(19)国家知识产权局

(12)发明专利

(10)授权公告号 CN 114672516 B
(45)授权公告日 2024.11.26

(21)申请号 202210504372.2
(22)申请日 2017.07.27
(65)同一申请的已公布的文献号
申请公布号 CN 114672516 A
(43)申请公布日 2022.06.28
(30)优先权数据
62/368,929 2016.07.29 US
(62)分案原申请数据
201780050806.3 2017.07.27
(73)专利权人 加利福尼亚大学董事会
地址 美国加利福尼亚
专利权人 宾夕法尼亚州大学理事会
(72)发明人 D·V·莎菲尔 J·G·弗兰纳里
W·A·贝尔特兰 L·C·拜内
M·菲泽尔
(74)专利代理机构 中国贸促会专利商标事务所有限公司 11038
专利代理师 陈晓娜
(51)Int.Cl.
C12N 15/864(2006.01)
C12N 7/01(2006.01)
C12N 15/35(2006.01)
C07K 14/015(2006.01)
A61K 48/00(2006.01)
A61P 27/02(2006.01)
A61P 27/06(2006.01)
C12R 1/93(2006.01)
(56)对比文件
CN 103561774 A,2014.02.05
CN 105330732 A,2016.02.17
审查员 颜泉梅

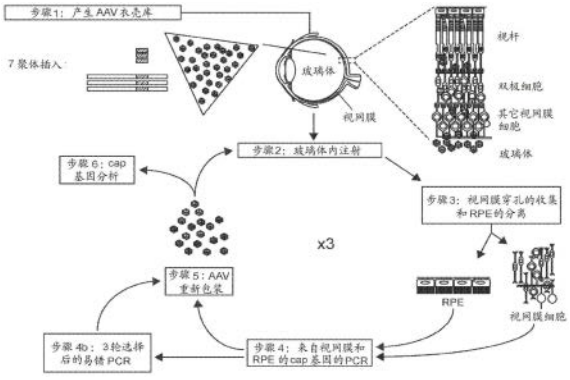
权利要求书2页 说明书37页
序列表103页 附图33页

(54)发明名称

具有变异衣壳的腺相关病毒病毒体和其使用方法

(57)摘要

本公开提供了具有改变的衣壳蛋白的腺相关病毒(AAV)病毒体,其中与野生型AAV相比,所述AAV病毒体展现对视网膜细胞更大的感染性。本公开还提供了将基因产物递送至个体中的视网膜细胞的方法,以及治疗眼病的方法。



CN 114672516 B

1.一种重组腺相关病毒rAAV病毒体,其包含:

a) 变异AAV衣壳蛋白,其中相对于对应的亲本AAV衣壳蛋白,所述变异AAV衣壳蛋白在衣壳蛋白GH环中包含异源肽的插入,

其中所述异源肽由SEQ ID NO: 53所示的氨基酸序列LAPDSTTRSA组成,

其中与包含所述对应的亲本AAV衣壳蛋白的对照AAV病毒体对视网膜细胞的感染性相比,所述变异衣壳蛋白赋予增加的对视网膜细胞的感染性;以及

b) 异源核酸,所述异源核酸包含编码异源基因产物的核苷酸序列。

2.根据权利要求1所述的rAAV病毒体,其中与包含所述对应的亲本AAV衣壳蛋白的对照AAV病毒体对视网膜细胞的感染性相比,所述rAAV病毒体展现增加至少5倍的对视网膜细胞的感染性,和/或其中与包含所述对应的亲本AAV衣壳蛋白的AAV病毒体定位至内核层、外核层、光感受器层、神经节细胞层或视网膜色素上皮细胞的程度相比,所述rAAV病毒体展现增加至少5倍的至内核层、外核层、光感受器层、神经节细胞层和视网膜色素上皮细胞中的一个或多个的定位。

3.根据权利要求1或2所述的rAAV病毒体,其中插入位点介于与AAV2的VP1的氨基酸570和611对应的氨基酸之间,或另一AAV血清型的衣壳蛋白VP1中的对应位置。

4.根据权利要求3所述的rAAV病毒体,其中所述插入位点位于与AAV2的VP1的氨基酸587和588对应的氨基酸之间,或另一AAV血清型的衣壳蛋白VP1中的对应位置。

5.根据权利要求1、2或4中任一项所述的rAAV病毒体,其中所述基因产物是:

a) 干扰RNA或适体;

b) 多肽;或

c) RNA引导的核酸内切酶和向导RNA。

6.根据权利要求5所述的rAAV病毒体,其中所述多肽为神经保护多肽、抗血管生成多肽、抗细胞凋亡多肽、或增强视网膜细胞的功能的多肽、或RNA引导的核酸内切酶。

7.根据权利要求1、2或4中任一项所述的rAAV病毒体,其中所述异源基因产物为神经胶质源性神经营养因子、成纤维细胞生长因子2、神经秩蛋白、睫状神经营养因子、神经生长因子、脑源性神经营养因子、表皮生长因子、视紫红质、X连锁凋亡抑制因子、视网膜劈裂蛋白、RPE65、视网膜色素变性GTP酶相互作用蛋白-1、外周蛋白、外周蛋白-2、RdCVF、视网膜色素变性GTP酶调控因子或音猬因子。

8.根据权利要求3所述的rAAV病毒体,其中所述基因产物是:

a) 干扰RNA或适体;

b) 多肽;或

c) RNA引导的核酸内切酶和向导RNA。

9.根据权利要求8所述的rAAV病毒体,其中所述多肽是神经保护多肽、抗血管生成多肽、抗细胞凋亡多肽、或增强视网膜细胞的功能的多肽、或RNA引导的核酸内切酶。

10.一种药物组合物,其包含:

a) 权利要求1至9中任一项所述的重组腺相关病毒rAAV病毒体;和

b) 药学上可接受的赋形剂。

11.权利要求1至9中任一项所述的重组腺相关病毒rAAV病毒体在制备用于将基因产物递送至个体中的视网膜细胞的方法的药物组合物中的用途,其中所述方法包括向所述个体

施用权利要求1至9中任一项所述的重组腺相关病毒rAAV病毒体。

12.权利要求1至9中任一项所述的重组腺相关病毒rAAV病毒体在制备用于治疗视网膜疾病的方法的药物组合物的用途,其中所述方法包括向有需要的个体施用有效量的权利要求1至9中任一项所述的重组腺相关病毒rAAV病毒体。

13.根据权利要求12所述的用途,其中所述施用是通过眼内注射进行。

14.根据权利要求12所述的用途,其中所述施用是通过玻璃体内注射进行。

15.根据权利要求12至14中任一项所述的用途,其中所述视网膜疾病为青光眼、视网膜色素变性、黄斑变性、视网膜劈裂症、利伯氏先天性黑朦、糖尿病性视网膜病、全色盲或色盲。

16.一种分离的核酸,其包含编码变异腺相关病毒AAV衣壳蛋白的核苷酸序列,其中相对于对应的亲本AAV衣壳蛋白,所述变异AAV衣壳蛋白在衣壳蛋白GH环中包含异源肽的插入,

其中所述异源肽由SEQ ID NO: 53所示的氨基酸序列LAPDSTTRSA组成,

其中所述变异衣壳蛋白在存在于AAV病毒体中时,提供所述AAV病毒体增加的对视网膜细胞的感染性。

17.根据权利要求16所述的分离的核酸,其中插入位点介于AAV2的VP1的氨基酸570与611之间,或另一AAV血清型的衣壳蛋白VP1中的对应位置。

18.根据权利要求17所述的分离的核酸,其中所述插入位点介于AAV2的VP1的氨基酸587与588之间、AAV1的VP1的氨基酸590与591之间、AAV5的VP1的氨基酸575与576之间、AAV6的VP1的氨基酸590与591之间、AAV7的VP1的氨基酸589与590之间、AAV8的VP1的氨基酸590与591之间、AAV9的VP1的氨基酸588与589之间或AAV10的VP1的氨基酸588与589之间。

19.一种分离的经遗传修饰的宿主细胞,其包含权利要求16至18中任一项所述的核酸。

20.根据权利要求19所述的分离的经遗传修饰的宿主细胞,其还包含编码AAV rep蛋白的核苷酸序列。

21.一种变异腺相关病毒AAV衣壳蛋白,其中相对于对应的亲本AAV衣壳蛋白,所述变异AAV衣壳蛋白在GH环中包含异源肽的插入,其中所述异源肽由SEQ ID NO: 53所示的氨基酸序列LAPDSTTRSA组成。

22.根据权利要求21所述的变异腺相关病毒AAV衣壳蛋白,其中所述插入位点介于AAV2的VP1的氨基酸570与611之间,或另一AAV血清型的衣壳蛋白VP1中的对应位置。

23.根据权利要求22所述的变异腺相关病毒AAV衣壳蛋白,其中插入位点介于AAV2的VP1的氨基酸587与588之间、AAV1的VP1的氨基酸590与591之间、AAV5的VP1的氨基酸575与576之间、AAV6的VP1的氨基酸590与591之间、AAV7的VP1的氨基酸589与590之间、AAV8的VP1的氨基酸590与591之间、AAV9的VP1的氨基酸588与589之间或AAV10的VP1的氨基酸588与589之间。

24.一种宿主细胞,其产生权利要求1至9中任一项所述的rAAV病毒体。

具有变异衣壳的腺相关病毒病毒体和其使用方法

[0001] 本申请是分案申请,其相应母案申请是申请号为201780050806.3的中国发明专利申请,申请日为2017年7月27日,发明名称为“具有变异衣壳的腺相关病毒病毒体和其使用方法”。

[0002] 交叉引用

[0003] 本申请要求2016年7月29日提交的美国临时专利申请No.62/368,929的权益,该申请以引用的方式整体并入本文中。

[0004] 关于联邦政府资助的研究的声明

[0005] 本发明是在政府支持下根据美国国家卫生研究院颁发的合同/许可No.EY022975、EY018241和EY06855进行的。政府在本发明中具有一定的权利。

背景技术

[0006] 光感受器是视网膜中接收和加工视觉信息的第一神经元,其将可见的电磁辐射通过光转换转变成超极化反应。绝大多数遗传性视网膜疾病引起这些细胞的丧失,直接引起,例如在影响视紫红蛋白折叠的显性突变中;或间接引起,例如在影响视网膜色素上皮细胞(retinal pigment epithelium,RPE)中的视网膜再循环通路的隐性突变中。

[0007] 腺相关病毒(Adeno-associated virus,AAV)属于成员需要与例如腺病毒等辅助病毒协同感染来促进复制的细小病毒科(Parvoviridae)和依赖性病毒(Dependovirus)属,且AAV在缺少辅助剂时建立潜伏性感染。病毒体由25nm二十面体衣壳环绕4.9kb单链DNA基因组与两个开放阅读框rep和cap构成。非结构性rep基因编码四种对病毒复制来说不可或缺的调节蛋白,而cap编码三种装配成60聚体衣壳的结构蛋白(VP1-3)。此病毒衣壳介导AAV载体克服病毒转导的许多生物障碍的能力,所述生物障碍包括细胞表面受体结合、胞吞作用、胞内运输和核中拆包。

发明内容

[0008] 本公开提供了具有改变的衣壳蛋白的重组腺相关病毒(AAV)病毒体,其中与野生型AAV相比,所述重组AAV(rAAV)病毒体展现更大的对视网膜细胞的感染性,且其中rAAV病毒体包含异源核酸。本公开还提供了将基因产物递送至个体中的视网膜细胞的方法,和治疗眼病的方法。本公开提供了一种rAAV病毒体,其中与包含对应的亲本AAV衣壳蛋白的AAV病毒体定位至内核层、外核层、光感受器层、神经节细胞层或视网膜色素上皮细胞的程度相比,所述rAAV病毒体展现增加至少5倍的至内核层、外核层、光感受器层、神经节细胞层和视网膜色素上皮细胞中的一个或多个的定位。

附图说明

[0009] 图1是用于研发与亲本AAV相比,展现增加的对眼细胞(例如视网膜细胞)的感染性的AAV变体的定向进化法的示意图。

[0010] 图2是含有绿色荧光蛋白(GFP)-条型码构建体的AAV变体的深度测序的示意图。

[0011] 图3描绘18成员AAV变体库对神经节细胞层、内核层、光感受器层和视网膜色素上皮细胞(RPE)层中细胞的感染。

[0012] 图4提供AAV2衣壳蛋白VP1的氨基酸序列。氨基酸587和588(NP)呈粗体且加下划线。

[0013] 图5提供与多种AAV血清型的AAV衣壳蛋白VP1的氨基酸570-610对应的氨基酸序列。

[0014] 图6A-6C提供AAV衣壳蛋白环IV(GH环)区的氨基酸序列的比对。插入位点以粗体和下划线显示。AAV1:SEQ ID NO:35;AAV6:SEQ ID NO:36;AAV3:SEQ ID NO:37;AAV2:SEQ ID NO:38;AAV8:SEQ ID NO:39;AAV8.1:SEQ ID NO:40;AAV8 rh8:SEQ ID NO:41;AAV10:SEQ ID NO:42;AAV7:SEQ ID NO:43;AAV9:SEQ ID NO:44;AAV 9.1:SEQ ID NO:45;AAV5:SEQ ID NO:46。

[0015] 图7A-7V提供例示性异源基因产物的氨基酸序列。

[0016] 图8A-8C提供例示性向导-RNA指导的核酸内切酶的氨基酸序列。

[0017] 定义

[0018] 术语“视网膜细胞”在本文中可以指包含视网膜的细胞类型中的任一种,例如视网膜神经节细胞;无长突细胞;水平细胞;双极细胞;包括视杆和视锥的感光细胞;米勒胶质细胞(Müller glial cell);星形细胞(例如视网膜星形细胞);和视网膜色素上皮细胞。

[0019] “AAV”是腺相关病毒的缩写,且可以用于指病毒本身或其衍生物。除非另外需要,否则该术语涵盖所有亚型和天然存在的形式与重组形式两者。缩写“rAAV”是指重组腺相关病毒,又称为重组AAV载体(或“rAAV载体”)。术语“AAV”包括AAV 1型(AAV-1)、AAV 2型(AAV-2)、AAV 3型(AAV-3)、AAV 4型(AAV-4)、AAV 5型(AAV-5)、AAV 6型(AAV-6)、AAV 7型(AAV-7)、AAV 8型(AAV-8)、AAV 9型(AAV-9)、鸟类AAV、牛类AAV、犬科AAV、马科AAV、灵长类AAV、非灵长类AAV和绵羊科AAV。“灵长类AAV”是指从灵长类动物分离的AAV,“非灵长类AAV”是指从非灵长类哺乳动物分离的AAV,“牛类AAV”是指从牛类哺乳动物(例如母牛)分离的AAV等等。

[0020] 如本文所用的“rAAV载体”是指包含非AAV来源的多核苷酸序列(即对AAV来说异源的多核苷酸),典型地用于细胞的遗传转化的所关注的序列的AAV载体。一般说来,异源多核苷酸侧接至少一个且一般侧接两个AAV反向末端重复序列(ITR)。术语rAAV载体涵盖rAAV载体粒子与rAAV载体质粒两者。

[0021] “AAV病毒”或“AAV病毒粒子”或“rAAV载体粒子”是指由至少一种AAV衣壳蛋白(典型地野生型AAV的全部衣壳蛋白)和包壳的多核苷酸rAAV载体构成的病毒粒子。如果粒子包含异源多核苷酸(即除野生型AAV基因组以外的多核苷酸,例如有待递送至哺乳动物细胞的转基因),那么其典型地称为“rAAV载体粒子”或简称为“rAAV载体”。因此,rAAV粒子的产生当然包括rAAV载体的产生,因为此类载体含于rAAV粒子内。

[0022] “包装”是指引起AAV粒子的装配和包壳的一系列细胞内事件。

[0023] AAV“rep”和“cap”基因是指编码腺相关病毒的复制和包壳蛋白的多核苷酸序列。AAV rep和cap在本文中称为AAV“包装基因”。

[0024] AAV“辅助病毒”是指允许哺乳动物细胞复制和包装AAV(例如野生型AAV)的病毒。多种此类AAV辅助病毒是本领域中已知的,包括腺病毒、疱疹病毒和痘病毒,例如牛痘。腺病毒涵盖许多不同的亚类,不过亚类C的腺病毒5型最常使用。已知人类、非人类哺乳动物和鸟

类来源的许多腺病毒,且可以从例如ATCC等保藏中心获得。疱疹科病毒包括例如单纯疱疹病毒(herpes simplex viruses,HSV)和埃-巴二氏病毒(Epstein-Barr virus,EBV)以及巨细胞病毒(cytomegalovirus,CMV)和假狂犬病毒(pseudorabies virus,PRV);其也可以从例如ATCC等保藏中心获得。

[0025] “辅助病毒功能”是指在辅助病毒基因组中编码的允许AAV复制和包装(结合对本文所述的复制和包装的其它需求)的功能。如本文所述,“辅助病毒功能”可以呈许多方式提供,包括通过提供辅助病毒或提供例如编码必需功能的多核苷酸序列至在转运中的生产细胞。

[0026] “感染”病毒或病毒粒子是包含能够递送至病毒物种向性的细胞中的多核苷酸组分的病毒或病毒粒子。该术语不一定暗示病毒的任何复制能力。如本文所用,“感染性”病毒或病毒粒子是可以接近靶细胞,可以感染靶细胞,且可以在靶细胞中表达异源核酸的病毒或病毒粒子。因此,“感染性”是指病毒粒子接近靶细胞、感染靶细胞和在靶细胞中表达异源核酸的能力。感染性可以指体外感染性或体内感染性。用于计数感染性病毒粒子的测定在本公开中和本领域中别处进行描述。病毒感染性可以表示为感染性病毒粒子与总病毒粒子的比率。总病毒粒子可以表示为病毒基因组(vg)拷贝的数目。病毒粒子在细胞中表达异源核酸的能力可以称为“转导”。病毒粒子在细胞中表达异源核酸的能力可以使用许多技术测定,所述技术包括评定标志物基因,例如绿色荧光蛋白(GFP)测定(例如其中病毒包含编码GFP的核苷酸序列),其中GFP在感染病毒粒子的细胞中产生且检测和/或测量;或例如通过酶联免疫吸附测定(ELISA)测量所产生的蛋白质。病毒感染性可以表示为感染性病毒粒子与总病毒粒子的比率。本领域中已知测定感染性病毒粒子与总病毒粒子的比率的方法。参见例如Grainger等人(2005)Mol.Ther.11:S337(描述TCID50感染滴度测定);和Zolotukhin等人(1999)Gene Ther.6:973。

[0027] “有复制能力”的病毒(例如有复制能力的AAV)是指具有感染性的表型野生型病毒,且在受感染细胞中也能够复制(即在辅助病毒或辅助病毒功能存在下)。在AAV情况下,复制能力一般需要功能性AAV包装基因的存在。一般说来,由于缺乏一种或多种AAV包装基因,如本文所述的rAAV载体在哺乳动物细胞(特别是人类细胞中)是不能复制的。典型地,此类rAAV载体缺乏任何AAV基因序列,从而使通过AAV包装基因与引入的rAAV载体之间的重组产生有复制能力的AAV的可能性降至最低。在许多实施方案中,如本文所述的rAAV载体制剂为含有即使有也极少数的有复制能力的AAV(rcAAV,又称为RCA)(例如每10^2rAAV粒子少于约1rcAAV、每10^4rAAV粒子少于约1rcAAV、每10^8rAAV粒子少于约1rcAAV、每10^{12}rAAV粒子少于约1rcAAV或无rcAAV)的制剂。

[0028] 术语“多核苷酸”是指任何长度的核苷酸的聚合物形式,包括脱氧核糖核苷酸或核糖核苷酸或其类似物。多核苷酸可以包含经修饰的核苷酸,例如甲基化核苷酸和核苷酸类似物,且可以间杂有非核苷酸组分。如果存在,那么可以在聚合物装配之前或之后给予核苷酸结构修饰。如本文所用的术语多核苷酸可互换地指双链和单链分子。除非另作说明或需要,作为多核苷酸的本文所述的本发明的任何实施方案涵盖双链形式和已知或预测组成双链形式的两种互补单链形式中的每一种。

[0029] 多核苷酸或多肽具有一定百分比的与另一多核苷酸或多肽的“序列一致性”,意指在比对时,当比较两种序列时该百分数的碱基或氨基酸相同。序列相似性可以用许多不同

的方式测定。为了测定序列一致性,可以使用包括可以在万维网的ncbi.nlm.nih.gov/BLAST/BLAST获得的BLAST在内的方法和计算机程序,比对序列。另一比对算法为FASTA,可以在来自Madison,Wisconsin,USA的Genetics Computing Group(GCG)程序包(Oxford Molecular Group公司的全资附属公司)获得。其它比对技术描述于Methods in Enzymology,第266卷:Computer Methods for Macromolecular Sequence Analysis (1996),编辑Doolittle,Academic Press公司,Harcourt Brace&Co.分公司,San Diego,California,USA。尤其关注允许序列中缺口的比对程序。Smith-Waterman为在序列比对中允许缺口的一类算法。参见Meth.Mol.Biol.70:173-187(1997)。此外,使用Needleman和Wunsch比对方法的GAP程序可以用于比对序列。参见J.Mol.Biol.48:443-453(1970)。

[0030] 关注BestFit程序,其使用Smith Waterman的局部同源性算法(Advances in Applied Mathematics 2:482-489(1981)来测定序列一致性。缺口产生罚分一般在1至5范围内,通常2至4且在许多实施方案中将为3。缺口延伸罚分一般在约0.01至0.20范围内,且在许多情况下将为0.10。程序具有由所输入的待比较的序列决定的缺省参数。优选地,使用由程序决定的缺省参数确定序列一致性。此程序也可以从来自Madison,Wisconsin,USA的Genetics Computing Group(GCG)程序包获得。

[0031] 另一所关注的程序为FastDB算法。FastDB描述于Current Methods in Sequence Comparison and Analysis,Macromolecule Sequencing and Synthesis,Selected Methods and Applications,第127-149页,1988,Alan R.Liss公司。序列一致性百分比通过FastDB基于以下参数计算:

[0032] 错配罚分:1.00;

[0033] 缺口罚分:1.00;

[0034] 缺口尺寸罚分:0.33;以及

[0035] 接合罚分:30.0。

[0036] “基因”是指含有至少一个能够在转录和翻译后编码特定蛋白质的开放阅读框的多核苷酸。

[0037] 如本文所用的术语“向导RNA”是指包含以下的RNA:i)结合于向导RNA指导的核酸内切酶(例如2类CRISPR/Cas核酸内切酶,例如II型、V型或VI型CRISPR/Cas核酸内切酶)且活化RNA指导的核酸内切酶的“活化”核苷酸序列;和ii)包含与靶核酸杂交的核苷酸序列的“靶”核苷酸序列。“活化”核苷酸序列和“靶”核苷酸序列可以在分开的RNA分子(例如“双向导RNA”)上;或可以在相同的RNA分子(“单向导RNA”)上。

[0038] “小干扰”或“短干扰RNA”或siRNA为靶向所关注的基因(“靶基因”)的核苷酸的RNA双链体。“RNA双链体”是指由RNA分子的两个区域之间的互补配对所形成的结构。siRNA由于siRNA的双链体部分的核苷酸序列与所靶向基因的核苷酸序列互补而“靶向”基因。在一些实施方案中,siRNA的双链体的长度少于30个核苷酸。在一些实施方案中,双链体长度可以为29个、28个、27个、26个、25个、24个、23个、22个、21个、20个、19个、18个、17个、16个、15个、14个、13个、12个、11个或10个核苷酸。在一些实施方案中,双链体的长度为19-25个核苷酸长。siRNA的RNA双链体部分可以为发夹结构的一部分。除双链体部分外,发夹结构可以含有环部分,该环部分位于形成双链体的两个序列之间。环的长度可以变化。在一些实施方案中,环长度为5个、6个、7个、8个、9个、10个、11个、12个或13个核苷酸。发夹结构还可以含有

3'或5'悬垂部分。

[0039] 在一些实施方案中,悬垂物为0个、1个、2个、3个、4个或5个核苷酸长的3'或5'悬垂物。

[0040] 如本文所用,术语"微型RNA"是指任何类型的干扰RNA,包括但不限于内源性微型RNA和人工微型RNA(例如合成miRNA)。内源性微型RNA为在基因组中天然编码的能够调节mRNA的生产性利用的小型RNA。人工微型RNA可以为除内源性微型RNA以外的能够调节mRNA的活性的任何类型的RNA序列。微型RNA序列可以为由这些序列中的任一种或多种构成的RNA分子。微型RNA(或"miRNA")序列已经描述于例如以下的出版物中:Lim等人,2003,Genes&Development,17,991-1008;Lim等人,2003,Science,299,1540;Lee和Ambrose,2001,Science,294,862;Lau等人,2001,Science294,858-861;Lagos-Quintana等人,2002,Current Biology,12,735-739;Lagos-Quintana等人,2001,Science,294,853-857;和Lagos-Quintana等人,2003,RNA,9,175-179。微型RNA的实例包括作为较大RNA的片段的任何RNA,或为miRNA、siRNA、stRNA、sncRNA、tncRNA、snoRNA、smRNA、shRNA、snRNA或其它小型非编码RNA。参见例如美国专利申请20050272923、20050266552、20050142581和20050075492。"微型RNA前体"(或"前驱miRNA")是指微型RNA序列并入其中的具有茎环结构的核酸。"成熟微型RNA"(或"成熟miRNA")包括已经从微型RNA前体("前驱miRNA")裂解或已经合成(例如在实验室中通过无细胞合成而合成)的微型RNA,且具有约19个核苷酸至约27个核苷酸的长度,例如成熟微型RNA可以具有19nt、20nt、21nt、22nt、23nt、24nt、25nt、26nt或27nt的长度。成熟微型RNA可以结合于靶mRNA且抑制靶mRNA的翻译。

[0041] 如应用于多核苷酸的"重组"意指多核苷酸为克隆、限制或连接步骤和产生与在自然界中发现的多核苷酸不同的构建体的其它程序的多种组合的产物。重组病毒为包含重组多核苷酸的病毒粒子。所述术语分别包括原始多核苷酸构建体的复制物和原始病毒构建体的后代。

[0042] "控制元件"或"控制序列"为参与促进多核苷酸的功能调控的分子的相互作用,包括多核苷酸的复制、重复、转录、剪接、翻译或降解的核苷酸序列。调控可以影响过程的频率、速度或特异性,且可以为增强性或抑制性的。本领域中已知的控制元件包括例如转录调控序列,例如启动子和增强子。启动子为在一定条件下能够结合核糖核酸聚合酶且开始通常位于启动子下游(在3'方向上)的编码区的转录的DNA区域。

[0043] "可操作地连接(Operatively linked)"或"可操作地连接(operably linked)"是指遗传元件的并置,其中所述元件处于允许其以预期方式操作的关系中。举例来说,如果启动子帮助开始编码序列的转录,那么启动子可操作地连接于编码区。在启动子与编码区之间可能有插入残基,只要维持此功能关系即可。

[0044] "表达载体"为包含编码所关注的多肽的区域的载体,且用于实现蛋白质在预期靶细胞中的表达。表达载体还包含可操作地连接于编码区以促进蛋白质在靶中的表达的控制元件。控制元件与其可操作地连接以求表达的基因的组合有时称为"表达盒",本领域中已知和可获得许多表达盒,或容易由本领域中可获得的组分构建。

[0045] "异源"意指衍生自一种实体,该实体在基因型上截然不同于正被比较实体的其余部分。举例来说,通过遗传工程技术引入源自于不同物种的质粒或载体中的多核苷酸为异源多核苷酸。从天然编码序列去除且可操作地连接于在自然界中未发现连接的编码序列的

启动子为异源启动子。因此,举例来说,包括编码异源基因产物的异源核酸的rAAV为包括天然存在的野生型AAV中通常不包括的核酸的rAAV,且编码的异源基因产物为天然存在的野生型AAV通常不编码的基因产物。作为另一实例,包含插入衣壳蛋白的GH环中的异源肽的变异AAV衣壳蛋白为包括天然存在的野生型AAV中通常不包括的肽插入的变异AAV衣壳蛋白。

[0046] 术语“遗传改变”和“遗传修饰”(和其语法变体)在本文中可互换使用,是指其中不通过有丝分裂或减数分裂,将遗传元件(例如多核苷酸)引入细胞的过程。所述元件可以与细胞异源,或其可能为细胞中已经存在的元件的额外拷贝或改进型式。遗传改变可以例如通过用重组质粒或其它多核苷酸通过本领域中已知的任何方法,例如电穿孔、磷酸钙沉淀或接触多核苷酸-脂质粒复合物转染细胞来实现。遗传改变还可以例如通过用DNA或RNA病毒或病毒载体转导或感染来实现。一般地,遗传元件被引入细胞中的染色体或极微染色体中;但改变细胞和其后代的表型和/或基因型的任何改变都包括在此术语中。

[0047] 如果在细胞的体外长期培养期间序列可以用来执行其功能,那么称细胞经遗传序列“稳定地”改变、转导、基因修饰或转化。一般地,此类细胞为“遗传上”改变(遗传上修饰),因为引入了所改变的细胞的后代也能够遗传的遗传改变。

[0048] 术语“多肽”、“肽”和“蛋白质”在本文中可互换使用,是指任何长度的氨基酸的聚合物。所述术语还涵盖已经修饰的氨基酸聚合物;例如二硫键形成、糖基化、脂质化、磷酸化或与标记组分偶联。在基因产物递送至哺乳动物受试者的背景下论述时例如抗血管生成多肽、神经保护多肽等多肽和其组合物是指相应的完整多肽或保留完整蛋白质的所需生物化学功能的其任何片段或基因工程衍生物。类似地,提及编码抗血管生成多肽的核酸、编码神经保护多肽的核酸和用于基因产物递送至哺乳动物受试者中的其它此类核酸(可以称为递送至受体细胞的“转基因”)包括编码完整多肽或具有所需生物化学功能的任何片段或基因工程衍生物的多核苷酸。

[0049] “分离”的质粒、核酸、载体、病毒、病毒体、宿主细胞或其它物质是指缺乏物质或类似物质天然存在或最初制备时也可能存在的其它组分中的至少一些的物质制剂。因此,举例来说,分离的物质可以通过使用纯化技术将其从来源混合物富集来制备。富集可以在绝对基础上测量,例如每体积溶液的重量,或其可以相对于来源混合物中存在的可能干扰的第二物质测量。本发明的实施方案的日益富集,日益更多地分离。在一些实施方案中,分离的质粒、核酸、载体、病毒、宿主细胞或其它物质经纯化,例如约80%至约90%纯、至少约90%纯、至少约95%纯、至少约98%纯或至少约99%纯或更纯。

[0050] 如本文所用,术语“治疗(treatment)”、“治疗(treating)”等等是指获得所需药理学和/或生理学作用。就完全或部分预防疾病或其症状而言,作用可以为预防性的,和/或就部分或完全治愈疾病和/或可归因于所述疾病的不利影响而言,作用可以为治疗性的。如本文所用,“治疗”涵盖哺乳动物、尤其人类中疾病的任何治疗,且包括:(a)预防疾病在易感染疾病或处于得病的风险中但尚未被诊断为患病的受试者中发生;(b)抑制疾病,即抑制其发展;和(c)减轻疾病,即引起疾病消退。

[0051] 术语“个体”、“宿主”、“受试者”和“患者”在本文中可互换使用,且是指哺乳动物,包括(但不限于)人类和非人类灵长类动物,包括猿和人类;哺乳动物运动动物(例如马、骆驼等);哺乳动物农畜(例如绵羊、山羊、母牛等);哺乳动物宠物(犬、猫等);和啮齿类动物(例如小鼠、大鼠等)。在一些情况下,个体为人类。

[0052] 在进一步描述本发明前,应了解本发明不局限于所述的具体实施方案,因而当然可以变化。还应了解本文中使用的术语仅仅是出于描述具体实施方案的目的,且不意图限制,因为本发明的范围仅仅受随附权利要求书限制。

[0053] 在提供值的范围的情况下,应了解除非上下文另外清楚地规定,否则本发明内涵盖该范围的上下限之间的每个中间值,至下限的单位的十分之一,和所说明范围内的任何其它所说明或中间值。这些较小范围的上下限可以独立地包括在较小范围中,且也涵盖于本发明内,服从于所说明范围中的任何特别排除的界限。在所说明的范围包括界限中的一个或两个的情况下,排除那些包括的界限中的任一个或两个的范围也包括在本发明中。

[0054] 除非另外定义,否则本文中使用的所有技术和科学术语都具有与本发明所属领域的一般技术人员通常所了解的含义相同的含义。虽然与本文所述的方法和材料类似或同等的任何方法和材料也可以用于实践或测试本发明,但是现在描述优选的方法和材料。本文中提到的所有出版物都以引用的方式并入本文中以公开和描述引用出版物所相关的方法和/或材料。

[0055] 必须指出如本文和随附权利要求书中所用,除非上下文另外清楚规定,否则单数形式“一种(a/an)”、“或”和“所述”包括多个指示物。因此,举例来说,提及“一种AAV衣壳”包括多个此类衣壳,且提及“所述AAV病毒体”包括提及一种或多种AAV病毒体和本领域的技术人员已知的其同等物等等。进一步指出,权利要求书可以被撰写成排除任何任选的要素。因而,此陈述意图作为与权利要求要素的叙述一起使用排他性术语如“单独地”、“仅”等,或采用“负面”限制的先前基础。

[0056] 应了解,为清楚起见,在分开实施方案的上下文中描述的本发明的某些特征也可能组合提供于单个实施方案。相反地,为简便起见,在单个实施方案的上下文中描述的本发明的多种特征也可以分开或呈任何合适的子组合提供。本发明特别涵盖关于本发明的实施方案的所有组合且在本文中公开,如同每个组合个别且明确地公开一般。另外,本发明也特别涵盖多种实施方案和其要素的所有子组合,且在本文中公开,如同每个此类子组合个别且明确地在本文中公开一般。

[0057] 本文中论述的出版物仅仅针对其在本申请的提交日期前的公开内容提供。本文中不应有内容解释为承认本发明无权借助在先发明而先于此类出版物。此外,所提供的公布日期可以与实际公布日期不同,实际公布日期可以独立地证实。

具体实施方式

[0058] 本公开提供了具有改变的衣壳蛋白的重组腺相关病毒(AAV)病毒体,其中与野生型AAV相比,所述重组AAV(rAAV)病毒体展现更大的对视网膜细胞的感染性;且其中rAAV病毒体包含异源核酸。与对应的野生型AAV对视网膜细胞的感染性相比,rAAV病毒体展现更大的对视网膜细胞的感染性。视网膜细胞可以为光感受器(例如视杆;视锥)、视网膜神经节细胞(RGC)、米勒细胞(米勒胶质细胞)、星形细胞(例如视网膜星形细胞)、双极细胞、无长突细胞、水平细胞或视网膜色素上皮细胞(RPE)。本公开还提供了将基因产物递送至个体中的视网膜细胞的方法,和治疗眼病的方法。本公开提供了一种具有改变的衣壳蛋白的rAAV病毒体,其中与包含对应的亲本AAV衣壳蛋白的AAV病毒体定位至内核层、外核层、光感受器层、神经节细胞层或视网膜色素上皮细胞的程度相比,所述rAAV病毒体展现增加至少5倍的至

内核层、外核层、光感受器层、神经节细胞层和视网膜色素上皮细胞中的一个或多个的定位;且其中所述rAAV病毒体包含异源核酸。

[0059] 变异AAV衣壳多肽

[0060] 本公开提供了一种变异AAV衣壳蛋白。本公开的变异AAV衣壳蛋白在亲本AAV衣壳蛋白的表面可及(例如溶剂可及)部分中的插入位点中包含5个氨基酸至20个氨基酸长的异源肽的插入,使得与包含对应的亲本AAV衣壳蛋白的AAV病毒体对视网膜细胞的感染性相比,所述变异衣壳蛋白在存在于AAV病毒体中时赋予增加的对视网膜细胞的感染性。在其它情况下,视网膜细胞为米勒细胞。其它视网膜细胞包括无长突细胞、双极细胞和水平细胞。"约5个氨基酸至约20个氨基酸的插入"在本文中也称为"肽插入"(例如异源肽插入)。"对应的亲本AAV衣壳蛋白"是指没有肽插入的相同AAV血清型的AAV衣壳蛋白。在许多情况下,变异AAV衣壳包含5个氨基酸至20个氨基酸(例如5至7个、7至10个、10至12个、12至15个或15至20个氨基酸)长的单一异源肽插入。

[0061] 插入位点在AAV衣壳蛋白的GH环或环IV中,例如AAV衣壳蛋白的GH环或环IV的溶剂可及部分中。关于AAV衣壳的GH环/环IV,参见例如van Vliet等人(2006)Mol.Ther.14:809;Padron等人(2005)J.Virol.79:5047;和Shen等人(2007)Mol.Ther.15:1955。举例来说,插入位点可以在AAV衣壳蛋白的氨基酸411-650内,如图6A-6C中所描绘。举例来说,插入位点可以在AAV2的氨基酸570-611内,AAV1的氨基酸571-612内,AAV5的氨基酸560-601内,AAV6的氨基酸571至612内,AAV7的氨基酸572至613内,AAV8的氨基酸573至614内,AAV9的氨基酸571至612内,或AAV10的氨基酸573至614内,如图5中所描绘。在一些情况下,插入位点介于AAV2衣壳蛋白的氨基酸588与589之间,或不同血清型的AAV中的对应插入位点。在一些情况下,插入位点介于AAV2衣壳蛋白的氨基酸587与588之间,或不同血清型的AAV中的对应插入位点。

[0062] 在一些情况下,相对于对应的亲本AAV衣壳蛋白,约5个氨基酸至约20个氨基酸(例如5至7个、7至10个、10至12个、12至15个或15至20个氨基酸)长的异源肽插入衣壳蛋白的GH环或环IV中的插入位点中。举例来说,插入位点可以介于AAV2的氨基酸587与588之间,或另一AAV血清型的衣壳子单元的对应位置。应注意到,插入位点587/588是基于AAV2衣壳蛋白。5个氨基酸至约20个氨基酸(例如5至7个、7至10个、10至12个、12至15个或15至20个氨基酸)长的异源肽可以插入除AAV2以外的AAV血清型(例如AAV8、AAV9等)中的对应位点中。基于多种AAV血清型的衣壳蛋白的氨基酸序列的比较,本领域的技术人员将知道"与AAV2的氨基酸587-588对应"的插入位点在任何既定的AAV血清型的衣壳蛋白中的位置。多种AAV血清型中与AAV2的衣壳蛋白VP1的氨基酸570-611(参见图4)对应的序列展示于图5中。参见例如GenBank登记号NP_049542,AAV1;GenBank登记号AAD13756,AAV5;GenBank登记号AAB95459,AAV6;GenBank登记号YP_077178,AAV7;GenBank登记号YP_077180,AAV8;GenBank登记号AAS99264,AAV9;和GenBank登记号AAT46337,AAV10。

[0063] 举例来说,插入位点可以介于AAV2的氨基酸587与588之间,AAV1的氨基酸590与591之间,AAV5的氨基酸575与576之间,AAV6的氨基酸590与591之间,AAV7的氨基酸589与590之间,AAV8的氨基酸590与591之间,AAV9的氨基酸588与589之间,或AAV10的氨基酸588与589之间。图5中插入位点加下划线;氨基酸编号是基于图5中描绘的编号。

[0064] 在一些实施方案中,主题衣壳蛋白包括氨基酸序列与图6A-6C中阐述的氨基酸序

列具有至少约85％、至少约90％、至少约95％、至少约98％、至少约99％或100％氨基酸序列一致性且插入5至20个氨基酸(例如5至7个、7至10个、10至12个、12至15个或15至20个氨基酸)长的异源肽的GH环。

[0065] 插入肽

[0066] 如上所述,将约5个氨基酸至约20个氨基酸长的异源肽插入AAV衣壳的GH环中。在一些情况下,插入肽具有5个氨基酸至20个氨基酸的长度。在一些情况下,插入肽具有7个氨基酸至15个氨基酸的长度。在一些情况下,插入肽具有9个氨基酸至15个氨基酸的长度。在一些情况下,插入肽具有9个氨基酸至12个氨基酸的长度。插入肽具有5个氨基酸、6个氨基酸、7个氨基酸、8个氨基酸、9个氨基酸、10个氨基酸、11个氨基酸、12个氨基酸、13个氨基酸、14个氨基酸、15个氨基酸、16个氨基酸、17个氨基酸、18个氨基酸、19个氨基酸或20个氨基酸的长度。在一些情况下,插入肽具有7个氨基酸的长度。在一些情况下,插入肽具有8个氨基酸的长度。在一些情况下,插入肽具有9个氨基酸的长度。在一些情况下,插入肽具有10个氨基酸的长度。在一些情况下,插入肽具有11个氨基酸的长度。在一些情况下,插入肽具有12个氨基酸的长度。在一些情况下,插入肽具有13个氨基酸的长度。在一些情况下,插入肽具有14个氨基酸的长度。在一些情况下,插入肽具有15个氨基酸的长度。

[0067] 在一些情况下,肽插入物为式I的肽:

[0068] $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$,其中:

[0069] X_1为Leu、Ile、Pro或Gln;

[0070] X_2为Ala、Pro、Ser、Asp、Gly、Thr或Val;

[0071] X_3为Lys、His、Thr、Ile、Pro、Val、Arg、Ala、Asp、Glu、Asn、Gln或Tyr;

[0072] X_4(如果存在)为Gln、Asp、Ser、Gly、Thr、Ile、Asn、Glu、Lys或Arg;

[0073] X_5为Asp、Ser、Gln、Val、Thr、Gly、Ala、Asn、Lys或Tyr;

[0074] X_6为Thr、Ala、Gln、Ser、Glu、Pro或Ile;

[0075] X_7为Thr、Ser、Asn、Pro、Leu、Gln、Lys、Ala或Cys;

[0076] X_8为Lys、Ser、Arg、Thr、Ala、Glu、Ile或Asn;

[0077] X_9为Asn、Pro、Ser、Lys、His、Ile、Thr或Ala;且

[0078] X_{10}为Ala、Phe、Asp、Thr、Val或Met。

[0079] 式I的肽插入物包括(但不限于)(1)LAKDATKNA(SEQ ID NO:47);(2)PAHQDTTKNA(SEQ ID NO:48);(3)LAHQDTTKNA(SEQ ID NO:49);(4)LATTSQNKPA(SEQ ID NO:50);(5)LAISDQTKHA(SEQ ID NO:51);(6)IARGVAPSSA(SEQ ID NO:52);(7)LAPDSTTRSA(SEQ ID NO:53);(8)LAKGTELKPA(SEQ ID NO:54);(9)LAIIDATKNA(SEQ ID NO:55);(10)LAVDGAQRSA(SEQ ID NO:56);(11)PAPQDTTKKA(SEQ ID NO:57);(12)LPHQDTTKNA(SEQ ID NO:58);(13)LAKDATKTIA(SEQ ID NO:59);(14)LAKQQSASTA(SEQ ID NO:60);(15)LAKSDQSKPA(SEQ ID NO:61);(16)LSHQDTTKNA(SEQ ID NO:62);(17)LAANQPSKPA(SEQ ID NO:63);(18)LAVSDSTKAA(SEQ ID NO:64);(19)LAAQGTAKKPA(SEQ ID NO:65);(20)LAPDQTTRNA(SEQ ID NO:66);(21)LAASDSTKAA(SEQ ID NO:67);(22)LAPQDTTKNA(SEQ ID NO:68);(23)LAKADETRPA(SEQ ID NO:69);(24)LAHQDTAKNA(SEQ ID NO:70);(25)LAHQDTKKNA(SEQ ID NO:71);(26)LAHQDTTKHA(SEQ ID NO:72);(27)LAHQDTTKKA(SEQ ID NO:73);(28)LAHQDTTRNA(SEQ ID NO:74);(29)LAHQDTTNA(SEQ ID NO:75);(30)LAHQGTTKNA(SEQ ID

NO:76)；(31)LAHQVTTKNA(SEQ ID NO:77)；(32)LAISDQSKPA(SEQ ID NO:78)；(33)LADATKTA(SEQ ID NO:79)；(34)LAKDTTKNA(SEQ ID NO:80)；(35)LAKSDQSRPA(SEQ ID NO:81)；(36)LAPQDTKKNA(SEQ ID NO:82)；(37)LATSDSTKAA(SEQ ID NO:83)；(38)LAVDGSQRSA(SEQ ID NO:84)；(39)LPISDQTKHA(SEQ ID NO:85)；(40)LPKDATKTIA(SEQ ID NO:86)；(41)LPPQDTTKNA(SEQ ID NO:87)；(42)PAPQDTTKNA(SEQ ID NO:88)；(43)QAHQDTTKNA(SEQ ID NO:89)；(44)LAHETSPRPA(SEQ ID NO:90)；(45)LAKSTSTAPA(SEQ ID NO:91)；(46)LADQDTTKNA(SEQ ID NO:92)；(47)LAESDQSKPA(SEQ ID NO:93)；(48)LAHKDTTKNA(SEQ ID NO:94)；(49)LAHKTQQKM(SEQ ID NO:95)；(50)LAHQDTTENA(SEQ ID NO:96)；(51)LAHQDTTINA(SEQ ID NO:97)；(52)LAHQDTTKKT(SEQ ID NO:98)；(53)LAHQDTTKND(SEQ ID NO:99)；(54)LAHQDTTKNT(SEQ ID NO:100)；(55)LAHQDTTKNV(SEQ ID NO:101)；(56)LAHQDTTKTM(SEQ ID NO:102)；(57)LAHQNTTKNA(SEQ ID NO:103)；(58)LAHRDTTKNA(SEQ ID NO:104)；(59)LAISDQTNHA(SEQ ID NO:105)；(60)LAKQKSASTA(SEQ ID NO:106)；(61)LAKSDQCKPA(SEQ ID NO:107)；(62)LAKSDQSKPD(SEQ ID NO:108)；(63)LAKSDQSNPA(SEQ ID NO:109)；(64)LAKSYQSKPA(SEQ ID NO:110)；(65)LANQDTTKNA(SEQ ID NO:111)；(66)LAPQNTTKNA(SEQ ID NO:112)；(67)LAPSSIQKPA(SEQ ID NO:113)；(68)LAQQDTTKNA(SEQ ID NO:114)；(69)LAYQDTTKNA(SEQ ID NO:115)；(70)LDHQDTTKNA(SEQ ID NO:116)；(71)LDHQDTTKSA(SEQ ID NO:117)；(72)LGHQDTTKNA(SEQ ID NO:118)；(73)LPHQDTTKND(SEQ ID NO:119)；(74)LPHQDTTKNT(SEQ ID NO:120)；(75)LPHQDTTNNA(SEQ ID NO:121)；(76)LTHQDTTKNA(SEQ ID NO:122)；(77)LTKDATKTIA(SEQ ID NO:123)；(78)LTPQDTTKNA(SEQ ID NO:124)；和(79)LVHQDTTKNA(SEQ ID NO:125)。

[0080] 在一些情况下,肽插入物为式II的肽:

[0081] $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$,其中:

[0082] X_1为Leu、Ile或Pro;

[0083] X_2为Ala、Pro或Ser;

[0084] X_3为Lys、His、Thr、Ile、Pro、Val、Arg或Ala;

[0085] X_4(如果存在)为Gln、Asp、Ser、Gly、Thr、Ile或Asn;

[0086] X_5为Asp、Ser、Gln、Val、Thr、Gly或Ala;

[0087] X_6为Thr、Ala、Gln、Ser、Glu或Pro;

[0088] X_7为Thr、Ser、Asn、Pro、Leu、Gln、Lys或Ala;

[0089] X_8为Lys、Ser、Arg或Thr;

[0090] X_9为Asn、Pro、Ser、Lys、His、Ile、Thr或Ala;且

[0091] X_{10}为Ala。

[0092] 式II的肽插入物包括(但不限于)(1)LAKDATKNA(SEQ ID NO:47)；(2)PAHQDTTKNA(SEQ ID NO:48)；(3)LAHQDTTKNA(SEQ ID NO:49)；(4)LATTSQNKPA(SEQ ID NO:50)；(5)LAISDQTKHA(SEQ ID NO:51)；(6)IARGVAPSSA(SEQ ID NO:52)；(7)LAPDSTTRSA(SEQ ID NO:53)；(8)LAKGTELKPA(SEQ ID NO:54)；(9)LAIIDATKNA(SEQ ID NO:55)；(10)LAVDGAQRSA(SEQ ID NO:56)；(11)PAPQDTTKKA(SEQ ID NO:57)；(12)LPHQDTTKNA(SEQ ID NO:58)；(13)LAKDATKTIA(SEQ ID NO:59)；(14)LAKQQSASTA(SEQ ID NO:60)；(15)LAKSDQSKPA(SEQ ID NO:61)；(16)LSHQDTTKNA(SEQ ID NO:62)；(17)LAANQPSKPA(SEQ ID NO:63)；(18)

LAVSDSTKAA(SEQ ID NO:64)；(19)LAAQGTAKKPA(SEQ ID NO:65)；(20)LAPDQTTRNA(SEQ ID NO:66)；(21)LAASDSTKAA(SEQ ID NO:67)；(22)LAPQDTTKNA(SEQ ID NO:68)；(23)LAKADETRPA(SEQ ID NO:69)；(24)LAHQDTAKNA(SEQ ID NO:70)；(25)LAHQDTKKNA(SEQ ID NO:71)；(26)LAHQDTTKHA(SEQ ID NO:72)；(27)LAHQDTTKKA(SEQ ID NO:73)；(28)LAHQDTTRNA(SEQ ID NO:74)；(29)LAHQDTTNA(SEQ ID NO:75)；(30)LAHQGTTKNA(SEQ ID NO:76)；(31)LAHQVTTKNA(SEQ ID NO:77)；(32)LAISDQSKPA(SEQ ID NO:78)；(33)LADATKTA(SEQ ID NO:79)；(34)LAKDTTKNA(SEQ ID NO:80)；(35)LAKSDQSRPA(SEQ ID NO:81)；(36)LAPQDTKKNA(SEQ ID NO:82)；(37)LATSDSTKAA(SEQ ID NO:83)；(38)LAVDGSQRSA(SEQ ID NO:84)；(39)LPISDQTKHA(SEQ ID NO:85)；(40)LPKDATKTIA(SEQ ID NO:86)；(41)LPPQDTTKNA(SEQ ID NO:87)；和(42)PAPQDTTKNA(SEQ ID NO:88)。

[0093] 式II的肽包括(但不限于)：(1)LAKDATKNA(SEQ ID NO:47)；(2)PAHQDTTKNA(SEQ ID NO:48)；(3)LAHQDTTKNA(SEQ ID NO:49)；(4)LATTSQNKPA(SEQ ID NO:50)；(5)LAISDQTKHA(SEQ ID NO:51)；(6)IARGVAPSSA(SEQ ID NO:52)；(7)LAPDSTTRSA(SEQ ID NO:53)；(8)LAKGTELKPA(SEQ ID NO:54)；(9)LAIIDATKNA(SEQ ID NO:55)；(10)LAVDGAQRSA(SEQ ID NO:56)；(11)PAPQDTTKKA(SEQ ID NO:57)；(12)LPHQDTTKNA(SEQ ID NO:58)；(13)LAKDATKTIA(SEQ ID NO:59)；(14)LAKQQSASTA(SEQ ID NO:60)；(15)LAKSDQSKPA(SEQ ID NO:61)；(16)LSHQDTTKNA(SEQ ID NO:62)；(17)LAANQPSKPA(SEQ ID NO:63)；和(18)LAVSDSTKAA(SEQ ID NO:64)。在一些情况下,肽插入物为(1)LAKDATKNA(SEQ ID NO:47)。在一些情况下,肽插入物为(2)PAHQDTTKNA(SEQ ID NO:48)。在一些情况下,肽插入物为(3)LAHQDTTKNA(SEQ ID NO:49)。在一些情况下,肽插入物为(4)LATTSQNKPA(SEQ ID NO:50)。在一些情况下,肽插入物为(5)LAISDQTKHA(SEQ ID NO:51)。在一些情况下,肽插入物为(6)IARGVAPSSA(SEQ ID NO:52)。在一些情况下,肽插入物为(7)LAPDSTTRSA(SEQ ID NO:53)。在一些情况下,肽插入物为(8)LAKGTELKPA(SEQ ID NO:54)。在一些情况下,肽插入物为(9)LAIIDATKNA(SEQ ID NO:55)。在一些情况下,肽插入物为(10)LAVDGAQRSA(SEQ ID NO:56)。在一些情况下,肽插入物为(11)PAPQDTTKKA(SEQ ID NO:57)。在一些情况下,肽插入物为(12)LPHQDTTKNA(SEQ ID NO:58)。在一些情况下,肽插入物为(13)LAKDATKTIA(SEQ ID NO:59)。在一些情况下,肽插入物为(14)LAKQQSASTA(SEQ ID NO:60)。在一些情况下,肽插入物为(15)LAKSDQSKPA(SEQ ID NO:61)。在一些情况下,肽插入物为(16)LSHQDTTKNA(SEQ ID NO:62)。在一些情况下,肽插入物为(17)LAANQPSKPA(SEQ ID NO:63)。在一些情况下,肽插入物为(18)LAVSDSTKAA(SEQ ID NO:64)。

[0094] 在一些情况下,肽插入物为式III的肽：

[0095] $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$,其中：

[0096] X_1为Leu、Ile或Pro；

[0097] X_2为Ala、Pro或Ser；

[0098] X_3为Lys、His、Thr、Ile、Pro、Val、Arg或Ala；

[0099] X_4(如果存在)为Gln、Asp、Ser、Gly、Thr、Ile或Asn；

[0100] X_5为Asp、Ser、Gln、Val、Thr、Gly或Ala；

[0101] X_6为Thr、Ala、Gln、Ser、Glu或Pro；

[0102] X_7为Thr、Ser、Asn、Pro、Leu、Gln、Lys或Ala；

[0103] X_8为Lys、Ser、Arg或Thr;

[0104] X_9为Asn、Pro、Ser、Lys、His、Ile、Thr或Ala;且

[0105] X10为Ala、Thr、Asp Val或Met。

[0106] 式III的肽插入物包括(但不限于)(1)LAKDATKNA(SEQ ID NO:47);(2)PAHQDTTKNA(SEQ ID NO:48);(3)LAHQDTTKNA(SEQ ID NO:49);(6)IARGVAPSSA(SEQ ID NO:52);(7)LAPDSTTRSA(SEQ ID NO:53);(8)LAKGTELKPA(SEQ ID NO:54);(9)LAIIDATKNA(SEQ ID NO:55);(10)LAVDGAQRSA(SEQ ID NO:56);(11)PAPQDTTKKA(SEQ ID NO:57);(12)LPHQDTTKNA(SEQ ID NO:58);(13)LAKDATKTIA(SEQ ID NO:59);(14)LAKQQSASTA(SEQ ID NO:60);(16)LSHQDTTKNA(SEQ ID NO:62);(17)LAANQPSKPA(SEQ ID NO:63);(18)LAVSDSTKAA(SEQ ID NO:64);(19)LAAQGTAKPA(SEQ ID NO:65);(20)LAPDQTTRNA(SEQ ID NO:66);(24)LAHQDTAKNA(SEQ ID NO:70);(25)LAHQDTKKNA(SEQ ID NO:71);(26)LAHQDTTKHA(SEQ ID NO:72);(27)LAHQDTTKKA(SEQ ID NO:73);(28)LAHQDTTRNA(SEQ ID NO:74);(29)LAHQDTTTNA(SEQ ID NO:75);(30)LAHQGTTKNA(SEQ ID NO:76);(21)LAASDSTKAA(SEQ ID NO:67);(22)LAPQDTTKNA(SEQ ID NO:68);(31)LAHQVTTKNA(SEQ ID NO:77);(33)LAKDATKTA(SEQ ID NO:79);(34)LAKDTTKNA(SEQ ID NO:80);(36)LAPQDTKKNA(SEQ ID NO:82);(37)LATSDSTKAA(SEQ ID NO:83);(38)LAVDGSQRSA(SEQ ID NO:84);(41)LPPQDTTKNA(SEQ ID NO:87);(42)PAPQDTTKNA(SEQ ID NO:88);(52)LAHQDTTKKT(SEQ ID NO:98);(53)LAHQDTTKND(SEQ ID NO:99);(54)LAHQDTTKNT(SEQ ID NO:100);(55)LAHQDTTKNV(SEQ ID NO:101);(56)LAHQDTTKTM(SEQ ID NO:102);(73)LPHQDTTKND(SEQ ID NO:119);和(74)LPHQDTTKNT(SEQ ID NO:120)。

[0107] 在一些情况下,肽插入物为式IV的肽:

[0108] $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$,其中:

[0109] X_1为Leu;

[0110] X_2为Ala;

[0111] X_3为Lys、His、Thr、Ile、Pro或Val;

[0112] X_4(如果存在)为Gln、Asp、Ser或Gly;

[0113] X_5为Asp、Ser或Gln;

[0114] X_6为Thr、Ala、Gln或Ser;

[0115] X_7为Thr或Ser;

[0116] X_8为Lys、Ser或Arg;

[0117] X_9为Asn、Pro或Ser;且

[0118] X_{10}为Ala。

[0119] 式IV的肽插入物包括(但不限于)(1)LAKDATKNA(SEQ ID NO:47);(3)LAHQDTTKNA(SEQ ID NO:49);(7)LAPDSTTRSA(SEQ ID NO:53);(15)LAKSDQSKPA(SEQ ID NO:61);(20)LAPDQTTRNA(SEQ ID NO:66);(22)LAPQDTTKNA(SEQ ID NO:68);(28)LAHQDTTRNA(SEQ ID NO:74);(32)LAISDQSKPA(SEQ ID NO:78);(34)LAKDTTKNA(SEQ ID NO:80);和(35)LAKSDQSRPA(SEQ ID NO:81)。

[0120] 在一些情况下,肽插入物为式V的肽:

[0121] $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$,其中:

[0122] X_1为Leu;

[0123] X_2为Ala;

[0124] X_3为Lys或His;

[0125] X_4(如果存在)为Gln、Asp、Ser或Gly;

[0126] X_5为Asp、Ser或Gln;

[0127] X_6为Thr、Ala、Gln或Ser;

[0128] X_7为Thr或Ser;

[0129] X_8为Lys、Ser或Arg;

[0130] X_9为Asn、Pro或Ser;且

[0131] X_{10}为Ala。

[0132] 式V的肽插入物包括(但不限于)(1)LAKDATKNA(SEQ ID NO:47);(15)LAKSDQSKPA(SEQ ID NO:51);(34)LAKDTTKNA(SEQ ID NO:80);和(35)LAKSDQSRPA(SEQ ID NO:81)。

[0133] 在一些情况下,肽插入物为式VI的肽:

[0134] $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$,其中:

[0135] X_1为Leu;

[0136] X_2为Ala;

[0137] X_3为Asn、Lys、Thr、Gln、Ser、Ile或Leu;

[0138] X_4为Ser、Ala、Thr、Glu、Gln、Gly、Lys或Pro;

[0139] X_5为Asp、Pro、Glu、Thr、Asn或Arg;

[0140] X_6为Ile、His、Thr、Gln、Asn、Tyr、Asp或Glu;

[0141] X_7为Gln、Thr、Asn、Ala或Lys;

[0142] X_8为Lys、Thr、Arg或Asp;

[0143] X_9为Pro、Asn、Thr、Arg、Lys或Ser;且

[0144] X_{10}为Ala。

[0145] 式VI的肽包括(但不限于):(80)LAKANQNTPA(SEQ ID NO:126);(81)LATTPITKPA(SEQ ID NO:127);(82)LATTPIAKPA(SEQ ID NO:128);(83)LAIEDHTKSA(SEQ ID NO:129);(84)LAQSEHQRPA(SEQ ID NO:130);(85)LAKSPNKDNA(SEQ ID NO:131);(86)LANQDYTKTA(SEQ ID NO:132);(87)LANSTDQTRA(SEQ ID NO:133);(88)LALGETTRPA(SEQ ID NO:134);(89)LANSTEQTRA(SEQ ID NO:135);(90)LAQADTTKNA(SEQ ID NO:136);(91)LASKDITKTA(SEQ ID NO:137);和(92)LASPRHNKKC(SEQ ID NO:138)。

[0146] 在一些情况下,肽插入物为式VII的肽:LAHQDTTK$X_1X_2X_3$(SEQ ID NO:148),其中X_1为Lys、Thr、Asn或His;X_2为Ala、Thr、Val、Ile、Met或Asp;且X_3如果存在,那么为Ala。式VII的肽包括(但不限于):(26)LAHQDTTKHA(SEQ ID NO:72);(27)LAHQDTTKKA(SEQ ID NO:73);(52)LAHQDTTKKT(SEQ ID NO:98);(53)LAHQDTTKND(SEQ ID NO:99);(54)LAHQDTTKNT(SEQ ID NO:100);(55)LAHQDTTKNV(SEQ ID NO:101);(56)LAHQDTTKTM(SEQ ID NO:102);和(93)LAHQDTTKTIA(SEQ ID NO:139)。

[0147] 在一些情况下,肽插入物为式VIII的肽:LAX_1QX_2T$X_3X_4X_5X_6$(SEQ ID NO:149),其中X_1为Ala、Pro、Asp或His;X_2为Gly或Asp;X_3为Ala、Thr或Lys;X_4为Asn、Glu、Lys、Arg或Thr;X_5为Leu、Asn、Lys或Thr;且X_6如果存在,那么为Ala、Thr、Asp、Val或Met。式VIII的肽包括(但

不限于)(94)LAAQGTANL(SEQ ID NO:140);(22)LAPQDTTKNA(SEQ ID NO:68);(46)LADQDTTKNA(SEQ ID NO:92);(24)LAHQDTAKNA(SEQ ID NO:70);(25)LAHQDTKKNA(SEQ ID NO:71);(26)LAHQDTTKHA(SEQ ID NO:72);(27)LAHQDTTKKA(SEQ ID NO:73);(28)LAHQDTTRNA(SEQ ID NO:74);(29)LAHQDTTTNA(SEQ ID NO:75);(50)LAHQDTTENA(SEQ ID NO:96);(51)LAHQDTTINA(SEQ ID NO:97);(52)LAHQDTTKKT(SEQ ID NO:98);(53)LAHQDTTKND(SEQ ID NO:99);(54)LAHQDTTKNT(SEQ ID NO:100);(55)LAHQDTTKNV(SEQ ID NO:101);和(56)LAHQDTTKTM(SEQ ID NO:102)。

[0148] 在一些情况下,肽插入物为式IX的肽:$X_1AX_2X_3DX_4TKX_5A$(SEQ ID NO:150),其中X_1为Val或Leu;X_2为Ile、Val、His或Asp;X_3为Glu、Ser、Lys或Gln;X_4为His、Ser或Thr;且X_5为Ser、Ala、Asn、His或Lys。式IX的肽包括(但不限于)(95)VAIEDHTKSA(SEQ ID NO:141);(18)LAVSDSTKAA(SEQ ID NO:64);(46)LADQDTTKNA(SEQ ID NO:92);(48)LAHKDTTKNA(SEQ ID NO:94);(26)LAHQDTTKHA(SEQ ID NO:72);和(27)LAHQDTTKKA(SEQ ID NO:73)。

[0149] 在一些情况下,肽插入物为式X的肽:$X_1X_2X_3AX_4QX_5TX_6KNA$(SEQ ID NO:151),其中X_1如果存在,那么为Leu;X_2如果存在,那么为Ala;X_3为Lys、Leu或Pro;X_4为Asn、His、Pro或Tyr;X_5为Asn、Gly、Val或Asp;且X_6为Pro或Thr。式X的肽包括(但不限于)(96)LAKANQNTPKNA(SEQ ID NO:142);(57)LAHQNTTKNA(SEQ ID NO:103);(66)LAPQNTTKNA(SEQ ID NO:112);(69)LAYQDTTKNA(SEQ ID NO:115);(30)LAHQGTTKNA(SEQ ID NO:76);(31)LAHQVTTKNA(SEQ ID NO:77);和(42)PAPQDTTKNA(SEQ ID NO:88)。

[0150] 在一些情况下,肽插入物为LAHQDTTKKX(SEQ ID NO:143),其中X为任何氨基酸。在一些情况下,肽插入物为LAHQDTTKKX(SEQ ID NO:143),其中X为Ala、Thr、Asp、Val或Met。在一些情况下,肽插入物为(27)LAHQDTTKKA(SEQ ID NO:73)。在一些情况下,肽插入物为(52)LAHQDTTKKT(SEQ ID NO:98)。在一些情况下,肽插入物为LAHQDTTKKD(SEQ ID NO:144)。在一些情况下,肽插入物为LAHQDTTKKV(SEQ ID NO:145)。在一些情况下,肽插入物为LAHQDTTKKM(SEQ ID NO:146)。

[0151] 在一些情况下,肽插入物不为(88)LALGETTRPA(SEQ ID NO:134)。在一些情况下,肽插入物不为LGETTRP(SEQ ID NO:147)。

[0152] 合适的肽插入物包括(但不限于)(1)LAKDATKNA(SEQ ID NO:47);(2)PAHQDTTKNA(SEQ ID NO:48);(3)LAHQDTTKNA(SEQ ID NO:49);(4)LATTSQNKPA(SEQ ID NO:50);(5)LAISDQTKHA(SEQ ID NO:51);(6)IARGVAPSSA(SEQ ID NO:52);(7)LAPDSTTRSA(SEQ ID NO:53);(8)LAKGTELKPA(SEQ ID NO:54);(9)LAIIDATKNA(SEQ ID NO:55);(10)LAVDGAQRSA(SEQ ID NO:56);(11)PAPQDTTKKA(SEQ ID NO:57);(12)LPHQDTTKNA(SEQ ID NO:58);(13)LAKDATKTIA(SEQ ID NO:59);(14)LAKQQSASTA(SEQ ID NO:60);(15)LAKSDQSKPA(SEQ ID NO:61);(16)LSHQDTTKNA(SEQ ID NO:62);(17)LAANQPSKPA(SEQ ID NO:63);(18)LAVSDSTKAA(SEQ ID NO:64);(19)LAAQGTAKKPA(SEQ ID NO:65);(20)LAPDQTTRNA(SEQ ID NO:66);(21)LAASDSTKAA(SEQ ID NO:67);(22)LAPQDTTKNA(SEQ ID NO:68);(23)LAKADETRPA(SEQ ID NO:69);(24)LAHQDTAKNA(SEQ ID NO:70);(25)LAHQDTKKNA(SEQ ID NO:71);(26)LAHQDTTKHA(SEQ ID NO:72);(27)LAHQDTTKKA(SEQ ID NO:73);(28)LAHQDTTRNA(SEQ ID NO:74);(29)LAHQDTTNA(SEQ ID NO:75);(30)LAHQGTTKNA(SEQ ID NO:76);(31)LAHQVTTKNA(SEQ ID NO:77);(32)LAISDQSKPA(SEQ ID NO:78);(33)LADATKTA

(SEQ ID NO:79)；(34)LAKDTTKNA(SEQ ID NO:80)；(35)LAKSDQSRPA(SEQ ID NO:81)；(36)LAPQDTKKNA(SEQ ID NO:82)；(37)LATSDSTKAA(SEQ ID NO:83)；(38)LAVDGSQRSA(SEQ ID NO:84)；(39)LPISDQTKHA(SEQ ID NO:85)；(40)LPKDATKTIA(SEQ ID NO:86)；(41)LPPQDTTKNA(SEQ ID NO:87)；(42)PAPQDTTKNA(SEQ ID NO:88)；(43)QAHQDTTKNA(SEQ ID NO:89)；(44)LAHETSPRPA(SEQ ID NO:90)；(45)LAKSTSTAPA(SEQ ID NO:91)；(46)LADQDTTKNA(SEQ ID NO:92)；(47)LAESDQSKPA(SEQ ID NO:93)；(48)LAHKDTTKNA(SEQ ID NO:94)；(49)LAHKTQQKM(SEQ ID NO:95)；(50)LAHQDTTENA(SEQ ID NO:96)；(51)LAHQDTTINA(SEQ ID NO:97)；(52)LAHQDTTKKT(SEQ ID NO:98)；(53)LAHQDTTKND(SEQ ID NO:99)；(54)LAHQDTTKNT(SEQ ID NO:100)；(55)LAHQDTTKNV(SEQ ID NO:101)；(56)LAHQDTTKTM(SEQ ID NO:102)；(57)LAHQNTTKNA(SEQ ID NO:103)；(58)LAHRDTTKNA(SEQ ID NO:104)；(59)LAISDQTNHA(SEQ ID NO:105)；(60)LAKQKSASTA(SEQ ID NO:106)；(61)LAKSDQCKPA(SEQ ID NO:107)；(62)LAKSDQSKPD(SEQ ID NO:108)；(63)LAKSDQSNPA(SEQ ID NO:109)；(64)LAKSYQSKPA(SEQ ID NO:110)；(65)LANQDTTKNA(SEQ ID NO:111)；(66)LAPQNTTKNA(SEQ ID NO:112)；(67)LAPSSIQKPA(SEQ ID NO:113)；(68)LAQQDTTKNA(SEQ ID NO:114)；(69)LAYQDTTKNA(SEQ ID NO:115)；(70)LDHQDTTKNA(SEQ ID NO:116)；(71)LDHQDTTKSA(SEQ ID NO:117)；(72)LGHQDTTKNA(SEQ ID NO:118)；(73)LPHQDTTKND(SEQ ID NO:119)；(74)LPHQDTTKNT(SEQ ID NO:120)；(75)LPHQDTTNNA(SEQ ID NO:121)；(76)LTHQDTTKNA(SEQ ID NO:122)；(77)LTKDATKTIA(SEQ ID NO:123)；(78)LTPQDTTKNA(SEQ ID NO:124)；(79)LVHQDTTKNA(SEQ ID NO:125)；(80)LAKANQNTPA(SEQ ID NO:126)；(81)LATTPITKPA(SEQ ID NO:127)；(82)LATTPIAKPA(SEQ ID NO:128)；(83)LAIEDHTKSA(SEQ ID NO:129)；(84)LAQSEHQRPA(SEQ ID NO:130)；(85)LAKSPNKDNA(SEQ ID NO:131)；(86)LANQDYTKTA(SEQ ID NO:132)；(87)LANSTDQTRA(SEQ ID NO:133)；(88)LALGETTRPA(SEQ ID NO:134)；(89)LANSTEQTRA(SEQ ID NO:135)；(90)LAQADTTKNA(SEQ ID NO:136)；(91)LASKDITKTA(SEQ ID NO:137)；(92)LASPRHNKKC(SEQ ID NO:138)；(93)LAHQDTTKTIA(SEQ ID NO:139)；(94)LAAQGTANL(SEQ ID NO:140)；(95)VAIEDHTKSA(SEQ ID NO:141)；和(96)LAKANQNTPKNA(SEQ ID NO:142)。

[0153] 在一些情况下,肽插入物为(11)PAPQDTTKKA(SEQ ID NO:57)。在一些情况下,肽插入物为(7)LAPDSTTRSA(SEQ ID NO:53)。

[0154] 在一些实施方案中,除相对于对应的亲本AAV衣壳蛋白,GH环或环IV中约5个氨基酸至约20个氨基酸(例如5个、6个、7个、8个、9个、10个、11个、12个、13个、14个、15个、16个、17个、18个、19个或20个氨基酸;例如9个氨基酸、10个氨基酸、11个氨基酸或12个氨基酸)的插入外,主题rAAV病毒体衣壳不包括任何其它的氨基酸取代、插入或缺失。在其它实施方案中,除相对于对应的亲本AAV衣壳蛋白,GH环或环IV中约5个氨基酸至约20个氨基酸(例如5个、6个、7个、8个、9个、10个、11个、12个、13个、14个、15个、16个、17个、18个、19个或20个氨基酸;例如9个氨基酸、10个氨基酸、11个氨基酸或12个氨基酸)的插入外,与亲本AAV衣壳蛋白相比,主题rAAV病毒体衣壳包括1至约25个氨基酸插入、缺失或取代。举例来说,在一些实施方案中,除相对于对应的亲本AAV衣壳蛋白,GH环或环IV中的约5个氨基酸至约20个氨基酸(例如5个、6个、7个、8个、9个、10个、11个、12个、13个、14个、15个、16个、17个、18个、19个或20个氨基酸;例如9个氨基酸、10个氨基酸、11个氨基酸或12个氨基酸)的插入外,与亲本

AAV衣壳蛋白相比,主题rAAV病毒体衣壳包括1至约5个、约5至约10个、约10至约15个、约15至约20个或约20至约25个氨基酸插入、缺失或取代。

[0155] 在一些情况下,主题rAAV病毒体衣壳不包括以下氨基酸取代中的一个、两个、三个或四个:Y273F、Y444F、Y500F和Y730F。

[0156] 在一些情况下,除如上所述的插入肽外,主题变异衣壳多肽包含以下氨基酸取代中的一个、两个、三个或四个:Y273F、Y444F、Y500F和Y730F。

[0157] 在一些情况下,主题rAAV病毒体衣壳为嵌合衣壳,例如衣壳包含第一AAV血清型的AAV衣壳的一部分和第二血清型的AAV衣壳的一部分;且相对于对应的亲本AAV衣壳蛋白,在GH环或环IV中包含约5个氨基酸至约20个氨基酸(例如5个、6个、7个、8个、9个、10个、11个、12个、13个、14个、15个、16个、17个、18个、19个或20个氨基酸;例如9个氨基酸、10个氨基酸、11个氨基酸或12个氨基酸)。

[0158] 在一些实施方案中,主题rAAV病毒体包含如下衣壳蛋白,其氨基酸序列具有与图4中提供的氨基酸序列至少约85%、至少约90%、至少约95%、至少约98%或至少约99%氨基酸序列一致性;且相对于对应的亲本AAV衣壳蛋白,在GH环或环IV中包含约5个氨基酸至约20个氨基酸(例如5个、6个、7个、8个、9个、10个、11个、12个、13个、14个、15个、16个、17个、18个、19个或20个氨基酸;例如9个氨基酸、10个氨基酸、11个氨基酸或12个氨基酸)的插入。在一些实施方案中,主题rAAV病毒体包含如下衣壳蛋白,其氨基酸序列具有与图4中提供的氨基酸序列至少约85%、至少约90%、至少约95%、至少约98%或至少约99%氨基酸序列一致性;且相对于图4中描绘的氨基酸序列,在氨基酸587与588之间,或在相对于对应的亲本AAV衣壳蛋白的对应位点,包含约5个氨基酸至约20个氨基酸(例如5个、6个、7个、8个、9个、10个、11个、12个、13个、14个、15个、16个、17个、18个、19个或20个氨基酸;例如9个氨基酸、10个氨基酸、11个氨基酸或12个氨基酸)的插入。

[0159] 在一些实施方案中,主题rAAV病毒体包含包括如下GH环的衣壳蛋白,所述GH环包含与图5中阐述的氨基酸序列具有至少约85%、至少约90%、至少约95%、至少约98%、至少约99%或100%氨基酸序列一致性的氨基酸序列,且在粗体与加下划线的氨基酸之间包含约5个氨基酸至约20个氨基酸(例如5个、6个、7个、8个、9个、10个、11个、12个、13个、14个、15个、16个、17个、18个、19个或20个氨基酸;例如9个氨基酸、10个氨基酸、11个氨基酸或12个氨基酸)的插入。

[0160] 在一些实施方案中,主题rAAV病毒体包含如下衣壳蛋白,其氨基酸序列具有与图6A-6C中提供的任一氨基酸序列至少约85%、至少约90%、至少约95%、至少约98%或至少约99%氨基酸序列一致性;且在AAV2的氨基酸587与588之间,或在相对于另一AAV基因型的对应位点,包含约5个氨基酸至约20个氨基酸(例如5个、6个、7个、8个、9个、10个、11个、12个、13个、14个、15个、16个、17个、18个、19个或20个氨基酸;例如9个氨基酸、10个氨基酸、11个氨基酸或12个氨基酸)的插入。在一些情况下,对应插入位点为如图6B中粗体文字和下划线所指示的位点。

[0161] 与包含对应的亲本AAV衣壳蛋白的AAV病毒体对视网膜细胞的感染性相比,主题rAAV病毒体展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对视网膜细胞的感染性。

[0162] 在一些情况下,与包含对应的亲本AAV衣壳蛋白的AAV病毒体在经由玻璃体内注射

进行施用时对视网膜细胞的感染性相比，主题rAAV病毒体在经由玻璃体内注射进行施用时展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对视网膜细胞的感染性。

[0163] 在一些实施方案中，与包含对应的亲本AAV衣壳蛋白的AAV病毒体对感光细胞的感染性相比，主题rAAV病毒体展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对感光(视杆或视锥)细胞的感染性。

[0164] 在一些实施方案中，与包含对应的亲本AAV衣壳蛋白的AAV病毒体在经由玻璃体内注射进行施用时对感光细胞的感染性相比，主题rAAV病毒体在经由玻璃体内注射进行施用时，展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对感光(视杆或视锥)细胞的感染性。

[0165] 在一些实施方案中，与包含对应的亲本AAV衣壳蛋白的AAV病毒体对RGC的感染性相比，主题rAAV病毒体展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对RGC的感染性。

[0166] 在一些实施方案中，与包含对应的亲本AAV衣壳蛋白的AAV病毒体在经由玻璃体内注射进行施用时对RGC的感染性相比，主题rAAV病毒体在经由玻璃体内注射进行施用时展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对RGC的感染性。

[0167] 在一些实施方案中，与包含对应的亲本AAV衣壳蛋白的AAV病毒体对RPE细胞的感染性相比，主题rAAV病毒体展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对RPE细胞的感染性。

[0168] 在一些实施方案中，与包含对应的亲本AAV衣壳蛋白的AAV病毒体在经由玻璃体内注射进行施用时对RPE细胞的感染性相比，主题rAAV病毒体在经由玻璃体内注射进行施用时展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对RPE细胞的感染性。

[0169] 在一些实施方案中，与包含对应的亲本AAV衣壳蛋白的AAV病毒体对米勒细胞的感染性相比，主题rAAV病毒体展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对米勒细胞的感染性。

[0170] 在一些实施方案中，与包含对应的亲本AAV衣壳蛋白的AAV病毒体在经由玻璃体内注射进行施用时对米勒细胞的感染性相比，主题rAAV病毒体在经由玻璃体内注射进行施用时展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对米勒细胞的感染性。

[0171] 在一些实施方案中，与包含对应的亲本AAV衣壳蛋白的AAV病毒体对双极细胞的感染性相比，主题rAAV病毒体展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对双极细胞的感染性。

[0172] 在一些实施方案中，与包含对应的亲本AAV衣壳蛋白的AAV病毒体在经由玻璃体内注射进行施用时对双极细胞的感染性相比，主题rAAV病毒体在经由玻璃体内注射进行施用时展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对双极细胞的感染性。

[0173] 在一些实施方案中，与包含对应的亲本AAV衣壳蛋白的AAV病毒体对无长突细胞的

感染性相比,主题rAAV病毒体展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对无长突细胞的感染性。

[0174] 在一些实施方案中,与包含对应的亲本AAV衣壳蛋白的AAV病毒体在经由玻璃体内注射进行施用时对无长突细胞的感染性相比,主题rAAV病毒体在经由玻璃体内注射进行施用时展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对无长突细胞的感染性。

[0175] 在一些实施方案中,与包含对应的亲本AAV衣壳蛋白的AAV病毒体对水平细胞的感染性相比,主题rAAV病毒体展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对水平细胞的感染性。

[0176] 在一些实施方案中,与包含对应的亲本AAV衣壳蛋白的AAV病毒体在经由玻璃体内注射进行施用时对水平细胞的感染性相比,主题rAAV病毒体在经由玻璃体内注射进行施用时展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对水平细胞的感染性。

[0177] 在一些实施方案中,与包含对应的亲本AAV衣壳蛋白的AAV病毒体对视网膜星形细胞的感染性相比,主题rAAV病毒体展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对视网膜星形细胞的感染性。

[0178] 在一些实施方案中,与包含对应的亲本AAV衣壳蛋白的AAV病毒体在经由玻璃体内注射进行施用时对视网膜星形细胞的感染性相比,主题rAAV病毒体在经由玻璃体内注射进行施用时展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对视网膜星形细胞的感染性。

[0179] 在一些情况下,与包含对应的亲本AAV衣壳蛋白的AAV病毒体跨越内界膜(ILM)的能力相比,主题rAAV病毒体展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的跨越ILM的能力。

[0180] 在一些情况下,与包含对应的亲本AAV衣壳蛋白的AAV病毒体在经由玻璃体内注射进行施用时跨越ILM的能力相比,主题rAAV病毒体在经由玻璃体内注射进行施用时,展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的跨越ILM的能力。

[0181] 主题rAAV病毒体可以跨越ILM,且还可以横越细胞层,包括米勒细胞、无长突细胞等等,到达感光细胞和或RPE细胞。举例来说,主题rAAV病毒体在经由玻璃体内注射进行施用时可以跨越ILM,且还可以横越细胞层,包括米勒细胞、无长突细胞等等,到达感光细胞和或RPE细胞。

[0182] 在一些情况下,与经玻璃体内注射的包含对应的亲本AAV衣壳蛋白的对照AAV病毒体经过ILM定位的程度相比,主题rAAV病毒体在经玻璃体内注射时,展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的经过ILM的定位。举例来说,在一些情况下,与经玻璃体内注射的包含对应的亲本AAV衣壳蛋白的对照AAV病毒体定位至视网膜色素上皮细胞(RPE)层的程度相比,主题rAAV病毒体在经玻璃体内注射时,展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的至RPE的定位。作为另一实例,在一些情况下,与经玻璃体内注射的包含对应的亲本AAV衣壳蛋白的对照AAV病毒体定位至光感受器(PR)层的程度相比,主题rAAV病毒体在经玻璃体内注射时,展现增

加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的至PR层的定位。作为另一实例,在一些情况下,与经玻璃体内注射的包含对应的亲本AAV衣壳蛋白的对照AAV病毒体定位至内核层的程度相比,主题rAAV病毒体在经玻璃体内注射时,展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的至内核层的定位。作为另一实例,在一些情况下,与经玻璃体内注射的包含对应的亲本AAV衣壳蛋白的对照AAV病毒体定位至外核层的程度相比,主题rAAV病毒体在经玻璃体内注射时,展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的至外核层的定位。作为另一实例,在一些情况下,与经玻璃体内注射的包含对应的亲本AAV衣壳蛋白的对照AAV病毒体定位至神经节细胞层的程度相比,主题rAAV病毒体在经玻璃体内注射时,展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的至神经节细胞层的定位。

[0183] 在一些实施方案中,主题rAAV病毒体选择性地感染视网膜细胞,例如主题rAAV病毒体以比非视网膜细胞(例如在眼睛外的细胞)大10倍、15倍、20倍、25倍、50倍或超过50倍的特异性感染视网膜细胞。举例来说,在一些实施方案中,主题rAAV病毒体选择性地感染视网膜细胞,例如主题rAAV病毒体以比非视网膜细胞(例如在眼睛外的细胞)大10倍、15倍、20倍、25倍、50倍或超过50倍的特异性感染感光细胞。

[0184] 在一些实施方案中,主题rAAV病毒体选择性地感染感光细胞,例如主题rAAV病毒体以比眼睛中存在的非感光细胞(例如视网膜神经节细胞、米勒细胞等)大10倍、15倍、20倍、25倍、50倍或超过50倍的特异性感染感光细胞。

[0185] 在一些实施方案中,与包含对应的亲本AAV衣壳蛋白的AAV病毒体在经由玻璃体内注射进行施用时对感光细胞的感染性相比,主题rAAV病毒体在经由玻璃体内注射进行施用时展现增加至少5倍、至少10倍、至少15倍、至少20倍、至少25倍、至少50倍或超过50倍的对感光细胞的感染性。

[0186] 基因产物

[0187] 主题rAAV病毒体包含异源核酸,所述异源核酸包含编码基因产物(异源基因产物)的核苷酸序列。在一些情况下,基因产物为多肽。

[0188] 在一些情况下,基因产物为RNA。在基因产物为RNA的情况下,在一些情况下,RNA基因产物编码多肽。在一些情况下,本公开的rAAV病毒体包含单个异源核酸,该单个异源核酸包含编码单个异源基因产物的核苷酸序列。在一些情况下,本公开的rAAV病毒体包含单个异源核酸,该单个异源核酸包含编码两个异源基因产物的核苷酸序列。在一些情况下,本公开的rAAV病毒体包含两个异源核酸,每个异源核酸包含编码异源基因产物的核苷酸序列。

[0189] 在一些实施方案中,基因产物为干扰RNA。在一些实施方案中,基因产物为适体。在一些实施方案中,基因产物为多肽。在一些实施方案中,基因产物为提供基因功能的位点特异性敲低的位点特异性核酸酶。在一些实施方案中,基因产物为提供靶核酸的修饰的RNA引导的核酸内切酶。

[0190] 干扰RNA

[0191] 在基因产物为干扰RNA(RNAi)的情况下,合适的RNAi包括降低细胞中细胞凋亡或血管生成因子的水平的RNAi。举例来说,RNAi可以为降低细胞中诱发或促进细胞凋亡的基因产物的水平的shRNA或siRNA。基因产物诱发或促进细胞凋亡的基因在本文中称为“促细

胞凋亡基因”,且那些基因的产物(mRNA;蛋白质)称为“促细胞凋亡基因产物”。促细胞凋亡基因产物包括例如Bax、Bid、Bak和Bad基因产物。参见例如美国专利No.7,846,730。

[0192] 干扰RNA还可以针对血管生成产物,例如血管内皮生长因子(VEGF)(例如Cand5;参见例如美国专利公布No.2011/0143400;美国专利公布No.2008/0188437;和Reich等人(2003)Mol.Vis.9:210);VEGF受体-1(VEGFR1)(例如Sirna-027;参见例如Kaiser等人(2010)Am.J.Ophthalmol.150:33;和Shen等人(2006)Gene Ther.13:225);或VEGF受体-2(VEGFR2)(Kou等人(2005)Biochem.44:15064)。又参见美国专利No.6,649,596、6,399,586、5,661,135、5,639,872和5,639,736;和美国专利No.7,947,659和7,919,473。

[0193] 适体

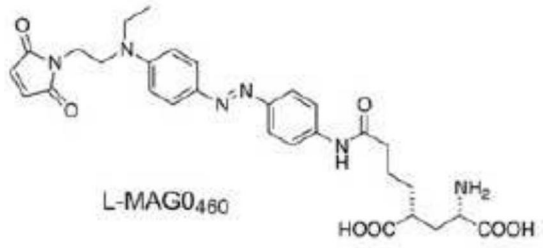
[0194] 在基因产物为适体的情况下,所关注的例示性适体包括针对VE GF的适体。参见例如Ng等人(2006)Nat.Rev.Drug Discovery 5:123;和Lee等人(2005)Proc.Natl.Acad.Sci.USA 102:18902。举例来说,VEGF适体可以包含核苷酸序列5’-cgcaaucagugaaugcuuauacau ccg-3’(SEQ ID NO://)。血小板源性生长因子(PDGF)特异性适体,例如E10030也是适用的;参见例如Ni和Hui(2009)Ophthalmologica223:401;和Akiyama等人(2006)J.Cell Physiol.207:407)。

[0195] 多肽

[0196] 在基因产物为多肽的情况下,多肽一般为增强视网膜细胞的功能,例如视杆或视锥感光细胞、视网膜神经节细胞、米勒细胞、双极细胞、无长突细胞、水平细胞或视网膜色素上皮细胞的功能的多肽。例示性多肽包括神经保护多肽(例如胶质细胞源性神经营养因子(GDNF)、睫状神经营养因子(CNTF)、神经营养素-4(NT4)、神经生长因子(NGF)和神经秩蛋白(neurturin,NTN));抗血管生成多肽(例如可溶性VEGF受体;VEGF结合抗体;VEGF结合抗体片段(例如单链抗VEGF抗体);内皮抑素(endostatin);肿瘤抑素(tumstatin);血管抑素(angiostatin);可溶性Flt多肽(Lai等人(2005)Mol.Ther.12:659);包含可溶性Flt多肽的Fc融合蛋白(参见例如Pechan等人(2009)Gene Ther.16:10);色素上皮衍生因子(PEDF);可溶性Tie-2受体等);组织金属蛋白酶抑制因子-3(TIMP-3);光反应性视蛋白,例如视紫红质;抗细胞凋亡多肽(例如Bcl-2、Bcl-Xl;XIAP)等等。合适的多肽包括(但不限于)神经胶质源性神经营养因子(GDNF);成纤维细胞生长因子;成纤维细胞生长因子2;神经秩蛋白(NTN);睫状神经营养因子(CNTF);神经生长因子(NGF);神经营养素-4(NT4);脑源性神经营养因子(BDNF;例如氨基酸序列具有与图7B中描绘的氨基酸序列(SEQ ID NO:11)的约200个氨基酸至247个氨基酸的相邻延伸至少约90%、至少约95%、至少约98%、至少约99%或100%氨基酸序列一致性的多肽);表皮生长因子;视紫红质;X连锁凋亡抑制因子;和音猬因子。

[0197] 合适的光反应性视蛋白包括例如如以下中所述的光反应性视蛋白:美国专利公布No.2007/0261127(例如光敏感通道-2;ChR2;Chop2);美国专利公布No.2001/0086421;美国专利公布No.2010/0015095;美国专利公布No.2016/0002302;美国专利公布No.2013/0347137;美国专利公布No.2013/0019325;和Diester等人(2011)Nat.Neurosci.14:387。参见Thyagarajan等人(2010)J Neurosci.30(26):8745-8758;Lagali等人(2008)Nat Neurosci.11(6):667-675;Doroudchi等人(2011)Mol Ther.19(7):1220-1229;Henriksen等人(2014)J.Ophthalmic Vis.Res.9:374;Tomita等人(2014)Mol.Ther.22:1434。

[0198] 合适的多肽包括光门控离子通道多肽。参见例如Gaub等人(2014)Proc.Natl.Acad.Sci.USA 111:E5574。举例来说,合适的多肽为光门控离子型谷氨酸受体(LiGluR)。在可光异构化化合物存在下LiGluR在视网膜神经节细胞和ON-双极细胞中的表达使细胞对光起反应。LiGluR包含L439C取代;参见Caporale等人(2011)Mol Ther.19:1212-1219;Volgraf等人(2006)Nat Chem Biol.2:47-52;和Gorostiza等人(2007)Proc Natl Acad Sci USA.104:10865-10870。可光异构化化合物包括例如在460nm下具有峰值效率的顺丁烯二酰亚胺-偶氮苯-谷氨酸酯0(MAG0$_{460}$)。MAG0$_{460}$具有以下结构:

[0199] 

。

[0200] 合适的多肽还包括视网膜劈裂蛋白(例如氨基酸序列具有与图7A中描绘的氨基酸序列(SEQ ID NO:10)的约200个氨基酸至224个氨基酸的相邻延伸至少约90%、至少约95%、至少约98%、至少约99%或100%氨基酸序列一致性的多肽)。合适的多肽包括例如视网膜色素变性GTP酶调控因子(RPGR)相互作用蛋白-1(参见例如GenBank登记号Q96KN7、Q9EPQ2和Q9GLM3)(例如氨基酸序列具有与图7F中描绘的氨基酸序列(SEQ ID NO:15)的约1150个氨基酸至1200个氨基酸或约1200个氨基酸至1286个氨基酸的相邻延伸至少约90%、至少约95%、至少约98%、至少约99%或100%氨基酸序列一致性的多肽);外周蛋白-2(Prph2)(参见例如GenBank登记号NP_000313(例如氨基酸序列具有与图7D中描绘的氨基酸序列(SEQ ID NO:13)的约300个氨基酸至346个氨基酸的相邻延伸至少约90%、至少约95%、至少约98%、至少约99%或100%氨基酸序列一致性的多肽;和Travis等人(1991)Genomics 10:733);外周蛋白(例如氨基酸序列具有与图7E中描绘的氨基酸序列(SEQ ID NO:14)的约400个氨基酸至约470个氨基酸的相邻延伸至少约90%、至少约95%、至少约98%、至少约99%或100%氨基酸序列一致性的多肽;视网膜色素上皮细胞特异性蛋白(RPE65)(例如氨基酸序列具有与图7C中描绘的氨基酸序列(SEQ ID NO:12)的约200个氨基酸至247个氨基酸的相邻延伸至少约90%、至少约95%、至少约98%、至少约99%或100%氨基酸序列一致性的多肽)(参见例如GenBank AAC39660;和Morimura等人(1998)Proc.Natl.Acad.Sci.USA 95:3088);视杆源性视锥细胞活力因子(RdCVF)(例如氨基酸序列具有与图7H、7I和7J中的任一个中描绘的氨基酸序列至少约90%、至少约95%、至少约98%、至少约99%或100%氨基酸序列一致性的多肽;无脉络膜(例如氨基酸序列具有与图7G中描绘的氨基酸序列至少约90%、至少约95%、至少约98%、至少约99%或100%氨基酸序列一致性的多肽);视网膜色素变性GTP酶调控因子(RPGR)(例如氨基酸序列具有与图7S-7V中的一个中描绘的氨基酸序列至少约90%、至少约95%、至少约98%、至少约99%或100%氨基酸序列一致性的多肽)等等。举例来说,在一些情况下,合适的RPGR多肽包含具有与图7S中描绘的氨基酸序列至少约90%、至少约95%、至少约98%、至少约99%或100%氨基酸序列一致性的氨基酸序列。作为另一实例,在一些情况下,合适的RPGR多肽包含具有与图7T中描绘的氨基酸序列至少约90%、至少约95%、至少约98%、至少约99%或100%氨基

酸序列一致性的氨基酸序列。举例来说,在一些情况下,合适的RPGR多肽包含具有与图7U中描绘的氨基酸序列至少约90％、至少约95％、至少约98％、至少约99％或100％氨基酸序列一致性的氨基酸序列。举例来说,在一些情况下,合适的RPGR多肽包含具有与图7V中描绘的氨基酸序列至少约90％、至少约95％、至少约98％、至少约99％或100％氨基酸序列一致性的氨基酸序列。

[0201] 合适的多肽还包括:CHM(无脉络膜(Rab护送蛋白1(REP1))),一种在有缺陷或缺失时引起无脉络膜的多肽(参见例如Donnelly等人(1994)Hum.Mol.Genet.3:1017;和van Bokhoven等人(1994)Hum.Mol.Genet.3:1041);和Crumbs同源物1(CRB1),一种在有缺陷或缺失时引起利伯氏先天性黑朦和色素性视网膜炎的多肽(参见例如den Hollander等人(1999)Nat.Genet.23:217;和GenBank登记号CAM23328)。举例来说,合适的REP1多肽可以包含具有与图7G中描绘的氨基酸序列组至少约90％、至少约95％、至少约98％、至少约99％或100％氨基酸序列一致性的氨基酸序列。

[0202] 合适的多肽包括视杆cGMP特异性3',5'-环状磷酸二酯酶子单元α(PDE6α)、视杆cGMP特异性3',5'-环状磷酸二酯酶子单元β同种型1(PDE6β同种型1)、视杆cGMP特异性3',5'-环状磷酸二酯酶子单元β同种型2(PDE6β同种型2)、视杆cGMP特异性3',5'-环状磷酸二酯酶子单元β同种型3(PDE6β同种型3)。举例来说,合适的PDE6α多肽可以包含具有与图7K中描绘的氨基酸序列组至少约90％、至少约95％、至少约98％、至少约99％或100％氨基酸序列一致性的氨基酸序列。作为另一实例,合适的PDE6β6同种型1多肽可以包含具有与图7L中描绘的氨基酸序列组至少约90％、至少约95％、至少约98％、至少约99％或100％氨基酸序列一致性的氨基酸序列。作为另一实例,合适的PDE6β6同种型2多肽可以包含具有与图7M中描绘的氨基酸序列组至少约90％、至少约95％、至少约98％、至少约99％或100％氨基酸序列一致性的氨基酸序列。作为另一实例,合适的PDE6β6同种型3多肽可以包含具有与图7N中描绘的氨基酸序列组至少约90％、至少约95％、至少约98％、至少约99％或100％氨基酸序列一致性的氨基酸序列。

[0203] 合适的多肽还包括当有缺陷或缺失时引起全色盲的多肽,其中此类多肽包括例如视锥光感受器cGMP门控通道子单元α(CNGA3)(参见例如GenBank登记号NP_001289;和Booij等人(2011)Ophthalmology 118:160-167);视锥光感受器cGMP门控阳离子通道β-子单元(CNGB3)(参见例如Kohl等人(2005)Eur J Hum Genet.13(3):302);鸟嘌呤核苷酸结合蛋白(G蛋白)、α转导活性多肽2(GNAT2)(ACHM4);和ACHM5;和当有缺陷或缺乏时引起色盲的多种形式的多肽(例如L-视蛋白、M-视蛋白和S-视蛋白)。参见Mancuso等人(2009)Nature 461(7265):784-787。

[0204] 举例来说,合适的CNGA3(又名ACHM2)同种型1多肽可以包含具有与图7O中描绘的氨基酸序列组至少约90％、至少约95％、至少约98％、至少约99％或100％氨基酸序列一致性的氨基酸序列。作为另一实例,合适的CNGA3(又名ACHM2)同种型2多肽可以包含具有与图7P中描绘的氨基酸序列组至少约90％、至少约95％、至少约98％、至少约99％或100％氨基酸序列一致性的氨基酸序列。

[0205] 作为另一实例,合适的CNGB3(又名ACHM3)多肽可以包含具有与图7Q中描绘的氨基酸序列组至少约90％、至少约95％、至少约98％、至少约99％或100％氨基酸序列一致性的氨基酸序列。作为另一实例,GNAT2(又名ACHM4)可以包含具有与图7R中描绘的氨基酸序列

组至少约90％、至少约95％、至少约98％、至少约99％或100％氨基酸序列一致性的氨基酸序列。

[0206] 位点特异性核酸内切酶

[0207] 在一些情况下,所关注的基因产物为提供基因功能的位点特异性敲低的位点特异性核酸内切酶,例如其中核酸内切酶敲除与视网膜疾病有关的等位基因。举例来说,在显性等位基因编码当野生型时为视网膜结构蛋白和/或提供正常的视网膜功能的基因的缺陷拷贝的情况下,位点特异性核酸内切酶可以靶向缺陷等位基因且敲出缺陷等位基因。在一些情况下,位点特异性核酸内切酶为RNA引导的核酸内切酶。

[0208] 除敲除缺陷等位基因外,位点特异性核酸酶还可以用于刺激与编码由缺陷等位基因编码的蛋白质的功能性拷贝的供体DNA的同源重组。因此,例如,主题rAAV病毒体可以用于递送敲除缺陷等位基因的位点特异性核酸内切酶,且可以用于递送缺陷等位基因的功能性拷贝,引起缺陷等位基因的修复,从而产生功能性视网膜蛋白(例如功能性视网膜劈裂蛋白、功能性RPE65、功能性外周蛋白等等)。参见例如Li等人(2011)Nature 475:217。在一些实施方案中,主题rAAV病毒体包含编码位点特异性核酸内切酶的异源核苷酸序列;和编码缺陷等位基因的功能性拷贝的异源核苷酸序列,其中功能性拷贝编码功能性视网膜蛋白。功能性视网膜蛋白包括例如视网膜劈裂蛋白、RPE65、视网膜色素变性GTP酶调控因子(RGPR)相互作用蛋白-1、外周蛋白、外周蛋白-2、RdCVF等等。

[0209] 适用的位点特异性核酸内切酶包括例如锌指核酸酶(ZFN);大范围核酸酶;和转录激活因子样效应物核酸酶(TALEN),其中此类位点特异性核酸内切酶并非天然存在的且经修饰以靶向特定基因。此类位点特异性核酸酶可以进行工程化以切割基因组内的特定位置,且接着非同源性末端接合可以在插入或缺失若干核苷酸时修复断裂。接着此类位点特异性核酸内切酶(又称为“INDEL”)将蛋白质抛出框,且有效地敲除基因。参见例如美国专利公布No.2011/0301073。合适的位点特异性核酸内切酶包括工程化的大范围核苷酸、再次工程化的归巢核酸内切酶。合适的核酸内切酶包括I-Tevl核酸酶。合适的大范围核酸酶包括I-Sce1(参见例如Bellaiche等人(1999)Genetics 152:1037);和I-Cre1(参见例如Heath等人(1997)Nature Sructural Biology 4:468)。

[0210] RNA引导的核酸内切酶

[0211] 在一些情况下,基因产物为RNA引导的核酸内切酶。在一些情况下,基因产物为包含编码RNA引导的核酸内切酶的核苷酸序列的RNA。在一些情况下,基因产物为向导RNA,例如单向导RNA。在一些情况下,基因产物为:1)向导RNA;和2)RNA引导的核酸内切酶。向导RNA可以包含:a)结合于RNA引导的核酸内切酶的蛋白结合区;和b)结合于靶核酸的区域。RNA引导的核酸内切酶在本文中又称为“基因组编辑核酸酶”。

[0212] 合适的基因组编辑核酸酶的实例为CRISPR/Cas核酸内切酶(例如2类CRISPR/Cas核酸内切酶,例如II型、V型或VI型CRISPR/Cas核酸内切酶)。因此,基因组靶向组合物可以包括CRISPR/Cas核酸内切酶(例如2类CRISPR/Cas核酸内切酶,例如II型、V型或VI型CRISPR/Cas核酸内切酶)。在一些情况下,基因组靶向组合物包括2类CRISPR/Cas核酸内切酶。在一些情况下,基因组靶向组合物包括2类II型CRISPR/Cas核酸内切酶(例如Cas9蛋白)。在一些情况下,基因组靶向组合物包括2类V型CRISPR/Cas核酸内切酶(例如Cpf1蛋白、C2c1蛋白或C2c3蛋白)。在一些情况下,基因组靶向组合物包括2类VI型CRISPR/Cas核酸内

切酶(例如C2c2蛋白)。

[0213] 在一些情况下,基因组编辑核酸酶为与异源多肽(又称为“融合搭配物”)融合的融合蛋白。在一些情况下,基因组编辑核酸酶与提供亚细胞定位的氨基酸序列(融合搭配物)融合,即融合搭配物为亚细胞定位序列(例如一种或多种用于靶向核的核定位信号(NLS)、两种或更多种NLS、三种或更多种NLS等)。

[0214] 在一些情况下,基因组编辑核酸内切酶为II型CRISPR/Case核酸内切酶。在一些情况下,基因组编辑核酸内切酶为Cas9多肽。Cas9蛋白由于与Cas9向导RNA的蛋白结合区段缔合而被引导至靶核酸序列(例如染色体序列或染色体外序列,例如游离体序列、微环序列、线粒体序列、叶绿体序列等)内的靶位点(例如稳定在靶位点)。在一些情况下,Cas9多肽包含具有与图8A中描绘的酿脓链球菌(Streptococcus pyogenes)Cas9至少50%、至少60%、至少70%、至少80%、至少90%、至少95%、至少98%、至少99%或超过99%氨基酸序列一致性的氨基酸序列。在一些情况下,用于本公开的组合物或方法中的Cas9多肽为金黄色葡萄球菌(Staphylococcus aureus)Cas9(saCas9)多肽。在一些情况下,saCas9多肽包含具有与图8B中描绘的saCas9氨基酸序列至少85%、至少90%、至少95%、至少98%、至少99%或100%氨基酸序列一致性的氨基酸序列。

[0215] 在一些情况下,合适的Cas9多肽为高保真度(HF)Cas9多肽。Kleinstiver等人(2016)Nature 529:490。举例来说,图8A中描绘的氨基酸序列的氨基酸N497、R661、Q695和Q926经例如丙氨酸取代。举例来说,HF Cas9多肽可以包含具有与图8A中描绘的氨基酸序列至少90%、至少95%、至少98%、至少99%或100%氨基酸序列一致性的氨基酸序列,其中氨基酸N497、R661、Q695和Q926经例如丙氨酸取代。

[0216] 在一些情况下,合适的Cas9多肽展现改变的PAM特异性。参见例如Kleinstiver等人(2015)Nature 523:481。

[0217] 在一些情况下,基因组编辑核酸内切酶为V型CRISPR/Cas核酸内切酶。在一些情况下,V型CRISPR/Cas核酸内切酶为Cpf1蛋白。在一些情况下,Cpf1蛋白包含具有与图8C中描绘的Cpf1氨基酸序列至少30%、至少35%、至少40%、至少45%、至少50%、至少55%、至少60%、至少65%、至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少90%或100%氨基酸序列一致性的氨基酸序列。

[0218] 结合于2类CRISPR/Cas核酸内切酶(例如Cas9蛋白;V型或VI型CRISPR/Cas蛋白;Cpf1蛋白等)且将复合物靶向靶核酸内的特定位置的核酸在本文中称为“向导RNA”或“CRISPR/Cas向导核酸”或“CRISPR/Cas向导RNA”。向导RNA通过包括靶向区段提供对复合物(RNP复合物)的特异性,所述靶向区段包括向导序列(在本文中又称为靶向序列),向导序列为与靶核酸的序列互补的核苷酸序列。

[0219] 在一些情况下,向导RNA包括两个分开的核酸分子:“活化子”和“靶向子”,且在本文中称为“双向导RNA”、“双分子向导RNA”、“两分子向导RNA”或“dgRNA”。在一些情况下,向导RNA为一个分子(例如对于一些2类CRISPR/Cas蛋白,对应的向导RNA为单一分子;且在一些情况下,活化子和靶向子彼此例如经由插入核苷酸而共价连接),且向导RNA称为“单向导RNA”、“单分子向导RNA”、“一分子向导RNA”或简称为“sgRNA”。

[0220] 在基因产物为RNA引导的核酸内切酶或为RNA引导的核酸内切酶与向导RNA的情况下,基因产物可以修饰靶核酸。在一些情况下,例如在靶核酸包含缺陷等位基因中的有害突

变(例如视网膜细胞靶核酸中的有害突变)的情况下,RNA引导的核酸内切酶/向导RNA复合物与包含校正有害突变的核苷酸序列的供体核酸(例如包含编码由缺陷等位基因编码的蛋白质的功能性拷贝的核苷酸序列的供体核酸)一起可以用于例如经由同源性定向修复(HDR)校正有害突变。

[0221] 在一些情况下,基因产物为RNA引导的核酸内切酶和2个分开的sgRNA,其中2个分开的sgRNA经由非同源性末端接合(NHEJ)提供靶核酸的缺失。

[0222] 本公开提供了一种修饰个体中的视网膜细胞中的靶核酸的方法,其中靶核酸包含有害突变,所述方法包括向所述个体施用(例如通过眼内、玻璃体内等施用)本公开的rAAV病毒体,其中所述rAAV病毒体包含含有以下的异源核酸:i)编码RNA引导的核酸内切酶(例如Cas9核酸内切酶)的核苷酸序列;ii)编码包含与靶核酸互补的核苷酸序列的sgRNA的核苷酸序列;和iii)编码包含校正有害突变的核苷酸序列的供体DNA模板的核苷酸序列。rAAV病毒体的施用通过HDR校正靶核酸中的有害突变。

[0223] 本公开提供了一种修饰个体中的视网膜细胞中的靶核酸的方法,其中靶核酸包含有害突变,所述方法包括向所述个体施用(例如通过眼内、玻璃体内等施用)本公开的rAAV病毒体,其中所述rAAV病毒体包含含有以下的异源核酸:i)编码RNA引导的核酸内切酶(例如Cas9核酸内切酶)的核苷酸序列;ii)编码包含与靶核酸中的第一序列互补的核苷酸序列的第一sgRNA的核苷酸序列;和iii)编码包含与靶核酸中的第二序列互补的核苷酸序列的第二sgRNA的核苷酸序列。rAAV病毒体的施用通过NHEJ切除靶核酸中的有害突变。

[0224] 调控序列

[0225] 在一些情况下,编码所关注的基因产物的核苷酸序列可操作地连接于转录控制元件。举例来说,在一些情况下,编码所关注的基因产物的核苷酸序列可操作地连接于组成型启动子。在其它情况下,编码所关注的基因产物的核苷酸序列可操作地连接于诱导型启动子。在一些情况下,编码所关注的基因产物的核苷酸序列可操作地连接于组织特异性或细胞类型特异性调控元件。举例来说,在一些情况下,编码所关注的基因产物的核苷酸序列可操作地连接于视网膜细胞特异性启动子。举例来说,在一些情况下,编码所关注的基因产物的核苷酸序列可操作地连接于光感受器特异性调控元件(例如光感受器特异性启动子),例如赋予可操作地连接的基因在感光细胞中选择性表达的调控元件。合适的光感受器特异性调控元件包括例如视紫红质启动子;视紫红质激酶启动子(Young等人(2003)Ophthalmol.Vis.Sci.44:4076);β磷酸二酯酶基因启动子(Nicoud等人(2007)J.Gene Med.9:1015);视网膜色素变性基因启动子(Nicoud等人(2007)上述);光感受器间类维生素A结合蛋白(IRBP)基因增强子(Nicoud等人(2007)上述);IRBP基因启动子(Yokoyama等人(1992)Exp Eye Res.55:225)。

[0226] 药物组合物

[0227] 本公开提供了一种药物组合物,其包含:a)如上所述的主题rAAV病毒体;和b)药学上可接受的载剂、稀释剂、赋形剂或缓冲剂。在一些实施方案中,药学上可接受的载剂、稀释剂、赋形剂或缓冲剂适合用于人类。

[0228] 此类赋形剂、载剂、稀释剂和缓冲剂包括可以施用而无过度毒性的任何制药剂。药学上可接受的赋形剂包括(但不限于)例如水、盐水、丙三醇和乙醇等液体。其中可以包括药学上可接受的盐,例如无机酸盐,例如盐酸盐、氢溴酸盐、磷酸盐、硫酸盐等等;和有机酸盐,

例如乙酸盐、丙酸盐、丙二酸盐、苯甲酸盐等等。另外,例如湿润剂或乳化剂、pH缓冲物质等等辅助物质可以存在于此类媒剂中。本领域中已知多种药学上可接受的赋形剂且本文中无需详细地论述。药学上可接受的赋形剂已经在多个公布中充分描述,所述公布包括例如A.Gennaro(2000)"Remington:The Science and Practice of Pharmacy,"第20版,Lippincott,Williams,&Wilkins;Pharmaceutical Dosage Forms and Drug Delivery Systems(1999)H.C.Ansel等人编辑,第7版,Lippincott,Williams,&Wilkins;和Handbook of Pharmaceutical Excipients(2000)A.H.Kibbe等人编辑,第3版Amer.Pharmaceutical Assoc。

[0229] 将基因产物递送至视网膜细胞的方法和治疗方法

[0230] 本公开提供了一种将基因产物递送至个体中的视网膜细胞的方法,所述方法包括向所述个体施用如上所述的主题rAAV病毒体。如上所述,基因产物可以是多肽或干扰RNA(例如shRNA、siRNA等等)、适体或位点特异性核酸内切酶(例如RNA引导的核酸内切酶)。基因产物递送至视网膜细胞可以治疗视网膜疾病。视网膜细胞可以是光感受器、视网膜神经节细胞、米勒细胞、双极细胞、无长突细胞、水平细胞或视网膜色素上皮细胞。在一些情况下,视网膜细胞为感光细胞,例如视杆或视锥细胞。

[0231] 本公开提供了一种修饰视网膜细胞中的靶核酸的方法,所述方法包括使视网膜细胞接触:1)本公开的rAAV病毒体,其中所述rAAV病毒体包含异源核酸,所述异源核酸包含编码结合向导RNA的RNA引导的核酸内切酶的核苷酸序列;和2)向导RNA。本公开提供了一种修饰视网膜细胞中的靶核酸的方法,所述方法包括使视网膜细胞接触本公开的rAAV病毒体,其中所述rAAV病毒体包含异源核酸,所述异源核酸包含编码以下的核苷酸序列:i)结合向导RNA的RNA引导的核酸内切酶;和ii)向导RNA。在一些情况下,所述方法包括使视网膜细胞与供体DNA模板接触。在一些情况下,RNA引导的核酸内切酶为Cas9多肽。在一些情况下,向导RNA为单向导RNA。

[0232] 本公开提供了一种治疗眼病(例如视网膜疾病)的方法,所述方法包括向有需要的个体施用有效量的如上所述的主题rAAV病毒体。主题rAAV病毒体可以经由眼球内注射、通过玻璃体内注射或通过任何其它合宜的施用模式或途径施用。其它合宜的施用模式或途径包括例如静脉内、鼻内等等。

[0233] "治疗有效量"将在可以通过实验和/或临床试验测定的相对广泛的范围内。举例来说,对于体内注射,即直接注射至眼中,治疗有效剂量将大约为约10^{6}至约10^{15}rAAV病毒体,例如约10^{8}至10^{12}rAAV病毒体。对于体外转导,待递送至细胞的rAAV病毒体的有效量将大约为约10^{8}至约10^{13}rAAV病毒体。其它有效剂量容易由本领域的一般技术人员通过常规试验,确定剂量反应曲线来确定。

[0234] 在一些实施方案中,超过一次施用(例如两次、三次、四次或更多次施用)可以用以实现所需的基因表达水平。在一些情况下,超过一次施用以多个时间间隔施用,例如每日、每周、半月、每月、每3个月、每6个月、每年施用等等。在一些情况下,多次施用在1个月至2个月、2个月至4个月、4个月至8个月、8个月至12个月、1年至2年、2年至5年或超过5年的时期内施用。

[0235] 可以使用主题方法治疗的眼病包括(但不限于)急性黄斑神经视网膜病变;白塞氏病(Behcet's disease);脉络膜新生血管;糖尿病性葡萄膜炎;组织胞浆菌病;黄斑变性,例

如急性黄斑变性、非渗出性年龄相关性黄斑变性和渗出性年龄相关性黄斑变性;水肿,例如黄斑水肿、黄斑囊样水肿和糖尿病性黄斑水肿;多灶性脉络膜炎;影响后眼位点或位置的眼外伤;眼肿瘤;视网膜病症,例如视网膜中央静脉阻塞、糖尿病性视网膜病(包括增生性糖尿病性视网膜病)、增生性玻璃体视网膜病变(PVR)、视网膜动脉阻塞性疾病、视网膜剥离、葡萄膜炎视网膜病;交感性眼炎;伏格特-小柳-原田(Vogt Koyanagi-Harada,VKH)综合征;葡萄膜扩散;由眼睛激光治疗引起或受其影响的后眼病状;由光动力学疗法引起或受其影响的后眼病状;光凝、辐射性视网膜病变;视网膜外膜病症;视网膜分支静脉阻塞;前部缺血性视神经病变;非视网膜病变的糖尿病性视网膜功能障碍;视网膜劈裂;视网膜色素变性;青光眼;尤塞氏综合征(Usher syndrome)、视锥-视杆营养不良;斯特格氏病(Stargardt disease)(眼底黄色斑点症);遗传性黄斑变性;脉络膜视网膜变性;利伯氏先天性黑朦;先天性静止性夜盲;无脉络膜;巴德-毕德氏综合征(Bardet-Biedl syndrome);黄斑毛细血管扩张;利伯氏遗传性视神经病变;早产儿视网膜病;色觉障碍,包括全色盲、红色盲、绿色盲和蓝色盲;和比蒂氏结晶样视网膜营养不良(Bietti's crystalline dystrophy)。

[0236] 核酸和宿主细胞

[0237] 本公开提供了一种分离的核酸,其包含编码如上所述的主题变异腺相关病毒(AAV)衣壳蛋白的核苷酸序列,其中相对于对应的亲本AAV衣壳蛋白,所述变异AAV衣壳蛋白在GH环或环IV中包含约5个氨基酸至约20个氨基酸的插入,且其中与包含对应的亲本AAV衣壳蛋白的AAV病毒体对视网膜细胞的感染性相比,所述变异衣壳蛋白在存在于AAV病毒体中时对视网膜细胞的感染性增加。主题分离的核酸可以为AAV载体,例如重组AAV载体。

[0238] 插入肽

[0239] 由主题核酸编码的变异AAV衣壳蛋白具有约5个氨基酸至约20个氨基酸长的插入肽,所述插入肽插入AAV衣壳的GH环中。插入肽具有5个氨基酸、6个氨基酸、7个氨基酸、8个氨基酸、9个氨基酸、10个氨基酸、11个氨基酸、12个氨基酸、13个氨基酸、14个氨基酸、15个氨基酸、16个氨基酸、17个氨基酸、18个氨基酸、19个氨基酸或20个氨基酸的长度。合适的插入肽如上所述。合适的插入肽包括如上所述的式I-X中的任一个的肽。

[0240] 主题重组AAV载体可以用于产生如上所述的主题重组AAV病毒体。因此,本公开提供一种重组AAV载体,其在引入合适的细胞中时,可以产生主题重组AAV病毒体。

[0241] 本发明还提供了宿主细胞,例如分离(经遗传修饰)的宿主细胞,其包含主题核酸。主题宿主细胞可以为分离的细胞,例如体外培养的细胞。主题宿主细胞可如下所述用于产生主题rAAV病毒体。在主题宿主细胞用于产生主题rAAV病毒体的情况下,其称为"包装细胞"。在一些实施方案中,主题宿主细胞稳定地经主题核酸遗传修饰。在其它实施方案中,主题宿主细胞短暂地经主题核酸遗传修饰。

[0242] 使用建立的技术,包括(但不限于)电穿孔、磷酸钙沉淀、脂质粒介导的转染等等将主题核酸稳定或短暂地引入宿主细胞中。为稳定转化,主题核酸一般还包括可选择的标志物,例如若干众所周知的可选择的标志物中的任一种,例如新霉素抗性等等。

[0243] 主题宿主细胞通过将主题核酸引入多种细胞中的任一种,例如哺乳动物细胞,包括例如鼠科细胞和灵长类动物细胞(例如人类细胞)中而产生。合适的哺乳动物细胞包括(但不限于)初级细胞和细胞系,其中合适的细胞系包括(但不限于)293细胞、COS细胞、HeLa细胞、Vero细胞、3T3小鼠成纤维细胞、C3H10T1/2成纤维细胞、CHO细胞等等。合适的宿主细

胞的非限制性实例包括例如HeLa细胞(例如美国菌种保藏中心(American Type Culture Collection,ATCC)No.CCL-2)、CHO细胞(例如ATCC No.CRL9618、CCL61、CRL9096)、293细胞(例如ATCC No.CRL-1573)、Vero细胞、NIH 3T3细胞(例如ATCC No.CRL-1658)、Huh-7细胞、BHK细胞(例如ATCC No.CCL10)、PC12细胞(ATCC No.CRL1721)、COS细胞、COS-7细胞(ATCC No.CRL1651)、RAT1细胞、小鼠L细胞(ATCC No.CCLI.3)、人类胚肾(HEK)细胞(ATCC No.CRL1573)、HLHepG2细胞等等。主题宿主细胞还可以使用杆状病毒感染昆虫细胞如Sf9细胞,产生AAV来制成(参见例如美国专利No.7,271,002;美国专利申请12/297,958)。

[0244] 在一些实施方案中,除包含编码如上所述的变异AAV衣壳蛋白的核苷酸序列的核酸外,主题经遗传修饰的宿主细胞还包括包含编码一种或多种AAV rep蛋白的核苷酸序列的核酸。在其它实施方案中,主题宿主细胞还包含rAAV载体。rAAV病毒体可以使用主题宿主细胞产生。产生rAAV病毒体的方法描述于例如美国专利公布No.2005/0053922和美国专利公布No.2009/0202490中。

[0245] 本公开的非限制性方面的实例

[0246] 包括实施方案在内的上述本发明的主题的方面在单独或与一个或多个其它方面或实施方案组合下可以为有益的。不限制以上描述,下文提供本公开编号1-34的某些非限制性方面。如本领域的技术人员在阅读本公开后将显而易见,可以使用每个个别编号的方面或与前面或后面个别编号的方面中的任一个组合。此意图为方面的所有此类组合提供支持且不局限于以下明确提供的方面的组合:

[0247] 方面1.一种重组腺相关病毒(rAAV)病毒体,其包含:a)变异AAV衣壳蛋白,其中相对于对应的亲本AAV衣壳蛋白,所述变异AAV衣壳蛋白在衣壳蛋白GH环中包含具有5个氨基酸至约20个氨基酸长度的异源肽的插入,且其中与包含对应的亲本AAV衣壳蛋白的对照AAV病毒体对视网膜细胞的感染性相比,所述变异衣壳蛋白对视网膜细胞的感染性增加;和b)包含编码异源基因产物的核苷酸序列的异源核酸。

[0248] 方面2.方面1的rAAV病毒体,其中与包含对应的亲本AAV衣壳蛋白的对照AAV病毒体对视网膜细胞的感染性相比,所述rAAV病毒体展现增加5倍的对视网膜细胞的感染性。

[0249] 方面3.方面1的rAAV病毒体,其中与包含对应的亲本AAV衣壳蛋白的AAV病毒体对视网膜细胞的感染性相比,所述rAAV病毒体展现增加至少10倍的对视网膜细胞的感染性。

[0250] 方面4.方面1至3中任一项的rAAV病毒体,其中与包含对应的亲本AAV衣壳蛋白的AAV病毒体定位至内核层、外核层、光感受器层、神经节细胞层或视网膜色素上皮细胞的程度相比,所述rAAV病毒体展现增加至少5倍的至内核层、外核层、光感受器层、神经节细胞层和视网膜色素上皮细胞中的一个或多个的定位。

[0251] 方面5.方面1至4中任一项的rAAV病毒体,其中插入位点介于与AAV2的VP1的氨基酸570和611对应的氨基酸之间,或另一AAV血清型的衣壳蛋白中的对应位置。

[0252] 方面6.方面1至5中任一项的rAAV病毒体,其中插入位点位于与AAV2的VP1的氨基酸587和588对应的氨基酸之间,或另一AAV血清型的衣壳蛋白中的对应位置。

[0253] 方面7.方面1至6中任一项的rAAV病毒体,其中基因产物为干扰RNA或适体。

[0254] 方面8.方面1至6中任一项的rAAV病毒体,其中所述基因产物为多肽。

[0255] 方面9.方面8的rAAV病毒体,其中所述多肽为神经保护多肽、抗血管生成多肽或增强视网膜细胞的功能的多肽。

[0256] 方面10.方面8的rAAV病毒体,其中所述多肽为RNA引导的核酸内切酶。

[0257] 方面11.方面10的rAAV病毒体,其中所述RNA引导的核酸内切酶为Cas9多肽。

[0258] 方面12.方面10的rAAV病毒体,其中所述基因产物为RNA引导的核酸内切酶和向导RNA。

[0259] 方面13.方面1至12中任一项的rAAV病毒体,其中插入GH环中的所述异源肽具有式I-X中的任一个。

[0260] 方面14.方面1至12中任一项的rAAV病毒体,其中所述异源肽为式I的肽:$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$,

[0261] 其中:

[0262] X_1为Leu、Ile、Pro或Gln;

[0263] X_2为Ala、Pro、Ser、Asp、Gly、Thr或Val;

[0264] X_3为Lys、His、Thr、Ile、Pro、Val、Arg、Ala、Asp、Glu、Asn、Gln或Tyr;

[0265] X_4如果存在,那么为Gln、Asp、Ser、Gly、Thr、Ile、Asn、Glu、Lys或Arg;

[0266] X_5为Asp、Ser、Gln、Val、Thr、Gly、Ala、Asn、Lys或Tyr;

[0267] X_6为Thr、Ala、Gln、Ser、Glu、Pro或Ile;

[0268] X_7为Thr、Ser、Asn、Pro、Leu、Gln、Lys、Ala或Cys;

[0269] X_8为Lys、Ser、Arg、Thr、Ala、Glu、Ile或Asn;

[0270] X_9为Asn、Pro、Ser、Lys、His、Ile、Thr或Ala;且

[0271] X_{10}为Ala、Phe、Asp、Thr、Val或Met。

[0272] 方面15.方面14的rAAV病毒体,其中所述异源肽包含以下氨基酸序列中的一种:(1)LAKDATKNA(SEQ ID NO:47);(2)PAHQDTTKNA(SEQ ID NO:48);(3)LAHQDTTKNA(SEQ ID NO:49);(4)LATTSQNKPA(SEQ ID NO:50);(5)LAISDQTKHA(SEQ ID NO:51);(6)IARGVAPSSA(SEQ ID NO:52);(7)LAPDSTTRSA(SEQ ID NO:53);(8)LAKGTELKPA(SEQ ID NO:54);(9)LAIIDATKNA(SEQ ID NO:55);(10)LAVDGAQRSA(SEQ ID NO:56);(11)PAPQDTTKKA(SEQ ID NO:57);(12)LPHQDTTKNA(SEQ ID NO:58);(13)LAKDATKTIA(SEQ ID NO:59);(14)LAKQQSASTA(SEQ ID NO:60);(15)LAKSDQSKPA(SEQ ID NO:61);(16)LSHQDTTKNA(SEQ ID NO:62);(17)LAANQPSKPA(SEQ ID NO:63);(18)LAVSDSTKAA(SEQ ID NO:64);(19)LAAQGTAKKPA(SEQ ID NO:65);(20)LAPDQTTRNA(SEQ ID NO:66);(21)LAASDSTKAA(SEQ ID NO:67);(22)LAPQDTTKNA(SEQ ID NO:68);(23)LAKADETRPA(SEQ ID NO:69);(24)LAHQDTAKNA(SEQ ID NO:70);(25)LAHQDTKKNA(SEQ ID NO:71);(26)LAHQDTTKHA(SEQ ID NO:72);(27)LAHQDTTKKA(SEQ ID NO:73);(28)LAHQDTTRNA(SEQ ID NO:74);(29)LAHQDTTNA(SEQ ID NO:75);(30)LAHQGTTKNA(SEQ ID NO:76);(31)LAHQVTTKNA(SEQ ID NO:77);(32)LAISDQSKPA(SEQ ID NO:78);(33)LADATKTA(SEQ ID NO:79);(34)LAKDTTKNA(SEQ ID NO:80);(35)LAKSDQSRPA(SEQ ID NO:81);(36)LAPQDTKKNA(SEQ ID NO:82);(37)LATSDSTKAA(SEQ ID NO:83);(38)LAVDGSQRSA(SEQ ID NO:84);(39)LPISDQTKHA(SEQ ID NO:85);(40)LPKDATKTIA(SEQ ID NO:86);(41)LPPQDTTKNA(SEQ ID NO:87);(42)PAPQDTTKNA(SEQ ID NO:88);(43)QAHQDTTKNA(SEQ ID NO:89);(44)LAHETSPRPA(SEQ ID NO:90);(45)LAKSTSTAPA(SEQ ID NO:91);(46)LADQDTTKNA(SEQ ID NO:92);(47)LAESDQSKPA(SEQ ID NO:93);(48)LAHKDTTKNA(SEQ ID NO:94);(49)LAHKTQQKM(SEQ ID

NO:95)；(50)LAHQDTTENA(SEQ ID NO:96)；(51)LAHQDTTINA(SEQ ID NO:97)；(52)LAHQDTTKKT(SEQ ID NO:98)；(53)LAHQDTTKND(SEQ ID NO:99)；(54)LAHQDTTKNT(SEQ ID NO:100)；(55)LAHQDTTKNV(SEQ ID NO:101)；(56)LAHQDTTKTM(SEQ ID NO:102)；(57)LAHQNTTKNA(SEQ ID NO:103)；(58)LAHRDTTKNA(SEQ ID NO:104)；(59)LAISDQTNHA(SEQ ID NO:105)；(60)LAKQKSASTA(SEQ ID NO:106)；(61)LAKSDQCKPA(SEQ ID NO:107)；(62)LAKSDQSKPD(SEQ ID NO:108)；(63)LAKSDQSNPA(SEQ ID NO:109)；(64)LAKSYQSKPA(SEQ ID NO:110)；(65)LANQDTTKNA(SEQ ID NO:111)；(66)LAPQNTTKNA(SEQ ID NO:112)；(67)LAPSSIQKPA(SEQ ID NO:113)；(68)LAQQDTTKNA(SEQ ID NO:114)；(69)LAYQDTTKNA(SEQ ID NO:115)；(70)LDHQDTTKNA(SEQ ID NO:116)；(71)LDHQDTTKSA(SEQ ID NO:117)；(72)LGHQDTTKNA(SEQ ID NO:118)；(73)LPHQDTTKND(SEQ ID NO:119)；(74)LPHQDTTKNT(SEQ ID NO:120)；(75)LPHQDTTNNA(SEQ ID NO:121)；(76)LTHQDTTKNA(SEQ ID NO:122)；(77)LTKDATKTIA(SEQ ID NO:123)；(78)LTPQDTTKNA(SEQ ID NO:124)；和(79)LVHQDTTKNA(SEQ ID NO:125)。

[0273] 方面16.方面1至12中任一项的rAAV病毒体,其中所述异源肽为式II的肽：

[0274] $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$,其中：

[0275] X_1为Leu、Ile或Pro；

[0276] X_2为Ala、Pro或Ser；

[0277] X_3为Lys、His、Thr、Ile、Pro、Val、Arg或Ala；

[0278] X_4(如果存在)为Gln、Asp、Ser、Gly、Thr、Ile或Asn；

[0279] X_5为Asp、Ser、Gln、Val、Thr、Gly或Ala；

[0280] X_6为Thr、Ala、Gln、Ser、Glu或Pro；

[0281] X_7为Thr、Ser、Asn、Pro、Leu、Gln、Lys或Ala；

[0282] X_8为Lys、Ser、Arg或Thr；

[0283] X_9为Asn、Pro、Ser、Lys、His、Ile、Thr或Ala;且

[0284] X_{10}为Ala。

[0285] 方面17.方面16的rAAV病毒体,其中所述肽包含以下氨基酸序列中的一种：(1)LAKDATKNA(SEQ ID NO:47)；(2)PAHQDTTKNA(SEQ ID NO:48)；(3)LAHQDTTKNA(SEQ ID NO:49)；(4)LATTSQNKPA(SEQ ID NO:50)；(5)LAISDQTKHA(SEQ ID NO:51)；(6)IARGVAPSSA(SEQ ID NO:52)；(7)LAPDSTTRSA(SEQ ID NO:53)；(8)LAKGTELKPA(SEQ ID NO:54)；(9)LAIIDATKNA(SEQ ID NO:55)；(10)LAVDGAQRSA(SEQ ID NO:56)；(11)PAPQDTTKKA(SEQ ID NO:57)；(12)LPHQDTTKNA(SEQ ID NO:58)；(13)LAKDATKTIA(SEQ ID NO:59)；(14)LAKQQSASTA(SEQ ID NO:60)；(15)LAKSDQSKPA(SEQ ID NO:61)；(16)LSHQDTTKNA(SEQ ID NO:62)；(17)LAANQPSKPA(SEQ ID NO:63)；(18)LAVSDSTKAA(SEQ ID NO:64)；(19)LAAQGTAKKPA(SEQ ID NO:65)；(20)LAPDQTTRNA(SEQ ID NO:66)；(21)LAASDSTKAA(SEQ ID NO:67)；(22)LAPQDTTKNA(SEQ ID NO:68)；(23)LAKADETRPA(SEQ ID NO:69)；(24)LAHQDTAKNA(SEQ ID NO:70)；(25)LAHQDTKKNA(SEQ ID NO:71)；(26)LAHQDTTKHA(SEQ ID NO:72)；(27)LAHQDTTKKA(SEQ ID NO:73)；(28)LAHQDTTRNA(SEQ ID NO:74)；(29)LAHQDTTNA(SEQ ID NO:75)；(30)LAHQGTTKNA(SEQ ID NO:76)；(31)LAHQVTTKNA(SEQ ID NO:77)；(32)LAISDQSKPA(SEQ ID NO:78)；(33)LADATKTA(SEQ ID NO:79)；(34)LAKDTTKNA

(SEQ ID NO:80)；(35)LAKSDQSRPA(SEQ ID NO:81)；(36)LAPQDTKKNA(SEQ ID NO:82)；(37)LATSDSTKAA(SEQ ID NO:83)；(38)LAVDGSQRSA(SEQ ID NO:84)；(39)LPISDQTKHA(SEQ ID NO:85)；(40)LPKDATKTIA(SEQ ID NO:86)；(41)LPPQDTTKNA(SEQ ID NO:87)；和(42)PAPQDTTKNA(SEQ ID NO:88)。

[0286] 方面18.方面16的rAAV病毒体，其中所述肽包含以下氨基酸序列中的一种：(1)LAKDATKNA(SEQ ID NO:47)；(2)PAHQDTTKNA(SEQ ID NO:48)；(3)LAHQDTTKNA(SEQ ID NO:49)；(4)LATTSQNKPA(SEQ ID NO:50)；(5)LAISDQTKHA(SEQ ID NO:51)；(6)IARGVAPSSA(SEQ ID NO:52)；(7)LAPDSTTRSA(SEQ ID NO:53)；(8)LAKGTELKPA(SEQ ID NO:54)；(9)LAIIDATKNA(SEQ ID NO:55)；(10)LAVDGAQRSA(SEQ ID NO:56)；(11)PAPQDTTKKA(SEQ ID NO:57)；(12)LPHQDTTKNA(SEQ ID NO:58)；(13)LAKDATKTIA(SEQ ID NO:59)；(14)LAKQQSASTA(SEQ ID NO:60)；(15)LAKSDQSKPA(SEQ ID NO:61)；(16)LSHQDTTKNA(SEQ ID NO:62)；(17)LAANQPSKPA(SEQ ID NO:63)；和(18)LAVSDSTKAA(SEQ ID NO:64)。

[0287] 方面19.一种药物组合物，其包含：a)方面1至18中任一项的重组腺相关病毒病毒体；和b)药学上可接受的赋形剂。

[0288] 方面20.一种将基因产物递送至个体中的视网膜细胞的方法，所述方法包括向所述个体施用方面1至18中任一项的重组腺相关病毒(rAAV)病毒体。

[0289] 方面21.方面20的方法，其中所述基因产物为多肽。

[0290] 方面22.方面20的方法，其中所述基因产物为短干扰RNA或适体。

[0291] 方面23.方面21的方法，其中所述多肽为神经保护因子、抗血管生成多肽、抗细胞凋亡因子或增强视网膜细胞的功能的多肽。

[0292] 方面24.方面21的方法，其中所述多肽为神经胶质源性神经营养因子、成纤维细胞生长因子2、神经秩蛋白、睫状神经营养因子、神经生长因子、脑源性神经营养因子、表皮生长因子、视紫红质、X连锁凋亡抑制因子、视网膜劈裂蛋白、RPE65、视网膜色素变性GTP酶相互作用蛋白-1、外周蛋白、外周蛋白-2、视紫红质、RdCVF、视网膜色素变性GTP酶调控因子(RPGR)或音猬因子。

[0293] 方面25.方面21的方法，其中所述多肽为RNA引导的核酸内切酶。

[0294] 方面26.一种治疗眼病的方法，所述方法包括向有需要的个体施用有效量的方面1至18中任一项所述的重组腺相关病毒(rAAV)病毒体。

[0295] 方面27.方面26的方法，其中所述施用是通过眼球内注射。

[0296] 方面28.方面26的方法，其中所述施用是通过玻璃体内注射。

[0297] 方面29.方面26的方法，其中所述眼病为青光眼、视网膜色素变性、黄斑变性、视网膜劈裂症、利伯氏先天性黑朦(Leber's Congenital Amaurosis)、糖尿病性视网膜病、全色盲或色盲。

[0298] 方面30.一种分离的核酸，其包含编码变异腺相关病毒(AAV)衣壳蛋白的核苷酸序列，其中所述变异AAV衣壳蛋白相对于对应的亲本AAV衣壳蛋白，在衣壳蛋白GH环中包含约5个氨基酸至约20个氨基酸的插入，且其中所述变异衣壳蛋白在存在于AAV病毒体中时，增加所述AAV病毒体对视网膜细胞的感染性，且其中所述氨基酸插入在天然AAV衣壳的GH环中，其中所述插入为具有式I-X中的任一个的肽。

[0299] 方面31.方面30的分离的核酸，其中所述插入位点介于AAV2的氨基酸587与588之

间、AAV1的氨基酸590与591之间、AAV5的氨基酸575与576之间、AAV6的氨基酸590与591之间、AAV7的氨基酸589与590之间、AAV8的氨基酸590与591之间、AAV9的氨基酸588与589之间或AAV10的氨基酸588与589之间。

[0300] 方面32.一种分离的经遗传修饰的宿主细胞,其包含方面30或方面31的核酸。

[0301] 方面33.一种变异腺相关病毒(AAV)衣壳蛋白,其中所述变异AAV衣壳蛋白包含约5个氨基酸至约20个氨基酸的插入,其中所述氨基酸插入在天然AAV衣壳的GH环中,其中所述插入为具有式I-X中的任一个的肽。

[0302] 方面34.在方面1至33中的任一项中,插入GH环中的所述异源肽可以具有式I-X中的一个,其中:

[0303] 式I为$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$,其中:

[0304] X_1为Leu、Ile、Pro或Gln;

[0305] X_2为Ala、Pro、Ser、Asp、Gly、Thr或Val;

[0306] X_3为Lys、His、Thr、Ile、Pro、Val、Arg、Ala、Asp、Glu、Asn、Gln或Tyr;

[0307] X_4(如果存在)为Gln、Asp、Ser、Gly、Thr、Ile、Asn、Glu、Lys或Arg;

[0308] X_5为Asp、Ser、Gln、Val、Thr、Gly、Ala、Asn、Lys或Tyr;

[0309] X_6为Thr、Ala、Gln、Ser、Glu、Pro或Ile;

[0310] X_7为Thr、Ser、Asn、Pro、Leu、Gln、Lys、Ala或Cys;

[0311] X_8为Lys、Ser、Arg、Thr、Ala、Glu、Ile或Asn;

[0312] X_9为Asn、Pro、Ser、Lys、His、Ile、Thr或Ala;且

[0313] X_{10}为Ala、Phe、Asp、Thr、Val或Met;

[0314] 式II为$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$,其中:

[0315] X_1为Leu、Ile或Pro;

[0316] X_2为Ala、Pro或Ser;

[0317] X_3为Lys、His、Thr、Ile、Pro、Val、Arg或Ala;

[0318] X_4(如果存在)为Gln、Asp、Ser、Gly、Thr、Ile或Asn;

[0319] X_5为Asp、Ser、Gln、Val、Thr、Gly或Ala;

[0320] X_6为Thr、Ala、Gln、Ser、Glu或Pro;

[0321] X_7为Thr、Ser、Asn、Pro、Leu、Gln、Lys或Ala;

[0322] X_8为Lys、Ser、Arg或Thr;

[0323] X_9为Asn、Pro、Ser、Lys、His、Ile、Thr或Ala;且

[0324] X_{10}为Ala;

[0325] 式III为$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$,其中:

[0326] X_1为Leu、Ile或Pro;

[0327] X_2为Ala、Pro或Ser;

[0328] X_3为Lys、His、Thr、Ile、Pro、Val、Arg或Ala;

[0329] X_4(如果存在)为Gln、Asp、Ser、Gly、Thr、Ile或Asn;

[0330] X_5为Asp、Ser、Gln、Val、Thr、Gly或Ala;

[0331] X_6为Thr、Ala、Gln、Ser、Glu或Pro;

[0332] X_7为Thr、Ser、Asn、Pro、Leu、Gln、Lys或Ala;

[0333] X_8为Lys、Ser、Arg或Thr;

[0334] X_9为Asn、Pro、Ser、Lys、His、Ile、Thr或Ala;且

[0335] X10为Ala、Thr、Asp Val或Met;

[0336] 式IV为$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$,其中:

[0337] X_1为Leu;

[0338] X_2为Ala;

[0339] X_3为Lys、His、Thr、Ile、Pro或Val;

[0340] X_4(如果存在)为Gln、Asp、Ser或Gly;

[0341] X_5为Asp、Ser或Gln;

[0342] X_6为Thr、Ala、Gln或Ser;

[0343] X_7为Thr或Ser;

[0344] X_8为Lys、Ser或Arg;

[0345] X_9为Asn、Pro或Ser;且

[0346] X_{10}为Ala;

[0347] 式V为$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$,其中:

[0348] X_1为Leu;

[0349] X_2为Ala;

[0350] X_3为Lys或His;

[0351] X_4(如果存在)为Gln、Asp、Ser或Gly;

[0352] X_5为Asp、Ser或Gln;

[0353] X_6为Thr、Ala、Gln或Ser;

[0354] X_7为Thr或Ser;

[0355] X_8为Lys、Ser或Arg;

[0356] X_9为Asn、Pro或Ser;且

[0357] X_{10}为Ala;

[0358] 式VI为$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$,其中:

[0359] X_1为Leu;

[0360] X_2为Ala;

[0361] X_3为Asn、Lys、Thr、Gln、Ser、Ile或Leu;

[0362] X_4为Ser、Ala、Thr、Glu、Gln、Gly、Lys或Pro;

[0363] X_5为Asp、Pro、Glu、Thr、Asn或Arg;

[0364] X_6为Ile、His、Thr、Gln、Asn、Tyr、Asp或Glu;

[0365] X_7为Gln、Thr、Asn、Ala或Lys;

[0366] X_8为Lys、Thr、Arg或Asp;

[0367] X_9为Pro、Asn、Thr、Arg、Lys或Ser;且

[0368] X_{10}为Ala;

[0369] 式VII为$LAHQDTTKX_1X_2X_3$(SEQ ID NO:148),其中X_1为Lys、Thr、Asn或His;X_2为Ala、Thr、Val、Ile、Met或Asp;且X_3如果存在,那么为Ala;

[0370] 式VIII为$LAX_1QX_2TX_3X_4X_5X_6$(SEQ ID NO:149),其中X_1为Ala、Pro、Asp或His;X_2为Gly

或Asp;X_3为Ala、Thr或Lys;X_4为Asn、Glu、Lys、Arg或Thr;X_5为Leu、Asn、Lys或Thr;且X_6如果存在,那么为Ala、Thr、Asp、Val或Met;

[0371] 式IX为$X_1AX_2X_3DX_4TKX_5A$(SEQ ID NO:150),其中X_1为Val或Leu;X_2为Ile、Val、His或Asp;X_3为Glu、Ser、Lys或Gln;X_4为His、Ser或Thr;且X_5为Ser、Ala、Asn、His或Lys;且

[0372] 式X为$X_1X_2X_3AX_4QX_5TX_6KNA$(SEQ ID NO:151),其中X_1如果存在,那么为Leu;X_2如果存在,那么为Ala;X_3为Lys、Leu或Pro;X_4为Asn、His、Pro或Tyr;X_5为Asn、Gly、Val或Asp;且X_6为Pro或Thr。

[0373] 实施例

[0374] 提出以下实施例以便为一般技术者提供关于如何进行和使用本发明的完整公开和描述,且既不意图限制本发明人视为其发明的范围,也不意图表示以下实验是所执行的全部或唯一实验。虽然努力确保关于所用数字(例如量、温度等)的准确性,但应考虑一些实验误差和偏差。除非另外指示,否则份为重量份,分子量为重量平均分子量,温度为摄氏温度,且压力为大气压或接近大气压。可能使用标准缩写,例如bp,碱基对;kb,千碱基;pl,皮升;s或sec,秒;min,分钟;h或hr,小时;aa,氨基酸;kb,千碱基;bp,碱基对;nt,核苷酸;i.m.,肌肉内;i.p.,腹膜内;s.c.,皮下等等。

[0375] 实施例1:具有AAV衣壳变体的AAV病毒体的产生和表征

[0376] 迭代体内筛选方法用于产生具有能克服显著和复杂障碍的衣壳变体的AAV,预防大型动物眼睛中的全视网膜AAV感染。犬为视网膜变性疾病重要的临床前模型,其眼睛尺寸和结构类似于人类,且视网膜疾病的许多形式在多种犬品种中是天然存在的。筛选法用于鉴别96种能够在犬科视网膜中进行全视网膜感染的AAV变体。深度测序用于定量来自筛选的AAV变体池的这些变体中的18种在犬科视网膜中的性能。基于玻璃体内注射后视网膜细胞中的病毒DNA和mRNA的水平定量感染性。这些变体可以用于大型动物和人眼中的多种基因递送策略。

[0377] 产生在AAV衣壳上的表面暴露位置含有随机21核苷酸插入(被5'6-核苷酸连接子和3'3-核苷酸连接子围绕)的肽呈现库。包装病毒,使得每个病毒基因组被包壳在该基因组编码的衣壳蛋白壳内。因此,通过选择而鉴别的功能改善可以连接于病毒衣壳内所含有的基因组序列。由此库,使用迭代体内筛选选择过程鉴别能够从玻璃体感染犬科视网膜的变体(图1)。每轮向犬科眼睛注射约250μL 10E+13-10E+14病毒基因组/mL(vg/mL)滴度病毒。注射三周后,摘出眼睛,且从视网膜的中央和边缘区域取出视网膜穿孔。将RPE细胞从视网膜组织分离,并将组织冷冻。接着从视网膜细胞收集DNA,且将cap基因从分离的样品进行聚合酶链反应(PCR)扩增。cap基因用于随后的AAV包装。

[0378] 图1.定向进化法的例示,用于研发犬科视网膜AAV变体。产生肽呈现库,包装成AAV载体,并经由玻璃体内注射来注射至犬科眼睛中。迭代数轮的选择用于从载体池阳性选择AAV变体。三轮选择后为一轮易错PCR,接着为额外的数轮选择。

[0379] 在5轮选择后,Illumina深度测序用于鉴别AAV变体库中相对表示在数轮中增加的变体。病毒库中表示的增加表明阳性选择和从玻璃体感染犬科视网膜的能力。从约10E+7变体的库中,在体内筛选中选择的最高96种变体提供于表1中。

[0380] 表1

		肽 No.	SEQ ID NO:
	LAKDATKNA	1	47
	PAHQDTTKNA	2	48
	LAHQDTTKNA	3	49
	LATTSQNKPA	4	50
	LAISDQTKHA	5	51
	IARGVAPSSA	6	52
	LAPDSTTRSA	7	53
	LAKGTELKPA	8	54
	LAIIDATKNA	9	55
	LAVDGAQRSA	10	56
	PAPQDTTKKA	11	57
	LPHQDTTKNA	12	58
	LAKDATKTIA	13	59
	LAKQQSASTA	14	60
	LAKSDQSKPA	15	61
	LSHQDTTKNA	16	62
	LAANQPSKPA	17	63
	LAVSDSTKAA	18	64
	LAAQGTAKPA	19	65
	LAPDQTTRNA	20	66
	LAASDSTKAA	21	67
	LAPQDTTKNA	22	68
[0381]	LAKADETRPA	23	69
	LAHQDTAKNA	24	70
	LAHQDTKKNA	25	71
	LAHQDTTKHA	26	72
	LAHQDTTKKA	27	73
	LAHQDTTRNA	28	74
	LAHQDTTTNA	29	75
	LAHQGTTKNA	30	76
	LAHQVTTKNA	31	77
	LAISDQSKPA	32	78
	LAKDATKTA	33	79
	LAKDTTKNA	34	80
	LAKSDQSRPA	35	81
	LAPQDTKKNA	36	82
	LATSDSTKAA	37	83
	LAVDGSQRSA	38	84
	LPISDQTKHA	39	85
	LPKDATKTIA	40	86
	LPPQDTTKNA	41	87
	PAPQDTTKNA	42	88
	QAHQDTTKNA	43	89
	LAHETSPRPA	44	90
	LAKSTSTAPA	45	91
	LADQDTTKNA	46	92

		肽 No.	SEQ ID NO:
	LAESDQSKPA	47	93
	LAHKDTTKNA	48	94
	LAHKTQQKM	49	95
	LAHQDTTENA	50	96
	LAHQDTTINA	51	97
	LAHQDTTKKT	52	98
	LAHQDTTKND	53	99
	LAHQDTTKNT	54	100
	LAHQDTTKNV	55	101
	LAHQDTTKTM	56	102
	LAHQNTTKNA	57	103
	LAHRDTTKNA	58	104
	LAISDQTNHA	59	105
	LAKQKSASTA	60	106
	LAKSDQCKPA	61	107
	LAKSDQSKPD	62	108
	LAKSDQSNPA	63	109
	LAKSYQSKPA	64	110
	LANQDTTKNA	65	111
	LAPQNTTKNA	66	112
	LAPSSIQKPA	67	113
	LAQQDTTKNA	68	114
	LAYQDTTKNA	69	115
[0382]	LDHQDTTKNA	70	116
	LDHQDTTKSA	71	117
	LGHQDTTKNA	72	118
	LPHQDTTKND	73	119
	LPHQDTTKNT	74	120
	LPHQDTTNNA	75	121
	LTHQDTTKNA	76	122
	LTKDATKTIA	77	123
	LTPQDTTKNA	78	124
	LVHQDTTKNA	79	125
	LAKANQNTPA	80	126
	LATTPITKPA	81	127
	LATTPIAKPA	82	128
	LAIEDHTKSA	83	129
	LAQSEHQRPA	84	130
	LAKSPNKDNA	85	131
	LANQDYTKTA	86	132
	LANSTDQTRA	87	133
	LALGETTRPA	88	134
	LANSTEQTRA	89	135
	LAQADTTKNA	90	136
	LASKDITKTA	91	137
	LASPRHNKKC	92	138
	LAHQDTTKTIA	93	139
	LAAQGTANL	94	140

		肽 No.	SEQ ID NO:
[0383]	VAIEDHTKSA	95	141
	LAKANQNTPKNA	96	142

[0384] 使用高通量测序进一步定量表1中描绘的96种变体中的最高18种变体感染犬科视网膜的能力。表2描绘选择用于进一步定量的最高18种变体。

[0385] 表2

[0386]

LAKDATKNA (SEQ ID NO:47)	LAPDSTTRSA (SEQ ID NO:53)	LAKDATKTIA (SEQ ID NO:59)
PAHQDTTKNA (SEQ ID NO:48)	LAKGTELKPA (SEQ ID NO:54)	LAKQQSASTA (SEQ ID NO:60)
LAHQDTTKNA (SEQ ID NO:49)	LAIIDATKNA (SEQ ID NO:55)	LAKSDQSKPA (SEQ ID NO:61)
LATTSQNKPA (SEQ ID NO:50)	LAVDGAQRSA (SEQ ID NO:56)	LSHQDTTKNA (SEQ ID NO:62)
LAISDQTKHA (SEQ ID NO:51)	PAPQDTTKKA (SEQ ID NO:57)	LAANQPSKPA (SEQ ID NO:63)
IARGVAPSSA (SEQ ID NO:52)	LPHQDTTKNA (SEQ ID NO:58)	LAVSDSTKAA (SEQ ID NO:64)

[0387] 用驱动GFP表达的普遍CAG启动子,包装十八种变体。GFP cDNA与独特的25碱基对条形码标识符融合。18种变体中的每一种用独特的GFP条型码包装。将包装的变体以同等比率混合,且与对照的基于AAV2的载体(代表天然存在的亲本血清型的阴性对照)一起注射至视网膜中。注射后,从光感受器和RPE细胞收集DNA和mRNA。对DNA和mRNA水平进行定量以测定犬科来源的载体递送DNA至视网膜和引起转基因表达的能力(图2)。

[0388] 图2.含有GFP-条型码构建体的变体的深度测序。犬科来源的变体对犬科视网膜的感染通过标记GFP cDNA和mRNA的深度测序来定量。

[0389] 使用冷冻的视网膜切片的共焦显微术将18成员库的表达成像。GFP表达表明18成员库靶向内视网膜中的视网膜细胞和外视网膜中的光感受器(图3)。

[0390] 图3.18成员犬科来源的AAV变体库感染神经节细胞层、内核层、光感受器层和RPE层中的细胞。

[0391] 在测试的最高18种变体中,2种变体引起最高水平的DNA和mRNA恢复。引起最高水平的DNA恢复的变体具有插入序列~588-PAPQDTTKKA(SEQ ID NO:57)。引起最高水平的mRNA表达的变体具有插入序列~588-LAPDSTTRSA(SEQ ID NO:53)。

[0392] 虽然本发明已经参考其特定的实施方案描述,但应了解本领域的技术人员可以进行多种改变且可以在不脱离本发明真实的精神和范围下用同等物替代。另外,可以进行许多改变以使具体的情况、材料、物质组合物、方法、方法步骤适应本发明的目标、精神和范围。所有这类的改变意图在这里附上的权利要求书的范围内。

[0001] 序列表

[0002] <110> 加利福尼亚大学董事会

[0003] 宾夕法尼亚州大学理事会

[0004] <120> 具有变异衣壳的腺相关病毒病毒体和其使用方法

[0005] <130> BERK-335WO

[0006] <150> 62/368,929

[0007] <151> 2016-07-29

[0008] <160> 152

[0009] <170> PatentIn 3.5版

[0010] <210> 1

[0011] <211> 733

[0012] <212> PRT

[0013] <213> 腺相关病毒-2

[0014] <400> 1

[0015] Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Thr Leu Ser

[0016] 1 5 10 15

[0017] Glu Gly Ile Arg Gln Trp Trp Lys Leu Lys Pro Gly Pro Pro Pro Pro

[0018] 20 25 30

[0019] Lys Pro Ala Glu Arg His Lys Asp Asp Ser Arg Gly Leu Val Leu Pro

[0020] 35 40 45

[0021] Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro

[0022] 50 55 60

[0023] Val Asn Glu Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp

[0024] 65 70 75 80

[0025] Arg Gln Leu Asp Ser Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala

[0026] 85 90 95

[0027] Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly

[0028] 100 105 110

[0029] Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro

[0030] 115 120 125

[0031] Leu Gly Leu Val Glu Glu Pro Val Lys Thr Ala Pro Gly Lys Lys Arg

[0032] 130 135 140

[0033] Pro Val Glu His Ser Pro Val Glu Pro Asp Ser Ser Ser Gly Thr Gly

[0034] 145 150 155 160

[0035] Lys Ala Gly Gln Gln Pro Ala Arg Lys Arg Leu Asn Phe Gly Gln Thr

[0036] 165 170 175

[0037] Gly Asp Ala Asp Ser Val Pro Asp Pro Gln Pro Leu Gly Gln Pro Pro

[0038] 180 185 190

[0039] Ala Ala Pro Ser Gly Leu Gly Thr Asn Thr Met Ala Thr Gly Ser Gly
[0040] 195 200 205
[0041] Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ser
[0042] 210 215 220
[0043] Ser Gly Asn Trp His Cys Asp Ser Thr Trp Met Gly Asp Arg Val Ile
[0044] 225 230 235 240
[0045] Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
[0046] 245 250 255
[0047] Tyr Lys Gln Ile Ser Ser Gln Ser Gly Ala Ser Asn Asp Asn His Tyr
[0048] 260 265 270
[0049] Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe His
[0050] 275 280 285
[0051] Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn Trp
[0052] 290 295 300
[0053] Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln Val
[0054] 305 310 315 320
[0055] Lys Glu Val Thr Gln Asn Asp Gly Thr Thr Thr Ile Ala Asn Asn Leu
[0056] 325 330 335
[0057] Thr Ser Thr Val Gln Val Phe Thr Asp Ser Glu Tyr Gln Leu Pro Tyr
[0058] 340 345 350
[0059] Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala Asp
[0060] 355 360 365
[0061] Val Phe Met Val Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly Ser
[0062] 370 375 380
[0063] Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro Ser
[0064] 385 390 395 400
[0065] Gln Met Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe Glu
[0066] 405 410 415
[0067] Asp Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp Arg
[0068] 420 425 430
[0069] Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser Arg Thr
[0070] 435 440 445
[0071] Asn Thr Pro Ser Gly Thr Thr Thr Gln Ser Arg Leu Gln Phe Ser Gln
[0072] 450 455 460
[0073] Ala Gly Ala Ser Asp Ile Arg Asp Gln Ser Arg Asn Trp Leu Pro Gly
[0074] 465 470 475 480
[0075] Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys Thr Ser Ala Asp Asn Asn
[0076] 485 490 495
[0077] Asn Ser Glu Tyr Ser Trp Thr Gly Ala Thr Lys Tyr His Leu Asn Gly

[0078] 500 505 510

[0079] Arg Asp Ser Leu Val Asn Pro Gly Pro Ala Met Ala Ser His Lys Asp

[0080] 515 520 525

[0081] Asp Glu Glu Lys Phe Phe Pro Gln Ser Gly Val Leu Ile Phe Gly Lys

[0082] 530 535 540

[0083] Gln Gly Ser Glu Lys Thr Asn Val Asp Ile Glu Lys Val Met Ile Thr

[0084] 545 550 555 560

[0085] Asp Glu Glu Glu Ile Arg Thr Thr Asn Pro Val Ala Thr Glu Gln Tyr

[0086] 565 570 575

[0087] Gly Ser Val Ser Thr Asn Leu Gln Arg Gly Asn Arg Gln Ala Ala Thr

[0088] 580 585 590

[0089] Ala Asp Val Asn Thr Gln Gly Val Leu Pro Gly Met Val Trp Gln Asp

[0090] 595 600 605

[0091] Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His Thr

[0092] 610 615 620

[0093] Asp Gly His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu Lys

[0094] 625 630 635 640

[0095] His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala Asn

[0096] 645 650 655

[0097] Pro Ser Thr Thr Phe Ser Ala Ala Lys Phe Ala Ser Phe Ile Thr Gln

[0098] 660 665 670

[0099] Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln Lys

[0100] 675 680 685

[0101] Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn Tyr

[0102] 690 695 700

[0103] Asn Lys Ser Val Asn Val Asp Phe Thr Val Asp Thr Asn Gly Val Tyr

[0104] 705 710 715 720

[0105] Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg

[0106] 725 730

[0107] <210> 2

[0108] <211> 42

[0109] <212> PRT

[0110] <213> 腺相关病毒-2

[0111] <400> 2

[0112] Pro Val Ala Thr Glu Gln Tyr Gly Ser Val Ser Thr Asn Leu Gln Arg

[0113] 1 5 10 15

[0114] Gly Asn Arg Gln Ala Ala Thr Ala Asp Val Asn Thr Gln Gly Val Leu

[0115] 20 25 30

[0116] Pro Gly Met Val Trp Gln Asp Arg Asp Val

[0117] 35 40

[0118] <210> 3

[0119] <211> 42

[0120] <212> PRT

[0121] <213> 腺相关病毒-1

[0122] <400> 3

[0123] Pro Val Ala Thr Glu Arg Phe Gly Thr Val Ala Val Asn Phe Gln Ser

[0124] 1 5 10 15

[0125] Ser Ser Thr Asp Pro Ala Thr Gly Asp Val His Ala Met Gly Ala Leu

[0126] 20 25 30

[0127] Pro Gly Met Val Trp Gln Asp Arg Asp Val

[0128] 35 40

[0129] <210> 4

[0130] <211> 42

[0131] <212> PRT

[0132] <213> 腺相关病毒-5

[0133] <400> 4

[0134] Arg Val Ala Tyr Asn Val Gly Gly Gln Met Ala Thr Asn Asn Gln Ser

[0135] 1 5 10 15

[0136] Ser Thr Thr Ala Pro Ala Thr Gly Thr Tyr Asn Leu Gln Glu Ile Val

[0137] 20 25 30

[0138] Pro Gly Ser Val Trp Met Glu Arg Asp Val

[0139] 35 40

[0140] <210> 5

[0141] <211> 42

[0142] <212> PRT

[0143] <213> 腺相关病毒-6

[0144] <400> 5

[0145] Pro Val Ala Thr Glu Arg Phe Gly Thr Val Ala Val Asn Leu Gln Ser

[0146] 1 5 10 15

[0147] Ser Ser Thr Asp Pro Ala Thr Gly Asp Val His Val Met Gly Ala Leu

[0148] 20 25 30

[0149] Pro Gly Met Val Trp Gln Asp Arg Asp Val

[0150] 35 40

[0151] <210> 6

[0152] <211> 42

[0153] <212> PRT

[0154] <213> 腺相关病毒-7

[0155] <400> 6

[0156] Pro Val Ala Thr Glu Glu Tyr Gly Ile Val Ser Ser Asn Leu Gln Ala
[0157] 1 5 10 15
[0158] Ala Asn Thr Ala Ala Gln Thr Gln Val Val Asn Asn Gln Gly Ala Leu
[0159] 20 25 30
[0160] Pro Gly Met Val Trp Gln Asn Arg Asp Val
[0161] 35 40
[0162] <210> 7
[0163] <211> 42
[0164] <212> PRT
[0165] <213> 腺相关病毒-8
[0166] <400> 7
[0167] Pro Val Ala Thr Glu Glu Tyr Gly Ile Val Ala Asp Asn Leu Gln Gln
[0168] 1 5 10 15
[0169] Gln Asn Thr Ala Pro Gln Ile Gly Thr Val Asn Ser Gln Gly Ala Leu
[0170] 20 25 30
[0171] Pro Gly Met Val Trp Gln Asn Arg Asp Val
[0172] 35 40
[0173] <210> 8
[0174] <211> 42
[0175] <212> PRT
[0176] <213> 腺相关病毒-9
[0177] <400> 8
[0178] Pro Val Ala Thr Glu Ser Tyr Gly Gln Val Ala Thr Asn His Gln Ser
[0179] 1 5 10 15
[0180] Ala Gln Ala Gln Ala Gln Thr Gly Trp Val Gln Asn Gln Gly Ile Leu
[0181] 20 25 30
[0182] Pro Gly Met Val Trp Gln Asp Arg Asp Val
[0183] 35 40
[0184] <210> 9
[0185] <211> 42
[0186] <212> PRT
[0187] <213> 腺相关病毒-10
[0188] <400> 9
[0189] Pro Val Ala Thr Glu Gln Tyr Gly Val Val Ala Asp Asn Leu Gln Gln
[0190] 1 5 10 15
[0191] Ala Asn Thr Gly Pro Ile Val Gly Asn Val Asn Ser Gln Gly Ala Leu
[0192] 20 25 30
[0193] Pro Gly Met Val Trp Gln Asn Arg Asp Val
[0194] 35 40

[0195] <210> 10

[0196] <211> 224

[0197] <212> PRT

[0198] <213> 智人

[0199] <400> 10

[0200] Met Ser Arg Lys Ile Glu Gly Phe Leu Leu Leu Leu Leu Phe Gly Tyr

[0201] 1 5 10 15

[0202] Glu Ala Thr Leu Gly Leu Ser Ser Thr Glu Asp Glu Gly Glu Asp Pro

[0203] 20 25 30

[0204] Trp Tyr Gln Lys Ala Cys Lys Cys Asp Cys Gln Gly Gly Pro Asn Ala

[0205] 35 40 45

[0206] Leu Trp Ser Ala Gly Ala Thr Ser Leu Asp Cys Ile Pro Glu Cys Pro

[0207] 50 55 60

[0208] Tyr His Lys Pro Leu Gly Phe Glu Ser Gly Glu Val Thr Pro Asp Gln

[0209] 65 70 75 80

[0210] Ile Thr Cys Ser Asn Pro Glu Gln Tyr Val Gly Trp Tyr Ser Ser Trp

[0211] 85 90 95

[0212] Thr Ala Asn Lys Ala Arg Leu Asn Ser Gln Gly Phe Gly Cys Ala Trp

[0213] 100 105 110

[0214] Leu Ser Lys Phe Gln Asp Ser Ser Gln Trp Leu Gln Ile Asp Leu Lys

[0215] 115 120 125

[0216] Glu Ile Lys Val Ile Ser Gly Ile Leu Thr Gln Gly Arg Cys Asp Ile

[0217] 130 135 140

[0218] Asp Glu Trp Met Thr Lys Tyr Ser Val Gln Tyr Arg Thr Asp Glu Arg

[0219] 145 150 155 160

[0220] Leu Asn Trp Ile Tyr Tyr Lys Asp Gln Thr Gly Asn Asn Arg Val Phe

[0221] 165 170 175

[0222] Tyr Gly Asn Ser Asp Arg Thr Ser Thr Val Gln Asn Leu Leu Arg Pro

[0223] 180 185 190

[0224] Pro Ile Ile Ser Arg Phe Ile Arg Leu Ile Pro Leu Gly Trp His Val

[0225] 195 200 205

[0226] Arg Ile Ala Ile Arg Met Glu Leu Leu Glu Cys Val Ser Lys Cys Ala

[0227] 210 215 220

[0228] <210> 11

[0229] <211> 247

[0230] <212> PRT

[0231] <213> 智人

[0232] <400> 11

[0233] Met Thr Ile Leu Phe Leu Thr Met Val Ile Ser Tyr Phe Gly Cys Met

[0234] 1 5 10 15

[0235] Lys Ala Ala Pro Met Lys Glu Ala Asn Ile Arg Gly Gln Gly Gly Leu

[0236] 20 25 30

[0237] Ala Tyr Pro Gly Val Arg Thr His Gly Thr Leu Glu Ser Val Asn Gly

[0238] 35 40 45

[0239] Pro Lys Ala Gly Ser Arg Gly Leu Thr Ser Leu Ala Asp Thr Phe Glu

[0240] 50 55 60

[0241] His Val Ile Glu Glu Leu Leu Asp Glu Asp His Lys Val Arg Pro Asn

[0242] 65 70 75 80

[0243] Glu Glu Asn Asn Lys Asp Ala Asp Leu Tyr Thr Ser Arg Val Met Leu

[0244] 85 90 95

[0245] Ser Ser Gln Val Pro Leu Glu Pro Pro Leu Leu Phe Leu Leu Glu Glu

[0246] 100 105 110

[0247] Tyr Lys Asn Tyr Leu Asp Ala Ala Asn Met Ser Met Met Val Leu Arg

[0248] 115 120 125

[0249] His Ser Asp Pro Ala Arg Arg Gly Glu Leu Ser Val Cys Asp Ser Ile

[0250] 130 135 140

[0251] Ser Glu Trp Val Thr Ala Ala Asp Lys Lys Thr Ala Val Asp Met Ser

[0252] 145 150 155 160

[0253] Gly Gly Thr Val Thr Val Leu Glu Lys Val Pro Val Ser Lys Gly Gln

[0254] 165 170 175

[0255] Leu Lys Gln Tyr Phe Tyr Glu Thr Lys Cys Asn Pro Met Gly Tyr Thr

[0256] 180 185 190

[0257] Lys Glu Gly Cys Arg Gly Ile Asp Lys Arg His Trp Asn Ser Gln Cys

[0258] 195 200 205

[0259] Arg Thr Thr Gln Ser Tyr Val Arg Ala Leu Thr Met Asp Ser Lys Lys

[0260] 210 215 220

[0261] Arg Ile Gly Trp Arg Phe Ile Arg Ile Asp Thr Ser Cys Val Cys Thr

[0262] 225 230 235 240

[0263] Leu Thr Ile Lys Arg Gly Arg

[0264] 245

[0265] <210> 12

[0266] <211> 533

[0267] <212> PRT

[0268] <213> 智人

[0269] <400> 12

[0270] Met Ser Ile Gln Val Glu His Pro Ala Gly Gly Tyr Lys Lys Leu Phe

[0271] 1 5 10 15

[0272] Glu Thr Val Glu Glu Leu Ser Ser Pro Leu Thr Ala His Val Thr Gly

[0273] 20 25 30

[0274] Arg Ile Pro Leu Trp Leu Thr Gly Ser Leu Leu Arg Cys Gly Pro Gly

[0275] 35 40 45

[0276] Leu Phe Glu Val Gly Ser Glu Pro Phe Tyr His Leu Phe Asp Gly Gln

[0277] 50 55 60

[0278] Ala Leu Leu His Lys Phe Asp Phe Lys Glu Gly His Val Thr Tyr His

[0279] 65 70 75 80

[0280] Arg Arg Phe Ile Arg Thr Asp Ala Tyr Val Arg Ala Met Thr Glu Lys

[0281] 85 90 95

[0282] Arg Ile Val Ile Thr Glu Phe Gly Thr Cys Ala Phe Pro Asp Pro Cys

[0283] 100 105 110

[0284] Lys Asn Ile Phe Ser Arg Phe Phe Ser Tyr Phe Arg Gly Val Glu Val

[0285] 115 120 125

[0286] Thr Asp Asn Ala Leu Val Asn Val Tyr Pro Val Gly Glu Asp Tyr Tyr

[0287] 130 135 140

[0288] Ala Cys Thr Glu Thr Asn Phe Ile Thr Lys Ile Asn Pro Glu Thr Leu

[0289] 145 150 155 160

[0290] Glu Thr Ile Lys Gln Val Asp Leu Cys Asn Tyr Val Ser Val Asn Gly

[0291] 165 170 175

[0292] Ala Thr Ala His Pro His Ile Glu Asn Asp Gly Thr Val Tyr Asn Ile

[0293] 180 185 190

[0294] Gly Asn Cys Phe Gly Lys Asn Phe Ser Ile Ala Tyr Asn Ile Val Lys

[0295] 195 200 205

[0296] Ile Pro Pro Leu Gln Ala Asp Lys Glu Asp Pro Ile Ser Lys Ser Glu

[0297] 210 215 220

[0298] Ile Val Val Gln Phe Pro Cys Ser Asp Arg Phe Lys Pro Ser Tyr Val

[0299] 225 230 235 240

[0300] His Ser Phe Gly Leu Thr Pro Asn Tyr Ile Val Phe Val Glu Thr Pro

[0301] 245 250 255

[0302] Val Lys Ile Asn Leu Phe Lys Phe Leu Ser Ser Trp Ser Leu Trp Gly

[0303] 260 265 270

[0304] Ala Asn Tyr Met Asp Cys Phe Glu Ser Asn Glu Thr Met Gly Val Trp

[0305] 275 280 285

[0306] Leu His Ile Ala Asp Lys Lys Arg Lys Lys Tyr Leu Asn Asn Lys Tyr

[0307] 290 295 300

[0308] Arg Thr Ser Pro Phe Asn Leu Phe His His Ile Asn Thr Tyr Glu Asp

[0309] 305 310 315 320

[0310] Asn Gly Phe Leu Ile Val Asp Leu Cys Cys Trp Lys Gly Phe Glu Phe

[0311] 325 330 335

[0312] Val Tyr Asn Tyr Leu Tyr Leu Ala Asn Leu Arg Glu Asn Trp Glu Glu
[0313] 340 345 350
[0314] Val Lys Lys Asn Ala Arg Lys Ala Pro Gln Pro Glu Val Arg Arg Tyr
[0315] 355 360 365
[0316] Val Leu Pro Leu Asn Ile Asp Lys Ala Asp Thr Gly Lys Asn Leu Val
[0317] 370 375 380
[0318] Thr Leu Pro Asn Thr Thr Ala Thr Ala Ile Leu Cys Ser Asp Glu Thr
[0319] 385 390 395 400
[0320] Ile Trp Leu Glu Pro Glu Val Leu Phe Ser Gly Pro Arg Gln Ala Phe
[0321] 405 410 415
[0322] Glu Phe Pro Gln Ile Asn Tyr Gln Lys Tyr Cys Gly Lys Pro Tyr Thr
[0323] 420 425 430
[0324] Tyr Ala Tyr Gly Leu Gly Leu Asn His Phe Val Pro Asp Arg Leu Cys
[0325] 435 440 445
[0326] Lys Leu Asn Val Lys Thr Lys Glu Thr Trp Val Trp Gln Glu Pro Asp
[0327] 450 455 460
[0328] Ser Tyr Pro Ser Glu Pro Ile Phe Val Ser His Pro Asp Ala Leu Glu
[0329] 465 470 475 480
[0330] Glu Asp Asp Gly Val Val Leu Ser Val Val Val Ser Pro Gly Ala Gly
[0331] 485 490 495
[0332] Gln Lys Pro Ala Tyr Leu Leu Ile Leu Asn Ala Lys Asp Leu Ser Glu
[0333] 500 505 510
[0334] Val Ala Arg Ala Glu Val Glu Ile Asn Ile Pro Val Thr Phe His Gly
[0335] 515 520 525
[0336] Leu Phe Lys Lys Ser
[0337] 530
[0338] <210> 13
[0339] <211> 346
[0340] <212> PRT
[0341] <213> 智人
[0342] <400> 13
[0343] Met Ala Leu Leu Lys Val Lys Phe Asp Gln Lys Lys Arg Val Lys Leu
[0344] 1 5 10 15
[0345] Ala Gln Gly Leu Trp Leu Met Asn Trp Phe Ser Val Leu Ala Gly Ile
[0346] 20 25 30
[0347] Ile Ile Phe Ser Leu Gly Leu Phe Leu Lys Ile Glu Leu Arg Lys Arg
[0348] 35 40 45
[0349] Ser Asp Val Met Asn Asn Ser Glu Ser His Phe Val Pro Asn Ser Leu
[0350] 50 55 60

[0351] Ile Gly Met Gly Val Leu Ser Cys Val Phe Asn Ser Leu Ala Gly Lys
[0352] 65 70 75 80
[0353] Ile Cys Tyr Asp Ala Leu Asp Pro Ala Lys Tyr Ala Arg Trp Lys Pro
[0354] 85 90 95
[0355] Trp Leu Lys Pro Tyr Leu Ala Ile Cys Val Leu Phe Asn Ile Ile Leu
[0356] 100 105 110
[0357] Phe Leu Val Ala Leu Cys Cys Phe Leu Leu Arg Gly Ser Leu Glu Asn
[0358] 115 120 125
[0359] Thr Leu Gly Gln Gly Leu Lys Asn Gly Met Lys Tyr Tyr Arg Asp Thr
[0360] 130 135 140
[0361] Asp Thr Pro Gly Arg Cys Phe Met Lys Lys Thr Ile Asp Met Leu Gln
[0362] 145 150 155 160
[0363] Ile Glu Phe Lys Cys Cys Gly Asn Asn Gly Phe Arg Asp Trp Phe Glu
[0364] 165 170 175
[0365] Ile Gln Trp Ile Ser Asn Arg Tyr Leu Asp Phe Ser Ser Lys Glu Val
[0366] 180 185 190
[0367] Lys Asp Arg Ile Lys Ser Asn Val Asp Gly Arg Tyr Leu Val Asp Gly
[0368] 195 200 205
[0369] Val Pro Phe Ser Cys Cys Asn Pro Ser Ser Pro Arg Pro Cys Ile Gln
[0370] 210 215 220
[0371] Tyr Gln Ile Thr Asn Asn Ser Ala His Tyr Ser Tyr Asp His Gln Thr
[0372] 225 230 235 240
[0373] Glu Glu Leu Asn Leu Trp Val Arg Gly Cys Arg Ala Ala Leu Leu Ser
[0374] 245 250 255
[0375] Tyr Tyr Ser Ser Leu Met Asn Ser Met Gly Val Val Thr Leu Leu Ile
[0376] 260 265 270
[0377] Trp Leu Phe Glu Val Thr Ile Thr Ile Gly Leu Arg Tyr Leu Gln Thr
[0378] 275 280 285
[0379] Ser Leu Asp Gly Val Ser Asn Pro Glu Glu Ser Glu Ser Glu Ser Gln
[0380] 290 295 300
[0381] Gly Trp Leu Leu Glu Arg Ser Val Pro Glu Thr Trp Lys Ala Phe Leu
[0382] 305 310 315 320
[0383] Glu Ser Val Lys Lys Leu Gly Lys Gly Asn Gln Val Glu Ala Glu Gly
[0384] 325 330 335
[0385] Ala Asp Ala Gly Gln Ala Pro Glu Ala Gly
[0386] 340 345
[0387] <210> 14
[0388] <211> 470
[0389] <212> PRT

[0390] <213> 智人

[0391] <400> 14

[0392] Met Ser His His Pro Ser Gly Leu Arg Ala Gly Phe Ser Ser Thr Ser

[0393] 1 5 10 15

[0394] Tyr Arg Arg Thr Phe Gly Pro Pro Pro Ser Leu Ser Pro Gly Ala Phe

[0395] 20 25 30

[0396] Ser Tyr Ser Ser Ser Ser Arg Phe Ser Ser Ser Arg Leu Leu Gly Ser

[0397] 35 40 45

[0398] Ala Ser Pro Ser Ser Ser Val Arg Leu Gly Ser Phe Arg Ser Pro Arg

[0399] 50 55 60

[0400] Ala Gly Ala Gly Ala Leu Leu Arg Leu Pro Ser Glu Arg Leu Asp Phe

[0401] 65 70 75 80

[0402] Ser Met Ala Glu Ala Leu Asn Gln Glu Phe Leu Ala Thr Arg Ser Asn

[0403] 85 90 95

[0404] Glu Lys Gln Glu Leu Gln Glu Leu Asn Asp Arg Phe Ala Asn Phe Ile

[0405] 100 105 110

[0406] Glu Lys Val Arg Phe Leu Glu Gln Gln Asn Ala Ala Leu Arg Gly Glu

[0407] 115 120 125

[0408] Leu Ser Gln Ala Arg Gly Gln Glu Pro Ala Arg Ala Asp Gln Leu Cys

[0409] 130 135 140

[0410] Gln Gln Glu Leu Arg Glu Leu Arg Arg Glu Leu Glu Leu Leu Gly Arg

[0411] 145 150 155 160

[0412] Glu Arg Asp Arg Val Gln Val Glu Arg Asp Gly Leu Ala Glu Asp Leu

[0413] 165 170 175

[0414] Ala Ala Leu Lys Gln Arg Leu Glu Glu Glu Thr Arg Lys Arg Glu Asp

[0415] 180 185 190

[0416] Ala Glu His Asn Leu Val Leu Phe Arg Lys Asp Val Asp Asp Ala Thr

[0417] 195 200 205

[0418] Leu Ser Arg Leu Glu Leu Glu Arg Lys Ile Glu Ser Leu Met Asp Glu

[0419] 210 215 220

[0420] Ile Glu Phe Leu Lys Lys Leu His Glu Glu Glu Leu Arg Asp Leu Gln

[0421] 225 230 235 240

[0422] Val Ser Val Glu Ser Gln Gln Val Gln Gln Val Glu Val Glu Ala Thr

[0423] 245 250 255

[0424] Val Lys Pro Glu Leu Thr Ala Ala Leu Arg Asp Ile Arg Ala Gln Tyr

[0425] 260 265 270

[0426] Glu Ser Ile Ala Ala Lys Asn Leu Gln Glu Ala Glu Glu Trp Tyr Lys

[0427] 275 280 285

[0428] Ser Lys Tyr Ala Asp Leu Ser Asp Ala Ala Asn Arg Asn His Glu Ala

[0429] 290 295 300

[0430] Leu Arg Gln Ala Lys Gln Glu Met Asn Glu Ser Arg Arg Gln Ile Gln

[0431] 305 310 315 320

[0432] Ser Leu Thr Cys Glu Val Asp Gly Leu Arg Gly Thr Asn Glu Ala Leu

[0433] 325 330 335

[0434] Leu Arg Gln Leu Arg Glu Leu Glu Glu Gln Phe Ala Leu Glu Ala Gly

[0435] 340 345 350

[0436] Gly Tyr Gln Ala Gly Ala Ala Arg Leu Glu Glu Glu Leu Arg Gln Leu

[0437] 355 360 365

[0438] Lys Glu Glu Met Ala Arg His Leu Arg Glu Tyr Gln Glu Leu Leu Asn

[0439] 370 375 380

[0440] Val Lys Met Ala Leu Asp Ile Glu Ile Ala Thr Tyr Arg Lys Leu Leu

[0441] 385 390 395 400

[0442] Glu Gly Glu Glu Ser Arg Ile Ser Val Pro Val His Ser Phe Ala Ser

[0443] 405 410 415

[0444] Leu Asn Ile Lys Thr Thr Val Pro Glu Val Glu Pro Pro Gln Asp Ser

[0445] 420 425 430

[0446] His Ser Arg Lys Thr Val Leu Ile Lys Thr Ile Glu Thr Arg Asn Gly

[0447] 435 440 445

[0448] Glu Val Val Thr Glu Ser Gln Lys Glu Gln Arg Ser Glu Leu Asp Lys

[0449] 450 455 460

[0450] Ser Ser Ala His Ser Tyr

[0451] 465 470

[0452] <210> 15

[0453] <211> 1286

[0454] <212> PRT

[0455] <213> 智人

[0456] <400> 15

[0457] Met Ser His Leu Val Asp Pro Thr Ser Gly Asp Leu Pro Val Arg Asp

[0458] 1 5 10 15

[0459] Ile Asp Ala Ile Pro Leu Val Leu Pro Ala Ser Lys Gly Lys Asn Met

[0460] 20 25 30

[0461] Lys Thr Gln Pro Pro Leu Ser Arg Met Asn Arg Glu Glu Leu Glu Asp

[0462] 35 40 45

[0463] Ser Phe Phe Arg Leu Arg Glu Asp His Met Leu Val Lys Glu Leu Ser

[0464] 50 55 60

[0465] Trp Lys Gln Gln Asp Glu Ile Lys Arg Leu Arg Thr Thr Leu Leu Arg

[0466] 65 70 75 80

[0467] Leu Thr Ala Ala Gly Arg Asp Leu Arg Val Ala Glu Glu Ala Ala Pro

[0468] 85 90 95

[0469] Leu Ser Glu Thr Ala Arg Arg Gly Gln Lys Ala Gly Trp Arg Gln Arg

[0470] 100 105 110

[0471] Leu Ser Met His Gln Arg Pro Gln Met His Arg Leu Gln Gly His Phe

[0472] 115 120 125

[0473] His Cys Val Gly Pro Ala Ser Pro Arg Arg Ala Gln Pro Arg Val Gln

[0474] 130 135 140

[0475] Val Gly His Arg Gln Leu His Thr Ala Gly Ala Pro Val Pro Glu Lys

[0476] 145 150 155 160

[0477] Pro Lys Arg Gly Pro Arg Asp Arg Leu Ser Tyr Thr Ala Pro Pro Ser

[0478] 165 170 175

[0479] Phe Lys Glu His Ala Thr Asn Glu Asn Arg Gly Glu Val Ala Ser Lys

[0480] 180 185 190

[0481] Pro Ser Glu Leu Val Ser Gly Ser Asn Ser Ile Ile Ser Phe Ser Ser

[0482] 195 200 205

[0483] Val Ile Ser Met Ala Lys Pro Ile Gly Leu Cys Met Pro Asn Ser Ala

[0484] 210 215 220

[0485] His Ile Met Ala Ser Asn Thr Met Gln Val Glu Glu Pro Pro Lys Ser

[0486] 225 230 235 240

[0487] Pro Glu Lys Met Trp Pro Lys Asp Glu Asn Phe Glu Gln Arg Ser Ser

[0488] 245 250 255

[0489] Leu Glu Cys Ala Gln Lys Ala Ala Glu Leu Arg Ala Ser Ile Lys Glu

[0490] 260 265 270

[0491] Lys Val Glu Leu Ile Arg Leu Lys Lys Leu Leu His Glu Arg Asn Ala

[0492] 275 280 285

[0493] Ser Leu Val Met Thr Lys Ala Gln Leu Thr Glu Val Gln Glu Ala Tyr

[0494] 290 295 300

[0495] Glu Thr Leu Leu Gln Lys Asn Gln Gly Ile Leu Ser Ala Ala His Glu

[0496] 305 310 315 320

[0497] Ala Leu Leu Lys Gln Val Asn Glu Leu Arg Ala Glu Leu Lys Glu Glu

[0498] 325 330 335

[0499] Ser Lys Lys Ala Val Ser Leu Lys Ser Gln Leu Glu Asp Val Ser Ile

[0500] 340 345 350

[0501] Leu Gln Met Thr Leu Lys Glu Phe Gln Glu Arg Val Glu Asp Leu Glu

[0502] 355 360 365

[0503] Lys Glu Arg Lys Leu Leu Asn Asp Asn Tyr Asp Lys Leu Leu Glu Ser

[0504] 370 375 380

[0505] Met Leu Asp Ser Ser Asp Ser Ser Ser Gln Pro His Trp Ser Asn Glu

[0506] 385 390 395 400

[0507] Leu Ile Ala Glu Gln Leu Gln Gln Gln Val Ser Gln Leu Gln Asp Gln
[0508] 405 410 415
[0509] Leu Asp Ala Glu Leu Glu Asp Lys Arg Lys Val Leu Leu Glu Leu Ser
[0510] 420 425 430
[0511] Arg Glu Lys Ala Gln Asn Glu Asp Leu Lys Leu Glu Val Thr Asn Ile
[0512] 435 440 445
[0513] Leu Gln Lys His Lys Gln Glu Val Glu Leu Leu Gln Asn Ala Ala Thr
[0514] 450 455 460
[0515] Ile Ser Gln Pro Pro Asp Arg Gln Ser Glu Pro Ala Thr His Pro Ala
[0516] 465 470 475 480
[0517] Val Leu Gln Glu Asn Thr Gln Ile Glu Pro Ser Glu Pro Lys Asn Gln
[0518] 485 490 495
[0519] Glu Glu Lys Lys Leu Ser Gln Val Leu Asn Glu Leu Gln Val Ser His
[0520] 500 505 510
[0521] Ala Glu Thr Thr Leu Glu Leu Glu Lys Thr Arg Asp Met Leu Ile Leu
[0522] 515 520 525
[0523] Gln Arg Lys Ile Asn Val Cys Tyr Gln Glu Glu Leu Glu Ala Met Met
[0524] 530 535 540
[0525] Thr Lys Ala Asp Asn Asp Asn Arg Asp His Lys Glu Lys Leu Glu Arg
[0526] 545 550 555 560
[0527] Leu Thr Arg Leu Leu Asp Leu Lys Asn Asn Arg Ile Lys Gln Leu Glu
[0528] 565 570 575
[0529] Gly Ile Leu Arg Ser His Asp Leu Pro Thr Ser Glu Gln Leu Lys Asp
[0530] 580 585 590
[0531] Val Ala Tyr Gly Thr Arg Pro Leu Ser Leu Cys Leu Glu Thr Leu Pro
[0532] 595 600 605
[0533] Ala His Gly Asp Glu Asp Lys Val Asp Ile Ser Leu Leu His Gln Gly
[0534] 610 615 620
[0535] Glu Asn Leu Phe Glu Leu His Ile His Gln Ala Phe Leu Thr Ser Ala
[0536] 625 630 635 640
[0537] Ala Leu Ala Gln Ala Gly Asp Thr Gln Pro Thr Thr Phe Cys Thr Tyr
[0538] 645 650 655
[0539] Ser Phe Tyr Asp Phe Glu Thr His Cys Thr Pro Leu Ser Val Gly Pro
[0540] 660 665 670
[0541] Gln Pro Leu Tyr Asp Phe Thr Ser Gln Tyr Val Met Glu Thr Asp Ser
[0542] 675 680 685
[0543] Leu Phe Leu His Tyr Leu Gln Glu Ala Ser Ala Arg Leu Asp Ile His
[0544] 690 695 700
[0545] Gln Ala Met Ala Ser Glu His Ser Thr Leu Ala Ala Gly Trp Ile Cys

[0546] 705 710 715 720
[0547] Phe Asp Arg Val Leu Glu Thr Val Glu Lys Val His Gly Leu Ala Thr
[0548] 725 730 735
[0549] Leu Ile Gly Ala Gly Gly Glu Glu Phe Gly Val Leu Glu Tyr Trp Met
[0550] 740 745 750
[0551] Arg Leu Arg Phe Pro Ile Lys Pro Ser Leu Gln Ala Cys Asn Lys Arg
[0552] 755 760 765
[0553] Lys Lys Ala Gln Val Tyr Leu Ser Thr Asp Val Leu Gly Gly Arg Lys
[0554] 770 775 780
[0555] Ala Gln Glu Glu Glu Phe Arg Ser Glu Ser Trp Glu Pro Gln Asn Glu
[0556] 785 790 795 800
[0557] Leu Trp Ile Glu Ile Thr Lys Cys Cys Gly Leu Arg Ser Arg Trp Leu
[0558] 805 810 815
[0559] Gly Thr Gln Pro Ser Pro Tyr Ala Val Tyr Arg Phe Phe Thr Phe Ser
[0560] 820 825 830
[0561] Asp His Asp Thr Ala Ile Ile Pro Ala Ser Asn Asn Pro Tyr Phe Arg
[0562] 835 840 845
[0563] Asp Gln Ala Arg Phe Pro Val Leu Val Thr Ser Asp Leu Asp His Tyr
[0564] 850 855 860
[0565] Leu Arg Arg Glu Ala Leu Ser Ile His Val Phe Asp Asp Glu Asp Leu
[0566] 865 870 875 880
[0567] Glu Pro Gly Ser Tyr Leu Gly Arg Ala Arg Val Pro Leu Leu Pro Leu
[0568] 885 890 895
[0569] Ala Lys Asn Glu Ser Ile Lys Gly Asp Phe Asn Leu Thr Asp Pro Ala
[0570] 900 905 910
[0571] Glu Lys Pro Asn Gly Ser Ile Gln Val Gln Leu Asp Trp Lys Phe Pro
[0572] 915 920 925
[0573] Tyr Ile Pro Pro Glu Ser Phe Leu Lys Pro Glu Ala Gln Thr Lys Gly
[0574] 930 935 940
[0575] Lys Asp Thr Lys Asp Ser Ser Lys Ile Ser Ser Glu Glu Glu Lys Ala
[0576] 945 950 955 960
[0577] Ser Phe Pro Ser Gln Asp Gln Met Ala Ser Pro Glu Val Pro Ile Glu
[0578] 965 970 975
[0579] Ala Gly Gln Tyr Arg Ser Lys Arg Lys Pro Pro His Gly Gly Glu Arg
[0580] 980 985 990
[0581] Lys Glu Lys Glu His Gln Val Val Ser Tyr Ser Arg Arg Lys His Gly
[0582] 995 1000 1005
[0583] Lys Arg Ile Gly Val Gln Gly Lys Asn Arg Met Glu Tyr Leu Ser
[0584] 1010 1015 1020

[0585] Leu Asn Ile Leu Asn Gly Asn Thr Pro Glu Gln Val Asn Tyr Thr
[0586] 1025 1030 1035
[0587] Glu Trp Lys Phe Ser Glu Thr Asn Ser Phe Ile Gly Asp Gly Phe
[0588] 1040 1045 1050
[0589] Lys Asn Gln His Glu Glu Glu Glu Met Thr Leu Ser His Ser Ala
[0590] 1055 1060 1065
[0591] Leu Lys Gln Lys Glu Pro Leu His Pro Val Asn Asp Lys Glu Ser
[0592] 1070 1075 1080
[0593] Ser Glu Gln Gly Ser Glu Val Ser Glu Ala Gln Thr Thr Asp Ser
[0594] 1085 1090 1095
[0595] Asp Asp Val Ile Val Pro Pro Met Ser Gln Lys Tyr Pro Lys Ala
[0596] 1100 1105 1110
[0597] Asp Ser Glu Lys Met Cys Ile Glu Ile Val Ser Leu Ala Phe Tyr
[0598] 1115 1120 1125
[0599] Pro Glu Ala Glu Val Met Ser Asp Glu Asn Ile Lys Gln Val Tyr
[0600] 1130 1135 1140
[0601] Val Glu Tyr Lys Phe Tyr Asp Leu Pro Leu Ser Glu Thr Glu Thr
[0602] 1145 1150 1155
[0603] Pro Val Ser Leu Arg Lys Pro Arg Ala Gly Glu Glu Ile His Phe
[0604] 1160 1165 1170
[0605] His Phe Ser Lys Val Ile Asp Leu Asp Pro Gln Glu Gln Gln Gly
[0606] 1175 1180 1185
[0607] Arg Arg Arg Phe Leu Phe Asp Met Leu Asn Gly Gln Asp Pro Asp
[0608] 1190 1195 1200
[0609] Gln Gly His Leu Lys Phe Thr Val Val Ser Asp Pro Leu Asp Glu
[0610] 1205 1210 1215
[0611] Glu Lys Lys Glu Cys Glu Glu Val Gly Tyr Ala Tyr Leu Gln Leu
[0612] 1220 1225 1230
[0613] Trp Gln Ile Leu Glu Ser Gly Arg Asp Ile Leu Glu Gln Glu Leu
[0614] 1235 1240 1245
[0615] Asp Ile Val Ser Pro Glu Asp Leu Ala Thr Pro Ile Gly Arg Leu
[0616] 1250 1255 1260
[0617] Lys Val Ser Leu Gln Ala Ala Ala Val Leu His Ala Ile Tyr Lys
[0618] 1265 1270 1275
[0619] Glu Met Thr Glu Asp Leu Phe Ser
[0620] 1280 1285
[0621] <210> 16
[0622] <211> 653
[0623] <212> PRT

[0624] <213> 智人

[0625] <400> 16

[0626] Met Ala Asp Thr Leu Pro Ser Glu Phe Asp Val Ile Val Ile Gly Thr

[0627] 1 5 10 15

[0628] Gly Leu Pro Glu Ser Ile Ile Ala Ala Ala Cys Ser Arg Ser Gly Arg

[0629] 20 25 30

[0630] Arg Val Leu His Val Asp Ser Arg Ser Tyr Tyr Gly Gly Asn Trp Ala

[0631] 35 40 45

[0632] Ser Phe Ser Phe Ser Gly Leu Leu Ser Trp Leu Lys Glu Tyr Gln Glu

[0633] 50 55 60

[0634] Asn Ser Asp Ile Val Ser Asp Ser Pro Val Trp Gln Asp Gln Ile Leu

[0635] 65 70 75 80

[0636] Glu Asn Glu Glu Ala Ile Ala Leu Ser Arg Lys Asp Lys Thr Ile Gln

[0637] 85 90 95

[0638] His Val Glu Val Phe Cys Tyr Ala Ser Gln Asp Leu His Glu Asp Val

[0639] 100 105 110

[0640] Glu Glu Ala Gly Ala Leu Gln Lys Asn His Ala Leu Val Thr Ser Ala

[0641] 115 120 125

[0642] Asn Ser Thr Glu Ala Ala Asp Ser Ala Phe Leu Pro Thr Glu Asp Glu

[0643] 130 135 140

[0644] Ser Leu Ser Thr Met Ser Cys Glu Met Leu Thr Glu Gln Thr Pro Ser

[0645] 145 150 155 160

[0646] Ser Asp Pro Glu Asn Ala Leu Glu Val Asn Gly Ala Glu Val Thr Gly

[0647] 165 170 175

[0648] Glu Lys Glu Asn His Cys Asp Asp Lys Thr Cys Val Pro Ser Thr Ser

[0649] 180 185 190

[0650] Ala Glu Asp Met Ser Glu Asn Val Pro Ile Ala Glu Asp Thr Thr Glu

[0651] 195 200 205

[0652] Gln Pro Lys Lys Asn Arg Ile Thr Tyr Ser Gln Ile Ile Lys Glu Gly

[0653] 210 215 220

[0654] Arg Arg Phe Asn Ile Asp Leu Val Ser Lys Leu Leu Tyr Ser Arg Gly

[0655] 225 230 235 240

[0656] Leu Leu Ile Asp Leu Leu Ile Lys Ser Asn Val Ser Arg Tyr Ala Glu

[0657] 245 250 255

[0658] Phe Lys Asn Ile Thr Arg Ile Leu Ala Phe Arg Glu Gly Arg Val Glu

[0659] 260 265 270

[0660] Gln Val Pro Cys Ser Arg Ala Asp Val Phe Asn Ser Lys Gln Leu Thr

[0661] 275 280 285

[0662] Met Val Glu Lys Arg Met Leu Met Lys Phe Leu Thr Phe Cys Met Glu

[0663] 290 295 300

[0664] Tyr Glu Lys Tyr Pro Asp Glu Tyr Lys Gly Tyr Glu Glu Ile Thr Phe

[0665] 305 310 315 320

[0666] Tyr Glu Tyr Leu Lys Thr Gln Lys Leu Thr Pro Asn Leu Gln Tyr Ile

[0667] 325 330 335

[0668] Val Met His Ser Ile Ala Met Thr Ser Glu Thr Ala Ser Ser Thr Ile

[0669] 340 345 350

[0670] Asp Gly Leu Lys Ala Thr Lys Asn Phe Leu His Cys Leu Gly Arg Tyr

[0671] 355 360 365

[0672] Gly Asn Thr Pro Phe Leu Phe Pro Leu Tyr Gly Gln Gly Glu Leu Pro

[0673] 370 375 380

[0674] Gln Cys Phe Cys Arg Met Cys Ala Val Phe Gly Gly Ile Tyr Cys Leu

[0675] 385 390 395 400

[0676] Arg His Ser Val Gln Cys Leu Val Val Asp Lys Glu Ser Arg Lys Cys

[0677] 405 410 415

[0678] Lys Ala Ile Ile Asp Gln Phe Gly Gln Arg Ile Ile Ser Glu His Phe

[0679] 420 425 430

[0680] Leu Val Glu Asp Ser Tyr Phe Pro Glu Asn Met Cys Ser Arg Val Gln

[0681] 435 440 445

[0682] Tyr Arg Gln Ile Ser Arg Ala Val Leu Ile Thr Asp Arg Ser Val Leu

[0683] 450 455 460

[0684] Lys Thr Asp Ser Asp Gln Gln Ile Ser Ile Leu Thr Val Pro Ala Glu

[0685] 465 470 475 480

[0686] Glu Pro Gly Thr Phe Ala Val Arg Val Ile Glu Leu Cys Ser Ser Thr

[0687] 485 490 495

[0688] Met Thr Cys Met Lys Gly Thr Tyr Leu Val His Leu Thr Cys Thr Ser

[0689] 500 505 510

[0690] Ser Lys Thr Ala Arg Glu Asp Leu Glu Ser Val Val Gln Lys Leu Phe

[0691] 515 520 525

[0692] Val Pro Tyr Thr Glu Met Glu Ile Glu Asn Glu Gln Val Glu Lys Pro

[0693] 530 535 540

[0694] Arg Ile Leu Trp Ala Leu Tyr Phe Asn Met Arg Asp Ser Ser Asp Ile

[0695] 545 550 555 560

[0696] Ser Arg Ser Cys Tyr Asn Asp Leu Pro Ser Asn Val Tyr Val Cys Ser

[0697] 565 570 575

[0698] Gly Pro Asp Cys Gly Leu Gly Asn Asp Asn Ala Val Lys Gln Ala Glu

[0699] 580 585 590

[0700] Thr Leu Phe Gln Glu Ile Cys Pro Asn Glu Asp Phe Cys Pro Pro Pro

[0701] 595 600 605

[0702] Pro Asn Pro Glu Asp Ile Ile Leu Asp Gly Asp Ser Leu Gln Pro Glu
[0703] 610 615 620
[0704] Ala Ser Glu Ser Ser Ala Ile Pro Glu Ala Asn Ser Glu Thr Phe Lys
[0705] 625 630 635 640
[0706] Glu Ser Thr Asn Leu Gly Asn Leu Glu Glu Ser Ser Glu
[0707] 645 650
[0708] <210> 17
[0709] <211> 212
[0710] <212> PRT
[0711] <213> 智人
[0712] <400> 17
[0713] Met Ala Ser Leu Phe Ser Gly Arg Ile Leu Ile Arg Asn Asn Ser Asp
[0714] 1 5 10 15
[0715] Gln Asp Glu Leu Asp Thr Glu Ala Glu Val Ser Arg Arg Leu Glu Asn
[0716] 20 25 30
[0717] Arg Leu Val Leu Leu Phe Phe Gly Ala Gly Ala Cys Pro Gln Cys Gln
[0718] 35 40 45
[0719] Ala Phe Val Pro Ile Leu Lys Asp Phe Phe Val Arg Leu Thr Asp Glu
[0720] 50 55 60
[0721] Phe Tyr Val Leu Arg Ala Ala Gln Leu Ala Leu Val Tyr Val Ser Gln
[0722] 65 70 75 80
[0723] Asp Ser Thr Glu Glu Gln Gln Asp Leu Phe Leu Lys Asp Met Pro Lys
[0724] 85 90 95
[0725] Lys Trp Leu Phe Leu Pro Phe Glu Asp Asp Leu Arg Arg Asp Leu Gly
[0726] 100 105 110
[0727] Arg Gln Phe Ser Val Glu Arg Leu Pro Ala Val Val Val Leu Lys Pro
[0728] 115 120 125
[0729] Asp Gly Asp Val Leu Thr Arg Asp Gly Ala Asp Glu Ile Gln Arg Leu
[0730] 130 135 140
[0731] Gly Thr Ala Cys Phe Ala Asn Trp Gln Glu Ala Ala Glu Val Leu Asp
[0732] 145 150 155 160
[0733] Arg Asn Phe Gln Leu Pro Glu Asp Leu Glu Asp Gln Glu Pro Arg Ser
[0734] 165 170 175
[0735] Leu Thr Glu Cys Leu Arg Arg His Lys Tyr Arg Val Glu Lys Ala Ala
[0736] 180 185 190
[0737] Arg Gly Gly Arg Asp Pro Gly Gly Gly Gly Gly Glu Glu Gly Gly Ala
[0738] 195 200 205
[0739] Gly Gly Leu Phe
[0740] 210

[0741] <210> 18

[0742] <211> 156

[0743] <212> PRT

[0744] <213> 智人

[0745] <400> 18

[0746] Met Val Asp Ile Leu Gly Glu Arg His Leu Val Thr Cys Lys Gly Ala

[0747] 1 5 10 15

[0748] Thr Val Glu Ala Glu Ala Ala Leu Gln Asn Lys Val Val Ala Leu Tyr

[0749] 20 25 30

[0750] Phe Ala Ala Ala Arg Cys Ala Pro Ser Arg Asp Phe Thr Pro Leu Leu

[0751] 35 40 45

[0752] Cys Asp Phe Tyr Thr Ala Leu Val Ala Glu Ala Arg Arg Pro Ala Pro

[0753] 50 55 60

[0754] Phe Glu Val Val Phe Val Ser Ala Asp Gly Ser Ser Gln Glu Met Leu

[0755] 65 70 75 80

[0756] Asp Phe Met Arg Glu Leu His Gly Ala Trp Leu Ala Leu Pro Phe His

[0757] 85 90 95

[0758] Asp Pro Tyr Arg His Glu Leu Arg Lys Arg Tyr Asn Val Thr Ala Ile

[0759] 100 105 110

[0760] Pro Lys Leu Val Ile Val Lys Gln Asn Gly Glu Val Ile Thr Asn Lys

[0761] 115 120 125

[0762] Gly Arg Lys Gln Ile Arg Glu Arg Gly Leu Ala Cys Phe Gln Asp Trp

[0763] 130 135 140

[0764] Val Glu Ala Ala Asp Ile Phe Gln Asn Phe Ser Val

[0765] 145 150 155

[0766] <210> 19

[0767] <211> 135

[0768] <212> PRT

[0769] <213> 智人

[0770] <400> 19

[0771] Met Val Asp Ile Leu Gly Glu Arg His Leu Val Thr Cys Lys Gly Ala

[0772] 1 5 10 15

[0773] Thr Val Glu Ala Glu Ala Ala Leu Gln Asn Lys Val Val Ala Leu Tyr

[0774] 20 25 30

[0775] Phe Ala Ala Ala Arg Cys Ala Pro Ser Arg Asp Phe Thr Pro Leu Leu

[0776] 35 40 45

[0777] Cys Asp Phe Tyr Thr Ala Leu Val Ala Glu Ala Arg Arg Pro Ala Pro

[0778] 50 55 60

[0779] Phe Glu Val Val Phe Val Ser Ala Asp Gly Ser Ser Gln Glu Met Leu

[0780] 65 70 75 80
[0781] Asp Phe Met Arg Glu Leu His Gly Ala Trp Leu Ala Leu Pro Phe His
[0782] 85 90 95
[0783] Asp Pro Tyr Arg Gln Arg Ser Leu Ala Leu Leu Pro Arg Leu Glu Cys
[0784] 100 105 110
[0785] Ser Gly Val Ile Leu Ala His Cys Asn Leu Cys Leu Leu Gly Ser Ser
[0786] 115 120 125
[0787] Asp Ser Leu Ala Leu Ala Ser
[0788] 130 135
[0789] <210> 20
[0790] <211> 860
[0791] <212> PRT
[0792] <213> 智人
[0793] <400> 20
[0794] Met Gly Glu Val Thr Ala Glu Glu Val Glu Lys Phe Leu Asp Ser Asn
[0795] 1 5 10 15
[0796] Ile Gly Phe Ala Lys Gln Tyr Tyr Asn Leu His Tyr Arg Ala Lys Leu
[0797] 20 25 30
[0798] Ile Ser Asp Leu Leu Gly Ala Lys Glu Ala Ala Val Asp Phe Ser Asn
[0799] 35 40 45
[0800] Tyr His Ser Pro Ser Ser Met Glu Glu Ser Glu Ile Ile Phe Asp Leu
[0801] 50 55 60
[0802] Leu Arg Asp Phe Gln Glu Asn Leu Gln Thr Glu Lys Cys Ile Phe Asn
[0803] 65 70 75 80
[0804] Val Met Lys Lys Leu Cys Phe Leu Leu Gln Ala Asp Arg Met Ser Leu
[0805] 85 90 95
[0806] Phe Met Tyr Arg Thr Arg Asn Gly Ile Ala Glu Leu Ala Thr Arg Leu
[0807] 100 105 110
[0808] Phe Asn Val His Lys Asp Ala Val Leu Glu Asp Cys Leu Val Met Pro
[0809] 115 120 125
[0810] Asp Gln Glu Ile Val Phe Pro Leu Asp Met Gly Ile Val Gly His Val
[0811] 130 135 140
[0812] Ala His Ser Lys Lys Ile Ala Asn Val Pro Asn Thr Glu Glu Asp Glu
[0813] 145 150 155 160
[0814] His Phe Cys Asp Phe Val Asp Ile Leu Thr Glu Tyr Lys Thr Lys Asn
[0815] 165 170 175
[0816] Ile Leu Ala Ser Pro Ile Met Asn Gly Lys Asp Val Val Ala Ile Ile
[0817] 180 185 190
[0818] Met Ala Val Asn Lys Val Asp Gly Ser His Phe Thr Lys Arg Asp Glu

[0819] 195 200 205

[0820] Glu Ile Leu Leu Lys Tyr Leu Asn Phe Ala Asn Leu Ile Met Lys Val

[0821] 210 215 220

[0822] Tyr His Leu Ser Tyr Leu His Asn Cys Glu Thr Arg Arg Gly Gln Ile

[0823] 225 230 235 240

[0824] Leu Leu Trp Ser Gly Ser Lys Val Phe Glu Glu Leu Thr Asp Ile Glu

[0825] 245 250 255

[0826] Arg Gln Phe His Lys Ala Leu Tyr Thr Val Arg Ala Phe Leu Asn Cys

[0827] 260 265 270

[0828] Asp Arg Tyr Ser Val Gly Leu Leu Asp Met Thr Lys Gln Lys Glu Phe

[0829] 275 280 285

[0830] Phe Asp Val Trp Pro Val Leu Met Gly Glu Val Pro Pro Tyr Ser Gly

[0831] 290 295 300

[0832] Pro Arg Thr Pro Asp Gly Arg Glu Ile Asn Phe Tyr Lys Val Ile Asp

[0833] 305 310 315 320

[0834] Tyr Ile Leu His Gly Lys Glu Asp Ile Lys Val Ile Pro Asn Pro Pro

[0835] 325 330 335

[0836] Pro Asp His Trp Ala Leu Val Ser Gly Leu Pro Ala Tyr Val Ala Gln

[0837] 340 345 350

[0838] Asn Gly Leu Ile Cys Asn Ile Met Asn Ala Pro Ala Glu Asp Phe Phe

[0839] 355 360 365

[0840] Ala Phe Gln Lys Glu Pro Leu Asp Glu Ser Gly Trp Met Ile Lys Asn

[0841] 370 375 380

[0842] Val Leu Ser Met Pro Ile Val Asn Lys Lys Glu Glu Ile Val Gly Val

[0843] 385 390 395 400

[0844] Ala Thr Phe Tyr Asn Arg Lys Asp Gly Lys Pro Phe Asp Glu Met Asp

[0845] 405 410 415

[0846] Glu Thr Leu Met Glu Ser Leu Thr Gln Phe Leu Gly Trp Ser Val Leu

[0847] 420 425 430

[0848] Asn Pro Asp Thr Tyr Glu Ser Met Asn Lys Leu Glu Asn Arg Lys Asp

[0849] 435 440 445

[0850] Ile Phe Gln Asp Ile Val Lys Tyr His Val Lys Cys Asp Asn Glu Glu

[0851] 450 455 460

[0852] Ile Gln Lys Ile Leu Lys Thr Arg Glu Val Tyr Gly Lys Glu Pro Trp

[0853] 465 470 475 480

[0854] Glu Cys Glu Glu Glu Glu Leu Ala Glu Ile Leu Gln Ala Glu Leu Pro

[0855] 485 490 495

[0856] Asp Ala Asp Lys Tyr Glu Ile Asn Lys Phe His Phe Ser Asp Leu Pro

[0857] 500 505 510

[0858] Leu Thr Glu Leu Glu Leu Val Lys Cys Gly Ile Gln Met Tyr Tyr Glu
[0859] 515 520 525
[0860] Leu Lys Val Val Asp Lys Phe His Ile Pro Gln Glu Ala Leu Val Arg
[0861] 530 535 540
[0862] Phe Met Tyr Ser Leu Ser Lys Gly Tyr Arg Lys Ile Thr Tyr His Asn
[0863] 545 550 555 560
[0864] Trp Arg His Gly Phe Asn Val Gly Gln Thr Met Phe Ser Leu Leu Val
[0865] 565 570 575
[0866] Thr Gly Lys Leu Lys Arg Tyr Phe Thr Asp Leu Glu Ala Leu Ala Met
[0867] 580 585 590
[0868] Val Thr Ala Ala Phe Cys His Asp Ile Asp His Arg Gly Thr Asn Asn
[0869] 595 600 605
[0870] Leu Tyr Gln Met Lys Ser Gln Asn Pro Leu Ala Lys Leu His Gly Ser
[0871] 610 615 620
[0872] Ser Ile Leu Glu Arg His His Leu Glu Phe Gly Lys Thr Leu Leu Arg
[0873] 625 630 635 640
[0874] Asp Glu Ser Leu Asn Ile Phe Gln Asn Leu Asn Arg Arg Gln His Glu
[0875] 645 650 655
[0876] His Ala Ile His Met Met Asp Ile Ala Ile Ile Ala Thr Asp Leu Ala
[0877] 660 665 670
[0878] Leu Tyr Phe Lys Lys Arg Thr Met Phe Gln Lys Ile Val Asp Gln Ser
[0879] 675 680 685
[0880] Lys Thr Tyr Glu Ser Glu Gln Glu Trp Thr Gln Tyr Met Met Leu Glu
[0881] 690 695 700
[0882] Gln Thr Arg Lys Glu Ile Val Met Ala Met Met Met Thr Ala Cys Asp
[0883] 705 710 715 720
[0884] Leu Ser Ala Ile Thr Lys Pro Trp Glu Val Gln Ser Gln Val Ala Leu
[0885] 725 730 735
[0886] Leu Val Ala Ala Glu Phe Trp Glu Gln Gly Asp Leu Glu Arg Thr Val
[0887] 740 745 750
[0888] Leu Gln Gln Asn Pro Ile Pro Met Met Asp Arg Asn Lys Ala Asp Glu
[0889] 755 760 765
[0890] Leu Pro Lys Leu Gln Val Gly Phe Ile Asp Phe Val Cys Thr Phe Val
[0891] 770 775 780
[0892] Tyr Lys Glu Phe Ser Arg Phe His Glu Glu Ile Thr Pro Met Leu Asp
[0893] 785 790 795 800
[0894] Gly Ile Thr Asn Asn Arg Lys Glu Trp Lys Ala Leu Ala Asp Glu Tyr
[0895] 805 810 815
[0896] Asp Ala Lys Met Lys Val Gln Glu Glu Lys Lys Gln Lys Gln Gln Ser

[0897] 820 825 830

[0898] Ala Lys Ser Ala Ala Ala Gly Asn Gln Pro Gly Gly Asn Pro Ser Pro

[0899] 835 840 845

[0900] Gly Gly Ala Thr Thr Ser Lys Ser Cys Cys Ile Gln

[0901] 850 855 860

[0902] <210> 21

[0903] <211> 854

[0904] <212> PRT

[0905] <213> 智人

[0906] <400> 21

[0907] Met Ser Leu Ser Glu Glu Gln Ala Arg Ser Phe Leu Asp Gln Asn Pro

[0908] 1 5 10 15

[0909] Asp Phe Ala Arg Gln Tyr Phe Gly Lys Lys Leu Ser Pro Glu Asn Val

[0910] 20 25 30

[0911] Ala Ala Ala Cys Glu Asp Gly Cys Pro Pro Asp Cys Asp Ser Leu Arg

[0912] 35 40 45

[0913] Asp Leu Cys Gln Val Glu Glu Ser Thr Ala Leu Leu Glu Leu Val Gln

[0914] 50 55 60

[0915] Asp Met Gln Glu Ser Ile Asn Met Glu Arg Val Val Phe Lys Val Leu

[0916] 65 70 75 80

[0917] Arg Arg Leu Cys Thr Leu Leu Gln Ala Asp Arg Cys Ser Leu Phe Met

[0918] 85 90 95

[0919] Tyr Arg Gln Arg Asn Gly Val Ala Glu Leu Ala Thr Arg Leu Phe Ser

[0920] 100 105 110

[0921] Val Gln Pro Asp Ser Val Leu Glu Asp Cys Leu Val Pro Pro Asp Ser

[0922] 115 120 125

[0923] Glu Ile Val Phe Pro Leu Asp Ile Gly Val Val Gly His Val Ala Gln

[0924] 130 135 140

[0925] Thr Lys Lys Met Val Asn Val Glu Asp Val Ala Glu Cys Pro His Phe

[0926] 145 150 155 160

[0927] Ser Ser Phe Ala Asp Glu Leu Thr Asp Tyr Lys Thr Lys Asn Met Leu

[0928] 165 170 175

[0929] Ala Thr Pro Ile Met Asn Gly Lys Asp Val Val Ala Val Ile Met Ala

[0930] 180 185 190

[0931] Val Asn Lys Leu Asn Gly Pro Phe Phe Thr Ser Glu Asp Glu Asp Val

[0932] 195 200 205

[0933] Phe Leu Lys Tyr Leu Asn Phe Ala Thr Leu Tyr Leu Lys Ile Tyr His

[0934] 210 215 220

[0935] Leu Ser Tyr Leu His Asn Cys Glu Thr Arg Arg Gly Gln Val Leu Leu

[0936] 225 230 235 240

[0937] Trp Ser Ala Asn Lys Val Phe Glu Glu Leu Thr Asp Ile Glu Arg Gln

[0938] 245 250 255

[0939] Phe His Lys Ala Phe Tyr Thr Val Arg Ala Tyr Leu Asn Cys Glu Arg

[0940] 260 265 270

[0941] Tyr Ser Val Gly Leu Leu Asp Met Thr Lys Glu Lys Glu Phe Phe Asp

[0942] 275 280 285

[0943] Val Trp Ser Val Leu Met Gly Glu Ser Gln Pro Tyr Ser Gly Pro Arg

[0944] 290 295 300

[0945] Thr Pro Asp Gly Arg Glu Ile Val Phe Tyr Lys Val Ile Asp Tyr Ile

[0946] 305 310 315 320

[0947] Leu His Gly Lys Glu Glu Ile Lys Val Ile Pro Thr Pro Ser Ala Asp

[0948] 325 330 335

[0949] His Trp Ala Leu Ala Ser Gly Leu Pro Ser Tyr Val Ala Glu Ser Gly

[0950] 340 345 350

[0951] Phe Ile Cys Asn Ile Met Asn Ala Ser Ala Asp Glu Met Phe Lys Phe

[0952] 355 360 365

[0953] Gln Glu Gly Ala Leu Asp Asp Ser Gly Trp Leu Ile Lys Asn Val Leu

[0954] 370 375 380

[0955] Ser Met Pro Ile Val Asn Lys Lys Glu Glu Ile Val Gly Val Ala Thr

[0956] 385 390 395 400

[0957] Phe Tyr Asn Arg Lys Asp Gly Lys Pro Phe Asp Glu Gln Asp Glu Val

[0958] 405 410 415

[0959] Leu Met Glu Ser Leu Thr Gln Phe Leu Gly Trp Ser Val Met Asn Thr

[0960] 420 425 430

[0961] Asp Thr Tyr Asp Lys Met Asn Lys Leu Glu Asn Arg Lys Asp Ile Ala

[0962] 435 440 445

[0963] Gln Asp Met Val Leu Tyr His Val Lys Cys Asp Arg Asp Glu Ile Gln

[0964] 450 455 460

[0965] Leu Ile Leu Pro Thr Arg Ala Arg Leu Gly Lys Glu Pro Ala Asp Cys

[0966] 465 470 475 480

[0967] Asp Glu Asp Glu Leu Gly Glu Ile Leu Lys Glu Glu Leu Pro Gly Pro

[0968] 485 490 495

[0969] Thr Thr Phe Asp Ile Tyr Glu Phe His Phe Ser Asp Leu Glu Cys Thr

[0970] 500 505 510

[0971] Glu Leu Asp Leu Val Lys Cys Gly Ile Gln Met Tyr Tyr Glu Leu Gly

[0972] 515 520 525

[0973] Val Val Arg Lys Phe Gln Ile Pro Gln Glu Val Leu Val Arg Phe Leu

[0974] 530 535 540

[0975] Phe Ser Ile Ser Lys Gly Tyr Arg Arg Ile Thr Tyr His Asn Trp Arg
[0976] 545 550 555 560
[0977] His Gly Phe Asn Val Ala Gln Thr Met Phe Thr Leu Leu Met Thr Gly
[0978] 565 570 575
[0979] Lys Leu Lys Ser Tyr Tyr Thr Asp Leu Glu Ala Phe Ala Met Val Thr
[0980] 580 585 590
[0981] Ala Gly Leu Cys His Asp Ile Asp His Arg Gly Thr Asn Asn Leu Tyr
[0982] 595 600 605
[0983] Gln Met Lys Ser Gln Asn Pro Leu Ala Lys Leu His Gly Ser Ser Ile
[0984] 610 615 620
[0985] Leu Glu Arg His His Leu Glu Phe Gly Lys Phe Leu Leu Ser Glu Glu
[0986] 625 630 635 640
[0987] Thr Leu Asn Ile Tyr Gln Asn Leu Asn Arg Arg Gln His Glu His Val
[0988] 645 650 655
[0989] Ile His Leu Met Asp Ile Ala Ile Ile Ala Thr Asp Leu Ala Leu Tyr
[0990] 660 665 670
[0991] Phe Lys Lys Arg Ala Met Phe Gln Lys Ile Val Asp Glu Ser Lys Asn
[0992] 675 680 685
[0993] Tyr Gln Asp Lys Lys Ser Trp Val Glu Tyr Leu Ser Leu Glu Thr Thr
[0994] 690 695 700
[0995] Arg Lys Glu Ile Val Met Ala Met Met Met Thr Ala Cys Asp Leu Ser
[0996] 705 710 715 720
[0997] Ala Ile Thr Lys Pro Trp Glu Val Gln Ser Lys Val Ala Leu Leu Val
[0998] 725 730 735
[0999] Ala Ala Glu Phe Trp Glu Gln Gly Asp Leu Glu Arg Thr Val Leu Asp
[1000] 740 745 750
[1001] Gln Gln Pro Ile Pro Met Met Asp Arg Asn Lys Ala Ala Glu Leu Pro
[1002] 755 760 765
[1003] Lys Leu Gln Val Gly Phe Ile Asp Phe Val Cys Thr Phe Val Tyr Lys
[1004] 770 775 780
[1005] Glu Phe Ser Arg Phe His Glu Glu Ile Leu Pro Met Phe Asp Arg Leu
[1006] 785 790 795 800
[1007] Gln Asn Asn Arg Lys Glu Trp Lys Ala Leu Ala Asp Glu Tyr Glu Ala
[1008] 805 810 815
[1009] Lys Val Lys Ala Leu Glu Glu Lys Glu Glu Glu Glu Arg Val Ala Ala
[1010] 820 825 830
[1011] Lys Lys Val Gly Thr Glu Ile Cys Asn Gly Gly Pro Ala Pro Lys Ser
[1012] 835 840 845
[1013] Ser Thr Cys Cys Ile Leu

[1014] 850

[1015] <210> 22

[1016] <211> 853

[1017] <212> PRT

[1018] <213> 智人

[1019] <400> 22

[1020] Met Ser Leu Ser Glu Glu Gln Ala Arg Ser Phe Leu Asp Gln Asn Pro

[1021] 1 5 10 15

[1022] Asp Phe Ala Arg Gln Tyr Phe Gly Lys Lys Leu Ser Pro Glu Asn Val

[1023] 20 25 30

[1024] Ala Ala Ala Cys Glu Asp Gly Cys Pro Pro Asp Cys Asp Ser Leu Arg

[1025] 35 40 45

[1026] Asp Leu Cys Gln Val Glu Glu Ser Thr Ala Leu Leu Glu Leu Val Gln

[1027] 50 55 60

[1028] Asp Met Gln Glu Ser Ile Asn Met Glu Arg Val Val Phe Lys Val Leu

[1029] 65 70 75 80

[1030] Arg Arg Leu Cys Thr Leu Leu Gln Ala Asp Arg Cys Ser Leu Phe Met

[1031] 85 90 95

[1032] Tyr Arg Gln Arg Asn Gly Val Ala Glu Leu Ala Thr Arg Leu Phe Ser

[1033] 100 105 110

[1034] Val Gln Pro Asp Ser Val Leu Glu Asp Cys Leu Val Pro Pro Asp Ser

[1035] 115 120 125

[1036] Glu Ile Val Phe Pro Leu Asp Ile Gly Val Val Gly His Val Ala Gln

[1037] 130 135 140

[1038] Thr Lys Lys Met Val Asn Val Glu Asp Val Ala Glu Cys Pro His Phe

[1039] 145 150 155 160

[1040] Ser Ser Phe Ala Asp Glu Leu Thr Asp Tyr Lys Thr Lys Asn Met Leu

[1041] 165 170 175

[1042] Ala Thr Pro Ile Met Asn Gly Lys Asp Val Val Ala Val Ile Met Ala

[1043] 180 185 190

[1044] Val Asn Lys Leu Asn Gly Pro Phe Phe Thr Ser Glu Asp Glu Asp Val

[1045] 195 200 205

[1046] Phe Leu Lys Tyr Leu Asn Phe Ala Thr Leu Tyr Leu Lys Ile Tyr His

[1047] 210 215 220

[1048] Leu Ser Tyr Leu His Asn Cys Glu Thr Arg Arg Gly Gln Val Leu Leu

[1049] 225 230 235 240

[1050] Trp Ser Ala Asn Lys Val Phe Glu Glu Leu Thr Asp Ile Glu Arg Gln

[1051] 245 250 255

[1052] Phe His Lys Ala Phe Tyr Thr Val Arg Ala Tyr Leu Asn Cys Glu Arg

[1053] 260 265 270
[1054] Tyr Ser Val Gly Leu Leu Asp Met Thr Lys Glu Lys Glu Phe Phe Asp
[1055] 275 280 285
[1056] Val Trp Ser Val Leu Met Gly Glu Ser Gln Pro Tyr Ser Gly Pro Arg
[1057] 290 295 300
[1058] Thr Pro Asp Gly Arg Glu Ile Val Phe Tyr Lys Val Ile Asp Tyr Ile
[1059] 305 310 315 320
[1060] Leu His Gly Lys Glu Glu Ile Lys Val Ile Pro Thr Pro Ser Ala Asp
[1061] 325 330 335
[1062] His Trp Ala Leu Ala Ser Gly Leu Pro Ser Tyr Val Ala Glu Ser Gly
[1063] 340 345 350
[1064] Phe Ile Cys Asn Ile Met Asn Ala Ser Ala Asp Glu Met Phe Lys Phe
[1065] 355 360 365
[1066] Gln Glu Gly Ala Leu Asp Asp Ser Gly Trp Leu Ile Lys Asn Val Leu
[1067] 370 375 380
[1068] Ser Met Pro Ile Val Asn Lys Lys Glu Glu Ile Val Gly Val Ala Thr
[1069] 385 390 395 400
[1070] Phe Tyr Asn Arg Lys Asp Gly Lys Pro Phe Asp Glu Gln Asp Glu Val
[1071] 405 410 415
[1072] Leu Met Glu Ser Leu Thr Gln Phe Leu Gly Trp Ser Val Met Asn Thr
[1073] 420 425 430
[1074] Asp Thr Tyr Asp Lys Met Asn Lys Leu Glu Asn Arg Lys Asp Ile Ala
[1075] 435 440 445
[1076] Gln Asp Met Val Leu Tyr His Val Lys Cys Asp Arg Asp Glu Ile Gln
[1077] 450 455 460
[1078] Leu Ile Leu Pro Thr Arg Ala Arg Leu Gly Lys Glu Pro Ala Asp Cys
[1079] 465 470 475 480
[1080] Asp Glu Asp Glu Leu Gly Glu Ile Leu Lys Glu Glu Leu Pro Gly Pro
[1081] 485 490 495
[1082] Thr Thr Phe Asp Ile Tyr Glu Phe His Phe Ser Asp Leu Glu Cys Thr
[1083] 500 505 510
[1084] Glu Leu Asp Leu Val Lys Cys Gly Ile Gln Met Tyr Tyr Glu Leu Gly
[1085] 515 520 525
[1086] Val Val Arg Lys Phe Gln Ile Pro Gln Glu Val Leu Val Arg Phe Leu
[1087] 530 535 540
[1088] Phe Ser Ile Ser Lys Gly Tyr Arg Arg Ile Thr Tyr His Asn Trp Arg
[1089] 545 550 555 560
[1090] His Gly Phe Asn Val Ala Gln Thr Met Phe Thr Leu Leu Met Thr Gly
[1091] 565 570 575

[1092] Lys Leu Lys Ser Tyr Tyr Thr Asp Leu Glu Ala Phe Ala Met Val Thr
[1093] 580 585 590
[1094] Ala Gly Leu Cys His Asp Ile Asp His Arg Gly Thr Asn Asn Leu Tyr
[1095] 595 600 605
[1096] Gln Met Lys Ser Gln Asn Pro Leu Ala Lys Leu His Gly Ser Ser Ile
[1097] 610 615 620
[1098] Leu Glu Arg His His Leu Glu Phe Gly Lys Phe Leu Leu Ser Glu Glu
[1099] 625 630 635 640
[1100] Thr Leu Asn Ile Tyr Gln Asn Leu Asn Arg Arg Gln His Glu His Val
[1101] 645 650 655
[1102] Ile His Leu Met Asp Ile Ala Ile Ile Ala Thr Asp Leu Ala Leu Tyr
[1103] 660 665 670
[1104] Phe Lys Lys Arg Ala Met Phe Gln Lys Ile Val Asp Glu Ser Lys Asn
[1105] 675 680 685
[1106] Tyr Gln Asp Lys Lys Ser Trp Val Glu Tyr Leu Ser Leu Glu Thr Thr
[1107] 690 695 700
[1108] Arg Lys Glu Ile Val Met Ala Met Met Met Thr Ala Cys Asp Leu Ser
[1109] 705 710 715 720
[1110] Ala Ile Thr Lys Pro Trp Glu Val Gln Ser Lys Val Ala Leu Leu Val
[1111] 725 730 735
[1112] Ala Ala Glu Phe Trp Glu Gln Gly Asp Leu Glu Arg Thr Val Leu Asp
[1113] 740 745 750
[1114] Gln Gln Pro Ile Pro Met Met Asp Arg Asn Lys Ala Ala Glu Leu Pro
[1115] 755 760 765
[1116] Lys Leu Gln Val Gly Phe Ile Asp Phe Val Cys Thr Phe Val Tyr Lys
[1117] 770 775 780
[1118] Glu Phe Ser Arg Phe His Glu Glu Ile Leu Pro Met Phe Asp Arg Leu
[1119] 785 790 795 800
[1120] Gln Asn Asn Arg Lys Glu Trp Lys Ala Leu Ala Asp Glu Tyr Glu Ala
[1121] 805 810 815
[1122] Lys Val Lys Ala Leu Glu Glu Lys Glu Glu Glu Glu Arg Val Ala Ala
[1123] 820 825 830
[1124] Lys Lys Gly Thr Glu Ile Cys Asn Gly Gly Pro Ala Pro Lys Ser Ser
[1125] 835 840 845
[1126] Thr Cys Cys Ile Leu
[1127] 850
[1128] <210> 23
[1129] <211> 575
[1130] <212> PRT

[1131] <213> 智人

[1132] <400> 23

[1133] Met Thr Lys Glu Lys Glu Phe Phe Asp Val Trp Ser Val Leu Met Gly

[1134] 1 5 10 15

[1135] Glu Ser Gln Pro Tyr Ser Gly Pro Arg Thr Pro Asp Gly Arg Glu Ile

[1136] 20 25 30

[1137] Val Phe Tyr Lys Val Ile Asp Tyr Ile Leu His Gly Lys Glu Glu Ile

[1138] 35 40 45

[1139] Lys Val Ile Pro Thr Pro Ser Ala Asp His Trp Ala Leu Ala Ser Gly

[1140] 50 55 60

[1141] Leu Pro Ser Tyr Val Ala Glu Ser Gly Phe Ile Cys Asn Ile Met Asn

[1142] 65 70 75 80

[1143] Ala Ser Ala Asp Glu Met Phe Lys Phe Gln Glu Gly Ala Leu Asp Asp

[1144] 85 90 95

[1145] Ser Gly Trp Leu Ile Lys Asn Val Leu Ser Met Pro Ile Val Asn Lys

[1146] 100 105 110

[1147] Lys Glu Glu Ile Val Gly Val Ala Thr Phe Tyr Asn Arg Lys Asp Gly

[1148] 115 120 125

[1149] Lys Pro Phe Asp Glu Gln Asp Glu Val Leu Met Glu Ser Leu Thr Gln

[1150] 130 135 140

[1151] Phe Leu Gly Trp Ser Val Met Asn Thr Asp Thr Tyr Asp Lys Met Asn

[1152] 145 150 155 160

[1153] Lys Leu Glu Asn Arg Lys Asp Ile Ala Gln Asp Met Val Leu Tyr His

[1154] 165 170 175

[1155] Val Lys Cys Asp Arg Asp Glu Ile Gln Leu Ile Leu Pro Thr Arg Ala

[1156] 180 185 190

[1157] Arg Leu Gly Lys Glu Pro Ala Asp Cys Asp Glu Asp Glu Leu Gly Glu

[1158] 195 200 205

[1159] Ile Leu Lys Glu Glu Leu Pro Gly Pro Thr Thr Phe Asp Ile Tyr Glu

[1160] 210 215 220

[1161] Phe His Phe Ser Asp Leu Glu Cys Thr Glu Leu Asp Leu Val Lys Cys

[1162] 225 230 235 240

[1163] Gly Ile Gln Met Tyr Tyr Glu Leu Gly Val Val Arg Lys Phe Gln Ile

[1164] 245 250 255

[1165] Pro Gln Glu Val Leu Val Arg Phe Leu Phe Ser Ile Ser Lys Gly Tyr

[1166] 260 265 270

[1167] Arg Arg Ile Thr Tyr His Asn Trp Arg His Gly Phe Asn Val Ala Gln

[1168] 275 280 285

[1169] Thr Met Phe Thr Leu Leu Met Thr Gly Lys Leu Lys Ser Tyr Tyr Thr

[1170] 290 295 300

[1171] Asp Leu Glu Ala Phe Ala Met Val Thr Ala Gly Leu Cys His Asp Ile

[1172] 305 310 315 320

[1173] Asp His Arg Gly Thr Asn Asn Leu Tyr Gln Met Lys Ser Gln Asn Pro

[1174] 325 330 335

[1175] Leu Ala Lys Leu His Gly Ser Ser Ile Leu Glu Arg His His Leu Glu

[1176] 340 345 350

[1177] Phe Gly Lys Phe Leu Leu Ser Glu Glu Thr Leu Asn Ile Tyr Gln Asn

[1178] 355 360 365

[1179] Leu Asn Arg Arg Gln His Glu His Val Ile His Leu Met Asp Ile Ala

[1180] 370 375 380

[1181] Ile Ile Ala Thr Asp Leu Ala Leu Tyr Phe Lys Lys Arg Ala Met Phe

[1182] 385 390 395 400

[1183] Gln Lys Ile Val Asp Glu Ser Lys Asn Tyr Gln Asp Lys Lys Ser Trp

[1184] 405 410 415

[1185] Val Glu Tyr Leu Ser Leu Glu Thr Thr Arg Lys Glu Ile Val Met Ala

[1186] 420 425 430

[1187] Met Met Met Thr Ala Cys Asp Leu Ser Ala Ile Thr Lys Pro Trp Glu

[1188] 435 440 445

[1189] Val Gln Ser Lys Val Ala Leu Leu Val Ala Ala Glu Phe Trp Glu Gln

[1190] 450 455 460

[1191] Gly Asp Leu Glu Arg Thr Val Leu Asp Gln Gln Pro Ile Pro Met Met

[1192] 465 470 475 480

[1193] Asp Arg Asn Lys Ala Ala Glu Leu Pro Lys Leu Gln Val Gly Phe Ile

[1194] 485 490 495

[1195] Asp Phe Val Cys Thr Phe Val Tyr Lys Glu Phe Ser Arg Phe His Glu

[1196] 500 505 510

[1197] Glu Ile Leu Pro Met Phe Asp Arg Leu Gln Asn Asn Arg Lys Glu Trp

[1198] 515 520 525

[1199] Lys Ala Leu Ala Asp Glu Tyr Glu Ala Lys Val Lys Ala Leu Glu Glu

[1200] 530 535 540

[1201] Lys Glu Glu Glu Glu Arg Val Ala Ala Lys Lys Val Gly Thr Glu Ile

[1202] 545 550 555 560

[1203] Cys Asn Gly Gly Pro Ala Pro Lys Ser Ser Thr Cys Cys Ile Leu

[1204] 565 570 575

[1205] <210> 24

[1206] <211> 694

[1207] <212> PRT

[1208] <213> 智人

[1209] <400> 24

[1210] Met Ala Lys Ile Asn Thr Gln Tyr Ser His Pro Ser Arg Thr His Leu

[1211] 1 5 10 15

[1212] Lys Val Lys Thr Ser Asp Arg Asp Leu Asn Arg Ala Glu Asn Gly Leu

[1213] 20 25 30

[1214] Ser Arg Ala His Ser Ser Ser Glu Glu Thr Ser Ser Val Leu Gln Pro

[1215] 35 40 45

[1216] Gly Ile Ala Met Glu Thr Arg Gly Leu Ala Asp Ser Gly Gln Gly Ser

[1217] 50 55 60

[1218] Phe Thr Gly Gln Gly Ile Ala Arg Leu Ser Arg Leu Ile Phe Leu Leu

[1219] 65 70 75 80

[1220] Arg Arg Trp Ala Ala Arg His Val His His Gln Asp Gln Gly Pro Asp

[1221] 85 90 95

[1222] Ser Phe Pro Asp Arg Phe Arg Gly Ala Glu Leu Lys Glu Val Ser Ser

[1223] 100 105 110

[1224] Gln Glu Ser Asn Ala Gln Ala Asn Val Gly Ser Gln Glu Pro Ala Asp

[1225] 115 120 125

[1226] Arg Gly Arg Ser Ala Trp Pro Leu Ala Lys Cys Asn Thr Asn Thr Ser

[1227] 130 135 140

[1228] Asn Asn Thr Glu Glu Glu Lys Lys Thr Lys Lys Lys Asp Ala Ile Val

[1229] 145 150 155 160

[1230] Val Asp Pro Ser Ser Asn Leu Tyr Tyr Arg Trp Leu Thr Ala Ile Ala

[1231] 165 170 175

[1232] Leu Pro Val Phe Tyr Asn Trp Tyr Leu Leu Ile Cys Arg Ala Cys Phe

[1233] 180 185 190

[1234] Asp Glu Leu Gln Ser Glu Tyr Leu Met Leu Trp Leu Val Leu Asp Tyr

[1235] 195 200 205

[1236] Ser Ala Asp Val Leu Tyr Val Leu Asp Val Leu Val Arg Ala Arg Thr

[1237] 210 215 220

[1238] Gly Phe Leu Glu Gln Gly Leu Met Val Ser Asp Thr Asn Arg Leu Trp

[1239] 225 230 235 240

[1240] Gln His Tyr Lys Thr Thr Thr Gln Phe Lys Leu Asp Val Leu Ser Leu

[1241] 245 250 255

[1242] Val Pro Thr Asp Leu Ala Tyr Leu Lys Val Gly Thr Asn Tyr Pro Glu

[1243] 260 265 270

[1244] Val Arg Phe Asn Arg Leu Leu Lys Phe Ser Arg Leu Phe Glu Phe Phe

[1245] 275 280 285

[1246] Asp Arg Thr Glu Thr Arg Thr Asn Tyr Pro Asn Met Phe Arg Ile Gly

[1247] 290 295 300

[1248] Asn Leu Val Leu Tyr Ile Leu Ile Ile Ile His Trp Asn Ala Cys Ile
[1249] 305 310 315 320
[1250] Tyr Phe Ala Ile Ser Lys Phe Ile Gly Phe Gly Thr Asp Ser Trp Val
[1251] 325 330 335
[1252] Tyr Pro Asn Ile Ser Ile Pro Glu His Gly Arg Leu Ser Arg Lys Tyr
[1253] 340 345 350
[1254] Ile Tyr Ser Leu Tyr Trp Ser Thr Leu Thr Leu Thr Thr Ile Gly Glu
[1255] 355 360 365
[1256] Thr Pro Pro Pro Val Lys Asp Glu Glu Tyr Leu Phe Val Val Val Asp
[1257] 370 375 380
[1258] Phe Leu Val Gly Val Leu Ile Phe Ala Thr Ile Val Gly Asn Val Gly
[1259] 385 390 395 400
[1260] Ser Met Ile Ser Asn Met Asn Ala Ser Arg Ala Glu Phe Gln Ala Lys
[1261] 405 410 415
[1262] Ile Asp Ser Ile Lys Gln Tyr Met Gln Phe Arg Lys Val Thr Lys Asp
[1263] 420 425 430
[1264] Leu Glu Thr Arg Val Ile Arg Trp Phe Asp Tyr Leu Trp Ala Asn Lys
[1265] 435 440 445
[1266] Lys Thr Val Asp Glu Lys Glu Val Leu Lys Ser Leu Pro Asp Lys Leu
[1267] 450 455 460
[1268] Lys Ala Glu Ile Ala Ile Asn Val His Leu Asp Thr Leu Lys Lys Val
[1269] 465 470 475 480
[1270] Arg Ile Phe Gln Asp Cys Glu Ala Gly Leu Leu Val Glu Leu Val Leu
[1271] 485 490 495
[1272] Lys Leu Arg Pro Thr Val Phe Ser Pro Gly Asp Tyr Ile Cys Lys Lys
[1273] 500 505 510
[1274] Gly Asp Ile Gly Lys Glu Met Tyr Ile Ile Asn Glu Gly Lys Leu Ala
[1275] 515 520 525
[1276] Val Val Ala Asp Asp Gly Val Thr Gln Phe Val Val Leu Ser Asp Gly
[1277] 530 535 540
[1278] Ser Tyr Phe Gly Glu Ile Ser Ile Leu Asn Ile Lys Gly Ser Lys Ser
[1279] 545 550 555 560
[1280] Gly Asn Arg Arg Thr Ala Asn Ile Arg Ser Ile Gly Tyr Ser Asp Leu
[1281] 565 570 575
[1282] Phe Cys Leu Ser Lys Asp Asp Leu Met Glu Ala Leu Thr Glu Tyr Pro
[1283] 580 585 590
[1284] Glu Ala Lys Lys Ala Leu Glu Glu Lys Gly Arg Gln Ile Leu Met Lys
[1285] 595 600 605
[1286] Asp Asn Leu Ile Asp Glu Glu Leu Ala Arg Ala Gly Ala Asp Pro Lys

[1287] 610 615 620

[1288] Asp Leu Glu Glu Lys Val Glu Gln Leu Gly Ser Ser Leu Asp Thr Leu

[1289] 625 630 635 640

[1290] Gln Thr Arg Phe Ala Arg Leu Leu Ala Glu Tyr Asn Ala Thr Gln Met

[1291] 645 650 655

[1292] Lys Met Lys Gln Arg Leu Ser Gln Leu Glu Ser Gln Val Lys Gly Gly

[1293] 660 665 670

[1294] Gly Asp Lys Pro Leu Ala Asp Gly Glu Val Pro Gly Asp Ala Thr Lys

[1295] 675 680 685

[1296] Thr Glu Asp Lys Gln Gln

[1297] 690

[1298] <210> 25

[1299] <211> 676

[1300] <212> PRT

[1301] <213> 智人

[1302] <400> 25

[1303] Met Ala Lys Ile Asn Thr Gln Tyr Ser His Pro Ser Arg Thr His Leu

[1304] 1 5 10 15

[1305] Lys Val Lys Thr Ser Asp Arg Asp Leu Asn Arg Ala Glu Asn Gly Leu

[1306] 20 25 30

[1307] Ser Arg Ala His Ser Ser Ser Glu Glu Thr Ser Ser Val Leu Gln Pro

[1308] 35 40 45

[1309] Gly Ile Ala Met Glu Thr Arg Gly Leu Ala Asp Ser Gly Gln Gly Ser

[1310] 50 55 60

[1311] Phe Thr Gly Gln Gly Ile Ala Arg Leu Ser Arg Leu Ile Phe Leu Leu

[1312] 65 70 75 80

[1313] Arg Arg Trp Ala Ala Arg His Val His His Gln Asp Gln Gly Pro Asp

[1314] 85 90 95

[1315] Ser Phe Pro Asp Arg Phe Arg Gly Ala Glu Leu Lys Glu Val Ser Ser

[1316] 100 105 110

[1317] Gln Glu Ser Asn Ala Gln Ala Asn Val Gly Ser Gln Glu Pro Ala Asp

[1318] 115 120 125

[1319] Arg Gly Arg Arg Lys Lys Thr Lys Lys Lys Asp Ala Ile Val Val Asp

[1320] 130 135 140

[1321] Pro Ser Ser Asn Leu Tyr Tyr Arg Trp Leu Thr Ala Ile Ala Leu Pro

[1322] 145 150 155 160

[1323] Val Phe Tyr Asn Trp Tyr Leu Leu Ile Cys Arg Ala Cys Phe Asp Glu

[1324] 165 170 175

[1325] Leu Gln Ser Glu Tyr Leu Met Leu Trp Leu Val Leu Asp Tyr Ser Ala

[1326] 180 185 190
[1327] Asp Val Leu Tyr Val Leu Asp Val Leu Val Arg Ala Arg Thr Gly Phe
[1328] 195 200 205
[1329] Leu Glu Gln Gly Leu Met Val Ser Asp Thr Asn Arg Leu Trp Gln His
[1330] 210 215 220
[1331] Tyr Lys Thr Thr Thr Gln Phe Lys Leu Asp Val Leu Ser Leu Val Pro
[1332] 225 230 235 240
[1333] Thr Asp Leu Ala Tyr Leu Lys Val Gly Thr Asn Tyr Pro Glu Val Arg
[1334] 245 250 255
[1335] Phe Asn Arg Leu Leu Lys Phe Ser Arg Leu Phe Glu Phe Phe Asp Arg
[1336] 260 265 270
[1337] Thr Glu Thr Arg Thr Asn Tyr Pro Asn Met Phe Arg Ile Gly Asn Leu
[1338] 275 280 285
[1339] Val Leu Tyr Ile Leu Ile Ile Ile His Trp Asn Ala Cys Ile Tyr Phe
[1340] 290 295 300
[1341] Ala Ile Ser Lys Phe Ile Gly Phe Gly Thr Asp Ser Trp Val Tyr Pro
[1342] 305 310 315 320
[1343] Asn Ile Ser Ile Pro Glu His Gly Arg Leu Ser Arg Lys Tyr Ile Tyr
[1344] 325 330 335
[1345] Ser Leu Tyr Trp Ser Thr Leu Thr Leu Thr Thr Ile Gly Glu Thr Pro
[1346] 340 345 350
[1347] Pro Pro Val Lys Asp Glu Glu Tyr Leu Phe Val Val Val Asp Phe Leu
[1348] 355 360 365
[1349] Val Gly Val Leu Ile Phe Ala Thr Ile Val Gly Asn Val Gly Ser Met
[1350] 370 375 380
[1351] Ile Ser Asn Met Asn Ala Ser Arg Ala Glu Phe Gln Ala Lys Ile Asp
[1352] 385 390 395 400
[1353] Ser Ile Lys Gln Tyr Met Gln Phe Arg Lys Val Thr Lys Asp Leu Glu
[1354] 405 410 415
[1355] Thr Arg Val Ile Arg Trp Phe Asp Tyr Leu Trp Ala Asn Lys Lys Thr
[1356] 420 425 430
[1357] Val Asp Glu Lys Glu Val Leu Lys Ser Leu Pro Asp Lys Leu Lys Ala
[1358] 435 440 445
[1359] Glu Ile Ala Ile Asn Val His Leu Asp Thr Leu Lys Lys Val Arg Ile
[1360] 450 455 460
[1361] Phe Gln Asp Cys Glu Ala Gly Leu Leu Val Glu Leu Val Leu Lys Leu
[1362] 465 470 475 480
[1363] Arg Pro Thr Val Phe Ser Pro Gly Asp Tyr Ile Cys Lys Lys Gly Asp
[1364] 485 490 495

[1365] Ile Gly Lys Glu Met Tyr Ile Ile Asn Glu Gly Lys Leu Ala Val Val
[1366] 500 505 510
[1367] Ala Asp Asp Gly Val Thr Gln Phe Val Val Leu Ser Asp Gly Ser Tyr
[1368] 515 520 525
[1369] Phe Gly Glu Ile Ser Ile Leu Asn Ile Lys Gly Ser Lys Ser Gly Asn
[1370] 530 535 540
[1371] Arg Arg Thr Ala Asn Ile Arg Ser Ile Gly Tyr Ser Asp Leu Phe Cys
[1372] 545 550 555 560
[1373] Leu Ser Lys Asp Asp Leu Met Glu Ala Leu Thr Glu Tyr Pro Glu Ala
[1374] 565 570 575
[1375] Lys Lys Ala Leu Glu Glu Lys Gly Arg Gln Ile Leu Met Lys Asp Asn
[1376] 580 585 590
[1377] Leu Ile Asp Glu Glu Leu Ala Arg Ala Gly Ala Asp Pro Lys Asp Leu
[1378] 595 600 605
[1379] Glu Glu Lys Val Glu Gln Leu Gly Ser Ser Leu Asp Thr Leu Gln Thr
[1380] 610 615 620
[1381] Arg Phe Ala Arg Leu Leu Ala Glu Tyr Asn Ala Thr Gln Met Lys Met
[1382] 625 630 635 640
[1383] Lys Gln Arg Leu Ser Gln Leu Glu Ser Gln Val Lys Gly Gly Gly Asp
[1384] 645 650 655
[1385] Lys Pro Leu Ala Asp Gly Glu Val Pro Gly Asp Ala Thr Lys Thr Glu
[1386] 660 665 670
[1387] Asp Lys Gln Gln
[1388] 675
[1389] <210> 26
[1390] <211> 809
[1391] <212> PRT
[1392] <213> 智人
[1393] <400> 26
[1394] Met Phe Lys Ser Leu Thr Lys Val Asn Lys Val Lys Pro Ile Gly Glu
[1395] 1 5 10 15
[1396] Asn Asn Glu Asn Glu Gln Ser Ser Arg Arg Asn Glu Glu Gly Ser His
[1397] 20 25 30
[1398] Pro Ser Asn Gln Ser Gln Gln Thr Thr Ala Gln Glu Glu Asn Lys Gly
[1399] 35 40 45
[1400] Glu Glu Lys Ser Leu Lys Thr Lys Ser Thr Pro Val Thr Ser Glu Glu
[1401] 50 55 60
[1402] Pro His Thr Asn Ile Gln Asp Lys Leu Ser Lys Lys Asn Ser Ser Gly
[1403] 65 70 75 80

[1404] Asp Leu Thr Thr Asn Pro Asp Pro Gln Asn Ala Ala Glu Pro Thr Gly
[1405] 85 90 95
[1406] Thr Val Pro Glu Gln Lys Glu Met Asp Pro Gly Lys Glu Gly Pro Asn
[1407] 100 105 110
[1408] Ser Pro Gln Asn Lys Pro Pro Ala Ala Pro Val Ile Asn Glu Tyr Ala
[1409] 115 120 125
[1410] Asp Ala Gln Leu His Asn Leu Val Lys Arg Met Arg Gln Arg Thr Ala
[1411] 130 135 140
[1412] Leu Tyr Lys Lys Lys Leu Val Glu Gly Asp Leu Ser Ser Pro Glu Ala
[1413] 145 150 155 160
[1414] Ser Pro Gln Thr Ala Lys Pro Thr Ala Val Pro Pro Val Lys Glu Ser
[1415] 165 170 175
[1416] Asp Asp Lys Pro Thr Glu His Tyr Tyr Arg Leu Leu Trp Phe Lys Val
[1417] 180 185 190
[1418] Lys Lys Met Pro Leu Thr Glu Tyr Leu Lys Arg Ile Lys Leu Pro Asn
[1419] 195 200 205
[1420] Ser Ile Asp Ser Tyr Thr Asp Arg Leu Tyr Leu Leu Trp Leu Leu Leu
[1421] 210 215 220
[1422] Val Thr Leu Ala Tyr Asn Trp Asn Cys Cys Phe Ile Pro Leu Arg Leu
[1423] 225 230 235 240
[1424] Val Phe Pro Tyr Gln Thr Ala Asp Asn Ile His Tyr Trp Leu Ile Ala
[1425] 245 250 255
[1426] Asp Ile Ile Cys Asp Ile Ile Tyr Leu Tyr Asp Met Leu Phe Ile Gln
[1427] 260 265 270
[1428] Pro Arg Leu Gln Phe Val Arg Gly Gly Asp Ile Ile Val Asp Ser Asn
[1429] 275 280 285
[1430] Glu Leu Arg Lys His Tyr Arg Thr Ser Thr Lys Phe Gln Leu Asp Val
[1431] 290 295 300
[1432] Ala Ser Ile Ile Pro Phe Asp Ile Cys Tyr Leu Phe Phe Gly Phe Asn
[1433] 305 310 315 320
[1434] Pro Met Phe Arg Ala Asn Arg Met Leu Lys Tyr Thr Ser Phe Phe Glu
[1435] 325 330 335
[1436] Phe Asn His His Leu Glu Ser Ile Met Asp Lys Ala Tyr Ile Tyr Arg
[1437] 340 345 350
[1438] Val Ile Arg Thr Thr Gly Tyr Leu Leu Phe Ile Leu His Ile Asn Ala
[1439] 355 360 365
[1440] Cys Val Tyr Tyr Trp Ala Ser Asn Tyr Glu Gly Ile Gly Thr Thr Arg
[1441] 370 375 380
[1442] Trp Val Tyr Asp Gly Glu Gly Asn Glu Tyr Leu Arg Cys Tyr Tyr Trp

[1443] 385 390 395 400
[1444] Ala Val Arg Thr Leu Ile Thr Ile Gly Gly Leu Pro Glu Pro Gln Thr
[1445] 405 410 415
[1446] Leu Phe Glu Ile Val Phe Gln Leu Leu Asn Phe Phe Ser Gly Val Phe
[1447] 420 425 430
[1448] Val Phe Ser Ser Leu Ile Gly Gln Met Arg Asp Val Ile Gly Ala Ala
[1449] 435 440 445
[1450] Thr Ala Asn Gln Asn Tyr Phe Arg Ala Cys Met Asp Asp Thr Ile Ala
[1451] 450 455 460
[1452] Tyr Met Asn Asn Tyr Ser Ile Pro Lys Leu Val Gln Lys Arg Val Arg
[1453] 465 470 475 480
[1454] Thr Trp Tyr Glu Tyr Thr Trp Asp Ser Gln Arg Met Leu Asp Glu Ser
[1455] 485 490 495
[1456] Asp Leu Leu Lys Thr Leu Pro Thr Thr Val Gln Leu Ala Leu Ala Ile
[1457] 500 505 510
[1458] Asp Val Asn Phe Ser Ile Ile Ser Lys Val Asp Leu Phe Lys Gly Cys
[1459] 515 520 525
[1460] Asp Thr Gln Met Ile Tyr Asp Met Leu Leu Arg Leu Lys Ser Val Leu
[1461] 530 535 540
[1462] Tyr Leu Pro Gly Asp Phe Val Cys Lys Lys Gly Glu Ile Gly Lys Glu
[1463] 545 550 555 560
[1464] Met Tyr Ile Ile Lys His Gly Glu Val Gln Val Leu Gly Gly Pro Asp
[1465] 565 570 575
[1466] Gly Thr Lys Val Leu Val Thr Leu Lys Ala Gly Ser Val Phe Gly Glu
[1467] 580 585 590
[1468] Ile Ser Leu Leu Ala Ala Gly Gly Gly Asn Arg Arg Thr Ala Asn Val
[1469] 595 600 605
[1470] Val Ala His Gly Phe Ala Asn Leu Leu Thr Leu Asp Lys Lys Thr Leu
[1471] 610 615 620
[1472] Gln Glu Ile Leu Val His Tyr Pro Asp Ser Glu Arg Ile Leu Met Lys
[1473] 625 630 635 640
[1474] Lys Ala Arg Val Leu Leu Lys Gln Lys Ala Lys Thr Ala Glu Ala Thr
[1475] 645 650 655
[1476] Pro Pro Arg Lys Asp Leu Ala Leu Leu Phe Pro Pro Lys Glu Glu Thr
[1477] 660 665 670
[1478] Pro Lys Leu Phe Lys Thr Leu Leu Gly Gly Thr Gly Lys Ala Ser Leu
[1479] 675 680 685
[1480] Ala Arg Leu Leu Lys Leu Lys Arg Glu Gln Ala Ala Gln Lys Lys Glu
[1481] 690 695 700

[1482] Asn Ser Glu Gly Gly Glu Glu Glu Gly Lys Glu Asn Glu Asp Lys Gln
[1483] 705 710 715 720
[1484] Lys Glu Asn Glu Asp Lys Gln Lys Glu Asn Glu Asp Lys Gly Lys Glu
[1485] 725 730 735
[1486] Asn Glu Asp Lys Asp Lys Gly Arg Glu Pro Glu Glu Lys Pro Leu Asp
[1487] 740 745 750
[1488] Arg Pro Glu Cys Thr Ala Ser Pro Ile Ala Val Glu Glu Glu Pro His
[1489] 755 760 765
[1490] Ser Val Arg Arg Thr Val Leu Pro Arg Gly Thr Ser Arg Gln Ser Leu
[1491] 770 775 780
[1492] Ile Ile Ser Met Ala Pro Ser Ala Glu Gly Gly Glu Glu Val Leu Thr
[1493] 785 790 795 800
[1494] Ile Glu Val Lys Glu Lys Ala Lys Gln
[1495] 805
[1496] <210> 27
[1497] <211> 354
[1498] <212> PRT
[1499] <213> 智人
[1500] <400> 27
[1501] Met Gly Ser Gly Ala Ser Ala Glu Asp Lys Glu Leu Ala Lys Arg Ser
[1502] 1 5 10 15
[1503] Lys Glu Leu Glu Lys Lys Leu Gln Glu Asp Ala Asp Lys Glu Ala Lys
[1504] 20 25 30
[1505] Thr Val Lys Leu Leu Leu Leu Gly Ala Gly Glu Ser Gly Lys Ser Thr
[1506] 35 40 45
[1507] Ile Val Lys Gln Met Lys Ile Ile His Gln Asp Gly Tyr Ser Pro Glu
[1508] 50 55 60
[1509] Glu Cys Leu Glu Phe Lys Ala Ile Ile Tyr Gly Asn Val Leu Gln Ser
[1510] 65 70 75 80
[1511] Ile Leu Ala Ile Ile Arg Ala Met Thr Thr Leu Gly Ile Asp Tyr Ala
[1512] 85 90 95
[1513] Glu Pro Ser Cys Ala Asp Asp Gly Arg Gln Leu Asn Asn Leu Ala Asp
[1514] 100 105 110
[1515] Ser Ile Glu Glu Gly Thr Met Pro Pro Glu Leu Val Glu Val Ile Arg
[1516] 115 120 125
[1517] Arg Leu Trp Lys Asp Gly Gly Val Gln Ala Cys Phe Glu Arg Ala Ala
[1518] 130 135 140
[1519] Glu Tyr Gln Leu Asn Asp Ser Ala Ser Tyr Tyr Leu Asn Gln Leu Glu
[1520] 145 150 155 160

[1521] Arg Ile Thr Asp Pro Glu Tyr Leu Pro Ser Glu Gln Asp Val Leu Arg
[1522] 165 170 175
[1523] Ser Arg Val Lys Thr Thr Gly Ile Ile Glu Thr Lys Phe Ser Val Lys
[1524] 180 185 190
[1525] Asp Leu Asn Phe Arg Met Phe Asp Val Gly Gly Gln Arg Ser Glu Arg
[1526] 195 200 205
[1527] Lys Lys Trp Ile His Cys Phe Glu Gly Val Thr Cys Ile Ile Phe Cys
[1528] 210 215 220
[1529] Ala Ala Leu Ser Ala Tyr Asp Met Val Leu Val Glu Asp Asp Glu Val
[1530] 225 230 235 240
[1531] Asn Arg Met His Glu Ser Leu His Leu Phe Asn Ser Ile Cys Asn His
[1532] 245 250 255
[1533] Lys Phe Phe Ala Ala Thr Ser Ile Val Leu Phe Leu Asn Lys Lys Asp
[1534] 260 265 270
[1535] Leu Phe Glu Glu Lys Ile Lys Lys Val His Leu Ser Ile Cys Phe Pro
[1536] 275 280 285
[1537] Glu Tyr Asp Gly Asn Asn Ser Tyr Asp Asp Ala Gly Asn Tyr Ile Lys
[1538] 290 295 300
[1539] Ser Gln Phe Leu Asp Leu Asn Met Arg Lys Asp Val Lys Glu Ile Tyr
[1540] 305 310 315 320
[1541] Ser His Met Thr Cys Ala Thr Asp Thr Gln Asn Val Lys Phe Val Phe
[1542] 325 330 335
[1543] Asp Ala Val Thr Asp Ile Ile Ile Lys Glu Asn Leu Lys Asp Cys Gly
[1544] 340 345 350
[1545] Leu Phe
[1546] <210> 28
[1547] <211> 815
[1548] <212> PRT
[1549] <213> 智人
[1550] <400> 28
[1551] Met Arg Glu Pro Glu Glu Leu Met Pro Asp Ser Gly Ala Val Phe Thr
[1552] 1 5 10 15
[1553] Phe Gly Lys Ser Lys Phe Ala Glu Asn Asn Pro Gly Lys Phe Trp Phe
[1554] 20 25 30
[1555] Lys Asn Asp Val Pro Val His Leu Ser Cys Gly Asp Glu His Ser Ala
[1556] 35 40 45
[1557] Val Val Thr Gly Asn Asn Lys Leu Tyr Met Phe Gly Ser Asn Asn Trp
[1558] 50 55 60
[1559] Gly Gln Leu Gly Leu Gly Ser Lys Ser Ala Ile Ser Lys Pro Thr Cys

[1560] 65 70 75 80
[1561] Val Lys Ala Leu Lys Pro Glu Lys Val Lys Leu Ala Ala Cys Gly Arg
[1562] 85 90 95
[1563] Asn His Thr Leu Val Ser Thr Glu Gly Gly Asn Val Tyr Ala Thr Gly
[1564] 100 105 110
[1565] Gly Asn Asn Glu Gly Gln Leu Gly Leu Gly Asp Thr Glu Glu Arg Asn
[1566] 115 120 125
[1567] Thr Phe His Val Ile Ser Phe Phe Thr Ser Glu His Lys Ile Lys Gln
[1568] 130 135 140
[1569] Leu Ser Ala Gly Ser Asn Thr Ser Ala Ala Leu Thr Glu Asp Gly Arg
[1570] 145 150 155 160
[1571] Leu Phe Met Trp Gly Asp Asn Ser Glu Gly Gln Ile Gly Leu Lys Asn
[1572] 165 170 175
[1573] Val Ser Asn Val Cys Val Pro Gln Gln Val Thr Ile Gly Lys Pro Val
[1574] 180 185 190
[1575] Ser Trp Ile Ser Cys Gly Tyr Tyr His Ser Ala Phe Val Thr Thr Asp
[1576] 195 200 205
[1577] Gly Glu Leu Tyr Val Phe Gly Glu Pro Glu Asn Gly Lys Leu Gly Leu
[1578] 210 215 220
[1579] Pro Asn Gln Leu Leu Gly Asn His Arg Thr Pro Gln Leu Val Ser Glu
[1580] 225 230 235 240
[1581] Ile Pro Glu Lys Val Ile Gln Val Ala Cys Gly Gly Glu His Thr Val
[1582] 245 250 255
[1583] Val Leu Thr Glu Asn Ala Val Tyr Thr Phe Gly Leu Gly Gln Phe Gly
[1584] 260 265 270
[1585] Gln Leu Gly Leu Gly Thr Phe Leu Phe Glu Thr Ser Glu Pro Lys Val
[1586] 275 280 285
[1587] Ile Glu Asn Ile Arg Asp Gln Thr Ile Ser Tyr Ile Ser Cys Gly Glu
[1588] 290 295 300
[1589] Asn His Thr Ala Leu Ile Thr Asp Ile Gly Leu Met Tyr Thr Phe Gly
[1590] 305 310 315 320
[1591] Asp Gly Arg His Gly Lys Leu Gly Leu Gly Leu Glu Asn Phe Thr Asn
[1592] 325 330 335
[1593] His Phe Ile Pro Thr Leu Cys Ser Asn Phe Leu Arg Phe Ile Val Lys
[1594] 340 345 350
[1595] Leu Val Ala Cys Gly Gly Cys His Met Val Val Phe Ala Ala Pro His
[1596] 355 360 365
[1597] Arg Gly Val Ala Lys Glu Ile Glu Phe Asp Glu Ile Asn Asp Thr Cys
[1598] 370 375 380

[1599] Leu Ser Val Ala Thr Phe Leu Pro Tyr Ser Ser Leu Thr Ser Gly Asn
[1600] 385 390 395 400
[1601] Val Leu Gln Arg Thr Leu Ser Ala Arg Met Arg Arg Arg Glu Arg Glu
[1602] 405 410 415
[1603] Arg Ser Pro Asp Ser Phe Ser Met Arg Arg Thr Leu Pro Pro Ile Glu
[1604] 420 425 430
[1605] Gly Thr Leu Gly Leu Ser Ala Cys Phe Leu Pro Asn Ser Val Phe Pro
[1606] 435 440 445
[1607] Arg Cys Ser Glu Arg Asn Leu Gln Glu Ser Val Leu Ser Glu Gln Asp
[1608] 450 455 460
[1609] Leu Met Gln Pro Glu Glu Pro Asp Tyr Leu Leu Asp Glu Met Thr Lys
[1610] 465 470 475 480
[1611] Glu Ala Glu Ile Asp Asn Ser Ser Thr Val Glu Ser Leu Gly Glu Thr
[1612] 485 490 495
[1613] Thr Asp Ile Leu Asn Met Thr His Ile Met Ser Leu Asn Ser Asn Glu
[1614] 500 505 510
[1615] Lys Ser Leu Lys Leu Ser Pro Val Gln Lys Gln Lys Lys Gln Gln Thr
[1616] 515 520 525
[1617] Ile Gly Glu Leu Thr Gln Asp Thr Ala Leu Thr Glu Asn Asp Asp Ser
[1618] 530 535 540
[1619] Asp Glu Tyr Glu Glu Met Ser Glu Met Lys Glu Gly Lys Ala Cys Lys
[1620] 545 550 555 560
[1621] Gln His Val Ser Gln Gly Ile Phe Met Thr Gln Pro Ala Thr Thr Ile
[1622] 565 570 575
[1623] Glu Ala Phe Ser Asp Glu Glu Val Glu Ile Pro Glu Glu Lys Glu Gly
[1624] 580 585 590
[1625] Ala Glu Asp Ser Lys Gly Asn Gly Ile Glu Glu Gln Glu Val Glu Ala
[1626] 595 600 605
[1627] Asn Glu Glu Asn Val Lys Val His Gly Gly Arg Lys Glu Lys Thr Glu
[1628] 610 615 620
[1629] Ile Leu Ser Asp Asp Leu Thr Asp Lys Ala Glu Asp His Glu Phe Ser
[1630] 625 630 635 640
[1631] Lys Thr Glu Glu Leu Lys Leu Glu Asp Val Asp Glu Glu Ile Asn Ala
[1632] 645 650 655
[1633] Glu Asn Val Glu Ser Lys Lys Lys Thr Val Gly Asp Asp Glu Ser Val
[1634] 660 665 670
[1635] Pro Thr Gly Tyr His Ser Lys Thr Glu Gly Ala Glu Arg Thr Asn Asp
[1636] 675 680 685
[1637] Asp Ser Ser Ala Glu Thr Ile Glu Lys Lys Glu Lys Ala Asn Leu Glu

690 695 700

Glu Arg Ala Ile Cys Glu Tyr Asn Glu Asn Pro Lys Gly Tyr Met Leu
705 710 715 720
Asp Asp Ala Asp Ser Ser Ser Leu Glu Ile Leu Glu Asn Ser Glu Thr
725 730 735
Thr Pro Ser Lys Asp Met Lys Lys Thr Lys Lys Ile Phe Leu Phe Lys
740 745 750
Arg Val Pro Ser Ile Asn Gln Lys Ile Val Lys Asn Asn Asn Glu Pro
755 760 765
Leu Pro Glu Ile Lys Ser Ile Gly Asp Gln Ile Ile Leu Lys Ser Asp
770 775 780
Asn Lys Asp Ala Asp Gln Asn His Met Ser Gln Asn His Gln Asn Ile
785 790 795 800
Pro Pro Thr Asn Thr Glu Arg Arg Ser Lys Ser Cys Thr Ile Leu
805 810 815

<210> 29
<211> 646
<212> PRT
<213> 智人
<400> 29

Met Arg Glu Pro Glu Glu Leu Met Pro Asp Ser Gly Ala Val Phe Thr
1 5 10 15
Phe Gly Lys Ser Lys Phe Ala Glu Asn Asn Pro Gly Lys Phe Trp Phe
20 25 30
Lys Asn Asp Val Pro Val His Leu Ser Cys Gly Asp Glu His Ser Ala
35 40 45
Val Val Thr Gly Asn Asn Lys Leu Tyr Met Phe Gly Ser Asn Asn Trp
50 55 60
Gly Gln Leu Gly Leu Gly Ser Lys Ser Ala Ile Ser Lys Pro Thr Cys
65 70 75 80
Val Lys Ala Leu Lys Pro Glu Lys Val Lys Leu Ala Ala Cys Gly Arg
85 90 95
Asn His Thr Leu Val Ser Thr Glu Gly Gly Asn Val Tyr Ala Thr Gly
100 105 110
Gly Asn Asn Glu Gly Gln Leu Gly Leu Gly Asp Thr Glu Glu Arg Asn
115 120 125
Thr Phe His Val Ile Ser Phe Phe Thr Ser Glu His Lys Ile Lys Gln
130 135 140
Leu Ser Ala Gly Ser Asn Thr Ser Ala Ala Leu Thr Glu Asp Gly Arg

[1677] 145 150 155 160
[1678] Leu Phe Met Trp Gly Asp Asn Ser Glu Gly Gln Ile Gly Leu Lys Asn
[1679] 165 170 175
[1680] Val Ser Asn Val Cys Val Pro Gln Gln Val Thr Ile Gly Lys Pro Val
[1681] 180 185 190
[1682] Ser Trp Ile Ser Cys Gly Tyr Tyr His Ser Ala Phe Val Thr Thr Asp
[1683] 195 200 205
[1684] Gly Glu Leu Tyr Val Phe Gly Glu Pro Glu Asn Gly Lys Leu Gly Leu
[1685] 210 215 220
[1686] Pro Asn Gln Leu Leu Gly Asn His Arg Thr Pro Gln Leu Val Ser Glu
[1687] 225 230 235 240
[1688] Ile Pro Glu Lys Val Ile Gln Val Ala Cys Gly Gly Glu His Thr Val
[1689] 245 250 255
[1690] Val Leu Thr Glu Asn Ala Val Tyr Thr Phe Gly Leu Gly Gln Phe Gly
[1691] 260 265 270
[1692] Gln Leu Gly Leu Gly Thr Phe Leu Phe Glu Thr Ser Glu Pro Lys Val
[1693] 275 280 285
[1694] Ile Glu Asn Ile Arg Asp Gln Thr Ile Ser Tyr Ile Ser Cys Gly Glu
[1695] 290 295 300
[1696] Asn His Thr Ala Leu Ile Thr Asp Ile Gly Leu Met Tyr Thr Phe Gly
[1697] 305 310 315 320
[1698] Asp Gly Arg His Gly Lys Leu Gly Leu Gly Leu Glu Asn Phe Thr Asn
[1699] 325 330 335
[1700] His Phe Ile Pro Thr Leu Cys Ser Asn Phe Leu Arg Phe Ile Val Lys
[1701] 340 345 350
[1702] Leu Val Ala Cys Gly Gly Cys His Met Val Val Phe Ala Ala Pro His
[1703] 355 360 365
[1704] Arg Gly Val Ala Lys Glu Ile Glu Phe Asp Glu Ile Asn Asp Thr Cys
[1705] 370 375 380
[1706] Leu Ser Val Ala Thr Phe Leu Pro Tyr Ser Ser Leu Thr Ser Gly Asn
[1707] 385 390 395 400
[1708] Val Leu Gln Arg Thr Leu Ser Ala Arg Met Arg Arg Arg Glu Arg Glu
[1709] 405 410 415
[1710] Arg Ser Pro Asp Ser Phe Ser Met Arg Arg Thr Leu Pro Pro Ile Glu
[1711] 420 425 430
[1712] Gly Thr Leu Gly Leu Ser Ala Cys Phe Leu Pro Asn Ser Val Phe Pro
[1713] 435 440 445
[1714] Arg Cys Ser Glu Arg Asn Leu Gln Glu Ser Val Leu Ser Glu Gln Asp
[1715] 450 455 460

[1716] Leu Met Gln Pro Glu Glu Pro Asp Tyr Leu Leu Asp Glu Met Thr Lys
[1717] 465 470 475 480
[1718] Glu Ala Glu Ile Asp Asn Ser Ser Thr Val Glu Ser Leu Gly Glu Thr
[1719] 485 490 495
[1720] Thr Asp Ile Leu Asn Met Thr His Ile Met Ser Leu Asn Ser Asn Glu
[1721] 500 505 510
[1722] Lys Ser Leu Lys Leu Ser Pro Val Gln Lys Gln Lys Lys Gln Gln Thr
[1723] 515 520 525
[1724] Ile Gly Glu Leu Thr Gln Asp Thr Ala Leu Thr Glu Asn Asp Asp Ser
[1725] 530 535 540
[1726] Asp Glu Tyr Glu Glu Met Ser Glu Met Lys Glu Gly Lys Ala Cys Lys
[1727] 545 550 555 560
[1728] Gln His Val Ser Gln Gly Ile Phe Met Thr Gln Pro Ala Thr Thr Ile
[1729] 565 570 575
[1730] Glu Ala Phe Ser Asp Glu Glu Val Glu Ile Pro Glu Glu Lys Glu Gly
[1731] 580 585 590
[1732] Ala Glu Asp Ser Lys Gly Asn Gly Ile Glu Glu Gln Glu Val Glu Ala
[1733] 595 600 605
[1734] Asn Glu Glu Asn Val Lys Val His Gly Gly Arg Lys Glu Lys Thr Glu
[1735] 610 615 620
[1736] Ile Leu Ser Asp Asp Leu Thr Asp Lys Ala Glu Tyr Ser Ala Ser His
[1737] 625 630 635 640
[1738] Ser Gln Ile Val Ser Val
[1739] 645
[1740] <210> 30
[1741] <211> 1152
[1742] <212> PRT
[1743] <213> 智人
[1744] <400> 30
[1745] Met Arg Glu Pro Glu Glu Leu Met Pro Asp Ser Gly Ala Val Phe Thr
[1746] 1 5 10 15
[1747] Phe Gly Lys Ser Lys Phe Ala Glu Asn Asn Pro Gly Lys Phe Trp Phe
[1748] 20 25 30
[1749] Lys Asn Asp Val Pro Val His Leu Ser Cys Gly Asp Glu His Ser Ala
[1750] 35 40 45
[1751] Val Val Thr Gly Asn Asn Lys Leu Tyr Met Phe Gly Ser Asn Asn Trp
[1752] 50 55 60
[1753] Gly Gln Leu Gly Leu Gly Ser Lys Ser Ala Ile Ser Lys Pro Thr Cys
[1754] 65 70 75 80

[1755] Val Lys Ala Leu Lys Pro Glu Lys Val Lys Leu Ala Ala Cys Gly Arg
[1756] 85 90 95
[1757] Asn His Thr Leu Val Ser Thr Glu Gly Gly Asn Val Tyr Ala Thr Gly
[1758] 100 105 110
[1759] Gly Asn Asn Glu Gly Gln Leu Gly Leu Gly Asp Thr Glu Glu Arg Asn
[1760] 115 120 125
[1761] Thr Phe His Val Ile Ser Phe Phe Thr Ser Glu His Lys Ile Lys Gln
[1762] 130 135 140
[1763] Leu Ser Ala Gly Ser Asn Thr Ser Ala Ala Leu Thr Glu Asp Gly Arg
[1764] 145 150 155 160
[1765] Leu Phe Met Trp Gly Asp Asn Ser Glu Gly Gln Ile Gly Leu Lys Asn
[1766] 165 170 175
[1767] Val Ser Asn Val Cys Val Pro Gln Gln Val Thr Ile Gly Lys Pro Val
[1768] 180 185 190
[1769] Ser Trp Ile Ser Cys Gly Tyr Tyr His Ser Ala Phe Val Thr Thr Asp
[1770] 195 200 205
[1771] Gly Glu Leu Tyr Val Phe Gly Glu Pro Glu Asn Gly Lys Leu Gly Leu
[1772] 210 215 220
[1773] Pro Asn Gln Leu Leu Gly Asn His Arg Thr Pro Gln Leu Val Ser Glu
[1774] 225 230 235 240
[1775] Ile Pro Glu Lys Val Ile Gln Val Ala Cys Gly Gly Glu His Thr Val
[1776] 245 250 255
[1777] Val Leu Thr Glu Asn Ala Val Tyr Thr Phe Gly Leu Gly Gln Phe Gly
[1778] 260 265 270
[1779] Gln Leu Gly Leu Gly Thr Phe Leu Phe Glu Thr Ser Glu Pro Lys Val
[1780] 275 280 285
[1781] Ile Glu Asn Ile Arg Asp Gln Thr Ile Ser Tyr Ile Ser Cys Gly Glu
[1782] 290 295 300
[1783] Asn His Thr Ala Leu Ile Thr Asp Ile Gly Leu Met Tyr Thr Phe Gly
[1784] 305 310 315 320
[1785] Asp Gly Arg His Gly Lys Leu Gly Leu Gly Leu Glu Asn Phe Thr Asn
[1786] 325 330 335
[1787] His Phe Ile Pro Thr Leu Cys Ser Asn Phe Leu Arg Phe Ile Val Lys
[1788] 340 345 350
[1789] Leu Val Ala Cys Gly Gly Cys His Met Val Val Phe Ala Ala Pro His
[1790] 355 360 365
[1791] Arg Gly Val Ala Lys Glu Ile Glu Phe Asp Glu Ile Asn Asp Thr Cys
[1792] 370 375 380
[1793] Leu Ser Val Ala Thr Phe Leu Pro Tyr Ser Ser Leu Thr Ser Gly Asn

[1794] 385 390 395 400
[1795] Val Leu Gln Arg Thr Leu Ser Ala Arg Met Arg Arg Arg Glu Arg Glu
[1796] 405 410 415
[1797] Arg Ser Pro Asp Ser Phe Ser Met Arg Arg Thr Leu Pro Pro Ile Glu
[1798] 420 425 430
[1799] Gly Thr Leu Gly Leu Ser Ala Cys Phe Leu Pro Asn Ser Val Phe Pro
[1800] 435 440 445
[1801] Arg Cys Ser Glu Arg Asn Leu Gln Glu Ser Val Leu Ser Glu Gln Asp
[1802] 450 455 460
[1803] Leu Met Gln Pro Glu Glu Pro Asp Tyr Leu Leu Asp Glu Met Thr Lys
[1804] 465 470 475 480
[1805] Glu Ala Glu Ile Asp Asn Ser Ser Thr Val Glu Ser Leu Gly Glu Thr
[1806] 485 490 495
[1807] Thr Asp Ile Leu Asn Met Thr His Ile Met Ser Leu Asn Ser Asn Glu
[1808] 500 505 510
[1809] Lys Ser Leu Lys Leu Ser Pro Val Gln Lys Gln Lys Lys Gln Gln Thr
[1810] 515 520 525
[1811] Ile Gly Glu Leu Thr Gln Asp Thr Ala Leu Thr Glu Asn Asp Asp Ser
[1812] 530 535 540
[1813] Asp Glu Tyr Glu Glu Met Ser Glu Met Lys Glu Gly Lys Ala Cys Lys
[1814] 545 550 555 560
[1815] Gln His Val Ser Gln Gly Ile Phe Met Thr Gln Pro Ala Thr Thr Ile
[1816] 565 570 575
[1817] Glu Ala Phe Ser Asp Glu Glu Val Glu Ile Pro Glu Glu Lys Glu Gly
[1818] 580 585 590
[1819] Ala Glu Asp Ser Lys Gly Asn Gly Ile Glu Glu Gln Glu Val Glu Ala
[1820] 595 600 605
[1821] Asn Glu Glu Asn Val Lys Val His Gly Gly Arg Lys Glu Lys Thr Glu
[1822] 610 615 620
[1823] Ile Leu Ser Asp Asp Leu Thr Asp Lys Ala Glu Val Ser Glu Gly Lys
[1824] 625 630 635 640
[1825] Ala Lys Ser Val Gly Glu Ala Glu Asp Gly Pro Glu Gly Arg Gly Asp
[1826] 645 650 655
[1827] Gly Thr Cys Glu Glu Gly Ser Ser Gly Ala Glu His Trp Gln Asp Glu
[1828] 660 665 670
[1829] Glu Arg Glu Lys Gly Glu Lys Asp Lys Gly Arg Gly Glu Met Glu Arg
[1830] 675 680 685
[1831] Pro Gly Glu Gly Glu Lys Glu Leu Ala Glu Lys Glu Glu Trp Lys Lys
[1832] 690 695 700

[1833] Arg Asp Gly Glu Glu Gln Glu Gln Lys Glu Arg Glu Gln Gly His Gln
[1834] 705 710 715 720
[1835] Lys Glu Arg Asn Gln Glu Met Glu Glu Gly Gly Glu Glu Glu His Gly
[1836] 725 730 735
[1837] Glu Gly Glu Glu Glu Glu Gly Asp Arg Glu Glu Glu Glu Glu Lys Glu
[1838] 740 745 750
[1839] Gly Glu Gly Lys Glu Glu Gly Glu Gly Glu Glu Val Glu Gly Glu Arg
[1840] 755 760 765
[1841] Glu Lys Glu Glu Gly Glu Arg Lys Lys Glu Glu Arg Ala Gly Lys Glu
[1842] 770 775 780
[1843] Glu Lys Gly Glu Glu Glu Gly Asp Gln Gly Glu Gly Glu Glu Glu Glu
[1844] 785 790 795 800
[1845] Thr Glu Gly Arg Gly Glu Glu Lys Glu Glu Gly Gly Glu Val Glu Gly
[1846] 805 810 815
[1847] Gly Glu Val Glu Glu Gly Lys Gly Glu Arg Glu Glu Glu Glu Glu Glu
[1848] 820 825 830
[1849] Gly Glu Gly Glu Glu Glu Glu Gly Glu Gly Glu Glu Glu Glu Gly Glu
[1850] 835 840 845
[1851] Gly Glu Glu Glu Glu Gly Glu Gly Lys Gly Glu Glu Glu Gly Glu Glu
[1852] 850 855 860
[1853] Gly Glu Gly Glu Glu Glu Gly Glu Glu Gly Glu Gly Glu Gly Glu Glu
[1854] 865 870 875 880
[1855] Glu Glu Gly Glu Gly Glu Gly Glu Glu Glu Gly Glu Gly Glu Gly Glu
[1856] 885 890 895
[1857] Glu Glu Glu Gly Glu Gly Glu Gly Glu Glu Glu Gly Glu Gly Glu Gly
[1858] 900 905 910
[1859] Glu Glu Glu Glu Gly Glu Gly Lys Gly Glu Glu Glu Gly Glu Glu Gly
[1860] 915 920 925
[1861] Glu Gly Glu Gly Glu Glu Glu Glu Gly Glu Gly Glu Gly Glu Asp Gly
[1862] 930 935 940
[1863] Glu Gly Glu Gly Glu Glu Glu Glu Gly Glu Trp Glu Gly Glu Glu Glu
[1864] 945 950 955 960
[1865] Glu Gly Glu Gly Glu Gly Glu Glu Glu Gly Glu Gly Glu Gly Glu Glu
[1866] 965 970 975
[1867] Gly Glu Gly Glu Gly Glu Glu Glu Glu Gly Glu Gly Glu Gly Glu Glu
[1868] 980 985 990
[1869] Glu Glu Gly Glu Glu Glu Gly Glu Glu Glu Gly Glu Gly Glu Glu Glu
[1870] 995 1000 1005
[1871] Gly Glu Gly Glu Gly Glu Glu Glu Glu Glu Gly Glu Val Glu Gly

[1872] 1010 1015 1020
[1873] Glu Val Glu Gly Glu Glu Gly Glu Gly Glu Gly Glu Glu Glu Glu
[1874] 1025 1030 1035
[1875] Gly Glu Glu Glu Gly Glu Glu Arg Glu Lys Glu Gly Glu Gly Glu
[1876] 1040 1045 1050
[1877] Glu Asn Arg Arg Asn Arg Glu Glu Glu Glu Glu Glu Glu Gly Lys
[1878] 1055 1060 1065
[1879] Tyr Gln Glu Thr Gly Glu Glu Glu Asn Glu Arg Gln Asp Gly Glu
[1880] 1070 1075 1080
[1881] Glu Tyr Lys Lys Val Ser Lys Ile Lys Gly Ser Val Lys Tyr Gly
[1882] 1085 1090 1095
[1883] Lys His Lys Thr Tyr Gln Lys Lys Ser Val Thr Asn Thr Gln Gly
[1884] 1100 1105 1110
[1885] Asn Gly Lys Glu Gln Arg Ser Lys Met Pro Val Gln Ser Lys Arg
[1886] 1115 1120 1125
[1887] Leu Leu Lys Asn Gly Pro Ser Gly Ser Lys Lys Phe Trp Asn Asn
[1888] 1130 1135 1140
[1889] Val Leu Pro His Tyr Leu Glu Leu Lys
[1890] 1145 1150
[1891] <210> 31
[1892] <211> 1020
[1893] <212> PRT
[1894] <213> 智人
[1895] <400> 31
[1896] Met Arg Glu Pro Glu Glu Leu Met Pro Asp Ser Gly Ala Val Phe Thr
[1897] 1 5 10 15
[1898] Phe Gly Lys Ser Lys Phe Ala Glu Asn Asn Pro Gly Lys Phe Trp Phe
[1899] 20 25 30
[1900] Lys Asn Asp Val Pro Val His Leu Ser Cys Gly Asp Glu His Ser Ala
[1901] 35 40 45
[1902] Val Val Thr Gly Asn Asn Lys Leu Tyr Met Phe Gly Ser Asn Asn Trp
[1903] 50 55 60
[1904] Gly Gln Leu Gly Leu Gly Ser Lys Ser Ala Ile Ser Lys Pro Thr Cys
[1905] 65 70 75 80
[1906] Val Lys Ala Leu Lys Pro Glu Lys Val Lys Leu Ala Ala Cys Gly Arg
[1907] 85 90 95
[1908] Asn His Thr Leu Val Ser Thr Glu Gly Gly Asn Val Tyr Ala Thr Gly
[1909] 100 105 110
[1910] Gly Asn Asn Glu Gly Gln Leu Gly Leu Gly Asp Thr Glu Glu Arg Asn

[1911] 115 120 125
[1912] Thr Phe His Val Ile Ser Phe Phe Thr Ser Glu His Lys Ile Lys Gln
[1913] 130 135 140
[1914] Leu Ser Ala Gly Ser Asn Thr Ser Ala Ala Leu Thr Glu Asp Gly Arg
[1915] 145 150 155 160
[1916] Leu Phe Met Trp Gly Asp Asn Ser Glu Gly Gln Ile Gly Leu Lys Asn
[1917] 165 170 175
[1918] Val Ser Asn Val Cys Val Pro Gln Gln Val Thr Ile Gly Lys Pro Val
[1919] 180 185 190
[1920] Ser Trp Ile Ser Cys Gly Tyr Tyr His Ser Ala Phe Val Thr Thr Asp
[1921] 195 200 205
[1922] Gly Glu Leu Tyr Val Phe Gly Glu Pro Glu Asn Gly Lys Leu Gly Leu
[1923] 210 215 220
[1924] Pro Asn Gln Leu Leu Gly Asn His Arg Thr Pro Gln Leu Val Ser Glu
[1925] 225 230 235 240
[1926] Ile Pro Glu Lys Val Ile Gln Val Ala Cys Gly Gly Glu His Thr Val
[1927] 245 250 255
[1928] Val Leu Thr Glu Asn Ala Val Tyr Thr Phe Gly Leu Gly Gln Phe Gly
[1929] 260 265 270
[1930] Gln Leu Gly Leu Gly Thr Phe Leu Phe Glu Thr Ser Glu Pro Lys Val
[1931] 275 280 285
[1932] Ile Glu Asn Ile Arg Asp Gln Thr Ile Ser Tyr Ile Ser Cys Gly Glu
[1933] 290 295 300
[1934] Asn His Thr Ala Leu Ile Thr Asp Ile Gly Leu Met Tyr Thr Phe Gly
[1935] 305 310 315 320
[1936] Asp Gly Arg His Gly Lys Leu Gly Leu Gly Leu Glu Asn Phe Thr Asn
[1937] 325 330 335
[1938] His Phe Ile Pro Thr Leu Cys Ser Asn Phe Leu Arg Phe Ile Val Lys
[1939] 340 345 350
[1940] Leu Val Ala Cys Gly Gly Cys His Met Val Val Phe Ala Ala Pro His
[1941] 355 360 365
[1942] Arg Gly Val Ala Lys Glu Ile Glu Phe Asp Glu Ile Asn Asp Thr Cys
[1943] 370 375 380
[1944] Leu Ser Val Ala Thr Phe Leu Pro Tyr Ser Ser Leu Thr Ser Gly Asn
[1945] 385 390 395 400
[1946] Val Leu Gln Arg Thr Leu Ser Ala Arg Met Arg Arg Arg Glu Arg Glu
[1947] 405 410 415
[1948] Arg Ser Pro Asp Ser Phe Ser Met Arg Arg Thr Leu Pro Pro Ile Glu
[1949] 420 425 430

[1950] Gly Thr Leu Gly Leu Ser Ala Cys Phe Leu Pro Asn Ser Val Phe Pro
[1951] 435 440 445
[1952] Arg Cys Ser Glu Arg Asn Leu Gln Glu Ser Val Leu Ser Glu Gln Asp
[1953] 450 455 460
[1954] Leu Met Gln Pro Glu Glu Pro Asp Tyr Leu Leu Asp Glu Met Thr Lys
[1955] 465 470 475 480
[1956] Glu Ala Glu Ile Asp Asn Ser Ser Thr Val Glu Ser Leu Gly Glu Thr
[1957] 485 490 495
[1958] Thr Asp Ile Leu Asn Met Thr His Ile Met Ser Leu Asn Ser Asn Glu
[1959] 500 505 510
[1960] Lys Ser Leu Lys Leu Ser Pro Val Gln Lys Gln Lys Lys Gln Gln Thr
[1961] 515 520 525
[1962] Ile Gly Glu Leu Thr Gln Asp Thr Ala Leu Thr Glu Asn Asp Asp Ser
[1963] 530 535 540
[1964] Asp Glu Tyr Glu Glu Met Ser Glu Met Lys Glu Gly Lys Ala Cys Lys
[1965] 545 550 555 560
[1966] Gln His Val Ser Gln Gly Ile Phe Met Thr Gln Pro Ala Thr Thr Ile
[1967] 565 570 575
[1968] Glu Ala Phe Ser Asp Glu Glu Val Gly Asn Asp Thr Gly Gln Val Gly
[1969] 580 585 590
[1970] Pro Gln Ala Asp Thr Asp Gly Glu Gly Leu Gln Lys Glu Val Tyr Arg
[1971] 595 600 605
[1972] His Glu Asn Asn Asn Gly Val Asp Gln Leu Asp Ala Lys Glu Ile Glu
[1973] 610 615 620
[1974] Lys Glu Ser Asp Gly Gly His Ser Gln Lys Glu Ser Glu Ala Glu Glu
[1975] 625 630 635 640
[1976] Ile Asp Ser Glu Lys Glu Thr Lys Leu Ala Glu Ile Ala Gly Met Lys
[1977] 645 650 655
[1978] Asp Leu Arg Glu Arg Glu Lys Ser Thr Lys Lys Met Ser Pro Phe Phe
[1979] 660 665 670
[1980] Gly Asn Leu Pro Asp Arg Gly Met Asn Thr Glu Ser Glu Glu Asn Lys
[1981] 675 680 685
[1982] Asp Phe Val Lys Lys Arg Glu Ser Cys Lys Gln Asp Val Ile Phe Asp
[1983] 690 695 700
[1984] Ser Glu Arg Glu Ser Val Glu Lys Pro Asp Ser Tyr Met Glu Gly Ala
[1985] 705 710 715 720
[1986] Ser Glu Ser Gln Gln Gly Ile Ala Asp Gly Phe Gln Gln Pro Glu Ala
[1987] 725 730 735
[1988] Ile Glu Phe Ser Ser Gly Glu Lys Glu Asp Asp Glu Val Glu Thr Asp

[1989] 740 745 750

[1990] Gln Asn Ile Arg Tyr Gly Arg Lys Leu Ile Glu Gln Gly Asn Glu Lys

[1991] 755 760 765

[1992] Glu Thr Lys Pro Ile Ile Ser Lys Ser Met Ala Lys Tyr Asp Phe Lys

[1993] 770 775 780

[1994] Cys Asp Arg Leu Ser Glu Ile Pro Glu Glu Lys Glu Gly Ala Glu Asp

[1995] 785 790 795 800

[1996] Ser Lys Gly Asn Gly Ile Glu Glu Gln Glu Val Glu Ala Asn Glu Glu

[1997] 805 810 815

[1998] Asn Val Lys Val His Gly Gly Arg Lys Glu Lys Thr Glu Ile Leu Ser

[1999] 820 825 830

[2000] Asp Asp Leu Thr Asp Lys Ala Glu Asp His Glu Phe Ser Lys Thr Glu

[2001] 835 840 845

[2002] Glu Leu Lys Leu Glu Asp Val Asp Glu Glu Ile Asn Ala Glu Asn Val

[2003] 850 855 860

[2004] Glu Ser Lys Lys Lys Thr Val Gly Asp Asp Glu Ser Val Pro Thr Gly

[2005] 865 870 875 880

[2006] Tyr His Ser Lys Thr Glu Gly Ala Glu Arg Thr Asn Asp Asp Ser Ser

[2007] 885 890 895

[2008] Ala Glu Thr Ile Glu Lys Lys Glu Lys Ala Asn Leu Glu Glu Arg Ala

[2009] 900 905 910

[2010] Ile Cys Glu Tyr Asn Glu Asn Pro Lys Gly Tyr Met Leu Asp Asp Ala

[2011] 915 920 925

[2012] Asp Ser Ser Ser Leu Glu Ile Leu Glu Asn Ser Glu Thr Thr Pro Ser

[2013] 930 935 940

[2014] Lys Asp Met Lys Lys Thr Lys Lys Ile Phe Leu Phe Lys Arg Val Pro

[2015] 945 950 955 960

[2016] Ser Ile Asn Gln Lys Ile Val Lys Asn Asn Asn Glu Pro Leu Pro Glu

[2017] 965 970 975

[2018] Ile Lys Ser Ile Gly Asp Gln Ile Ile Leu Lys Ser Asp Asn Lys Asp

[2019] 980 985 990

[2020] Ala Asp Gln Asn His Met Ser Gln Asn His Gln Asn Ile Pro Pro Thr

[2021] 995 1000 1005

[2022] Asn Thr Glu Arg Arg Ser Lys Ser Cys Thr Ile Leu

[2023] 1010 1015 1020

[2024] <210> 32

[2025] <211> 1368

[2026] <212> PRT

[2027] <213> 酿脓链球菌

[2028] <400> 32

[2029] Met Asp Lys Lys Tyr Ser Ile Gly Leu Asp Ile Gly Thr Asn Ser Val
[2030] 1 5 10 15
[2031] Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
[2032] 20 25 30
[2033] Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
[2034] 35 40 45
[2035] Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
[2036] 50 55 60
[2037] Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
[2038] 65 70 75 80
[2039] Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
[2040] 85 90 95
[2041] Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
[2042] 100 105 110
[2043] His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
[2044] 115 120 125
[2045] His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
[2046] 130 135 140
[2047] Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
[2048] 145 150 155 160
[2049] Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
[2050] 165 170 175
[2051] Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
[2052] 180 185 190
[2053] Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
[2054] 195 200 205
[2055] Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
[2056] 210 215 220
[2057] Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
[2058] 225 230 235 240
[2059] Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
[2060] 245 250 255
[2061] Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
[2062] 260 265 270
[2063] Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
[2064] 275 280 285
[2065] Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
[2066] 290 295 300

[2067] Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
[2068] 305 310 315 320
[2069] Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
[2070] 325 330 335
[2071] Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
[2072] 340 345 350
[2073] Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
[2074] 355 360 365
[2075] Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
[2076] 370 375 380
[2077] Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
[2078] 385 390 395 400
[2079] Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
[2080] 405 410 415
[2081] Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
[2082] 420 425 430
[2083] Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
[2084] 435 440 445
[2085] Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
[2086] 450 455 460
[2087] Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
[2088] 465 470 475 480
[2089] Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
[2090] 485 490 495
[2091] Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
[2092] 500 505 510
[2093] Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
[2094] 515 520 525
[2095] Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
[2096] 530 535 540
[2097] Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
[2098] 545 550 555 560
[2099] Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
[2100] 565 570 575
[2101] Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
[2102] 580 585 590
[2103] Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
[2104] 595 600 605
[2105] Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr

[2106] 610 615 620
[2107] Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
[2108] 625 630 635 640
[2109] His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
[2110] 645 650 655
[2111] Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
[2112] 660 665 670
[2113] Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
[2114] 675 680 685
[2115] Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
[2116] 690 695 700
[2117] Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
[2118] 705 710 715 720
[2119] His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
[2120] 725 730 735
[2121] Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
[2122] 740 745 750
[2123] Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
[2124] 755 760 765
[2125] Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
[2126] 770 775 780
[2127] Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
[2128] 785 790 795 800
[2129] Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
[2130] 805 810 815
[2131] Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
[2132] 820 825 830
[2133] Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
[2134] 835 840 845
[2135] Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
[2136] 850 855 860
[2137] Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
[2138] 865 870 875 880
[2139] Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
[2140] 885 890 895
[2141] Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
[2142] 900 905 910
[2143] Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
[2144] 915 920 925

[2145] Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
[2146] 930 935 940
[2147] Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
[2148] 945 950 955 960
[2149] Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
[2150] 965 970 975
[2151] Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
[2152] 980 985 990
[2153] Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe
[2154] 995 1000 1005
[2155] Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala
[2156] 1010 1015 1020
[2157] Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe
[2158] 1025 1030 1035
[2159] Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala
[2160] 1040 1045 1050
[2161] Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu
[2162] 1055 1060 1065
[2163] Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val
[2164] 1070 1075 1080
[2165] Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val Lys Lys Thr
[2166] 1085 1090 1095
[2167] Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys
[2168] 1100 1105 1110
[2169] Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp Asp Pro
[2170] 1115 1120 1125
[2171] Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val
[2172] 1130 1135 1140
[2173] Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys
[2174] 1145 1150 1155
[2175] Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser
[2176] 1160 1165 1170
[2177] Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys
[2178] 1175 1180 1185
[2179] Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu
[2180] 1190 1195 1200
[2181] Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly
[2182] 1205 1210 1215
[2183] Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val

[2184] 1220 1225 1230
[2185] Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser
[2186] 1235 1240 1245
[2187] Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys
[2188] 1250 1255 1260
[2189] His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys
[2190] 1265 1270 1275
[2191] Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala
[2192] 1280 1285 1290
[2193] Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn
[2194] 1295 1300 1305
[2195] Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala
[2196] 1310 1315 1320
[2197] Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser
[2198] 1325 1330 1335
[2199] Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr
[2200] 1340 1345 1350
[2201] Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp
[2202] 1355 1360 1365
[2203] <210> 33
[2204] <211> 1053
[2205] <212> PRT
[2206] <213> 金黄色葡萄球菌
[2207] <400> 33
[2208] Met Lys Arg Asn Tyr Ile Leu Gly Leu Asp Ile Gly Ile Thr Ser Val
[2209] 1 5 10 15
[2210] Gly Tyr Gly Ile Ile Asp Tyr Glu Thr Arg Asp Val Ile Asp Ala Gly
[2211] 20 25 30
[2212] Val Arg Leu Phe Lys Glu Ala Asn Val Glu Asn Asn Glu Gly Arg Arg
[2213] 35 40 45
[2214] Ser Lys Arg Gly Ala Arg Arg Leu Lys Arg Arg Arg Arg His Arg Ile
[2215] 50 55 60
[2216] Gln Arg Val Lys Lys Leu Leu Phe Asp Tyr Asn Leu Leu Thr Asp His
[2217] 65 70 75 80
[2218] Ser Glu Leu Ser Gly Ile Asn Pro Tyr Glu Ala Arg Val Lys Gly Leu
[2219] 85 90 95
[2220] Ser Gln Lys Leu Ser Glu Glu Glu Phe Ser Ala Ala Leu Leu His Leu
[2221] 100 105 110
[2222] Ala Lys Arg Arg Gly Val His Asn Val Asn Glu Val Glu Glu Asp Thr

[2223] 115 120 125

[2224] Gly Asn Glu Leu Ser Thr Lys Glu Gln Ile Ser Arg Asn Ser Lys Ala

[2225] 130 135 140

[2226] Leu Glu Glu Lys Tyr Val Ala Glu Leu Gln Leu Glu Arg Leu Lys Lys

[2227] 145 150 155 160

[2228] Asp Gly Glu Val Arg Gly Ser Ile Asn Arg Phe Lys Thr Ser Asp Tyr

[2229] 165 170 175

[2230] Val Lys Glu Ala Lys Gln Leu Leu Lys Val Gln Lys Ala Tyr His Gln

[2231] 180 185 190

[2232] Leu Asp Gln Ser Phe Ile Asp Thr Tyr Ile Asp Leu Leu Glu Thr Arg

[2233] 195 200 205

[2234] Arg Thr Tyr Tyr Glu Gly Pro Gly Glu Gly Ser Pro Phe Gly Trp Lys

[2235] 210 215 220

[2236] Asp Ile Lys Glu Trp Tyr Glu Met Leu Met Gly His Cys Thr Tyr Phe

[2237] 225 230 235 240

[2238] Pro Glu Glu Leu Arg Ser Val Lys Tyr Ala Tyr Asn Ala Asp Leu Tyr

[2239] 245 250 255

[2240] Asn Ala Leu Asn Asp Leu Asn Asn Leu Val Ile Thr Arg Asp Glu Asn

[2241] 260 265 270

[2242] Glu Lys Leu Glu Tyr Tyr Glu Lys Phe Gln Ile Ile Glu Asn Val Phe

[2243] 275 280 285

[2244] Lys Gln Lys Lys Lys Pro Thr Leu Lys Gln Ile Ala Lys Glu Ile Leu

[2245] 290 295 300

[2246] Val Asn Glu Glu Asp Ile Lys Gly Tyr Arg Val Thr Ser Thr Gly Lys

[2247] 305 310 315 320

[2248] Pro Glu Phe Thr Asn Leu Lys Val Tyr His Asp Ile Lys Asp Ile Thr

[2249] 325 330 335

[2250] Ala Arg Lys Glu Ile Ile Glu Asn Ala Glu Leu Leu Asp Gln Ile Ala

[2251] 340 345 350

[2252] Lys Ile Leu Thr Ile Tyr Gln Ser Ser Glu Asp Ile Gln Glu Glu Leu

[2253] 355 360 365

[2254] Thr Asn Leu Asn Ser Glu Leu Thr Gln Glu Glu Ile Glu Gln Ile Ser

[2255] 370 375 380

[2256] Asn Leu Lys Gly Tyr Thr Gly Thr His Asn Leu Ser Leu Lys Ala Ile

[2257] 385 390 395 400

[2258] Asn Leu Ile Leu Asp Glu Leu Trp His Thr Asn Asp Asn Gln Ile Ala

[2259] 405 410 415

[2260] Ile Phe Asn Arg Leu Lys Leu Val Pro Lys Lys Val Asp Leu Ser Gln

[2261] 420 425 430

[2262] Gln Lys Glu Ile Pro Thr Thr Leu Val Asp Asp Phe Ile Leu Ser Pro
[2263] 435 440 445
[2264] Val Val Lys Arg Ser Phe Ile Gln Ser Ile Lys Val Ile Asn Ala Ile
[2265] 450 455 460
[2266] Ile Lys Lys Tyr Gly Leu Pro Asn Asp Ile Ile Ile Glu Leu Ala Arg
[2267] 465 470 475 480
[2268] Glu Lys Asn Ser Lys Asp Ala Gln Lys Met Ile Asn Glu Met Gln Lys
[2269] 485 490 495
[2270] Arg Asn Arg Gln Thr Asn Glu Arg Ile Glu Glu Ile Ile Arg Thr Thr
[2271] 500 505 510
[2272] Gly Lys Glu Asn Ala Lys Tyr Leu Ile Glu Lys Ile Lys Leu His Asp
[2273] 515 520 525
[2274] Met Gln Glu Gly Lys Cys Leu Tyr Ser Leu Glu Ala Ile Pro Leu Glu
[2275] 530 535 540
[2276] Asp Leu Leu Asn Asn Pro Phe Asn Tyr Glu Val Asp His Ile Ile Pro
[2277] 545 550 555 560
[2278] Arg Ser Val Ser Phe Asp Asn Ser Phe Asn Asn Lys Val Leu Val Lys
[2279] 565 570 575
[2280] Gln Glu Glu Asn Ser Lys Lys Gly Asn Arg Thr Pro Phe Gln Tyr Leu
[2281] 580 585 590
[2282] Ser Ser Ser Asp Ser Lys Ile Ser Tyr Glu Thr Phe Lys Lys His Ile
[2283] 595 600 605
[2284] Leu Asn Leu Ala Lys Gly Lys Gly Arg Ile Ser Lys Thr Lys Lys Glu
[2285] 610 615 620
[2286] Tyr Leu Leu Glu Glu Arg Asp Ile Asn Arg Phe Ser Val Gln Lys Asp
[2287] 625 630 635 640
[2288] Phe Ile Asn Arg Asn Leu Val Asp Thr Arg Tyr Ala Thr Arg Gly Leu
[2289] 645 650 655
[2290] Met Asn Leu Leu Arg Ser Tyr Phe Arg Val Asn Asn Leu Asp Val Lys
[2291] 660 665 670
[2292] Val Lys Ser Ile Asn Gly Gly Phe Thr Ser Phe Leu Arg Arg Lys Trp
[2293] 675 680 685
[2294] Lys Phe Lys Lys Glu Arg Asn Lys Gly Tyr Lys His His Ala Glu Asp
[2295] 690 695 700
[2296] Ala Leu Ile Ile Ala Asn Ala Asp Phe Ile Phe Lys Glu Trp Lys Lys
[2297] 705 710 715 720
[2298] Leu Asp Lys Ala Lys Lys Val Met Glu Asn Gln Met Phe Glu Glu Lys
[2299] 725 730 735
[2300] Gln Ala Glu Ser Met Pro Glu Ile Glu Thr Glu Gln Glu Tyr Lys Glu

[2301] 740 745 750
[2302] Ile Phe Ile Thr Pro His Gln Ile Lys His Ile Lys Asp Phe Lys Asp
[2303] 755 760 765
[2304] Tyr Lys Tyr Ser His Arg Val Asp Lys Lys Pro Asn Arg Glu Leu Ile
[2305] 770 775 780
[2306] Asn Asp Thr Leu Tyr Ser Thr Arg Lys Asp Asp Lys Gly Asn Thr Leu
[2307] 785 790 795 800
[2308] Ile Val Asn Asn Leu Asn Gly Leu Tyr Asp Lys Asp Asn Asp Lys Leu
[2309] 805 810 815
[2310] Lys Lys Leu Ile Asn Lys Ser Pro Glu Lys Leu Leu Met Tyr His His
[2311] 820 825 830
[2312] Asp Pro Gln Thr Tyr Gln Lys Leu Lys Leu Ile Met Glu Gln Tyr Gly
[2313] 835 840 845
[2314] Asp Glu Lys Asn Pro Leu Tyr Lys Tyr Tyr Glu Glu Thr Gly Asn Tyr
[2315] 850 855 860
[2316] Leu Thr Lys Tyr Ser Lys Lys Asp Asn Gly Pro Val Ile Lys Lys Ile
[2317] 865 870 875 880
[2318] Lys Tyr Tyr Gly Asn Lys Leu Asn Ala His Leu Asp Ile Thr Asp Asp
[2319] 885 890 895
[2320] Tyr Pro Asn Ser Arg Asn Lys Val Val Lys Leu Ser Leu Lys Pro Tyr
[2321] 900 905 910
[2322] Arg Phe Asp Val Tyr Leu Asp Asn Gly Val Tyr Lys Phe Val Thr Val
[2323] 915 920 925
[2324] Lys Asn Leu Asp Val Ile Lys Lys Glu Asn Tyr Tyr Glu Val Asn Ser
[2325] 930 935 940
[2326] Lys Cys Tyr Glu Glu Ala Lys Lys Leu Lys Lys Ile Ser Asn Gln Ala
[2327] 945 950 955 960
[2328] Glu Phe Ile Ala Ser Phe Tyr Asn Asn Asp Leu Ile Lys Ile Asn Gly
[2329] 965 970 975
[2330] Glu Leu Tyr Arg Val Ile Gly Val Asn Asn Asp Leu Leu Asn Arg Ile
[2331] 980 985 990
[2332] Glu Val Asn Met Ile Asp Ile Thr Tyr Arg Glu Tyr Leu Glu Asn Met
[2333] 995 1000 1005
[2334] Asn Asp Lys Arg Pro Pro Arg Ile Ile Lys Thr Ile Ala Ser Lys
[2335] 1010 1015 1020
[2336] Thr Gln Ser Ile Lys Lys Tyr Ser Thr Asp Ile Leu Gly Asn Leu
[2337] 1025 1030 1035
[2338] Tyr Glu Val Lys Ser Lys Lys His Pro Gln Ile Ile Lys Lys Gly
[2339] 1040 1045 1050

[2340] <210> 34

[2341] <211> 1300

[2342] <212> PRT

[2343] <213> 土拉热弗朗西丝菌

[2344] <400> 34

[2345] Met Ser Ile Tyr Gln Glu Phe Val Asn Lys Tyr Ser Leu Ser Lys Thr

[2346] 1 5 10 15

[2347] Leu Arg Phe Glu Leu Ile Pro Gln Gly Lys Thr Leu Glu Asn Ile Lys

[2348] 20 25 30

[2349] Ala Arg Gly Leu Ile Leu Asp Asp Glu Lys Arg Ala Lys Asp Tyr Lys

[2350] 35 40 45

[2351] Lys Ala Lys Gln Ile Ile Asp Lys Tyr His Gln Phe Phe Ile Glu Glu

[2352] 50 55 60

[2353] Ile Leu Ser Ser Val Cys Ile Ser Glu Asp Leu Leu Gln Asn Tyr Ser

[2354] 65 70 75 80

[2355] Asp Val Tyr Phe Lys Leu Lys Lys Ser Asp Asp Asp Asn Leu Gln Lys

[2356] 85 90 95

[2357] Asp Phe Lys Ser Ala Lys Asp Thr Ile Lys Lys Gln Ile Ser Glu Tyr

[2358] 100 105 110

[2359] Ile Lys Asp Ser Glu Lys Phe Lys Asn Leu Phe Asn Gln Asn Leu Ile

[2360] 115 120 125

[2361] Asp Ala Lys Lys Gly Gln Glu Ser Asp Leu Ile Leu Trp Leu Lys Gln

[2362] 130 135 140

[2363] Ser Lys Asp Asn Gly Ile Glu Leu Phe Lys Ala Asn Ser Asp Ile Thr

[2364] 145 150 155 160

[2365] Asp Ile Asp Glu Ala Leu Glu Ile Ile Lys Ser Phe Lys Gly Trp Thr

[2366] 165 170 175

[2367] Thr Tyr Phe Lys Gly Phe His Glu Asn Arg Lys Asn Val Tyr Ser Ser

[2368] 180 185 190

[2369] Asn Asp Ile Pro Thr Ser Ile Ile Tyr Arg Ile Val Asp Asp Asn Leu

[2370] 195 200 205

[2371] Pro Lys Phe Leu Glu Asn Lys Ala Lys Tyr Glu Ser Leu Lys Asp Lys

[2372] 210 215 220

[2373] Ala Pro Glu Ala Ile Asn Tyr Glu Gln Ile Lys Lys Asp Leu Ala Glu

[2374] 225 230 235 240

[2375] Glu Leu Thr Phe Asp Ile Asp Tyr Lys Thr Ser Glu Val Asn Gln Arg

[2376] 245 250 255

[2377] Val Phe Ser Leu Asp Glu Val Phe Glu Ile Ala Asn Phe Asn Asn Tyr

[2378] 260 265 270

[2379] Leu Asn Gln Ser Gly Ile Thr Lys Phe Asn Thr Ile Ile Gly Gly Lys
[2380] 275 280 285
[2381] Phe Val Asn Gly Glu Asn Thr Lys Arg Lys Gly Ile Asn Glu Tyr Ile
[2382] 290 295 300
[2383] Asn Leu Tyr Ser Gln Gln Ile Asn Asp Lys Thr Leu Lys Lys Tyr Lys
[2384] 305 310 315 320
[2385] Met Ser Val Leu Phe Lys Gln Ile Leu Ser Asp Thr Glu Ser Lys Ser
[2386] 325 330 335
[2387] Phe Val Ile Asp Lys Leu Glu Asp Asp Ser Asp Val Val Thr Thr Met
[2388] 340 345 350
[2389] Gln Ser Phe Tyr Glu Gln Ile Ala Ala Phe Lys Thr Val Glu Glu Lys
[2390] 355 360 365
[2391] Ser Ile Lys Glu Thr Leu Ser Leu Leu Phe Asp Asp Leu Lys Ala Gln
[2392] 370 375 380
[2393] Lys Leu Asp Leu Ser Lys Ile Tyr Phe Lys Asn Asp Lys Ser Leu Thr
[2394] 385 390 395 400
[2395] Asp Leu Ser Gln Gln Val Phe Asp Asp Tyr Ser Val Ile Gly Thr Ala
[2396] 405 410 415
[2397] Val Leu Glu Tyr Ile Thr Gln Gln Ile Ala Pro Lys Asn Leu Asp Asn
[2398] 420 425 430
[2399] Pro Ser Lys Lys Glu Gln Glu Leu Ile Ala Lys Lys Thr Glu Lys Ala
[2400] 435 440 445
[2401] Lys Tyr Leu Ser Leu Glu Thr Ile Lys Leu Ala Leu Glu Glu Phe Asn
[2402] 450 455 460
[2403] Lys His Arg Asp Ile Asp Lys Gln Cys Arg Phe Glu Glu Ile Leu Ala
[2404] 465 470 475 480
[2405] Asn Phe Ala Ala Ile Pro Met Ile Phe Asp Glu Ile Ala Gln Asn Lys
[2406] 485 490 495
[2407] Asp Asn Leu Ala Gln Ile Ser Ile Lys Tyr Gln Asn Gln Gly Lys Lys
[2408] 500 505 510
[2409] Asp Leu Leu Gln Ala Ser Ala Glu Asp Asp Val Lys Ala Ile Lys Asp
[2410] 515 520 525
[2411] Leu Leu Asp Gln Thr Asn Asn Leu Leu His Lys Leu Lys Ile Phe His
[2412] 530 535 540
[2413] Ile Ser Gln Ser Glu Asp Lys Ala Asn Ile Leu Asp Lys Asp Glu His
[2414] 545 550 555 560
[2415] Phe Tyr Leu Val Phe Glu Glu Cys Tyr Phe Glu Leu Ala Asn Ile Val
[2416] 565 570 575
[2417] Pro Leu Tyr Asn Lys Ile Arg Asn Tyr Ile Thr Gln Lys Pro Tyr Ser

[2418] 580 585 590
[2419] Asp Glu Lys Phe Lys Leu Asn Phe Glu Asn Ser Thr Leu Ala Asn Gly
[2420] 595 600 605
[2421] Trp Asp Lys Asn Lys Glu Pro Asp Asn Thr Ala Ile Leu Phe Ile Lys
[2422] 610 615 620
[2423] Asp Asp Lys Tyr Tyr Leu Gly Val Met Asn Lys Lys Asn Asn Lys Ile
[2424] 625 630 635 640
[2425] Phe Asp Asp Lys Ala Ile Lys Glu Asn Lys Gly Glu Gly Tyr Lys Lys
[2426] 645 650 655
[2427] Ile Val Tyr Lys Leu Leu Pro Gly Ala Asn Lys Met Leu Pro Lys Val
[2428] 660 665 670
[2429] Phe Phe Ser Ala Lys Ser Ile Lys Phe Tyr Asn Pro Ser Glu Asp Ile
[2430] 675 680 685
[2431] Leu Arg Ile Arg Asn His Ser Thr His Thr Lys Asn Gly Ser Pro Gln
[2432] 690 695 700
[2433] Lys Gly Tyr Glu Lys Phe Glu Phe Asn Ile Glu Asp Cys Arg Lys Phe
[2434] 705 710 715 720
[2435] Ile Asp Phe Tyr Lys Gln Ser Ile Ser Lys His Pro Glu Trp Lys Asp
[2436] 725 730 735
[2437] Phe Gly Phe Arg Phe Ser Asp Thr Gln Arg Tyr Asn Ser Ile Asp Glu
[2438] 740 745 750
[2439] Phe Tyr Arg Glu Val Glu Asn Gln Gly Tyr Lys Leu Thr Phe Glu Asn
[2440] 755 760 765
[2441] Ile Ser Glu Ser Tyr Ile Asp Ser Val Val Asn Gln Gly Lys Leu Tyr
[2442] 770 775 780
[2443] Leu Phe Gln Ile Tyr Asn Lys Asp Phe Ser Ala Tyr Ser Lys Gly Arg
[2444] 785 790 795 800
[2445] Pro Asn Leu His Thr Leu Tyr Trp Lys Ala Leu Phe Asp Glu Arg Asn
[2446] 805 810 815
[2447] Leu Gln Asp Val Val Tyr Lys Leu Asn Gly Glu Ala Glu Leu Phe Tyr
[2448] 820 825 830
[2449] Arg Lys Gln Ser Ile Pro Lys Lys Ile Thr His Pro Ala Lys Glu Ala
[2450] 835 840 845
[2451] Ile Ala Asn Lys Asn Lys Asp Asn Pro Lys Lys Glu Ser Val Phe Glu
[2452] 850 855 860
[2453] Tyr Asp Leu Ile Lys Asp Lys Arg Phe Thr Glu Asp Lys Phe Phe Phe
[2454] 865 870 875 880
[2455] His Cys Pro Ile Thr Ile Asn Phe Lys Ser Ser Gly Ala Asn Lys Phe
[2456] 885 890 895

[2457] Asn Asp Glu Ile Asn Leu Leu Leu Lys Glu Lys Ala Asn Asp Val His
[2458] 900 905 910
[2459] Ile Leu Ser Ile Asp Arg Gly Glu Arg His Leu Ala Tyr Tyr Thr Leu
[2460] 915 920 925
[2461] Val Asp Gly Lys Gly Asn Ile Ile Lys Gln Asp Thr Phe Asn Ile Ile
[2462] 930 935 940
[2463] Gly Asn Asp Arg Met Lys Thr Asn Tyr His Asp Lys Leu Ala Ala Ile
[2464] 945 950 955 960
[2465] Glu Lys Asp Arg Asp Ser Ala Arg Lys Asp Trp Lys Lys Ile Asn Asn
[2466] 965 970 975
[2467] Ile Lys Glu Met Lys Glu Gly Tyr Leu Ser Gln Val Val His Glu Ile
[2468] 980 985 990
[2469] Ala Lys Leu Val Ile Glu Tyr Asn Ala Ile Val Val Phe Glu Asp Leu
[2470] 995 1000 1005
[2471] Asn Phe Gly Phe Lys Arg Gly Arg Phe Lys Val Glu Lys Gln Val
[2472] 1010 1015 1020
[2473] Tyr Gln Lys Leu Glu Lys Met Leu Ile Glu Lys Leu Asn Tyr Leu
[2474] 1025 1030 1035
[2475] Val Phe Lys Asp Asn Glu Phe Asp Lys Thr Gly Gly Val Leu Arg
[2476] 1040 1045 1050
[2477] Ala Tyr Gln Leu Thr Ala Pro Phe Glu Thr Phe Lys Lys Met Gly
[2478] 1055 1060 1065
[2479] Lys Gln Thr Gly Ile Ile Tyr Tyr Val Pro Ala Gly Phe Thr Ser
[2480] 1070 1075 1080
[2481] Lys Ile Cys Pro Val Thr Gly Phe Val Asn Gln Leu Tyr Pro Lys
[2482] 1085 1090 1095
[2483] Tyr Glu Ser Val Ser Lys Ser Gln Glu Phe Phe Ser Lys Phe Asp
[2484] 1100 1105 1110
[2485] Lys Ile Cys Tyr Asn Leu Asp Lys Gly Tyr Phe Glu Phe Ser Phe
[2486] 1115 1120 1125
[2487] Asp Tyr Lys Asn Phe Gly Asp Lys Ala Ala Lys Gly Lys Trp Thr
[2488] 1130 1135 1140
[2489] Ile Ala Ser Phe Gly Ser Arg Leu Ile Asn Phe Arg Asn Ser Asp
[2490] 1145 1150 1155
[2491] Lys Asn His Asn Trp Asp Thr Arg Glu Val Tyr Pro Thr Lys Glu
[2492] 1160 1165 1170
[2493] Leu Glu Lys Leu Leu Lys Asp Tyr Ser Ile Glu Tyr Gly His Gly
[2494] 1175 1180 1185
[2495] Glu Cys Ile Lys Ala Ala Ile Cys Gly Glu Ser Asp Lys Lys Phe

[2496] 1190 1195 1200
[2497] Phe Ala Lys Leu Thr Ser Val Leu Asn Thr Ile Leu Gln Met Arg
[2498] 1205 1210 1215
[2499] Asn Ser Lys Thr Gly Thr Glu Leu Asp Tyr Leu Ile Ser Pro Val
[2500] 1220 1225 1230
[2501] Ala Asp Val Asn Gly Asn Phe Phe Asp Ser Arg Gln Ala Pro Lys
[2502] 1235 1240 1245
[2503] Asn Met Pro Gln Asp Ala Asp Ala Asn Gly Ala Tyr His Ile Gly
[2504] 1250 1255 1260
[2505] Leu Lys Gly Leu Met Leu Leu Gly Arg Ile Lys Asn Asn Gln Glu
[2506] 1265 1270 1275
[2507] Gly Lys Lys Leu Asn Leu Val Ile Lys Asn Glu Glu Tyr Phe Glu
[2508] 1280 1285 1290
[2509] Phe Val Gln Asn Arg Asn Asn
[2510] 1295 1300
[2511] <210> 35
[2512] <211> 297
[2513] <212> PRT
[2514] <213> 腺相关病毒-1
[2515] <400> 35
[2516] Thr Phe Ser Tyr Thr Phe Glu Glu Val Pro Phe His Ser Ser Tyr Ala
[2517] 1 5 10 15
[2518] His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr
[2519] 20 25 30
[2520] Leu Tyr Tyr Leu Asn Arg Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn
[2521] 35 40 45
[2522] Lys Asp Leu Leu Phe Ser Arg Gly Ser Pro Ala Gly Met Ser Val Gln
[2523] 50 55 60
[2524] Pro Lys Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser
[2525] 65 70 75 80
[2526] Lys Thr Lys Thr Asp Asn Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala
[2527] 85 90 95
[2528] Ser Lys Tyr Asn Leu Asn Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr
[2529] 100 105 110
[2530] Ala Met Ala Ser His Lys Asp Asp Glu Asp Lys Phe Phe Pro Met Ser
[2531] 115 120 125
[2532] Gly Val Met Ile Phe Gly Lys Glu Ser Ala Gly Ala Ser Asn Thr Ala
[2533] 130 135 140
[2534] Leu Asp Asn Val Met Ile Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn

[2535] 145 150 155 160
[2536] Pro Val Ala Thr Glu Arg Phe Gly Thr Val Ala Val Asn Phe Lys Asp
[2537] 165 170 175
[2538] Asp Glu Asp Lys Phe Phe Pro Met Ser Gly Val Met Ile Phe Gly Lys
[2539] 180 185 190
[2540] Glu Ser Ala Gly Ala Ser Asn Thr Ala Leu Asp Asn Val Met Ile Thr
[2541] 195 200 205
[2542] Asp Glu Glu Glu Ile Lys Ala Thr Asn Pro Val Ala Thr Glu Arg Phe
[2543] 210 215 220
[2544] Gly Thr Val Ala Val Asn Phe Gln Ser Ser Ser Thr Asp Pro Ala Thr
[2545] 225 230 235 240
[2546] Gly Asp Val His Ala Met Gly Ala Leu Pro Gly Met Val Trp Gln Asp
[2547] 245 250 255
[2548] Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His Thr
[2549] 260 265 270
[2550] Asp Gly His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu Lys
[2551] 275 280 285
[2552] Asn Pro Pro Pro Gln Ile Leu Ile Lys
[2553] 290 295
[2554] <210> 36
[2555] <211> 240
[2556] <212> PRT
[2557] <213> 腺相关病毒-6
[2558] <400> 36
[2559] Thr Phe Ser Tyr Thr Phe Glu Asp Val Pro Phe His Ser Ser Tyr Ala
[2560] 1 5 10 15
[2561] His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr
[2562] 20 25 30
[2563] Leu Tyr Tyr Leu Asn Arg Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn
[2564] 35 40 45
[2565] Lys Asp Leu Leu Phe Ser Arg Gly Ser Pro Ala Gly Met Ser Val Gln
[2566] 50 55 60
[2567] Pro Lys Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser
[2568] 65 70 75 80
[2569] Lys Thr Lys Thr Asp Asn Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala
[2570] 85 90 95
[2571] Ser Lys Tyr Asn Leu Asn Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr
[2572] 100 105 110
[2573] Ala Met Ala Ser His Lys Asp Asp Lys Asp Lys Phe Phe Pro Met Ser

[2574] 115 120 125
[2575] Gly Val Met Ile Phe Gly Lys Glu Ser Ala Gly Ala Ser Asn Thr Ala
[2576] 130 135 140
[2577] Leu Asp Asn Val Met Ile Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn
[2578] 145 150 155 160
[2579] Pro Val Ala Thr Glu Arg Phe Gly Thr Val Ala Val Asn Leu Gln Ser
[2580] 165 170 175
[2581] Ser Ser Thr Asp Pro Ala Thr Gly Asp Val His Val Met Gly Ala Leu
[2582] 180 185 190
[2583] Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile
[2584] 195 200 205
[2585] Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser Pro Leu
[2586] 210 215 220
[2587] Met Gly Gly Phe Gly Leu Lys His Pro Pro Pro Gln Ile Leu Ile Lys
[2588] 225 230 235 240
[2589] <210> 37
[2590] <211> 240
[2591] <212> PRT
[2592] <213> 腺相关病毒-3
[2593] <400> 37
[2594] Phe Ser Tyr Thr Phe Glu Asp Val Pro Phe His Ser Ser Tyr Ala His
[2595] 1 5 10 15
[2596] Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu
[2597] 20 25 30
[2598] Tyr Tyr Leu Asn Arg Thr Gln Gly Thr Thr Ser Gly Thr Thr Asn Gln
[2599] 35 40 45
[2600] Ser Arg Leu Leu Phe Ser Gln Ala Gly Pro Gln Ser Met Ser Leu Gln
[2601] 50 55 60
[2602] Ala Arg Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Leu Ser
[2603] 65 70 75 80
[2604] Lys Thr Ala Asn Asp Asn Asn Asn Ser Asn Phe Pro Trp Thr Ala Ala
[2605] 85 90 95
[2606] Ser Lys Tyr His Leu Asn Gly Arg Asp Ser Leu Val Asn Pro Gly Pro
[2607] 100 105 110
[2608] Ala Met Ala Ser His Lys Asp Asp Glu Glu Lys Phe Phe Pro Met His
[2609] 115 120 125
[2610] Gly Asn Leu Ile Phe Gly Lys Glu Gly Thr Thr Ala Ser Asn Ala Glu
[2611] 130 135 140
[2612] Leu Asp Asn Val Met Ile Thr Asp Glu Glu Glu Ile Arg Thr Thr Asn

[2613] 145 150 155 160
[2614] Pro Val Ala Thr Glu Gln Tyr Gly Thr Val Ala Asn Asn Leu Gln Ser
[2615] 165 170 175
[2616] Ser Asn Thr Ala Pro Thr Thr Gly Thr Val Asn His Gln Gly Ala Leu
[2617] 180 185 190
[2618] Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile
[2619] 195 200 205
[2620] Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser Pro Leu
[2621] 210 215 220
[2622] Met Gly Gly Phe Gly Leu Lys His Pro Pro Pro Gln Ile Met Ile Lys
[2623] 225 230 235 240
[2624] <210> 38
[2625] <211> 240
[2626] <212> PRT
[2627] <213> 腺相关病毒-2
[2628] <400> 38
[2629] Phe Ser Tyr Thr Phe Glu Asp Val Pro Phe His Ser Ser Tyr Ala His
[2630] 1 5 10 15
[2631] Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu
[2632] 20 25 30
[2633] Tyr Tyr Leu Ser Arg Thr Asn Thr Pro Ser Gly Thr Thr Thr Gln Ser
[2634] 35 40 45
[2635] Arg Leu Gln Phe Ser Gln Ala Gly Ala Ser Asp Ile Arg Asp Gln Ser
[2636] 50 55 60
[2637] Arg Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys
[2638] 65 70 75 80
[2639] Thr Ser Ala Asp Asn Asn Asn Ser Glu Tyr Ser Trp Thr Gly Ala Thr
[2640] 85 90 95
[2641] Lys Tyr His Leu Asn Gly Arg Asp Ser Leu Val Asn Pro Gly Pro Ala
[2642] 100 105 110
[2643] Met Ala Ser His Lys Asp Asp Glu Glu Lys Phe Phe Pro Gln Ser Gly
[2644] 115 120 125
[2645] Val Leu Ile Phe Gly Lys Gln Gly Ser Glu Lys Thr Asn Val Asp Ile
[2646] 130 135 140
[2647] Glu Lys Val Met Ile Thr Asp Glu Glu Glu Ile Arg Thr Thr Asn Pro
[2648] 145 150 155 160
[2649] Val Ala Thr Glu Gln Tyr Gly Ser Val Ser Thr Asn Leu Gln Arg Gly
[2650] 165 170 175
[2651] Asn Arg Gln Ala Ala Thr Ala Asp Val Asn Thr Gln Gly Val Leu Pro

[2652] 180 185 190
[2653] Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp
[2654] 195 200 205
[2655] Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser Pro Leu Met
[2656] 210 215 220
[2657] Gly Gly Phe Gly Leu Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn
[2658] 225 230 235 240
[2659] <210> 39
[2660] <211> 243
[2661] <212> PRT
[2662] <213> 腺相关病毒-8
[2663] <400> 39
[2664] Asn Phe Gln Phe Thr Tyr Thr Phe Glu Asp Val Pro Phe His Ser Ser
[2665] 1 5 10 15
[2666] Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp
[2667] 20 25 30
[2668] Gln Tyr Leu Tyr Tyr Leu Ser Arg Thr Gln Thr Thr Gly Gly Thr Ala
[2669] 35 40 45
[2670] Asn Thr Gln Thr Leu Gly Phe Ser Gln Gly Gly Pro Asn Thr Met Ala
[2671] 50 55 60
[2672] Asn Gln Ala Lys Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg
[2673] 65 70 75 80
[2674] Val Ser Thr Thr Thr Gly Gln Asn Asn Asn Ser Asn Phe Ala Trp Thr
[2675] 85 90 95
[2676] Ala Gly Thr Lys Tyr His Leu Asn Gly Arg Asn Ser Leu Ala Asn Pro
[2677] 100 105 110
[2678] Gly Ile Ala Met Ala Thr His Lys Asp Asp Glu Glu Arg Phe Phe Pro
[2679] 115 120 125
[2680] Ser Asn Gly Ile Leu Ile Phe Gly Lys Gln Asn Ala Ala Arg Asp Asn
[2681] 130 135 140
[2682] Ala Asp Tyr Ser Asp Val Met Leu Thr Ser Glu Glu Glu Ile Lys Thr
[2683] 145 150 155 160
[2684] Thr Asn Pro Val Ala Thr Glu Glu Tyr Gly Ile Val Ala Asp Asn Leu
[2685] 165 170 175
[2686] Gln Gln Gln Asn Thr Ala Pro Gln Ile Gly Thr Val Asn Ser Gln Gly
[2687] 180 185 190
[2688] Ala Leu Pro Gly Met Val Trp Gln Asn Arg Asp Val Tyr Leu Gln Gly
[2689] 195 200 205
[2690] Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly Asn Phe His Pro Ser

[2691] 210 215 220
[2692] Pro Leu Met Gly Gly Phe Gly Leu Lys His Pro Pro Pro Gln Ile Leu
[2693] 225 230 235 240
[2694] Ile Lys Asn
[2695] <210> 40
[2696] <211> 243
[2697] <212> PRT
[2698] <213> 腺相关病毒-8.1
[2699] <400> 40
[2700] Asn Phe Gln Phe Thr Tyr Thr Phe Glu Asp Val Pro Phe His Ser Ser
[2701] 1 5 10 15
[2702] Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp
[2703] 20 25 30
[2704] Gln Tyr Leu Tyr Tyr Leu Ser Arg Thr Gln Thr Thr Gly Gly Thr Ala
[2705] 35 40 45
[2706] Asn Thr Gln Thr Leu Gly Phe Ser Gln Gly Gly Pro Asn Thr Met Ala
[2707] 50 55 60
[2708] Asn Gln Ala Lys Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg
[2709] 65 70 75 80
[2710] Val Ser Thr Thr Thr Gly Gln Asn Asn Asn Ser Asn Phe Ala Trp Thr
[2711] 85 90 95
[2712] Ala Gly Thr Lys Tyr His Leu Asn Gly Arg Asn Ser Leu Ala Asn Pro
[2713] 100 105 110
[2714] Gly Ile Ala Met Ala Thr His Lys Asp Asp Glu Glu Arg Phe Phe Pro
[2715] 115 120 125
[2716] Ser Asn Gly Ile Leu Ile Phe Gly Lys Gln Asn Ala Ala Arg Asp Asn
[2717] 130 135 140
[2718] Ala Asp Tyr Ser Asp Val Met Leu Thr Ser Glu Glu Glu Ile Lys Thr
[2719] 145 150 155 160
[2720] Thr Asn Pro Val Ala Thr Glu Glu Tyr Gly Ile Val Ala Asp Asn Leu
[2721] 165 170 175
[2722] Gln Gly Gln Arg Gln Ala Ala Gln Ile Gly Thr Val Asn Ser Gln Gly
[2723] 180 185 190
[2724] Ala Leu Pro Gly Met Val Trp Gln Asn Arg Asp Val Tyr Leu Gln Gly
[2725] 195 200 205
[2726] Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly Asn Phe His Pro Ser
[2727] 210 215 220
[2728] Pro Leu Met Gly Gly Phe Gly Leu Lys His Pro Pro Pro Gln Ile Leu
[2729] 225 230 235 240

[2730] Ile Lys Asn
[2731] <210> 41
[2732] <211> 241
[2733] <212> PRT
[2734] <213> 腺相关病毒-8 Rh8
[2735] <400> 41
[2736] Phe Gln Phe Ser Tyr Thr Phe Glu Asp Val Pro Phe His Ser Ser Tyr
[2737] 1 5 10 15
[2738] Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln
[2739] 20 25 30
[2740] Tyr Leu Tyr Tyr Leu Val Arg Thr Gln Thr Thr Gly Thr Gly Gly Thr
[2741] 35 40 45
[2742] Gln Thr Leu Ala Phe Ser Gln Ala Gly Pro Ser Ser Met Ala Asn Gln
[2743] 50 55 60
[2744] Ala Arg Asn Trp Val Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser
[2745] 65 70 75 80
[2746] Thr Thr Thr Asn Gln Asn Asn Asn Ser Asn Phe Ala Trp Thr Gly Ala
[2747] 85 90 95
[2748] Ala Lys Phe Lys Leu Asn Gly Arg Asp Ser Leu Met Asn Pro Gly Val
[2749] 100 105 110
[2750] Ala Met Ala Ser His Lys Asp Asp Asp Asp Arg Phe Phe Pro Ser Ser
[2751] 115 120 125
[2752] Gly Val Leu Ile Phe Gly Lys Gln Gly Ala Gly Asn Asp Gly Val Asp
[2753] 130 135 140
[2754] Tyr Ser Gln Val Leu Ile Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn
[2755] 145 150 155 160
[2756] Pro Val Ala Thr Glu Glu Tyr Gly Ala Val Ala Ile Asn Asn Gln Ala
[2757] 165 170 175
[2758] Ala Asn Thr Gln Ala Gln Thr Gly Leu Val His Asn Gln Gly Val Ile
[2759] 180 185 190
[2760] Pro Gly Met Val Trp Gln Asn Arg Asp Val Tyr Leu Gln Gly Pro Ile
[2761] 195 200 205
[2762] Trp Ala Lys Ile Pro His Thr Asp Gly Asn Phe His Pro Ser Pro Leu
[2763] 210 215 220
[2764] Met Gly Gly Phe Gly Leu Lys His Pro Pro Pro Gln Ile Leu Ile Lys
[2765] 225 230 235 240
[2766] Asn
[2767] <210> 42
[2768] <211> 243

[2769] <212> PRT

[2770] <213> 腺相关病毒-10

[2771] <400> 42

[2772] Asn Phe Glu Phe Ser Tyr Thr Phe Glu Asp Val Pro Phe His Ser Ser

[2773] 1 5 10 15

[2774] Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp

[2775] 20 25 30

[2776] Gln Tyr Leu Tyr Tyr Leu Ser Arg Thr Gln Ser Thr Gly Gly Thr Gln

[2777] 35 40 45

[2778] Gly Thr Gln Gln Leu Leu Phe Ser Gln Ala Gly Pro Ala Asn Met Ser

[2779] 50 55 60

[2780] Ala Gln Ala Lys Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg

[2781] 65 70 75 80

[2782] Val Ser Thr Thr Leu Ser Gln Asn Asn Asn Ser Asn Phe Ala Trp Thr

[2783] 85 90 95

[2784] Gly Ala Thr Lys Tyr His Leu Asn Gly Arg Asp Ser Leu Val Asn Pro

[2785] 100 105 110

[2786] Gly Val Ala Met Ala Thr His Lys Asp Asp Glu Glu Arg Phe Phe Pro

[2787] 115 120 125

[2788] Ser Ser Gly Val Leu Met Phe Gly Lys Gln Gly Ala Gly Arg Asp Asn

[2789] 130 135 140

[2790] Val Asp Tyr Ser Ser Val Met Leu Thr Ser Glu Glu Glu Ile Lys Thr

[2791] 145 150 155 160

[2792] Thr Asn Pro Val Ala Thr Glu Gln Tyr Gly Val Val Ala Asp Asn Leu

[2793] 165 170 175

[2794] Gln Gln Ala Asn Thr Gly Pro Ile Val Gly Asn Val Asn Ser Gln Gly

[2795] 180 185 190

[2796] Ala Leu Pro Gly Met Val Trp Gln Asn Arg Asp Val Tyr Leu Gln Gly

[2797] 195 200 205

[2798] Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly Asn Phe His Pro Ser

[2799] 210 215 220

[2800] Pro Leu Met Gly Gly Phe Gly Leu Lys His Pro Pro Pro Gln Ile Leu

[2801] 225 230 235 240

[2802] Ile Lys Asn

[2803] <210> 43

[2804] <211> 242

[2805] <212> PRT

[2806] <213> 腺相关病毒-7

[2807] <400> 43

[2808] Phe Glu Phe Ser Tyr Ser Phe Glu Asp Val Pro Phe His Ser Ser Tyr
[2809] 1 5 10 15
[2810] Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln
[2811] 20 25 30
[2812] Tyr Leu Tyr Tyr Leu Ala Arg Thr Gln Ser Asn Pro Gly Gly Thr Ala
[2813] 35 40 45
[2814] Gly Asn Arg Glu Leu Gln Phe Tyr Gln Gly Gly Pro Ser Thr Met Ala
[2815] 50 55 60
[2816] Glu Gln Ala Lys Asn Trp Leu Pro Gly Pro Cys Phe Arg Gln Gln Arg
[2817] 65 70 75 80
[2818] Val Ser Lys Thr Leu Asp Gln Asn Asn Asn Ser Asn Phe Ala Trp Thr
[2819] 85 90 95
[2820] Gly Ala Thr Lys Tyr His Leu Asn Gly Arg Asn Ser Leu Val Asn Pro
[2821] 100 105 110
[2822] Gly Val Ala Met Ala Thr His Lys Asp Asp Glu Asp Arg Phe Phe Pro
[2823] 115 120 125
[2824] Ser Ser Gly Val Leu Ile Phe Gly Lys Thr Gly Ala Thr Asn Lys Thr
[2825] 130 135 140
[2826] Thr Leu Glu Asn Val Leu Met Thr Asn Glu Glu Glu Ile Arg Pro Thr
[2827] 145 150 155 160
[2828] Asn Pro Val Ala Thr Glu Glu Tyr Gly Ile Val Ser Ser Asn Leu Gln
[2829] 165 170 175
[2830] Ala Ala Asn Thr Ala Ala Gln Thr Gln Val Val Asn Asn Gln Gly Ala
[2831] 180 185 190
[2832] Leu Pro Gly Met Val Trp Gln Asn Arg Asp Val Tyr Leu Gln Gly Pro
[2833] 195 200 205
[2834] Ile Trp Ala Lys Ile Pro His Thr Asp Gly Asn Phe His Pro Ser Pro
[2835] 210 215 220
[2836] Leu Met Gly Gly Phe Gly Leu Lys His Pro Pro Pro Gln Ile Leu Ile
[2837] 225 230 235 240
[2838] Lys Asn
[2839] <210> 44
[2840] <211> 240
[2841] <212> PRT
[2842] <213> 腺相关病毒-9
[2843] <400> 44
[2844] Phe Gln Phe Ser Tyr Glu Phe Glu Asn Val Pro Phe His Ser Ser Tyr
[2845] 1 5 10 15
[2846] Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln

[2847] 20 25 30
[2848] Tyr Leu Tyr Tyr Leu Ser Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln
[2849] 35 40 45
[2850] Gln Thr Leu Lys Phe Ser Val Ala Gly Pro Ser Asn Met Ala Val Gln
[2851] 50 55 60
[2852] Gly Arg Asn Tyr Ile Pro Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser
[2853] 65 70 75 80
[2854] Thr Thr Val Thr Gln Asn Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala
[2855] 85 90 95
[2856] Ser Ser Trp Ala Leu Asn Gly Arg Asn Ser Leu Met Asn Pro Gly Pro
[2857] 100 105 110
[2858] Ala Met Ala Ser His Lys Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser
[2859] 115 120 125
[2860] Gly Ser Leu Ile Phe Gly Lys Gln Gly Thr Gly Arg Asp Asn Val Asp
[2861] 130 135 140
[2862] Ala Asp Lys Val Met Ile Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn
[2863] 145 150 155 160
[2864] Pro Val Ala Thr Glu Ser Tyr Gly Gln Val Ala Thr Asn His Gln Ser
[2865] 165 170 175
[2866] Ala Gln Ala Gln Ala Gln Thr Gly Trp Val Gln Asn Gln Gly Ile Leu
[2867] 180 185 190
[2868] Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile
[2869] 195 200 205
[2870] Trp Ala Lys Ile Pro His Thr Asp Gly Asn Phe His Pro Ser Pro Leu
[2871] 210 215 220
[2872] Met Gly Gly Phe Gly Met Lys His Pro Pro Pro Gln Ile Leu Ile Lys
[2873] 225 230 235 240
[2874] <210> 45
[2875] <211> 240
[2876] <212> PRT
[2877] <213> 腺相关病毒-9.1
[2878] <400> 45
[2879] Phe Gln Phe Ser Tyr Glu Phe Glu Asn Val Pro Phe His Ser Ser Tyr
[2880] 1 5 10 15
[2881] Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln
[2882] 20 25 30
[2883] Tyr Leu Tyr Tyr Leu Ser Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln
[2884] 35 40 45
[2885] Gln Thr Leu Lys Phe Ser Val Ala Gly Pro Ser Asn Met Ala Val Gln

[2886] 50 55 60

[2887] Gly Arg Asn Tyr Ile Pro Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser

[2888] 65 70 75 80

[2889] Thr Thr Val Thr Gln Asn Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala

[2890] 85 90 95

[2891] Ser Ser Trp Ala Leu Asn Gly Arg Asn Ser Leu Met Asn Pro Gly Pro

[2892] 100 105 110

[2893] Ala Met Ala Ser His Lys Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser

[2894] 115 120 125

[2895] Gly Ser Leu Ile Phe Gly Lys Gln Gly Thr Gly Arg Asp Asn Val Asp

[2896] 130 135 140

[2897] Ala Asp Lys Val Met Ile Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn

[2898] 145 150 155 160

[2899] Pro Val Ala Thr Glu Ser Tyr Gly Gln Val Ala Thr Asn His Gln Ser

[2900] 165 170 175

[2901] Gly Gln Ala Gln Ala Ala Thr Gly Trp Val Gln Asn Gln Gly Ile Leu

[2902] 180 185 190

[2903] Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile

[2904] 195 200 205

[2905] Trp Ala Lys Ile Pro His Thr Asp Gly Asn Phe His Pro Ser Pro Leu

[2906] 210 215 220

[2907] Met Gly Gly Phe Gly Met Lys His Pro Pro Pro Gln Ile Leu Ile Lys

[2908] 225 230 235 240

[2909] <210> 46

[2910] <211> 240

[2911] <212> PRT

[2912] <213> 腺相关病毒-5

[2913] <400> 46

[2914] Asn Phe Glu Phe Thr Tyr Asn Phe Glu Glu Val Pro Phe His Ser Ser

[2915] 1 5 10 15

[2916] Phe Ala Pro Ser Gln Asn Leu Phe Lys Leu Ala Asn Pro Leu Val Asp

[2917] 20 25 30

[2918] Gln Tyr Leu Tyr Arg Phe Val Ser Thr Asn Asn Thr Gly Gly Val Gln

[2919] 35 40 45

[2920] Phe Asn Lys Asn Leu Ala Gly Arg Tyr Ala Asn Thr Tyr Lys Asn Trp

[2921] 50 55 60

[2922] Phe Pro Gly Pro Met Gly Arg Thr Gln Gly Trp Asn Leu Gly Ser Gly

[2923] 65 70 75 80

[2924] Val Asn Arg Ala Ser Val Ser Ala Phe Ala Thr Thr Asn Arg Met Glu

[2925] 85 90 95

[2926] Leu Glu Gly Ala Ser Tyr Gln Val Pro Pro Gln Pro Asn Gly Met Thr

[2927] 100 105 110

[2928] Asn Asn Leu Gln Gly Ser Asn Thr Tyr Ala Leu Glu Asn Thr Met Ile

[2929] 115 120 125

[2930] Phe Asn Ser Gln Pro Ala Asn Pro Gly Thr Thr Ala Thr Tyr Leu Glu

[2931] 130 135 140

[2932] Gly Asn Met Leu Ile Thr Ser Glu Ser Glu Thr Gln Pro Val Asn Arg

[2933] 145 150 155 160

[2934] Val Ala Tyr Asn Val Gly Gly Gln Met Ala Thr Asn Asn Gln Ser Ser

[2935] 165 170 175

[2936] Thr Thr Ala Pro Ala Thr Gly Thr Tyr Asn Leu Gln Glu Ile Val Pro

[2937] 180 185 190

[2938] Gly Ser Val Trp Met Glu Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp

[2939] 195 200 205

[2940] Ala Lys Ile Pro Glu Thr Gly Ala His Phe His Pro Ser Pro Ala Met

[2941] 210 215 220

[2942] Gly Gly Phe Gly Leu Lys His Pro Pro Pro Met Met Leu Ile Lys Asn

[2943] 225 230 235 240

[2944] <210> 47

[2945] <211> 9

[2946] <212> PRT

[2947] <213> 人工序列

[2948] <220>

[2949] <223> 合成肽

[2950] <400> 47

[2951] Leu Ala Lys Asp Ala Thr Lys Asn Ala

[2952] 1 5

[2953] <210> 48

[2954] <211> 10

[2955] <212> PRT

[2956] <213> 人工序列

[2957] <220>

[2958] <223> 合成肽

[2959] <400> 48

[2960] Pro Ala His Gln Asp Thr Thr Lys Asn Ala

[2961] 1 5 10

[2962] <210> 49

[2963] <211> 10

[2964] <212> PRT
[2965] <213> 人工序列
[2966] <220>
[2967] <223> 合成肽
[2968] <400> 49
[2969] Leu Ala His Gln Asp Thr Thr Lys Asn Ala
[2970] 1 5 10
[2971] <210> 50
[2972] <211> 10
[2973] <212> PRT
[2974] <213> 人工序列
[2975] <220>
[2976] <223> 合成肽
[2977] <400> 50
[2978] Leu Ala Thr Thr Ser Gln Asn Lys Pro Ala
[2979] 1 5 10
[2980] <210> 51
[2981] <211> 10
[2982] <212> PRT
[2983] <213> 人工序列
[2984] <220>
[2985] <223> 合成肽
[2986] <400> 51
[2987] Leu Ala Ile Ser Asp Gln Thr Lys His Ala
[2988] 1 5 10
[2989] <210> 52
[2990] <211> 10
[2991] <212> PRT
[2992] <213> 人工序列
[2993] <220>
[2994] <223> 合成肽
[2995] <400> 52
[2996] Ile Ala Arg Gly Val Ala Pro Ser Ser Ala
[2997] 1 5 10
[2998] <210> 53
[2999] <211> 10
[3000] <212> PRT
[3001] <213> 人工序列
[3002] <220>

[3003] <223> 合成肽

[3004] <400> 53

[3005] Leu Ala Pro Asp Ser Thr Thr Arg Ser Ala

[3006] 1 5 10

[3007] <210> 54

[3008] <211> 10

[3009] <212> PRT

[3010] <213> 人工序列

[3011] <220>

[3012] <223> 合成肽

[3013] <400> 54

[3014] Leu Ala Lys Gly Thr Glu Leu Lys Pro Ala

[3015] 1 5 10

[3016] <210> 55

[3017] <211> 10

[3018] <212> PRT

[3019] <213> 人工序列

[3020] <220>

[3021] <223> 合成肽

[3022] <400> 55

[3023] Leu Ala Ile Ile Asp Ala Thr Lys Asn Ala

[3024] 1 5 10

[3025] <210> 56

[3026] <211> 10

[3027] <212> PRT

[3028] <213> 人工序列

[3029] <220>

[3030] <223> 合成肽

[3031] <400> 56

[3032] Leu Ala Val Asp Gly Ala Gln Arg Ser Ala

[3033] 1 5 10

[3034] <210> 57

[3035] <211> 10

[3036] <212> PRT

[3037] <213> 人工序列

[3038] <220>

[3039] <223> 合成肽

[3040] <400> 57

[3041] Pro Ala Pro Gln Asp Thr Thr Lys Lys Ala

[3042] 1 5 10

[3043] <210> 58

[3044] <211> 10

[3045] <212> PRT

[3046] <213> 人工序列

[3047] <220>

[3048] <223> 合成肽

[3049] <400> 58

[3050] Leu Pro His Gln Asp Thr Thr Lys Asn Ala

[3051] 1 5 10

[3052] <210> 59

[3053] <211> 10

[3054] <212> PRT

[3055] <213> 人工序列

[3056] <220>

[3057] <223> 合成肽

[3058] <400> 59

[3059] Leu Ala Lys Asp Ala Thr Lys Thr Ile Ala

[3060] 1 5 10

[3061] <210> 60

[3062] <211> 10

[3063] <212> PRT

[3064] <213> 人工序列

[3065] <220>

[3066] <223> 合成肽

[3067] <400> 60

[3068] Leu Ala Lys Gln Gln Ser Ala Ser Thr Ala

[3069] 1 5 10

[3070] <210> 61

[3071] <211> 10

[3072] <212> PRT

[3073] <213> 人工序列

[3074] <220>

[3075] <223> 合成肽

[3076] <400> 61

[3077] Leu Ala Lys Ser Asp Gln Ser Lys Pro Ala

[3078] 1 5 10

[3079] <210> 62

[3080] <211> 10

[3081] <212> PRT
[3082] <213> 人工序列
[3083] <220>
[3084] <223> 合成肽
[3085] <400> 62
[3086] Leu Ser His Gln Asp Thr Thr Lys Asn Ala
[3087] 1 5 10
[3088] <210> 63
[3089] <211> 10
[3090] <212> PRT
[3091] <213> 人工序列
[3092] <220>
[3093] <223> 合成肽
[3094] <400> 63
[3095] Leu Ala Ala Asn Gln Pro Ser Lys Pro Ala
[3096] 1 5 10
[3097] <210> 64
[3098] <211> 10
[3099] <212> PRT
[3100] <213> 人工序列
[3101] <220>
[3102] <223> 合成肽
[3103] <400> 64
[3104] Leu Ala Val Ser Asp Ser Thr Lys Ala Ala
[3105] 1 5 10
[3106] <210> 65
[3107] <211> 10
[3108] <212> PRT
[3109] <213> 人工序列
[3110] <220>
[3111] <223> 合成肽
[3112] <400> 65
[3113] Leu Ala Ala Gln Gly Thr Ala Lys Pro Ala
[3114] 1 5 10
[3115] <210> 66
[3116] <211> 10
[3117] <212> PRT
[3118] <213> 人工序列
[3119] <220>

[3120] <223> 合成肽
[3121] <400> 66
[3122] Leu Ala Pro Asp Gln Thr Thr Arg Asn Ala
[3123] 1 5 10
[3124] <210> 67
[3125] <211> 10
[3126] <212> PRT
[3127] <213> 人工序列
[3128] <220>
[3129] <223> 合成肽
[3130] <400> 67
[3131] Leu Ala Ala Ser Asp Ser Thr Lys Ala Ala
[3132] 1 5 10
[3133] <210> 68
[3134] <211> 10
[3135] <212> PRT
[3136] <213> 人工序列
[3137] <220>
[3138] <223> 合成肽
[3139] <400> 68
[3140] Leu Ala Pro Gln Asp Thr Thr Lys Asn Ala
[3141] 1 5 10
[3142] <210> 69
[3143] <211> 10
[3144] <212> PRT
[3145] <213> 人工序列
[3146] <220>
[3147] <223> 合成肽
[3148] <400> 69
[3149] Leu Ala Lys Ala Asp Glu Thr Arg Pro Ala
[3150] 1 5 10
[3151] <210> 70
[3152] <211> 10
[3153] <212> PRT
[3154] <213> 人工序列
[3155] <220>
[3156] <223> 合成肽
[3157] <400> 70
[3158] Leu Ala His Gln Asp Thr Ala Lys Asn Ala

[3159] 1 5 10

[3160] <210> 71

[3161] <211> 10

[3162] <212> PRT

[3163] <213> 人工序列

[3164] <220>

[3165] <223> 合成肽

[3166] <400> 71

[3167] Leu Ala His Gln Asp Thr Lys Lys Asn Ala

[3168] 1 5 10

[3169] <210> 72

[3170] <211> 10

[3171] <212> PRT

[3172] <213> 人工序列

[3173] <220>

[3174] <223> 合成肽

[3175] <400> 72

[3176] Leu Ala His Gln Asp Thr Thr Lys His Ala

[3177] 1 5 10

[3178] <210> 73

[3179] <211> 10

[3180] <212> PRT

[3181] <213> 人工序列

[3182] <220>

[3183] <223> 合成肽

[3184] <400> 73

[3185] Leu Ala His Gln Asp Thr Thr Lys Lys Ala

[3186] 1 5 10

[3187] <210> 74

[3188] <211> 10

[3189] <212> PRT

[3190] <213> 人工序列

[3191] <220>

[3192] <223> 合成肽

[3193] <400> 74

[3194] Leu Ala His Gln Asp Thr Thr Arg Asn Ala

[3195] 1 5 10

[3196] <210> 75

[3197] <211> 10

[3198] <212> PRT
[3199] <213> 人工序列
[3200] <220>
[3201] <223> 合成肽
[3202] <400> 75
[3203] Leu Ala His Gln Asp Thr Thr Thr Asn Ala
[3204] 1 5 10
[3205] <210> 76
[3206] <211> 10
[3207] <212> PRT
[3208] <213> 人工序列
[3209] <220>
[3210] <223> 合成肽
[3211] <400> 76
[3212] Leu Ala His Gln Gly Thr Thr Lys Asn Ala
[3213] 1 5 10
[3214] <210> 77
[3215] <211> 10
[3216] <212> PRT
[3217] <213> 人工序列
[3218] <220>
[3219] <223> 合成肽
[3220] <400> 77
[3221] Leu Ala His Gln Val Thr Thr Lys Asn Ala
[3222] 1 5 10
[3223] <210> 78
[3224] <211> 10
[3225] <212> PRT
[3226] <213> 人工序列
[3227] <220>
[3228] <223> 合成肽
[3229] <400> 78
[3230] Leu Ala Ile Ser Asp Gln Ser Lys Pro Ala
[3231] 1 5 10
[3232] <210> 79
[3233] <211> 9
[3234] <212> PRT
[3235] <213> 人工序列
[3236] <220>

[3237] <223> 合成肽
[3238] <400> 79
[3239] Leu Ala Lys Asp Ala Thr Lys Thr Ala
[3240] 1 5
[3241] <210> 80
[3242] <211> 9
[3243] <212> PRT
[3244] <213> 人工序列
[3245] <220>
[3246] <223> 合成肽
[3247] <400> 80
[3248] Leu Ala Lys Asp Thr Thr Lys Asn Ala
[3249] 1 5
[3250] <210> 81
[3251] <211> 10
[3252] <212> PRT
[3253] <213> 人工序列
[3254] <220>
[3255] <223> 合成肽
[3256] <400> 81
[3257] Leu Ala Lys Ser Asp Gln Ser Arg Pro Ala
[3258] 1 5 10
[3259] <210> 82
[3260] <211> 10
[3261] <212> PRT
[3262] <213> 人工序列
[3263] <220>
[3264] <223> 合成肽
[3265] <400> 82
[3266] Leu Ala Pro Gln Asp Thr Lys Lys Asn Ala
[3267] 1 5 10
[3268] <210> 83
[3269] <211> 10
[3270] <212> PRT
[3271] <213> 人工序列
[3272] <220>
[3273] <223> 合成肽
[3274] <400> 83
[3275] Leu Ala Thr Ser Asp Ser Thr Lys Ala Ala

[3276] 1 5 10

[3277] <210> 84

[3278] <211> 10

[3279] <212> PRT

[3280] <213> 人工序列

[3281] <220>

[3282] <223> 合成肽

[3283] <400> 84

[3284] Leu Ala Val Asp Gly Ser Gln Arg Ser Ala

[3285] 1 5 10

[3286] <210> 85

[3287] <211> 10

[3288] <212> PRT

[3289] <213> 人工序列

[3290] <220>

[3291] <223> 合成肽

[3292] <400> 85

[3293] Leu Pro Ile Ser Asp Gln Thr Lys His Ala

[3294] 1 5 10

[3295] <210> 86

[3296] <211> 10

[3297] <212> PRT

[3298] <213> 人工序列

[3299] <220>

[3300] <223> 合成肽

[3301] <400> 86

[3302] Leu Pro Lys Asp Ala Thr Lys Thr Ile Ala

[3303] 1 5 10

[3304] <210> 87

[3305] <211> 10

[3306] <212> PRT

[3307] <213> 人工序列

[3308] <220>

[3309] <223> 合成肽

[3310] <400> 87

[3311] Leu Pro Pro Gln Asp Thr Thr Lys Asn Ala

[3312] 1 5 10

[3313] <210> 88

[3314] <211> 10

[3315] <212> PRT
[3316] <213> 人工序列
[3317] <220>
[3318] <223> 合成肽
[3319] <400> 88
[3320] Pro Ala Pro Gln Asp Thr Thr Lys Asn Ala
[3321] 1 5 10
[3322] <210> 89
[3323] <211> 10
[3324] <212> PRT
[3325] <213> 人工序列
[3326] <220>
[3327] <223> 合成肽
[3328] <400> 89
[3329] Gln Ala His Gln Asp Thr Thr Lys Asn Ala
[3330] 1 5 10
[3331] <210> 90
[3332] <211> 10
[3333] <212> PRT
[3334] <213> 人工序列
[3335] <220>
[3336] <223> 合成肽
[3337] <400> 90
[3338] Leu Ala His Glu Thr Ser Pro Arg Pro Ala
[3339] 1 5 10
[3340] <210> 91
[3341] <211> 10
[3342] <212> PRT
[3343] <213> 人工序列
[3344] <220>
[3345] <223> 合成肽
[3346] <400> 91
[3347] Leu Ala Lys Ser Thr Ser Thr Ala Pro Ala
[3348] 1 5 10
[3349] <210> 92
[3350] <211> 10
[3351] <212> PRT
[3352] <213> 人工序列
[3353] <220>

[3354] <223> 合成肽
[3355] <400> 92
[3356] Leu Ala Asp Gln Asp Thr Thr Lys Asn Ala
[3357] 1 5 10
[3358] <210> 93
[3359] <211> 10
[3360] <212> PRT
[3361] <213> 人工序列
[3362] <220>
[3363] <223> 合成肽
[3364] <400> 93
[3365] Leu Ala Glu Ser Asp Gln Ser Lys Pro Ala
[3366] 1 5 10
[3367] <210> 94
[3368] <211> 10
[3369] <212> PRT
[3370] <213> 人工序列
[3371] <220>
[3372] <223> 合成肽
[3373] <400> 94
[3374] Leu Ala His Lys Asp Thr Thr Lys Asn Ala
[3375] 1 5 10
[3376] <210> 95
[3377] <211> 9
[3378] <212> PRT
[3379] <213> 人工序列
[3380] <220>
[3381] <223> 合成肽
[3382] <400> 95
[3383] Leu Ala His Lys Thr Gln Gln Lys Met
[3384] 1 5
[3385] <210> 96
[3386] <211> 10
[3387] <212> PRT
[3388] <213> 人工序列
[3389] <220>
[3390] <223> 合成肽
[3391] <400> 96
[3392] Leu Ala His Gln Asp Thr Thr Glu Asn Ala

[3393] 1 5 10

[3394] <210> 97

[3395] <211> 10

[3396] <212> PRT

[3397] <213> 人工序列

[3398] <220>

[3399] <223> 合成肽

[3400] <400> 97

[3401] Leu Ala His Gln Asp Thr Thr Ile Asn Ala

[3402] 1 5 10

[3403] <210> 98

[3404] <211> 10

[3405] <212> PRT

[3406] <213> 人工序列

[3407] <220>

[3408] <223> 合成肽

[3409] <400> 98

[3410] Leu Ala His Gln Asp Thr Thr Lys Lys Thr

[3411] 1 5 10

[3412] <210> 99

[3413] <211> 10

[3414] <212> PRT

[3415] <213> 人工序列

[3416] <220>

[3417] <223> 合成肽

[3418] <400> 99

[3419] Leu Ala His Gln Asp Thr Thr Lys Asn Asp

[3420] 1 5 10

[3421] <210> 100

[3422] <211> 10

[3423] <212> PRT

[3424] <213> 人工序列

[3425] <220>

[3426] <223> 合成肽

[3427] <400> 100

[3428] Leu Ala His Gln Asp Thr Thr Lys Asn Thr

[3429] 1 5 10

[3430] <210> 101

[3431] <211> 10

[3432] <212> PRT
[3433] <213> 人工序列
[3434] <220>
[3435] <223> 合成肽
[3436] <400> 101
[3437] Leu Ala His Gln Asp Thr Thr Lys Asn Val
[3438] 1 5 10
[3439] <210> 102
[3440] <211> 10
[3441] <212> PRT
[3442] <213> 人工序列
[3443] <220>
[3444] <223> 合成肽
[3445] <400> 102
[3446] Leu Ala His Gln Asp Thr Thr Lys Thr Met
[3447] 1 5 10
[3448] <210> 103
[3449] <211> 10
[3450] <212> PRT
[3451] <213> 人工序列
[3452] <220>
[3453] <223> 合成肽
[3454] <400> 103
[3455] Leu Ala His Gln Asn Thr Thr Lys Asn Ala
[3456] 1 5 10
[3457] <210> 104
[3458] <211> 10
[3459] <212> PRT
[3460] <213> 人工序列
[3461] <220>
[3462] <223> 合成肽
[3463] <400> 104
[3464] Leu Ala His Arg Asp Thr Thr Lys Asn Ala
[3465] 1 5 10
[3466] <210> 105
[3467] <211> 10
[3468] <212> PRT
[3469] <213> 人工序列
[3470] <220>

[3471] <223> 合成肽

[3472] <400> 105

[3473] Leu Ala Ile Ser Asp Gln Thr Asn His Ala

[3474] 1 5 10

[3475] <210> 106

[3476] <211> 10

[3477] <212> PRT

[3478] <213> 人工序列

[3479] <220>

[3480] <223> 合成肽

[3481] <400> 106

[3482] Leu Ala Lys Gln Lys Ser Ala Ser Thr Ala

[3483] 1 5 10

[3484] <210> 107

[3485] <211> 10

[3486] <212> PRT

[3487] <213> 人工序列

[3488] <220>

[3489] <223> 合成肽

[3490] <400> 107

[3491] Leu Ala Lys Ser Asp Gln Cys Lys Pro Ala

[3492] 1 5 10

[3493] <210> 108

[3494] <211> 10

[3495] <212> PRT

[3496] <213> 人工序列

[3497] <220>

[3498] <223> 合成肽

[3499] <400> 108

[3500] Leu Ala Lys Ser Asp Gln Ser Lys Pro Asp

[3501] 1 5 10

[3502] <210> 109

[3503] <211> 10

[3504] <212> PRT

[3505] <213> 人工序列

[3506] <220>

[3507] <223> 合成肽

[3508] <400> 109

[3509] Leu Ala Lys Ser Asp Gln Ser Asn Pro Ala

[3510] 1 5 10

[3511] <210> 110

[3512] <211> 10

[3513] <212> PRT

[3514] <213> 人工序列

[3515] <220>

[3516] <223> 合成肽

[3517] <400> 110

[3518] Leu Ala Lys Ser Tyr Gln Ser Lys Pro Ala

[3519] 1 5 10

[3520] <210> 111

[3521] <211> 10

[3522] <212> PRT

[3523] <213> 人工序列

[3524] <220>

[3525] <223> 合成肽

[3526] <400> 111

[3527] Leu Ala Asn Gln Asp Thr Thr Lys Asn Ala

[3528] 1 5 10

[3529] <210> 112

[3530] <211> 10

[3531] <212> PRT

[3532] <213> 人工序列

[3533] <220>

[3534] <223> 合成肽

[3535] <400> 112

[3536] Leu Ala Pro Gln Asn Thr Thr Lys Asn Ala

[3537] 1 5 10

[3538] <210> 113

[3539] <211> 10

[3540] <212> PRT

[3541] <213> 人工序列

[3542] <220>

[3543] <223> 合成肽

[3544] <400> 113

[3545] Leu Ala Pro Ser Ser Ile Gln Lys Pro Ala

[3546] 1 5 10

[3547] <210> 114

[3548] <211> 10

[3549] <212> PRT
[3550] <213> 人工序列
[3551] <220>
[3552] <223> 合成肽
[3553] <400> 114
[3554] Leu Ala Gln Gln Asp Thr Thr Lys Asn Ala
[3555] 1 5 10
[3556] <210> 115
[3557] <211> 10
[3558] <212> PRT
[3559] <213> 人工序列
[3560] <220>
[3561] <223> 合成肽
[3562] <400> 115
[3563] Leu Ala Tyr Gln Asp Thr Thr Lys Asn Ala
[3564] 1 5 10
[3565] <210> 116
[3566] <211> 10
[3567] <212> PRT
[3568] <213> 人工序列
[3569] <220>
[3570] <223> 合成肽
[3571] <400> 116
[3572] Leu Asp His Gln Asp Thr Thr Lys Asn Ala
[3573] 1 5 10
[3574] <210> 117
[3575] <211> 10
[3576] <212> PRT
[3577] <213> 人工序列
[3578] <220>
[3579] <223> 合成肽
[3580] <400> 117
[3581] Leu Asp His Gln Asp Thr Thr Lys Ser Ala
[3582] 1 5 10
[3583] <210> 118
[3584] <211> 10
[3585] <212> PRT
[3586] <213> 人工序列
[3587] <220>

[3588] <223> 合成肽
[3589] <400> 118
[3590] Leu Gly His Gln Asp Thr Thr Lys Asn Ala
[3591] 1 5 10
[3592] <210> 119
[3593] <211> 10
[3594] <212> PRT
[3595] <213> 人工序列
[3596] <220>
[3597] <223> 合成肽
[3598] <400> 119
[3599] Leu Pro His Gln Asp Thr Thr Lys Asn Asp
[3600] 1 5 10
[3601] <210> 120
[3602] <211> 10
[3603] <212> PRT
[3604] <213> 人工序列
[3605] <220>
[3606] <223> 合成肽
[3607] <400> 120
[3608] Leu Pro His Gln Asp Thr Thr Lys Asn Thr
[3609] 1 5 10
[3610] <210> 121
[3611] <211> 10
[3612] <212> PRT
[3613] <213> 人工序列
[3614] <220>
[3615] <223> 合成肽
[3616] <400> 121
[3617] Leu Pro His Gln Asp Thr Thr Asn Asn Ala
[3618] 1 5 10
[3619] <210> 122
[3620] <211> 10
[3621] <212> PRT
[3622] <213> 人工序列
[3623] <220>
[3624] <223> 合成肽
[3625] <400> 122
[3626] Leu Thr His Gln Asp Thr Thr Lys Asn Ala

[3627] 1 5 10

[3628] <210> 123

[3629] <211> 10

[3630] <212> PRT

[3631] <213> 人工序列

[3632] <220>

[3633] <223> 合成肽

[3634] <400> 123

[3635] Leu Thr Lys Asp Ala Thr Lys Thr Ile Ala

[3636] 1 5 10

[3637] <210> 124

[3638] <211> 10

[3639] <212> PRT

[3640] <213> 人工序列

[3641] <220>

[3642] <223> 合成肽

[3643] <400> 124

[3644] Leu Thr Pro Gln Asp Thr Thr Lys Asn Ala

[3645] 1 5 10

[3646] <210> 125

[3647] <211> 10

[3648] <212> PRT

[3649] <213> 人工序列

[3650] <220>

[3651] <223> 合成肽

[3652] <400> 125

[3653] Leu Val His Gln Asp Thr Thr Lys Asn Ala

[3654] 1 5 10

[3655] <210> 126

[3656] <211> 10

[3657] <212> PRT

[3658] <213> 人工序列

[3659] <220>

[3660] <223> 合成肽

[3661] <400> 126

[3662] Leu Ala Lys Ala Asn Gln Asn Thr Pro Ala

[3663] 1 5 10

[3664] <210> 127

[3665] <211> 10

[3666] <212> PRT
[3667] <213> 人工序列
[3668] <220>
[3669] <223> 合成肽
[3670] <400> 127
[3671] Leu Ala Thr Thr Pro Ile Thr Lys Pro Ala
[3672] 1 5 10
[3673] <210> 128
[3674] <211> 10
[3675] <212> PRT
[3676] <213> 人工序列
[3677] <220>
[3678] <223> 合成肽
[3679] <400> 128
[3680] Leu Ala Thr Thr Pro Ile Ala Lys Pro Ala
[3681] 1 5 10
[3682] <210> 129
[3683] <211> 10
[3684] <212> PRT
[3685] <213> 人工序列
[3686] <220>
[3687] <223> 合成肽
[3688] <400> 129
[3689] Leu Ala Ile Glu Asp His Thr Lys Ser Ala
[3690] 1 5 10
[3691] <210> 130
[3692] <211> 10
[3693] <212> PRT
[3694] <213> 人工序列
[3695] <220>
[3696] <223> 合成肽
[3697] <400> 130
[3698] Leu Ala Gln Ser Glu His Gln Arg Pro Ala
[3699] 1 5 10
[3700] <210> 131
[3701] <211> 10
[3702] <212> PRT
[3703] <213> 人工序列
[3704] <220>

[3705] <223> 合成肽
[3706] <400> 131
[3707] Leu Ala Lys Ser Pro Asn Lys Asp Asn Ala
[3708] 1 5 10
[3709] <210> 132
[3710] <211> 10
[3711] <212> PRT
[3712] <213> 人工序列
[3713] <220>
[3714] <223> 合成肽
[3715] <400> 132
[3716] Leu Ala Asn Gln Asp Tyr Thr Lys Thr Ala
[3717] 1 5 10
[3718] <210> 133
[3719] <211> 10
[3720] <212> PRT
[3721] <213> 人工序列
[3722] <220>
[3723] <223> 合成肽
[3724] <400> 133
[3725] Leu Ala Asn Ser Thr Asp Gln Thr Arg Ala
[3726] 1 5 10
[3727] <210> 134
[3728] <211> 10
[3729] <212> PRT
[3730] <213> 人工序列
[3731] <220>
[3732] <223> 合成肽
[3733] <400> 134
[3734] Leu Ala Leu Gly Glu Thr Thr Arg Pro Ala
[3735] 1 5 10
[3736] <210> 135
[3737] <211> 10
[3738] <212> PRT
[3739] <213> 人工序列
[3740] <220>
[3741] <223> 合成肽
[3742] <400> 135
[3743] Leu Ala Asn Ser Thr Glu Gln Thr Arg Ala

[3744] 1 5 10

[3745] <210> 136

[3746] <211> 10

[3747] <212> PRT

[3748] <213> 人工序列

[3749] <220>

[3750] <223> 合成肽

[3751] <400> 136

[3752] Leu Ala Gln Ala Asp Thr Thr Lys Asn Ala

[3753] 1 5 10

[3754] <210> 137

[3755] <211> 10

[3756] <212> PRT

[3757] <213> 人工序列

[3758] <220>

[3759] <223> 合成肽

[3760] <400> 137

[3761] Leu Ala Ser Lys Asp Ile Thr Lys Thr Ala

[3762] 1 5 10

[3763] <210> 138

[3764] <211> 10

[3765] <212> PRT

[3766] <213> 人工序列

[3767] <220>

[3768] <223> 合成肽

[3769] <400> 138

[3770] Leu Ala Ser Pro Arg His Asn Lys Lys Cys

[3771] 1 5 10

[3772] <210> 139

[3773] <211> 11

[3774] <212> PRT

[3775] <213> 人工序列

[3776] <220>

[3777] <223> 合成肽

[3778] <400> 139

[3779] Leu Ala His Gln Asp Thr Thr Lys Thr Ile Ala

[3780] 1 5 10

[3781] <210> 140

[3782] <211> 9

[3783] <212> PRT
[3784] <213> 人工序列
[3785] <220>
[3786] <223> 合成肽
[3787] <400> 140
[3788] Leu Ala Ala Gln Gly Thr Ala Asn Leu
[3789] 1 5
[3790] <210> 141
[3791] <211> 10
[3792] <212> PRT
[3793] <213> 人工序列
[3794] <220>
[3795] <223> 合成肽
[3796] <400> 141
[3797] Val Ala Ile Glu Asp His Thr Lys Ser Ala
[3798] 1 5 10
[3799] <210> 142
[3800] <211> 12
[3801] <212> PRT
[3802] <213> 人工序列
[3803] <220>
[3804] <223> 合成肽
[3805] <400> 142
[3806] Leu Ala Lys Ala Asn Gln Asn Thr Pro Lys Asn Ala
[3807] 1 5 10
[3808] <210> 143
[3809] <211> 10
[3810] <212> PRT
[3811] <213> 人工序列
[3812] <220>
[3813] <223> 合成肽
[3814] <220>
[3815] <221> Misc_feature
[3816] <222> (10)..(10)
[3817] <223> Xaa为任何氨基酸
[3818] <400> 143
[3819] Leu Ala His Gln Asp Thr Thr Lys Lys Xaa
[3820] 1 5 10
[3821] <210> 144

[3822] <211> 10
[3823] <212> PRT
[3824] <213> 人工序列
[3825] <220>
[3826] <223> 合成肽
[3827] <400> 144
[3828] Leu Ala His Gln Asp Thr Thr Lys Lys Asp
[3829] 1 5 10
[3830] <210> 145
[3831] <211> 10
[3832] <212> PRT
[3833] <213> 人工序列
[3834] <220>
[3835] <223> 合成肽
[3836] <400> 145
[3837] Leu Ala His Gln Asp Thr Thr Lys Lys Val
[3838] 1 5 10
[3839] <210> 146
[3840] <211> 10
[3841] <212> PRT
[3842] <213> 人工序列
[3843] <220>
[3844] <223> 合成肽
[3845] <400> 146
[3846] Leu Ala His Gln Asp Thr Thr Lys Lys Met
[3847] 1 5 10
[3848] <210> 147
[3849] <211> 7
[3850] <212> PRT
[3851] <213> 人工序列
[3852] <220>
[3853] <223> 合成肽
[3854] <400> 147
[3855] Leu Gly Glu Thr Thr Arg Pro
[3856] 1 5
[3857] <210> 148
[3858] <211> 11
[3859] <212> PRT
[3860] <213> 人工序列

[3861] <220>
[3862] <223> 合成肽
[3863] <220>
[3864] <221> Misc_feature
[3865] <222> (9)..(9)
[3866] <223> Xaa为Lys、Thr、Asn或His
[3867] <220>
[3868] <221> Misc_feature
[3869] <222> (10)..(10)
[3870] <223> Xaa为Ala、Thr、Val、Ile、Met或Asp
[3871] <220>
[3872] <221> Misc_feature
[3873] <222> (11)..(11)
[3874] <223> Xaa为Ala
[3875] <400> 148
[3876] Leu Ala His Gln Asp Thr Thr Lys Xaa Xaa Xaa
[3877] 1 5 10
[3878] <210> 149
[3879] <211> 10
[3880] <212> PRT
[3881] <213> 人工序列
[3882] <220>
[3883] <223> 合成肽
[3884] <220>
[3885] <221> Misc_feature
[3886] <222> (3)..(3)
[3887] <223> Xaa为Ala、Pro、Asp或His
[3888] <220>
[3889] <221> Misc_feature
[3890] <222> (5)..(5)
[3891] <223> Xaa为Gly或Asp
[3892] <220>
[3893] <221> Misc_feature
[3894] <222> (7)..(7)
[3895] <223> Xaa为Ala、Thr或Lys
[3896] <220>
[3897] <221> Misc_feature
[3898] <222> (8)..(8)
[3899] <223> Xaa为Asn、Glu、Lys、Arg或Thr

[3900] <220>
[3901] <221> Misc_feature
[3902] <222> (9)..(9)
[3903] <223> Xaa为Leu、Asn、Lys或Thr
[3904] <220>
[3905] <221> Misc_feature
[3906] <222> (10)..(10)
[3907] <223> Xaa为Ala、Thr、Asp、Val或Met
[3908] <400> 149
[3909] Leu Ala Xaa Gln Xaa Thr Xaa Xaa Xaa Xaa
[3910] 1 5 10
[3911] <210> 150
[3912] <211> 10
[3913] <212> PRT
[3914] <213> 人工序列
[3915] <220>
[3916] <223> 合成肽
[3917] <220>
[3918] <221> Misc_feature
[3919] <222> (1)..(1)
[3920] <223> Xaa为Val或Leu
[3921] <220>
[3922] <221> Misc_feature
[3923] <222> (3)..(3)
[3924] <223> Xaa为Ile、Val、His或Asp
[3925] <220>
[3926] <221> Misc_feature
[3927] <222> (4)..(4)
[3928] <223> Xaa为Glu、Ser、Lys或Gln
[3929] <220>
[3930] <221> Misc_feature
[3931] <222> (6)..(6)
[3932] <223> Xaa为His、Ser或Thr
[3933] <220>
[3934] <221> Misc_feature
[3935] <222> (9)..(9)
[3936] <223> Xaa为Ser、Ala、Asn、His或Lys
[3937] <400> 150
[3938] Xaa Ala Xaa Xaa Asp Xaa Thr Lys Xaa Ala

[3939] 1 5 10

[3940] <210> 151

[3941] <211> 12

[3942] <212> PRT

[3943] <213> 人工序列

[3944] <220>

[3945] <223> 合成肽

[3946] <220>

[3947] <221> Misc_feature

[3948] <222> (1)..(1)

[3949] <223> Xaa为Leu

[3950] <220>

[3951] <221> Misc_feature

[3952] <222> (2)..(2)

[3953] <223> Xaa为Ala

[3954] <220>

[3955] <221> Misc_feature

[3956] <222> (3)..(3)

[3957] <223> Xaa为 Lys、Leu或Pro

[3958] <220>

[3959] <221> Misc_feature

[3960] <222> (5)..(5)

[3961] <223> Xaa为 Asn、His、Pro或Tyr

[3962] <220>

[3963] <221> Misc_feature

[3964] <222> (7)..(7)

[3965] <223> Xaa为 Asn、Gly、Val或Asp

[3966] <220>

[3967] <221> Misc_feature

[3968] <222> (9)..(9)

[3969] <223> Xaa为 Pro或Thr

[3970] <400> 151

[3971] Xaa Xaa Xaa Ala Xaa Gln Xaa Thr Xaa Lys Asn Ala

[3972] 1 5 10

[3973] <210> 152

[3974] <211> 27

[3975] <212> RNA

[3976] <213> 人工序列

[3977] <220>

[3978] <223> 合成序列

[3979] <400> 152

[3980] cgcaaucagu gaaugcuuau acauccg 27

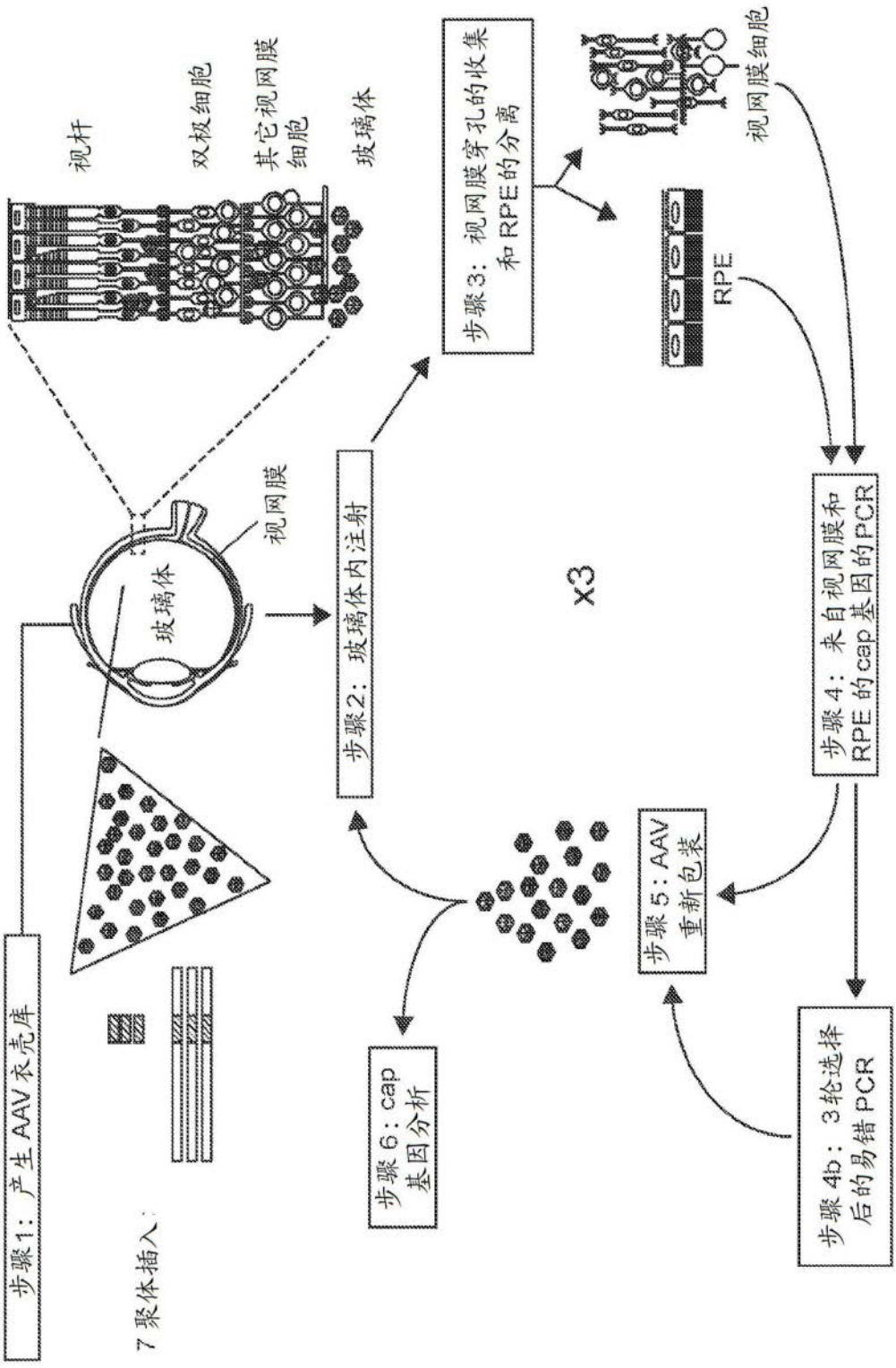

视杆
双极细胞
其它视网膜细胞
玻璃体
视网膜细胞
RPE
视网膜
玻璃体
步骤1：产生AAV衣壳库
7聚体插入
步骤2：玻璃体内注射
步骤3：视网膜穿孔的收集和RPE的分离
x3
步骤4：来自视网膜和RPE的cap基因的PCR
步骤5：AAV重新包装
步骤6：cap基因分析
步骤4b：3轮选择后的易错PCR

图1

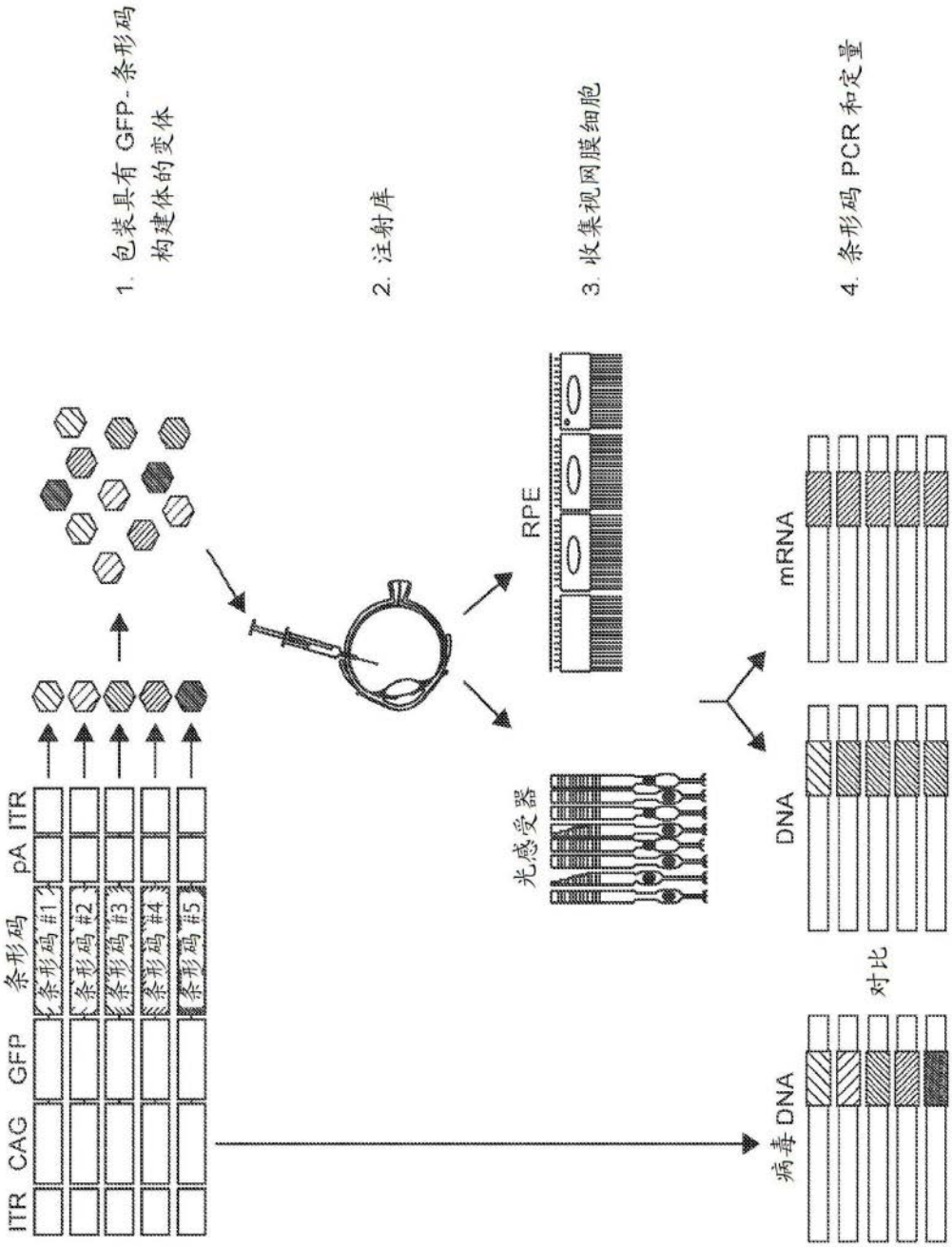

1. 包装具有 GFP-条形码
构建体的变体
2. 注射库
3. 收集视网膜细胞
4. 条形码 PCR 和定量
ITR
CAG
GFP
条形码
pA
ITR
条形码#1
条形码#2
条形码#3
条形码#4
条形码#5
RPE
光感受器
mRNA
DNA
病毒 DNA
对比

图2

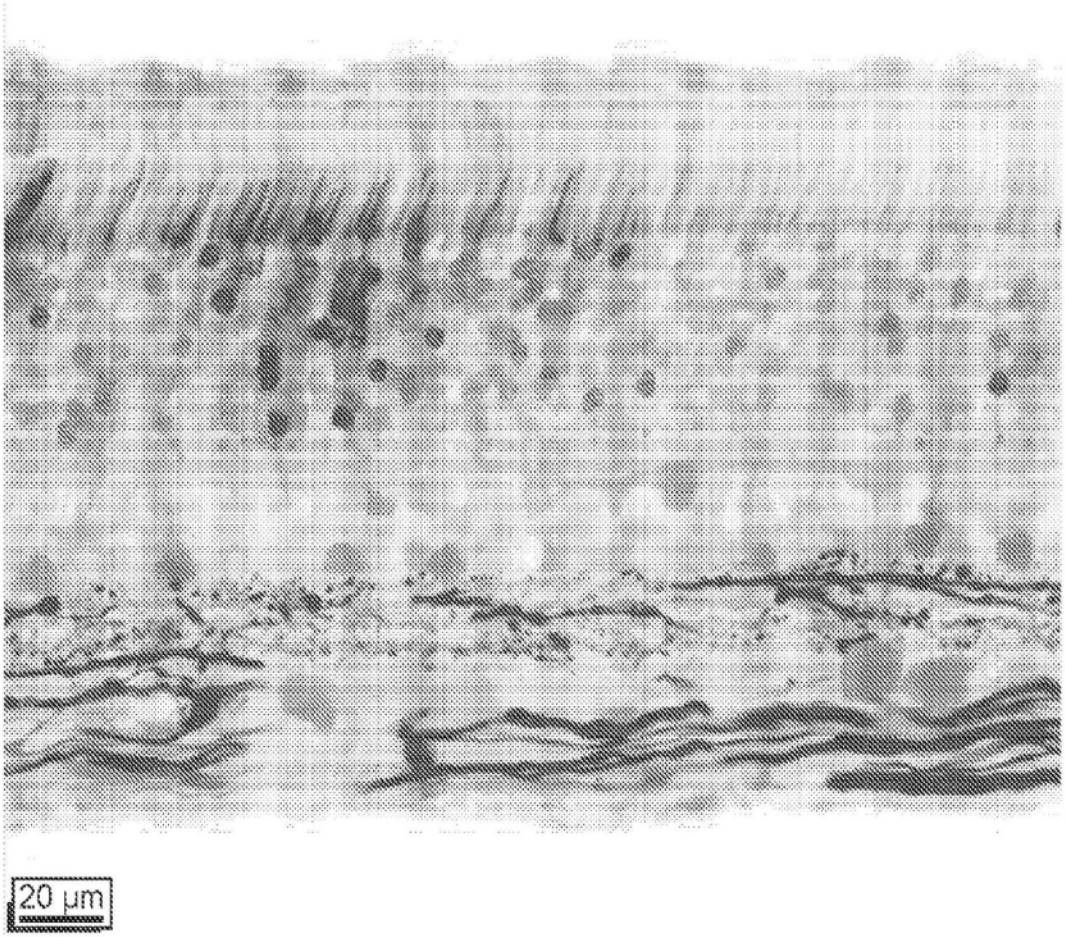


图3

```
AAV2 VP1     1 MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPFNGLD
AAV2 VP1    61 KGEPVNEADAAALEHDKAYDRQLDSGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQ
AAV2 VP1   121 AKKRVLEPLGLVEEPVKTAPGKKRPVEHSPVEPDSSSGTGKAGQQPARKRLNFGQTGDAD
AAV2 VP1   181 SVPDPQPLGQPPAAPSGLGTNTMATGSGAPMADNNEGADGVGNSSGNWHCDSTWMGDRVI
AAV2 VP1   241 TTSTRTWALPTYNNHLYKQISSQSGASNDNHYFGYSTPWGYFDFNRFHCHFSPRDWQRLI
AAV2 VP1   301 NNNWGFRPKRLNFKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGSAHQG
AAV2 VP1   361 CLPPFPADVFMVPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFTFSYTFEDVPF
AAV2 VP1   421 HSSYAHSQSLDRLMNPLIDQYLYYLSRTNTPSGTTTQSRLQFSQAGASDIRDQSRNWLPG
AAV2 VP1   481 PCYRQQRVSKTSADNNNSEYSWTGATKYHLNGRDSLVNPGPAMASHKDDEEKFFPQSGVL
AAV2 VP1   541 IFGKQGSEKTNVDIEKVMITDEEEIRTTNPVATEQYGSVSTNLQRGNRQAATADVNTQGV
AAV2 VP1   601 LPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPPPQILIKNTPVPANPSTT
AAV2 VP1   661 FSAAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYNKSVNVDFTVDTNGVY
AAV2 VP1   721 SEPRPIGTRYLTR  (SEQ ID NO:1)
```

图4

```
AAV-2    570  PVATEQYGSVSTNLQRGNRQAATADVNTQGVLPGMVWQDRDV  611  (SEQ ID NO:2)
AAV-1    571  PVATEREGTVAVNFQSSSTDPATGDVHAMGALPGMVWQDRDV  612  (SEQ ID NO:3)
AAV-5    560  RVAYNVGGQMATNNQSSTTAPATGTYNLQEIVPGSVWMERDV  601  (SEQ ID NO:4)
AAV-6    571  PVATEREGTVAVNLQSSSTDPATGDVHVMGALPGMVWQDRDV  612  (SEQ ID NO:5)
AAV-7    572  PVATEEYGIVSSNLQAANTAAQTQVVNNQGALPGMVWQNRDV  613  (SEQ ID NO:6)
AAV-8    573  PVATEEYGIVADNLQQQNTAPQIGTVNSQGALPGMVWQNRDV  614  (SEQ ID NO:7)
AAV-9    571  PVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDRDV  612  (SEQ ID NO:8)
AAV-10   573  PVATEQYGVVADNLQQANTGPIVGNVNSQGALPGMVWQNRDV  614  (SEQ ID NO:9)
```

图5

```
AAV1      --TFSYTFEEVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQ--NQSGSAQNKDLLFSRGS 467
AAV6      --TFSYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQ-NQSGSAQNKDLLFSRGS 467
AAV3      ---FSYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQGTTSGTTNQSRLLFSQAG 467
AAV2      ---FSYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTN-TPSGTTTQSRLQFSQAG 466
AAV8      NFQFTYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQTT-GGTANTQTLGFSQGG 469
AAV8.1    NFQFTYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQTT-GGTANTQTLGFSQGG 469
AAV8_rh8    FQFSYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLVRTQTTGTGGTQTLAFSQAGPS 469
AAV10     NFEFSYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQST-GGTQGTQQLLFSQAG 469
AAV7      --FEFSYSFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLARTQSNPGGTAGNRELQFYQGG 469
AAV9      -FQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSKTI--NGSGQNQQTLKFSVAG 467
AAV9.1    -FQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSKTI--NGSGQNQQTLKFSVAG 467
AAV5      NFEFTYNFEEVPFHSSFAPSQNLFKLANPLVDQYLYRFVSTN----------NTGGVQFNKNL 453
                    *:*  **:*******:* **.* :* ***:*****  :   *       : *

AAV1      PAGMSVQPKNWLPGPCYRQQRVSKTKTDNNNSNFTWTGASKYNLNGRESIINPGTAMASH 527
AAV6      PAGMSVQPKNWLPGPCYRQQRVSKTKTDNNNSNFTWTGASKYNLNGRESIINPGTAMASH 527
AAV3      PQSMSLQARNWLPGPCYRQQRLSKTANDNNNSNFPWTAASKYHLNGRDSLVNPGPAMASH 527
AAV2      ASDIRDQSRNWLPGPCYRQQRVSKTSADNNNSEYSWTGATKYHLNGRDSLVNPGPAMASH 526
AAV8      PNTMANQAKNWLPGPCYRQQRVSTTTGQNNNSNFAWTAGTKYHLNGRNSLANPGIAMATH 529
AAV8.1    PNTMANQAKNWLPGPCYRQQRVSTTTGQNNNSNFAWTAGTKYHLNGRNSLANPGIAMATH 529
AAV8_rh8  S--MANQARNWVPGPCYRQQRVSTTTNQNNNSNFAWTGAAKTKLNGRDSLMNPGVAMASH 527
AAV10     PANMSAQAKNWLPGPCYRQQRVSTTLSQNNNSNFAWTGATKYHLNGRDSLVNPGVAMATH 529
AAV7      PSTMAEQAKNWLPGPCFRQQRVSKTLDQNNNSNFAWTGATKYHLNGRNSLVNPGVAMATH 529
AAV9      PSNMAVQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASH 527
AAV9.1    PSNMAVQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASH 527
AAV5      AGRYANTYKNWFPGPMGRTQGWNLGSGVNRASVSAFATTNRMELEGASYQVPPQPNGMTN 513
                    :*::***  * *  .  *. *  .::.  .  *:* .  *     ::
```

图6A

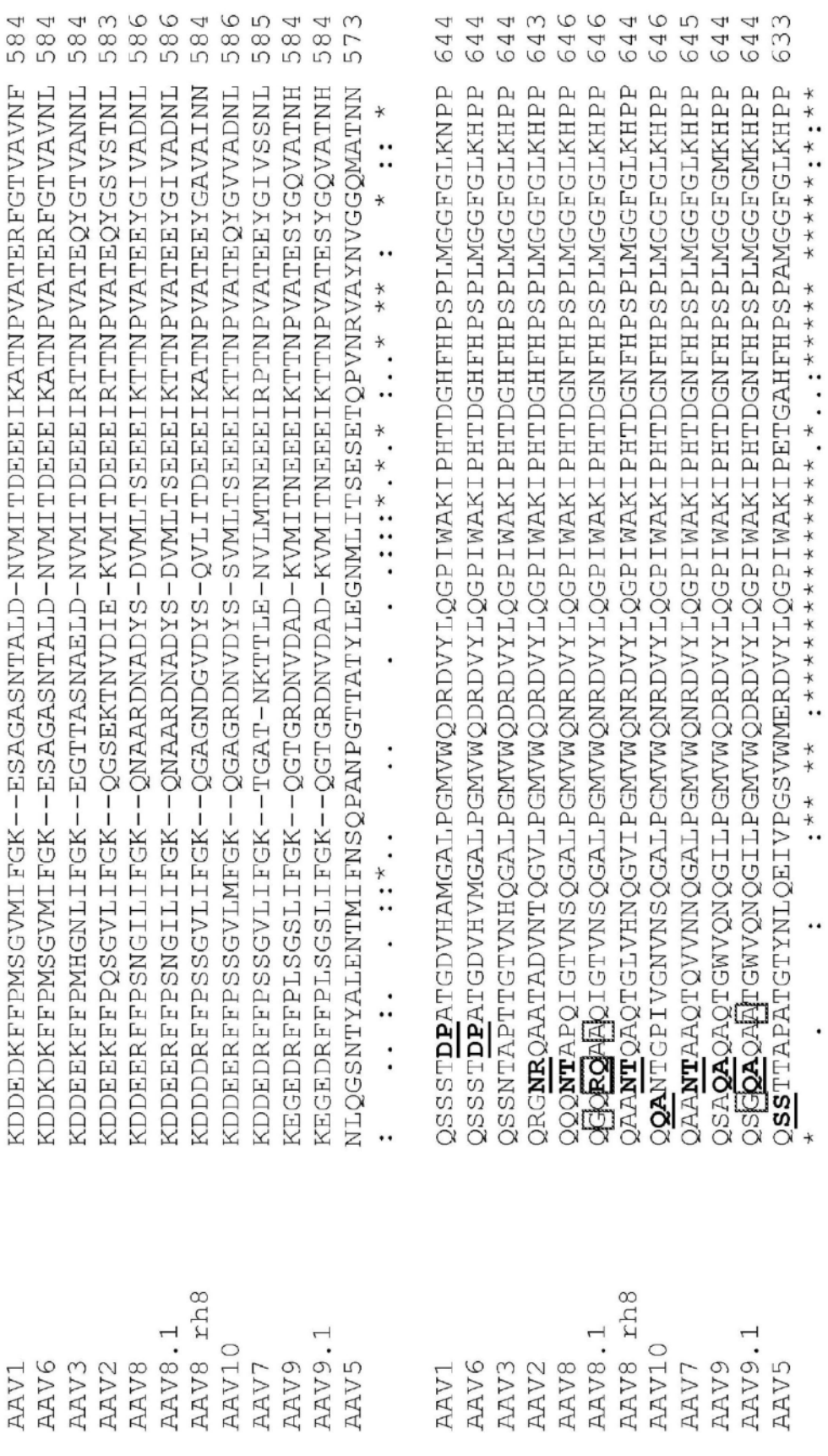

AAV1 KDDEDKFFPMSGVMIFGK--ESAGASNTALD-NVMITDEEEIKATNPVATERFGTVAVNF 584
AAV6 KDDKDKFFPMSGVMIFGK--ESAGASNTALD-NVMITDEEEIKATNPVATERFGTVAVNL 584
AAV3 KDDEEKFFPMHGNLIFGK--EGTTASNAELD-NVMITDEEEIRTTNPVATEQYGTVANNL 584
AAV2 KDDEEKFFPQSGVLIFGK--QGSEKTNVDIE-KVMITDEEEIRTTNPVATEQYGSVSTNL 583
AAV8 KDDEERFFPSNGILIFGK--QNAARDNADYS-DVMLTSEEEIKTTNPVATEEYGIVADNL 586
AAV8.1 KDDEERFFPSNGILIFGK--QNAARDNADYS-DVMLTSEEEIKTTNPVATEEYGIVADNL 586
AAV8 rh8 KDDDDRFFPSSGVLIFGK--QGAGNDGVDYS-QVLITDEEEIKATNPVATEEYGAVAINN 584
AAV10 KDDEERFFPSSGVLMFGK--QGAGRDNVDYS-SVMLTSEEEIKTTNPVATEQYGVVADNL 586
AAV7 KDDEDRFFPSSGVLIFGK--TGAT-NKTTLE-NVLMTNEEEIRPTNPVATEEYGIVSSNL 585
AAV9 KEGEDRFFPLSGSLIFGK--QGTGRDNVDAD-KVMITNEEEIKTTNPVATESYGQVATNH 584
AAV9.1 KEGEDRFFPLSGSLIFGK--QGTGRDNVDAD-KVMITNEEEIKTTNPVATESYGQVATNH 584
AAV5 NLQGSNTYALENTMIFNSQPANPGTTATYLEGNMLITSESETQPVNRVAYNVGGQMATNN 573
: .. :. . ::*.. .. . . .:::*.*.* :..* ** : * :: *
AAV1 QSSSTDPATGDVHAMGALPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKNPP 644
AAV6 QSSSTDPATGDVHVMGALPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPP 644
AAV3 QSSNTAPTTGTVNHQGALPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPP 644
AAV2 QRGNRQAATADVNTQGVLPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPP 643
AAV8 QQQNTAPQIGTVNSQGALPGMVWQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPP 646
AAV8.1 QGQRQAAQIGTVNSQGALPGMVWQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPP 646
AAV8 rh8 QAANTQAQTGLVHNQGVIPGMVWQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPP 644
AAV10 QQANTGPIVGNVNSQGALPGMVWQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPP 646
AAV7 QAANTAAQTQVVNNQGALPGMVWQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPP 645
AAV9 QSAQAQAQTGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPP 644
AAV9.1 QSGQAQAQTGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPP 644
AAV5 QSSTTAPATGTYNLQEIVPGSVWMERDVYLQGPIWAKIPETGAHFHPSPAMGGFGLKHPP 633
* . : :** ** :********** .*..:***** ***** *:*:**

图6B

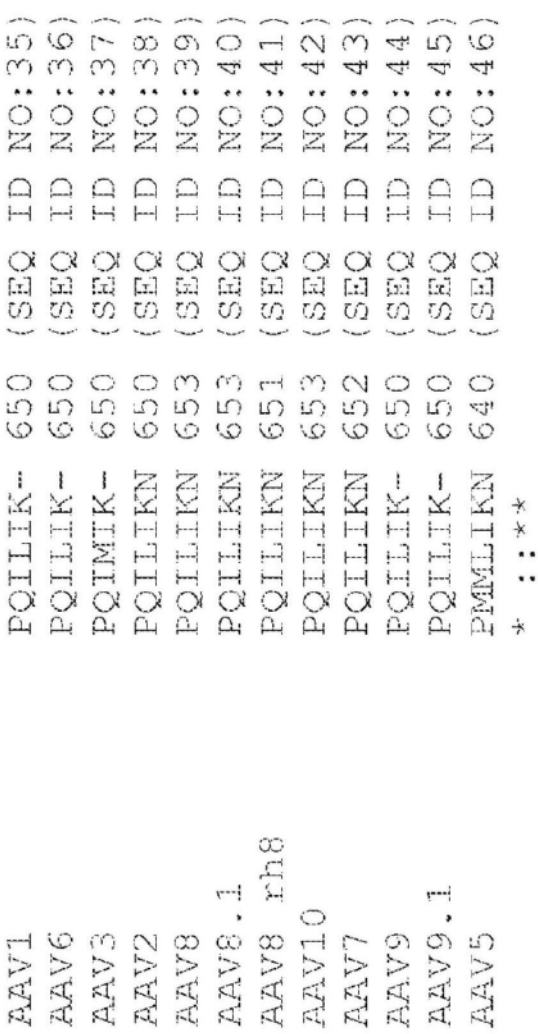

AAV1 PQILIK- 650 (SEQ ID NO:35)
AAV6 PQILIK- 650 (SEQ ID NO:36)
AAV3 PQIMIK- 650 (SEQ ID NO:37)
AAV2 PQILIKN 650 (SEQ ID NO:38)
AAV8 PQILIKN 653 (SEQ ID NO:39)
AAV8.1 PQILIKN 653 (SEQ ID NO:40)
AAV8 rh8 PQILIKN 651 (SEQ ID NO:41)
AAV10 PQILIKN 653 (SEQ ID NO:42)
AAV7 PQILIKN 652 (SEQ ID NO:43)
AAV9 PQILIK- 650 (SEQ ID NO:44)
AAV9.1 PQILIK- 650 (SEQ ID NO:45)
AAV5 PMMLIKN 640 (SEQ ID NO:46)
* ::**

图6C

视网膜劈裂蛋白-1
智人

```
  1 msrkiegfll llifgyeatl glsstedege dpwyqkackc dcgggpnalw sagatsldci
 61 pecpyhkplg fesgevtpdq itcsnpeqyv gwysswtank arlnsqgfgc awlskfqdss
121 qwlqidlkei kvisgiltgg rcdidewmtk ysvqyrtder lnwiyykdqt gnnrvfygns
181 drtstvqntl rppiisrfir liplqwhvri airmellecv skca (SEQ ID NO:10)
```

图7A

BDNF
智人

```
  1 mtilfltmvi syfgcmkaap mkeanirgqg glaypgvrth gtlesvngpk agsrgltsla
 61 dtfehvieel ldedhkvrpn eemnkdadly tsrvmlssqv plepplfll eeyknyldaa
121 nmsmmvlrhs dparrgelsv cdsisewvta adkktavdms ggtvtvlekv pvskgqlkqy
181 fyetkcnpmg ytkegcrgid krhwnsqcrt tqsyvralтm dskkrigwrf iridtscvct
241 ltikrgr (SEQ ID NO:11)
```

图7B

RPE65
智人

```
   1 msiqvehpag gykklfetve elsspltahv tgriplwltg sllrcgpglf evgsepfyhl
  61 fdgqallhkf dfkeghvtyh rrfirtdayv ramtekrivi tefgtcafpd pcknifsrff
 121 syfrgvevtd nalvnvypvg edyyactetn fitkinpetl etikqvdlcn yvsvngatah
 181 phiendgtvy nignefgknf siaynivkip plqadkedpi skseivvqfp csdrfkpsyv
 241 hsfgltpnyi vfvetpvkin lfkflsswsl wganymdcfe snetmgvwlh iadkkrkkyl
 301 nnkyrtspfn lfhhintyed ngfllvdlcc wkgfefvyny lylanlrenw eevkknarka
 361 pqpevrryvl plnidkadtg knlvtlpntt atailcsdet iwlepevlfs gprqafefpq
 421 inyqkycgkp ytyayglgln hfvpdrlckl nvktketwvw qepdsypsep ifvshpdale
 481 eddqvvlsvv vspgaggkpa yllllnakdl sevaraevei nipvtfhglf kks
        (SEQ ID NO:12)
```

图7C

外周蛋白-2
智人

```
   1 mallkvkfdq kkrvklaqgl wlmnwfsvla giiifslglf lkielrkrsd vmnnseshfv
  61 pnsliqmgvl scvfnslagk icydaldpak yarwkppwlkp ylaicvlfni illflvalccf
 121 llrgslentl gqglkngmky yrdtdtpgrc fmkktidmlq iefkccqnng frdwfeiqwi
 181 snryldfssk evkdriksnv dgrylvdgvp fsccnpsspr pciqyqitnn sahysydhqt
 241 eelnlwvrgc raallsyyss lmnsmgvvtl liwlfevtit iglrylqtsl dgvsnpeese
 301 sesqgwller svpetwkafl esvkkliqkqn qveaeqgadaq qapeaq (SEQ ID NO:13)
```

图7D

外周蛋白
智人

```
   1 mshhpsglra gfsstsyyrt fgpppslspg afsyssssrf ssslgsas psssvrlgsf
  61 rspragagal lrlpseridf smaealngef latrsnekqe lgelndrfan flekvrfleq
 121 qnaalrgels qargqeqara dqlcqgelre lrrelellgr erdrvgverd glaedlaalk
 181 qrleeetrkr edaehnlvlf rkdvddatls rlelerkies lmdeieflkk lheeelrdlq
 241 vsvesqqvqq veveatvkpe ltaalrdira gyesiaaknl qeaeewyksk yadlsdaaar
 301 nhealrgakq emaesrrqlq sltcevdgLr gtneallrql releqfaLe aggyqagaar
 361 leelrqlke emarhlreyq ellnvkmald ieiatyrkll egeesrisvp vhsfaslnik
 421 ttvpevepqq dshszktvli ktietrngev vtesqkegrs eldkssahsy (SEQ ID NO:14)
```

图7E

RPGR-相互作用蛋白-1
智人

```
   1 mshlvdptsg dlpvrdidai plvlpaskgk nmktqpplsr mnreeledsf frlredhmlv
  61 kelswkqqde ikrlrttllr ltaagrdlrv aeeaaplset arrgqkagwr qrlsmhqrpq
 121 mhrlqghfhc vgpasprrag prvqvghrql htagapvpek pkrgprdrls ytappsfkeh
 181 atnenrgeva skpselvsgs nsiisfssvi smakpiglcm pnsahimasn tmqveeppks
 241 pekmwpkden feqrssleca qkaaelrasi kekvelirlk klihernasl vmtkaqltev
 301 qeayetllqk nqgilsaahe allkqvnelr aelkeeskka vslksqledv silqmtlkef
 361 qervedleke rkllndnydk llesmldssd sssqphwsne liaeqlqqqv sqlqdqldae
 421 ledkrkvlle lsrekaqned lklevtnilq khkqevellq naatisqppd rqsepathpa
 481 vlqentqiep sepknqeekk lsqvlnelqv shaettlele ktrdmlilqr kinvcyqeel
 541 eammtkadnd nrdhkekler ltrlldlknn rikqlegilr shdlptseql kdvaygtrpl
 601 slcletlpah gdedkvdisl lhqgenlfel nihqafltsa alaqaqdtqp ttfctysfyd
 661 fethctplsv gpqplydfts qyvmetdsif lhylqeasar ldihqamase hstlaagwic
 721 fdrvletvek vhglatliqa ggeefgvley wmrlrfpikp slqacnkrkk aqvylstdvl
 781 ggrkaqeeef rseswepqme lwieitkccg lrsrwlqtqp spyavyrfft fsdhdtaiip
 841 asmpyfrdq arfpvlvtsd ldhylrreal sihvfddedl epgsylqrar vpllplakne
 901 sikgdfnltd paekpngsiq vqldwkfpyi ppesflkpea qtkgkdtkds skisseeeka
 961 sfpsqdqmas pevpieaggy rskrkpphgg erkekehqvv sysrrkhgkr igvqgknrme
1021 ylslnilngn tpeqvnytew kfsetnsfig dgfknqheee emtlshsalk qkeplhpvnd
1081 kesseqgsev seaqttdsdd vivppmsqky pkadsekmci eivslafype aevmsdenik
1141 qvyveykfyd lplsetetpv slrkpragee ihfhfskvid ldpqeqggrr rflfdmlngq
1201 dpdqghlkft vvsdpldeek keceevgyay lqlwqilesg rdileqeldi vspedlatpi
1261 grlkvslqaa avlhaiykem tedlfs (SEQ ID NO:15)
```

图7F

Rab 护送蛋白-1

```
   1 madtlpsefd vivigtglpe siiaaacsrs qrrvlhvdsr syyggnwasf sfsgllswlk
  61 eyqensdivs dspvwqdqil eneeaialsr kdktiqhvev fcyasqdlhe dveeagalqk
 121 nhalvtsans teaadsaflp tedeslstms cemlteqtps sdpenalevn gaevtgeken
 181 hcddktcvps tsaedmsenv piaedtteqp kknritysqi ikegrrfnid lvsklysrg
 241 llidlliksn vsryaefkni trilafregr veqvpcsrad vfnskqltmv ekrmimkflt
 301 fcmeyekypd eykgyeeitf yeylktqklt pnlqyivmhs iamtsetass tidglkatkn
 361 flhclgrygn tpflfplygq gelpqcfcrm cavfggiycl rhsvqclvvd kesrkckaii
 421 dqfqqriise hflvedsyfp enmcsrvqyr qisravlitd rsvlktdsdq qisiltvpae
 481 epgtfavrvi elcsstmtcm kgtylvhltc tsskt aredl esvvqklfvp ytemeieneq
 541 vekprilwal yfnmrdssdi srscyndlps nvyvcsgpdc glgndnavkq aetlfqeicp
 601 nedfcppppn pediildgds lqpeasessa ipeansetfk estnlgnlee sse
                    (SEQ ID NO:16)
```

图7G

RdCVF的212氨基酸同种型

```
   1 maslfsgril irnnsdqdel dteaevsrrl enrlvllffg agacpqcqaf vpilkdffvr
  61 ltdefyvlra aqlalvyvsq dsteeqqdlf lkdmpkkwlf lpfeddlrrd lgrqfsverl
 121 pavvvlkpdg dvltrdgade iqrlgtacfa nwqeaaevld rnfqlpedle dqeprsltec
 181 lrrhkyrvek aarggrdpgg gggeeggagg lf (SEQ ID NO:17)
```

图7H

RdCVF的156氨基酸同种型(同种型1)

```
  1 mvdilgerhl vtckgatvea eaalqmkvva lyfaaarcap srdftpllcd fytalvaear
 61 rpapfevvfv sadgssqeml dfmrelhgaw lalpfhdpyr helrkrynvt aipklvivkq
121 ngevitnkgr kqirerglac fqdwveaadi fqnfsv (SEQ ID NO:18)
```

图7I

RdCVF 的135氨基酸同种型（同种型2）

```
   1 mvdilgerhl vtckgatvea eaalqnkvva lyfaaarcap srdftpllcd fytalvaear
  61 rpapfevvfv sadgssqeml dfmrelhgaw lalpfhdpyr qrslallprl ecsgvilahc
 121 nicllgssds lalas (SEQ ID NO:19)
```

图7J

视杆cGMP特异性3',5'-环状磷酸二酯酶子单元α (PDE6α)
GenBank NP_000431

```
   1 mgevtaeeve kfldsnigfa kqyynlhyra klisdilgak eaavdfsnyh spssmeesei
  61 ifdllrdfqe nlqtekcifn vmkklcfllq adrmslfmyr trngiaelat rlfnvhkdav
 121 ledclvmpdq eivfpldmgi vghvahskki anvpnteede hfcdfvdilt eyktknilas
 181 pimngkdvva iimavnkvdg shftkrdeei llkylnfanl imkvyhlsyl hncetrrgqi
 241 llwsgskvfe eltdierqfh kalytvrafl ncdrysvgll dmtkqkeffd vwpvlmgevp
 301 pysqprtpdg reinfykvid yilhqkedik vipnpppdhw alvsqlpayv aqnqlicnim
 361 napaedffaf qkepldesqw miknvlsmpi vnkkeeivgv atfynrkdqk pfdemdetlm
 421 eslqflgws vlnpdtyesm nklenrkdif qdivkyhvkc dneeiqkilk trevygkepw
 481 eceeeelaei lqaelpdadk yeinkfhfsd lpltelelvk cgiqmyyelk vvdkfhipqe
 541 alvrfmysls kgyrkityhn wrhgfnvgqt mfslivtgkl kryftdleal amvtaafchd
 601 idhrgtnnly qmksqnplak lhgssilerh hlefgktllr deslnifqnl nrrqhehaih
 661 mmdiaiiatd lalyfkkrtm fqkivdqskt yeseqewtqy mnleqtrkei vmammmtacd
 721 lsaitkpwev qsqvallvaa efweqgdler tvlqqnpipm mdrnkadeip klqvvgfidfv
 781 ctfvykefsr fheeitpmld qitmnrkewk aladeydakm kvqeekkqkq qsaksaaagn
 841 qpgqnpspgg attskscciq (SEQ ID NO:20)
```

图7K

视杆 cGMP 特异性 3',5'- 环状磷酸二酯酶子单元 β 同种型 1 (PDE6β 同种型 1)
GenBank NP_000274

```
   1 mslseegars fldqmpdfar qyfgkklspe nvaaacedgc ppdcdslrdl cqveestall
  61 elvqdmqesi nmervvfkvl rrlctllqad rcslfmyrqr ngvaelatrl fsvqpdsvle
 121 dclvppdsei vfpldigvvg hvaqtkkmvn vedvaecphf ssfadeltdy ktknmlatpi
 181 mngkdvvavi mavnklngpf ftsededvfl kylnfatlyl kiyhlsylhn cetrrgqvll
 241 wsankvfeel tdierqfhka fytvraylnc erysvglldm tkekeffdvw svlmgesqpy
 301 sgprtpdgre ivfykvidyi lhgkeeikvi ptpsadhwal asglpsyvae sgficnimma
 361 sademfkfqe galddsgwli knvismpivn kkeeivgvat fynrkdgkpf degdevlmes
 421 ltqflqwsvm ntdtydkmnk lenrkdiaqd mvlyhvkcdr deiqliptr arlqkepadc
 481 dedelgeilk eelpgpttfd iyefhfsdle cteldlvkcg iqmyyelgvv rkfqipqevl
 541 vrflfsiskg yrrityhnwr hgfnvaqtmf tllmtgklks yytdleafam vtaglchdid
 601 hrgtnnlyqm ksqmplaklh gssllerhhl efgkflisee tlniyqnlnr rqhehvihlm
 661 diaiiatdla lyfkkramfq kivdesknyq dkkswvcyls lcttrkcivm ammtacdls
 721 aitkpwevqs kvallvaaef weqqdlertv ldqqpipmmd rnkaaelpkl qvgfidfvct
 781 fvykefsrfh eeilpmfdrl qnnrkewkal adeyeakvka leekeeeerv aakkvgteic
 841 nggpapksst ccil (SEQ ID NO:21)
```

图7L

视杆 cGMP 特异性 3',5'- 环状磷酸二酯酶子单元 β 同种型 2 (PDE6β 同种型 2)
GenBank NP_001138763

```
   1 mslseeqars fldqnpdfar qyfgkklspe nvaaacedgc ppdcdslrdl cqveestall
  61 elvqdmqesi nmervvfkvl rrlctllqad rcslfmyrqr ngvaelatrl fsvqpdsvle
 121 dclvppdsei vfpldigvvg hvaqtkkmvn vedvaecphf ssfadeltdy ktknmlatpi
 181 mngkdvvavi mavnklngpf ftsededvfl kylnfatlyi kiyhlsylhn cetrrgqvll
 241 wsankvfeel tdierqfhka fytvraylnc erysvglldm tkekeffdvw svlmgesqpy
 301 sgprtpdgre ivfykvidyi lhgkeeikvi ptpsadhwal asgipsyvae sgficnimna
 361 sademfkfqe galddsgwli knvlsmpivn kkeeivgvat fynrkdgkpf deqdevlmes
 421 ltqflqwsvm ntdtydkmnk lenrkdiaqd mvlyhvvkcdr deiqlilptr arlgkepadc
 481 dedelqeilk eelpgpttfd iyefhfsdie cteldlvkcq iqmyyelqvv rkfqipqevl
 541 vrflfsiskg yrrityhnwr hgfnvaqtmf tllmtgklks yytdleafam vtaglchdid
 601 hrgtnnlyqm ksqnplaklh gssilerhhl efgkfllsee tlniyqnlnr rqhehvihlm
 661 diaiiatdla lyfkkramfq kivdesknyq dkkswveyls lettrkeivm ammmtacdls
 721 aitkpwevqs kvallvaaef weqqdlertv ldqqpipmmd rnkaaelpkl qvqfidfvct
 781 fvykefsrfh eeilpmfdrl qnnrkewkal adeyeakvka leekeeeerv aakkqteicn
 841 ggpapksstc cil (SEQ ID NO:22)
```

图7M

视杆 cGMP 特异性 3',5'- 环状磷酸二酯酶子单元 β 同种型 3 (PDE6β 同种型 3)
GenBank NP_001138764

```
   1 mtkekefdv wsvlmgesqp ysgprtpdgr eivfykvidy ilhgkeeikv iptpsadhwa
  61 lasqipsyva esqficnimn asademfkfq egaiddsgwl iknvlsmpiv nkkeeivgva
 121 tfynrkdgkp fdeqdevlme sltqflgwsv nntdtydkmm klenrkdiaq dmvlyhvkcd
 181 rdeiqlilpt rarlgkepad cdedelgeil keelpgptif diycfhfsdl ecteldlvkc
 241 giqmyyelgv vrkfqipqev lvrflfsisk gyrrityhnw rhgfnvaqtm ftllmtgklk
 301 syytdleafa mvtaglchdi dhrgtnnlyq mksqnplakl hgssilerhh lefgkfllse
 361 etlniyqnln rrqhehvihl mdiaiiatdl alyfkkramf qkivdeskny qdkkswveyl
 421 sletirkeiv mammmtacdl saitkpwevq skvallvaae fweqgdlert vldqqpipmm
 481 drnkaaelpk lqvyfidfvc tfvykefsrf heeilpmfdr lqnnrkewka ladeyeakvk
 541 aleekeeeer vaakkvgtei cnggpapkss tccil (SEQ ID NO:23)
```

图7N

环核苷酸门控阳离子通道 α-3 同种型 1 (CNGA3同种型 1)
GenBank NP_001289

```
   1 makintqysh psrthlkvkt sdrdlnraen glsrahssse etssvlqpgi ametrglads
  61 qqgsftgqgi arlsrlifll rrwaarhvhh qdqgpdsfpd rfrgaelkev ssqesnaqan
 121 vqsqepadrg rsawplakcn tntsnnteee kktkkkdaiv vdpssnlyyr wltaialpvf
 181 ynwyllicra cfdelqseyl mlwlvldysa dvlyvldvlv rartqfleqg lmvsdtnrlw
 241 qhyktttqfk ldvlslvptd laylkvgtny pevrfnrlik fsrlfeffdr tetrtnypnm
 301 friqnlvlyi liithwnaci yfaiskfigf qtdswvypni sipehgrlsr kyiyslywst
 361 ltlttigetp ppvkdeeylf vvvdflvqvl ifativqnvg smisnmnasr aefqakidsi
 421 kqymqfrkvt kdletrvirw fdylwankkt vdekevlksl pdklkaeiai nvhldtlkkv
 481 rifqdceagl lvelvlklrp tvfspgdyic kkgdigkemy iinegklavv addgvtqfvv
 541 isdgsyfgei silnikgsks qnrrtanirs igysdlfcls kddlmealte ypeakkalee
 601 kqrqilmkdn lideelarag adpkdleekv eqlgssldtl qtrfarllae ynatqmkmkq
 661 rlsqlesqvk gggdkpladg evpgdatkte dkqq (SEQ ID NO:24)
```

图70

环核苷酸门控阳离子通道α-3同种型2（CNGA3同种型2）
GenBank NP_001073347

```
   1 makintqysh psrthlkvkt sdrdlnraen glsrahssse etssvlqpgi ametrglads
  61 qggsftgqqi arlsrlifli rrwaarhvhh qdqgpqdsfpd rfrgaelkev ssqesnaqan
 121 vgsqepadrg rrkktkkkda ivvdpssnly yrwltaialp vfynwyllic racfdelqse
 181 ylmlwlvldy sadvlyvldv lvrartgfle qglmvsdtnr lwqhyktttq fkldvlslvp
 241 tdlaylkvgt nypevrfnrl lkfsrlfeff drtetrtnyp nmfriqnlvl yiliihwna
 301 ciyfaiskfi gfqtdswvyp nisipehgrl srkyiyslyw stltttige tppvkdeey
 361 lfvvvdflvg vlifativgn vgsmisnmna sraefqakid sikqymqfrk vtkdletrvi
 421 rwfdylwank ktvdekevlk slpdklkaei ainvhldtlk kvrifqdcea qlvelvlkl
 481 rptvfspgdy ickkqdigke myiinegkla vvaddgvtqf vvlsdgsyfg eisilnikgs
 541 ksgnrrtani rsigysdifc lskddlmeal teypeakkal eekgrqilmk dnlideelar
 601 agadpkdlee kveqlgssld tlqtrfarll aeynatqmkm kqrlsqlesq vkgggdkpla
 661 dgevpgdatk tedkqq (SEQ ID NO:25)
```

图7P

环核苷酸门控阳离子通道β-3 (CNGB3)
GenBank NP_061971

```
   1 mfksltkvnk vkpigennen eqssrrneeg shpsnqsqqt taqeenkgee kslktkstpv
  61 tseephtniq dklskknssg dlttnpdpqn aaeptqtvpe qkemdpqkeg pnspqnkppa
 121 apvineyada qlhnlvkrmr qrtalykkkl vegdlsspea spqtakptav ppvkesddkp
 181 tehyyrilwf kvkkmpltey lkrikiprsi dsytdrlyll wlllvtlayn wnccfiplri
 241 vfpyqtadni hywliadiic diiylydmlf iqprlqfvrq gdiivdsnel rkhyrtstkf
 301 qldvasiipf dicylffgfn pmfranrmlk ytsffefnhh lesimdkayi yrvirttgyl
 361 lfilhinacv yywasnyegi gttrwvydge gneylrcyyw avrtlitigg lpepqtlfei
 421 vfqllnffsg vfvfssligq mrdvigaata nqnyfracmd dtiaymnnys ipkivqkrvr
 481 twyeytwdsq rmldesdllk tlpttvqlal aidvnfsiis kvdlfkgcdt qmiydmllrl
 541 ksvlylpgdf vckkgeigke myiikhgevq vlggpdgtkv lvtlkagsvf geisllaagg
 601 gnrrtanvva hqfanlitld kktlqeilvh ypdserilmk karvlikqka ktaeatpprk
 661 dlallfppke etpklfktll ggtgkaslar llklkreqaa qkkensegge eegkenedkq
 721 kenedkqken edkgkenedk dkgrepeekp ldrpectasp iaveeephsv rrtvlprgts
 781 rqsliismap saeggeevlt ievkekakq (SEQ ID NO:26)
```

图7Q

鸟嘌呤核苷酸结合蛋白G(t)子单元 α-2 (GNAT2)
GenBank NP_005263

```
   1 mgsgasaedk elakrskele kklqedadke aktvkllllg agesgkstiv kqmkihqdg
  61 yspeeclefk aiiygnvlqs ilaiiramtt lgidyaepsc addqrqlnnl adsieegtmp
 121 pelvevirrl wkdggvqacf eraaeyqlnd sasyylnqle ritdpeylps eqdvlrsrvk
 181 ttgiietkfs vkdlnfrmfd vggqrserkk wihcfegvtc iifcaalsay dmvlveddev
 241 nrmheslhlf nsicnhkffa atsivlflnk kdlfeekikk vhlsicfpey dgnnsyddag
 301 nyiksqfldl nmrkdvkeiy shmtcatdtq nvkfvfdavt diiikenlkd cglf
```

(SEQ ID NO:27)

图7R

RPGR – 815 氨基酸
GenBank NP_000319

```
   1 mrepeelmpd sgavftfgks kfaennpgkf wfkndvpvhl scgdehsavv tgnnklymfg
  61 snnwgqlglg sksaiskptc vkalkpekvk laacgrnhtl vsteggnvya tggnnegqlg
 121 lgdteerntf hvisfftseh kikqlsagsn tsaaltedgr lfmwgdnseg qiglknvsnv
 181 cvpgqvtigk pvswiscgyy hsafvttdge lyvfgepeng klglpnqlig nhrtpqlvse
 241 ipekviqvac ggehtvvlte navytfglgq fgqlglgtfl fetsepkvie nirdqtisyi
 301 scgenhtali tdiglmytfg dgrhgklglg lenftnhfip tlcsnflrfi vklvacggch
 361 mvvfaaphrq vakeiefdei ndtclsvatf lpyssltsgn vlqrtlsarm rrrererspd
 421 sfsmrrtlpp ieqtiglsac flpnsvfprc sernlqesvl seqqdlmqpee pdylldemtk
 481 eaeidnsstv eslgettdil nmthimslns nekslklspv qkqkkqqtig eltqdtalte
 541 nddsdeyeem semkegkack qhvsqgifmt qpattieafs deeveipeek egaedskgmg
 601 ieeqeveane envkvhggrk ekteilsddl tdkaedhefs kteelkledv deeinaenve
 661 skkktvgdde svptgyhskt egaertndds saetiekkek anleeraice ynempkgyml
 721 ddadssslei lensettpsk dmkktkkifl fkrvpsinqk ivknmneplp eiksigdqii
 781 lksdnkdadq nnmsqnhqni pptnterrsk sctil (SEQ ID NO:28)
```

图7S

RPGR—646 氨基酸
GenBank CAB54002

```
   1 mrepeelmpd sgavftfgks kfaennpgkf wfkndvpvhl scgdehsavv tgmnklymfg
  61 snnwgqlglg sksaiskptc vkalkpekvk laacgrnhtl vsteggnvya tggmnegqlg
 121 lgdteexntf hvisfftseh kikqlsagsn tsaaltedgr lfmwgdnseg qiglknvsnv
 181 cvpqqvtiqk pvswiscgyy hsafvttdge lyvfgepeng klglpnqllg nhrtpqlvse
 241 ipekviqvac ggehtvvlte navytfglgq fgqlglgtfl fetsepkvie nirdqtisyi
 301 scgenhtali tdiglmytfg dgrhgklglg lenftnhfip tlcsmflrfi vklvacggch
 361 mvvfaaphrg vakeiefdei ndtclsvatf lpyssltsgn vlqrtlsarm rrrererspd
 421 sfsmrrtlpp iegtlglsac flpnsvfpnc sernlqesvl seqdlmqpee pdyildemtk
 481 eaeidnsstv eslgettdil nmthimslns nekslklspv qkqkkqqtig eltqdtalte
 541 nddsdeyeem semkegkack qhvsqqgifmt qpattieafs deeveipeek egaedskgng
 601 ieeqeveane envkvhggrk ektеilsddl tdkaeysash sqivsv (SEQ ID NO:29)
```

图7T

RPGR—1152 氨基酸

```
   1 mrepeelmpd sgavftfgks kfaennpgkf wfkndvpvhl scgdehsavv tgnnklymfg
  61 snnwgqlglg sksaiskptc vkalkpekvk laacgrnhtl vsteggnvya tggnnegqlg
 121 lgdteerntf hvisfftseh kikqlsaqsn tsaaltedgr lfmwgdnseq qiglknvsnv
 181 cvpqqvtigk pvswiscgyy hsafvttdge lyvfgepeng klglpnqlig fetsepkvie
 241 ipekviqvac ggehtvvlte navytfglgq fgqlglgtfl nirdqtisyi vsteggnvya
 301 scgenhtali tdiglmytfg dgrhgklglg lenftnhfip tlcsnflrfi vklvacggch
 361 mvvfaaphrg vakeiefdei ndtclsvatf lpyssltsgn vlgrtlsarm rrrererspd
 421 sfsmrrtlpp iegtlglsac flpnsvfpro sernlgesvl seqqdlmqpee pdyilcdemtk
 481 eaeidnsstv eslgettdil nmthimslns nekslklspv qkqkkqqtig eltqptalte
 541 nddsdeyeem semkegkack qhvsqqifmt qpattieafs deeveipeek egaedskgng
 601 ieeqeveane envkvhggrk ektellsddl tdkaevsegk aksvgeaedg pegrgdgtce
 661 egssgaehwq deerakgekd kgrgemerpg egekelaeke ewkkrdgeeb eqkereqghq
 721 kernqemeeg geeehgegee eegdreeeee kegegkeege geevegeerek eegerkkeer
 781 agkeekgeee gdqgegeeee tegrgeekee ggevegggeve egkgeereeee eeggeeeeeg
 841 egeeeegegge eeegagkgee egeegegegee geegegegeee eegegegeee gegggeeeeg
 901 egggeeegeg egeeeegegk geeeggeegg egeeeegegge ggpggggggee eeggewggeee
 961 eggggeeeeb eggggeeggeb geeeggeggb eeeggggeeggbe eggggeeeeeggbe
1021 vggevegeeg eggeeeeege eegeerekeg egeeenrrnre eeeeeggkyb etgeeenerb
1081 dgeeykkvsk ikgsvkvgkh ktyqkksvtn tqgngkegrs rnqvvqsskrll kmgpsgskkf
1141 wnnvlphyle lk (SEQ ID NO:30)
```

图7U

RPGR – 1020 氨基酸

```
   1 mrepeelmpd sgavftfgks kfaennpgkf wfkndvpvhl scgdehsavv tqnnklymfg
  61 snnwqqiglg sksaiskptc vkalkpekvk laacgrnhtl vstegqnvya tqqnnegqlg
 121 lgdteerntf hvisfftseh kikqlsagsn tsaaltedgr lfmwqdnseg qiglknvsnv
 181 cvpqqvtigk pvswiscgyy hsafvttdge lyvfgepeng klglpnqlig nhrtpqlvse
 241 ipekviqvac ggehtvvlte navytfglgq fgqlglgtfl fetsepkvie nirdqtisyi
 301 scgenhtali tdiglmytfq dgrhgklglg lenftnhfip tlcsnflrfi vklvacqgch
 361 mvvfaaphrg vakeiefdei ndtclsvatf lpyssltsqn vlqrtlsarm rrrererspd
 421 sfsmrrtlpp iegtlglsac flpnsvfprc sernlqesvl seqdlmqpee pdylldemtk
 481 eaeidnsstv eslgettdil nmthimsins nekslklspv qkqkkqqtig eltqdtalte
 541 ndqsdeyeem semkeqkack qhvsqqgifmt qpattieafs deevqndtgq vqpqadtdge
 601 glqkevyrhe nnngvdqqlda keiekesdqg hsqkeseaee idseketkla eiaqmkdlre
 661 rekstkkmsp ffqnlpdrqm nteseenkdf vkkresckqd vifdseresv ekpdsymega
 721 sesqqqiadg fqqpeaiefs sgekeddeve tdqniryqrk lieqqneket kpiisksmak
 781 ydfkcdrlse ipeekegaed skqnqieeqe veaneenvkv hqqrkektei lsddltdkae
 841 dhefskteel kledvdeein aenveskkkt vqddesvptq yhsktegaer tnddssaeti
 901 ekkekanlee raiceynenp kqymlddads ssleilense ttpskdmkkt kkiflfkrvp
 961 sinqkivknn neplpeiksi gdqiilksdn kdadqnhmsq nhqnipptnt errsksctil
```

(SEQ ID NO:31)

图7V

酿脓链球菌 Cas9

```
   1 mdkkysigld igtnsvgwav itdeykvpsk kfkvlgntdr hsikknliga llfdsgetae
  61 atrlkrtarr rytrrknric yiqeifsnem akvddsffhr leesflveed kkherhpifg
 121 nivdevayhe kyptiyhlrk klvdstdkad lrliylalah mikfrghfli egdlnpdnsd
 181 vdklfiqlvq tynqlfeenp inasgvdaka ilsarlsksr rlenliaqlp gekknglfgn
 241 lialslgltp nfksnfdlae dakiqlskdt yddldnlla qigdqyadlf laaknlsdai
 301 llsdilrvnt eitkaplsas mikrydehhq dltllkalvr qqlpekykei ffdqskngya
 361 gyidggasqe efykfikpil ekmdgteell vklnredllr kqrtfdngsi phqihlgelh
 421 ailrrqedfy pflkdnreki ekiltfripy yvgplargns rfawmtrkse etitpwnfee
 481 vvdkgasaqs fiermtnfdk nlpnekvlpk hsllyeyftv yneltkvkyv tegmrkpafl
 541 sgeqkkaivd llfktnrkvt vkqlkedyfk kiecfdsvei sgvedrfnas lgtyhdllki
 601 ikdkdfldne enedilediv ltltlfedre mieerlktya hlfddkvmkq lkrrrytgwg
 661 rlsrklingi rdkqsgktil dflksdgfan rnfmqlihdd sltfkediqk aqvsgqgdsl
 721 hehianlags paikkgilqt vkvvdelvkv mgrhkpeniv iemarenqtt qkgqknsrer
 781 mkrieegike lgsqilkehp ventqlqnek lylyylqngr dmyvdqeldi nrlsdydvdh
 841 ivpqsflkdd sidnkvltrs dknrgksdnv pseevvkkmk nywrqllnak litqrkfdnl
 901 tkaergglse ldkagfikrq lvetrqitkh vaqildsrmn tkydendkli revkvitlks
 961 klvsdfrkdf qfykvreinn yhhahdayln avvgtalikk ypklesefvy gdykvydvrk
1021 miakseqeig katakyffys nimnffktei tlangeirkr plietngetg eivwdkgrdf
1081 atvrkvlsmp qvnivkktev qtggfskesi lpkrnsdkli arkkdwdpkk yggfdsptva
1141 ysvlvvakve kgkskklksv kellgitime rssfeknpid fleakgykev kkdliiklpk
1201 yslfelengr krmlasagel qkgnelalps kyvnflylas hyeklkgspe dneqkqlfve
1261 qhkhyldeii eqisefskrv iladanldkv lsaynkhrdk pireqaenii hlftltnlga
1321 paafkyfdtt idrkrytstk evldatlihq sitglyetri dlsqlggd
```

(SEQ ID NO:32)

图8A

金黄色葡萄球菌 Cas9

```
   1 mkrnyilgld igitsvgygi idyetrdvid agvrifkean vennegrrsk rgarrlkrrr
  61 rhriqrvkkl lfdynlltdh selsginpye arvkglsqkl seeefsaall hlakrrgvhn
 121 vneveedtgn elstkeqisr nskaleekyv aelqlerlkk dgevrgsinr fktsdyvkea
 181 kqllkvqkay hqldqsfidt yidlletrrt yyeqpgegsp fgwkdikewy emlmghctyf
 241 peelrsvkya ynadlynaln dlnnlvitrd enekleyyek fqiienvfkq kkkptlkqia
 301 keilvneedi kgyrvtstgk peftnlkvyh dikditarke iienaelldq iakiltiyqs
 361 sediqeeltn lnseltqeei eqisnlkgyt gthnlslkai nlildelwht ndnqiaifnr
 421 lklvpkkvdl sqqkeipttl vddfilspvv krsfiqsikv inaiikkyql pndiiielar
 481 eknskdaqkm inemqkrnrq tnerieeiir ttgkenakyl iekiklhdmq egkclyslea
 541 ipledllnnp fnyevdhiip rsvsfdnsfn nkvlvkqeen skkgnrtpfq ylsssdskis
 601 yetfkkhiln lakgkgrisk tkkeylleer dinrfsvqkd finrnlvdtr yatrglmnll
 661 rsyfrvnnld vkvksinggf tsflrrkwkf kkernkgykh haedaliian adfifkewkk
 721 ldkakkvmen qmfeekqaes mpeieteqey keifitphqi khikdfkdyk yshrvdkkpn
 781 relindtlys trkddkgntl ivnnlnglyd kdndklkkli nkspeklimy hhdpqtyqkl
 841 klimeqygde knplykyyee tqnyltkysk kdngpvikki kyygnklnah ldittddypns
 901 rnkvvklslk pyrfdvyldn gvykfvtvkn ldvikkenyy evnskcyeea kklkkisnqa
 961 efiasfymnd likingelyr vigvnndlln rievnmidit yreylenmnd krppriikti
1021 asktqsikky stdilgnlye vkskkhpqii kkg (SEQ ID NO:33)
```

图8B

土拉热弗朗西丝菌 Cpf1

```
   1 msiyqefvnk yslsktlrfe lipqgktlen ikargllddd ekrakdykka kqiidkyhqf
  61 fieeilssvc isedllqmys dvyfklkksd ddnlqkdfks akdtikkqis eyikdsekfk
 121 nlfnqnlida kkqqesdlil wlkqskdngi elfkansdit didealeiik sfkgwttyfk
 181 gfhenrknvy ssndiptsii yrivddnlpk flenkakyes lkdkapeain yeqikkdlae
 241 eltfdidykt sevnqrvfsl devfeianfn nylnqsqitk fntiiggkfv ngentkrkgi
 301 neyinlysqq indktlkkyk msvlfkqils dtesksfvid kleddsdvvt tmqsfyeqia
 361 afktveeksi ketlsllfdd lkaqkidlsk iyfkndkslt dlsqqvfddy svigtavley
 421 itqqiapknl dnpskkeqel iakktekaky lsletiklal eefnkhrdid kqcrfeeila
 481 nfaaipmifd eiaqnkdnla qisikyqnqg kkdllqasae ddvkaikdll dqtnnllhkl
 541 kifhisqsed kanildkdeh fylvfeecyf elanivplyn kirnyitqkp ysdekfklnf
 601 enstlangwd knkepdntai lfikddkyyl qvmnkknnki fddkaikenk gegykkivyk
 661 llpgankmip kvffsaksik fynpsedilr irnhsthtkn gspqkqyekf efniedcrkf
 721 idfykqsisk hpewkdfqfr fsdtqrynsi defyrevenq gykltfenis esyidsvvnq
 781 gklylfqiyn kdfsayskgr pnlhtlywka lfdernlqdv vyklngeael fyrkqsipkk
 841 ithpakeaia nknkdnpkke svfeydlikd krftedkfff hcpitinfks sgankfndei
 901 nlllkekand vnilsidrge rhlayytlvd gkqnlikqdt fniignddrmk tnyhdklaai
 961 ekdrdsarkd wkkinnikem kegylsqvvh eiaklvieyn aivvfedlnf gfkrqrfkve
1021 kqvyqklekm lieklnylvf kdnefdktgg vlrayqltap fetfkkmgkq tgiiyyvpag
1081 ftskicpvtg fvnqlypkye svsksqeffs kfdkicynld kgyfefsfdy knfqdkaakg
1141 kwtiasfgsr linfrnsdkn hnwdtrevyp tkelekllkd ysieyghgec ikaaicgesd
1201 kkffaktsv lntilqmrns ktqteldyli spvadvngnf fdsrqapknm pqdadangay
1261 higlkglmll grikknqegk klnlvikkee yfefvqnrnn (SEQ ID NO:34)
```

图8C