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(54)发明名称

针对STEAP1的嵌合受体及其使用方法

(57)摘要

根据本发明,披露了针对STEAP1的抗原结合分子、嵌合受体和工程化的免疫细胞。本发明进一步涉及使用这些STEAP1抗原结合分子和工程化的免疫细胞的载体、组合物和治疗和/或检测方法。

CN 112771080 B

1.一种嵌合抗原受体,该嵌合抗原受体包含抗原结合分子,该抗原结合分子特异性结合到STEAP1、共刺激结构域和激活结构域,所述激活结构域是CD3ξ的信号传导结构域,其中该抗原结合分子包含:

a)可变重链区和可变轻链区,所述可变重链区包含氨基酸序列分别如SEQ ID NO:89、SEQ ID NO:90和SEQ ID NO:91所示的互补决定区("CDR")1、2和3,和所述可变轻链区包含氨基酸序列分别如SEQ ID NO:94、SEQ ID NO:95和SEQ ID:96所示的CDR 1、2和3;或

b)如SEQ ID NO:88所示的VH区和如SEQ ID NO:93所示的VL区;

和共刺激结构域,其中所述共刺激结构域是CD28共刺激结构域,其包含SEQ ID NO:2、SEQ ID NO:4、SEQ ID NO:6或SEQ ID NO:8的序列;或者CD8共刺激结构域,其包含SEQ ID NO:14的序列;或4-1BB共刺激结构域,其包含SEQ ID NO:16的序列。

2.根据权利要求1所述的嵌合抗原受体,其中该CD3ξ包含SEQ ID NO:10。

3.一种多核苷酸,该多核苷酸编码根据权利要求1所述的嵌合抗原受体。

4.一种载体,该载体包含根据权利要求3所述的多核苷酸。

5.根据权利要求4所述的载体,其包含质粒。

6.根据权利要求4所述的载体,该载体为逆转录病毒载体、DNA载体、RNA载体、腺病毒载体、腺病毒相关载体、慢病毒载体、或其任何组合。

7.一种免疫细胞,该免疫细胞包含根据权利要求4所述的载体。

8.根据权利要求7所述的免疫细胞,其中该免疫细胞是T细胞。

9.根据权利要求7所述的免疫细胞,其中该免疫细胞是NK细胞。

10.根据权利要求7所述的免疫细胞,其中该免疫细胞是肿瘤浸润淋巴细胞(TIL)、表达TCR的细胞或树突状细胞。

11.根据权利要求7所述的免疫细胞,其中该免疫细胞是NK-T细胞。

12.根据权利要求7所述的免疫细胞,其中该细胞是自体T细胞。

13.根据权利要求7所述的免疫细胞,其中该细胞是同种异体T细胞。

14.根据权利要求7所述的免疫细胞,其中该载体被引入细胞中,所述细胞是从患者身体分离的细胞或是从取自患者身体的样品生长的细胞。

15.根据权利要求7所述的免疫细胞,其中该载体被引入细胞中,所述细胞是从供体身体分离的细胞。

16.一种药物组合物,该药物组合物包含根据权利要求7所述的免疫细胞。

17.根据权利要求1所述的嵌合抗原受体,其中该VH和VL区通过至少一个接头连接。

18.根据权利要求17所述的嵌合抗原受体,其中该接头包含scFv G4S接头或scFv惠特洛接头。

19.根据权利要求3所述的多核苷酸在制备用于治疗有需要的受试者中的前列腺癌的药物中的用途。

20.根据权利要求4所述的载体在制备用于治疗有需要的受试者中的前列腺癌的药物中的用途。

21.根据权利要求1所述的嵌合抗原受体在制备用于治疗有需要的受试者中的前列腺癌的药物中的用途。

22.根据权利要求7所述的免疫细胞在制备用于治疗有需要的受试者中的前列腺癌的

药物中的用途。

23.根据权利要求16所述的药物组合物在制备用于治疗有需要的受试者中的前列腺癌的药物中的用途。

24.根据权利要求19-23中任一项所述的用途,其中该前列腺癌是转移性去势抵抗性前列腺癌。

针对STEAP1的嵌合受体及其使用方法

背景技术

[0001] 除了皮肤癌,前列腺癌是男性中最常被诊断出的癌症。前列腺癌是男性癌症死亡的第二大原因,在2012年,导致估计28,170人死亡。激素疗法、化学疗法、放射或这些治疗的组合用于治疗更晚期的疾病。尽管在前列腺癌疗法方面取得了上述经鉴定的进展,但仍需要能够有效抑制前列腺癌进展(包括未经雄激素受体抑制剂治疗的前列腺癌)的另外的治疗剂。

[0002] 工程化的免疫细胞已显示在治疗性处理中特别是在肿瘤学中具有所希望的性质。两种主要类型的工程化的免疫细胞是含有嵌合抗原受体(称为“CAR”或“CAR-T”)和T-细胞受体(“TCR”)的细胞。这些工程化的细胞被设计用来赋予它们抗原特异性,同时保留或增强它们识别和杀伤靶细胞的能力。嵌合抗原受体可以包括,例如,(i)抗原特异性成分(“抗原结合分子”)、(ii)一个或多个共刺激结构域、以及(iii)一个或多个激活结构域。每个结构域可能是异源的,即由来自不同蛋白质链的序列构成。表达嵌合抗原受体的免疫细胞(诸如T细胞)可用于各种治疗,包括癌症治疗。应当认识到的是,如本文所定义的共刺激多肽可用于增强针对靶抗原的、表达CAR的细胞的激活,从而提高过继性免疫疗法的效力。

[0003] T细胞可以被设计成对一个或多个所希望的靶标具有特异性。例如,T细胞可以用编码抗原结合分子的DNA或其他遗传物质(诸如抗体的一个或多个单链可变片段(“scFv”)联合一个或多个信号传导分子和/或一个或多个激活结构域(诸如CD3ξ)转导。

[0004] 除了CAR-T细胞识别和破坏靶细胞的能力外,成功的T细胞疗法还得益于CAR-T细胞在对抗原的应答中坚持和维持增殖能力的能力。

[0005] 存在对用于鉴定治疗STEAP1相关疾病和障碍的新颖疗法和改进疗法的需求。

发明内容

[0006] 本发明涉及对STEAP1具有特异性的工程化的免疫细胞(诸如CAR或TCR)、抗原结合分子(包括但不限于抗体、scFv、重链和/或轻链以及这些抗原结合分子的CDR)。

[0007] 本发明的嵌合抗原受体通常包括:(i)STEAP1特异性抗原结合分子、(ii)一个或多个共刺激结构域、以及(iii)一个或多个激活结构域。应当认识到的是,每个结构域可能是异源的,因此,其由来自不同蛋白质链的序列组成。

[0008] 在一些实施例中,本发明涉及嵌合抗原受体,该嵌合抗原受体包含抗原结合分子,该抗原结合分子特异性结合到STEAP1上,其中该抗原结合分子包含以下至少一种:(a)可变重链CDR1,其包含与SEQ ID NO:89、99、109、119、129、或139的氨基酸序列差异不超过3、2、1、或0个氨基酸残基的氨基酸序列;(b)可变重链CDR2,其包含与SEQ ID NO:90、100、110、120、130、或140的氨基酸序列差异不超过3、2、1、或0个氨基酸残基的氨基酸序列;(c)可变重链CDR3,其包含与SEQ ID NO:91、101、111、121、131、或141的氨基酸序列差异不超过3、2、1、或0个氨基酸残基的氨基酸序列;(d)可变轻链CDR1,其包含与SEQ ID NO:94、104、114、124、134、或14的氨基酸序列差异不超过3、2、1、或0个氨基酸残基的氨基酸序列;(e)可变轻链CDR2,其包含与SEQ ID NO:95、105、115、125、135、或145的氨基酸序列差异不超过3、2、1、

或0个氨基酸残基的氨基酸序列;(f)可变轻链CDR3,其包含与SEQ ID:96、106、116、126、136、或146的氨基酸序列差异不超过3、2、1、或0个氨基酸残基的氨基酸序列。

[0009] 在其他实施例中,该嵌合抗原受体进一步包括至少一个共刺激结构域。在另外的实施例中,该嵌合抗原受体进一步包括至少一个激活结构域。

[0010] 在某些实施例中,该共刺激结构域是以下的信号传导区:CD28、CD28T、OX-40、4-1BB/CD137、CD2、CD7、CD27、CD30、CD40、程序性死亡-1(PD-1)、T细胞可诱导共刺激因子(ICOS)、淋巴细胞功能相关抗原-1(LFA-1、CD1-1a/CD18)、CD3γ、CD3δ、CD3ε、CD247、CD276(B7-H3)、LIGHT、(TNFSF14)、NKG2C、Igα(CD79a)、DAP-10、Fcγ受体、MHC 1类分子、TNF受体蛋白、免疫球蛋白、细胞因子受体、整合素、信号传导淋巴细胞活化分子(SLAM蛋白)、激活型NK细胞受体、BTLA、Toll配体受体、ICAM-1、B7-H3、CDS、ICAM-1、GITR、BAFFR、LIGHT、HVEM(LIGHTR)、KIRDS2、SLAMF7、NKp80(KLRF1)、NKp44、NKp30、NKp46、CD19、CD4、CD8α、CD8β、IL-2Rβ、IL-2Rγ、IL-7Rα、ITGA4、VLA1、CD49a、ITGA4、IA4、CD49D、ITGA6、VLA-6、CD49f、ITGAD、CD1 1d、ITGAE、CD103、ITGAL、CD1 1a、LFA-1、ITGAM、CD1 1b、ITGAX、CD1 1c、ITGB1、CD29、ITGB2、CD18、LFA-1、ITGB7、NKG2D、TNFR2、TRANCE/RANKL、DNAM1(CD226)、SLAMF4(CD244、2B4)、CD84、CD96(Tactile)、CEACAM1、CRT AM、Ly9(CD229)、CD160(BY55)、PSGL1、CD100(SEMA4D)、CD69、SLAMF6(NTB-A、Ly108)、SLAM(SLAMF1、CD150、IPO-3)、BLAME(SLAMF8)、SELPLG(CD162)、LTBR、LAT、GADS、SLP-76、PAG/Cbp、CD19a、与CD83特异性结合的配体、或其任何组合。

[0011] 在一些实施例中,该共刺激结构域来自4-1BB。在其他实施例中,该共刺激结构域来自OX40。还参见Hombach等人,Oncoimmunology.[肿瘤免疫学]2012年7月1日;1(4):458-466。在仍然其他实施例中,该共刺激结构域包含ICOS,如描述于Guedan等人,2014年8月14日;Blood[血液]:124(7)以及Shen等人,Journal of Hematology&Oncology[血液学与肿瘤学杂志](2013)6:33。在仍然其他实施例中,该共刺激结构域包含CD27,如描述于Song等人,Oncoimmunology.[肿瘤免疫学]2012年7月1日;1(4):547-549。

[0012] 在某些实施例中,该CD28共刺激结构域包含SEQ ID NO:2、SEQ ID NO:4、SEQ ID NO:6或SEQ ID NO:8。在另外的实施例中,该CD8共刺激结构域包含SEQ ID NO:14。在另外的实施例中,该激活结构域包含CD3、CD3ξ、或具有SEQ ID NO:10中列出的序列的CD3ξ。

[0013] 在其他实施例中,本发明涉及嵌合抗原受体,其中该共刺激结构域包含SEQ ID NO:2且激活结构域包含SEQ ID NO:10。

[0014] 本发明进一步涉及编码嵌合抗原受体的多核苷酸以及包含该多核苷酸的载体。例如,该载体可以是逆转录病毒载体、DNA载体、质粒、RNA载体、腺病毒载体、腺病毒相关载体、慢病毒载体、或其任何组合。本发明进一步涉及包含该载体的免疫细胞。在一些实施例中,该慢病毒载体是pGAR载体。

[0015] 示例性免疫细胞包括但不限于T细胞、肿瘤浸润淋巴细胞(TIL)、NK细胞、表达TCR的细胞、树突状细胞或NK-T细胞。所述T细胞可以是自体、同种异体或异源的。在其他实施例中,本发明涉及包含本文所述免疫细胞的药物组合物。

[0016] 在某些实施例中,本发明涉及抗原结合分子(以及包含这些分子的嵌合抗原受体),该抗原结合分子包括以下中的至少一种:

[0017] (a)VH区,其与2F3的VH区的氨基酸序列差异不超过10、9、8、7、6、5、4、3、2、1或0个

氨基酸残基,和VL区,其与2F3的VL区的氨基酸序列差异不超过10、9、8、7、6、5、4、3、2、1、或0个氨基酸残基;

[0018] (b)VH区,其与11C2的VH区的氨基酸序列差异不超过10、9、8、7、6、5、4、3、2、1或0个氨基酸残基,和VL区,其与11C2的VL区的氨基酸序列差异不超过10、9、8、7、6、5、4、3、2、1、或0个氨基酸残基;

[0019] (c)VH区,其与1A1的VH区的氨基酸序列差异不超过10、9、8、7、6、5、4、3、2、1或0个氨基酸残基,和VL区,其与1A1的VL区的氨基酸序列差异不超过10、9、8、7、6、5、4、3、2、1、或0个氨基酸残基;

[0020] (d)VH区,其与7A4的VH区的氨基酸序列差异不超过10、9、8、7、6、5、4、3、2、1或0个氨基酸残基,和VL区,其与7A4的VL区的氨基酸序列差异不超过10、9、8、7、6、5、4、3、2、1、或0个氨基酸残基;以及

[0021] (e)VH区,其与7A5的VH区的氨基酸序列差异不超过10、9、8、7、6、5、4、3、2、1或0个氨基酸残基,和VL区,其与7A5的VL区的氨基酸序列差异不超过10、9、8、7、6、5、4、3、2、1、或0个氨基酸残基;

[0022] (f)VH区,其与14C1的VH区的氨基酸序列差异不超过10、9、8、7、6、5、4、3、2、1或0个氨基酸残基,和VL区,其与14C1的VL区的氨基酸序列差异不超过10、9、8、7、6、5、4、3、2、1、或0个氨基酸残基;

[0023] 并且其中该一个或多个VH和VL区通过至少一个接头连接。

[0024] 在其他实施例中,本发明涉及抗原结合分子(以及包含这些分子的嵌合抗原受体),其中该接头包含scFv G4S接头和scFv惠特洛(Whitlow)接头中的至少一个。

[0025] 在其他实施例中,本发明涉及编码本发明多肽的载体以及包含这些多肽的免疫细胞。优选的免疫细胞包括T细胞、肿瘤浸润淋巴细胞(TIL)、NK细胞、表达TCR的细胞、树突状细胞或NK-T细胞。所述T细胞可以是自体、同种异体或异源的。

[0026] 在其他实施例中,本发明涉及编码包含特异性结合至STEAP1的抗原结合分子的嵌合抗原受体(CAR)或T细胞受体(TCR)的分离的多核苷酸,其中该抗原结合分子包含可变重(V_H)链CDR3,该可变重(V_H)链CDR3包含SEQ ID NO:19或SEQ ID NO:27的氨基酸序列。该多核苷酸可以进一步包含激活结构域。在优选实施例中,该激活结构域是CD3,更优选为CD3ξ,更优选为SEQ ID NO:9中列出的氨基酸序列。

[0027] 在其他实施例中,本发明包括共刺激结构域,例如CD28、CD28T、OX40、4-1BB/CD137、CD2、CD3(α、β、δ、ε、γ、ξ)、CD4、CD5、CD7、CD9、CD16、CD22、CD27、CD30、CD 33、CD37、CD40、CD 45、CD64、CD80、CD86、CD134、CD137、CD154、PD-1、ICOS、淋巴细胞功能相关抗原-1(LFA-1(CDl la/CD18)、CD247、CD276(B7-H3)、LIGHT(肿瘤坏死因子超家族成员14;TNFSF14)、NKG2C、Igα(CD79a)、DAP-10、Fcγ受体、MHC I类分子、TNF、TNFr、整合素、信号传导淋巴细胞活化分子、BTLA、Toll配体受体、ICAM-1、B7-H3、CDS、ICAM-1、GITR、BAFFR、LIGHT、HVEM(LIGHTR)、KIRDS2、SLAMF7、NKp80(KLRF1)、NKp44、NKp30、NKp46、CD19、CD4、CD8α、CD8β、IL-2Rβ、IL-2R γ、IL-7Rα、ITGA4、VLA1、CD49a、ITGA4、IA4、CD49D、ITGA6、VLA-6、CD49f、ITGAD、CDl-ld、ITGAE、CD103、ITGAL、CDl-la、LFA-1、ITGAM、CDl-lb、ITGAX、CDl-lc、ITGB1、CD29、ITGB2、CD18、LFA-1、ITGB7、NKG2D、TNFR2、TRANCE/RANKL、DNAM1(CD226)、SLAMF4(CD244、2B4)、CD84、CD96(Tactile)、CEACAM1、CRT AM、Ly9(CD229)、CD160(BY55)、

PSGL1、CD100(SEMA4D)、CD69、SLAMF6(NTB-A、Ly108)、SLAM(SLAMF1、CD150、IPO-3)、BLAME(SLAMF8)、SELPLG(CD162)、LTBR、LAT、GADS、SLP-76、PAG/Cbp、CD19a、CD83配体、或其片段或组合。优选的共刺激结构域是如下文所列举的。

[0028] 本发明进一步涉及治疗有需要的受试者中的疾病或障碍的方法,该方法包括向该受试者施用根据本发明的抗原结合分子、CAR、TCR、多核苷酸、载体、细胞或组合物。适合治疗的疾病包括但不限于:前列腺癌,包括转移性去势抵抗性前列腺癌。

附图说明

[0029] 图1描绘了人细胞系上STEAP1细胞表面表达的流式细胞术分析。

[0030] 图2描绘了经编码多种CAR的mRNA电穿孔的原代人T细胞中的CAR表达。

[0031] 图3描绘了经电穿孔的CAR T细胞针对多种细胞系的细胞溶解活性。

[0032] 图4由图3A和图3B构成,描绘了通过电穿孔的CAR T细胞产生IFNγ、IL-2和TNFα。

[0033] 图5描绘了来自两个健康供体的慢病毒转导的原代人T细胞中的CAR表达。

[0034] 图6描绘了pGAR载体图谱。

具体实施方式

[0035] 应当认识到的是,嵌合抗原受体(CAR或CAR-T)和T细胞受体(TCR)是基因工程化的受体。这些工程化受体可以根据本领域已知的技术很容易地插入免疫细胞并通过免疫细胞表达,所述免疫细胞包括T细胞。通过CAR,单一的受体可以被编程,使其既能识别特定的抗原,又能在与该抗原结合时激活免疫细胞,攻击并摧毁携带该抗原的细胞。当这些抗原存在于肿瘤细胞上时,表达CAR的免疫细胞可以靶向并杀伤肿瘤细胞。

[0036] 通过掺入与靶抗原相互作用的抗原结合分子,CAR可以被工程化以结合抗原(诸如细胞表面抗原)。优选地,该抗原结合分子是其抗体片段,并且更优选地是一个或多个单链抗体片段(“scFv”)。scFv是单链抗体片段,它具有连接在一起的抗体重链和轻链的可变区。参见美国专利号7,741,465、和6,319,494以及Eshhar等人,Cancer Immunol Immunotherapy[癌症免疫免疫疗法](1997)45:131-136。scFv保留了亲本抗体与靶抗原特异性相互作用的能力。scFv优选用于在嵌合抗原受体中使用,因为它们可以被工程化以作为单链的部分与其他CAR成分被表达。同上还参见Krause等人,J.Exp.Med.[实验医学杂志],第188卷,第4期,1998(619-626);Finney等人,Journal of Immunology[免疫学杂志],1998,161:2791-2797。应当认识到的是,抗原结合分子通常包含在CAR的细胞外部分中,这样它就能够识别和结合目的抗原。在本发明的范围内考虑到的是具有对多于一个目的靶标具有特异性的双特异性和多特异性CAR。

[0037] 共刺激结构域。嵌合抗原受体可以掺入共刺激(信号传导)结构域来增强其效力。参见美国专利号7,741,465、和6,319,494,以及Krause等人和Finney等人(同上),Song等人,Blood[血液]119:696-706(2012);Kalos等人,Sci Transl.Med.[科学转化医学]3:95(2011);Porter等人,N.Engl.J.Med.[新英格兰医学杂志]365:725-33(2011),以及Gross等人,Annu.Rev.Pharmacol.Toxicol.[药理学与毒理学年评]56:59-83(2016)。例如,CD28是一种天然存在于T细胞上的共刺激蛋白。CD28的完整天然氨基酸序列描述于NCBI参考序列:NP_006130.1。完整的天然CD28核酸序列描述于NCBI参考序列:NM_006139.1。

[0038] 某些CD28结构域已被用于嵌合抗原受体。在一个实施例中,可以使用称为“CD28T”的新颖CD28细胞外结构域,并且出乎意料地发现当其用于CAR构建体时可以提供某些益处。

[0039] CD28T分子的核苷酸序列(包括细胞外CD28T结构域、CD28跨膜结构域和细胞内结构域)在SEQ ID NO:1中列出:

CTTGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAA

[0040] GCACCTCTGTCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTC
GTAGTGGGTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCT
TCTGGGTTAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTC

[0041] CACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATT
TCGCTGCCTATCGGAGC

[0042] 相应的氨基酸序列在SEQ ID NO:2中列出:

[0043] LDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY MNMTPRRPGPTRKHYQPYAPPRDFAAYRS

[0044] CD28T的细胞外部分的核苷酸序列在SEQ ID NO:3中列出:

[0045] CTTGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTG TTCCCTGGTCCATCCAAGCCA

[0046] CD28T细胞外结构域的相应的氨基酸序列在SEQ ID NO:4中列出:LDNEKSNGTI IHVKGKHLCP SPLFPGPSKP

[0047] CD28跨膜结构域的核苷酸序列在SEQ ID NO:5中列出:

[0048] TTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATA ATCTTCTGGGTT

[0049] CD28跨膜结构域的氨基酸序列在以下中列出

[0050] SEQ ID NO:6:FWVLVVVGGVLACYSLLVTVAFIIFWV

[0051] CD28细胞内信号传导结构域的核苷酸序列在SEQ ID NO:7中列出:

[0052] AGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCCCACA AGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATCGGAGC

[0053] CD28细胞内信号传导结构域的氨基酸序列在SEQ ID NO:8中列出:RSKRSRLLHSDY MNMTPRRPGPTRKHYQPYAPPRDFAAYRS

[0054] 适用于本发明的另外的CD28序列包括CD28核苷酸序列,其在SEQ ID NO:11中列出:

[0055] ATTGAGGTGATGTATCCACCGCCTTACCTGGATAACGAAAAGAGTAACGGTACCATCATTCACGTGAAA GGTAAACACCTGTGTCCTTCTCCCCTCTTCCCCGGGCCATCAAAGCCC

[0056] 相应的氨基酸序列在SEQ ID NO:12中列出:

[0057] IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKP

[0058] 其他的适合的细胞外或跨膜序列可以来自CD8。适合的CD8细胞外和跨膜结构域的核苷酸序列在SEQ ID NO:13中列出:

[0059] GCTGCAGCATTGAGCAACTCAATAATGTATTTTAGTCACTTTGTACCAGTGTTCTTGCCGGCTAAGCCT ACTACCACACCCGCTCCACGGCCACCTACCCCAGCTCCTACCATCGCTTCACAGCCTCTGTCCCTGCGCCCAGAGGC TTGCCGACCGGCCGCAGGGGGCGCTGTTCATACCAGAGGACTGGATTTCGCCTGCGATATCTATATCTGGGCACCCC

TGGCCGGAACCTGCGGCGTACTCCTGCTGTCCCTGGTCATCACGCTCTATTGTAATCACAGGAAC

[0060] 相应的氨基酸序列在SEQ ID NO:14中列出：

[0061] AAALSNSIMYFSHFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDI YIWAPLAGTCGVLLLSLVITLYCNHRN

[0062] 其他的适合的细胞内信号传导序列可以来自41-BB。适合的41-BB细胞内信号传导结构域的核苷酸序列在SEQ ID NO:15中列出：

[0063] CGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATGAGGCCG GTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTG

[0064] 相应的氨基酸序列在SEQ ID NO:16中列出：

[0065] RFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL

[0066] 本发明范围内的适合的共刺激结构域可以来自(除其他来源外)CD28、CD28T、OX40、4-1BB/CD137、CD2、CD3(α、β、δ、ε、γ、ξ)、CD4、CD5、CD7、CD9、CD16、CD22、CD27、CD30、CD33、CD37、CD40、CD 45、CD64、CD80、CD86、CD134、CD137、CD154、PD-1、ICOS、淋巴细胞功能相关抗原-1(LFA-1(CD1 1a/CD18)、CD247、CD276(B7-H3)、LIGHT(肿瘤坏死因子超家族成员14;TNFSF14)、NKG2C、Igα(CD79a)、DAP-10、Fcγ受体、MHC I类分子、TNF、TNFr、整合素、信号传导淋巴细胞活化分子、BTLA、Toll配体受体、ICAM-1、B7-H3、CDS、ICAM-1、GITR、BAFFR、LIGHT、HVEM(LIGHTR)、KIRDS2、SLAMF7、NKp80(KLRF1)、NKp44、NKp30、NKp46、CD19、CD4、CD8α、CD8β、IL-2Rβ、IL-2R γ、IL-7Rα、ITGA4、VLA1、CD49a、ITGA4、IA4、CD49D、ITGA6、VLA-6、CD49f、ITGAD、CD1-1d、ITGAE、CD103、ITGAL、CD1-1a、LFA-1、ITGAM、CD1-1b、ITGAX、CD1-1c、ITGB1、CD29、ITGB2、CD18、LFA-1、ITGB7、NKG2D、TNFR2、TRANCE/RANKL、DNAM1(CD226)、SLAMF4(CD244、2B4)、CD84、CD96(Tactile)、CEACAM1、CRT AM、Ly9(CD229)、CD160(BY55)、PSGL1、CD100(SEMA4D)、CD69、SLAMF6(NTB-A、Ly108)、SLAM(SLAMF1、CD150、IPO-3)、BLAME(SLAMF8)、SELPLG(CD162)、LTBR、LAT、GADS、SLP-76、PAG/Cbp、CD19a、CD83配体、或其片段或组合。

[0067] 激活结构域。

[0068] CD3是天然T细胞上T细胞受体的元件,并且已显示是CAR内重要的细胞内激活元件。在优选的实施例中,CD3是CD3ξ,其核苷酸序列在SEQ ID NO:9中列出：

[0069] AGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGC CAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTT GGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAAC CCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCT GAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACC AGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGC CACCTAGG

[0070] 细胞内CD3ξ的相应的氨基酸在SEQ ID NO:10中列出：

[0071] RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPR

[0072] RKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

[0073] 结构域取向

[0074] 应当认识到的是在结构上,这些结构域对应于免疫细胞相关的位置。因此,这些结

构域可以是(i)“铰链”或细胞外(EC)结构域、(ii)跨膜(TM)结构域、和/或(iii)细胞内(IC)(细胞质)结构域的部分。细胞内成分通常部分包含CD3家族的成员,优选为CD3ξ,该CD3ξ能够在抗原结合分子与其靶标结合后激活T细胞。在一个实施例中,该铰链结构域通常由如本文定义的至少一个共刺激结构域构成。

[0075] 还应当认识到的是铰链区也可能包含免疫球蛋白家族的一些或全部成员,诸如IgG1、IgG2、IgG3、IgG4、IgA、IgD、IgE、IgM或其片段。

[0076] 根据本发明的示例性CAR构建体在表1中列出。

[0077] 表1

[0078]

构建体名称	scFv	共刺激结构域	激活结构域
2F3-CD28T-CD28-41BB	2F3	CD28T、4-1BB	CD3 ξ
2F3-CD28T-CD28	2F3	CD28T	CD3 ξ
2F3-CD28T-41BB	2F3	4-1BB	CD3 ξ
2F3-C8K-CD28	2F3	CD28T	CD3 ξ
2F3-C8K-41BB	2F3	4-1BB	CD3 ξ
11C2-CD28T-CD28-41BB	11C2	CD28T、4-1BB	CD3 ξ
11C2-CD28T-CD28	11C2	CD28T	CD3 ξ
11C2-CD28T-41BB	11C2	4-1BB	CD3 ξ
11C2-C8K-CD28	11C2	CD28T	CD3 ξ
11C2-C8K-41BB	11C2	4-1BB	CD3 ξ
1A1-CD28T-CD28-41BB	1A1	CD28T、4-1BB	CD3 ξ
1A1-CD28T-CD28	1A1	CD28T	CD3 ξ
1A1-CD28T-41BB	1A1	4-1BB	CD3 ξ
1A1-C8K-CD28	1A1	CD28T	CD3 ξ
1A1-C8K-41BB	1A1	4-1BB	CD3 ξ
7A4-CD28T-CD28-41BB	7A4	CD28T、4-1BB	CD3 ξ
7A4-CD28T-CD28	7A4	CD28T	CD3 ξ
7A4-CD28T-41BB	7A4	4-1BB	CD3 ξ
7A4-C8K-CD28	7A4	CD28T	CD3 ξ
7A4-C8K-41BB	7A4	4-1BB	CD3 ξ
7A5-CD28T-CD28-41BB	7A5	CD28T、4-1BB	CD3 ξ
7A5-CD28T-CD28	7A5	CD28T	CD3 ξ
7A5-CD28T-41BB	7A5	4-1BB	CD3 ξ
7A5-C8K-CD28	7A5	CD28T	CD3 ξ
7A5-C8K-41BB	7A5	4-1BB	CD3 ξ
14C1-CD28T-CD28-41BB	14C1	CD28T、4-1BB	CD3 ξ
14C1-CD28T-CD28	14C1	CD28T	CD3 ξ
14C1-CD28T-41BB	14C1	4-1BB	CD3 ξ

[0079]

14C1-C8K-CD28	14C1	CD28T	CD3 ξ
14C1-C8K-41BB	14C1	4-1BB	CD3 ξ

[0080] 与细胞相关的结构域

[0081] 应当认识到的是,相对于携带受体的细胞,本发明的工程化的T细胞包括抗原结合分子(诸如scFv)、细胞外结构域(可能包括“铰链”结构域)、跨膜结构域和细胞内结构域。细胞内结构域至少部分地包含激活结构域,该激活结构域优选地由CD3家族成员(诸如CD3ξ、CD3ε、CD3γ、或其部分)构成。进一步应当认识到的是抗原结合分子(例如,一个或多个scFv)被工程化使其位于分子/构建体的细胞外部分,从而能够识别和结合到其一个或多个靶标上。

[0082] 细胞外结构域。细胞外结构域有利于信号传导和淋巴细胞对抗原的有效应答。本发明中特别有用的细胞外结构域可以来自(即包括):CD28、CD28T、CD8、OX-40、4-1BB/CD137、CD2、CD7、CD27、CD30、CD40、程序性死亡-1(PD-1)、T细胞可诱导共刺激因子(ICOS)、淋巴细胞功能相关抗原-1(LFA-1、CD1-1a/CD18)、CD3γ、CD3δ、CD3ε、CD247、CD276(B7-H3)、LIGHT、(TNFSF14)、NKG2C、Igα(CD79a)、DAP-10、Fcγ受体、MHC 1类分子、TNF受体蛋白、免疫球蛋白、细胞因子受体、整合素、信号传导淋巴细胞活化分子(SLAM蛋白)、激活型NK细胞受体、BTLA、Toll配体受体、ICAM-1、B7-H3、CDS、ICAM-1、GITR、BAFFR、LIGHT、HVEM(LIGHTR)、KIRDS2、SLAMF7、NKp80(KLRF1)、NKp44、NKp30、NKp46、CD19、CD4、CD8α、CD8β、IL-2Rβ、IL-2Rγ、IL-7Rα、ITGA4、VLA1、CD49a、ITGA4、IA4、CD49D、ITGA6、VLA-6、CD49f、ITGAD、CD1 1d、ITGAE、CD103、ITGAL、CD1 1a、LFA-1、ITGAM、CD1 1b、ITGAX、CD1 1c、ITGB1、CD29、ITGB2、CD18、LFA-1、ITGB7、NKG2D、TNFR2、TRANCE/RANKL、DNAM1(CD226)、SLAMF4(CD244、2B4)、CD84、CD96(Tactile)、CEACAM1、CRT AM、Ly9(CD229)、CD160(BY55)、PSGL1、CD100(SEMA4D)、CD69、SLAMF6(NTB-A、Ly108)、SLAM(SLAMF1、CD150、IPO-3)、BLAME(SLAMF8)、SELPLG(CD162)、LTBR、LAT、GADS、SLP-76、PAG/Cbp、CD19a、与CD83特异性结合的配体、或其任何组合。细胞外结构域可来自天然来源或合成来源。

[0083] 如本文所述,细胞外结构域通常包含铰链部分。这是细胞外结构域的一部分,有时称为“间隔子”区。根据本发明可以使用多种铰链,包括如上文所述的共刺激分子,以及免疫球蛋白(Ig)序列或其他适合的分子,以达到所希望的与靶细胞的特殊距离。在一些实施例中,整个细胞外区域包括铰链区。在一些实施例中,该铰链区包含CD28T或CD28的EC结构域。

[0084] 跨膜结构域。CAR可被设计成包括融合到该CAR的细胞外结构域的跨膜结构域。它可以类似地融合到CAR的细胞内结构域。在一个实施例中,使用自然与CAR中的一个结构域相关的跨膜结构域。在一些情况下,可以通过氨基酸取代来选择或修饰跨膜结构域,以避免此类结构域与相同或不同表面膜蛋白的跨膜结构域的结合以最小化与受体复合物的其他成员的相互作用。跨膜结构域可来自天然来源或合成来源。在来源是天然的情况下,结构域可以衍生自任何膜结合或跨膜蛋白。本发明中特别有用的跨膜区可以来自(即包括):CD28、CD28T、CD8、OX-40、4-1BB/CD137、CD2、CD7、CD27、CD30、CD40、程序性死亡-1(PD-1)、T细胞可诱导共刺激因子(ICOS)、淋巴细胞功能相关抗原-1(LFA-1、CD1-1a/CD18)、CD3γ、CD3δ、CD3ε、CD247、CD276(B7-H3)、LIGHT、(TNFSF14)、NKG2C、Igα(CD79a)、DAP-10、Fcγ受体、MHC 1类分子、TNF受体蛋白、免疫球蛋白、细胞因子受体、整合素、信号传导淋巴细胞活化分子(SLAM蛋白)、激活型NK细胞受体、BTLA、Toll配体受体、ICAM-1、B7-H3、CDS、ICAM-1、GITR、BAFFR、LIGHT、HVEM(LIGHTR)、KIRDS2、SLAMF7、NKp80(KLRF1)、NKp44、NKp30、NKp46、CD19、CD4、CD8α、CD8β、IL-2Rβ、IL-2Rγ、IL-7Rα、ITGA4、VLA1、CD49a、ITGA4、IA4、CD49D、ITGA6、VLA-6、CD49f、ITGAD、CD1 1d、ITGAE、CD103、ITGAL、CD1 1a、LFA-1、ITGAM、CD1 1b、ITGAX、CD1 1c、

ITGB1、CD29、ITGB2、CD18、LFA-1、ITGB7、NKG2D、TNFR2、TRANCE/RANKL、DNAM1(CD226)、SLAMF4(CD244、2B4)、CD84、CD96(Tactile)、CEACAM1、CRT AM、Ly9(CD229)、CD160(BY55)、PSGL1、CD100(SEMA4D)、CD69、SLAMF6(NTB-A、Ly108)、SLAM(SLAMF1、CD150、IPO-3)、BLAME(SLAMF8)、SELPLG(CD162)、LTBR、LAT、GADS、SLP-76、PAG/Cbp、CD19a、与CD83特异性结合的配体、或其任何组合。

[0085] 任选地,短接头可以在CAR的任何或部分细胞外、跨膜和细胞内结构域之间形成连接。

[0086] 在一个实施例中,本发明的CAR中的跨膜结构域为CD8跨膜结构域。在一个实施例中,该CD8跨膜结构域包含SEQ ID NO:13的核酸序列的跨膜部分。在另一个实施例中,该CD8跨膜结构域包含编码SEQ ID NO:14中包含的跨膜氨基酸序列的核酸序列。

[0087] 在某些实施例中,本发明的CAR中的跨膜结构域为CD28跨膜结构域。在一个实施例中,该CD28跨膜结构域包含SEQ ID NO:5的核酸序列。在一个实施例中,该CD28跨膜结构域包含编码SEQ ID NO:6的氨基酸序列的核酸序列。在另一个实施例中,该CD28跨膜结构域包含SEQ ID NO:6的氨基酸序列。

[0088] 细胞内(细胞质)结构域。本发明的工程化的T细胞的细胞内(细胞质)结构域可提供免疫细胞的至少一种正常效应功能的激活。T细胞的效应子功能例如可以是包括细胞因子的分泌的细胞溶解活性或辅助活性。

[0089] 应当认识到的是,适合的细胞内分子包括(即包含)但不限于CD28、CD28T、CD8、OX-40、4-1BB/CD137、CD2、CD7、CD27、CD30、CD40、程序性死亡-1(PD-1)、T细胞可诱导共刺激因子(ICOS)、淋巴细胞功能相关抗原-1(LFA-1、CD1-1a/CD18)、CD3γ、CD3δ、CD3ε、CD247、CD276(B7-H3)、LIGHT、(TNFSF14)、NKG2C、Igα(CD79a)、DAP-10、Fcγ受体、MHC 1类分子、TNF受体蛋白、免疫球蛋白、细胞因子受体、整合素、信号传导淋巴细胞活化分子(SLAM蛋白)、激活型NK细胞受体、BTLA、Toll配体受体、ICAM-1、B7-H3、CDS、ICAM-1、GITR、BAFFR、LIGHT、HVEM(LIGHTR)、KIRDS2、SLAMF7、NKp80(KLRF1)、NKp44、NKp30、NKp46、CD19、CD4、CD8α、CD8β、IL-2Rβ、IL-2R γ、IL-7Rα、ITGA4、VLA1、CD49a、ITGA4、IA4、CD49D、ITGA6、VLA-6、CD49f、ITGAD、CD1 1d、ITGAE、CD103、ITGAL、CD1 1a、LFA-1、ITGAM、CD1 1b、ITGAX、CD1 1c、ITGB1、CD29、ITGB2、CD18、LFA-1、ITGB7、NKG2D、TNFR2、TRANCE/RANKL、DNAM1(CD226)、SLAMF4(CD244、2B4)、CD84、CD96(Tactile)、CEACAM1、CRT AM、Ly9(CD229)、CD160(BY55)、PSGL1、CD100(SEMA4D)、CD69、SLAMF6(NTB-A、Ly108)、SLAM(SLAMF1、CD150、IPO-3)、BLAME(SLAMF8)、SELPLG(CD162)、LTBR、LAT、GADS、SLP-76、PAG/Cbp、CD19a、与CD83特异性结合的配体、或其任何组合。

[0090] 在优选的实施例中,所述CAR的细胞质结构域可被设计为包含CD3ξ信号传导结构域本身,或与在本发明的CAR上下文中有用的任何其他所希望的一个或多个细胞质结构域组合。例如,CAR的细胞质结构域可以包含CD3ξ链部分和共刺激信号传导区。

[0091] 本发明的CAR的细胞质信号传导部分内的细胞质信号传导序列可以按随机或指定的顺序相互连接。

[0092] 在一个优选的实施例中,该细胞质结构域被设计为包含CD3ξ的信号传导结构域和CD28的信号传导结构域。在另一个实施例中,该细胞质结构域被设计为包含CD3ξ的信号传导结构域和4-1BB的信号传导结构域,其中该细胞质CD28包含在SEQ ID NO:15中列出的核

酸序列和在SEQ ID NO:16中列出的氨基酸序列。。在另一个实施例中,本发明的CAR中的细胞质结构域被设计为包括CD28和CD3ξ的一部分,其中该细胞质CD28包含在SEQ ID NO:7中列出的核酸序列和在SEQ ID NO:8中列出的氨基酸序列。CD3ξ核酸序列在SEQ ID NO:9中列出,且氨基酸序列在SEQ ID NO:8中列出。

[0093] 应当认识到的是,根据本发明的CAR的一个优选的取向包括抗原结合结构域(诸如scFv)与共刺激结构域和激活结构域串联。共刺激结构域可包含细胞外部分、跨膜部分和细胞内部分的一个或多个。进一步应当认识到的是可以串联使用多个共刺激结构域。

[0094] 在一些实施例中,提供的核酸包括可操作地连接到编码抗原结合分子的第一多核苷酸的启动子、至少一个共刺激分子和激活结构域。

[0095] 在一些实施例中,该核酸构建体包含在病毒载体中。在一些实施例中,该病毒载体选自下组,该组由以下组成:逆转录病毒载体、小鼠白血病病毒载体、SFG载体、腺病毒载体、慢病毒载体、腺相关病毒(AAV)载体、疱疹病毒载体和牛痘病毒载体。在一些实施例中,该核酸包含在质粒中。

[0096] 本发明进一步涉及编码嵌合抗原受体的分离的多核苷酸以及包含该多核苷酸的载体。任何本领域已知的载体都适用于本发明。在一些实施例中,该载体是病毒载体。在一些实施例中,该载体是逆转录病毒载体(诸如pMSVG1)、DNA载体、小鼠白血病病毒载体、SFG载体、质粒、RNA载体、腺病毒载体、杆状病毒载体、Epstein Barr病毒载体、乳头多瘤空泡病毒载体、牛痘病毒载体、单纯疱疹病毒载体、腺病毒相关载体(AAV)、慢病毒载体(诸如pGAR)、或其任何组合。pGAR载体图谱如图6所示。pGAR序列如下:

[0097]
CTGACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGC
GTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCT
TTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGG
GTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTAGGGTGATGG

TTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCC
ACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCG
GTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCTATTGGTTAAAAAATG
AGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGCTTACAATTT
GCCATTCGCCATTCAGGCTGCGCAACTGTTGGGAAGGGCGATCGGTGCGGGCCTCTT
CGCTATTACGCCAGCTGGCGAAAGGGGGATGTGCTGCAAGGCGATTAAGTTGGGTA
ACGCCAGGGTTTTCCCAGTCACGACGTTGTAAAACGACGGCCAGTGAATTGTAATAC
GACTCACTATAGGGCGACCCGGGGATGGCGCGCCAGTAATCAATTACGGGGTCATT

AGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGCC
TGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCAT
AGTAACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAAC
TGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGT
CAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTT
TCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACCATGCTGATGCGGTTT
TGGCAGTACATCAATGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTC
CACCCCATTGACGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCA
AAATGTCGTAACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTG
[0098] GGAGGTCTATATAAGCAGAGCTGGTTTAGTGAACCGGGGTCTCTCTGGTTAGACCAG
ATCTGAGCCTGGGAGCTCTCTGGCTAACTAGGGAACCCACTGCTTAAGCCTCAATAA
AGCTTGCCTTGAGTGCTTCAAGTAGTGTGTGCCCGTCTGTTGTGTGACTCTGGTAACT
AGAGATCCCTCAGACCCTTTTAGTCAGTGTGGAAAATCTCTAGCAGTGGCGCCCGAA
CAGGGACTTGAAAGCGAAAGGGAAACCAGAGGAGCTCTCTCGACGCAGGACTCGGC
TTGCTGAAGCGCGCACGGCAAGAGGCGAGGGGCGGCGACTGGTGAGTACGCCAAAA
ATTTTGACTAGCGGAGGCTAGAAGGAGAGAGATGGGTGCGAGAGCGTCAGTATTAA
GCGGGGGAGAATTAGATCGCGATGGGAAAAAATTCGGTTAAGGCCAGGGGGAAAG
AAAAAATATAAATTAAAACATATAGTATGGGCAAGCAGGGAGCTAGAACGATTCGC
AGTTAATCCTGGCCTGTTAGAAACATCAGAAGGCTGTAGACAAATACTGGGACAGC
TACAACCATCCCTTCAGACAGGATCAGAAGAACTTAGATCATTATATAATACAGTAG
CAACCCTCTATTGTGTGCATCAAAGGATAGAGATAAAAGACACCAAGGAAGCTTTA
GACAAGATAGAGGAAGAGCAAAACAAAAGTAAGACCACCGCACAGCAAGCCGCCG
CTGATCTTCAGACCTGGAGGAGGAGATATGAGGGACAATTGGAGAAGTGAATTATA
TAAATATAAAGTAGTAAAAATTGAACCATTAGGAGTAGCACCCACCAAGGCAAAGA
GAAGAGTGGTGCAGAGAGAAAAAAGAGCAGTGGGAATAGGAGCTTTGTTCCTTGGG
TTCTTGGGAGCAGCAGGAAGCACTATGGGCGCAGCGTCAATGACGCTGACGGTACA
GGCCAGACAATTATTGTCTGGTATAGTGCAGCAGCAGAACAATTTGCTGAGGGCTAT
TGAGGCGCAACAGCATCTGTTGCAACTCACAGTCTGGGGCATCAAGCAGCTCCAGG

[0099]

CAAGAATCCTGGCTGTGGAAAGATACCTAAAGGATCAACAGCTCCTGGGGATTTGG
GGTTGCTCTGGAAAACTCATTTGCACCACTGCTGTGCCTTGGAATGCTAGTTGGAGT
AATAAATCTCTGGAACAGATTTGGAATCACACGACCTGGATGGAGTGGGACAGAGA
AATTAACAATTACACAAGCTTAATACACTCCTTAATTGAAGAATCGCAAAACCAGCA
AGAAAAGAATGAACAAGAATTATTGGAATTAGATAAATGGGCAAGTTTGTGGAATT
GGTTTAACATAACAAATTGGCTGTGGTATATAAAATTATTCATAATGATAGTAGGAG
GCTTGGTAGGTTTAAGAATAGTTTTTGCTGTACTTTCTATAGTGAATAGAGTTAGGCA
GGGATATTCACCATTATCGTTTCAGACCCACCTCCCAACCCCGAGGGGACCCGACAG
GCCCGAAGGAATAGAAGAAGAAGGTGGAGAGAGAGACAGAGACAGATCCATTCGA
TTAGTGAACGGATCTCGACGGTATCGGTTAACTTTTAAAAGAAAAGGGGGGATTGG
GGGGTACAGTGCAGGGGAAAGAATAGTAGACATAATAGCAACAGACATACAAACT
AAAGAATTACAAAAACAAATTACAAAATTCAAAATTTTATCGCGATCGCGGAATGA
AAGACCCCACCTGTAGGTTTGGCAAGCTAGCTTAAGTAACGCCATTTTGCAAGGCAT
GGAAAATACATAACTGAGAATAGAGAAGTTCAGATCAAGGTTAGGAACAGAGAGA
CAGCAGAATATGGGCCAAACAGGATATCTGTGGTAAGCAGTTCCTGCCCCGGCTCA
GGGCCAAGAACAGATGGTCCCCAGATGCGGTCCCGCCCTCAGCAGTTTCTAGAGAA
CCATCAGATGTTTCCAGGGTGCCCCAAGGACCTGAAAATGACCCTGTGCCTTATTTG
AACTAACCAATCAGTTCGCTTCTCGCTTCTGTTCGCGCGCTTCTGCTCCCCGAGCTCA
ATAAAAGAGCCCACAACCCCTCACTCGGCGCGCCAGTCCTTCGAAGTAGATCTTTGT
CGATCCTACCATCCACTCGACACACCCGCCAGCGGCCGCTGCCAAGCTTCCGAGCTC
TCGAATTAATTCACGGTACCCACCATGGCCTAGGGAGACTAGTCGAATCGATATCAA
CCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTT
TTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTAT
GGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTGCTGTCTCTTTATGAGGAGTTGT
GGCCCGTTGTCAGGCAACGTGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCA
CTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCT
CCCTATTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGC
TCGGCTGTTGGGCACTGACAATTCCGTGGTGTTGTCGGGGAAGCTGACGTCCTTTTC
ATGGCTGCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTC
CCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTGCGGC
CTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTCGGATCTCCCTTTGGGCCGCCTC
CCCGCCTGGTTAATTAAAGTACCTTTAAGACCAATGACTTACAAGGCAGCTGTAGAT
CTTAGCCACTTTTTAAAAGAAAAGGGGGGACTGGAAGGGCGAATTCACTCCCAACG
AAGACAAGATCTGCTTTTTGCTTGTACTGGGTCTCTCTGGTTAGACCAGATCTGAGCC
TGGGAGCTCTCTGGCTAACTAGGGAACCCACTGCTTAAGCCTCAATAAAGCTTGCCT
TGAGTGCTTCAAGTAGTGTGTGCCCGTCTGTTGTGTGACTCTGGTAACTAGAGATCC

CTCAGACCCTTTTAGTCAGTGTGGAAAATCTCTAGCAGGCATGCCAGACATGATAAG

ATACATTGATGAGTTTGGACAAACCACAACTAGAATGCAGTGAAAAAAATGCTTTAT

TTGTGAAATTTGTGATGCTATTGCTTTATTTGTAACCATTATAAGCTGCAATAAACAA

GTTAACAACAACAATTGCATTCATTTTATGTTTCAGGTTCAGGGGGAGGTGTGGGAG

GTTTTTTGGCGCGCCATCGTCGAGGTTCCCTTTAGTGAGGGTTAATTGCGAGCTTGGC

GTAATCATGGTCATAGCTGTTTCCTGTGTGAAATTGTTATCCGCTCACAATTCCACAC

AACATACGAGCCGGAAGCATAAAGTGTAAAGCCTGGGGTGCCTAATGAGTGAGCTA

ACTCACATTAATTGCGTTGCGCTCACTGCCCGCTTTCCAGTCGGGAAACCTGTCGTGC

CAGCTGCATTAATGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGGGCG

CTCTTCCGCTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGCTGCGGCGAGCG

GTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAACGC

AGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCC

GCGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATCGA

CGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGTTTCC

CCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCGGATACCTG

TCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTCATAGCTCACGCTGTAGGTATC

TCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGGGCTGTGTGCACGAACCCCCCGTTC

[0100] AGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTGAGTCCAACCCGGTAAGAC

ACGACTTATCGCCACTGGCAGCAGCCACTGGTAACAGGATTAGCAGAGCGAGGTAT

GTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAACTACGGCTACACTAGAAG

AACAGTATTTGGTATCTGCGCTCTGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGG

TAGCTCTTGATCCGGCAAACAAACCACCGCTGGTAGCGGTGGTTTTTTTGTTTGCAA

GCAGCAGATTACGCGCAGAAAAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTAC

GGGGTCTGACGCTCAGTGGAACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATT

ATCAAAAAGGATCTTCACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAATCAAT

CTAAAGTATATATGAGTAAACTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGC

ACCTATCTCAGCGATCTGTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTG

TAGATAACTACGATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCG

CGAGACCCACGCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAAG

GGCCGAGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTG

TTGCCGGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGC

CATTGCTACAGGCATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCTCC

GGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCAAAAAAGCGGTT

AGCTCCTTCGGTCCTCCGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGTTATCACTC

ATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCATGCCATCCGTAAGATGCTTTT

[0101] CTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAATAGTGTATGCGGCGACCGA GTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGCCACATAGCAGAACTTTAA AAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGAAAACTCTCAAGGATCTTACCGC TGTTGAGATCCAGTTCGATGTAACCCACTCGTGCACCCAACTGATCTTCAGCATCTTT TACTTTCACCAGCGTTTCTGGGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAA AGGGAATAAGGGCGACACGGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATT ATTGAAGCATTTATCAGGGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTA GAAAAATAAACAAATAGGGGTTCCGCGCACATTTCCCCGAAAAGTGCCAC (SEQ ID NO:147)

[0102] 适合的另外的示例性载体包括,例如pBABE-puro、pBABE-neo largeTcDNA、pBABE-hygro-hTERT、pMKO.1GFP、MSCV-IRES-GFP、pMSCV PIG(Puro IRES GFP空质粒)、pMSCV-loxp-dsRed-loxp-eGFP-Puro-WPRE、MSCV IRES荧光素酶、pMIG、MDH1-PGK-GFP_2.0、TtRMPVIR、pMSCV-IRES-mCherry FP、pRetroX GFP T2A Cre、pRXTN、pLncEXP、和pLXIN-Luc。

[0103] 在一些实施例中,该工程化的细胞是T细胞、肿瘤浸润淋巴细胞(TIL)、NK细胞、表达TCR的细胞、树突状细胞或NK-T细胞。在一些实施例中,该细胞获得自外周血或由外周血制备。在一些实施例中,该细胞获得自外周血单核细胞(PBMC)或由外周血单核细胞(PBMC)制备。在一些实施例中,该细胞获得自骨髓或由骨髓制备。在一些实施例中,该细胞获得自脐带血或由脐带血制备。在一些实施例中,该细胞是人细胞。在一些实施例中,使用选自下组的方法用核酸载体转染或转导细胞,该组由以下组成:电穿孔、声孔效应、生物弹射(例如基因枪)、脂质转染、聚合物转染、纳米颗粒或复合物。

[0104] 在一些实施例中,嵌合抗原受体在包含本申请的核酸的工程化的免疫细胞中表达。在一些实施例中,本应用的这些嵌合抗原受体可以包括,(i)抗原结合分子(诸如scFv)、(ii)跨膜区、和(iii)T细胞活化分子或区域。

[0105] 抗原结合分子

[0106] 抗原结合分子在本发明的范围内。

[0107] 如本文所用的“抗原结合分子”意指任何结合特定靶抗原的蛋白质。在本申请中,指定的靶抗原是STEAP1蛋白或其片段。抗原结合分子包括但不限于抗体及其结合部分,例如免疫功能片段。肽体(即,包含肽结合结构域的Fc融合分子)是合适的抗原结合分子的另一个实例。

[0108] 在一些实施例中,该抗原结合分子结合至肿瘤细胞上的抗原。在一些实施例中,该抗原结合分子结合至与过度增殖性疾病有关的细胞上的抗原或结合至病毒或细菌抗原。在某些实施例中,该抗原结合分子结合至STEAP1。在另外的实施例中,该抗原结合分子是抗体或其片段,包括其一个或多个互补决定区(CDR)。在另外的实施例中,该抗原结合分子是单链可变片段(scFv)。

[0109] 术语抗原结合分子的“免疫功能片段”(或“片段”)是包含抗体的部分(无论该部分如何获得或合成)抗原结合分子的一种,所述抗体至少缺乏一些存在于全长链上的氨基酸,但仍有能力与抗原特异性结合。此类片段具有生物活性,因为它们与靶抗原结合,并可以与其他抗原结合分子(包括完整的抗体)竞争结合到给定的表位。在一些实施例中,该片段是中和片段。在一些实施例中,该片段可以阻断或降低STEAP1的活性。在一个方面,此类片段

将保留存在于全长轻链或重链中的至少一个CDR,并且在一些实施例中将包含单个重链和/或轻链或其部分。这些片段可以通过重组DNA技术产生,或可以通过抗原结合分子(包括完整的抗体)的酶促或化学裂解产生。

[0110] 免疫功能免疫球蛋白片段包括,但不限于:scFv片段、Fab片段(Fab'、$F(ab')_2$等)、一个或多个CDR、双抗体(与轻链可变结构域相同的多肽上的重链可变结构域,经由短肽接头,该接头太短,不允许同一链上的两个结构域之间的配对)、结构域抗体、和单链抗体。这些片段可以来自任何哺乳动物,包括但不限于人、小鼠、大鼠、骆驼或兔。如本领域普通技术人员所理解的,抗原结合分子可以包括非蛋白成分。

[0111] 抗原结合分子的变体也在本发明的范围内,如可变轻链和/或可变重链,每条链与本文所述序列的氨基酸序列具有至少70%-80%、80%-85%、85%-90%、90%-95%、95%-97%、97%-99%或99%以上的同一性。在一些情况下,此类分子包括至少一个重链和一个轻链,而在其他情况下,这些变体形式含有两个相同的轻链和两个相同的重链(或其子部分)。本领域技术人员将能够使用熟知的技术如在此所陈述的确定抗原结合分子的合适的变体。在某些实施例中,本领域技术人员可以鉴定分子的合适的区域,这些区域通过靶向被认为对活性不重要的区域在不破坏活性的情况下被改变。

[0112] 在某些实施例中,抗原结合分子的多肽结构基于抗体,包括但不限于:单克隆抗体、双特异性抗体、迷你抗体、结构域抗体、合成抗体(有时在本文中称为"抗体模拟物")、嵌合抗体、人源化抗体、人抗体、抗体融合(有时在本文中称为"抗体缀合物")、及分别地其片段。在一些实施例中,该抗原结合分子包含亲和多聚体(avimer)或由亲和多聚体组成。

[0113] 在一些实施例中,单独施用STEAP1的抗原结合分子。在其他实施例中,作为CAR、TCR、或其他免疫细胞的部分施用STEAP1的抗原结合分子。在此类免疫细胞中,STEAP1的抗原分子可以在相同启动子区域或单独的启动子的控制下。在某些实施例中,编码蛋白质制剂的基因和/或STEAP1的抗原结合分子可以位于分开的载体中。

[0114] 本发明进一步提供了包含STEAP1的抗原结合分子以及药学上可接受的稀释剂、载体、增溶剂、乳化剂、防腐剂和/或佐剂的药物组合物。在某些实施例中,药物组合物将包括多于一种的不同的STEAP1抗原结合分子。在某些实施例中,药物组合物将包括多于一种的STEAP1的抗原结合分子,其中STEAP1抗原结合分子结合多于一个表位。在一些实施例中,各抗原结合分子不会相互竞争结合STEAP1。

[0115] 在其他实施例中,可以选择用于胃肠外递送、用于吸入或用于通过消化道(如口服)递送的药物组合物。此类药物可接受的组合物的制备是在本领域技术人员的能力范围内的。在某些实施例中,使用缓冲液将组合物维持在生理pH值或稍低的pH值,通常pH值范围为从约5至约8。在某些实施例中,当考虑进行胃肠外施用时,治疗组合物可以采用无热原的、胃肠外可接受的水溶液的形式,该水溶液包含在药学上可接受的载体中(含有或不含有另外的治疗剂)的所希望的STEAP1抗原结合分子。在某些实施例中,用于胃肠外注射的载体是无菌蒸馏水,STEAP1的抗原结合分子处于其中,含有或不含有至少一种另外的治疗剂,配制为无菌、等渗溶液,适当保存。在某些实施例中,该制备可以涉及用可以提供用于产物(该产物可以经由储库注射来递送)的受控或持续释放的聚合物化合物(诸如聚乳酸或聚乙醇酸)、珠粒或脂质体配制所希望分子。在某些实施例中,可植入药物递送装置可用于引入所希望的分子。

[0116] 在一些实施例中,该抗原结合分子用作诊断或验证工具。该抗原结合分子可用于测定样品和/或受试者中存在的STEAP1的量。在一些实施例中,诊断性抗原结合分子不被中和。在一些实施例中,在测定试剂盒和/或用于检测哺乳动物组织或细胞中的STEAP1的方法中使用或提供本文披露的抗原结合分子,以筛选/诊断与STEAP1水平变化相关的疾病或障碍。所述试剂盒可包含结合STEAP1的抗原结合分子,以及指示抗原结合分子与STEAP1结合的手段和任选的STEAP1蛋白(如果存在)水平。

[0117] 鉴于下面的定义和描述,将进一步理解抗原结合分子。

[0118] "Fc"区包含两个重链片段,其包含抗体的CH1和CH2结构域。两个重链片段通过两个或更多个二硫键并通过CH3结构域的疏水相互作用保持在一起。

[0119] "Fab片段"包含一条轻链和一条重链的CH1和可变区。Fab分子的重链不能与另一个重链分子形成二硫键。"Fab'片段"包含一条轻链和一条重链的一部分,该部分含有VH结构域和CH1结构域以及CH1和CH2结构域之间的区域,使得可以在两个Fab'片段的两个重链之间形成链间二硫键以形成$F(ab')_2$分子。"$F(ab')_2$片段"含有两条轻链和两条重链,该两条重链含有CH1和CH2结构域之间的恒定区的一部分,使得在两条重链之间形成链间二硫键。因此,$F(ab')_2$片段由两个Fab'片段构成,这两个Fab'片段通过两条重链之间的二硫键保持在一起。

[0120] "Fv区"包含来自重链和轻链的可变区,但缺少恒定区。

[0121] "单链可变片段"("scFv",也称为"单链抗体")是指Fv分子,其中重链和轻链可变区通过柔性接头连接形成单个多肽链,其形成抗原结合区。参见PCT申请WO 88/01649和美国专利号4,946,778和5,260,203,这些披露内容通过引用以其全文结合在此。

[0122] "二价抗原结合分子"包含两个抗原结合位点。在一些情况下,两个结合位点具有相同的抗原特异性。二价抗原结合分子可以是双特异性的。"多特异性抗原结合分子"是靶向多于一种抗原或表位的抗原结合分子。"双特异性"、"双重特异性"或"双功能性"抗原结合分子分别是具有两种不同抗原结合位点的杂合抗原结合分子或抗体。双特异性抗原结合分子的两个结合位点将结合两种不同的表位,其可以存在于相同或不同的蛋白质靶标上。

[0123] 当解离常数(K_d)为约1 x 10^{-7}M时,抗原结合分子被说成"特异性结合"其靶抗原。当K_d为1-5x10^{-9}M时,抗原结合分子以"高亲和力"特异性结合抗原,并且当K_d为1-5x10^{-10}M时,抗原结合分子以"非常高亲和力"特异性结合抗原。在一个实施例中,抗原结合分子具有K_d为10^{-9}M。在一个实施例中,解离速率为<1x10^{-5}。在其他实施例中,该抗原结合分子将与人STEAP1结合,K_d为约10^{-7}M和10^{-13}M之间,并且在又另一个实施例中,该抗原结合分子将以1.0-5x10^{-10}的K_d结合。

[0124] 当抗原结合分子与一个靶标结合比与第二个靶标结合更紧密时,称其是"选择性的"。

[0125] 术语"抗体"是指任何同种型的完整免疫球蛋白,或其可以与完整抗体竞争地特异性结合靶抗原的片段并且包括例如嵌合的、人源化的、完全人的和双特异性的抗体。"抗体"是如本文所定义的抗原结合分子的种类。完整抗体通常包含至少两条全长重链和两条全长轻链,但在一些情况下可包括更少的链,例如天然存在于骆驼科动物中的抗体,其可仅包含重链。抗体可以仅来自单一来源,或者可以是嵌合的,即,抗体的不同部分可以来自如下文进一步描述的两种不同的抗体。抗原结合分子、抗体或结合片段可以在杂交瘤中通过重组

DNA技术或通过完整抗体的酶促或化学切割产生。除非另有说明,否则术语“抗体”除了包含两条全长重链和两条全长轻链的抗体外,还包括其衍生物、变体、片段和突变蛋白,其实例如下所述。此外,除非明确排除,抗体包括:单克隆抗体、双特异性抗体、迷你抗体、结构域抗体、合成抗体(有时在本文中称为“抗体模拟物”)、嵌合抗体、人源化抗体、人类抗体、抗体融合(有时在本文中称为“抗体缀合物”)、及分别地其片段。

[0126] 可变区通常表现出通过3个高变区(即“CDR”)连接的相对保守的框架区(FR)的相同的一般结构。来自每对的两条链的CDR通常通过框架区对齐,这可以使得能够结合特定的表位。从N末端到C末端,轻链和重链可变区通常包含结构域FR1、CDR1、FR2、CDR2、FR3、CDR3和FR4。按照惯例,重链中的CDR区通常称为HC CDR1、CDR2和CDR3。轻链中的CDR区通常称为LC CDR1、CDR2和CDR3。每个结构域的氨基酸的分配通常根据Kabat的定义(Seqs ofProteins of Immunological Interest[感兴趣的免疫蛋白质的序列](NIH,Bethesda,MD(1987和1991)),或Chothia(J.Mol.Biol.[分子生物学杂志],196:901-917(1987);Chothia等人,Nature[自然],342:878-883(1989))。可以采用各种分析方法来鉴定或估计CDR区,不仅包括Kabat或Chothia,还包括AbM定义。

[0127] 术语“轻链”包括全长轻链及其片段,该片段具有足够的可变区序列赋予结合特异性。全长轻链包括可变区结构域V_L和恒定区结构域C_L。轻链的可变区结构域位于多肽的氨基末端。轻链包括κ链和λ链。

[0128] 术语“重链”包括全长重链及其片段,该片段具有足够的可变区序列赋予结合特异性。全长重链包括可变区结构域V_H和三个恒定区结构域CH1、CH2和CH3。V_H结构域位于多肽的氨基末端,C_H结构域位于羧基末端,CH3最接近多肽的羧基末端。重链可以是任何同种型,包括IgG(包括IgG1、IgG2、IgG3和IgG4亚型)、IgA(包括IgA1和IgA2亚型)、IgM和IgE。

[0129] 术语“可变区”或“可变结构域”是指抗体的轻链和/或重链的一部分,通常包括重链中氨基末端大约120至130个氨基酸和轻链中大约100至110个氨基末端氨基酸。抗体的可变区通常确定特定抗体对其靶标的特异性。

[0130] 可变性在整个抗体的可变结构域中并不均匀分布;它集中在重链可变区和轻链可变区中的每一个的子结构域中。这些子结构域称为“超变区”或“互补决定区”(CDR)。可变结构域的更保守的(即非超变)部分称为“框架”区(FRM或FR),并且为三维空间中的六个CDR提供支架以形成抗原结合表面。天然存在的重链和轻链的可变结构域各自包含四个FRM区(FR1、FR2、FR3和FR4),这四个FRM区主要采用β-片层构型,通过三个超变区连接,这三个超变区形成连接β-片层结构的环,并且在一些情况下形成β-片层结构的一部分。每条链中的超变区通过FRM紧密靠近在一起,并与来自另一条链的超变区一起有助于抗原结合位点的形成(参见Kabat等人,上述引文)。

[0131] 术语“CDR”及其复数“CDR”是指其中三个构成轻链可变区(CDR-L1、CDR-L2和CDR-L3)的结合特征并且三个构成重链可变区(CDRH1、CDR-H2和CDR-H3)的结合特征的互补决定区。CDR含有大部分负责抗体与抗原特异性相互作用的残基,并且因此有助于抗体分子的功能活性:它们是抗原特异性的主要决定因素。

[0132] 准确定义的CDR边界和长度受制于不同的分类和编号系统。因此,CDR可以通过Kabat、Chothia、contact或任何其他边界定义(包括本文所述的编号系统)来引用。尽管有不同的边界,但这些系统中的每一者在构成可变序列内所谓的“超变区”的方面具有一定程

度的重叠。因此,根据这些系统的CDR定义可以在相对于相邻框架区的长度和边界区域中不同。参见,例如Kabat(一种基于跨物种序列变异性的方法)、Chothia(一种基于抗原-抗体复合物的晶体学研究的方法)和/或MacCallum(Kabat等人,上述引文;Chothia等人,J.MoI.Biol[分子生物学杂志],1987,196:901-917;和MacCallum等人,J.MoI.Biol[分子生物学杂志],1996,262:732)。表征抗原结合位点的还另一标准是由牛津大学分子公司(Oxfbrd Molecular)的AbM抗体建模软件使用的AbM定义。参见例如,Protein Sequence and Structure Analysis of Antibody Variable Domains[抗体可变结构域的蛋白质序列和结构分析]在:Antibody Engineering Lab Manual[抗体工程实验室手册](编辑:Duebel,S.和Kontermann,R.,施普林格出版社(Springer-Verlag),海德尔堡)。就两种残基鉴定技术定义重叠区而非相同区而言,可以将它们组合以定义杂合CDR。然而,根据所谓的Kabat系统进行编号是优选的。

[0133] 典型地,CDR形成可以分类为规范结构的环结构。术语“规范结构”是指由抗原结合(CDR)环所采用的主链构象。从比较结构研究中,已经发现六个抗原结合环中的五个仅具有有限的可用构象组库。每个规范结构可以通过多肽骨架的扭转角来表征。因此,抗体之间的对应环可能具有非常相似的三维结构,但环的大多数部分具有高的氨基酸序列可变性(Chothia和Lesk,J.MoI.Biol.[分子生物学杂志],1987,196:901;Chothia等人,Nature[自然],1989,342:877;Martin和Thornton,J.MoI.Biol[分子生物学杂志],1996,263:800)。此外,所采用的环结构与其周围的氨基酸序列之间存在关系。特定规范类别的构象由环的长度和位于环内关键位置以及保守框架内(即,环外)的氨基酸残基决定。因此,可以基于这些关键氨基酸残基的存在对特定的规范类别进行分配。

[0134] 术语“规范结构”还可以包括关于抗体的线性序列的考虑因素,例如,如通过Kabat(Kabat等人,上述引文)编目的。Kabat编号方案(系统)是以一致方式对抗体可变结构域的氨基酸残基进行编号的广泛采用的标准,并且是本发明应用的优选方案,也如本文其他地方所提及。另外的结构考虑因素也可以用于确定抗体的规范结构。例如,Kabat编号未完全反映的那些差异可以通过Chothia等人的编号系统来描述,并且/或者通过其他技术(例如结晶学和二维或三维计算建模)来揭示。因此,可以将给定的抗体序列置于规范的类别中,该类别尤其允许鉴定适当的基础结构(chassis)序列(例如,基于在文库中包括多种规范结构的期望)。文献中描述了抗体氨基酸序列的Kabat编号和如由Chothia等人,上述引文所述的结构考虑因素以及其参与解释抗体结构的规范方面。不同类别免疫球蛋白的亚单位结构和三维构型在本领域中是熟知的。关于抗体结构的综述,参见Antibodies:A Laboratory Manual[抗体:实验室手册],Cold Spring Harbor Laboratory[冷泉港实验室],Harlow等人编辑,1988。

[0135] 轻链的CDR3以及特别是重链的CDR3可以构成轻链可变区和重链可变区内抗原结合中最重要的决定簇。在一些抗体构建体中,重链CDR3似乎构成抗原与抗体之间主要的接触区域。其中单独改变CDR3的体外选择方案可以用于改变抗体的结合特性或确定哪些残基有助于抗原的结合。因此,CDR3典型地是抗体结合位点内分子多样性的最大来源。例如,H3可以短至两个氨基酸残基或多于26个氨基酸。

[0136] 术语“中和”分别指抗原结合分子、scFv或抗体,其结合配体并防止或降低该配体的生物学效应。这可以通过例如直接阻断配体上的结合位点或通过结合配体并通过间接方

式(例如配体中的结构或能量改变)改变配体结合的能力来完成。在一些实施例中,该术语还可以表示抗原结合分子,其阻止与其结合的蛋白质发挥生物学功能。

[0137] 术语“靶标”或“抗原”是指能够被抗原结合分子结合的分子或分子的一部分。在某些实施例中,靶标可具有一个或多个表位。

[0138] 当用于竞争相同表位的抗原结合分子的上下文中时,术语“竞争”意指抗原结合分子之间的竞争,该竞争通过其中待测试的抗原结合分子(例如,其抗体或免疫功能片段)阻止或抑制(例如,降低)参考抗原结合分子与抗原的特异性结合的测定而确定。许多类型的竞争性结合测定可用于确定一种抗原结合分子是否与另一种抗原结合分子竞争,例如:固相直接或间接放射免疫测定(RIA)、固相直接或间接酶免疫测定(EIA),夹心法竞争测定(Stahli等人,1983,Methods in Enzymology[酶学方法]9:242-253);固相直接生物素-抗生物素蛋白EIA(Kirkland等人,1986,J.Immunol.[免疫学杂志]137:3614-3619)、固相直接标记测定、固相直接标记夹心法测定(Harlow和Lane,1988,Antibodies,A Laboratory Manual,Cold Spring Harbor Press[抗体,实验室手册,冷泉港出版社]);使用1-125标记固相直接标记RIA(Morel等人,1988,Molec.Immunol.[分子免疫学]25:7-15);固相直接生物素-抗生物素蛋白EIA(Cheung,等人,1990,Virology[病毒学]176:546-552);和直接标记的RIA(Moldenhauer等人,1990,Scand.J.Immunol.[斯堪的纳维亚免疫学杂志]32:77-82)。术语“表位”包括能够被抗原结合分子结合的任何决定簇,例如本发明的scFv、抗体或免疫细胞。表位是靶向抗原的抗原结合分子结合的该抗原的区域,并且当该抗原是蛋白质时,其包括直接接触抗原结合分子的特定氨基酸。

[0139] 如本文所用,术语“标记”或“标记的”是指掺入可检测标记物,例如通过掺入放射性标记的氨基酸或附着于生物素部分的多肽(其可以通过标记的抗生物素蛋白(例如含有荧光标志物或可通过光学或比色法检测的酶活性的链霉亲和素)检测)。在某些实施例中,标记或标志物也可以是治疗性的。标记多肽和糖蛋白的各种方法是本领域已知的并且可以使用。

[0140] 根据本发明,本文可以包括开-关或其他类型的控制转换技术。这些技术可以使用二聚化结构域和此类结构域二聚化的任选的活化剂。这些技术包括例如Wu等人,Science[科学]2014350(6258)utilizing FKBP/Rapalog dimerization systems in certain cells[在某些细胞中使用FKBP/Rapalog二聚化系统]描述的那些技术,其内容通过引用以其整体结合在此。另外的二聚化技术描述于例如Fegan等人Chem.Rev.[化学评论]2010,110,3315-3336以及美国专利号5,830,462;5,834,266;5,869,337;和6,165,787,其内容也通过引用以其整体结合在此。另外的二聚化对可包括环孢菌素-A/亲环蛋白受体、雌激素/雌激素受体(任选使用他莫昔芬)、糖皮质激素/糖皮质激素受体、四环素/四环素受体、维生素D/维生素D受体。二聚化技术的其他实例可以在例如WO 2014/127261、WO 2015/090229、US 2014/0286987、US 2015/0266973、US 2016/0046700、美国专利号8,486,693、US 2014/0171649、和US 2012/0130076中找到,其内容通过引用以其整体进一步结合在此。

[0141] 治疗方法

[0142] 使用过继性免疫疗法,天然T细胞可以(i)从患者体内中移除、(ii)基因工程化以表达与至少一种肿瘤抗原结合的嵌合抗原受体(CAR)、(iii)离体扩增为更大的工程化T细胞群体、以及(iv)重新引入患者体内。参见例如美国专利号7,741,465、和6,319,494,

Eshhar等人(Cancer Immunol[癌症免疫学],同上);Krause等人(同上);Finney等人(同上)。在将工程化的T细胞重新引入患者体内后,它们介导针对表达肿瘤抗原的细胞的免疫应答。参见例如Krause等人,J.Exp.Med.[实验医学杂志],第188卷,第4期,1998(619-626)。该免疫应答包括T细胞分泌IL-2和其他细胞因子,识别肿瘤抗原的T细胞的克隆扩增,以及T细胞介导的阳性靶细胞的特异性杀伤。参见Hombach等人,Journal ofImmun.[免疫学杂志]167:6123-6131(2001)。

[0143] 在一些方面,本发明因此包括治疗或预防与患者中不希望的和/或升高的STEAP1水平相关的病症的方法,该方法包括向有需要的患者施用有效量的至少一种本文披露的分离的抗原结合分子、CAR、或TCR。

[0144] 提供了用于治疗疾病或障碍(包括癌症)的方法。在一些实施例中,本发明涉及在受试者中产生T细胞介导的免疫应答,包括向受试者施用有效量的本申请的工程化的免疫细胞。在一些实施例中,T细胞介导的免疫应答直接针对靶细胞或细胞。在一些实施例中,该工程化的免疫细胞包含嵌合抗原受体(CAR)、或T细胞受体(TCR)。在一些实施例中,该靶细胞是肿瘤细胞。在一些方面,本发明包括治疗或预防恶性肿瘤的方法,所述方法包括向有需要的受试者施用有效量的至少一种本文所述的分离的抗原结合分子。在一些方面,本发明包括治疗或预防恶性肿瘤的方法,所述方法包括向有需要的受试者施用有效量的至少一种免疫细胞,其中该免疫细胞包含至少一种如本文所述的嵌合抗原受体、T细胞受体和/或分离的抗原结合分子。

[0145] 在一些方面,本发明包括药物组合物,其包含至少一种如本文所述的抗原结合分子和药学上可接受的赋形剂。在一些实施例中,该药物组合物进一步包含另外的活性剂。

[0146] 本发明的抗原结合分子、CAR、TCR、免疫细胞等可用于治疗表达STEAP1的疾病,包括但不限于:前列腺癌,且在一个优选的实施例中,转移性去势抵抗性前列腺癌。

[0147] 应当认识到的是,$CAR^+/CAR\text{-}T^+/TCR^+$细胞的靶剂量的范围可以从$1x10^6$-$2x10^{10}$个细胞/kg,优选$2x10^6$个细胞/kg,更优选。应当认识到的是,高于和低于该范围的剂量可能适合于某些受试者,并且适当的剂量水平可以由健康护理提供者根据需要确定。另外,根据本发明可以提供多剂量的细胞。

[0148] 还提供了用于减小受试者中肿瘤大小的方法,该方法包括向受试者施用本发明的工程化的细胞,其中该细胞包含嵌合抗原受体、T细胞受体、或基于T细胞受体的嵌合抗原受体(其包含与肿瘤上的抗原结合的抗原结合分子)。在一些实施例中,该受试者患有实体瘤或血液恶性肿瘤,例如淋巴瘤或白血病。在一些实施例中,将该工程化的细胞递送至瘤床。在一些实施例中,该癌症存在于受试者的骨髓中。

[0149] 在一些实施例中,该工程化的细胞是自体T细胞。在一些实施例中,该工程化的细胞是同种异体T细胞。在一些实施例中,该工程化的细胞是异源T细胞。在一些实施例中,本申请的工程化的细胞在体内转染或转导。在其他实施例中,该工程化的细胞离体转染或转导。

[0150] 该方法可以进一步包括施用一种或多种化学治疗剂。在某些实施例中,该化学治疗剂是淋巴细胞耗尽(预调节)化学治疗剂。有益的预调节治疗方案以及相关的有益生物标志物描述于美国临时专利申请62/262,143和62/167,750中,其通过引用整体并入本文。这些描述了例如调节需要T细胞疗法的患者的方法,该方法包括向患者施用指定的有益剂量

的环磷酰胺(200mg/m^2/天和2000mg/m^2/天之间)和特定剂量的氟达拉滨(20mg/m^2/天和900mg/m^2/天之间)。优选的剂量方案包括治疗患者,包括每天向患者施用约500mg/m^2/天的环磷酰胺和约60mg/m^2/天的氟达拉滨,持续3天,然后向患者施用治疗有效量的工程化的T细胞。

[0151] 在其他实施例中,抗原结合分子、转导的(或以其他方式工程化的)细胞(例如CAR或TCR)和化学治疗剂各自以有效量施用以治疗受试者的疾病或病症。

[0152] 在某些实施例中,本文披露的包含表达CAR的免疫效应细胞的组合物可与任意数量的化学治疗剂联合施用。化学治疗剂的实例包括烷基化剂,诸如噻替哌和环磷酰胺(CYTOXAN™);烷基磺酸酯,例如白消安、英丙舒凡(improsulfan)和哌泊舒凡(piposulfan);氮丙啶,例如苯佐替哌(benzodopa)、卡波醌、美妥替哌(meturedopa)和乌瑞替哌(uredopa);乙撑亚胺和甲基蜜胺(methylamelamine),包括六甲蜜胺、三乙撑蜜胺、三乙撑磷酰胺、三乙撑硫代磷酰胺(triethylenethiophosphaoramide)和三羟甲基蜜胺(trimethylolomelamine);氮芥,例如苯丁酸氮芥、萘氮芥、氯磷酰胺(cholophosphamide)、雌氮芥、异环磷酰胺、二氯甲基二乙胺、盐酸甲氧氮芥(mechlorethamine oxide hydrochloride)、美法仑、新恩比兴(novembichin)、苯芥胆甾醇(phenesterine)、泼尼莫司汀、曲磷胺、尿嘧啶氮芥;亚硝基脲,例如卡莫司汀、氯脲霉素、福莫司汀、洛莫司汀、尼莫司汀、雷莫司汀;抗生素,诸如阿克拉霉素(aclacinomysin)、放线菌素、安曲霉素(authramycin)、重氮丝氨酸、博来霉素、放线菌素(cactinomycin)、卡奇霉素(calicheamicin)、卡柔比星(carabicin)、洋红霉素(caminomycin)、嗜癌菌素、色霉素、更生霉素、道诺霉素、地托比星(detorubicin)、6-重氮-5-氧代-L-正亮氨酸、多柔比星、表柔比星、依索比星、伊达比星、麻西罗霉素、丝裂霉素、霉酚酸、诺加霉素、橄榄霉素、培洛霉素、泊非霉素(potfiromycin)、嘌呤霉素、三铁阿霉素、罗多比星、链黑菌素、链脲霉素、杀结核菌素、乌苯美司、净司他丁、佐柔比星;抗代谢药,例如甲氨蝶呤和5-氟尿嘧啶(5-FU);叶酸类似物,例如二甲叶酸(denopterin)、甲氨蝶呤、蝶罗呤、三甲曲沙;嘌呤类似物,例如氟达拉滨、6-巯嘌呤、硫咪嘌呤、硫鸟嘌呤;嘧啶类似物,诸如安西他滨、阿扎胞苷、6-氮杂尿苷、卡莫氟、阿糖胞苷、二脱氧尿苷、去氧氟尿苷、依诺他滨、氟尿苷、5-FU;雄激素,诸如卡鲁睾酮、屈他雄酮丙酸酯、环硫雄醇、美雄烷、睾内酯;抗肾上腺药,例如氨鲁米特、米托坦、曲洛司坦;叶酸补充剂,例如亚叶酸(frolinic acid);醋葡醛内酯;醛磷酰胺糖苷;氨基乙酰丙酸;安吖啶;倍曲布西(bestrabucil);比生群;依达曲沙(edatraxate);地磷酰胺(defofamine);秋水仙胺;地吖醌(diaziquone);依氟鸟氨酸(elformithine);依利醋铵;依托格鲁;硝酸镓;羟基脲;香菇多糖;氯尼达明;米托胍腙(mitoguazone);米托蒽醌;莫哌达醇;硝氨丙吖啶(nitracrine);喷司他丁;蛋氨氮芥(phenamet);吡柔比星;鬼臼酸(podophyllinic acid);2-乙基酰肼;丙卡巴肼;PSK®;丙亚胺;西佐喃;锗螺胺;细交链孢菌酮酸;三亚胺醌;2,2',2"-三氯三乙胺;乌拉坦(urethan);长春地辛;达卡巴嗪;甘露莫司汀;二溴甘露醇;二溴卫矛醇;哌泊溴烷;加赛特辛(gacytosine);阿拉伯糖苷("Ara-C");环磷酰胺;噻替派;紫杉烷,例如紫杉醇(TAXOL™,百时美施贵宝公司(Bristol-Myers Squibb))和多西他赛(doxetaxel)(TAXOTERE®,罗纳普朗克公司(Rhone-Poulenc Rorer));苯丁酸氮芥;吉西他滨;6-硫鸟嘌呤;巯嘌呤;甲氨蝶呤;铂类似物,例如顺铂和卡

铂;长春碱;铂;依托泊苷(VP-16);异环磷酰胺;丝裂霉素C;米托蒽醌;长春新碱;长春瑞滨;诺维本;诺安托(novantrone);替尼泊苷;道诺霉素;氨基蝶呤;希罗达(xeloda);伊班膦酸盐;CPT-11;拓扑异构酶抑制剂RFS2000;二氟甲基鸟氨酸(DMFO);视黄酸衍生物诸如Targretin™(蓓萨罗丁)、Panretin™、(阿利维A酸);ONTAK™(地尼白介素);埃斯波霉素(esperamicin);卡培他滨;以及上述任何一种的药学上可接受的盐、酸或衍生物。该定义中还包括用于调控或抑制激素对肿瘤的作用的抗激素剂,诸如抗雌激素剂,包括例如,他莫昔芬、雷洛西芬(raloxifene)、芳香化酶抑制性4(5)-咪唑、4-羟基他莫昔芬、曲沃昔芬、雷洛昔芬(keoxifene)、LY117018、奥那司酮和托瑞米芬(法乐通);和抗雄激素药,例如氟他胺、尼鲁米特、比卡鲁胺、亮丙瑞林和戈舍瑞林;以及上述任何一种的药学上可接受的盐、酸或衍生物。在适当的情况下也施用化学治疗剂的组合,包括但不限于CHOP(即环磷酰胺(Cytoxan®))、多柔比星(羟基多柔比星)、长春新碱(Oncovin®)、和泼尼松。

[0153] 在一些实施例中,该化学治疗剂在施用工程化的细胞或核酸的同一时间或一周内施用。在其他实施例中,该化学治疗剂在施用工程化的细胞或核酸后的1至4周或1周至1个月、1周至2个月、1周至3个月、1周至6个月、1周至9个月或1周至12个月施用。在其他实施例中,该化学治疗剂在施用细胞或核酸之前至少1个月施用。在一些实施例中,该方法进一步包括施用两种或更多种化学治疗剂。

[0154] 多种另外的治疗剂可以与本文所述的组合物结合使用。例如,潜在有用的另外的治疗剂包括PD-1抑制剂,例如纳武单抗(Opdivo®)、兰洛利珠单抗(Keytruda®)、兰洛利珠单抗、匹地利珠单抗、和阿特利珠单抗,和CTLA-4抑制剂,例如易普利姆玛(Yervoy®)。

[0155] 适合与本发明组合使用的另外的治疗剂包括但不限于:醋酸阿比特龙、阿帕鲁胺(apalutamide)、比卡鲁胺(bicalutamide)、卡巴紫杉醇(cabazitaxel)、康士得(casodex)(比卡鲁胺(bicalutamide))、地加瑞克(degarelix)、多西紫杉醇(docetaxel)、恩扎鲁胺(enzalutamide)、Erleada®(阿帕鲁胺(apalutamide))、氟他胺(flutamide)、醋酸戈舍瑞林(goserelin acetate)、Jevtana®(卡巴紫杉醇(cabazitaxel))、醋酸亮丙瑞林(leuprolide acetate)、Lupron®(醋酸亮丙瑞林)、Lupron Depot(醋酸亮丙瑞林)、Lupron Depot-Ped(醋酸亮丙瑞林)、盐酸米托蒽醌(mitoxantrone hydrochloride)、Nilandron®(尼鲁米特(nilutamide))、尼鲁米特、Provenge®(西普鲁塞(Sipuleucel-T))、二氯化镭223、西普鲁塞、泰素帝(taxotere)(多西紫杉醇)、亮丙瑞林(Viadur)(醋酸亮丙瑞林)、Xofigo(二氯化镭223)、安可坦(Xtandi)(恩扎鲁胺(enzalutamide))、诺雷德(Zoladex)(醋酸戈舍瑞林(goserelin acetate))、或Zytiga(醋酸阿比特龙)。

[0156] 在另外的实施例中,包含含有CAR的免疫的组合物可以与抗炎剂一起施用。抗炎剂或药物包括但不限于类固醇和糖皮质激素(包括倍他米松、布地奈德、地塞米松、醋酸氢化可的松、氢化可的松、氢化可的松、甲基强的松龙、泼尼松龙、泼尼松、曲安奈德)、非甾体类抗炎药(NSAIDS)(包括阿司匹林、布洛芬、萘普生、甲氨蝶呤、柳氮磺胺吡啶、来氟米特、抗TNF药物、环磷酰胺和霉酚酸酯。示例性NSAID包括布洛芬、萘普生、萘普生钠、Cox-2抑制剂和唾液酸盐。示例性镇痛药包括对乙酰氨基酚、羟考酮、盐酸丙氧芬的曲马多。示例性糖皮质激素包括可的松、地塞米松、氢化可的松、甲基强的松龙、泼尼松龙或泼尼松。示例性生物

应答调节剂包括直接针对细胞表面标志物(例如,CD4、CD5等)的分子,细胞因子抑制剂例如TNF拮抗剂(例如依那西普(ENBREL®)、阿达木单抗(HUMIRA®)和英夫利昔单抗(REMICADE®)),趋化因子抑制剂和粘附分子抑制剂。生物应答调节剂包括单克隆抗体以及重组形式的分子。示例性DMARD包括咪唑硫嘌呤、环磷酰胺、环孢菌素、甲氨蝶呤、青霉胺、来氟米特、柳氮磺胺吡啶、羟化氯喹、金(口服(金诺芬)和肌内)和米诺环素。

[0157] 在某些实施例中,本文所述的组合物与细胞因子结合施用。如本文所用,"细胞因子"意指由一个细胞群释放的蛋白质,其作为细胞间介质作用于另外细胞。细胞因子的实例是淋巴因子、单核因子和传统的多肽激素。细胞因子中包括生长激素,如人生长激素,N-甲硫氨酰人生长激素和牛生长激素;甲状旁腺激素;甲状腺素;胰岛素;胰岛素原;松弛素;松弛素原;糖蛋白激素,如促卵泡激素(FSH)、促甲状腺激素(TSH)和促黄体激素(LH);肝脏生长因子(HGF);纤维母细胞生长因子(FGF);催乳素;胎盘催乳素;苗勒抑制物质;小鼠促性腺激素相关肽;抑制素;激活素;血管内皮生长因子;整合素;血小板生成素(TPO);神经生长因子(NGFs)如NGF-β;血小板生长因子;转化生长因子(TGFs)如TGF-α和TGF-β;胰岛素生长因子I和II;促红细胞生成素(EPO);骨诱导因子;干扰素如干扰素-α、β、和-γ;集落刺激因子(CSF)如巨噬细胞-CSF(M-CSF);粒细胞-巨噬细胞-CSF(GM-CSF);和粒细胞-CSF(G-CSF);白介素(IL)如IL-1、IL-1α、IL-2、IL-3、IL-4、IL-5、IL-6、IL-7、IL-8、IL-9、IL-10、IL-11、IL-12;IL-15,肿瘤坏死因子如TNF-α或TNF-β;和其他多肽因子,包括LIF和kit配体(KL)。如本文所用,术语细胞因子包括来自天然来源或来自重组细胞培养物的蛋白质,以及天然序列细胞因子的生物活性等同物。

[0158] 在一些方面,本发明包括以小于100pM的K_d与STEAP1结合的抗原结合分子。在一些实施例中,该抗原结合分子以小于10pM的K_d结合。在其他实施例中,该抗原结合分子以小于5pM的K_d结合。

[0159] 制备方法

[0160] 可以使用多种已知技术制备根据本发明的多核苷酸、多肽、载体、抗原结合分子、免疫细胞、组合物等。

[0161] 在本文所述的免疫细胞的体外操作或遗传修饰之前,可以从受试者获得细胞。在一些实施例中,免疫细胞包含T细胞。T细胞可以从许多来源获得,包括外周血单核细胞(PBMC)、骨髓、淋巴结组织、脐带血、胸腺组织、来自感染部位的组织、腹水、胸腔积液、脾组织和肿瘤。在某些实施例中,T细胞可以使用本领域技术人员已知的任何数量的技术(例如FICOLL™分离)从受试者收集的血液单位获得。细胞可优选地通过单采从个体的循环血液中获得。单采产物通常含有淋巴细胞(包括T细胞)、单核细胞、粒细胞、B细胞、其他有核白细胞、红细胞、和血小板。在某些实施例中,可以洗涤通过单采收集的细胞以除去血浆级分,并将其置于合适的缓冲液或培养基中用于后续处理。可以用PBS洗涤细胞。应当认识到的是,可以使用洗涤步骤,例如通过使用半自动流通式离心机-例如Cobe™ 2991细胞处理器,Baxter CytoMate™等。洗涤后,可将细胞重悬于多种生物相容性缓冲液或含有或不含缓冲液的其它盐水溶液中。在某些实施例中,可以去除单采样品的不希望的组分。

[0162] 在某些实施例中,通过裂解红细胞和耗尽单核细胞从PBMC分离T细胞,例如,使用通过PERCOLL™梯度的离心。可以通过本领域已知的阳性或阴性选择技术进一步分离T细胞

的特定子群,如CD28+、CD4+、$CD8^+$、$CD45RA^+$和$CD45RO^+$T细胞。例如,通过阴性选择富集T细胞群可以用针对阴性选择的细胞特有的表面标志物的抗体组合来实现。本文使用的一种方法是经由阴性磁免疫粘附或流式细胞术进行细胞分选和/或选择,其使用针对阴性选择的细胞上存在的细胞表面标志物的单克隆抗体混合物。例如,为了通过阴性选择富集$CD4^+$细胞,单克隆抗体混合物通常包括针对CD14、CD20、CD11b、CD16、HLA-DR和CD8的抗体。流式细胞术和细胞分选也可用于分离用于本发明的目的细胞群。

[0163] 可以直接使用PBMC用于使用本文所述的方法在免疫细胞情况下的遗传修饰(如CAR或TCR)。在某些实施例中,在分离PBMC后,可以进一步分离T淋巴细胞,并且可以在遗传修饰和/或扩增之前或之后将细胞毒性和辅助性T淋巴细胞分选为初始、记忆和效应T细胞亚群。

[0164] 在一些实施例中,通过鉴定与这些类型的$CD8^+$细胞中的每一种相关的细胞表面抗原,将$CD8^+$细胞进一步分选为初始、中枢记忆和效应细胞。在一些实施例中,中枢记忆T细胞的表型标志物的表达包括CD45RO、CD62L、CCR7、CD28、CD3和CD127,并且对于颗粒酶B是阴性的。在一些实施例中,中枢记忆T细胞是$CD45RO^+$、$CD62L^+$、$CD8^+$T细胞。在一些实施例中,效应T细胞对CD62L、CCR7、CD28和CD127是阴性的,对于颗粒酶B和穿孔素是阳性的。在某些实施例中,$CD4^+$T细胞进一步分选为亚群。例如,通过鉴定具有细胞表面抗原的细胞群,可以将$CD4^+$T辅助性细胞分选为初始、中枢记忆和效应细胞。

[0165] 免疫细胞,例如T细胞,可以在使用已知方法分离后进行遗传修饰,或者免疫细胞可以在进行遗传修饰之前在体外活化和扩增(或在祖细胞的情况下分化)。在另一个实施例中,免疫细胞,例如T细胞,用本文所述的嵌合抗原受体进行遗传修饰(例如,用包含一个或多个编码CAR的核苷酸序列的病毒载体转导),然后在体外活化和/或扩增。用于激活和扩增T细胞的方法是本领域已知的,并且描述于例如美国专利号6,905,874;和美国专利号6,867,041;美国专利号6,797,514;和PCT WO 2012/079000,其内容通过引用整体并入本文。通常,此类方法包括在具有适当细胞因子例如IL-2的培养基中使PBMC或分离的T细胞与刺激剂和共刺激剂接触,例如抗CD3和抗CD28抗体,通常附着于珠子或其他表面。附着于相同珠子的抗CD3和抗CD28抗体充当“替代”抗原呈递细胞(APC)。一个例子是Dynabeads®系统,一种用于人T细胞生理激活的CD3/CD28激活剂/刺激系统。

[0166] 在其他实施例中,可以用饲养细胞和适当的抗体和细胞因子使用例如如下所述的那些的方法激活和刺激T细胞增殖:美国专利号6,040,177;美国专利号5,827,642;和WO 2012129514,其内容通过引用整体并入本文。

[0167] 用于制备本发明的构建体和工程化的免疫细胞的某些方法描述于PCT申请PCT/US15/14520中,其内容通过引用整体并入本文。制备构建体和细胞的另外的方法可以在美国临时专利申请号62/244036中发现,其内容通过引用整体并入本文。

[0168] 应当认识到的是,PBMC可以进一步包括其他细胞毒性淋巴细胞,例如NK细胞或NKT细胞。携带如本文披露的嵌合受体的编码序列的表达载体可以引入人供体T细胞、NK细胞或NKT细胞的群。携带表达载体的成功转导的T细胞可以使用流式细胞术分选以分离CD3阳性T细胞,然后除了使用抗CD3抗体和IL-2或本文其他地方描述的本领域已知的其他方法的细胞激活外还进一步繁殖以增加这些表达CAR的T细胞的数量。使用标准程序用于冷藏保存表达CAR的T细胞,用于储存和/或制备用于在人受试者中使用。在一个实施例中,T细胞的体外

转导、培养和/或扩增在不存在非人动物衍生产物(例如胎牛血清(fetal calf serum)和胎牛血清(fetal bovine serum))的情况下进行。

[0169] 为了克隆多核苷酸,可以将载体导入宿主细胞(分离的宿主细胞)中以允许载体自身复制,从而扩增其中含有的多核苷酸的拷贝。克隆载体可含有序列组分,这些序列组分通常包括但不限于复制起点、启动子序列、转录起始序列、增强子序列和选择标志物。这些元件可以由本领域普通技术人员适当选择。例如,可以选择复制起点以促进载体在宿主细胞中的自主复制。

[0170] 在某些实施例中,本披露提供了含有本文提供的载体的分离的宿主细胞。含有载体的宿主细胞可用于表达或克隆载体中含有的多核苷酸。合适的宿主细胞可包括但不限于原核细胞、真菌细胞、酵母细胞或更高等真核细胞,如哺乳动物细胞。用于此目的的合适的原核细胞包括但不限于真细菌,例如革兰氏阴性或革兰氏阳性生物,例如肠杆菌科(Enterobacteriaceae)像埃希氏杆菌属(Escherichia),例如大肠杆菌(E.coli)、肠杆菌属(Enterobacter)、欧文氏菌属(Erwinia)、克雷白氏杆菌属(Klebsiella)、变形杆菌属(Proteus)、沙门氏菌属(Salmonella),例如鼠伤寒沙门氏菌(Salmonella typhimurium)、沙雷氏菌属(Serratia),例如如粘质沙雷氏菌(Serratia marcescans)、和志贺氏杆菌(Shigella)、还有芽孢杆菌属(Bacillus),例如枯草芽孢杆菌(B.subtilis)和地衣芽孢杆菌(B.licheniformis)、假单胞菌属(Pseudomonas)(如铜绿假单胞菌)、和链霉菌属(Streptomyces)。

[0171] 可以使用本领域已知的任何合适的方法将载体引入宿主细胞,这些方法包括但不限于DEAE-葡聚糖介导的递送、磷酸钙沉淀法、阳离子脂质介导的递送、脂质体介导的转染、电穿孔、基因枪法、受体介导的基因递送、由聚赖氨酸、组蛋白、壳聚糖和肽介导的递送。用于表达目的载体的细胞的转染和转化的标准方法是本领域熟知的。在另外的实施例中,不同表达载体的混合物可用于遗传修饰供体免疫效应细胞群,其中每个载体编码如本文披露的不同CAR。得到的转导的免疫效应细胞形成混合的工程化的细胞群,其中一部分工程化的细胞表达多于一种不同的CAR。

[0172] 在一个实施例中,本发明提供了一种储存表达靶向STEAP1蛋白的CAR或TCR的基因工程化的细胞的方法。这涉及冷藏保存免疫细胞,使细胞在解冻后保持活力。表达CAR的一部分免疫细胞可以通过本领域已知的方法冷藏保存,以提供此类细胞的永久来源,用于将来治疗患有恶性肿瘤的患者。需要时,冷藏保存的转化免疫细胞可以解冻、生长和扩增以获得更多此类细胞。

[0173] 如本文所用,“冷藏保存”是指通过冷却至零下的温度来保存细胞,例如(通常)77开尔文或-196℃(液氮的沸点)。低温保护剂通常在零下的温度下使用,以保护细胞免受因低温冷冻或升温至室温而受到损坏。冷藏保存剂和最佳冷却速率可以防止细胞损伤。根据本发明可以使用的低温保护剂包括但不限于:二甲亚砜(DMSO)(Lovelock&Bishop,Nature[自然](1959);183:1394-1395;Ashwood-Smith,Nature[自然](1961);190:1204-1205)、甘油、聚乙烯吡咯烷酮(Rinfret,Ann.N.Y.Acad.Sci.[纽约科学院年报](1960);85:576)、和聚乙二醇(Sloviter&Ravdin,Nature[自然](1962);196:48)。优选冷却速度为1℃-3℃/分钟。

[0174] 术语“基本上纯的”用于表示给定组分以高水平存在。该组分理想地是组合物中存

在的主要组分。优选其以多于30％、多于50％、多于75％、多于90％、或甚至多于95％的水平存在,所述水平关于正在考虑的总组合物以干重/干重进行确定。以非常高的水平(例如,大于90％、大于95％或大于99％的水平)的该组分可被视为“纯的形式”。本发明的生物活性物质(包括多肽、核酸分子、抗原结合分子、部分)可以以基本上不含一种或多种污染物的形式提供,该物质可能以其他方式与之相关。当组合物实质上不含给定的污染物时,污染物将处于很低的水平(例如,以如上所述的干重/干重计小于10％、小于5％或小于1％的水平)。

[0175] 在一些实施例中,通过首先从其培养基中收获细胞,然后将细胞洗涤并浓缩在适于施用的培养基和容器系统(“药学上可接受的”载体)中以治疗有效量来配制细胞。合适的输注介质可以是任何等渗培养基配制品,通常是生理盐水,Normosol™ R(Abbott)或Plasma-Lyte™ A(Baxter),但也可以使用5％葡萄糖水溶液或林格氏乳酸盐。输注介质可以补充人血清白蛋白。

[0176] 组合物中所希望的治疗量的细胞通常为至少2个细胞(例如,至少1个$CD8^+$中枢记忆T细胞和至少1个$CD4^+$辅助性T细胞亚群)或更通常大于10^2个细胞,并且高达10^6个,多达并且包括10^8或10^9个细胞,并且可以超过10^{10}个细胞。细胞数量取决于组合物所希望的用途,以及其中包含的细胞类型。所希望的细胞的密度通常大于10^6个细胞/ml,并且通常大于10^7个细胞/ml,通常为10^8个细胞/ml或更多。临床相关数量的免疫细胞可以分配到累积等于或超过10^5、10^6、10^7、10^8、10^9、10^{10}、10^{11}、或10^{12}个细胞的多次输注中。在本发明的一些方面,特别是因为所有输注的细胞将被重定向至特定的靶抗原(STEAP1),可以施用较低数量的细胞,范围为10^6个细胞/千克(每个患者10^6-10^{11})。CAR治疗可以在这些范围内的剂量下多次施用。对于在进行治疗的患者,该细胞可以是自体、同种异体或异源的。

[0177] 本发明的表达CAR的细胞群可以单独施用,或作为药物组合物与稀释剂和/或与其他组分如IL-2或其他细胞因子或细胞群组合施用。本发明的药物组合物可包含表达CAR或TCR的细胞群,如本文所述的T细胞,与一种或多种药学上或生理学上可接受的载体、稀释剂或赋形剂的组合。此类组合物可包含缓冲液,例如中性缓冲盐水、磷酸盐缓冲盐水等;碳水化合物,如葡萄糖、甘露糖、蔗糖或葡聚糖、甘露醇;蛋白质;多肽或氨基酸,如甘氨酸;抗氧化剂;螯合剂,如EDTA或谷胱甘肽;佐剂(例如氢氧化铝);和防腐剂。优选将本发明的组合物配制为用于静脉内施用。

[0178] 药物组合物(溶液、悬浮液等)可包括下列中的一种或多种:无菌稀释剂,例如注射用水、盐溶液,优选生理盐水、林格氏溶液、等渗氯化钠、固定油,例如可用作溶剂或悬浮介质的合成的单甘油酯或二甘油酯、聚乙二醇、甘油、丙二醇或其他溶剂;抗菌剂,如苯甲醇或对羟基苯甲酸甲酯;抗氧化剂,如抗坏血酸或亚硫酸氢钠;螯合剂,如乙二胺四乙酸;缓冲剂,如乙酸盐、柠檬酸盐或磷酸盐;以及用于调节张力的试剂,如氯化钠或葡萄糖。胃肠外制剂可以被封装在由玻璃或塑料制成的安瓿、一次性注射器或多剂量小瓶中。可注射药物组合物优选是无菌的。

[0179] 应当认识到的是,通过用自杀基因转导免疫细胞(含有一种或多种CAR或TCR)可以使不良事件最小化。还可能需要将诱导型“开启”或“加速器”开关掺入免疫细胞中。合适的技术包括在用本发明的CAR构建体转导细胞之前、之后或同时使用诱导型胱天蛋白酶-9(美国申请2011/0286980)或胸苷激酶。用于引入自杀基因和/或“开启”开关的另外的方法包括TALENS、锌指、RNAi、siRNA、shRNA、反义技术和本领域已知的其他技术。

[0180] 应理解的是,本文的描述都只是示例性和说明性的,并且不限制如所要求的本发明。在本申请中,除非另外特别说明,单数的使用包括复数。

[0181] 在此使用的章节标题只是出于组织的目的,而不应解释为限制所描述的主题内容。在本申请中所引用的所有文件或文件的部分,包括但不局限于专利、专利申请、论文、书籍、和专著,都特此出于任何目的通过引用将其全部内容清楚地结合在此。如根据本披露使用的,除非另外指明,否则以下术语应当被理解为具有以下含义:

[0182] 在本申请中,"或"的使用意指"和/或",除非另外说明。此外,术语"包括(including)"、以及其他形式如"包括(includes)"和"包括(included)"的使用不是限制性的。同样,术语如"元件"或"组分"涵盖包含一个单位的元件和组分以及包含超过一个亚单位的元件和组分两者,除非另外明确说明。

[0183] 术语"STEAP1活性"包括STEAP1的任何生物学效应。在某些实施例中,STEAP1活性包括STEAP1与底物或受体相互作用或结合的能力。

[0184] 术语"多核苷酸"、"核苷酸"或"核酸"包括单链和双链核苷酸聚合物。包含多核苷酸的核苷酸可以是核糖核苷酸和脱氧核糖核苷酸或任一类型核苷酸的修饰形式。所述修饰包括碱基修饰(例如溴尿嘧啶核苷和肌苷衍生物)、核糖修饰(例如2',3'-双脱氧核糖)和核苷酸间连接修饰(例如硫代磷酸、二硫代磷酸、硒代磷酸、二硒代磷酸、阿尼洛硫代磷酸(phosphoro-anilothioate)、阿尼洛磷酸(phoshoraniladate)和磷酰胺)。

[0185] 术语"寡核苷酸"是指包含200个或更少核苷酸的多核苷酸。寡核苷酸可以是单链或双链的,例如用于构建突变基因。寡核苷酸可以是正义或反义寡核苷酸。寡核苷酸可包括用于检测测定的标记,包括放射性标记、荧光标记、半抗原或抗原标记。寡核苷酸可用作例如PCR引物、克隆引物或杂交探针。

[0186] 术语"控制序列"是指可以影响与其连接的编码序列的表达和加工的多核苷酸序列。此类控制序列的性质可取决于宿主生物体。在具体的实施例中,原核生物的控制序列可包括启动子、核糖体结合位点和转录终止序列。例如,真核生物的控制序列可包括启动子,其包含转录因子、转录增强子序列和转录终止序列的一个或多个识别位点。"控制序列"可包括前导序列(信号肽)和/或融合伴侣序列。

[0187] 如本文所用,"可操作地连接"意指应用该术语的组分处于允许它们在合适条件下实现其固有功能的关系中。

[0188] 术语"载体"意指用于将蛋白质编码信息转移到宿主细胞中的任何分子或实体(例如,核酸、质粒、噬菌体或病毒)。术语"表达载体"或"表达构建体"是指适合转化宿主细胞的载体,并含有指导和/或控制(与宿主细胞结合)一个或多个与其可操作地连接的异源编码区表达的核酸序列。表达构建体可包括但不限于影响或控制转录、翻译的序列,并且如果存在内含子,则影响与其可操作地连接的编码区的RNA剪接。

[0189] 术语"宿主细胞"是指已经用核酸序列转化或能够被转化的细胞,从而表达目的基因。该术语包括亲本细胞的后代,无论后代是否与原始亲本细胞在形态上或遗传构成方面相同,只要存在目的基因即可。

[0190] 术语"转化"是指细胞遗传特性的改变,当细胞被修饰以含有新的DNA或RNA时,则该细胞就被转化了。例如,细胞经由转染、转导或其他技术引入新的遗传材料,由其原始状态进行基因修饰,则该细胞就被转化了。转染或转导后,转化的DNA可以通过物理整合进入

细胞染色体与细胞的DNA重组,或者可以作为一个不被复制的游离元件被暂时维持,或者可以作为质粒独立复制。当转化的DNA随着细胞的分裂而复制时,细胞被认为已经“稳定地转化”了。

[0191] 术语“转染”是指通过细胞吸收外来或外源性DNA。许多转染技术在本领域中是熟知的,并在本文中披露。参见例如Graham等人,1973,Virology[ ]52:456;Sambrook等人,2001,Molecular Cloning:A Laboratory Manual[分子克隆:实验室手册],同上;Davis等人,1986,Basic Methods in Molecular Biology[分子生物学基本方法],思唯尔(Elsevier);Chu等人,1981,Gene[基因]13:197。

[0192] 术语“转导”是指外来DNA经由病毒载体被引入细胞的过程。参见Jones等人,(1998).Genetics:principles and analysis.[遗传学:原理与分析。]波士顿:Jones&Bartlett Publ.[Jones&Bartlett出版社]。

[0193] 术语“多肽”或“蛋白质”是指具有蛋白质的氨基酸序列的大分子,其包括天然序列的一个或多个氨基酸的缺失、添加和/或取代。术语“多肽”和“蛋白质”特别涵盖STEAP1抗原结合分子、抗体或抗原结合蛋白的一个或多个氨基酸被缺失、添加和/或取代的序列。术语“多肽片段”是指与全长天然蛋白质相比具有氨基末端缺失、羧基末端缺失和/或内部缺失的多肽。与天然蛋白质相比,此类片段还可含有修饰的氨基酸。有用的多肽片段包括抗原结合分子的免疫功能片段。有用的片段包括但不限于一个或多个CDR区、重链和/或轻链的可变结构域、抗体链的其他部分的一部分等。

[0194] 术语“分离的”是指(i)不含至少一些通常与其一起被发现的蛋白质,(ii)基本上不含来自相同来源的其他蛋白质,例如来自相同物种,(iii)与至少约50%的在自然界与其相关的多核苷酸、脂质、碳水化合物或其他物质分离,(iv)可操作地与在自然界与其不相关的多肽相关(通过共价或非共价相互作用),或(v)在自然界中不存在。

[0195] 多肽的“变体”(如抗原结合分子或抗体)包含氨基酸序列,其中相对于另一个多肽序列,该氨基酸序列中插入、缺失和/或取代一个或多个氨基酸残基到。变体包括融合蛋白。

[0196] 术语“同一性”意指两个或更多个多肽分子或两个或更多个核酸分子的序列之间的通过比对和比较序列来确定的关系。“百分比同一性”意指比较的分子中氨基酸或核苷酸之间相同残基的百分比,并且是基于比较的最小分子的大小来计算的。在这些计算中,优选通过特定的数学模型或计算机程序(即“算法”)解决的空位比对(如果有的话)。

[0197] 为了计算百分比同一性,被比较的序列通常以给出序列之间最大匹配的方式比对。可用于确定百分比同一性的计算机程序的一个实例是GCG程序包,其包括GAP(Devereux等人,1984,Nucl.Acid Res.[核酸研究]12:387;Genetics Computer Group,University of Wisconsin,Madison,Wis.[遗传学计算机组,威斯康星大学,麦迪逊,威斯康星州])。计算机算法GAP是用来比对其百分比序列同一性待确定的两个多肽或多核苷酸。比对序列以使它们各自的氨基酸或核苷酸达到最佳匹配(提供算法确定的“匹配范围”)。在某些实施例中,本算法使用标准比较矩阵(参见Dayhoff等人,1978,Atlas ofProtein Sequence and Structure[蛋白质序列和结构图谱]5:345-352用于PAM 250比较矩阵;Henikoff等人,1992,Proc.Natl.Acad.Sci.U.S.A.[美国国家科学院院刊]89:10915-10919用于BLOSUM 62比较矩阵)。

[0198] 如本文所用,二十种常规(如天然存在的)氨基酸及其缩写遵循常规用法。参见

Immunology-A Synthesis[免疫学-合成](第2版,Golub和Gren编辑,席娜欧出版公司(Sinauer Assoc.),桑德兰,Mass.(1991)),出于任何目的将其通过引用结合在此。二十种常规氨基酸的立体异构体(如D-氨基酸)、α-,α-二取代氨基酸、N-烷基氨基酸、乳酸等非天然氨基酸以及其他非常规氨基酸也可作为本发明多肽的合适组分。非常规氨基酸的实例包括:4-羟基脯氨酸、γ-羧基谷氨酸、ε-N,N,N-三甲基赖氨酸、e-N-乙酰基赖氨酸、O-磷酸丝氨酸、N-乙酰丝氨酸、N-甲酰基甲硫氨酸、3-甲基组氨酸、5-羟基赖氨酸、σ-N-甲基精氨酸、和其他类似的氨基酸和亚氨基酸(例如,4-羟基脯氨酸)。本文使用的多肽表示法中,按照标准用法和惯例,左手方向是氨基末端方向,右手方向是羧基末端方向。

[0199] 保守氨基酸取代可以涵盖非天然存在的氨基酸残基,这些残基通常是通过化学肽合成而非生物系统合成而掺入。这些包括肽模拟物和氨基酸部分的其他反向或逆向形式。基于共同的侧链特性可以将天然存在的残基分类:

[0200] a)疏水性:正亮氨酸、Met、Ala、Val、Leu、Ile;

[0201] b)中性亲水性:Cys、Ser、Thr、Asn、Gln;

[0202] c)酸性:Asp、Glu;

[0203] d)碱性:His、Lys、Arg;

[0204] e)影响链取向的残基:Gly、Pro;以及

[0205] f)芳香族:Trp、Tyr、Phe。

[0206] 例如,非保守取代可以涉及到用这些类之一的成员交换另一个类中的成员。例如,此类被取代的残基可以被引入至与非人抗体同源的人抗体的区域,或者引入至分子的非同源区域。

[0207] 在改变抗原结合分子、工程化的T细胞的共刺激结构域或激活结构域时,可根据某些实施例考虑氨基酸的亲水指数。根据每种氨基酸的疏水性和荷电特性,确定了其亲水指数。它们是:异亮氨酸(+4.5);缬氨酸(+4.2);亮氨酸(+3.8);苯丙氨酸(+2.8);半胱氨酸/胱氨酸(+2.5);蛋氨酸(+1.9);丙氨酸(+1.8);甘氨酸(-0.4);苏氨酸(-0.7);丝氨酸(-0.8);色氨酸(-0.9);酪氨酸(-1.3);脯氨酸(-1.6);组氨酸(-3.2);谷氨酸(-3.5);谷氨酰胺(-3.5);天冬氨酸(-3.5);天冬酰胺(-3.5);赖氨酸(-3.9);和精氨酸(-4.5)。参见Kyte等人,J.Mol.Biol.[分子生物学杂志],157:105-131(1982)。已知某些氨基酸可以取代具有相似的亲水指数或得分的其他氨基酸,并且仍然保留相似的生物活性。本领域还应理解,可以基于亲水性有效地进行相似氨基酸的取代,特别是在由此产生的生物学功能蛋白质或肽旨在用于如在本发明的情况中的免疫学实施例时。示例性氨基酸取代在表2中列出。

[0208] 表2

[0209]

原始残基	示例性取代	优选的取代
Ala	Val、Leu、Ile	Val
Arg	Lys、Gln、Asn	Lys
Asn	Gln	Gln
Asp	Glu	Glu
Cys	Ser、Ala	Ser
Gln	Asn	Asn
Glu	Asp	Asp
Gly	Pro、Ala	Ala
His	Asn、Gln、Lys、Arg	Arg
Ile	Leu、Val、Met、Ala、Phe、正亮氨酸	Leu
Leu	正亮氨酸、Ile、Val、Met、Ala、Phe	Ile
Lys	Arg、1,4 二氨基-丁酸、	Arg
	Gln、Asn	
Met	Leu、Phe、Ile	Leu
Phe	Leu、Val、Ile、Ala、	Leu
	Tyr	
Pro	Ala	Gly
Ser	Thr、Ala、Cys	Thr
Thr	Ser	Ser
Trp	Tyr、Phe	Tyr

[0210]

Tyr	Trp、Phe、Thr、Ser	Phe
Val	Ile、Met、Leu、Phe、	Leu
	Ala、正亮氨酸	

[0211] 术语“衍生物”意指包括除了氨基酸(或核酸)的插入、缺失或置换以外的化学修饰的分子。在某些实施例中,衍生物包含共价修饰,包括但不限于与聚合物、脂类或其他有机或无机部分的化学键合。在某些实施例中,经化学修饰的抗原结合分子比未经化学修饰的抗原结合分子具有更大的循环半衰期。在一些实施例中,将衍生物抗原结合分子共价修饰使其包括一个或多个水溶性聚合物附着体,包括但不限于聚乙二醇、聚氧乙烯二醇或聚氧丙烯二醇。

[0212] 肽类似物在医药工业中作为非肽类药物被广泛应用,其性质与模板肽类似。这些类型的非肽化合物被称为“肽的模拟物(peptide mimetics)”或“肽模拟物(peptidomimetics)”。Fauchere,J.,Adv.Drug Res.[药物研究前沿],15:29(1986);Veber&Freidinger,TINS[神经科学发展],第392页(1985);以及Evans等人,J.Med.Chem.[药物化学期刊],30:1229(1987),出于任何目的将其通过引用结合在此。

[0213] 术语“治疗有效量”意指确定在哺乳动物体内产生治疗应答的STEAP1抗原结合分子的量。此类治疗有效量是由本领域普通技术人员容易确定的。

[0214] 术语“患者”和“受试者”可互换地使用,并包括人和非人动物受试者,以及那些具有正式诊断的障碍的受试者,那些没有正式确认的障碍的受试者,那些接受医疗救助的受试者,那些有发育障碍风险的受试者等。

[0215] 术语“治疗”和“治疗”包括治疗性治疗、预防性治疗,以及应用于降低受试者罹患障碍或其他风险因素的风险。治疗不需要障碍的完全治愈,并涵盖减少症状或潜在风险因素的实施例。术语“预防”并不要求100%事件消除的可能性。相反,它表示在化合物或方法存在的情况下,事件发生的可能性已经降低。

[0216] 标准技术可用于重组DNA、寡核苷酸合成、以及组织培养和转化(如电穿孔、脂质转染)。酶促反应和纯化技术可以根据制造商的说明书进行,或如本领域中通常所实现或如在此所描述进行的。前述技术和方法一般是根据本领域中众所周知的常规方法并且如本说明书全篇所引用并且论述的不同通用和更特定的参考文献中所描述来进行。参见例如,Sambrook等人,Molecular Cloning:A Laboratory Manual[分子克隆:实验室手册](第2版,冷泉港实验室出版社(Cold Spring Harbor Laboratory Press),冷泉港(Cold Spring Harbor),纽约州(1989)),出于任何目的将其通过引用结合在此。

[0217] 如下序列将进一步说明本发明。

[0218] CD28T DNA细胞外、跨膜、细胞内

CTTGATAATGAAAAGTC

AAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACC

CTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGT

[0219] GGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCT

TCTGGGTTAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGA

ATATGACTCCACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTT

ACGCACCACCTAGAGATTTCGCTGCCTATCGGAGC (SEQ ID NO:1)

[0220] CD28T细胞外、跨膜、细胞内AA：

LDNEKSNGTI IHVKGKHLCP SPLFPGPSKP FWVLVVVGGV

[0221] LACYSLLVTV AFIIFWVRSK RSRLLHSDYM NMTPRRPGPT

RKHYQPYAPP RDFAAYRS (SEQ ID NO:2)

[0222] CD28T DNA-细胞外

CTTGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAA

[0223] GCACCTCTGTCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCA (SEQ ID NO:3)

[0224] CD28T AA-细胞外

[0225] LDNEKSNGTI IHVKGKHLCP SPLFPGPSKP(SEQ ID NO:4)

[0226] CD28 DNA跨膜结构域

[0227] TTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCTTGTTACTCTCTGC

TCGTCACCGTGGCTTTTATAATCTTCTGGGTT (SEQ ID NO:5)

[0228] CD28 AA跨膜结构域：

[0229] FWVLVVVGGV LACYSLLVTV AFIIFWV(SEQ ID NO:6)

[0230] CD28 DNA细胞内结构域：

AGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACT

[0231] CCACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCA

CCTAGAGATTTCGCTGCCTATCGGAGC (SEQ ID NO:7)

[0232] CD28 AA细胞内结构域

[0233] RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS(SEQ ID NO:8)

[0234] CD3ξDNA

AGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGC
CAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTA
TGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCA

[0235] AACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAG
AAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGA
GCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCA
CTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCAC
CTAGG (SEQ ID NO:9)

[0236] CD3ξAA

RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK

[0237] PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTA
TKDTYDALHMQALPPR (SEQ ID NO:10)

[0238] CD28 DNA

ATTGAGGTGATGTATCCACCGCCTTACCTGGATAACGAAAAGAGTAAC

[0239] GGTACCATCATTCACGTGAAAGGTAAACACCTGTGTCCTTCTCCCCTCT
TCCCCGGGCCATCAAAGCCC (SEQ ID NO:11)

[0240] CD28 AA

[0241] IEVMYPPPYL DNEKSNGTII HVKGKHLCPS PLFPGPSKP(SEQ ID NO:12)

[0242] CD8 DNA细胞外&跨膜结构域

GCTGCAGCATTGAGCAACTCAATAATGTATTTTAGTCACTTTGTACCAG
TGTTCTTGCCGGCTAAGCCTACTACCACACCCGCTCCACGGCCACCTAC
CCCAGCTCCTACCATCGCTTCACAGCCTCTGTCCCTGCGCCCAGAGGCT

[0243] TGCCGACCGGCCGCAGGGGGCGCTGTTCATACCAGAGGACTGGATTTC
GCCTGCGATATCTATATCTGGGCACCCCTGGCCGGAACCTGCGGCGTA
CTCCTGCTGTCCCTGGTCATCACGCTCTATTGTAATCACAGGAAC (SEQ
ID NO:13)

[0244] CD8 AA细胞外&跨膜结构域

AAALSNSIMYFSHFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPA

[0245] AGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHRN (SEQ ID
NO:14)

[0246] 4-1BB DNA细胞内结构域

CGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTC

[0247] AAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGG
CTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTG
(SEQ ID NO:15)

[0248] 4-1BB AA细胞内结构域

[0249] RFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL(SEQ ID NO:16)

[0250] 克隆2F3 HC DNA

[0251] CAGGTTCAGCTGCAGCAGTCTGGAGCTGAGATGATGAAGCCTGGGGCC
TCAGTGAAGATATCCTGCAAGGCTACTGGCTACACATTCAGTACCTAC
TGGATAGAGTGGGTAAAGCAGAGGCCTGGACATGGCCTTGAGTGGAT
TGGAGAGATTTTACCTGGAAGTGGTAATACTGACTTCAATGAGAAGTT
CAAGGGCAAGGCCACATTCACTGCAGATACATCCTCCGACACAGCCTA
CATGCATCTCAGCAGCCTGACATCTGAGGACTCTGCCGTCTATTACTGT
ACAAGATGGGGGTACTACGGTACTAGGGGGTACTTCAATGTCTGGGGC
GCAGGGTCCACGGTCACCGTCTCCTCA (SEQ ID NO: 87)

[0252] 克隆2F3 HC AA-CDR加下划线

[0253] QVQLVQSGAEVKKPGASVKVSCKASGYTFSTYWIEWVRQAPGQRLEWM
GEILPGSGNTDFNEKFQGRVTFTADTSSDTAYMELSSLRSEDTAVYYCTR
WGYYGTRGYFNVWGQGTLVTVSS (SEQ ID NO: 88)

[0254] 克隆2F3 HC AA CDR1:TYWIE(SEQ ID NO:89)

[0255] 克隆2F3 HC AA CDR2:EILPGSGNTDFNEKFQG(SEQ ID NO:90)

[0256] 克隆2F3 HC AA CDR3:WGYYGTRGYFNV(SEQ ID NO:91)

[0257] 克隆2F3 LC DNA

[0258] CAAATTGTTCTCACCCAGTCTCCAGCAATCATGTCTGCATCTCCAGGGG
AGAAGGTCACCATAACGTGCAGTGCCAGCTCAAGTGTAAGTTACATGC
ACTGGTTCCAGCAGAAGCCAGGCACTTCTCCCAAACTCTGGATTTATA
GCACCTCCAACCTGGCTTCTGGAGTCCCTGCTCGCTTCAGTGGCAGTG
GATCTGGGACCTCTTACTCTCTCACAATCAGCCGAATGGAGGCTGAAG
ATGCTGCCACTTATTACTGCCAGCAAAGGCGTAGTTTCCCGTACACGTT
CGGAGGGGGGACCAAGCTGGAAATTAAA (SEQ ID NO: 92)

[0259] 克隆2F3 LC AA(CDR加下划线)

[0260] EIVLTQSPATLSLSPGERATLSCRASSSVSYMHWFQQKPGQAPRLLIYSTS
NLASGIPARFSGSGSGTDYTLTISSLEPEDFAVYYCQQRRSFPYTFGQGTKL
EIK (SEQ ID NO: 93)

[0261] 克隆2F3 LC CDR1 AA:RASSSVSYMH(SEQ ID NO:94)

[0262] 克隆2F3 LC CDR2 AA:STSNLAS(SEQ ID NO:95)

[0263] 克隆2F3 LC CDR3 AA:QQRRSFPYT(SEQ ID NO:96)

[0264] 克隆11C2 HC DNA

[0265] CAGATCCAGTTGGTGCAGTCTGGACCTGAACTGAAGAAGCCTGGAGA
GACAGTCAAGATCTCCTGCAAGGCTTCTGGATATACCTTCACAAACTA
TGGAATGAACTGGGTGAAGCAGGCTCCAGGAAAGGGTTTACAGTGGA
TGGGCTGGATGAACACTTATACTGGAGAGCCAACATATGCTGATGACT
TCAAGGGACGGTTTGCCTTCTCTTTGGAAACCTCTGCCAGAACTGTCTC
TTTGGACATCAACGACCTCAAAAATGAGGACACGGCTACATATTTCTG
TACAAGAGCAGGGGGACAACTCAGGCCCGGGGCTATGGACTACTGGG
GTCAAGGAACCTCAGTCACCGTCTCCTCA (SEQ ID NO:97)

[0266] 克隆11C2 HC AA(CDR加下划线)
QLVQSGAEVKKPGATVKISCKASGYTFTNYGMNWVQQAPGQGLEWMG

[0267] WMNTYTGEPTYADKFQGRVTFTLDTSARTVYMELSSLRSEDTAVYFCAR
AGGQLRPGAMDYWGQGTMVTVSS (SEQ ID NO:98)

[0268] 克隆11C2 HC AA CDR1:NYGMN(SEQ ID NO:99)

[0269] 克隆11C2 HC AA CDR2:WMNTYTGEPTYADKFQG(SEQ ID NO:100)

[0270] 克隆11C2 HC AA CDR3:AGGQLRPGAMDY(SEQ ID NO:101)

[0271] 克隆11C2 LC DNA
GACATTGTGCTGACCCAATCTCCAGCTTCTTTGGCTGTGTCTCTAGGG
CAGAGGGCCACCATCTCCTGCAAGGCCAGCCAAAGTGTTGATTATGA
TGGTGATAGTTTTATGAACTGGTACCAACAGAAACCAGGACAGCCAC
CCAAACTCCTCATCTATGTTGCATCCAATCTAGAATCTGGGATCCCAG
ACAGGTTTAGTGGCAGTGGGTCTGGGACAGACTTCACCCTCAACATCC
ATCCTGTGGAGGAGGAGGATGCTGCAACCTATTATTGTCAGCAAAGT
AATGAGGAACCTCCGACGTTCGGTGGAGGCACCAAGCTGGAAATCAA
A (SEQ ID NO: 102)

[0273] 克隆11C2 LC AA(CDR加下划线)
DIVLTQTPLSLSVTPGQPASISCKASQSVDYDGDSFMNWYLQKPGQPPQLL

[0274] IYVASNLESGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSNEEPPTFGQGTKLE
IK (SEQ ID NO: 103)

[0275] 克隆11C2 LC AA CDR1:KASQSVDYDGDSFMN(SEQ ID NO:104)

[0276] 克隆11C2 LC AA CDR2:VASNLES(SEQ ID NO:105)

[0277] 克隆11C2 LHC AA CDR3:QQSNEEPPT(SEQ ID NO:106)

[0278] 克隆1A1 HC DNA

CAGATACAACTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAG
GTCCCTGAGACTCTCCTGTGTAGCGTCTGGATTCACCTTCAAGAACTATGGCATG
CACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATTTGG
[0279] TATGATGGAAGTAATGAATACTATGGAGACCCCGTGAAGGGCCGATTCACCATC
TCCAGAGACAACTCCAAGAACATGTTGTATCTGCAAATGAACAGCCTGAGAGCC
GATGACACGGCTGTGTATTACTGTGCGAGGTCGGGAATAGCAGTGGCTGGGGCC
TTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA (SEQ ID NO: 107)

[0280] 克隆1A1 HC AA(CDR加下划线)

[0281] QVQLVQSGAEVKKPGASVKVSCKASGYTFTTYWMHWVRQAPGQGLEW

[0282] MGEINPSSGRTNYNEKFKTRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAKLGPGPQ
YYAMDYWGQGTMVTVSS (SEQ ID NO: 108)

[0283] 克隆1A1 HC AA CDR1:TYWMH(SEQ ID NO:109)

[0284] 克隆1A1 HC AA CDR2:EINPSSGRTNYNEKFKT(SEQ ID NO:110)

[0285] 克隆1A1 HC AA CDR3:LGPGPQYYAMDY(SEQ ID NO:111)

[0286] 克隆1A1 LC DNA

GAAATTGTGTTGACGCAGTCTCCAGACACCCTGTCTTTGTCTCCAGGG
GAAAAAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAGCTTCTTG
GCCTGGTACCAGCAGAAACCTGGACAGGCTCCCAGTCTCCTCATCTATGTTGCAT
[0287] CCAGAAGGGCCGCTGGCATCCCTGACAGGTTCAGTGGCAGTGGGTCTGGGACAG
ACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGGAATGTTTTACTG
TCAACACTATGGTAGGACACCATTCACTTTCGGCCCTGGGACCAAAGTGGATATC
AAACGA (SEQ ID NO: 112)

[0288] 克隆1A1 LC AA(CDR加下划线)

DIQMTQSPSSLSASVGDRVTITCHASQNINVWLSWYQQKPGKAPKLLIYK

[0289] ASKLHTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGQSYPWTFGQGTKLEIK
(SEQ ID NO:113)

[0290] 克隆1A1 LC AA CDR1:HASQNINVWLS(SEQ ID NO:114)

[0291] 克隆1A1 LC AA CDR2:KASKLHT(SEQ ID NO:115)

[0292] 克隆1A1 LC AA CDR3:QQGQSYPWT(SEQ ID NO:116)

[0293] 克隆7A4 HC DNA

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGC
CTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATATA
CACTGGGTGCGACAGGCCCCTGAACAAGGGCTTGAGTGGATGGGATGGATCAAC

[0294] CCTAACAGTGGTGGCACAAACTATGCACAGAAGTTTCAGGGCAGGGTCACCATG
GCCAGGGACACGTCCATCAGCACAGTTTACATGGACCTGAGCAGGCTGAGATCT
GACGACACGGCCGTGTATTACTGTGCGAGAATACGCGGTGGTAACTCGGTCTTTG
ACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA (SEQ ID NO: 117)

[0295] 克隆7A4 HC AA(CDR加下划线)

QVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDINWVRQATGQGLEWM

[0296] GWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRSEDTAVYYCGRAGYYY
YFGMDVWGQGTTVTVSS (SEQ ID NO: 118)

[0297] 克隆7A4 HC AA CDR1:SYDIN(SEQ ID NO:119)

[0298] 克隆7A4 HC AA CDR2:WMNPNSGNTGYAQKFQG(SEQ ID NO:120)

[0299] 克隆7A4 HC AA CDR3:AGYYYYFGMDV(SEQ ID NO:121)

[0300] 克隆7A4 LC DNA

GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGC
GAGAGGGCCACCATCAACTGCAAGTCCACCCAGAGTATTTTATACACCTCCAAC
AATAAGAACTTCTTAGCTTGGTACCAGCAGAAACCAGGGCAGCCTCCTAAACTG

[0301] CTCATTTCCTGGGCATCTATCCGGGAATCCGGGGTCCCTGACCGATTCAGTGGCA
GCGGGTCTGGGACAGATTTCGCTCTCACCATCAGCAGCCTGCAGGCTGAAGATGT
GGCAGTTTATTACTGTCAACAATATTTTAGTACTATGTTCAGTTTTGGCCAGGGG
ACCAAGCTGGAGATCAAACGA (SEQ ID NO: 122)

[0302] 克隆7A4 LC AA(CDR加下划线)

EIVLTQSPGTLSLSPGERATLSCRAGQSVTSSSFAWYQQKPGQAPRLLIYQ

[0303] TSTRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGGSRSFGQGTKVELKR
(SEQ ID NO: 123)

[0304] 克隆7A4 LC AA CDR1:RAGQSVTSSSFA(SEQ ID NO:124)

[0305] 克隆7A4 LC AA CDR2:QTSTRAT(SEQ ID NO:125)

[0306] 克隆7A4 LC AA CDR3:QQYGGSRS(SEQ ID NO:126)

[0307] 克隆7A5 HC DNA

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACA
GACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTGGTGCATAC
TACTGGACTTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGATTGGGTAC

[0308] ATCCATTACAGTGGGAGCACCTACTCCAACCCGTCCCTCAAGAGTCGAATTACCA
TATCGTTAGACACGTCTAAGAACCAGTTCTCCCTGAAGCTGAACTCTGTGACTGC
CGCGGACACGGCCGTGTATTACTGTGCGAGACAAGAGGACTACGGTGGTTTGTTT
GACTACTGGGGCCAGGGAACCCTGGTCACCGTTTCCTCA (SEQ ID NO: 127)

[0309] 克隆7A5 HC AA(CDR加下划线)

QVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDINWVRQATGQGLEWM

[0310] GWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRSEDTAVYYCGRAGYYY YFGMDVWGQGTTVTVSS (SEQ ID NO: 128)

[0311] 克隆7A5 HC AA CDR1:SYDIN(SEQ ID NO:129)

[0312] 克隆7A5 HC AA CDR2:WMNPNSGNTGYAQKFQG(SEQ ID NO:130)

[0313] 克隆7A5 HC AA CDR3:AGYYYYFGMDV(SEQ ID NO:131)

[0314] 克隆7A5 LC DNA

GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGG GAAAGAATCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTACCACCGACTTAGCCT GGTACCAGCAGATGCCTGGACAGGCTCCCCGGCTCCTCATCTATGATGCTTCCAC

[0315] CAGGGCCACTGGTTTCCCAGCCAGATTCAGTGGCAGTGGGTCTGGGACAGACTTC ACGCTCACCATCAGCAGCCTGCAGGCTGAAGATTTTGCAGTTTATTACTGTCAAC ATTATAAAACCTGGCCTCTCACTTTCGGCGGAGGGACTAAGGTGGAGATCAAAC GA (SEQ ID NO: 132)

[0316] 克隆7A5 LC AA(CDR加下划线)

EIVLTQSPGTLSLSPGERATLSCRAGQSVTSSSLAWYQQKPGQAPRLLIYQ

[0317] TSTRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGGSRAFGQGTKVELKR (SEQ ID NO: 133)

[0318] 克隆7A5 LC AA CDR1:RAGQSVTSSSLA(SEQ ID NO:134)

[0319] 克隆7A5 LC AA CDR2:QTSTRAT(SEQ ID NO:135)

[0320] 克隆7A5 LC AA CDR3:QQYGGSRA(SEQ ID NO:136)

[0321] 克隆14C11 HC DNA

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACA GACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTGGTGCATAC TACTGGACTTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGATTGGGTAC

[0322] ATCCATTACAGTGGGAGCACCTACTCCAACCCGTCCCTCAAGAGTCGAATTACCA TATCGTTAGACACGTCTAAGAACCAGTTCTCCCTGAAGCTGAACTCTGTGACTGC CGCGGACACGGCCGTGTATTACTGTGCGAGACAAGAGGACTACGGTGGTTTGTTT GACTACTGGGGCCAGGGAACCCTGGTCACCGTTTCCTCA (SEQ ID NO: 137)

[0323] 克隆14C11 HC AA(CDR加下划线)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEW

[0324] MGWINPNSGGTNSAQKFQGRVTMTRDTSISTAYMELNRLRSDDTAVYYCARGWLQ TYYFDNWGQGTLVTVSS (SEQ ID NO: 138)

[0325] 克隆14C11 HC AA CDR1:GYYMH(SEQ ID NO:139)

[0326] 克隆14C1 HC AA CDR2:WINPNSGGTNSAQKFQG(SEQ ID NO:140)

[0327] 克隆14C1 HC AA CDR3:GWLQTYYFDN(SEQ ID NO:141)

[0328] 克隆14C11 LC DNA

GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGG
GAAAGAATCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTACCACCGACTTAGCCT
GGTACCAGCAGATGCCTGGACAGGCTCCCCGGCTCCTCATCTATGATGCTTCCAC

[0329] CAGGGCCACTGGTTTCCCAGCCAGATTCAGTGGCAGTGGGTCTGGGACAGACTTC
ACGCTCACCATCAGCAGCCTGCAGGCTGAAGATTTTGCAGTTTATTACTGTCAAC
ATTATAAAACCTGGCCTCTCACTTTCGGCGGAGGGACTAAGGTGGAGATCAAAC
GA (SEQ ID NO: 142)

[0330] 克隆14C11 LC AA(CDR加下划线)

DIVMTQSPDSLAVSLGERATIYCKSSQTVLTSSNNKNFLAWYQQKLGQPP

[0331] KLLISWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAIYYCQHYYTSPLTFGGGT
KVEIKR (SEQ ID NO: 143)

[0332] 克隆14C11 LC AA CDR1:TVLTSSNNKNFLA(SEQ ID NO:144)

[0333] 克隆14C1 LC AA CDR2:WASTRES(SEQ ID NO:145)

[0334] 克隆14C1 LC AA CDR3:QHYYTSPLT(SEQ ID NO:146)

[0335] 构建体S1-2F3-CD28T-CD28-41BB DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAGAAGCCCGGA
GCCAGCGTGAAGGTGAGCTGCAAAGCCAGCGGCTACACCTTCTCCACCTACTGG
ATCGAGTGGGTGAGACAGGCCCCGGACAGAGGCTGGAATGGATGGGAGAGATC
CTGCCCGGCAGCGGCAACACCGACTTCAACGAGAAGTTCCAGGGCAGAGTGACC
TTCACCGCCGATACCAGCAGCGACACCGCCTACATGGAACTGAGCAGCCTGAGA
AGCGAGGATACCGCCGTCTACTACTGCACCAGATGGGGCTACTACGGCACCAGG
GGCTATTTCAACGTGTGGGGCCAGGGAACCCTCGTGACCGTGAGCAGCGGAGGC

[0336] GGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGAGATTGTGCTGACC
CAGAGCCCTGCTACACTGAGCCTGAGCCCCGGCGAGAGAGCCACACTGAGCTGC
AGAGCCAGCAGCAGCGTGAGCTACATGCACTGGTTCCAGCAAAAGCCCGGCCAG
GCCCCTAGGCTGCTGATCTACAGCACATCCAACCTGGCCAGCGGCATCCCTGCCA
GATTCAGCGGTTCTGGCTCCGGCACCGACTACACCCTGACCATCTCCAGCCTGGA
GCCCGAGGACTTTGCCGTGTATTACTGCCAGCAGAGGAGGAGCTTCCCCTACACA
TTCGGCCAGGGCACCAAACTGGAGATCAAGGCCGCTGCCCTTGATAATGAAAAG
TCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTGT
TCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGC

TTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTAGATCCAAAA
GAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCC
CACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATCGG
AGCCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAAC
AGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCC
GCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGAT
CTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCA
ACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGAC
CCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAAT
GAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGA
GAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGC
TACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAA
GAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGA
AGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCC
[0337] GCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCC
TGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTG

GCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCC
TGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTG
TACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGAT
GCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGT
GAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATA
AGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCG
AACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGC
TGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGAT
GGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCC
AAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCG
TGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCG
ACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGT
AGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:17)

[0338] 构建体S1-2F3-CD28T-CD28-41BB AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFSTYWI

[0339] EWVRQAPGQRLEWMGEILPGSGNTDFNEKFQGRVTFTADTSSDTAYMELSSLRSED
TAVYYCTRWGYYGTRGYFNVWGQGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPA

[0340] TLSLSPGERATLSCRASSSVSYMHWFQQKPGQAPRLLIYSTSNLASGIPARFSGSGSGT
DYTLTISSLEPEDFAVYYCQQRRSFPYTFGQGTKLEIKAAALDNEKSNGTIIHVKGKH
LCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTP
RRPGPTRKHYQPYAPPRDFAAYRSRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGC
SCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRD
PEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTAT
KDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRL
LLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSV
TFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRV
CEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRW
ADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPV
VTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:18)

[0341] 构建体S1-2F3-CD28T-CD28 DNA(信号序列以粗体显示)

[0342] ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAGAAGCCCGGA
GCCAGCGTGAAGGTGAGCTGCAAAGCCAGCGGCTACACCTTCTCCACCTACTGG
ATCGAGTGGGTGAGACAGGCCCCCGGACAGAGGCTGGAATGGATGGGAGAGAT
CCTGCCCGGCAGCGGCAACACCGACTTCAACGAGAAGTTCCAGGGCAGAGTGAC
CTTCACCGCCGATACCAGCAGCGACACCGCCTACATGGAACTGAGCAGCCTGAG
AAGCGAGGATACCGCCGTCTACTACTGCACCAGATGGGGCTACTACGGCACCAG
GGGCTATTTCAACGTGTGGGGCCAGGGAACCCTCGTGACCGTGAGCAGCGGAGG
CGGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGAGATTGTGCTGAC
CCAGAGCCCTGCTACACTGAGCCTGAGCCCCGGCGAGAGAGCCACACTGAGCTG
CAGAGCCAGCAGCAGCGTGAGCTACATGCACTGGTTCCAGCAAAAGCCCGGCCA
GGCCCCTAGGCTGCTGATCTACAGCACATCCAACCTGGCCAGCGGCATCCCTGCC
AGATTCAGCGGTTCTGGCTCCGGCACCGACTACACCCTGACCATCTCCAGCCTGG
AGCCCGAGGACTTTGCCGTGTATTACTGCCAGCAGAGGAGGAGCTTCCCCTACAC
ATTCGGCCAGGGCACCAAACTGGAGATCAAGGCCGCTGCCCTTGATAATGAAAA
GTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTG
TTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCG
CTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTAGATCCAAA
AGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCC
CCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATCG
GAGCAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCA
GAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTT

[0343] GGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAA
ACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCT
ATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGT
TTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGC
AAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCT
CTCCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCC
ACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGT
CTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGA
ATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAAC
CAGACAGTCTGTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAG
CCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGC
CCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAG
GACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGC
CTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGAC
GGAACCTACAGCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTC
TGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAG
TGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCA
GACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTG
ATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAG
TCGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGC
AGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA
(SEQ ID NO:19)

[0344] 构建体S1-2F3-CD28T-CD28 AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFSTYWI
EWVRQAPGQRLEWMGEILPGSGNTDFNEKFQGRVTFTADTSSDTAYMELSSLRSED
TAVYYCTRWGYYGTRGYFNVWGQGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPA
TLSLSPGERATLSCRASSSVSYMHWFQQKPGQAPRLLIYSTSNLASGIPARFSGSGSGT
DYTLTISSLEPEDFAVYYCQQRRSFPYTFGQGTKLEIKAAALDNEKSNGTIIHVKGKH

[0345] LCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTP
RRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEY
DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH
DGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAG
ATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGA
NQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQ
DETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCE

[0346] DTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAG
VVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:20)

[0347] 构建体S1-2F3-CD28T-41BB DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAGAAGCCCGGA
GCCAGCGTGAAGGTGAGCTGCAAAGCCAGCGGCTACACCTTCTCCACCTACTGG
ATCGAGTGGGTGAGACAGGCCCCCGGACAGAGGCTGGAATGGATGGGAGAGAT
CCTGCCCGGCAGCGGCAACACCGACTTCAACGAGAAGTTCCAGGGCAGAGTGAC
CTTCACCGCCGATACCAGCAGCGACACCGCCTACATGGAACTGAGCAGCCTGAG
AAGCGAGGATACCGCCGTCTACTACTGCACCAGATGGGGCTACTACGGCACCAG
GGGCTATTTCAACGTGTGGGGCCAGGGAACCCTCGTGACCGTGAGCAGCGGAGG
CGGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGAGATTGTGCTGAC
CCAGAGCCCTGCTACACTGAGCCTGAGCCCCGGCGAGAGAGCCACACTGAGCTG
CAGAGCCAGCAGCAGCGTGAGCTACATGCACTGGTTCCAGCAAAAGCCCGGCCA
GGCCCCTAGGCTGCTGATCTACAGCACATCCAACCTGGCCAGCGGCATCCCTGCC
AGATTCAGCGGTTCTGGCTCCGGCACCGACTACACCCTGACCATCTCCAGCCTGG
AGCCCGAGGACTTTGCCGTGTATTACTGCCAGCAGAGGAGGAGCTTCCCCTACAC

[0348] ATTCGGCCAGGGCACCAAACTGGAGATCAAGGCCGCTGCCCTTGATAATGAAAA
GTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTG
TTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCG
CTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTCGCTTTTCCG
TCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATGA
GGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCCGCTTTCCTGAGG
AGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGATCTGCAGATGCAC
CAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCA
GGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTG
GCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAG
GATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAG
GGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATAC
TTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAG
CGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAATCCGGG
GCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCT

CCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGC
CTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCG
CACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTGAC
ATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTG
GGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGAT
GTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGG
TGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGT

[0349] ATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTCGACCC
TTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTAC
GCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAG
CACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGC
CCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTC
ATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCT
GTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCT
TTAAGAGATGACCTAGGTAA (SEQ ID NO:21)

[0350] 构建体S1-2F3-CD28T-41BB AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFSTYWI
EWVRQAPGQRLEWMGEILPGSGNTDFNEKFQGRVTFTADTSSDTAYMELSSLRSED
TAVYYCTRWGYYGTRGYFNVWGQGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPA
TLSLSPGERATLSCRASSSVSYMHWFQQKPGQAPRLLIYSTSNLASGIPARFSGSGSGT
DYTLTISSLEPEDFAVYYCQQRRSFPYTFGQGTKLEIKAAALDNEKSNGTIIHVKGKH
LCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRFSVVKRGRKKLLYIFKQ
PFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLG

[0351] RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRR
GKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGP
MGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQ
PCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAY
GYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPC
TVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIAS
TVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID
NO:22)

[0352] 构建体S1-2F3-C8K-CD28 DNA(信号序列以粗体显示)

[0353]

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAGAAGCCCGGA
GCCAGCGTGAAGGTGAGCTGCAAAGCCAGCGGCTACACCTTCTCCACCTACTGG
ATCGAGTGGGTGAGACAGGCCCCCGGACAGAGGCTGGAATGGATGGGAGAGAT
CCTGCCCGGCAGCGGCAACACCGACTTCAACGAGAAGTTCCAGGGCAGAGTGAC
CTTCACCGCCGATACCAGCAGCGACACCGCCTACATGGAACTGAGCAGCCTGAG
AAGCGAGGATACCGCCGTCTACTACTGCACCAGATGGGGCTACTACGGCACCAG
GGGCTATTTCAACGTGTGGGGCCAGGGAACCCTCGTGACCGTGAGCAGCGGAGG
CGGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGAGATTGTGCTGAC
CCAGAGCCCTGCTACACTGAGCCTGAGCCCCGGCGAGAGAGCCACACTGAGCTG
CAGAGCCAGCAGCAGCGTGAGCTACATGCACTGGTTCCAGCAAAAGCCCGGCCA
GGCCCCTAGGCTGCTGATCTACAGCACATCCAACCTGGCCAGCGGCATCCCTGCC
AGATTCAGCGGTTCTGGCTCCGGCACCGACTACACCCTGACCATCTCCAGCCTGG
AGCCCGAGGACTTTGCCGTGTATTACTGCCAGCAGAGGAGGAGCTTCCCCTACAC
ATTCGGCCAGGGCACCAAACTGGAGATCAAGGCCGCTGCCTTCGTGCCTGTTTTT
CTGCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCAACTCCTGCACCAA
CTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAGG
CGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGCC
CCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTACT
GCAACCACAGAAACAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGA
ATATGACTCCACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCAC
CACCTAGAGATTTCGCTGCCTATCGGAGCAGGGTGAAGTTTTCCAGATCTGCAGA
TGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGG
ACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGAT
GGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCA
GAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGA
GAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAG
GATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGT
GGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAAT
CCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTG
CTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAA
CGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGG
CGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCA
GTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAAT

GTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTG
CAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTG
CCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAA
CACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGT
CGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGA

[0354] GTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCAC
CCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACC
GGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGAC
GACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCT
GATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTAC
ATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:23)

[0355] 构建体S1-2F3-C8K-CD28 AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFSTYWI
EWVRQAPGQRLEWMGEILPGSGNTDFNEKFQGRVTFTADTSSDTAYMELSSLRSED
TAVYYCTRWGYYGTRGYFNVWGQGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPA
TLSLSPGERATLSCRASSSVSYMHWFQQKPGQAPRLLIYSTSNLASGIPARFSGSGSGT
DYTLTISSLEPEDFAVYYCQQRRSFPYTFGQGTKLEIKAAAFVPVFLPAKPTTTPAPRP
PTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITL
YCNHRNRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSAD

[0356] APAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQK
DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSG
EGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYT
HSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQS
MSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEEC
PDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDS
TAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVG
LVAYIAFKR (SEQ ID NO:24)

[0357] 构建体S1-2F3-C8K-41BB DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG

[0358] CACGCCCGCAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAGAAGCCCGGA
GCCAGCGTGAAGGTGAGCTGCAAAGCCAGCGGCTACACCTTCTCCACCTACTGG
ATCGAGTGGGTGAGACAGGCCCCCGGACAGAGGCTGGAATGGATGGGAGAGAT

[0359]

CCTGCCCGGCAGCGGCAACACCGACTTCAACGAGAAGTTCCAGGGCAGAGTGAC
CTTCACCGCCGATACCAGCAGCGACACCGCCTACATGGAACTGAGCAGCCTGAG
AAGCGAGGATACCGCCGTCTACTACTGCACCAGATGGGGCTACTACGGCACCAG
GGGCTATTTCAACGTGTGGGGCCAGGGAACCCTCGTGACCGTGAGCAGCGGAGG
CGGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGAGATTGTGCTGAC
CCAGAGCCCTGCTACACTGAGCCTGAGCCCCGGCGAGAGAGCCACACTGAGCTG
CAGAGCCAGCAGCAGCGTGAGCTACATGCACTGGTTCCAGCAAAAGCCCGGCCA
GGCCCCTAGGCTGCTGATCTACAGCACATCCAACCTGGCCAGCGGCATCCCTGCC
AGATTCAGCGGTTCTGGCTCCGGCACCGACTACACCCTGACCATCTCCAGCCTGG
AGCCCGAGGACTTTGCCGTGTATTACTGCCAGCAGAGGAGGAGCTTCCCCTACAC
ATTCGGCCAGGGCACCAAACTGGAGATCAAGGCCGCTGCCTTCGTGCCTGTTTTT
CTGCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCAACTCCTGCACCAA
CTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAGG
CGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGCC
CCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTACT
GCAACCACAGAAACCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGT
ACATTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACG
GCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGA
AGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGT
ATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCA
GAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAG
GGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATA
GGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGG
ACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCA
CCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGT
GGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGC
TATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGC
GCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAA
GCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCT
GTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCC
TTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTC
GAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACT
ACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCA
GTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACA

GCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATA
CCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAG
ATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACA
GCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCT

[0360] ACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACG
CGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGG
TCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:25)

[0361] 构建体S1-2F3-C8K-41BB AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFSTYWI
EWVRQAPGQRLEWMGEILPGSGNTDFNEKFQGRVTFTADTSSDTAYMELSSLRSED
TAVYYCTRWGYYGTRGYFNVWGQGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPA
TLSLSPGERATLSCRASSSVSYMHWFQQKPGQAPRLLIYSTSNLASGIPARFSGSGSGT
DYTLTISSLEPEDFAVYYCQQRRSFPYTFGQGTKLEIKAAAFVPVFLPAKPTTTPAPRP
PTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITL
YCNHRNRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKF

[0362] SRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLY
NELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRA
KRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLGVSLGGAKEAC
PTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTEC
VGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNT
VCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTP
PEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILA
AVVVGLVAYIAFKR (SEQ ID NO:26)

[0363] 构建体S1-11C2-CD28T-CD28-41BB DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGGAGATTCAGCTGGTGCAGAGCGGCGCCGAGGTGAAAAAGCCCGGA
GCCACCGTGAAGATCAGCTGCAAGGCCAGCGGCTACACATTCACCAACTACGGC
ATGAACTGGGTGCAACAGGCCCCCGGCCAGGGACTGGAGTGGATGGGCTGGATG

[0364] AACACATACACCGGCGAGCCCACCTACGCCGACAAGTTCCAGGGCAGGGTGACA
TTCACACTCGATACCAGCGCCAGAACCGTGTATATGGAACTGAGCAGCCTGAGG
AGCGAGGACACCGCTGTGTACTTCTGCGCAAGGGCTGGAGGCCAGCTGAGACCT
GGCGCTATGGACTACTGGGGCCAGGGCACCATGGTGACCGTGAGCTCCGGAGGC
GGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCGTGCTGACC

CAGACACCTCTCTCCCTGTCCGTGACCCCCGGACAGCCTGCCTCCATTTCCTGTA
AGGCCTCCCAGAGCGTGGACTATGACGGCGACAGCTTCATGAACTGGTACCTGC
AGAAGCCCGGACAACCCCCCCAGCTGCTGATCTACGTGGCCAGCAACCTGGAGT
CCGGCGTGCCTGACAGGTTTTCCGGCTCCGGCAGCGGCACCGACTTCACCCTGAA
GATCAGCAGGGTGGAAGCCGAGGACGTGGGCGTGTACTACTGCCAGCAGAGCAA
CGAGGAGCCCCCTACCTTCGGACAGGGCACCAAGCTGGAGATCAAGGCCGCTGC
CCTTGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCT
CTGTCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAG
TGGGTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTC
TGGGTTAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTC
CACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAG
ATTTCGCTGCCTATCGGAGCCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCT
GCTGTACATTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGA
GGACGGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAG
GGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCA
ACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAA

[0365] GCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCC
AGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTG
AAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTAC
CAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCC
CTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTT
ACATGTGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGA
AGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCG
GAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTT
GCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGA
CAGTCTGTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCAC
CGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCC
TGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGAC
GAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTC
GTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGA
ACCTACAGCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCG
AGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCG
AGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACA
GTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCG
CTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGT

[0366] GACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCC
GTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ
ID NO:27)

[0367] 构建体S1-11C2-CD28T-CD28-41BB AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPEIQLVQSGAEVKKPGATVKISCKASGYTFTNYGM
NWVQQAPGQGLEWMGWMNTYTGEPTYADKFQGRVTFTLDTSARTVYMELSSLRS
EDTAVYFCARAGGQLRPGAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIVLTQ
TPLSLSVTPGQPASISCKASQSVDYDGDSFMNWYLQKPGQPPQLLIYVASNLESGVP
DRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSNEEPPTFGQGTKLEIKAAALDNEKS
NGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRL
LHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRFSVVKRGRKKLLYIFKQPFMR

[0368] PVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREE
YDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG
HDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGA
GATGRAMDGPRLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCG
ANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYY
QDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVC
EDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVA
GVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:28)

[0369] 构建体S1-11C2-CD28T-CD28 DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGGAGATTCAGCTGGTGCAGAGCGGCGCCGAGGTGAAAAAGCCCGGA
GCCACCGTGAAGATCAGCTGCAAGGCCAGCGGCTACACATTCACCAACTACGGC

[0370] ATGAACTGGGTGCAACAGGCCCCCGGCCAGGGACTGGAGTGGATGGGCTGGATG
AACACATACACCGGCGAGCCCACCTACGCCGACAAGTTCCAGGGCAGGGTGACA
TTCACACTCGATACCAGCGCCAGAACCGTGTATATGGAACTGAGCAGCCTGAGG
AGCGAGGACACCGCTGTGTACTTCTGCGCAAGGGCTGGAGGCCAGCTGAGACCT

GGCGCTATGGACTACTGGGGCCAGGGCACCATGGTGACCGTGAGCTCCGGAGGC
GGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCGTGCTGACC
CAGACACCTCTCTCCCTGTCCGTGACCCCCGGACAGCCTGCCTCCATTTCCTGTA
AGGCCTCCCAGAGCGTGGACTATGACGGCGACAGCTTCATGAACTGGTACCTGC
AGAAGCCCGGACAACCCCCCCAGCTGCTGATCTACGTGGCCAGCAACCTGGAGT
CCGGCGTGCCTGACAGGTTTTCCGGCTCCGGCAGCGGCACCGACTTCACCCTGAA
GATCAGCAGGGTGGAAGCCGAGGACGTGGGCGTGTACTACTGCCAGCAGAGCAA
CGAGGAGCCCCCTACCTTCGGACAGGGCACCAAGCTGGAGATCAAGGCCGCTGC
CCTTGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCT
CTGTCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAG
TGGGTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTC
TGGGTTAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTC
CACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAG
ATTTCGCTGCCTATCGGAGCAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGC
GTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGA
AGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAA
[0371] ACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAA
GATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAA
AAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATG
ACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGG
AGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCCTA
TGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCT
GTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTAC
ACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAA
CCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTGACATTCA
GCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCT
TCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCC
TATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGT
GAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGT
GAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTCGACCCTTGC
TTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGC
TGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACA
CCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCT
CCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATG
[0372] GGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCT
ACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAA
GAGATGACCTAGGTAA (SEQ ID NO:29)

[0373] 构建体S1-11C2-CD28T-CD28 AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPEIQLVQSGAEVKKPGATVKISCKASGYTFTNYGM
NWVQQAPGQGLEWMGWMNTYTGEPTYADKFQGRVTFTLDTSARTVYMELSSLRS
EDTAVYFCARAGGQLRPGAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIVLTQ
TPLSLSVTPGQPASISCKASQSVDYDGDSFMNWYLQKPGQPPQLLIYVASNLESGVP
DRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSNEEPPTFGQGTKLEIKAAALDNEKS
NGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRL
LHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLY

[0374] NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM
KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDV
EENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLG
EGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAV
CRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHV
DPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPE
QDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ
ID NO:30)

[0375] 构建体S1-11C2-CD28T-41BB DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGGAGATTCAGCTGGTGCAGAGCGGCGCCGAGGTGAAAAAGCCCGGA
GCCACCGTGAAGATCAGCTGCAAGGCCAGCGGCTACACATTCACCAACTACGGC
ATGAACTGGGTGCAACAGGCCCCCGGCCAGGGACTGGAGTGGATGGGCTGGATG

[0376] AACACATACACCGGCGAGCCCACCTACGCCGACAAGTTCCAGGGCAGGGTGACA
TTCACACTCGATACCAGCGCCAGAACCGTGTATATGGAACTGAGCAGCCTGAGG
AGCGAGGACACCGCTGTGTACTTCTGCGCAAGGGCTGGAGGCCAGCTGAGACCT
GGCGCTATGGACTACTGGGGCCAGGGCACCATGGTGACCGTGAGCTCCGGAGGC
GGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCGTGCTGACC
CAGACACCTCTCTCCCTGTCCGTGACCCCCGGACAGCCTGCCTCCATTTCCTGTA

AGGCCTCCCAGAGCGTGGACTATGACGGCGACAGCTTCATGAACTGGTACCTGC
AGAAGCCCGGACAACCCCCCCAGCTGCTGATCTACGTGGCCAGCAACCTGGAGT
CCGGCGTGCCTGACAGGTTTTCCGGCTCCGGCAGCGGCACCGACTTCACCCTGAA
GATCAGCAGGGTGGAAGCCGAGGACGTGGGCGTGTACTACTGCCAGCAGAGCAA
CGAGGAGCCCCCTACCTTCGGACAGGGCACCAAGCTGGAGATCAAGGCCGCTGC
CCTTGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCT
CTGTCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAG
TGGGTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTC
TGGGTTCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCA
AACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCT
GCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCA
GATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGC
TCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGG
ACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATA
ATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAG
GAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACT
GCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCA
[0377] AGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGG
AAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCC
CGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGC
CTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTT
GGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGC
CTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTT
GTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGA
TGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTG
TGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGAT
AAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGC
GAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCA
GCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAG
ATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTAC
CCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGG
CGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAAC

CGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTG
GTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:31)

[0378] 构建体S1-11C2-CD28T-41BB AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPEIQLVQSGAEVKKPGATVKISCKASGYTFTNYGM
NWVQQAPGQGLEWMGWMNTYTGEPTYADKFQGRVTFTLDTSARTVYMELSSLRS
EDTAVYFCARAGGQLRPGAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIVLTQ
TPLSLSVTPGQPASISCKASQSVDYDGDSFMNWYLQKPGQPPQLLIYVASNLESGVP
DRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSNEEPPTFGQGTKLEIKAAALDNEKS
NGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRFSVVKR
GRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQ

[0379] NQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYS
EIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTC
GDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKA
CNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEA
DDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDE
ANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEP
EAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFK
R (SEQ ID NO:32)

[0380] 构建体S1-11C2-C8K-CD28 DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGGAGATTCAGCTGGTGCAGAGCGGCGCCGAGGTGAAAAAGCCCGGA
GCCACCGTGAAGATCAGCTGCAAGGCCAGCGGCTACACATTCACCAACTACGGC
ATGAACTGGGTGCAACAGGCCCCCGGCCAGGGACTGGAGTGGATGGGCTGGATG
AACACATACACCGGCGAGCCCACCTACGCCGACAAGTTCCAGGGCAGGGTGACA

[0381] TTCACACTCGATACCAGCGCCAGAACCGTGTATATGGAACTGAGCAGCCTGAGG
AGCGAGGACACCGCTGTGTACTTCTGCGCAAGGGCTGGAGGCCAGCTGAGACCT
GGCGCTATGGACTACTGGGGCCAGGGCACCATGGTGACCGTGAGCTCCGGAGGC
GGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCGTGCTGACC
CAGACACCTCTCTCCCTGTCCGTGACCCCCGGACAGCCTGCCTCCATTTCCTGTA
AGGCCTCCCAGAGCGTGGACTATGACGGCGACAGCTTCATGAACTGGTACCTGC

AGAAGCCCGGACAACCCCCCCAGCTGCTGATCTACGTGGCCAGCAACCTGGAGT
CCGGCGTGCCTGACAGGTTTTCCGGCTCCGGCAGCGGCACCGACTTCACCCTGAA
GATCAGCAGGGTGGAAGCCGAGGACGTGGGCGTGTACTACTGCCAGCAGAGCAA
CGAGGAGCCCCCTACCTTCGGACAGGGCACCAAGCTGGAGATCAAGGCCGCTGC
CTTCGTGCCTGTTTTTCTGCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCC
CAACTCCTGCACCAACTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATG
CCGCCCCGCGGCAGGCGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGA
TATTTATATCTGGGCCCCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTG
GTGATTACCCTCTACTGCAACCACAGAAACAGATCCAAAAGAAGCCGCCTGCTC
CATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCCCACAAGGAAACAC
TACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATCGGAGCAGGGTGAAGT
TTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATA
ACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAG
GACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGT
CTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGC
ATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACT
CAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCT
[0382] AGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGG
GACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATG
GATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTA
AGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTG
TAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGA
ACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGC
AAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAG
CCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCG
GGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTG
CCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGA
CGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGA
ACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCC
TGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCC
GAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGT
TGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGG

CACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTG
GGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:33)

[0383] 构建体S1-11C2-C8K-CD28 AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPEIQLVQSGAEVKKPGATVKISCKASGYTFTNYGM
NWVQQAPGQGLEWMGWMNTYTGEPTYADKFQGRVTFTLDTSARTVYMELSSLRS
EDTAVYFCARAGGQLRPGAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIVLTQ
TPLSLSVTPGQPASISCKASQSVDYDGDSFMNWYLQKPGQPPQLLIYVASNLESGVP
DRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSNEEPPTFGQGTKLEIKAAAFVPVFLP
AKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGT
CGVLLLSLVITLYCNHRNRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAA
[0384] YRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRK
NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM
QALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSL
GGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATE
PCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFS
CQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPG
RWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLI
PVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:34)

[0385] 构建体S1-11C2-C8K-41BB DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGGAGATTCAGCTGGTGCAGAGCGGCGCCGAGGTGAAAAAGCCCGGA
GCCACCGTGAAGATCAGCTGCAAGGCCAGCGGCTACACATTCACCAACTACGGC
ATGAACTGGGTGCAACAGGCCCCCGGCCAGGGACTGGAGTGGATGGGCTGGATG
AACACATACACCGGCGAGCCCACCTACGCCGACAAGTTCCAGGGCAGGGTGACA
[0386] TTCACACTCGATACCAGCGCCAGAACCGTGTATATGGAACTGAGCAGCCTGAGG
AGCGAGGACACCGCTGTGTACTTCTGCGCAAGGGCTGGAGGCCAGCTGAGACCT
GGCGCTATGGACTACTGGGGCCAGGGCACCATGGTGACCGTGAGCTCCGGAGGC
GGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCGTGCTGACC
CAGACACCTCTCTCCCTGTCCGTGACCCCCGGACAGCCTGCCTCCATTTCCTGTA
AGGCCTCCCAGAGCGTGGACTATGACGGCGACAGCTTCATGAACTGGTACCTGC
AGAAGCCCGGACAACCCCCCCAGCTGCTGATCTACGTGGCCAGCAACCTGGAGT

[0387] CCGGCGTGCCTGACAGGTTTTCCGGCTCCGGCAGCGGCACCGACTTCACCCTGAA
GATCAGCAGGGTGGAAGCCGAGGACGTGGGCGTGTACTACTGCCAGCAGAGCAA
CGAGGAGCCCCCTACCTTCGGACAGGGCACCAAGCTGGAGATCAAGGCCGCTGC
CTTCGTGCCTGTTTTTCTGCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCC
CAACTCCTGCACCAACTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATG
CCGCCCCGCGGCAGGCGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGA
TATTTATATCTGGGCCCCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTG
GTGATTACCCTCTACTGCAACCACAGAAACCGCTTTTCCGTCGTTAAGCGGGGGA
GAAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGA
CTCAGGAAGAGGACGGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGT
GCGAACTGAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGG
GCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACG
TTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGA
AAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAA
GCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGA
CGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCAC
ATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGG
ATCTCTCCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGG
CGCCACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGC
GTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCG
GTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGC
TAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTC
TCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGT
CCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTA
CCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTC
TGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCC
AGACGGAACCTACAGCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCAC
CGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGC
TGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGG
ATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGA
CCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAA
CCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCT
TGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAG
GTAA (SEQ ID NO:35)

[0388] 构建体S1-11C2-C8K-41BB AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPEIQLVQSGAEVKKPGATVKISCKASGYTFTNYGM
NWVQQAPGQGLEWMGWMNTYTGEPTYADKFQGRVTFTLDTSARTVYMELSSLRS
EDTAVYFCARAGGQLRPGAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIVLTQ
TPLSLSVTPGQPASISCKASQSVDYDGDSFMNWYLQKPGQPPQLLIYVASNLESGVP
DRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSNEEPPTFGQGTKLEIKAAAFVPVFLP
AKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGT
CGVLLLSLVITLYCNHRNRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE

[0389] EEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK
PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDA
LHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLG
VSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVS
ATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSG
LVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECE
EIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTT
DNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:36)

[0390] 构建体S2-1A1-CD28T-CD28-41BB DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCCGGCGCCGAAGTGAAGAAGCCCGGAG
CCAGCGTGAAGGTGAGCTGCAAGGCCTCCGGCTACACCTTCACCACCTACTGGAT
GCACTGGGTCAGACAGGCTCCCGGACAGGGCCTGGAATGGATGGGCGAAATCAA
CCCCTCCTCCGGCAGGACCAACTACAACGAGAAGTTCAAGACCAGGGTGACCAT

[0391] GACCAGGGACACCAGCACCAGCACCGTGTACATGGAGCTGTCCAGCCTGAGGAG
CGAGGACACCGCCGTGTACTACTGTGCCAAGCTGGGACCCGGCCCCCAGTACTA
TGCCATGGACTACTGGGGCCAAGGCACCATGGTGACCGTGAGCAGCGGAGGCGG
AGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCCAGATGACCCA
GAGCCCCTCCAGCCTGTCCGCTAGCGTGGGCGACAGGGTCACCATTACCTGCCAC
GCCAGCCAGAACATCAACGTGTGGCTGAGCTGGTATCAGCAGAAACCCGGCAAG
GCTCCCAAGCTGCTGATCTACAAGGCCAGCAAGCTGCACACCGGCGTGCCCAGC

AGGTTTAGCGGTTCTGGCTCCGGCACCGACTTCACCCTCACCATCAGCAGCCTGC
AGCCCGAAGACTTCGCTACCTACTACTGCCAGCAGGGACAAAGCTACCCCTGGA
CCTTCGGCCAGGGAACCAAGCTGGAAATCAAGGCCGCTGCCCTTGATAATGAAA
AGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTT
GTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTC
GCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTAGATCCAA
AAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGC
CCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATC
GGAGCCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAA
ACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTG
CCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAG
ATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCT
CAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGG
ACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATA
ATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAG
GAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACT
GCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCA
[0392] AGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGG
AAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCC
CGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGC
CTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTT
GGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGC
CTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTT
GTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGA
TGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTG
TGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGAT
AAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGC
GAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCA
GCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAG
ATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTAC
CCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGG
CGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAAC

CGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTG
GTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:37)

[0393] 构建体S2-1A1-CD28T-CD28-41BB AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTTYW
MHWVRQAPGQGLEWMGEINPSSGRTNYNEKFKTRVTMTRDTSTSTVYMELSSLRSE
DTAVYYCAKLGPGPQYYAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIQMTQS
PSSLSASVGDRVTITCHASQNINVWLSWYQQKPGKAPKLLIYKASKLHTGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQGQSYPWTFGQGTKLEIKAAALDNEKSNGTIIH
VKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY
MNMTPRRPGPTRKHYQPYAPPRDFAAYRSRFSVVKRGRKKLLYIFKQPFMRPVQTT

[0394] QEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLD
KRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLY
QGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGR
AMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTV
CEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETT
GRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTER
QLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTT
VMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:38)

[0395] 构建体S2-1A1-CD28T-CD28 DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCCGGCGCCGAAGTGAAGAAGCCCGGAG
CCAGCGTGAAGGTGAGCTGCAAGGCCTCCGGCTACACCTTCACCACCTACTGGAT
GCACTGGGTCAGACAGGCTCCCGGACAGGGCCTGGAATGGATGGGCGAAATCAA
CCCCTCCTCCGGCAGGACCAACTACAACGAGAAGTTCAAGACCAGGGTGACCAT

[0396] GACCAGGGACACCAGCACCAGCACCGTGTACATGGAGCTGTCCAGCCTGAGGAG
CGAGGACACCGCCGTGTACTACTGTGCCAAGCTGGGACCCGGCCCCCAGTACTA
TGCCATGGACTACTGGGGCCAAGGCACCATGGTGACCGTGAGCAGCGGAGGCGG
AGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCCAGATGACCCA
GAGCCCCTCCAGCCTGTCCGCTAGCGTGGGCGACAGGGTCACCATTACCTGCCAC
GCCAGCCAGAACATCAACGTGTGGCTGAGCTGGTATCAGCAGAAACCCGGCAAG

GCTCCCAAGCTGCTGATCTACAAGGCCAGCAAGCTGCACACCGGCGTGCCCAGC
AGGTTTAGCGGTTCTGGCTCCGGCACCGACTTCACCCTCACCATCAGCAGCCTGC
AGCCCGAAGACTTCGCTACCTACTACTGCCAGCAGGGACAAAGCTACCCCTGGA
CCTTCGGCCAGGGAACCAAGCTGGAAATCAAGGCCGCTGCCCTTGATAATGAAA
AGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTT
GTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTC
GCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTAGATCCAA
AAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGC
CCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATC
GGAGCAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCC
AGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTT
TGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAA
AACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCC
TATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGG
TTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATG
CAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATC

[0397] TCTCCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGC
CACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTG
TCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTG
AATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAA
CCAGACAGTCTGTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCA
GCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCG
CCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCA
GGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGG
CCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGA
CGGAACCTACAGCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGT
CTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGA
GTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATC
AGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCT
GATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCA
GTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGG
CAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTA
A (SEQ ID NO:39)

[0398] 构建体S2-1A1-CD28T-CD28 AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTTYW
MHWVRQAPGQGLEWMGEINPSSGRTNYNEKFKTRVTMTRDTSTSTVYMELSSLRSE
DTAVYYCAKLGPGPQYYAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIQMTQS
PSSLSASVGDRVTITCHASQNINVWLSWYQQKPGKAPKLLIYKASKLHTGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQGQSYPWTFGQGTKLEIKAAALDNEKSNGTIIH
VKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY
MNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNELNL

[0399] GRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR
RGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGP
MGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQ
PCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAY
GYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPC
TVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIAS
TVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID
NO:40)

[0400] 构建体S2-1A1-CD28T-41BB DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCCGGCGCCGAAGTGAAGAAGCCCGGAG
CCAGCGTGAAGGTGAGCTGCAAGGCCTCCGGCTACACCTTCACCACCTACTGGAT
GCACTGGGTCAGACAGGCTCCCGGACAGGGCCTGGAATGGATGGGCGAAATCAA
CCCCTCCTCCGGCAGGACCAACTACAACGAGAAGTTCAAGACCAGGGTGACCAT
GACCAGGGACACCAGCACCAGCACCGTGTACATGGAGCTGTCCAGCCTGAGGAG
CGAGGACACCGCCGTGTACTACTGTGCCAAGCTGGGACCCGGCCCCCAGTACTA

[0401] TGCCATGGACTACTGGGGCCAAGGCACCATGGTGACCGTGAGCAGCGGAGGCGG
AGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCCAGATGACCCA
GAGCCCCTCCAGCCTGTCCGCTAGCGTGGGCGACAGGGTCACCATTACCTGCCAC
GCCAGCCAGAACATCAACGTGTGGCTGAGCTGGTATCAGCAGAAACCCGGCAAG
GCTCCCAAGCTGCTGATCTACAAGGCCAGCAAGCTGCACACCGGCGTGCCCAGC
AGGTTTAGCGGTTCTGGCTCCGGCACCGACTTCACCCTCACCATCAGCAGCCTGC
AGCCCGAAGACTTCGCTACCTACTACTGCCAGCAGGGACAAAGCTACCCCTGGA
CCTTCGGCCAGGGAACCAAGCTGGAAATCAAGGCCGCTGCCCTTGATAATGAAA

AGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTT
GTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTC
GCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTCGCTTTTCC
GTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATG
AGGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCCGCTTTCCTGAG
GAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGATCTGCAGATGCA
CCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGC
AGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGT
GGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAA
GGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAA
GGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATA
CTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCA
GCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAATCCGG
GGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTGCTTC

[0402] TCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGG
CCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTC
GCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTGA
CATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGT
GGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGA
TGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGG
GTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACA
GTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTCGAC
CCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGT
ACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGG
AGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAG
GCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAG
TCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTC
CTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGC
CTTTAAGAGATGACCTAGGTAA (SEQ ID NO:41)

[0403] 构建体S2-1A1-CD28T-41BB AA(信号序列以粗体显示;CDR加下划线)

[0404] **MALPVTALLLPLALLLHAARP**QVQLVQSGAEVKKPGASVKVSCKASGYTFTTYW
MHWVRQAPGQGLEWMGEINPSSGRTNYNEKFKTRVTMTRDTSTSTVYMELSSLRSE

DTAVYYCAKLGPGPQYYAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIQMTQS
PSSLSASVGDRVTITCHASQNINVWLSWYQQKPGKAPKLLIYKASKLHTGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQGQSYPWTFGQGTKLEIKAAALDNEKSNGTIIH
VKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRFSVVKRGRKKL
LYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYN
ELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMK

[0405] GERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVE
ENPGPMGAGATGRAMDGPRLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGE
GVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVC
RCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVD
PCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQ
DLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ
ID NO:42)

[0406] 构建体S2-1A1-C8K-CD28 DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCCGGCGCCGAAGTGAAGAAGCCCGGAG
CCAGCGTGAAGGTGAGCTGCAAGGCCTCCGGCTACACCTTCACCACCTACTGGAT
GCACTGGGTCAGACAGGCTCCCGGACAGGGCCTGGAATGGATGGGCGAAATCAA
CCCCTCCTCCGGCAGGACCAACTACAACGAGAAGTTCAAGACCAGGGTGACCAT
GACCAGGGACACCAGCACCAGCACCGTGTACATGGAGCTGTCCAGCCTGAGGAG
CGAGGACACCGCCGTGTACTACTGTGCCAAGCTGGGACCCGGCCCCCAGTACTA
TGCCATGGACTACTGGGGCCAAGGCACCATGGTGACCGTGAGCAGCGGAGGCGG
AGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCCAGATGACCCA

[0407] GAGCCCCTCCAGCCTGTCCGCTAGCGTGGGCGACAGGGTCACCATTACCTGCCAC
GCCAGCCAGAACATCAACGTGTGGCTGAGCTGGTATCAGCAGAAACCCGGCAAG
GCTCCCAAGCTGCTGATCTACAAGGCCAGCAAGCTGCACACCGGCGTGCCCAGC
AGGTTTAGCGGTTCTGGCTCCGGCACCGACTTCACCCTCACCATCAGCAGCCTGC
AGCCCGAAGACTTCGCTACCTACTACTGCCAGCAGGGACAAAGCTACCCCTGGA
CCTTCGGCCAGGGAACCAAGCTGGAAATCAAGGCCGCTGCCTTCGTGCCTGTTTT
TCTGCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCAACTCCTGCACCA
ACTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAG
GCGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGC

CCCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTAC
TGCAACCACAGAAACAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATG
AATATGACTCCACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCA
CCACCTAGAGATTTCGCTGCCTATCGGAGCAGGGTGAAGTTTTCCAGATCTGCAG
ATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGG
GACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAG
ATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTG
CAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCG
GAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGA
AGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAA
GTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAA
ATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGAC
TGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCC

[0408] AACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAG
GGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATT
CAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGA
ATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTG
TGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCC
TGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAA
ACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACG
TCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAG
AGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCA
CCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAAC
CGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGAC
GACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCT
GATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTAC
ATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:43)

[0409] 构建体S2-1A1-C8K-CD28 AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTTYW
MHWVRQAPGQGLEWMGEINPSSGRTNYNEKFKTRVTMTRDTSTSTVYMELSSLRSE

[0410] DTAVYYCAKLGPGPQYYAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIQMTQS
PSSLSASVGDRVTITCHASQNINVWLSWYQQKPGKAPKLLIYKASKLHTGVPSRFSG

SGSGTDFTLTISSLQPEDFATYYCQQGQSYPWTFGQGTKLEIKAAAFVPVFLPAKPTT
TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLL
LSLVITLYCNHRNRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRV
KFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEG
LYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

[0411] AKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEA
CPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTE
CVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQN
TVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRST
PPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSIL
AAVVVGLVAYIAFKR (SEQ ID NO:44)

[0412] 构建体S2-1A1-C8K-41BB DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCCGGCGCCGAAGTGAAGAAGCCCGGAG
CCAGCGTGAAGGTGAGCTGCAAGGCCTCCGGCTACACCTTCACCACCTACTGGAT
GCACTGGGTCAGACAGGCTCCCGGACAGGGCCTGGAATGGATGGGCGAAATCAA
CCCCTCCTCCGGCAGGACCAACTACAACGAGAAGTTCAAGACCAGGGTGACCAT
GACCAGGGACACCAGCACCAGCACCGTGTACATGGAGCTGTCCAGCCTGAGGAG
CGAGGACACCGCCGTGTACTACTGTGCCAAGCTGGGACCCGGCCCCCAGTACTA
TGCCATGGACTACTGGGGCCAAGGCACCATGGTGACCGTGAGCAGCGGAGGCGG
AGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCCAGATGACCCA
GAGCCCCTCCAGCCTGTCCGCTAGCGTGGGCGACAGGGTCACCATTACCTGCCAC

[0413] GCCAGCCAGAACATCAACGTGTGGCTGAGCTGGTATCAGCAGAAACCCGGCAAG
GCTCCCAAGCTGCTGATCTACAAGGCCAGCAAGCTGCACACCGGCGTGCCCAGC
AGGTTTAGCGGTTCTGGCTCCGGCACCGACTTCACCCTCACCATCAGCAGCCTGC
AGCCCGAAGACTTCGCTACCTACTACTGCCAGCAGGGACAAAGCTACCCCTGGA
CCTTCGGCCAGGGAACCAAGCTGGAAATCAAGGCCGCTGCCTTCGTGCCTGTTTT
TCTGCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCAACTCCTGCACCA
ACTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAG
GCGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGC
CCCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTAC
TGCAACCACAGAAACCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTG

[0414] TACATTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGAC
GGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTG
AAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTG
TATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGC
AGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGA
GGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAAT
AGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGG
GACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCC
ACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATG
TGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGG
CTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGG
CGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAA
GCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCT
GTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCC
TTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTC
GAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACT
ACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCA
GTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACA
GCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATA
CCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAG
ATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACA
GCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCT
ACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACG
CGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGG
TCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:45)

[0415] 构建体S2-1A1-C8K-41BB AA(信号序列以粗体显示;CDR加下划线)

[0416] **MALPVTALLLPLALLLHAARP**QVQLVQSGAEVKKPGASVKVSCKASGYTFTTYW
MHWVRQAPGQGLEWMGEINPSSGRTNYNEKFKTRVTMTRDTSTSTVYMELSSLRSE
DTAVYYCAKLGPGPQYYAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIQMTQS
PSSLSASVGDRVTITCHASQNINVWLSWYQQKPGKAPKLLIYKASKLHTGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQGQSYPWTFGQGTKLEIKAAAFVPVFLPAKPTT

TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLL
LSLVITLYCNHRNRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGC
ELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN
PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ
ALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLG
[0417] GAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEP
CKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFS
CQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPG
RWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLI
PVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:46)

[0418] 构建体S2-7A4-CD28T-CD28-41BB DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT
CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA
CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT
GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC
TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT
ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT
TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT
CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG
[0419] GTCAGAGTGTTACCAGCAGCTCCTTTGCTTGGTACCAACAGAAACCTGGCCAGGC
TCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAGG
TTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAGC
CTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGTCGTTCGG
CCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCCTTGATAATGAAAAGTC
AAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTGTTC
CCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCTT
GTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTAGATCCAAAAGA
AGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCCCA
CAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATCGGA
GCCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAACA

GCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCCG
CTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGATC
TGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAA
CCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCC
TGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGA
GCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGA
GCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTAC
GAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAG
AAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGA
AAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCG
ACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGT
CCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCG

[0420] AGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGG
ATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTAC
CGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCA
GTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAG
GCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGC
AAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAAC
CACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGA
GAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGA
TCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAG
AACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGT
GACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAA
TCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCC
TACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:47)

[0421] 构建体S2-7A4-CD28T-CD28-41BB AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDI
NWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRS

[0422] EDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP
GTLSLSPGERATLSCRAGQSVTSSSFAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYGGSRSFGQGTKVELKRAAALDNEKSNGTIIHV

KGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYM
NMTPRRPGPTRKHYQPYAPPRDFAAYRSRFSVVKRGRKKLLYIFKQPFMRPVQTTQE
EDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKR
RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQG
LSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAM
[0423] DGPRLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEP
CLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRC
EACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLR
ECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVM
GSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:48)

[0424] 构建体S2-7A4-CD28T-CD28 DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT
CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA
CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT
GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC
TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT
ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT
TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT
CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG
[0425] GTCAGAGTGTTACCAGCAGCTCCTTTGCTTGGTACCAACAGAAACCTGGCCAGGC
TCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAGG
TTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAGC
CTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGTCGTTCGG
CCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCCTTGATAATGAAAAGTC
AAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTGTTC
CCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCTT
GTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTAGATCCAAAAGA
AGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCCCA
CAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATCGGA
GCAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGA

ACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGG
ACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAAC
CCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTAT
TCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTT
GTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCA
AGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCT
CCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCAC
GGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCT
CTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAA
TGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACC
AGACAGTCTGTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGC

[0426] CACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCC
CCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGG
ACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCC
TCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACG
GAACCTACAGCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCT
GCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGT
GCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAG
ACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGA
TCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGT
CGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCA
GCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA
(SEQ ID NO:49)

[0427] 构建体S2-7A4-CD28T-CD28 AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDI
NWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRS
EDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP

[0428] GTLSLSPGERATLSCRAGQSVTSSSFAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYGGSRSFGQGTKVELKRAAALDNEKSNGTIIHV
KGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYM
NMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNELNLGR
REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRG

[0429] KGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPM GAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQP CGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYG YYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCT VCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIAST VAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:50)

[0430] 构建体S2-7A4-CD28T-41BB DNA(信号序列以粗体显示)

[0431] ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG GTCAGAGTGTTACCAGCAGCTCCTTTGCTTGGTACCAACAGAAACCTGGCCAGGC TCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAGG TTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAGC CTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGTCGTTCGG CCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCCTTGATAATGAAAAGTC AAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTGTTC CCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCTT GTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTCGCTTTTCCGTC GTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATGAGG CCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCCGCTTTCCTGAGGAG GAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGATCTGCAGATGCACCA GCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGG GAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGC AAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGAT

AAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGG
AAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTA
TGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGG
GGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCC
TATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCT
GCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTC
TACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCAC
AACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTGACATT
CAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGC
[0432] CTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTG
CCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGT
GTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTAT
GTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTCGACCCTT
GCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGC
GCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCA
CACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCC
CTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCAT
GGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGT
CTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTT
AAGAGATGACCTAGGTAA (SEQ ID NO:51)

[0433] 构建体S2-7A4-CD28T-41BB AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDI
NWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRS
EDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP
GTLSLSPGERATLSCRAGQSVTSSSFAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYGGSRSFGQGTKVELKRAAALDNEKSNGTIIHV
[0434] KGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRFSVVKRGRKKLL
YIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNE
LNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKG
ERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEE
NPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGE
GVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVC
RCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVD
PCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQ
[0435] DLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ
ID NO:52)

[0436] 构建体S2-7A4-C8K-CD28 DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG

CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG

CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT

CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA

CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT

GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC

TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT

ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT

TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT

CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG

GTCAGAGTGTTACCAGCAGCTCCTTTGCTTGGTACCAACAGAAACCTGGCCAGGC

TCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAGG

TTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAGC

[0437] CTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGTCGTTCGG

CCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCTTCGTGCCTGTTTTTCTG

CCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCAACTCCTGCACCAACTA

TCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAGGCGG

CGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGCCCCC

CTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTACTGCA

ACCACAGAAACAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATA

TGACTCCACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCAC

CTAGAGATTTCGCTGCCTATCGGAGCAGGGTGAAGTTTTCCAGATCTGCAGATGC

ACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACG

CAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGG

GTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGA

AGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGA

AGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGAT

ACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGC
AGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAATCCG
GGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTGCTT
CTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGG
GCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGT
CGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTG
ACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTG
TGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAG
[0438] ATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCG
GGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACAC
AGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTCGA
CCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGT
ACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGG
AGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAG
GCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAG
TCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTC
CTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGC
CTTTAAGAGATGACCTAGGTAA (SEQ ID NO:53)

[0439] 构建体S2-7A4-C8K-CD28 AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDI
NWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRS
EDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP
GTLSLSPGERATLSCRAGQSVTSSSFAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYGGSRSFGQGTKVELKRAAAFVPVFLPAKPTTT
PAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL
[0440] SLVITLYCNHRNRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKF
SRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLY
NELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRA
KRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEAC
PTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTEC
VGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNT
VCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTP
PEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILA
[0441] AVVVGLVAYIAFKR (SEQ ID NO:54)

[0442] 构建体S2-7A4-C8K-41BB DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG

CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG

CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT

CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA

CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT

GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC

TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT

ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT

TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT

CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG

GTCAGAGTGTTACCAGCAGCTCCTTTGCTTGGTACCAACAGAAACCTGGCCAGGC

TCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAGG

TTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAGC

CTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGTCGTTCGG

[0443] CCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCTTCGTGCCTGTTTTTCTG

CCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCAACTCCTGCACCAACTA

TCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAGGCGG

CGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGCCCCC

CTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTACTGCA

ACCACAGAAACCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACA

TTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGCT

GCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGT

TTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATA

ACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAG

GACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGT

CTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGC

ATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACT

CAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCT

AGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGG

[0444] GACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATG
GATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTA
AGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTG
TAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGA
ACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGC
AAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAG
CCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCG
GGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTG
CCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGA
CGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGA
ACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCC
TGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCC
GAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGT
TGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGG
CACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTG
GGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:55)

[0445] 构建体S2-7A4-C8K-41BB AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDI
NWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRS
EDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP
GTLSLSPGERATLSCRAGQSVTSSSFAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYGGSRSFGQGTKVELKRAAAFVPVFLPAKPTTT
PAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL
SLVITLYCNHRNRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCE
[0446] LRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNP
QEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA
LPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGG
AKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPC
KPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSC
QDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGR
WITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIP
VYCSILAAVVVGLVAYIAFKR (SEQ ID NO:56)

[0447] 构建体S2-7A5-CD28T-CD28-41BB DNA(信号序列以粗体显示)

[0448]

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT
CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA
CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT
GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC
TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT
ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT
TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT
CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG
GTCAGAGTGTTACCAGCAGCTCCTTAGCTTGGTACCAGCAGAAACCTGGCCAGG
CTCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAG
GTTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAG
CCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGGCGTTCG
GCCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCCTTGATAATGAAAAGT
CAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTGTT
CCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCT
TGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTAGATCCAAAAG
AAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCCC
ACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATCGG
AGCCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAAC
AGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCC
GCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGAT
CTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCA
ACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGAC
CCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAAT
GAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGA
GAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGC
TACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAA
GAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGA
AGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCC
GCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCC

[0449] TGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTG
GCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCC
TGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTG
TACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGAT
GCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGT
GAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATA
AGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCG
AACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGC
TGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGAT
GGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCC
AAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCG
TGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCG
ACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGT
AGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:57)

[0450] 构建体S2-7A5-CD28T-CD28-41BB AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDI
NWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRS
EDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP
GTLSLSPGERATLSCRAGQSVTSSSLAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYGGSRAFGQGTKVELKRAAALDNEKSNGTIIH
VKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY
MNMTPRRPGPTRKHYQPYAPPRDFAAYRSRFSVVKRGRKKLLYIFKQPFMRPVQTT

[0451] QEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLD
KRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLY
QGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGR
AMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTV
CEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETT
GRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTER
QLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTT
VMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:58)

[0452] 构建体S2-7A5-CD28T-CD28 DNA(信号序列以粗体显示)

[0453]

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT
CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA
CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT
GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC
TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT
ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT
TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT
CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG
GTCAGAGTGTTACCAGCAGCTCCTTAGCTTGGTACCAGCAGAAACCTGGCCAGG
CTCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAG
GTTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAG
CCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGGCGTTCG
GCCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCCTTGATAATGAAAAGT
CAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTGTT
CCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCT
TGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTAGATCCAAAAG
AAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCCC
ACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATCGG
AGCAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAG
AACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTG
GACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAA
CCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTA
TTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTT
TGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCA
AGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCT
CCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCAC
GGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCT
CTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAA
TGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACC
AGACAGTCTGTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGC

[0454] CACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCC
CCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGG
ACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCC
TCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACG
GAACCTACAGCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCT
GCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGT
GCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAG
ACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGA
TCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGT
CGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCA
GCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA
(SEQ ID NO:59)

[0455] 构建体S2-7A5-CD28T-CD28 AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDI
NWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRS
EDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP
GTLSLSPGERATLSCRAGQSVTSSSLAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYGGSRAFGQGTKVELKRAAALDNEKSNGTIIH
VKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY
MNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNELNL
[0456] GRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR
RGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGP
MGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQ
PCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAY
GYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPC
TVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIAS
TVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID
NO:60)

[0457] 构建体S2-7A5-CD28T-41BB DNA(信号序列以粗体显示)

[0458] ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG

CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT

CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA

CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT

GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC

TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT

ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT

TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT

CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG

GTCAGAGTGTTACCAGCAGCTCCTTAGCTTGGTACCAGCAGAAACCTGGCCAGG

CTCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAG

GTTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAG

CCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGGCGTTCG

GCCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCCTTGATAATGAAAAGT

CAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTGTT

CCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCT

TGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTCGCTTTTCCGTC

[0459] GTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATGAGG

CCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCCGCTTTCCTGAGGAG

GAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGATCTGCAGATGCACCA

GCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGG

GAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGC

AAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGAT

AAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGG

AAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTA

TGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGG

GGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCC

TATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCT

GCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTC

TACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCAC

AACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTGACATT

CAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGC

CTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTG

CCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGT

GTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTAT
GTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTCGACCCTT
GCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGC
GCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCA

[0460] CACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCC
CTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCAT
GGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGT
CTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTT
AAGAGATGACCTAGGTAA (SEQ ID NO:61)

[0461] 构建体S2-7A5-CD28T-41BB AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDI
NWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRS
EDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP
GTLSLSPGERATLSCRAGQSVTSSSLAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYGGSRAFGQGTKVELKRAAALDNEKSNGTIIH
VKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRFSVVKRGRKKL
LYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYN

[0462] ELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMK
GERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVE
ENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGE
GVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVC
RCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVD
PCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQ
DLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ
ID NO:62)

[0463] 构建体S2-7A5-C8K-CD28 DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG

[0464] CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT
CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA
CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT

GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC

TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT

ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT

TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT

CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG

GTCAGAGTGTTACCAGCAGCTCCTTAGCTTGGTACCAGCAGAAACCTGGCCAGG

CTCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAG

GTTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAG

CCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGGCGTTCG

GCCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCTTCGTGCCTGTTTTTCT

GCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCAACTCCTGCACCAACT

ATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAGGCG

GCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGCCCC

CCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTACTGC

AACCACAGAAACAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAAT

ATGACTCCACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCA

[0465] CCTAGAGATTTCGCTGCCTATCGGAGCAGGGTGAAGTTTTCCAGATCTGCAGATG

CACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGAC

GCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATG

GGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAG

AAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAG

AAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGG

ATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTG

GCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAATC

CGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTGC

TTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAAC

GGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGC

GTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAG

TGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATG

TGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGC

AGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGC

CGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAAC

ACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTC

GACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAG
TGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACC
CGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCG

[0466] GAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACG
ACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTG
ATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACA
TCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:63)

[0467] 构建体S2-7A5-C8K-CD28 AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDI
NWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRS
EDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP
GTLSLSPGERATLSCRAGQSVTSSSLAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYGGSRAFGQGTKVELKRAAAFVPVFLPAKPTT
TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLL
LSLVITLYCNHRNRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRV

[0468] KFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEG
LYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
AKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLGVSLGGAKEA
CPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTE
CVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQN
TVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRST
PPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSIL
AAVVVGLVAYIAFKR (SEQ ID NO:64)

[0469] 构建体S2-7A5-C8K-41BB DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT

[0470] CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA
CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT
GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC
TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT

ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT
TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT
CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG
GTCAGAGTGTTACCAGCAGCTCCTTAGCTTGGTACCAGCAGAAACCTGGCCAGG
CTCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAG
GTTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAG
CCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGGCGTTCG
GCCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCTTCGTGCCTGTTTTTCT
GCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCAACTCCTGCACCAACT
ATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAGGCG
GCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGCCCC
CCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTACTGC
AACCACAGAAACCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTAC
ATTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGC
TGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAG
TTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATA

[0471] ACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAG
GACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGT
CTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGC
ATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACT
CAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCT
AGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGG
GACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATG
GATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTA
AGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTG
TAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGA
ACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGC
AAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAG
CCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCG
GGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTG
CCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGA
CGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGA
ACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCC
TGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCC
GAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGT

[0472] TGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGG
CACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTG
GGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:65)

[0473] 构建体S2-7A5-C8K-41BB AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDI
NWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRS
EDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP
GTLSLSPGERATLSCRAGQSVTSSSLAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYGGSRAFGQGTKVELKRAAAFVPVFLPAKPTT
TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLL
LSLVITLYCNHRNRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGC

[0474] ELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN
PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ
ALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLG
GAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEP
CKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFS
CQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPG
RWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLI
PVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:66)

[0475] 构建体S2-14C1-CD28T-CD28-41BB DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATAT
GCACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAA

[0476] CCCTAATAGTGGTGGCACAAACTCTGCACAGAAGTTTCAGGGCAGGGTCACCAT
GACCAGGGACACGTCCATCAGTACAGCCTACATGGAGCTGAACAGGCTGAGATC
TGACGACACGGCCGTTTATTACTGTGCGAGAGGATGGCTACAGACGTACTACTTT
GACAACTGGGGCCAGGGAACCCTGGTCACCGTATCCTCAGGAGGCGGCGGTTCA
GGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGACATCGTGATGACCCAGTCTCCA

GACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCTACTGCAAGTCCAGCC

AGACTGTTTTGACCAGCTCCAACAATAAGAACTTCTTAGCTTGGTACCAACAGAA

ACTAGGACAGCCTCCTAAGCTGCTCATTTCCTGGGCCTCTACCCGGGAATCCGGG

GTCCCTGACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCA

GCAGCCTGCAGGCTGAAGATGTGGCAATTTATTACTGTCAGCACTATTATACTAG

TCCACTCACTTTCGGCGGCGGGACCAAGGTGGAGATCAAACGAGCCGCTGCCCT

TGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTG

TCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGG

GTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGG

GTTAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCAC

GCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATT

TCGCTGCCTATCGGAGCCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCT

GTACATTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGA

CGGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGT

GAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACT

GTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCG

[0477] CAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGG

AGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAA

TAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAG

GGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGC

CACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACAT

GTGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGG

GCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAG

GCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAA

AGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGT

CTGTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAG

CCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTG

TCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAA

CTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTT

CAGTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTA

CAGCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGA

TACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGA

GATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTAC

AGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTC
TACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGAC

[0478] GCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTG
GTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:67)

[0479] 构建体S2-14C1-CD28T-CD28-41BB AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTGYY
MHWVRQAPGQGLEWMGWINPNSGGTNSAQKFQGRVTMTRDTSISTAYMELNRLRS
DDTAVYYCARGWLQTYYFDNWGQGTLVTVSSGGGGSGGGGSGGGGSDIVMTQSP
DSLAVSLGERATIYCKSSQTVLTSSNNKNFLAWYQQKLGQPPKLLISWASTRESGVP
DRFSGSGSGTDFTLTISSLQAEDVAIYYCQHYYTSPLTFGGGTKVEIKRAAALDNEKS
NGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRL
LHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRFSVVKRGRKKLLYIFKQPFMR

[0480] PVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREE
YDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG
HDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGA
GATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCG
ANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYY
QDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVC
EDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVA
GVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:68)

[0481] 构建体S2-14C1-CD28T-CD28 DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATAT

[0482] GCACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAA
CCCTAATAGTGGTGGCACAAACTCTGCACAGAAGTTTCAGGGCAGGGTCACCAT
GACCAGGGACACGTCCATCAGTACAGCCTACATGGAGCTGAACAGGCTGAGATC
TGACGACACGGCCGTTTATTACTGTGCGAGAGGATGGCTACAGACGTACTACTTT

GACAACTGGGGCCAGGGAACCCTGGTCACCGTATCCTCAGGAGGCGGCGGTTCA
GGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGACATCGTGATGACCCAGTCTCCA
GACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCTACTGCAAGTCCAGCC
AGACTGTTTTGACCAGCTCCAACAATAAGAACTTCTTAGCTTGGTACCAACAGAA
ACTAGGACAGCCTCCTAAGCTGCTCATTTCCTGGGCCTCTACCCGGGAATCCGGG
GTCCCTGACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCA
GCAGCCTGCAGGCTGAAGATGTGGCAATTTATTACTGTCAGCACTATTATACTAG
TCCACTCACTTTCGGCGGCGGGACCAAGGTGGAGATCAAACGAGCCGCTGCCCT
TGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTG
TCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGG
GTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGG
GTTAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCAC
GCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATT
TCGCTGCCTATCGGAGCAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTA
TCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGA
GTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACC
[0483] AAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGAT
GGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAG
GGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACG
CTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGG
GCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCCTATGG
GTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTT
GTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACT
CACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTT
GTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTGACATTCAGCGA
TGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAG
TCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATG
GATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAG
CCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGTGAGG
AGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTCGACCCTTGCTTGC
CGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGG
CAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTC
CTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAG
AGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATC
[0484] CTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGT
AGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGAT
GACCTAGGTAA (SEQ ID NO:69)

[0485] 构建体S2-14C1-CD28T-CD28 AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTGYY
MHWVRQAPGQGLEWMGWINPNSGGTNSAQKFQGRVTMTRDTSISTAYMELNRLRS
DDTAVYYCARGWLQTYYFDNWGQGTLVTVSSGGGGSGGGGSGGGGSDIVMTQSP
DSLAVSLGERATIYCKSSQTVLTSSNNKNFLAWYQQKLGQPPKLLISWASTRESGVP
DRFSGSGSGTDFTLTISSLQAEDVAIYYCQHYYTSPLTFGGGTKVEIKRAAALDNEKS
NGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRL
LHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLY

[0486] NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM
KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDV
EENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLG
EGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAV
CRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHV
DPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPE
QDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ
ID NO:70)

[0487] 构建体S2-14C1-CD28T-41BB DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATAT
GCACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAA
CCCTAATAGTGGTGGCACAAACTCTGCACAGAAGTTTCAGGGCAGGGTCACCAT

[0488] GACCAGGGACACGTCCATCAGTACAGCCTACATGGAGCTGAACAGGCTGAGATC
TGACGACACGGCCGTTTATTACTGTGCGAGAGGATGGCTACAGACGTACTACTTT
GACAACTGGGGCCAGGGAACCCTGGTCACCGTATCCTCAGGAGGCGGCGGTTCA
GGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGACATCGTGATGACCCAGTCTCCA
GACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCTACTGCAAGTCCAGCC

AGACTGTTTTGACCAGCTCCAACAATAAGAACTTCTTAGCTTGGTACCAACAGAA
ACTAGGACAGCCTCCTAAGCTGCTCATTTCCTGGGCCTCTACCCGGGAATCCGGG
GTCCCTGACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCA
GCAGCCTGCAGGCTGAAGATGTGGCAATTTATTACTGTCAGCACTATTATACTAG
TCCACTCACTTTCGGCGGCGGGACCAAGGTGGAGATCAAACGAGCCGCTGCCCT
TGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTG
TCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGG
GTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGG
GTTCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAAC
AGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCC
GCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGAT
CTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCA
ACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGAC
CCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAAT
GAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGA
GAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGC
TACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAA
[0489] GAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGA
AGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCC
GCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCC
TGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTG
GCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCC
TGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTG
TACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGAT
GCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGT
GAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATA
AGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCG
AACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGC
TGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGAT
GGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCC
AAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCG
TGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCG

ACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGT
AGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:71)

[0490] 构建体S2-14C1-CD28T-41BB AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTGYY
MHWVRQAPGQGLEWMGWINPNSGGTNSAQKFQGRVTMTRDTSISTAYMELNRLRS
DDTAVYYCARGWLQTYYFDNWGQGTLVTVSSGGGGSGGGGSGGGGSDIVMTQSP
DSLAVSLGERATIYCKSSQTVLTSSNNKNFLAWYQQKLGQPPKLLISWASTRESGVP
DRFSGSGSGTDFTLTISSLQAEDVAIYYCQHYYTSPLTFGGGTKVEIKRAAALDNEKS
NGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRFSVVKR
GRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQ
[0491] NQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYS
EIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTC
GDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKA
CNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEA
DDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDE
ANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEP
EAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFK
R (SEQ ID NO:72)

[0492] 构建体S2-14C1-C8K-CD28 DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATAT
GCACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAA
CCCTAATAGTGGTGGCACAAACTCTGCACAGAAGTTTCAGGGCAGGGTCACCAT
[0493] GACCAGGGACACGTCCATCAGTACAGCCTACATGGAGCTGAACAGGCTGAGATC
TGACGACACGGCCGTTTATTACTGTGCGAGAGGATGGCTACAGACGTACTACTTT
GACAACTGGGGCCAGGGAACCCTGGTCACCGTATCCTCAGGAGGCGGCGGTTCA
GGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGACATCGTGATGACCCAGTCTCCA
GACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCTACTGCAAGTCCAGCC
AGACTGTTTTGACCAGCTCCAACAATAAGAACTTCTTAGCTTGGTACCAACAGAA
ACTAGGACAGCCTCCTAAGCTGCTCATTTCCTGGGCCTCTACCCGGGAATCCGGG

GTCCCTGACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCA
GCAGCCTGCAGGCTGAAGATGTGGCAATTTATTACTGTCAGCACTATTATACTAG
TCCACTCACTTTCGGCGGCGGGACCAAGGTGGAGATCAAACGAGCCGCTGCCTT
CGTGCCTGTTTTTCTGCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCA
ACTCCTGCACCAACTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCC
GCCCCGCGGCAGGCGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATA
TTTATATCTGGGCCCCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGT
GATTACCCTCTACTGCAACCACAGAAACAGATCCAAAAGAAGCCGCCTGCTCCA
TAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCCCACAAGGAAACACTA
CCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATCGGAGCAGGGTGAAGTTT
TCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAAC
GAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGA
CGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCT
CTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCAT
GAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCA
GCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAG

[0494] GGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGA
CGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGA
TGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAG
GAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTA
ACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAAC
CATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAA
GCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCC
GATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGG
CGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCC
AGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGAC
GAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAA
CGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCT
GGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCG
AGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTT
GCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGC
ACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGG
GCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:73)

[0495] 构建体S2-14C1-C8K-CD28 AA(信号序列以粗体显示;CDR加下划线)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTGYY
MHWVRQAPGQGLEWMGWINPNSGGTNSAQKFQGRVTMTRDTSISTAYMELNRLRS
DDTAVYYCARGWLQTYYFDNWGQGTLVTVSSGGGGSGGGGSGGGGSDIVMTQSP
DSLAVSLGERATIYCKSSQTVLTSSNNKNFLAWYQQKLGQPPKLLISWASTRESGVP
DRFSGSGSGTDFTLTISSLQAEDVAIYYCQHYYTSPLTFGGGTKVEIKRAAAFVPVFL
PAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGT
CGVLLLSLVITLYCNHRNRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAA
[0496] YRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRK
NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM
QALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSL
GGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATE
PCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFS
CQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPG
RWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLI
PVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:74)

[0497] 构建体S2-14C1-C8K-41BB DNA(信号序列以粗体显示)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATAT
GCACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAA
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AGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTT
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GTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGG
CAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTA
A (SEQ ID NO:75)

[0500] 构建体S2-14C1-C8K-41BB AA(信号序列以粗体显示;CDR加下划线)

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DRFSGSGSGTDFTLTISSLQAEDVAIYYCQHYYTSPLTFGGGTKVEIKRAAAFVPVFL
PAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGT
CGVLLLSLVITLYCNHRNRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE
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PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDA
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ATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSG
LVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECE
EIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTT
DNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:76)

[0502] 人STEAP1NM_012449(NP_036581)AA
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PILVINKVLPMVSITLLALVYLPGVIAAIVQLHNGTKYKKFPHWLDKWMLTRKQFGL
[0503] LSFFFAVLHAIYSLSYPMRRSYRYKLLNWAYQQVQQNKEDAWIEHDVWRMEIYVSL
GIVGLAILALLAVTSIPSVSDSLTWREFHYIQSKLGIVSLLLGTIHALIFAWNKWIDIKQ
FVWYTPPTFMIAVFLPIVVLIFKSILFLPCLRKKILKIRHGWEDVTKINKTEICSQL (SEQ
ID NO:77)

[0504] CAR信号肽DNA

[0505] ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCG (SEQ ID NO:78)

[0506] CAR信号肽:MALPVTALLLPLALLLHAARP(SEQ ID NO:79)

[0507] scFv G4S接头DNA

[0508] GGCGGTGGAGGCTCCGGAGGGGGGGGCTCTGGCGGAGGGGGCTCC(SEQ ID NO:80)

[0509] scFv G4s接头:GGGGSGGGGSGGGGS(SEQ ID NO:81)

[0510] scFv惠特洛接头DNA

[0511] GGGTCTACATCCGGCTCCGGGAAGCCCGGAAGTGGCGAAGGTAGTACAAAGGGG
(SEQ ID NO:82)

[0512] scFv惠特洛接头:GSTSGSGKPGSGEGSTKG(SEQ ID NO:83)

[0513] 4-1BB核酸序列(细胞内结构域)

AAGCGCGGCAGGAAGAAGCTCCTCTACATTTTTAAGCAGCCTTTTATGAGGCCCG

[0514] TACAGACAACACAGGAGGAAGATGGCTGTAGCTGCAGATTTCCCGAGGAGGAGG

AAGGTGGGTGCGAGCTG (SEQ ID NO:84)

[0515] 4-1BB AA(细胞内结构域)

[0516] KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL(SEQ ID NO:85)

[0517] OX40 AA

[0518] RRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLAKI(SEQ ID NO:86)

[0519] 通过引用结合

[0520] 本说明书中提到的所有出版物、专利和专利申请都通过引入结合在此,如同每一单独的出版物、专利或专利申请具体且单独地通过引入结合在此。然而,在此的参考文献的引用不能理解为承认此类参考文献是本发明的现有技术。通过引用结合的参考文献中提供的任何定义或术语与本文提供的术语和讨论发生冲突的程度上,以为本术语和定义为准。

[0521] 等同物

[0522] 前述书面说明书被认为满足能使本领域技术人员实践本发明。本发明的某些优选实施例中详细描述了前述描述和实例并描述了诸位发明人考虑的最佳模式。然而,将领会到的是,不论前述事项可以在文中看起来如何详尽,本发明可以按多种方式进行实践,并且应该依据所附权利要求书及其任何等同物来解释。

[0523] 以下实例,包括进行的实验和实现的结果,仅提供解释说明目的,并且不应被解释为限制本发明。

[0524] 实例1

[0525] 将PNT-2、LNCaP、PC-3、22Rv1、C4-2B和DU145细胞系在RPMI1640(龙沙公司(Lonza))+10%FBS(康宁公司(Corning))+1X青霉素链霉素L-谷氨酰胺(康宁公司)(R10)培养基中培养并维持细胞密度在0.5-2.0x10^6个细胞/ml之间。PNT-2和DU145是阴性对照细胞系。为了检查细胞表面STEAP1表达,将细胞与抗STEAP1抗体(2F3)或IgG1同种型对照抗体(BD Pharmingen公司)在染色缓冲液(BD Pharmingen公司)中在4℃下孵育30分钟。数据采集前,洗涤细胞并重悬于含有碘化丙啶(BD Pharmingen公司)的染色缓冲液中。靶细胞上的STEAP1表达如图1所示。

[0526] 实例2

[0527] 通过用EcoRI和BamHI(NEB)过夜消化10μg DNA,使编码T7启动子、CAR构建体和β珠蛋白稳定序列的质粒线性化。然后在50℃下用蛋白酶K(赛默飞世尔科技公司(Thermo Scientific),600U/ml)将DNA消化2小时,用苯酚/氯仿纯化,并通过添加乙酸钠和2体积的乙醇沉淀。然后将沉淀干燥,重悬浮于不含RNA酶/DNA酶的水中并使用NanoDrop定量。然后使用mMESSAGE mMACHINE T7Ultra(赛默飞世尔科技公司)按照制造商的说明将1μg线性DNA用于体外转录。使用MEGAClear试剂盒(赛默飞世尔科技公司)按照制造商的说明进一步纯化RNA,并使用NanoDrop定量。使用琼脂糖凝胶上的迁移率评估mRNA完整性。根据制造商的说明书,使用ficoll-paque密度离心法从健康供体leukopaks(Hemacare)中分离出PBMC。使用OKT3(50ng/ml,美天旎生物技术公司(Miltenyi Biotec))于R10培养基+IL-2(300IU/ml,Proleukin®, Prometheus®治疗诊断公司(Prometheus® Therapeutics and Diagnostics))中刺激PBMC。刺激后7天,将T细胞在Opti-MEM培养基(赛默飞世尔科技公司)中洗涤两次,并

在Opti-MEM培养基中以2.5x10^7个细胞/ml的终浓度重悬。每次电穿孔使用10μg的mRNA。使用Gemini X2系统(哈佛仪器公司(Harvard Apparatus BTX))进行细胞的电穿孔,以在2mm比色皿(哈佛仪器公司)中递送单个400V脉冲0.5ms。立即将细胞转移到R10+IL-2培养基中并允许其恢复6小时。为检测CAR表达,在染色缓冲液(BD Pharmingen公司)中使用LNGFR或生物素化蛋白L(赛默飞世尔科技公司)在4℃下染色T细胞30分钟。然后洗涤细胞并在染色缓冲液中使用抗LNGFR-PE或PE链霉亲和素(BD Pharmingen公司)在4℃下染色30分钟。数据采集前,洗涤细胞并重悬于含有碘化丙啶(BD Pharmingen公司)的染色缓冲液中。STEAP1CAR在电穿孔的T细胞中的表达显示在图2中。

[0528] 实例3

[0529] 为了检测电穿孔的STEAP1 CAR T细胞的细胞溶解活性,将效应细胞与靶细胞按1:1的E:T比在R10培养基中培养。共培养十六小时后,通过Luminex(EMD密理博公司(EMD Millipore))分析上清液,并通过被CD-3阴性细胞吸收的碘化丙啶(PI)的流式细胞术评估靶细胞存活率。电穿孔的CAR T细胞的细胞溶解活性显示在图3中,并且细胞因子产生显示在图4中。

[0530] 实例4

[0531] 为了评估对表达STEAP1的靶细胞应答的CAR T细胞增殖,在R10培养基中以1:1的E:T比与靶细胞共培养前,用CFSE标记T细胞。五天后,通过CFSE稀释的流式细胞术评估T细胞增殖情况。STEAP1 CAR T细胞的增殖情况如图5所示。

序列表

<110> 美商安进公司（AMGEN INC.）

<120> 针对STEAP1的嵌合受体及其使用方法

<130> A-2280-WO-PCT

<140> PCT/US2019/042245
<141> 2019-07-17

<150> 62/700,178
<151> 2018-07-18

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ctcgcttgtt actctctgct cgtcaccgtg gcttttataa tcttctgggt tagatccaaa 180

agaagccgcc tgctccatag cgattacatg aatatgactc cacgccgccc tggccccaca 240

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His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp
20 25 30

Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val
35 40 45

[0002]

Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu
50 55 60

Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr
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[0003]

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20 25 30

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[0004]

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35 40

[0005]

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cgggaccctg agatgggtgg caaaccaaga cgaaaaaacc cccaggaggg tctctataat 180

gagctgcaga aggataagat ggctgaagcc tattctgaaa taggcatgaa aggagagcgg 240

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20 25 30

[0006]

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
35 40 45

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
50 55 60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65 70 75 80

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
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Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
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Phe Pro Gly Pro Ser Lys Pro
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35 40 45

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
50 55 60

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
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Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn
85 90 95

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Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
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35 40 45

Thr Phe Ser Thr Tyr Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Gln
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Arg Leu Glu Trp Met Gly Glu Ile Leu Pro Gly Ser Gly Asn Thr Asp
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Ser Asp Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

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145 150 155 160

Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala
165 170 175

Thr Leu Ser Cys Arg Ala Ser Ser Ser Val Ser Tyr Met His Trp Phe
180 185 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Ser Thr Ser

195 200 205

Asn Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
210 215 220

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
225 230 235 240

Val Tyr Tyr Cys Gln Gln Arg Arg Ser Phe Pro Tyr Thr Phe Gly Gln
245 250 255

Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Leu Asp Asn Glu Lys Ser
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Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro
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Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile
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Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
325 330 335

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
340 345 350

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val
355 360 365

Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
370 375 380

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
385 390 395 400

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
405 410 415

Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
420 425 430

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
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Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
485 490 495

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
500 505 510

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

Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu

530 535 540

Asn Pro Gly Pro Met Gly Ala Gly Ala Thr Gly Arg Ala Met Asp Gly
545 550 555 560

Pro Arg Leu Leu Leu Leu Leu Leu Leu Gly Val Ser Leu Gly Gly Ala
565 570 575

Lys Glu Ala Cys Pro Thr Gly Leu Tyr Thr His Ser Gly Glu Cys Cys
580 585 590

Lys Ala Cys Asn Leu Gly Glu Gly Val Ala Gln Pro Cys Gly Ala Asn
595 600 605

Gln Thr Val Cys Glu Pro Cys Leu Asp Ser Val Thr Phe Ser Asp Val
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Val Ser Ala Thr Glu Pro Cys Lys Pro Cys Thr Glu Cys Val Gly Leu
625 630 635 640

Gln Ser Met Ser Ala Pro Cys Val Glu Ala Asp Asp Ala Val Cys Arg
645 650 655

Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys Glu Ala
660 665 670

Cys Arg Val Cys Glu Ala Gly Ser Gly Leu Val Phe Ser Cys Gln Asp
675 680 685

Lys Gln Asn Thr Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser Asp
690 695 700

Glu Ala Asn His Val Asp Pro Cys Leu Pro Cys Thr Val Cys Glu Asp
705 710 715 720

Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala Glu Cys
725 730 735

Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro Glu Gly
740 745 750

Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro Pro Glu
755 760 765

Gln Asp Leu Ile Ala Ser Thr Val Ala Gly Val Val Thr Thr Val Met
770 775 780

[0017] Gly Ser Ser Gln Pro Val Val Thr Arg Gly Thr Thr Asp Asn Leu Ile
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35 40 45

[0020] Thr Phe Ser Thr Tyr Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Gln
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Arg Leu Glu Trp Met Gly Glu Ile Leu Pro Gly Ser Gly Asn Thr Asp
65 70 75 80

Phe Asn Glu Lys Phe Gln Gly Arg Val Thr Phe Thr Ala Asp Thr Ser
85 90 95

Ser Asp Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Thr Arg Trp Gly Tyr Tyr Gly Thr Arg Gly Tyr
115 120 125

Phe Asn Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
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Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val
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Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala
165 170 175

Thr Leu Ser Cys Arg Ala Ser Ser Ser Val Ser Tyr Met His Trp Phe
180 185 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Ser Thr Ser
195 200 205

Asn Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
210 215 220

[0021]

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
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Val Tyr Tyr Cys Gln Gln Arg Arg Ser Phe Pro Tyr Thr Phe Gly Gln
245 250 255

Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Leu Asp Asn Glu Lys Ser
260 265 270

Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro
275 280 285

Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly
290 295 300

Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile
305 310 315 320

Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
325 330 335

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
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Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe
355 360 365

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
370 375 380

[0022] Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
385 390 395 400

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
405 410 415

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
420 425 430

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
435 440 445

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
450 455 460

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Ala Lys Arg Ser
465 470 475 480

Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu
485 490 495

Glu Asn Pro Gly Pro Met Gly Ala Gly Ala Thr Gly Arg Ala Met Asp
500 505 510

Gly Pro Arg Leu Leu Leu Leu Leu Leu Leu Leu Gly Val Ser Leu Gly Gly
515 520 525

Ala Lys Glu Ala Cys Pro Thr Gly Leu Tyr Thr His Ser Gly Glu Cys
530 535 540

Cys Lys Ala Cys Asn Leu Gly Glu Gly Val Ala Gln Pro Cys Gly Ala
545 550 555 560

[0023]

Asn Gln Thr Val Cys Glu Pro Cys Leu Asp Ser Val Thr Phe Ser Asp
565 570 575

Val Val Ser Ala Thr Glu Pro Cys Lys Pro Cys Thr Glu Cys Val Gly
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Leu Gln Ser Met Ser Ala Pro Cys Val Glu Ala Asp Asp Ala Val Cys
595 600 605

Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys Glu
610 615 620

Ala Cys Arg Val Cys Glu Ala Gly Ser Gly Leu Val Phe Ser Cys Gln
625 630 635 640

Asp Lys Gln Asn Thr Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser
645 650 655

Asp Glu Ala Asn His Val Asp Pro Cys Leu Pro Cys Thr Val Cys Glu
660 665 670

Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala Glu
675 680 685

Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro Glu
690 695 700

Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro Pro
705 710 715 720

[0024] Glu Gln Asp Leu Ile Ala Ser Thr Val Ala Gly Val Val Thr Thr Val
725 730 735

Met Gly Ser Ser Gln Pro Val Val Thr Arg Gly Thr Thr Asp Asn Leu
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65 70 75 80

Phe Asn Glu Lys Phe Gln Gly Arg Val Thr Phe Thr Ala Asp Thr Ser
85 90 95

Ser Asp Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
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Ala Val Tyr Tyr Cys Thr Arg Trp Gly Tyr Tyr Gly Thr Arg Gly Tyr

115 120 125

Phe Asn Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
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145 150 155 160

Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala
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Thr Leu Ser Cys Arg Ala Ser Ser Ser Val Ser Tyr Met His Trp Phe
180 185 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Ser Thr Ser
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245 250 255

Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Leu Asp Asn Glu Lys Ser
260 265 270

Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro
275 280 285

Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly
290 295 300

Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile
305 310 315 320

Phe Trp Val Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu
325 330 335

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
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Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
355 360 365

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Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
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Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
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Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser

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Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
465 470 475 480

Pro Arg Ala Lys Arg Ser Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu
485 490 495

Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Met Gly Ala Gly Ala
500 505 510

Thr Gly Arg Ala Met Asp Gly Pro Arg Leu Leu Leu Leu Leu Leu Leu
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Gly Val Ser Leu Gly Gly Ala Lys Glu Ala Cys Pro Thr Gly Leu Tyr
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Ala Gln Pro Cys Gly Ala Asn Gln Thr Val Cys Glu Pro Cys Leu Asp
565 570 575

Ser Val Thr Phe Ser Asp Val Val Ser Ala Thr Glu Pro Cys Lys Pro
580 585 590

Cys Thr Glu Cys Val Gly Leu Gln Ser Met Ser Ala Pro Cys Val Glu
595 600 605

Ala Asp Asp Ala Val Cys Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu
610 615 620

Thr Thr Gly Arg Cys Glu Ala Cys Arg Val Cys Glu Ala Gly Ser Gly
625 630 635 640

Leu Val Phe Ser Cys Gln Asp Lys Gln Asn Thr Val Cys Glu Glu Cys
645 650 655

Pro Asp Gly Thr Tyr Ser Asp Glu Ala Asn His Val Asp Pro Cys Leu
660 665 670

Pro Cys Thr Val Cys Glu Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr
675 680 685

Arg Trp Ala Asp Ala Glu Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr
690 695 700

[0031] Arg Ser Thr Pro Pro Glu Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln
705 710 715 720

Glu Pro Glu Ala Pro Pro Glu Gln Asp Leu Ile Ala Ser Thr Val Ala
725 730 735

Gly Val Val Thr Thr Val Met Gly Ser Ser Gln Pro Val Val Thr Arg
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Gly Thr Thr Asp Asn Leu Ile Pro Val Tyr Cys Ser Ile Leu Ala Ala
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Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
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Thr Phe Ser Thr Tyr Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Arg Leu Glu Trp Met Gly Glu Ile Leu Pro Gly Ser Gly Asn Thr Asp
65 70 75 80

Phe Asn Glu Lys Phe Gln Gly Arg Val Thr Phe Thr Ala Asp Thr Ser
85 90 95

Ser Asp Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Thr Arg Trp Gly Tyr Tyr Gly Thr Arg Gly Tyr
115 120 125

Phe Asn Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
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Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val
145 150 155 160

Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala
165 170 175

[0035]

Thr Leu Ser Cys Arg Ala Ser Ser Ser Val Ser Tyr Met His Trp Phe
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Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Ser Thr Ser
195 200 205

Asn Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
210 215 220

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
225 230 235 240

Val Tyr Tyr Cys Gln Gln Arg Arg Ser Phe Pro Tyr Thr Phe Gly Gln
245 250 255

Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Phe Val Pro Val Phe Leu
260 265 270

Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
275 280 285

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
290 295 300

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
305 310 315 320

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
325 330 335

[0036] Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Ser Lys
340 345 350

Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg
355 360 365

Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp
370 375 380

Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
385 390 395 400

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
405 410 415

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
420 425 430

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
435 440 445

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
450 455 460

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
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Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
485 490 495

Gln Ala Leu Pro Pro Arg Ala Lys Arg Ser Gly Ser Gly Glu Gly Arg
500 505 510

[0037]

Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Met
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Gly Ala Gly Ala Thr Gly Arg Ala Met Asp Gly Pro Arg Leu Leu Leu
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Leu Leu Leu Leu Gly Val Ser Leu Gly Gly Ala Lys Glu Ala Cys Pro
545 550 555 560

Thr Gly Leu Tyr Thr His Ser Gly Glu Cys Cys Lys Ala Cys Asn Leu
565 570 575

Gly Glu Gly Val Ala Gln Pro Cys Gly Ala Asn Gln Thr Val Cys Glu
580 585 590

Pro Cys Leu Asp Ser Val Thr Phe Ser Asp Val Val Ser Ala Thr Glu
595 600 605

Pro Cys Lys Pro Cys Thr Glu Cys Val Gly Leu Gln Ser Met Ser Ala
610 615 620

Pro Cys Val Glu Ala Asp Asp Ala Val Cys Arg Cys Ala Tyr Gly Tyr
625 630 635 640

Tyr Gln Asp Glu Thr Thr Gly Arg Cys Glu Ala Cys Arg Val Cys Glu
645 650 655

Ala Gly Ser Gly Leu Val Phe Ser Cys Gln Asp Lys Gln Asn Thr Val
660 665 670

[0038]

Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser Asp Glu Ala Asn His Val
675 680 685

Asp Pro Cys Leu Pro Cys Thr Val Cys Glu Asp Thr Glu Arg Gln Leu
690 695 700

Arg Glu Cys Thr Arg Trp Ala Asp Ala Glu Cys Glu Glu Ile Pro Gly
705 710 715 720

Arg Trp Ile Thr Arg Ser Thr Pro Pro Glu Gly Ser Asp Ser Thr Ala
725 730 735

Pro Ser Thr Gln Glu Pro Glu Ala Pro Pro Glu Gln Asp Leu Ile Ala
740 745 750

Ser Thr Val Ala Gly Val Val Thr Thr Val Met Gly Ser Ser Gln Pro
755 760 765

Val Val Thr Arg Gly Thr Thr Asp Asn Leu Ile Pro Val Tyr Cys Ser
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Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Ser Thr Tyr Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Arg Leu Glu Trp Met Gly Glu Ile Leu Pro Gly Ser Gly Asn Thr Asp
65 70 75 80

Phe Asn Glu Lys Phe Gln Gly Arg Val Thr Phe Thr Ala Asp Thr Ser
85 90 95

Ser Asp Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

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Phe Asn Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
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Gly Gly Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val
145 150 155 160

Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala
165 170 175

Thr Leu Ser Cys Arg Ala Ser Ser Ser Val Ser Tyr Met His Trp Phe
180 185 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Ser Thr Ser

195 200 205

Asn Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
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Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
225 230 235 240

Val Tyr Tyr Cys Gln Gln Arg Arg Ser Phe Pro Tyr Thr Phe Gly Gln
245 250 255

Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Phe Val Pro Val Phe Leu
260 265 270

Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
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Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
290 295 300

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
305 310 315 320

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
325 330 335

Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Phe Ser
340 345 350

Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
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Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
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Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
435 440 445

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485 490 495

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Ala Lys Arg Ser
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Glu Asn Pro Gly Pro Met Gly Ala Gly Ala Thr Gly Arg Ala Met Asp

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Gly Pro Arg Leu Leu Leu Leu Leu Leu Leu Gly Val Ser Leu Gly Gly
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Ala Lys Glu Ala Cys Pro Thr Gly Leu Tyr Thr His Ser Gly Glu Cys
565 570 575

Cys Lys Ala Cys Asn Leu Gly Glu Gly Val Ala Gln Pro Cys Gly Ala
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Asn Gln Thr Val Cys Glu Pro Cys Leu Asp Ser Val Thr Phe Ser Asp
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Val Val Ser Ala Thr Glu Pro Cys Lys Pro Cys Thr Glu Cys Val Gly
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Leu Gln Ser Met Ser Ala Pro Cys Val Glu Ala Asp Asp Ala Val Cys
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Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys Glu
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Ala Cys Arg Val Cys Glu Ala Gly Ser Gly Leu Val Phe Ser Cys Gln
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Asp Lys Gln Asn Thr Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser
675 680 685

Asp Glu Ala Asn His Val Asp Pro Cys Leu Pro Cys Thr Val Cys Glu
690 695 700

Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala Glu
705 710 715 720

Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro Glu
725 730 735

Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro Pro
740 745 750

Glu Gln Asp Leu Ile Ala Ser Thr Val Ala Gly Val Val Thr Thr Val
755 760 765

Met Gly Ser Ser Gln Pro Val Val Thr Arg Gly Thr Thr Asp Asn Leu
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[0046]

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Ala Tyr Ile Ala Phe Lys Arg
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Gly Leu Glu Trp Met Gly Trp Met Asn Thr Tyr Thr Gly Glu Pro Thr
65 70 75 80

Tyr Ala Asp Lys Phe Gln Gly Arg Val Thr Phe Thr Leu Asp Thr Ser
85 90 95

Ala Arg Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Phe Cys Ala Arg Ala Gly Gly Gln Leu Arg Pro Gly Ala
115 120 125

Met Asp Tyr Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
145 150 155 160

Leu Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly Gln Pro Ala
165 170 175

Ser Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser
180 185 190

Phe Met Asn Trp Tyr Leu Gln Lys Pro Gly Gln Pro Pro Gln Leu Leu
195 200 205

[0050]

Ile Tyr Val Ala Ser Asn Leu Glu Ser Gly Val Pro Asp Arg Phe Ser
210 215 220

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu
225 230 235 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Ser Asn Glu Glu Pro
245 250 255

Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Leu
260 265 270

Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His
275 280 285

Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val
290 295 300

Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr
305 310 315 320

Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu
325 330 335

His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg
340 345 350

Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg
355 360 365

Ser Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile
370 375 380

[0051]

Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp
385 390 395 400

Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
405 410 415

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
420 425 430

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
435 440 445

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
450 455 460

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
465 470 475 480

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
485 490 495

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
500 505 510

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
515 520 525

Ala Lys Arg Ser Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys
530 535 540

[0052]

Gly Asp Val Glu Glu Asn Pro Gly Pro Met Gly Ala Gly Ala Thr Gly
545 550 555 560

Arg Ala Met Asp Gly Pro Arg Leu Leu Leu Leu Leu Leu Leu Leu Gly Val
565 570 575

Ser Leu Gly Gly Ala Lys Glu Ala Cys Pro Thr Gly Leu Tyr Thr His
580 585 590

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

Pro Cys Gly Ala Asn Gln Thr Val Cys Glu Pro Cys Leu Asp Ser Val
610 615 620

Thr Phe Ser Asp Val Val Ser Ala Thr Glu Pro Cys Lys Pro Cys Thr
625 630 635 640

Glu Cys Val Gly Leu Gln Ser Met Ser Ala Pro Cys Val Glu Ala Asp
645 650 655

Asp Ala Val Cys Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu Thr Thr
660 665 670

Gly Arg Cys Glu Ala Cys Arg Val Cys Glu Ala Gly Ser Gly Leu Val
675 680 685

Phe Ser Cys Gln Asp Lys Gln Asn Thr Val Cys Glu Glu Cys Pro Asp
690 695 700

Gly Thr Tyr Ser Asp Glu Ala Asn His Val Asp Pro Cys Leu Pro Cys
705 710 715 720

[0053]

Thr Val Cys Glu Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg Trp
725 730 735

Ala Asp Ala Glu Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg Ser
740 745 750

Thr Pro Pro Glu Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu Pro
755 760 765

Glu Ala Pro Pro Glu Gln Asp Leu Ile Ala Ser Thr Val Ala Gly Val
770 775 780

Val Thr Thr Val Met Gly Ser Ser Gln Pro Val Val Thr Arg Gly Thr
785 790 795 800

Thr Asp Asn Leu Ile Pro Val Tyr Cys Ser Ile Leu Ala Ala Val Val
805 810 815

Val Gly Leu Val Ala Tyr Ile Ala Phe Lys Arg
820 825

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多核苷酸"

<400> 29

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atcagctgca aggccagcgg ctacacattc accaactacg gcatgaactg ggtgcaacag 180

gcccccggcc agggactgga gtggatgggc tggatgaaca catacaccgg cgagcccacc 240

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tatatggaac tgagcagcct gaggagcgag gacaccgctg tgtacttctg cgcaagggct 360

ggaggccagc tgagacctgg cgctatggac tactggggcc agggcaccat ggtgaccgtg 420

agctccggag gcggaggatc tggtggcggt ggttctggcg gcggaggctc cgacatcgtg 480

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ccattctggg tgttggtcgt agtgggtgga gtcctcgctt gttactctct gctcgtcacc 960

gtggctttta taatcttctg ggttagatcc aaaagaagcc gcctgctcca tagcgattac 1020

atgaatatga ctccacgccg ccctggcccc acaaggaaac actaccagcc ttacgcacca 1080

cctagagatt tcgctgccta tcggagcagg gtgaagtttt ccagatctgc agatgcacca 1140

gcgtatcagc agggccagaa ccaactgtat aacgagctca acctgggacg cagggaagag 1200

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gtgttcagtt gccaggataa gcaaaacaca gtatgtgagg agtgtccaga cggaacctac 1980

agcgacgagg cgaaccacgt cgacccttgc ttgccgtgca ccgtctgcga ggataccgaa 2040

cgccagctga gagagtgtac gcgctgggca gacgctgagt gcgaggagat ccctgggaga 2100

tggatcaccc ggagcacacc tcctgaggga tcagacagta cagccccgag tacccaagaa 2160

ccggaggccc ctccagagca ggacctgatc gcttctacag ttgctggcgt ggtgacgaca 2220

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[0056]

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<223> /注释="对人工序列的描述: 合成
多肽"

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His Ala Ala Arg Pro Glu Ile Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Gln Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Trp Met Asn Thr Tyr Thr Gly Glu Pro Thr
65 70 75 80

Tyr Ala Asp Lys Phe Gln Gly Arg Val Thr Phe Thr Leu Asp Thr Ser
85 90 95

Ala Arg Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Phe Cys Ala Arg Ala Gly Gly Gln Leu Arg Pro Gly Ala
115 120 125

Met Asp Tyr Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly
130 135 140

[0057] Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
145 150 155 160

Leu Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly Gln Pro Ala
165 170 175

Ser Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser
180 185 190

Phe Met Asn Trp Tyr Leu Gln Lys Pro Gly Gln Pro Pro Gln Leu Leu
195 200 205

Ile Tyr Val Ala Ser Asn Leu Glu Ser Gly Val Pro Asp Arg Phe Ser
210 215 220

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu

225 230 235 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Ser Asn Glu Glu Pro
245 250 255

Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Leu
260 265 270

Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His
275 280 285

Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val
290 295 300

Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr
[0058] 305 310 315 320

Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu
325 330 335

His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg
340 345 350

Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg
355 360 365

Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
370 375 380

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
385 390 395 400

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
405 410 415

Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
420 425 430

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
435 440 445

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
450 455 460

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
465 470 475 480

[0059] Arg Ala Lys Arg Ser Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr
485 490 495

Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Met Gly Ala Gly Ala Thr
500 505 510

Gly Arg Ala Met Asp Gly Pro Arg Leu Leu Leu Leu Leu Leu Leu Gly
515 520 525

Val Ser Leu Gly Gly Ala Lys Glu Ala Cys Pro Thr Gly Leu Tyr Thr
530 535 540

His Ser Gly Glu Cys Cys Lys Ala Cys Asn Leu Gly Glu Gly Val Ala
545 550 555 560

Gln Pro Cys Gly Ala Asn Gln Thr Val Cys Glu Pro Cys Leu Asp Ser

565 570 575

Val Thr Phe Ser Asp Val Val Ser Ala Thr Glu Pro Cys Lys Pro Cys
580 585 590

Thr Glu Cys Val Gly Leu Gln Ser Met Ser Ala Pro Cys Val Glu Ala
595 600 605

Asp Asp Ala Val Cys Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu Thr
610 615 620

Thr Gly Arg Cys Glu Ala Cys Arg Val Cys Glu Ala Gly Ser Gly Leu
625 630 635 640

Val Phe Ser Cys Gln Asp Lys Gln Asn Thr Val Cys Glu Glu Cys Pro
[0060] 645 650 655

Asp Gly Thr Tyr Ser Asp Glu Ala Asn His Val Asp Pro Cys Leu Pro
660 665 670

Cys Thr Val Cys Glu Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg
675 680 685

Trp Ala Asp Ala Glu Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg
690 695 700

Ser Thr Pro Pro Glu Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu
705 710 715 720

Pro Glu Ala Pro Pro Glu Gln Asp Leu Ile Ala Ser Thr Val Ala Gly
725 730 735

Val Val Thr Thr Val Met Gly Ser Ser Gln Pro Val Val Thr Arg Gly
740 745 750

Thr Thr Asp Asn Leu Ile Pro Val Tyr Cys Ser Ile Leu Ala Ala Val
755 760 765

Val Val Gly Leu Val Ala Tyr Ile Ala Phe Lys Arg
770 775 780

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<220>
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[0061] <223> /注释="对人工序列的描述: 合成多核苷酸"

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atcagctgca aggccagcgg ctacacattc accaactacg gcatgaactg ggtgcaacag 180

gcccccggcc agggactgga gtggatgggc tggatgaaca catacaccgg cgagcccacc 240

tacgccgaca agttccaggg cagggtgaca ttcacactcg ataccagcgc cagaaccgtg 300

tatatggaac tgagcagcct gaggagcgag gacaccgctg tgtacttctg cgcaagggct 360

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ctgtacattt tcaaacagcc gtttatgagg ccggtccaaa cgactcagga agaggacggc 1080

tgctcctgcc gctttcctga ggaggaggag ggcgggtgcg aactgagggt gaagttttcc 1140

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ggtggcaaac caagacgaaa aaacccccag gagggtctct ataatgagct gcagaaggat 1320

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[0063]

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多肽"

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His Ala Ala Arg Pro Glu Ile Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Gln Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Trp Met Asn Thr Tyr Thr Gly Glu Pro Thr
65 70 75 80

Tyr Ala Asp Lys Phe Gln Gly Arg Val Thr Phe Thr Leu Asp Thr Ser
85 90 95

Ala Arg Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Phe Cys Ala Arg Ala Gly Gly Gln Leu Arg Pro Gly Ala
115 120 125

[0064]

Met Asp Tyr Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
145 150 155 160

Leu Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly Gln Pro Ala
165 170 175

Ser Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser
180 185 190

Phe Met Asn Trp Tyr Leu Gln Lys Pro Gly Gln Pro Pro Gln Leu Leu
195 200 205

Ile Tyr Val Ala Ser Asn Leu Glu Ser Gly Val Pro Asp Arg Phe Ser
210 215 220

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu
225 230 235 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Ser Asn Glu Glu Pro
245 250 255

Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Leu
260 265 270

Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His
275 280 285

[0065] Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val
290 295 300

Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr
305 310 315 320

Val Ala Phe Ile Ile Phe Trp Val Arg Phe Ser Val Val Lys Arg Gly
325 330 335

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
340 345 350

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
355 360 365

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
370 375 380

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
385 390 395 400

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
405 410 415

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
420 425 430

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
435 440 445

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
450 455 460

[0066]

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
465 470 475 480

Met Gln Ala Leu Pro Pro Arg Ala Lys Arg Ser Gly Ser Gly Glu Gly
485 490 495

Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro
500 505 510

Met Gly Ala Gly Ala Thr Gly Arg Ala Met Asp Gly Pro Arg Leu Leu
515 520 525

Leu Leu Leu Leu Leu Gly Val Ser Leu Gly Gly Ala Lys Glu Ala Cys
530 535 540

Pro Thr Gly Leu Tyr Thr His Ser Gly Glu Cys Cys Lys Ala Cys Asn
545 550 555 560

Leu Gly Glu Gly Val Ala Gln Pro Cys Gly Ala Asn Gln Thr Val Cys
565 570 575

Glu Pro Cys Leu Asp Ser Val Thr Phe Ser Asp Val Val Ser Ala Thr
580 585 590

Glu Pro Cys Lys Pro Cys Thr Glu Cys Val Gly Leu Gln Ser Met Ser
595 600 605

Ala Pro Cys Val Glu Ala Asp Asp Ala Val Cys Arg Cys Ala Tyr Gly
610 615 620

[0067] Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys Glu Ala Cys Arg Val Cys
625 630 635 640

Glu Ala Gly Ser Gly Leu Val Phe Ser Cys Gln Asp Lys Gln Asn Thr
645 650 655

Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser Asp Glu Ala Asn His
660 665 670

Val Asp Pro Cys Leu Pro Cys Thr Val Cys Glu Asp Thr Glu Arg Gln
675 680 685

Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala Glu Cys Glu Glu Ile Pro
690 695 700

Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro Glu Gly Ser Asp Ser Thr
705 710 715 720

Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro Pro Glu Gln Asp Leu Ile
725 730 735

Ala Ser Thr Val Ala Gly Val Val Thr Thr Val Met Gly Ser Ser Gln
740 745 750

Pro Val Val Thr Arg Gly Thr Thr Asp Asn Leu Ile Pro Val Tyr Cys
755 760 765

Ser Ile Leu Ala Ala Val Val Val Gly Leu Val Ala Tyr Ile Ala Phe
770 775 780

Lys Arg
785

[0068]

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多核苷酸"

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gccccggcc agggactgga gtggatgggc tggatgaaca catacaccgg cgagcccacc 240

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cccggacaac ccccccagct gctgatctac gtggccagca acctggagtc cggcgtgcct 660

gacaggtttt ccggctccgg cagcggcacc gacttcaccc tgaagatcag cagggtggaa 720

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ctgctccata gcgattacat gaatatgact ccacgccgcc ctggccccac aaggaaacac 1140

taccagcctt acgcaccacc tagagatttc gctgcctatc ggagcagggt gaagttttcc 1200

agatctgcag atgcaccagc gtatcagcag ggccagaacc aactgtataa cgagctcaac 1260

ctgggacgca gggaagagta tgacgttttg gacaagcgca gaggacggga ccctgagatg 1320

ggtggcaaac caagacgaaa aaacccccag gagggtctct ataatgagct gcagaaggat 1380

aagatggctg aagcctattc tgaaataggc atgaaaggag agcggagaag gggaaaaggg 1440

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Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Gln Gln Ala Pro Gly Gln
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Gly Leu Glu Trp Met Gly Trp Met Asn Thr Tyr Thr Gly Glu Pro Thr
65 70 75 80

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100 105 110

Ala Val Tyr Phe Cys Ala Arg Ala Gly Gly Gln Leu Arg Pro Gly Ala
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145 150 155 160

Leu Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly Gln Pro Ala

165 170 175

Ser Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser
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Ile Tyr Val Ala Ser Asn Leu Glu Ser Gly Val Pro Asp Arg Phe Ser
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Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Phe
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Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg
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Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
290 295 300

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
305 310 315 320

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
325 330 335

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His
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Arg Asn Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn
355 360 365

Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr
370 375 380

Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser
385 390 395 400

Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
405 410 415

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Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
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Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
465 470 475 480

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
485 490 495

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Ala Lys Arg Ser Gly

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Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu
515 520 525

Asn Pro Gly Pro Met Gly Ala Gly Ala Thr Gly Arg Ala Met Asp Gly
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Pro Arg Leu Leu Leu Leu Leu Leu Leu Gly Val Ser Leu Gly Gly Ala
545 550 555 560

Lys Glu Ala Cys Pro Thr Gly Leu Tyr Thr His Ser Gly Glu Cys Cys
565 570 575

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

Val Ser Ala Thr Glu Pro Cys Lys Pro Cys Thr Glu Cys Val Gly Leu
610 615 620

Gln Ser Met Ser Ala Pro Cys Val Glu Ala Asp Asp Ala Val Cys Arg
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Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys Glu Ala
645 650 655

Cys Arg Val Cys Glu Ala Gly Ser Gly Leu Val Phe Ser Cys Gln Asp
660 665 670

Lys Gln Asn Thr Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser Asp
675 680 685

Glu Ala Asn His Val Asp Pro Cys Leu Pro Cys Thr Val Cys Glu Asp
690 695 700

Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala Glu Cys
705 710 715 720

Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro Glu Gly
725 730 735

Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro Pro Glu
740 745 750

[0075]

Gln Asp Leu Ile Ala Ser Thr Val Ala Gly Val Val Thr Thr Val Met
755 760 765

Gly Ser Ser Gln Pro Val Val Thr Arg Gly Thr Thr Asp Asn Leu Ile
770 775 780

Pro Val Tyr Cys Ser Ile Leu Ala Ala Val Val Val Gly Leu Val Ala
785 790 795 800

Tyr Ile Ala Phe Lys Arg
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Lys Lys Pro Gly Ala Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
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Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Gln Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Trp Met Asn Thr Tyr Thr Gly Glu Pro Thr
65 70 75 80

Tyr Ala Asp Lys Phe Gln Gly Arg Val Thr Phe Thr Leu Asp Thr Ser
85 90 95

Ala Arg Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Phe Cys Ala Arg Ala Gly Gly Gln Leu Arg Pro Gly Ala
115 120 125

Met Asp Tyr Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
145 150 155 160

Leu Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly Gln Pro Ala
165 170 175

Ser Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser
180 185 190

[0079]

Phe Met Asn Trp Tyr Leu Gln Lys Pro Gly Gln Pro Pro Gln Leu Leu
195 200 205

Ile Tyr Val Ala Ser Asn Leu Glu Ser Gly Val Pro Asp Arg Phe Ser
210 215 220

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu
225 230 235 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Ser Asn Glu Glu Pro
245 250 255

Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Phe
260 265 270

Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg
275 280 285

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
290 295 300

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
305 310 315 320

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
325 330 335

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His
340 345 350

[0080] Arg Asn Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr
355 360 365

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
370 375 380

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
385 390 395 400

Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
405 410 415

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
420 425 430

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
435 440 445

Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
450 455 460

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
465 470 475 480

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
485 490 495

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
500 505 510

Arg Ala Lys Arg Ser Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr
515 520 525

[0081]

Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Met Gly Ala Gly Ala Thr
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Gly Arg Ala Met Asp Gly Pro Arg Leu Leu Leu Leu Leu Leu Leu Gly
545 550 555 560

Val Ser Leu Gly Gly Ala Lys Glu Ala Cys Pro Thr Gly Leu Tyr Thr
565 570 575

His Ser Gly Glu Cys Cys Lys Ala Cys Asn Leu Gly Glu Gly Val Ala
580 585 590

Gln Pro Cys Gly Ala Asn Gln Thr Val Cys Glu Pro Cys Leu Asp Ser
595 600 605

Val Thr Phe Ser Asp Val Val Ser Ala Thr Glu Pro Cys Lys Pro Cys
610 615 620

Thr Glu Cys Val Gly Leu Gln Ser Met Ser Ala Pro Cys Val Glu Ala
625 630 635 640

Asp Asp Ala Val Cys Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu Thr
645 650 655

Thr Gly Arg Cys Glu Ala Cys Arg Val Cys Glu Ala Gly Ser Gly Leu
660 665 670

Val Phe Ser Cys Gln Asp Lys Gln Asn Thr Val Cys Glu Glu Cys Pro
675 680 685

[0082]

Asp Gly Thr Tyr Ser Asp Glu Ala Asn His Val Asp Pro Cys Leu Pro
690 695 700

Cys Thr Val Cys Glu Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg
705 710 715 720

Trp Ala Asp Ala Glu Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg
725 730 735

Ser Thr Pro Pro Glu Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu
740 745 750

Pro Glu Ala Pro Pro Glu Gln Asp Leu Ile Ala Ser Thr Val Ala Gly
755 760 765

Val Val Thr Thr Val Met Gly Ser Ser Gln Pro Val Val Thr Arg Gly
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Thr Phe Thr Thr Tyr Trp Met His Trp Val Arg Gln Ala Pro Gly Gln
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Tyr Asn Glu Lys Phe Lys Thr Arg Val Thr Met Thr Arg Asp Thr Ser
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Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
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Ala Val Tyr Tyr Cys Ala Lys Leu Gly Pro Gly Pro Gln Tyr Tyr Ala
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130 135 140

Gly Gly Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln
145 150 155 160

Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
165 170 175

Thr Ile Thr Cys His Ala Ser Gln Asn Ile Asn Val Trp Leu Ser Trp
180 185 190

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala
195 200 205

Ser Lys Leu His Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
210 215 220

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe
225 230 235 240

Ala Thr Tyr Tyr Cys Gln Gln Gly Gln Ser Tyr Pro Trp Thr Phe Gly
245 250 255

Gln Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Leu Asp Asn Glu Lys
260 265 270

Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser
275 280 285

[0087] Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val
290 295 300

Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile
305 310 315 320

Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr
325 330 335

Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln
340 345 350

Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser
355 360 365

Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro

370 375 380

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
385 390 395 400

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
405 410 415

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
420 425 430

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
435 440 445

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
[0088] 450 455 460

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Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
485 490 495

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
500 505 510

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Ala Lys Arg Ser
515 520 525

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545 550 555 560

Gly Pro Arg Leu Leu Leu Leu Leu Leu Leu Gly Val Ser Leu Gly Gly
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Ala Lys Glu Ala Cys Pro Thr Gly Leu Tyr Thr His Ser Gly Glu Cys
580 585 590

Cys Lys Ala Cys Asn Leu Gly Glu Gly Val Ala Gln Pro Cys Gly Ala
595 600 605

Asn Gln Thr Val Cys Glu Pro Cys Leu Asp Ser Val Thr Phe Ser Asp
610 615 620

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625 630 635 640

Leu Gln Ser Met Ser Ala Pro Cys Val Glu Ala Asp Asp Ala Val Cys
645 650 655

Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys Glu
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675 680 685

Asp Lys Gln Asn Thr Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser
690 695 700

Asp Glu Ala Asn His Val Asp Pro Cys Leu Pro Cys Thr Val Cys Glu

705 710 715 720

Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala Glu
725 730 735

Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro Glu
740 745 750

Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro Pro
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770 775 780

Met Gly Ser Ser Gln Pro Val Val Thr Arg Gly Thr Thr Asp Asn Leu
785 790 795 800

[0090]

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Ala Tyr Ile Ala Phe Lys Arg
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多核苷酸"

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gtgagctgca aggcctccgg ctacaccttc accacctact ggatgcactg ggtcagacag 180

gctcccggac agggcctgga atggatgggc gaaatcaacc cctcctccgg caggaccaac 240

tacaacgaga agttcaagac cagggtgacc atgaccaggg acaccagcac cagcaccgtg 300

tacatggagc tgtccagcct gaggagcgag gacaccgccg tgtactactg tgccaagctg 360

ggacccggcc cccagtacta tgccatggac tactggggcc aaggcaccat ggtgaccgtg 420

agcagcggag gcggaggatc tggtggcggt ggttctggcg gcggaggctc cgacatccag 480

atgacccaga gcccctccag cctgtccgct agcgtgggcg acagggtcac cattacctgc 540

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Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Thr Tyr Trp Met His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

[0093]

Gly Leu Glu Trp Met Gly Glu Ile Asn Pro Ser Ser Gly Arg Thr Asn
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Tyr Asn Glu Lys Phe Lys Thr Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Lys Leu Gly Pro Gly Pro Gln Tyr Tyr Ala
115 120 125

Met Asp Tyr Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln
145 150 155 160

Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
165 170 175

Thr Ile Thr Cys His Ala Ser Gln Asn Ile Asn Val Trp Leu Ser Trp
180 185 190

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala
195 200 205

Ser Lys Leu His Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
210 215 220

[0094] Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe
225 230 235 240

Ala Thr Tyr Tyr Cys Gln Gln Gly Gln Ser Tyr Pro Trp Thr Phe Gly
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Gln Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Leu Asp Asn Glu Lys
260 265 270

Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser
275 280 285

Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val
290 295 300

Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile
305 310 315 320

Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr
325 330 335

Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln
340 345 350

Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys
355 360 365

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
370 375 380

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
385 390 395 400

[0095]

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
405 410 415

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
420 425 430

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
435 440 445

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
450 455 460

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Ala Lys Arg
465 470 475 480

Ser Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val
485 490 495

Glu Glu Asn Pro Gly Pro Met Gly Ala Gly Ala Thr Gly Arg Ala Met
500 505 510

Asp Gly Pro Arg Leu Leu Leu Leu Leu Leu Leu Gly Val Ser Leu Gly
515 520 525

Gly Ala Lys Glu Ala Cys Pro Thr Gly Leu Tyr Thr His Ser Gly Glu
530 535 540

Cys Cys Lys Ala Cys Asn Leu Gly Glu Gly Val Ala Gln Pro Cys Gly
545 550 555 560

[0096] Ala Asn Gln Thr Val Cys Glu Pro Cys Leu Asp Ser Val Thr Phe Ser
565 570 575

Asp Val Val Ser Ala Thr Glu Pro Cys Lys Pro Cys Thr Glu Cys Val
580 585 590

Gly Leu Gln Ser Met Ser Ala Pro Cys Val Glu Ala Asp Asp Ala Val
595 600 605

Cys Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys
610 615 620

Glu Ala Cys Arg Val Cys Glu Ala Gly Ser Gly Leu Val Phe Ser Cys
625 630 635 640

Gln Asp Lys Gln Asn Thr Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr
645 650 655

Ser Asp Glu Ala Asn His Val Asp Pro Cys Leu Pro Cys Thr Val Cys
660 665 670

Glu Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala
675 680 685

Glu Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro
690 695 700

Glu Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro
705 710 715 720

Pro Glu Gln Asp Leu Ile Ala Ser Thr Val Ala Gly Val Val Thr Thr
725 730 735

[0097]

Val Met Gly Ser Ser Gln Pro Val Val Thr Arg Gly Thr Thr Asp Asn
740 745 750

Leu Ile Pro Val Tyr Cys Ser Ile Leu Ala Ala Val Val Val Gly Leu
755 760 765

Val Ala Tyr Ile Ala Phe Lys Arg
770 775

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gtgagctgca aggcctccgg ctacaccttc accacctact ggatgcactg ggtcagacag 180

gctcccggac agggcctgga atggatgggc gaaatcaacc cctcctccgg caggaccaac 240

tacaacgaga agttcaagac cagggtgacc atgaccaggg acaccagcac cagcaccgtg 300

tacatggagc tgtccagcct gaggagcgag gacaccgccg tgtactactg tgccaagctg 360

ggacccggcc cccagtacta tgccatggac tactggggcc aaggcaccat ggtgaccgtg 420

agcagcggag gcggaggatc tggtggcggt ggttctggcg gcggaggctc cgacatccag 480

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Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
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Thr Phe Thr Thr Tyr Trp Met His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Glu Ile Asn Pro Ser Ser Gly Arg Thr Asn
65 70 75 80

Tyr Asn Glu Lys Phe Lys Thr Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Lys Leu Gly Pro Gly Pro Gln Tyr Tyr Ala
115 120 125

Met Asp Tyr Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln
145 150 155 160

Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
165 170 175

Thr Ile Thr Cys His Ala Ser Gln Asn Ile Asn Val Trp Leu Ser Trp
180 185 190

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala
195 200 205

[0101] Ser Lys Leu His Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
210 215 220

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe
225 230 235 240

Ala Thr Tyr Tyr Cys Gln Gln Gly Gln Ser Tyr Pro Trp Thr Phe Gly
245 250 255

Gln Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Leu Asp Asn Glu Lys
260 265 270

Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser
275 280 285

Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val

290 295 300

Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile
305 310 315 320

Ile Phe Trp Val Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu
325 330 335

Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln
340 345 350

Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly
355 360 365

Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
[0102] 370 375 380

Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
385 390 395 400

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
405 410 415

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
420 425 430

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
435 440 445

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
450 455 460

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
465 470 475 480

Pro Pro Arg Ala Lys Arg Ser Gly Ser Gly Glu Gly Arg Gly Ser Leu
485 490 495

Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Met Gly Ala Gly
500 505 510

Ala Thr Gly Arg Ala Met Asp Gly Pro Arg Leu Leu Leu Leu Leu Leu
515 520 525

Leu Gly Val Ser Leu Gly Gly Ala Lys Glu Ala Cys Pro Thr Gly Leu
530 535 540

[0103] Tyr Thr His Ser Gly Glu Cys Cys Lys Ala Cys Asn Leu Gly Glu Gly
545 550 555 560

Val Ala Gln Pro Cys Gly Ala Asn Gln Thr Val Cys Glu Pro Cys Leu
565 570 575

Asp Ser Val Thr Phe Ser Asp Val Val Ser Ala Thr Glu Pro Cys Lys
580 585 590

Pro Cys Thr Glu Cys Val Gly Leu Gln Ser Met Ser Ala Pro Cys Val
595 600 605

Glu Ala Asp Asp Ala Val Cys Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp
610 615 620

Glu Thr Thr Gly Arg Cys Glu Ala Cys Arg Val Cys Glu Ala Gly Ser

625 630 635 640

Gly Leu Val Phe Ser Cys Gln Asp Lys Gln Asn Thr Val Cys Glu Glu
645 650 655

Cys Pro Asp Gly Thr Tyr Ser Asp Glu Ala Asn His Val Asp Pro Cys
660 665 670

Leu Pro Cys Thr Val Cys Glu Asp Thr Glu Arg Gln Leu Arg Glu Cys
675 680 685

Thr Arg Trp Ala Asp Ala Glu Cys Glu Glu Ile Pro Gly Arg Trp Ile
690 695 700

[0104]

Thr Arg Ser Thr Pro Pro Glu Gly Ser Asp Ser Thr Ala Pro Ser Thr
705 710 715 720

Gln Glu Pro Glu Ala Pro Pro Glu Gln Asp Leu Ile Ala Ser Thr Val
725 730 735

Ala Gly Val Val Thr Thr Val Met Gly Ser Ser Gln Pro Val Val Thr
740 745 750

Arg Gly Thr Thr Asp Asn Leu Ile Pro Val Tyr Cys Ser Ile Leu Ala
755 760 765

Ala Val Val Val Gly Leu Val Ala Tyr Ile Ala Phe Lys Arg
770 775 780

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gctcccggac agggcctgga atggatgggc gaaatcaacc cctcctccgg caggaccaac 240

tacaacgaga agttcaagac cagggtgacc atgaccaggg acaccagcac cagcaccgtg 300

tacatggagc tgtccagcct gaggagcgag gacaccgccg tgtactactg tgccaagctg 360

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多肽"

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20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Thr Tyr Trp Met His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Glu Ile Asn Pro Ser Ser Gly Arg Thr Asn
65 70 75 80

Tyr Asn Glu Lys Phe Lys Thr Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Lys Leu Gly Pro Gly Pro Gln Tyr Tyr Ala
115 120 125

Met Asp Tyr Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln
145 150 155 160

Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
165 170 175

[0108] Thr Ile Thr Cys His Ala Ser Gln Asn Ile Asn Val Trp Leu Ser Trp
180 185 190

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala
195 200 205

Ser Lys Leu His Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
210 215 220

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe
225 230 235 240

Ala Thr Tyr Tyr Cys Gln Gln Gly Gln Ser Tyr Pro Trp Thr Phe Gly
245 250 255

Gln Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Phe Val Pro Val Phe
260 265 270

Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
275 280 285

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
290 295 300

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
305 310 315 320

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
325 330 335

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Ser
340 345 350

[0109]

Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg
355 360 365

Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg
370 375 380

Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp
385 390 395 400

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
405 410 415

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
420 425 430

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
435 440 445

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
450 455 460

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
465 470 475 480

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
485 490 495

Met Gln Ala Leu Pro Pro Arg Ala Lys Arg Ser Gly Ser Gly Glu Gly
500 505 510

[0110] Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro
515 520 525

Met Gly Ala Gly Ala Thr Gly Arg Ala Met Asp Gly Pro Arg Leu Leu
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Leu Leu Leu Leu Leu Gly Val Ser Leu Gly Gly Ala Lys Glu Ala Cys
545 550 555 560

Pro Thr Gly Leu Tyr Thr His Ser Gly Glu Cys Cys Lys Ala Cys Asn
565 570 575

Leu Gly Glu Gly Val Ala Gln Pro Cys Gly Ala Asn Gln Thr Val Cys
580 585 590

Glu Pro Cys Leu Asp Ser Val Thr Phe Ser Asp Val Val Ser Ala Thr
595 600 605

Glu Pro Cys Lys Pro Cys Thr Glu Cys Val Gly Leu Gln Ser Met Ser
610 615 620

Ala Pro Cys Val Glu Ala Asp Asp Ala Val Cys Arg Cys Ala Tyr Gly
625 630 635 640

Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys Glu Ala Cys Arg Val Cys
645 650 655

Glu Ala Gly Ser Gly Leu Val Phe Ser Cys Gln Asp Lys Gln Asn Thr
660 665 670

Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser Asp Glu Ala Asn His
675 680 685

[0111]

Val Asp Pro Cys Leu Pro Cys Thr Val Cys Glu Asp Thr Glu Arg Gln
690 695 700

Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala Glu Cys Glu Glu Ile Pro
705 710 715 720

Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro Glu Gly Ser Asp Ser Thr
725 730 735

Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro Pro Glu Gln Asp Leu Ile
740 745 750

Ala Ser Thr Val Ala Gly Val Val Thr Thr Val Met Gly Ser Ser Gln
755 760 765

Pro Val Val Thr Arg Gly Thr Thr Asp Asn Leu Ile Pro Val Tyr Cys
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Lys Arg

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Thr Phe Thr Thr Tyr Trp Met His Trp Val Arg Gln Ala Pro Gly Gln
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Gly Leu Glu Trp Met Gly Glu Ile Asn Pro Ser Ser Gly Arg Thr Asn
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Tyr Asn Glu Lys Phe Lys Thr Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
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Ala Val Tyr Tyr Cys Ala Lys Leu Gly Pro Gly Pro Gln Tyr Tyr Ala
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Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala
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Ser Lys Leu His Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
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Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe
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Ala Thr Tyr Tyr Cys Gln Gln Gly Gln Ser Tyr Pro Trp Thr Phe Gly
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Gln Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Phe Val Pro Val Phe
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Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
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Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
325 330 335

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Phe
340 345 350

Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln
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Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser

370 375 380

Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys
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Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
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Ser Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val
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Asp Gly Pro Arg Leu Leu Leu Leu Leu Leu Leu Gly Val Ser Leu Gly
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Cys Cys Lys Ala Cys Asn Leu Gly Glu Gly Val Ala Gln Pro Cys Gly
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Glu Ala Cys Arg Val Cys Glu Ala Gly Ser Gly Leu Val Phe Ser Cys
660 665 670

Gln Asp Lys Gln Asn Thr Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr
675 680 685

Ser Asp Glu Ala Asn His Val Asp Pro Cys Leu Pro Cys Thr Val Cys
690 695 700

Glu Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala

705 710 715 720

Glu Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro
725 730 735

Glu Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro
740 745 750

Pro Glu Gln Asp Leu Ile Ala Ser Thr Val Ala Gly Val Val Thr Thr
755 760 765

Val Met Gly Ser Ser Gln Pro Val Val Thr Arg Gly Thr Thr Asp Asn
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Gly Leu Glu Trp Met Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly
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Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
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Ile Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
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Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gln Thr
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Ser Thr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser
210 215 220

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245 250 255

Gly Thr Lys Val Glu Leu Lys Arg Ala Ala Ala Leu Asp Asn Glu Lys
260 265 270

Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser
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Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val
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Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile
305 310 315 320

Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr
325 330 335

Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln
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Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser
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Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
370 375 380

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385 390 395 400

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
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Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
435 440 445

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
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Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
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Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
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Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Ala Lys Arg Ser
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Glu Asn Pro Gly Pro Met Gly Ala Gly Ala Thr Gly Arg Ala Met Asp
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Asn Gln Thr Val Cys Glu Pro Cys Leu Asp Ser Val Thr Phe Ser Asp
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Val Val Ser Ala Thr Glu Pro Cys Lys Pro Cys Thr Glu Cys Val Gly
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Leu Gln Ser Met Ser Ala Pro Cys Val Glu Ala Asp Asp Ala Val Cys
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Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys Glu
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Ala Cys Arg Val Cys Glu Ala Gly Ser Gly Leu Val Phe Ser Cys Gln
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Asp Lys Gln Asn Thr Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser
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Glu Gln Asp Leu Ile Ala Ser Thr Val Ala Gly Val Val Thr Thr Val
770 775 780

Met Gly Ser Ser Gln Pro Val Val Thr Arg Gly Thr Thr Asp Asn Leu
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[0129]

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His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ser Phe Thr Ser Tyr Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly
65 70 75 80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Ile Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Gly Arg Ala Gly Tyr Tyr Tyr Tyr Phe Gly Met
115 120 125

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu
145 150 155 160

[0130] Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
165 170 175

Leu Ser Cys Arg Ala Gly Gln Ser Val Thr Ser Ser Ser Phe Ala Trp
180 185 190

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gln Thr
195 200 205

Ser Thr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser
210 215 220

Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe
225 230 235 240

Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Gly Ser Arg Ser Phe Gly Gln

245 250 255

Gly Thr Lys Val Glu Leu Lys Arg Ala Ala Ala Leu Asp Asn Glu Lys
260 265 270

Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser
275 280 285

Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val
290 295 300

Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile
305 310 315 320

Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr
[0131] 325 330 335

Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln
340 345 350

Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys
355 360 365

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
370 375 380

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
385 390 395 400

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
405 410 415

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
420 425 430

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
435 440 445

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
450 455 460

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Ala Lys Arg
465 470 475 480

Ser Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val
485 490 495

[0132] Glu Glu Asn Pro Gly Pro Met Gly Ala Gly Ala Thr Gly Arg Ala Met
500 505 510

Asp Gly Pro Arg Leu Leu Leu Leu Leu Leu Leu Leu Gly Val Ser Leu Gly
515 520 525

Gly Ala Lys Glu Ala Cys Pro Thr Gly Leu Tyr Thr His Ser Gly Glu
530 535 540

Cys Cys Lys Ala Cys Asn Leu Gly Glu Gly Val Ala Gln Pro Cys Gly
545 550 555 560

Ala Asn Gln Thr Val Cys Glu Pro Cys Leu Asp Ser Val Thr Phe Ser
565 570 575

Asp Val Val Ser Ala Thr Glu Pro Cys Lys Pro Cys Thr Glu Cys Val

580 585 590

Gly Leu Gln Ser Met Ser Ala Pro Cys Val Glu Ala Asp Asp Ala Val
595 600 605

Cys Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys
610 615 620

Glu Ala Cys Arg Val Cys Glu Ala Gly Ser Gly Leu Val Phe Ser Cys
625 630 635 640

Gln Asp Lys Gln Asn Thr Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr
645 650 655

Ser Asp Glu Ala Asn His Val Asp Pro Cys Leu Pro Cys Thr Val Cys
[0133] 660 665 670

Glu Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala
675 680 685

Glu Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro
690 695 700

Glu Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro
705 710 715 720

Pro Glu Gln Asp Leu Ile Ala Ser Thr Val Ala Gly Val Val Thr Thr
725 730 735

Val Met Gly Ser Ser Gln Pro Val Val Thr Arg Gly Thr Thr Asp Asn
740 745 750

Leu Ile Pro Val Tyr Cys Ser Ile Leu Ala Ala Val Val Val Gly Leu
755 760 765

Val Ala Tyr Ile Ala Phe Lys Arg
770 775

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多核苷酸"

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gtgtcctgca aggcttctgg atacagcttc accagttatg atatcaactg ggtgcgacag 180

gccactggac aagggcttga gtggatgggg tggatgaacc cgaacagtgg taacacaggc 240

tatgcacaga agttccaggg cagagtcacc atgaccaggg acacctccat aagcacagcc 300

tacatggaac tgagcagcct gagatctgag gacacggccg tgtattactg tgggagagcc 360

ggttactact actacttcgg tatggacgtc tggggccaag ggaccacggt caccgtatcc 420

tcaggaggcg gcggttcagg cggaggtggc tctggcggtg gcggaagtga aattgtgttg 480

acgcagtctc caggcaccct gtctttgtct ccaggggaaa gagccaccct ctcctgcagg 540

gccggtcaga gtgttaccag cagctccttt gcttggtacc aacagaaacc tggccaggct 600

cccaggctcc tcatctatca gacatccacc agggccactg gcatcccaga caggttcagt 660

ggcagtgggt ctgggacaga tttcactctc accatcagca gactggagcc tgaagatttt 720

gcagtgtatt actgtcagca gtatggtggc tcacggtcgt tcggccaagg gaccaaggtg 780

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ttggtcgtag tgggtggagt cctcgcttgt tactctctgc tcgtcaccgt ggcttttata 960

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aaacagccgt ttatgaggcc ggtccaaacg actcaggaag aggacggctg ctcctgccgc 1080

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gcaccagcgt atcagcaggg ccagaaccaa ctgtataacg agctcaacct gggacgcagg 1200

gaagagtatg acgttttgga caagcgcaga ggacgggacc ctgagatggg tggcaaacca 1260

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taccagggac tcagcactgc tacgaaggat acttatgacg ctctccacat gcaagccctg 1440

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gacgtggaag aaaatccggg gcctatgggt gccggcgcca cgggaagggc tatggatggc 1560

ccgcgactgc ttctcctgct gttgttgggc gtgtctctcg gaggcgctaa ggaggcctgt 1620

ccaacgggcc tctacactca ctccggtgaa tgttgcaaag cctgtaacct tggcgagggc 1680

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tattaccagg acgaaactac cgggcggtgt gaggcctgcc gggtgtgtga agccggctct 1920

ggcctcgtgt tcagttgcca ggataagcaa aacacagtat gtgaggagtg tccagacgga 1980

acctacagcg acgaggcgaa ccacgtcgac ccttgcttgc cgtgcaccgt ctgcgaggat 2040

accgaacgcc agctgagaga gtgtacgcgc tgggcagacg ctgagtgcga ggagatccct 2100

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caagaaccgg aggcccctcc agagcaggac ctgatcgctt ctacagttgc tggcgtggtg 2220

acgacagtca tgggatcctc acaaccagtc gtgacgcggg gcacaaccga caatctgatt 2280

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多肽"

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His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ser Phe Thr Ser Tyr Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly
65 70 75 80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Ile Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Gly Arg Ala Gly Tyr Tyr Tyr Tyr Phe Gly Met
115 120 125

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly
130 135 140

[0137]

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu
145 150 155 160

Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
165 170 175

Leu Ser Cys Arg Ala Gly Gln Ser Val Thr Ser Ser Ser Phe Ala Trp
180 185 190

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gln Thr
195 200 205

Ser Thr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser
210 215 220

Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe
225 230 235 240

Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Gly Ser Arg Ser Phe Gly Gln
245 250 255

Gly Thr Lys Val Glu Leu Lys Arg Ala Ala Ala Leu Asp Asn Glu Lys
260 265 270

Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser
275 280 285

Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val
290 295 300

[0138] Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile
305 310 315 320

Ile Phe Trp Val Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu
325 330 335

Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln
340 345 350

Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly
355 360 365

Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
370 375 380

Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
385 390 395 400

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
405 410 415

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
420 425 430

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
435 440 445

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
450 455 460

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
465 470 475 480

[0139]

Pro Pro Arg Ala Lys Arg Ser Gly Ser Gly Glu Gly Arg Gly Ser Leu
485 490 495

Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Met Gly Ala Gly
500 505 510

Ala Thr Gly Arg Ala Met Asp Gly Pro Arg Leu Leu Leu Leu Leu Leu
515 520 525

Leu Gly Val Ser Leu Gly Gly Ala Lys Glu Ala Cys Pro Thr Gly Leu
530 535 540

Tyr Thr His Ser Gly Glu Cys Cys Lys Ala Cys Asn Leu Gly Glu Gly
545 550 555 560

Val Ala Gln Pro Cys Gly Ala Asn Gln Thr Val Cys Glu Pro Cys Leu
565 570 575

Asp Ser Val Thr Phe Ser Asp Val Val Ser Ala Thr Glu Pro Cys Lys
580 585 590

Pro Cys Thr Glu Cys Val Gly Leu Gln Ser Met Ser Ala Pro Cys Val
595 600 605

Glu Ala Asp Asp Ala Val Cys Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp
610 615 620

Glu Thr Thr Gly Arg Cys Glu Ala Cys Arg Val Cys Glu Ala Gly Ser
625 630 635 640

[0140] Gly Leu Val Phe Ser Cys Gln Asp Lys Gln Asn Thr Val Cys Glu Glu
645 650 655

Cys Pro Asp Gly Thr Tyr Ser Asp Glu Ala Asn His Val Asp Pro Cys
660 665 670

Leu Pro Cys Thr Val Cys Glu Asp Thr Glu Arg Gln Leu Arg Glu Cys
675 680 685

Thr Arg Trp Ala Asp Ala Glu Cys Glu Glu Ile Pro Gly Arg Trp Ile
690 695 700

Thr Arg Ser Thr Pro Pro Glu Gly Ser Asp Ser Thr Ala Pro Ser Thr
705 710 715 720

Gln Glu Pro Glu Ala Pro Pro Glu Gln Asp Leu Ile Ala Ser Thr Val
725 730 735

Ala Gly Val Val Thr Thr Val Met Gly Ser Ser Gln Pro Val Val Thr
740 745 750

Arg Gly Thr Thr Asp Asn Leu Ile Pro Val Tyr Cys Ser Ile Leu Ala
755 760 765

Ala Val Val Val Gly Leu Val Ala Tyr Ile Ala Phe Lys Arg
770 775 780

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[0141]

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gtgtcctgca aggcttctgg atacagcttc accagttatg atatcaactg ggtgcgacag 180

gccactggac aagggcttga gtggatgggg tggatgaacc cgaacagtgg taacacaggc 240

tatgcacaga agttccaggg cagagtcacc atgaccaggg acacctccat aagcacagcc 300

tacatggaac tgagcagcct gagatctgag gacacggccg tgtattactg tgggagagcc 360

ggttactact actacttcgg tatggacgtc tggggccaag ggaccacggt caccgtatcc 420

tcaggaggcg gcggttcagg cggaggtggc tctggcggtg gcggaagtga aattgtgttg 480

acgcagtctc caggcaccct gtctttgtct ccaggggaaa gagccaccct ctcctgcagg 540

gccggtcaga gtgttaccag cagctccttt gcttggtacc aacagaaacc tggccaggct 600

cccaggctcc tcatctatca gacatccacc agggccactg gcatcccaga caggttcagt 660

ggcagtgggt ctgggacaga tttcactctc accatcagca gactggagcc tgaagatttt 720

gcagtgtatt actgtcagca gtatggtggc tcacggtcgt tcggccaagg gaccaaggtg 780

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gtgattaccc tctactgcaa ccacagaaac agatccaaaa gaagccgcct gctccatagc 1080

gattacatga atatgactcc acgccgccct ggccccacaa ggaaacacta ccagccttac 1140

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gaagagtatg acgttttgga caagcgcaga ggacgggacc ctgagatggg tggcaaacca 1320

agacgaaaaa acccccagga gggtctctat aatgagctgc agaaggataa gatggctgaa 1380

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taccagggac tcagcactgc tacgaaggat acttatgacg ctctccacat gcaagccctg 1500

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ccgcgactgc ttctcctgct gttgttgggc gtgtctctcg gaggcgctaa ggaggcctgt 1680

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[0143] aagagatgac ctaggtaa 2418

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多肽"

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His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ser Phe Thr Ser Tyr Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly
65 70 75 80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Ile Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

[0144] Ala Val Tyr Tyr Cys Gly Arg Ala Gly Tyr Tyr Tyr Tyr Phe Gly Met
115 120 125

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu
145 150 155 160

Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
165 170 175

Leu Ser Cys Arg Ala Gly Gln Ser Val Thr Ser Ser Ser Phe Ala Trp
180 185 190

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gln Thr

195 200 205

Ser Thr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser
210 215 220

Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe
225 230 235 240

Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Gly Ser Arg Ser Phe Gly Gln
245 250 255

Gly Thr Lys Val Glu Leu Lys Arg Ala Ala Ala Phe Val Pro Val Phe
260 265 270

Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
[0145] 275 280 285

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
290 295 300

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
305 310 315 320

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
325 330 335

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Ser
340 345 350

Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg
355 360 365

Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg
370 375 380

Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp
385 390 395 400

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
405 410 415

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
420 425 430

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
435 440 445

[0146] Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
450 455 460

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
465 470 475 480

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
485 490 495

Met Gln Ala Leu Pro Pro Arg Ala Lys Arg Ser Gly Ser Gly Glu Gly
500 505 510

Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro
515 520 525

Met Gly Ala Gly Ala Thr Gly Arg Ala Met Asp Gly Pro Arg Leu Leu

530 535 540

Leu Leu Leu Leu Leu Gly Val Ser Leu Gly Gly Ala Lys Glu Ala Cys
545 550 555 560

Pro Thr Gly Leu Tyr Thr His Ser Gly Glu Cys Cys Lys Ala Cys Asn
565 570 575

Leu Gly Glu Gly Val Ala Gln Pro Cys Gly Ala Asn Gln Thr Val Cys
580 585 590

Glu Pro Cys Leu Asp Ser Val Thr Phe Ser Asp Val Val Ser Ala Thr
595 600 605

Glu Pro Cys Lys Pro Cys Thr Glu Cys Val Gly Leu Gln Ser Met Ser
[0147] 610 615 620

Ala Pro Cys Val Glu Ala Asp Asp Ala Val Cys Arg Cys Ala Tyr Gly
625 630 635 640

Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys Glu Ala Cys Arg Val Cys
645 650 655

Glu Ala Gly Ser Gly Leu Val Phe Ser Cys Gln Asp Lys Gln Asn Thr
660 665 670

Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser Asp Glu Ala Asn His
675 680 685

Val Asp Pro Cys Leu Pro Cys Thr Val Cys Glu Asp Thr Glu Arg Gln
690 695 700

Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala Glu Cys Glu Glu Ile Pro
705 710 715 720

Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro Glu Gly Ser Asp Ser Thr
725 730 735

Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro Pro Glu Gln Asp Leu Ile
740 745 750

Ala Ser Thr Val Ala Gly Val Val Thr Thr Val Met Gly Ser Ser Gln
755 760 765

Pro Val Val Thr Arg Gly Thr Thr Asp Asn Leu Ile Pro Val Tyr Cys
770 775 780

[0148]

Ser Ile Leu Ala Ala Val Val Val Gly Leu Val Ala Tyr Ile Ala Phe
785 790 795 800

Lys Arg

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<211> 2436
<212> DNA
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<220>
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多核苷酸"

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gtgtcctgca aggcttctgg atacagcttc accagttatg atatcaactg ggtgcgacag 180

gccactggac aagggcttga gtggatgggg tggatgaacc cgaacagtgg taacacaggc 240

tatgcacaga agttccaggg cagagtcacc atgaccaggg acacctccat aagcacagcc 300

tacatggaac tgagcagcct gagatctgag gacacggccg tgtattactg tgggagagcc 360

ggttactact actacttcgg tatggacgtc tggggccaag ggaccacggt caccgtatcc 420

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gccggtcaga gtgttaccag cagctccttt gcttggtacc aacagaaacc tggccaggct 600

cccaggctcc tcatctatca gacatccacc agggccactg gcatcccaga caggttcagt 660

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tgcgatattt atatctgggc ccccccttgcc gggacatgcg gggtactgct gctgtctctg 1020

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[0151]

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65 70 75 80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Ile Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
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Ala Val Tyr Tyr Cys Gly Arg Ala Gly Tyr Tyr Tyr Tyr Phe Gly Met
115 120 125

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly
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Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu
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Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
165 170 175

Leu Ser Cys Arg Ala Gly Gln Ser Val Thr Ser Ser Ser Phe Ala Trp
180 185 190

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gln Thr
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Ser Thr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser
210 215 220

[0152]

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245 250 255

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260 265 270

Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
275 280 285

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
290 295 300

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
305 310 315 320

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
325 330 335

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Phe
340 345 350

Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln
355 360 365

Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser
370 375 380

[0153] Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys
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Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
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Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
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Glu Glu Asn Pro Gly Pro Met Gly Ala Gly Ala Thr Gly Arg Ala Met
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Asp Gly Pro Arg Leu Leu Leu Leu Leu Leu Leu Leu Gly Val Ser Leu Gly
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[0154]

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565 570 575

Cys Cys Lys Ala Cys Asn Leu Gly Glu Gly Val Ala Gln Pro Cys Gly
580 585 590

Ala Asn Gln Thr Val Cys Glu Pro Cys Leu Asp Ser Val Thr Phe Ser
595 600 605

Asp Val Val Ser Ala Thr Glu Pro Cys Lys Pro Cys Thr Glu Cys Val
610 615 620

Gly Leu Gln Ser Met Ser Ala Pro Cys Val Glu Ala Asp Asp Ala Val
625 630 635 640

Cys Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys
645 650 655

Glu Ala Cys Arg Val Cys Glu Ala Gly Ser Gly Leu Val Phe Ser Cys
660 665 670

Gln Asp Lys Gln Asn Thr Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr
675 680 685

Ser Asp Glu Ala Asn His Val Asp Pro Cys Leu Pro Cys Thr Val Cys
690 695 700

Glu Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala
705 710 715 720

[0155]

Glu Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro
725 730 735

Glu Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro
740 745 750

Pro Glu Gln Asp Leu Ile Ala Ser Thr Val Ala Gly Val Val Thr Thr
755 760 765

Val Met Gly Ser Ser Gln Pro Val Val Thr Arg Gly Thr Thr Asp Asn
770 775 780

Leu Ile Pro Val Tyr Cys Ser Ile Leu Ala Ala Val Val Val Gly Leu
785 790 795 800

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Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ser Phe Thr Ser Tyr Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly

65 70 75 80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
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Ile Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
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Ala Val Tyr Tyr Cys Gly Arg Ala Gly Tyr Tyr Tyr Tyr Phe Gly Met
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Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly
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180 185 190

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gln Thr
195 200 205

Ser Thr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser
210 215 220

Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe
225 230 235 240

Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Gly Ser Arg Ala Phe Gly Gln
245 250 255

Gly Thr Lys Val Glu Leu Lys Arg Ala Ala Ala Leu Asp Asn Glu Lys
260 265 270

Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser
275 280 285

Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val
290 295 300

Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile
305 310 315 320

[0160] Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr
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Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln
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Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser
355 360 365

Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
370 375 380

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
385 390 395 400

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe

405 410 415

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
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Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
435 440 445

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
450 455 460

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
465 470 475 480

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
[0161] 485 490 495

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Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Ala Lys Arg Ser
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Glu Asn Pro Gly Pro Met Gly Ala Gly Ala Thr Gly Arg Ala Met Asp
545 550 555 560

Gly Pro Arg Leu Leu Leu Leu Leu Leu Leu Leu Gly Val Ser Leu Gly Gly
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Ala Lys Glu Ala Cys Pro Thr Gly Leu Tyr Thr His Ser Gly Glu Cys
580 585 590

Cys Lys Ala Cys Asn Leu Gly Glu Gly Val Ala Gln Pro Cys Gly Ala
595 600 605

Asn Gln Thr Val Cys Glu Pro Cys Leu Asp Ser Val Thr Phe Ser Asp
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Val Val Ser Ala Thr Glu Pro Cys Lys Pro Cys Thr Glu Cys Val Gly
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Leu Gln Ser Met Ser Ala Pro Cys Val Glu Ala Asp Asp Ala Val Cys
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[0162] Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys Glu
660 665 670

Ala Cys Arg Val Cys Glu Ala Gly Ser Gly Leu Val Phe Ser Cys Gln
675 680 685

Asp Lys Gln Asn Thr Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser
690 695 700

Asp Glu Ala Asn His Val Asp Pro Cys Leu Pro Cys Thr Val Cys Glu
705 710 715 720

Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala Glu
725 730 735

Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro Glu

740 745 750

Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro Pro
755 760 765

Glu Gln Asp Leu Ile Ala Ser Thr Val Ala Gly Val Val Thr Thr Val
770 775 780

Met Gly Ser Ser Gln Pro Val Val Thr Arg Gly Thr Thr Asp Asn Leu
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Ala Tyr Ile Ala Phe Lys Arg
[0163] 820

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Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
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[0166]

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195 200 205

Ser Thr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser
210 215 220

Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe
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Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Gly Ser Arg Ala Phe Gly Gln
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260 265 270

Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser
275 280 285

Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val
290 295 300

Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile
305 310 315 320

Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr
325 330 335

Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln
340 345 350

Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys
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Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
370 375 380

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
385 390 395 400

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
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Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
420 425 430

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Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
450 455 460

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Ala Lys Arg
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Glu Glu Asn Pro Gly Pro Met Gly Ala Gly Ala Thr Gly Arg Ala Met
500 505 510

Asp Gly Pro Arg Leu Leu Leu Leu Leu Leu Leu Gly Val Ser Leu Gly
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Gly Ala Lys Glu Ala Cys Pro Thr Gly Leu Tyr Thr His Ser Gly Glu
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Cys Cys Lys Ala Cys Asn Leu Gly Glu Gly Val Ala Gln Pro Cys Gly
545 550 555 560

Ala Asn Gln Thr Val Cys Glu Pro Cys Leu Asp Ser Val Thr Phe Ser
565 570 575

Asp Val Val Ser Ala Thr Glu Pro Cys Lys Pro Cys Thr Glu Cys Val
580 585 590

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595 600 605

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Glu Ala Cys Arg Val Cys Glu Ala Gly Ser Gly Leu Val Phe Ser Cys
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Gln Asp Lys Gln Asn Thr Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr
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Glu Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala
675 680 685

Glu Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro
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Glu Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro
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Pro Glu Gln Asp Leu Ile Ala Ser Thr Val Ala Gly Val Val Thr Thr
725 730 735

Val Met Gly Ser Ser Gln Pro Val Val Thr Arg Gly Thr Thr Asp Asn
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Leu Ile Pro Val Tyr Cys Ser Ile Leu Ala Ala Val Val Val Gly Leu
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[0170]

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Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser
275 280 285

Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val
290 295 300

Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile
305 310 315 320

Ile Phe Trp Val Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu

325 330 335

Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln
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Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly
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Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
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Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
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Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Met Gly Ala Gly
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Tyr Thr His Ser Gly Glu Cys Cys Lys Ala Cys Asn Leu Gly Glu Gly
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565 570 575

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Glu Thr Thr Gly Arg Cys Glu Ala Cys Arg Val Cys Glu Ala Gly Ser
625 630 635 640

Gly Leu Val Phe Ser Cys Gln Asp Lys Gln Asn Thr Val Cys Glu Glu
645 650 655

Cys Pro Asp Gly Thr Tyr Ser Asp Glu Ala Asn His Val Asp Pro Cys

660 665 670

Leu Pro Cys Thr Val Cys Glu Asp Thr Glu Arg Gln Leu Arg Glu Cys
675 680 685

Thr Arg Trp Ala Asp Ala Glu Cys Glu Glu Ile Pro Gly Arg Trp Ile
690 695 700

Thr Arg Ser Thr Pro Pro Glu Gly Ser Asp Ser Thr Ala Pro Ser Thr
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Gln Glu Pro Glu Ala Pro Pro Glu Gln Asp Leu Ile Ala Ser Thr Val
725 730 735

Ala Gly Val Val Thr Thr Val Met Gly Ser Ser Gln Pro Val Val Thr
740 745 750

[0177]

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Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gln Thr
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[0181] Ser Thr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser
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Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Gly Ser Arg Ala Phe Gly Gln
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Gly Thr Lys Val Glu Leu Lys Arg Ala Ala Ala Phe Val Pro Val Phe
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Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
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Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
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Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
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Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
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Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Ser
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Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg
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Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg
370 375 380

[0182]

Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp
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Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
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Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
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Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro
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Glu Pro Cys Leu Asp Ser Val Thr Phe Ser Asp Val Val Ser Ala Thr
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Glu Pro Cys Lys Pro Cys Thr Glu Cys Val Gly Leu Gln Ser Met Ser
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Ala Pro Cys Val Glu Ala Asp Asp Ala Val Cys Arg Cys Ala Tyr Gly
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Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser Asp Glu Ala Asn His
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690 695 700

Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala Glu Cys Glu Glu Ile Pro
705 710 715 720

[0184]

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Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro Pro Glu Gln Asp Leu Ile
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755 760 765

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Ser Phe Thr Ser Tyr Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln
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Ser Thr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser
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Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe
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Gly Thr Lys Val Glu Leu Lys Arg Ala Ala Ala Phe Val Pro Val Phe
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Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
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Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
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Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln
355 360 365

Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser
370 375 380

Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys
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Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln

405 410 415

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
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Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
435 440 445

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
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Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
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Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
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Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Ala Lys Arg
500 505 510

Ser Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val
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Glu Glu Asn Pro Gly Pro Met Gly Ala Gly Ala Thr Gly Arg Ala Met
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Asp Gly Pro Arg Leu Leu Leu Leu Leu Leu Leu Gly Val Ser Leu Gly
545 550 555 560

Gly Ala Lys Glu Ala Cys Pro Thr Gly Leu Tyr Thr His Ser Gly Glu
565 570 575

Cys Cys Lys Ala Cys Asn Leu Gly Glu Gly Val Ala Gln Pro Cys Gly
580 585 590

Ala Asn Gln Thr Val Cys Glu Pro Cys Leu Asp Ser Val Thr Phe Ser
595 600 605

Asp Val Val Ser Ala Thr Glu Pro Cys Lys Pro Cys Thr Glu Cys Val
610 615 620

Gly Leu Gln Ser Met Ser Ala Pro Cys Val Glu Ala Asp Asp Ala Val
625 630 635 640

Cys Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys
645 650 655

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660 665 670

Gln Asp Lys Gln Asn Thr Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr
675 680 685

Ser Asp Glu Ala Asn His Val Asp Pro Cys Leu Pro Cys Thr Val Cys
690 695 700

Glu Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala
705 710 715 720

Glu Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro
725 730 735

Glu Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro

740 745 750

Pro Glu Gln Asp Leu Ile Ala Ser Thr Val Ala Gly Val Val Thr Thr
755 760 765

Val Met Gly Ser Ser Gln Pro Val Val Thr Arg Gly Thr Thr Asp Asn
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785 790 795 800

Val Ala Tyr Ile Ala Phe Lys Arg
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Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
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Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn
65 70 75 80

[0195] Ser Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Ile Ser Thr Ala Tyr Met Glu Leu Asn Arg Leu Arg Ser Asp Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Gly Trp Leu Gln Thr Tyr Tyr Phe Asp
115 120 125

Asn Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
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Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr
145 150 155 160

Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile
165 170 175

Tyr Cys Lys Ser Ser Gln Thr Val Leu Thr Ser Ser Asn Asn Lys Asn
180 185 190

Phe Leu Ala Trp Tyr Gln Gln Lys Leu Gly Gln Pro Pro Lys Leu Leu
195 200 205

Ile Ser Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser
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Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
225 230 235 240

Ala Glu Asp Val Ala Ile Tyr Tyr Cys Gln His Tyr Tyr Thr Ser Pro
245 250 255

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260 265 270

Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys
275 280 285

His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp
290 295 300

Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val
305 310 315 320

Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu
325 330 335

Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr
340 345 350

Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr
355 360 365

Arg Ser Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr
370 375 380

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
385 390 395 400

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
405 410 415

[0197] Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
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Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
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Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
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Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
465 470 475 480

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
485 490 495

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
500 505 510

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
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Arg Ala Lys Arg Ser Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr
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Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Met Gly Ala Gly Ala Thr
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Gly Arg Ala Met Asp Gly Pro Arg Leu Leu Leu Leu Leu Leu Leu Gly
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Val Ser Leu Gly Gly Ala Lys Glu Ala Cys Pro Thr Gly Leu Tyr Thr
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[0198]

His Ser Gly Glu Cys Cys Lys Ala Cys Asn Leu Gly Glu Gly Val Ala
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Gln Pro Cys Gly Ala Asn Gln Thr Val Cys Glu Pro Cys Leu Asp Ser
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Val Thr Phe Ser Asp Val Val Ser Ala Thr Glu Pro Cys Lys Pro Cys
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Thr Glu Cys Val Gly Leu Gln Ser Met Ser Ala Pro Cys Val Glu Ala
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Asp Asp Ala Val Cys Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu Thr
660 665 670

Thr Gly Arg Cys Glu Ala Cys Arg Val Cys Glu Ala Gly Ser Gly Leu
675 680 685

Val Phe Ser Cys Gln Asp Lys Gln Asn Thr Val Cys Glu Glu Cys Pro
690 695 700

Asp Gly Thr Tyr Ser Asp Glu Ala Asn His Val Asp Pro Cys Leu Pro
705 710 715 720

Cys Thr Val Cys Glu Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg
725 730 735

Trp Ala Asp Ala Glu Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg
740 745 750

[0199] Ser Thr Pro Pro Glu Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu
755 760 765

Pro Glu Ala Pro Pro Glu Gln Asp Leu Ile Ala Ser Thr Val Ala Gly
770 775 780

Val Val Thr Thr Val Met Gly Ser Ser Gln Pro Val Val Thr Arg Gly
785 790 795 800

Thr Thr Asp Asn Leu Ile Pro Val Tyr Cys Ser Ile Leu Ala Ala Val
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Val Val Gly Leu Val Ala Tyr Ile Ala Phe Lys Arg
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Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
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Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn
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Ser Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
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Ala Val Tyr Tyr Cys Ala Arg Gly Trp Leu Gln Thr Tyr Tyr Phe Asp
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Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile
165 170 175

Tyr Cys Lys Ser Ser Gln Thr Val Leu Thr Ser Ser Asn Asn Lys Asn
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Phe Leu Ala Trp Tyr Gln Gln Lys Leu Gly Gln Pro Pro Lys Leu Leu
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225 230 235 240

Ala Glu Asp Val Ala Ile Tyr Tyr Cys Gln His Tyr Tyr Thr Ser Pro
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Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Ala Ala Ala
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Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys
275 280 285

His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp
290 295 300

Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val
305 310 315 320

Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu
325 330 335

Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr
340 345 350

[0204] Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr
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Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
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Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
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Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
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Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
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Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
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Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
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Pro Arg Ala Lys Arg Ser Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu
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Gly Val Ser Leu Gly Gly Ala Lys Glu Ala Cys Pro Thr Gly Leu Tyr
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Ser Val Thr Phe Ser Asp Val Val Ser Ala Thr Glu Pro Cys Lys Pro
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Cys Thr Glu Cys Val Gly Leu Gln Ser Met Ser Ala Pro Cys Val Glu
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Ala Asp Asp Ala Val Cys Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu
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Thr Thr Gly Arg Cys Glu Ala Cys Arg Val Cys Glu Ala Gly Ser Gly
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Leu Val Phe Ser Cys Gln Asp Lys Gln Asn Thr Val Cys Glu Glu Cys
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Pro Asp Gly Thr Tyr Ser Asp Glu Ala Asn His Val Asp Pro Cys Leu
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Pro Cys Thr Val Cys Glu Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr
675 680 685

[0206] Arg Trp Ala Asp Ala Glu Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr
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Arg Ser Thr Pro Pro Glu Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln
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Gly Val Val Thr Thr Val Met Gly Ser Ser Gln Pro Val Val Thr Arg
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gagtgtccag acggaaccta cagcgacgag gcgaaccacg tcgacccttg cttgccgtgc 2040

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tgcgaggaga tccctgggag atggatcacc cggagcacac ctcctgaggg atcagacagt 2160

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gttgctggcg tggtgacgac agtcatggga tcctcacaac cagtcgtgac gcggggcaca 2280

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[0209]

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20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn
65 70 75 80

Ser Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Ile Ser Thr Ala Tyr Met Glu Leu Asn Arg Leu Arg Ser Asp Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Gly Trp Leu Gln Thr Tyr Tyr Phe Asp
115 120 125

Asn Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr
145 150 155 160

[0210]

Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile
165 170 175

Tyr Cys Lys Ser Ser Gln Thr Val Leu Thr Ser Ser Asn Asn Lys Asn
180 185 190

Phe Leu Ala Trp Tyr Gln Gln Lys Leu Gly Gln Pro Pro Lys Leu Leu
195 200 205

Ile Ser Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser
210 215 220

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
225 230 235 240

Ala Glu Asp Val Ala Ile Tyr Tyr Cys Gln His Tyr Tyr Thr Ser Pro
245 250 255

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Ala Ala Ala
260 265 270

Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys
275 280 285

His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp
290 295 300

Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val
305 310 315 320

Thr Val Ala Phe Ile Ile Phe Trp Val Arg Phe Ser Val Val Lys Arg
325 330 335

[0211]

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
340 345 350

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
355 360 365

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
370 375 380

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
385 390 395 400

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
405 410 415

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
420 425 430

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
435 440 445

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
450 455 460

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
465 470 475 480

His Met Gln Ala Leu Pro Pro Arg Ala Lys Arg Ser Gly Ser Gly Glu
485 490 495

[0212] Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly
500 505 510

Pro Met Gly Ala Gly Ala Thr Gly Arg Ala Met Asp Gly Pro Arg Leu
515 520 525

Leu Leu Leu Leu Leu Leu Gly Val Ser Leu Gly Gly Ala Lys Glu Ala
530 535 540

Cys Pro Thr Gly Leu Tyr Thr His Ser Gly Glu Cys Cys Lys Ala Cys
545 550 555 560

Asn Leu Gly Glu Gly Val Ala Gln Pro Cys Gly Ala Asn Gln Thr Val
565 570 575

Cys Glu Pro Cys Leu Asp Ser Val Thr Phe Ser Asp Val Val Ser Ala
580 585 590

Thr Glu Pro Cys Lys Pro Cys Thr Glu Cys Val Gly Leu Gln Ser Met
595 600 605

Ser Ala Pro Cys Val Glu Ala Asp Asp Ala Val Cys Arg Cys Ala Tyr
610 615 620

Gly Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys Glu Ala Cys Arg Val
625 630 635 640

Cys Glu Ala Gly Ser Gly Leu Val Phe Ser Cys Gln Asp Lys Gln Asn
645 650 655

Thr Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser Asp Glu Ala Asn
660 665 670

[0213]

His Val Asp Pro Cys Leu Pro Cys Thr Val Cys Glu Asp Thr Glu Arg
675 680 685

Gln Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala Glu Cys Glu Glu Ile
690 695 700

Pro Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro Glu Gly Ser Asp Ser
705 710 715 720

Thr Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro Pro Glu Gln Asp Leu
725 730 735

Ile Ala Ser Thr Val Ala Gly Val Val Thr Thr Val Met Gly Ser Ser
740 745 750

Gln Pro Val Val Thr Arg Gly Thr Thr Asp Asn Leu Ile Pro Val Tyr
755 760 765

Cys Ser Ile Leu Ala Ala Val Val Val Gly Leu Val Ala Tyr Ile Ala
770 775 780

Phe Lys Arg
785

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多核苷酸"

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gtgtcctgca aggcttctgg atacaccttc accggctact atatgcactg ggtgcgacag 180

gcccctggac aagggcttga gtggatggga tggatcaacc ctaatagtgg tggcacaaac 240

tctgcacaga agtttcaggg cagggtcacc atgaccaggg acacgtccat cagtacagcc 300

tacatggagc tgaacaggct gagatctgac gacacggccg tttattactg tgcgagagga 360

tggctacaga cgtactactt tgacaactgg ggccagggaa ccctggtcac cgtatcctca 420

ggaggcggcg gttcaggcgg aggtggctct ggcggtggcg gaagtgacat cgtgatgacc 480

cagtctccag actccctggc tgtgtctctg ggcgagaggg ccaccatcta ctgcaagtcc 540

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ctaggacagc ctcctaagct gctcatttcc tgggcctcta cccgggaatc cggggtccct 660

gaccgattca gtggcagcgg gtctgggaca gatttcactc tcaccatcag cagcctgcag 720

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cgcctgctcc atagcgatta catgaatatg actccacgcc gccctggccc cacaaggaaa 1140

cactaccagc cttacgcacc acctagagat ttcgctgcct atcggagcag ggtgaagttt 1200

[0215] tccagatctg cagatgcacc agcgtatcag cagggccaga accaactgta taacgagctc 1260

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atgggtggca aaccaagacg aaaaaacccc caggagggtc tctataatga gctgcagaag 1380

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cacatgcaag ccctgccacc tagggccaag agaagtggca gcggggaggg ccggggatct 1560

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tgtgaagccg gctctggcct cgtgttcagt tgccaggata agcaaaacac agtatgtgag 2040

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accgtctgcg aggataccga acgccagctg agagagtgta cgcgctgggc agacgctgag 2160

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[0216]

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多肽"

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Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr

35 40 45

Thr Phe Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn
65 70 75 80

Ser Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Ile Ser Thr Ala Tyr Met Glu Leu Asn Arg Leu Arg Ser Asp Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Gly Trp Leu Gln Thr Tyr Tyr Phe Asp
[0217] 115 120 125

Asn Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr
145 150 155 160

Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile
165 170 175

Tyr Cys Lys Ser Ser Gln Thr Val Leu Thr Ser Ser Asn Asn Lys Asn
180 185 190

Phe Leu Ala Trp Tyr Gln Gln Lys Leu Gly Gln Pro Pro Lys Leu Leu
195 200 205

Ile Ser Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser
210 215 220

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
225 230 235 240

Ala Glu Asp Val Ala Ile Tyr Tyr Cys Gln His Tyr Tyr Thr Ser Pro
245 250 255

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Ala Ala Ala
260 265 270

Phe Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro
275 280 285

[0218] Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
290 295 300

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
305 310 315 320

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
325 330 335

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn
340 345 350

His Arg Asn Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
355 360 365

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro

370 375 380

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe
385 390 395 400

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
405 410 415

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
420 425 430

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
435 440 445

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
[0219] 450 455 460

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
465 470 475 480

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
485 490 495

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Ala Lys Arg Ser
500 505 510

Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu
515 520 525

Glu Asn Pro Gly Pro Met Gly Ala Gly Ala Thr Gly Arg Ala Met Asp
530 535 540

Gly Pro Arg Leu Leu Leu Leu Leu Leu Leu Gly Val Ser Leu Gly Gly
545 550 555 560

Ala Lys Glu Ala Cys Pro Thr Gly Leu Tyr Thr His Ser Gly Glu Cys
565 570 575

Cys Lys Ala Cys Asn Leu Gly Glu Gly Val Ala Gln Pro Cys Gly Ala
580 585 590

Asn Gln Thr Val Cys Glu Pro Cys Leu Asp Ser Val Thr Phe Ser Asp
595 600 605

Val Val Ser Ala Thr Glu Pro Cys Lys Pro Cys Thr Glu Cys Val Gly
610 615 620

[0220] Leu Gln Ser Met Ser Ala Pro Cys Val Glu Ala Asp Asp Ala Val Cys
625 630 635 640

Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys Glu
645 650 655

Ala Cys Arg Val Cys Glu Ala Gly Ser Gly Leu Val Phe Ser Cys Gln
660 665 670

Asp Lys Gln Asn Thr Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser
675 680 685

Asp Glu Ala Asn His Val Asp Pro Cys Leu Pro Cys Thr Val Cys Glu
690 695 700

Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala Glu

705 710 715 720

Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro Glu
725 730 735

Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro Pro
740 745 750

Glu Gln Asp Leu Ile Ala Ser Thr Val Ala Gly Val Val Thr Thr Val
755 760 765

Met Gly Ser Ser Gln Pro Val Val Thr Arg Gly Thr Thr Asp Asn Leu
770 775 780

Ile Pro Val Tyr Cys Ser Ile Leu Ala Ala Val Val Val Gly Leu Val
[0221] 785 790 795 800

Ala Tyr Ile Ala Phe Lys Arg
805

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多核苷酸"

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gtgtcctgca aggcttctgg atacaccttc accggctact atatgcactg ggtgcgacag 180

gcccctggac aagggcttga gtggatggga tggatcaacc ctaatagtgg tggcacaaac 240

tctgcacaga agtttcaggg cagggtcacc atgaccaggg acacgtccat cagtacagcc 300

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tggctacaga cgtactactt tgacaactgg ggccagggaa ccctggtcac cgtatcctca 420

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gaccgattca gtggcagcgg gtctgggaca gatttcactc tcaccatcag cagcctgcag 720

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gacccttgct tgccgtgcac cgtctgcgag gataccgaac gccagctgag agagtgtacg 2160

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gtcgtgacgc ggggcacaac cgacaatctg attcctgtct actgtagcat cttggcagcc 2400

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多肽"

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His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
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Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

[0224]

Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn
65 70 75 80

Ser Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Ile Ser Thr Ala Tyr Met Glu Leu Asn Arg Leu Arg Ser Asp Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Gly Trp Leu Gln Thr Tyr Tyr Phe Asp
115 120 125

Asn Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr
145 150 155 160

Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile
165 170 175

Tyr Cys Lys Ser Ser Gln Thr Val Leu Thr Ser Ser Asn Asn Lys Asn
180 185 190

Phe Leu Ala Trp Tyr Gln Gln Lys Leu Gly Gln Pro Pro Lys Leu Leu
195 200 205

Ile Ser Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser
210 215 220

[0225] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
225 230 235 240

Ala Glu Asp Val Ala Ile Tyr Tyr Cys Gln His Tyr Tyr Thr Ser Pro
245 250 255

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Ala Ala Ala
260 265 270

Phe Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro
275 280 285

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
290 295 300

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
305 310 315 320

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
325 330 335

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn
340 345 350

His Arg Asn Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu
355 360 365

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
370 375 380

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
385 390 395 400

[0226]

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
405 410 415

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
420 425 430

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
435 440 445

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
450 455 460

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
465 470 475 480

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
485 490 495

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
500 505 510

Pro Arg Ala Lys Arg Ser Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu
515 520 525

Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Met Gly Ala Gly Ala
530 535 540

Thr Gly Arg Ala Met Asp Gly Pro Arg Leu Leu Leu Leu Leu Leu Leu
545 550 555 560

[0227] Gly Val Ser Leu Gly Gly Ala Lys Glu Ala Cys Pro Thr Gly Leu Tyr
565 570 575

Thr His Ser Gly Glu Cys Cys Lys Ala Cys Asn Leu Gly Glu Gly Val
580 585 590

Ala Gln Pro Cys Gly Ala Asn Gln Thr Val Cys Glu Pro Cys Leu Asp
595 600 605

Ser Val Thr Phe Ser Asp Val Val Ser Ala Thr Glu Pro Cys Lys Pro
610 615 620

Cys Thr Glu Cys Val Gly Leu Gln Ser Met Ser Ala Pro Cys Val Glu
625 630 635 640

Ala Asp Asp Ala Val Cys Arg Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu
645 650 655

Thr Thr Gly Arg Cys Glu Ala Cys Arg Val Cys Glu Ala Gly Ser Gly
660 665 670

Leu Val Phe Ser Cys Gln Asp Lys Gln Asn Thr Val Cys Glu Glu Cys
675 680 685

Pro Asp Gly Thr Tyr Ser Asp Glu Ala Asn His Val Asp Pro Cys Leu
690 695 700

Pro Cys Thr Val Cys Glu Asp Thr Glu Arg Gln Leu Arg Glu Cys Thr
705 710 715 720

Arg Trp Ala Asp Ala Glu Cys Glu Glu Ile Pro Gly Arg Trp Ile Thr
725 730 735

[0228]

Arg Ser Thr Pro Pro Glu Gly Ser Asp Ser Thr Ala Pro Ser Thr Gln
740 745 750

Glu Pro Glu Ala Pro Pro Glu Gln Asp Leu Ile Ala Ser Thr Val Ala
755 760 765

Gly Val Val Thr Thr Val Met Gly Ser Ser Gln Pro Val Val Thr Arg
770 775 780

Gly Thr Thr Asp Asn Leu Ile Pro Val Tyr Cys Ser Ile Leu Ala Ala
785 790 795 800

Val Val Val Gly Leu Val Ala Tyr Ile Ala Phe Lys Arg
805 810

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Lys Pro Arg Arg Asn Leu Glu Glu Asp Asp Tyr Leu His Lys Asp Thr
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Gly Glu Thr Ser Met Leu Lys Arg Pro Val Leu Leu His Leu His Gln
35 40 45

Thr Ala His Ala Asp Glu Phe Asp Cys Pro Ser Glu Leu Gln His Thr
50 55 60

[0229]

Gln Glu Leu Phe Pro Gln Trp His Leu Pro Ile Lys Ile Ala Ala Ile
65 70 75 80

Ile Ala Ser Leu Thr Phe Leu Tyr Thr Leu Leu Arg Glu Val Ile His
85 90 95

Pro Leu Ala Thr Ser His Gln Gln Tyr Phe Tyr Lys Ile Pro Ile Leu
100 105 110

Val Ile Asn Lys Val Leu Pro Met Val Ser Ile Thr Leu Leu Ala Leu
115 120 125

Val Tyr Leu Pro Gly Val Ile Ala Ala Ile Val Gln Leu His Asn Gly
130 135 140

Thr Lys Tyr Lys Lys Phe Pro His Trp Leu Asp Lys Trp Met Leu Thr
145 150 155 160

Arg Lys Gln Phe Gly Leu Leu Ser Phe Phe Phe Ala Val Leu His Ala
165 170 175

Ile Tyr Ser Leu Ser Tyr Pro Met Arg Arg Ser Tyr Arg Tyr Lys Leu
180 185 190

Leu Asn Trp Ala Tyr Gln Gln Val Gln Gln Asn Lys Glu Asp Ala Trp
195 200 205

Ile Glu His Asp Val Trp Arg Met Glu Ile Tyr Val Ser Leu Gly Ile
210 215 220

[0230] Val Gly Leu Ala Ile Leu Ala Leu Leu Ala Val Thr Ser Ile Pro Ser
225 230 235 240

Val Ser Asp Ser Leu Thr Trp Arg Glu Phe His Tyr Ile Gln Ser Lys
245 250 255

Leu Gly Ile Val Ser Leu Leu Leu Gly Thr Ile His Ala Leu Ile Phe
260 265 270

Ala Trp Asn Lys Trp Ile Asp Ile Lys Gln Phe Val Trp Tyr Thr Pro
275 280 285

Pro Thr Phe Met Ile Ala Val Phe Leu Pro Ile Val Val Leu Ile Phe
290 295 300

Lys Ser Ile Leu Phe Leu Pro Cys Leu Arg Lys Lys Ile Leu Lys Ile
305 310 315 320

Arg His Gly Trp Glu Asp Val Thr Lys Ile Asn Lys Thr Glu Ile Cys
325 330 335

Ser Gln Leu

<210> 78
<211> 63
<212> DNA
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成寡核苷酸"

<400> 78
[0231] atggcactcc ccgtaactgc tctgctgctg ccgttggcat tgctcctgca cgccgcacgc 60

ccg 63

<210> 79
<211> 21
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 79
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro

20

<210> 80
<211> 45
<212> DNA
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成寡核苷酸"

<400> 80
ggcggtggag gctccggagg gggggctct ggcggagggg gctcc 45

<210> 81
<211> 15
<212> PRT
[0232] <213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 81
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 82
<211> 54
<212> DNA
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成寡核苷酸"

<400> 82
gggtctacat ccggctccgg gaagcccgga agtggcgaag gtagtacaaa gggg 54

<210> 83
<211> 18
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
肽"

<400> 83
Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr
1 5 10 15

Lys Gly

[0233]

<210> 84
<211> 126
<212> DNA
<213> 未知的

<220>
<221> 来源
<223> /注释="对未知的描述:
4-1BB序列"

<400> 84
aagcgcggca ggaagaagct cctctacatt tttaagcagc cttttatgag gcccgtacag 60

acaacacagg aggaagatgg ctgtagctgc agatttcccg aggaggagga aggtgggtgc 120

gagctg 126

<210> 85

<211> 42
<212> PRT
<213> 未知的

<220>
<221> 来源
<223> /注释="对未知的描述:
4-1BB序列"

<400> 85
Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
1 5 10 15

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
20 25 30

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
35 40

[0234]

<210> 86
<211> 37
<212> PRT
<213> 未知的

<220>
<221> 来源
<223> /注释="对未知的描述:
OX40 序列"

<400> 86
Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala His Lys Pro Pro Gly Gly
1 5 10 15

Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu Gln Ala Asp Ala His Ser
20 25 30

Thr Leu Ala Lys Ile

35

<210> 87
<211> 363
<212> DNA
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多核苷酸"

<400> 87

[0235]

caggttcagc tgcagcagtc tggagctgag atgatgaagc ctggggcctc agtgaagata 60

tcctgcaagg ctactggcta cacattcagt acctactgga tagagtgggt aaagcagagg 120

cctggacatg gccttgagtg gattggagag attttacctg gaagtggtaa tactgacttc 180

aatgagaagt tcaagggcaa ggccacattc actgcagata catcctccga cacagcctac 240

atgcatctca gcagcctgac atctgaggac tctgccgtct attactgtac aagatggggg 300

tactacggta ctaggggta cttcaatgtc tggggcgcag ggtccacggt caccgtctcc 360

tca 363

<210> 88
<211> 121
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多肽"

<400> 88

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

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

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

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

Gln Gly Arg Val Thr Phe Thr Ala Asp Thr Ser Ser Asp Thr Ala Tyr
65 70 75 80

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

[0236]

Thr Arg Trp Gly Tyr Tyr Gly Thr Arg Gly Tyr Phe Asn Val Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 89
<211> 5
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 89
Thr Tyr Trp Ile Glu

1 5

<210> 90
<211> 17
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 90
Glu Ile Leu Pro Gly Ser Gly Asn Thr Asp Phe Asn Glu Lys Phe Gln
1 5 10 15

Gly

[0237]

<210> 91
<211> 12
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 91
Trp Gly Tyr Tyr Gly Thr Arg Gly Tyr Phe Asn Val
1 5 10

<210> 92
<211> 318
<212> DNA
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多核苷酸"

<400> 92
caaattgttc tcacccagtc tccagcaatc atgtctgcat ctccagggga gaaggtcacc 60

ataacgtgca gtgccagctc aagtgtaagt tacatgcact ggttccagca gaagccaggc 120

acttctccca aactctggat ttatagcacc tccaacctgg cttctggagt ccctgctcgc 180

ttcagtggca gtggatctgg gacctcttac tctctcacaa tcagccgaat ggaggctgaa 240

gatgctgcca cttattactg ccagcaaagg cgtagtttcc cgtacacgtt cggaggggg 300

accaagctgg aaattaaa 318

[0238]

<210> 93
<211> 106
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多肽"

<400> 93
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

His Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
35 40 45

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

Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu
65 70 75 80

Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Arg Ser Phe Pro Tyr Thr
85 90 95

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 94
<211> 10
<212> PRT
<213> 人工序列

[0239]

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 94
Arg Ala Ser Ser Ser Val Ser Tyr Met His
1 5 10

<210> 95
<211> 7
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 95

Ser Thr Ser Asn Leu Ala Ser
1 5

<210> 96
<211> 9
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 96
Gln Gln Arg Arg Ser Phe Pro Tyr Thr
1 5

[0240]

<210> 97
<211> 363
<212> DNA
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成多核苷酸"

<400> 97
cagatccagt tggtgcagtc tggacctgaa ctgaagaagc ctggagagac agtcaagatc 60

tcctgcaagg cttctggata taccttcaca aactatggaa tgaactgggt gaagcaggct 120

ccaggaaagg gtttacagtg gatgggctgg atgaacactt atactggaga gccaacatat 180

gctgatgact tcaagggacg gtttgccttc tctttggaaa cctctgccag aactgtctct 240

ttggacatca acgacctcaa aaatgaggac acggctacat atttctgtac aagagcaggg 300

ggacaactca ggcccggggc tatggactac tggggtcaag gaacctcagt caccgtctcc 360

tca 363

<210> 98
<211> 119
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多肽"

<400> 98
Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Thr Val
1 5 10 15

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

[0241]

Asn Trp Val Gln Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Trp
35 40 45

Met Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe Gln Gly
50 55 60

Arg Val Thr Phe Thr Leu Asp Thr Ser Ala Arg Thr Val Tyr Met Glu
65 70 75 80

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg
85 90 95

Ala Gly Gly Gln Leu Arg Pro Gly Ala Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Met Val Thr Val Ser Ser
115

<210> 99
<211> 5
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 99
Asn Tyr Gly Met Asn
1 5

[0242]

<210> 100
<211> 17
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 100
Trp Met Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe Gln
1 5 10 15

Gly

<210> 101
<211> 12
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
肽"

<400> 101
Ala Gly Gly Gln Leu Arg Pro Gly Ala Met Asp Tyr
1 5 10

<210> 102
<211> 333
<212> DNA
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多核苷酸"

[0243] <400> 102
gacattgtgc tgacccaatc tccagcttct ttggctgtgt ctctagggca gagggccacc 60

atctcctgca aggccagcca aagtgttgat tatgatggtg atagttttat gaactggtac 120

caacagaaac caggacagcc acccaaactc ctcatctatg ttgcatccaa tctagaatct 180

gggatcccag acaggtttag tggcagtggg tctgggacag acttcaccct caacatccat 240

cctgtggagg aggaggatgc tgcaacctat tattgtcagc aaagtaatga ggaacctccg 300

acgttcggtg gaggcaccaa gctggaaatc aaa 333

<210> 103
<211> 111
<212> PRT
<213> 人工序列

<220>
<221> 来源

<223> /注释="对人工序列的描述: 合成
多肽"

<400> 103
Asp Ile Val Leu Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20 25 30

Gly Asp Ser Phe Met Asn Trp Tyr Leu Gln Lys Pro Gly Gln Pro Pro
35 40 45

Gln Leu Leu Ile Tyr Val Ala Ser Asn Leu Glu Ser Gly Val Pro Asp
50 55 60

[0244] Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser
65 70 75 80

Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Ser Asn
85 90 95

Glu Glu Pro Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 104
<211> 15
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
肽"

<400> 104
Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Phe Met Asn
1 5 10 15

<210> 105
<211> 7
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 105
Val Ala Ser Asn Leu Glu Ser
1 5

[0245]

<210> 106
<211> 9
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 106
Gln Gln Ser Asn Glu Glu Pro Pro Thr
1 5

<210> 107
<211> 360
<212> DNA
<213> 人工序列

<220>
<221> 来源

<223> /注释="对人工序列的描述: 合成
多核苷酸"

<400> 107
cagatacaac tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgtag cgtctggatt caccttcaag aactatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atttggtatg atggaagtaa tgaatactat 180

ggagaccccg tgaagggccg attcaccatc tccagagaca actccaagaa catgttgtat 240

ctgcaaatga acagcctgag agccgatgac acggctgtgt attactgtgc gaggtcggga 300

atagcagtgg ctggggcctt tgactactgg ggccagggaa ccctggtcac cgtctcctca 360

[0246]

<210> 108
<211> 121
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多肽"

<400> 108
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

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

Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Glu Ile Asn Pro Ser Ser Gly Arg Thr Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Thr Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

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

Ala Lys Leu Gly Pro Gly Pro Gln Tyr Tyr Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser
115 120

[0247]

<210> 109
<211> 5
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 109
Thr Tyr Trp Met His
1 5

<210> 110
<211> 17
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 110
Glu Ile Asn Pro Ser Ser Gly Arg Thr Asn Tyr Asn Glu Lys Phe Lys
1 5 10 15

Thr

<210> 111
<211> 12
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

[0248]

<400> 111
Leu Gly Pro Gly Pro Gln Tyr Tyr Ala Met Asp Tyr
1 5 10

<210> 112
<211> 327
<212> DNA
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成多核苷酸"

<400> 112
gaaattgtgt tgacgcagtc tccagacacc ctgtctttgt ctccagggga aaaagccacc 60

ctctcctgca gggccagtca gagtgttagc agcagcttct tggcctggta ccagcagaaa 120

cctggacagg ctcccagtct cctcatctat gttgcatcca gaagggccgc tggcatccct 180

gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240

cctgaagatt ttggaatgtt ttactgtcaa cactatggta ggacaccatt cactttcggc 300

cctgggacca aagtggatat caaacga 327

<210> 113
<211> 107
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多肽"

<400> 113
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

[0249]

Asp Arg Val Thr Ile Thr Cys His Ala Ser Gln Asn Ile Asn Val Trp
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Lys Leu His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Gln Ser Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 114
<211> 11
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 114
His Ala Ser Gln Asn Ile Asn Val Trp Leu Ser
1 5 10

[0250]

<210> 115
<211> 7
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 115
Lys Ala Ser Lys Leu His Thr
1 5

<210> 116
<211> 9
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成

肽"

<400> 116
Gln Gln Gly Gln Ser Tyr Pro Trp Thr
1 5

<210> 117
<211> 357
<212> DNA
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多核苷酸"

<400> 117
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

[0251] tcctgcaagg cttctggata caccttcacc ggctactata tacactgggt gcgacaggcc 120

cctgaacaag ggcttgagtg gatgggatgg atcaacccta acagtggtgg cacaaactat 180

gcacagaagt ttcagggcag ggtcaccatg gccagggaca cgtccatcag cacagtttac 240

atggacctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagaatacgc 300

ggtggtaact cggtctttga ctactggggc cagggaaccc tggtcaccgt ctcctca 357

<210> 118
<211> 120
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多肽"

<400> 118

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

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

Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

[0252] Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Gly Arg Ala Gly Tyr Tyr Tyr Tyr Phe Gly Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 119
<211> 5
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
肽"

<400> 119
Ser Tyr Asp Ile Asn
1 5

<210> 120
<211> 17
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 120
Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

[0253] Gly

<210> 121
<211> 11
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 121
Ala Gly Tyr Tyr Tyr Tyr Phe Gly Met Asp Val
1 5 10

<210> 122
<211> 342
<212> DNA

<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多核苷酸"

<400> 122
gacatcgtga tgacccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60

atcaactgca agtccaccca gagtatttta tacacctcca acaataagaa cttcttagct 120

tggtaccagc agaaaccagg gcagcctcct aaactgctca tttcctgggc atctatccgg 180

gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cgctctcacc 240

atcagcagcc tgcaggctga agatgtggca gtttattact gtcaacaata ttttagtact 300

atgttcagtt ttggccaggg gaccaagctg gagatcaaac ga 342

[0254]

<210> 123
<211> 108
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多肽"

<400> 123
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Gly Gln Ser Val Thr Ser Ser
20 25 30

Ser Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

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

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Gly Ser Arg
85 90 95

Ser Phe Gly Gln Gly Thr Lys Val Glu Leu Lys Arg
100 105

[0255]

<210> 124
<211> 12
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 124
Arg Ala Gly Gln Ser Val Thr Ser Ser Ser Phe Ala
1 5 10

<210> 125
<211> 7
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 125
Gln Thr Ser Thr Arg Ala Thr
1 5

<210> 126
<211> 8
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 126
Gln Gln Tyr Gly Gly Ser Arg Ser
1 5

[0256]

<210> 127
<211> 360
<212> DNA
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成多核苷酸"

<400> 127
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt agtggtgcat actactggac ttggatccgc 120

cagcacccag ggaagggcct ggagtggatt gggtacatcc attacagtgg gagcacctac 180

tccaacccgt ccctcaagag tcgaattacc atatcgttag acacgtctaa gaaccagttc 240

tccctgaagc tgaactctgt gactgccgcg gacacggccg tgtattactg tgcgagacaa 300

gaggactacg gtggtttgtt tgactactgg ggccagggaa ccctggtcac cgtttcctca 360

<210> 128
<211> 120
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多肽"

<400> 128
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

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

[0257]

Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Gly Arg Ala Gly Tyr Tyr Tyr Tyr Phe Gly Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 129
<211> 5
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 129
Ser Tyr Asp Ile Asn
1 5

[0258]

<210> 130
<211> 17
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 130
Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 131
<211> 11
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
肽"

<400> 131
Ala Gly Tyr Tyr Tyr Tyr Phe Gly Met Asp Val
1 5 10

<210> 132
<211> 324
<212> DNA
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多核苷酸"

[0259] <400> 132
gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagaatcacc 60

ctctcctgca gggccagtca gagtgttacc accgacttag cctggtacca gcagatgcct 120

ggacaggctc cccggctcct catctatgat gcttccacca gggccactgg tttcccagcc 180

agattcagtg gcagtgggtc tgggacagac ttcacgctca ccatcagcag cctgcaggct 240

gaagattttg cagtttatta ctgtcaacat tataaaacct ggcctctcac tttcggcgga 300

gggactaagg tggagatcaa acga 324

<210> 133
<211> 108
<212> PRT
<213> 人工序列

<220>
<221> 来源

<223> /注释="对人工序列的描述: 合成
多肽"

<400> 133
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Gly Gln Ser Val Thr Ser Ser
20 25 30

Ser Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

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

[0260] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Gly Ser Arg
85 90 95

Ala Phe Gly Gln Gly Thr Lys Val Glu Leu Lys Arg
100 105

<210> 134
<211> 12
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
肽"

<400> 134
Arg Ala Gly Gln Ser Val Thr Ser Ser Ser Leu Ala
1 5 10

<210> 135
<211> 7
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 135
Gln Thr Ser Thr Arg Ala Thr
1 5

[0261]

<210> 136
<211> 8
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 136
Gln Gln Tyr Gly Gly Ser Arg Ala
1 5

<210> 137
<211> 360
<212> DNA
<213> 人工序列

<220>
<221> 来源

<223> /注释="对人工序列的描述: 合成
多核苷酸"

<400> 137
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt agtggtgcat actactggac ttggatccgc 120

cagcacccag ggaagggcct ggagtggatt gggtacatcc attacagtgg gagcacctac 180

tccaacccgt ccctcaagag tcgaattacc atatcgttag acacgtctaa gaaccagttc 240

tccctgaagc tgaactctgt gactgccgcg gacacggccg tgtattactg tgcgagacaa 300

gaggactacg gtggtttgtt tgactactgg ggccagggaa ccctggtcac cgtttcctca 360

<210> 138
<211> 119
<212> PRT
[0262] <213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多肽"

<400> 138
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

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

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Gly Trp Leu Gln Thr Tyr Tyr Phe Asp Asn Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

[0263]

<210> 139
<211> 5
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 139
Gly Tyr Tyr Met His
1 5

<210> 140
<211> 17
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 140
Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Ser Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 141
<211> 10
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
肽"

[0264]

<400> 141
Gly Trp Leu Gln Thr Tyr Tyr Phe Asp Asn
1 5 10

<210> 142
<211> 324
<212> DNA
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多核苷酸"

<400> 142
gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagaatcacc 60

ctctcctgca gggccagtca gagtgttacc accgacttag cctggtacca gcagatgcct 120

ggacaggctc cccggctcct catctatgat gcttccacca gggccactgg tttcccagcc 180

agattcagtg gcagtgggtc tgggacagac ttcacgctca ccatcagcag cctgcaggct 240

gaagattttg cagtttatta ctgtcaacat tataaaacct ggcctctcac tttcggcgga 300

gggactaagg tggagatcaa acga 324

<210> 143
<211> 114
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多肽"

<400> 143
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

[0265]

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

Ser Asn Asn Lys Asn Phe Leu Ala Trp Tyr Gln Gln Lys Leu Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Ser Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Ile Tyr Tyr Cys Gln His
85 90 95

Tyr Tyr Thr Ser Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
100 105 110

Lys Arg

<210> 144
<211> 13
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 144
Thr Val Leu Thr Ser Ser Asn Asn Lys Asn Phe Leu Ala
1 5 10

[0266]

<210> 145
<211> 7
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成肽"

<400> 145
Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 146
<211> 9
<212> PRT
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
肽"

<400> 146
Gln His Tyr Tyr Thr Ser Pro Leu Thr
1 5

<210> 147
<211> 6762
<212> DNA
<213> 人工序列

<220>
<221> 来源
<223> /注释="对人工序列的描述: 合成
多核苷酸"

[0267]

<400> 147
ctgacgcgcc ctgtagcggc gcattaagcg cggcgggtgt ggtggttacg cgcagcgtga 60

ccgctacact tgccagcgcc ctagcgcccg ctcctttcgc tttcttccct tcctttctcg 120

ccacgttcgc cggctttccc cgtcaagctc taaatcgggg gctcccttta gggttccgat 180

ttagtgcttt acggcacctc gaccccaaaa aacttgatta gggtgatggt tcacgtagtg 240

ggccatcgcc ctgatagacg gtttttcgcc ctttgacgtt ggagtccacg ttctttaata 300

gtggactctt gttccaaact ggaacaacac tcaaccctat ctcggtctat tcttttgatt 360

tataagggat tttgccgatt tcggcctatt ggttaaaaaa tgagctgatt taacaaaaat 420

ttaacgcgaa ttttaacaaa atattaacgc ttacaatttg ccattcgcca ttcaggctgc 480

gcaactgttg ggaagggcga tcggtgcggg cctcttcgct attacgccag ctggcgaaag 540

ggggatgtgc tgcaaggcga ttaagttggg taacgccagg gttttcccag tcacgacgtt 600

gtaaaacgac ggccagtgaa ttgtaatacg actcactata gggcgacccg gggatggcgc 660

gccagtaatc aattacgggg tcattagttc atagcccata tatggagttc cgcgttacat 720

aacttacggt aaatggcccg cctggctgac cgcccaacga cccccgccca ttgacgtcaa 780

taatgacgta tgttcccata gtaacgccaa tagggacttt ccattgacgt caatgggtgg 840

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cccctattga cgtcaatgac ggtaaatggc ccgcctggca ttatgcccag tacatgacct 960

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gtctccaccc cattgacgtc aatgggagtt tgttttggca ccaaaatcaa cgggactttc 1140

caaaatgtcg taacaactcc gccccattga cgcaaatggg cggtaggcgt gtacggtggg 1200

[0268] aggtctatat aagcagagct ggtttagtga accggggtct ctctggttag accagatctg 1260

agcctgggag ctctctggct aactagggaa cccactgctt aagcctcaat aaagcttgcc 1320

ttgagtgctt caagtagtgt gtgcccgtct gttgtgtgac tctggtaact agagatccct 1380

cagacccttt tagtcagtgt ggaaaatctc tagcagtggc gcccgaacag ggacttgaaa 1440

gcgaaaggga aaccagagga gctctctcga cgcaggactc ggcttgctga agcgcgcacg 1500

gcaagaggcg aggggcggcg actggtgagt acgccaaaaa ttttgactag cggaggctag 1560

aaggagagag atgggtgcga gagcgtcagt attaagcggg ggagaattag atcgcgatgg 1620

gaaaaaattc ggttaaggcc aggggggaaag aaaaaatata aattaaaaca tatagtatgg 1680

gcaagcaggg agctagaacg attcgcagtt aatcctggcc tgttagaaac atcagaaggc 1740

tgtagacaaa tactgggaca gctacaacca tcccttcaga caggatcaga agaacttaga 1800

tcattatata atacagtagc aaccctctat tgtgtgcatc aaaggataga gataaaagac 1860

accaaggaag ctttagacaa gatagaggaa gagcaaaaca aaagtaagac caccgcacag 1920

caagccgccg ctgatcttca gacctggagg aggagatatg agggacaatt ggagaagtga 1980

attatataaa tataaagtag taaaaattga accattagga gtagcaccca ccaaggcaaa 2040

gagaagagtg gtgcagagag aaaaaagagc agtgggaata ggagctttgt tccttgggtt 2100

cttgggagca gcaggaagca ctatgggcgc agcgtcaatg acgctgacgg tacaggccag 2160

acaattattg tctggtatag tgcagcagca gaacaatttg ctgagggcta ttgaggcgca 2220

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tgtggaaaga tacctaaagg atcaacagct cctggggatt tggggttgct ctggaaaact 2340

catttgcacc actgctgtgc cttggaatgc tagttggagt aataaatctc tggaacagat 2400

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gaatatgggc caaacaggat atctgtggta agcagttcct gccccggctc agggccaaga 3120

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gcgcggggag aggcggtttg cgtattgggc gctcttccgc ttcctcgctc actgactcgc 4860

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tatccacaga atcaggggat aacgcaggaa agaacatgtg agcaaaaggc cagcaaaagg 4980

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gatccggcaa acaaaccacc gctggtagcg gtggtttttt tgtttgcaag cagcagatta 5580

cgcgcagaaa aaaaggatct caagaagatc ctttgatctt ttctacgggg tctgacgctc 5640

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taccatctgg ccccagtgct gcaatgatac cgcgagaccc acgctcaccg gctccagatt 5940

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ccgcctccat ccagtctatt aattgttgcc gggaagctag agtaagtagt tcgccagtta 6060

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gtatggcttc attcagctcc ggttcccaac gatcaaggcg agttacatga tcccccatgt 6180

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cagtgttatc actcatggtt atggcagcac tgcataattc tcttactgtc atgccatccg 6300

taagatgctt ttctgtgact ggtgagtact caaccaagtc attctgagaa tagtgtatgc 6360

ggcgaccgag ttgctcttgc ccggcgtcaa tacgggataa taccgcgcca catagcagaa 6420

ctttaaaagt gctcatcatt ggaaaacgtt cttcggggcg aaaactctca aggatcttac 6480

cgctgttgag atccagttcg atgtaaccca ctcgtgcacc caactgatct tcagcatctt 6540

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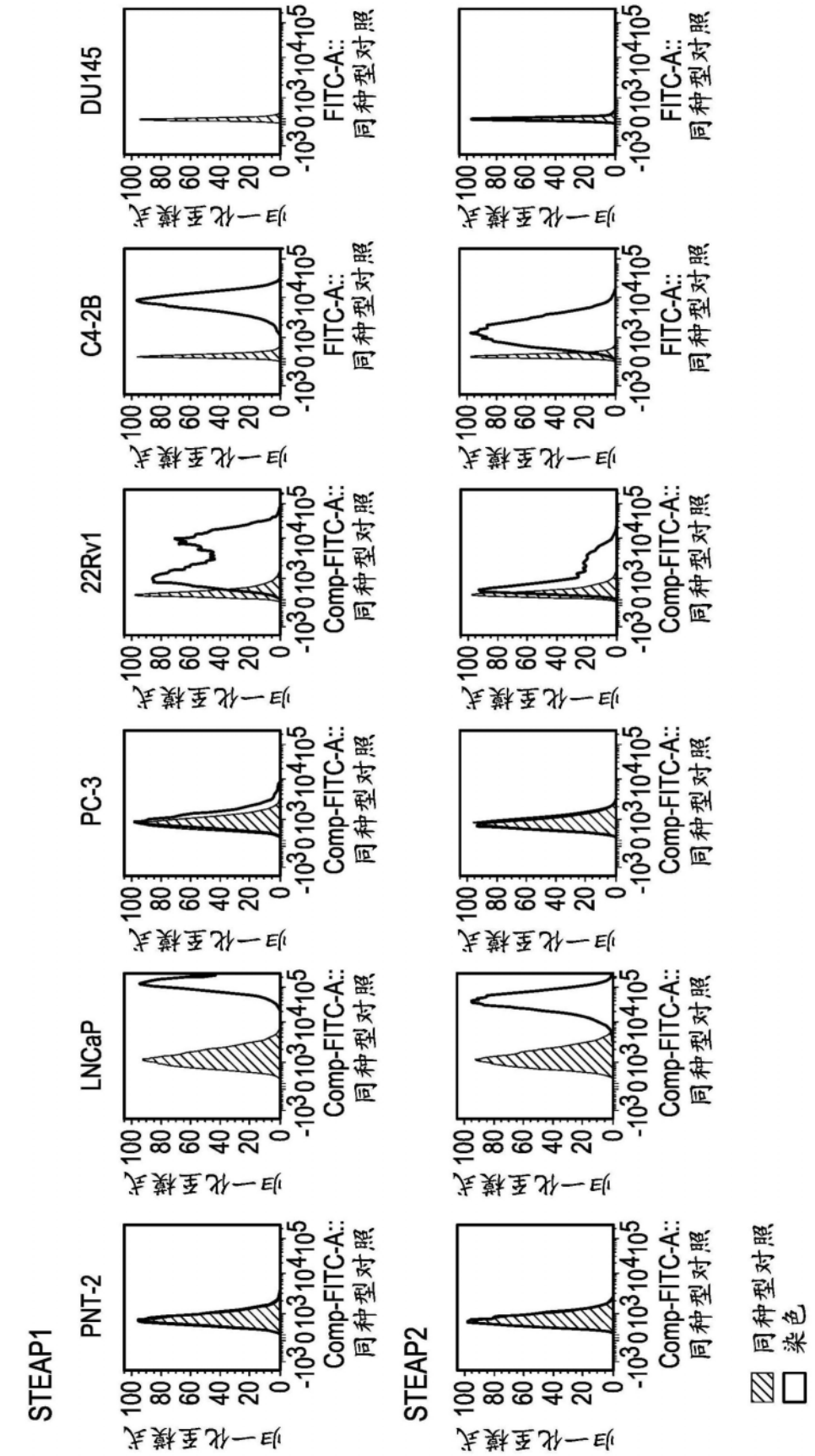
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STEAP2
PNT-2
LNCaP
PC-3
22Rv1
C4-2B
DU145
归一化至模式
Comp-FITC-A::
FITC-A::
同种型对照
同种型对照
染色

图1

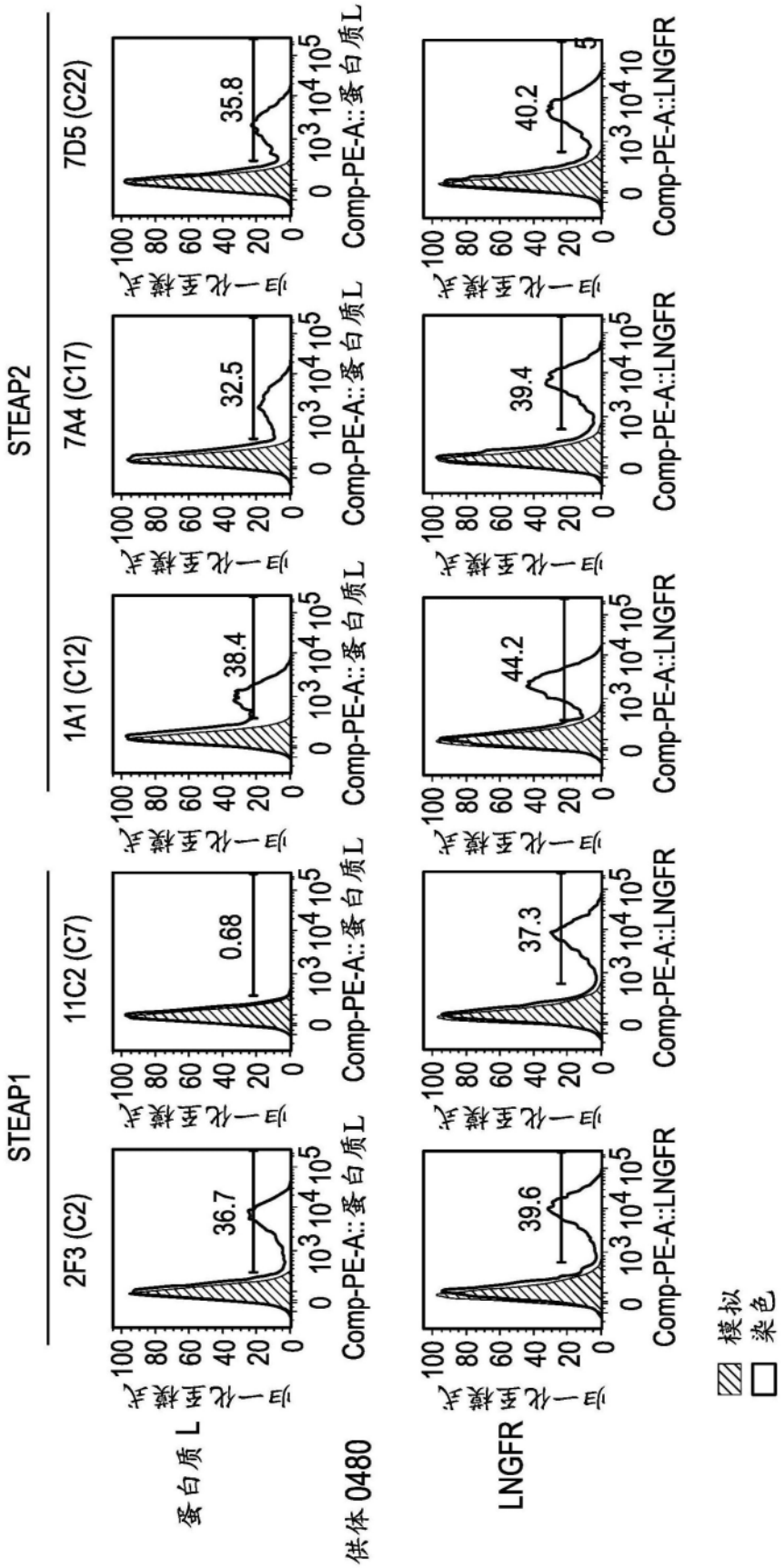
STEAP1
STEAP2
2F3 (C2)
11C2 (C7)
1A1 (C12)
7A4 (C17)
7D5 (C22)
蛋白质 L
LNGFR
供体 0480
36.7
0.68
38.4
32.5
35.8
39.6
37.3
44.2
39.4
40.2
归一化至模式
Comp-PE-A::蛋白质L
Comp-PE-A::LNGFR
模拟
染色

图2

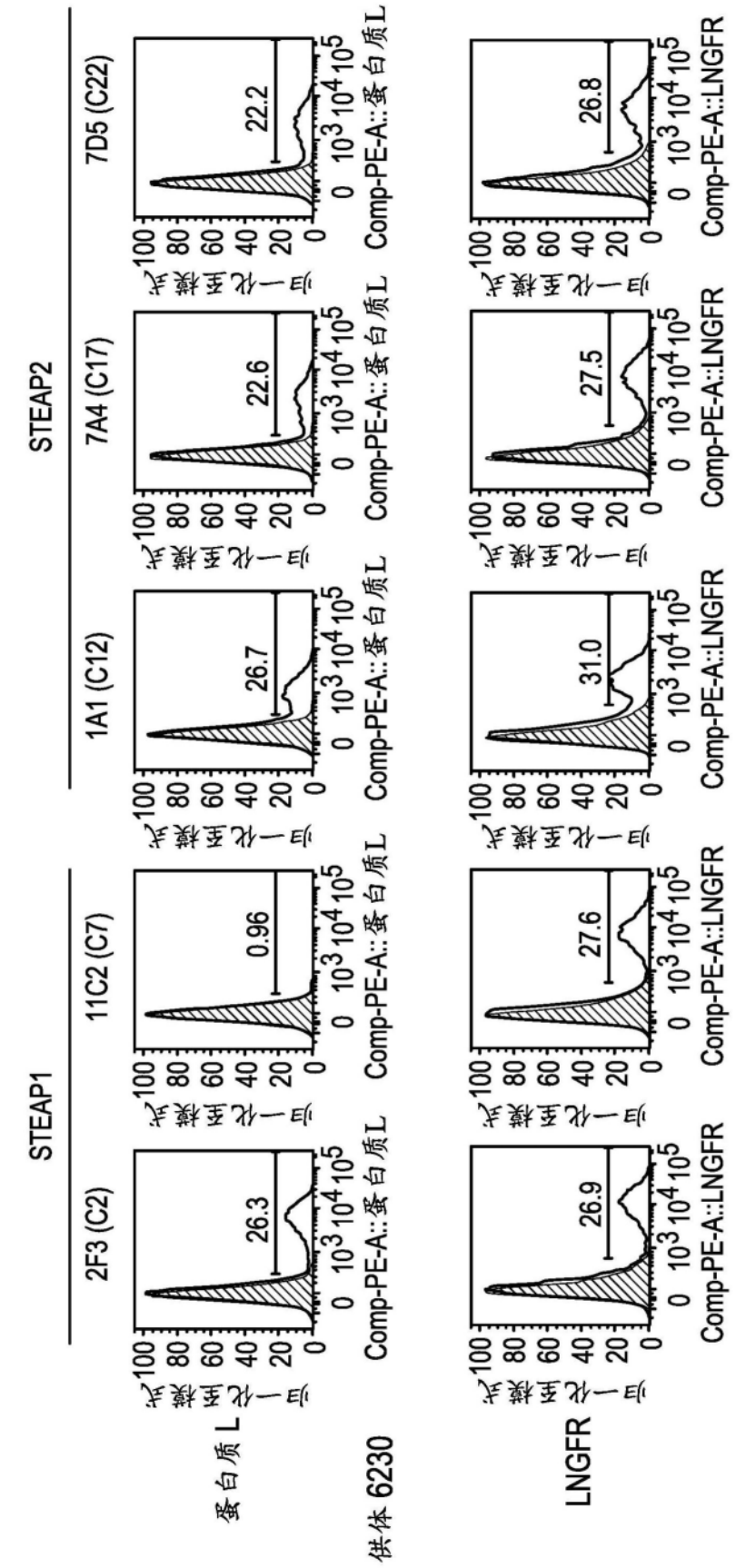
STEAP1
STEAP2
2F3 (C2)
11C2 (C7)
1A1 (C12)
7A4 (C17)
7D5 (C22)
蛋白质 L
LNGFR
供体 6230
归一化至模式
Comp-PE-A::蛋白质L
Comp-PE-A::LNGFR
26.3
0.96
26.7
22.6
22.2
26.9
27.6
31.0
27.5
26.8
模拟
染色

图2续

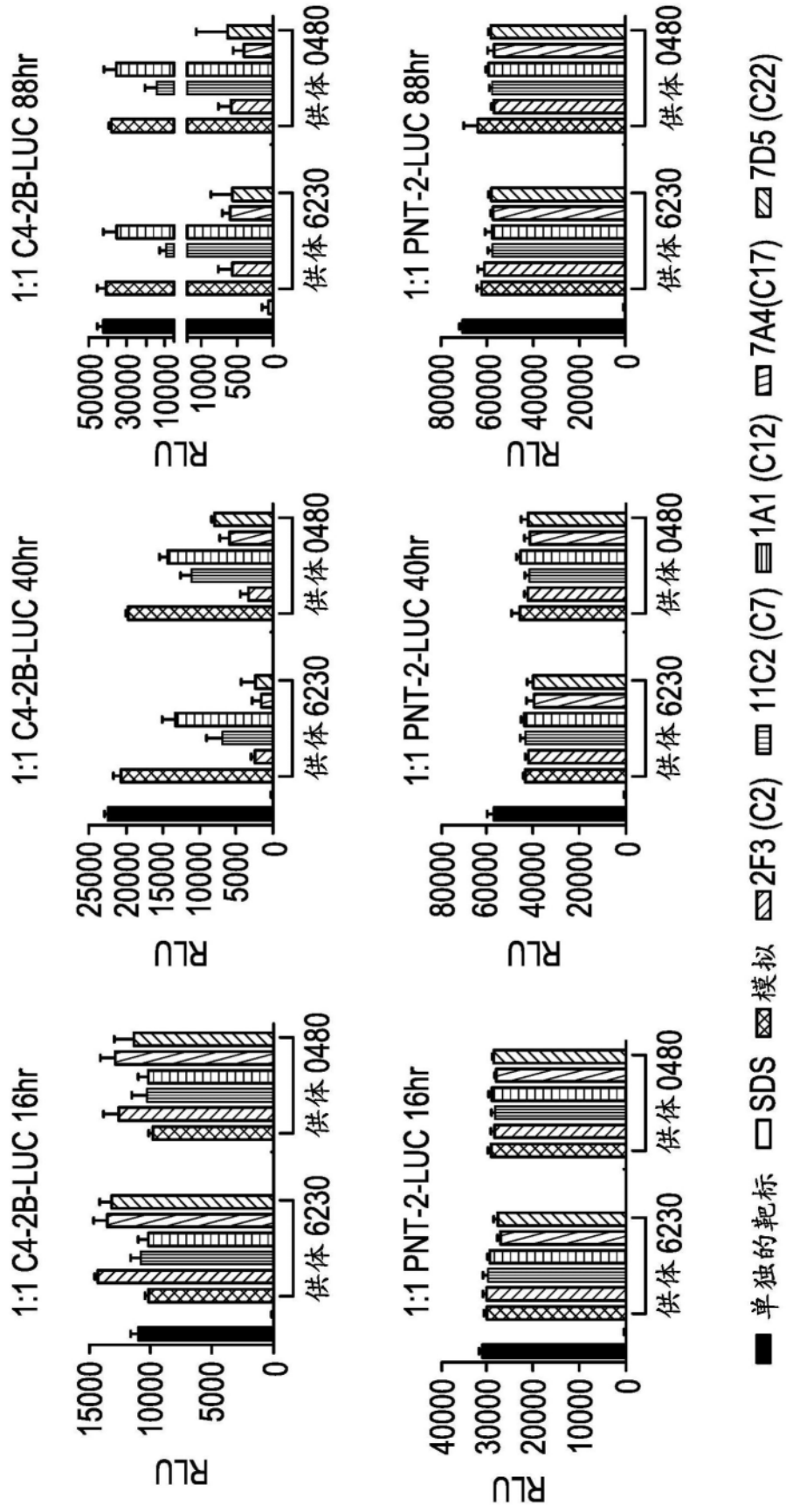
1:1 C4-2B-LUC 16hr
1:1 C4-2B-LUC 40hr
1:1 C4-2B-LUC 88hr
1:1 PNT-2-LUC 16hr
1:1 PNT-2-LUC 40hr
1:1 PNT-2-LUC 88hr
RLU
供体 6230
供体 0480
单独的靶标
SDS
模拟
2F3 (C2)
11C2 (C7)
1A1 (C12)
7A4(C17)
7D5 (C22)

图3

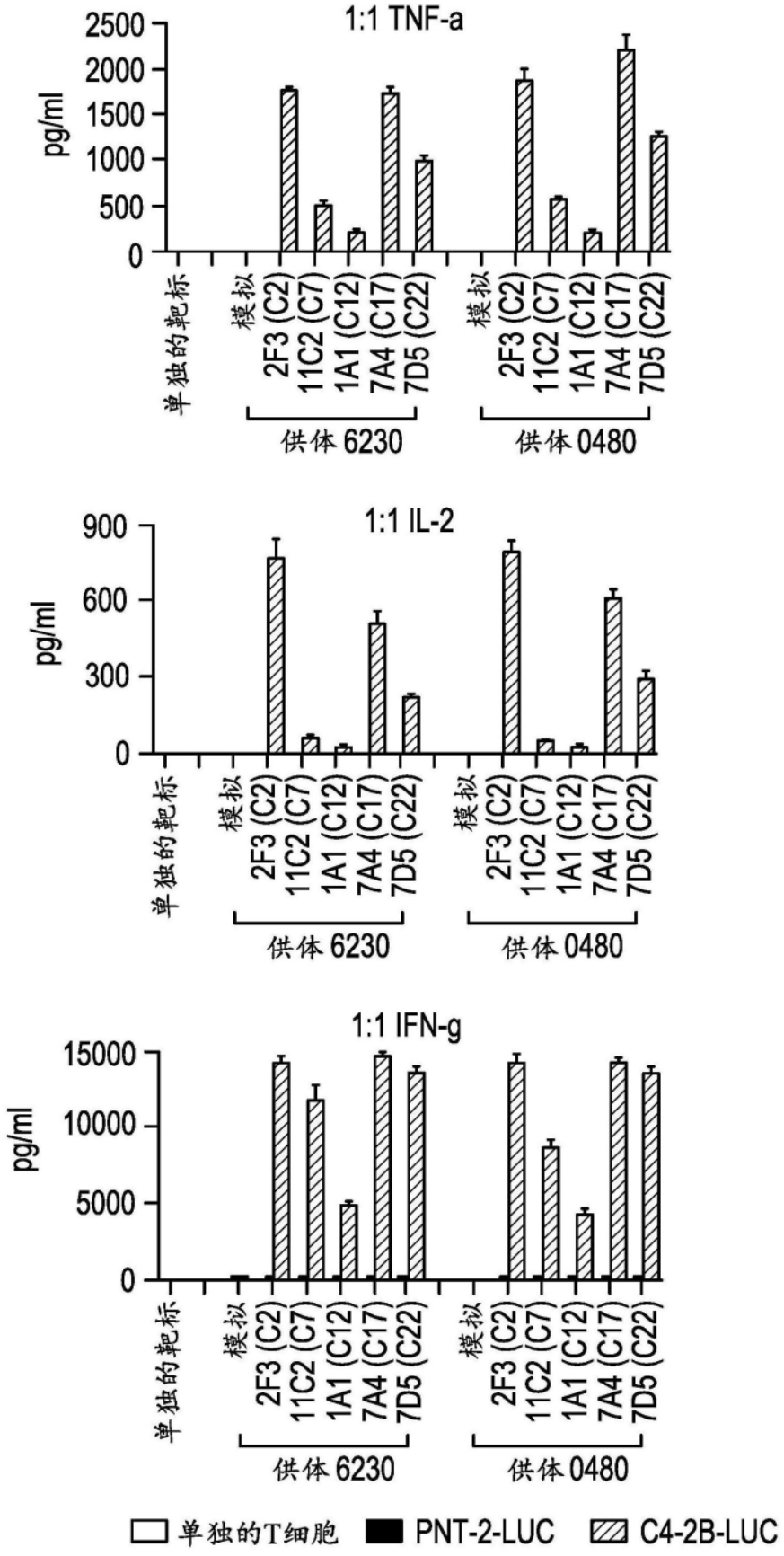
1:1 TNF-a
pg/ml
2500
2000
1500
1000
500
0
单独的靶标
模拟
2F3 (C2)
11C2 (C7)
1A1 (C12)
7A4 (C17)
7D5 (C22)
供体 6230
供体 0480
1:1 IL-2
900
600
300
1:1 IFN-g
15000
10000
5000
□ 单独的T细胞 ■ PNT-2-LUC ▨ C4-2B-LUC

图4

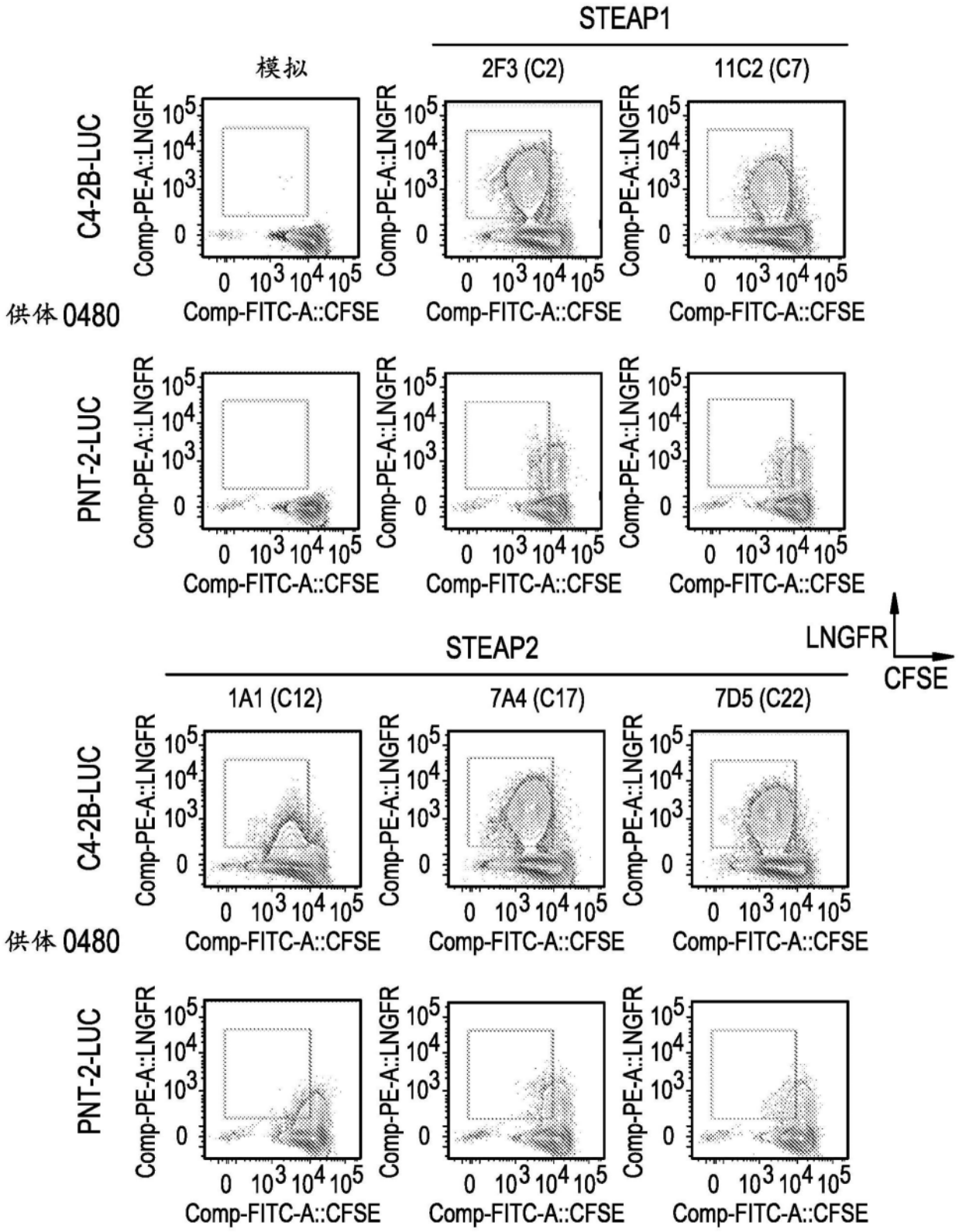
STEAP1
模拟
2F3 (C2)
11C2 (C7)
C4-2B-LUC
PNT-2-LUC
供体 0480
Comp-PE-A::LNGFR
Comp-FITC-A::CFSE
STEAP2
1A1 (C12)
7A4 (C17)
7D5 (C22)
LNGFR
CFSE

图5

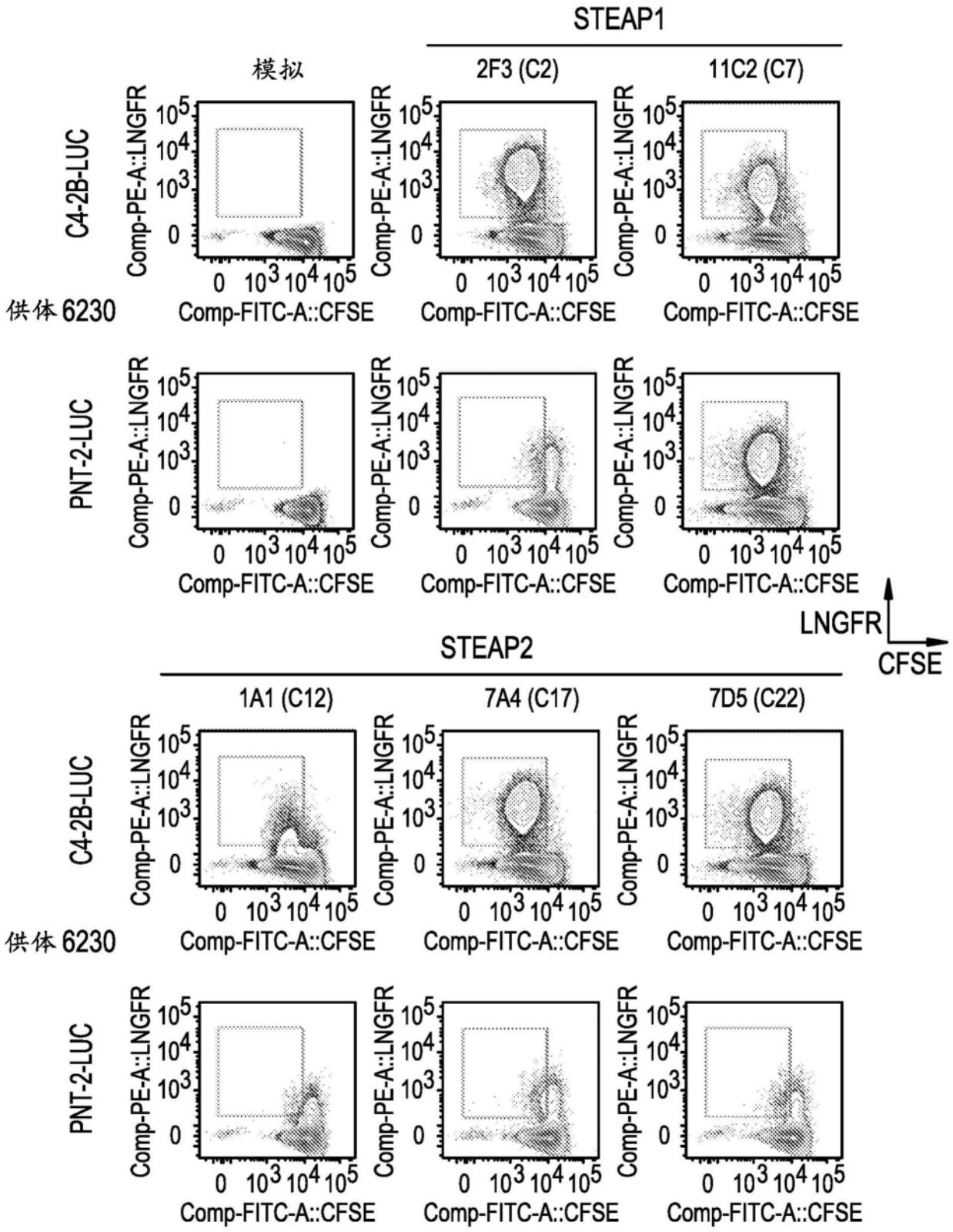
STEAP1
模拟
2F3 (C2)
11C2 (C7)
C4-2B-LUC
PNT-2-LUC
供体6230
Comp-PE-A::LNGFR
Comp-FITC-A::CFSE
LNGFR
CFSE
STEAP2
1A1 (C12)
7A4 (C17)
7D5 (C22)

图5续

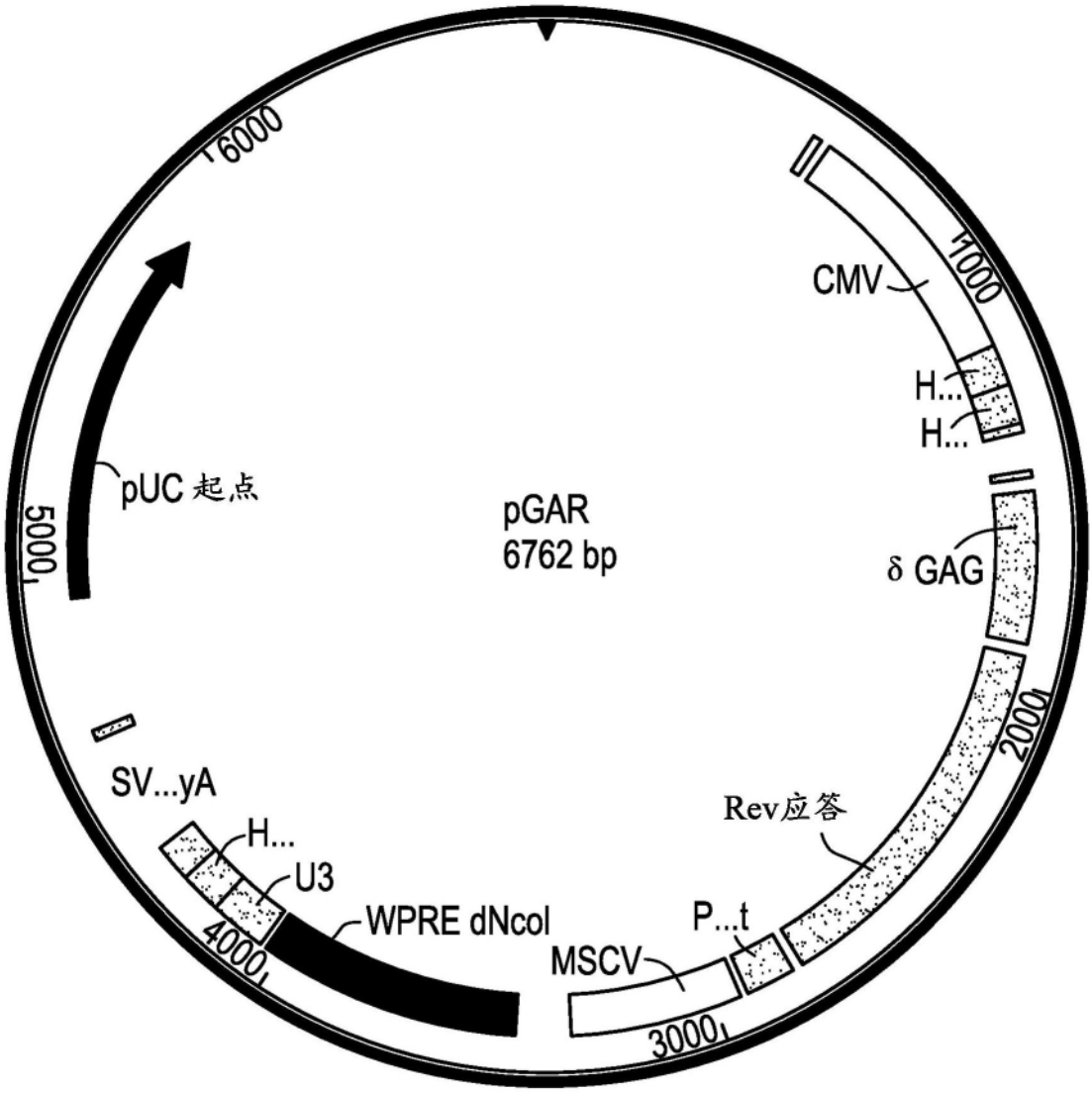
6000
1000
CMV
H...
H...
pUC 起点
pGAR
6762 bp
δ GAG
5000
2000
SV...yA
Rev应答
H...
U3
WPRE dNcol
P...t
MSCV
4000
3000

图6