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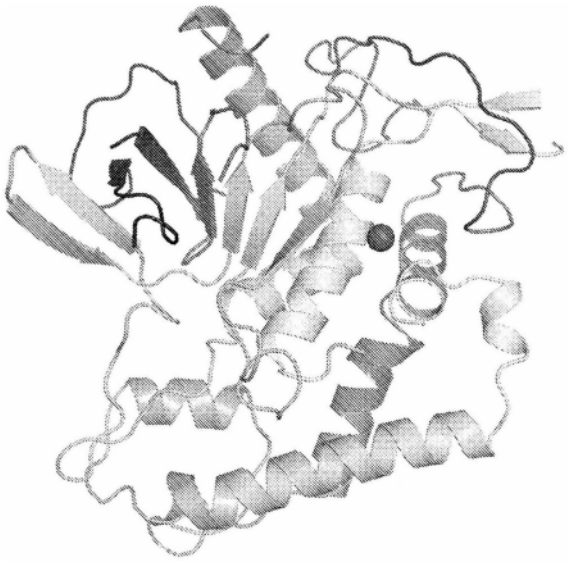
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(54)发明名称

新的肉毒神经毒素及其衍生物

(57)摘要

本文中提供了新血清型(BoNT/X)的肉毒梭菌神经毒素(BoNT)多肽以及制备和使用所述BoNT多肽的方法(例如在治疗应用中)。



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1.一种经修饰BoNT多肽,其由SEQ ID NO:4至17中任一个的氨基酸序列组成。

2.一种多肽,其由权利要求1所述的经修饰BoNT多肽与亲和标签融合而形成。

3.一种经修饰BoNT多肽,其由SEQ ID NO:18至21中任一个的氨基酸序列组成。

4.一种经修饰BoNT多肽,其由SEQ ID NO:31的氨基酸序列组成。

5.一种多肽,其由权利要求4所述的经修饰BoNT多肽与亲和标签融合而形成。

6.核酸分子,其编码权利要求1至5中任一项所述的多肽。

7.核酸载体,其包含权利要求6所述的核酸分子。

8.细胞,其包含权利要求6所述的核酸分子或权利要求7所述的核酸载体。

9.细胞,其表达权利要求1至5中任一项所述的多肽。

10.产生多肽的方法,所述方法包括在其中产生所述多肽的条件下培养权利要求9所述细胞的步骤。

11.权利要求10所述的方法,其还包括从培养物中回收所述多肽。

12.权利要求4或5所述的多肽在制备作为用于将治疗剂递送到神经元中的递送载剂的药物中的用途。

13.药物组合物,其包含权利要求1至5中任一项所述的多肽。

14.权利要求13所述的药物组合物,其还包含可药用赋形剂。

15.药盒,其包含权利要求13或权利要求14所述的药物组合物以及用于治疗性施用所述药物组合物的用法说明书。

16.治疗有效量的SEQ ID NO:1-3中任一氨基酸序列的分离的BoNT多肽,或者权利要求1至3中任一项所述的多肽在制备用于治疗病症的药物中的用途,所述药物配制成向对象施用以治疗所述病症,其中所述病症选自:痉挛性发声障碍、痉挛性斜颈、喉肌张力障碍、口下颌发声困难、舌肌张力障碍、颈肌张力障碍、局灶性手肌张力障碍、眼睑痉挛、斜视、偏侧面肌痉挛、眼睑疾病、大脑性瘫痪、局灶性痉挛状态和其他发声障碍、痉挛性结肠炎、神经源性膀胱、肛门痉挛、肢体痉挛状态、抽搐、震颤、夜磨牙症、肛裂、失弛缓症、吞咽困难和其他肌张力障碍以及特征为肌肉群不自主运动的其他障碍、流泪、多汗、过度流涎、过度胃肠分泌、分泌紊乱、肌痉挛引起的疼痛、头痛、皮肤病学或美学/美容病症、肥胖/食欲减退、银屑病、变态反应、嗜红细胞淋巴组织细胞增生症和酒精性胰腺疾病。

17.权利要求16所述的用途,其中所述药物配制成通过注射到达存在不期望的神经元活动的地方来进行施用。

18.SEQ ID NO:1-3中任一个的分离的BoNT多肽,或者权利要求1至3中任一项所述的多肽在制备用于治疗与不期望的神经元活动相关的病症的药物中的用途,其中所述病症选自:痉挛性发声障碍、痉挛性斜颈、喉肌张力障碍、口下颌发声困难、舌肌张力障碍、颈肌张力障碍、局灶性手肌张力障碍、眼睑痉挛、斜视、偏侧面肌痉挛、眼睑疾病、大脑性瘫痪、局灶性痉挛状态和其他发声障碍、痉挛性结肠炎、神经源性膀胱、肛门痉挛、肢体痉挛状态、抽搐、震颤、夜磨牙症、肛裂、失弛缓症、吞咽困难和其他肌张力障碍以及特征为肌肉群不自主运动的其他障碍、流泪、多汗、过度流涎、过度胃肠分泌、分泌紊乱、肌痉挛引起的疼痛、头痛、皮肤病学或美学/美容病症、肥胖/食欲减退。

新的肉毒神经毒素及其衍生物

[0001] 相关申请

[0002] 本申请根据35 U.S.C§119(e)要求于2016年7月8日提交的美国临时申请号62/360,239的权益,其通过引用整体并入本文。

[0003] 政府支持

[0004] 本发明是在国立卫生研究院(National Institutes of Health)授予的R01NS080833的政府支持下完成的。政府对本发明享有某些权利。

背景技术

[0005] 肉毒梭菌神经毒素(Clostridial Botulinum neurotoxin,BoNT)是最危险的潜在生物恐怖剂(bioterrorism agent)并且在临床上也用于治疗越来越多的医学病症。迄今为止已知有七种BoNT的血清型(BoNT/A-G)。近年来,BoNT已被广泛用于治疗越来越多的医学病症:局部注射少量毒素可减弱靶区域中的神经元活动(neuronal activity),这在许多医学病症中以及对于美容目的都是有益的。随着BoNT的应用不断增长,已经报道了多种限制和不良作用。主要的限制是在患者中产生中和抗体,这使得将来的治疗无效。终止使用BoNT往往使患者没有其他有效的方法来治疗/缓解他们的疾病。与BoNT使用相关的不良作用范围从短暂的非严重事件(例如上睑下垂(ptosis)和复视)直到危及生命的事件甚至死亡。BoNT的限制和不良作用在很大程度上与剂量相关。对于开发新的BoNT类型作为治疗性毒素存在相当大的兴趣。在过去的45年里,没有确认新的BoNT类型。

发明内容

[0006] 本公开内容至少部分地基于通过搜索肉毒梭菌(Clostridium Botulinum)菌株的基因组数据库鉴定新的BoNT血清型BoNT/X。BoNT/X与其他BoNT具有最低的序列同一性,且其未被针对已知BoNT类型的抗血清识别。如同其他BoNT那样,BoNT/X切割SNARE蛋白。然而,BoNT/X还切割其他BoNT不能切割的数种SNARE蛋白,例如VAMP4、VAMP5和Ykt6。提供了用于使用BoNT/X来治疗疾病的组合物和方法。本文中还提供了制备BoNT/X的方法。

[0007] 因此,本公开内容的一些方面提供了包含SEQ ID NO:1的氨基酸序列的分离的肉毒梭菌神经毒素(BoNT)多肽。

[0008] 本公开内容的一些方面提供了分离的BoNT多肽,其包含与SEQ ID NO:1具有至少85%、至少86%、至少87%、至少88%、至少89%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或至少99.5%同一性的氨基酸序列。在一些实施方案中,分离的BoNT多肽由SEQ ID NO:1的氨基酸序列组成。

[0009] 本公开内容的一些方面提供了包含SEQ ID NO:2的氨基酸序列的分离的BoNT多肽。本公开内容的一些方面提供了分离的BoNT多肽,其包含与SEQ ID NO:2具有至少85%、至少86%、至少87%、至少88%、至少89%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少96%、至少97%、至少98%、至少99%或至少99.5%同一性的氨基酸序列。在一些实施方案中,分离的BoNT多肽由SEQ ID NO:2的氨基酸序列组成。

[0010] 本公开内容的一些方面提供了包含SEQ ID NO:3的氨基酸序列的分离的BoNT多肽。本公开内容的一些方面提供了分离的BoNT多肽，其包含与SEQ ID NO:3具有至少85％、至少86％、至少87％、至少88％、至少89％、至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少96％、至少97％、至少98％、至少99％或至少99.5％同一性的氨基酸序列。在一些实施方案中，分离的BoNT多肽由SEQ ID NO:3的氨基酸序列组成。

[0011] 本公开内容的一些方面提供了经修饰BoNT多肽，其在对应于SEQ ID NO:1的C461、C467和C1240的位置处包含一个或更多个替换突变。在一些实施方案中，替换突变对应于SEQ ID NO:1中的C461S、C461A、C467S、C467A、C1240S、C1240A、C461S/C1240S、C416S/C1240A、C461A/C1240S、C461A/C1240A、C467S/C1240S、C461S/C1240A、C467A/C1240S或C467A/C1240A。

[0012] 在一些实施方案中，经修饰BoNT多肽包含SEQ ID NO:4至17中任一个的氨基酸序列。在一些实施方案中，经修饰BoNT多肽包含与SEQ ID NO:4至17中任一个具有至少85％、至少86％、至少87％、至少88％、至少89％、至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％、至少99％或至少99.5％同一性的氨基酸序列，其中所述多肽不具有SEQ ID NO:1的氨基酸序列。在一些实施方案中，经修饰BoNT多肽由SEQ ID NO:4至17中任一个的氨基酸序列组成。

[0013] 本公开内容的一些方面提供了经修饰BoNT多肽，其在对应于SEQ ID NO:2的C461或C467的位置处包含单替换突变。

[0014] 在一些实施方案中，替换突变对应于SEQ ID NO:2中的C461S、C461A、C467S、C467A、C1240S、C1240A、C461S/C1240S、C416S/C1240A、C461A/C1240S、C461A/C1240A、C467S/C1240S、C461S/C1240A、C467A/C1240S或C467A/C1240A。

[0015] 在一些实施方案中，经修饰BoNT多肽包含SEQ ID NO:18至21中任一个的氨基酸序列。在一些实施方案中，经修饰BoNT多肽包含与SEQ ID NO:18至21中任一个具有至少85％、至少86％、至少87％、至少88％、至少89％、至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％、至少99％或至少99.5％同一性的氨基酸序列，其中所述多肽不具有SEQ ID NO:2的氨基酸序列。在一些实施方案中，经修饰BoNT多肽由SEQ ID NO:18至21中任一个的氨基酸序列组成。

[0016] 本公开内容的一些方面提供了嵌合BoNT多肽，其包含SEQ ID NO:22至24中任一个的氨基酸序列。在一些实施方案中，嵌合BoNT多肽包含与SEQ ID NO:22至24中任一个具有至少85％、至少86％、至少87％、至少88％、至少89％、至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％、至少99％或至少99.5％同一性的氨基酸序列，其中所述多肽不具有SEQ ID NO:1或SEQ ID NO:2的氨基酸序列。在一些实施方案中，嵌合BoNT多肽由SEQ ID NO:22至24中任一个的氨基酸序列组成。

[0017] 在一些实施方案中，嵌合BoNT多肽还在对应于SEQ ID NO:2中的C461或C467的位置处包含单替换突变。

[0018] 在一些实施方案中，嵌合BoNT多肽包含SEQ ID NO:25至30中任一个的氨基酸序列。在一些实施方案中，嵌合BoNT多肽包含与SEQ ID NO:25至30中任一个具有至少85％、至少86％、至少87％、至少88％、至少89％、至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％、至少99％或至少99.5％同一性的氨基酸序

列。在一些实施方案中,嵌合BoNT多肽由SEQ ID NO:25至30中任一个的氨基酸序列组成。

[0019] 在一些实施方案中,BoNT多肽进入细胞。在一些实施方案中,BoNT多肽切割细胞中的SNARE蛋白。在一些实施方案中,SNARE蛋白选自:SNAP-25、VAMP1、VAMP2、VAMP3、VAMP4、VAMP5、Ykt6和突触融合蛋白1(syntaxin 1)。

[0020] 在一些实施方案中,SNARE蛋白是VAMP1。在一些实施方案中,BoNT在对应于SEQ ID NO:39的R66和A67的氨基酸残基之间切割。

[0021] 在一些实施方案中,SNARE蛋白是VAMP2。在一些实施方案中,BoNT在对应于SEQ ID NO:40的R66和A67的氨基酸残基之间切割。

[0022] 在一些实施方案中,SNARE蛋白是VAMP3。在一些实施方案中,BoNT在对应于SEQ ID NO:41的R66和A67的氨基酸残基之间切割。

[0023] 在一些实施方案中,SNARE蛋白是VAMP4。在一些实施方案中,BoNT在对应于SEQ ID NO:42的K87和S88的氨基酸残基之间切割。

[0024] 在一些实施方案中,SNARE蛋白是VAMP5。在一些实施方案中,BoNT在对应于SEQ ID NO:43的R40和S41的氨基酸残基之间切割。

[0025] 在一些实施方案中,SNARE蛋白是Ykt6。在一些实施方案中,BoNT在对应于SEQ ID NO:44的K173和S174的氨基酸残基之间切割。

[0026] 在一些实施方案中,BoNT多肽与其相应的野生型BoNT多肽相比具有提高的稳定性。

[0027] 在一些实施方案中,细胞是分泌细胞。在一些实施方案中,细胞是神经元细胞。在一些实施方案中,细胞是免疫细胞。在一些实施方案中,BoNT多肽抑制神经元活动。在一些实施方案中,BoNT多肽诱导松弛性瘫痪(flaccid paralysis)。在一些实施方案中,细胞是培养的细胞。在一些实施方案中,细胞是体内的。在一些实施方案中,细胞来自哺乳动物。在一些实施方案中,哺乳动物是人。在一些实施方案中,哺乳动物是啮齿动物。在一些实施方案中,啮齿动物是小鼠。在一些实施方案中,啮齿动物是大鼠。

[0028] 在一些实施方案中,BoNT多肽不与针对BoNT血清型A、B、C、D、E、F或G的抗体交叉反应。

[0029] 本公开内容的另一些方面提供了核酸分子,其包含编码多肽的多核苷酸,所述多肽包含与本文中所述的BoNT多肽具有至少85%、至少86%、至少87%、至少88%、至少89%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或至少99.5%或100%同一性的氨基酸序列。提供了包含这样核酸分子的核酸载体。提供了包含本文中所述的核酸分子或核酸载体的细胞。在一些实施方案中,这样的细胞表达本文中所述的BoNT多肽。

[0030] 提供了产生本公开内容的BoNT多肽的方法。这样的方法包括在其中产生所述BoNT多肽的条件下培养表达BoNT多肽的细胞的步骤。在一些实施方案中,所述方法还包括从培养物中回收BoNT多肽。

[0031] 本公开内容的另一些方面提供了经修饰BoNT多肽,其包含:(a)蛋白酶结构域;(b)经修饰接头区;以及(c)易位结构域(translocation domain);其中(a)、(b)和(c)来自BoNT血清型X,并且其中经修饰接头区在对应于SEQ ID NO:1的C461或C467的位置处包含一个单替换突变。

[0032] 在一些实施方案中,经修饰BoNT多肽还包含:(d)受体结合结构域。

[0033] 在一些实施方案中,经修饰接头区包含对应于SEQ ID NO:1中的C461S或C461A的替换突变。在一些实施方案中,经修饰接头区包含对应于SEQ ID NO:1中的C467S或C467A的替换突变。

[0034] 在一些实施方案中,受体结合结构域来自BoNT/X。在一些实施方案中,受体结合结构域是经修饰的。在一些实施方案中,受体结合结构域包含对应于SEQ ID NO:1中的C1240S或C1240A的替换突变。

[0035] 在一些实施方案中,受体结合结构域来自选自A、B、C、D、E、F和G的血清型。

[0036] 在一些实施方案中,经修饰BoNT多肽进入细胞。在一些实施方案中,经修饰BoNT多肽切割细胞中的SNARE蛋白。在一些实施方案中,SNARE蛋白选自:SNAP-25、VAMP1、VAMP2、VAMP3、VAMP4、VAMP5、Ykt6和突触融合蛋白1。

[0037] 在一些实施方案中,SNARE蛋白是VAMP1。在一些实施方案中,BoNT在对应于SEQ ID NO:39的R66和A67的氨基酸残基之间切割。

[0038] 在一些实施方案中,SNARE蛋白是VAMP2。在一些实施方案中,BoNT在对应于SEQ ID NO:40的R66和A67的氨基酸残基之间切割。

[0039] 在一些实施方案中,SNARE蛋白是VAMP3。在一些实施方案中,BoNT在对应于SEQ ID NO:41的R66和A67的氨基酸残基之间切割。

[0040] 在一些实施方案中,SNARE蛋白是VAMP4。在一些实施方案中,BoNT在对应于SEQ ID NO:42的K87和S88的氨基酸残基之间切割。

[0041] 在一些实施方案中,SNARE蛋白是VAMP5。在一些实施方案中,BoNT在对应于SEQ ID NO:43的R40和S41的氨基酸残基之间切割。

[0042] 在一些实施方案中,SNARE蛋白是Ykt6。在一些实施方案中,BoNT在对应于SEQ ID NO:44的K173和S174的氨基酸残基之间切割。

[0043] 在一些实施方案中,BoNT多肽与其相应的野生型BoNT多肽相比具有提高的稳定性。

[0044] 在一些实施方案中,细胞是分泌细胞。在一些实施方案中,细胞是神经元细胞。在一些实施方案中,细胞是免疫细胞。在一些实施方案中,BoNT多肽抑制神经元活动。在一些实施方案中,BoNT多肽诱导松弛性瘫痪。在一些实施方案中,细胞是培养的细胞。在一些实施方案中,细胞是体内的。在一些实施方案中,细胞来自哺乳动物。在一些实施方案中,哺乳动物是人。在一些实施方案中,哺乳动物是啮齿动物。在一些实施方案中,啮齿动物是小鼠。在一些实施方案中,啮齿动物是大鼠。

[0045] 在一些实施方案中,BoNT多肽不与针对BoNT血清型A、B、C、D、E、F或G的抗体交叉反应。

[0046] 在一些实施方案中,经修饰接头区包含人工接头。在一些实施方案中,人工接头含有蛋白酶的切割位点。在一些实施方案中,蛋白酶选自凝血酶、TEV、PreScission(3C蛋白酶)、因子Xa、MMP-12、MMP-13、MMP-17、MMP-20、颗粒酶-B(Granzyme-B)和肠激酶。在一些实施方案中,接头包含SEQ ID NO:50至60中任一个的氨基酸序列。

[0047] 本公开内容的另一些方面提供了核酸分子,其包含编码多肽的多核苷酸,所述多肽包含与本文中所述的BoNT多肽具有至少85%、至少86%、至少87%、至少88%、至少89%、

至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％、至少99％或至少99.5％或100％同一性的氨基酸序列。提供了包含这样核酸分子的核酸载体。提供了包含本文中所述的核酸分子或核酸载体的细胞。在一些实施方案中，这样的细胞表达本文中所述的BoNT多肽。

[0048] 提供了产生本公开内容的BoNT多肽的方法。这样的方法包括在其中产生所述BoNT多肽的条件下培养表达BoNT多肽的细胞的步骤。在一些实施方案中，所述方法还包括从培养物中回收BoNT多肽。

[0049] 本公开内容的另一些方面提供了经修饰BoNT多肽，其在对应于SEQ ID NO:1中的R360、Y363、H227、E228或H231的位置处包含一个或更多个替换突变。在一些实施方案中，所述一个或更多个替换突变对应于SEQ ID NO:1中的R360A/Y363F、H227Y、E228Q或H231Y。

[0050] 在一些实施方案中，经修饰BoNT多肽包含SEQ ID NO:31至38中任一个的氨基酸序列。在一些实施方案中，经修饰BoNT多肽包含与SEQ ID NO:31至38中任一个具有至少85％、至少86％、至少87％、至少88％、至少89％、至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％、至少99％或至少99.5％同一性的氨基酸序列，其中所述多肽不具有SEQ ID NO:1或SEQ ID NO:2的氨基酸序列。在一些实施方案中，经修饰BoNT多肽由SEQ ID NO:31至38中任一个的氨基酸序列组成。

[0051] 本公开内容的另一些方面提供了经修饰BoNT/X多肽，其包含：a)无活性蛋白酶结构域；b)接头区；以及c)易位结构域。在一些实施方案中，经修饰BoNT/X还包含受体结合结构域。

[0052] 在一些实施方案中，无活性蛋白酶结构域在对应于SEQ ID NO:1的R360、Y363、H227、E228或H231的位置处包含一个或更多个替换突变。在一些实施方案中，一个或更多个替换突变对应于SEQ ID NO:1的R360A/Y363F、H227Y、E228Q或H231Y。

[0053] 在一些实施方案中，经修饰BoNT多肽进入细胞。在一些实施方案中，经修饰BoNT多肽不切割SNARE蛋白。

[0054] 在一些实施方案中，经修饰BoNT/X多肽还在(b)的接头区中包含修饰。在一些实施方案中，接头区中的修饰包含在对应于SEQ ID NO:1的C461或C467的位置处的一个单替换突变。在一些实施方案中，单替换突变对应于SEQ ID NO:1的C461A、C461S、C467A或C467S。在一些实施方案中，经修饰BoNT/X多肽还在(d)的受体结合结构域中包含修饰。

[0055] 在一些实施方案中，受体结合结构域中的修饰包含在对应于SEQ ID NO:1的C1240的位置处的替换突变。

[0056] 本公开内容的另一些方面提供了核酸分子，其包含编码多肽的多核苷酸，所述多肽包含与本文中所述的BoNT多肽具有至少85％、至少86％、至少87％、至少88％、至少89％、至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％、至少99％或至少99.5％或100％同一性的氨基酸序列。提供了包含这样核酸分子的核酸载体。提供了包含本文中所述的核酸分子或核酸载体的细胞。在一些实施方案中，这样的细胞表达本文中所述的BoNT多肽。

[0057] 提供了产生本公开内容的BoNT多肽的方法。这样的方法包括在其中产生所述BoNT多肽的条件下培养表达BoNT多肽的细胞的步骤。在一些实施方案中，所述方法还包括从培养物中回收BoNT多肽。

[0058] 本文中还提供了本文中所述的经修饰BoNT多肽作为用于将治疗剂递送到神经元中的递送载体的用途。

[0059] 本公开内容的一些方面提供了嵌合分子,其包含与第二部分连接的第一部分,其中所述第一部分是本文中所述的经修饰BoNT多肽。

[0060] 在一些实施方案中,第一部分与第二部分共价连接。在一些实施方案中,第一部分与第二部分非共价连接。

[0061] 在一些实施方案中,其中第二部分选自小分子、核酸、短多肽和蛋白质。在一些实施方案中,第二部分是生物活性分子。在一些实施方案中,第二部分是非多肽药物。在一些实施方案中,第二部分是治疗性多肽。

[0062] 本公开内容的另一些方面提供了核酸分子,其包含编码多肽的多核苷酸,所述多肽包含与本文中所述的嵌合BoNT多肽具有至少85%、至少86%、至少87%、至少88%、至少89%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或至少99.5%或100%同一性的氨基酸序列。提供了包含这样核酸分子的核酸载体。提供了包含本文中所述的核酸分子或核酸载体的细胞。在一些实施方案中,这样的细胞表达本文中所述的嵌合BoNT多肽。

[0063] 提供了产生本公开内容的嵌合BoNT多肽的方法。这样的方法包括在其中产生所述嵌合BoNT多肽的条件下培养表达嵌合BoNT多肽的细胞的步骤。在一些实施方案中,所述方法还包括从培养物中回收嵌合BoNT多肽。

[0064] 本公开内容的另一些方面提供了包含本文中所述的BoNT多肽的药物组合物。

[0065] 在一些实施方案中,药物组合物还包含可药用赋形剂。

[0066] 还提供了包含这样的药物组合物的药盒(kit)以及用于治疗性施用所述药物组合物的用法说明书(directions)。

[0067] 本公开内容的一些方面提供了治疗病症的方法,其包括向对象施用治疗有效量的本文中所述的BoNT多肽、嵌合分子或药物组合物以治疗所述病症。

[0068] 在一些实施方案中,所述病症与过度活动的神经元或腺体相关。在一些实施方案中,所述病症选自:痉挛性发声障碍(spasmodic dysphonia)、痉挛性斜颈(spasmodic torticollis)、喉肌张力障碍(laryngeal dystonia)、口下颌发声困难(oromandibular dysphonia)、舌肌张力障碍(lingual dystonia)、颈肌张力障碍(cervical dystonia)、局灶性手肌张力障碍(focal hand dystonia)、眼睑痉挛(blepharospasm)、斜视(strabismus)、偏侧面肌痉挛(hemifacial spasm)、眼睑疾病(eyelid disorder)、大脑性瘫痪(cerebral palsy)、局灶性痉挛状态(focal spasticity)和其他发声障碍(voice disorder)、痉挛性结肠炎(spasmodic colitis)、神经源性膀胱(neurogenic bladder)、肛门痉挛(anismus)、肢体痉挛状态(limb spasticity)、抽搐(tic)、震颤(tremor)、夜磨牙症(bruxism)、肛裂(anal fissure)、失弛缓症(achalasia)、吞咽困难(dysphagia)和其他肌张力障碍(muscle tone disorder)以及特征为肌肉群不自主运动(involuntary movement)的其他障碍、流泪(lacrimation)、多汗(hyperhydrosis)、过度流涎(excessive salivation)、过度胃肠分泌(excessive gastrointestinal secretion)、分泌紊乱(secretory disorder)、肌痉挛引起的疼痛、头痛、皮肤病学或美学/美容病症(dermatological or aesthetic/cosmetic condition)以及肥胖/食欲减退(reduced

appetite)。

[0069] 在一些实施方案中,所述病症与不需要的神经元活动无关。在一些实施方案中,所述病症选自:银屑病(psoriasis)、变态反应(allergy)、嗜红细胞淋巴组织细胞增生症(haemophagocytic lymphohistiocytosis)和酒精性胰腺疾病(alcoholic pancreatic disease)。

[0070] 在一些实施方案中,施用是通过注射到达存在不期望的神经元活动的地方。

[0071] 本公开内容的另一些方面提供了产生肉毒梭菌神经毒素(BoNT)多肽的方法,所述方法包括:

[0072] (i)获得包含重链的N端结构域(H_N)和轻链(LC)的第一BoNT片段,其中所述第一BoNT片段包含C端LPXTGG(SEQ ID NO:60)基序;

[0073] (ii)获得包含重链的C端结构域(H_C)的第二BoNT片段;其中所述第二BoNT片段在其N端包含特异性蛋白酶切割位点;

[0074] (iii)用特异性蛋白酶切割第二BoNT片段,其中所述切割在N端产生游离的甘氨酸残基;以及

[0075] (iv)在存在转肽酶的情况下使第一BoNT片段与第二BoNT片段接触,从而将第一BoNT片段与第二BoNT片段连接以形成连接的BoNT。

[0076] 在一些实施方案中,第一BoNT片段还包含亲和标签。在一些实施方案中,亲和标签与第一BoNT片段在N端融合。在一些实施方案中,亲和标签与第一BoNT片段在C端融合。在一些实施方案中,亲和标签选自:His6、GST、Avi、Strep、S、MBP、Sumo、FLAG、HA、Myc、SBP、E、钙调蛋白、Softag 1、Softag 3、TC、V5、VSV、Xpress、Halo和Fc。

[0077] 在一些实施方案中,第二BoNT片段还包含亲和标签。在一些实施方案中,亲和标签与第一BoNT片段在N端融合。在一些实施方案中,亲和标签与第二BoNT片段在C端融合。在一些实施方案中,亲和标签选自:His6、GST、Avi、Strep、S、MBP、Sumo、FLAG、HA、Myc、SBP、E、钙调蛋白、Softag 1、Softag 3、TC、V5、VSV、Xpress、Halo和Fc。

[0078] 在一些实施方案中,蛋白酶选自:凝血酶、TEV、PreScission、MMP-12、MMP-13、MMP-17、MMP-20、颗粒酶-B、肠激酶和SUMO蛋白酶。在一些实施方案中,同源蛋白酶是凝血酶。

[0079] 在一些实施方案中,第一BoNT片段来自BoNT血清型A、B、C、D、E、F、G或X。在一些实施方案中,第一BoNT片段来自BoNT/X。在一些实施方案中,第二BoNT片段来自BoNT血清型A、B、C、D、E、F、G或X。在一些实施方案中,第二BoNT片段来自BoNT/A。在一些实施方案中,第二BoNT片段来自BoNT/B。在一些实施方案中,第二BoNT片段来自BoNT/C。在一些实施方案中,第二BoNT片段来自BoNT/X。

[0080] 在一些实施方案中,转肽酶是定位酶(sortase)。在一些实施方案中,定位酶来自金黄色葡萄球菌(Staphylococcus aureus)(SrtA)。

[0081] 参考发明详述,本公开内容的这些和其他方面以及多种优点和效用将是明显的。如将理解的,本公开内容的每个方面都可涵盖多个实施方案。

[0082] 本申请中标识的所有文献通过引用整体并入本文。

附图说明

[0083] 以下附图构成本说明书的一部分并且包括在内以进一步示出本公开内容的某些

方面，其可通过与本文中示出的一些具体实施方案的详细描述组合参照这些附图中的一幅或更多幅来更好地理解。

[0084] 图1A-1E示出了BoNT/X鉴定为新的BoNT。图1A示出了通过ClustalW方法分析的BoNT/A-G、BoNT/F5、TeNT和BoNT/X的蛋白质序列比对的系统发生树。在每种毒素之后指示了每种毒素与BoNT/X之间的序列同一性百分比。还标记了BoNT/E与BoNT/F之间以及BoNT/B与BoNT/G之间的序列同一性百分比。图1B，上图，示出了BoNT/X的三个结构域的示意图，标记了L_C中的保守的蛋白酶基序以及H_C中的神经节苷脂结合基序。图1B，下图，示出了滑动序列比较窗(sliding sequence comparison window)，示出BoNT/X相对于所有其他七种BoNT和TeNT具有沿其序列均匀分布的低相似性。图1C是携带BoNT/X基因的orf基因簇的示意图(上图)，其与两种已知的orfX簇变体(中图和下图)相比具有两个独特的特征：(1)位于BoNT/X基因之后存在另外的orfX2蛋白(指定为orfX2b)；(2)orfX基因的阅读框与BoNT/X基因具有相同的方向。图1D是示出在BoNT/X中发现的独特基因方向性和另外的OrfX2基因的示意图。图1E示出了BoNT/X轻链的初步结构。黑点代表活性位点锌。该结构以1.9Å的分辨率示出。

[0085] 图2A-2J示出了BoNT/X的LC(X-LC)在独特位点处切割VAMP。图2A示出了用或不用EDTA预处理的与大鼠脑洗涤剂提取物(brain detergent extract，BDE)一起孵育的X-LC。进行免疫印迹分析以检测突触融合蛋白1、SNAP-25和VAMP2。还检测突触小泡蛋白(Synaptophysin，Syp)作为上样对照。并行地分析BoNT/A的LC(A-LC)和BoNT/B的LC(B-LC)。通过B-LC切割VAMP2导致丧失免疫印迹信号，而通过A-LC切割SNAP-25产生仍可在免疫印迹上检测到的SNAP-25的较小片段(用星号标记)。与X-LC孵育导致丧失VAMP2免疫印迹信号，表明X-LC切割VAMP2。EDTA阻断了X-、A-和B-LC的活性。图2B示出了纯化为His6标记的重组蛋白并与X-LC一起孵育的VAMP2(残基1-96)。通过SDS-PAGE和考马斯蓝染色对样品进行分析。X-LC将VAMP2(1-96)转化为两个较小的片段，表明X-LC切割VAMP2。图2C-2E示出了与X-LC一起孵育的VAMP2(1-96)。然后通过质谱(LC-MS/MS)分析全蛋白样品以确定切割片段的精确分子量。在图2C中绘制了在运行时间(RT，X轴)中来自HPLC柱的洗脱的肽峰。两种切割产物的质谱数据分别在图2D和2E中示出，其中对于每个信号标记了质荷比(m/z)。通过用m乘以z，然后减去z来推出分子量。两种切割产物的蛋白质序列从上到下对应于SEQ ID NO：61和62，并在图2C中示出。图2F示出了VAMP 1、2、3、4、5、7、8、Sec22b和Ykt6之间的序列比对，其中BoNT/B、D、F、G和X的切割位点加下划线，并且两个SNARE基序加框。序列从上到下对应于SEQ ID NO:63至71。图2G示出了HA标记的VAMP 1、3、7和8以及myc标记的Sec22b和通过瞬时转染在HEK293细胞中表达的Ykt6。将细胞裂解物与X-LC一起孵育，并进行检测HA或Myc标签的免疫印迹分析。肌动蛋白用作上样对照。X-LC切割VAMP 1、3和Ykt6，但不切割VAMP 7、8和Sec22。图2H示出与X-LC(100nM)一起孵育指定时间的GST标记的Ykt6。通过SDS-PAGE和考马斯蓝染色对样品进行分析。X-LC切割Ykt6。图2I示出与X-LC一起孵育指定时间的VAMP2(33-86)、VAMP4(1-115)和VAMP5(1-70)的GST标记的细胞质结构域。通过SDS-PAGE和考马斯蓝染色对样品进行分析。X-LC切割VAMP4和VAMP5二者。切割大多数VAMP5需要更长的孵育时间(360分钟)。注意到VAMP5蛋白含有另外的条带，其是降解产物或细菌蛋白质污染物，其在SDS-PAGE上的运行与切割产物接近(但不相同)。图2J示出了如图2A中所述进行的实验，不同之处在于检测到VAMP4和Sec22b。检测作为上样对照的突触结合蛋白

(Synaptotagmin I,Syt I)。X-LC切割BDE中的天然VAMP4。

[0086] 图3A-3E示出通过蛋白水解切割LC与H_N之间的接头区来活化BoNT/X。图3A示出了七种BoNT和BoNT/X的LC与H_N之间的接头区的序列比对。序列从上到下对应于SEQ ID NO:72至79。BoNT/X在所有BoNT中具有最长的接头区,其除了LC和H_N中的两个保守的半胱氨酸外还含有额外的半胱氨酸。通过质谱法鉴定在有限的蛋白水解下的Lys-C切割位点。图3B示出了在介质中暴露于指定浓度的X-LC-H_N持续12小时的培养的大鼠皮质神经元。收获细胞裂解物并进行免疫印迹分析以检查神经元中的突触融合蛋白1、SNAP-25和VAMP2。肌动蛋白用作上样对照。并行地分析胰蛋白酶活化的BoNT/A的LC-H_N(A-LC-H_N)和BoNT/B的LC-H_N(B-LC-H_N)作为对照。X-LC-H_N进入神经元并切割VAMP2,如通过VAMP2免疫印迹信号丧失所表明的。由Lys-C活化的X-LC-H_N示出比未活化的X-LC-H_N显著提高的效力。X-LC-H_N比胰蛋白酶活化的B-LC-H_N和A-LC-H_N更强效,其在相同测定浓度下未示出在神经元中其SNARE底物的任何可检出的切割。图3C示出在有或没有DTT的情况下,通过有限的蛋白水解活化并通过SDS-PAGE和考马斯蓝染色分析的具有指示的半胱氨酸突变的X-LC-H_N突变体以及WT X-LC-H_N。在有或没有DTT的情况下,C423S突变导致两个50kDa片段。在没有DTT的情况下,携带C461S或C467S的突变体在100kDa处显示单条带,并且在存在DTT的情况下,其分离成两条～50kDa条带,表明H_N上的C461和C467二者均可与LC上的C423形成链间二硫键。一部分WT X-LC-H_N在SDS-PAGE凝胶的顶部形成聚集体。这些聚集体是由于分子间二硫键的形成,因为它们在存在DTT的情况下消失。突变三个半胱氨酸中的任一个消除了聚集体,表明分子间二硫键的形成是由于在接头区中存在额外的半胱氨酸。大多数活化的WT X-LC-H_N在没有DTT的情况下在SDS-PAGE凝胶上也分离成两个～50kDa条带。这是由于图3D中描述的二硫键混编(shuffling)。图3D示出了通过有限的蛋白水解活化,然后与指定浓度的NEM预孵育以阻断二硫键混编的WT X-LC-H_N。然后在存在或不存在DTT的情况下通过SDS-PAGE和考马斯蓝染色对样品进行分析。在没有DTT的情况下,在NEM处理后大多数WT X-LC-H_N以100kDa的单条带存在,这表明WT X-LC-H_N主要含有链间二硫键。图3E示出了如图3B中所述进行的实验,不同之处在于将神经元暴露于WT或指定的X-LC-H_N突变体。使LC上的半胱氨酸(C423)突变消除了X-LC-H_N的活性,而使H_N上的两个半胱氨酸之一(C461或C467)突变则不影响X-LC-H_N对神经元的活性。这些结果证实,链间二硫键的形成对于X-LC-H_N的活性是必需的。

[0087] 图4A-4F示出了全长BoNT/X对培养的神经元和在小鼠体内有活性。序列如下:LVPR-GS(SEQ ID NO:80)、LPETGG-His6(SEQ ID NO:81)、GG-His6(SEQ ID NO:82)和LPETGS(SEQ ID NO:59)。图4A示出了使用定位酶连接方法合成全长BoNT/X的示意图。图4B示出了通过SDS-PAGE和考马斯蓝染色分析定位酶连接反应混合物和指定的对照组分。星号标记由于分子间二硫键引起的蛋白质的聚集体,因为这些聚集体在存在DTT的情况下消失。分子量标志物在泳道1中(从左侧开始)。全长BoNT/X(X-FL)仅出现在定位酶连接混合物中(泳道7和泳道14)。图4C示出了在介质中暴露于相同量(5μl)的定位酶连接混合物或指定的对照组分12小时的神经元。通过免疫印迹分析细胞裂解物。由于X-LC-HN在反应混合物中的高浓度,因此X-LC-HN单独切割一些VAMP2。与单独的X-LC-HN相比,含有X-LC-HN和X-HC二者但不含定位酶的对照混合物略微增强了VAMP2的切割,可能是因为X-HC通过非共价相互作用与X-LC-HN缔合。相对于没有定位酶的X-LC-HN和X-HC的混合物,通过定位酶连接X-LC-HN和X-HC增强了VAMP2的切割,表明连接的X-FL在神经元中是有功能的。图4D示出如在图b(泳道7)

中所述制备的定位酶反应混合物在小鼠中使用DAS测定法进行分析在体内是有活性的。注射的肢体出现松弛性瘫痪，且脚趾在12小时内未扩散。左侧肢体没有注射毒素，用作对照。图4E示出使BoNT/AG、镶嵌毒素(mosaic toxin)BoNT/DC和BoNT/X进行斑点印迹分析(每种毒素0.2μg，点在硝酸纤维素膜上)，使用四种马抗血清(三价抗BoNT/A、B和E、抗BoNT/C、抗BoNT/DC和抗BoNT/F)，以及两种山羊抗血清(抗BoNT/G和抗BoNT/D)。BoNT/X由纯化的X-LC-HN和X-HC以1:1的比例构成。这些抗血清识别其相应的靶毒素，但它们都没有识别BoNT/X。图4F示出在大肠杆菌中纯化全长无活性形式的BoNT/X(BoNT/XRY)作为His6标记的重组蛋白，并在有或没有DTT的情况下，通过SDS-PAGE和考马斯蓝染色进行分析。

[0088] 图5是示出了梭菌神经毒素的分布和关系的系统发生树。该树表示来自Jackhmmer搜索的不同BoNT和TeNT序列的关系。BoNT/X被圈出。

[0089] 图6示出完整VAMP2(1-96)的质谱分析。通过LC-MS/MS质谱分析His6标记的VAMP2(1-96)。HPLC谱与蛋白质序列一起列在左图中。全长VAMP2(1-96)的质谱数据在右图中示出，并对应于SEQ ID NO:83，其中为每个信号标记m/z值。

[0090] 图7A-7F示出了通过X-LC鉴定GST-VAMP2(33-86)上的切割位点。图7A示出了与或不与X-LC一起孵育的GST标记的VAMP2(33-86)。通过SDS-PAGE和考马斯蓝染色对样品进行分析。图7B-7C示出了通过LC-MS/MS质谱分析的完整GST标记的VAMP2(33-86)。HPLC谱在图7B中示出。质谱数据在图7C中示出，图7C中标记了蛋白质序列(SEQ ID NO:84)。标记了VAMP2(33-66)和VAMP2(67-86)。图7D-7E示出用X-LC孵育的GST标记的VAMP2(33-86)。然后通过LC-MS/MS质谱对样品进行分析。HPLC谱在图7D中示出。由X-LC产生的C端片段(SEQ ID NO:85)的质谱数据在图7E中示出。N端片段(SEQ ID NO:86)的质谱数据在图7F中示出。C端和N端片段的蛋白质序列在图7E-7F中示出，并分别对应于SEQ ID NO:85和86。

[0091] 图8A-8B示出XA嵌合毒素对神经元有活性。图8A示出通过定位酶将X-LC-H_N与A-H_C连接而产生的XA嵌合毒素，类似于产生如图4A所述的X-FL。通过SDS-PAGE和考马斯蓝染色分析定位酶连接混合物和指定的对照组分。连接是高效的，因为大多数X-LC-H_N连接到XA嵌合毒素中。图8B示出了在介质中暴露于指定的对照组分或定位酶连接的XA混合物(5μl)12小时的大鼠皮质神经元。通过免疫印迹分析细胞裂解物。由于X-LC-H_N在反应混合物中的高浓度，因此X-LC-H_N单独切割一些VAMP2。连接的XA切割神经元中的VAMP2。

[0092] 图9示出了使H_N中的额外半胱氨酸和H_C中的半胱氨酸突变不影响BoNT/X的活性。通过定位酶连接将X-H_C(C1240S)与WT X-LC-H_N、X-LC-H_N(C461S)或X-LC-H_N(C467S)连接。在介质中将神经元暴露于定位酶连接混合物或对照组分(5μl)12小时。通过免疫印迹分析细胞裂解物。使C1240和H_N上的一个半胱氨酸(C461或C467)突变不影响BoNT/X的活性，因为连接的突变体毒素能够进入神经元并切割VAMP2。

[0093] 图10示出了针对BoNT的七种血清型产生的抗血清中和神经元上的其靶BoNT。将培养的大鼠皮质神经元暴露于指定的BoNT，与或没有与指定的抗血清预孵育。12小时后收获细胞裂解物并进行免疫印迹分析。所有的抗血清均特异性中和其靶BoNT，而不影响不同BoNT血清型的活性，从而验证这些抗血清的特异性和效力。BoNT的浓度为:BoNT/A(50pM)、BoNT/B(2nM)、BoNT/C(1.5nM)、BoNT/D(100pM)、BoNT/E(0.5nM)、BoNT/F(0.5nM)、BoNT/G(5nM)。针对BoNT/A/B/E的抗血清以每孔20μl使用。所有其他抗血清以每孔10μl使用。将BoNT与指定的抗血清在37℃下预孵育30分钟，然后添加到培养基中。

[0094] 图11A-11C示出了BoNT/X_{RY}对神经元没有活性。图11A示出了以指定浓度暴露于BoNT/X_{RY}的培养的大鼠皮质神经元。通过免疫印迹分析细胞裂解物。VAMP2未被切割，表明BoNT/X_{RY}对神经元没有活性。图11B示出了BoNT/X_{RY}(4-12％BisTris，MOPS缓冲液)的细胞裂解物和上清液(S/N)表达的SDS-PAGE分析。对应于BoNT/X的150kDa条带在裂

[0095] 解物和可溶性级分二者中都清晰可见。图11C示出了高度纯化的BoNT/X_{RY}(4-12％BisTris，MOPS缓冲液)的最终样品的SDS-PAGE分析。

[0096] 对应于BoNT/X的150kDa的单条带清晰可见并显示～90％的纯度。

[0097] 图12A-12F示出了BoNT/X与所有四种脑神经节苷脂结合。图12A-12D分别示出了与GD1a(图12A)、GT1b(图12B)、GD1b(图12C)和GM1(图12D)结合的BoNT/X(正方形)和A-Hc(圆形)。曲线对应于一式三份ELISA测定的平均值，并用Prism7(GraphPad软件)进行拟合。图12E示出了与图12F中BoNT/A的总结合相比，所有四种神经节苷脂的BoNT/X结合的总结。

[0098] 图13A-13D示出了通过质谱分析鉴定Ykt6上X-LC的切割位点。图13A-13D示出了在SDS-PAGE上分离的10μg GST-标记的Ykt6(1-192)，与或没有与X-LC预孵育(图13A)。如所示切下蛋白质条带并用胰凝乳蛋白酶消化。将消化的肽脱盐并通过反相HPLC通过与ESI-MS偶联的C18柱进行分析。未用X-LC预处理的GST-Ykt6的HPLC谱在图13B中示出，且用X-LC预处理的样品在图13C中示出。在用X-LC预处理的样品中，一种肽被鉴定为比未暴露于X-LC的样品(用星号表示)高约100倍强度。该肽在37分钟RT洗脱，m/z＝611(图13D)，其仅符合Ykt6中的肽序列ESLLERGEKLDDLVSK(SEQ ID NO:87)，表明这是位于X-LC的切割位点的N端侧的肽。因此，切割位点是Ykt6中的K173-S174。

[0099] 图14A-14E示出了通过质谱分析鉴定在VAMP4和VAMP5上X-LC的切割位点。图14A-14E示出了如图13中所述进行的实验，不同之处在于分析了VAMP4(图14B，14C)和VAMP5(图14D，14E)。图14B是标记VAMP4中切割位点的N端位点的肽。肽DELQDK的序列对应于SEQ ID NO:88。图14C是标记VAMP4中切割位点的C端位点的肽。肽SESLSDNATAF的序列对应于SEQ ID NO:89。图14D是标记VAMP5中切割位点的N端位点的肽。肽AELQQR的序列对应于SEQ ID NO:90。图14E是标记VAMP5中切割位点的C端位点的肽。肽SDQLLDMSSTF的序列对应于SEQ ID NO:91。因此，切割位点被确定为VAMP4中的K87-S88和VAMP5中的R40-S41。

具体实施方式

[0100] 肉毒梭菌神经毒素(BoNT)是由梭菌属细菌产生的细菌毒素家族，具有七种确立的血清型(BoNT/A-G)[1-3]。它们是最危险的潜在生物恐怖剂之一，被美国疾病控制中心(Center for Disease Control，CDC)列为“A类”选择剂[4]。这些毒素是作为单一多肽产生的，并且可通过细菌或宿主蛋白酶分成轻链(LC，～50kDa)和重链(H_C，～100kDa)。这两条链通过链间二硫键保持连接。H_C含有两个亚结构域：N端H_N结构域，其介导LC跨内体膜的易位；以及C端H_C结构域，其介导与神经元上的受体的结合。一旦LC易位进入到胞质溶胶中，则链间二硫键就会还原[5,6]。释放的LC充当蛋白酶以特异性切割一组神经元蛋白：BoNT/A、C和E在称为SNAP-25的蛋白质上的不同位点处切割；BoNT/B、D、F和G在囊泡蛋白VAMP的不同位点处切割；并且BoNT/C也切割跨膜蛋白质突触融合蛋白1[1-3]。这三种蛋白质形成复合物，称为SNARE复合物，这对于释放神经递质至关重要[7,8]。切割这三种SNARE蛋白中的任何一种阻断神经递质从神经元释放，因此使肌肉瘫痪。

[0101] BoNT是已知的最强效的毒素，并导致称为肉毒中毒(botulism)的人和动物疾病[3]。肉毒中毒的主要形式是摄入受BoNT污染的食物(食物肉毒中毒)。还存在其他形式，例如婴儿肉毒中毒，其是由于婴儿中产生毒素之细菌的肠定植。BoNT总是与另一种称为NTNHA(无毒非血凝素蛋白(non-toxic non-hemagglutinin protein))的150kDa蛋白质一起产生，该蛋白质与BoNT形成pH依赖性复合物并保护BoNT免受胃肠道中蛋白酶的影响[9]。在两种类型的基因簇中发现编码BoNT和NTNHA的基因：(1)HA簇，其含有三种保守蛋白HA17、HA33和HA70的基因，其与BoNT/NTNHA形成复合物并促进毒素穿过肠上皮屏障的吸收[10-12]。(2)OrfX簇，其编码具有未知功能的保守的OrfX1、OrfX2、OrfX3和P47蛋白[13]。

[0102] 由于局部注射微量的毒素可削弱靶区域的神经元活动，因此BoNT已被用于治疗越来越多的医学病症[14-16]，包括肌痉挛、慢性疼痛、膀胱活动过度症(overactive bladder)问题以及用于化妆品应用。BoNT的销售在2011年已超过15亿美元，且预计到2018年达到29亿。

[0103] BoNT传统上通过小鼠中的中和测定来进行分型，通过在有或没有针对已知BoNT的抗血清的情况下将梭菌属细菌的培养上清液注射到小鼠中。由Georgina Burke于1919年建立第一个著名的血清型BoNT/A和BoNT/B[18]。七种类型的最后一种BoNT/G于1969年从阿根廷的土壤样品中识别[19]。自1970年以来一直没有识别新的BoNT血清型。在1990年代确定每种BoNT的蛋白质序列后，该分类仍然适用。七种BoNT中任意两对之间的序列同一性为32％至65.3％。在其医学用途时代之前，已经鉴定并表征了所有七种BoNT。因此，没有关于这些毒素中任一种的任何专利。任何公司都可自由地生产和销售这七种BoNT中的任一种。在七种类型中，BoNT/A和BoNT/B是目前FDA批准用于人的两种毒素[14-16]。BoNT/A是用于医疗和化妆品应用二者的主要类型，以来自Allergan Inc.的Botox、来自IPSEN Inc.的Dysport和来自Merz Inc的Xeomin销售。BoNT/B由USWorld Med以Myobloc销售。由于以下两个主要原因，对于开发其他BoNT类型作为治疗性毒素有相当大的兴趣：

[0104] (1)治疗的主要限制是在患者中产生针对BoNT/A或BoNT/B的中和抗体，这使得使用相同毒素的将来的治疗无效[20]。在这种情况下，患者将需要用不同类型BoNT进行治疗。这就是为什么BoNT/B经常用于治疗在治疗期间产生针对BoNT/A之中和抗体的患者，但是对于已经产生针对BoNT/A和BoNT/B之抗体的患者需要替代的毒素。

[0105] (2)尽管所有BoNT共有相同的结构和功能，但它们之间也存在相当大的差异。例如，BoNT/A切割SNAP-25并使用蛋白质SV2作为其受体，而BoNT/B切割VAMP并使用蛋白质突触结合蛋白(Syt)作为其受体[21-27]。这些功能变化可转化为靶向不同类型神经元的治疗效力的潜在差异。此外，七种毒素之间的稳定性和治疗持续时间也可以不同。因此，不同的毒素类型可具有其优于BoNT/A和BoNT/B的优势。

[0106] 近年来基因组测序的迅速进展揭示了BoNT的显著多样性[28,29]。首先，存在多种亚型，其可被相同的抗血清识别，但在蛋白质序列上含有显著的变化水平(差异为2.6％～31.6％)[28,30]。例如，BoNT/A含有8种已知的亚型，称为BoNT/A1至A8[13]。此外，存在多种镶嵌毒素，可能源自毒素基因的重组。例如，2013年报告了“H型”，但后来它被认为是嵌合毒素，因为它的LC与BoNT/F亚型BoNT/F5的LC共有约80％的同一性，并且其H_C与BoNT/A1的H_C共有约84％同一性[31-34]。与此一致，这种毒素可被针对BoNT/A的可用抗血清识别并中和[33]。

[0107] 编码BoNT的基因簇可在质粒、细菌噬菌体或染色体上，表明毒素基因是可移动的并且可进行水平基因转移(horizontal gene transfer)[13]。还存在梭菌属细菌菌株含有两

种甚至三种不同毒素基因的情况[32,35,36]。在这些情况下，一种毒素(用大写字母标出)通常较其他毒素(用小写字母标出)以更高水平表达。例如，表达高水平BoNT/B和低水平BoNT/F的菌株被称为BoNT/Bf菌株。还存在如下情况，一种毒素被表达，但另一种毒素未被表达，其被称为沉默毒素(通常用()标记)。例如，加利福尼亚州对婴儿肉毒中毒病例的调查显示，8％的菌株是BoNT/A(B)，这意味着这些菌株含有BoNT/A和BoNT/B这两种基因，但仅表达可检出水平的BoNT/A[37-39]。

[0108] 如本公开内容的附图和实施例中所示，搜索公布的梭菌属细菌基因组序列数据库，并鉴定在肉毒梭菌菌株111的染色体上编码的新BoNT基因(下文中称为“BoNT/X”)。菌株111于1996年在日本首次从婴儿肉毒中毒患者中分离出来[40]。已经表明，来自小鼠中的菌株111的毒性可被BoNT/B抗血清中和[40]。后来证实该菌株表达在质粒上编码的BoNT/B的亚型BoNT/B2[41,42]。作为菌株111的基因组序列的一部分，BoNT/X的序列于2015年2月存入PubMed数据库中。之前未对BoNT/X进行表征。尚不清楚它是否在菌株111中表达以及它是否是功能性毒素。

[0109] 本文中还提供了BoNT/X在功能水平的表征。发现其LC在与所有其他BoNT的已知靶位点不同的位点处切割VAMP。发现通过定位酶通过共价连接无毒片段产生的全长毒素进入培养的神经元并切割神经元中的VAMP，诱导小鼠中的松弛性瘫痪。最后，发现毒素不被针对所有七种已知BoNT产生的抗血清识别，将BoNT/X确立为新的BoNT血清型。它的鉴定对开发有效的对策提出了紧迫的挑战。它还有可能被开发成新的治疗性毒素，并可用于产生具有潜在不同药理学特性的嵌合毒素。

[0110] 本文中使用的术语“肉毒梭菌神经毒素(BoNT)多肽”涵盖来自本文中所述的肉毒神经毒素的任何多肽或片段。在一些实施方案中，术语BoNT是指全长BoNT。在一些实施方案中，术语BoNT是指其中可执行BoNT进入神经元并抑制神经递质释放的总细胞机制的BoNT片段。在一些实施方案中，术语BoNT仅指BoNT的片段，而不需要该片段具有任何特定功能或活性。例如，BoNT多肽可以指BoNT(例如，BoNT/X)的轻链(LC)。在整个本公开内容中对于“肉毒梭菌神经毒素”可用的其他术语可以是BoNT、肉毒毒素或肉毒梭菌(C.Botulium)毒素。应理解，这些术语可互换使用。“BoNT/X”是指在本公开内容中描述和表征的新的BoNT血清型。还提供了BoNT/X蛋白序列(GenBank No.BAQ12790.1；四个半胱氨酸加下划线并为粗体)：

[0111] MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPERYNFTNNTNDLNIPSEPIME
ADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKPEGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNI
VSNLQANLVIYGPGPDIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFVKRE
FAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFEELLTFGGIDSKAISSLIIKKIIET
AKNNYTTLISERLNTVTVENDLLKYIKNKIPVQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVR
KHYLKERPIDPIYVNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNGLLYNAI
YRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGCIEVENKDLFLISNKDSLNDINLSEEKIKPETTVFFKD
KLPPQDITLSNYDFTEANSIPSISQQNILERNEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIR
VELTDSVDEALSNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKSSDTLAIVP
YIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVIGGELAREQVEAIVNNALDKRDQKWA
EVYNITKAQWWGTIHLQINTRLAHTYKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLN
KSVEQAMKNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTNLSSSLRRKVSIR
LNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGKIKDLSGTTSDINIGSDIELADGRENKAIKIK
GSENSTIKIAMNKYLRFSATDNFSISFWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDH
NNSIKIVTPDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRLKNNRDTQAFTLLD
QFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYNKKYYLQTQDKPGKGLIREYWSSFGYDYVILS
DSKTITFPNNIRYGALYNGSKVLIKNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTH
DLTTDFEIIQRQEKYRNYCQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSAWYFQNYENLNLRKHT
KTNWYFIPKDEGWDED (SEQ ID NO: 1)

[0112] “经修饰肉毒梭菌神经毒素(BoNT)”涵盖在氨基酸序列中包含的任何修饰(例如截短、添加、氨基酸替换及其任何组合)的BoNT。例如,在C461或C467处包含氨基酸替换突变的BoNT/X是经修饰BoNT。在另一个实例中,全长BoNT的片段或结构域(例如,蛋白酶结构域或LC)被认为是经修饰BoNT。在一些实施方案中,BoNT的结构域还可包含氨基酸替换突变,例如在BoNT/X的C461或C467位置处包含替换突变的蛋白酶结构域。

[0113] 当用于描述本公开内容的BoNT的作用时,术语“进入细胞”涵盖BoNT与低或高亲和力受体复合物的结合、BoNT与神经节苷脂的结合、毒素内化、毒素轻链易位进入到细胞质中以及BoNT底物的酶促修饰。

[0114] 本文中使用的术语“肉毒梭菌神经毒素(BoNT)蛋白酶结构域”与“轻链(LC)”同义。BoNT蛋白酶结构域位于BoNT的轻链中,并因此也称为LC。该术语意指可执行中毒过程的酶促靶标修饰步骤的BoNT结构域。如果提及来自特定BoNT血清型的LC,则使用术语“血清型-LC”。例如,“X-LC”意指来自BoNT/X的LC多肽。BoNT蛋白酶结构域特异性靶向肉毒梭菌毒素底物并且涵盖肉毒梭菌毒素底物(例如,SNARE蛋白例如SNAP-25底物、VAMP底物和突触融合蛋白底物)的蛋白水解切割。在BoNT(例如,BoNT/X、BoNT/A、BoNT/B、BoNT/C等)中,蛋白酶结构域或LC被认为对应于BoNT/X的约第1至439位氨基酸。结构域边界可变化约25个氨基酸。例如,蛋白酶结构域可对应于BoNT/X的第1至414或1至464位氨基酸。在一些实施方案中,蛋白酶结构域可对应于BoNT/X的第1至438、1-至437、1至436、1至435、1至434、1至433、1至432、1至431、1至430、1至429、1至439、1至440、1至441、1至442、1至443、1至444、1至445、1至446、1至447、1至448或1至449位氨基酸。

[0115] 本文中使用的术语“肉毒梭菌神经毒素(BoNT)易位结构域”与“H_N结构域”同义,并且意指可执行中毒过程的易位步骤(其介导BoNT轻链易位)的BoNT结构域。因此,H_N促进BoNT轻链移动穿过膜进入到细胞的细胞质。H_N的非限制性实例包括BoNT/A H_N、BoNT/B H_N、

BoNT/C1 H_N、BoNT/D H_N、BoNT/E H_N、BoNT/F H_N、BoNT/G H_N、和BoNT/X H_N。易位结构域位于重链(H_C)的N端，并因此也称为H_N。应理解，这些术语在本文中可互换使用。

[0116] 本文中使用的术语“接头区”是指BoNT蛋白酶结构域和易位结构域之间的氨基酸序列。接头在第461和467位包含两个半胱氨酸，其中一个与蛋白酶结构域中的半胱氨酸C423形成分子间二硫键(C461-C423二硫键或C467-C423二硫键)。这种二硫键的形成对于BoNT/X的活性是必不可少的。

[0117] 本文中使用的术语“LC-H_N”是指包含蛋白酶结构域、接头区和易位结构域的BoNT多肽。如果提及来自特定BoNT血清型的LC-H_N，则使用术语“血清型-LC-H_N”。例如，“X-LC-H_N”意指来自BoNT/X的LC-H_N多肽。LC-H_N多肽被认为对应于BoNT/X的约第1至892位氨基酸。结构域边界可变化约25个氨基酸。例如，LC-H_N多肽可对应于BoNT/X的约第1至917或1至867位氨基酸。在一些实施方案中，LC-H_N多肽可对应于BoNT/X的第1至893、1至894、1至895、1至896、1至897、1至898、1至899、1至900、1至901、1至902、1至892、1至891、1至890、1至889、1至888、1至887、1至886、1至885、1至884或1至883位氨基酸。

[0118] 本文中使用的术语“肉毒梭菌神经毒素(BoNT)受体结合结构域”与“H_C结构域”同义，并且意指可执行中毒过程的细胞结合(包括例如BoNT与位于靶细胞质膜表面上的BoNT特异性受体系统的结合)步骤的任何天然存在的BoNT受体结合结构域。本公开内容的一些方面涉及来自血清型X(BoNT/X)的经修饰BoNT受体结合结构域。在一些实施方案中，“经修饰BoNT/X受体结合结构域”在对应于BoNT/X(SEQ ID NO:1)中C1240的位置处包含氨基酸替换。受体结合结构域或H_C被认为对应于BoNT/X的约第893至1306位氨基酸。结构域边界可变化约25个氨基酸。例如，受体结合结构域或H_C可对应于第868至1306或918至1306位氨基酸。在一些实施方案中，受体结合结构域或H_C可对应于BoNT/X的第893至1306、894至1306、895至1306、896至1306、897至1306、898至1306、899至1306、900至1306、901至1306、902至1306、892至1306、891至1306、890至1306、889至1306、888至1306、887至1306、886至1306、885至1306、884至1306或883至1306位氨基酸。

[0119] “分离的”意指对于在天然状态下存在的通常与其相伴的组分具有不同游离度的物质。“分离”表示与原始来源或周围环境的分隔度(degree of separation)，例如，与细胞或与侧翼DNA或DNA的天然来源的分隔度。术语“纯化的”用于指物质(例如多肽)相对于制剂的其他组分(例如，其他多肽)而言是“基本上纯的”。它可以指多肽相对于其他组分而言是至少约50％、60％＞、70％＞或75％、优选至少约85％、更优选至少约90％、并且最优选至少约95％纯的。对于多肽而言，术语“基本上纯的”或“基本上纯化的”是指制剂含有低于约20％、更优选低于约15％、10％、8％、7％、最优低于约约5％、4％、3％、2％、1％或低于1％的一种或更多种其他组分(例如，其他多肽或细胞组分)。

[0120] 不指代特定氨基酸，术语“替换突变”可包括通常位于该位置处的野生型残基以外的任何氨基酸。这样的替换可用非极性(疏水性)氨基酸(例如甘氨酸、丙氨酸、缬氨酸、亮氨酸、异亮氨酸、甲硫氨酸、苯丙氨酸、色氨酸和脯氨酸)进行替代。替换可用极性(亲水性)氨基酸(例如丝氨酸、苏氨酸、半胱氨酸、酪氨酸、天冬酰胺和谷氨酰胺)进行替代。替换可用带电氨基酸(例如，带负电荷的氨基酸，例如天冬氨酸和谷氨酸；以及带正电荷的氨基酸，例如赖氨酸、精氨酸和组氨酸)进行替代。

[0121] 本文中所述的替换突变通常是以不同的天然存在的氨基酸残基进行替换，但在某

些情况下，也可替换非天然存在的氨基酸残基。本文中使用的术语非天然氨基酸是指天然存在或化学合成的非产生蛋白质(即非蛋白编码)的氨基酸。实例包括但不限于β-氨基酸(β3和β2)、高氨基酸(homo-amino acid)、脯氨酸和丙酮酸衍生物、3-取代的丙氨酸衍生物、甘氨酸衍生物、环取代的苯丙氨酸和酪氨酸衍生物、线性核心氨基酸、二氨基酸、D-氨基酸和N-甲基氨基酸。在一些实施方案中，氨基酸可以是经取代的或未经取代的。取代的氨基酸或取代基可以是卤代芳香族氨基酸或脂肪族氨基酸；疏水侧链上的卤代脂肪族或芳香族修饰；或者脂肪族或芳香族修饰。

[0122] 使用在Karlin和Altschul.Proc.Natl.Acad.Sci.USA 90:5873-77,1993中修改的Karlin和Altschul.Proc.Natl.Acad.Sci.USA 87:2264-68,1990的算法确定两个氨基酸序列的“同一性百分比”。这样的算法被并入到Altschul等J.Mol.Biol.215:403-10,1990的NBLAST和XBLAST程序(2.0版)中。可用XBLAST程序，得分＝50，字长＝3进行BLAST蛋白质搜索以获得与目标蛋白质分子同源的氨基酸序列。当两个序列之间存在空位时，可如Altschul等,Nucleic Acids Res.25(17):3389-3402,1997中所述使用Gapped BLAST。当使用BLAST和Gapped BLAST程序时，可使用各个程序(例如，XBLAST和NBLAST)的缺省参数(default parameter)。

[0123] 因此，本公开内容的一些方面提供了分离的BoNT多肽。在一些实施方案中，分离的BoNT多肽是全长BoNT/X多肽。在一些实施方案中，分离的BoNT多肽包含SEQ ID NO:1的氨基酸序列。在一些实施方案中，分离的BoNT/X多肽包含与SEQ ID NO:1具有至少85％同一性的氨基酸序列。例如，分离的BoNT多肽可包含与SEQ ID NO:1具有至少85％、至少86％、至少87％、至少88％、至少89％、至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％、至少99％或至少99.5％同一性的氨基酸序列。在一些实施方案中，分离的BoNT多肽包含与SEQ ID NO:1具有85％、86％、87％、88％、89％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％或100％同一性的氨基酸序列。在一些实施方案中，分离的BoNT多肽由SEQ ID NO:1的氨基酸序列组成。

[0124] 在一些实施方案中，分离的BoNT多肽是X-LC-H_N多肽。在一些实施方案中，分离的BoNT多肽包含SEQ ID NO:2的氨基酸序列。在一些实施方案中，分离的BoNT多肽包含与SEQ ID NO:2具有至少85％同一性的氨基酸序列。例如，分离的BoNT多肽可包含与SEQ ID NO:2具有至少85％、至少86％、至少87％、至少88％、至少89％、至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％、至少99％或至少99.5％同一性的氨基酸序列。在一些实施方案中，分离的BoNT多肽包含与SEQ ID NO:2具有85％、86％、87％、88％、89％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％或100％同一性的氨基酸序列。在一些实施方案中，分离的BoNT多肽由SEQ ID NO:2的氨基酸序列组成。

[0125] 在一些实施方案中，分离的BoNT多肽是X-LC多肽。在一些实施方案中，分离的BoNT多肽包含SEQ ID NO:3的氨基酸序列。在一些实施方案中，分离的BoNT多肽包含与SEQ ID NO:3具有至少85％同一性的氨基酸序列。例如，分离的BoNT多肽可包含与SEQ ID NO:3具有至少85％、至少86％、至少87％、至少88％、至少89％、至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％、至少99％或至少99.5％同一性的氨基酸序列。在一些实施方案中，分离的BoNT多肽包含与SEQ ID NO:3具有85％、86％、

87％、88％、89％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％或100％同一性的氨基酸序列。在一些实施方案中，分离的BoNT多肽由SEQ ID NO:3的氨基酸序列组成。

[0126] 可通过本领域中任何已知的表达外源蛋白质的技术(例如，通过慢病毒载体、通过AAV载体使LC编码序列直接转染到细胞中，或将X-LC与细胞穿透肽融合)将X-LC多肽单独引入其中出于研究或治疗目的期望切割BoNT底物(例如，SNARE蛋白)的细胞中。

[0127] 在一些实施方案中，本公开内容的BoNT多肽是全长BoNT/X，其包含蛋白酶结构域(LC)、接头区、易位结构域(H_N)和受体结合结构域(H_C)，其中所述接头区位于蛋白酶结构域与易位结构域之间。与其他BoNT一样，BoNT/X最初作为单多肽产生，并且通过裂解LC与H_N之间的接头区(细菌或宿主蛋白酶)而被活化。该过程被称为“活化”并且对于BoNT/X的活性是必需的。在切割后，LC与H_N通过链间二硫键保持连接，然后将LC易位进入到细胞的胞质溶胶中，其中二硫键被还原以便将LC释放到胞质溶胶中。与其他BoNT、C423和C467相比，BoNT/X含有两个保守的半胱氨酸。有趣的是，BoNT/X还含有额外的半胱氨酸(C461)，这是BoNT/X独有的。对于BoNT/X活性，需要形成链间二硫键(C423-C461或C423-C467)。

[0128] 除了接头区中的半胱氨酸之外，BoNT的受体结合结构域还含有另一个半胱氨酸C1240，其也可与BoNT/X中的其他半胱氨酸形成分子间二硫键。这些分子间二硫键导致BoNT/X聚集并使蛋白质不稳定(图4B)。替换对于BoNT/X活性不需要的半胱氨酸可产生具有提高的稳定性的BoNT/X多肽。

[0129] 因此，本公开内容的一些方面提供了经修饰BoNT/X多肽，其包含C461、C467或C1240中的一个或更多个替换突变，其比野生型BoNT/X更稳定且具有相当的活性。半胱氨酸可被消除二硫键形成的任何氨基酸替换。在一些实施方案中，半胱氨酸被丝氨酸(S)或丙氨酸(A)替换。可存在于本公开内容的经修饰BoNT中的替换突变的可能组合是但不限于：C461S、C461A、C467S、C467A、C1240S、C1240A、C461S/C1240S、C461A/C1240S、C461S/C1240A、C467A/C1240A、C467S/C1240S、C467A/C1240S、C467S/C1240A和C467A/C1240A。“/”表示双重突变。在一些实施方案中，本公开内容的经修饰BoNT/X多肽包含SEQ ID NO:4至17中任一个的氨基酸序列。在一些实施方案中，经修饰BoNT/X多肽包含与SEQ ID NO:4至17中任一个具有至少85％同一性的氨基酸序列，并且不具有SEQ ID NO:1的氨基酸序列。例如，经修饰BoNT/X多肽可包含与SEQ ID NO:4至17中任一个具有至少85％、至少86％、至少87％、至少88％、至少89％、至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％、至少99％或至少99.5％同一性的氨基酸序列，并且不具有SEQ ID NO:1的氨基酸序列。在一些实施方案中，经修饰BoNT/X多肽包含与SEQ ID NO:4至17中任一个具有85％、86％、87％、88％、89％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％或100％同一性的氨基酸序列，并且不具有SEQ ID NO:1的氨基酸序列。在一些实施方案中，经修饰BoNT/X多肽由SEQ ID NO:4至17中任一个的氨基酸序列组成。

[0130] 在一些实施方案中，本公开内容的经修饰BoNT多肽是包含本文中所述的替换突变的经修饰BoNT/X-LC-H_N多肽。在一些实施方案中，经修饰BoNT/X-LC-H_N在对应于SEQ ID NO:2中的C461或C467的位置处包含一个单替换突变。在一些实施方案中，经修饰BoNT/X-LC-H_N包含对应于SEQ ID NO:2中的C461A、C461S、C467A或C467S的一个单替换突变。在一些实施方案中，本公开内容的经修饰BoNT/X多肽包含SEQ ID NO:18至21中任一个的氨基酸序列。

在一些实施方案中，经修饰BoNT/X-LC-H_N多肽包含与SEQ ID NO:18至21中任一个具有至少85％同一性的氨基酸序列，并且不具有SEQ ID NO:2的氨基酸序列。例如，经修饰BoNT/X-LC-H_N多肽可包含与SEQ ID NO:18至21中任一个具有至少85％、至少86％、至少87％、至少88％、至少89％、至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％、至少99％或至少99.5％同一性的氨基酸序列，并且不具有SEQ ID NO:2的氨基酸序列。在一些实施方案中，经修饰BoNT/X-LC-H_N多肽包含与SEQ ID NO:18至21中任一个具有85％、86％、87％、88％、89％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％或100％同一性的氨基酸序列，并且不具有SEQ ID NO:2的氨基酸序列。在一些实施方案中，经修饰BoNT/X-LC-H_N多肽由SEQ ID NO:18至21中任一个的氨基酸序列组成。

[0131] 包含一个或更多个本文中所述的替换突变(例如，在C461、C467或C1240中)的经修饰BoNT多肽不形成引起蛋白质聚集的分子间二硫键，并因此比其相应的野生型蛋白质更稳定。BoNT多肽的活性不受半胱氨酸中的替换突变的影响。因此，经修饰BoNT/X由于其提高的稳定性可比野生型BoNT/X更适合于治疗用途。

[0132] 本公开内容的另一些方面提供了包含本文中所述的BoNT/X-LC-H_N和来自不同BoNT的受体结合结构域(H_C)的嵌合BoNT。例如，受体结合结构域可来自BoNT/A、BoNT/B、BoNT/C、BoNT/D、BoNT/E、BoNT/E、BoNT/F和BoNT/G中任一种。因此，本文中考虑的嵌合BoNT包括BoNT/X-LC-H_N-A-H_C、BoNT/X-LC-H_N-B-H_C、BoNT/X-LC-H_N-C-H_C、BoNT/X-LC-H_N-D-H_C、BoNT/X-LC-H_N-E-H_C、BoNT/X-LC-H_N-F-H_C和BoNT/X-LC-H_N-G-H_C。应理解，七种已知血清型(例如A、B、C、D、E、F或G)的任何亚型的H_C结构域适用于嵌合毒素。当提及BoNT/A、BoNT/B、BoNT/C、BoNT/D、BoNT/E、BoNT/F或BoNT/G时，它涵盖所有亚型。例如，BoNT/A有8种亚型，BoNT/A1、BoNT/A2、BoNT/A3、BoNT/A4、BoNT/A5、BoNT/A6、BoNT/A7或BoNT/A8，并且这些BoNT/A亚型中任一种的H_C适用于本公开内容的嵌合BoNT。类似地，BoNT/B的8种亚型(即BoNT/B1、BoNT/B2、BoNT/B3、BoNT/B4、BoNT/B5、BoNT/B6、BoNT/B7或BoNT/B8)中任一种的H_C适用于本公开内容的嵌合BoNT。

[0133] 在一些实施方案中，提供了BoNT/X-LC-H_N-A1-H_C(SEQ ID NO:22)、BoNT/X-LC-H_N-B1-H_C(SEQ ID NO:23)和BoNT/X-LC-H_N-C1-H_C(SEQ ID NO:24)。在一些实施方案中，嵌合BoNT多肽包含与SEQ ID NO:22至24中任一个具有至少85％同一性的氨基酸序列。例如，嵌合BoNT多肽可包含与SEQ ID NO:22至24中任一个具有至少85％、至少86％、至少87％、至少88％、至少89％、至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％、至少99％或至少99.5％同一性的氨基酸序列。在一些实施方案中，嵌合BoNT多肽包含与SEQ ID NO:22至24中任一个具有85％、86％、87％、88％、89％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％或100％同一性的氨基酸序列。在一些实施方案中，嵌合BoNT多肽由SEQ ID NO:22至24中任一个的氨基酸序列组成。

[0134] 在一些实施方案中，本公开内容的嵌合BoNT包含经修饰BoNT/X-LC-H_N，其在接头区中(例如在对应于SEQ ID NO:2的C461或C467的位置处)包含替换突变。例如，嵌合BoNT中的BoNT/X-LC-H_N可包含对应于SEQ ID NO:2的C461A、C467A、C461S或C467S的替换突变。例如，本公开内容的嵌合BoNT多肽可包含SEQ ID NO:25至30中任一个的氨基酸序列。在一些实施方案中，嵌合BoNT多肽包含与SEQ ID NO:25至30中任一个具有至少85％同一性的氨基

酸序列。例如，嵌合BoNT多肽可包含与SEQ ID NO:25至30中任一个具有至少85％、至少86％、至少87％、至少88％、至少89％、至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％、至少99％或至少99.5％同一性的氨基酸序列。在一些实施方案中，嵌合BoNT多肽包含与SEQ ID NO:25至30中任一个具有85％、86％、87％、88％、89％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％或100％同一性的氨基酸序列。在一些实施方案中，嵌合BoNT多肽由SEQ ID NO:25至30中任一个的氨基酸序列组成。

[0135] 为了产生嵌合毒素，例如BoNT/X-LC-H_N-A1-H_C毒素，将包含第约1至892位氨基酸(SEQ ID NO:2)的X-LC-H_N片段与BoNT/A、BoNT/B、BoNT/C、BoNT/D、BoNT/E、BoNT/E、BoNT/F和BoNT/G中任一种的受体结合结构域融合。不同BoNT的受体结合结构域对应于BoNT/B1的第约860至1291位氨基酸。应理解，X-LC-H_N片段和/或受体结合结构域的边界可变化1至25个氨基酸。例如，可用于嵌合毒素的X-LC-H_N片段可包含BoNT/X的第1至917或1至867位氨基酸。在一些实施方案中，可用于嵌合毒素的X-LC-H_N片段可包含BoNT/X的第1至893、1至894、1至895、1至896、1至897、1至898、1至899、1至900、1至901、1至902、1至892、1至891、1至890、1至889、1至888、1至887、1至886、1至885、1至884或1至883位氨基酸。类似地，可用于嵌合毒素的受体结合可包含对应于BoNT/X的第885至1291或835至1291位氨基酸。在一些实施方案中，可用于嵌合毒素的受体结合可包含对应于BoNT/B的第860至1291、861至1291、862至1291、863至1291、864至1291、865至1291、866至1291、867至1291、868至1291、869至1291、870至1291、860至1291、859至1291、858至1291、857至1291、856至1291、855至1291、854至1291、853至1291、852至1291或851至1291位的氨基酸。技术人员能够基于他/她在蛋白质同源性方面的知识，在有或没有序列比对软件的帮助下鉴定可用于本公开内容的嵌合毒素的结构域。使片段融合的方法是本领域技术人员公知的标准重组技术。

[0136] 本文中还考虑了经修饰BoNT/X多肽，其包含经修饰接头区，其中接头区包含特异性的蛋白酶切割位点。本文中使用的“特异性蛋白酶切割位点”是指特异性蛋白酶的识别和切割位点，与其相对的是超过一种非特异性蛋白酶识别和切割的序列。这样的特异性蛋白酶包括但不限于：凝血酶、TEV、PreScission、因子Xa、MMP-12、MMP-13、MMP-17、MMP-20、颗粒酶-B和肠激酶。可通过插入或替换接头区中的现有氨基酸(例如，替换BoNT/X多肽的第424至460位氨基酸)将特异性蛋白酶的切割位点添加至BoNT/X多肽的接头区。还提供了特异性蛋白酶切割位点序列的序列：LVPR|GS(凝血酶，SEQ ID NO:50)、ENLYFQ|G(TEV，SEQ ID NO:51)、LEVLFQ|GP(PreScission，SEQ ID NO:52)、IEGR|或IDGR|(因子Xa，SEQ ID NO:53或54)，DDDDK|(肠激酶，SEQ ID NO:55)和AHREQIGG|(SUMO蛋白酶，SEQ ID NO:56)。“|”表示发生切割的位置。

[0137] 本公开内容的另一些方面提供了BoNT/X多肽的功能表征。本公开内容的BoNT/X多肽、经修饰BoNT/X多肽和嵌合BoNT多肽可结合并进入靶细胞(例如，神经元)并切割其底物蛋白质，例如SNARE蛋白。本文中使用的术语“SNARE蛋白”是指SNAP(可溶性NSF附着蛋白(Soluble NSF Attachment Protein))受体，其是在酵母和哺乳动物细胞中由超过60个成员组成的大的蛋白质超家族。SNARE蛋白的主要作用是介导囊泡融合，即囊泡与其靶膜结合区室(例如溶酶体)的融合。研究最充分的SNARE蛋白是介导神经元中突触小泡与突触前膜对接的那些，例如SNAP-25、VAMP1、VAMP2、VAMP3、VAMP4、VAMP5、VAMP7、VAMP8、突触融合蛋白

1和Ykt6。这些SNARE蛋白中的数种是BoNT的底物。例如，已表明VAMP1、VAMP2、VAMP3、SNAP-25和突触融合蛋白1被已知的BoNT(例如，BoNT/A和BoNT/B)切割。

[0138] 本文中提供的数据显示BoNT/X切割作为BoNT的已知底物的SNARE蛋白。本公开内容的一个出人意料的发现是BoNT/X能够切割其他BoNT不能切割的数种SNARE蛋白，例如VAMP4、VAMP5和Ykt6。VAMP4广泛地表达并且已知其介导反式高尔基体网络(trans-Golgi network，TGN)与内体之间的囊泡融合，以及内体的同型融合。传统上已知BoNT限于靶向介导囊泡胞吐到质膜上的SNARE。BoNT/X是第一个能够切割介导细胞内的其他类型融合事件而不是以质膜作为目的地(destine)的SNARE的BoNT。VAMP4也可有助于异步的(asynchronous)突触囊泡胞吐作用、扩大体(enlargeosome)胞吐作用和神经元中活性依赖性的大量胞吞作用(activity-dependent bulk endocytosis，ADBE)。此外，VAMP4与免疫细胞中的颗粒释放有关。因此，BoNT/X可能在所有BoNT中具有调节免疫细胞中炎性分泌的独特潜力，其可在治疗上被利用。VAMP5主要在肌肉中表达，且其功能尚待确定。BoNT/X将是用于研究VAMP4和VAMP5功能的独特工具。Ykt6在内质网向高尔基体(Golgi)转运中发挥作用。它还在早期/将内体再循环至TGN转运中发挥作用。鉴定Ykt6作为本文中所述的BoNT多肽的底物是重要的，因为它开辟了用于通过BoNT在多种细胞中阻断分泌的新治疗应用。

[0139] 本公开内容的另一个出人意料的发现是BoNT/X在先前未描述的新位点切割SNARE蛋白。如本公开内容的实施例和附图中所示，BoNT/X在VAMP1、VAMP2和VAMP3中的氨基酸R66至S67之间切割。R66至A67是与所有其他BoNT的已确立的靶位点不同的新的切割位点(图2F)。它也是位于先前称为SNARE基序的区域内的唯一BoNT切割位点(图2F)。

[0140] 因此，本公开内容的BoNT多肽具有扩展的靶细胞和底物的谱。在一些实施方案中，BoNT多肽切割细胞中的SNARE蛋白。在一些实施方案中，BoNT多肽切割选自以下的SNARE蛋白：SNAP-25、VAMP1、VAMP2、VAMP3、VAMP4、VAMP5、Ykt6和突触融合蛋白1。在一些实施方案中，BoNT多肽切割VAMP1(SEQ ID NO:39)。在一些实施方案中，BoNT多肽在对应于SEQ ID NO:39的R66和A67的氨基酸残基之间切割VAMP1。在一些实施方案中，BoNT多肽切割VAMP2(SEQ ID NO:40)。在一些实施方案中，BoNT多肽在对应于SEQ ID NO:40的R66和A67的氨基酸残基之间切割VAMP2。在一些实施方案中，BoNT多肽切割VAMP3(SEQ ID NO:31)。在一些实施方案中，BoNT多肽在对应于SEQ ID NO:41的R66和A67的氨基酸残基之间切割VAMP3。在一些实施方案中，BoNT多肽切割VAMP4(SEQ ID NO:42)。在一些实施方案中，BoNT多肽在对应于SEQ ID NO:42的K87和S88的氨基酸残基之间切割VAMP4。在一些实施方案中，BoNT多肽切割VAMP5(SEQ ID NO:43)。在一些实施方案中，BoNT多肽在对应于SEQ ID NO:43的R40和S41的氨基酸残基之间切割VAMP5。在一些实施方案中，BoNT多肽切割Ykt6(SEQ ID NO:44)。在一些实施方案中，BoNT多肽在对应于SEQ ID NO:44的K173和S174的氨基酸残基之间切割Ykt6。

[0141] 在一些实施方案中，本公开内容的BoNT多肽切割靶细胞中的SNARE蛋白。本文中使用的“靶细胞”意指BoNT能够进入或使中毒的天然存在的细胞的细胞。在一些实施方案中，靶细胞是分泌细胞，例如神经元或分泌性免疫细胞。可以是BoNT靶细胞的神经元的实例包括但不限于运动神经元；感觉神经元；自主神经元；例如交感神经元和副交感神经元；非肽能神经元，例如胆碱能神经元、肾上腺素能神经元、去甲肾上腺素能神经元、血清素能神经元、GABA能神经元；以及肽能神经元，例如物质P神经元、降钙素基因相关肽神经元、血管活

性肠肽神经元、神经肽Y神经元、缩胆囊素神经元。

[0142] 本公开内容的BoNT多肽(例如BoNT/X或经修饰BoNT/X多肽),由于其切割VAMP4或Ykt6的能力,能够靶向除神经元之外的其他类型的分泌细胞。在一些实施方案中,由BoNT多肽靶向的分泌细胞是分泌性免疫细胞。本文中使用的"分泌性免疫细胞"是指分泌细胞因子、趋化因子或抗体的免疫细胞。这样的分泌性免疫细胞可以是固有免疫细胞,包括但不限于自然杀伤细胞、肥大细胞、嗜酸性粒细胞、嗜碱性粒细胞、巨噬细胞、中性粒细胞和树突细胞。本公开内容的BoNT多肽也可靶向分泌抗体的分泌性免疫细胞(例如,白细胞)。抗体分泌细胞的非限制性实例包括但不限于血浆B细胞、浆细胞(plasmocyte)、浆细胞(plasmacyte)和效应B细胞。在一些实施方案中,靶细胞是培养的细胞,例如培养的神经元或培养的分泌性免疫细胞。在一些实施方案中,靶细胞是体内的。在一些实施方案中,靶细胞来自哺乳动物。在一些实施方案中,哺乳动物是人。在实施方案中,哺乳动物是啮齿动物,例如小鼠或大鼠。

[0143] 在一些实施方案中,BoNT多肽抑制神经元活动。在一些实施方案中,BoNT多肽调节免疫应答。在一些实施方案中,BoNT多肽诱导松弛性瘫痪。"松弛性瘫痪"是指临床表现的特征为无力或瘫痪并且肌张力降低而没有其他明显原因(例如,创伤)。

[0144] 本公开内容的另一些方面提供了包含无活性蛋白酶结构域的经修饰BoNT/X多肽。这样的BoNT/X多肽(在本文中也称为"无活性BoNT/X")可进入靶细胞但由于蛋白酶结构域失活而不能切割底物蛋白质(例如,SNARE蛋白)。在一些实施方案中,无活性BoNT/X是X-LC-H_N片段,其包含:a)无活性蛋白酶结构域;b)接头区;以及c)易位结构域。在一些实施方案中,无活性BoNT/X是全长BoNT/X多肽,其包含:a)无活性蛋白酶结构域;b)接头区;c)易位结构域;以及d)受体结合结构域。在一些实施方案中,无活性蛋白酶结构域在对应于SEQ ID NO:1的R360、Y363、H227、E228或H231的位置处包含一个或更多个替换突变。在一些实施方案中,一个或更多个替换突变对应于SEQ ID NO:1中的R360A/Y363F、H227Y、E228Q或H231Y。应理解,无活性BoNT/X多肽可包含使蛋白酶结构域失活的任何突变。

[0145] 在一些实施方案中,无活性BoNT/X多肽包含SEQ ID NO:31至38中任一个的氨基酸序列。在一些实施方案中,无活性BoNT/X多肽包含与SEQ ID NO:31至38中任一个具有至少85%同一性的氨基酸序列。例如,无活性BoNT/X多肽可包含与SEQ ID NO:31至38中任一个具有至少85%、至少86%、至少87%、至少88%、至少89%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或至少99.5%同一性的氨基酸序列。在一些实施方案中,无活性BoNT/X多肽包含与SEQ ID NO:31至38中任一个具有85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、99.5%或100%同一性的氨基酸序列。在一些实施方案中,无活性BoNT/X多肽由SEQ ID NO:31至38中任一个的氨基酸序列组成。

[0146] 在一些实施方案中,无活性BoNT/X(例如,无活性X-LC-H_N或无活性全长BoNT/X)还在接头区中包含突变。在一些实施方案中,接头区中的修饰包含在对应于SEQ ID NO:1的C461或C467的位置处的一个单替换突变。在一些实施方案中,单替换突变对应于SEQ ID NO:1中的C461A、C461S、C467A或C467S。在一些实施方案中,无活性BoNT/X(例如,无活性全长BoNT/X)还在受体结合结构域中包含修饰。在一些实施方案中,受体结合结构域中的修饰包含在对应于SEQ ID NO:1的C1240的位置处的替换突变。

[0147] 还考虑包含本文中所述的无活性蛋白酶结构域的经修饰BoNT/X多肽可用作靶向人中细胞(例如,神经元)的递送工具。例如,经修饰BoNT/X可与其他治疗剂共价地或非共价地连接,并且充当靶向载剂以将治疗剂递送至人中的靶细胞。

[0148] 因此,本公开内容的另一方面涉及嵌合多肽分子,其包含与第二部分连接的无活性BoNT/X的第一部分,所述第一部分包含一个或更多个使蛋白酶结构域失活的替换突变。该分子的第二部分可以是生物活性分子,例如治疗剂(例如,多肽或非多肽药物)。分子的第一部分与第二部分的连接可以是共价的(例如,以融合蛋白的形式)或非共价的。这样连接的方法是本领域中已知的,并且本领域技术人员可容易地应用。当嵌合分子的第二部分是多肽并且嵌合分子是蛋白质形式时,提供了编码这样嵌合分子的核酸和核酸载体。

[0149] 还提供了包含核酸或核酸载体的细胞,以及表达这样嵌合分子的细胞。融合蛋白形式的嵌合分子可使用本文中公开的方法表达和分离。

[0150] 本公开内容的经修饰BoNT/X多肽、嵌合BoNT多肽或包含作为多肽(例如但不限于,包含SEQ ID NO:1至38中任一个的氨基酸序列的多肽)的第二部分的嵌合分子通常将通过在合适的细胞(例如,大肠杆菌(E.coli)或昆虫细胞)中表达形式的重组核酸产生并分离。可通过本领域中已知的任何方法获得编码本文中所述多肽的核酸,并确定核酸的核苷酸序列。

[0151] 本文中还提供了编码本文中公开的任何BoNT多肽的分离的和/或重组的核酸。编码本公开内容的分离的多肽片段的核酸可以是双链或单链的DNA或RNA。在某些方面,编码分离的多肽片段的主题核酸进一步理解为包括编码本文中所述的任一个经修饰BoNT多肽之变体的多肽的核酸。

[0152] 变体核苷酸序列包括通过一个或更多个核苷酸替换、添加或缺失而不同的序列,例如等位基因变体。在一些实施方案中,本公开内容的分离的核酸分子包含编码多肽的多核苷酸,其包含与SEQ ID NO:1至38中任一个具有至少85%、至少86%、至少87%、至少88%、至少89%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或至少99.5%同一性的氨基酸序列。在一些实施方案中,本公开内容的分离的核酸分子包含编码多肽的多核苷酸,其包含与SEQ ID NO:1至38中任一个具有85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%或100%同一性的氨基酸序列。

[0153] 在一些实施方案中,核酸包含在载体(例如表达载体)内。在一些实施方案中,载体包含与核酸可操作地连接的启动子。

[0154] 多种启动子可用于表达本文中所述的多肽,其包括但不限于巨细胞病毒(cytomegalovirus,CMV)中间早期启动子(intermediate early promoter)、病毒LTR(例如劳斯肉瘤病毒LTR、HIV-LTR、HTLV-1 LTR)、猿猴病毒40(simian virus 40,SV40)早期启动子、大肠杆菌lac UV5启动子和单纯疱疹tk病毒启动子。还可使用可调节的启动子。这样的可调节的启动子包括使用来自大肠杆菌的lac阻遏物作为转录调节子来调节携带lac操纵基因(lac operator)的哺乳动物细胞启动子的转录的那些[Brown,M.等,Cell,49:603-612(1987)]、使用四环素阻遏物(tetR)的那些[Gossen,M.,和Bujard,H.,Proc.Natl.Acad.Sci.USA 89:5547-5551(1992);Yao,F.等,Human Gene Therapy,9:1939-1950(1998);Shockelt,P.,等,Proc.Natl.Acad.Sci.USA,92:6522-6526(1995)]。

[0155] 其他系统包括FK506二聚体、使用astradiol、RU486、diphenol murislerone的VP16或p65或雷帕霉素。可诱导的系统可从Invitrogen、Clontech和Ariad获得。可使用包括具有操纵子的阻遏物的可调节启动子。在一个实施方案中，来自大肠杆菌的lac阻遏物可作为转录调节子发挥作用来调节携带lac操纵基因的哺乳动物细胞启动子的转录[M.Brown等，Cell，49:603-612(1987)]；Gossen和Bujard(1992)；[M.Gossen等，Natl.Acad.Sci.USA，89:5547-5551(1992)]将四环素阻遏物(tetR)与转录激活因子(VP16)组合以产生tetR-哺乳动物细胞转录激活子融合蛋白tTa(tetR-VP16)，与来自人巨细胞病毒(HCMV)主要立即早期启动子的携带tetO的最小启动子组合以产生tetR-tet操纵基因系统从而控制哺乳动物细胞中的基因表达。在一个实施方案中，使用四环素诱导型开关(Yao等，Human Gene Therapy；Gossen等，Natl.Acad.Sci.USA，89:5547-5551(1992)；Shockett等，Proc.Natl.Acad.Sci.USA，92:6522-6526(1995))。

[0156] 另外，载体可含有例如以下的一些或全部：选择标记基因，例如用于在哺乳动物细胞中选择稳定或瞬时转染子的新霉素基因；用于高水平的转录的来自人CMV的立即早期基因的增强子/启动子序列；用于mRNA稳定性的来自SV40的转录终止和RNA加工信号；用于合适的附加体复制(episomal replication)的SV40多瘤复制起点和ColE1；内部核糖体结合位点(internal ribosome binding site，IRES)、多功能多克隆位点；以及用于有义和反义RNA的体外转录的T7和SP6 RNA启动子。合适载体和用于产生含有转基因之载体的方法是本领域中公知且可获得的。

[0157] 可通过常规技术(例如，电穿孔、脂质体转染和磷酸钙沉淀)将包含核酸的表达载体转移至宿主细胞，并随后通过常规技术培养转染的细胞以产生本文中所述的多肽。在一些实施方案中，本文中所述多肽的表达受组成型、诱导型或组织特异性启动子的调节。

[0158] 用于表达本文中所述的分离的多肽的宿主细胞可以是细菌细胞(例如大肠杆菌)，或优选真核细胞。特别地，与例如来自人巨细胞病毒的主要中间早期基因启动子元件的载体联合的哺乳动物细胞，例如中国仓鼠卵巢细胞(CHO)是免疫球蛋白的有效表达系统(Foecking等(1986)“Powerful And Versatile Enhancer-Promoter Unit For Mammalian Expression Vectors，”Gene 45:101-106；Cockett等(1990)“High Level Expression Of Tissue Inhibitor Of Metalloproteinases In Chinese Hamster Ovary Cells Using Glutamine Synthetase Gene Amplification，”Biotechnology 8:662-667)。多种宿主表达载体系统可用于表达本文中所述的分离的多肽。这样的宿主表达系统代表可通过其产生和随后纯化本文中所述的分离的多肽的编码序列的载体，但也代表当用合适的核苷酸编码序列转化或转染时可原位表达本文中所述的分离的多肽的细胞。这些包括但不限于用含有本文中所述的分离的多肽的编码序列的重组噬菌体DNA、质粒DNA或黏粒DNA表达载体转化的微生物，例如细菌(例如，大肠杆菌和枯草芽孢杆菌(B.subtilis))；用含有编码本文中所述的分离的多肽的序列的重组酵母表达载体转化的酵母(例如，Saccharomyces pichia)；用含有编码本文中所述的分离的多肽的序列的重组病毒表达载体(例如，杆状病毒)感染的昆虫细胞系统；用含有编码本文中所述的分离的多肽的序列的重组病毒表达载体(例如，花椰菜花叶病毒(cauliflower mosaic virus，CaMV)和烟草花叶病毒(tobacco mosaic virus，TMV))感染的或用重组质粒表达载体(例如，Ti质粒)转化的植物细胞系统；或携带有重组表达构建体的哺乳动物细胞系统(例如，COS、CHO、BHK、293、293T、3T3细胞、淋巴细胞

(参见美国专利No.5,807,715)、Per C.6细胞(由Crucell开发的人视网膜细胞),所述重组表达构建体含有来自哺乳动物细胞的基因组的启动子(例如,金属硫蛋白启动子)或来自哺乳动物病毒的基因组的启动子(例如,腺病毒晚期启动子;牛痘病毒7.5K启动子)。

[0159] 在细菌系统中,根据所表达的多肽的预期用途,可有利地选择许多表达载体。例如,当要产生大量这样的蛋白质时,为了产生本文中所述的多肽的药物组合物,可期望指导易于纯化的高水平融合蛋白产物的表达的载体。这样的载体包括但不限于大肠杆菌表达载体pUR278(Rüther等(1983)"Easy Identification Of cDNA Clones,"EMBO J.2:1791-1794),其中编码序列可单个地连接到载体中并与lac Z编码区同框,从而产生融合蛋白;pIN载体(Inouye等(1985)"Up-Promoter Mutations In The lpp Gene Of Escherichia Coli,"Nucleic Acids Res.13:3101-3110;Van Heeke等(1989)"Expression Of Human Asparagine Synthetase In Escherichia Coli,"J.Biol.Chem.24:5503-5509);等。pGEX载体也可用于将外源多肽表达为与谷胱甘肽S-转移酶(glutathione S-transferase,GST)的融合蛋白。一般而言,这样的融合蛋白是可溶的,并且可通过吸附和结合至基质谷胱甘肽-琼脂糖珠然后在游离谷胱甘肽存在下洗脱而容易地从裂解的细胞中纯化。

[0160] 设计pGEX载体以包含凝血酶或因子Xa蛋白酶切割位点,使得克隆的靶基因产物可从GST部分(GST moiety)中释放。在昆虫系统中,苜蓿银纹夜蛾核型多角体病毒(Autographa californica nuclear polyhedrosis virus,AcNPV)用作表达外源基因的载体。病毒在草地贪夜蛾(Spodoptera frugiperda)细胞中生长。编码序列可单独克隆到病毒的非必需区域(例如,多角体蛋白基因)中,并置于AcNPV启动子(例如,多角体蛋白启动子)的控制下。

[0161] 在哺乳动物宿主细胞中,可使用许多基于病毒的表达系统。在其中使用腺病毒作为表达载体的情况下,目的编码序列可连接至腺病毒转录/翻译控制复合物,例如晚期启动子和三联前导序列(tripartite leader sequence)。然后可通过体外或体内重组将该嵌合基因插入到腺病毒基因组中。插入病毒基因组的非必需区域(例如,E1或E3区)将得到重组病毒,其可存活并且能够在受感染的宿主中表达免疫球蛋白分子(例如,参见Logan等(1984)"Adenovirus Tripartite Leader Sequence Enhances Translation Of mRNAs Late After Infection,"Proc.Natl.Acad.Sci.USA 81:3655-3659)。为了高效翻译插入的抗体编码序列,还可需要特定的起始信号。这些信号包括ATG起始密码子和相邻序列。此外,起始密码子必须与所期望编码序列的阅读框同相(in phase),以确保整个插入片段(insert)的翻译。这些外源翻译控制信号和起始密码子可具有多种来源(天然的和合成的二者)。

[0162] 通过包含合适的转录增强子元件、转录终止子等可增强表达效率(参见Bitter等(1987)"Expression And Secretion Vectors For Yeast,"Methods in Enzymol.153:516-544)。另外,可选择调节插入序列的表达,或以所期望的特定方式修饰和加工基因产物的宿主细胞株。蛋白质产物的这种修饰(例如,糖基化)和加工(例如,切割)对于蛋白质的功能可以是重要的。例如,在某些实施方案中,本文中所述的多肽可表达为单基因产物(例如,作为单多肽链,即作为多蛋白前体(polyprotein precursor)),这需要通过天然或重组细胞机制进行蛋白水解切割以形成本文中所述的单独多肽。

[0163] 因此,本公开内容涵盖工程改造核酸序列以编码包含本文中所述多肽的多蛋白前

体分子,其包含能够指导所述多蛋白前体的翻译后切割的编码序列。多蛋白前体的翻译后切割产生本文中所述的多肽。包含本文中所述多肽的前体分子的翻译后切割可在体内发生(即,在宿主细胞内通过天然或重组细胞系统/机制,例如在适当位点的弗林蛋白酶(furin)切割);或可在体外发生(例如,在包含已知活性的蛋白酶或肽酶的组合物中和/或在包含已知促进所期望的蛋白水解作用的条件或试剂的组合物中孵育所述多肽链)。

[0164] 重组蛋白的纯化和修饰是本领域中公知的,使得多蛋白前体的设计可包括技术人员容易理解的许多实施方案。本领域中已知的任何已知蛋白酶或肽酶可用于前体分子的所述修饰,所述前体分子例如凝血酶或因子Xa(Nagai等(1985)"Oxygen Binding Properties Of Human Mutant Hemoglobins Synthesized In Escherichia Coli," Proc.Nat.Acad.Sci.USA 82:7252-7255,并在Jenny等(2003)"A Critical Review Of The Methods For Cleavage Of Fusion Proteins With Thrombin And Factor Xa,"Protein Expr.Purif.31:1-11(2003)中进行了综述,其各自通过引用整体并入本文)、肠激酶(Collins-Racie等(1995)"Production Of Recombinant Bovine Enterokinase Catalytic Subunit In Escherichia Coli Using The Novel Secretory Fusion Partner DsbA,"Biotechnology 13:982-987,其通过引用在此整体并入本文)、弗林蛋白酶和AcTEV(Parks等(1994)"Release Of Proteins And Peptides From Fusion Proteins Using A Recombinant Plant Virus Proteinase,"Anal.Biochem.216:413-417,其通过引用在此整体并入本文))和口蹄疫病毒蛋白酶C3。

[0165] 不同的宿主细胞具有用于蛋白质和基因产物的翻译后加工和修饰的特征性和特异的机制。可选择合适的细胞系或宿主系统以确保表达的外源蛋白质的正确修饰和加工。为此,可使用具有用于正确加工基因产物的初级转录物、糖基化和磷酸化的细胞机器(cellular machinery)的真核宿主细胞。这样的哺乳动物宿主细胞包括但不限于CHO、VERY、BHK、HeLa、COS、MDCK、293、293T、3T3、WI38、BT483、Hs578T、HTB2、BT20和T47D、CRL7030和Hs578Bst。

[0166] 对于重组蛋白的长期高产率产生,优选稳定表达。例如,可工程改造稳定表达本文中所述多肽的细胞系。不使用含有病毒复制起点的表达载体,而是可以用适当的表达控制元件(例如,启动子、增强子、序列、转录终止子、多腺苷酸化位点等)和选择标志控制的DNA转化宿主细胞。在引入外源DNA后,可使工程改造细胞在富集培养基中生长1至2天,并随后转换至选择性培养基。重组质粒中的选择标志赋予对选择的抗性,并允许细胞将质粒稳定地整合到它们的染色体中并生长形成灶(foci),其进而可被克隆并扩增到细胞系中。该方法可有利地用于工程改造表达本文中所述多肽的细胞系。这样的工程改造细胞系可特别地用于筛选和评价与本文中所述多肽直接或间接相互作用的多肽。

[0167] 可使用许多选择系统,包括但不限于单纯疱疹病毒胸苷激酶(Wigler等(1977)"Transfer Of Purified Herpes Virus Thymidine Kinase Gene To Cultured Mouse Cells,"Cell 11:223-232)、次黄嘌呤-鸟嘌呤磷酸核糖基转移酶(Szybalska等(1992)"Use Of The HPRT Gene And The HAT Selection Technique In DNA-Mediated Transformation Of Mammalian Cells First Steps Toward Developing Hybridoma Techniques And Gene Therapy,"Bioessays 14:495-500)和腺嘌呤磷酸核糖基转移酶(Lowy等(1980)"Isolation Of Transforming DNA:Cloning The Hamster aprt Gene,"

Cell 22:817-823)基因可分别用于tk-、hgprt-或aprt-细胞。此外,抗代谢物抗性可用作选择以下基因的基础:dhfr,其赋予对甲氨蝶呤的抗性(Wigler等(1980)“Transformation Of Mammalian Cells With An Amplifiable Dominant-Acting Gene,”Proc.Natl.Acad.Sci.USA 77:3567-3570;O′Hare等(1981)“Transformation Of Mouse Fibroblasts To Methotrexate Resistance By A Recombinant Plasmid Expressing A Prokaryotic Dihydrofolate Reductase,”Proc.Natl.Acad.Sci.USA 78:1527-1531);gpt,其赋予对霉酚酸的抗性(Mulligan等(1981)“Selection For Animal Cells That Express The Escherichia coli Gene Coding For Xanthine-Guanine Phosphoribosyltransferase,”Proc.Natl.Acad.Sci.USA 78:2072-2076;neo,其赋予对氨基糖苷类G-418的抗性(Tolstoshev(1993)“Gene Therapy,Concepts,Current Trials And Future Directions,”Ann.Rev.Pharmacol.Toxicol.32:573-596;Mulligan(1993)“The Basic Science Of Gene Therapy,”Science 260:926-932;以及Morgan等(1993)“Human Gene Therapy,”Ann.Rev.Biochem.62:191-217)”Human Gene Therapy,“Ann.Rev.Biochem.62:191-217)和hygro,其赋予对潮霉素的抗性(Santerre等(1984)“Expression Of Prokaryotic Genes For Hygromycin B And G418 Resistance As Dominant-Selection Markers In Mouse L Cells,”Gene 30:147-156)。可使用的重组DNA技术领域中公知的方法描述于Ausubel等(编辑.),1993,Current Protocols in Molecular Biology,John Wiley&Sons,NY;Kriegler,1990,Gene Transfer and Expression,A Laboratory Manual,Stockton Press,NY;以及在第12和13章,Dracopoli等(编辑),1994,Current Protocols in Human Genetics,John Wiley&Sons,NY.;Colberre-Garapin等(1981)“A New Dominant Hybrid Selective Marker For Higher Eukaryotic Cells,”J.Mol.Biol.150:1-14中。

[0168] 本文中所述多肽的表达水平可通过载体扩增来提高(综述参见Bebbington和Hentschel,The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning,第3卷(Academic Press,New York,1987)。当表达本文中所述多肽的载体系统中的标志物是可扩增的时,宿主细胞培养物中存在的抑制剂水平的提高将提高标志物基因的拷贝数。由于扩增的区域是与本文中所述多肽的核苷酸序列或本文中所述多肽相关,多肽的产生也将提高(Crouse等(1983)“Expression And Amplification Of Engineered Mouse Dihydrofolate Reductase Minigenes,”Mol.Cell.Biol.3:257-266)。

[0169] 一旦重组表达本文中所述的多肽,可通过本领域中已知的用于纯化多肽、多蛋白或抗体的任何方法(例如,类似于基于抗原选择性的抗体纯化方案),例如通过色谱法(例如,离子交换、亲和力,特别是通过对特异性抗原的亲和力(任选地在其中多肽包含Fc结构域(或其部分)的蛋白A选择后)和大小柱色谱法(sizing column chromatography))、离心、差异溶解度或通过用于纯化多肽或抗体的任何其他标准技术。本公开内容的另一些方面涉及包含本文中所述核酸或本文中所述载体的细胞。

[0170] 所述细胞可以是原核细胞或真核细胞。在一些实施方案中,细胞是哺乳动物细胞。本文中描述了示例性细胞类型。本公开内容的另一些方面涉及表达本文中所述经修饰BoNT多肽的细胞。细胞可以是原核细胞或真核细胞。在一些实施方案中,细胞是哺乳动物细胞。

本文中描述了示例性细胞类型。细胞可用于核酸的扩增(propagation)或用于核酸的表达，或这两者。这样的细胞包括但不限于原核细胞，包括但不限于需氧、微需氧、嗜二氧化碳的(capnophilic)、兼性、厌氧、革兰氏阴性和革兰氏阳性细菌细胞，例如来自例如大肠杆菌(Escherichia coli)、枯草芽孢杆菌(Bacillus subtilis)、地衣芽孢杆菌(Bacillus licheniformis)、脆弱拟杆菌(Bacteroides fragilis)、产气荚梭菌(Clostridia perfringens)、艰难梭菌(Clostridia difficile)、新月柄杆菌(Caulobacter crescentus)、乳酸乳球菌(Lactococcus lactis)、扭脱甲基杆菌(Methylobacterium extorquens)、脑膜炎奈瑟球菌(Neisseria meningirulls)、脑膜炎奈瑟菌(Neisseria meningitidis)、荧光假单胞菌(Pseudomonas fluorescens)和鼠伤寒沙门氏菌(Salmonella typhimurium)的那些;以及真核细胞，包括但不限于酵母菌株，例如来自巴斯德毕赤酵母(Pichia pastoris)、甲醇毕赤酵母(Pichia methanolica)、安格斯毕赤酵母(Pichia angusta)、粟酒裂殖酵母(Schizosaccharomyces pombe)、酿酒酵母(Saccharomyces cerevisiae)和解脂耶氏酵母(Yarrowia lipolytica)的那些;昆虫细胞和来自昆虫的细胞系，例如来自草地夜蛾(Spodoptera frugiperda)、粉纹夜蛾(Trichoplusia ni)、黑腹果蝇(Drosophila melanogaster)和烟草天蛾(Manduca sexta)的那些;以及哺乳动物细胞和来自哺乳动物细胞的细胞系，例如来自小鼠、大鼠、仓鼠、猪、牛、马、灵长类和人的那些。细胞系可从美国典型培养物保藏中心(Arnerican Type Culture Collection)、欧洲细胞培养物保藏中心(European Collection of Cell Cultures)和德国微生物和细胞培养物保藏中心(German Collection of Microorganisms and Cell Cultures)获得。用于选择、制备和使用合适细胞系的特定方案的一些非限制性实例描述于例如INSECT CELL CULTURE ENGINEERING(Mattheus F.A.Goosen等编辑，Marcel Dekker,1993);INSECT CELL CULTURES:FUNDAMENTAL AND APPLIED ASPECTS(J.M.Vlak等编辑,Kluwer Academic Publishers,1996);Maureen A.Harrison&Ian F.Rae,GENERAL TECHNIQUES OF CELL CULTURE(Cambridge University Press,1997);CELL AND TISSUE CULTURE:LABORATORY PROCEDURES(Alan Doyle等编辑.,John Wiley and Sons,1998);R.Ian Freshney,CULTURE OF ANIMAL CELLS:A MANUAL OF BASIC TECHNIQUE(Wiley-Liss,第4版.2000);ANIMAL CELL CULTURE:A PRACTICAL APPROACH(John R.W.Masters编辑.,Oxford University Press,第3版.2000);MOLECULAR CLONING A LABORATORY MANUAL,同上,(2001);BASIC CELL CULTURE:A PRACTICAL APPROACH(John M.Davis,Oxford Press,第2版.2002);以及CURRENT PROTOCOLS IN MOLECULAR BIOLOGY,同上,(2004)。

[0171] 这些方案是本领域技术人员范围内和根据本文中教导的常规操作。本公开内容的另一些方面涉及产生本文中所述多肽的方法，所述方法包括获得本文中所述的细胞并在所述细胞中表达本文中所述的核酸。在一些实施方案中，所述方法还包括分离和纯化本文中所述的多肽。

[0172] 在一些实施方案中，肉毒神经毒素可通过在发酵罐中建立和培养肉毒梭菌培养物并随后根据已知操作收获和纯化经发酵混合物来获得。所有肉毒毒素血清型最初合成为无活性单链蛋白，其必须被蛋白酶切割或切开以变得具有神经活性的。

[0173] 制造肉毒毒素血清型A和G的细菌菌株具有内源性蛋白酶，并因此血清型A和G可主

要以其活性形式从细菌培养物中回收。相反，肉毒毒素血清型C、D和E由非蛋白水解菌株合成，并因此当从培养物中回收时通常是无活性。血清型B和F由蛋白水解和非蛋白水解菌株二者产生，并因此可以以活性或无活性形式回收。产生例如B型肉毒毒素血清型的蛋白水解菌株可仅切割一部分所产生的毒素。本文中考虑了使用这些菌株产生BoNT/X多肽。

[0174] 带切口与未带切口分子的确切比例取决于孵育的长度和培养物的温度。因此，一定百分比的例如B型毒素肉毒毒素的制备物可以是无活性的。在一个实施方案中，本公开内容的神经毒素处于活性状态。在一个实施方案中，神经毒素处于无活性状态。在一个实施方案中，考虑了活性和无活性神经毒素的组合。

[0175] 本公开内容的一个方面提供了通过连接两个无毒BoNT片段的体外转肽酶反应产生BoNT的新方法。这样的方法包括以下步骤：(i)获得包含重链的N端结构域(H_N)和轻链(LC)的第一BoNT片段，其中所述第一BoNT片段包含C端LPXTGG(SEQ ID NO:60)基序；(ii)获得包含重链(HC)的C端结构域的第二BoNT片段；其中所述第二BoNT片段在其N端包含特异性蛋白酶切割位点；(iii)用特异性蛋白酶切割第二BoNT片段，其中切割在N端产生游离甘氨酸残基；以及(iv)在存在转肽酶的情况下，使第一BoNT片段与第二BoNT片段接触，从而将第一BoNT片段与第二BoNT片段连接以形成连接的BoNT。

[0176] 在一些实施方案中，第一BoNT片段包含与C端LPXTGG(SEQ ID NO:60)基序(例如，SEQ ID NO:45)或其任何变体融合的本文中所述X-LC-H_N多肽。在一些实施方案中，第二BoNT片段包含本文中所述的H_C多肽或其任何变体(例如，SEQ ID NO:46)。应理解，可使用本文中所述的方法连接任何BoNT片段或结构域。

[0177] 本文中所述的方法也可用于产生嵌合BoNT。例如，第一BoNT片段可来自BoNT血清型A、B、C、D、E、F、G或X。类似地，第二BoNT片段可来自BoNT血清型A、B、C、D、E、F、G或X。本领域技术人员将能够辨别可进行的组合。在一些实施方案中，使用这种方法制备本文中描述的嵌合BoNT多肽(例如，BoNT/X-LC-H_N-A1-H_C、BoNT/X-LC-H_N-B1-H_C或BoNT/X-LC-H_N-C1-H_C)。

[0178] 在一些实施方案中，转肽酶是定位酶。在一些实施方案中，定位酶来自金黄色葡萄球菌(Staphylococcus aureus)(SrtA)。

[0179] 本领域中可用的其他肽连接系统也可用于连接两个无毒BoNT片段。例如，内含肽介导的蛋白质连接反应允许通过天然肽键将合成肽或具有N端半胱氨酸残基的蛋白质连接至经细菌表达的蛋白质的C端(Evans等，(1998)Protein Sci.7,2256-2264，Dawson等，(1994)Science266,776-779；Tam等，(1995)Proc.Natl.Acad.Sci.USA92,12485-12489，Muir等，(1998)Proe.Natl.Acad.Sci.USA95,6705-6710；Severinov和Muir(1998)J.Biol.Chem.273,16205-16209，其全部内容通过引用并入本文)。用于内含肽介导的蛋白质连接反应的药盒可商购获得(例如，来自New England Biolabs)。

[0180] 在一些实施方案中，第一BoNT片段还包含亲和标签。在一些实施方案中，亲和标签与第一BoNT片段在N端融合。在一些实施方案中，亲和标签与与第一BoNT片段在C端融合。在亲和标签与第一BoNT片段的C端融合的情况下，转肽酶在LPXTGG(SEQ ID NO:60)基序中的T与G之间切割并除去亲和标签，然后将第一BoNT片段与第二BoNT片段连接。

[0181] 在一些实施方案中，第二BoNT片段还包含亲和标签。在一些实施方案中，亲和标签与第一BoNT片段在N端融合。在一些实施方案中，亲和标签与第二BoNT片段在C端融合。在亲和标签与第一BoNT片段的N端融合的情况下，特异性蛋白酶在特异性蛋白酶切割位点处切

割并除去亲和标签，然后通过转肽酶将第一BoNT片段与第二BoNT片段连接。

[0182] 本文中使用的“亲和标签”是指可特异性与物质或部分结合的多肽序列，例如包含与Ni^{2+}特异性结合的六个组氨酸的标签。可将亲和标签附加至蛋白质以促进其分离。亲和标签通常通过本领域技术人员已知的重组DNA技术与蛋白质融合。使用亲和标签来促进蛋白质分离也是本领域中公知的。可根据本公开内容使用的合适的亲和标签包括但不限于His6、GST、Avi、Strep、S、MBP、Sumo、FLAG、HA、Myc、SBP、E、钙调蛋白、Softag 1、Softag 3、TC、V5、VSV、Xpress、Halo和Fc。

[0183] 第二BoNT片段在N端具有特异性蛋白酶切割。通过特异性蛋白酶切割位点导致在第二BoNT片段的N端的游离甘氨酸残基。根据本发明可使用的合适的特异性蛋白酶包括但不限于：凝血酶、TEV、PreScission、肠激酶和SUMO蛋白酶。在一些实施方案中，特异性蛋白酶是凝血酶，并且切割位点是：LVPR|GS(SEQ ID NO:50)。

[0184] 本文中所述的BoNT/X多肽提供治疗用途的潜力。例如，与其他BoNT血清型相比，BoNT/X可能更强效。BoNT/X更通用并且由于其能够切割比其他BoNT血清型更多的底物，因此可在很多种细胞中更有效。

[0185] 因此，本公开内容还考虑了包含本公开内容的BoNT/X多肽或嵌合分子的药物组合物。如在后面的本公开内容中也变得清楚的，本公开内容的药物组合物还可包含适合于这种组合物被设计用于治疗的特定疾病的其他治疗剂。在一些实施方案中，本公开内容的药物组合物还包含可药用载体。

[0186] 本文中使用的术语“可药用载体”意指可药用材料、组合物或载剂，例如液体或固体填充剂、稀释剂、赋形剂、制造助剂(例如，润滑剂、滑石镁、硬脂酸钙或硬脂酸锌或硬脂酸)、或参与将多肽从身体的一个部位(例如，递送部位)携带或运输至另一个部位(例如，器官、组织或身体的一部分)的溶剂包封材料。

[0187] 可药用载体在与制剂的其他成分相容方面是“可接受的”，并且对对象的组织无害(例如，生理学相容的、无菌的、生理pH等)。可用作可药用载体的材料的一些实例包括：(1)糖，例如乳糖、葡萄糖和蔗糖；(2)淀粉，例如玉米淀粉和马铃薯淀粉；(3)纤维素及其衍生物，例如羧甲基纤维素钠、甲基纤维素、乙基纤维素、微晶纤维素和醋酸纤维素；(4)粉末西黄蓍胶；(5)麦芽；(6)明胶；(7)润滑剂，例如硬脂酸镁、月桂基硫酸钠和滑石；(8)赋形剂，例如可可豆脂和栓剂蜡；(9)油类，例如花生油、棉籽油、红花油、芝麻油、橄榄油、玉米油和大豆油；(10)二醇类，例如丙二醇；(11)多元醇类，例如甘油、山梨糖醇、甘露糖醇和聚乙二醇(PEG)；(12)酯类，例如油酸乙酯和月桂酸乙酯；(13)琼脂；(14)缓冲剂，例如氢氧化镁和氢氧化铝；(15)藻酸；(16)无热原水；(17)等张盐水；(18)林格液(Ringer's solution)；(19)乙醇；(20)pH缓冲溶液；(21)聚酯、聚碳酸酯和/或聚酸酐；(22)填充剂，例如多肽和氨基酸(23)血清成分，例如血清白蛋白、HDL和LDL；(22)C2-C12醇类，例如乙醇；以及(23)药物制剂中使用的其他无毒相容物质。润湿剂、着色剂、脱模剂、包衣剂、甜味剂、矫味剂、芳香剂、防腐剂和抗氧化剂也可存在于制剂中。术语例如“赋形剂”、“载体”、“可药用载体”等在本文中可互换使用。在一些实施方案中，组合物中本公开内容的BoNT多肽通过注射、通过导管、通过栓剂或通过植入物施用，所述植入物是多孔的、无孔的或凝胶状材料，包括膜，例如硅橡胶膜(sialastic membrane)或纤维。

[0188] 通常来说，当施用所述组合物时，使用本公开内容的多肽不吸收的材料。在另一些

实施方案中，本公开内容的经修饰BoNT多肽在控释系统中递送。这样的组合物和施用方法在美国专利公开No.2007/0020295中提供，其内容通过引用并入本文。在一个实施方案中，可使用泵(参见，例如，Langer，1990，Science 249:1527-1533;Sefton，1989，CRC Crit.Ref.Biomed.Eng.14:201;Buchwald等，1980，Surgery 88:507;Saudek等，1989，N.Engl.J.Med.321:574)。在另一个实施方案中，可使用聚合物材料。(参见，例如，Medical Applications of Controlled Release(Langer和Wise编辑.，CRC Press，Boca Raton，Fla.，1974);Controlled Drug Bioavailability，Drug Product Design and Performance(Smolen和Ball编辑.，Wiley，New York，1984);Ranger和Peppas，1983，Macromol.Sci.Rev.Macromol.Chem.23:61.另参见Levy等，1985，Science 228:190;During等，1989，Ann.Neurol.25:351;Howard等，1989，J.Neurosurg.71:105.)。其他控释系统在例如Langer(同上)中讨论。

[0189] 本公开内容的BoNT多肽可作为药物组合物施用，所述药物组合物包含治疗有效量的黏合剂和一种或更多种药学上相容的成分。在一些典型的实施方案中，药物组合物根据常规操作配制成适合于向对象(例如，人)进行静脉内或皮下施用的药物组合物。

[0190] 通常来说，通过注射施用的组合物是无菌等张水性缓冲液中的溶液。必要时，药物还可包含增溶剂和局部麻醉剂(例如利多卡因)以缓解注射部位的疼痛。通常来说，成分单独地或混合在一起，以单位剂量形式在表明活性剂之量的密封容器(例如安瓿或小袋(sachette))中(例如作为干燥的冻干粉末或无水浓缩物)供应。当药物通过输注施用时，其可用含有无菌药用级水或盐水的输液瓶分配。当药物通过注射施用时，可提供一安瓿的无菌注射用水或盐水以便在施用前混合各成分。用于全身施用的药物组合物可以是液体，例如无菌盐水、乳酸林格液或汉克氏液(Hank's solution)。此外，药物组合物可以是固体形式，并在使用前立即再溶解或混悬。还考虑了冻干形式。药物组合物可包含在脂质颗粒或囊泡(例如脂质体或微晶)中，其也适用于肠胃外施用。颗粒可以是任何合适的结构，例如单层或多层，只要其中含有组合物即可。

[0191] 本公开内容的多肽可包埋在含有促融性脂质二油酰磷脂酰乙醇胺(DOPE)、低水平(5至10mol％)的阳离子脂质的“稳定化质粒-脂质颗粒”(stabilized plasmid-lipid particle，SPLP)中，并通过聚乙二醇(PEG)包衣稳定化(Zhang Y P等，Gene Ther.1999，6:1438-47)。带正电荷的脂质(例如N-[1-(2，3-二油酰氧基)丙基]-N，N，N-三甲基-甲基硫酸铵或“DOTAP”)特别优选用于这样的颗粒和囊泡。这样的脂质颗粒的制备是公知的。参见，例如，美国专利No.4，880，635、4，906，477、4，911，928、4，917，951、4，920，016和4，921，757。例如，本公开内容的药物组合物可作为单位剂量施用或包装。

[0192] 当用于提及本公开内容的药物组合物时，术语“单位剂量”是指适合用于对象的单位剂量的物理上离散的单元，每个单元含有预定量的经计算可与所需的稀释剂(即，载体或载剂)联合产生所期望治疗效果的活性物质。在一些实施方案中，本文中所述的BoNT/X多肽可与治疗部分(例如，抗生素)缀合。将这样的治疗性部分与多肽(包括例如Fc结构域)缀合的技术是公知的;参见例如Amon等，“Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy”，in Monoclonal Antibodies And Cancer Therapy，Reisfeld等(编辑.)，1985，第243-56页，Alan R.Liss，Inc.);Hellstrom等，“Antibodies For Drug Delivery”，in Controlled Drug Delivery(第2版.)，Robinson等(编辑.)，1987，第623-53

页,Marcel Dekker,Inc.);Thorpe,“Antibody Carriers Of Cytotoxic Agents In Cancer Therapy:A Review”,in Monoclonal Antibodies′84:Biological And Clinical Applications,Pinchera等(编辑.),1985,第475-506页);“Analysis,Results,And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy”,in Monoclonal Antibodies For Cancer Detection And Therapy,Baldwin等(编辑.),1985,第303-16页,Academic Press;以及Thorpe等(1982)“The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates,”Immunol.Rev.,62:119-158。此外,药物组合物可作为药盒(pharmaceutical kit)提供,所述药盒包含(a)含有冻干形式的本公开内容的多肽的容器和(b)含有用于注射的可药用稀释剂(例如,无菌水)的第二容器。可药用稀释剂可用于重构或稀释本公开内容的冻干多肽。任选地,这样的容器可伴随具有由管理药物或生物制品的生产、使用或销售的政府机构所规定的形式的通知,该通知反映了该机构对于用于人施用的生产、使用或销售的批准。另一方面,包括含有可用于治疗上述疾病的物质的制品。在一些实施方案中,制品包括容器和标签。

[0193] 合适的容器包括例如瓶子、小瓶、注射器和试管。容器可由多种材料(例如玻璃或塑料)形成。在一些实施方案中,容器容纳有效治疗本文中所述疾病的组合物,并且可具有无菌进入口。例如,容器可以是静脉内溶液袋或具有可由皮下注射针刺穿的塞子的小瓶。组合物中的活性剂是本公开内容的分离的多肽。在一些实施方案中,容器上或与容器缔合的标签表明该组合物用于治疗所选的疾病。所述制品还可包含第二容器,所述第二容器包含可药用缓冲液,例如磷酸缓冲盐水、林格液或葡萄糖溶液。它还可包含从商业和用户角度所期望的其他材料,包括其他缓冲液、稀释剂、过滤器、针、注射器和具有使用说明的包装插件(package insert)。

[0194] 本公开内容的BoNT多肽(例如,BoNT/X多肽)、嵌合分子和药物组合物可用于治疗与不期望的神经元活动相关的病症。因此,本文中还提供了治疗与不期望的神经元活动相关的病症的方法,所述方法包括施用治疗有效量的本文中所述的BoNT多肽、嵌合分子或药物组合物从而治疗所述病症。在一些实施方案中,本公开内容的BoNT多肽、嵌合分子和药物组合物与一种或更多种表现出不期望的神经元活动的神经元接触。

[0195] 通常用神经毒素治疗的病症(例如,骨骼肌病症、平滑肌病症、腺体病症、神经肌肉病症、自主神经病症、疼痛或美学/美容病症)与不期望的神经元活动相关,如技术人员所确定的。通过使有效量的组合物与表现出不期望活性的神经元相接触的途径施用。在一些实施方案中,所述病症可与过度活动的神经元或腺体相关。考虑通过本文中讨论的方法治疗的具体病症包括但不限于:痉挛性发声障碍、痉挛性斜颈、喉肌张力障碍、口下颌发声困难、舌肌张力障碍、颈肌张力障碍、局灶性手肌张力障碍、眼睑痉挛、斜视、偏侧面肌痉挛、眼睑疾病、大脑性瘫痪、局灶性痉挛状态和其他发声障碍、痉挛性结肠炎、神经源性膀胱、肛门痉挛、肢体痉挛状态、抽搐、震颤、夜磨牙症、肛裂、失弛缓症、吞咽困难和其他肌张力障碍以及特征为肌肉群不自主运动的其他障碍、流泪、多汗、过度流涎、过度胃肠分泌以及其他分泌紊乱、肌痉挛引起的疼痛、头痛。此外,本公开内容可用于治疗皮肤病学或美学/美容病症,例如减轻眉头皱纹(brow furrow)、减轻皮肤皱纹(skin wrinke)。

[0196] 本公开内容的BoNT/X多肽的一个独特性质是其切割VAMP4、VAMP5和Ykt6的能力。因此,本文中还考虑了BoNT/X多肽在与很多种细胞中的不期望的分泌活性相关的病症中的

治疗用途。在一些实施方案中，不期望的分泌是免疫分泌。与不期望的免疫分泌相关的病症包括但不限于：炎症、银屑病、变态反应、嗜红细胞淋巴组织细胞增生症和酒精性胰腺疾病。

[0197] 本公开内容还可用于治疗运动损伤。Borodic美国专利No.5,053,005公开了使用A型肉毒用于治疗幼年脊柱弯曲(即脊柱侧弯)的方法。Borodic的公开内容通过引用整体并入本文。在一个实施方案中，使用与Borodic公开的基本相似的方法，可将BoNT多肽施用于哺乳动物(优选人)以治疗脊柱弯曲。在一个合适的实施方案中，施用包含与基于亮氨酸的基序融合的E型肉毒的BoNT多肽。甚至更优选地，将包含具有融合至其轻链羧基端的基于亮氨酸之基序的A至E型肉毒的BoNT多肽施用于哺乳动物(优选人)以治疗脊柱弯曲。

[0198] 此外，可使用通常用A型肉毒梭菌进行的公知技术施用BoNT多肽以治疗神经肌肉病症。例如，本公开内容可用于治疗疼痛，例如头痛、肌痉挛引起的疼痛以及多种形式的炎性疼痛。例如，Aoki美国专利No.5,721,215和Aoki美国专利No.6,113,915公开了使用A型肉毒毒素治疗疼痛的方法。这两个专利的公开内容通过引用整体并入本文。

[0199] 自主神经系统疾病还可用经修饰神经毒素进行治疗。例如，腺体功能障碍是自主神经系统疾病。腺体功能障碍包括过度出汗和过度流涎。呼吸功能障碍是自主神经系统病症的另一个实例。呼吸功能障碍包括慢性阻塞性肺病和哮喘。Sanders等公开了用于治疗自主神经系统的方法；例如，使用天然存在的肉毒毒素治疗自主神经系统病症，例如过度出汗、过度流涎、哮喘等。Sander等的公开内容通过引用整体引入本文。

[0200] 在一个实施方案中，可使用基本上类似于Sanders等的方法，但是使用BoNT多肽来治疗自主神经系统病症，例如上面讨论的病症。例如，BoNT多肽可以以足以使自主神经系统的胆碱能神经元(其控制鼻腔中的黏液分泌)退化的量局部施用于哺乳动物的鼻腔。可通过经修饰神经毒素治疗的疼痛包括由肌肉紧张或痉挛引起的疼痛或与肌痉挛无关的疼痛。例如，Binder在美国专利No.5,714,468中公开了由血管紊乱、肌紧张、神经痛和神经病变引起的头痛可用天然存在的肉毒毒素(例如A型肉毒)进行治疗。Binder的公开内容通过引用整体并入本文。

[0201] 在一个实施方案中，可使用基本上类似于Binder的方法，但是使用本文中所述的BoNT多肽来治疗头痛，尤其是由血管紊乱、肌紧张、神经痛和神经病变引起的头痛。肌痉挛引起的疼痛还可通过施用本文中所述的BoNT多肽来治疗。例如，与基于亮氨酸的基序融合的E型肉毒(优选在E型肉毒轻链的羧基端)可在疼痛/痉挛位置肌内施用以减轻疼痛。此外，可将经修饰神经毒素施用于哺乳动物以治疗与肌肉疾病(例如痉挛)无关的疼痛。

[0202] 在一个广泛的实施方案中，治疗非痉挛相关疼痛的本公开内容方法包括中枢施用或外周施用BoNT多肽。例如，Foster等在美国专利No.5,989,545中公开了可在中枢(鞘内)施用的与靶向部分缀合的肉毒毒素以减轻疼痛。Foster等的公开内容通过引用整体并入本文。

[0203] 在一个实施方案中，可使用基本上类似于Foster等的方法，但使用本文中所述的组合物来治疗疼痛。待治疗的疼痛可以是急性疼痛或慢性疼痛。与肌痉挛无关的急性或慢性疼痛也可通过将经修饰神经毒素局部外周施用至哺乳动物的实际或感知的疼痛位置来减轻。

[0204] 在一个实施方案中，BoNT多肽在疼痛位置处或附近(例如，在切口处或切口附近)皮下施用。在一些实施方案中，经修饰神经毒素在哺乳动物的疼痛位置处或附近(例如，挫

伤(bruise)位置处或附近)肌内施用。在一些实施方案中,将BoNT多肽直接注射到哺乳动物的关节中用于治疗或减轻由关节炎病症引起的疼痛。而且,频繁地将经修饰神经毒素重复注射或输注至外周疼痛位置也在本公开内容的范围内。这样方法的施用途径是本领域中已知的并且本领域技术人员容易对本文中所述的方法进行修改(例如,参见Harrison′s Principles of Internal Medicine(1998),由Anthony Fauci等编辑.,第14版,由McGraw Hill出版)。

[0205] 作为非限制性实例,神经肌肉病症的治疗可包括向肌肉或肌肉群局部施用有效量的分子的步骤,自主神经病症的治疗可包括局部施用对腺体或一些腺体有效的分子的步骤,并且疼痛的治疗可包括向疼痛部位施用有效量的分子的步骤。另外,疼痛的治疗可包括向脊髓施用有效量的经修饰神经毒素的步骤。

[0206] 本文中使用的“治疗有效量”是指本公开内容的每种治疗剂单独或与一种或更多种其他治疗剂组合赋予对象治疗效果所需的量。如本领域技术人员所认识到的,有效量根据所治疗的具体病症、病症的严重程度、个体对象参数(包括年龄、身体状况、身材大小、性别和体重、治疗持续时间、同时治疗(如果有的话)的性质、具体的施用途径等在健康从业者的知识和专长中的相似因素。这些因素是本领域普通技术人员所公知的,并且可仅通过常规实验来解决。通常优选使用最大剂量的各组分或其组合,即根据合理的医学判断的最高安全剂量。然而,本领域普通技术人员将理解,对象可出于医学原因、心理原因或实际上任何其他原因坚持较低剂量或可耐受剂量。经验考虑因素(例如半衰期)通常将有助于确定剂量。例如,可使用与人免疫系统相容的治疗剂,例如包含来自人源化抗体或完全人抗体的区域的多肽来延长多肽的半衰期并防止多肽被宿主的免疫系统攻击。

[0207] 施用的频率可在治疗过程中确定和调整,并且通常但不是必须基于疾病的治疗和/或抑制和/或改善和/或延迟。或者,多肽的持续连续释放制剂可以是合适的。用于实现持续释放的多种制剂和装置是本领域中已知的。在一些实施方案中,剂量是每天、每隔一天、每三天、每四天、每五天或每六天。在一些实施方案中,给药频率是每周一次、每2周一次、每4周一次、每5周一次、每6周一次、每7周一次、每8周一次、每9周一次或每10周一次;或每月一次、每2个月一次、或每3个月或更长时间一次。通过常规技术和测定可容易地监测该治疗的进展。

[0208] 给药方案(包括使用的多肽)可随时间变化。在一些实施方案中,对于正常体重的成年对象,可施用范围为约0.01至1000mg/kg的剂量。在一些实施方案中,剂量为1至200mg。具体的剂量方案(即剂量、时机和重复)将取决于具体的对象和对象的病史,以及多肽的性质(例如多肽的半衰期以及本领域中公知的其他考虑因素)。

[0209] 为了本公开内容的目的,如本文中所述的治疗剂的合适剂量将取决于所用的具体药剂(或其组合物)、制剂和施用途径、疾病的类型和严重程度、所述多肽是用于预防还是治疗目的、先前的治疗、对象的临床病史和对拮抗剂的响应以及主治医师的判定。通常来说,临床医生将施用多肽直至达到实现所期望结果的剂量。

[0210] 一种或更多种多肽的施用可以是连续的或间歇的,这取决于例如接受者的生理状况、施用的目的是治疗性的还是预防性的、以及技术人员已知的其他因素。多肽的施用可在预选的时间段内基本上连续,或者可以是一系列间隔剂量,例如在疾病发生之前、期间或之后。本文中使用的术语“治疗”是指将多肽或包含所述多肽的组合物应用或施用于有此需要

的对象。

[0211] “有此需要的对象”是指患有疾病、疾病的症状或对疾病有倾向的个体，其目的是治疗、治愈、缓和、减轻、改变、补救、改善、改进或影响疾病、疾病的症状或对疾病的倾向。在一些实施方案中，对象患有CDI。在一些实施方案中，对象患有癌症。在一些实施方案中，对象是哺乳动物。在一些实施方案中，对象是非人灵长类。在一些实施方案中，对象是人。减轻疾病包括延迟疾病的发生或发展，或降低疾病严重程度。减轻疾病并不一定需要治愈性结果。

[0212] 其中使用的“延迟”疾病的发生意味着推迟、阻碍、减缓、延缓、稳定和/或推迟疾病的进展。这种延迟可具有不同的时间长度，这取决于病史和/或被治疗的个体。“延迟”或减轻疾病的发生或延迟疾病发作的方法是，与不使用该方法相比，在给定时间框架内降低发生一种或更多种疾病症状的可能性和/或在给定的时间框架内降低症状程度的方法。这样的比较通常基于临床研究，使用足以给出统计学显著性结果的许多对象。

[0213] 疾病的“发生”或“发展”意指疾病的初始表现和/或随后的进展。可使用本领域中公知的标准临床技术检测和评估疾病的发生。然而，发生也指可以是不可检出的进展。对于本公开内容的目的，发生或发展是指症状的生物学过程。“发生”包括发生、复发和发作。

[0214] 本文中使用的疾病的“发作”或“发生”包括初始发作和/或复发。可使用医学领域普通技术人员已知的常规操作将分离的多肽或药物组合物施用于对象，这取决于待治疗的疾病类型或疾病的部位。该组合物还可通过其他常规途径施用，例如经口、肠胃外、通过吸入喷雾、表面、经直肠、经鼻、口含、经阴道或通过植入的储库(implanted reservoir)施用。

[0215] 本文中使用的术语“肠胃外”包括皮下、皮内、静脉内、肌内、关节内、动脉内、滑膜内、胸骨内、鞘内、病灶内和颅内注射或输注技术。另外，它可通过可注射的储库(injectable depoit)施用途径施用于对象，例如使用1个月、3个月或6个月储库可注射或可生物降解的材料和方法。

[0216] 本文中使用的“对象”是指人或动物。通常动物是脊椎动物，例如灵长类、啮齿动物、家畜或狩猎动物(game animal)。灵长类包括黑猩猩、食蟹猴、蜘蛛猴和狨猴，例如恒河猴(Rhesus)。啮齿动物包括小鼠、大鼠、土拨鼠(woodchuck)、雪貂(ferret)、兔和仓鼠。家养和野生动物包括牛、马、猪、鹿、野牛(bison)、水牛、猫科动物(例如家猫)、犬科动物(例如狗、狐狸、狼)、鸟类(例如鸡、鸸鹋、鸵鸟)和鱼(例如鳟鱼、鲶鱼和鲑鱼)。患者或对象包括前述的任何子集，例如以上所有，但不包括一个或更多个组或物种，例如人、灵长类或啮齿动物。在本文中所述一些方面的某些实施方案中，对象是哺乳动物，例如灵长类(例如，人)。

[0217] 术语“患者”和“对象”在本文中可互换使用。对象可以是雄性或雌性。对象可以是完全发育的对象(例如，成人)或经历发育过程的对象(例如，儿童、婴儿或胎儿)。优选地，对象是哺乳动物。哺乳动物可以是人、非人灵长类、小鼠、大鼠、狗、猫、马或牛，但不限于这些实例。除人之外的哺乳动物可有利地用作代表与不期望的神经元活动相关的病症的动物模型的对象。此外，本文中所述的方法和组合物可用于治疗家养动物和/或宠物。

[0218] 以下实施例旨在举例说明某些实施方案，并且是非限制性的。在贯穿本申请中引用的所有参考文献(包括参考文献、授权专利、公开的专利申请和共同未决的专利申请)的全部内容在此通过引用明确地并入。

[0219] 实施例

[0220] 表1 BoNT多肽序列

[0221]

SEQ ID NO.	描述	序列
1	WT BoNT/X	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGCIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGK IKDLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNF SISFWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIK IVTPDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRL KNNRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYN KKYYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSK VLIKNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDL TTDFEIIQRQEKYRNYCQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSA WYFQNYENLNLRKHTKTNWYFIPKDEGWDED
2	WT BoNT/X LC-H_N	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP

[0222]

		EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGCIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEI
3	WT BoNT/X LC	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKN
4	WT BoNT/X C461S	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPSSLLNGCIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGK IKDLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNF SISFWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKI VTPDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRL KNNRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYN KKYYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSK VLIKNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDL TTDFEIIQRQEKYRNYCQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSA WYFQNYENLNLRKHTKTNWYFIPKDEGWDED
5	WT BoNT/X C461A	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPASLLNGCIEVENKDLFLISN

[0223]

		KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGK IKDLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNF SISFWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKI VTPDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRL KNNRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYN KKYYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSK VLIKNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDL TTDFEIIQRQEKYRNYCQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSA WYFQNYENLNLRKHTKTNWYFIPKDEGWDED
6	WT BoNT/X C467S	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGSIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGK IKDLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNF SISFWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKI VTPDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRL KNNRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYN KKYYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSK VLIKNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDL TTDFEIIQRQEKYRNYCQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSA WYFQNYENLNLRKHTKTNWYFIPKDEGWDED
7	WT BoNT/X C467A	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGAIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGK IKDLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNF

[0224]

		SISFWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKI VTPDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRL KNNRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYN KKYYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSK VLIKNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDL TTDFEIIQRQEKYRNYCQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSA WYFQNYENLNLRKHTKTNWYFIPKDEGWDED
8	WT BoNT/X C1240S	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGCIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGK IKDLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNF SISFWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKI VTPDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRL KNNRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYN KKYYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSK VLIKNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDL TTDFEIIQRQEKYRNYSQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSA WYFQNYENLNLRKHTKTNWYFIPKDEGWDED
9	WT BoNT/X C1240S	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGCIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGK IKDLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNF SISFWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKI VTPDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRL KNNRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYN KKYYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSK

[0225]

		VLIKNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDL TTDFEIIQRQEKYRNYAQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSA WYFQNYENLNLRKHTKTNWYFIPKDEGWDED
10	WT BoNT/X C461S/C1240A	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPSSLLNGCIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGK IKDLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNF SISFWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKI VTPDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRL KNNRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYN KKYYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSK VLIKNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDL TTDFEIIQRQEKYRNYAQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSA WYFQNYENLNLRKHTKTNWYFIPKDEGWDED
11	WT BoNT/X C461S/C1240S	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPSSLLNGCIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGK IKDLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNF SISFWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKI VTPDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRL KNNRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYN KKYYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSK VLIKNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDL TTDFEIIQRQEKYRNYSQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSA WYFQNYENLNLRKHTKTNWYFIPKDEGWDED

[0226]

12	WT BoNT/X C461A/C1240S	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPASLLNGCIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGK IKDLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNF SISFWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKI VTPDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRL KNNRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYN KKYYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSK VLIKNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDL TTDFEIIQRQEKYRNYSQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSA WYFQNYENLNLRKHTKTNWYFIPKDEGWDED
13	WT BoNT/X C461A/C1240A	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPASLLNGCIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGK IKDLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNF SISFWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKI VTPDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRL KNNRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYN KKYYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSK VLIKNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDL TTDFEIIQRQEKYRNYAQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSA WYFQNYENLNLRKHTKTNWYFIPKDEGWDED
14	WT BoNT/X C467S/C1240A	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP

[0227]

		DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGSIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGK IKDLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNF SISFWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKI VTPDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRL KNNRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYN KKYYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSK VLIKNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDL TTDFEIIQRQEKYRNYAQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSA WYFQNYENLNLRKHTKTNWYFIPKDEGWDED
15	WT BoNT/X C467S/C1240S	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGSIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGK IKDLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNF SISFWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKI VTPDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRL KNNRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYN KKYYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSK VLIKNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDL TTDFEIIQRQEKYRNYSQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSA WYFQNYENLNLRKHTKTNWYFIPKDEGWDED
16	WT BoNT/X C467A/C1240S	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP

[0228]

		VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGAIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGK IKDLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNF SISFWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKI VTPDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRL KNNRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYN KKYYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSK VLIKNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDL TTDFEIIQRQEKYRNYSQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSA WYFQNYENLNLRKHTKTNWYFIPKDEGWDED
17	WT BoNT/X C467A/C1240A	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGAIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGK IKDLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNF SISFWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKI VTPDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRL KNNRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYN KKYYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSK VLIKNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDL TTDFEIIQRQEKYRNYAQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSA WYFQNYENLNLRKHTKTNWYFIPKDEGWDED
18	WT BoNT/X LC-H_N C461A	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPASLLNGCIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER

[0229]

		NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEI
19	WT BoNT/X LC-H_N C461S	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPSSLLNGCIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEI
20	WT BoNT/X LC-H_N C467A	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGAIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEI
21	WT BoNT/X LC-H_N C467S	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGSIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEI
22	BoNT/X-LC-	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER

[0230]

	H_N-A1-Hc	YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGCIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIIINTSILNLRYESNHL IDLSRYASKINIGSKVNFDPIDKNQIQLFNLESSKIEVILKNAIVYNSMYENFS TSFWIRIPKYFNSISLNNEYTIINCMENNSGWKVSLNYGEIIWTLQDTQEIKQ RVVFKYSQMINISDYINRWIFVTITNNRLNNSKIYINGRLIDQKPISNLGNIHA SNNIMFKLDGCRDTHRYIWIKYFNLFDKELNEKEIKDLYDNQSNSGILKDFW GDYLQYDKPYYMLNLYDPNKYVDVNNVGIRGYMYLKGPRGSVMTTNIYL NSSLYRGTKFIIKKYASGNKDNIVRNNDRVYINVVVKNKEYRLATNASQAG VEKILSALEIPDVGNLSQVVVMKSKNDQGITNKCKMNLQDNNGNDIGFIGF HQFNNIAKLVASNWYNRQIERSSRTLGCSWEFIPVDDGWGERPL
23	BoNT/X-LC-H_N-B1-Hc	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGCIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIILNNIILNLRYKDNN LIDLSGYGAKVEVYDGVELNDKNQFKLTSSANSKIRVTQNQNIIFNSVFLDF SVSFWIRIPKYKNDGIQNYIHNEYTIINCMKNNSGWKISIRGNRIIWTLIDING KTKSVFFEYNIREDISEYINRWFFVTITNNLNNAKIYINGKLESNTDIKDIREVI ANGEIIFKLDGDIDRTQFIWMKYFSIFNTELSQSNIEERYKIQSYSEYLKDFW GNPLMYNKEYYMFNAGNKNSYIKLKKDSPVGEILTRSKYNQNSKYINYRDL YIGEKFIIRRKSNSQSINDDIVRKEDYIYLDFFNLNQEWRVYTYKYFKKEEEK LFLAPISDSDEFYNTIQIKEYDEQPTYSCQLLFKKDEESTDEIGLIGIHRFYESG IVFEEYKDYFCISKWYLKEVKRKPYNLKLGCNWQFIPKDEGWTE
24	BoNT/X-LC-H_N-C1-Hc	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGCIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER

[0231]

		NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIINDSKILSLQNRKNT LVDTSGYNAEVSEEGDVQLNPIFPFDFKLGSSGEDRGKVIVTQNENIVYNSM YESFSISFWIRINKWVSNLPGYTIIDSVKNNSGWSIGIISNFLVFTLKQNEDSE QSINFSYDISNNAPGYNKWFFVTVTNNMMGNMKIYINGKLIDTIKVKELTGI NFSKTITFEINKIPDTGLITSDSDNINMWIRDFYIFAKELDGKDINILFNSLQYT NVVKDYWGNDLRYNKEYYMVNIDYLNRYMYANSRQIVFNTRRNNNDFNE GYKIIIKRIRGNTNDTRVRGGDILYFDMTINNKAYNLFMKNETMYADNHST EDIYAIGLREQTKDINDNIIFQIQPMNNTYYYASQIFKSNFNGENISGICSIGTY RFRLGGDWYRHNYLVPTVKQGNYASLLESTSTHWGFVPVSE
25	BoNT/X-LC-H_N-A1-Hc C461S	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPSSLLNGCIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIIINTSILNLRYESNHL IDLSRYASKINIGSKVNFDPIDKNQIQLFNLESSKIEVILKNAIVYNSMYENFS TSFWIRIPKYFNSISLNNEYTIINCMENNSGWKVSLNYGEIIWTLQDTQEIKQ RVVFKYSQMINISDYINRWIFVTITNNRLNNSKIYINGRLIDQKPISNLGNIHA SNNIMFKLDGCRDTHRYIWIKYFNLFDKELNEKEIKDLYDNQSNSGILKDFW GDYLQYDKPYYMLNLYDPNKYVDVNNVGIRGYMYLKGPRGSVMTTNIYL NSSLYRGTKFIIKKYASGNKDNIVRNNDRVYINVVVKNKEYRLATNASQAG VEKILSALEIPDVGNLSQVVVMKSKNDQGITNKCKMNLQDNNGNDIGFIGF HQFNNIAKLVASNWYNRQIERSSRTLGCSWEFIPVDDGWGERPL
26	BoNT/X-LC-H_N-B1-Hc C461S	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIP VQGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIY VNILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNG LLYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPSSLLNGCIEVENKDLFLISN KDSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILER NEELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEAL SNPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKS SDTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVI GGELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHT YKALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAM KNTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTN LSSSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIILNNIILNLRYKDNN

[0232]

		LIDLSGYGAKVEVYDGVELNDKNQFKLTSSANSKIRVTQNQNIIFNSVFLDF SVSFWIRIPKYKNDGIQNYIHNEYTIINCMKNNSGWKISIRGNRIIWTLIDING KTKSVFFEYNIREDISEYINRWFFVTITNNLNNAKIYINGKLESNTDIKDIREVI ANGEIIFKLDGDIDRTQFIWMKYFSIFNTELSQSNIEERYKIQSYSEYLKDFW GNPLMYNKEYYMFNAGNKNSYIKLKKDSPVGEILTRSKYNQNSKYINYRDL YIGEKFIIRRKSNSQSINDDIVRKEDYIYLDFFNLNQEWRVYTYKYFKKEEEK LFLAPISDSDEFYNTIQIKEYDEQPTYSCQLLFKKDEESTDEIGLIGIHRFYESG IVFEEYKDYFCISKWYLKEVKRKPYNLKLGCNWQFIPKDEGWTE
27	BoNT/X-LC-H_N-C1-Hc C461S	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFEE LLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIPV QGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIYV NILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNGL LYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPSSLLNGCIEVENKDLFLISNK DSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILERN EELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEALS NPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKSS DTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVIG GELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHTY KALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAMK NTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTNLS SSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIINDSKILSLQNRKNTLV DTSGYNAEVSEEGDVQLNPIFPFDFKLGSSGEDRGKVIVTQNENIVYNSMYE SFSISFWIRINKWVSNLPGYTIIDSVKNNSGWSIGIISNFLVFTLKQNEDSEQSI NFSYDISNNAPGYNKWFFVTVTNNMMGNMKIYINGKLIDTIKVKELTGINFS KTITFEINKIPDTGLITSDSDNINMWIRDFYIFAKELDGKDINILFNSLQYTNVV KDYWGNDLRYNKEYYMVNIDYLNRYMYANSRQIVFNTRRNNNDFNEGYK IIIKRIRGNTNDTRVRGGDILYFDMTINNKAYNLFMKNETMYADNHSTEDIY AIGLREQTKDINDNIIFQIQPMNNTYYYASQIFKSNFNGENISGICSIGTYRFRL GGDWYRHNYLVPTVKQGNYASLLESTSTHWGFVPVSE
28	BoNT/X-LC-H_N-A1-Hc C467S	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFEE LLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIPV QGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIYV NILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNGL LYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGSIEVENKDLFLISNK DSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILERN EELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEALS NPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKSS DTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVIG GELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHTY KALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAMK NTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTNLS SSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIIINTSILNLRYESNHLID LSRYASKINIGSKVNFDPIDKNQIQLFNLESSKIEVILKNAIVYNSMYENFSTS FWIRIPKYFNSISLNNEYTIINCMENNSGWKVSLNYGEIIWTLQDTQEIKQRV VFKYSQMINISDYINRWIFVTITNNRLNNSKIYINGRLIDQKPISNLGNIHASN NIMFKLDGCRDTHRYIWIKYFNLFDKELNEKEIKDLYDNQSNSGILKDFWG DYLQYDKPYYMLNLYDPNKYVDVNNVGIRGYMYLKGPRGSVMTTNIYLN

[0233]

		SSLYRGTKFIIKKYASGNKDNIVRNNDRVYINVVVKNKEYRLATNASQAGV EKILSALEIPDVGNLSQVVVMKSKNDQGITNKCKMNLQDNNGNDIGFIGFH QFNNIAKLVASNWYNRQIERSSRTLGCSWEFIPVDDGWGERPL
29	BoNT/X-LC-H_N-B1-Hc C467S	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFEE LLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIPV QGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIYV NILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNGL LYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGSIEVENKDLFLISNK DSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILERN EELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEALS NPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKSS DTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVIG GELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHTY KALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAMK NTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTNLS SSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIINLNNIILNLRYKDNNLID LSGYGAKVEVYDGVELNDKNQFKLTSSANSKIRVTQNQNIIFNSVFLDFSVS FWIRIPKYKNDGIQNYIHNEYTIINCMKNNSGWKISIRGNRIIWTLIDINGKTK SVFFEYNIREDISEYINRWFFVTITNNLNNAKIYINGKLESNTDIKDIREVIANG EIIFKLDGDIDRTQFIWMKYFSIFNTELSQSNIEERYKIQSYSEYLKDFWGNPL MYNKEYYMFNAGNKNSYIKLKKDSPVGEILTRSKYNQNSKYINYRDLYIGE KFIIRRKSNSQSINDDIVRKEDYIYLDFFNLNQEWRVYTYKYFKKEEEKLFLA PISDSDEFYNTIQIKEYDEQPTYSCQLLFKKDEESTDEIGLIGIHRFYESGIVFE EYKDYFCISKWYLKEVKRKPYNLKLGCNWQFIPKDEGWTE
30	BoNT/X-LC-H_N-C1-Hc C467S	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFEE LLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIPV QGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIYV NILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNGL LYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGSIEVENKDLFLISNK DSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILERN EELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEALS NPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKSS DTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVIG GELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHTY KALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAMK NTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTNLS SSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIINDSKILSLQNRKNTLV DTSGYNAEVSEEGDVQLNPIFPFDFKLGSSGEDRGKVIVTQNENIVYNSMYE SFSISFWIRINKWVSNLPGYTIIDSVKNNSGWSIGIISNFLVFTLKQNEDSEQSI NFSYDISNNAPGYNKWFFVTVTNNMMGNMKIYINGKLIDTIKVKELTGINFS KTITFEINKIPDTGLITSDSDNINMWIRDFYIFAKELDGKDINILFNSLQYTNVV KDYWGNDLRYNKEYYMVNIDYLNRYMYANSRQIVFNTRRNNNDFNEGYK IIIKRIRGNTNDTRVRGGDILYFDMTINNKAYNLFMKNETMYADNHSTEDIY AIGLREQTKDINDNIIFQIQPMNNTYYYASQIFKSNFNGENISGICSIGTYRFRL

[0234]

		GGDWYRHNYLVPTVKQGNYASLLESTSTHWGFVPVSE
31	BoNT/X R360A/Y363F	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFEE LLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIPV QGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVAKHFLKERPIDPIYV NILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNGL LYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGCIEVENKDLFLISNK DSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILERN EELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEALS NPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKSS DTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVIG GELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHTY KALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAMK NTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTNLS SSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGKIK DLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNFSIS FWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKIVT PDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRLKN NRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYNKK YYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSKVLI KNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDLTTD FEIIQRQEKYRNYCQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSAWYF QNYENLNLRKHTKTNWYFIPKDEGWDED
32	BoNT/X H227Y	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMYELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFEE LLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIPV QGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIYV NILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNGL LYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGCIEVENKDLFLISNK DSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILERN EELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEALS NPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKSS DTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVIG GELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHTY KALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAMK NTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTNLS SSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGKIK DLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNFSIS FWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKIVT PDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRLKN NRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYNKK YYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSKVLI KNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDLTTD FEIIQRQEKYRNYCQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSAWYF QNYENLNLRKHTKTNWYFIPKDEGWDED
33	BoNT/X E228Q	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV

[0235]

		KREFAPDPASTLMHQLVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIPV QGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIYV NILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNGL LYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGCIEVENKDLFLISNK DSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILERN EELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEALS NPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKSS DTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVIG GELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHTY KALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAMK NTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTNLS SSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGKIK DLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNFSIS FWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKIVT PDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRLKN NRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYNKK YYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSKVLI KNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDLTTD FEIIQRQEKYRNYCQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSAWYF QNYENLNLRKHTKTNWYFIPKDEGWDED
34	BoNT/X H231Y	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVYVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFEE LLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIPV QGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIYV NILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNGL LYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGCIEVENKDLFLISNK DSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILERN EELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEALS NPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKSS DTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVIG GELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHTY KALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAMK NTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTNLS SSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEIEDYEVLNLGAEDGKIK DLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIKIAMNKYLRFSATDNFSIS FWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQDSKLIWYLRDHNNSIKIVT PDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDISSIWNTEVDDPIIFRLKN NRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFNSNYIRDIWGNPLQYNKK YYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTITFPNNIRYGALYNGSKVLI KNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNEDTNYIGTTYGTTHDLTTD FEIIQRQEKYRNYCQLKTPYNIFHKSGLMSTETSKPTFHDYRDWVYSSAWYF QNYENLNLRKHTKTNWYFIPKDEGWDED
35	BoNT/X-LC-H_N R360A/Y363F	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFEE LLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIPV QGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVAKHFLKERPIDPIYV NILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNGL LYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGCIEVENKDLFLISNK

[0236]

		DSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILERN EELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEALS NPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKSS DTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVIG GELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHTY KALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAMK NTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTNLS SSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEI
36	BoNT/X-LC-H_N H227Y	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMYELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFEE LLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIPV QGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIYV NILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNGL LYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGCIEVENKDLFLISNK DSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILERN EELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEALS NPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKSS DTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVIG GELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHTY KALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAMK NTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTNLS SSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEI
37	BoNT/X-LC-H_N E228Q	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHQLVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFE ELLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIPV QGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIYV NILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNGL LYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGCIEVENKDLFLISNK DSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILERN EELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEALS NPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKSS DTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVIG GELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHTY KALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAMK NTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTNLS SSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEI
38	BoNT/X-LC-H_N H231Y	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVYVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFEE LLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIPV QGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIYV NILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNGL LYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGCIEVENKDLFLISNK DSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILERN EELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEALS NPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKSS DTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVIG

[0237]

		GELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHTY KALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAMK NTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTNLS SSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEI
39	VAMP1	MSAPAQPPAEGTEGTAPGGGPPGPPPNMTSNRRLQQTQAQVEEVVDIIRVN VDKVLERDQKLSELDDRADALQAGASQFESSAAKLKRKYWWKNCKMMIM LGAICAIIVVVIVIYFFT
40	VAMP2	MSATAATAPPAAPAGEGGPPAPPPNLTSNRRLQQTQAQVDEVVDIMRVNV DKVLERDQKLSELDDRADALQAGASQFETSAAKLKRKYWWKNLKMMIIL GVICAIILIIIVYFSS
41	VAMP3	MSTGVPSGSSAATGSNRRLQQTQNQVDEVVDIMRVNVDKVLERDQKLSEL DDRADALQAGASQFETSAAKLKRKYWWKNCKMWAIGISVLVIIVIIIVWC VS
42	VAMP4	MPPKFKRHLNDDDVTGSVKSERRNLLEDDSDEEEDFFLRGPSGPRFGPRND KIKHVQNQVDEVIDVMQENITKVIERGERLDELQDKSESLSDNATAFSNRSK QLRRQMWWRGCKIKAIMALVAAILLLVIIILIVMKYRT
43	VAMP5	MAGIELERCQQQANEVTEIMRNNFGKVLERGVKLAELQQRSDQLLDMSSTF NKTTQNLAQKKCWENIRYRICVGLVVVGVLLIILIVLLVVFLPQSSDSSSAPR TQDAGIASGPGN
44	Ykt6	MKLYSLSVLYKGEAKVVLLKAAYDVSSFSFFQRSSVQEFMTFTSQLIVERSS KGTRASVKEQDYLCHVYVRNDSLAGVVIADNEYPSRVAFTLLEKVLDEFSK QVDRIDWPVGSPATIHYPALDGHLSRYQNPREADPMTKVQAELDETKIILHN TMESLLERGEKLDDLVSKSEVLGTQSKAFYKTARKQNSCCAII
45	BoNT/X-LC-H_N-LPETGG	MKLEINKFNYNDPIDGINVITMRPPRHSDKINKGKGPFKAFQVIKNIWIVPER YNFTNNTNDLNIPSEPIMEADAIYNPNYLNTPSEKDEFLQGVIKVLERIKSKP EGEKLLELISSSIPLPLVSNGALTLSDNETIAYQENNNIVSNLQANLVIYGPGP DIANNATYGLYSTPISNGEGTLSEVSFSPFYLKPFDESYGNYRSLVNIVNKFV KREFAPDPASTLMHELVHVTHNLYGISNRNFYYNFDTGKIETSRQQNSLIFEE LLTFGGIDSKAISSLIIKKIIETAKNNYTTLISERLNTVTVENDLLKYIKNKIPV QGRLGNFKLDTAEFEKKLNTILFVLNESNLAQRFSILVRKHYLKERPIDPIYV NILDDNSYSTLEGFNISSQGSNDFQGQLLESSYFEKIESNALRAFIKICPRNGL LYNAIYRNSKNYLNNIDLEDKKTTSKTNVSYPCSLLNGCIEVENKDLFLISNK DSLNDINLSEEKIKPETTVFFKDKLPPQDITLSNYDFTEANSIPSISQQNILERN EELYEPIRNSLFEIKTIYVDKLTTFHFLEAQNIDESIDSSKIRVELTDSVDEALS NPNKVYSPFKNMSNTINSIETGITSTYIFYQWLRSIVKDFSDETGKIDVIDKSS DTLAIVPYIGPLLNIGNDIRHGDFVGAIELAGITALLEYVPEFTIPILVGLEVIG GELAREQVEAIVNNALDKRDQKWAEVYNITKAQWWGTIHLQINTRLAHTY KALSRQANAIKMNMEFQLANYKGNIDDKAKIKNAISETEILLNKSVEQAMK NTEKFMIKLSNSYLTKEMIPKVQDNLKNFDLETKKTLDKFIKEKEDILGTNLS SSLRRKVSIRLNKNIAFDINDIPFSEFDDLINQYKNEILPETGG
46	G-BoNT/X-Hc	GEDYEVLNLGAEDGKIKDLSGTTSDINIGSDIELADGRENKAIKIKGSENSTIK IAMNKYLRFSATDNFSISFWIKHPKPTNLLNNGIEYTLVENFNQRGWKISIQD SKLIWYLRDHNNSIKIVTPDYIAFNGWNLITITNNRSKGSIVYVNGSKIEEKDI SSIWNTEVDDPIIFRLKNNRDTQAFTLLDQFSIYRKELNQNEVVKLYNYYFN SNYIRDIWGNPLQYNKKYYLQTQDKPGKGLIREYWSSFGYDYVILSDSKTIT FPNNIRYGALYNGSKVLIKNSKKLDGLVRNKDFIQLEIDGYNMGISADRFNE DTNYIGTTYGTTHDLTTDFEIIQRQEKYRNYCQLKTPYNIFHKSGLMSTETSK PTFHDYRDWVYSSAWYFQNYENLNLRKHTKTNWYFIPKDEGWDED
47	BoNT/A1-Hc	IINTSILNLRYESNHLIDLSRYASKINIGSKVNFDPIDKNQIQLFNLESSKIEVIL KNAIVYNSMYENFSTSFWIRIPKYFNSISLNNEYTIINCMENNSGWKVSLNYG EIIWTLQDTQEIKQRVVFKYSQMINISDYINRWIFVTITNNRLNNSKIYINGRLI DQKPISNLGNIHASNNIMFKLDGCRDTHRYIWIKYFNLFDKELNEKEIKDLY DNQSNSGILKDFWGDYLQYDKPYYMLNLYDPNKYVDVNNVGIRGYMYLK GPRGSVMTTNIYLNSSLYRGTKFIIKKYASGNKDNIVRNNDRVYINVVVKNK EYRLATNASQAGVEKILSALEIPDVGNLSQVVVMKSKNDQGITNKCKMNLQ DNNGNDIGFIGFHQFNNIAKLVASNWYNRQIERSSRTLGCSWEFIPVDDGWG

[0238]

		ERPL
48	BoNT/B1-Hc	ILNNIILNLRYKDNNLIDLSGYGAKVEVYDGVELNDKNQFKLTSSANSKIRV TQNQNIIFNSVFLDFSVSFWIRIPKYKNDGIQNYIHNEYTIINCMKNNSGWKIS IRGNRIIWTLIDINGKTKSVFFEYNIREDISEYINRWFFVTITNNLNNAKIYING KLESNTDIKDIREVIANGEIIFKLDGDIDRTQFIWMKYFSIFNTELSQSNIEERY KIQSYSEYLKDFWGNPLMYNKEYYMFNAGNKNSYIKLKKDSPVGEILTRSK YNQNSKYINYRDLYIGEKFIIRRKSNSQSINDDIVRKEDYIYLDFFNLNQEWR VYTYKYFKKEEEKLFLAPISDSDEFYNTIQIKEYDEQPTYSCQLLFKKDEEST DEIGLIGIHRFYESGIVFEEYKDYFCISKWYLKEVKRKPYNLKLGCNWQFIPK DEGWTE
49	BoNT/C1-Hc	INDSKILSLQNRKNTLVDTSGYNAEVSEEGDVQLNPIFPFDFKLGSSGEDRGK VIVTQNENIVYNSMYESFSISFWIRINKWVSNLPGYTIIDSVKNNSGWSIGIIS NFLVFTLKQNEDSEQSINFSYDISNNAPGYNKWFFVTVTNNMMGNMKIYIN GKLIDTIKVKELTGINFSKTITFEINKIPDTGLITSDSDNINMWIRDFYIFAKEL DGKDINILFNSLQYTNVVKDYWGNDLRYNKEYYMVNIDYLNRYMYANSR QIVFNTRRNNNDFNEGYKIIIKRIRGNTNDTRVRGGDILYFDMTINNKAYNLF MKNETMYADNHSTEDIYAIGLREQTKDINDNIIFQIQPMNNTYYYASQIFKS NFNGENISGICSIGTYRFRLGGDWYRHNYLVPTVKQGNYASLLESTSTHWGF VPVSE
50	凝血酶 切割位点	LVPR|GS
51	TEV	ENLYFQ|G
52	PreScission 切割位点	LEVLFQ|GP
53	因子Xa 切割位点	IEGR|
54	因子Xa 切割位点	IDGR|
55	肠激酶 切割位点	DDDDK|
56	SUMO 蛋白酶 切割位点	AHREQ|GG|

[0239] *通过加下划线来表示突变

[0240] 新的肉毒神经毒素及其衍生物

[0241] 肉毒神经毒素(BoNT)是最危险的潜在生物恐怖剂之一,并且临床上也将其用于治疗越来越多的医学病症。到目前为止已知有七种BoNT血清型(BoNT/A-G),并且在过去的45年中没有识别出新的类型。肉毒梭菌菌株的基因组数据库检索揭示了被称为BoNT/X的新的BoNT类型。该毒素显示出与其他BoNT的最低序列同一性,并且未被针对已知BoNT类型产生的抗血清识别。其切割神经元中的囊泡相关膜蛋白(vesicle associated membrane protein,VAMP),所述VAMP也是BoNT/B/D/F/G的靶标,但是BoNT/X在对该毒素来说是独特的位点(VAMP2上的Arg66至Ala67之间)处切割。为了验证BoNT/X的活性,通过使用转肽酶(定位酶)将BoNT/X的两个无毒片段共价连接而组装有限量的全长BoNT/X。经组装的BoNT/X进入培养的神经元并切割VAMP2,并在小鼠中引起通过趾外展评分(Digit Abduction Score)测定测量的松弛性瘫痪。这些数据一起将BoNT/X确定为新的BoNT类型。它的发现为开发有效的对策提出了紧迫的挑战,并且也为潜在的治疗应用提供了新的工具。

[0242] 检索基因组数据库揭示了新的BoNT基因

[0243] 为了调查BoNT的进化情况,利用七种BoNT的序列作为探针,对PubMed序列数据库进行迭代隐马尔可夫模型(iterative Hidden Markov model)检索。该检索成功确定了主要的BoNT血清型、亚型和镶嵌毒素,以及相关的破伤风神经毒素(tetanus neurotoxin,TeNT)(图5)。出乎意料的是,它还揭示了来自最近报道的肉毒梭菌菌株111的基因组序列的新BoNT基因(GenBank No.BAQ12790.1)。该毒素基因在本文中定名为BoNT/X。

[0244] 系统发生分析揭示BoNT/X明显不同于所有其他BoNT和TeNT(图1A)。它在BoNT/TeNT家族内的成对比较中与任何其他BoNT具有最小的蛋白质序列同一性(＜31％)(图1A)。例如,BoNT/A和BoNT/B共享39％的序列同一性,并且BoNT/B和BoNT/G具有58％的序列同一性。此外,滑动序列比较窗口示出,与其他七种BoNT和TeNT相比,低相似性沿BoNT/X序列均匀分布(图1B),表明它不是镶嵌毒素。

[0245] 尽管具有低的序列同一性,但是在BoNT/X中,BoNT的整体结构域排列和一些关键特征显示是保守的(图1B),其包括:(1)保守的锌依赖性蛋白酶基序HExxH(第227至231位残基,HELVH(SEQ ID NO:92))位于推定的LC中;(2)两个保守的半胱氨酸(其可形成必需的链间二硫键)位于推定的LC与HC之间的边界处;(3)保守受体结合基序SxWY(其识别脂质辅助受体(co-receptor)神经节苷脂)存在于推定的H_C(第1274至1277位残基,SAWY(SEQ ID NO:93))中[43,44]。

[0246] 正如预期的,在BoNT/X基因之前的是推定的NTNHA基因(图1C)。它们位于OrfX基因簇中。然而,与其他两个已知的OrfX簇相比,BoNT/X的OrfX基因簇具有两个独特的特征(图1C):(1)在BoNT/X基因旁边有另外的OrfX2蛋白(定名为OrfX2b),这在任何其他OrfX簇中还没有被报道过;(2)OrfX基因的阅读框与BoNT/X基因的具有相同的方向,而它们通常与其他OrfX簇中BoNT基因的方向相反(图1C)。这些特征一起表明BoNT/X可构成BoNT家族的独特进化分支。

[0247] BoNT/X的LC在新位点处切割VAMP2

[0248] 接下来检查BoNT/X是否是功能性毒素。首先,研究BoNT/X的LC(X-LC)。通过与其他BoNT的序列比对确定LC的边界(第1至439位残基)。合成编码LC的cDNA,并在大肠杆菌中产生LC作为His6标记的重组蛋白。将X-LC与大鼠脑洗涤剂提取物(BDE)一起孵育,并使用免疫印迹分析以检查脑中的三种主要SNARE蛋白SNAP-25、VAMP2和突触融合蛋白1是否被切割。将BoNT/A的LC(A-LC)和BoNT/B的LC(B-LC)平行作为对照进行测定。BoNT/A对SNAP-25的切割产生较小的片段,其仍然可在免疫印迹上识别,而BoNT/B对VAMP2的切割消除了VAMP2的免疫印迹信号(图2A)。还对突触小泡蛋白(Syp)(一种突触囊泡蛋白)作为内部上样对照进行检测。X-LC与大鼠脑DTE的孵育不影响突触融合蛋白1或SNAP-25,但是消除了VAMP2信号(图2A)。BoNT的LC是锌依赖性蛋白酶[25]。正如预期的,EDTA防止X-、A-和B-LC对SNARE蛋白的切割(图2A)。为了进一步证实X-LC切割VAMP2,将作为His6标记蛋白质的VAMP2的胞质结构域(第1至96位残基)进行纯化。VAMP2(1至96)与X-LC的孵育将VAMP2条带转化为SDS-PAGE凝胶上的两个较低分子量条带(图2B),这证实X-LC切割VAMP2。

[0249] 为了确定VAMP2上的切割位点,通过液相色谱-串联质谱(LC-MS/MS),在与或不与X-LC一起预孵育的情况下分析VAMP2(1至96)蛋白质(图2C至2E,详见下文)。在与X-LC一起孵育后出现单个主肽峰(图2C、2E和图6)。确定其分子量为3081.7,其仅符合VAMP2的残基A67至L96的肽序列(图2C,2E)。一致地,还检测到从His6标签开始至VAMP2的残基R66的另一个片段(图2D)。为了进一步证实该结果,用以下不同的VAMP2片段进行重复测定:GST标记的重组VAMP2(33至86)(图7)。与X-LC一起孵育产生单主峰,分子量为2063.1,其仅符合VAMP2的残基A67至R86的肽序列(图7D至7E)。正如预期的,还检测到从GST标签开始至VAMP2的残基R66的另一个片段(图7F)。这些结果一起表明X-LC在R66和A67之间的VAMP2上具有单切割位点。

[0250] R66至A67是与所有其他BoNT的已建立的靶位点不同的新切割位点(图2F)。它也是位于先前已知为SNARE基序的区域内的唯一BoNT切割位点(图2F,阴影区域)[45]。VAMP家族蛋白包括VAMP1、2、3、4、5、7、8以及相关的Sec22b和Ykt6。R66至A67在与VAMP2高度同源的VAMP1和VAMP3中是保守的,但在其他VAMP同源物(例如VAMP7和VAMP8)中则不是保守的。为了验证X-LC的特异性,通过瞬时转染在HEK293细胞中表达HA标记的全长VAMP1、3、7、8和myc标记的Sec22b和Ykt6。将细胞裂解物与X-LC一起孵育(图2G)。如免疫印迹信号向较低分子量的移动所证实的,VAMP1和3二者均被X-LC切割,而VAMP7、VAMP8和Sec22B对X-LC具有抗性(图2G)。

[0251] 出乎意料的是,Ykt6被X-LC切割(图2G)。使用经纯化的GST标记的Ykt6片段证实了该发现,该片段在与X-LC一起孵育后移动至较低分子量条带(图2H)。通过完整Ykt6相对于X-LC切割的Ykt6的质谱分析确定切割位点为K173至S174(图13A)。这是VAMP2中切割位点的同源位点(图2F),表明切割位点的位置在不同的VAMP之间是保守的。在VAMP成员之间,VAMP4在该位点包含与Ykt6相同的残基对(K87至S88)。发现,通过X-LC高效地切割VAMP4的GST标记的胞质结构域(图2I)。一致地,X-LC切割BDE中的天然VAMP4(图4J)。作为对照,Sec22b未被BDE中的X-LC切割。另外,VAMP5的GST标记的胞质结构域也被切割,尽管是以比VAMP2和VAMP4更慢的速度(图2I)。通过质谱分析证实切割位点是VAMP4中的K87至S88和VAMP5中的R40至S41(图14)。这两者都是VAMP2中切割位点的同源位点(图2F)。X-LC切割VAMP4、VAMP5和Ykt6的能力高度地不寻常,因为它们的序列与VAMP1/2/3显著不同。BoNT/X是第一个可切割典型靶标VAMP1/2/3以外的VAMP的BoNT[66]。X-LC还切割BDE中的VAMP4,并且EDTA阻断该切割(图2J)。

[0252] BoNT/X的显著特征是其独特的切割VAMP4和Ykt6的能力。VAMP4被广泛表达并且已知其介导反面高尔基网(trans-Golgi network,TGN)于内体之间的囊泡融合,以及内体的同型融合[59,60]。Ykt6是不具有跨膜结构域的非典型SNARE[67-70]。它通过脂化锚定于膜,这允许动态调节其膜缔合。Ykt6是酵母中的关键蛋白质,其参与多种膜融合事件,包括ER-高尔基体、内高尔基体、内体-高尔基体-液泡、以及自噬体的形成。其在哺乳动物细胞中的功能仍有待确定。传统上已知BoNT限于靶向介导囊泡胞吐到质膜上的SNARE。BoNT/X是第一个能够切割介导多种细胞内膜运输事件之SNARE的BoNT。

[0253] 有趣的是,VAMP4和Ykt6二者均都在神经元中富含。最近的研究表明,VAMP4也可有助于神经元中的异步的突触囊泡胞吐作用、扩大体胞吐作用和活性依赖性大量胞吞作用(activity-dependent bulk endocytosis,ADBE)[61-63]。Ykt6在神经元中的作用仍有待确定,但已显示其可抑制帕金森病(Parkinson's disease)模型中α-突触核蛋白(α-synuclein)的毒性[71-72]。BoNT/X的另一种底物VAMP5主要在肌细胞中表达,并且其功能仍有待确定[64]。BoNT/X将成为研究VAMP4、Ykt6和VAMP5功能以及相关膜运输事件的有力工具。此外,VAMP4参与免疫细胞中的颗粒释放[65],因此BoNT/X可能在所有BoNT中具有调节免疫细胞中炎性分泌的独特潜力。

[0254] BoNT/X的蛋白水解活化

[0255] BoNT最初作为单一多肽产生。LC与H_N之间的接头区需要在已知为“活化”的过程中被细菌或宿主蛋白酶切割,这对于BoNT的活性是必需的。在将LC易位到细胞的胞质溶胶中之前,BoNT的LC和H_N通过链间二硫键保持连接,其中二硫键被还原以将LC释放到胞质溶胶

中。序列比对揭示，与所有其他BoNT相比，BoNT/X包含两个保守半胱氨酸之间最长的接头区(C423至C467，图3A)。另外，BoNT/X的接头区包含另外的半胱氨酸(C461)，其对BoNT/X来说是独特的。

[0256] 为了检查BoNT/X的LC与H_N之间的接头区是否易受蛋白水解切割的影响，在大肠杆菌中产生重组X-LC-H_N片段(第1至891位残基)并通过内蛋白酶Lys-C对其进行限制性蛋白酶解，所述内蛋白酶Lys-C在赖氨酸残基的C端侧进行切割。为了在受限的蛋白酶解条件下确定易受影响的切割位点，使用串联质量标签(Tandem Mass Tag，TMT)标记和串联质谱法对X-LC-H_N进行分析。TMT标记游离的N端(和赖氨酸)。Lys-C的受限蛋白酶解产生另外的游离N端，其在完整的X-LC-H_N样品中不存在(详见下文)。简单地说，用轻TMT标记完整的X-LC-H_N样品，并将等量的X-LC-H_N样品暴露于Lys-C，并随后用重(heavy)TMT标记。然后将这两个样品用胰凝乳蛋白酶消化，合并在一起，并对其进行定量质谱分析。确定的肽的列表示于下表2中。对于每种肽，轻TMT:重TMT比值通常在彼此的2倍之内，除了以N439开始的5种肽对轻TMT标记未显示信号，表明这是通过Lys-C切割产生的新的N端(图3A，表2)。因此，在受限的蛋白水解条件下，Lys-C优先切割K438至N439，表明接头区易受蛋白酶的影响(图3A)。

[0257] 接下来检查这种蛋白水解活化对BoNT/X的功能是否重要。先前已经显示，高浓度的BoNT的LC-H_N与培养的神经元的孵育导致LC-H_N进入到神经元中，可能通过非特异性摄取进入到神经元中[46,47]。使用该方法，比较完整与活化的X-LC-H_N对培养的大鼠皮质神经元的效力。将神经元暴露于培养基中的X-LC-H_N持续12小时。收获细胞裂解物并进行免疫印迹分析以检查SNARE蛋白的切割。如图3B中所示，X-LC-H_N以浓度依赖性方式进入神经元并切割VAMP2。由Lys-C活化的X-LC-H_N显示出比完整X-LC-H_N显著提高的效力:10nM活化的X-LC-H_N切割与150nM完整X-LC-H_N相似水平的VAMP2(图3B)。注意，完整的X-LC-H_N可能易受细胞表面蛋白酶的蛋白水解切割的影响，这就是为什么它在高浓度下仍然对神经元有活性的原因。有趣的是，活化的X-LC-H_N显示出比活化的BoNT/A的LC-H_N(A-LC-H_N)和BoNT/B的LC-H_N(B-LC-H_N)更强效，在相同测定条件下，后二者没有显示出对它们在神经元中的SNARE底物的任何可检测到的切割(图3B)。

[0258] 表2.通过TMT标记和定量质谱分析受限蛋白酶解下的X-LC-H_N的肽片段。

[0259] 用轻TMT标记His6标记的重组X-LC-H_N。将等量的X-LC-H_N样品暴露于Lys-C并随后用重TMT标记。然后将这两个样品用胰凝乳蛋白酶消化，合并在一起，并对其进行定量质谱分析。示出了确定的肽的列表。对于所有肽，轻TMT:重TMT比值在彼此的2倍内，除了以N439开始的五种肽(具有下划线)。这五种肽对轻TMT标记未显示信号，表明N439是通过Lys-C切割产生的新的N端。表2中的肽序列从上到下对应于SEQ ID NO:94至226。

[0260]

ScanF	z	理论 m/z	PPM	X Corr	Δ Corr	Ref.	肽	开始位置	结束位置	最大重	最大轻	H/L 比值
16633	2	611.384	1.46	1.751	0.651	xLcHN	K.L]EINK#F.N	3	8	4.03E+04	2.92E+04	1.38
16638	2	606.3736	0.95	1.71	0.654	xLcHN	K.LEINKF.N	3	8	4.03E+04	2.92E+04	1.38
15946	2	912.456	2.74	4.083	0.877	xLcHN	F.N]YNDPIDGINVITM*.R	9	22	4.34E+05	9.26E+05	0.47
15942	2	909.9508	2.28	4.546	0.661	xLcHN	F.NYNDPIDGINVITM*.R	9	22	4.34E+05	9.26E+05	0.47
17201	2	785.9092	1.26	2.455	0.273	xLcHN	F.NYNDPIDGINVLT	9	20	1.14E+06	1.94E+06	0.59
11082	2	679.833	1.17	1.74	0.754	xLcHN	F.NYNDPIDGIN.V	9	18	8.01E+05	1.20E+06	0.67
11083	2	682.3382	0.96	2.6	0.742	xLcHN	F.N]YNDPIDGIN.V	9	18	8.01E+05	1.20E+06	0.67
19628	2	535.3264	0.97	1.391	0.701	xLcHN	D.P]IDGINVLT	13	20	6.55E+04	1.23E+05	0.53
19626	2	532.8211	0.68	1.474	0.608	xLcHN	D.PIDGINVLT	13	20	6.55E+04	1.23E+05	0.53
20815	4	802.2073	2.19	2.962	0.582	xLcHN	Y.N]PNYLNTPSEK#DEFLQGVIK#VL.E	78	99	4.57E+04	1.21E+05	0.38
20463	4	802.2073	1.96	2.726	0.385	xLcHN	Y.N]PNYLNTPSEK#DEFLQGVIK#VL.E	78	99	2.96E+04	8.18E+04	0.36
20799	4	798.4495	1.91	3.647	0.659	xLcHN	Y.NPNYLNTPSEKDEFLQGVIKVL.E	78	99	4.57E+04	1.21E+05	0.38
20568	4	798.4495	1.63	2.639	0.419	xLcH	Y.NPNYLNTPSEKD	78	99	2.96E+04	8.18E+04	0.36

[0261]

						N	EFLQGVI KVLE					
22720	2	753.4631	1.96	2.339	0.222	xLcH N	L.LELISSS IPLPL.V	112	123	1.40E+04	2.80E+04	0.50
21170	2	696.9211	1.9	1.781	0.326	xLcH N	L.ELISSSI PLPL.V	113	123	2.75E+04	4.15E+04	0.66
21281	2	696.9211	1.86	2.099	0.282	xLcH N	L.ELISSSI PLPL.V	113	123	2.75E+04	4.15E+04	0.66
21378	2	696.9211	1.83	1.593	0.149	xLcH N	L.ELISSSI PLPL.V	113	123	2.75E+04	4.15E+04	0.66
19246	2	578.363	1.18	1.443	0.27	xLcH N	L.I]SSSIPL PL.V	115	123	1.61E+04	4.12E+04	0.39
19365	2	578.363	1.08	1.624	0.135	xLcH N	L.I]SSSIPL PL.V	115	123	1.61E+04	4.12E+04	0.39
19241	2	575.8577	1	1.484	0.209	xLcH N	L.ISSSIPL PL.V	115	123	1.61E+04	4.12E+04	0.39
19360	2	575.8577	0.91	1.673	0.298	xLcH N	L.ISSSIPL PL.V	115	123	1.61E+04	4.12E+04	0.39
13952	2	948.9912	2.47	2.562	0.54	xLcH N	L.V]SNGA LTLSDNE TIAY.Q	124	139	2.51E+05	3.67E+05	0.68
13949	2	946.486	2.42	1.729	0.599	xLcH N	L.VSNGA LTLSDNE TIAY.Q	124	139	2.51E+05	3.67E+05	0.68
6712	2	392.7318	0.19	1.523	0.206	xLcH N	L.VSNGA L.T	124	129	1.18E+05	2.03E+05	0.58
10243	2	678.3482	0.73	1.499	0.616	xLcH N	L.T]LSDN ETIAY.Q	130	139	2.14E+05	3.67E+05	0.58
10242	2	675.843	0.69	1.594	0.842	xLcH N	L.TLSDNE TIAY.Q	130	139	2.14E+05	3.67E+05	0.58
15890	2	1110.579	2.74	2.243	0.6	xLcH N	L.Q]ANLV IYGPGPDI ANNATY. G	150	168	5.20E+04	9.82E+04	0.53
15881	2	1108.073	1.86	2.121	0.673	xLcH N	L.QANLVI YGPGPDI ANNATY.	150	168	5.20E+04	9.82E+04	0.53

[0262]

							G					
11142	2	727.3879	1.39	1.945	0.635	xLcH N	L.VIYGPG PDIANN.A	154	165	1.91E+04	3.90E+04	0.49
12879	2	894.962	1.24	2.673	0.731	xLcH N	L.VIYGPG PDIANNA TY.G	154	168	6.62E+05	1.25E+06	0.53
10964	2	707.3541	2.8	1.39	0.466	xLcH N	Y.GPGPDI ANNATY. G	157	168	1.42E+04	2.24E+04	0.63
11091	2	456.2473	0.78	1.352	0.765	xLcH N	N.ATYGL Y.S	166	171	3.55E+04	8.08E+04	0.44
17435	2	1094.055	2.53	3.418	0.69	xLcH N	Y.GJLYST PISNGEGT LSEVSF.S	169	187	1.55E+05	2.27E+05	0.68
17410	2	1091.549	2.48	3.748	0.738	xLcH N	Y.GLYSTP ISNGEGT LSEVSF.S	169	187	1.55E+05	2.27E+05	0.68
19830	2	1259.631	2.15	2.885	0.676	xLcH N	Y.GJLYST PISNGEGT LSEVSFSP F.Y	169	190	1.98E+04	2.46E+04	0.81
20131	3	838.4197	2.08	2.781	0.742	xLcH N	Y.GLYSTP ISNGEGT LSEVSFSP F.Y	169	190	4.60E+05	5.32E+05	0.86
12546	2	862.9488	1.9	1.817	0.401	xLcH N	Y.GJLYST PISNGEGT LS.E	169	183	7.95E+04	7.83E+04	1.02
12571	2	860.4436	1.84	1.528	0.588	xLcH N	Y.GLYSTP ISNGEGT LS.E	169	183	7.95E+04	7.83E+04	1.02
19819	3	838.4197	1.61	2.655	0.662	xLcH N	Y.GLYSTP ISNGEGT LSEVSFSP F.Y	169	190	4.13E+04	4.59E+04	0.90
9948	2	851.4307	2.54	2.044	0.765	xLcH N	Y.STPISN GEGTLSE VS.F	172	186	1.92E+04	2.39E+04	0.81
18409	2	1090.541	2.45	4.434	0.844	xLcH N	Y.STPISN GEGTLSE VSFSPF.Y	172	190	8.21E+05	9.22E+05	0.89
18417	2	1090.541	2.39	3.307	0.82	xLcH N	Y.STPISN GEGTLSE VSFSPF.Y	172	190	8.21E+05	9.22E+05	0.89
18418	2	1093.047	2.39	2.983	0.845	xLcH	Y.STPISN GEGTLSE	172	190	8.21E+05	9.22E+05	0.89

[0263]

						N	VSFSPF.Y					
18876	2	1093.047	1.97	1.841	0.679	xLcH N	Y.S]TPISN GEGTLSE VSFSPF.Y	172	190	8.21E+05	9.22E+05	0.89
14591	2	927.4701	1.96	3.362	0.646	xLcH N	Y.S]TPISN GEGTLSE VSF.S	172	187	2.09E+05	1.42E+05	1.48
14803	2	924.9649	1.88	1.934	0.462	xLcH N	Y.STPISN GEGTLSE VSF.S	172	187	2.96E+05	4.65E+05	0.64
14852	2	924.9649	1.87	1.538	0.369	xLcH N	Y.STPISN GEGTLSE VSF.S	172	187	2.96E+05	4.65E+05	0.64
18554	2	1093.047	1.72	3.044	0.86	xLcH N	Y.S]TPISN GEGTLSE VSFSPF.Y	172	190	8.21E+05	9.22E+05	0.89
18552	2	1090.541	1.68	3.643	0.813	xLcH N	Y.STPISN GEGTLSE VSFSPF.Y	172	190	8.21E+05	9.22E+05	0.89
14978	2	927.4701	1.68	1.401	0.31	xLcH N	Y.S]TPISN GEGTLSE VSF.S	172	187	4.96E+04	7.37E+04	0.67
18680	2	1093.047	1.66	1.656	0.717	xLcH N	Y.S]TPISN GEGTLSE VSFSPF.Y	172	190	8.21E+05	9.22E+05	0.89
20660	2	1093.047	1.63	2.182	0.831	xLcH N	Y.S]TPISN GEGTLSE VSFSPF.Y	172	190	5.24E+05	5.44E+05	0.96
17226	2	924.9649	1.62	2.459	0.698	xLcH N	Y.STPISN GEGTLSE VSF.S	172	187	3.25E+05	5.31E+05	0.61
17306	2	924.9649	1.62	2.126	0.588	xLcH N	Y.STPISN GEGTLSE VSF.S	172	187	3.25E+05	5.31E+05	0.61
10139	2	696.3644	1.61	1.942	0.628	xLcH N	Y.S]TPISN GEGTLS.E	172	183	6.39E+04	8.46E+04	0.76
18674	2	1090.541	1.59	2.423	0.765	xLcH N	Y.STPISN GEGTLSE VSFSPF.Y	172	190	8.21E+05	9.22E+05	0.89
20642	2	1090.541	1.55	2.608	0.823	xLcH N	Y.STPISN GEGTLSE VSFSPF.Y	172	190	5.24E+05	5.44E+05	0.96
8077	2	696.3644	1.54	1.763	0.707	xLcH N	Y.S]TPISN GEGTLS.E	172	183	1.09E+05	1.29E+05	0.84
18476	2	562.2872	1.17	1.812	0.784	xLcH	L.SEVSFS PF.Y	183	190	4.49E+04	7.11E+04	0.63

[0264]

						N						
18478	2	564.7924	0.95	1.57	0.965	xLcH N	L.S]EVSFS PF.Y	183	190	4.49E+04	7.11E+04	0.63
13190	3	652.0048	0.97	2.099	0.697	xLcH N	F.Y]LK#PF DESYGNY .R	191	202	1.98E+06	3.09E+06	0.64
12839	3	540.6289	0.38	2.441	0.423	xLcH N	F.Y]LK#PF DESY.G	191	199	2.43E+05	5.45E+05	0.44
7115	2	538.7403	0.69	1.476	0.615	xLcH N	F.D]ESYG NY.R	196	202	1.44E+05	3.14E+05	0.46
16124	3	661.3911	1.14	2.123	0.575	xLcH N	Y.G]NYRS LVNIVNK #F.V	200	212	2.81E+04	2.27E+04	1.24
11646	3	474.5894	0.49	2.077	0.602	xLcH N	H.NLYGIS NRNF.Y	235	244	2.80E+05	4.38E+05	0.64
10091	4	603.8103	1.23	2.98	0.756	xLcH N	F.YYNFD TGKIETSR QQN.S	245	260	3.05E+05	1.94E+05	1.57
9932	4	603.8103	1.08	2.5	0.638	xLcH N	F.YYNFD TGKIETSR QQN.S	245	260	3.05E+05	1.94E+05	1.57
10782	3	820.4359	0.65	2.156	0.438	xLcH N	Y.Y]NFDT GK#IETSR QQNSL.I	246	262	7.40E+04	1.33E+05	0.56
15039	3	819.1317	1.41	2.281	0.516	xLcH N	L.ISERLN TVTVEND LLKY.I	298	314	1.45E+05	2.76E+05	0.53
13824	3	619.6838	1.27	2.021	0.44	xLcH N	L.NTVTV ENDLLKY .I	303	314	3.10E+04	5.07E+04	0.61
10975	2	760.4251	1.45	2.089	0.663	xLcH N	F.V]LNES NLAQRF.S	345	355	4.63E+05	6.60E+05	0.70
17696	3	966.86	2.14	2.704	0.532	xLcH N	H.Y]LK#E RPIDPIYV NILDDNS Y.S	363	382	8.61E+04	1.42E+05	0.61
20823	2	827.9299	2.21	2.495	0.806	xLcH N	D.P]IYVNI LDDNSY. S	371	382	7.80E+04	8.16E+04	0.96
20825	2	825.4247	2.17	2.958	0.881	xLcH N	D.PIYVNI LDDNSY. S	371	382	7.80E+04	8.16E+04	0.96

[0265]

12614	2	685.3561	1.34	1.843	0.609	xLcH N	N.I]LDDN SYSTL.E	376	385	1.01E+05	2.57E+05	0.39
11272	2	441.7421	1.48	1.795	0.903	xLcH N	Y.S]TLEG F.N	383	388	4.45E+04	1.36E+05	0.33
11261	2	439.2369	1.08	1.536	0.514	xLcH N	Y.STLEGF .N	383	388	4.45E+04	1.36E+05	0.33
14260	2	441.7421	0.49	1.462	0.848	xLcH N	Y.S]TLEG F.N	383	388	5.41E+04	1.32E+05	0.41
14246	2	439.2369	0.38	1.46	0.844	xLcH N	Y.STLEGF .N	383	388	5.41E+04	1.32E+05	0.41
13808	2	916.4629	2.48	2.036	0.498	xLcH N	F.NISSQG SNDFQGQ LL.E	389	403	2.86E+04	6.39E+04	0.45
17314	3	815.7238	2.05	2.149	0.621	xLcH N	F.NISSQG SNDFQGQ LLESSYF. E	389	408	1.26E+05	2.71E+05	0.47
6340	2	803.3788	0.75	2.554	0.721	xLcH N	F.NISSQG SNDFQGQ .L	389	401	1.03E+04	2.21E+04	0.47
11696	2	493.2814	0.67	1.62	0.518	xLcH N	L.L]YNAI Y.R	429	434	1.19E+05	1.87E+05	0.63
11692	2	490.7762	0.6	1.57	0.118	xLcH N	L.LYNAIY .R	429	434	1.19E+05	1.87E+05	0.63
14021	3	756.4332	2.14	2.305	0.363	xLcH N	K.N]YLNN IDLEDK# K#T.T	439	451	6.85E+05	5.12E+03	133. 95
12997	3	1009.909	1.93	3.044	0.553	xLcH N	K.N]YLNN IDLEDK# K#TTSK#T N.V	439	456	4.24E+05	0.00E+00	#DI V/0!
12932	3	1009.909	1.92	4.251	0.695	xLcH N	K.N]YLNN IDLEDK# K#TTSK#T N.V	439	456	4.24E+05	0.00E+00	#DI V/0!
14003	3	790.1157	1.59	2.894	0.542	xLcH N	K.N]YLNN IDLEDK# K#TT.S	439	452	4.40E+06	1.13E+04	389. 24
13105	4	729.173	1	3	0.599	xLcH N	K.N]YLNN IDLEDK# K#TTSK#T	439	455	3.39E+06	3.14E+03	1078 .97

[0266]

							.N					
11567	3	747.091	1.33	2.711	0.518	xLcH N	N.YLNNID LEDKKTT .S	440	452	1.22E+04	9.52E+04	0.13
11515	3	747.091	1.33	2.729	0.496	xLcH N	N.YLNNID LEDKKTT .S	440	452	1.22E+04	9.52E+04	0.13
17001	2	857.9579	1.99	1.967	0.713	xLcH N	G.CIEVEN KDLF.L	467	476	3.29E+04	1.64E+05	0.20
16337	4	941.793	1.76	2.419	0.135	xLcH N	F.L]ISNK# DSLNDIN LSEEK#IK #PETTVF. F	477	501	1.27E+06	1.06E+06	1.19
16394	4	941.793	1.72	2.19	0.391	xLcH N	F.L]ISNK# DSLNDIN LSEEK#IK #PETTVF. F	477	501	1.27E+06	1.06E+06	1.19
17983	3	993.888	2.4	3.193	0.657	xLcH N	K.D]SLND INLSEEK# IK#PETTV F.F	482	501	3.27E+04	2.59E+03	12.64
18031	3	955.5456	2.06	3.607	0.764	xLcH N	D.S]LNDI NLSEEK#I K#PETTV F.F	483	501	4.90E+04	4.12E+04	1.19
11720	2	834.8912	2.14	1.689	0.726	xLcH N	L.SNYDFT EANSIPS.I	514	526	2.91E+04	2.50E+04	1.17
13409	2	1065.513	2.12	4.742	0.769	xLcH N	L.S]NYDF TEANSIPS ISQQ.N	514	530	7.05E+04	7.52E+04	0.94
8896	2	642.7908	1.42	1.851	0.708	xLcH N	L.SNYDFT EAN.S	514	522	2.12E+05	2.27E+05	0.94
8883	2	645.296	1.39	2.362	0.879	xLcH N	L.S]NYDF TEAN.S	514	522	2.12E+05	2.27E+05	0.94
17774	2	1051.044	2.7	1.967	0.9	xLcH N	Y.DFTEA NSIPSISQ QNIL.E	517	533	3.52E+04	3.28E+04	1.07
17438	2	1051.044	2.55	1.944	0.665	xLcH N	Y.DFTEA NSIPSISQ QNIL.E	517	533	9.04E+04	8.08E+04	1.12
12784	2	880.9387	1.87	2.537	0.778	xLcH	Y.DFTEA NSIPSISQ	517	530	4.72E+05	5.06E+05	0.93

[0267]

						N	Q.N					
12779	2	883.4439	1.73	3.423	0.797	xLcH N	Y.D]FTEA NSIPSISQ Q.N	517	530	4.72E+05	5.06E+05	0.93
16126	4	911.7114	1.6	3.934	0.579	xLcH N	Y.DFTEA NSIPSISQ QNILERN EELYEPIR N.S	517	545	5.41E+05	2.02E+05	2.67
12449	2	937.9602	1.56	3.012	0.73	xLcH N	Y.DFTEA NSIPSISQ QN.I	517	531	5.16E+05	5.72E+05	0.90
12151	2	940.4654	1.47	1.476	0.458	xLcH N	Y.D]FTEA NSIPSISQ QN.I	517	531	4.65E+05	4.96E+05	0.94
20080	3	1106.923	2.52	3.592	0.677	xLcH N	N.S]IPSIS QQNILER NEELYEPI RNSLF.E	523	548	1.86E+04	1.52E+04	1.23
11314	3	700.7002	1.59	2.563	0.763	xLcH N	L.TDSVDE ALSNPNK VY.S	583	597	1.74E+05	1.84E+05	0.95
11315	3	704.0405	1.56	2.444	0.262	xLcH N	L.TJDSVD EALSNPN K#VY.S	583	597	1.74E+05	1.84E+05	0.95
11916	3	700.7002	1.52	2.049	0.508	xLcH N	L.TDSVDE ALSNPNK VY.S	583	597	2.27E+05	2.78E+05	0.82
7902	2	635.3637	0.25	1.478	0.567	xLcH N	L.SNPNK VY.S	591	597	6.79E+05	8.90E+05	0.76
7903	2	640.3742	0.25	1.485	0.282	xLcH N	L.S]NPNK #VY.S	591	597	6.79E+05	8.90E+05	0.76
14536	3	927.1457	1.59	2.027	0.553	xLcH N	Y.S]PFK# NM*SNTI NSIETGIT STY.I	598	618	1.47E+05	8.07E+04	1.83
14487	3	923.8054	1.54	2.35	0.708	xLcH N	Y.SPFKN M*SNTIN SIETGITS TY.I	598	618	1.47E+05	8.07E+04	1.83
13108	3	813.421	2.03	2.046	0.548	xLcH N	F.KNM*S NTINSIET GITSTY.I	601	618	2.41E+06	2.42E+06	1.00
12962	3	813.421	1.98	2.378	0.482	xLcH N	F.KNM*S NTINSIET GITSTY.I	601	618	2.41E+06	2.42E+06	1.00

[0268]

13079	3	813.421	1.98	2.245	0.617	xLcH N	F.KNM*S NTINSIET GITSTY.I	601	618	2.41E+06	2.42E+06	1.00
13194	2	915.4701	2.12	1.504	0.654	xLcH N	M.S]NTIN SIETGITS TY.I	604	618	1.74E+05	3.22E+05	0.54
13170	2	912.9649	1.99	1.791	0.699	xLcH N	M.SNTINS IETGITST Y.I	604	618	1.74E+05	3.22E+05	0.54
12405	2	812.4274	2.38	1.349	0.781	xLcH N	N.TINSIET GITSTY.I	606	618	2.94E+04	3.41E+04	0.86
14318	3	837.465	1.53	2.439	0.647	xLcH N	F.SJDETG K#IDVIDK #SSDTL.A	632	648	2.23E+04	1.55E+04	1.44
19535	2	586.368	0.52	1.753	0.731	xLcH N	L.A]IVPY1 GPL.L	649	657	7.93E+05	1.16E+06	0.69
19564	2	442.268	0.43	1.498	0.892	xLcH N	V.PYIGPL. L	652	657	1.30E+04	2.64E+04	0.49
9998	2	715.396	1.76	2.148	0.33	xLcH N	V.I]GGEL AREQVE. A	699	709	8.53E+04	1.32E+04	6.44
5372	3	494.9536	0.34	2.943	0.626	xLcH N	L.SRQAN AIKM*.N	754	762	2.50E+05	1.57E+04	15.97
5363	3	494.9536	0.32	3.357	0.734	xLcH N	L.SRQAN AIKM*.N	754	762	2.50E+05	1.57E+04	15.97
17794	2	734.3537	1.89	2.212	0.79	xLcH N	F.SEFDDL INQY.K	879	888	3.00E+05	4.05E+05	0.74
14171	4	757.641	0.97	2.289	0.421	xLcH N	F.DDLINQ YKNEGSI LPETGGL EHH.H	882	904	1.02E+04	3.96E+04	0.26
7676	4	679.3532	1.49	2.624	0.624	xLcH N	Y.KNEGSI LPETGGL EHHHHH H.-	889	908	3.63E+04	3.74E+04	0.97
13193	3	588.3365	1.18	2.307	0.629	xLcH N	Y.KNEGSI LPETGGL. E	889	901	2.81E+05	3.08E+05	0.91
10362	3	677.037	1.15	2.582	0.615	xLcH N	Y.KNEGSI LPETGGL EH.H	889	903	8.01E+05	1.17E+06	0.68
9325	4	542.2943	1.06	2.617	0.58	xLcH	Y.KNEGSI	889	904	2.17E+05	2.96E+05	0.73

						N	LPETGGL EHH.H					

[0269] BoNT/X中二硫键的独特特征

[0270] BoNT/X的接头区包含另外的半胱氨酸(C461)，其对BoNT/X来说是独特的。为了确定哪个半胱氨酸形成连接LC和HC的二硫键，产生三种X-LC-H_N突变体，其中三个半胱氨酸残基中的每一个发生了突变(C423S、C461S和C467S)。对这三种半胱氨酸突变体以及野生型(WT)X-LC-H_N进行受限的蛋白酶解，并随后在有或没有还原剂DTT的情况下，通过SDS-PAGE和考马斯蓝染色(Coomassie Blue staining)对其进行分析(图3C)。发现，在有或没有DTT的情况下，LC上的半胱氨酸(C423S)突变得到分离成两个～50kDa条带的蛋白质，表明C423S消除了链间二硫键。相反，包含C461S或C467S的突变体在不存在DTT的情况下显示出在100kDa处的单条带，存在DTT的情况下分离成两个～50kDa条带，表明H_N上的C461和C467二者均可与LC上的C423形成链间二硫键。此外，X-LC-H_N(C423S)突变体显示出比C461S和C467S突变体二者更易受Lys-C影响，导致蛋白质的进一步降解(图3C)。该结果表明，失去链间二硫键可提高LC和H_N的自由度，从而暴露更多的表面区域。此外，一部分WT X-LC-H_N在SDS-PAGE凝胶的顶部形成聚集体(图3C)。这些聚集体是由于分子间二硫键的形成，因为它们在存在DTT的情况下消失(图3C，+DTT)。C423、C461和C467是X-LC-H_N中仅有的三个半胱氨酸。三个半胱氨酸中的任何一个突变消除了X-LC-H_N聚集体(图3C，-DTT)，表明分子间二硫键的形成是由于在接头区中存在额外的半胱氨酸。

[0271] 在没有DTT的情况下，大多数活化的WT X-LC-H_N也在SDS-PAGE凝胶上分离成两个～50kDa条带(图3C)。另一方面，WT X-LC-H_N对Lys-C的抗性与C461S和C467S突变体类似，并且它没有显示出如C423S突变体的进一步降解(图3C，+DTT)，表明WT X-LC-H_N与C423S突变体不同。一种可能的解释是由于在H_N上存在两个靠近各自的半胱氨酸(C461和C467)，所以二硫键发生了混编，在变性条件下其可将二硫键从链间C423至C467或C423至C467重排为链内C461至C467[48,49]。为了测试该假设，使用烷基化试剂N-乙基马来酰亚胺(N-Ethylmaleimide,NEM)，其与游离半胱氨酸的巯基反应并永久阻断任何游离半胱氨酸。如图3D中所示，用NEM预处理的WT X-LC-H_N在不存在DTT的情况下主要显示为在100kDa处的单条带，并且在存在DTT的情况下分离成两个～50kDa条带。这些结果确认了天然WT X-LC-H_N主要包含链间二硫键，由于在接头区中存在第三半胱氨酸，其易受二硫键混编的影响。

[0272] 最后，检查了三种X-LC-H_N半胱氨酸突变体对培养的神经元的活性。如图3E中所示，使LC上的半胱氨酸(C423S)突变消除了X-LC-H_N的活性，如在神经元中缺乏VAMP2切割所证明的。与野生型(WT)X-LC-H_N相比，使H_N上两个半胱氨酸中的一个(C461或C467)突变没有显著影响X-LC-H_N的效力(图3E)。这些结果确定了链间二硫键对BoNT/X的活性是必需的，并且表明了可以通过C423至C461或C423至C467形成功能性链间二硫键。

[0273] 通过定位酶介导的连接产生全长BoNT/X.

[0274] 为了评价BoNT/X是否是功能性毒素，有必要产生并测试全长BoNT/X。然而，BoNT是最危险的潜在生物恐怖剂之一。因此，采取了必要的预防措施，并且未产生全长活性毒素基因。相反，开发了通过酶促连接两个无毒的BoNT片段在受控条件下在试管中产生有限量的全长BoNT的方法。该方法利用已知为定位酶的转肽酶，其识别特定的肽基序并通过形成天然肽键将两个肽共价连接在一起(图4A)。该方法先前已用于产生嵌合毒素和其他融合蛋白[50,51]。

[0275] 产生来自金黄色葡萄球菌的称为SrtA*的工程定位酶A[51]。SrtA*识别肽基序LPXTG(SEQ ID NO:57)，在T-G之间切割，并且同时在包含LPXTG的蛋白质(SEQ ID NO:57)与包含

一个或更多个N端甘氨酸的其他蛋白质/肽之间形成新的肽键(图4A)。产生BoNT/X的两个无毒片段:(1)具有与C端融合的LPETGG(SEQ ID NO:58)基序和His6-标签的LC-H_N;(2)在其N端具有GST标签和凝血酶切割位点的BoNT/X的H_C(X-H_C)。通过凝血酶切割在N端释放具有游离甘氨酸的X-H_C。这两个片段与SrtA*的孵育产生有限量的～150kD全长BoNT/X,其在LC-H_N与H_C之间包含短接头(LPETGS,SEQ ID NO:59)(图4A至4B)。

[0276] 观察到,一旦从GST标签切割下来,X-H_C由于未知的原因在溶液中显示出强烈的聚集趋势,这可能是BoNT/X的连接效率低的原因(图4B)。相反,使用相同的方法将X-LC-H_N与BoNT/A的H_C(A-H_C)连接实现了更高的效率,其中大多数X-LC-H_N连接成全长XA嵌合毒素(图8A)。BoNT/X对培养的神经元有活性

[0277] 为了分析全长BoNT/X的活性,使用培养的大鼠皮质神经元作为模型系统。将神经元暴露于定位酶连接混合物和培养基中的不同对照混合物。12小时后收获细胞裂解物并进行免疫印迹分析以检查SNARE蛋白的切割。如图4C中所示,单独的X-LC-H_N切割一些VAMP2,因为其在反应混合物中浓度高。与单独的X-LC-H_N相比,包含X-LC-H_N和X-H_C但不包含定位酶的对照混合物略微增强了VAMP2的切割。该结果表明X-H_C可能通过非共价相互作用与X-LC-H_N缔合。该相互作用显示是特异性的,因为包含X-LC-H_N和A-H_C的对照混合物显示出与单独的X-LC-H_N相同的VAMP2切割水平(图8B)。通过定位酶将X-LC-H_N与X-H_C连接相对于在不含定位酶的X-LC-H_N和X-H_C的混合物增强对VAMP2的切割(图4C),表明连接的全长BoNT/X可进入神经元并切割VAMP2。类似地,连接的全长XA嵌合毒素也进入神经元并切割VAMP2(图8B)。

[0278] 与单独的X-LC-H_N相比,将X-H_C与X-LC-H_N混合提高了SDS-PAGE凝胶顶部的聚集体的量。这些聚集体在存在DTT的情况下消失,表明一部分X-H_C与X-LC-H_N形成分子间二硫键。DTT的存在还提高了连接的全长BoNT/X的量,表明一部分BoNT/X通过分子间二硫键聚集(图4B)。这些聚集体的形成可显著降低溶液中的有效毒素单体浓度。这可以是BoNT/X序列的内在弱点。X-H_C包含单个半胱氨酸(C1240)并且使该半胱氨酸突变不影响连接的BoNT/X的活性(图9)。此外,C1240S突变体可与X-LC-H_N中的C461S或C467S突变组合以产生没有游离半胱氨酸的经修饰BoNT/X(图9)。这些突变体毒素维持与WT BoNT/X相同的活性水平,但作为单体在溶液中比WT BoNT/X更稳定。

[0279] BoNT/X在小鼠体内诱导松弛性瘫痪

[0280] 使用在小鼠中公认的称为趾外展评分(DAS)的非致死性测定检查BoNT/X在体内是否具有活性。该测定测量将BoNT注射到小鼠后肢肌肉后的局部肌肉瘫痪[52,53]。BoNT引起肢体肌肉的松弛性瘫痪,这可通过在惊吓响应(startle response)期间无法伸展脚趾来检测。将活化的定位酶反应混合物(图4B,泳道7)注射到小鼠右后肢的腓肠肌中。在12小时内,右肢发生典型的松弛性瘫痪并且脚趾无法伸展(图4D)。这些结果确认BoNT/X能够如其他BoNT一样在体内引起松弛性瘫痪。

[0281] BoNT/X未被针对所有已知BoNT产生的抗血清识别

[0282] 为了进一步确定BoNT/X是血清学上独特的BoNT,使用针对已知BoNT产生的抗血清进行斑点印迹测定,所述已知BoNT包括所有七种血清型以及一种镶嵌毒素(BoNT/DC)。使用四种马抗血清(三价抗BoNT/A、B和E,抗BoNT/C,抗BoNT/DC和抗BoNT/F),以及两种山羊抗血清(抗BoNT/G和抗BoNT/D)。这些抗血清都能够中和其相应的靶BoNT并防止神经元中SNARE蛋白的切割(图10),因此验证它们的特异性和效力。如图4E中所示,这些抗血清识别了它们

相应的靶毒素，但它们中没有一个识别出BoNT/X。注意，针对BoNT/DC和BoNT/C产生的抗血清相互交叉反应，因为它们在其H_C中共有高度的相似性。这些结果将BoNT/X确定为新的BoNT血清型。

[0283] 全长无活性BoNT/X

[0284] 最后，检查了是否可产生全长BoNT/X作为可溶性蛋白质。为了确保生物安全性要求，引入了使其毒性失活的BoNT/X的LC突变。已经显示，BoNT/A中两个残基的突变R362A/Y365F使体外LC的蛋白酶活性失活，并且在小鼠体内消除了全长BoNT/A的毒性[54-56]。这两个残基在包括BoNT/X在内的所有BoNT中都是保守的。因此，在这两个位点引入相应的突变(BoNT/X中的R360A/Y363F)。如图4F中所示，产生这种全长灭活形式的BoNT/X(BoNT/X_{RY})，并在大肠杆菌中重组纯化为His6标记的蛋白质。它对神经元没有任何活性，因为VAMP2在神经元中未被切割(图11)。

[0285] 大部分BoNT/X_{RY}在SDS-PAGE凝胶的顶部形成聚集体(图4F)。这可能是由于从接头区中的额外半胱氨酸和H_C中的半胱氨酸形成分子间二硫键，因为添加DTT将聚集体转化为单体BoNT/X_{RY}(图4F)。使这些半胱氨酸突变不影响BoNT/X的活性(图9)，并且具有防止分子间二硫键形成和BoNT/X聚集的益处。

[0286] 无活性形式的BoNT/X可用作用于将治疗剂递送到神经元中的载剂。失活可通过在以下残基中任何一个或其组合处的突变来实现：R360、Y363、H227、E228或H231，后三个残基形成保守的蛋白酶基序。

[0287] 在工业规模上纯化全长无活性BoNT/X

[0288] 研究了是否可将全长BoNT/X纯化至高纯度并具有良好的收率，这对于作为治疗性毒素的BoNT/X(或其衍生物)的工业生产将是重要的。测试了细胞生长和表达的数个参数，例如温度、诱导时间和IPTG浓度。选择用于蛋白质表达的最佳参数是在37℃下培养细胞直至它们达到指数生长，在该阶段将温度降至18℃并通过向培养基添加1mM IPTG诱导表达。然后，在收获前将细胞培养16至18小时。通过SDS-PAGE验证BoNT/X的存在，并且其在可溶性级分中显示高水平的过表达(图11B)。

[0289] 进行了数项小规模的纯化试验以优化生产过程。使用Emulsiflex-C3(Avestin，Mannheim，Germany)的机械细胞裂解是细胞内蛋白质提取的优选方法，并且显示比超声处理更高效。为了BoNT/X的最佳回收，还必须评估多种缓冲条件。还原剂包含在整个纯化过程中，并且其大大降低了不需要的聚集的倾向。另外，在纯化过程的早期阶段将甘油用作添加剂并改善蛋白质稳定性。

[0290] 表达具有HIS6标签的BoNT/X构建体，所述HIS6标签可作为第一纯化步骤用于亲和色谱。对于小规模试验，使用5ml HIsTrapFF柱(GE Healthcare，Danderyd，Sweden)。为了从初始色谱获得最高纯度，测试了多种浓度的咪唑。将BoNT/X从浓度为100mM的咪唑洗脱；然而，很容易将主要的污染物与毒素共纯化。该污染物显示出与BoNT/X非特异性相互作用，并通过质谱法将其确定为大肠杆菌宿主蛋白质(双功能多黏菌素抗性蛋白AmA)。随着高盐浓度(500mM NaCl)的引入以及通过在纯化期间在100mM咪唑下进行另外的洗涤步骤，显著降低了该污染物的存在。这允许在250mM咪唑下洗脱更纯的BoNT/X级分。然后可通过尺寸排阻色谱对该后一级分进行改进(polish)。

[0291] 一旦到位，该方案通过用上述条件表达多至12L的培养基而扩大。另外，制备了由

15ml的Protino® Ni-NTA琼脂糖(Macherey-Nagel,Düren,Germany)组成的更大的亲和色谱基质以提高BoNT/X回收的收率。使用Superdex200-16/60柱(GE Healthcare,Danderyd,Sweden)通过尺寸排阻色谱进行最终的纯化步骤。使用该方法,获得85%至90%的纯度(图11C)。可对蛋白质进行浓缩(使用具有100kDa截止的Vivaspin浓缩器;GE Healthcare,Danderyd,Sweden)并且其显示高至10mg/ml是稳定的。以下描述蛋白质产生过程的完整细节。获得的BoNT/X的收率约为每升细胞培养物3mg。这些结果一起表明BoNT/X可在工业规模上纯化至高纯度。

[0292] 注意,纯化是在存在还原剂的情况下进行的,这会降低LC与HC之间的二硫键,因此经纯化的毒素将不是活性的。然而,在没有还原剂的情况下,将能够对包含在半胱氨酸位点处突变(C461或C467处的一个突变,与突变的C1240组合)的设计的BoNT/X衍生物进行纯化。注意,无活性形式的BoNT/X(及其半胱氨酸突变衍生物)可用作用于将治疗剂递送到神经元中的载剂。失活可通过使任何一个以下残基或其组合突变来实现:R360、Y363、H227、E228、或H231(后三个残基形成保守的蛋白酶基序)。确定神经节苷脂为BoNT/X的受体

[0293] 神经节苷脂是所有BoNT的公认的脂质辅助受体,并且神经节苷脂结合基序在BoNT/X中是充分保守的(图1C)。将经高度纯化的全长无活性BoNT/X用于检查BoNT/X是否通过神经节苷脂与神经元细胞结合。开发体外ELISA测定以对与以下四种主要脑神经节苷脂的相互作用进行测试:GD1a、GD1b、GT1b和GM1。将A-LC用作阴性对照以评估非特异性结合。还进行了与BoNT/A(A-HC)的受体结合结构域的直接比较。使用抗His6标签抗体检测蛋白质的结合。发现,BoNT/X在A-LC的非特异性结合水平上显示出对所有四种神经节苷脂的剂量依赖性结合(图12),表明BoNT/X能够利用所有四种脑神经节苷脂作为辅助受体。根据先前报道,BoNT/A对GD1a和GT1b(图12F)及其末端NAcGal-Gal-NAcNeu部分呈现相等的偏好(当用S形剂量-响应模型进行拟合时,其表观EC_{50}值分别为0.7和1.0μM)。相反,BoNT/X对GD1b和GM1显示出比对GD1a和GT1b更高的亲和力(图12E)。这表明BoNT/X具有优选的唾液酸识别模式,其也见于BoNT/B和TeNT中。BoNT/X在与其他毒素之一的同源位置处具有保守的SxWY基序。虽然具有低亲和力,但它可识别所有四种神经节苷脂的事实可以是多个碳水化合物结合位点的指示。

[0294] 讨论

[0295] 在确定最后一种主要的BoNT血清型之后经过45年,第8种BoNT血清型已被确定。BoNT/X与该毒素家族中的任何其他BoNT和TeNT具有最低的蛋白质序列同一性,并且这种低水平的同一性沿着毒素序列均匀分布。正如预期的,BoNT/X未被任何针对已知BoNT产生的抗血清识别。它清楚地代表了毒素家族唯一且独特的进化分支。

[0296] 通过检索肉毒梭菌菌株的基因组序列揭露了BoNT/X,并且其代表了通过基因组测序和生物信息学方法确定的第一种主要毒素类型。包含BoNT/X基因的菌株111最初是在20世纪90年代从婴儿肉毒中毒患者中确定。先前使用经典中和测定的表征已经将BoNT/B2确定为该菌株的主要毒素。BoNT/X很可能是沉默的毒素基因,或者其在实验室的培养条件下不以可检出的毒性水平表达。因此,它只可通过测序菌株111来确定。这说明了基因组测序和生物信息学方法对于理解微生物毒力因子的重要性。

[0297] 先前在多种肉毒梭菌菌株中经常发现沉默的BoNT基因。尚不清楚为什么这些细菌会保持沉默的毒素基因。它可能是进化上退化的基因。当沉默毒素基因包含过早的终止码

突变时，显然就是这种情况。然而，也存在沉默基因编码全长BoNT的情况。这些沉默的全长BoNT是否可能在某些环境条件下表达并表现出毒性仍然是引起兴趣的问题。

[0298] BoNT的一般三结构域结构和功能在BoNT/X中是充分保守的，但它还具有一些独特的特征：(1)它与BoNT/B、D、F和G在神经元中共享VAMP作为其靶标，但它在新的位点(VAMP2中的R66至A67)切割VAMP，这个新位点对该毒素来说是独特。这进一步扩展了可用于在不同位点切除(ablate)VAMP的毒素库。(2)连接LC和H_N的链间二硫键在BoNT/X中是保守的，但它在接头区还包含独特的另外的半胱氨酸，这可导致二硫键混编。H_N上的额外半胱氨酸对于LC-H_N的活性不是必需的(图3D)，并且使其突变具有防止形成分子间二硫键的益处(图3D，4B)。

[0299] His6标记的X-LC-H_N片段作为重组蛋白在缓冲液中是稳定的。它对神经元显示出比对A-LC-H_N和B-LC-H_N二者更高的活性水平(图3B)，表明其膜易位和/或蛋白酶活性可能比BoNT/A和BoNT/B中的相应片段更高效。X-LC-H_N可以是在广泛的细胞类型和组织中靶向VAMP1/2/3的可用试剂，因为其进入可能不限于神经元。例如，它可通过靶向感觉神经元和分泌炎性信号的其他细胞来潜在地用于减轻局部区域的疼痛。它还可用于产生嵌合毒素，例如XA(图8)。

[0300] X-HC具有功能，因为与单独的LC-H_N相比，其存在增强了神经元中VAMP2的切割(图4C)。然而，X-H_C可具有一些不利的特征，这仍有待进一步评价。例如，只有当它与GST(已知其促进蛋白质折叠/溶解度)而不是与His6标签融合时才产生足够水平的可溶性X-H_C。一旦从GST标签中释放，X-H_C就容易聚集。另外，X-H_C中的半胱氨酸也可形成分子间二硫键(图4B)。全长无活性BoNT/X可被纯化并作为可溶性蛋白质存在，表明X-H_C的溶解度问题可能至少部分归因于该结构域与X-LC-H_N的分离。例如，X-LC-H_N可能与X-H_C相互作用并在全长情况中覆盖其潜在的疏水区段，这对于多结构域蛋白质来说并不少见。

[0301] 神经节苷脂长期以来被确定为所有BoNT亚型的神经元受体。表明BoNT/X可与所有以下四种最丰富的神经节苷脂结合：GD1a、GD1b、GT1b、和GM1。另外，当与BoNT/A相比时，其亲和力和特异性有显著差异。这是一个有趣的特性，因为其他BoNT显示出对神经节苷脂亚组有不同程度的偏好。例如，BoNT/A、E、F和G优选GD1a和GT1b。与其他BoNT相比，BoNT/X可能潜在地识别更广泛的神经元类型。

[0302] BoNT/X可能在体内具有低毒性，这可能解释了为什么在对菌株111的原始研究中未检测到BoNT/X活性。如果是这种情况，毒性降低很可能是由于其H_C结构域，因为X-LC-H_N显示出比A-LC-H_N和B-LC-H_N二者都更有活性。分子间二硫键的形成也可能降低有效毒素浓度。为了确定其体内效力，有必要产生全长天然BoNT/X，但在产生全长毒素之前使用无毒的BoNT/X片段产生中和抗血清是重要的。

[0303] 将全长活性毒素基因引入到任何表达系统/生物体始终是重要的生物安全问题，并且它已成为生物毒素结构-功能研究的强大障碍。这特别对于BoNT来说是重要的考虑因素，因为它们是六种A类潜在生物恐怖剂之一[4]。在此开发了从两个互补且无毒的片段生物化学地组装有限量全长毒素的方法。将每个片段单独表达并纯化，并随后在试管中通过定位酶连接在一起。也可使用其他蛋白质连接方法，例如断裂内含肽系统(split intein system)，其通过蛋白质反式剪接将两个蛋白质片段融合[57]。通过控制反应中前体片段的量，可严格地控制经连接的全长毒素的量。这种“半合成”方法可用于在受控条件下产生多结构

域生物毒素和其他有毒蛋白质。它还提供了用于产生融合和嵌合毒素的通用平台，例如交换两个BoNT的H_C、用其他靶向蛋白质替换BoNT的H_C、或将另外的载物(cargo)与毒素附接。由于在细菌或任何其他活生物体中从未产生过全长毒素cDNA，也没有毒素的表达，这种方法显著减轻了与产生野生型和突变毒素相关的生物安全问题，并将极大地促进生物毒素和有毒蛋白质的结构功能研究。

[0304] 材料和方法

[0305] 材料：用于突触融合蛋白1(HPC-1)、SNAP-25(C171.2)和VAMP2(C169.1)的小鼠单克隆抗体由E.Chapman(Madison,WI)慷慨提供，并且可从Synaptic Systems(Goettingen,Germany)获得。用于肌动蛋白的小鼠单克隆抗体购自Sigma(AC-15)。针对BoNT/A/B/E、BoNT/C、BoNT/DC、BoNT/F的马多克隆抗血清和针对BoNT/G的山羊多克隆抗血清获自FDA。针对BoNT/D的山羊多克隆抗体购自Fisher Scientific(NB10062469)。BoNT/A、BoNT/B、BoNT/C、BoNT/DC、BoNT/E、BoNT/F和BoNT/G购自Metabiologics(Madison,WI)。BoNT/D由E.Johnson(Madison,WI)慷慨提供。

[0306] cDNA和构建体：合成编码X-LC(第1至439位残基)和X-H_C(第893至1306位残基)的cDNA。编码X-H_N的cDNA是使用Gibson组装方法在内部(in-house)产生的。编码A-LC(第1至425位残基，M30196)和B-LC(第1至439位残基，AB232927)的cDNA由GenScript(New Brunswick,NJ)合成。将这些LC克隆到pET28载体中用于作为His6标记的蛋白质表达。将X-H_C克隆到pGEX4T中以作为GST标记的蛋白质表达。将X-LC-H_N、A-LC-H_N和B-LC-H_N亚克隆到pET28载体中(使肽序列LPETGG(SEQ ID NO:58)与其C端融合)，并将其纯化为His6-标记的蛋白质。全长无活性形式的BoNT/X由突变的X-LC(R360A/Y363F)、X-H_N和X-H_C在内部组装。将其克隆到pET28载体中，其中使His6-标签与BoNT/X的C端融合。编码大鼠VAMP2的cDNA由E.Chapman(Madison,WI)慷慨提供。将VAMP2(1至96)克隆到pET28载体中并表达为His6标记的蛋白质。将VAMP2(33至86)克隆到pGEX4T载体中并表达为GST标记的蛋白质。编码小鼠VAMP1、VAMP3，大鼠VAMP7和VAMP8的cDNA由C.Hu(Louisville,KY)慷慨提供。将它们克隆到经修饰pcDNA3.1载体中，使HA标签与其C端融合。编码His6标记的定位酶(SrtA*)的构建体由B.Pentelute(Boston,MA)慷慨提供，并且先前已有描述[51]。

[0307] 生物信息学：使用BoNT A型序列(Uniprot登录号A5HZZ9)在HMMER网络服务器上用jackhmmer检索Uniprot数据库直至收敛。返回的序列与Clustal Omega和用SplitsTree4评估的NeighborNet系统发生网络匹配。

[0308] 蛋白质纯化：利用大肠杆菌BL21(DE3)进行蛋白质表达。在22℃下过夜用0.1mM IPTG进行诱导表达。通过超声处理使细菌沉淀物在裂解缓冲液(50mM Tris pH 7.5,150mM NaCl)中破碎，并在4℃下以20000g离心30分钟之后收集上清液。使用AKTA Prime FPLC系统(GE)进行蛋白质纯化，并将经纯化的蛋白质用PD-10柱(GE,17-0851-01)进一步脱盐。具体地，将全长无活性BoNT/X(BoNT/X_{RY})克隆到pET22b载体中。将相应的质粒转化到大肠杆菌BL21(DE3)感受态细胞中。将所得菌落用于在250ml摇瓶中接种含有100μg/ml羧苄青霉素的TB培养基的100ml过夜培养物，并在37℃下培养。首先使用LEX Bioreactor(Epiphyte3,Ontario,Canada)在37℃下在1.5L TB培养基中培养用于表达的培养物，直至OD_{600}达到0.8。然后将温度降至18℃用于用1mM IPTG诱导表达，并培养16至17小时。收获细胞并将其在50mM HEPES pH 7.2,500mM NaCl,25mM咪唑,5％甘油,2mM TCEP中于冰上重悬，以使得能够

在20,000psi下用Emulsiflex-C3(Avestin,Mannheim,German)进行细胞裂解。在4℃下将裂解物以200,000g超速离心45分钟。将上清液加载到15ml Protino®Ni-NTA琼脂糖(Macherey-Nagen,Düren,Germany)柱上,然后用50mM HEPES pH 7.2,500mM NaCl,100mM咪唑,5%甘油,1mM TCEP洗涤。用50mM HEPES pH 7.2,500mM NaCl,250mM咪唑,5%甘油,1mM TCEP进行洗脱。在4℃下,将洗脱液在50mM HEPES pH 7.2,500mM NaCl,5%甘油,0.5mM TCEP中透析过夜。使用Vivaspin浓缩器(100kDa截止,GE Healthcare,Danderyd,Sweden)浓缩透析液,然后将其加载到在与用于透析的相同缓冲液中预平衡的Superdex200-16/60柱(GE Healthcare,Danderyd,Sweden)上。收集对应于BoNT/X的洗脱峰并浓缩,使得最终样品的浓度为10mg/ml。将样品等分并在液氮中快速冷冻以在-80℃下储存。

[0309] 神经节苷脂结合测定:将经纯化的神经节苷脂GD1a、GD1b、GT1b、和GM1(Carbosynth,Compton,UK)溶解在DMSO中并在甲醇中稀释至达到终浓度为2.5μg/ml;将100μL施加于96孔PVC测定板(目录号2595,Corning;Corning,NY)的每个孔。在21℃下蒸发溶剂后,用200μL PBS/0.1%(w/v)BSA洗涤孔。通过在4℃下在200μL PBS/2%(w/v)BSA中孵育2.5小时来封闭非特异性结合位点。在4℃下,在含有浓度范围为6μM至0.05μM(以连续2倍稀释)的样品(一式三份)的100μL PBS/0.1%(w/v)BSA/孔中进行1小时结合测定。孵育后,用PBS/0.1%(w/v)BSA洗涤孔三次,并在4℃下与HRP缀合的抗-6xHis单克隆抗体(1:2000,ThermoFisher)一起孵育1小时。在用PBS/0.1%(w/v)BSA进行三次洗涤步骤之后,使用Ultra-TMB(100vL/孔,ThermoFisher)作为底物检测结合的样品。15分钟后通过添加100μL 0.2M H_2SO_4使反应终止,并使用Infinite M200PRO读板仪(Tecan,Männedorf,Switzerland)测量450nm处的吸光度。用Prism7(GraphPad软件)对数据进行分析。

[0310] 大鼠脑洗涤剂提取物(BDE)中SNARE蛋白的切割:如先前所述[58],从新鲜解剖的成年大鼠脑中制备大鼠BDE。简单地说,将大鼠脑在15ml 320mM蔗糖缓冲液中匀浆,然后在4℃下以5000rpm离心2分钟。收集上清液并以11,000rpm离心12分钟。收集沉淀物并在15ml Tris缓冲盐水(TBS:20mM Tris,150mM NaCl)加2%Triton X-100和蛋白酶抑制剂混合物(Roche,CA)中溶解30分钟。随后将样品以17,000rpm离心20分钟以除去不溶物质。最终的BDE浓度为~2mg/ml蛋白质。在37℃下,将BDE(60μL)分别与X-LC(0.5μM)、A-LC(1μM)或B-LC(1μM)一起孵育1小时,并随后通过使用增强化学发光(ECL)方法(Pierce)的免疫印迹对其进行分析。作为对照,在室温(RT)下将LC与20mM EDTA一起预孵育20分钟,以在将其添加到BDE中之前使其活性失活。

[0311] 通过X-LC切割重组的VAMP:将VAMP2(1至96)作为His6标记的蛋白质表达并纯化,并且将VAMP2(33至86)作为GST标记的蛋白质表达并纯化。在37℃下,将这些蛋白质(0.6mg/ml)与在TBS缓冲液中的0.1μM X-LC一起孵育1小时。通过SDS-PAGE凝胶和考马斯蓝染色对样品进行分析,或者对样品进行质谱分析。

[0312] 细胞裂解物中VAMP的切割:按照制造商的说明书,使用PolyJet转染试剂(SignaGen,MD)将全长HA标记的VAMP1、3、7和8转染到HEK293细胞中。48小时后在RIPA缓冲液(50mM Tris,1%NP40,150mM NaCl,0.5%脱氧胆酸钠,0.1%SDS,每10cm血400μL)加蛋白酶抑制剂混合物(Sigma-Aldrich)中收获细胞裂解物。在37℃下,将细胞裂解物(250μL)与X-LC(0.5μM)一起孵育1小时。然后通过免疫印迹对样品进行分析。

[0313] 通过LC-MS/MS进行的全蛋白质分析:在哈佛医学院(Harvard Medical School)的Taplin Biological Mass Spectrometry Core Facility处对样品进行分析。简单地说,使用压力元件(pressure cell)将全蛋白样品加载到100μM内径C18反相HPLC柱上,该柱用3cm离线珠填充。将柱重新附接至Accela 600泵(Thermo Fisher Scientific,Waltham,MA)。使用迅速递增梯度的乙腈从HPLC柱洗脱蛋白质/肽。当洗脱肽时,将它们进行电喷射离子化,并随后进入到LTQ Orbitrap Velos Pro离子阱质谱仪(Thermo Fisher Scientific,Waltham,MA)中以获得60000分辨率的高分辨率FTMS扫描、离子阱中低分辨率的第二扫描、以及最终的扫描以进行数据依赖性的MS/MS。人工对电荷状态包络(charge state envelope)进行去卷积以在可能时获得单同位素质量或者以获得蛋白质的平均质量。肽和蛋白质的同一性通过软件程序Sequest(Thermo Fisher Scientific)将蛋白质数据库与获得的片段化模式匹配而确定。所有数据库都包括所有序列的反转版本(reversed version),并且数据被过滤到1%至2%的肽错误发现率。

[0314] 确定LC与H_N之间的蛋白酶切割位点:将His6标记的重组X-LC-H_N片段(第1至891位残基)在大肠杆菌中进行纯化,并通过内蛋白酶Lys-C进行受限的蛋白酶解(Sigma P2289,100:1(毒素:Lys-C)摩尔比,在室温下25分钟)。通过串联质量标签(Tandem Mass Tag,TMT)标记和串联质谱法确定切割位点。简单地说,用轻TMT标记完整的X-LC-H_N样品,并将等量的X-LC-H_N样品暴露于Lys-C,并随后用重TMT标记。然后将这两个样品用胰凝乳蛋白酶消化,合并在一起,并进行定量质谱分析。

[0315] 通过NEM进行半胱氨酸烷基化:在含或不含指定浓度的NEM(20、10、和5mM)的情况下,将Lys-C活化的X-LC-H_N片段以0.3mg/ml的终浓度稀释到磷酸钠缓冲液(10mM,pH 6.5)中,并在RT下孵育10分钟。NEM是在磷酸钠缓冲液中新鲜制备的。将样品与3×中性载样染料(200mM Tris pH 6.8、30%甘油、6%十二烷基硫酸锂、10mM NEM和0.06%BPB)混合。对于不含NEM的样品,使用相同的不含NEM的3×SDS载样染料。将样品进一步在室温下与载样染料一起孵育10分钟,在55℃下加热10分钟,并随后通过SDS-PAGE和考马斯蓝染色进行分析。

[0316] 神经元培养和免疫印迹分析:如我们先前所述的,使用木瓜蛋白酶解离试剂盒(Worthington Biochemical,NJ)从E18-19胚胎制备原代大鼠皮质神经元[58]。实验在DIV 14-16上进行。将神经元暴露于培养基中的BoNT/X片段或定位酶连接混合物持续12小时。然后用RIPA缓冲液(50mM Tris、1%NP40、150mM NaCl、0.5%脱氧胆酸钠、0.1%SDS)加蛋白酶抑制剂混合物(Sigma-Aldrich)对细胞进行洗涤并裂解。在4℃下,使用微型离心机以最大速度将裂解物离心10分钟。对上清液进行SDS-PAG和免疫印迹分析。

[0317] 斑点印迹:将BoNT(在1μL中0.2μg)点在硝酸纤维素膜上并干燥(在室温下10分钟)。用含5%乳的TBST(TBS加0.05%吐温20)封闭膜30分钟,并随后与指定的抗血清(1:500稀释)一起孵育30分钟。然后将膜用TBST洗涤三次,并与HRP(辣根过氧化物酶)缀合的二抗一起孵育30分钟,用TBST再洗涤三次,并用ECL法(Pierce)进行分析。我们注意到,BoNT/X样品由1:1比例的经纯化的X-LC-H_N和X-HC组成。

[0318] 定位酶介导的连接:将GST-X-H_C在4℃下由凝血酶切割过夜,然后将其添加到蛋白质混合物中。在RT下,在添加有X-LC-H_N(8μM)、凝血酶切割的GST-X-H_C(25μM)、Ca^{2+}(10mM)、和定位酶(10μM)的50μL TBS缓冲液中建立连接反应持续40分钟。在图4C中,将神经元暴露于培养基中的5μL混合物持续12小时。在图4D中所述的DAS测定中,将25μL混合物注射到小

鼠的后腿中。

[0319] DAS测定:首先使用胰蛋白酶(60:1摩尔比(蛋白质的总量:胰蛋白酶),在RT下30分钟)以受限的蛋白酶解活化定位酶连接混合物。在此我们选择胰蛋白酶代替Lys-C,因为我们可通过添加胰蛋白酶抑制剂(大豆胰蛋白酶抑制剂,1:10比例(胰蛋白酶:胰蛋白酶抑制剂))来终止蛋白酶解。将小鼠(CD-1品系,21至25g,n=6)用异氟烷(3%至4%)麻醉,并使用附接至无菌Hamilton注射器的30号针将定位酶连接混合物注注射到右后肢的腓肠肌中。BoNT导致惊吓响应中后爪瘫痪。如先前所述,在注射之后12小时内观察到肌肉瘫痪[52,53]。

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[0393] 其他实施方案

[0394] 本说明书中公开的所有特征可以以任何组合进行组合。本说明书中公开的每个特征可被达到相同、等同或相似目的的替代特征所代替。因此,除非另有明确说明,否则所公开的每个特征仅是通用系列的等效或类似特征中的一个实例。

[0395] 根据以上描述,本领域技术人员可容易地确定本公开内容的基本特征,并且在不脱离其精神和范围的情况下,可对本公开内容做出多种改变和修改以使其适应多种用途和条件。因此,其他实施方案也在权利要求内。

[0396] 等同方案和范围

[0397] 虽然本文中描述并举例说明了本发明的数个实施方案,但是本领域普通技术人员将容易想到用于执行所述功能和/或获得所述结果和/或本文中所述的一个或更多个优点的多种其他方式和/或结构,并且每种这样的变化和/或修改都被视为在本文中描述的本发明的实施方案范围之内。更一般地,本领域的技术人员将容易理解,本文中所描述的所有参数、尺寸、材料和构造意为示例性的且实际的参数、尺寸、材料和/或构造将取决于使用本发明教导的具体应用。本领域的技术人员将认识到或能够仅使用常规实验确定许多与本文中所描述的本发明具体实施方案等同的方案。因此,应理解的是,前述实施方案仅通过示例的方式给出,且在所附权利要求书及其等同方案的范围之内,可以以除了具体描述和要求保护的其他方式来实施本发明的实施方案。本公开内容的本发明实施方案是针对本文中所述的每个单独的特征、系统、制品、材料、药盒和/或方法。此外,如果这类特征、系统、制品、材料、药盒和/或方法相互不矛盾,则两个或更多个这类特征、系统、制品、材料、药盒和/或方法的任意组合也包括在本公开内容的本发明范围内。

[0398] 本文中定义和使用的所有定义应理解为优先于于字典的定义、通过引用并入的文献中的定义、和/或所定义术语的普通含义。

[0399] 本文中公开的所有参考文献、专利和专利申请关于其各自所记载的主题均通过引用并入本文,在某些情况下可涵盖整个文件。

[0400] 除非明确指出相反,否则如本文在说明书和权利要求书中使用的没有数量词修饰的名词表示“至少一个/种”。

[0401] 如本文中在说明书和权利要求书中使用的短语“和/或”应被理解为意指如此结合起来的要素,即,在一些情况下联合存在而另一些情况下分开存在的要素的“任一种或二者”。用“和/或”列出的多个元素应以相同的方式解释,即,如此结合的“一个/种或更多个/种”元素。除了通过由“和/或”句子表述所具体确定的要素之外,其他要素也可任选地存在,无论其与具体确定的那些要素相关或不相关。因此,作为非限制性实例,当与开放式语言(例如“包含”)联合使用时,提及“A和/或B”在一个实施方案中可以指A B(任选地包括除了B之外的元素);在另一个实施方案中,可以指B(任选包括除了A之外的元素);在另一个实施方案中,可以指A和B二者(任选包括其他要素);等。

[0402] 如本文中在说明书和权利要求书中使用的“或”应被理解为具有与如上所定义“和/或”相同的含义。例如,当分离列表中的项目时,“或”或“和/或”应被解释为包括性的,即包括数字或要素列表中的至少一个,但还包括了多于一个,并且任选地包括其他未列出

的项目。只有明确表述示相反的术语，例如“仅之一”或“正好之一”，或者，在权利要求书中使用“由.....组成”时，才指仅包括要素或要素的列表中的一个要素。一般而言，当前面有排他性的术语例如“任一”、“之一”、“仅有之一”或“恰好之一”时，本文中所使用的术语“或”应该仅解释为表示排他性的替代选择(即“一个或另一个但不是二者”)。当在权利要求书中使用时，“基本由.....组成”应具有其在专利法领域中所使用的通常含义。

[0403] 关于一个或更多个要素的列表，如本文中在说明书和权利要求书中使用的短语“至少一个/种”应理解为意指选自要素列表中任意一个/种或更多个/种要素中的至少一个/种要素，但是不一定包括要素列表内具体列出的各个/种要素和每个/种要素中的至少一个/种，并且不排除要素列表中的要素的任意组合。该定义还允许除了短语“至少一个/种”所指的要素列表内的明确指出的要素之外，可任选地存在其他的要素，不论其与那些明确指出的要素相关或不相关。因此，作为一个非限制性的实例，“A和B中的至少一个”(或等同地，“A或B中的至少一个”或等同地，“A和/或B中的至少一个”)在一个实施方案中可以指，至少一个A，任选包括多于一个A，而不存在B(并任选地包括除了B之外的要素)；在另一个实施方案中，可以指至少一个B，任选包括多于一个B，而不存在A(且任选地包括除A之外的要素)；在另一个实施方案中，可以指至少一个A，任选地包括多于一个A，以及至少一个B，任选包括多于一个B(且任选地包括其他要素)；等。

[0404] 还应理解，除非明确指出相反，否则在本文中所要求保护的任何包括多于一个步骤或作用的方法中，所述方法的步骤或动作的顺序不一定限于所记载的方法的步骤或动作的顺序。

[0405] 在权利要求书以及在上述说明书中，所有的连接词例如“包含”、“包括”、“携带”、“具有”、“含有”、“涉及”、“持有”、“由...构成”等应理解为开放式的，即意指包括但不限制于。仅连接词“由.....组成”和“基本上由...组成”应分别是封闭的或半封闭的连接词，如美国专利局专利审查程序手册2111.03部分(United States Patent Office Manual of Patent Examining Procedures，Section 2111.03)所述。

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Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
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Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

[0008] Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile
885 890

<210> 3
<211> 439
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<220>
<223> 合成的多肽

<400> 3

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

[0009] Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

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Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305                 310                 315                 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
                325                 330                 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
            340                 345                 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
        355                 360                 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
    370                 375                 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385                 390                 395                 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
                405                 410                 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
            420                 425                 430

Ile Tyr Arg Asn Ser Lys Asn
        435
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[0010]

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<211> 1306
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<220>
<223> 合成的多肽

<400> 4

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Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1               5                   10                  15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
            20                  25                  30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
        35                  40                  45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
    50                  55                  60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65                  70                  75                  80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
                85                  90                  95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
            100                 105                 110
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Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

[0011] Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Ser Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

[0012] Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp

705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

[0013] Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly
900 905 910

Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His
995 1000 1005

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu
1085 1090 1095

Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly
1130 1135 1140

[0014]

Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln
1220 1225 1230

Glu Lys Tyr Arg Asn Tyr Cys Gln Leu Lys Thr Pro Tyr Asn Ile
1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

<210> 5
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<220>
<223> 合成的多肽

<400> 5

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
[0015] 85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

[0016] Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Ala Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

[0017] Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly
900 905 910

Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

[0018] Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His
995 1000 1005

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu
1085 1090 1095

Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly

1130 1135 1140

Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln
1220 1225 1230

Glu Lys Tyr Arg Asn Tyr Cys Gln Leu Lys Thr Pro Tyr Asn Ile
1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

[0019]

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

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<220>
<223> 合成的多肽

<400> 6

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

[0020] Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr

370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Ser Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

[0021] Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

[0022] Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly
900 905 910

Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His
995 1000 1005

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu
1085 1090 1095

Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

[0023]

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly
1130 1135 1140

Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln
1220 1225 1230

Glu Lys Tyr Arg Asn Tyr Cys Gln Leu Lys Thr Pro Tyr Asn Ile
1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

<210> 7
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<400> 7

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
[0024] 50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

[0025] Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Ala Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

[0026] Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr

805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly
900 905 910

Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

[0027] Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His
995 1000 1005

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu
1085 1090 1095

Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly
1130 1135 1140

Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln
1220 1225 1230

Glu Lys Tyr Arg Asn Tyr Cys Gln Leu Lys Thr Pro Tyr Asn Ile
[0028] 1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

<210> 8
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Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp

35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

[0029] Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

[0030] Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

[0031] Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly
900 905 910

Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His
995 1000 1005

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

[0032] Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu
1085 1090 1095

Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly
1130 1135 1140

Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln

1220 1225 1230

Glu Lys Tyr Arg Asn Tyr Ser Gln Leu Lys Thr Pro Tyr Asn Ile
1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

<210> 9
<211> 1306
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<220>
<223> 合成的多肽

<400> 9

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

[0033] Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

[0034] Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn

465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

[0035] Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly
900 905 910

[0036] Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His
995 1000 1005

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu
1085 1090 1095

Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly
1130 1135 1140

Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

[0037] Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln
1220 1225 1230

Glu Lys Tyr Arg Asn Tyr Ala Gln Leu Lys Thr Pro Tyr Asn Ile
1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

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<400> 10

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

[0038] Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

[0039] Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Ser Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

[0040] Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly

900 905 910

Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His
995 1000 1005

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

[0041] Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu
1085 1090 1095

Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly
1130 1135 1140

Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln
1220 1225 1230

Glu Lys Tyr Arg Asn Tyr Ala Gln Leu Lys Thr Pro Tyr Asn Ile
1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

<210> 11
<211> 1306
<212> PRT
<213> 人工序列

[0042] <220>
<223> 合成的多肽

<400> 11

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn

130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

[0043] Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Ser Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

[0044] Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

[0045] Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly
900 905 910

Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His
995 1000 1005

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu
1085 1090 1095

Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly
1130 1135 1140

Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

[0046] Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln
1220 1225 1230

Glu Lys Tyr Arg Asn Tyr Ser Gln Leu Lys Thr Pro Tyr Asn Ile
1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

<210> 12

<211> 1306
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 12

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

[0047] Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

[0048] Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Ala Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser

565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

[0049] Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly
900 905 910

Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His
995 1000 1005

[0050]

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu
1085 1090 1095

Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly
1130 1135 1140

Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln
1220 1225 1230

Glu Lys Tyr Arg Asn Tyr Ser Gln Leu Lys Thr Pro Tyr Asn Ile
1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

[0051] Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

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Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

[0052] Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Ala Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

[0053] Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

[0054] Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly
900 905 910

Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His

995 1000 1005

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu
1085 1090 1095

Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

[0055] Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly
1130 1135 1140

Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln
1220 1225 1230

Glu Lys Tyr Arg Asn Tyr Ala Gln Leu Lys Thr Pro Tyr Asn Ile
1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

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Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

[0056]

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser

225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

[0057] Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Ser Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

[0058] Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly
900 905 910

Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

[0059] Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His
995 1000 1005

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu
1085 1090 1095

Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly
1130 1135 1140

Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln
1220 1225 1230

Glu Lys Tyr Arg Asn Tyr Ala Gln Leu Lys Thr Pro Tyr Asn Ile
1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

[0060]

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

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Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

[0061] Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Ser Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

[0062] Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala

660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

[0063] Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly
900 905 910

Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His
995 1000 1005

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu
1085 1090 1095

[0064] Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly
1130 1135 1140

Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln
1220 1225 1230

Glu Lys Tyr Arg Asn Tyr Ser Gln Leu Lys Thr Pro Tyr Asn Ile
1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

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<223> 合成的多肽

<400> 16

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
[0065] 35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

[0066] Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Ala Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

[0067] Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly
900 905 910

Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

[0068] Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His
995 1000 1005

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu

1085 1090 1095

Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly
1130 1135 1140

Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln
1220 1225 1230

[0069]

Glu Lys Tyr Arg Asn Tyr Ser Gln Leu Lys Thr Pro Tyr Asn Ile
1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

<210> 17
<211> 1306
<212> PRT
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<220>
<223> 合成的多肽

<400> 17

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

[0070] Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu

325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

[0071] Asn Gly Ala Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

[0072] Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly
900 905 910

Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His
995 1000 1005

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

[0073]

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu
1085 1090 1095

Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly
1130 1135 1140

Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln
1220 1225 1230

Glu Lys Tyr Arg Asn Tyr Ala Gln Leu Lys Thr Pro Tyr Asn Ile
1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

<210> 18
<211> 892
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 18

[0074]

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

[0075] Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Ala Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

[0076] Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu

755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile
885 890

<210> 19
<211> 892
[0077] <212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 19

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

[0078] Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala

420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Ser Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

[0079] Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

[0080] Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile
885 890

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Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile

85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

[0081]
Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Ala Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

[0082] Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

[0083]

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile
885 890

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<400> 21

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
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Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

[0084] Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Ser Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

[0085] Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

[0086]

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile
885 890

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<220>
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<400> 22

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

[0087] Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

[0088] Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu

610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

[0089] Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Ile Ile Asn Thr
885 890 895

Ser Ile Leu Asn Leu Arg Tyr Glu Ser Asn His Leu Ile Asp Leu Ser
900 905 910

Arg Tyr Ala Ser Lys Ile Asn Ile Gly Ser Lys Val Asn Phe Asp Pro
915 920 925

Ile Asp Lys Asn Gln Ile Gln Leu Phe Asn Leu Glu Ser Ser Lys Ile
930 935 940

Glu Val Ile Leu Lys Asn Ala Ile Val Tyr Asn Ser Met Tyr Glu Asn
945 950 955 960

Phe Ser Thr Ser Phe Trp Ile Arg Ile Pro Lys Tyr Phe Asn Ser Ile
965 970 975

Ser Leu Asn Asn Glu Tyr Thr Ile Ile Asn Cys Met Glu Asn Asn Ser
980 985 990

Gly Trp Lys Val Ser Leu Asn Tyr Gly Glu Ile Ile Trp Thr Leu Gln
995 1000 1005

Asp Thr Gln Glu Ile Lys Gln Arg Val Val Phe Lys Tyr Ser Gln
1010 1015 1020

Met Ile Asn Ile Ser Asp Tyr Ile Asn Arg Trp Ile Phe Val Thr
1025 1030 1035

Ile Thr Asn Asn Arg Leu Asn Asn Ser Lys Ile Tyr Ile Asn Gly
1040 1045 1050

[0090] Arg Leu Ile Asp Gln Lys Pro Ile Ser Asn Leu Gly Asn Ile His
1055 1060 1065

Ala Ser Asn Asn Ile Met Phe Lys Leu Asp Gly Cys Arg Asp Thr
1070 1075 1080

His Arg Tyr Ile Trp Ile Lys Tyr Phe Asn Leu Phe Asp Lys Glu
1085 1090 1095

Leu Asn Glu Lys Glu Ile Lys Asp Leu Tyr Asp Asn Gln Ser Asn
1100 1105 1110

Ser Gly Ile Leu Lys Asp Phe Trp Gly Asp Tyr Leu Gln Tyr Asp
1115 1120 1125

Lys Pro Tyr Tyr Met Leu Asn Leu Tyr Asp Pro Asn Lys Tyr Val
1130 1135 1140

Asp Val Asn Asn Val Gly Ile Arg Gly Tyr Met Tyr Leu Lys Gly
1145 1150 1155

Pro Arg Gly Ser Val Met Thr Thr Asn Ile Tyr Leu Asn Ser Ser
1160 1165 1170

Leu Tyr Arg Gly Thr Lys Phe Ile Ile Lys Lys Tyr Ala Ser Gly
1175 1180 1185

Asn Lys Asp Asn Ile Val Arg Asn Asn Asp Arg Val Tyr Ile Asn
1190 1195 1200

Val Val Val Lys Asn Lys Glu Tyr Arg Leu Ala Thr Asn Ala Ser
1205 1210 1215

Gln Ala Gly Val Glu Lys Ile Leu Ser Ala Leu Glu Ile Pro Asp
1220 1225 1230

Val Gly Asn Leu Ser Gln Val Val Val Met Lys Ser Lys Asn Asp
1235 1240 1245

Gln Gly Ile Thr Asn Lys Cys Lys Met Asn Leu Gln Asp Asn Asn
1250 1255 1260

Gly Asn Asp Ile Gly Phe Ile Gly Phe His Gln Phe Asn Asn Ile
1265 1270 1275

Ala Lys Leu Val Ala Ser Asn Trp Tyr Asn Arg Gln Ile Glu Arg
1280 1285 1290

Ser Ser Arg Thr Leu Gly Cys Ser Trp Glu Phe Ile Pro Val Asp
1295 1300 1305

Asp Gly Trp Gly Glu Arg Pro Leu
1310 1315

[0091]

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<220>
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<400> 23

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

[0092] Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

[0093] Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

[0094] Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Ile Leu Asn Asn
885 890 895

Ile Ile Leu Asn Leu Arg Tyr Lys Asp Asn Asn Leu Ile Asp Leu Ser
900 905 910

Gly Tyr Gly Ala Lys Val Glu Val Tyr Asp Gly Val Glu Leu Asn Asp
915 920 925

Lys Asn Gln Phe Lys Leu Thr Ser Ser Ala Asn Ser Lys Ile Arg Val
930 935 940

Thr Gln Asn Gln Asn Ile Ile Phe Asn Ser Val Phe Leu Asp Phe Ser
945 950 955 960

Val Ser Phe Trp Ile Arg Ile Pro Lys Tyr Lys Asn Asp Gly Ile Gln
965 970 975

Asn Tyr Ile His Asn Glu Tyr Thr Ile Ile Asn Cys Met Lys Asn Asn
980 985 990

Ser Gly Trp Lys Ile Ser Ile Arg Gly Asn Arg Ile Ile Trp Thr Leu
995 1000 1005

Ile Asp Ile Asn Gly Lys Thr Lys Ser Val Phe Phe Glu Tyr Asn
1010 1015 1020

Ile Arg Glu Asp Ile Ser Glu Tyr Ile Asn Arg Trp Phe Phe Val

1025 1030 1035

Thr Ile Thr Asn Asn Leu Asn Asn Ala Lys Ile Tyr Ile Asn Gly
1040 1045 1050

Lys Leu Glu Ser Asn Thr Asp Ile Lys Asp Ile Arg Glu Val Ile
1055 1060 1065

Ala Asn Gly Glu Ile Ile Phe Lys Leu Asp Gly Asp Ile Asp Arg
1070 1075 1080

Thr Gln Phe Ile Trp Met Lys Tyr Phe Ser Ile Phe Asn Thr Glu
1085 1090 1095

Leu Ser Gln Ser Asn Ile Glu Glu Arg Tyr Lys Ile Gln Ser Tyr
1100 1105 1110

Ser Glu Tyr Leu Lys Asp Phe Trp Gly Asn Pro Leu Met Tyr Asn
1115 1120 1125

Lys Glu Tyr Tyr Met Phe Asn Ala Gly Asn Lys Asn Ser Tyr Ile
1130 1135 1140

Lys Leu Lys Lys Asp Ser Pro Val Gly Glu Ile Leu Thr Arg Ser
1145 1150 1155

[0095] Lys Tyr Asn Gln Asn Ser Lys Tyr Ile Asn Tyr Arg Asp Leu Tyr
1160 1165 1170

Ile Gly Glu Lys Phe Ile Ile Arg Arg Lys Ser Asn Ser Gln Ser
1175 1180 1185

Ile Asn Asp Asp Ile Val Arg Lys Glu Asp Tyr Ile Tyr Leu Asp
1190 1195 1200

Phe Phe Asn Leu Asn Gln Glu Trp Arg Val Tyr Thr Tyr Lys Tyr
1205 1210 1215

Phe Lys Lys Glu Glu Glu Lys Leu Phe Leu Ala Pro Ile Ser Asp
1220 1225 1230

Ser Asp Glu Phe Tyr Asn Thr Ile Gln Ile Lys Glu Tyr Asp Glu
1235 1240 1245

Gln Pro Thr Tyr Ser Cys Gln Leu Leu Phe Lys Lys Asp Glu Glu
1250 1255 1260

Ser Thr Asp Glu Ile Gly Leu Ile Gly Ile His Arg Phe Tyr Glu
1265 1270 1275

Ser Gly Ile Val Phe Glu Glu Tyr Lys Asp Tyr Phe Cys Ile Ser
1280 1285 1290

Lys Trp Tyr Leu Lys Glu Val Lys Arg Lys Pro Tyr Asn Leu Lys
1295 1300 1305

Leu Gly Cys Asn Trp Gln Phe Ile Pro Lys Asp Glu Gly Trp Thr
1310 1315 1320

Glu

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<220>
<223> 合成的多肽

<400> 24

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

[0096]

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser

225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

[0097] Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

[0098] Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Ile Asn Asp Ser
885 890 895

Lys Ile Leu Ser Leu Gln Asn Arg Lys Asn Thr Leu Val Asp Thr Ser
900 905 910

Gly Tyr Asn Ala Glu Val Ser Glu Glu Gly Asp Val Gln Leu Asn Pro
915 920 925

Ile Phe Pro Phe Asp Phe Lys Leu Gly Ser Ser Gly Glu Asp Arg Gly
930 935 940

Lys Val Ile Val Thr Gln Asn Glu Asn Ile Val Tyr Asn Ser Met Tyr
945 950 955 960

Glu Ser Phe Ser Ile Ser Phe Trp Ile Arg Ile Asn Lys Trp Val Ser
965 970 975

[0099] Asn Leu Pro Gly Tyr Thr Ile Ile Asp Ser Val Lys Asn Asn Ser Gly
980 985 990

Trp Ser Ile Gly Ile Ile Ser Asn Phe Leu Val Phe Thr Leu Lys Gln
995 1000 1005

Asn Glu Asp Ser Glu Gln Ser Ile Asn Phe Ser Tyr Asp Ile Ser
1010 1015 1020

Asn Asn Ala Pro Gly Tyr Asn Lys Trp Phe Phe Val Thr Val Thr
1025 1030 1035

Asn Asn Met Met Gly Asn Met Lys Ile Tyr Ile Asn Gly Lys Leu
1040 1045 1050

Ile Asp Thr Ile Lys Val Lys Glu Leu Thr Gly Ile Asn Phe Ser
1055 1060 1065

Lys Thr Ile Thr Phe Glu Ile Asn Lys Ile Pro Asp Thr Gly Leu
1070 1075 1080

Ile Thr Ser Asp Ser Asp Asn Ile Asn Met Trp Ile Arg Asp Phe
1085 1090 1095

Tyr Ile Phe Ala Lys Glu Leu Asp Gly Lys Asp Ile Asn Ile Leu
1100 1105 1110

Phe Asn Ser Leu Gln Tyr Thr Asn Val Val Lys Asp Tyr Trp Gly
1115 1120 1125

Asn Asp Leu Arg Tyr Asn Lys Glu Tyr Tyr Met Val Asn Ile Asp
1130 1135 1140

Tyr Leu Asn Arg Tyr Met Tyr Ala Asn Ser Arg Gln Ile Val Phe
1145 1150 1155

Asn Thr Arg Arg Asn Asn Asn Asp Phe Asn Glu Gly Tyr Lys Ile
1160 1165 1170

Ile Ile Lys Arg Ile Arg Gly Asn Thr Asn Asp Thr Arg Val Arg
1175 1180 1185

Gly Gly Asp Ile Leu Tyr Phe Asp Met Thr Ile Asn Asn Lys Ala
1190 1195 1200

Tyr Asn Leu Phe Met Lys Asn Glu Thr Met Tyr Ala Asp Asn His
1205 1210 1215

Ser Thr Glu Asp Ile Tyr Ala Ile Gly Leu Arg Glu Gln Thr Lys
1220 1225 1230

Asp Ile Asn Asp Asn Ile Ile Phe Gln Ile Gln Pro Met Asn Asn
1235 1240 1245

Thr Tyr Tyr Tyr Ala Ser Gln Ile Phe Lys Ser Asn Phe Asn Gly
1250 1255 1260

[0100]

Glu Asn Ile Ser Gly Ile Cys Ser Ile Gly Thr Tyr Arg Phe Arg
1265 1270 1275

Leu Gly Gly Asp Trp Tyr Arg His Asn Tyr Leu Val Pro Thr Val
1280 1285 1290

Lys Gln Gly Asn Tyr Ala Ser Leu Leu Glu Ser Thr Ser Thr His
1295 1300 1305

Trp Gly Phe Val Pro Val Ser Glu
1310 1315

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<400> 25

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

[0101] Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Ser Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

[0102] Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro

645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

[0103] Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Ile Ile Asn Thr
885 890 895

Ser Ile Leu Asn Leu Arg Tyr Glu Ser Asn His Leu Ile Asp Leu Ser
900 905 910

Arg Tyr Ala Ser Lys Ile Asn Ile Gly Ser Lys Val Asn Phe Asp Pro
915 920 925

Ile Asp Lys Asn Gln Ile Gln Leu Phe Asn Leu Glu Ser Ser Lys Ile
930 935 940

Glu Val Ile Leu Lys Asn Ala Ile Val Tyr Asn Ser Met Tyr Glu Asn
945 950 955 960

Phe Ser Thr Ser Phe Trp Ile Arg Ile Pro Lys Tyr Phe Asn Ser Ile
965 970 975

Ser Leu Asn Asn Glu Tyr Thr Ile Ile Asn Cys Met Glu Asn Asn Ser
980 985 990

Gly Trp Lys Val Ser Leu Asn Tyr Gly Glu Ile Ile Trp Thr Leu Gln
995 1000 1005

Asp Thr Gln Glu Ile Lys Gln Arg Val Val Phe Lys Tyr Ser Gln
1010 1015 1020

Met Ile Asn Ile Ser Asp Tyr Ile Asn Arg Trp Ile Phe Val Thr
1025 1030 1035

Ile Thr Asn Asn Arg Leu Asn Asn Ser Lys Ile Tyr Ile Asn Gly
1040 1045 1050

Arg Leu Ile Asp Gln Lys Pro Ile Ser Asn Leu Gly Asn Ile His
1055 1060 1065

Ala Ser Asn Asn Ile Met Phe Lys Leu Asp Gly Cys Arg Asp Thr
1070 1075 1080

[0104] His Arg Tyr Ile Trp Ile Lys Tyr Phe Asn Leu Phe Asp Lys Glu
1085 1090 1095

Leu Asn Glu Lys Glu Ile Lys Asp Leu Tyr Asp Asn Gln Ser Asn
1100 1105 1110

Ser Gly Ile Leu Lys Asp Phe Trp Gly Asp Tyr Leu Gln Tyr Asp
1115 1120 1125

Lys Pro Tyr Tyr Met Leu Asn Leu Tyr Asp Pro Asn Lys Tyr Val
1130 1135 1140

Asp Val Asn Asn Val Gly Ile Arg Gly Tyr Met Tyr Leu Lys Gly
1145 1150 1155

Pro Arg Gly Ser Val Met Thr Thr Asn Ile Tyr Leu Asn Ser Ser
1160 1165 1170

Leu Tyr Arg Gly Thr Lys Phe Ile Ile Lys Lys Tyr Ala Ser Gly
1175 1180 1185

Asn Lys Asp Asn Ile Val Arg Asn Asn Asp Arg Val Tyr Ile Asn
1190 1195 1200

Val Val Val Lys Asn Lys Glu Tyr Arg Leu Ala Thr Asn Ala Ser
1205 1210 1215

Gln Ala Gly Val Glu Lys Ile Leu Ser Ala Leu Glu Ile Pro Asp
1220 1225 1230

Val Gly Asn Leu Ser Gln Val Val Val Met Lys Ser Lys Asn Asp
1235 1240 1245

Gln Gly Ile Thr Asn Lys Cys Lys Met Asn Leu Gln Asp Asn Asn
1250 1255 1260

Gly Asn Asp Ile Gly Phe Ile Gly Phe His Gln Phe Asn Asn Ile
1265 1270 1275

Ala Lys Leu Val Ala Ser Asn Trp Tyr Asn Arg Gln Ile Glu Arg
1280 1285 1290

Ser Ser Arg Thr Leu Gly Cys Ser Trp Glu Phe Ile Pro Val Asp
1295 1300 1305

Asp Gly Trp Gly Glu Arg Pro Leu
1310 1315

<210> 26
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<220>
<223> 合成的多肽

<400> 26

[0105]
Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

[0106] Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Ser Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

[0107] Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Ile Leu Asn Asn
885 890 895

Ile Ile Leu Asn Leu Arg Tyr Lys Asp Asn Asn Leu Ile Asp Leu Ser
900 905 910

[0108] Gly Tyr Gly Ala Lys Val Glu Val Tyr Asp Gly Val Glu Leu Asn Asp
915 920 925

Lys Asn Gln Phe Lys Leu Thr Ser Ser Ala Asn Ser Lys Ile Arg Val
930 935 940

Thr Gln Asn Gln Asn Ile Ile Phe Asn Ser Val Phe Leu Asp Phe Ser
945 950 955 960

Val Ser Phe Trp Ile Arg Ile Pro Lys Tyr Lys Asn Asp Gly Ile Gln
965 970 975

Asn Tyr Ile His Asn Glu Tyr Thr Ile Ile Asn Cys Met Lys Asn Asn
980 985 990

Ser Gly Trp Lys Ile Ser Ile Arg Gly Asn Arg Ile Ile Trp Thr Leu
995 1000 1005

Ile Asp Ile Asn Gly Lys Thr Lys Ser Val Phe Phe Glu Tyr Asn
1010 1015 1020

Ile Arg Glu Asp Ile Ser Glu Tyr Ile Asn Arg Trp Phe Phe Val
1025 1030 1035

Thr Ile Thr Asn Asn Leu Asn Asn Ala Lys Ile Tyr Ile Asn Gly
1040 1045 1050

Lys Leu Glu Ser Asn Thr Asp Ile Lys Asp Ile Arg Glu Val Ile

1055 1060 1065

Ala Asn Gly Glu Ile Ile Phe Lys Leu Asp Gly Asp Ile Asp Arg
1070 1075 1080

Thr Gln Phe Ile Trp Met Lys Tyr Phe Ser Ile Phe Asn Thr Glu
1085 1090 1095

Leu Ser Gln Ser Asn Ile Glu Glu Arg Tyr Lys Ile Gln Ser Tyr
1100 1105 1110

Ser Glu Tyr Leu Lys Asp Phe Trp Gly Asn Pro Leu Met Tyr Asn
1115 1120 1125

Lys Glu Tyr Tyr Met Phe Asn Ala Gly Asn Lys Asn Ser Tyr Ile
1130 1135 1140

Lys Leu Lys Lys Asp Ser Pro Val Gly Glu Ile Leu Thr Arg Ser
1145 1150 1155

Lys Tyr Asn Gln Asn Ser Lys Tyr Ile Asn Tyr Arg Asp Leu Tyr
1160 1165 1170

Ile Gly Glu Lys Phe Ile Ile Arg Arg Lys Ser Asn Ser Gln Ser
1175 1180 1185

[0109] Ile Asn Asp Asp Ile Val Arg Lys Glu Asp Tyr Ile Tyr Leu Asp
1190 1195 1200

Phe Phe Asn Leu Asn Gln Glu Trp Arg Val Tyr Thr Tyr Lys Tyr
1205 1210 1215

Phe Lys Lys Glu Glu Glu Lys Leu Phe Leu Ala Pro Ile Ser Asp
1220 1225 1230

Ser Asp Glu Phe Tyr Asn Thr Ile Gln Ile Lys Glu Tyr Asp Glu
1235 1240 1245

Gln Pro Thr Tyr Ser Cys Gln Leu Leu Phe Lys Lys Asp Glu Glu
1250 1255 1260

Ser Thr Asp Glu Ile Gly Leu Ile Gly Ile His Arg Phe Tyr Glu
1265 1270 1275

Ser Gly Ile Val Phe Glu Glu Tyr Lys Asp Tyr Phe Cys Ile Ser
1280 1285 1290

Lys Trp Tyr Leu Lys Glu Val Lys Arg Lys Pro Tyr Asn Leu Lys
1295 1300 1305

Leu Gly Cys Asn Trp Gln Phe Ile Pro Lys Asp Glu Gly Trp Thr
1310 1315 1320

Glu

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Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

[0110]

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly

260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

[0111] Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Ser Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

[0112] Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Ile Asn Asp Ser
885 890 895

Lys Ile Leu Ser Leu Gln Asn Arg Lys Asn Thr Leu Val Asp Thr Ser
900 905 910

Gly Tyr Asn Ala Glu Val Ser Glu Glu Gly Asp Val Gln Leu Asn Pro
915 920 925

Ile Phe Pro Phe Asp Phe Lys Leu Gly Ser Ser Gly Glu Asp Arg Gly
930 935 940

Lys Val Ile Val Thr Gln Asn Glu Asn Ile Val Tyr Asn Ser Met Tyr
945 950 955 960

Glu Ser Phe Ser Ile Ser Phe Trp Ile Arg Ile Asn Lys Trp Val Ser
965 970 975

Asn Leu Pro Gly Tyr Thr Ile Ile Asp Ser Val Lys Asn Asn Ser Gly
980 985 990

Trp Ser Ile Gly Ile Ile Ser Asn Phe Leu Val Phe Thr Leu Lys Gln
995 1000 1005

[0113]

Asn Glu Asp Ser Glu Gln Ser Ile Asn Phe Ser Tyr Asp Ile Ser
1010 1015 1020

Asn Asn Ala Pro Gly Tyr Asn Lys Trp Phe Phe Val Thr Val Thr
1025 1030 1035

Asn Asn Met Met Gly Asn Met Lys Ile Tyr Ile Asn Gly Lys Leu
1040 1045 1050

Ile Asp Thr Ile Lys Val Lys Glu Leu Thr Gly Ile Asn Phe Ser
1055 1060 1065

Lys Thr Ile Thr Phe Glu Ile Asn Lys Ile Pro Asp Thr Gly Leu
1070 1075 1080

Ile Thr Ser Asp Ser Asp Asn Ile Asn Met Trp Ile Arg Asp Phe
1085 1090 1095

Tyr Ile Phe Ala Lys Glu Leu Asp Gly Lys Asp Ile Asn Ile Leu
1100 1105 1110

Phe Asn Ser Leu Gln Tyr Thr Asn Val Val Lys Asp Tyr Trp Gly
1115 1120 1125

Asn Asp Leu Arg Tyr Asn Lys Glu Tyr Tyr Met Val Asn Ile Asp
1130 1135 1140

Tyr Leu Asn Arg Tyr Met Tyr Ala Asn Ser Arg Gln Ile Val Phe
1145 1150 1155

Asn Thr Arg Arg Asn Asn Asn Asp Phe Asn Glu Gly Tyr Lys Ile
1160 1165 1170

Ile Ile Lys Arg Ile Arg Gly Asn Thr Asn Asp Thr Arg Val Arg
1175 1180 1185

Gly Gly Asp Ile Leu Tyr Phe Asp Met Thr Ile Asn Asn Lys Ala
1190 1195 1200

Tyr Asn Leu Phe Met Lys Asn Glu Thr Met Tyr Ala Asp Asn His
1205 1210 1215

Ser Thr Glu Asp Ile Tyr Ala Ile Gly Leu Arg Glu Gln Thr Lys
1220 1225 1230

Asp Ile Asn Asp Asn Ile Ile Phe Gln Ile Gln Pro Met Asn Asn
1235 1240 1245

Thr Tyr Tyr Tyr Ala Ser Gln Ile Phe Lys Ser Asn Phe Asn Gly
1250 1255 1260

Glu Asn Ile Ser Gly Ile Cys Ser Ile Gly Thr Tyr Arg Phe Arg
1265 1270 1275

Leu Gly Gly Asp Trp Tyr Arg His Asn Tyr Leu Val Pro Thr Val
1280 1285 1290

[0114]

Lys Gln Gly Asn Tyr Ala Ser Leu Leu Glu Ser Thr Ser Thr His
1295 1300 1305

Trp Gly Phe Val Pro Val Ser Glu
1310 1315

<210> 28
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Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

[0115] Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Ser Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

[0116] Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe

675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

[0117] Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Ile Ile Asn Thr
885 890 895

Ser Ile Leu Asn Leu Arg Tyr Glu Ser Asn His Leu Ile Asp Leu Ser
900 905 910

Arg Tyr Ala Ser Lys Ile Asn Ile Gly Ser Lys Val Asn Phe Asp Pro
915 920 925

Ile Asp Lys Asn Gln Ile Gln Leu Phe Asn Leu Glu Ser Ser Lys Ile
930 935 940

Glu Val Ile Leu Lys Asn Ala Ile Val Tyr Asn Ser Met Tyr Glu Asn
945 950 955 960

Phe Ser Thr Ser Phe Trp Ile Arg Ile Pro Lys Tyr Phe Asn Ser Ile
965 970 975

Ser Leu Asn Asn Glu Tyr Thr Ile Ile Asn Cys Met Glu Asn Asn Ser
980 985 990

Gly Trp Lys Val Ser Leu Asn Tyr Gly Glu Ile Ile Trp Thr Leu Gln
995 1000 1005

Asp Thr Gln Glu Ile Lys Gln Arg Val Val Phe Lys Tyr Ser Gln
1010 1015 1020

Met Ile Asn Ile Ser Asp Tyr Ile Asn Arg Trp Ile Phe Val Thr
1025 1030 1035

Ile Thr Asn Asn Arg Leu Asn Asn Ser Lys Ile Tyr Ile Asn Gly
1040 1045 1050

Arg Leu Ile Asp Gln Lys Pro Ile Ser Asn Leu Gly Asn Ile His
1055 1060 1065

Ala Ser Asn Asn Ile Met Phe Lys Leu Asp Gly Cys Arg Asp Thr
1070 1075 1080

His Arg Tyr Ile Trp Ile Lys Tyr Phe Asn Leu Phe Asp Lys Glu
1085 1090 1095

Leu Asn Glu Lys Glu Ile Lys Asp Leu Tyr Asp Asn Gln Ser Asn
1100 1105 1110

[0118]

Ser Gly Ile Leu Lys Asp Phe Trp Gly Asp Tyr Leu Gln Tyr Asp
1115 1120 1125

Lys Pro Tyr Tyr Met Leu Asn Leu Tyr Asp Pro Asn Lys Tyr Val
1130 1135 1140

Asp Val Asn Asn Val Gly Ile Arg Gly Tyr Met Tyr Leu Lys Gly
1145 1150 1155

Pro Arg Gly Ser Val Met Thr Thr Asn Ile Tyr Leu Asn Ser Ser
1160 1165 1170

Leu Tyr Arg Gly Thr Lys Phe Ile Ile Lys Lys Tyr Ala Ser Gly
1175 1180 1185

Asn Lys Asp Asn Ile Val Arg Asn Asn Asp Arg Val Tyr Ile Asn
1190 1195 1200

Val Val Val Lys Asn Lys Glu Tyr Arg Leu Ala Thr Asn Ala Ser
1205 1210 1215

Gln Ala Gly Val Glu Lys Ile Leu Ser Ala Leu Glu Ile Pro Asp
1220 1225 1230

Val Gly Asn Leu Ser Gln Val Val Val Met Lys Ser Lys Asn Asp
1235 1240 1245

Gln Gly Ile Thr Asn Lys Cys Lys Met Asn Leu Gln Asp Asn Asn
1250 1255 1260

Gly Asn Asp Ile Gly Phe Ile Gly Phe His Gln Phe Asn Asn Ile
1265 1270 1275

Ala Lys Leu Val Ala Ser Asn Trp Tyr Asn Arg Gln Ile Glu Arg
1280 1285 1290

Ser Ser Arg Thr Leu Gly Cys Ser Trp Glu Phe Ile Pro Val Asp
1295 1300 1305

Asp Gly Trp Gly Glu Arg Pro Leu
1310 1315

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<220>
<223> 合成的多肽

<400> 29

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

[0119]

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

[0120] Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Ser Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

[0121] Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Ile Leu Asn Asn
885 890 895

Ile Ile Leu Asn Leu Arg Tyr Lys Asp Asn Asn Leu Ile Asp Leu Ser
900 905 910

Gly Tyr Gly Ala Lys Val Glu Val Tyr Asp Gly Val Glu Leu Asn Asp
915 920 925

Lys Asn Gln Phe Lys Leu Thr Ser Ser Ala Asn Ser Lys Ile Arg Val
930 935 940

[0122] Thr Gln Asn Gln Asn Ile Ile Phe Asn Ser Val Phe Leu Asp Phe Ser
945 950 955 960

Val Ser Phe Trp Ile Arg Ile Pro Lys Tyr Lys Asn Asp Gly Ile Gln
965 970 975

Asn Tyr Ile His Asn Glu Tyr Thr Ile Ile Asn Cys Met Lys Asn Asn
980 985 990

Ser Gly Trp Lys Ile Ser Ile Arg Gly Asn Arg Ile Ile Trp Thr Leu
995 1000 1005

Ile Asp Ile Asn Gly Lys Thr Lys Ser Val Phe Phe Glu Tyr Asn
1010 1015 1020

Ile Arg Glu Asp Ile Ser Glu Tyr Ile Asn Arg Trp Phe Phe Val
1025 1030 1035

Thr Ile Thr Asn Asn Leu Asn Asn Ala Lys Ile Tyr Ile Asn Gly
1040 1045 1050

Lys Leu Glu Ser Asn Thr Asp Ile Lys Asp Ile Arg Glu Val Ile
1055 1060 1065

Ala Asn Gly Glu Ile Ile Phe Lys Leu Asp Gly Asp Ile Asp Arg
1070 1075 1080

Thr Gln Phe Ile Trp Met Lys Tyr Phe Ser Ile Phe Asn Thr Glu

1085 1090 1095

Leu Ser Gln Ser Asn Ile Glu Glu Arg Tyr Lys Ile Gln Ser Tyr
1100 1105 1110

Ser Glu Tyr Leu Lys Asp Phe Trp Gly Asn Pro Leu Met Tyr Asn
1115 1120 1125

Lys Glu Tyr Tyr Met Phe Asn Ala Gly Asn Lys Asn Ser Tyr Ile
1130 1135 1140

Lys Leu Lys Lys Asp Ser Pro Val Gly Glu Ile Leu Thr Arg Ser
1145 1150 1155

Lys Tyr Asn Gln Asn Ser Lys Tyr Ile Asn Tyr Arg Asp Leu Tyr
1160 1165 1170

Ile Gly Glu Lys Phe Ile Ile Arg Arg Lys Ser Asn Ser Gln Ser
1175 1180 1185

Ile Asn Asp Asp Ile Val Arg Lys Glu Asp Tyr Ile Tyr Leu Asp
1190 1195 1200

Phe Phe Asn Leu Asn Gln Glu Trp Arg Val Tyr Thr Tyr Lys Tyr
1205 1210 1215

Phe Lys Lys Glu Glu Glu Lys Leu Phe Leu Ala Pro Ile Ser Asp
[0123] 1220 1225 1230

Ser Asp Glu Phe Tyr Asn Thr Ile Gln Ile Lys Glu Tyr Asp Glu
1235 1240 1245

Gln Pro Thr Tyr Ser Cys Gln Leu Leu Phe Lys Lys Asp Glu Glu
1250 1255 1260

Ser Thr Asp Glu Ile Gly Leu Ile Gly Ile His Arg Phe Tyr Glu
1265 1270 1275

Ser Gly Ile Val Phe Glu Glu Tyr Lys Asp Tyr Phe Cys Ile Ser
1280 1285 1290

Lys Trp Tyr Leu Lys Glu Val Lys Arg Lys Pro Tyr Asn Leu Lys
1295 1300 1305

Leu Gly Cys Asn Trp Gln Phe Ile Pro Lys Asp Glu Gly Trp Thr
1310 1315 1320

Glu

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Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

[0124]

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr

290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

[0125] Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Ser Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

[0126] Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Ile Asn Asp Ser
885 890 895

Lys Ile Leu Ser Leu Gln Asn Arg Lys Asn Thr Leu Val Asp Thr Ser
900 905 910

Gly Tyr Asn Ala Glu Val Ser Glu Glu Gly Asp Val Gln Leu Asn Pro
915 920 925

Ile Phe Pro Phe Asp Phe Lys Leu Gly Ser Ser Gly Glu Asp Arg Gly
930 935 940

Lys Val Ile Val Thr Gln Asn Glu Asn Ile Val Tyr Asn Ser Met Tyr
945 950 955 960

Glu Ser Phe Ser Ile Ser Phe Trp Ile Arg Ile Asn Lys Trp Val Ser
965 970 975

Asn Leu Pro Gly Tyr Thr Ile Ile Asp Ser Val Lys Asn Asn Ser Gly
980 985 990

Trp Ser Ile Gly Ile Ile Ser Asn Phe Leu Val Phe Thr Leu Lys Gln
995 1000 1005

Asn Glu Asp Ser Glu Gln Ser Ile Asn Phe Ser Tyr Asp Ile Ser
1010 1015 1020

Asn Asn Ala Pro Gly Tyr Asn Lys Trp Phe Phe Val Thr Val Thr
1025 1030 1035

[0127] Asn Asn Met Met Gly Asn Met Lys Ile Tyr Ile Asn Gly Lys Leu
1040 1045 1050

Ile Asp Thr Ile Lys Val Lys Glu Leu Thr Gly Ile Asn Phe Ser
1055 1060 1065

Lys Thr Ile Thr Phe Glu Ile Asn Lys Ile Pro Asp Thr Gly Leu
1070 1075 1080

Ile Thr Ser Asp Ser Asp Asn Ile Asn Met Trp Ile Arg Asp Phe
1085 1090 1095

Tyr Ile Phe Ala Lys Glu Leu Asp Gly Lys Asp Ile Asn Ile Leu
1100 1105 1110

Phe Asn Ser Leu Gln Tyr Thr Asn Val Val Lys Asp Tyr Trp Gly
1115 1120 1125

Asn Asp Leu Arg Tyr Asn Lys Glu Tyr Tyr Met Val Asn Ile Asp
1130 1135 1140

Tyr Leu Asn Arg Tyr Met Tyr Ala Asn Ser Arg Gln Ile Val Phe
1145 1150 1155

Asn Thr Arg Arg Asn Asn Asn Asp Phe Asn Glu Gly Tyr Lys Ile
1160 1165 1170

Ile Ile Lys Arg Ile Arg Gly Asn Thr Asn Asp Thr Arg Val Arg
1175 1180 1185

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Gly Gly  Asp Ile Leu Tyr Phe  Asp Met Thr Ile Asn  Asn Lys Ala
    1190                 1195                 1200

Tyr Asn  Leu Phe Met Lys Asn  Glu Thr Met Tyr Ala  Asp Asn His
    1205                 1210                 1215

Ser Thr  Glu Asp Ile Tyr Ala  Ile Gly Leu Arg Glu  Gln Thr Lys
    1220                 1225                 1230

Asp Ile  Asn Asp Asn Ile Ile  Phe Gln Ile Gln Pro  Met Asn Asn
    1235                 1240                 1245

Thr Tyr  Tyr Tyr Ala Ser Gln  Ile Phe Lys Ser Asn  Phe Asn Gly
    1250                 1255                 1260

Glu Asn  Ile Ser Gly Ile Cys  Ser Ile Gly Thr Tyr  Arg Phe Arg
    1265                 1270                 1275

Leu Gly  Gly Asp Trp Tyr Arg  His Asn Tyr Leu Val  Pro Thr Val
    1280                 1285                 1290

Lys Gln  Gly Asn Tyr Ala Ser  Leu Leu Glu Ser Thr  Ser Thr His
    1295                 1300                 1305

Trp Gly  Phe Val Pro Val Ser  Glu
    1310                 1315
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[0128]

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Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
            20                  25                  30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
        35                  40                  45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
    50                  55                  60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65                  70                  75                  80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
                85                  90                  95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
            100                 105                 110
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Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

[0129] Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Ala Lys His Phe Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

[0130] Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp

705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

[0131] Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly
900 905 910

Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His
995 1000 1005

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu
1085 1090 1095

Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly
1130 1135 1140

[0132] Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln
1220 1225 1230

Glu Lys Tyr Arg Asn Tyr Cys Gln Leu Lys Thr Pro Tyr Asn Ile
1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

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Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
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Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
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Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
[0133] 85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met Tyr Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

[0134] Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

[0135] Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly
900 905 910

Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

[0136] Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His
995 1000 1005

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu
1085 1090 1095

Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly

1130 1135 1140

Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln
1220 1225 1230

Glu Lys Tyr Arg Asn Tyr Cys Gln Leu Lys Thr Pro Tyr Asn Ile
1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

[0137]

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

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Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

[0138] Leu Met His Gln Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr

370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

[0139] Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

[0140] Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly
900 905 910

Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His
995 1000 1005

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu
1085 1090 1095

Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

[0141]

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly
1130 1135 1140

Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln
1220 1225 1230

Glu Lys Tyr Arg Asn Tyr Cys Gln Leu Lys Thr Pro Tyr Asn Ile
1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

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Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
[0142] 50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val Tyr Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

[0143] Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

[0144] Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr

805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Glu Asp Tyr Glu
885 890 895

Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile Lys Asp Leu Ser Gly
900 905 910

Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile Glu Leu Ala Asp Gly
915 920 925

Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser Glu Asn Ser Thr Ile
930 935 940

[0145] Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser Ala Thr Asp Asn Phe
945 950 955 960

Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro Thr Asn Leu Leu Asn
965 970 975

Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe Asn Gln Arg Gly Trp
980 985 990

Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp Tyr Leu Arg Asp His
995 1000 1005

Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr Ile Ala Phe Asn
1010 1015 1020

Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser Lys Gly Ser
1025 1030 1035

Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp Ile Ser
1040 1045 1050

Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg Leu
1055 1060 1065

Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
1070 1075 1080

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu
1085 1090 1095

Tyr Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly
1100 1105 1110

Asn Pro Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp
1115 1120 1125

Lys Pro Gly Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly
1130 1135 1140

Tyr Asp Tyr Val Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro
1145 1150 1155

Asn Asn Ile Arg Tyr Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu
1160 1165 1170

Ile Lys Asn Ser Lys Lys Leu Asp Gly Leu Val Arg Asn Lys Asp
1175 1180 1185

Phe Ile Gln Leu Glu Ile Asp Gly Tyr Asn Met Gly Ile Ser Ala
1190 1195 1200

Asp Arg Phe Asn Glu Asp Thr Asn Tyr Ile Gly Thr Thr Tyr Gly
1205 1210 1215

Thr Thr His Asp Leu Thr Thr Asp Phe Glu Ile Ile Gln Arg Gln
1220 1225 1230

Glu Lys Tyr Arg Asn Tyr Cys Gln Leu Lys Thr Pro Tyr Asn Ile
[0146] 1235 1240 1245

Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr Ser Lys Pro Thr
1250 1255 1260

Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala Trp Tyr Phe
1265 1270 1275

Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys Thr Asn
1280 1285 1290

Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
1295 1300 1305

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Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp

35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

[0147] Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Ala Lys His Phe Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

[0148] Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

[0149] Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile
885 890

<210> 36
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<223> 合成的多肽

<400> 36

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Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
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Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
            20                  25                  30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
        35                  40                  45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
    50                  55                  60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65                  70                  75                  80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
                85                  90                  95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
            100                 105                 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
        115                 120                 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
    130                 135                 140
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[0150]

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Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145                 150                 155                 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
                165                 170                 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
            180                 185                 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
        195                 200                 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
    210                 215                 220

Leu Met Tyr Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225                 230                 235                 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
                245                 250                 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
            260                 265                 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
        275                 280                 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
    290                 295                 300
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Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

[0151] Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

[0152] Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile
885 890

<210> 37

<211> 892
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 37

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

[0153] Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Gln Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

[0154] Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser

565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

[0155] Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile
885 890

<210> 38
<211> 892
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 38

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly
1 5 10 15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
20 25 30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
35 40 45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
50 55 60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65 70 75 80

[0156]

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
85 90 95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
100 105 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
115 120 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
130 135 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145 150 155 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
165 170 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
180 185 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
195 200 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
210 215 220

Leu Met His Glu Leu Val Tyr Val Thr His Asn Leu Tyr Gly Ile Ser

225 230 235 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
245 250 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
260 265 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
275 280 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
290 295 300

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

[0157] Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

[0158] Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile
885 890

<210> 39
<211> 118
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 39

Met Ser Ala Pro Ala Gln Pro Pro Ala Glu Gly Thr Glu Gly Thr Ala
1 5 10 15

Pro Gly Gly Gly Pro Pro Gly Pro Pro Pro Asn Met Thr Ser Asn Arg
20 25 30

Arg Leu Gln Gln Thr Gln Ala Gln Val Glu Glu Val Val Asp Ile Ile
35 40 45

[0159]

Arg Val Asn Val Asp Lys Val Leu Glu Arg Asp Gln Lys Leu Ser Glu
50 55 60

Leu Asp Asp Arg Ala Asp Ala Leu Gln Ala Gly Ala Ser Gln Phe Glu
65 70 75 80

Ser Ser Ala Ala Lys Leu Lys Arg Lys Tyr Trp Trp Lys Asn Cys Lys
85 90 95

Met Met Ile Met Leu Gly Ala Ile Cys Ala Ile Ile Val Val Val Ile
100 105 110

Val Ile Tyr Phe Phe Thr
115

<210> 40
<211> 116
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 40

Met Ser Ala Thr Ala Ala Thr Ala Pro Pro Ala Ala Pro Ala Gly Glu
1 5 10 15

Gly Gly Pro Pro Ala Pro Pro Pro Asn Leu Thr Ser Asn Arg Arg Leu
20 25 30

Gln Gln Thr Gln Ala Gln Val Asp Glu Val Val Asp Ile Met Arg Val
35 40 45

Asn Val Asp Lys Val Leu Glu Arg Asp Gln Lys Leu Ser Glu Leu Asp
50 55 60

Asp Arg Ala Asp Ala Leu Gln Ala Gly Ala Ser Gln Phe Glu Thr Ser
65 70 75 80

Ala Ala Lys Leu Lys Arg Lys Tyr Trp Trp Lys Asn Leu Lys Met Met
85 90 95

Ile Ile Leu Gly Val Ile Cys Ala Ile Ile Leu Ile Ile Ile Ile Val
100 105 110

Tyr Phe Ser Ser
115

<210> 41
<211> 103
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 41

Met Ser Thr Gly Val Pro Ser Gly Ser Ser Ala Ala Thr Gly Ser Asn
1 5 10 15

[0160]

Arg Arg Leu Gln Gln Thr Gln Asn Gln Val Asp Glu Val Val Asp Ile
20 25 30

Met Arg Val Asn Val Asp Lys Val Leu Glu Arg Asp Gln Lys Leu Ser
35 40 45

Glu Leu Asp Asp Arg Ala Asp Ala Leu Gln Ala Gly Ala Ser Gln Phe
50 55 60

Glu Thr Ser Ala Ala Lys Leu Lys Arg Lys Tyr Trp Trp Lys Asn Cys
65 70 75 80

Lys Met Trp Ala Ile Gly Ile Ser Val Leu Val Ile Ile Val Ile Ile
85 90 95

Ile Ile Val Trp Cys Val Ser
100

<210> 42
<211> 141
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 42

Met Pro Pro Lys Phe Lys Arg His Leu Asn Asp Asp Asp Val Thr Gly

1 5 10 15

Ser Val Lys Ser Glu Arg Arg Asn Leu Leu Glu Asp Asp Ser Asp Glu
20 25 30

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

Arg Asn Asp Lys Ile Lys His Val Gln Asn Gln Val Asp Glu Val Ile
50 55 60

Asp Val Met Gln Glu Asn Ile Thr Lys Val Ile Glu Arg Gly Glu Arg
65 70 75 80

Leu Asp Glu Leu Gln Asp Lys Ser Glu Ser Leu Ser Asp Asn Ala Thr
85 90 95

Ala Phe Ser Asn Arg Ser Lys Gln Leu Arg Arg Gln Met Trp Trp Arg
100 105 110

Gly Cys Lys Ile Lys Ala Ile Met Ala Leu Val Ala Ala Ile Leu Leu
115 120 125

Leu Val Ile Ile Ile Leu Ile Val Met Lys Tyr Arg Thr
130 135 140

[0161]

<210> 43
<211> 116
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 43

Met Ala Gly Ile Glu Leu Glu Arg Cys Gln Gln Gln Ala Asn Glu Val
1 5 10 15

Thr Glu Ile Met Arg Asn Asn Phe Gly Lys Val Leu Glu Arg Gly Val
20 25 30

Lys Leu Ala Glu Leu Gln Gln Arg Ser Asp Gln Leu Leu Asp Met Ser
35 40 45

Ser Thr Phe Asn Lys Thr Thr Gln Asn Leu Ala Gln Lys Lys Cys Trp
50 55 60

Glu Asn Ile Arg Tyr Arg Ile Cys Val Gly Leu Val Val Val Gly Val
65 70 75 80

Leu Leu Ile Ile Leu Ile Val Leu Leu Val Val Phe Leu Pro Gln Ser
85 90 95

Ser Asp Ser Ser Ser Ala Pro Arg Thr Gln Asp Ala Gly Ile Ala Ser
100 105 110

Gly Pro Gly Asn
115

<210> 44
<211> 198
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 44

Met Lys Leu Tyr Ser Leu Ser Val Leu Tyr Lys Gly Glu Ala Lys Val
1 5 10 15

Val Leu Leu Lys Ala Ala Tyr Asp Val Ser Ser Phe Ser Phe Phe Gln
20 25 30

Arg Ser Ser Val Gln Glu Phe Met Thr Phe Thr Ser Gln Leu Ile Val
35 40 45

Glu Arg Ser Ser Lys Gly Thr Arg Ala Ser Val Lys Glu Gln Asp Tyr
50 55 60

Leu Cys His Val Tyr Val Arg Asn Asp Ser Leu Ala Gly Val Val Ile
65 70 75 80

Ala Asp Asn Glu Tyr Pro Ser Arg Val Ala Phe Thr Leu Leu Glu Lys
85 90 95

Val Leu Asp Glu Phe Ser Lys Gln Val Asp Arg Ile Asp Trp Pro Val
100 105 110

[0162]

Gly Ser Pro Ala Thr Ile His Tyr Pro Ala Leu Asp Gly His Leu Ser
115 120 125

Arg Tyr Gln Asn Pro Arg Glu Ala Asp Pro Met Thr Lys Val Gln Ala
130 135 140

Glu Leu Asp Glu Thr Lys Ile Ile Leu His Asn Thr Met Glu Ser Leu
145 150 155 160

Leu Glu Arg Gly Glu Lys Leu Asp Asp Leu Val Ser Lys Ser Glu Val
165 170 175

Leu Gly Thr Gln Ser Lys Ala Phe Tyr Lys Thr Ala Arg Lys Gln Asn
180 185 190

Ser Cys Cys Ala Ile Ile
195

<210> 45
<211> 898
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 45

Met Lys Leu Glu Ile Asn Lys Phe Asn Tyr Asn Asp Pro Ile Asp Gly

```
1               5                  10                  15

Ile Asn Val Ile Thr Met Arg Pro Pro Arg His Ser Asp Lys Ile Asn
            20                  25                  30

Lys Gly Lys Gly Pro Phe Lys Ala Phe Gln Val Ile Lys Asn Ile Trp
        35                  40                  45

Ile Val Pro Glu Arg Tyr Asn Phe Thr Asn Asn Thr Asn Asp Leu Asn
    50                  55                  60

Ile Pro Ser Glu Pro Ile Met Glu Ala Asp Ala Ile Tyr Asn Pro Asn
65                  70                  75                  80

Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu Gln Gly Val Ile
                85                  90                  95

Lys Val Leu Glu Arg Ile Lys Ser Lys Pro Glu Gly Glu Lys Leu Leu
            100                 105                 110

Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val Ser Asn Gly Ala
        115                 120                 125

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln Glu Asn Asn Asn
    130                 135                 140

Ile Val Ser Asn Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro
145                 150                 155                 160

Asp Ile Ala Asn Asn Ala Thr Tyr Gly Leu Tyr Ser Thr Pro Ile Ser
                165                 170                 175

Asn Gly Glu Gly Thr Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr Leu
            180                 185                 190

Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile
        195                 200                 205

Val Asn Lys Phe Val Lys Arg Glu Phe Ala Pro Asp Pro Ala Ser Thr
    210                 215                 220

Leu Met His Glu Leu Val His Val Thr His Asn Leu Tyr Gly Ile Ser
225                 230                 235                 240

Asn Arg Asn Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser
                245                 250                 255

Arg Gln Gln Asn Ser Leu Ile Phe Glu Glu Leu Leu Thr Phe Gly Gly
            260                 265                 270

Ile Asp Ser Lys Ala Ile Ser Ser Leu Ile Ile Lys Lys Ile Ile Glu
        275                 280                 285

Thr Ala Lys Asn Asn Tyr Thr Thr Leu Ile Ser Glu Arg Leu Asn Thr
    290                 295                 300
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[0163]

Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile Lys Asn Lys Ile Pro
305 310 315 320

Val Gln Gly Arg Leu Gly Asn Phe Lys Leu Asp Thr Ala Glu Phe Glu
325 330 335

Lys Lys Leu Asn Thr Ile Leu Phe Val Leu Asn Glu Ser Asn Leu Ala
340 345 350

Gln Arg Phe Ser Ile Leu Val Arg Lys His Tyr Leu Lys Glu Arg Pro
355 360 365

Ile Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr
370 375 380

Leu Glu Gly Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly
385 390 395 400

Gln Leu Leu Glu Ser Ser Tyr Phe Glu Lys Ile Glu Ser Asn Ala Leu
405 410 415

Arg Ala Phe Ile Lys Ile Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala
420 425 430

Ile Tyr Arg Asn Ser Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp
435 440 445

[0164] Lys Lys Thr Thr Ser Lys Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu
450 455 460

Asn Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu Ile Ser Asn
465 470 475 480

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
485 490 495

Glu Thr Thr Val Phe Phe Lys Asp Lys Leu Pro Pro Gln Asp Ile Thr
500 505 510

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
515 520 525

Gln Gln Asn Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg
530 535 540

Asn Ser Leu Phe Glu Ile Lys Thr Ile Tyr Val Asp Lys Leu Thr Thr
545 550 555 560

Phe His Phe Leu Glu Ala Gln Asn Ile Asp Glu Ser Ile Asp Ser Ser
565 570 575

Lys Ile Arg Val Glu Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn
580 585 590

Pro Asn Lys Val Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn
595 600 605

Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile Phe Tyr Gln Trp Leu
610 615 620

Arg Ser Ile Val Lys Asp Phe Ser Asp Glu Thr Gly Lys Ile Asp Val
625 630 635 640

Ile Asp Lys Ser Ser Asp Thr Leu Ala Ile Val Pro Tyr Ile Gly Pro
645 650 655

Leu Leu Asn Ile Gly Asn Asp Ile Arg His Gly Asp Phe Val Gly Ala
660 665 670

Ile Glu Leu Ala Gly Ile Thr Ala Leu Leu Glu Tyr Val Pro Glu Phe
675 680 685

Thr Ile Pro Ile Leu Val Gly Leu Glu Val Ile Gly Gly Glu Leu Ala
690 695 700

Arg Glu Gln Val Glu Ala Ile Val Asn Asn Ala Leu Asp Lys Arg Asp
705 710 715 720

Gln Lys Trp Ala Glu Val Tyr Asn Ile Thr Lys Ala Gln Trp Trp Gly
725 730 735

Thr Ile His Leu Gln Ile Asn Thr Arg Leu Ala His Thr Tyr Lys Ala
740 745 750

[0165] Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn Met Glu Phe Gln Leu
755 760 765

Ala Asn Tyr Lys Gly Asn Ile Asp Asp Lys Ala Lys Ile Lys Asn Ala
770 775 780

Ile Ser Glu Thr Glu Ile Leu Leu Asn Lys Ser Val Glu Gln Ala Met
785 790 795 800

Lys Asn Thr Glu Lys Phe Met Ile Lys Leu Ser Asn Ser Tyr Leu Thr
805 810 815

Lys Glu Met Ile Pro Lys Val Gln Asp Asn Leu Lys Asn Phe Asp Leu
820 825 830

Glu Thr Lys Lys Thr Leu Asp Lys Phe Ile Lys Glu Lys Glu Asp Ile
835 840 845

Leu Gly Thr Asn Leu Ser Ser Ser Leu Arg Arg Lys Val Ser Ile Arg
850 855 860

Leu Asn Lys Asn Ile Ala Phe Asp Ile Asn Asp Ile Pro Phe Ser Glu
865 870 875 880

Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Ile Leu Pro Glu Thr
885 890 895

Gly Gly

<210> 46
<211> 415
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 46

Gly Glu Asp Tyr Glu Val Leu Asn Leu Gly Ala Glu Asp Gly Lys Ile
1 5 10 15

Lys Asp Leu Ser Gly Thr Thr Ser Asp Ile Asn Ile Gly Ser Asp Ile
20 25 30

Glu Leu Ala Asp Gly Arg Glu Asn Lys Ala Ile Lys Ile Lys Gly Ser
35 40 45

Glu Asn Ser Thr Ile Lys Ile Ala Met Asn Lys Tyr Leu Arg Phe Ser
50 55 60

Ala Thr Asp Asn Phe Ser Ile Ser Phe Trp Ile Lys His Pro Lys Pro
65 70 75 80

Thr Asn Leu Leu Asn Asn Gly Ile Glu Tyr Thr Leu Val Glu Asn Phe
85 90 95

Asn Gln Arg Gly Trp Lys Ile Ser Ile Gln Asp Ser Lys Leu Ile Trp
[0166] 100 105 110

Tyr Leu Arg Asp His Asn Asn Ser Ile Lys Ile Val Thr Pro Asp Tyr
115 120 125

Ile Ala Phe Asn Gly Trp Asn Leu Ile Thr Ile Thr Asn Asn Arg Ser
130 135 140

Lys Gly Ser Ile Val Tyr Val Asn Gly Ser Lys Ile Glu Glu Lys Asp
145 150 155 160

Ile Ser Ser Ile Trp Asn Thr Glu Val Asp Asp Pro Ile Ile Phe Arg
165 170 175

Leu Lys Asn Asn Arg Asp Thr Gln Ala Phe Thr Leu Leu Asp Gln Phe
180 185 190

Ser Ile Tyr Arg Lys Glu Leu Asn Gln Asn Glu Val Val Lys Leu Tyr
195 200 205

Asn Tyr Tyr Phe Asn Ser Asn Tyr Ile Arg Asp Ile Trp Gly Asn Pro
210 215 220

Leu Gln Tyr Asn Lys Lys Tyr Tyr Leu Gln Thr Gln Asp Lys Pro Gly
225 230 235 240

Lys Gly Leu Ile Arg Glu Tyr Trp Ser Ser Phe Gly Tyr Asp Tyr Val
245 250 255

Ile Leu Ser Asp Ser Lys Thr Ile Thr Phe Pro Asn Asn Ile Arg Tyr
260 265 270

Gly Ala Leu Tyr Asn Gly Ser Lys Val Leu Ile Lys Asn Ser Lys Lys
275 280 285

Leu Asp Gly Leu Val Arg Asn Lys Asp Phe Ile Gln Leu Glu Ile Asp
290 295 300

Gly Tyr Asn Met Gly Ile Ser Ala Asp Arg Phe Asn Glu Asp Thr Asn
305 310 315 320

Tyr Ile Gly Thr Thr Tyr Gly Thr Thr His Asp Leu Thr Thr Asp Phe
325 330 335

Glu Ile Ile Gln Arg Gln Glu Lys Tyr Arg Asn Tyr Cys Gln Leu Lys
340 345 350

Thr Pro Tyr Asn Ile Phe His Lys Ser Gly Leu Met Ser Thr Glu Thr
355 360 365

Ser Lys Pro Thr Phe His Asp Tyr Arg Asp Trp Val Tyr Ser Ser Ala
370 375 380

Trp Tyr Phe Gln Asn Tyr Glu Asn Leu Asn Leu Arg Lys His Thr Lys
385 390 395 400

[0167] Thr Asn Trp Tyr Phe Ile Pro Lys Asp Glu Gly Trp Asp Glu Asp
405 410 415

<210> 47
<211> 424
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 47

Ile Ile Asn Thr Ser Ile Leu Asn Leu Arg Tyr Glu Ser Asn His Leu
1 5 10 15

Ile Asp Leu Ser Arg Tyr Ala Ser Lys Ile Asn Ile Gly Ser Lys Val
20 25 30

Asn Phe Asp Pro Ile Asp Lys Asn Gln Ile Gln Leu Phe Asn Leu Glu
35 40 45

Ser Ser Lys Ile Glu Val Ile Leu Lys Asn Ala Ile Val Tyr Asn Ser
50 55 60

Met Tyr Glu Asn Phe Ser Thr Ser Phe Trp Ile Arg Ile Pro Lys Tyr
65 70 75 80

Phe Asn Ser Ile Ser Leu Asn Asn Glu Tyr Thr Ile Ile Asn Cys Met
85 90 95

Glu Asn Asn Ser Gly Trp Lys Val Ser Leu Asn Tyr Gly Glu Ile Ile
100 105 110

Trp Thr Leu Gln Asp Thr Gln Glu Ile Lys Gln Arg Val Val Phe Lys
115 120 125

Tyr Ser Gln Met Ile Asn Ile Ser Asp Tyr Ile Asn Arg Trp Ile Phe
130 135 140

Val Thr Ile Thr Asn Asn Arg Leu Asn Asn Ser Lys Ile Tyr Ile Asn
145 150 155 160

Gly Arg Leu Ile Asp Gln Lys Pro Ile Ser Asn Leu Gly Asn Ile His
165 170 175

Ala Ser Asn Asn Ile Met Phe Lys Leu Asp Gly Cys Arg Asp Thr His
180 185 190

Arg Tyr Ile Trp Ile Lys Tyr Phe Asn Leu Phe Asp Lys Glu Leu Asn
195 200 205

Glu Lys Glu Ile Lys Asp Leu Tyr Asp Asn Gln Ser Asn Ser Gly Ile
210 215 220

Leu Lys Asp Phe Trp Gly Asp Tyr Leu Gln Tyr Asp Lys Pro Tyr Tyr
225 230 235 240

[0168] Met Leu Asn Leu Tyr Asp Pro Asn Lys Tyr Val Asp Val Asn Asn Val
245 250 255

Gly Ile Arg Gly Tyr Met Tyr Leu Lys Gly Pro Arg Gly Ser Val Met
260 265 270

Thr Thr Asn Ile Tyr Leu Asn Ser Ser Leu Tyr Arg Gly Thr Lys Phe
275 280 285

Ile Ile Lys Lys Tyr Ala Ser Gly Asn Lys Asp Asn Ile Val Arg Asn
290 295 300

Asn Asp Arg Val Tyr Ile Asn Val Val Val Lys Asn Lys Glu Tyr Arg
305 310 315 320

Leu Ala Thr Asn Ala Ser Gln Ala Gly Val Glu Lys Ile Leu Ser Ala
325 330 335

Leu Glu Ile Pro Asp Val Gly Asn Leu Ser Gln Val Val Val Met Lys
340 345 350

Ser Lys Asn Asp Gln Gly Ile Thr Asn Lys Cys Lys Met Asn Leu Gln
355 360 365

Asp Asn Asn Gly Asn Asp Ile Gly Phe Ile Gly Phe His Gln Phe Asn
370 375 380

Asn Ile Ala Lys Leu Val Ala Ser Asn Trp Tyr Asn Arg Gln Ile Glu
385 390 395 400

Arg Ser Ser Arg Thr Leu Gly Cys Ser Trp Glu Phe Ile Pro Val Asp
405 410 415

Asp Gly Trp Gly Glu Arg Pro Leu
420

<210> 48
<211> 432
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 48

Ile Leu Asn Asn Ile Ile Leu Asn Leu Arg Tyr Lys Asp Asn Asn Leu
1 5 10 15

Ile Asp Leu Ser Gly Tyr Gly Ala Lys Val Glu Val Tyr Asp Gly Val
20 25 30

Glu Leu Asn Asp Lys Asn Gln Phe Lys Leu Thr Ser Ser Ala Asn Ser
35 40 45

Lys Ile Arg Val Thr Gln Asn Gln Asn Ile Ile Phe Asn Ser Val Phe
50 55 60

Leu Asp Phe Ser Val Ser Phe Trp Ile Arg Ile Pro Lys Tyr Lys Asn
[0169] 65 70 75 80

Asp Gly Ile Gln Asn Tyr Ile His Asn Glu Tyr Thr Ile Ile Asn Cys
85 90 95

Met Lys Asn Asn Ser Gly Trp Lys Ile Ser Ile Arg Gly Asn Arg Ile
100 105 110

Ile Trp Thr Leu Ile Asp Ile Asn Gly Lys Thr Lys Ser Val Phe Phe
115 120 125

Glu Tyr Asn Ile Arg Glu Asp Ile Ser Glu Tyr Ile Asn Arg Trp Phe
130 135 140

Phe Val Thr Ile Thr Asn Asn Leu Asn Asn Ala Lys Ile Tyr Ile Asn
145 150 155 160

Gly Lys Leu Glu Ser Asn Thr Asp Ile Lys Asp Ile Arg Glu Val Ile
165 170 175

Ala Asn Gly Glu Ile Ile Phe Lys Leu Asp Gly Asp Ile Asp Arg Thr
180 185 190

Gln Phe Ile Trp Met Lys Tyr Phe Ser Ile Phe Asn Thr Glu Leu Ser
195 200 205

Gln Ser Asn Ile Glu Glu Arg Tyr Lys Ile Gln Ser Tyr Ser Glu Tyr
210 215 220

Leu Lys Asp Phe Trp Gly Asn Pro Leu Met Tyr Asn Lys Glu Tyr Tyr
225 230 235 240

Met Phe Asn Ala Gly Asn Lys Asn Ser Tyr Ile Lys Leu Lys Lys Asp
245 250 255

Ser Pro Val Gly Glu Ile Leu Thr Arg Ser Lys Tyr Asn Gln Asn Ser
260 265 270

Lys Tyr Ile Asn Tyr Arg Asp Leu Tyr Ile Gly Glu Lys Phe Ile Ile
275 280 285

Arg Arg Lys Ser Asn Ser Gln Ser Ile Asn Asp Asp Ile Val Arg Lys
290 295 300

Glu Asp Tyr Ile Tyr Leu Asp Phe Phe Asn Leu Asn Gln Glu Trp Arg
305 310 315 320

Val Tyr Thr Tyr Lys Tyr Phe Lys Lys Glu Glu Glu Lys Leu Phe Leu
325 330 335

Ala Pro Ile Ser Asp Ser Asp Glu Phe Tyr Asn Thr Ile Gln Ile Lys
340 345 350

Glu Tyr Asp Glu Gln Pro Thr Tyr Ser Cys Gln Leu Leu Phe Lys Lys
355 360 365

[0170] Asp Glu Glu Ser Thr Asp Glu Ile Gly Leu Ile Gly Ile His Arg Phe
370 375 380

Tyr Glu Ser Gly Ile Val Phe Glu Glu Tyr Lys Asp Tyr Phe Cys Ile
385 390 395 400

Ser Lys Trp Tyr Leu Lys Glu Val Lys Arg Lys Pro Tyr Asn Leu Lys
405 410 415

Leu Gly Cys Asn Trp Gln Phe Ile Pro Lys Asp Glu Gly Trp Thr Glu
420 425 430

<210> 49
<211> 424
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 49

Ile Asn Asp Ser Lys Ile Leu Ser Leu Gln Asn Arg Lys Asn Thr Leu
1 5 10 15

Val Asp Thr Ser Gly Tyr Asn Ala Glu Val Ser Glu Glu Gly Asp Val
20 25 30

Gln Leu Asn Pro Ile Phe Pro Phe Asp Phe Lys Leu Gly Ser Ser Gly
35 40 45

Glu Asp Arg Gly Lys Val Ile Val Thr Gln Asn Glu Asn Ile Val Tyr

50 55 60

Asn Ser Met Tyr Glu Ser Phe Ser Ile Ser Phe Trp Ile Arg Ile Asn
65 70 75 80

Lys Trp Val Ser Asn Leu Pro Gly Tyr Thr Ile Ile Asp Ser Val Lys
85 90 95

Asn Asn Ser Gly Trp Ser Ile Gly Ile Ile Ser Asn Phe Leu Val Phe
100 105 110

Thr Leu Lys Gln Asn Glu Asp Ser Glu Gln Ser Ile Asn Phe Ser Tyr
115 120 125

Asp Ile Ser Asn Asn Ala Pro Gly Tyr Asn Lys Trp Phe Phe Val Thr
130 135 140

Val Thr Asn Asn Met Met Gly Asn Met Lys Ile Tyr Ile Asn Gly Lys
145 150 155 160

Leu Ile Asp Thr Ile Lys Val Lys Glu Leu Thr Gly Ile Asn Phe Ser
165 170 175

Lys Thr Ile Thr Phe Glu Ile Asn Lys Ile Pro Asp Thr Gly Leu Ile
180 185 190

[0171] Thr Ser Asp Ser Asp Asn Ile Asn Met Trp Ile Arg Asp Phe Tyr Ile
195 200 205

Phe Ala Lys Glu Leu Asp Gly Lys Asp Ile Asn Ile Leu Phe Asn Ser
210 215 220

Leu Gln Tyr Thr Asn Val Val Lys Asp Tyr Trp Gly Asn Asp Leu Arg
225 230 235 240

Tyr Asn Lys Glu Tyr Tyr Met Val Asn Ile Asp Tyr Leu Asn Arg Tyr
245 250 255

Met Tyr Ala Asn Ser Arg Gln Ile Val Phe Asn Thr Arg Arg Asn Asn
260 265 270

Asn Asp Phe Asn Glu Gly Tyr Lys Ile Ile Ile Lys Arg Ile Arg Gly
275 280 285

Asn Thr Asn Asp Thr Arg Val Arg Gly Gly Asp Ile Leu Tyr Phe Asp
290 295 300

Met Thr Ile Asn Asn Lys Ala Tyr Asn Leu Phe Met Lys Asn Glu Thr
305 310 315 320

Met Tyr Ala Asp Asn His Ser Thr Glu Asp Ile Tyr Ala Ile Gly Leu
325 330 335

Arg Glu Gln Thr Lys Asp Ile Asn Asp Asn Ile Ile Phe Gln Ile Gln
340 345 350

Pro Met Asn Asn Thr Tyr Tyr Tyr Ala Ser Gln Ile Phe Lys Ser Asn
355 360 365

Phe Asn Gly Glu Asn Ile Ser Gly Ile Cys Ser Ile Gly Thr Tyr Arg
370 375 380

Phe Arg Leu Gly Gly Asp Trp Tyr Arg His Asn Tyr Leu Val Pro Thr
385 390 395 400

Val Lys Gln Gly Asn Tyr Ala Ser Leu Leu Glu Ser Thr Ser Thr His
405 410 415

Trp Gly Phe Val Pro Val Ser Glu
420

<210> 50
<211> 6
<212> PRT
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<220>
<223> 合成的多肽

<400> 50

Leu Val Pro Arg Gly Ser
1 5

<210> 51
<211> 7
<212> PRT
[0172] <213> 人工序列

<220>
<223> 合成的多肽

<400> 51

Glu Asn Leu Tyr Phe Gln Gly
1 5

<210> 52
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 52

Leu Glu Val Leu Phe Gln Gly Pro
1 5

<210> 53
<211> 4
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 53

Ile Glu Gly Arg
1

<210> 54
<211> 4
<212> PRT
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<220>
<223> 合成的多肽

<400> 54

Ile Asp Gly Arg
1

<210> 55
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 55

Asp Asp Asp Asp Lys
1 5

<210> 56
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

[0173] <400> 56

Ala His Arg Glu Gln Ile Gly Gly
1 5

<210> 57
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<220>
<221> misc_feature
<222> (3)..(3)
<223> Xaa可以是任何天然存在的氨基酸

<400> 57

Leu Pro Xaa Thr Gly
1 5

<210> 58
<211> 6
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 58

Leu Pro Glu Thr Gly Gly
1 5

<210> 59
<211> 6
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 59

Leu Pro Glu Thr Gly Ser
1 5

<210> 60
<211> 6
<212> PRT
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<220>
<223> 合成的多肽

<220>
<221> misc_feature
<222> (3)..(3)
<223> Xaa可以是任何天然存在的氨基酸

<400> 60

Leu Pro Xaa Thr Gly Gly
1 5

<210> 61
<211> 101
[0174] <212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 61

Gly Gly Ser His His His His His His Gly Met Ala Ser Met Thr Gly
1 5 10 15

Gly Gln Gln Met Gly Arg Asp Leu Tyr Asp Asp Asp Asp Lys Asp Arg
20 25 30

Trp Gly Ser Met Ser Ala Thr Ala Ala Thr Val Pro Pro Ala Ala Pro
35 40 45

Ala Gly Glu Gly Gly Pro Pro Ala Pro Pro Pro Asn Leu Thr Ser Asn
50 55 60

Arg Arg Leu Gln Gln Thr Gln Ala Gln Val Asp Glu Val Val Asp Ile
65 70 75 80

Met Arg Val Asn Val Asp Lys Val Leu Glu Arg Asp Gln Lys Leu Ser
85 90 95

Glu Leu Asp Asp Arg
100

<210> 62

<211> 27
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 62

Ala Asp Ala Leu Gln Ala Gly Ala Ser Gln Phe Glu Thr Ser Ala Ala
1 5 10 15

Lys Leu Lys Arg Lys Tyr Trp Trp Lys Asn Leu
20 25

<210> 63
<211> 54
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 63

Gln Gln Thr Gln Ala Gln Val Asp Glu Val Val Asp Ile Met Arg Val
1 5 10 15

Asn Val Asp Lys Val Leu Glu Arg Asp Gln Lys Leu Ser Glu Leu Asp
20 25 30

Asp Arg Ala Asp Ala Leu Gln Ala Gly Ala Ser Gln Phe Glu Thr Ser
35 40 45

[0175]

Ala Ala Lys Leu Lys Arg
50

<210> 64
<211> 54
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 64

Gln Gln Thr Gln Ala Gln Val Glu Glu Val Val Asp Ile Met Arg Val
1 5 10 15

Asn Val Asp Lys Val Leu Glu Arg Asp Gln Lys Leu Ser Glu Leu Asp
20 25 30

Asp Arg Ala Asp Ala Leu Gln Ala Gly Ala Ser Gln Phe Glu Ser Ser
35 40 45

Ala Ala Lys Leu Lys Arg
50

<210> 65
<211> 54
<212> PRT
<213> 人工序列

<220>

<223> 合成的多肽

<400> 65

Gln Gln Thr Gln Asn Gln Val Asp Glu Val Val Asp Ile Met Arg Val
1 5 10 15

Asn Val Asp Lys Val Leu Glu Arg Asp Gln Lys Leu Ser Glu Leu Asp
20 25 30

Asp Arg Ala Asp Ala Leu Gln Ala Gly Ala Ser Gln Phe Glu Thr Ser
35 40 45

Ala Ala Lys Leu Lys Arg
50

<210> 66
<211> 54
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 66

Lys His Val Gln Asn Gln Val Asp Glu Val Ile Asp Val Met Gln Glu
1 5 10 15

Asn Ile Thr Lys Val Ile Glu Arg Gly Glu Arg Leu Asp Glu Leu Gln
20 25 30

[0176]

Asp Lys Ser Glu Ser Leu Ser Asp Asn Ala Thr Ala Phe Ser Asn Arg
35 40 45

Ser Lys Gln Leu Arg Arg
50

<210> 67
<211> 54
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 67

Glu Arg Cys Gln Gln Gln Ala Asn Glu Val Thr Glu Ile Met Arg Asn
1 5 10 15

Asn Phe Gly Lys Val Leu Glu Arg Gly Val Lys Leu Ala Glu Leu Gln
20 25 30

Gln Arg Ser Asp Gln Leu Leu Asp Met Ser Ser Thr Phe Asn Lys Thr
35 40 45

Thr Gln Asn Leu Ala Gln
50

<210> 68
<211> 54
<212> PRT

<213> 人工序列

<220>
<223> 合成的多肽

<400> 68

Thr Glu Thr Gln Ala Gln Val Asp Glu Leu Lys Gly Ile Met Val Arg
1 5 10 15

Asn Ile Asp Leu Val Ala Gln Arg Gly Glu Arg Leu Glu Leu Leu Ile
20 25 30

Asp Lys Thr Glu Asn Leu Val Asp Ser Ser Val Thr Phe Lys Thr Thr
35 40 45

Ser Arg Asn Leu Ala Arg
50

<210> 69
<211> 54
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 69

Arg Asn Leu Gln Ser Glu Val Glu Gly Val Lys Asn Ile Met Thr Gln
1 5 10 15

[0177]

Asn Val Glu Arg Ile Leu Ala Arg Gly Glu Asn Leu Asp His Leu Arg
20 25 30

Asn Lys Thr Glu Asp Leu Glu Ala Thr Ser Glu His Phe Lys Thr Thr
35 40 45

Ser Gln Lys Val Ala Arg
50

<210> 70
<211> 54
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 70

Gly Ser Ile Asn Thr Glu Leu Gln Asp Val Gln Arg Ile Met Val Ala
1 5 10 15

Asn Ile Glu Glu Val Leu Gln Arg Gly Glu Ala Leu Ser Ala Leu Asp
20 25 30

Ser Lys Ala Asn Asn Leu Ser Ser Leu Ser Lys Lys Tyr Arg Gln Asp
35 40 45

Ala Lys Tyr Leu Asn Met
50

<210> 71
<211> 50
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 71

Ser Lys Val Gln Ala Glu Leu Asp Glu Thr Lys Ile Ile Leu His Asn
1 5 10 15

Thr Met Glu Ser Leu Leu Glu Arg Gly Glu Lys Leu Asp Asp Leu Val
20 25 30

Ser Lys Ser Glu Val Leu Gly Thr Gln Ser Lys Ala Phe Tyr Lys Thr
35 40 45

Ala Arg
50

<210> 72
<211> 25
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 72

[0178] Cys Val Arg Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Asp Lys Gly
1 5 10 15

Tyr Asn Lys Ala Leu Asn Asp Leu Cys
20 25

<210> 73
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 73

Cys Lys Ser Val Lys Ala Pro Gly Ile Cys
1 5 10

<210> 74
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 74

Cys His Lys Ala Ile Asp Gly Arg Ser Leu Tyr Asn Lys Thr Leu Asp
1 5 10 15

Cys

<210> 75
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 75

Cys Leu Arg Leu Thr Lys Asn Ser Arg Asp Asp Ser Thr Cys
1 5 10

<210> 76
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 76

Cys Lys Asn Ile Val Ser Val Lys Gly Ile Arg Lys Ser Ile Cys
1 5 10 15

<210> 77
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

[0179]

<400> 77

Cys Lys Ser Val Ile Pro Arg Lys Gly Thr Lys Ala Pro Pro Arg Leu
1 5 10 15

Cys

<210> 78
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 78

Cys Lys Pro Val Met Tyr Lys Asn Thr Gly Lys Ser Glu Gln Cys
1 5 10 15

<210> 79
<211> 45
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 79

Cys Pro Arg Asn Gly Leu Leu Tyr Asn Ala Ile Tyr Arg Asn Ser Lys
1 5 10 15

Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp Lys Lys Thr Thr Ser Lys
20 25 30

Thr Asn Val Ser Tyr Pro Cys Ser Leu Leu Asn Gly Cys
35 40 45

<210> 80
<211> 6
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> 被GST修饰

<400> 80

Leu Val Pro Arg Gly Ser
1 5

<210> 81
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 81

[0180]

Leu Pro Glu Thr Gly Gly His His His His His His
1 5 10

<210> 82
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 82

Gly Gly His His His His His His
1 5

<210> 83
<211> 128
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 83

Gly Gly Ser His His His His His His Gly Met Ala Ser Met Thr Gly
1 5 10 15

Gly Gln Gln Met Gly Arg Asp Leu Tyr Asp Asp Asp Asp Lys Asp Arg
20 25 30

Trp Gly Ser Met Ser Ala Thr Ala Ala Thr Val Pro Pro Ala Ala Pro

35 40 45

Ala Gly Glu Gly Gly Pro Pro Ala Pro Pro Pro Asn Leu Thr Ser Asn
50 55 60

Arg Arg Leu Gln Gln Thr Gln Ala Gln Val Asp Glu Val Val Asp Ile
65 70 75 80

Met Arg Val Asn Val Asp Lys Val Leu Glu Arg Asp Gln Lys Leu Ser
85 90 95

Glu Leu Asp Asp Arg Ala Asp Ala Leu Gln Ala Gly Ala Ser Gln Phe
100 105 110

Glu Thr Ser Ala Ala Lys Leu Lys Arg Lys Tyr Trp Trp Lys Asn Leu
115 120 125

<210> 84
<211> 280
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 84

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1 5 10 15

[0181] Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
20 25 30

Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
35 40 45

Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
50 55 60

Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65 70 75 80

Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85 90 95

Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100 105 110

Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115 120 125

Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130 135 140

Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145 150 155 160

Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165 170 175

Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180 185 190

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

Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
210 215 220

Gly Ser Gln Gln Thr Gln Ala Gln Val Asp Glu Val Val Asp Ile Met
225 230 235 240

Arg Val Asn Val Asp Lys Val Leu Glu Arg Asp Gln Lys Leu Ser Glu
245 250 255

Leu Asp Asp Arg Ala Asp Ala Leu Gln Ala Gly Ala Ser Gln Phe Glu
260 265 270

Thr Ser Ala Ala Lys Leu Lys Arg
275 280

<210> 85
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

[0182] <400> 85

Ala Asp Ala Leu Gln Ala Gly Ala Ser Gln Phe Glu Thr Ser Ala Ala
1 5 10 15

Lys Leu Lys Arg
20

<210> 86
<211> 260
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 86

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1 5 10 15

Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
20 25 30

Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
35 40 45

Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
50 55 60

Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn

65 70 75 80

Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85 90 95

Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100 105 110

Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115 120 125

Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130 135 140

Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145 150 155 160

Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165 170 175

Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180 185 190

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

Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
[0183] 210 215 220

Gly Ser Gln Gln Thr Gln Ala Gln Val Asp Glu Val Val Asp Ile Met
225 230 235 240

Arg Val Asn Val Asp Lys Val Leu Glu Arg Asp Gln Lys Leu Ser Glu
245 250 255

Leu Asp Asp Arg
260

<210> 87
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 87

Glu Ser Leu Leu Glu Arg Gly Glu Lys Leu Asp Asp Leu Val Ser Lys
1 5 10 15

<210> 88
<211> 6
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 88

Asp Glu Leu Gln Asp Lys
1 5

<210> 89
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 89

Ser Glu Ser Leu Ser Asp Asn Ala Thr Ala Phe
1 5 10

<210> 90
<211> 6
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 90

Ala Glu Leu Gln Gln Arg
1 5

<210> 91
<211> 11
<212> PRT
<213> 人工序列

[0184] <220>
<223> 合成的多肽

<400> 91

Ser Asp Gln Leu Leu Asp Met Ser Ser Thr Phe
1 5 10

<210> 92
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 92

His Glu Leu Val His
1 5

<210> 93
<211> 4
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 93

Ser Ala Trp Tyr
1

<210> 94

<210> 8
<212> PRT
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<220>
<223> 合成的多肽

<400> 94

Lys Leu Glu Ile Asn Lys Phe Asn
1 5

<210> 95
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 95

Lys Leu Glu Ile Asn Lys Phe Asn
1 5

<210> 96
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 96

[0185] Phe Asn Tyr Asn Asp Pro Ile Asp Gly Ile Asn Val Ile Thr Met Arg
1 5 10 15

<210> 97
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 97

Phe Asn Tyr Asn Asp Pro Ile Asp Gly Ile Asn Val Ile Thr Met Arg
1 5 10 15

<210> 98
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 98

Phe Asn Tyr Asn Asp Pro Ile Asp Gly Ile Asn Val Ile Thr
1 5 10

<210> 99
<211> 12
<212> PRT
<213> 人工序列

<220>

<223> 合成的多肽

<400> 99

Phe Asn Tyr Asn Asp Pro Ile Asp Gly Ile Asn Val
1 5 10

<210> 100
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 100

Phe Asn Tyr Asn Asp Pro Ile Asp Gly Ile Asn Val
1 5 10

<210> 101
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 101

Asp Pro Ile Asp Gly Ile Asn Val Ile Thr
1 5 10

[0186]

<210> 102
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 102

Asp Pro Ile Asp Gly Ile Asn Val Ile Thr
1 5 10

<210> 103
<211> 24
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 103

Tyr Asn Pro Asn Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu
1 5 10 15

Gln Gly Val Ile Lys Val Leu Glu
20

<210> 104
<211> 24
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 104

Tyr Asn Pro Asn Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu
1 5 10 15

Gln Gly Val Ile Lys Val Leu Glu
20

<210> 105
<211> 24
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 105

Tyr Asn Pro Asn Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu
1 5 10 15

Gln Gly Val Ile Lys Val Leu Glu
20

<210> 106
<211> 24
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

[0187]

<400> 106

Tyr Asn Pro Asn Tyr Leu Asn Thr Pro Ser Glu Lys Asp Glu Phe Leu
1 5 10 15

Gln Gly Val Ile Lys Val Leu Glu
20

<210> 107
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 107

Leu Leu Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val
1 5 10

<210> 108
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 108

Leu Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val
1 5 10

<210> 109
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 109

Leu Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val
1 5 10

<210> 110
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 110

Leu Glu Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val
1 5 10

<210> 111
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

[0188] <400> 111

Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val
1 5 10

<210> 112
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 112

Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val
1 5 10

<210> 113
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 113

Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val
1 5 10

<210> 114
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 114

Leu Ile Ser Ser Ser Ile Pro Leu Pro Leu Val
1 5 10

<210> 115
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 115

Leu Val Ser Asn Gly Ala Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala
1 5 10 15

Tyr Gln

<210> 116
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 116

[0189] Leu Val Ser Asn Gly Ala Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala
1 5 10 15

Tyr Gln

<210> 117
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 117

Leu Val Ser Asn Gly Ala Leu Thr
1 5

<210> 118
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 118

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln
1 5 10

<210> 119
<211> 12

<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 119

Leu Thr Leu Ser Asp Asn Glu Thr Ile Ala Tyr Gln
1 5 10

<210> 120
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 120

Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro Asp Ile Ala Asn
1 5 10 15

Asn Ala Thr Tyr Gly
20

<210> 121
<211> 21
<212> PRT
<213> 人工序列

<220>
[0190] <223> 合成的多肽

<400> 121

Leu Gln Ala Asn Leu Val Ile Tyr Gly Pro Gly Pro Asp Ile Ala Asn
1 5 10 15

Asn Ala Thr Tyr Gly
20

<210> 122
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 122

Leu Val Ile Tyr Gly Pro Gly Pro Asp Ile Ala Asn Asn Ala
1 5 10

<210> 123
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 123

Leu Val Ile Tyr Gly Pro Gly Pro Asp Ile Ala Asn Asn Ala Thr Tyr
1 5 10 15

Gly

<210> 124
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 124

Tyr Gly Pro Gly Pro Asp Ile Ala Asn Asn Ala Thr Tyr Gly
1 5 10

<210> 125
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 125

Asn Ala Thr Tyr Gly Leu Tyr Ser
1 5

<210> 126
<211> 21
<212> PRT
<213> 人工序列

[0191]

<220>
<223> 合成的多肽

<400> 126

Tyr Gly Leu Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser
1 5 10 15

Glu Val Ser Phe Ser
20

<210> 127
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 127

Tyr Gly Leu Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser
1 5 10 15

Glu Val Ser Phe Ser
20

<210> 128
<211> 24
<212> PRT
<213> 人工序列

<220>

<223> 合成的多肽

<400> 128

Tyr Gly Leu Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser
1 5 10 15

Glu Val Ser Phe Ser Pro Phe Tyr
20

<210> 129
<211> 24
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 129

Tyr Gly Leu Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser
1 5 10 15

Glu Val Ser Phe Ser Pro Phe Tyr
20

<210> 130
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

[0192]

<400> 130

Tyr Gly Leu Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser
1 5 10 15

Glu

<210> 131
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 131

Tyr Gly Leu Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser
1 5 10 15

Glu

<210> 132
<211> 24
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 132

Tyr Gly Leu Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser
1 5 10 15

Glu Val Ser Phe Ser Pro Phe Tyr
20

<210> 133
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 133

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu Val Ser
1 5 10 15

Phe

<210> 134
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 134

[0193] Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu Val Ser
1 5 10 15

Phe Ser Pro Phe Tyr
20

<210> 135
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 135

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu Val Ser
1 5 10 15

Phe Ser Pro Phe Tyr
20

<210> 136
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 136

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu Val Ser
1 5 10 15

Phe Ser Pro Phe Tyr
20

<210> 137
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 137

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu Val Ser
1 5 10 15

Phe Ser Pro Phe Tyr
20

<210> 138
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 138

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu Val Ser
1 5 10 15

[0194] Phe Ser

<210> 139
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 139

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu Val Ser
1 5 10 15

Phe Ser

<210> 140
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 140

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu Val Ser
1 5 10 15

Phe Ser

<210> 141
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 141

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu Val Ser
1 5 10 15

Phe Ser Pro Phe Tyr
20

<210> 142
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 142

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu Val Ser
1 5 10 15

Phe Ser Pro Phe Tyr
20

[0195]

<210> 143
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 143

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu Val Ser
1 5 10 15

Phe Ser

<210> 144
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 144

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu Val Ser
1 5 10 15

Phe Ser Pro Phe Tyr
20

<210> 145
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 145

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu Val Ser
1 5 10 15

Phe Ser Pro Phe Tyr
20

<210> 146
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 146

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu Val Ser
1 5 10 15

Phe Ser

[0196]

<210> 147
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 147

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu Val Ser
1 5 10 15

Phe Ser

<210> 148
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 148

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu
1 5 10

<210> 149
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 149

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu Val Ser
1 5 10 15

Phe Ser Pro Phe Tyr
20

<210> 150
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 150

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu Val Ser
1 5 10 15

Phe Ser Pro Phe Tyr
20

<210> 151
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

[0197] <400> 151

Tyr Ser Thr Pro Ile Ser Asn Gly Glu Gly Thr Leu Ser Glu
1 5 10

<210> 152
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 152

Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr
1 5 10

<210> 153
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 153

Leu Ser Glu Val Ser Phe Ser Pro Phe Tyr
1 5 10

<210> 154
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 154

Phe Tyr Leu Lys Pro Phe Asp Glu Ser Tyr Gly Asn Tyr Arg
1 5 10

<210> 155
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 155

Phe Tyr Leu Lys Pro Phe Asp Glu Ser Tyr Gly
1 5 10

<210> 156
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 156

Phe Asp Glu Ser Tyr Gly Asn Tyr Arg
1 5

[0198]

<210> 157
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 157

Tyr Gly Asn Tyr Arg Ser Leu Val Asn Ile Val Asn Lys Phe Val
1 5 10 15

<210> 158
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 158

His Asn Leu Tyr Gly Ile Ser Asn Arg Asn Phe Tyr
1 5 10

<210> 159
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 159

Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser Arg Gln Gln
1 5 10 15

Asn Ser

<210> 160
<211> 18
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 160

Phe Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser Arg Gln Gln
1 5 10 15

Asn Ser

<210> 161
<211> 19
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 161

[0199] Tyr Tyr Asn Phe Asp Thr Gly Lys Ile Glu Thr Ser Arg Gln Gln Asn
1 5 10 15

Ser Leu Ile

<210> 162
<211> 19
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 162

Leu Ile Ser Glu Arg Leu Asn Thr Val Thr Val Glu Asn Asp Leu Leu
1 5 10 15

Lys Tyr Ile

<210> 163
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 163

Leu Asn Thr Val Thr Val Glu Asn Asp Leu Leu Lys Tyr Ile
1 5 10

<210> 164
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 164

Phe Val Leu Asn Glu Ser Asn Leu Ala Gln Arg Phe Ser
1 5 10

<210> 165
<211> 22
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 165

His Tyr Leu Lys Glu Arg Pro Ile Asp Pro Ile Tyr Val Asn Ile Leu
1 5 10 15

Asp Asp Asn Ser Tyr Ser
20

<210> 166
<211> 14
<212> PRT
<213> 人工序列

[0200]

<220>
<223> 合成的多肽

<400> 166

Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser
1 5 10

<210> 167
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 167

Asp Pro Ile Tyr Val Asn Ile Leu Asp Asp Asn Ser Tyr Ser
1 5 10

<210> 168
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 168

Asn Ile Leu Asp Asp Asn Ser Tyr Ser Thr Leu Glu
1 5 10

<210> 169
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 169

Tyr Ser Thr Leu Glu Gly Phe Asn
1 5

<210> 170
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 170

Tyr Ser Thr Leu Glu Gly Phe Asn
1 5

<210> 171
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

[0201]

<400> 171

Tyr Ser Thr Leu Glu Gly Phe Asn
1 5

<210> 172
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 172

Tyr Ser Thr Leu Glu Gly Phe Asn
1 5

<210> 173
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 173

Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly Gln Leu Leu
1 5 10 15

Glu

<210> 174
<211> 22
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 174

Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly Gln Leu Leu
1 5 10 15

Glu Ser Ser Tyr Phe Glu
20

<210> 175
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 175

Phe Asn Ile Ser Ser Gln Gly Ser Asn Asp Phe Gln Gly Gln Leu
1 5 10 15

<210> 176
<211> 8
<212> PRT
<213> 人工序列

[0202] <220>
<223> 合成的多肽

<400> 176

Leu Leu Tyr Asn Ala Ile Tyr Arg
1 5

<210> 177
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 177

Leu Leu Tyr Asn Ala Ile Tyr Arg
1 5

<210> 178
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 178

Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp Lys Lys Thr Thr
1 5 10 15

<210> 179

<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 179

Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp Lys Lys Thr Thr Ser
1 5 10 15

Lys Thr Asn Val
20

<210> 180
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 180

Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp Lys Lys Thr Thr Ser
1 5 10 15

Lys Thr Asn Val
20

[0203]

<210> 181
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 181

Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp Lys Lys Thr Thr Ser
1 5 10 15

<210> 182
<211> 19
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 182

Lys Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp Lys Lys Thr Thr Ser
1 5 10 15

Lys Thr Asn

<210> 183
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 183

Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp Lys Lys Thr Thr Ser
1 5 10 15

<210> 184
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 184

Asn Tyr Leu Asn Asn Ile Asp Leu Glu Asp Lys Lys Thr Thr Ser
1 5 10 15

<210> 185
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 185

Gly Cys Ile Glu Val Glu Asn Lys Asp Leu Phe Leu
1 5 10

<210> 186
<211> 27
[0204] <212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 186

Phe Leu Ile Ser Asn Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu
1 5 10 15

Glu Lys Ile Lys Pro Glu Thr Thr Val Phe Phe
20 25

<210> 187
<211> 27
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 187

Phe Leu Ile Ser Asn Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu
1 5 10 15

Glu Lys Ile Lys Pro Glu Thr Thr Val Phe Phe
20 25

<210> 188
<211> 22
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 188

Lys Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro
1 5 10 15

Glu Thr Thr Val Phe Phe
20

<210> 189
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 189

Asp Ser Leu Asn Asp Ile Asn Leu Ser Glu Glu Lys Ile Lys Pro Glu
1 5 10 15

Thr Thr Val Phe Phe
20

<210> 190
<211> 15
<212> PRT
<213> 人工序列

<220>
[0205] <223> 合成的多肽

<400> 190

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile
1 5 10 15

<210> 191
<211> 19
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 191

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser
1 5 10 15

Gln Gln Asn

<210> 192
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 192

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser
1 5 10

<210> 193
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 193

Leu Ser Asn Tyr Asp Phe Thr Glu Ala Asn Ser
1 5 10

<210> 194
<211> 19
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 194

Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser Gln Gln Asn
1 5 10 15

Ile Leu Glu

<210> 195
<211> 19
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[0206]

<220>
<223> 合成的多肽

<400> 195

Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser Gln Gln Asn
1 5 10 15

Ile Leu Glu

<210> 196
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 196

Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser Gln Gln Asn
1 5 10 15

<210> 197
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 197

Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser Gln Gln Asn
1 5 10 15

<210> 198
<211> 31
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 198

Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser Gln Gln Asn
1 5 10 15

Ile Leu Glu Arg Asn Glu Glu Leu Tyr Glu Pro Ile Arg Asn Ser
20 25 30

<210> 199
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 199

Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser Gln Gln Asn
1 5 10 15

[0207] Ile

<210> 200
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 200

Tyr Asp Phe Thr Glu Ala Asn Ser Ile Pro Ser Ile Ser Gln Gln Asn
1 5 10 15

Ile

<210> 201
<211> 28
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 201

Asn Ser Ile Pro Ser Ile Ser Gln Gln Asn Ile Leu Glu Arg Asn Glu
1 5 10 15

Glu Leu Tyr Glu Pro Ile Arg Asn Ser Leu Phe Glu
20 25

<210> 202
<211> 17
<212> PRT
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<220>
<223> 合成的多肽

<400> 202

Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn Pro Asn Lys Val Tyr
1 5 10 15

Ser

<210> 203
<211> 17
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<220>
<223> 合成的多肽

<400> 203

Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn Pro Asn Lys Val Tyr
1 5 10 15

Ser

[0208]

<210> 204
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 204

Leu Thr Asp Ser Val Asp Glu Ala Leu Ser Asn Pro Asn Lys Val Tyr
1 5 10 15

Ser

<210> 205
<211> 9
<212> PRT
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<220>
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<400> 205

Leu Ser Asn Pro Asn Lys Val Tyr Ser
1 5

<210> 206
<211> 9
<212> PRT
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<220>
<223> 合成的多肽

<400> 206

Leu Ser Asn Pro Asn Lys Val Tyr Ser
1 5

<210> 207
<211> 23
<212> PRT
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<220>
<223> 合成的多肽

<400> 207

Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn Ser Ile Glu Thr
1 5 10 15

Gly Ile Thr Ser Thr Tyr Ile
20

<210> 208
<211> 23
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 208

[0209] Tyr Ser Pro Phe Lys Asn Met Ser Asn Thr Ile Asn Ser Ile Glu Thr
1 5 10 15

Gly Ile Thr Ser Thr Tyr Ile
20

<210> 209
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 209

Phe Lys Asn Met Ser Asn Thr Ile Asn Ser Ile Glu Thr Gly Ile Thr
1 5 10 15

Ser Thr Tyr Ile
20

<210> 210
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 210

Phe Lys Asn Met Ser Asn Thr Ile Asn Ser Ile Glu Thr Gly Ile Thr
1 5 10 15

Ser Thr Tyr Ile
20

<210> 211
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 211

Phe Lys Asn Met Ser Asn Thr Ile Asn Ser Ile Glu Thr Gly Ile Thr
1 5 10 15

Ser Thr Tyr Ile
20

<210> 212
<211> 17
<212> PRT
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<220>
<223> 合成的多肽

<400> 212

Met Ser Asn Thr Ile Asn Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr
1 5 10 15

[0210] Ile

<210> 213
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 213

Met Ser Asn Thr Ile Asn Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr
1 5 10 15

Ile

<210> 214
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 214

Asn Thr Ile Asn Ser Ile Glu Thr Gly Ile Thr Ser Thr Tyr Ile
1 5 10 15

<210> 215

<211> 19
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 215

Phe Ser Asp Glu Thr Gly Lys Ile Asp Val Ile Asp Lys Ser Ser Asp
1 5 10 15

Thr Leu Ala

<210> 216
<211> 11
<212> PRT
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<220>
<223> 合成的多肽

<400> 216

Leu Ala Ile Val Pro Tyr Ile Gly Pro Leu Leu
1 5 10

<210> 217
<211> 8
<212> PRT
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<220>
[0211] <223> 合成的多肽

<400> 217

Val Pro Tyr Ile Gly Pro Leu Leu
1 5

<210> 218
<211> 13
<212> PRT
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<220>
<223> 合成的多肽

<400> 218

Val Ile Gly Gly Glu Leu Ala Arg Glu Gln Val Glu Ala
1 5 10

<210> 219
<211> 11
<212> PRT
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<220>
<223> 合成的多肽

<400> 219

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn
1 5 10

<210> 220
<211> 11

<212> PRT
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<220>
<223> 合成的多肽

<400> 220

Leu Ser Arg Gln Ala Asn Ala Ile Lys Met Asn
1 5 10

<210> 221
<211> 12
<212> PRT
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<220>
<223> 合成的多肽

<400> 221

Phe Ser Glu Phe Asp Asp Leu Ile Asn Gln Tyr Lys
1 5 10

<210> 222
<211> 25
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 222

[0212] Phe Asp Asp Leu Ile Asn Gln Tyr Lys Asn Glu Gly Ser Ile Leu Pro
1 5 10 15

Glu Thr Gly Gly Leu Glu His His His
20 25

<210> 223
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 223

Tyr Lys Asn Glu Gly Ser Ile Leu Pro Glu Thr Gly Gly Leu Glu His
1 5 10 15

His His His His His
20

<210> 224
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 224

Tyr Lys Asn Glu Gly Ser Ile Leu Pro Glu Thr Gly Gly Leu Glu
1 5 10 15

<210> 225
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成的多肽

<400> 225

Tyr Lys Asn Glu Gly Ser Ile Leu Pro Glu Thr Gly Gly Leu Glu His
1 5 10 15

His

[0213]

<210> 226
<211> 18
<212> PRT
<213> 人工序列

<220>
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<400> 226

Tyr Lys Asn Glu Gly Ser Ile Leu Pro Glu Thr Gly Gly Leu Glu His
1 5 10 15

His His

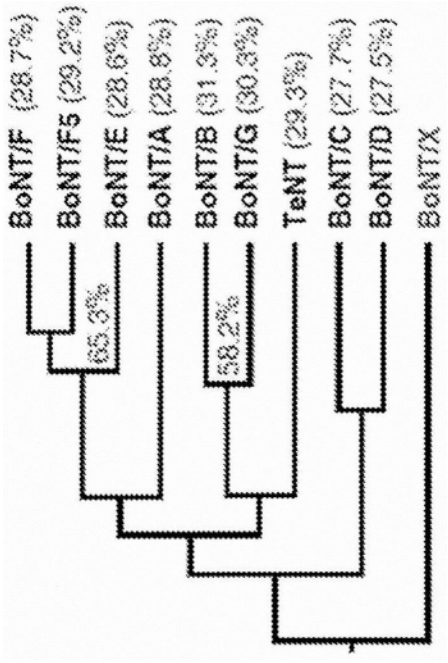

BoNT/F (28.7%)
BoNT/F5 (29.2%)
BoNT/E (28.6%)
BoNT/A (28.8%)
BoNT/B (31.3%)
BoNT/G (30.3%)
TeNT (29.3%)
BoNT/C (27.7%)
BoNT/D (27.5%)
BoNT/X
65.3%
58.2%

图1A

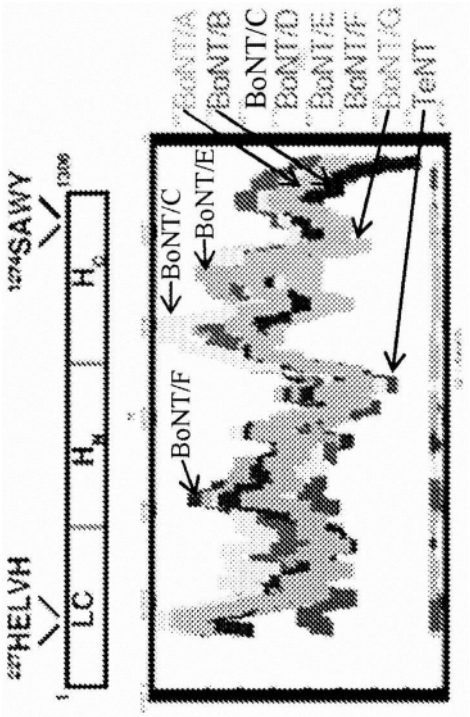

BoNT/A
BoNT/B
BoNT/C
BoNT/D
BoNT/E
BoNT/F
BoNT/G
TeNT
BoNT/C
BoNT/E
BoNT/F
1274SAWY
1306
227HELVH
LC
H
H

图1B

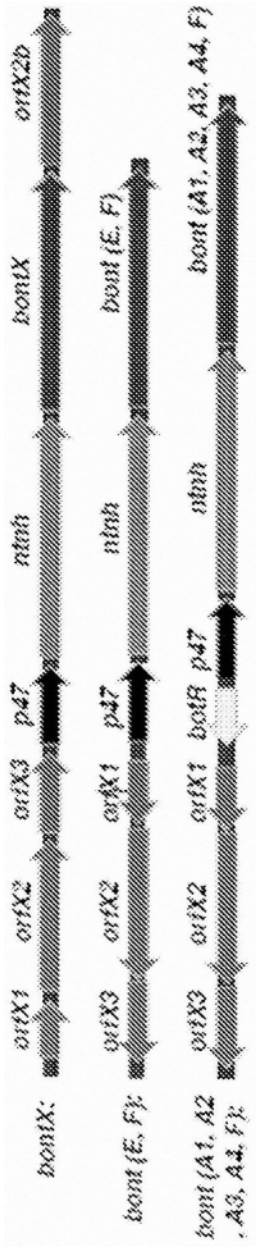

orfX2b
bontX
ntnh
p47
orfX3
orfX2
orfX1
bontX
bont (E, F)
bont (A1, A2, A3, A4, F)

图1C

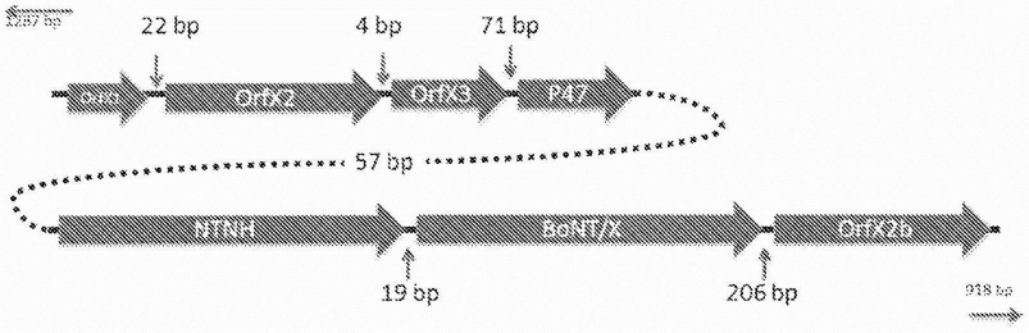

22 bp
4 bp
71 bp
OrfX1
OrfX2
OrfX3
P47
57 bp
NTNH
BoNT/X
OrfX2b
19 bp
206 bp

图1D

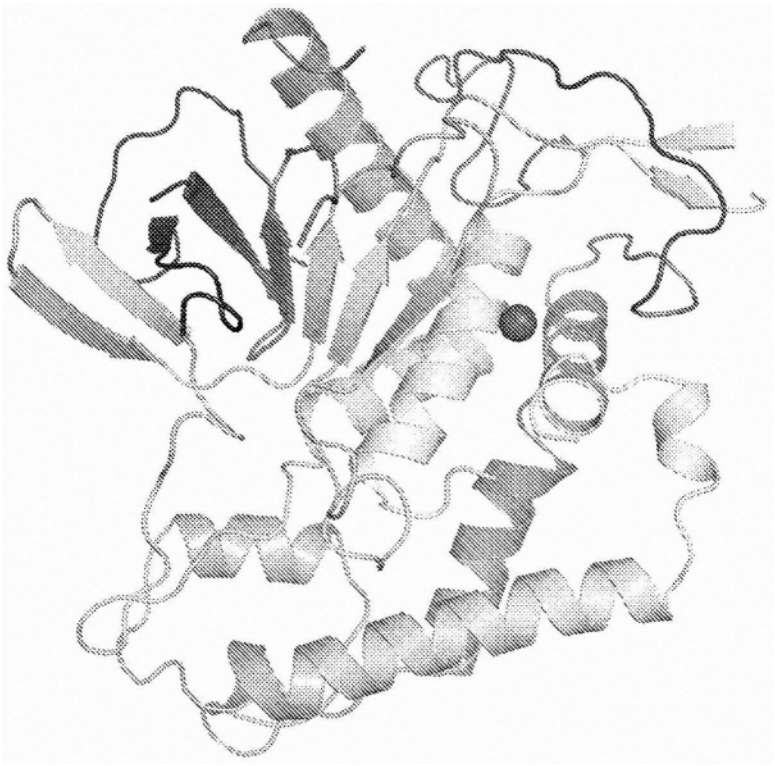


图1E

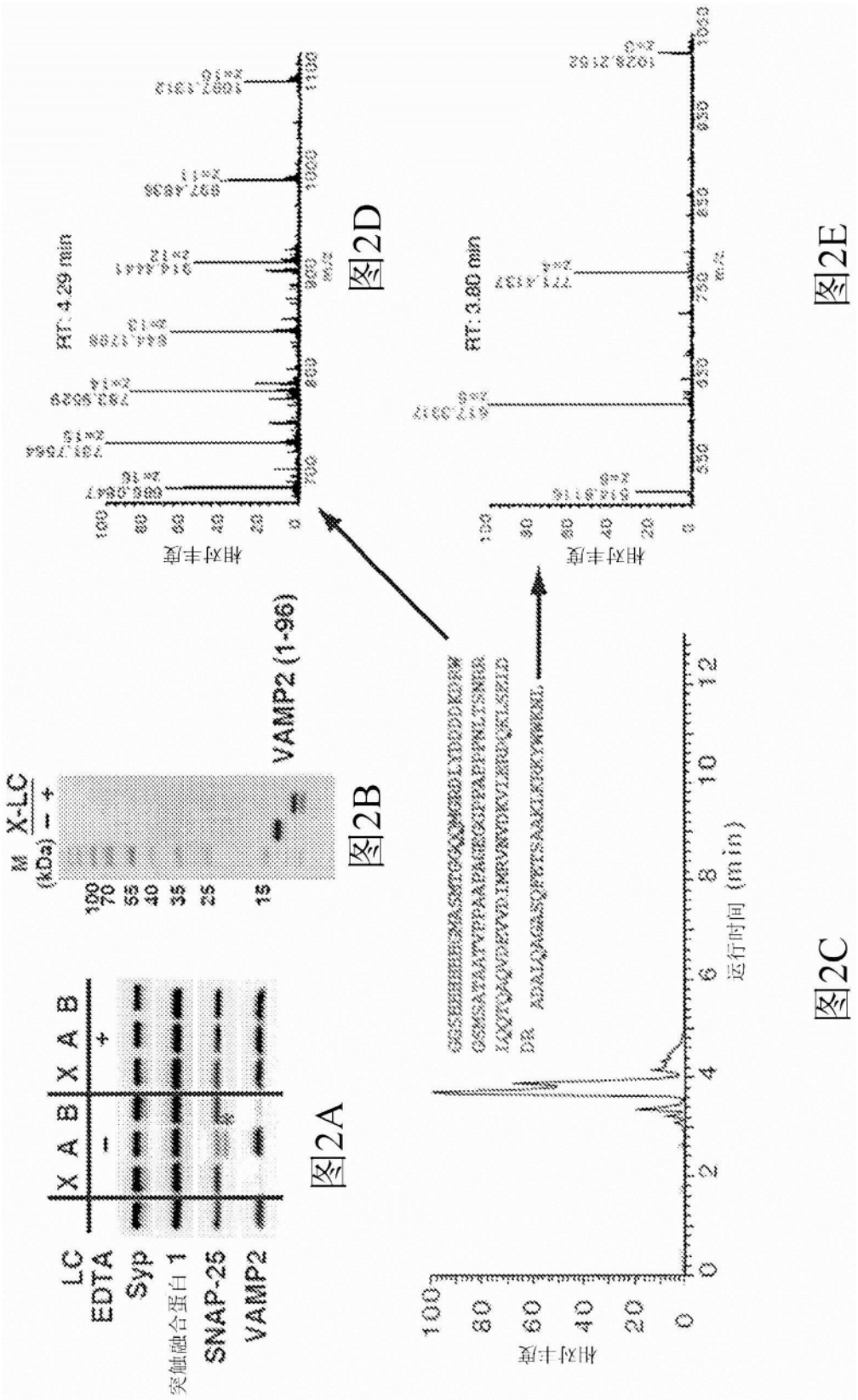


图2A 图2B 图2C 图2D 图2E

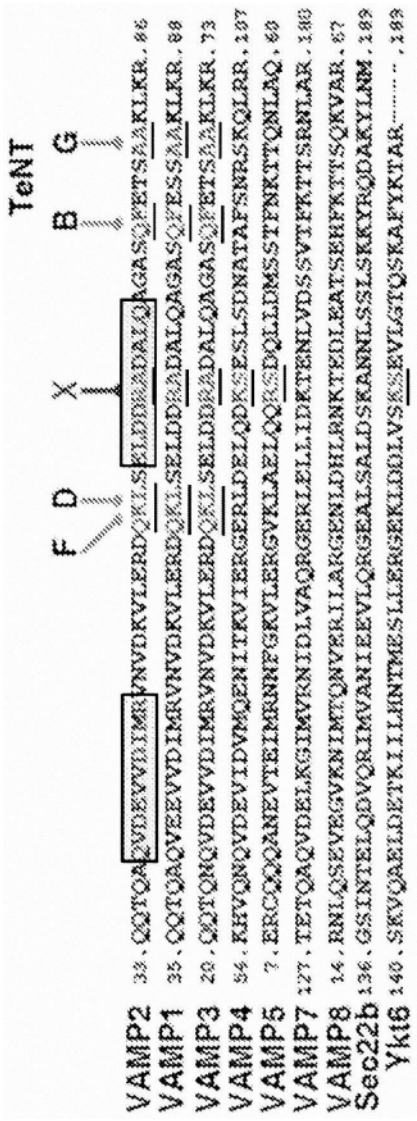

TeNT
F
D
X
B
G
VAMP2
VAMP1
VAMP3
VAMP4
VAMP5
VAMP7
VAMP8
Sec22b
Ykt6

图2F

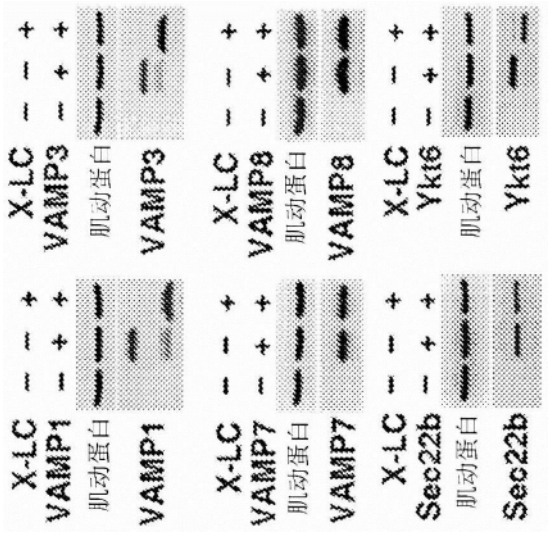

X-LC
VAMP3
肌动蛋白
VAMP3
X-LC
VAMP8
肌动蛋白
VAMP8
X-LC
Ykt6
肌动蛋白
Ykt6
X-LC
VAMP1
肌动蛋白
VAMP1
X-LC
VAMP7
肌动蛋白
VAMP7
X-LC
Sec22b
肌动蛋白
Sec22b

图2G

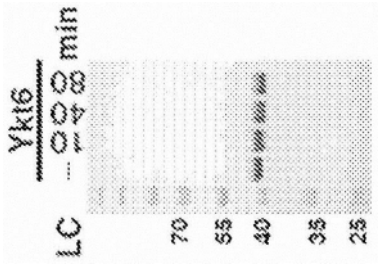

Ykt6
0 2 4 8 min
LC
70
55
40
35
25

图2H

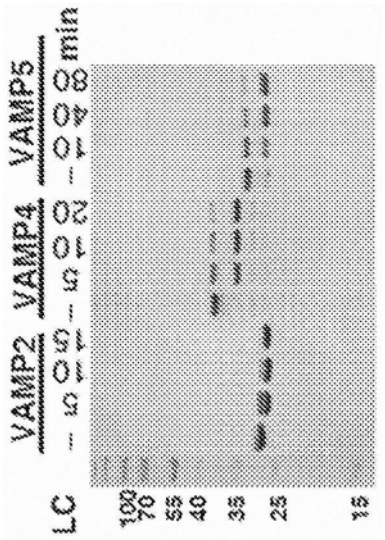

VAMP2
VAMP4
VAMP5
0 2 5 10 15 0 2 5 10 15 0 2 4 8 min
LC
100
70
55
40
35
25
15

图2I

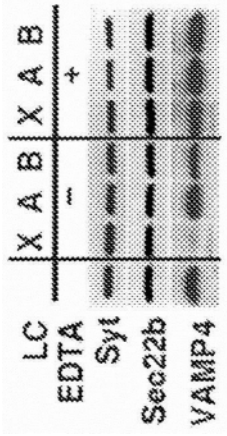


图2J

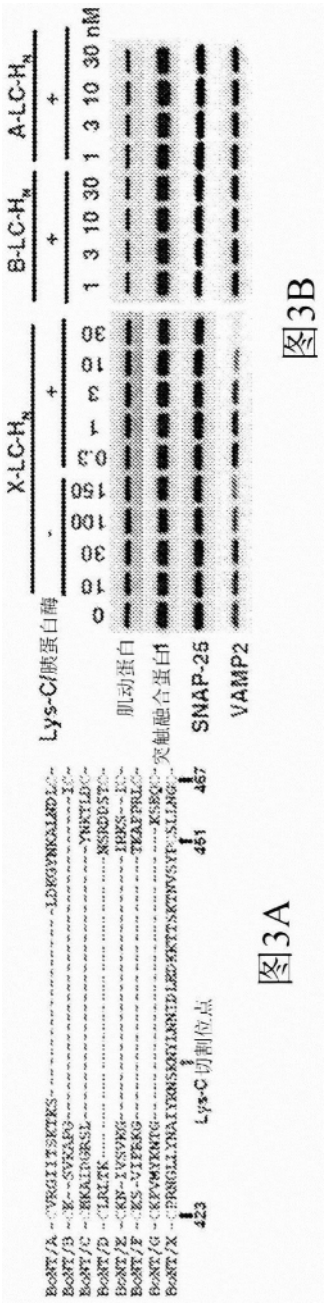

X-LC-Hx
B-LC-Hx
A-LC-Hx
Lys-C肽酶白酶
肌动蛋白
突触融合蛋白1
SNAP-25
VAMP2
Lys-C切割位点
423
451
467
0 10 30 100 150
0.3 1 3 10 30
1 3 10 30
1 3 10 30 nM

图3A

图3B

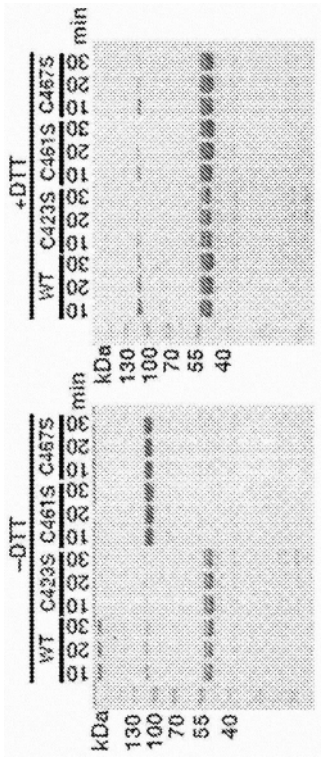

+DTT
WT C423S C461S C467S
10 20 30 10 20 30 10 20 30 10 20 30 min
-DTT
WT C423S C461S C467S
10 20 30 10 20 30 10 20 30 10 20 30 min
kDa
130
100
70
55
40

图3C

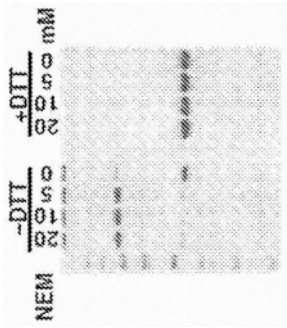

NEM
-DTT
0 5 10 20
+DTT
0 5 10 20 mM

图3D

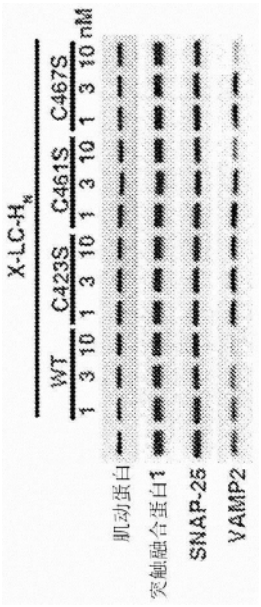

X-LC-H$_N$
WT
C423S
C461S
C467S
1 3 10 1 3 10 1 3 10 1 3 10 nM
肌动蛋白
突触融合蛋白1
SNAP-25
VAMP2

图3E

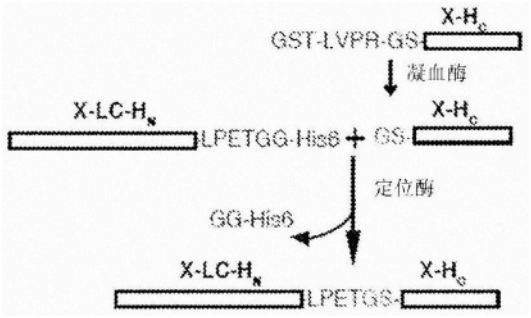

X-H$_C$
GST-LVPR-GS
凝血酶
X-LC-H$_N$
LPETGG-His6
GS-
X-H$_C$
定位酶
GG-His6
X-LC-H$_N$
X-H$_C$
LPETGS-

图4A

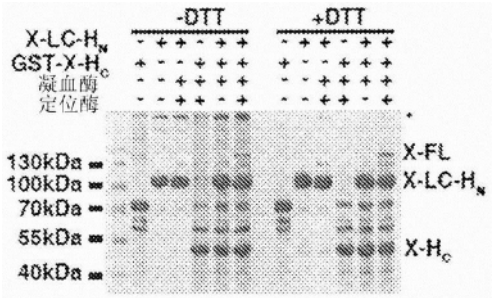

-DTT
+DTT
X-LC-H$_N$
GST-X-H$_C$
凝血酶
定位酶
130kDa
100kDa
70kDa
55kDa
40kDa
X-FL
X-LC-H$_N$
X-H$_C$

图4B

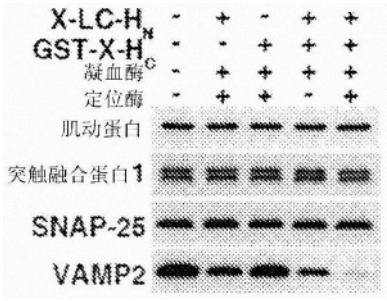


图4C

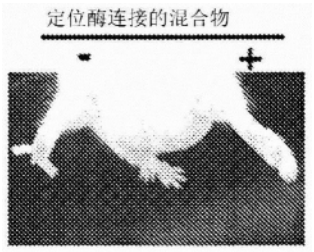


图4D

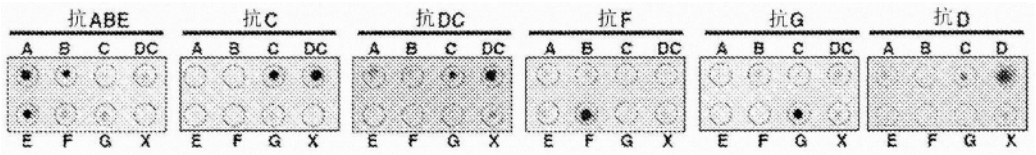


图4E

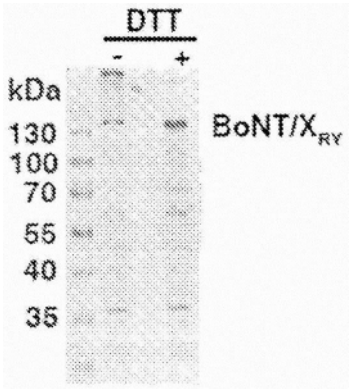


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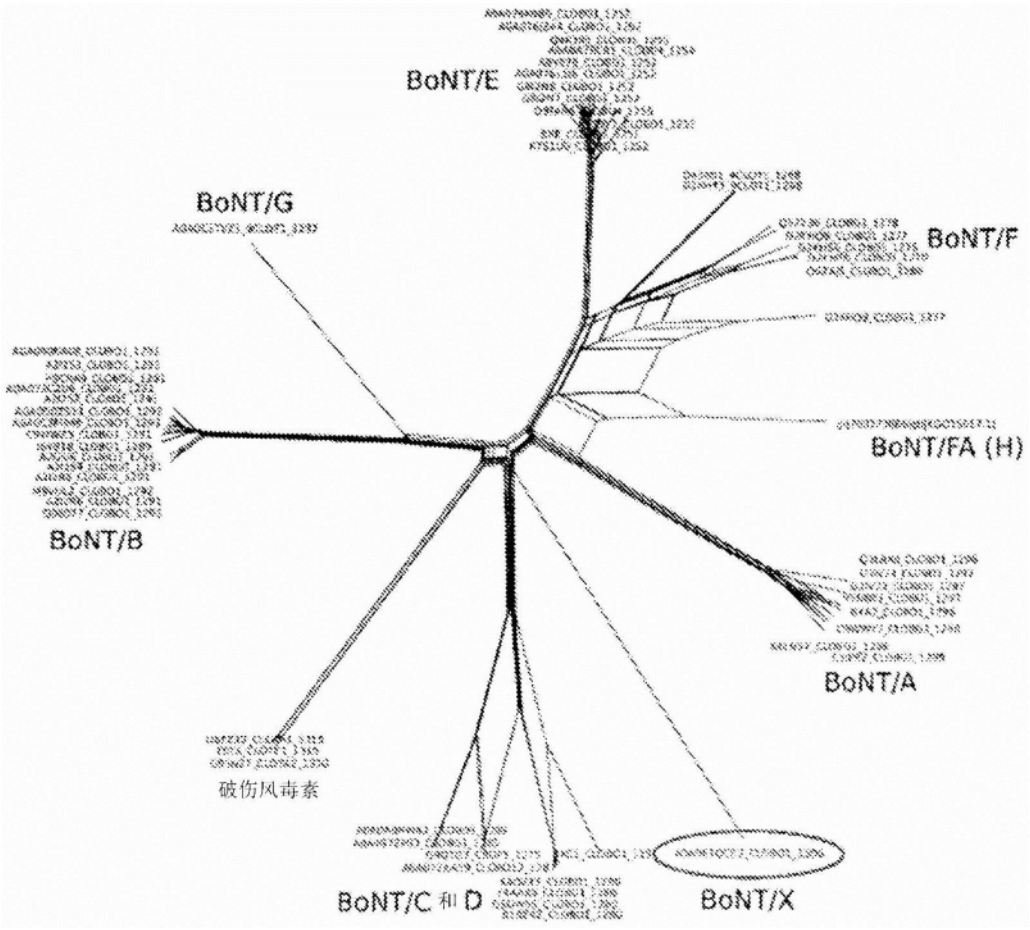


图5

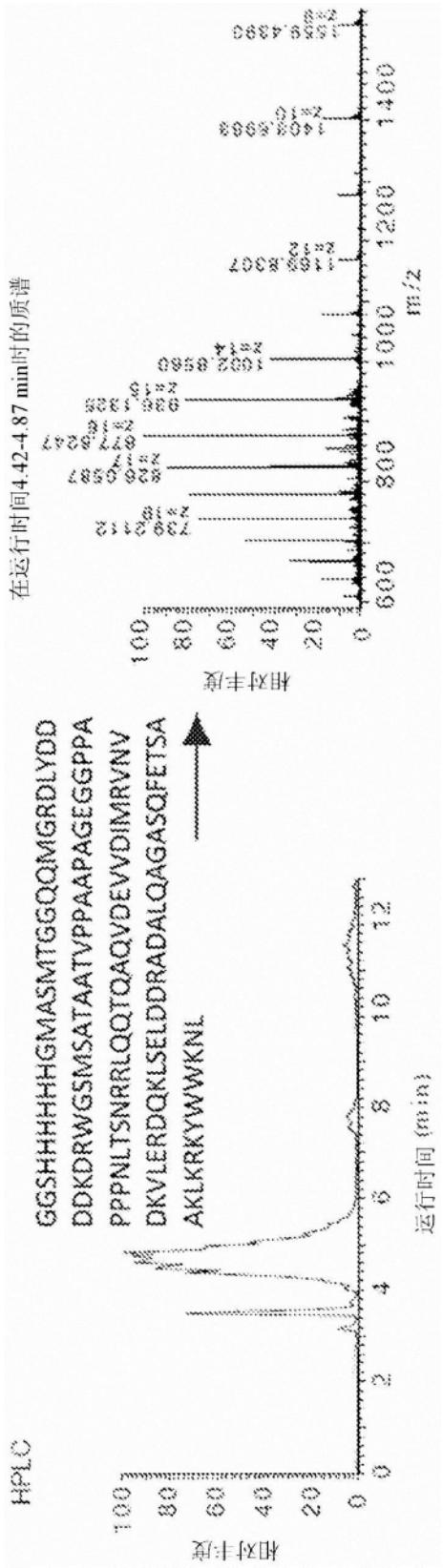

HPLC
相对丰度
运行时间 (min)
GGSHHHHHHGMASMTGGQQMGRDLYDD
DDKDRWGSMSATAATVPPAAPAGEGGPPA
PPPNLTSNRRLQQTQAQVDEVVDIMRVNV
DKVLERDQKLSELDDRADALQAGASQFETSA
AKLKRKYWWKNL
在运行时间4.42-4.87 min时的质谱
相对丰度
m/z

图6

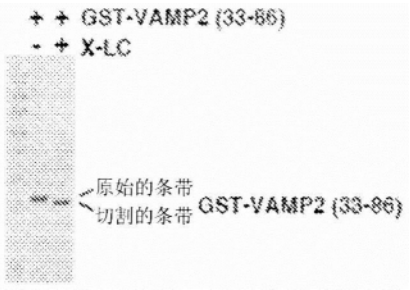

+ + GST-VAMP2 (33-66)
- + X-LC
原始的条带
切割的条带
GST-VAMP2 (33-66)

图7A

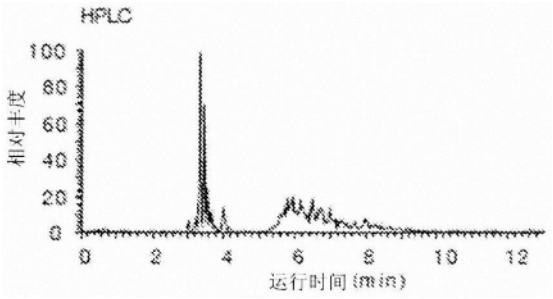

HPLC
相对丰度
运行时间 (min)

图7B

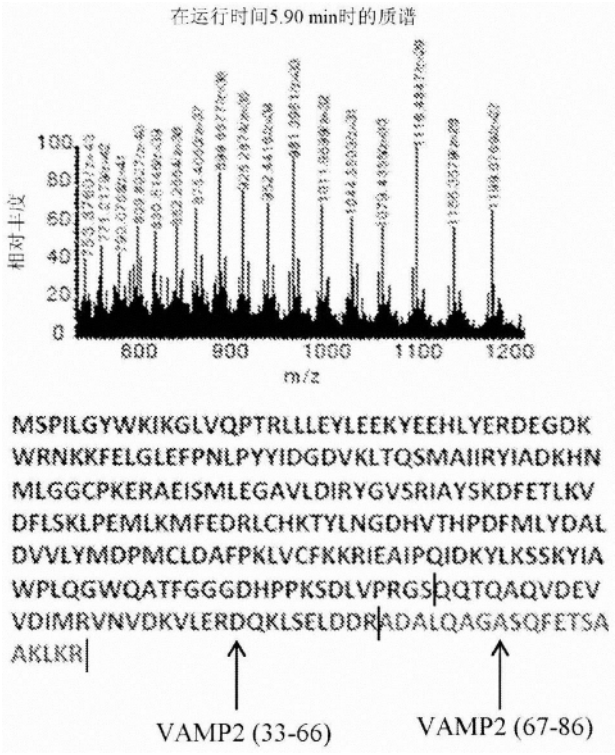

在运行时间5.90 min时的质谱
相对丰度
m/z
MSPILGYWKIKGLVQPTRLLLEYLEEKYEEHLYERDEGDK
WRNKKFELGLEFPNLPYYIDGDVKLTQSMAIIRYIADKHN
MLGGCPKERAEISMLEGAVLDIRYGVSRIAYSKDFETLKV
DFLSKLPEMLKMFEDRLCHKTYLNGDHVTHPDFMLYDAL
DVVLYMDPMCLDAFPKLVCFKKRIEAIPQIDKYLKSSKYIA
WPLQGWQATFGGGDHPPKSDLVPRGSQQTQAQVDEV
VDIMRVNVDKVLERDQKLSELDDRADALQAGASQFETSA
AKLKR
VAMP2 (33-66)
VAMP2 (67-86)

图7C

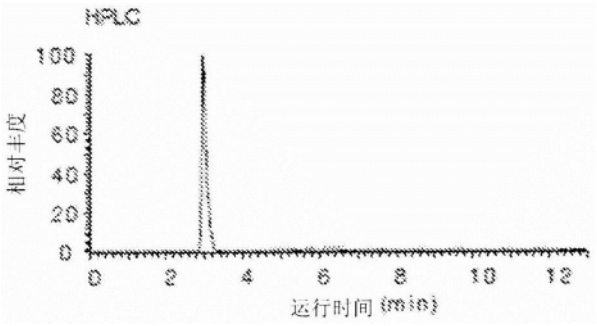

HPLC
相对丰度
运行时间 (min)

图7D

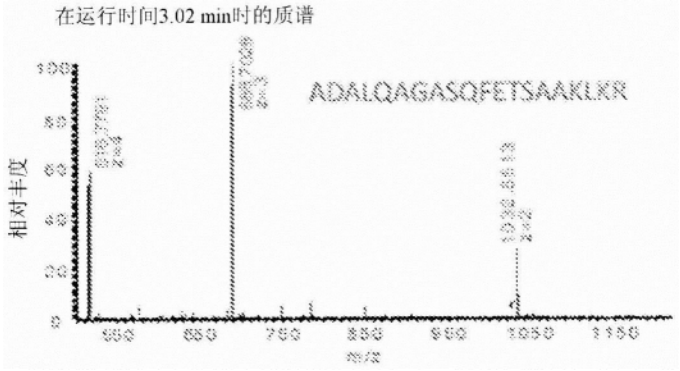

在运行时间3.02 min时的质谱
ADALQAGASQFETSAAKLKR
相对丰度
m/z

图7E

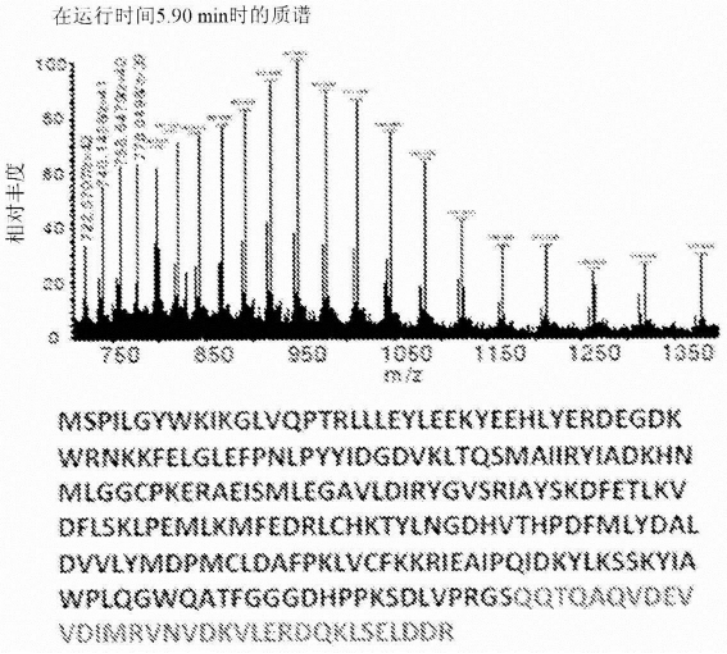

在运行时间5.90 min时的质谱
相对丰度
m/z
MSPILGYWKIKGLVQPTRLLLEYLEEKYEEHLYERDEGDK
WRNKKFELGLEFPNLPYYIDGDVKLTQSMAIIRYIADKHN
MLGGCPKERAEISMLEGAVLDIRYGVSRIAYSKDFETLKV
DFLSKLPEMLKMFEDRLCHKTYLNGDHVTHPDFMLYDAL
DVVLYMDPMCLDAFPKLVCFKKRIEAIPQIDKYLKSSKYIA
WPLQGWQATFGGGDHPPKSDLVPRGSQQTQAQVDEV
VDIMRVNVDKVLERDQKLSELDDR

图7F

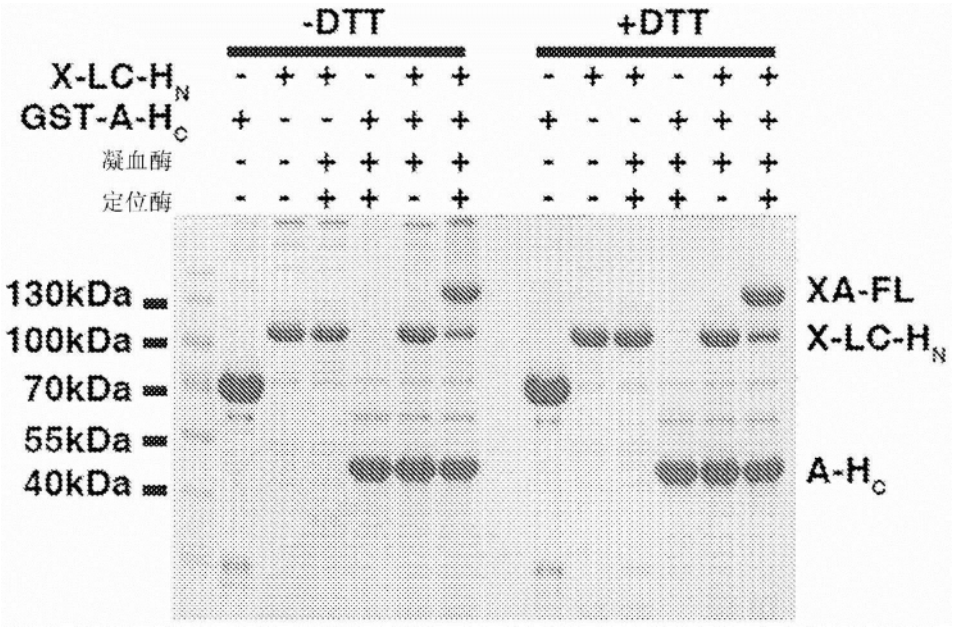

-DTT
+DTT
X-LC-H$_N$
GST-A-H$_C$
凝血酶
定位酶
130kDa
100kDa
70kDa
55kDa
40kDa
XA-FL
X-LC-H$_N$
A-H$_C$

图8A

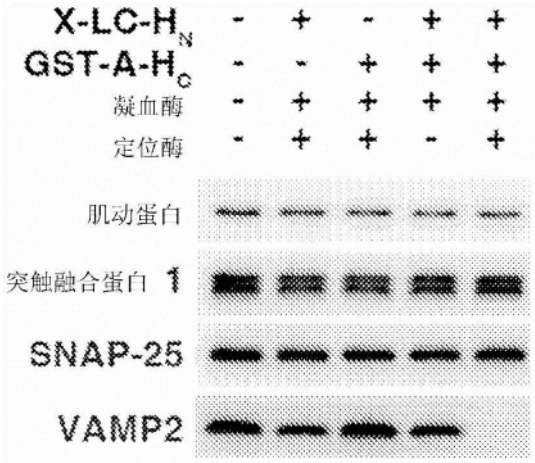

X-LC-H$_N$
GST-A-H$_C$
凝血酶
定位酶
肌动蛋白
突触融合蛋白 1
SNAP-25
VAMP2

图8B

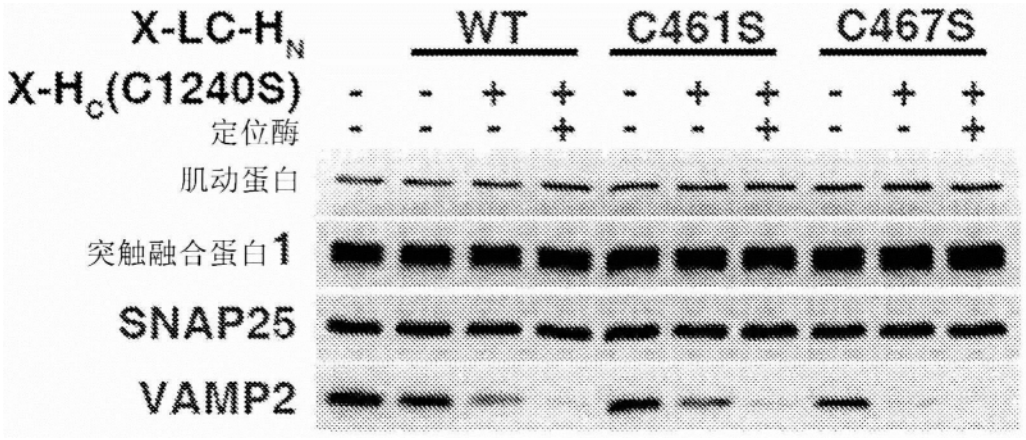

X-LC-H$_N$
WT
C461S
C467S
X-H$_C$(C1240S)
- - + + - + + - + +
定位酶
- - - + - - + - - +
肌动蛋白
突触融合蛋白1
SNAP25
VAMP2

图9

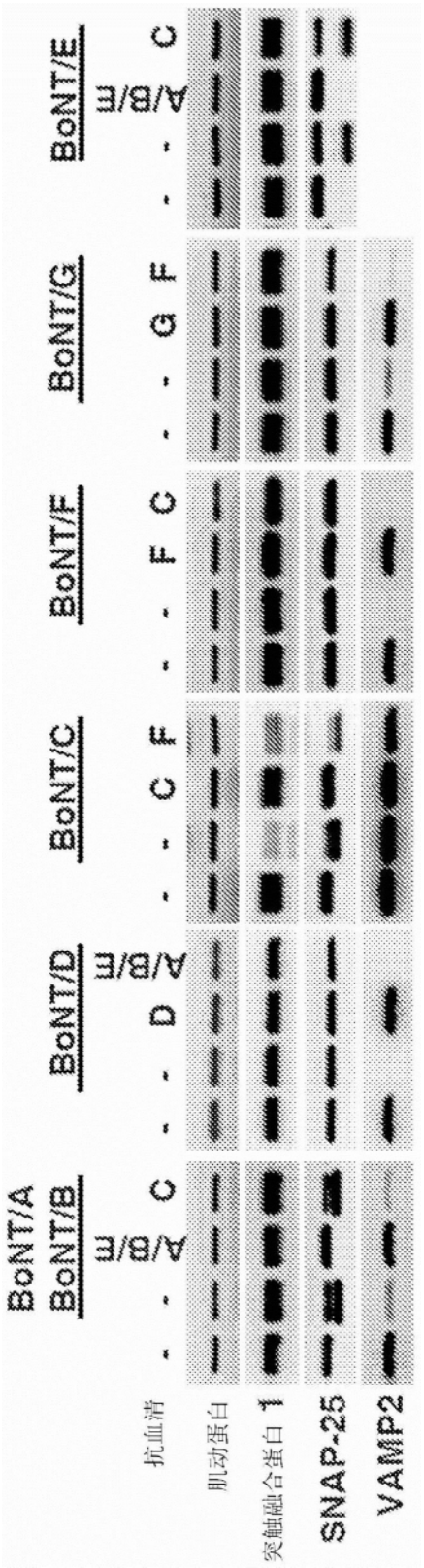

BoNT/A
BoNT/B
A/B/E
C
D
BoNT/D
A/B/E
C
F
BoNT/C
F
C
BoNT/F
G
F
BoNT/G
A/B/E
C
BoNT/E
抗血清
肌动蛋白
突触融合蛋白 1
SNAP-25
VAMP2

图10

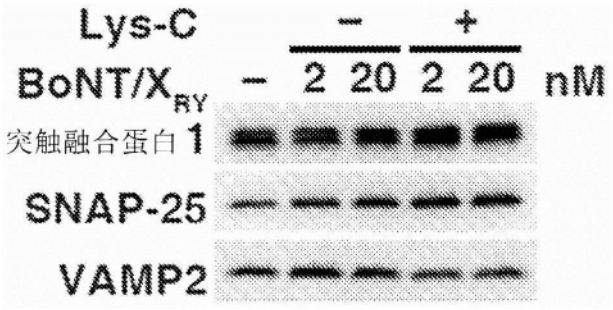

Lys-C
–
+
BoNT/X$_{RY}$
– 2 20 2 20 nM
突触融合蛋白1
SNAP-25
VAMP2

图11A

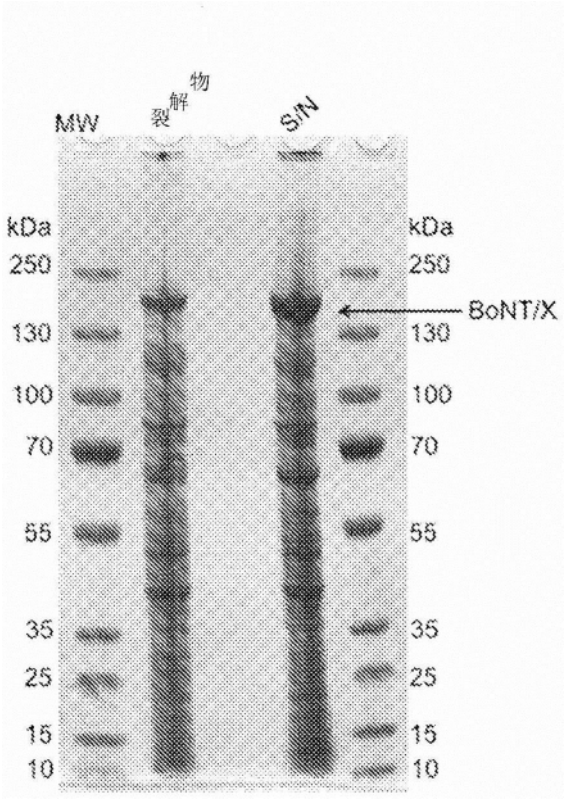

MW
裂解物
S/N
kDa
250
130
100
70
55
35
25
15
10
BoNT/X

图11B

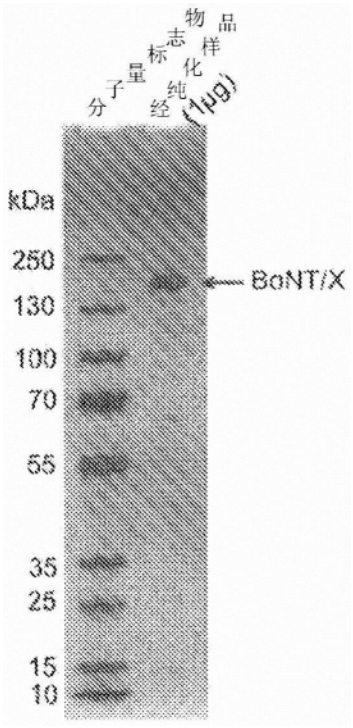

分子量标志物
经纯化样品
(1μg)
kDa
250
130
100
70
55
35
25
15
10
BoNT/X

图11C

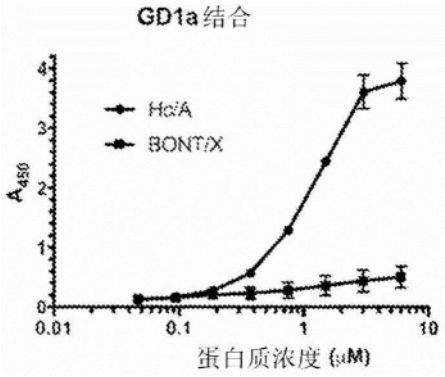

GD1a结合
Hc/A
BONT/X
A450
0
1
2
3
4
0.01
0.1
1
10
蛋白质浓度 (μM)

图12A

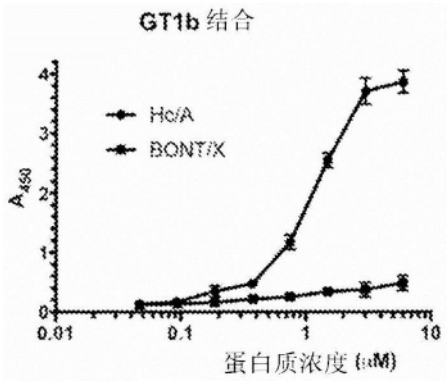


图12B

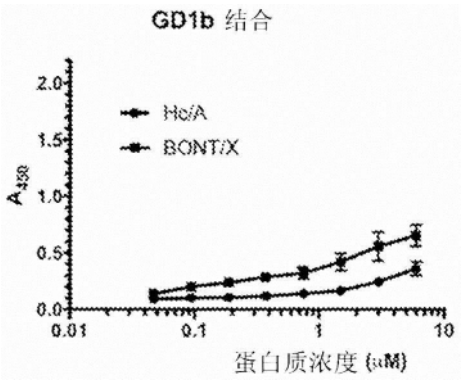


图12C

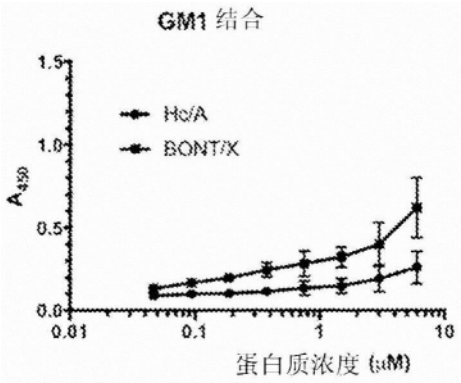


图12D

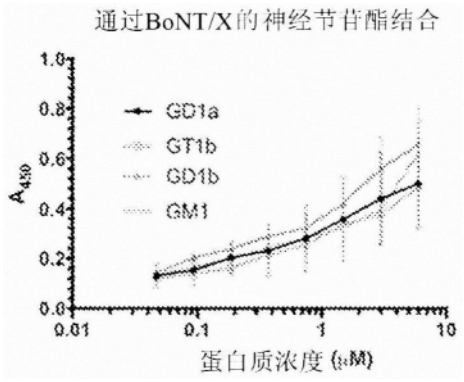


图12E

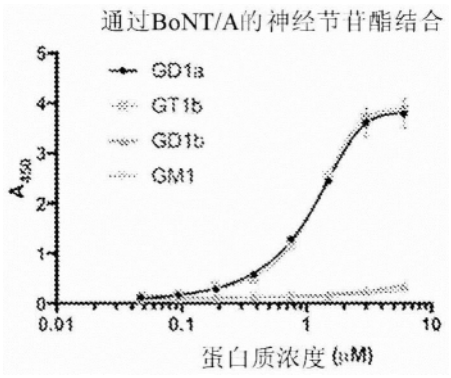


图12F

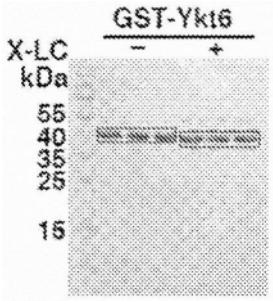


图13A

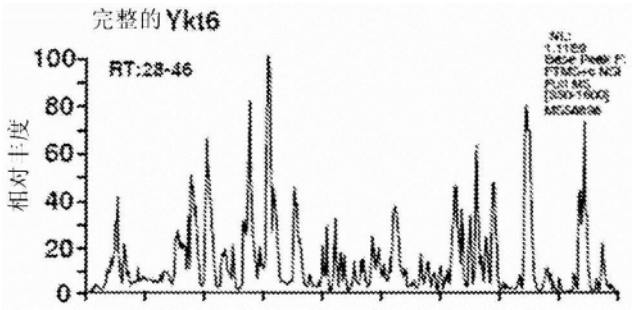


图13B

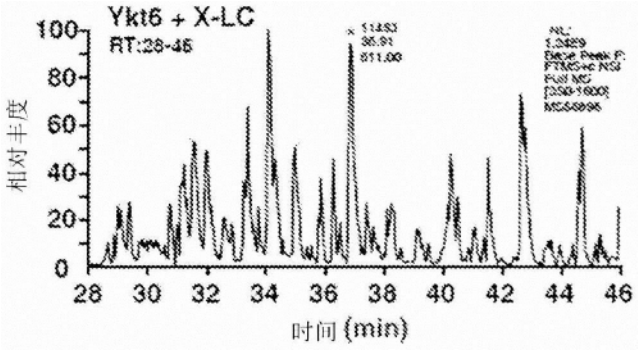


图13C

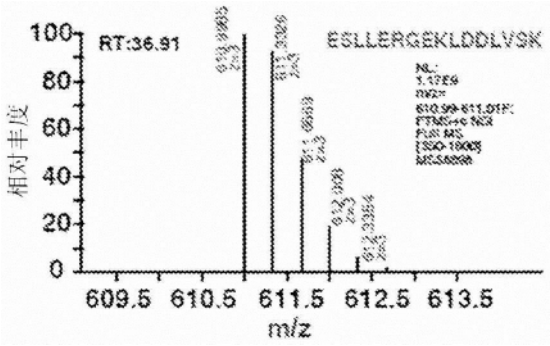


图13D

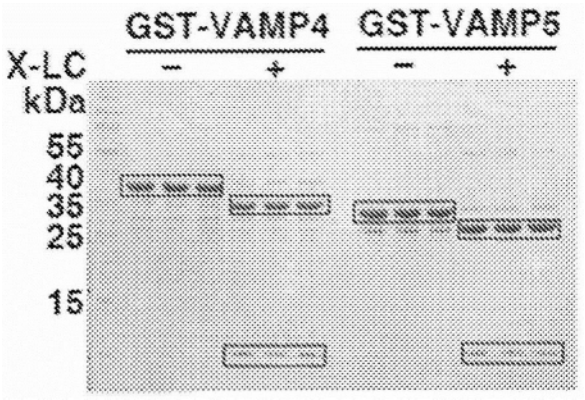


图14A

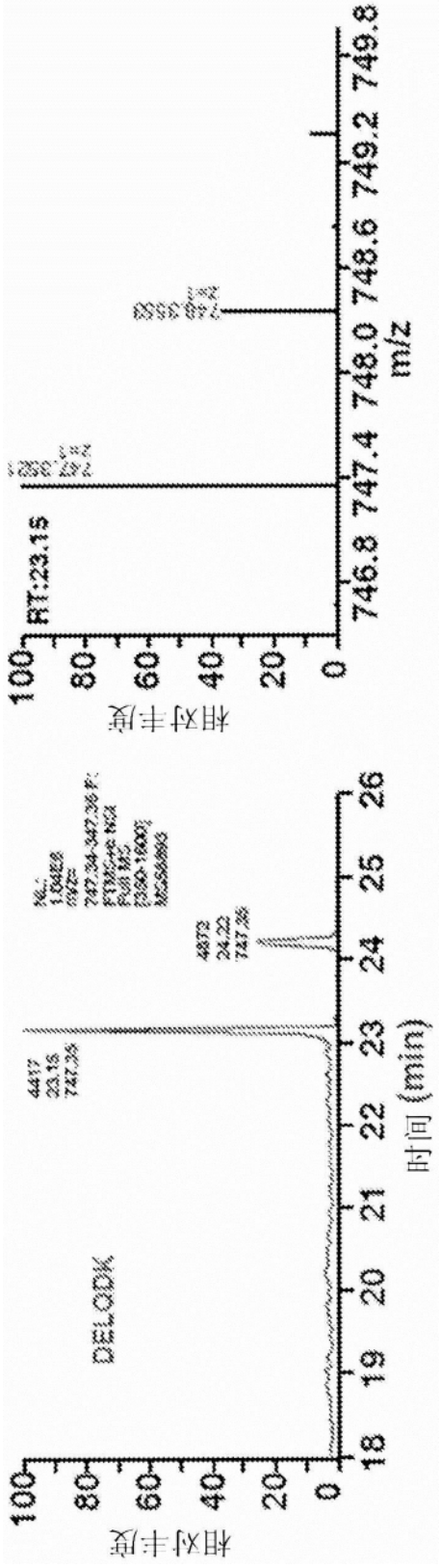


图14B

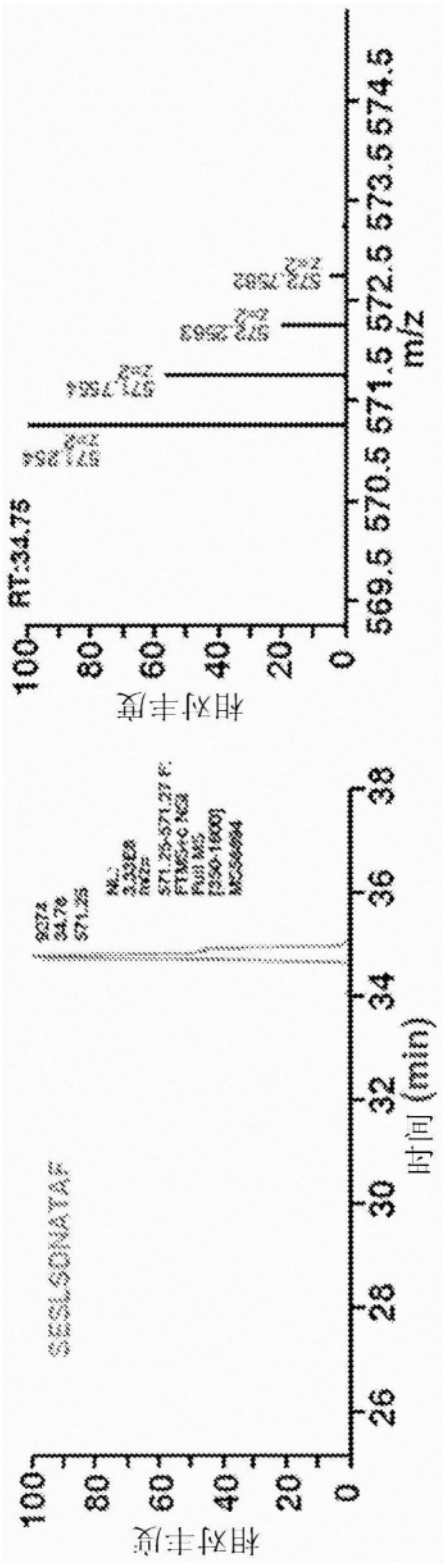

RT:34.75
相对丰度
m/z
569.5 570.5 571.5 572.5 573.5 574.5
SESLSDNATAF
时间 (min)
26 28 30 32 34 36 38

图14C

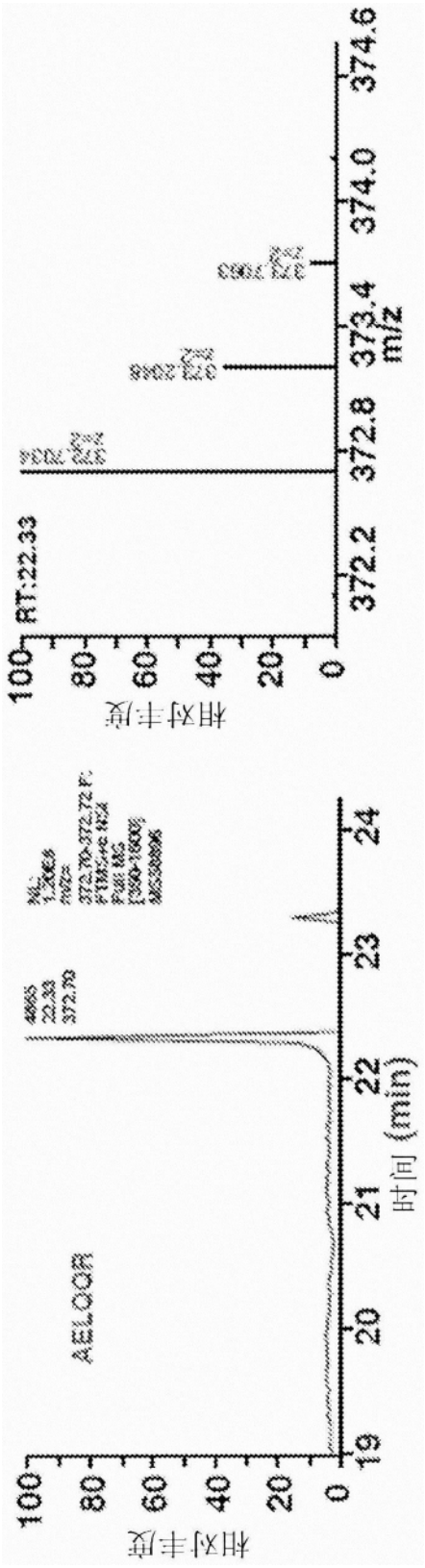


图14D

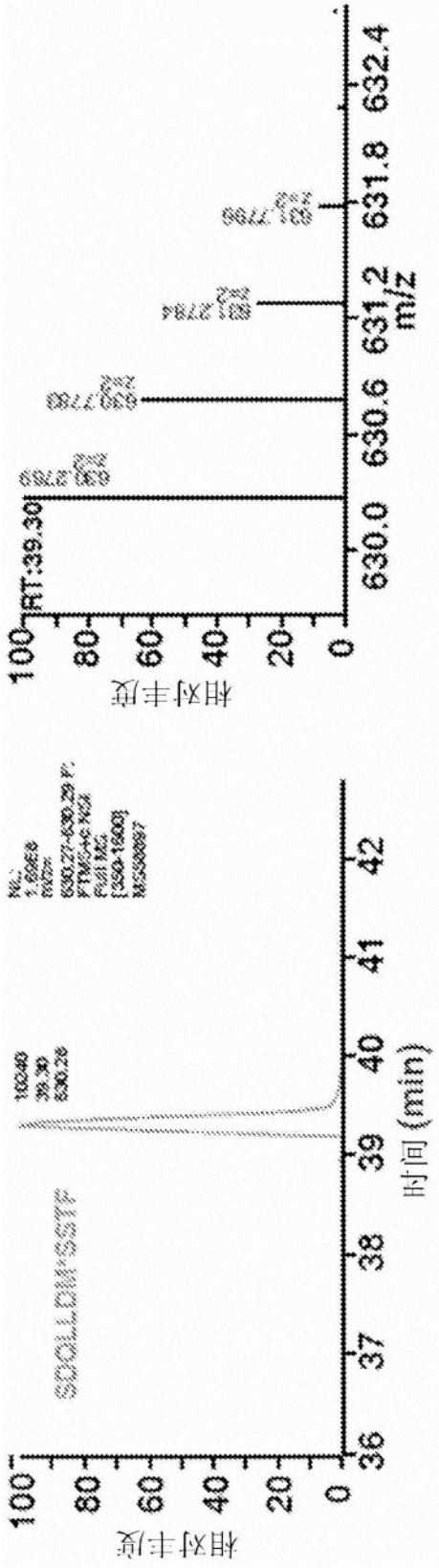

RT:39.30
630.0
630.6
631.2
631.8
632.4
m/z
相对丰度
100
80
60
40
20
0
SOLLDW-SSTF
36
37
38
39
40
41
42
时间 (min)

图14E