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(54)发明名称

溶瘤病毒及其应用

(57)摘要

本申请涉及生物医药的技术领域,具体公开了一种溶瘤病毒及其应用。该溶瘤病毒包括M蛋白,所述M蛋白与SEQ ID NO 1所示的氨基酸序列相比,包含以下一个或多个位点的氨基酸取代:第32位、第33位、第49位、第54位、第133位、第225位。以及该溶瘤病毒的表达载体、生产该溶瘤病毒的病毒生产细胞、包括该溶瘤病毒的药物组合物;以及上述溶瘤病毒、溶瘤病毒表达载体、病毒生产细胞和/或药物组合物的制备方法和用途。本申请能够有效提高溶瘤病毒的安全性和治愈率。

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1.溶瘤病毒,其特征在于,所述溶瘤病毒包含M蛋白、G蛋白、N蛋白、P蛋白和L蛋白;

与SEQ ID NO 1所示的氨基酸序列相比,所述M蛋白的氨基酸取代为N32S、N49D、M51R、H54Y、V221F、V225I、S226R;

与SEQ ID NO 31所示的氨基酸序列相比,所述G蛋白的氨基酸取代为V53I、A141V、D172Y、K217E、D232G、V331A、V371E、G436D、T438S、F453L、T471I、Y487H;

与SEQ ID NO 55所示的氨基酸序列相比,所述N蛋白的氨基酸取代为I14V、R155K、S353N;

与SEQ ID NO 61所示的氨基酸序列相比,所述P蛋白的氨基酸取代为R50K、V76A、D99E、L126S、L140S、H151Y、I168M、K170E、Y189S、N237D;

与SEQ ID NO 81所示的氨基酸序列相比,所述L蛋白的氨基酸取代为以下组中的任一项:

1)所述L蛋白的氨基酸取代为S87P;

2)所述L蛋白的氨基酸取代为S87P、I487T;

3)所述L蛋白的氨基酸取代为I487T。

2.根据权利要求1所述的溶瘤病毒,其特征在于,所述溶瘤病毒包含棒状病毒。

3.根据权利要求1所述的溶瘤病毒,其特征在于:所述溶瘤病毒包含水疱性口炎病毒。

4.根据权利要求1所述的溶瘤病毒,其特征在于:所述溶瘤病毒包含VSV病毒Indiana MuddSummer亚型。

5.根据权利要求1所述的溶瘤病毒,其特征在于:所述溶瘤病毒包含或表达外源目的蛋白。

6.根据权利要求5所述的溶瘤病毒,其特征在于:编码所述外源目的蛋白的核酸序列位于编码具有氨基酸取代的M蛋白的核酸序列、和/或编码具有氨基酸取代的G蛋白的核酸序列、和/或编码具有氨基酸取代的N蛋白的核酸序列、和/或编码具有氨基酸取代的P蛋白的核酸序列、和/或编码具有氨基酸取代的L蛋白的核酸序列之间。

7.溶瘤病毒表达载体,其特征在于,所述溶瘤病毒表达载体能够表达权利要求1-6中任一项所述的溶瘤病毒。

8.病毒生产细胞,其特征在于:所述病毒生产细胞能够产生权利要求1-6中任一项所述的溶瘤病毒。

9.药物组合物,其特征在于:所述药物组合物包括权利要求1-6中任一项所述的溶瘤病毒,以及任选地药学上可接受的载剂。

10.权利要求1-6中任一项所述的溶瘤病毒、权利要求7所述的溶瘤病毒表达载体、权利要求8所述的病毒生产细胞和/或权利要求9所述的药物组合物的制备方法。

11.权利要求1-6中任一项所述的溶瘤病毒、权利要求7所述的溶瘤病毒表达载体、权利要求8所述的病毒生产细胞和/或权利要求9所述的药物组合物在制备用于预防和/或治疗疾病和/或病症的药物中用于持续杀伤异常细胞的用途。

12.根据权利要求11所述的用途,其特征在于:所述溶瘤病毒、所述溶瘤病毒表达载体、所述病毒生产细胞和/或所述药物组合物用于持续杀伤异常增生性细胞的方法中。

13.根据权利要求12所述的用途,其特征在于:所述异常增生性细胞选自肿瘤细胞或肿瘤组织的相关细胞。

14.根据权利要求13所述的用途,其特征在于:所述肿瘤包括实体瘤或血液瘤。

溶瘤病毒及其应用

技术领域

[0001] 本申请涉及生物医药的技术领域,更具体地说,它涉及一种溶瘤病毒及其应用。

背景技术

[0002] 溶瘤病毒是一类具有复制能力的肿瘤杀伤性病毒,目前已被大众接受作为肿瘤免疫治疗的重要分支。溶瘤病毒能够特异性地靶向感染肿瘤细胞,例如利用肿瘤细胞中抑癌基因的失活或缺陷,从而选择性地感染肿瘤细胞;溶瘤病毒感染肿瘤细胞后,会在肿瘤细胞内大量复制并最终摧毁肿瘤细胞,从而杀死肿瘤细胞。同时,溶瘤病毒还可以提供提高宿主自身抗癌反应所必需的免疫刺激信号,从而吸引更多的免疫细胞来继续杀死残余的肿瘤细胞。

[0003] 虽然溶瘤病毒在肿瘤免疫治疗方面具有较好的应用前景,但野生型溶瘤病毒往往会引起机体神经系统炎症等问题,在利用野生型病毒感染肿瘤细胞的过程中,还存在较大的致病风险。因此,为进一步推进溶瘤病毒的临床应用,需要对野生型溶瘤病毒进行改造,以获得减毒后的溶瘤病毒。将减毒后的溶瘤病毒用于临床应用,从而降低溶瘤病毒的致病风险,提高溶瘤病毒的安全性。

[0004] 然而,在对溶瘤病毒改造的过程中,若仅是对野生型溶瘤病毒随机进行基因修饰,虽然能够降低其毒性,但改造后的溶瘤病毒可能治愈率效果不佳,甚至改造后的溶瘤病毒无法进行包装,不利于推进溶瘤病毒的临床应用。因此,提供一种安全性能良好,同时治愈率高的改造后的溶瘤病毒,对肿瘤免疫治疗领域具有重要的科研价值和应用意义。

发明内容

[0005] 为了提高溶瘤病毒的安全性和治愈率,本申请提供一种溶瘤病毒及其应用。

[0006] 第一方面,本申请提供的一种溶瘤病毒,采用如下的技术方案:

[0007] 一种溶瘤病毒,所述溶瘤病毒包括M蛋白,所述M蛋白与SEQ ID NO 1所示的氨基酸序列相比,包含以下一个或多个位点的氨基酸取代:第32位、第33位、第49位、第54位、第133位、第225位。

[0008] 在一些具体的实施方案中,所述M蛋白的氨基酸取代包含在第32位的天冬酰胺突变为丝氨酸(N32S);和/或,在第33位的甲硫氨酸突变为丙氨酸(M33A);和/或,在第49位的天冬酰胺突变为天冬氨酸(N49D);和/或,在第54位的组氨酸突变为酪氨酸(H54Y);和/或,在第133位的丙氨酸突变为苏氨酸(A133T);和/或,在第225位的缬氨酸突变为异亮氨酸(V225I)。

[0009] 进一步地,所述M蛋白还包含以下一个或多个位点的氨基酸取代:第21位、第51位、第111位、第221位和第226位。

[0010] 在一些具体的实施方案中,所述M蛋白的氨基酸取代还包含在第21位的甘氨酸突变为谷氨酸(G21E);和/或,所述M蛋白的氨基酸取代包含在第51位的甲硫氨酸突变为精氨酸(M51R);和/或,在第51位的甲硫氨酸突变为丙氨酸(M51A);和/或,包含在第111位的亮氨

酸突变为丙氨酸(L111A);和/或,在第221位的缬氨酸突变为苯丙氨酸(V221F);和/或,在第226位的丝氨酸突变为精氨酸(S226R)。

[0011] 在一个具体的实施方案中,所述M蛋白的氨基酸取代包含在第21位的甘氨酸突变为谷氨酸(G21E)。

[0012] 在一个具体的实施方案中,所述M蛋白的氨基酸取代包含在第32位的天冬酰胺突变为丝氨酸(N32S)。

[0013] 在一个具体的实施方案中,所述M蛋白的氨基酸取代包含在第33位的甲硫氨酸突变为丙氨酸(M33A)。

[0014] 在一个具体的实施方案中,所述M蛋白的氨基酸取代包含在第49位的天冬酰胺突变为天冬氨酸(N49D)。

[0015] 在一个具体的实施方案中,所述M蛋白的氨基酸取代包含在第54位的组氨酸突变为酪氨酸(H54Y)。

[0016] 在一个具体的实施方案中,所述M蛋白的氨基酸取代包含在第111位的亮氨酸突变为丙氨酸(L111A)。

[0017] 在一个具体的实施方案中,所述M蛋白的氨基酸取代包含在第133位的丙氨酸突变为苏氨酸(A133T)。

[0018] 在一个具体的实施方案中,所述M蛋白的氨基酸取代包含在第225位的缬氨酸突变为异亮氨酸(V225I)。

[0019] 在一个具体的实施方案中,所述M蛋白的氨基酸取代包含在第51位的甲硫氨酸突变为精氨酸(M51R)。

[0020] 在一个具体的实施方案中,所述M蛋白的氨基酸取代包含在第51位的甲硫氨酸突变为丙氨酸(M51A)。

[0021] 在一个具体的实施方案中,所述M蛋白的氨基酸取代包含在第221位的缬氨酸突变为苯丙氨酸(V221F)。

[0022] 在一个具体的实施方案中,所述M蛋白的氨基酸取代包含在第226位的丝氨酸突变为精氨酸(S226R)。

[0023] 在一个具体的实施方案中,所述M蛋白的氨基酸取代包含在第226位的丝氨酸突变为甘氨酸(S226G)。

[0024] 在一个具体的实施方案中,所述M蛋白具有G21E的氨基酸取代。

[0025] 在一个具体的实施方案中,所述M蛋白具有G21E、N32S的氨基酸取代。

[0026] 在一个具体的实施方案中,所述M蛋白具有G21E、N32S、M33A的氨基酸取代。

[0027] 在一个具体的实施方案中,所述M蛋白具有G21E、N32S、M33A、N49D的氨基酸取代。

[0028] 在一个具体的实施方案中,所述M蛋白具有G21E、N32S、M33A、N49D、H54Y的氨基酸取代。

[0029] 在一个具体的实施方案中,所述M蛋白具有G21E、N32S、M33A、N49D、H54Y、L111A的氨基酸取代。

[0030] 在一个具体的实施方案中,所述M蛋白具有G21E、N32S、M33A、N49D、H54Y、L111A、A133T的氨基酸取代。

[0031] 在一个具体的实施方案中,所述M蛋白具有G21E、N32S、M33A、N49D、H54Y、L111A、

A133T、V225I的氨基酸取代。

[0032] 在一个具体的实施方案中,所述M蛋白具有G21E、N32S、M33A、N49D、M51R、H54Y、L111A、A133T、V225I氨基酸取代。

[0033] 在一个具体的实施方案中,所述M蛋白具有G21E、N32S、M33A、N49D、M51R、H54Y、L111A、A133T、V221F、V225I的氨基酸取代。

[0034] 在一个具体的实施方案中,所述M蛋白具有G21E、N32S、M33A、N49D、M51R、H54Y、L111A、A133T、V221F、V225I、S226R的氨基酸取代。

[0035] 在一个具体的实施方案中,所述M蛋白具有N32S、M33A、N49D、M51R、H54Y、L111A、A133T、V221F、V225I、S226R的氨基酸取代。

[0036] 在一个具体的实施方案中,所述M蛋白具有M33A、N49D、M51R、H54Y、L111A、A133T、V221F、V225I、S226R的氨基酸取代。

[0037] 在一个具体的实施方案中,所述M蛋白具有N49D、M51R、H54Y、L111A、A133T、V221F、V225I、S226R的氨基酸取代。

[0038] 在一个具体的实施方案中,所述M蛋白具有M51R、H54Y、L111A、A133T、V221F、V225I、S226R的氨基酸取代。

[0039] 在一个具体的实施方案中,所述M蛋白具有H54Y、L111A、A133T、V221F、V225I、S226R的氨基酸取代。

[0040] 在一个具体的实施方案中,所述M蛋白具有L111A、A133T、V221F、V225I、S226R的氨基酸取代。

[0041] 在一个具体的实施方案中,所述M蛋白具有A133T、V221F、V225I、S226R的氨基酸取代。

[0042] 在一个具体的实施方案中,所述M蛋白具有V221F、V225I、S226R的氨基酸取代。

[0043] 在一个具体的实施方案中,所述M蛋白具有V225I、S226R的氨基酸取代。

[0044] 在一个具体的实施方案中,所述M蛋白具有S226R的氨基酸取代。

[0045] 在一个具体的实施方案中,所述M蛋白具有N32S、N49D、H54Y、V225I的氨基酸取代。

[0046] 在一个具体的实施方案中,所述M蛋白具有N32S、N49D、H54Y、V225I、S226G的氨基酸取代。

[0047] 在一个具体的实施方案中,所述M蛋白具有N32S、N49D、M51R、H54Y、V221F、V225I、S226R的氨基酸取代。

[0048] 在一个具体的实施方案中,所述M蛋白具有N32S、M33A、N49D、M51R、H54Y、V221F、V225I、S226R的氨基酸取代。

[0049] 在一个具体的实施方案中,所述M蛋白具有N32S、N49D、M51R、H54Y、A133T、V221F、V225I、S226R的氨基酸取代。

[0050] 在一个具体的实施方案中,所述M蛋白具有N32S、M33A、N49D、M51R、H54Y、A133T、V221F、V225I、S226R的氨基酸取代。

[0051] 在一个具体的实施方案中,所述M蛋白具有G21E、N32S、N49D、M51A、H54Y、L111A、V225I、S226R的氨基酸取代。

[0052] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 2所示的氨基酸序列。

[0053] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 3所示的氨基酸序列。

[0054] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 4所示的氨基酸序列。

[0055] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 5所示的氨基酸序列。

[0056] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 6所示的氨基酸序列。

[0057] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 7所示的氨基酸序列。

[0058] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 8所示的氨基酸序列。

[0059] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 9所示的氨基酸序列。

[0060] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 10所示的氨基酸序列。

[0061] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 11所示的氨基酸序列。

[0062] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 12所示的氨基酸序列。

[0063] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 13所示的氨基酸序列。

[0064] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 14所示的氨基酸序列。

[0065] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 15所示的氨基酸序列。

[0066] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 16所示的氨基酸序列。

[0067] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 17所示的氨基酸序列。

[0068] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 18所示的氨基酸序列。

[0069] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 19所示的氨基酸序列。

[0070] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 20所示的氨基酸序列。

[0071] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 21所示的氨基酸序列。

[0072] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 22所示的氨基酸序列。

[0073] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 23所示的氨基酸序列。

[0074] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 24所示的氨基酸序列。

[0075] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 25所示的氨基酸序列。

[0076] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 26所示的氨基酸序列。

[0077] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 27所示的氨基酸序列。

[0078] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 28所示的氨基酸序列。

[0079] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 29所示的氨基酸序列。

[0080] 在一个具体的实施方案中,所述M蛋白包含如SEQ ID NO 30所示的氨基酸序列。

[0081] 一种溶瘤病毒,包含上述M蛋白;所述溶瘤病毒还包括G蛋白;所述G蛋白与SEQ ID NO 31所示的氨基酸序列相比,包含以下一个或多个位点的氨基酸取代:第438位、第453位、第471位和第487位。

[0082] 在一些具体的实施方案中,所述G蛋白还包含以下一个或多个位点的氨基酸取代:第53位、第141位、第172位、第217位、第232位、第331位、第371位、第436位。

[0083] 在一些具体的实施方案中,所述G蛋白的氨基酸取代包含在第53位的缬氨酸突变为异亮氨酸(V53I);和/或,在第141位的丙氨酸突变为缬氨酸(A141V);和/或,在第172位的天冬氨酸突变为酪氨酸(D172Y);和/或,在第217位的赖氨酸突变为谷氨酸(K217E);和/或,在第232位的天冬氨酸突变为甘氨酸(D232G);和/或,在第331位的缬氨酸突变为丙氨酸(V331A);和/或,在第371位的缬氨酸突变为谷氨酸(V371E);和/或,在第436位的甘氨酸突变为天冬氨酸(G436D);和/或,在第438位的苏氨酸突变为丝氨酸(T438S);和/或,在第453位的苯丙氨酸突变为亮氨酸(F453L);和/或,在第471位的苏氨酸突变为异亮氨酸(T471I);

和/或,在第487位的酪氨酸突变为组氨酸(Y487H)。

[0084] 在一个具体的实施方案中,所述G蛋白的氨基酸取代包含在第53位的缬氨酸突变为异亮氨酸(V53I)。

[0085] 在一个具体的实施方案中,所述G蛋白的氨基酸取代包含在第141位的丙氨酸突变为缬氨酸(A141V)。

[0086] 在一个具体的实施方案中,所述G蛋白的氨基酸取代包含在第172位的天冬氨酸突变为酪氨酸(D172Y)。

[0087] 在一个具体的实施方案中,所述G蛋白的氨基酸取代包含在第217位的赖氨酸突变为谷氨酸(K217E)。

[0088] 在一个具体的实施方案中,所述G蛋白的氨基酸取代包含在第232位的天冬氨酸突变为甘氨酸(D232G)。

[0089] 在一个具体的实施方案中,所述G蛋白的氨基酸取代包含在第331位的缬氨酸突变为丙氨酸(V331A)。

[0090] 在一个具体的实施方案中,所述G蛋白的氨基酸取代包含在第371位的缬氨酸突变为谷氨酸(V371E)。

[0091] 在一个具体的实施方案中,所述G蛋白的氨基酸取代包含在第436位的甘氨酸突变为天冬氨酸(G436D)。

[0092] 在一个具体的实施方案中,所述G蛋白的氨基酸取代包含在第438位的苏氨酸突变为丝氨酸(T438S)。

[0093] 在一个具体的实施方案中,所述G蛋白的氨基酸取代包含在第453位的苯丙氨酸突变为亮氨酸(F453L)。

[0094] 在一个具体的实施方案中,所述G蛋白的氨基酸取代包含在第471位的苏氨酸突变为异亮氨酸(T471I)。

[0095] 在一个具体的实施方案中,所述G蛋白的氨基酸取代包含在第487位的酪氨酸突变为组氨酸(Y487H)。

[0096] 在一个具体的实施方案中,所述G蛋白具有V53I的氨基酸取代。

[0097] 在一个具体的实施方案中,所述G蛋白具有V53I、A141V的氨基酸取代。

[0098] 在一个具体的实施方案中,所述G蛋白具有V53I、A141V、D172Y的氨基酸取代。

[0099] 在一个具体的实施方案中,所述G蛋白具有V53I、A141V、D172Y、K217E的氨基酸取代。

[0100] 在一个具体的实施方案中,所述G蛋白具有V53I、A141V、D172Y、K217E、D232G的氨基酸取代。

[0101] 在一个具体的实施方案中,所述G蛋白具有V53I、A141V、D172Y、K217E、D232G、V331A的氨基酸取代。

[0102] 在一个具体的实施方案中,所述G蛋白具有V53I、A141V、D172Y、K217E、D232G、V331A、V371E的氨基酸取代。

[0103] 在一个具体的实施方案中,所述G蛋白具有V53I、A141V、D172Y、K217E、D232G、V331A、V371E、G436D的氨基酸取代。

[0104] 在一个具体的实施方案中,所述G蛋白具有V53I、A141V、D172Y、K217E、D232G、

V331A、V371E、G436D、T438S的氨基酸取代。

[0105] 在一个具体的实施方案中,所述G蛋白具有V53I、A141V、D172Y、K217E、D232G、V331A、V371E、G436D、T438S、F453L的氨基酸取代。

[0106] 在一个具体的实施方案中,所述G蛋白具有V53I、A141V、D172Y、K217E、D232G、V331A、V371E、G436D、T438S、F453L、T471I的氨基酸取代。

[0107] 在一个具体的实施方案中,所述G蛋白具有V53I、A141V、D172Y、K217E、D232G、V331A、V371E、G436D、T438S、F453L、T471I、Y487H的氨基酸取代。

[0108] 在一个具体的实施方案中,所述G蛋白具有A141V、D172Y、K217E、D232G、V331A、V371E、G436D、T438S、F453L、T471I、Y487H的氨基酸取代。

[0109] 在一个具体的实施方案中,所述G蛋白具有D172Y、K217E、D232G、V331A、V371E、G436D、T438S、F453L、T471I、Y487H的氨基酸取代。

[0110] 在一个具体的实施方案中,所述G蛋白具有K217E、D232G、V331A、V371E、G436D、T438S、F453L、T471I、Y487H的氨基酸取代。

[0111] 在一个具体的实施方案中,所述G蛋白具有D232G、V331A、V371E、G436D、T438S、F453L、T471I、Y487H的氨基酸取代。

[0112] 在一个具体的实施方案中,所述G蛋白具有V331A、V371E、G436D、T438S、F453L、T471I、Y487H的氨基酸取代。

[0113] 在一个具体的实施方案中,所述G蛋白具有V371E、G436D、T438S、F453L、T471I、Y487H的氨基酸取代。

[0114] 在一个具体的实施方案中,所述G蛋白具有G436D、T438S、F453L、T471I、Y487H的氨基酸取代。

[0115] 在一个具体的实施方案中,所述G蛋白具有T438S、F453L、T471I、Y487H的氨基酸取代。

[0116] 在一个具体的实施方案中,所述G蛋白具有F453L、T471I、Y487H的氨基酸取代。

[0117] 在一个具体的实施方案中,所述G蛋白具有T471I、Y487H的氨基酸取代。

[0118] 在一个具体的实施方案中,所述G蛋白具有Y487H的氨基酸取代。

[0119] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 32所示的氨基酸序列。

[0120] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 33所示的氨基酸序列。

[0121] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 34所示的氨基酸序列。

[0122] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 35所示的氨基酸序列。

[0123] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 36所示的氨基酸序列。

[0124] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 37所示的氨基酸序列。

[0125] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 38所示的氨基酸序列。

[0126] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 39所示的氨基酸序列。

[0127] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 40所示的氨基酸序列。

[0128] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 41所示的氨基酸序列。

[0129] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 42所示的氨基酸序列。

[0130] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 43所示的氨基酸序列。

[0131] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 44所示的氨基酸序列。

[0132] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 45所示的氨基酸序列。

[0133] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 46所示的氨基酸序列。

[0134] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 47所示的氨基酸序列。

[0135] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 48所示的氨基酸序列。

[0136] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 49所示的氨基酸序列。

[0137] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 50所示的氨基酸序列。

[0138] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 51所示的氨基酸序列。

[0139] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 52所示的氨基酸序列。

[0140] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 53所示的氨基酸序列。

[0141] 在一个具体的实施方案中,所述G蛋白如SEQ ID NO 54所示的氨基酸序列。

[0142] 一种溶瘤病毒,包含上述M蛋白、或M蛋白和G蛋白;所述溶瘤病毒还包括N蛋白;所述N蛋白与SEQ ID NO 55所示的氨基酸序列相比,包含以下一个或多个位点的氨基酸取代:第14位、第155位、第353位。

[0143] 在一些具体的实施方案中,所述N蛋白的氨基酸取代包含在第14位的异亮氨酸突变为缬氨酸(I14V);和/或,在第155位的精氨酸突变为赖氨酸(R155K);和/或,在第353位的丝氨酸突变为天冬酰胺(S353N)。

[0144] 在一个具体的实施方案中,所述N蛋白的氨基酸取代包含在第14位的异亮氨酸突变为缬氨酸(I14V)。

[0145] 在一个具体的实施方案中,所述N蛋白的氨基酸取代包含在第155位的精氨酸突变为赖氨酸(R155K)。

[0146] 在一个具体的实施方案中,所述N蛋白的氨基酸取代包含在第353位的丝氨酸突变为天冬酰胺(S353N)。

[0147] 在一个具体的实施方案中,所述N蛋白具有I14V的氨基酸取代。

[0148] 在一个具体的实施方案中,所述N蛋白具有I14V、R155K的氨基酸取代。

[0149] 在一个具体的实施方案中,所述N蛋白具有I14V、R155K、S353N的氨基酸取代。

[0150] 在一个具体的实施方案中,所述N蛋白具有R155K、S353N的氨基酸取代。

[0151] 在一个具体的实施方案中,所述N蛋白具有S353N的氨基酸取代。

[0152] 在一个具体的实施方案中,所述N蛋白包含如SEQ ID NO 56所示的氨基酸序列。

[0153] 在一个具体的实施方案中,所述N蛋白包含如SEQ ID NO 57所示的氨基酸序列。

[0154] 在一个具体的实施方案中,所述N蛋白包含如SEQ ID NO 58所示的氨基酸序列。

[0155] 在一个具体的实施方案中,所述N蛋白包含如SEQ ID NO 59所示的氨基酸序列。

[0156] 在一个具体的实施方案中,所述N蛋白包含如SEQ ID NO 60所示的氨基酸序列。

[0157] 一种溶瘤病毒,包含上述M蛋白、或M蛋白和G蛋白、或M蛋白、G蛋白和N蛋白、或M蛋白和N蛋白;所述溶瘤病毒还包括P蛋白;所述P蛋白与SEQ ID NO 61所示的氨基酸序列相比,包括以下一个或多个位点的氨基酸取代:第50位、第76位、第99位、第126位、第140位、第151位、第168位、第170位、第189位、第237位。

[0158] 在一些具体的实施方案中,所述P蛋白的氨基酸取代包含在第50位的精氨酸突变为赖氨酸(R50K);和/或,在第76位的缬氨酸突变为丙氨酸(V76A);和/或,在第99位的天冬酰胺突变为谷氨酸(D99E);和/或,在第126位的亮氨酸突变为丝氨酸(L126S);和/或,在第

140位的亮氨酸突变为丝氨酸(L140S);和/或,在第151位的组氨酸突变为酪氨酸(H151Y);和/或,在第168位的异亮氨酸突变为甲硫氨酸(I168M);和/或,在第170位的赖氨酸突变为谷氨酸(K170E);和/或,在第189位的酪氨酸突变为丝氨酸(Y189S);和/或,在第237位的天冬酰胺突变为天冬氨酸(N237D)。

[0159] 在一个具体的实施方案中,所述P蛋白的氨基酸取代包含在第50位的精氨酸突变为赖氨酸(R50K)。

[0160] 在一个具体的实施方案中,所述P蛋白的氨基酸取代包含在第76位的缬氨酸突变为丙氨酸(V76A)。

[0161] 在一个具体的实施方案中,所述P蛋白的氨基酸取代包含在第99位的天冬酰胺突变为谷氨酸(D99E)。

[0162] 在一个具体的实施方案中,所述P蛋白的氨基酸取代包含在第126位的亮氨酸突变为丝氨酸(L126S)。

[0163] 在一个具体的实施方案中,所述P蛋白的氨基酸取代包含在第140位的亮氨酸突变为丝氨酸(L140S)。

[0164] 在一个具体的实施方案中,所述P蛋白的氨基酸取代包含在第151位的组氨酸突变为酪氨酸(H151Y)。

[0165] 在一个具体的实施方案中,所述P蛋白的氨基酸取代包含在第168位的异亮氨酸突变为甲硫氨酸(I168M)。

[0166] 在一个具体的实施方案中,所述P蛋白的氨基酸取代包含在第170位的赖氨酸突变为谷氨酸(K170E)。

[0167] 在一个具体的实施方案中,所述P蛋白的氨基酸取代包含在第189位的酪氨酸突变为丝氨酸(Y189S)。

[0168] 在一个具体的实施方案中,所述P蛋白的氨基酸取代包含在第237位的天冬酰胺突变为天冬氨酸(N237D)。

[0169] 在一个具体的实施方案中,所述P蛋白具有R50K的氨基酸取代。

[0170] 在一个具体的实施方案中,所述P蛋白具有R50K、V76A的氨基酸取代。

[0171] 在一个具体的实施方案中,所述P蛋白具有R50K、V76A、D99E的氨基酸取代。

[0172] 在一个具体的实施方案中,所述P蛋白具有R50K、V76A、D99E、L126S的氨基酸取代。

[0173] 在一个具体的实施方案中,所述P蛋白具有R50K、V76A、D99E、L126S、L140S的氨基酸取代。

[0174] 在一个具体的实施方案中,所述P蛋白具有R50K、V76A、D99E、L126S、L140S、H151Y的氨基酸取代。

[0175] 在一个具体的实施方案中,所述P蛋白具有R50K、V76A、D99E、L126S、L140S、H151Y、I168M的氨基酸取代。

[0176] 在一个具体的实施方案中,所述P蛋白具有R50K、V76A、D99E、L126S、L140S、H151Y、I168M、K170E的氨基酸取代。

[0177] 在一个具体的实施方案中,所述P蛋白具有R50K、V76A、D99E、L126S、L140S、H151Y、I168M、K170E、Y189S的氨基酸取代。

[0178] 在一个具体的实施方案中,所述P蛋白具有R50K、V76A、D99E、L126S、L140S、H151Y、

I168M、K170E、Y189S、N237D的氨基酸取代。

[0179] 在一个具体的实施方案中,所述P蛋白具有V76A、D99E、L126S、L140S、H151Y、I168M、K170E、Y189S、N237D的氨基酸取代。

[0180] 在一个具体的实施方案中,所述P蛋白具有D99E、L126S、L140S、H151Y、I168M、K170E、Y189S、N237D的氨基酸取代。

[0181] 在一个具体的实施方案中,所述P蛋白具有L126S、L140S、H151Y、I168M、K170E、Y189S、N237D的氨基酸取代。

[0182] 在一个具体的实施方案中,所述P蛋白具有L140S、H151Y、I168M、K170E、Y189S、N237D的氨基酸取代。

[0183] 在一个具体的实施方案中,所述P蛋白具有H151Y、I168M、K170E、Y189S、N237D的氨基酸取代。

[0184] 在一个具体的实施方案中,所述P蛋白具有I168M、K170E、Y189S、N237D的氨基酸取代。

[0185] 在一个具体的实施方案中,所述P蛋白具有K170E、Y189S、N237D的氨基酸取代。

[0186] 在一个具体的实施方案中,所述P蛋白具有Y189S、N237D的氨基酸取代。

[0187] 在一个具体的实施方案中,所述P蛋白具有N237D的氨基酸取代。

[0188] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 62所示的氨基酸序列。

[0189] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 63所示的氨基酸序列。

[0190] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 64所示的氨基酸序列。

[0191] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 65所示的氨基酸序列。

[0192] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 66所示的氨基酸序列。

[0193] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 67所示的氨基酸序列。

[0194] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 68所示的氨基酸序列。

[0195] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 69所示的氨基酸序列。

[0196] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 70所示的氨基酸序列。

[0197] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 71所示的氨基酸序列。

[0198] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 72所示的氨基酸序列。

[0199] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 73所示的氨基酸序列。

[0200] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 74所示的氨基酸序列。

[0201] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 75所示的氨基酸序列。

[0202] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 76所示的氨基酸序列。

[0203] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 77所示的氨基酸序列。

[0204] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 78所示的氨基酸序列。

[0205] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 79所示的氨基酸序列。

[0206] 在一个具体的实施方案中,所述P蛋白包含如SEQ ID NO 80所示的氨基酸序列。

[0207] 一种溶瘤病毒,包含上述M蛋白,或M蛋白和G蛋白,或M蛋白、G蛋白和N蛋白,或M蛋白、G蛋白、N蛋白和P蛋白,或M蛋白和N蛋白,或M蛋白和P蛋白,或M蛋白、G蛋白和P蛋白,或M蛋白、N蛋白和P蛋白;所述溶瘤病毒还包括L蛋白;所述L蛋白与SEQ ID NO 81所示的氨基酸序列相比,包括以下一个或多个位点的氨基酸取代:第87位、第487位。

[0208] 在一些具体的实施方案中,所述L蛋白的氨基酸取代包含在第87位的丝氨酸突变为脯氨酸(S87P);和/或,在第487位的异亮氨酸突变为苏氨酸(I487T)。

[0209] 在一个具体的实施方案中,所述L蛋白的氨基酸取代包含在第87位的丝氨酸突变为脯氨酸(S87P)。

[0210] 在一个具体的实施方案中,所述L蛋白的氨基酸取代包含在第487位的异亮氨酸突变为苏氨酸(I487T)。

[0211] 在一个具体的实施方案中,所述L蛋白具有S87P的氨基酸取代。

[0212] 在一个具体的实施方案中,所述L蛋白具有S87P、I487T的氨基酸取代。

[0213] 在一个具体的实施方案中,所述L蛋白具有I487T的氨基酸取代。

[0214] 在一个具体的实施方案中,所述L蛋白包含如SEQ ID NO 82所示的氨基酸序列。

[0215] 在一个具体的实施方案中,所述L蛋白包含如SEQ ID NO 83所示的氨基酸序列。

[0216] 在一个具体的实施方案中,所述L蛋白包含如SEQ ID NO 84所示的氨基酸序列。

[0217] 在一些具体的实施方案中,所述溶瘤病毒是以棒状病毒为基础,进行定点突变后获得的。

[0218] 在一些具体的实施方案中,所述溶瘤病毒是以Vesicular Stomatitis Virus(简称“VSV”)病毒为基础,进行定点突变后获得的。

[0219] 在一些具体的实施方案中,所述溶瘤病毒是以VSV病毒Indiana MuddSummer亚型为基础,进行定点突变后获得的。

[0220] 在一些具体的实施方案中,所述溶瘤病毒包含或表达外源目的蛋白。

[0221] 在一些具体的实施方案中,所述溶瘤病毒包含核酸分子,所述核酸分子包含编码所述具有氨基酸取代的M蛋白的核酸序列、和/或编码所述具有氨基酸取代的G蛋白的核酸序列、和/或编码所述具有氨基酸取代的N蛋白的核酸序列、和/或编码所述具有氨基酸取代的P蛋白的核酸序列、和/或编码所述具有氨基酸取代的L蛋白的核酸序列。

[0222] 在一些具体的实施方案中,所述核酸分子包含编码所述外源目的蛋白的核酸序列。

[0223] 在一些具体的实施方案中,所述核酸分子中所述编码外源目的蛋白的核酸序列位于编码所述具有氨基酸取代的M蛋白的核酸序列、和/或编码所述具有氨基酸取代的G蛋白的核酸序列、和/或编码所述具有氨基酸取代的N蛋白的核酸序列、和/或编码所述具有氨基酸取代的P蛋白的核酸序列、和/或编码所述具有氨基酸取代的L蛋白的核酸序列之间。

[0224] 第二方面,本申请提供一种溶瘤病毒表达载体,采用如下的技术方案:

[0225] 一种溶瘤病毒表达载体,所述溶瘤病毒表达载体能够产生本申请所述的任一项溶瘤病毒。

[0226] 第三方面,本申请提供一种病毒生产细胞,采用如下的技术方案:

[0227] 一种病毒生产细胞,所述病毒生产细胞能够产生本申请所述的任一项溶瘤病毒。

[0228] 第四方面,本申请提供一种药物组合物,采用如下的技术方案:

[0229] 一种药物组合物,所述药物组合物包括本申请所述的任一项溶瘤病毒,以及任选地药学上可接受的载剂。

[0230] 第五方面,本申请提供上述溶瘤病毒、溶瘤病毒表达载体、病毒生产细胞和/或药物组合物的制备方法。

[0231] 第六方面,本申请提供上述溶瘤病毒、溶瘤病毒表达载体、病毒生产细胞和/或药物组合物在制备用于预防和/或治疗疾病和/或病症的药物中的用途。

[0232] 在一些具体的实施方案中,所述溶瘤病毒、溶瘤病毒表达载体、病毒生产细胞和/或药物组合物用于缓慢持续杀伤异常增生性细胞的方法中。

[0233] 在一些具体的实施方案中,所述疾病和/或病症包括:异常增生性细胞,选自肿瘤细胞或肿瘤组织的相关细胞;优选的,所述肿瘤细胞是癌细胞;更优选的,所述癌细胞是转移性癌细胞。

[0234] 在一些具体的实施方案中,所述肿瘤包括实体瘤和/或血液瘤。

[0235] 综上所述,本申请具有以下有益效果:

[0236] 本申请提供的溶瘤病毒均对异常增生性LLC细胞、4T1细胞、MC38细胞以及Hela细胞具有较好的侵染能力、体外杀伤能力,且在LLC细胞、4T1细胞、MC38细胞以及Hela细胞内均不容易清除。并且,本申请提供的溶瘤病毒均对正常MEF细胞的侵染能力较差,体外杀伤能力较差,且本申请提供的溶瘤病毒在正常MEF细胞内均容易清除。因此,本申请提供的溶瘤病毒能够较好的用于肿瘤、癌症等细胞的侵染和杀伤,且在肿瘤、癌症等细胞内不易清除,进一步提高了溶瘤病毒对肿瘤、癌症等细胞的治愈率;同时,上述提供的溶瘤病毒不会损伤正常细胞,且在正常细胞内时更加容易清除,进一步保证了正常细胞的安全性。

附图说明

[0237] 图1为本申请制备的溶瘤病毒以及野生型溶瘤病毒对LLC细胞的侵染能力的检测结果。

[0238] 图2为本申请制备的溶瘤病毒以及野生型溶瘤病毒对4T1细胞的侵染能力的检测结果。

[0239] 图3为本申请制备的溶瘤病毒以及野生型溶瘤病毒对MC38细胞的侵染能力的检测结果。

[0240] 图4为本申请制备的溶瘤病毒以及野生型溶瘤病毒对Hela细胞的侵染能力的检测结果。

[0241] 图5为本申请制备的溶瘤病毒以及野生型溶瘤病毒对MEF细胞的侵染能力的检测结果。

[0242] 图6为本申请制备的溶瘤病毒以及野生型溶瘤病毒对LLC细胞的体外杀伤能力的检测结果。

[0243] 图7为本申请制备的溶瘤病毒以及野生型溶瘤病毒对4T1细胞的体外杀伤能力的检测结果。

[0244] 图8为本申请制备的溶瘤病毒以及野生型溶瘤病毒对MC38细胞的体外杀伤能力的检测结果。

[0245] 图9为本申请制备的溶瘤病毒以及野生型溶瘤病毒对Hela细胞的体外杀伤能力的检测结果。

[0246] 图10为本申请制备的溶瘤病毒以及野生型溶瘤病毒对MEF细胞的体外杀伤能力的检测结果。

[0247] 图11为本申请制备的溶瘤病毒以及野生型溶瘤病毒在LLC细胞内诱导IFN-β的表

达情况。

[0248] 图12为本申请制备的溶瘤病毒以及野生型溶瘤病毒在4T1细胞内诱导IFN-β的表达情况。

[0249] 图13为本申请制备的溶瘤病毒以及野生型溶瘤病毒在MC38细胞内诱导IFN-β的表达情况。

[0250] 图14为本申请制备的溶瘤病毒以及野生型溶瘤病毒在Hela细胞内诱导IFN-β的表达情况。

[0251] 图15为本申请制备的溶瘤病毒以及野生型溶瘤病毒在MEF细胞内诱导IFN-β的表达情况。

[0252] 以上附图中,横坐标上0号表示野生型溶瘤病毒;横坐标1-79号分别表示制备例1-79制备的溶瘤病毒。

[0253] 纵坐标Log_{10}TCID50表示利用Karber法计算得出的TCID50值,Log_{10}TCID50的值越大,表示溶瘤病毒对该细胞的侵染能力越好;Log_{10}TCID50的值越小,表示溶瘤病毒对该细胞的侵染能力越差;

[0254] 纵坐标OD_{570}表示细胞的OD值,OD_{570}的值越大,表示溶瘤病毒对该细胞的杀伤能力越差;OD_{570}的值越小,表示溶瘤病毒对该细胞的杀伤能力越好。

[0255] 纵坐标IFN-β水平表示IFN-β基因的表达情况,IFN-β水平的值越大,表示溶瘤病毒在该细胞内繁殖能力越弱,越容易清除;IFN-β水平的值越小,表示溶瘤病毒在该细胞内繁殖能力越强,越不容易清除。

[0256] 本领域技术人员能够从下文的详细描述中容易地洞察到本申请的其它方面和优势。下文的详细描述中仅显示和描述了本申请的示例性实施方式。如本领域技术人员将认识到的,本申请的内容使得本领域技术人员能够对所公开的具体实施方式进行改动而不脱离本申请所涉及发明的精神和范围。相应地,本申请的附图和说明书中的描述仅仅是示例性的,而非为限制性的。

具体实施方式

[0257] 以下由特定的具体实施例说明本申请发明的实施方式,本领域技术人员可由本说明书所公开的内容容易地了解本申请发明的其他优点及效果。

[0258] 术语定义

[0259] 在本申请中,术语“溶瘤病毒”通常指能够在肿瘤细胞中复制并杀死肿瘤细胞的病毒。溶瘤病毒包括但不限于:水疱性口炎病毒(Vesicular Stomatitis Virus,简称“VSV病毒”)、痘病毒、单纯疱疹病毒、麻疹病毒、塞姆利基森林病毒、脊髓灰质炎病毒、呼肠孤病毒、塞内卡谷病毒、埃可型肠道病毒、柯萨奇病毒、新城疫病毒和马拉巴病毒。在某些实施方案中,所述溶瘤病毒被改造以提高对肿瘤细胞的选择性。在某些实施方案中,所述溶瘤病毒被改造以降低其免疫原性。在一些实施方案中,本申请所述溶瘤病毒为VSV病毒。在一些实施方案中,VSV病毒为VSV病毒Indiana MuddSummer亚型株的突变体。在一些实施方案中,可以对VSV病毒的M蛋白、和/或G蛋白、和/或N蛋白、和/或P蛋白、和/或L蛋白进行定点基因突变。

[0260] 在某些实施方式中,本申请所述溶瘤病毒可以是经过基因水平改造的溶瘤病毒,如经过一个或多个基因的修饰来改造,从而提高其肿瘤选择性和/或在分裂细胞中优先复

制。所述基因水平的改造可以为修饰参与DNA复制、核酸代谢、宿主向性、表面附着、毒力、裂解和扩散过程的基因,也可以为整合外源基因的改造。所述外源基因可以包括外源免疫调节基因、外源筛选基因、外源报告基因等。所述经过改造的溶瘤病毒也可以是经过氨基酸水平改造的溶瘤病毒,如一个或多个氨基酸的插入、缺失、置换。

[0261] 在本申请中,术语“M蛋白”通常指VSV病毒基质蛋白。M蛋白是VSV病毒重要的毒力因子,也是VSV病毒中已知可干扰小鼠天然免疫应答的蛋白。术语“M蛋白”还包括其同源物、直系同源物、变体、功能活性片段等。在本申请中,野生型VSV病毒IndianaMuddSummer亚型M蛋白可以包含如SEQ ID NO 1所示的氨基酸序列。在本申请中,所述溶瘤病毒的M蛋白可以包含如SEQ ID NO 2-29所示的氨基酸序列。

[0262] 在本申请中,术语“G蛋白”通常指水VSV病毒的糖蛋白,也称包膜蛋白。术语“G蛋白”还包括其同源物、直系同源物、变体、功能活性片段等。在本申请中,野生型VSV病毒Indiana MuddSummer亚型G蛋白可以包含如SEQ ID NO 31所示的氨基酸序列。在本申请中,所述溶瘤病毒的G蛋白可以包含如SEQ ID NO 32-54所示的氨基酸序列。

[0263] 在本申请中,术语“N蛋白”通常指VSV病毒的核衣壳蛋白。术语“N蛋白”还包括其同源物,直系同源物、变体、功能活性片段等。在本申请中,野生型VSV病毒Indiana MuddSummer亚型N蛋白可以包含如SEQ ID NO 55所示的氨基酸序列。在本申请中,所述溶瘤病毒的N蛋白可以包含如SEQ ID NO 56-60所示的氨基酸序列。

[0264] 在本申请中,术语“P蛋白”通常指VSV病毒的磷酸蛋白。术语“P蛋白”还包括其同源物,直系同源物、变体、功能活性片段等。在本申请中,野生型VSV病毒Indiana MuddSummer亚型P蛋白可以包含如SEQ ID NO 61所示的氨基酸序列。在本申请中,所述溶瘤病毒的P蛋白可以包含如SEQ ID NO 62-80所示的氨基酸序列。

[0265] 在本申请中,术语“L蛋白”通常指VSV病毒RNA聚合酶蛋白。VSV病毒的L基因编码RNApoly E蛋白。术语“L蛋白”还包括其同源物,直系同源物、变体、功能活性片段等。在本申请中,野生型VSV病毒Indiana MuddSummer亚型L蛋白可以包含如SEQ ID NO 81所示的氨基酸序列。在本申请中,所述溶瘤病毒的L蛋白可以包含如SEQ ID NO 82-84所示的氨基酸序列。

[0266] 在本申请中,蛋白突变位点的表述通常由“氨基酸+氨基酸位数+(突变后的氨基酸)”来表述。在本申请中,所述突变可以包括但不限于氨基酸的增加、替换、缺失和/或删除。例如,术语“M51R”通常指第51位甲硫氨酸M突变为精氨酸R。

[0267] 在本申请中,术语“氨基酸取代”通常是指用另一个氨基酸残基替代存在于亲本序列中的一个氨基酸残基。亲本序列中的氨基酸可以是例如经由化学肽合成或通过本领域已知的重组方法来取代。因此,“在xx位置处取代”通常是指用替代性氨基酸残基取代存在于位置xx处的氨基酸。在本申请中,所述氨基酸取代可以包括氨基酸突变。

[0268] 在本申请中,术语“突变”通常是指改变野生型分子的核苷酸或氨基酸序列。氨基酸变化可以包括氨基酸的置换、删除、缺失、插入、添加、截短、或蛋白质的加工或切割。

[0269] 在本申请中,术语“核酸分子”通常指任何长度的核苷酸。在本申请中,术语“核酸分子”可以编码所述溶瘤病毒包含的蛋白。在本申请中,所述核酸分子可以包含DNA和/或RNA。在某些情形下,所述RNA可以包含单链RNA(ssRNA),也可以包含双链RNA(dsRNA),单链RNA可以包含正义RNA,也可以包含反义RNA(anti-sense RNA),也可以包含双义RNA。

[0270] 在本申请中,术语“表达载体”通常指一种核酸载体。在适当的条件下,其通常能够表达目标基因和/或目标蛋白。在本申请的某些实施方式中,所述表达载体包括用于表达病毒(例如,溶瘤病毒)的一种或多种组分的核酸分子。例如,所述表达载体可包括至少一个病毒基因组元件,并可以被包装入病毒或被包装为病毒粒子。

[0271] 在本申请中,术语“病毒生产细胞”通常指可以或已经含有包括本申请所述的核酸分子或表达载体,或能够表达本申请所述溶瘤病毒的细胞、细胞系或细胞培养物。所述细胞可以包括单个宿主细胞的子代。所述细胞可以通过使用本申请所述的表达载体体外转染而得到。

[0272] 在本申请中,术语“药物组合物”通常指以允许活性成分的生物学活性有效的形式存在的制剂,并且其不含有对所述制剂待施用的受试者有不可接受的毒性的另外成分。在某些实施方案中,这些制剂可以包含药物的活性组分以及药学上可接受的载剂。在某些实施方式中,所述药物产品包含肠胃外、经皮、腔内、动脉内、鞘内和/或鼻内施用或直接注射到组织中的药物产品。所述药物产品可以通过不同方式给药,例如静脉内、腹膜内、皮下、肌肉内、局部或真皮内施用。

[0273] 在本申请中,术语“预防”通常是指通过预先采取某些措施而防止疾病或其一种或多种症状的产生和发作,复发,和/或扩散。在本申请中,术语“治疗”通常指消除或改善疾病,或与疾病相关的一种或多种症状。在某些实施方案中,治疗通常指向患有这种疾病的患者施用一种或多种药物使得疾病消除或缓解。在某些实施方案中,“治疗”可以是在特定疾病的症状发作后,在其他药物存在或不存在的情况下施用所述药物组合和/或药物产品。例如,使用本申请所述药物组合和/或药物产品防止肿瘤的产生,发展,复发和/或转移。

[0274] 在本申请中,术语“肿瘤”通常是指任何新的病理性的组织增生。肿瘤可能是良性的,也可能是恶性的。在本申请中,所述肿瘤可以是实体瘤和/或血液瘤。用于研究时,可通过本领域技术人员熟知的方法从易于获得的资源中将这些组织分离出来。

[0275] 发明详述

[0276] 本申请提供了一种溶瘤病毒,所述溶瘤病毒是以野生型VSV病毒为基础,具体以VSV病毒印第安纳株,VSV病毒Indiana MuddSummer亚型株为基础,通过对其M蛋白、G蛋白、N蛋白、P蛋白、L蛋白的氨基酸序列上的位点进行突变获得的。其M蛋白的氨基酸序列如SEQ ID NO 1所示;其G蛋白的氨基酸序列如SEQ ID NO 31所示;其N蛋白的氨基酸序列如SEQ ID NO 55所示;其P蛋白的氨基酸序列如SEQ ID NO 61所示;其L蛋白的氨基酸序列如SEQ ID NO 81所示。在本申请中,所述M蛋白、G蛋白、N蛋白、P蛋白、L蛋白均可以被改造。

[0277] 本申请对所述VSV病毒进行如下修饰,以获得溶瘤病毒。

[0278] 一种溶瘤病毒,溶瘤病毒包括M蛋白,所述M蛋白与SEQ ID NO 1所示的氨基酸序列相比,包含以下一个或多个位点的氨基酸取代:第32位、第33位、第49位、第54位、第133位、第225位。所述M蛋白还包含以下一个或多个位点的氨基酸取代:第21位、第51位、第111位、第221位和第226位。

[0279] 所述M蛋白的氨基酸取代包含在第32位的天冬酰胺突变为丝氨酸(N32S);和/或,在第33位的甲硫氨酸突变为丙氨酸(M33A);和/或,在第49位的天冬酰胺突变为天冬氨酸(N49D);和/或,在第54位的组氨酸突变为酪氨酸(H54Y);和/或,在第133位的丙氨酸突变为苏氨酸(A133T);和/或,在第225位的缬氨酸突变为异亮氨酸(V225I);所述M蛋白的氨基酸

取代还包含在第21位的甘氨酸突变为谷氨酸(G21E);和/或,所述M蛋白的氨基酸取代包含在第51位的甲硫氨酸突变为精氨酸(M51R);和/或,在第51位的甲硫氨酸突变为丙氨酸(M51A);和/或,包含在第111位的亮氨酸突变为丙氨酸(L111A);和/或,在第221位的缬氨酸突变为苯丙氨酸(V221F);和/或,在第226位的丝氨酸突变为精氨酸(S226R)。

[0280] 在本申请中,所述M蛋白可以包含第21位的氨基酸突变。

[0281] 在本申请中,所述M蛋白可以包含第21位、第32位的氨基酸突变。

[0282] 在本申请中,所述M蛋白可以包含第21位、第32位和第33位的氨基酸突变。

[0283] 在本申请中,所述M蛋白可以包含第21位、第32位、第33位和第49位的氨基酸突变。

[0284] 在本申请中,所述M蛋白可以包含第21位、第32位、第33位、第49位和第54位的氨基酸突变。

[0285] 在本申请中,所述M蛋白可以包含第21位、第32位、第33位、第49位、第54位和第111位的氨基酸突变。

[0286] 在本申请中,所述M蛋白可以包含第21位、第32位、第33位、第49位、第54位、第111位和第133位的氨基酸突变。

[0287] 在本申请中,所述M蛋白可以包含第21位、第32位、第33位、第49位、第54位、第111位、第133位和第225位的氨基酸突变。

[0288] 在本申请中,所述M蛋白可以包含第21位、第32位、第33位、第49位、第51位、第54位、第111位、第133位和第225位的氨基酸突变。

[0289] 在本申请中,所述M蛋白可以包含第21位、第32位、第33位、第49位、第51位、第54位、第111位、第133位、第221位和第225位的氨基酸突变。

[0290] 在本申请中,所述M蛋白可以包含第21位、第32位、第33位、第49位、第51位、第54位、第111位、第133位、第221位、第225位和第226位的氨基酸突变。

[0291] 在本申请中,所述M蛋白可以包含第32位、第33位、第49位、第51位、第54位、第111位、第133位、第221位、第225位和第226位的氨基酸突变。

[0292] 在本申请中,所述M蛋白可以包含第33位、第49位、第51位、第54位、第111位、第133位、第221位、第225位和第226位的氨基酸突变。

[0293] 在本申请中,所述M蛋白可以包含第49位、第51位、第54位、第111位、第133位、第221位、第225位和第226位的氨基酸突变。

[0294] 在本申请中,所述M蛋白可以包含第51位、第54位、第111位、第133位、第221位、第225位和第226位的氨基酸突变。

[0295] 在本申请中,所述M蛋白可以包含第54位、第111位、第133位、第221位、第225位和第226位的氨基酸突变。

[0296] 在本申请中,所述M蛋白可以包含第111位、第133位、第221位、第225位和第226位的氨基酸突变。

[0297] 在本申请中,所述M蛋白可以包含第133位、第221位、第225位和第226位的氨基酸突变。

[0298] 在本申请中,所述M蛋白可以包含第221位、第225位和第226位的氨基酸突变。

[0299] 在本申请中,所述M蛋白可以包含第225位和第226位的氨基酸突变。

[0300] 在本申请中,所述M蛋白可以包含第226位的氨基酸突变。

[0301] 在本申请中,所述M蛋白可以包含第32位、第49位、第54位和第225位的氨基酸突变。

[0302] 在本申请中,所述M蛋白可以包含第32位、第49位、第54位、第225位和第226位的氨基酸突变。

[0303] 在本申请中,所述M蛋白可以包含第32位、第49位、第51位、第54位、第221位、第225位和第226位的氨基酸突变。

[0304] 在本申请中,所述M蛋白可以包含第32位、第33位、第49位、第51位、第54位、第221位、第225位和第226位的氨基酸突变。

[0305] 在本申请中,所述M蛋白可以包含第32位、第49位、第51位、第54位、第133位、第221位、第225位和第226位的氨基酸突变。

[0306] 在本申请中,所述M蛋白可以包含第32位、第33位、第49位、第51位、第54位、第133位、第221位、第225位和第226位的氨基酸突变。

[0307] 在本申请中,所述M蛋白可以包含第21位、第32位、第49位、第51位、第54位、第111位、第225位和第226位的氨基酸突变。

[0308] 在本申请中,所述M蛋白还可以包含其他位置的氨基酸取代。

[0309] 所述溶瘤病毒还包括G蛋白;所述G蛋白与SEQ ID NO 31所示的氨基酸序列相比,包含以下一个或多个位点的氨基酸取代:第438位、第453位、第471位和第487位。

[0310] 在本申请中,所述G蛋白的氨基酸取代包含在第53位的缬氨酸突变为异亮氨酸(V53I);和/或,在第141位的丙氨酸突变为缬氨酸(A141V);和/或,在第172位的天冬氨酸突变为酪氨酸(D172Y);和/或,在第217位的赖氨酸突变为谷氨酸(K217E);和/或,在第232位的天冬氨酸突变为甘氨酸(D232G);和/或,在第331位的缬氨酸突变为丙氨酸(V331A);和/或,在第371位的缬氨酸突变为谷氨酸(V371E);和/或,在第436位的甘氨酸突变为天冬氨酸(G436D);和/或,在第438位的苏氨酸突变为丝氨酸(T438S);和/或,在第453位的苯丙氨酸突变为亮氨酸(F453L);和/或,在第471位的苏氨酸突变为异亮氨酸(T471I);和/或,在第487位的酪氨酸突变为组氨酸(Y487H)。例如,所述G蛋白如SEQ ID NO 43所示的氨基酸序列。

[0311] 在本申请中,所述G蛋白可以包含第53位的氨基酸突变。

[0312] 在本申请中,所述G蛋白可以包含第53位和第141位的氨基酸突变。

[0313] 在本申请中,所述G蛋白可以包含第53位、第141位和第172位的氨基酸突变。

[0314] 在本申请中,所述G蛋白可以包含第53位、第141位、第172位和第217位的氨基酸突变。

[0315] 在本申请中,所述G蛋白可以包含第53位、第141位、第172位、第217位和第232位的氨基酸突变。

[0316] 在本申请中,所述G蛋白可以包含第53位、第141位、第172位、第217位、第232位和第331位的氨基酸突变。

[0317] 在本申请中,所述G蛋白可以包含第53位、第141位、第172位、第217位、第232位、第331位和第371位的氨基酸突变。

[0318] 在本申请中,所述G蛋白可以包含第53位、第141位、第172位、第217位、第232位、第331位、第371位和第436位的氨基酸突变。

[0319] 在本申请中,所述G蛋白可以包含第53位、第141位、第172位、第217位、第232位、第331位、第371位、第436位和第438位的氨基酸突变。

[0320] 在本申请中,所述G蛋白可以包含第53位、第141位、第172位、第217位、第232位、第331位、第371位、第436位、第438位和第453位的氨基酸突变。

[0321] 在本申请中,所述G蛋白可以包含第53位、第141位、第172位、第217位、第232位、第331位、第371位、第436位、第438位、第453位和第471位的氨基酸突变。

[0322] 在本申请中,所述G蛋白可以包含第53位、第141位、第172位、第217位、第232位、第331位、第371位、第436位、第438位、第453位、第471位和第487位的氨基酸突变。

[0323] 在本申请中,所述G蛋白可以包含第141位、第172位、第217位、第232位、第331位、第371位、第436位、第438位、第453位、第471位和第487位的氨基酸突变。

[0324] 在本申请中,所述G蛋白可以包含第172位、第217位、第232位、第331位、第371位、第436位、第438位、第453位、第471位和第487位的氨基酸突变。

[0325] 在本申请中,所述G蛋白可以包含第217位、第232位、第331位、第371位、第436位、第438位、第453位、第471位和第487位的氨基酸突变。

[0326] 在本申请中,所述G蛋白可以包含第232位、第331位、第371位、第436位、第438位、第453位、第471位和第487位的氨基酸突变。

[0327] 在本申请中,所述G蛋白可以包含第331位、第371位、第436位、第438位、第453位、第471位和第487位的氨基酸突变。

[0328] 在本申请中,所述G蛋白可以包含第371位、第436位、第438位、第453位、第471位和第487位的氨基酸突变。

[0329] 在本申请中,所述G蛋白可以包含第436位、第438位、第453位、第471位和第487位的氨基酸突变。

[0330] 在本申请中,所述G蛋白可以包含第438位、第453位、第471位和第487位的氨基酸突变。

[0331] 在本申请中,所述G蛋白可以包含第453位、第471位和第487位的氨基酸突变。

[0332] 在本申请中,所述G蛋白可以包含第471位、第487位的氨基酸突变。

[0333] 在本申请中,所述G蛋白可以包含第487位的氨基酸突变。

[0334] 在本申请中,所述G蛋白还可以包含其他位置的氨基酸取代。

[0335] 在某些实施方式中,所述G蛋白至少包含在保守区的一个或多个氨基酸取代。例如,所述保守区可以包含G蛋白的第437-461位氨基酸。在某些实施方式中,所述G蛋白至少包含在胞质域的截短区的一个或多个氨基酸取代。例如,所述胞质域的截短区可以包含G蛋白的第483-511位氨基酸。

[0336] 在本申请中,所述G蛋白可以至少包含在第438、第453位、第471位和第487位的氨基酸取代。

[0337] 所述溶瘤病毒还包括N蛋白;所述N蛋白与SEQ ID NO 55所示的氨基酸序列相比,包含以下一个或多个位点的氨基酸取代:第14位、第155位、第353位。

[0338] 本申请中,所述N蛋白的氨基酸取代包含在第14位的异亮氨酸突变为缬氨酸(I14V);和/或,在第155位的精氨酸突变为赖氨酸(R155K);和/或,在第353位的丝氨酸突变为天冬酰胺(S353N)。例如,所述N蛋白包含如SEQ ID NO 58所示的氨基酸序列。

[0339] 在本申请中,所述N蛋白可以包含第14位的氨基酸突变。

[0340] 在本申请中,所述N蛋白可以包含第14位和第155位的氨基酸突变。

[0341] 在本申请中,所述N蛋白可以包含第14位、第155位和第353位的氨基酸突变。

[0342] 在本申请中,所述N蛋白可以包含第155位和第353位的氨基酸突变。

[0343] 在本申请中,所述N蛋白可以包含第353位的氨基酸突变。

[0344] 在本申请中,所述N蛋白还可以包含其他位置的氨基酸取代。

[0345] 所述溶瘤病毒还包括P蛋白;所述P蛋白与SEQ ID NO 61所示的氨基酸序列相比,包括以下一个或多个位点的氨基酸取代:第50位、第76位、第99位、第126位、第140位、第151位、第168位、第170位、第189位、第237位。

[0346] 在本申请中,所述P蛋白的氨基酸取代包含在第50位的精氨酸突变为赖氨酸(R50K);和/或,在第76位的缬氨酸突变为丙氨酸(V76A);和/或,在第99位的天冬酰胺突变为谷氨酸(D99E);和/或,在第126位的亮氨酸突变为丝氨酸(L126S);和/或,在第140位的亮氨酸突变为丝氨酸(L140S);和/或,在第151位的组氨酸突变为酪氨酸(H151Y);和/或,在第168位的异亮氨酸突变为甲硫氨酸(I168M);和/或,在第170位的赖氨酸突变为谷氨酸(K170E);和/或,在第189位的酪氨酸突变为丝氨酸(Y189S);和/或,在第237位的天冬酰胺突变为天冬氨酸(N237D)。例如,所述P蛋白包含如SEQ ID NO 71所示的氨基酸序列。

[0347] 在本申请中,所述P蛋白可以包含第50位的氨基酸突变。

[0348] 在本申请中,所述P蛋白可以包含第50位和第76位的氨基酸突变。

[0349] 在本申请中,所述P蛋白可以包含第50位、第76位和第99位的氨基酸突变。

[0350] 在本申请中,所述P蛋白可以包含第50位、第76位、第99位和第126位的氨基酸突变。

[0351] 在本申请中,所述P蛋白可以包含第50位、第76位、第99位、第126位和第140位的氨基酸突变。

[0352] 在本申请中,所述P蛋白可以包含第50位、第76位、第99位、第126位、第140位和第151位的氨基酸突变。

[0353] 在本申请中,所述P蛋白可以包含第50位、第76位、第99位、第126位、第140位、第151位和第168位的氨基酸突变。

[0354] 在本申请中,所述P蛋白可以包含第50位、第76位、第99位、第126位、第140位、第151位、第168位和第170位的氨基酸突变。

[0355] 在本申请中,所述P蛋白可以包含第50位、第76位、第99位、第126位、第140位、第151位、第168位、第170位和第189位的氨基酸突变。

[0356] 在本申请中,所述P蛋白可以包含第50位、第76位、第99位、第126位、第140位、第151位、第168位、第170位、第189位和第237位的氨基酸突变。

[0357] 在本申请中,所述P蛋白可以包含第76位、第99位、第126位、第140位、第151位、第168位、第170位、第189位和第237位的氨基酸突变。

[0358] 在本申请中,所述P蛋白可以包含第99位、第126位、第140位、第151位、第168位、第170位、第189位和第237位的氨基酸突变。

[0359] 在本申请中,所述P蛋白可以包含第126位、第140位、第151位、第168位、第170位、第189位和第237位的氨基酸突变。

[0360] 在本申请中,所述P蛋白可以包含第140位、第151位、第168位、第170位、第189位和第237位的氨基酸突变。

[0361] 在本申请中,所述P蛋白可以包含第151位、第168位、第170位、第189位和第237位的氨基酸突变。

[0362] 在本申请中,所述P蛋白可以包含第168位、第170位、第189位和第237位的氨基酸突变。

[0363] 在本申请中,所述P蛋白可以包含第170位、第189位和第237位的氨基酸突变。

[0364] 在本申请中,所述P蛋白可以包含第189位和第237位的氨基酸突变。

[0365] 在本申请中,所述P蛋白可以包含第237位的氨基酸突变。

[0366] 在本申请中,所述P蛋白还可以包含其他位置的氨基酸取代。

[0367] 所述溶瘤病毒还包括L蛋白;所述L蛋白与SEQ ID NO 81所示的氨基酸序列相比,包括以下一个或多个位点的氨基酸取代:第87位、第487位。例如,所述L蛋白包含如SEQ ID NO 83所示的氨基酸序列。

[0368] 在本申请中,所述L蛋白的氨基酸取代包含在第87位的丝氨酸突变为脯氨酸(S87P);和/或,在第487位的异亮氨酸突变为苏氨酸(I487T)。

[0369] 在本申请中,所述P蛋白可以包含第87位的氨基酸突变。

[0370] 在本申请中,所述P蛋白可以包含第87位和第487位的氨基酸突变。

[0371] 在本申请中,所述P蛋白可以包含第487位的氨基酸突变。

[0372] 在本申请中,所述P蛋白还可以包含其他位置的氨基酸取代。

[0373] 所述溶瘤病毒还可以包含核酸分子和外源目的蛋白。核酸分子包含编码所述具有氨基酸取代的M蛋白的核酸序列、和/或编码所述具有氨基酸取代的G蛋白的核酸序列、和/或编码所述具有氨基酸取代的N蛋白的核酸序列、和/或编码所述具有氨基酸取代的P蛋白的核酸序列、和/或编码所述具有氨基酸取代的L蛋白的核酸序列。

[0374] 进一步地,该核酸分子包含编码所述外源目的蛋白的核酸序列。所述编码外源目的蛋白的核酸序列位于编码所述具有氨基酸取代的M蛋白的核酸序列、和/或编码所述具有氨基酸取代的G蛋白的核酸序列、和/或编码所述具有氨基酸取代的N蛋白的核酸序列、和/或编码所述具有氨基酸取代的P蛋白的核酸序列、和/或编码所述具有氨基酸取代的L蛋白的核酸序列之间。

[0375] 在本申请中,可以通过病毒包装过程和病毒拯救过程获得本申请所述的溶瘤病毒。具体过程可以包括用表达T7 RNA聚合酶的痘病毒vTF7-3感染接种BSR-T7细胞,使用分别克隆VSV N、VSV P、VSV L基因的表达质粒和骨架质粒进行lipofectamine转染,获得目的溶瘤病毒。

[0376] 本申请还提供了一种溶瘤病毒表达载体、一种病毒生产细胞以及一种药物组合物。

[0377] 所述溶瘤病毒表达载体可以包含编码所述溶瘤病毒的M蛋白和G蛋白的核酸序列;所述溶瘤病毒表达载体还可以包含编码所述溶瘤病毒的N蛋白、P蛋白和L蛋白的核酸序列。

[0378] 所述病毒生产细胞能够产生上述的溶瘤病毒;所述病毒生产细胞可以包含BSR-T7细胞、Vero细胞、293细胞、MRC-5细胞、WI38细胞。

[0379] 所述药物组合物包括上述的溶瘤病毒,以及任选地药学上可接受的载剂。

[0380] 在某些实施方案中,所述药物组合物可以包括一种或多种(药学上有效的)佐剂、稳定剂、赋形剂、稀释剂、增溶剂、表面活性剂、乳化剂和/或防腐剂的合适的制剂。药物组合物的可接受成分在所用剂量和浓度下优选对接受者无毒。本申请的药物组合物包括但不限于液体、冷冻和冻干组合物。

[0381] 在某些实施方案中,所述药学上可接受的载剂可以包括与药物给药相容的任何和所有的溶剂、分散介质、包衣、等渗剂和吸收延迟剂,通常安全、无毒。

[0382] 所述药物组合物包括上述的溶瘤病毒,以及任选地药学上可接受的其它药物。

[0383] 上述药物组合物可用于进行联合治疗疾病,包括但不限于治疗肿瘤。

[0384] 在某些实施方案中,所述药物组合物可以包含肠胃外、经皮下、腔内、动脉内、静脉内、鞘内和/或鼻内施用或直接注射到组织中。例如,所述药物组合物可以通过输注或注射施用于患者或者受试者。在某些实施方案中,所述药物组合物的施用可以通过不同的方式进行,例如静脉内、腹膜内、皮下、肌肉内、局部或真皮内施用。在某些实施方案中,所述药物组合物可以不间断施用。所述不间断(或连续)施用可以通过患者佩戴的小泵系统来实现,以测量流入患者体内的治疗剂,如WO2015/036583所述。

[0385] 此外,本申请还提供了上述溶瘤病毒的制备方法,该制备方法可以包括溶瘤病毒表达载体、病毒生产细胞和/或药物组合物的制备方法。任何适于生产溶瘤病毒的方法都可用于产生本申请的溶瘤病毒。例如,可以向细胞中加入表达T7 RNA聚合酶的痘病毒进行转染,加入表达所述溶瘤病毒N蛋白、L蛋白和P蛋白的质粒以及骨架质粒进行转染,通过病毒拯救过程获得本申请的溶瘤病毒。

[0386] 本申请还提供了上述溶瘤病毒、溶瘤病毒表达载体、病毒生产细胞和/或药物组合物在制备用于预防和/或治疗疾病和/或病症的药物中的用途。

[0387] 本申请提供的溶瘤病毒分别对溶瘤病毒的M蛋白、G蛋白、N蛋白、P蛋白、L蛋白上的氨基酸进行定点突变,从而进一步提高了溶瘤病毒对异常增生性LLC细胞、4T1细胞、MC38细胞以及Hela细胞的侵染能力。同时,上述制备的溶瘤病毒对正常细胞正常MEF细胞的侵染能力均较差,说明本申请制备的溶瘤病毒能够较好的用于肿瘤、癌症等细胞的侵染,同时不会损伤正常细胞,具有广泛的应用前景。

[0388] 本申请提供的溶瘤病毒分别对溶瘤病毒的M蛋白、G蛋白、N蛋白、P蛋白、L蛋白上的氨基酸进行定点突变,从而进一步提高了溶瘤病毒对异常增生性LLC细胞、4T1细胞、MC38细胞以及Hela细胞的侵染能力。从而进一步提高了溶瘤病毒对LLC细胞、4T1细胞、MC38细胞以及Hela细胞的体外杀伤能力。同时,上述制备的溶瘤病毒对正常MEF细胞几乎无影响,说明本申请制备的溶瘤病毒能够较好的用于肿瘤、癌症等非正常细胞的损伤和杀死,同时不会损伤正常细胞。

[0389] 本申请提供的溶瘤病毒在异常增生性LLC细胞、4T1细胞、MC38细胞以及Hela细胞内均不易清除。相对而言,野生型溶瘤病毒在LLC细胞、MC38细胞以及Hela细胞内更容易清除。而本申请提供的溶瘤病毒分别对溶瘤病毒的M蛋白、G蛋白、N蛋白、P蛋白、L蛋白上的氨基酸进行定点突变,使得溶瘤病毒在LLC细胞、4T1细胞、MC38细胞以及Hela细胞内更加不容易清除,进一步保证溶瘤病毒能够在LLC细胞、4T1细胞、MC38细胞以及Hela细胞内更好的发挥侵染和杀伤能力;同时,本申请提供的溶瘤病毒在正常MEF细胞内更加容易清除,进一步保证了正常MEF细胞的安全性,从而提高了溶瘤病毒的安全性。

[0390] 以下结合制备例1-80、实施例1-3以及附图1-15对本申请作进一步详细说明。

[0391] 制备例

[0392] 制备例1-29

[0393] 制备例1-29分别提供了一种溶瘤病毒,其不同之处主要在于:野生型溶瘤病毒M蛋白上氨基酸定点突变的位点。各制备例对应的溶瘤病毒的构建方法具体如下:

[0394] (1)构建质粒

[0395] 以pRV-core质粒(BioVectorNTCC质粒载体菌种细胞基因保藏中心)为模板,利用PCR技术引入如表1所示的突变位点。将pRV-core质粒分别与载有各突变位点的引物进行PCR;然后将PCR产物进行1%琼脂糖凝胶电泳;再利用凝胶回收试剂盒进行割胶回收,从而获得具有M蛋白不同突变位点的质粒,获得构建好的质粒pRV-core Mut。

[0396] 表1制备例1-29中溶瘤病毒M蛋白的突变情况表

[0397]

制备例	突变位点及突变后的氨基酸	突变位点数	氨基酸序列
1	G21E	1	SEQ ID NO 2
2	G21E、N32S	2	SEQ ID NO 3
3	G21E、N32S、M33A	3	SEQ ID NO 4
4	G21E、N32S、M33A、N49D	4	SEQ ID NO 5
5	G21E、N32S、M33A、N49D、H54Y	5	SEQ ID NO 6
6	G21E、N32S、M33A、N49D、H54Y、L111A	6	SEQ ID NO 7
7	G21E、N32S、M33A、N49D、H54Y、L111A、A133T	7	SEQ ID NO 8
8	G21E、N32S、M33A、N49D、H54Y、L111A、A133T、V225I	8	SEQ ID NO 9
9	G21E、N32S、M33A、N49D、M51R、H54Y、L111A、A133T、V225I	9	SEQ ID NO 10
10	G21E、N32S、M33A、N49D、M51R、H54Y、L111A、A133T、V221F、V225I	10	SEQ ID NO 11
11	G21E、N32S、M33A、N49D、M51R、H54Y、L111A、A133T、V221F、V225I、S226R	11	SEQ ID NO 12
12	N32S、M33A、N49D、M51R、H54Y、L111A、A133T、V221F、V225I、S226R	10	SEQ ID NO 13
13	M33A、N49D、M51R、H54Y、L111A、A133T、V221F、V225I、S226R	9	SEQ ID NO 14
14	N49D、M51R、H54Y、L111A、A133T、V221F、	8	SEQ ID NO 15

[0398]

	V225I、S226R		
15	M51R、H54Y、L111A、A133T、V221F、V225I、S226R	7	SEQ ID NO 16
16	H54Y、L111A、A133T、V221F、V225I、S226R	6	SEQ ID NO 17
17	L111A、A133T、V221F、V225I、S226R	5	SEQ ID NO 18
18	A133T、V221F、V225I、S226R	4	SEQ ID NO 19
19	V221F、V225I、S226R	3	SEQ ID NO 20
20	V225I、S226R	2	SEQ ID NO 21
21	S226R	1	SEQ ID NO 22
22	N32S、N49D、H54Y、V225I	4	SEQ ID NO 23
23	N32S、N49D、H54Y、V225I、S226G	5	SEQ ID NO 24
24	N32S、N49D、M51R、H54Y、V221F、V225I、S226R	7	SEQ ID NO 25
25	N32S、M33A、N49D、M51R、H54Y、V221F、V225I、S226R	8	SEQ ID NO 26
26	N32S、N49D、M51R、H54Y、A133T、V221F、V225I、S226R	8	SEQ ID NO 27
27	N32S、M33A、N49D、M51R、H54Y、A133T、V221F、V225I、S226R	9	SEQ ID NO 28
28	G21E、N32S、N49D、M51A、H54Y、L111A、V225I、S226R	8	SEQ ID NO 29
29	M51R、V221F、S226R	3	SEQ ID NO 30

[0399] (2)病毒拯救

[0400] 利用磷酸钙转染试剂盒(Thermo Fisher Scientific),通过细胞转染技术,将构建好的质粒pRV-core Mut转染至BSR-T7细胞(购自ATCC,美国菌种保藏中心,又称美国模式菌种收集中心)。

[0401] 按照pRV-core Mut、pP、pN、pL的质量比例为10:5:4:1,将四种质粒混合,质粒总量为5μg;使用200μl opti-MEM培养基(Thermo Fisher Scientific)稀释质粒,并加入7.5μl转染试剂Plus Reagent(Life Technologies),获得转染质粒预混液;其中,pP(载有棒状病毒磷酸蛋白基因的质粒)、pN(载有棒状病毒核蛋白基因的质粒)、pL(载有棒状病毒聚合酶蛋白基因的质粒);pN、pP、pL三种质粒对应的母体载体均为pCAGGS(购自ATCC);

[0402] 利用200μl opti-MEM培养基稀释Lipofectamine LTX 10μl(Thermo Fisher Scientific),获得LTX混合液;

[0403] 按照Lipofectamine LTX使用说明书所述的方法进行质粒转染,6h后利用PBS清洗BSR-T7细胞两次,进一步接种于10%胎牛血清的DMEM培养基(Thermo Fisher Scientific)中培养3天;

[0404] 将培养BSR-T7细胞获得的的细胞上清转移到Vero细胞(Thermo Fisher Scientific)中,并将Vero细胞置于37℃的环境条件下培养3天,荧光显微镜观察细胞中绿色荧光确定病毒拯救的情况;进一步将拯救的突变棒状病毒库,通过Vero细胞传代,在建立的噬菌斑筛选系统中挑取单克隆病毒株。

[0405] (3)M蛋白基因测序。利用Trizol试剂盒抽提病毒基因组RNA,用随机引物进行逆转

录反应,用针对M蛋白基因序列设计的引物对逆转录出来的cDNA进行PCR;

[0406] 引物序列为:

[0407] PF:ATGAGTTCCTTAAAGAA;

[0408] PR:TCATTTGAAGTGG。

[0409] 产物经1%琼脂糖凝胶电泳后回收,并送往测序公司进行测序。测序结果如表1所示。

[0410] 制备例30-52

[0411] 制备例30-52分别提供了一种溶瘤病毒,其不同之处主要在于:野生型溶瘤病毒M蛋白和G蛋白上氨基酸定点突变的位点。其中,M蛋白的突变位点与制备例24中相应的突变位点相同,G蛋白的突变位点如表2所示。

[0412] 上述制备例提供的溶瘤病毒的构建方法同制备例11的构建方法,不同之处在于:

[0413] 步骤(1)的构建质粒中利用PCR技术引入如表2所示的突变位点;

[0414] 步骤(3)为G蛋白基因测序。利用Trizol试剂盒抽提病毒基因组RNA,用随机引物进行逆转录反应,用针对G蛋白基因序列设计的引物对逆转录出来的cDNA进行PCR;

[0415] 引物序列为:

[0416] PF:ATGAAGTGCCTTTTGTACTTAG;

[0417] PR:TTACTTTCCAAGTCGGTTCATCT。

[0418] 产物经1%琼脂糖凝胶电泳后回收,并送往测序公司进行测序。测序结果如表2所示。

[0419] 表2制备例30-52中溶瘤病毒G蛋白的突变情况表

[0420]

制备例	突变位点及突变后的氨基酸	突变位点数	氨基酸序列
30	V53I	1	SEQ ID NO 32
31	V53I、A141V	2	SEQ ID NO 33
32	V53I、A141V、D172Y	3	SEQ ID NO 34
33	V53I、A141V、D172Y、K217E	4	SEQ ID NO 35
34	V53I、A141V、D172Y、K217E、D232G	5	SEQ ID NO 36
35	V53I、A141V、D172Y、K217E、D232G、V331A	6	SEQ ID NO 37
36	V53I、A141V、D172Y、K217E、D232G、V331A、V371E	7	SEQ ID NO 38
37	V53I、A141V、D172Y、K217E、D232G、V331A、V371E、G436D	8	SEQ ID NO 39
38	V53I、A141V、D172Y、K217E、D232G、V331A、V371E、G436D、T438S	9	SEQ ID NO 40
39	V53I、A141V、D172Y、K217E、D232G、V331A、V371E、G436D、T438S、F453L	10	SEQ ID NO 41
40	V53I、A141V、D172Y、K217E、D232G、V331A、V371E、G436D、T438S、F453L、T471I	11	SEQ ID NO 42
41	V53I、A141V、D172Y、K217E、D232G、V331A、V371E、G436D、T438S、F453L、T471I、Y487H	12	SEQ ID NO 43
42	A141V、D172Y、K217E、D232G、V331A、V371E、G436D、T438S、F453L、T471I、Y487H	11	SEQ ID NO 44
43	D172Y、K217E、D232G、V331A、V371E、G436D、T438S、F453L、T471I、Y487H	10	SEQ ID NO 45
44	K217E、D232G、V331A、V371E、G436D、T438S、F453L、T471I、Y487H	9	SEQ ID NO 46
45	D232G、V331A、V371E、G436D、T438S、F453L、T471I、Y487H	8	SEQ ID NO 47
46	V331A、V371E、G436D、T438S、F453L、T471I、Y487H	7	SEQ ID NO 48
47	V371E、G436D、T438S、F453L、T471I、Y487H	6	SEQ ID NO 49

[0421]

48	G436D、T438S、F453L、T471I、Y487H	5	SEQ ID NO 50
49	T438S、F453L、T471I、Y487H	4	SEQ ID NO 51
50	F453L、T471I、Y487H	3	SEQ ID NO 52
51	T471I、Y487H	2	SEQ ID NO 53
52	Y487H	1	SEQ ID NO 54

[0422] 制备例53-57

[0423] 制备例53-57分别提供了一种溶瘤病毒,其不同之处主要在于:野生型溶瘤病毒M蛋白、G蛋白、N蛋白上氨基酸定点突变的位点。其中,M蛋白、G蛋白的突变位点与制备例41中相应的突变位点相同,N蛋白的突变位点如表3所示。

[0424] 上述制备例提供的溶瘤病毒的构建方法同制备例41的构建方法,不同之处在于:

[0425] 步骤(1)的构建质粒中利用PCR技术引入如表3所示的突变位点;

[0426] 步骤(3)为N蛋白基因测序。利用Trizol试剂盒抽提病毒基因组RNA,用随机引物进

行逆转录反应,用针对N蛋白基因序列设计的引物对逆转录出来的cDNA进行PCR;

[0427] 引物序列为:

[0428] PF:ATGTCTGTTACAGTCAAGAG;

[0429] PR:TCATTTGTCAAATTCTGACTT。

[0430] 产物经1%琼脂糖凝胶电泳后回收,并送往测序公司进行测序。测序结果如表3所示。

[0431] 表3制备例53-57中溶瘤病毒N蛋白的突变情况表

[0432]

制备例	突变位点及突变后的氨基酸	突变位点数	氨基酸序列
53	I14V	1	SEQ ID NO 56
54	I14V、R155K	2	SEQ ID NO 57
55	I14V、R155K、S353N	3	SEQ ID NO 58
56	R155K、S353N	2	SEQ ID NO 59
57	S353N	1	SEQ ID NO 60

[0433] 制备例58-76

[0434] 制备例58-76分别提供了一种溶瘤病毒,其不同之处主要在于:野生型溶瘤病毒M蛋白、G蛋白、N蛋白、P蛋白上氨基酸定点突变的位点。其中,M蛋白、G蛋白、N蛋白的突变位点与制备例55中相应的突变位点相同,P蛋白的突变位点如表4所示。

[0435] 上述制备例提供的溶瘤病毒的构建方法同制备例55的构建方法,不同之处在于:

[0436] 步骤(1)的构建质粒中利用PCR技术引入如表4所示的突变位点;

[0437] 步骤(3)为P蛋白基因测序。利用Trizol试剂盒抽提病毒基因组RNA,用随机引物进行逆转录反应,用针对P蛋白基因序列设计的引物对逆转录出来的cDNA进行PCR;

[0438] 引物序列为:

[0439] PF:ATGGATAATCTCACAAAAGTTCG;

[0440] PR:CTACAGAGAATATTTGACTCTCG。

[0441] 产物经1%琼脂糖凝胶电泳后回收,并送往测序公司进行测序。测序结果如表4所示。

[0442] 表4制备例58-76中溶瘤病毒P蛋白的突变情况表

[0443]

制备例	突变位点及突变后的氨基酸	突变位点数	氨基酸序列
58	R50K	1	SEQ ID NO 62
59	R50K、V76A	2	SEQ ID NO 63
60	R50K、V76A、D99E	3	SEQ ID NO 64
61	R50K、V76A、D99E、L126S	4	SEQ ID NO 65

[0444]

62	R50K、V76A、D99E、L126S、L140S	5	SEQ ID NO 66
63	R50K、V76A、D99E、L126S、L140S、H151Y	6	SEQ ID NO 67
64	R50K、V76A、D99E、L126S、L140S、H151Y、I168M	7	SEQ ID NO 68
65	R50K、V76A、D99E、L126S、L140S、H151Y、I168M、K170E	8	SEQ ID NO 69
66	R50K、V76A、D99E、L126S、L140S、H151Y、I168M、K170E、Y189S	9	SEQ ID NO 70
67	R50K、V76A、D99E、L126S、L140S、H151Y、I168M、K170E、Y189S、N237D	10	SEQ ID NO 71
68	V76A、D99E、L126S、L140S、H151Y、I168M、K170E、Y189S、N237D	9	SEQ ID NO 72
69	D99E、L126S、L140S、H151Y、I168M、K170E、Y189S、N237D	8	SEQ ID NO 73
70	L126S、L140S、H151Y、I168M、K170E、Y189S、N237D	7	SEQ ID NO 74
71	L140S、H151Y、I168M、K170E、Y189S、N237D	6	SEQ ID NO 75
72	H151Y、I168M、K170E、Y189S、N237D	5	SEQ ID NO 76
73	I168M、K170E、Y189S、N237D	4	SEQ ID NO 77
74	K170E、Y189S、N237D	3	SEQ ID NO 78
75	Y189S、N237D	2	SEQ ID NO 79
76	N237D	1	SEQ ID NO 80

[0445] 制备例77-79

[0446] 制备例77-79分别提供了一种溶瘤病毒,其不同之处主要在于:野生型溶瘤病毒M蛋白、G蛋白、N蛋白、P蛋白、L蛋白上氨基酸定点突变的位点。其中,M蛋白、G蛋白、N蛋白、P蛋白的突变位点与制备例67中相应的突变位点相同,L蛋白的突变位点如表5所示。

[0447] 上述制备例提供的溶瘤病毒的构建方法同制备例67的构建方法,不同之处在于:

[0448] 步骤(1)的构建质粒中利用PCR技术引入如表5所示的突变位点;

[0449] 步骤(3)为L蛋白基因测序。利用Trizol试剂盒抽提病毒基因组RNA,用随机引物进行逆转录反应,用针对L蛋白基因序列设计的引物对逆转录出来的cDNA进行PCR;

[0450] 引物序列为:

[0451] PF:ATGGAAGTCCACGATTTTGAGA;

[0452] PR:TTAATCTCTCCAAGAGTTTTCCT。

[0453] 产物经1%琼脂糖凝胶电泳后回收,并送往测序公司进行测序。测序结果如表5所示。

[0454] 表5制备例77-79中溶瘤病毒L蛋白的突变情况表

[0455]

制备例	突变位点及突变后的氨基酸	突变位点数	氨基酸序列
77	S87P	1	SEQ ID NO 82
78	S87P、I487T	2	SEQ ID NO 83
79	I487T	1	SEQ ID NO 84

[0456] 制备例80

[0457] 本制备例提供了利用上述制备例1-79中任一制备例制备的溶瘤病毒的包装过程，具体包括以下步骤：

[0458] 1)利用表达T7 RNA聚合酶的痘病毒vTF7-3(BioVectorNTCC质粒载体菌种细胞基因保藏中心)感染接种BSR-T7细胞(购自ATCC)

[0459] 具体步骤如下：将BSR-T7细胞铺在6孔板上，控制每孔细胞量达到3×10^5个；铺板14-16h后加入表达T7 RNA聚合酶的痘病毒vTF7-3，进行痘病毒vTF7-3对BSR-T7细胞的感染；感染6h后，使用DPBS缓冲液(Thermo Fisher Scientific)漂洗一次BSR-T7细胞，进行转染。

[0460] 2)转染过程

[0461] 具体包括以下步骤：按照pRV-core Mut、pP、pN、pL的质量比例为10:5:4:1，将四种质粒混合，质粒总量为5μg；使用200μl opti-MEM培养基(Thermo Fisher Scientific)稀释质粒，并加入7.5μl转染试剂Plus Reagent(Life Technologies)，获得转染质粒预混液；其中，pP(载有棒状病毒磷酸蛋白基因的质粒)、pN(载有棒状病毒核蛋白基因的质粒)、pL(载有棒状病毒聚合酶蛋白基因的质粒)；pN、pP、pL三种质粒对应的母体载体均为pCAGGS(购自ATCC)；

[0462] 利用200μl opti-MEM培养基稀释Lipofectamine LTX 10μl(Thermo Fisher Scientific)，获得LTX混合液；

[0463] 将LTX混合液200μl与转染质粒预混液200μl混合，室温孵育15min，获得LTX-DNA混合液；

[0464] 将步骤1)的6孔板中的DPBS缓冲液换成Opti-MEM培养基，将LTX-DNA混合液逐滴加入培养BSR-T7细胞的6孔板中，轻轻摇动6孔板，使LTX-DNA混合液均匀分布在6孔板内；转染6-8h后，吸去转染试剂，加入3ml新鲜的完全培养基(Thermo Fisher Scientific)；72h后收获BSR-T7细胞的细胞上清，使用0.22μm滤器进行过滤，获得制备例1-79各自对应的溶瘤病毒。

[0465] 实施例

[0466] 实施例1

[0467] 本实施例分别利用制备例1-79制得的溶瘤病毒以及野生型溶瘤病毒对不同细胞的侵染能力进行试验检测。

[0468] 检测方法为TCID50检测法，即在不同细胞的培养液中，分别加入制备例1-79以及野生型溶瘤病毒各200pfu，检测各溶瘤病毒产生的半数组织培养感染剂量(Tissue culture infective dose，TCID50)。

[0469] 所检测的细胞包括：LLC细胞(鼠源肺癌细胞系)、4T1细胞(鼠源乳腺癌细胞系)、MC38细胞(鼠源结肠癌细胞系)、Hela细胞(人源宫颈癌细胞系)、MEF细胞(人源成纤维细胞系)。

[0470] 具体检测方法为：

[0471] (1)分别在6孔培养板中加入Vero(LLC/4T1/MC38/Hela/MEF)细胞悬液3mL，使细胞量达到4×10^5个/孔，共6个孔，其中MEF细胞2个孔；将6孔培养板置于37℃、5％CO_2的环境条件下培养16h；

[0472] (2)分别向6孔培养板的每个孔中加入制备例制得的溶瘤病毒200pfu；在24h收获

MEF细胞以及每种Vero细胞的上清100μl;将收获的上清分别加入96孔培养板的孔中,使各种细胞的细胞量达到1×10^4个/ml,将96孔培养板置于37℃、5%CO_2的环境条件下培养16h;

[0473] (3)在1.5ml EP管中将步骤(2)收获的上清作连续10倍的稀释,从10^{-1}~10^{-11},共11个滴度;将稀释好的上清接种到96孔培养板中,每一稀释度接种一列共8孔,每孔接种100μl;

[0474] (4)48h后观察每孔细胞的荧光情况,有荧光则记为此孔被感染;按Karber法计算TCID50。

[0475] 检测结果如图1-图5所示。其中,横坐标0表示野生型溶瘤病毒;横坐标1-79分别表示制备例1-79制备的溶瘤病毒;纵坐标Log_{10} TCID50表示利用Karber法计算得出的TCID50值,Log_{10} TCID50的值越大,表示溶瘤病毒对该细胞的侵染能力越好;Log_{10} TCID50的值越小,表示溶瘤病毒对该细胞的侵染能力越差。

[0476] 图1为本申请制备的溶瘤病毒以及野生型溶瘤病毒对LLC细胞的侵染能力的检测结果。

[0477] 图2为本申请制备的溶瘤病毒以及野生型溶瘤病毒对4T1细胞的侵染能力的检测结果。

[0478] 图3为本申请制备的溶瘤病毒以及野生型溶瘤病毒对MC38细胞的侵染能力的检测结果。

[0479] 图4为本申请制备的溶瘤病毒以及野生型溶瘤病毒对Hela细胞的侵染能力的检测结果。

[0480] 图5为本申请制备的溶瘤病毒以及野生型溶瘤病毒对MEF细胞的侵染能力的检测结果。

[0481] 通过上述附图可知,本申请制备例1-79制备的溶瘤病毒均对LLC细胞、4T1细胞、MC38细胞以及Hela细胞具有较好的侵染能力,尤其是制备例77-79提供的溶瘤病毒对LLC细胞、4T1细胞、MC38细胞以及Hela细胞的侵染能力达到了野生型溶瘤病毒的侵染能力。同时,上述制备的溶瘤病毒均对MEF细胞的侵染能力较差,尤其是制备例77-79提供的溶瘤病毒,说明本申请制备的溶瘤病毒能够较好的用于肿瘤、癌症等细胞的侵染,同时不会损伤正常细胞,具有广泛的应用前景。

[0482] 实施例2

[0483] 本实施例分别利用制备例1-79制得的溶瘤病毒以及野生型溶瘤病毒对不同细胞进行体外杀伤试验检测。

[0484] 检测方法为MTT检测法,即在不同细胞的培养液中,分别加入制备例1-79以及野生型溶瘤病毒各200pfu,24h后利用MTT检测法检测细胞活性。

[0485] 所检测的细胞包括:LLC细胞、4T1细胞、MC38细胞、Hela细胞、MEF细胞。

[0486] 具体检测方法为:

[0487] (1)分别在96孔培养板中加入Vero(LLC/4T1/MC38/Hela/MEF)细胞悬液100μl,使细胞量达到1×10^4个/孔,将96孔培养板置于37℃、5%CO_2的环境条件下培养16h;

[0488] (2)将制备例制得的溶瘤病毒稀释到MOI(感染复数)分别为0.001、0.01、0.1、1.0,将每一稀释梯度的溶瘤病毒分别接种到步骤(1)的96孔培养板上,每一稀释梯度接种4个孔,每孔100μl,将96孔培养板置于37℃、5%CO_2的环境条件下培养40h;

[0489] (3)将步骤(2)的96孔培养板中的细胞上清取出,并向96孔培养板中加入新鲜培养基和MTT溶液,加入量为20μL/孔,将96孔培养板置于37℃、5%CO_2的环境条件下培养4h;

[0490] (4)将96孔培养板于室温下离心5min,设置转速为2500rpm/min,用1mL一次性无菌注射器轻轻吸掉上清;然后向96孔培养板的每个孔中加入DMSO,加入量为100ul/孔,37℃的环境条件下放置10min。使用多功能酶标仪,震荡2min,在570nm或490nm波长下测定96孔培养板上各孔的OD值。

[0491] 检测结果如图6-图10所示。其中,横坐标0表示野生型溶瘤病毒;横坐标1-79分别表示制备例1-79制备的溶瘤病毒;纵坐标OD_{570}表示细胞的OD值,OD_{570}的值越大,表示溶瘤病毒对该细胞的杀伤能力越差;OD_{570}的值越小,表示溶瘤病毒对该细胞的杀伤能力越好。

[0492] 图6为本申请制备的溶瘤病毒以及野生型溶瘤病毒对LLC细胞的体外杀伤能力的检测结果。

[0493] 图7为本申请制备的溶瘤病毒以及野生型溶瘤病毒对4T1细胞的体外杀伤能力的检测结果。

[0494] 图8为本申请制备的溶瘤病毒以及野生型溶瘤病毒对MC38细胞的体外杀伤能力的检测结果。

[0495] 图9为本申请制备的溶瘤病毒以及野生型溶瘤病毒对Hela细胞的体外杀伤能力的检测结果。

[0496] 图10为本申请制备的溶瘤病毒以及野生型溶瘤病毒对MEF细胞的体外杀伤能力的检测结果。

[0497] 通过上述附图可知,本申请制备例1-79制备的溶瘤病毒均对LLC细胞、4T1细胞、MC38细胞以及Hela细胞均具有较好的体外杀伤能力,尤其是制备例77-79提供的溶瘤病毒对LLC细胞、4T1细胞、MC38细胞以及Hela细胞的体外杀伤能力超过了野生型溶瘤病毒的体外杀伤能力。同时,上述制备的溶瘤病毒对MEF细胞几乎无杀伤作用,说明本申请制备的溶瘤病毒能够较好的用于肿瘤、癌症等非正常细胞的损伤和杀死,同时不会损伤正常细胞。

[0498] 虽然野生型溶瘤病毒对LLC细胞、MC38细胞以及4T1细胞已具有较好的体外杀伤能力,但其在损伤和杀死上述细胞的同时,还会很大程度地损伤和杀死MEF细胞,限制了野生型溶瘤病毒的临床应用。因此,本申请对野生型溶瘤病毒的改造,在保证溶瘤病毒对正常细胞的安全性的同时,还保证了溶瘤病毒对肿瘤、癌症细胞的杀伤能力,具有广泛的临床应用前景。

[0499] 实施例3

[0500] 本实施例对制备例1-79制得的溶瘤病毒以及野生型溶瘤病毒在不同细胞内诱导IFN-β的表达情况进行试验检测。

[0501] 检测指标为基因IFN-β在不同细胞内的表达情况。基因IFN-β是细胞产生的具有广泛的抗病毒、抗肿瘤和免疫调节作用的可溶性糖蛋白的基因,通过基因IFN-β的表达情况可判断细胞对溶瘤病毒的清除能力:当基因IFN-β的表达较高时,表明溶瘤病毒在细胞内容易清除;当基因IFN-β的表达较低时,表示溶瘤病毒在细胞内不容易清除。

[0502] 所检测的细胞包括:LLC细胞、4T1细胞、MC38细胞、Hela细胞、MEF细胞。

[0503] 具体检测方法为:

[0504] (1)分别在96孔培养板中加入Vero(LLC/4T1/MC38/Hela/MEF)细胞悬液100μl,使

细胞量达到1×10^4个/孔,将96孔培养板置于37℃、5%CO_2的环境条件下培养16h;

[0505] (2)将制备例制得的溶瘤病毒稀释到MOI(感染复数)分别为0.001、0.01、0.1、1.0,将每一稀释梯度的溶瘤病毒分别接种到步骤(1)的96孔培养板上,每一稀释梯度接种4个孔,每孔100μl,将96孔培养板置于37℃、5%CO_2的环境条件下培养40h;

[0506] (3)将步骤(2)培养获得的各组细胞破碎,并利用TRIzol(Invitrogen)从各细胞中提取总RNA,利用PrimeScriptRT ReagentKitwith DNAEraser(Takara)反转录试剂盒逆转录成cDNA,并用LightCycler 480SYBR Green I Master(Roche)染料进行染色,在LightCycler 480定量PCR仪上检测各个基因的Ct值。用ΔΔCt法计算目的基因IFN-β的相对表达量。

[0507] 检测结果如图11-图15所示。其中,横坐标0表示野生型溶瘤病毒;横坐标1-79分别表示制备例1-79制备的溶瘤病毒;纵坐标IFN-β水平表示IFN-β基因的表达情况,IFN-β水平的值越大,表示溶瘤病毒在该细胞内繁殖能力越弱,越容易清除;IFN-β水平的值越小,表示溶瘤病毒在该细胞内繁殖能力越强,越不容易清除。

[0508] 图11为本申请制备的溶瘤病毒以及野生型溶瘤病毒在LLC细胞内诱导IFN-β的表达情况。

[0509] 图12为本申请制备的溶瘤病毒以及野生型溶瘤病毒在4T1细胞内诱导IFN-β的表达情况。

[0510] 图13为本申请制备的溶瘤病毒以及野生型溶瘤病毒在MC38细胞内诱导IFN-β的表达情况。

[0511] 图14为本申请制备的溶瘤病毒以及野生型溶瘤病毒在Hela细胞内诱导IFN-β的表达情况。

[0512] 图15为本申请制备的溶瘤病毒以及野生型溶瘤病毒在MEF细胞内诱导IFN-β的表达情况。

[0513] 通过上述附图可知,本申请制备例1和制备例21提供的溶瘤病毒以及野生型溶瘤病毒在LLC细胞、4T1细胞、MC38细胞以及Hela细胞内繁殖能力较弱,均容易被清除。相对而言,制备例2-20、22-79提供的溶瘤病毒在LLC细胞、4T1细胞、MC38细胞以及Hela细胞内更不容易清除。尤其是制备例77-79提供的溶瘤病毒在LLC细胞、4T1细胞、MC38细胞以及Hela细胞内更加不容易清除,进一步保证溶瘤病毒能够在LLC细胞、4T1细胞、MC38细胞以及Hela细胞内更好的发挥侵染和杀伤的能力。同时,本申请提供的溶瘤病毒在MEF细胞内更加容易清除,进一步保证了MEF细胞的安全性,从而提高了溶瘤病毒的安全性。

[0514] 本具体实施例仅仅是对本申请的解释,其并不是对本申请的限制,本领域技术人员在阅读完本说明书后可以根据需要对本实施例做出没有创造性贡献的修改,但只要在本申请的权利要求范围内都受到专利法的保护。

[0001] 序列表

[0002] <110> 上海荣瑞医药科技有限公司

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[0049] 20 25 30

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[0051] 35 40 45

[0052] Asn Glu Met Asp Thr His Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

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[0054] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr

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[0072] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Val Leu Asp Ser

[0073] 210 215 220

[0074] Val Ser His Phe Lys

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[0084] 20 25 30

[0085] Met Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val

[0086] 35 40 45

[0087] Asn Glu Met Asp Thr His Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

[0088] 50 55 60

[0089] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr

[0090] 65 70 75 80

[0091] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile

[0092] 85 90 95

[0093] Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Leu Gly

[0094] 100 105 110

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[0096] 115 120 125

[0097] Pro Glu Tyr His Ala His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg

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[0104] 180 185 190

[0105] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe

[0106] 195 200 205

[0107] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Val Leu Asp Ser

[0108] 210 215 220

[0109] Val Ser His Phe Lys

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[0119] 20 25 30

[0120] Ala Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val

[0121] 35 40 45

[0122] Asn Glu Met Asp Thr His Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

[0123] 50 55 60

[0124] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr

[0125] 65 70 75 80

[0126] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile

[0127] 85 90 95

[0128] Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Leu Gly

[0129] 100 105 110

[0130] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln

[0131] 115 120 125

[0132] Pro Glu Tyr His Ala His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg

[0133] 130 135 140

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[0135] 145 150 155 160

[0136] Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Ile Glu Leu Thr Met Thr

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[0138] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His

[0139] 180 185 190

[0140] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe

[0141] 195 200 205

[0142] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Val Leu Asp Ser

[0143] 210 215 220

[0144] Val Ser His Phe Lys

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[0154] 20 25 30

[0155] Ala Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val

[0156] 35 40 45

[0157] Asp Glu Met Asp Thr His Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

[0158] 50 55 60

[0159] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr

[0160] 65 70 75 80

[0161] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile

[0162] 85 90 95

[0163] Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Leu Gly

[0164] 100 105 110

[0165] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln

[0166] 115 120 125

[0167] Pro Glu Tyr His Ala His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg

[0168] 130 135 140

[0169] Met Gly Lys Thr Pro Pro Met Leu Asn Val Pro Glu His Phe Arg Arg

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[0173] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His

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[0175] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe

[0176] 195 200 205

[0177] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Val Leu Asp Ser

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[0179] Val Ser His Phe Lys

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[0189] 20 25 30

[0190] Ala Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val

[0191] 35 40 45

[0192] Asp Glu Met Asp Thr Tyr Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

[0193] 50 55 60

[0194] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr

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[0208] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His
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[0225] Ala Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val
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[0227] Asp Glu Met Asp Thr Tyr Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe
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[0229] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr
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[0233] Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Ala Gly

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[0235] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln

[0236] 115 120 125

[0237] Pro Glu Tyr His Ala His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg

[0238] 130 135 140

[0239] Met Gly Lys Thr Pro Pro Met Leu Asn Val Pro Glu His Phe Arg Arg

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[0241] Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Ile Glu Leu Thr Met Thr

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[0243] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His

[0244] 180 185 190

[0245] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe

[0246] 195 200 205

[0247] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Val Leu Asp Ser

[0248] 210 215 220

[0249] Val Ser His Phe Lys

[0250] 225

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[0258] Ser Lys Lys Leu Glu Ile Ala Pro Pro Pro Tyr Glu Glu Asp Thr Ser

[0259] 20 25 30

[0260] Ala Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val

[0261] 35 40 45

[0262] Asp Glu Met Asp Thr Tyr Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

[0263] 50 55 60

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[0265] 65 70 75 80

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[0267] 85 90 95

[0268] Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Ala Gly

[0269] 100 105 110

[0270] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln

[0271] 115 120 125

[0272] Pro Glu Tyr His Thr His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg

[0273] 130 135 140

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[0275] 145 150 155 160

[0276] Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Ile Glu Leu Thr Met Thr

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[0278] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His

[0279] 180 185 190

[0280] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe

[0281] 195 200 205

[0282] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Val Leu Asp Ser

[0283] 210 215 220

[0284] Val Ser His Phe Lys

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[0292] 1 5 10 15

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[0294] 20 25 30

[0295] Ala Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val

[0296] 35 40 45

[0297] Asp Glu Met Asp Thr Tyr Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

[0298] 50 55 60

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[0304] 100 105 110

[0305] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln

[0306] 115 120 125

[0307] Pro Glu Tyr His Thr His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg

[0308] 130 135 140

[0309] Met Gly Lys Thr Pro Pro Met Leu Asn Val Pro Glu His Phe Arg Arg

[0310] 145 150 155 160

[0311] Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Ile Glu Leu Thr Met Thr

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[0313] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His

[0314] 180 185 190

[0315] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe

[0316] 195 200 205

[0317] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Val Leu Asp Ser

[0318] 210 215 220

[0319] Ile Ser His Phe Lys

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[0323] <212> PRT

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[0328] Ser Lys Lys Leu Glu Ile Ala Pro Pro Pro Tyr Glu Glu Asp Thr Ser

[0329] 20 25 30

[0330] Ala Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val

[0331] 35 40 45

[0332] Asp Glu Arg Asp Thr Tyr Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

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[0334] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr

[0335] 65 70 75 80

[0336] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile

[0337] 85 90 95

[0338] Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Ala Gly

[0339] 100 105 110

[0340] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln

[0341] 115 120 125

[0342] Pro Glu Tyr His Thr His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg

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[0344] Met Gly Lys Thr Pro Pro Met Leu Asn Val Pro Glu His Phe Arg Arg

[0345] 145 150 155 160

[0346] Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Ile Glu Leu Thr Met Thr

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[0348] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His

[0349] 180 185 190

[0350] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe

[0351] 195 200 205

[0352] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Val Leu Asp Ser

[0353] 210 215 220

[0354] Ile Ser His Phe Lys

[0355] 225

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[0363] Ser Lys Lys Leu Glu Ile Ala Pro Pro Pro Tyr Glu Glu Asp Thr Ser

[0364] 20 25 30

[0365] Ala Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val

[0366] 35 40 45

[0367] Asp Glu Arg Asp Thr Tyr Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

[0368] 50 55 60

[0369] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr

[0370] 65 70 75 80

[0371] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile

[0372] 85 90 95

[0373] Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Ala Gly

[0374] 100 105 110

[0375] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln

[0376] 115 120 125

[0377] Pro Glu Tyr His Thr His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg

[0378] 130 135 140

[0379] Met Gly Lys Thr Pro Pro Met Leu Asn Val Pro Glu His Phe Arg Arg

[0380] 145 150 155 160

[0381] Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Ile Glu Leu Thr Met Thr

[0382] 165 170 175

[0383] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His

[0384] 180 185 190

[0385] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe

[0386] 195 200 205

[0387] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Phe Leu Asp Ser

[0388] 210 215 220

[0389] Ile Ser His Phe Lys

[0390] 225

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[0394] <213> 人工序列(Artificial Sequence)

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[0397] 1 5 10 15

[0398] Ser Lys Lys Leu Glu Ile Ala Pro Pro Pro Tyr Glu Glu Asp Thr Ser

[0399] 20 25 30

[0400] Ala Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val

[0401] 35 40 45

[0402] Asp Glu Arg Asp Thr Tyr Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

[0403] 50 55 60

[0404] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr

[0405] 65 70 75 80

[0406] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile

[0407] 85 90 95

[0408] Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Ala Gly

[0409] 100 105 110

[0410] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln

[0411] 115 120 125

[0412] Pro Glu Tyr His Thr His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg

[0413] 130 135 140

[0414] Met Gly Lys Thr Pro Pro Met Leu Asn Val Pro Glu His Phe Arg Arg

[0415] 145 150 155 160

[0416] Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Ile Glu Leu Thr Met Thr

[0417] 165 170 175

[0418] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His

[0419] 180 185 190

[0420] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe

[0421] 195 200 205

[0422] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Phe Leu Asp Ser

[0423] 210 215 220

[0424] Ile Arg His Phe Lys

[0425] 225

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[0427] <211> 229

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[0429] <213> 人工序列(Artificial Sequence)

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[0432] 1 5 10 15

[0433] Ser Lys Lys Leu Gly Ile Ala Pro Pro Pro Tyr Glu Glu Asp Thr Ser

[0434] 20 25 30

[0435] Ala Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val

[0436] 35 40 45

[0437] Asp Glu Arg Asp Thr Tyr Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

[0438] 50 55 60

[0439] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr

[0440] 65 70 75 80

[0441] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile

[0442] 85 90 95

[0443] Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Ala Gly

[0444] 100 105 110

[0445] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln

[0446] 115 120 125

[0447] Pro Glu Tyr His Thr His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg

[0448] 130 135 140

[0449] Met Gly Lys Thr Pro Pro Met Leu Asn Val Pro Glu His Phe Arg Arg

[0450] 145 150 155 160

[0451] Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Ile Glu Leu Thr Met Thr

[0452] 165 170 175

[0453] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His

[0454] 180 185 190

[0455] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe

[0456] 195 200 205

[0457] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Phe Leu Asp Ser

[0458] 210 215 220

[0459] Ile Arg His Phe Lys

[0460] 225

[0461] <210> 14

[0462] <211> 229

[0463] <212> PRT

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[0466] Met Ser Ser Leu Lys Lys Ile Leu Gly Leu Lys Gly Lys Gly Lys Lys

[0467] 1 5 10 15

[0468] Ser Lys Lys Leu Gly Ile Ala Pro Pro Pro Tyr Glu Glu Asp Thr Asn
[0469] 20 25 30
[0470] Ala Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val
[0471] 35 40 45
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[0541] 35 40 45
[0542] Asn Glu Arg Asp Thr Tyr Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe
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[0577] Asn Glu Met Asp Thr Tyr Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe
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[0580] 65 70 75 80
[0581] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile
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[0599] Ile Arg His Phe Lys
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[0611] 35 40 45
[0612] Asn Glu Met Asp Thr His Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe
[0613] 50 55 60
[0614] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr
[0615] 65 70 75 80
[0616] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile
[0617] 85 90 95
[0618] Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Ala Gly
[0619] 100 105 110
[0620] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln
[0621] 115 120 125
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[0632] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Phe Leu Asp Ser
[0633] 210 215 220
[0634] Ile Arg His Phe Lys
[0635] 225
[0636] <210> 19
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[0644] 20 25 30
[0645] Ala Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val
[0646] 35 40 45
[0647] Asn Glu Met Asp Thr His Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe
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[0649] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr
[0650] 65 70 75 80
[0651] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile
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[0655] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln
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[0657] Pro Glu Tyr His Thr His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg
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[0667] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Phe Leu Asp Ser
[0668] 210 215 220
[0669] Ile Arg His Phe Lys
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[0700] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe
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[0702] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Phe Leu Asp Ser
[0703] 210 215 220
[0704] Ile Arg His Phe Lys
[0705] 225
[0706] <210> 21
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[0714] 20 25 30
[0715] Ala Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val
[0716] 35 40 45
[0717] Asn Glu Met Asp Thr His Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe
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[0719] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr
[0720] 65 70 75 80
[0721] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile
[0722] 85 90 95
[0723] Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Leu Gly
[0724] 100 105 110
[0725] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln
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[0727] Pro Glu Tyr His Ala His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg
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[0729] Met Gly Lys Thr Pro Pro Met Leu Asn Val Pro Glu His Phe Arg Arg
[0730] 145 150 155 160
[0731] Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Ile Glu Leu Thr Met Thr
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[0733] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His
[0734] 180 185 190
[0735] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe
[0736] 195 200 205
[0737] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Val Leu Asp Ser
[0738] 210 215 220
[0739] Ile Arg His Phe Lys
[0740] 225

[0741] <210> 22

[0742] <211> 229

[0743] <212> PRT

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[0749] 20 25 30

[0750] Ala Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val

[0751] 35 40 45

[0752] Asn Glu Met Asp Thr His Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

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[0754] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr

[0755] 65 70 75 80

[0756] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile

[0757] 85 90 95

[0758] Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Leu Gly

[0759] 100 105 110

[0760] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln

[0761] 115 120 125

[0762] Pro Glu Tyr His Ala His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg

[0763] 130 135 140

[0764] Met Gly Lys Thr Pro Pro Met Leu Asn Val Pro Glu His Phe Arg Arg

[0765] 145 150 155 160

[0766] Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Ile Glu Leu Thr Met Thr

[0767] 165 170 175

[0768] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His

[0769] 180 185 190

[0770] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe

[0771] 195 200 205

[0772] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Val Leu Asp Ser

[0773] 210 215 220

[0774] Val Arg His Phe Lys

[0775] 225

[0776] <210> 23

[0777] <211> 229

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[0783] Ser Lys Lys Leu Gly Ile Ala Pro Pro Pro Tyr Glu Glu Asp Thr Ser

[0784] 20 25 30

[0785] Met Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val

[0786] 35 40 45

[0787] Asp Glu Met Asp Thr Tyr Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

[0788] 50 55 60

[0789] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr

[0790] 65 70 75 80

[0791] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile

[0792] 85 90 95

[0793] Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Leu Gly

[0794] 100 105 110

[0795] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln

[0796] 115 120 125

[0797] Pro Glu Tyr His Ala His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg

[0798] 130 135 140

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[0801] Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Ile Glu Leu Thr Met Thr

[0802] 165 170 175

[0803] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His

[0804] 180 185 190

[0805] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe

[0806] 195 200 205

[0807] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Val Leu Asp Ser

[0808] 210 215 220

[0809] Ile Ser His Phe Lys

[0810] 225

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[0812] <211> 229

[0813] <212> PRT

[0814] <213> 人工序列(Artificial Sequence)

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[0818] Ser Lys Lys Leu Gly Ile Ala Pro Pro Pro Tyr Glu Glu Asp Thr Ser

[0819] 20 25 30

[0820] Met Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val

[0821] 35 40 45

[0822] Asp Glu Met Asp Thr Tyr Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

[0823] 50 55 60

[0824] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr

[0825] 65 70 75 80

[0826] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile

[0827] 85 90 95

[0828] Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Leu Gly

[0829] 100 105 110

[0830] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln

[0831] 115 120 125

[0832] Pro Glu Tyr His Ala His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg

[0833] 130 135 140

[0834] Met Gly Lys Thr Pro Pro Met Leu Asn Val Pro Glu His Phe Arg Arg

[0835] 145 150 155 160

[0836] Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Ile Glu Leu Thr Met Thr

[0837] 165 170 175

[0838] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His

[0839] 180 185 190

[0840] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe

[0841] 195 200 205

[0842] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Val Leu Asp Ser

[0843] 210 215 220

[0844] Ile Gly His Phe Lys

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[0847] <211> 229

[0848] <212> PRT

[0849] <213> 人工序列(Artificial Sequence)

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[0852] 1 5 10 15

[0853] Ser Lys Lys Leu Gly Ile Ala Pro Pro Pro Tyr Glu Glu Asp Thr Ser

[0854] 20 25 30

[0855] Met Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val

[0856] 35 40 45

[0857] Asp Glu Arg Asp Thr Tyr Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

[0858] 50 55 60

[0859] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr

[0860] 65 70 75 80

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[0865] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln

[0866] 115 120 125

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[0872] 165 170 175

[0873] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His

[0874] 180 185 190

[0875] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe

[0876] 195 200 205

[0877] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Phe Leu Asp Ser

[0878] 210 215 220

[0879] Ile Arg His Phe Lys

[0880] 225

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[0882] <211> 229

[0883] <212> PRT

[0884] <213> 人工序列(Artificial Sequence)

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[0887] 1 5 10 15

[0888] Ser Lys Lys Leu Gly Ile Ala Pro Pro Pro Tyr Glu Glu Asp Thr Ser

[0889] 20 25 30

[0890] Ala Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val

[0891] 35 40 45

[0892] Asp Glu Arg Asp Thr Tyr Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

[0893] 50 55 60

[0894] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr

[0895] 65 70 75 80

[0896] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile

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[0900] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln

[0901] 115 120 125

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[0903] 130 135 140

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[0905] 145 150 155 160

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[0907] 165 170 175

[0908] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His

[0909] 180 185 190

[0910] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe

[0911] 195 200 205

[0912] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Phe Leu Asp Ser

[0913] 210 215 220

[0914] Ile Arg His Phe Lys

[0915] 225

[0916] <210> 27

[0917] <211> 229

[0918] <212> PRT

[0919] <213> 人工序列(Artificial Sequence)

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[0922] 1 5 10 15

[0923] Ser Lys Lys Leu Gly Ile Ala Pro Pro Pro Tyr Glu Glu Asp Thr Ser

[0924] 20 25 30

[0925] Met Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val

[0926] 35 40 45

[0927] Asp Glu Arg Asp Thr Tyr Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

[0928] 50 55 60

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[0930] 65 70 75 80

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[0932] 85 90 95

[0933] Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Leu Gly

[0934] 100 105 110

[0935] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln

[0936] 115 120 125

[0937] Pro Glu Tyr His Thr His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg

[0938] 130 135 140

[0939] Met Gly Lys Thr Pro Pro Met Leu Asn Val Pro Glu His Phe Arg Arg

[0940] 145 150 155 160

[0941] Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Ile Glu Leu Thr Met Thr

[0942] 165 170 175

[0943] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His

[0944] 180 185 190

[0945] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe

[0946] 195 200 205

[0947] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Phe Leu Asp Ser

[0948] 210 215 220

[0949] Ile Arg His Phe Lys

[0950] 225

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[0952] <211> 229

[0953] <212> PRT

[0954] <213> 人工序列(Artificial Sequence)

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[0957] 1 5 10 15

[0958] Ser Lys Lys Leu Gly Ile Ala Pro Pro Pro Tyr Glu Glu Asp Thr Ser

[0959] 20 25 30

[0960] Ala Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val

[0961] 35 40 45

[0962] Asp Glu Arg Asp Thr Tyr Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe

[0963] 50 55 60

[0964] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr

[0965] 65 70 75 80

[0966] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile

[0967] 85 90 95

[0968] Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Leu Gly

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[0970] Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln

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[0972] Pro Glu Tyr His Thr His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg

[0973] 130 135 140

[0974] Met Gly Lys Thr Pro Pro Met Leu Asn Val Pro Glu His Phe Arg Arg

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[0978] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His
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[0980] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe
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[0984] Ile Arg His Phe Lys
[0985] 225
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[0996] 35 40 45
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[0999] Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr
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[1001] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile
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[1003] Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Ala Gly
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[1007] Pro Glu Tyr His Ala His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg
[1008] 130 135 140
[1009] Met Gly Lys Thr Pro Pro Met Leu Asn Val Pro Glu His Phe Arg Arg
[1010] 145 150 155 160
[1011] Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Ile Glu Leu Thr Met Thr
[1012] 165 170 175
[1013] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His

[1014] 180 185 190
[1015] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe
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[1017] Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Val Leu Asp Ser
[1018] 210 215 220
[1019] Ile Arg His Phe Lys
[1020] 225
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[1031] 35 40 45
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[1035] 65 70 75 80
[1036] Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile
[1037] 85 90 95
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[1039] 100 105 110
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[1044] Met Gly Lys Thr Pro Pro Met Leu Asn Val Pro Glu His Phe Arg Arg
[1045] 145 150 155 160
[1046] Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Ile Glu Leu Thr Met Thr
[1047] 165 170 175
[1048] Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His
[1049] 180 185 190
[1050] Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe
[1051] 195 200 205
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[1054] Val Arg His Phe Lys

[1055] 225

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[1064] 20 25 30

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[1066] 35 40 45

[1067] His Asn Asp Leu Val Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser

[1068] 50 55 60

[1069] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp

[1070] 65 70 75 80

[1071] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His

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[1073] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile

[1074] 100 105 110

[1075] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln

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[1077] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Ala Ile Val Gln

[1078] 130 135 140

[1079] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val

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[1081] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Asp Ile Cys Pro Thr

[1082] 165 170 175

[1083] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu

[1084] 180 185 190

[1085] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp

[1086] 195 200 205

[1087] Gly Glu Leu Ser Ser Leu Gly Lys Lys Gly Thr Gly Phe Arg Ser Asn

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[1093] Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly
[1094] 260 265 270
[1095] Ser Ser Ile Ser Ala Pro Ser Gln Thr Ser Val Asp Val Ser Leu Ile
[1096] 275 280 285
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[1099] Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr
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[1102] 325 330 335
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[1104] 340 345 350
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[1106] 355 360 365
[1107] Glu Arg Val Leu Trp Asp Asp Trp Ala Pro Tyr Glu Asp Val Glu Ile
[1108] 370 375 380
[1109] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu
[1110] 385 390 395 400
[1111] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser
[1112] 405 410 415
[1113] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
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[1117] Asn Pro Ile Glu Phe Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser
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[1119] Ile Ala Ser Phe Phe Phe Thr Ile Gly Leu Ile Ile Gly Leu Phe Leu
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[1122] 485 490 495
[1123] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
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[1134] Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp
[1135] 35 40 45
[1136] His Asn Asp Leu Ile Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser
[1137] 50 55 60
[1138] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
[1139] 65 70 75 80
[1140] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His
[1141] 85 90 95
[1142] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile
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[1144] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln
[1145] 115 120 125
[1146] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Ala Ile Val Gln
[1147] 130 135 140
[1148] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val
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[1150] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Asp Ile Cys Pro Thr
[1151] 165 170 175
[1152] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu
[1153] 180 185 190
[1154] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp
[1155] 195 200 205
[1156] Gly Glu Leu Ser Ser Leu Gly Lys Lys Gly Thr Gly Phe Arg Ser Asn
[1157] 210 215 220
[1158] Tyr Phe Ala Tyr Glu Thr Gly Asp Lys Ala Cys Lys Met Gln Tyr Cys
[1159] 225 230 235 240
[1160] Lys His Trp Gly Val Arg Leu Pro Ser Gly Val Trp Phe Glu Met Ala
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[1162] Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly
[1163] 260 265 270
[1164] Ser Ser Ile Ser Ala Pro Ser Gln Thr Ser Val Asp Val Ser Leu Ile
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[1171] 325 330 335
[1172] Gly Thr Leu Lys Tyr Phe Glu Thr Arg Tyr Ile Arg Val Asp Ile Ala
[1173] 340 345 350
[1174] Ala Pro Ile Leu Ser Arg Met Val Gly Met Ile Ser Gly Thr Thr Thr
[1175] 355 360 365
[1176] Glu Arg Val Leu Trp Asp Asp Trp Ala Pro Tyr Glu Asp Val Glu Ile
[1177] 370 375 380
[1178] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu
[1179] 385 390 395 400
[1180] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser
[1181] 405 410 415
[1182] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
[1183] 420 425 430
[1184] Leu Pro Asp Gly Glu Thr Leu Phe Phe Gly Asp Thr Gly Leu Ser Lys
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[1186] Asn Pro Ile Glu Phe Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser
[1187] 450 455 460
[1188] Ile Ala Ser Phe Phe Phe Thr Ile Gly Leu Ile Ile Gly Leu Phe Leu
[1189] 465 470 475 480
[1190] Val Leu Arg Val Gly Ile Tyr Leu Cys Ile Lys Leu Lys His Thr Lys
[1191] 485 490 495
[1192] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
[1193] 500 505 510
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[1203] Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp
[1204] 35 40 45
[1205] His Asn Asp Leu Ile Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser
[1206] 50 55 60
[1207] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
[1208] 65 70 75 80

[1209] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His
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[1214] 115 120 125
[1215] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Val Ile Val Gln
[1216] 130 135 140
[1217] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val
[1218] 145 150 155 160
[1219] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Asp Ile Cys Pro Thr
[1220] 165 170 175
[1221] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu
[1222] 180 185 190
[1223] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp
[1224] 195 200 205
[1225] Gly Glu Leu Ser Ser Leu Gly Lys Lys Gly Thr Gly Phe Arg Ser Asn
[1226] 210 215 220
[1227] Tyr Phe Ala Tyr Glu Thr Gly Asp Lys Ala Cys Lys Met Gln Tyr Cys
[1228] 225 230 235 240
[1229] Lys His Trp Gly Val Arg Leu Pro Ser Gly Val Trp Phe Glu Met Ala
[1230] 245 250 255
[1231] Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly
[1232] 260 265 270
[1233] Ser Ser Ile Ser Ala Pro Ser Gln Thr Ser Val Asp Val Ser Leu Ile
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[1236] 290 295 300
[1237] Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr
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[1239] Leu Ala Pro Lys Asn Pro Gly Thr Gly Pro Val Phe Thr Ile Ile Asn
[1240] 325 330 335
[1241] Gly Thr Leu Lys Tyr Phe Glu Thr Arg Tyr Ile Arg Val Asp Ile Ala
[1242] 340 345 350
[1243] Ala Pro Ile Leu Ser Arg Met Val Gly Met Ile Ser Gly Thr Thr Thr
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[1245] Glu Arg Val Leu Trp Asp Asp Trp Ala Pro Tyr Glu Asp Val Glu Ile
[1246] 370 375 380
[1247] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu

[1248] 385 390 395 400
[1249] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser
[1250] 405 410 415
[1251] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
[1252] 420 425 430
[1253] Leu Pro Asp Gly Glu Thr Leu Phe Phe Gly Asp Thr Gly Leu Ser Lys
[1254] 435 440 445
[1255] Asn Pro Ile Glu Phe Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser
[1256] 450 455 460
[1257] Ile Ala Ser Phe Phe Phe Thr Ile Gly Leu Ile Ile Gly Leu Phe Leu
[1258] 465 470 475 480
[1259] Val Leu Arg Val Gly Ile Tyr Leu Cys Ile Lys Leu Lys His Thr Lys
[1260] 485 490 495
[1261] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
[1262] 500 505 510
[1263] <210> 34
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[1274] His Asn Asp Leu Ile Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser
[1275] 50 55 60
[1276] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
[1277] 65 70 75 80
[1278] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His
[1279] 85 90 95
[1280] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile
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[1282] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln
[1283] 115 120 125
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[1287] 145 150 155 160
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[1291] 180 185 190
[1292] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp
[1293] 195 200 205
[1294] Gly Glu Leu Ser Ser Leu Gly Lys Lys Gly Thr Gly Phe Arg Ser Asn
[1295] 210 215 220
[1296] Tyr Phe Ala Tyr Glu Thr Gly Asp Lys Ala Cys Lys Met Gln Tyr Cys
[1297] 225 230 235 240
[1298] Lys His Trp Gly Val Arg Leu Pro Ser Gly Val Trp Phe Glu Met Ala
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[1304] Gln Asp Val Glu Arg Ile Leu Asp Tyr Ser Leu Cys Gln Glu Thr Trp
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[1306] Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr
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[1310] Gly Thr Leu Lys Tyr Phe Glu Thr Arg Tyr Ile Arg Val Asp Ile Ala
[1311] 340 345 350
[1312] Ala Pro Ile Leu Ser Arg Met Val Gly Met Ile Ser Gly Thr Thr Thr
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[1314] Glu Arg Val Leu Trp Asp Asp Trp Ala Pro Tyr Glu Asp Val Glu Ile
[1315] 370 375 380
[1316] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu
[1317] 385 390 395 400
[1318] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser
[1319] 405 410 415
[1320] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
[1321] 420 425 430
[1322] Leu Pro Asp Gly Glu Thr Leu Phe Phe Gly Asp Thr Gly Leu Ser Lys
[1323] 435 440 445
[1324] Asn Pro Ile Glu Phe Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser
[1325] 450 455 460

[1326] Ile Ala Ser Phe Phe Phe Thr Ile Gly Leu Ile Ile Gly Leu Phe Leu
[1327] 465 470 475 480
[1328] Val Leu Arg Val Gly Ile Tyr Leu Cys Ile Lys Leu Lys His Thr Lys
[1329] 485 490 495
[1330] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
[1331] 500 505 510
[1332] <210> 35
[1333] <211> 511
[1334] <212> PRT
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[1339] Lys Phe Thr Ile Val Phe Pro His Asn Gln Lys Gly Asn Trp Lys Asn
[1340] 20 25 30
[1341] Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp
[1342] 35 40 45
[1343] His Asn Asp Leu Ile Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser
[1344] 50 55 60
[1345] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
[1346] 65 70 75 80
[1347] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His
[1348] 85 90 95
[1349] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile
[1350] 100 105 110
[1351] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln
[1352] 115 120 125
[1353] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Val Ile Val Gln
[1354] 130 135 140
[1355] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val
[1356] 145 150 155 160
[1357] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Tyr Ile Cys Pro Thr
[1358] 165 170 175
[1359] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu
[1360] 180 185 190
[1361] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp
[1362] 195 200 205
[1363] Gly Glu Leu Ser Ser Leu Gly Lys Glu Gly Thr Gly Phe Arg Ser Asn
[1364] 210 215 220

[1365] Tyr Phe Ala Tyr Glu Thr Gly Asp Lys Ala Cys Lys Met Gln Tyr Cys
[1366] 225 230 235 240
[1367] Lys His Trp Gly Val Arg Leu Pro Ser Gly Val Trp Phe Glu Met Ala
[1368] 245 250 255
[1369] Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly
[1370] 260 265 270
[1371] Ser Ser Ile Ser Ala Pro Ser Gln Thr Ser Val Asp Val Ser Leu Ile
[1372] 275 280 285
[1373] Gln Asp Val Glu Arg Ile Leu Asp Tyr Ser Leu Cys Gln Glu Thr Trp
[1374] 290 295 300
[1375] Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr
[1376] 305 310 315 320
[1377] Leu Ala Pro Lys Asn Pro Gly Thr Gly Pro Val Phe Thr Ile Ile Asn
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[1379] Gly Thr Leu Lys Tyr Phe Glu Thr Arg Tyr Ile Arg Val Asp Ile Ala
[1380] 340 345 350
[1381] Ala Pro Ile Leu Ser Arg Met Val Gly Met Ile Ser Gly Thr Thr Thr
[1382] 355 360 365
[1383] Glu Arg Val Leu Trp Asp Asp Trp Ala Pro Tyr Glu Asp Val Glu Ile
[1384] 370 375 380
[1385] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu
[1386] 385 390 395 400
[1387] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser
[1388] 405 410 415
[1389] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
[1390] 420 425 430
[1391] Leu Pro Asp Gly Glu Thr Leu Phe Phe Gly Asp Thr Gly Leu Ser Lys
[1392] 435 440 445
[1393] Asn Pro Ile Glu Phe Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser
[1394] 450 455 460
[1395] Ile Ala Ser Phe Phe Phe Thr Ile Gly Leu Ile Ile Gly Leu Phe Leu
[1396] 465 470 475 480
[1397] Val Leu Arg Val Gly Ile Tyr Leu Cys Ile Lys Leu Lys His Thr Lys
[1398] 485 490 495
[1399] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
[1400] 500 505 510
[1401] <210> 36
[1402] <211> 511
[1403] <212> PRT

[1404] <213> 人工序列(Artificial Sequence)

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[1410] Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp
[1411] 35 40 45
[1412] His Asn Asp Leu Ile Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser
[1413] 50 55 60
[1414] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
[1415] 65 70 75 80
[1416] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His
[1417] 85 90 95
[1418] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile
[1419] 100 105 110
[1420] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln
[1421] 115 120 125
[1422] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Val Ile Val Gln
[1423] 130 135 140
[1424] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val
[1425] 145 150 155 160
[1426] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Tyr Ile Cys Pro Thr
[1427] 165 170 175
[1428] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu
[1429] 180 185 190
[1430] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp
[1431] 195 200 205
[1432] Gly Glu Leu Ser Ser Leu Gly Lys Glu Gly Thr Gly Phe Arg Ser Asn
[1433] 210 215 220
[1434] Tyr Phe Ala Tyr Glu Thr Gly Gly Lys Ala Cys Lys Met Gln Tyr Cys
[1435] 225 230 235 240
[1436] Lys His Trp Gly Val Arg Leu Pro Ser Gly Val Trp Phe Glu Met Ala
[1437] 245 250 255
[1438] Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly
[1439] 260 265 270
[1440] Ser Ser Ile Ser Ala Pro Ser Gln Thr Ser Val Asp Val Ser Leu Ile
[1441] 275 280 285
[1442] Gln Asp Val Glu Arg Ile Leu Asp Tyr Ser Leu Cys Gln Glu Thr Trp

[1443] 290 295 300

[1444] Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr

[1445] 305 310 315 320

[1446] Leu Ala Pro Lys Asn Pro Gly Thr Gly Pro Val Phe Thr Ile Ile Asn

[1447] 325 330 335

[1448] Gly Thr Leu Lys Tyr Phe Glu Thr Arg Tyr Ile Arg Val Asp Ile Ala

[1449] 340 345 350

[1450] Ala Pro Ile Leu Ser Arg Met Val Gly Met Ile Ser Gly Thr Thr Thr

[1451] 355 360 365

[1452] Glu Arg Val Leu Trp Asp Asp Trp Ala Pro Tyr Glu Asp Val Glu Ile

[1453] 370 375 380

[1454] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu

[1455] 385 390 395 400

[1456] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser

[1457] 405 410 415

[1458] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln

[1459] 420 425 430

[1460] Leu Pro Asp Gly Glu Thr Leu Phe Phe Gly Asp Thr Gly Leu Ser Lys

[1461] 435 440 445

[1462] Asn Pro Ile Glu Phe Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser

[1463] 450 455 460

[1464] Ile Ala Ser Phe Phe Phe Thr Ile Gly Leu Ile Ile Gly Leu Phe Leu

[1465] 465 470 475 480

[1466] Val Leu Arg Val Gly Ile Tyr Leu Cys Ile Lys Leu Lys His Thr Lys

[1467] 485 490 495

[1468] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys

[1469] 500 505 510

[1470] <210> 37

[1471] <211> 511

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[1477] Lys Phe Thr Ile Val Phe Pro His Asn Gln Lys Gly Asn Trp Lys Asn

[1478] 20 25 30

[1479] Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp

[1480] 35 40 45

[1481] His Asn Asp Leu Ile Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser

[1482] 50 55 60
[1483] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
[1484] 65 70 75 80
[1485] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His
[1486] 85 90 95
[1487] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile
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[1489] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln
[1490] 115 120 125
[1491] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Val Ile Val Gln
[1492] 130 135 140
[1493] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val
[1494] 145 150 155 160
[1495] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Tyr Ile Cys Pro Thr
[1496] 165 170 175
[1497] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu
[1498] 180 185 190
[1499] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp
[1500] 195 200 205
[1501] Gly Glu Leu Ser Ser Leu Gly Lys Glu Gly Thr Gly Phe Arg Ser Asn
[1502] 210 215 220
[1503] Tyr Phe Ala Tyr Glu Thr Gly Gly Lys Ala Cys Lys Met Gln Tyr Cys
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[1505] Lys His Trp Gly Val Arg Leu Pro Ser Gly Val Trp Phe Glu Met Ala
[1506] 245 250 255
[1507] Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly
[1508] 260 265 270
[1509] Ser Ser Ile Ser Ala Pro Ser Gln Thr Ser Val Asp Val Ser Leu Ile
[1510] 275 280 285
[1511] Gln Asp Val Glu Arg Ile Leu Asp Tyr Ser Leu Cys Gln Glu Thr Trp
[1512] 290 295 300
[1513] Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr
[1514] 305 310 315 320
[1515] Leu Ala Pro Lys Asn Pro Gly Thr Gly Pro Ala Phe Thr Ile Ile Asn
[1516] 325 330 335
[1517] Gly Thr Leu Lys Tyr Phe Glu Thr Arg Tyr Ile Arg Val Asp Ile Ala
[1518] 340 345 350
[1519] Ala Pro Ile Leu Ser Arg Met Val Gly Met Ile Ser Gly Thr Thr Thr
[1520] 355 360 365

[1521] Glu Arg Val Leu Trp Asp Asp Trp Ala Pro Tyr Glu Asp Val Glu Ile
[1522] 370 375 380
[1523] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu
[1524] 385 390 395 400
[1525] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser
[1526] 405 410 415
[1527] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
[1528] 420 425 430
[1529] Leu Pro Asp Gly Glu Thr Leu Phe Phe Gly Asp Thr Gly Leu Ser Lys
[1530] 435 440 445
[1531] Asn Pro Ile Glu Phe Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser
[1532] 450 455 460
[1533] Ile Ala Ser Phe Phe Phe Thr Ile Gly Leu Ile Ile Gly Leu Phe Leu
[1534] 465 470 475 480
[1535] Val Leu Arg Val Gly Ile Tyr Leu Cys Ile Lys Leu Lys His Thr Lys
[1536] 485 490 495
[1537] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
[1538] 500 505 510
[1539] <210> 38
[1540] <211> 511
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[1546] Lys Phe Thr Ile Val Phe Pro His Asn Gln Lys Gly Asn Trp Lys Asn
[1547] 20 25 30
[1548] Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp
[1549] 35 40 45
[1550] His Asn Asp Leu Ile Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser
[1551] 50 55 60
[1552] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
[1553] 65 70 75 80
[1554] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His
[1555] 85 90 95
[1556] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile
[1557] 100 105 110
[1558] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln
[1559] 115 120 125

[1560] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Val Ile Val Gln
[1561] 130 135 140
[1562] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val
[1563] 145 150 155 160
[1564] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Tyr Ile Cys Pro Thr
[1565] 165 170 175
[1566] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu
[1567] 180 185 190
[1568] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp
[1569] 195 200 205
[1570] Gly Glu Leu Ser Ser Leu Gly Lys Glu Gly Thr Gly Phe Arg Ser Asn
[1571] 210 215 220
[1572] Tyr Phe Ala Tyr Glu Thr Gly Gly Lys Ala Cys Lys Met Gln Tyr Cys
[1573] 225 230 235 240
[1574] Lys His Trp Gly Val Arg Leu Pro Ser Gly Val Trp Phe Glu Met Ala
[1575] 245 250 255
[1576] Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly
[1577] 260 265 270
[1578] Ser Ser Ile Ser Ala Pro Ser Gln Thr Ser Val Asp Val Ser Leu Ile
[1579] 275 280 285
[1580] Gln Asp Val Glu Arg Ile Leu Asp Tyr Ser Leu Cys Gln Glu Thr Trp
[1581] 290 295 300
[1582] Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr
[1583] 305 310 315 320
[1584] Leu Ala Pro Lys Asn Pro Gly Thr Gly Pro Ala Phe Thr Ile Ile Asn
[1585] 325 330 335
[1586] Gly Thr Leu Lys Tyr Phe Glu Thr Arg Tyr Ile Arg Val Asp Ile Ala
[1587] 340 345 350
[1588] Ala Pro Ile Leu Ser Arg Met Val Gly Met Ile Ser Gly Thr Thr Thr
[1589] 355 360 365
[1590] Glu Arg Glu Leu Trp Asp Asp Trp Ala Pro Tyr Glu Asp Val Glu Ile
[1591] 370 375 380
[1592] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu
[1593] 385 390 395 400
[1594] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser
[1595] 405 410 415
[1596] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
[1597] 420 425 430
[1598] Leu Pro Asp Gly Glu Thr Leu Phe Phe Gly Asp Thr Gly Leu Ser Lys

[1599] 435 440 445

[1600] Asn Pro Ile Glu Phe Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser

[1601] 450 455 460

[1602] Ile Ala Ser Phe Phe Phe Thr Ile Gly Leu Ile Ile Gly Leu Phe Leu

[1603] 465 470 475 480

[1604] Val Leu Arg Val Gly Ile Tyr Leu Cys Ile Lys Leu Lys His Thr Lys

[1605] 485 490 495

[1606] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys

[1607] 500 505 510

[1608] <210> 39

[1609] <211> 511

[1610] <212> PRT

[1611] <213> 人工序列(Artificial Sequence)

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[1614] 1 5 10 15

[1615] Lys Phe Thr Ile Val Phe Pro His Asn Gln Lys Gly Asn Trp Lys Asn

[1616] 20 25 30

[1617] Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp

[1618] 35 40 45

[1619] His Asn Asp Leu Ile Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser

[1620] 50 55 60

[1621] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp

[1622] 65 70 75 80

[1623] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His

[1624] 85 90 95

[1625] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile

[1626] 100 105 110

[1627] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln

[1628] 115 120 125

[1629] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Val Ile Val Gln

[1630] 130 135 140

[1631] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val

[1632] 145 150 155 160

[1633] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Tyr Ile Cys Pro Thr

[1634] 165 170 175

[1635] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu

[1636] 180 185 190

[1637] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp

[1638] 195 200 205
[1639] Gly Glu Leu Ser Ser Leu Gly Lys Glu Gly Thr Gly Phe Arg Ser Asn
[1640] 210 215 220
[1641] Tyr Phe Ala Tyr Glu Thr Gly Gly Lys Ala Cys Lys Met Gln Tyr Cys
[1642] 225 230 235 240
[1643] Lys His Trp Gly Val Arg Leu Pro Ser Gly Val Trp Phe Glu Met Ala
[1644] 245 250 255
[1645] Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly
[1646] 260 265 270
[1647] Ser Ser Ile Ser Ala Pro Ser Gln Thr Ser Val Asp Val Ser Leu Ile
[1648] 275 280 285
[1649] Gln Asp Val Glu Arg Ile Leu Asp Tyr Ser Leu Cys Gln Glu Thr Trp
[1650] 290 295 300
[1651] Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr
[1652] 305 310 315 320
[1653] Leu Ala Pro Lys Asn Pro Gly Thr Gly Pro Ala Phe Thr Ile Ile Asn
[1654] 325 330 335
[1655] Gly Thr Leu Lys Tyr Phe Glu Thr Arg Tyr Ile Arg Val Asp Ile Ala
[1656] 340 345 350
[1657] Ala Pro Ile Leu Ser Arg Met Val Gly Met Ile Ser Gly Thr Thr Thr
[1658] 355 360 365
[1659] Glu Arg Glu Leu Trp Asp Asp Trp Ala Pro Tyr Glu Asp Val Glu Ile
[1660] 370 375 380
[1661] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu
[1662] 385 390 395 400
[1663] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser
[1664] 405 410 415
[1665] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
[1666] 420 425 430
[1667] Leu Pro Asp Asp Glu Thr Leu Phe Phe Gly Asp Thr Gly Leu Ser Lys
[1668] 435 440 445
[1669] Asn Pro Ile Glu Phe Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser
[1670] 450 455 460
[1671] Ile Ala Ser Phe Phe Phe Thr Ile Gly Leu Ile Ile Gly Leu Phe Leu
[1672] 465 470 475 480
[1673] Val Leu Arg Val Gly Ile Tyr Leu Cys Ile Lys Leu Lys His Thr Lys
[1674] 485 490 495
[1675] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
[1676] 500 505 510

[1677] <210> 40

[1678] <211> 511

[1679] <212> PRT

[1680] <213> 人工序列(Artificial Sequence)

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[1683] 1 5 10 15

[1684] Lys Phe Thr Ile Val Phe Pro His Asn Gln Lys Gly Asn Trp Lys Asn

[1685] 20 25 30

[1686] Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp

[1687] 35 40 45

[1688] His Asn Asp Leu Ile Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser

[1689] 50 55 60

[1690] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp

[1691] 65 70 75 80

[1692] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His

[1693] 85 90 95

[1694] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile

[1695] 100 105 110

[1696] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln

[1697] 115 120 125

[1698] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Val Ile Val Gln

[1699] 130 135 140

[1700] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val

[1701] 145 150 155 160

[1702] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Tyr Ile Cys Pro Thr

[1703] 165 170 175

[1704] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu

[1705] 180 185 190

[1706] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp

[1707] 195 200 205

[1708] Gly Glu Leu Ser Ser Leu Gly Lys Glu Gly Thr Gly Phe Arg Ser Asn

[1709] 210 215 220

[1710] Tyr Phe Ala Tyr Glu Thr Gly Gly Lys Ala Cys Lys Met Gln Tyr Cys

[1711] 225 230 235 240

[1712] Lys His Trp Gly Val Arg Leu Pro Ser Gly Val Trp Phe Glu Met Ala

[1713] 245 250 255

[1714] Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly

[1715] 260 265 270

[1716] Ser Ser Ile Ser Ala Pro Ser Gln Thr Ser Val Asp Val Ser Leu Ile
[1717] 275 280 285
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[1719] 290 295 300
[1720] Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr
[1721] 305 310 315 320
[1722] Leu Ala Pro Lys Asn Pro Gly Thr Gly Pro Ala Phe Thr Ile Ile Asn
[1723] 325 330 335
[1724] Gly Thr Leu Lys Tyr Phe Glu Thr Arg Tyr Ile Arg Val Asp Ile Ala
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[1726] Ala Pro Ile Leu Ser Arg Met Val Gly Met Ile Ser Gly Thr Thr Thr
[1727] 355 360 365
[1728] Glu Arg Glu Leu Trp Asp Asp Trp Ala Pro Tyr Glu Asp Val Glu Ile
[1729] 370 375 380
[1730] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu
[1731] 385 390 395 400
[1732] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser
[1733] 405 410 415
[1734] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
[1735] 420 425 430
[1736] Leu Pro Asp Asp Glu Ser Leu Phe Phe Gly Asp Thr Gly Leu Ser Lys
[1737] 435 440 445
[1738] Asn Pro Ile Glu Phe Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser
[1739] 450 455 460
[1740] Ile Ala Ser Phe Phe Phe Thr Ile Gly Leu Ile Ile Gly Leu Phe Leu
[1741] 465 470 475 480
[1742] Val Leu Arg Val Gly Ile Tyr Leu Cys Ile Lys Leu Lys His Thr Lys
[1743] 485 490 495
[1744] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
[1745] 500 505 510
[1746] <210> 41
[1747] <211> 511
[1748] <212> PRT
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[1753] Lys Phe Thr Ile Val Phe Pro His Asn Gln Lys Gly Asn Trp Lys Asn
[1754] 20 25 30

[1755] Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp
[1756] 35 40 45
[1757] His Asn Asp Leu Ile Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser
[1758] 50 55 60
[1759] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
[1760] 65 70 75 80
[1761] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His
[1762] 85 90 95
[1763] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile
[1764] 100 105 110
[1765] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln
[1766] 115 120 125
[1767] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Val Ile Val Gln
[1768] 130 135 140
[1769] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val
[1770] 145 150 155 160
[1771] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Tyr Ile Cys Pro Thr
[1772] 165 170 175
[1773] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu
[1774] 180 185 190
[1775] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp
[1776] 195 200 205
[1777] Gly Glu Leu Ser Ser Leu Gly Lys Glu Gly Thr Gly Phe Arg Ser Asn
[1778] 210 215 220
[1779] Tyr Phe Ala Tyr Glu Thr Gly Gly Lys Ala Cys Lys Met Gln Tyr Cys
[1780] 225 230 235 240
[1781] Lys His Trp Gly Val Arg Leu Pro Ser Gly Val Trp Phe Glu Met Ala
[1782] 245 250 255
[1783] Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly
[1784] 260 265 270
[1785] Ser Ser Ile Ser Ala Pro Ser Gln Thr Ser Val Asp Val Ser Leu Ile
[1786] 275 280 285
[1787] Gln Asp Val Glu Arg Ile Leu Asp Tyr Ser Leu Cys Gln Glu Thr Trp
[1788] 290 295 300
[1789] Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr
[1790] 305 310 315 320
[1791] Leu Ala Pro Lys Asn Pro Gly Thr Gly Pro Ala Phe Thr Ile Ile Asn
[1792] 325 330 335
[1793] Gly Thr Leu Lys Tyr Phe Glu Thr Arg Tyr Ile Arg Val Asp Ile Ala

[1794] 340 345 350
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[1796] 355 360 365
[1797] Glu Arg Glu Leu Trp Asp Asp Trp Ala Pro Tyr Glu Asp Val Glu Ile
[1798] 370 375 380
[1799] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu
[1800] 385 390 395 400
[1801] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser
[1802] 405 410 415
[1803] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
[1804] 420 425 430
[1805] Leu Pro Asp Asp Glu Ser Leu Phe Phe Gly Asp Thr Gly Leu Ser Lys
[1806] 435 440 445
[1807] Asn Pro Ile Glu Leu Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser
[1808] 450 455 460
[1809] Ile Ala Ser Phe Phe Phe Thr Ile Gly Leu Ile Ile Gly Leu Phe Leu
[1810] 465 470 475 480
[1811] Val Leu Arg Val Gly Ile Tyr Leu Cys Ile Lys Leu Lys His Thr Lys
[1812] 485 490 495
[1813] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
[1814] 500 505 510
[1815] <210> 42
[1816] <211> 511
[1817] <212> PRT
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[1822] Lys Phe Thr Ile Val Phe Pro His Asn Gln Lys Gly Asn Trp Lys Asn
[1823] 20 25 30
[1824] Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp
[1825] 35 40 45
[1826] His Asn Asp Leu Ile Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser
[1827] 50 55 60
[1828] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
[1829] 65 70 75 80
[1830] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His
[1831] 85 90 95
[1832] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile

[1833] 100 105 110
[1834] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln
[1835] 115 120 125
[1836] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Val Ile Val Gln
[1837] 130 135 140
[1838] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val
[1839] 145 150 155 160
[1840] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Tyr Ile Cys Pro Thr
[1841] 165 170 175
[1842] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu
[1843] 180 185 190
[1844] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp
[1845] 195 200 205
[1846] Gly Glu Leu Ser Ser Leu Gly Lys Glu Gly Thr Gly Phe Arg Ser Asn
[1847] 210 215 220
[1848] Tyr Phe Ala Tyr Glu Thr Gly Gly Lys Ala Cys Lys Met Gln Tyr Cys
[1849] 225 230 235 240
[1850] Lys His Trp Gly Val Arg Leu Pro Ser Gly Val Trp Phe Glu Met Ala
[1851] 245 250 255
[1852] Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly
[1853] 260 265 270
[1854] Ser Ser Ile Ser Ala Pro Ser Gln Thr Ser Val Asp Val Ser Leu Ile
[1855] 275 280 285
[1856] Gln Asp Val Glu Arg Ile Leu Asp Tyr Ser Leu Cys Gln Glu Thr Trp
[1857] 290 295 300
[1858] Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr
[1859] 305 310 315 320
[1860] Leu Ala Pro Lys Asn Pro Gly Thr Gly Pro Ala Phe Thr Ile Ile Asn
[1861] 325 330 335
[1862] Gly Thr Leu Lys Tyr Phe Glu Thr Arg Tyr Ile Arg Val Asp Ile Ala
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[1864] Ala Pro Ile Leu Ser Arg Met Val Gly Met Ile Ser Gly Thr Thr Thr
[1865] 355 360 365
[1866] Glu Arg Glu Leu Trp Asp Asp Trp Ala Pro Tyr Glu Asp Val Glu Ile
[1867] 370 375 380
[1868] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu
[1869] 385 390 395 400
[1870] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser
[1871] 405 410 415

[1872] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
[1873] 420 425 430
[1874] Leu Pro Asp Asp Glu Ser Leu Phe Phe Gly Asp Thr Gly Leu Ser Lys
[1875] 435 440 445
[1876] Asn Pro Ile Glu Leu Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser
[1877] 450 455 460
[1878] Ile Ala Ser Phe Phe Phe Ile Ile Gly Leu Ile Ile Gly Leu Phe Leu
[1879] 465 470 475 480
[1880] Val Leu Arg Val Gly Ile Tyr Leu Cys Ile Lys Leu Lys His Thr Lys
[1881] 485 490 495
[1882] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
[1883] 500 505 510
[1884] <210> 43
[1885] <211> 511
[1886] <212> PRT
[1887] <213> 人工序列(Artificial Sequence)
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[1891] Lys Phe Thr Ile Val Phe Pro His Asn Gln Lys Gly Asn Trp Lys Asn
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[1893] Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp
[1894] 35 40 45
[1895] His Asn Asp Leu Ile Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser
[1896] 50 55 60
[1897] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
[1898] 65 70 75 80
[1899] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His
[1900] 85 90 95
[1901] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile
[1902] 100 105 110
[1903] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln
[1904] 115 120 125
[1905] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Val Ile Val Gln
[1906] 130 135 140
[1907] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val
[1908] 145 150 155 160
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[1915] Gly Glu Leu Ser Ser Leu Gly Lys Glu Gly Thr Gly Phe Arg Ser Asn
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[1926] 290 295 300
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[1940] 405 410 415
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[1942] 420 425 430
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[1944] 435 440 445
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[1950] 485 490 495

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[1963] 35 40 45

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[1965] 50 55 60

[1966] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp

[1967] 65 70 75 80

[1968] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His

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[1970] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile

[1971] 100 105 110

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[1973] 115 120 125

[1974] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Val Ile Val Gln

[1975] 130 135 140

[1976] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val

[1977] 145 150 155 160

[1978] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Tyr Ile Cys Pro Thr

[1979] 165 170 175

[1980] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu

[1981] 180 185 190

[1982] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp

[1983] 195 200 205

[1984] Gly Glu Leu Ser Ser Leu Gly Lys Glu Gly Thr Gly Phe Arg Ser Asn

[1985] 210 215 220

[1986] Tyr Phe Ala Tyr Glu Thr Gly Gly Lys Ala Cys Lys Met Gln Tyr Cys

[1987] 225 230 235 240

[1988] Lys His Trp Gly Val Arg Leu Pro Ser Gly Val Trp Phe Glu Met Ala

[1989] 245 250 255
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[1991] 260 265 270
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[1993] 275 280 285
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[1996] Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr
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[2005] 370 375 380
[2006] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu
[2007] 385 390 395 400
[2008] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser
[2009] 405 410 415
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[2011] 420 425 430
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[2013] 435 440 445
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[2015] 450 455 460
[2016] Ile Ala Ser Phe Phe Phe Ile Ile Gly Leu Ile Ile Gly Leu Phe Leu
[2017] 465 470 475 480
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[2032] 35 40 45

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[2035] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp

[2036] 65 70 75 80

[2037] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His

[2038] 85 90 95

[2039] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile

[2040] 100 105 110

[2041] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln

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[2046] 145 150 155 160

[2047] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Tyr Ile Cys Pro Thr

[2048] 165 170 175

[2049] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu

[2050] 180 185 190

[2051] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp

[2052] 195 200 205

[2053] Gly Glu Leu Ser Ser Leu Gly Lys Glu Gly Thr Gly Phe Arg Ser Asn

[2054] 210 215 220

[2055] Tyr Phe Ala Tyr Glu Thr Gly Gly Lys Ala Cys Lys Met Gln Tyr Cys

[2056] 225 230 235 240

[2057] Lys His Trp Gly Val Arg Leu Pro Ser Gly Val Trp Phe Glu Met Ala

[2058] 245 250 255

[2059] Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly

[2060] 260 265 270

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[2062] 275 280 285

[2063] Gln Asp Val Glu Arg Ile Leu Asp Tyr Ser Leu Cys Gln Glu Thr Trp

[2064] 290 295 300

[2065] Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr

[2066] 305 310 315 320

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[2068] 325 330 335
[2069] Gly Thr Leu Lys Tyr Phe Glu Thr Arg Tyr Ile Arg Val Asp Ile Ala
[2070] 340 345 350
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[2072] 355 360 365
[2073] Glu Arg Glu Leu Trp Asp Asp Trp Ala Pro Tyr Glu Asp Val Glu Ile
[2074] 370 375 380
[2075] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu
[2076] 385 390 395 400
[2077] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser
[2078] 405 410 415
[2079] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
[2080] 420 425 430
[2081] Leu Pro Asp Asp Glu Ser Leu Phe Phe Gly Asp Thr Gly Leu Ser Lys
[2082] 435 440 445
[2083] Asn Pro Ile Glu Leu Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser
[2084] 450 455 460
[2085] Ile Ala Ser Phe Phe Phe Ile Ile Gly Leu Ile Ile Gly Leu Phe Leu
[2086] 465 470 475 480
[2087] Val Leu Arg Val Gly Ile His Leu Cys Ile Lys Leu Lys His Thr Lys
[2088] 485 490 495
[2089] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
[2090] 500 505 510
[2091] <210> 46
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[2098] Lys Phe Thr Ile Val Phe Pro His Asn Gln Lys Gly Asn Trp Lys Asn
[2099] 20 25 30
[2100] Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp
[2101] 35 40 45
[2102] His Asn Asp Leu Val Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser
[2103] 50 55 60
[2104] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
[2105] 65 70 75 80

[2106] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His
[2107] 85 90 95
[2108] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile
[2109] 100 105 110
[2110] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln
[2111] 115 120 125
[2112] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Ala Ile Val Gln
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[2114] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val
[2115] 145 150 155 160
[2116] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Asp Ile Cys Pro Thr
[2117] 165 170 175
[2118] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu
[2119] 180 185 190
[2120] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp
[2121] 195 200 205
[2122] Gly Glu Leu Ser Ser Leu Gly Lys Glu Gly Thr Gly Phe Arg Ser Asn
[2123] 210 215 220
[2124] Tyr Phe Ala Tyr Glu Thr Gly Gly Lys Ala Cys Lys Met Gln Tyr Cys
[2125] 225 230 235 240
[2126] Lys His Trp Gly Val Arg Leu Pro Ser Gly Val Trp Phe Glu Met Ala
[2127] 245 250 255
[2128] Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly
[2129] 260 265 270
[2130] Ser Ser Ile Ser Ala Pro Ser Gln Thr Ser Val Asp Val Ser Leu Ile
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[2133] 290 295 300
[2134] Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr
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[2136] Leu Ala Pro Lys Asn Pro Gly Thr Gly Pro Ala Phe Thr Ile Ile Asn
[2137] 325 330 335
[2138] Gly Thr Leu Lys Tyr Phe Glu Thr Arg Tyr Ile Arg Val Asp Ile Ala
[2139] 340 345 350
[2140] Ala Pro Ile Leu Ser Arg Met Val Gly Met Ile Ser Gly Thr Thr Thr
[2141] 355 360 365
[2142] Glu Arg Glu Leu Trp Asp Asp Trp Ala Pro Tyr Glu Asp Val Glu Ile
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[2144] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu

[2145] 385 390 395 400
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[2147] 405 410 415
[2148] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
[2149] 420 425 430
[2150] Leu Pro Asp Asp Glu Ser Leu Phe Phe Gly Asp Thr Gly Leu Ser Lys
[2151] 435 440 445
[2152] Asn Pro Ile Glu Leu Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser
[2153] 450 455 460
[2154] Ile Ala Ser Phe Phe Phe Ile Ile Gly Leu Ile Ile Gly Leu Phe Leu
[2155] 465 470 475 480
[2156] Val Leu Arg Val Gly Ile His Leu Cys Ile Lys Leu Lys His Thr Lys
[2157] 485 490 495
[2158] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
[2159] 500 505 510
[2160] <210> 47
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[2162] <212> PRT
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[2167] Lys Phe Thr Ile Val Phe Pro His Asn Gln Lys Gly Asn Trp Lys Asn
[2168] 20 25 30
[2169] Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp
[2170] 35 40 45
[2171] His Asn Asp Leu Val Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser
[2172] 50 55 60
[2173] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
[2174] 65 70 75 80
[2175] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His
[2176] 85 90 95
[2177] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile
[2178] 100 105 110
[2179] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln
[2180] 115 120 125
[2181] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Ala Ile Val Gln
[2182] 130 135 140
[2183] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val

[2184] 145 150 155 160
[2185] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Asp Ile Cys Pro Thr
[2186] 165 170 175
[2187] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu
[2188] 180 185 190
[2189] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp
[2190] 195 200 205
[2191] Gly Glu Leu Ser Ser Leu Gly Lys Lys Gly Thr Gly Phe Arg Ser Asn
[2192] 210 215 220
[2193] Tyr Phe Ala Tyr Glu Thr Gly Gly Lys Ala Cys Lys Met Gln Tyr Cys
[2194] 225 230 235 240
[2195] Lys His Trp Gly Val Arg Leu Pro Ser Gly Val Trp Phe Glu Met Ala
[2196] 245 250 255
[2197] Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly
[2198] 260 265 270
[2199] Ser Ser Ile Ser Ala Pro Ser Gln Thr Ser Val Asp Val Ser Leu Ile
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[2201] Gln Asp Val Glu Arg Ile Leu Asp Tyr Ser Leu Cys Gln Glu Thr Trp
[2202] 290 295 300
[2203] Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr
[2204] 305 310 315 320
[2205] Leu Ala Pro Lys Asn Pro Gly Thr Gly Pro Ala Phe Thr Ile Ile Asn
[2206] 325 330 335
[2207] Gly Thr Leu Lys Tyr Phe Glu Thr Arg Tyr Ile Arg Val Asp Ile Ala
[2208] 340 345 350
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[2211] Glu Arg Glu Leu Trp Asp Asp Trp Ala Pro Tyr Glu Asp Val Glu Ile
[2212] 370 375 380
[2213] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu
[2214] 385 390 395 400
[2215] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser
[2216] 405 410 415
[2217] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
[2218] 420 425 430
[2219] Leu Pro Asp Asp Glu Ser Leu Phe Phe Gly Asp Thr Gly Leu Ser Lys
[2220] 435 440 445
[2221] Asn Pro Ile Glu Leu Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser
[2222] 450 455 460

[2223] Ile Ala Ser Phe Phe Phe Ile Ile Gly Leu Ile Ile Gly Leu Phe Leu
[2224] 465 470 475 480
[2225] Val Leu Arg Val Gly Ile His Leu Cys Ile Lys Leu Lys His Thr Lys
[2226] 485 490 495
[2227] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
[2228] 500 505 510
[2229] <210> 48
[2230] <211> 511
[2231] <212> PRT
[2232] <213> 人工序列(Artificial Sequence)
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[2236] Lys Phe Thr Ile Val Phe Pro His Asn Gln Lys Gly Asn Trp Lys Asn
[2237] 20 25 30
[2238] Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp
[2239] 35 40 45
[2240] His Asn Asp Leu Val Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser
[2241] 50 55 60
[2242] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
[2243] 65 70 75 80
[2244] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His
[2245] 85 90 95
[2246] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile
[2247] 100 105 110
[2248] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln
[2249] 115 120 125
[2250] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Ala Ile Val Gln
[2251] 130 135 140
[2252] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val
[2253] 145 150 155 160
[2254] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Asp Ile Cys Pro Thr
[2255] 165 170 175
[2256] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu
[2257] 180 185 190
[2258] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp
[2259] 195 200 205
[2260] Gly Glu Leu Ser Ser Leu Gly Lys Lys Gly Thr Gly Phe Arg Ser Asn
[2261] 210 215 220

[2262] Tyr Phe Ala Tyr Glu Thr Gly Asp Lys Ala Cys Lys Met Gln Tyr Cys
[2263] 225 230 235 240
[2264] Lys His Trp Gly Val Arg Leu Pro Ser Gly Val Trp Phe Glu Met Ala
[2265] 245 250 255
[2266] Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly
[2267] 260 265 270
[2268] Ser Ser Ile Ser Ala Pro Ser Gln Thr Ser Val Asp Val Ser Leu Ile
[2269] 275 280 285
[2270] Gln Asp Val Glu Arg Ile Leu Asp Tyr Ser Leu Cys Gln Glu Thr Trp
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[2281] 370 375 380
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[2285] 405 410 415
[2286] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
[2287] 420 425 430
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[2292] Ile Ala Ser Phe Phe Phe Ile Ile Gly Leu Ile Ile Gly Leu Phe Leu
[2293] 465 470 475 480
[2294] Val Leu Arg Val Gly Ile His Leu Cys Ile Lys Leu Lys His Thr Lys
[2295] 485 490 495
[2296] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
[2297] 500 505 510
[2298] <210> 49
[2299] <211> 511
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[2306] 20 25 30

[2307] Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp

[2308] 35 40 45

[2309] His Asn Asp Leu Val Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser

[2310] 50 55 60

[2311] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp

[2312] 65 70 75 80

[2313] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His

[2314] 85 90 95

[2315] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile

[2316] 100 105 110

[2317] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln

[2318] 115 120 125

[2319] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Ala Ile Val Gln

[2320] 130 135 140

[2321] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val

[2322] 145 150 155 160

[2323] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Asp Ile Cys Pro Thr

[2324] 165 170 175

[2325] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu

[2326] 180 185 190

[2327] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp

[2328] 195 200 205

[2329] Gly Glu Leu Ser Ser Leu Gly Lys Lys Gly Thr Gly Phe Arg Ser Asn

[2330] 210 215 220

[2331] Tyr Phe Ala Tyr Glu Thr Gly Asp Lys Ala Cys Lys Met Gln Tyr Cys

[2332] 225 230 235 240

[2333] Lys His Trp Gly Val Arg Leu Pro Ser Gly Val Trp Phe Glu Met Ala

[2334] 245 250 255

[2335] Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly

[2336] 260 265 270

[2337] Ser Ser Ile Ser Ala Pro Ser Gln Thr Ser Val Asp Val Ser Leu Ile

[2338] 275 280 285

[2339] Gln Asp Val Glu Arg Ile Leu Asp Tyr Ser Leu Cys Gln Glu Thr Trp

[2340] 290 295 300
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[2344] 325 330 335
[2345] Gly Thr Leu Lys Tyr Phe Glu Thr Arg Tyr Ile Arg Val Asp Ile Ala
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[2347] Ala Pro Ile Leu Ser Arg Met Val Gly Met Ile Ser Gly Thr Thr Thr
[2348] 355 360 365
[2349] Glu Arg Glu Leu Trp Asp Asp Trp Ala Pro Tyr Glu Asp Val Glu Ile
[2350] 370 375 380
[2351] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu
[2352] 385 390 395 400
[2353] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser
[2354] 405 410 415
[2355] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
[2356] 420 425 430
[2357] Leu Pro Asp Asp Glu Ser Leu Phe Phe Gly Asp Thr Gly Leu Ser Lys
[2358] 435 440 445
[2359] Asn Pro Ile Glu Leu Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser
[2360] 450 455 460
[2361] Ile Ala Ser Phe Phe Phe Ile Ile Gly Leu Ile Ile Gly Leu Phe Leu
[2362] 465 470 475 480
[2363] Val Leu Arg Val Gly Ile His Leu Cys Ile Lys Leu Lys His Thr Lys
[2364] 485 490 495
[2365] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
[2366] 500 505 510
[2367] <210> 50
[2368] <211> 511
[2369] <212> PRT
[2370] <213> 人工序列(Artificial Sequence)
[2371] <400> 50
[2372] Met Lys Cys Leu Leu Tyr Leu Ala Phe Leu Phe Ile Gly Val Asn Cys
[2373] 1 5 10 15
[2374] Lys Phe Thr Ile Val Phe Pro His Asn Gln Lys Gly Asn Trp Lys Asn
[2375] 20 25 30
[2376] Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp
[2377] 35 40 45
[2378] His Asn Asp Leu Val Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser

[2379] 50 55 60

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[2381] 65 70 75 80

[2382] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His

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[2384] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile

[2385] 100 105 110

[2386] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln

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[2388] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Ala Ile Val Gln

[2389] 130 135 140

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[2393] 165 170 175

[2394] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu

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[2397] 195 200 205

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[2405] 260 265 270

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[2410] Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr

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[2412] Leu Ala Pro Lys Asn Pro Gly Thr Gly Pro Val Phe Thr Ile Ile Asn

[2413] 325 330 335

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[2416] Ala Pro Ile Leu Ser Arg Met Val Gly Met Ile Ser Gly Thr Thr Thr

[2417] 355 360 365

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[2448] 50 55 60
[2449] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
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[2451] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His
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[2466] 195 200 205
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[2473] Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly
[2474] 260 265 270
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[2493] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
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[2502] 485 490 495
[2503] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
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[2514] Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp
[2515] 35 40 45
[2516] His Asn Asp Leu Val Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser
[2517] 50 55 60
[2518] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
[2519] 65 70 75 80
[2520] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His
[2521] 85 90 95
[2522] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile
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[2524] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln
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[2531] 165 170 175
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[2535] 195 200 205

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[2537] 210 215 220

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[2539] 225 230 235 240

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[2541] 245 250 255

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[2543] 260 265 270

[2544] Ser Ser Ile Ser Ala Pro Ser Gln Thr Ser Val Asp Val Ser Leu Ile

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[2547] 290 295 300

[2548] Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr

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[2551] 325 330 335

[2552] Gly Thr Leu Lys Tyr Phe Glu Thr Arg Tyr Ile Arg Val Asp Ile Ala

[2553] 340 345 350

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[2555] 355 360 365

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[2557] 370 375 380

[2558] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu

[2559] 385 390 395 400

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[2561] 405 410 415

[2562] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln

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[2565] 435 440 445

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[2567] 450 455 460

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[2571] 485 490 495

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[2584] 35 40 45

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[2587] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp

[2588] 65 70 75 80

[2589] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His

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[2591] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile

[2592] 100 105 110

[2593] Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln

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[2595] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Ala Ile Val Gln

[2596] 130 135 140

[2597] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val

[2598] 145 150 155 160

[2599] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Asp Ile Cys Pro Thr

[2600] 165 170 175

[2601] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu

[2602] 180 185 190

[2603] Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp

[2604] 195 200 205

[2605] Gly Glu Leu Ser Ser Leu Gly Lys Lys Gly Thr Gly Phe Arg Ser Asn

[2606] 210 215 220

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[2612] 260 265 270

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[2625] Glu Arg Val Leu Trp Asp Asp Trp Ala Pro Tyr Glu Asp Val Glu Ile
[2626] 370 375 380
[2627] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu
[2628] 385 390 395 400
[2629] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser
[2630] 405 410 415
[2631] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
[2632] 420 425 430
[2633] Leu Pro Asp Gly Glu Thr Leu Phe Phe Gly Asp Thr Gly Leu Ser Lys
[2634] 435 440 445
[2635] Asn Pro Ile Glu Phe Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser
[2636] 450 455 460
[2637] Ile Ala Ser Phe Phe Phe Ile Ile Gly Leu Ile Ile Gly Leu Phe Leu
[2638] 465 470 475 480
[2639] Val Leu Arg Val Gly Ile His Leu Cys Ile Lys Leu Lys His Thr Lys
[2640] 485 490 495
[2641] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
[2642] 500 505 510
[2643] <210> 54
[2644] <211> 511
[2645] <212> PRT
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[2653] 35 40 45
[2654] His Asn Asp Leu Val Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser
[2655] 50 55 60
[2656] His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
[2657] 65 70 75 80
[2658] Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His
[2659] 85 90 95
[2660] Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile
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[2663] 115 120 125
[2664] Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Ala Ile Val Gln
[2665] 130 135 140
[2666] Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val
[2667] 145 150 155 160
[2668] Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Asp Ile Cys Pro Thr
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[2670] Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu
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[2673] 195 200 205
[2674] Gly Glu Leu Ser Ser Leu Gly Lys Lys Gly Thr Gly Phe Arg Ser Asn
[2675] 210 215 220
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[2677] 225 230 235 240
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[2695] 370 375 380
[2696] Gly Pro Asn Gly Val Leu Arg Thr Ser Ser Gly Tyr Lys Phe Pro Leu
[2697] 385 390 395 400
[2698] Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser
[2699] 405 410 415
[2700] Lys Ala Gln Val Phe Glu His Pro His Ile Gln Asp Ala Ala Ser Gln
[2701] 420 425 430
[2702] Leu Pro Asp Gly Glu Thr Leu Phe Phe Gly Asp Thr Gly Leu Ser Lys
[2703] 435 440 445
[2704] Asn Pro Ile Glu Phe Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser
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[2706] Ile Ala Ser Phe Phe Phe Thr Ile Gly Leu Ile Ile Gly Leu Phe Leu
[2707] 465 470 475 480
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[2709] 485 490 495
[2710] Lys Arg Gln Ile Tyr Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
[2711] 500 505 510
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[2721] Arg Lys Ser Lys Glu Ile Pro Leu Tyr Ile Asn Thr Thr Lys Ser Leu
[2722] 35 40 45
[2723] Ser Asp Leu Arg Gly Tyr Val Tyr Gln Gly Leu Lys Ser Gly Asn Val
[2724] 50 55 60
[2725] Ser Ile Ile His Val Asn Ser Tyr Leu Tyr Gly Ala Leu Lys Asp Ile
[2726] 65 70 75 80
[2727] Arg Gly Lys Leu Asp Lys Asp Trp Ser Ser Phe Gly Ile Asn Ile Gly
[2728] 85 90 95
[2729] Lys Ala Gly Asp Thr Ile Gly Ile Phe Asp Leu Val Ser Leu Lys Ala

[2730] 100 105 110
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[2732] 115 120 125
[2733] Ala Asp Asp Lys Trp Leu Pro Leu Tyr Leu Leu Gly Leu Tyr Arg Val
[2734] 130 135 140
[2735] Gly Arg Thr Gln Met Pro Glu Tyr Arg Lys Arg Leu Met Asp Gly Leu
[2736] 145 150 155 160
[2737] Thr Asn Gln Cys Lys Met Ile Asn Glu Gln Phe Glu Pro Leu Val Pro
[2738] 165 170 175
[2739] Glu Gly Arg Asp Ile Phe Asp Val Trp Gly Asn Asp Ser Asn Tyr Thr
[2740] 180 185 190
[2741] Lys Ile Val Ala Ala Val Asp Met Phe Phe His Met Phe Lys Lys His
[2742] 195 200 205
[2743] Glu Cys Ala Ser Phe Arg Tyr Gly Thr Ile Val Ser Arg Phe Lys Asp
[2744] 210 215 220
[2745] Cys Ala Ala Leu Ala Thr Phe Gly His Leu Cys Lys Ile Thr Gly Met
[2746] 225 230 235 240
[2747] Ser Thr Glu Asp Val Thr Thr Trp Ile Leu Asn Arg Glu Val Ala Asp
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[2750] 260 265 270
[2751] Ser Tyr Met Pro Tyr Leu Ile Asp Phe Gly Leu Ser Ser Lys Ser Pro
[2752] 275 280 285
[2753] Tyr Ser Ser Val Lys Asn Pro Ala Phe His Phe Trp Gly Gln Leu Thr
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[2755] Ala Leu Leu Leu Arg Ser Thr Arg Ala Arg Asn Ala Arg Gln Pro Asp
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[2764] 370 375 380
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[2780] Arg Lys Ser Lys Glu Ile Pro Leu Tyr Ile Asn Thr Thr Lys Ser Leu
[2781] 35 40 45
[2782] Ser Asp Leu Arg Gly Tyr Val Tyr Gln Gly Leu Lys Ser Gly Asn Val
[2783] 50 55 60
[2784] Ser Ile Ile His Val Asn Ser Tyr Leu Tyr Gly Ala Leu Lys Asp Ile
[2785] 65 70 75 80
[2786] Arg Gly Lys Leu Asp Lys Asp Trp Ser Ser Phe Gly Ile Asn Ile Gly
[2787] 85 90 95
[2788] Lys Ala Gly Asp Thr Ile Gly Ile Phe Asp Leu Val Ser Leu Lys Ala
[2789] 100 105 110
[2790] Leu Asp Gly Val Leu Pro Asp Gly Val Ser Asp Ala Ser Arg Thr Ser
[2791] 115 120 125
[2792] Ala Asp Asp Lys Trp Leu Pro Leu Tyr Leu Leu Gly Leu Tyr Arg Val
[2793] 130 135 140
[2794] Gly Arg Thr Gln Met Pro Glu Tyr Arg Lys Arg Leu Met Asp Gly Leu
[2795] 145 150 155 160
[2796] Thr Asn Gln Cys Lys Met Ile Asn Glu Gln Phe Glu Pro Leu Val Pro
[2797] 165 170 175
[2798] Glu Gly Arg Asp Ile Phe Asp Val Trp Gly Asn Asp Ser Asn Tyr Thr
[2799] 180 185 190
[2800] Lys Ile Val Ala Ala Val Asp Met Phe Phe His Met Phe Lys Lys His
[2801] 195 200 205
[2802] Glu Cys Ala Ser Phe Arg Tyr Gly Thr Ile Val Ser Arg Phe Lys Asp
[2803] 210 215 220
[2804] Cys Ala Ala Leu Ala Thr Phe Gly His Leu Cys Lys Ile Thr Gly Met
[2805] 225 230 235 240
[2806] Ser Thr Glu Asp Val Thr Thr Trp Ile Leu Asn Arg Glu Val Ala Asp
[2807] 245 250 255

[2808] Glu Met Val Gln Met Met Leu Pro Gly Gln Glu Ile Asp Lys Ala Asp
[2809] 260 265 270
[2810] Ser Tyr Met Pro Tyr Leu Ile Asp Phe Gly Leu Ser Ser Lys Ser Pro
[2811] 275 280 285
[2812] Tyr Ser Ser Val Lys Asn Pro Ala Phe His Phe Trp Gly Gln Leu Thr
[2813] 290 295 300
[2814] Ala Leu Leu Leu Arg Ser Thr Arg Ala Arg Asn Ala Arg Gln Pro Asp
[2815] 305 310 315 320
[2816] Asp Ile Glu Tyr Thr Ser Leu Thr Thr Ala Gly Leu Leu Tyr Ala Tyr
[2817] 325 330 335
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[2819] 340 345 350
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[2823] 370 375 380
[2824] Gln Asn Arg Lys Pro Thr Pro Asp Met Met Gln Tyr Ala Lys Arg Ala
[2825] 385 390 395 400
[2826] Val Met Ser Leu Gln Gly Leu Arg Glu Lys Thr Ile Gly Lys Tyr Ala
[2827] 405 410 415
[2828] Lys Ser Glu Phe Asp Lys
[2829] 420
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[2840] 35 40 45
[2841] Ser Asp Leu Arg Gly Tyr Val Tyr Gln Gly Leu Lys Ser Gly Asn Val
[2842] 50 55 60
[2843] Ser Ile Ile His Val Asn Ser Tyr Leu Tyr Gly Ala Leu Lys Asp Ile
[2844] 65 70 75 80
[2845] Arg Gly Lys Leu Asp Lys Asp Trp Ser Ser Phe Gly Ile Asn Ile Gly
[2846] 85 90 95

[2847] Lys Ala Gly Asp Thr Ile Gly Ile Phe Asp Leu Val Ser Leu Lys Ala
[2848] 100 105 110
[2849] Leu Asp Gly Val Leu Pro Asp Gly Val Ser Asp Ala Ser Arg Thr Ser
[2850] 115 120 125
[2851] Ala Asp Asp Lys Trp Leu Pro Leu Tyr Leu Leu Gly Leu Tyr Arg Val
[2852] 130 135 140
[2853] Gly Arg Thr Gln Met Pro Glu Tyr Arg Lys Lys Leu Met Asp Gly Leu
[2854] 145 150 155 160
[2855] Thr Asn Gln Cys Lys Met Ile Asn Glu Gln Phe Glu Pro Leu Val Pro
[2856] 165 170 175
[2857] Glu Gly Arg Asp Ile Phe Asp Val Trp Gly Asn Asp Ser Asn Tyr Thr
[2858] 180 185 190
[2859] Lys Ile Val Ala Ala Val Asp Met Phe Phe His Met Phe Lys Lys His
[2860] 195 200 205
[2861] Glu Cys Ala Ser Phe Arg Tyr Gly Thr Ile Val Ser Arg Phe Lys Asp
[2862] 210 215 220
[2863] Cys Ala Ala Leu Ala Thr Phe Gly His Leu Cys Lys Ile Thr Gly Met
[2864] 225 230 235 240
[2865] Ser Thr Glu Asp Val Thr Thr Trp Ile Leu Asn Arg Glu Val Ala Asp
[2866] 245 250 255
[2867] Glu Met Val Gln Met Met Leu Pro Gly Gln Glu Ile Asp Lys Ala Asp
[2868] 260 265 270
[2869] Ser Tyr Met Pro Tyr Leu Ile Asp Phe Gly Leu Ser Ser Lys Ser Pro
[2870] 275 280 285
[2871] Tyr Ser Ser Val Lys Asn Pro Ala Phe His Phe Trp Gly Gln Leu Thr
[2872] 290 295 300
[2873] Ala Leu Leu Leu Arg Ser Thr Arg Ala Arg Asn Ala Arg Gln Pro Asp
[2874] 305 310 315 320
[2875] Asp Ile Glu Tyr Thr Ser Leu Thr Thr Ala Gly Leu Leu Tyr Ala Tyr
[2876] 325 330 335
[2877] Ala Val Gly Ser Ser Ala Asp Leu Ala Gln Gln Phe Cys Val Gly Asp
[2878] 340 345 350
[2879] Ser Lys Tyr Thr Pro Asp Asp Ser Thr Gly Gly Leu Thr Thr Asn Ala
[2880] 355 360 365
[2881] Pro Pro Gln Gly Arg Asp Val Val Glu Trp Leu Gly Trp Phe Glu Asp
[2882] 370 375 380
[2883] Gln Asn Arg Lys Pro Thr Pro Asp Met Met Gln Tyr Ala Lys Arg Ala
[2884] 385 390 395 400
[2885] Val Met Ser Leu Gln Gly Leu Arg Glu Lys Thr Ile Gly Lys Tyr Ala

[2886] 405 410 415

[2887] Lys Ser Glu Phe Asp Lys

[2888] 420

[2889] <210> 58

[2890] <211> 422

[2891] <212> PRT

[2892] <213> 人工序列(Artificial Sequence)

[2893] <400> 58

[2894] Met Ser Val Thr Val Lys Arg Ile Ile Asp Asn Thr Val Val Val Pro

[2895] 1 5 10 15

[2896] Lys Leu Pro Ala Asn Glu Asp Pro Val Glu Tyr Pro Ala Asp Tyr Phe

[2897] 20 25 30

[2898] Arg Lys Ser Lys Glu Ile Pro Leu Tyr Ile Asn Thr Thr Lys Ser Leu

[2899] 35 40 45

[2900] Ser Asp Leu Arg Gly Tyr Val Tyr Gln Gly Leu Lys Ser Gly Asn Val

[2901] 50 55 60

[2902] Ser Ile Ile His Val Asn Ser Tyr Leu Tyr Gly Ala Leu Lys Asp Ile

[2903] 65 70 75 80

[2904] Arg Gly Lys Leu Asp Lys Asp Trp Ser Ser Phe Gly Ile Asn Ile Gly

[2905] 85 90 95

[2906] Lys Ala Gly Asp Thr Ile Gly Ile Phe Asp Leu Val Ser Leu Lys Ala

[2907] 100 105 110

[2908] Leu Asp Gly Val Leu Pro Asp Gly Val Ser Asp Ala Ser Arg Thr Ser

[2909] 115 120 125

[2910] Ala Asp Asp Lys Trp Leu Pro Leu Tyr Leu Leu Gly Leu Tyr Arg Val

[2911] 130 135 140

[2912] Gly Arg Thr Gln Met Pro Glu Tyr Arg Lys Lys Leu Met Asp Gly Leu

[2913] 145 150 155 160

[2914] Thr Asn Gln Cys Lys Met Ile Asn Glu Gln Phe Glu Pro Leu Val Pro

[2915] 165 170 175

[2916] Glu Gly Arg Asp Ile Phe Asp Val Trp Gly Asn Asp Ser Asn Tyr Thr

[2917] 180 185 190

[2918] Lys Ile Val Ala Ala Val Asp Met Phe Phe His Met Phe Lys Lys His

[2919] 195 200 205

[2920] Glu Cys Ala Ser Phe Arg Tyr Gly Thr Ile Val Ser Arg Phe Lys Asp

[2921] 210 215 220

[2922] Cys Ala Ala Leu Ala Thr Phe Gly His Leu Cys Lys Ile Thr Gly Met

[2923] 225 230 235 240

[2924] Ser Thr Glu Asp Val Thr Thr Trp Ile Leu Asn Arg Glu Val Ala Asp

[2925] 245 250 255
[2926] Glu Met Val Gln Met Met Leu Pro Gly Gln Glu Ile Asp Lys Ala Asp
[2927] 260 265 270
[2928] Ser Tyr Met Pro Tyr Leu Ile Asp Phe Gly Leu Ser Ser Lys Ser Pro
[2929] 275 280 285
[2930] Tyr Ser Ser Val Lys Asn Pro Ala Phe His Phe Trp Gly Gln Leu Thr
[2931] 290 295 300
[2932] Ala Leu Leu Leu Arg Ser Thr Arg Ala Arg Asn Ala Arg Gln Pro Asp
[2933] 305 310 315 320
[2934] Asp Ile Glu Tyr Thr Ser Leu Thr Thr Ala Gly Leu Leu Tyr Ala Tyr
[2935] 325 330 335
[2936] Ala Val Gly Ser Ser Ala Asp Leu Ala Gln Gln Phe Cys Val Gly Asp
[2937] 340 345 350
[2938] Asn Lys Tyr Thr Pro Asp Asp Ser Thr Gly Gly Leu Thr Thr Asn Ala
[2939] 355 360 365
[2940] Pro Pro Gln Gly Arg Asp Val Val Glu Trp Leu Gly Trp Phe Glu Asp
[2941] 370 375 380
[2942] Gln Asn Arg Lys Pro Thr Pro Asp Met Met Gln Tyr Ala Lys Arg Ala
[2943] 385 390 395 400
[2944] Val Met Ser Leu Gln Gly Leu Arg Glu Lys Thr Ile Gly Lys Tyr Ala
[2945] 405 410 415
[2946] Lys Ser Glu Phe Asp Lys
[2947] 420
[2948] <210> 59
[2949] <211> 422
[2950] <212> PRT
[2951] <213> 人工序列(Artificial Sequence)
[2952] <400> 59
[2953] Met Ser Val Thr Val Lys Arg Ile Ile Asp Asn Thr Val Ile Val Pro
[2954] 1 5 10 15
[2955] Lys Leu Pro Ala Asn Glu Asp Pro Val Glu Tyr Pro Ala Asp Tyr Phe
[2956] 20 25 30
[2957] Arg Lys Ser Lys Glu Ile Pro Leu Tyr Ile Asn Thr Thr Lys Ser Leu
[2958] 35 40 45
[2959] Ser Asp Leu Arg Gly Tyr Val Tyr Gln Gly Leu Lys Ser Gly Asn Val
[2960] 50 55 60
[2961] Ser Ile Ile His Val Asn Ser Tyr Leu Tyr Gly Ala Leu Lys Asp Ile
[2962] 65 70 75 80
[2963] Arg Gly Lys Leu Asp Lys Asp Trp Ser Ser Phe Gly Ile Asn Ile Gly

[2964] 85 90 95

[2965] Lys Ala Gly Asp Thr Ile Gly Ile Phe Asp Leu Val Ser Leu Lys Ala

[2966] 100 105 110

[2967] Leu Asp Gly Val Leu Pro Asp Gly Val Ser Asp Ala Ser Arg Thr Ser

[2968] 115 120 125

[2969] Ala Asp Asp Lys Trp Leu Pro Leu Tyr Leu Leu Gly Leu Tyr Arg Val

[2970] 130 135 140

[2971] Gly Arg Thr Gln Met Pro Glu Tyr Arg Lys Lys Leu Met Asp Gly Leu

[2972] 145 150 155 160

[2973] Thr Asn Gln Cys Lys Met Ile Asn Glu Gln Phe Glu Pro Leu Val Pro

[2974] 165 170 175

[2975] Glu Gly Arg Asp Ile Phe Asp Val Trp Gly Asn Asp Ser Asn Tyr Thr

[2976] 180 185 190

[2977] Lys Ile Val Ala Ala Val Asp Met Phe Phe His Met Phe Lys Lys His

[2978] 195 200 205

[2979] Glu Cys Ala Ser Phe Arg Tyr Gly Thr Ile Val Ser Arg Phe Lys Asp

[2980] 210 215 220

[2981] Cys Ala Ala Leu Ala Thr Phe Gly His Leu Cys Lys Ile Thr Gly Met

[2982] 225 230 235 240

[2983] Ser Thr Glu Asp Val Thr Thr Trp Ile Leu Asn Arg Glu Val Ala Asp

[2984] 245 250 255

[2985] Glu Met Val Gln Met Met Leu Pro Gly Gln Glu Ile Asp Lys Ala Asp

[2986] 260 265 270

[2987] Ser Tyr Met Pro Tyr Leu Ile Asp Phe Gly Leu Ser Ser Lys Ser Pro

[2988] 275 280 285

[2989] Tyr Ser Ser Val Lys Asn Pro Ala Phe His Phe Trp Gly Gln Leu Thr

[2990] 290 295 300

[2991] Ala Leu Leu Leu Arg Ser Thr Arg Ala Arg Asn Ala Arg Gln Pro Asp

[2992] 305 310 315 320

[2993] Asp Ile Glu Tyr Thr Ser Leu Thr Thr Ala Gly Leu Leu Tyr Ala Tyr

[2994] 325 330 335

[2995] Ala Val Gly Ser Ser Ala Asp Leu Ala Gln Gln Phe Cys Val Gly Asp

[2996] 340 345 350

[2997] Asn Lys Tyr Thr Pro Asp Asp Ser Thr Gly Gly Leu Thr Thr Asn Ala

[2998] 355 360 365

[2999] Pro Pro Gln Gly Arg Asp Val Val Glu Trp Leu Gly Trp Phe Glu Asp

[3000] 370 375 380

[3001] Gln Asn Arg Lys Pro Thr Pro Asp Met Met Gln Tyr Ala Lys Arg Ala

[3002] 385 390 395 400

[3003] Val Met Ser Leu Gln Gly Leu Arg Glu Lys Thr Ile Gly Lys Tyr Ala
[3004] 405 410 415
[3005] Lys Ser Glu Phe Asp Lys
[3006] 420
[3007] <210> 60
[3008] <211> 422
[3009] <212> PRT
[3010] <213> 人工序列(Artificial Sequence)
[3011] <400> 60
[3012] Met Ser Val Thr Val Lys Arg Ile Ile Asp Asn Thr Val Ile Val Pro
[3013] 1 5 10 15
[3014] Lys Leu Pro Ala Asn Glu Asp Pro Val Glu Tyr Pro Ala Asp Tyr Phe
[3015] 20 25 30
[3016] Arg Lys Ser Lys Glu Ile Pro Leu Tyr Ile Asn Thr Thr Lys Ser Leu
[3017] 35 40 45
[3018] Ser Asp Leu Arg Gly Tyr Val Tyr Gln Gly Leu Lys Ser Gly Asn Val
[3019] 50 55 60
[3020] Ser Ile Ile His Val Asn Ser Tyr Leu Tyr Gly Ala Leu Lys Asp Ile
[3021] 65 70 75 80
[3022] Arg Gly Lys Leu Asp Lys Asp Trp Ser Ser Phe Gly Ile Asn Ile Gly
[3023] 85 90 95
[3024] Lys Ala Gly Asp Thr Ile Gly Ile Phe Asp Leu Val Ser Leu Lys Ala
[3025] 100 105 110
[3026] Leu Asp Gly Val Leu Pro Asp Gly Val Ser Asp Ala Ser Arg Thr Ser
[3027] 115 120 125
[3028] Ala Asp Asp Lys Trp Leu Pro Leu Tyr Leu Leu Gly Leu Tyr Arg Val
[3029] 130 135 140
[3030] Gly Arg Thr Gln Met Pro Glu Tyr Arg Lys Arg Leu Met Asp Gly Leu
[3031] 145 150 155 160
[3032] Thr Asn Gln Cys Lys Met Ile Asn Glu Gln Phe Glu Pro Leu Val Pro
[3033] 165 170 175
[3034] Glu Gly Arg Asp Ile Phe Asp Val Trp Gly Asn Asp Ser Asn Tyr Thr
[3035] 180 185 190
[3036] Lys Ile Val Ala Ala Val Asp Met Phe Phe His Met Phe Lys Lys His
[3037] 195 200 205
[3038] Glu Cys Ala Ser Phe Arg Tyr Gly Thr Ile Val Ser Arg Phe Lys Asp
[3039] 210 215 220
[3040] Cys Ala Ala Leu Ala Thr Phe Gly His Leu Cys Lys Ile Thr Gly Met
[3041] 225 230 235 240

[3042] Ser Thr Glu Asp Val Thr Thr Trp Ile Leu Asn Arg Glu Val Ala Asp
[3043] 245 250 255
[3044] Glu Met Val Gln Met Met Leu Pro Gly Gln Glu Ile Asp Lys Ala Asp
[3045] 260 265 270
[3046] Ser Tyr Met Pro Tyr Leu Ile Asp Phe Gly Leu Ser Ser Lys Ser Pro
[3047] 275 280 285
[3048] Tyr Ser Ser Val Lys Asn Pro Ala Phe His Phe Trp Gly Gln Leu Thr
[3049] 290 295 300
[3050] Ala Leu Leu Leu Arg Ser Thr Arg Ala Arg Asn Ala Arg Gln Pro Asp
[3051] 305 310 315 320
[3052] Asp Ile Glu Tyr Thr Ser Leu Thr Thr Ala Gly Leu Leu Tyr Ala Tyr
[3053] 325 330 335
[3054] Ala Val Gly Ser Ser Ala Asp Leu Ala Gln Gln Phe Cys Val Gly Asp
[3055] 340 345 350
[3056] Asn Lys Tyr Thr Pro Asp Asp Ser Thr Gly Gly Leu Thr Thr Asn Ala
[3057] 355 360 365
[3058] Pro Pro Gln Gly Arg Asp Val Val Glu Trp Leu Gly Trp Phe Glu Asp
[3059] 370 375 380
[3060] Gln Asn Arg Lys Pro Thr Pro Asp Met Met Gln Tyr Ala Lys Arg Ala
[3061] 385 390 395 400
[3062] Val Met Ser Leu Gln Gly Leu Arg Glu Lys Thr Ile Gly Lys Tyr Ala
[3063] 405 410 415
[3064] Lys Ser Glu Phe Asp Lys
[3065] 420
[3066] <210> 61
[3067] <211> 265
[3068] <212> PRT
[3069] <213> Vesicular Stomatitis Virus
[3070] <400> 61
[3071] Met Asp Asn Leu Thr Lys Val Arg Glu Tyr Leu Lys Ser Tyr Ser Arg
[3072] 1 5 10 15
[3073] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3074] 20 25 30
[3075] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3076] 35 40 45
[3077] Thr Arg Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3078] 50 55 60
[3079] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Val Pro Asp Pro Glu
[3080] 65 70 75 80

[3081] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3082] 85 90 95
[3083] Asp Glu Asp Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3084] 100 105 110
[3085] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Leu Pro Glu
[3086] 115 120 125
[3087] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Leu Thr Ile Lys Ala
[3088] 130 135 140
[3089] Val Val Gln Ser Ala Lys His Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3090] 145 150 155 160
[3091] Ala Ser Gly Glu Gly Val Ile Ile Lys Lys Arg Gln Ile Thr Pro Asp
[3092] 165 170 175
[3093] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Tyr Gln Ser Glu
[3094] 180 185 190
[3095] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3096] 195 200 205
[3097] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3098] 210 215 220
[3099] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asn Gly Arg Met
[3100] 225 230 235 240
[3101] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3102] 245 250 255
[3103] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3104] 260 265
[3105] <210> 62
[3106] <211> 265
[3107] <212> PRT
[3108] <213> 人工序列(Artificial Sequence)
[3109] <400> 62
[3110] Met Asp Asn Leu Thr Lys Val Arg Glu Tyr Leu Lys Ser Tyr Ser Arg
[3111] 1 5 10 15
[3112] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3113] 20 25 30
[3114] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3115] 35 40 45
[3116] Thr Lys Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3117] 50 55 60
[3118] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Val Pro Asp Pro Glu
[3119] 65 70 75 80

[3120] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3121] 85 90 95
[3122] Asp Glu Asp Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3123] 100 105 110
[3124] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Leu Pro Glu
[3125] 115 120 125
[3126] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Leu Thr Ile Lys Ala
[3127] 130 135 140
[3128] Val Val Gln Ser Ala Lys His Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3129] 145 150 155 160
[3130] Ala Ser Gly Glu Gly Val Ile Ile Lys Lys Arg Gln Ile Thr Pro Asp
[3131] 165 170 175
[3132] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Tyr Gln Ser Glu
[3133] 180 185 190
[3134] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3135] 195 200 205
[3136] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3137] 210 215 220
[3138] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asn Gly Arg Met
[3139] 225 230 235 240
[3140] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3141] 245 250 255
[3142] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3143] 260 265
[3144] <210> 63
[3145] <211> 265
[3146] <212> PRT
[3147] <213> 人工序列(Artificial Sequence)
[3148] <400> 63
[3149] Met Asp Asn Leu Thr Lys Val Arg Glu Tyr Leu Lys Ser Tyr Ser Arg
[3150] 1 5 10 15
[3151] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3152] 20 25 30
[3153] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3154] 35 40 45
[3155] Thr Lys Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3156] 50 55 60
[3157] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Ala Pro Asp Pro Glu
[3158] 65 70 75 80

[3159] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3160] 85 90 95
[3161] Asp Glu Asp Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3162] 100 105 110
[3163] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Leu Pro Glu
[3164] 115 120 125
[3165] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Leu Thr Ile Lys Ala
[3166] 130 135 140
[3167] Val Val Gln Ser Ala Lys His Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3168] 145 150 155 160
[3169] Ala Ser Gly Glu Gly Val Ile Ile Lys Lys Arg Gln Ile Thr Pro Asp
[3170] 165 170 175
[3171] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Tyr Gln Ser Glu
[3172] 180 185 190
[3173] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3174] 195 200 205
[3175] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3176] 210 215 220
[3177] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asn Gly Arg Met
[3178] 225 230 235 240
[3179] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3180] 245 250 255
[3181] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3182] 260 265
[3183] <210> 64
[3184] <211> 265
[3185] <212> PRT
[3186] <213> 人工序列(Artificial Sequence)
[3187] <400> 64
[3188] Met Asp Asn Leu Thr Lys Val Arg Glu Tyr Leu Lys Ser Tyr Ser Arg
[3189] 1 5 10 15
[3190] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3191] 20 25 30
[3192] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3193] 35 40 45
[3194] Thr Lys Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3195] 50 55 60
[3196] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Ala Pro Asp Pro Glu
[3197] 65 70 75 80

[3198] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3199] 85 90 95
[3200] Asp Glu Glu Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3201] 100 105 110
[3202] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Leu Pro Glu
[3203] 115 120 125
[3204] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Leu Thr Ile Lys Ala
[3205] 130 135 140
[3206] Val Val Gln Ser Ala Lys His Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3207] 145 150 155 160
[3208] Ala Ser Gly Glu Gly Val Ile Ile Lys Lys Arg Gln Ile Thr Pro Asp
[3209] 165 170 175
[3210] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Tyr Gln Ser Glu
[3211] 180 185 190
[3212] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3213] 195 200 205
[3214] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3215] 210 215 220
[3216] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asn Gly Arg Met
[3217] 225 230 235 240
[3218] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3219] 245 250 255
[3220] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3221] 260 265
[3222] <210> 65
[3223] <211> 265
[3224] <212> PRT
[3225] <213> 人工序列(Artificial Sequence)
[3226] <400> 65
[3227] Met Asp Asn Leu Thr Lys Val Arg Glu Tyr Leu Lys Ser Tyr Ser Arg
[3228] 1 5 10 15
[3229] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3230] 20 25 30
[3231] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3232] 35 40 45
[3233] Thr Lys Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3234] 50 55 60
[3235] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Ala Pro Asp Pro Glu
[3236] 65 70 75 80

[3237] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3238] 85 90 95
[3239] Asp Glu Glu Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3240] 100 105 110
[3241] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Ser Pro Glu
[3242] 115 120 125
[3243] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Leu Thr Ile Lys Ala
[3244] 130 135 140
[3245] Val Val Gln Ser Ala Lys His Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3246] 145 150 155 160
[3247] Ala Ser Gly Glu Gly Val Ile Ile Lys Lys Arg Gln Ile Thr Pro Asp
[3248] 165 170 175
[3249] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Tyr Gln Ser Glu
[3250] 180 185 190
[3251] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3252] 195 200 205
[3253] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3254] 210 215 220
[3255] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asn Gly Arg Met
[3256] 225 230 235 240
[3257] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3258] 245 250 255
[3259] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3260] 260 265
[3261] <210> 66
[3262] <211> 265
[3263] <212> PRT
[3264] <213> 人工序列(Artificial Sequence)
[3265] <400> 66
[3266] Met Asp Asn Leu Thr Lys Val Arg Glu Tyr Leu Lys Ser Tyr Ser Arg
[3267] 1 5 10 15
[3268] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3269] 20 25 30
[3270] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3271] 35 40 45
[3272] Thr Lys Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3273] 50 55 60
[3274] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Ala Pro Asp Pro Glu
[3275] 65 70 75 80

[3276] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3277] 85 90 95
[3278] Asp Glu Glu Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3279] 100 105 110
[3280] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Ser Pro Glu
[3281] 115 120 125
[3282] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Ser Thr Ile Lys Ala
[3283] 130 135 140
[3284] Val Val Gln Ser Ala Lys His Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3285] 145 150 155 160
[3286] Ala Ser Gly Glu Gly Val Ile Ile Lys Lys Arg Gln Ile Thr Pro Asp
[3287] 165 170 175
[3288] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Tyr Gln Ser Glu
[3289] 180 185 190
[3290] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3291] 195 200 205
[3292] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3293] 210 215 220
[3294] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asn Gly Arg Met
[3295] 225 230 235 240
[3296] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3297] 245 250 255
[3298] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3299] 260 265
[3300] <210> 67
[3301] <211> 265
[3302] <212> PRT
[3303] <213> 人工序列(Artificial Sequence)
[3304] <400> 67
[3305] Met Asp Asn Leu Thr Lys Val Arg Glu Tyr Leu Lys Ser Tyr Ser Arg
[3306] 1 5 10 15
[3307] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3308] 20 25 30
[3309] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3310] 35 40 45
[3311] Thr Lys Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3312] 50 55 60
[3313] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Ala Pro Asp Pro Glu
[3314] 65 70 75 80

[3315] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3316] 85 90 95
[3317] Asp Glu Glu Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3318] 100 105 110
[3319] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Ser Pro Glu
[3320] 115 120 125
[3321] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Ser Thr Ile Lys Ala
[3322] 130 135 140
[3323] Val Val Gln Ser Ala Lys Tyr Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3324] 145 150 155 160
[3325] Ala Ser Gly Glu Gly Val Ile Ile Lys Lys Arg Gln Ile Thr Pro Asp
[3326] 165 170 175
[3327] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Tyr Gln Ser Glu
[3328] 180 185 190
[3329] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3330] 195 200 205
[3331] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3332] 210 215 220
[3333] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asn Gly Arg Met
[3334] 225 230 235 240
[3335] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3336] 245 250 255
[3337] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3338] 260 265
[3339] <210> 68
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[3346] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3347] 20 25 30
[3348] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3349] 35 40 45
[3350] Thr Lys Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3351] 50 55 60
[3352] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Ala Pro Asp Pro Glu
[3353] 65 70 75 80

[3354] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3355] 85 90 95
[3356] Asp Glu Glu Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3357] 100 105 110
[3358] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Ser Pro Glu
[3359] 115 120 125
[3360] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Ser Thr Ile Lys Ala
[3361] 130 135 140
[3362] Val Val Gln Ser Ala Lys Tyr Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3363] 145 150 155 160
[3364] Ala Ser Gly Glu Gly Val Ile Met Lys Lys Arg Gln Ile Thr Pro Asp
[3365] 165 170 175
[3366] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Tyr Gln Ser Glu
[3367] 180 185 190
[3368] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3369] 195 200 205
[3370] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3371] 210 215 220
[3372] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asn Gly Arg Met
[3373] 225 230 235 240
[3374] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3375] 245 250 255
[3376] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3377] 260 265
[3378] <210> 69
[3379] <211> 265
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[3385] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
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[3387] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3388] 35 40 45
[3389] Thr Lys Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3390] 50 55 60
[3391] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Ala Pro Asp Pro Glu
[3392] 65 70 75 80

[3393] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3394] 85 90 95
[3395] Asp Glu Glu Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3396] 100 105 110
[3397] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Ser Pro Glu
[3398] 115 120 125
[3399] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Ser Thr Ile Lys Ala
[3400] 130 135 140
[3401] Val Val Gln Ser Ala Lys Tyr Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3402] 145 150 155 160
[3403] Ala Ser Gly Glu Gly Val Ile Met Lys Glu Arg Gln Ile Thr Pro Asp
[3404] 165 170 175
[3405] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Tyr Gln Ser Glu
[3406] 180 185 190
[3407] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3408] 195 200 205
[3409] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3410] 210 215 220
[3411] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asn Gly Arg Met
[3412] 225 230 235 240
[3413] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3414] 245 250 255
[3415] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3416] 260 265
[3417] <210> 70
[3418] <211> 265
[3419] <212> PRT
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[3423] 1 5 10 15
[3424] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3425] 20 25 30
[3426] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3427] 35 40 45
[3428] Thr Lys Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3429] 50 55 60
[3430] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Ala Pro Asp Pro Glu
[3431] 65 70 75 80

[3432] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3433] 85 90 95
[3434] Asp Glu Glu Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3435] 100 105 110
[3436] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Ser Pro Glu
[3437] 115 120 125
[3438] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Ser Thr Ile Lys Ala
[3439] 130 135 140
[3440] Val Val Gln Ser Ala Lys Tyr Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3441] 145 150 155 160
[3442] Ala Ser Gly Glu Gly Val Ile Met Lys Glu Arg Gln Ile Thr Pro Asp
[3443] 165 170 175
[3444] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Ser Gln Ser Glu
[3445] 180 185 190
[3446] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3447] 195 200 205
[3448] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3449] 210 215 220
[3450] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asn Gly Arg Met
[3451] 225 230 235 240
[3452] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3453] 245 250 255
[3454] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3455] 260 265
[3456] <210> 71
[3457] <211> 265
[3458] <212> PRT
[3459] <213> 人工序列(Artificial Sequence)
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[3462] 1 5 10 15
[3463] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3464] 20 25 30
[3465] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3466] 35 40 45
[3467] Thr Lys Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3468] 50 55 60
[3469] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Ala Pro Asp Pro Glu
[3470] 65 70 75 80

[3471] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3472] 85 90 95
[3473] Asp Glu Glu Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3474] 100 105 110
[3475] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Ser Pro Glu
[3476] 115 120 125
[3477] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Ser Thr Ile Lys Ala
[3478] 130 135 140
[3479] Val Val Gln Ser Ala Lys Tyr Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3480] 145 150 155 160
[3481] Ala Ser Gly Glu Gly Val Ile Met Lys Glu Arg Gln Ile Thr Pro Asp
[3482] 165 170 175
[3483] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Ser Gln Ser Glu
[3484] 180 185 190
[3485] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3486] 195 200 205
[3487] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3488] 210 215 220
[3489] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asp Gly Arg Met
[3490] 225 230 235 240
[3491] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3492] 245 250 255
[3493] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3494] 260 265
[3495] <210> 72
[3496] <211> 264
[3497] <212> PRT
[3498] <213> 人工序列(Artificial Sequence)
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[3502] Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala Glu
[3503] 20 25 30
[3504] Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His Thr
[3505] 35 40 45
[3506] Arg Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser Glu
[3507] 50 55 60
[3508] Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Ala Pro Asp Pro Glu Ala
[3509] 65 70 75 80

[3510] Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala Asp
[3511] 85 90 95
[3512] Glu Glu Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu Leu
[3513] 100 105 110
[3514] Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Ser Pro Glu Gly
[3515] 115 120 125
[3516] Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Ser Thr Ile Lys Ala Val
[3517] 130 135 140
[3518] Val Gln Ser Ala Lys Tyr Trp Asn Leu Ala Glu Cys Thr Phe Glu Ala
[3519] 145 150 155 160
[3520] Ser Gly Glu Gly Val Ile Met Lys Glu Arg Gln Ile Thr Pro Asp Val
[3521] 165 170 175
[3522] Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Ser Gln Ser Glu Ala
[3523] 180 185 190
[3524] Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln Pro
[3525] 195 200 205
[3526] Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu Phe
[3527] 210 215 220
[3528] Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asp Gly Arg Met Ser
[3529] 225 230 235 240
[3530] His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr Asn
[3531] 245 250 255
[3532] Gln Ala Arg Val Lys Tyr Ser Leu
[3533] 260
[3534] <210> 73
[3535] <211> 265
[3536] <212> PRT
[3537] <213> 人工序列(Artificial Sequence)
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[3540] 1 5 10 15
[3541] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3542] 20 25 30
[3543] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3544] 35 40 45
[3545] Thr Arg Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3546] 50 55 60
[3547] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Val Pro Asp Pro Glu
[3548] 65 70 75 80

[3549] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3550] 85 90 95
[3551] Asp Glu Glu Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3552] 100 105 110
[3553] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Ser Pro Glu
[3554] 115 120 125
[3555] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Ser Thr Ile Lys Ala
[3556] 130 135 140
[3557] Val Val Gln Ser Ala Lys Tyr Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3558] 145 150 155 160
[3559] Ala Ser Gly Glu Gly Val Ile Met Lys Glu Arg Gln Ile Thr Pro Asp
[3560] 165 170 175
[3561] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Ser Gln Ser Glu
[3562] 180 185 190
[3563] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3564] 195 200 205
[3565] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3566] 210 215 220
[3567] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asp Gly Arg Met
[3568] 225 230 235 240
[3569] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3570] 245 250 255
[3571] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3572] 260 265
[3573] <210> 74
[3574] <211> 265
[3575] <212> PRT
[3576] <213> 人工序列(Artificial Sequence)
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[3578] Met Asp Asn Leu Thr Lys Val Arg Glu Tyr Leu Lys Ser Tyr Ser Arg
[3579] 1 5 10 15
[3580] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3581] 20 25 30
[3582] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3583] 35 40 45
[3584] Thr Arg Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3585] 50 55 60
[3586] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Val Pro Asp Pro Glu
[3587] 65 70 75 80

[3588] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3589] 85 90 95
[3590] Asp Glu Asp Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3591] 100 105 110
[3592] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Ser Pro Glu
[3593] 115 120 125
[3594] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Ser Thr Ile Lys Ala
[3595] 130 135 140
[3596] Val Val Gln Ser Ala Lys Tyr Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3597] 145 150 155 160
[3598] Ala Ser Gly Glu Gly Val Ile Met Lys Glu Arg Gln Ile Thr Pro Asp
[3599] 165 170 175
[3600] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Ser Gln Ser Glu
[3601] 180 185 190
[3602] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3603] 195 200 205
[3604] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3605] 210 215 220
[3606] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asp Gly Arg Met
[3607] 225 230 235 240
[3608] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3609] 245 250 255
[3610] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3611] 260 265
[3612] <210> 75
[3613] <211> 265
[3614] <212> PRT
[3615] <213> 人工序列(Artificial Sequence)
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[3618] 1 5 10 15
[3619] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3620] 20 25 30
[3621] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3622] 35 40 45
[3623] Thr Arg Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3624] 50 55 60
[3625] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Val Pro Asp Pro Glu
[3626] 65 70 75 80

[3627] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3628] 85 90 95
[3629] Asp Glu Asp Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3630] 100 105 110
[3631] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Leu Pro Glu
[3632] 115 120 125
[3633] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Ser Thr Ile Lys Ala
[3634] 130 135 140
[3635] Val Val Gln Ser Ala Lys Tyr Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3636] 145 150 155 160
[3637] Ala Ser Gly Glu Gly Val Ile Met Lys Glu Arg Gln Ile Thr Pro Asp
[3638] 165 170 175
[3639] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Ser Gln Ser Glu
[3640] 180 185 190
[3641] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3642] 195 200 205
[3643] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3644] 210 215 220
[3645] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asp Gly Arg Met
[3646] 225 230 235 240
[3647] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3648] 245 250 255
[3649] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3650] 260 265
[3651] <210> 76
[3652] <211> 265
[3653] <212> PRT
[3654] <213> 人工序列(Artificial Sequence)
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[3656] Met Asp Asn Leu Thr Lys Val Arg Glu Tyr Leu Lys Ser Tyr Ser Arg
[3657] 1 5 10 15
[3658] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3659] 20 25 30
[3660] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3661] 35 40 45
[3662] Thr Arg Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3663] 50 55 60
[3664] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Val Pro Asp Pro Glu
[3665] 65 70 75 80

[3666] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3667] 85 90 95
[3668] Asp Glu Asp Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3669] 100 105 110
[3670] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Leu Pro Glu
[3671] 115 120 125
[3672] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Leu Thr Ile Lys Ala
[3673] 130 135 140
[3674] Val Val Gln Ser Ala Lys Tyr Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3675] 145 150 155 160
[3676] Ala Ser Gly Glu Gly Val Ile Met Lys Glu Arg Gln Ile Thr Pro Asp
[3677] 165 170 175
[3678] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Ser Gln Ser Glu
[3679] 180 185 190
[3680] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3681] 195 200 205
[3682] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3683] 210 215 220
[3684] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asp Gly Arg Met
[3685] 225 230 235 240
[3686] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3687] 245 250 255
[3688] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3689] 260 265
[3690] <210> 77
[3691] <211> 265
[3692] <212> PRT
[3693] <213> 人工序列(Artificial Sequence)
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[3696] 1 5 10 15
[3697] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3698] 20 25 30
[3699] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3700] 35 40 45
[3701] Thr Arg Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3702] 50 55 60
[3703] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Val Pro Asp Pro Glu
[3704] 65 70 75 80

[3705] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3706] 85 90 95
[3707] Asp Glu Asp Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3708] 100 105 110
[3709] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Leu Pro Glu
[3710] 115 120 125
[3711] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Leu Thr Ile Lys Ala
[3712] 130 135 140
[3713] Val Val Gln Ser Ala Lys His Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3714] 145 150 155 160
[3715] Ala Ser Gly Glu Gly Val Ile Met Lys Glu Arg Gln Ile Thr Pro Asp
[3716] 165 170 175
[3717] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Ser Gln Ser Glu
[3718] 180 185 190
[3719] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3720] 195 200 205
[3721] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3722] 210 215 220
[3723] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asp Gly Arg Met
[3724] 225 230 235 240
[3725] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3726] 245 250 255
[3727] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3728] 260 265
[3729] <210> 78
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[3732] <213> 人工序列(Artificial Sequence)
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[3734] Met Asp Asn Leu Thr Lys Val Arg Glu Tyr Leu Lys Ser Tyr Ser Arg
[3735] 1 5 10 15
[3736] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3737] 20 25 30
[3738] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3739] 35 40 45
[3740] Thr Arg Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3741] 50 55 60
[3742] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Val Pro Asp Pro Glu
[3743] 65 70 75 80

[3744] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3745] 85 90 95
[3746] Asp Glu Asp Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3747] 100 105 110
[3748] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Leu Pro Glu
[3749] 115 120 125
[3750] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Leu Thr Ile Lys Ala
[3751] 130 135 140
[3752] Val Val Gln Ser Ala Lys His Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3753] 145 150 155 160
[3754] Ala Ser Gly Glu Gly Val Ile Ile Lys Glu Arg Gln Ile Thr Pro Asp
[3755] 165 170 175
[3756] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Ser Gln Ser Glu
[3757] 180 185 190
[3758] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3759] 195 200 205
[3760] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3761] 210 215 220
[3762] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asp Gly Arg Met
[3763] 225 230 235 240
[3764] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3765] 245 250 255
[3766] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3767] 260 265
[3768] <210> 79
[3769] <211> 265
[3770] <212> PRT
[3771] <213> 人工序列(Artificial Sequence)
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[3773] Met Asp Asn Leu Thr Lys Val Arg Glu Tyr Leu Lys Ser Tyr Ser Arg
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[3775] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3776] 20 25 30
[3777] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3778] 35 40 45
[3779] Thr Arg Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
[3780] 50 55 60
[3781] Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Val Pro Asp Pro Glu
[3782] 65 70 75 80

[3783] Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
[3784] 85 90 95
[3785] Asp Glu Asp Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
[3786] 100 105 110
[3787] Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Leu Pro Glu
[3788] 115 120 125
[3789] Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Leu Thr Ile Lys Ala
[3790] 130 135 140
[3791] Val Val Gln Ser Ala Lys His Trp Asn Leu Ala Glu Cys Thr Phe Glu
[3792] 145 150 155 160
[3793] Ala Ser Gly Glu Gly Val Ile Ile Lys Lys Arg Gln Ile Thr Pro Asp
[3794] 165 170 175
[3795] Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Ser Gln Ser Glu
[3796] 180 185 190
[3797] Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
[3798] 195 200 205
[3799] Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
[3800] 210 215 220
[3801] Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asp Gly Arg Met
[3802] 225 230 235 240
[3803] Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
[3804] 245 250 255
[3805] Asn Gln Ala Arg Val Lys Tyr Ser Leu
[3806] 260 265
[3807] <210> 80
[3808] <211> 265
[3809] <212> PRT
[3810] <213> 人工序列(Artificial Sequence)
[3811] <400> 80
[3812] Met Asp Asn Leu Thr Lys Val Arg Glu Tyr Leu Lys Ser Tyr Ser Arg
[3813] 1 5 10 15
[3814] Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
[3815] 20 25 30
[3816] Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
[3817] 35 40 45
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[3819] 50 55 60
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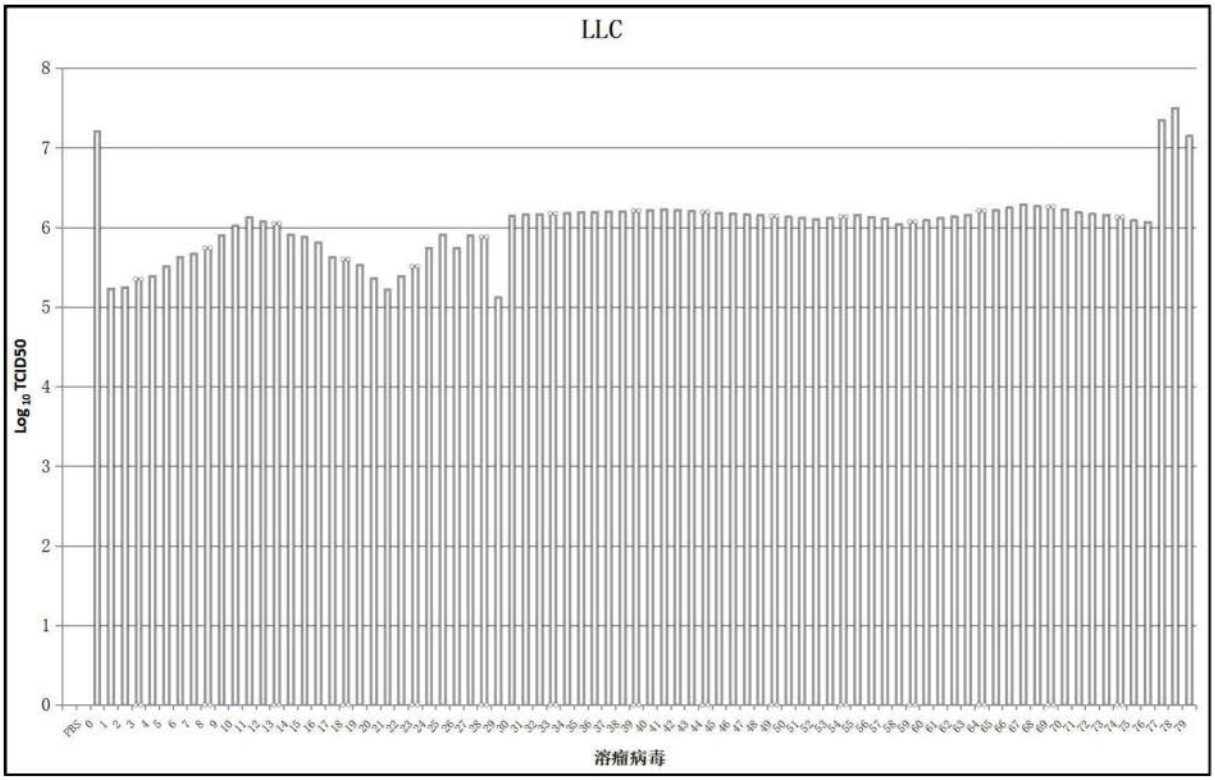


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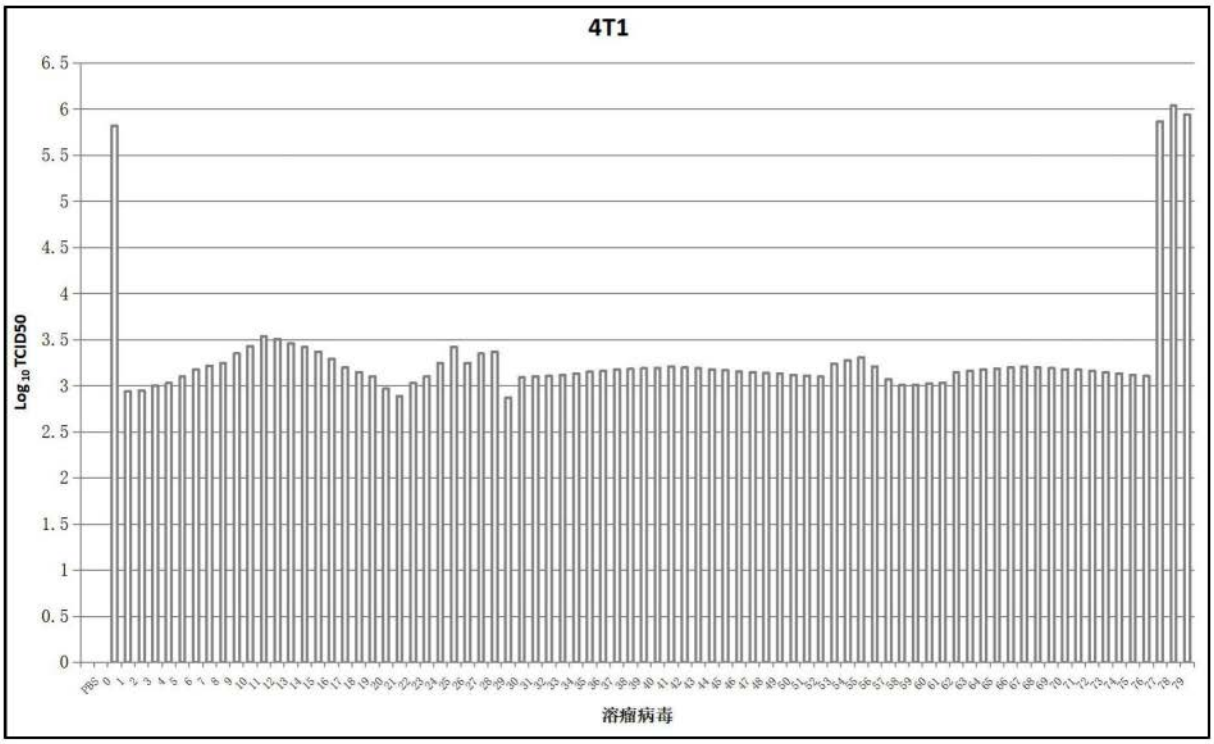


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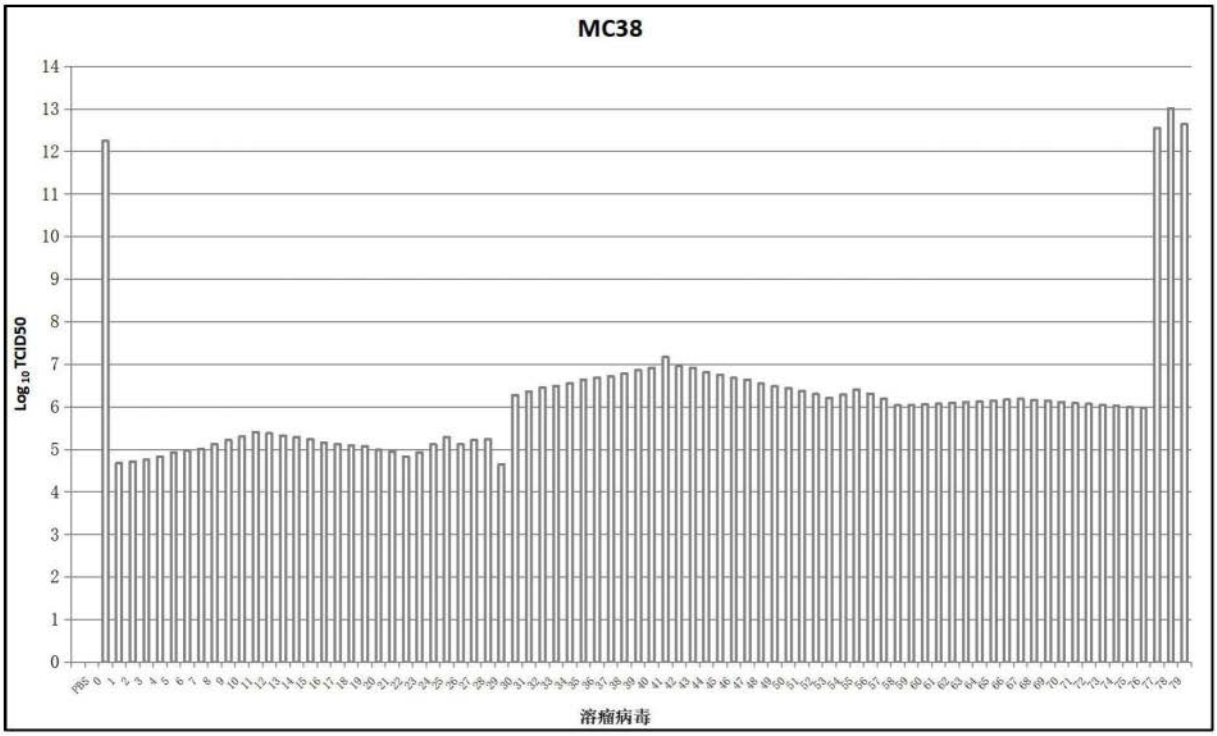


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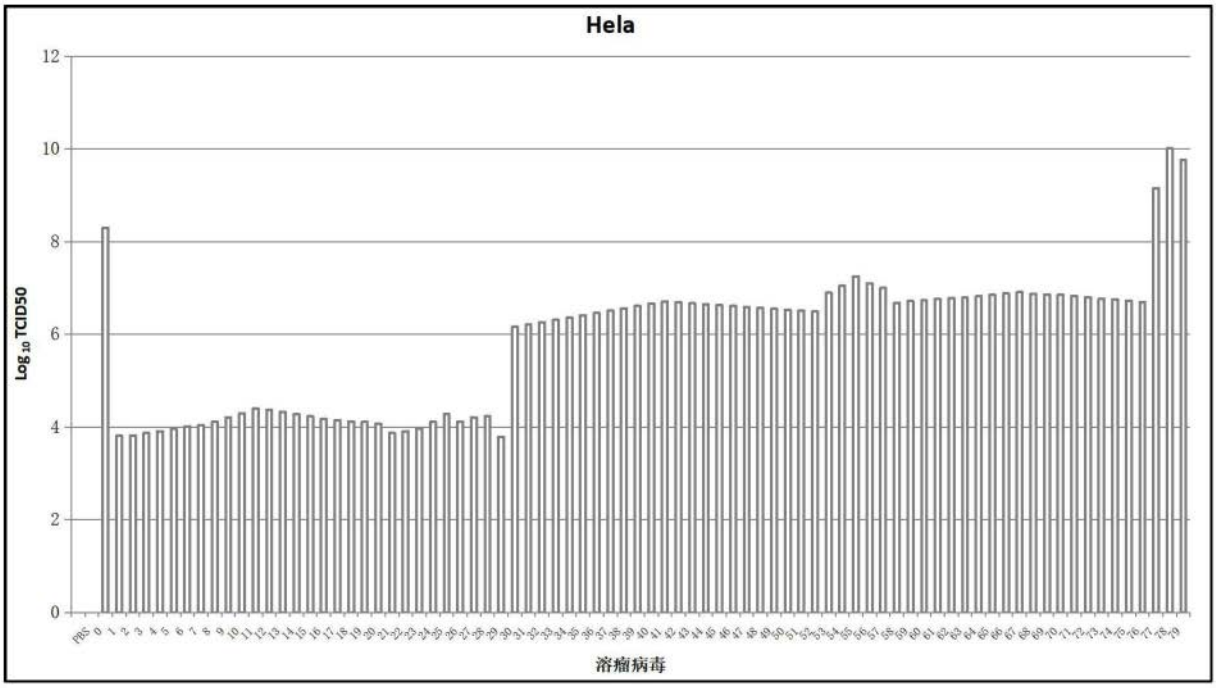


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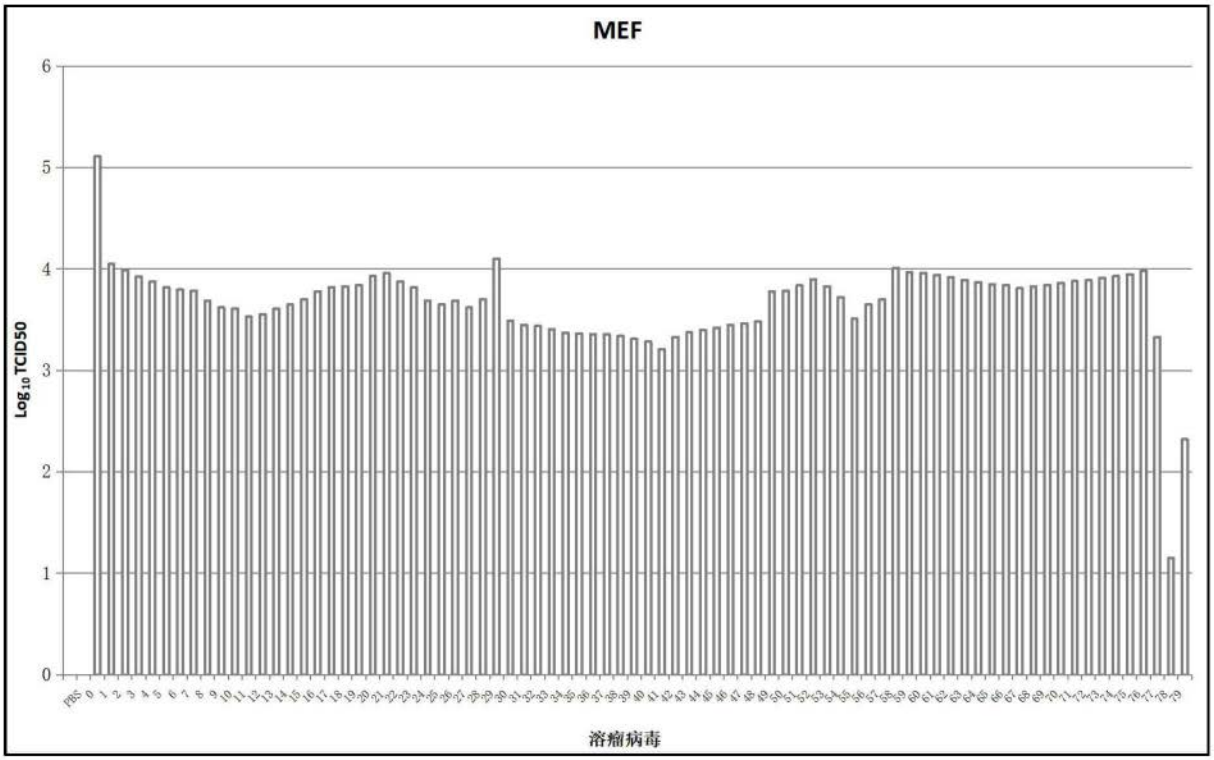


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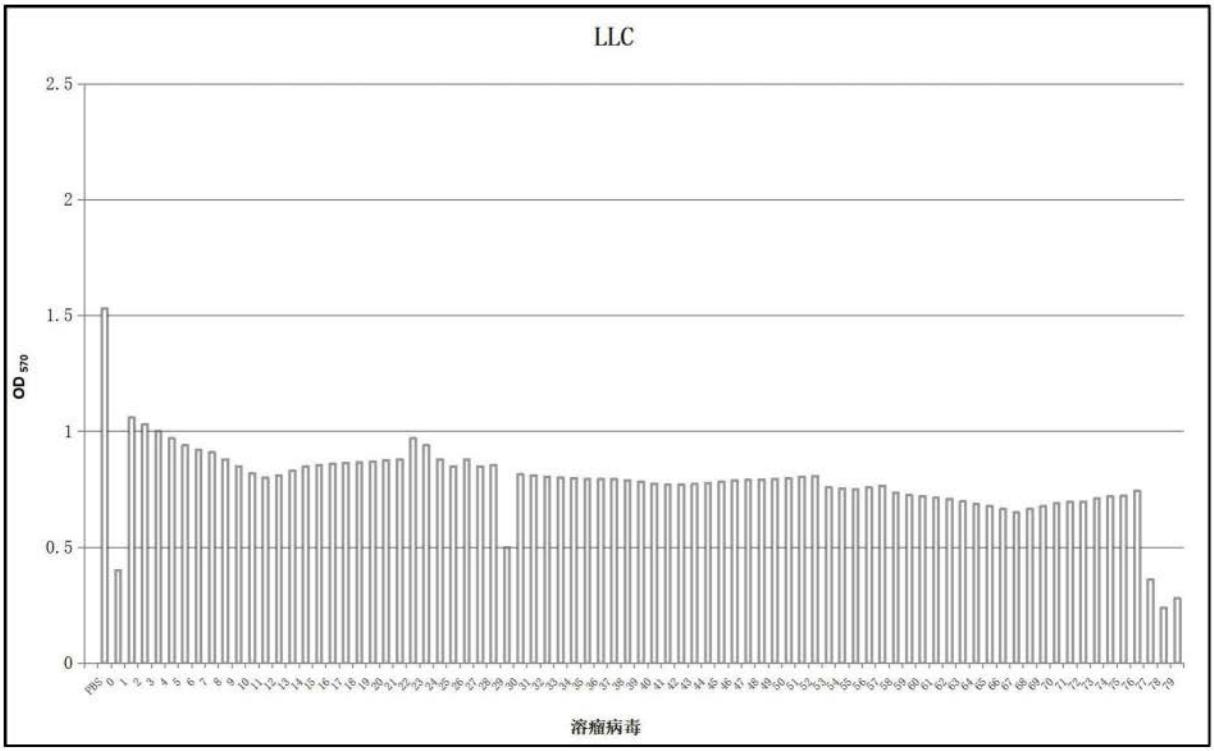


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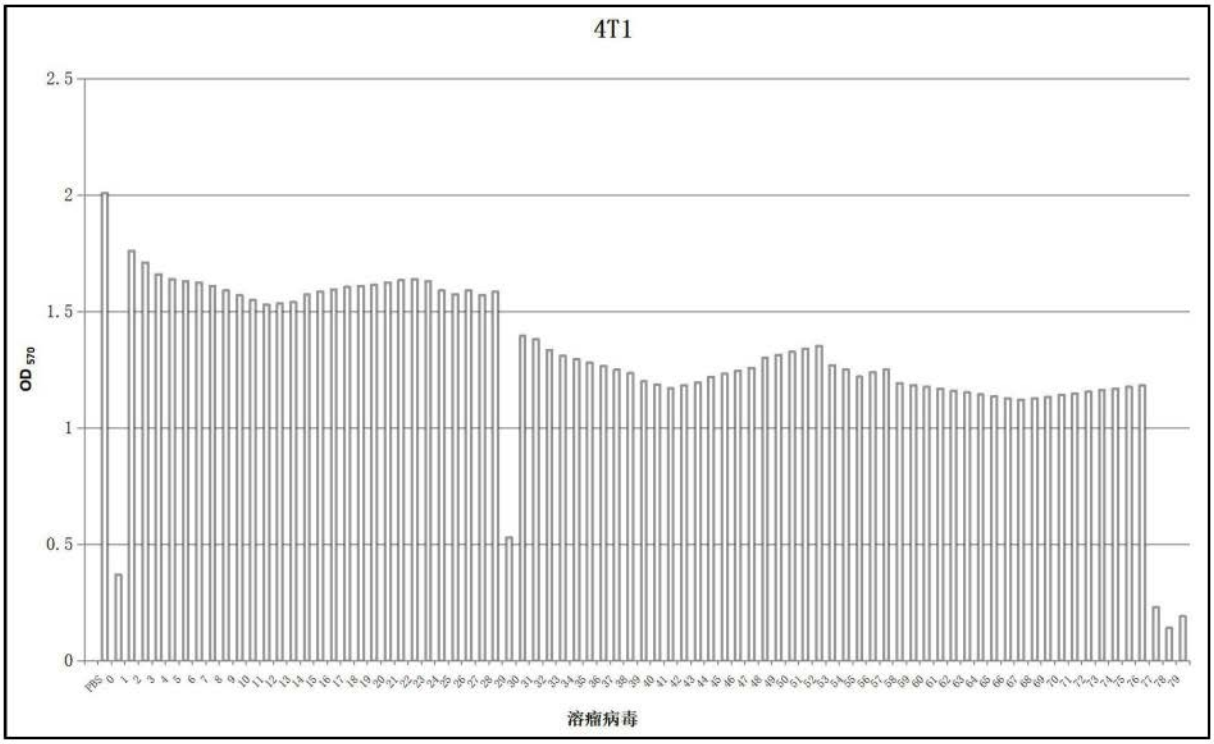

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溶瘤病毒

图7

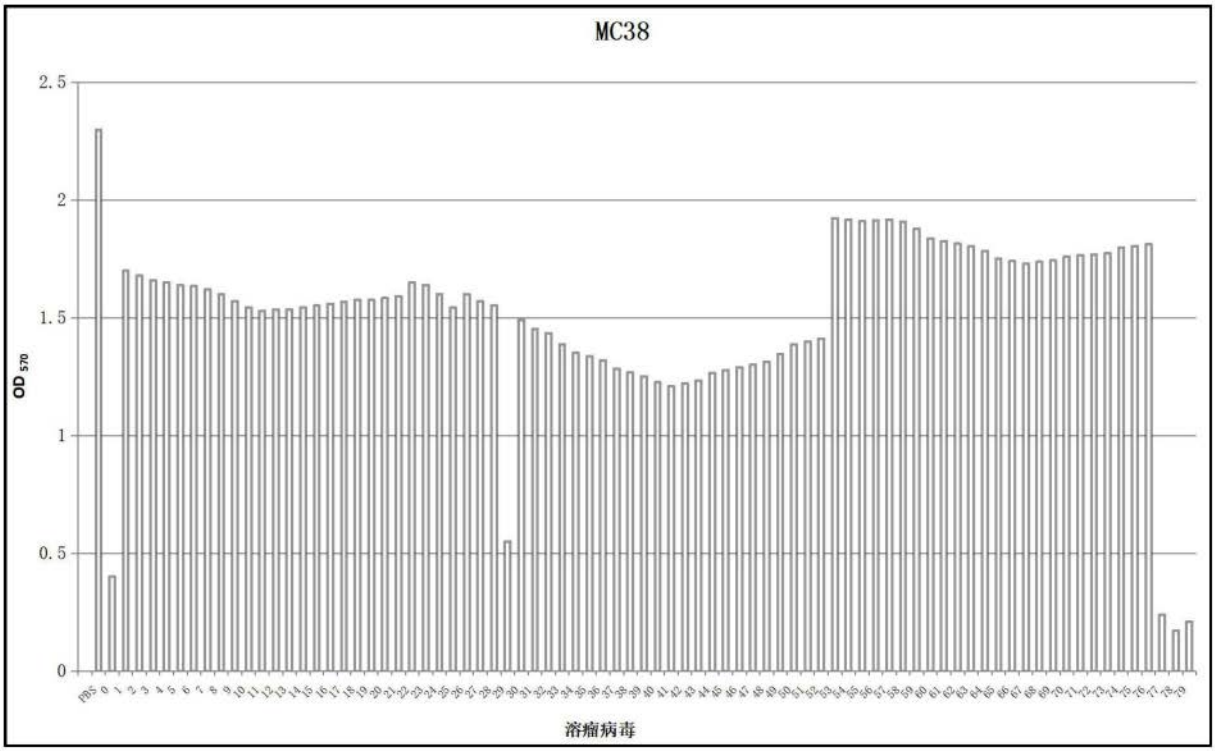

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溶瘤病毒

图8

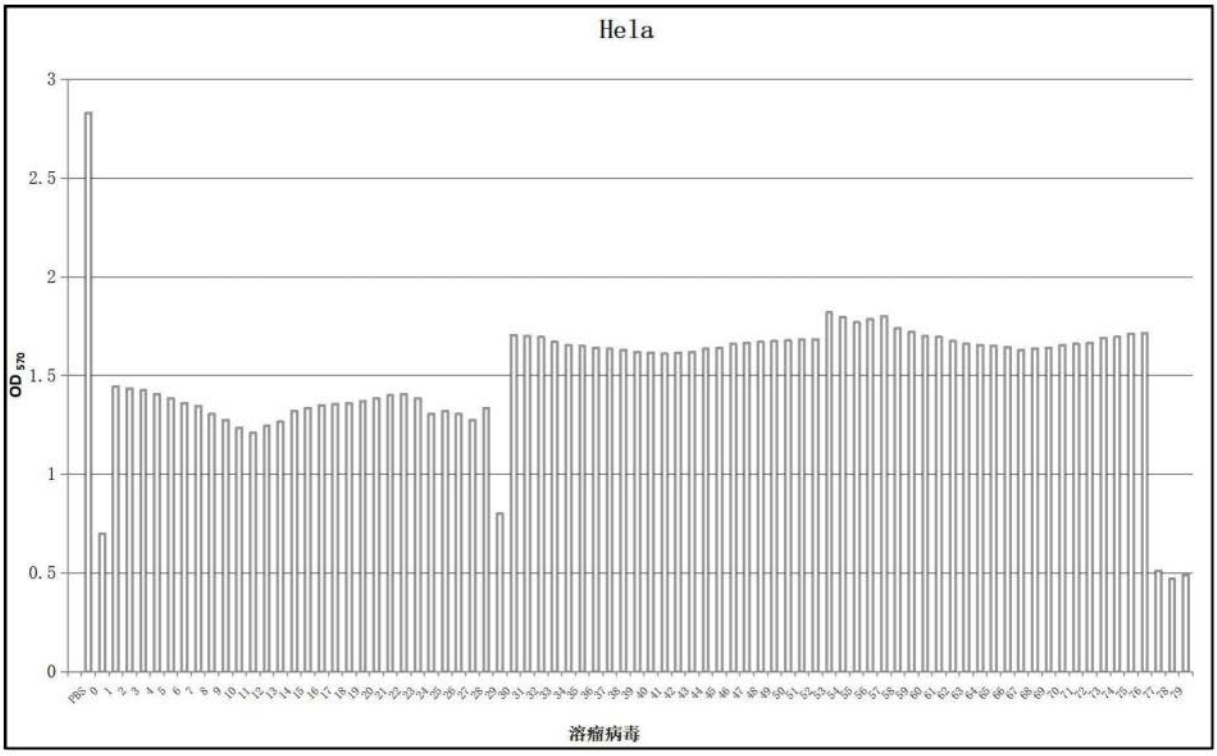


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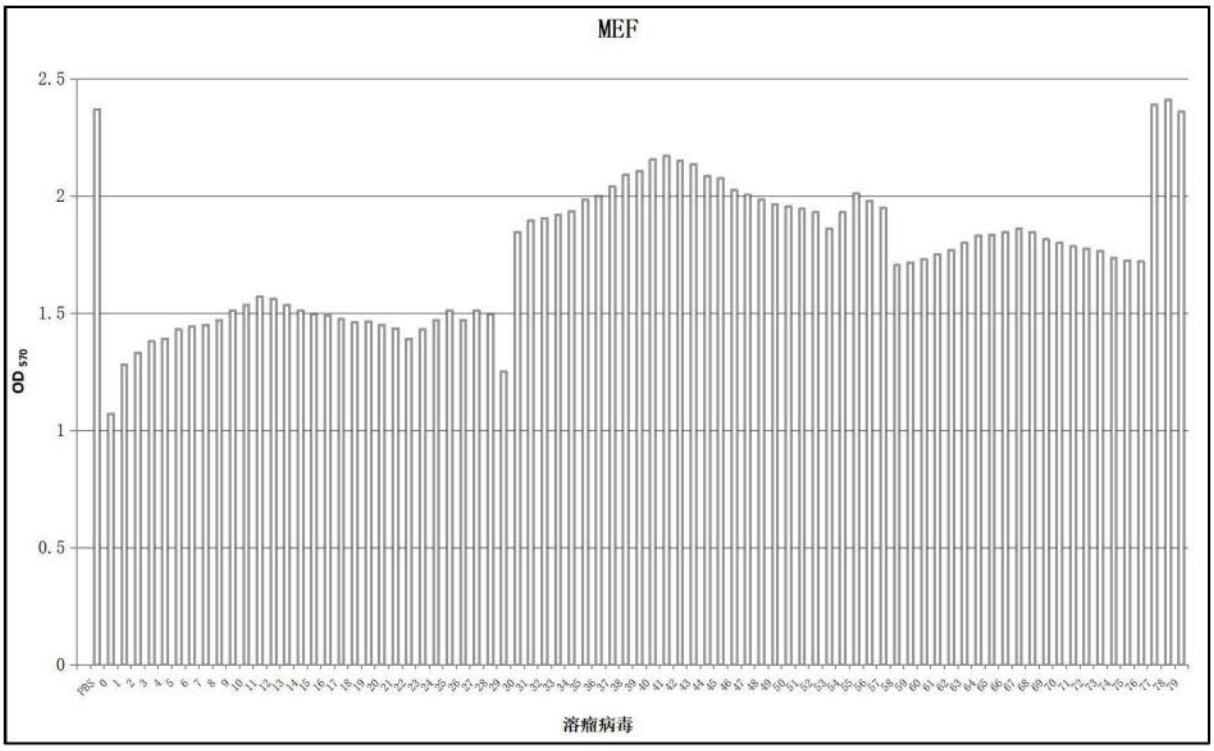


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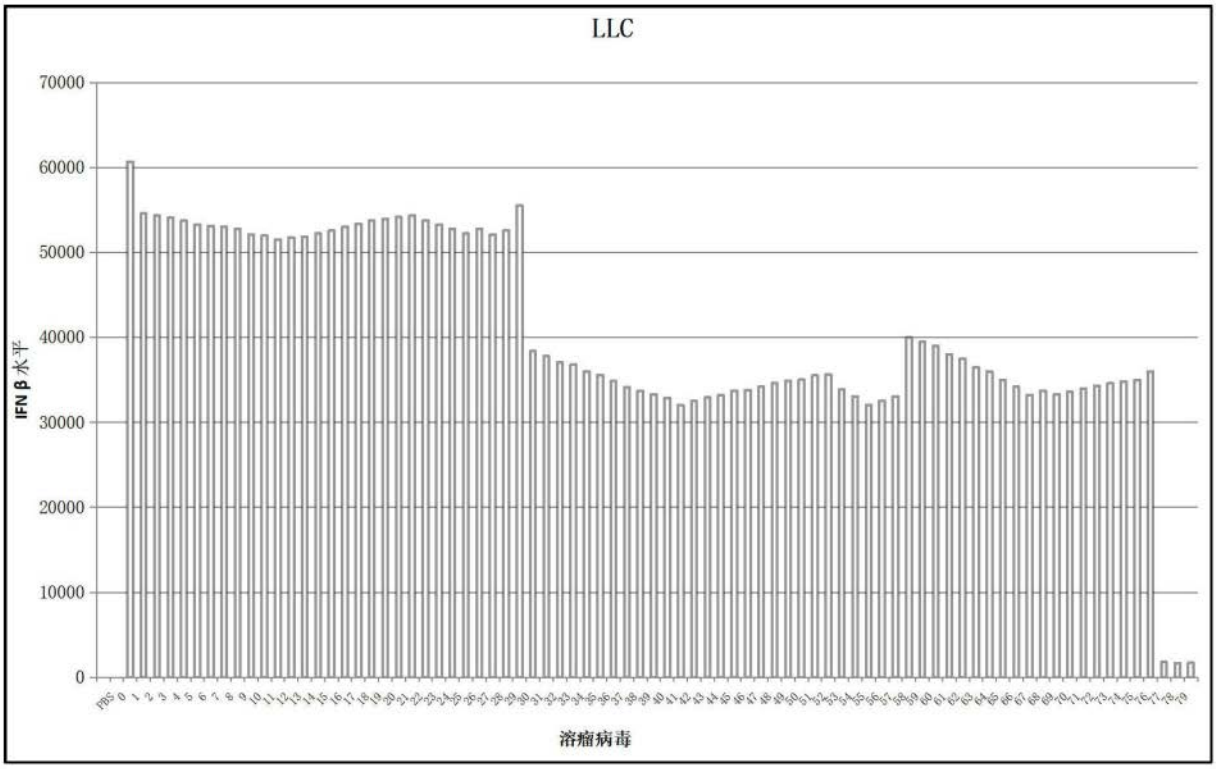

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20000
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IFN β 水平
溶瘤病毒

图11

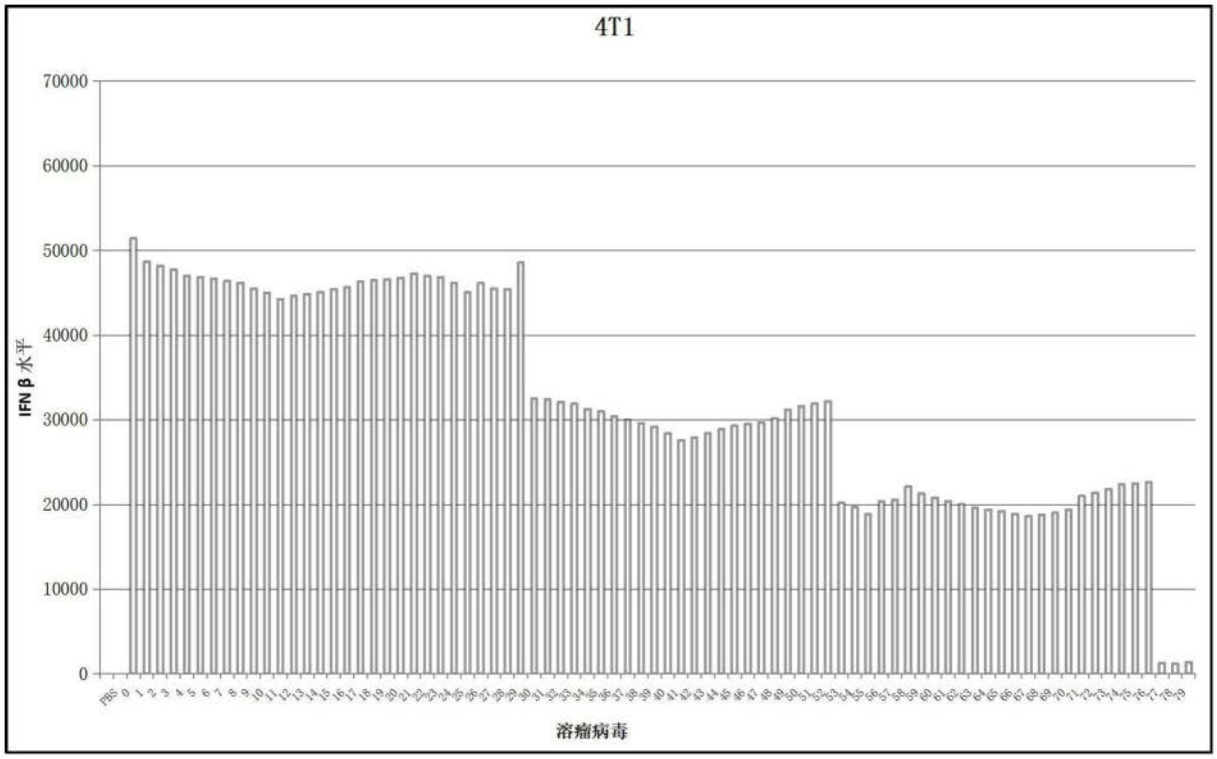

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溶瘤病毒

图12

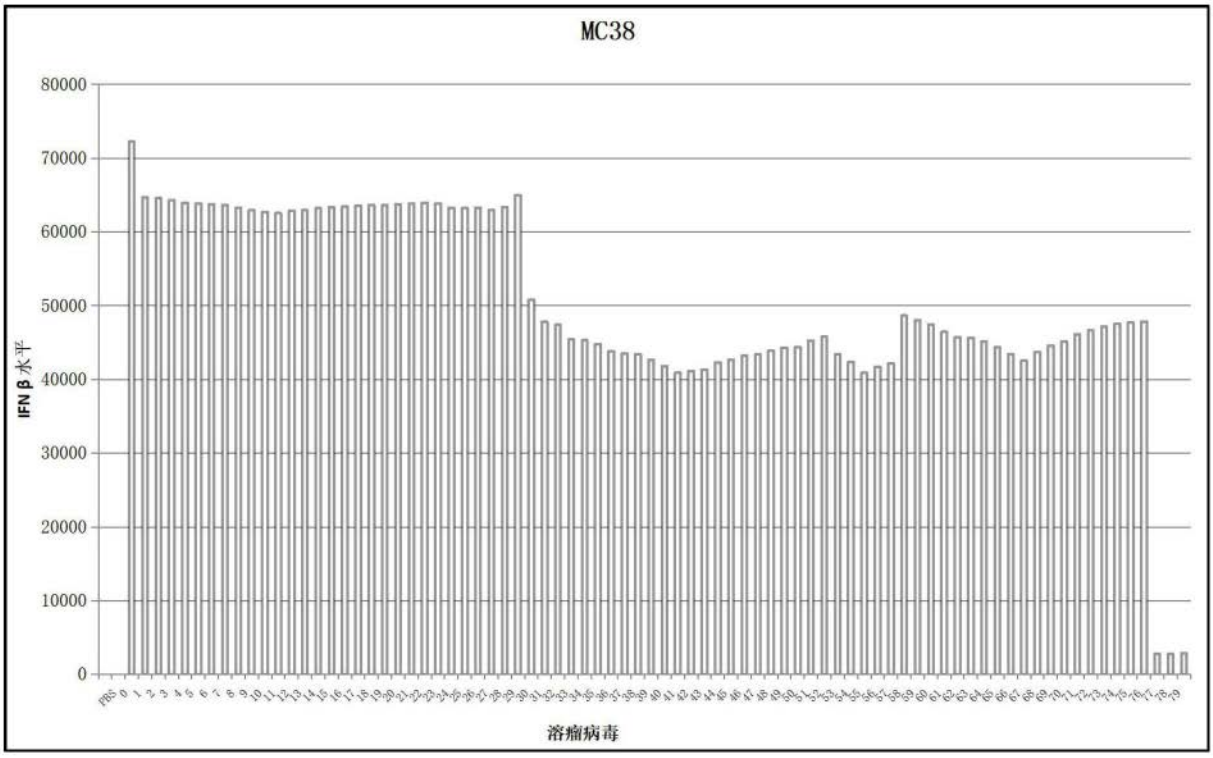

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20000
10000
0
PBS
溶瘤病毒

图13

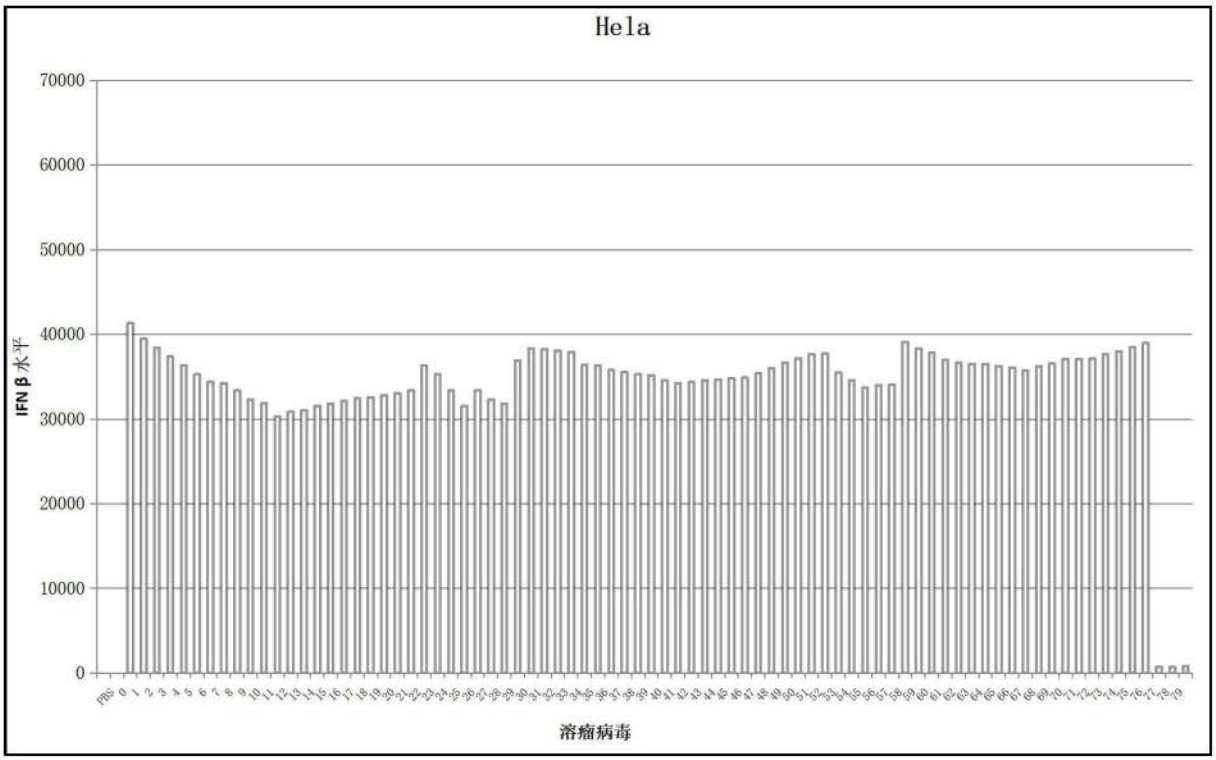

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PBS
溶瘤病毒

图14

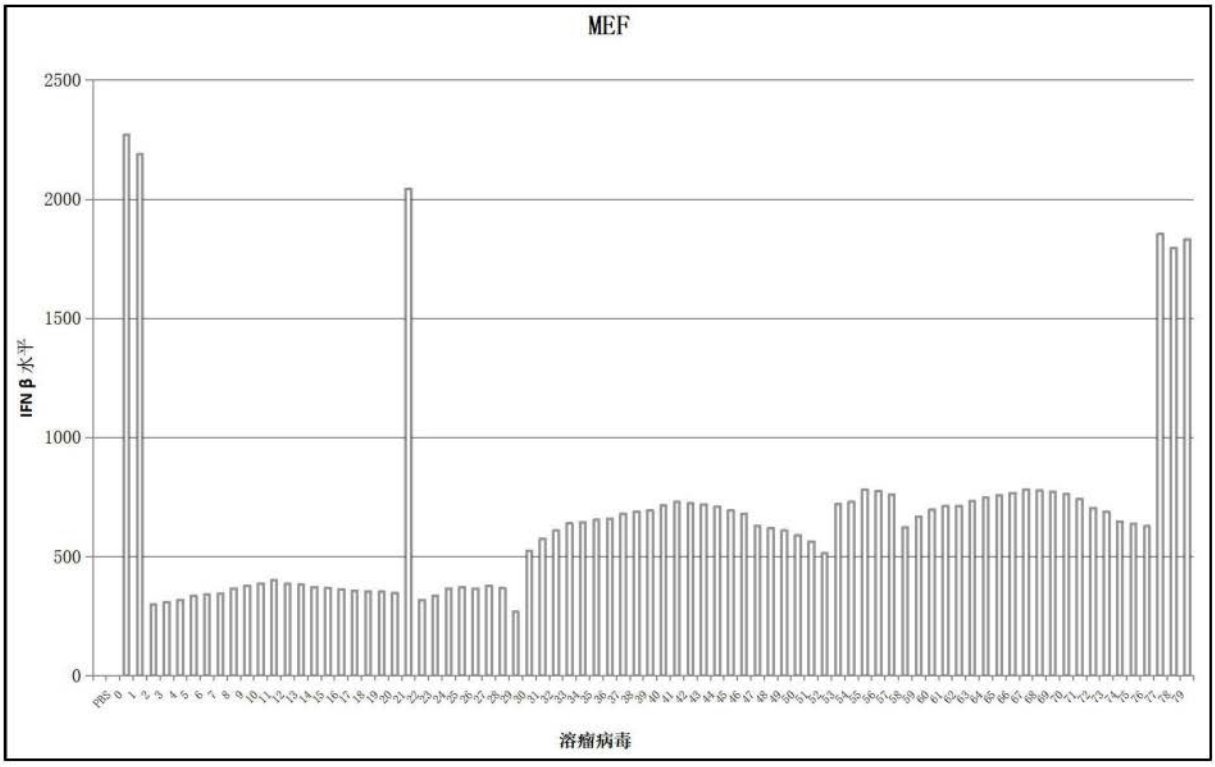

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IFN β 水平
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溶瘤病毒

图15