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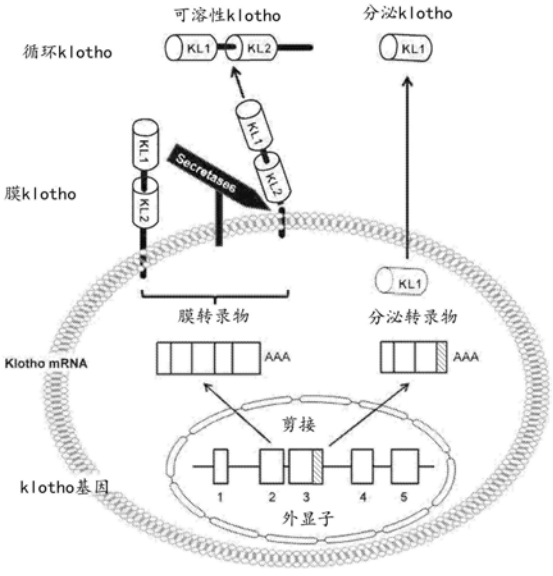
(54)发明名称

治疗性重组KLOTHO蛋白及其组合物和方法

(57)摘要

本发明公开了重组Klotho蛋白质及其变体、编码它的核酸、表达它的细胞系和悬浮培养物、和其制造和施用方法。蛋白质包括溶解性或延长半衰期的特征，如糖基化和融合蛋白标签。蛋白质与人αKlotho同种型1的一部分具有至少85%的氨基酸序列同一性。治疗方案包括测定受试者中的血清可溶性Klotho水平，计算足以将受试者中的血清可溶性Klotho水平提高至预定水平的蛋白质的剂量，向受试者施用蛋白质的剂量，例如通过推注或渐进注射，确定施用第一剂量后受试者血清中Klotho蛋白质下降的速率，计算Klotho蛋白质的后续剂量的时间和量，以及将后续剂量的Klotho蛋白质施用于受试者。



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1.一种制备重组Klotho蛋白的方法,所述方法包括:

在中国仓鼠卵巢(CHO)细胞中产生重组Klotho蛋白,

优选在二氢叶酸还原酶(DHFR)缺陷型CHO细胞中,更优选在CHO-S细胞中,或

优选在谷氨酰胺合成酶(GS)缺陷型CHO细胞中,更优选在GS-/-CHO细胞中,

所述蛋白质优选地与SEQ ID NO:2至SEQ ID NO:70之一具有至少85%的氨基酸序列同一性。

2.根据权利要求1所述的方法,其中所述蛋白质包含与其连接的一种或多种聚糖。

3.根据权利要求1或2所述的方法,其中所述CHO细胞含有外源核酸,其编码:

启动子,优选强启动子;

与SEQ ID NO:2至SEQ ID NO:70之一具有至少85%氨基酸序列同一性的多肽;和

任选地,功能性二氢叶酸还原酶(DHFR)酶或功能性谷氨酰胺合成酶(GS)酶,

其中产生所述重组Klotho蛋白包含表达由所述核酸编码的所述多肽。

4.根据权利要求3所述的方法,还包括选自以下的一个或多个步骤:

将所述外源核酸导入所述CHO细胞,优选通过转染;和

在液体培养基中培养CHO细胞,优选在无血清和/或无动物蛋白成分的培养基中,其中所述液体培养基优选包含碳源、氮源和一种或多种维生素、矿物质、盐、氨基酸、补充剂或添加剂,更优选其中所述液体培养基缺乏次黄嘌呤、胸苷和/或谷氨酰胺。

5.根据权利要求4所述的方法,其中所述蛋白质从CHO细胞分泌到液体培养基中,优选浓度为每升液体培养基200-500mg蛋白质,更优选浓度为500-2000mg蛋白质,更优选浓度为2000-5000毫克蛋白质,而不浓缩蛋白质。

6.根据权利要求4所述的方法,还包括将有效量的甲氨蝶呤(MTX)和/或甲硫氨酸亚砜亚胺(MSX)引入液体培养基中,优选浓度为约1nM-1μM,更优选浓度为约10μM-100nM。

7.根据权利要求4所述的方法,还包括选择在液体培养基中生长的活CHO细胞的悬浮培养物,其中所选悬浮培养物的培养基中蛋白质的浓度为在不浓缩蛋白质的情况下,至少200mg/L、优选至少500mg/L、更优选至少1000mg/L、甚至更优选至少2000mg/L、还更优选至少5000mg/L。

8.根据权利要求7所述的方法,其中所选择的悬浮培养物的活CHO细胞含有至少约2至10个拷贝、优选至少约10至20个拷贝、更优选至少约20至30个拷贝、甚至更优选至少约30至50个拷贝的外源核酸/细胞。

9.根据权利要求4所述的方法,进一步包括从CHO细胞、液体培养基或两者中纯化含有重组Klotho蛋白的提取物,所述提取物优选包含:

至少约98%干重的所述蛋白质;和/或

小于约1-100ppm的CHO宿主细胞蛋白(HCP)。

10.根据权利要求9所述的方法,其中纯化提取物维持蛋白质的糖基化。

11.根据权利要求4所述的方法,其中生长所述CHO细胞包括在生物反应器中培养CHO细胞,所述生物反应器的体积或工作体积为至少10升,优选至少25升,更优选至少50升,甚至更优选至少100升,还更优选至少250升,还更优选至少500升,还更优选至少1,000升,还更优选至少2,000升,还更优选至少2500升,还更优选至少5,000升,还更优选至少10,000升。

12.根据权利要求1至11中任一项所述的方法,其中所述核酸包含转基因或cDNA,其与

SEQ ID NO:76至SEQ ID NO:96之一优选地具有至少85%、更优选至少90%、甚至更优选至少95%、仍甚至更优选至少98%、还更优选至少99%、最优选100%核酸序列同一性。

13.根据权利要求1至12中任一项所述的方法,其中所述蛋白与SEQ ID NO:2至SEQ ID NO:70之一具有至少90%、优选至少95%、更优选至少98%、甚至更优选至少99%、更优选100%核酸序列同一性。

14.一种细胞系,其包括:

多个中国仓鼠卵巢(CHO)细胞,

优选在二氢叶酸还原酶(DHFR)缺陷型CHO细胞中,更优选在CHO-S细胞中,或

优选在谷氨酰胺合成酶(GS)缺陷型CHO细胞中,更优选在GS-/-CHO细胞中,

含有外源核酸的所述CHO细胞包含启动子,优选强启动子,并且编码:

多肽,至少一部分所述多肽与SEQ ID NO:2至SEQ ID NO:70之一具有至少85%的氨基酸序列同一性;和

任选地,功能性二氢叶酸还原酶(DHFR)酶或功能性谷氨酰胺合成酶(GS)酶。

15.根据权利要求14所述的细胞系,其中所述CHO细胞含有或选择含有至少约2至10个拷贝、优选至少约10至20个拷贝、更优选至少约20至30个拷贝、甚至更优选至少约30至50个拷贝的外源核酸/细胞。

16.根据权利要求14所述的细胞系,其中所述核酸编码与SEQ ID NO:2至SEQ ID NO:70之一具有至少90%、优选至少95%、更优选至少98%、甚至更优选至少99%、更优选100%核酸序列同一性的多肽。

17.根据权利要求14所述的细胞系,其中所述核酸包含转基因或cDNA,其与SEQ ID NO:76至SEQ ID NO:96之一优选地具有至少85%、更优选至少90%、甚至更优选至少95%、仍甚至更优选至少98%、还更优选至少99%、最优选100%核酸序列同一性。

18.一种悬浮细胞培养物,包括:

液体培养基,优选无血清和/或无动物蛋白成分的液体培养基,其中所述液体培养基优选包含碳源、氮源和一种或多种维生素、矿物质、盐、氨基酸、补充剂或添加剂,更优选其中所述液体培养基缺乏次黄嘌呤、胸苷和/或谷氨酰胺;和

权利要求14-17中任一项所述的细胞系,其在所述液体培养基中生长以使得所述CHO细胞表达由所述核酸编码的所述多肽,所述多肽包含重组Klotho蛋白。

19.根据权利要求18所述的悬浮细胞培养物,其中所述CHO细胞将所述蛋白质分泌到所述液体培养基中,优选浓度为每升液体培养基200-500mg蛋白质,更优选浓度为500-2000mg蛋白质,仍更优选浓度为2000-5000mg蛋白质,而不浓缩蛋白质,和/或其中蛋白质以下述浓度存在于液体培养基中:每升液体培养基200-500mg蛋白质,更优选浓度为500-2000mg蛋白质,更优选浓度为2000-5000毫克蛋白质,而不浓缩蛋白质。

20.根据权利要求18或19所述的悬浮细胞培养物,其中所述蛋白质包含与其连接的一种或多种聚糖。

21.根据权利要求18至20中任一项所述的悬浮细胞培养物,其中所述液体培养基还包含有效量的甲氨蝶呤(MTX)和/或甲硫氨酸亚砜亚胺(MSX),优选浓度为约1nM-1μM,更优选浓度约为10nM-100nM。

22.根据权利要求18-21中任一项所述的悬浮细胞培养物,其中所述蛋白质与SEQ ID

NO:2至SEQ ID NO:70之一具有至少85%、优选至少90%、更优选至少95%、甚至更优选至少98%、仍更优选至少99%、更优选100%的氨基酸序列同一性。

23.一种重组Klotho蛋白,其中至少一部分所述蛋白质与SEQ ID NO:2至SEQ ID NO:70之一具有至少80%的氨基酸序列同一性。

24.根据权利要求23所述的重组Klotho蛋白,其中所述蛋白:

调节IGF-1和/或Wnt信号传导途径;

表现出β-葡萄糖醛酸酶和/或唾液酸酶活性;

抑制p53/p21信号传导途径;和/或

减少H_2O_2诱导的细胞衰老和凋亡,优选通过抑制p53/p21信号传导途径。

25.根据权利要求23或24所述的重组Klotho蛋白,其中所述蛋白质作为体液因子起作用,优选表现出多效活性,优选调节氧化应激,生长因子信号传导,离子稳态,和/或调节细胞表面上一种或多种糖蛋白活性,优选地一种或多离子通道蛋白和/或生长因子受体,优选地胰岛素/胰岛素样生长因子-1受体。

26.根据权利要求23-25中任一项所述的重组Klotho蛋白,其中至少一部分所述蛋白质与SEQ ID NO:2至SEQ ID NO:70之一具有至少85%、优选至少90%、更优选至少95%、甚至更优选至少98%、仍更优选至少99%、更优选100%的氨基酸序列同一性。

27.一种治疗衰老相关或其他病症、疾病或病症的方法,所述方法包括向有需要的受试者施用药学有效量的根据权利要求23-26中任一项所述的重组Klotho蛋白。

28.一种治疗衰老相关或其他病症、疾病或病症的方法,所述方法包括向有需要的受试者施用药学有效量的可溶性重组Klotho蛋白,其至少与人αKlotho同种型1的氨基酸残基1-981的子集具有至少80%氨基酸序列同一性。

29.一种治疗衰老相关或其他病症、疾病或病症的方法,所述方法包括向有需要的受试者施用药学有效量的可溶性重组Klotho蛋白,其与SEQ ID NO:2至SEQ ID NO:70之一具有至少80%的氨基酸序列同一性。

30.根据权利要求27至29中任一项所述的方法,其中所述蛋白质与SEQ ID NO:2至SEQ ID NO:70之一具有至少85%、优选至少90%、更优选至少95%、甚至更优选至少98%、仍更优选至少99%、更优选100%的氨基酸序列同一性。

31.根据权利要求30所述的方法,其中所述药学有效量足以:

将受试者的血清可溶性Klotho蛋白浓度提高到预定水平;和

优选地,将受试者的血清可溶性Klotho蛋白浓度维持在预定阈值或高于预定阈值达预定时间段。

32.根据权利要求31所述的方法,其中所述预定水平大于或等于每毫升血清约1000皮克可溶性Klotho蛋白。

33.根据权利要求31所述的方法,其中所述预定水平大约大于、等于或在以下之间:

每毫升血清50、100、250、500、750、1000、1250、1500、1750、2000、2250、2500、2750、3000、3500、4000、4500、5000、5500、6000、6500、7000、7500、8000、8500、9000、9500、10000、11000、12000、13000、14000、15000、20000、25000、30000、40000、50000、75000、100000皮克可溶性Klotho蛋白质;和/或

比血清中典型健康水平的可溶性Klotho蛋白质高约5%、10%、15%、20%、25%、30%、

40％、50％、60％、70％、80％、90％、100％、150％、200％、250％、300％、400％、500％、600％、700％、800％、900％、1000％、1200％、1500％、2000％、2500％、3000％、4000％、5000％。

34.根据权利要求31所述的方法，还包括以下中的一个或多个：

确定所述受试者的血清可溶性Klotho蛋白浓度；

计算足以将所述受试者的血清可溶性Klotho蛋白浓度提高到第一预定水平的药学有效量，其中所述第一预定水平优选大于或等于每毫升血清约1000皮克可溶性Klotho蛋白；

确定所述受试者的血清中可溶性Klotho蛋白质下降和/或代谢的速率；

基于所确定的速率计算所述受试者的血清可溶性Klotho蛋白浓度将处于或低于第二预定水平的后续剂量时间；和

计算足以将所述受试者的血清可溶性Klotho蛋白浓度从第二预定水平升高至第一预定水平的蛋白质的后续剂量。

35.根据权利要求34所述的方法，还包括将所述后续剂量量的蛋白质给予受试者。

36.根据权利要求31所述的方法，还包括以下中的一个或多个：

将外源核酸引入中国仓鼠卵巢(CHO)细胞，优选通过转染，所述核酸优选地包括转基因或cDNA，所述核酸编码与SEQ ID NO:2至SEQ ID NO:70之一具有至少85％、优选至少90％、更优选至少95％、甚至更优选至少98％、还更优选至少99％、最优选100％氨基酸序列同一性的多肽，所述核酸与SEQ ID NO:76至SEQ ID NO:96之一具有优选至少85％、更优选至少90％、甚至更优选至少95％、还更优选至少98％、还更优选至少99％、最优选100％的核酸序列同一性；

在液体培养基中培养CHO细胞，优选在无血清和/或无动物蛋白成分的液体培养基中，其中所述液体培养基优选包含碳源、氮源和一种或多种维生素、矿物质、盐、氨基酸、补充剂或添加剂，更优选其中所述液体培养基缺乏次黄嘌呤、胸苷和/或谷氨酰胺，

所述CHO细胞优选为：

二氢叶酸还原酶(DHFR)缺陷型CHO细胞，更优选在CHO-S细胞中，或

谷氨酰胺合成酶(GS)缺陷型CHO细胞，更优选在GS-/-CHO细胞中；

将有效量的甲氨蝶呤(MTX)和/或甲硫氨酸亚砜亚胺(MSX)引入液体培养基中，优选浓度为约1nM-1μM，更优选浓度为约10μM-100nM；

通过细胞选择过程选择在液体培养基中生长的活CHO细胞的悬浮培养物，其中所选悬浮培养物的培养基中蛋白质的浓度为在不浓缩蛋白质的情况下，至少200mg/L、优选至少500mg/L、更优选至少1000mg/L、甚至更优选至少2000mg/L、还更优选至少5000mg/L；

在所述CHO细胞中产生所述重组可溶性Klotho蛋白，其中所述蛋白优选地从CHO细胞分泌到液体培养基中，优选浓度为每升液体培养基200-500mg蛋白质，更优选浓度为500-2000mg蛋白质，更优选浓度为2000-5000毫克蛋白质，而不浓缩蛋白质；和

从CHO细胞、液体培养基或两者中纯化含有重组Klotho蛋白的提取物，所述提取物优选包含：

至少约98％干重的重组可溶性Klotho蛋白；和/或

小于约1-100ppm的CHO宿主细胞蛋白(HCP)，

其中纯化所述提取物优选地维持所述蛋白质的糖基化，所述蛋白质具有与其连接的一

个或多个聚糖。

37.根据权利要求31所述的方法，其中所述预定时间段是至少约6小时，优选至少约12小时，更优选至少约18小时，甚至更优选至少约24小时，还更优选至少约30小时，还更优选至少约36小时，更优选至少约42小时，还更优选至少约48小时，还更优选至少约54小时，还更优选至少约60小时，还更优选至少约66小时，更优选至少约72小时。

38.根据权利要求31所述的方法，其中所述预定时间段大于或等于约1-120天。

39.根据权利要求31所述的方法，其中所述预定时间段大于或等于约6个月、9个月或1年。

40.根据权利要求30-39中任一项所述的方法，其中所述受试者是人、非人动物或非人哺乳动物。

41.根据权利要求30至40中任一项所述的方法，其中所述蛋白质在药学上可接受的载体中施用或与其一起施用。

42.根据权利要求30至41中任一项所述的方法，其中所述与衰老相关的或其他的病症、疾病或障碍选自：

脆弱；
骨密度减少；
骨矿物密度减少；
体重减轻；
肌肉萎缩；
肌肉退化；
肌肉质量下降；
肌肉力量下降；
手部力量下降；
腿部力量下降；
身体素质下降；
运动减少；
行动自由下降；
生活质量评估下降；
射血分数下降；
运动能力下降；
学习下降；
学习能力下降；
记忆力下降；
智商下降；
认知恶化；
健忘；
认知能力下降；
认知功能下降；
突触可塑性下降；

突触功能下降;和

细胞衰老。

43.根据权利要求30至41中任一项所述的方法,其中所述与衰老相关的或其他的病症、疾病或障碍选自:

慢性肾脏病(CKD);

多囊肾病(PKD);

常染色体显性多囊肾病(ADPKD);

急性肾损伤(AKI);

急性肾小管坏死(ATN);

急性过敏性间质性肾炎(AAIN);

肾小球肾炎;

肾脏疾病;

肾功能衰竭;

非低尿性肾功能衰竭;

酗酒;

高磷血症;

肌营养不良症(MS);

1型糖尿病;

2型糖尿病;

心血管疾病(CVD);

心血管钙化;

脑血管功能不全;

血管钙化;

冠状动脉疾病;

血压异常;

盐敏感性高血压;

组织钙化;

钙化动脉粥样硬化斑块负担;

钙质沉着;

家族性肿瘤性钙质沉着症;

癌症;

一个或多个肿瘤;

髓鞘相关疾病;

脱髓鞘疾病;

神经退行性疾病;

神经血管疾病;

进行性核上性麻痹(PSP);

庞培病;

尼曼-皮克病;

小神经胶质细胞；
法伯病(FD)；
骨质疾病；
骨质疏松症；
骨质疏松；
骨质减少(特别是皮质骨BMD的丧失)；
肺气肿；
肺纤维化；
皮肤萎缩；
胸腺萎缩；
肾间质基质的积累；
肾小球硬化；
贫血；
白蛋白尿；
蛋白尿；
不孕；
阿尔茨海默氏病；
帕金森病；
痴呆；
血管性痴呆；
肌萎缩侧索硬化症(ALS)；
运动神经元病(MND)；
心房颤动；
慢性阻塞性肺病(COPD)；
纤维肌痛；
成年型糖尿病；
关节炎；
类风湿关节炎；
骨关节炎；
青光眼；
白内障；
黄斑变性；
多发性硬化症(MS)；
狼疮；
溃疡性结肠炎；
恶病质；
肥胖；
维生素D相关病症；
骨病；

通过骨重建的骨病；

干细胞耗竭；

晕船；

空间适应综合症(SAS)；

恶心；和

眩晕。

44.根据权利要求30-43中任一项所述的方法，还包括施用或共同施用一种或多种附加活性成分。

45.根据权利要求44所述的方法，其中所述一种或多种附加活性成分选自药物、抗体、激素、放射性造影剂、医药、天然化合物、合成化合物或药物组合物。

46.一种药物组合物，其包括：

药学有效量的权利要求23-25中任一项所述的重组Klotho蛋白；和

药学上可接受的载体。

47.一种药物组合物，其包括：

药学有效量的重组可溶性Klotho蛋白质，至少一部分所述蛋白质与下述具有至少85％的氨基酸序列同一性：

人αKlotho同种型1的氨基酸残基1-981、29-981、34-981、36-981、131-981、1-549、29-549、34-549、36-549或131-549的至少子集；或

SEQ ID NO:2至SEQ ID NO:70之一的至少一部分；和药学上可接受的载体。

48.根据权利要求46或47所述的药物组合物，其中至少一部分所述蛋白质与SEQ ID NO:2至SEQ ID NO:70之一的至少一部分具有至少85％、优选至少88％、更优选至少90％、甚至更优选至少92％、还更优选至少95％、还更优选至少98％、仍更优选至少99％、最优选100％的氨基酸序列同一性。

49.根据权利要求46至48中任一项所述的药物组合物，其进一步包含一种或多种附加活性成分。

50.根据权利要求46-49中任一项所述的药物组合物，其用于治疗选自以下的与衰老有关的或其他的病症，疾病或障碍：

脆弱；

骨密度减少；

骨矿物密度减少；

体重减轻；

肌肉萎缩；

肌肉退化；

肌肉质量下降；

肌肉力量下降；

手部力量下降；

腿部力量下降；

身体素质下降；

运动减少；

行动自由下降；
生活质量评估下降；
射血分数下降；
运动能力下降；
学习下降；
学习能力下降；
记忆力下降；
智商下降；
认知恶化；
健忘；
认知能力下降；
认知功能下降；
突触可塑性下降；
突触功能下降；
细胞衰老；
慢性肾脏病(CKD)；
多囊肾病(PKD)；
常染色体显性多囊肾病(ADPKD)；
急性肾损伤(AKI)；
急性肾小管坏死(ATN)；
急性过敏性间质性肾炎(AAIN)；
肾小球肾炎；
肾脏疾病；
肾功能衰竭；
非低尿性肾功能衰竭；
酗酒；
高磷血症；
肌营养不良症(MS)；
1型糖尿病；
2型糖尿病；
心血管疾病(CVD)；
心血管钙化；
脑血管功能不全；
血管钙化；
冠状动脉疾病；
血压异常；
盐敏感性高血压；
组织钙化；
钙化动脉粥样硬化斑块负担；

钙质沉着；
家族性肿瘤性钙质沉着症；
癌症；
一个或多个肿瘤；
髓鞘相关疾病；
脱髓鞘疾病；
神经退行性疾病；
神经血管疾病；
进行性核上性麻痹(PSP)；
庞培病；
尼曼-皮克病；
小神经胶质细胞；
法伯病(FD)；
骨质疾病；
骨质疏松症；
骨质疏松；
骨质减少(特别是皮质骨BMD的丧失)；
肺气肿；
肺纤维化；
皮肤萎缩；
胸腺萎缩；
肾间质基质的积累；
肾小球硬化；
贫血；
白蛋白尿；
蛋白尿；
不孕；
阿尔茨海默氏病；
帕金森病；
痴呆；
血管性痴呆；
肌萎缩侧索硬化症(ALS)；
运动神经元病(MND)；
心房颤动；
慢性阻塞性肺病(COPD)；
纤维肌痛；
成年型糖尿病；
关节炎；
类风湿关节炎；

骨关节炎；

青光眼；

白内障；

黄斑变性；

多发性硬化症(MS)；

狼疮；

溃疡性结肠炎；

恶病质；

肥胖；

维生素D相关病症；

骨病；

通过骨重建的骨病；

干细胞耗竭；

晕船；

空间适应综合症(SAS)；

恶心;和

眩晕。

51.根据权利要求46-49中任一项的药物组合物,其用于治疗或预防急性肾损伤(AKI)。

52.一种治疗或预防急性肾损伤(AKI)或其他病症的方法,所述方法包括：

向有需要的受试者施用药学有效量的重组Klotho蛋白质,至少一部分所述蛋白质与以下具有至少85％、86％、88％、90％、92％、95％、98％、99％、或优选100％的氨基酸序列同一性：

人αKlotho同种型1的氨基酸残基1-981、29-981、34-981、36-981、131-981、1-549、29-549、34-549、36-549或131-549的至少子集;或

SEQ ID NO:2至SEQ ID NO:70之一的至少一部分。

53.根据权利要求52所述的方法,还包括与药学有效量的重组可溶性Klotho蛋白共同施用一种或多种附加活性成分。

54.根据权利要求53所述的方法,其中将所述蛋白质和所述一种或多种附加活性成分配制成组合产品或组合物。

55.根据权利要求53所述的方法,其中所述蛋白质和所述一种或多种附加活性成分是单独的组分。

56.根据权利要求53所述的方法,其中混合所述蛋白质和所述一种或多种附加活性成分。

57.根据权利要求53所述的方法,其中所述蛋白质和一种或多种附加活性成分被配置用于共同施用,其中所述共同施用包括：

同时施用;或

不同的施用,优选分开一段时间。

58.根据权利要求53所述的方法,其中所述一种或多种附加活性成分选自药物、抗体、激素、放射性造影剂、医药或组合物。

59.根据权利要求52或53所述的方法，其中所述病症包括：

急性肾小管坏死(ATN)、肾炎、急性过敏性间质性肾炎(AAIN)、肾小球肾炎和/或肾毒性；或

AKI，其至少部分来自肾移植或其他手术、急性肾小管坏死(ATN)、肾炎、急性过敏性间质性肾炎(AAIN)、肾小球肾炎、肾毒性或低血压。

60.根据权利要求52或53所述的方法，其中所述肾毒性包括药物诱导的肾毒性。

61.根据权利要求60所述的方法，其中所述药物诱导的肾毒性包括抗微生物剂诱导的肾毒性。

62.根据权利要求60所述的方法，其中所述药物诱导的肾毒性包括氨基糖苷类诱导的肾毒性。

63.根据权利要求52或53所述的方法，其中施用步骤包括选自以下的一个或多个步骤：

确定所述受试者的血清可溶性Klotho水平；

计算足以将受试者中血清可溶性Klotho水平升高至预定水平或正常水平百分比的所述蛋白质的第一剂量；

向所述受试者施用第一剂量的蛋白质，优选通过推注或逐渐施用，更优选通过注射；

确定所述受试者的血清中可溶性Klotho下降的速率，优选在施用第一剂量后；

计算蛋白质后续剂量的时间和/或量；和

根据计算的时间和/或量将后续剂量的蛋白质给予所述受试者。

64.根据权利要求52或53所述的方法，其中施用步骤足以使受试者的血清可溶性Klotho蛋白浓度升高和/或维持在预定水平或阈值或高于预定水平或阈值，任选地持续预定时间段。

65.根据权利要求64所述的方法，其中所述预定水平或阈值大约大于、等于或在以下之间：

每毫升血清50、100、250、500、750、1000、1250、1500、1750、2000、2250、2500、2750、3000、3500、4000、4500、5000、5500、6000、6500、7000、7500、8000、8500、9000、9500、10000、11000、12000、13000、14000、15000、20000、25000、30000、40000、50000、75000、100000皮克可溶性Klotho蛋白质；或

比血清中典型健康水平的可溶性Klotho蛋白质高约5％、10％、15％、20％、25％、30％、40％、50％、60％、70％、80％、90％、100％、150％、200％、250％、300％、400％、500％、600％、700％、800％、900％、1000％、1200％、1500％、2000％、2500％、3000％、4000％、5000％。

66.根据权利要求64所述的方法，其中所述预定时间段大于或等于约6小时、12小时、18小时、1天、2天、3天、4天、5天、6天、7天、8天。天、9天、10天、12天、14天、21天、30天、45天、60天、90天、120天、6个月、9个月、1年、2年、3年、4年、或5年。

67.根据权利要求52或53所述的方法，其中施用所述蛋白质：

预防性地，在肾移植或施用肾毒素之前；和/或

肾移植或施用肾毒素后。

68.根据权利要求67所述的方法，其中所述肾毒素包括：

一种或多种氨基糖苷类，优选选自巴龙霉素、妥布霉素、庆大霉素、阿米卡星、卡那霉素

和新霉素；

一种或多种抗真菌剂，优选选自两性霉素B和氟胞嘧啶；

一种或多种造影剂，优选选自碘化放射性造影介质，碘与分子比率为约1.5:1的高渗透压造影介质(HOCM)，碘与分子比约3:1的非离子造影剂(LOCM)，和碘与分子比约为6:1的等渗(等渗透性)造影剂(IOCM)；

一种或多种抗逆转录病毒剂，优选选自阿德福韦、西多福韦、替诺福韦和膦甲酸；

一种或多种癌症(或化学)治疗剂，优选选自顺铂、卡铂、奥沙利铂、烷化剂、苯达莫司汀、环磷酰胺、异环磷酰胺、亚硝基脲、替莫唑胺、美法仑、抗肿瘤抗生素、丝裂霉素C、博来霉素、蒽环霉素抗代谢物、卡培他滨、羟基脲、甲氨蝶呤、培美曲塞、普拉曲沙、喷司他丁、氟达拉滨、克拉屈滨、吉西他滨、阿糖胞苷、长春花生物碱、拓扑替康、依托泊苷、紫杉烷类、伊立替康、来那度胺、艾日布林、三氧化二砷或伊沙唑嗪；

一种或多种二膦酸盐或其衍生物，优选选自唑来膦酸盐/唑来膦酸、伊班膦酸盐、阿仑膦酸盐、阿仑膦酸盐/胆钙化醇、依替膦酸盐、利塞膦酸盐，利塞膦酸盐碳酸钙、帕米膦酸盐和替鲁膦酸盐；和/或

一种或多种麻醉剂或阿片类药物，优选选自可卡因和海洛因。

69.根据权利要求52或53所述的方法，其中所述蛋白质包括：

C370S，优选不含F352V，更优选含F352；和/或

H193，或H193R变体以外的蛋白质。

70.一种治疗衰老个体的方法，所述衰老个体在编码Klotho蛋白的基因中具有纯合或杂合突变，所述方法包括：

给予治疗浓度的与SEQ ID NO:2至SEQ ID NO:70之一具有至少85％、优选至少90％、更优选至少95％、甚至更优选至少98％、还更优选至少99％、最优选100％氨基酸序列同一性的多肽。

71.根据权利要求70所述的方法，还包括确定基因的表达水平。

72.根据权利要求71所述的方法，其中给予治疗浓度的步骤取决于基因的表达水平。

治疗性重组KLOTHO蛋白及其组合物和方法

背景

1.技术领域

本公开涉及重组人Klotho蛋白组合物作为治疗剂的生产和施用。具体地，本公开涉及包含CGMP级人重组可溶性α-Klotho蛋白或其变体的组合物，以及制备和施用于人或非人受试者的方法。

2.相关技术

Klotho(或alpha-Klotho，α-Klotho等)是最近表征的由KL(或klotho)基因编码的蛋白质，位于人13号染色体上。已经鉴定了通过替代RNA剪接从单个klotho基因产生的两个转录物。见图1和2。第一转录被预测编码Klotho同种型1——全长1012个氨基酸、单次跨膜膜蛋白，具有短胞质尾(人残基1003至1012)、跨膜(TM)结构域(人残基982-1002)和细胞外区域或结构域(人残基1-981)，其包含两个同源(内部重复)结构域(称为KL1(人残基56-506，长450个残基)和KL2(人残基515-953，长438个残基)，其各自与β-葡糖苷酶具有20％-40％的氨基酸序列同源性，但缺乏葡糖苷酶催化活性)和信号序列(SS)结构域(人残基1-33)。含有SS、KL1和KL2结构域的细胞外区域(人残基1-981)可被α/β-分泌酶酶促切割，并作为130kDa循环蛋白释放到循环流中，称为可溶性klotho(或sKlotho、s-Klotho、alpha可溶性-Klotho等)。细胞外区域也可以切割成单独的68kDa蛋白质(KL1+SS)和64kDa蛋白质(KL2)。

第二个转录物是α-klotho mRNA的剪接变体，编码Klotho蛋白的第二个同种型，主要对应于KL1结构域。认为内部剪接供体位点位于klotho基因的外显子3中。得到的可变剪接转录物在外显子3(图1;灰色)后含有50bp插入，在其末端具有符合读框的终止密码子。表达的蛋白质产物分泌到循环中并称为分泌的Klotho(或Klotho同种型2)。因此，在任何给定时间，在循环中可能存在许多不同的Klotho蛋白，这取决于基因表达、RNA剪接和酶促切割。尽管存在各种形式的α-Klotho蛋白，但已知只有全长、膜结合的同种型1与成纤维细胞生长因子(FGF)受体形成复合物，并且用作FGF23的必需共受体——骨来源激素，其诱导尿液排出磷酸盐并对P_i和维生素D代谢具有调节作用。

Klotho在肾脏、大脑中以及在其他器官中的较小程度上高度表达，并且也可以在哺乳动物的脑脊髓液和尿液中发现。哺乳动物中可溶性Klotho蛋白的循环水平被认为随着年龄而降低。此外，Klotho缺陷小鼠表现出加速的衰老表型，而小鼠中klotho的过表达已显示延长寿命。此外，Klotho还涉及许多与衰老相关的细胞过程。鉴于上述情况，发展中的假设认为可溶性Klotho可以在人体中起抗衰老化合物的作用。

衰老是一种不可避免的渐进式生物过程，导致几乎所有组织和器官的功能障碍和破坏，最终导致死亡。例如，人体的衰老与细胞功能的衰退有关，这可导致各种疾病的发展。衰老被认为是由遗传和获得因素之间严格调节和复杂的相互作用驱动的，其特征通常在于衰老的增加、干细胞的定量和定性降低以及组织水平的异常结构。

随着所谓的“婴儿潮一代”一代人在年龄上不断发展，老龄人(例如，年龄在60-65岁)的人口在全球范围内迅速增加。这一老龄化人口对医疗保健需求的增加给任何医疗保健系统

带来了巨大的经济负担。重组klotho蛋白可以提供有希望的治疗剂以对抗与年龄相关的健康状况。基于可溶性Klotho的生产和纯化(例如,基本同质性)开发策略和健康干预方法以及在日益老化的人群中向受试者施用该蛋白质可有助于改善这种情况和与之相关的问题。

目前,不存在用于提供人Klotho蛋白质的外源形式的方法,如重组可溶性人α-Klotho蛋白质或蛋白质变体,特别是作为现行良好制造规范(cGMP)的规定标准的蛋白质,如由美国食品和药物管理局(FDA)确定和强制执行的,无论是单独使用还是与一种或多种其他活性成分组合使用。基于对受试者施用重组S-Klotho发展策略和健康干预方法,尤其是在日益老龄化的人群中,可能有助于改善这种情况。

发明内容

本公开的实施方案利用重组人Klotho蛋白、蛋白质片段和/或蛋白质变体、表达核酸构建体和/或载体、细胞系和/或细胞悬浮液,以及其制备、纯化和施用其至(人或非人动物)受试者的方法,解决了一个或多个上述或本领域中的其他问题。

例如,本公开的一些实施方案可以包括:

重组人α可溶性Klotho蛋白、蛋白片段和/或蛋白质变体;

重组人α可溶性Klotho蛋白的药物(或治疗组合物,例如制剂);

重组人α可溶性Klotho蛋白和至少一种另外的(活性)成分的组合物;

编码重组人α可溶性Klotho蛋白的核酸构建体或载体;

细胞系,其含有(i)编码重组人α可溶性Klotho蛋白的核酸构建体或载体和/或(ii)表达重组人α可溶性Klotho蛋白;

细胞的细胞悬浮培养物,其含有(i)编码重组人α可溶性Klotho蛋白的核酸构建体或载体和/或(ii)表达重组人α可溶性Klotho蛋白;

一种制备和任选纯化重组人α可溶性Klotho蛋白的方法;

一种制备重组人α可溶性Klotho蛋白的药物(或治疗组合物,即制剂)的方法;

将重组人α可溶性Klotho蛋白质施用至(人或非人动物)受试者的方法;

用于确定受试者中Klotho蛋白缺乏的诊断方法;

一种诊断受试者中Klotho蛋白缺乏的方法;

一种诊断受试者需要通过施用接受重组人α可溶性Klotho蛋白的方法;

用于评估有效性和/或确定蛋白质对有需要的受试者的有效剂量的方法;

重组人α可溶性Klotho蛋白,用于治疗特定的医学或其他疾病;和/或

重组人α可溶性Klotho蛋白质在制备用于治疗特定的医疗或其它状况的药物中的用途。

一些实施方案可包括制备重组Klotho蛋白的方法,该方法包括在中国仓鼠卵巢(CHO)细胞中产生重组Klotho蛋白,优选在二氢叶酸还原酶(DHFR)缺陷型CHO细胞中,更优选在CHO-S细胞中,或优选在谷氨酰胺合成酶(GS)缺陷型CHO细胞中,更优选在GS-/-CHO细胞中,所述蛋白质优选地与SEQ ID NO:2至SEQ ID NO:70的一种具有至少85%氨基酸序列同一性。

一些实施方案可以包括一种细胞系,其包括多个中国仓鼠卵巢(CHO)细胞,优选在二氢叶酸还原酶(DHFR)缺陷型CHO细胞,更优选在CHO-S细胞,或优选地在谷氨酰胺合成酶(GS)

缺陷型CHO细胞，更优选在GS-/-CHO细胞中，含有外源核酸的所述CHO细胞包含启动子，优选强启动子，并编码多肽，至少一部分多肽与SEQ ID NO:2至SEQ ID NO:70的一种具有至少85％的氨基酸序列同一性，和任选地，功能性二氢叶酸还原酶(DHFR)酶或功能性谷氨酰胺合成酶(GS)酶。

一些实施方案可包括悬浮细胞培养物，其包含液体培养基，优选无血清和/或无动物蛋白成分的液体培养基，其中液体培养基优选包含碳源、氮源和一种或多种维生素、矿物质、盐、氨基酸、补充物、或添加剂，更优选其中所述液体培养基缺乏次黄嘌呤、胸苷和/或谷氨酰胺以及权利要求14-17中任一项所述的细胞系在液体培养基中生长以使得CHO细胞表达由核酸编码的多肽，该多肽包含重组Klotho蛋白。

一些实施方案可包括重组Klotho蛋白，其中至少一部分所述蛋白质与SEQ ID NO:2至SEQ ID NO:70之一具有至少80％的氨基酸序列同一性。

一些实施方案可包括治疗衰老相关或其他病症、疾病或病症的方法，该方法包括向有需要的受试者施用药学有效量的如本文所述的重组Klotho蛋白。

一些实施方案可包括治疗衰老相关或其他病症、疾病或病症的方法，该方法包括向有需要的受试者施用药学有效量的可溶性重组Klotho蛋白，其至少与人αKlotho同种型1的氨基酸残基1-981的子集具有至少80％氨基酸序列同一性的。

一些实施方案可包括治疗衰老相关或其他病症、疾病或病症的方法，该方法包括向有需要的受试者施用药学有效量的可溶性重组Klotho蛋白，其与SEQ ID NO:2至SEQ ID NO:70之一具有至少80％、85％、90％、95％、97％、98％或99％的氨基酸序列同一性。

一些实施方案可包括药物组合物，其包含药学有效量的如本文所述的重组Klotho蛋白和药学上可接受的载体。

一些实施方案可包括药物组合物，其包含药学有效量的重组可溶性Klotho蛋白，至少一部分蛋白与人αKlotho同种型1的氨基酸残基1-981、29-981、34-981、36-981、131-981、1-549、29-549、34-549、36-549或131-549的至少子集或SEQ ID NO:2至SEQ ID NO:70的一种的至少一部分具有至少85％的氨基酸序列同一性，和药学上可接受的载体。

一些实施方案可以包括用于治疗或预防急性肾损伤(AKI)或其它病症的方法，所述方法包括向有需要的受试者施用药学上有效量的重组Klotho蛋白质，至少一部分蛋白与人αKlotho同种型1的氨基酸残基1-981、29-981、34-981、36-981、131-981、1-549、29-549、34-549、36-549或131-549的至少子集或SEQ ID NO:2至SEQ ID NO:70的一种的至少一部分具有至少85％、86％、88％、90％、92％、95％、98％、99％、或优选地100％的氨基酸序列同一性。

一些实施方案可包括组合物，其含有治疗性Klotho蛋白，例如CGMP级人重组可溶性α-Klotho蛋白，和至少一种其他活性组分，例如药物、抗体、激素、人细胞、组织、基于细胞或组织的产品(HCT/Ps)等，和/或将其施用于人或非人受试者的方法。组合的组合物和方法可用于治疗患有年龄相关病症或病症、代谢障碍、慢性病、急性损伤等的受试者。对没有明显病症或障碍的受试者预防性施用组合治疗也可用于延迟或预防本文所述的某些病症或障碍。

一些实施方案可包括核酸或核酸构建体。例如，实施方案可包括表达载体或核酸。核酸可以编码重组人α可溶性Klotho蛋白、蛋白片段或蛋白质变体。核酸可以编码天然或非天然信号传导序列。例如，核酸可编码在编码的Klotho蛋白质序列的上游(或N端)的非天然信号

传导序列。

一些实施方案可包括制备重组人α可溶性Klotho蛋白的方法。该制造方法可以包括在液体培养基中生长中国仓鼠卵巢(CHO)细胞,在CHO细胞中产生重组可溶性Klotho蛋白质,和/或从CHO细胞、液体培养基或两者纯化含重组可溶性Klotho蛋白的提取物。提取物可包括至少约98%干重的重组可溶性Klotho蛋白和/或小于约1-100ppmCHO宿主细胞蛋白(HCP)。CHO细胞可以是二氢叶酸还原酶(DHFR)缺陷型CHO细胞,如CHO-S细胞,或谷氨酰胺合成酶(GS)缺陷型CHO细胞,如GS-/-CHO细胞。产生的(表达的)蛋白质可以从CHO细胞释放(例如,分泌)到液体培养基中和/或可以具有一个或多个与其连接的β-聚糖。

CHO细胞可以含有一种或多种编码蛋白质的外源核酸,以及任选的功能酶,例如二氢叶酸还原酶、谷氨酰胺合成酶(GS)等。外源核酸可以包括启动子(例如,强启动子、弱启动子等),例如通常或典型用于在CHO细胞中表达外源蛋白的启动子。外源核酸可包括转基因或cDNA(例如,在启动子的控制下),优选与SEQ ID NO:76至SEQ ID NO:96之一具有至少85%的核酸序列同一性,或任何其他合适的核酸,其编码如本文所述的Klotho蛋白(例如,S-Klotho变体)。

该方法可包括例如通过转染将外源核酸引入CHO细胞中。该方法可以包括在液体培养基中生长CHO细胞,如无(人、(胎)牛或其他)血清和/或无动物(或动物衍生的)蛋白质(组分)的培养基。培养基优选包含碳源、氮源、和/或一种或多种维生素、矿物质、盐、氨基酸、补充物或添加剂,优选在生物反应器中。根据具体的CHO细胞系,方法可包括:将有效量的甲氨蝶呤(MTX)、蛋氨酸亚砜亚胺(MSX)或其他药剂引入液体培养基和/或选择(例如,通过CHO细胞亚克隆、有限稀释、荧光激活细胞分选(FACS)等)在液体培养基中生长的活CHO细胞的悬浮培养物。

在一些实施方案中,选择和/或基因扩增可以通过在选择培养基中培养转染的细胞来进行,所述选择培养基例如缺少次黄嘌呤和/或胸苷(例如,-HT培养基)、谷氨酰胺等的培养基。在至少一个实施方案中,可以添加或使用低浓度的MTX来扩增转染的核酸(或其基因),从而选择增加的蛋白质表达(例如,用DHFR转基因转染的DHFR缺陷型CHO细胞)。可选地(或另外),可以通过将MSX((内源)谷氨酰胺合成酶(GS)的抑制剂)添加到具有至少一种(外源)谷氨酰胺合成酶(GS)转基因的CHO细胞的悬浮培养物中来进行选择和/或基因扩增。

该方法可包括亚培养存活细胞或培养物(例如,MTX抗性和/或MSX抗性细胞或培养物)。选择的悬浮培养物和/或选择的CHO细胞可以具有或表现出蛋白质产量的增加(例如,通过CHO细胞),蛋白质浓度增加(例如,在液体培养基中),和/或外源核酸的拷贝数增加(例如,每个细胞)(例如,相比于未选择的悬浮培养或CHO细胞)。

某些实施方案可包括含有多个CHO细胞的细胞系。例如,CHO细胞可以是DHFR缺陷型CHO细胞,例如CHO-S细胞。CHO细胞可以包含一种或多种外源核酸(拷贝数)(包含转基因或cDNA),其编码与SEQ ID NO:2至SEQ ID NO:70之一具有至少85%的氨基酸序列同一性的多肽。该多肽可以包含人重组α可溶性Klotho蛋白。外源核酸可包括转基因或cDNA,优选与SEQ ID NO:76至SEQ ID NO:96之一具有至少85%的核酸序列同一性。在一些实施方案中,核酸可以(也)包括或编码启动子(与转基因相关)和/或任选的(外源)酶,例如(功能性)二氢叶酸还原酶(DHFR)酶、谷氨酰胺合成酶(GS)酶等。

至少一个实施方案包括悬浮细胞培养物,其包含在液体培养基中生长的细胞系,液体

培养基优选包含碳源、氮源和/或一种或多种维生素、矿物质、盐、氨基酸、补充物或添加剂，使得CHO细胞表达由所述核酸编码的多肽。液体培养基可以是无(人、(胎)牛或其他)血清和/或无动物(或动物衍生的)蛋白质(组分)的。例如，液体培养基可以不含牛血清白蛋白、人血清白蛋白等。

在一些实施方案中液体培养基还可以包括有效量的MTX和/或MSX。悬浮培养物(或其CHO细胞)可以(被选择以)：表现出蛋白质产量的增加(例如，通过CHO细胞)；表现出增加的蛋白质浓度(例如，在液体培养基中)；分泌蛋白质(例如，进入液体培养基)；和/或具有外源核酸的增加拷贝数(例如，每个细胞)，优选相比于未选择的悬浮培养物。蛋白质可以具有一个或多个与其连接的β-聚糖。

一些实施方式包括悬浮细胞培养物的CHO细胞、液体培养基或两者的或来自其的提取物，提取物含有与SEQ ID NO:2至SEQ ID NO:70之一具有至少85％的氨基酸序列同一性的重组蛋白。某些实施方案包括来自(例如悬浮细胞培养物的)CHO细胞、液体培养基或两者的含有人重组α可溶性Klotho蛋白的提取物。至少一个实施方案包括与SEQ ID NO:2至SEQ ID NO:70之一具有至少85％的氨基酸序列同一性的分离的重组蛋白。

一些实施方案可以包括施用重组人α可溶性Klotho蛋白质至需要其的人或非人动物受试者的方法。施用Klotho蛋白质的受试者可能患有各种病症或具有多种病症的风险(例如，障碍、疾病、损伤、生病等)。例如，一些实施方案包括治疗一种或多种慢性疾病和/或与衰老相关的病症的方法，例如与(人)老化相关联的物理、精神、神经其它病症。一些实施方案可通过一种或多种机制或作用促进愈合、恢复、长寿和/或其他有益结果。实施方案可包括例如向有需要的受试者(例如，具有病症的受试者或处于发生病症的风险的受试者)施用药学有效量的重组可溶性Klotho蛋白质或蛋白质变体。施用这种蛋白质或蛋白质变体可以对病症的过程和结果具有积极的治疗效果，包括慢性和/或与年龄相关的疾病和人受试者的寿命，以及其表征。

药学有效量可以是足以提高血清可溶性Klotho蛋白质浓度至预定水平，如大于、等于或在每毫升血清约50至3000微微克可溶性Klotho蛋白质之间。该量还可以或可选地足以将受试者的血清可溶性Klotho蛋白质浓度维持在预定阈值或高于预定阈值达预定时间段。实施方案还可包括施用所述蛋白质至有需要的受试者，从而保持受试者的血清可溶性Klotho蛋白质浓度在预定阈值或高于预定阈值预定的时间段。

实施方案还可以包括确定受试者的血清的可溶性Klotho蛋白质浓度，计算药学有效量，确定受试者的血清中的可溶性Klotho蛋白质下降的速率，基于所确定的速率计算受试者的血清可溶性Klotho蛋白质的浓度将处于或低于第二预定水平的后续剂量时间，计算足以将受试者的血清可溶性Klotho蛋白浓度从第二预定水平升高至第一预定水平的蛋白质的后续剂量量，和/或将后续剂量的蛋白质施用给受试者。

该蛋白可以(有效)调节IGF-1和/或Wnt信号传导途径，表现出β-葡萄糖醛酸酶和/或唾液酸酶活性，抑制p53/p21信号传导途径，和/或减少H_2O_2诱导的细胞衰老和凋亡，优选通过抑制p53/p21信号传导途径。该蛋白质可以作为或作为体液因子起作用，优选表现出多效活性和/或优选调节氧化应激，生长因子信号传导，离子稳态，和/或调节细胞表面上糖蛋白活性，例如一种或更多离子通道蛋白和/或生长因子受体，例如胰岛素/胰岛素样生长因子-1受体。

该蛋白质还可以有效治疗一种或多种与衰老相关的病症(或与(人)衰老相关的病症),例如脆弱,骨密度丧失或骨矿物质密度丧失,体重减轻,肌肉萎缩或变性,肌肉量减少,肌肉力量、手部力量、腿部力量或身体素质下降,运动、活动自由度、生活评估质量、射血分数或运动能力下降,学习、学习能力、记忆力或智商下降,认知恶化或遗忘,认知能力或功能下降,突触可塑性或突触功能下降,以及细胞衰老。

该蛋白质还可以有效治疗一种或多种与衰老相关的疾病(或与(人)衰老有关的疾病),如阿尔茨海默病、帕金森病、痴呆或血管性痴呆、肌萎缩侧索硬化症(ALS)或运动神经元疾病(MND)、心房颤动、慢性阻塞性肺病(COPD)、纤维肌痛、成人发病的糖尿病、关节炎或类风湿性关节炎、骨关节炎、骨质疏松症、青光眼、白内障、黄斑变性和其他眼病/病症、多发性硬化症(MS)、狼疮和/或溃疡性结肠炎。

因此,实施方案还可以包括在治疗一种或多种衰老相关的病症中使用的组合物。该组合物可以包括重组可溶性Klotho蛋白质(例如,其与SEQ ID NO:2至SEQ ID NO:70之一具有至少85%的氨基酸序列同一性)和药学上可接受的载体。

一些实施方案可包括组合物,其含有治疗性Klotho蛋白,例如CGMP级人重组可溶性α-Klotho蛋白,和至少一种其他活性组分,例如药物、抗体、激素、激素、人细胞、组织、基于细胞或组织的产品(HCT/Ps)等,和将其施用于人或非人受试者的方法。组合的组合物和方法可用于治疗患有年龄相关病症或病症、代谢障碍、慢性病、急性损伤等的受试者。对没有明显病症或障碍的受试者预防性施用组合治疗也可用于延迟或预防本文所述的某些病症或障碍。

在本公开的各种实施方案中,无论是产物还是方法,重组Klotho蛋白可以包含具有与SEQ ID NO:1至SEQ ID NO:38之一具有80%-100%序列同一性的序列的Klotho蛋白之一,优选具有与SEQ ID NO:74或SEQ ID NO:75的序列之一具有80%-100%序列同一性的C-末端标签,任选地具有与SEQ ID NO:73具有80%-100%序列同一性的接头序列置于其间。蛋白质可任选地包含或表达与SEQ ID NO:71或SEQ ID NO:72具有80%-100%序列同一性的信号传导序列。优选地,(制造、生产、表达或施用的)蛋白质与SEQ ID NO:39至SEQ ID NO:70之一具有80%-100%的序列同一性。

制造重组Klotho蛋白质的一种示例性的方法包括:在中国仓鼠卵巢(CHO)细胞中产生重组Klotho蛋白,优选在二氢叶酸还原酶(DHFR)缺陷型CHO细胞中,更优选在CHO-S细胞中,或优选在谷氨酰胺合成酶(GS)缺陷型CHO细胞中,更优选在GS-/-CHO细胞中,所述蛋白质优选地与SEQ ID NO:2至SEQ ID NO:70的一种具有至少85%氨基酸序列同一性。

示例性细胞系包含:多个中国仓鼠卵巢(CHO)细胞,优选在二氢叶酸还原酶(DHFR)缺陷型CHO细胞,更优选在CHO-S细胞,或优选地在谷氨酰胺合成酶(GS)缺陷型CHO细胞,更优选在GS-/-CHO细胞中,含有外源核酸的所述CHO细胞包含启动子,优选强启动子,并编码多肽,至少一部分多肽与SEQ ID NO:2至SEQ ID NO:70的一种具有至少85%的氨基酸序列同一性,和任选地,功能性二氢叶酸还原酶(DHFR)酶或功能性谷氨酰胺合成酶(GS)酶。

示例性的悬浮细胞培养物包含:液体培养基,优选无血清和/或无动物蛋白成分的液体培养基,其中液体培养基优选包含碳源、氮源和一种或多种维生素、矿物质、盐、氨基酸、补充物、或添加剂,更优选其中所述液体培养基缺乏次黄嘌呤、胸苷和/或谷氨酰胺以及权利要求14-17中任一项所述的细胞系在液体培养基中生长以使得CHO细胞表达由核酸编码的

多肽，该多肽包含重组Klotho蛋白。

示例性重组Klotho蛋白质包括与SEQ ID NO:2至SEQ ID NO:70之一具有至少80％的氨基酸序列同一性。

治疗衰老相关或其他病症、疾病或病症的示例性方法，该方法包括向有需要的受试者施用药学有效量的可溶性重组Klotho蛋白，其至少与人αKlotho同种型1的氨基酸残基1-981的子集具有至少80％氨基酸序列同一性的。

治疗衰老相关或其他病症、疾病或病症的示例性方法，该方法包括向有需要的受试者施用药学有效量的可溶性重组Klotho蛋白，其与SEQ ID NO:2至SEQ ID NO:70之一具有至少80％的氨基酸序列同一性。

示例性药物组合物包含：药学有效量的重组可溶性Klotho蛋白，至少一部分蛋白与人αKlotho同种型1的氨基酸残基1-981、29-981、34-981、36-981、131-981、1-549、29-549、34-549、36-549或131-549的至少子集；或SEQ ID NO:2至SEQ ID NO:70的一种的至少一部分具有至少85％的氨基酸序列同一性，和药学上可接受的载体。

治疗或预防急性肾损伤(AKI)或其它病症的示例性方法包括：向有需要的受试者施用药学上有效量的重组Klotho蛋白质，至少一部分蛋白与人αKlotho同种型1的氨基酸残基1-981、29-981、34-981、36-981、131-981、1-549、29-549、34-549、36-549或131-549的至少子集或SEQ ID NO:2至SEQ ID NO:70的一种的至少一部分具有至少85％、86％、88％、90％、92％、95％、98％、99％、或优选地100％的氨基酸序列同一性。

治疗衰老个体的示例性方法，所述衰老个体在编码Klotho蛋白的基因中具有纯合或杂合突变。该方法包括给予治疗浓度的与SEQ ID NO:2至SEQ ID NO:70之一具有至少85％、优选至少90％、更优选至少95％、甚至更优选至少98％、还更优选至少99％、最优选100％氨基酸序列同一性的多肽。

一些实施方案可以包括在本公开的其他地方阐述的(包括在本公开的其他方面或实施方案中的)任何特征、选项和/或可能性。还应注意，本文描述的前述、后续和/或其他特征中的每一个代表本公开的不同实施方案。此外，这些特征中的任何两个或更多个的组合代表本公开的不同实施方案。在不脱离本公开的范围的情况下，这些特征或实施方案也可以以任何合适的组合和/或顺序进行组合。因此，本文描述的每个特征可以以任何合适的组合和/或顺序与本文描述的任何一个或多个其他特征组合。因此，本公开不限于在此详细描述的示例性实施方案的特定组合。

本公开的示例性实施方案的附加特征和优点将在随后的描述中阐述，并且部分地将从描述中显而易见，或者可以通过这些示例性实施方案的实践来学习。借助于所附权利要求中特别指出的仪器和组合，可以实现和获得这些实施方案的特征和优点。根据以下描述和所附权利要求，这些和其他特征将变得更加明显，或者可以通过实践下文阐述的这种示例性实施方案来学习。

附图说明

为了描述可以获得本公开的上述和其他优点和特征的方式，将通过参考在附图中示出的其特定实施方案来呈现上面简要描述的实施方案的更具体的描述。为了更好地理解，在整个附图中，相同的元件由相同的附图标记表示。应理解，这些附图仅描绘了本发明的典型

实施方案，因此不应认为是对其范围的限制，将通过使用附图以附加特性和细节来描述和解释本公开，在附图中：

图1描绘了示意图，示出根据本公开的实施方案的各种Klotho蛋白质的细胞生产；

图2(A-D)描绘了：A)人α-Klotho的同种型1和同种型2的示意性结构，以及用于产生C-D的抗体结合的表位的位置(残基800至900)；B)1012个氨基酸的全长α-Klotho蛋白质序列，KL1和KL2分别以红色和绿色显示，并且TM突出显示(黑色)；C)和D)人细胞裂解物(C)和人体组织的蛋白质印迹分析(D)；

图3A显示了2010年接受某些氨基糖苷类的成年患者的数量；

图3B说明了接受图3A中所示的氨基糖苷类的成年患者的年龄分布；和

图4说明了在接受图3A中呈现的氨基糖苷类的成年患者上收集的治疗数据。

具体实施方式

在详细描述本公开的各种实施方案之前，应理解，本公开不仅限于特定示例的系统、方法和/或产品的具体参数、措辞和描述，其可在一个实施方案到下一个实施方案变化。因此，尽管对本公开的某些实施方案进行详细地描述，参考具体的特征(例如，配置、参数、性质、步骤、组分、成分、构件、元件、部件、和/或部分等)，但该描述是说明性的，不应解释为限制本公开和/或要求保护的发明的范围。另外，这里使用的术语是为了描述实施方案，并不一定是为了限制本公开和/或要求保护的发明的范围。

除非另外定义，否则本文使用的所有技术和科学术语具有与本公开所属领域的普通技术人员通常理解的含义相同的含义。

可以参考一个或多个本质上是示例性的实施方案来说明本公开的各个方面，包括系统、方法和/或产品。如本文所使用的，术语“实施方案”意味着“用作示例、实例或说明”，并且不应被解释为比本文公开的其他方面更优选或更具优势。另外，对本公开或发明的“实施方案”的提及旨在提供说明性示例，而不限制由所附权利要求指示的本发明的范围。

如在本说明书和所附权利要求中所使用的，单数形式“一”，“一个”和“该”均考虑、包括并具体地公开单数和复数指示物，除非上下文另有明确说明。例如，提及“蛋白质”考虑并具体地公开了一种蛋白质，以及多种(例如，两种或更多种、三种或更多种)蛋白质。类似地，除非上下文另有明确规定，否则复数指示物的使用不一定需要多个这样的指示物，而是包括、具体地公开和/或提供对单个以及多个这种指示物的支持。

如贯穿本公开所使用的，词语“可”和“可以”以允许的意义使用(即，意味着可能)，而不是强制意义(即，意义着必须)。另外，术语“包括”、“具有”、“涉及”、“含有”、“特征在于”、其变体以及本文(包括权利要求)所用的类似术语应具有包容性和/或开放性，与“包含”及其变体的含义相同，并且例如，不排除其他未陈述的元素或方法步骤。

为简洁起见，仅本公开可以列举数值的列表或范围。然而，应当理解，在公开或陈述了这样的列表或数值范围(例如大于、小于、至多、至少和/或大约某个值，和/或在两个列举的值之间)的情况，同样具体地公开和考虑了落入所公开的值或列表或值范围内的任何特定值或值范围。因此，小于或等于约10个单位或0到10个单位的说明性测量(例如，长度、宽度、厚度等)的公开说明性地包括以下具体公开：(i)9个单位、5个单位、1个单位或0到10个单位之间的任何其他值的测量，包括0个单位和/或10个单位；和/或(ii)9个单位和1个单位之

间、8个单位和2个单位之间、6个单位和4个单位、和/或0到10个单位之间的任何其他值范围之间的测量。

为了便于理解，在可能的情况下，已经使用类似的参考(即，组件和/或元件的类似命名)来指定与本公开的不同实施方案共同的相同元件。类似地，在可能的情况下，类似的组件或具有相同功能的组件将被提供有类似的参考标记。这里将使用特定语言来描述示例性实施方案。然而，应该理解，不打算由此限制本公开的范围。而是，应理解，用于描述示例性实施方案的语言仅是说明性的，不应被解释为限制本公开的范围(除非这种语言在本文中明确地描述为必要的)。

虽然详细说明被分成章节，每个章节内的段标题和内容被仅用于组织目的，并且不旨在是自包含的描述和实施方案或限制本说明书或权利要求的范围。而是，详细描述中的每个章节的内容旨在被阅读和理解为总体性整体，其中一个章节的元素可以属于和/或预示其他章节。因此，在一个章节内具体公开的实施方案还可以涉及和/或用作具有相同和/或类似产品、方法和/或术语的另一章节中的附加和/或替代实施方案。

本公开内容的实施方案包括产品、组合物和/或制造和/或使用重组人Klotho的蛋白质的方法，如(现行良好制造实践(CGMP)等级)人重组可溶性α-Klotho蛋白质、蛋白质片段和/或蛋白质变体。

基因治疗可以在动物研究中有效。然而，基因治疗的安全性，尤其是人类治疗的安全性仍然值得怀疑。与将klotho基因病毒递送至动物(细胞)相比，在人中施用外源和/或重组Klotho蛋白可以是更安全、更容易和更直接的恢复(内分泌)klotho水平的方式。因此，类似于施用促红细胞生成素或红细胞生成刺激剂以纠正CKD患者和/或胰岛素中的贫血以维持I型糖尿病患者的正常葡萄糖代谢，外源性(人重组α可溶性)Klotho蛋白的施用可能是在不久的将来用于治疗衰老和/或衰老相关疾病的可行且有效的选项。例如，向人类施用外源(人重组α可溶性)Klotho蛋白可能是逆转或延缓干细胞耗竭和/或减轻与年龄相关的脆弱或其他病理过程的有效策略。

临床前数据支持可溶性Klotho蛋白质对于与年龄有关的疾病和缺乏Klotho相关的疾病的治疗潜力。流行病学数据显示，老年人可溶性Klotho低于年轻成人，可溶性Klotho水平与年龄呈负相关，表明衰老与可溶性Klotho下降有关。

已定义术语的缩略列表

为了帮助理解前述和即将出现的书面描述和所附权利要求的范围和内容，下面直接定义选择的几个术语。

术语“病症”是指本领域技术人员所理解的在患者中表现或预期的任何障碍症、疾病、损伤或生病。这种病症的表现形式可以是本领域已知的早期、中期或晚期表现，包括病前症状、体征或标志物。预期这种病症可以是或包括其预测的、预料的、预想的、推测的、假设的和/或猜测的发生，无论是在科学或医学证据、风险评估中发现，还是仅仅是担忧或恐惧。

术语“患者”通常是指在医生的护理下的任何动物，如该术语在本文中定义，特别是指在医生或其他相关医学专业人员的护理下的人。

本文使用的术语“医师”通常是指医生。在上下文适用的情况下，该术语可包括任何医疗专业人员，包括肿瘤科医生、外科医生，或任何执业医疗专业人员，例如医生助理、护士、抽血师、兽医等。

术语“癌症”是指细胞的异常，通常是不受控制的生长。如本文所用的“癌细胞”包括具有异常的、通常不受控制的生长的恶性细胞。因此，术语癌症是涵盖多种不同的独特疾病的总称，其特征在于恶性细胞以通常不受控制的方式生长。

术语“共同施用”和类似术语是指两种或更多种组分的同时、顺序和/或组合施用。例如，可以通过并行、同时或依次(例如，分开一段时间的不同施用)以单独的剂量施用每种组分来共同施用两种组分。该段时间可以是非常小的(例如，基本上、立即第一次施用后)或更长的(例如，1-60秒、1-60分钟、1-24小时、1-7天、1-4周、1-12个月等，或其间的任何值或值范围)。并行或同时施用可包括用于两个或更多个组分的重叠施用时间，或包含两种或多种组分的混合物的组合产品的施用。

如本文所用，“核酸”和类似术语是指天然存在的或合成的寡核苷酸或多核苷酸，无论是DNA还是RNA或DNA-RNA杂合体、单链或双链、有义或反义。特别地，核酸可包括但不限于DNA、RNA、cDNA、gDNA、ssDNA、dsDNA或其任何组合。本公开内容的核酸还可包括本领域已知的核苷酸或核酸类似物(例如BrdU)和非磷酸二酯(核苷间)键或主链(例如，肽核酸(PNA)或硫代二酯键)。

如本文所用，术语“标准氨基酸”包括：丙氨酸-ala-A；精氨酸-arg-R；天冬酰胺酸-asn-N；天冬氨酸-asp-D；半胱氨酸-cys-C；谷氨酰胺酸-gln-Q；谷氨酸-glu-E；甘氨酸-gly-G；组氨酸-his-H；异亮氨酸-ile-I；亮氨酸-leu-L；赖氨酸-lys-K；蛋氨酸-met-M；苯丙氨酸-phe-F；脯氨酸-pro-P；丝氨酸-ser-S；苏氨酸-thr-T；色氨酸-trp-W；酪氨酸-tyr-Y；和缬氨酸-val-V。

如本文所用，“密码子优化的”或“密码子优化”是指将核苷酸序列中的密码子修饰或改变为优选或更接近地匹配用于表达分子的生物体中密码子使用模式的密码子的过程。因此，可以基于生物体中已知的密码子使用来优化密码子以用于需要表达的特定生物体中，以增强核酸表达的有效性，例如，以实现更快的翻译速率和高准确度。特定生物体中的密码子使用是已知的。

编码核酸分子可以是经修饰的野生型或密码子优化的序列，其中密码子被优化用于在特定宿主细胞中表达，例如哺乳动物细胞，例如CHO细胞或293细胞，或在酵母或植物细胞、真核细胞中。

在特定实例中，核酸序列可以是密码子优化的，例如，以增加编码序列的表达水平。特定密码子使用依赖于表达修饰多肽的宿主生物。本领域技术人员熟悉用于在哺乳动物或人细胞、细菌或酵母中表达的最佳密码子，包括例如大肠杆菌或酿酒酵母(Saccharomyces cerevisiae)。例如，密码子使用信息可从kazusa.or.jp.codon获得的密码子使用数据库获得(参见例如Richmond(2000)Genome Biology，1:241，以获得数据库的描述。还参见Forsburg(2004)Yeast，10:1045-1047；布朗等人(1991)Nucleic Acids Research，19:4298；夏普等人(1988)Nucleic Acids Res.，12:8207-8211；夏普等人(1991)Yeast，657-78)。

治疗性蛋白质

本公开的实施方案可包括一种或多种治疗性和/或重组人α可溶性Klotho蛋白、蛋白片段和/或蛋白质变体。

该蛋白可包含人αKlotho同种型1的氨基酸残基1-1012、1-981、29-981、34-981、36-

981、131-981、1-549、29-549、34-549、36-549或131-549的全部或子集。该蛋白可具有与人αKlotho同种型1的氨基酸残基1-1012、1-981、29-981、34-981、36-981、131-981、1-549、29-549、34-549、36-549或131-549的全部或子集至少或约85％、86％、87％、88％、89％、90％、91％、92％、93％、94％、95％、96％、97％、98％、或99％、或100％的氨基酸序列同一性。例如，至少一部分所述蛋白质与SEQ ID NO:2至SEQ ID NO:70之一或其两种或更多种的组合具有至少85％的氨基酸序列同一性。本文也可考虑在本申请中描述的蛋白质序列的其它部分或片段。例如，一些实施方案可包括具有与SEQ ID NOS:1-75中的一种或其两种或更多种的组合的任何合适部分具有至少85％的氨基酸序列同一性的至少一部分的蛋白质。

一些实施方案可包括与人αKlotho同种型1相比具有一个或多个氨基酸变异的蛋白质。说明性地，蛋白质可包含人C370变体。例如，蛋白质可包括C370S改变，从而包含S370。在一些实施方案中，蛋白质可包括人F352或除F352V以外的蛋白质。在至少一个实施方案中，蛋白质可包括C370S改变，从而包含S370，不含F352V变体，优选含有F352。蛋白质可包括H193或H193R变体以外的蛋白质。考虑并在本文中明确公开了在人αKlotho同种型1的氨基酸残基(或位置)193、352和/或370处的所有其他标准氨基酸取代。

一些实施方案可包括人αKlotho同种型1的氨基酸残基45的变异。在45位，残基可以是缬氨酸(Val;V)、苯丙氨酸(Phe;F)或另一种氨基酸。

蛋白质还可包括一种或多种聚糖(与其连接)。例如，天然人αKlotho同种型1可具有在氨基酸106、159、283、344、604、612和/或694处连接(通过糖基化)的聚糖。因此，本公开的蛋白质或其Klotho蛋白质序列可具有一个或多个相同(或相似)的聚糖(通过糖基化)与其连接(例如，在相同的氨基酸位置)。在一个优选的实施方案中，蛋白质包括在相同氨基酸位置连接的所有相同或相似(天然型)聚糖。

在一些实施方案中，蛋白质可包括信号肽或信号传导序列。例如，蛋白质可包括天然Klotho信号传导序列。蛋白质可包括非天然或合成的信号传导序列。在一些实施方案中，信号传导序列可以是N末端信号传导序列和/或Klotho蛋白质序列的上游(或N末端)。在其他实施方案中，信号传导序列可以是C-末端或以其他方式设置。优选地，信号传导序列可以是、包括、或具有与天然人αKlotho同种型1信号传导序列、天然人αKlotho同种型2信号传导序列、SEQID NO:71或SEQ ID NO:72至少80％、85％、90％、95％、98％、或99％的氨基酸序列同一性。

在一些实施方案中，蛋白质可包括氨基酸标签。标签可以是C-末端标签和/或Klotho蛋白质序列的下游(或C-末端)。在其他实施方案中，标签可以是N-末端或以其他方式设置。标签可以是或包含Fc融合蛋白。例如，标签可以是或包含IgG1-Fc蛋白质序列。优选地，所述标签可以是、包括、或具有与SEQ ID NO:74至少80％、85％、90％、95％、98％、或99％的氨基酸序列同一性。

标签也可以或替代地是或包含TEV-双胞胎链霉素(twinstrep)蛋白质序列(例如，如本领域中已知的)。优选地，信号传导序列可以是、包括、或具有与SEQ ID NO:75至少80％、85％、90％、95％、98％、或99％的氨基酸序列同一性。

在至少一个实施方案中，标签可以从蛋白质上切割下来。在其他实施方案中，标签可以保留为蛋白质的一部分。在一些实施方案中，标签可以增强蛋白质的溶解度和/或(血清)半衰期。在一些实施方案中，可以在蛋白质纯化期间利用标签(例如，作为纯化机制的一部

分)。

在一些实施方案中,蛋白质可包括置于Klotho蛋白质序列和氨基酸标签之间的接头(例如,氨基酸接头)。说明性地,接头可包含1至40个氨基酸,优选5至20个氨基酸,更优选8至12个氨基酸,最优选约10个氨基酸。在一些实施方案中,接头可以是或包含GS接头。优选地,接头可以是、包括、或具有与SEQ ID NO:73至少70%、80%、90%、或100%的氨基酸序列同一性。

在至少一个实施方案中,蛋白质可以是符合CGMP规范的,如美国食品和药物管理局(FDA)所确定和实施的。例如,Klotho蛋白可以是干重至少95%、96%、97%、98%、或99%纯的。在一些实施方案中,Klotho蛋白质样品可以包括少于约1-100百万分率(ppm),少于约100-1000十亿分率(ppb),或小于约1-100ppb的CHO宿主细胞蛋白(HCP)、核酸和/或其他细胞组分,或其间的任何值或值范围。

核酸和表达载体

一些实施方案可包括核酸或核酸构建体。例如,实施方案可包括表达载体或核酸构建体。如本文所述,核酸可编码重组人α可溶性Klotho蛋白、蛋白片段或蛋白质变体。在至少一个实施方案中,核酸可编码Klotho蛋白质序列、任选的(天然或非天然的)信号传导序列(例如,在Klotho蛋白质序列的N末端或N末端)、任选的接头序列(例如,GS接头)和/或氨基酸标签(例如,IgG1-Fc或TEV-双胞胎链霉素),如本文所述。

在一些实施方案中,核酸可以表达的蛋白质包含人αKlotho同种型1的氨基酸残基1-1012、1-981、29-981、34-981、36-981、131-981、1-549、29-549、34-549、36-549或131-549的全部或子集。至少一部分蛋白质可具有与人αKlotho同种型1的氨基酸残基1-1012、1-981、29-981、34-981、36-981、131-981、1-549、29-549、34-549、36-549或131-549的全部或子集至少或约85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%、98%、或99%、或100%的氨基酸序列同一性。例如,至少一部分蛋白质可以具有与SEQ ID NO:1至SEQ ID NO:75之一或其两种或更多种的组合的全部或部分至少和/或约85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%、98%、或99%、或100%的氨基酸序列同一性。在优选的实施方案中,蛋白质可以具有与SEQ ID NO:2至SEQ ID NO:70之一的全部或部分至少和/或约85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%、98%、或99%、或100%的氨基酸序列同一性。

在一些实施方案中,至少一部分核酸可以具有与SEQ ID NO:76至SEQ ID NO:101之一或其两种或更多种的组合至少和/或约85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%、98%、或99%、或100%的核苷酸序列同一性。在优选的实施方案中,核酸可以具有与SEQ ID NO:76至SEQ ID NO:96之一至少和/或约85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%、98%、或99%、或100%的核苷酸序列同一性。

本公开的核酸序列还可以包括本领域已知的终止密码子(例如,TGA、TAG、TAA)。

细胞系和制造方法

本公开的实施方案可包括细胞系。细胞系可包含任何合适的细胞类型,例如CHO细胞、HEK细胞、HL-60细胞或本领域已知的其他细胞系。说明性地,该细胞系可包括CHO细胞(例如,多个CHO细胞)。在一些实施方案中,CHO细胞可(各)包含(一个或多个拷贝)的外源核酸。

核酸可以编码具有与SEQ ID NO:1至SEQ ID NO:75之一或其两种或更多种的组合(优选地与SEQ ID NO:2至SEQ ID NO:70之一)至少和/或约85％、86％、87％、88％、89％、90％、91％、92％、93％、94％、95％、96％、97％、98％、或99％、或100％的氨基酸序列同一性的多肽。

核酸可包含至少一种转基因或cDNA。在一些实施方案中,至少一部分核酸可以具有与SEQ ID NO:76至SEQ ID NO:101之一或其两种或更多种的组合(优选地与SEQ ID NO:76至SEQ ID NO:96之一)至少和/或约85％、86％、87％、88％、89％、90％、91％、92％、93％、94％、95％、96％、97％、98％、或99％、或100％的核酸序列同一性。核酸可以是或包含质粒或其他(结构)形式的核酸。

在一些实施方案中,外源性核酸可以编码功能性的酶,例如二氢叶酸还原酶(DHFR)和/或谷氨酰胺合成酶(GS)。在至少一个实施方案中,CHO细胞可以是或包括二氢叶酸还原酶(DHFR)缺陷型CHO细胞,如CHO-S细胞。所述核酸可以包括启动子(例如,弱到强启动子,如本领域技术人员所理解的)。例如,在一些实施方案中,核酸可以包括与SEQ ID NO:2至SEQ ID NO:70之一具有至少85％等的核酸序列同一性的转基因相关联的(强)启动子。因此,转基因可以在启动子的控制下。

为方便起见,在整个本公开中提及CHO细胞和/或细胞系。然而,应注意,其他细胞、细胞系和/或宿主细胞(除CHO细胞外)也涵盖在本发明的范围内。因此,对CHO细胞和/或细胞系的提及也考虑参考和/或使用其他已知细胞、细胞系和/或宿主细胞。

转染

制造CHO细胞系的方法可以包括引入外源核酸至CHO细胞中,优选通过转染,或其它技术,如本领域中已知的。在至少一个实施方案中,CHO细胞系的无血清生长优化的细胞悬浮液用作宿主细胞系用于插入含有启动子的核酸(质粒),编码人αS-klotho转基因的多肽——其具有与SEQ ID NO:2至SEQ ID NO:70之一至少85％氨基酸序列同一性,和可选择的(酶)标记。转基因分别编码人α可溶性Klotho的氨基酸1至981、29至981或34至981。在具体实施方案中,转基因具有对应于SEQ ID NO:76至SEQ ID NO:96之一的序列(或具有与SEQ ID NO:76至SEQ ID NO:96中的一种至少85％核酸序列同一性)。对于DHFR缺陷型CHO细胞系(如CHO-S细胞系),可选择(酶)标记是外源性DHFR。对于其他CHO细胞系,可选择的(酶)标记是外源GS。

生长、选择和/或基因扩增

一些实施方案可以包括在固体培养基上和/或在液体培养基中(例如在悬浮细胞培养物中)生长细胞(例如,转染和/或CHO细胞),优选在无血清和/或无动物(或动物衍生的)蛋白质(成分)培养基中。例如,细胞可以在固体生长培养基上铺板一段时间。细胞也可以或可选地在悬浮培养物和/或液体培养基中生长。液体培养基优选包含碳源、氮源、和一种或多种维生素、矿物质、盐、氨基酸、补充物或添加剂。在一些实施方案中,培养基还可以缺少次黄嘌呤和胸苷(HT)、谷氨酰胺等。

在至少一个实施方案中,在一定的时间段之后(例如,48小时转染后),可将细胞聚集(例如,分离),任选地离心(例如,在100×g下5分钟),和/或接种(例如,以约2000个细胞/孔),例如到96孔贴壁培养板(例如,含有补充血清的-HT和/或谷氨酰胺培养基)中。在某些实施方案中,培养基还可以包括MTX和/或MSX。未转染的细胞可在选择后7-14天内死亡(例

如,在-HT和/或谷氨酰胺培养基中暴露于MTX和/或MSX后)。

在某些实施方案中,CHO细胞可以(被选择为)含有至少约2至10个拷贝、至少约10至20个拷贝、至少约20至30个拷贝、或至少约30至50个拷贝的外源核酸(例如,每个细胞)。因此,该方法可以包括选择含有至少约2至10个拷贝、至少约10至20个拷贝、至少约20至30个拷贝、或至少约30到50个拷贝的外源核酸(例如,每个细胞)的CHO细胞。例如,可以向细胞施用(连续增加的水平)MTX和/或MSX(例如,浓度为约1nM-1μM、约10-100nM等)。

用外源DHFR转染的DHFR缺陷型CHO细胞(如CHO-S细胞系)中的二氢叶酸还原酶(DHFR)基因扩增是通过在生长培养基中连续增加甲氨蝶呤(MTX)的水平来完成的。因为质粒含有DHFR,所以这允许在暴露于MTX(10-100nM)时扩增宿主细胞内的S-klotho基因(片段)。GS基因表达系统也用于扩增用外源GS转染的CHO细胞(例如,暴露于MSX时)。或者,也使用GS-/-宿主细胞系,这消除了对MSX的需要。这些步骤导致产生大量拷贝的S-klotho基因(例如,每个细胞10至30个拷贝的基因),并导致转基因细胞系中S-klotho蛋白的高水平表达。

在一些实施方案中,在悬浮培养物中,蛋白可以从CHO细胞分泌到液体培养基中。例如,本公开的某些CHO细胞和/或细胞系可以分泌(或选择分泌)高达每升液体培养基200-500mg蛋白质的浓度,每升液体培养基500-2000mg蛋白质的浓度,每升液体培养基2000-5000mg蛋白质的浓度,或其间的任何值或值范围(未浓缩蛋白)。在至少一个实施方案中,可以选择高产细胞系(或悬浮培养物),使得培养基(所选细胞系的一种或多种所选悬浮培养物)中人重组α可溶性Klotho蛋白的浓度为在不浓缩蛋白质的情况下,至少200mg/L、优选至少500mg/L、更优选至少1000mg/L、甚至更优选至少2000mg/L、还更优选至少5000mg/L。

通过有限的细胞稀释对所得的高S-klotho产生的含转基因的菌落进行亚克隆,以进一步产生分泌在500至2000mg/L S-klotho范围内的分泌S-klotho的CHO细胞系至细胞条件培养基中。对所有细胞构建体进行限制性消化并验证序列。

在一些实施方案中,CHO细胞可以在生物反应器中生长,所述生物反应器的体积或工作体积为至少10升,优选至少25升,更优选至少50升,甚至更优选至少100升,还更优选至少250升,还更优选至少500升,还更优选至少1,000升,还更优选至少2,000升,还更优选至少2500升,还更优选至少5,000升,还更优选至少10,000升。

细胞系维护

对于扩增的高产S-Klotho细胞系(例如,由DHFR/MTX或GS/MSX系统产生),任选随后进行细胞亚克隆,明智地使用浓缩培养基饲料在扩大规模期间向生产细胞系施用在无血清和无动物蛋白成分的基础培养基中进行最终的生物反应器运行。

通过在摇瓶中或在波袋(Wave Bag)系统中的细胞悬浮液中的细胞接种物扩增进行高产生细胞系的放大,然后连续接种在100L然后500L容量的生物反应器中产生的细胞。在摇瓶、波袋或生物反应器中,在整个生长周期中细胞活力维持在大于85%的活细胞;然后在CHO S细胞生长的平台阶段期间生物反应器中的活细胞计数为80%或更高,伴随产生高达1-3g/L的S-klotho产生(称为“高产者”)。

蛋白质生产

某些实施方案可采用利用强启动子序列和/或高拷贝数质粒的重组DNA策略,用于在哺乳动物(例如,CHO)细胞中生产治疗量的的Klotho蛋白质。在至少一个实施方案中,例如,DHFR缺陷型CHO细胞中的二氢叶酸还原酶(DHFR)基因扩增可包括提供和/或使用(连续增加

水平的)甲氨蝶呤(MTX)。类似地,含外源谷氨酰胺合成酶(GS)基因的CHO细胞可以与甲硫氨酸砜亚胺(MSX)处理。

所述Klotho蛋白质还可以包括一种或多种聚糖(连接到其上)。例如,天然人αKlotho同种型1(SEQ ID NO:1)可具有在氨基酸106、159、283、344、604、612和/或694处连接(通过糖基化)的聚糖。本公开内容的Klotho蛋白可具有一个或多个相同(或相似)的聚糖(通过糖基化)与其连接(例如,在相同的氨基酸处)。

在至少一个实施方案中,蛋白质可以是符合CGMP规范的,如美国食品和药物管理局(FDA)所确定和实施的。例如,Klotho蛋白可以是干重至少95%、96%、97%、98%、或99%纯的。在一些实施方案中,Klotho蛋白质样品可以包括少于约1-100百万分率(ppm),少于约100-1000十亿分率(ppb),或小于约1-100ppb的CHO宿主细胞蛋白(HCP)、核酸和/或其他细胞组分,或其间的任何值或值范围。

与从人体液体(即血液、血清、尿液、脑脊髓液)分离的天然S-klotho结构上的结构相比,所产生的S-Klotho蛋白质存在的聚糖结构可以是相似或相同的。在至少一个实施方案中,天然样聚糖的确认可确保在S CHO细胞产生的S-Klotho蛋白中产生并稳定维持正确的天然翻译后修饰(PTM)。

Klotho蛋白的溶解度和/或半衰期延长

公开了用于延长人S-Klotho蛋白的半衰期和增加其溶解度的方法和组合物。而且,如此产生以实现这些结果的蛋白质构建体的纯化和表征也是本公开的主题。关于在klotho基因或核酸构建体的序列中进行的核酸变化的相关信息(参见SEQ ID NOS:76-96)和/或Klotho蛋白的氨基酸序列中的变化或化学改变(参见SEQ ID NOS:1-70),和/或在Klotho蛋白的氨基酸序列中添加或减少化学基团、肽或蛋白质在本公开内容中教导,以获得所得的人Klotho变体蛋白质(新组合物),与天然Klotho分子相比,生物基质(如血液、脑脊液、尿液或各种人体组织)中的生物半衰期或溶解度增加。这些新颖的组合物可以通过本文所述的用于修饰S-Klotho蛋白的方法制备。

融合蛋白构建体可以通过将S-Klotho蛋白与抗体(IgG)的Fc结构域组合来产生。

通过将S-Klotho蛋白与人血清白蛋白(HSA)组合产生融合蛋白构建体。

通过将S-Klotho蛋白与人转铁蛋白(TF)组合产生融合蛋白构建体。

通过将S-Klotho蛋白与专有重组多肽如XTEN®组合产生融合蛋白。

通过聚乙二醇化产生新型S-Klotho蛋白。

利用上述和其他半衰期延长方法以几种方式改善S-Klotho蛋白的性能,例如:

增加S-Klotho给药间隔,提供优越的患者便利性和可能的依从性。

减少给药频率导致总体药物使用量降低,并降低商品成本。

在与母体蛋白相同的给药间隔内降低药物量。

简化剂量配方并实现皮下配方。

使用与母体蛋白相同的剂量和给药间隔的更高药物水平,导致更长的药物暴露和可能更好的功效。

降低S-Klotho的免疫原性。

产生S-Klotho的Fc结构域融合蛋白构建体

测试抗体Fc结构域和人血清白蛋白(HSA)在延长半衰期和增加人S-Klotho蛋白的溶解

度方面的有效性。Fc融合体涉及肽、蛋白质或受体外部结构域与抗体Fc部分的融合。Fc和白蛋白融合物不仅通过增加肽药物的大小而实现延长的半衰期，而且还通过将延伸的蛋白质与新生儿Fc受体FcRn结合而利用身体的天然再循环机制。在延伸的蛋白质与FcRn受体结合后，防止了细胞内体中融合蛋白的降解。基于添加Fc或白蛋白的融合可导致3-16天的生物半衰期，比已报道的典型聚乙二醇化或脂化肽的寿命长得多。对于描述使用蛋白质融合技术如Fc融合蛋白、与人血清白蛋白融合、与羧基末端肽融合以及其他多肽融合方法以制备具有更理想的药代动力学特征的生物质药物的综述，参见Strohl WR.Fusion Proteins for Half-Life Extension of Biologics as a Strategy to Make Biobetters(生物制剂半衰期延长的融合蛋白作为制备生物质药物的策略)，Biodrugs.2015;29(4):215-239，其全部内容通过具体引用并入本文。

因此将Fc结构域添加到我们的亲本蛋白(S-Klotho)中以增加对Fc受体(FcRn)的结合亲和力。FcRn存在于血管内皮细胞的溶酶体内，并起到拯救抗体降解的作用，其使大多数蛋白质在循环中短暂存在。由于与FcRn的相互作用，蛋白质具有从几天到几周的半衰期，与不具有这种新产生的物质组合物的生物制剂相比，允许延长形式的蛋白质药物的给药频率更低。

Fc和白蛋白之间的主要差异是Fc的二聚体性质与HSA的单体结构相比，导致Fc融合肽作为二聚体或单体呈现，与HSA形成对比。如果S-Klotho的靶受体足够紧密地间隔开或者它们本身是特定人靶器官的二聚体，则肽Fc融合体的二聚体性质可以产生亲合力效应。取决于靶标，这可能是合乎需要的或不合乎需要的。

在本公开中还教导了S-Klotho蛋白与抗体Fc的融合，以改善S-Klotho的溶解度和稳定性。向S-Klotho添加Fc结构域还将允许融合蛋白在人受试者中施用后具有较低的免疫原性。

S-Klotho蛋白与人血清白蛋白(HSA)的缀合

与人IgG相似，66.5kDa蛋白质HSA在19天的范围内具有长的平均半衰期。在浓度为约50mg/mL(约600μM)时，HSA是人血浆中最丰富的蛋白质，其具有多种功能，包括维持血浆pH、代谢物和脂肪酸转运，以及维持血压的作用。HSA(肾脏对肾小球滤过蛋白质的尺寸上限)也是强阴离子的，这更有助于延缓肾脏的过滤。与IgG类似，HSA也以pH依赖性方式结合FcRn，尽管在与IgG结合不同的位点并且通过与IgG结合不同的机制，并且与IgG类似地再循环，导致其延长的半衰期。HSA也倾向于在肿瘤和发炎组织中积累，这表明与白蛋白融合或结合可能有助于将蛋白质或肽靶向这些位点。

自20世纪90年代初以来，人们已经广泛研究了具有固有的短半衰期性质的肽或蛋白质与HSA的融合以延长这些分子的血清半衰期。从那时起，许多不同的肽和小蛋白质已经融合到HSA作为创新和潜在的改良抗体(biobetter)分子。批准上市的第一种HSA-肽或蛋白质融合产物是Tanzeum®(在欧盟销售为Eperzan®)，Human Genome Sciences发现的一种DPP-4抗性GLP-1-HSA融合蛋白，由葛兰素史克公司(GlaxoSmithKline)开发和销售。Tanzeum®(阿必鲁肽(albiglutide))分别于2014年3月和4月获得欧洲药品管理局(EMA)和FDA的批准。因此，HSA将药理学活性GLP-1的半衰期从天然GLP-1的1-2分钟改善至4-7天，这允许每周一次给药。其他七种已知的HSA融合蛋白产物候选物正在开发中或最近已经开发中。此外，Novozyme一直在开发具有改进的FcRn结合的重组HSA的修饰形式，用于构建可

具有甚至更长的半衰期特性的“下一代”HSA-蛋白质融合体。这是基于使用HSA的K573P突变体，发现其对FcRn具有大12倍的亲和力，在小鼠和食蟹猴中赋予HSA的半衰期比野生型分子更长。期望HSA的这些较长半衰期的突变体可以进一步用作融合蛋白以改善融合蛋白的半衰期。

因此，本发明人公开了我们可以将我们的Klotho蛋白融合至野生型HSA或HSA的突变形式以产生Klotho融合分子，其在人血液、脑脊髓液和其他人生物基质中具有显著延长的半衰期，以产生战略性治疗益处，例如优越的患者便利性和可能的依从性，减少给药频率，导致总体药物使用较少，和/或降低商品成本。与母体蛋白质相同的给药间隔的更低药物量也可以简化剂量配方并且能够实现皮下制剂或降低S-Klotho的免疫原性。

S-Klotho蛋白与人转铁蛋白(TF)的缀合

转铁蛋白是一种高度丰富的血清糖蛋白，在血清中发现3-4mg/mL，可以紧密但可逆地结合铁，并起到将铁运送到组织的作用。转铁蛋白具有679个氨基酸残基，大小约为80kDa，并且具有两个高亲和力的Fe3+结合位点，一个位于N-末端结构域，另一个位于C-末端结构域。据报道，人转铁蛋白的半衰期为7-10天或10-12天。人转铁蛋白的非糖基化形式占总转铁蛋白库的约2-8％，具有略长的14-17天的半衰期。转铁蛋白在人血清中的持续延长是由于网格蛋白依赖性转铁蛋白受体介导的机制，其将受体结合的转铁蛋白再循环回到循环中。

已经对人转铁蛋白与N-和C-末端以及将转铁蛋白的两个主瓣连接在一起的中心定位的铰链区进行了肽和蛋白质的融合。转铁蛋白的N末端是游离的并且可以直接融合。C末端更加埋藏并受到附近二硫键的约束，因此当蛋白质与C末端融合时通常使用柔性接头。通过制备针对特定靶标的肽文库，然后将来自这些文库的结合物融合到糖基转铁蛋白(N-末端、C-末端、环或接头区域)以开发成具有延长的半衰期的治疗性融合蛋白，扩展了这种能力。

生物技术公司BioRexis Technologies，Inc.成立于2002年，旨在开发转铁蛋白融合蛋白平台，它被称为“Trans Body”平台，作为治疗平台。他们的先导分子BRX-0585是转铁蛋白-GLP-1融合蛋白，用于治疗2型糖尿病(T2DM)。GLP-1与转铁蛋白的融合被证明显著增强GLP-1的半衰期。BioRexis于2007年3月被辉瑞公司收购。至今可以确定，目前没有BioRexis衍生的融合蛋白在临床中。Klotho蛋白可以与人转铁蛋白融合以产生Klotho融合分子并临床施用以显著延长体内人生物基质的半衰期或稳定性。

S-Klotho蛋白与来自Amunix的XTEN的缀合

XTEN®是一种专有的重组多肽，可延长治疗性有效载荷的体内半衰期。XTEN由天然存在的亲水性氨基酸组成，可生物降解。可以通过化学缀合或遗传融合将诸如蛋白质、肽和合成化合物的药物XTEN化。XTEN蛋白质缺乏二级和三级结构，它们的溶液行为类似于具有非常大的流体动力学半径的化学制备的聚合物。通过尺寸排阻色谱，XTEN蛋白质聚合物看起来比具有相似分子量的典型球状蛋白质大得多。XTEN的膨胀效应大大降低了附着分子的肾清除率，从而大大增加了它们的体内半衰期。在本发明中，添加到Klotho蛋白质中的XTEN聚合物的长度将被定制以优化药代动力学以及附着的Klotho蛋白质有效负载的生物分布。

因此，XTEN可以与我们的S-Klotho蛋白重组融合，以增加体内半衰期的分子。一个益处是利用遗传S-Klotho-XTEN融合构建体，产生了一种分子，其具有包括治疗和扩大部分在内的单个分子的表达、纯化和表征的便利性。重组融合允许每个蛋白质在精确定义的位置连

接多个XTEN链，已经被治疗药物制造商成功使用，其产生了最佳的药代动力学，例如XTEN化的生长激素(Somavaratan，与Versartis公司)和FVIII-XTEN(Biogen公司)所示例。例如，在接受不同剂量的XTEN化生长激素(Somavaratan，Versartis)的儿童中进行的药代动力学已经显示出Somavaratan分子的优化，以减少除肾脏清除之外的受体介导的消除，从而产生最佳的半衰期。

XTEN蛋白质聚合物可以作为游离中间体产生，用于与肽、肽模拟物和其他合成分子的化学缀合。通过将半胱氨酸或赖氨酸残基引入XTEN编码基因，将反应基团(硫醇、胺)插入精确限定的位置。Amunix已开发出含有1至9个硫醇基团的XTEN，这些硫醇基团具有不同的间距，可供合作伙伴使用。因此，在本发明中，XTEN中与氨基和巯基的正交缀合将促进我们的Klotho-XTEN分子的产生。

蛋白质的纯化

所述Klotho蛋白质可以从(例如，CHO细胞系的)CHO细胞的细胞悬浮培养中提取。CHO细胞可以产生并任选地分泌Klotho蛋白质(例如，进入液体培养基中)。还观察到S-klotho分泌到高达200-500mg/L的细胞用过的培养基中。

本公开的重组蛋白的纯化可以通过本领域已知的或本文描述的任何合适的方法进行，例如，涉及提取、沉淀、色谱和/或电泳的任何常规方法。可用于纯化蛋白质的进一步纯化方法包括使用结合靶蛋白质的单克隆抗体的亲和层析。一些实施方案可包括可通过亲和层析纯化的IgG标记的蛋白质。通常，含有重组蛋白的粗制剂通过其上固定有合适的单克隆抗体的柱。蛋白质通常通过特异性抗体与柱结合而杂质通过。洗涤柱后，通过改变pH或离子强度从凝胶中洗脱蛋白质。例如，来自CHO-S高产细胞系的用过的培养基通过切向流过滤浓缩；通过亲和层析，然后通过离子交换柱或柱层析纯化S-klotho蛋白。尺寸排阻色谱也可用于纯化蛋白质。

在备选方案中，进行一个或多个亲和前或后亲和纯化步骤。这些步骤可包括，例如，(超)离心、透析、膜和/或切向流过滤、色谱分离例如离子交换、液-液萃取例如(水性)两相萃取，或其他已知的纯化步骤。在某些实施方案中进行一个或多个后纯化处理步骤。这种后纯化处理步骤可包括，例如，串联阴离子/阳离子流通色谱(不同于结合-洗脱色谱)，通过膜过滤除去病毒和/或细菌(例如，0.2微米、0.1微米等)，或通过本领域普通技术人员已知的其他方式。

分析Klotho蛋白质

蛋白质纯度可通过SDS-PAGE或本领域已知的其他测定或手段证明。例如，在至少一个实施方案中，将Klotho蛋白质样品(50μg)在预制SDS-PAGE凝胶(4-15％，10个孔；目录号456-1083；BioRad)上分级分离并用考马斯(Coomassie)蓝染色剂染色。所有样品均在其间或在单独的凝胶上的空泳道中运行，以避免样品与样品的污染。如通过考马斯蓝色染色和光密度测定法追踪，或通过银染色可视化，或通过HPLC或RP-HPLC测定，显示大于98％的S-klotho从CHO S条件培养基中分离。为了获得序列信息，可以用溴化氰、胰蛋白酶和/或蛋白酶K切割蛋白质(还原和S-羧甲基化后)，并根据蛋白质化学的已知方法通过HPLC分离肽。然后在自动气相微测序装置(Applied Biosystems Model 470A，ABI，Foster City，CA，USA)中使用连接到插座的在线自动HPLC PTH氨基酸分析仪(Applied Biosystems Model 120，ABI见上文)对如此制备的样品进行测序。

还通过质谱法分析蛋白质。关于质谱的样品制备，为了限制对正确的S-klotho蛋白质的分析，仅切除75和150kDa之间的凝胶条带用于分析。用无菌刀片浸渍凝胶级分并进行凝胶内消化。通过用80μL 50％乙腈(ACN)/50mm碳酸氢铵洗涤三次使凝胶级分脱色，并用100％ACN洗涤。鉴于不存在来自靶α-Klotho肽的半胱氨酸残基，省略了烷基化步骤。胰蛋白酶消化在37℃下用60μL胰蛋白酶在50毫米碳酸氢铵(0.005微克/微升)中进行过夜(测序级改良，目录号为V511A;Promega)。该过程产生25μL，其中5μL(对于S-Klotho为1μL)在连接至nanoLC(Dionex Ultimate 3000UHPLC)的Orbitrap nano-ESI Q-Exactive质谱仪(Thermo Scientific)中进行液相色谱-电喷雾电离串联质谱(MS/MS)和PRM分析。MS/MS分析证实，通过本公开内容的实施方案产生的人重组αS-klotho与人血液、血清、尿液或脑脊髓液中发现的人重组αS-klotho基本上相似(例如，在相应的氨基酸序列中相同)。

使用上述纯化方法，确定污染的CHO宿主细胞蛋白(HCP)的水平在纯化的S-Klotho蛋白中是可接受的。在最终的S-Klotho产品中，HCP被除去至<1-100ppm。从用过的CHO S生产细胞系(细胞和/或液体培养基)中分离纯度为98+％的S-klotho蛋白质产物。具体地，产生并纯化具有适合于人受试者临床施用的分析特征的CGMP级人αS-klotho。例如，人重组αS-Klotho的分析谱在ProteomeXchange数据库中用参考号PXD002775表示，其可以在http://proteomecentral.proteomexchange.org/cgi/GetDataset?ID＝PXD002775中找到。NIH完整的S-Klotho蛋白质数据集位于http://www.ncbi.nlm.nih.gov/protein/Q9UEF7

适用于临床施用的S-Klotho的分析图谱和在本公开的实施方案中获得的分析图谱包括小于0.1ng/μg(1EU/μg)的S-Klotho的内毒素水平。此外，还通过SDS PAGE显示纯化的人重组体S-Klotho具有≥98％的纯度。

存在于CHO S细胞产生的S-Klotho上的聚糖结构与从人体液体(即血液、血清、尿液和脑脊髓液)分离的天然S-Klotho上的结构相比是相同的。这确保了在S CHO细胞产生的S-Klotho蛋白中产生并稳定维持相同的天然翻译后修饰(PTM)。因此，使用本文所述的生产和纯化方法，我们已成功地生产cGMP级人S-klotho，其具有适合于人受试者临床施用的分析特征。

治疗组合物

本公开的一些实施方案可包括药物组合物，例如治疗组合物。本公开的药物组合物通常可包括治疗有效量的重组可溶性αKlotho蛋白质混合物与媒介物或载体，其由一种或多种另外的组分组成。组分可包括一种或多种聚集抑制剂、缓冲剂、张力调节剂和另外的赋形剂。载体中的主要溶剂可以是水性或非水性的。可以通过将本公开的纯化的Klotho蛋白质与药学上可接受的载体组合来制备组合物。

本领域普通技术人员将理解，组合物中包含的各种组分的组合可以以任何适当的顺序进行，即，缓冲剂可以首先、中间或最后添加，并且张力调节剂也可以首先、中间或最后添加。本领域普通技术人员还应理解，这些化学品中的一些在某些组合中可能是不相容的，因此，易于用具有相似性质但在相关混合物中相容的不同化学品替代。

聚集抑制剂降低多肽在不适当或不需要的三元或四元复合物中缔合的倾向。氨基酸L-精氨酸和/或L-半胱氨酸可用于在制剂中长时间(例如，两年或更长)地减少含Fc结构域的多肽的聚集。制剂中聚集抑制剂的浓度优选为约1mM至1M，更优选约10mM至约200mM，更优选约10mM至约100mM，甚至更优选约15mM至约75mM，和更优选约25mM。这些化合物可从商业供

应商处获得。

本公开的组合物可包含缓冲剂。缓冲剂将pH维持在所需范围内。适用于本公开的药物组合物的各种缓冲剂包括组氨酸、磷酸钾、碱金属盐、磷酸钠或磷酸钾或其氢或二氢盐、柠檬酸钠或柠檬酸钾/柠檬酸、乙酸钠/乙酸、马来酸、乙酸铵、三-(羟甲基)-氨基甲烷(tris)、各种形式的乙酸盐和二乙醇胺,以及本领域已知的任何其它药学上可接受的pH缓冲剂,以将溶液的pH保持在所需范围内。也可以使用这些缓冲剂的混合物。

在组合物中有用的缓冲剂的量在很大程度上取决于所用的特定缓冲剂和溶液的pH。例如,乙酸盐在pH 5下比pH 6更有效,因此在pH 5的溶液中可以使用比在pH 6下更少的乙酸盐。优选制剂的优选pH范围为4.0-5.0,并且还可包括pH调节剂如盐酸、柠檬酸、氢氧化钠或其盐,以获得所需的pH。

一种优选的缓冲剂是磷酸钠,因为其缓冲能力为pH6.2或接近pH6.2。然而,应当理解,可以选择其他缓冲液以实现任何所需的pH缓冲。制剂中缓冲液的浓度优选为约1mM至约1M,更优选约10mM至约200mM。缓冲剂在本领域中是公知的,并且通过已知方法制造并且可从商业供应商处获得。

当药物组合物的pH设定在或接近生理水平时,施用时患者的舒适度最大化。特别地,优选在约5.8至8.4的pH范围内,优选约6.2至7.4,然而,应理解在特定制剂中可以根据需要调节pH以使多肽的稳定性和溶解度最大化,因此,在生理范围之外但患者仍可耐受的pH在本公开的范围内。

本公开的制剂可以进一步包括一种或多种张力调节剂(例如,使溶液与患者的血液等渗以进行注射)。张力调节剂应理解为是有助于溶液重量摩尔渗透压的分子。优选调节药物组合物的重量摩尔渗透压浓度,以使活性成分的稳定性最大化,并使给药时患者的不适最小化。其中血清约为每公斤300+/-50毫渗透压(milliosmolals)。通常优选药物组合物与血清等渗,即具有相同或相似的重量摩尔渗透压浓度,其通过添加张力调节剂来实现,因此考虑重量摩尔渗透压浓度可为约180至约420毫渗透压,但是应理解,当特定条件需要时,重量摩尔渗透压浓度可以更高或更低。

典型的张力调节剂是本领域熟知的,包括但不限于各种盐、氨基酸或多糖。合适的氨基酸的非限制性实例包括甘氨酸。合适的多糖的非限制性实例包括蔗糖、甘露醇和山梨糖醇。应当理解,可以一次使用一种以上的张力调节剂,例如,山梨糖醇和甘氨酸可以组合使用以改变制剂的张力。

适用于改变重量摩尔渗透压浓度的张力调节剂的其他实例包括但不限于氨基酸(例如精氨酸、半胱氨酸、组氨酸和甘氨酸)、盐(例如氯化钠、氯化钾和柠檬酸钠)和/或糖类(例如蔗糖、葡萄糖和甘露醇)。制剂中张力调节剂的浓度优选为约1mM至1M,更优选约10mM至约200mM。张力调节剂在本领域中是公知的,并且通过已知方法制造并且可从商业供应商处获得。

也可以将在溶液中(也以干燥或冷冻形式)稳定多肽的赋形剂(也称为化学添加剂、共溶质或共溶剂)加入药物组合物中。赋形剂在本文中定义为添加到药物组合物中的非治疗剂,以提供所需的效果,例如稳定化、等渗性。所需赋形剂的共同属性是水溶性、无毒性、非反应性、从体内快速清除以及不存在免疫原性。此外,赋形剂应该能够稳定蛋白质的天然构象,从而在加工、储存和给予患者的过程中保持药物的功效和安全性。实例包括但不限于

糖/多元醇,例如:蔗糖,乳糖,甘油,木糖醇,山梨糖醇,甘露糖醇,麦芽糖,肌醇,海藻糖,葡萄糖;聚合物如:血清白蛋白(牛血清白蛋白(BSA)、人SA或重组HA),葡聚糖,PVA,羟丙基甲基纤维素(HPMC),聚乙烯亚胺,明胶,聚乙烯吡咯烷酮(PVP),羟乙基纤维素(HEC);非水溶剂,例如:多元醇(例如,PEG、乙二醇和甘油),二甲基亚砜(DMSO)和二甲基甲酰胺(DMF);氨基酸如:脯氨酸,L-丝氨酸,谷氨酸钠,丙氨酸,甘氨酸,赖氨酸盐酸盐,肌氨酸和γ-氨基丁酸;表面活性剂如:吐温-80™(聚山梨醇酯80),吐温-20™(聚山梨醇酯20),SDS,聚山梨醇酯,聚氧乙烯共聚物;和其他辅料,如:磷酸钾,醋酸钠,硫酸铵,硫酸镁,硫酸钠,三甲胺N-氧化物,甜菜碱,金属离子(如锌、铜、钙、锰和镁),CHAPS,单月桂酸酯,2-O-β-甘露糖苷酸或上述的任何组合。

本公开制剂中一种或多种赋形剂的浓度优选为约0.001至5重量%,更优选约0.1至2重量%。赋形剂在本领域中是众所周知的,并且通过已知方法制造并且可从商业供应商获得。

在一个示例性实施方案中,本公开的制剂可包含用HEPES、MES或Tris-HCl缓冲至pH7.3-7.4的约150mM NaCl,和任选地,如本文所述的一种或多种另外的组分。

在一个示例性实施方案中,本公开的制剂可包含约25至约50mg TNFR:Fc(依那西普),约10mM至约100mM L-精氨酸,约10mM至约50mM磷酸钠,约0.75%至约1.25%蔗糖,约50mM至约150mM NaCl,在约pH6.0至约pH7.0下。在另一个实施方案中,L-精氨酸可以在制剂中用L-半胱氨酸(约1至约500微摩尔)代替。在又一个实施方案中,pH可以为约pH 7.0。在另一个具体实施方案中,本发明的制剂可包含约25mg/ml TNFR:Fc,约25mM L-精氨酸,约25mM磷酸钠,约98mM氯化钠和约1%蔗糖,约pH6.2。

在另一个实施方案中,本公开的制剂可包含在约10mM至约100mM L-精氨酸、约10mM至约50mM磷酸钠、约0.75%至约1.25%蔗糖、约50mM至约150mM NaCl中的约10至约100mg/mL的RANK:Fc,在约pH6至约pH7。在一个具体实施方案中,本发明的制剂包含在约25mM L-精氨酸、约25mM磷酸钠、约98mM氯化钠和约1%蔗糖中的50mg/ml RANK:Fc,pH约6.2。

在另一个实施方案中,本公开的制剂可包含有效量的含Fc结构域的多肽,约10mM至约100mM L-精氨酸,约10mM至约50mM磷酸钠,约0至5%甘露醇和0至0.2%Tween-20™(聚山梨醇酯20),在约pH 6至7下。在另一个实施方案中,本公开的制剂可包含有效量的抗体,例如Emab(抗CD22特异性抗体),约25mM L-精氨酸,约25mM磷酸钠,约4%甘露醇,约0.02%Tween-20™(聚山梨醇酯20)和在约pH 6.0。

在另一个实施方案中,本公开内容提供了治疗哺乳动物的方法,其包括施用治疗有效量的本文所述的药物组合物,其中所述哺乳动物患有可以用在组合物中的含有Fc结构域的多肽有益地治疗的疾病或病症。在另一个实施方案中,含有Fc结构域的多肽衍生自与用该组合物处理的哺乳动物的相同种类。在一个具体实施方案中,哺乳动物是需要治疗的人类患者。当组合物的含有Fc结构域的多肽是TNFR:Fc时,可以治疗的疾病或病症的实例包括但不限于类风湿性关节炎、银屑病关节炎、强直性脊柱炎、韦格纳病(肉芽肿病)、克罗恩病(或炎性肠病)、慢性阻塞性肺病(COPD)、丙型肝炎、子宫内膜异位症、哮喘、恶病质、牛皮癣和特应性皮炎,或具有一种或多种Klotho基因突变的遗传疾病的人。可以用TNFR:Fc治疗的其他疾病或病症包括WO 00/62790、WO01/62272和美国专利申请2001/0021380中描述的那些,其相关部分通过引用并入本文。

在另一个实施方案中,本公开内容提供了用于加速稳定性测试本公开的药物组合物中

含有Fc结构域的多肽的稳定性的方法，其包括下述步骤：在储存之前即时间为零、将组合物在37℃下储存一个月，测试根据本公开配制的多肽的活性，和测量多肽的稳定性，并比较时间零点与一个月时间点的稳定性。此信息有助于尽早消除最初似乎具有良好稳定性但不能长期存放的批次或一批。

此外，药物组合物提供长期储存，使得活性成分例如含有Fc结构域的多肽在储存过程中在液体或冷冻状态下是稳定的。如本文所用，短语“长期”储存应理解为意指药物组合物可储存三个月或更长时间，六个月或更长时间，一年或更长时间，优选两年或更长时间。长期储存也应理解为药物组合物以2-8℃的液体储存或冷冻，例如-20℃或更冷(例如-20℃或-80℃)。还考虑组合物可以冷冻和解冻不止一次。关于长期储存的术语“稳定”应理解为意指相对于储存开始时组合物的活性，药物组合物的活性多肽不会损失超过20％，或更优选15％，或甚至更优选10％，最优选5％。

一种或多种抗氧化剂可包括在本公开的制剂中。考虑用于制备制剂的抗氧化剂包括氨基酸如甘氨酸和赖氨酸，螯合剂如EDTA和DTPA，和自由基清除剂如山梨糖醇和甘露糖醇。

还设想了其他有效的给药形式，例如肠胃外缓释制剂、吸入雾剂、口服活性制剂或栓剂。因此，制剂还可以包括聚合化合物的颗粒制剂，例如整体侵蚀聚合物(例如，聚(乳酸-共聚-羟基乙酸)(PLGA)共聚物，PLGA聚合物共混物，PEG以及乳酸和乙醇酸的嵌段共聚物，聚(氰基丙烯酸酯))；表面腐蚀聚合物(例如，聚(酸酐)和聚(原酸酯))；水凝胶酯(例如，聚氧丙烯聚氧乙烯共聚物(pluronic)多元醇，聚(乙烯醇)，聚(乙烯基吡咯烷酮)，马来酸酐-烷基乙烯基醚共聚物，纤维素，透明质酸衍生物，藻酸盐，胶原，明胶，白蛋白，以及淀粉和葡聚糖)及其组合物系统；或脂质体或微球的制剂。此类制剂可影响本发明蛋白质和衍生物的物理状态、稳定性、体内释放速率和体内清除速率。用于所需蛋白质的最佳药物制剂可由本领域技术人员根据给药途径和所需剂量确定。示例性药物制剂公开于Remington’s Pharmaceutical Sciences，第18版，(1990)，Mack Publishing Co.，Easton，Pa.18042，第1435-1712页，其公开内容通过引用结合在此。

生物活性

用于评估功效和/或确定人重组α可溶性Klotho的有效剂量(对于表现出与年龄相关的病症或代谢病症的患者、受试者或个体)的方法可以(初步地)包括进行基于生物体的测定(例如使用哺乳动物(例如小鼠、大鼠、灵长类动物或一些其他非人类)或其他动物(例如非洲爪蟾、斑马鱼或无脊椎动物例如苍蝇(例如黑腹果蝇)或线虫(例如秀丽隐杆线虫(Caenorhabditis elegans)。Klotho蛋白质可以一次或作为方案(规则或不规则)施用于生物体。例如，蛋白质可以在给定的时间段内(例如每月、半月、每周、半周、每天等)施用合适的次数(例如一次、两次等)。然后可以评估生物体的参数(例如年龄相关参数)。感兴趣的Klotho蛋白可以相对于参照(例如，对照生物的参数)实现或导致参数的变化。还可以评估其他参数(例如与毒性、清除和药代动力学相关)。

本发明的klotho蛋白质可以使用具有或表现出特定障碍或病症的动物(模型)来评估，例如年龄有关或年龄相关的障碍或病症、代谢紊乱或病症等。这些障碍和病症还可以提供致敏系统，其中可以观察到蛋白质对生理学的影响。示例性病症包括例如去神经支配，废用性萎缩，代谢紊乱(例如肥胖和/或糖尿病动物的病症，例如db/db小鼠、ob/ob小鼠等)，脑疾病，肝脏缺血或其他肝脏疾病，顺铂/紫杉醇/长春新碱模型，各种组织(异种移植)移植，转

基因骨模型，疼痛综合征(例如炎症和神经性病症)，百草枯，遗传毒性，氧化应激模型和肿瘤(I)模型。

为了评估本公开的S-Klotho蛋白质，可以将蛋白质施用于合适的动物(适合的治疗期)并评估动物的参数，例如在合适的一段时间后，例如10至60分钟、1至24小时、1至30天、1至12个月、1至5年，或其间的任何值或值范围。动物可以随意或正常喂食(例如，不受热量限制，尽管可以在这样的条件下评估一些参数)。通常，将一组这样的动物用于测定。通常，如果测试多肽影响受热量限制的类似动物的表型方向的参数，则可以指示测试多肽有利地改变动物的寿命调节。此类测试多肽可以引起热量限制的至少一些寿命调节作用(例如，这种效应的子集)，而不必剥夺生物体的热量摄入。

待测试的参数可以是年龄相关或疾病相关参数(例如，与动物模型相关的病症的症状)。有利地指出的测试蛋白质相对于未用多肽处理的类似参考动物可以引起症状的改善。与疾病或衰老相关的其他参数可包括：抗氧化剂水平(例如抗氧化酶水平或活性)，抗应激性(例如，百草枯抗性)，核心体温，葡萄糖水平，胰岛素水平，促甲状腺激素水平，催乳素水平和促黄体激素水平。

为了测量本公开的S-Klotho蛋白质用于治疗年龄相关病症的有效性，可以使用具有降低的Klotho表达的动物(例如，具有突变或缺失的klotho基因的小鼠)。例如，可以将测试蛋白质施用于突变小鼠，并监测年龄相关参数。有利地指出的测试蛋白质相对于未用蛋白质处理的类似参考动物可以引起症状的改善。

与代谢紊乱或衰老相关的参数可以通过测量体重，获得生殖能力的检查，血糖水平的测量，寿命的观察，皮肤的观察，运动功能(例如步行)的观察等等来评估。评估还可以通过测量胸腺重量、观察胸腔内表面上形成的钙化结节的大小等来进行。此外，定量测定klotho基因或Klotho蛋白的mRNA也可用于评估。

其他(体内)模型和生物测定包括评估动物的代谢参数，例如与胰岛素病症、II型糖尿病相关的参数。示例性代谢参数包括：葡萄糖浓度、胰岛素浓度和胰岛素敏感性。

在评估测试蛋白质是否能够改变寿命调节时，可以监测或评估许多与年龄相关的参数或生物标志物。示例性年龄相关参数包括：(i)细胞或生物的寿命；(ii)具有生物学年龄依赖性表达模式的细胞或生物体中基因转录物或基因产物的存在或丰度；(iii)细胞或生物对压力的抵抗力；(iv)细胞或生物体的一种或多种代谢参数(示例性参数包括循环胰岛素水平，血糖水平；脂肪含量；核心体温等)；(v)生物体中存在的细胞或一组细胞的增殖能力；和(vi)细胞或生物体的外观或行为。

术语“平均寿命”是指一组生物的平均死亡年龄。在某些情况下，在受控环境条件下使用一组遗传相同的生物来评估“平均寿命”。由于事故导致的死亡被丢弃。在受控环境条件下无法确定平均寿命(例如，对于人类)的情况下，对于足够大的群体，可以使用可靠的统计信息(例如，来自精算表)作为平均寿命。

两种此类生物(例如，一种参照生物和一种用S-Klotho蛋白处理的生物)之间的分子差异的表征可揭示生物的生理状态的差异。参考生物和经处理的生物通常具有相同(或基本相同)的实际年龄和/或性别。本文所用的术语“实足年龄”是指自预选的事件以来经过的时间，例如受孕，确定的胚胎或胎儿阶段，或更优选地，出生。可以使用各种标准来确定生物体是否具有用于比较分析的“相同”实足年龄。

通常，所需的准确度是野生型生物的平均寿命的函数。例如，对于线虫秀丽隐杆线虫(C.elegans)，实验室野生型菌株N2在某些受控条件下平均生活约16天，相同年龄的生物可能已经存活相同的天数。对于小鼠，相同年龄的生物可能已经存活了相同的数周或数月；对于灵长类动物或人类，相同的年数(或在2年、3年或5年内)；等等。通常，相同实际年龄的生物可以在该物种的野生型生物的平均寿命的15％、10％、5％、3％、2％或1％内存活一段时间。优选地，生物体是成体生物体(例如，生物体已经存活至少一段时间，其中平均野生型生物体已经成熟至其有能力繁殖的年龄)。

可以在生物体表现出明显的衰老物理特征之前进行生物筛选试验。例如，生物可以是仅生活在相同物种的野生型生物的平均寿命的10％、30％、40％、50％、60％或70％的成体生物。报道了年龄相关的代谢、免疫能力和染色体结构的变化。可以在测试受试者中(例如，对于基于生物体的测定)，或在用本文描述的治疗剂(例如，对于(人或哺乳动物)患者)治疗之前、期间或之后评估任何这些变化。

还可以在筛选测定(或治疗的受试者)的受试生物中评估与热量限制相关的标志物。尽管这些标志物可能与年龄无关，但它们可能表示当调节Klotho或Klotho相关途径时改变的生理状态。标记物可以是mRNA或蛋白质，其在热量限制的动物中的丰度发生变化。衍生自本文所述动物细胞或类似于本文所述动物模型的细胞模型可用于基于细胞的测定。

用于评估测试蛋白质对肌肉萎缩的影响的模型包括：1)由去神经支配导致的大鼠内侧腓肠肌质量损失，例如通过切断大腿中部的右侧坐骨神经；2)由固定引起的大鼠内侧腓肠肌质量损失(例如，通过在90度屈曲时固定右踝关节)；3)大鼠内侧腓肠肌质量损失由后肢悬吊引起；4)由恶病质细胞因子白细胞介素-1(IL-1)治疗引起的骨骼肌萎缩；5)由糖皮质激素、地塞米松治疗引起的骨骼肌萎缩。

施用外源性S-Klotho

本公开涉及S-Klotho制剂、临床剂量和施用(例如，增加和/或维持S-Klotho的血清浓度在正常和/或年轻(例如18-30岁)人范围内(例如没有任何慢性病)。

本公开的方面或实施方案包括，例如，将(cGMP-级和/或临床级)人重组α可溶性Klotho蛋白或蛋白片段(同种型1)给予有需要的(人)受试者。实施方案还可以包括测量(在(人)受试者中)血清S-Klotho水平或浓度(例如通过质谱(MS)或ELISA)。这种测量可以在S-Klotho施用之前、之后和/或期间发生，并且可以根据需要重复进行，以确定血清S-Klotho水平和/或血清S-Klotho水平的代谢、降解或降低速率。MS是本领域熟知的技术。MS可用于鉴定甚至定量受试者血清中一种或多种(天然和/或重组)Klotho蛋白的水平。

还可以在受试者的血清中测量一种或多种另外的蛋白质。例如，一种或多种Klotho相关和/或衰老相关蛋白(例如FGF21、GDF-11、TIMP2、NAD+、CCL11、激素睾酮、雌激素等)和/或肾功能蛋白(例如KIM-1、胱抑素-C、肌酸酐、BUN、肌酸酐、NGAL等)可以与测量血清中的Klotho分开测量或组合测量。

在至少一个实施方案中，获得血清样品，例如血液样品。如本领域已知的，可以通过抽血获得样品。在优选的实施方案中，可以使用手指刺或其他侵入性较小的获得血液样品的方法。因此，可以更频繁地采集血液样品(例如全天和/或每0.5、1、2、3、4、5、6、7、8、9、10、11或12小时)。MS可用于测量总Klotho蛋白质血清浓度，以及各种αKlotho蛋白质种类的血清浓度，例如天然Klotho物种(例如可溶性Klotho、裂解的Klotho、分泌的Klotho等)和/或一

种或更多本公开的Klotho蛋白质。在一些实施方案中，Klotho水平可以在治疗性重组Klotho蛋白施用之前测量并且再次在整天中和/或在施用后每0.5、1、2、3、4、5、6、7、8、9、10、11或12小时测量。

实施方案还可以包括确定这样的速率和/或计算治疗方案(例如，包括S-Klotho的(后续)施用的频率、量和/或持续时间)以维持该受试者的血清中的S-Klotho浓度在正常年轻人的S-Klotho血清浓度范围内。在至少一个实施方案中，S-Klotho的浓度可维持在每毫升血清约1000皮克(S-Klotho)蛋白质(pg/mL)。

在至少一个实施方案中，S-Klotho施用策略(在人中)可包括测量S-Klotho的一种或多种药代动力学参数。例如，可以测量响应于S-Klotho施用的血清、尿液和脑脊髓液中S-Klotho水平的体内变化。一些实施方案可包括测量S-Klotho施用对一种或多种临床指标的有效性。各种病症、疾病和障碍的临床指标是本领域已知的并在本文中进一步描述。

实施方案还可包括进行(基线)S-Klotho水平测量(例如，在零时间(在任何外源性S-Klotho施用之前)和/或在治疗方案之前和/或整个过程中的一天中的不同时间(例如，在施用S-Klotho之前和之后)以便考虑(人)受试者中的任何昼夜节律效应。

实施方案还可以包括确定S-Klotho施用的合适频率、量和/或持续时间。例如，可以给予具有低S-Klotho血清水平(例如通过MS或ELISA免疫测定定量测定)的受试者(例如，通过静脉内、真皮内、腹膜内、肌肉内、皮内和/或皮下注射或其他施用)第一次施用klotho，其配置和/或适于使受试者血清S-Klotho水平达到第一预定水平(例如，约1000pg/mL)，测量受试者中血清S-Klotho浓度(产生的变化)(例如通过MS或ELISA)，测量血清S-Klotho水平的代谢、降解或降低的水平和/或速率(在第一次施用后)，计算施用的S-Klotho的半衰期，和/或确定应当给予S-Klotho的第二次随后给药的频率和/或时间范围(例如，为了将血清S-Klotho水平维持在第二预定水平以上)。在至少一个实施方案中，第二预定水平可以在第一预定水平的以下之间和/或可以是以下：约95％、90％、85％、80％、75％、70％、65％、60％、55％、50％、45％、40％、35％、30％、25％、20％、15％、10％和/或5％。

可以在适合于在受试者中产生(长期)S-Klotho血清水平的时间范围内给予进一步的施用，所述血清水平等同于正常性别匹配的年轻人的血清维持水平(例如，约1000pg/ml)。S-Klotho施用(对(人)受试者)的总时间跨度可以为1天至5年或更长。还可以在时间范围内基于临床脆弱性评分的使用和其他测量来测量和/或确定受试者的脆弱性。

本公开的实施方案还包括增加S-Klotho剂量以维持S-Klotho水平高于正常范围(1000pg/ml)的5％、10％、15％、20％、25％、30％、35％、40％、45％、50％、55％、60％、65％、70％、75％、80％、85％、90％、95％、100％或更多的提高。

某些实施方案包括在单次推注或延长(IV)注射中施用S-Klotho蛋白质(例如，在延长的时间段内滴注)。在至少一个实施方案中，每个受试者可以每次治疗施用1、2、2.5、2.75、3、3.5、4、4.5、5或更多微克的S-Klotho。可以通过本领域已知的一种或多种方法计算合适的给药量。一种这样的方法是异速生长缩放方法。例如，在大鼠实验中，每次给药0.01mg S-Klotho/kg体重，或10μg/kg。使用人类异速生物标度等效值0.16，说明性地，人等效剂量(HED)＝10ug/kg×0.16＝1.6ug/kg。因此，说明性地，70kg的人类需要70kg×1.6ug/kg＝112ug，60kg的人需要60kg×1.6＝96ug。

使用归一化至体表面积来建立HED，该过程由Reagan-Shaw(2008)描述，通过引用并入

本文。该过程称为异速生长标度，校正不同物种之间代谢率的基础差异，并且可能优于简单剂量外推法。说明性地，当HED为0.4mg/kg时，使用异速生长标度，对于70kg体重的个体，人体等效剂量为0.4mg/kg或28mg，对于60kg体重的个体，人体等效剂量为24mg。

在确定、测量和/或估计S-Klotho在人体中的量(和/或生物利用度)(重组蛋白质施用之前和/或之后)、要施用的S-Klotho的总量和/或浓度、和/或重组蛋白施用后(随时间推移)的血清水平反应中，可以考虑或考察多种因素。这些因素可包括例如稀释剂的组成、给药途径、给药部位、分布到受试者的组织和器官、受试者的代谢或其他速率、药代动力学(PK)、药效学(PD)、毒理学(Tox)等等。

在至少一个实施方案中，(正常)浓度的S-Klotho(例如，在健康的年轻(18-30岁)人类成人中)在血清中可以是约1000pg/ml。典型的成年人可以具有大约5升的血容量，女性通常具有比男性更少的血容量。大约55％的人血可以由血清组成。因此，(5升血液/成人)×(0.55血清/升血液)＝2.75升(2750ml)血清/成人。假设没有内源性血清S-klotho，要在总血清中达到1000pg/ml的终浓度；每个成人受试者施用2750ml×1000pg/ml＝2,750,000pg(或2750ng，或2.75μg)外源性S-Klotho。

为了将可溶性Klotho增加至比典型健康水平高50％(例如，至1500pg/ml血清)，可以施用4.125微克/受试者的剂量。为了将可溶性Klotho增加至比典型健康水平高100％(例如，至2000pg/ml血清)，可施用5.5微克/受试者的剂量，等等。

可以施用药学上有效和/或足量的纯化的重组S-klotho蛋白，以便将受试者的血清可溶性Klotho蛋白浓度提高至任何合适的水平，例如大于、等于或在以下之间：每毫升血清约50、100、250、500、750、1000、1250、1500、1750、2000、2250、2500、2750、3000、3500、4000、4500、5000、5500、6000、6500、7000、7500、8000、8500、9000、9500、10000、11000、12000、13000、14000、15000、20000、25000、30000、40000、50000、75000、100000或更多皮克可溶性Klotho蛋白质，或大于、等于或在以下之间：比血清中典型健康水平的可溶性Klotho蛋白质高约5％、10％、15％、20％、25％、30％、40％、50％、60％、70％、80％、90％、100％、150％、200％、250％、300％、400％、500％、600％、700％、800％、900％、1000％、1200％、1500％、2000％、2500％、3000％、4000％、5000％或更多。

在一些实施方案中，受试者可以施用一次或多次(推注)静脉内、真皮内、腹膜内、肌肉内、皮内、皮下和/或其他注射重组人S-Klotho蛋白，剂量大于、等于约0.01mg/kg体重或在其间，其在合适体积的Klotho缓冲液(例如，150mM NaCl和10mM HEPES pH 7.4)或其他药学上可接受的载体中。因此，施用给160磅受试者(即72.57kg体重)每次给药(推注)注射约0.73mg S-Klotho(基于0.01mg S-Klotho/kg×72.57kg体重的计算)。同样，170磅的人每次给药可以接受0.77毫克的S-Klotho。给药的总次数和频率可以基于实现和维持血清中浓度为例如1000pg/ml的S-Klotho(相当于0.000001mg/ml血清)来确定。后者可通过MS或人S-Klotho ELISA测定法测定。

在其他实施方案中，剂量可以大于、等于或在以下之间：约0.0001-10mg/kg体重、0.0001-10μg/kg体重、0.0001-10ng/kg体重、0.0001-10pg/kg体重，或其间的任何值或值范围。可以在一个或多个时间点收集尿液和/或血液，例如医疗程序或首次给药(剂量)重组Klotho蛋白之后大于、小于、等于、在其间、和/或大约5分钟、10分钟、15分钟、20分钟、25分钟、30分钟、40分钟、45分钟、60分钟、90分钟、2小时、3小时、4小时、5小时、6小时、9小时、12

小时、18小时、24小时、36小时、48小时、2.5天、3天、5天、7天、10天、14天、21天、4周、1个月、2个月、3个月或更长(例如以测量、测试和/或确定血清S-Klotho水平以及响应给药和/或随时间的变化)。

一个或多个实施方案包括生产和/或(后续)施用S-Klotho活性药物产品的独特制剂和/或与药学上可接受的载体组合。载体可适用于IV和/或弹丸注射。实施方案还可以包括生产和/或(后续)施用S-Klotho的独特的无活性前药制剂和/或与药学上可接受的载体组合(使得可以在体内活化无活性的S-Klotho以在生物学上释放在动物或人类受试者中有效的S-Klotho)。这种前药制剂可包括包衣或定时释放制剂。

施用外源性S-Klotho治疗人类与年龄相关的脆弱性

本公开的示例性实施方案涉及施用外源Klotho蛋白以治疗与年龄相关的脆弱性(例如,在人或非人动物中)。S-Klotho可以在人类疾病的动物模型中拯救生肌干细胞,改善肌肉修复和/或抑制纤维化。因此,S-Klotho可能是一种有前景的治疗剂,用于对抗衰老的人类受试者的肌肉退化,其显示出虚弱的迹象。

例如,本公开涉及S-Klotho制剂、临床剂量、以及对脆弱和/或老年人(例如60-95岁)人的施用,以便在前者中保持维持血清浓度为S-Klotho在正常和/或年轻(例如18-30岁)人的范围内(例如没有任何慢性病)。

[0001] 长时间的Klotho治疗可以恢复和/或改善老年人体弱或其他生理老化中的一种或多种与衰老相关的指标或状况。

施用外源性S-Klotho治疗(减少)人肌肉萎缩

本公开的示例性实施方案涉及外源性Klotho蛋白的施用以治疗人的肌肉萎缩(例如降低(其速率)),这通过骨骼肌组织质量和同时使用上述蛋白质和分子指示剂来测量,以提供关于Klotho给药对抗肌肉萎缩的影响的指导。

肌肉萎缩可包括许多神经肌肉、代谢、免疫和神经障碍和疾病以及饥饿、营养缺乏、代谢应激、糖尿病、衰老、肌营养不良或肌病。在衰老过程中可能发生肌肉萎缩。肌肉萎缩也可能是由于肌肉的使用减少或不使用造成的。症状包括骨骼肌组织质量下降。在人类男性中,肌肉质量在50到80岁之间下降了三分之一。肌肉萎缩的一些分子特征可包括泛素连接酶的上调和肌原纤维蛋白的丧失。可以监测这些蛋白质的分解(例如通过测量肌动蛋白的特定成分的3-甲基-组氨酸产生),例如在肌球蛋白的某些肌肉中。肌酸激酶(细胞损伤标记物)的释放也可以是指示。

施用外源性S-Klotho用于治疗老年和/或整个人类寿命期间的精神和/或认知衰退

本公开的示例性实施方案涉及外源性Klotho蛋白的施用以改善和/或抵消(衰老相关的)认知功能的下降。在本公开时,尚不清楚外源性Klotho蛋白的施用是否可以抵消人类的认知衰退。然而,在多次学习和记忆测试中,具有系统性klotho过表达的转基因小鼠比对照表现更好。在小鼠中升高klotho也增强了长期增强作用,这是突触可塑性的一种形式,以及富含突触GluN2B,一种N-甲基-D-天冬氨酸受体(NMDAR)亚基,在学习和记忆中具有关键功能。阻断GluN2B消除了klotho介导的作用。

Klotho调节的途径可能与减缓阿尔茨海默病和其他形式的痴呆的进展有关。对超过400名年龄在53岁及以上的健康男性和女性进行的脑部扫描发现,那些携带特定Klotho基因变体的单一拷贝的人有更大的脑区来处理规划和决策。对该组进行的进一步测试发现右

侧背外侧前额叶皮质(rDLPFC)扩大的患者在一系列心理任务中表现更好。

大约五分之一的人遗传了单拷贝的基因变异或等位基因,称为KL-VS,它可以改善心脏和肾脏的功能,平均可以增加人体寿命约三年。然而,对于大脑功能,拥有更大的rDLPFC仅占人们心理测试分数改善的12%,而另一方面,正如社论指出的那样,携带一拷贝KL-VS等位基因似乎赋予了对rDLPFC结构和功能预期下降的几十年的抵御能力。因此,KL-VS杂合性似乎与右背外侧前额叶皮质(rDLPFC)中的更大体积相关。

由于rDLPFC对执行功能很重要,因此研究人员还分析了个体的工作记忆和处理速度。KL-VS杂合性可能与检查的整个生命周期中的执行功能增强有关。简而言之,结果可能表明klotho基因的变异可能与更大的脑容量和更好的功能相关。

本公开的示例性实施方案涉及外源性Klotho蛋白的施用以增强体内klotho水平和/或(细胞、分子和/或下游)效应(例如,以增强认知并抵消整个人寿命中的认知缺陷)。临床级S-Klotho的外源性施用保留和/或改善认知功能(例如,在人类中)。

施用外源性S-Klotho以治疗(延长)人类寿命和/或生命周期

本公开的示例性实施方案涉及外源性Klotho蛋白质按时间顺序(例如,出生年龄匹配)和性别匹配的人类受试者施用以改善平均寿命。因为人口足够多,Klotho施用(人类受试者的实验组)获得的平均寿命结果可以与未接受Klotho外源性施用的个体(对照组)和/或统计信息(例如,来自精算表)可靠地比较。

施用外源性S-Klotho治疗其他临床适应症

本公开的示例性实施方案涉及外源性S-Klotho的施用以治疗任何与年龄相关或非年龄相关的病症,包括但不限于人类脆弱(增加)、寿命(减少)、细胞衰老期(减少)、肌肉力量(衰退)、骨质流失或密度(减少)、认知(减少)、肌肉质量(下降)、体力(下降)、手力(下降)、腿部力量(下降)等等。本公开内容还涉及施用S-Klotho以增加骨矿物质密度(BMD)(例如,在女性中但不在男性中),以增加BMD(例如,在老年女性中)(其在绝经后减少),以再生或减少(退行性)骨骼肌的退化,改善步行步态,改善空间学习和记忆(或减少其下降)、运动、运动自由度、生活质量评估、射血分数,运动变化,运动改善等等。本公开进一步涉及施用S-Klotho以减少认知恶化或健忘,增加认知能力,改善认知功能和突触可塑性,减少学习、学习能力或智商的下降,以改善学习、学习能力或智商,等等。

施用外源性S-Klotho治疗遗传缺陷

本公开的示例性实施方案涉及外源性S-Klotho的施用以治疗(例如,纠正)已知的人类遗传缺陷。例如,报道了一名患有家族性肿瘤性钙质沉着症和Klotho突变的13岁女孩。家族性肿瘤性钙质沉着症是一种常染色体隐性代谢疾病,其特征在于由于FGF23或GALNT3中的失活突变导致的异位钙化和高磷血症。FGF23是肾脏排泄磷酸盐所必需的激素,而GALNT是一种有助于FGF23成熟和分泌的酶。KLOTHO基因中的纯合突变已在该13岁女孩中被鉴定出来。KLOTHO编码FGF23向其受体发射信号所必需的分泌蛋白。外源性人重组S-Klotho的施用构成了针对家族性肿瘤性钙质沉着症的功能障碍和症状的高度靶向和有效的疗法。

施用外源性S-Klotho治疗急性肾损伤(AKI)

急性肾损伤(AKI),以前称为急性肾衰竭(ARF),通常被定义为肾功能不全的突然发作,范围从轻微的功能丧失到衰竭。AKI是一种常见的临床并发症,每年约有4%-7%的住院患者发生并且预后可能较差。与AKI相关的死亡率范围为20%-35%。在AKI后,已显示肾

Klotho表达被抑制。Klotho的腺病毒基因转移在AKI中可以是细胞保护性的。

据报道，急性肾损伤(AKI)每年约占4.9％-7％的住院患者。(住院)老年人的AKI率可高达60％，老年人或危重病人的AKI率可高达20-30％。AKI还与死亡率、住院时间(LOS)和住院费用增加有关。

AKI可能至少部分来自肾移植或其他手术，急性肾小管坏死(ATN)、急性过敏性间质性肾炎(AAIN)、肾炎(如肾小球肾炎)、肾毒性(如药物性肾毒性)、低血压或其他促成因素。肾移植和其他手术可导致肾脏急性损伤或损伤，引起肾脏疾病和/或衰竭。肾毒性可导致AKI、ATN、AAIN、肾炎等。据报道，药物(例如，临床给药、处方药、非法药物或其他药物)与所有AKI病例的15％至25％相关。仅造影剂占医院获得性急性肾功能衰竭的所有原因的10％(例如，通过造影剂引起的急性肾损伤CIAKI)，并且是肾灌注减少和术后肾功能不全导致院内肾功能恶化的第三大原因。

在一些情况下，药物诱导的AKI可以是或包含抗微生物剂诱导的肾毒性(由抗微生物剂治疗产生)。例如，某些(革兰氏阴性)细菌感染可以用一种或多种氨基糖苷类治疗，例如巴龙霉素、妥布霉素、庆大霉素、阿米卡星、卡那霉素、新霉素等。已显示氨基糖苷类是肾毒性的。如图4所示，例如，接受阿米卡星(一种常见的氨基糖苷类)治疗的近23％的患者出现急性肾病，超过17％的阿米卡星治疗患者在出院前死亡。其他氨基糖苷类，包括庆大霉素和妥布霉素也诱导(或与之相关或促成)肾病。如图3A和3B所示，在2010年，超过120万不同年龄组的成年患者用氨基糖苷类治疗。其他抗微生物剂包括，例如，青霉素、氨苄青霉素、头孢菌素、磺胺、环丙沙星、万古霉素、大环内酯类、四环素、利福平等。

药物诱导的肾毒性也可以通过用一种或多种非类固醇抗炎药(NSAID)治疗导致，例如阿司匹林(乙酰水杨酸)、塞来昔布、双氯芬酸、二氟尼柳、乙哚乙酸、布洛芬、吲哚美辛、酮洛芬、酮咯酸、萘丁酮、萘普生、奥沙普秦、吡罗昔康、莎莎酸、舒林酸、托美汀等。

药物诱导的肾毒性也可以通过用以下治疗引起：一种或多种环加氧酶-2(COX-2)抑制剂(例如伐地考昔、罗非考昔、塞来昔布等)，质子泵抑制剂(例如奥美拉唑、兰索拉唑等)，抗惊厥药(例如，苯妥英、丙戊酸等)，组胺H2受体拮抗剂(例如，尼扎替丁、雷尼替丁、法莫替丁、西咪替丁等)，利尿剂(例如，碳酸酐酶抑制剂、袢利尿剂(例如布美他尼、乙基丙烯酸、托拉塞米、呋塞米等)，保钾利尿剂(如三苯乙烯、螺内酯、阿米洛利等)，噻嗪类利尿剂(如吲达帕胺、氯噻酮、美托拉宗、甲基噻嗪、氢氯噻嗪、氯噻嗪、苄氟噻嗪、聚噻嗪、氢氟噻嗪等)或其他利尿剂，如帕马溴、甘露醇等。

药物引起的肾毒性也可以由锂治疗引起，锂可以影响钠通过体内的神经和肌肉细胞的流动，并且可以用于治疗双相情感障碍的躁狂发作，通常表现为活动过度、言语冲突、判断力差、睡眠需求减少、攻击和愤怒。锂还可以帮助预防或减轻躁狂发作的强度。药物引起的肾毒性也可能由金、汞、铜或其他元素物质的治疗或暴露引起。

药物诱导的肾毒性也可以由以下的治疗引起：(D-)青霉胺；螯合剂类药物，其可用于治疗硬皮病、威尔森氏病(通过与累积的铜结合以通过尿液消除)、胱氨酸尿症(通过与半胱氨酸结合产生比半胱氨酸更易溶的混合二硫化物)，直接-作用平滑肌松弛剂(例如肼苯哒嗪)，解痉剂(例如卡立普多、环苯扎林、美他沙酮、甲基卡巴胺)，苯并二氮杂卓，例如地西泮、可乐定和其他咪唑啉化合物，替扎尼定，巴氯芬，乙内酰脲衍生物，丹曲林等。

其他形式的药物诱导的肾毒性可包括，例如：造影剂诱导的肾毒性(例如，暴露于(碘化

的)造影剂后,也称为放射性造影剂诱导的肾病(CIN));麻醉-(阿片类药物)诱发肾毒性(例如,使用或滥用某些麻醉品(如阿片类药物),如可卡因、海洛因等);化学疗法引起的肾毒性(例如,用癌症治疗剂治疗后,例如:顺铂;卡铂;奥沙利铂;烷化剂,如苯达莫司汀、环磷酰胺、异环磷酰胺、亚硝基脲、替莫唑胺、美法仑等;抗肿瘤抗生素,如丝裂霉素C、博来霉素、蒽环霉素和相关药剂等;抗代谢物,如卡培他滨、羟基脲、甲氨蝶呤、培美曲塞、普拉曲沙、喷司他丁、氟达拉滨、克拉屈滨、吉西他滨、阿糖胞苷等;长春花生物碱;拓扑替康;依托泊苷;紫杉烷;伊立替康;来那度胺;艾日布林;三氧化二砷;伊沙唑嗪等);等等。实际上,各种各样的肾毒性药物都可以诱发肾毒性,从而导致AKI。如果不进行治疗,药物引起的肾毒性(和其他形式的AKI)可能会危及生命,并且可能会(给患者、医院和保险公司)带来巨大的治疗成本。

本公开的实施方案可包括治疗或预防(预防性)急性肾损伤(AKI)或其他病症的方法。该方法可包括将重组(可溶性)Klotho蛋白质给予有需要的受试者。例如,该方法可以包括向需要其的受试者施用药学有效量的与SEQ ID NO:2至SEQ ID NO:70之一具有至少85%的氨基酸序列同一性的重组可溶性Klotho蛋白质(例如,以便将受试者的血清可溶性Klotho蛋白质浓度升高和/或维持在预定阈值或高于预定阈值达预定时间段)。该病症可包括:(i)急性肾小管坏死(ATN)、急性过敏性间质性肾炎(AAIN)、肾炎、肾小球肾炎和/或肾毒性;或(ii)至少部分由肾移植或其他手术、急性肾小管坏死(ATN)、急性过敏性间质性肾炎(AAIN)、肾炎、肾小球肾炎、肾毒性或低血压引起的AKI。该病症可包括药物诱导的(例如,氨基糖苷类诱导的)肾毒性。蛋白质可以预防性施用,例如,在肾移植、肾毒素施用或其他已知或预期引起或促成AKI的活动、治疗或事件之前施用。可选地,或另外,蛋白质可以响应于AKI(例如在肾移植或其他手术后)、氨基糖苷类或其他肾毒素施用、或已知或预期引起或促成AKI的其他活动、治疗或事件进行施用。

在一些实施方案中,肾毒素或其他药物可以是或包含,例如:

一种或多种氨基糖苷类(例如巴龙霉素、妥布霉素、庆大霉素、阿米卡星、卡那霉素、新霉素等);

一种或多种抗真菌剂(如两性霉素B、氟胞嘧啶等);

一种或多种造影剂(例如,(碘化的)放射性造影介质,碘与分子比率为约1.5:1的高渗透压造影介质(HOCM),碘与分子比约3:1的低渗透压非离子造影剂(LOCM),碘与分子比约为6:1的等渗(等渗透性)造影剂(IOCM)等);

一种或多种抗逆转录病毒药物(如阿德福韦、西多福韦、替诺福韦、膦甲酸等);

一种或多种癌症(或化疗)治疗药物(如顺铂,卡铂,奥沙利铂,烷化剂(如苯达莫司汀、环磷酰胺、异环磷酰胺、亚硝基脲、替莫唑胺、美法仑等)),抗肿瘤抗生素(如丝裂霉素C、博来霉素、蒽环类抗生素和相关药剂等),抗代谢物(如卡培他滨、羟基脲、甲氨蝶呤、培美曲塞、普拉曲沙、喷司他丁、氟达拉滨、克拉屈滨、吉西他滨、阿糖胞苷等),长春花生物碱,托泊替康,依托泊苷,紫杉烷,伊立替康,来那度胺,艾日布林,三氧化二砷,伊沙唑嗪等);

一种或多种二膦酸盐或其衍生物(例如,唑来膦酸盐/唑来膦酸,伊班膦酸盐,阿仑膦酸盐,阿仑膦酸盐/胆钙化醇,依替膦酸盐,利塞膦酸盐(任选地,用碳酸钙),帕米膦酸盐,替鲁膦酸盐等);和/或

一种或多种麻醉剂(如阿片类药物),如可卡因、海洛因等);

本公开的实施方案可包括给予治疗性重组(α可溶性)Klotho蛋白质的方法(例如,与人

αKlotho同种型1的氨基酸残基1-981或其子集具有至少85％氨基酸序列同一性)。该方法可以包括将治疗性Klotho蛋白给予人或非人类受试者以治疗或预防(预防性)AKI或一种或多种与AKI相关的病症。该方法可以包括:确定受试者中血清可溶性klotho水平的水平,计算足以将受试者中的血清可溶性klotho水平升高至预定水平或正常水平百分比的第一剂量的蛋白质,对受试者施用第一剂量的蛋白质,例如通过推注或逐渐施用,确定受试者血清中可溶性Klotho下降的速率,例如在施用第一剂量后,计算随后的剂量时间和量,和/或对受试者施用随后的蛋白质剂量。

施用外源性S-Klotho治疗慢性肾脏病(CKD)

如Neyra和Hu“Klotho在人类慢性肾病中的潜在应用”,Bone(2017)所述,其通过引用整体并入本文,可溶性Klotho在循环中在慢性肾病(CKD)阶段2的早期开始下降和尿Klotho可能甚至更早在CKD阶段1下降。因此,可溶性Klotho可以作为肾功能衰退的早期和敏感标志物。此外,临床前动物数据支持Klotho缺乏不仅仅是一种生物标志物,而且是CKD进展和肾外CKD并发症的致病因素,包括心血管疾病和干扰的矿物质代谢。预防Klotho下降,内源性Klotho产生的再激活或外源性Klotho的补充都与动物模型中肾纤维化的减弱、CKD进展的延迟、矿物质代谢的改善、心肌病的改善和CKD中的血管钙化的减轻有关。

CKD的特征在于肾功能的进行性恶化,具有高ESRD风险。CKD风险随着年龄的增长而增加,大约一半的CKD期≥3病例发生在N70岁以上的受试者中。CKD可以被视为加速老化的状态。25至34岁透析患者的心血管死亡率的相对风险与N75岁的非CKD患者相似。心血管疾病是CKD和ESRD患者的主要杀手。CKD和ESRD患者具有低肾Klotho表达和低水平的循环Klotho。CKD早期的肾Klotho缺乏可能主要归因于Klotho表达的抑制而不是活肾小管的丧失。此外,一些透析患者仍然具有可检测的循环Klotho,表明肾Klotho表达未被完全抑制,并且Klotho可能来自肾外来源,尽管其起源迄今尚不清楚。建立Klotho的肾外来源并描述当肾脏产生失败时如何上调它是至关重要的。

施用本公开的外源Klotho蛋白可有助于预防、延缓和减轻CKD中共病的负担。

组合物和治疗,其包括S-Klotho与其他成分的组合

Klotho还可以与其他化合物和/或组分以添加剂或协同物质起作用,以影响人类健康和福祉的一个或多个方面。例如,包括治疗性人重组可溶性αKlotho(S-Klotho)蛋白质与一种或多种另外的活性组分组合和/或同时可以使人类患者受益。此类治疗可以是预防性的或对Klotho蛋白和/或其他组分可以具有治疗效果的任何人类病症有反应。这些病症可包括例如年龄相关病症、代谢病症、慢性或急性病症等。本文公开了具体病症的非限制性实例。

S-klotho可以与其他血源性抗衰老化合物如生长/分化因子11(GDF-11)一起存在于人体内。因此,在某些实施方案中,治疗性S-klotho可与治疗性GDF-11共同施用(例如,同时、依次和/或组合)。在一些实施方案中,这种施用可具有加成或协同抗衰老或其他作用。同样,与CCL11的(中和)抗体或抑制剂共同施用S-klotho至人类受试者可以协同工作以对抗衰老或其他病症(因为CCL11(也称为嗜酸性粒细胞趋化因子-1)被理解为干细胞恢复的负调节因子。S-klotho还可以或替代地与其他嗜酸性粒细胞趋化因子共同施用,例如嗜酸性粒细胞趋化因子-2(CCL24)和/或嗜酸性粒细胞趋化因子-3(CCL26)。

在一些实施方案中,S-klotho可与转化生长因子β-1(TGF-β1)的抑制剂或抗体共同施

用。S-klotho施用可以抵抗参与内源性抗细胞上皮-间质转化(抗EMT)的TGF-β1信号途径的作用,其导致肾和其他组织纤维化。抗EMT在癌细胞中也是相关的,其中抑制EMT可赋予癌细胞转移的能力-后一过程被理解为与klotho相反。因此,共同施用S-klotho和转化生长因子β-1(TGF-β1)的抑制剂或抗体可以具有协同或累加效应。

在一些实施方案中,S-klotho可与胰岛素生长因子-1(IGF-1)的抗体或抑制剂共同施用。Klotho被理解为抑制细胞内胰岛素/IGF-1信号传导级联的激素,并且这种抑制增加了哺乳动物细胞和生物体水平对氧化应激的抗性;一种被认为在延长寿命方面具有进化保守性的机制。因此,共同施用S-klotho和胰岛素生长因子-1(IGF-1)的抑制剂或抗体可以具有协同或累加效应。

在一些实施方案中,S-klotho可以与维生素D(例如,维生素D3)或1,25-二羟基维生素D_3[1,25(OH)$_2$$D_3$]、FGF-15、FGF-19和/或Klothoβ共同施用;这是由于大量研究揭示了矿物稳态的综合调控方案,涉及Klothoα-K1、FGF23和1,25(OH)$_2$D和/或类似调节网络的相互调节的正/负反馈作用,该类似调节网络由Klothoβ-K1、FGF15/人FGF19和调节胆汁酸/胆固醇代谢的胆汁酸组成。这种共同施用可以对体内的许多病症和/或过程具有协同或累加效应。在一些实施方案中,S-klotho可以与FGF-21组合施用,

在一些实施方案中,S-klotho可与碳酸酐酶抑制剂共同施用,例如乙酰唑胺、甲醋唑胺、二氯苯胺、多佐胺、布林佐胺和/或托吡酯。这种组合施用可用于治疗强直性脊柱炎(AS)、类风湿性关节炎(RA)和各种其他病症。各种研究表明,骨吸收增加是AS和RA的特征,并且碳酸酐酶抑制剂通过抑制骨吸收而发挥抗关节炎作用。在骨水平,通过不同的机制,S-klotho通过作用于TRPV5刺激骨吸收和磷酸盐释放,TRPV5是最近发现的破骨细胞功能调节剂。由S-Klotho施用引起的1,25(OH)$_2$$D_3$水平的增加也可以刺激破骨细胞分化和骨吸收,从而刺激磷酸盐释放。因此,S-Klotho和碳酸酐酶抑制剂的共同施用可以具有累加或协同作用,特别是在促进骨骼健康方面,特别是在AS和RA中。

S-Klotho可与一种或多种改善疾病的抗风湿药(DMARDs)联合给药-用于治疗严重的活动性类风湿性关节炎。

S-Klotho可与环孢菌素联合给药,因为环孢菌素降低klotho mRNA和蛋白质并增加氧化应激,导致环孢菌素诱导的肾损伤(CsA)。klotho mRNA和蛋白质的相关减少和增加的氧化应激可以通过外源性共同施用S-Klotho来抵消。

在一些实施方案中,S-klotho可与氯沙坦和/或环孢菌素共同施用。用氯沙坦(一种血管紧张素II 1型(AT1)受体阻滞剂)治疗可逆转环孢菌素所见的klotho表达的下降。氯沙坦也同时改善了肾组织学(氯沙坦降低了由环孢菌素引起的肾小管间质纤维化)。

在一些实施方案中,S-klotho可与一种或多种氨基糖苷类如阿米卡星、庆大霉素、妥布霉素等共同给药。当使用氨基糖苷类药物治疗(革兰氏阴性)病原体感染时,这种治疗可用于预防肾毒性和/或急性肾损伤(AKI),这可以大大扩展氨基糖甙类药物治疗感染的用途。已经用于阻断AKI的S-Klotho与维拉帕米和/或地尔硫卓的给药可以治疗和/或预防AKI的肾功能障碍。

在一些实施方案中,S-klotho可与睾酮或雄激素受体(AR)上调化合物共同施用。最近的报道表明,在人格、心理健康或情绪方面,没有观察到男性睾酮治疗的有益效果。此外,对于心血管健康、性功能、身体功能、情绪或认知功能的低T补充睾酮的处方被认为是没有随

机临床试验的支持。然而，一直发现补充睾酮可增加肌肉力量，但对身体功能没有有益作用。S-Klotho与睾酮和/或雄激素受体(AR)上调化合物联合使用可显著增加老年人、体弱者或低T男性的肌肉力量和/或身体机能，超过在这些治疗组中单独使用的睾丸激素或S-Klotho可能产生的任何影响。

在一些实施方案中，S-klotho可与雌激素或雌性激素(例如雌二醇、雌三醇、雌酮等)共同施用。这种共同施用可以改善女性的健康指标(例如，月经、绝经或绝经过渡期妇女)和/或治疗不育症、多囊性卵巢疾病或病症、肥胖症、激素失衡和相关病症和/或其他女性健康状况。

在一些实施方案中，S-klotho可与一种或多种益智药共同施用-也称为智能药物或认知增强剂。益智药、补充剂和/或其他物质可以改善认知功能，特别是执行功能、记忆力、创造力、主动性、任务显著性(执行任务的动机)，表现(特别是需要高度努力的繁琐任务)，并且可用于治疗由阿尔茨海默病、帕金森病、亨廷顿舞蹈病和ADHD等疾病引起的认知或运动功能障碍。已知可以改善认知某些方面的最常用的一类药物是兴奋剂，尤其是通过作为前额皮质中多巴胺受体D1、肾上腺素受体A2或两者的直接激动剂或间接激动剂而在人体中表现出认知增强作用的兴奋剂类别。兴奋剂包括，例如:安非他明类(例如安非他明、右旋安非他明，赖斯他那胺等)，其可以有益于一系列认知功能(例如，抑制性控制、情景记忆、工作记忆和注意力方面)，尤其是在多动症个体中;二甲基胺(DMAA)，如1,3-二甲基胺，其可以改善体能、警觉性、反应时间等;

哌甲酯-一种取代的苯乙胺，可以改善一系列认知功能(例如，工作记忆、情景记忆、抑制性控制、注意力方面和计划潜伏期);eugeroics(例如，阿莫达非尼、莫达非尼等)，其可以作为唤醒促进剂，可以提高警觉性，特别是在睡眠不足的个体，促进推理和解决问题，治疗嗜睡症，转移睡眠障碍和睡眠后的白天嗜睡呼吸暂停治疗，等等;黄嘌呤(例如，咖啡因等)，其可以提高警觉性、表现和/或记忆力;尼古丁等等。

在一些实施方案中，如本领域已知的，S-klotho可与一种或多种骨质疏松症和/或骨质减少药物共同施用。Klotho可在调节骨矿物质密度方面发挥作用，因为缺乏Klotho可导致动物骨密度降低。例如，Klotho敲除小鼠随着时间的推移显示骨矿物质密度降低。在Klotho敲除动物中，Klotho表达可以拯救骨缺陷，例如Klotho敲除小鼠随时间显示骨矿物质密度降低。流行病学研究表明，各种Klotho基因变异与骨矿物质密度和手骨关节炎患病率的变化之间存在关联。

S-Klotho可以与一种或多种抗癌治疗和/或预防组合施用，例如化学治疗剂。例如，在肺癌中，例如非小细胞肺癌(NSCLC)，S-klotho施用可以影响肺癌细胞对顺铂和/或其他化学疗法的抗性。此外，S-klotho可以在肺癌、胃癌、胰腺癌(腺癌)和其他形式的癌症中起潜在的肿瘤抑制剂的作用。S-Klotho可与索拉非尼化疗联合给药，用于治疗肝细胞癌(HCC)。klotho的过表达以及用可溶性klotho蛋白处理可以在体外和体内减少肝细胞瘤细胞的生长。可以用S-klotho共同给药治疗的其他癌症类型包括肝细胞癌(HCC)、中枢神经系统(CNS)癌症(例如脑(例如神经胶质瘤、颅咽管瘤、成神经管细胞瘤和脑膜瘤)、脊髓和其他肿瘤、淋巴瘤等)、(转移性)结肠癌等。

S-Klotho还可以与化学治疗剂联合给药，以治疗癌症患者的化疗诱导的脆弱性。还可以施用S-Klotho以在其他已知治疗之后治疗癌症患者的癌症诱发的脆弱性。

S-Klotho可以与肾透析或其他程序组合施用。可以施用S-Klotho来治疗透析患者的虚弱,因为脆弱与透析患者的不良结果相关。

S-Klotho可以与一种或多种阿尔茨海默氏病治疗或预防一起给药,或与脑源性神经营养因子(BDNF)联合给药,因为足量的BDNF可以帮助发展和维持大脑中正常的神经元回路。

S-Klotho可以与一种或多种分子组合施用,所述分子增加klotho穿过血脑屏障的能力,以增加klotho进入中枢神经系统(CNS)以治疗或预防CNS相关病症的能力。例如,已知S-Klotho和BDNF都不会穿过血脑屏障。本公开内容的实施方案包括利用血脑屏障递送技术将S-klotho和/或S-klotho与BDNF一起施用于CNS以治疗阿尔茨海默病和/或改善未受阿尔茨海默氏病影响的个体的认知。

S-Klotho可与5'腺苷一磷酸激活蛋白激酶(AMPK)或AMPK激活药物或成分一起给药,这些药物或成分可正调节补充细胞ATP供应的信号通路,包括脂肪酸氧化和自噬;或负调节ATP消耗的生物合成过程,包括糖异生、脂质和蛋白质合成。

S-Klotho可以与一种或多种抗糖尿病药物如胰岛素、根皮苷或抗氧化剂药物联合给药,这些联合治疗可具有预防糖尿病疾病中产生的氧化应激引起的肾损伤的优点。S-Klotho与其他1型糖尿病的抗糖尿病药物的共同给药可以通过激活整联蛋白β1-FAK/Akt途径抑制β细胞凋亡来保护β细胞,从而抑制胱天蛋白酶3的裂解。

S-Klotho可以与一种或多种2型抗糖尿病药物如二甲双胍联合给药,用于改善超重和肥胖糖尿病受试者的血糖控制和血管功能。

S-Klotho可以与一种或多种血压药物、钙调节剂或慢性肾病(CKD)的治疗或预防组合施用。例如,软组织钙化是CKD的一个突出特征,Klotho可以通过增强磷酸尿,保留肾小球滤过和直接抑制血管平滑肌摄取磷酸盐来改善血管钙化。

S-Klotho可与TM5441或其他PAI-1抑制剂(纤溶酶原激活物1)联合使用,因为认为PAI-1抑制或缺乏可延缓衰老的发展并保护器官结构和功能,同时延长Klotho缺陷型(kl/kl)小鼠寿命。

S-Klotho可以与sirtuin1(SIRT1)或SIRT1活化化合物(STAC)如白藜芦醇组合施用。SIRT1是一种III型蛋白质脱乙酰酶,被认为是一种新型抗衰老蛋白,参与调节细胞衰老/衰老和炎症。在氧化应激引起的肺部炎症期间,SIRT1水平和活性降低。SIRT1介导的抗炎症保护机制与炎症的调节、过早衰老、端粒磨损、衰老相关的分泌表型和DNA损伤反应有关。多种膳食多酚和药理活化剂被证明可以调节SIRT1,从而干预与炎症相关的2型糖尿病、癌症、心血管疾病和慢性阻塞性肺病的进展。因此,通过与S-Klotho一起给予SIRT1和/或SIRTI活化化合物的共同施用,可以增强SIRT-1的一些或所有健康益处。

如FDA所认可的,S-Klotho可与一种或多种人细胞、组织和细胞和组织产品(HCT/Ps)组合施用。这些产品可包括,例如,一种或多种骨(包括脱矿骨、韧带、肌腱、筋膜、软骨、眼组织(角膜和巩膜),皮肤,血管移植物(静脉和动脉)(除了保留的脐带静脉),心包膜,羊膜(单独使用(不添加细胞)用于眼部修复),硬脑膜,心脏瓣膜同种异体移植物,源自自外周或脐带血的造血干细胞,精液,卵母细胞或胚胎。在至少一个实施方案中,HCT/P可以是或包含一种或多种干细胞。受损的身体组织和器官的干细胞治疗继续普及。与干细胞组合施用治疗性重组Klotho蛋白为有此需要的受试者提供了令人惊讶、意外和甚至协同的结果。

本公开的实施方案还包括组合产品,其包含与人干细胞组合的治疗性重组Klotho蛋

白。组合物还可包含如本文所述的药学上可接受的载体。如FDA所认可的，此类组合物可包含或归类为再生药物，以治疗、改变、逆转或治愈严重或危及生命的疾病或病症。初步临床证据表明，该组合物(药物)有可能解决这种疾病或病症的未满足的医疗需求。

说明性地，干细胞可以是或包含间充质干细胞(MSC)，例如来自人脐带或胎盘。在至少一个实施方案中，包含huMSC和本公开的治疗性重组Klotho蛋白的组合物减弱AKI中发生的炎性和氧化应激反应，和/或减少衰老相关蛋白和微小RNA的表达。

S-Klotho可以与一种或多种衰老抑制剂组合施用。例如，Klotho蛋白可以与Pin1-FOXM1和/或其他衰老抑制剂组合以增强接受这种治疗的患者的结果。

S-Klotho可以与以下一种或多种组合施用:Klotho刺激剂(Vit.D、氯沙坦、睾酮)，GDF-11，曲古抑菌素A抗真菌(GDF-11刺激剂)，TIMP-2，CCL-11抑制剂/抗体，达沙替尼，烟酰胺核苷(NAD+)，烟酰胺单核苷酸(NMN)(NDA+)，AMPK刺激剂(白藜芦醇、阿司匹林、水杨酸盐、植物化学物质、DR)，C60富勒烯，雷帕霉素，FGF抑制剂，Senolytics药物/化合物如FOXO4-p53干扰肽(如FOXO4-DRI)，抗凋亡蛋白BCL-2和BCL-xL的抑制剂。

任何前述或其他治疗或共同施用可以比单独的任何治疗具有累加或协同效应。例如，Klotho蛋白与一种或多种前述物质的共同施用可导致治疗结果大于单独以相似浓度施用组分的个体结果的总和。此外，协同效应可包括类似于单独施用组分的个体结果的治疗结果，但是浓度较低。协同效应还可包括增加一种或多种组分的最大有效剂量，降低一种或多种组分的毒性，或任何其它有益结果，其不仅仅是单独治疗结果的累加效应。此外，各个治疗结果的累加效应可以包括协同效应，其中考虑到各个组分的性质和理解，不预测或预期这种加和效应。

如本文中所使用的，组合治疗或共同给药可以包括包含Klotho蛋白质和一种或多种附加活性成分的组合产品、组合物或制剂的治疗或施用。所述一个或多个附加活性成分可以从本文所述或本领域中已知的组分、药物、物质、治疗组合物等中选择。例如，Klotho蛋白质和一种或多种附加活性成分可以共同配制成可注射的(例如，肌内、静脉内等)、可摄入的、经皮的、吸入的、局部的或其它的制剂。

或者，联合治疗或共同给药可包括治疗或给予Klotho蛋白和一种或多种附加活性成分，但Klotho蛋白和一种或多种附加活性成分不被组合或配制成组合产品、组合物或制剂。例如，Klotho蛋白质和一种或多种附加活性成分可各自包括或者是在一个单独的注射的(例如，肌内、静脉内等)、可摄入的、经皮的、吸入的、局部的或其它的制剂中。

还将理解的是，共同施用可包括同时施用两个或多个组分，或不同施用两个或多个组分，所述不同施用优选隔开一段时间。在一些实施方案中，该时间段可以非常小。例如，第二组分的Klotho蛋白质和一种或多种附加活性成分可以基本上紧接第一组分的Klotho蛋白质和一个或多个附加活性成分的施用而施用(注射)。或者，第一次和第二次施用可以分开1-60秒、1-60分钟、1-24小时、1-7天、1-4周、1-12个月等的时间段，或者其间的任何值或值范围。类似地，同时施用可以包括两个或更多个组分的重叠施用时间。

Klotho蛋白质变体

各种长度的治疗性S-Klotho蛋白(例如S-Klotho1-981、29-981、34-981、36-981、131-981、1-549、29-549、34-549、36-549、131-549等))可以以各种方式被修饰以实现在天然Klotho蛋白质未展现的各种有益效果和/或结果。说明性地，QuickChange XL定点诱变试剂

盒(Stratagene)可用于改变各种S-Klotho构建体的核酸序列。也可以使用本领域已知的其他诱变方法和试剂盒。例如,各种亚克隆方法和试剂盒是本领域已知的并且可商购获得。

在本公开的至少一个实施方案中,蛋白质用一个或多个C-末端标签和/或N-末端标签修饰。此类标签可用于延长蛋白质的血清和/或可溶性半衰期(在一种或多种治疗或其他环境中)。标签还可用作蛋白质的存在或诊断定位、蛋白质的分离或去除、蛋白质的递送或转运、蛋白质与一种或多种靶标(例如蛋白质、核酸、细胞器、细胞结构组分等)结合、酶促加工或裂解等的标记物。在至少一个实施方案中,蛋白质的C末端可以用TEV-双胞胎链霉素和/或Fc-融合物标记,如本领域已知的并且在本文中进一步描述。另外的描述可以在文章"Fusion Proteins for Half-Life Extension of Biologics as a Strategy to Make Biobetters"、"What is the future of PEGylated therapies?"和"Strategies for extended serum half-life of protein therapeutics"中找到,其全部内容通过具体参考并入本文。在某些实施方案中,接头或接头肽可以插入和/或置于(天然或变体)Klotho蛋白质序列和标签之间。

在一些实施方案中,修饰的Klotho蛋白可包括替代(例如,天然的、非天然的和/或合成的)信号肽。例如,在一些实施方案中,天然信号肽序列可以用替代信号肽或信号序列(SS)替换和/或补充。在一些实施方案中,可以除去Klotho蛋白的天然甲硫氨酸残基,并且可以包括SS的N末端的甲硫氨酸残基。另外的描述可以在论文"Generation of high expressing CHO cell lines for the production of recombinant antibodies using optimized signal peptides and a novel ER stress based selection system"中找到,其全部内容通过具体参考并入本文。在某些实施方案中,接头或接头肽可以插入和/或置于(天然或变体)Klotho蛋白质序列和备选SS之间。

一些实施方案可包括一种或多种氨基酸变体。应理解,本公开考虑任何所公开的Klotho蛋白中的任何一种或多种天然氨基酸与任何其他氨基酸的变体,无论是天然存在的、合成的还是以其他方式配置的。

S-Klotho C370S蛋白质变体

在人类中,Klotho基因定位于染色体13q12上。大约15%的白种人中存在称为KL-VS的变体。该变体由六个单核苷酸多态性(SNP)组成,其中两个引起氨基酸取代(即F352V和C370S-苯丙氨酸352变为缬氨酸,而半胱氨酸370变为丝氨酸)。体外转染测定显示,对于V352变体,klotho的分泌水平降低了6倍,而对于S370形式,它们几乎增加了3倍。然而,人KLOTHO基因中的这两种变体一起分离并形成KL-VS单倍型,其使klotho分泌增加1.6倍。例如,据报道,在筛选来自地理和/或种族不同的群组的300多个个体中,未发现单个个体仅包含V352变体或S370变体中的一个。

本公开的一个实施方案包括具有C370S同源性的重组S-Klotho蛋白(即,不存在(或缺失)F352V变体)。可以在本文所述的任何蛋白质构建体的背景下产生和/或表达C370S变体。例如,C370S变体可以在S-Klotho 1-981、29-981、34-981、36-981、131-981、1-549、29-549、34-549、36-549、131-549等的背景下产生或表达,有或没有Fc融合和/或TEV-双胞胎链霉素。因此,表达蛋白质的核酸构建体或cDNA可以具有相应的长度。

实施方式可包括制造S370杂合或纯的变体构建体,转移(例如,通过转染)得到的构建体(其编码S-Klotho的C370S蛋白)到适当的表达系统(例如CHO细胞),和/或瞬时表达S-

KlothoS370蛋白。S370Klotho蛋白质可以在比F352V/C370S蛋白和/或野生型F352/C370蛋白更高的水平被表达。实施方案可以包括纯化(和任选的质量控制测试)用于治疗性施用的表达的蛋白质。实施方案可以包括施用给需要其的受试者治疗量或治疗有效量的S-Klotho的C370S蛋白。例如,受试者可以包藏或表达KL-VS变体。或者,受试者可以是野生型的其他突变型或变体型。重组S-KlothoC370S蛋白的施用会导致血液中的S-Klotho水平的有益增加。因此,S-Klotho在接收该治疗性的重组S-Klotho C370S蛋白的受试者中的循环浓度可以不经受当存在F352V变体时所观察到的稀释作用。

高磷血症家族性肿瘤钙粘蛋白(HFTC)的治疗处理

在受影响的人类个体中,HFTC是由S-Klotho-rs121908423的氨基酸(AA)位置193处的组氨酸(H)至精氨酸(R)突变引起的。不受任何理论束缚,认为HFTC个体中的H193R突变损害了S-Klotho与FGF23和FGFR1c形成三元复合物的能力,其损害KL依赖性FGF23信号传导。结果,受影响的受试者呈现严重的代谢紊乱,其表现为皮肤和皮下组织中的高磷血症和大量钙沉积。一些患者表现出与骨膜反应和皮质骨肥厚和无皮肤受累的影像学发现相关的长骨的复发性、短暂性、疼痛性肿胀。

本公开的一个实施方案包括具有H193的S-Klotho蛋白。H193蛋白可以在本文所述的任何蛋白质构建体的背景下产生或表达。例如,H193变体可以在S-Klotho 1-981、29-981、34-981、36-981、131-981、1-549、29-549、34-549、36-549、131-549等的背景下产生或表达,有或没有Fc融合和/或TEV-双胞胎链霉素。因此,表达蛋白质的核酸构建体或cDNA可以具有相应的构型。

实施方式可包括制造H193杂合或纯的变体构建体,转移(例如,通过转染)得到的构建体(其编码S-Klotho的H193蛋白)到适当的表达系统(例如CHO细胞),和/或瞬时表达S-KlothoH193蛋白。该H193Klotho蛋白质也可以在比R193(或H193R)蛋白更高的水平表达。实施方案可以包括纯化(和任选的质量控制测试)用于治疗性施用的表达的蛋白质。实施方案可包括施用治疗量或治疗有效量的S-Klotho H193蛋白至需要其的受试者(例如,HFTC个体、诊断患有HFTC的个体或携带H193R(rs121908423)或其他变体的患者)。或者,受试者可以是野生型的其他突变型或变体型。重组S-KlothoH193蛋白的施用会导致血液中的S-Klotho水平的有益增加。给药可以逆转或抵消由在HFTC个体中转录和循环的R193突变的有害作用,这是由于受HFTC影响的个体中人klotho基因中发现的H-至-R193点突变。因此,S-Klotho H193的循环浓度可能有助于抵消H193R或HFTC个体中观察到的影响。

CC基因型终末期肾病患者(ESRD)的治疗处理

大约350,000名终末期肾病(ESRD)患者在慢性血液透析的第一年遭受异常高的死亡率。维生素D和成纤维细胞生长因子(FGF)-23水平都与这些患者的存活率相关。不受任何理论束缚,Klotho是维生素D/FGF-23信号传导途径中的蛋白质,与动物模型中的加速老化和早期死亡率相关。据推测,Klotho基因的遗传变异可能与ESRD患者的生存相关。研究人员测试了Klotho基因中的12个单核苷酸多态性(SNP)与一组ESRD患者(n=1307白人和亚洲人)在血液透析期间第一年的死亡率之间的关联。在一个标签SNP的CC基因型、rs577912(位于内含子1中的Klotho基因序列中具有次要等位基因频率[MAF]>0.05的常见HapMap变体)以及1年死亡率的风险增加之间发现了显著的关联(RR,1.76;95%CI,1.19-2.59;p=0.003)。对于未接受活性维生素D补充治疗的患者,具有CC基因型的个体的这种效应甚至更显著

(HR,2.51;95％CI,1.18-5.34;p＝0.005)。在源自HapMap受试者的淋巴母细胞样细胞系中,与AA或AC基因型相比,CC基因型与Klotho表达降低16-21％相关性。然而,上述rs577912SNP核苷酸变化均未导致Klotho蛋白质的氨基酸变化。因此,该功能性SNP(rs577912)可定量地影响mRNA水平的Klotho基因表达。

本公开的一个实施方案包括由AA或AC基因型表达的S-Klotho蛋白。蛋白质可以在本文所述的任何蛋白质构建体的背景下产生或表达。例如,蛋白质可以在S-Klotho 1-981、29-981、34-981、36-981、131-981、1-549、29-549、34-549、36-549、131-549等的背景下产生或表达,有或没有Fc融合和/或TEV-双胞胎链霉素。因此,表达蛋白质的核酸构建体或cDNA可以具有相应的长度。

实施方式可包括制造AA或AC杂合或纯合构建体,转移(例如,通过转染)得到的构建体(其编码S-Klotho的蛋白)到适当的表达系统(例如CHO细胞),和/或瞬时表达S-Klotho蛋白。在AA或AC杂合或纯合细胞中表达的Klotho蛋白可以比在CC细胞中更高的水平表达。实施方案可以包括纯化(和任选的质量控制测试)用于治疗性施用的表达的蛋白质。实施方案可以包括施用治疗量或治疗有效量的S-Klotho蛋白至需要其的受试者(例如,在一个标签SNP、rs577912包藏CC突变的个体或患者,其具有低的内源性S-Klotho蛋白表达和/或终末期肾病(ESRD))。或者,受试者可以是野生型的其他突变型或变体型。重组S-Klotho蛋白的施用会导致血液中的S-Klotho水平的有益增加。给药可以逆转或抵消由于在受影响的个体中人klotho基因中发现的点突变而在个体中转录和传播的CC突变的有害作用。因此,S-Klotho的循环浓度可能有助于对抗CC个体中观察到的影响,特别是那些患有终末期肾病(ESRD)的患者,即接受慢性血液透析的ESRD患者第一年的死亡率。

放射性手骨关节炎(OA)和骨赘的治疗处理

骨关节炎(OA)是一种常见的复杂疾病,具有强烈的可遗传成分。研究人员研究了klotho基因中的四种假定功能遗传变异与大个女性高加索人群中的手OA之间的关联。研究人员发现SNP G-395A与射线照相手OA和骨赘形成的存在与否之间存在显著关联。等位基因G显著增加射线照相手OA和骨赘的风险,优势比(ORs)分别为1.44(P＝0.008,95％置信区间(CI)1.09-1.91)和1.36(P＝0.006,95％CI 1.09-1.70)。从逻辑回归模型来看,与基因型AA相比,基因型GG显示放射照相手OA(OR＝3.10,95％CI 1.10-8.76)和骨赘(OR＝3.10,95％CI1.10-8.75)的风险增加超过三倍。根据年龄调整后,基因型GG的OR值进一步增加至射线照相手OA的4.39(P＝0.006,95％CI 1.51-12.74)和骨赘的4.47(P＝0.005,95％CI 1.56-12.77)。研究人员还提出,klotho基因中的一个变体(SNP G-395A)与手OA的易感性相关,并且似乎通过骨赘形成而不是软骨损伤起作用。

本公开的一个实施方案包括由具有SNP G395A的构建体表达的S-Klotho蛋白。可以在本文所述的任何蛋白质构建体的背景下产生或表达所得蛋白质。例如,A395变体可以在S-Klotho 1-981、29-981、34-981、36-981、131-981、1-549、29-549、34-549、36-549、131-549等的背景下产生或表达,有或没有Fc融合和/或TEV-双胞胎链霉素。因此,表达蛋白质的核酸构建体或cDNA可以具有相应的长度。

实施方式可包括制造A395杂合或纯合构建体,转移(例如,通过转染)得到的构建体(其编码S-Klotho的蛋白)到适当的表达系统(例如CHO细胞),和/或瞬时表达S-Klotho蛋白。在A395杂合或纯合细胞中表达的Klotho蛋白质可以在比在G396细胞中更高的水平表达。实施

方案可以包括纯化(和任选的质量控制测试)用于治疗性施用的表达的蛋白质。实施方案可以包括施用治疗量或治疗有效量的S-Klotho的蛋白至需要其的受试者(例如,携带G395SNP和/或(处于发展的风险)的射线照相手骨关节炎(OA)和/或骨赘的个体或患者)。或者,受试者可以是野生型的其他突变型或变体型。重组S-Klotho蛋白的施用会导致血液中的S-Klotho水平的有益增加。给药可以逆转或抵消在受影响的个体中转录和传播的G395SNP的有害作用。因此,S-Klotho的循环浓度可能有助于对抗在G395个体中观察到的影响,特别是那些有发展放射性手部骨关节炎(OA)和/或骨赘的风险的人。因此,施用G-395A S-Klotho蛋白可降低患者(例如,携带G395SNP的患者)的放射线手骨关节炎(OA)和骨赘形成的风险。

代谢综合征的治疗

代谢综合征(MetS)的风险和/或发病率是一组心脏代谢风险因素,包括腹部肥胖、高血糖、血脂异常和高血压,其随着年龄的增长而增加。在老年人中,MetS不仅增加了心血管疾病和2型糖尿病的风险,而且还与认知能力下降和残疾有关。目前的证据表明,MetS部分可遗传,遗传因素比环境因素对MetS的发病率起着更大的作用。研究人员在一群中国九十老年人和百岁老人中发现G-395A多态性与代谢综合征(MetS)存在关联。受试者来自都江堰的长寿和老龄工程(PLAD)。使用TaqMan等位基因鉴别分析进行Klotho基因启动子区域中G-395A(rs1207568)的基因分型。MetS根据国际糖尿病联盟标准诊断。包括年龄为93.5±3.2岁的695名受试者。G和A等位基因频率分别为0.852和0.148。在整个人群中,GG和GA+AA基因型组的MetS频率分别为10.8%和5.9%(p=0.004)。-395A等位基因携带者在整个人群中具有显著较低的MetS风险(优势比[OR]0.50,95%置信区间[CI]0.25至0.98)并且在女性中(OR0.51,95%CI 0.24至0.97),但不是在男性中(OR 0.42,95%CI 0.05至3.85)。在整个人群和女性中,Klotho G-395A SNP与MetS之间的关系可能是由于其对高血压(分别地,OR 0.48,95%CI 0.34至0.67;OR 0.47,95%CI 0.31至0.71)和高甘油三酯血症(分别地OR 0.66,95%CI 0.39至0.95;OR 0.54,95%CI 0.31至0.98)的影响。在男性中,这种关系可能是由于其对高血压(OR 0.47,95%CI 0.25-0.90)和低HDL-C(OR 0.69,95%CI 0.27-0.93)的影响。研究人员得出结论,Klotho基因的-395A等位基因携带者与中国九十多岁老年人和百岁老人的MetS风险降低相关,尤其是女性。

本公开的一个实施方案包括由具有-395A等位基因的构建体表达的S-Klotho蛋白。可以在本文所述的任何蛋白质构建体的背景下产生或表达所得蛋白质。例如,A395等位基因质可以在S-Klotho 1-981、29-981、34-981、36-981、131-981、1-549、29-549、34-549、36-549、131-549等的背景下产生或表达,有或没有Fc融合和/或TEV-双胞胎链霉素。因此,表达蛋白质的核酸构建体或cDNA可以具有相应的长度。

实施方式可包括制造-395A杂合或纯合构建体,转移(例如,通过转染)得到的构建体(其编码S-Klotho的蛋白)到适当的表达系统(例如CHO细胞),和/或瞬时表达S-Klotho蛋白。在A395杂合或纯合细胞中表达的Klotho蛋白质可以在比在G396细胞中更高的水平表达。实施方案可以包括纯化(和任选的质量控制测试)用于治疗性施用的表达的蛋白质。实施方案可以包括施用治疗量或治疗有效量的S-Klotho的蛋白至需要其的受试者(例如,携带G395SNP和/或(处于发展的风险)代谢综合征(MetS)的个体或患者)。或者,受试者可以是野生型的其他突变型或变体型。重组S-Klotho蛋白的施用会导致血液中的S-Klotho水平的有益增加。给药可以逆转或抵消在受影响的个体中转录和传播的G395SNP的有害作用。因

此,S-Klotho的循环浓度可能有助于对抗G395个体中观察到的影响,特别是那些有发展代谢综合征(MetS)风险的个体。因此,施用G-395A S-Klotho蛋白可以降低患者(例如,在老年人和/或女性中携带G395SNP的患者)的代谢综合征(MetS)的风险。

癌症的治疗性治疗

S-Klotho被认为抑制基础Wnt信号传导活性,从而起到结肠直肠癌(CRC)的肿瘤抑制剂的作用。此外,与寿命差异相关的klotho基因变异可能抑制丁酸盐介导的Wnt过度活化,从而增加CRC的风险。已经假设以这种方式,存在的klotho变体的类型及其相对表达可以与来自饮食的丁酸盐水平相互作用以改变CRC风险。此外,mTOR信号传导也与人类衰老有关,Wnt和mTOR信号传导之间的串扰可能影响结肠肿瘤发生。

KL-VS变体或其他构建体可用作研究哪些SNP(例如,在KL-VS内)负责影响S-Klotho以产生基础Wnt信号传导的减少和/或抑制丁酸盐介导的Wnt过度活化的载体——后者Wnt相关活性与S-Klotho肿瘤抑制相关。实施方案包括修饰适当的氨基酸(例如,在S-Klotho的KL-VS段中),其显示影响KL-VS变体的肿瘤抑制作用。本公开的一个实施方案包括重组S-Klotho蛋白,其在6个SNP的KL-VS区段中具有一个或多个氨基酸改变。可以在本文所述的任何蛋白质构建体的背景下产生和/或表达蛋白质。例如,蛋白质可以在S-Klotho 1-981、29-981、34-981、36-981、131-981、1-549、29-549、34-549、36-549、131-549等的背景下产生或表达,有或没有Fc融合和/或TEV-双胞胎链霉素。因此,表达蛋白质的核酸构建体或cDNA可以具有相应的长度。

实施方式可包括制造杂合或纯的变体构建体,转移(例如,通过转染)得到的构建体(其编码S-Klotho的蛋白)到适当的表达系统(例如CHO细胞),和/或瞬时表达S-Klotho蛋白。所述Klotho蛋白质可以以比其它的Klotho蛋白质更高的水平表达,包括野生型。实施方案可以包括纯化(和任选的质量控制测试)用于治疗性施用的表达的蛋白质。实施方案可以包括施用治疗量或治疗有效量的S-Klotho至需要其的受试者(例如,具有或处于发展结肠直肠癌(CRC)或其他肿瘤的风险的患者)。受试者可以例如包藏或表达具有降低的Wnt抑制活性的Klotho变体。或者,受试者可以是野生型的其他突变型或变体型。重组S-Klotho蛋白的施用会导致血液中的S-Klotho水平的有益增加。

年龄相关疾病的治疗

研究人员发现Klotho与生物学参数之间存在关联,这些参数通常被认为是住院老年患者临床状态的指标。研究人员对连续就诊于老年病房的594例住院老年患者(65-99岁)的单核苷酸多态性(SNPs)rs9536314/rs1207568和rs564481进行了基因分型,并测试了这些KL变异与生物定量的相关性,其使用协方差分析和遗传风险评分模型。观察到rs9536314与血红蛋白、白蛋白和高密度脂蛋白胆固醇(HDL-C)血清水平的显著相关性以及rs564481与血红蛋白、空腹胰岛素和空腹血糖血清水平的显著相关性。性别隔离分析证实了这些相关性,并表明KL基因型与HDL-C、空腹血糖和空腹胰岛素水平的关联可能由女性性别驱动,而与血清血红蛋白水平的关联可能由男性性别驱动。在女性中发现了KL基因型与肌酸水平的关联,而在男性中发现了与胰岛素样生长因子-1(IGF-1)和淋巴细胞计数(LC)的关联。遗传风险评分(GRS)模型进一步证实了KL SNP与血红蛋白、总胆固醇和HDL-C之间的显著相关性。采用GRS标记方法的性别隔离分析证实了女性的HDL-C、空腹血糖和空腹胰岛素水平以及男性血红蛋白和LC的相关性。研究结果表明,KL位点可能影响住院老年患者例如脂质、空腹血

糖、白蛋白和血红蛋白的血清水平的数量性状，肌酸、IGF-1水平和LC存在性别差异，因此是遗传因素之一，可能导致与年龄有关的疾病和长寿。

本公开的一个实施方案包括如本文所述的S-Klotho蛋白。实施方式可包括产生合适的klotho构建体，转移(例如，通过转染)所述构建体(其编码S-Klotho的蛋白)到适当的表达系统(例如CHO细胞)，和/或瞬时表达S-Klotho蛋白。实施方案可以包括纯化(和任选的质量控制测试)用于治疗性施用的表达的蛋白质。实施方案可以包括将治疗或治疗有效量的S-Klotho蛋白质给予有需要的受试者(例如，个体或患者，任选地老年人和/或患有与衰老相关的病症、低内源性S-Klotho蛋白质表达和/或年龄相关病症的症状或寿命降低)。重组S-Klotho蛋白的施用会导致血液中的S-Klotho水平的有益增加。给药可逆转或抵消衰老相关病症的有害影响和/或以积极的治疗方式影响数量性状，如总胆固醇、HDL-C、空腹血糖、空腹胰岛素、白蛋白、肌酸、IGF-1、血红蛋白和淋巴细胞计数的血清水平(例如，在住院和/或老年患者中)。

应当理解，在本文所述的一种或多种治疗方法中，待治疗的个体可以具有Klotho基因的突变(例如，基因组编码的杂合突变或纯合突变)，并且治疗方案可以包括给予治疗剂量的包含野生型Klotho和/或本文公开的Klotho的任何一种或多种变体的肽，包括例如与个体表达的突变相似的变体。或者，待治疗的个体可编码/表达野生型Klotho，并且治疗方案可包括施用治疗剂量的包含野生型Klotho的肽和/或本文公开的Klotho的任何一种或多种变体。在一些实施方案中，并且无论个体表达的Klotho是天然野生型或突变体形式，治疗方法可包括确定循环和/或细胞结合的Klotho蛋白的低水平(例如，与对照组相比)以及施用治疗剂量，该治疗剂量可操作地将循环和/或细胞结合的Klotho的浓度恢复至至少稳态水平。在一些实施方案中，这可以包括在施用治疗浓度之前确定Klotho的水平(例如，基因表达水平、蛋白质表达水平、循环水平等)。另外，治疗剂量可取决于个体中测定的Klotho水平。在一些实施方案中，治疗剂量超过稳态水平例如稳态水平的标量倍数(例如，1.5倍多、2倍多、3倍多、4倍多、5倍多、6倍多、7倍多、8倍多、9倍多、10倍多、15倍多、20倍多、25倍多、30倍多、40倍多、50倍多、75倍多、100倍多、500倍多、1000倍多、10,000倍多等)。

更具体地，应当理解，年龄相关病症的治疗性治疗可包括给予治疗浓度的一种或多种Klotho变体。在一些实施方式中，这可以包括用本文公开的治疗浓度的Klotho变体(或Klotho变体的组合)治疗患者，例如选自SEQ ID NO:2至SEQ ID NO:70中的任何一个或多个的肽。应当理解，年龄相关病症可以用Klotho变体治疗，所述Klotho变体与具有年龄相关病症的个体表达和/或编码的Klotho变体相同或不同。例如，患有年龄相关病症的个体可以遗传编码一种或多种野生型或Klotho变体，并且个体可以在稳态水平(与对照组相比)、低于稳态水平或根本没有表达野生型和/或变体Klotho蛋白。旨在治疗个体年龄相关病症的治疗方案可包括施用本文公开的一种或多种Klotho变体。

预防性S-Klotho给药

除了前述之外，本公开的实施方案可以包括将治疗量或治疗有效量的S-Klotho蛋白质给予有需要的个体或受试者，用于预防目的和/或维持某些健康属性。例如，某些S-Klotho蛋白的施用可以帮助维持未患有诊断的衰老相关病症的任选老年患者的年轻。因此，尽管本公开的某些实施方案可以涉及和/或包括治疗患者的病症，但是其他实施方案可以涉及和/或包括预防、抑制发展和/或预防性地解决一种或多种病症。例如，S-Klotho可以施用于

具有一种或多种Klotho基因突变的遗传疾病的人。

实施例

实施例1

表1说明了在HEK和/或CHO细胞系中所述Klotho变体的表达和纯化的结果。在下表1中提供的结果中,遵循以下缩写方案。

对于Fc融合蛋白,使用标准ATUM方法将蛋白质表达载体转染到HEK293.sus或CHO中。简言之,使细胞生长7天并收获。细胞计数在注释部分给出。用1M Hepes pH 7.4调节上清液pH并加入叠氮化钠。KanCap A树脂用于捕获蛋白质。用PBS洗涤树脂。用PBS加1M NaCl洗涤树脂。用PBS洗涤树脂。用50mM柠檬酸盐pH 3.5,100mM NaCl洗脱蛋白质。立即用1M Tris pH 8,0.5M精氨酸中和蛋白质。在该阶段除去SDS PAGE凝胶样品。将蛋白质缓冲液交换到PBS中。通过OD280定量蛋白质,使用计算的消光系数确定数量和浓度。使用还原和未还原的SDS-PAGE(Biorad标准Tris/甘氨酸/SDS,4-20%)测定纯度和近似分子量。通过HPLC测定聚集状态,使用Sepax Zenix-C SEC-300,3um,300Å,4.6×150mm尺寸排阻柱和PBS运行缓冲液在280nm处检测。过滤灭菌后,将蛋白质作为等分试样运输,在液氮中快速冷冻。应当注意,对于Fc标记的蛋白质,如在前一轮纯化中,在脱盐到PBS期间观察到蛋白质的损失,如在纯化之前和之后在SDS-PAGE上运行的样品所测定的。表达这些蛋白质,但是从HPLC中,在PBS中的二氧化硅HPLC柱的脱盐或测定期间出现问题。因此,可以优化缓冲液选择。

对于链霉素标记蛋白,使用标准ATUM方法将蛋白质表达载体转染到HEK293.sus或CHO中。简言之,使细胞生长7天并收获。用1M Hepes pH 7.4调节上清液pH并加入叠氮化钠。添加BioLock生物素隔离试剂。StrepTactin Superflow树脂用于捕获蛋白质。用100mM Tris pH 8,150mM NaCl,1mM EDTA洗涤树脂。用100mM Tris pH 8,150mM NaCl,1mM EDTA加2.5mM脱硫生物素(Desthiobiotin)洗脱蛋白质。通过OD280定量蛋白质,使用计算的消光系数确定数量和浓度。使用还原和未还原的SDS-PAGE(Biorad标准Tris/甘氨酸/SDS,4-20%)测定纯度和近似分子量。通过HPLC测定聚集状态,使用Sepax Zenix-C SEC-300,3um,300Å,4.6×150mm尺寸排阻柱和PBS运行缓冲液在280nm处检测。过滤灭菌后,将蛋白质作为等分试样运输,在液氮中快速冷冻。应注意,对于链霉素标记的蛋白质,在洗脱缓冲液中测定样品。该洗脱缓冲液非常“中性”,对蛋白质无害。此外,SEC柱的运行缓冲液是PBS,因此蛋白质在测定期间进行缓冲液交换。时间7分钟以上的吸光度是小分子。

表1.Klotho瞬态表达谱

蛋白质名称	OD280nm	浓度 (mg/mL)	消光系数	分子量(Da)	滴度 (mg/L)
天然Klotho ECD(34-981)-天然SS-链霉素-HEK	2.01	0.95	246780	116615	6.18
天然Klotho ECD(34-981)-ATUMSS-链霉素-HEK	1.73	0.79	246780	113119	5.16
Klotho ECD变体-1(36-981)-ATUMSS-链霉素-HEK	0.89	0.41	246780	112893	2.64
天然分泌/同种型2(34-549)-天然链霉素-HEK	1.33	0.63	140510	66255	4.07

天然分泌的/同种型2(34-549)-ATUMSS-链霉素-HEK	2.84	1.27	140510	62760	8.24
分泌的变体(36-549)-ATUMSS-链霉素-HEK	1.40	0.62	140510	62534	4.04
Klotho ECD变体-2(131-981)-ATUMSS-链霉素-HEK	1.12	0.52	221800	103079	3.40
天然Klotho ECD(34-981)-天然SS-Fc-HEK	0.02	0.01	270075	138668	0.27
天然Klotho ECD(34-981)-ATUMSS-Fc-HEK	0.01	0.00	270075	135172	0.12
Klotho ECD变体-1(36-981)-ATUMSS-Fc-HEK	-0.04	-0.02	270075	134946	-0.48
天然分泌的/同种型2(34-549)-天然SS-Fc-HEK	0.03	0.02	163805	88308	0.43
天然分泌/同种型2(34-549)-ATUMSS-FC-HEK	0.05	0.03	163805	84813	0.76
分泌的变体(36-549)-ATUMSS-Fc-HEK	-0.01	-0.00	163805	84587	-0.08
Klotho ECD变体-2(131-981)-ATUMSS-Fc-HEK	-0.01	-0.01	245095	125132	-0.15
天然Klotho ECD(34-981)-天然SS-链霉素-CHO	0.42	0.20	246780	116615	1.97
天然Klotho ECD(34-981)-ATUMSS-链霉素-CHO	0.28	0.13	246780	113119	1.30
Klotho ECD变体-1(36-981)-ATUMSS-链霉素-CHO	0.15	0.07	246780	112893	0.68
天然分泌/同种型2(34-549)-天然SS - 链霉素-CHO	0.26	0.12	140510	66255	1.24
天然分泌/同种型2(34-549)-ATUMSS-链霉素-CHO	0.36	0.16	140510	62760	1.61

分泌的变体(36-549)-ATUMSS-链霉素-CHO	0.22	0.10	140510	62534	0.98
Klotho ECD变体-2(131-981)-ATUMSS-链霉素-CHO	0.19	0.09	221800	103079	0.86
天然分泌的/同种型2(34-549)-天然SS-Fc-CHO	0.12	0.06	163805	88308	1.54
天然分泌的/同种型2(34-549)-ATUMSS-Fc-CHO	0.16	0.08	163805	84813	2.05

应当理解,除了本文公开但未在表1中显示的一种或多种其他Klotho变体之外,表1中公开的Klotho变体的表达和/或纯化可以在一些实施方案中产生优于表达和/或纯化天然Klotho的优势。例如,当表达和/或纯化Klotho变体时,可以减少替代产品的数量和/或类型。另外或可替代地,与天然Klotho的表达水平相比,期望的Klotho变体的表达水平可以增加。另外或可替代地,在相当的条件和方法下,以更纯的形式表达和/或纯化所需的Klotho变体(例如,所需Klotho变体的浓度随着表达和/或纯化的副产物的伴随减少而增加)。

实施例2

即将到来的实施例包括限定所公开发明的范围的示例性权利要求组。然而,如本文所提供的,本发明的范围由所附权利要求而不是由即将提出的实施例或前述说明书指出。

1.一种制造重组Klotho蛋白质的示例性方法,所述方法包括:在中国仓鼠卵巢(CHO)细胞中产生重组Klotho蛋白,优选在二氢叶酸还原酶(DHFR)缺陷型CHO细胞中,更优选在CHO-S细胞中,或优选在谷氨酰胺合成酶(GS)缺陷型CHO细胞中,更优选在GS-/-CHO细胞中,所述蛋白质优选地与SEQ ID NO:2至SEQ ID NO:70的一种具有至少85%氨基酸序列同一性。

2.根据权利要求1所述的方法,其中所述蛋白质包含与其连接的一种或多种聚糖。

3.根据权利要求1或2所述的方法,其中所述CHO细胞含有编码以下的外源核酸:启动子,优选强启动子;与SEQ ID NO:2至SEQ ID NO:70之一具有至少85%氨基酸序列同一性的多肽;任选地,功能性二氢叶酸还原酶(DHFR)酶或功能性谷氨酰胺合成酶(GS)酶,其中产生重组Klotho蛋白包括表达由核酸编码的多肽。

4.根据权利要求3所述的方法,进一步包括选自以下的一个或多个步骤:将外源核酸引入CHO细胞,优选通过转染;和在液体培养基中培养CHO细胞,优选在无血清和/或无动物蛋白成分的培养基中,其中液体培养基优选包含碳源、氮源和一种或多种维生素、矿物质、盐、氨基酸、补充剂或添加剂,更优选其中液体培养基缺乏次黄嘌呤、胸苷和/或谷氨酰胺。

5.根据权利要求4所述的方法,其中所述蛋白质从CHO细胞分泌到液体培养基中,优选浓度为每升液体培养基200-500mg蛋白质,更优选浓度为500-2000mg蛋白质,更优选浓度为2000-5000毫克蛋白质,而不浓缩蛋白质。

6.根据权利要求4所述的方法,还包括将有效量的甲氨蝶呤(MTX)和/或甲硫氨酸亚砜亚胺(MSX)引入液体培养基中,优选浓度为约1nM-1μM,更优选浓度为约10μM-100nM。

7.根据权利要求4所述的方法,还包括选择在液体培养基中生长的活CHO细胞的悬浮培养物,其中所选悬浮培养物的培养基中蛋白质的浓度为在不浓缩蛋白质的情况下,至少

200mg/L、优选至少500mg/L、更优选至少1000mg/L、甚至更优选至少2000mg/L、还更优选至少5000mg/L。

8.根据权利要求7所述的方法，其中所选择的悬浮培养物的活CHO细胞含有至少约2至10个拷贝、优选至少约10至20个拷贝、更优选至少约20至30个拷贝、甚至更优选至少约30至50个拷贝的外源核酸/细胞。

9.根据权利要求4所述的方法，进一步包括从CHO细胞、液体培养基或两者中纯化含有重组Klotho蛋白的提取物，所述提取物优选包含：至少约98％干重的蛋白质；和/或小于约1-100ppm的CHO宿主细胞蛋白(HCP)。

10.根据权利要求9所述的方法，其中纯化提取物维持蛋白质的糖基化。

11.根据权利要求4所述的方法，其中生长所述CHO细胞包括在生物反应器中培养CHO细胞，所述生物反应器的体积或工作体积为至少10升，优选至少25升，更优选至少50升，甚至更优选至少100升，还更优选至少250升，还更优选至少500升，还更优选至少1,000升，还更优选至少2,000升，还更优选至少2500升，还更优选至少5,000升，还更优选至少10,000升。

12.根据权利要求1至11中任一项所述的方法，其中所述核酸包含转基因或cDNA，其与SEQ ID NO:76至SEQ ID NO:96之一优选地具有至少85％、更优选至少90％、甚至更优选至少95％、仍甚至更优选至少98％、还更优选至少99％、最优选100％核酸序列同一性。

13.根据权利要求1至12中任一项所述的方法，其中所述蛋白与SEQ ID NO:2至SEQ ID NO:70之一具有至少90％、优选至少95％、更优选至少98％、甚至更优选至少99％、更优选100％核酸序列同一性。

14.一种细胞系，其包括：多个中国仓鼠卵巢(CHO)细胞，优选在二氢叶酸还原酶(DHFR)缺陷型CHO细胞，更优选在CHO-S细胞，或优选地在谷氨酰胺合成酶(GS)缺陷型CHO细胞，更优选在GS-/-CHO细胞中，含有外源核酸的所述CHO细胞包含启动子，优选强启动子，并编码：多肽，至少一部分多肽与SEQ ID NO:2至SEQ ID NO:70的一种具有至少85％的氨基酸序列同一性；和任选地，功能性二氢叶酸还原酶(DHFR)酶或功能性谷氨酰胺合成酶(GS)酶。

15.根据权利要求14所述的细胞系，其中所述CHO细胞含有或选择含有至少约2至10个拷贝、优选至少约10至20个拷贝、更优选至少约20至30个拷贝、甚至更优选至少约30至50个拷贝的外源核酸/细胞。

16.根据权利要求14所述的细胞系，其中所述核酸编码与SEQ ID NO:2至SEQ ID NO:70之一具有至少90％、优选至少95％、更优选至少98％、甚至更优选至少99％、更优选100％核酸序列同一性的多肽。

17.根据权利要求14所述的细胞系，其中所述核酸包含转基因或cDNA，其与SEQ ID NO:76至SEQ ID NO:96之一优选地具有至少85％、更优选至少90％、甚至更优选至少95％、仍甚至更优选至少98％、还更优选至少99％、最优选100％核酸序列同一性。

18.一种悬浮细胞培养物，其包含：液体培养基，优选无血清和/或无动物蛋白成分的液体培养基，其中液体培养基优选包含碳源、氮源和一种或多种维生素、矿物质、盐、氨基酸、补充物、或添加剂，更优选其中所述液体培养基缺乏次黄嘌呤、胸苷和/或谷氨酰胺；以及权利要求14-17中任一项所述的细胞系在液体培养基中生长以使得CHO细胞表达由核酸编码的多肽，该多肽包含重组Klotho蛋白。

19.根据权利要求18所述的悬浮细胞培养物，其中所述CHO细胞将所述蛋白质分泌到所

述液体培养基中，优选浓度为每升液体培养基200-500mg蛋白质，更优选浓度为500-2000mg蛋白质，仍更优选浓度为2000-5000mg蛋白质，而不浓缩蛋白质，和/或其中蛋白质以下述浓度存在于液体培养基中：每升液体培养基200-500mg蛋白质，更优选浓度为500-2000mg蛋白质，更优选浓度为2000-5000毫克蛋白质，而不浓缩蛋白质。

20.根据权利要求18或19所述的悬浮细胞培养物，其中所述蛋白质包含与其连接的一种或多种聚糖。

21.根据权利要求18至20中任一项所述的悬浮细胞培养物，其中所述液体培养基还包含有效量的甲氨蝶呤(MTX)和/或甲硫氨酸亚砜亚胺(MSX)，优选浓度为约1nM-1μM，更优选浓度约为10nM-100nM。

22.根据权利要求18-21中任一项所述的悬浮细胞培养物，其中所述蛋白质与SEQ ID NO:2至SEQ ID NO:70之一具有至少85％、优选至少90％、更优选至少95％、甚至更优选至少98％、仍更优选至少99％、更优选100％的氨基酸序列同一性。

23.一种重组Klotho蛋白，其中至少一部分所述蛋白质与SEQ ID NO:2至SEQ ID NO:70之一具有至少80％的氨基酸序列同一性。

24.根据权利要求23所述的重组Klotho蛋白，其中所述蛋白质：调节IGF-1和/或Wnt信号传导途径；表现出β-葡萄糖醛酸酶和/或唾液酸酶活性；抑制p53/p21信号传导途径；和/或减少H2O2诱导的细胞衰老和凋亡，优选通过抑制p53/p21信号传导途径。

25.根据权利要求23或24所述的重组Klotho蛋白，其中所述蛋白质作为体液因子起作用，优选表现出多效活性，优选调节氧化应激，生长因子信号传导，离子稳态，和/或调节细胞表面上一种或多种糖蛋白活性，优选地一种或多离子通道蛋白和/或生长因子受体，优选地胰岛素/胰岛素样生长因子-1受体。

26.根据权利要求23-25中任一项所述的重组Klotho蛋白，其中至少一部分所述蛋白质与SEQ ID NO:2至SEQ ID NO:70之一具有至少85％、优选至少90％、更优选至少95％、甚至更优选至少98％、仍更优选至少99％、更优选100％的氨基酸序列同一性。

27.一种治疗衰老相关或其他病症、疾病或病症的方法，所述方法包括向有需要的受试者施用药学有效量的根据权利要求23-26中任一项所述的重组Klotho蛋白。

28.一种治疗衰老相关或其他病症、疾病或病症的方法，所述方法包括向有需要的受试者施用药学有效量的可溶性重组Klotho蛋白，其至少与人αKlotho同种型1的氨基酸残基1-981的子集具有至少80％氨基酸序列同一性。

29.一种治疗衰老相关或其他病症、疾病或病症的方法，所述方法包括向有需要的受试者施用药学有效量的可溶性重组Klotho蛋白，其与SEQ ID NO:2至SEQ ID NO:70之一具有至少80％的氨基酸序列同一性。

30.根据权利要求27至29中任一项所述的方法，其中所述蛋白质与SEQ ID NO:2至SEQ ID NO:70之一具有至少85％、优选至少90％、更优选至少95％、甚至更优选至少98％、仍更优选至少99％、更优选100％的氨基酸序列同一性。

31.根据权利要求30所述的方法，其中所述药学有效量足以：将所述受试者的血清可溶性Klotho蛋白浓度升高至预定水平；优选地，将所述受试者的血清可溶性Klotho蛋白质浓度维持在预定阈值或高于预定阈值一段预定时间。

32.根据权利要求31所述的方法，其中所述预定水平大于或等于每毫升血清约1000皮

克可溶性Klotho蛋白。

33.根据权利要求31所述的方法，其中，所述预定水平大于、等于或在以下之间：每毫升血清约50、100、250、500、750、1000、1250、1500、1750、2000、2250、2500、2750、3000、3500、4000、4500、5000、5500、6000、6500、7000、7500、8000、8500、9000、9500、10000、11000、12000、13000、14000、15000、20000、25000、30000、40000、50000、75000、100000皮克可溶性Klotho蛋白质；和/或比血清中典型健康水平的可溶性Klotho蛋白质高约5％、10％、15％、20％、25％、30％、40％、50％、60％、70％、80％、90％、100％、150％、200％、250％、300％、400％、500％、600％、700％、800％、900％、1000％、1200％、1500％、2000％、2500％、3000％、4000％、5000％。

34.根据权利要求31所述的方法，还包括以下一种或多种：确定所述受试者的血清可溶性Klotho蛋白质浓度；计算足以使受试者的血清可溶性Klotho蛋白质浓度升高至第一预定水平的蛋白质的药学有效量，其中第一预定水平优选大于或等于每毫升血清约1000皮克可溶性Klotho蛋白质；确定受试者血清中可溶性Klotho蛋白质下降和/或代谢的速率；基于所确定的速率计算受试者的血清可溶性Klotho蛋白质的浓度将处于或低于第二预定水平的后续剂量时间；和计算足以将受试者的血清可溶性Klotho蛋白浓度从第二预定水平升高至第一预定水平的蛋白质的后续剂量量。

35.根据权利要求34所述的方法，还包括将所述后续剂量量的蛋白质给予受试者。

36.根据权利要求31所述的方法，还包括以下一种或多种：将外源核酸引入中国仓鼠卵巢(CHO)细胞，优选通过转染，所述核酸优选包含转基因或cDNA，所述核酸编码与SEQ ID NO:2至SEQ ID NO:70之一具有至少85％、优选至少90％、更优选至少95％、甚至更优选至少98％、仍更优选至少99％、更优选100％氨基酸序列同一性的多肽，所述核酸与SEQ ID NO:76至SEQ ID NO:96之一具有优选至少85％、更优选至少90％、甚至更优选至少95％、仍更优选至少98％、仍更优选至少99％、最优选100％的核酸序列同一性；在液体培养基中培养CHO细胞，优选在无血清和/或无动物蛋白成分的液体培养基中，其中液体培养基优选包含碳源、氮源和一种或多种维生素、矿物质、盐、氨基酸、补充剂或添加剂，更优选其中液体培养基缺乏次黄嘌呤、胸苷和/或谷氨酰胺，所述CHO细胞优选为：二氢叶酸还原酶(DHFR)缺陷型CHO细胞，更优选在CHO-S细胞中，或谷氨酰胺合成酶(GS)缺陷型CHO细胞，更优选在GS-/-CHO细胞中；将有效量的甲氨蝶呤(MTX)和/或甲硫氨酸亚砜亚胺(MSX)引入液体培养基中，优选浓度为约1nM-1μM，更优选浓度为约10-100nM；通过细胞选择过程选择在液体培养基中生长的活CHO细胞的悬浮培养物，其中所选悬浮培养基的培养基中蛋白质的浓度为至少200mg/L，优选至少500mg/L，更优选至少1000mg/L，甚至更优选至少2000mg/L，还更优选至少5000mg/L，而不浓缩蛋白质；在CHO细胞中产生重组可溶性Klotho蛋白，其中所述蛋白质优选从CHO细胞分泌到液体培养基中，优选浓度为每升液体培养基200-500mg蛋白质，更优选浓度为500-2000mg蛋白质，仍更优选地浓度为2000-5000mg蛋白质，而不浓缩蛋白质；以及从CHO细胞、液体培养基或两者中纯化含有重组可溶性Klotho蛋白的提取物，所述提取物优选包含：至少约98％干重的重组可溶性Klotho蛋白；和/或小于约1-100ppm的CHO宿主细胞蛋白(HCP)，其中纯化提取物优选保持蛋白质的糖基化，所述蛋白质具有与其连接的一个或多个聚糖。

37.根据权利要求31所述的方法，其中所述预定时间段是至少约6小时，优选至少约12

小时，更优选至少约18小时，甚至更优选至少约24小时，还更优选至少约30小时，还更优选至少约36小时，更优选至少约42小时，还更优选至少约48小时，还更优选至少约54小时，还更优选至少约60小时，还更优选至少约66小时，更优选至少约72小时。

38.根据权利要求31所述的方法，其中所述预定时间段大于或等于约1-120天。

39.根据权利要求31所述的方法，其中所述预定时间段大于或等于约6个月、9个月或1年。

40.根据权利要求30-39中任一项所述的方法，其中所述受试者是人、非人动物或非人哺乳动物。

41.根据权利要求30至40中任一项所述的方法，其中所述蛋白质在药学上可接受的载体中施用或与其一起施用。

42.根据权利要求30至41中任一项所述的方法，其中所述与衰老有关的或其他的病症、疾病或障碍包括以下一种或多种：脆弱；骨密度丧失；骨矿物质密度丧失；体重减轻；肌肉萎缩或变性；肌肉量减少；肌肉力量下降；手部力量下降；腿部力量下降；身体素质下降；运动下降；活动自由度下降；生活评估质量下降；射血分数下降；运动能力下降；学习下降；学习能力下降；记忆力下降；智商下降；认知恶化；遗忘；认知能力下降；功能下降；突触可塑性下降；突触功能下降；以及细胞衰老。

43.根据权利要求30-41中任一项所述的方法，其中所述与衰老有关的或其他的病症、疾病或障碍包括以下一种或多种：慢性肾病(CKD)；多囊肾病(PKD)；常染色体显性多囊肾病(ADPKD)；急性肾损伤(AKI)；急性肾小管坏死(ATN)；急性过敏性间质性肾炎(AAIN)；肾小球肾炎；肾脏疾病；肾功能衰竭；非低尿性肾功能衰竭；酗酒；高磷血症；肌营养不良症(MS)；1型糖尿病；2型糖尿病；心血管疾病(CVD)；心血管钙化；脑血管功能不全；血管钙化；冠状动脉疾病；血压异常；盐敏感性高血压；组织钙化；钙化动脉粥样硬化斑块负担；钙质沉着；家族性肿瘤性钙质沉着症；癌症；一个或多个肿瘤；髓鞘相关疾病；脱髓鞘疾病；神经退行性疾病；神经血管疾病；进行性核上性麻痹(PSP)；庞培病；尼曼-皮克病；小神经胶质细胞；法伯病(FD)；骨质疾病；骨质疏松症；骨质疏松；骨质减少(特别是皮质骨BMD的丧失)；肺气肿；肺纤维化；皮肤萎缩；胸腺萎缩；肾间质基质的积累；肾小球硬化；贫血；白蛋白尿；蛋白尿；不孕；阿尔茨海默氏病；帕金森病；痴呆；血管性痴呆；肌萎缩侧索硬化症(ALS)；运动神经元病(MND)；心房颤动；慢性阻塞性肺病(COPD)；纤维肌痛；成年型糖尿病；关节炎；类风湿关节炎；骨关节炎；青光眼；白内障；黄斑变性；多发性硬化症(MS)；狼疮；溃疡性结肠炎；恶病质；肥胖；维生素D相关病症；骨病；通过骨重建的骨病；干细胞耗竭；晕船；空间适应综合症(SAS)；恶心；和眩晕。

44.根据权利要求30-43中任一项所述的方法，还包括施用或共同施用一种或多种附加活性成分。

45.根据权利要求44所述的方法，其中所述一种或多种附加活性成分选自药物、抗体、激素、放射性造影剂、医药、天然化合物、合成化合物或药物组合物。

46.一种药物组合物，其包含：药学有效量的权利要求23-25中任一项所述的重组Klotho蛋白；和药学上可接受的载体。

47.一种药物组合物，其包含：药学有效量的重组可溶性Klotho蛋白，至少一部分蛋白与人αKlotho同种型1的氨基酸残基1-981、29-981、34-981、36-981、131-981、1-549、29-

549、34-549、36-549或131-549的至少子集或SEQ ID NO:2至SEQ ID NO:70的一种的至少一部分具有至少85％的氨基酸序列同一性，和药学上可接受的载体。

48.根据权利要求46或47所述的药物组合物，其中至少一部分蛋白质与SEQ ID NO:2至SEQ ID NO:70之一的至少一部分具有至少85％、优选至少88％、更优选至少90％、甚至更优选至少92％、还更优选至少95％、更优选至少98％、还更优选至少99％、最优选100％的氨基酸序列同一性。

49.根据权利要求46-48中任一项所述的药物组合物，还包含一种或多种附加活性成分。

50.根据权利要求46-49中任一项的药物组合物，其用于治疗与衰老有关的或其他的病症、疾病或障碍，其包括以下一种或多种：脆弱；骨密度减少；骨矿物质密度减少；减肥；肌肉萎缩；肌肉退化；肌肉质量下降；肌肉力量下降；手部力量下降；腿部力量下降；身体素质下降；运动减少；行动自由度下降；生活质量评估下降；射血分数下降；运动能力下降；学习下降；学习能力下降；记忆力下降；智商下降；认知恶化；健忘；认知能力下降；认知功能下降；突触可塑性下降；突触功能下降；细胞衰老；慢性肾脏病(CKD)；多囊肾病(PKD)；常染色体显性多囊肾病(ADPKD)；急性肾损伤(AKI)；急性肾小管坏死(ATN)；急性过敏性间质性肾炎(AAIN)；肾小球肾炎；肾脏疾病；肾功能衰竭；非低尿性肾功能衰竭；酗酒；高磷血症；肌营养不良症(MS)；1型糖尿病；2型糖尿病；心血管疾病(CVD)；心血管钙化；脑血管功能不全；血管钙化；冠状动脉疾病；血压异常；盐敏感性高血压；组织钙化；钙化动脉粥样硬化斑块负担；钙质沉着；家族性肿瘤性钙质沉着症；癌症；一个或多个肿瘤；髓鞘相关疾病；脱髓鞘疾病；神经退行性疾病；神经血管疾病；进行性核上性麻痹(PSP)；庞培病；尼曼-皮克病；小神经胶质细胞；法伯病(FD)；骨质疾病；骨质疏松症；骨质疏松；骨质减少(特别是皮质骨BMD的丧失)；肺气肿；肺纤维化；皮肤萎缩；胸腺萎缩；肾间质基质的积累；肾小球硬化；贫血；白蛋白尿；蛋白尿；不孕；阿尔茨海默氏病；帕金森病；痴呆；血管性痴呆；肌萎缩侧索硬化症(ALS)；运动神经元病(MND)；心房颤动；慢性阻塞性肺病(COPD)；纤维肌痛；成年型糖尿病；关节炎；类风湿关节炎；骨关节炎；青光眼；白内障；黄斑变性；多发性硬化症(MS)；狼疮；溃疡性结肠炎；恶病质；肥胖；维生素D相关病症；骨病；通过骨重建的骨病；干细胞耗竭；晕船；空间适应综合症(SAS)；恶心；和眩晕。

51.根据权利要求46-49中任一项的药物组合物，其用于治疗或预防急性肾损伤(AKI)。

52.一种治疗或预防急性肾损伤(AKI)或其它病症的方法，所述方法包括向有需要的受试者施用药学上有效量的重组Klotho蛋白质，至少一部分蛋白与人αKlotho同种型1的氨基酸残基1-981、29-981、34-981、36-981、131-981、1-549、29-549、34-549、36-549或131-549的至少子集或SEQ ID NO:2至SEQ ID NO:70的一种的至少一部分具有至少85％、86％、88％、90％、92％、95％、98％、99％、或优选地100％的氨基酸序列同一性。

53.根据权利要求52所述的方法，还包括与药学有效量的重组可溶性Klotho蛋白共同施用一种或多种附加活性成分。

54.根据权利要求53所述的方法，其中将所述蛋白质和所述一种或多种附加活性成分配制成组合产品或组合物。

55.根据权利要求53所述的方法，其中所述蛋白质和所述一种或多种附加活性成分是单独的组分。

56.根据权利要求53所述的方法，其中混合所述蛋白质和所述一种或多种附加活性成分。

57.根据权利要求53所述的方法，其中所述蛋白质和所述一种或多种附加活性成分被配置用于共同施用，其中共同施用包括：同时施用；或不同的施用，优选间隔一段时间。

58.根据权利要求53所述的方法，其中所述一种或多种附加活性成分选自药物、抗体、激素、放射性造影剂、医药或组合物。

59.根据权利要求52或53所述的方法，其中所述病症包括：急性肾小管坏死(ATN)、肾炎、急性过敏性间质性肾炎(AAIN)、肾小球肾炎和/或肾毒性；或AKI至少部分来自肾移植或其他手术、急性肾小管坏死(ATN)、肾炎、急性过敏性间质性肾炎(AAIN)、肾小球肾炎、肾毒性或低血压。

60.根据权利要求52或53所述的方法，其中所述肾毒性包括药物诱导的肾毒性。

61.根据权利要求60所述的方法，其中所述药物诱导的肾毒性包括抗微生物剂诱导的肾毒性。

62.根据权利要求60所述的方法，其中所述药物诱导的肾毒性包括氨基糖苷类诱导的肾毒性。

63.根据权利要求52或53所述的方法，其中施用步骤包括选自以下的一个或多个步骤：确定受试者中的血清可溶性Klotho水平；计算足以将受试者中血清可溶性Klotho水平升高至预定水平或正常水平百分比的所述蛋白质的第一剂量；向受试者施用第一剂量的蛋白质，优选通过推注或逐渐施用，更优选通过注射；确定受试者血清中可溶性Klotho下降的速率，优选在施用第一剂量后；计算蛋白质后续剂量的时间和/或量；根据计算的时间和/或量，将后续剂量的蛋白质给予受试者。

64.根据权利要求52或53所述的方法，其中施用步骤足以使受试者的血清可溶性Klotho蛋白浓度升高和/或维持在预定水平或阈值或高于预定水平或阈值，任选地持续预定时间段。

65.根据权利要求64所述的方法，其中，所述预定水平或阈值大于、等于和/或在以下之间：每毫升血清约50、100、250、500、750、1000、1250、1500、1750、2000、2250、2500、2750、3000、3500、4000、4500、5000、5500、6000、6500、7000、7500、8000、8500、9000、9500、10000、11000、12000、13000、14000、15000、20000、25000、30000、40000、50000、75000、100000皮克可溶性Klotho蛋白质；或比血清中典型健康水平的可溶性Klotho蛋白质高约5％、10％、15％、20％、25％、30％、40％、50％、60％、70％、80％、90％、100％、150％、200％、250％、300％、400％、500％、600％、700％、800％、900％、1000％、1200％、1500％、2000％、2500％、3000％、4000％或5000％。

66.根据权利要求64所述的方法，其中所述预定时间段大于或等于约6小时、12小时、18小时、1天、2天、3天、4天、5天、6天、7天、8天。天、9天、10天、12天、14天、21天、30天、45天、60天、90天、120天、6个月、9个月、1年、2年、3年、4年、或5年。

67.根据权利要求52或53所述的方法，其中在肾移植或给予肾毒素之前；和/或肾移植或给予肾毒素后预防性地给予所述蛋白质。

68.根据权利要求67所述的方法，其中所述肾毒素包括：一种或多种氨基糖苷类，优选选自巴龙霉素、妥布霉素、庆大霉素、阿米卡星、卡那霉素和新霉素；一种或多种抗真菌剂，

优选选自两性霉素B和氟胞嘧啶;一种或多种造影剂,优选选自碘化放射性造影介质、碘与分子比为约1.5:1的高渗透压造影剂(HOCM)、碘与分子比约为3:1的低渗透压非离子造影剂(LOCM)、和碘与分子比约为6:1的等渗(等渗透性)造影剂(IOCM);一种或多种抗逆转录病毒剂,优选选自阿德福韦、西多福韦、替诺福韦和膦甲酸;一种或多种癌症(或化学)治疗剂,优选选自顺铂、卡铂、奥沙利铂、烷化剂、苯达莫司汀、环磷酰胺、异环磷酰胺、亚硝基脲、替莫唑胺、美法仑、抗肿瘤抗生素、丝裂霉素C、博来霉素、蒽环霉素抗代谢物、卡培他滨、羟基脲、甲氨蝶呤、培美曲塞、普拉曲沙、喷司他丁、氟达拉滨、克拉屈滨、吉西他滨、阿糖胞苷、长春花生物碱、拓扑替康、依托泊苷、紫杉烷类、伊立替康、来那度胺、艾日布林、三氧化二砷或伊沙唑嗪;一种或多种二膦酸盐或其衍生物,优选选自唑来膦酸盐/唑来膦酸、伊班膦酸盐、阿仑膦酸盐、阿仑膦酸盐/胆钙化醇、依替膦酸盐、利塞膦酸盐、利塞膦酸盐碳酸钙、帕米膦酸盐和替鲁膦酸盐;和/或一种或多种麻醉剂或阿片类药物,优选选自可卡因和海洛因。

69.根据权利要求52或53所述的方法,其中所述蛋白质包含:C370S,优选不含F352V,更优选含有F352;和/或H193,或H193R变体以外的其他变体。

70.一种治疗衰老个体的方法,所述衰老个体在编码Klotho蛋白的基因中具有纯合或杂合突变,所述方法包括:给予治疗浓度的与SEQ ID NO:2至SEQ ID NO:70之一具有至少85%、优选至少90%、更优选至少95%、甚至更优选至少98%、还更优选至少99%、最优选100%氨基酸序列同一性的多肽。

71.根据权利要求70所述的方法,还包括确定基因的表达水平。

72.根据权利要求71所述的方法,其中给予治疗浓度的步骤取决于基因的表达水平。

结论

尽管前面的详细描述参考特定的示例性实施方案,但本公开可以具体化为其他具体形式而不背离其精神或必要特征。因此,所描述的实施方案在所有方面都应被视为仅是说明性的而非限制性的。例如,在不脱离由所附权利要求限定的本公开的精神和范围的情况下,可以对所描述和/或示出的实施方案进行本文描述和/或示出的发明特征的各种替换、变更和/或修改,以及本文描述和/或示出的原理的附加应用,这将是相关领域的和具有本公开的技术人员想到的。这样的替换、改变和/或修改在本公开的范围内予以考虑。

因此,本发明的范围由所附权利要求而不是前面的描述表示。权利要求中记载的限制应基于权利要求中采用的语言广义地解释,并且不限于前述详细描述中描述的具体实例,这些实例应被解释为非排他性的且非穷举性的。在权利要求的含义和等同范围内的所有变化都包含在其范围内。

还应当理解,某些实施方案的各种特征可以与本公开的其他实施方案兼容、组合、包括在其中和/或并入本公开的其他实施方案中。例如,根据本公开的某些实施方案的系统、方法和/或产品可以包括、结合或以其他方式包括在本文公开和/或描述的其他实施方案中描述的特征。因此,相对于本公开的特定实施方案的某些特征的公开不应被解释为限制所述特征应用或包含到该特定实施方案。

另外,除非在特定实施方案中描述了特征为必需的,否则在各个实施方案中描述的特征可以是可选的,并且可以不包括在本公开的其他实施方案中。此外,除非将特征描述为需要与其组合的另一特征,否则本文的任何特征可与本文公开的相同或不同实施方案的任何其他特征组合。应当理解,虽然在某些实施方案中特征可以是可选的,但是当在这样的实施

方案中包括特征时，可以要求它们具有如本公开中描述的特定配置。

同样，本文中所描述和/或权利要求中陈述的任何方法或过程中所述的任何步骤可以以任何合适的顺序来执行，并且不必限于所描述和/或陈述的顺序，除非另有说明(明确地或隐含地)。然而，在本公开的某些实施方案中，还可以要求以特定顺序或任何合适的顺序执行这些步骤。

此外，这里没有特别详细地描述说明性系统、方法、产品等的各种公知方面，以避免模糊示例实施方案的各方面。然而，这些方面也在本文中考虑。

序列表

<110> WNT治疗公司(WNT Therapeutics, Inc.)

约瑟夫 F.塔斯索(Tarsio, Joseph F.)

<120> 治疗性重组KLOTHO蛋白及其组合物和方法

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Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln
35 40 45

Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60

Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80

Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95

Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110

His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125

Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140

Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160

Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175

Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190

His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205

Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220

Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu

225 230 235 240
Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255
Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270
Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285
Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
290 295 300
Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305 310 315 320
Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335
Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350
Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365
Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380
Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385 390 395 400
Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415
Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430
Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445
Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460
Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480
Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495
Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
500 505 510
Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp
515 520 525
Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala
530 535 540

Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
545 550 555 560
Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
565 570 575
Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
580 585 590
Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met
595 600 605
Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
610 615 620
Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
625 630 635 640
Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu
645 650 655
Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
660 665 670
Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
675 680 685
Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
690 695 700
Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
705 710 715 720
Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
725 730 735
Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
740 745 750
Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765
Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780
Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800
Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
805 810 815
Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
820 825 830
Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
835 840 845
Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu

850 855 860
Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
865 870 875 880
Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
885 890 895
Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
900 905 910
Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
915 920 925
Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His
930 935 940
Thr Arg Lys Ser
945

<210> 5
<211> 946
<212> PRT
<213> 智人(Homo sapiens)
<400> 5
Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro Pro Ala Pro
1 5 10 15
Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe Leu Trp
20 25 30
Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His
35 40 45
Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala
50 55 60
Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser
65 70 75 80
Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn
85 90 95
Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr
100 105 110
Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly
115 120 125
Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg
130 135 140
Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp Asp
145 150 155 160
Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala

165 170 175
Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe
180 185 190
Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val
195 200 205
Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly
210 215 220
Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala His
225 230 235 240
Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly
245 250 255
Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg
260 265 270
Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val
275 280 285
Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu
290 295 300
Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser
305 310 315 320
Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Cys Phe
325 330 335
Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg
340 345 350
Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu
355 360 365
Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val
370 375 380
Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys
385 390 395 400
Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp
405 410 415
Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His
420 425 430
Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser
435 440 445
Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys
450 455 460
Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu
465 470 475 480

Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr
485 490 495
Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr
500 505 510
Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp Gly Val
515 520 525
Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln
530 535 540
Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe Arg Phe
545 550 555 560
Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln Val
565 570 575
Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val
580 585 590
Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met Ala Pro
595 600 605
Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn
610 615 620
Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln
625 630 635 640
Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr
645 650 655
Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys Ala His
660 665 670
Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala Gln Asn
675 680 685
Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys
690 695 700
Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu Glu Phe
705 710 715 720
Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro
725 730 735
Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro
740 745 750
Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe
755 760 765
Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu Lys Glu
770 775 780
Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met Thr Asp

785 790 795 800
Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro Trp Gly
805 810 815
Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp Leu Pro
820 825 830
Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala Glu Asp
835 840 845
Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu Ala Leu
850 855 860
Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe Ala Tyr
865 870 875 880
Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg Tyr Ala
885 890 895
Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg Lys Ile
900 905 910
Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg Phe Cys
915 920 925
Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His Thr Arg
930 935 940
Lys Ser
945

<210> 6
<211> 851
<212> PRT
<213> 智人(Homo sapiens)
<400> 6
Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His
1 5 10 15
Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala
20 25 30
Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu
35 40 45
Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp
50 55 60
Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg
65 70 75 80
Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His
85 90 95
Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val

100 105 110

Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg

115 120 125

Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala

130 135 140

His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln

145 150 155 160

Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg

165 170 175

Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe

180 185 190

Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro

195 200 205

Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu

210 215 220

Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Cys

225 230 235 240

Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe

245 250 255

Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp

260 265 270

Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe

275 280 285

Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu

290 295 300

Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val

305 310 315 320

Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp

325 330 335

His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu

340 345 350

Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln

355 360 365

Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro

370 375 380

Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn

385 390 395 400

Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn Val

405 410 415

Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp Gly
420 425 430
Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile
435 440 445
Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe Arg
450 455 460
Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln
465 470 475 480
Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu
485 490 495
Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met Ala
500 505 510
Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu
515 520 525
Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe
530 535 540
Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu Pro
545 550 555 560
Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys Ala
565 570 575
His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala Gln
580 585 590
Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala
595 600 605
Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu Glu
610 615 620
Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp Tyr
625 630 635 640
Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu
645 650 655
Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe Asp
660 665 670
Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu Lys
675 680 685
Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met Thr
690 695 700
Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro Trp
705 710 715 720
Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp Leu

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

<210> 7
<211> 549
<212> PRT
<213> 智人(Homo sapiens)
<400> 7
Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1 5 10 15
Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg
20 25 30
Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
35 40 45
Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60
Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80
Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95
Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110
Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125
Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val

130 135 140
Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160
Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175
Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190
His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
195 200 205
Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
210 215 220
Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225 230 235 240
Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
245 250 255
Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
260 265 270
Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
275 280 285
Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
290 295 300
Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305 310 315 320
Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
325 330 335
Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
340 345 350
Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
355 360 365
Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
370 375 380
Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385 390 395 400
Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
405 410 415
Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
420 425 430
Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
435 440 445

Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
450 455 460
Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465 470 475 480
Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495
Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510
Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525
Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540
Asn Val Tyr Leu Trp
545

<210> 8
<211> 521
<212> PRT
<213> 智人(Homo sapiens)
<400> 8

Arg Arg Leu Arg Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg
1 5 10 15
Phe Ser Arg Pro Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr
20 25 30
Phe Pro Asp Gly Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr
35 40 45
Glu Gly Gly Trp Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr
50 55 60
Phe Thr His His Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser
65 70 75 80
Leu Pro Leu Gly Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val
85 90 95
Ala Ser Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg
100 105 110
Glu Leu Gly Val Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val
115 120 125
Leu Pro Asn Gly Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr
130 135 140
Tyr Arg Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val
145 150 155 160

Val Thr Leu Tyr His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr
165 170 175
Gly Gly Trp Ala Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala
180 185 190
Glu Leu Cys Phe Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr
195 200 205
Ile Asp Asn Pro Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg
210 215 220
Leu Ala Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala
225 230 235 240
His Asn Leu Leu Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr
245 250 255
Ser Phe Arg Pro Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser
260 265 270
His Trp Ile Asn Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys
275 280 285
Gln Lys Ser Leu Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe
290 295 300
Ile Asp Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile
305 310 315 320
Leu Pro Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala
325 330 335
Asp Phe Phe Ala Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu
340 345 350
Asp Pro His Met Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln
355 360 365
Leu Leu Ser Trp Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile
370 375 380
Val Glu Asn Gly Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala
385 390 395 400
Lys Tyr Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala
405 410 415
Ile Lys Leu Asp Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu
420 425 430
Met Asp Gly Phe Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu
435 440 445
Phe Tyr Val Asp Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser
450 455 460
Ser Ala Leu Phe Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro

465 470 475 480
Leu Pro Glu Asn Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala
485 490 495
Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln
500 505 510
Phe Thr Asp Leu Asn Val Tyr Leu Trp
515 520

<210> 9
<211> 516
<212> PRT
<213> 智人(Homo sapiens)
<400> 9
Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro Pro
1 5 10 15
Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe
20 25 30
Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln
35 40 45
Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60
Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80
Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95
Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110
His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125
Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140
Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160
Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175
Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190
His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205
Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile

210 215 220

Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240

Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255

Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270

Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285

Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
290 295 300

Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305 310 315 320

Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335

Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350

Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365

Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380

Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385 390 395 400

Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415

Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430

Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445

Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460

Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480

Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495

Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
500 505 510

Val Tyr Leu Trp
515

<210> 10
<211> 514
<212> PRT
<213> 智人(Homo sapiens)
<400> 10

Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro Pro Ala Pro
1 5 10 15
Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe Leu Trp
20 25 30
Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His
35 40 45
Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala
50 55 60
Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser
65 70 75 80
Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn
85 90 95
Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr
100 105 110
Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly
115 120 125
Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg
130 135 140
Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp Asp
145 150 155 160
Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala
165 170 175
Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe
180 185 190
Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val
195 200 205
Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly
210 215 220
Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala His
225 230 235 240
Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly
245 250 255
Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg
260 265 270

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

<210> 11
<211> 419
<212> PRT
<213> 智人(Homo sapiens)
<400> 11

Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His
1 5 10 15
Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala

20 25 30

Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu

35 40 45

Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp

50 55 60

Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg

65 70 75 80

Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His

85 90 95

Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val

100 105 110

Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg

115 120 125

Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala

130 135 140

His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln

145 150 155 160

Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg

165 170 175

Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe

180 185 190

Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro

195 200 205

Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu

210 215 220

Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Cys

225 230 235 240

Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe

245 250 255

Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp

260 265 270

Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe

275 280 285

Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu

290 295 300

Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val

305 310 315 320

Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp

325 330 335

His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu
340 345 350
Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln
355 360 365
Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro
370 375 380
Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn
385 390 395 400
Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn Val
405 410 415
Tyr Leu Trp

<210> 12
<211> 981
<212> PRT
<213> 智人(Homo sapiens)
<400> 12

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1 5 10 15
Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg
20 25 30
Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
35 40 45
Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60
Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80
Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95
Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110
Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125
Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140
Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160
Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175
Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr

180 185 190

His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala

195 200 205

Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe

210 215 220

Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro

225 230 235 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly

245 250 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu

260 265 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro

275 280 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn

290 295 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu

305 310 315 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp

325 330 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe

340 345 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala

355 360 365

Leu Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met

370 375 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp

385 390 395 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly

405 410 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr

420 425 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp

435 440 445

Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe

450 455 460

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp

465 470 475 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe

485 490 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510
Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525
Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540
Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545 550 555 560
Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
565 570 575
Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
580 585 590
Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
595 600 605
Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
610 615 620
Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
625 630 635 640
Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
645 650 655
Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
660 665 670
Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
675 680 685
Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
690 695 700
Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
705 710 715 720
Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
725 730 735
Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
740 745 750
Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
755 760 765
Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
770 775 780
Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
785 790 795 800
Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser

805 810 815
Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
820 825 830
Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
835 840 845
Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
850 855 860
Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
865 870 875 880
Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
885 890 895
Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
900 905 910
Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
915 920 925
Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
930 935 940
Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945 950 955 960
Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
965 970 975
His Thr Arg Lys Ser
980

<210> 13
<211> 953
<212> PRT
<213> 智人(Homo sapiens)
<400> 13
Arg Arg Leu Arg Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg
1 5 10 15
Phe Ser Arg Pro Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr
20 25 30
Phe Pro Asp Gly Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr
35 40 45
Glu Gly Gly Trp Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr
50 55 60
Phe Thr His His Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser
65 70 75 80
Leu Pro Leu Gly Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val

85 90 95

Ala Ser Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg
100 105 110

Glu Leu Gly Val Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val
115 120 125

Leu Pro Asn Gly Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr
130 135 140

Tyr Arg Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val
145 150 155 160

Val Thr Leu Tyr His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr
165 170 175

Gly Gly Trp Ala Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala
180 185 190

Glu Leu Cys Phe Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr
195 200 205

Ile Asp Asn Pro Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg
210 215 220

Leu Ala Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala
225 230 235 240

His Asn Leu Leu Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr
245 250 255

Ser Phe Arg Pro Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser
260 265 270

His Trp Ile Asn Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys
275 280 285

Gln Lys Ser Leu Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe
290 295 300

Ile Asp Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile
305 310 315 320

Leu Pro Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala
325 330 335

Asp Phe Phe Ala Leu Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu
340 345 350

Asp Pro His Met Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln
355 360 365

Leu Leu Ser Trp Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile
370 375 380

Val Glu Asn Gly Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala
385 390 395 400

Lys Tyr Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala
405 410 415
Ile Lys Leu Asp Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu
420 425 430
Met Asp Gly Phe Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu
435 440 445
Phe Tyr Val Asp Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser
450 455 460
Ser Ala Leu Phe Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro
465 470 475 480
Leu Pro Glu Asn Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala
485 490 495
Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln
500 505 510
Phe Thr Asp Leu Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg
515 520 525
Leu Ile Lys Val Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys
530 535 540
Val Asp Phe Ala Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met
545 550 555 560
His Val Thr His Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro
565 570 575
Leu Gly Asn Gln Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg
580 585 590
Cys Met Ala Ser Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala
595 600 605
Leu Trp Gln Pro Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala
610 615 620
Arg Gln Gly Ala Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu
625 630 635 640
Tyr Ala Arg Leu Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp
645 650 655
Ile Thr Met Asn Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly
660 665 670
His Asn Leu Leu Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu
675 680 685
Lys Phe Arg His Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala
690 695 700
Asp Trp Ile Glu Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val

705 710 715 720
Ala Glu Arg Val Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile
725 730 735
Phe Gly Ser Gly Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln
740 745 750
Arg Asn Asn Phe Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu
755 760 765
Ile Gln Gly Thr Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile
770 775 780
Leu Val Asp Ser Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu
785 790 795 800
Glu Val Gln Glu Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln
805 810 815
Val Ala Val Val Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys
820 825 830
Phe Lys Tyr Gly Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp
835 840 845
Asp Gly Leu His Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln
850 855 860
Asn Tyr Ile Asn Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn
865 870 875 880
Leu Cys Gly Tyr Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg
885 890 895
Phe Gly Leu Tyr Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser
900 905 910
Met Lys His Tyr Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro
915 920 925
Glu Thr Leu Glu Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu
930 935 940
Cys Ser Phe Phe His Thr Arg Lys Ser
945 950

<210> 14
<211> 948
<212> PRT
<213> 智人(Homo sapiens)
<400> 14
Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro Pro
1 5 10 15
Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe

20 25 30

Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln
35 40 45

Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60

Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80

Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95

Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110

His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125

Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140

Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160

Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175

Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190

His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205

Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220

Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240

Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255

Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270

Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285

Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
290 295 300

Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305 310 315 320

Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335

Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350
Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365
Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380
Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385 390 395 400
Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415
Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430
Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445
Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460
Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480
Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495
Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
500 505 510
Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp
515 520 525
Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala
530 535 540
Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
545 550 555 560
Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
565 570 575
Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
580 585 590
Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met
595 600 605
Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
610 615 620
Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
625 630 635 640
Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu

645 650 655
Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
660 665 670
Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
675 680 685
Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
690 695 700
Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
705 710 715 720
Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
725 730 735
Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
740 745 750
Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765
Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780
Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800
Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
805 810 815
Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
820 825 830
Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
835 840 845
Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
850 855 860
Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
865 870 875 880
Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
885 890 895
Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
900 905 910
Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
915 920 925
Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His
930 935 940
Thr Arg Lys Ser
945

<210> 15
<211> 946
<212> PRT
<213> 智人(Homo sapiens)
<400> 15

Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro Pro Ala Pro
1 5 10 15
Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe Leu Trp
20 25 30
Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His
35 40 45
Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala
50 55 60
Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser
65 70 75 80
Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn
85 90 95
Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr
100 105 110
Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly
115 120 125
Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg
130 135 140
Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp Asp
145 150 155 160
Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala
165 170 175
Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe
180 185 190
Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val
195 200 205
Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly
210 215 220
Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala His
225 230 235 240
Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly
245 250 255
Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg
260 265 270

Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val
275 280 285
Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu
290 295 300
Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser
305 310 315 320
Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Ser Phe
325 330 335
Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg
340 345 350
Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu
355 360 365
Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val
370 375 380
Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys
385 390 395 400
Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp
405 410 415
Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His
420 425 430
Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser
435 440 445
Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys
450 455 460
Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu
465 470 475 480
Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr
485 490 495
Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr
500 505 510
Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp Gly Val
515 520 525
Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln
530 535 540
Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe Arg Phe
545 550 555 560
Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln Val
565 570 575
Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val

580 585 590
Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met Ala Pro
595 600 605
Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn
610 615 620
Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln
625 630 635 640
Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr
645 650 655
Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys Ala His
660 665 670
Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala Gln Asn
675 680 685
Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys
690 695 700
Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu Glu Phe
705 710 715 720
Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro
725 730 735
Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro
740 745 750
Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe
755 760 765
Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu Lys Glu
770 775 780
Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met Thr Asp
785 790 795 800
Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro Trp Gly
805 810 815
Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp Leu Pro
820 825 830
Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala Glu Asp
835 840 845
Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu Ala Leu
850 855 860
Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe Ala Tyr
865 870 875 880
Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg Tyr Ala
885 890 895

Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg Lys Ile
900 905 910
Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg Phe Cys
915 920 925
Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His Thr Arg
930 935 940
Lys Ser
945

<210> 16
<211> 851
<212> PRT
<213> 智人(Homo sapiens)
<400> 16

Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His
1 5 10 15
Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala
20 25 30
Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu
35 40 45
Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp
50 55 60
Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg
65 70 75 80
Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His
85 90 95
Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val
100 105 110
Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg
115 120 125
Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala
130 135 140
His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln
145 150 155 160
Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg
165 170 175
Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe
180 185 190
Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro
195 200 205

Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu
210 215 220
Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Ser
225 230 235 240
Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe
245 250 255
Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp
260 265 270
Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe
275 280 285
Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu
290 295 300
Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val
305 310 315 320
Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp
325 330 335
His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu
340 345 350
Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln
355 360 365
Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro
370 375 380
Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn
385 390 395 400
Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn Val
405 410 415
Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp Gly
420 425 430
Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile
435 440 445
Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe Arg
450 455 460
Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln
465 470 475 480
Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu
485 490 495
Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met Ala
500 505 510
Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu

515 520 525

Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe

530 535 540

Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu Pro

545 550 555 560

Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys Ala

565 570 575

His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala Gln

580 585 590

Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala

595 600 605

Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu Glu

610 615 620

Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp Tyr

625 630 635 640

Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu

645 650 655

Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe Asp

660 665 670

Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu Lys

675 680 685

Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met Thr

690 695 700

Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro Trp

705 710 715 720

Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp Leu

725 730 735

Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala Glu

740 745 750

Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu Ala

755 760 765

Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe Ala

770 775 780

Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg Tyr

785 790 795 800

Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg Lys

805 810 815

Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg Phe

820 825 830

Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His Thr
835 840 845
Arg Lys Ser
850

<210> 17
<211> 549
<212> PRT
<213> 智人(Homo sapiens)
<400> 17

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1 5 10 15
Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg
20 25 30
Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
35 40 45
Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60
Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80
Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95
Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110
Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125
Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140
Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160
Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175
Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190
His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
195 200 205
Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
210 215 220
Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225 230 235 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
245 250 255
Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
260 265 270
Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
275 280 285
Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
290 295 300
Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305 310 315 320
Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
325 330 335
Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
340 345 350
Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
355 360 365
Leu Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
370 375 380
Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385 390 395 400
Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
405 410 415
Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
420 425 430
Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
435 440 445
Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
450 455 460
Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465 470 475 480
Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495
Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510
Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525
Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540
Asn Val Tyr Leu Trp

545

<210> 18

<211> 521

<212> PRT

<213> 智人(Homo sapiens)

<400> 18

Arg Arg Leu Arg Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg
1 5 10 15

Phe Ser Arg Pro Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr
20 25 30

Phe Pro Asp Gly Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr
35 40 45

Glu Gly Gly Trp Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr
50 55 60

Phe Thr His His Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser
65 70 75 80

Leu Pro Leu Gly Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val
85 90 95

Ala Ser Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg
100 105 110

Glu Leu Gly Val Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val
115 120 125

Leu Pro Asn Gly Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr
130 135 140

Tyr Arg Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val
145 150 155 160

Val Thr Leu Tyr His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr
165 170 175

Gly Gly Trp Ala Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala
180 185 190

Glu Leu Cys Phe Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr
195 200 205

Ile Asp Asn Pro Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg
210 215 220

Leu Ala Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala
225 230 235 240

His Asn Leu Leu Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr
245 250 255

Ser Phe Arg Pro Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser

260 265 270

His Trp Ile Asn Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys
275 280 285

Gln Lys Ser Leu Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe
290 295 300

Ile Asp Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile
305 310 315 320

Leu Pro Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala
325 330 335

Asp Phe Phe Ala Leu Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu
340 345 350

Asp Pro His Met Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln
355 360 365

Leu Leu Ser Trp Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile
370 375 380

Val Glu Asn Gly Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala
385 390 395 400

Lys Tyr Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala
405 410 415

Ile Lys Leu Asp Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu
420 425 430

Met Asp Gly Phe Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu
435 440 445

Phe Tyr Val Asp Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser
450 455 460

Ser Ala Leu Phe Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro
465 470 475 480

Leu Pro Glu Asn Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala
485 490 495

Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln
500 505 510

Phe Thr Asp Leu Asn Val Tyr Leu Trp
515 520

<210> 19

<211> 516

<212> PRT

<213> 智人(Homo sapiens)

<400> 19

Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro Pro

1 5 10 15
Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe
20 25 30
Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln
35 40 45
Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60
Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80
Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95
Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110
His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125
Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140
Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160
Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175
Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190
His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205
Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220
Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240
Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255
Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270
Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285
Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
290 295 300
Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305 310 315 320

Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335
Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350
Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365
Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380
Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385 390 395 400
Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415
Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430
Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445
Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460
Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480
Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495
Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
500 505 510
Val Tyr Leu Trp
515

<210> 20
<211> 514
<212> PRT
<213> 智人(Homo sapiens)
<400> 20

Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro Pro Ala Pro
1 5 10 15
Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe Leu Trp
20 25 30
Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His
35 40 45
Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala
50 55 60

Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser
65 70 75 80
Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn
85 90 95
Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr
100 105 110
Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly
115 120 125
Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg
130 135 140
Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp Asp
145 150 155 160
Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala
165 170 175
Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe
180 185 190
Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val
195 200 205
Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly
210 215 220
Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala His
225 230 235 240
Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly
245 250 255
Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg
260 265 270
Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val
275 280 285
Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu
290 295 300
Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser
305 310 315 320
Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Ser Phe
325 330 335
Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg
340 345 350
Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu
355 360 365
Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val

370 375 380
Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys
385 390 395 400
Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp
405 410 415
Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His
420 425 430
Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser
435 440 445
Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys
450 455 460
Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu
465 470 475 480
Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr
485 490 495
Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr
500 505 510
Leu Trp

<210> 21
<211> 419
<212> PRT
<213> 智人(Homo sapiens)
<400> 21
Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His
1 5 10 15
Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala
20 25 30
Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu
35 40 45
Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp
50 55 60
Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg
65 70 75 80
Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His
85 90 95
Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val
100 105 110
Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg
115 120 125

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

<210> 22

<211> 1012

<212> PRT

<213> 智人(Homo sapiens)

<400> 22

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1 5 10 15
Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg
20 25 30
Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Val Ser Arg Pro
35 40 45
Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60
Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80
Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95
Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110
Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125
Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140
Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160
Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175
Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190
His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
195 200 205
Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
210 215 220
Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225 230 235 240
Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
245 250 255
Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
260 265 270
Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
275 280 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
290 295 300
Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305 310 315 320
Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
325 330 335
Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
340 345 350
Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
355 360 365
Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
370 375 380
Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385 390 395 400
Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
405 410 415
Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
420 425 430
Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
435 440 445
Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
450 455 460
Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465 470 475 480
Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495
Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510
Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525
Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540
Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545 550 555 560
Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
565 570 575
Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
580 585 590
Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln

595 600 605

Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser

610 615 620

Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro

625 630 635 640

Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala

645 650 655

Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu

660 665 670

Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn

675 680 685

Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu

690 695 700

Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His

705 710 715 720

Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu

725 730 735

Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val

740 745 750

Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly

755 760 765

Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe

770 775 780

Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr

785 790 795 800

Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser

805 810 815

Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu

820 825 830

Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val

835 840 845

Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly

850 855 860

Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His

865 870 875 880

Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn

885 890 895

Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr

900 905 910

Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
915 920 925
Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
930 935 940
Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945 950 955 960
Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
965 970 975
His Thr Arg Lys Ser Leu Leu Ala Phe Ile Ala Phe Leu Phe Phe Ala
980 985 990
Ser Ile Ile Ser Leu Ser Leu Ile Phe Tyr Tyr Ser Lys Lys Gly Arg
995 1000 1005
Arg Ser Tyr Lys
1010

<210> 23
<211> 981
<212> PRT
<213> 智人(Homo sapiens)
<400> 23

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Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg
20 25 30
Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Val Ser Arg Pro
35 40 45
Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60
Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80
Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95
Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110
Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125
Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140
Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160

Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175
Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190
His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
195 200 205
Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
210 215 220
Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225 230 235 240
Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
245 250 255
Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
260 265 270
Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
275 280 285
Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
290 295 300
Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305 310 315 320
Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
325 330 335
Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
340 345 350
Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
355 360 365
Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
370 375 380
Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385 390 395 400
Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
405 410 415
Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
420 425 430
Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
435 440 445
Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
450 455 460
Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp

465 470 475 480
Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495
Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510
Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525
Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540
Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545 550 555 560
Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
565 570 575
Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
580 585 590
Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
595 600 605
Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
610 615 620
Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
625 630 635 640
Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
645 650 655
Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
660 665 670
Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
675 680 685
Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
690 695 700
Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
705 710 715 720
Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
725 730 735
Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
740 745 750
Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
755 760 765
Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
770 775 780

Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
785 790 795 800
Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
805 810 815
Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
820 825 830
Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
835 840 845
Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
850 855 860
Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
865 870 875 880
Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
885 890 895
Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
900 905 910
Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
915 920 925
Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
930 935 940
Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945 950 955 960
Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
965 970 975
His Thr Arg Lys Ser
980

<210> 24
<211> 953
<212> PRT
<213> 智人(Homo sapiens)
<400> 24
Arg Arg Leu Arg Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg
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Val Ser Arg Pro Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr
20 25 30
Phe Pro Asp Gly Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr
35 40 45
Glu Gly Gly Trp Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr
50 55 60

Phe Thr His His Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser
65 70 75 80
Leu Pro Leu Gly Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val
85 90 95
Ala Ser Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg
100 105 110
Glu Leu Gly Val Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val
115 120 125
Leu Pro Asn Gly Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr
130 135 140
Tyr Arg Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val
145 150 155 160
Val Thr Leu Tyr His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr
165 170 175
Gly Gly Trp Ala Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala
180 185 190
Glu Leu Cys Phe Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr
195 200 205
Ile Asp Asn Pro Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg
210 215 220
Leu Ala Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala
225 230 235 240
His Asn Leu Leu Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr
245 250 255
Ser Phe Arg Pro Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser
260 265 270
His Trp Ile Asn Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys
275 280 285
Gln Lys Ser Leu Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe
290 295 300
Ile Asp Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile
305 310 315 320
Leu Pro Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala
325 330 335
Asp Phe Phe Ala Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu
340 345 350
Asp Pro His Met Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln
355 360 365
Leu Leu Ser Trp Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile

370 375 380

Val Glu Asn Gly Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala
385 390 395 400

Lys Tyr Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala
405 410 415

Ile Lys Leu Asp Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu
420 425 430

Met Asp Gly Phe Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu
435 440 445

Phe Tyr Val Asp Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser
450 455 460

Ser Ala Leu Phe Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro
465 470 475 480

Leu Pro Glu Asn Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala
485 490 495

Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln
500 505 510

Phe Thr Asp Leu Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg
515 520 525

Leu Ile Lys Val Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys
530 535 540

Val Asp Phe Ala Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met
545 550 555 560

His Val Thr His Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro
565 570 575

Leu Gly Asn Gln Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg
580 585 590

Cys Met Ala Ser Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala
595 600 605

Leu Trp Gln Pro Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala
610 615 620

Arg Gln Gly Ala Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu
625 630 635 640

Tyr Ala Arg Leu Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp
645 650 655

Ile Thr Met Asn Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly
660 665 670

His Asn Leu Leu Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu
675 680 685

Lys Phe Arg His Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala
690 695 700
Asp Trp Ile Glu Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val
705 710 715 720
Ala Glu Arg Val Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile
725 730 735
Phe Gly Ser Gly Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln
740 745 750
Arg Asn Asn Phe Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu
755 760 765
Ile Gln Gly Thr Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile
770 775 780
Leu Val Asp Ser Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu
785 790 795 800
Glu Val Gln Glu Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln
805 810 815
Val Ala Val Val Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys
820 825 830
Phe Lys Tyr Gly Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp
835 840 845
Asp Gly Leu His Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln
850 855 860
Asn Tyr Ile Asn Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn
865 870 875 880
Leu Cys Gly Tyr Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg
885 890 895
Phe Gly Leu Tyr Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser
900 905 910
Met Lys His Tyr Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro
915 920 925
Glu Thr Leu Glu Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu
930 935 940
Cys Ser Phe Phe His Thr Arg Lys Ser
945 950

<210> 25
<211> 948
<212> PRT
<213> 智人(Homo sapiens)
<400> 25

Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Val Ser Arg Pro Pro
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Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe
20 25 30
Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln
35 40 45
Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60
Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80
Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95
Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110
His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125
Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140
Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160
Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175
Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190
His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205
Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220
Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240
Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255
Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270
Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285
Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
290 295 300
Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr

305 310 315 320
Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335
Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350
Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365
Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380
Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385 390 395 400
Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415
Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430
Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445
Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460
Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480
Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495
Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
500 505 510
Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp
515 520 525
Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala
530 535 540
Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
545 550 555 560
Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
565 570 575
Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
580 585 590
Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met
595 600 605
Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
610 615 620

Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
625 630 635 640
Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu
645 650 655
Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
660 665 670
Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
675 680 685
Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
690 695 700
Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
705 710 715 720
Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
725 730 735
Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
740 745 750
Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765
Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780
Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800
Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
805 810 815
Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
820 825 830
Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
835 840 845
Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
850 855 860
Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
865 870 875 880
Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
885 890 895
Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
900 905 910
Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
915 920 925
Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His

930 935 940

Thr Arg Lys Ser
945

<210> 26
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<212> PRT
<213> 智人(Homo sapiens)
<400> 26

Gly Asp Gly Ala Gln Thr Trp Ala Arg Val Ser Arg Pro Pro Ala Pro
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Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe Leu Trp
20 25 30
Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His
35 40 45
Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala
50 55 60
Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser
65 70 75 80
Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn
85 90 95
Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr
100 105 110
Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly
115 120 125
Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg
130 135 140
Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp Asp
145 150 155 160
Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala
165 170 175
Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe
180 185 190
Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val
195 200 205
Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly
210 215 220
Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala His
225 230 235 240
Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly

245 250 255
Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg
260 265 270
Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val
275 280 285
Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu
290 295 300
Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser
305 310 315 320
Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Cys Phe
325 330 335
Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg
340 345 350
Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu
355 360 365
Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val
370 375 380
Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys
385 390 395 400
Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp
405 410 415
Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His
420 425 430
Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser
435 440 445
Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys
450 455 460
Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu
465 470 475 480
Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr
485 490 495
Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr
500 505 510
Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp Gly Val
515 520 525
Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln
530 535 540
Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe Arg Phe
545 550 555 560

Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln Val
565 570 575
Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val
580 585 590
Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met Ala Pro
595 600 605
Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn
610 615 620
Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln
625 630 635 640
Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr
645 650 655
Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys Ala His
660 665 670
Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala Gln Asn
675 680 685
Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys
690 695 700
Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu Glu Phe
705 710 715 720
Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro
725 730 735
Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro
740 745 750
Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe
755 760 765
Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu Lys Glu
770 775 780
Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met Thr Asp
785 790 795 800
Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro Trp Gly
805 810 815
Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp Leu Pro
820 825 830
Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala Glu Asp
835 840 845
Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu Ala Leu
850 855 860
Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe Ala Tyr

865 870 875 880
Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg Tyr Ala
885 890 895
Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg Lys Ile
900 905 910
Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg Phe Cys
915 920 925
Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His Thr Arg
930 935 940
Lys Ser
945

<210> 27
<211> 549
<212> PRT
<213> 智人(Homo sapiens)
<400> 27
Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
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Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg
20 25 30
Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Val Ser Arg Pro
35 40 45
Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60
Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80
Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95
Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110
Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125
Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140
Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160
Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175
Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr

180 185 190

His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala

195 200 205

Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe

210 215 220

Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro

225 230 235 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly

245 250 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu

260 265 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro

275 280 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn

290 295 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu

305 310 315 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp

325 330 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe

340 345 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala

355 360 365

Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met

370 375 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp

385 390 395 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly

405 410 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr

420 425 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp

435 440 445

Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe

450 455 460

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp

465 470 475 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe

485 490 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510
Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525
Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540
Asn Val Tyr Leu Trp
545

<210> 28
<211> 521
<212> PRT
<213> 智人(Homo sapiens)
<400> 28

Arg Arg Leu Arg Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg
1 5 10 15
Val Ser Arg Pro Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr
20 25 30
Phe Pro Asp Gly Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr
35 40 45
Glu Gly Gly Trp Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr
50 55 60
Phe Thr His His Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser
65 70 75 80
Leu Pro Leu Gly Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val
85 90 95
Ala Ser Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg
100 105 110
Glu Leu Gly Val Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val
115 120 125
Leu Pro Asn Gly Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr
130 135 140
Tyr Arg Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val
145 150 155 160
Val Thr Leu Tyr His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr
165 170 175
Gly Gly Trp Ala Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala
180 185 190
Glu Leu Cys Phe Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr
195 200 205

Ile Asp Asn Pro Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg
210 215 220
Leu Ala Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala
225 230 235 240
His Asn Leu Leu Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr
245 250 255
Ser Phe Arg Pro Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser
260 265 270
His Trp Ile Asn Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys
275 280 285
Gln Lys Ser Leu Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe
290 295 300
Ile Asp Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile
305 310 315 320
Leu Pro Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala
325 330 335
Asp Phe Phe Ala Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu
340 345 350
Asp Pro His Met Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln
355 360 365
Leu Leu Ser Trp Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile
370 375 380
Val Glu Asn Gly Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala
385 390 395 400
Lys Tyr Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala
405 410 415
Ile Lys Leu Asp Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu
420 425 430
Met Asp Gly Phe Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu
435 440 445
Phe Tyr Val Asp Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser
450 455 460
Ser Ala Leu Phe Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro
465 470 475 480
Leu Pro Glu Asn Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala
485 490 495
Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln
500 505 510
Phe Thr Asp Leu Asn Val Tyr Leu Trp

515 520

<210> 29

<211> 516

<212> PRT

<213> 智人(Homo sapiens)

<400> 29

Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Val Ser Arg Pro Pro
1 5 10 15
Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe
20 25 30
Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln
35 40 45
Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60
Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80
Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95
Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110
His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125
Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140
Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160
Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175
Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190
His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205
Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220
Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240
Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255
Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro

260 265 270

Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp

275 280 285

Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr

290 295 300

Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr

305 310 315 320

Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu

325 330 335

Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys

340 345 350

Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile

355 360 365

Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp

370 375 380

Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr

385 390 395 400

Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly

405 410 415

Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu

420 425 430

Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe

435 440 445

Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr

450 455 460

Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln

465 470 475 480

Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp

485 490 495

Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn

500 505 510

Val Tyr Leu Trp

515

<210> 30

<211> 514

<212> PRT

<213> 智人(Homo sapiens)

<400> 30

Gly Asp Gly Ala Gln Thr Trp Ala Arg Val Ser Arg Pro Pro Ala Pro

1 5 10 15
Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe Leu Trp
20 25 30
Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His
35 40 45
Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala
50 55 60
Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser
65 70 75 80
Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn
85 90 95
Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr
100 105 110
Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly
115 120 125
Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg
130 135 140
Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp Asp
145 150 155 160
Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala
165 170 175
Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe
180 185 190
Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val
195 200 205
Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly
210 215 220
Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala His
225 230 235 240
Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly
245 250 255
Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg
260 265 270
Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val
275 280 285
Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu
290 295 300
Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser
305 310 315 320

Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Cys Phe
325 330 335
Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg
340 345 350
Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu
355 360 365
Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val
370 375 380
Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys
385 390 395 400
Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp
405 410 415
Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His
420 425 430
Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser
435 440 445
Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys
450 455 460
Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu
465 470 475 480
Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr
485 490 495
Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr
500 505 510
Leu Trp

<210> 31
<211> 981
<212> PRT
<213> 智人(Homo sapiens)
<400> 31

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1 5 10 15
Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg
20 25 30
Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Val Ser Arg Pro
35 40 45
Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60
Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp

65 70 75 80
Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95
Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110
Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125
Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140
Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160
Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175
Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190
His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
195 200 205
Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
210 215 220
Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225 230 235 240
Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
245 250 255
Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
260 265 270
Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
275 280 285
Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
290 295 300
Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305 310 315 320
Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
325 330 335
Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
340 345 350
Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
355 360 365
Leu Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
370 375 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385 390 395 400
Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
405 410 415
Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
420 425 430
Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
435 440 445
Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
450 455 460
Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465 470 475 480
Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495
Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510
Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525
Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540
Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545 550 555 560
Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
565 570 575
Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
580 585 590
Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
595 600 605
Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
610 615 620
Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
625 630 635 640
Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
645 650 655
Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
660 665 670
Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
675 680 685
Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu

690 695 700

Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
705 710 715 720
Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
725 730 735
Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
740 745 750
Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
755 760 765
Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
770 775 780
Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
785 790 795 800
Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
805 810 815
Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
820 825 830
Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
835 840 845
Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
850 855 860
Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
865 870 875 880
Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
885 890 895
Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
900 905 910
Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
915 920 925
Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
930 935 940
Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945 950 955 960
Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
965 970 975
His Thr Arg Lys Ser
980

<210> 32

<211> 953

<212> PRT

<213> 智人(Homo sapiens)

<400> 32

Arg Arg Leu Arg Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg
1 5 10 15
Val Ser Arg Pro Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr
20 25 30
Phe Pro Asp Gly Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr
35 40 45
Glu Gly Gly Trp Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr
50 55 60
Phe Thr His His Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser
65 70 75 80
Leu Pro Leu Gly Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val
85 90 95
Ala Ser Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg
100 105 110
Glu Leu Gly Val Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val
115 120 125
Leu Pro Asn Gly Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr
130 135 140
Tyr Arg Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val
145 150 155 160
Val Thr Leu Tyr His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr
165 170 175
Gly Gly Trp Ala Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala
180 185 190
Glu Leu Cys Phe Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr
195 200 205
Ile Asp Asn Pro Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg
210 215 220
Leu Ala Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala
225 230 235 240
His Asn Leu Leu Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr
245 250 255
Ser Phe Arg Pro Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser
260 265 270
His Trp Ile Asn Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys
275 280 285

Gln Lys Ser Leu Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe
290 295 300
Ile Asp Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile
305 310 315 320
Leu Pro Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala
325 330 335
Asp Phe Phe Ala Leu Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu
340 345 350
Asp Pro His Met Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln
355 360 365
Leu Leu Ser Trp Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile
370 375 380
Val Glu Asn Gly Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala
385 390 395 400
Lys Tyr Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala
405 410 415
Ile Lys Leu Asp Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu
420 425 430
Met Asp Gly Phe Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu
435 440 445
Phe Tyr Val Asp Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser
450 455 460
Ser Ala Leu Phe Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro
465 470 475 480
Leu Pro Glu Asn Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala
485 490 495
Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln
500 505 510
Phe Thr Asp Leu Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg
515 520 525
Leu Ile Lys Val Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys
530 535 540
Val Asp Phe Ala Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met
545 550 555 560
His Val Thr His Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro
565 570 575
Leu Gly Asn Gln Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg
580 585 590
Cys Met Ala Ser Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala

595 600 605

Leu Trp Gln Pro Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala
610 615 620

Arg Gln Gly Ala Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu
625 630 635 640

Tyr Ala Arg Leu Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp
645 650 655

Ile Thr Met Asn Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly
660 665 670

His Asn Leu Leu Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu
675 680 685

Lys Phe Arg His Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala
690 695 700

Asp Trp Ile Glu Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val
705 710 715 720

Ala Glu Arg Val Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile
725 730 735

Phe Gly Ser Gly Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln
740 745 750

Arg Asn Asn Phe Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu
755 760 765

Ile Gln Gly Thr Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile
770 775 780

Leu Val Asp Ser Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu
785 790 795 800

Glu Val Gln Glu Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln
805 810 815

Val Ala Val Val Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys
820 825 830

Phe Lys Tyr Gly Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp
835 840 845

Asp Gly Leu His Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln
850 855 860

Asn Tyr Ile Asn Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn
865 870 875 880

Leu Cys Gly Tyr Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg
885 890 895

Phe Gly Leu Tyr Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser
900 905 910

Met Lys His Tyr Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro
915 920 925
Glu Thr Leu Glu Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu
930 935 940
Cys Ser Phe Phe His Thr Arg Lys Ser
945 950

<210> 33
<211> 948
<212> PRT
<213> 智人(Homo sapiens)
<400> 33

Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Val Ser Arg Pro Pro
1 5 10 15
Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe
20 25 30
Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln
35 40 45
Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60
Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80
Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95
Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110
His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125
Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140
Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160
Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175
Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190
His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205
Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220

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

530 535 540

Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
545 550 555 560

Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
565 570 575

Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
580 585 590

Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met
595 600 605

Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
610 615 620

Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
625 630 635 640

Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu
645 650 655

Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
660 665 670

Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
675 680 685

Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
690 695 700

Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
705 710 715 720

Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
725 730 735

Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
740 745 750

Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765

Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780

Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800

Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
805 810 815

Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
820 825 830

Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
835 840 845

Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
850 855 860
Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
865 870 875 880
Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
885 890 895
Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
900 905 910
Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
915 920 925
Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His
930 935 940
Thr Arg Lys Ser
945

<210> 34
<211> 946
<212> PRT
<213> 智人(Homo sapiens)
<400> 34

Gly Asp Gly Ala Gln Thr Trp Ala Arg Val Ser Arg Pro Pro Ala Pro
1 5 10 15
Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe Leu Trp
20 25 30
Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His
35 40 45
Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala
50 55 60
Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser
65 70 75 80
Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn
85 90 95
Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr
100 105 110
Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly
115 120 125
Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg
130 135 140
Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp Asp
145 150 155 160

Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala
165 170 175
Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe
180 185 190
Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val
195 200 205
Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly
210 215 220
Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala His
225 230 235 240
Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly
245 250 255
Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg
260 265 270
Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val
275 280 285
Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu
290 295 300
Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser
305 310 315 320
Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Ser Phe
325 330 335
Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg
340 345 350
Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu
355 360 365
Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val
370 375 380
Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys
385 390 395 400
Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp
405 410 415
Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His
420 425 430
Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser
435 440 445
Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys
450 455 460
Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu

465 470 475 480
Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr
485 490 495
Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr
500 505 510
Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp Gly Val
515 520 525
Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln
530 535 540
Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe Arg Phe
545 550 555 560
Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln Val
565 570 575
Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val
580 585 590
Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met Ala Pro
595 600 605
Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn
610 615 620
Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln
625 630 635 640
Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr
645 650 655
Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys Ala His
660 665 670
Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala Gln Asn
675 680 685
Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys
690 695 700
Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu Glu Phe
705 710 715 720
Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro
725 730 735
Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro
740 745 750
Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe
755 760 765
Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu Lys Glu
770 775 780

Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met Thr Asp
785 790 795 800
Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro Trp Gly
805 810 815
Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp Leu Pro
820 825 830
Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala Glu Asp
835 840 845
Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu Ala Leu
850 855 860
Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe Ala Tyr
865 870 875 880
Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg Tyr Ala
885 890 895
Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg Lys Ile
900 905 910
Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg Phe Cys
915 920 925
Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His Thr Arg
930 935 940
Lys Ser
945

<210> 35
<211> 549
<212> PRT
<213> 智人(Homo sapiens)
<400> 35

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1 5 10 15
Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg
20 25 30
Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Val Ser Arg Pro
35 40 45
Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60
Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80
Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95

Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110
Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125
Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140
Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160
Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175
Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190
His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
195 200 205
Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
210 215 220
Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225 230 235 240
Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
245 250 255
Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
260 265 270
Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
275 280 285
Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
290 295 300
Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305 310 315 320
Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
325 330 335
Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
340 345 350
Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
355 360 365
Leu Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
370 375 380
Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385 390 395 400
Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly

405 410 415
Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
420 425 430
Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
435 440 445
Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
450 455 460
Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465 470 475 480
Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495
Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510
Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525
Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540
Asn Val Tyr Leu Trp
545

<210> 36
<211> 521
<212> PRT
<213> 智人(Homo sapiens)
<400> 36
Arg Arg Leu Arg Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg
1 5 10 15
Val Ser Arg Pro Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr
20 25 30
Phe Pro Asp Gly Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr
35 40 45
Glu Gly Gly Trp Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr
50 55 60
Phe Thr His His Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser
65 70 75 80
Leu Pro Leu Gly Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val
85 90 95
Ala Ser Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg
100 105 110
Glu Leu Gly Val Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val

115 120 125

Leu Pro Asn Gly Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr

130 135 140

Tyr Arg Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val

145 150 155 160

Val Thr Leu Tyr His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr

165 170 175

Gly Gly Trp Ala Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala

180 185 190

Glu Leu Cys Phe Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr

195 200 205

Ile Asp Asn Pro Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg

210 215 220

Leu Ala Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala

225 230 235 240

His Asn Leu Leu Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr

245 250 255

Ser Phe Arg Pro Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser

260 265 270

His Trp Ile Asn Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys

275 280 285

Gln Lys Ser Leu Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe

290 295 300

Ile Asp Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile

305 310 315 320

Leu Pro Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala

325 330 335

Asp Phe Phe Ala Leu Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu

340 345 350

Asp Pro His Met Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln

355 360 365

Leu Leu Ser Trp Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile

370 375 380

Val Glu Asn Gly Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala

385 390 395 400

Lys Tyr Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala

405 410 415

Ile Lys Leu Asp Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu

420 425 430

Met Asp Gly Phe Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu
435 440 445
Phe Tyr Val Asp Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser
450 455 460
Ser Ala Leu Phe Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro
465 470 475 480
Leu Pro Glu Asn Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala
485 490 495
Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln
500 505 510
Phe Thr Asp Leu Asn Val Tyr Leu Trp
515 520

<210> 37
<211> 516
<212> PRT
<213> 智人(Homo sapiens)
<400> 37

Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Val Ser Arg Pro Pro
1 5 10 15
Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe
20 25 30
Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln
35 40 45
Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60
Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80
Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95
Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110
His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125
Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140
Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160
Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175

Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190
His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205
Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220
Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240
Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255
Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270
Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285
Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
290 295 300
Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305 310 315 320
Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335
Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350
Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365
Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380
Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385 390 395 400
Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415
Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430
Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445
Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460
Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480
Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp

485 490 495
Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
500 505 510
Val Tyr Leu Trp
515
<210> 38
<211> 514
<212> PRT
<213> 智人(Homo sapiens)
<400> 38
Gly Asp Gly Ala Gln Thr Trp Ala Arg Val Ser Arg Pro Pro Ala Pro
1 5 10 15
Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe Leu Trp
20 25 30
Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His
35 40 45
Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala
50 55 60
Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser
65 70 75 80
Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn
85 90 95
Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr
100 105 110
Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly
115 120 125
Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg
130 135 140
Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp Asp
145 150 155 160
Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala
165 170 175
Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe
180 185 190
Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val
195 200 205
Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly
210 215 220
Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala His

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

<210> 39
<211> 1218
<212> PRT

<213> 人工序列(Artificial Sequence)
<220>
<221> PEPTIDE
<222> ()..()
<223> 蛋白质_天然_SS_34_981V_GS_IgG1_noCH1_Fc_融合
<400> 39

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1 5 10 15
Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg
20 25 30
Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Val Ser Arg Pro
35 40 45
Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60
Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80
Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95
Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110
Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125
Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140
Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160
Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175
Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190
His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
195 200 205
Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
210 215 220
Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225 230 235 240
Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
245 250 255
Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu

260 265 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
275 280 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
290 295 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305 310 315 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
325 330 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
340 345 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
355 360 365

Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
370 375 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385 390 395 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
405 410 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
420 425 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
435 440 445

Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
450 455 460

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465 470 475 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510

Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525

Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540

Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545 550 555 560

Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
565 570 575

Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
580 585 590
Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
595 600 605
Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
610 615 620
Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
625 630 635 640
Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
645 650 655
Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
660 665 670
Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
675 680 685
Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
690 695 700
Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
705 710 715 720
Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
725 730 735
Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
740 745 750
Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
755 760 765
Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
770 775 780
Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
785 790 795 800
Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
805 810 815
Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
820 825 830
Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
835 840 845
Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
850 855 860
Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
865 870 875 880
Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn

885 890 895
Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
900 905 910
Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
915 920 925
Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
930 935 940
Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945 950 955 960
Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
965 970 975
His Thr Arg Lys Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp
980 985 990
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
995 1000 1005
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1010 1015 1020
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Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
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Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
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Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
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Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
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Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
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Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
1155 1160 1165
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1170 1175 1180
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
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35 40 45

Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60

Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80

Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95

Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110

His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125

Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140

Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160

Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175

Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190

His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205

Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile

210 215 220
Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240
Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255
Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270
Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285
Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
290 295 300
Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305 310 315 320
Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335
Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350
Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365
Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380
Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385 390 395 400
Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415
Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430
Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445
Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460
Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480
Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495
Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
500 505 510
Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp
515 520 525

Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala
530 535 540
Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
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Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
565 570 575
Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
580 585 590
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595 600 605
Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
610 615 620
Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
625 630 635 640
Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu
645 650 655
Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
660 665 670
Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
675 680 685
Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
690 695 700
Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
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Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
725 730 735
Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
740 745 750
Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765
Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780
Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800
Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
805 810 815
Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
820 825 830
Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala

835 840 845

Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
850 855 860

Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
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Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
885 890 895

Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
900 905 910

Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
915 920 925

Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His
930 935 940

Thr Arg Lys Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys
945 950 955 960

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
965 970 975

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
980 985 990

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
995 1000 1005

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
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Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
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Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
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Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
1060 1065 1070

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
1075 1080 1085

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
1090 1095 1100

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

His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
195 200 205
Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
210 215 220
Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225 230 235 240
Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
245 250 255
Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
260 265 270
Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
275 280 285
Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
290 295 300
Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
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Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
325 330 335
Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
340 345 350
Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
355 360 365
Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
370 375 380
Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385 390 395 400
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405 410 415
Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
420 425 430
Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
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Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
450 455 460
Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465 470 475 480
Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495
Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn

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Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val

515 520 525

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

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Thr Lys Pro Tyr His Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp

545 550 555 560

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly

565 570 575

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile

580 585 590

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu

595 600 605

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His

610 615 620

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg

625 630 635 640

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys

645 650 655

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu

660 665 670

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr

675 680 685

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu

690 695 700

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp

705 710 715 720

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val

725 730 735

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp

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Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
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65 70 75 80
Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95
Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110
His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
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Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
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145 150 155 160
Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175
Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
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His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205
Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220
Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240
Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255

Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270
Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285
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Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305 310 315 320
Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
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Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350
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Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
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Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
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Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445
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Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480
Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495
Asn Tyr Ile Gln Val Ser Gln Leu Thr Lys Pro Ile Ser Ser Leu Thr
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Lys Pro Tyr His Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys
515 520 525
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
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Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
545 550 555 560
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp

565 570 575
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
580 585 590
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
595 600 605
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
610 615 620
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
625 630 635 640
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
645 650 655
Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
660 665 670
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
675 680 685
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
690 695 700
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
705 710 715 720
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Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
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Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80
Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95
Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110
Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125
Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140
Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
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Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
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Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190
His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
195 200 205
Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
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Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225 230 235 240
Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
245 250 255
Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
260 265 270
Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
275 280 285
Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
290 295 300
Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
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Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
325 330 335
Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
340 345 350
Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala

355 360 365

Leu Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met

370 375 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp

385 390 395 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly

405 410 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr

420 425 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp

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Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe

450 455 460

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp

465 470 475 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe

485 490 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn

500 505 510

Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val

515 520 525

Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu

530 535 540

Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val

545 550 555 560

Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala

565 570 575

Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His

580 585 590

Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln

595 600 605

Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser

610 615 620

Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro

625 630 635 640

Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala

645 650 655

Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu

660 665 670

Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
675 680 685
Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
690 695 700
Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
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Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
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Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
740 745 750
Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
755 760 765
Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
770 775 780
Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
785 790 795 800
Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
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Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
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835 840 845
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885 890 895
Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
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915 920 925
Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
930 935 940
Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945 950 955 960
Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
965 970 975
His Thr Arg Lys Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp

980 985 990
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
995 1000 1005
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
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Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
1060 1065 1070
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
1075 1080 1085
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
1090 1095 1100
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
1105 1110 1115 1120
Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
1125 1130 1135
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
1140 1145 1150
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
1155 1160 1165
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
1170 1175 1180
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
1185 1190 1195 1200
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
1205 1210 1215
Gly Lys

<210> 44
<211> 1185
<212> PRT
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<221> PEPTIDE
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<223> 蛋白质_34_981V_C370S_GS_IgG1_noCH1_Fc_融合
<400> 44

Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Val Ser Arg Pro Pro
1 5 10 15
Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe
20 25 30
Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln
35 40 45
Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60
Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80
Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95
Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110
His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125
Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140
Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160
Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175
Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190
His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205
Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220
Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240
Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255
Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270
Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285
Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
290 295 300
Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr

305 310 315 320
Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335
Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350
Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365
Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380
Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385 390 395 400
Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415
Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430
Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445
Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460
Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480
Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495
Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
500 505 510
Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp
515 520 525
Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala
530 535 540
Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
545 550 555 560
Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
565 570 575
Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
580 585 590
Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met
595 600 605
Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
610 615 620

Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
625 630 635 640
Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu
645 650 655
Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
660 665 670
Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
675 680 685
Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
690 695 700
Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
705 710 715 720
Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
725 730 735
Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
740 745 750
Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765
Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780
Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800
Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
805 810 815
Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
820 825 830
Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
835 840 845
Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
850 855 860
Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
865 870 875 880
Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
885 890 895
Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
900 905 910
Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
915 920 925
Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His

930 935 940
Thr Arg Lys Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys
945 950 955 960
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
965 970 975
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
980 985 990
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
995 1000 1005
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
1010 1015 1020
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
1025 1030 1035 1040
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
1045 1050 1055
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
1060 1065 1070
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
1075 1080 1085
Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
1090 1095 1100
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
1105 1110 1115 1120
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
1125 1130 1135
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
1140 1145 1150
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
1155 1160 1165
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
1170 1175 1180
Lys
1185

<210> 45
<211> 786
<212> PRT
<213> 人工序列(Artificial Sequence)
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<221> PEPTIDE

<222> ()..()

<223> 蛋白质_天然_SS_34_549V_C370S_GS_IgG1_noCH1_Fc_融合

<400> 45

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1 5 10 15
Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg
20 25 30
Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Val Ser Arg Pro
35 40 45
Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60
Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80
Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95
Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110
Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125
Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140
Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160
Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175
Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190
His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
195 200 205
Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
210 215 220
Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225 230 235 240
Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
245 250 255
Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
260 265 270
Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
275 280 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
290 295 300
Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305 310 315 320
Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
325 330 335
Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
340 345 350
Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
355 360 365
Leu Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
370 375 380
Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385 390 395 400
Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
405 410 415
Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
420 425 430
Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
435 440 445
Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
450 455 460
Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465 470 475 480
Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495
Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510
Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525
Asp Asn Tyr Ile Gln Val Ser Gln Leu Thr Lys Pro Ile Ser Ser Leu
530 535 540
Thr Lys Pro Tyr His Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp
545 550 555 560
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
565 570 575
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
580 585 590
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu

595 600 605
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
610 615 620
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
625 630 635 640
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
645 650 655
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
660 665 670
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
675 680 685
Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
690 695 700
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
705 710 715 720
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
725 730 735
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
740 745 750
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
755 760 765
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
770 775 780
Gly Lys
785

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Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Val Ser Arg Pro Pro
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Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe
20 25 30
Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln

35 40 45

Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60
Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80
Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95
Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110
His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125
Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140
Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160
Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175
Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190
His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205
Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220
Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240
Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255
Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270
Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285
Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
290 295 300
Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305 310 315 320
Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335
Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350

Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365
Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380
Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385 390 395 400
Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415
Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430
Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445
Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460
Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480
Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495
Asn Tyr Ile Gln Val Ser Gln Leu Thr Lys Pro Ile Ser Ser Leu Thr
500 505 510
Lys Pro Tyr His Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys
515 520 525
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
530 535 540
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
545 550 555 560
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
565 570 575
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
580 585 590
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
595 600 605
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
610 615 620
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
625 630 635 640
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
645 650 655
Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr

660 665 670

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
675 680 685

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
690 695 700

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
705 710 715 720

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
725 730 735

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
740 745 750

Lys

<210> 47

<211> 1183

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<221> PEPTIDE

<222> ()..()

<223> 蛋白质_36_981V_GS_IgG1_noCH1_Fc_融合

<400> 47

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

Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His
35 40 45

Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala
50 55 60

Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser
65 70 75 80

Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn
85 90 95

Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr
100 105 110

Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly
115 120 125

Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg
130 135 140

Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp Asp
145 150 155 160
Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala
165 170 175
Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe
180 185 190
Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val
195 200 205
Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly
210 215 220
Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala His
225 230 235 240
Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly
245 250 255
Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg
260 265 270
Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val
275 280 285
Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu
290 295 300
Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser
305 310 315 320
Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Cys Phe
325 330 335
Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg
340 345 350
Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu
355 360 365
Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val
370 375 380
Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys
385 390 395 400
Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp
405 410 415
Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His
420 425 430
Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser
435 440 445
Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys

450 455 460

Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu
465 470 475 480

Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr
485 490 495

Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr
500 505 510

Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp Gly Val
515 520 525

Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln
530 535 540

Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe Arg Phe
545 550 555 560

Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln Val
565 570 575

Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val
580 585 590

Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met Ala Pro
595 600 605

Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn
610 615 620

Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln
625 630 635 640

Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr
645 650 655

Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys Ala His
660 665 670

Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala Gln Asn
675 680 685

Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys
690 695 700

Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu Glu Phe
705 710 715 720

Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro
725 730 735

Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro
740 745 750

Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe
755 760 765

Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu Lys Glu
770 775 780
Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met Thr Asp
785 790 795 800
Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro Trp Gly
805 810 815
Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp Leu Pro
820 825 830
Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala Glu Asp
835 840 845
Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu Ala Leu
850 855 860
Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe Ala Tyr
865 870 875 880
Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg Tyr Ala
885 890 895
Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg Lys Ile
900 905 910
Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg Phe Cys
915 920 925
Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His Thr Arg
930 935 940
Lys Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His
945 950 955 960
Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
965 970 975
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
980 985 990
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
995 1000 1005
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
1010 1015 1020
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
1025 1030 1035 1040
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
1045 1050 1055
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
1060 1065 1070
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro

1075 1080 1085

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
1090 1095 1100

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
1105 1110 1115 1120

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
1125 1130 1135

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
1140 1145 1150

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
1155 1160 1165

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
1170 1175 1180

<210> 48

<211> 1183

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<221> PEPTIDE

<222> ()..()

<223> 蛋白质_36_981V_C370S_GS_IgG1_noCH1_Fc_融合

<400> 48

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

Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His
35 40 45

Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala
50 55 60

Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser
65 70 75 80

Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn
85 90 95

Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr
100 105 110

Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly
115 120 125

Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg

130 135 140

Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp Asp
145 150 155 160
Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala
165 170 175
Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe
180 185 190
Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val
195 200 205
Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly
210 215 220
Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala His
225 230 235 240
Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly
245 250 255
Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg
260 265 270
Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val
275 280 285
Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu
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Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser
305 310 315 320
Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Ser Phe
325 330 335
Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg
340 345 350
Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu
355 360 365
Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val
370 375 380
Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys
385 390 395 400
Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp
405 410 415
Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His
420 425 430
Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser
435 440 445

Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys
450 455 460
Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu
465 470 475 480
Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr
485 490 495
Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr
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Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp Gly Val
515 520 525
Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln
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Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe Arg Phe
545 550 555 560
Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln Val
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Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val
580 585 590
Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met Ala Pro
595 600 605
Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn
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Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln
625 630 635 640
Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr
645 650 655
Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys Ala His
660 665 670
Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala Gln Asn
675 680 685
Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys
690 695 700
Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu Glu Phe
705 710 715 720
Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro
725 730 735
Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro
740 745 750
Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe

755 760 765

Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu Lys Glu
770 775 780

Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met Thr Asp
785 790 795 800

Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro Trp Gly
805 810 815

Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp Leu Pro
820 825 830

Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala Glu Asp
835 840 845

Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu Ala Leu
850 855 860

Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe Ala Tyr
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Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg Tyr Ala
885 890 895

Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg Lys Ile
900 905 910

Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg Phe Cys
915 920 925

Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His Thr Arg
930 935 940

Lys Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His
945 950 955 960

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
965 970 975

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
980 985 990

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
995 1000 1005

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
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Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
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Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
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Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
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Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
1075 1080 1085
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
1090 1095 1100
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
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Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
1125 1130 1135
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
1140 1145 1150
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35 40 45
Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala
50 55 60
Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser
65 70 75 80
Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn
85 90 95
Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr
100 105 110
Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly
115 120 125

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

435 440 445

Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys

450 455 460

Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu

465 470 475 480

Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr

485 490 495

Ile Gln Val Ser Gln Leu Thr Lys Pro Ile Ser Ser Leu Thr Lys Pro

500 505 510

Tyr His Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His

515 520 525

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val

530 535 540

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr

545 550 555 560

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu

565 570 575

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys

580 585 590

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser

595 600 605

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys

610 615 620

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile

625 630 635 640

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro

645 650 655

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu

660 665 670

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn

675 680 685

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser

690 695 700

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg

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35 40 45
Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala
50 55 60
Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser
65 70 75 80
Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn
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Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr
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Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly
115 120 125
Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg
130 135 140
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145 150 155 160
Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala
165 170 175
Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe
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Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val
195 200 205
Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly
210 215 220
Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala His
225 230 235 240

Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly
245 250 255
Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg
260 265 270
Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val
275 280 285
Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu
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Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser
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Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Ser Phe
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Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg
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Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu
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Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val
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Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys
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Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp
405 410 415
Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His
420 425 430
Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser
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Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys
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Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu
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Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr
485 490 495
Ile Gln Val Ser Gln Leu Thr Lys Pro Ile Ser Ser Leu Thr Lys Pro
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Tyr His Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His
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Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
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Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr

545 550 555 560
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
565 570 575
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
580 585 590
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
595 600 605
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
610 615 620
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
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Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
645 650 655
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
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Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
675 680 685
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
690 695 700
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
705 710 715 720
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Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
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Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
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Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
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Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
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Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140

Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
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Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175

Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190

His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
195 200 205

Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
210 215 220

Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225 230 235 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
245 250 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
260 265 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
275 280 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
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Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305 310 315 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
325 330 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
340 345 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
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Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
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450 455 460
Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
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Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
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545 550 555 560
Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
565 570 575
Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
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Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
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Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
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Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
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Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
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Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu

660 665 670

Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn

675 680 685

Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu

690 695 700

Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His

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Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe

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Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser

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Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu

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Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly

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Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn

885 890 895

Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr

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Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr

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945 950 955 960

Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe

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

Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
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Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335
Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
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Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
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385 390 395 400
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405 410 415
Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
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Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
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Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
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Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
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Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
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Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp
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Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
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Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
565 570 575
Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
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Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp

610 615 620
Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
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Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu
645 650 655
Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
660 665 670
Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
675 680 685
Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
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Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
705 710 715 720
Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
725 730 735
Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
740 745 750
Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765
Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780
Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800
Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
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Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
850 855 860
Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
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885 890 895
Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
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Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
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Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
980 985 990
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
995 1000 1005
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1140 1145 1150
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Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60
Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80
Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95
Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110
Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125
Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140
Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160
Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175
Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190
His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
195 200 205
Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
210 215 220
Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225 230 235 240
Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
245 250 255
Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
260 265 270
Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro

275 280 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn

290 295 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu

305 310 315 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp

325 330 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe

340 345 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala

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Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp

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Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly

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Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr

420 425 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp

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450 455 460

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp

465 470 475 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe

485 490 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn

500 505 510

Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val

515 520 525

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

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Thr Lys Pro Tyr His Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp

545 550 555 560

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly

565 570 575

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Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
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Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
625 630 635 640
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645 650 655
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
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Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
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Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
690 695 700
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
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Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
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Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
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Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
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Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
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Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
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His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
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Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
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165 170 175
Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
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195 200 205
Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220
Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240
Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255
Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270
Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285
Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
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Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305 310 315 320
Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335
Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys

340 345 350

Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365

Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380

Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385 390 395 400

Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415

Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430

Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445

Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
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Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480

Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495

Asn Tyr Ile Gln Val Ser Gln Leu Thr Lys Pro Ile Ser Ser Leu Thr
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Lys Pro Tyr His Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys
515 520 525

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
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Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
545 550 555 560

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
565 570 575

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
580 585 590

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
595 600 605

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
610 615 620

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
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Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
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Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
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Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
675 680 685
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
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Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
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Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
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Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
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Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val

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Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
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His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
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Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
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Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
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Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
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Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
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Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
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Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
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Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
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Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
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Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
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465 470 475 480
Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
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Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
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545 550 555 560
Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
565 570 575
Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
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Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
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Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
610 615 620
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Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
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Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
660 665 670
Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
675 680 685
Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
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Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
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Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
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Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe

770 775 780

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Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly

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Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn

885 890 895

Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr

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Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr

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Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu

945 950 955 960

Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe

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His Thr Arg Lys Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp

980 985 990

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly

995 1000 1005

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile

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Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu

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Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg

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

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Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
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His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
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Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
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Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
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Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
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Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
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His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205

Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220

Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240

Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255

Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270

Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
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Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
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Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
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Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
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Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
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Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
660 665 670
Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
675 680 685
Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
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740 745 750
Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765
Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780
Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800
Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
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835 840 845
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930 935 940
Thr Arg Lys Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys
945 950 955 960
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
965 970 975
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
980 985 990
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
995 1000 1005
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
1010 1015 1020

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
1025 1030 1035 1040
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
1045 1050 1055
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
1060 1065 1070
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
1075 1080 1085
Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
1090 1095 1100
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
1105 1110 1115 1120
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
1125 1130 1135
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
1140 1145 1150
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
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Lys
1185

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35 40 45
Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60

Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80
Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95
Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110
Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125
Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140
Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160
Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175
Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190
His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
195 200 205
Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
210 215 220
Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225 230 235 240
Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
245 250 255
Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
260 265 270
Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
275 280 285
Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
290 295 300
Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305 310 315 320
Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
325 330 335
Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
340 345 350
Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
355 360 365
Leu Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met

370 375 380
Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385 390 395 400
Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
405 410 415
Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
420 425 430
Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
435 440 445
Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
450 455 460
Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465 470 475 480
Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495
Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510
Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525
Asp Asn Tyr Ile Gln Val Ser Gln Leu Thr Lys Pro Ile Ser Ser Leu
530 535 540
Thr Lys Pro Tyr His Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp
545 550 555 560
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
565 570 575
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
580 585 590
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
595 600 605
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
610 615 620
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
625 630 635 640
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
645 650 655
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
660 665 670
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
675 680 685

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
690 695 700
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
705 710 715 720
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
725 730 735
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
740 745 750
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
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Gly Lys
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35 40 45
Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60
Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80
Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95
Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110
His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125

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

435 440 445

Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460

Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480

Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495

Asn Tyr Ile Gln Val Ser Gln Leu Thr Lys Pro Ile Ser Ser Leu Thr
500 505 510

Lys Pro Tyr His Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys
515 520 525

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
530 535 540

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
545 550 555 560

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
565 570 575

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
580 585 590

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
595 600 605

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
610 615 620

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
625 630 635 640

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
645 650 655

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
660 665 670

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
675 680 685

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
690 695 700

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
705 710 715 720

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

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<212> PRT

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

225 230 235 240
Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly
245 250 255
Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg
260 265 270
Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val
275 280 285
Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu
290 295 300
Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser
305 310 315 320
Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Cys Phe
325 330 335
Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg
340 345 350
Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu
355 360 365
Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val
370 375 380
Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys
385 390 395 400
Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp
405 410 415
Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His
420 425 430
Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser
435 440 445
Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys
450 455 460
Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu
465 470 475 480
Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr
485 490 495
Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr
500 505 510
Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp Gly Val
515 520 525
Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln
530 535 540

Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe Arg Phe
545 550 555 560
Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln Val
565 570 575
Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val
580 585 590
Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met Ala Pro
595 600 605
Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn
610 615 620
Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln
625 630 635 640
Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr
645 650 655
Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys Ala His
660 665 670
Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala Gln Asn
675 680 685
Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys
690 695 700
Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu Glu Phe
705 710 715 720
Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro
725 730 735
Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro
740 745 750
Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe
755 760 765
Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu Lys Glu
770 775 780
Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met Thr Asp
785 790 795 800
Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro Trp Gly
805 810 815
Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp Leu Pro
820 825 830
Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala Glu Asp
835 840 845
Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu Ala Leu

850 855 860
Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe Ala Tyr
865 870 875 880
Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg Tyr Ala
885 890 895
Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg Lys Ile
900 905 910
Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg Phe Cys
915 920 925
Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His Thr Arg
930 935 940
Lys Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His
945 950 955 960
Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
965 970 975
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
980 985 990
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
995 1000 1005
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
1010 1015 1020
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
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Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
1045 1050 1055
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
1060 1065 1070
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
1075 1080 1085
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
1090 1095 1100
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
1105 1110 1115 1120
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
1125 1130 1135
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
1140 1145 1150
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
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His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
1170 1175 1180

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

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

530 535 540

Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe Arg Phe
545 550 555 560

Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln Val
565 570 575

Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val
580 585 590

Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met Ala Pro
595 600 605

Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn
610 615 620

Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln
625 630 635 640

Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr
645 650 655

Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys Ala His
660 665 670

Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala Gln Asn
675 680 685

Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys
690 695 700

Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu Glu Phe
705 710 715 720

Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro
725 730 735

Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro
740 745 750

Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe
755 760 765

Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu Lys Glu
770 775 780

Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met Thr Asp
785 790 795 800

Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro Trp Gly
805 810 815

Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp Leu Pro
820 825 830

Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala Glu Asp
835 840 845

Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu Ala Leu
850 855 860
Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe Ala Tyr
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Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg Tyr Ala
885 890 895
Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg Lys Ile
900 905 910
Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg Phe Cys
915 920 925
Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His Thr Arg
930 935 940
Lys Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His
945 950 955 960
Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
965 970 975
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
980 985 990
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
995 1000 1005
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
1010 1015 1020
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
1025 1030 1035 1040
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
1045 1050 1055
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
1060 1065 1070
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
1075 1080 1085
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
1090 1095 1100
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
1105 1110 1115 1120
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
1125 1130 1135
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
1140 1145 1150
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu

1155 1160 1165

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
1170 1175 1180

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<400> 61

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20 25 30
Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His
35 40 45
Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala
50 55 60
Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser
65 70 75 80
Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn
85 90 95
Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr
100 105 110
Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly
115 120 125
Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg
130 135 140
Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp Asp
145 150 155 160
Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala
165 170 175
Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe
180 185 190
Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val
195 200 205
Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly

210 215 220
Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala His
225 230 235 240
Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly
245 250 255
Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg
260 265 270
Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val
275 280 285
Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu
290 295 300
Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser
305 310 315 320
Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Cys Phe
325 330 335
Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg
340 345 350
Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu
355 360 365
Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val
370 375 380
Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys
385 390 395 400
Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp
405 410 415
Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His
420 425 430
Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser
435 440 445
Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys
450 455 460
Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu
465 470 475 480
Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr
485 490 495
Ile Gln Val Ser Gln Leu Thr Lys Pro Ile Ser Ser Leu Thr Lys Pro
500 505 510
Tyr His Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His
515 520 525

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
530 535 540
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
545 550 555 560
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
565 570 575
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
580 585 590
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
595 600 605
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
610 615 620
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
625 630 635 640
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
645 650 655
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
660 665 670
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
675 680 685
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
690 695 700
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
705 710 715 720
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
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Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His
35 40 45
Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala
50 55 60
Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser
65 70 75 80
Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn
85 90 95
Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr
100 105 110
Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly
115 120 125
Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg
130 135 140
Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp Asp
145 150 155 160
Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala
165 170 175
Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe
180 185 190
Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val
195 200 205
Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly
210 215 220
Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala His
225 230 235 240
Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly
245 250 255
Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg
260 265 270
Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val
275 280 285
Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu
290 295 300
Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser
305 310 315 320
Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Ser Phe

325 330 335
Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg
340 345 350
Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu
355 360 365
Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val
370 375 380
Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys
385 390 395 400
Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp
405 410 415
Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His
420 425 430
Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser
435 440 445
Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys
450 455 460
Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu
465 470 475 480
Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr
485 490 495
Ile Gln Val Ser Gln Leu Thr Lys Pro Ile Ser Ser Leu Thr Lys Pro
500 505 510
Tyr His Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His
515 520 525
Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
530 535 540
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
545 550 555 560
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
565 570 575
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
580 585 590
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
595 600 605
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
610 615 620
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
625 630 635 640

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
645 650 655
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
660 665 670
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
675 680 685
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
690 695 700
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
705 710 715 720
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
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His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
740 745 750

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

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

435 440 445

Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460

Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480

Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495

Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
500 505 510

Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp
515 520 525

Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala
530 535 540

Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
545 550 555 560

Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
565 570 575

Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
580 585 590

Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met
595 600 605

Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
610 615 620

Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
625 630 635 640

Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu
645 650 655

Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
660 665 670

Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
675 680 685

Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
690 695 700

Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
705 710 715 720

Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
725 730 735

Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
740 745 750

Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765
Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780
Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800
Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
805 810 815
Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
820 825 830
Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
835 840 845
Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
850 855 860
Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
865 870 875 880
Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
885 890 895
Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
900 905 910
Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
915 920 925
Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His
930 935 940
Thr Arg Lys Ser Gly Gly Glu Asn Leu Tyr Phe Gln Ser Ser Ala Trp
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Ser His Pro Gln Phe Glu Lys Gly Gly Gly Ser Gly Gly Gly Ser Gly
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Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln
35 40 45
Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60
Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80
Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95
Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110
His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125
Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140
Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160
Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175
Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190
His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205
Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220
Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240
Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255
Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270
Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285
Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
290 295 300
Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr

305 310 315 320
Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335
Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350
Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365
Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380
Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385 390 395 400
Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415
Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430
Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445
Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460
Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480
Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495
Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
500 505 510
Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp
515 520 525
Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala
530 535 540
Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
545 550 555 560
Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
565 570 575
Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
580 585 590
Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met
595 600 605
Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
610 615 620

Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
625 630 635 640
Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu
645 650 655
Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
660 665 670
Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
675 680 685
Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
690 695 700
Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
705 710 715 720
Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
725 730 735
Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
740 745 750
Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765
Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780
Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800
Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
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Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
820 825 830
Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
835 840 845
Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
850 855 860
Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
865 870 875 880
Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
885 890 895
Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
900 905 910
Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
915 920 925
Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His

930 935 940

Thr Arg Lys Ser Gly Gly Glu Asn Leu Tyr Phe Gln
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Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln
35 40 45

Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60

Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80

Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95

Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110

His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125

Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140

Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160

Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175

Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190

His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205

Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile

210 215 220

Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240

Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255

Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270

Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285

Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
290 295 300

Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305 310 315 320

Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335

Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350

Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365

Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380

Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385 390 395 400

Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415

Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430

Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445

Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460

Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480

Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495

Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
500 505 510

Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp
515 520 525

Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala
530 535 540
Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
545 550 555 560
Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
565 570 575
Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
580 585 590
Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met
595 600 605
Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
610 615 620
Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
625 630 635 640
Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu
645 650 655
Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
660 665 670
Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
675 680 685
Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
690 695 700
Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
705 710 715 720
Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
725 730 735
Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
740 745 750
Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765
Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780
Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800
Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
805 810 815
Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
820 825 830
Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala

835 840 845

Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
850 855 860

Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
865 870 875 880

Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
885 890 895

Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
900 905 910

Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
915 920 925

Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His
930 935 940

Thr Arg Lys Ser Gly Gly Glu Asn Leu Tyr Phe Gln Ser Ser Ala Trp
945 950 955 960

Ser His Pro Gln Phe Glu Lys Gly Gly Gly Ser Gly Gly Gly Ser Gly
965 970 975

Gly Ser Ser Ala Trp Ser His Pro Gln Phe Glu Lys
980 985

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Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln
35 40 45

Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60

Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80

Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr

85 90 95

Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110

His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125

Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140

Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160

Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175

Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190

His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205

Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220

Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240

Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255

Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270

Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285

Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
290 295 300

Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305 310 315 320

Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335

Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350

Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365

Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380

Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385 390 395 400

Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415
Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430
Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445
Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460
Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480
Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495
Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
500 505 510
Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp
515 520 525
Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala
530 535 540
Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
545 550 555 560
Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
565 570 575
Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
580 585 590
Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met
595 600 605
Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
610 615 620
Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
625 630 635 640
Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu
645 650 655
Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
660 665 670
Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
675 680 685
Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
690 695 700
Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu

705 710 715 720
Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
725 730 735
Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
740 745 750
Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765
Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780
Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800
Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
805 810 815
Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
820 825 830
Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
835 840 845
Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
850 855 860
Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
865 870 875 880
Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
885 890 895
Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
900 905 910
Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
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Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His
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Thr Arg Lys Ser Gly Gly Glu Asn Leu Tyr Phe Gln
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35 40 45
Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60
Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80
Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95
Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110
His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125
Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140
Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160
Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175
Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190
His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205
Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220
Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240
Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255
Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270
Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285
Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
290 295 300

Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305 310 315 320
Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335
Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350
Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365
Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380
Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385 390 395 400
Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415
Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430
Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445
Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460
Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480
Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495
Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
500 505 510
Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp
515 520 525
Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala
530 535 540
Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
545 550 555 560
Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
565 570 575
Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
580 585 590
Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met
595 600 605
Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp

610 615 620
Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
625 630 635 640
Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu
645 650 655
Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
660 665 670
Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
675 680 685
Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
690 695 700
Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
705 710 715 720
Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
725 730 735
Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
740 745 750
Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765
Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780
Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800
Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
805 810 815
Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
820 825 830
Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
835 840 845
Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
850 855 860
Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
865 870 875 880
Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
885 890 895
Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
900 905 910
Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
915 920 925

Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His
930 935 940
Thr Arg Lys Ser Gly Gly Glu Asn Leu Tyr Phe Gln Ser Ser Ala Trp
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Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln
35 40 45
Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60
Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80
Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95
Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110
His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125
Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140
Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160
Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175

Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190
His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205
Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220
Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240
Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255
Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270
Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285
Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
290 295 300
Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305 310 315 320
Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335
Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350
Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365
Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380
Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385 390 395 400
Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415
Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430
Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445
Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460
Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480
Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp

485 490 495

Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn

500 505 510

Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp

515 520 525

Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala

530 535 540

Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe

545 550 555 560

Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser

565 570 575

Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu

580 585 590

Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met

595 600 605

Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp

610 615 620

Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys

625 630 635 640

Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu

645 650 655

Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys

660 665 670

Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala

675 680 685

Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro

690 695 700

Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu

705 710 715 720

Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp

725 730 735

Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu

740 745 750

Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe

755 760 765

Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu

770 775 780

Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met

785 790 795 800

Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
805 810 815
Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
820 825 830
Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
835 840 845
Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
850 855 860
Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
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Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
885 890 895
Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
900 905 910
Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
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Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His
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35 40 45
Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60
Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80

Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95
Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110
His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125
Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140
Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160
Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175
Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190
His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205
Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220
Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240
Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255
Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270
Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285
Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
290 295 300
Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305 310 315 320
Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335
Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350
Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365
Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380
Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr

385 390 395 400
Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415
Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430
Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445
Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460
Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
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Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495
Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
500 505 510
Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp
515 520 525
Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala
530 535 540
Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
545 550 555 560
Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
565 570 575
Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
580 585 590
Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met
595 600 605
Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
610 615 620
Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
625 630 635 640
Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu
645 650 655
Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
660 665 670
Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
675 680 685
Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
690 695 700

Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
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Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
725 730 735
Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
740 745 750
Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765
Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780
Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800
Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
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Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
820 825 830
Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
835 840 845
Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
850 855 860
Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
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Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
885 890 895
Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
900 905 910
Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
915 920 925
Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His
930 935 940
Thr Arg Lys Ser Gly Gly Glu Asn Leu Tyr Phe Gln Ser Ser Ala Trp
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Gly Ser Ser Ala Trp Ser His Pro Gln Phe Glu Lys
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35 40 45
Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60
Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80
Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95
Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110
His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125
Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140
Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160
Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175
Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190
His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205
Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220
Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240
Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255
Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro

260 265 270

Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp

275 280 285

Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr

290 295 300

Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr

305 310 315 320

Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu

325 330 335

Ser Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys

340 345 350

Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile

355 360 365

Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp

370 375 380

Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr

385 390 395 400

Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly

405 410 415

Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu

420 425 430

Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe

435 440 445

Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr

450 455 460

Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln

465 470 475 480

Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp

485 490 495

Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn

500 505 510

Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp

515 520 525

Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala

530 535 540

Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe

545 550 555 560

Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser

565 570 575

Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
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Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
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625 630 635 640
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645 650 655
Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
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Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
675 680 685
Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
690 695 700
Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
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Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
725 730 735
Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
740 745 750
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755 760 765
Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780
Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800
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835 840 845
Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
850 855 860
Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
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Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg

885 890 895
Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
900 905 910
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Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
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Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125
Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
130 135 140
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145 150 155 160
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165 170 175
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
180 185 190
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
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210 215 220

Pro Gly Lys

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<210> 75

<211> 40

<212> PRT

<213> 人工序列(Artificial Sequence)

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<400> 75

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<210> 76

<211> 3036

<212> DNA

<213> 智人(Homo sapiens)

<400> 76

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<211> 2943
<212> DNA
<213> 智人(Homo sapiens)

<400> 77

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<211> 2859
<212> DNA
<213> 智人(Homo sapiens)
<400> 78

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<211> 2844
<212> DNA
<213> 智人(Homo sapiens)
<400> 79

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<211> 2838

<212> DNA

<213> 智人(Homo sapiens)

<400> 80

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<211> 2553
<212> DNA
<213> 智人(Homo sapiens)
<400> 81

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<210> 82
<211> 1648
<212> DNA
<213> 智人(Homo sapiens)
<400> 82

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<210> 83
<211> 1564
<212> DNA
<213> 智人(Homo sapiens)

<400> 83
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<211> 1549
<212> DNA
<213> 智人(Homo sapiens)
<400> 84

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<210> 85
<211> 1543
<212> DNA
<213> 智人(Homo sapiens)
<400> 85

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<400> 94

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<211> 2553
<212> DNA
<213> 智人(Homo sapiens)
<400> 95

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<210> 96
<211> 1257
<212> DNA
<213> 智人(Homo sapiens)
<400> 96

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<210> 98
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<210> 99
<211> 681
<212> DNA
<213> 人工序列(Artificial Sequence)
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<223> DNA_ IgG1_noCH1_Fc_融合
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<210> 100
<211> 57
<212> DNA
<213> 人工序列(Artificial Sequence)
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<221> gene
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<210> 101
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<212> DNA
<213> 人工序列(Artificial Sequence)
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<221> gene
<222> ()..()
<223> DNA_双胞胎链霉素_标签
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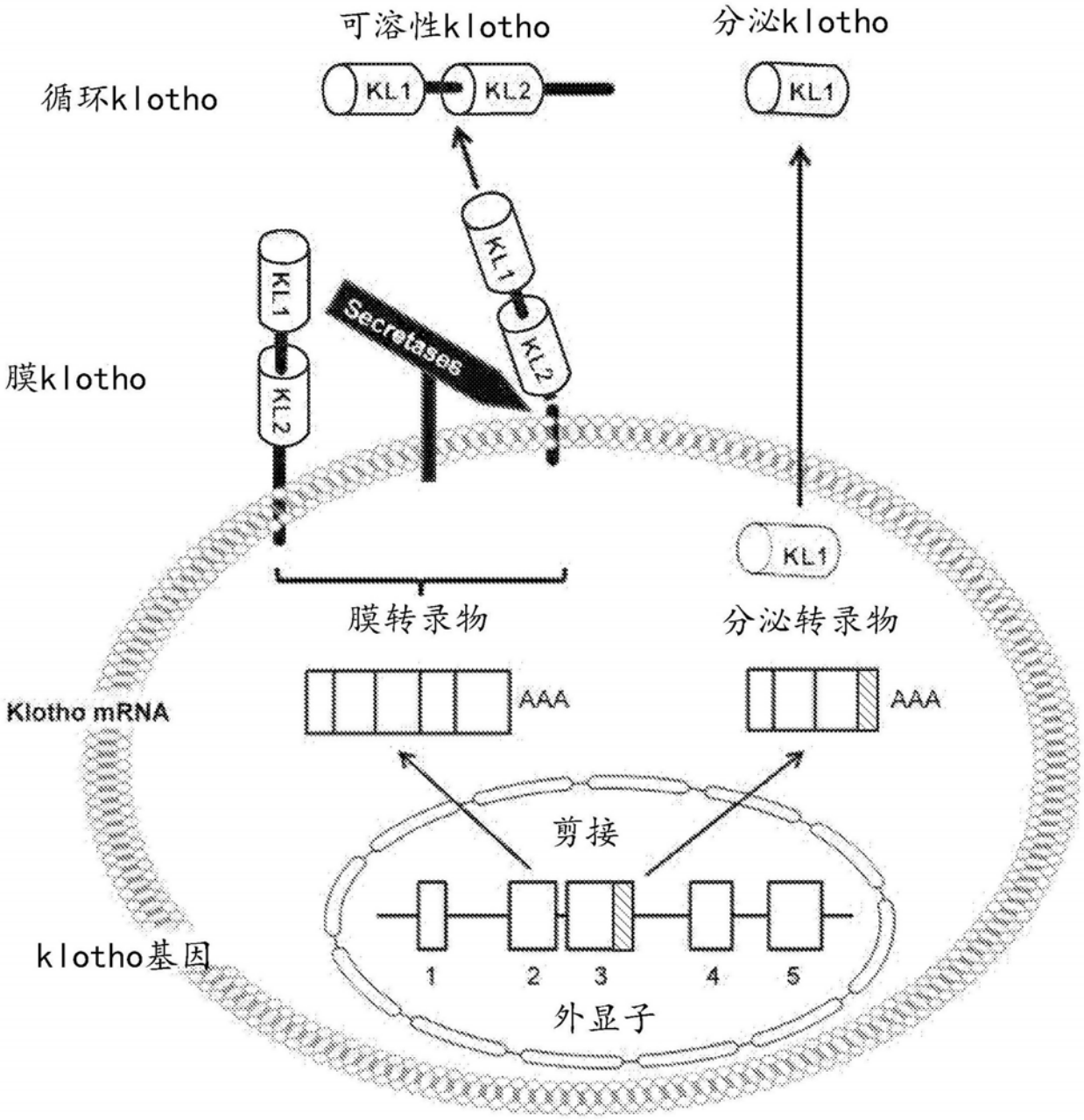

可溶性klotho
分泌klotho
循环klotho
KL1
KL2
KL1
膜klotho
KL1
KL2
Secretases
KL2
KL1
膜转录物
分泌转录物
Klotho mRNA
AAA
AAA
剪接
klotho基因
1
2
3
4
5
外显子

图1

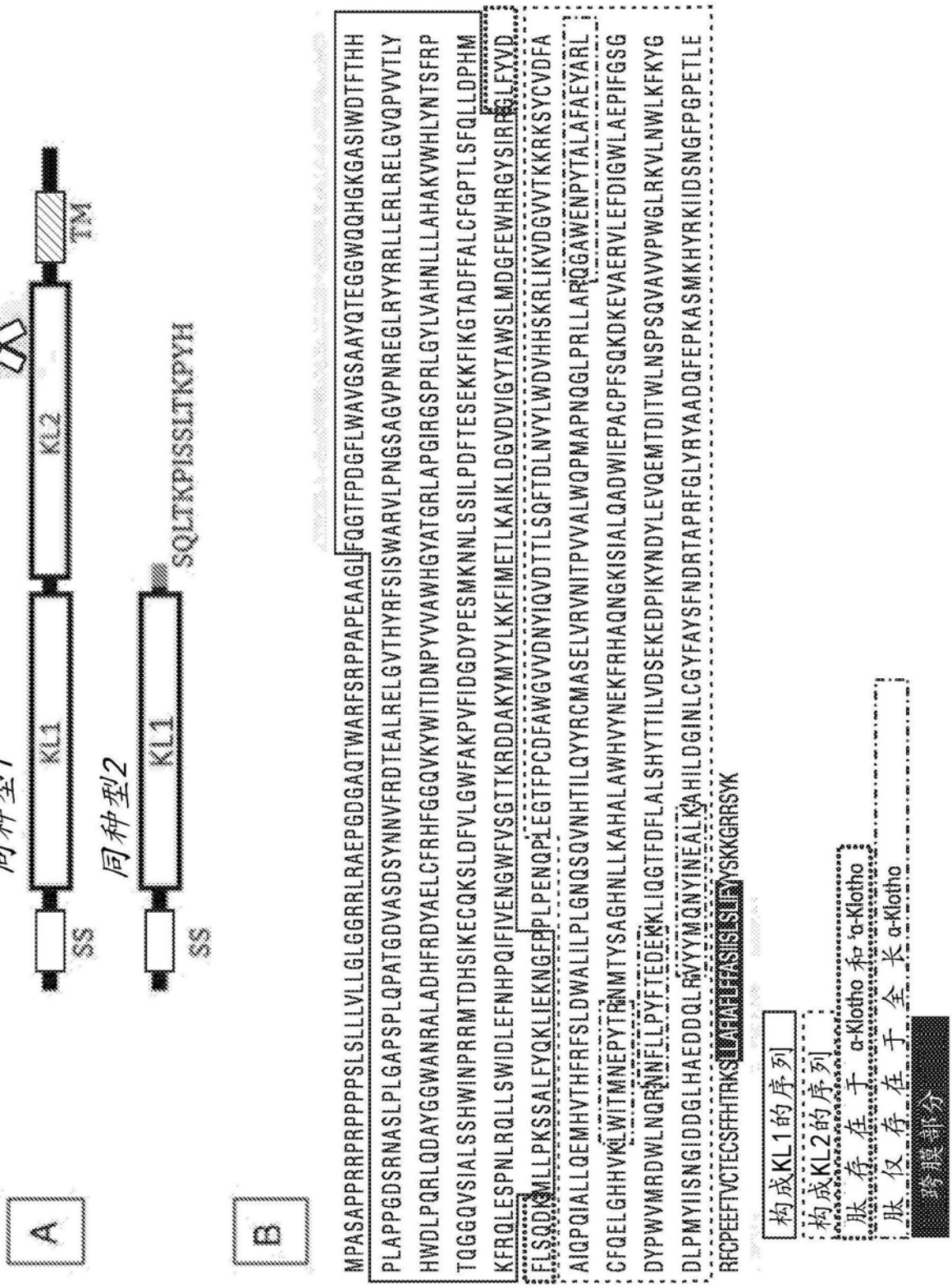
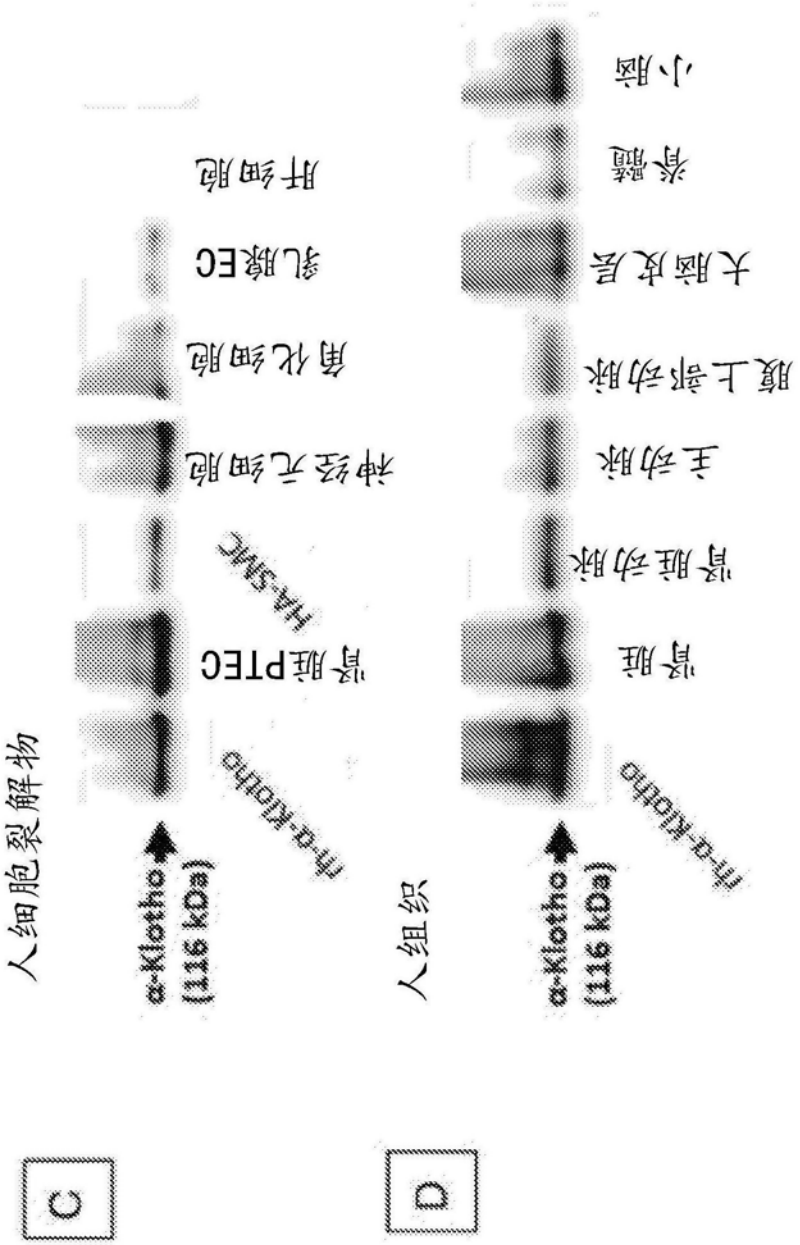

A
同种型1
SS
KL1
KL2
TM
同种型2
SS
KL1
SQLTKPISSLTKPYH
B
构成KL1的序列
构成KL2的序列
肽存在于 α-Klotho 和 β-Klotho
肽仅存在于全长 α-Klotho
跨膜部分

图2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人细胞裂解物
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(116 kDa)
抗-α-Klotho
肾脏PTEC
HA-SMC
神经元细胞
角化细胞
乳腺EC
肝细胞
D
人组织
α-Klotho
(116 kDa)
抗-α-Klotho
肾脏
肾脏动脉
主动脉
腹上部动脉
大脑皮层
脊髓
小脑

图2,续

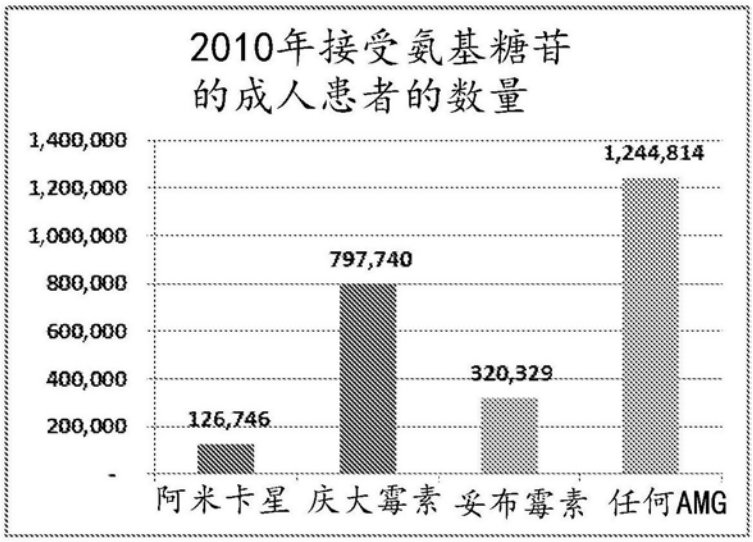
2010年接受氨基糖苷
的成人患者的数量
1,400,000
1,200,000
1,000,000
800,000
600,000
400,000
200,000
-
126,746
797,740
320,329
1,244,814
阿米卡星
庆大霉素
妥布霉素
任何AMG

图3A

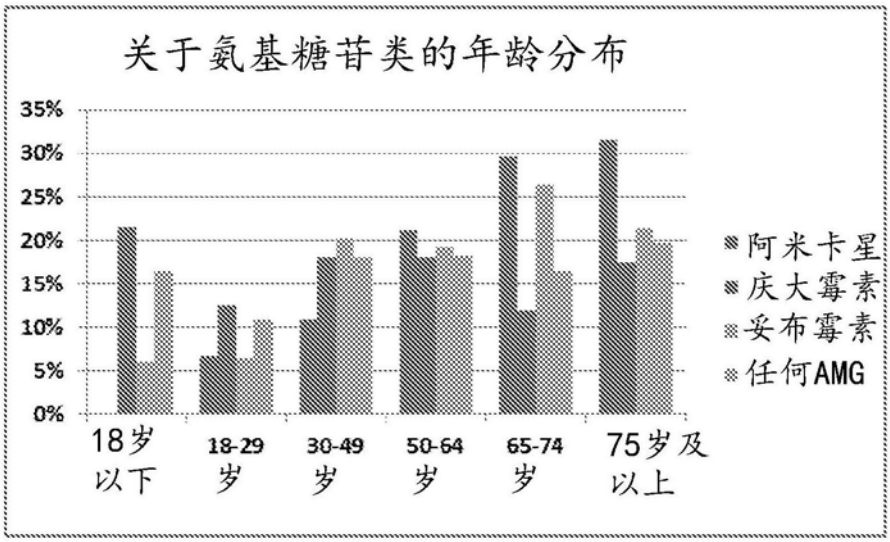
关于氨基糖苷类的年龄分布
35%
30%
25%
20%
15%
10%
5%
0%
18岁
以下
18-29
岁
30-49
岁
50-64
岁
65-74
岁
75岁及
以上
阿米卡星
庆大霉素
妥布霉素
任何AMG

图3B

	阿米卡星	庆大霉素	妥布霉素	氨基糖苷类
留置长度	11.8	8.7	10.4	9.2
出院回家	55.1%	72.0%	62.6%	68.9%
死亡	17.1%	4.1%	6.3%	5.8%
ICU	21.8%	18.2%	21.8%	18.7%
儿童患者(18岁以下)	0.0%	21.6%	6.1%	16.5%
在家护理患者	22.1%	12.5%	20.2%	14.6%
肾病	22.9%	13.5%	16.5%	14.8%
前5 Dx	UTI/膀胱炎 脓毒病 肺炎 皮肤感染 盆腔感染	UTI/膀胱炎 脓毒病 皮肤感染 肺炎 FUO	肺炎 UTI/膀胱炎 脓毒病 皮肤感染 盆腔感染	UTI/膀胱炎 脓毒病 肺炎 皮肤感染 盆腔感染

图4