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(54) 发明名称

IL-1 拮抗剂制剂

(57) 摘要

提供了白介素-1(IL-1)拮抗剂制剂,包括预冻干制剂、复原冻干制剂和稳定的液体制剂。优选地,所述IL-1拮抗剂是由2种融合蛋白的二聚体组成的IL-1捕获剂,所述融合蛋白具有选自SEQ ID NO:2、4、6、8、10、12、14、16、18、20、22、24和26的氨基酸序列。最优选地,融合蛋白具有SEQ ID NO:10的序列。

1. 一种适合于冻干的制剂,其包含约 20mM 组氨酸、约 1.5% PEG3350、约 0.5% 甘氨酸、约 25mM 精氨酸、约 1.0% 蔗糖和约 40mg/ml IL-1 捕获剂,其中所述 IL-1 捕获剂为序列如 SEQ ID NO:10 所示的融合蛋白或所述融合蛋白的二聚体。
2. 权利要求 1 的制剂,其不包含磷酸盐缓冲液、超过约 1.5% 的蔗糖、超过约 0.15mM 的柠檬酸盐和超过约 0.005% 的聚山梨醇酯 20。
3. 权利要求 1 或 2 的制剂,其中 pH 为 6-6.75。
4. 权利要求 3 的制剂,其中 pH 为 6-6.5。
5. 权利要求 4 的制剂,其中 pH 为 6.5。
6. 通过将权利要求 1-5 中任一项的预冻干制剂进行冻干可获得的冻干制剂。
7. 一种生产 IL-1 拮抗剂的冻干制剂的方法,其包括将权利要求 1-5 中任一项的预冻干制剂进行冻干以产生冻干的 IL-1 拮抗剂制剂。
8. 一种生产 IL-1 拮抗剂的复原的冻干制剂的方法,其包括将权利要求 6 的冻干制剂或通过权利要求 7 的方法而获得的冻干制剂复原成复原制剂。
9. 权利要求 8 的方法,其中所述复原制剂包含约 20-120mg/ml IL-1 捕获剂。
10. 权利要求 8 的方法,其中所述复原制剂的浓度为所述预冻干制剂的浓度的 2 倍或 3 倍。
11. IL-1 捕获剂的液体制剂,所述制剂包含约 40mM 组氨酸、约 3% PEG 3350、约 1% 甘氨酸、约 50mM 精氨酸、约 2.0% 蔗糖和约 80mg/ml 所述 IL-1 捕获剂,其中所述 IL-1 捕获剂为序列如 SEQ ID NO:10 所示的融合蛋白或所述融合蛋白的二聚体。
12. IL-1 捕获剂的稳定的液体制剂,所述制剂包含 10mM 磷酸盐缓冲液、3% PEG 3350、50mM NaCl、20% 蔗糖和 10-100mg/ml IL-1 捕获剂,其中所述 IL-1 捕获剂为序列如 SEQ ID NO:10 所示的融合蛋白或所述融合蛋白的二聚体。
13. 权利要求 12 的液体制剂,其中在将 50mg/ml IL-1 捕获剂制剂于 5°C 储存 2.9 个月后,依据目检所述 IL-1 拮抗剂显示少于 4% 的聚集。

IL-1 拮抗剂制剂

[0001] 发明背景

发明领域

[0002] 本发明旨在包含能够抑制白介素 -1 (IL-1) 的试剂的药物制剂, 以及制造和使用此类制剂的方法。

[0003] 相关领域的陈述

[0004] 能够阻断或抑制 IL-1 的生物学作用的白介素 -1 (IL-1) 拮抗剂已得到描述。2003 年 7 月 31 日公开的美国专利公开号 2003/0143697 中描述了 IL-1 拮抗剂的实例——IL-1 捕获剂。IL-1 捕获剂是包括两种 IL-1 受体组分和多聚化组分的 IL-1 特异性融合蛋白。

[0005] 冻干法 (在受控的条件下冷冻干燥) 通常用于蛋白质的长期储存。冻干的蛋白质基本上耐降解、聚集、氧化以及冷冻干燥状态时的其他变性过程 (参见, 例如 U. S. 6, 436, 897)。

[0006] 发明简述

[0007] 本文提供了白介素 -1 (IL-1) 拮抗剂的稳定制剂。本发明的药物学上可接受的制剂包含 IL-1 捕获剂以及药物学上可接受的载体。在具体实施方案中, 提供了液体和冷冻干燥的、或冻干的制剂。

[0008] 在第一个实例方面, 本发明的特征在于白介素 -1 (IL-1) 拮抗剂的预冻干制剂, 其包含能够结合并抑制 IL-1 的生物学作用的 IL-1 蛋白拮抗剂、缓冲剂、有机共溶剂或填充剂、和一种或多种冻干保护剂 (lyoprotectant)。在一个具体实施方案中, IL-1 拮抗剂是能够结合 IL-1 的融合蛋白, 缓冲剂是组氨酸, 有机共溶剂或填充剂是 PEG, 和冻干保护剂是甘氨酸、精氨酸和蔗糖中的至少一种。在一个实施方案中, 本发明的预冻干制剂不包含防腐剂。

[0009] 在本发明预冻干制剂的一个实施方案中, 该制剂包含 5-100mM 组氨酸、0.5-3.0% PEG、0.25-3.0% 甘氨酸、5-50mM 精氨酸、0.5-30.0% 蔗糖和 5-50mg/ml IL-1 拮抗剂, pH 为约 6.5。在一个实施方案中, 所述预冻干制剂可以进一步包含高达 5mM 的柠檬酸盐和 / 或 0.003-0.005% 聚山梨醇酯。在此, 聚山梨醇酯可以是例如聚山梨醇酯 20 或 80。

[0010] 在一个更具体的实施方案中, IL-1 拮抗剂的预冻干制剂包含约 20mM 组氨酸、约 1.5% PEG 3350、约 0.5% 甘氨酸、约 25mM 精氨酸、约 1.0% 蔗糖和约 40mg/ml IL-1 捕获剂, pH 为约 6.5。在一个具体实施方案中, IL-1 拮抗剂是如 SEQ ID NO :2、4、6、8、10、12、14、16、18、20、22、24、26 中所示的 IL-1 捕获剂融合蛋白。更优选地, IL-1 捕获剂是 SEQ ID NO :10 中所示的捕获剂。

[0011] 在一个优选实施方案中, 预冻干 IL-1 拮抗剂制剂基本上由约 20mM 组氨酸、约 1.5% PEG 3350、约 0.5% 甘氨酸、约 25mM 精氨酸、约 1.0% 蔗糖和约 40mg/ml 具有 SEQ ID NO :10 的序列的 IL-1 融合蛋白组成, pH 为约 6.5。可以存在柠檬酸盐 (小于或等于约 0.15mM) 和聚山梨醇酯 (小于或等于约 0.005%)。

[0012] 在第二个方面, 本发明的特征在于预冻干 IL-1 拮抗剂制剂, 所述制剂基本上由约

20mM 组氨酸、约 1.5% PEG 3350、约 0.5% 甘氨酸、约 25mM 精氨酸、约 1.0% 蔗糖和约 40mg/ml 具有 SEQ ID NO:10 的序列的 IL-1 融合蛋白组成, pH 为约 6.5, 其中预冻干制剂不包含防腐剂、磷酸盐缓冲液、超过痕量的 NaCl、和 / 或超过 1.5% 的蔗糖。可以存在小于约 0.15mM 的量的柠檬酸盐, 和还可以存在高达约 0.005-0.01% 的聚山梨醇酯 20。

[0013] 在第三个方面, 本发明的特征在于生产 IL-1 拮抗剂的冻干制剂的方法, 所述方法包括对本发明的预冻干 IL-1 拮抗剂制剂实施冻干以产生冻干的 IL-1 拮抗剂制剂。冻干的制剂可以通过本领域已知用于冻干液体的任何方法来冻干。

[0014] 在第四个相关方面, 本发明的特征在于生产 IL-1 拮抗剂的复原的 (reconstituted) 冻干制剂的方法, 其包括将本发明的冻干制剂复原为复原制剂。在一个实施方案中, 复原制剂是预冻干制剂浓度的两倍, 例如, 本发明方法包括: (a) 产生 IL-1 拮抗剂的预冻干制剂, 所述制剂由约 20mM 组氨酸、约 1.5% PEG 3350、约 0.5% 甘氨酸、约 25mM 精氨酸、约 1.0% 蔗糖和约 40mg/ml IL-1 蛋白拮抗剂组成, pH 为约 6.5; (b) 对步骤 (a) 的预冻干制剂实施冻干; 以及 (c) 将步骤 (b) 的冻干制剂复原为由约 40mM 组氨酸、约 3% PEG 3350、约 1% 甘氨酸、约 50mM 精氨酸、约 2.0% 蔗糖和约 80mg/ml IL-1 蛋白拮抗剂组成的混合物, 其中复原制剂可以进一步包含约 0.2mM 柠檬酸盐和 / 或约 0.008% 聚山梨醇酯 20。在一个具体实施方案中, IL-1 拮抗剂是如 SEQ ID NO:2、4、6、8、10、12、14、16、18、20、22、24、26 中所示的 IL-1 捕获剂融合蛋白。更优选地, IL-1 捕获剂是 SEQ ID NO:10 中所示的捕获剂。在另外实施方案中, 复原制剂是预冻干制剂浓度的 3 倍, 例如, 将 20mg IL-1 拮抗剂蛋白质 /ml 预冻干制剂复原为 60mg IL-1 拮抗剂蛋白质 /ml 的最终制剂。一般地, 冻干制剂用适合于注射的无菌水复原。在一个实施方案中, 复原液可以是抑菌水。

[0015] 在生产复原的冻干制剂的方法的具体实施方案中, 预冻干溶液以 40mg IL-1 拮抗剂蛋白质 /ml 预冻干制剂溶液存在于管形瓶中, 它被冻干并复原为 80mg/ml 溶液。在另一实施方案中, 20mg/ml 预冻干溶液被冻干并复原为 40mg/ml 溶液。在另一实施方案中, 25mg/ml 预冻干溶液被冻干并复原为 50mg/ml 溶液。在另一实施方案中, 12.5mg/ml 预冻干溶液被冻干并复原为 25mg/ml 溶液。在另一实施方案中, 12.5mg/ml 预冻干溶液被冻干并复原为 50mg/ml 溶液。在另一实施方案中, 25mg/ml 预冻干溶液被冻干并复原为 75mg/ml 溶液。在另一实施方案中, 40mg/ml 预冻干溶液被冻干并复原为 120mg/ml 溶液。在另一实施方案中, 40mg/ml 预冻干溶液被冻干并复原为 20mg/ml 溶液。优选地, 复原的冻干制剂不包含防腐剂。在另一实施方案中, 复原制剂包括高达 30% 的蔗糖以及一种或多种防腐剂。

[0016] 在第五个方面, 本发明的特征在于 IL-1 拮抗剂的稳定液体制剂, 所述液体制剂包含能够结合并抑制 IL-1 的生物学作用的 IL-1 拮抗剂蛋白质、缓冲剂、有机共溶剂以及一种或多种热稳定剂。在一个具体实施方案中, IL-1 拮抗剂是如 SEQ ID NO:2、4、6、8、10、12、14、16、18、20、22、24、26 中所示的 IL-1 捕获剂融合蛋白。更优选地, IL-1 捕获剂是 SEQ ID NO:10 中所示的捕获剂。在一个实施方案中, 缓冲剂是磷酸盐缓冲液。在一个实施方案中, 有机共溶剂是 PEG, 优选 PEG 3350。在一个实施方案中, 热稳定剂是 NaCl 和 / 或蔗糖。更优选地, 热稳定剂是 NaCl 和蔗糖。

[0017] 在一个具体实施方案中, IL-1 拮抗剂的稳定液体制剂包含 5-100mM 磷酸盐缓冲液、0.5-3.0% PEG、25-150mM NaCl、5-30% 蔗糖、10-500mg/ml IL-1 捕获剂蛋白质, pH 为约 6-6.5。在一个更具体的实施方案中, IL-1 拮抗剂的稳定液体制剂包含 10mM 磷酸盐缓冲液、

3% PEG 3350、50mM NaCl、5-20%蔗糖、12.5-50mg/ml IL-1 捕获剂蛋白质，pH 为约 6-6.5。另外，可以存在低或痕量的柠檬酸盐缓冲液或聚山梨醇酯。在 50mg/ml IL-1 捕获剂制剂于 5°C 储存高达约 29 个月后，根据目检确定本发明的 IL-1 拮抗剂稳定液体制剂显示很少或没有沉淀。进一步地，在 50mg/ml IL-1 捕获剂制剂于 5°C 储存高达约 24 个月后，根据大小排阻层析例如 HPLC 的测定，观察到很少或没有聚集。

[0018] 其他目的和优点经参阅随后的详细描述将是显而易见的。

[0019] 发明详述

[0020] 本发明不限于所描述的具体方法和实验条件，因为此类方法和条件可以改变。还应当理解本文所使用的术语仅用于描述具体实施方案，并不希望用于限制，除非另有说明，因为本发明的范围将仅由所附的权利要求来限定。

[0021] 如本说明书和所附权利要求中所使用的，除非上下文明确说明，否则单数形式“a”、“an”和“the”包括复数。因此，例如提及“一种方法”包括本文所描述的和 / 或阅读本公开内容后对于本领域技术人员将是显而易见的类型的一种或多种方法和 / 或步骤。

[0022] 除非另外定义，本文所使用的所有技术和科学术语具有与本发明所属领域普通技术人员通常理解相同的含义。尽管与本文所述那些类似或等同的任何方法和材料均可用于本发明的实践或测试中，但现在还是描述优选的方法和材料。

[0023] 一般描述

[0024] 包含蛋白质的制剂的安全操作和施用代表了对于药物配方设计师来说的重大挑战。蛋白质具有存在稳定性问题的独特化学和物理特性：存在蛋白质的各种降解途径，牵涉到化学和物理不稳定性。化学不稳定性包括脱氨作用、聚集、肽主链的剪断以及甲硫氨酸残基的氧化。物理不稳定性包括许多现象，包括例如聚集。

[0025] 通过从蛋白质中去除水可以促进化学和物理稳定性。冻干法（在受控条件下的冷冻干燥）通常用于蛋白质的长期储存。冻干的蛋白质基本上耐降解、聚集、氧化以及冷冻干燥状态时的其他变性过程。冻干的蛋白质通常在施用前用任选包含抑菌性防腐剂（例如苯甲醇）的水来复原。

[0026] 定义

[0027] 术语“治疗上或药物学上有效剂量”指产生施用其所期望的效果的剂量。确切的剂量将取决于治疗的目的，并且将可由本领域技术人员利用已知技术来确定（参见，例如 Lloyd(1999) The Art, Science and Technology of Pharmaceutical Compounding）。

[0028] 术语“阻滞剂”、“抑制剂”或“拮抗剂”是指延缓或阻止化学或生理反应或应答的物质。通常的阻滞剂或抑制剂包括但不限于反义分子、抗体、拮抗剂及其衍生物。

[0029] 术语“药物学上可接受的”包括指经联邦或州政府管理机构批准的或者在美国药典或其他普遍公认的药典中列出的用于动物并且更具体而言用于人的。

[0030] 术语“载体 (carrier)”指稀释剂、佐剂、赋形剂或用于与组合物一起施用的媒介物。载体可以包括无菌的液体，例如水和油，包括石油，动物、植物或合成来源的油，例如花生油、大豆油、矿物油、芝麻油等。

[0031] 术语“赋形剂”包括加入到药物组合物中以提供所需稠度或稳定效果的非治疗试剂。合适的药物赋形剂包括，例如淀粉、葡萄糖、乳糖、蔗糖、明胶、麦芽、米、面粉、白垩、硅胶、硬脂酸钠、单硬脂酸甘油酯、滑石、氯化钠、脱脂奶粉、甘油、丙二醇、水、乙醇等。

[0032] 术语“冻干的”或“冷冻干燥的”包括已经历干燥操作例如冻干的物质的状态，其中至少 50% 的水分已被去除。

[0033] 术语“填充剂”包括药物学上可接受且增加冻干团块 (lyo cake) 体积的化合物。一般地，本领域已知的可接受的填充剂包括，例如碳水化合物，包括单糖例如右旋糖、核糖、果糖等，醇糖例如甘露醇、肌醇和山梨糖醇，二糖包括海藻糖、蔗糖和乳糖，天然发生的聚合物例如淀粉、葡聚糖、壳聚糖、透明质酸盐、蛋白质（例如明胶和血清白蛋白）、糖原，以及合成的单体和聚合物。在本发明的制剂中，PEG3350 是一种有机共溶剂，其用于在搅动、混合或处理时稳定 IL-1 蛋白拮抗剂，并且作为填充剂以帮助产生可接受的体积。

[0034] 术语“冻干保护剂”包括可以加入冷冻干燥或冻干的制剂中以帮助在冷冻干燥或冻干时维持蛋白质结构的物质。

[0035] “防腐剂”包括抑菌、杀菌、抑真菌或杀真菌的化合物，它们一般加入制剂以延缓或消除制剂中细菌或其他污染微生物的生长。防腐剂包括，例如苯甲醇、苯酚、苯扎氯铵、间甲酚、硫柳汞 (thimerosal)、三氯叔丁醇、羟基苯甲酸甲酯、羟基苯甲酸丙酯等。药物学上可接受的防腐剂的其他实例可以在 USP 中找到。

[0036] IL-1 拮抗剂

[0037] IL-1 拮抗剂是能够阻断或抑制 IL-1 的生物学作用的化合物，包括能够捕获 IL-1 的融合蛋白，例如 IL-1 捕获剂。在一个优选实施方案中，IL-1 捕获剂是包括两种 IL-1 受体组分和多聚化组分的 IL-1 特异性融合蛋白，例如 2003 年 7 月 31 日公开的美国专利公开号 2003/0143697 中描述的 IL-1 捕获剂。在一个具体实施方案中，IL-1 捕获剂是 SEQ ID NO :2、4、6、8、10、12、14、16、18、20、22、24、26 中所示的融合蛋白。优选的 IL-1 捕获剂显示于 SEQ ID NO :10 中。本发明包括基本上等同于 SEQ ID NO :2、4、6、8、10、12、14、16、18、20、22、24、26 的蛋白质的 IL-1 捕获剂的用途，即与 SEQ ID NO :2、4、6、8、10、12、14、16、18、20、22、24、26 的蛋白质具有至少 95% 同一性、优选至少 97% 同一性、和更优选至少 98% 同一性，并且能够结合并抑制 IL-1 的蛋白质。进一步地，在具体实施方案中，IL-1 拮抗剂是经修饰的 IL-1 捕获剂，其包括一种或多种受体组分以及一种或多种对于 IL-1 和 / 或 IL-1 受体来说特异的免疫球蛋白来源组分。在另一实施方案中，IL-1 拮抗剂是经修饰的 IL-1 捕获剂，其包括一种或多种对于 IL-1 和 / 或 IL-1 受体来说特异的免疫球蛋白来源组分。

[0038] 本发明方法和制剂的 IL-1 捕获剂可以通过本领域已知或将会已知的、可用于制备 IL-1 捕获剂的任何合适方法进行制备。IL-1 捕获剂在用于制备药物学上可接受的制剂时优选基本上不含蛋白质污染物。“基本上不含蛋白质污染物”优选地指，用于制造包含 IL-1 捕获剂的制剂的 IL-1 捕获剂制备物中至少 90 重量% 蛋白质是 IL-1 捕获剂蛋白质，更优选至少 95%，最优选至少 99%。IL-1 捕获剂优选基本上不含聚集物。“基本上不含聚集物”指，在 IL-1 捕获剂用于制备药物学上有效的制剂时至少 90 重量% 的 IL-1 捕获剂蛋白质不以聚集物的形式存在。本发明方法和制剂的 IL-1 捕获剂可以包含由于纯化过程而引起的低或痕量化合物，例如低或痕量的柠檬酸盐和 / 或聚山梨醇酯。在包含约 40mg IL-1 捕获剂 /ml 的本发明预冻干制剂的一个实施方案中，柠檬酸盐可以以约 0.1mM 的浓度存在，和 / 或聚山梨醇酯可以以约 0.004% 的浓度存在。如果预冻干制剂在冻干后复原为原始体积的一半（例如 80mg/ml 的 IL-1 捕获剂），则所得到的浓度可以是 0.2mM 柠檬酸盐和 / 或 0.008% 聚山梨醇酯。如果预冻干制剂在冻干后复原为原始体积的三分之一（例如 120mg/

ml 的 IL-1 捕获剂), 则所得到的浓度可以是 0.6mM 柠檬酸盐和 / 或 0.012% 聚山梨醇酯。

[0039] 冻干过程和冻干制剂

[0040] 在本发明的一个方面, 提供了包含 IL-1 捕获剂的药物学上可接受的制剂, 其中该制剂是冷冻干燥或冻干的制剂。优选地, 冷冻干燥或冻干的制剂包含药物学上有效量的 IL-1 捕获剂。冻干制剂可以复原为溶液、悬浮液、乳状液或适合于施用或使用的任何其他适当形式。冻干制剂一般首先制备为液体, 然后冷冻并冻干。冻干前的总液体体积可以少于、等于或多于冻干制剂的最终复原体积。冻干方法是本领域普通技术人员众所周知的, 并且一般包括在受控条件下水从冷冻制剂中的升华。

[0041] 冻干制剂可以储存在宽的温度范围内。冻干制剂可以在等于或低于 30°C 的温度下储存, 例如于 4°C 冷藏, 或于室温 (例如大约 25°C) 储存。优选地, 冻干制剂储存在低于约 25°C, 更优选地, 在约 4-20°C; 低于约 4°C; 低于约 -20°C; 约 -40°C; 或约 -70°C。

[0042] 冻干制剂一般通过添加水溶液以溶解冻干制剂, 从而复原以供使用。可以使用多种多样的水溶液来复原冻干制剂。优选地, 冻干制剂可以用水复原。冻干制剂优选基本上由水 (例如 USP WFI 或注射用水) 或抑菌水 (例如含 0.9% 苯甲醇的 USP WFI) 组成的溶液复原。然而, 还可使用包含缓冲剂和 / 或赋形剂和 / 或一种或多种药物学上可接受的载体的溶液。

[0043] 冷冻干燥或冻干的制剂一般从液体, 即从溶液、悬浮液、乳状液等制备。因此, 待经历冷冻干燥或冻干的液体优选包含最终复原液体制剂中所需的所有组分。因此, 在复原时, 冷冻干燥或冻干的制剂在复原后将提供所需的液体制剂。用于产生冷冻干燥或冻干的制剂的优选液体制剂包含药物学上有效量的 IL-1 捕获剂、缓冲剂、稳定剂和填充剂。冷冻干燥或冻干的制剂优选包含组氨酸, 因为当 IL-1 捕获剂被冻干时, 与磷酸盐相比, 组氨酸在稳定 IL-1 捕获剂方面更有效。有机共溶剂, 例如 PEG 3350 用于在搅动、混合或处理时稳定 IL-1 捕获剂。冻干保护剂优选用于冷冻干燥或冻干的制剂中。在冷冻干燥或冻干时, 冻干保护剂帮助维持蛋白质的二级结构。冻干保护剂的三个优选实例是甘氨酸、精氨酸和蔗糖, 它们优选一起使用。

[0044] 稳定的液体制剂

[0045] 在一个方面, 本发明提供了包含 IL-1 捕获剂的稳定的药物学上可接受的制剂, 其中该制剂是液体制剂。优选地, 所述液体制剂包含药物学上有效量的 IL-1 捕获剂。该制剂还可包含一种或多种药物学上可接受的载体、缓冲剂、填充剂、稳定剂、防腐剂和 / 或赋形剂。包含 IL-1 捕获剂的药物学上可接受的液体制剂的实例包含药物学上有效量的 IL-1 捕获剂、缓冲剂、共溶剂以及一种或多种稳定剂。

[0046] 优选的液体制剂包含磷酸盐缓冲液、有机共溶剂、和一种或多种热稳定剂、以及约 12.5mg/ml- 约 50mg/ml IL-1 捕获剂, 所述热稳定剂用于在储存时将聚集物以及低分子量产物的形成降至最低, 其中该制剂的 pH 为约 6.0- 约 6.75。更优选的液体制剂包含 10mM 磷酸盐缓冲液、3% PEG、50mM NaCl、5-20% 蔗糖、10-100mg/ml IL-1 捕获剂, 其中该制剂的 pH 为约 6.0- 约 6.5。尽管 NaCl 或蔗糖均可用作稳定剂, 但已确定 NaCl 和蔗糖的组合比单独的任何单个稳定剂更有效地稳定 IL-1 捕获剂。优选地, PEG 是 PEG 3350, 已确定它增强 IL-1 捕获剂稳定性。

[0047] 表 1 显示了如当在 5°C 孵育时于长达 24 个月的时间内所测定的, 在包含 5 或 20%

蔗糖的样品中天然 IL-1 捕获剂的百分比或聚集的 IL-1 捕获剂的百分比。在 20%蔗糖存在下,天然(非聚集)形式的 IL-1 捕获剂从第 0 天的 92.6%降至 24 个月时的 88.9%,并且聚集物的百分比在相同时间内从 2.3%增至 3.4%。5%蔗糖制剂的天然(非聚集)形式的 IL-1 捕获剂从第 0 天的 92.4%降至 24 个月时的 86.9%,并且聚集物的百分比在相同时间内从 2.6%增至 3.6%。

[0048] 表 1

[0049]

在 5℃ 时的孵育时间 (月)	%天然的 (20%蔗糖)	%聚集物 (20%蔗糖)	%天然的 (5%蔗糖)	%聚集物 (5%蔗糖)
0	92.6	2.3	92.4	2.6
1.0	92.6	2.4	92.5	2.5
2.0	91.9	2.6	91.5	2.9
6.0	91.6	2.8	91.0	2.9
18	91.8	3.2	90.7	3.6
21.0	91.3	2.9	89.5	3.6
24.0	88.9	3.4	86.9	3.6

[0050] 表 2 显示了如当在 5℃孵育时于长达 2.9 个月的时间内所测定的,在包含 0.5 或 20%蔗糖的样品中天然 IL-1 捕获剂的百分比 (50mg/ml IL-1 捕获剂、10mM 磷酸盐、0.2%聚山梨醇酯-20、50 或 135 (含 0%蔗糖)mM NaCl, pH 6.5。在 0%蔗糖存在下,天然(非聚集)形式的 IL-1 捕获剂从第 0 天的 96.4%降至 2.9 个月时的 0.5%。5%蔗糖制剂的天然(非聚集)形式的 IL-1 捕获剂从第 0 天的 96.5%降至 2.9 个月时的 39.2%。20%蔗糖制剂的天然(非聚集)形式的 IL-1 捕获剂从第 0 天的 96.4%降至 2.9 个月时的 95.3%。

[0051] 表 2

[0052]

孵育时间 (月)	%天然的 (0%蔗糖)	%天然的 (5%蔗糖)	%天然的 (20%蔗糖)
0	96.4	96.5	96.4
1	96.7	89.3	96.2
2.9	0.5	39.2	95.3

[0053] 液体或冷冻干燥的和冻干的制剂可以储存在去除氧的环境中。去除氧的环境可以通过将制剂储存在惰性气体下而产生,所述惰性气体例如为氩、氮或氦。

[0054] 测定预冻干和冻干的制剂的稳定性。包含 40mg/ml IL-1 捕获剂 (SEQ ID NO:10)、20mM 组氨酸、1.5% PEG-3350、1%蔗糖、0.5%甘氨酸、25mM 精氨酸-HCl, pH 6.5 的预冻干制剂在 5℃孵育 0-52 周。如表 3 中所示,天然(非聚集)形式的 IL-1 从 94.9(0 周)降至 92.3(52 周),并且聚集物的百分比在相同时间内从 1%增至 1.8%。

[0055] 表 3

[0056]

孵育时间 (周, 于 5℃)	%天然的	%聚集物
0	94.9	1.0
4	94.3	1.3
12	93.5	1.7
24	93.3	1.5
36	92.6	1.5
52	92.3	1.8

[0057] 包含 40mg/ml IL-1 捕获剂 (SEQ ID NO :10)、20mM 组氨酸、1.5% PEG-3350、1% 蔗糖、0.5% 甘氨酸、25mM 精氨酸-HCl, pH 6.5 (预冻干浓度) 的冻干制剂的稳定性在 25℃ 孵育 0-56 周。如表 4 中所示,天然 (非聚集) 形式的 IL-1 从 97.0 (0 周) 降至 94.0 (56 周), 并且聚集物的百分比在相同时间内从 0.8% 增至 3.6%。

[0058] 表 4

[0059]

孵育时间 (周, 于 25℃)	%天然的	%聚集物
0	97.0	0.8
3.9	96.3	1.4
6.1	95.5	1.5
12.3	95.4	1.9
25.7	94.7	2.2
39.3	94.4	2.9
56	94.0	3.6

[0060] 尽管前述发明已通过图表和实施例得到相当详细的描述,但对于本领域普通技术人员将会显而易见的是,可对本发明的教导进行某些改变和修改,而不离开所附权利要求的精神或范围。

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530	535	540
His Ala Ser Tyr Thr Tyr Leu Gly Lys Gln Tyr Pro Ile Thr Arg Val		
545	550	555
Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys Pro Thr Arg Pro Val Ile		
565	570	575
Val Ser Pro Ala Asn Glu Thr Met Glu Val Asp Leu Gly Ser Gln Ile		
580	585	590
Gln Leu Ile Cys Asn Val Thr Gly Gln Leu Ser Asp Ile Ala Tyr Trp		
595	600	605
Lys Trp Asn Gly Ser Val Ile Asp Glu Asp Asp Pro Val Leu Gly Glu		
610	615	620
Asp Tyr Tyr Ser Val Glu Asn Pro Ala Asn Lys Arg Arg Ser Thr Leu		

625	630	635	640
Ile Thr Val Leu Asn Ile Ser Glu Ile Glu Ser Arg Phe Tyr Lys His			
	645	650	655
Pro Phe Thr Cys Phe Ala Lys Asn Thr His Gly Ile Asp Ala Ala Tyr			
	660	665	670
Ile Gln Leu Ile Tyr Pro Val Thr Asn Ser Gly Asp Lys Thr His Thr			
	675	680	685
Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe			
	690	695	700
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro			
705	710	715	720
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val			
	725	730	735
Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr			
	740	745	750
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val			
	755	760	765
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys			
	770	775	780
Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser			
785	790	795	800
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro			
	805	810	815
Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val			
	820	825	830
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly			
	835	840	845
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			
	885	890	895
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys			
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<211>2703

<212>DNA

<213> 智人

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agcaagacac ctgtatctac agaacaagcc tccaggattc atcaacacaa agagaaactt 240
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tcttactgcc tcagaattaa aataagtgc aaatttgtgg agaattgagc taacttatgt 360
tataatgcac aagccatatt taagcagaaa ctaccctgtg caggagacgg aggacttgtg 420
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<211>900

<212>PRT

<213> 智人

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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

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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		
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
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 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	
850	855 860
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	
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Ser Pro Gly Lys	
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<211>2709

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cgteccctgtc ctcttaaccc aatgaacac aaaggcacta taacttggta taaggatgac	180
agcaagacac ctgtatctac agaacaagcc tccaggattc atcaacacaa agagaaactt	240
tggtttgttc ctgctaaggt ggaggattca ggacattact attgcgtggg aagaaattca	300
tcttactgcc tcagaattaa aataagtgc aaatttgtgg agaattgagc taacttatgt	360
tataatgcac aagccatatt taagcagaaa ctaccggtg caggagacgg aggacttgtg	420
tgcccttata tggagttttt taaaatgaa aataatgagt tacctaaatt acagtgggtat	480
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<212>PRT

<213> 智人

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20           25           30

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

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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		
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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		
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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 TyrPhe 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		
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		
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Asn Asp His Val Val Tyr Glu Lys Glu Pro Gly Glu Glu Leu Leu Ile		
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Pro Cys Thr Val Tyr Phe Ser Phe Leu Met Asp Ser Arg Asn Glu Val		
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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		
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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
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
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
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu		
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Ser Leu Ser Leu Gly Lys		
900		

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<211>2709

<212>DNA

<213> 智人

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tgcccttata	tggagttttt	taaaaatgaa	aataatgagt	tacctaaatt	acagtggat	480
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2709

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<210>8

<211>902

<212>PRT

<213> 智人

<400>8

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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

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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		
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
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
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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 ValAsp 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	
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<210>9

<211>2703

<212>DNA

<213> 智人

<400>9

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<210>10

<211>900

<212>PRT

<213> 智人

<400>10

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           20           25           30
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

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50	55	60
Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu		
65	70	75
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
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
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
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
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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
				565						570				575	
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
				610						615				620	
Lys	Arg	Arg	Ser	Thr	Leu	Ile	Thr	Val	Leu	Asn	Ile	Ser	Glu	Ile	Glu
625					630					635					640
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		
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<211>2709

<212>DNA

<213> 智人

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gcatatatcc	agttaatatata	tccagtcact	aattccggag	agtcacaaata	cggtcgcca	2040
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<210>12

<211>902

<212>PRT

<213> 智人

<400>12

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Arg	Gln	Ile	Gln	Val	Phe	Glu	Asp	Glu	Pro	Ala	Arg	Ile	Lys	Cys	Pro
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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			
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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			
	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			
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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			
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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			
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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	
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Pro Thr Arg Pro Val Ile Val Ser Pro Ala Asn Glu Thr Met Glu Val		560
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Asp Leu Gly Ser Gln Ile Gln Leu Ile Cys Asn Val Thr Gly Gln Leu		575
	580	585
Ser Asp Ile Ala Tyr Trp Lys Trp Asn Gly Ser Val Ile Asp Glu Asp		590
	595	600
Asp Pro Val Leu Gly Glu Asp Tyr Tyr Ser Val Glu Asn Pro Ala Asn		605
	610	615
Lys Arg Arg Ser Thr Leu Ile Thr Val Leu Asn Ile Ser Glu Ile Glu		620
625	630	635
Ser Arg Phe Tyr Lys His Pro Phe Thr Cys Phe Ala Lys Asn Thr His		640
	645	650
Gly Ile Asp Ala Ala Tyr Ile Gln Leu Ile Tyr Pro Val Thr Asn Ser		655
	660	665
Gly Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu		670
	675	680
Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp		685
	690	695
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp		700
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Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly		720
	725	730
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn		735
	740	745
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp		750
	755	760
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro		765
	770	775
Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu		780
785	790	795
Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn		800
	805	810
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile		815
	820	825
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr		830
	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
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 Ser Leu Ser Leu Gly Lys
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<210>13

<211>2709

<212>DNA

<213> 智人

<400>13

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aatgcacaag ccatatttaa gcagaaacta ccggttgag gagacggagg acttgtgtgc 1440

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<210>14

<211>902

<212>PRT

<213> 智人

<400>14

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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

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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		
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
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
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
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			
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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			
	565	570	575
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			
	610	615	620
Lys Arg Arg Ser Thr Leu Ile Thr Val Leu Asn Ile Ser Glu Ile Glu			
625	630	635	640
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 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
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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
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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
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Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg
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865					870					875					880
Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu
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<210>15

<211>2748

<212>DNA

<213> 智人

<400>15

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2748

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<212>PRT

<213> 智人

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Arg	His	Tyr	Lys	Arg	Glu	Phe	Arg	Leu	Glu	Gly	Glu	Pro	Val	Ala	Leu
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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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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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Glu	Leu	Arg	Ile	Lys	Lys	Lys	Lys	Glu	Glu	Thr	Ile	Pro	Val	Ile	Ile
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Arg Val Thr Glu Gly Pro Arg Gln Glu Tyr Ser Glu Asn Asn Glu Asn			
	290	295	300
Tyr Ile Glu Val Pro Leu Ile Phe Asp Pro Val Thr Arg Glu Asp Leu			
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His Met Asp Phe Lys Cys Val Val His Asn Thr Leu Ser Phe Gln Thr			
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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			
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Thr Arg Gln Asp Arg Asp Leu Glu Glu Pro Ile Asn Phe Arg Leu Pro			
	405	410	415
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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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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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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675	680	685	
Asp Lys Thr His Thr Cys Pro ProCys Pro Ala Pro Glu Leu Leu Gly			
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Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His			
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Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val			
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His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr			
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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			
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Pro Gly Lys			
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<212>PRT

<213> 智人

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

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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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	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	800
Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro			
	805	810	815
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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Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser			
	885	890	895
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser			
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<213> 智人

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<211>917

<212>PRT

<213> 智人

<400>20

Met	Val	Arg	Leu	Tyr	Val	Leu	Val	Met	Gly	Val	Ser	Ala	Phe	Thr	Leu
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Gln	Pro	Ala	Ala	His	Thr	Gly	Ala	Ala	Arg	Ser	Cys	Arg	Phe	Arg	Gly
				20					25					30	
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
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
			165					170						175	
Asp	Lys	Asp	Asn	Glu	Lys	Phe	Leu	Ser	Val	Arg	Gly	Thr	Thr	His	Leu
			180					185						190	
Leu	Val	His	Asp	Val	Ala	Leu	Glu	Asp	Ala	Gly	Tyr	Tyr	Arg	Cys	Val
			195					200					205		
Leu	Thr	Phe	Ala	His	Glu	Gly	Gln	Gln	Tyr	Asn	Ile	Thr	Arg	Ser	Ile
			210				215						220		
Glu	Leu	Arg	Ile	Lys	Lys	Lys	Lys	Glu	Glu	Thr	Ile	Pro	Val	Ile	Ile
225					230					235				240	

Ser Pro Leu Lys Thr Ile Ser Ala Ser Leu Gly Ser Arg Leu Thr Ile		
245	250	255
Pro Cys Lys Val Phe Leu Gly Thr Gly Thr Pro Leu Thr Thr Met Leu		
260	265	270
Trp Trp Thr Ala Asn Asp Thr His Ile Glu Ser Ala Tyr Pro Gly Gly		
275	280	285
Arg Val Thr Glu Gly Pro Arg Gln Glu Tyr Ser Glu Asn Asn Glu Asn		
290	295	300
Tyr Ile Glu Val Pro Leu Ile Phe Asp Pro Val Thr Arg Glu Asp Leu		
305	310	315
His Met Asp Phe Lys Cys Val Val His Asn Thr Leu Ser Phe Gln Thr		
325	330	335
Leu Arg Thr Thr Val Lys Glu Ala Ser Ser Thr Phe Ser Glu Arg Cys		
340	345	350
Asp Asp Trp Gly Leu Asp Thr Met Arg Gln Ile Gln Val Phe Glu Asp		
355	360	365
Glu Pro Ala Arg Ile Lys Cys Pro Leu Phe Glu His Phe Leu Lys Phe		
370	375	380
Asn Tyr Ser Thr Ala His Ser Ala Gly Leu Thr Leu Ile Trp Tyr Trp		
385	390	395
Thr Arg Gln Asp Arg Asp Leu Glu Glu Pro Ile Asn Phe Arg Leu Pro		
405	410	415
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		
435	440	445
Tyr Cys Ser Lys Val Ala Phe Pro Leu Glu Val Val Gln Lys Asp Ser		
450	455	460
Cys Phe Asn Ser Pro Met Lys Leu Pro Val His Lys Leu Tyr Ile Glu		
465	470	475
Tyr Gly Ile Gln Arg Ile Thr Cys Pro Asn Val Asp Gly Tyr Phe Pro		
485	490	495
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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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			
	580	585	590
Pro Cys Thr Val Tyr Phe Ser Phe Leu Met Asp Ser Arg Asn Glu Val			
	595	600	605
Trp Trp Thr Ile Asp Gly Lys Lys Pro Asp Asp Ile Thr Ile Asp Val			
	610	615	620
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			
	645	650	655
Ser Tyr Val Cys His Ala Arg Ser Ala Lys Gly Glu Val Ala Lys Ala			
	660	665	670
Ala Lys Val Lys Gln Lys Val Pro Ala Pro Arg Tyr Thr Val Ser Gly			
	675	680	685
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro 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	800
Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro			
	805	810	815
Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln			
	820	825	830
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala			
	835	840	845
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
 865 870 875 880
 Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
 885 890 895
 Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
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 Leu Ser Leu Gly Lys
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<210>21

<211>2748

<212>DNA

<213> 智人

<400>21

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<210>22

<211>915

<212>PRT

<213> 智人

<400>22

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           20           25           30
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

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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		
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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
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
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
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			
	450	455	460
Glu Asn Thr Asp Ala Phe Leu Pro Phe Ile Ser Tyr Pro Gln Ile Leu			
465	470	475	480
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			
	530	535	540
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			
	580	585	590
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			
	610	615	620
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			
	660	665	670
Gln Thr Leu Arg Thr Thr Val Lys Glu Ala Ser Ser Thr Phe Ser Gly			
	675	680	685
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
 705 710 715 720
 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
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 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
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 Pro Gly Lys
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<210>23

<211>2754

<212>DNA

<213> 智人

<400>23

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<210>24

<211>917

<212>PRT

<213> 智人

<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			
	450	455	460
Glu Asn Thr Asp Ala Phe Leu Pro Phe Ile Ser Tyr Pro Gln Ile Leu			
465	470	475	480
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			
	530	535	540

Cys Val Leu Thr Phe	Ala His Glu Gly Gln Gln Tyr Asn Ile Thr Arg
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Ser Ile Glu Leu Arg Ile Lys Lys Lys Lys Glu Glu Thr Ile Pro Val	
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Ile Ile Ser Pro Leu Lys Thr Ile Ser Ala Ser Leu Gly Ser Arg Leu	
580	585 590
Thr Ile Pro Cys Lys Val Phe Leu Gly Thr Gly Thr Pro Leu Thr Thr	
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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	
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Glu Asn Tyr Ile Glu Val Pro Leu Ile Phe Asp Pro Val Thr Arg Glu	
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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	
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Glu Ser Lys Tyr Gly Pro ProCys Pro Ser Cys Pro Ala Pro Glu Phe	
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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	790 795 800
Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro	
805	810 815
Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln	
820	825 830
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala	
835	840 845
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		
865	870	875
Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser		
	885	890
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser		
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Leu Ser Leu Gly Lys		910
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<211>2754

<212>DNA

<213> 智人

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<211>917

<212>PRT

<213> 智人

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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
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Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu

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

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Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr		
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Leu Met Ile Ser Arg Thr ProGlu 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		
	740	745
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Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser		
785	790	795
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Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu		
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Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser		
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Leu Ser Leu Gly Lys		910
915		