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(54)发明名称

具有增加的比活性的抗血友病因子VIII的新型变体

(57)摘要

本发明在血友病疗法的领域中。其涉及相较于已知的因子VIII产品具有增加的比活性的抗血友病因子VIII的新型变体。

1. 一种分离的且重组的猪因子VIII (FVIII) 变体, 所述FVIII变体的氨基酸序列如SEQ ID NO:1所示。
2. 一种多核苷酸, 其编码根据权利要求1所述FVIII变体。
3. 一种表达载体, 其包含根据权利要求2所述的多核苷酸。
4. 一种哺乳动物细胞, 其包含根据权利要求3所述的表达载体。
5. 一种用于产生FVIII变体的方法, 其包括步骤:
  - a. 培养根据权利要求4所述的哺乳动物细胞; 和
  - b. 从所述哺乳动物细胞分离FVIII变体。
6. 根据权利要求5所述的方法, 其还包括步骤
  - c. 将所述FVIII变体与适当的赋形剂一起配制到药物组合物中。
7. 一种药物组合物, 其包含根据权利要求1所述的FVIII变体。
8. 根据权利要求1所述的FVIII变体在制备治疗有此需要的患者的血友病的药物中的应用。
9. 根据权利要求8所述的应用, 其中所述血友病是甲型血友病。
10. 根据权利要求8所述的应用, 其中所述血友病是获得性血友病。
11. 根据权利要求8至10中任一项所述的应用, 其中所述患者已产生人FVIII抗体。
12. 根据权利要求8至10中任一项所述的应用, 其中以不超过200 $\mu$ g/剂量或150 $\mu$ g/剂量或140 $\mu$ g/剂量的量施用所述FVIII变体。

## 具有增加的比活性的抗血友病因子VIII的新型变体

### 发明领域

[0001] 本发明在凝血因子和血友病的领域中。其涉及在本文中称为rFVIIIv3的抗血友病因子VIII (FVIII) 的新变体,该变体相较于已知的因子VIII产品具有增加的比活性。

### [0002] 发明背景

[0003] 当血小板在损伤位置附着至受伤血管的切壁 (cut wall) 时,凝血开始。随后,在酶促调节的反应的级联中,可溶性血纤蛋白原分子被酶凝血酶转化成血纤蛋白的不溶性链,其将血小板在血栓中保持在一起。在级联的每一个步骤中,变体前体被转化成在一系列中裂解下一个变体前体的蛋白酶。在大部分步骤中需要辅因子。

[0004] 因子VIII (也称为抗血友病因子VIII或FVIII) 作为无活性前体在血液中循环,紧密地非共价地结合至血管性血友病因子 (von Willebrand factor)。因子VIII被凝血酶或因子Xa蛋白水解激活,所述凝血酶或凝血酶因子Xa使其与血管性血友病因子分离,并且在级联中激活其促凝血功能。活性形式的变体因子VIIIa是使因子IXa向因子X激活的催化效率增加数个数量级的辅因子。

[0005] 人FVIII的克隆已显示变体包含组织在许多结构域 (具有顺序A1-A2-B-A3-C1-C2) 内的2332个氨基酸 (Vehar等人,1984,Nature312,337-342;Toole等人,1984,Nature312,342-347和Wood等人,1984,Nature312,330-337)。大多数FVIII在血浆中是异二聚体,包含轻链和各种重链衍生物。异源二聚体结构归因于前体在精氨酸1648处的蛋白水解性裂解,从而导致分别包含A1-A2-B和A3-C1-C2的重链和轻链。重链内的异质性可通过其羧基末端B结构域内的限制性蛋白水解来解释。

[0006] 为了用作因子X激活的辅因子,FVIII需要通过因子Xa或凝血酶产生的限制性蛋白水解。该激活包括在重链上的位置372和740处和轻链上的位置1689处的精氨酸处的裂解。已确定与无活性前体相比较,活性FVIII辅因子缺乏轻链片段1649-1689和完整的B结构域 (Mertens等人,1993)。

[0007] 未利用因子VIII治疗的在因子VIII或针对因子VIII的抗体中具有缺陷的人遭受不受控制的内出血,其可引起一系列严重症状,从关节中的炎症反应至早逝。在美国共计约10,000个严重的血友病患者可通过输注人因子VIII来治疗,如果以充足的频率和浓度施用,这可恢复血液的正常凝血能力。事实上,因子VIII的经典定义是存在于正常血浆中修正来源于患有甲型血友病的个体的血浆的凝血缺陷的物质。

[0008] 几种具有不同程度的纯度的人血浆源性因子VIII的制剂可商购获得用于治疗甲型血友病。此类制剂包括来源于许多供体的混合血液的部分纯化的因子VIII,所述血液针对病毒进行了热处理和去垢剂处理但包含显著水平的抗原性变体;具有更低水平的抗原性杂质和病毒污染的单克隆抗体纯化的因子VIII;和重组人因子VIII。

[0009] 抑制因子VIII的活性的抗体 (“抑制剂”或“抑制性抗体”) 的产生是血友病患者治疗中的严重并发症。

[0010] 同种抗体 (Alloantibody) 响应因子VIII的治疗性输注在约20%的甲型血友病患者中产生。在产生抑制剂的先前未治疗的甲型血友病患者中,抑制剂通常在一年的治疗内

产生。此外,使因子VIII失活的抗体(自身抗体)偶尔在具有先前正常因子VIII水平的个体中产生。如果抑制剂滴度足够低,则患者可通过增加因子VIII的剂量来治疗。然而,通常地抑制剂滴度是如此之高,以至于其不能被因子VIII压制。可选的策略是在正常止血过程中使用激活的凝血酶原复合物浓缩制剂(例如,KONYNE (Cutter Laboratories)、FEIBA (Baxter Healthcare)、PROPLEX (Baxter Healthcare))或重组人因子VIIa来绕过对因子VIII的需要。此外,由于猪因子VIII通常具有比人因子VIII显著更小的与抑制剂的反应性,因此已使用部分纯化的猪因子VIII制剂(HYATE:C (IPSEN Pharma))。已利用猪因子VIII成功地治疗了许多已产生针对人因子VIII的抑制性抗体的患者,这些患者已长期耐受这样的治疗。

[0011] 然而,关于病毒或其它血液传播污染物的危险的公共卫生问题已限制了从猪血液纯化的猪因子VIII的有用性。因此开发了重组猪因子VIII变体,其被称为“OBI-1”并且描述于例如WO 01/68109中。OBI-1是部分B结构域缺失的猪FVIII。该分子目前正处于临床开发中。

[0012] 已知B结构域缺失的因子VIII变体保持因子VIII的前凝血剂和辅因子活性。除此以外,Mertens等人(British Journal of Haematology 1993, 85, 133-142)描述了缺乏B结构域和横跨赖氨酸713至精氨酸740的重链序列的重组人因子VIII变体。

[0013] 许多血友病患者需要每天替换因子VIII以阻止出血和所造成的致畸形血友病性关节炎(resulting deforming hemophilic arthropathy)。鉴于此,存在对更具效力的因子VIII分子的需要。

[0014] 发明概述

[0015] 在第一方面,本发明涉及分离的重组的完全或部分B结构域缺失的因子VIII (FVIII)变体、缺乏多达27个氨基酸序列(对应于如图2中描述的猪因子VIII的氨基酸716至742或SEQ ID NO:7的氨基酸714至740)的FVIII变体。该27个氨基酸序列NTGDYEDSYEDISAYLLSKNNAIEPR (SEQ ID NO:10)可部分或完全缺失。

[0016] 在一个实施方案中,本发明涉及分离的重组的完全或部分B结构域缺失的FVIII变体,FVIII变体缺乏多达27个氨基酸的序列,该序列对应于如图2中描述的猪因子VIII的氨基酸716至742或SEQ ID NO:7的氨基酸714至740,其中可缺失27、26、25、24、23、22、21、20、19、18、17、16、15、14、13、12、11、10、9、8、7、6、5、4、3、2或1个氨基酸。在另一个实施方案中,可缺失27、26、25、24、23、22、21或20个氨基酸。在另一个实施方案中,缺失27、26或25个氨基酸。在另一个实施方案中,缺失对应于DIGDYDNTYEDIPGFLLSGKNVIEPR (SEQ ID NO:10)的27个氨基酸。

[0017] 在一个实施方案中,本发明涉及分离的重组的完全或部分B结构域缺失的FVIII变体,FVIII变体缺乏多达27个氨基酸的序列,该序列对应于如图2中描述的人因子VIII的氨基酸716至742或SEQ ID NO:8的氨基酸714至740,其中可缺失27、26、25、24、23、22、21、20、19、18、17、16、15、14、13、12、11、10、9、8、7、6、5、4、3、2或1个氨基酸。在另一个实施方案中,缺失27、26、25、24、23、22、21或20个氨基酸。在另一个实施方案中,缺失27、26或25个氨基酸。在另一个实施方案中,缺失对应于NTGDYEDSYEDISAYLLSKNNAIEPR (SEQ ID NO:11)的27个氨基酸。

[0018] 在另一个实施方案中,本发明涉及分离的重组的完全或部分B结构域缺失的猪

FVIII变体,该变体完全缺乏对应于DIGDYDNTYEDIPGFLLSGKNVIEPR (SEQ ID NO:10)的27个氨基酸。

[0019] 在另一个实施方案中,本发明涉及分离的重组的完全或部分B结构域缺失的人FVIII变体,该变体完全缺乏对应于NTGDYEDSYEDISAYLLSKNNAIEPR (SEQ ID NO:11)的27个氨基酸。

[0020] 在另一个实施方案中,本发明涉及分离的重组的完全或部分B结构域缺失的犬FVIII变体,该变体完全缺乏对应于NIDDYEDTYEDIPTPLNENNVIKPR (SEQ ID NO:12)的27个氨基酸。

[0021] 本发明的第二方面涉及编码第一方面中定义的多肽的多核苷酸和描述的实施方案。

[0022] 在第三方面,本发明涉及包含第二方面中定义的多核苷酸的表达载体。

[0023] 本发明的第四方面涉及包含第三方面中定义的表达载体的哺乳动物细胞。

[0024] 在第五方面,本发明涉及用于产生第一方面中定义FVIII的方法,其包括步骤:

[0025] a. 培养根据第四方面的哺乳动物细胞;和

[0026] b. 从哺乳动物细胞分离FVIII变体。

[0027] 本发明的第六方面涉及包含第一方面中定义FVIII变体的药物组合物。

[0028] 在第七方面,本发明涉及治疗患有血友病的患者的方法,包括给有此需要的患者施用治疗有效量的根据本发明的第一方面的FVIII变体,从而治疗所述患者的血友病。

[0029] 在第八方面,本发明涉及用于治疗血友病的根据第一方面的FVIII变体。

[0030] 附图简述

[0031] 图1显示对于5种已知的FVIII产品(空白柱)和新型rpFVIIIv3(混杂柱)所需的以 $\mu$ g/剂量表示的蛋白质的量。BDD=缺失的B结构域;FL=全长; $u=\mu$ ;

[0032] 图2a-e是相同序列的连续。图2a-e显示来自人(智人)、猪(野猪)、小鼠(小家鼠)和狗(家犬)的因子VIII序列之间的序列比对。该序列比对获自HADB (aka HAMSTeRS) 2010,甲型血友病突变数据库和关于因子VIII的资料来源位置的主页(hadb.org.uk)。编号按照人序列并且与列表中的序列的氨基酸编号不相同。粗体加双下划线标示的序列描述了在本发明的重组FVIIIv3变体中失去的序列。下划线标示的序列是B结构域的序列。以灰色突出显示的序列是来自B结构域的部分,其可被保留在本发明的部分B结构域缺失的FVIIIv3序列中;和

[0033] 图3显示了实施例5中描述的校准标准的SEC特征谱和校准曲线的线性回归的典型实例。

[0034] 序列概述

[0035] SEQ ID NO:1显示猪的部分B结构域缺失的FVIIIv3的序列;

[0036] SEQ ID NO:2显示人B结构域缺失的FVIIIv3的序列;

[0037] SEQ ID NO:3显示犬B结构域缺失的FVIIIv3的序列;

[0038] SEQ ID NO:4显示来自猪FVIII B结构域的序列,其可存在于本发明的部分B结构域缺失的FVIII分子(所谓的“B结构域接头”);

[0039] SEQ ID NO:5显示来自人FVIII B结构域的B结构域接头序列,其可存在于本发明的部分B结构域缺失的FVIII分子中;

[0040] SEQ ID NO:6显示来自犬FVIII B结构域的B结构域接头序列,其可存在于本发明的部分B结构域缺失的FVIII分子中;

[0041] SEQ ID NO:7显示全长猪FVIII的氨基酸序列;

[0042] SEQ ID NO:8显示全长人FVIII的氨基酸序列;

[0043] SEQ ID NO:9显示全长犬FVIII的氨基酸序列;

[0044] SEQ ID NO:10显示27肽序列,其对应于图2中描述的猪因子VIII的氨基酸716至742或SEQ ID NO:7的氨基酸714至740;

[0045] SEQ ID NO:11显示27肽序列,其对应于图2中描述的人因子VIII的氨基酸714至740或SEQ ID NO:8的氨基酸714至740;和

[0046] SEQ ID NO:12显示27肽序列,其对应于图2中描述的犬因子VIII的氨基酸714至740或SEQ ID NO:9的氨基酸708至734。

[0047] 发明详述

[0048] 本发明基于部分B结构域缺失的重组猪因子VIII蛋白的变体的发现,所述变体包含特别的27个氨基酸的缺失。已显示该变体(其在本文中称为rpFVIIIv3)相较于包含27个氨基酸的区段(stretch)的类似蛋白(即称为“OBI-1”的部分B结构域缺失的重组猪FVIII)具有增加的比活性。已知OBI-1、其氨基酸序列和编码OBI-1的多核苷酸例如来自US 6,458,563。

[0049] 本发明涉及分离的重组的完全或部分B结构域缺失的因子VIII (FVIII) 变体,其中FVIII变体缺乏对应于图2中描述的猪因子VIII的氨基酸716至742或SEQ ID NO:7的氨基酸714至740的氨基酸序列。

[0050] 此外,本发明涉及分离的重组的完全或部分B结构域缺失的FVIII变体,FVIII变体缺乏对应于图2中描述的猪因子VIII的氨基酸716至742或SEQ ID NO:7的氨基酸714至740的27个氨基酸的序列,其中可缺失27、26、25、24、23、22、21、20、19、18、17、16、15、14、13、12、11、10、9、8、7、6、5、4、3、2或1个氨基酸。在一个变体中,缺失27、26、25、24、23、22、21或20个氨基酸。在另一个变体中,缺失27、26或25个氨基酸。在rpFVIIIv3变体中,缺失对应于DIGDYDNTYEDIPGFLLSGKNVIEPR (SEQ ID NO:10) 的27个氨基酸。

[0051] 此外,本发明涉及分离的重组的完全或部分B结构域缺失的FVIII变体,FVIII变体缺乏对应于图2中描述的人因子VIII的氨基酸714至740或SEQ ID NO:8的氨基酸714至740的27个氨基酸的序列,其中可缺失27、26、25、24、23、22、21、20、19、18、17、16、15、14、13、12、11、10、9、8、7、6、5、4、3、2或1个氨基酸。在一个变体中,缺失27、26、25、24、23、22、21或20个氨基酸。在另一个变体中,缺失27、26或25个氨基酸。在人FVIIIv3变体(rhFVIIIv3)中,缺失对应于NTGDYEDSYEDISAYLLSKNNAIEPR (SEQ ID NO:11) 的27个氨基酸。

[0052] 此外,本发明涉及分离的重组的完全或部分B结构域缺失的FVIII变体,FVIII变体缺失对应于图2中描述的犬因子VIII的氨基酸714至740或SEQ ID NO:9的氨基酸708至734的27个氨基酸的序列,其中可缺失27、26、25、24、23、22、21、20、19、18、17、16、15、14、13、12、11、10、9、8、7、6、5、4、3、2或1个氨基酸。在一个变体中,缺失27、26、25、24、23、22、21或20个氨基酸。在另一个变体中,缺失27、26或25个氨基酸。在犬FVIIIv3变体(rcFVIIIv3)中,缺失对应于NIDDYEDTYEDIPTPLLNNVVIKPR (SEQ ID NO:12) 的27个氨基酸。

[0053] 此类变体具有相较于包含完整的27个氨基酸的序列的类似变体升高的比活性。优

选地,比活性增加超过25%或30%或35%或40%或45%或50%或55%或60%。

[0054] 如本文中所用,术语“比活性”是指可修正人因子VIII缺乏的血浆的凝血不良的活性。在其中将人因子VIII缺乏的血浆的凝血时间与正常人血浆的凝血时间相比较的标准测定中,将比活性测量为凝血活性的单位每毫克总因子VIII变体。被FDA接受用于高纯度的FVIII浓缩物的用于测量FVIII产品的效力的适当标准测定称为一期凝血测定(one-stage clotting assay) (OSCA;参见实施例5;Langdell RD,Wagner RH,Brinkhous KM.,Effect of antihemophilic factor on one-stage clotting tests:a presumptive test for hemophilia and a simple one-stage antihemophilic assay procedure,J Lab Clin Med,1953;41:637-47;Brand JT,Measurement of factor VIII:a potential risk factor for vascular disease,Arch Pathol Lab Med,1993;117:48-51;Preston FE,Kitchen S,Quality control and factor VIII assays,Haemophilia,1998;4:651-3;National Committee for Clinical Laboratory Standards (NCCLS USA).Determination of factor coagulant activities;Approved guideline,NCCLS Document H-48-A1997;17:1-36.)。存在于样品中的FVIII蛋白的量可以例如利用SEC HPLC(大小排阻高效液相色谱)来测量。

[0055] 一个单位的因子VIII活性是存在于1毫升的正常人血浆中的活性。在测定中,血块形成的时间越短,则待测定的因子VIII的活性越大。猪因子VIII在人因子VIII测定中具有凝固活性。

[0056] 与本发明一致,术语“蛋白质”和“多肽”可互换使用。

[0057] “缺乏对应于图2中描述的氨基酸716至742的氨基酸序列”意指在本发明的FVIII变体中,缺失了(即不包括)氨基酸716和742以及这些位置之间的氨基酸。该氨基酸区段从而由本发明的FVIII变体所缺乏的27个氨基酸组成。

[0058] 本发明的因子VIII变体在本文中总体称为“FVIII变体”或“FVIIIv3”或“rFVIIIv3”。它们可以是猪、人、犬、鼠或适用于人或动物疗法的任何其它来源的。图2描述了人、猪、鼠和犬来源的FVIII序列的序列比对。

[0059] 本发明的FVIII变体中缺失的序列以粗体突出显示并且以双下划线标示。可由本领域技术人员,通过将其它物种的FVIII序列与例如猪或人序列比对,然后获取对应于按照本专利申请的图2的氨基酸716至742的氨基酸来鉴定其它物种的FVIII变体的该氨基酸区段。

[0060] 本发明的实施方案涉及猪、人或犬来源的FVIII变体。

[0061] 在实施方案中,根据本发明的FVIII变体包含SEQ ID NO:1的序列,或其包含与SEQ ID NO:1具有至少90%的同一性的序列的变体。应理解,10%的变异性涉及缺失的氨基酸区段外部的序列,即变体完全缺乏DIGDYDNTYEDIPGFLLSGKNVIEPR (SEQ ID NO:10) (对应于图2中描述的猪因子VIII的氨基酸716至742或SEQ ID NO:7的氨基酸714至740的氨基酸序列)。

[0062] 在其它实施方案中,本发明的FVIII变体包含SEQ ID NO:2的序列,或其包含与SEQ ID NO:2具有至少90%的同一性的序列的变体。再次地,变体理解为完全缺乏对应于图2中描述的人因子VIII的氨基酸714至740或SEQ ID NO:8的氨基酸714至740的氨基酸序列NTGDYEDSYEDISAYLLSKNNAIEPR (SEQ ID NO:11)。

[0063] 在又其它实施方案中,本发明的FVIII变体包含SEQ ID NO:3的序列,或其包含与SEQ ID NO:3具有至少90%的同一性的序列的变体。再次地,变体理解为完全缺乏对应于图2中描述的犬因子VIII的氨基酸714至740或SEQ ID NO:9的氨基酸708至734的氨基酸序列NIDDYYEDTYEDIPTLLNENNVIKPR (SEQ ID NO:12)。

[0064] 本发明的FVIII变体还可包含与SEQ ID NO:7、8或9的序列具有至少91、92、93、94、95、96、97、98、99、99.5、99.6、99.7、99.8或99.9%的同一性的序列。

[0065] 为了测定两个多肽/蛋白质的同一性百分比,为了最佳的比较目的,将氨基酸序列比对(例如,可将空位引入第一氨基酸序列的序列以与第二氨基酸序列进行最佳比对)。随后比较对应氨基酸位置处的氨基酸残基。当第一序列中的位置被与第二序列中对应位置相同的氨基酸残基占据时,则分子在该位置处是相同的。两个序列之间的同一性百分比是由序列共有的相同位置的数目的函数(即,同一性% = 相同位置的数目/总的位置数目(例如,(重叠位置) × 100))。

[0066] 两个序列之间的同一性百分比的测定可使用数学算法来实现。用于两个序列的比較的数学算法的优选非限定性实例是在Karlin和Altschul (1993) Proc. Natl. Acad. Sci. USA 90:5873-5877中改进的Karlin和Altschul (1990) Proc. Natl. Acad. Sci. USA 87:2264-2268的算法。这样的算法被整合至Altschul, 等人 (1990) J. Mol. Biol. 215:403-410的NBLAST和XBLAST程序中。BLAST核苷酸搜寻可利用NBLAST程序,评分=100,字长=12来进行,以获得与本发明的核酸分子同源的核苷酸序列。BLAST变体搜寻可利用XBLAST程序,评分=50,字长=3来进行,以获得与本发明的变体分子同源的氨基酸序列。为了获得空位比对(为了比较目的),可如Altschul等人 (1997) Nucleic Acids Res. 25:3389-3402中所述使用Gapped BLAST。或者,可使用PSI-Blast进行迭代搜寻,所述搜寻检测分子之间的远缘谱系关系(distant relationship)。当使用BLAST、Gapped BLAST和PSI-Blast程序时,可使用各自程序(例如,XBLAST和NBLAST)的缺省参数。用于序列比較的数学算法的另一个优选的非限定性实例是Myers和Miller, (1988) CABIOS 4:11-17的算法。将这样的算法整合至作为GCG序列比对软件包的部分的ALIGN程序(2.0版)中。当使用ALIGN程序比较氨基酸序列时,可使用PAM120权重残基表(weight residue table)、为12的空位长度罚分以及为4的空位罚分。用于鉴定局部序列相似性和比对的区域的另一个有用的算法是Pearson和Lipman (1988) Proc. Natl. Acad. Sci. USA 85:2444-2448中描述的FASTA算法。当使用FASTA算法比较核苷酸或氨基酸序列时,可以例如将PAM120权重残基表与为2的k-元组值(k-tuple value)一起使用。

[0067] 两个序列之间的同一性百分比可使用类似于上述技术的技术,提供或不提供空位来进行测定。在计算百分比同一性中,仅计数完全匹配(exact match)。

[0068] 本发明的FVIII变体可以是部分或完全B结构域缺失的。这意指缺失整个B结构域,或在FVIII变体中保留B结构域的部分。B结构域的剩余(保留的)部分例如选自彼此融合于读框内的B结构域的20、15、12、10或5个N末端氨基酸和20、15、12、10或5个C末端氨基酸。

[0069] 因此,优选地,在本发明的部分B结构域缺失的FVIII变体中,除去约900个氨基酸的B结构域的大部分。在本发明的实施方案中,少于5%或少于4%或少于3%或少于2%或少于1%的B结构域仍然存在于FVIII变体中。

[0070] 在本发明的实施方案中,B结构域的剩余部分选自由SEQ ID NO:4或SEQ ID NO:5

或SEQ ID NO:6组成的序列。

[0071] 在其它方面,本发明涉及编码上述多肽/蛋白质的多核苷酸。多核苷酸可以是RNA或DNA分子,根据遗传密码的已知关系,其核苷酸序列体现了至宿主细胞的本发明的变体的氨基酸序列的编码信息。

[0072] 在其它方面,本发明涉及包含上述多核苷酸的表达载体。

[0073] “表达载体”是通常具有环状结构的DNA元件,其具有在期望的宿主细胞中自主复制,或整合到宿主基因组中的能力,并且还具有一项或多项在适当位点并且以适当的方向插入载体序列的编码DNA表达的某些公知特征。此类特征可包括但不限于一个或多个指导编码DNA的转录起始的启动子序列和其它DNA元件例如增强子、多腺苷酸化位点等,这在本领域全都是公知的。术语“表达载体”用于表示可使待表达的DNA编码序列插入其序列内的载体,和可使必需表达控制元件相对于插入位点这样排列以便其可用于表达插入该位点的任何编码DNA的载体,所述表达载体在本领域都是公知的。因此,例如,缺乏启动子的载体可通过插入与编码DNA组合的启动子变成表达载体。如本文中所示,表达载体还可以是病毒载体。

[0074] 优选在哺乳动物细胞培养物中进行本发明的重组FVIII变体的表达。

[0075] 因此,在其它方面,本发明涉及包含上述表达载体的哺乳动物细胞。例如,CHO(中国仓鼠卵巢)细胞和BHK细胞(幼仓鼠肾细胞)是在本发明的上下文中为适当的宿主细胞的哺乳动物细胞。

[0076] 根据本发明的另一个方面,用于产生本发明的FVIII变体的方法包括步骤:

[0077] a. 培养上述哺乳动物细胞;和

[0078] b. 从哺乳动物细胞分离FVIII变体。

[0079] 在实施方案中,方法还包括步骤

[0080] c. 将因子VIII变体与适当的赋形剂一起配制成药物组合物。

[0081] 适合于人或动物施用的赋形剂是例如药物稳定化合物、防腐剂、递送媒介物和/或载体媒介物。因子VIII产品的一种适当的制剂例如描述于WO 03/080108(将其通过引用并入本文中)中。

[0082] 在其它方面,本发明涉及包含本发明的FVIII变体的药物组合物。

[0083] 本发明的其它方面涉及治疗具有因子VIII缺乏症的患者,包括给有此需要的患者施用治疗有效量的本发明的FVIII变体,从而治疗所述患者的因子VIII缺乏症。

[0084] 如本文中所示,术语“治疗有效量”意指足以在患者中显示可测量的改善或保护作用(例如,终止出血)的具有FVIII缺乏症的患者血浆中的FVIII水平,所述患者已接受FVIII变体的药物组合物。具有FVIII缺乏症的患者通常是先天性甲型血友病患者但也包括经诊断患有“获得性血友病”(其中非先天性血友病患者那些患者自发地对它们的FVIII产生抑制性抗体,从而产生严重的FVIII缺乏症的病症)的受试者。

[0085] 本发明还涉及用于治疗因子VIII缺乏症的本发明的FVIII变体。

[0086] 治疗可采取单次静脉内施用组合物或必要时在一段延长的时期中定期或连续施用的形式。优选地,FVIII变体的施用是通过静脉内途径。

[0087] 如本文中所示,“因子VIII缺乏症”包括因缺陷型因子VIII的产生,因因子VIII的不足或未产生,或因抑制剂对因子VIII的部分或完全抑制而引起的凝血活性的缺乏。甲型血友病是由X连锁基因的缺乏以及其编码的因子VIII变体的不存在或不足而引起的一种类

型的因子VIII缺乏症。

[0088] 本发明的FVIII变体用于治疗血友病患者的因因子VIII缺乏而引起的不受控制的出血(例如,关节内、颅内或或胃肠道出血)。

[0089] 在本发明的实施方案中,因子VIII缺乏症是甲型血友病。

[0090] 在另一个实施方案中,因子VIII缺乏症是获得性血友病。

[0091] 在实施方案中,治疗已产生人FVIII抗体的患者的因子VIII缺乏症。

[0092] 如上文中提及的,本发明的FVIII变体具有增加比活性。因此可能施用减少量的FVIII变体,以治疗根据本发明的VIII缺乏症。相较于利用不包含本发明的多达27个氨基酸缺失的FVIII产品的疗法,FVIII变体的量可减少至少30%、35%、40%、45%、50%、55%、60%。

[0093] 减少FVIII变体的量的疗法具有预期的减小的免疫原性的有利方面,即预期患者中产生针对FVIII替代疗法的抑制性抗体的概率显著减小。

[0094] 在实施方案中,以不超过200 $\mu$ g/剂量或150 $\mu$ g/剂量或145 $\mu$ g/剂量或140 $\mu$ g/剂量或136 $\mu$ g/剂量或130 $\mu$ g/剂量的量施用本发明的因子VIII变体。

[0095] 现已完全描述了本发明,本领域技术人员应理解,在不背离本发明的精神和范围以及无需过度实验的情况下可在宽范围的等同参数、浓度和条件内进行本发明。

[0096] 虽然已结合其特定实施方案描述了本发明,但应理解其能够进行进一步改进。本申请意欲包括总体上遵从本发明的原理并且包括这样的与本公开内容的背离的本发明的任何变化、用途或改造,这在本发明所属的领域内的已知或常规实践内并且这可应用于上文中所示的基本特征(这落在所附权利要求的范围内)。

[0097] 本文中引用的所有参考资料,包括期刊论文或摘要、公布的或未公布的美国或外国专利申请、发布的美国或外国专利或任何其它参考资料通过引用整体并入本文,包括在引用的参考资料中呈现的所有数据、表格、附图和文本文件。此外,本文中引用的参考资料的完整内容通过引用整体并入本文。

[0098] 参考已知的方法步骤、常规方法步骤、已知的方法或常规方法绝不是承认在相关领域公开、教导或建议本发明的任何方面、描述或实施方案。

[0099] 具体实施方案的前述描述如此全面地揭示了本发明的一般性质,以至于其他人在无需过度实验,在不背离本发明的一般概念的情况下,可通过应用本领域技术人员掌握的知识(包括本文中引用的参考资料的内容)容易地改进和/或改造(为了各种应用)此类具体实施方案。因此,基于本文中提供的教导和指导方针,此类改造和改进意欲在公开的实施方案的等同物的范围内。应理解,本文中的措辞或术语是为了说明目的而非限制,以便本说明书中的术语或措辞将由本领域技术人员根据本文中提供的教导和指导方针,结合本领域技术人员的知识来进行解释。

## 实施例

[0100] 实施例1:重组猪部分B结构域缺失的FVIII(OBI-1)的表达及3种变体蛋白(rpVIIIv1、v2和v3)的分离

[0101] 基本上如US 6,458,563中所述在BHK细胞中进行OBI-1的表达。在产生的材料中检测到3种变体(rpVIIIv1、v2和v3)。分离变体,通过离子交换层析将其纯化至大于95%的纯

度。为了进行纯化,使用利用MonoQ HR10/10半制备型阴离子交换柱(现为Mono Q10/100GL, GE Healthcare Lifesciences#17-5167-01)的AKTA Explorer系统(AKTA Explorer10,GE Healthcare Lifesciences#17-5167-01)。利用两种下列缓冲液进行梯度洗脱:

[0102] 缓冲液A:10mM TRIS,pH7.0,0.01%聚山梨酯80

[0103] 缓冲液B:缓冲液A和1M氯化钠。

[0104] 纯化法的特征概述于表1中。

[0105] 表1:rpFVIII变体的纯化法

[0106]	AKTA 法:	LoopMQ1010	
	流动:	4 ml/分钟	
	平衡柱	8 CV	
	上样流量	4ml/分钟	
	样品体积	40 - 1000 ml	
	洗涤柱	10CV	
	梯度	柱体积(CV)	%B
		7	45
		4	50
	[0107]		4
		6	52
		4	52
		2	55
		7	60
		1	65
		5	65
		1	70
		5	70
		1	100
		7	100
		1	10
		4	10
	总运行	59 CV	
	柱温度	不受控制	

[0108] 实施例2:变体3(rpVIIIv3)具有比变体1和2显著更高的比活性

[0109] 通过将由一期凝血测定(OSCA)评估的效能除以每方法通过SECHPLC测量的蛋白质浓度来评估每一种变体的比活性。如实施例5的“材料和方法”中所述,进行OSCA和SEC HPLC法。

[0110] 结果

[0111] 比活性的结果示于表2中。

[0112] 表2:从两个不同批次的rpFVIII获得的纯化的变体1、2和3的比活性(OSCA法)

	基于 SEC 的 样品	OSCA 单位 /ml	%RSD*	比活性单位/ml	%RSD*	
[0113]	V1-批次 1	1060	1.5	11956	1.7	
	V2-批次 1	715	2.7	17267	3.3	
	V3-批次 1	216	1.2	25926	2.8	
	OBI-1	513	1	18150	1.3	
	V1-批次 2	980	1.2	12532	1.5	
	V2-批次 2	613	0.6	16089	1.3	
	V3-批次 2	280	2.9	19718	4.1	
	[0114]	OBI-1	565	4.0	14427	4.4

[0115] \*相对标准偏差

[0116] OSCA测定中变体3的显著更高的比活性的观察是明确和一致的。由于OSCA法对于人中凝固过程是预测性和代表性的,因此预期变体3是具有有效值(significant value)的产品。预期效力的1.5-2.0倍的增加减少了给患者施用的FVIII的量,从而可能间接减少免疫副作用的发生。

[0117] 实施例3:rpFVIIIv3的序列测定

[0118] 通过肽图谱,然后通过Q-TOF Ultima质谱仪上进行LCMS(液相色谱质谱)和LCMS/MS(液相色谱质谱/质谱),运行MassLynx4.0(Waters Corporation,Milford,MA)来测定纯化的v3的序列。

[0119] 使用具有10,000MWC0滤膜(Millipore Corporation,Billerica,MA)的Amicon, Centricon YM-10浓缩器将约250µg的变体3浓缩成小于100µL的体积。将样品与450µL的6M盐酸胍/0.002M EDTA(乙二胺四乙酸)/0.02M Tris缓冲液pH8混合,转移至2.0mL聚丙烯管中。将1M DTT(二硫苏糖醇)添加至每一个样品至10mM的终浓度,在37°C下孵育1小时。还原后,将2M碘乙酰胺添加至每一个管至20mM的终浓度,在室温下再孵育1小时。将还原的和烷基化的样品转移至透析盒(dialysis cassette),针对1L50mM的含有1.0M尿素,pH8的碳酸氢铵透析缓冲液透析1小时。随后在维持恒定搅拌的同时将样品在室温下针对1L透析缓冲液透析过夜。透析后,终体积为各自约0.5mL。将样品分成两个125µg的等分。

[0120] 透析后,将蛋白质样品包含在对于利用胰蛋白酶的蛋白水解消化是最佳的基质中。将胰蛋白酶以1:20(w:w)的酶底物比添加至每一个样品,在37°C下孵育8小时。将所有样品转移至HPLC小瓶,通过HPLC-MS进行分析。

[0121] 将还原的和烷基化的蛋白质注射至Vydac C18反相柱(Grace,Deerfield,IL)上。在样品注射之前,分析空白样品(移动相A;含有0.2%(v:v)甲酸的去离子水)以平衡柱子和显示干涉峰(interfering peak)的不存在。

[0122] 以阳离子模式使用电喷射离子化(ESI)在Q-TOF API-US质谱仪或Q-TOF Ultima质谱仪(Waters Corporation,Milford,MA)上收集质谱数据。在进行样品分析之前,使用对覆盖175至1285m/z的范围的Glu-血纤蛋白原肽的碎片离子的五阶拟合(5th order fit)来校准质谱。为了校准以通过规范(specification),要求肽碎片质量的质量的RMS(均方根)误差小于5ppm。软件包Masslynx4.0™ SP2和SP4(Waters Corporation,Milford,MA)用于数据获取和分析。

[0123] 使用单个液相色谱 (LC) 运行收集MS和MS/MS数据。从200-1950m/z收集全质谱 (MS) 测量扫描。

[0124] rpFVIII的序列经测定对应于SEQ ID NO:1。该序列相较于OBI-1序列包含27个氨基酸的缺失。

[0125] 实施例4:rpFVIIIv3具有比其它已知的FVIII产品更高的比活性

[0126] 将rpFVIIIv3的比活性与3种商购可得FVIII产品即Xynthia® (重组的B结构域缺失的人FVIII, 来自WyethPharmaceuticals (Philadelphia, PA))、Kogenate FS® (全长人FVIII, 来自Bayer Healthcare (Tarrytown, NY)) 和Advate® (全长人FVIII, 来自Baxter (Westlake Village, CA)) 以及与目前处于临床开发中的OBI-1 (重组的部分B结构域缺失的猪FVIII) 和B结构域缺失的犬因子VIII (Denise E. Sabatino等人, Recombinant canine B domain-deleted FVIII exhibits high specific activity and is safe in the canine hemophilia A model, Blood, 2009年11月12日, 第114卷, No. 20, 第4562-4565页) 相比较。

[0127] OBI-1和rpFVIIIv3的比活性通过实施例5中描述的方法来进行测定。

[0128] 结果描述于表3和图1中。由于其增加的比活性, 因此可给患者施用每剂量更低的rpFVIIIv3的量。预期剂量的减少将导致减小的免疫原性, 即导致更低的患者产生抑制性抗体的概率。

[0129] 表3: 与rpFVIIIv3相比较的FVIII产品的比活性

	以IU/mg 蛋白质表示的比活性	Amt 蛋白质 $\mu\text{g}/\text{剂量}^{\wedge}$
Xynthia	7500	400
Kogenate FS	4000	750
Advate	4000	750
OBI-1	11000	273
rpFVIIIv3	22000	136
犬 BDD*FVIII	34000	88

[0131]  $\wedge$ Amt蛋白 = xxx $\mu\text{g}/\text{剂量}$ 。对于rpFVIII3栏中显示的数目表示将需要136 $\mu\text{g}/\text{剂量}$ 的量。一个剂量是使血液因子VIII水平从0%升至100%所需要的量, 即比活性 (XXX个单位/mg) 越高, 需要的量 (以 $\mu\text{g}$ 表示) 越少。要指出的是1mg = 1000 $\mu\text{g}$ 。假定典型剂量为3000个单位/患者, 则实际需要的蛋白质的量 = 3000/22000 = 0.136mg = 136 $\mu\text{g}$ 。

[0132] \*BDD代表B结构域缺失以及FL代表全长。

[0133] 总之, 这些结果显示rpFVIIIv3具有比目前商业化的或处于临床开发中 (以用于FVIII替代疗法) 的测试产品显著更高的比活性。

[0134] 具体地, 高度令人惊讶地存在于rpFVIIIv3而非OBI-1中的27个氨基酸的缺失导致50%的比活性的增加 (如通过OSCA测定测量的)。

[0135] 实施例5:材料和方法

[0136] 一期凝血测定-OSCA-法

[0137] 1.将参照标准于测定缓冲液(10%的因子VIII缺乏血浆+每升Owren's Veronal缓冲液28mmol的巴比妥钠和125mmol的NaCl,pH7.35)中稀释至1.0个单位/mL的目标效力。

[0138] 2.将检查标准、活性对照和样品在测定缓冲液中稀释至目标效力。

[0139] 3.将校准标准(参照)和试剂上样至Symex仪内部的适当的孔中。(Sysmex CA-1500,Coagulation Analyzer,Dade Behring#B4260-1500(Siemans Corporation,Deerfield,IL))。

[0140] 4.将检查标准、对照和样品上样至Symex仪外部的支架(rack)上。

[0141] 5.测定顺序如下在仪器内部自动地进行:

[0142] a.将5uL的样品在反应管的内部稀释至45uL的测定缓冲液中

[0143] b.将50uL的因子VIII缺乏的血浆添加至反应管

[0144] c.50uL的Dade Actin FS( $1.0 \times 10^{-4}$ M鞣花酸激活剂中的纯化的大豆磷脂,Dade Behring,Liederbach,Germany)激活的部分促凝血酶原激酶时间试剂添加至反应管中并且孵育60秒。

[0145] d.将50uL的氯化钙(0.025M,Dade Behring,Liederbach,Germany)添加至反应管中,孵育240秒。

[0146] e.测量凝血时间多达300秒的最长时间。

[0147] 6.随后使凝血时间与通过参照标准校正曲线产生的效力相关联。

[0148] 大小排阻 (SEC) HPLC法

[0149] 将Agilent1100(Agilent Technologies,Santa Clara,CA)或Waters Bioalliance HPLC系统(Waters Corporation,Milford,MA)用于以及通常用于大小排阻法,以测定蛋白质浓度。使用的典型的大小排阻柱为来自GE的Superdex 200(Superdex20010.300GL,10X300mm,Cat#17-5175-01(GE Healthcare Lifesciences,Piscataway,NJ))。一般的测定方案如下:

[0150] 1.制备包含400mM NaCl与20mM TRIS,pH7.4和0.01%聚山梨酯80的典型流动相。

[0151] 2.将流动相运行通过HPLC系统和柱子直至观察到基线的平衡。

[0152] 3.运行标准以建立系统适用性,对于每一个样品使用30分钟的典型运行时间。

[0153] 4.通常将样品上样至自动取样器上,控制室温度为4℃。

[0154] 5.将已知浓度的包含不同量的标准样品(通常1、3、5、10和25μg的蛋白质)的校准标准以10至50μL的体积上样至柱子上。

[0155] 6.也将未知浓度的样品通常以30至50μL的体积上样至柱子中。

[0156] 7.HPLC系统经编程以按照设立的顺序自动地运行样品。

[0157] 8.基于荧光检测(利用分别在280nm和340nm上的激发和发射)测定校准标准和未知样品的峰面积。

[0158] 9.产生校准标准的线性回归,对照该校准曲线测定未知样品的浓度。

[0159] 校正标准的SEC曲线和校准曲线的线性回归的典型实例示于图3中。

[0160] 实施例6:与血管性血友病因子的结合

[0161] 血管性血友病因子(vWF)是多功能糖蛋白,其作为与因子VIII(FVIII/vWF复合物)

复合的多聚体形式在血浆中循环。FVIII/vWF复合物用于在体内循环中保护结合的FVIII免受早期蛋白水解。

[0162] 大小排阻层析 (SEC) 用于表征FVIII/vWF复合物中的结合。因其已知的生物相容性和4000万道尔顿的高排阻极限 (流动相配制缓冲液: 2mM CaCl<sub>2</sub>、10mM Tris pH7.0、300mM NaCl、0.01% PSB-80、11mM蔗糖、10mM柠檬酸三钠) 而选择Superose6柱 (Superose610/300GL, GE Healthcare#17-5172-01, 流速=0.5mL/分钟)。血管性血友病因子 (二聚体@~500kD, Fitzgerald目录号30C-CP4003U, 批次号A09121050, 单体分子量=~260kD, 浓度=77μg/mL) 与rpFVIII (~160kD) 之间的分子量的差异足以分辨两个种类。

[0163] 通过利用递增量的rpFVIII滴定恒定量的vWF来测定结合的化学计量学。根据SEC层析谱和适当的峰的积分测定rpFVIII与vWF之间复合物形成的特征谱。将所得的混合物在上清液中的可溶性形式用于测定复合物形成的终点 (根据利用递增量的rpFVIII进行的滴定)。rpFVIII与vWF之间形成的更大的稳定复合物从正常保留时间迁移至柱子的排阻极限。当饱和发生时, 将在SEC层析中观察到递增量的未结合的rpFVIII。该方法用于区分变体性质的差异和相似性。

[0164] 实施例7: 凝血酶消化动力学

[0165] SDS-PAGE

[0166] 重组猪因子VIII (rpFVIII) 分子是约160kD的由78.5kD分子量的轻链 (A3-C1-C2, 765-1448) 和分子量从86.7kD变化的重链 (A1-A2) 组成的异二聚体。rpFVIII的重链是异源的并且由3个主要变体组成, 所述变体从细胞分泌后形成并且可被称为PACE (配对的碱性氨基酸裂解酶) 的枯草杆菌蛋白酶家族的膜结合蛋白酶裂解。

[0167] 与人因子VIII一样, 通过从凝血酶限制性蛋白水解将rpFVIII转化成活性形式。rpFVIII的凝血酶激活对于Arg (372) -Ser (373) 处的重链的裂解位点是特异性的。轻链在Arg (805) -Ser (806) 处的裂解区释放765-804 (~4.4kD) 的小的40个氨基酸肽片段。这些由凝血酶产生的初始裂解的组合将激活的重组猪因子VIII形成为称为A1 (~50kD)、A2 (~40kD) 和A3-C1-C2 (~70kD) 的亚单位的异三聚体。裂解的rpFVIII A1和A3-C1-C2亚单位保留二价金属离子依赖性连接, 然而A2亚单位主要通过静电相互作用与A1-A3-C1-C2二聚体较弱地缔合。在SDS-PAGE中, 此类亚单位显示为3条不同的条带。rpFVIII (2个肽单位) 至3个肽单位的转化的效力是产品的凝血酶激活的特征。该方法区分个体变体之间的相似性和差异。

[0168] 两个其它正交法可用于对FVIII的凝血酶消化的动力学作图。可使用变性反相HPLC; 预期峰特征谱与SDS-PAGE的相似。还可使用阴离子交换层析, 其保留肽的天然形式。

[0169] 反相HPLC

[0170] 设备:

[0171] 1. HPLC1100系列: Agilent Technologies, Santa Clara, CA, USA; 型号61312A, 系列号DE10907753。

[0172] 2. Poroshell15um2.1X75mm柱: Agilent Technologies, Santa Clara, CA, USA; 产品编号 (Part No.) 660750-909, 系列号USVV001988。

[0173] 试剂:

[0174] 1. 缓冲液A: 0.1%的水中的TFA (JT B Baker, Phillisburg, NJ; 目录号94700-00,

批次号J23J00)

[0175] 2.缓冲液B:0.1%的乙腈中的TFA(JTBaker,Phillisburg,NJ;目录号9017-03,批次号J38807)。

[0176] 步骤:

[0177] 1.使用99%A和1%B以1ml/分钟平衡柱子,进行60分钟。

[0178] 2.以50 $\mu$ l的体积进行样品注射;25 $\mu$ l的参照标准用作对照。

[0179] 3.用于运行样品的方法的实例示于表4中。

[0180] 表4:

注射	时间(分钟)	流量(ml/分钟)	%A	%B
1	0.00	2	99	1
2	2.00	2	99	1
3	3.00	2	64	36
4	3.50	2	64	36
5	4.00	2	61	39
6	5.00	2	61	39
[0181] 7	5.10	2	58	42
8	6.50	2	58	42
9	6.51	2	56	44
10	7.20	2	56	44
11	7.21	2	40	60
12	8.50	2	40	60
13	8.51	2	10	90
14	9.00	2	10	90
15	9.10	2	99	1
16	10.00	2	99	1

[0182] 阴离子交换层析

[0183] 设备:

[0184] 1.AllianceBio HPLC,Waters corporation,Milford,MA,USA;型号2796;系列号M08BA1199M。

[0185] 2.Protein Pak Hi Res Q5um4.6X100mm柱:Waters Corporation,Milford,MA,USA;产品编号186004931,系列号502N112561VE04。

[0186] 试剂:

[0187] 缓冲液A:

[0188] 10mM Tris碱(1.211g/L)

[0189] 2mM氯化钙(0.588g/L)

[0190] 0.01%聚山梨酯80(1ml的10%PS-80/L)

[0191] 多达1L的过滤水,pH7.0

[0192] 缓冲液B:

[0193] 10mM Tris碱(1.211g/L)

[0194] 2mM氯化钙(0.588g/L)

[0195] 0.01%的聚山梨酯80(1ml的10%PS-80/L)

[0196] 1M氯化钠 (58.44g/L)

[0197] 多达1L的过滤水, pH7.0

[0198] 步骤:

[0199] 1. 使用70%A和30%B以0.5ml/分钟平衡柱子, 进行60分钟

[0200] 2. 以50 $\mu$ l的体积进行样品注射; 将10 $\mu$ l的参照标准用作对照。

[0201] 3. 用于运行样品的方法的实例示于表5中。

[0202] 表5:

注射	时间(分钟)	流量(ml/分钟)	%A	%B
1	0.01	0.5	70	30
2	0.50	0.5	70	30
3	3.50	0.5	60	40
4	5.00	0.5	60	40
5	10.00	0.5	30	70
6	10.10	0.5	1	99
7	12.00	0.5	1	99
8	12.10	0.5	70	30
9	17.00	0.5	70	30

[0205] 本领域技术人员将知道并且理解这些以及其它方法可用于达到理解本文中描述的重组因子VIII蛋白。

## 序列表

<110> Ipsen Pharma S.A.S.  
 <120> 具有增加的比活性的抗血友病因子 VIII 的新型变体  
 <130> IPH 021  
 <160> 12  
 <170> PatentIn 3.5 版  
 <210> 1  
 <211> 1421  
 <212> PRT  
 <213> 野猪  
 <400> 1

[0001]

Ala Ile Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser Trp Asp Tyr  
 1                    5                    10                    15

Arg Gln Ser Glu Leu Leu Arg Glu Leu His Val Asp Thr Arg Phe Pro  
                   20                    25                    30

Ala Thr Ala Pro Gly Ala Leu Pro Leu Gly Pro Ser Val Leu Tyr Lys  
                   35                    40                    45

Lys Thr Val Phe Val Glu Phe Thr Asp Gln Leu Phe Ser Val Ala Arg  
                   50                    55                    60

Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu  
 65                    70                    75                    80

Val Tyr Asp Thr Val Val Val Thr Leu Lys Asn Met Ala Ser His Pro  
                   85                    90                    95

Val Ser Leu His Ala Val Gly Val Ser Phe Trp Lys Ser Ser Glu Gly  
 100 105 110

Ala Glu Tyr Glu Asp His Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys  
 115 120 125

Val Leu Pro Gly Lys Ser Gln Thr Tyr Val Trp Gln Val Leu Lys Glu  
 130 135 140

Asn Gly Pro Thr Ala Ser Asp Pro Pro Cys Leu Thr Tyr Ser Tyr Leu  
 145 150 155 160

Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala  
 165 170 175

[0002] Leu Leu Val Cys Arg Glu Gly Ser Leu Thr Arg Glu Arg Thr Gln Asn  
 180 185 190

Leu His Glu Phe Val Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser  
 195 200 205

Trp His Ser Ala Arg Asn Asp Ser Trp Thr Arg Ala Met Asp Pro Ala  
 210 215 220

Pro Ala Arg Ala Gln Pro Ala Met His Thr Val Asn Gly Tyr Val Asn  
 225 230 235 240

Arg Ser Leu Pro Gly Leu Ile Gly Cys His Lys Lys Ser Val Tyr Trp  
 245 250 255

His Val Ile Gly Met Gly Thr Ser Pro Glu Val His Ser Ile Phe Leu  
 260 265 270

Glu Gly His Thr Phe Leu Val Arg His His Arg Gln Ala Ser Leu Glu  
 275 280 285

Ile Ser Pro Leu Thr Phe Leu Thr Ala Gln Thr Phe Leu Met Asp Leu  
 290 295 300

Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His His His Gly Gly  
 305 310 315 320

Met Glu Ala His Val Arg Val Glu Ser Cys Ala Glu Glu Pro Gln Leu  
 325 330 335

Arg Arg Lys Ala Asp Glu Glu Glu Asp Tyr Asp Asp Asn Leu Tyr Asp  
 340 345 350

[0003] Ser Asp Met Asp Val Val Arg Leu Asp Gly Asp Asp Val Ser Pro Phe  
 355 360 365

Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr Trp Val His  
 370 375 380

Tyr Ile Ser Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro Ala Val Pro  
 385 390 395 400

Ser Pro Ser Asp Arg Ser Tyr Lys Ser Leu Tyr Leu Asn Ser Gly Pro  
 405 410 415

Gln Arg Ile Gly Arg Lys Tyr Lys Lys Ala Arg Phe Val Ala Tyr Thr  
 420 425 430

Asp Val Thr Phe Lys Thr Arg Lys Ala Ile Pro Tyr Glu Ser Gly Ile  
 435 440 445

Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu Leu Ile Ile  
 450 455 460

Phe Lys Asn Lys Ala Ser Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile  
 465 470 475 480

Thr Asp Val Ser Ala Leu His Pro Gly Arg Leu Leu Lys Gly Trp Lys  
 485 490 495

His Leu Lys Asp Met Pro Ile Leu Pro Gly Glu Thr Phe Lys Tyr Lys  
 500 505 510

Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys  
 515 520 525

[0004] Leu Thr Arg Tyr Tyr Ser Ser Ser Ile Asn Leu Glu Lys Asp Leu Ala  
 530 535 540

Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Val Asp  
 545 550 555 560

Gln Arg Gly Asn Gln Met Met Ser Asp Lys Arg Asn Val Ile Leu Phe  
 565 570 575

Ser Val Phe Asp Glu Asn Gln Ser Trp Tyr Leu Ala Glu Asn Ile Gln  
 580 585 590

Arg Phe Leu Pro Asn Pro Asp Gly Leu Gln Pro Gln Asp Pro Glu Phe  
 595 600 605

Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val Phe Asp Ser  
 610 615 620

Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp Tyr Ile Leu  
625                      630                      635                      640

Ser Val Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr  
                    645                      650                      655

Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro  
                    660                      665                      670

Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu Trp  
                    675                      680                      685

Val Leu Gly Cys His Asn Ser Asp Leu Arg Asn Arg Gly Met Thr Ala  
                    690                      695                      700

[0005] Leu Leu Lys Val Tyr Ser Cys Asp Arg Ser Phe Ala Gln Asn Ser Arg  
705                      710                      715                      720

Pro Pro Ser Ala Ser Ala Pro Lys Pro Pro Val Leu Arg Arg His Gln  
                    725                      730                      735

Arg Asp Ile Ser Leu Pro Thr Phe Gln Pro Glu Glu Asp Lys Met Asp  
                    740                      745                      750

Tyr Asp Asp Ile Phe Ser Thr Glu Thr Lys Gly Glu Asp Phe Asp Ile  
                    755                      760                      765

Tyr Gly Glu Asp Glu Asn Gln Asp Pro Arg Ser Phe Gln Lys Arg Thr  
                    770                      775                      780

Arg His Tyr Phe Ile Ala Ala Val Glu Gln Leu Trp Asp Tyr Gly Met  
785                      790                      795                      800

Ser Glu Ser Pro Arg Ala Leu Arg Asn Arg Ala Gln Asn Gly Glu Val  
805 810 815

Pro Arg Phe Lys Lys Val Val Phe Arg Glu Phe Ala Asp Gly Ser Phe  
820 825 830

Thr Gln Pro Ser Tyr Arg Gly Glu Leu Asn Lys His Leu Gly Leu Leu  
835 840 845

Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr Phe  
850 855 860

Lys Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile Ser  
865 870 875 880

[0006] Tyr Pro Asp Asp Gln Glu Gln Gly Ala Glu Pro Arg His Asn Phe Val  
885 890 895

Gln Pro Asn Glu Thr Arg Thr Tyr Phe Trp Lys Val Gln His His Met  
900 905 910

Ala Pro Thr Glu Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe Ser  
915 920 925

Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro Leu  
930 935 940

Leu Ile Cys Arg Ala Asn Thr Leu Asn Ala Ala His Gly Arg Gln Val  
945 950 955 960

Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr Lys  
965 970 975

Ser Trp Tyr Phe Thr Glu Asn Val Glu Arg Asn Cys Arg Ala Pro Cys  
 980 985 990

His Leu Gln Met Glu Asp Pro Thr Leu Lys Glu Asn Tyr Arg Phe His  
 995 1000 1005

Ala Ile Asn Gly Tyr Val Met Asp Thr Leu Pro Gly Leu Val Met  
 1010 1015 1020

Ala Gln Asn Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met Gly Ser  
 1025 1030 1035

Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val Phe Ser  
 1040 1045 1050

[0007] Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Val Tyr Asn Leu Tyr  
 1055 1060 1065

Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys Val Gly  
 1070 1075 1080

Ile Trp Arg Ile Glu Cys Leu Ile Gly Glu His Leu Gln Ala Gly  
 1085 1090 1095

Met Ser Thr Thr Phe Leu Val Tyr Ser Lys Glu Cys Gln Ala Pro  
 1100 1105 1110

Leu Gly Met Ala Ser Gly Arg Ile Arg Asp Phe Gln Ile Thr Ala  
 1115 1120 1125

Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg Leu His  
 1130 1135 1140

	Tyr Ser Gly Ser Ile Asn Ala	Trp Ser Thr Lys Asp	Pro His Ser
	1145	1150	1155
	Trp Ile Lys Val Asp Leu Leu	Ala Pro Met Ile Ile	His Gly Ile
	1160	1165	1170
	Met Thr Gln Gly Ala Arg Gln	Lys Phe Ser Ser Leu	Tyr Ile Ser
	1175	1180	1185
	Gln Phe Ile Ile Met Tyr Ser	Leu Asp Gly Arg Asn	Trp Gln Ser
	1190	1195	1200
	Tyr Arg Gly Asn Ser Thr Gly	Thr Leu Met Val Phe	Phe Gly Asn
	1205	1210	1215
[0008]	Val Asp Ala Ser Gly Ile Lys	His Asn Ile Phe Asn	Pro Pro Ile
	1220	1225	1230
	Val Ala Arg Tyr Ile Arg Leu	His Pro Thr His Tyr	Ser Ile Arg
	1235	1240	1245
	Ser Thr Leu Arg Met Glu Leu	Met Gly Cys Asp Leu	Asn Ser Cys
	1250	1255	1260
	Ser Met Pro Leu Gly Met Gln	Asn Lys Ala Ile Ser	Asp Ser Gln
	1265	1270	1275
	Ile Thr Ala Ser Ser His Leu	Ser Asn Ile Phe Ala	Thr Trp Ser
	1280	1285	1290
	Pro Ser Gln Ala Arg Leu His	Leu Gln Gly Arg Thr	Asn Ala Trp
	1295	1300	1305

Arg Pro Arg Val Ser Ser Ala Glu Glu Trp Leu Gln Val Asp Leu  
1310 1315 1320

Gln Lys Thr Val Lys Val Thr Gly Ile Thr Thr Gln Gly Val Lys  
1325 1330 1335

Ser Leu Leu Ser Ser Met Tyr Val Lys Glu Phe Leu Val Ser Ser  
1340 1345 1350

Ser Gln Asp Gly Arg Arg Trp Thr Leu Phe Leu Gln Asp Gly His  
1355 1360 1365

Thr Lys Val Phe Gln Gly Asn Gln Asp Ser Ser Thr Pro Val Val  
1370 1375 1380

Asn Ala Leu Asp Pro Pro Leu Phe Thr Arg Tyr Leu Arg Ile His  
1385 1390 1395

[0009]

Pro Thr Ser Trp Ala Gln His Ile Ala Leu Arg Leu Glu Val Leu  
1400 1405 1410

Gly Cys Glu Ala Gln Asp Leu Tyr  
1415 1420

&lt;210&gt; 2

&lt;211&gt; 1397

&lt;212&gt; PRT

&lt;213&gt; 智人

&lt;400&gt; 2

Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser Trp Asp Tyr  
1 5 10 15

Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg Phe Pro Pro

20 25 30

Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val Tyr Lys Lys  
35 40 45

Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile Ala Lys Pro  
50 55 60

Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu Val  
65 70 75 80

Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser His Pro Val  
85 90 95

Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser Glu Gly Ala  
100 105 110

[0010]

Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys Val  
115 120 125

Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu Asn  
130 135 140

Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser Tyr Leu Ser  
145 150 155 160

His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala Leu  
165 170 175

Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr Gln Thr Leu  
180 185 190

His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser Trp

195                      200                      205

His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp Ala Ala Ser  
210                      215                      220

Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr Val Asn Arg  
225                      230                      235                      240

Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val Tyr Trp His  
245                      250                      255

Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile Phe Leu Glu  
260                      265                      270

Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser Leu Glu Ile  
275                      280                      285

[0011]

Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met Asp Leu Gly  
290                      295                      300

Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His Asp Gly Met  
305                      310                      315                      320

Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro Gln Leu Arg  
325                      330                      335

Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp Leu Thr Asp  
340                      345                      350

Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser Pro Ser Phe  
355                      360                      365

Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr Trp Val His

370                      375                      380

Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro Leu Val Leu  
385                      390                      395                      400

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

Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met Ala Tyr Thr  
420                      425                      430

Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu Ser Gly Ile  
435                      440                      445

Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu Leu Ile Ile  
450                      455                      460

[0012]

Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile  
465                      470                      475                      480

Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys Gly Val Lys  
485                      490                      495

His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe Lys Tyr Lys  
500                      505                      510

Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys  
515                      520                      525

Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg Asp Leu Ala  
530                      535                      540

Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Val Asp

545                      550                      555                      560  
 Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val Ile Leu Phe  
                                  565                      570                      575  
 Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu Asn Ile Gln  
                                  580                      585                      590  
 Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp Pro Glu Phe  
                                  595                      600                      605  
 Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val Phe Asp Ser  
                                  610                      615                      620  
 Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp Tyr Ile Leu  
 625                      630                      635                      640  
 [0013]  
 Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr  
                                  645                      650                      655  
 Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro  
                                  660                      665                      670  
 Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu Trp  
                                  675                      680                      685  
 Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly Met Thr Ala  
                                  690                      695                      700  
 Leu Leu Lys Val Ser Ser Cys Asp Lys Glu Ile Thr Arg Thr Thr Leu  
 705                      710                      715                      720  
 Gln Ser Asp Gln Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu

725 730 735

Met Lys Lys Glu Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser  
740 745 750

Pro Arg Ser Phe Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val  
755 760 765

Glu Arg Leu Trp Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg  
770 775 780

Asn Arg Ala Gln Ser Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe  
785 790 795 800

Gln Glu Phe Thr Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu  
805 810 815

[0014]

Leu Asn Glu His Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val  
820 825 830

Glu Asp Asn Ile Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr  
835 840 845

Ser Phe Tyr Ser Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly  
850 855 860

Ala Glu Pro Arg Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr  
865 870 875 880

Phe Trp Lys Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp  
885 890 895

Cys Lys Ala Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val

900 905 910

His Ser Gly Leu Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu

915 920 925

Asn Pro Ala His Gly Arg Gln Val Thr Val Gln Glu Phe Ala Leu Phe

930 935 940

Phe Thr Ile Phe Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu Asn Met

945 950 955 960

Glu Arg Asn Cys Arg Ala Pro Cys Asn Ile Gln Met Glu Asp Pro Thr

965 970 975

Phe Lys Glu Asn Tyr Arg Phe His Ala Ile Asn Gly Tyr Ile Met Asp

980 985 990

[0015]

Thr Leu Pro Gly Leu Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr

995 1000 1005

Leu Leu Ser Met Gly Ser Asn Glu Asn Ile His Ser Ile His Phe

1010 1015 1020

Ser Gly His Val Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met

1025 1030 1035

Ala Leu Tyr Asn Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met

1040 1045 1050

Leu Pro Ser Lys Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly

1055 1060 1065

Glu His Leu His Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser

1070	1075	1080
Asn Lys Cys Gln Thr Pro Leu	Gly Met Ala Ser Gly	His Ile Arg
1085	1090	1095
Asp Phe Gln Ile Thr Ala Ser	Gly Gln Tyr Gly Gln	Trp Ala Pro
1100	1105	1110
Lys Leu Ala Arg Leu His Tyr	Ser Gly Ser Ile Asn	Ala Trp Ser
1115	1120	1125
Thr Lys Glu Pro Phe Ser Trp	Ile Lys Val Asp Leu	Leu Ala Pro
1130	1135	1140
Met Ile Ile His Gly Ile Lys	Thr Gln Gly Ala Arg	Gln Lys Phe
1145	1150	1155
[0016]		
Ser Ser Leu Tyr Ile Ser Gln	Phe Ile Ile Met Tyr	Ser Leu Asp
1160	1165	1170
Gly Lys Lys Trp Gln Thr Tyr	Arg Gly Asn Ser Thr	Gly Thr Leu
1175	1180	1185
Met Val Phe Phe Gly Asn Val	Asp Ser Ser Gly Ile	Lys His Asn
1190	1195	1200
Ile Phe Asn Pro Pro Ile Ile	Ala Arg Tyr Ile Arg	Leu His Pro
1205	1210	1215
Thr His Tyr Ser Ile Arg Ser	Thr Leu Arg Met Glu	Leu Met Gly
1220	1225	1230
Cys Asp Leu Asn Ser Cys Ser	Met Pro Leu Gly Met	Glu Ser Lys

1235                      1240                      1245

Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn

1250                      1255                      1260

Met Phe Ala Thr Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln

1265                      1270                      1275

Gly Arg Ser Asn Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu

1280                      1285                      1290

Trp Leu Gln Val Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val

1295                      1300                      1305

Thr Thr Gln Gly Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys

1310                      1315                      1320

[0017]

Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu

1325                      1330                      1335

Phe Phe Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp

1340                      1345                      1350

Ser Phe Thr Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr

1355                      1360                      1365

Arg Tyr Leu Arg Ile His Pro Gln Ser Trp Val His Gln Ile Ala

1370                      1375                      1380

Leu Arg Met Glu Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr

1385                      1390                      1395

<210> 3

&lt;211&gt; 1397

&lt;212&gt; PRT

&lt;213&gt; 家犬

&lt;400&gt; 3

Ala Thr Arg Lys Tyr Tyr Leu Gly Ala Val Glu Leu Ser Trp Asp Tyr  
 1                    5                    10                    15

Met Gln Ser Asp Leu Leu Ser Ala Leu His Ala Asp Thr Ser Phe Ser  
                   20                    25                    30

Ser Arg Val Pro Gly Ser Leu Pro Leu Thr Thr Ser Val Thr Tyr Arg  
                   35                    40                    45

Lys Thr Val Phe Val Glu Phe Thr Asp Asp Leu Phe Asn Ile Ala Lys  
                   50                    55                    60

[0018]

Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu  
 65                    70                    75                    80

Val Tyr Asp Thr Val Val Ile Val Leu Lys Asn Met Ala Ser His Pro  
                   85                    90                    95

Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser Glu Gly  
                   100                    105                    110

Ala Glu Tyr Glu Asp Gln Thr Ser Gln Lys Glu Lys Glu Asp Asp Asn  
                   115                    120                    125

Val Ile Pro Gly Glu Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu  
                   130                    135                    140

Asn Gly Pro Met Ala Ser Asp Pro Pro Cys Leu Thr Tyr Ser Tyr Phe  
 145                    150                    155                    160

Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala  
 165 170 175

Leu Leu Val Cys Lys Glu Gly Ser Leu Ala Lys Glu Arg Thr Gln Thr  
 180 185 190

Leu Gln Glu Phe Val Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser  
 195 200 205

Trp His Ser Glu Thr Asn Ala Ser Leu Thr Gln Ala Glu Ala Gln His  
 210 215 220

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

[0019] Thr Val Cys His Lys Arg Ser Val Tyr Trp His Val Ile Gly Met Gly  
 245 250 255

Thr Thr Pro Glu Val His Ser Ile Phe Leu Glu Gly His Thr Phe Leu  
 260 265 270

Val Arg Asn His Arg Gln Ala Ser Leu Glu Ile Ser Pro Ile Thr Phe  
 275 280 285

Leu Thr Ala Gln Thr Phe Leu Met Asp Leu Gly Gln Phe Leu Leu Phe  
 290 295 300

Cys His Ile Pro Ser His Gln His Asp Gly Met Glu Ala Tyr Val Lys  
 305 310 315 320

Val Asp Ser Cys Pro Glu Glu Pro Gln Leu Arg Met Lys Asn Asn Glu  
 325 330 335

Asp Lys Asp Tyr Asp Asp Gly Leu Tyr Asp Ser Asp Met Asp Val Val  
 340 345 350

Ser Phe Asp Asp Asp Ser Ser Ser Pro Phe Ile Gln Ile Arg Ser Val  
 355 360 365

Ala Lys Lys His Pro Lys Thr Trp Val His Tyr Ile Ala Ala Glu Glu  
 370 375 380

Glu Asp Trp Asp Tyr Ala Pro Ser Gly Pro Thr Pro Asn Asp Arg Ser  
 385 390 395 400

His Lys Asn Leu Tyr Leu Asn Asn Gly Pro Gln Arg Ile Gly Lys Lys  
 405 410 415

[0020] Tyr Lys Lys Val Arg Phe Val Ala Tyr Thr Asp Glu Thr Phe Lys Thr  
 420 425 430

Arg Glu Ala Ile Gln Tyr Glu Ser Gly Ile Leu Gly Pro Leu Leu Tyr  
 435 440 445

Gly Glu Val Gly Asp Thr Leu Leu Ile Ile Phe Lys Asn Gln Ala Ser  
 450 455 460

Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile Asn Tyr Val Thr Pro Leu  
 465 470 475 480

His Thr Gly Arg Leu Pro Lys Gly Val Lys His Leu Lys Asp Met Pro  
 485 490 495

Ile Leu Pro Gly Glu Ile Phe Lys Tyr Lys Trp Thr Val Thr Val Glu  
 500 505 510

Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys Leu Thr Arg Tyr Tyr Ser  
515 520 525

Ser Phe Ile Asn Leu Glu Arg Asp Leu Ala Ser Gly Leu Ile Gly Pro  
530 535 540

Leu Leu Ile Cys Tyr Lys Glu Ser Val Asp Gln Arg Gly Asn Gln Met  
545 550 555 560

Met Ser Asp Lys Arg Asn Val Ile Leu Phe Ser Val Phe Asp Glu Asn  
565 570 575

Arg Ser Trp Tyr Leu Thr Glu Asn Met Gln Arg Phe Leu Pro Asn Ala  
580 585 590

[0021] Asp Val Val Gln Pro His Asp Pro Glu Phe Gln Leu Ser Asn Ile Met  
595 600 605

His Ser Ile Asn Gly Tyr Val Phe Asp Asn Leu Gln Leu Ser Val Cys  
610 615 620

Leu His Glu Val Ala Tyr Trp Tyr Ile Leu Ser Val Gly Ala Gln Thr  
625 630 635 640

Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr Thr Phe Lys His Lys Met  
645 650 655

Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro Phe Ser Gly Glu Thr Val  
660 665 670

Phe Met Ser Met Glu Asn Pro Gly Leu Trp Val Leu Gly Cys His Asn  
675 680 685

Ser Asp Phe Arg Asn Phe Val Ile Ile Ile Asn Arg Gly Met Thr Ala  
690 695 700

Leu Leu Lys Val Ser Ser Cys Asn Arg Glu Ile Thr Val Thr Thr Leu  
705 710 715 720

Gln Pro Glu Glu Asp Lys Phe Glu Tyr Asp Asp Thr Phe Ser Ile Glu  
725 730 735

Met Lys Arg Glu Asp Phe Asp Ile Tyr Gly Asp Tyr Glu Asn Gln Gly  
740 745 750

Leu Arg Ser Phe Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val  
755 760 765

[0022] Glu Arg Leu Trp Asp Tyr Gly Met Ser Arg Ser Pro His Ile Leu Arg  
770 775 780

Asn Arg Ala Gln Ser Gly Asp Val Gln Gln Phe Lys Lys Val Val Phe  
785 790 795 800

Gln Glu Phe Thr Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu  
805 810 815

Leu Asn Glu His Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val  
820 825 830

Glu Asp Asn Ile Val Val Thr Phe Lys Asn Gln Ala Ser Arg Pro Tyr  
835 840 845

Ser Phe Tyr Ser Ser Leu Ile Ser Tyr Asp Glu Asp Glu Gly Gln Gly  
850 855 860

Ala Glu Pro Arg Arg Lys Phe Val Asn Pro Asn Glu Thr Lys Ile Tyr  
865 870 875 880

Phe Trp Lys Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp  
885 890 895

Cys Lys Ala Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val  
900 905 910

His Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Arg Ser Asn Thr Leu  
915 920 925

Asn Pro Ala His Gly Arg Gln Val Thr Val Gln Glu Phe Ala Leu Val  
930 935 940

[0023] Phe Thr Ile Phe Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu Asn Leu  
945 950 955 960

Glu Arg Asn Cys Arg Ala Pro Cys Asn Val Gln Lys Glu Asp Pro Thr  
965 970 975

Leu Lys Glu Asn Phe Arg Phe His Ala Ile Asn Gly Tyr Val Lys Asp  
980 985 990

Thr Leu Pro Gly Leu Val Met Ala Gln Asp Gln Lys Val Arg Trp Tyr  
995 1000 1005

Leu Leu Ser Met Gly Ser Asn Glu Asn Ile His Ser Ile His Phe  
1010 1015 1020

Ser Gly His Val Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met  
1025 1030 1035

Ala Val Tyr Asn Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met  
1040 1045 1050

Leu Pro Ser Gln Val Gly Ile Trp Arg Ile Glu Cys Leu Ile Gly  
1055 1060 1065

Glu His Leu Gln Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser  
1070 1075 1080

Lys Lys Cys Gln Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg  
1085 1090 1095

Asp Phe Gln Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro  
1100 1105 1110

[0024] Lys Leu Ala Arg Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser  
1115 1120 1125

Thr Lys Asp Pro Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro  
1130 1135 1140

Met Ile Ile His Gly Ile Met Thr Gln Gly Ala Arg Gln Lys Phe  
1145 1150 1155

Ser Ser Leu Tyr Val Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp  
1160 1165 1170

Gly Asn Lys Trp His Ser Tyr Arg Gly Asn Ser Thr Gly Thr Leu  
1175 1180 1185

Met Val Phe Phe Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn  
1190 1195 1200

Ile Phe Asn Pro Pro Ile Ile Ala Gln Tyr Ile Arg Leu His Pro  
1205 1210 1215

Thr His Tyr Ser Ile Arg Ser Thr Leu Arg Met Glu Leu Leu Gly  
1220 1225 1230

Cys Asp Phe Asn Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys  
1235 1240 1245

Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser Ser Tyr Leu Ser Ser  
1250 1255 1260

Met Leu Ala Thr Trp Ser Pro Ser Gln Ala Arg Leu His Leu Gln  
1265 1270 1275

[0025] Gly Arg Thr Asn Ala Trp Arg Pro Gln Ala Asn Asn Pro Lys Glu  
1280 1285 1290

Trp Leu Gln Val Asp Phe Arg Lys Thr Met Lys Val Thr Gly Ile  
1295 1300 1305

Thr Thr Gln Gly Val Lys Ser Leu Leu Ile Ser Met Tyr Val Lys  
1310 1315 1320

Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly His Asn Trp Thr Leu  
1325 1330 1335

Phe Leu Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn Arg Asp  
1340 1345 1350

Ser Ser Thr Pro Val Arg Asn Arg Leu Glu Pro Pro Leu Val Ala  
1355 1360 1365

Arg Tyr Val Arg Leu His Pro Gln Ser Trp Ala His His Ile Ala  
 1370 1375 1380

Leu Arg Leu Glu Val Leu Gly Cys Asp Thr Gln Gln Pro Ala  
 1385 1390 1395

<210> 4  
 <211> 24  
 <212> PRT  
 <213> 野豬

<400> 4

Ser Phe Ala Gln Asn Ser Arg Pro Pro Ser Ala Ser Ala Pro Lys Pro  
 1 5 10 15

Pro Val Leu Arg Arg His Gln Arg  
 20

[0026]

<210> 5  
 <211> 24  
 <212> PRT  
 <213> 智人

<400> 5

Ser Phe Ser Gln Asn Ser Arg His Pro Ser Thr Arg Ser Gln Asn Pro  
 1 5 10 15

Pro Val Leu Lys Arg His Gln Arg  
 20

<210> 6  
 <211> 24  
 <212> PRT  
 <213> 家犬

&lt;400&gt; 6

Ser Phe Ser Gln Asn Ser Arg His Pro Ser Thr Lys Ser Gln Asn Pro  
 1                    5                    10                    15

Pro Val Ser Lys His His Gln Arg  
 20

&lt;210&gt; 7

&lt;211&gt; 2114

&lt;212&gt; PRT

&lt;213&gt; 野豬

&lt;400&gt; 7

Ala Ile Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser Trp Asp Tyr  
 1                    5                    10                    15

[0027] Arg Gln Ser Glu Leu Leu Arg Glu Leu His Val Asp Thr Arg Phe Pro  
                   20                    25                    30

Ala Thr Ala Pro Gly Ala Leu Pro Leu Gly Pro Ser Val Leu Tyr Lys  
 35                    40                    45

Lys Thr Val Phe Val Glu Phe Thr Asp Gln Leu Phe Ser Val Ala Arg  
 50                    55                    60

Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu  
 65                    70                    75                    80

Val Tyr Asp Thr Val Val Val Thr Leu Lys Asn Met Ala Ser His Pro  
                   85                    90                    95

Val Ser Leu His Ala Val Gly Val Ser Phe Trp Lys Ser Ser Glu Gly  
                   100                    105                    110

Ala Glu Tyr Glu Asp His Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys  
 115 120 125

Val Leu Pro Gly Lys Ser Gln Thr Tyr Val Trp Gln Val Leu Lys Glu  
 130 135 140

Asn Gly Pro Thr Ala Ser Asp Pro Pro Cys Leu Thr Tyr Ser Tyr Leu  
 145 150 155 160

Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala  
 165 170 175

Leu Leu Val Cys Arg Glu Gly Ser Leu Thr Arg Glu Arg Thr Gln Asn  
 180 185 190

[0028] Leu His Glu Phe Val Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser  
 195 200 205

Trp His Ser Ala Arg Asn Asp Ser Trp Thr Arg Ala Met Asp Pro Ala  
 210 215 220

Pro Ala Arg Ala Gln Pro Ala Met His Thr Val Asn Gly Tyr Val Asn  
 225 230 235 240

Arg Ser Leu Pro Gly Leu Ile Gly Cys His Lys Lys Ser Val Tyr Trp  
 245 250 255

His Val Ile Gly Met Gly Thr Ser Pro Glu Val His Ser Ile Phe Leu  
 260 265 270

Glu Gly His Thr Phe Leu Val Arg His His Arg Gln Ala Ser Leu Glu  
 275 280 285

Ile Ser Pro Leu Thr Phe Leu Thr Ala Gln Thr Phe Leu Met Asp Leu  
290 295 300

Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His His His Gly Gly  
305 310 315 320

Met Glu Ala His Val Arg Val Glu Ser Cys Ala Glu Glu Pro Gln Leu  
325 330 335

Arg Arg Lys Ala Asp Glu Glu Glu Asp Tyr Asp Asp Asn Leu Tyr Asp  
340 345 350

Ser Asp Met Asp Val Val Arg Leu Asp Gly Asp Asp Val Ser Pro Phe  
355 360 365

[0029] Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr Trp Val His  
370 375 380

Tyr Ile Ser Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro Ala Val Pro  
385 390 395 400

Ser Pro Ser Asp Arg Ser Tyr Lys Ser Leu Tyr Leu Asn Ser Gly Pro  
405 410 415

Gln Arg Ile Gly Arg Lys Tyr Lys Lys Ala Arg Phe Val Ala Tyr Thr  
420 425 430

Asp Val Thr Phe Lys Thr Arg Lys Ala Ile Pro Tyr Glu Ser Gly Ile  
435 440 445

Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu Leu Ile Ile  
450 455 460

Phe Lys Asn Lys Ala Ser Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile  
465                      470                      475                      480

Thr Asp Val Ser Ala Leu His Pro Gly Arg Leu Leu Lys Gly Trp Lys  
                                 485                      490                      495

His Leu Lys Asp Met Pro Ile Leu Pro Gly Glu Thr Phe Lys Tyr Lys  
                                 500                      505                      510

Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys  
                                 515                      520                      525

Leu Thr Arg Tyr Tyr Ser Ser Ser Ile Asn Leu Glu Lys Asp Leu Ala  
                                 530                      535                      540

[0030] Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Val Asp  
545                      550                      555                      560

Gln Arg Gly Asn Gln Met Met Ser Asp Lys Arg Asn Val Ile Leu Phe  
                                 565                      570                      575

Ser Val Phe Asp Glu Asn Gln Ser Trp Tyr Leu Ala Glu Asn Ile Gln  
                                 580                      585                      590

Arg Phe Leu Pro Asn Pro Asp Gly Leu Gln Pro Gln Asp Pro Glu Phe  
                                 595                      600                      605

Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val Phe Asp Ser  
                                 610                      615                      620

Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp Tyr Ile Leu  
625                      630                      635                      640

Ser Val Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr  
645 650 655

Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro  
660 665 670

Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu Trp  
675 680 685

Val Leu Gly Cys His Asn Ser Asp Leu Arg Asn Arg Gly Met Thr Ala  
690 695 700

Leu Leu Lys Val Tyr Ser Cys Asp Arg Asp Ile Gly Asp Tyr Tyr Asp  
705 710 715 720

[0031] Asn Thr Tyr Glu Asp Ile Pro Gly Phe Leu Leu Ser Gly Lys Asn Val  
725 730 735

Ile Glu Pro Arg Ser Phe Ala Gln Asn Ser Arg Pro Pro Ser Ala Ser  
740 745 750

Gln Lys Gln Phe Gln Thr Ile Thr Ser Pro Glu Asp Asp Val Glu Leu  
755 760 765

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

Pro Ser Gly Asp Gly Ser Met Leu Leu Gly Gln Asn Pro Ala Pro His  
785 790 795 800

Gly Ser Ser Ser Ser Asp Leu Gln Glu Ala Arg Asn Glu Ala Asp Asp  
805 810 815

Tyr Leu Pro Gly Ala Arg Glu Arg Asn Thr Ala Pro Ser Ala Ala Ala  
820 825 830

Arg Leu Arg Pro Glu Leu His His Ser Ala Glu Arg Val Leu Thr Pro  
835 840 845

Glu Pro Glu Lys Glu Leu Lys Lys Leu Asp Ser Lys Met Ser Ser Ser  
850 855 860

Ser Asp Leu Leu Lys Thr Ser Pro Thr Ile Pro Ser Asp Thr Leu Ser  
865 870 875 880

Ala Glu Thr Glu Arg Thr His Ser Leu Gly Pro Pro His Pro Gln Val  
885 890 895

[0032] Asn Phe Arg Ser Gln Leu Gly Ala Ile Val Leu Gly Lys Asn Ser Ser  
900 905 910

His Phe Ile Gly Ala Gly Val Pro Leu Gly Ser Thr Glu Glu Asp His  
915 920 925

Glu Ser Ser Leu Gly Glu Asn Val Ser Pro Val Glu Ser Asp Gly Ile  
930 935 940

Phe Glu Lys Glu Arg Ala His Gly Pro Ala Ser Leu Thr Lys Asp Asp  
945 950 955 960

Val Leu Phe Lys Val Asn Ile Ser Leu Val Lys Thr Asn Lys Ala Arg  
965 970 975

Val Tyr Leu Lys Thr Asn Arg Lys Ile His Ile Asp Asp Ala Ala Leu  
980 985 990

Leu Thr Glu Asn Arg Ala Ser Ala Thr Phe Met Asp Lys Asn Thr Thr  
 995 1000 1005

Ala Ser Gly Leu Asn His Val Ser Asn Trp Ile Lys Gly Pro Leu  
 1010 1015 1020

Gly Lys Asn Pro Leu Ser Ser Glu Arg Gly Pro Ser Pro Glu Leu  
 1025 1030 1035

Leu Thr Ser Ser Gly Ser Gly Lys Ser Val Lys Gly Gln Ser Ser  
 1040 1045 1050

Gly Gln Gly Arg Ile Arg Val Ala Val Glu Glu Glu Glu Leu Ser  
 1055 1060 1065

[0033] Lys Gly Lys Glu Met Met Leu Pro Asn Ser Glu Leu Thr Phe Leu  
 1070 1075 1080

Thr Asn Ser Ala Asp Val Gln Gly Asn Asp Thr His Ser Gln Gly  
 1085 1090 1095

Lys Lys Ser Arg Glu Glu Met Glu Arg Arg Glu Lys Leu Val Gln  
 1100 1105 1110

Glu Lys Val Asp Leu Pro Gln Val Tyr Thr Ala Thr Gly Thr Lys  
 1115 1120 1125

Asn Phe Leu Arg Asn Ile Phe His Gln Ser Thr Glu Pro Ser Val  
 1130 1135 1140

Glu Gly Phe Asp Gly Gly Ser His Ala Pro Val Pro Gln Asp Ser  
 1145 1150 1155

	Arg Ser	Leu Asn Asp Ser Ala	Glu Arg Ala Glu Thr	His Ile Ala
	1160	1165	1170	
	His Phe	Ser Ala Ile Arg Glu	Glu Ala Pro Leu Glu	Ala Pro Gly
	1175	1180	1185	
	Asn Arg	Thr Gly Pro Gly Pro	Arg Ser Ala Val Pro	Arg Arg Val
	1190	1195	1200	
	Lys Gln	Ser Leu Lys Gln Ile	Arg Leu Pro Leu Glu	Glu Ile Lys
	1205	1210	1215	
	Pro Glu	Arg Gly Val Val Leu	Asn Ala Thr Ser Thr	Arg Trp Ser
	1220	1225	1230	
[0034]	Glu Ser	Ser Pro Ile Leu Gln	Gly Ala Lys Arg Asn	Asn Leu Ser
	1235	1240	1245	
	Leu Pro	Phe Leu Thr Leu Glu	Met Ala Gly Gly Gln	Gly Lys Ile
	1250	1255	1260	
	Ser Ala	Leu Gly Lys Ser Ala	Ala Gly Pro Leu Ala	Ser Gly Lys
	1265	1270	1275	
	Leu Glu	Lys Ala Val Leu Ser	Ser Ala Gly Leu Ser	Glu Ala Ser
	1280	1285	1290	
	Gly Lys	Ala Glu Phe Leu Pro	Lys Val Arg Val His	Arg Glu Asp
	1295	1300	1305	
	Leu Leu	Pro Gln Lys Thr Ser	Asn Val Ser Cys Ala	His Gly Asp
	1310	1315	1320	

	Leu Gly	Gln Glu Ile Phe Leu	Gln Lys Thr Arg Gly	Pro Val Asn
	1325	1330	1335	
	Leu Asn	Lys Val Asn Arg Pro	Gly Arg Thr Pro Ser	Lys Leu Leu
	1340	1345	1350	
	Gly Pro	Pro Met Pro Lys Glu	Trp Glu Ser Leu Glu	Lys Ser Pro
	1355	1360	1365	
	Lys Ser	Thr Ala Leu Arg Thr	Lys Asp Ile Ile Ser	Leu Pro Leu
	1370	1375	1380	
	Asp Arg	His Glu Ser Asn His	Ser Ile Ala Ala Lys	Asn Glu Gly
	1385	1390	1395	
[0035]	Gln Ala	Glu Thr Gln Arg Glu	Ala Ala Trp Thr Lys	Gln Gly Gly
	1400	1405	1410	
	Pro Gly	Arg Leu Cys Ala Pro	Lys Pro Pro Val Leu	Arg Arg His
	1415	1420	1425	
	Gln Arg	Asp Ile Ser Leu Pro	Thr Phe Gln Pro Glu	Glu Asp Lys
	1430	1435	1440	
	Met Asp	Tyr Asp Asp Ile Phe	Ser Thr Glu Thr Lys	Gly Glu Asp
	1445	1450	1455	
	Phe Asp	Ile Tyr Gly Glu Asp	Glu Asn Gln Asp Pro	Arg Ser Phe
	1460	1465	1470	
	Gln Lys	Arg Thr Arg His Tyr	Phe Ile Ala Ala Val	Glu Gln Leu
	1475	1480	1485	

	Trp Asp	Tyr Gly Met Ser Glu	Ser Pro Arg Ala Leu	Arg Asn Arg
	1490	1495	1500	
	Ala Gln	Asn Gly Glu Val Pro	Arg Phe Lys Lys Val	Val Phe Arg
	1505	1510	1515	
	Glu Phe	Ala Asp Gly Ser Phe	Thr Gln Pro Ser Tyr	Arg Gly Glu
	1520	1525	1530	
	Leu Asn	Lys His Leu Gly Leu	Leu Gly Pro Tyr Ile	Arg Ala Glu
	1535	1540	1545	
	Val Glu	Asp Asn Ile Met Val	Thr Phe Lys Asn Gln	Ala Ser Arg
	1550	1555	1560	
[0036]	Pro Tyr	Ser Phe Tyr Ser Ser	Leu Ile Ser Tyr Pro	Asp Asp Gln
	1565	1570	1575	
	Glu Gln	Gly Ala Glu Pro Arg	His Asn Phe Val Gln	Pro Asn Glu
	1580	1585	1590	
	Thr Arg	Thr Tyr Phe Trp Lys	Val Gln His His Met	Ala Pro Thr
	1595	1600	1605	
	Glu Asp	Glu Phe Asp Cys Lys	Ala Trp Ala Tyr Phe	Ser Asp Val
	1610	1615	1620	
	Asp Leu	Glu Lys Asp Val His	Ser Gly Leu Ile Gly	Pro Leu Leu
	1625	1630	1635	
	Ile Cys	Arg Ala Asn Thr Leu	Asn Ala Ala His Gly	Arg Gln Val
	1640	1645	1650	

	Thr Val	Gln Glu Phe Ala Leu	Phe Phe Thr Ile Phe	Asp Glu Thr
	1655	1660	1665	
	Lys Ser	Trp Tyr Phe Thr Glu	Asn Val Glu Arg Asn	Cys Arg Ala
	1670	1675	1680	
	Pro Cys	His Leu Gln Met Glu	Asp Pro Thr Leu Lys	Glu Asn Tyr
	1685	1690	1695	
	Arg Phe	His Ala Ile Asn Gly	Tyr Val Met Asp Thr	Leu Pro Gly
	1700	1705	1710	
	Leu Val	Met Ala Gln Asn Gln	Arg Ile Arg Trp Tyr	Leu Leu Ser
	1715	1720	1725	
[0037]	Met Gly	Ser Asn Glu Asn Ile	His Ser Ile His Phe	Ser Gly His
	1730	1735	1740	
	Val Phe	Ser Val Arg Lys Lys	Glu Glu Tyr Lys Met	Ala Val Tyr
	1745	1750	1755	
	Asn Leu	Tyr Pro Gly Val Phe	Glu Thr Val Glu Met	Leu Pro Ser
	1760	1765	1770	
	Lys Val	Gly Ile Trp Arg Ile	Glu Cys Leu Ile Gly	Glu His Leu
	1775	1780	1785	
	Gln Ala	Gly Met Ser Thr Thr	Phe Leu Val Tyr Ser	Lys Glu Cys
	1790	1795	1800	
	Gln Ala	Pro Leu Gly Met Ala	Ser Gly Arg Ile Arg	Asp Phe Gln
	1805	1810	1815	

Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala  
1820 1825 1830

Arg Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Asp  
1835 1840 1845

Pro His Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile  
1850 1855 1860

His Gly Ile Met Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu  
1865 1870 1875

Tyr Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Arg Asn  
1880 1885 1890

[0038] Trp Gln Ser Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe  
1895 1900 1905

Phe Gly Asn Val Asp Ala Ser Gly Ile Lys His Asn Ile Phe Asn  
1910 1915 1920

Pro Pro Ile Val Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr  
1925 1930 1935

Ser Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu  
1940 1945 1950

Asn Ser Cys Ser Met Pro Leu Gly Met Gln Asn Lys Ala Ile Ser  
1955 1960 1965

Asp Ser Gln Ile Thr Ala Ser Ser His Leu Ser Asn Ile Phe Ala  
1970 1975 1980

Thr Trp Ser Pro Ser Gln Ala Arg Leu His Leu Gln Gly Arg Thr  
 1985 1990 1995

Asn Ala Trp Arg Pro Arg Val Ser Ser Ala Glu Glu Trp Leu Gln  
 2000 2005 2010

Val Asp Leu Gln Lys Thr Val Lys Val Thr Gly Ile Thr Thr Gln  
 2015 2020 2025

Gly Val Lys Ser Leu Leu Ser Ser Met Tyr Val Lys Glu Phe Leu  
 2030 2035 2040

Val Ser Ser Ser Gln Asp Gly Arg Arg Trp Thr Leu Phe Leu Gln  
 2045 2050 2055

[0039] Asp Gly His Thr Lys Val Phe Gln Gly Asn Gln Asp Ser Ser Thr  
 2060 2065 2070

Pro Val Val Asn Ala Leu Asp Pro Pro Leu Phe Thr Arg Tyr Leu  
 2075 2080 2085

Arg Ile His Pro Thr Ser Trp Ala Gln His Ile Ala Leu Arg Leu  
 2090 2095 2100

Glu Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr  
 2105 2110

<210> 8

<211> 2332

<212> PRT

<213> 智人

<400> 8

Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser Trp Asp Tyr  
1                    5                    10                    15

Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg Phe Pro Pro  
                  20                    25                    30

Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val Tyr Lys Lys  
                  35                    40                    45

Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile Ala Lys Pro  
                  50                    55                    60

Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu Val  
65                    70                    75                    80

[0040] Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser His Pro Val  
                  85                    90                    95

Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser Glu Gly Ala  
                  100                    105                    110

Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys Val  
                  115                    120                    125

Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu Asn  
                  130                    135                    140

Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser Tyr Leu Ser  
145                    150                    155                    160

His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala Leu  
                  165                    170                    175

Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr Gln Thr Leu  
 180 185 190

His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser Trp  
 195 200 205

His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp Ala Ala Ser  
 210 215 220

Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr Val Asn Arg  
 225 230 235 240

Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val Tyr Trp His  
 245 250 255

[0041] Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile Phe Leu Glu  
 260 265 270

Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser Leu Glu Ile  
 275 280 285

Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met Asp Leu Gly  
 290 295 300

Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His Asp Gly Met  
 305 310 315 320

Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro Gln Leu Arg  
 325 330 335

Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp Leu Thr Asp  
 340 345 350

Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser Pro Ser Phe  
 355 360 365

Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr Trp Val His  
 370 375 380

Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro Leu Val Leu  
 385 390 395 400

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

Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met Ala Tyr Thr  
 420 425 430

[0042] Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu Ser Gly Ile  
 435 440 445

Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu Leu Ile Ile  
 450 455 460

Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile  
 465 470 475 480

Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys Gly Val Lys  
 485 490 495

His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe Lys Tyr Lys  
 500 505 510

Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys  
 515 520 525

Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg Asp Leu Ala  
 530 535 540

Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Val Asp  
 545 550 555 560

Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val Ile Leu Phe  
 565 570 575

Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu Asn Ile Gln  
 580 585 590

Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp Pro Glu Phe  
 595 600 605

[0043] Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val Phe Asp Ser  
 610 615 620

Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp Tyr Ile Leu  
 625 630 635 640

Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr  
 645 650 655

Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro  
 660 665 670

Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu Trp  
 675 680 685

Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly Met Thr Ala  
 690 695 700

Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp Tyr Tyr Glu  
705                      710                      715                      720

Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala  
                    725                      730                      735

Ile Glu Pro Arg Ser Phe Ser Gln Asn Ser Arg His Pro Ser Thr Arg  
                    740                      745                      750

Gln Lys Gln Phe Asn Ala Thr Thr Ile Pro Glu Asn Asp Ile Glu Lys  
                    755                      760                      765

Thr Asp Pro Trp Phe Ala His Arg Thr Pro Met Pro Lys Ile Gln Asn  
                    770                      775                      780

[0044] Val Ser Ser Ser Asp Leu Leu Met Leu Leu Arg Gln Ser Pro Thr Pro  
785                      790                      795                      800

His Gly Leu Ser Leu Ser Asp Leu Gln Glu Ala Lys Tyr Glu Thr Phe  
                    805                      810                      815

Ser Asp Asp Pro Ser Pro Gly Ala Ile Asp Ser Asn Asn Ser Leu Ser  
                    820                      825                      830

Glu Met Thr His Phe Arg Pro Gln Leu His His Ser Gly Asp Met Val  
                    835                      840                      845

Phe Thr Pro Glu Ser Gly Leu Gln Leu Arg Leu Asn Glu Lys Leu Gly  
                    850                      855                      860

Thr Thr Ala Ala Thr Glu Leu Lys Lys Leu Asp Phe Lys Val Ser Ser  
865                      870                      875                      880

Thr Ser Asn Asn Leu Ile Ser Thr Ile Pro Ser Asp Asn Leu Ala Ala  
885 890 895

Gly Thr Asp Asn Thr Ser Ser Leu Gly Pro Pro Ser Met Pro Val His  
900 905 910

Tyr Asp Ser Gln Leu Asp Thr Thr Leu Phe Gly Lys Lys Ser Ser Pro  
915 920 925

Leu Thr Glu Ser Gly Gly Pro Leu Ser Leu Ser Glu Glu Asn Asn Asp  
930 935 940

Ser Lys Leu Leu Glu Ser Gly Leu Met Asn Ser Gln Glu Ser Ser Trp  
945 950 955 960

[0045] Gly Lys Asn Val Ser Ser Thr Glu Ser Gly Arg Leu Phe Lys Gly Lys  
965 970 975

Arg Ala His Gly Pro Ala Leu Leu Thr Lys Asp Asn Ala Leu Phe Lys  
980 985 990

Val Ser Ile Ser Leu Leu Lys Thr Asn Lys Thr Ser Asn Asn Ser Ala  
995 1000 1005

Thr Asn Arg Lys Thr His Ile Asp Gly Pro Ser Leu Leu Ile Glu  
1010 1015 1020

Asn Ser Pro Ser Val Trp Gln Asn Ile Leu Glu Ser Asp Thr Glu  
1025 1030 1035

Phe Lys Lys Val Thr Pro Leu Ile His Asp Arg Met Leu Met Asp  
1040 1045 1050

	Lys Asn	Ala Thr Ala Leu Arg	Leu Asn His Met Ser	Asn Lys Thr
	1055	1060	1065	
	Thr Ser	Ser Lys Asn Met Glu	Met Val Gln Gln Lys	Lys Glu Gly
	1070	1075	1080	
	Pro Ile	Pro Pro Asp Ala Gln	Asn Pro Asp Met Ser	Phe Phe Lys
	1085	1090	1095	
	Met Leu	Phe Leu Pro Glu Ser	Ala Arg Trp Ile Gln	Arg Thr His
	1100	1105	1110	
	Gly Lys	Asn Ser Leu Asn Ser	Gly Gln Gly Pro Ser	Pro Lys Gln
	1115	1120	1125	
[0046]	Leu Val	Ser Leu Gly Pro Glu	Lys Ser Val Glu Gly	Gln Asn Phe
	1130	1135	1140	
	Leu Ser	Glu Lys Asn Lys Val	Val Val Gly Lys Gly	Glu Phe Thr
	1145	1150	1155	
	Lys Asp	Val Gly Leu Lys Glu	Met Val Phe Pro Ser	Ser Arg Asn
	1160	1165	1170	
	Leu Phe	Leu Thr Asn Leu Asp	Asn Leu His Glu Asn	Asn Thr His
	1175	1180	1185	
	Asn Gln	Glu Lys Lys Ile Gln	Glu Glu Ile Glu Lys	Lys Glu Thr
	1190	1195	1200	
	Leu Ile	Gln Glu Asn Val Val	Leu Pro Gln Ile His	Thr Val Thr
	1205	1210	1215	

	Gly Thr	Lys Asn Phe Met Lys	Asn Leu Phe Leu Leu	Ser Thr Arg
	1220	1225	1230	
	Gln Asn	Val Glu Gly Ser Tyr	Asp Gly Ala Tyr Ala	Pro Val Leu
	1235	1240	1245	
	Gln Asp	Phe Arg Ser Leu Asn	Asp Ser Thr Asn Arg	Thr Lys Lys
	1250	1255	1260	
	His Thr	Ala His Phe Ser Lys	Lys Gly Glu Glu Glu	Asn Leu Glu
	1265	1270	1275	
	Gly Leu	Gly Asn Gln Thr Lys	Gln Ile Val Glu Lys	Tyr Ala Cys
	1280	1285	1290	
[0047]	Thr Thr	Arg Ile Ser Pro Asn	Thr Ser Gln Gln Asn	Phe Val Thr
	1295	1300	1305	
	Gln Arg	Ser Lys Arg Ala Leu	Lys Gln Phe Arg Leu	Pro Leu Glu
	1310	1315	1320	
	Glu Thr	Glu Leu Glu Lys Arg	Ile Ile Val Asp Asp	Thr Ser Thr
	1325	1330	1335	
	Gln Trp	Ser Lys Asn Met Lys	His Leu Thr Pro Ser	Thr Leu Thr
	1340	1345	1350	
	Gln Ile	Asp Tyr Asn Glu Lys	Glu Lys Gly Ala Ile	Thr Gln Ser
	1355	1360	1365	
	Pro Leu	Ser Asp Cys Leu Thr	Arg Ser His Ser Ile	Pro Gln Ala
	1370	1375	1380	

	Asn Arg	Ser Pro Leu Pro Ile	Ala Lys Val Ser Ser	Phe Pro Ser
	1385	1390	1395	
	Ile Arg	Pro Ile Tyr Leu Thr	Arg Val Leu Phe Gln	Asp Asn Ser
	1400	1405	1410	
	Ser His	Leu Pro Ala Ala Ser	Tyr Arg Lys Lys Asp	Ser Gly Val
	1415	1420	1425	
	Gln Glu	Ser Ser His Phe Leu	Gln Gly Ala Lys Lys	Asn Asn Leu
	1430	1435	1440	
	Ser Leu	Ala Ile Leu Thr Leu	Glu Met Thr Gly Asp	Gln Arg Glu
	1445	1450	1455	
[0048]	Val Gly	Ser Leu Gly Thr Ser	Ala Thr Asn Ser Val	Thr Tyr Lys
	1460	1465	1470	
	Lys Val	Glu Asn Thr Val Leu	Pro Lys Pro Asp Leu	Pro Lys Thr
	1475	1480	1485	
	Ser Gly	Lys Val Glu Leu Leu	Pro Lys Val His Ile	Tyr Gln Lys
	1490	1495	1500	
	Asp Leu	Phe Pro Thr Glu Thr	Ser Asn Gly Ser Pro	Gly His Leu
	1505	1510	1515	
	Asp Leu	Val Glu Gly Ser Leu	Leu Gln Gly Thr Glu	Gly Ala Ile
	1520	1525	1530	
	Lys Trp	Asn Glu Ala Asn Arg	Pro Gly Lys Val Pro	Phe Leu Arg
	1535	1540	1545	

	Val Ala Thr Glu Ser Ser Ala	Lys Thr Pro Ser Lys	Leu Leu Asp
	1550	1555	1560
	Pro Leu Ala Trp Asp Asn His	Tyr Gly Thr Gln Ile	Pro Lys Glu
	1565	1570	1575
	Glu Trp Lys Ser Gln Glu Lys	Ser Pro Glu Lys Thr	Ala Phe Lys
	1580	1585	1590
	Lys Lys Asp Thr Ile Leu Ser	Leu Asn Ala Cys Glu	Ser Asn His
	1595	1600	1605
	Ala Ile Ala Ala Ile Asn Glu	Gly Gln Asn Lys Pro	Glu Ile Glu
	1610	1615	1620
[0049]	Val Thr Trp Ala Lys Gln Gly	Arg Thr Glu Arg Leu	Cys Ser Gln
	1625	1630	1635
	Asn Pro Pro Val Leu Lys Arg	His Gln Arg Glu Ile	Thr Arg Thr
	1640	1645	1650
	Thr Leu Gln Ser Asp Gln Glu	Glu Ile Asp Tyr Asp	Asp Thr Ile
	1655	1660	1665
	Ser Val Glu Met Lys Lys Glu	Asp Phe Asp Ile Tyr	Asp Glu Asp
	1670	1675	1680
	Glu Asn Gln Ser Pro Arg Ser	Phe Gln Lys Lys Thr	Arg His Tyr
	1685	1690	1695
	Phe Ile Ala Ala Val Glu Arg	Leu Trp Asp Tyr Gly	Met Ser Ser
	1700	1705	1710

	Ser Pro	His Val Leu Arg Asn	Arg Ala Gln Ser Gly	Ser Val Pro
	1715	1720	1725	
	Gln Phe	Lys Lys Val Val Phe	Gln Glu Phe Thr Asp	Gly Ser Phe
	1730	1735	1740	
	Thr Gln	Pro Leu Tyr Arg Gly	Glu Leu Asn Glu His	Leu Gly Leu
	1745	1750	1755	
	Leu Gly	Pro Tyr Ile Arg Ala	Glu Val Glu Asp Asn	Ile Met Val
	1760	1765	1770	
	Thr Phe	Arg Asn Gln Ala Ser	Arg Pro Tyr Ser Phe	Tyr Ser Ser
	1775	1780	1785	
[0050]	Leu Ile	Ser Tyr Glu Glu Asp	Gln Arg Gln Gly Ala	Glu Pro Arg
	1790	1795	1800	
	Lys Asn	Phe Val Lys Pro Asn	Glu Thr Lys Thr Tyr	Phe Trp Lys
	1805	1810	1815	
	Val Gln	His His Met Ala Pro	Thr Lys Asp Glu Phe	Asp Cys Lys
	1820	1825	1830	
	Ala Trp	Ala Tyr Phe Ser Asp	Val Asp Leu Glu Lys	Asp Val His
	1835	1840	1845	
	Ser Gly	Leu Ile Gly Pro Leu	Leu Val Cys His Thr	Asn Thr Leu
	1850	1855	1860	
	Asn Pro	Ala His Gly Arg Gln	Val Thr Val Gln Glu	Phe Ala Leu
	1865	1870	1875	

	Phe Phe	Thr Ile Phe Asp Glu	Thr Lys Ser Trp Tyr	Phe Thr Glu
	1880	1885	1890	
	Asn Met	Glu Arg Asn Cys Arg	Ala Pro Cys Asn Ile	Gln Met Glu
	1895	1900	1905	
	Asp Pro	Thr Phe Lys Glu Asn	Tyr Arg Phe His Ala	Ile Asn Gly
	1910	1915	1920	
	Tyr Ile	Met Asp Thr Leu Pro	Gly Leu Val Met Ala	Gln Asp Gln
	1925	1930	1935	
	Arg Ile	Arg Trp Tyr Leu Leu	Ser Met Gly Ser Asn	Glu Asn Ile
	1940	1945	1950	
[0051]	His Ser	Ile His Phe Ser Gly	His Val Phe Thr Val	Arg Lys Lys
	1955	1960	1965	
	Glu Glu	Tyr Lys Met Ala Leu	Tyr Asn Leu Tyr Pro	Gly Val Phe
	1970	1975	1980	
	Glu Thr	Val Glu Met Leu Pro	Ser Lys Ala Gly Ile	Trp Arg Val
	1985	1990	1995	
	Glu Cys	Leu Ile Gly Glu His	Leu His Ala Gly Met	Ser Thr Leu
	2000	2005	2010	
	Phe Leu	Val Tyr Ser Asn Lys	Cys Gln Thr Pro Leu	Gly Met Ala
	2015	2020	2025	
	Ser Gly	His Ile Arg Asp Phe	Gln Ile Thr Ala Ser	Gly Gln Tyr
	2030	2035	2040	

	Gly Gln	Trp Ala Pro Lys Leu	Ala Arg Leu His Tyr	Ser Gly Ser
	2045	2050	2055	
	Ile Asn	Ala Trp Ser Thr Lys	Glu Pro Phe Ser Trp	Ile Lys Val
	2060	2065	2070	
	Asp Leu	Leu Ala Pro Met Ile	Ile His Gly Ile Lys	Thr Gln Gly
	2075	2080	2085	
	Ala Arg	Gln Lys Phe Ser Ser	Leu Tyr Ile Ser Gln	Phe Ile Ile
	2090	2095	2100	
	Met Tyr	Ser Leu Asp Gly Lys	Lys Trp Gln Thr Tyr	Arg Gly Asn
	2105	2110	2115	
[0052]	Ser Thr	Gly Thr Leu Met Val	Phe Phe Gly Asn Val	Asp Ser Ser
	2120	2125	2130	
	Gly Ile	Lys His Asn Ile Phe	Asn Pro Pro Ile Ile	Ala Arg Tyr
	2135	2140	2145	
	Ile Arg	Leu His Pro Thr His	Tyr Ser Ile Arg Ser	Thr Leu Arg
	2150	2155	2160	
	Met Glu	Leu Met Gly Cys Asp	Leu Asn Ser Cys Ser	Met Pro Leu
	2165	2170	2175	
	Gly Met	Glu Ser Lys Ala Ile	Ser Asp Ala Gln Ile	Thr Ala Ser
	2180	2185	2190	
	Ser Tyr	Phe Thr Asn Met Phe	Ala Thr Trp Ser Pro	Ser Lys Ala
	2195	2200	2205	

Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp Arg Pro Gln Val  
 2210 2215 2220

Asn Asn Pro Lys Glu Trp Leu Gln Val Asp Phe Gln Lys Thr Met  
 2225 2230 2235

Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys Ser Leu Leu Thr  
 2240 2245 2250

Ser Met Tyr Val Lys Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly  
 2255 2260 2265

His Gln Trp Thr Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe  
 2270 2275 2280

[0053] Gln Gly Asn Gln Asp Ser Phe Thr Pro Val Val Asn Ser Leu Asp  
 2285 2290 2295

Pro Pro Leu Leu Thr Arg Tyr Leu Arg Ile His Pro Gln Ser Trp  
 2300 2305 2310

Val His Gln Ile Ala Leu Arg Met Glu Val Leu Gly Cys Glu Ala  
 2315 2320 2325

Gln Asp Leu Tyr  
 2330

<210> 9

<211> 2324

<212> PRT

<213> 家犬

<400> 9

Ala Thr Arg Lys Tyr Tyr Leu Gly Ala Val Glu Leu Ser Trp Asp Tyr  
1                    5                    10                    15

Met Gln Ser Asp Leu Leu Ser Ala Leu His Ala Asp Thr Ser Phe Ser  
                  20                    25                    30

Ser Arg Val Pro Gly Ser Leu Pro Leu Thr Thr Ser Val Thr Tyr Arg  
                  35                    40                    45

Lys Thr Val Phe Val Glu Phe Thr Asp Asp Leu Phe Asn Ile Ala Lys  
                  50                    55                    60

Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu  
65                    70                    75                    80

[0054] Val Tyr Asp Thr Val Val Ile Val Leu Lys Asn Met Ala Ser His Pro  
                  85                    90                    95

Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser Glu Gly  
                  100                    105                    110

Ala Glu Tyr Glu Asp Gln Thr Ser Gln Lys Glu Lys Glu Asp Asp Asn  
                  115                    120                    125

Val Ile Pro Gly Glu Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu  
                  130                    135                    140

Asn Gly Pro Met Ala Ser Asp Pro Pro Cys Leu Thr Tyr Ser Tyr Phe  
145                    150                    155                    160

Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala  
                  165                    170                    175

Leu Leu Val Cys Lys Glu Gly Ser Leu Ala Lys Glu Arg Thr Gln Thr  
 180 185 190

Leu Gln Glu Phe Val Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser  
 195 200 205

Trp His Ser Glu Thr Asn Ala Ser Leu Thr Gln Ala Glu Ala Gln His  
 210 215 220

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

Thr Val Cys His Lys Arg Ser Val Tyr Trp His Val Ile Gly Met Gly  
 245 250 255

[0055] Thr Thr Pro Glu Val His Ser Ile Phe Leu Glu Gly His Thr Phe Leu  
 260 265 270

Val Arg Asn His Arg Gln Ala Ser Leu Glu Ile Ser Pro Ile Thr Phe  
 275 280 285

Leu Thr Ala Gln Thr Phe Leu Met Asp Leu Gly Gln Phe Leu Leu Phe  
 290 295 300

Cys His Ile Pro Ser His Gln His Asp Gly Met Glu Ala Tyr Val Lys  
 305 310 315 320

Val Asp Ser Cys Pro Glu Glu Pro Gln Leu Arg Met Lys Asn Asn Glu  
 325 330 335

Asp Lys Asp Tyr Asp Asp Gly Leu Tyr Asp Ser Asp Met Asp Val Val  
 340 345 350

Ser Phe Asp Asp Asp Ser Ser Ser Pro Phe Ile Gln Ile Arg Ser Val  
 355 360 365

Ala Lys Lys His Pro Lys Thr Trp Val His Tyr Ile Ala Ala Glu Glu  
 370 375 380

Glu Asp Trp Asp Tyr Ala Pro Ser Gly Pro Thr Pro Asn Asp Arg Ser  
 385 390 395 400

His Lys Asn Leu Tyr Leu Asn Asn Gly Pro Gln Arg Ile Gly Lys Lys  
 405 410 415

Tyr Lys Lys Val Arg Phe Val Ala Tyr Thr Asp Glu Thr Phe Lys Thr  
 420 425 430

[0056] Arg Glu Ala Ile Gln Tyr Glu Ser Gly Ile Leu Gly Pro Leu Leu Tyr  
 435 440 445

Gly Glu Val Gly Asp Thr Leu Leu Ile Ile Phe Lys Asn Gln Ala Ser  
 450 455 460

Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile Asn Tyr Val Thr Pro Leu  
 465 470 475 480

His Thr Gly Arg Leu Pro Lys Gly Val Lys His Leu Lys Asp Met Pro  
 485 490 495

Ile Leu Pro Gly Glu Ile Phe Lys Tyr Lys Trp Thr Val Thr Val Glu  
 500 505 510

Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys Leu Thr Arg Tyr Tyr Ser  
 515 520 525

Ser Phe Ile Asn Leu Glu Arg Asp Leu Ala Ser Gly Leu Ile Gly Pro  
530 535 540

Leu Leu Ile Cys Tyr Lys Glu Ser Val Asp Gln Arg Gly Asn Gln Met  
545 550 555 560

Met Ser Asp Lys Arg Asn Val Ile Leu Phe Ser Val Phe Asp Glu Asn  
565 570 575

Arg Ser Trp Tyr Leu Thr Glu Asn Met Gln Arg Phe Leu Pro Asn Ala  
580 585 590

Asp Val Val Gln Pro His Asp Pro Glu Phe Gln Leu Ser Asn Ile Met  
595 600 605

[0057] His Ser Ile Asn Gly Tyr Val Phe Asp Asn Leu Gln Leu Ser Val Cys  
610 615 620

Leu His Glu Val Ala Tyr Trp Tyr Ile Leu Ser Val Gly Ala Gln Thr  
625 630 635 640

Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr Thr Phe Lys His Lys Met  
645 650 655

Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro Phe Ser Gly Glu Thr Val  
660 665 670

Phe Met Ser Met Glu Asn Pro Gly Leu Trp Val Leu Gly Cys His Asn  
675 680 685

Ser Asp Phe Arg Asn Arg Gly Met Thr Ala Leu Leu Lys Val Ser Ser  
690 695 700

Cys Asn Arg Asn Ile Asp Asp Tyr Tyr Glu Asp Thr Tyr Glu Asp Ile  
705                      710                      715                      720

Pro Thr Pro Leu Leu Asn Glu Asn Asn Val Ile Lys Pro Arg Ser Phe  
                                 725                      730                      735

Ser Gln Asn Ser Arg His Pro Ser Thr Lys Glu Lys Gln Leu Lys Ala  
                                 740                      745                      750

Thr Thr Thr Pro Glu Asn Asp Ile Glu Lys Ile Asp Leu Gln Ser Gly  
                                 755                      760                      765

Glu Arg Thr Gln Leu Ile Lys Ala Gln Ser Val Ser Ser Ser Asp Leu  
                                 770                      775                      780

[0058] Leu Met Leu Leu Gly Gln Asn Pro Thr Pro Arg Gly Leu Phe Leu Ser  
785                      790                      795                      800

Asp Leu Arg Glu Ala Thr Asp Arg Ala Asp Asp His Ser Arg Gly Ala  
                                 805                      810                      815

Ile Glu Arg Asn Lys Gly Pro Pro Glu Val Ala Ser Leu Arg Pro Glu  
                                 820                      825                      830

Leu Arg His Ser Glu Asp Arg Glu Phe Thr Pro Glu Pro Glu Leu Gln  
                                 835                      840                      845

Leu Arg Leu Asn Glu Asn Leu Gly Thr Asn Thr Thr Val Glu Leu Lys  
                                 850                      855                      860

Lys Leu Asp Leu Lys Ile Ser Ser Ser Ser Asp Ser Leu Met Thr Ser  
865                      870                      875                      880

Pro Thr Ile Pro Ser Asp Lys Leu Ala Ala Ala Thr Glu Lys Thr Gly  
885 890 895

Ser Leu Gly Pro Pro Asn Met Ser Val His Phe Asn Ser His Leu Gly  
900 905 910

Thr Ile Val Phe Gly Asn Asn Ser Ser His Leu Ile Gln Ser Gly Val  
915 920 925

Pro Leu Glu Leu Ser Glu Glu Asp Asn Asp Ser Lys Leu Leu Glu Ala  
930 935 940

Pro Leu Met Asn Ile Gln Glu Ser Ser Leu Arg Glu Asn Val Leu Ser  
945 950 955 960

[0059] Met Glu Ser Asn Arg Leu Phe Lys Glu Glu Arg Ile Arg Gly Pro Ala  
965 970 975

Ser Leu Ile Lys Asp Asn Ala Leu Phe Lys Val Asn Ile Ser Ser Val  
980 985 990

Lys Thr Asn Arg Ala Pro Val Asn Leu Thr Thr Asn Arg Lys Thr Arg  
995 1000 1005

Val Ala Ile Pro Thr Leu Leu Ile Glu Asn Ser Thr Ser Val Trp  
1010 1015 1020

Gln Asp Ile Met Leu Glu Arg Asn Thr Glu Phe Lys Glu Val Thr  
1025 1030 1035

Ser Leu Ile His Asn Glu Thr Phe Met Asp Arg Asn Thr Thr Ala  
1040 1045 1050

	Leu Gly	Leu Asn His Val Ser	Asn Lys Thr Thr Leu	Ser Lys Asn
	1055	1060	1065	
	Val Glu	Met Ala His Gln Lys	Lys Glu Asp Pro Val	Pro Leu Arg
	1070	1075	1080	
	Ala Glu	Asn Pro Asp Leu Ser	Ser Ser Lys Ile Pro	Phe Leu Pro
	1085	1090	1095	
	Asp Trp	Ile Lys Thr His Gly	Lys Asn Ser Leu Ser	Ser Glu Gln
	1100	1105	1110	
	Arg Pro	Ser Pro Lys Gln Leu	Thr Ser Leu Gly Ser	Glu Lys Ser
	1115	1120	1125	
[0060]	Val Lys	Asp Gln Asn Phe Leu	Ser Glu Glu Lys Val	Val Val Gly
	1130	1135	1140	
	Glu Asp	Glu Phe Thr Lys Asp	Thr Glu Leu Gln Glu	Ile Phe Pro
	1145	1150	1155	
	Asn Asn	Lys Ser Ile Phe Phe	Ala Asn Leu Ala Asn	Val Gln Glu
	1160	1165	1170	
	Asn Asp	Thr Tyr Asn Gln Glu	Lys Lys Ser Pro Glu	Glu Ile Glu
	1175	1180	1185	
	Arg Lys	Glu Lys Leu Thr Gln	Glu Asn Val Ala Leu	Pro Gln Ala
	1190	1195	1200	
	His Thr	Met Ile Gly Thr Lys	Asn Phe Leu Lys Asn	Leu Phe Leu
	1205	1210	1215	

Leu Ser Thr Lys Gln Asn Val Ala Gly Leu Glu Glu Gln Pro Tyr  
 1220 1225 1230

Thr Pro Ile Leu Gln Asp Thr Arg Ser Leu Asn Asp Ser Pro His  
 1235 1240 1245

Ser Glu Gly Ile His Met Ala Asn Phe Ser Lys Ile Arg Glu Glu  
 1250 1255 1260

Ala Asn Leu Glu Gly Leu Gly Asn Gln Thr Asn Gln Met Val Glu  
 1265 1270 1275

Arg Phe Pro Ser Thr Thr Arg Met Ser Ser Asn Ala Ser Gln His  
 1280 1285 1290

[0061] Val Ile Thr Gln Arg Gly Lys Arg Ser Leu Lys Gln Pro Arg Leu  
 1295 1300 1305

Ser Gln Gly Glu Ile Lys Phe Glu Arg Lys Val Ile Ala Asn Asp  
 1310 1315 1320

Thr Ser Thr Gln Trp Ser Lys Asn Met Asn Tyr Leu Ala Gln Gly  
 1325 1330 1335

Thr Leu Thr Gln Ile Glu Tyr Asn Glu Lys Glu Lys Arg Ala Ile  
 1340 1345 1350

Thr Gln Ser Pro Leu Ser Asp Cys Ser Met Arg Asn His Val Thr  
 1355 1360 1365

Ile Gln Met Asn Asp Ser Ala Leu Pro Val Ala Lys Glu Ser Ala  
 1370 1375 1380

	Ser Pro	Ser Val Arg His Thr	Asp Leu Thr Lys Ile	Pro Ser Gln
	1385	1390	1395	
	His Asn	Ser Ser His Leu Pro	Ala Ser Ala Cys Asn	Tyr Thr Phe
	1400	1405	1410	
	Arg Glu	Arg Thr Ser Gly Val	Gln Glu Gly Ser His	Phe Leu Gln
	1415	1420	1425	
	Glu Ala	Lys Arg Asn Asn Leu	Ser Leu Ala Phe Val	Thr Leu Gly
	1430	1435	1440	
	Ile Thr	Glu Gly Gln Gly Lys	Phe Ser Ser Leu Gly	Lys Ser Ala
	1445	1450	1455	
[0062]	Thr Asn	Gln Pro Met Tyr Lys	Lys Leu Glu Asn Thr	Val Leu Leu
	1460	1465	1470	
	Gln Pro	Gly Leu Ser Glu Thr	Ser Asp Lys Val Glu	Leu Leu Ser
	1475	1480	1485	
	Gln Val	His Val Asp Gln Glu	Asp Ser Phe Pro Thr	Lys Thr Ser
	1490	1495	1500	
	Asn Asp	Ser Pro Gly His Leu	Asp Leu Met Gly Lys	Ile Phe Leu
	1505	1510	1515	
	Gln Lys	Thr Gln Gly Pro Val	Lys Met Asn Lys Thr	Asn Ser Pro
	1520	1525	1530	
	Gly Lys	Val Pro Phe Leu Lys	Trp Ala Thr Glu Ser	Ser Glu Lys
	1535	1540	1545	

	Ile Pro	Ser Lys	Leu Leu	Gly	Val Leu	Ala Trp	Asp	Asn His	Tyr
	1550			1555			1560		
	Asp Thr	Gln Ile	Pro Ser	Glu	Glu Trp	Lys Ser	Gln	Lys Lys	Ser
	1565			1570			1575		
	Gln Thr	Asn Thr	Ala Phe	Lys	Arg Lys	Asp Thr	Ile	Leu Pro	Leu
	1580			1585			1590		
	Gly Pro	Cys Glu	Asn Asn	Asp	Ser Thr	Ala Ala	Ile	Asn Glu	Gly
	1595			1600			1605		
	Gln Asp	Lys Pro	Gln Arg	Glu	Ala Met	Trp Ala	Lys	Gln Gly	Glu
	1610			1615			1620		
[0063]	Pro Gly	Arg Leu	Cys Ser	Gln	Asn Pro	Pro Val	Ser	Lys His	His
	1625			1630			1635		
	Gln Arg	Glu Ile	Thr Val	Thr	Thr Leu	Gln Pro	Glu	Glu Asp	Lys
	1640			1645			1650		
	Phe Glu	Tyr Asp	Asp Thr	Phe	Ser Ile	Glu Met	Lys	Arg Glu	Asp
	1655			1660			1665		
	Phe Asp	Ile Tyr	Gly Asp	Tyr	Glu Asn	Gln Gly	Leu	Arg Ser	Phe
	1670			1675			1680		
	Gln Lys	Lys Thr	Arg His	Tyr	Phe Ile	Ala Ala	Val	Glu Arg	Leu
	1685			1690			1695		
	Trp Asp	Tyr Gly	Met Ser	Arg	Ser Pro	His Ile	Leu	Arg Asn	Arg
	1700			1705			1710		

	Ala Gln Ser Gly Asp Val Gln	Gln Phe Lys Lys Val	Val Phe Gln
	1715	1720	1725
	Glu Phe Thr Asp Gly Ser Phe	Thr Gln Pro Leu Tyr	Arg Gly Glu
	1730	1735	1740
	Leu Asn Glu His Leu Gly Leu	Leu Gly Pro Tyr Ile	Arg Ala Glu
	1745	1750	1755
	Val Glu Asp Asn Ile Val Val	Thr Phe Lys Asn Gln	Ala Ser Arg
	1760	1765	1770
	Pro Tyr Ser Phe Tyr Ser Ser	Leu Ile Ser Tyr Asp	Glu Asp Glu
	1775	1780	1785
[0064]	Gly Gln Gly Ala Glu Pro Arg	Arg Lys Phe Val Asn	Pro Asn Glu
	1790	1795	1800
	Thr Lys Ile Tyr Phe Trp Lys	Val Gln His His Met	Ala Pro Thr
	1805	1810	1815
	Lys Asp Glu Phe Asp Cys Lys	Ala Trp Ala Tyr Phe	Ser Asp Val
	1820	1825	1830
	Asp Leu Glu Lys Asp Val His	Ser Gly Leu Ile Gly	Pro Leu Leu
	1835	1840	1845
	Ile Cys Arg Ser Asn Thr Leu	Asn Pro Ala His Gly	Arg Gln Val
	1850	1855	1860
	Thr Val Gln Glu Phe Ala Leu	Val Phe Thr Ile Phe	Asp Glu Thr
	1865	1870	1875

	Lys Ser	Trp Tyr Phe Thr Glu	Asn Leu Glu Arg Asn	Cys Arg Ala
	1880	1885	1890	
	Pro Cys	Asn Val Gln Lys Glu	Asp Pro Thr Leu Lys	Glu Asn Phe
	1895	1900	1905	
	Arg Phe	His Ala Ile Asn Gly	Tyr Val Lys Asp Thr	Leu Pro Gly
	1910	1915	1920	
	Leu Val	Met Ala Gln Asp Gln	Lys Val Arg Trp Tyr	Leu Leu Ser
	1925	1930	1935	
	Met Gly	Ser Asn Glu Asn Ile	His Ser Ile His Phe	Ser Gly His
	1940	1945	1950	
[0065]	Val Phe	Thr Val Arg Lys Lys	Glu Glu Tyr Lys Met	Ala Val Tyr
	1955	1960	1965	
	Asn Leu	Tyr Pro Gly Val Phe	Glu Thr Val Glu Met	Leu Pro Ser
	1970	1975	1980	
	Gln Val	Gly Ile Trp Arg Ile	Glu Cys Leu Ile Gly	Glu His Leu
	1985	1990	1995	
	Gln Ala	Gly Met Ser Thr Leu	Phe Leu Val Tyr Ser	Lys Lys Cys
	2000	2005	2010	
	Gln Thr	Pro Leu Gly Met Ala	Ser Gly His Ile Arg	Asp Phe Gln
	2015	2020	2025	
	Ile Thr	Ala Ser Gly Gln Tyr	Gly Gln Trp Ala Pro	Lys Leu Ala
	2030	2035	2040	

	Arg Leu	His Tyr Ser Gly Ser	Ile Asn Ala Trp Ser	Thr Lys Asp
	2045	2050	2055	
	Pro Phe	Ser Trp Ile Lys Val	Asp Leu Leu Ala Pro	Met Ile Ile
	2060	2065	2070	
	His Gly	Ile Met Thr Gln Gly	Ala Arg Gln Lys Phe	Ser Ser Leu
	2075	2080	2085	
	Tyr Val	Ser Gln Phe Ile Ile	Met Tyr Ser Leu Asp	Gly Asn Lys
	2090	2095	2100	
	Trp His	Ser Tyr Arg Gly Asn	Ser Thr Gly Thr Leu	Met Val Phe
	2105	2110	2115	
[0066]	Phe Gly	Asn Val Asp Ser Ser	Gly Ile Lys His Asn	Ile Phe Asn
	2120	2125	2130	
	Pro Pro	Ile Ile Ala Gln Tyr	Ile Arg Leu His Pro	Thr His Tyr
	2135	2140	2145	
	Ser Ile	Arg Ser Thr Leu Arg	Met Glu Leu Leu Gly	Cys Asp Phe
	2150	2155	2160	
	Asn Ser	Cys Ser Met Pro Leu	Gly Met Glu Ser Lys	Ala Ile Ser
	2165	2170	2175	
	Asp Ala	Gln Ile Thr Ala Ser	Ser Tyr Leu Ser Ser	Met Leu Ala
	2180	2185	2190	
	Thr Trp	Ser Pro Ser Gln Ala	Arg Leu His Leu Gln	Gly Arg Thr
	2195	2200	2205	

Asn Ala Trp Arg Pro Gln Ala Asn Asn Pro Lys Glu Trp Leu Gln  
 2210 2215 2220

Val Asp Phe Arg Lys Thr Met Lys Val Thr Gly Ile Thr Thr Gln  
 2225 2230 2235

Gly Val Lys Ser Leu Leu Ile Ser Met Tyr Val Lys Glu Phe Leu  
 2240 2245 2250

Ile Ser Ser Ser Gln Asp Gly His Asn Trp Thr Leu Phe Leu Gln  
 2255 2260 2265

Asn Gly Lys Val Lys Val Phe Gln Gly Asn Arg Asp Ser Ser Thr  
 2270 2275 2280

Pro Val Arg Asn Arg Leu Glu Pro Pro Leu Val Ala Arg Tyr Val  
 2285 2290 2295

[0067]

Arg Leu His Pro Gln Ser Trp Ala His His Ile Ala Leu Arg Leu  
 2300 2305 2310

Glu Val Leu Gly Cys Asp Thr Gln Gln Pro Ala  
 2315 2320

&lt;210&gt; 10

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; 野猪

&lt;400&gt; 10

Asp Ile Gly Asp Tyr Tyr Asp Asn Thr Tyr Glu Asp Ile Pro Gly Phe  
 1 5 10 15

Leu Leu Ser Gly Lys Asn Val Ile Glu Pro Arg

20

25

&lt;210&gt; 11

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; 智人

&lt;400&gt; 11

Asn Thr Gly Asp Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr

1

5

10

15

Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg

[0068]

20

25

&lt;210&gt; 12

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; 家犬

&lt;400&gt; 12

Asn Ile Asp Asp Tyr Tyr Glu Asp Thr Tyr Glu Asp Ile Pro Thr Pro

1

5

10

15

Leu Leu Asn Glu Asn Asn Val Ile Lys Pro Arg

20

25

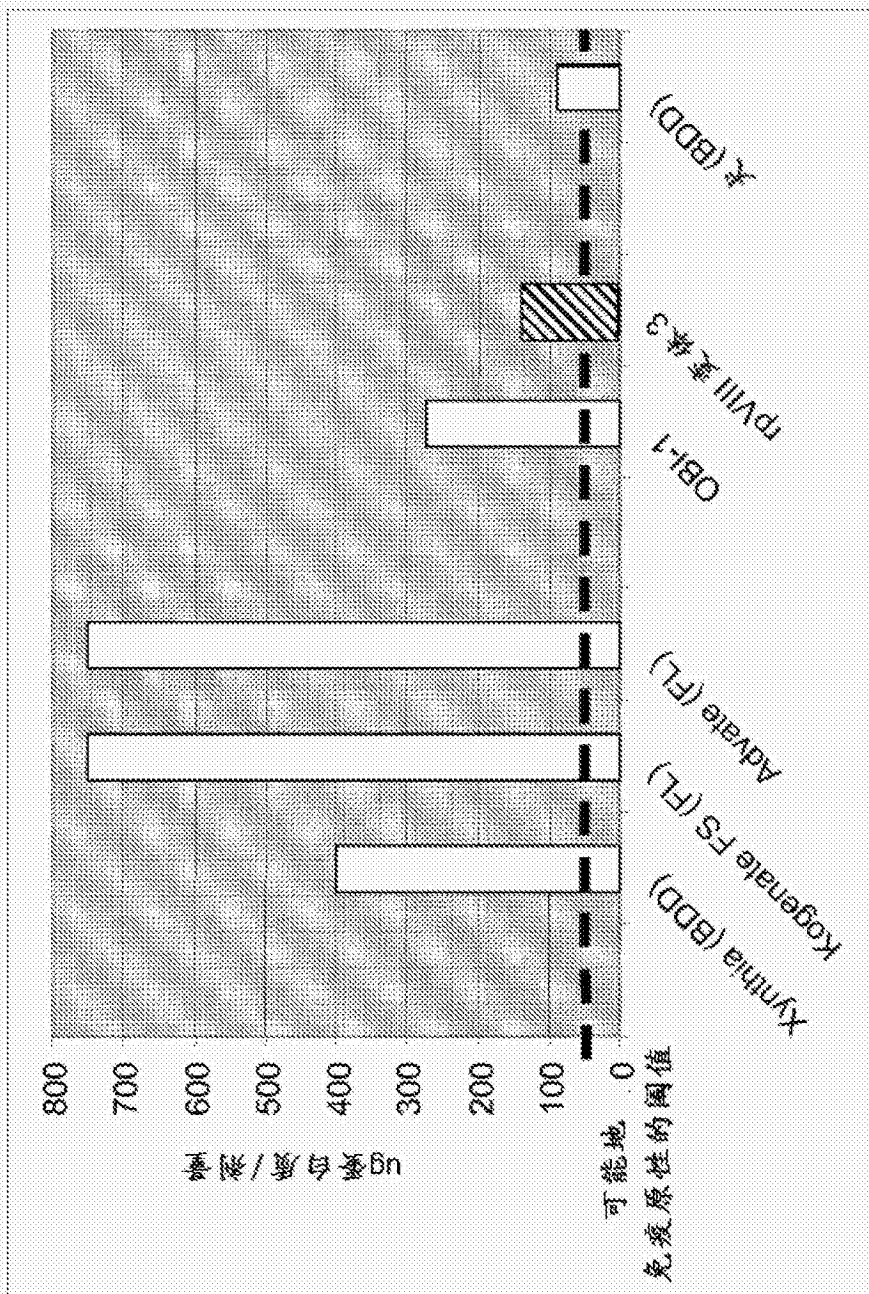


图1

	1				50
HUMFVIII	AFKRYLLGAV	ELSWDYMQSD	.LGELFVDAR	FFFPVFKSFF	FNTSVVYKKT
PIGFVIII	AIKRYLLGAV	ELSWDYRQSE	LLRELHVDTR	FPATAPGALP	LGPSVLYKKT
MURFVIII	AIKRYLLGAV	ELSWNYIQSD	LLQVLHTDSR	FLFRMSTSPF	FNTSVMYKKT
CANFVIII	AFKRYLLGAV	ELSWDYMQSD	LLSALHADFS	FSSKVPGLSP	LTTEVYTKKT
	51				100
HUMFVIII	LFVEETDHLF	NIAKPRFPWM	GLLGFTIQAE	VYDTPVITLK	NMASHFVSLH
PIGFVIII	VPVEFTDQLF	SVAKPRFPWM	GLLGFTIQAE	VYDTPVVITLK	NMASHFVSLH
MURFVIII	VFVEYKQQLF	NIAKPRFPWM	GLLGFTIWFTE	VHDTPVITLK	NMASHFVSLH
CANFVIII	VFVEFTDHLF	NIAKPRFPWM	GLLGFTIQAE	VYDTPVIVLK	NMASHFVSLH
	101				150
HUMFVIII	AVGVSYWEAS	EGAEYDDQTS	QREKEDDKVF	PGGSHTYVWQ	VLKENGPMAS
PIGFVIII	AVGVSPWESE	EGAEYEDHTS	QREKEDDKVL	PGESQTYVWQ	VLKENGPTAS
MURFVIII	AVGVSYWEAS	EGDEYEDQTS	QMEKEDEKVF	PGESHTYVWQ	VLKENGPMAS
CANFVIII	AVGVSYWEAS	EGAEYEDQTS	QREKEDDQVI	PGESHTYVWQ	VLKENGPMAS
	151				200
HUMFVIII	DPLCLTYSYL	SHVDLVKDLN	SGLIGALLVC	REGSLAKERT	QTLRKFILLF
PIGFVIII	DPFCLTYSYL	SHVDLVKDLN	SGLIGALLVC	REGSLTRERT	QNLNEFVLLF
MURFVIII	DPFCLTYSYM	SHVDLVKDLN	SGLIGALLVC	KESLSKERT	QMLYQFVLLF
CANFVIII	DPFCLTYSYF	SHVDLVKDLN	SGLIGALLVC	KESLSAKERT	QTLQRFVLLF
	201				250
HUMFVIII	AVFDEGKSWH	SETKNSLMQD	NDASARAWP	KMHTVNGYVN	RSLEGLIGCH
PIGFVIII	AVFDEGKSWH	SARNDSWFEA	MDPAPARAQP	AMHTVNGYVN	RSLEGLIGCH
MURFVIII	AVFDEGKSWH	SETINDSYTQS	MDSASAKDWF	KMHTVNGYVN	RSLEGLIGCH
CANFVIII	AVFDEGKSWH	SETNASLTQ.	... .AEAQH	ELHTINGYVN	RSLEGLTVCH
	251				300
HUMFVIII	KKSVMYWHVIG	MGTTFEVHSI	FLEGHFFLVR	NHRQASLEIS	PITFLTAQTL
PIGFVIII	KKSVMYWHVIG	MGTGPEVHSI	FLEGHFFLVR	NHRQASLEIS	PLTFLTAQTF
MURFVIII	KKSVMYWHVIG	MGTTFEIHSI	FLEGHFFVVR	NHRQASLEIS	PITFLTAQTL
CANFVIII	KKSVMYWHVIG	MGTTFEVHSI	FLEGHFFLVR	NHRQASLEIS	PITFLTAQTF
	301				350
HUMFVIII	LMDLQQFLLF	CHISSHQHDS	MEAYVVDSC	PEEPQLRMK.	NNEEAEDYDD
PIGFVIII	LMDLQQFLLF	CHISSHHNGG	MEAHVVEESC	AEEPQLRKK.	ADEE.EDYDD
MURFVIII	LIDLQQFLLF	CHISSHHHDS	MEAYVVDSC	PEESQWQEN	NNEEMEDYDD
CANFVIII	LMDLQQFLLF	CHISSHQHDS	MEAYVVDSC	PEEPQLRMK.	NNED.RDYDD
	351				400
HUMFVIII	DLTQSEMDDV	RFDDDSPPF	IQIRSVAKKH	PKTWVHYIAA	EEEDWDYAPS
PIGFVIII	NLYQSEMDDV	RLDGDDVQPF	IQIRSVAKKH	PKTWVHYISA	EEEDWDYABA
MURFVIII	DLY. SEMDMF	FLDYD. SSPF	IQIRSVAKKY	PKTWVHYISA	EEEDWDYAPS
CANFVIII	GLYDSDMDVV	SPDDDSPPF	IQIRSVAKKH	PKTWVHYIAA	EEEDWDYAPS
	401				450
HUMFVIII	VLAPDERSYK	SOYLNSGPQR	IGRKYKVRV	WAYTDETFET	REAIQHEGGI
PIGFVIII	VSPSPDRSYK	SLYLNSGPQR	IGREYKVARF	WAYTDVTFET	REAIPTESGI
MURFVIII	VPTSDNGSYK	SOYLNSGPHR	IGREYKVRV	IAYTDETFET	RETIQRESGL
CANFVIII	GPTENDRSHK	NLYLNSGPQR	IGRKYKVRV	VAYTDETFKT	REAIQYESGI
	451				500
HUMFVIII	LGFLLYGEVG	DTLLIIFKNQ	ASRPYNIYPH	GITDVRFLYS	RLLENGVKNL
PIGFVIII	LGFLLYGEVG	DTLLIIFKNK	ASRPYNIYPH	GITDVSALRF	GRLLGQVKNL
MURFVIII	LGFLLYGEVG	DTLLIIFKNQ	ASRPYNIYPH	GITDVSPLHA	RKLPKGIKRV
CANFVIII	LGFLLYGEVG	DTLLIIFKNQ	ASRPYNIYPH	GINVTPLHT	GRLPKGVKHL
	501				550

图2a

HUMFVIII	KDFPILPGEI	FRYKWTVTVE	DGPTKSDPRC	LTRYSSFPVN	MERDLASGLI
FIGFVIII	KDMPILPGET	FRYKWTVTVE	DGPTKSDPRC	LTRYSSSEIN	LERDLASGLI
MURFVIII	KDLFIHSGEI	FRYKWTVTVE	DGPTKSDPRC	LTRYSSFIN	PERDLASGLI
CANFVIII	KDMPILPGEI	FRYKWTVTVE	DGPTKSDPRC	LTRYSSFIN	LERDLASGLI
	551				600
HUMFVIII	GFLLCYKES	VDQRGNQIMS	DKRNVILFSV	FDENRQSWYL	ENIQRFLENF
FIGFVIII	GFLLCYKES	VDQRGNQIMS	DKRNVILFSV	FDENRQSWYLA	ENIQRFLENF
MURFVIII	GFLLCYKES	VDQRGNQIMS	DKRNVILFSI	FDENRQSWYIT	ENMQRFLENA
CANFVIII	GFLLCYKES	VDQRGNQIMS	DKRNVILFSV	FDENRQSWYL	ENMQRFLENA
	601				650
HUMFVIII	AGVQLEDPEF	QASNIMHSIN	GYVFDLQLS	VCLHEVAYWY	ILSVGAQTDF
FIGFVIII	DGLQPDPEF	QASNIMHSIN	GYVFDLQLS	VCLHEVAYWY	ILSVGAQTDF
MURFVIII	AKTQPDPEF	QASNIMHSIN	GYVFDLQLS	VCLHEVAYWH	ILSVGAQTDF
CANFVIII	DVVQPDPEF	QLSNIMHSIN	GYVFDLQLS	VCLHEVAYWY	ILSVGAQTDF
	651				700
HUMFVIII	LSVFFSGYTF	KHKMVEYDTL	TLFFPSGETV	FMSMENPGLW	VLGCHNSDFR
FIGFVIII	LSVFFSGYTF	KHKMVEYDTL	TLFFPSGETV	FMSMENPGLW	VLGCHNSDLR
MURFVIII	LSLFFSGYTF	KHKMVEYDTL	TLFFPSGETV	FMSMENPGLW	VLGCHNSDFR
CANFVIII	LSVFFSGYTF	KHKMVEYDTL	TLFFPSGETV	FMSMENPGLW	VLGCHNSDFR
	701				750
HUMFVIII	NRGNTALLKV	SSCDKNTGDY	YEDSYEDISA	YLLSKNNAIK	PR
FIGFVIII	NRGNTALLKV	YECURDIGDY	YDNTYEDIPG	FLLSCKNVIE	PR
MURFVIII	KRGNTALLKV	SSCDKNTSDY	YREIYEDIPT	QLVNENNVID	PR
CANFVIII	NRGNTALLKV	SSCDKNTIDDY	YEDTYEDIPT	FLLNENNVIK	PR
	751				800
HUMFVIII	QKQFNA	YTFENDIEK	EDPWFARPTF	MFKIQNVSS	DLMLLQCS.
FIGFVIII	QKQFQFQ	YTFPRDVE.	LDQSGERTG	ALRELSVPSG	DGSMLLGN.
MURFVIII	ENTKREKFD	STPKNDMEK	IEPQFEELAE	NLKVQSVSVS	DLMLLQCSH
CANFVIII	ETREKQLEA	YTFENDIEK	IDLQSGERTG	LIRAQSVSS	DLMLLQGN.
	801				850
HUMFVIII	ETPHGLSLSD	LQEARNEYFS	DDPSEGAIDS	NMSLCEMTRF	RFQLHRSGDM
FIGFVIII	FAPHGSSSD	LQEARNE..A	DDYLPGAREP	RTAFSAAAARL	RFRLHNSAER
MURFVIII	ETPHGLFLSD	GQEAIEAIE	DDHSPNAIDS	NEGPKVTFQL	RPESHHSEKI
CANFVIII	ETPHGLFLSD	LREA..TDR	DDHSPGAIER	NRGPFVAVSL	RPELHRSEDE
	851				900
HUMFVIII	VTFPESGLQL	PLNEKLGTTA	ATELKKLDK	VSSSTNNLI.	STFIPSDLA
FIGFVIII	VLTFEPE...	.....	.KELKKLDSE	MSSSDILLKT	SPFIPSDTLS
MURFVIII	VTFPESGLQL	RSNKSLETNI	EVKWKLGLO	VSLFSLMNT	TFILSDNLEK
CANFVIII	ETTFEPELQL	RLNENLGTTF	TVELKKLDL	ISSSDSLMT	SPFIPSDLA
	901				950
HUMFVIII	AGTNTSSLG	PPSMFVHYDS	QLDTTLFGKK	SSPLTESGGF	LSLSEEDNDS
FIGFVIII	AETERTHSLG	PEHPQVNEFS	QLGAIYLGKN	SSHFIGAGVF	LGSTEED...
MURFVIII	ATTEKTSQSG	PPDMFVHSSG	KLSTTATGKN	AYSLVGSHPV	LRASEENSQS
CANFVIII	ATEKTSLSG	PPMMSVHFS	HGTTIVFGNN	SSHLIQSGVF	LSLSEEDNDS
	951				1000
HUMFVIII	KLLESGLMS	QESSWEKNVS	STESGRLEK	KPARGFALLT	KDNALFKVSI
FIGFVIII	.....	HESSLGENVS	PVESDGIPEK	ERARGFASLT	EDDVLKVNHI
MURFVIII	NILDSTLMS	QESLFRONIL	GIENDKLLPE	KRFNGIALLT	KDNTLFRDNY
CANFVIII	KLLEAFPMNI	QESSLRENVL	SMESMELFKE	ERIRGFASLI	KDNALFKVNI

图2b

	1050	1050
HUMFVIII	SLKTKNETSN NSATNPKTHI DGPSLLIENS FSVWQNI.LE SDTEFKKVTY	
FIGFVIII	SLVKTNEAKV YLKTNRKAIH DGAALLTEMP ASA.....	
MURFVIII	SLMETNKTYN NSTTNEKLNH ESPT.SIENS TTOLQDAILK VNSEIQEYTA	
CANFVIII	SGVKTNRAPV NLTNKRKTFV AIPTLLIENS FSVWQDIME ENTEFKKVTY	
	1051	1100
HUMFVIII	LHDERMLMDK NATALRLNHM SNETTSSENM EMVQOKKEGF IPPDAQRPM	
FIGFVIII	.....TFMDK NTPASGLNHV SN.....	
MURFVIII	LHDSGTLGK NPTYLRLNHM LNRFTSTENK DIPHRKDEDP IPQDERNTIM	
CANFVIII	LHNETFMDR NPTALGLNHV SNETTLSKNV EMARQKKEDE VPLKAEKPOL	
	1101	1150
HUMFVIII	SFFKMLFLPE SARNTQKTHG KNSLNSGQGP SFFQLVSLQP ERSVEGQRFL	
FIGFVIII	.....WIEGFLS KNPSSSERGF SPELLTSEGS QKSVKQSSSG	
MURFVIII	SFSKMLFLSE SNNWFKETNG KNSLNSQDQH SFFQVYVLMF KKYVENQSVL	
CANFVIII	SSSKIFFLED WL...KTHG KNSLSSEQRP SFFCLTSLGS ERSVKIQRFL	
	1151	1200
HUMFVIII	SEKMKVAVGK DEFTKDVGLK EMVFPSEKNI FLTNLDNLHE NNTHNQEKKI	
FIGFVIII	QQRIRVAVEE EELSKG...K EMMLENSELT FLTNSADVOG NDTNSQGRKS	
MURFVIII	SEKMKVYVEQ DQFTKNIGLK DMAPFHNMSI FLTFLSNVBE NGRBRQEKKI	
CANFVIII	SE.EKVYVGE DEFTKDELO E.IFPNNSI PFANLANVQE NDTYNQEKKS	
	1201	1250
HUMFVIII	QEEIEKEETL IQENVVLPQI STVTGTRNFM KNLFLLSFRQ NVEGSDYDGY	
FIGFVIII	REEMERREEL VQEKVDLPQV YIATGTRNPL KNIFHQSTEP SVEGFLGGSH	
MURFVIII	QEEIE.KEAL IEEKVVLPOV HEATGSKNHL KDILILGTRQ NIELYE..VH	
CANFVIII	VEEIEEKEEL TQENVALPOA NYMIGTRNPL KNLFLLSFRQ NVAGLEQGF	
	1251	1300
HUMFVIII	APVLDQFRSL NDSYRPTKTH TANFSEKQ.. EENLEGLGN QTNQIVRYA	
FIGFVIII	APVQDERSL NDSRERAETH IANFSAIR.. EEPLEAFGN RT.....	
MURFVIII	YFVLQNTSI NNSYNTVQIH MEHFTKREED KETNSEGLVN FTREMYRY.	
CANFVIII	TFILQDTRSL NDSYRSEGIH MANFSAIR.. EEMLEGLGN QTNQIVRYA	
	1301	1350
HUMFVIII	CTNRISFNTE QCNVYVOREK NALQPPFLFL ETELEKRII VDETQFQWK	
FIGFVIII	.....GGG PRSAVPRVVE QSLQKRLFL ETEKPERGVV LMATSTKWS.	
MURFVIII	.....PS QKNITQSK NALQPPFL.. ..STQRLK	
CANFVIII	STRMESNAS QH.VITQSK NALQPPFLSQ GEIKPERVI ANETQFQWK	
	1351	1400
HUMFVIII	NMKHLPESTL TQIDYNEEEK GAITQSPLEB CLTRSHSLPQ ANKSELPYAK	
FIGFVIII	.....	
MURFVIII	TINCSTQCII KQIDHSEKEM KPIKSELSQ SSVLK.SFTQ TNGSDENIVK	
CANFVIII	NMNYLAQGET TQIEYNEEEK RAITQSELSQ CSMRNHVITQ MNDALPYAK	
	1401	1450
HUMFVIII	VSSFPSIFPI YLEFVLFQDN SSSLFAAS.. .YRKKDSGV QESSHFLOQA	
FIGFVIII	.....ESSEFLQGA	
MURFVIII	TSAPP...PI DLKNSPFONK FSHVQASSYI YDEPKSSRI QESNFKLET	
CANFVIII	ESAGPSVRHT DLKIFPSQHN SSSLPASACN YFPRERTSGV QEGSHFLOQA	
	1451	1500
HUMFVIII	KRNMLSLAIL TLEMTDQRE YGGLGTEATH SVTYKVENT VLPKPDLPKT	
FIGFVIII	KRNMLSLPFL TLEMAGGQEK ISALGKSAAG PLASGKLEKA VLSSAGLSEA	
MURFVIII	KRNMLSLAIL FNMMEYDQEK FTSFGKSNTH SVTYKRENI IFLKPTLPEE	
CANFVIII	KRNMLSLAFV TLGITEGQEK FSSLGKSAFN QFMYKRENT VLLQPLGET	
	1501	1550

图2c

HUMFVIII	SGKVELLQKV	HIYQKDLFPT	FTSNSSPGHL	DLVEGSLIQG	TEGAIKWNNA
PIGFVIII	SGEAEFLPKV	KVNRKDLLEQ	KTSNVSCANG	DLQGEIFLQK	TQGVVHLNEV
MURFVIII	SGKIELLPQV	SIQKKEILFT	FTSNSSPGHL	NLMKEVELOK	IQGVTKWNNA
CANFVIII	SDKVELLSQV	HVDQEDSEPT	KTSNDSFGHL	DLMGKILFQK	TQGVVEMNRT
	1551				1600
HUMFVIII	NRFGVEVFLK	VATESSAKTF	SKLLDPLAWD	NHYGTQIFKE	ENFSQEKSPK
PIGFVIII	NRFG.....	.....RTF	SKLLGFPM..	.....FK	ENFSLEKSPK
MURFVIII	KRHGES..IK	GRTRSSKNTB	SKLLNHRAWD	YHYAAQIFKD	MNKSKKESPK
CANFVIII	NSFGKVPFLK	WATESSSEKIF	SKLLGVLAWD	NHYDTQIFSE	ENFSQEKSKQ
	1601				1650
HUMFVIII	NTAFKFKDTI	.LSLNACEGN	NATAAINEGQ	NKFEIEVTTWA	KQGFTEPLCK
PIGFVIII	STALETKDII	GLFLDKHESN	NSIAAKNEGQ	NETQREAAWT	KQGFGRGLCK
MURFVIII	LIISIEQEDTI	.LSLRFHGNB	NSIGA.NEKQ	NWPCRETTWV	KQGFQORTCK
CANFVIII	NTAFKFKDTI	.LPLGFCEKN	NSIAAINEGQ	NKPCREAAWV	KQGFGRGLCK
	1651				1700
HUMFVIII	QV.....	REITFTTLQK	DQEEIDYDQI	ISVEMKKEQF	DIYDEDENGK
PIGFVIII	QV.....	DISLPTPQK	EECKMDYDQI	FETETFGEDF	DIYGEDENGK
MURFVIII	QV.....	ELS..AFQK	EQEATDYDDA	ITITETLEDF	DIYSEDIRQK
CANFVIII	QV.....	REITFTTLQK	EEDEFEYDQI	FSIEMKKEQF	DIYQDYENQK
	1701				1750
HUMFVIII	FRSPQKTPK	YFIAAVERLW	DYGMSSSPHV	LRNKAQGGSV	QQPKKVVPEK
PIGFVIII	FRSPQKTPK	YFIAAAVEQLW	DYGMSESPRA	LRNKAQNGEV	QPKKVVVTEK
MURFVIII	FRSPQKTPK	YFIAAVERLW	DYGMSTLHW	LRNRYQSDNV	QQPKKVVPEK
CANFVIII	LRSFQKTPK	YFIAAVERLW	DYGMSSSPHI	LRNKAQGGDV	QQPKKVVPEK
	1751				1800
HUMFVIII	FTDGSFTQFL	YRGRINERLQ	LLGPIYIPAV	EDNIMVTFKN	QASKPYSPYS
PIGFVIII	FADGSFTQFS	YRGLINKRLG	LLGPIYIPAV	EDNIMVTFKN	QASKPYSPYS
MURFVIII	FTDGSFTQFL	YRGLMEHLG	LLGPIYIPAV	EDNIMVTFKN	QASKPYSPYS
CANFVIII	FTDGSFTQEL	YRGLMEHLG	LLGPIYIPAV	EDNIVVTFKN	QASKPYSPYS
	1801				1850
HUMFVIII	SLISYEEDQK	QGAEPKKNV	KPNETKIYFW	KVQRHMAFTK	DEYDCKAWAY
PIGFVIII	SLISYFDDQK	QGAEPKKNV	QPNETKIYFW	KVQRHMAFTE	DEYDCKAWAY
MURFVIII	SLISYKEDQ.	EGEFPKKNV	KPNETKIYFW	KVQRHMAFTE	DEYDCKAWAY
CANFVIII	SLISYDEDEK	QGAEPKKNV	NEPETKIYFW	KVQRHMAFTK	DEYDCKAWAY
	1851				1900
HUMFVIII	FSDVDLEKDV	HSGLIGFLLY	CHNTLNPAK	GRQVTVQEFA	LVFTIYDETK
PIGFVIII	FSDVDLEKDV	HSGLIGFLLI	CRANTLNAAK	GRQVTVQEFA	LVFTIYDETK
MURFVIII	FSDVDLERDM	HSGLIGFLLI	CHANTLNPAK	GRQVTVQEFA	LVFTIYDETK
CANFVIII	FSDVDLEEDV	HSGLIGFLLI	CRSNTLNPAK	GRQVTVQEFA	LVFTIYDETK
	1901				1950
HUMFVIII	SWYFTENMEK	NCRAPCRIQM	EDFTLEENYK	FRAINGYVMD	TLPGLVMAQK
PIGFVIII	SWYFTENVER	NCRAPCHLQM	EDFTLEENYK	FRAINGYVMD	TLPGLVMAQK
MURFVIII	SWYFTENYK	NCKYPCNEQM	EDFTLEENYK	FRAINGYVMD	TLPGLVMAQK
CANFVIII	SWYFTENLEK	NCKAPCNVQK	EDFTLEENYK	FRAINGYVMD	TLPGLVMAQK
	1951				2000
HUMFVIII	QRIRWYLLSM	GSNENIHSIR	FSGHVFTVVK	KEEYKMAVYN	LYPGVFETVE
PIGFVIII	QRIRWYLLSM	GSNENIHSIR	FSGHVFSVVK	KEEYKMAVYN	LYPGVFETVE
MURFVIII	QRIRWYLLSM	GNENIHSIR	FSGHVFTVVK	KEEYKMAVYN	LYPGVFETVE
CANFVIII	QKVRWYLLSM	GSNENIHSIR	FSGHVFTVVK	KEEYKMAVYN	LYPGVFETVE
	2001				2050
HUMFVIII	MLPSEAGIWR	VECLIGERLH	AGMSTLFLVY	SNKQTFPLGM	ASGRIRDFOI

图2d

FIGFVIII	MLPSKVGIWR	IECLIGEHLO	AGMSTLFLVY	SKKQQAFLGM	ASGRIRDFQI
MURFVIII	MLPSRAGIWR	VECLIGEHLO	AGMSTLFLVY	SKQQQIFLGM	ASGSIRDFQI
CANFVIII	MLPSQVGIWR	IECLIGEHLO	AGMSTLFLVY	SKKQQYFLGM	ASGHIRDFQI
	2051				2100
HUMFVIII	TASGQYQWA	FKLARLHYSG	SINAWSTKEP	FSWIKVDLLA	FMIINGINTQ
FIGFVIII	TASGQYQWA	FKLARLHYSG	SINAWSTKDF	HSWIKVDLLA	FMIINGINTQ
MURFVIII	TASGHYQWA	FRLARLHYSG	SINAWSTKEF	FSWIKVDLLA	FMIYHGIKTQ
CANFVIII	TASGQYQWA	FKLARLHYSG	SINAWSTKDF	FSWIKVDLLA	FMIINGINTQ
	2101				2150
HUMFVIII	GARQKPFSSLY	ISQPIIMYSL	DGKKNQTYRG	NSTGTLMVFF	GNVDSSGIKH
FIGFVIII	GARQKPFSSLY	ISQPIIMYSL	DGRNWQSYRG	NSTGTLMVFF	GNVDASGIKH
MURFVIII	GARQKPFSSLY	ISQPIIMYSL	DGKKNWLSYQG	NSTGTLMVFF	GNVDSSGIKH
CANFVIII	GARQKPFSSLY	YSQPIIMYSL	DGNKNWHSYRG	NSTGTLMVFF	GNVDSSGIKH
	2151				2200
HUMFVIII	NIFNPPFIAR	YIRLHPHYS	IRSTLRMELM	GCDLNSCSMP	LGMESKAISSD
FIGFVIII	NIFNPPFIVAR	YIRLHPHYS	IRSTLRMELM	GCDLNSCSMP	LGMQNKAISSD
MURFVIII	NSPNPPFIAR	YIRLHPHSS	IRSTLRMELM	GCDLNSCSIF	LGMESKVISSD
CANFVIII	NIFNPPFIIAQ	YIRLHPHYS	IRSTLRMELL	GCDFNSCSMP	LGMESKAISSD
	2201				2250
HUMFVIII	AQITASSYPT	NMFATWSPSK	ARLHLQGRFN	AWRPQVNNPK	EWLQVDLQKT
FIGFVIII	SOITASSHLS	NIFATWSPSQ	ARLHLQGRFN	AWRPVSSAE	EWLQVDLQKT
MURFVIII	TQITASSYPT	NMFATWSPSQ	ARLHLQGRFN	AWRPQVNDPK	QWLQVDLQKT
CANFVIII	AQITASSYLS	SMLATWSPSQ	ARLHLQGRFN	AWRPQANNPK	EWLQVDLQKT
	2251				2300
HUMFVIII	MKVYIGVITQG	VKSLLSMYV	KEFLISSSQD	GHWTLFLOQ	GKVKVFOGNG
FIGFVIII	VKYIGIITQG	VKSLLSMYV	KEFLVSSSQD	GHWTLFLOQ	GHTKVIQGNQ
MURFVIII	MKVYIGIITQG	VKSLFTSMFV	KEFLISSSQD	GHWTOIILYN	GKVKVFOGNG
CANFVIII	MKVYIGIITQG	VKSLLSMYV	KEFLISSSQD	GHWTLFLOQ	GKVKVFOGNG
	2301				2345
HUMFVIII	DSTFPVNSL	DFPLLTRYLK	IRFQSWVHQI	ALRMEVLGCE	AQDLY
FIGFVIII	DSTFPVNSL	DFPLLTRYLK	IRFQSWAQHI	ALRLEVIGCE	AQDLY
MURFVIII	DSTFMMNSL	DFELLTRYLK	IRFQIWEHQI	ALREILGCE	AQQY
CANFVIII	DSTFVRNRL	EPFLVARYVR	LRFQSWAHHI	ALRLEVIGCD	TQQPA

图2e

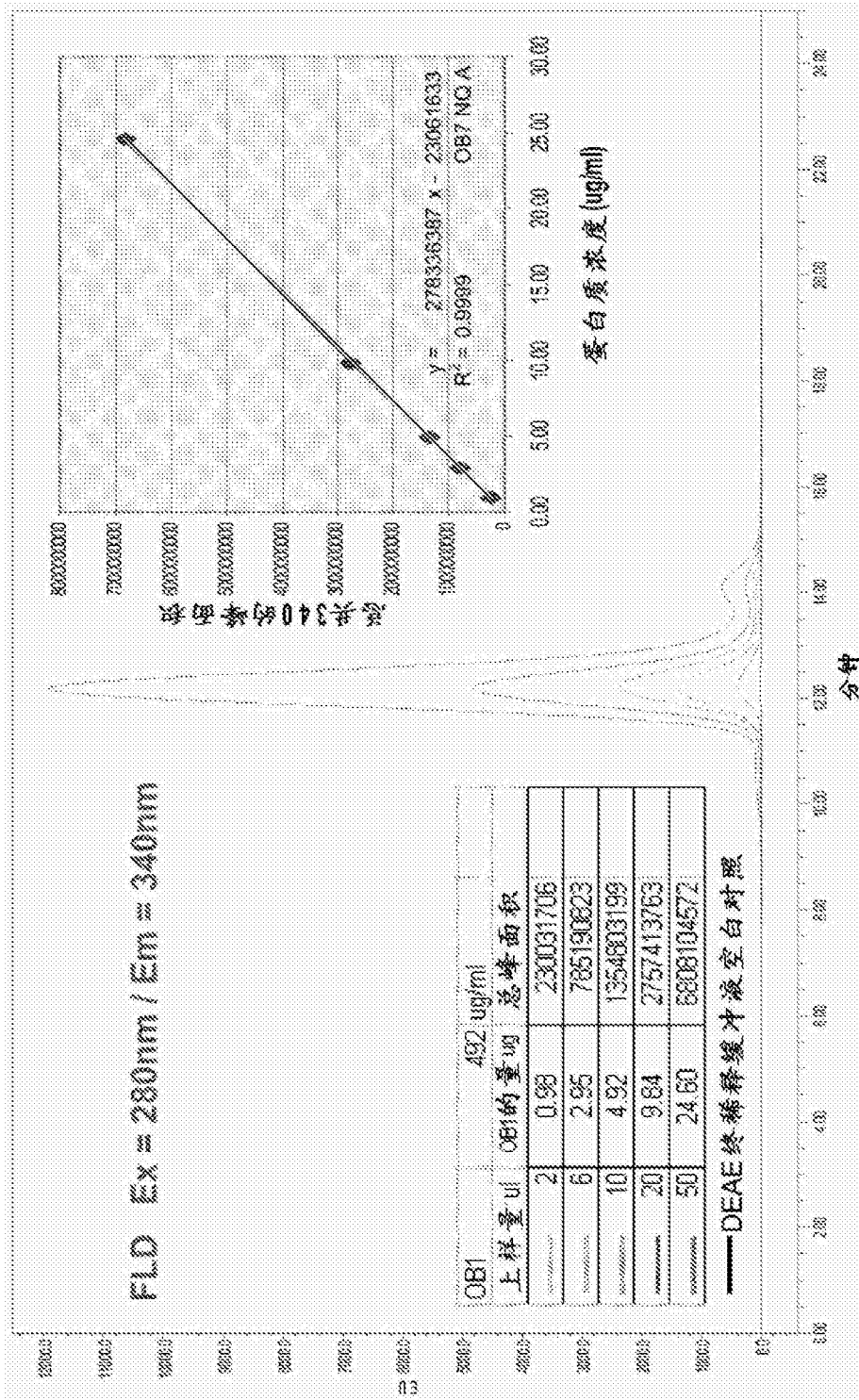


图3