



(12) 发明专利

(10) 授权公告号 CN 101528252 B

(45) 授权公告日 2014. 05. 28

(21) 申请号 200780039016. 1

(22) 申请日 2007. 10. 19

(30) 优先权数据

60/853, 385 2006. 10. 20 US

(85) PCT国际申请进入国家阶段日

2009. 04. 20

(86) PCT国际申请的申请数据

PCT/US2007/022377 2007. 10. 19

(87) PCT国际申请的公布数据

W02008/051496 EN 2008. 05. 02

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(51) Int. Cl.

A61K 38/17(2006. 01)

A61K 38/20(2006. 01)

A61P 19/06(2006. 01)

A61P 19/02(2006. 01)

(56) 对比文件

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审查员 潘浩

权利要求书1页 说明书8页

序列表59页

(54) 发明名称

IL-1 拮抗剂在治疗痛风中的应用

(57) 摘要

治疗, 抑制或改善有此需要的人受试者中的痛风, 包括慢性剧烈 (顽固性) 痛风或假痛风的方法, 包括对需要的受试者给予治疗量的白细胞介素 1(IL-1) 拮抗剂, 其中痛风或假痛风得到抑制或改善。优选 IL-1 拮抗剂为 SEQ ID NO :10 的蛋白质 (利洛纳塞)。

1. 白细胞介素 1 (IL-1) 拮抗剂在制备用于治疗、抑制或改善与高尿酸血症相关的代谢性风湿病的药物中的应用, 其中 IL-1 拮抗剂为融合蛋白, 其包含人 IL-1RAcP 胞外域的 IL-1 结合部分、人 IL-1R1 胞外域的 IL-1 结合部分和多聚化成分, 并且所述的代谢性风湿病为痛风, 其中所述的 IL-1 拮抗剂为由 SEQ ID NO :10 的氨基酸序列组成的融合蛋白。

2. 权利要求 1 的应用, 其中所述的代谢性风湿病为顽固性痛风。

3. 权利要求 1-2 中任意一项的应用, 其中给药是通过皮下或静脉内给药。

4. 权利要求 3 的应用, 其中给药是通过单次或多次皮下注射或静脉内输注。

5. 权利要求 4 的应用, 其中给药包括通过皮下给予的 250-500mg IL-1 拮抗剂的初始剂量, 随后是通过皮下给予的 125-250mg 的一个或多个剂量。

6. 如权利要求 1 中所定义的 IL-1 拮抗剂作为第一种治疗剂和一种或多种选自另一种 IL-1 拮抗剂、皮质类固醇、非类固醇消炎药 (NSAID) 和秋水仙碱的额外治疗剂在制备用于治疗、抑制或改善与高尿酸血症相关的代谢性风湿病的药物中的应用, 其中所述的代谢性风湿病为痛风。

IL-1 拮抗剂在治疗痛风中的应用

[0001] 背景

[0002] 发明领域

[0003] 本发明涉及使用白细胞介素 -1 (IL-1) 拮抗剂治疗与高尿酸血症相关的代谢性风湿病,包括痛风和慢性活动性(顽固性)痛风的方法。本发明还包括治疗诸如假痛风这类疾患的方法。

[0004] 相关领域的描述

[0005] 与高尿酸血症相关的代谢性风湿病,诸如痛风的特征在于嘌呤代谢反常,导致高尿酸血症,即血液中的尿酸过量,急性关节炎发作和在关节软骨中形成白垩样沉积物。这些沉积物主要由尿酸盐或尿素构成。

[0006] 已知治疗痛风的方法包括使用尿酸合成抑制剂抑制体内尿素蓄积并且使用尿酸排泄促进剂加速体内蓄积的尿酸快速排泄。别嘌醇为尿酸合成抑制剂的实例。丙磺舒,磺吡酮和苯溴马隆为尿酸排泄促进剂的实例。已经提出白细胞介素 -6 (IL-6) 作为血清尿酸减少剂用于治疗痛风(参见美国专利 US 6,007,804)。

[0007] 假痛风为高尿酸血症紊乱,并且涉及焦磷酸钙沉积。

[0008] 发明概述

[0009] 本发明在第一个方面中的特征在于治疗,抑制或改善与高尿酸血症相关的代谢性风湿病的方法,包括对有此需要的受试者给予需要的白细胞介素 1 (IL-1) 拮抗剂。IL-1 拮抗剂为能够阻断或抑制 IL-1 生物作用的化合物,包括能够俘获 IL-1 的融合蛋白,诸如 IL-1 “俘获物”。在一个优选的实施方案中,IL-1 俘获物为包含两种 IL-1 受体成分和多聚化成分的 IL-1- 特异性融合蛋白,例如描述在美国专利 US6,927,044 中的 IL-1 俘获物。IL-1 俘获物融合蛋白包含人 IL-1RAcP 胞外域的 IL-1 结合部分,人 IL-1RI 胞外域的 IL-1 结合部分和多聚化成分。在一个具体的实施方案中,IL-1 俘获物为 SEQ ID NO:10 中所示的融合蛋白(利洛纳塞(rilonacept))或与 SEQ ID NO:10 的蛋白质具有至少 95% 同一性并且能够结合和抑制 IL-1 的蛋白质。IL-1 俘获物治疗痛风的应用因几个原因而提供了比现有技术 IL-1 拮抗剂的应用令人意外的优点,包括能够使得痛风症状随给药频率的下降而缓解,减少副作用,诸如,例如减轻注射部位炎症或减轻免疫原性。

[0010] 在一个优选的实施方案中,与高尿酸血症相关的代谢性风湿病为痛风。所治疗的受试者最优选为诊断为患有痛风,例如慢性活动性痛风的人。本发明的方法包括预防或改善患有该病的人受试者的痛风或高尿酸血症。

[0011] 本发明在第二个方面中的特征在于治疗,抑制或改善假痛风的方法,包括对有此需要的受试者给予需要的白细胞介素 1 (IL-1) 拮抗剂。

[0012] 本发明的方法包括通过本领域公知的任意方式,例如皮下,肌内,静脉内,透皮给药或口服给药途径给予 IL-1 拮抗剂。优选通过皮下或静脉内注射或静脉内输注给药。

[0013] 在本发明的治疗方法的具体实施方案中,使用 IL-1 俘获物和第二种治疗剂的组合治疗受试者。第二种治疗剂为:额外的 IL-1 拮抗剂和/或共-疗法,如尿酸合成抑制剂,以便抑制体内尿酸蓄积,例如尿酸排泄促进剂别嘌醇,以便加速体内蓄积的尿酸快速排泄,

例如丙磺舒,磺吡酮和 / 或苯溴马隆为尿酸排泄促进剂的实例 ;皮质类固醇 ;非类固醇类消炎药 (NSAID) ;和 / 或秋水仙碱。

[0014] 本发明在第三个方面中的特征在于白细胞介素 1(IL-1) 拮抗剂在制备用于治疗,抑制或改善与高尿酸血症相关的代谢性风湿病的药物中的应用,其中 IL-1 拮抗剂为包含人 IL-1RAcP 胞外域的 IL-1 结合部分,人 IL-1R1 胞外域的 IL-1 结合部分和多聚化成分的融合蛋白,并且所述的代谢性风湿病为痛风或高尿酸血症。优选 IL-1 拮抗剂为 SEQ ID NO: 10 的氨基酸序列中所示的融合蛋白(利洛纳塞)。在一个优选的实施方案中,所述的代谢性风湿病为慢性活动性(顽固性)痛风。更具体地说,在一个优选的实施方案中,将利洛纳塞以约 250-500mg 的初始剂量皮下给药,随后通过皮下给予 125-250mg 的一个或多个剂量。

[0015] 本发明在第四个方面中提供了作为第一种治疗剂的如上所定义的 IL-1 拮抗剂和选自另一种 IL-1 拮抗剂,皮质类固醇,非类固醇消炎药 (NSAID) 和秋水仙碱的一种或多种另外的治疗剂在制备用于治疗,抑制或改善与高尿酸血症相关的代谢性风湿病的药物中的应用。第一种和第二种治疗剂的给药可以单独,同时或依次进行。

[0016] 其它目的和优点从随后的详细描述中将变得显而易见。

[0017] 详细描述

[0018] 在描述本发明的方法前,应理解本发明并不限于特定的方法和所述的实验条件,因为这类方法和条件可以改变。还应理解本文所用的术语的目的仅在于描述特定的实施方案,并不意欲起限定作用,因为本发明的范围仅由所附的权利要求限定。

[0019] 除非上下文中另有清楚的描述,否则在本说明书和所附的权利要求中所用的单数形式“一种”和“所述的”包括复数对应物。因此,例如,对“一种方法”的提及包括一种或多种方法和 / 或本文所述和 / 或对本领域技术人员而言在阅读本说明书时显而易见等类型的步骤。

[0020] 除非另作定义,否则本文所用的所有技术和科学术语都具有与本发明所属技术领域的普通技术人员通常理解的相同的含义。尽管任何与本文所述的那些类似或等效的方法和材料都可以用于实施或测试本发明,但是现在描述的是优选的方法和材料。

[0021] 与高尿酸血症相关的代谢性风湿病

[0022] 痛风为一类与高尿酸血症相关的代谢性风湿病,并且是中年男性中炎性关节病的最常见的原因。痛风主要为尿酸盐代谢障碍。尿酸盐结晶在血尿酸过多个体中的沉积导致急性痛风,其特征在于极度疼痛和炎症快速发作,最常见的是侵袭第一跖趾关节。高尿酸血症与发生痛风的风险增加相关并且它随高尿酸血症的程度和持续时间而增加。

[0023] 治疗痛风的目的在于缓解疼痛和炎症急性发作,并且使反复发作的发生率下降。膳食和药理学降低尿酸的疗法的目的主要在于预防临床关节损害。治疗急性痛风的常用手段为皮质类固醇,非类固醇消炎药 (NSAID) 和秋水仙碱。这些药物的副作用,特别是在经历急性痛风发病率最高的虚弱的中老年群体中可能是严重的。预防复发性痛风的手段是使用黄嘌呤氧化酶抑制剂别嘌醇。然而,别嘌醇可能存在严重的副作用,诸如别嘌醇超敏反应综合征(例如,参见 Arellano 等 (1993) Ann Pharmacother 27 :337-343)。

[0024] 预防痛风的备选药物包括受其副作用分布限制的排尿酸剂磺吡酮和苯溴马隆和丙磺舒。已经提出将一种在治疗各种形式高脂血症中众所周知的药物非诺贝特用于治疗高尿酸血症。

[0025] 假痛风

[0026] 假痛风为一种类型的关节炎,作为该名称其意指可能导致与痛风类似,但在反应上与不同类型的结晶沉积物类似的症状。假痛风,有时称作焦磷酸钙沉着病可以导致局部痛和肿胀的重度发作,从而导致丧失能力数天或数周。它还可以导致类似于骨关节炎或类风湿性关节炎的更为慢性的关节炎。最常涉及膝,但可以侵袭腕,双肩,踝,肘或手。假痛风在焦磷酸钙结晶沉积物蓄积在关节中时产生。

[0027] IL-1 俘获物拮抗剂

[0028] 白细胞介素-1 (IL-1) 俘获物为含有 IL-1 受体成分和能够与存在于另一种融合蛋白中的多聚化成分发生相互作用而形成高级结构的多聚化成分的融合蛋白的多聚体,诸如二聚体。细胞因子俘获物为受体-Fc 融合概念的新扩展,即它们包括结合单一细胞因子的两种不同受体成分,导致拮抗剂产生,这些拮抗剂具有的亲和力明显增加,超过了单一成分试剂所提供的亲和力。实际上,在曾经描述的大多数有效细胞因子阻断剂中有本文所述的细胞因子俘获物。简言之,称作 IL-1 俘获物的细胞因子俘获物由人 IL-1R I 型 (IL-1RI) 或 II 型 (IL-1RII) 的胞外域,随后是人 IL-1 辅助蛋白 (IL-1AcP) 的胞外域,随后是多聚化成分组成。在一个优选的实施方案中,多聚化成分为免疫球蛋白衍生的结构域,诸如,例如人 IgG 的 Fc 区,包括部分铰链区,CH2 和 CH3 结构域。免疫球蛋白衍生的结构域可以选自主要类别的免疫球蛋白中的任一种,包括 IgA, IgD, IgE, IgG 和 IgM 以及任意亚类或同种型,例如 IgG1, IgG2, IgG3 和 IgG4; IgA-1 和 IgA-2。或者, IL-1 俘获物由人 IL-1AcP 的胞外域,随后是人 IL-1RI 或 IL-1RII 的胞外域,随后是多聚化成分组成。就 IL-1 俘获物的更详细描述而言,参见 W000/18932。优选的 IL-1 俘获物具有 SEQ ID NOs :2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 和 26 中所示的氨基酸序列,或与 SEQ IDNO :2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 或 26 的序列具有至少 95% 同一性,并且能够结合和抑制 IL1 的基本上相同的蛋白质。最优选 IL-1 拮抗剂为 SEQ ID NO :10 的蛋白质 (利洛纳塞)。

[0029] 在具体的实施方案中, IL-1 拮抗剂包含能够结合 IL-1 α , IL-1 β , IL-1RI 和/或 IL-1RAcp 或其片段的抗体片段。优选的实施方案可以为 IL-1 β 的拮抗剂。包含一种或多种抗体片段,例如单链 Fv (scFv) 的 IL-1 拮抗剂的一个实施方案描述在美国专利 US 6, 472, 179 中。在包含一种或多种抗体衍生的对 IL-1 或 IL-1 受体具有特异性的成分的所有 IL-1 拮抗剂实施方案中,所述的成分可以按照多种结构排列,例如 IL-1 受体成分-scFv(s)-多聚化成分;IL-1 受体成分-多聚化成分-scFv(s);scFv(s)-IL-1 受体成分-多聚化成分, ScFv-ScFv-Fc 等,只要所述的分子或多聚体能够抑制 IL-1 的生物活性。

[0030] 治疗群体

[0031] 本发明的方法提供了治疗患有与高尿酸血症相关的假痛风 and 代谢性风湿病的人类患者的方法。该治疗群体因此为诊断为患有假痛风, 痛风或高尿酸血症的人受试者。本发明包括治疗处于患有复发性痛风发作或发生痛风或假痛风风险中的人受试者。

[0032] 给药方法

[0033] 本发明提供了治疗方法,包括对受试者给予有效量的本发明的活性剂。在一个优选的方面中,所述的活性剂基本上为纯化的(例如,基本上不含限制其作用或产生不需要的副作用的物质)。

[0034] 各种递送系统为已知的并且可以用于给予本发明的活性剂,例如在脂质体中包

囊,微粒,微囊,能够表达化合物的重组细胞,受体介导的胞吞(例如,参见 Wu 和 Wu,1987, J. Biol. Chem. 262 :4429-4432),构建核酸作为逆转录病毒或其它载体的组成部分等。导入方法可以为经肠或非肠道并且包括,但不限于透皮,肌内,腹膜内,静脉内,皮下,硬膜外和口服途径。可以通过任意便利的途径,例如通过输注或快速浓注,通过经上皮或皮肤粘膜内层(例如,口腔粘膜,直肠和肠粘膜等)吸收给予化合物,并且可以与其它生物活性剂共同给药。给药可以为全身或局部的。此外,期望通过任何合适的途径,包括心室内和鞘内注射将本发明的药物组合物导入中枢神经系统;可以通过导管,例如与储器,诸如奥马耶贮器连接的导管促进心室内注射。还可以使用肺部给药,例如通过使用吸入器或喷雾器和具有雾化剂的制剂。

[0035] 在一个具体的实施方案中,将本发明的药物组合物经局部施用于需要治疗的区域可能是理想的;例如可以实现这一目的,并且并非作为限定,通过在手术过程中局部输注,局部施用,例如通过注射,通过导管或通过植入物,所述的植入物为多孔,非多孔或胶凝状材料,包括膜,诸如 sialastic 膜,纤维,商品皮肤替代物或血管成形术气囊或支架。

[0036] 在另一个实施方案中,可以以囊泡,特别是脂质体的形式递送活性剂(参见 Langer(1990)Science 249 :1527-1533)。在另一个实施方案中,可以以控释系统递送活性剂。在一个实施方案中,可以使用泵(参见 Langer(1990),上文)。在另一个实施方案中,可以使用聚合物材料(参见 Howard 等(1989)J. Neurosurg. 71 :105)。在本发明的活性剂为编码蛋白质的核酸的另一个实施方案中,可以体内给予核酸以便促进其编码的蛋白质表达,该过程通过下列步骤进行:构建它作为适当核酸表达载体的一部分并且给予它以便例如通过使用逆转录病毒载体(例如,参见美国专利 US4,980,286)或通过直接注射或通过使用微粒轰击(例如基因枪;Biolistic, Dupont)使其成为胞内的或用脂质或细胞表面受体或转染剂包被或通过给予它而连接于已知进入核的同源异型框样肽(例如,参见 Joliot 等 1991, Proc. Natl. Acad. Sci. USA 88 :1864-1868)等。或者,可以在胞内导入核酸并且将其掺入宿主细胞 DNA 以便通过同源重组表达。

[0037] 联合疗法

[0038] 在许多实施方案中,可以将本发明的 IL-1 拮抗剂与一种或多种额外的化合物或疗法一起给予。联合疗法可以为单独的,同时的或依次的。可以将本发明的 IL-1 俘获物与例如 TNF- 抑制剂,诸如依那西普(ENBREL®, Amgen),英夫利昔单抗(REMICADE®, Centocor), HUMIRA® (Abbott) 联用。联合疗法还可以包括使用同时用于治疗或预防痛风的药物治疗,包括皮质类固醇,非类固醇消炎药(NSAID);秋水仙碱;黄嘌呤氧化酶抑制剂,诸如别嘌醇;促尿酸尿药磺吡酮,苯溴马隆和丙磺舒;和非诺贝特。优选的共同疗法包括 NSAID,类固醇和/或秋水仙碱。

[0039] 药物组合物

[0040] 本发明还提供了药物组合物。这类组合物包含治疗有效量的活性剂和药学上可接受的载体。术语“药学上可接受的”意指由联邦或州政府管理局批准或美国药典或其它一般公认用于动物,且更具体地说是用于人的药典中所列的。术语“载体”意指给予与治疗剂一起给予的稀释剂,佐剂,赋形剂或媒介物。这类药用载体可以为无菌液体,诸如水和油,包括石油,动物,植物或合成来源的那些,诸如花生油、大豆油、矿物油、芝麻油等。合适的药用赋形剂包括淀粉、葡萄糖、乳糖、蔗糖、明胶、麦芽、稻米、面粉、白垩、硅胶、硬脂酸钠、单

硬脂酸甘油酯、滑石粉、氯化钠、脱脂奶、甘油、丙二醇、水和乙醇等。如果需要、组合物还可以包含少量湿润剂或乳化剂或 pH 缓冲剂。这些组合物可以采用溶液、混悬液、乳剂、片剂、丸剂、胶囊、粉末、缓释制剂等形式。可以使用传统的粘合剂和载体、诸如甘油三酯将组合物配制成栓剂。口服制剂可以包括标准载体、诸如药用级甘露糖醇、乳糖、淀粉、硬脂酸镁、糖精钠、纤维素、碳酸镁等。合适的药用载体的实例描述在 E. W. Martin 的“Remington’s Pharmaceutical Sciences”中。

[0041] 在一个优选的实施方案中,按照常规操作将组合物配制成适合于对人给药的药物组合物。如果必要,该组合物还可以包括增溶剂和局部麻醉剂,诸如利多卡因以便缓解注射部位的疼痛。如果通过注射给予组合物,那么可以用含有无菌药用级水或盐水的输注瓶调配。如果通过注射给予该组合物,那么可以制成无菌注射用水或盐水的安瓿,以便在给药前混合组分。

[0042] 可以将本发明的活性剂配制成中性或盐形式。药学上可接受的盐包括与游离氨基形成的那些,诸如衍生自盐酸、磷酸、乙酸、草酸、酒石酸等的那些,和与游离羧基形成的那些,诸如衍生自钠、钾、铵、钙、铁氢氧化物,异丙胺、三乙胺、2-乙氨基乙醇、组氨酸、普鲁卡因等的那些。

[0043] 可以通过给予本说明书的标准临床技术测定可有效治疗迟发型过敏反应的本发明活性剂的用量。此外,体外测定可以任选地用于辅助鉴定最佳剂量范围。用于制剂的精确剂量还取决于给药途径和疾患的严重性,并且应根据临床医师的判断和每位受试者的情况决定。

[0044] 就全身给药而言,最初可以根据体外测定估计治疗有效剂量。例如,可以在动物模型中配制剂量以便实现包括在细胞培养物中测定的 IC_{50} 的循环浓度范围。这类信息可以用于更精确地测定在人体中的有用剂量。还可以根据体内数据,例如动物模型,使用本领域众所周知的技术估计初始剂量。本领域的普通技术人员易于基于动物数据优化对人的给药。

[0045] 实施例

[0046] 给出下列实施例是为了给本领域技术人员提供如何实施和利用本发明的方法和组合物的完整披露内容和描述,并非打算限制本发明人视为其发明的范围。已经进行了尝试以确保在所用数值(例如用量,温度等)方面的精确性,但应考虑某些实验误差和偏差。除非另外指明,否则份数为重量份,分子量为平均分子量,温度为摄氏度,且压力为大气压或接近大气压。

[0047] 实施例 1. 利洛纳塞在治疗慢性活动性痛风中的安全性,耐受性和临床活性的 I/II 期安慰剂对照的引导研究

[0048] 痛风为发病率逐步增加的常见疾病。约 5MM 的美国人患有痛风。医疗需求尚未完全得到满足;大量个体对目前的治疗或预防策略而言不耐受或并非良好的候选者。本研究研究了利洛纳塞在痛风范围的一个目标中的活性:慢性活动性(顽固性)痛风。从本研究的结果中可以暗示,也可以不暗示利洛纳塞在急性活动性痛风或预防痛风潮红中的潜在应用性;然而,在这种情况下中的活性提示了潜在的有益性。慢性活动性(顽固性)痛风群体尽管较小,但是代表了医疗需求的真实状况。

[0049] 主要目的:为了评价利洛纳塞在具有慢性活动性痛风,至少一个关节持续发炎的受试者中的安全性。

[0050] 次要目的: (1) 为了在安慰剂试验期与活性成分治疗期过程中自我报告的疼痛评分 (VAS) 改变的受试者中进行比较; (2) 为了在安慰剂试验期与活性成分治疗期过程中评价受试者和临床医师综合评价中的改变; (3) 为了在具有慢性活动性痛风的受试者中评价利洛纳塞对 C- 反应蛋白 (CRP) 和红细胞沉降率 (ESR) 的作用。

[0051] 研究种类和组: 在第 7 天时筛选受试者; 2 周单盲安慰剂试验在基线访问时开始 (就利洛纳塞 SQ 而言, 2 x 2ml 的安慰剂); 在第 2 周访问时经皮下给予单盲利洛纳塞 320mg, 且然后受试者在家中自我注射 160mg/ 周。每 2 周进行一次访问, 直到第 8 周为止。在筛选访问时评价 PPD 皮试, CXR 和选择 / 排除标准。在筛选和基线时教导了自我注射技术。在筛选, 基线, 第 2, 4 和 8 周时进行实验室样品采集。在第 14 周时进行随访。

[0052] 样品大小和部位数量: 在美国 N = 5, 从至多 5 个地点开始。

[0053] 药物提供: 安慰剂: 5 位受试者 x 2 支小瓶 = 10 支小瓶 + 30% 过量 = 13 支小瓶; 利洛纳塞: 5 位受试者 x 8 支小瓶 = 48 支小瓶 + 30% 过量 = 66 支小瓶, 3 支小瓶 / 试剂盒。

[0054] 受试者合格中选条件标准选择标准: (1) 男性或女性 ≥ 21 岁; (2) 慢性剧烈单关节或多关节痛风 (≥ 1 因痛风而持续关节发炎, \pm 痛风石); (3) 因关节疼痛 / 发炎而 VAS 10- 点疼痛等级评分 ≥ 3 (即中度或中度以上); (4) 标准疗法无效或预涉及副作用的风险相关的受试者。

[0055] 排除标准: (1) 器官移植接受者; (2) 目前剧烈感染; (3) 血清肌酸酐 < 2.5 mg/dL; (4) 可能干扰评价的其它关节炎疾患。

[0056] 主要终点: 利洛纳塞的耐受和安全特性。

[0057] 次要终点: (1) 在受试者疼痛评分中从基线到第 8 周的改变 (10cm VAS 等级); (2) 在受试者总体评价中从基线到第 8 周的改变; (3) 在临床医师总体评价中从基线到第 8 周的改变; (4) 在 ESR 和 CRP 中从基线到第 8 周的改变。

[0058] 实施例 2. 利洛纳塞在具有慢性剧烈痛风性关节炎的受试者中的安全性

[0059] 利洛纳塞在具有慢性剧烈单关节或多关节痛风性关节炎的受试者中的 14 周, 多中心, 非随机化, 单盲, 安慰剂对照的单次序交叉研究。受试者接受 2 周单盲安慰剂, 随后接受负荷剂量的皮下注射 320mg 利洛纳塞, 随后每周接受皮下注射 160mg 利洛纳塞, 持续 5 周。研究群体。研究群体包括由临床医师诊断具有慢性剧烈单关节或多关节痛风性关节炎至少 6 个月的成年受试者 (年龄至少 18 岁, 男性或女性), 其中至少一个关节持续发炎 (自我报告, 否则是未报告) ≥ 4 周, 痛风的诊断基于滑膜液分析中存在结晶的历史, 长期升高的血清尿酸和 / 或痛风石; 因在筛选和基线访问时关节疼痛 / 发炎而产生的直观模拟标度尺递增疼痛等级评分和针对痛风的标准疗法低于有效或与涉及副作用的风险相关的受试者。

[0060] 研究设计 本研究为 IL-1 俘获物 (利洛纳塞) 在具有慢性剧烈单关节或多关节痛风性关节炎的受试者中的 14 周, 多中心, 非随机化, 单盲, 安慰剂对照的单次序交叉研究。受试者接受 2 周单盲安慰剂, 随后接受负荷剂量的皮下注射 320mg 利洛纳塞, 随后每周接受皮下注射 160mg 利洛纳塞, 持续 5 周。本研究在美国的约 12 个地点进行。本研究包括为登记受试者的单次序交叉设计; 治疗 1: 安慰剂注射 2 周; 治疗 2: 注射利洛纳塞 6 周。描述统计学用于评价利洛纳塞在痛风周的安全性和功效。约 10 位受试者登记在本研究过程者接受皮下给予安慰剂 (2 周) 和利洛纳塞 (6 周)。受试者接受总计 2 个剂量的安慰剂 (在第 0

和第 7 天研究时) 和在第 14, 21, 28, 35, 42 和 49 天时 6 个剂量的利洛纳塞。不允许剂量抗比例上升。定期给予临床观察结果和实验室测定, 包括抗 - 利洛纳塞抗体, hs-CRP 和 ESR 评价受试者的功效和安全性。本研究的总体结构包括如下期限: 筛选期: 在研究开始的 7 天那进行筛选操作并且包括获得知情许可和评价以便确定确定用于研究参予的合格中选条件。基线: 在基线访问 (第 0 天) 时, 证实合格中选条件, 并且受试者登记。进行基线评价。给予第一次安慰剂注射, 并且调配安慰剂小瓶。安慰剂治疗期: 在治疗期过程周 (第 0 天到第 2 周), 患者接受安慰剂研究药物, 取功效评价; 取安全性和耐受性评价, 包括尿和血样用于临床实验室测试。活性成分治疗期: 在治疗期过程中 (第 2 周到第 8 周), 患者接受活性研究药物, 取功效评价; 取安全性和耐受性评价, 包括尿和血样用于临床实验室测试。采集血样的生物标记, IL-1 俘获物 (利洛纳塞) 血浆水平和利洛纳塞抗体。随访: 在第 14 周时, 取生命体征, 体重, 不良反应和伴随用药评价。采集血样的生物标记, 利洛纳塞血浆水平和利洛纳塞抗体。结果如表 1 中所示。第一栏列出了评价参数; 第二栏 (安慰剂反应) 比较了在第 2 周时获得的参数测量值与在第 0 天时测定的测量值; 第 3 栏 (利洛纳塞反应) 比较了在第 8 周时获得的参数测量值与在第 2 周时的那些值; 且第 4 栏 (从使用利洛纳塞治疗撤药的作用) 比较了在第 14 周时获得的参数测量值与在第 2 周时的那些值。

[0061] 结果在使用安慰剂治疗的过程中, 在任何临床参数与 CRP 中均没有明显的改善的倾向。此外, 在使用安慰剂治疗的过程中, 无改善证据。在使用利洛纳塞治疗结束时, 反应者比例明显优于 10% 的安慰剂反应, 与如何确定反应无关 ($p < 0.01$)。此外, 在患者自我报告的疼痛中存在显著性减轻 ($p = 0.02$)。当从使用利洛纳塞治疗中撤药时, 功效的趋向下降并且疼痛复发。这些结果提示安慰剂反应最小, 且未观察到疼痛减轻, 直到给予利洛纳塞治疗时为止。

[0062] 表 1

[0063]

评价	安慰剂反应	利洛纳塞反应			撤除利洛纳塞治疗的效应
		第 0 天-第 2 周的变化	第 2-4 周的变化	第 2-4 周的变化	
受试者的疼痛评价	0.96	0.046	0.07	0.02	0.07
临床医师的总体评价	0.09	0.4	0.8	0.2	0.02
受试者的总体评价	1.0	0.07	0.14	0.06	0.02
受侵袭的关节的数量	0.3	0.7	0.9	0.099	0.95
受侵袭的关节的症状调节的评分(每个关节最大值为 3)	0.2	0.7	0.8	0.04	0.3
受侵袭的关节的严重性和症状调节的评分(每个关节最大值为 9)	0.2	0.2	0.8	0.04	0.14
从基线 CRP 的改变	0.5	0.002	0.004	0.004	0.04

序列表

<110>Regeneron Pharmaceuticals, Inc.

<120>IL-1 拮抗剂治疗痛风和假痛风的用途

<130>5060A-WO

<140>待指定

<141>2006-10-19

<150>60/853, 385

<151>2006-10-20

<160>26

<170>FastSEQ for Windows Version 3.0

<210>1

<211>2733

<212>DNA

<213>人

<400>1

atg gtg ctt ctg tgg tgt gta gtg agt ctc tac ttt tat gga atc ctg	48
caa agt gat gcc tca gaa cgc tgc gat gac tgg gga cta gac acc atg	96
agg caa atc caa gtg ttt gaa gat gag cca gct cgc atc aag tgc cca	144
ctc ttt gaa cac ttc ttg aaa ttc aac tac agc aca gcc cat tca get	192
ggc ctt act ctg atc tgg tat tgg act agg cag gac cgg gac ctt gag	240
gag cca att aac ttc cgc ctc ccc gag aac cgc att agt aag gag aaa	288
gat gtg ctg tgg ttc cgg ccc act ctc ctc aat gac act ggc aac tat	336
acc tgc atg tta agg aac act aca tat tgc agc aaa gtt gca ttt ccc	384
ttg gaa gtt gtt caa aaa gac agc tgt ttc aat tcc ccc atg aaa ctc	432
cca gtg cat aaa ctg tat ata gaa tat ggc att cag agg atc act tgt	480
cca aat gta gat gga tat ttt cct tcc agt gtc aaa ccg act atc act	528
tgg tat atg ggc tgt tat aaa ata cag aat ttt aat aat gta ata ccc	576
gaa ggt atg aac ttg agt ttc ctc att gcc tta att tca aat aat gga	624
aat tac aca tgt gtt gtt aca tat cca gaa aat gga cgt acg ttt cat	672
ctc acc agg act ctg act gta aag gta gta ggc tct cca aaa aat gca	720

gtg ccc cct gtg atc cat tea cct aat gat cat gtg gtc tat gag aaa	768
gaa cca gga gag gag cta ctc att ccc tgt acg gtc tat ttt agt ttt	816
ctg atg gat tct cgc aat gag gtt tgg tgg acc att gat gga aaa aaa	864
cct gat gac atc act att gat gtc acc att aac gaa agt ata agt cat	912
agt aga aca gaa gat gaa aca aga act cag att ttg agc atc aag aaa	960
gtt acc tct gag gat ctc aag cgc agc tat gtc tgt cat gct aga agt	1008
gcc aaa ggc gaa gtt gcc aaa gca gcc aag gtg aag cag aaa gtg cca	1056
gct cca aga tac aca gtg tcc ggt ggc gcg cct atg ctg agc gag gct	1104
gat aaa tgc aag gaa cgt gaa gaa aaa ata att tta gtg tca tct gca	1152
aat gaa att gat gtt cgt ccc tgt cct ctt aac cca aat gaa cac aaa	1200
ggc act ata act tgg tat aag gat gac agc aag aca cct gta tct aca	1248
gaa caa gcc tcc agg att cat caa cac aaa gag aaa ctt tgg ttt gtt	1296
cct gct aag gtg gag gat tca gga cat tac tat tgc gtg gta aga aat	1344
tca tct tac tgc ctc aga att aaa ata agt gca aaa ttt gtg gag aat	1392
gag cct aac tta tgt tat aat gca caa gcc ata ttt aag cag aaa cta	1440
ccc gtt gca gga gac gga gga ctt gtg tgc cct tat atg gag ttt ttt	1488
aaa aat gaa aat aat gag tta cct aaa tta cag tgg tat aag gat tgc	1536
aaa cct cta ctt ctt gac aat ata cac ttt agt gga gtc aaa gat agg	1584
ctc atc gtg atg aat gtg gct gaa aag cat aga ggg aac tat act tgt	1632
cat gca tcc tac aca tac ttg ggc aag caa tat cct att acc cgg gta	1680
ata gaa ttt att act cta gag gaa aac aaa ccc aca agg cct gtg att	1728
gtg agc cca gct aat gag aca atg gaa gta gac ttg gga tcc cag ata	1776
caa ttg atc tgt aat gtc acc ggc cag ttg agt gac att gct tac tgg	1824
aag tgg aat ggg tca gta att gat gaa gat gac cca gtg cta ggg gaa	1872
gac tat tac agt gtg gaa aat cct gca aac aaa aga agg agt acc ctc	1920
atc aca gtg ctt aat ata tcg gaa att gag agt aga ttt tat aaa cat	1968
cca ttt acc tgt ttt gcc aag aat aca cat ggt ata gat gca gca tat	2016
atc cag tta ata tat cca gtc act aat tcc gga gac aaa act cac aca	2064
tgc cca ccg tgc cca gca cct gaa ctc ctg ggg gga ccg tca gtc ttc	2112
ctc ttc ccc cca aaa ccc aag gac acc ctc atg atc tcc cgg acc cct	2160
gag gtc aca tgc gtg gtg gtg gac gtg agc cac gaa gac cct gag gtc	2208
aag ttc aac tgg tac gtg gac ggc gtg gag gtg cat aat gcc aag aca	2256
aag ccg cgg gag gag cag tac aac agc acg tac cgt gtg gtc agc gtc	2304
ctc acc gtc ctg cac cag gac tgg ctg aat ggc aag gag tac aag tgc	2352
aag gtc tcc aac aaa gcc ctc cca gcc ccc atc gag aaa acc atc tcc	2400
aaa gcc aaa ggg cag ccc cga gaa cca cag gtg tac acc ctg ccc cca	2448
tcc cgg gag gag atg acc aag aac cag gtc agc ctg acc tgc ctg gtc	2496
aaa ggc ttc tat ccc agc gac atc gcc gtg gag tgg gag agc aat ggg	2544
cag ccg gag aac aac tac aag acc acg cct ccc gtg ctg gac tcc gac	2592

ggc tcc ttc ttc ctc tat agc aag ctc acc gtg gac aag agc agg tgg	2640
cag cag ggg aac gtc ttc tea tgc tcc gtg atg cat gag gct ctg cac	2688
aac cac tac acg cag aag agc ctc tcc ctg tct ccg ggt aaa	2730
tga	2733

<210>2

<211>910

<212>PRT

<213>人

<400>2

Met Val Leu Leu Trp Cys Val Val Ser Leu Tyr PheTyr Gly Ile Leu			
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Gln Ser Asp Ala Ser Glu Arg Cys Asp Asp Trp Gly Leu Asp Thr Met			
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Arg Gln Ile Gln Val Phe Glu Asp Glu Pro Ala Arg Ile Lys Cys Pro			
	35	40	45
Leu Phe Glu His Phe Leu Lys Phe Asn Tyr Ser Thr Ala His Ser Ala			
	50	55	60
Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu			
65	70	75	80
Glu Pro Ile Asn Phe Arg Leu Pro Glu Asn Arg Ile Ser Lys Glu Lys			
	85	90	95
Asp Val Leu Trp Phe Arg Pro Thr Leu Leu Asn Asp Thr Gly Asn Tyr			
	100	105	110
Thr Cys Met Leu Arg Asn Thr Thr Tyr Cys Ser Lys Val Ala Phe Pro			
	115	120	125
Leu Glu Val Val Gln Lys Asp Ser Cys Phe Asn Ser Pro Met Lys Leu			
	130	135	140
Pro Val His Lys Leu Tyr Ile Glu Tyr Gly Ile Gln Arg Ile Thr Cys			
145	150	155	160
Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Thr Ile Thr			
	165	170	175
Trp Tyr Met Gly Cys Tyr Lys Ile Gln Asn Phe Asn Asn Val Ile Pro			
	180	185	190
Glu Gly Met Asn Leu Ser Phe Leu Ile Ala Leu Ile Ser Asn Asn Gly			
	195	200	205
Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Thr Phe His			
	210	215	220

Leu Thr Arg Thr Leu Thr Val Lys Val Val Gly Ser Pro Lys Asn Ala
 225 230 235 240
 Val Pro Pro Val Ile His Ser Pro Asn Asp His Val Val Tyr Glu Lys
 245 250 255
 Glu Pro Gly Glu Glu Leu Leu Ile Pro Cys Thr Val Tyr Phe Ser Phe
 260 265 270
 Leu Met Asp Ser Arg Asn Glu Val Trp Trp Thr Ile Asp Gly Lys Lys
 275 280 285
 Pro Asp Asp Ile Thr Ile Asp Val Thr Ile Asn Glu Ser Ile Ser His
 290 295 300
 Ser Arg Thr Glu Asp Glu Thr Arg Thr Gln Ile Leu Ser Ile Lys Lys
 305 310 315 320
 Val Thr Ser Glu Asp Leu Lys Arg Ser Tyr Val Cys His Ala Arg Ser
 325 330 335
 Ala Lys Gly Glu Val Ala Lys Ala Ala Lys Val Lys Gln Lys Val Pro
 340 345 350
 Ala Pro Arg Tyr Thr Val Ser Gly Gly Ala Pro Met Leu Ser Glu Ala
 355 360 365
 Asp Lys Cys Lys Glu Arg Glu Glu Lys Ile Ile Leu Val Ser Ser Ala
 370 375 380
 Asn Glu Ile Asp Val Arg Pro Cys Pro Leu Asn Pro Asn Glu His Lys
 385 390 395 400
 Gly Thr Ile Thr Trp Tyr Lys Asp Asp Ser Lys Thr Pro Val Ser Thr
 405 410 415
 Glu Gln Ala Ser Arg Ile His Gln His Lys Glu Lys Leu Trp Phe Val
 420 425 430
 Pro Ala Lys Val Glu Asp Ser Gly His Tyr Tyr Cys Val Val Arg Asn
 435 440 445
 Ser Ser Tyr Cys Leu Arg Ile Lys Ile Ser Ala Lys Phe Val Glu Asn
 450 455 460
 Glu Pro Asn Leu Cys Tyr Asn Ala Gln Ala Ile Phe Lys Gln Lys Leu
 465 470 475 480
 Pro Val Ala Gly Asp Gly Gly Leu Val Cys Pro Tyr Met Glu Phe Phe
 485 490 495
 Lys Asn Glu Asn Asn Glu Lcu Pro Lys Leu Gln Trp Tyr Lys Asp Cys
 500 505 510
 Lys Pro Leu Leu Leu Asp Asn Ilc His Phe Ser Gly Val Lys Asp Arg
 515 520 525
 Leu Ile Val Met Asn Val Ala Glu Lys His Arg Gly Asn Tyr Thr Cys

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
 850 855 860
 Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
 865 870 875 880
 Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
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 Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 900 905 910

<210>3

<211>2703

<212>DNA

<213>人

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 cgtccctgtc ctcttaacce aatgaacac aaaggcacta taacttggtg taaggatgac 180
 agcaagacac ctgtatctac agaacaagcc tccaggattc atcaacacaa agagaaactt 240
 tggtttgttc ctgctaaggt ggaggattca ggacattact attgcggtgt aagaaattca 300
 tcttactgcc tcagaattaa aataagtgca aaatttgtgg agaatgagcc taacttatgt 360
 tataatgcac aagccatatt taagcagaaa ctaccggttg caggagacgg aggacttgtg 420
 tgcccttata tggagttttt taaaatgaa aataatgagt tacctaaatt acagtgggat 480
 aaggattgca aaccttact tcttgacaat atacacttta gtggagtcaa agataggctc 540
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 tacttgggca agcaatatec tattaccceg gtaatagaat ttattactct agaggaaaac 660
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Trp Phe Val Pro Ala Lys Val Glu Asp Ser Gly His Tyr Tyr Cys Val
 85 90 95
 Val Arg Asn Ser Ser Tyr Cys Leu Arg Ile Lys Ile Ser Ala Lys Phe
 100 105 110
 Val Glu Asn Glu Pro Asn Leu Cys Tyr Asn Ala Gln Ala Ile Phe Lys
 115 120 125
 Gln Lys Leu Pro Val Ala Gly Asp Gly Gly Leu Val Cys Pro Tyr Met
 130 135 140
 Glu Phe Phe Lys Asn Glu Asn Asn Glu Leu Pro Lys Leu Gln Trp Tyr
 145 150 155 160
 Lys Asp Cys Lys Pro Leu Leu Leu Asp Asn Ile His Phe Ser Gly Val
 165 170 175
 Lys Asp Arg Leu Ile Val Met Asn Val Ala Glu Lys His Arg Gly Asn
 180 185 190
 Tyr Thr Cys His Ala Ser Tyr Thr Tyr Leu Gly Lys Gln Tyr Pro Ile
 195 200 205
 Thr Arg Val Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys Pro Thr Arg
 210 215 220
 Pro Val Ile Val Ser Pro Ala Asn Glu Thr Met Glu Val Asp Leu Gly
 225 230 235 240
 Ser Gln Ile Gln Leu Ile Cys Asn Val Thr Gly Gln Leu Ser Asp Ile
 245 250 255
 Ala Tyr Trp Lys Trp Asn Gly Ser Val Ile Asp Glu Asp Asp Pro Val
 260 265 270
 Leu Gly Glu Asp Tyr Tyr Ser Val Glu Asn Pro Ala Asn Lys Arg Arg
 275 280 285
 Ser Thr Leu Ile Thr Val Leu Asn Ile Ser Glu Ile Glu Ser Arg Phe
 290 295 300
 Tyr Lys His Pro Phe Thr Cys Phe Ala Lys Asn Thr His Gly Ile Asp
 305 310 315 320
 Ala Ala Tyr Ile Gln Leu Ile Tyr Pro Val Thr Asn Ser Glu Arg Cys
 325 330 335
 Asp Asp Trp Gly Leu Asp Thr Met Arg Gln Ile Gln Val Phe Glu Asp
 340 345 350
 Glu Pro Ala Arg Ile Lys Cys Pro Leu Phe Glu His Phe Leu Lys Phe
 355 360 365
 Asn Tyr Ser Thr Ala His Ser Ala Gly Leu Thr Leu Ile Trp Tyr Trp
 370 375 380
 Thr Arg Gln Asp Arg Asp Leu Glu Glu Pro Ile Asn Phe Arg Leu Pro

385	390	395	400
Glu Asn Arg Ile Ser Lys Glu Lys Asp Val Leu Trp Phe Arg Pro Thr			
	405	410	415
Leu Leu Asn Asp Thr Gly Asn Tyr Thr Cys Met Leu Arg Asn Thr Thr			
	420	425	430
Tyr Cys Ser Lys Val Ala Phe Pro Leu Glu Val Val Gln Lys Asp Ser			
	435	440	445
Cys Phe Asn Ser Pro Met Lys Leu Pro Val His Lys Leu Tyr Ile Glu			
	450	455	460
Tyr Gly Ile Gln Arg Ile Thr Cys Pro Asn Val Asp Gly Tyr Phe Pro			
465	470	475	480
Ser Ser Val Lys Pro Thr Ile Thr Trp Tyr Met Gly Cys Tyr Lys Ile			
	485	490	495
Gln Asn Phe Asn Asn Val Ile Pro Glu Gly Met Asn Leu Ser Phe Leu			
	500	505	510
Ile Ala Leu Ile Ser Asn Asn Gly Asn Tyr Thr Cys Val Val Thr Tyr			
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Pro Glu Asn Gly Arg Thr Phe His Leu Thr Arg Thr Leu Thr Val Lys			
	530	535	540
Val Val Gly Ser Pro Lys Asn Ala Val Pro Pro Val Ile His Ser Pro			
545	550	555	560
Asn Asp His Val Val Tyr Glu Lys Glu Pro Gly Glu Glu Leu Leu Ile			
	565	570	575
Pro Cys Thr Val Tyr Phe Ser Phe Leu Met Asp Ser Arg Asn Glu Val			
	580	585	590
Trp Trp Thr Ile Asp Gly Lys Lys Pro Asp Asp Ile Thr Ile Asp Val			
	595	600	605
Thr Ile Asn Glu Ser Ile Ser His Ser Arg Thr Glu Asp Glu Thr Arg			
	610	615	620
Thr Gln Ile Leu Ser Ile Lys Lys Val Thr Ser Glu Asp Leu Lys Arg			
625	630	635	640
Ser Tyr Val Cys His Ala Arg Ser Ala Lys Gly Glu Val Ala Lys Ala			
	645	650	655
Ala Lys Val Lys Gln Lys Val Pro Ala Pro Arg Tyr Thr Val Glu Ser			
	660	665	670
Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu			
	675	680	685
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu			
	690	695	700

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser																	
705					710						715						720
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu																	
					725						730						735
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr																	
					740						745						750
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn																	
					755						760						765
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro																	
					770						775						780
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln																	
785					790						795						800
Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val																	
					805						810						815
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val																	
					820						825						830
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro																	
					835						840						845
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr																	
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Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val																	
865					870						875						880
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu																	
					885						890						895
Ser Pro Gly Lys																	
					900												

<210>5

<211>2709

<212>DNA

<213>人

<400>5

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cgtcctgtgc ctcttaaccc aatgaacac aaaggcacta taacttggtg taagatgac	180
agcaagacac ctgtatctac agaacaagcc tccaggattc atcaacacaa agagaaactt	240
tggttttgttc ctgctaaggt ggaggattca ggacattact attgcgtggt aagaaattca	300
tcttactgcc tcagaattaa aataagtgc aaatttgtgg agaatgagcc taacttatgt	360

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tgcccttata	tggagttttt	taaaaatgaa	aataatgagt	tacctaaatt	acagtgggat	480
aaggattgca	aacctctact	tcttgacaat	atacacttta	gtggagtcaa	agataggctc	540
atcgtgatga	atgtggctga	aaagcataga	gggaactata	cttgtcatgc	atcctacaca	600
tacttgggca	agcaatatec	tattacecgg	gtaatagaat	ttattactct	agaggaaaac	660
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gaaaatcctg	caaacaaaag	aaggagtacc	ctcatcacag	tgcttaatat	atcggaaatt	900
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gcagcatata	tccagttaat	atatccagtc	actaattcag	aacgctgcga	tgactgggga	1020
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tccgtgatgc	atgaggctct	gcacaaccac	tacacacaga	agagcctctc	cctgtctctg	2700

ggtaaatga

2709

<210>6

<211>902

<212>PRT

<213>人

<400>6

Met Val Leu Leu Arg Leu Ile Cys Phe Ile Ala Leu Leu Ile Ser Ser

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Leu Glu Ala Asp Lys Cys Lys Glu Arg Glu Glu Lys Ile Ile Leu Val

20 25 30

Ser Ser Ala Asn Glu Ile Asp Val Arg Pro Cys Pro Leu Asn Pro Asn

35 40 45

Glu His Lys Gly Thr Ile Thr Trp Tyr Lys Asp Asp Ser Lys Thr Pro

50 55 60

Val Ser Thr Glu Gln Ala Ser Arg Ile His Gln His Lys Glu Lys Leu

65 70 75 80

Trp Phe Val Pro Ala Lys Val Glu Asp Ser Gly His Tyr Tyr Cys Val

85 90 95

Val Arg Asn Ser Ser Tyr Cys Leu Arg Ile Lys Ile Ser Ala Lys Phe

100 105 110

Val Glu Asn Glu Pro Asn Leu Cys Tyr Asn Ala Gln Ala Ile Phe Lys

115 120 125

Gln Lys Leu Pro Val Ala Gly Asp Gly Gly Leu Val Cys Pro Tyr Met

130 135 140

Glu Phe Phe Lys Asn Glu Asn Asn Glu Leu Pro Lys Leu Gln Trp Tyr

145 150 155 160

Lys Asp Cys Lys Pro Leu Leu Leu Asp Asn Ile His Phe Ser Gly Val

165 170 175

Lys Asp Arg Leu Ile Val Met Asn Val Ala Glu Lys His Arg Gly Asn

180 185 190

Tyr Thr Cys His Ala Ser Tyr Thr Tyr Leu Gly Lys Gln Tyr Pro Ile

195 200 205

Thr Arg Val Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys Pro Thr Arg

210 215 220

Pro Val Ile Val Ser Pro Ala Asn Glu Thr Met Glu Val Asp Leu Gly

225 230 235 240

Ser Gln Ile Gln Leu Ile Cys Asn Val Thr Gly Gln Leu Ser Asp Ile

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Ala Tyr Trp Lys Trp Asn Gly Ser Val Ile Asp Glu Asp Asp Pro Val			
	260	265	270
Leu Gly Glu Asp Tyr Tyr Ser Val Glu Asn Pro Ala Asn Lys Arg Arg			
	275	280	285
Ser Thr Leu Ile Thr Val Leu Asn Ile Ser Glu Ile Glu Ser Arg Phe			
	290	295	300
Tyr Lys His Pro Phe Thr Cys Phe Ala Lys Asn Thr His Gly Ile Asp			
305	310	315	320
Ala Ala Tyr Ile Gln Leu Ile Tyr Pro Val Thr Asn Ser Glu Arg Cys			
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Asp Asp Trp Gly Leu Asp Thr Met Arg Gln Ile Gln Val Phe Glu Asp			
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Glu Pro Ala Arg Ile Lys Cys Pro Leu Phe Glu His Phe Leu Lys Phe			
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Asn Tyr Ser Thr Ala His Ser Ala Gly Leu Thr Leu Ile Trp Tyr Trp			
	370	375	380
Thr Arg Gln Asp Arg Asp Leu Glu Glu Pro Ile Asn Phe Arg Leu Pro			
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Glu Asn Arg Ile Ser Lys Glu Lys Asp Val Leu Trp Phe Arg Pro Thr			
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Leu Leu Asn Asp Thr Gly Asn Tyr Thr Cys Met Leu Arg Asn Thr Thr			
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Tyr Cys Ser Lys Val Ala Phe Pro Leu Glu Val Val Gln Lys Asp Ser			
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Cys Phe Asn Ser Pro Met Lys Leu Pro Val His Lys Leu Tyr Ile Glu			
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Tyr Gly Ile Gln Arg Ile Thr Cys Pro Asn Val Asp Gly Tyr Phe Pro			
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Ser Ser Val Lys Pro Thr Ile Thr Trp Tyr Met Gly Cys Tyr Lys Ile			
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Gln Asn Phe Asn Asn Val Ile Pro Glu Gly Met Asn Leu Ser Phe Leu			
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Ile Ala Leu Ile Ser Asn Asn Gly Asn Tyr Thr Cys Val Val Thr Tyr			
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Pro Glu Asn Gly Arg Thr Phe His Leu Thr Arg Thr Leu Thr Val Lys			
	530	535	540
Val Val Gly Ser Pro Lys Asn Ala Val Pro Pro Val Ile His Ser Pro			
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Asn Asp His Val Val Tyr Glu Lys Glu Pro Gly Glu Glu Leu Leu Ile
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 580 585 590
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 595 600 605
 Thr Ile Asn Glu Ser Ile Ser His Ser Arg Thr Glu Asp Glu Thr Arg
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 Thr Gln Ile Leu Ser Ile Lys Lys Val Thr Ser Glu Asp Leu Lys Arg
 625 630 635 640
 Ser Tyr Val Cys His Ala Arg Ser Ala Lys Gly Glu Val Ala Lys Ala
 645 650 655
 Ala Lys Val Lys Gln Lys Val Pro Ala Pro Arg Tyr Thr Val Glu Ser
 660 665 670
 Gly Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu
 675 680 685
 Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
 690 695 700
 Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 705 710 715 720
 Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
 725 730 735
 Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
 740 745 750
 Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
 755 760 765
 Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
 770 775 780
 Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
 785 790 795 800
 Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn
 805 810 815
 Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
 820 825 830
 Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
 835 840 845
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 850 855 860
 Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys

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 ggtaaata 2709

<210>8

<211>902

<212>PRT

<213>人

<400>8

Met Val Leu Leu Arg Leu Ile Cys Phe Ile Ala Leu Leu Ile Ser Ser
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 Leu Glu Ala Asp Lys Cys Lys Glu Arg Glu Glu Lys Ile Ile Leu Val
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 Ser Ser Ala Asn Glu Ile Asp Val Arg Pro Cys Pro Leu Asn Pro Asn
 35 40 45
 Glu His Lys Gly Thr Ile Thr Trp Tyr Lys Asp Asp Ser Lys Thr Pro
 50 55 60
 Val Ser Thr Glu Gln Ala Ser Arg Ile His Gln His Lys Glu Lys Leu
 65 70 75 80
 Trp Phe Val Pro Ala Lys Val Glu Asp Ser Gly His Tyr Tyr Cys Val
 85 90 95
 Val Arg Asn Ser Ser Tyr Cys Leu Arg Ile Lys Ile Ser Ala Lys Phe

100	105	110
Val Glu Asn Glu Pro Asn Leu Cys Tyr Asn Ala Gln Ala Ile Phe Lys		
115	120	125
Gln Lys Leu Pro Val Ala Gly Asp Gly Gly Leu Val Cys Pro Tyr Met		
130	135	140
Glu Phe Phe Lys Asn Glu Asn Asn Glu Leu Pro Lys Leu Gln Trp Tyr		
145	150	155
Lys Asp Cys Lys Pro Leu Leu Leu Asp Asn Ile His Phe Ser Gly Val		
165	170	175
Lys Asp Arg Leu Ile Val Met Asn Val Ala Glu Lys His Arg Gly Asn		
180	185	190
Tyr Thr Cys His Ala Ser Tyr Thr Tyr Leu Gly Lys Gln Tyr Pro Ile		
195	200	205
Thr Arg Val Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys Pro Thr Arg		
210	215	220
Pro Val Ile Val Ser Pro Ala Asn Glu Thr Met Glu Val Asp Leu Gly		
225	230	235
Ser Gln Ile Gln Leu Ile Cys Asn Val Thr Gly Gln Leu Ser Asp Ile		
245	250	255
Ala Tyr Trp Lys Trp Asn Gly Ser Val Ile Asp Glu Asp Asp Pro Val		
260	265	270
Leu Gly Glu Asp Tyr Tyr Ser Val Glu Asn Pro Ala Asn Lys Arg Arg		
275	280	285
Ser Thr Leu Ile Thr Val Leu Asn Ile Ser Glu Ile Glu Ser Arg Phe		
290	295	300
Tyr Lys His Pro Phe Thr Cys Phe Ala Lys Asn Thr His Gly Ile Asp		
305	310	315
Ala Ala Tyr Ile Gln Leu Ile Tyr Pro Val Thr Asn Ser Glu Arg Cys		
325	330	335
Asp Asp Trp Gly Leu Asp Thr Met Arg Gln Ile Gln Val Phe Glu Asp		
340	345	350
Glu Pro Ala Arg Ile Lys Cys Pro Leu Phe Glu His Phe Leu Lys Phe		
355	360	365
Asn Tyr Ser Thr Ala His Ser Ala Gly Leu Thr Leu Ile Trp Tyr Trp		
370	375	380
Thr Arg Gln Asp Arg Asp Leu Glu Glu Pro Ile Asn Phe Arg Leu Pro		
385	390	395
Glu Asn Arg Ile Ser Lys Glu Lys Asp Val Leu Trp Phe Arg Pro Thr		
405	410	415

Leu Leu Asn Asp Thr Gly Asn Tyr Thr Cys Met Leu Arg Asn Thr Thr
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 Tyr Cys Ser Lys Val Ala Phe Pro Leu Glu Val Val Gln Lys Asp Ser
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 Cys Phe Asn Ser Pro Met Lys Leu Pro Val His Lys Leu Tyr Ile Glu
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 Tyr Gly Ile Gln Arg Ile Thr Cys Pro Asn Val Asp Gly Tyr Phe Pro
 465 470 475 480
 Ser Ser Val Lys Pro Thr Ile Thr Trp Tyr Met Gly Cys Tyr Lys Ile
 485 490 495
 Gln Asn Phe Asn Asn Val Ile Pro Glu Gly Met Asn Leu Ser Phe Leu
 500 505 510
 Ile Ala Leu Ile Ser Asn Asn Gly Asn Tyr Thr Cys Val Val Thr Tyr
 515 520 525
 Pro Glu Asn Gly Arg Thr Phe His Leu Thr Arg Thr Leu Thr Val Lys
 530 535 540
 Val Val Gly Ser Pro Lys Asn Ala Val Pro Pro Val Ile His Ser Pro
 545 550 555 560
 Asn Asp His Val Val Tyr Glu Lys Glu Pro Gly Glu Glu Leu Leu Ile
 565 570 575
 Pro Cys Thr Val Tyr Phe Ser Phe Leu Met Asp Ser Arg Asn Glu Val
 580 585 590
 Trp Trp Thr Ile Asp Gly Lys Lys Pro Asp Asp Ile Thr Ile Asp Val
 595 600 605
 Thr Ile Asn Glu Ser Ile Ser His Ser Arg Thr Glu Asp Glu Thr Arg
 610 615 620
 Thr Gln Ile Leu Ser Ile Lys Lys Val Thr Ser Glu Asp Leu Lys Arg
 625 630 635 640
 Ser Tyr Val Cys His Ala Arg Ser Ala Lys Gly Glu Val Ala Lys Ala
 645 650 655
 Ala Lys Val Lys Gln Lys Val Pro Ala Pro Arg Tyr Thr Val Glu Ser
 660 665 670
 Gly Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu
 675 680 685
 Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
 690 695 700
 Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 705 710 715 720
 Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly

	725	730	735
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn			
	740	745	750
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp			
	755	760	765
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro			
	770	775	780
Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu			
785	790	795	800
Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn			
	805	810	815
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile			
	820	825	830
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr			
	835	840	845
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg			
	850	855	860
Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys			
865	870	875	880
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu			
	885	890	895
Ser Leu Ser Leu Gly Lys			
	900		

<210>9

<211>2703

<212>DNA

<213>人

<400>9

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gagccagctc gcatcaagtg cccactcttt gaacacttct tgaattcaa ctacagcaca	180
gcccattcag ctggccttac tctgatctgg tattggacta ggcaggaccg ggaccttgag	240
gagccaatta acttccgcct ccccgagaac cgcattagta aggagaaaga tgtgctgtgg	300
ttccggceca ctctctcaa tgacactggc aactatacct gcatgttaag gaactactaca	360
tattgcagca aagttgcatt tcccttgga gttgttcaaa aagacagctg tttcaattec	420
cccatgaaac tcccagtgc taaactgtat atagaatatg gcattcagag gatcaactgt	480
ccaaatgtag atggatattt tccttccagt gtcaaaccga ctatcacttg gtatatgggc	540

tgttataaaa	tacagaat	tt	taataatgta	atacccgaag	gtatgaactt	gagtttcctc	600	
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cgtacgtttc	atctcaccag	gactctgact	gtaaaggtag	taggctctcc	aaaaaatgca		720	
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gagctactca	ttccctgtac	ggtctat	tttt	agttttctga	tggattctcg	caatgaggtt	840	
tggtggacca	ttgatggaaa	aaaacctgat	gacatcacta	ttgatgtcac	cattaacgaa		900	
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gcatat	atcc	agttaatata	tccagtcact	aattccggag	acaaaactca	cacatgcccc		2040
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tga							2703	

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<211>900

<212>PRT

<213>人

<400>10

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 35 40 45
 Leu Phe Glu His Phe Leu Lys Phe Asn Tyr Ser Thr Ala His Ser Ala
 50 55 60
 Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu
 65 70 75 80
 Glu Pro Ile Asn Phe Arg Leu Pro Glu Asn Arg Ile Ser Lys Glu Lys
 85 90 95
 Asp Val Leu Trp Phe Arg Pro Thr Leu Leu Asn Asp Thr Gly Asn Tyr
 100 105 110
 Thr Cys Met Leu Arg Asn Thr Thr Tyr Cys Ser Lys Val Ala Phe Pro
 115 120 125
 Leu Glu Val Val Gln Lys Asp Ser Cys Phe Asn Ser Pro Met Lys Leu
 130 135 140
 Pro Val His Lys Leu Tyr Ile Glu Tyr Gly Ile Gln Arg Ile Thr Cys
 145 150 155 160
 Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Thr Ile Thr
 165 170 175
 Trp Tyr Met Gly Cys Tyr Lys Ile Gln Asn Phe Asn Asn Val Ile Pro
 180 185 190
 Glu Gly Met Asn Leu Ser Phe Leu Ile Ala Leu Ile Ser Asn Asn Gly
 195 200 205
 Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Thr Phe His
 210 215 220
 Leu Thr Arg Thr Leu Thr Val Lys Val Val Gly Ser Pro Lys Asn Ala
 225 230 235 240
 Val Pro Pro Val Ile His Ser Pro Asn Asp His Val Val Tyr Glu Lys
 245 250 255
 Glu Pro Gly Glu Glu Leu Leu Ile Pro Cys Thr Val Tyr Phe Ser Phe
 260 265 270

Leu Met Asp Ser Arg Asn Glu Val Trp Trp Thr Ile Asp Gly Lys Lys
 275 280 285
 Pro Asp Asp Ile Thr Ile Asp Val Thr Ile Asn Glu Ser Ile Ser His
 290 295 300
 Ser Arg Thr Glu Asp Glu Thr Arg Thr Gln Ile Leu Ser Ile Lys Lys
 305 310 315 320
 Val Thr Ser Glu Asp Leu Lys Arg Ser Tyr Val Cys His Ala Arg Ser
 325 330 335
 Ala Lys Gly Glu Val Ala Lys Ala Ala Lys Val Lys Gln Lys Val Pro
 340 345 350
 Ala Pro Arg Tyr Thr Val Glu Lys Cys Lys Glu Arg Glu Glu Lys Ile
 355 360 365
 Ile Leu Val Ser Ser Ala Asn Glu Ile Asp Val Arg Pro Cys Pro Leu
 370 375 380
 Asn Pro Asn Glu His Lys Gly Thr Ile Thr Trp Tyr Lys Asp Asp Ser
 385 390 395 400
 Lys Thr Pro Val Ser Thr Glu Gln Ala Ser Arg Ile His Gln His Lys
 405 410 415
 Glu Lys Leu Trp Phe Val Pro Ala Lys Val Glu Asp Ser Gly His Tyr
 420 425 430
 Tyr Cys Val Val Arg Asn Ser Ser Tyr Cys Leu Arg Ile Lys Ile Ser
 435 440 445
 Ala Lys Phe Val Glu Asn Glu Pro Asn Leu Cys Tyr Asn Ala Gln Ala
 450 455 460
 Ile Phe Lys Gln Lys Leu Pro Val Ala Gly Asp Gly Gly Leu Val Cys
 465 470 475 480
 Pro Tyr Met Glu Phe Phe Lys Asn Glu Asn Asn Glu Leu Pro Lys Leu
 485 490 495
 Gln Trp Tyr Lys Asp Cys Lys Pro Leu Leu Leu Asp Asn Ile His Phe
 500 505 510
 Ser Gly Val Lys Asp Arg Leu Ile Val Met Asn Val Ala Glu Lys His
 515 520 525
 Arg Gly Asn Tyr Thr Cys His Ala Ser Tyr Thr Tyr Leu Gly Lys Gln
 530 535 540
 Tyr Pro Ile Thr Arg Val Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys
 545 550 555 560
 Pro Thr Arg Pro Val Ile Val Ser Pro Ala Asn Glu Thr Met Glu Val
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 Asp Leu Gly Ser Gln Ile Gln Leu Ile Cys Asn Val Thr Gly Gln Leu

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595	600	605
Asp Pro Val Leu Gly Glu Asp Tyr Tyr Ser Val Glu Asn Pro Ala Asn		
610	615	620
Lys Arg Arg Ser Thr Leu Ile Thr Val Leu Asn Ile Ser Glu Ile Glu		
625	630	635
Ser Arg Phe Tyr Lys His Pro Phe Thr Cys Phe Ala Lys Asn Thr His		
645	650	655
Gly Ile Asp Ala Ala Tyr Ile Gln Leu Ile Tyr Pro Val Thr Asn Ser		
660	665	670
Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu		
675	680	685
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu		
690	695	700
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser		
705	710	715
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu		
725	730	735
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr		
740	745	750
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn		
755	760	765
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro		
770	775	780
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln		
785	790	795
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val		
805	810	815
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val		
820	825	830
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro		
835	840	845
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr		
850	855	860
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val		
865	870	875
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu		
885	890	895

Ser Pro Gly Lys

900

<210>11

<211>2709

<212>DNA

<213> 人

<400>11

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gagccagctc	gcatcaagtg	cccactcttt	gaacacttct	tgaaattcaa	ctacagcaca	180
gcccattcag	ctggccttac	tctgatctgg	tattggacta	ggcaggaccg	ggaccttgag	240
gagccaatta	acttccgcct	ccccgagaac	cgcattagta	aggagaaaga	tgtgctgtgg	300
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tattgcagca	aagttgcatt	tccttggaa	gttgttcaaa	aagacagctg	ttcaattcc	420
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tgttataaaa	tacagaattt	taataatgta	atacccgaag	gtatgaactt	gagtttcctc	600
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ggtaaataga 2709

<210>12

<211>902

<212>PRT

<213>人

<400>12

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Arg Gln Ile Gln Val Phe Glu Asp Glu Pro Ala Arg Ile Lys Cys Pro
35 40 45
Leu Phe Glu His Phe Leu Lys Phe Asn Tyr Ser Thr Ala His Ser Ala
50 55 60
Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu
65 70 75 80
Glu Pro Ile Asn Phe Arg Leu Pro Glu Asn Arg Ile Ser Lys Glu Lys
85 90 95
Asp Val Leu Trp Phe Arg Pro Thr Leu Leu Asn Asp Thr Gly Asn Tyr
100 105 110
Thr Cys Met Leu Arg Asn Thr Thr Tyr Cys Ser Lys Val Ala Phe Pro
115 120 125

Leu Glu Val Val Gln Lys Asp Ser Cys Phe Asn Ser Pro Met Lys Leu
 130 135 140
 Pro Val His Lys Leu Tyr Ile Glu Tyr Gly Ile Gln Arg Ile Thr Cys
 145 150 155 160
 Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Thr Ile Thr
 165 170 175
 Trp Tyr Met Gly Cys Tyr Lys Ile Gln Asn Phe Asn Asn Val Ile Pro
 180 185 190
 Glu Gly Met Asn Leu Ser Phe Leu Ile Ala Leu Ile Ser Asn Asn Gly
 195 200 205
 Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Thr Phe His
 210 215 220
 Leu Thr Arg Thr Leu Thr Val Lys Val Val Gly Ser Pro Lys Asn Ala
 225 230 235 240
 Val Pro Pro Val Ile His Ser Pro Asn Asp His Val Val Tyr Glu Lys
 245 250 255
 Glu Pro Gly Glu Glu Leu Leu Ile Pro Cys Thr Val Tyr Phe Ser Phe
 260 265 270
 Leu Met Asp Ser Arg Asn Glu Val Trp Trp Thr Ile Asp Gly Lys Lys
 275 280 285
 Pro Asp Asp Ile Thr Ile Asp Val Thr Ile Asn Glu Ser Ile Ser His
 290 295 300
 Ser Arg Thr Glu Asp Glu Thr Arg Thr Gln Ile Leu Ser Ile Lys Lys
 305 310 315 320
 Val Thr Ser Glu Asp Leu Lys Arg Ser Tyr Val Cys His Ala Arg Ser
 325 330 335
 Ala Lys Gly Glu Val Ala Lys Ala Ala Lys Val Lys Gln Lys Val Pro
 340 345 350
 Ala Pro Arg Tyr Thr Val Glu Lys Cys Lys Glu Arg Glu Glu Lys Ile
 355 360 365
 Ile Leu Val Ser Ser Ala Asn Glu Ile Asp Val Arg Pro Cys Pro Leu
 370 375 380
 Asn Pro Asn Glu His Lys Gly Thr Ile Thr Trp Tyr Lys Asp Asp Ser
 385 390 395 400
 Lys Thr Pro Val Ser Thr Glu Gln Ala Ser Arg Ile His Gln His Lys
 405 410 415
 Glu Lys Leu Trp Phe Val Pro Ala Lys Val Glu Asp Ser Gly His Tyr
 420 425 430
 Tyr Cys Val Val Arg Asn Ser Ser Tyr Cys Leu Arg Ile Lys Ile Ser

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Ala Lys Phe Val Glu Asn Glu Pro Asn Leu Cys Tyr Asn Ala Gln Ala		
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Ile Phe Lys Gln Lys Leu Pro Val Ala Gly Asp Gly Gly Leu Val Cys		
465	470	475
Pro Tyr Met Glu Phe Phe Lys Asn Glu Asn Asn Glu Leu Pro Lys Leu		
485	490	495
Gln Trp Tyr Lys Asp Cys Lys Pro Leu Leu Leu Asp Asn Ile His Phe		
500	505	510
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515	520	525
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Tyr Pro Ile Thr Arg Val Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys		
545	550	555
Pro Thr Arg Pro Val Ile Val Ser Pro Ala Asn Glu Thr Met Glu Val		
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Asp Leu Gly Ser Gln Ile Gln Leu Ile Cys Asn Val Thr Gly Gln Leu		
580	585	590
Ser Asp Ile Ala Tyr Trp Lys Trp Asn Gly Ser Val Ile Asp Glu Asp		
595	600	605
Asp Pro Val Leu Gly Glu Asp Tyr Tyr Ser Val Glu Asn Pro Ala Asn		
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Lys Arg Arg Ser Thr Leu Ile Thr Val Leu Asn Ile Ser Glu Ile Glu		
625	630	635
Ser Arg Phe Tyr Lys His Pro Phe Thr Cys Phe Ala Lys Asn Thr His		
645	650	655
Gly Ile Asp Ala Ala Tyr Ile Gln Leu Ile Tyr Pro Val Thr Asn Ser		
660	665	670
Gly Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu		
675	680	685
Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp		
690	695	700
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp		
705	710	715
Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly		
725	730	735
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn		
740	745	750

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
 755 760 765
 Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
 770 775 780
 Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
 785 790 795 800
 Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn
 805 810 815
 Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
 820 825 830
 Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
 835 840 845
 Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg
 850 855 860
 Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys
 865 870 875 880
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 Ser Leu Ser Leu Gly Lys
 900

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<211>2709

<212>DNA

<213> 人

<400>13

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 gccattcag ctggccttac tctgatctgg tattggacta ggcaggaccg ggaccttgag 240
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<211>902

<212>PRT

<213>人

<400>14

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 35 40 45
 Leu Phe Glu His Phe Leu Lys Phe Asn Tyr Ser Thr Ala His Ser Ala
 50 55 60
 Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu
 65 70 75 80
 Glu Pro Ile Asn Phe Arg Leu Pro Glu Asn Arg Ile Ser Lys Glu Lys
 85 90 95
 Asp Val Leu Trp Phe Arg Pro Thr Leu Leu Asn Asp Thr Gly Asn Tyr
 100 105 110
 Thr Cys Met Leu Arg Asn Thr Thr Tyr Cys Ser Lys Val Ala Phe Pro
 115 120 125
 Leu Glu Val Val Gln Lys Asp Ser Cys Phe Asn Ser Pro Met Lys Leu
 130 135 140
 Pro Val His Lys Leu Tyr Ile Glu Tyr Gly Ile Gln Arg Ile Thr Cys
 145 150 155 160
 Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Thr Ile Thr
 165 170 175
 Trp Tyr Met Gly Cys Tyr Lys Ile Gln Asn Phe Asn Asn Val Ile Pro
 180 185 190
 Glu Gly Met Asn Leu Ser Phe Leu Ile Ala Leu Ile Ser Asn Asn Gly
 195 200 205
 Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Thr Phe His
 210 215 220
 Leu Thr Arg Thr Leu Thr Val Lys Val Val Gly Ser Pro Lys Asn Ala
 225 230 235 240
 Val Pro Pro Val Ile His Ser Pro Asn Asp His Val Val Tyr Glu Lys
 245 250 255
 Glu Pro Gly Glu Glu Leu Leu Ile Pro Cys Thr Val Tyr Phe Ser Phe
 260 265 270
 Leu Met Asp Ser Arg Asn Glu Val Trp Trp Thr Ile Asp Gly Lys Lys
 275 280 285
 Pro Asp Asp Ile Thr Ile Asp Val Thr Ile Asn Glu Ser Ile Ser His

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Val Thr Ser Glu Asp Leu Lys Arg Ser Tyr Val Cys His Ala Arg Ser		
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Ala Lys Gly Glu Val Ala Lys Ala Ala Lys Val Lys Gln Lys Val Pro		
	340	345
Ala Pro Arg Tyr Thr Val Glu Lys Cys Lys Glu Arg Glu Glu Lys Ile		
	355	360
Ile Leu Val Ser Ser Ala Asn Glu Ile Asp Val Arg Pro Cys Pro Leu		
	370	375
Asn Pro Asn Glu His Lys Gly Thr Ile Thr Trp Tyr Lys Asp Asp Ser		
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Lys Thr Pro Val Ser Thr Glu Gln Ala Ser Arg Ile His Gln His Lys		
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Glu Lys Leu Trp Phe Val Pro Ala Lys Val Glu Asp Ser Gly His Tyr		
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Tyr Cys Val Val Arg Asn Ser Ser Tyr Cys Leu Arg Ile Lys Ile Ser		
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Ala Lys Phe Val Glu Asn Glu Pro Asn Leu Cys Tyr Asn Ala Gln Ala		
	450	455
Ile Phe Lys Gln Lys Leu Pro Val Ala Gly Asp Gly Gly Leu Val Cys		
465	470	475
Pro Tyr Met Glu Phe Phe Lys Asn Glu Asn Asn Glu Leu Pro Lys Leu		
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Gln Trp Tyr Lys Asp Cys Lys Pro Leu Leu Leu Asp Asn Ile His Phe		
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Ser Gly Val Lys Asp Arg Leu Ile Val Met Asn Val Ala Glu Lys His		
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Arg Gly Asn Tyr Thr Cys His Ala Ser Tyr Thr Tyr Leu Gly Lys Gln		
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Tyr Pro Ile Thr Arg Val Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys		
545	550	555
Pro Thr Arg Pro Val Ile Val Ser Pro Ala Asn Glu Thr Met Glu Val		
	565	570
Asp Leu Gly Ser Gln Ile Gln Leu Ile Cys Asn Val Thr Gly Gln Leu		
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Ser Asp Ile Ala Tyr Trp Lys Trp Asn Gly Ser Val Ile Asp Glu Asp		
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		605

Asp Pro Val Leu Gly Glu Asp Tyr Tyr Ser Val Glu Asn Pro Ala Asn
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 Lys Arg Arg Ser Thr Leu Ile Thr Val Leu Asn Ile Ser Glu Ile Glu
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 Ser Arg Phe Tyr Lys His Pro Phe Thr Cys Phe Ala Lys Asn Thr His
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 660 665 670
 Gly Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu
 675 680 685
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 690 695 700
 Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 705 710 715 720
 Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
 725 730 735
 Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
 740 745 750
 Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
 755 760 765
 Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
 770 775 780
 Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
 785 790 795 800
 Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn
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 Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
 820 825 830
 Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
 835 840 845
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 885 890 895
 Ser Leu Ser Leu Gly Lys
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<211>2748

<212>DNA

<213> 人

<400>15

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gaagaagaga	cacggatgtg	ggcccaggac	ggtgctctgt	ggcttctgcc	agccttgtag	300
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<212>PRT

<213>人

<400>16

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 Arg Cys Pro Gln Val Pro Tyr Trp Leu Trp Ala Ser Val Ser Pro Arg
 50 55 60
 Ile Asn Leu Thr Trp His Lys Asn Asp Ser Ala Arg Thr Val Pro Gly
 65 70 75 80
 Glu Glu Glu Thr Arg Met Trp Ala Gln Asp Gly Ala Leu Trp Leu Leu
 85 90 95
 Pro Ala Leu Gln Glu Asp Ser Gly Thr Tyr Val Cys Thr Thr Arg Asn
 100 105 110
 Ala Ser Tyr Cys Asp Lys Met Ser Ile Glu Leu Arg Val Phe Glu Asn
 115 120 125
 Thr Asp Ala Phe Leu Pro Phe Ile Ser Tyr Pro Gln Ile Leu Thr Leu
 130 135 140
 Ser Thr Ser Gly Val Leu Val Cys Pro Asp Leu Ser Glu Phe Thr Arg

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Asp Lys Thr Asp Val Lys Ile Gln Trp Tyr Lys Asp Ser Leu Leu Leu			
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Asp Lys Asp Asn Glu Lys Phe Leu Ser Val Arg Gly Thr Thr His Leu			
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Leu Val His Asp Val Ala Leu Glu Asp Ala Gly Tyr Tyr Arg Cys Val			
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Leu Thr Phe Ala His Glu Gly Gln Gln Tyr Asn Ile Thr Arg Ser Ile			
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Glu Leu Arg Ile Lys Lys Lys Lys Glu Glu Thr Ile Pro Val Ile Ile			
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Ser Pro Leu Lys Thr Ile Ser Ala Ser Leu Gly Ser Arg Leu Thr Ile			
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Pro Cys Lys Val Phe Leu Gly Thr Gly Thr Pro Leu Thr Thr Met Leu			
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Trp Trp Thr Ala Asn Asp Thr His Ile Glu Ser Ala Tyr Pro Gly Gly			
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Arg Val Thr Glu Gly Pro Arg Gln Glu Tyr Ser Glu Asn Asn Glu Asn			
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Tyr Ile Glu Val Pro Leu Ile Phe Asp Pro Val Thr Arg Glu Asp Leu			
305	310	315	320
His Met Asp Phe Lys Cys Val Val His Asn Thr Leu Ser Phe Gln Thr			
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Leu Arg Thr Thr Val Lys Glu Ala Ser Ser Thr Phe Ser Glu Arg Cys			
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Asp Asp Trp Gly Leu Asp Thr Met Arg Gln Ile Gln Val Phe Glu Asp			
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Asn Tyr Ser Thr Ala His Ser Ala Gly Leu Thr Leu Ile Trp Tyr Trp			
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Thr Arg Gln Asp Arg Asp Leu Glu Glu Pro Ile Asn Phe Arg Leu Pro			
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Glu Asn Arg Ile Ser Lys Glu Lys Asp Val Leu Trp Phe Arg Pro Thr			
	420	425	430
Leu Leu Asn Asp Thr Gly Asn Tyr Thr Cys Met Leu Arg Asn Thr Thr			
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Tyr Cys Ser Lys Val Ala Phe Pro Leu Glu Val Val Gln Lys Asp Ser			
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Ser Ser Val Lys Pro Thr Ile Thr Trp Tyr Met Gly Cys Tyr Lys Ile																	
					500					505							510
Gln Asn Phe Asn Asn Val Ile Pro Glu Gly Met Asn Leu Ser Phe Leu																	
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Pro Cys Thr Val Tyr Phe Ser Phe Leu Met Asp Ser Arg Asn Glu Val																	
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Thr Ile Asn Glu Ser Ile Ser His Ser Arg Thr Glu Asp Glu Thr Arg																	
625					630					635							640
Thr Gln Ile Leu Ser Ile Lys Lys Val Thr Ser Glu Asp Leu Lys Arg																	
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Ser Tyr Val Cys His Ala Arg Ser Ala Lys Gly Glu Val Ala Lys Ala																	
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Ala Lys Val Lys Gln Lys Val Pro Ala Pro Arg Tyr Thr Val Ser Gly																	
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Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly																	
					690					695							700
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met																	
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Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His																	
					725					730							735
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val																	
					740					745							750
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr																	
					755					760							765
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly																	

770	775	780			
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile					
785	790	795	800		
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val					
	805	810	815		
Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser					
	820	825	830		
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu					
	835	840	845		
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro					
850	855	860			
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val					
865	870	875	880		
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met					
	885	890	895		
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser					
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915					

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<211>2754

<212>DNA

<213>人

<400>17

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ctggaagggg agcctgtagc cctgaggtgc ccccaggtgc cctactgggt gtgggcctct      180
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 Arg Cys Pro Gln Val Pro Tyr Trp Leu Trp Ala Ser Val Ser Pro Arg
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 Ile Asn Leu Thr Trp His Lys Asn Asp Ser Ala Arg Thr Val Pro Gly
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 Glu Glu Glu Thr Arg Met Trp Ala Gln Asp Gly Ala Leu Trp Leu Leu
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 Pro Ala Leu Gln Glu Asp Ser Gly Thr Tyr Val Cys Thr Thr Arg Asn
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 Ala Ser Tyr Cys Asp Lys Met Ser Ile Glu Leu Arg Val Phe Glu Asn
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 Ser Thr Ser Gly Val Leu Val Cys Pro Asp Leu Ser Glu Phe Thr Arg
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 Asp Lys Thr Asp Val Lys Ile Gln Trp Tyr Lys Asp Ser Leu Leu Leu
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 Asp Lys Asp Asn Glu Lys Phe Leu Ser Val Arg Gly Thr Thr His Leu
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 Leu Val His Asp Val Ala Leu Glu Asp Ala Gly Tyr Tyr Arg Cys Val
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 Leu Thr Phe Ala His Glu Gly Gln Gln Tyr Asn Ile Thr Arg Ser Ile
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 Glu Leu Arg Ile Lys Lys Lys Lys Glu Glu Thr Ile Pro Val Ile Ile
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 Ser Pro Leu Lys Thr Ile Ser Ala Ser Leu Gly Ser Arg Leu Thr Ile
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<213> 人

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<211>917

<212>PRT

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Arg His Tyr Lys Arg Glu Phe Arg Leu Glu Gly Glu Pro Val Ala Leu
           35           40           45
Arg Cys Pro Gln Val Pro Tyr Trp Leu Trp Ala Ser Val Ser Pro Arg
           50           55           60
Ile Asn Leu Thr Trp His Lys Asn Asp Ser Ala Arg Thr Val Pro Gly
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Glu Glu Glu Thr Arg Met Trp Ala Gln Asp Gly Ala Leu Trp Leu Leu
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Pro Ala Leu Gln Glu Asp Ser Gly Thr Tyr Val Cys Thr Thr Arg Asn
           100          105          110
Ala Ser Tyr Cys Asp Lys Met Ser Ile Glu Leu Arg Val Phe Glu Asn
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Thr Asp Ala Phe Leu Pro Phe Ile Ser Tyr Pro Gln Ile Leu Thr Leu
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 Glu Leu Arg Ile Lys Lys Lys Lys Glu Glu Thr Ile Pro Val Ile Ile
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Ser Ser Val Lys Pro Thr Ile Thr Trp Tyr Met Gly Cys Tyr Lys Ile		
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Gln Asn Phe Asn Asn Val Ile Pro Glu Gly Met Asn Leu Ser Phe Leu		
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Ile Ala Leu Ile Ser Asn Asn Gly Asn Tyr Thr Cys Val Val Thr Tyr		
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Pro Glu Asn Gly Arg Thr Phe His Leu Thr Arg Thr Leu Thr Val Lys		
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Val Val Gly Ser Pro Lys Asn Ala Val Pro Pro Val Ile His Ser Pro		
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Asn Asp His Val Val Tyr Glu Lys Glu Pro Gly Glu Glu Leu Leu Ile		
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Thr Gln Ile Leu Ser Ile Lys Lys Val Thr Ser Glu Asp Leu Lys Arg		
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Ser Tyr Val Cys His Ala Arg Ser Ala Lys Gly Glu Val Ala Lys Ala		
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Ala Lys Val Lys Gln Lys Val Pro Ala Pro Arg Tyr Thr Val Ser Gly		
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Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe		
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Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val		
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Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val		
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Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser		
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Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
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 785 790 795 800
 Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
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 Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
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 Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
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 Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
 850 855 860
 Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
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<212>DNA

<213>人

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<213>人

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Leu Phe Glu His Phe Leu Lys Phe Asn Tyr Ser Thr Ala His Ser Ala
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Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu
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Glu Pro Ile Asn Phe Arg Leu Pro Glu Asn Arg Ile Ser Lys Glu Lys
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Asp Val Leu Trp Phe Arg Pro Thr Leu Leu Asn Asp Thr Gly Asn Tyr
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Thr Cys Met Leu Arg Asn Thr Thr Tyr Cys Ser Lys Val Ala Phe Pro
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Pro Val His Lys Leu Tyr Ile Glu Tyr Gly Ile Gln Arg Ile Thr Cys
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Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Thr Ile Thr
 165 170 175

Trp Tyr Met Gly Cys Tyr Lys Ile Gln Asn Phe Asn Asn Val Ile Pro
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Glu Gly Met Asn Leu Ser Phe Leu Ile Ala Leu Ile Ser Asn Asn Gly
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Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Thr Phe His
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Leu Thr Arg Thr Leu Thr Val Lys Val Val Gly Ser Pro Lys Asn Ala
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Val Pro Pro Val Ile His Ser Pro Asn Asp His Val Val Tyr Glu Lys
 245 250 255

Glu Pro Gly Glu Glu Leu Leu Ile Pro Cys Thr Val Tyr Phe Ser Phe
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<213> 人

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<212>PRT

<213>人

<400>24

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

145	150	155	160
Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Thr Ile Thr			
	165	170	175
Trp Tyr Met Gly Cys Tyr Lys Ile Gln Asn Phe Asn Asn Val Ile Pro			
	180	185	190
Glu Gly Met Asn Leu Ser Phe Leu Ile Ala Leu Ile Ser Asn Asn Gly			
	195	200	205
Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Thr Phe His			
210	215	220	
Leu Thr Arg Thr Leu Thr Val Lys Val Val Gly Ser Pro Lys Asn Ala			
225	230	235	240
Val Pro Pro Val Ile His Ser Pro Asn Asp His Val Val Tyr Glu Lys			
	245	250	255
Glu Pro Gly Glu Glu Leu Leu Ile Pro Cys Thr Val Tyr Phe Ser Phe			
	260	265	270
Leu Met Asp Ser Arg Asn Glu Val Trp Trp Thr Ile Asp Gly Lys Lys			
	275	280	285
Pro Asp Asp Ile Thr Ile Asp Val Thr Ile Asn Glu Ser Ile Ser His			
290	295	300	
Ser Arg Thr Glu Asp Glu Thr Arg Thr Gln Ile Leu Ser Ile Lys Lys			
305	310	315	320
Val Thr Ser Glu Asp Leu Lys Arg Ser Tyr Val Cys His Ala Arg Ser			
	325	330	335
Ala Lys Gly Glu Val Ala Lys Ala Ala Lys Val Lys Gln Lys Val Pro			
	340	345	350
Ala Pro Arg Tyr Thr Val His Thr Gly Ala Ala Arg Ser Cys Arg Phe			
	355	360	365
Arg Gly Arg His Tyr Lys Arg Glu Phe Arg Leu Glu Gly Glu Pro Val			
370	375	380	
Ala Leu Arg Cys Pro Gln Val Pro Tyr Trp Leu Trp Ala Ser Val Ser			
385	390	395	400
Pro Arg Ile Asn Leu Thr Trp His Lys Asn Asp Ser Ala Arg Thr Val			
	405	410	415
Pro Gly Glu Glu Glu Thr Arg Met Trp Ala Gln Asp Gly Ala Leu Trp			
	420	425	430
Leu Leu Pro Ala Leu Gln Glu Asp Ser Gly Thr Tyr Val Cys Thr Thr			
	435	440	445
Arg Asn Ala Ser Tyr Cys Asp Lys Met Ser Ile Glu Leu Arg Val Phe			
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Glu Asn Thr Asp Ala Phe Leu Pro Phe Ile Ser Tyr Pro Gln Ile Leu
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 Thr Leu Ser Thr Ser Gly Val Leu Val Cys Pro Asp Leu Ser Glu Phe
 485 490 495
 Thr Arg Asp Lys Thr Asp Val Lys Ile Gln Trp Tyr Lys Asp Ser Leu
 500 505 510
 Leu Leu Asp Lys Asp Asn Glu Lys Phe Leu Ser Val Arg Gly Thr Thr
 515 520 525
 His Leu Leu Val His Asp Val Ala Leu Glu Asp Ala Gly Tyr Tyr Arg
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 Cys Val Leu Thr Phe Ala His Glu Gly Gln Gln Tyr Asn Ile Thr Arg
 545 550 555 560
 Ser Ile Glu Leu Arg Ile Lys Lys Lys Lys Glu Glu Thr Ile Pro Val
 565 570 575
 Ile Ile Ser Pro Leu Lys Thr Ile Ser Ala Ser Leu Gly Ser Arg Leu
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 Thr Ile Pro Cys Lys Val Phe Leu Gly Thr Gly Thr Pro Leu Thr Thr
 595 600 605
 Met Leu Trp Trp Thr Ala Asn Asp Thr His Ile Glu Ser Ala Tyr Pro
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 Gly Gly Arg Val Thr Glu Gly Pro Arg Gln Glu Tyr Ser Glu Asn Asn
 625 630 635 640
 Glu Asn Tyr Ile Glu Val Pro Leu Ile Phe Asp Pro Val Thr Arg Glu
 645 650 655
 Asp Leu His Met Asp Phe Lys Cys Val Val His Asn Thr Leu Ser Phe
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 Gln Thr Leu Arg Thr Thr Val Lys Glu Ala Ser Ser Thr Phe Ser Gly
 675 680 685
 Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe
 690 695 700
 Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
 705 710 715 720
 Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
 725 730 735
 Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
 740 745 750
 Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
 755 760 765
 Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu

770	775	780
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser		
785	790	795
Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro		800
	805	810
Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln		815
	820	825
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala		830
	835	840
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr		845
	850	855
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu		860
865	870	875
Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser		880
	885	890
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser		895
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Leu Ser Leu Gly Lys		910
915		

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<212>DNA

<213>人

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<211>917

<212>PRT

<213>人

<400>26

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 35 40 45
 Leu Phe Glu His Phe Leu Lys Phe Asn Tyr Ser Thr Ala His Ser Ala
 50 55 60
 Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu
 65 70 75 80
 Glu Pro Ile Asn Phe Arg Leu Pro Glu Asn Arg Ile Ser Lys Glu Lys
 85 90 95
 Asp Val Leu Trp Phe Arg Pro Thr Leu Leu Asn Asp Thr Gly Asn Tyr
 100 105 110
 Thr Cys Met Leu Arg Asn Thr Thr Tyr Cys Ser Lys Val Ala Phe Pro
 115 120 125
 Leu Glu Val Val Gln Lys Asp Ser Cys Phe Asn Ser Pro Met Lys Leu
 130 135 140
 Pro Val His Lys Leu Tyr Ile Glu Tyr Gly Ile Gln Arg Ile Thr Cys
 145 150 155 160
 Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Thr Ile Thr
 165 170 175
 Trp Tyr Met Gly Cys Tyr Lys Ile Gln Asn Phe Asn Asn Val Ile Pro
 180 185 190
 Glu Gly Met Asn Leu Ser Phe Leu Ile Ala Leu Ile Ser Asn Asn Gly
 195 200 205
 Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Thr Phe His
 210 215 220
 Leu Thr Arg Thr Leu Thr Val Lys Val Val Gly Ser Pro Lys Asn Ala
 225 230 235 240
 Val Pro Pro Val Ile His Ser Pro Asn Asp His Val Val Tyr Glu Lys
 245 250 255
 Glu Pro Gly Glu Glu Leu Leu Ile Pro Cys Thr Val Tyr Phe Ser Phe
 260 265 270
 Leu Met Asp Ser Arg Asn Glu Val Trp Trp Thr Ile Asp Gly Lys Lys
 275 280 285
 Pro Asp Asp Ile Thr Ile Asp Val Thr Ile Asn Glu Ser Ile Ser His
 290 295 300

