scFv掩蔽的PD-1抗体-IL-15融合分子(215γ)、不含掩蔽部分的Fc-IL-15融合分子(215βref)、不含掩蔽部分的PD-1抗体-IL-15融合分子(PD1/IL15mutein(M2))进行预处理。图5A为不表达PD-1的$CD4^+$T细胞中的Ki67活性;图5B为表达PD-1的$CD4^+$T细胞中的Ki67活性;图5C为不同待测样品处理的表达及不表达PD-1的$CD4^+$T细胞的$EC_{50}$值,同时也列出了表达及不表达PD-1的$CD4^+$T细胞的$EC_{50}$值的倍数关系。

[0053] 图6A和图6B为PBMC中的$CD4^+$T细胞的Ki67活性,其中PBMC用PD-1抗体(PD-1),阴性对照(IgG1抗体),及以IL-2受体β胞外域(IL-2Rβ-ECD)为掩蔽部分的PD-1抗体-IL-2突变蛋白融合分子(PD-1/IL2V*)进行预处理。图6A为不表达PD-1的$CD4^+$T细胞中的Ki67活性;图6B为表达PD-1的$CD4^+$T细胞中的Ki67活性。

[0054] 图7阐述了前药通过“顺式结合(cis-binding)”进行活化的原理。靶细胞(右侧)同时表达对载体部分有靶向性的抗原和细胞因子受体。前药通过和细胞表面抗原结合来接近细胞表面的细胞因子受体,使细胞因子受体以竞争性的优势取代掩蔽部分,进而实现其与细胞因子受体结合的信号传导作用。所述前药无需蛋白酶切割去除掩蔽部分。在仅表达细胞因子受体不表达抗原(左侧)的细胞中,前药的细胞因子处于被掩蔽而无活性的状态。

[0055] 发明详述

[0056] 本文及权利要求书中使用的单数形式“一个”,“或”和“这”包括复数所指物,除非上下文另有明确规定。

[0057] 此处“约”一个值或参数的引用包括(并描述了)该值或参数本身的变体。例如,“约X”的描述包括“X”的描述。此外,在任何一组数字前面使用“约”也包括在这一组所引用的数字中使用“约”。例如,“约X、Y或Z”的描述意在描述“约X、约Y或约Z”。

[0058] 术语“抗原结合部分”是指多肽或一组相互作用的多肽,其与抗原特异性结合,包括但不限于抗体(例如,单克隆抗体、多克隆抗体、多特异性抗体、双特异性抗体、抗独特型抗体或双功能混合抗体),或其抗原结合片段(例如Fab,Fab',F(ab')2,Fv,二硫键连接的Fv,scFv,单域抗体(dAb),双抗体,单链抗体和含Fc的多肽(比如免疫粘附素))。在一些实施例中,抗体可以是任何重链种型(例如,IgG,IgA,IgM,IgE或IgD)或亚型(例如,IgG1,IgG2,IgG3或IgG4)。在一些实施方案中,抗体可以是任何轻链种型(例如kappa或lambda)。抗体可以是人的,非人的(例如,来自小鼠,大鼠,兔,山羊或其他非人的动物),嵌合的(例如,具有非人可变区和人源恒定区)或人源化的(例如,具有非人CDR,人源构架和恒定区)。在一些实施例中,抗体是衍生的抗体。

[0059] 本发明在表述两个分子相互作用时使用的词汇“抗”,“结合”,“特异性结合”指的是用本领域惯常手段(如表面等离子共振,Elisa等)测得的$K_D$值不超过1000nM(如不超过100,10或1nM,例如小于1nM,1-10nM,10-100nM,或100-1000nM)。

[0060] “细胞因子激动剂多肽”一词是指野生型细胞因子或其类似物。野生型细胞因子的类似物与野生型细胞因子具有相同的生物学特异性(例如,结合到相同的受体并激活相同的靶细胞),尽管其活性水平可能与野生型细胞因子不同。类似物可为,例如,野生型细胞因子的一种突变蛋白质(即突变多肽),并可能相对于野生型细胞因子包括至少一个、至少两个、至少三个、至少有四个、至少5个、至少6个、至少7个、至少8个、至少九个或者至少十个突变。

[0061] “细胞因子拮抗剂”,“掩蔽部分”,或“细胞因子掩蔽部分”是指与细胞因子结合的部分(如多肽),当拮抗剂或掩蔽部分与细胞因子结合时,可抑制细胞因子与靶细胞表面受体结合和/或抑制其发挥生物学功能。细胞因子拮抗剂或掩蔽部分的例子,包括但不限于,从细胞因子自然受体的胞外结构域衍生的与细胞因子作用的多肽。

[0062] 术语“有效量”或“治疗有效量”是指足以治疗特定失调、状况或疾病(如改善、缓和、减轻和/或延缓一种或多种症状)的化合物或组合物的量。关于疾病如癌症,有效量可能是一个足以延缓癌症发展或进展(例如减少肿瘤的生长速度,和/或延迟或阻止肿瘤血管生成、转移、或肿瘤细胞渗透到周边器官),减少上皮样细胞,达到癌症消退(例如减少或消除肿瘤),和/或防止或延缓癌症的发生或复发。有效剂量可一次或多次给予。

[0063] “功能性类似物”是指具有与对照分子相同的生物学特异性(如与相同配体结合)和/或活性(如激活或抑制靶细胞)的分子。

[0064] 关于两个多肽序列的术语“融合”(fused)或“融合”(fusion),其是指两个多肽序列通过主链肽键的连接。两个多肽可以直接融合,亦可以通过一个或多个氨基酸长度的肽连接物融合。融合多肽可以通过重组技术,由包含着两个融合部份体的各自编码序列的一段编码序列制备,其间可具或不具肽连接物的编码序列。在一些实施方案中,融合涵盖化学

缀合。

[0065] “药学上可接受的赋形剂”指的是用来指组合物中的一个成分,适用于给予受试者,包括人体,对受试者没有过度的有害副作用、不影响药物活性成分(API)的生物活性。

[0066] 术语“前药”指的是在体外或血液循环没有活性或具有较低活性,而在病灶位点的环境中活性增强的治疗性物质。

[0067] “受试者”一词指哺乳动物,包括但不限于人类、宠物(如犬、猫)、农场动物(如牛、马)、啮齿动物或灵长类动物。

[0068] 此处使用的“治疗”(treatment)或“治疗”(treating)是一种获得有益或预期临床结果的方法。有益或期望的临床结果包括但不限于以下一项或多项:减轻疾病带来的一个或多个症状,减少疾病的程度,改善疾病状态,稳定疾病(例如预防或延缓疾病的恶化或进展),预防或延迟一种疾病的传播(如转移),预防或延缓疾病的复发,实现疾病部分或全部缓解,减少治疗疾病所需的一个或多个其他药物剂量,提高患者的生活质量,和/或延长生存时间。本公开方法思考了治疗的一个或多个方面。

[0069] 应该理解,这里描述的各种实施例中的一个、一些或所有属性可以组合起来形成本发明的其他实施例。此处使用的章节标题为了组织的目的而并不应该被解释成限定本申请所描述的主题。

[0070] I.细胞因子前药

[0071] 本发明提供的细胞因子前药在病灶位点的活性增强。该前药包括细胞因子激动剂多肽(细胞因子部分),载体部分和掩蔽部分。细胞因子部分通过或不通过肽连接物(如不可切割肽连接物)和载体部分连接,并被掩蔽部分掩蔽(结合)。掩蔽部分通过或不通过肽连接物(如不可切割肽连接物)和细胞因子部分或载体部分连接。或者细胞因子部分通过或不通过肽连接物(如不可切割肽连接物)和掩蔽部分连接,所述掩蔽部分通过或不通过肽连接物(如不可切割肽连接物)和载体部分连接。

[0072] 载体部分包括可与靶细胞(如肿瘤细胞或免疫细胞)抗原结合的抗原结合域。在一些实施例中,载体包括的抗体,如图1A所示。在一些实施例中,载体部分包括的可结合两个不同抗原的双特异性抗体,如图1B和图1C所示。

[0073] 掩蔽部分例如可以包括细胞因子受体胞外域(ECD),其中ECD和细胞因子部分(如图1D和图1E)连接,和/或通过不可切割肽连接物与载体部分连接(如图1A-C和图1E)。掩蔽部分和细胞因子部分结合并抑制其生物学功能。前药通过与细胞表面表达的细胞因子受体和抗原的顺式结合来吸引靶细胞,在无需切割掉或去除掩蔽部分的条件下可增加前药的活性。前药的细胞因子部分在靶位点(如在肿瘤位点或周围环境)的活性增加,其中对载体有靶向性的抗原和细胞因子受体表达在同一细胞上。相关前药的实施例表述在图1A-E中,图7阐述了所述顺式结合的原理。

[0074] A前药的细胞因子部分

[0075] 在一些实施例中,细胞因子部分包括IL-2激动剂多肽。在一些实施例中,IL-2激动剂多肽为具有R38S/F42A/Y45A/E62A或F42A/Y45A/L72G突变的IL-2突变体(序号和SEQ ID NO:6一致)。在一些实施例中,本发明披露的IL-2突变体包括选自T3,D20,K35,R38,F42,F44,Y45,E62,E68,L72,A73,N88,N90,C125,和Q126(序号和SEQ ID NO:6一致)位点的突变。在某些实施例中,新的IL-2突变体包括在R38,F42,Y45,和A73(序号和SEQ ID NO:6一致)位

点的突变。

[0076] 在一些实施例中,前药的细胞因子部分包括IL-15激动剂多肽。在一些实施例中,人IL-15多肽包括选自N1A,N1D,N4A,N4D,I6T,S7A,D8A,D8T,D8E,D8N,K10A,K10D,K11A,K11D,E46,V49,L45,S51,L52,D61A,D61N,T62L,T62A,E64A,E64L,E64K,E64Q,N65A,N65L,N65D,L66D,L66E,I 67D,I67E,I68S,I68E,L69S,L69E,N72A,N72D,V63E,V63D,L66E,L66D,I67E,I67D,Q108E,N112A,N1D/D61N,N1D/E64Q,N4D/D61N,N4D/E64Q,D8N/D61N,D8N/E64Q,D61N/E64Q,E64Q/Q108E,N1D/N4D/D8N,D61N/E64Q/N65D,N1D/D61N/E64Q,N1D/Q108E,N1D/D61N/E64Q/Q108E,N4D/D61N/E64Q/Q108E,和D30N/E64Q/N65D(序号和SEQ ID NO:7一致)中的一个或多个突变。在一些实施例中,IL-15前药进一步包括Sushi域。在一些实施例中,Sushi域包括SEQ ID NO:8或与其具有至少95%同源性的氨基酸序列。

[0077] 在一些实施例中,细胞因子部分包括IL-21激动剂多肽。在一些实施例中,IL-21激动剂多肽可以为野生型IL-21多肽,如野生型人IL-21(如SEQ ID NO:1),或为衍生自人IL-21的IL-21突变体,如选自SEQ ID NO:2-5任一条氨基酸序列。IL-21突变体相较于野生型IL-21明显降低了其对IL-2Rα或IL-21RαRγ的亲和力。在一些实施例中,IL-21突变体相较于野生型IL-21对高亲和力IL-2Rα的亲和力降低为1/5、1/10、1/20、1/50、1/100、1/300、1/500、1/1000或1/10000。除非另有其他说明,本发明涉及的IL-21和IL-21突变体中残基序号和SEQ ID NO:1一致。

[0078] B.前药的掩蔽部分

[0079] 本发明中的掩蔽部分包括与前药中细胞因子部分结合的肽、抗体或抗体片段,通过掩蔽细胞因子来抑制其生物学功能。在一些实施例中,所述掩蔽部分可操作地通过不可切割肽连接物和所述前药的其他部分连接。

[0080] 例如,前药包括IL-2激动剂多肽,掩蔽部分包括与IL-2结合以影响IL-2与其同源受体结合的肽、抗体或其抗原结合片段。在一些实施例中,掩蔽部分降低被掩蔽的IL-2部分的生物学活性。在一些实施例中,IL-2拮抗剂包括IL-2Rβ或IL-2Rγ胞外域或其功能类似物,例如可以来自于人IL-2Rβ或人IL-2Rγ(如SEQ ID NO:11或13)。在一些实施例中,IL-2掩蔽部分包括从肽文库筛选出来的肽。在一些实施例中,IL-2掩蔽部分包括抑制IL-2或IL-2突变体和IL-2受体结合的抗体或其片段。在一些实施例中,掩蔽部分包括抗IL-2抗体的scFv。在一些实施例中,掩蔽部分包括SEQ ID NO:22或23,或与其具有至少95%同源性的氨基酸序列。

[0081] 又比如,前药包括IL-21激动剂多肽,掩蔽部分包括与IL-21结合以影响IL-21与其同源受体结合的肽、抗体或其抗原结合片段。在一些实施例中,掩蔽部分降低被掩蔽的IL-21部分的生物学活性。在一些实施例中,IL-21拮抗剂包括IL-21Rα或IL-21Rγ胞外域或其功能类似物,例如可以来自于人IL-21Rα或人IL-21Rγ(如SEQ ID NO:12或13)。在一些实施例中,IL-21掩蔽部分包括从肽文库筛选出来的肽。在一些实施例中,IL-21掩蔽部分包括抑制IL-21或IL-21突变体和IL-21受体结合的抗体或其片段。在一些实施例中,掩蔽部分包括抗IL-21抗体的scFv。在一些实施例中,掩蔽部分包括SEQ ID NO:20或21,或与其具有至少95%同源性的氨基酸序列。

[0082] 再比如,前药包括本发明披露任一细胞因子的掩蔽部分,所述细胞因子包括但不限于选自于IL-7激动剂多肽、IL-9激动剂多肽、IL-15激动剂多肽、IL-1α激动剂多肽、IL-1β

激动剂多肽、IL-4激动剂多肽、IL-5激动剂多肽、IL-6激动剂多肽、IL-8激动剂多肽、IL-10激动剂多肽、IL-12激动剂多肽、IL-17激动剂多肽、IL-18激动剂多肽、IL-22激动剂多肽、IL-23激动剂多肽、IL-31激动剂多肽、IL-33激动剂多肽、IL-36激动剂多肽、干扰素α激动剂多肽、干扰素γ激动剂多肽、4-1BB配体,OX-40配体或CD-40配体。

[0083] C.前药的载体部分

[0084] 前药的载体部分包括抗原结合域和可选的其他结构域。载体部分可改善PK如血清中细胞因子激动剂多肽的半衰期,以及将细胞因子激动剂多肽靶向递送至身体的靶点部位,如肿瘤位点。

[0085] 1.载体部分的抗原结合域

[0086] 载体部分包括抗原结合结构域,可以是抗体或其抗原结合片段,或免疫粘附素。在一些实施例中,抗原结合载体部分是一个具有两条重链和两条轻链的全长抗体、一个Fab片段、一个Fab'片段、一个$F(ab')_2$片段、一个Fv片段、一个二硫键连接的Fv片段、一个单域抗体、一个纳米体或一个单链可变片段(scFv)。在一些实施例中,抗原结合部分为双特异性抗原结合部分,可与两种不同抗原或同一抗原上的两种不同表位结合。抗原结合部分可能为细胞因子激动剂多肽提供附加和潜在的协同治疗效果。

[0087] 细胞因子激动剂多肽及其掩蔽部分可以与抗原结合部分的轻链和/或重链的N末端或C末端融合。例如,IIL-21激动剂多肽及其掩蔽部分可以与抗体重链或其抗原结合片段融合,也可以与抗体轻链或其抗原结合片段融合。举例来说,IL-21激动剂多肽及其掩蔽部分可以与抗体重链或其抗原结合片段融合,也可以与抗体轻链或其抗原结合片段融合。在一些实施例中,IL-21激动剂多肽的一个末端与抗体的一个或两个重链的C端融合,IL-21掩蔽通过一个不可切掉的肽连接物与IL-21激动剂多肽的另一个末端融合。在一些实施例中,IL-21受体激动剂多肽融合到抗体的一个重链的C端上,IL-21保护单位通过一个不可切掉的肽连接物与抗体的另一个重链的C端融合,其中两个重链包含突变,允许两个不同重链的特殊配对。

[0088] 形成异二聚体的策略是众所周知的(参见,例如,Spies et al.,Mol Imm.67(2)(A):95-106(2015))。例如,前药中的两个重链多肽可以通过“knobs-into-holes”突变形成稳定的异二聚体。进行“knobs-into-holes”突变以促进抗体重链的异二聚体的形成,并且普遍用于制造双特异性抗体(参见,例如,美国专利号8,642,745)。例如,抗体的Fc结构域可在“knob chian”的CH3结构域中包含T366W突变,而在“hole chain”的CH3结构域中包含T366S,L368A和/或Y407V突变。还可以使用CH3域之间的另一个链间二硫桥,例如,通过将Y349C突变引入“knobs chain”的CH3域,并将E356C或S354C突变引入“hole chain”的CH3域中(参见,例如,Merchant et al.,Nature Biotech16:677-81(1998))。在其他实施方案中,抗体部分可在两个CH3结构域之一中包含Y349C和/或T366W突变,在另一个CH3结构域中包含E356C,T366S,L368A和/或Y407V突变。在某些特定实施例中,抗体部分可在两个CH3结构域之一中包含Y349C和/或T366W突变,在另一个CH3结构域中包含S354C(或E356C),T366S,L368A和/或Y407V突变;当一个CH3结构域上额外的Y349C突变,和另一个CH3结构域上额外的E356C或S354C突变,形成一个链间二硫键(编号始终根据Kabat的EU索引编号;Kabat et al.,“Sequences of Proteins of Immunological Interest,”5th ed.,Public Health Service,National Institutes of Health,Bethesda,Md.(1991))。其他knobs-in-holes

技术,比如EP1870459A1中所述的,均可以替代或附加地使用。于是,抗体部分的knobs-in-holes突变的另一个例子是在“knob chain”的CH3域中带有R409D/K370E突变,在“hole chain”的CH3域中带有D399K/E357K突变(EU编号)。

[0089] 在一些实施例中,前药的抗原结合部分包括抗体,其Fc结构域具有L234A和L235A(“LALA”)突变。LALA突变可消除补体结合和固定以及Fcγ依赖性ADCC(见Hezareh et al.J.Virol.(2001)75(24):12161-8)。在进一步实施例中,除了knobs-into-holes突变外,抗体部分还存在LALA突变。

[0090] 在一些实施例中,该抗原结合部分包括Fc结构域的M252Y/S254T/T256E(“YTE”)突变。YTE突变允许同时调节血清半衰期、组织分布和IgG1活性(见Dall'Acqua et al.,J Biol Chem.(2006)281:23514-24;and Robbie et al.,Antimicrob Agents Chemother.(2013)57(12):6147-53)。在进一步实施例中,除了knobs-into-holes突变外,在抗体部分中还存在YTE突变。在具体实施例中,抗体部分具有YTE、LALA和knobs-into-holes突变或它们的任何组合。

[0091] 在特定实施例中,抗原结合部分为结合靶细胞(如免疫细胞)表面抗原的抗体或其抗原结合片段,其中免疫细胞为公知常识。在非限制性实施例中,免疫细胞包括T细胞、NK细胞和巨噬细胞。抗原结合部分能够激活免疫细胞并增强其抗肿瘤活性。抗体可能具有或不具有ADCC活性。抗原结合部分进一步可以和细胞毒性药物结合。在一些实施例中,抗原结合部分可以与PD-1、LAG-3、TIM-3、TIGIT、CTLA-4或TGF-beta结合。在其他实施例中,抗原结合部分可以与靶细胞(如肿瘤细胞)表面抗原结合。例如,抗原结合部分可与FAPα、5T4、Trop-2、PD-L1、HER-2、EGFR、Claudin18.2、DLL-3、GCP3或癌胚抗原(CEA)结合。-

[0092] 在一些实施例中,抗原结合部分可结合于脒基环化酶C(GCC),糖类抗原19-9(CA19-9),糖蛋白A33(gpA33),粘蛋白1(MUC1)、胰岛素样生长因子1受体(IGF1-R),人类表皮生长因子受体2(HER2),人类表皮生长因子受体3(HER3),delta-like蛋白3(DLL3),delta-like蛋白4(DLL4)、表皮生长因子受体(EGFR),蛋白多糖-3(GPC3),c-MET,血管内皮生长因子受体1(VEGFR1),血管内皮生长因子受体2(VEGFR2)、Nectin-4、Liv-1、糖蛋白NMB(GPNMB)、前列腺特异性膜抗原(PSMA)、Trop-2、碳酸酐酶IX(CA9),内皮素B受体(ETBR),前列腺1的6个跨膜上皮抗原(STEAP1),叶酸受体α(FR-α),SLIT和NTRK类蛋白6(SLITRK6)碳酸酐酶VI(CA6),磷酸二酯酶家族成员3(ENPP3),间皮素,滋养层糖蛋白(TPBG),CD19,CD20,CD22,CD33,CD40,CD56,CD66e,CD70,CD74,CD79b,CD98,CD123,CD138,CD352,CD47,信号调节蛋白(SIRPα),Claudin 18.2,Claudin 6,BCMA或EPCAM。在一些实施例中,抗原结合部分与DLL3的表皮生长因子(EGF)-样结构域结合。在一些实施例中,抗原结合部分与DLL3的Delta/Serrate/Lag2(DSL)-样结构域结合。在一些实施例中,抗原结合部分与位于GPC3的第374个氨基酸后的一个表位结合。在一些实施例中,抗原结合部分与GPC3的硫酸肝素聚糖结合。在一些实施例中,抗原结合部分与Claudin 18.2结合,但不与Claudin 18.1结合。在一些实施例中,抗原结合部分与Claudin 18.1的结合亲和力,比与Claudin 18.2的结合亲和力至少弱10倍。

[0093] 示例性的抗原结合部分包括曲妥珠单抗、利妥昔单抗、伯妥昔单抗、西妥昔单抗、帕尼单抗、GC33(或其人源化版本)、抗EGFR抗体mAb806(或其人源化版本)、抗dPNAG抗体F598及其抗原结合片段。在一些实施例中,抗原结合部分至少有90%、91%、92%、93%、

94％、95％、96％、97％、98％或99％与曲妥珠单抗、利妥昔单抗、伯妥昔单抗、西妥昔单抗或帕尼单抗、GC33(或其人源化版本)、抗EGFR抗体mAb806(或其人源化版本)、抗-dPNAG抗体F598或其片段一致。在一些实施例中,抗原结合部分有一个抗体重链,其至少有90％,91％,92％,93％,94％,95％,96％,97％,98％或99％与曲妥珠单抗,利妥昔单抗,本妥昔单抗,西妥昔单抗,帕尼单抗,GC33(或其人源化版本),抗-EGFR抗体mAb806(或其人源化版本),抗-dPNAG抗体F598或片段的抗体重链一致。在一些实施例中,抗原结合部分有一个抗体轻链,其至少有90％,91％,92％,93％,94％,95％,96％,97％,98％或99％与曲妥珠单抗抗体,利妥昔单抗,本妥昔单抗,西妥昔单抗,帕尼单抗,GC33(或其人源化版本),抗-EGFR抗体mAb806(或其人源化版本),抗-dPNAG抗体F598或片段的抗体轻链一致。抗原结合部分被融合到IL-2激动剂多肽上。在一些实施例中,抗原结合部分包括曲妥珠单抗、利妥昔单抗、本妥昔单抗、西妥昔单抗、帕尼单抗、GC33、抗EGFR抗体mAb806或抗dPNAG抗体F598的6个互补决定区(CDRs)。

[0094] 许多CDR描述是本领域已知的,并且在本文中涵盖。本领域技术人员可以基于重链或轻链可变区的序列,轻易地确定所给定描述的CDR。“Kabat”CDR乃基于序列可变性且最为常用(Kabat et al.,Sequences of Proteins of Immunological Interest,5th Ed.Public Health Service,National Institutes of Health,Bethesda,Md.(1991))。“Chothia”CDR是指结构环的位置(Chothia&Lesk,Canonical structures for the hypervariable regions of immunoglobulins,J.Mol.Biol.,vol.196,pp.901-917(1987))。“AbM”CDR代表了Kabat CDR和Chothia结构环之间的折衷,其亦被牛津分子(Oxford Molecular)的AbM抗体建模软件使用。“Contact”CDR为基于对可用复杂晶体结构的分析。参考常见的抗体编号方案,这些CDR的各个残基在下表1中列出。除非本文另有说明,否则抗体中的氨基酸编号是指如上文Kabat等人所述的Kabat编号方案,其包括当参照Kabat,Chothia,AbM或Contact方案进行CDR描述时。使用该编号系统,实际的线性氨基酸序列可以包含较少或额外的氨基酸,其对应于可变结构域的框架区(FR)或CDR的缩短或插入。例如,重链可变域可以包括在H2的残基52之后的单个氨基酸插入(根据Kabat的残基52a),亦包括在重链FR残基82之后的插入的残基(例如,根据Kabat的残基82a,82b和82c等)。对于所给定的抗体,通过在抗体序列同源区域与“标准”Kabat编号序列进行比对,可以确定其抗体残基的Kabat编号。

[0095] 表1:不同编号方案的CDR描述

[0096]

| CDR | Kabat | AbM | Chothia | Contact |
|---|---|---|---|---|
| VL-CDR1 | L24—L34 | L24—L34 | L26—L32 | L30—L36 |
| VL-CDR2 | L50—L56 | L50—L56 | L50—L52 | L46—L55 |
| VL-CDR3 | L89—L97 | L89—L97 | L91—L96 | L89—L96 |
| VH-CDR1(Kabat nos.) | H31—H35B | H26—H35B | H26—H32 | H30—H35B |
| VH-CDR1(Chothia nos.) | H31—H35 | H26—H35 | H26—H32 | H30—H35 |
| VH-CDR2 | H50—H65 | H50—H58 | H53—H55 | H47—H58 |
| VH-CDR3 | H95—H102 | H95—H102 | H95—H101 | H93—H101 |

[0097] 在一些实施例中,CDRs是“扩展的CDRs”,包含根据不同方案开始或结束区域。例如,扩展的CDR可如下所示:L24—L36,L26—L34,或L26—L36(VL-CDR1);L46—L52,L46—

L56,或L50—L55(VL-CDR2);L91—L97(VL-CDR3);H47—H55,H47—H65,H50—H55,H53—H58,或H53—H65(VH-CDR2;和/或H93—H102(VH-CDR3)。

[0098] 在一些实施例中,与PDL1结合的抗原结合部分,包括一条与SEQ ID NO:45的氨基酸序列或其片段具有至少90%,91%,92%,93%,94%,95%,96%,97%,98%,或99%同一性的轻链,和一条与SEQ ID NO:46的氨基酸序列或其片段具有至少90%,91%,92%,93%,94%,95%,96%,97%,98%,或99%同一性的重链。在一些实施例中,抗原结合域包括SEQ ID NO:45的CDR1、CDR2和CDR3,以及SEQ ID NO:46的CDR1、CDR2和CDR3。

[0099] 在一些实施例中,与PD-1结合的抗原结合部分,包括一条与SEQ ID NO:44的氨基酸序列或其片段具有至少90%,91%,92%,93%,94%,95%,96%,97%,98%,或99%同一性的轻链,和一条与SEQ ID NO:47的氨基酸序列或其片段具有至少90%,91%,92%,93%,94%,95%,96%,97%,98%,或99%同一性的重链。在一些实施例中,抗原结合域包括SEQ ID NO:44的CDR1、CDR2和CDR3,以及SEQ ID NO:47的CDR1、CDR2和CDR3。

[0100] 在一些实施例中,与PD-1结合的抗原结合部分,包括一条与SEQ ID NO:48的氨基酸序列或其片段具有至少90%,91%,92%,93%,94%,95%,96%,97%,98%,或99%同一性的轻链,和一条与SEQ ID NO:49的氨基酸序列或其片段具有至少90%,91%,92%,93%,94%,95%,96%,97%,98%,或99%同一性的重链。在一些实施例中,抗原结合域包括SEQ ID NO:48的CDR1、CDR2和CDR3,以及SEQ ID NO:49的CDR1、CDR2和CDR3。

[0101] 在一些实施例中,抗原结合部分包括一个、两个或三个抗原结合结构域。例如,抗原结合部分是双特异性的,可与两种不同的抗原结合,这两种抗原分别选自CD3,HER2,HER3,EGFR,5T4,FAP alpha,Trop-2,GPC3,VEGFR2,Claudin 18.2以及PD-L1。在一些实施例中,双特异性抗原结合部分与HER2的两个不同表位结合。在其他实施例中,抗原结合部分是双特异性的,可以与两种不同的抗原结合,这两种抗原分别选自PD-1,PD-L1,CTLA-4,CD47,CD3,TIM-3,LAG-3以及TIGIT。

[0102] 2.其他载体部分

[0103] 载体部分也可以包括其他非抗原结合结构域。例如,抗体Fc结构域(例如人IgG1,IgG2,IgG3或IgG4Fc),聚合物(例如PEG),白蛋白(例如人白蛋白),或其片段,或纳米颗粒,均可使用。

[0104] 例如,可以将细胞因子激动剂多肽(如IL-2、IL-21、IL-5、或本发明披露的其他任何细胞因子)和其拮抗剂与抗体Fc结构域融合,形成Fc融合蛋白。在一些实施例中细胞因子激动剂多肽与Fc结构域其中一条多肽链的C端或N端融合(直接融合或通过肽连接物),而细胞因子掩蔽部分则通过可切割的肽连接物,与另一条Fc结构域多肽链相应的C端或N端融合,其中两条Fc结构域多肽链包含了允许两条不同的Fc链特异性配对的突变。在一些实施例中,Fc结构域包含上述的holes-into-holes突变。在一些进一步实施例中,Fc结构域亦可包含上述的YTE和/或LALA突变。

[0105] 前药的载体部分可包含白蛋白(例如人血清白蛋白)或其片段。在一些实施例中,载体部分包括白蛋白片段(如人血清白蛋白片段),其具有约10或更多,20或更多,30或更多,40或更多,50或更多,60或更多,70或更多,80或更多,90或更多,100或更多,120或更多,140或更多,160或更多,180或更多,200或更多,250或更多,300或更多,350或更多,400或更多长度为450或更多,500或更多或550或更多的氨基酸。在一些实施例中,所述白蛋白片段

的长度在约10个氨基酸与约584个氨基酸之间(例如在约10与约20,约20与约40,约40与约80,约80与约160,约160与约250,约250和约350,约350和约450,或约450和约550个氨基酸之间)。在一些实施例中,白蛋白片段包括Sudlow I结构域或其片段,或Sudlow II结构域或其片段。

[0106] D.前药的连接部分

[0107] 细胞因子激动剂多肽可以在具有或不具有肽连接物的情况下与载体部分融合。肽连接物可以是不可切割的。在一些实施例中,肽连接物选自SEQ ID NO:27-34。在一些特定的实施例中,肽连接物包含氨基酸序列GGGGSGGGGSGGGGS(SEQ ID NO:30)

[0108] 掩蔽部分可以通过不可切割肽连接物或不经过肽连接物和细胞因子部分或载体部分融合。

[0109] II.药物组合物

[0110] 药物组合物包括本发明所述前药和突变蛋白(例如,活性药物成分或API),可藉将所需纯度的API与一或多种可选择的药学上可接受赋形剂混合来制备(例如参见,Remington's Pharmaceutical Sciences,16th Edition.,Osol,A.Ed.(1980))成冻干制剂或水溶液。药学上可接受的赋形剂(或载体)通常在使用的剂量和浓度下对给予者无毒,包括但不限于:缓冲液含有例如,磷酸盐,柠檬酸盐,琥珀酸盐,组氨酸,乙酸盐或另一种无机或有机酸或其盐;抗氧化剂,包括抗坏血酸和蛋氨酸;防腐剂(例如十八烷基二甲基苄基氯化铵;六甲基氯化铵;苯扎氯铵;苄索氯铵;苯酚,丁醇或苄醇;对羟基苯甲酸烷基酯如对羟基苯甲酸甲酯或对羟基苯甲酸丙酯;邻苯二酚;间苯二酚;间苯二酚;3-戊醇和间甲酚);低分子量(少于约10个残基)多肽;蛋白质,例如血清白蛋白,明胶或免疫球蛋白;亲水性聚合物,例如聚乙烯吡咯烷酮;氨基酸,例如甘氨酸,谷氨酰胺,天冬酰胺,组氨酸,精氨酸或赖氨酸;单糖,二糖和其他碳水化合物,包括蔗糖,葡萄糖,甘露糖或糊精;螯合剂,如EDTA;糖,例如蔗糖,甘露醇,海藻糖或山梨糖醇;成盐的抗衡离子,例如钠;金属配合物(例如锌-蛋白配合物);和/或非离子表面活性剂,例如聚乙二醇(PEG)。

[0111] 缓冲液用于将pH控制在最佳的治疗效果范围内,特别是当稳定性依赖于pH时。缓冲液浓度最好在50mM到250mM之间。适用于与本发明一起使用的缓冲剂包括有机和无机酸及其盐类,如柠檬酸盐、磷酸盐、琥珀酸盐、酒石酸盐、富马酸盐、葡萄糖酸盐、草酸盐、乳酸盐和醋酸盐。此外,缓冲液可包括组氨酸和三甲胺盐,如三羟甲基氨基甲烷。

[0112] 添加防腐剂以减缓微生物的生长,通常在0.2%-1.0%(w/v)范围内存在。本发明使用的适用防腐剂包括十八烷基二甲基苄基氯化铵;六甲铵氯化物;苯扎卤铵(如氯、溴、碘)、苯扎氯铵;硫柳汞、苯酚、丁基或苄醇;羟苯甲酸甲酯或羟苯甲酸丙酯;邻苯二酚;间苯二酚;环己醇,3-戊醇和间甲酚。

[0113] 张度剂,有时称为"稳定剂",是用以调节或维持成分中液体的张力。当其与带电荷的生物大分子(如蛋白质和抗体)一起使用时,它们通常被称为"稳定剂",因其可与氨基酸侧链的带电基团相互作用,从而降低了分子间和分子内相互作用的可能性。当考虑其他成分的相对量时,张度剂可在0.1%至25%重量比之间的任何量使用,或更优选于1%至5%重量比之间。优选的张度剂包括多元糖醇,更优选地为三元或更高级的糖醇,例如甘油,赤藓糖醇,阿拉伯糖醇,木糖醇,山梨糖醇和甘露糖醇。

[0114] 非离子表面活性剂或去污剂(也称为"湿润剂"),被用以帮助溶解治疗剂,并保护

治疗蛋白避免因搅动所导致的聚集,其亦允许了该制剂配方可暴露于剪切表面应力而不引起活性治疗性蛋白或抗体的变性。非离子表面活性剂的使用范围为约0.05mg/ml至约1.0mg/ml,优选地为约0.07mg/ml至约0.2mg/ml。

[0115] 合适的非离子表面活性剂包括聚山梨酸酯(20、40、60、65、80等),泊咯沙姆(184、188等),普朗尼克多元醇,曲拉通,聚氧乙烯山梨糖醇单醚(吐温-20,吐温-80等),聚桂醇400,聚氧化烯硬脂酸酯40,聚氧乙烯氢化蓖麻油10、50和60,单硬脂酸甘油酯,蔗糖脂肪酸酯,甲基纤维素和羧甲基纤维素。可使用的阴离子去污剂包括月桂基硫酸钠,磺基琥珀酸二辛酯钠和磺酸二辛基钠。阳离子去污剂包括苯扎氯铵或苄索氯铵。

[0116] 药物载体、赋形剂或稀释剂的选择可根据预定的给药途径和标准制药实践。药物组合物还可包括适合的粘合剂、润滑剂、悬浮剂、涂层剂或增溶剂。

[0117] 根据不同的药物传递系统,可能需要不同的组合物/制剂要求。举例来说,本发明中有用的药物成分可被配制成适用于微型泵或通过粘膜途径传递,例如,作为鼻用喷雾剂或气雾剂的吸入剂或可吸收溶液,亦或配制成注射形式的成分以肠胃外地给药,其藉由例如静脉内,肌内或皮下途径传递。

[0118] 在一些实施例中,本发明的药物组合是一种冻干蛋白制剂。在其他实施例中,所述药物组合物可以是水相液体制剂。

[0119] III.治疗方法

[0120] 细胞因子前药及融合分子可用于治疗疾病,其取决于抗原结合结构域所结合的抗原。在一些实施例中,细胞因子前药或融合分子用于治疗癌症。在一些实施例中,细胞因子前药或融合分子用于治疗感染。

[0121] 在一些实施例中,治疗疾病(例如癌症,寄生虫感染,病毒感染或细菌感染)的方法包含向对象施用有效量的细胞因子前药或融合分子。

[0122] 在一些实施例中,癌症是实体癌。在一些实施例中,癌症是血液癌或实体瘤。可治疗的示例性癌症包括但不限于,白血病,淋巴瘤,肾癌,膀胱癌,泌尿道癌,子宫颈癌,脑癌,头颈癌,皮肤癌,子宫癌,睾丸癌,食道癌,肝癌,大肠癌,胃癌,鳞状细胞癌,前列腺癌,胰腺癌,肺癌(例如非小细胞肺癌),胆管癌,乳腺癌和卵巢癌。

[0123] 在一些实施例中,细胞因子前药或融合分子用于治疗病毒感染。在一些实施例中,引起病毒感染的病毒是丙型肝炎病毒(HCV)、乙型肝炎病毒(HBV)、人体免疫缺陷病毒(HIV)或人类乳头瘤病毒(HPV)。在一些实施例中,抗原结合部分与病毒抗原相结合。

[0124] 在一些实施例中,细胞因子前药或融合分子用于治疗细菌感染,如脓毒症。在一些实施例中,引起细菌感染的细菌是耐药细菌。在一些实施例中,抗原结合部分与细菌抗原结合。

[0125] 一般来说,现有药物的给药剂量和给药途径是根据受试者的情况和条件,按照标准的药学实践确定。在一些实施例中,药物成分给予是通过一个给药路径,包括口服、皮下、吸入、静脉注射、动脉内的、肌内、直接应用于伤口,应用手术部位、腹腔内、栓剂、皮下、皮内注射、经皮、雾化、胸膜腔内、脑室、关节内的、眼内、颅内或脊柱内。在一些实施例中,药物被静脉注射给受试者。

[0126] 在一些实施例中,药物组合物的剂量是单剂量或多剂量。在一些实施例中,剂量为每天一次,每天两次,每天三次,或每天四次或更多次给予给药对象。在一些实施方案中,一

周内给予约1次或更多(例如约2、3、4、5、6或7或更多)剂量。在一些实施例中,药物组合物以每周一次,每两周一次,每三周一次,每四周一次,每周一次(三周中的两周中的每周),或每周一次(四周中的三周中的每周),来实施给药。在一些实施例中,多剂量于几天,几周,几个月或几年的过程中给予。在一些实施方案中,治疗过程为约1或更多剂量(例如约2、3、4、5、7、10、15或20或更多剂量)。

[0127] 除非本文另外定义,否则与本发明相关的科学和技术术语,应具有本领域普通技术人员通常理解的含义。示例性方法和材料如下所描述,但与本文描述的那些类似或等同的方法和材料亦可被用于本发明的实践或试验中。如有冲突,以本规范说明,包括定义,为准。通常,本文所述相关于细胞和组织培养,分子生物学,免疫学,微生物学,遗传学,分析化学,合成有机化学,医学和药物化学,以及蛋白质和核酸化学,以及杂交混合的术语和技术均为本领域众所周知和常用的。酶促反应和纯化技术乃根据制造商的规范说明执行,如本领域通常达成的或如本文所述。此外,除非上下文另外要求,否则单数术语应包括复数,并且复数术语应包括单数。在整个规范说明和实施方案中,词语"具有"和"包含",或其同义、替代词及变体,将被理解为暗示着包括了所述整数或整数组,但不排除任何其他整数或整数组。应当理解,本文所述发明的方面和变化包括"由……组成"和/或"基本上由……组成"的方面和变化。尽管本文引用了许多文件,但该引用并不构成承认这些文件中的任何文件形成本领域公知常识的一部分。

[0128] IV.示例性实施方案

[0129] 本发明的其他特定实施例描述如下。这些实施方案旨在说明本发明中描述的成分和方法,而并非旨在限制本发明的范围。

[0130] 1、前药,包括细胞因子部分、掩蔽部分和载体部分,其中,

[0131] a)掩蔽部分结合细胞因子部分并抑制该细胞因子的生物学活性;

[0132] b)载体部分包括抗原结合部分,其可以与细胞表面表达的抗原结合,且

[0133] c)掩蔽部分通过不可切割肽连接物或不通过肽连接物直接或间接地和载体部分结合;

[0134] 其中,前药对同时表达对载体部分有靶向性的抗原及细胞因子受体的细胞的活化相较于其对仅表达细胞因子受体而不表达对载体部分有靶向性抗原的细胞的活化具有更高的活性。

[0135] 2、前药,包括细胞因子部分,掩蔽部分和载体部分,其中,

[0136] a)掩蔽部分和细胞因子部分结合并抑制细胞因子生物学活性;

[0137] b)载体部分包括抗原结合部分,其可与细胞表面表达的抗原结合;且,

[0138] c)掩蔽部分通过不可切割肽连接物或不通过肽连接物直接或间接和载体部分结合;

[0139] 其中,前药在病灶位点被活化,或者前药在病灶位点的生物学功能增加至少2倍、至少5倍或至少10倍,所述病灶位点的细胞同时表达对载体部分有靶向性的抗原和细胞因子受体。

[0140] 3、实施例1或2所述的前药,其中细胞因子部分的受体包括两个或多个亚基。

[0141] 4、实施例1或2所述的前药,其中载体部分包括免疫细胞表达抗原的抗原结合部分,

[0142] 5、实施例1或2所述的前药,其中载体部分包括抗原结合部分,抗原选自PD-1,PD-L1,CTLA-4,TIGIT,TIM-3,LAG-3,CD25,CD16a,CD16b,NKG2D,NKP44,NKP30,CD19,CD20,CD38和BCMA。

[0143] 6、实施例1-5任一项所述的前药,其中细胞因子部分包括选自IL-2激动剂多肽、IL-7激动剂多肽、IL-9激动剂多肽、IL-15激动剂多肽及IL-21激动剂多肽的细胞因子。

[0144] 7、实施例1-5任一项所述的前药,其中细胞因子选自IL-1α激动剂多肽,IL-1β激动剂多肽,IL-4激动剂多肽,IL-5激动剂多肽,IL-6激动剂多肽,IL-8激动剂多肽,IL-10激动剂多肽,IL-12激动剂多肽,IL-17激动剂多肽,IL-18激动剂多肽,IL-22激动剂多肽,IL-23激动剂多肽,IL-31激动剂多肽,IL-33激动剂多肽,IL-36激动剂多肽,干扰素-α激动剂多肽,干扰素γ激动剂多肽,4-1BB配体,OX-40配体和CD-40配体。

[0145] 8、实施例1-7任一项所述的前药,其中掩蔽部分为细胞因子受体胞外域。

[0146] 9、实施例1-6任一项所述的前药,其中细胞因子为IL-7激动剂多肽,掩蔽部分为IL-7受体α胞外域(IL-7RαECD)或其功能类似物。

[0147] 10、实施例1-6任一项所述的前药,其中细胞因子为IL-21激动剂多肽,掩蔽部分为IL-21受体α胞外域(IL-21RαECD)或其功能类似物。

[0148] 11、实施例1-6任一项所述的前药,其中细胞因子为IL-2激动剂多肽或IL-15激动剂多肽,掩蔽部分为IL-2受体β胞外域(IL-2RβECD)。

[0149] 12、实施例1-6任一项所述的前药,其中细胞因子为IL-21激动剂多肽,掩蔽部分为抗IL-21的Fab,单链Fv(scFv),或单域抗体。

[0150] 13、实施例1-6任一项所述的前药,其中细胞因子为IL-2激动剂多肽,掩蔽部分为抗IL-2的Fab,单链Fv(scFv),或单域抗体。

[0151] 14、实施例1-6任一项所述的前药,其中细胞因子为IL-15激动剂多肽,掩蔽部分为抗IL-15的Fab,单链Fv(scFv),或单域抗体。

[0152] 15、实施例1-6、11或14任一项所述的前药,其中细胞因子包括IL-15激动剂多肽,融合分子进一步包括IL-15受体α的sushi域(IL-15Rαsushi域)。

[0153] 16、实施例10或12任一项所述的前药,其中IL-21激动剂多肽包括SEQ ID NO:1或与其具有至少90%同源性的氨基酸序列。

[0154] 17、实施例10或16所述的前药,其中掩蔽部分为IL-21RαECD或其功能类似物,其包括SEQ ID NO:12,63-72和73,或与SEQ ID NO:12具有至少90%同源性的氨基酸序列。

[0155] 18、实施例12或16所述的前药,其中掩蔽部分为结合人IL-21的scFv,所述scFv包括氨基酸序列SEQ ID NO:20或21。

[0156] 19、实施例11或13所述的前药,其中IL-2激动剂多肽包括SEQ ID NO:6或61,或与其具有至少95%同源性的氨基酸序列。

[0157] 20、实施例11或14所述的前药,其中IL-15激动剂多肽包括SEQ ID NO:7或与其具有至少95%同源性的氨基酸序列。

[0158] 21、实施例11,19或20所述的前药,其中掩蔽部分包括IL-2Rβ-ECD或其功能类似物,IL-2Rβ-ECD包括SEQ ID NO:11或与其具有至少95%同源性的氨基酸序列。

[0159] 22、实施例6、13或19任一项所述的前药,其中掩蔽部分为结合IL-2的scFv,所述scFv抑制或干扰IL-2及IL-2Rγ的相互作用,IL-2及IL-2Rβ的相互作用,和/或IL-2及IL-2R

γ的相互作用。

[0160] 23、实施例6,14,15或20任一项所述的前药,其中掩蔽部分为结合IL-15的scFv,所述scFv抑制或干扰IL-15及IL-2Rβ,和/或IL-2及IL-2Rγ的相互作用。

[0161] 24、实施例6,12或16任一项所述的前药,其中掩蔽部分为结合IL-21的scFv,所述scFv抑制或干扰IL-21及IL-21Rα,和/或IL-21及IL-2Rγ的相互作用。

[0162] 25、实施例6所述的前药,其中掩蔽部分为结合选自IL-2,IL-7,IL-9,IL-15,或IL-21细胞因子的scFv,所述scFv抑制或干扰所述细胞因子和IL-2Rγ的相互作用,所述前药相较于野生型细胞因子在非人类灵长动物或人体内的半衰期增加至少20倍、至少50倍、至少100倍、至少150倍或至少200倍。

[0163] 26、前药,包括载体部分、细胞因子部分、和掩蔽部分,其中,

[0164] a)细胞因子选自IL-2激动剂多肽,IL-7激动剂多肽,IL-9激动剂多肽,IL-15激动剂多肽,IL-21激动剂多肽;

[0165] b)掩蔽部分为结合所述细胞因子部分的scFv;

[0166] c)所述scFv抑制或干扰细胞因子和IL-2Rγ的相互作用;以及

[0167] d)所述前药相较于野生型细胞因子在非人类灵长动物或人体内的半衰期增加至少20倍、至少50倍、至少100倍、至少150倍或至少200倍。

[0168] 27、实施例22-25任一项所述的前药,其中scFv以$K_D$为1-10nM和细胞因子结合。

[0169] 28、实施例22-25任一项所述的前药,其中scFv以$K_D$为10-100nM和细胞因子结合.

[0170] 29、实施例22-25任一项所述的前药,其中scFv以$K_D$为100-1000nM和细胞因子结合。

[0171] 30、实施例13或19所述的前药,其中掩蔽部分为结合IL-2的scFv,所述scFv包括和杂交瘤4E12B2D10相同的重链和轻链CDR。

[0172] 31实施例13或19所述的前药,其中掩蔽部分为结合IL-2的scFv,所述scFv包括SEQ ID NO:22或23,或与其具有至少95%同源性的氨基酸序列。

[0173] 32、实施例14或20所述的前药,其中掩蔽部分为结合IL-15的scFv,所述scFv包括和IL-15抗体146B7,146H5,或404E4相同的重链和轻链CDR。

[0174] 33、实施例14或20所述的前药,其中掩蔽部分为结合IL-15的scFv,所述scFv包括氨基酸序列SEQ ID NO:18或19。

[0175] 34、实施例1-32任一项所述的前药,其中所述前药不含可切割肽连接物。

[0176] 35、实施例1所述的前药,其中所述前药包括的两条轻链的氨基酸序列为SEQ ID NO:44,重链多肽链的氨基酸序列分别为:

[0177] SEQ ID NO:33和36;

[0178] SEQ ID NO:37和36;

[0179] SEQ ID NO:37和38;

[0180] SEQ ID NO:39和41;或

[0181] SEQ ID NO:42和43。

[0182] 36、实施例1所述的前药,其中所述前药包括的两条轻链的氨基酸序列为SEQ ID NO:50,重链多肽链的氨基酸序列分别为:

[0183] SEQ ID NO:51和54;

[0184] SEQ ID NO:51和55;

[0185] SEQ ID NO:51和56;

[0186] SEQ ID NO:52和54;

[0187] SEQ ID NO:53和58;

[0188] SEQ ID NO:53和59;或

[0189] SEQ ID NO:52和57。

[0190] 37、包括实施例1-36任一项所述前药和药学上可接受的赋形剂的药物组合物。

[0191] 38、编码实施例1-36任一项所述前药的多核苷酸。

[0192] 39、包括实施例38所述多核苷酸的表达载体。

[0193] 40、包括实施例39所述表达载体的宿主细胞。

[0194] 41、制备实施例1-36任一项所述前药的方法,包括:

[0195] 在允许所述前药表达的条件下培养实施例46所述的宿主细胞,其中宿主细胞为哺乳动物细胞,和

[0196] 分离所述前药。

[0197] 42、对有需要患者治疗癌症、自身免疫性疾病或感染性疾病或刺激免疫系统的方法,包括向患者施用有效剂量的实施例37所述的药物组合物。

[0198] 43、实施例1-36任一项所述的前药,对有需要的患者在治疗癌症、自身免疫疾病、感染性疾病或刺激免疫系统中的应用。

[0199] 44、实施例1-36任一项所述前药在制备对有需要的患者治疗癌症、自身免疫疾病、感染性疾病或刺激免疫系统药物中的应用。

[0200] 45、实施例41所述的方法,权利要求42中前药的应用或权利要求43中融合分子的应用,或权利要求44前药的应用,所述患者患有HIV、HBV、HCV或HPV感染性疾病;选自红斑狼疮、I型糖尿病、银屑病、皮肌炎、GvHD、类风湿病的自身免疫系统疾病;选自乳腺癌、肺癌、胰腺癌、食道癌、甲状腺髓样癌、卵巢癌、子宫癌、前列腺癌、睾丸癌、结肠直肠癌和胃癌的癌症。

[0201] 46、前药,包括载体部分、细胞因子部分和掩蔽部分,其中,

[0202] a)细胞因子部分选自IL-2激动剂多肽、IL-7激动剂多肽、IL-9激动剂多肽、IL-15激动剂多肽、IL-21激动剂多肽;

[0203] b)掩蔽部分为结合细胞因子的scFv;

[0204] c)所述scFv抑制或干扰细胞因子和IL-2Rγ的相互作用,以及

[0205] d)所述前药在非人灵长动物或人体内的曲线下面积(AUC)相较于野生型细胞因子增加至少20倍、至少50倍、至少100倍、至少150倍或至少200倍。

[0206] 为了本发明可被更好地理解,于此阐述以下示例。这些示例仅出于说明目的,而不应以任何方式解释为限制本发明的范围。

## 实施例

[0207] 实施例1和实施例2所用到的材料和方法如下所述:

[0208] SEC-HPLC分析

[0209] SEC-HPLC的分析是在Agilent 1100系列HPLC系统上进行并配以Tosoh

Bioscience的TSKgel G3000SWXL色谱柱(7.8mmIDX 30cm,粒径5μm)。上样至多100μl,色谱柱的流动相为200mM $K_3PO_4$、250mM KCl,pH 6.5的缓冲液。流速设定为0.5ml/min。柱温为室温。

[0210] 蛋白水解处理

[0211] 蛋白酶,人MMP2,人MMP9,小鼠MMP2和小鼠MMP9购自R&D systems。蛋白酶消化的步骤如下,将10μg-50μg的前药蛋白与1μg人MMP2、人MMP9、小鼠MMP2或小鼠MMP9,加入含2mM $CaCl_2$和10μM $ZnCl_2$的HBS缓冲液中(20mM HEPES,150mM $NaCl_2$,pH 7.4),在37度培养12个小时。

[0212] 细胞活性测定

[0213] 采用细胞活性测定法检测蛋白酶消化前后的前药和对照样品。简单地说,NK92细胞在PRMI-1640培养基中生长,培养基中添加L-谷氨酰胺、10%胎牛血清、10%非必需氨基酸、10%丙酮酸钠和55μM巯基乙醇。NK92细胞不贴壁,在IL-2浓度为100ng/ml的培养基中维持在1x $10^5$-1x $10^6$细胞/ml。一般来说,细胞每周分裂两次。对于生物测定,最好使用传代后不少于48小时的细胞。将NK92细胞以5×$10^4$个细胞/孔培养,连续稀释样品,在固定量的IL-2存在下培养2天,测定IL-21的功能活性。上层液然后用ELISA检测干扰素-γ。

[0214] Mino IL-21活力分析

[0215] Mino细胞活力分析按照如下步骤进行:

[0216] a)将在50μL分析培养基(RPMI 1640,10%胎牛血清,NEAA,丙酮酸钠,55μM b-巯基乙醇)中连续稀释的待测样品加入96孔板中;

[0217] b)向每孔加入50μL含有20,000个Mino细胞的分析培养基;

[0218] c)培养3至5天;

[0219] d)向每孔加入100μL的Cell Titer Glo(Promega),Cell Titer Glo通过对ATP的定量评估来提供细胞活力的测量方法;

[0220] e)测量荧光度。

[0221] PBMC原始细胞分析Ki67活性

[0222] 人PBMC用浓度为100ng/mL的抗CD3抗体(OKT3)活化2天,清洗3遍后,用常规细胞培养基在37℃,5%$CO_2$的培养箱中静置3天。活化/静置后的PBMC以200K细胞/孔的密度接种至96孔板中,分别用不同浓度的待测样品处理上述PBMC,培养五天后,染色并流式细胞技术分析PD-$1^+$$CD4^+$细胞和PD-$1^-$$CD4^+$细胞中的Ki67(所有用于细胞染色的单抗购自BD)。

[0223] 实施例1:构建抗PD-1抗体-IL-21前药融合分子

[0224] 用两条相同的轻链(氨基酸序列如SEQ ID NO:44所示),第一重链多肽链(氨基酸序列如SEQ ID NO:42所示)和第二重链多肽链(氨基酸序列如SEQ ID NO:76所示)构建了基于抗PD-1抗体的IL-21前药。瞬时表达并纯化该分子((lot#PW04-38)。

[0225] 第二个基于抗PD-1抗体的IL-21前药的掩蔽部分为scFv,表达并纯化该分子(Lot#PW05-68)。

[0226] 另外,对照品为不含有掩蔽部分的抗PD-1抗体-IL-21融合分子,表达并纯化该分子(Lot#PW05-67)。

[0227] 进一步地,第二个对照品为不含有掩蔽部分的抗PD-1抗体-IL-21突变体(R9ER76A)融合分子,表达并纯化该分子(Lot#PW09-02)。

[0228] 实施例2.抗PD-1抗体-IL-21前药融合分子的生物学活性

[0229] 用FACS检测分析所述前药分子和多种对照分子与Mino细胞的结合。图2所示的结果显示PD-1抗体和Fc-IL-21融合分子均能够和Mino细胞结合,说明Mino细胞可表达PD-1和IL-21受体。结果显示基于Fc-IL-21前药分子不与该细胞结合,说明IL-21细胞因子被相应掩蔽部分掩蔽。然而基于PD-1抗体-IL-21前药分子和融合分子能够和Mino细胞结合。

[0230] 用NK92细胞和自然杀伤细胞(NK)检测分析所述分子的细胞活性,图3所示的结果显示,在未被活化条件下,以IL-21αECD作为掩蔽部分(Lot#PW04-38)的前药分子有最低限度的活性,而以scFv作为掩蔽部分(Lot#PW05-68)的活性为不含有掩蔽部分(PW04-67)的约1/1000。结果表明用蛋白酶MMP2处理后的前药的生物活性明显增强。

[0231] 用Mino细胞检测融合分子对肿瘤的杀伤活性。Mino为套细胞淋巴瘤细胞系,其可表达PD-1和IL-21受体(Harington et al.,Leuk Lymphoma(2019)60(10):2498-2507and Gelebart et al.,Leukemia(2009)23:1836-1846)。图4A和图4B为Mino细胞活力分析结果。令人意外的,抗PD-1抗体-IL-21前药(Lots#PW04-38和PW05-68)在活化前具有明显活性,而对照分子(PD-1抗体-IL-21R9E/R76A融合分子,Lot#PW09-02)没有或具有可忽略不计的活性。结果表明抗PD-1-IL-21融合分子通过“顺式结合(cis-binding)”被活化,比如通过同时和PD-1和IL-21受体结合。PD-1抗体和细胞表面PD-1抗原以及细胞因子和同一细胞表面的细胞因子受体的顺式结合可去除掩蔽部分的掩蔽效应。由于相应局部的免疫细胞同时表达对载体有靶向性的抗原及结合细胞因子部分的受体,因此不含可切割肽连接物的前药在病灶位点(如肿瘤)被活化。

[0232] 实施例3.构建抗PD-1抗体-IL-15前药融合分子

[0233] 构建一组抗PD-1抗体-IL-15前药,其中IL-15分子(i)被scFv 215β掩蔽;(ii)被scFv 215γ掩蔽;(iii)不含掩蔽部分(215βRef);或者(iv)包括突变但不含掩蔽部分(PD1/IL15突变体(M2))。所述前药的抗PD-1抗体包括两条相同轻链,氨基酸序列为SEQ ID NO:44,和两条相同重链,氨基酸序列为SEQ ID NO:47。

[0234] 基于Fc的前药215β为包括氨基酸序列SEQ ID NO:16和17的异二聚体。

[0235] 基于抗PD-1抗体的前药215γ包括两条相同轻链(SEQ ID NO:44),第一重链融合多肽链的氨基酸序列为SEQ ID NO:37,第二重链融合多肽链的氨基酸序列为SEQ ID NO:75。

[0236] 215βRef为IL-15突变体(D30N/E64Q/N65D)Fc融合分子。

[0237] PD1/IL15突变体(M2)为与IL-15突变体融合的抗PD-1抗体,其中IL-15激动剂包括E46G,V49R,E64Q,D30N,及N1G突变。

[0238] 上述物质均由CHO细胞表达,并依次通过蛋白A柱亲和层析和附加层析步骤进行纯化。

[0239] 实施例4.抗PD-1抗体-IL-15前药融合分子的生物学活性

[0240] 评估分析IL-15前药对激活人PBMC表达Ki67的作用效果。图5A-5C为处理过的PBMC中$CD4^+$T细胞的Ki67活性;图5A为不表达PD-1的$CD4^+$T细胞的Ki67活性;图5B为表达PD-1的$CD4^+$T细胞的Ki67活性;图5C分别为不同待测样品处理的表达和不表达PD-1的$CD4^+$T细胞的$EC_{50}$值,同时也列出了表达及不表达PD-1的$CD4^+$T细胞的$EC_{50}$值的倍数关系。数据表明215γ对表达PD-1的$CD4^+$细胞的Ki67的活性明显高于其对不表达PD-1的$CD4^+$细胞的Ki67活性,说

明前药215γ在同时表达PD-1抗原和IL-15细胞因子受体的细胞中活化而无需蛋白酶水解。

[0241] 实施例5.抗PD-1抗体-IL-2前药融合分子

[0242] 以类似的方法构建抗PD-1抗体-IL-2前药,所述前药PD-1/IL-2v*包括两条相同轻链(SEQ ID NO:44)和两条重链融合多肽(分别为SEQ ID NO:24和25)。IL-2部分为IL-2突变体,且所述前药中的掩蔽部分为IL-2受体β胞外域。分析IL-2前药对激活人PBMC表达Ki67的活性。

[0243] 图6A和图6B给出了分别用PD-1抗体(PD-1)、阴性对照、或PD-1/IL-2v*处理过的PBMC中的$CD4^+$T细胞的Ki67活性。阴性对照为抗人Claudin 18.2的IgG1抗体。上述物质均由CHO细胞表达,并依次通过蛋白A柱亲和层析和附加层析步骤进行纯化。图6A为不表达PD-1的$CD4^+$T细胞的Ki67活性;图6B为表达PD-1的$CD4^+$T细胞的Ki67活性。数据显示前药PD-1/IL2V*对表达PD-1的$CD4^+$细胞的Ki67诱导活性明显高于不表达PD-1的细胞。说明PD-1/IL-2v*在同时表达PD-1抗原和IL-2细胞因子受体的细胞中活化而无需蛋白酶水解。

[0244] 以上数据说明细胞因子前药在同时表达细胞因子受体和对载体部分有靶向性抗原的细胞处可被活化。以抗原结合部分作为载体的前药在无需蛋白酶水解条件下可被活化。尽管不希望受理论的约束,可以做如下预判:载体部分的抗原结合域将前药分子靶向至表达抗原的细胞表面,进而使细胞表面的细胞因子受体和前药的掩蔽部分竞争性结合细胞因子。如图7所示,不发生蛋白酶水解反应的前药通过细胞表面的细胞因子受体取代掩蔽部分以完成整个活化过程。

[0245] 细胞,如耗竭性Teff细胞,同时表达抗原(如PD-1)和细胞因子受体(如IL-2Rβ和IL-2Rγ)。耗竭性Teff细胞一般存在肿瘤微环境中而非正常组织。表达抗原和细胞因子受体的细胞在体内分布的差异性使前药在病灶位点特异性活化。所述靶特异性也进一步加强了细胞因子治疗的安全性。

[0246] 序列表

[0247] SEQ ID NO:1-人IL-21

QGQDRHMIRM RQLIDIVDQL KNYVNDLVPE FLPAPEDVET NCEWSAFSCF QKAQLKSANT

[0248] GNNERIINVS IKKLKRKPPS TNAGRRQKHR LTCPSCDSYE KKPPKEFLER FKSLLQKMIH QHLSSRTHGS EDS

[0249] SEQ ID NO:2-IL-21突变体A

QGQDRHMIRM RQLIDIVAQL KNYVNDLVPE FLPAPEDVET NCEWSAFSCF QKAQLKSANT

[0250] GNNERIINVS IKKLKRKPPS TNAGRRQKHR LTCPSCDSYE KKPPKEFLER FKSLLQKMIH QHLSSRTHGS EDS

[0251] SEQ ID NO:3-IL-21突变体B

QGQDRHMIRM RQLIDIVKQL KNYVNDLVPE FLPAPEDVET NCEWSAFSCF QKAQLKSANT

[0252] GNNERIINVS IKKLKRKPPS TNAGRRQKHR LTCPSCDSYE KKPPKEFLER FKSLLQKMIH QHLSSRTHGS EDS

[0253] SEQ ID NO:4-IL-21突变体C

QGQDRHMIRM RQLIDIVDQL KNYVNDLVPE FLPAPEDVET NCEWSAFSCF QKAQLKSANT

[0254] GNNERIINVS IKKLKRKPPS TNAGRRQKHR LTCPSCDSYE KKPPKEFLRR FKSLLQKMIH QHLSSRTHGS EDS

[0255] SEQ ID NO:5-IL-21突变体D

[0256] QGQDRHMIRM RQLIDIVDKL KNYVNDLVPE FLPAPEDVET NCEWSAFSCF QKAQLKSANT GNNERIINVS IKKLKRKPPS TNAGRRQKHR LTCPSCDSYE KKPPKEFLRR FKSLLQKMIH QHLSSRTHGS EDS

[0257] SEQ ID NO:6-人IL-2

[0258] APTSSSTKKT QLQLEHLLLD LQMILNGINN YKNPKLTRML TFKFYMPKKA TELKHLQCLE EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE TATIVEFLNR WITFCQSIIS TLT

[0259] SEQ ID NO:7-人IL-15

[0260] NWVNVISDLK KIEDLIQSMH IDATLYTESD VHPSCKVTAM KCFLLELQVI SLESGDASIH DTVENLIILA NNSLSSNGNV TESGCKECEE LEEKNIKEFL QSFVHIVQMF INT

[0261] SEQ ID NO:8-人IL-15Rαsushi域

[0262] ITCPPPMSVE HADIWVKSYS LYSRERYICN SGFKRKAGTS SLTECVLNKA TNVAHWTTPS LKCIRDPALV HQRPA

[0263] SEQ ID NO:9-人IL-7

[0264] DCDIEGKDGK QYESVLMVSI DQLLDSMKEI GSNCLNNEFN FFKRHICDAN KEGMFLFRAA RKLRQFLKMN STGDFDLHLL KVSEGTTILL NCTGQVKGRK PAALGEAQPT KSLEENKSLK EQKKLNDLCF LKRLLQEIKT CWNKILMGTK EH

[0265] SEQ ID NO:10-人IL-9

[0266] QGCPTLAGIL DINFLINKMQ EDPASKCHCS ANVTSCLCLG IPSDNCTRPC FSERLSQMTN TTMQTRYPLI FSRVKKSVEV LKNNKCPYFS CEQPCNQTTA GNALTFLKSL LEIFQKEKMR GMRGKI

[0267] SEQ ID NO:11-IL-2RβECD

[0268] AVNGTSQFTC FYNSRANISC VWSQDGALQD TSCQVHAWPD RRRWNQTCEL LPVSQASWAC NLILGAPDSQ KLTTVDIVTL RVLCREGVRW RVMAIQDFKP FENLRLMAPI SLQVVHVETH RCNISWEISQ ASHYFERHLE FEARTLSPGH TWEEAPLLTL KQKQEWICLE TLTPDTQYEF QVRVKPLQGE FTTWSPWSQP LAFRTKPAAL GKDT

[0269] SEQ ID NO:12-IL-21RαECD(来源:uniprot.org/uniprot/Q9HBE5)

[0270] CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR SDYEDPAFYM LKGKLQYELQ YRNRGDPWAV SPRRKLISVD SRSVSLLPLE FRKDSSYELQ VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

[0271] SEQ ID NO:13-人IL-21Rγ ECD

[0272] LNTTILTPNG NEDTTADFFL TTMPTDSLSV STLPLPEVQC FVFNVEYMNC TWNSSSEPQP TNLTLHYWYK NSDNDKVQKC SHYLFSEEIT SGCQLQKKEI HLYQTFVVQL QDPREPRRQA TQMLKLQNLV IPWAPENLTL HKLSESQLEL NWNNRFLNHC LEHLVQYRTD WDHSWTEQSV DYRHKFSLPS VDGQKRYTFR VRSRFNPLCG SAQHWSEWSH PIHWGSNTSK ENPFLFALEA

[0273] SEQ ID NO:14-IL-7α受体ECD(来源:https://www.uniprot.org/uniprot/P16871)

ESGYAQNGDL EDAELDDYSF SCYSQLEVNG SQHSLTCAFE DPDVNITNLE FEICGALVEV

[0274] KCLNFRKLQE IYFIETKKFL LIGKSNICVK VGEKSLTCKK IDLTTIVKPE APFDLSVVYR EGANDFVVTF NTSHLQKKYV KVLMHDVAYR QEKDENKWTH VNLSSTKLTL LQRKLQPAAM YEIKVRSIPD HYFKGFWSEW SPSYYFRTPE INNSSGEMD

[0275] SEQ ID NO:15-IL-9α受体ECD(来源:)

SVTGEGQGPR SRTFTCLTNN ILRIDCHWSA PELGQGSSPW LLFTSNQAPG GTHKCILRGS

[0276] ECTVVLPPEA VLVPSDNFTI TFHHCMSGRE QVSLVDPEYL PRRHVKLDPP SDLQSNISSG HCILTWSISP ALEPMTTLLS YELAFKKQEE AWEQAQHRDH IVGVTWLILE AFELDPGFIH EARLRVQMAT LEDDVVEEER YTGQWSEWSQ PVCFQAPQRQ GPLIPPWGWP

[0277] SEQ ID NO:16Fc-抗IL-15scFv2

DKTHTCPPCP APEAAGGPSV FLFPPKPKDT LYITREPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVCT LPPSREEMTK NQVSLSCAVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLVSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGAGGG GSVHMPLGFL

[0278] GPRQARVVNG GGGGSGGGGS EIVLTQSPGT LSLSPGERAT LSCRASQSVS SSYLAWYQQK PGQAPRLLIY GASRRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ RYGSSHTFGQ GTKLEISGGG GSGGGGSGGG GSEVQLVQSG AEVKKPGESL KISCKVSGYF FTTYWIGWVR QMPGKGLEYM GIIYPGDSDT RYSPSFQGQV TISADKSIST AYLQWSSLKA SDTAMYYCAR GGNWNCFDYW GQGTLVTVSS

[0279] SEQ ID NO:17Fc-IL-15N65D

DKTHTCPPCP APEAAGGPSV FLFPPKPKDT LYITREPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPCREEMTK NQVSLWCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS

[0280] DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGAGGG GSGGGGSGGG GSITCPPPMS VEHADIWVKS YSLYSRERYI CNSGFKRKAG TSSLTECVLN KATNVAHWTT PSLKCIRGGG GSGGGSGGGG SAAGGGGSGG GGSGGGGSNW VNVISDLKKI EDLIQSMHID ATLYTESDVH PSCKVTAMKC FLLELQVISL ESGDASIHDT VEDLIILANN SLSSNGNVTE SGCKECEELE EKNIKEFLQS FVHIVQMFIN TS

[0281] SEQ ID NO:18抗IL-15scFv1(斜体部分为:VH和VL)

*EVQLVQSGAE VKKPGESLKI SCKVSGYFFT TYWIGWVRQM PGKGLEYMGI IYPGDSDTRY*

[0282] *SPSFQGQVTI SADKSISTAY LQWSSLKASD TAMYYCARGG NWNCFDYWGQ GTLVTVSS*GG GGSGGGGSGG GGS*GIVLTQS PGTLSLSPGE RATLSCRASQ SVSSSYLAWY QQKPGQAPRL LIYGASRRAT GIPDRFSGSG SGTDFTLTIS RLEPEDFAVY YCQRYGSSHT FGQGTKLEIS*

[0283] SEQ ID NO:19抗IL-15scFv2(斜体部分为:VH和VL)

*EIVLTQSPGT LSLSPGERAT LSCRASQSVS SSYLAWYQQK PGQAPRLLIY GASRRATGIP*

[0284] *DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ RYGSSHTFGQ GTKLEIS*GGG GSGGGGSGGG GS*EVQLVQSG AEVKKPGESL KISCKVSGYF FTTYWIGWVR QMPGKGLEYM GIIYPGDSDT RYSPSFQGQV TISADKSIS TAYLQWSSLK ASDTAMYYCA RGGNWNCFDY WGQGTLVTVSS*

[0285] SEQ ID NO:20抗IL-21scFv1(斜体部分为:VH和VL)

*QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAF IWYDGSDKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARDG DSSDWYGDYY FGMDVWGQGT*

[0286] *TVTVSS*GGGG SGGGGSGGGG *SEIVLTQSPG TLSLSPGERA TLSCRASQSV SSSYLAWYQQ KPGQAPRLLI YGASSRATGI PDRFSGSGSG TDFTLTISRL EPEDFAVYYC QQYGSWTFGQ GTKVEIK*

[0287] SEQ ID NO:21抗IL-21scFv2(斜体部分为:VH和VL)

*EIVLTQSPGT LSLSPGERAT LSCRASQSVS SSYLAWYQQK PGQAPRLLIY GASSRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSWTFGQG TKVEIK*GGGG SGGGGSGGGG

[0288] *SQVQLVESGG GVVQPGRSLR LSCAASGFTF SSYGMHWVRQ APGKGLEWVA FIWYDGSDKY YADSVKGRFT ISRDNSKNTL YLQMNSLRAE DTAVYYCARD GDSSDWYGDY YFGMDVWGQG TTVTVSS*

[0289] SEQ ID NO:22抗IL-2scFv1(下划线为:HCDR1-3和LCDR1-3;斜体:VH和VL)

*QVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPIFGTANY AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARVD RYYNWNYFLG SFDYWGQGTL*

[0290] *VTVSS*GGGGS GGGGSGGGGS *SYVLTQPPSV SVAPGKTARI TCGGNNIRSK SVHWYQQKPG QAPVVVIYYD SDRPSGIPER ISGSNSGNTA TLTISRVEAG DEADYFCQVW DSSSDHHVFG GGTKLTVL*

[0291] SEQ ID NO:23抗IL-2scFv2(下划线为:LCDR1-3和HCDR1-3;斜体:VL和VH)

*SYVLTQPPSV SVAPGKTARI TCGGNNIRSK SVHWYQQKPG QAPVVVIYYD SDRPSGIPER ISGSNSGNTA TLTISRVEAG DEADYFCQVW DSSSDHHVFG GGTKLTVL*GG GGSGGGGSGGG

[0292] GS*QVQLVQSG AEVKKPGSSV KVSCKASGGT FSSYAISWVR QAPGQGLEWM GGIIPIFGTA NYAQKFQGRV TITADESTST AYMELSSLRS EDTAVYYCAR VDRYYNWNYF LGSFDYWGQG TLVTVSS*

[0293] SEQ ID NO:24PD1-HC-IL-2v(CX3.58.1)

QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSSASTKGPS VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPCQEE MTKNQVSLWC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV MHEALHNHYT QKSLSLSLGK GGGGSGGGGS GGGGSAPASS STKKTQLQLE HLLLDLQMIL NGINNYKNPK LTSMLTAKFA MPKKATELKH LQCLEEALKP LEEVLNLAQS KNFHLRPRDL ISNINVIVLE LKGSETTFMC EYADETATIV EFLNRWITFS QSIISTLT

[0294]

[0295] SEQ ID NO:25PD1-HC-IL-2Rβ-ECD(CX3.58.3)

[0296] QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSSASTKGPS VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VCTLPPSQEE MTKNQVSLSC AVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLV SRLTVDKSRW QEGNVFSCSV MHEALHNHYT QKSLSLSLGK GGGGSGPLGV RGGGGSGGGG SAVNGTSQFT CFYNSRANIS CVWSQDGALQ DTSCQVHAWP DRRRWNQTCE LLPVSQASWA CNLILGAPDS QKLTTVDIVT LRVLCREGVR WRVMAIQDFK PFENLRLMAP ISLQVVHVET HRCNISWEIS QASHYFERHL EFEARTLSPG HTWEEAPLLT LKQKQEWICL ETLTPDTQYE FQVRVKPLQG EFTTWSPWSQ PLAFRTKPAA LGKDT

[0297] SEQ ID NO:26含有不可切割肽连接物的PD1-HC-IL-21RαECD

[0298] MGVKVLFALI CIAVAEAQVQ LVESGGGVVQ PGRSLRLDCK ASGITFSNSG MHWVRQAPGK GLEWVAVIWY DGSKRYYADS VKGRFTISRD NSKNTLFLQM NSLRAEDTAV YYCATNDDYW GQGTLVTVSS ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPPCP APEFLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT LPPSQEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSRL TVDKSRWQEG NVFSCSVMHE ALHNHYTQKS LSLSLGAGGG GSGGGGSAAG GGGSGGGGSC PDLVCYTDYL QTVICILEMW NLHPSTLTLT WQDQYEELKD EATSCSLHRS AHNATHATYT CHMDVFHFMA DDIFSVNITD QSGNYSQECG SFLLAESIKP APPFNVTVTF SGQYNISWRS DYEDPAFYML KGKLQYELQY RNRGDPWAVS PRRKLISVDS RSVSLLPLEF RKDSSYELQV RAGPMPGSSY QGTWSEWSDP VIFQTQSEEL KE

[0299] SEQ ID NO:27-34肽连接物$(GGGGS)_n$(SEQ ID NO:27),其中,n=1,2,3,and 4GGGGS(SEQ ID NO:28)

[0300] GGGGSGGGGS(SEQ ID NO:29)

[0301] GGGGSGGGGSGGGGS(SEQ ID NO:30)

[0302] GGGGSGGGGSXXGGGGSGGGGS(SEQ ID NO:31),X=A或N

[0303] GGGGSGGGGSGGGGSXXGGGGSGGGGS(SEQ ID NO:32),X=A或N

[0304] GGGGSGGGGSGGGGSXXGGGGSGGGGSGGGGS(SEQ ID NO:33),X=A或N

[0305] GGGGSGGGGXGGGGYGGGGS(SEQ ID NO:34),X=S,A or N,and Y=A或N SEQ ID NO:35PD1-HC-IL-2v

QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSSASTKGPS VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT

[0306] VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV MHEALHNHYT QKSLSLSLA(GGGGS)$_{n1}$X$_1$X$_2$(GGGGS)$_{n2}$APX$_{aa3}$SSSTKKTQL QLEHLLLDLQ MILNGINNYK NPX$_{aa35}$LTRMLTX$_{aa42}$KFX$_{aa45}$M PKKATELKH LQCLEEELKP LEEVLNX$_{aa72}$X$_{aa73}$QSKNFHLR PRDLISNINV IVLELKGSET TFMCEYADET ATIVEFLNRW ITFX$_{aa125}$QSIIS TLT

[0307] 其中Xaa3为N或A;Xaa125为A或S;Xaa35选自K和N;Xaa42选自A,G、S、T、Q、E、N、D、R和K;Xaa45选自A、G、S、T、Q、E、N、D、R和K;Xaa72选自A、GS、T、Q、E、N、D、R和K;Xaa73选自A和T;$n_1$=0、1、2或3;$n_2$=0、1、2或3;$X_1$为丙氨酸或缺失;$X_2$为丙氨酸或缺失。

[0308] SEQ ID NO:36-PD1-HC-IL-2Rβ-ECD

QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSSASTKGPS VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT

[0309] VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV MHEALHNHYT QKSLSLSLGA(GGGGS)$_{n1}$X$_1$X$_2$(GGGGS)$_{n2}$AV NGTSQFTCFY NSRANISCVW SQDGALQDTS CQVHAWPDRR RWNQTCELLP VSQASWACNL ILGAPDSQKL TTVDIVTLRV LCREGVRWRV MAIQDFKPFE NLRLMAPISL QVVHVETHRC NISWEISQAS HYFERHLEFE ARTLSPGHTW EEAPLLTLKQ KQEWICLETL TPDTQYEFQV RVKPLQGEFT TWSPWSQPLA FRTKPAALGK DT

[0310] 其中$n_1$=0、1、2、或3;$n_2$=0、1、2或3;$X_1$为丙氨酸或缺失;$X_2$为丙氨酸或缺失。

[0311] SEQ ID NO:37PD1-HC with-sushi-IL-15v

QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSSASTKGPS
VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP
KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
[0312] VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC
LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV
MHEALHNHYT QKSLSLSLGA GGGGSGGGGS GGGGSITCPP PMSVEHADIW VKSYSLYSRE
RYICNSGFKR KAGTSSLTEC VLNKATNVAH WTTPSLKCIR GGGGSGGGSG GGGSAAGGGG
SGGGGSGGGG SNWVNVISDL KKIEDLIQSM HIDATLYTES DVHPSCKVTA MKCFLLELQV
ISLESGDASI HDTVEDLIIL ANNSLSSNGN VTESGCKECE ELEEKNIKEF LQSFVHIVQM
FINTS

[0313] SEQ ID NO:38PD1-HC-抗IL-15scFV2

QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSSASTKGPS
VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP
KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC
[0314] LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV
MHEALHNHYT QKSLSLSLGA(GGGGS)$_{n1}$X$_1$X$_2$(GGGGS)$_{n2}$EI VLTQSPGTLS LSPGERATLS
CRASQSVSSS YLAWYQQKPG QAPRLLIYGA SRRATGIPDR FSGSGSGTDF TLTISRLEPE
DFAVYYCQRY GSSHTFGQGT KLEISGGGGS GGGGSGGGGS EVQLVQSGAE VKKPGESLKI
SCKVSGYFFT TYWIGWVRQM PGKGLEYMGI IYPGDSDTRY SPSFQGQVTI SADKSISTAY
LQWSSLKASD TAMYYCARGG NWNCFDYWGQ GTLVTVSS

[0315] 其中$n_1$＝0、1、2或3;$n_2$＝0、1、2或3;$X_1$为丙氨酸或缺失;$X_2$为丙氨酸或缺失。

[0316] SEQ ID NO:39PD1-HC-IL-21

MGVKVLFALI CIAVAEAQVQ LVESGGGVVQ PGRSLRLDCK ASGITFSNSG MHWVRQAPGK
GLEWVAVIWY DGSKRYYADS VKGRFTISRD NSKNTLFLQM NSLRAEDTAV YYCATNDDYW
GQGTLVTVSS ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV
HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPPCP
APEFLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK
[0317] PREEQFNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT
LPPSQEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSRL
TVDKSRWQEG NVFSCSVMHE ALHNHYTQKS LSLSLGAGGG GSGGGGSGGG GSQGQDRHMI
RMRQLIDIVD QLKNYVNDLV PEFLPAPEDV ETNCEWSAFS CFQKAQLKSA NTGNNERIIN
VSIKKLKRKP PSTNAGRRQK HRLTCPSCDS YEKKPPKEFL ERFKSLLQKM IHQHLSSRTH
GSEDS

[0318] SEQ ID NO:40含有可切割肽连接物的PD1-HC-IL-21RαECD

MGVKVLFALICIAVAEA
QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSSASTKGPS
VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP
KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT

[0319] VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC
LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV
MHEALHNHYT QKSLSLSLGA GGGGSGGGGS GPLGVRGGGG SCPDLVCYTD YLQTVICILE
MWNLHPSTLT LTWQDQYEEL KDEATSCSLH RSAHNATHAT YTCHMDVFHF MADDIFSVNI
TDQSGNYSQE CGSFLLAESI KPAPPFNVTV TFSGQYNISW RSDYEDPAFY MLKGKLQYEL
QYRNRGDPWA VSPRRKLISV DSRSVSLLPL EFRKDSSYEL QVRAGPMPGS SYQGTWSEWS
DPVIFQTQSE ELKE

[0320] SEQ ID NO:41PD1-HC-抗IL-21scFv21

MGVKVLFALI CIAVAEAQVQ LVESGGGVV QPGRSLRLDC KASGITFSNS GMHWVRQAPG
KGLEWVAVIW YDGSKRYYAD SVKGRFTIS RDNSKNTLFL QMNSLRAEDT AVYYCATNDD
YWGQGTLVTV SSASTKGPSV FPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT
SGVHTFPAVL QSSGLYSLSS VVTVPSSSL GTKTYTCNVD HKPSNTKVDK RVESKYGPPC
PPCPAPEFLG GPSVFLFPPK PKDTLMISR TPEVTCVVVD VSQEDPEVQF NWYVDGVEVH
NAKTKPREEQ FNSTYRVVSV LTVLHQDWL NGKEYKCKVS NKGLPSSIEK TISKAKGQPR

[0321] EPQVYTLPPS QEEMTKNQVS LTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS
FFLYSRLTVD KSRWQEGNVF SCSVMHEAL HNHYTQKSLS LSLGAGGGGS GGGGSAAGGG
GSGGGGSEIV LTQSPGTLSL SPGERATLS CRASQSVSSS YLAWYQQKPG QAPRLLIYGA
SSRATGIPDR FSGSGSGTDF TLTISRLEP EDFAVYYCQQ YGSWTFGQGT KVEIKGGGGS
GGGGSGGGGS QVQLVESGGG VVQPGRSLR LSCAASGFTF SSYGMHWVRQ APGKGLEWVA
FIWYDGSDKY YADSVKGRFT ISRDNSKNT LYLQMNSLRA EDTAVYYCAR DGDSSDWYGD
YYFGMDVWGQ GTTVTVSS

[0322] SEQ ID NO:42包括knob突变的PD1-HC-IL-21

QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSSASTKGPS
VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP
KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT

[0323] VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPCQEE MTKNQVSLWC
LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV
MHEALHNHYT QKSLSLSLGA GGGGSGGGGS GGGGSQGQDR HMIRMRQLID IVDQLKNYVN
DLVPEFLPAP EDVETNCEWS AFSCFQKAQL KSANTGNNER IINVSIKKLK RKPPSTNAGR
RQKHRLTCPS CDSYEKKPPK EFLERFKSLL QKMIHQHLSS RTHGSEDS

[0324] SEQ ID NO:43包括hole突变的PD1-HC-IL-21RαECD

QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSSASTKGPS
VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP
KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
[0325] VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VCTLPPSQEE MTKNQVSLSC
AVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLV SRLTVDKSRW QEGNVFSCSV
MHEALHNHYT QKSLSLSLGA GGGGSGGGGS AAGGGGSGGG GSCPDLVCYT DYLQTVICIL
EMWNLHPSTL TLTWQDQYEE LKDEATSCSL HRSAHNATHA TYTCHMDVFH FMADDIFSVN
ITDQSGNYSQ ECGSFLLAES IKPAPPFNVT VTFSGQYNIS WRSDYEDPAF YMLKGKLQYE
LQYRNRGDPW AVSPRRKLIS VDSRSVSLLP LEFRKDSSYE LQVRAGPMPG SSYQGTWSEW
SDPVIFQTQS EELKE

[0326] SEQ ID NO:44PD1-LC

EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA
[0327] RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ SSNWPRTFGQ GTKVEIKRTV AAPSVFIFPP
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC

[0328] SEQ ID NO:45抗PDL1阿特珠单抗LC

DIQMTQSPSS LSASVGDRVT ITCRASQDVS TAVAWYQQKP GKAPKLLIYS ASFLYSGVPS
[0329] RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YLYHPATFGQ GTKVEIKRTV AAPSVFIFPP
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC

[0330] SEQ ID NO:46抗PDL1阿特珠单抗HC

EVQLVESGGG LVQPGGSLRL SCAASGFTFS DSWIHWVRQA PGKGLEWVAW ISPYGGSTYY
ADSVKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCARRH WPGGFDYWGQ GTLVTVSSAS
TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
[0331] YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKKVEPKS CDKTHTCPPC PAPELLGGPS
VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYAST
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSREEMT
KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
GNVFSCSVMH EALHNHYTQK SLSLSPGK

[0332] SEQ ID NO:47抗PD-1Nivolumab HC

QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSSASTKGPS
VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
[0333] VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP
KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC
LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV
MHEALHNHYT QKSLSLSLGK

[0334] SEQ ID NO:48抗PD-1Pembrolizumab LC

[0335] EIVLTQSPAT LSLSPGERAT LSCRASKGVS TSGYSYLHWY QQKPGQAPRL LIYLASYLES GVPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQHSRDLPL TFGGGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC

[0336] SEQ ID NO:49抗PD-1Pembrolizumab HC

[0337] QVQLVQSGVE VKKPGASVKV SCKASGYTFT NYYMYWVRQA PGQGLEWMGG INPSNGGTNF NEKFKNRVTL TTDSSTTTAY MELKSLQFDD TAVYYCARRD YRFDMGFDYW GQGTTVTVSS ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPPCP APEFLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT LPPSQEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSRL TVDKSRWQEG NVFSCSVMHE ALHNHYTQKS LSLSLGK

[0338] SEQ ID NO:50CTLA-4抗体Ipilimumab LC

[0339] EIVLTQSPGT LSLSPGERAT LSCRASQSVG SSYLAWYQQK PGQAPRLLIY GAFSRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSPWTFG QGTKVEIKRT VAAPSVFIFP PSDEQLKSGT ASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYSLSSTL TLSKADYEKH KVYACEVTHQ GLSSPVTKSF NRGEC

[0340] SEQ ID NO:51CTLA-4抗体Ipilimumab HC-IL2v

[0341] QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGA(GGGGS)$_{n1}$X$_1$X$_2$(GGGGS)$_{n2}$APX$_{aa3}$ SSSTKKTQLQ LEHLLLDLQM ILNGINNYKN PX$_{aa35}$LTRMLTX$_{aa42}$KFX$_{aa45}$M PKKATELKHLQ CLEEELKPLE EVLNX$_{aa72}$X$_{aa73}$QSKNFHLRPR DLISNINVIV LELKGSETTF MCEYADETATI VEFLNRWITF X$_{aa125}$QSIIST LT

[0342] 其中Xaa3为N或A;Xaa125为A或S;Xaa35选自K和N;Xaa42选自A、G、S、T、Q、E、N、D、R和K;Xaa45选自A、G、S、T、Q、E、N、D、R和K;

[0343] Xaa72选自A、G、S、T、Q、E、N、D、R和K;Xaa73选自A和T;$n_1$＝0、1、2或3;$n_2$＝0、1、2或3;以及$X_1$为丙氨酸或缺失;$X_2$为丙氨酸或缺失。

[0344] SEQ ID NO:52CTLA-4抗体Ipilimumab HC-IL15v

[0345] QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGAGG GGSGGGGSGG GGSITCPPPM SVEHADIWVK SYSLYSRERY ICNSGFKRKA GTSSLTECVL NKATNVAHWT TPSLKCIRGG GGSGGGSGGG GS**AA**GGGGSG GGGSGGGGSN WVNVISDLKK IEDLIQSMHI DATLYTESDV HPSCKVTAMK CFLLELQVIS LESGDASIHD TVEDLIILAN NSLSSNGNVT ESGCKECEEL EEKNIKEFLQ SFVHIVQMFI NTS

[0346] SEQ ID NO:53CTLA-4抗体Ipilimumab HC-IL-21

QVQLVESGGG VVQPGRSLR LSCAASGFTF SSYTMHWVRQ APGKGLEWVT FISYDGNNKYY ADSVKGRFTI SRDNSKNTL YLQMNSLRAE DTAIYYCART GWLGPFDYWG QGTLVTVSSAS TKGPSVFPLA PSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSGL YSLSSVVTVP SSSLGTQTY ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGPS VFLFPPKPKD TLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNST YRVVSVLTVL HQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDELT KNQVSLTCLV KGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQQ GNVFSCSVMH EALHNHYTQ KSLSLSPGA(GGGGS)$_{n1}$X$_1$X$_2$(GGGGS)$_{n2}$QGQDRHMIRM RQLI DIVDQLKNYV NDLVPEFLP APEDVETNCE WSAFSCFQKA QLKSANTGNN ERIINVSIKKL KRKPPSTNAG RRQKHRLTC PSCDSYEKKP PKEFLERFKS LLQKMIHQHL SSRTHGSEDS

[0347]

[0348] 其中$n_1$=0、1、2或3;$n_2$=0、1、2或3;$X_1$为丙氨酸或缺失;$X_2$为丙氨酸或缺失。SEQ ID NO:54CTLA-4抗体Ipilimumab HC-IL-2Rβ-ECD

QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGA(GGGGS)$_{n1}$X$_1$X$_2$(GGGGS)$_{n2}$ AVNG TSQFTCFYNS RANISCVWSQ DGALQDTSCQ VHAWPDRRRW NQTCELLPVS QASWACNLIL GAPDSQKLTT VDIVTLRVLC REGVRWRVMA IQDFKPFENL RLMAPISLQV VHVETHRCNI SWEISQASHY FERHLEFEAR TLSPGHTWEE APLLTLKQKQ EWICLETLTP DTQYEFQVRV KPLQGEFTTW SPWSQPLAFR TKPAALGKDT

[0349]

[0350] 其中$n_1$=0、1、2或3;$n_2$=0、1、2或3;$X_1$为丙氨酸或缺失;$X_2$为丙氨酸或缺失。

[0351] SEQ ID NO:55CTLA-4抗体Ipilimumab HC-抗IL-2scFv1(scFV中,下划线部分为:HCDR1-3和LCDR1-3;斜体部分为:VH和VL)

[0352] QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGA $(GGGGS)_{n1}X_1X_2(GGGGS)_{n2}$ *QVQ LVQSGAEVKK PGSSVKVSCK ASGGTFSSYA ISWVRQAPGQ GLEWMGGIIP IFGTANYAQK FQGRVTITAD ESTSTAYMEL SSLRSEDTAV YYCARVDRYY NWNYFLGSFD YWGQGTLVTV SS*GGGGSGGG GSGGGGS*SYV LTQPPSVSVA PGKTARITCG GNNIRSKSVH WYQQKPGQAP VVVIYYDSDR PSGIPERISG SNSGNTATLTISRVEAGDEADYFCQVWDSSSDHHVFGGGTKLTVL*;

[0353] 其中$n_1$=0、1、2或3;$n_2$=0、1、2或3;$X_1$为丙氨酸或缺失;$X_2$为丙氨酸或缺失。

[0354] SEQ ID NO:56CTLA-4抗体Ipilimumab HC-抗IL-2scFv2(下划线部分为:LCDR1-3和HCDR1-3;斜体部分为:VL和VH)

[0355] QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGA(GGGGS)$_{n1}X_1X_2$(GGGGS)$_{n2}$ *SYVL TQPPSVSVAP GKTARITCGG NNIRSKSVHW YQQKPGQAPV VVIYYDSDRP SGIPERISGS NSGNTATLTI SRVEAGDEAD YFCQVWDSSS DHHVFGGGTK LTVL*GGGGSG GGGSGGGGS*Q VQLVQSGAEV KKPGSSVKVS CKASGGTFSS YAISWVRQAP GQGLEWMGGI IPIFGTANYA QKFQGRVTIT ADESTSTAYM ELSSLRSEDT AVYYCARVDR YYNWNYFLGS FDYWGQGTLV TVSS*;

[0356] 其中$n_1$=0,1,2,或3;$n_2$=0,1,2,或3;$X_1$为丙氨酸或缺失;$X_2$为丙氨酸或缺失.

[0357] SEQ ID NO:57CTLA-4抗体Ipilimumab HC-抗IL-15scFv2

[0358] QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGA(GGGGS)$_{n1}$X$_1$X$_2$(GGGGS)$_{n2}$EIVL TQSPGTLSLS PGERATLSCR ASQSVSSSYL AWYQQKPGQA PRLLIYGASR RATGIPDRFS GSGSGTDFTL TISRLEPEDF AVYYCQRYGS SHTFGQGTKL EISGGGGSGG GGSGGGGSEV QLVQSGAEVK KPGESLKISC KVSGYFFTTY WIGWVRQMPG KGLEYMGIIY PGDSDTRYSP SFQGQVTISA DKSISTAYLQ WSSLKASDTA MYYCARGGNW NCFDYWGQGT LVTVSS

[0359] 其中$n_1$＝0、1、2或3;$n_2$＝0、1、2或3;$X_1$为丙氨酸或缺失;$X_2$为丙氨酸或缺失。

[0360] SEQ ID NO:58CTLA-4抗体Ipilimumab HC-IL-21Rα-ECD

[0361] QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGAGG GGSGGGGSAA GGGGSGGGGS CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR SDYEDPAFYM LKGKLQYELQ YRNRGDPWAV SPRRKLISVD SRSVSLLPLE FRKDSSYELQ VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

[0362] SEQ ID NO:59CTLA-4抗体Ipilimumab HC-抗IL-21scFv2

[0363] QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGAGG GGSGGGGSAA GGGGSGGGGS EIVLTQSPGT LSLSPGERAT LSCRASQSVS SSYLAWYQQK PGQAPRLLIY GASSRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSWTFGQG TKVEIKGGGG SGGGGSGGGG SQVQLVESGG GVVQPGRSLR LSCAASGFTF SSYGMHWVRQ APGKGLEWVA FIWYDGSDKY YADSVKGRFT ISRDNSKNTL YLQMNSLRAE DTAVYYCARD GDSSDWYGDY YFGMDVW-GQGTTVTVSS

[0364] SEQ ID NO:604E12B2D10抗-IL2HC可变区(下划线部分:HCDR1-3)

EVQLQQSGAE LVRPGASVKL SCTASGFNIK DDYLHWVRQR PEQGLEWIGR IDPANGNTKY

[0365] APKFQDKATI TADTSSNTAY LQLSILTSED TAVYYCAARF GYFYGSSFYA VAYWGQGTSV TVSS

[0366] SEQ ID NO:614E12B2D10抗-IL2LC可变区(下划线部分:LCDR1-3)

QIVLTQSPAI MSASPGEKVT MTCSASSSVS YMHWYQQKSG TSPKRWIYDT SKLASGVPAR

[0367] FSGSGSGTSY SLTISSMEAE DAATYYCQQW SSNPYTFGGGTKLEIK

[0368] SEQ ID NO:62IL-2激动剂多肽

APX$_{aa3}$SSSTK KTQLQLEHLL LDLQMILNGI NNYKNPX$_{aa35}$LTRMLTX$_{aa42}$KFX$_{aa45}$MPKKATEL

[0369] KHLQCLEEEL KPLEEVLNX$_{aa72}$X$_{aa73}$QSKNFH LRPRDLISNI NVIVLELKGSE TTFMCEYADE TATIVEFLNR WITFX$_{aa125}$QS IISTLT

[0370] 其中Xaa3为N或A;Xaa125为C、A或S;Xaa35选自K和N;Xaa42选自A、G、S、T、Q、E、N、D、R和K;Xaa45选自A、G、S、T、Q、E、N、D、R和K;Xaa72选自A、G、S、T、Q、E、N、D、R和K;以及Xaa73选自A和T。

[0371] SEQ ID NO:63IL-21受体αECD突变体1(突变部分下划线标记)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY

[0372] TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR SDYEDPAFYM LKGKLQYELQ YRNRGD**GSG**V SPRRKLISVD SRSVSLLPLE FRKDSSYELQ VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

[0373] SEQ ID NO:64IL-21受体αECD突变体2(突变部分下划线标记)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY

[0374] TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR SDYEDPAFYM LKGKLQYELQ YRNRGD**N**A**S**V SPRRKLISVD SRSVSLLPLE FRKDSSYELQ VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

[0375] SEQ ID NO:65IL-21受体αECD突变体3(突变部分下划线标记)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY

[0376] TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR SDYEDPAFYM LKGKLQYELQ YRNRGD**NGS**V SPRRKLISVD SRSVSLLPLE FRKDSSYELQ VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

[0377] SEQ ID NO:66IL-21受体αECD突变体4(突变部分下划线标记)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSL**N**R SAHNATHATY

[0378] TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR SDYEDPAFYM LKGKLQYELQ YRNRGD**N**A**S**V SPRRKLISVD SRSVSLLPLE FRKDSSYELQ VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

[0379] SEQ ID NO:67IL-21受体αECD突变体5(突变部分下划线标记)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY

[0380] TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR SDYEDPAFYM LKGKLQYELQ YRNRGDP**S**AV SPRRKLISVD SRSVSLLPLE FRKDSSYELQ VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

[0381] SEQ ID NO:68IL-21受体αECD突变体6(突变部分下划线标记)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR SDYEDPAFYM LKGKLQYELQ YRNRGDP**SG**V SPRRKLISVD SRSVSLLPLE FRKDSSYELQ VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

[0382]

[0383] SEQ ID NO:69IL-21受体αECD突变体7(突变部分下划线标记)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR S**A**YEDPAFYM LKGKLQYELQ YRNRGD**GSG**V SPRRKLISVD SRSVSLLPLE FRKDSSYELQ VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

[0384]

[0385] SEQ ID NO:70IL-21受体αECD突变体8(突变部分下划线标记)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR S**I**YEDPAFYM LKGKLQYELQ YRNRGD**GSG**V SPRRKLISVD SRSVSLLPLE FRKDSSYELQ VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

[0386]

[0387] SEQ ID NO:71IL-21受体αECD突变体9(突变部分下划线标记)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR S**W**YEDPAFYM LKGKLQYELQ YRNRGD**GSG**V SPRRKLISVD SRSVSLLPLE FRKDSSYELQ VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

[0388]

[0389] SEQ ID NO:72IL-21受体αECD突变体10(突变部分下划线标记)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR S**F**YEDPAFYM LKGKLQYELQ YRNRGD**GSG**V SPRRKLISVD SRSVSLLPLE FRKDSSYELQ VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

[0390]

[0391] SEQ ID NO:73IL-21受体αECD突变体11

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR S**Y**YEDPAFYM LKGKLQYELQ YRNRGD**GSG**V SPRRKLISVD SRSVSLLPLE FRKDSSYELQ VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

[0392]

[0393] SEQ ID NO:74含有hole突变的PD1-HC-IL-21RαECD

QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSSASTKGPS
VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP
KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VCTLPPSQEE MTKNQVSLSC
AVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLV SRLTVDKSRW QEGNVFSCSV
MHEALHNHYT QKSLSLSLGA GGGGSGGGGS GPLGVRGGGG SCPDLVCYTD YLQTVICILE
MWNLHPSTLT LTWQDQYEEL KDEATSCSLH RSAHNATHAT YTCHMDVFHF MADDIFSVNI
TDQSGNYSQE CGSFLLAESI KPAPPFNVTV TFSGQYNISW RSDYEDPAFY MLKGKLQYEL
QYRNRGDPWA VSPRRKLISV DSRSVSLLPL EFRKDSSYEL QVRAGPMPGS SYQGTWSEWS
DPVIFQTQSE ELKE

[0394]

[0395] SEQ ID NO:75抗IL-15的scFv2-PD1-HC融合多肽

QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSSASTKGPS
VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP
KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC
LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV
MHEALHNHYT QKSLSLSLGA GGGGSGGGGS GPLGVRGGGG SGGGGSEIVL TQSPGTLSLS
PGERATLSCR ASQSVSSSYL AWYQQKPGQA PRLLIYGASR RATGIPDRFS GSGSGTDFTL
TISRLEPEDF AVYYCQRYGS SHTFGQGTKL EISGGGGSGG GGSGGGGSEV QLVQSGAEVK
KPGESLKISC KVSGYFFTTY WIGWVRQMPG KGLEYMGIIY PGDSDTRYSP SFQGQVTISA
DKSISTAYLQ WSSLKASDTA MYYCARGGNW NCFDYWGQGT LVTVSS

[0396]

[0397] SEQ ID NO:76抗IL-15抗体146B7HC CDR1(蛋白序列)

[0398] TYWIG

[0399] SEQ ID NO:77抗IL-15抗体146B7HC CDR2(蛋白序列)

[0400] IIYPGDSDTR YSPSFQG

[0401] SEQ ID NO:78抗IL-15抗体146B7HC CDR3(蛋白序列)

[0402] GNWNCFDY

[0403] SEQ ID NO:79抗IL-15抗体146B7LC CDR1(蛋白序列)

[0404] RASQSVSSSY LA

[0405] SEQ ID NO:80抗IL-15抗体146B7LC CDR2(蛋白序列)

[0406] GASRRAT

[0407] SEQ ID NO:81抗IL-15抗体146B7LC CDR3(蛋白序列)

[0408] QRYGSSHT

[0409] SEQ ID NO:82抗IL-15抗体146B7HC CDR3的版本二(蛋白序列)GNWNSFDY

[0410] SEQ ID NO:83抗IL-15抗体146B7HC可变区(下划线部分为:HCDR1-3)

[0411] EVQLVQSGAE VKKPGESLKI SCKVSGYFFT TYWIGWVRQM PGKGLEYMGI IYPGDSDTRY SPSFQGQVTI SADKSISTAY LQWSSLKASD TAMYYCARGG NWNCFDYWGQ GTLVTVSS

[0412] SEQ ID NO:84抗IL-15抗体146B7LC可变区(下划线部分为:LCDR1-3)

[0413] EIVLTQSPGT LSLSPGREAT LSCRASQSVS SSYLAWYQQK PGQAPRLLIY GASRRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ RYGSSHTFGQ GTKLEISRTV AAPSVFIFP

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[0181] 65 70 75 80

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[0217] Lys Val Ser Glu Gly Thr Thr Ile Leu Leu Asn Cys Thr Gly Gln Val

[0218] 85 90 95

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[0220] 100 105 110

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[0223] Cys Phe Leu Lys Arg Leu Leu Gln Glu Ile Lys Thr Cys Trp Asn Lys

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[0244] Gln Thr Thr Ala Gly Asn Ala Leu Thr Phe Leu Lys Ser Leu Leu Glu
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[0259] Glu Leu Leu Pro Val Ser Gln Ala Ser Trp Ala Cys Asn Leu Ile Leu
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[0268] 115 120 125
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[0291] 35 40 45
[0292] His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met
[0293] 50 55 60
[0294] Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr
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[0296] Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala
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[0336] 130 135 140
[0337] Glu Ser Gln Leu Glu Leu Asn Trp Asn Asn Arg Phe Leu Asn His Cys
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[0366] Thr Cys Lys Lys Ile Asp Leu Thr Thr Ile Val Lys Pro Glu Ala Pro

[0367] 100 105 110

[0368] Phe Asp Leu Ser Val Val Tyr Arg Glu Gly Ala Asn Asp Phe Val Val

[0369] 115 120 125

[0370] Thr Phe Asn Thr Ser His Leu Gln Lys Lys Tyr Val Lys Val Leu Met

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[0372] His Asp Val Ala Tyr Arg Gln Glu Lys Asp Glu Asn Lys Trp Thr His

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[1091] <212> PRT

[1092] <213> 人工序列
[1093] <220>
[1094] <221> 来源
[1095] <223> 人工序列说明:合成多肽
[1096] <400> 29
[1097] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[1098] 1 5 10
[1099] <210> 30
[1100] <211> 15
[1101] <212> PRT
[1102] <213> 人工序列
[1103] <220>
[1104] <221> 来源
[1105] <223> 人工序列说明:合成多肽
[1106] <400> 30
[1107] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[1108] 1 5 10 15
[1109] <210> 31
[1110] <211> 22
[1111] <212> PRT
[1112] <213> 人工序列
[1113] <220>
[1114] <221> 来源
[1115] <223> 人工序列说明:合成多肽
[1116] <220>
[1117] <221> 突变
[1118] <222> (11)..(12)
[1119] <223> 用"N"取代
[1120] <220>
[1121] <221> SITE
[1122] <222> (1)..(22)
[1123] <223> 序列中可变位点的可变残基并不偏好性使用注释中提供的氨基酸残基
[1124] <400> 31
[1125] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ala Gly Gly Gly Gly
[1126] 1 5 10 15
[1127] Ser Gly Gly Gly Gly Ser
[1128] 20
[1129] <210> 32
[1130] <211> 27

[1131] <212> PRT
[1132] <213> 人工序列
[1133] <220>
[1134] <221> 来源
[1135] <223> 人工序列说明:合成多肽
[1136] <220>
[1137] <221> 突变
[1138] <222> (16)..(17)
[1139] <223> 用"N"取代
[1140] <220>
[1141] <221> SITE
[1142] <222> (1)..(27)
[1143] <223> 序列中可变位点的可变残基并不偏好性使用注释中提供的氨基酸残基
[1144] <400> 32
[1145] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
[1146] 1 5 10 15
[1147] Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[1148] 20 25
[1149] <210> 33
[1150] <211> 32
[1151] <212> PRT
[1152] <213> 人工序列
[1153] <220>
[1154] <221> 来源
[1155] <223> 人工序列说明:合成多肽
[1156] <220>
[1157] <221> 突变
[1158] <222> (16)..(17)
[1159] <223> 用"N"取代
[1160] <220>
[1161] <221> SITE
[1162] <222> (1)..(32)
[1163] <223> 序列中可变位点的可变残基并不偏好性使用注释中提供的氨基酸残基
[1164] <400> 33
[1165] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
[1166] 1 5 10 15
[1167] Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[1168] 20 25 30
[1169] <210> 34

[1170] <211> 20
[1171] <212> PRT
[1172] <213> 人工序列
[1173] <220>
[1174] <221> 来源
[1175] <223> 人工序列说明:合成多肽
[1176] <220>
[1177] <221> 突变
[1178] <222> (10)..(10)
[1179] <223> 用"A" 或 "N"取代
[1180] <220>
[1181] <221> 突变
[1182] <222> (15)..(15)
[1183] <223> 用"N"取代
[1184] <220>
[1185] <221> SITE
[1186] <222> (1)..(20)
[1187] <223> 序列中可变位点的可变残基并不偏好性使用注释中提供的氨基酸残基
[1188] <400> 34
[1189] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ala Gly
[1190] 1 5 10 15
[1191] Gly Gly Gly Ser
[1192] 20
[1193] <210> 35
[1194] <211> 604
[1195] <212> PRT
[1196] <213> 人工序列
[1197] <220>
[1198] <221> 来源
[1199] <223> 人工序列说明:合成多肽
[1200] <220>
[1201] <221> SITE
[1202] <222> (440)..(454)
[1203] <223> 该区域包括 0-3 'Gly Gly Gly Gly Ser'重复单元
[1204] <220>
[1205] <221> 突变
[1206] <222> (455)..(455)
[1207] <223> 用" "取代
[1208] <220>

[1209] <221> 突变
[1210] <222> (456)..(456)
[1211] <223> 用" "取代
[1212] <220>
[1213] <221> SITE
[1214] <222> (457)..(471)
[1215] <223> 该区域包括 0-3 'Gly Gly Gly Gly Ser'重复单元
[1216] <220>
[1217] <221> 突变
[1218] <222> (474)..(474)
[1219] <223> 用"A"取代
[1220] <220>
[1221] <221> 突变
[1222] <222> (506)..(506)
[1223] <223> 用"N"取代
[1224] <220>
[1225] <221> 突变
[1226] <222> (513)..(513)
[1227] <223> 用"G" o或 "S" 或 "T" 或 "Q" 或 "E" 或 "N" 或
[1228] "D" 或 "R" 或 "K"取代
[1229] <220>
[1230] <221> 突变
[1231] <222> (516)..(516)
[1232] <223> 用"G" 或 "S" 或 "T" 或 "Q" 或 "E" 或 "N" 或
[1233] "D" 或 "R" 或 "K"取代
[1234] <220>
[1235] <221> 突变
[1236] <222> (543)..(543)
[1237] <223> 用"G" 或 "S" 或 "T" 或 "Q" 或 "E" 或 "N" 或
[1238] "D" 或 "R" 或 "K"取代
[1239] <220>
[1240] <221> 突变
[1241] <222> (544)..(544)
[1242] <223> 用"T"取代
[1243] <220>
[1244] <221> 突变
[1245] <222> (596)..(596)
[1246] <223> 用"S"取代
[1247] <220>

[1248] <221> SITE

[1249] <222> (1)..(604)

[1250] <223> 序列中可变位点的可变残基并不偏好性使用注释中提供的氨基酸残基

[1251] <400> 35

[1252] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

[1253] 1 5 10 15

[1254] Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser

[1255] 20 25 30

[1256] Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[1257] 35 40 45

[1258] Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val

[1259] 50 55 60

[1260] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe

[1261] 65 70 75 80

[1262] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[1263] 85 90 95

[1264] Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser

[1265] 100 105 110

[1266] Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser

[1267] 115 120 125

[1268] Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp

[1269] 130 135 140

[1270] Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr

[1271] 145 150 155 160

[1272] Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr

[1273] 165 170 175

[1274] Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys

[1275] 180 185 190

[1276] Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp

[1277] 195 200 205

[1278] Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala

[1279] 210 215 220

[1280] Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro

[1281] 225 230 235 240

[1282] Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val

[1283] 245 250 255

[1284] Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val

[1285] 260 265 270

[1286] Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln

[1287] 275 280 285
[1288] Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
[1289] 290 295 300
[1290] Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
[1291] 305 310 315 320
[1292] Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
[1293] 325 330 335
[1294] Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
[1295] 340 345 350
[1296] Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
[1297] 355 360 365
[1298] Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
[1299] 370 375 380
[1300] Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
[1301] 385 390 395 400
[1302] Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
[1303] 405 410 415
[1304] Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
[1305] 420 425 430
[1306] Ser Leu Ser Leu Ser Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly
[1307] 435 440 445
[1308] Ser Gly Gly Gly Gly Ser Ala Ala Gly Gly Gly Gly Ser Gly Gly Gly
[1309] 450 455 460
[1310] Gly Ser Gly Gly Gly Gly Ser Ala Pro Asn Ser Ser Ser Thr Lys Lys
[1311] 465 470 475 480
[1312] Thr Gln Leu Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu
[1313] 485 490 495
[1314] Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr
[1315] 500 505 510
[1316] Ala Lys Phe Ala Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln
[1317] 515 520 525
[1318] Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Ala Ala
[1319] 530 535 540
[1320] Gln Ser Lys Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile
[1321] 545 550 555 560
[1322] Asn Val Ile Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys
[1323] 565 570 575
[1324] Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp
[1325] 580 585 590

[1326] Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr Leu Thr
[1327] 595 600
[1328] <210> 36
[1329] <211> 686
[1330] <212> PRT
[1331] <213> 人工序列
[1332] <220>
[1333] <221> 来源
[1334] <223> 人工序列说明:合成多肽
[1335] <220>
[1336] <221> SITE
[1337] <222> (441)..(455)
[1338] <223> 该区域包括 0-3 'Gly Gly Gly Gly Ser'重复单元
[1339] <220>
[1340] <221> 突变
[1341] <222> (456)..(456)
[1342] <223> 用" "取代
[1343] <220>
[1344] <221> 突变
[1345] <222> (457)..(457)
[1346] <223> 用" "取代
[1347] <220>
[1348] <221> SITE
[1349] <222> (458)..(472)
[1350] <223> 该区域包括 0-3 'Gly Gly Gly Gly Ser'重复单元
[1351] <220>
[1352] <221> SITE
[1353] <222> (1)..(686)
[1354] <223> 序列中可变位点的可变残基并不偏好性使用注释中提供的氨基酸残基
[1355] <400> 36
[1356] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
[1357] 1 5 10 15
[1358] Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
[1359] 20 25 30
[1360] Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[1361] 35 40 45
[1362] Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
[1363] 50 55 60
[1364] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe

[1365] 65 70 75 80
[1366] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[1367] 85 90 95
[1368] Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
[1369] 100 105 110
[1370] Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
[1371] 115 120 125
[1372] Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
[1373] 130 135 140
[1374] Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
[1375] 145 150 155 160
[1376] Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
[1377] 165 170 175
[1378] Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
[1379] 180 185 190
[1380] Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
[1381] 195 200 205
[1382] Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
[1383] 210 215 220
[1384] Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
[1385] 225 230 235 240
[1386] Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
[1387] 245 250 255
[1388] Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
[1389] 260 265 270
[1390] Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
[1391] 275 280 285
[1392] Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
[1393] 290 295 300
[1394] Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
[1395] 305 310 315 320
[1396] Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
[1397] 325 330 335
[1398] Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
[1399] 340 345 350
[1400] Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
[1401] 355 360 365
[1402] Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
[1403] 370 375 380

[1404] Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
[1405] 385 390 395 400
[1406] Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
[1407] 405 410 415
[1408] Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
[1409] 420 425 430
[1410] Ser Leu Ser Leu Ser Leu Gly Ala Gly Gly Gly Gly Ser Gly Gly Gly
[1411] 435 440 445
[1412] Gly Ser Gly Gly Gly Gly Ser Ala Ala Gly Gly Gly Gly Ser Gly Gly
[1413] 450 455 460
[1414] Gly Gly Ser Gly Gly Gly Gly Ser Ala Val Asn Gly Thr Ser Gln Phe
[1415] 465 470 475 480
[1416] Thr Cys Phe Tyr Asn Ser Arg Ala Asn Ile Ser Cys Val Trp Ser Gln
[1417] 485 490 495
[1418] Asp Gly Ala Leu Gln Asp Thr Ser Cys Gln Val His Ala Trp Pro Asp
[1419] 500 505 510
[1420] Arg Arg Arg Trp Asn Gln Thr Cys Glu Leu Leu Pro Val Ser Gln Ala
[1421] 515 520 525
[1422] Ser Trp Ala Cys Asn Leu Ile Leu Gly Ala Pro Asp Ser Gln Lys Leu
[1423] 530 535 540
[1424] Thr Thr Val Asp Ile Val Thr Leu Arg Val Leu Cys Arg Glu Gly Val
[1425] 545 550 555 560
[1426] Arg Trp Arg Val Met Ala Ile Gln Asp Phe Lys Pro Phe Glu Asn Leu
[1427] 565 570 575
[1428] Arg Leu Met Ala Pro Ile Ser Leu Gln Val Val His Val Glu Thr His
[1429] 580 585 590
[1430] Arg Cys Asn Ile Ser Trp Glu Ile Ser Gln Ala Ser His Tyr Phe Glu
[1431] 595 600 605
[1432] Arg His Leu Glu Phe Glu Ala Arg Thr Leu Ser Pro Gly His Thr Trp
[1433] 610 615 620
[1434] Glu Glu Ala Pro Leu Leu Thr Leu Lys Gln Lys Gln Glu Trp Ile Cys
[1435] 625 630 635 640
[1436] Leu Glu Thr Leu Thr Pro Asp Thr Gln Tyr Glu Phe Gln Val Arg Val
[1437] 645 650 655
[1438] Lys Pro Leu Gln Gly Glu Phe Thr Thr Trp Ser Pro Trp Ser Gln Pro
[1439] 660 665 670
[1440] Leu Ala Phe Arg Thr Lys Pro Ala Ala Leu Gly Lys Asp Thr
[1441] 675 680 685
[1442] <210> 37

[1443] <211> 665

[1444] <212> PRT

[1445] <213> 人工序列

[1446] <220>

[1447] <221> 来源

[1448] <223> 人工序列说明:合成多肽

[1449] <400> 37

[1450] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

[1451] 1 5 10 15

[1452] Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser

[1453] 20 25 30

[1454] Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[1455] 35 40 45

[1456] Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val

[1457] 50 55 60

[1458] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe

[1459] 65 70 75 80

[1460] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[1461] 85 90 95

[1462] Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser

[1463] 100 105 110

[1464] Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser

[1465] 115 120 125

[1466] Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp

[1467] 130 135 140

[1468] Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr

[1469] 145 150 155 160

[1470] Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr

[1471] 165 170 175

[1472] Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys

[1473] 180 185 190

[1474] Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp

[1475] 195 200 205

[1476] Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala

[1477] 210 215 220

[1478] Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro

[1479] 225 230 235 240

[1480] Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val

[1481] 245 250 255

[1482] Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
[1483] 260 265 270
[1484] Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
[1485] 275 280 285
[1486] Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
[1487] 290 295 300
[1488] Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
[1489] 305 310 315 320
[1490] Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
[1491] 325 330 335
[1492] Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
[1493] 340 345 350
[1494] Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
[1495] 355 360 365
[1496] Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
[1497] 370 375 380
[1498] Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
[1499] 385 390 395 400
[1500] Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
[1501] 405 410 415
[1502] Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
[1503] 420 425 430
[1504] Ser Leu Ser Leu Ser Leu Gly Ala Gly Gly Gly Gly Ser Gly Gly Gly
[1505] 435 440 445
[1506] Gly Ser Gly Gly Gly Gly Ser Ile Thr Cys Pro Pro Pro Met Ser Val
[1507] 450 455 460
[1508] Glu His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu
[1509] 465 470 475 480
[1510] Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Ser Ser
[1511] 485 490 495
[1512] Leu Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr
[1513] 500 505 510
[1514] Thr Pro Ser Leu Lys Cys Ile Arg Gly Gly Gly Gly Ser Gly Gly Gly
[1515] 515 520 525
[1516] Ser Gly Gly Gly Gly Ser Ala Ala Gly Gly Gly Gly Ser Gly Gly Gly
[1517] 530 535 540
[1518] Gly Ser Gly Gly Gly Gly Ser Asn Trp Val Asn Val Ile Ser Asp Leu
[1519] 545 550 555 560
[1520] Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu

[1521] 565 570 575

[1522] Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys

[1523] 580 585 590

[1524] Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala

[1525] 595 600 605

[1526] Ser Ile His Asp Thr Val Glu Asp Leu Ile Ile Leu Ala Asn Asn Ser

[1527] 610 615 620

[1528] Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu

[1529] 625 630 635 640

[1530] Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His

[1531] 645 650 655

[1532] Ile Val Gln Met Phe Ile Asn Thr Ser

[1533] 660 665

[1534] <210> 38

[1535] <211> 712

[1536] <212> PRT

[1537] <213> 人工序列

[1538] <220>

[1539] <221> 来源

[1540] <223> 人工序列说明:合成多肽

[1541] <220>

[1542] <221> SITE

[1543] <222> (441)..(455)

[1544] <223> 该区域包括 0-3 'Gly Gly Gly Gly Ser'重复单元

[1545] <220>

[1546] <221> 突变

[1547] <222> (456)..(456)

[1548] <223> 用" "取代

[1549] <220>

[1550] <221> 突变

[1551] <222> (457)..(457)

[1552] <223> 用" "取代

[1553] <220>

[1554] <221> SITE

[1555] <222> (458)..(472)

[1556] <223> 该区域包括0-3 'Gly Gly Gly Gly Ser'重复单元

[1557] <220>

[1558] <221> SITE

[1559] <222> (1)..(712)

[1560] <223> 序列中可变位点的可变残基并不偏好性使用注释中提供的氨基酸残基

[1561] <400> 38

[1562] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

[1563] 1 5 10 15

[1564] Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser

[1565] 20 25 30

[1566] Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[1567] 35 40 45

[1568] Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val

[1569] 50 55 60

[1570] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe

[1571] 65 70 75 80

[1572] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[1573] 85 90 95

[1574] Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser

[1575] 100 105 110

[1576] Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser

[1577] 115 120 125

[1578] Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp

[1579] 130 135 140

[1580] Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr

[1581] 145 150 155 160

[1582] Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr

[1583] 165 170 175

[1584] Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys

[1585] 180 185 190

[1586] Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp

[1587] 195 200 205

[1588] Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala

[1589] 210 215 220

[1590] Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro

[1591] 225 230 235 240

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[2568] 515 520 525
[2569] Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys
[2570] 530 535 540
[2571] Pro Leu Glu Glu Val Leu Asn Ala Ala Gln Ser Lys Asn Phe His Leu
[2572] 545 550 555 560
[2573] Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu

[2574] 565 570 575
[2575] Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala
[2576] 580 585 590
[2577] Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile
[2578] 595 600 605
[2579] Ile Ser Thr Leu Thr
[2580] 610
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[2590] 1 5 10 15
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[2592] 20 25 30
[2593] Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[2594] 35 40 45
[2595] Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
[2596] 50 55 60
[2597] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[2598] 65 70 75 80
[2599] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
[2600] 85 90 95
[2601] Ala Arg Thr Gly Trp Leu Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
[2602] 100 105 110
[2603] Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
[2604] 115 120 125
[2605] Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
[2606] 130 135 140
[2607] Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
[2608] 145 150 155 160
[2609] Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
[2610] 165 170 175
[2611] Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
[2612] 180 185 190

[2613] Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
[2614] 195 200 205
[2615] Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
[2616] 210 215 220
[2617] His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
[2618] 225 230 235 240
[2619] Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
[2620] 245 250 255
[2621] Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
[2622] 260 265 270
[2623] Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
[2624] 275 280 285
[2625] Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
[2626] 290 295 300
[2627] Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
[2628] 305 310 315 320
[2629] Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
[2630] 325 330 335
[2631] Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[2632] 340 345 350
[2633] Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
[2634] 355 360 365
[2635] Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
[2636] 370 375 380
[2637] Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
[2638] 385 390 395 400
[2639] Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
[2640] 405 410 415
[2641] Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
[2642] 420 425 430
[2643] Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala
[2644] 435 440 445
[2645] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ile
[2646] 450 455 460
[2647] Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys
[2648] 465 470 475 480
[2649] Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe
[2650] 485 490 495
[2651] Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys

[2652] 500 505 510
[2653] Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
[2654] 515 520 525
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[2656] 530 535 540
[2657] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asn
[2658] 545 550 555 560
[2659] Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln
[2660] 565 570 575
[2661] Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro
[2662] 580 585 590
[2663] Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val
[2664] 595 600 605
[2665] Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asp
[2666] 610 615 620
[2667] Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr
[2668] 625 630 635 640
[2669] Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys
[2670] 645 650 655
[2671] Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr
[2672] 660 665 670
[2673] Ser
[2674] <210> 53
[2675] <211> 613
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[2680] <223> 人工序列说明:合成多肽
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[2682] <221> SITE
[2683] <222> (449)..(463)
[2684] <223> 该区域包括 0-3 'Gly Gly Gly Gly Ser'重复单元
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[2687] <222> (464)..(464)
[2688] <223> 用" "取代
[2689] <220>
[2690] <221> 突变

[2691] <222> (465)..(465)
[2692] <223> 用" "取代
[2693] <220>
[2694] <221> SITE
[2695] <222> (466)..(480)
[2696] <223> 该区域包括 0-3 'Gly Gly Gly Gly Ser'重复单元
[2697] <220>
[2698] <221> SITE
[2699] <222> (1)..(613)
[2700] <223> 序列中可变位点的可变残基并不偏好性使用注释中提供的氨基酸残基
[2701] <400> 53

[2702] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
[2703] 1 5 10 15
[2704] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[2705] 20 25 30
[2706] Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[2707] 35 40 45
[2708] Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
[2709] 50 55 60
[2710] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[2711] 65 70 75 80
[2712] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
[2713] 85 90 95
[2714] Ala Arg Thr Gly Trp Leu Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
[2715] 100 105 110
[2716] Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
[2717] 115 120 125
[2718] Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
[2719] 130 135 140
[2720] Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
[2721] 145 150 155 160
[2722] Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
[2723] 165 170 175
[2724] Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
[2725] 180 185 190
[2726] Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
[2727] 195 200 205
[2728] Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
[2729] 210 215 220

[2730] His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
[2731] 225 230 235 240
[2732] Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
[2733] 245 250 255
[2734] Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
[2735] 260 265 270
[2736] Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
[2737] 275 280 285
[2738] Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
[2739] 290 295 300
[2740] Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
[2741] 305 310 315 320
[2742] Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
[2743] 325 330 335
[2744] Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[2745] 340 345 350
[2746] Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
[2747] 355 360 365
[2748] Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
[2749] 370 375 380
[2750] Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
[2751] 385 390 395 400
[2752] Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
[2753] 405 410 415
[2754] Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
[2755] 420 425 430
[2756] Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala
[2757] 435 440 445
[2758] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
[2759] 450 455 460
[2760] Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[2761] 465 470 475 480
[2762] Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
[2763] 485 490 495
[2764] Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
[2765] 500 505 510
[2766] Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
[2767] 515 520 525
[2768] Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu

[2769] 530 535 540

[2770] Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser

[2771] 545 550 555 560

[2772] Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys

[2773] 565 570 575

[2774] Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys

[2775] 580 585 590

[2776] Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His

[2777] 595 600 605

[2778] Gly Ser Glu Asp Ser

[2779] 610

[2780] <210> 54

[2781] <211> 694

[2782] <212> PRT

[2783] <213> 人工序列

[2784] <220>

[2785] <221> 来源

[2786] <223> 人工序列说明:合成多肽

[2787] <220>

[2788] <221> SITE

[2789] <222> (449)..(463)

[2790] <223> 该区域包括 0-3 'Gly Gly Gly Gly Ser'重复单元

[2791] <220>

[2792] <221> 突变

[2793] <222> (464)..(464)

[2794] <223> 用" "取代

[2795] <220>

[2796] <221> 突变

[2797] <222> (465)..(465)

[2798] <223> 用" "取代

[2799] <220>

[2800] <221> SITE

[2801] <222> (466)..(480)

[2802] <223> 该区域包括 0-3 'Gly Gly Gly Gly Ser'重复单元

[2803] <220>

[2804] <221> SITE

[2805] <222> (1)..(694)

[2806] <223> 序列中可变位点的可变残基并不偏好性使用注释中提供的氨基酸残基

[2807] <400> 54

[2808] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
[2809] 1 5 10 15
[2810] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[2811] 20 25 30
[2812] Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[2813] 35 40 45
[2814] Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
[2815] 50 55 60
[2816] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[2817] 65 70 75 80
[2818] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
[2819] 85 90 95
[2820] Ala Arg Thr Gly Trp Leu Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
[2821] 100 105 110
[2822] Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
[2823] 115 120 125
[2824] Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
[2825] 130 135 140
[2826] Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
[2827] 145 150 155 160
[2828] Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
[2829] 165 170 175
[2830] Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
[2831] 180 185 190
[2832] Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
[2833] 195 200 205
[2834] Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
[2835] 210 215 220
[2836] His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
[2837] 225 230 235 240
[2838] Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
[2839] 245 250 255
[2840] Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
[2841] 260 265 270
[2842] Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
[2843] 275 280 285
[2844] Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
[2845] 290 295 300
[2846] Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr

[2847] 305 310 315 320
[2848] Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
[2849] 325 330 335
[2850] Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[2851] 340 345 350
[2852] Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
[2853] 355 360 365
[2854] Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
[2855] 370 375 380
[2856] Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
[2857] 385 390 395 400
[2858] Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
[2859] 405 410 415
[2860] Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
[2861] 420 425 430
[2862] Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala
[2863] 435 440 445
[2864] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
[2865] 450 455 460
[2866] Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[2867] 465 470 475 480
[2868] Ala Val Asn Gly Thr Ser Gln Phe Thr Cys Phe Tyr Asn Ser Arg Ala
[2869] 485 490 495
[2870] Asn Ile Ser Cys Val Trp Ser Gln Asp Gly Ala Leu Gln Asp Thr Ser
[2871] 500 505 510
[2872] Cys Gln Val His Ala Trp Pro Asp Arg Arg Arg Trp Asn Gln Thr Cys
[2873] 515 520 525
[2874] Glu Leu Leu Pro Val Ser Gln Ala Ser Trp Ala Cys Asn Leu Ile Leu
[2875] 530 535 540
[2876] Gly Ala Pro Asp Ser Gln Lys Leu Thr Thr Val Asp Ile Val Thr Leu
[2877] 545 550 555 560
[2878] Arg Val Leu Cys Arg Glu Gly Val Arg Trp Arg Val Met Ala Ile Gln
[2879] 565 570 575
[2880] Asp Phe Lys Pro Phe Glu Asn Leu Arg Leu Met Ala Pro Ile Ser Leu
[2881] 580 585 590
[2882] Gln Val Val His Val Glu Thr His Arg Cys Asn Ile Ser Trp Glu Ile
[2883] 595 600 605
[2884] Ser Gln Ala Ser His Tyr Phe Glu Arg His Leu Glu Phe Glu Ala Arg
[2885] 610 615 620

[2886] Thr Leu Ser Pro Gly His Thr Trp Glu Glu Ala Pro Leu Leu Thr Leu
[2887] 625 630 635 640
[2888] Lys Gln Lys Gln Glu Trp Ile Cys Leu Glu Thr Leu Thr Pro Asp Thr
[2889] 645 650 655
[2890] Gln Tyr Glu Phe Gln Val Arg Val Lys Pro Leu Gln Gly Glu Phe Thr
[2891] 660 665 670
[2892] Thr Trp Ser Pro Trp Ser Gln Pro Leu Ala Phe Arg Thr Lys Pro Ala
[2893] 675 680 685
[2894] Ala Leu Gly Lys Asp Thr
[2895] 690
[2896] <210> 55
[2897] <211> 728
[2898] <212> PRT
[2899] <213> 人工序列
[2900] <220>
[2901] <221> 来源
[2902] <223> 人工序列说明:合成多肽
[2903] <220>
[2904] <221> SITE
[2905] <222> (449)..(463)
[2906] <223> 该区域包括 0-3 'Gly Gly Gly Gly Ser'重复单元
[2907] <220>
[2908] <221> 突变
[2909] <222> (464)..(464)
[2910] <223> 用" "取代
[2911] <220>
[2912] <221> 突变
[2913] <222> (465)..(465)
[2914] <223> 用" "取代
[2915] <220>
[2916] <221> SITE
[2917] <222> (466)..(480)
[2918] <223> 该区域包括 0-3 'Gly Gly Gly Gly Ser'重复单元
[2919] <220>
[2920] <221> SITE
[2921] <222> (1)..(728)
[2922] <223> 序列中可变位点的可变残基并不偏好性使用注释中提供的氨基酸残基
[2923] <400> 55
[2924] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

[2925] 1 5 10 15
[2926] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[2927] 20 25 30
[2928] Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[2929] 35 40 45
[2930] Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
[2931] 50 55 60
[2932] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[2933] 65 70 75 80
[2934] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
[2935] 85 90 95
[2936] Ala Arg Thr Gly Trp Leu Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
[2937] 100 105 110
[2938] Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
[2939] 115 120 125
[2940] Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
[2941] 130 135 140
[2942] Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
[2943] 145 150 155 160
[2944] Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
[2945] 165 170 175
[2946] Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
[2947] 180 185 190
[2948] Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
[2949] 195 200 205
[2950] Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
[2951] 210 215 220
[2952] His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
[2953] 225 230 235 240
[2954] Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
[2955] 245 250 255
[2956] Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
[2957] 260 265 270
[2958] Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
[2959] 275 280 285
[2960] Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
[2961] 290 295 300
[2962] Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
[2963] 305 310 315 320

[2964] Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
[2965] 325 330 335
[2966] Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[2967] 340 345 350
[2968] Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
[2969] 355 360 365
[2970] Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
[2971] 370 375 380
[2972] Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
[2973] 385 390 395 400
[2974] Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
[2975] 405 410 415
[2976] Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
[2977] 420 425 430
[2978] Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala
[2979] 435 440 445
[2980] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
[2981] 450 455 460
[2982] Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[2983] 465 470 475 480
[2984] Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
[2985] 485 490 495
[2986] Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
[2987] 500 505 510
[2988] Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
[2989] 515 520 525
[2990] Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
[2991] 530 535 540
[2992] Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
[2993] 545 550 555 560
[2994] Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
[2995] 565 570 575
[2996] Ala Arg Val Asp Arg Tyr Tyr Asn Trp Asn Tyr Phe Leu Gly Ser Phe
[2997] 580 585 590
[2998] Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
[2999] 595 600 605
[3000] Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Val Leu
[3001] 610 615 620
[3002] Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys Thr Ala Arg Ile

[3003] 625 630 635 640
[3004] Thr Cys Gly Gly Asn Asn Ile Arg Ser Lys Ser Val His Trp Tyr Gln
[3005] 645 650 655
[3006] Gln Lys Pro Gly Gln Ala Pro Val Val Val Ile Tyr Tyr Asp Ser Asp
[3007] 660 665 670
[3008] Arg Pro Ser Gly Ile Pro Glu Arg Ile Ser Gly Ser Asn Ser Gly Asn
[3009] 675 680 685
[3010] Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly Asp Glu Ala Asp
[3011] 690 695 700
[3012] Tyr Phe Cys Gln Val Trp Asp Ser Ser Ser Asp His His Val Phe Gly
[3013] 705 710 715 720
[3014] Gly Gly Thr Lys Leu Thr Val Leu
[3015] 725
[3016] <210> 56
[3017] <211> 728
[3018] <212> PRT
[3019] <213> 人工序列
[3020] <220>
[3021] <221> 来源
[3022] <223> 人工序列说明:合成多肽
[3023] <220>
[3024] <221> SITE
[3025] <222> (449)..(463)
[3026] <223> 该区域包括 0-3 'Gly Gly Gly Gly Ser'重复单元
[3027] <220>
[3028] <221> 突变
[3029] <222> (464)..(464)
[3030] <223> 用" "取代
[3031] <220>
[3032] <221> 突变
[3033] <222> (465)..(465)
[3034] <223> 用" "取代
[3035] <220>
[3036] <221> SITE
[3037] <222> (466)..(480)
[3038] <223> 该区域包括 0-3 'Gly Gly Gly Gly Ser'重复单元
[3039] <220>
[3040] <221> SITE
[3041] <222> (1)..(728)

[3042] <223> 序列中可变位点的可变残基并不偏好性使用注释中提供的氨基酸残基

[3043] <400> 56

[3044] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

[3045] 1 5 10 15

[3046] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr

[3047] 20 25 30

[3048] Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[3049] 35 40 45

[3050] Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val

[3051] 50 55 60

[3052] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

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[3549] Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Cys Gln Ser Ile
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[3564] 20 25 30
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[3574] 100 105 110
[3575] Gly Gln Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala Phe
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[3581] Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser
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[3583] Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln
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[3600] 20 25 30

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[3604] 50 55 60

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[3606] 65 70 75 80

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[3611] Gly Gln Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala Phe

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[3614] 130 135 140

[3615] Gly Asp Asn Ala Ser Val Ser Pro Arg Arg Lys Leu Ile Ser Val Asp

[3616] 145 150 155 160

[3617] Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser

[3618] 165 170 175

[3619] Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln

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[3621] Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser

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[3636] 20 25 30
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[3640] 50 55 60
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[3643] Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala
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[3646] 100 105 110
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[3650] 130 135 140
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[3656] 180 185 190
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[3658] 195 200 205
[3659] Glu Glu Leu Lys Glu
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[3672] 20 25 30

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[3676] 50 55 60

[3677] Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr

[3678] 65 70 75 80

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[3682] 100 105 110

[3683] Gly Gln Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala Phe

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[3685] Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg

[3686] 130 135 140

[3687] Gly Asp Asn Ala Ser Val Ser Pro Arg Arg Lys Leu Ile Ser Val Asp

[3688] 145 150 155 160

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[3690] 165 170 175

[3691] Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln

[3692] 180 185 190

[3693] Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser

[3694] 195 200 205

[3695] Glu Glu Leu Lys Glu

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[3709] Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu
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[3712] 50 55 60
[3713] Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr
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[3718] 100 105 110
[3719] Gly Gln Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala Phe
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[3721] Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg
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[3730] 195 200 205
[3731] Glu Glu Leu Lys Glu
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[3753] Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser
[3754] 100 105 110
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[3762] 165 170 175
[3763] Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln
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[3766] 195 200 205
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[3833] Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser
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[3835] Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln
[3836] 180 185 190
[3837] Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser
[3838] 195 200 205
[3839] Glu Glu Leu Lys Glu
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[3856] 50 55 60
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[3862] 100 105 110
[3863] Gly Gln Tyr Asn Ile Ser Trp Arg Ser Trp Tyr Glu Asp Pro Ala Phe
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[3865] Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg
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[3910] 195 200 205
[3911] Glu Glu Leu Lys Glu
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[4031] Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg Gly Asp Pro
[4032] 595 600 605
[4033] Trp Ala Val Ser Pro Arg Arg Lys Leu Ile Ser Val Asp Ser Arg Ser
[4034] 610 615 620
[4035] Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser Tyr Glu Leu
[4036] 625 630 635 640
[4037] Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln Gly Thr Trp
[4038] 645 650 655
[4039] Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser Glu Glu Leu
[4040] 660 665 670
[4041] Lys Glu
[4042] <210> 75
[4043] <211> 706
[4044] <212> PRT
[4045] <213> 人工序列
[4046] <220>
[4047] <221> 来源
[4048] <223> 人工序列说明:合成多肽
[4049] <400> 75
[4050] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
[4051] 1 5 10 15
[4052] Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
[4053] 20 25 30
[4054] Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[4055] 35 40 45

[4056] Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
[4057] 50 55 60
[4058] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
[4059] 65 70 75 80
[4060] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[4061] 85 90 95
[4062] Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
[4063] 100 105 110
[4064] Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
[4065] 115 120 125
[4066] Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
[4067] 130 135 140
[4068] Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
[4069] 145 150 155 160
[4070] Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
[4071] 165 170 175
[4072] Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
[4073] 180 185 190
[4074] Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
[4075] 195 200 205
[4076] Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
[4077] 210 215 220
[4078] Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
[4079] 225 230 235 240
[4080] Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
[4081] 245 250 255
[4082] Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
[4083] 260 265 270
[4084] Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
[4085] 275 280 285
[4086] Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
[4087] 290 295 300
[4088] Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
[4089] 305 310 315 320
[4090] Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
[4091] 325 330 335
[4092] Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
[4093] 340 345 350
[4094] Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser

[4095] 355 360 365
[4096] Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
[4097] 370 375 380
[4098] Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
[4099] 385 390 395 400
[4100] Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
[4101] 405 410 415
[4102] Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
[4103] 420 425 430
[4104] Ser Leu Ser Leu Ser Leu Gly Ala Gly Gly Gly Gly Ser Gly Gly Gly
[4105] 435 440 445
[4106] Gly Ser Gly Pro Leu Gly Val Arg Gly Gly Gly Gly Ser Gly Gly Gly
[4107] 450 455 460
[4108] Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser
[4109] 465 470 475 480
[4110] Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser
[4111] 485 490 495
[4112] Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg
[4113] 500 505 510
[4114] Leu Leu Ile Tyr Gly Ala Ser Arg Arg Ala Thr Gly Ile Pro Asp Arg
[4115] 515 520 525
[4116] Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg
[4117] 530 535 540
[4118] Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Arg Tyr Gly Ser
[4119] 545 550 555 560
[4120] Ser His Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Ser Gly Gly Gly
[4121] 565 570 575
[4122] Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu
[4123] 580 585 590
[4124] Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile
[4125] 595 600 605
[4126] Ser Cys Lys Val Ser Gly Tyr Phe Phe Thr Thr Tyr Trp Ile Gly Trp
[4127] 610 615 620
[4128] Val Arg Gln Met Pro Gly Lys Gly Leu Glu Tyr Met Gly Ile Ile Tyr
[4129] 625 630 635 640
[4130] Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln Gly Gln Val
[4131] 645 650 655
[4132] Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser
[4133] 660 665 670

[4134] Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly
[4135] 675 680 685
[4136] Asn Trp Asn Cys Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
[4137] 690 695 700
[4138] Ser Ser
[4139] 705
[4140] <210> 76
[4141] <211> 5
[4142] <212> PRT
[4143] <213> 人工序列
[4144] <220>
[4145] <221> 来源
[4146] <223> 人工序列说明:合成肽
[4147] <400> 76
[4148] Thr Tyr Trp Ile Gly
[4149] 1 5
[4150] <210> 77
[4151] <211> 17
[4152] <212> PRT
[4153] <213> 人工序列
[4154] <220>
[4155] <221> 来源
[4156] <223> 人工序列说明:合成肽
[4157] <400> 77
[4158] Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln
[4159] 1 5 10 15
[4160] Gly
[4161] <210> 78
[4162] <211> 8
[4163] <212> PRT
[4164] <213> 人工序列
[4165] <220>
[4166] <221> 来源
[4167] <223> 人工序列说明:合成肽
[4168] <400> 78
[4169] Gly Asn Trp Asn Cys Phe Asp Tyr
[4170] 1 5
[4171] <210> 79
[4172] <211> 12

[4173] <212> PRT
[4174] <213> 人工序列
[4175] <220>
[4176] <221> 来源
[4177] <223> 人工序列说明:合成肽
[4178] <400> 79
[4179] Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
[4180] 1 5 10
[4181] <210> 80
[4182] <211> 7
[4183] <212> PRT
[4184] <213> 人工序列
[4185] <220>
[4186] <221> 来源
[4187] <223> 人工序列说明:合成肽
[4188] <400> 80
[4189] Gly Ala Ser Arg Arg Ala Thr
[4190] 1 5
[4191] <210> 81
[4192] <211> 8
[4193] <212> PRT
[4194] <213> 人工序列
[4195] <220>
[4196] <221> 来源
[4197] <223> 人工序列说明:合成肽
[4198] <400> 81
[4199] Gln Arg Tyr Gly Ser Ser His Thr
[4200] 1 5
[4201] <210> 82
[4202] <211> 8
[4203] <212> PRT
[4204] <213> 人工序列
[4205] <220>
[4206] <221> 来源
[4207] <223> 人工序列说明:合成肽
[4208] <400> 82
[4209] Gly Asn Trp Asn Ser Phe Asp Tyr
[4210] 1 5
[4211] <210> 83

[4212] <211> 118
[4213] <212> PRT
[4214] <213> 人工序列
[4215] <220>
[4216] <221> 来源
[4217] <223> 人工序列说明:合成多肽
[4218] <400> 83
[4219] Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
[4220] 1 5 10 15
[4221] Ser Leu Lys Ile Ser Cys Lys Val Ser Gly Tyr Phe Phe Thr Thr Tyr
[4222] 20 25 30
[4223] Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Tyr Met
[4224] 35 40 45
[4225] Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
[4226] 50 55 60
[4227] Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
[4228] 65 70 75 80
[4229] Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
[4230] 85 90 95
[4231] Ala Arg Gly Gly Asn Trp Asn Cys Phe Asp Tyr Trp Gly Gln Gly Thr
[4232] 100 105 110
[4233] Leu Val Thr Val Ser Ser
[4234] 115
[4235] <210> 84
[4236] <211> 119
[4237] <212> PRT
[4238] <213> 人工序列
[4239] <220>
[4240] <221> 来源
[4241] <223> 人工序列说明:合成多肽
[4242] <400> 84
[4243] Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
[4244] 1 5 10 15
[4245] Arg Glu Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
[4246] 20 25 30
[4247] Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
[4248] 35 40 45
[4249] Ile Tyr Gly Ala Ser Arg Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
[4250] 50 55 60

[4251] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu

[4252] 65 70 75 80

[4253] Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Arg Tyr Gly Ser Ser His

[4254] 85 90 95

[4255] Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Ser Arg Thr Val Ala Ala

[4256] 100 105 110

[4257] Pro Ser Val Phe Ile Phe Pro

[4258] 115

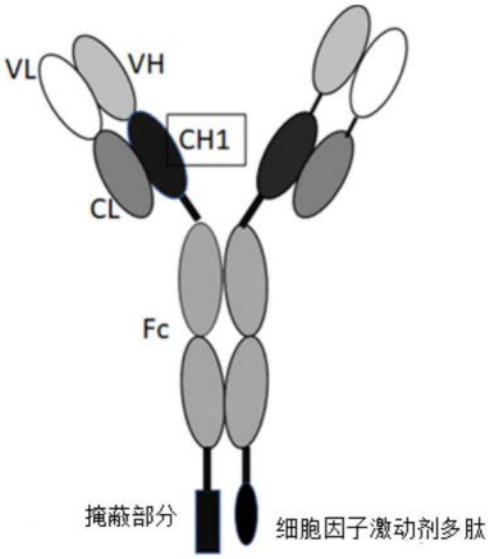

VL
VH
CH1
CL
Fc
掩蔽部分
细胞因子激动剂多肽

图1A

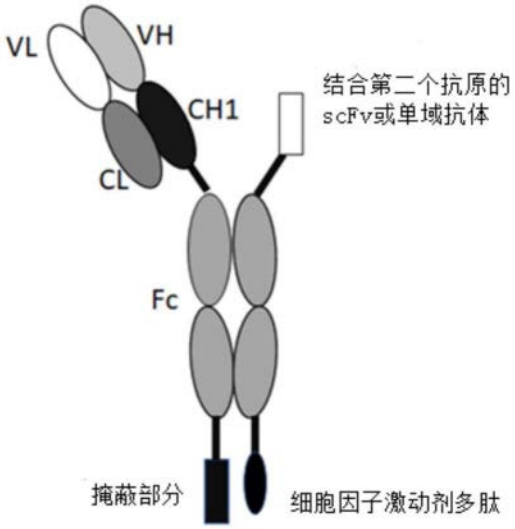

VL
VH
CH1
CL
结合第二个抗原的
scFv或单域抗体
Fc
掩蔽部分
细胞因子激动剂多肽

图1B

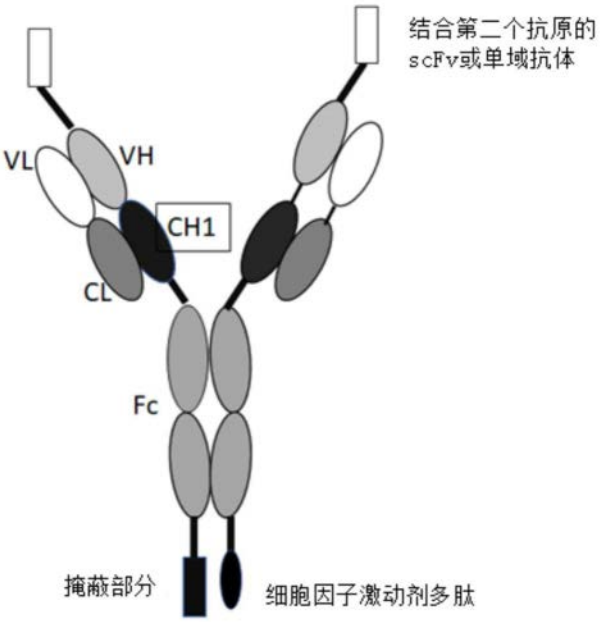

结合第二个抗原的
scFv或单域抗体
VL
VH
CH1
CL
Fc
掩蔽部分
细胞因子激动剂多肽

图1C

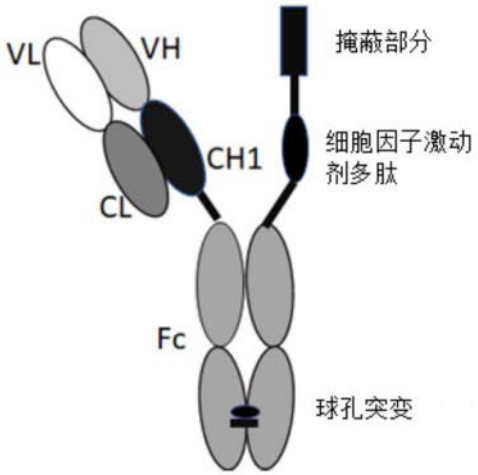

VL
VH
掩蔽部分
细胞因子激动
剂多肽
CH1
CL
Fc
球孔突变

图1D

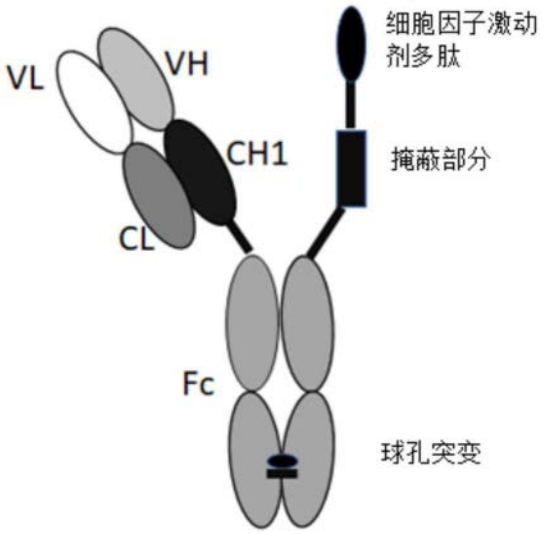

细胞因子激动
剂多肽
VL
VH
CH1
掩蔽部分
CL
Fc
球孔突变

图1E

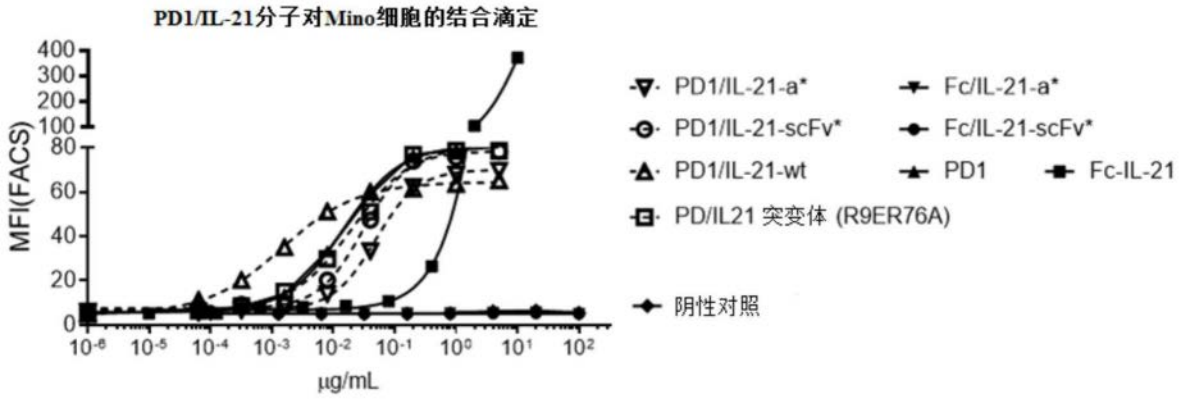

PD1/IL-21分子对Mino细胞的结合滴定
MFI(FACS)
400
300
200
100
80
60
40
20
0
10-6 10-5 10-4 10-3 10-2 10-1 100 101 102
μg/mL
PD1/IL-21-a*
Fc/IL-21-a*
PD1/IL-21-scFv*
Fc/IL-21-scFv*
PD1/IL-21-wt
PD1
Fc-IL-21
PD/IL21 突变体 (R9ER76A)
阴性对照

图2

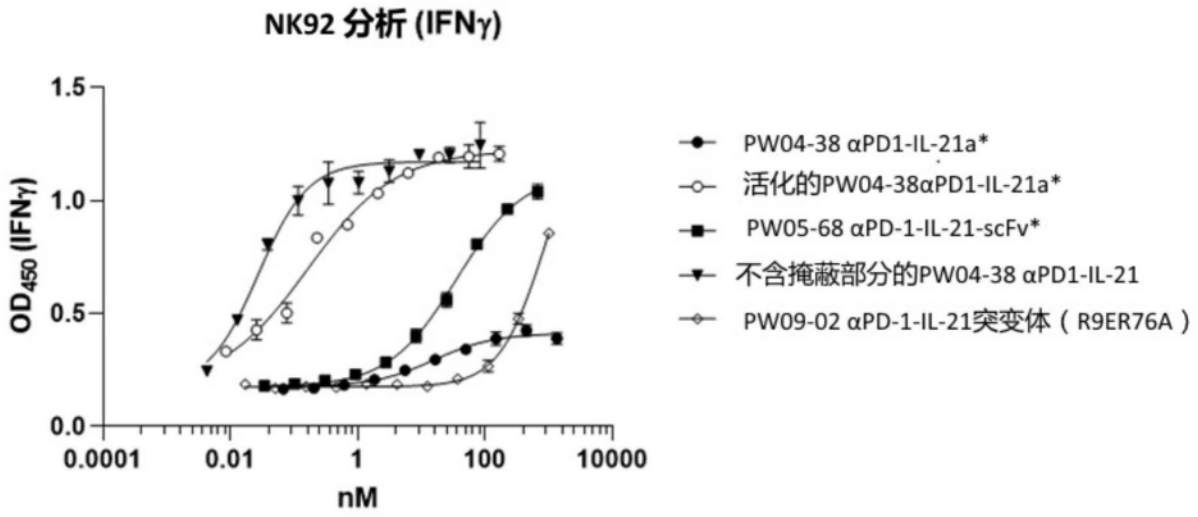

NK92 分析 (IFNγ)
OD450 (IFNγ)
1.5
1.0
0.5
0.0
0.0001
0.01
1
100
10000
nM
PW04-38 αPD1-IL-21a*
活化的PW04-38αPD1-IL-21a*
PW05-68 αPD-1-IL-21-scFv*
不含掩蔽部分的PW04-38 αPD1-IL-21
PW09-02 αPD-1-IL-21突变体（R9ER76A）

图3

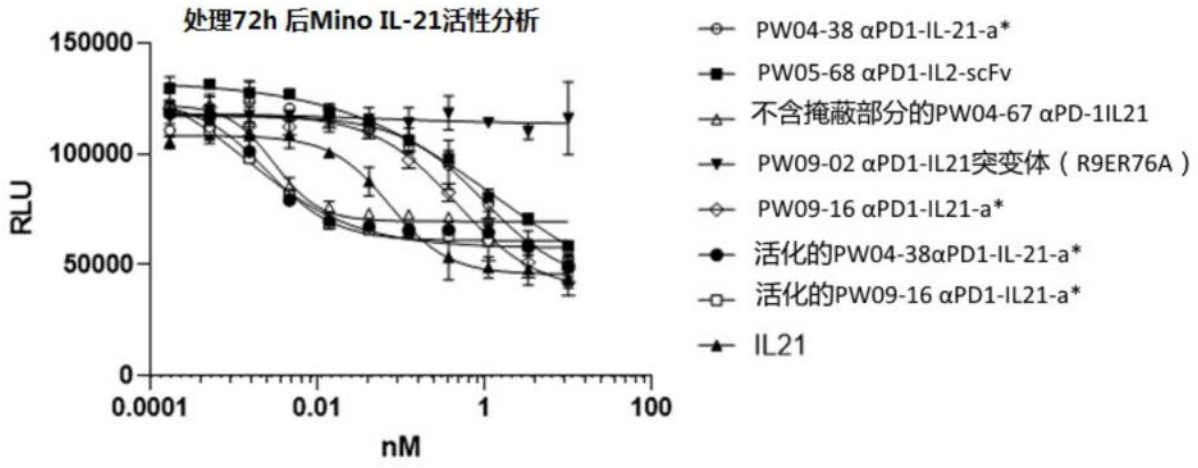

处理72h 后Mino IL-21活性分析
RLU
150000
100000
50000
0
0.0001
0.01
1
100
nM
PW04-38 αPD1-IL-21-a*
PW05-68 αPD1-IL2-scFv
不含掩蔽部分的PW04-67 αPD-1IL21
PW09-02 αPD1-IL21突变体（R9ER76A）
PW09-16 αPD1-IL21-a*
活化的PW04-38αPD1-IL-21-a*
活化的PW09-16 αPD1-IL21-a*
IL21

图4A

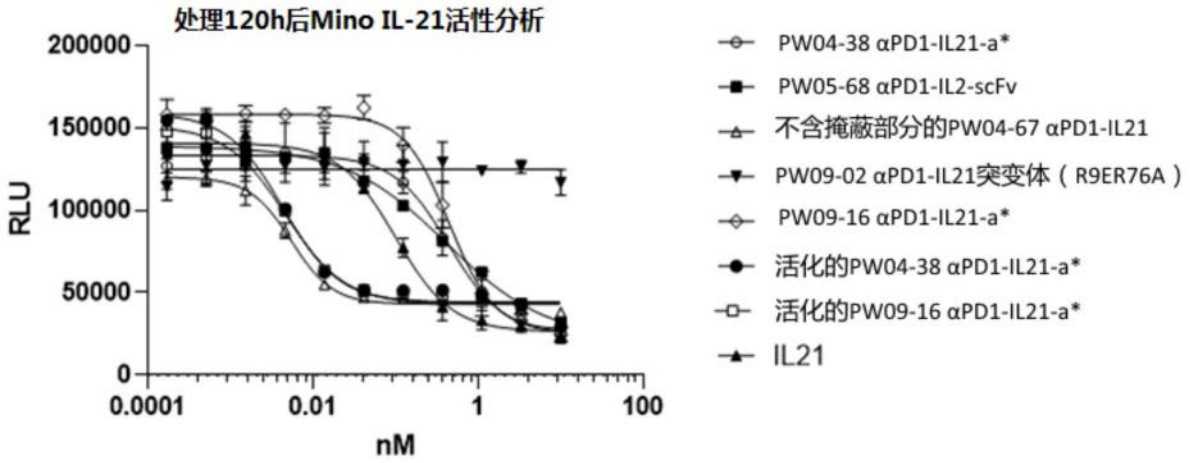

处理120h后Mino IL-21活性分析
RLU
200000
150000
100000
50000
0
0.0001
0.01
1
100
nM
PW04-38 αPD1-IL21-a*
PW05-68 αPD1-IL2-scFv
不含掩蔽部分的PW04-67 αPD1-IL21
PW09-02 αPD1-IL21突变体（R9ER76A）
PW09-16 αPD1-IL21-a*
活化的PW04-38 αPD1-IL21-a*
活化的PW09-16 αPD1-IL21-a*
IL21

图4B

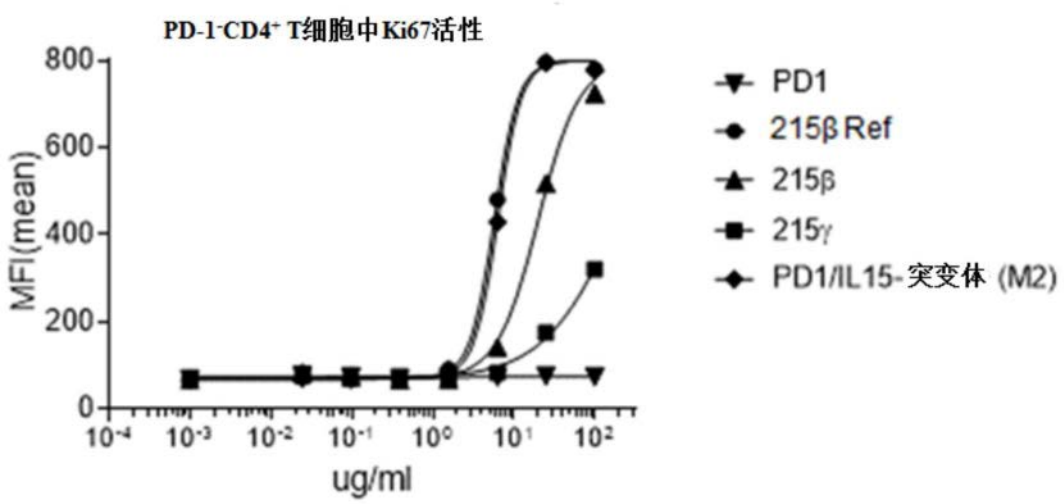

PD-1-CD4+ T细胞中Ki67活性
MFI(mean)
800
600
400
200
0
10-4
10-3
10-2
10-1
100
101
102
ug/ml
PD1
215β Ref
215β
215γ
PD1/IL15-突变体 (M2)

图5A

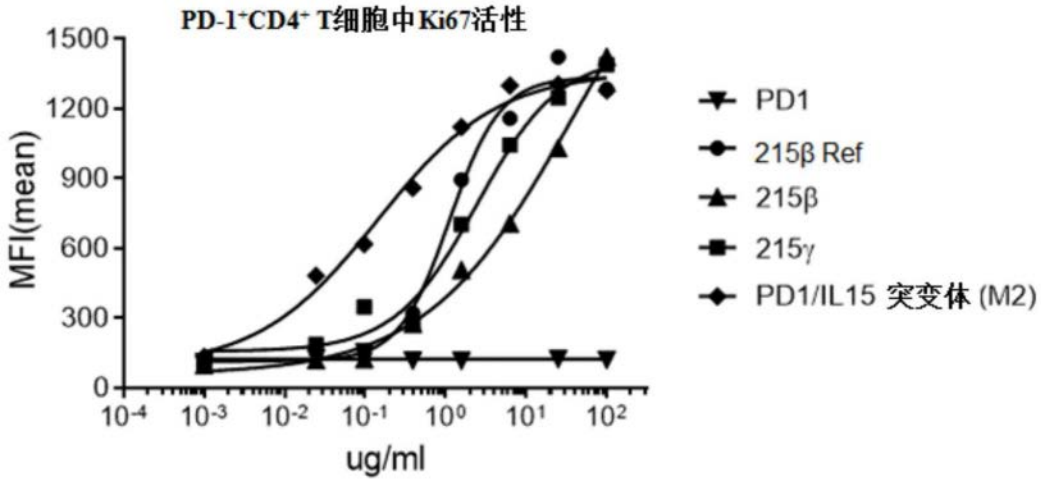



图5B

| | PD-1$^+$ T 细胞（$EC_{50}$ μg/ml） | PD-1$^-$ T 细胞（$EC_{50}$ μg/ml） | 倍数关系（$EC_{50}$ PD-1$^-$/$EC_{50}$ PD-1$^+$） |
|---|---|---|---|
| **PD-1** | ＞10,000 | ＞10,000 | N/A |
| **215β Ref** | 1.12 | 5.72 | 5X ↑ |
| **215β** | 38.48 | 20 | 2X ↓ |
| **215γ** | 2.47 | 195 | 79X ↑ |
| **PD/15 突变体（M2）** | 0.14 | 6.25 | 44X ↑ |

图5C

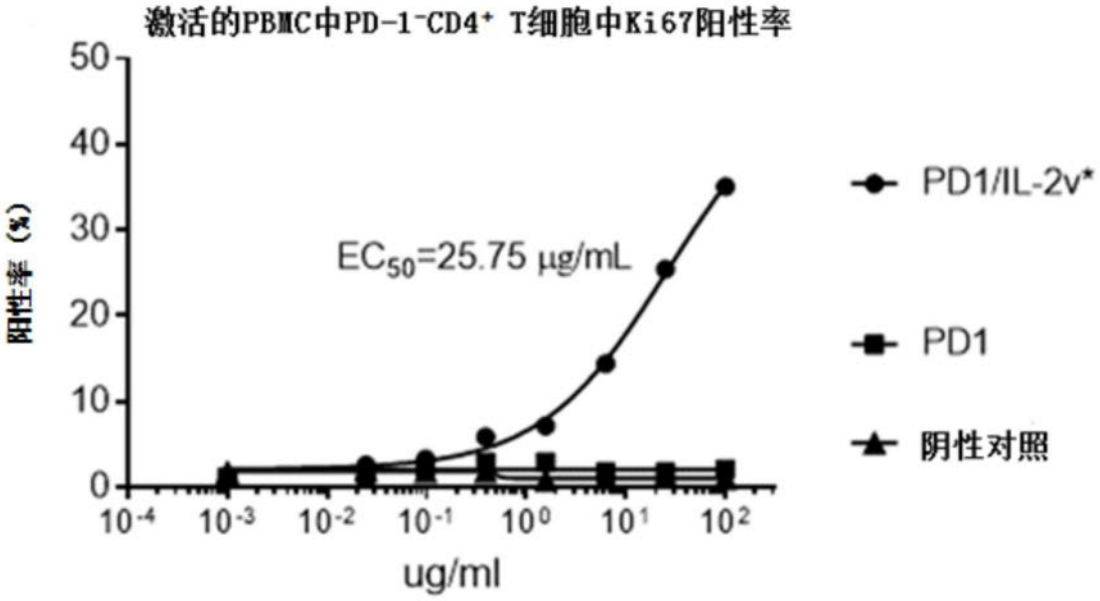

激活的PBMC中PD-1⁻CD4⁺ T细胞中Ki67阳性率
阳性率（%）
50
40
30
20
10
0
EC50=25.75 μg/mL
PD1/IL-2v*
PD1
阴性对照
10-4 10-3 10-2 10-1 100 101 102
ug/ml

图6A

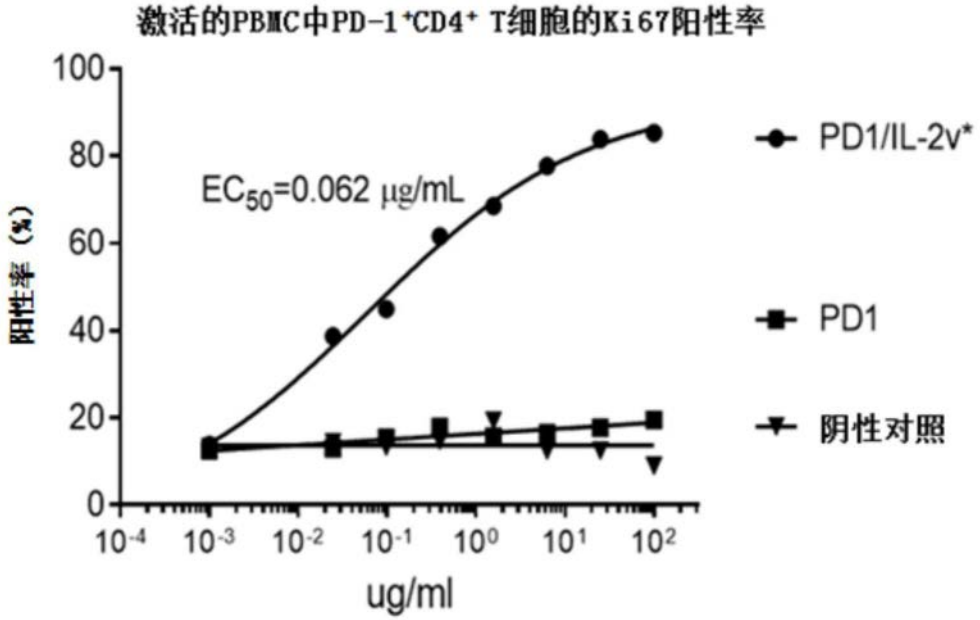

激活的PBMC中PD-1⁺CD4⁺ T细胞的Ki67阳性率
阳性率（%）
100
80
60
40
20
0
EC50=0.062 μg/mL
PD1/IL-2v*
PD1
阴性对照
10-4 10-3 10-2 10-1 100 101 102
ug/ml

图6B

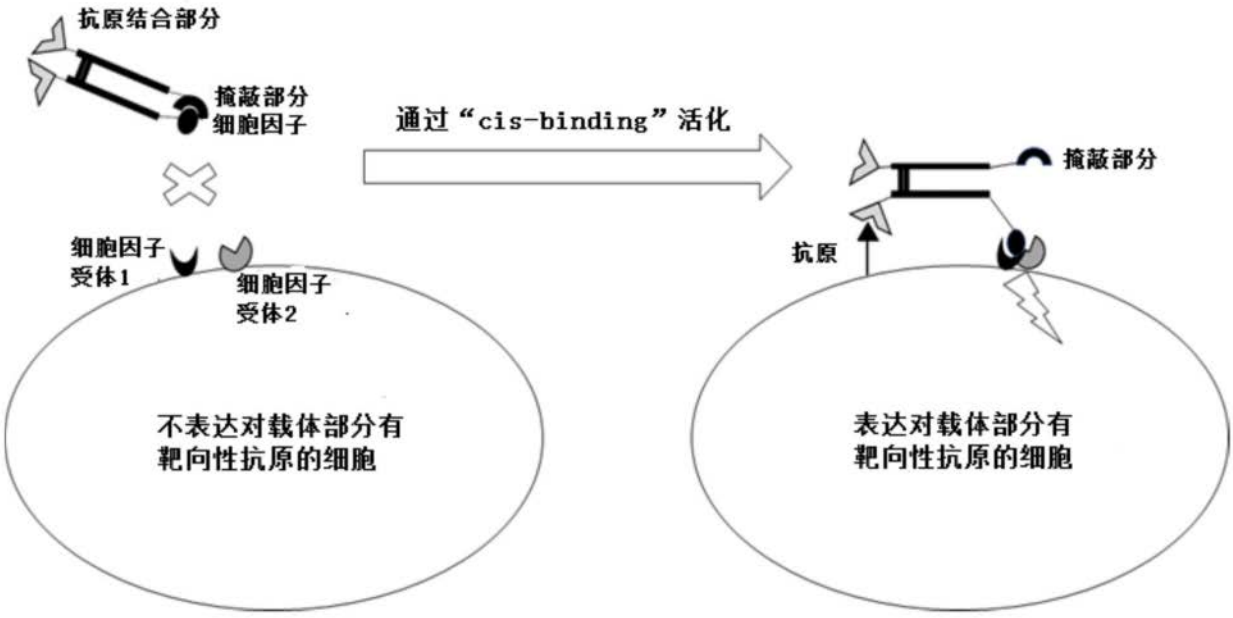

抗原结合部分
掩蔽部分
细胞因子
通过“cis-binding”活化
掩蔽部分
细胞因子
受体1
细胞因子
受体2
抗原
不表达对载体部分有
靶向性抗原的细胞
表达对载体部分有
靶向性抗原的细胞

图7