



(12) 发明专利

(10) 授权公告号 CN 111050784 B

(45) 授权公告日 2024. 03. 19

(21) 申请号 201880051871.2

C12N 9/82 (2006.01)

(22) 申请日 2018.08.10

(56) 对比文件

(65) 同一申请的已公布的文献号
申请公布号 CN 111050784 A

EP 0811687 A2,1997.12.10
JP H1057080 A,1998.03.03
WO 2012170640 A1,2012.12.13
WO 2015164588 A1,2015.10.29
JP 2015503333 A,2015.02.02
JP 2010501191 A,2010.01.21
JP 2016117718 A,2016.06.30
WO 2004112717 A2,2004.12.29
WO 2012075173 A2,2012.06.07

(43) 申请公布日 2020.04.21

(30) 优先权数据
62/544,411 2017.08.11 US
62/544,396 2017.08.11 US

(85) PCT国际申请进入国家阶段日
2020.02.10

(86) PCT国际申请的申请数据
PCT/US2018/046196 2018.08.10

(87) PCT国际申请的公布数据
W02019/032952 EN 2019.02.14

(73) 专利权人 伊利诺伊大学理事会
地址 美国伊利诺伊州
专利权人 美国政府代表退伍军人事务部

堤康央・真弓忠範. フェージ表面提示法を
駆使した機能性人工蛋白質の創出とDDSへの展
開.《Drug Delivery System》.2003,第18卷(第6
期),第536-544页.

K.Terpe.Overview of tag protein
fusions: from molecular and biochemical
fundamentals to commercial systems.《Appl
Microbiol Biotechnol》.2002,第60卷第523-
533页.

(续)

(72) 发明人 阿尔农・拉维 海恩-安哈・源
阿曼达・沙尔克

审查员 贾星航

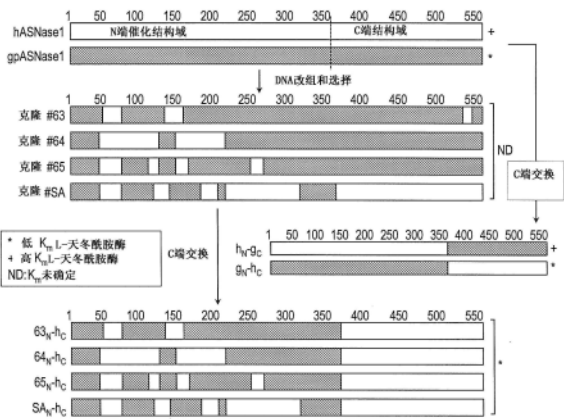
(74) 专利代理机构 中原信达知识产权代理有限
责任公司 11219
专利代理师 金海霞 刘慧

(51) Int.Cl.
A61K 38/17 (2006.01)

权利要求书1页 说明书30页
序列表95页 附图3页

(54) 发明名称
截短的豚鼠L-天冬酰胺酶变体及其使用方法

(57) 摘要
本文描述了截短并人源化的变体豚鼠L-天冬酰胺酶和含有所述L-天冬酰胺酶的融合蛋白,以及所述L-天冬酰胺酶在治疗癌症例如急性成淋巴细胞性白血病和急性髓性白血病中的用途。



CN 111050784 B

[接上页]

(56) 对比文件

Michiyoshi Kouno 等.Targeted Delivery of Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand to Keratinocytes with a Pemphigus mAb.《Journal of Investigative Dermatology》.2013,第1页摘要.

Sebastian Meier 等.Foldon, The Natural Trimerization Domain of T4 Fibrin, Dissociates into a Monomeric A-state Form containing a Stable β -Hairpin: Atomic Details of Trimer Dissociation and

Local β -Hairpin Stability from Residual Dipolar Couplings.《J. Mol. Biol》.2004,第344卷第1051-1069页.

Amanda M. Schalk 等.Identification and Structural Analysis of an L-Asparaginase Enzyme from Guinea Pig with Putative Tumor Cell Killing Properties.《THE JOURNAL OF BIOLOGICAL CHEMISTRY》.2014,第289卷(第48期),第33175页摘要.

龙水清等.点突变H125L和E145A对L-天冬酰胺酶酶活和热稳定性的改善.《食品与发酵工业》.2016,第42卷(第05期),第6-11页.

1. 一种豚鼠L-天冬酰胺酶GpA变体,其中所述GpA变体由选自SEQ ID NO:37、39-42、45-65和86的氨基酸序列构成。
2. 一种融合蛋白,其包含权利要求1的GpA变体,以及组氨酸标签、SUMO标签、白蛋白结合结构域或其组合。
3. 一种融合蛋白,其包含权利要求1的GpA变体,以及3个串联的TRAIL可溶性结构域,其中所述TRAIL可溶性结构域的序列如SEQ ID NO:80所示。
4. 一种核酸分子,其由编码权利要求1的GpA变体或者权利要求2或3的融合蛋白的核苷酸序列组成。
5. 一种表达载体,其包含权利要求4的核酸分子。
6. 一种分离的宿主细胞,其包含权利要求4的核酸分子。
7. 一种药物组合物,其包含权利要求1的GpA变体或者权利要求2或3的融合蛋白和可药用赋形剂。
8. 权利要求1的GpA变体或者权利要求2或3的融合蛋白在制备用于在对象中治疗急性成淋巴细胞性白血病的药物中的用途。

截短的豚鼠L-天冬酰胺酶变体及其使用方法

技术领域

[0001] 本申请要求2017年8月11日提交的美国临时申请号62/544,396和2017年8月11日提交的美国临时申请号62/544,411的优先权利益,所述美国临时申请的内容以其整体通过引用并入本文。

[0002] 本发明在美国国立卫生研究院(National Institutes of Health)授予的资助号为EB013685和美国退伍军人事务部(Department of Veteran Affairs)授予的资助号为BX001919的政府支持下做出。美国政府在本发明中具有一定权利。

背景技术

[0003] 某些癌症例如急性成淋巴细胞性白血病(ALL)依赖于从血液中清除Asn,这是最常归因于此类癌症中天冬酰胺合成酶的缺乏/表达低下的因素。因此,在这些癌症的治疗中,L-天冬酰胺酶已被鉴定为关键组分。所有可商购的L-天冬酰胺酶都具有双重活性。主要活性即L-天冬酰胺酶活性将氨基酸L-天冬酰胺(Asn)水解成L-天冬氨酸(Asp)和氨。次要活性是L-谷氨酰胺酶活性,其将L-谷氨酰胺(Gln)水解成L-谷氨酸(Glu)和氨。对于FDA批准的酶例如ELSPAR®(从大肠埃希氏杆菌(*Escherichia coli*)获得的酶)和ERWINAZE®(从菊欧文氏菌(*Erwinia chrysanthemi*)获得的酶)来说,L-谷氨酰胺酶活性在主要的L-天冬酰胺酶活性的2至10%的范围内。尽管这些药物的L-天冬酰胺酶活性的重要性已被接受,但关于L-谷氨酰胺酶活性在杀死白血病细胞中的重要性的报道相互矛盾。此外,已将L-谷氨酰胺酶活性与L-天冬酰胺酶的大量临床毒性相关联。事实上,L-天冬酰胺酶治疗的毒副作用严重限制了这种抗癌药物的使用。

[0004] 使用细菌的酶作为治疗剂的另一个缺点是它们的免疫原性,由于超敏反应直至过敏性休克,这可能导致对患者的直接威胁。此外,产生的抗体可以失活并清除所述酶药物,从而降低或甚至消除它的有效性。已开发了降低这些严重副作用的方法,例如将大肠杆菌酶与聚乙二醇偶联(PEG化)或通过野生型大肠杆菌酶的第115、118、120、123、215、219、307和312位残基的突变进行去免疫化(WO 2012/075173A2)。然而,需要具有降低的免疫原性和降低的L-谷氨酰胺酶活性的可替换L-天冬酰胺酶制剂。

[0005] 豚鼠L-天冬酰胺酶已从豚鼠血清纯化并表征(Zhang等,(1995)Comp.Biochem.Physiol.B Biochem.Mol.Biol.112(4):607-12)。被注释为H0W0T5_CAVP0的豚鼠酶表现出抗肿瘤活性,对天冬酰胺具有低的 K_m 值,并缺乏L-谷氨酰胺酶活性(Schalk等,(2014)J.Biol.Chem.289:33175-33186)。也参见EP 0726313 B1和US 6,537,547。

[0006] 使用L-天冬酰胺酶治疗癌症的其他方法包括L-天冬酰胺酶与TNF相关凋亡诱导配体(TRAIL)激动剂或TRAIL受体激动剂例如3个可溶性TRAIL结构域和另外的功能性结构域例如抗体片段的共同给药。参见US2015/0337027、US2009/0131317和WO 2012/170640。就此而言,在对L-天冬酰胺酶单一治疗有抗性的神经胶质瘤细胞中,显示出L-天冬酰胺酶克服了对于由Bcl-2/Bcl-xL抑制剂ABT263诱导的内在凋亡和由TRAIL介导的外在凋亡两者的抗性(Karpel-Massler等,(2016)Oncotarget 7(23):33512-28)。

发明内容

[0007] 本发明提供了一种C端截短的豚鼠L-天冬酰胺酶(GpA)变体,其与SEQ ID NO:1的第1至359位残基共享至少85%的序列同一性。在某些实施方式中,所述C端截短在SEQ ID NO:1的第359至396位之间的位置处。在某些实施方式中,所述C端截短在SEQ ID NO:1的第369位处。在其他实施方式中,所述截短的GpA变体还包括相对于SEQ ID NO:1的至少一个氨基酸替换,例如在第7、10、23、25、48、49、52、53、54、57、58、59、60、62、92、98、101、102、106、108、121、122、134、147、193、198、217、233、236、250、257、281、301、311、340、344、360、362、363、364、365、366、367或368位或其组合处。在特定实施方式中,所述相对于SEQ ID NO:1的至少一个氨基酸替换是H10R、Q23R、K25E、K48E、Q52R、Q54R、P57S、D58E、H59D、A60T、A62V、D91A、D92E、K98Q、E101K、Q108H、S121F、G122A、H134Q、R147H、K193R、C198A、C198S、C198V、D217E、N233S、H236Q、S250A、Q288E、R301Q、E344D、L360P、T362S、A363V、D364E、L365E、H366R、Q367R或S368P或其组合。在其他实施方式中,所述相对于SEQ ID NO:1的至少一个氨基酸替换包括:(a)在第49、52、225、257、281或340位或其组合处的半胱氨酸残基;或(b)在第7、53、54、57、58、98、106、233、250、257、281、311或340位或其组合处的赖氨酸残基。理想情况下,所述变体具有等于或高于野生型GpA的催化活性。任选地,所述截短的GpA变体还可以包括组氨酸标签、SUMO标签、白蛋白结合结构域、3个串联的TRAIL可溶性结构域(例如人类TRAIL的第115-281位残基)或其组合。

[0008] 还提供了核酸分子、表达载体、宿主细胞和含有所述截短的GpA变体或融合蛋白的药物组合物,并且还提供了通过任选地与稳定形式的TRAIL组合向需要治疗的对象给药有效量的所述截短的GpA变体或融合蛋白来治疗癌症的方法。

附图说明

[0009] 图1是从DNA改组方法和C端结构域交换获得的克隆的示意图。hASNase1序列是空心框,gpASNase1是阴影框。从选择分离的克隆(#63、64、65和SA)或通过C端交换产生的克隆(63-hC、64-hC、65-hC和SA-hC)是hASNase1(空心框)与gpASNase1(实心框)序列之间的改组。

[0010] 图2A和2B示出了hASNase1(hASN)、gpASNase1(GpA)和选择的人源化克隆的氨基酸序列比对。下划线的残基是源自于GpA的残基。

[0011] 发明详述

[0012] L-天冬酰胺酶是一种用于治疗急性成淋巴细胞性白血病(ALL)的化疗药物。L-天冬酰胺酶的临床效能的主要先决条件是对天冬酰胺的微摩尔 K_m 允许完全剥夺血液中的这种氨基酸。由于当前批准的L-天冬酰胺酶是细菌来源的,因此免疫原性是一种挑战,其可以通过人类的酶来减轻。然而,所有人类L-天冬酰胺酶都对天冬酰胺具有毫摩尔 K_m 。已鉴定到低 K_m 的豚鼠L-天冬酰胺酶(gpASNase1),其与人类L-天冬酰胺酶1(hASNase1)共享~70%的氨基酸同一性。与人类酶相同,gpASNase1含有两个结构域:L-天冬酰胺酶活性居于其中的~360个残基的N端结构域,和未知功能的~200个残基的C端结构域。为了改进半衰期,寻求更短但稳定的GpA版本。因此,将GpA进行C端截短以鉴定保留活性的最短的GpA片段。这项分析表明,359个氨基酸残基的N端催化结构域可以与SUMO标签一起表达并保留野生型活性。然而,在除去所述SUMO标签后,所述蛋白质变得不稳定。将截短延长到第369位残基提供了

既稳定又有活性的酶。

[0013] 为了降低截短的GpA变体的免疫原性,采取了两种不同方法将所述酶人源化:DNA改组和表面残基的基于结构的突变。GpA的人源化产生的变体与hASNase1共享大约80%的序列同一性,具有野生型GpA活性,对天冬酰胺具有低 K_m 值并且没有可检测的L-谷氨酰胺酶活性。在引入半胱氨酸或赖氨酸残基并偶联到PEG后,所述截短的GpA变体维持它们的L-天冬酰胺酶活性并且在某些情况下表现出所述活性的提高。此外,修饰例如组氨酸标签、SUMO标签和/或白蛋白结合结构域的N或C端添加可以增加体内循环时间,并且将所述截短的GpA变体融合到3个串联的TRAIL可溶性结构域,可以通过为内在凋亡级联提供必需的信号(L-天冬酰胺酶)和诱导外在凋亡级联(TRAIL)两者来促进细胞死亡。

[0014] 因此,本发明提供了截短的GpA变体及其融合蛋白,用于治疗依赖于存在Asn的外部供应的癌症例如淋巴瘤和白血病。本发明的L-天冬酰胺酶的改进的安全性将为当前患者群体(例如患有儿童ALL的患者)提供益处,并在其他患者群体(例如成人ALL、AML和其他癌症)中提供扩展用途。

[0015] 正如在本领域中已知的,L-天冬酰胺酶(L-天冬酰胺氨基水解酶,E.C.3.5.1.1)是水解Asn中的酰胺键产生Asp和氨的酰胺酶(Kumar&Verma (2012) Asian J. Biochem. Pharma Res. 3:197-205)。在本文中被称为“gpASNase1”或“GpA”的野生型豚鼠(*Cavia porcellus*) L-天冬酰胺酶是一种565个氨基酸残基的蛋白质,其可以在Uniprot登记号H0W0T5_CAVPO下和SEQ ID NO:1中获得。GpA表现出抗肿瘤活性,对天冬酰胺具有低 K_m 值,并缺乏L-谷氨酰胺酶活性。然而,野生型GpA与hASNase1仅共享大约70%的序列同一性。因此,本发明提供了一种截短的GpA,其在某些实施方式中被人源化以降低免疫原性。具体来说,本发明提供了一种截短的GpA变体,其与SEQ ID NO:1的第1至359位残基共享至少85%的序列同一性。

[0016] “GpA变体”是指GpA的一种非天然存在的形式,其表现出L-天冬酰胺酶活性,对Asn具有低 K_m ,并缺乏L-谷氨酰胺酶活性。作为比较,“野生型”GpA是指所述L-天冬酰胺酶从天然存在的来源分离时的典型形式。野生型是在天然群体中最频繁观察到的形式,因此被随意地指定为正常或野生型形式。野生型GpA对Asn具有约 $39s^{-1}$ 的反应速率(k_{cat})和 $58\mu M$ 的 K_m (Schalk等,(2014) J. Biol. Chem. 289:33175-33186)。本发明的截短的GpA变体通常表现出野生型GpA酶的至少75%、80%、85%、90%、95%或100%的 k_{cat} ,并对Asn表现出低于 $250\mu M$ 、 $200\mu M$ 、 $150\mu M$ 、 $100\mu M$ 、 $80\mu M$ 或 $60\mu M$ 的 K_m 。

[0017] 在最低限度,GpA变体被截短。“截短的GpA”是指其中约206个C端氨基酸残基中的全部或一部分已被去除的GpA。在某些实施方式中,截短的GpA蛋白保留了N端359个氨基酸残基的催化结构域。理想情况下,所述全长GpA(SEQ ID NO:1)在第359至396位残基之间的位置处被C端截短。具体来说,所述全长GpA(SEQ ID NO:1)在第359、367、369、374、384、392或396位处被C端截短。在某些实施方式中,截短的GpA变体在第369位处被C端截短。示例性的截短的GpA变体提供在SEQ ID NO:3 (GpA359)、SEQ ID NO:4 (GpA367)、SEQ ID NO:5 (GpA369)、SEQ ID NO:6 (GpA374)、SEQ ID NO:7 (GpA384)、SEQ ID NO:8 (GpA392)和SEQ ID NO:9 (GpA396)中。在某些实施方式中,C端截短的GpA变体包含SEQ ID NO:3或由其构成。在某些实施方式中,C端截短的GpA变体包含SEQ ID NO:5或由其构成。

[0018] 根据本发明的其他方面,GpA变体被截短,并包括提高稳定性、提高与hASNase1的序列同一性和/或与野生型GpA酶相比提高GpA的体内循环时间的至少一个氨基酸替换或修

饰(例如PEG化或蛋白质融合)。正如在本文中证实的,将位于GpA的表面上的氨基酸残基突变,以将GpA人源化和/或提供适合于PEG化的位点。此外,GpA与蛋白质标签或三聚体TRAIL的融合提供了稳定性和/或提高的肿瘤细胞杀伤活性。

[0019] 因此,在某些方面,GpA变体相对于野生型GpA(SEQ ID NO:1)具有至少一个氨基酸替换。在特定实施方式中,所述被替换的氨基酸残基是表面残基。术语“表面残基”是指位于蛋白质表面上的残基。相反,埋藏的残基是不位于蛋白质表面上的残基。表面残基通常包括亲水性侧链。在操作上,可以从蛋白质的结构模型通过计算来鉴定表面残基,所述表面残基是接触卷在分子结构表面上的水合球的残基。还可以通过使用氘交换研究或各种不同的标记试剂例如亲水性烷基化剂的可接近性,通过实验来鉴定表面残基。在特定实施方式中,所述氨基酸替换不在活性位点残基例如Thr19、Ser85、Ser86、Thr116、Asp117、Ala142、Lys188、Asn272和Tyr308之一处。

[0020] GpA的可以被替换以产生本发明的GpA变体的表面残基包括但不限于在SEQ ID NO:1的第7、10、23、25、40、48、49、52、53、54、57、58、59、60、62、92、98、101、106、108、121、122、131、132、134、147、193、198、217、221、222、223、224、225、226、233、236、250、253、257、261、281、282、283、284、301、311、340、344、345、347、352、358、359、360、362、363、364、365、366、367或368位处的氨基酸残基。在某些实施方式中,GpA变体包括至少一个氨基酸替换。在其他实施方式中,GpA变体包括约1至50、1至45、1至40、1至35、1至30、1至25、1至20、1至15、1至10、1至7或1至4个氨基酸替换。在特定实施方式中,GpA变体包括在SEQ ID NO:1的第7、10、23、25、48、49、52、53、54、57、58、59、60、62、92、98、101、106、108、121、122、134、147、193、198、217、233、236、250、257、281、301、311、340、344、360、362、363、364、365、366、367和368位中的一个或多个位置处的氨基酸替换。

[0021] 正如本文中指明的,截短的GpA369与hASNase1的N端371个氨基酸残基共享约72%的序列同一性。理想情况下,所述GpA的至少一个氨基酸替换产生与野生型GpA相比与hASNase1具有提高的氨基酸序列同一性的GpA变体。因此,本发明的一个方面提供了GpA的人源化。根据本发明的这个方面,所述截短的GpA变体优选地与hASNase1的N端371个氨基酸残基具有至少70%、72%、74%、76%、78%、80%、82%或84%的氨基酸序列同一性。此外,所述截短的GpA变体与野生型截短的GpA共享至少85%、87%、89%、91%、93%、95%、97%或99%的序列同一性。

[0022] 优选地,截短的GpA的人源化通过将野生型GpA的一个或多个表面残基用hASNase1的对应表面残基代替来实现。具体来说,截短的GpA的人源化通过将野生型GpA残基H10、Q23、K25、K48、Q52、Q54、D91、D92、K98、E101、Q108、S121、G122、H134、R147、K193、D217、N233、H236、S250、Q288、R301、E344、L360、T362、A363、L365、H366、Q367或S368或其任何组合用hASNase1的对应表面残基代替来实现。具体来说,截短的GpA的人源化通过对野生型GpA进行一个或多个下述氨基酸替换来实现:H10R,Q23R,K25E,K48E,Q52R,Q54R,D91A,D92E,K98Q,E101K,Q108H,S121F,G122A,H134Q,R147H,K193R,D217E,N233S,H236Q,S250A,Q288E,R301Q,E344D,L360P,T362S,A363V,L365E,H366R,Q367R和/或S368P。示例性的截短且人源化的GpA变体被提供在SEQ ID NO:45、SEQ ID NO:46、SEQ ID NO:47、SEQ ID NO:48、SEQ ID NO:49、SEQ ID NO:50、SEQ ID NO:58、SEQ ID NO:59、SEQ ID NO:60、SEQ ID NO:61、SEQ ID NO:62、SEQ ID NO:64、SEQ ID NO:65和SEQ ID NO:86中。

[0023] 已显示,L-天冬酰胺酶的PEG化增加了体内循环时间。术语“PEG化的”或“PEG化”是指L-天冬酰胺酶与聚乙二醇(PEG)的偶联。“PEG”或“聚乙二醇”是指任何水溶性聚(乙二醇)或聚(环氧乙烷)。因此,表述PEG包含了结构 $(\text{CH}_2\text{CH}_2\text{O})_n$,其中n是2至约1000的整数。常用的PEG是封端的PEG,其中所述PEG端的一个末端用相对无活性的基团例如烷氧基封端,而另一个末端是可能被连接物组成部分进一步修饰的羟基。在一个实施方式中,所述封端基团是甲氧基,并且所述相应的封端PEG被表示为mPEG。因此,mPEG是 $\text{CH}_3\text{O}(\text{CH}_2\text{CH}_2\text{O})_n$,其中n是2至约1000的整数。在另一个实施方式中,所述封端基团是羟基,并且所述相应的封端PEG是羟基PEG。后面跟有数字(不是下标)的“PEG”指示具有等于所述数字乘以1,000的近似分子量的PEG组成部分。因此,“PEG40”或“PEG40K”是具有40kDa的近似分子量的PEG组成部分。可用于确定PEG分子量的方法的实例包括但不限于质谱术,例如TOF-MS。PEG可以例如由NOF Corporation,Tokyo,Japan,Creative PEG-works,Winston Salem,NC和Nanocs,Boston,MA提供。

[0024] 在一个实施方式中,所述PEG组成部分可以通过亲核取代(酰化)附连到N端 α -氨基上或 γ -位上的赖氨酸残基上,例如使用OSu活化的酯。在另一个实施方式中,可以使用PEG-醛试剂和还原剂例如氰基硼氢化钠,通过还原烷基化将所述PEG组成部分附连到所述GpA蛋白中存在的氨基上。在另一个实施方式中,可以使用例如PEG马来酰亚胺试剂,在迈克尔加成反应中将所述PEG组成部分附连到未配对的半胱氨酸残基的侧链。其他PEG化方法包括但不限于桥接PEG化、转谷氨酰胺酶PEG化、糖基PEG化、使用遗传工程的PEG化、可释放连接物PEG化。对于PEG化方法的综述,参见Pasut&Veronese (2012) J. Contr. Rel. 161:461-472;和Roberts等,(2012) Adv. Drug Del. Rev. 64:116-127。在一个实施方式中,所述PEG组成部分被附连到赖氨酸或半胱氨酸残基的侧链。

[0025] “连接物”是指将所述GpA蛋白的-HN-基团与PEG组成部分的-O-基团相连的化学组成部分。在优选实施方式中,所述连接物对GpA的活性没有任何不利影响。所述连接物通常是羧酸的衍生物,其中所述羧酸官能团被用于通过酰胺键附连到所述GpA蛋白。连接物的实例包括但不限于连接基元为 CH_2CO 的乙酸组成部分、连接基元为 $\text{CH}_2\text{CH}_2\text{CO}$ 或 CHCH_3CO 的丙酸组成部分、连接基元为 $\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}$ 或 $\text{CH}_2\text{CHCH}_3\text{CO}$ 的丁酸组成部分、CO基团、N-(氨基羰基)琥珀酰亚胺衍生物(例如N-(N-丙基丙酰胺)琥珀酰亚胺、N-(N-丙基己酰胺)琥珀酰亚胺和N-(N-乙基丙酰胺)琥珀酰亚胺)、戊酸($(\text{CH}_2)_5\text{CO}$)、 α -甲基丁酸($\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{CO}$)、琥珀酸($\text{CO}(\text{CH}_2)_2\text{CO}$)、戊二酸($\text{CO}(\text{CH}_2)_3\text{CO}$)、琥珀酰胺衍生物(例如 $(\text{CH}_2)_2\text{NHCO}(\text{CH}_2)_2\text{CO}$)、戊二酰胺衍生物(例如 $(\text{CH}_2)_3\text{NHCO}(\text{CH}_2)_3\text{CO}$ 和 $(\text{CH}_2)_2\text{NHCO}(\text{CH}_2)_3\text{CO}$)。在本发明中使用的示例性PEG分子包括但不限于甲氧基PEG琥珀酰亚胺基碳酸酯(mPEG-SC)、mPEG-琥珀酰亚胺基羧基甲基酯(mPEG-SCM)和mPEG-琥珀酰胺琥珀酰亚胺基酯(mPEG-SAS)。

[0026] 可用于PEG化本发明的L-天冬酰胺酶的PEG化方法提供在例如US 4,179,337、US 5,766,897、US2002/0065397和US2009/0054590中。理想情况下,PEG化的GpA变体通过将PEG与截短的GpA变体根据PEG的大小以约20:1至100:1或更特别地20:1至50:1或最特别地20:1的PEG:GpA比例反应来产生。在某些情况下,所述GpA变体具有至少一个半胱氨酸残基,所述PEG是马来酰亚胺PEG,所述反应在不存在甘氨酸或天冬氨酸的情况下进行,并将反应产物用 β -巯基乙醇处理。在其他情况下,所述GpA变体具有至少一个赖氨酸残基,所述PEG是mPEG-SC、mPEG-SCM或mPEG-SAS,并且所述反应在不存在DTT和甘油的情况下进行。

[0027] 正如本文中所公开的,L-天冬酰胺酶可以通过位点特异性PEG化,在通过氨基酸替换引入到所述L-天冬酰胺酶的氨基酸序列中的1至6个半胱氨酸或10至30个赖氨酸残基处PEG化。参见实施例4和5。具体来说,截短的GpA或人源化且截短的GpA可以通过引入下述残基PEG化:(a)在第49、52、225、257、281和/或340位处的半胱氨酸残基;或(b)在第7、53、54、57、58、98、106、233、250、257、281、311和/或340位处的赖氨酸残基。除了在特定位置处引入半胱氨酸或赖氨酸残基之外,可以将内源的半胱氨酸或赖氨酸残基突变(即用另一个残基替换),以在所述蛋白质的长度内更均匀地分配所述PEG化位点。就此而言,某些实施方式包括将残基Cys198用Ala、Val或Ser代替和/或将残基Lys223用Asp代替。在一个实施方式中,将Cys198用Ala代替,并且将所述L-天冬酰胺酶衍生物在Cys79处PEG化。在其他实施方式中,将Cys198用Ala代替,并将第49、225和340位处的氨基酸残基中的一者或多者用半胱氨酸代替。适合于PEG化的示例性的截短的GpA变体提供在SEQ ID NO:51(GpA369-C198A)、SEQ ID NO:52(GpA369-C198S)、SEQ ID NO:53(GpA369-C198V)、SEQ ID NO:54(GpA369-C198A+K225C)、SEQ ID NO:55(GpA369-C198A+K225C+E340C)、SEQ ID NO:56(GpA369-C198A+K225C+E340C+E49C)、SEQ ID NO:57(GpA369-C198A+K225C+E340C+E49C+Q257C)、SEQ ID NO:58(GpA369(hum)-组1+2+3-C198A)、SEQ ID NO:59、SEQ ID NO:60、SEQ ID NO:61、SEQ ID NO:62、SEQ ID NO:63、SEQ ID NO:64、SEQ ID NO:65和SEQ ID NO:86中。

[0028] 为了增加截短的GpA的体内循环时间,本发明还提供了具有组氨酸标签(His)、SUMO标签(SUMO)、白蛋白结合结构域(ABD)或其组合的变体,特别是截短的GpA变体。所述截短的GpA变体可以在其C端、N端和/或所述GpA序列中的内部位置处包括所述组氨酸标签、SUMO标签和/或白蛋白结合结构域。理想情况下,当His标签、SUMO标签或ABD被插入到所述GpA序列内(即不在N或C端处)时,所述插入在所述GpA蛋白的一个或多个柔性环中。举例说明,所述截短的GpA变体可以具有SUMO-天冬酰胺酶-ABD、His-SUMO-ABD-天冬酰胺酶、His-SUMO-天冬酰胺酶-ABD、His-SUMO-天冬酰胺酶、His-ABD-天冬酰胺酶、ABD-天冬酰胺酶、ABD-SUMO-天冬酰胺酶、天冬酰胺酶¹⁻²²⁵-ABD-天冬酰胺酶²²⁶⁻³⁶⁹、天冬酰胺酶¹⁻³⁴⁰-ABD-天冬酰胺酶³⁴¹⁻³⁶⁹等的N至C端结构。编码所述His、SUMO或ABD的核酸可以被同框插入到编码所述截短的GpA变体的核酸的5'或3',从而产生融合蛋白。

[0029] 理想情况下,组氨酸标签、SUMO标签、白蛋白结合结构域中的一者或多者或其组合的包含,可以显著增加L-天冬酰胺酶的体内循环时间。换句话说,所述变体与以等量的蛋白质剂量给药的野生型L-天冬酰胺酶相比具有更长的t_{1/2}。当在本文中使用术语“t_{1/2}”或“半衰期”是指在体外或体内例如注射到哺乳动物中后,截短的GpA变体或其融合蛋白的浓度下降一半所需的时间。考虑到L-天冬酰胺酶的效能与所述药物的体内半衰期相关,本发明的截短的GpA变体在癌症例如白血病和淋巴瘤的治疗中特别有用。

[0030] 当在本文中使用术语“组氨酸标签”是指由至少一个组氨酸(His)残基、优选地至少6个His残基构成的氨基酸基序。所述组氨酸标签包括6(六组氨酸标签、6xHis标签或His₆标签)、7、8、9、10或多达20个组氨酸残基的聚组氨酸。

[0031] “SUMO标签”是指将SUMO(小泛素相关修饰物)蛋白融合到感兴趣的蛋白质以提高所述感兴趣的蛋白质的溶解性/稳定性。SUMO标签的包含可以使用已知的表达系统例如CHAMPION pET SUMO表达系统(Invitrogen)、EXPRESSO T7 SUMO克隆和表达系统(Lucigen)或pET His6 SUMO TEV LIC克隆载体(Addgene)来实现。除了SUMO标签之外,还设想了可以

使用其他的Ub1蛋白,包括但不限于Ub、Rub1、Hub1、ISG15、Ubi-L(MNSF)、FAT10、Apg12、Apg8和Urm1(Larsen&Wang(2002)J.Proteome Res.1(5):411-9)。也参见整体通过引用并入本文的US 7,655,413。示例性的SUMO标签阐述在SEQ ID NO:66、SEQ ID NO:67、SEQ ID NO:68、SEQ ID NO:69和SEQ ID NO:70中。

[0032] “白蛋白结合结构域”或“ABD”是指在体内或体外结合白蛋白并提高治疗剂的血清半衰期和生物分布的多肽。白蛋白可以源自于任何动物物种,例如人、猴或啮齿动物。白蛋白结合结构域描述在例如US 6,267,964、WO 1991/19741、WO 2005/097202、WO 2001/45746、WO 2013/043071和US2004/0001827中。此外,US 9,156,887公开了非天然的白蛋白结合结构域,其可用于本发明。在某些实施方式中,所述白蛋白结合结构域具有在SEQ ID NO:71、SEQ ID NO:72或SEQ ID NO:73中阐述的氨基酸序列。

[0033] 本文公开的截短的GpA变体的增强的细胞毒性活性,可以通过将所述GpA偶联或融合到3个串联的TRAIL可溶性结构域或将所述GpA与稳定形式的TRAIL共同给药来实现。与缺少所述3个串联的TRAIL可溶性结构域的截短的GpA变体相比,所得到的融合蛋白可以提供IC₅₀值的至少20、25、30、35或40倍的降低。因此,融合到3个串联的TRAIL可溶性结构域的截短的GpA变体在癌症、特别是对L-天冬酰胺酶不敏感的癌症的治疗中特别有用。

[0034] “融合蛋白”是指含有以非本源方式可操作连接的蛋白质或蛋白质片段(例如GpA变体)的嵌合蛋白。根据本发明的融合蛋白,将3个串联的TRAIL可溶性结构域(TRAIL_{三聚体})与截短的GpA变体同框融合。理想情况下,将甘氨酸或丝氨酸残基插入到每个TRAIL重复序列之间,以便于所述TRAIL三聚体的折叠(参见例如SEQ ID NO:87和SEQ ID NO:88)。任选地,所述TRAIL三聚体和天冬酰胺酶组分可以被如SEQ ID NO:81、SEQ ID NO:82、SEQ ID NO:83或SEQ ID NO:84中所阐述的连接物隔开。所述融合蛋白可以包括融合到GpA的C端(GpA-TRAIL_{三聚体};例如SEQ ID NO:89和SEQ ID NO:90)或N端(TRAIL_{三聚体}-GpA;例如SEQ ID NO:91和SEQ ID NO:92)的TRAIL三聚体,其中所述GpA组分可以是任何上文描述的变体。当进一步与标签或修饰组合使用时,所述融合蛋白可以具有下述结构:SUMO-TRAIL_{三聚体}-GpA-ABD,His-SUMO-ABD-TRAIL_{三聚体}-GpA,His-SUMO-TRAIL_{三聚体}-GpA-ABD,His-SUMO-GpA-TRAIL_{三聚体},His-ABD-TRAIL_{三聚体}-GpA,ABD-GpA-TRAIL_{三聚体},ABD-SUMO-TRAIL_{三聚体}-GpA等。除了被插入在N或C端处之外,所述ABD肽可以被嫁接在GpA变体的一个或多个柔性环中。在一个实例中,所述柔性环跨越第215至228位残基。在另一个实例中,所述柔性环跨越GpA的第337至342位残基。参见例如SEQ ID NO:94。编码TRAIL特别是TRAIL_{三聚体}的核酸可以被同框插入到编码所述L-天冬酰胺酶的核酸的5'或3',从而产生所述融合蛋白。

[0035] 优选地,所述TRAIL可溶性结构域源自于哺乳动物、特别是人类TRAIL,包括其等位基因变体和/或衍生物。所述可溶性结构域包括TRAIL的细胞外部分,包括受体结合结构域而没有膜定位结构域。与TNF超家族的其他蛋白质类似,TRAIL通过15-30个氨基酸的N端部分、即所谓的茎区,锚定到膜。所述茎区对三聚体化有贡献,并提供了与细胞膜的一定距离。然而,所述茎区不是受体结合结构域(RBD)的一部分。因此,所述可溶性TRAIL结构域优选地包括TRAIL的受体结合结构域并缺少来自于茎区的任何氨基酸(参见US2015/0337027)。

[0036] 所述可溶性TRAIL结构域可以源自于人类TRAIL。优选地,所述可溶性TRAIL结构域源自于人类TRAIL,特别是从人类TRAIL的第115-122位氨基酸残基开始,并包括第115-281、120-281、121-281或122-281位氨基酸残基。在某些实施方式中,TRAIL_{三聚体}的每个可溶性结

构域由人类TRAIL的第115-281位残基构成。人类TRAIL的第115-281位残基在本文中阐述在SEQ ID NO:80中。为了促进正确折叠,可以将甘氨酸或丝氨酸残基插入到每个TRAIL重复序列之间。参见例如SEQ ID NO:87和SEQ ID NO:88。

[0037] 设想了结合死亡受体的TRAIL结构域的所有衍生物和变体,并且可以通过改变它们的氨基酸序列来制造所述衍生物和变体,所述改变通过替换、添加和/或缺失/截短或通过引入产生功能上等同的多肽的化学修饰来进行。本领域普通技术人员将会理解,任何多肽的序列中的某些氨基酸可以被替换为其他氨基酸而对所述多肽的活性没有不利影响。

[0038] 本文中公开的TRAIL结构域包括所公开的序列中的一个或多个氨基酸的替换。专业技术人员能够使用公知的技术确定本文中阐述的肽的适合的序列变体。在某些实施方式中,专业技术人员可以通过靶向据信对活性不重要的区域,来鉴定所述分子的可以被改变而不破坏活性的适合区域。在其他实施方式中,专业技术人员可以鉴定所述分子的在相似多肽之间保守的残基和部分。在其他实施方式中,即使是对生物学活性或对结构来说重要的氨基酸残基也可能经历保守氨基酸替换,而不破坏其生物学活性或对肽结构没有不利影响。

[0039] 所述三个TRAIL可溶性结构域优选地通过由1至8个氨基酸残基构成的肽连接基团彼此相连。同样地,TRAIL_{三聚体}优选地通过由1至20个氨基酸残基构成的肽连接基团连接到所述L-天冬酰胺酶。术语“肽连接基团”或“连接物”意指充当分子桥梁以将两个不同分子可操作连接在一起的肽组成部分。理想地,本发明的连接物由甘氨酸或丝氨酸或其组合构成。在特定实施方式中,TRAIL_{三聚体}的每个可溶性结构域优选地通过单个甘氨酸或单个丝氨酸残基彼此相连。示例性的TRAIL_{三聚体}在所述三个可溶性TRAIL结构域之间包括单个丝氨酸残基(SEQ ID NO:88)。对位于所述TRAIL_{三聚体}与L-天冬酰胺酶之间的肽连接基团来说,理想地该连接物是柔性连接物。所述柔性连接物优选地具有1至20个氨基酸残基的长度,特别是6、9、12、15或18个氨基酸残基的长度。所述柔性连接物优选为甘氨酸/丝氨酸连接物,即主要由氨基酸甘氨酸和丝氨酸构成的肽连接物。在特定实施方式中,所述TRAIL_{三聚体}与L-天冬酰胺酶之间的连接物是(GGGS)_n连接物(SEQ ID NO:81),其中n是1至4,或其排列包括例如GGGS(GGGGS)_n(SEQ ID NO:82),其中n是1至4。在某些实施方式中,所述TRAIL_{三聚体}与L-天冬酰胺酶之间的连接物具有SEQ ID NO:83中阐述的氨基酸序列。在其他实施方式中,所述TRAIL_{三聚体}与L-天冬酰胺酶之间的连接物具有SEQ ID NO:84中阐述的氨基酸序列。TRAIL_{三聚体}-GpA变体融合蛋白的实例具有N端TRAIL_{三聚体},其包括在所述三个可溶性TRAIL结构域之间的单个甘氨酸或丝氨酸残基和所述TRAIL_{三聚体}与截短的GpA变体之间的甘氨酸/丝氨酸连接物。参见例如SEQ ID NO:89、SEQ ID NO:90、SEQ ID NO:91和SEQ ID NO:92。

[0040] 稳定形式的TRAIL意指促进三聚体化的TRAIL形式。具体来说,为了促进TRAIL的三聚体化,已显示一个小的三聚体化结构域即FOLDON序列(GYIPEAPRDGQAYVRKDGEWVLLSTFL; SEQ ID NO:85)在37℃下维持TRAIL的稳定性和生物学活性至少48小时(Kouno等,(2013) J. Invest. Dermatol. 133 (9):2212-2220)。因此,将所述FOLDON肽插入到His-SUMO标签与TRAIL的N端之间,以产生His-SUMO-FOLDON-TRAIL融合蛋白。将所述融合蛋白表达,并在细胞培养物中获得>10mg/L的融合蛋白产量。所述蛋白非常稳定,显示出FOLDON的包含产生稳定形式的TRAIL。因此,稳定形式的TRAIL可以与截短的GpA变体共同给药和/或合并并在药物组合物中,以提高所述GpA的细胞毒性活性。

[0041] 本文中公开的截短的GpA变体和融合蛋白可以通过常规的重组蛋白技术容易地制备,其中将重组宿主细胞用带有编码所述变体或融合蛋白的核酸分子的表达构建物或载体转化或转导,将所述重组宿主细胞在适合条件下生长以提供所述变体或融合蛋白的表达,随后将所述变体或融合蛋白分离并任选地纯化。因此,本发明还提供了编码截短的GpA变体或其融合蛋白的核酸分子,以及含有它们的表达盒和/或表达载体。理想情况下,所述表达盒和表达载体含有必需的调控序列(例如启动子、终止子等)以促进在感兴趣的宿主细胞中的表达。包含编码截短的GpA变体或融合蛋白的核酸分子的宿主细胞,也被包括在本发明的范围之内。宿主细胞可以包括真核细胞(例如哺乳动物、真菌或酵母细胞)或原核细胞(例如大肠埃希氏杆菌)。

[0042] 在生产和分离/纯化后,本发明的截短的GpA变体和/或融合蛋白可以原样使用或配制在含有可药用赋形剂的药物组合物中。本文中提供的药物组合物可以被特别配制用于静脉内给药的固体或液体形式或用于静脉内注射。最适的药物组合物可以由本领域技术人员根据例如所打算的给药途径、递送格式和所需剂量来确定。参见例如《雷明顿制药学》(Remington's Pharmaceutical Sciences)(第19版,1995)。

[0043] 所述截短的GpA变体和/或融合蛋白可以被并入到常规的系统剂型例如注射用制剂中。所述剂型也可以包括必需的生理上可接受的载剂材料、赋形剂、润滑剂、缓冲剂、表面活性剂、抗菌剂、增量剂(例如甘露糖醇)、抗氧化剂(抗坏血酸或亚硫酸氢钠)等。

[0044] 药物组合物中的主要载剂或赋形剂在本质上可以是水性或非水性的。例如,适合的载体或赋形剂可以是注射用水、生理盐水溶液或人造脑脊液,并可能增补有在用于肠胃外给药的组合物中常用的其他材料。中性缓冲盐水或与血清白蛋白混合的盐水是另外的示例性媒剂。药物组合物可以包括约pH 7.0-8.5的Tris缓冲液或约pH 4.0-5.5的乙酸盐缓冲液,其可以进一步包括山梨糖醇或其适合的替代物。本发明的药物组合物可以通过将具有所需纯度的所选组合物与任选的配制剂(《雷明顿制药学》(Remington's Pharmaceutical Sciences),同上)混合制备成冻干饼或水性溶液的形式,以备储存。此外,可以使用适合的赋形剂例如蔗糖或甘氨酸,将本发明的截短的GpA变体或融合蛋白配制成冻干物。

[0045] 用于本发明的截短的GpA变体、融合蛋白或药物组合物的给药途径包括通过静脉内、腹膜内、脑内(实质内)、脑室内、肌肉内、眼内、动脉内、门静脉内或病灶内途径的注射,通过持续释放系统或通过植入装置。组合物可以通过快速浓注或连续输注或植入装置来给药。组合物也可以通过其上吸收或包封有所需分子的膜、海绵或其它适合材料的植入,局部地给药。在使用植入装置的情况下,所述装置可以被植入到任何适合的组织或器官中,并且所需分子的递送可以通过扩散、定时释放丸剂或连续给药来进行。

[0046] 本发明的组合物可以肠胃外递送。当考虑肠胃外给药时,在本发明中使用的治疗性组合物可以采取无热原、肠胃外可接受的水性溶液的形式,其在可药用媒剂中包含在本发明的筛选方法中鉴定到的所需化合物。特别适合于肠胃外注射的媒剂是无菌蒸馏水,将在本发明的筛选方法中鉴定到的化合物在其中配制成无菌等渗溶液,适合地保存。制备可以包括将所需分子与可以提供产品的受控或持续释放的试剂例如可注射微球、生物溶蚀性粒子、聚合化合物(例如聚乳酸或聚乙醇酸)、珠子或脂质体制剂,它们然后可以通过储库注射来递送。含有透明质酸的剂型具有促进在循环中的持续时间的效果。可植入的药物递送装置可用于引入所需分子。

[0047] 所述组合物也可以配制成用于吸入。在这些实施方式中,将所述截短的GpA变体或融合蛋白配制成用于吸入的干粉,或者也可以使用推进剂配制成吸入溶液,用于气溶胶递送例如通过喷雾递送。肺部给药被进一步描述在WO 1994/020069中,其描述了化学修饰的蛋白质的肺部递送。

[0048] 本发明的组合物可以通过消化道例如经口递送。这类可药用组合物的制备在本领域的技术范围之内。以这种方式给药的本发明的截短的GpA变体或融合蛋白,可以使用或不使用在固体剂型例如片剂和胶囊的混料中常规使用的载剂来配制。胶囊可以被设计成在胃肠道中生物可利用性被最大化并且系统前降解被最小化的位点处释放所述剂型的活性部分。可以包含另外的试剂以促进本文公开的本发明的肽的吸收。还可以使用稀释剂、调味剂、低熔点蜡、植物油、润滑剂、悬浮剂、片剂崩解剂和粘合剂。

[0049] 这些组合物也可以含有辅助剂例如防腐剂、润湿剂、乳化剂和分散剂。微生物作用的阻止可以通过包含各种不同的抗细菌和抗真菌剂例如对羟基苯甲酸酯、氯丁醇、苯酚、山梨酸等来确保。包括等渗剂例如糖类、氯化钠等,可能也是合乎需要的。注射药物形式的延长吸收,可以通过包含延迟吸收的试剂例如单硬脂酸铝和明胶来产生。

[0050] 本发明的截短的GpA变体和/或融合蛋白在可以通过剥夺天冬酰胺来治疗的疾病或病状的治疗中特别有用。因此,本发明还提供了用于治疗疾病、特别是癌症的方法,所述方法通过向需要治疗的对象给药有效量的截短的GpA变体或融合蛋白。“有效量”在本文中用于指称活性成分的足以实现预期目的的量,所述目的是:(a)减轻所述病症的严重性;(b)限制或阻止正在被治疗的病症的特征性症状的发展;(c)抑制正在被治疗的病症的特征性症状的恶化;(d)在以前患过所述病症的患者中限制或阻止所述病症的复发;(e)在以前具有所述病症的症状的患者中限制或阻止症状的复发;(f)降低疾病或病症出现后的死亡率;(g)治愈;和(h)疾病的预防。在每个单独情况下,所述有效量可以由专业技术人员根据本领域中已确立的方法凭经验确定。当在本发明的情形中使用,“给药”包括体内给药到个体以及在体外或离体直接给药到细胞或组织。截短的GpA变体或融合蛋白的有效量通常是在癌细胞或对象的肿瘤中诱导凋亡并减少循环L-天冬酰胺的量。临床医生可以调整剂量或给药途径以获得最佳治疗效果。

[0051] 在某些实施方式中,所述截短的GpA变体或融合蛋白可用于治疗或制造药物以用于治疗癌症例如成人和儿童两者中的急性成淋巴细胞性白血病(ALL)以及预期天冬酰胺贫化在其中具有有用效果的其他病症。这些病症包括但不限于恶性肿瘤或癌症,包括但不限于血液恶性肿瘤、非霍奇金淋巴瘤、NK淋巴瘤、胰腺癌、卵巢癌、霍奇金病、急性髓细胞性白血病、急性髓单核细胞性白血病、慢性淋巴细胞性白血病、淋巴肉瘤、网状细胞肉瘤和黑素肉瘤。对天冬酰胺贫化有响应的代表性的非恶性血液疾病包括免疫系统介导的血液疾病例如传染病,例如由HIV感染引起的传染病(即AIDS)。与天冬酰胺依赖性相关的非血液疾病包括自体免疫疾病例如类风湿性关节炎、SLE、自体免疫、胶原血管病、AIDS等。其他自体免疫疾病包括骨关节炎、艾萨克斯综合征、银屑病、胰岛素依赖型糖尿病、多发性硬化症、硬化性全脑炎、系统性红斑狼疮、风湿热、炎性肠病(例如溃疡性结肠炎和克罗恩病)、原发性胆汁性肝硬化、慢性活动性肝炎、肾小球肾炎、重症肌无力、寻常型天疱疮和格雷夫斯病。在特定实施方式中,所述截短的GpA变体或融合蛋白被用于治疗非霍奇金淋巴瘤、白血病、急性成淋巴细胞性白血病、急性髓性白血病、B细胞淋巴瘤、伯基特淋巴瘤、慢性髓细胞性白血病、

慢性淋巴细胞性白血病和毛细胞白血病。

[0052] 怀疑引起疾病的细胞可以在任何适合的体外或体内测定法中测试天冬酰胺依赖性,例如其中生长培养基缺少天冬酰胺的体外测定法。因此,一方面,本发明涉及一种在患者中治疗可治疗疾病的方法,所述方法包括向所述患者给药有效量的本发明的截短的GpA变体或融合蛋白。在特定实施方式中,所述疾病是ALL。在特定实施方式中,在可以通过天冬酰胺剥夺治疗的疾病的治疗中使用的截短的GpA变体或融合蛋白包括来自于豚鼠的截短的GpA变体。

[0053] 所述截短的GpA变体或融合蛋白可以根据从约每周三次至约每月一次、通常为每周一次或每隔周一次的时间表,作为单一药剂(例如单药疗法)或作为与化疗药物的组合的一部分来给药,所述化疗药物包括但不限于糖皮质激素、皮质类固醇、抗癌化合物或其他药剂包括但不限于甲氨蝶呤、地塞米松、泼尼松、泼尼松龙、长春新碱、环磷酰胺和蒽环类药物。作为实例,患有ALL的患者将在包括诱导、巩固或强化和维持的3个化疗阶段中,作为多药剂化疗的组分给药本发明的截短的GpA变体或融合蛋白。在特定实例中,所述截短的GpA变体或融合蛋白不与天冬酰胺合成酶抑制剂一起给药(例如参见WO 2007/103290)。在另一个特定实例中,所述截短的GpA变体或融合蛋白不与天冬酰胺合成酶抑制剂一起给药,但与其他化疗药物一起给药。所述截短的GpA变体或融合蛋白可以在作为多药剂化疗方案的一部分的其他化合物之前、之后或同时给药。

[0054] 在特定实施方式中,所述方法包括以约1U/kg至约1000U/kg的量给药本发明的截短的GpA变体或融合蛋白。在更特定实施方式中,所述截短的GpA变体或融合蛋白以选自约20、50、60、70、100、200、300、400、500和600U/kg的量给药。在另一个特定实施方式中,所述截短的GpA变体或融合蛋白以约1000IU/m²至约20000IU/m²范围内的剂量(例如1000IU/m²、2000IU/m²、3000IU/m²、4000IU/m²、5000IU/m²、6000IU/m²、7000IU/m²、8000IU/m²、9000IU/m²、10000IU/m²、11000IU/m²、12000IU/m²、13000IU/m²、14000IU/m²、15000IU/m²、16000IU/m²、17000IU/m²、18000IU/m²、19000IU/m²或20000IU/m²)给药。在另一个特定实施方式中,所述截短的GpA变体或融合蛋白以在约3天至约10天(例如3、4、5、6、7、8、9或10天)的时间段中将Asn贫化至不可检测的水平的剂量单剂给药。在另一个实施方式中,所述方法包括给药本发明的截短的GpA变体或融合蛋白,其与野生型L-天冬酰胺酶相比在单剂后具有更长的体内循环半衰期。

[0055] 提供了下述非限制性实施例以进一步说明本发明。

[0056] 实施例1:有活性的C端截短的GpA的产生

[0057] 哺乳动物L-天冬酰胺酶例如人类L-天冬酰胺酶(hASNase1;UNIPROT登记号Q86U10;SEQ ID NO:2)和豚鼠L-天冬酰胺酶(gpASNase1或GpA;UNIPROT登记号H0W0T5;SEQ ID NO:1)含有两个结构域:L-天冬酰胺酶活性居于其中的~360个残基的N端结构域,和功能未知的~200个残基的C端结构域。作为比较,来自于大肠埃希氏杆菌和菊欧文氏菌(*Erwinia chrysanthemi*)的临床上相关的细菌L-天冬酰胺酶长度为约350个氨基酸残基,并且不含这种C端结构域。

[0058] 可注射生物治疗剂的挑战之一来自于短的半衰期,其导致不良的生物可利用性。清除主要由蛋白水解、肾滤过或免疫系统的中和引起。更大的外来序列分子具有更大机会被免疫系统检测并从系统快速清除。鉴定较短但仍稳定版本的GpA预期会提供更好的治疗

剂,特别是在全长蛋白的C端结构域功能未知的情况下。

[0059] 为了评估GpA的C端残基的功能,构建了C端截短的GpA变体并分析其稳定性和完整L-天冬酰胺酶活性。hASNase1、GpA、大肠杆菌L-天冬酰胺酶和欧文氏菌L-天冬酰胺酶的序列比对和晶体结构分析表明催化结构域结束于第359位残基。由GpA的第1-359位残基(SEQ ID NO:3)构成的构建物被重组表达,但纯化的C-截短的酶是不稳定的。因此,制备了融合到SUM0标签的另外的C端截短的GpA构建物(表1)。

[0060] 表1

GpA	残基*	SEQ ID NO:
全长GpA	1-565	1
GpA359	1-359	3
GpA367	1-367	4
GpA369	1-369	5
GpA374	1-374	6
GpA384	1-384	7
GpA392	1-392	8
GpA396	1-396	9

[0062] *相对于SEQ ID NO:1。

[0063] 这些C端截短的GpA构建物的重组过表达表明所有蛋白质都被良好地过表达,并被纯化到>95%的纯度(通过SDS-PAGE测量)。尽管在稳定性SUM0标签被切掉后GpA367在数分钟内快速沉淀,但更长的变体显示出与全长蛋白可比的出色的稳定性和活性。值得注意的是,带有额外的Cys388的较长构建物倾向于形成非特异性二硫键,改变了L-天冬酰胺酶活性所必需的四聚体形式。尽管正如在本文中证实的由至少第1-369位残基构成的C端截短的GpA产生具有L-天冬酰胺酶活性的稳定的GpA酶,但由第1-359或1-367位残基构成的C端截短的GpA的稳定性可以通过与异源肽/蛋白质(例如SUM0标签或白蛋白)的融合或化学修饰(例如PEG化)而被稳定化。

[0064] 实施例2:通过定向进化产生的人源化GpA变体

[0065] 概述。定向进化或在实验室中模拟自然进化过程的过程,被广泛用于改进酶的性能。参见例如Dalby(2011)Curr.Opin.Struct.Biol.21:473-480;Goldsmith&Tawfik(2012)Curr.Opin.Struct.Biol.22:406-412;Labrou(2010)Curr.Protein Pept.Sci.11:91-100;Wang&Zhao(2012)Bioresour.Technol.115:117-125。由于在文库生成、筛选技术方面的进展,最重要的是对自然蛋白质进化的机制的更好的理解,已获得经进化的催化活性的大大提高(相对于起点,并根据绝对 k_{cat}/K_m 值)(Fasan等,(2008)J.Mol.Biol.383:1069-80;Bar-Even等,(2011)Biochemistry(Mosc.)50:4402-10)。

[0066] 为了克服免疫原性,通过定向进化方法产生了具有与II型大肠杆菌L-天冬酰胺酶相近的动力学性质的人类样L-天冬酰胺酶。使用DNA家族改组,鉴定到与hASNase1具有高的序列同一性但具有gpASNase1的低 K_m 性质的几个克隆。

[0067] 菌株。染色体基因缺失使用 λ -red重组酶系统来进行(Datsenko&Wanner(2000)Proc.Natl.Acad.Sci.U.S.A.97:6640-6645)。将酪氨酸氨基转移酶基因tyrB、天冬氨酸氨基转移酶基因aspC和L-天冬酰胺酶基因ansA、ansB、iaaA从大肠杆菌BW25113 F⁻,DE(araD-

araB) 567, lacZ4787 (del)::rrnB-3, LAM-, rph-1, DE(rhaD-rhaB) 568, hsdR514 的染色体中缺失, 得到大肠杆菌 BW5 Δ 。简单来说, 按照已知方法, 使用引物对来扩增被来自于适合的 keio 菌株的卡那霉素抗性表达盒代替的基因 (Datsenko & Wanner (2000) Proc. Natl. Acad. Sci. U.S.A. 97:6640-6645)。然后, 将所述线性 PCR 产物用于代替 BW25113 染色体上被靶向基因的整个开放阅读框。将含有正确基因缺失的菌落用 FLP 重组酶质粒 pCP20 转化以除去卡那霉素抗性标志物, 然后将 pCP20 从得到的菌株中消除。遵照相同的过程并在基因 ansA 和 ansB 缺失后获得大肠杆菌菌株 BW2 Δ 。

[0068] 将 hASNase1 和 gpASNase1 克隆到 BW2 Δ 和 BW5 Δ 中。使用引物 NdeI-hA_F1 和 hA-BamHI_R573 以及引物 NdeI-gpA_F1 和 gpA-BamHI_R565 分别扩增编码 hASNase1 的密码子优化序列和 gpASNase1 的密码子优化序列的基因 (表 2)。在 BamHI/NdeI 消化后, 将 PCR 产物插入到 pBAD 载体中。然后将得到的载体用于转化菌株 BW5 Δ 和 BW2 Δ , 得到菌株 BW5 Δ pBAD_hASNase1、BW5 Δ pBAD_gpASNase1、BW2 Δ pBAD_hASNase1 和 BW2 Δ pBAD_gpASNase1。还将 BW5 Δ 和 BW2 Δ 用 pBAD 空载体转化以充当对照。

[0069] 表 2

[0070]

引物	序列 (5'→3')	SEQ ID NO:
gpA-BamHI_R565	AACGTCGGATCCTTAAATAGCCGG CGGGACTTC	10
gpA_F	ATGGCACGCGCTTCGGGCTCGGAA	11
gpA_R	CCAGATTACGCAGCAGAGC	12
hA-F	GCTCGTGCTGTGGGTCCGGAA	13
hA_R	GACACCCGGCAGCACTTC	14
gpA360-367_R	CTGATGCAGGTCTGCCGTCGGCAG CGTCATTTACCGCGCAGGT	15
hA354-361_F	AAGGACCTGCGCGGTGAAATGAC GCTGCCGACGGCAGACCTGC	16
hA362-369_R	GCGACGTTCTTCCACAGACGGCGG GGTCATTTACCCACGCAGATC	17
gpA352-359_F	AAAGATCTGCGTGGTGAAATGACC CCGCCGTCTGTGGAAGAACG	18
Lib1 M22R23_F	TACACCGGCGGCACCATTTGGCANNK NNKAGTGAGCTCGGCGTGCTTGTG	19
Lib1 M22R23_R	CACAAGCACGCCGAGCTCACTMN NMNNGCCAATGGTGCCGCCGGTG TA	20
Lib2 D84S86_F	CTGGAGTGCCAGCCCCTCTTCNNK TCCNNKGACATGACCATCGCTGAG TGG	21

[0071]

Lib2 D84S86 R	CCACTCAGCGATGGTCATGTCMNN GGAMNNGAAGAGGGGCTGGCACT CCAG	22
Lib3 H114G115_F	CAGTACCACGGCTTTGTGGTCATC NNKNNKACCGACACCATGGCCTTT GCTGCC	23
Lib3 H114G115_R	GGCAGCAAAGGCCATGGTGTCGG TMNNMNNGATGACCACAAAGCCG TGGTACTG	24
Lib4 A142Q143V144_F	AGAAGACTGTCATCCTCACTGGGN NKNNKNNKCCCATCCATGCCCTGT GGAGC	25
Lib4 A142Q143V144_R	GCTCCACAGGGCATGATGGGMNN MNNMNNCCCAGTGAGGATGACAG TCTTCT	26
Lib5 A191R192_F	GCAACCGGGCAACCAAGGTAGAC NNKNNKAGGTTCGCAGCTTTCTGC TCCCC	27
Lib5 A191R192_R	GGGGAGCAGAAAGCTGCGAACCT MNNMNGTCTACCTTGGTTGCCC GGTTGC	28
Lib6 T118F121_F	TCATCCACGGCACCGACNNKATGG CCNNKGCTGCCTCGATGCTGTCC	29
Lib6 T118F121_R	GGACAGCATCGAGGCAGCMNNGG CCATMNNGTCGGTGCCGTGGATG A	30
Lib7 A91C95T99_F	TCCAGTGACATGACCATCNNKGAG TGGGTTNNKCTTGCCCAGNNKATC AAGAGGCACTACGAG	31
Lib7	CTCGTAGTGCCTCTTGATMNNCTG	32

[0072]	A91C95T99_R	GGCAAGMNNAACCCACTCMNNGA TGGTCATGTCACTGGA	
	Lib8 R23E25L26_F	GGCGGCACCATTTGGCATGNNKAG TNNKNNKGGCGTGCTTGTGCCCCGG G	33
	Lib8 R23E25L26_R	CCCGGGCACAAGCACGCCMNNMN NACTMNNCATGCCAATGGTGCCG CC	34

[0073] 培养基和生长实验。M9完全培养基由M9最低盐(Sigma)制成,并增补有0.4%甘油、2 μ M硫胺素、1mM MgSO₄、0.1mM CaCl₂和100 μ g/mL氨苄青霉素。对于完全M9平板来说,添加15g/L的琼脂。对于使用菌株BW2 Δ 的实验来说,制造不含NH₄Cl的M9培养基。在需要时,向M9培养基添加不同浓度的L-天冬酰胺酶。为了诱导克隆在pBAD载体中的hASNase1和gpASNase1的表达,向所述M9培养基添加0.02%阿拉伯糖。对于在完全M9琼脂平板上的生长实验来说,将所述菌株首先在LB中在37 $^{\circ}$ C下生长过夜,离心下来并在M9培养基中清洗。然后将该悬液的适当稀释液铺展在M9平板上,以便为每种菌株获得相同的菌落数目。将平板在37 $^{\circ}$ C温育48至96小时。

[0074] DNA改组。DNA改组按照描述(Meyer等,(2014) Curr. Protoc. Mol. Biol., Ausubel (ed) 105:Unit-15.12)并做出略微调整来进行。简单来说,将hASNase1和GpA基因的等摩尔混合物用0.5U DNase (NEB) 消化2分30秒。使用QIAQUICK凝胶提取试剂盒(Qiagen)提取100bp至200bp之间的片段,通过PCR组装,然后使用对GpA基因特异的引物或对hASNase1基因的引物扩增。使用Megawhop方法(Miyazaki (2003) Methods Mol. Biol. 231:23-28)将得到的改组片段克隆到pBAD载体中。简单来说,将100至300ng的改组的片段用作大引物,使用pBAD_hASNase1或pBAD_gpASNase1作为模板运行全质粒PCR。在用DpnI消化所述模板后,将20至40ng的含有所述改组序列的新合成的质粒用于转化电转感受态BW5 Δ 细胞。在电脉冲后,将细胞重悬浮在1ml SOC培养基中,并在37 $^{\circ}$ C下振荡温育1小时。然后将细胞以4000x g离心4分钟,并轻柔重悬浮在200 μ L M9培养基中。将100 μ L铺板于增补有0.2mM Asn或2mM Asn的M9平板上。在将所述板在37 $^{\circ}$ C温育4天后,从2mM Asn平板分离菌落并汇集在200 μ L新鲜M9培养基中。连续进行两次稀释并将其用于铺板新鲜的0.2mM Asn M9平板。在37 $^{\circ}$ C下温育4天并在室温下温育另外3天后,将能够在0.2mM Asn平板上生长的克隆分离并在LB平板上划线。

[0075] C端结构域交换。为了建立克隆h_N-g_C,使用引物NdeI-hA_F1和gpA360-367_R扩增对应于hASNase1的N端结构域(h_N,第1-361位残基)的序列,并使用引物hA354-361_F和gpA-BamHI_R565扩增对应于gpASNase1的C端结构域(g_C,第360-565位残基)的序列。为了建立克隆g_N-h_C,使用引物NdeI-gpA_F1和hA362-369_R扩增对应于gpASNase1的N端结构域(g_N,第1-359位残基)的序列,并使用引物gpA352-359_F和hA_BamHI_R573扩增对应于hASNase1的C端结构域(h_C,第362-573位残基)的序列。引物被列于表2中。然后使用适合的引物通过片段h_N和g_C或g_N和h_C的PCR融合来构建嵌合体,然后克隆到pBAD和pET载体中。

[0076] 所选克隆的克隆和表达。将分离的克隆进行培养;提取质粒并测序。将相应的基因转移到pET载体(改良的pET14b以包括His-SUMO标签,使用与用于克隆到pBAD载体中的引物相同的引物),以允许在C41(DE3)细胞中表达带有His标签的蛋白。在增补有100 μ g/mL氨苄青霉素的1L 2YT培养基中进行培养。使用0.1mM IPTG诱导表达,并将细胞在18 $^{\circ}$ C生长过夜。按照以前对野生型gpASNase1所描述的将细胞收获、裂解并纯化(Schalk等,(2014) J.Biol.Chem.289:33175-86)。将所述蛋白质在25mM Tris-HCl pH 7.5,200mM KCl,500mM 咪唑缓冲液中洗脱,并针对不含咪唑但含有1mM DTT的相同缓冲液透析。大肠杆菌ansB酶的表达和纯化以前已描述过(Schalk等,(2014) J.Biol.Chem.289:33175-86)。

[0077] 动力学测定法。所述克隆的催化活性使用光谱学NADH依赖性酶偶联测定法来确定(Fernandez等,(2013) Int.J.Clin.Exp.Med.6:478-487;Hejazi等,(2002) Biochem.J.364:129-136),所述测定法通过还原型NADH的1:1氧化来测量L-天冬氨酸(Asp)的生产。NADH向NAD的转化通过分光光度法被测量为在37 $^{\circ}$ C下340nm处吸收值的降低。所有测量在含有100mM Tris pH 7.5,0.4mM α -酮戊二酸和0.4mM NADH以及50nM(hASNase1,hN-gC)、10nM(gpASNase1,gN-hC、63-hC、64-hC、65-hC,SA-hC)或3nM(ansB)酶的缓冲液中一式三份进行。谷草转氨酶(Sigma)和苹果酸脱氢酶(Sigma)是用于偶联酶反应的辅助酶,分别使用5单位和1单位。使用SigmaPlot(Systat Software Inc)将数据拟合到米氏方程。由于hASNase1的协同本性,该酶使用希尔方程来分析。

[0078] 细胞培养。LOUCY(Ben-Bassat等,(1990) Cancer Genet.Cytogenet.49(2):241-8)和SUP-B15(ATCC CRL-1929)细胞系在现有技术中已被描述。将所有细胞系通过STR(短串联重复序列)进行分析,并确认与来自于Global Bioresource Center ATCC的相应STR剖析数据100%匹配。所有细胞系被核实为无支原体。LOUCY和SUP-B15细胞系在加湿气氛(5%CO₂,37 $^{\circ}$ C)中,使用增补有10%FBS(Hyclone)和1x青霉素-链霉素溶液(Invitrogen)的RPMI 1640培养基培养。L-谷氨酰胺被直接添加到细胞培养物中至终浓度为2mM。将细胞悬浮液(5 $\times$ 10⁵个细胞/mL)的90 μ L等分试样在圆底96孔微量滴定板中,在10 μ L DPBS(Dulbecco的磷酸盐缓冲盐水,Mediatech)或终浓度在0.00001至0.1IU/mL范围内的不同L-天冬酰胺酶存在下进行一式三份培养。在将所述板在37 $^{\circ}$ C和含有5%CO₂的加湿空气中温育4天后,添加11 μ L Alamar Blue(Invitrogen)至终浓度为10%(v/v),并将所述板继续温育2小时,然后读取荧光信号。白血病细胞存活率被计算为在L-天冬酰胺酶存在下相比于在DPBS对照中的荧光计数的百分率。

[0079] 选择系统的开发。为了产生用于L-天冬酰胺酶活性的选择系统,需要其生长依赖于酶反应的任何产物的细菌菌株。由于L-天冬酰胺酶催化Asn水解成Asp和氨,开发并测试了两个选择系统:一个系统利用依赖于反应产物铵作为唯一氮源的细菌菌株,另一个系统使用对Asp营养缺陷的菌株。

[0080] 菌株BW2 Δ :在氮源方面对L-天冬酰胺酶反应的依赖性。所有生命形式都需要氮源。对于在最低培养基例如M9中生长的大肠杆菌来说,氮源通常以NH₄Cl盐的形式获得。然而,在不存在NH₄Cl的情况下,验证了在本研究中使用的大肠杆菌BW菌株可以使用培养基中的2mM Asn生长。这证实了大肠杆菌可以通过它的内源L-天冬酰胺酶的活性使用Asn作为氮源。为了制造依赖于由外源L-天冬酰胺酶活性产生的NH₄Cl的BW大肠杆菌菌株,从大肠杆菌BW亲代菌株缺失两个内源L-天冬酰胺酶基因(ansA和ansB),其在此后文中被称为BW2 Δ 。值得

注意的是,第三种内源L-天冬酰胺酶(iiiA)未被缺失,因为它对Asn具有非常高的 K_m 值。事实上,在实验条件下,即使在培养基中使用2mM Asn,BW2 Δ 菌株的生长也极大受损。

[0081] 菌株BW5:在天冬氨酸方面对L-天冬酰胺酶反应的依赖性。大肠杆菌可以通过水解Asn(L-天冬酰胺酶反应)或通过氨基转移酶反应产生Asp。事实上,亲代BW菌株独立地在M9培养基中良好生长,并且Asp增补没有影响。为了产生对Asp营养缺陷的大肠杆菌菌株,将所有3个内源L-天冬酰胺酶基因(ansA、ansB和iiiA)缺失,并且也将两个相关的氨基转移酶基因(aspC和tyrB)缺失。这5个基因被缺失的菌株被称为菌株BW5 Δ 。为了确保菌株BW5 Δ 获得Asp营养缺陷,在增补和未增补Asp的最低培养基M9中测试生长。观察到在未用Asp增补培养基的情况下BW5 Δ 不能生长。然而,在增补Asp的条件下观察到生长。

[0082] 使用BW2 Δ 和BW5 Δ 菌株选择表达L-天冬酰胺酶的克隆。为了调查这些细菌菌株是否可用作针对L-天冬酰胺酶活性的选择系统以及最重要的是调查它们是否允许在 K_m 性质的基础上在L-天冬酰胺酶之间做出区分,分析了表达具有低 K_m 的L-天冬酰胺酶或具有高 K_m 的L-天冬酰胺酶的BW2 Δ 和BW5 Δ 菌株的生长。待进化的蛋白靶人类I型L-天冬酰胺酶(hASNase1)的特征在于对Asn的 K_m 在毫摩尔范围内(Karamitros&Konrad(2014) J.Biol.Chem.289:12962-75;Schalk等,(2014) J.Biol.Chem.289:33175-86),并因此被用作高 K_m L-天冬酰胺酶。豚鼠L-天冬酰胺酶I(gpASNase1)的特征在于对Asn的 K_m 在微摩尔范围内(Schalk等,(2014) J.Biol.Chem.289:33175-86),并因此被用作低 K_m L-天冬酰胺酶。将编码相应的L-天冬酰胺酶的两个基因克隆到pBAD载体中,以便得到良好受控的蛋白质表达。

[0083] 在基于L-天冬酰胺酶反应供应唯一氮源的第一个筛选系统中,将BW2 Δ 用pBAD(对照载体)、pBAD_hASNase1(高 K_m 酶)或pBAD_gpASNase1(低 K_m 酶)转化。将所转化的细胞在缺少 NH_4Cl 但增补有浓度逐渐提高的Asn的M9培养基中生长。预期是低Asn浓度将优先促进带有编码低 K_m 酶的pBAD_gpASNase1质粒的细菌的生长。结果显示,BW2 Δ pBAD_hASNase1和pBAD_gpASNase1两者的生长事实上都依赖于Asn的浓度(即Asn浓度的提高导致更好的生长)。然而,根据Asn浓度,在BW2 Δ pBAD_hASNase1与pBAD_gpASNase1之间不存在显著的生长差异,例如在0.2mM Asn下,表达低 K_m gpASNase1酶的BW2 Δ 细菌与表达高 K_m hASNase1酶的细菌相比不形成明显更多或更大的菌落。总而言之,发现这种筛选系统不适合于区分Asn K_m 值有差异的L-天冬酰胺酶。

[0084] 在基于Asp营养缺陷的第二种筛选系统中,将BW5 Δ 同样地用pBAD、pBAD_hASNase1或pBAD_gpASNase1转化。将所转化的细胞在增补有浓度逐渐提高的Asn的完全M9培养基中。发现BW5 Δ pBAD_hASNase1和pBAD_gpASNase1的生长依赖于Asn的浓度。有趣的是,在代表了豚鼠酶被底物饱和($K_m = 50\mu\text{M}$)并且人类酶仅仅被部分饱和($K_m = 3,500\mu\text{M}$)的浓度的2mM Asn下,hASNase1和gpASNase1转化的BW5 Δ 菌株显示出相近的生长。换句话说,在这个相对高的Asn浓度下,BW5 Δ 菌株不能用于将表达低 K_m L-天冬酰胺酶的细菌与表达高 K_m 酶的细菌区分开。相反,在较低的底物Asn浓度下,只有BW5 Δ pBAD_gpASNase1能够生长。事实上,在0.2mM Asn,即远低于hASNase1的 K_m 但高于gpASNase1的 K_m 的Asn浓度下,BW5 Δ pBAD_gpASNase1的菌落生成,而BW5 Δ pBAD_hASNase1不能生长。值得注意的是,发现这种生长差异不依赖于酶表达水平,因为当以0.0002%-0.2%的范围使用阿拉伯糖(蛋白质表达的诱导物)时,没有注意到生长的变化。总之,所述结果表明在最低培养基平板上在表达hASNase1的BW5 Δ 与表达

gpASNase1的BW5 Δ 之间看到的生长差异直接反映了相应地表达的L-天冬酰胺酶的 K_m 。

[0085] 来自于该最初一组实验的结论是基于所述L-天冬酰胺酶反应供应氮的筛选(使用BW2 Δ 菌株)不能足够好地区分高和低 K_m 的酶,而基于所述L-天冬酰胺酶反应供应氨基酸Asp的筛选(使用BW5 Δ 菌株),在低Asn浓度下确实可以区分对Asn具有不同亲和性的酶,只有表达低 K_m L-天冬酰胺酶的细菌形成菌落。因此,旨在发现已获得低 K_m 的人类L-天冬酰胺酶变体的所有进一步的选择工作,都使用BW5 Δ 大肠杆菌菌株来进行。

[0086] DNA家族改组。DNA家族改组是一种用于产生遗传多样性的可替代方法。hASNase1和gpASNase1的蛋白质序列分别含有573和565个氨基酸,并且在氨基酸水平上具有69.8%同一性(相差170个氨基酸)。使用hASNase1(SEQ ID NO:35)和gpASNase1(SEQ ID NO:36)两者的合成的密码子优化版本工作,编码hASNase1和gpASNase1的基因在DNA水平上显示出75%同一性。正如在本文中提到的,hASNase1对Asn具有3.5mM的 K_m ,而豚鼠酶的 K_m 被确定是50 μ M(表3)。将DNA改组方法用于重组所述两种L-天冬酰胺酶,以便获得表现出豚鼠的低 K_m 但与人类酶具有尽可能高的氨基酸同源性的嵌合体。然后将所述改组的片段克隆到pBAD载体中。将得到的嵌合文库用于转化BW5 Δ 菌株。具有低 K_m 的突变体的存在使用如上所述的选择方案来发现。在0.2mM的Asn浓度下,从M9平板分离到4个克隆(#63、#64、#65和#SA)。这些克隆的序列分析揭示出重组事件主要发生在N端(即催化)结构域中的改组模式;所选的克隆之一(#SA)带有在催化结构域之外引入过早终止密码子(STOP)的突变(图1)。

[0087] C端结构域的交流。为了最小化针对GpA的免疫原性,搜寻了与人类L-天冬酰胺酶尽可能一致,但具有豚鼠/大肠杆菌II型酶的低 K_m 性质的酶。改组实验表明在人类C端结构域之前具有豚鼠L-天冬酰胺酶结构域的嵌合体仍会保留gpASNase1的有利的动力学性质,但会与人类酶具有提高的序列同一性。

[0088] 因此,产生了两种嵌合体,一种被称为 h_N-g_C 并包括融合到豚鼠C端结构域的人类N端结构域,第二种被称为 g_N-h_C 并包括融合到人类C端结构域的豚鼠N端结构域(图1、表3)。这些嵌合体的体外动力学表征证实了预测,其中 h_N-g_C 表现出与hASNase1相似的动力学性质, g_N-h_C 表现出与gpASNase1相似的动力学性质(表4)。

[0089] 这个结果证实了GpA的C端结构域不影响L-天冬酰胺酶的催化活性,并且最重要的是不负面影响 K_m 。由于目标是鉴定具有gpASNase1动力学性质但与hASNase1具有最高序列同源性的克隆,因此通过将其改组的C端结构域用人类C端结构域的精确序列代替,对所述4个克隆#63、#64、#65和#SA进行了工程化改造(图1)。所述工程化的克隆即 63_N-h_C 、 64_N-h_C 、 65_N-h_C 和 SA_N-h_C 与野生型hASNase1序列分别表现出85.7%、91.1%、87.1%和91.6%的同一性(表3和图2A-2B)。

[0090] 表3

[0091]	酶名称	残基的数目	与 hASNase1 的同一性%	SEQ ID NO:
	hASNase1	573	100	2

[0092]

ansB	326	26.9	-
gpASNase1	565	69.8	1
g _N -h _C	571	83.4	37
h _N -g _C	567	86.5	38
63 _N -h _C	571	85.7	39
64 _N -h _C	571	91.1	40
65 _N -h _C	571	87.1	41
SA _N -h _C	571	91.6	42

[0093] 变体的催化性质。为了确定63_N-h_C、64_N-h_C、65_N-h_C和SA_N-h_C的精确的动力学性质,将编码这些酶的基因亚克隆在pET14b表达载体中,并在C41大肠杆菌细胞中表达。测试纯化的克隆的L-天冬酰胺酶活性(表4)。还包括了大肠杆菌L-天冬酰胺酶ansB以便将所述克隆与被批准用于癌症疗法的L-天冬酰胺酶进行比较。观察到所述通过定向进化选择并带有hASNase1的C端结构域的4个克隆与hASNase1表呈现出高的序列同一性(>85%),但动力学性质类似于具有毫摩尔范围内的K_m的gpASNase1。克隆63_N-h_C(与hASNase1序列具有85.7%同一性)表现出47μM的最低K_m。克隆SA_N-h_C与hASNase1具有最高的序列同一性(91.6%同一性),但这个克隆具有165μM的略微高些的Asn K_m。对所述酶在50μM Asn下观察到的Asn水解速率(k_{obs@50μM})进行比较,因为该浓度是相关的血液Asn浓度(Ollenschläger (1988) Eur. J. Clin. Invest. 18:512-6)。发现大肠杆菌ansB的k_{obs@50μM}为41±0.3sec⁻¹,并且野生型gpASNase1的所述速率为20sec⁻¹。重要的是,所述人源化克隆的k_{obs@50μM}值也在这个范围内,对于克隆63_N-h_C、64_N-h_C、65_N-h_C和SA_N-h_C来说分别为17sec⁻¹、10sec⁻¹、17sec⁻¹和6sec⁻¹。

[0094] 表4

[0095]

酶名称	k _{cat} (sec ⁻¹)	K _m (μM)	k _{cat} /K _m (sec ⁻¹ μM ⁻¹)	k _{obs} (sec ⁻¹) @50 μM
hASNase1*	17±0.8	3500±300	0.005	ND
ansB	48±1	11±1	4.4	41±0.3

[0096]	gpASNase1	41±2	50±7	0.8	20±1
	g _N -h _C	24±1	35±4	0.7	14±1
	h _N -g _C	14±0.5	3800±120	0.004	ND
	63 _N -h _C	32±0.6	47±3	0.7	17±0.5
	64 _N -h _C	60±2	202±17	0.3	10±1
	65 _N -h _C	40±1	74±5	0.5	17±1
	SA _N -h _C	32±2	165±19	0.2	6±1

[0097] *使用希尔方程的动力学参数 (n=2.1)

[0098] ND: 未确定

[0099] 人源化L-天冬酰胺酶克隆的细胞培养评估。为了确定GpA酶是否表现出抗ALL活性,将人类T-ALL LOUCY和B-ALL SUP-B15细胞系暴露于浓度逐渐提高的gpASNase1。这项分析的结果表明gpASNase1对LOUCY和SUP-B15细胞系分别表现出0.00015IU/ml和0.00036IU/ml的IC₅₀ (表5)。值得注意的是,这些IC₅₀值与大肠杆菌II型酶的IC₅₀值可比。

[0100] 还评估了hASNase1和gpASNase1的嵌合体的抗ALL效能。为这些实验选择了克隆g_N-h_C、63_N-h_C和65_N-h_C,因为这些克隆具有最低的Asn K_m (分别为35、47和74μM),并因此具有最接近于gpASNase1 (50μM) 的活性。由于65_N-h_C的较高的K_m值,这个克隆与其他酶相比具有最高的IC₅₀值,但在杀死T-ALL和B-ALL细胞两者方面仍然非常有效 (IC₅₀在mIU/mL范围内;表5)。克隆g_N-h_C和63_N-h_C被证明在它们的细胞杀死能力方面与gpASNase1相比非常相似。对于克隆63_N-h_C来说这一点是特别值得注意的,因为这个克隆将与hASNase1的百分同一性从gpASNase1中所呈现的69.8%提高到85.7%。

[0101] 表5

[0102]	酶名称	IC ₅₀ 值 (IU/mL x 10 ⁻⁴)	
		LOUCY	SUB-B15
	gpASNase1	1.5	3.6
[0103]	g _N -h _C	2.9	5.7
	63 _N -h _C	3.8	6.0
	65 _N -h _C	85.3	13.0
	<i>E. coli</i> type II	3.5	3.7

[0104] 概括来说,这项分析鉴定了GpA的具有所需低K_m性质的人源化变体。2个鉴定到的克隆63_N-h_C和65_N-h_C分别与hA-FL共享85.7%和87.1%的氨基酸序列同一性,但具有与全长GpA相近的K_m。与全长hASNase1相比,这些克隆具有提高100至140倍的催化效率。值得注意的是,这些高度类似人类的L-天冬酰胺酶维持它们的体外ALL杀灭潜力。

[0105] 实施例3:通过基于结构化的方法产生的人源化GpA变体

[0106] 作为DNA改组和结构域交换的替代方法,采取了基于结构的方法将所述GpA酶人源化并降低其免疫原性。对于这种方法来说,对截短的GpA369变体 (SEQ ID NO:5) 进行修饰。检查了GpA的晶体结构,并对所述酶表面处的哪些残基可以被突变成hASNase1中的相应氨基酸并且其存在不会有害于所述酶的活性或稳定性做出预测。所述候选表面残基在对GpA的活性或稳定性具有可能影响的可能性的基础上分为三组 (第1组,无影响;第2组,很可能无影响;和第3组,有可能影响) (表6)。

[0107] 表6

	第 1 组		第 2 组		第 3 组	
	GpA 残基 ¹	人类残基 ²	GpA 残基 ¹	人类残基 ²	GpA 残基 ¹	人类残基 ²
[0108]	Q23	R23	H10	R10	R147	H147
	K25	E25	D91	A91	K193	R193
	K48	E48	D92	E92	D217	E217
	Q52	R52	Q108	H108	R301	Q301
	Q54	R54	H236	Q236		
	K98	Q98	S250	A250		
[0109]	E101	K101				
	S121	F121				
	G122	A122				
	H134	Q134				
	N233	S233				
	Q288	E288				
	E344	D346				
	L360	P362				
	T362	S364				
	A363	V365				
	D364	E366				
	L365	E367				
	H366	R368				
	Q367	R369				
	S368	P370				

[0110] ¹参考序列GpA369 (SEQ ID NO:5)。

[0111] ²参考序列hASNase1 (SEQ ID NO:2) 中的相应残基。

[0112] 制备了含有所有第1组突变、第1和2组突变的组合以及第1、2和3组突变的组合的

GpA变体(表7)。将所述GpA变体重组表达,并发现保留了100%的野生型活性和稳定性。

[0113] 体内稳定性数据暗示,存在于GpA酶中的表面暴露的环之一可能被断裂。具体来说,数据表明具有hASNase1中呈现的环1的序列(环1^{hum},第57-62位残基:SEDTLV(SEQ ID NO:43))的蛋白质与具有GpA中呈现的序列(环1^{sp},第57-62位残基:PDHALA(SEQ ID NO:44))的蛋白质之间的不同稳定性。因此,含有第1、2和3组突变的组合的GpA变体被进一步突变以包含环1^{hum}序列(表7)。同样地,将所述环1GpA变体重组表达,并发现其保留100%的野生型活性和稳定性。

[0114] 表7

变体名称	同一性的%		SEQ ID NO:
	GpA359*	hASNase1 ⁺	
GpA369	100%	72.2%	5
GpA369(hum)-组 1	96.4%	77.9%	45
GpA369(hum)-组 1+2	94.7%	79.5%	46
GpA369(hum)-组 1+2+3	93.6%	80.6%	47
GpA369(hum)-组 1-环 1 ^{hum}	95.0%	79.2%	48
GpA369(hum)-组 1+2-环 1 ^{hum}	93.3%	80.9%	49
GpA369(hum)-组 1+2+3-环 1 ^{hum}	92.2%	81.9%	50

[0116] *与GpA359(SEQ ID NO:3)相比,在变体的催化结构域的整个长度(第1-359位残基)上确定的同一性。

[0117] ⁺与hASNase1的第1-371位残基相比,在变体的整个长度上确定的同一性,因为所述人类酶在第311位残基处具有两个残基插入。

[0118] 实施例4:用于PEG化的表面半胱氨酸残基的突变

[0119] 已知PEG化增加体内循环时间。PEG分子可以通过基于马来酰亚胺的PEG化化学被容易地偶联到感兴趣的蛋白质的半胱氨酸残基。GpA369和人源化GpA369变体含有5个固有的半胱氨酸残基Cys79、Cys173、Cys198、Cys296和Cys299。基于晶体结构分析,Cys173和Cys296被埋藏,并因此预计不影响PEG化。Cys299被认为与Cys198相比不太容易接近并且对四聚体稳定化有贡献。将Cys299更换为Ala或Ser以避免该位点处的PEG化的尝试产生不稳定的蛋白质。相反,将第198位处的半胱氨酸残基突变成丙氨酸(GpA369-C198A,SEQ ID NO:51)、丝氨酸(GpA369-C198S,SEQ ID NO:52)或缬氨酸(GpA369-C198V,SEQ ID NO:53)产生与参比GpA369酶相比同等稳定且有活性的蛋白质。此外,现在仅含有单个反应性表面半胱氨酸(Cys79)的GpA369-C198A、GpA369-C198S和GpA369-C198V蛋白的马来酰亚胺-PEG化,产生均质的产物。

[0120] PEG化对生物制剂的保护程度取决于所述PEG药剂的结构和复杂度,但在大多数情况下,单一位点PEG化不足以覆盖整个大分子。因此,产生了另外的GpA变体,其含有1至5个之间的表面半胱氨酸残基。在这种情况下,分析了GpA的结构以便鉴定可以被突变成半胱氨酸以获得多位点PEG化产物的残基的区域。有用的区域必须在表面上,必须远离寡聚化界面

(GpA是四聚体,因此将界面附近的残基PEG化可能对酶的活性有害),并包括指向外部的残基。满足这些标准的GpA区域列于表8中。

[0121] 表8

	区域				
	1	2	3	4	5
[0122]	R40	E131	R253	E340	S358
	K48	N132	Q257	E344	S359
	E49	K221-D226	K261	R345	
	Q52	N233	Q281-R284	Q347	
	Q54		Q288	K352	
	D58				

[0123] 在可以被突变的可能残基(表8)中,来自于区域1的E49、来自于区域2的K225、来自于区域3的Q257和来自于区域4的E340被鉴定为用于突变成半胱氨酸的良好候选者。产生了包括K225C、E340C、E49C和Q257C突变中的一者或多者的GpA369-C198和GpA369(hum) -组1+2+3-C198的变体(表9)。

[0124] 表9

	变体名称	同一性的%		SEQ ID NO:
		GpA359*	hASNase1 ⁺	
[0125]	GpA369-C198A	99.7%	72.0%	51
	GpA369-C198A+K225C	99.4%	71.7%	54
	GpA369-C198A+K225C+E340C	99.2%	71.7%	55

[0126]	GpA369-C198A+K225C+E340C+E49C	98.9%	71.4%	56
	GpA369-C198A+K225C+E340C+E49C+Q257C	98.6%	71.2%	57
	GpA369(hum)-组 1+2+3-环 1 ^{hum} -C198A	91.9%	81.7%	58
	GpA369(hum)- 组 1+2+3- 环 1 ^{hum} -C198A+R52C	91.9%	81.4%	59
	GpA369(hum)-组 1+2+3-环 1 ^{hum} -C198A+R52C+K225C	91.6%	81.1%	60
	GpA369(hum)-组 1+2+3-环 1 ^{hum} -C198A+R52C+K225C+E340C	91.4%	81.1%	61
	GpA369(hum)-组 1+2+3-环 1 ^{hum} -C198A+R52C+K225C+E340C+Q281C	91.1%	80.9%	62

[0127] *与GpA359 (SEQ ID NO:3) 相比,在变体的催化结构域的整体长度(第1-359位残基)上确定的同一性。

[0128] ⁺与hASNase1的第1-371位残基相比,在变体的整体长度上确定的同一性,因为所述人类酶在第311位残基处具有两个残基插入。

[0129] 表9中列出的每个变体被重组表达、纯化并使用mPEG-10K、mPEG-20K和mPEG-40K中的一者或多者PEG化(表10)。正如通过SDS-PAGE分析所确定的,PEG化的酶的大小随着活性半胱氨酸的数目增加而提高。例如,使用马来酰亚胺-PEG10K, GpA369(hum)-C198A在PEG化之后以较高的分子量迁移(由于由PEG提供的额外10K Da),并且GpA369(hum)-C198A+R52C以甚至更高的表观分子量迁移,因为这种变体可以与两个PEG分子反应(由连接到酶的两个10K分子提供的额外的总共20K Da)。值得注意的是,所述GpA369-C198A-K225C-E340C-E49C-Q257C突变体被制备、表达、纯化,并用mPEG-10K进行PEG化。然而,用mPEG-10K对这种变体的PEG化产生多种产物。伴侣蛋白60KDa以1:1的比例与这种蛋白质一起出现,表明GpA369-C198A-K225C-E340C-E49C-Q257C突变体未被良好地折叠。

[0130] 表10

[0131]	变体	在 2mM ASN 下的 k_{obs} (sec^{-1})	与 GpA-FL 相比的%
	全长 GpA (GpA-FL)	41	100
	GpA369	44	107.3
	GpA369-C198A	43.3	105.6
	GpA369-C198A+K225C	41.4	100.9
	GpA369-C198A+K225C+E340C	42.4	103.4
	GpA369-C198A+K225C+E340C+E49C	41.6	101.5
	10K-PEG 化-GpA369-C198A	83.3	203.2
	20K-PEG 化-GpA369-C198A	83.7	204.1
	40K-PEG 化-GpA369-C198A	76.5	186.6
	10K-PEG 化-GpA369-C198A+K225C	92.6	225.9
	20K-PEG 化-GpA369-C198A+K225C	88.0	214.6
	40K-PEG 化-GpA369-C198A+K225C	92.8	226.3
	10K-PEG 化-GpA369-C198A+K225C+E340C	84.9	207.1
	10K-PEG 化-GpA369-C198A+K225C+E340C +E49C	83.9	204.6

[0132] *PEG化使用直链PEG。

[0133] 为了进一步评估所述变体的PEG化,使用了不同的PEG:蛋白质比例。对于这项分析来说,使用了2mg/mL的GpA369-C198A以及2、10和20倍过量的直链m-PEG10K。此外,进行了分析以确定在PEG化反应完成后添加5mM β -巯基乙醇和在PEG化反应期间包括添加剂例如10mM或100mM甘氨酸或10mM天冬氨酸的效果。这项分析表明,为了确保GpA369变体的完全PEG化需要20:1的马来酰亚胺PEG:蛋白质的摩尔比。此外,发现 β -巯基乙醇的添加提供了均质产物,而甘氨酸或天冬氨酸应该被排除在PEG化反应之外。

[0134] 除了直链马来酰亚胺-PEG10K之外,还将GpA369变体用直链马来酰亚胺-PEG20K、直链马来酰亚胺-PEG40K、双支链马来酰亚胺-PEG20K、四臂马来酰亚胺-PEG10K和Y形马来酰亚胺-PEG40K进行PEG化。观察到了使用每种这些不同类型的PEG的PEG化。值得注意的是,所述PEG化变体与GpA369的裸变体相比显示出L-天冬酰胺酶活性的显著提高(表10)。

[0135] 实施例5:用于PEG化的表面赖氨酸残基的突变

[0136] 大多数常规生物治疗剂在赖氨酸残基上被PEG化,其中所述赖氨酸侧链的 ϵ 氨基与PEG分子反应。赖氨酸是存在于蛋白质表面处的常见氨基酸。因此,使用这种策略的PEG化常常产生低均质性的产物,连接到所述蛋白质的PEG分子具有可变的数目。

[0137] 为了提高均质性,将GpA的紧邻另一个赖氨酸残基的赖氨酸残基用不与PEG反应的

残基代替。此外,将对四聚体L-天冬酰胺酶的结构完整性以及因此酶活性具有可能的负面影响的残基用表面赖氨酸残基代替,以使整个酶的表面受到完全且均匀的保护。

[0138] 使用这种策略,考虑了将具有表11中列出的突变的截短的GpA变体用于本发明。

[0139] 表11

变体名称	同一性的%		SEQ ID
	GpA359*	hASNase1 ⁺	NO:
GpA369-Q54K+D91K+K223D+S311K	98.9%	72.5%	63
[0140] GpA369(hum)- 组 1+2+3-C198A-R54K+A91K+K223D+S311K	92.8%	80.1%	64
GpA369(hum)- 组 1+2+3- 环 1 ^{hum} -C198A-R54K+A91K+K223D+S311K	91.4%	81.4%	65
GpA369(hum)- 组 1+2+3- 环 1 ^{hum} -	90.3%	79.2%	86
[0141] C198A-S7K+A53K+E58K+Q98K+Q106K+S233K+Q257K+Q281K+S311K+E340K			

[0142] *与GpA359 (SEQ ID NO:3) 相比,在变体的催化结构域的整体长度(第1-359位残基)上确定的同一性。

[0143] ⁺与hASNase1的第1-371位残基相比,在变体的整体长度上确定的同一性,因为所述人类酶在第311位残基处具有两个残基插入。

[0144] 为了证实活性、稳定性和通过赖氨酸残基的PEG化,产生了GpA369(hum)-组1+2+3-C198A-R54K+A91K+K223D+S311K变体,将其重组表达、纯化,并使用不同的PEG:蛋白质比例进行PEG化。这项分析显示,为了确保GpA369变体的完全PEG化,需要超过20:1的胺PEG与蛋白质的摩尔比。还观察到添加剂例如DTT和甘油应该被排除在PEG化反应之外。试验了不同的尺寸和连接物类型,包括甲氧基PEG琥珀酰亚胺基碳酸酯10K (mPEG-SC-10K)、mPEG-琥珀酰亚胺基羧基甲基酯5K (mPEG-SCM-5K) 和mPEG-琥珀酰亚胺琥珀酰亚胺基酯5K (mPEG-SAS-5K)。值得注意的是,所述PEG化产物与裸露的版本相比均未表现出L-天冬酰胺酶活性的任何损失(表12)。

[0145] 表12

[0146]	变体	在 2mM ASN 下的 k_{obs} (sec^{-1})	与 GpA-FL 相比的%
	全长 GpA (Gpa-FL)	41	100
	GpA369(hum)- 组 1+2+3-C198A-R54K+A91K+K223D+S311K	69.5	169.5
	mPEG-SC-10K-PEG 化-GpA369(hum)-组 1+2+3-C198A-R54K+A91K+K223D+S311K	69.3	169.1
	mPEG-SCM-5K-PEG 化-GpA369(hum)-组 1+2+3-C198A-R54K+A91K+K223D+S311K	70.9	172.9
	mPEG-SAS-5K-PEG 化 -GpA369(hum)- 组	66.9	163.2
[0147]	1+2+3-C198A-R54K+A91K+K223D+S311K		

[0148] 实施例6:用于增加体内半衰期的标签

[0149] L-天冬酰胺酶的效能与药物的体内半衰期相关;半衰期越长,酶发挥作用水解血液天冬酰胺的时间越长。因此,为了增加本文公开的L-天冬酰胺酶变体的体内半衰期,将标签融合到所述L-天冬酰胺酶的N端。这些标签包括组氨酸标签、酵母SUMO标签、人类SUMO标签、His₆-人类SUMO标签(其中所述SUMO标签可以是人类中存在的4个同源SUMO结构域(SUMO-1、SUMO-2、SUMO-3或SUMO-4)之一)和白蛋白结合肽标签。每个所述标签都可以增加所述L-天冬酰胺酶的循环时间。此外,可以使用标签的组合。具体来说,可以将SA21和SUMO标签组合以获得具有甚至进一步延长的半衰期的变体。

[0150] 组氨酸标签。指定了一串6至9个组氨酸残基的DNA序列经常被用于生产重组蛋白的载体中。结果是具有融合到N端或C端的6xHis或多His标签的重组蛋白的表达。

[0151] 表达的带有His标签的蛋白可以被纯化并容易地检测,从而提供了不使用蛋白特异性抗体或探针来特异性纯化或检测所述重组蛋白的手段。对于带有His标签的蛋白来说,试剂盒是可商购的。

[0152] SUMO修饰。已发现,在显著提高蛋白质稳定性和溶解性的基础上,作为N端融合配偶体的SUMO在原核和真核表达系统中提高有功能蛋白的生产。

[0153] 在所述融合蛋白的表达和纯化后,所述SUMO标签可以被特异性(SUMO)蛋白酶通过它们的内切肽酶活性在体外切掉,以产生释放的蛋白质配偶体的所需的N端。SUMO标签表达系统是可商购的。在某些实施方式中,所述SUMO标签是酵母SUMO标签(例如Smt3 (SEQ ID NO:66))。在其他实施方式中,所述SUMO标签是人类SUMO标签(例如SUMO-1 (SEQ ID NO:67)、SUMO-2 (SEQ ID NO:68),SUMO-3 (SEQ ID NO:69)或SUMO-4 (SEQ ID NO:70))。

[0154] His-SUMO修饰。将组氨酸(例如1x-6xHis)标签与SUMO修饰组合提供了L-天冬酰胺酶的高效纯化、提高的表达和溶解性以及增加的半衰期。用于为感兴趣的蛋白提供His-SUMO修饰的表达系统是可商购的。参见例如CHAMPION pET SUMO蛋白表达系统

(Invitrogen)。

[0155] 白蛋白结合结构域。使用噬菌体展示,已鉴定到来自于多个物种的结合血清白蛋白的一系列肽(Dennis等,(2002)J.Biol.Chem.277(38):35035-35043;US2016/0185874和US2004/0001827)。已发现这些肽中被称为SA21的一种肽具有延长的血清半衰期。示例性的白蛋白结合肽包括但不限于SA20(QRLIEDICLPWGCLWEDDF;SEQ ID NO:71)、SA21(RLIEDICLPWGCLWEDD;SEQ ID NO:72)和SA31(RLIEDICLPWGCLW;SEQ ID NO:73)。通过将这些结构域融合到本文公开的L-天冬酰胺酶,预期药代动力学通过与白蛋白的非共价结合得以改善。参见Dennis等,(2002)J.Biol.Chem.277(38):35035-35043,US2016/0185874和US2004/0001827。

[0156] 带有各种不同标签的示例性的截短的GpA变体提供在表13中。

[0157] 表13

	GpA 变体	标签	SEQ ID
			NO:
[0158]	GpA369-C79K-C198A	N 端酵母 SUMO + 1X-His	74
	GpA369-C79K-C198A	N 端人类 SUMO-1 + 1X-His	75
	GpA369-C198A	N 端 SA21	76
	GpA369-C198A	C 端 SA21	77
	GpA369-C79A-C198A	N 端酵母 SUMO + 1X-His, C 端 SA21	78
	GpA369-C198A	N 端人类 SUMO-1 + 1X-His, C 端 SA21	79
[0159]	GpA(hum) ₁₋₂₂₅ -SA21-GpA(hum) ₂₂₆₋₃₆₉	嫁接在 GpA 的第 225 和 226 位残基之间的 SA21	93
	GpA(hum) ₁₋₃₄₀ -SA21-GpA(hum) ₃₄₁₋₃₆₉	嫁接在 GpA 的第 340 和 341 位残基之间的 SA21	94

[0160] 实施例7:TRAIL-GpA融合蛋白

[0161] TRAIL (TNF相关凋亡诱导配体)是一种通过凋亡诱导细胞死亡的蛋白质。因此,产生了一种TRAIL-天冬酰胺酶融合蛋白以合并这两种蛋白质的活性。使用这种融合蛋白,所述L-天冬酰胺酶组分向细胞传导信号以经历凋亡,并且所述TRAIL组分诱导细胞死亡。举例说明,将3个串联的TRAIL可溶性结构域(TRAIL_{三聚体})与截短并人源化的豚鼠L-天冬酰胺酶例如GpA369(hum)-组1+2+3(SEQ ID NO:47)或GpA369(hum)-组1+2+3-环1^{hum}(SEQ ID NO:50)同框融合,以产生TRAIL_{三聚体}-GpA或GpA-TRAIL_{三聚体}融合蛋白。

[0162] 通过将急性髓性白血病MV4;11细胞在终浓度在0.0001至2.5IU/ml范围内的融合蛋白存在下进行培养,来评估融合蛋白的效能。在将板在37℃下在含有5%CO₂的加湿空气

中温育4天后,添加Alamar Blue(Invitrogen)至终浓度为10%v/v,并将板继续温育4小时,然后读取荧光信号。白血病细胞的存活率被计算为在L-天冬酰胺酶存在下的荧光计数与在DPBS对照中的荧光计数相比的百分率。这项分析证实了与单独的所述截短且人源化的豚鼠L-天冬酰胺酶相比,所述有活性的融合蛋白对MV4;11细胞系具有明显更好的杀灭活性。

[0163] 融合蛋白杀死白血病细胞的体内效能如下进行评估:用含有 5×10^6 个萤光素酶阳性MV4;11细胞的150 μ L DPBS,注射4-10只6周龄非肥胖糖尿病/严重综合免疫缺陷 γ (NSG)小鼠(The Jackson Laboratory)。在规则的时间点使用IVIS Lumina II成像系统(PerkinElmer)测量生物发光。在植入后(第0天),将小鼠每天用15IU/小鼠的所述融合蛋白i.p.注射处理一周。在第0天和第7天测量生物发光信号。这项分析的结果证实所述融合蛋白对MV4;11细胞的显著杀灭效应。

[0164] 所述融合蛋白针对实体癌症例如胰腺癌和卵巢癌的效能也被确定。将胰腺癌细胞系例如Panc-1和MiaPaca2和卵巢癌细胞系例如OVCAR3和OVCAR4用终浓度在0.0001至2.5IU/ml范围内的融合蛋白或单独的GpA或用浓度与用于所述融合蛋白的浓度相对应的TRAIL_{三聚体}处理。在将板在37°C下在含有5%CO₂的加湿空气中温育4天后,添加Alamar Blue(Invitrogen)至终浓度为10%v/v,并将板继续温育4小时,然后读取荧光信号。癌细胞存活率被计算为在所述融合蛋白存在下的荧光计数与在DPBS对照中的荧光计数相比的百分率。这项分析证实与TRAIL_{三聚体}或单独的GpA相比,所述有活性的融合蛋白对癌细胞系具有明显更好的杀灭活性。

[0001]	序列表
[0002]	<110> 伊利诺伊大学理事会(The Board of Trustees of the University of Illinois)
[0003]	<120> 截短的豚鼠L-天冬酰胺酶变体及其使用方法
[0004]	<130> UIC0074W0
[0005]	<150> US 62/544,396
[0006]	<151> 2017-08-11
[0007]	<150> US 62/544,411
[0008]	<151> 2017-08-11
[0009]	<160> 94
[0010]	<170> PatentIn version 3.5
[0011]	<210> 1
[0012]	<211> 565
[0013]	<212> PRT
[0014]	<213> 豚鼠(Cavia porcellus)
[0015]	<400> 1
[0016]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr
[0017]	1 5 10 15
[0018]	Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro Gly
[0019]	20 25 30
[0020]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Lys
[0021]	35 40 45
[0022]	Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu Ala Leu Pro
[0023]	50 55 60
[0024]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln
[0025]	65 70 75 80
[0026]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile Arg Ile
[0027]	85 90 95
[0028]	Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly Phe Val Val
[0029]	100 105 110
[0030]	Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu Ser Phe
[0031]	115 120 125
[0032]	Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala Gln Val
[0033]	130 135 140
[0034]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala
[0035]	145 150 155 160
[0036]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met
[0037]	165 170 175
[0038]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln
[0039]	180 185 190
[0040]	Lys Phe Glu Ala Phe Cys Ser Pro Asn Leu Ser Pro Leu Ala Thr Val

[0041]	195	200	205
[0042]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys Trp		
[0043]	210	215	220
[0044]	Lys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp Val Ala Leu		
[0045]	225	230	235
[0046]	240		
[0047]	245	250	255
[0048]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn		
[0049]	260	265	270
[0050]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Gln		
[0051]	275	280	285
[0052]	290		
[0053]	295	300	
[0054]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly		
[0055]	305	310	315
[0056]	320		
[0057]	325	330	335
[0058]	Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys		
[0059]	340	345	350
[0060]	355		
[0061]	360	365	
[0062]	Ser Pro Pro Gly Ser Thr Leu Gly Gln Gly Val Ala Arg Leu Phe Ser		
[0063]	370	375	380
[0064]	385		
[0065]	390	395	400
[0066]	Ser Leu Ala Leu Ala Leu Ala His Ala Gly Glu Leu Glu Ala Leu Gln		
[0067]	405	410	415
[0068]	420		
[0069]	425	430	
[0070]	Gln Thr Leu Leu His Val Ala Ala Arg Asn Gly Arg Asp Gly Val Val		
[0071]	435	440	445
[0072]	450		
[0073]	455	460	
[0074]	Gly Leu Ser Pro Leu Leu Leu Ala Val Gln Gly Arg His Arg Glu Cys		
[0075]	465	470	475
[0076]	480		
[0077]	485	490	495
[0078]	Lys Asp Ala Gly Thr Glu Leu Cys Arg Leu Ala Ser Arg Ala Asp Met		
[0079]	500	505	510
[0080]	Glu Gly Leu Gln Ala Trp Gly Gln Ala Gly Ala Asp Leu Gln Gln Pro		
[0081]	515	520	525
[0082]	Gly Tyr Asp Gly Arg Ser Ala Leu Cys Val Ala Glu Ala Ala Gly Asn		

[0083]	530	535	540
[0084]	Gln Glu Val Leu Ala Leu Leu Arg Asn Leu Ala Leu Val Gly Pro Glu		
[0085]	545	550	555 560
[0086]	Val Pro Pro Ala Ile		
[0087]	565		
[0088]	<210> 2		
[0089]	<211> 573		
[0090]	<212> PRT		
[0091]	<213> 智人 (Homo sapiens)		
[0092]	<400> 2		
[0093]	Met Ala Arg Ala Val Gly Pro Glu Arg Arg Leu Leu Ala Val Tyr Thr		
[0094]	1 5 10 15		
[0095]	Gly Gly Thr Ile Gly Met Arg Ser Glu Leu Gly Val Leu Val Pro Gly		
[0096]	20 25 30		
[0097]	Thr Gly Leu Ala Ala Ile Leu Arg Thr Leu Pro Met Phe His Asp Glu		
[0098]	35 40 45		
[0099]	Glu His Ala Arg Ala Arg Gly Leu Ser Glu Asp Thr Leu Val Leu Pro		
[0100]	50 55 60		
[0101]	Pro Ala Ser Arg Asn Gln Arg Ile Leu Tyr Thr Val Leu Glu Cys Gln		
[0102]	65 70 75 80		
[0103]	Pro Leu Phe Asp Ser Ser Asp Met Thr Ile Ala Glu Trp Val Cys Leu		
[0104]	85 90 95		
[0105]	Ala Gln Thr Ile Lys Arg His Tyr Glu Gln Tyr His Gly Phe Val Val		
[0106]	100 105 110		
[0107]	Ile His Gly Thr Asp Thr Met Ala Phe Ala Ala Ser Met Leu Ser Phe		
[0108]	115 120 125		
[0109]	Met Leu Glu Asn Leu Gln Lys Thr Val Ile Leu Thr Gly Ala Gln Val		
[0110]	130 135 140		
[0111]	Pro Ile His Ala Leu Trp Ser Asp Gly Arg Glu Asn Leu Leu Gly Ala		
[0112]	145 150 155 160		
[0113]	Leu Leu Met Ala Gly Gln Tyr Val Ile Pro Glu Val Cys Leu Phe Phe		
[0114]	165 170 175		
[0115]	Gln Asn Gln Leu Phe Arg Gly Asn Arg Ala Thr Lys Val Asp Ala Arg		
[0116]	180 185 190		
[0117]	Arg Phe Ala Ala Phe Cys Ser Pro Asn Leu Leu Pro Leu Ala Thr Val		
[0118]	195 200 205		
[0119]	Gly Ala Asp Ile Thr Ile Asn Arg Glu Leu Val Arg Lys Val Asp Gly		
[0120]	210 215 220		
[0121]	Lys Ala Gly Leu Val Val His Ser Ser Met Glu Gln Asp Val Gly Leu		
[0122]	225 230 235 240		
[0123]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ala Leu Val Arg Ala Phe Leu		
[0124]	245 250 255		

[0125]	Gln Pro Pro Leu Lys Gly Val Val Met Glu Thr Phe Gly Ser Gly Asn		
[0126]		260	265 270
[0127]	Gly Pro Thr Lys Pro Asp Leu Leu Gln Glu Leu Arg Val Ala Thr Glu		
[0128]		275	280 285
[0129]	Arg Gly Leu Val Ile Val Asn Cys Thr His Cys Leu Gln Gly Ala Val		
[0130]		290	295 300
[0131]	Thr Thr Asp Tyr Ala Ala Gly Met Ala Met Ala Gly Ala Gly Val Ile		
[0132]		305	310 315 320
[0133]	Ser Gly Phe Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr		
[0134]		325	330 335
[0135]	Val Leu Gly Gln Pro Gly Leu Ser Leu Asp Val Arg Lys Glu Leu Leu		
[0136]		340	345 350
[0137]	Thr Lys Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg		
[0138]		355	360 365
[0139]	Arg Pro Ser Leu Gln Gly Asn Thr Leu Gly Gly Gly Val Ser Trp Leu		
[0140]		370	375 380
[0141]	Leu Ser Leu Ser Gly Ser Gln Glu Ala Asp Ala Leu Arg Asn Ala Leu		
[0142]		385	390 395 400
[0143]	Val Pro Ser Leu Ala Cys Ala Ala Ala His Ala Gly Asp Val Glu Ala		
[0144]		405	410 415
[0145]	Leu Gln Ala Leu Val Glu Leu Gly Ser Asp Leu Gly Leu Val Asp Phe		
[0146]		420	425 430
[0147]	Asn Gly Gln Thr Pro Leu His Ala Ala Ala Arg Gly Gly His Thr Glu		
[0148]		435	440 445
[0149]	Ala Val Thr Met Leu Leu Gln Arg Gly Val Asp Val Asn Thr Arg Asp		
[0150]		450	455 460
[0151]	Thr Asp Gly Phe Ser Pro Leu Leu Leu Ala Val Arg Gly Arg His Pro		
[0152]		465	470 475 480
[0153]	Gly Val Ile Gly Leu Leu Arg Glu Ala Gly Ala Ser Leu Ser Thr Gln		
[0154]		485	490 495
[0155]	Glu Leu Glu Glu Ala Gly Thr Glu Leu Cys Arg Leu Ala Tyr Arg Ala		
[0156]		500	505 510
[0157]	Asp Leu Glu Gly Leu Gln Val Trp Trp Gln Ala Gly Ala Asp Leu Gly		
[0158]		515	520 525
[0159]	Gln Pro Gly Tyr Asp Gly His Ser Ala Leu His Val Ala Glu Ala Ala		
[0160]		530	535 540
[0161]	Gly Asn Leu Ala Val Val Ala Phe Leu Gln Ser Leu Glu Gly Ala Val		
[0162]		545	550 555 560
[0163]	Gly Ala Gln Ala Pro Cys Pro Glu Val Leu Pro Gly Val		
[0164]		565	570
[0165]	<210> 3		
[0166]	<211> 359		

[0167]	<212> PRT																			
[0168]	<213> 人工序列																			
[0169]	<220>																			
[0170]	<223> 合成多肽																			
[0171]	<400> 3																			
[0172]	Met	Ala	Arg	Ala	Ser	Gly	Ser	Glu	Arg	His	Leu	Leu	Leu	Ile	Tyr	Thr				
[0173]	1				5					10					15					
[0174]	Gly	Gly	Thr	Leu	Gly	Met	Gln	Ser	Lys	Gly	Gly	Val	Leu	Val	Pro	Gly				
[0175]				20					25					30						
[0176]	Pro	Gly	Leu	Val	Thr	Leu	Leu	Arg	Thr	Leu	Pro	Met	Phe	His	Asp	Lys				
[0177]			35					40					45							
[0178]	Glu	Phe	Ala	Gln	Ala	Gln	Gly	Leu	Pro	Asp	His	Ala	Leu	Ala	Leu	Pro				
[0179]		50					55					60								
[0180]	Pro	Ala	Ser	His	Gly	Pro	Arg	Val	Leu	Tyr	Thr	Val	Leu	Glu	Cys	Gln				
[0181]	65					70				75				80						
[0182]	Pro	Leu	Leu	Asp	Ser	Ser	Asp	Met	Thr	Ile	Asp	Asp	Trp	Ile	Arg	Ile				
[0183]				85					90					95						
[0184]	Ala	Lys	Ile	Ile	Glu	Arg	His	Tyr	Glu	Gln	Tyr	Gln	Gly	Phe	Val	Val				
[0185]			100					105					110							
[0186]	Ile	His	Gly	Thr	Asp	Thr	Met	Ala	Ser	Gly	Ala	Ser	Met	Leu	Ser	Phe				
[0187]		115					120					125								
[0188]	Met	Leu	Glu	Asn	Leu	His	Lys	Pro	Val	Ile	Leu	Thr	Gly	Ala	Gln	Val				
[0189]		130					135					140								
[0190]	Pro	Ile	Arg	Val	Leu	Trp	Asn	Asp	Ala	Arg	Glu	Asn	Leu	Leu	Gly	Ala				
[0191]	145					150				155				160						
[0192]	Leu	Leu	Val	Ala	Gly	Gln	Tyr	Ile	Ile	Pro	Glu	Val	Cys	Leu	Phe	Met				
[0193]				165					170					175						
[0194]	Asn	Ser	Gln	Leu	Phe	Arg	Gly	Asn	Arg	Val	Thr	Lys	Val	Asp	Ser	Gln				
[0195]			180						185					190						
[0196]	Lys	Phe	Glu	Ala	Phe	Cys	Ser	Pro	Asn	Leu	Ser	Pro	Leu	Ala	Thr	Val				
[0197]			195					200					205							
[0198]	Gly	Ala	Asp	Val	Thr	Ile	Ala	Trp	Asp	Leu	Val	Arg	Lys	Val	Lys	Trp				
[0199]		210					215					220								
[0200]	Lys	Asp	Pro	Leu	Val	Val	His	Ser	Asn	Met	Glu	His	Asp	Val	Ala	Leu				
[0201]	225					230					235			240						
[0202]	Leu	Arg	Leu	Tyr	Pro	Gly	Ile	Pro	Ala	Ser	Leu	Val	Arg	Ala	Phe	Leu				
[0203]				245					250					255						
[0204]	Gln	Pro	Pro	Leu	Lys	Gly	Val	Val	Leu	Glu	Thr	Phe	Gly	Ser	Gly	Asn				
[0205]				260					265					270						
[0206]	Gly	Pro	Ser	Lys	Pro	Asp	Leu	Leu	Gln	Glu	Leu	Arg	Ala	Ala	Ala	Gln				
[0207]			275						280					285						
[0208]	Arg	Gly	Leu	Ile	Met	Val	Asn	Cys	Ser	Gln	Cys	Leu	Arg	Gly	Ser	Val				

[0209]	290	295	300
[0210]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly		
[0211]	305	310	315
[0212]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu		
[0213]	325	330	335
[0214]	Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys		
[0215]	340	345	350
[0216]	Asp Leu Arg Gly Glu Met Thr		
[0217]	355		
[0218]	<210> 4		
[0219]	<211> 367		
[0220]	<212> PRT		
[0221]	<213> 人工序列		
[0222]	<220>		
[0223]	<223> 合成多肽		
[0224]	<400> 4		
[0225]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr		
[0226]	1	5	10
[0227]	Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro Gly		
[0228]	20	25	30
[0229]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Lys		
[0230]	35	40	45
[0231]	Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu Ala Leu Pro		
[0232]	50	55	60
[0233]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln		
[0234]	65	70	75
[0235]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile Arg Ile		
[0236]	85	90	95
[0237]	Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly Phe Val Val		
[0238]	100	105	110
[0239]	Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu Ser Phe		
[0240]	115	120	125
[0241]	Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala Gln Val		
[0242]	130	135	140
[0243]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala		
[0244]	145	150	155
[0245]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met		
[0246]	165	170	175
[0247]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln		
[0248]	180	185	190
[0249]	Lys Phe Glu Ala Phe Cys Ser Pro Asn Leu Ser Pro Leu Ala Thr Val		
[0250]	195	200	205

[0251]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys Trp
[0252]	210 215 220
[0253]	Lys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp Val Ala Leu
[0254]	225 230 235 240
[0255]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala Phe Leu
[0256]	245 250 255
[0257]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn
[0258]	260 265 270
[0259]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Gln
[0260]	275 280 285
[0261]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val
[0262]	290 295 300
[0263]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly
[0264]	305 310 315 320
[0265]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu
[0266]	325 330 335
[0267]	Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys
[0268]	340 345 350
[0269]	Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu His Gln
[0270]	355 360 365
[0271]	<210> 5
[0272]	<211> 369
[0273]	<212> PRT
[0274]	<213> 人工序列
[0275]	<220>
[0276]	<223> 合成多肽
[0277]	<400> 5
[0278]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr
[0279]	1 5 10 15
[0280]	Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro Gly
[0281]	20 25 30
[0282]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Lys
[0283]	35 40 45
[0284]	Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu Ala Leu Pro
[0285]	50 55 60
[0286]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln
[0287]	65 70 75 80
[0288]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile Arg Ile
[0289]	85 90 95
[0290]	Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly Phe Val Val
[0291]	100 105 110
[0292]	Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu Ser Phe

[0293]	115	120	125
[0294]	Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala Gln Val		
[0295]	130	135	140
[0296]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala		
[0297]	145	150	155
[0298]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met		
[0299]	165	170	175
[0300]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln		
[0301]	180	185	190
[0302]	Lys Phe Glu Ala Phe Cys Ser Pro Asn Leu Ser Pro Leu Ala Thr Val		
[0303]	195	200	205
[0304]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys Trp		
[0305]	210	215	220
[0306]	Lys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp Val Ala Leu		
[0307]	225	230	235
[0308]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala Phe Leu		
[0309]	245	250	255
[0310]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn		
[0311]	260	265	270
[0312]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Gln		
[0313]	275	280	285
[0314]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val		
[0315]	290	295	300
[0316]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly		
[0317]	305	310	315
[0318]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu		
[0319]	325	330	335
[0320]	Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys		
[0321]	340	345	350
[0322]	Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu His Gln Ser		
[0323]	355	360	365
[0324]	Ser		
[0325]	<210> 6		
[0326]	<211> 374		
[0327]	<212> PRT		
[0328]	<213> 人工序列		
[0329]	<220>		
[0330]	<223> 合成多肽		
[0331]	<400> 6		
[0332]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr		
[0333]	1	5	10
[0334]	Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro Gly		

[0335]	20	25	30
[0336]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Lys		
[0337]	35	40	45
[0338]	Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu Ala Leu Pro		
[0339]	50	55	60
[0340]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln		
[0341]	65	70	75
[0342]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile Arg Ile		
[0343]	85	90	95
[0344]	Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly Phe Val Val		
[0345]	100	105	110
[0346]	Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu Ser Phe		
[0347]	115	120	125
[0348]	Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala Gln Val		
[0349]	130	135	140
[0350]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala		
[0351]	145	150	155
[0352]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met		
[0353]	165	170	175
[0354]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln		
[0355]	180	185	190
[0356]	Lys Phe Glu Ala Phe Cys Ser Pro Asn Leu Ser Pro Leu Ala Thr Val		
[0357]	195	200	205
[0358]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys Trp		
[0359]	210	215	220
[0360]	Lys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp Val Ala Leu		
[0361]	225	230	235
[0362]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala Phe Leu		
[0363]	245	250	255
[0364]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn		
[0365]	260	265	270
[0366]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Gln		
[0367]	275	280	285
[0368]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val		
[0369]	290	295	300
[0370]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly		
[0371]	305	310	315
[0372]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu		
[0373]	325	330	335
[0374]	Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys		
[0375]	340	345	350
[0376]	Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu His Gln Ser		

[0377]	355	360	365
[0378]	Ser Pro Pro Gly Ser Thr		
[0379]	370		
[0380]	<210> 7		
[0381]	<211> 384		
[0382]	<212> PRT		
[0383]	<213> 人工序列		
[0384]	<220>		
[0385]	<223> 合成多肽		
[0386]	<400> 7		
[0387]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr		
[0388]	1 5 10 15		
[0389]	Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro Gly		
[0390]	20 25 30		
[0391]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Lys		
[0392]	35 40 45		
[0393]	Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu Ala Leu Pro		
[0394]	50 55 60		
[0395]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln		
[0396]	65 70 75 80		
[0397]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile Arg Ile		
[0398]	85 90 95		
[0399]	Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly Phe Val Val		
[0400]	100 105 110		
[0401]	Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu Ser Phe		
[0402]	115 120 125		
[0403]	Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala Gln Val		
[0404]	130 135 140		
[0405]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala		
[0406]	145 150 155 160		
[0407]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met		
[0408]	165 170 175		
[0409]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln		
[0410]	180 185 190		
[0411]	Lys Phe Glu Ala Phe Cys Ser Pro Asn Leu Ser Pro Leu Ala Thr Val		
[0412]	195 200 205		
[0413]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys Trp		
[0414]	210 215 220		
[0415]	Lys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp Val Ala Leu		
[0416]	225 230 235 240		
[0417]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala Phe Leu		
[0418]	245 250 255		

[0419]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn
[0420]	260 265 270
[0421]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Gln
[0422]	275 280 285
[0423]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val
[0424]	290 295 300
[0425]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly
[0426]	305 310 315 320
[0427]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu
[0428]	325 330 335
[0429]	Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys
[0430]	340 345 350
[0431]	Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu His Gln Ser
[0432]	355 360 365
[0433]	Ser Pro Pro Gly Ser Thr Leu Gly Gln Gly Val Ala Arg Leu Phe Ser
[0434]	370 375 380
[0435]	<210> 8
[0436]	<211> 392
[0437]	<212> PRT
[0438]	<213> 人工序列
[0439]	<220>
[0440]	<223> 合成多肽
[0441]	<400> 8
[0442]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr
[0443]	1 5 10 15
[0444]	Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro Gly
[0445]	20 25 30
[0446]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Lys
[0447]	35 40 45
[0448]	Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu Ala Leu Pro
[0449]	50 55 60
[0450]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln
[0451]	65 70 75 80
[0452]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile Arg Ile
[0453]	85 90 95
[0454]	Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly Phe Val Val
[0455]	100 105 110
[0456]	Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu Ser Phe
[0457]	115 120 125
[0458]	Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala Gln Val
[0459]	130 135 140
[0460]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala

[0461]	145	150	155	160
[0462]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met			
[0463]		165	170	175
[0464]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln			
[0465]		180	185	190
[0466]	Lys Phe Glu Ala Phe Cys Ser Pro Asn Leu Ser Pro Leu Ala Thr Val			
[0467]		195	200	205
[0468]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys Trp			
[0469]		210	215	220
[0470]	Lys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp Val Ala Leu			
[0471]	225	230	235	240
[0472]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala Phe Leu			
[0473]		245	250	255
[0474]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn			
[0475]		260	265	270
[0476]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Gln			
[0477]		275	280	285
[0478]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val			
[0479]		290	295	300
[0480]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly			
[0481]	305	310	315	320
[0482]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu			
[0483]		325	330	335
[0484]	Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys			
[0485]		340	345	350
[0486]	Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu His Gln Ser			
[0487]		355	360	365
[0488]	Ser Pro Pro Gly Ser Thr Leu Gly Gln Gly Val Ala Arg Leu Phe Ser			
[0489]		370	375	380
[0490]	Leu Phe Gly Cys Gln Glu Glu Asp			
[0491]	385	390		
[0492]	<210> 9			
[0493]	<211> 396			
[0494]	<212> PRT			
[0495]	<213> 人工序列			
[0496]	<220>			
[0497]	<223> 合成多肽			
[0498]	<400> 9			
[0499]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr			
[0500]	1	5	10	15
[0501]	Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro Gly			
[0502]		20	25	30

[0503]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Lys		
[0504]	35	40	45
[0505]	Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu Ala Leu Pro		
[0506]	50	55	60
[0507]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln		
[0508]	65	70	75
[0509]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile Arg Ile		
[0510]	85	90	95
[0511]	Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly Phe Val Val		
[0512]	100	105	110
[0513]	Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu Ser Phe		
[0514]	115	120	125
[0515]	Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala Gln Val		
[0516]	130	135	140
[0517]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala		
[0518]	145	150	155
[0519]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met		
[0520]	165	170	175
[0521]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln		
[0522]	180	185	190
[0523]	Lys Phe Glu Ala Phe Cys Ser Pro Asn Leu Ser Pro Leu Ala Thr Val		
[0524]	195	200	205
[0525]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys Trp		
[0526]	210	215	220
[0527]	Lys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp Val Ala Leu		
[0528]	225	230	235
[0529]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala Phe Leu		
[0530]	245	250	255
[0531]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn		
[0532]	260	265	270
[0533]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Gln		
[0534]	275	280	285
[0535]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val		
[0536]	290	295	300
[0537]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly		
[0538]	305	310	315
[0539]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu		
[0540]	325	330	335
[0541]	Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys		
[0542]	340	345	350
[0543]	Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu His Gln Ser		
[0544]	355	360	365

[0545]	Ser Pro Pro Gly Ser Thr Leu Gly Gln Gly Val Ala Arg Leu Phe Ser
[0546]	370 375 380
[0547]	Leu Phe Gly Cys Gln Glu Glu Asp Ser Val Gln Asp
[0548]	385 390 395
[0549]	<210> 10
[0550]	<211> 33
[0551]	<212> DNA
[0552]	<213> 人工序列
[0553]	<220>
[0554]	<223> 合成寡核苷酸
[0555]	<400> 10
[0556]	aacgtcggat ccttaaatacg ccggcgggac ttc 33
[0557]	<210> 11
[0558]	<211> 24
[0559]	<212> DNA
[0560]	<213> 人工序列
[0561]	<220>
[0562]	<223> 合成寡核苷酸
[0563]	<400> 11
[0564]	atggcacgag cttcgggctc ggaa 24
[0565]	<210> 12
[0566]	<211> 19
[0567]	<212> DNA
[0568]	<213> 人工序列
[0569]	<220>
[0570]	<223> 合成寡核苷酸
[0571]	<400> 12
[0572]	ccagattacg cagcagagc 19
[0573]	<210> 13
[0574]	<211> 21
[0575]	<212> DNA
[0576]	<213> 人工序列
[0577]	<220>
[0578]	<223> 合成寡核苷酸
[0579]	<400> 13
[0580]	gctcgtgctg tgggtccgga a 21
[0581]	<210> 14
[0582]	<211> 18
[0583]	<212> DNA
[0584]	<213> 人工序列
[0585]	<220>
[0586]	<223> 合成寡核苷酸

[0587] <400> 14
[0588] gacacccggc agcacttc 18
[0589] <210> 15
[0590] <211> 44
[0591] <212> DNA
[0592] <213> 人工序列
[0593] <220>
[0594] <223> 合成寡核苷酸
[0595] <400> 15
[0596] ctgatgcagg tctgccgtcg gcagcgcat ttcaccgcgc aggt 44
[0597] <210> 16
[0598] <211> 43
[0599] <212> DNA
[0600] <213> 人工序列
[0601] <220>
[0602] <223> 合成寡核苷酸
[0603] <400> 16
[0604] aaggacctgc gcggtgaaat gacgctgccg acggcagacc tgc 43
[0605] <210> 17
[0606] <211> 45
[0607] <212> DNA
[0608] <213> 人工序列
[0609] <220>
[0610] <223> 合成寡核苷酸
[0611] <400> 17
[0612] gcgacgttct tccacagacg gcggggcat ttcaccacgc agatc 45
[0613] <210> 18
[0614] <211> 44
[0615] <212> DNA
[0616] <213> 人工序列
[0617] <220>
[0618] <223> 合成寡核苷酸
[0619] <400> 18
[0620] aaagatctgc gtggtgaaat gaccccgccg tctgtggaag aacg 44
[0621] <210> 19
[0622] <211> 48
[0623] <212> DNA
[0624] <213> 人工序列
[0625] <220>
[0626] <223> 合成寡核苷酸
[0627] <220>
[0628] <221> misc_feature

[0629]	<222> (22) .. (23)
[0630]	<223> n是a、c、g或t
[0631]	<220>
[0632]	<221> misc_feature
[0633]	<222> (25) .. (26)
[0634]	<223> n是a、c、g或t
[0635]	<400> 19
[0636]	tacaccggcg gcaccattgg cnnknnkagt gagctcggcg tgcttgtg 48
[0637]	<210> 20
[0638]	<211> 48
[0639]	<212> DNA
[0640]	<213> 人工序列
[0641]	<220>
[0642]	<223> 合成寡核苷酸
[0643]	<220>
[0644]	<221> misc_feature
[0645]	<222> (23) .. (24)
[0646]	<223> n是a、c、g或t
[0647]	<220>
[0648]	<221> misc_feature
[0649]	<222> (26) .. (27)
[0650]	<223> n是a、c、g或t
[0651]	<400> 20
[0652]	cacaagcacg ccgagctcac tmnnmnngcc aatggtgccg ccggtgta 48
[0653]	<210> 21
[0654]	<211> 51
[0655]	<212> DNA
[0656]	<213> 人工序列
[0657]	<220>
[0658]	<223> 合成寡核苷酸
[0659]	<220>
[0660]	<221> misc_feature
[0661]	<222> (22) .. (23)
[0662]	<223> n是a、c、g或t
[0663]	<220>
[0664]	<221> misc_feature
[0665]	<222> (28) .. (29)
[0666]	<223> n是a、c、g或t
[0667]	<400> 21
[0668]	ctggagtgcc agcccctctt cnnktcnnk gacatgacca tcgctgagtg g 51
[0669]	<210> 22
[0670]	<211> 51

[0671] <212> DNA
[0672] <213> 人工序列
[0673] <220>
[0674] <223> 合成寡核苷酸
[0675] <220>
[0676] <221> misc_feature
[0677] <222> (23) .. (24)
[0678] <223> n是a、c、g或t
[0679] <220>
[0680] <221> misc_feature
[0681] <222> (29) .. (30)
[0682] <223> n是a、c、g或t
[0683] <400> 22
[0684] ccactcagcg atgggtcatgt cmnnggamnn gaagaggggc tggcactcca g 51
[0685] <210> 23
[0686] <211> 54
[0687] <212> DNA
[0688] <213> 人工序列
[0689] <220>
[0690] <223> 合成寡核苷酸
[0691] <220>
[0692] <221> misc_feature
[0693] <222> (25) .. (26)
[0694] <223> n是a、c、g或t
[0695] <220>
[0696] <221> misc_feature
[0697] <222> (28) .. (29)
[0698] <223> n是a、c、g或t
[0699] <400> 23
[0700] cagtaccacg gctttgtggt catcnnknnk accgacacca tggcctttgc tgcc 54
[0701] <210> 24
[0702] <211> 54
[0703] <212> DNA
[0704] <213> 人工序列
[0705] <220>
[0706] <223> 合成寡核苷酸
[0707] <220>
[0708] <221> misc_feature
[0709] <222> (26) .. (27)
[0710] <223> n是a、c、g或t
[0711] <220>
[0712] <221> misc_feature

[0713] <222> (29) .. (30)
[0714] <223> n是a、c、g或t
[0715] <400> 24
[0716] ggcagcaaag gccatggtgt cggtmnnmnn gatgaccaca aagccgtggt actg 54
[0717] <210> 25
[0718] <211> 53
[0719] <212> DNA
[0720] <213> 人工序列
[0721] <220>
[0722] <223> 合成寡核苷酸
[0723] <220>
[0724] <221> misc_feature
[0725] <222> (24) .. (25)
[0726] <223> n是a、c、g或t
[0727] <220>
[0728] <221> misc_feature
[0729] <222> (27) .. (28)
[0730] <223> n是a、c、g或t
[0731] <220>
[0732] <221> misc_feature
[0733] <222> (30) .. (31)
[0734] <223> n是a、c、g或t
[0735] <400> 25
[0736] agaagactgt catcctcact gggnnknnkn nkcccatcca tgccctgtgg agc 53
[0737] <210> 26
[0738] <211> 52
[0739] <212> DNA
[0740] <213> 人工序列
[0741] <220>
[0742] <223> 合成寡核苷酸
[0743] <220>
[0744] <221> misc_feature
[0745] <222> (22) .. (23)
[0746] <223> n是a、c、g或t
[0747] <220>
[0748] <221> misc_feature
[0749] <222> (25) .. (26)
[0750] <223> n是a、c、g或t
[0751] <220>
[0752] <221> misc_feature
[0753] <222> (28) .. (29)
[0754] <223> n是a、c、g或t

[0755] <400> 26
[0756] gctccacagg gcatgatggg mnnmnnmnncc cagtgagga tgacagtctt ct 52
[0757] <210> 27
[0758] <211> 52
[0759] <212> DNA
[0760] <213> 人工序列
[0761] <220>
[0762] <223> 合成寡核苷酸
[0763] <220>
[0764] <221> misc_feature
[0765] <222> (24) .. (25)
[0766] <223> n是a、c、g或t
[0767] <220>
[0768] <221> misc_feature
[0769] <222> (27) .. (28)
[0770] <223> n是a、c、g或t
[0771] <400> 27
[0772] gcaaccgggc aaccaaggta gacnnknka ggttcgcagc tttctgctcc cc 52
[0773] <210> 28
[0774] <211> 52
[0775] <212> DNA
[0776] <213> 人工序列
[0777] <220>
[0778] <223> 合成寡核苷酸
[0779] <220>
[0780] <221> misc_feature
[0781] <222> (25) .. (26)
[0782] <223> n是a、c、g或t
[0783] <220>
[0784] <221> misc_feature
[0785] <222> (28) .. (29)
[0786] <223> n是a、c、g或t
[0787] <400> 28
[0788] ggggagcaga aagctgcgaa cctmnnmnnng tctaccttgg ttgcccgtt gc 52
[0789] <210> 29
[0790] <211> 47
[0791] <212> DNA
[0792] <213> 人工序列
[0793] <220>
[0794] <223> 合成寡核苷酸
[0795] <220>
[0796] <221> misc_feature

[0797] <222> (18) .. (19)
[0798] <223> n是a、c、g或t
[0799] <220>
[0800] <221> misc_feature
[0801] <222> (27) .. (28)
[0802] <223> n是a、c、g或t
[0803] <400> 29
[0804] tcatccacgg caccgacnnk atggccnnkg ctgcctcgat gctgtcc 47
[0805] <210> 30
[0806] <211> 47
[0807] <212> DNA
[0808] <213> 人工序列
[0809] <220>
[0810] <223> 合成寡核苷酸
[0811] <220>
[0812] <221> misc_feature
[0813] <222> (20) .. (21)
[0814] <223> n是a、c、g或t
[0815] <220>
[0816] <221> misc_feature
[0817] <222> (29) .. (30)
[0818] <223> n是a、c、g或t
[0819] <400> 30
[0820] ggacagcatc gaggcagcmn nggccaatmnn gtcggtgccg tggatga 47
[0821] <210> 31
[0822] <211> 63
[0823] <212> DNA
[0824] <213> 人工序列
[0825] <220>
[0826] <223> 合成寡核苷酸
[0827] <220>
[0828] <221> misc_feature
[0829] <222> (19) .. (20)
[0830] <223> n是a、c、g或t
[0831] <220>
[0832] <221> misc_feature
[0833] <222> (31) .. (32)
[0834] <223> n是a、c、g或t
[0835] <220>
[0836] <221> misc_feature
[0837] <222> (43) .. (44)
[0838] <223> n是a、c、g或t

- [0839] <400> 31
[0840] tccagtgaca tgaccatcnn kgagtgggtt nnkcttgccc agnnkatcaa gaggcactac 60
[0841] gag 63
[0842] <210> 32
[0843] <211> 63
[0844] <212> DNA
[0845] <213> 人工序列
[0846] <220>
[0847] <223> 合成寡核苷酸
[0848] <220>
[0849] <221> misc_feature
[0850] <222> (20) .. (21)
[0851] <223> n是a、c、g或t
[0852] <220>
[0853] <221> misc_feature
[0854] <222> (32) .. (33)
[0855] <223> n是a、c、g或t
[0856] <220>
[0857] <221> misc_feature
[0858] <222> (44) .. (45)
[0859] <223> n是a、c、g或t
[0860] <400> 32
[0861] ctctgtagtgc ctcttgatmn nctgggcaag mnnaaccac tcmngatgg tcatgtcact 60
[0862] gga 63
[0863] <210> 33
[0864] <211> 48
[0865] <212> DNA
[0866] <213> 人工序列
[0867] <220>
[0868] <223> 合成寡核苷酸
[0869] <220>
[0870] <221> misc_feature
[0871] <222> (19) .. (20)
[0872] <223> n是a、c、g或t
[0873] <220>
[0874] <221> misc_feature
[0875] <222> (25) .. (26)
[0876] <223> n是a、c、g或t
[0877] <220>
[0878] <221> misc_feature
[0879] <222> (28) .. (29)
[0880] <223> n是a、c、g或t

[0881] <400> 33
 [0882] ggcggcacca ttggcatgnn kagtnnknk ggcgtgcttg tgcccggg 48
 [0883] <210> 34
 [0884] <211> 48
 [0885] <212> DNA
 [0886] <213> 人工序列
 [0887] <220>
 [0888] <223> 合成寡核苷酸
 [0889] <220>
 [0890] <221> misc_feature
 [0891] <222> (20) .. (21)
 [0892] <223> n是a、c、g或t
 [0893] <220>
 [0894] <221> misc_feature
 [0895] <222> (23) .. (24)
 [0896] <223> n是a、c、g或t
 [0897] <220>
 [0898] <221> misc_feature
 [0899] <222> (29) .. (30)
 [0900] <223> n是a、c、g或t
 [0901] <400> 34
 [0902] cccgggcaca agcacgccmn nmnnactmnn catgccaatg gtgccgcc 48
 [0903] <210> 35
 [0904] <211> 1722
 [0905] <212> DNA
 [0906] <213> 人工序列
 [0907] <220>
 [0908] <223> 合成多核苷酸
 [0909] <400> 35
 [0910] atggctcgtg ctgtgggtcc ggaacgccgc ctgctggctg tctatacggg tggtacgatt 60
 [0911] ggtatgcgct ctgaactggg tgtcctggtg ccgggtaccg gtctggcagc aattctgcgt 120
 [0912] acgctgccga tgtttcatga tgaagaacac gcacgtgcac gcggtctgtc ggaagacacc 180
 [0913] ctggtgctgc cgccggcaag ccgtaaccag cgcactctgt ataccgttct ggaatgccaa 240
 [0914] ccgctgtttg atagctctga catgaccatt gccgaatggg tttgtctggc acagacgac 300
 [0915] aaacgtcatt atgaacaata ccacggttgc gtggttattc atggcaccga tacgatggcc 360
 [0916] tttgcagctt ccatgtctgc attcatgctg gaaaacctgc agaagaccgt tattctgacg 420
 [0917] ggcgtcaag tcccgatcca cgcactgtgg agcgacggtc gcgaaaatct gctgggcgcc 480
 [0918] ctgtgatgg caggccagta tgtcatcccg gaagtgtgcc tgtttttcca gaaccaactg 540
 [0919] ttccgtggta atcgcgtac caaagtcgat gcgcgtcgtt ttgcggcctt ctgtagcccc 600
 [0920] aacctgctgc cgctggctac cgttggtgca gatattacga tcaatcgtga actggtgcgc 660
 [0921] aaagttgacg gcaaggcagg tctggtcgtg catagttcca tggaacagga tgtcggcctg 720
 [0922] ctgcgtctgt acccggtat tccggcagct ctggtgcgtg cttttctgca gccgccgctg 780

[0923]	aaaggtgttg tcatggaaac cttcggttct ggcaacggtc cgacgaagcc ggatctgctg	840
[0924]	caggaactgc gtgtggcaac cgaacgcggc ctggtcattg tgaattgcac gcactgtctg	900
[0925]	caagcgcag ttaccacgga ttatgcagcc ggtatggcaa tggctgggtgc ggggtgtcatc	960
[0926]	tccggttttg acatgaccag cgaagcagct ctggcgaaac tgtcctacgt tctgggccag	1020
[0927]	ccgggtctgt cactggatgt ccgtaaagaa ctgctgacca aggacctgcg cggtgaaatg	1080
[0928]	acgccgccgt ctgtggaaga acgtcgcccg agtctgcagg gtaacaccct gggcgggtggc	1140
[0929]	gtttcttggc tgctgtcact gtcgggcagc caagaagccg atgcactgcg caatgcactg	1200
[0930]	gtgccgagtc tggcatgcgc agcagcacat gcaggtagc tggaaagtct gcaggcgtg	1260
[0931]	gttgaactgg gttccgatct gggcctgggt gactttaacg gtcaaaccct gctgcatgct	1320
[0932]	gcagcacgtg gtggccacac cgaagcagtt acgatgctgc tgcagcgtgg cgttgatgct	1380
[0933]	aatacccgcg atacggacgg ttctagtcgc ctgctgctgg cagtccgtgg tcgtcatccg	1440
[0934]	ggcgtgatcg gtctgctgcg cgaagctggt gcgtctctga gtaccagga actggaagaa	1500
[0935]	gcgggcacgg aactgtgtcg tctggcctat cgcgcagatc tggaaagcct gcaagtgtgg	1560
[0936]	tggcaagcag gtgcagatct gggtcagccg ggttacgacg gtcatagcgc cctgcacgtt	1620
[0937]	gcagaagcag ctggtaatct ggctgtggtt gcgtttctgc aaagtctgga aggtgccgtc	1680
[0938]	ggtgcccgaag cgccgtgccc ggaagtgtg cgggtgtct aa	1722
[0939]	<210>	36
[0940]	<211>	1698
[0941]	<212>	DNA
[0942]	<213>	人工序列
[0943]	<220>	
[0944]	<223>	合成多核苷酸
[0945]	<400>	36
[0946]	atggcacgcg cttcgggctc ggaacgtcat ctgctgctga tctacacggg tggcacgctg	60
[0947]	ggtatgcaat ccaagggtgg tgttctggtc ccgggtccgg gtctggtgac cctgctgcgt	120
[0948]	acgtgccga tgtttcatga taaagaattc gcacaggcac aaggcctgcc ggaccatgct	180
[0949]	ctggcgtgctgc cgccggcctc tcacggtcgc cgctgctgt ataccgttct ggaatgccag	240
[0950]	ccgtgctgctgg atagctctga catgacgatt gatgactgga ttcgtatcgc gaagattatc	300
[0951]	gaacgccatt atgaacagta ccaaggtttt gtggttatcc acggcaccga tacgatggtc	360
[0952]	tcaggcgcgt cgatgctgag cttcatgctg gaaaacctgc acaaaccggt gattctgacc	420
[0953]	ggtgcccagg tcccgatccg tgtgctgtgg aacgatgcac gcgaaaatct gctgggtgcc	480
[0954]	ctgctgggtg caggccagta tattatcccg gaagtctgcc tgtttatgaa ctgcgaactg	540
[0955]	ttccgtggca atcgctcac gaaggtggat agccagaaat ttgaagcatt ctgttctccg	600
[0956]	aacctgagtc cgctggctac cgttggtgcg gatgtcacga ttgcgtggga cctggttcgt	660
[0957]	aaagtcaagt ggaaagatcc gctggtcgtg cattccaata tggaaacacga cgtcgcactg	720
[0958]	ctgcgtctgt acccgggcat cccggctagc ctggttcgtg cgtttctgca gccgccgtg	780
[0959]	aagggtgttg tcttgaaac cttcggtcc ggtaatggcc cgtcaaaacc ggatctgctg	840
[0960]	caggaactgc gtgcagcagc acaacgcggc ctgattatgg tgaactgctc gcagtgtctg	900
[0961]	cgcgtagcgc ttacccggg ttatgccacg agcctggcag gtgcaaatat cgtgtctggc	960
[0962]	ctggatatga ccagtgaagc tgcgtggcg aagctgtctt acgttctggg cctgccggaa	1020
[0963]	ctgagtctgg aacgtcgcca ggaactgtg gctaaagatc tgcgtggtga aatgaccctg	1080
[0964]	ccgacggcag acctgcatca gatttccccg ccgggtcca cctgggtca aggcgtggcc	1140

[0965]	cgccctgtttt cactgttcgg ttgtcaggaa gaagattcgg tgcaagacgc agttatgccg	1200
[0966]	agcctggctc tggcactggc acacgcaggt gaactggaag ccctgcaagc actgatggaa	1260
[0967]	ctgggttccg atctgcgtct gaaagactca aacggccaga cctgctgca tgttgccgca	1320
[0968]	cgtaatggtc gcgatggcgt ggttacgatg ctgctgcacc gcggtatgga cgtgaacgca	1380
[0969]	cgtgatcgtg acggtctgtc accgctgctg ctggcagttc aaggtcgtca tcgcgaatgc	1440
[0970]	attcgtctgc tgcgcaaggc tggcgcgtgt ctgtctccgc aggatctgaa agacgcgggt	1500
[0971]	accgaactgt gccgtctggc tagtcgcgcg gatatggaag gtctgcaggc atgggggtcaa	1560
[0972]	gcaggtgcag atctgcagca accgggttac gacggccgta gtgccctgtg tgtggcagaa	1620
[0973]	gctgcgggta atcaggaagt gctggctctg ctgcgtaatc tggctctggt tggcccggaa	1680
[0974]	gtcccgcgg ctatttaa	1698
[0975]	<210>	37
[0976]	<211>	571
[0977]	<212>	PRT
[0978]	<213>	人工序列
[0979]	<220>	
[0980]	<223>	合成多肽
[0981]	<400>	37
[0982]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr	
[0983]	1 5 10 15	
[0984]	Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro Gly	
[0985]	20 25 30	
[0986]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Lys	
[0987]	35 40 45	
[0988]	Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu Ala Leu Pro	
[0989]	50 55 60	
[0990]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln	
[0991]	65 70 75 80	
[0992]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile Arg Ile	
[0993]	85 90 95	
[0994]	Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly Phe Val Val	
[0995]	100 105 110	
[0996]	Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu Ser Phe	
[0997]	115 120 125	
[0998]	Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala Gln Val	
[0999]	130 135 140	
[1000]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala	
[1001]	145 150 155 160	
[1002]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met	
[1003]	165 170 175	
[1004]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln	
[1005]	180 185 190	
[1006]	Lys Phe Glu Ala Phe Cys Ser Pro Asn Leu Ser Pro Leu Ala Thr Val	

[1007]	195	200	205
[1008]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys Trp		
[1009]	210	215	220
[1010]	Lys Asp Pro Leu Val Val His Ser Ser Met Glu Gln Asp Val Gly Leu		
[1011]	225	230	235
[1012]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala Phe Leu		
[1013]	245	250	255
[1014]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn		
[1015]	260	265	270
[1016]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Glu		
[1017]	275	280	285
[1018]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val		
[1019]	290	295	300
[1020]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly		
[1021]	305	310	315
[1022]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu		
[1023]	325	330	335
[1024]	Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys		
[1025]	340	345	350
[1026]	Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg Arg Pro		
[1027]	355	360	365
[1028]	Ser Leu Gln Gly Asn Thr Leu Gly Gly Gly Val Ser Trp Leu Leu Ser		
[1029]	370	375	380
[1030]	Leu Ser Gly Ser Gln Glu Ala Asp Ala Leu Arg Asn Ala Leu Val Pro		
[1031]	385	390	395
[1032]	Ser Leu Ala Cys Ala Ala Ala His Ala Gly Asp Val Glu Ala Leu Gln		
[1033]	405	410	415
[1034]	Ala Leu Val Glu Leu Gly Ser Asp Leu Gly Leu Val Asp Phe Asn Gly		
[1035]	420	425	430
[1036]	Gln Thr Pro Leu His Ala Ala Ala Arg Gly Gly His Thr Glu Ala Val		
[1037]	435	440	445
[1038]	Thr Met Leu Leu Gln Arg Gly Val Asp Val Asn Thr Arg Asp Thr Asp		
[1039]	450	455	460
[1040]	Gly Phe Ser Pro Leu Leu Leu Ala Val Arg Gly Arg His Pro Gly Val		
[1041]	465	470	475
[1042]	Ile Gly Leu Leu Arg Glu Ala Gly Ala Ser Leu Ser Thr Gln Glu Leu		
[1043]	485	490	495
[1044]	Glu Glu Ala Gly Thr Glu Leu Cys Arg Leu Ala Tyr Arg Ala Asp Leu		
[1045]	500	505	510
[1046]	Glu Gly Leu Gln Val Trp Trp Gln Ala Gly Ala Asp Leu Gly Gln Pro		
[1047]	515	520	525
[1048]	Gly Tyr Asp Gly His Ser Ala Leu His Val Ala Glu Ala Ala Gly Asn		

[1049]	530	535	540
[1050]	Leu Ala Val Val Ala Phe Leu Gln Ser Leu Glu Gly Ala Val Gly Ala		
[1051]	545	550	555 560
[1052]	Gln Ala Pro Cys Pro Glu Val Leu Pro Gly Val		
[1053]	565	570	
[1054]	<210> 38		
[1055]	<211> 567		
[1056]	<212> PRT		
[1057]	<213> 人工序列		
[1058]	<220>		
[1059]	<223> 合成多肽		
[1060]	<400> 38		
[1061]	Met Ala Arg Ala Val Gly Pro Glu Arg Arg Leu Leu Ala Val Tyr Thr		
[1062]	1 5 10 15		
[1063]	Gly Gly Thr Ile Gly Met Arg Ser Glu Leu Gly Val Leu Val Pro Gly		
[1064]	20 25 30		
[1065]	Thr Gly Leu Ala Ala Ile Leu Arg Thr Leu Pro Met Phe His Asp Glu		
[1066]	35 40 45		
[1067]	Glu His Ala Arg Ala Arg Gly Leu Ser Glu Asp Thr Leu Val Leu Pro		
[1068]	50 55 60		
[1069]	Pro Ala Ser Arg Asn Gln Arg Ile Leu Tyr Thr Val Leu Glu Cys Gln		
[1070]	65 70 75 80		
[1071]	Pro Leu Phe Asp Ser Ser Asp Met Thr Ile Ala Glu Trp Val Cys Leu		
[1072]	85 90 95		
[1073]	Ala Gln Thr Ile Lys Arg His Tyr Glu Gln Tyr His Gly Phe Val Val		
[1074]	100 105 110		
[1075]	Ile His Gly Thr Asp Thr Met Ala Phe Ala Ala Ser Met Leu Ser Phe		
[1076]	115 120 125		
[1077]	Met Leu Glu Asn Leu Gln Lys Thr Val Ile Leu Thr Gly Ala Gln Val		
[1078]	130 135 140		
[1079]	Pro Ile His Ala Leu Trp Ser Asp Gly Arg Glu Asn Leu Leu Gly Ala		
[1080]	145 150 155 160		
[1081]	Leu Leu Met Ala Gly Gln Tyr Val Ile Pro Glu Val Cys Leu Phe Phe		
[1082]	165 170 175		
[1083]	Gln Asn Gln Leu Phe Arg Gly Asn Arg Ala Thr Lys Val Asp Ala Arg		
[1084]	180 185 190		
[1085]	Arg Phe Ala Ala Phe Cys Ser Pro Asn Leu Leu Pro Leu Ala Thr Val		
[1086]	195 200 205		
[1087]	Gly Ala Asp Ile Thr Ile Asn Arg Glu Leu Val Arg Lys Val Asp Gly		
[1088]	210 215 220		
[1089]	Lys Ala Gly Leu Val Val His Ser Ser Met Glu Gln Asp Val Gly Leu		
[1090]	225 230 235 240		

[1091]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ala Leu Val Arg Ala Phe Leu
[1092]	245 250 255
[1093]	Gln Pro Pro Leu Lys Gly Val Val Met Glu Thr Phe Gly Ser Gly Asn
[1094]	260 265 270
[1095]	Gly Pro Thr Lys Pro Asp Leu Leu Gln Glu Leu Arg Val Ala Thr Glu
[1096]	275 280 285
[1097]	Arg Gly Leu Val Ile Val Asn Cys Thr His Cys Leu Gln Gly Ala Val
[1098]	290 295 300
[1099]	Thr Thr Asp Tyr Ala Ala Gly Met Ala Met Ala Gly Ala Gly Val Ile
[1100]	305 310 315 320
[1101]	Ser Gly Phe Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr
[1102]	325 330 335
[1103]	Val Leu Gly Gln Pro Gly Leu Ser Leu Asp Val Arg Lys Glu Leu Leu
[1104]	340 345 350
[1105]	Thr Lys Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu His
[1106]	355 360 365
[1107]	Gln Ser Ser Pro Pro Gly Ser Thr Leu Gly Gln Gly Val Ala Arg Leu
[1108]	370 375 380
[1109]	Phe Ser Leu Phe Gly Cys Gln Glu Glu Asp Ser Val Gln Asp Ala Val
[1110]	385 390 395 400
[1111]	Met Pro Ser Leu Ala Leu Ala Leu Ala His Ala Gly Glu Leu Glu Ala
[1112]	405 410 415
[1113]	Leu Gln Ala Leu Met Glu Leu Gly Ser Asp Leu Arg Leu Lys Asp Ser
[1114]	420 425 430
[1115]	Asn Gly Gln Thr Leu Leu His Val Ala Ala Arg Asn Gly Arg Asp Gly
[1116]	435 440 445
[1117]	Val Val Thr Met Leu Leu His Arg Gly Met Asp Val Asn Ala Arg Asp
[1118]	450 455 460
[1119]	Arg Asp Gly Leu Ser Pro Leu Leu Leu Ala Val Gln Gly Arg His Arg
[1120]	465 470 475 480
[1121]	Glu Cys Ile Arg Leu Leu Arg Lys Ala Gly Ala Cys Leu Ser Pro Gln
[1122]	485 490 495
[1123]	Asp Leu Lys Asp Ala Gly Thr Glu Leu Cys Arg Leu Ala Ser Arg Ala
[1124]	500 505 510
[1125]	Asp Met Glu Gly Leu Gln Ala Trp Gly Gln Ala Gly Ala Asp Leu Gln
[1126]	515 520 525
[1127]	Gln Pro Gly Tyr Asp Gly Arg Ser Ala Leu Cys Val Ala Glu Ala Ala
[1128]	530 535 540
[1129]	Gly Asn Gln Glu Val Leu Ala Leu Leu Arg Asn Leu Ala Leu Val Gly
[1130]	545 550 555 560
[1131]	Pro Glu Val Pro Pro Ala Ile
[1132]	565

[1133]	<210> 39															
[1134]	<211> 571															
[1135]	<212> PRT															
[1136]	<213> 人工序列															
[1137]	<220>															
[1138]	<223> 合成多肽															
[1139]	<400> 39															
[1140]	Met	Ala	Arg	Ala	Ser	Gly	Ser	Glu	Arg	His	Leu	Leu	Leu	Ile	Tyr	Thr
[1141]	1				5				10					15		
[1142]	Gly	Gly	Thr	Leu	Gly	Met	Gln	Ser	Lys	Gly	Gly	Val	Leu	Val	Pro	Gly
[1143]				20					25					30		
[1144]	Pro	Gly	Leu	Val	Thr	Leu	Leu	Arg	Thr	Leu	Pro	Met	Phe	His	Asp	Lys
[1145]			35					40					45			
[1146]	Glu	Phe	Ala	Arg	Ala	Arg	Gly	Leu	Ser	Glu	Asp	Thr	Leu	Val	Leu	Pro
[1147]		50					55				60					
[1148]	Pro	Ala	Ser	Arg	Asn	Gln	Arg	Ile	Leu	Tyr	Thr	Val	Leu	Glu	Cys	Gln
[1149]	65					70				75					80	
[1150]	Pro	Leu	Leu	Asp	Ser	Ser	Asp	Met	Thr	Ile	Asp	Asp	Trp	Ile	Arg	Ile
[1151]				85					90					95		
[1152]	Ala	Lys	Ile	Ile	Glu	Arg	His	Tyr	Glu	Gln	Tyr	Gln	Gly	Phe	Val	Val
[1153]				100					105					110		
[1154]	Ile	His	Gly	Thr	Asp	Thr	Met	Ala	Phe	Ala	Ala	Ser	Met	Leu	Ser	Phe
[1155]			115					120					125			
[1156]	Met	Leu	Glu	Asn	Leu	His	Lys	Pro	Val	Ile	Leu	Thr	Gly	Ala	Gln	Val
[1157]		130					135					140				
[1158]	Pro	Ile	Arg	Val	Leu	Trp	Asn	Asp	Ala	Arg	Glu	Asn	Leu	Leu	Gly	Ala
[1159]	145					150				155					160	
[1160]	Leu	Leu	Val	Ala	Gly	Gln	Tyr	Ile	Ile	Pro	Glu	Val	Cys	Leu	Phe	Met
[1161]				165					170					175		
[1162]	Asn	Ser	Gln	Leu	Phe	Arg	Gly	Asn	Arg	Val	Thr	Lys	Val	Asp	Ser	Gln
[1163]				180					185					190		
[1164]	Lys	Phe	Glu	Ala	Phe	Cys	Ser	Pro	Asn	Leu	Ser	Pro	Leu	Ala	Thr	Val
[1165]			195					200					205			
[1166]	Gly	Ala	Asp	Val	Thr	Ile	Ala	Trp	Asp	Leu	Val	Arg	Lys	Val	Lys	Trp
[1167]		210					215					220				
[1168]	Lys	Asp	Pro	Leu	Val	Val	His	Ser	Ser	Met	Glu	Gln	Asp	Val	Gly	Leu
[1169]	225					230				235					240	
[1170]	Leu	Arg	Leu	Tyr	Pro	Gly	Ile	Pro	Ala	Ser	Leu	Val	Arg	Ala	Phe	Leu
[1171]				245					250						255	
[1172]	Gln	Pro	Pro	Leu	Lys	Gly	Val	Val	Leu	Glu	Thr	Phe	Gly	Ser	Gly	Asn
[1173]				260					265					270		
[1174]	Gly	Pro	Ser	Lys	Pro	Asp	Leu	Leu	Gln	Glu	Leu	Arg	Ala	Ala	Ala	Glu

[1175]	275	280	285
[1176]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val		
[1177]	290	295	300
[1178]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly		
[1179]	305	310	315
[1180]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu		
[1181]	325	330	335
[1182]	Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys		
[1183]	340	345	350
[1184]	Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg Arg Pro		
[1185]	355	360	365
[1186]	Ser Leu Gln Gly Asn Thr Leu Gly Gly Gly Val Ser Trp Leu Leu Ser		
[1187]	370	375	380
[1188]	Leu Ser Gly Ser Gln Glu Ala Asp Ala Leu Arg Asn Ala Leu Val Pro		
[1189]	385	390	395
[1190]	Ser Leu Ala Cys Ala Ala Ala His Ala Gly Asp Val Glu Ala Leu Gln		
[1191]	405	410	415
[1192]	Ala Leu Val Glu Leu Gly Ser Asp Leu Gly Leu Val Asp Phe Asn Gly		
[1193]	420	425	430
[1194]	Gln Thr Pro Leu His Ala Ala Ala Arg Gly Gly His Thr Glu Ala Val		
[1195]	435	440	445
[1196]	Thr Met Leu Leu Gln Arg Gly Val Asp Val Asn Thr Arg Asp Thr Asp		
[1197]	450	455	460
[1198]	Gly Phe Ser Pro Leu Leu Leu Ala Val Arg Gly Arg His Pro Gly Val		
[1199]	465	470	475
[1200]	Ile Gly Leu Leu Arg Glu Ala Gly Ala Ser Leu Ser Thr Gln Glu Leu		
[1201]	485	490	495
[1202]	Glu Glu Ala Gly Thr Glu Leu Cys Arg Leu Ala Tyr Arg Ala Asp Leu		
[1203]	500	505	510
[1204]	Glu Gly Leu Gln Val Trp Trp Gln Ala Gly Ala Asp Leu Gly Gln Pro		
[1205]	515	520	525
[1206]	Gly Tyr Asp Gly His Ser Ala Leu His Val Ala Glu Ala Ala Gly Asn		
[1207]	530	535	540
[1208]	Leu Ala Val Val Ala Phe Leu Gln Ser Leu Glu Gly Ala Val Gly Ala		
[1209]	545	550	555
[1210]	Gln Ala Pro Cys Pro Glu Val Leu Pro Gly Val		
[1211]	565	570	
[1212]	<210> 40		
[1213]	<211> 513		
[1214]	<212> PRT		
[1215]	<213> 人工序列		
[1216]	<220>		

[1217]	<223> 合成多肽															
[1218]	<400> 40															
[1219]	Met	Ala	Arg	Ala	Ser	Gly	Ser	Glu	Arg	His	Leu	Leu	Leu	Ile	Tyr	Thr
[1220]	1				5					10					15	
[1221]	Gly	Gly	Thr	Leu	Gly	Met	Gln	Ser	Lys	Gly	Gly	Val	Leu	Val	Pro	Gly
[1222]				20					25					30		
[1223]	Pro	Gly	Leu	Val	Thr	Leu	Leu	Arg	Thr	Leu	Pro	Met	Phe	His	Asp	Glu
[1224]			35					40					45			
[1225]	Glu	His	Ala	Arg	Ala	Arg	Gly	Leu	Ser	Glu	Asp	Thr	Leu	Val	Leu	Pro
[1226]		50					55					60				
[1227]	Pro	Ala	Ser	Arg	Asn	Gln	Arg	Ile	Leu	Tyr	Thr	Val	Leu	Glu	Cys	Gln
[1228]	65					70					75				80	
[1229]	Pro	Leu	Leu	Asp	Ser	Ser	Asp	Met	Thr	Ile	Asp	Asp	Trp	Ile	Arg	Ile
[1230]				85					90						95	
[1231]	Ala	Lys	Ile	Ile	Glu	Arg	His	Tyr	Glu	Gln	Tyr	Gln	Gly	Phe	Val	Val
[1232]				100					105					110		
[1233]	Ile	His	Gly	Thr	Asp	Thr	Met	Ala	Phe	Ala	Ala	Ser	Met	Leu	Ser	Phe
[1234]			115					120					125			
[1235]	Met	Leu	Glu	Asn	Leu	His	Lys	Pro	Val	Ile	Leu	Thr	Gly	Ala	Gln	Val
[1236]		130					135					140				
[1237]	Pro	Ile	His	Ala	Leu	Trp	Ser	Asp	Gly	Arg	Glu	Asn	Leu	Leu	Gly	Ala
[1238]	145					150					155				160	
[1239]	Leu	Leu	Val	Ala	Gly	Gln	Tyr	Ile	Ile	Pro	Glu	Val	Cys	Leu	Phe	Met
[1240]				165					170					175		
[1241]	Asn	Ser	Gln	Leu	Phe	Arg	Gly	Asn	Arg	Val	Thr	Lys	Val	Asp	Ser	Gln
[1242]			180						185					190		
[1243]	Lys	Phe	Glu	Ala	Phe	Cys	Ser	Pro	Asn	Leu	Ser	Pro	Leu	Ala	Thr	Val
[1244]		195						200					205			
[1245]	Gly	Ala	Asp	Val	Thr	Ile	Ala	Trp	Asp	Leu	Val	Arg	Lys	Val	Lys	Trp
[1246]		210					215					220				
[1247]	Lys	Asp	Pro	Leu	Val	Val	His	Ser	Ser	Met	Glu	Gln	Asp	Val	Gly	Leu
[1248]	225					230					235				240	
[1249]	Leu	Arg	Leu	Tyr	Pro	Gly	Ile	Pro	Ala	Ser	Leu	Val	Arg	Ala	Phe	Leu
[1250]				245					250					255		
[1251]	Gln	Pro	Pro	Leu	Lys	Gly	Val	Val	Met	Glu	Thr	Phe	Gly	Ser	Gly	Asn
[1252]				260					265					270		
[1253]	Gly	Pro	Thr	Lys	Pro	Asp	Leu	Leu	Gln	Glu	Leu	Arg	Ala	Ala	Ala	Glu
[1254]			275						280				285			
[1255]	Arg	Gly	Leu	Ile	Met	Val	Asn	Cys	Ser	Gln	Cys	Leu	Arg	Gly	Ser	Val
[1256]		290						295				300				
[1257]	Thr	Pro	Gly	Tyr	Ala	Thr	Ser	Leu	Ala	Gly	Ala	Asn	Ile	Val	Ser	Gly
[1258]	305					310					315				320	

[1259]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu		
[1260]		325	330
[1261]	Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys		335
[1262]		340	345
[1263]	Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg Arg Pro		350
[1264]		355	360
[1265]	Ser Leu Gln Gly Asn Thr Leu Gly Gly Gly Val Ser Trp Leu Leu Ser		365
[1266]		370	375
[1267]	Leu Ser Gly Ser Gln Glu Ala Asp Ala Leu Arg Asn Ala Leu Val Pro		380
[1268]		385	390
[1269]	Ser Leu Ala Cys Ala Ala Ala His Ala Gly Asp Val Glu Ala Leu Gln		395
[1270]		405	410
[1271]	Ala Leu Val Glu Leu Gly Ser Asp Leu Gly Leu Val Asp Phe Asn Gly		415
[1272]		420	425
[1273]	Gln Thr Pro Leu His Ala Ala Ala Arg Gly Gly His Thr Glu Ala Val		430
[1274]		435	440
[1275]	Thr Met Leu Leu Gln Arg Gly Val Asp Val Asn Thr Arg Asp Thr Asp		445
[1276]		450	455
[1277]	Gly Phe Ser Pro Leu Leu Leu Ala Val Arg Gly Arg His Pro Gly Val		460
[1278]		465	470
[1279]	Ile Gly Leu Leu Arg Glu Ala Gly Ala Ser Leu Ser Thr Gln Glu Leu		475
[1280]		485	490
[1281]	Glu Glu Ala Gly Thr Glu Leu Cys Arg Leu Ala Tyr Arg Ala Asp Leu		495
[1282]		500	505
[1283]	Glu		510
[1284]	<210> 41		
[1285]	<211> 571		
[1286]	<212> PRT		
[1287]	<213> 人工序列		
[1288]	<220>		
[1289]	<223> 合成多肽		
[1290]	<400> 41		
[1291]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr		
[1292]	1	5	10
[1293]	Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro Gly		15
[1294]		20	25
[1295]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Glu		30
[1296]		35	40
[1297]	Glu His Ala Arg Ala Arg Gly Leu Ser Glu Asp Thr Leu Val Leu Pro		45
[1298]		50	55
[1299]	Pro Ala Ser Arg Asn Gln Arg Ile Leu Tyr Thr Val Leu Glu Cys Gln		60
[1300]	65	70	75
			80

[1301]	Pro	Leu	Phe	Asp	Ser	Ser	Asp	Met	Thr	Ile	Ala	Glu	Trp	Val	Cys	Leu
[1302]					85					90					95	
[1303]	Ala	Gln	Thr	Ile	Lys	Arg	His	Tyr	Glu	Gln	Tyr	His	Gly	Phe	Val	Val
[1304]					100					105					110	
[1305]	Ile	His	Gly	Thr	Asp	Thr	Met	Ala	Phe	Ala	Ala	Ser	Met	Leu	Ser	Phe
[1306]					115					120					125	
[1307]	Met	Leu	Glu	Asn	Leu	His	Lys	Pro	Val	Ile	Leu	Thr	Gly	Ala	Gln	Val
[1308]					130					135					140	
[1309]	Pro	Ile	His	Ala	Leu	Trp	Ser	Asp	Gly	Arg	Glu	Asn	Leu	Leu	Gly	Ala
[1310]					145					150					155	160
[1311]	Leu	Leu	Met	Ala	Gly	Gln	Tyr	Val	Ile	Pro	Glu	Val	Cys	Leu	Phe	Phe
[1312]					165					170					175	
[1313]	Gln	Asn	Gln	Leu	Phe	Arg	Gly	Asn	Arg	Ala	Thr	Lys	Val	Asp	Ala	Arg
[1314]					180					185					190	
[1315]	Arg	Phe	Ala	Ala	Phe	Cys	Ser	Pro	Asn	Leu	Leu	Pro	Leu	Ala	Thr	Val
[1316]					195					200					205	
[1317]	Gly	Ala	Asp	Val	Thr	Ile	Ala	Trp	Asp	Leu	Val	Arg	Lys	Val	Lys	Trp
[1318]					210					215					220	
[1319]	Lys	Asp	Pro	Leu	Val	Val	His	Ser	Asn	Met	Glu	His	Asp	Val	Ala	Leu
[1320]					225					230					235	240
[1321]	Leu	Arg	Leu	Tyr	Pro	Gly	Ile	Pro	Ala	Ala	Leu	Val	Arg	Ala	Phe	Leu
[1322]					245					250					255	
[1323]	Gln	Pro	Pro	Leu	Lys	Gly	Val	Val	Leu	Glu	Thr	Phe	Gly	Ser	Gly	Asn
[1324]					260					265					270	
[1325]	Gly	Pro	Ser	Lys	Pro	Asp	Leu	Leu	Gln	Glu	Leu	Arg	Ala	Ala	Ala	Glu
[1326]					275					280					285	
[1327]	Arg	Gly	Leu	Ile	Met	Val	Asn	Cys	Ser	Gln	Cys	Leu	Arg	Gly	Ser	Val
[1328]					290					295					300	
[1329]	Thr	Pro	Gly	Tyr	Ala	Thr	Ser	Leu	Ala	Gly	Ala	Asn	Ile	Val	Ser	Gly
[1330]					305					310					315	320
[1331]	Leu	Asp	Met	Thr	Ser	Glu	Ala	Ala	Leu	Ala	Lys	Leu	Ser	Tyr	Val	Leu
[1332]					325					330					335	
[1333]	Gly	Leu	Pro	Glu	Leu	Ser	Leu	Glu	Arg	Arg	Gln	Glu	Leu	Leu	Ala	Lys
[1334]					340					345					350	
[1335]	Asp	Leu	Arg	Gly	Glu	Met	Thr	Pro	Pro	Ser	Val	Glu	Glu	Arg	Arg	Pro
[1336]					355					360					365	
[1337]	Ser	Leu	Gln	Gly	Asn	Thr	Leu	Gly	Gly	Gly	Val	Ser	Trp	Leu	Leu	Ser
[1338]					370					375					380	
[1339]	Leu	Ser	Gly	Ser	Gln	Glu	Ala	Asp	Ala	Leu	Arg	Asn	Ala	Leu	Val	Pro
[1340]					385					390					395	400
[1341]	Ser	Leu	Ala	Cys	Ala	Ala	Ala	His	Ala	Gly	Asp	Val	Glu	Ala	Leu	Gln
[1342]					405					410					415	

[1343]	Ala Leu Val Glu Leu Gly Ser Asp Leu Gly Leu Val Asp Phe Asn Gly
[1344]	420 425 430
[1345]	Gln Thr Pro Leu His Ala Ala Ala Arg Gly Gly His Thr Glu Ala Val
[1346]	435 440 445
[1347]	Thr Met Leu Leu Gln Arg Gly Val Asp Val Asn Thr Arg Asp Thr Asp
[1348]	450 455 460
[1349]	Gly Phe Ser Pro Leu Leu Leu Ala Val Arg Gly Arg His Pro Gly Val
[1350]	465 470 475 480
[1351]	Ile Gly Leu Leu Arg Glu Ala Gly Ala Ser Leu Ser Thr Gln Glu Leu
[1352]	485 490 495
[1353]	Glu Glu Ala Gly Thr Glu Leu Cys Arg Leu Ala Tyr Arg Ala Asp Leu
[1354]	500 505 510
[1355]	Glu Gly Leu Gln Val Trp Trp Gln Ala Gly Ala Asp Leu Gly Gln Pro
[1356]	515 520 525
[1357]	Gly Tyr Asp Gly His Ser Ala Leu His Val Ala Glu Ala Ala Gly Asn
[1358]	530 535 540
[1359]	Leu Ala Val Val Ala Phe Leu Gln Ser Leu Glu Gly Ala Val Gly Ala
[1360]	545 550 555 560
[1361]	Gln Ala Pro Cys Pro Glu Val Leu Pro Gly Val
[1362]	565 570
[1363]	<210> 42
[1364]	<211> 571
[1365]	<212> PRT
[1366]	<213> 人工序列
[1367]	<220>
[1368]	<223> 合成多肽
[1369]	<400> 42
[1370]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr
[1371]	1 5 10 15
[1372]	Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro Gly
[1373]	20 25 30
[1374]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Glu
[1375]	35 40 45
[1376]	Glu His Ala Arg Ala Arg Gly Leu Ser Glu Asp Thr Leu Val Leu Pro
[1377]	50 55 60
[1378]	Pro Ala Ser Arg Asn Gln Arg Ile Leu Tyr Thr Val Leu Glu Cys Gln
[1379]	65 70 75 80
[1380]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile Arg Ile
[1381]	85 90 95
[1382]	Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr His Gly Phe Val Val
[1383]	100 105 110
[1384]	Ile His Gly Thr Asp Thr Met Ala Phe Ala Ala Ser Met Leu Ser Phe

[1385]	115	120	125
[1386]	Met Leu Glu Asn Leu Gln Lys Thr Val Ile Leu Thr Gly Ala Gln Val		
[1387]	130	135	140
[1388]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala		
[1389]	145	150	155
[1390]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met		
[1391]	165	170	175
[1392]	Ser Asn Gln Leu Phe Arg Gly Asn Arg Ala Thr Lys Val Asp Ala Arg		
[1393]	180	185	190
[1394]	Arg Phe Ala Ala Phe Cys Ser Pro Asn Leu Ser Pro Leu Ala Thr Val		
[1395]	195	200	205
[1396]	Gly Ala Asp Ile Thr Ile Asn Arg Glu Leu Val Arg Lys Val Asp Gly		
[1397]	210	215	220
[1398]	Lys Ala Gly Leu Val Val His Ser Ser Met Glu Gln Asp Val Gly Leu		
[1399]	225	230	235
[1400]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ala Leu Val Arg Ala Phe Leu		
[1401]	245	250	255
[1402]	Gln Pro Pro Leu Lys Gly Val Val Met Glu Thr Phe Gly Ser Gly Asn		
[1403]	260	265	270
[1404]	Gly Pro Thr Lys Pro Asp Leu Leu Gln Glu Leu Arg Val Ala Thr Glu		
[1405]	275	280	285
[1406]	Arg Gly Leu Val Ile Val Asn Cys Thr His Cys Leu Gln Gly Ala Val		
[1407]	290	295	300
[1408]	Thr Thr Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly		
[1409]	305	310	315
[1410]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu		
[1411]	325	330	335
[1412]	Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys		
[1413]	340	345	350
[1414]	Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg Arg Pro		
[1415]	355	360	365
[1416]	Ser Leu Gln Gly Asn Thr Leu Gly Gly Gly Val Ser Trp Leu Leu Ser		
[1417]	370	375	380
[1418]	Leu Ser Gly Ser Gln Glu Ala Asp Ala Leu Arg Asn Ala Leu Val Pro		
[1419]	385	390	395
[1420]	Ser Leu Ala Cys Ala Ala Ala His Ala Gly Asp Val Glu Ala Leu Gln		
[1421]	405	410	415
[1422]	Ala Leu Val Glu Leu Gly Ser Asp Leu Gly Leu Val Asp Phe Asn Gly		
[1423]	420	425	430
[1424]	Gln Thr Pro Leu His Ala Ala Ala Arg Gly Gly His Thr Glu Ala Val		
[1425]	435	440	445
[1426]	Thr Met Leu Leu Gln Arg Gly Val Asp Val Asn Thr Arg Asp Thr Asp		

[1427]	450	455	460
[1428]	Gly Phe Ser Pro Leu Leu Leu Ala Val Arg Gly Arg His Pro Gly Val		
[1429]	465	470	475 480
[1430]	Ile Gly Leu Leu Arg Glu Ala Gly Ala Ser Leu Ser Thr Gln Glu Leu		
[1431]		485	490 495
[1432]	Glu Glu Ala Gly Thr Glu Leu Cys Arg Leu Ala Tyr Arg Ala Asp Leu		
[1433]		500	505 510
[1434]	Glu Gly Leu Gln Val Trp Trp Gln Ala Gly Ala Asp Leu Gly Gln Pro		
[1435]		515	520 525
[1436]	Gly Tyr Asp Gly His Ser Ala Leu His Val Ala Glu Ala Ala Gly Asn		
[1437]	530	535	540
[1438]	Leu Ala Val Val Ala Phe Leu Gln Ser Leu Glu Gly Ala Val Gly Ala		
[1439]	545	550	555 560
[1440]	Gln Ala Pro Cys Pro Glu Val Leu Pro Gly Val		
[1441]		565	570
[1442]	<210> 43		
[1443]	<211> 6		
[1444]	<212> PRT		
[1445]	<213> 人工序列		
[1446]	<220>		
[1447]	<223> 合成肽		
[1448]	<400> 43		
[1449]	Ser Glu Asp Thr Leu Val		
[1450]	1	5	
[1451]	<210> 44		
[1452]	<211> 6		
[1453]	<212> PRT		
[1454]	<213> 人工序列		
[1455]	<220>		
[1456]	<223> 合成肽		
[1457]	<400> 44		
[1458]	Pro Asp His Ala Leu Ala		
[1459]	1	5	
[1460]	<210> 45		
[1461]	<211> 369		
[1462]	<212> PRT		
[1463]	<213> 人工序列		
[1464]	<220>		
[1465]	<223> 合成多肽		
[1466]	<400> 45		
[1467]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr		
[1468]	1	5	10 15

[1469]	Gly Gly Thr Leu Gly Met Arg Ser Glu Gly Gly Val Leu Val Pro Gly
[1470]	20 25 30
[1471]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Glu
[1472]	35 40 45
[1473]	Glu Phe Ala Arg Ala Arg Gly Leu Pro Asp His Ala Leu Ala Leu Pro
[1474]	50 55 60
[1475]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln
[1476]	65 70 75 80
[1477]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile Arg Ile
[1478]	85 90 95
[1479]	Ala Gln Ile Ile Lys Arg His Tyr Glu Gln Tyr Gln Gly Phe Val Val
[1480]	100 105 110
[1481]	Ile His Gly Thr Asp Thr Met Ala Phe Ala Ala Ser Met Leu Ser Phe
[1482]	115 120 125
[1483]	Met Leu Glu Asn Leu Gln Lys Pro Val Ile Leu Thr Gly Ala Gln Val
[1484]	130 135 140
[1485]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala
[1486]	145 150 155 160
[1487]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met
[1488]	165 170 175
[1489]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln
[1490]	180 185 190
[1491]	Lys Phe Glu Ala Phe Cys Ser Pro Asn Leu Ser Pro Leu Ala Thr Val
[1492]	195 200 205
[1493]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys Trp
[1494]	210 215 220
[1495]	Lys Asp Pro Leu Val Val His Ser Ser Met Glu His Asp Val Ala Leu
[1496]	225 230 235 240
[1497]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala Phe Leu
[1498]	245 250 255
[1499]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn
[1500]	260 265 270
[1501]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Glu
[1502]	275 280 285
[1503]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val
[1504]	290 295 300
[1505]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly
[1506]	305 310 315 320
[1507]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu
[1508]	325 330 335
[1509]	Gly Leu Pro Glu Leu Ser Leu Asp Arg Arg Gln Glu Leu Leu Ala Lys
[1510]	340 345 350

[1511]	Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg Arg Pro
[1512]	355 360 365
[1513]	Ser
[1514]	<210> 46
[1515]	<211> 369
[1516]	<212> PRT
[1517]	<213> 人工序列
[1518]	<220>
[1519]	<223> 合成多肽
[1520]	<400> 46
[1521]	Met Ala Arg Ala Ser Gly Ser Glu Arg Arg Leu Leu Leu Ile Tyr Thr
[1522]	1 5 10 15
[1523]	Gly Gly Thr Leu Gly Met Arg Ser Glu Gly Gly Val Leu Val Pro Gly
[1524]	20 25 30
[1525]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Glu
[1526]	35 40 45
[1527]	Glu Phe Ala Arg Ala Arg Gly Leu Pro Asp His Ala Leu Ala Leu Pro
[1528]	50 55 60
[1529]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln
[1530]	65 70 75 80
[1531]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Ala Glu Trp Ile Arg Ile
[1532]	85 90 95
[1533]	Ala Gln Ile Ile Lys Arg His Tyr Glu Gln Tyr His Gly Phe Val Val
[1534]	100 105 110
[1535]	Ile His Gly Thr Asp Thr Met Ala Phe Ala Ala Ser Met Leu Ser Phe
[1536]	115 120 125
[1537]	Met Leu Glu Asn Leu Gln Lys Pro Val Ile Leu Thr Gly Ala Gln Val
[1538]	130 135 140
[1539]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala
[1540]	145 150 155 160
[1541]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met
[1542]	165 170 175
[1543]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln
[1544]	180 185 190
[1545]	Lys Phe Glu Ala Phe Cys Ser Pro Asn Leu Ser Pro Leu Ala Thr Val
[1546]	195 200 205
[1547]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys Trp
[1548]	210 215 220
[1549]	Lys Asp Pro Leu Val Val His Ser Ser Met Glu Gln Asp Val Ala Leu
[1550]	225 230 235 240
[1551]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ala Leu Val Arg Ala Phe Leu
[1552]	245 250 255

[1553]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn
[1554]	260 265 270
[1555]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Glu
[1556]	275 280 285
[1557]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val
[1558]	290 295 300
[1559]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly
[1560]	305 310 315 320
[1561]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu
[1562]	325 330 335
[1563]	Gly Leu Pro Glu Leu Ser Leu Asp Arg Arg Gln Glu Leu Leu Ala Lys
[1564]	340 345 350
[1565]	Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg Arg Pro
[1566]	355 360 365
[1567]	Ser
[1568]	<210> 47
[1569]	<211> 369
[1570]	<212> PRT
[1571]	<213> 人工序列
[1572]	<220>
[1573]	<223> 合成多肽
[1574]	<400> 47
[1575]	Met Ala Arg Ala Ser Gly Ser Glu Arg Arg Leu Leu Leu Ile Tyr Thr
[1576]	1 5 10 15
[1577]	Gly Gly Thr Leu Gly Met Arg Ser Glu Gly Gly Val Leu Val Pro Gly
[1578]	20 25 30
[1579]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Glu
[1580]	35 40 45
[1581]	Glu Phe Ala Arg Ala Arg Gly Leu Pro Asp His Ala Leu Ala Leu Pro
[1582]	50 55 60
[1583]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln
[1584]	65 70 75 80
[1585]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Ala Glu Trp Ile Arg Ile
[1586]	85 90 95
[1587]	Ala Gln Ile Ile Lys Arg His Tyr Glu Gln Tyr His Gly Phe Val Val
[1588]	100 105 110
[1589]	Ile His Gly Thr Asp Thr Met Ala Phe Ala Ala Ser Met Leu Ser Phe
[1590]	115 120 125
[1591]	Met Leu Glu Asn Leu Gln Lys Pro Val Ile Leu Thr Gly Ala Gln Val
[1592]	130 135 140
[1593]	Pro Ile His Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala
[1594]	145 150 155 160

[1595]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met		
[1596]		165	170
[1597]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln		
[1598]		180	185
[1599]	Arg Phe Glu Ala Phe Cys Ser Pro Asn Leu Ser Pro Leu Ala Thr Val		
[1600]		195	200
[1601]	Gly Ala Asp Val Thr Ile Ala Trp Glu Leu Val Arg Lys Val Lys Trp		
[1602]		210	215
[1603]	Lys Asp Pro Leu Val Val His Ser Ser Met Glu Gln Asp Val Ala Leu		
[1604]		225	230
[1605]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ala Leu Val Arg Ala Phe Leu		
[1606]		245	250
[1607]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn		
[1608]		260	265
[1609]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Glu		
[1610]		275	280
[1611]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Gln Gly Ser Val		
[1612]		290	295
[1613]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly		
[1614]		305	310
[1615]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu		
[1616]		325	330
[1617]	Gly Leu Pro Glu Leu Ser Leu Asp Arg Arg Gln Glu Leu Leu Ala Lys		
[1618]		340	345
[1619]	Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg Arg Pro		
[1620]		355	360
[1621]	Ser		
[1622]	<210> 48		
[1623]	<211> 369		
[1624]	<212> PRT		
[1625]	<213> 人工序列		
[1626]	<220>		
[1627]	<223> 合成多肽		
[1628]	<400> 48		
[1629]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr		
[1630]		1	5
[1631]	Gly Gly Thr Leu Gly Met Arg Ser Glu Gly Gly Val Leu Val Pro Gly		
[1632]		20	25
[1633]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Glu		
[1634]		35	40
[1635]	Glu Phe Ala Arg Ala Arg Gly Leu Ser Glu Asp Thr Leu Val Leu Pro		
[1636]		50	55

[1637]	Pro	Ala	Ser	His	Gly	Pro	Arg	Val	Leu	Tyr	Thr	Val	Leu	Glu	Cys	Gln
[1638]	65					70					75					80
[1639]	Pro	Leu	Leu	Asp	Ser	Ser	Asp	Met	Thr	Ile	Asp	Asp	Trp	Ile	Arg	Ile
[1640]					85					90						95
[1641]	Ala	Gln	Ile	Ile	Lys	Arg	His	Tyr	Glu	Gln	Tyr	Gln	Gly	Phe	Val	Val
[1642]					100					105						110
[1643]	Ile	His	Gly	Thr	Asp	Thr	Met	Ala	Phe	Ala	Ala	Ser	Met	Leu	Ser	Phe
[1644]					115					120						125
[1645]	Met	Leu	Glu	Asn	Leu	Gln	Lys	Pro	Val	Ile	Leu	Thr	Gly	Ala	Gln	Val
[1646]					130					135						140
[1647]	Pro	Ile	Arg	Val	Leu	Trp	Asn	Asp	Ala	Arg	Glu	Asn	Leu	Leu	Gly	Ala
[1648]					145					150						160
[1649]	Leu	Leu	Val	Ala	Gly	Gln	Tyr	Ile	Ile	Pro	Glu	Val	Cys	Leu	Phe	Met
[1650]					165					170						175
[1651]	Asn	Ser	Gln	Leu	Phe	Arg	Gly	Asn	Arg	Val	Thr	Lys	Val	Asp	Ser	Gln
[1652]					180					185						190
[1653]	Lys	Phe	Glu	Ala	Phe	Cys	Ser	Pro	Asn	Leu	Ser	Pro	Leu	Ala	Thr	Val
[1654]					195					200						205
[1655]	Gly	Ala	Asp	Val	Thr	Ile	Ala	Trp	Asp	Leu	Val	Arg	Lys	Val	Lys	Trp
[1656]					210					215						220
[1657]	Lys	Asp	Pro	Leu	Val	Val	His	Ser	Ser	Met	Glu	His	Asp	Val	Ala	Leu
[1658]					225					230						240
[1659]	Leu	Arg	Leu	Tyr	Pro	Gly	Ile	Pro	Ala	Ser	Leu	Val	Arg	Ala	Phe	Leu
[1660]					245					250						255
[1661]	Gln	Pro	Pro	Leu	Lys	Gly	Val	Val	Leu	Glu	Thr	Phe	Gly	Ser	Gly	Asn
[1662]					260					265						270
[1663]	Gly	Pro	Ser	Lys	Pro	Asp	Leu	Leu	Gln	Glu	Leu	Arg	Ala	Ala	Ala	Glu
[1664]					275					280						285
[1665]	Arg	Gly	Leu	Ile	Met	Val	Asn	Cys	Ser	Gln	Cys	Leu	Arg	Gly	Ser	Val
[1666]					290					295						300
[1667]	Thr	Pro	Gly	Tyr	Ala	Thr	Ser	Leu	Ala	Gly	Ala	Asn	Ile	Val	Ser	Gly
[1668]					305					310						320
[1669]	Leu	Asp	Met	Thr	Ser	Glu	Ala	Ala	Leu	Ala	Lys	Leu	Ser	Tyr	Val	Leu
[1670]					325					330						335
[1671]	Gly	Leu	Pro	Glu	Leu	Ser	Leu	Asp	Arg	Arg	Gln	Glu	Leu	Leu	Ala	Lys
[1672]					340					345						350
[1673]	Asp	Leu	Arg	Gly	Glu	Met	Thr	Pro	Pro	Ser	Val	Glu	Glu	Arg	Arg	Pro
[1674]					355					360						365
[1675]	Ser															
[1676]	<210>	49														
[1677]	<211>	369														
[1678]	<212>	PRT														

[1679]	<213>	人工序列
[1680]	<220>	
[1681]	<223>	合成多肽
[1682]	<400>	49
[1683]	Met Ala Arg Ala Ser Gly Ser Glu Arg Arg Leu Leu Leu Ile Tyr Thr	
[1684]	1	5 10 15
[1685]	Gly Gly Thr Leu Gly Met Arg Ser Glu Gly Gly Val Leu Val Pro Gly	
[1686]	20	25 30
[1687]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Glu	
[1688]	35	40 45
[1689]	Glu Phe Ala Arg Ala Arg Gly Leu Ser Glu Asp Thr Leu Val Leu Pro	
[1690]	50	55 60
[1691]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln	
[1692]	65	70 75 80
[1693]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Ala Glu Trp Ile Arg Ile	
[1694]	85	90 95
[1695]	Ala Gln Ile Ile Lys Arg His Tyr Glu Gln Tyr His Gly Phe Val Val	
[1696]	100	105 110
[1697]	Ile His Gly Thr Asp Thr Met Ala Phe Ala Ala Ser Met Leu Ser Phe	
[1698]	115	120 125
[1699]	Met Leu Glu Asn Leu Gln Lys Pro Val Ile Leu Thr Gly Ala Gln Val	
[1700]	130	135 140
[1701]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala	
[1702]	145	150 155 160
[1703]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met	
[1704]	165	170 175
[1705]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln	
[1706]	180	185 190
[1707]	Lys Phe Glu Ala Phe Cys Ser Pro Asn Leu Ser Pro Leu Ala Thr Val	
[1708]	195	200 205
[1709]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys Trp	
[1710]	210	215 220
[1711]	Lys Asp Pro Leu Val Val His Ser Ser Met Glu Gln Asp Val Ala Leu	
[1712]	225	230 235 240
[1713]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ala Leu Val Arg Ala Phe Leu	
[1714]	245	250 255
[1715]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn	
[1716]	260	265 270
[1717]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Glu	
[1718]	275	280 285
[1719]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val	
[1720]	290	295 300

[1721]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly
[1722]	305 310 315 320
[1723]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu
[1724]	325 330 335
[1725]	Gly Leu Pro Glu Leu Ser Leu Asp Arg Arg Gln Glu Leu Leu Ala Lys
[1726]	340 345 350
[1727]	Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg Arg Pro
[1728]	355 360 365
[1729]	Ser
[1730]	<210> 50
[1731]	<211> 369
[1732]	<212> PRT
[1733]	<213> 人工序列
[1734]	<220>
[1735]	<223> 合成多肽
[1736]	<400> 50
[1737]	Met Ala Arg Ala Ser Gly Ser Glu Arg Arg Leu Leu Leu Ile Tyr Thr
[1738]	1 5 10 15
[1739]	Gly Gly Thr Leu Gly Met Arg Ser Glu Gly Gly Val Leu Val Pro Gly
[1740]	20 25 30
[1741]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Glu
[1742]	35 40 45
[1743]	Glu Phe Ala Arg Ala Arg Gly Leu Ser Glu Asp Thr Leu Val Leu Pro
[1744]	50 55 60
[1745]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln
[1746]	65 70 75 80
[1747]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Ala Glu Trp Ile Arg Ile
[1748]	85 90 95
[1749]	Ala Gln Ile Ile Lys Arg His Tyr Glu Gln Tyr His Gly Phe Val Val
[1750]	100 105 110
[1751]	Ile His Gly Thr Asp Thr Met Ala Phe Ala Ala Ser Met Leu Ser Phe
[1752]	115 120 125
[1753]	Met Leu Glu Asn Leu Gln Lys Pro Val Ile Leu Thr Gly Ala Gln Val
[1754]	130 135 140
[1755]	Pro Ile His Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala
[1756]	145 150 155 160
[1757]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met
[1758]	165 170 175
[1759]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln
[1760]	180 185 190
[1761]	Arg Phe Glu Ala Phe Cys Ser Pro Asn Leu Ser Pro Leu Ala Thr Val
[1762]	195 200 205

[1763]	Gly	Ala	Asp	Val	Thr	Ile	Ala	Trp	Glu	Leu	Val	Arg	Lys	Val	Lys	Trp
[1764]	210						215					220				
[1765]	Lys	Asp	Pro	Leu	Val	Val	His	Ser	Ser	Met	Glu	Gln	Asp	Val	Ala	Leu
[1766]	225					230					235					240
[1767]	Leu	Arg	Leu	Tyr	Pro	Gly	Ile	Pro	Ala	Ala	Leu	Val	Arg	Ala	Phe	Leu
[1768]					245					250					255	
[1769]	Gln	Pro	Pro	Leu	Lys	Gly	Val	Val	Leu	Glu	Thr	Phe	Gly	Ser	Gly	Asn
[1770]				260					265					270		
[1771]	Gly	Pro	Ser	Lys	Pro	Asp	Leu	Leu	Gln	Glu	Leu	Arg	Ala	Ala	Ala	Glu
[1772]			275					280					285			
[1773]	Arg	Gly	Leu	Ile	Met	Val	Asn	Cys	Ser	Gln	Cys	Leu	Gln	Gly	Ser	Val
[1774]	290					295						300				
[1775]	Thr	Pro	Gly	Tyr	Ala	Thr	Ser	Leu	Ala	Gly	Ala	Asn	Ile	Val	Ser	Gly
[1776]	305				310					315						320
[1777]	Leu	Asp	Met	Thr	Ser	Glu	Ala	Ala	Leu	Ala	Lys	Leu	Ser	Tyr	Val	Leu
[1778]				325					330					335		
[1779]	Gly	Leu	Pro	Glu	Leu	Ser	Leu	Asp	Arg	Arg	Gln	Glu	Leu	Leu	Ala	Lys
[1780]			340						345					350		
[1781]	Asp	Leu	Arg	Gly	Glu	Met	Thr	Pro	Pro	Ser	Val	Glu	Glu	Arg	Arg	Pro
[1782]		355					360						365			
[1783]	Ser															
[1784]	<210>	51														
[1785]	<211>	369														
[1786]	<212>	PRT														
[1787]	<213>	人工序列														
[1788]	<220>															
[1789]	<223>	合成多肽														
[1790]	<400>	51														
[1791]	Met	Ala	Arg	Ala	Ser	Gly	Ser	Glu	Arg	His	Leu	Leu	Leu	Ile	Tyr	Thr
[1792]	1			5					10					15		
[1793]	Gly	Gly	Thr	Leu	Gly	Met	Gln	Ser	Lys	Gly	Gly	Val	Leu	Val	Pro	Gly
[1794]			20					25					30			
[1795]	Pro	Gly	Leu	Val	Thr	Leu	Leu	Arg	Thr	Leu	Pro	Met	Phe	His	Asp	Lys
[1796]		35					40					45				
[1797]	Glu	Phe	Ala	Gln	Ala	Gln	Gly	Leu	Pro	Asp	His	Ala	Leu	Ala	Leu	Pro
[1798]	50					55					60					
[1799]	Pro	Ala	Ser	His	Gly	Pro	Arg	Val	Leu	Tyr	Thr	Val	Leu	Glu	Cys	Gln
[1800]	65				70					75					80	
[1801]	Pro	Leu	Leu	Asp	Ser	Ser	Asp	Met	Thr	Ile	Asp	Asp	Trp	Ile	Arg	Ile
[1802]				85					90					95		
[1803]	Ala	Lys	Ile	Ile	Glu	Arg	His	Tyr	Glu	Gln	Tyr	Gln	Gly	Phe	Val	Val
[1804]			100						105					110		

[1805]	Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu Ser Phe		
[1806]	115	120	125
[1807]	Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala Gln Val		
[1808]	130	135	140
[1809]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala		
[1810]	145	150	155
[1811]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met		
[1812]	165	170	175
[1813]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln		
[1814]	180	185	190
[1815]	Lys Phe Glu Ala Phe Ala Ser Pro Asn Leu Ser Pro Leu Ala Thr Val		
[1816]	195	200	205
[1817]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys Trp		
[1818]	210	215	220
[1819]	Lys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp Val Ala Leu		
[1820]	225	230	235
[1821]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala Phe Leu		
[1822]	245	250	255
[1823]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn		
[1824]	260	265	270
[1825]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Gln		
[1826]	275	280	285
[1827]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val		
[1828]	290	295	300
[1829]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly		
[1830]	305	310	315
[1831]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu		
[1832]	325	330	335
[1833]	Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys		
[1834]	340	345	350
[1835]	Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu His Gln Ser		
[1836]	355	360	365
[1837]	Ser		
[1838]	<210> 52		
[1839]	<211> 369		
[1840]	<212> PRT		
[1841]	<213> 人工序列		
[1842]	<220>		
[1843]	<223> 合成多肽		
[1844]	<400> 52		
[1845]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr		
[1846]	1	5	10
			15

[1847]	Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro Gly
[1848]	20 25 30
[1849]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Lys
[1850]	35 40 45
[1851]	Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu Ala Leu Pro
[1852]	50 55 60
[1853]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln
[1854]	65 70 75 80
[1855]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile Arg Ile
[1856]	85 90 95
[1857]	Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly Phe Val Val
[1858]	100 105 110
[1859]	Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu Ser Phe
[1860]	115 120 125
[1861]	Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala Gln Val
[1862]	130 135 140
[1863]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala
[1864]	145 150 155 160
[1865]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met
[1866]	165 170 175
[1867]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln
[1868]	180 185 190
[1869]	Lys Phe Glu Ala Phe Ser Ser Pro Asn Leu Ser Pro Leu Ala Thr Val
[1870]	195 200 205
[1871]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys Trp
[1872]	210 215 220
[1873]	Lys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp Val Ala Leu
[1874]	225 230 235 240
[1875]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala Phe Leu
[1876]	245 250 255
[1877]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn
[1878]	260 265 270
[1879]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Gln
[1880]	275 280 285
[1881]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val
[1882]	290 295 300
[1883]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly
[1884]	305 310 315 320
[1885]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu
[1886]	325 330 335
[1887]	Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys
[1888]	340 345 350

[1889]	Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu His Gln Ser
[1890]	355 360 365
[1891]	Ser
[1892]	<210> 53
[1893]	<211> 369
[1894]	<212> PRT
[1895]	<213> 人工序列
[1896]	<220>
[1897]	<223> 合成多肽
[1898]	<400> 53
[1899]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr
[1900]	1 5 10 15
[1901]	Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro Gly
[1902]	20 25 30
[1903]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Lys
[1904]	35 40 45
[1905]	Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu Ala Leu Pro
[1906]	50 55 60
[1907]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln
[1908]	65 70 75 80
[1909]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile Arg Ile
[1910]	85 90 95
[1911]	Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly Phe Val Val
[1912]	100 105 110
[1913]	Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu Ser Phe
[1914]	115 120 125
[1915]	Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala Gln Val
[1916]	130 135 140
[1917]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala
[1918]	145 150 155 160
[1919]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met
[1920]	165 170 175
[1921]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln
[1922]	180 185 190
[1923]	Lys Phe Glu Ala Phe Val Ser Pro Asn Leu Ser Pro Leu Ala Thr Val
[1924]	195 200 205
[1925]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys Trp
[1926]	210 215 220
[1927]	Lys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp Val Ala Leu
[1928]	225 230 235 240
[1929]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala Phe Leu
[1930]	245 250 255

[1931]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn
[1932]	260 265 270
[1933]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Gln
[1934]	275 280 285
[1935]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val
[1936]	290 295 300
[1937]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly
[1938]	305 310 315 320
[1939]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu
[1940]	325 330 335
[1941]	Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys
[1942]	340 345 350
[1943]	Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu His Gln Ser
[1944]	355 360 365
[1945]	Ser
[1946]	<210> 54
[1947]	<211> 369
[1948]	<212> PRT
[1949]	<213> 人工序列
[1950]	<220>
[1951]	<223> 合成多肽
[1952]	<400> 54
[1953]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr
[1954]	1 5 10 15
[1955]	Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro Gly
[1956]	20 25 30
[1957]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Lys
[1958]	35 40 45
[1959]	Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu Ala Leu Pro
[1960]	50 55 60
[1961]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln
[1962]	65 70 75 80
[1963]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile Arg Ile
[1964]	85 90 95
[1965]	Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly Phe Val Val
[1966]	100 105 110
[1967]	Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu Ser Phe
[1968]	115 120 125
[1969]	Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala Gln Val
[1970]	130 135 140
[1971]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala
[1972]	145 150 155 160

[1973]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met		
[1974]		165	170
[1975]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln		175
[1976]		180	185
[1977]	Lys Phe Glu Ala Phe Ala Ser Pro Asn Leu Ser Pro Leu Ala Thr Val		190
[1978]		195	200
[1979]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys Trp		205
[1980]		210	215
[1981]	Cys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp Val Ala Leu		220
[1982]		225	230
[1983]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala Phe Leu		235
[1984]		245	250
[1985]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn		255
[1986]		260	265
[1987]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Gln		270
[1988]		275	280
[1989]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val		285
[1990]		290	295
[1991]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly		300
[1992]		305	310
[1993]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu		315
[1994]		325	330
[1995]	Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys		335
[1996]		340	345
[1997]	Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu His Gln Ser		350
[1998]		355	360
[1999]	Ser		365
[2000]	<210> 55		
[2001]	<211> 369		
[2002]	<212> PRT		
[2003]	<213> 人工序列		
[2004]	<220>		
[2005]	<223> 合成多肽		
[2006]	<400> 55		
[2007]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr		
[2008]		1	5
[2009]	Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro Gly		10
[2010]		20	25
[2011]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Lys		30
[2012]		35	40
[2013]	Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu Ala Leu Pro		45
[2014]		50	55
			60

[2015]	Pro	Ala	Ser	His	Gly	Pro	Arg	Val	Leu	Tyr	Thr	Val	Leu	Glu	Cys	Gln
[2016]	65					70					75					80
[2017]	Pro	Leu	Leu	Asp	Ser	Ser	Asp	Met	Thr	Ile	Asp	Asp	Trp	Ile	Arg	Ile
[2018]					85					90						95
[2019]	Ala	Lys	Ile	Ile	Glu	Arg	His	Tyr	Glu	Gln	Tyr	Gln	Gly	Phe	Val	Val
[2020]					100					105						110
[2021]	Ile	His	Gly	Thr	Asp	Thr	Met	Ala	Ser	Gly	Ala	Ser	Met	Leu	Ser	Phe
[2022]					115					120						125
[2023]	Met	Leu	Glu	Asn	Leu	His	Lys	Pro	Val	Ile	Leu	Thr	Gly	Ala	Gln	Val
[2024]					130					135						140
[2025]	Pro	Ile	Arg	Val	Leu	Trp	Asn	Asp	Ala	Arg	Glu	Asn	Leu	Leu	Gly	Ala
[2026]	145									150						160
[2027]	Leu	Leu	Val	Ala	Gly	Gln	Tyr	Ile	Ile	Pro	Glu	Val	Cys	Leu	Phe	Met
[2028]										165						175
[2029]	Asn	Ser	Gln	Leu	Phe	Arg	Gly	Asn	Arg	Val	Thr	Lys	Val	Asp	Ser	Gln
[2030]					180					185						190
[2031]	Lys	Phe	Glu	Ala	Phe	Ala	Ser	Pro	Asn	Leu	Ser	Pro	Leu	Ala	Thr	Val
[2032]					195					200						205
[2033]	Gly	Ala	Asp	Val	Thr	Ile	Ala	Trp	Asp	Leu	Val	Arg	Lys	Val	Lys	Trp
[2034]					210					215						220
[2035]	Cys	Asp	Pro	Leu	Val	Val	His	Ser	Asn	Met	Glu	His	Asp	Val	Ala	Leu
[2036]	225									230						240
[2037]	Leu	Arg	Leu	Tyr	Pro	Gly	Ile	Pro	Ala	Ser	Leu	Val	Arg	Ala	Phe	Leu
[2038]										245						255
[2039]	Gln	Pro	Pro	Leu	Lys	Gly	Val	Val	Leu	Glu	Thr	Phe	Gly	Ser	Gly	Asn
[2040]					260					265						270
[2041]	Gly	Pro	Ser	Lys	Pro	Asp	Leu	Leu	Gln	Glu	Leu	Arg	Ala	Ala	Ala	Gln
[2042]					275					280						285
[2043]	Arg	Gly	Leu	Ile	Met	Val	Asn	Cys	Ser	Gln	Cys	Leu	Arg	Gly	Ser	Val
[2044]					290					295						300
[2045]	Thr	Pro	Gly	Tyr	Ala	Thr	Ser	Leu	Ala	Gly	Ala	Asn	Ile	Val	Ser	Gly
[2046]	305									310						320
[2047]	Leu	Asp	Met	Thr	Ser	Glu	Ala	Ala	Leu	Ala	Lys	Leu	Ser	Tyr	Val	Leu
[2048]										325						335
[2049]	Gly	Leu	Pro	Cys	Leu	Ser	Leu	Glu	Arg	Arg	Gln	Glu	Leu	Leu	Ala	Lys
[2050]					340					345						350
[2051]	Asp	Leu	Arg	Gly	Glu	Met	Thr	Leu	Pro	Thr	Ala	Asp	Leu	His	Gln	Ser
[2052]					355					360						365
[2053]	Ser															
[2054]	<210>	56														
[2055]	<211>	369														
[2056]	<212>	PRT														

[2057]	<213> 人工序列															
[2058]	<220>															
[2059]	<223> 合成多肽															
[2060]	<400> 56															
[2061]	Met	Ala	Arg	Ala	Ser	Gly	Ser	Glu	Arg	His	Leu	Leu	Leu	Ile	Tyr	Thr
[2062]	1				5					10					15	
[2063]	Gly	Gly	Thr	Leu	Gly	Met	Gln	Ser	Lys	Gly	Gly	Val	Leu	Val	Pro	Gly
[2064]				20					25					30		
[2065]	Pro	Gly	Leu	Val	Thr	Leu	Leu	Arg	Thr	Leu	Pro	Met	Phe	His	Asp	Lys
[2066]			35					40					45			
[2067]	Cys	Phe	Ala	Gln	Ala	Gln	Gly	Leu	Pro	Asp	His	Ala	Leu	Ala	Leu	Pro
[2068]		50					55					60				
[2069]	Pro	Ala	Ser	His	Gly	Pro	Arg	Val	Leu	Tyr	Thr	Val	Leu	Glu	Cys	Gln
[2070]	65				70					75				80		
[2071]	Pro	Leu	Leu	Asp	Ser	Ser	Asp	Met	Thr	Ile	Asp	Asp	Trp	Ile	Arg	Ile
[2072]				85					90					95		
[2073]	Ala	Lys	Ile	Ile	Glu	Arg	His	Tyr	Glu	Gln	Tyr	Gln	Gly	Phe	Val	Val
[2074]			100					105					110			
[2075]	Ile	His	Gly	Thr	Asp	Thr	Met	Ala	Ser	Gly	Ala	Ser	Met	Leu	Ser	Phe
[2076]		115					120					125				
[2077]	Met	Leu	Glu	Asn	Leu	His	Lys	Pro	Val	Ile	Leu	Thr	Gly	Ala	Gln	Val
[2078]		130					135					140				
[2079]	Pro	Ile	Arg	Val	Leu	Trp	Asn	Asp	Ala	Arg	Glu	Asn	Leu	Leu	Gly	Ala
[2080]	145				150					155				160		
[2081]	Leu	Leu	Val	Ala	Gly	Gln	Tyr	Ile	Ile	Pro	Glu	Val	Cys	Leu	Phe	Met
[2082]				165					170				175			
[2083]	Asn	Ser	Gln	Leu	Phe	Arg	Gly	Asn	Arg	Val	Thr	Lys	Val	Asp	Ser	Gln
[2084]			180						185				190			
[2085]	Lys	Phe	Glu	Ala	Phe	Ala	Ser	Pro	Asn	Leu	Ser	Pro	Leu	Ala	Thr	Val
[2086]		195					200					205				
[2087]	Gly	Ala	Asp	Val	Thr	Ile	Ala	Trp	Asp	Leu	Val	Arg	Lys	Val	Lys	Trp
[2088]		210					215					220				
[2089]	Cys	Asp	Pro	Leu	Val	Val	His	Ser	Asn	Met	Glu	His	Asp	Val	Ala	Leu
[2090]	225				230					235				240		
[2091]	Leu	Arg	Leu	Tyr	Pro	Gly	Ile	Pro	Ala	Ser	Leu	Val	Arg	Ala	Phe	Leu
[2092]				245					250				255			
[2093]	Gln	Pro	Pro	Leu	Lys	Gly	Val	Val	Leu	Glu	Thr	Phe	Gly	Ser	Gly	Asn
[2094]			260						265				270			
[2095]	Gly	Pro	Ser	Lys	Pro	Asp	Leu	Leu	Gln	Glu	Leu	Arg	Ala	Ala	Ala	Gln
[2096]			275						280				285			
[2097]	Arg	Gly	Leu	Ile	Met	Val	Asn	Cys	Ser	Gln	Cys	Leu	Arg	Gly	Ser	Val
[2098]		290					295					300				

[2099]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly
[2100]	305 310 315 320
[2101]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu
[2102]	325 330 335
[2103]	Gly Leu Pro Cys Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys
[2104]	340 345 350
[2105]	Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu His Gln Ser
[2106]	355 360 365
[2107]	Ser
[2108]	<210> 57
[2109]	<211> 369
[2110]	<212> PRT
[2111]	<213> 人工序列
[2112]	<220>
[2113]	<223> 合成多肽
[2114]	<400> 57
[2115]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr
[2116]	1 5 10 15
[2117]	Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro Gly
[2118]	20 25 30
[2119]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Lys
[2120]	35 40 45
[2121]	Cys Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu Ala Leu Pro
[2122]	50 55 60
[2123]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln
[2124]	65 70 75 80
[2125]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile Arg Ile
[2126]	85 90 95
[2127]	Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly Phe Val Val
[2128]	100 105 110
[2129]	Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu Ser Phe
[2130]	115 120 125
[2131]	Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala Gln Val
[2132]	130 135 140
[2133]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala
[2134]	145 150 155 160
[2135]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met
[2136]	165 170 175
[2137]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln
[2138]	180 185 190
[2139]	Lys Phe Glu Ala Phe Ala Ser Pro Asn Leu Ser Pro Leu Ala Thr Val
[2140]	195 200 205

[2141]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys Trp
[2142]	210 215 220
[2143]	Cys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp Val Ala Leu
[2144]	225 230 235 240
[2145]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala Phe Leu
[2146]	245 250 255
[2147]	Cys Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn
[2148]	260 265 270
[2149]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Gln
[2150]	275 280 285
[2151]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val
[2152]	290 295 300
[2153]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly
[2154]	305 310 315 320
[2155]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu
[2156]	325 330 335
[2157]	Gly Leu Pro Cys Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys
[2158]	340 345 350
[2159]	Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu His Gln Ser
[2160]	355 360 365
[2161]	Ser
[2162]	<210> 58
[2163]	<211> 369
[2164]	<212> PRT
[2165]	<213> 人工序列
[2166]	<220>
[2167]	<223> 合成多肽
[2168]	<400> 58
[2169]	Met Ala Arg Ala Ser Gly Ser Glu Arg Arg Leu Leu Leu Ile Tyr Thr
[2170]	1 5 10 15
[2171]	Gly Gly Thr Leu Gly Met Arg Ser Glu Gly Gly Val Leu Val Pro Gly
[2172]	20 25 30
[2173]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Glu
[2174]	35 40 45
[2175]	Glu Phe Ala Arg Ala Arg Gly Leu Ser Glu Asp Thr Leu Val Leu Pro
[2176]	50 55 60
[2177]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln
[2178]	65 70 75 80
[2179]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Ala Glu Trp Ile Arg Ile
[2180]	85 90 95
[2181]	Ala Gln Ile Ile Lys Arg His Tyr Glu Gln Tyr His Gly Phe Val Val
[2182]	100 105 110

[2183]	Ile His Gly Thr Asp Thr Met Ala Phe Ala Ala Ser Met Leu Ser Phe		
[2184]	115	120	125
[2185]	Met Leu Glu Asn Leu Gln Lys Pro Val Ile Leu Thr Gly Ala Gln Val		
[2186]	130	135	140
[2187]	Pro Ile His Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala		
[2188]	145	150	155
[2189]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met		
[2190]	165	170	175
[2191]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln		
[2192]	180	185	190
[2193]	Arg Phe Glu Ala Phe Ala Ser Pro Asn Leu Ser Pro Leu Ala Thr Val		
[2194]	195	200	205
[2195]	Gly Ala Asp Val Thr Ile Ala Trp Glu Leu Val Arg Lys Val Lys Trp		
[2196]	210	215	220
[2197]	Lys Asp Pro Leu Val Val His Ser Ser Met Glu Gln Asp Val Ala Leu		
[2198]	225	230	235
[2199]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ala Leu Val Arg Ala Phe Leu		
[2200]	245	250	255
[2201]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn		
[2202]	260	265	270
[2203]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Glu		
[2204]	275	280	285
[2205]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Gln Gly Ser Val		
[2206]	290	295	300
[2207]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly		
[2208]	305	310	315
[2209]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu		
[2210]	325	330	335
[2211]	Gly Leu Pro Glu Leu Ser Leu Asp Arg Arg Gln Glu Leu Leu Ala Lys		
[2212]	340	345	350
[2213]	Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg Arg Pro		
[2214]	355	360	365
[2215]	Ser		
[2216]	<210> 59		
[2217]	<211> 369		
[2218]	<212> PRT		
[2219]	<213> 人工序列		
[2220]	<220>		
[2221]	<223> 合成多肽		
[2222]	<400> 59		
[2223]	Met Ala Arg Ala Ser Gly Ser Glu Arg Arg Leu Leu Leu Ile Tyr Thr		
[2224]	1	5	10
			15

[2225]	Gly Gly Thr Leu Gly Met Arg Ser Glu Gly Gly Val Leu Val Pro Gly		
[2226]		20	25 30
[2227]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Glu		
[2228]		35	40 45
[2229]	Glu Phe Ala Cys Ala Arg Gly Leu Ser Glu Asp Thr Leu Val Leu Pro		
[2230]		50	55 60
[2231]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln		
[2232]		65	70 75 80
[2233]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Ala Glu Trp Ile Arg Ile		
[2234]		85	90 95
[2235]	Ala Gln Ile Ile Lys Arg His Tyr Glu Gln Tyr His Gly Phe Val Val		
[2236]		100	105 110
[2237]	Ile His Gly Thr Asp Thr Met Ala Phe Ala Ala Ser Met Leu Ser Phe		
[2238]		115	120 125
[2239]	Met Leu Glu Asn Leu Gln Lys Pro Val Ile Leu Thr Gly Ala Gln Val		
[2240]		130	135 140
[2241]	Pro Ile His Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala		
[2242]		145	150 155 160
[2243]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met		
[2244]		165	170 175
[2245]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln		
[2246]		180	185 190
[2247]	Arg Phe Glu Ala Phe Ala Ser Pro Asn Leu Ser Pro Leu Ala Thr Val		
[2248]		195	200 205
[2249]	Gly Ala Asp Val Thr Ile Ala Trp Glu Leu Val Arg Lys Val Lys Trp		
[2250]		210	215 220
[2251]	Lys Asp Pro Leu Val Val His Ser Ser Met Glu Gln Asp Val Ala Leu		
[2252]		225	230 235 240
[2253]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ala Leu Val Arg Ala Phe Leu		
[2254]		245	250 255
[2255]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn		
[2256]		260	265 270
[2257]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Glu		
[2258]		275	280 285
[2259]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Gln Gly Ser Val		
[2260]		290	295 300
[2261]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly		
[2262]		305	310 315 320
[2263]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu		
[2264]		325	330 335
[2265]	Gly Leu Pro Glu Leu Ser Leu Asp Arg Arg Gln Glu Leu Leu Ala Lys		
[2266]		340	345 350

[2267]	Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg Arg Pro
[2268]	355 360 365
[2269]	Ser
[2270]	<210> 60
[2271]	<211> 369
[2272]	<212> PRT
[2273]	<213> 人工序列
[2274]	<220>
[2275]	<223> 合成多肽
[2276]	<400> 60
[2277]	Met Ala Arg Ala Ser Gly Ser Glu Arg Arg Leu Leu Leu Ile Tyr Thr
[2278]	1 5 10 15
[2279]	Gly Gly Thr Leu Gly Met Arg Ser Glu Gly Gly Val Leu Val Pro Gly
[2280]	20 25 30
[2281]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Glu
[2282]	35 40 45
[2283]	Glu Phe Ala Cys Ala Arg Gly Leu Ser Glu Asp Thr Leu Val Leu Pro
[2284]	50 55 60
[2285]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln
[2286]	65 70 75 80
[2287]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Ala Glu Trp Ile Arg Ile
[2288]	85 90 95
[2289]	Ala Gln Ile Ile Lys Arg His Tyr Glu Gln Tyr His Gly Phe Val Val
[2290]	100 105 110
[2291]	Ile His Gly Thr Asp Thr Met Ala Phe Ala Ala Ser Met Leu Ser Phe
[2292]	115 120 125
[2293]	Met Leu Glu Asn Leu Gln Lys Pro Val Ile Leu Thr Gly Ala Gln Val
[2294]	130 135 140
[2295]	Pro Ile His Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala
[2296]	145 150 155 160
[2297]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met
[2298]	165 170 175
[2299]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln
[2300]	180 185 190
[2301]	Arg Phe Glu Ala Phe Ala Ser Pro Asn Leu Ser Pro Leu Ala Thr Val
[2302]	195 200 205
[2303]	Gly Ala Asp Val Thr Ile Ala Trp Glu Leu Val Arg Lys Val Lys Trp
[2304]	210 215 220
[2305]	Cys Asp Pro Leu Val Val His Ser Ser Met Glu Gln Asp Val Ala Leu
[2306]	225 230 235 240
[2307]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ala Leu Val Arg Ala Phe Leu
[2308]	245 250 255

[2309]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn
[2310]	260 265 270
[2311]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Glu
[2312]	275 280 285
[2313]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Gln Gly Ser Val
[2314]	290 295 300
[2315]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly
[2316]	305 310 315 320
[2317]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu
[2318]	325 330 335
[2319]	Gly Leu Pro Glu Leu Ser Leu Asp Arg Arg Gln Glu Leu Leu Ala Lys
[2320]	340 345 350
[2321]	Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg Arg Pro
[2322]	355 360 365
[2323]	Ser
[2324]	<210> 61
[2325]	<211> 369
[2326]	<212> PRT
[2327]	<213> 人工序列
[2328]	<220>
[2329]	<223> 合成多肽
[2330]	<400> 61
[2331]	Met Ala Arg Ala Ser Gly Ser Glu Arg Arg Leu Leu Leu Ile Tyr Thr
[2332]	1 5 10 15
[2333]	Gly Gly Thr Leu Gly Met Arg Ser Glu Gly Gly Val Leu Val Pro Gly
[2334]	20 25 30
[2335]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Glu
[2336]	35 40 45
[2337]	Glu Phe Ala Cys Ala Arg Gly Leu Ser Glu Asp Thr Leu Val Leu Pro
[2338]	50 55 60
[2339]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln
[2340]	65 70 75 80
[2341]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Ala Glu Trp Ile Arg Ile
[2342]	85 90 95
[2343]	Ala Gln Ile Ile Lys Arg His Tyr Glu Gln Tyr His Gly Phe Val Val
[2344]	100 105 110
[2345]	Ile His Gly Thr Asp Thr Met Ala Phe Ala Ala Ser Met Leu Ser Phe
[2346]	115 120 125
[2347]	Met Leu Glu Asn Leu Gln Lys Pro Val Ile Leu Thr Gly Ala Gln Val
[2348]	130 135 140
[2349]	Pro Ile His Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala
[2350]	145 150 155 160

[2351]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met		
[2352]		165	170
[2353]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln		
[2354]		180	185
[2355]	Arg Phe Glu Ala Phe Ala Ser Pro Asn Leu Ser Pro Leu Ala Thr Val		
[2356]		195	200
[2357]	Gly Ala Asp Val Thr Ile Ala Trp Glu Leu Val Arg Lys Val Lys Trp		
[2358]		210	215
[2359]	Cys Asp Pro Leu Val Val His Ser Ser Met Glu Gln Asp Val Ala Leu		
[2360]		225	230
[2361]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ala Leu Val Arg Ala Phe Leu		
[2362]		245	250
[2363]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn		
[2364]		260	265
[2365]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Glu		
[2366]		275	280
[2367]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Gln Gly Ser Val		
[2368]		290	295
[2369]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly		
[2370]		305	310
[2371]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu		
[2372]		325	330
[2373]	Gly Leu Pro Cys Leu Ser Leu Asp Arg Arg Gln Glu Leu Leu Ala Lys		
[2374]		340	345
[2375]	Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg Arg Pro		
[2376]		355	360
[2377]	Ser		
[2378]	<210> 62		
[2379]	<211> 369		
[2380]	<212> PRT		
[2381]	<213> 人工序列		
[2382]	<220>		
[2383]	<223> 合成多肽		
[2384]	<400> 62		
[2385]	Met Ala Arg Ala Ser Gly Ser Glu Arg Arg Leu Leu Leu Ile Tyr Thr		
[2386]		1	5
[2387]	Gly Gly Thr Leu Gly Met Arg Ser Glu Gly Gly Val Leu Val Pro Gly		
[2388]		20	25
[2389]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Glu		
[2390]		35	40
[2391]	Glu Phe Ala Cys Ala Arg Gly Leu Ser Glu Asp Thr Leu Val Leu Pro		
[2392]		50	55

[2393]	Pro	Ala	Ser	His	Gly	Pro	Arg	Val	Leu	Tyr	Thr	Val	Leu	Glu	Cys	Gln
[2394]	65					70					75					80
[2395]	Pro	Leu	Leu	Asp	Ser	Ser	Asp	Met	Thr	Ile	Ala	Glu	Trp	Ile	Arg	Ile
[2396]					85					90						95
[2397]	Ala	Gln	Ile	Ile	Lys	Arg	His	Tyr	Glu	Gln	Tyr	His	Gly	Phe	Val	Val
[2398]					100					105						110
[2399]	Ile	His	Gly	Thr	Asp	Thr	Met	Ala	Phe	Ala	Ala	Ser	Met	Leu	Ser	Phe
[2400]					115					120						125
[2401]	Met	Leu	Glu	Asn	Leu	Gln	Lys	Pro	Val	Ile	Leu	Thr	Gly	Ala	Gln	Val
[2402]					130					135						140
[2403]	Pro	Ile	His	Val	Leu	Trp	Asn	Asp	Ala	Arg	Glu	Asn	Leu	Leu	Gly	Ala
[2404]	145									150						160
[2405]	Leu	Leu	Val	Ala	Gly	Gln	Tyr	Ile	Ile	Pro	Glu	Val	Cys	Leu	Phe	Met
[2406]					165					170						175
[2407]	Asn	Ser	Gln	Leu	Phe	Arg	Gly	Asn	Arg	Val	Thr	Lys	Val	Asp	Ser	Gln
[2408]					180					185						190
[2409]	Arg	Phe	Glu	Ala	Phe	Ala	Ser	Pro	Asn	Leu	Ser	Pro	Leu	Ala	Thr	Val
[2410]					195					200						205
[2411]	Gly	Ala	Asp	Val	Thr	Ile	Ala	Trp	Glu	Leu	Val	Arg	Lys	Val	Lys	Trp
[2412]					210					215						220
[2413]	Cys	Asp	Pro	Leu	Val	Val	His	Ser	Ser	Met	Glu	Gln	Asp	Val	Ala	Leu
[2414]	225									230						240
[2415]	Leu	Arg	Leu	Tyr	Pro	Gly	Ile	Pro	Ala	Ala	Leu	Val	Arg	Ala	Phe	Leu
[2416]					245					250						255
[2417]	Gln	Pro	Pro	Leu	Lys	Gly	Val	Val	Leu	Glu	Thr	Phe	Gly	Ser	Gly	Asn
[2418]					260					265						270
[2419]	Gly	Pro	Ser	Lys	Pro	Asp	Leu	Leu	Cys	Glu	Leu	Arg	Ala	Ala	Ala	Glu
[2420]					275					280						285
[2421]	Arg	Gly	Leu	Ile	Met	Val	Asn	Cys	Ser	Gln	Cys	Leu	Gln	Gly	Ser	Val
[2422]					290					295						300
[2423]	Thr	Pro	Gly	Tyr	Ala	Thr	Ser	Leu	Ala	Gly	Ala	Asn	Ile	Val	Ser	Gly
[2424]	305									310						320
[2425]	Leu	Asp	Met	Thr	Ser	Glu	Ala	Ala	Leu	Ala	Lys	Leu	Ser	Tyr	Val	Leu
[2426]					325					330						335
[2427]	Gly	Leu	Pro	Cys	Leu	Ser	Leu	Asp	Arg	Arg	Gln	Glu	Leu	Leu	Ala	Lys
[2428]					340					345						350
[2429]	Asp	Leu	Arg	Gly	Glu	Met	Thr	Pro	Pro	Ser	Val	Glu	Glu	Arg	Arg	Pro
[2430]					355					360						365
[2431]	Ser															
[2432]	<210>	63														
[2433]	<211>	369														
[2434]	<212>	PRT														

[2435]	<213>	人工序列
[2436]	<220>	
[2437]	<223>	合成多肽
[2438]	<400>	63
[2439]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr	
[2440]	1 5 10 15	
[2441]	Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro Gly	
[2442]	20 25 30	
[2443]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Lys	
[2444]	35 40 45	
[2445]	Glu Phe Ala Gln Ala Lys Gly Leu Pro Asp His Ala Leu Ala Leu Pro	
[2446]	50 55 60	
[2447]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln	
[2448]	65 70 75 80	
[2449]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Lys Asp Trp Ile Arg Ile	
[2450]	85 90 95	
[2451]	Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly Phe Val Val	
[2452]	100 105 110	
[2453]	Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu Ser Phe	
[2454]	115 120 125	
[2455]	Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala Gln Val	
[2456]	130 135 140	
[2457]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala	
[2458]	145 150 155 160	
[2459]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met	
[2460]	165 170 175	
[2461]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln	
[2462]	180 185 190	
[2463]	Lys Phe Glu Ala Phe Cys Ser Pro Asn Leu Ser Pro Leu Ala Thr Val	
[2464]	195 200 205	
[2465]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Asp Trp	
[2466]	210 215 220	
[2467]	Lys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp Val Ala Leu	
[2468]	225 230 235 240	
[2469]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala Phe Leu	
[2470]	245 250 255	
[2471]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn	
[2472]	260 265 270	
[2473]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Gln	
[2474]	275 280 285	
[2475]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val	
[2476]	290 295 300	

[2477]	Thr	Pro	Gly	Tyr	Ala	Thr	Lys	Leu	Ala	Gly	Ala	Asn	Ile	Val	Ser	Gly
[2478]	305					310				315						320
[2479]	Leu	Asp	Met	Thr	Ser	Glu	Ala	Ala	Leu	Ala	Lys	Leu	Ser	Tyr	Val	Leu
[2480]					325					330						335
[2481]	Gly	Leu	Pro	Glu	Leu	Ser	Leu	Glu	Arg	Arg	Gln	Glu	Leu	Leu	Ala	Lys
[2482]				340					345					350		
[2483]	Asp	Leu	Arg	Gly	Glu	Met	Thr	Leu	Pro	Thr	Ala	Asp	Leu	His	Gln	Ser
[2484]			355					360					365			
[2485]	Ser															
[2486]	<210>	64														
[2487]	<211>	369														
[2488]	<212>	PRT														
[2489]	<213>	人工序列														
[2490]	<220>															
[2491]	<223>	合成多肽														
[2492]	<400>	64														
[2493]	Met	Ala	Arg	Ala	Ser	Gly	Ser	Glu	Arg	Arg	Leu	Leu	Leu	Ile	Tyr	Thr
[2494]	1				5					10					15	
[2495]	Gly	Gly	Thr	Leu	Gly	Met	Arg	Ser	Glu	Gly	Gly	Val	Leu	Val	Pro	Gly
[2496]				20					25					30		
[2497]	Pro	Gly	Leu	Val	Thr	Leu	Leu	Arg	Thr	Leu	Pro	Met	Phe	His	Asp	Glu
[2498]			35					40					45			
[2499]	Glu	Phe	Ala	Arg	Ala	Lys	Gly	Leu	Pro	Asp	His	Ala	Leu	Ala	Leu	Pro
[2500]		50					55				60					
[2501]	Pro	Ala	Ser	His	Gly	Pro	Arg	Val	Leu	Tyr	Thr	Val	Leu	Glu	Cys	Gln
[2502]	65					70				75						80
[2503]	Pro	Leu	Leu	Asp	Ser	Ser	Asp	Met	Thr	Ile	Lys	Glu	Trp	Ile	Arg	Ile
[2504]				85						90						95
[2505]	Ala	Gln	Ile	Ile	Lys	Arg	His	Tyr	Glu	Gln	Tyr	His	Gly	Phe	Val	Val
[2506]				100					105					110		
[2507]	Ile	His	Gly	Thr	Asp	Thr	Met	Ala	Phe	Ala	Ala	Ser	Met	Leu	Ser	Phe
[2508]			115					120					125			
[2509]	Met	Leu	Glu	Asn	Leu	Gln	Lys	Pro	Val	Ile	Leu	Thr	Gly	Ala	Gln	Val
[2510]		130					135					140				
[2511]	Pro	Ile	His	Val	Leu	Trp	Asn	Asp	Ala	Arg	Glu	Asn	Leu	Leu	Gly	Ala
[2512]	145					150				155						160
[2513]	Leu	Leu	Val	Ala	Gly	Gln	Tyr	Ile	Ile	Pro	Glu	Val	Cys	Leu	Phe	Met
[2514]				165						170					175	
[2515]	Asn	Ser	Gln	Leu	Phe	Arg	Gly	Asn	Arg	Val	Thr	Lys	Val	Asp	Ser	Gln
[2516]				180					185					190		
[2517]	Arg	Phe	Glu	Ala	Phe	Ala	Ser	Pro	Asn	Leu	Ser	Pro	Leu	Ala	Thr	Val
[2518]			195					200					205			

[2519]	Gly Ala Asp Val Thr Ile Ala Trp Glu Leu Val Arg Lys Val Asp Trp		
[2520]	210	215	220
[2521]	Lys Asp Pro Leu Val Val His Ser Ser Met Glu Gln Asp Val Ala Leu		
[2522]	225	230	235 240
[2523]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ala Leu Val Arg Ala Phe Leu		
[2524]	245	250	255
[2525]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn		
[2526]	260	265	270
[2527]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Glu		
[2528]	275	280	285
[2529]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Gln Gly Ser Val		
[2530]	290	295	300
[2531]	Thr Pro Gly Tyr Ala Thr Lys Leu Ala Gly Ala Asn Ile Val Ser Gly		
[2532]	305	310	315 320
[2533]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu		
[2534]	325	330	335
[2535]	Gly Leu Pro Glu Leu Ser Leu Asp Arg Arg Gln Glu Leu Leu Ala Lys		
[2536]	340	345	350
[2537]	Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg Arg Pro		
[2538]	355	360	365
[2539]	Ser		
[2540]	<210> 65		
[2541]	<211> 369		
[2542]	<212> PRT		
[2543]	<213> 人工序列		
[2544]	<220>		
[2545]	<223> 合成多肽		
[2546]	<400> 65		
[2547]	Met Ala Arg Ala Ser Gly Ser Glu Arg Arg Leu Leu Leu Ile Tyr Thr		
[2548]	1	5	10 15
[2549]	Gly Gly Thr Leu Gly Met Arg Ser Glu Gly Gly Val Leu Val Pro Gly		
[2550]	20	25	30
[2551]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Glu		
[2552]	35	40	45
[2553]	Glu Phe Ala Arg Ala Lys Gly Leu Ser Glu Asp Thr Leu Val Leu Pro		
[2554]	50	55	60
[2555]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln		
[2556]	65	70	75 80
[2557]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Lys Glu Trp Ile Arg Ile		
[2558]	85	90	95
[2559]	Ala Gln Ile Ile Lys Arg His Tyr Glu Gln Tyr His Gly Phe Val Val		
[2560]	100	105	110

[2561]	Ile His Gly Thr Asp Thr Met Ala Phe Ala Ala Ser Met Leu Ser Phe		
[2562]	115	120	125
[2563]	Met Leu Glu Asn Leu Gln Lys Pro Val Ile Leu Thr Gly Ala Gln Val		
[2564]	130	135	140
[2565]	Pro Ile His Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala		
[2566]	145	150	155
[2567]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met		
[2568]	165	170	175
[2569]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln		
[2570]	180	185	190
[2571]	Arg Phe Glu Ala Phe Ala Ser Pro Asn Leu Ser Pro Leu Ala Thr Val		
[2572]	195	200	205
[2573]	Gly Ala Asp Val Thr Ile Ala Trp Glu Leu Val Arg Lys Val Asp Trp		
[2574]	210	215	220
[2575]	Lys Asp Pro Leu Val Val His Ser Ser Met Glu Gln Asp Val Ala Leu		
[2576]	225	230	235
[2577]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ala Leu Val Arg Ala Phe Leu		
[2578]	245	250	255
[2579]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn		
[2580]	260	265	270
[2581]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Glu		
[2582]	275	280	285
[2583]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Gln Gly Ser Val		
[2584]	290	295	300
[2585]	Thr Pro Gly Tyr Ala Thr Lys Leu Ala Gly Ala Asn Ile Val Ser Gly		
[2586]	305	310	315
[2587]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu		
[2588]	325	330	335
[2589]	Gly Leu Pro Glu Leu Ser Leu Asp Arg Arg Gln Glu Leu Leu Ala Lys		
[2590]	340	345	350
[2591]	Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg Arg Pro		
[2592]	355	360	365
[2593]	Ser		
[2594]	<210> 66		
[2595]	<211> 98		
[2596]	<212> PRT		
[2597]	<213> 人工序列		
[2598]	<220>		
[2599]	<223> 合成多肽		
[2600]	<400> 66		
[2601]	Met Ser Asp Ser Glu Val Asn Gln Glu Ala Lys Pro Glu Val Lys Pro		
[2602]	1	5	10
			15

[2603]	Glu Val Lys Pro Glu Thr His Ile Asn Leu Lys Val Ser Asp Gly Ser
[2604]	20 25 30
[2605]	Ser Glu Ile Phe Phe Lys Ile Lys Lys Thr Thr Pro Leu Arg Arg Leu
[2606]	35 40 45
[2607]	Met Glu Ala Phe Ala Lys Arg Gln Gly Lys Glu Met Asp Ser Leu Arg
[2608]	50 55 60
[2609]	Phe Leu Tyr Asp Gly Ile Arg Ile Gln Ala Asp Gln Thr Pro Glu Asp
[2610]	65 70 75 80
[2611]	Leu Asp Met Glu Asp Asn Asp Ile Ile Glu Ala His Arg Glu Gln Ile
[2612]	85 90 95
[2613]	Gly Gly
[2614]	<210> 67
[2615]	<211> 97
[2616]	<212> PRT
[2617]	<213> 人工序列
[2618]	<220>
[2619]	<223> 合成多肽
[2620]	<400> 67
[2621]	Met Ser Asp Gln Glu Ala Lys Pro Ser Thr Glu Asp Leu Gly Asp Lys
[2622]	1 5 10 15
[2623]	Lys Glu Gly Glu Tyr Ile Lys Leu Lys Val Ile Gly Gln Asp Ser Ser
[2624]	20 25 30
[2625]	Glu Ile His Phe Lys Val Lys Met Thr Thr His Leu Lys Lys Leu Lys
[2626]	35 40 45
[2627]	Glu Ser Tyr Cys Gln Arg Gln Gly Val Pro Met Asn Ser Leu Arg Phe
[2628]	50 55 60
[2629]	Leu Phe Glu Gly Gln Arg Ile Ala Asp Asn His Thr Pro Lys Glu Leu
[2630]	65 70 75 80
[2631]	Gly Met Glu Glu Glu Asp Val Ile Glu Val Tyr Gln Glu Gln Thr Gly
[2632]	85 90 95
[2633]	Gly
[2634]	<210> 68
[2635]	<211> 95
[2636]	<212> PRT
[2637]	<213> 人工序列
[2638]	<220>
[2639]	<223> 合成多肽
[2640]	<400> 68
[2641]	Met Ala Asp Glu Lys Pro Lys Glu Gly Val Lys Thr Glu Asn Asn Asp
[2642]	1 5 10 15
[2643]	His Ile Asn Leu Lys Val Ala Gly Gln Asp Gly Ser Val Val Gln Phe
[2644]	20 25 30

[2645]	Lys Ile Lys Arg His Thr Pro Leu Ser Lys Leu Met Lys Ala Tyr Cys
[2646]	35 40 45
[2647]	Glu Arg Gln Gly Leu Ser Met Arg Gln Ile Arg Phe Arg Phe Asp Gly
[2648]	50 55 60
[2649]	Gln Pro Ile Asn Glu Thr Asp Thr Pro Ala Gln Leu Glu Met Glu Asp
[2650]	65 70 75 80
[2651]	Glu Asp Thr Ile Asp Val Phe Gln Gln Gln Thr Gly Gly Val Tyr
[2652]	85 90 95
[2653]	<210> 69
[2654]	<211> 103
[2655]	<212> PRT
[2656]	<213> 人工序列
[2657]	<220>
[2658]	<223> 合成多肽
[2659]	<400> 69
[2660]	Met Ser Glu Glu Lys Pro Lys Glu Gly Val Lys Thr Glu Asn Asp His
[2661]	1 5 10 15
[2662]	Ile Asn Leu Lys Val Ala Gly Gln Asp Gly Ser Val Val Gln Phe Lys
[2663]	20 25 30
[2664]	Ile Lys Arg His Thr Pro Leu Ser Lys Leu Met Lys Ala Tyr Cys Glu
[2665]	35 40 45
[2666]	Arg Gln Gly Leu Ser Met Arg Gln Ile Arg Phe Arg Phe Asp Gly Gln
[2667]	50 55 60
[2668]	Pro Ile Asn Glu Thr Asp Thr Pro Ala Gln Leu Glu Met Glu Asp Glu
[2669]	65 70 75 80
[2670]	Asp Thr Ile Asp Val Phe Gln Gln Gln Thr Gly Gly Val Pro Glu Ser
[2671]	85 90 95
[2672]	Ser Leu Ala Gly His Ser Phe
[2673]	100
[2674]	<210> 70
[2675]	<211> 95
[2676]	<212> PRT
[2677]	<213> 人工序列
[2678]	<220>
[2679]	<223> 合成多肽
[2680]	<400> 70
[2681]	Met Ala Asn Glu Lys Pro Thr Glu Glu Val Lys Thr Glu Asn Asn Asn
[2682]	1 5 10 15
[2683]	His Ile Asn Leu Lys Val Ala Gly Gln Asp Gly Ser Val Val Gln Phe
[2684]	20 25 30
[2685]	Lys Ile Lys Arg Gln Thr Pro Leu Ser Lys Leu Met Lys Ala Tyr Cys
[2686]	35 40 45

[2687]	Glu Pro Arg Gly Leu Ser Met Lys Gln Ile Arg Phe Arg Phe Gly Gly
[2688]	50 55 60
[2689]	Gln Pro Ile Ser Gly Thr Asp Lys Pro Ala Gln Leu Glu Met Glu Asp
[2690]	65 70 75 80
[2691]	Glu Asp Thr Ile Asp Val Phe Gln Gln Pro Thr Gly Gly Val Tyr
[2692]	85 90 95
[2693]	<210> 71
[2694]	<211> 20
[2695]	<212> PRT
[2696]	<213> 人工序列
[2697]	<220>
[2698]	<223> 合成肽
[2699]	<400> 71
[2700]	Gln Arg Leu Ile Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp
[2701]	1 5 10 15
[2702]	Glu Asp Asp Phe
[2703]	20
[2704]	<210> 72
[2705]	<211> 18
[2706]	<212> PRT
[2707]	<213> 人工序列
[2708]	<220>
[2709]	<223> 合成肽
[2710]	<400> 72
[2711]	Arg Leu Ile Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp Glu
[2712]	1 5 10 15
[2713]	Asp Asp
[2714]	<210> 73
[2715]	<211> 15
[2716]	<212> PRT
[2717]	<213> 人工序列
[2718]	<220>
[2719]	<223> 合成肽
[2720]	<400> 73
[2721]	Arg Leu Ile Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp
[2722]	1 5 10 15
[2723]	<210> 74
[2724]	<211> 468
[2725]	<212> PRT
[2726]	<213> 人工序列
[2727]	<220>
[2728]	<223> 合成多肽

[2729]	<400> 74
[2730]	Met Ser Asp Ser Glu Val Asn Gln Glu Ala Lys Pro Glu Val Lys Pro
[2731]	1 5 10 15
[2732]	Glu Val Lys Pro Glu Thr His Ile Asn Leu Lys Val Ser Asp Gly Ser
[2733]	20 25 30
[2734]	Ser Glu Ile Phe Phe Lys Ile Lys Lys Thr Thr Pro Leu Arg Arg Leu
[2735]	35 40 45
[2736]	Met Glu Ala Phe Ala Lys Arg Gln Gly Lys Glu Met Asp Ser Leu Arg
[2737]	50 55 60
[2738]	Phe Leu Tyr Asp Gly Ile Arg Ile Gln Ala Asp Gln Thr Pro Glu Asp
[2739]	65 70 75 80
[2740]	Leu Asp Met Glu Asp Asn Asp Ile Ile Glu Ala His Arg Glu Gln Ile
[2741]	85 90 95
[2742]	Gly Gly His Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu
[2743]	100 105 110
[2744]	Ile Tyr Thr Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu
[2745]	115 120 125
[2746]	Val Pro Gly Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe
[2747]	130 135 140
[2748]	His Asp Lys Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu
[2749]	145 150 155 160
[2750]	Ala Leu Pro Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu
[2751]	165 170 175
[2752]	Glu Lys Gln Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp
[2753]	180 185 190
[2754]	Ile Arg Ile Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly
[2755]	195 200 205
[2756]	Phe Val Val Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met
[2757]	210 215 220
[2758]	Leu Ser Phe Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly
[2759]	225 230 235 240
[2760]	Ala Gln Val Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu
[2761]	245 250 255
[2762]	Leu Gly Ala Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys
[2763]	260 265 270
[2764]	Leu Phe Met Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val
[2765]	275 280 285
[2766]	Asp Ser Gln Lys Phe Glu Ala Phe Ala Ser Pro Asn Leu Ser Pro Leu
[2767]	290 295 300
[2768]	Ala Thr Val Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys
[2769]	305 310 315 320
[2770]	Val Lys Trp Lys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp

[2771]	325								330				335			
[2772]	Val	Ala	Leu	Leu	Arg	Leu	Tyr	Pro	Gly	Ile	Pro	Ala	Ser	Leu	Val	Arg
[2773]	340								345				350			
[2774]	Ala	Phe	Leu	Gln	Pro	Pro	Leu	Lys	Gly	Val	Val	Leu	Glu	Thr	Phe	Gly
[2775]	355								360				365			
[2776]	Ser	Gly	Asn	Gly	Pro	Ser	Lys	Pro	Asp	Leu	Leu	Gln	Glu	Leu	Arg	Ala
[2777]	370								375				380			
[2778]	Ala	Ala	Gln	Arg	Gly	Leu	Ile	Met	Val	Asn	Cys	Ser	Gln	Cys	Leu	Arg
[2779]	385				390				395				400			
[2780]	Gly	Ser	Val	Thr	Pro	Gly	Tyr	Ala	Thr	Ser	Leu	Ala	Gly	Ala	Asn	Ile
[2781]	405								410				415			
[2782]	Val	Ser	Gly	Leu	Asp	Met	Thr	Ser	Glu	Ala	Ala	Leu	Ala	Lys	Leu	Ser
[2783]	420								425				430			
[2784]	Tyr	Val	Leu	Gly	Leu	Pro	Glu	Leu	Ser	Leu	Glu	Arg	Arg	Gln	Glu	Leu
[2785]	435								440				445			
[2786]	Leu	Ala	Lys	Asp	Leu	Arg	Gly	Glu	Met	Thr	Leu	Pro	Thr	Ala	Asp	Leu
[2787]	450								455				460			
[2788]	His	Gln	Ser	Ser												
[2789]	465															
[2790]	<210> 75															
[2791]	<211> 467															
[2792]	<212> PRT															
[2793]	<213> 人工序列															
[2794]	<220>															
[2795]	<223> 合成多肽															
[2796]	<400> 75															
[2797]	Met	Ser	Asp	Gln	Glu	Ala	Lys	Pro	Ser	Thr	Glu	Asp	Leu	Gly	Asp	Lys
[2798]	1		5				10				15					
[2799]	Lys	Glu	Gly	Glu	Tyr	Ile	Lys	Leu	Lys	Val	Ile	Gly	Gln	Asp	Ser	Ser
[2800]	20								25				30			
[2801]	Glu	Ile	His	Phe	Lys	Val	Lys	Met	Thr	Thr	His	Leu	Lys	Lys	Leu	Lys
[2802]	35								40				45			
[2803]	Glu	Ser	Tyr	Cys	Gln	Arg	Gln	Gly	Val	Pro	Met	Asn	Ser	Leu	Arg	Phe
[2804]	50				55				60							
[2805]	Leu	Phe	Glu	Gly	Gln	Arg	Ile	Ala	Asp	Asn	His	Thr	Pro	Lys	Glu	Leu
[2806]	65				70				75				80			
[2807]	Gly	Met	Glu	Glu	Glu	Asp	Val	Ile	Glu	Val	Tyr	Gln	Glu	Gln	Thr	Gly
[2808]	85								90				95			
[2809]	Gly	His	Met	Ala	Arg	Ala	Ser	Gly	Ser	Glu	Arg	His	Leu	Leu	Leu	Ile
[2810]	100								105				110			
[2811]	Tyr	Thr	Gly	Gly	Thr	Leu	Gly	Met	Gln	Ser	Lys	Gly	Gly	Val	Leu	Val
[2812]	115				120				125							

[2813]	Pro Gly Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His		
[2814]	130	135	140
[2815]	Asp Lys Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu Ala		
[2816]	145	150	155
[2817]	Leu Pro Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu		
[2818]	165	170	175
[2819]	Lys Gln Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile		
[2820]	180	185	190
[2821]	Arg Ile Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly Phe		
[2822]	195	200	205
[2823]	Val Val Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu		
[2824]	210	215	220
[2825]	Ser Phe Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala		
[2826]	225	230	235
[2827]	Gln Val Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu		
[2828]	245	250	255
[2829]	Gly Ala Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu		
[2830]	260	265	270
[2831]	Phe Met Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp		
[2832]	275	280	285
[2833]	Ser Gln Lys Phe Glu Ala Phe Ala Ser Pro Asn Leu Ser Pro Leu Ala		
[2834]	290	295	300
[2835]	Thr Val Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val		
[2836]	305	310	315
[2837]	Lys Trp Lys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp Val		
[2838]	325	330	335
[2839]	Ala Leu Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala		
[2840]	340	345	350
[2841]	Phe Leu Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser		
[2842]	355	360	365
[2843]	Gly Asn Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala		
[2844]	370	375	380
[2845]	Ala Gln Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly		
[2846]	385	390	395
[2847]	Ser Val Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val		
[2848]	405	410	415
[2849]	Ser Gly Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr		
[2850]	420	425	430
[2851]	Val Leu Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu		
[2852]	435	440	445
[2853]	Ala Lys Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu His		
[2854]	450	455	460

[2855]	Gln Ser Ser
[2856]	465
[2857]	<210> 76
[2858]	<211> 386
[2859]	<212> PRT
[2860]	<213> 人工序列
[2861]	<220>
[2862]	<223> 合成多肽
[2863]	<400> 76
[2864]	Arg Leu Ile Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp Glu
[2865]	1 5 10 15
[2866]	Asp Asp Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr
[2867]	20 25 30
[2868]	Thr Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro
[2869]	35 40 45
[2870]	Gly Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp
[2871]	50 55 60
[2872]	Lys Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu Ala Leu
[2873]	65 70 75 80
[2874]	Pro Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys
[2875]	85 90 95
[2876]	Gln Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile Arg
[2877]	100 105 110
[2878]	Ile Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly Phe Val
[2879]	115 120 125
[2880]	Val Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu Ser
[2881]	130 135 140
[2882]	Phe Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala Gln
[2883]	145 150 155 160
[2884]	Val Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly
[2885]	165 170 175
[2886]	Ala Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe
[2887]	180 185 190
[2888]	Met Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser
[2889]	195 200 205
[2890]	Gln Lys Phe Glu Ala Phe Ala Ser Pro Asn Leu Ser Pro Leu Ala Thr
[2891]	210 215 220
[2892]	Val Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys
[2893]	225 230 235 240
[2894]	Trp Lys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp Val Ala
[2895]	245 250 255
[2896]	Leu Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala Phe

[2897]	260	265	270
[2898]	Leu Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly		
[2899]	275	280	285
[2900]	Asn Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala		
[2901]	290	295	300
[2902]	Gln Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser		
[2903]	305	310	315
[2904]	Val Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser		
[2905]	325	330	335
[2906]	Gly Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val		
[2907]	340	345	350
[2908]	Leu Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala		
[2909]	355	360	365
[2910]	Lys Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu His Gln		
[2911]	370	375	380
[2912]	Ser Ser		
[2913]	385		
[2914]	<210> 77		
[2915]	<211> 387		
[2916]	<212> PRT		
[2917]	<213> 人工序列		
[2918]	<220>		
[2919]	<223> 合成多肽		
[2920]	<400> 77		
[2921]	Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile Tyr Thr		
[2922]	1	5	10
[2923]	Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val Pro Gly		
[2924]	20	25	30
[2925]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Lys		
[2926]	35	40	45
[2927]	Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu Ala Leu Pro		
[2928]	50	55	60
[2929]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln		
[2930]	65	70	75
[2931]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile Arg Ile		
[2932]	85	90	95
[2933]	Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly Phe Val Val		
[2934]	100	105	110
[2935]	Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu Ser Phe		
[2936]	115	120	125
[2937]	Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala Gln Val		
[2938]	130	135	140

[2939]	Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala		
[2940]	145	150	155 160
[2941]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met		
[2942]		165	170 175
[2943]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln		
[2944]		180	185 190
[2945]	Lys Phe Glu Ala Phe Ala Ser Pro Asn Leu Ser Pro Leu Ala Thr Val		
[2946]		195	200 205
[2947]	Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val Lys Trp		
[2948]		210	215 220
[2949]	Lys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp Val Ala Leu		
[2950]		225	230 235 240
[2951]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala Phe Leu		
[2952]		245	250 255
[2953]	Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn		
[2954]		260	265 270
[2955]	Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala Ala Gln		
[2956]		275	280 285
[2957]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly Ser Val		
[2958]		290	295 300
[2959]	Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val Ser Gly		
[2960]		305	310 315 320
[2961]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu		
[2962]		325	330 335
[2963]	Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu Ala Lys		
[2964]		340	345 350
[2965]	Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu His Gln Ser		
[2966]		355	360 365
[2967]	Ser Arg Leu Ile Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp		
[2968]		370	375 380
[2969]	Glu Asp Asp		
[2970]	385		
[2971]	<210> 78		
[2972]	<211> 486		
[2973]	<212> PRT		
[2974]	<213> 人工序列		
[2975]	<220>		
[2976]	<223> 合成多肽		
[2977]	<400> 78		
[2978]	Met Ser Asp Ser Glu Val Asn Gln Glu Ala Lys Pro Glu Val Lys Pro		
[2979]	1	5	10 15
[2980]	Glu Val Lys Pro Glu Thr His Ile Asn Leu Lys Val Ser Asp Gly Ser		

[2981]	20	25	30
[2982]	Ser Glu Ile Phe Phe Lys Ile Lys Lys Thr Thr Pro Leu Arg Arg Leu		
[2983]	35	40	45
[2984]	Met Glu Ala Phe Ala Lys Arg Gln Gly Lys Glu Met Asp Ser Leu Arg		
[2985]	50	55	60
[2986]	Phe Leu Tyr Asp Gly Ile Arg Ile Gln Ala Asp Gln Thr Pro Glu Asp		
[2987]	65	70	75
[2988]	Leu Asp Met Glu Asp Asn Asp Ile Ile Glu Ala His Arg Glu Gln Ile		
[2989]	85	90	95
[2990]	Gly Gly His Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu		
[2991]	100	105	110
[2992]	Ile Tyr Thr Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu		
[2993]	115	120	125
[2994]	Val Pro Gly Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe		
[2995]	130	135	140
[2996]	His Asp Lys Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu		
[2997]	145	150	155
[2998]	Ala Leu Pro Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu		
[2999]	165	170	175
[3000]	Glu Cys Gln Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp		
[3001]	180	185	190
[3002]	Ile Arg Ile Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly		
[3003]	195	200	205
[3004]	Phe Val Val Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met		
[3005]	210	215	220
[3006]	Leu Ser Phe Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly		
[3007]	225	230	235
[3008]	Ala Gln Val Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu		
[3009]	245	250	255
[3010]	Leu Gly Ala Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys		
[3011]	260	265	270
[3012]	Leu Phe Met Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val		
[3013]	275	280	285
[3014]	Asp Ser Gln Lys Phe Glu Ala Phe Ala Ser Pro Asn Leu Ser Pro Leu		
[3015]	290	295	300
[3016]	Ala Thr Val Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys		
[3017]	305	310	315
[3018]	Val Lys Trp Lys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp		
[3019]	325	330	335
[3020]	Val Ala Leu Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg		
[3021]	340	345	350
[3022]	Ala Phe Leu Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly		

[3023]	355	360	365
[3024]	Ser Gly Asn Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala		
[3025]	370	375	380
[3026]	Ala Ala Gln Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg		
[3027]	385	390	395
[3028]	Gly Ser Val Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile		
[3029]	405	410	415
[3030]	Val Ser Gly Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser		
[3031]	420	425	430
[3032]	Tyr Val Leu Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu		
[3033]	435	440	445
[3034]	Leu Ala Lys Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu		
[3035]	450	455	460
[3036]	His Gln Ser Ser Arg Leu Ile Glu Asp Ile Cys Leu Pro Arg Trp Gly		
[3037]	465	470	475
[3038]	Cys Leu Trp Glu Asp Asp		480
[3039]	485		
[3040]	<210> 79		
[3041]	<211> 485		
[3042]	<212> PRT		
[3043]	<213> 人工序列		
[3044]	<220>		
[3045]	<223> 合成多肽		
[3046]	<400> 79		
[3047]	Met Ser Asp Gln Glu Ala Lys Pro Ser Thr Glu Asp Leu Gly Asp Lys		
[3048]	1	5	10
[3049]	Lys Glu Gly Glu Tyr Ile Lys Leu Lys Val Ile Gly Gln Asp Ser Ser		
[3050]	20	25	30
[3051]	Glu Ile His Phe Lys Val Lys Met Thr Thr His Leu Lys Lys Leu Lys		
[3052]	35	40	45
[3053]	Glu Ser Tyr Cys Gln Arg Gln Gly Val Pro Met Asn Ser Leu Arg Phe		
[3054]	50	55	60
[3055]	Leu Phe Glu Gly Gln Arg Ile Ala Asp Asn His Thr Pro Lys Glu Leu		
[3056]	65	70	75
[3057]	Gly Met Glu Glu Glu Asp Val Ile Glu Val Tyr Gln Glu Gln Thr Gly		
[3058]	85	90	95
[3059]	Gly His Met Ala Arg Ala Ser Gly Ser Glu Arg His Leu Leu Leu Ile		
[3060]	100	105	110
[3061]	Tyr Thr Gly Gly Thr Leu Gly Met Gln Ser Lys Gly Gly Val Leu Val		
[3062]	115	120	125
[3063]	Pro Gly Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His		
[3064]	130	135	140

[3065]	Asp Lys Glu Phe Ala Gln Ala Gln Gly Leu Pro Asp His Ala Leu Ala		
[3066]	145	150	155 160
[3067]	Leu Pro Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu		
[3068]		165 170	175
[3069]	Cys Gln Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Asp Asp Trp Ile		
[3070]		180 185	190
[3071]	Arg Ile Ala Lys Ile Ile Glu Arg His Tyr Glu Gln Tyr Gln Gly Phe		
[3072]		195 200	205
[3073]	Val Val Ile His Gly Thr Asp Thr Met Ala Ser Gly Ala Ser Met Leu		
[3074]		210 215	220
[3075]	Ser Phe Met Leu Glu Asn Leu His Lys Pro Val Ile Leu Thr Gly Ala		
[3076]	225	230 235	240
[3077]	Gln Val Pro Ile Arg Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu		
[3078]		245 250	255
[3079]	Gly Ala Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu		
[3080]		260 265	270
[3081]	Phe Met Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp		
[3082]		275 280	285
[3083]	Ser Gln Lys Phe Glu Ala Phe Ala Ser Pro Asn Leu Ser Pro Leu Ala		
[3084]		290 295	300
[3085]	Thr Val Gly Ala Asp Val Thr Ile Ala Trp Asp Leu Val Arg Lys Val		
[3086]	305	310 315	320
[3087]	Lys Trp Lys Asp Pro Leu Val Val His Ser Asn Met Glu His Asp Val		
[3088]		325 330	335
[3089]	Ala Leu Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ser Leu Val Arg Ala		
[3090]		340 345	350
[3091]	Phe Leu Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser		
[3092]		355 360	365
[3093]	Gly Asn Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala		
[3094]		370 375	380
[3095]	Ala Gln Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Arg Gly		
[3096]	385	390 395	400
[3097]	Ser Val Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val		
[3098]		405 410	415
[3099]	Ser Gly Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr		
[3100]		420 425	430
[3101]	Val Leu Gly Leu Pro Glu Leu Ser Leu Glu Arg Arg Gln Glu Leu Leu		
[3102]		435 440	445
[3103]	Ala Lys Asp Leu Arg Gly Glu Met Thr Leu Pro Thr Ala Asp Leu His		
[3104]		450 455	460
[3105]	Gln Ser Ser Arg Leu Ile Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys		
[3106]	465	470 475	480

[3107]	Leu Trp Glu Asp Asp
[3108]	485
[3109]	<210> 80
[3110]	<211> 167
[3111]	<212> PRT
[3112]	<213> 人工序列
[3113]	<220>
[3114]	<223> 合成多肽
[3115]	<400> 80
[3116]	Arg Glu Arg Gly Pro Gln Arg Val Ala Ala His Ile Thr Gly Thr Arg
[3117]	1 5 10 15
[3118]	Gly Arg Ser Asn Thr Leu Ser Ser Pro Asn Ser Lys Asn Glu Lys Ala
[3119]	20 25 30
[3120]	Leu Gly Arg Lys Ile Asn Ser Trp Glu Ser Ser Arg Ser Gly His Ser
[3121]	35 40 45
[3122]	Phe Leu Ser Asn Leu His Leu Arg Asn Gly Glu Leu Val Ile His Glu
[3123]	50 55 60
[3124]	Lys Gly Phe Tyr Tyr Ile Tyr Ser Gln Thr Tyr Phe Arg Phe Gln Glu
[3125]	65 70 75 80
[3126]	Glu Ile Lys Glu Asn Thr Lys Asn Asp Lys Gln Met Val Gln Tyr Ile
[3127]	85 90 95
[3128]	Tyr Lys Tyr Thr Ser Tyr Pro Asp Pro Ile Leu Leu Met Lys Ser Ala
[3129]	100 105 110
[3130]	Arg Asn Ser Cys Trp Ser Lys Asp Ala Glu Tyr Gly Leu Tyr Ser Ile
[3131]	115 120 125
[3132]	Tyr Gln Gly Gly Ile Phe Glu Leu Lys Glu Asn Asp Arg Ile Phe Val
[3133]	130 135 140
[3134]	Ser Val Thr Asn Glu His Leu Ile Asp Met Asp His Glu Ala Ser Phe
[3135]	145 150 155 160
[3136]	Phe Gly Ala Phe Leu Val Gly
[3137]	165
[3138]	<210> 81
[3139]	<211> 16
[3140]	<212> PRT
[3141]	<213> 人工序列
[3142]	<220>
[3143]	<223> 合成肽
[3144]	<220>
[3145]	<221> MISC_FEATURE
[3146]	<222> (5) .. (16)
[3147]	<223> 残基可以存在或不存在
[3148]	<400> 81

[3149]	Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
[3150]	1 5 10 15
[3151]	<210> 82
[3152]	<211> 24
[3153]	<212> PRT
[3154]	<213> 人工序列
[3155]	<220>
[3156]	<223> 合成肽
[3157]	<220>
[3158]	<221> MISC_FEATURE
[3159]	<222> (10) .. (24)
[3160]	<223> 残基可以存在或不存在
[3161]	<400> 82
[3162]	Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
[3163]	1 5 10 15
[3164]	Gly Gly Ser Gly Gly Gly Gly Ser
[3165]	20
[3166]	<210> 83
[3167]	<211> 24
[3168]	<212> PRT
[3169]	<213> 人工序列
[3170]	<220>
[3171]	<223> 合成肽
[3172]	<400> 83
[3173]	Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
[3174]	1 5 10 15
[3175]	Gly Gly Ser Gly Gly Gly Gly Ser
[3176]	20
[3177]	<210> 84
[3178]	<211> 19
[3179]	<212> PRT
[3180]	<213> 人工序列
[3181]	<220>
[3182]	<223> 合成肽
[3183]	<400> 84
[3184]	Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly
[3185]	1 5 10 15
[3186]	Ser Gly Ser
[3187]	<210> 85
[3188]	<211> 27
[3189]	<212> PRT
[3190]	<213> 人工序列

[3191]	<220>															
[3192]	<223> 合成肽															
[3193]	<400> 85															
[3194]	Gly	Tyr	Ile	Pro	Glu	Ala	Pro	Arg	Asp	Gly	Gln	Ala	Tyr	Val	Arg	Lys
[3195]	1				5					10					15	
[3196]	Asp	Gly	Glu	Trp	Val	Leu	Leu	Ser	Thr	Phe	Leu					
[3197]				20					25							
[3198]	<210> 86															
[3199]	<211> 369															
[3200]	<212> PRT															
[3201]	<213> 人工序列															
[3202]	<220>															
[3203]	<223> 合成多肽															
[3204]	<400> 86															
[3205]	Met	Ala	Arg	Ala	Ser	Gly	Lys	Glu	Arg	Arg	Leu	Leu	Leu	Ile	Tyr	Thr
[3206]	1				5					10					15	
[3207]	Gly	Gly	Thr	Leu	Gly	Met	Arg	Ser	Glu	Gly	Gly	Val	Leu	Val	Pro	Gly
[3208]				20					25					30		
[3209]	Pro	Gly	Leu	Val	Thr	Leu	Leu	Arg	Thr	Leu	Pro	Met	Phe	His	Asp	Glu
[3210]			35					40					45			
[3211]	Glu	Phe	Ala	Arg	Lys	Lys	Gly	Leu	Lys	Lys	Asp	Thr	Leu	Val	Leu	Pro
[3212]		50					55				60					
[3213]	Pro	Ala	Ser	His	Gly	Pro	Arg	Val	Leu	Tyr	Thr	Val	Leu	Glu	Cys	Gln
[3214]	65					70				75						80
[3215]	Pro	Leu	Leu	Asp	Ser	Ser	Asp	Met	Thr	Ile	Ala	Glu	Trp	Ile	Arg	Ile
[3216]				85					90						95	
[3217]	Ala	Lys	Ile	Ile	Lys	Arg	His	Tyr	Glu	Lys	Tyr	His	Gly	Phe	Val	Val
[3218]				100					105					110		
[3219]	Ile	His	Gly	Thr	Asp	Thr	Met	Ala	Phe	Ala	Ala	Ser	Met	Leu	Ser	Phe
[3220]			115					120					125			
[3221]	Met	Leu	Glu	Asn	Leu	Gln	Lys	Pro	Val	Ile	Leu	Thr	Gly	Ala	Gln	Val
[3222]		130					135					140				
[3223]	Pro	Ile	His	Val	Leu	Trp	Asn	Asp	Ala	Arg	Glu	Asn	Leu	Leu	Gly	Ala
[3224]	145					150				155						160
[3225]	Leu	Leu	Val	Ala	Gly	Gln	Tyr	Ile	Ile	Pro	Glu	Val	Cys	Leu	Phe	Met
[3226]				165					170					175		
[3227]	Asn	Ser	Gln	Leu	Phe	Arg	Gly	Asn	Arg	Val	Thr	Lys	Val	Asp	Ser	Gln
[3228]				180					185					190		
[3229]	Arg	Phe	Glu	Ala	Phe	Ala	Ser	Pro	Asn	Leu	Ser	Pro	Leu	Ala	Thr	Val
[3230]			195					200					205			
[3231]	Gly	Ala	Asp	Val	Thr	Ile	Ala	Trp	Glu	Leu	Val	Arg	Lys	Val	Lys	Trp
[3232]		210					215					220				

[3233]	Lys Asp Pro Leu Val Val His Ser Lys Met Glu Gln Asp Val Ala Leu
[3234]	225 230 235 240
[3235]	Leu Arg Leu Tyr Pro Gly Ile Pro Ala Lys Leu Val Arg Ala Phe Leu
[3236]	245 250 255
[3237]	Lys Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser Gly Asn
[3238]	260 265 270
[3239]	Gly Pro Ser Lys Pro Asp Leu Leu Lys Glu Leu Arg Ala Ala Ala Glu
[3240]	275 280 285
[3241]	Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Gln Gly Ser Val
[3242]	290 295 300
[3243]	Thr Pro Gly Tyr Ala Thr Lys Leu Ala Gly Ala Asn Ile Val Ser Gly
[3244]	305 310 315 320
[3245]	Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu
[3246]	325 330 335
[3247]	Gly Leu Pro Lys Leu Ser Leu Asp Arg Arg Gln Glu Leu Leu Ala Lys
[3248]	340 345 350
[3249]	Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg Arg Pro
[3250]	355 360 365
[3251]	Ser
[3252]	<210> 87
[3253]	<211> 503
[3254]	<212> PRT
[3255]	<213> 人工序列
[3256]	<220>
[3257]	<223> 合成多肽
[3258]	<400> 87
[3259]	Arg Glu Arg Gly Pro Gln Arg Val Ala Ala His Ile Thr Gly Thr Arg
[3260]	1 5 10 15
[3261]	Gly Arg Ser Asn Thr Leu Ser Ser Pro Asn Ser Lys Asn Glu Lys Ala
[3262]	20 25 30
[3263]	Leu Gly Arg Lys Ile Asn Ser Trp Glu Ser Ser Arg Ser Gly His Ser
[3264]	35 40 45
[3265]	Phe Leu Ser Asn Leu His Leu Arg Asn Gly Glu Leu Val Ile His Glu
[3266]	50 55 60
[3267]	Lys Gly Phe Tyr Tyr Ile Tyr Ser Gln Thr Tyr Phe Arg Phe Gln Glu
[3268]	65 70 75 80
[3269]	Glu Ile Lys Glu Asn Thr Lys Asn Asp Lys Gln Met Val Gln Tyr Ile
[3270]	85 90 95
[3271]	Tyr Lys Tyr Thr Ser Tyr Pro Asp Pro Ile Leu Leu Met Lys Ser Ala
[3272]	100 105 110
[3273]	Arg Asn Ser Cys Trp Ser Lys Asp Ala Glu Tyr Gly Leu Tyr Ser Ile
[3274]	115 120 125

[3275]	Tyr	Gln	Gly	Gly	Ile	Phe	Glu	Leu	Lys	Glu	Asn	Asp	Arg	Ile	Phe	Val
[3276]	130						135				140					
[3277]	Ser	Val	Thr	Asn	Glu	His	Leu	Ile	Asp	Met	Asp	His	Glu	Ala	Ser	Phe
[3278]	145					150					155					160
[3279]	Phe	Gly	Ala	Phe	Leu	Val	Gly	Gly	Arg	Glu	Arg	Gly	Pro	Gln	Arg	Val
[3280]					165					170					175	
[3281]	Ala	Ala	His	Ile	Thr	Gly	Thr	Arg	Gly	Arg	Ser	Asn	Thr	Leu	Ser	Ser
[3282]				180					185					190		
[3283]	Pro	Asn	Ser	Lys	Asn	Glu	Lys	Ala	Leu	Gly	Arg	Lys	Ile	Asn	Ser	Trp
[3284]		195						200					205			
[3285]	Glu	Ser	Ser	Arg	Ser	Gly	His	Ser	Phe	Leu	Ser	Asn	Leu	His	Leu	Arg
[3286]	210						215					220				
[3287]	Asn	Gly	Glu	Leu	Val	Ile	His	Glu	Lys	Gly	Phe	Tyr	Tyr	Ile	Tyr	Ser
[3288]	225					230					235					240
[3289]	Gln	Thr	Tyr	Phe	Arg	Phe	Gln	Glu	Glu	Ile	Lys	Glu	Asn	Thr	Lys	Asn
[3290]				245						250					255	
[3291]	Asp	Lys	Gln	Met	Val	Gln	Tyr	Ile	Tyr	Lys	Tyr	Thr	Ser	Tyr	Pro	Asp
[3292]			260						265					270		
[3293]	Pro	Ile	Leu	Leu	Met	Lys	Ser	Ala	Arg	Asn	Ser	Cys	Trp	Ser	Lys	Asp
[3294]		275						280						285		
[3295]	Ala	Glu	Tyr	Gly	Leu	Tyr	Ser	Ile	Tyr	Gln	Gly	Gly	Ile	Phe	Glu	Leu
[3296]	290						295					300				
[3297]	Lys	Glu	Asn	Asp	Arg	Ile	Phe	Val	Ser	Val	Thr	Asn	Glu	His	Leu	Ile
[3298]	305					310					315					320
[3299]	Asp	Met	Asp	His	Glu	Ala	Ser	Phe	Phe	Gly	Ala	Phe	Leu	Val	Gly	Ser
[3300]				325						330				335		
[3301]	Arg	Glu	Arg	Gly	Pro	Gln	Arg	Val	Ala	Ala	His	Ile	Thr	Gly	Thr	Arg
[3302]			340							345				350		
[3303]	Gly	Arg	Ser	Asn	Thr	Leu	Ser	Ser	Pro	Asn	Ser	Lys	Asn	Glu	Lys	Ala
[3304]			355							360				365		
[3305]	Leu	Gly	Arg	Lys	Ile	Asn	Ser	Trp	Glu	Ser	Ser	Arg	Ser	Gly	His	Ser
[3306]	370						375					380				
[3307]	Phe	Leu	Ser	Asn	Leu	His	Leu	Arg	Asn	Gly	Glu	Leu	Val	Ile	His	Glu
[3308]	385					390					395					400
[3309]	Lys	Gly	Phe	Tyr	Tyr	Ile	Tyr	Ser	Gln	Thr	Tyr	Phe	Arg	Phe	Gln	Glu
[3310]				405						410				415		
[3311]	Glu	Ile	Lys	Glu	Asn	Thr	Lys	Asn	Asp	Lys	Gln	Met	Val	Gln	Tyr	Ile
[3312]				420						425				430		
[3313]	Tyr	Lys	Tyr	Thr	Ser	Tyr	Pro	Asp	Pro	Ile	Leu	Leu	Met	Lys	Ser	Ala
[3314]			435							440				445		
[3315]	Arg	Asn	Ser	Cys	Trp	Ser	Lys	Asp	Ala	Glu	Tyr	Gly	Leu	Tyr	Ser	Ile
[3316]	450						455					460				

[3317]	Tyr	Gln	Gly	Gly	Ile	Phe	Glu	Leu	Lys	Glu	Asn	Asp	Arg	Ile	Phe	Val
[3318]	465						470					475				480
[3319]	Ser	Val	Thr	Asn	Glu	His	Leu	Ile	Asp	Met	Asp	His	Glu	Ala	Ser	Phe
[3320]							485					490				495
[3321]	Phe	Gly	Ala	Phe	Leu	Val	Gly									
[3322]							500									
[3323]	<210>	88														
[3324]	<211>	503														
[3325]	<212>	PRT														
[3326]	<213>	人工序列														
[3327]	<220>															
[3328]	<223>	合成多肽														
[3329]	<400>	88														
[3330]	Arg	Glu	Arg	Gly	Pro	Gln	Arg	Val	Ala	Ala	His	Ile	Thr	Gly	Thr	Arg
[3331]	1					5					10				15	
[3332]	Gly	Arg	Ser	Asn	Thr	Leu	Ser	Ser	Pro	Asn	Ser	Lys	Asn	Glu	Lys	Ala
[3333]						20					25				30	
[3334]	Leu	Gly	Arg	Lys	Ile	Asn	Ser	Trp	Glu	Ser	Ser	Arg	Ser	Gly	His	Ser
[3335]						35					40				45	
[3336]	Phe	Leu	Ser	Asn	Leu	His	Leu	Arg	Asn	Gly	Glu	Leu	Val	Ile	His	Glu
[3337]						50					55				60	
[3338]	Lys	Gly	Phe	Tyr	Tyr	Ile	Tyr	Ser	Gln	Thr	Tyr	Phe	Arg	Phe	Gln	Glu
[3339]	65					70					75				80	
[3340]	Glu	Ile	Lys	Glu	Asn	Thr	Lys	Asn	Asp	Lys	Gln	Met	Val	Gln	Tyr	Ile
[3341]						85					90				95	
[3342]	Tyr	Lys	Tyr	Thr	Ser	Tyr	Pro	Asp	Pro	Ile	Leu	Leu	Met	Lys	Ser	Ala
[3343]						100					105				110	
[3344]	Arg	Asn	Ser	Cys	Trp	Ser	Lys	Asp	Ala	Glu	Tyr	Gly	Leu	Tyr	Ser	Ile
[3345]						115					120				125	
[3346]	Tyr	Gln	Gly	Gly	Ile	Phe	Glu	Leu	Lys	Glu	Asn	Asp	Arg	Ile	Phe	Val
[3347]						130					135				140	
[3348]	Ser	Val	Thr	Asn	Glu	His	Leu	Ile	Asp	Met	Asp	His	Glu	Ala	Ser	Phe
[3349]	145					150					155				160	
[3350]	Phe	Gly	Ala	Phe	Leu	Val	Gly	Ser	Arg	Glu	Arg	Gly	Pro	Gln	Arg	Val
[3351]						165					170				175	
[3352]	Ala	Ala	His	Ile	Thr	Gly	Thr	Arg	Gly	Arg	Ser	Asn	Thr	Leu	Ser	Ser
[3353]						180					185				190	
[3354]	Pro	Asn	Ser	Lys	Asn	Glu	Lys	Ala	Leu	Gly	Arg	Lys	Ile	Asn	Ser	Trp
[3355]						195					200				205	
[3356]	Glu	Ser	Ser	Arg	Ser	Gly	His	Ser	Phe	Leu	Ser	Asn	Leu	His	Leu	Arg
[3357]						210					215				220	
[3358]	Asn	Gly	Glu	Leu	Val	Ile	His	Glu	Lys	Gly	Phe	Tyr	Tyr	Ile	Tyr	Ser

[3359]	225	230	235	240
[3360]	Gln Thr Tyr Phe Arg Phe Gln Glu Glu Ile Lys Glu Asn Thr Lys Asn			
[3361]		245	250	255
[3362]	Asp Lys Gln Met Val Gln Tyr Ile Tyr Lys Tyr Thr Ser Tyr Pro Asp			
[3363]		260	265	270
[3364]	Pro Ile Leu Leu Met Lys Ser Ala Arg Asn Ser Cys Trp Ser Lys Asp			
[3365]		275	280	285
[3366]	Ala Glu Tyr Gly Leu Tyr Ser Ile Tyr Gln Gly Gly Ile Phe Glu Leu			
[3367]		290	295	300
[3368]	Lys Glu Asn Asp Arg Ile Phe Val Ser Val Thr Asn Glu His Leu Ile			
[3369]	305	310	315	320
[3370]	Asp Met Asp His Glu Ala Ser Phe Phe Gly Ala Phe Leu Val Gly Ser			
[3371]		325	330	335
[3372]	Arg Glu Arg Gly Pro Gln Arg Val Ala Ala His Ile Thr Gly Thr Arg			
[3373]		340	345	350
[3374]	Gly Arg Ser Asn Thr Leu Ser Ser Pro Asn Ser Lys Asn Glu Lys Ala			
[3375]		355	360	365
[3376]	Leu Gly Arg Lys Ile Asn Ser Trp Glu Ser Ser Arg Ser Gly His Ser			
[3377]		370	375	380
[3378]	Phe Leu Ser Asn Leu His Leu Arg Asn Gly Glu Leu Val Ile His Glu			
[3379]	385	390	395	400
[3380]	Lys Gly Phe Tyr Tyr Ile Tyr Ser Gln Thr Tyr Phe Arg Phe Gln Glu			
[3381]		405	410	415
[3382]	Glu Ile Lys Glu Asn Thr Lys Asn Asp Lys Gln Met Val Gln Tyr Ile			
[3383]		420	425	430
[3384]	Tyr Lys Tyr Thr Ser Tyr Pro Asp Pro Ile Leu Leu Met Lys Ser Ala			
[3385]		435	440	445
[3386]	Arg Asn Ser Cys Trp Ser Lys Asp Ala Glu Tyr Gly Leu Tyr Ser Ile			
[3387]		450	455	460
[3388]	Tyr Gln Gly Gly Ile Phe Glu Leu Lys Glu Asn Asp Arg Ile Phe Val			
[3389]	465	470	475	480
[3390]	Ser Val Thr Asn Glu His Leu Ile Asp Met Asp His Glu Ala Ser Phe			
[3391]		485	490	495
[3392]	Phe Gly Ala Phe Leu Val Gly			
[3393]		500		
[3394]	<210> 89			
[3395]	<211> 874			
[3396]	<212> PRT			
[3397]	<213> 人工序列			
[3398]	<220>			
[3399]	<223> 合成多肽			
[3400]	<400> 89			

[3401]	Met	Ala	Arg	Ala	Ser	Gly	Ser	Glu	Arg	Arg	Leu	Leu	Leu	Ile	Tyr	Thr
[3402]	1				5					10					15	
[3403]	Gly	Gly	Thr	Leu	Gly	Met	Arg	Ser	Glu	Gly	Gly	Val	Leu	Val	Pro	Gly
[3404]				20					25						30	
[3405]	Pro	Gly	Leu	Val	Thr	Leu	Leu	Arg	Thr	Leu	Pro	Met	Phe	His	Asp	Glu
[3406]			35					40					45			
[3407]	Glu	Phe	Ala	Arg	Ala	Arg	Gly	Leu	Ser	Glu	Asp	Thr	Leu	Val	Leu	Pro
[3408]			50				55						60			
[3409]	Pro	Ala	Ser	His	Gly	Pro	Arg	Val	Leu	Tyr	Thr	Val	Leu	Glu	Cys	Gln
[3410]	65					70					75				80	
[3411]	Pro	Leu	Leu	Asp	Ser	Ser	Asp	Met	Thr	Ile	Ala	Glu	Trp	Ile	Arg	Ile
[3412]					85					90					95	
[3413]	Ala	Gln	Ile	Ile	Lys	Arg	His	Tyr	Glu	Gln	Tyr	His	Gly	Phe	Val	Val
[3414]					100					105					110	
[3415]	Ile	His	Gly	Thr	Asp	Thr	Met	Ala	Phe	Ala	Ala	Ser	Met	Leu	Ser	Phe
[3416]			115					120					125			
[3417]	Met	Leu	Glu	Asn	Leu	Gln	Lys	Pro	Val	Ile	Leu	Thr	Gly	Ala	Gln	Val
[3418]			130					135					140			
[3419]	Pro	Ile	His	Val	Leu	Trp	Asn	Asp	Ala	Arg	Glu	Asn	Leu	Leu	Gly	Ala
[3420]	145					150					155				160	
[3421]	Leu	Leu	Val	Ala	Gly	Gln	Tyr	Ile	Ile	Pro	Glu	Val	Cys	Leu	Phe	Met
[3422]					165					170					175	
[3423]	Asn	Ser	Gln	Leu	Phe	Arg	Gly	Asn	Arg	Val	Thr	Lys	Val	Asp	Ser	Gln
[3424]				180						185					190	
[3425]	Arg	Phe	Glu	Ala	Phe	Ala	Ser	Pro	Asn	Leu	Ser	Pro	Leu	Ala	Thr	Val
[3426]			195					200					205			
[3427]	Gly	Ala	Asp	Val	Thr	Ile	Ala	Trp	Glu	Leu	Val	Arg	Lys	Val	Lys	Trp
[3428]			210					215					220			
[3429]	Lys	Asp	Pro	Leu	Val	Val	His	Ser	Ser	Met	Glu	Gln	Asp	Val	Ala	Leu
[3430]	225					230					235				240	
[3431]	Leu	Arg	Leu	Tyr	Pro	Gly	Ile	Pro	Ala	Ala	Leu	Val	Arg	Ala	Phe	Leu
[3432]				245						250					255	
[3433]	Gln	Pro	Pro	Leu	Lys	Gly	Val	Val	Leu	Glu	Thr	Phe	Gly	Ser	Gly	Asn
[3434]				260						265					270	
[3435]	Gly	Pro	Ser	Lys	Pro	Asp	Leu	Leu	Gln	Glu	Leu	Arg	Ala	Ala	Ala	Glu
[3436]			275					280					285			
[3437]	Arg	Gly	Leu	Ile	Met	Val	Asn	Cys	Ser	Gln	Cys	Leu	Gln	Gly	Ser	Val
[3438]			290					295					300			
[3439]	Thr	Pro	Gly	Tyr	Ala	Thr	Ser	Leu	Ala	Gly	Ala	Asn	Ile	Val	Ser	Gly
[3440]	305					310					315				320	
[3441]	Leu	Asp	Met	Thr	Ser	Glu	Ala	Ala	Leu	Ala	Lys	Leu	Ser	Tyr	Val	Leu
[3442]					325					330					335	

[3443]	Gly Leu Pro Glu Leu Ser Leu Asp Arg Arg Gln Glu Leu Leu Ala Lys		
[3444]		340	345
[3445]	Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg Arg Pro		350
[3446]		355	360
[3447]	Ser Thr Ser Arg Glu Arg Gly Pro Gln Arg Val Ala Ala His Ile Thr		365
[3448]		370	375
[3449]	Gly Thr Arg Gly Arg Ser Asn Thr Leu Ser Ser Pro Asn Ser Lys Asn		380
[3450]		385	390
[3451]	Glu Lys Ala Leu Gly Arg Lys Ile Asn Ser Trp Glu Ser Ser Arg Ser		395
[3452]		405	410
[3453]	Gly His Ser Phe Leu Ser Asn Leu His Leu Arg Asn Gly Glu Leu Val		415
[3454]		420	425
[3455]	Ile His Glu Lys Gly Phe Tyr Tyr Ile Tyr Ser Gln Thr Tyr Phe Arg		430
[3456]		435	440
[3457]	Phe Gln Glu Glu Ile Lys Glu Asn Thr Lys Asn Asp Lys Gln Met Val		445
[3458]		450	455
[3459]	Gln Tyr Ile Tyr Lys Tyr Thr Ser Tyr Pro Asp Pro Ile Leu Leu Met		460
[3460]		465	470
[3461]	Lys Ser Ala Arg Asn Ser Cys Trp Ser Lys Asp Ala Glu Tyr Gly Leu		475
[3462]		485	490
[3463]	Tyr Ser Ile Tyr Gln Gly Gly Ile Phe Glu Leu Lys Glu Asn Asp Arg		495
[3464]		500	505
[3465]	Ile Phe Val Ser Val Thr Asn Glu His Leu Ile Asp Met Asp His Glu		510
[3466]		515	520
[3467]	Ala Ser Phe Phe Gly Ala Phe Leu Val Gly Gly Arg Glu Arg Gly Pro		525
[3468]		530	535
[3469]	Gln Arg Val Ala Ala His Ile Thr Gly Thr Arg Gly Arg Ser Asn Thr		540
[3470]		545	550
[3471]	Leu Ser Ser Pro Asn Ser Lys Asn Glu Lys Ala Leu Gly Arg Lys Ile		555
[3472]		565	570
[3473]	Asn Ser Trp Glu Ser Ser Arg Ser Gly His Ser Phe Leu Ser Asn Leu		575
[3474]		580	585
[3475]	His Leu Arg Asn Gly Glu Leu Val Ile His Glu Lys Gly Phe Tyr Tyr		590
[3476]		595	600
[3477]	Ile Tyr Ser Gln Thr Tyr Phe Arg Phe Gln Glu Glu Ile Lys Glu Asn		605
[3478]		610	615
[3479]	Thr Lys Asn Asp Lys Gln Met Val Gln Tyr Ile Tyr Lys Tyr Thr Ser		620
[3480]		625	630
[3481]	Tyr Pro Asp Pro Ile Leu Leu Met Lys Ser Ala Arg Asn Ser Cys Trp		635
[3482]		645	650
[3483]	Ser Lys Asp Ala Glu Tyr Gly Leu Tyr Ser Ile Tyr Gln Gly Gly Ile		655
[3484]		660	665
			670

[3485]	Phe Glu Leu Lys Glu Asn Asp Arg Ile Phe Val Ser Val Thr Asn Glu		
[3486]	675	680	685
[3487]	His Leu Ile Asp Met Asp His Glu Ala Ser Phe Phe Gly Ala Phe Leu		
[3488]	690	695	700
[3489]	Val Gly Ser Arg Glu Arg Gly Pro Gln Arg Val Ala Ala His Ile Thr		
[3490]	705	710	715
[3491]	Gly Thr Arg Gly Arg Ser Asn Thr Leu Ser Ser Pro Asn Ser Lys Asn		
[3492]	725	730	735
[3493]	Glu Lys Ala Leu Gly Arg Lys Ile Asn Ser Trp Glu Ser Ser Arg Ser		
[3494]	740	745	750
[3495]	Gly His Ser Phe Leu Ser Asn Leu His Leu Arg Asn Gly Glu Leu Val		
[3496]	755	760	765
[3497]	Ile His Glu Lys Gly Phe Tyr Tyr Ile Tyr Ser Gln Thr Tyr Phe Arg		
[3498]	770	775	780
[3499]	Phe Gln Glu Glu Ile Lys Glu Asn Thr Lys Asn Asp Lys Gln Met Val		
[3500]	785	790	795
[3501]	Gln Tyr Ile Tyr Lys Tyr Thr Ser Tyr Pro Asp Pro Ile Leu Leu Met		
[3502]	805	810	815
[3503]	Lys Ser Ala Arg Asn Ser Cys Trp Ser Lys Asp Ala Glu Tyr Gly Leu		
[3504]	820	825	830
[3505]	Tyr Ser Ile Tyr Gln Gly Gly Ile Phe Glu Leu Lys Glu Asn Asp Arg		
[3506]	835	840	845
[3507]	Ile Phe Val Ser Val Thr Asn Glu His Leu Ile Asp Met Asp His Glu		
[3508]	850	855	860
[3509]	Ala Ser Phe Phe Gly Ala Phe Leu Val Gly		
[3510]	865	870	
[3511]	<210> 90		
[3512]	<211> 883		
[3513]	<212> PRT		
[3514]	<213> 人工序列		
[3515]	<220>		
[3516]	<223> 合成多肽		
[3517]	<400> 90		
[3518]	Ser Glu Arg Arg Leu Leu Leu Ile Tyr Thr Gly Gly Thr Leu Gly Met		
[3519]	1	5	10
[3520]	Arg Ser Glu Gly Gly Val Leu Val Pro Gly Pro Gly Leu Val Thr Leu		
[3521]	20	25	30
[3522]	Leu Arg Thr Leu Pro Met Phe His Asp Glu Glu Phe Ala Arg Ala Arg		
[3523]	35	40	45
[3524]	Gly Leu Ser Glu Asp Thr Leu Val Leu Pro Pro Ala Ser His Gly Pro		
[3525]	50	55	60
[3526]	Arg Val Leu Tyr Thr Val Leu Glu Cys Gln Pro Leu Leu Asp Ser Ser		

[3527]	65	70	75	80
[3528]	Asp Met Thr Ile Ala Glu Trp Ile Arg Ile Ala Gln Ile Ile Lys Arg			
[3529]		85	90	95
[3530]	His Tyr Glu Gln Tyr His Gly Phe Val Val Ile His Gly Thr Asp Thr			
[3531]		100	105	110
[3532]	Met Ala Phe Ala Ala Ser Met Leu Ser Phe Met Leu Glu Asn Leu Gln			
[3533]		115	120	125
[3534]	Lys Pro Val Ile Leu Thr Gly Ala Gln Val Pro Ile His Val Leu Trp			
[3535]		130	135	140
[3536]	Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala Leu Leu Val Ala Gly Gln			
[3537]	145	150	155	160
[3538]	Tyr Ile Ile Pro Glu Val Cys Leu Phe Met Asn Ser Gln Leu Phe Arg			
[3539]		165	170	175
[3540]	Gly Asn Arg Val Thr Lys Val Asp Ser Gln Arg Phe Glu Ala Phe Ala			
[3541]		180	185	190
[3542]	Ser Pro Asn Leu Ser Pro Leu Ala Thr Val Gly Ala Asp Val Thr Ile			
[3543]		195	200	205
[3544]	Ala Trp Glu Leu Val Arg Lys Val Lys Trp Lys Asp Pro Leu Val Val			
[3545]		210	215	220
[3546]	His Ser Ser Met Glu Gln Asp Val Ala Leu Leu Arg Leu Tyr Pro Gly			
[3547]	225	230	235	240
[3548]	Ile Pro Ala Ala Leu Val Arg Ala Phe Leu Gln Pro Pro Leu Lys Gly			
[3549]		245	250	255
[3550]	Val Val Leu Glu Thr Phe Gly Ser Gly Asn Gly Pro Ser Lys Pro Asp			
[3551]		260	265	270
[3552]	Leu Leu Gln Glu Leu Arg Ala Ala Ala Glu Arg Gly Leu Ile Met Val			
[3553]		275	280	285
[3554]	Asn Cys Ser Gln Cys Leu Gln Gly Ser Val Thr Pro Gly Tyr Ala Thr			
[3555]		290	295	300
[3556]	Ser Leu Ala Gly Ala Asn Ile Val Ser Gly Leu Asp Met Thr Ser Glu			
[3557]	305	310	315	320
[3558]	Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu Gly Leu Pro Glu Leu Ser			
[3559]		325	330	335
[3560]	Leu Asp Arg Arg Gln Glu Leu Leu Ala Lys Asp Leu Arg Gly Glu Met			
[3561]		340	345	350
[3562]	Thr Pro Pro Ser Val Glu Glu Arg Arg Pro Ser Leu Gln Gly Asn Thr			
[3563]		355	360	365
[3564]	Leu Gly Gly Gly Val Ser Trp Leu Leu Ser Thr Ser Arg Glu Arg Gly			
[3565]		370	375	380
[3566]	Pro Gln Arg Val Ala Ala His Ile Thr Gly Thr Arg Gly Arg Ser Asn			
[3567]	385	390	395	400
[3568]	Thr Leu Ser Ser Pro Asn Ser Lys Asn Glu Lys Ala Leu Gly Arg Lys			

[3569]		405		410		415
[3570]	Ile Asn Ser Trp Glu Ser Ser Arg Ser Gly His Ser Phe Leu Ser Asn					
[3571]		420		425		430
[3572]	Leu His Leu Arg Asn Gly Glu Leu Val Ile His Glu Lys Gly Phe Tyr					
[3573]		435		440		445
[3574]	Tyr Ile Tyr Ser Gln Thr Tyr Phe Arg Phe Gln Glu Glu Ile Lys Glu					
[3575]		450		455		460
[3576]	Asn Thr Lys Asn Asp Lys Gln Met Val Gln Tyr Ile Tyr Lys Tyr Thr					
[3577]	465		470		475	480
[3578]	Ser Tyr Pro Asp Pro Ile Leu Leu Met Lys Ser Ala Arg Asn Ser Cys					
[3579]		485		490		495
[3580]	Trp Ser Lys Asp Ala Glu Tyr Gly Leu Tyr Ser Ile Tyr Gln Gly Gly					
[3581]		500		505		510
[3582]	Ile Phe Glu Leu Lys Glu Asn Asp Arg Ile Phe Val Ser Val Thr Asn					
[3583]		515		520		525
[3584]	Glu His Leu Ile Asp Met Asp His Glu Ala Ser Phe Phe Gly Ala Phe					
[3585]		530		535		540
[3586]	Leu Val Gly Ser Arg Glu Arg Gly Pro Gln Arg Val Ala Ala His Ile					
[3587]	545		550		555	560
[3588]	Thr Gly Thr Arg Gly Arg Ser Asn Thr Leu Ser Ser Pro Asn Ser Lys					
[3589]		565		570		575
[3590]	Asn Glu Lys Ala Leu Gly Arg Lys Ile Asn Ser Trp Glu Ser Ser Arg					
[3591]		580		585		590
[3592]	Ser Gly His Ser Phe Leu Ser Asn Leu His Leu Arg Asn Gly Glu Leu					
[3593]		595		600		605
[3594]	Val Ile His Glu Lys Gly Phe Tyr Tyr Ile Tyr Ser Gln Thr Tyr Phe					
[3595]		610		615		620
[3596]	Arg Phe Gln Glu Glu Ile Lys Glu Asn Thr Lys Asn Asp Lys Gln Met					
[3597]	625		630		635	640
[3598]	Val Gln Tyr Ile Tyr Lys Tyr Thr Ser Tyr Pro Asp Pro Ile Leu Leu					
[3599]		645		650		655
[3600]	Met Lys Ser Ala Arg Asn Ser Cys Trp Ser Lys Asp Ala Glu Tyr Gly					
[3601]		660		665		670
[3602]	Leu Tyr Ser Ile Tyr Gln Gly Gly Ile Phe Glu Leu Lys Glu Asn Asp					
[3603]		675		680		685
[3604]	Arg Ile Phe Val Ser Val Thr Asn Glu His Leu Ile Asp Met Asp His					
[3605]		690		695		700
[3606]	Glu Ala Ser Phe Phe Gly Ala Phe Leu Val Gly Ser Arg Glu Arg Gly					
[3607]	705		710		715	720
[3608]	Pro Gln Arg Val Ala Ala His Ile Thr Gly Thr Arg Gly Arg Ser Asn					
[3609]		725		730		735
[3610]	Thr Leu Ser Ser Pro Asn Ser Lys Asn Glu Lys Ala Leu Gly Arg Lys					

[3611]	740	745	750
[3612]	Ile Asn Ser Trp Glu Ser Ser Arg Ser Gly His Ser Phe Leu Ser Asn		
[3613]	755	760	765
[3614]	Leu His Leu Arg Asn Gly Glu Leu Val Ile His Glu Lys Gly Phe Tyr		
[3615]	770	775	780
[3616]	Tyr Ile Tyr Ser Gln Thr Tyr Phe Arg Phe Gln Glu Glu Ile Lys Glu		
[3617]	785	790	795 800
[3618]	Asn Thr Lys Asn Asp Lys Gln Met Val Gln Tyr Ile Tyr Lys Tyr Thr		
[3619]	805	810	815
[3620]	Ser Tyr Pro Asp Pro Ile Leu Leu Met Lys Ser Ala Arg Asn Ser Cys		
[3621]	820	825	830
[3622]	Trp Ser Lys Asp Ala Glu Tyr Gly Leu Tyr Ser Ile Tyr Gln Gly Gly		
[3623]	835	840	845
[3624]	Ile Phe Glu Leu Lys Glu Asn Asp Arg Ile Phe Val Ser Val Thr Asn		
[3625]	850	855	860
[3626]	Glu His Leu Ile Asp Met Asp His Glu Ala Ser Phe Phe Gly Ala Phe		
[3627]	865	870	875 880
[3628]	Leu Val Gly		
[3629]	<210> 91		
[3630]	<211> 872		
[3631]	<212> PRT		
[3632]	<213> 人工序列		
[3633]	<220>		
[3634]	<223> 合成多肽		
[3635]	<400> 91		
[3636]	Arg Glu Arg Gly Pro Gln Arg Val Ala Ala His Ile Thr Gly Thr Arg		
[3637]	1 5 10 15		
[3638]	Gly Arg Ser Asn Thr Leu Ser Ser Pro Asn Ser Lys Asn Glu Lys Ala		
[3639]	20 25 30		
[3640]	Leu Gly Arg Lys Ile Asn Ser Trp Glu Ser Ser Arg Ser Gly His Ser		
[3641]	35 40 45		
[3642]	Phe Leu Ser Asn Leu His Leu Arg Asn Gly Glu Leu Val Ile His Glu		
[3643]	50 55 60		
[3644]	Lys Gly Phe Tyr Tyr Ile Tyr Ser Gln Thr Tyr Phe Arg Phe Gln Glu		
[3645]	65 70 75 80		
[3646]	Glu Ile Lys Glu Asn Thr Lys Asn Asp Lys Gln Met Val Gln Tyr Ile		
[3647]	85 90 95		
[3648]	Tyr Lys Tyr Thr Ser Tyr Pro Asp Pro Ile Leu Leu Met Lys Ser Ala		
[3649]	100 105 110		
[3650]	Arg Asn Ser Cys Trp Ser Lys Asp Ala Glu Tyr Gly Leu Tyr Ser Ile		
[3651]	115 120 125		
[3652]	Tyr Gln Gly Gly Ile Phe Glu Leu Lys Glu Asn Asp Arg Ile Phe Val		

[3653]	130	135	140
[3654]	Ser Val Thr Asn Glu His Leu Ile Asp Met Asp His Glu Ala Ser Phe		
[3655]	145	150	155
[3656]	Phe Gly Ala Phe Leu Val Gly Ser Arg Glu Arg Gly Pro Gln Arg Val		
[3657]		165	170
[3658]	Ala Ala His Ile Thr Gly Thr Arg Gly Arg Ser Asn Thr Leu Ser Ser		
[3659]		180	185
[3660]	Pro Asn Ser Lys Asn Glu Lys Ala Leu Gly Arg Lys Ile Asn Ser Trp		
[3661]		195	200
[3662]	Glu Ser Ser Arg Ser Gly His Ser Phe Leu Ser Asn Leu His Leu Arg		
[3663]	210	215	220
[3664]	Asn Gly Glu Leu Val Ile His Glu Lys Gly Phe Tyr Tyr Ile Tyr Ser		
[3665]	225	230	235
[3666]	Gln Thr Tyr Phe Arg Phe Gln Glu Glu Ile Lys Glu Asn Thr Lys Asn		
[3667]		245	250
[3668]	Asp Lys Gln Met Val Gln Tyr Ile Tyr Lys Tyr Thr Ser Tyr Pro Asp		
[3669]		260	265
[3670]	Pro Ile Leu Leu Met Lys Ser Ala Arg Asn Ser Cys Trp Ser Lys Asp		
[3671]		275	280
[3672]	Ala Glu Tyr Gly Leu Tyr Ser Ile Tyr Gln Gly Gly Ile Phe Glu Leu		
[3673]	290	295	300
[3674]	Lys Glu Asn Asp Arg Ile Phe Val Ser Val Thr Asn Glu His Leu Ile		
[3675]	305	310	315
[3676]	Asp Met Asp His Glu Ala Ser Phe Phe Gly Ala Phe Leu Val Gly Ser		
[3677]		325	330
[3678]	Arg Glu Arg Gly Pro Gln Arg Val Ala Ala His Ile Thr Gly Thr Arg		
[3679]		340	345
[3680]	Gly Arg Ser Asn Thr Leu Ser Ser Pro Asn Ser Lys Asn Glu Lys Ala		
[3681]		355	360
[3682]	Leu Gly Arg Lys Ile Asn Ser Trp Glu Ser Ser Arg Ser Gly His Ser		
[3683]	370	375	380
[3684]	Phe Leu Ser Asn Leu His Leu Arg Asn Gly Glu Leu Val Ile His Glu		
[3685]	385	390	395
[3686]	Lys Gly Phe Tyr Tyr Ile Tyr Ser Gln Thr Tyr Phe Arg Phe Gln Glu		
[3687]		405	410
[3688]	Glu Ile Lys Glu Asn Thr Lys Asn Asp Lys Gln Met Val Gln Tyr Ile		
[3689]		420	425
[3690]	Tyr Lys Tyr Thr Ser Tyr Pro Asp Pro Ile Leu Leu Met Lys Ser Ala		
[3691]		435	440
[3692]	Arg Asn Ser Cys Trp Ser Lys Asp Ala Glu Tyr Gly Leu Tyr Ser Ile		
[3693]	450	455	460
[3694]	Tyr Gln Gly Gly Ile Phe Glu Leu Lys Glu Asn Asp Arg Ile Phe Val		

[3695]	465	470	475	480
[3696]	Ser Val Thr Asn Glu His Leu Ile Asp Met Asp His Glu Ala Ser Phe			
[3697]		485	490	495
[3698]	Phe Gly Ala Phe Leu Val Gly Met Ala Arg Ala Ser Gly Ser Glu Arg			
[3699]		500	505	510
[3700]	Arg Leu Leu Leu Ile Tyr Thr Gly Gly Thr Leu Gly Met Arg Ser Glu			
[3701]		515	520	525
[3702]	Gly Gly Val Leu Val Pro Gly Pro Gly Leu Val Thr Leu Leu Arg Thr			
[3703]		530	535	540
[3704]	Leu Pro Met Phe His Asp Glu Glu Phe Ala Arg Ala Arg Gly Leu Ser			
[3705]	545	550	555	560
[3706]	Glu Asp Thr Leu Val Leu Pro Pro Ala Ser His Gly Pro Arg Val Leu			
[3707]		565	570	575
[3708]	Tyr Thr Val Leu Glu Cys Gln Pro Leu Leu Asp Ser Ser Asp Met Thr			
[3709]		580	585	590
[3710]	Ile Ala Glu Trp Ile Arg Ile Ala Gln Ile Ile Lys Arg His Tyr Glu			
[3711]		595	600	605
[3712]	Gln Tyr His Gly Phe Val Val Ile His Gly Thr Asp Thr Met Ala Phe			
[3713]		610	615	620
[3714]	Ala Ala Ser Met Leu Ser Phe Met Leu Glu Asn Leu Gln Lys Pro Val			
[3715]	625	630	635	640
[3716]	Ile Leu Thr Gly Ala Gln Val Pro Ile His Val Leu Trp Asn Asp Ala			
[3717]		645	650	655
[3718]	Arg Glu Asn Leu Leu Gly Ala Leu Leu Val Ala Gly Gln Tyr Ile Ile			
[3719]		660	665	670
[3720]	Pro Glu Val Cys Leu Phe Met Asn Ser Gln Leu Phe Arg Gly Asn Arg			
[3721]		675	680	685
[3722]	Val Thr Lys Val Asp Ser Gln Arg Phe Glu Ala Phe Ala Ser Pro Asn			
[3723]		690	695	700
[3724]	Leu Ser Pro Leu Ala Thr Val Gly Ala Asp Val Thr Ile Ala Trp Glu			
[3725]	705	710	715	720
[3726]	Leu Val Arg Lys Val Lys Trp Lys Asp Pro Leu Val Val His Ser Ser			
[3727]		725	730	735
[3728]	Met Glu Gln Asp Val Ala Leu Leu Arg Leu Tyr Pro Gly Ile Pro Ala			
[3729]		740	745	750
[3730]	Ala Leu Val Arg Ala Phe Leu Gln Pro Pro Leu Lys Gly Val Val Leu			
[3731]		755	760	765
[3732]	Glu Thr Phe Gly Ser Gly Asn Gly Pro Ser Lys Pro Asp Leu Leu Gln			
[3733]		770	775	780
[3734]	Glu Leu Arg Ala Ala Ala Glu Arg Gly Leu Ile Met Val Asn Cys Ser			
[3735]	785	790	795	800
[3736]	Gln Cys Leu Gln Gly Ser Val Thr Pro Gly Tyr Ala Thr Ser Leu Ala			

[3737]	805	810	815
[3738]	Gly Ala Asn Ile Val Ser Gly Leu Asp Met Thr Ser Glu Ala Ala Leu		
[3739]	820	825	830
[3740]	Ala Lys Leu Ser Tyr Val Leu Gly Leu Pro Glu Leu Ser Leu Asp Arg		
[3741]	835	840	845
[3742]	Arg Gln Glu Leu Leu Ala Lys Asp Leu Arg Gly Glu Met Thr Pro Pro		
[3743]	850	855	860
[3744]	Ser Val Glu Glu Arg Arg Pro Ser		
[3745]	865	870	
[3746]	<210> 92		
[3747]	<211> 891		
[3748]	<212> PRT		
[3749]	<213> 人工序列		
[3750]	<220>		
[3751]	<223> 合成多肽		
[3752]	<400> 92		
[3753]	Arg Glu Arg Gly Pro Gln Arg Val Ala Ala His Ile Thr Gly Thr Arg		
[3754]	1 5 10 15		
[3755]	Gly Arg Ser Asn Thr Leu Ser Ser Pro Asn Ser Lys Asn Glu Lys Ala		
[3756]	20 25 30		
[3757]	Leu Gly Arg Lys Ile Asn Ser Trp Glu Ser Ser Arg Ser Gly His Ser		
[3758]	35 40 45		
[3759]	Phe Leu Ser Asn Leu His Leu Arg Asn Gly Glu Leu Val Ile His Glu		
[3760]	50 55 60		
[3761]	Lys Gly Phe Tyr Tyr Ile Tyr Ser Gln Thr Tyr Phe Arg Phe Gln Glu		
[3762]	65 70 75 80		
[3763]	Glu Ile Lys Glu Asn Thr Lys Asn Asp Lys Gln Met Val Gln Tyr Ile		
[3764]	85 90 95		
[3765]	Tyr Lys Tyr Thr Ser Tyr Pro Asp Pro Ile Leu Leu Met Lys Ser Ala		
[3766]	100 105 110		
[3767]	Arg Asn Ser Cys Trp Ser Lys Asp Ala Glu Tyr Gly Leu Tyr Ser Ile		
[3768]	115 120 125		
[3769]	Tyr Gln Gly Gly Ile Phe Glu Leu Lys Glu Asn Asp Arg Ile Phe Val		
[3770]	130 135 140		
[3771]	Ser Val Thr Asn Glu His Leu Ile Asp Met Asp His Glu Ala Ser Phe		
[3772]	145 150 155 160		
[3773]	Phe Gly Ala Phe Leu Val Gly Ser Arg Glu Arg Gly Pro Gln Arg Val		
[3774]	165 170 175		
[3775]	Ala Ala His Ile Thr Gly Thr Arg Gly Arg Ser Asn Thr Leu Ser Ser		
[3776]	180 185 190		
[3777]	Pro Asn Ser Lys Asn Glu Lys Ala Leu Gly Arg Lys Ile Asn Ser Trp		
[3778]	195 200 205		

[3779]	Glu Ser Ser Arg Ser Gly His Ser Phe Leu Ser Asn Leu His Leu Arg		
[3780]	210	215	220
[3781]	Asn Gly Glu Leu Val Ile His Glu Lys Gly Phe Tyr Tyr Ile Tyr Ser		
[3782]	225	230	235 240
[3783]	Gln Thr Tyr Phe Arg Phe Gln Glu Glu Ile Lys Glu Asn Thr Lys Asn		
[3784]	245	250	255
[3785]	Asp Lys Gln Met Val Gln Tyr Ile Tyr Lys Tyr Thr Ser Tyr Pro Asp		
[3786]	260	265	270
[3787]	Pro Ile Leu Leu Met Lys Ser Ala Arg Asn Ser Cys Trp Ser Lys Asp		
[3788]	275	280	285
[3789]	Ala Glu Tyr Gly Leu Tyr Ser Ile Tyr Gln Gly Gly Ile Phe Glu Leu		
[3790]	290	295	300
[3791]	Lys Glu Asn Asp Arg Ile Phe Val Ser Val Thr Asn Glu His Leu Ile		
[3792]	305	310	315 320
[3793]	Asp Met Asp His Glu Ala Ser Phe Phe Gly Ala Phe Leu Val Gly Ser		
[3794]	325	330	335
[3795]	Arg Glu Arg Gly Pro Gln Arg Val Ala Ala His Ile Thr Gly Thr Arg		
[3796]	340	345	350
[3797]	Gly Arg Ser Asn Thr Leu Ser Ser Pro Asn Ser Lys Asn Glu Lys Ala		
[3798]	355	360	365
[3799]	Leu Gly Arg Lys Ile Asn Ser Trp Glu Ser Ser Arg Ser Gly His Ser		
[3800]	370	375	380
[3801]	Phe Leu Ser Asn Leu His Leu Arg Asn Gly Glu Leu Val Ile His Glu		
[3802]	385	390	395 400
[3803]	Lys Gly Phe Tyr Tyr Ile Tyr Ser Gln Thr Tyr Phe Arg Phe Gln Glu		
[3804]	405	410	415
[3805]	Glu Ile Lys Glu Asn Thr Lys Asn Asp Lys Gln Met Val Gln Tyr Ile		
[3806]	420	425	430
[3807]	Tyr Lys Tyr Thr Ser Tyr Pro Asp Pro Ile Leu Leu Met Lys Ser Ala		
[3808]	435	440	445
[3809]	Arg Asn Ser Cys Trp Ser Lys Asp Ala Glu Tyr Gly Leu Tyr Ser Ile		
[3810]	450	455	460
[3811]	Tyr Gln Gly Gly Ile Phe Glu Leu Lys Glu Asn Asp Arg Ile Phe Val		
[3812]	465	470	475 480
[3813]	Ser Val Thr Asn Glu His Leu Ile Asp Met Asp His Glu Ala Ser Phe		
[3814]	485	490	495
[3815]	Phe Gly Ala Phe Leu Val Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser		
[3816]	500	505	510
[3817]	Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Met Ala Arg Ala Ser Gly		
[3818]	515	520	525
[3819]	Ser Glu Arg Arg Leu Leu Leu Ile Tyr Thr Gly Gly Thr Leu Gly Met		
[3820]	530	535	540

[3821]	Arg Ser Glu Gly Gly Val Leu Val Pro Gly Pro Gly Leu Val Thr Leu		
[3822]	545	550	555 560
[3823]	Leu Arg Thr Leu Pro Met Phe His Asp Glu Glu Phe Ala Arg Ala Arg		
[3824]	565	570	575
[3825]	Gly Leu Ser Glu Asp Thr Leu Val Leu Pro Pro Ala Ser His Gly Pro		
[3826]	580	585	590
[3827]	Arg Val Leu Tyr Thr Val Leu Glu Cys Gln Pro Leu Leu Asp Ser Ser		
[3828]	595	600	605
[3829]	Asp Met Thr Ile Ala Glu Trp Ile Arg Ile Ala Gln Ile Ile Lys Arg		
[3830]	610	615	620
[3831]	His Tyr Glu Gln Tyr His Gly Phe Val Val Ile His Gly Thr Asp Thr		
[3832]	625	630	635 640
[3833]	Met Ala Phe Ala Ala Ser Met Leu Ser Phe Met Leu Glu Asn Leu Gln		
[3834]	645	650	655
[3835]	Lys Pro Val Ile Leu Thr Gly Ala Gln Val Pro Ile His Val Leu Trp		
[3836]	660	665	670
[3837]	Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala Leu Leu Val Ala Gly Gln		
[3838]	675	680	685
[3839]	Tyr Ile Ile Pro Glu Val Cys Leu Phe Met Asn Ser Gln Leu Phe Arg		
[3840]	690	695	700
[3841]	Gly Asn Arg Val Thr Lys Val Asp Ser Gln Arg Phe Glu Ala Phe Ala		
[3842]	705	710	715 720
[3843]	Ser Pro Asn Leu Ser Pro Leu Ala Thr Val Gly Ala Asp Val Thr Ile		
[3844]	725	730	735
[3845]	Ala Trp Glu Leu Val Arg Lys Val Lys Trp Lys Asp Pro Leu Val Val		
[3846]	740	745	750
[3847]	His Ser Ser Met Glu Gln Asp Val Ala Leu Leu Arg Leu Tyr Pro Gly		
[3848]	755	760	765
[3849]	Ile Pro Ala Ala Leu Val Arg Ala Phe Leu Gln Pro Pro Leu Lys Gly		
[3850]	770	775	780
[3851]	Val Val Leu Glu Thr Phe Gly Ser Gly Asn Gly Pro Ser Lys Pro Asp		
[3852]	785	790	795 800
[3853]	Leu Leu Gln Glu Leu Arg Ala Ala Ala Glu Arg Gly Leu Ile Met Val		
[3854]	805	810	815
[3855]	Asn Cys Ser Gln Cys Leu Gln Gly Ser Val Thr Pro Gly Tyr Ala Thr		
[3856]	820	825	830
[3857]	Ser Leu Ala Gly Ala Asn Ile Val Ser Gly Leu Asp Met Thr Ser Glu		
[3858]	835	840	845
[3859]	Ala Ala Leu Ala Lys Leu Ser Tyr Val Leu Gly Leu Pro Glu Leu Ser		
[3860]	850	855	860
[3861]	Leu Asp Arg Arg Gln Glu Leu Leu Ala Lys Asp Leu Arg Gly Glu Met		
[3862]	865	870	875 880

[3863]	Thr Pro Pro Ser Val Glu Glu Arg Arg Pro Ser
[3864]	885 890
[3865]	<210> 93
[3866]	<211> 387
[3867]	<212> PRT
[3868]	<213> 人工序列
[3869]	<220>
[3870]	<223> 合成多肽
[3871]	<400> 93
[3872]	Met Ala Arg Ala Ser Gly Ser Glu Arg Arg Leu Leu Leu Ile Tyr Thr
[3873]	1 5 10 15
[3874]	Gly Gly Thr Leu Gly Met Arg Ser Glu Gly Gly Val Leu Val Pro Gly
[3875]	20 25 30
[3876]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Glu
[3877]	35 40 45
[3878]	Glu Phe Ala Arg Ala Arg Gly Leu Ser Glu Asp Thr Leu Val Leu Pro
[3879]	50 55 60
[3880]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln
[3881]	65 70 75 80
[3882]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Ala Glu Trp Ile Arg Ile
[3883]	85 90 95
[3884]	Ala Gln Ile Ile Lys Arg His Tyr Glu Gln Tyr His Gly Phe Val Val
[3885]	100 105 110
[3886]	Ile His Gly Thr Asp Thr Met Ala Phe Ala Ala Ser Met Leu Ser Phe
[3887]	115 120 125
[3888]	Met Leu Glu Asn Leu Gln Lys Pro Val Ile Leu Thr Gly Ala Gln Val
[3889]	130 135 140
[3890]	Pro Ile His Val Leu Trp Asn Asp Ala Arg Glu Asn Leu Leu Gly Ala
[3891]	145 150 155 160
[3892]	Leu Leu Val Ala Gly Gln Tyr Ile Ile Pro Glu Val Cys Leu Phe Met
[3893]	165 170 175
[3894]	Asn Ser Gln Leu Phe Arg Gly Asn Arg Val Thr Lys Val Asp Ser Gln
[3895]	180 185 190
[3896]	Arg Phe Glu Ala Phe Ala Ser Pro Asn Leu Ser Pro Leu Ala Thr Val
[3897]	195 200 205
[3898]	Gly Ala Asp Val Thr Ile Ala Trp Glu Leu Val Arg Lys Val Lys Trp
[3899]	210 215 220
[3900]	Lys Arg Leu Ile Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp
[3901]	225 230 235 240
[3902]	Glu Asp Asp Asp Pro Leu Val Val His Ser Ser Met Glu Gln Asp Val
[3903]	245 250 255
[3904]	Ala Leu Leu Arg Leu Tyr Pro Gly Ile Pro Ala Ala Leu Val Arg Ala

[3905]	260	265	270
[3906]	Phe Leu Gln Pro Pro Leu Lys Gly Val Val Leu Glu Thr Phe Gly Ser		
[3907]	275	280	285
[3908]	Gly Asn Gly Pro Ser Lys Pro Asp Leu Leu Gln Glu Leu Arg Ala Ala		
[3909]	290	295	300
[3910]	Ala Glu Arg Gly Leu Ile Met Val Asn Cys Ser Gln Cys Leu Gln Gly		
[3911]	305	310	315
[3912]	Ser Val Thr Pro Gly Tyr Ala Thr Ser Leu Ala Gly Ala Asn Ile Val		
[3913]	325	330	335
[3914]	Ser Gly Leu Asp Met Thr Ser Glu Ala Ala Leu Ala Lys Leu Ser Tyr		
[3915]	340	345	350
[3916]	Val Leu Gly Leu Pro Glu Leu Ser Leu Asp Arg Arg Gln Glu Leu Leu		
[3917]	355	360	365
[3918]	Ala Lys Asp Leu Arg Gly Glu Met Thr Pro Pro Ser Val Glu Glu Arg		
[3919]	370	375	380
[3920]	Arg Pro Ser		
[3921]	385		
[3922]	<210> 94		
[3923]	<211> 387		
[3924]	<212> PRT		
[3925]	<213> 人工序列		
[3926]	<220>		
[3927]	<223> 合成多肽		
[3928]	<400> 94		
[3929]	Met Ala Arg Ala Ser Gly Ser Glu Arg Arg Leu Leu Leu Ile Tyr Thr		
[3930]	1	5	10
[3931]	Gly Gly Thr Leu Gly Met Arg Ser Glu Gly Gly Val Leu Val Pro Gly		
[3932]	20	25	30
[3933]	Pro Gly Leu Val Thr Leu Leu Arg Thr Leu Pro Met Phe His Asp Glu		
[3934]	35	40	45
[3935]	Glu Phe Ala Arg Ala Arg Gly Leu Ser Glu Asp Thr Leu Val Leu Pro		
[3936]	50	55	60
[3937]	Pro Ala Ser His Gly Pro Arg Val Leu Tyr Thr Val Leu Glu Cys Gln		
[3938]	65	70	75
[3939]	Pro Leu Leu Asp Ser Ser Asp Met Thr Ile Ala Glu Trp Ile Arg Ile		
[3940]	85	90	95
[3941]	Ala Gln Ile Ile Lys Arg His Tyr Glu Gln Tyr His Gly Phe Val Val		
[3942]	100	105	110
[3943]	Ile His Gly Thr Asp Thr Met Ala Phe Ala Ala Ser Met Leu Ser Phe		
[3944]	115	120	125
[3945]	Met Leu Glu Asn Leu Gln Lys Pro Val Ile Leu Thr Gly Ala Gln Val		
[3946]	130	135	140

[3947]	Pro	Ile	His	Val	Leu	Trp	Asn	Asp	Ala	Arg	Glu	Asn	Leu	Leu	Gly	Ala
[3948]	145					150					155					160
[3949]	Leu	Leu	Val	Ala	Gly	Gln	Tyr	Ile	Ile	Pro	Glu	Val	Cys	Leu	Phe	Met
[3950]					165					170						175
[3951]	Asn	Ser	Gln	Leu	Phe	Arg	Gly	Asn	Arg	Val	Thr	Lys	Val	Asp	Ser	Gln
[3952]				180					185							190
[3953]	Arg	Phe	Glu	Ala	Phe	Ala	Ser	Pro	Asn	Leu	Ser	Pro	Leu	Ala	Thr	Val
[3954]			195					200						205		
[3955]	Gly	Ala	Asp	Val	Thr	Ile	Ala	Trp	Glu	Leu	Val	Arg	Lys	Val	Lys	Trp
[3956]		210					215					220				
[3957]	Lys	Asp	Pro	Leu	Val	Val	His	Ser	Ser	Met	Glu	Gln	Asp	Val	Ala	Leu
[3958]	225					230					235					240
[3959]	Leu	Arg	Leu	Tyr	Pro	Gly	Ile	Pro	Ala	Ala	Leu	Val	Arg	Ala	Phe	Leu
[3960]					245					250						255
[3961]	Gln	Pro	Pro	Leu	Lys	Gly	Val	Val	Leu	Glu	Thr	Phe	Gly	Ser	Gly	Asn
[3962]				260					265							270
[3963]	Gly	Pro	Ser	Lys	Pro	Asp	Leu	Leu	Gln	Glu	Leu	Arg	Ala	Ala	Ala	Glu
[3964]			275					280					285			
[3965]	Arg	Gly	Leu	Ile	Met	Val	Asn	Cys	Ser	Gln	Cys	Leu	Gln	Gly	Ser	Val
[3966]		290					295						300			
[3967]	Thr	Pro	Gly	Tyr	Ala	Thr	Ser	Leu	Ala	Gly	Ala	Asn	Ile	Val	Ser	Gly
[3968]	305					310					315					320
[3969]	Leu	Asp	Met	Thr	Ser	Glu	Ala	Ala	Leu	Ala	Lys	Leu	Ser	Tyr	Val	Leu
[3970]					325					330						335
[3971]	Gly	Leu	Pro	Glu	Arg	Leu	Ile	Glu	Asp	Ile	Cys	Leu	Pro	Arg	Trp	Gly
[3972]				340					345							350
[3973]	Cys	Leu	Trp	Glu	Asp	Asp	Leu	Ser	Leu	Asp	Arg	Arg	Gln	Glu	Leu	Leu
[3974]			355					360						365		
[3975]	Ala	Lys	Asp	Leu	Arg	Gly	Glu	Met	Thr	Pro	Pro	Ser	Val	Glu	Glu	Arg
[3976]		370					375						380			
[3977]	Arg	Pro	Ser													
[3978]	385															

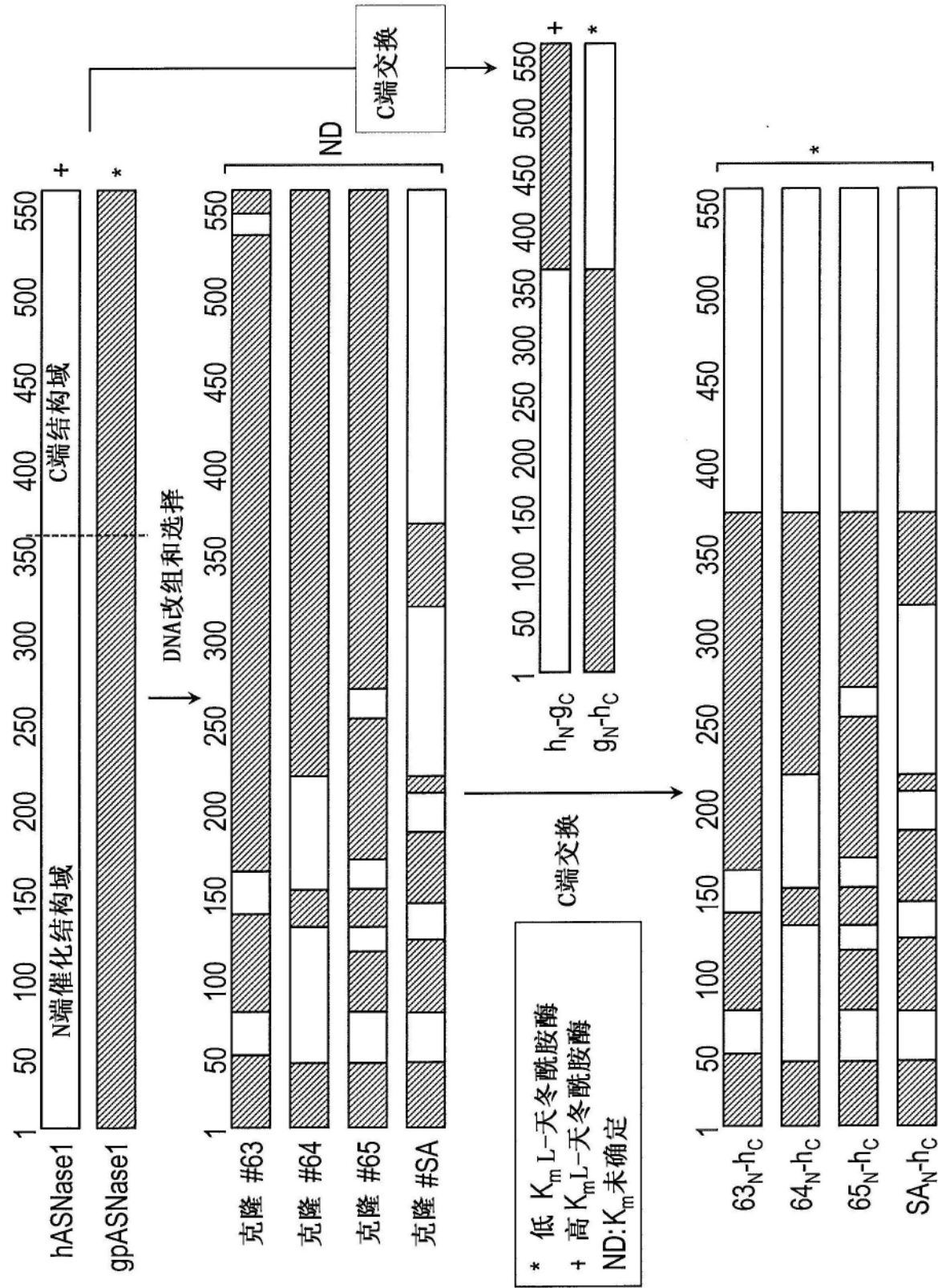


图1

hASN	MARAVGPERLLAVYTGGTIGMRSELGVLVPGTGLAAILRTLPMFHDEEH
GpA	MARASGSERHLLLIYTGGTLGMQSKGGVLVPGPGLVTLLRTLPMFHDKEF
h _N -g _C	MARAVGPERLLAVYTGGTIGMRSELGVLVPGTGLAAILRTLPMFHDEEH
g _N -h _C	MARASGSERHLLLIYTGGTLGMQSKGGVLVPGPGLVTLLRTLPMFHDKEF
63-h _C	MARASGSERHLLLIYTGGTLGMQSKGGVLVPGPGLVTLLRTLPMFHDKEF
64-h _C	MARASGSERHLLLIYTGGTLGMQSKGGVLVPGPGLVTLLRTLPMFHDEEH
65-h _C	MARASGSERHLLLIYTGGTLGMQSKGGVLVPGPGLVTLLRTLPMFHDEEH
SA-h _C	MARASGSERHLLLIYTGGTLGMQSKGGVLVPGPGLVTLLRTLPMFHDEEH ****-*.**.*:*****:*.*:*****.*.*.:*****:*
hASN	ARARGLSEDTLVLPPASRNQRILYTVLECCQLFDSSDMTIAEWVCLAQTI
GpA	AQAQGLPDHALALPPASHGPRVLYTVLECCQLLDSSDMTIDDWIRIAKII
h _N -g _C	ARARGLSEDTLVLPPASRNQRILYTVLECCQLFDSSDMTIAEWVCLAQTI
g _N -h _C	AQAQGLPDHALALPPASHGPRVLYTVLECCQLLDSSDMTIDDWIRIAKII
63-h _C	ARARGLSEDTLVLPPASRNQRILYTVLECCQLLDSSDMTIDDWIRIAKII
64-h _C	ARARGLSEDTLVLPPASRNQRILYTVLECCQLLDSSDMTIDDWIRIAKII
65-h _C	ARARGLSEDTLVLPPASRNQRILYTVLECCQLFDSSDMTIAEWVCLAQTI
SA-h _C	ARARGLSEDTLVLPPASRNQRILYTVLECCQLLDSSDMTIDDWIRIAKII *.*.**.:*.*****.*:*****:*****:*.*:*****:*
hASN	KRHYEQYHGFVVIHGTDMAFAASMLSFMLENLQKTVILTGAQVPIHALW
GpA	ERHYEQYQGFVVIHGTDMAFGASMLSFMLENLHKPVILTGAQVPIRVLW
h _N -g _C	KRHYEQYHGFVVIHGTDMAFAASMLSFMLENLQKTVILTGAQVPIHALW
g _N -h _C	ERHYEQYQGFVVIHGTDMAFGASMLSFMLENLHKPVILTGAQVPIRVLW
63-h _C	ERHYEQYQGFVVIHGTDMAFAASMLSFMLENLHKPVILTGAQVPIRVLW
64-h _C	ERHYEQYQGFVVIHGTDMAFAASMLSFMLENLHKPVILTGAQVPIHALW
65-h _C	KRHYEQYHGFVVIHGTDMAFAASMLSFMLENLHKPVILTGAQVPIHALW
SA-h _C	ERHYEQYHGFVVIHGTDMAFAASMLSFMLENLQKTVILTGAQVPIRVLW :*****:*****.*.*****:*.*****.*.*
hASN	SDGRENLLGALLMAGQYVIPEVCLFFQNQLFRGNRATKVDARRFAAFCSP
GpA	NDARENLLGALLVAGQYIIPEVCLFMNSQLFRGNRVTKVDSQKFEAFCSP
h _N -g _C	SDGRENLLGALLMAGQYVIPEVCLFFQNQLFRGNRATKVDARRFAAFCSP
g _N -h _C	NDARENLLGALLVAGQYIIPEVCLFMNSQLFRGNRVTKVDSQKFEAFCSP
63-h _C	NDARENLLGALLVAGQYIIPEVCLFMNSQLFRGNRVTKVDSQKFEAFCSP
64-h _C	SDGRENLLGALLVAGQYIIPEVCLFMNSQLFRGNRVTKVDSQKFEAFCSP
65-h _C	SDGRENLLGALLMAGQYVIPEVCLFFQNQLFRGNRATKVDARRFAAFCSP
SA-h _C	NDARENLLGALLVAGQYIIPEVCLFMNSQLFRGNRATKVDARRFAAFCSP .*.*****:*****:*****:..*****.*.*:..* *****
hASN	NLLPLATVGADITINRELVRKVDGKAGLVVHSSMEQDVGLLRLYPGIPAA
GpA	NLSPLATVGADVTIAWDLVRKVWKDPLVVHSSMEQDVGLLRLYPGIPAS
h _N -g _C	NLLPLATVGADITINRELVRKVDGKAGLVVHSSMEQDVGLLRLYPGIPAA
g _N -h _C	NLSPLATVGADVTIAWDLVRKVWKDPLVVHSSMEQDVGLLRLYPGIPAS
63-h _C	NLSPLATVGADVTIAWDLVRKVWKDPLVVHSSMEQDVGLLRLYPGIPAS
64-h _C	NLSPLATVGADVTIAWDLVRKVWKDPLVVHSSMEQDVGLLRLYPGIPAS
65-h _C	NLLPLATVGADVTIAWDLVRKVWKDPLVVHSSMEQDVGLLRLYPGIPAA
SA-h _C	NLSPLATVGADITINRELVRKVDGKAGLVVHSSMEQDVGLLRLYPGIPAA **~*****:*.*:*****.* *****.*.*:*****:*
hASN	LVRAFLQPPLKGVVMEFTFGSGNGPTKPDLLQELRVATERGLVIVNCTHCL
GpA	LVRAFLQPPLKGVVLETFGSGNGPSKPDLLQELRAAAQRLIMVNC SQCL
h _N -g _C	LVRAFLQPPLKGVVMEFTFGSGNGPTKPDLLQELRVATERGLVIVNCTHCL
g _N -h _C	LVRAFLQPPLKGVVLETFGSGNGPSKPDLLQELRAAAERGLIMVNC SQCL
63-h _C	LVRAFLQPPLKGVVLETFGSGNGPSKPDLLQELRAAAERGLIMVNC SQCL
64-h _C	LVRAFLQPPLKGVVMEFTFGSGNGPTKPDLLQELRAAAERGLIMVNC SQCL
65-h _C	LVRAFLQPPLKGVVLETFGSGNGPSKPDLLQELRAAAERGLIMVNC SQCL
SA-h _C	LVRAFLQPPLKGVVMEFTFGSGNGPTKPDLLQELRVATERGLVIVNCTHCL *****:*****:*****.*.:***:***:***:***:***

图2A

131