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(54)发明名称

用于诊断脑损伤或神经退行性变的方法和组合物

(57)摘要

提供用于诊断对象的脑损伤、神经退行性变;或其倾向的方法和组合物。特别地,本发明涉及可用于诊断对象的脑损伤、神经退行性变;或其倾向的特异性抗原抗体反应性。

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1.一种用于诊断对象的脑损伤的方法,所述方法包含下列步骤:

(i)从对象获取样本;

(ii)确定所述样本中的抗体对选自由SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的异构体、其片段、或其组合所组成群组中的至少一种抗原的反应性;以及

(iii)将所述样本中的所述抗体的反应性与健康对照的反应性比较;

其中,与所述健康对照的所述反应性相比,所述样本中所述抗体的显着差异的反应性是所述对象患有脑损伤的指征。

2.如权利要求1所述的方法,其中,所述抗体的所述反应性包含IgG反应性和IgM反应性。

3.如权利要求1所述的方法,其中,所述样本中的所述抗体的所述显着差异的反应性包含差异性的IgG反应性和IgM反应性。

4.如权利要求1所述的方法,其中,所述脑损伤是选自由下列所组成的群组:脑震荡、慢性创伤性脑病、轻度创伤性脑损伤、中度创伤性脑损伤、重度创伤性脑损伤、头部创伤、震荡性损伤及脑神经退行性病症。

5.如权利要求4所述的方法,其中,所述脑神经退行性病症进一步包括记忆或运动功能的衰退。

6.如权利要求5所述的方法,其中,所述神经退行性病症选自下列所组成的群组:阿兹海默症、亨廷顿症、帕金森症、脱髓鞘病、HTLV-1相关的脊髓病(HAM)、多发性硬化(MS)、肌萎缩性脊髓侧索硬化症、损伤或创伤后的病理学神经学症状、脑病和病毒性脑病。

7.如权利要求1所述的方法,其中,所述样本是选自下列所组成的群组:血液、血清、血浆、脑脊液(CSF)、尿液和唾液样本。

8.如权利要求1所述的方法,其中,所述样本是血清样本。

9.如权利要求1所述的方法,其中,健康对照的反应性是选自下列所组成的群组:至少一位健康个体的反应性、来自相同个体的基线样本、来自健康个体集合的一组对照样本、及来自健康对照个体的一组存储数据。

10.如权利要求1所述的方法,包含确定所述样本中抗体对复数种抗原的反应性。

11.如权利要求10所述的方法,其中,所述复数种抗原是以抗原探针集合、抗原阵列、或抗原芯片的形式使用。

12.如权利要求1所述的方法,进一步包含测量所述样本中的一种或多种生物标记物的水平;以及将所述一种或多种生物标记物的所述水平与相同生物标记物的与患有脑损伤的对象关联的预先定义的水平比较及与相同生物标记物的与健康对照关联的预先定义的水平比较,其中与所述预先定义的水平中的一者的关联提供了所述诊断。

13.如权利要求12所述的方法,其中,所述一种或多种生物标记物是选自由下列所组成的群组:胶质原纤维酸性蛋白(GFAP)、突触核蛋白β(Sncb)、金属硫蛋白-3(MT3)、神经颗粒素(NRGN)、细胞间粘附分子-5(ICAM5)和脑源性神经营养因子(BDNF)、或其瓜氨酸化形式。

14.一种抗原探针集合,包含复数种选自由下列所组成的抗原探针:SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的异构体、其片段、或其组合。

15.一种制品,包含如权利要求14所述的抗原集合。

16.如权利要求15所述的制品,进一步包含选自由下列所组成组的一种或多种生物标

记物:胶质原纤维酸性蛋白(GFAP)、突触核蛋白β(Sncb)、金属硫蛋白-3(MT3)、神经颗粒素(NRGN)、细胞间粘附分子-5(ICAM5)和脑源性神经营养因子(BDNF)、或其瓜氨酸化形式。

17.如权利要求15所述的制品,是抗原探针阵列形式或抗原芯片形式或浸染棒形式或侧流测试形式。

18.如权利要求17所述的制品,是试剂盒形式,所述试剂盒进一步包含用于实施如权利要求1所述方法的手段,或使用该试剂盒诊断脑损伤的使用说明书。

19.一种描述对象脑损伤状态的方法,所述方法包含下述步骤:

(i)从所述对象获取样本;

(ii)测定所述样本中的抗体对选自由SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的异构体、其片段、或其组合所组成群组中的至少一种抗原的反应性;以及

将所述样本中的所述抗体的所述反应性与选自有脑损伤、无脑损伤、脑损伤倾向、亚急性脑损伤、急性脑损伤、创伤后脑损伤、进行性脑损伤、退化性脑损伤、亚临床脑损伤、轻度脑损伤、中度脑损伤、重度脑损伤和慢性脑损伤所组成群组中的一种或多种脑损伤状态相关的预先定义的反应性比较,其中,与所述预先定义的反应性中的一者的关联确定了所述对象的所述脑损伤状态。

20.如权利要求19所述的方法,进一步包含测量所述样本中的一种或多种生物标记物的水平;以及,将所述一种或多种生物标记物的水平与相同生物标记物的与一种或多种脑损伤状态关联的预先定义的水平比较,其中,与所述预先定义的水平中的一者的关联确定了所述对象的所述脑损伤状态。

21.如权利要求20所述的方法,其中,所述一种或多种生物标记物是选自由下列所组成的群组:胶质原纤维酸性蛋白(GFAP)、突触核蛋白β(Sncb)、金属硫蛋白-3(MT3)、神经颗粒素(NRGN)、细胞间粘附分子-5(ICAM5)和脑源性神经营养因子(BDNF)、或其瓜氨酸化形式。

22.一种检测对象从脑损伤恢复的方法,所述方法包含下述步骤:

(i)从所述对象获取样本;

(ii)测定所述样本中的抗体对选自由SEQ ID NO:10、SEQ ID NO:61、SEQ ID NO:104、其异构体、其转译后修饰的形式、其片段、或其组合所组成群组中的至少一种抗原的反应性;以及

(iii)将所述样本中的所述抗体的所述反应性与预先定义的反应性阈值比较;其中,所述样本中的所述抗体的相较于所述预先定义的反应性阈值的显着差异的反应性是所述对象体内从脑损伤恢复的指征。

23.如权利要求22所述的方法,其中,所述抗体的反应性包含IgG反应性和IgM反应性。

24.如权利要求22所述的方法,其中,所述样本中的所述抗体的所述显着差异的反应性包含不同的IgG反应性和IgM反应性。

25.如权利要求22所述的方法,进一步包含测量所述样本中一种或多种生物标记物的水平;以及,将所述一种或多种生物标记物的所述水平与相同标记物的与从脑损伤恢复相关联的预先定义的水平比较,其中,与所述预先定义的水平中的一者的关联是所述受验者从脑损伤恢复的指征。

26.如权利要求25所述的方法,其中,所述一种或多种生物标记物是选自由下列所组成的群组:胶质原纤维酸性蛋白(GFAP)、突触核蛋白β(Sncb)、金属硫蛋白-3(MT3)、神经颗粒

素(NRGN)、细胞间粘附分子-5(ICAM5)和脑源性神经营养因子(BDNF)、或其瓜氨酸化形式。

27.如权利要求1、19或22中任一项所述的方法,其中,所述比较是使用至少一种分类算法执行的。

28.如权利要求27所述的方法,其中,所述至少一种分类算法是选自由下列所组成的群组:决策树分类法、逻辑回归分类法(LR)、最近邻分类法、神经网络分类法、高斯混合模型(GMM)、支持向量机(SVM)分类法、最小中值距离分类法、线性回归分类法、线性判别分析(LDA)分类法、二次判别分析(QDA)分类法、和随机森林分类法。

用于诊断脑损伤或神经退行性变的方法和组合物

技术领域

[0001] 本发明涉及用于诊断脑损伤、神经退行性变、或其倾向的方法和组合物，更具体地，涉及用于确定脑损伤或神经退行性变的存在和类型的临床方法。

背景技术

[0002] 脑损伤是复杂的，且可能具有多种严重的临床结局。大脑和脊髓的损伤可能是来自头部创伤、卒中、出生时创伤(traumatic birth)、心脏手术、心搏停止、及需要使用心室辅助装置或体外模式氧合(ECMO)支持的患者。

[0003] 每年大约170万美国人遭受轻度至重度的创伤性脑损伤(TBI)，而且这一数字并不包括大约360,000位牵涉入战斗作业的士兵和从恐怖袭击中幸存的公共安全工作者，而这些人发展出爆炸(震荡)冲击的继发性轻度TBI。这造成了全部损伤相关死亡中的大约30％，且每年耗费约600亿美元。至少230,000人由于TBI住院治疗且存活；超过一百万人进行TBI的急诊(ED)治疗，且80,000至90,000美国人承受由TBI造成的长期失能。

[0004] 近年来进行了研究以确定TBI评估在美国急诊中的维度。每年对480万随访者进行TBI评估；而在82％的TBI评估(每年390万随访者)中进行了头部CT扫描。52％的评估(每年250万随访者)中诊断出TBI。接受头部CT扫描的那些人中，9％具有创伤性异常情况的CT证据。在已经拥有格拉斯哥昏迷量表(GIasgow Coma ScaIe)分数记录的进行TBI评估的患者中，94.5％分类为患有轻度TBI，2.1％患有中度TBI，且3.5％患有重度TBI。在患有《国际疾病分类(第九修订临床修正版)》(CIassification of Diseases,Ninth Revision, CIinicaI Modification)中疾病的患者中，头部简略损伤尺度(Abbreviated Injury ScaIe)分数计算为9.0％、85.0％、2.5％、3.2％、0.3％、及0％的代码分别具有1、2、3、4、5、和6的头部简略损伤尺度分数。在进行TBI评估的患者中，31％具有其它头部/面部/颈部损伤，10％具有脊椎和背部损伤，7％具有躯干损伤，且14％具有极端损伤(KorIey et aI., Sep 10,2015,J Head Trauma RehabiI)。

[0005] TBI是钝击、摇晃或超压冲击头部的结果，其令脑功能紊乱。轻度TBI(mTBI)的子集已经表现更难以诊断TBI的部分。头部损伤的严重度是从精神状态或意识的简要变化到无意识和失忆症的范围内。在重度或多种震荡的情况下，可能出现具有毁灭性结果的人格改变。认知减退被公认为损伤后症状的一部分。

[0006] TBI损伤的妥善处理需要对被影响结构的精确诊断。TBI中的损伤机制造成周边前庭神经机制、中枢前庭结构、眼球运动神经束(ocuIar-motor tracts)、小脑、以及与这些结构沟通的全部脑域中的多种异常情况。前庭神经缺陷的发作通常在损伤后7至10天内出现。尽管有报导，眩晕症状在三个月后解决，15％的人在一年后仍具有顽固症状。

[0007] 目前，当有创伤性脑损伤的怀疑时，尤其主观且并非完全有效的诊断过程之一牵涉大量检查技术。该患者接受可能由下列组成的神经学检查：1)精神状态；2)运动功能；3)感觉检查；4)深部腱反射；5)站立、步态、和平衡；以及6)脑神经功能。该神经状态检查可包括：a)意识水平；b)短期和长期记忆；c)患者和住所信息；以及d)对头痛、眩晕、眼花等症状

提出问题。此外，该患者也可进行放射学研究，该研究可包括头部的CT扫描、MRI、PET扫描。已经有报导，在(尤其是轻度)创伤性脑损伤的早期，成像技术的敏感度可能不足以检测异常情况。此外，患者的认知能力最初可能未受损，且如果有症状，可能存在很少的症状。一般观察患者24至48小时，并每隔一段时间(如，每3至4小时)唤起患者，以确保他们能被唤醒。不给予用于头痛或其它疼痛的麻醉剂，因此，他们的作用不会遮蔽患者清醒状态的问题。一般采用测定认知水平和反应时间的计算机测试来重复检查。

[0008] 使用这一途径诊断潜在的创伤性脑损伤的问题之一是，该途径并不总是提供精确、及时的客观信息。该途径也存在源自人与人之间的个体差异。此外，如果一个人在当时无症状，则结论可能是并不存在问题，且该个体可能被鼓励回归正常活动。这一引导可能对该人的健康有潜在损伤，且甚至可能导致致命性后果。

[0009] 一旦患者被诊断具有脑损伤，为了最小化永久性损伤或死亡的风险，以及时、有效的方式治疗该患者即变得重要。

[0010] 尽管存在前述已知规程，对于早期且有效地确定个体是否罹患脑损伤、其可能的严重程度的方法以及一旦发现该损伤存在时有效治疗该患者的方法仍存在非常实际且本质的需求。

发明内容

[0011] 本发明提供用于诊断脑损伤或神经退行性变的方法和试剂盒。本发明进一步提供用于实践该诊断的抗原探针阵列，以及用于生成该阵列的抗原探针集合。

[0012] 本发明的抗原探针集合可用以概括，在罹患脑损伤或神经退行性变疾病的患者体内，由于破坏解剖结构的任何或全部组分以及检测跨越血脑屏障的要素的能力而得的抗体对于所述抗原的应答。这一抗体应答概况(profiIe)可用于诊断、监控及管理脑损伤。根据一些具体实施例，该抗体模式反映了在损伤当时的患者状态。该抗体应答的模式可在任何平台上测量，该平台包括但不限于微阵列或任何阵列芯片。

[0013] 本发明部分地基于将罹患脑损伤的患者的抗体反应性与健康对照的对比测试而获取的意外结果。令人惊奇的是，在所测试的脑损伤患者中，发现了与健康对照不同的对于特定抗原的免疫球蛋白G(IgG)反应性和IgM反应性。本发明还基于下述发现：将对于个体对特定脑相关分子的抗体应答模式的分析与免疫应答标记物组合，提供了新颖、可靠的探知脑损伤和其它神经退行性变病症的特性和程度的方法。因此，本发明提供指征脑损伤的独特抗原。本发明进一步提供与脑损伤相关的抗原-自身抗体反应性模式。特定的具体实施例中，本发明提供用于诊断或健康脑损伤的高度特异性、可靠、准确及有辨识力的化验，该化验基于该指征性抗原或其反应性模式而进行。根据一些具体实施例，监控在损伤当时的患者状态的“预先存在”。

[0014] 因此，根据本发明的一些具体实施例，提供了用于诊断和监控脑损伤进展的新颖方法。根据本发明的一些具体实施例，该方法包含测定从对象获取或派生的抗体对于本文中揭示的至少一种抗原的反应性。本发明的方法进一步包含将样本中抗体对至少一种抗原的反应性与对照物对于所述至少一种抗原的反应性比较的步骤。根据某些具体实施例，与健康对照的反应或来自相同患者的基线样本的反应性相比，样本中抗体的显着差异的反应性，是该对象为脑损伤所苦的指征。

[0015] 根据某些具体实施例，来自相同患者的基线样本可用于[随时间而测量]，以预测事件的进展、解决以及病程的缓解。

[0016] 根据某些具体实施例，本发明的方法可区别哪些具有脑损伤的患者需要进行头部CT扫描，以将颅内出血与仅存脑震荡区隔。如果作为初始应答(如，在急诊科(ED)环境)或后期应答(如，神经内科)而实施，本发明的方法将减少头部CT扫描的使用，从而减少医疗保健费用和辐射曝露。

[0017] 因此，根据第一方面，本发明提供诊断对象脑损伤的方法，该方法包含下述步骤：从该对象获取样本；确定样本中的抗体与选自由SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的异构体、其片段、或其组合所组成群组中的至少一种抗原的反应性；以及，将该样本中抗体的反应性与健康对照的反应性比较；其中，与健康对照的反应性相比，样本中抗体的显着差异的反应性是该对象患有脑损伤的指征。

[0018] 某些具体实施例中，该至少一种抗原是选自由SEQ ID NO:2、SEQ ID NO:14、SEQ ID NO:28、SEQ ID NO:42、SEQ ID NO:85、SEQ ID NO:86、或其任意组合所组成的群组。

[0019] 某些具体实施例中，所述方法进一步包含测量该样本中一种或多种生物标记物的水平；以及将该一种或多种与相同生物标记物的与患有脑损伤的对象关联的预先定义的水平与相同生物标记物的与健康对照关联的预先定义的水平比较，其中与预先定义中的一种水平的关联提供了该诊断。

[0020] 某些具体实施例中，所述脑损伤是选自由下列所组成的群组：脑震荡、慢性创伤性脑病、轻度创伤性脑损伤、中度创伤性脑损伤、重度创伤性脑损伤、头部创伤、震荡性损伤及脑神经退行性病症。

[0021] 某些具体实施例中，所述脑损伤造成血脑屏障的破坏。

[0022] 某些具体实施例中，该脑神经退行性变病症进一步包含记忆或运动功能的衰退和认知减退。

[0023] 某些具体实施例中，该神经退行性病症是选自由下列所组成的群组：阿兹海默症、亨廷顿症、帕金森症、脱髓鞘病、HTLV-1相关的脊髓病(HAM)、多发性硬化(MS)、肌萎缩性脊髓侧索硬化症(ALS)、损伤或创伤后的病理学神经学症状、脑病和病毒性脑病。

[0024] 某些具体实施例中，样本中抗体的反应性显着高于健康对照的反应性，是对象受苦于脑损伤的可能性增加的指征。其它某些具体实施例中，若样本中抗体的反应性并未显着高于健康对照的反应性，妥样本中抗体的反应性与健康对照的反应性相同，若样本中抗体的反应性低于健康对照的反应性，或者，样本中抗体的反应性显着低于健康对照的反应性，是对象受苦于脑损伤的可能性降低的指征。每一可能性均代表本发明的一种独立具体实施例。

[0025] 本发明方法的某些具体实施例中，该方法是以包含从对象获取或得到样本的步骤为先导。某些具体实施例中，该样本是通过非侵入性手段或方法从对象获取或得到的。

[0026] 某些具体实施例中，所述获取在头部受创2小时内完成。某些具体实施例中，所述获取在头部受创4小时内完成。某些具体实施例中，所述获取在头部受创24小时内完成。某些具体实施例中，所述获取在头部受创72小时内完成。某些具体实施例中，所述获取在急症护理过程中完成。

[0027] 某些具体实施例中，该对象在所述获取的时间是清醒的。

[0028] 某些具体实施例中，测定样本中抗体对复数种抗原的反应性，产生了用于对象脑损伤的诊断的反应性模式。因此，根据本发明的例示性具体实施例，将该样本中抗体对于复数种抗原的反应性模式与健康对照对象的样本中抗体对于所述复数种抗原的反应性模式比较，其中，该样本的反应性模式与健康对照的反应性模式间的显着差异表明，该对象受苦于脑损伤，或在其它具体实施例中，具有脑损伤的可能性增加。传统上，使用例如本文中揭示的学习和模式识别算法来计算并比较该反应性模式。

[0029] 根据另一具体实施例，该反应性包含IgG反应性和IgM反应性。根据另一具体实施例，样本中抗体的显着较高的反应性包含差异性的IgG反应性及/或IgM反应性。根据另一具体实施例，该增加的IgM反应性是相对于选自下列所组成组的至少一种抗原的：SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的异构体、其片段、或前述任意组合。根据另一具体实施例，该增加的IgG反应性是相对于选自下列所组成组的至少一种抗原的：SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的异构体、其片段、或前述任意组合。每一可能性表示本发明的一种独立具体实施例。

[0030] 根据本发明方法的另外的具体实施例，从对象获取的样本是生物体液。根据一些具体实施例，该样本是选自血浆、血清、血液、脑脊液、滑液、精液、尿液、唾液、泪液、淋巴样本、或该领域中已知的任何其它生物体液。每一可能性表示本发明的一种独立具体实施例。根据某些具体实施例，从对象获取的样本选自血清、血浆和血液组成的群组。根据一种具体实施例，该样本是血清样本。某些具体实施例中，通过非侵入性手段或方法从对象获取或派生样本。

[0031] 根据本发明方法的某些具体实施例，该对照选自下列所组成的群组：来自至少一个健康个体的样本、来自相同对象的基线样本、来自一群健康个体的一组对照样本、以及存储的来自健康个体的数据集。每一可能性表示本发明的一种独立具体实施例。典型地，健康个体是不受苦于脑损伤的对象。另一具体实施例中，健康个体是不受苦于神经退行性变疾病的对象。

[0032] 根据另一具体实施例，该方法包含测定该样本中抗体对于复数种抗原的反应性。

[0033] 根据另一具体实施例，该方法包含测定样本中抗体对于选自由下列所组成群组的至少一种抗原的反应性：SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的异构体、其片段、或前述任意组合。根据另一具体实施例，该方法包含测定样本中抗体对于选自下列所组成组的至少两种抗原的反应性：SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的异构体、其片段、或前述任意组合。

[0034] 根据另一具体实施例，该复数种抗原是以抗体探针集合、抗原阵列、或抗原芯片的形式使用。

[0035] 根据另一方面，本发明提供抗原探针集合，其包含选自由下列所组成群组的复数种抗原：SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的异构体、其片段、或前述任意组合。另一具体实施例中，该抗原探针集合包含SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的异构体、其片段、或前述任意组合的抗原探针。

[0036] 根据另一方面，本发明提供包含上文揭示的抗原探针集合的制品。

[0037] 某些具体实施例中，该制品进一步包含选自由下列所组成群组的一种或多种生物标记物：胶质原纤维酸性蛋白(GFAP)、突触核蛋白β(Sncb)、金属硫蛋白-3(MT3)、神经颗粒

素(NRGN)、细胞间粘附分子-5(ICAM5)和脑源性神经营养因子(BDNF)、或其瓜氨酸化形式。

[0038] 某些具体实施例中，该制品是抗原探针阵列形式；或抗原芯片形式；或浸染棒形式；或侧流测试形式；或ELISA板形式；或Quanterix系统、AgiIent读板器、介观尺度诊断平台、或该领域技术人员所知的任何其它平台形式。某些具体实施例中，该制品是试剂盒形式。

[0039] 根据某些具体实施例，该试剂盒进一步包含测定样本中抗体对于复数种抗原中至少一种抗原的反应性的手段。根据另一具体实施例，该试剂盒进一步包含测定不同样本中抗体对于复数种抗原中至少一种抗原的反应性的手段。根据另一具体实施例，该试剂盒进一步包含使用该试剂盒诊断脑损伤的使用说明书。

[0040] 根据另一方面，提供选自SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的异构体、其片段、或前述任意组合所组成组的至少一种抗原的用途；其用于制备用于诊断对象脑损伤的诊断试剂盒。每一可能性表示本发明的一种独立具体实施例。一些具体实施例中，该诊断试剂盒可用于测定样本中抗体的反应性，从而测定该样本对于该至少一种抗原的反应性模式。一些具体实施例中，样本的反应性模式与对照样本的反应性模式之间的显着差异(如，增加)是脑损伤的指征。

[0041] 根据另一方面，提供一种描述对象脑损伤状态的方法，该方法包含下述步骤：从该对象获取样本；确定样本中的抗体与选自由SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的异构体、其片段、或前述任意组合所组成群组中的至少一种抗原的反应性；以及，将样本中抗体的反应性与和选自由脑损伤、无脑损伤、脑损伤倾向、亚急性脑损伤、急性脑损伤、创伤后脑损伤、进行性脑损伤、退化性脑损伤、亚临床脑损伤、轻度脑损伤、中度脑损伤、重度脑损伤和慢性脑损伤所组成群组的一种或多种脑损伤状态相关的预先定义的反应性比较，其中，与预先定义的反应性之一的关联确定了该对象的脑损伤状态。

[0042] 某些具体实施例中，所述方法进一步包含测量该样本中一种或多种生物标记物的水平；以及，将该一种或多种生物标记物的水平与预先定义的相同生物标记物与一种或多种脑损伤状态关联的水平比较，其特征在于，与预先定义的水平之一的关联确定了该对象的脑损伤状态。

[0043] 根据另一方面，一种检测对象体内从脑损伤恢复的方法，该方法包含下述步骤：从该对象获取样本；测定该样本中的抗体与选自SEQ ID NO:10、SEQ ID NO:44、SEQ ID NO:61、SEQ ID NO:66、SEQ ID NO:102、SEQ ID NO:104、其异构体、其转译后修饰的形式、其片段、或其组合所组成组的至少一种抗原的反应性；以及，将该样本中抗体的反应性与预先定义的反应性阈值比较；其中，该样本中抗体的较之于该预先定义的反应性阈值显着差异的反应性是所述对象体内从脑损伤恢复的指征。

[0044] 某些具体实施例中，所述方法进一步包含测量该样本中一种或多种生物标记物的水平；以及，将该一种或多种生物标记物的水平与预先定义的相同标记物的与从脑损伤恢复相关联的水平比较，其特征在于，与预先定义的水平之一的关联是该受验者从脑损伤恢复的指征。

[0045] 某些具体实施例中，该一种或多种生物标记物选自下列所组成的群组：胶质原纤维酸性蛋白(GFAP)、突触核蛋白β(Sncb)、金属硫蛋白-3(MT3)、神经颗粒素(NRGN)、细胞间粘附分子-5(ICAM5)和脑源性神经营养因子(BDNF)、或其瓜氨酸化形式。

[0046] 某些具体实施例中，使用一种或多种抗体与一种或多种生物标记物的组合。

[0047] 根据某些具体实施例，该比较是使用至少一种分离算法执行的。

[0048] 根据某些具体实施例，该至少一种算法选自下列所组成的群组：决策树分类法、逻辑回归分类法、最近邻分类法、神经网络分类法、高斯混合模型(GMM)、支持向量机(SVM)分类法、最小中值距离分类法、线性回归分类法、线性判别分析(LDA)分类法、二次判别分析(QDA)分类法、和随机森林分类法。

[0049] 从下述说明和附图，本发明的其它目的、特征和优势将变得清晰。

附图说明

[0050] 图1例示性说明，在脑损伤后第30天，抗脂肪酸结合蛋白(FABP-3，SEQ ID No:61)IgM自身抗体的水平。格拉斯哥结局量表扩展(GIasgow Outcome ScaIe Extended(GOSE))分数小于8的TBI患者(十字)表示比GOSE分数为8的患者(圆点)低的IgM水平。

[0051] 图2例示性说明，在脑损伤后第30天，抗髓磷脂碱性蛋白(MBPR149，SEQ ID No:10)派生的BSA缀合肽IgM自身抗体的水平。格拉斯哥结局量表扩展(GOSE)分数小于8的TBI患者(十字)表示比GOSE分数为8的患者(圆点)低的IgM水平。

[0052] 图3例示性说明，从TBI患者(圆点)与健康对照(十字)获取的血清样本中抗髓过氧化物酶(MPO，SEQ ID No:85)IgM自身抗体的水平的比较。

[0053] 图4A例示性说明，在损伤后第30天和第90天，从TBI患者(圆点)(N＝142)与健康对照(十字)(N＝21)获取的血清样本中抗CMV(SEQ ID No:86)IgG自身抗体的水平的比较。

[0054] 图4B通过抗巨细胞病毒(CMV)IgG自身抗体水平的受试者工作特征(ROC)曲线而显示上述分离性能。T测试分离P值为3.746E-07，FDR校正后为5.02E-05。

[0055] KruskaI-WaIIis测试分离P值为4.567E-05，FDR校正后为0.0081593。

[0056] 图5A表明，基于在损伤后第30天从TBI患者获取的血清样本中抗TNFRSF12A(SEQ ID No:104)IgM自身抗体的水平，对TBI患者在损伤后第90天的临床状态的预测。将在损伤后第90天具有GOSE<8的TBI患者(圆点)(N＝52)与在损伤后第90天具有GOSE＝8的TBI患者(十字)(N＝15)比较。

[0057] 图5B通过抗TNFRSF12A IgM自身抗体水平的受试者工作特征(ROC)曲线而显示上述分离性能。T测试分离P值为6.808E-06，FDR校正后为0.0036493。

[0058] KruskaI-WaIIis测试分离P值为0.0004082，FDR校正后为0.1541973。

[0059] 图6显示六种分类方法(SVM、LR、QDA、CART、RF和LDA)的基于100次迭代的70:30交叉验证的受试者工作特征(ROC)曲线下面积。根据特征的中值得分或模型内含的频率而将特征排名，采用何种参数取决于所使用的方法。

[0060] 将在时间0(t0，N＝85)从TBI患者获取的血清样本与从健康对照(HC，N＝21)获取的血清样本比较。基于464iChip特征(232抗原、IgM和IgG)以及四种ELISA特征进行分析。iChip数据是基于两个阻断复本的平均，再进行校正过程而获得。ELISA特征是基于数据可应用性而选择的；仅使用具有可用于>80％的iChip样本的数据的特征。从该分析中移除ELISA数据缺失的样本。

[0061] 图7显示，六种分类方法(SVM、LR、QDA、CART、RF和LDA)的基于100次迭代的70:30交叉验证的ROC曲线。根据特征的中值得分或模型内含的频率而将特征排名，采用何种参数取

决于所使用的方法。将在时间0(t0)从TBI患者获取的CT结果异常的血清样本与在时间0(t0)从TBI患者获取的CT结果正常的样本比较。基于464iChip特征(232抗原、IgM和IgG)以及四种ELISA特征进行分析。iChip数据是基于两个阻断复本的平均,再进行校正过程而获得。ELISA特征是基于数据可应用性而选择的;仅使用具有可用于>80%的iChip样本的数据的特征。从该分析中移除ELISA数据缺失的样本。

具体实施方式

[0062] 本发明提供诊断对象脑损伤或伸进退行性病变的方法。本发明进一步提供用于实践该诊断的抗原探针集合或阵列,且检定用于生成该集合或阵列的具体抗原探针集合。

[0063] 不欲受缚于任何理论或作用机制,本发明部分地基于对在健康对象与罹患脑损伤的患者间具有高度差异的独特抗原的发现。本发明进一步基于下述发现:罹患脑损伤的患者血清中的抗体反应性概况明显不同于健康对照个体。尽管脑损伤患者的蛋白标记物已经被广泛研究,本文中揭示的独特抗体免疫现象在之前未被揭示。较佳地,本公开的独特抗体现象对脑损伤的诊断提供高敏感性和特异性化验。

[0064] 一些具体实施例中,本发明提供独特的抗原-抗体反应性模式,特别是与脑损伤相关的模式。在具体抗体的研究进程中,发明人使用抗原微阵列和信息学分析,检查了健康人和被诊断具有脑损伤的那些人的血清中IgM和IgG相对于多种抗原的反应性。

[0065] 定义

[0066] 应理解,本文中使用的术语仅用于揭示特定具体实施例的目的而非限制。必须注意,如在说明书和权利要求书中所使用的,除非明确排除,单数形式“一”和“该”包括复数形式。

[0067] 本文中使用的术语“约”意为数量术语加减5%,或在另一具体实施例中为加减10%,或在另一具体实施例中为加减15%,或在另一具体实施例中为加减20%。

[0068] 本文中,术语“自身抗体”指的是能与个体自身组织或细胞的抗原性构成进行对抗反应的抗体(如,识别并结合至“自身抗原”的抗体)。

[0069] 术语“脑损伤”指的是一种情况,该情况下,大脑因为由事件造成的损伤而受损。本文中所使用,“损伤”是细胞或分子完整性、活性、水平、鲁棒性、状态、或其它可追踪至事件的改变。例如,损伤包括细胞或分子特征的物理性、机械性、化学性、生物性、功能性、传染性、或其它调整。事件可包括物理性创伤如冲击(敲击或震荡),或生物学异常情况如血管阻塞或渗漏造成的卒中。视需要,事件是通过传染因子(infectious agent)造成的传染。该领域技术人员知道术语损伤或事件所涵盖的众多等效事件。

[0070] 根据本发明的方法的一些具体实施例,也诊断健康对象将来脑损伤发作的倾向。根据一些具体实施例,所述倾向的原因是早前的损伤或家族史。

[0071] 更具体地,术语“脑损伤”指的是导致中枢神经系统受损的病症,而不考虑其病理生理学基础如何。“脑损伤”的最常见肇因是卒中和创伤性脑损伤(TBI)。“卒中”分为出血性卒中和非出血性卒中。出血性卒中的实例包括脑出血、蛛网膜下出血、及作为脑动脉畸形继发症的颅内出血,而非出血性卒中包括脑梗死。

[0072] 术语“脑损伤”也指的是亚临床脑损伤、及缺氧缺血性脑损伤。术语“亚临床脑损伤”(SCI)指的是不具有明显脑损伤临床证据的脑损伤。当脑损伤确实存在时,脑损伤临床

证据的缺失可能是损伤程度、损伤类型、意识水平、以及药物治疗特别是镇静和麻醉造成的结果。这些原因多数可导致慢性创伤性脑病(CTE)。

[0073] 本文中所使用,术语“创伤性脑损伤”应意为由一次或多次直接或间接的冲击载荷造成的脑损伤,该冲击载荷被施加至脑而造成该载荷迅速移动且非自然地进入患者颅骨内,且创伤性脑损伤应明显包括,但不限于,通过下列造成的脑损伤:(a)贯穿颅骨的物体,如子弹、箭头、及其它穿过颅骨并进入脑内的物体;(b)施加至头部或患者身体其它部位的冲击载荷;(c)外科手术诱发的创伤;(d)造成个体站立处相对较近距离内大地重大震颤的爆炸,如可能在战争中存在的通过手榴弹、炸弹、及其它爆炸物的冲击产生的爆炸,以及类似的由非爆炸手段如运动损伤、交通事故、建筑物倒塌和地震造成的震颤。创伤性脑损伤的结果可能是各种类型的,但在每个实例中,将包括脑正常工作的能力的临时性或永久性下降且可造成死亡。

[0074] 由于对脑的冲击造成内皮细胞的渗透性增加,从而令流体可以从血管结构进入脑内,因此创伤性脑损伤的常见后果之一是脑内炎症的产生。这些渗漏出现的常见原因是创伤造成血管孔隙度增加,从而令血清从血管渗漏至脑域中。随着这一机制的建立,可产生脑的炎症和肿胀,而这些可能需要手术干预。

[0075] 临床上,基于包括意识丧失(LOC)、格拉斯哥昏迷量表(GCS)和创伤后应激性失忆症的持续时间的TBI变量,创伤性脑损伤可分为轻度、中度或重度。

[0076] 本文中所使用,“二次脑创伤”指的是,在急性脑损伤后,即TBI的二次损伤期内,对患者脑部的损害。

[0077] “慢性创伤性脑病(CTE)”是在曝露于重复的头部碰撞的个体,如拳击手和足球运动员,死后尸检中最常被鉴定的神经退行性疾病。CTE的神经病理学特征为,与其它神经退行性疾病包括阿兹海默症截然不同的模式而过度磷酸化的tau蛋白的蓄积。CTE的临床特征往往是累进性的,导致情绪、行为和认知的巨大改变,常常造成退行性痴呆的结果。一些例子中,也可能存在运动机能特征,包括震颤麻痹。

[0078] “非创伤性脑损伤”指的是并不牵涉局部缺血或外部机械力的脑损伤(如,卒中、阿兹海默症、帕金森症、亨廷顿症、多发性硬化、肌萎缩性脊髓侧索硬化症、脑出血、脑感染等)。

[0079] “卒中”指的是作为脑内出血或梗死的结果的脑组织损毁。卒中是发达国家中死亡的首要肇因。卒中可能是脑部一个区域内血流减少或组织死亡(梗死)所造成的。卒中的肇因包括在脑内血管中形成的血块(血栓)和从其它位置移动到脑部的血块或多个动脉粥样硬化斑块或其它材料(栓塞)。脑内流血(出血)也可造成类似卒中的症状。

[0080] “阿兹海默症(AD)”是非常普遍的、仍不可逆的、进展性脑部疾病,其缓慢地摧毁记忆力和思考能力,并最终摧毁完成最简单任务的能力。AD是老年人群体中痴呆的最常见肇因,其造成认知功能性思考、记住、和推理能力的丧失,丧失程度为妨碍日常生活和活动。预测人数有所不同,但专家认为多达510万美国人可能患有AD。目前,对罹患AD或其早期阶段或具有家族性AD病史的人群、或罹患遗忘性轻度认知功能障碍(MCI)的人群进行的脑部成像,正在开始检测其脑部的改变。AD的临床性痴呆与老年斑的明显病理学配合。AD的特征为淀粉体β在脑实质和脑毛细血管中的的异常蓄积和沉积,其导致血脑屏障(BBB)受损。

[0081] 本文中所使用,“慢性脑损伤”指的是对象从损伤后三天即遭受脑损伤之苦,到至

少12个月之前，仍持续存在脑损伤的症状。

[0082] 本文中所使用，“亚急性脑损伤”指的是对象在损伤后2至5天遭受脑损伤之苦。

[0083] 本文中所使用，“有意识的”具有传统意义，如Plum,et al.,The Diagnosis of Stupor and Coma,CNS Series,Philadelphia:Davis(1982)中所详述，该文献通过引用并入本文。有意识的患者包括那些具有能证明其自我意识或所处环境的可靠、可再生、互动行为的患者。有意识的患者包括恢复意识且具有较不严重的脑损伤的患者，但不包括引物其认知功能被损害而无法独立生活的患者。有意识的患者不包括展现觉醒状态但缺乏互动的那些(如，被认为处于持续性植物状态的那些人)。

[0084] 在曝露于头部创伤后仍有意识的对象可能没有任何可观察的创伤性脑损伤症状。相反，该对象也可能展现多种脑损伤症状和认知功能障碍。

[0085] 这与在获取时没有意识的对象相反，该没有意识的对象以诸如脑震荡或颅内出血状况(如，轴向内血肿、硬膜外血肿、及硬脑膜下血肿)为指征。

[0086] 短语“脑损伤状态”包括状况的任何可区别的表现形式，该状况包括不具有脑损伤。例如，脑损伤状态包括而不限于，患者体内脑损伤的存在或不存在、发展出脑损伤的风险、脑损伤的节段或严重性、脑损伤的进展(如，脑损伤随时间的进展)和脑损伤治疗的有效性或应答(如，治疗后对脑损伤的临床跟踪和监督)。基于这一状态，可指明进一步的规程，包括另外的诊断性测试或治疗性规程或方案。

[0087] “脊髓损伤”指的是一种状况，在该状况下，脊髓受到由椎骨骨折或脱臼造成的压迫/磨损而造成机能障碍。本文中所使用，术语“缺氧缺血性脑损伤”指的是对脑组织的供氧匮乏导致脑功能受损，且包括脑缺氧。例如，缺氧缺血性脑损伤包括局灶性脑缺血、全局性脑缺血、乏氧性缺氧(即，环境中有限的氧造成脑功能的下降，如潜水员、飞行员、登山者、和消防员，全部处于这种脑缺氧的风险之下)、肺功能障碍(如，噎、勒杀、气管破碎造成的缺氧)。

[0088] 术语“脑损伤生物标记物(BIB)”、“脑损伤生物标记蛋白”、“脑损伤生物标记肽”、“脑损伤生物标记多肽”等指的是一种蛋白质，包括本文中揭示的那些，其可用于本发明的方法中如诊断患者的脑损伤。脑损伤生物标记蛋白包括，但不限于，SNCB、GFAP、S100B、MT3、ICAM5、BDNF、及/或NSE。该术语也包括该领域中已知的其它脑损伤生物标记蛋白，包括神经颗粒素(NRGN)、髓鞘碱性蛋白(MBP)、PAD-2、微管蛋白β-4B链、微管蛋白α-IB链、CNPase、PPIA、Septin-7、伸长因子I-α2、TPPP、TPPP3、Ermin异构体2、NDRG2异构体2、星形肌动蛋白1(ASTN1)、脑血管生成抑制剂3(BAD)、肌肽二肽酶1(CNDP 1)、ERMTN、谷氨酸受体代谢型3(GRM3)、类科尔奇蛋白32(KLH32)、黑素瘤抗原家族E,2(MAGE2)、神经调节蛋白3(NRG3)、少突细胞髓磷脂糖蛋白(OMG)、溶质载剂家族39(锌转运子)、内质网膜蛋白1(RTN1)、及肽酰精氨酸脱亚氨酶(1型至4型、6型)(PAD)。

[0089] 此外，术语“脑损伤生物标记物”还包括前述任一者的异构体及/或转译后修饰的形式。本发明关注未修饰和修饰的(如，瓜氨酸化或其它转译后修饰)蛋白质/多肽/肽以及对于前述任一者的自身抗体的检测、测量、定量、测定等。某些具体实施例中，理解为，关于对生物标记物的检测、测量、测定等，泛指对蛋白质/多肽/肽(修饰及/或未修饰)的检测。其它具体实施例中，关于生物标记物的检测、测量、测定等，泛指对该蛋白质/多肽/肽的自身抗体的检测。

[0090] 本文中所使用，术语“比较”指的是，对来自患者的样本中抗体的反应性与标准样本或对照样本中相应抗体的反应性如何关联做出评估。例如，“比较”可以指，评估来自患者样本的抗体对一种或多种抗原的反应性是否等于、高于或低于、或不同于来自标准样本或对照样本的相应抗体的反应性。更具体地，该术语可以指，评估来自患者的样本的抗体对于一种或多种抗原的反应性是否等于、高于或低于、不同于、或反而对应于(或不对应于)抗体的预先定义的反应性，该抗体的预先定义的反应性与例如具有亚临床脑损伤(SCI)、不具有SCI、响应对SCI的治疗、不响应对SCI的治疗、似乎响应/不响应特定的SCI治疗、或具有/不具有另一疾病或病症的患者相对应。

[0091] 本文中所使用，关于参数如来自患者的样本中抗体的经调整的反应性的术语“表明”或“相关”(根据语境，或“指示”或“关联”或“指征”或“相互关系”)，可以意为该患者具有脑损伤。具体的具体实施例中，该参数可包含抗体对本发明的一种或多种抗原的反应性。抗体对一种或多种抗原的特定反应性可表明患者具有脑损伤(即，与患者具有脑损伤相关)。其它具体实施例中，抗体对一种或多种抗原的特定反应性可能与患者未受影响相关(即，表明患者不具有脑损伤)。某些具体实施例中，如根据本发明而使用的“表明”或“相关”，可以是通过描述抗体反应性水平与标准、对照或比较性值之间关系的任何线性或非线性的方法，进行对该诊断的评估、脑损伤或脑损伤进展的预测、临床治疗功效的评估、对可能相应特定的治疗方案或药剂的患者的鉴定、监控治疗进展、以及在筛选化验情境中用于抗脑损伤治疗性的鉴定。

[0092] 根据一些具体实施例，对脑损伤进展的监控是在损伤后第7至20天的时间点进行的，在那时神经循环重新连接开始出现。根据一些具体实施例，预测到对于神经循环系统的损害。

[0093] 术语“患者”、“个体”、或“对象”在本文中可互换使用，且指的是哺乳动物，特别是人。该患者可能具有轻度、中度或重度疾病。该患者可以是初治、正在对任何形式的治疗产生应答、或难治。基于特定症状或家族史，该患者可以是需要治疗或需要诊断的个体。一些例子中，该术语可以指治疗实验动物、兽医应用中的动物、及用于疾病的动物模型研发中的动物，包括但不限于，啮齿动物，包括小鼠、大鼠和仓鼠；以及灵长类动物。

[0094] 本文中所使用，术语“健康对照”指的是健康个体；来自相同个体的基线；复数个健康个体；与一个或多个健康个体相关或自其获取的数据集合或值。

[0095] 本文中所使用，术语“扩展格拉斯哥结局量表(GOSE)”将TBI后的功能性失能分为级别1至8，其中，1为死亡，而8为恢复高于良好。将GOSE分数<8的定义为功能性失能。

[0096] 术语“测量”、“检测”和“测定”通篇可互换使用，且指代是包括获取患者样本并检测样本中抗体反应性的方法。一些具体实施例中，该术语指的是获取患者样本并检测该样本中抗体对一种或多种抗原的反应性。可通过该领域已知的方法和本文中进一步揭示的那些来实施测量。

[0097] 术语“样本”、“患者样本”、“生物样本”等，涵盖从患者、个体或对象获取的多种样本类型，且可用于诊断或监控化验中。患者样本可从健康对象、患病的患者或具有脑损伤相关症状的患者获取。此外，从患者获取的样本可分成几部分，并仅将一部分用于诊断。再者，该样本或其部分可在一定条件下存储以保存样本以供后续分析。该定义具体地涵盖血液和生物来源的其它液体样本(包括但不限于，外周血、血清、血浆、脑脊液、尿液、唾液、粪便和

滑液)。特定具体实施例中,样本包含血液样本。另一具体实施例中,使用血清样本。该定义也包括已经在其取得之后以任何途径操作的样本,如通过离心、过滤、沉淀、渗析、色谱、使用试剂处理、洗涤、或富集某些细胞群体操作的样本。该术语进一步涵盖临床样本,还包括培养物中的细胞、细胞上清液、组织样本、器官等。样本也可包含新鲜冷冻及/或福尔马林固定、石蜡包埋的组织块,如从临床或活体组织切片制备的块,制备用于病理学分析或通过免疫组化进行研究。

[0098] 该样本可在采集后立即测试,或在4℃、-20℃、或-80℃储存后测试。在储存24小时、1周、1个月、1年、10年、或长达30年后测试。

[0099] 本发明的多种方法包括牵涉将值、水平、特征、特点、性质等与"适当对照"比较的步骤,本文中可互换地指代为"适宜对照"或"对照样本"。"适当对照"、"适宜对照"或"对照样本"是该领域技术人员所熟知的用于比较目标的任何对照或标准。一种具体实施例中,"适当对照"或"适宜对照"是在细胞、器官、或患者如对照或正常细胞、器官或患者中测定的展现俩人正常特质的值、水平、特征、特点、性质等。例如,来自未受影响的个体(UI)或正常对照个体(NC)(本文中两个术语可互换使用)的样本中抗体的反应性。另一具体实施例中,"适当对照"或"适宜对照"是在对患者实施治疗(如,对脑损伤的治疗)之前测定的值、水平、特征、特点、性质等。又一具体实施例中,可在对细胞、器官、或患者给予治疗之前、之中或之后,测定转录速率、mRNA水平、转译速率、蛋白质水平、生物学活性、细胞特点或性质、基因型、表型等。再一具体实施例中,"适当对照"或"适宜对照"是预先定义的值、水平、特征、特点、性质等。"适当对照"可以是抗体对至少一种与脑损伤关联的抗原的反应性概况或模式,患者样本可与该至少一种抗原比较。该患者样本也可与阴性对照比较,该阴性对照即为与不具有脑损伤相关联的概况。

[0100] 可使用该领域中广为人知的方法来纯化或合成待用于本发明化验中的抗原探针。例如,可使用已知的重组或合成方法生产抗原性蛋白或肽,该方法包括但不限于,固相(如,Boc或f-Moc化学)和溶液相合成方法(Stewart and Young,1963;Meienhofer,1973;Schroder and Lupke,1965;Sambrook et aI.,2001)。该领域技术人员将掌握所需要的专门知识以获取或合成本发明的抗原探针。一些抗原探针也可商购,如从Sigma(St.Louis,Mo.,USA)、Prospec(Ness-Ziona,IsraeI)、Abnova(Taipei City,Taiwan)、Matreya LLC(PIeasant Gap,Pa.,USA)、Avanti PoIar Lipids(AIabaster,AIa.,USA)、CaIbiochem(San Diego,CaIif.,USA)、Chemicon(TemecuIa,CaIif.,USA)、GeneTex(San Antonio,Tex.,USA)、Novus BioIogicaIs(LittIeton,CoIo.,USA)、Assay Designs(Ann Arbor,Mich.,USA)、ProSci Inc.(Poway,CaIif.,USA)、EMD Biosciences(San Diego,CaIif.,USA)、Cayman ChemicaI(Ann Arbor,Mich.,USA)、HyTest(Turku,FinIand)、Meridian Life Science(Memphis,Tenn.USA)和Biodesign InternationaI(Saco,Me.,USA)获取,如下文详述。

[0101] 应注意,本发明使用抗原探针及其同源物、片段、部分序列、突变形式、修饰形式和衍生物,只要这些同源物、片段、部分序列、突变形式、修饰形式和衍生物与这些抗原探针可免疫地交叉反应。本文中使用的术语"免疫地交叉反应"指的是,通过相同抗体特异性键结的两种或多种抗原。本文中使用的术语"同源物"指的是,具有与抗原氨基酸序列的至少70%、至少75%、至少80%、至少85%或至少90%一致性的肽。可通过大量免疫化验技术的

任一者如竞争化验(测量所测试抗原竞争性抑制抗体与其已知抗原的结合的能力)测定交叉反应性。

[0102] 术语“肽”典型指的是长度最多为约50个氨基酸残基的多肽。根据特定的具体实施例,本发明的抗原性肽的长度可以是10至50个氨基酸,典型地,长度为约10至30个或约15至25个氨基酸。

[0103] 该术语涵盖原生肽(降解产物、合成性合成肽、或重组肽)、模拟肽(典型为合成性合成肽)、及肽类似物类肽和半类肽,且可具有例如令该肽在身体内更稳定或更能渗透入细胞内的修饰。此类修饰包括,但不限于:N端修饰;C端修饰;肽键修饰;骨架修饰;以及残基修饰。

[0104] 本发明中的肽抗原可具有末端羧基;可作为羧基酰胺使用;可作为还原的末端羟基使用;或可作为药学可接受的盐,如金属盐,包括钠盐、钾盐、锂盐或钙盐,或作为与有机酸的盐,或作为与矿物酸包括硫酸、盐酸或磷酸的盐,或作为与有机酸如醋酸或马来酸的盐。根据一些具体实施例,本发明的肽抗原是BSA缀合肽。

[0105] 功能性衍生物由对氨基酸侧链及/或羧基及/或所述肽的氨基部分的化学修饰组成。此类衍生化的分子包括,例如,其中游离氨基已经被衍生为形成胺盐酸盐、对甲苯磺酰基、苄氧羰基、叔丁氧羰基、氯乙酰基或甲酰基的那些分子。将游离的羧基可衍生以形成盐、甲酯、乙酯、或其它类型的酯或酰肼。将游离的羟基可衍生以形成O-酰基或O-烷基衍生物。组氨酸的咪唑氮可衍生以形成N-im-苄基组氨酸。还包括的化学衍生物为含有天然存在的20种标准氨基酸残基或其修饰的氨基酸衍生物。例如:4-羟基脯氨酸可以替代脯氨酸;羟基赖氨酸可以替代赖氨酸;3-甲基组氨酸可以替代组氨酸;高丝氨酸可以替代丝氨酸;以及,鸟氨酸可以替代赖氨酸。

[0106] 除非明确排除,本文中揭示的氨基酸残基是“L”同分异构型式。然而,“D”同分异构型式的残基可替代任何L-氨基酸残基,只要该肽基本保留所希望的抗体特异性即可。

[0107] 通过当下标准肽合成方法和设备或重组方法可轻易合成适当的类似物。关于其氨基酸序列,全部这些类似物将主要基于本发明的抗原,但将具有一个或多个被删除、替代、或加入的氨基酸残基。当氨基酸残基被替代时,所设想的此类保守置换为那些并不显着改变该多肽的结构或抗原性的置换。例如,碱性氨基酸将被替换为其它碱性氨基酸,酸性氨基酸被替换为其它酸性氨基酸,而中性氨基酸被替换为其它中性氨基酸。处理包含上述保守替代的类似物之外,进一步设想了包含非保守氨基酸替代的类似物,只要这些类似物可与本发明的肽抗原进行免疫交叉反应即可。

[0108] 另一方面,提供编码这些肽的核酸、包含这些核酸的载体、以及含有该载体的宿主细胞。这些核酸、载体和宿主细胞可通过该领域中已知的重组技术轻易生产(间,如,Sambrook et aI.,2001)。例如,编码本发明抗原的分离的核酸序列可从其天然来源作为完整(即,完全)基因或其一部分而获取。核酸分子也可使用重组DNA技术(如,聚合酶链反应(PCR)扩增、克隆)或化学合成生产。核酸序列包括天然核酸序列及其同源物,包括但不限于,天然等位基因突变体和修饰核酸序列,其中,核苷酸已经被插入、删除、替代、及/或反转,以此方式,这些修饰并不显着干扰该核酸分子编码本发明的功能性肽的能力。

[0109] 本文中所使用,本发明的多肽或肽抗原的“功能等效突变体”是具有部分序列同源性的多肽或肽、具有一个或多个特异性保守及/或非保守氨基酸变化的多肽或肽、以及并不

改变该多肽或肽的生物学性质或结构性质的多肽或肽缀合产物。

[0110] 对于术语“功能性类似物”，该领域技术人员很好地理解，生物学功能性多肽或肽类似物的定义中所固有的是下述概念，对于可在分子所定义部位内作成的且仍导致分子具有可接受的等效生物学活性水平的改变的数目存在限制。根据本发明，可容易做出和使用复数种具有不同替代的有区别的多肽或肽。还应理解，某些残基对于多肽的生物学性质或结构性质尤其重要，且这些残基通常不可交换。

[0111] 可通过保守或非保守氨基酸替代生成功能性类似物。氨基酸替代通常基于氨基酸侧链取代基的相对相似性，例如，它们的疏水性、亲水性、电荷、体积等。因此，在本发明的范畴内，保守氨基酸变化意为，特定位置的氨基酸变化为与最初存在者相同类型的氨基酸；即，疏水性氨基酸交换为疏水性氨基酸，碱性氨基酸交换为碱性氨基酸等。保守替代的实例包括，非极性(疏水性)残基如异亮氨酸、缬氨酸、亮氨酸或甲硫氨酸替代为另一非极性(疏水性)残基；一个极性(亲水性)残基替代为另一个极性(亲水性)残基，如精氨酸与赖氨酸之间、谷氨酰胺与天冬氨酰胺之间、甘氨酸与丝氨酸之间；一个碱性残基如赖氨酸、精氨酸或组氨酸替代为另一个碱性残基；一个酸性残基如天冬氨酸或谷氨酸替代为另一个酸性残基；支链氨基酸如异亮氨酸、亮氨酸或缬氨酸替代为另一个支链氨基酸；或者，一个芳香族氨基酸如苯丙氨酸、酪氨酸或色氨酸替代为另一个芳香族氨基酸。氨基酸的这些变化得到了功能性类似物，其中，它们并不显着改变该多肽的整体电荷及/或构型。此类保守变化的实例是该领域技术人员所熟知的，且处于本发明的范畴内。保守替代也包括使用化学衍生残基代替非衍生残基，但须满足，所得多肽与该多肽抗原是生物学功能等效的。

[0112] 因此，“瓜氨酸化多肽”涵盖一种多肽，该多肽所具有的氨基酸序列与本文中提供的序列的差别在于一个或多个保守氨基酸替代。瓜氨酸化多肽也涵盖一种具有与本文中提供的序列相差一个突变的氨基酸序列的多肽，其中，该一个突变表示一个氨基酸删除、插入或替代。

[0113] 可通过该领域技术人员已知的方法作成瓜氨酸化的肽，最特别且优选的是使用蛋白质化学领域广为人知的技术通过化学合成如固相合成(Merrifield et al,65J.AM.CHEM.ASSOC.2149(1964);Merrifield et al,85J.AMER.CHEM.SOC.2149(1963);及Merrifield et al,35lNT.J.PEPTlDE PROTElN RES.161-214(1990))或在均相溶液合成(METHODS OF ORGANlC CHEMlSTRY,E.Wansch(Ed.)Vol.15,pts.l and ll,Thieme,Stuttgart(1987))来生成合成肽。瓜氨酸是转译后修饰的精氨酸，它是通过由肽酰基精氨酸脱亚氨酶4(PAD-4)催化的脱亚氨过程创建的，该过程从精氨酸移除一个正电荷并令所得瓜氨酸事实上是极性的。

[0114] 一种具体实施例中，可从已知的可商购来源制作瓜氨酸化的肽。在这方面，将冻干蛋白质在适宜的加入有该肽酰基精氨酸脱亚氨酶4的缓冲液中重建。或者，将Ca^{2+}加入PAD-4溶液中。令该溶液在适宜温度静置一段时间，该时间足以造成精氨酸残基修饰为瓜氨酸并因此创建瓜氨酸化的蛋白质。随后，使用高分子量膜移除该酶以分隔该酶或其它色谱方法来分离瓜氨酸化的蛋白质。该领域技术人员将理解，可依据被脱亚氨化的蛋白质，改动培养温度、缓冲条件和培养时间(Masson-Bessiere et al,166J.lMMUNOL.4177-4184(2001))。

[0115] 可通过基于其由序列决定的性质而选择的方法，进一步分离和纯化瓜氨酸化的蛋白质。可通过蛋白质纯化过程如色谱方法(凝胶过滤、离子交换、和免疫亲和性)、高效液相

色谱(HPLC、RP-HPLC、离子交换HPLC、体积排阻HPLC、高效层析聚焦和疏水作用色谱)或通过沉淀(免疫沉淀)实现纯化。

[0116] 聚酰胺凝胶电泳也可用来基于蛋白质的分子量、电荷性质和疏水性而分离瓜氨酸化的蛋白质。经纯化的瓜氨酸化的蛋白质可用于进一步的生物化学分析中,以确立二级结构和三级结构,而该结构可能有助于药物与该蛋白质相互作用、改变蛋白质电荷构型或与其它蛋白质的电荷相互作用、或改变其功能。

[0117] 本文中所使用,术语"寡核苷酸抗原"指的是,某一长度的邻接核苷酸的伸展。除非明确排除,本文中使用的术语"寡核苷酸抗原"涉及长度为15至40个核苷酸之间、或者长度为17至28个核苷酸之间、或长度为18至25个核苷酸之间的核苷酸序列。某些具体实施例中,寡核苷酸抗原由至少4个、至少5个、至少6个、至少7个、至少8个、至少9个、至少10个、至少16个、或更多个邻接核苷酸组成。每一种可能性表示本发明的一种独立具体实施例。某些具体实施例中,抗原由不超过50个、不超过45个、不超过40个、不超过35个、不超过30个、不超过25个、不超过20个、不超过16个、或更少个邻接核苷酸组成。每一种可能性表示本发明的一种独立具体实施例。某些具体实施例中,抗原由10至30个、15至25个、或17至20个邻接核苷酸组成。某些具体实施例中,抗原由17、18、19、或20个邻接核苷酸组成。

[0118] 本文中所使用,相对于"抗原"或"复数种抗原"的"样本中多种抗体的反应性"或"样本中抗体的反应性"指的是,样本中至少一种抗体性对于选自复数种抗原的至少一种特异性抗原的免疫反应性。该抗体相对于抗原的免疫反应性,即该抗体特异性结合至抗原的能力,可用来测定样本中该抗体的量。样本中每一种所测试抗体的计算水平,统统指代为该样本相对于这些抗原的反应性模式。该样本的反应性模式反映该样本中每一种所测试抗体的水平,从而提供定量检验。优选的具体实施例中,该抗体被定量测定。

[0119] 在不同的具体实施例中,反应性模式间的"显着差异"指的是统计学显着差异,或在其它具体实施例中,指的是为该领域技术人员所公认的显着差异。其它具体实施例中,从对象获取的样本的反应性模式与对照反应性模式间的显着差异是该对象受苦于脑损伤的指征。特定具体实施例中,样本中抗体相对于抗原的反应性上调或更高的反应性指的是,比对照中抗原相对于抗原的反应性水平高(即,大)约至少2倍、约至少3倍、约至少4倍、或约至少5倍的增长(即,提升)。另一具体实施例中,样本中抗体相对于抗原的反应性下调或更低的反应性指的是,比对照中抗原相对于抗原的反应性水平低约至少2倍、约至少3倍、约至少4倍、或约至少5倍的下降(即,减少)。

[0120] 根据一些具体实施例,该至少一种寡核苷酸抗原是包含至少5、6、7、8、9、10、11、12、13、14、15、16、17、18、19或20个邻接腺嘌呤核苷酸的寡核苷酸序列。根据另一具体实施例,该寡核苷酸序列包含至多20个邻接腺嘌呤核苷酸。根据另外的具体实施例,该至少一种寡核苷酸抗原是包含至少5、6、7、8、9、10、11、12、13、14、15、16、17、18、19或20个邻接胸腺嘧啶核苷酸的寡核苷酸序列。根据另一具体实施例,该寡核苷酸序列包含至多20个邻接胸腺嘧啶核苷酸。

[0121] 根据另外的具体实施例,该至少一种寡核苷酸抗原是包含至少5、6、7、8、9、10、11、12、13、14、15、16、17、18、19或20个邻接胞嘧啶核苷酸的寡核苷酸序列。根据另一具体实施例,该寡核苷酸序列包含至多20个邻接胞嘧啶核苷酸。根据另外的具体实施例,该至少一种寡核苷酸抗原是包含5至17、6至17、7至17、8至17、9至17、10至17、11至17、12至17、13至17、

14至17、15至17、16至17、或至多17个邻接鸟嘌呤核苷酸的寡核苷酸序列。

[0122] 根据一些具体实施例，该至少一种抗原选自SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的形式、其片段、或前述的任意组合所组成的群组。

[0123] 根据一些具体实施例，该抗原选自蛋白质、寡核苷酸抗原、或其任意组合。

[0124] 应理解，根据本发明的每一抗原可与从所测试对象获取或排除的样本中发现或分离的IgM抗体及/或IgG抗体结合。由于针对某一表位或抗原的IgM抗体和IgG抗体的相对量随时间进程而变，根据本发明的每一抗原可与IgM抗体、IgG抗体或两者结合。某些具体实施例中，抗体的反应性意为IgG抗体的反应性。某些具体实施例中，抗体的反应性意为IgM抗体的反应性。根据另一具体实施例，样本中抗体的显着较高的反应性意为增加的IgG反应性。根据另一具体实施例，样本中抗体的显着较高的反应性意为增加的IgM反应性。

[0125] 根据另一具体实施例，该增加的IgM反应性是相对于选自SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的形式、或前述的任意组合所组成组的至少一种抗原的反应性。

[0126] 根据另一具体实施例，该增加的IgG反应性是相对于选自SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的形式、或前述的任意组合所组成组的至少一种抗原的反应性。

[0127] 某些具体实施例中，该增加的IgM和IgG反应性是相对于选自SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的形式、其片段、或前述的任意组合所组成组的至少一种抗原的反应性。某些具体实施例中，该增加的IgM反应性是相对于选自SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的形式、其片段、或前述的任意组合所组成组的至少一种抗原的反应性。每一可能性表示本发明的一种独立具体实施例。

[0128] 应理解，为了实施本发明的方法，从对象获取或派生的样本必须包含由该对象自身产生的抗体。因此，样本可从天然地包含该对象抗体至少一个子集的任何组织、器官或液体中获取或派生。某些具体实施例中，该取自对象的样本是生物体液。根据一些具体实施例，该样本选自血浆、血清、血液、脑脊液、滑液、痰液、尿液、唾液、泪液、淋巴标本、或该领域中已知的任何其它生物体液所组成的群组。每一可能性表示本发明的一种独立具体实施例。根据某些具体实施例，该取自对象的样本选自血清、血浆和血液所组成的群组。根据一种具体实施例，该样本是血清样本。获取和分离适宜样本的方法完全处于该领域技术人员的能力之内。

[0129] 根据本发明方法的某些具体实施例，该对照选自下列所组成的群组：来自至少一个健康个体的样本、相同对象的基线、来自一群健康个体的一组对照样本、以及存储的来自健康个体的数据集。每一可能性表示本发明的一种独立具体实施例。典型地，健康个体是未受苦于脑损伤的对象。

[0130] 特定的具体实施例中，使用至少85％、优选至少90％的阳性预测值(PPV)截留来测定该显着差异。测定对于所选标记物(如，抗原)的PPV是该领域技术人员所熟知的，且在下文揭示的方法中举例说明。典型地，若在具体研究子群中超过10％的对象中检出所选截留值如PPV≥90％，则确定为抗原阳性。例如，当与不同测试组B比较时，如果在A组中检出至少10％的对象的PPV≥90％，则确定A组为抗原i特异性表征组。A组中对于抗原i的PPV≥90％截留的对象被认为是相对于抗原i为阳性。

[0131] 本文中所使用，“被指向”抗原的抗体是能特异性结合至该抗原的抗体。对抗体被指向复数种抗原的水平的测定，包括测量样本中每一抗体的水平，其中，每一抗体被指向本发明的具体抗原。典型使用免疫化验实施这一步骤，如本文中所详述。

[0132] 其它具体实施例中，通过包含下述的过程实施对样本中抗体相对于至少一种抗原的反应性(和样本中每一种所测试抗体的水平)的测定：在可形成特异性抗原-抗体复合物的条件下，令该样本与至少一种抗原(或当使用复数种抗原时，与包含该复数种抗原的抗原探针集合)接触；以及，将关于每一抗原探针形成的抗原-抗体复合物的量进行定量。抗原-抗体复合物的量是样本中所测试抗体水平(或该样本与该抗原的反应性)的指征。

[0133] 另一具体实施例中，该方法包含测定样本中至少一种lgG抗体和至少一种lgM抗体对于复数种抗原的反应性。另一具体实施例中，该方法包含测定样本中复数种lgG抗体和至少一种lgM抗原对于复数种抗原的反应性。另一具体实施例中，该方法包含测定样本中至少一种lgG抗体和复数种lgM抗体相对于复数种抗原的反应性。根据另一具体实施例，该方法包含测定样本中抗体相对于复数种抗原的反应性。

[0134] 典型地，使用免疫化验实施对样本中抗体对于至少一种抗原的反应性的测定。较佳地，当使用复数种抗原时，该复数种抗原可以抗原阵列的形式使用。

[0135] 抗原探针和抗原探针集合

[0136] 根据其它具体实施例，本发明提供可用于如本文所详述而用于诊断脑损伤的抗原探针和抗原探针集合。

[0137] 本发明进一步提供复数种抗原，本文中也指代为抗原探针集合。这些抗原探针集合包含复数种抗原，该抗原可与患有脑损伤的对象的血清进行特异性反应。根据本发明的原则，该复数种抗原较佳可以抗原阵列形式使用。根据一些具体实施例，该抗原阵列以抗原芯片的形式便利地排列。

[0138] 本文中所使用，“探针”意为能特异性结合至一种组分的任何化合物。根据一方面，本发明提供包含选自下列所组成组的复数种抗原的抗原探针集合：SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的形式、其片段、或前述的任意组合。根据某些具体实施例，该抗原探针集合包含本发明抗原的子集。特定的具体实施例中，该抗原的子集由下列组成：SEQ ID NO:1至SEQ ID NO:24、SEQ ID NO:27至SEQ ID NO:30、SEQ ID NO:42、SEQ ID NO:75、SEQ ID NO:76、其异构体、其转译后修饰的形式、其片段、或前述的任意组合。

[0139] 一些具体实施例中，抗原探针集合由多达300种抗原组成。一些具体实施例中，该抗原探针集合由2至5种抗原组成。

[0140] 根据另一具体实施例，本发明的方法包含测定样本中抗体对于选自SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的形式、其片段、或前述的任意组合所组成组的至少一种抗原的反应性。

[0141] 可根据该领域中已知的技术，测定本发明的抗体对于复数种抗原的反应性。

[0142] 优选地，本发明方法和试剂盒的复数种抗原包含一组本文中揭露的抗原。其它具体实施例中，该复数种抗原(或抗原探针集合)包含其子集或由其子集组成，如3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25,26、27、28、29、30、31、32、33,34、35、36、37、38、39、40、41、42、43、44、45、46、47、48、49、50、51、52、53、54、55、56、57、58、59、60、61、62、63、64、65、66或115中不同的抗原，各自选自本发明的抗原，其中，每一可能性

表示本发明的一种独立具体实施例。可选择此类子集，以获得诊断化验的最佳灵敏度及/或特异性。

[0143] 待用于本发明化验中的抗原探针可使用该领域中众所周知的方法合成或纯化。

[0144] 应注意，本发明使用抗原探针及其同源物、片段和衍生物，只要这些同源物、片段和衍生物可与这些抗原探针进行免疫交叉反应即可。本文中所使用，术语“f”指的是，由相同抗体特异性结合的两种或更多种抗原。本文中所使用，术语“同源物”指的是，具有至少80％、至少85％或至少90％的与抗原序列或结构的一致性的抗原探针。通过大量免疫化验技术如竞争化验(测量测试抗原竞争性抑制抗体与其已知抗原集合的能力)来测定交叉反应性。

[0145] 本文中所使用，术语“片段”指的是抗原的一部分或抗原类似物，其保留与抗原探针的免疫学交叉反应性，如免疫特异性识别靶标抗原。该片段可具有对应抗原长度的约80％、约85％、约90％、或约95％。

[0146] 根据另一方面，本发明提供抗原探针集合，其包含选自SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的形式、其片段、或前述的任意组合所组成组的复数种抗原探针。

[0147] 根据另一相关方面，本发明提供抗原探针集合，其包含选自SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的形式、其片段、或前述的任意组合所组成组的至少一种抗原探针。

[0148] 根据另一方面，本发明提供一种制品，其包含上文揭示的至少一种抗原探针集合。

[0149] 某些具体实施例中，该制品是抗原探针阵列形式、或抗原芯片形式、或浸染棒形式、或侧流测试形式、或该领域技术人员所知的任何其它平台形式。“抗原探针阵列”通常指的是复数种抗体探针，其或在单一容器内混合或布置在一个或多个容器内。“抗原芯片”通常指的是其上附加或粘附有复数种抗原的大体上二维的表面。“浸染棒”通常指的是一种其上附加或粘附有复数种抗原的物体，将其浸没于液体中以实施化学测试或提供对该液体中发现的数量的测量。“侧流测试”通常指的是装置，其打算用来检测样本(基质)中靶标分析质的存在(或不存在)而无需专业且昂贵的配置。某些具体实施例中，该制品是试剂盒形式。

[0150] 根据某些具体实施例，该试剂盒进一步包含用于检测样本中抗体对于复数种抗原的至少一种抗原的反应性的手段。根据另一具体实施例，该试剂盒进一步包含用于将不同样本中抗体对于复数种抗原的至少一种抗原的反应性进行比较的手段。根据另一具体实施例，该试剂盒进一步包含使用说明书。例如，前述手段可包括试剂、可检测的标签及/或容器，其可用于测量抗体与本发明抗原探针的特异性结合。本文中所使用，“手段”也可指代用来实施生物学或化学化验的装置、试剂和化学品，如小瓶、缓冲液和书面协议或使用说明书。

[0151] 根据另一方面，提供选自下列所组成组的至少一种抗原的用途：SEQ ID NO:1至SEQ ID NO:115、其异构体、其转译后修饰的形式、其片段、或前述的任意组合；用于制备用于诊断对象脑损伤的诊断试剂盒。一些具体实施例中，该诊断试剂盒可用于测定样本中抗体的反应性，从而测定样本对至少一种抗原的反应性模式。一些具体实施例中，样本的反应性模式较之于对照样本的反应性模式的显着差异(如，增加)是脑损伤的指征。

[0152] 其它具体实施例中，该抗体探针集合中包含的复数种抗原包含多达50、55、60、70、

80、90或100种不同抗原或由这些不同抗原组成。其它具体实施例中，该抗体探针集合中包含的复数种抗原包含至少50、100、150、200或500中不同抗原或由这些不同抗原组成。

[0153] 其它方面，提供包含本发明的寡核苷酸的核酸载体及含有该载体的宿主细胞。这些核酸、载体和宿主细胞是通过该领域中已知的重组方法生产的。聚核酸分子也可使用重组DNA技术(如，聚合酶链反应(PCR)扩增、克隆)或化学合成生产。核酸序列包括天然核酸序列及其同源物，包括但不限于，天然等位基因突变体和修饰核酸序列，其中，核酸已经被插入、删除、替代、及/或反转，且修饰方式为这些修饰大体上并不干扰核酸分子实施本发明方法的能力。

[0154] 根据本发明，该试剂盒包含复数种抗原，本文中也指代为抗原探针集合。这些包含复数种抗原的抗原探针集合可与患有脑损伤的对象的血清进行特异性反应。一些具体实施例中，该抗原探针集合可区分患有脑损伤的对象的血清与正常对象的血清。根据本发明的原则，该复数种抗原较佳可以抗原阵列形式使用。根据一些具体实施例，该抗原阵列以抗原芯片的方式便利地排列。

[0155] 其它具体实施例中，该试剂盒进一步包含用于检测样本中抗体对于复数种抗原的反应性的手段。例如，该试剂盒可含有试剂、可检测的标签及/或容器，其可用于测量抗体对于本发明抗原探针的特异性结合。特定的具体实施例中，该试剂盒是抗原阵列形式。

[0156] 一些具体实施例中，该试剂盒包含用于将不同样本中抗体对于复数种抗原的反应性模式进行比较的手段。其它具体实施例中，该试剂盒可进一步包含阴性及/或阳性对照样本。例如，阴性对照样本可含有来自至少一个健康个体(如，未受苦于脑损伤的个体)的样本。阳性对照可含有来自至少一个受苦于正在被诊断的脑损伤或脑损伤子类型的个体的样本。其它非限制性实例是一组来自一群健康个体或患病个体的对照样本，或来自对照个体的存储数据集。

[0157] 抗体、样本和免疫化验

[0158] 抗体，或免疫球蛋白，包含两个通过二硫键链接在一起的重链和两个轻链，每一轻链通过二硫键以“Y”形的构型链接至一条重链。每一重链在一端具有一可变域(VH)，接着是多个恒定域(CH)。每一轻链在一端具有一可变域(VL)而在其另一端具有一恒定域(CL)，该轻链可变域与该重链可变域对准，且该轻链恒定域与该重链的第一恒定域(CH1)对准。每一对轻链和重链的可变域形成抗原结合位点。

[0159] 该重链的同种型(γ、α、δ、ε或μ)决定了免疫球蛋白类别(分别为IgG、IgA、IgD、IgE或IgM)。该轻链是全部抗体类别中发现的两种同种型(κ或λ)的一种。

[0160] 应理解，当使用“抗体”或“多种抗体”时，其倾向于包括完整抗体，如多克隆抗体或单克隆抗体(mAbs)，及其蛋白水解性片段如Fab片段或$F(ab')_2$片段。本发明的范畴进一步包括(例如，作为免疫化验试剂，如本文中所详述)，嵌合抗体、重组和工程抗体、及其片段。

[0161] 包含轻重两条链的完整或基本完整的可变域的例示性功能性抗体片段定义如下：(i)Fv，定义为由该轻链可变域和该重链可变域组成的表达为两条链的基因工程片段；(ii)单链Fv(“scFv”)，包括通过适当的多肽链结基链接的该轻链可变域和该重链可变域的基因工程单链分子；(iii)Fab，含有抗体分子的单价抗体结合部位的抗体分子片段，通过使用木瓜蛋白酶处理完整抗体以获得完整轻链和重链Fd片段而得，由该可变域及其CH1域组成；(iv)Fab'，含有抗体分子的单价抗原结合部位的抗体分子片段，通过使用胃蛋白酶处理完

整抗体之后再还原(每一抗体分子得到两个Fab'片段)而得;以及(v)F(ab')$_2$,含有抗体分子的单价抗原结合部位的抗体分子片段,通过使用胃蛋白酶处理完整抗体而得(即,通过两个二硫键保持在一起的Fab'片段的二聚体)。

[0162] 本文中所使用,术语"抗原"是能结合抗体的分子或分子的一部分。抗原典型能诱导动物生产能结合至该抗原表位的抗体。上文中指代的特异性反应意为,指出该抗原将以高选择性的模式与其相关抗体反应而不与可能被其它抗原诱发的多数其它抗体反应。"抗原肽"是能特异性结合抗体的肽。

[0163] 另一具体实施例中,可通过将特异性抗原-抗体复合物的形成定量而实施对抗体特异性结合抗原探针的能力的检测。本文中所使用,术语"特异性结合"意为抗体与特异性抗原探针的该结合不受不相关分子存在的影响。

[0164] 某些具体实施例中,通过测定本发明抗原特异性结合至从对象分离的lgG表位的抗体的能力,或在其它具体实施例中结合至lgM抗体的能力,实施本发明的方法。

[0165] 从对象获取含抗体的适当生物样本的方法完全处于该领域技术人员的能力之内。典型地,适当的样本包含全血及自其排除的产品如血浆和血清。其它具体实施例中,可使用其它含抗体的样本,如CSF、尿液和唾液样本。

[0166] 大量众所周知的流体采集方法可用来从对象采集生物样本,以实施本发明的方法。

[0167] 根据本发明,任何适当的免疫化验可与该对象抗原合用。此类技术是该领域技术人员众所周知的,且已经揭示于很多标准免疫学手册和教科书中。某些优选具体实施例中,使用基于抗原探针阵列的方法来实施对抗体特异性结合该抗原探针的能力的测定。优选地,将该阵列以经适当稀释的对象血清培养,以允许该血清中含有的抗体与固定化的抗原探针之间进行特异性结合,从该阵列洗除未结合的血清,使用所希望表位抗体的接合有可检测标签的配体培养经洗涤的阵列,从该阵列洗除未结合的标签,以及测量结合至每一抗原探针的标签的水平。

[0168] 多种具体实施例中,本发明的方法进一步包含在实施该测定步骤前稀释样本。一种具体实施例中,例如,将样本使用PBS以1:2稀释。另一具体实施例中,将样本以1:4、1:6、1:8、1:15、1:20、1:50、或优选1:10进行稀释。每一可能性表示本发明的一种独立具体实施例。另一具体实施例中,样本在2倍至10倍范围内稀释。另一具体实施例中,样本在4倍至10倍范围内稀释。另一具体实施例中,样本在6倍至10倍范围内稀释。另一具体实施例中,样本在8倍至10倍范围内稀释。

[0169] 抗原芯片

[0170] 抗原微阵列用于免疫应答的高通量表征(Robinson et al.,2002,Nat Med 8,295-301),且已经被用来分析接种疫苗和自体免疫疾病中的免疫应答(Robinson et al.,2002;Robinson et al.,2003,Nat Biotechnol.21,1033-9;Quintana et al.,2004;Kanter et al.,2006,Nat Med 12,138-43)。已经假定,多重反应性的模式可能比单一抗原-抗体关系更具启迪作用(Quintana et al.,2006,Lupus 15,428-30),如早先对于健康和患病小鼠(Quintana et al.,2004;Quintana et al.,2001,J Autoimmun 17,191-7)和人(Merbl et al.,2007,J Clin lnvest 117,712-8;Quintana et al.,2003,J Autoimmun 21,65-75)自体免疫库的分析中所示。因此,自身抗体库具有提供重新深入理解该疾病发病

机理的潜力，以及用作该疾病进程的免疫生物标记物(Cohen,2007,Nat Rev lmmunol.7,569-74)的潜力。

[0171] 根据一些方面，可使用WO 02/08755和U.S.2005/0260770中揭露的抗原阵列实践本发明的一些方法，这两篇专利的内容通过引用并入本文。WO 02/08755针对用于聚类的系统和制品，从而鉴别可与源自需要进行疾病诊断或治疗监控的患者的血清的待定免疫球蛋白反应的预先定义抗原。进一步揭露诊断方法，以及可用于这些方法中的系统，采用将复数种抗原的抗原子集聚类的步骤，该抗原子集可与源自复数个患者的复数种抗体反应，以及将对象的抗体与所得集群关联或取消关联。

[0172] U.S.2005/0260770揭露一种抗原阵列系统及其诊断用途。该申请提供了诊断对象体内免疫疾病特别是1型糖尿病或其倾向的方法，包含测定该对象的免疫球蛋白特异性结合抗原探针集合的每一抗原探针的能力。该公开的教导乳糖本中详述者而以其整体并入本文。

[0173] 其它具体实施例中，可使用各种其它免疫化验，包括而不限于，酶联免疫吸附化验(ELlSA)；使用多重微珠的流式细胞计(如Luminex制作的系统)；表面等离子体共振(SPR)；椭圆测量术；以及各种其它免疫化验，其采用例如激光扫描、光检测、经由光电倍增管的光子检测、使用基于数码相机的系统或视频系统进行的摄影、辐射计数、荧光检测、电磁检测、和允许对抗原-抗体结合进行定量测量的任何其它系统。

[0174] 已经研发了多种方法用于制备适用于本发明方法的阵列。最先进的方法牵涉使用机械设备以将含有抗原探针的不同溶液施加或“点”在平面支撑物表面上密集的可访问位置，该平面支撑物典型为玻璃支撑物如显微镜载玻片，之后通过适当的热处理及/或化学处理进行加工以将抗原探针附加至该支撑物表面。首先，通过化学处理将该保留表面活化，将一层反应性基团如环氧基留在该表面上，而该反应性基团共价结合含有游离胺基或巯基的任何分子。适当的支撑物也可包括硅、硝基纤维素、纸张、纤维质支撑物等。

[0175] 优选地，为了令统计学上具有说服力的数据的产生称为可能，将附加至该阵列的具体可访问位置上的每一抗原探针或本发明抗原探针的不同子集独立附加在该阵列的至少两个、更优选至少三个分隔的具体可访问位置。

[0176] 根据另外的具体实施例，该抗原探针集合包含至少5、至少25、至少100、至少150、至少200、至少250、至少300种或更多种抗原，包括一种或复数种本发明提供的抗原。

[0177] 该阵列除了包括本发明的抗原探针外，可较佳地包括对照抗原探针或其它标准化学品。此类对照抗原探针可包括标准化对照探针。从该标准化对照探针获取的信号，提供用于结合条件、标签强度、“读取”效率和其它可造成给定结合的抗体-探针配体相互反应信号改变的因素中变化的对照。例如，从该抗原探针阵列全部其它抗原探针读取的信号如荧光强度除以来自该标准化对照探针的信号(如，荧光强度)，从而将测量值标准化。标准化对照探针可结合至该抗原探针阵列上的各种可访问位置，以控制抗体-配体探针效率的空间变化。优选地，标准化对照探针被置于该阵列的角落或边缘以控制边缘效应，以及该阵列的中部。

[0178] 标记的抗体配体可以是各种适当类型的抗体配体的任一种。优选地，该抗体配体是能特异性结合所使用的对象抗体的Fc部位的抗体。例如，若该对象的抗体是lgM表型，则该抗体配体优选为能特异性结合至该对象lgM抗体Fc区域的抗体。

[0179] 该对象抗体的配体可与各种类型可检测标签的任一种接合。该标签优选为荧光团，最优选Cy3。或者，该荧光团可以是各种荧光团的任一种，包括Cy5、Dy5、异硫氰酸荧光素(FlTC)、藻红蛋白(PE)、若丹明、Texas红等。适用于特异性同种型抗体的接合有荧光团的适当抗体可从供应商处广泛购买，且它们的生产方法已经被完善地构建。

[0180] 依据用途和目的，可分离对象的抗体，用于分析其以各种途径结合抗原探针的能力。虽然对象的抗体可以适当且便利地作为血清或血浆或其稀释物(如，1:10稀释)形式存在，仍可在测试该抗体特异性结合抗原探针的能力之前，对抗抗体进行任何所希望程度的纯化。可使用对象的全抗体或该对象的包含抗体可变区的抗体片段实践本发明的方法。

[0181] 对从对象获取的样本中一种或多种抗体水平与一种或多种生物标记物水平的联合测量

[0182] 本发明至少部分地基于下述发现：对从对象获取的样本中一种或多种抗体水平与一种或多种生物标记物水平的联合测量可测量该对象的实时背景生理学和急性事件状态。

[0183] 在具有脑损伤的患者体内，对损伤和从该损伤恢复的过程的应答取决于该损伤特性和该个体在损伤前的状态的组合。在停留在“健康”背景上损伤的患者将很可能具有比在“病态”或“先前受损”背景上损伤的患者更高(更快、更完全)的恢复情况。

[0184] 对患者自身抗体概况的测定可用作该患者在脑损伤之前的替代指标(surrogate measurement)，而对在损伤后短期内循环抗原水平的测定可用作损伤特点/程度的替代指标。将关于患者在损伤前状态的信息与该损伤特点/程度组合的算法可用来预测结局。

[0185] 可使用其中抗原结合至表面的任何平台实施对自身抗体概况的测定，循环抗体结合至该抗原并使用示踪二次抗体进行检测。可以任何包括捕捉抗体和检测抗体的ElISA型夹心化验格式进行对循环抗原概况的测定。

[0186] 用于抗体和抗原检测的平台可以是独立的(如，用于自身抗体的iCHIP、用于抗原的MSD ElSA或任何基于ElISA的相关平台)，或者可以组合为单一平台以同步测量循环自身抗体和抗原。这可通过下述进行：打印具有相关抗原和捕捉抗体两者的iCHIP，令血清与打印的表面接触，因此，循环抗体将结合至该表面结合的抗原，且循环抗原将结合至该表面结合的捕捉抗体。可使用二次抗体和检测抗体的混合物进行检测。

[0187] 在需要测量自身抗体对显示疾病状态信息的相同抗原的反应性的例子中，这些测量可在两个分隔的腔中进行。来自多次测试的数据联合用于用以最终预测该患者的状态的算法分析目的。

[0188] 用于检测生物标记物的试剂盒

[0189] 另一方面，本发明提供用于描述脑损伤状态的试剂盒，该试剂盒用来检测本文中揭示的生物标记物。特定具体实施例中，该试剂盒提供为包含本发明生物标记物的抗体的ElISA试剂盒，该生物标记物包括但不限于，胶质原纤维酸性蛋白(GFAP)和突触核蛋白β(Sncb)。

[0190] 一种候选具体实施例中，该组生物标记物包含BDNF、GFAP、MT3和SNCB。另一具体实施例中，该组生物标记物包含BDNF、GFAP、NRGN和SNCB。又一具体实施例中，该组生物标记物包含BDNF、ICAM5、MT3和SNCB。

[0191] ElISA试剂盒可包含其上附加有生物标记物捕捉试剂的固体支撑物，如芯片、微量滴定板(如，96孔板)、微珠、或树脂。

[0192] 该试剂盒可进一步包含一种用于检测生物标记物的手段如抗体，以及二次抗体-信号复合物如辣根过氧化酶(HRP)-缀合的羊抗兔IgG抗体和作为HRP底物的四甲基联苯胺(TMB)。

[0193] 该试剂盒可提供为包含其上固定有抗体的膜的免疫层析条带，以及用于检测的手段如金颗粒结合的抗体，其中，该膜包括NC膜和PVDF膜。该试剂盒可包含其上固定有样本施加垫的塑料板、暂时固定在玻璃纤维过滤器上的金颗粒结合的抗体、其上顾客有抗体带和二次抗体带的硝基纤维素膜，以及，吸收剂垫以连续方式放置以保持血清的连续毛细流动。

[0194] 数据分析

[0195] 较佳地，为了区别健康对照对象与那些具有脑损伤的患者的反应性模式，本发明的方法可采用学习和模式识别分析、聚类算法等。如此，该术语具体包括通过例如测定测试样本中抗体对复数种抗原的反应性，并使用测量算法及/或分析将所得反应性模式与阴性和阳性对照样本(如，分别从未受苦于脑损伤的对照对象或受苦于脑损伤的患者获取的样本)的反应性模式比较，从而测量的差异。该差异也可通过将测试样本的反应性模式与以此方式获取的预先定义分类相比较而测量。

[0196] 一些具体实施例中，为了区别具有子类型的脑损伤的对象与对照对象的反应性模式，本发明的方法可采用学习和模式识别分析、聚类算法等。例如，该方法可包括测定测试样本中抗体对复数种抗原的反应性，并使用此类算法及/或分析将所得模式与阴性和阳性对照样本的反应性模式比较。

[0197] 因此，另一具体实施例中，测试样本反应性模式与对照样本反应性活性相比的显着差异，其中该差异是使用学习和模式识别算法计算的，表明该对象受苦于脑损伤。例如，该算法可包括而不限于，监督或非监督分类，包括统计算法包括主成分分析(PCA)、偏最小二乘法(PLS)、多元线性回归(MLR)、主成分回归(PCR)、判别函数分析(DFA)，包括线性判别分析(LDA)、和聚类分析包括最近邻算法、人工神经网络、耦合双向聚类算法、多层感知(MLP)、广义回归神经网络(GRNN)、模糊推理系统(FIS)、自组织映射(SOM)、遗传算法(GAS)、神经模糊系统(NFS)、自适应共振理论(ART)。

[0198] 某些具体实施例中，一种或多种算法或计算机程序可用来将测试样本中定量的每一抗体的量与预先定义的截留(或与一定数目的预先定义的截留)比较。或者，可提供一种或多种用于人手动实施必需步骤的使用说明书。

[0199] 用于测定和比较模式分析的算法包括，但不限于，主成分分析、费舍尔线性分析、神经网络算法、遗传算法、模糊逻辑模式识别等。分析完成后，所得信息可例如在显示器上显示、传输至主机、或存储在存储装置中用于后续取回。

[0200] 该算法大多为基于神经网络的算法。神经网络具有输入层、处理层和输出层。神经网络中的信息分散在整个处理层中。该处理层由通过互连至其节点而模拟神经元的节点所组成。与展现一批数据中基本模式的统计分析相似，神经网络基于预先约定的准则锁定一批数据中的一贯模式。

[0201] 适当的模式识别算法包括，但不限于，主成分分析(PCA)、费舍尔线性判别分析(FLDA)、簇类独立软模式法(SIMCA)、K最近邻算法(KNN)、神经网络、遗传算法、模糊逻辑、及其它模式识别算法。一些具体实施例中，使用费舍尔线性判别分析(FLDA)和典型判别分析(CDA)以及其组合来比较输出信号与来自数据库的可用数据。

[0202] 其它具体实施例中，使用主成分分析。主成分分析(PCA)牵涉将若干相关联的变量转换为较少数目的不相关联的变量的数学技术。该较少数目的不相关联的变量称为主成分。第一主成分或特征向量尽可能多地占据该数据中的可变性，且每一接续成分(succeeding component)尽可能多地占据剩余的可变性。PCA的主要目标是减少数据集的维度和鉴定新的基础变量。

[0203] 主成分分析以分层方式比较两个或多个协方差矩阵的结构。例如，一个矩阵可能会与另一矩阵相同，但在后者中，前者的每一矩阵元均乘以一个常数。两个矩阵因此彼此成正比。更特别地，两个矩阵共享相同的特征向量(或主成分)，但其特征值相差一个常数。两个矩阵间的另一关系是，它们共享共有的主成分，但它们的特征值不同。主成分分析中使用的数学技术称为特征分析。与最大特征值相关联的特征向量具有与第一主成分相同的方向。与第二大特征值相关联的特征向量决定第二主成分相同的方向。特征值之和等于方阵的迹(trace)，而特征向量的最大数目等于这一矩阵的行数。

[0204] 另一具体实施例中，该算法是分类器。一种类型的分类器是通过使用来自训练集合且其效能被使用测试集合数据评估的数据“训练”该算法而创建。与本发明合用的分类器的实例是判别分析、决策树分析、受试者工作曲线或其拆分曲线、及成绩分析。

[0205] 术语“决策树”指的是采取用于分类法的类似流程图的树结构的分类器。决策树由数据集重复分段的子集所组成。每一分段由应用至一个变量的简单规则组成，如，“如果“变量1”的值大于“阈值1”，则向左，否则向右”。据此，给定特征空间被分割为一组矩形，且每一矩形被分配给一类。

[0206] 术语“测试集合”或“未知”或“确认集合”指的是全体可用数据集的子集，该数据集由未包括于训练集合中的全体。测试数据用来评估分类器效能。

[0207] 术语“训练集合”或“已知集合”或“参考集合”指的是各自全体可用数据集的子集。这一子集典型是随机选择的，且独自用于分类器构建的目的。

[0208] 诊断方法

[0209] 本文中所使用，术语“诊断”(diagnosing或diagnosis)指的是，通过其征兆、症状且特别是来自多种诊断过程的结果鉴定身体状况或疾病(如，脑损伤)的进程，包括，例如，检测从个体获取的生物样本(如，血清)中抗体对一种或多种抗原的反应性。此外，本文中所使用，术语“诊断”涵盖疾病的筛选、检测疾病的存在或严重性、区分一种疾病与包括那些可能具有一种或多种相似或相同症状的疾病的其它疾病、提供疾病的预后、监控疾病进展或复发，以及评估疗效及/或疾病、病变或病症的复发，以及选择对疾病的治疗及/或处置、对给定疾病疗法(剂量/计划)的优化、监控对疾病的治疗、及/或预测疗法对于特定患者或亚种群的适用性、或测定治疗性产品在患者或亚种群中的适宜给药剂量。

[0210] 一种具体实施例中，诊断脑损伤进一步容许评估所述脑损伤进化为脑损害并导致长期机能障碍的风险。另一具体实施例中，对所述脑损伤进化为长期机能障碍的风险的评估容许在早期进行的治疗性干预。

[0211] 面对已经遭受TBI的患者的最直接的问题是，测定再震荡性损伤后何时可以恢复至高风险活动而没有在细胞层面出现的永久性脑损害的风险。根据一些具体实施例，本发明提供广泛的免疫系统测试以监控、评估慢性结局及核实重新工作或比赛的安全性。

[0212] 对于确定适宜的临床关联以及预测长期结局，对TBI后的病理学和神经功能缺损

的评估是关键。在头部损伤中最常用的结局测量措施是格拉斯哥昏迷量表(GCS)、格拉斯哥结局量表(GOS)、计算机断层扫描、和磁共振成像(MR1)以检测颅内病理学。但是，尽管有基于这些结局测量措施的显着改良的急诊分类系统，大多数TB1遭受长期缺损，且尽管基于GOS预测为“恢复良好”，大量TB1幸存者仍严重受损。此外，CT和MR1昂贵且不能在急诊室环境中快速采用。另外，在于战斗相关联的简陋医疗环境中，TB1的确诊将会是对伤员进行适宜分类的必要先决条件。

[0213] 一种具体实施例中，与脑损伤相关的脑损害类型是白质结构异常。另一具体实施例中，该白质结构异常或损害处于胼胝体区域内。另一具体实施例中，该异常或损害处于钩束内。另一具体实施例中，该异常或损害处于右脑额叶内。另一具体实施例中，该异常或损害处于左脑额叶内。另一具体实施例中，该异常或损害是弥漫性轴索损伤(DA1)。另一具体实施例中，该异常或损害是弥漫性血管损伤。

[0214] 一些具体实施例中，该脑损伤是轻度TB1，一种具体实施例中，脑震荡是轻度TB1。另一具体实施例中，轻度TB1是由头部损伤造成的，其中，该头部损伤是，另一具体实施例中，钝挫伤、加速力或减速力。能够了解，此类头部损伤可以具有一个或多个下述条件为特征：(1)观察到的或自报的挫伤、定向障碍、或损伤当下的意识缺失、记忆丧失、意识丧失持续时间短于30分钟；以及，(2)在损伤不久后的症状如头痛、眩晕、疲惫、易怒、和注意力难以集中。基于使用格拉斯哥昏迷量表的临床检查，该头部损伤也可被归类为轻度。一种具体实施例中，在急诊中心检查时，该头部损伤的格拉色哥昏迷量表(GCS)分数为13至15，头部CT未见异常，意识丧失的持续时间不超过30分钟，创伤后记忆缺失短于24小时，且简明损伤量表(A1S)S3和1SS<12修改以排除该头部区域。

[0215] 诊断方法的灵敏度和特异性不同。诊断系统的“灵敏度”是测试呈阳性的患病个体的百分比(“真阳性”的百分比)。该化验未检出的患病个体为“假阴性”。未患病且在该化验中测试呈阴性的对象称为“真阴性”。诊断化验的“特异性”是1减去假阳性率，其中，该“假阳性”率定义为那些未患病但测试呈阳性的比例。尽管特定的诊断方法可能不提供对病症的最终诊断，但若该方法提供有助于诊断的阳性指示即足够。诊断化验的“准确性”是测量结果与真实值的接近度。诊断化验的“p值”是获取所观察的样本结果为零假设是事实真实时(或更极端的结果)的可能性。

[0216] 某些具体实施例中，使用本发明提供的抗原探针集合或本发明提供的抗原探针阵列，导致脑损伤指示性的(p值≤1.00E-08)、灵敏的(≥0.600)、特异性的(≥0.700)且准确的(≥0.600)抗体反应性概况。某些具体实施例中，该使用导致更加脑损伤指示性的(p值≤1.00E-10)、灵敏的(≥0.700)、特异性的(≥0.800)且准确的(≥0.700)抗体反应性概况。某些具体实施例中，该使用导致甚至更加脑损伤指示性的(p值≤1.00E-12)、灵敏的(≥0.800)、特异性的(≥0.900)且准确的(≥0.700)抗体反应性概况。某些具体实施例中，该使用导致再更加脑损伤指示性的(p值≤1.00E-14)、灵敏的(≥0.900)、特异性的(≥0.950)且准确的(≥0.900)抗体反应性概况。某些具体实施例中，该使用导致再更加脑损伤指示性的(p值≤1.00E-16)、灵敏的(≥0.950)、特异性的(≥0.990)且准确的(≥0.950)抗体反应性概况。每一可能性表示本发明的一种独立具体实施例。

[0217] 某些具体实施例中，本发明提供的抗原或本发明提供的抗原模式是脑损伤指示性的(p值≤1.87E-08)、灵敏的(≥0.609)、特异性的(≥0.769)且准确的(≥0.687)。某些具体

实施例中，本发明提供的抗原或本发明提供的抗原模式是脑损伤指示性的(p值≤2.81E-12)、灵敏的(≥0.657)、特异性的(≥0.798)且准确的(≥0.725)。某些具体实施例中，本发明提供的抗原或本发明提供的抗原模式是脑损伤指示性的(p值≤8.00E-14)、灵敏的(≥0.663)、特异性的(≥0.814)且准确的(≥0.738)。

[0218] 另一具体实施例中，该方法可导致对脑损伤进展水平的测定。又一具体实施例中，该方法可导致提供用于监控脑损伤进展的实体的比较。这些具体实施例中，该方法可用来例如区分具有进行性脑损伤的对象与具有退化性脑损伤的对象。

[0219] 一种具体实施例中，正在根据本发明方法进行诊断的对象是有症状的。其它具体实施例中，该对象是无症状的。某些具体实施例中，该对象显示直接症状。某些具体实施例中，该对象显示迟发症状。某些具体实施例中，该对象现在或过去未接受治疗。

[0220] 本文中所使用，术语“治疗”可涵盖治愈、预防、减少疾病的发病率；减轻疾病的症状；诱发疾病的缓解；或迟缓疾病的进展。术语“减少”、“压制”和“抑制”指的是裁减或缩减。

[0221] 诊断过程可在体内或体外实施，优选在体外实施。本发明方法的某些具体实施例中，通过非侵入性手段或方法实施该诊断过程。

[0222] 本发明的诊断过程和平台可能适用于作为护理装置方向或在诊所、医师办公室、医院实验室、或商业诊断实验室中服务方向使用。

[0223] 下述实施例仅为了更完全地例示性说明本发明的一些具体实施例而存在。然而，它们决不应解释为限制本发明范畴的广度。

[0224] [实施例]

[0225] 材料和方法

[0226] 人类对象

[0227] 该研究由参与临床单位的机构审查委员会批准；获取了来自全部参与者的知情同意书。在初始研究中，使用包括228种抗原(见表1)的抗原微阵列测试血清，该血清源自从健康对象获取的血液样本和从遭受脑损伤的对象在损伤后不同时间获取的血液样本，且具有不同的GOSE分数。

[0228] 在HeadSMART试验中从到达约翰霍普金斯医院(Johns Hopkins Hospital)急诊科(ED)的患者(JHH,Baltimore；n＝61)或在COBRlT临床试验的一个参与中心(n＝31；如JAMA.2012;308(19):1993-2000中所揭示)采集血液样本和临床数据。

[0229] 将确定的人血清样本用于本研究。回顾分析来自成年TBl患者的样本。从贝勒医学院(Baylor College of Medicine)(Houston,TX;n＝21)获取评估为未主诉TBl的健康对照组患者。

[0230] 待认定为进行HeadSMART试验的TBl患者，必须符合下述准则：18岁或更年长、损伤后24小时内存在TBl、符合美国急诊医师血液(American College of Emergency Physicians(ACEP))对于获取TBl的头部CT扫描的准则。排除患有脑瘤、进行过脑部外科手术、怀孕的、不以英语为母语的患者。在从登记至长达6个月的期间内，从61位TBl患者采集连续的血清样本。对于每一患者，在脑损伤后不同的8个时间点分别采集3个样本，挑选样本用于该分析。对于COBRlT试验样本，使用下述准则，接受准则为：该患者曾患有非穿透性创伤性脑损伤、年龄18岁(阿拉巴马州为19岁)至70岁、如协议中说明的启用/不启用GCS准则的中风患者、损伤后6个月在网络中心完成结局测量的合理预期、24小时时间窗口内登记的

合理预期、且以英语为母语。排除准则包括:GCS运动评分为6且不符合CT准则的插管患者、双侧固定且瞳孔扩张的、妊娠测试阳性的、已知怀孕的、或正在哺乳的、证明患有干扰结局评估的疾病的、正在使用乙酰胆碱酯酶抑制剂的、濒死或当下患有威胁生命的疾病的、当下登记在另一研究中的、或囚犯。对于健康对照,在贝勒医学院,招募了21位至少18岁的非TBI个体,并签署知情同意书。从每一对照个体采集一份血液样本,并加工以获取血清和血浆的复制瓶装小样,小样在-80℃储存直至使用。全部患者身份信息保密。

[0231] 抗原和血清测试

[0232] 使用Scienion S-11非接触式微阵列打印机(Scienion AG,Germany)将228种不同的抗原点在室内生产的环氧已基三乙氧基硅烷(EHTES)活化的环氧树脂载片上。随后,使用1%酪蛋白将该微阵列在室温封闭1小时。在37℃,将1%酪蛋白封闭缓冲液中的测试血清样本(1:20稀释)在盖玻片下培养1小时。随后,洗涤该阵列,并在37℃使用混合在一起的两种抗体的1:500稀释物培养1小时,该两种抗体是羊抗人IgG Cy3缀合抗体和羊抗人IgM AF647缀合抗体(两者均购自杰克逊免疫研究实验室(Jackson lmmunoResearch Laboratories lnc.,West Grove,PA))。通过激光器(Agilent Technologies,Santa Clara,CA)在530nm和630nm两个波长实施图像采集,使用Genepix pro 7软件(Molecular devices,Sunnyvale,CA)分析结果。结合至每一抗原点的信号强度的定量范围是0至65,000;这一检测范围令使用以1:20稀释的测试血清样本获得可靠数据成为可能。

[0233] 图像分析和数据处理

[0234] 将每一点的强度表示为,减除其局部背景中位数之后进行Log2变换的像素均值。输入具有类背景强度的阴性点(背景减除后)。对于各点,减去背景强度以获得纯信号。对于每一载片中的每一抗原,移除异常值点。异常值点定义为具有Z分>2或<-2。在移除异常值的点后,通过中位数将多个点的强度组合起来。将每一抗原的多个点的前景强度和背景强度平均,并计算前景与背景之间的差异。将所得值作为抗体结合至该点抗原的抗原反应性。在大量载片中,全部抗原均显示有意义的反应性;因此没有抗原被排除。

[0235] 抗体结果的统计分析

[0236] 鉴别与其它子群相比具有更高或更低反应性的特异性研究子群中的抗原。在T测试中使用单变量分析来分离抗原。实现并测定了允许设定分类阈值如阳性预测值(PPV)≥90%且灵敏度≥20%的抗原,以显着表征具体的子群。对于额外的限制,仅选择其双侧t测试的p值(在多重假设的Benjamini-Hochberg校正后)小于0.05的抗原。

[0237] ELISA板化验方法

[0238] 通过比色检测法、荧光检测法、化学发光检测费、或电化学发光检测法测试生物标记物。对于比色检测方法,使用Maxisorb 96孔板。对于荧光化验,使用黑色不透明壁的板。对于基于发光的化验,使用适用于发光的微量滴定板。如下述者制备板。使用对于每一板类型为特异性的涂覆缓冲液冲洗该板一次。将捕获抗体以最优浓度在最优时间段内加热各孔中。通常,在40℃涂覆缓冲液中实施超过12小时的涂覆。涂覆时期之后,移除过量抗体,以经优化的封闭缓冲液封闭该板,该封闭缓冲液由缓冲盐水与下列之一组成:酪蛋白、牛血清白蛋白、物种特异性全血清、或经过滤的脱脂奶粉、或其它封闭剂、及/或非离子型洗涤剂。使用最理想长度的一系列相继培养以令:1)屏蔽非特异性结合位点(即,封闭);2)捕获抗体-抗原结合;3)抗原的结合,之后洗涤以移除过量和未结合的抗原;4)抗-抗原检测抗体溶液

和检测标签的培养;5)洗涤,以移除过量的未结合检测抗体和标签;以及,6)加入检测底物(ELISA)或优化的检测溶液(荧光或发光)。通过测量有色底物对适宜波长的光的吸光度,在微量滴定板阅读器上实施比色检测。使用基于荧光的读板器实施荧光化验。在基于发光的阅读器上检测发光。收集数据,并使用已知浓度的重组蛋白质的标准曲线测定生物标记物浓度。

[0239] 实施例1:FABP(SEQ ID No:61)与具有TBI结局的MBPR149(SEQ ID No:10)之间的关联

[0240] 为了勾勒每一患者自身抗体在损伤后随时间改变的情况,对每一患者在其自测时间点进行概况性描述。在特定时间点(损伤后3个月/1个月),将来自扩展格拉斯哥结局量表(GOSE)等于8的TBI患者的样本与来自GOSE小于8的TBI患者的样本比较。

[0241] 抗体的结合

[0242] 测试来自健康对象和具有不同GOSE分数的脑损伤患者在受损后不同时间的血清样本中,血清IgG抗体及/或IgM抗体对表1中揭露的不同抗原的结合。

[0243] 表1:脑损伤相关抗原的清单

[0244]

抗原	氨基酸序列或产品(产品目录号)	SEQ ID NO:
MBP (髓磷脂碱性蛋白)	MASQKRPSQRHGSKYLATASTMDHARHGFLPRHRDTGILDSIG RFFGGDRGAPKRGSGKVPWLKPGRSPL PSHARSQPGLCNMYKDSHHPARTAHYGSLPQKSHGRTQDENPV VHFFKNIVTPRTPPPSQGKGRGLSLSR FSWGAEGQRPGFGYGGRASDYKSAHKGFKGVDAQGTLSKIFKL GGRDSRSGSPMARR Enzo LS (ALX-200-606-M001)	1
MBP-体外瓜氨酸化	Enzo LS 中一个或多个精氨酸的转译后瓜氨酸化 (ALX-200-606-M001)	2
MBP R26	Ac-TMDHA(Cit)HGFLPC-酰胺	3
MBP R32, R34	Ac-GFLP(Cit)H(Cit)DTGIC-酰胺	4
MBP R44	Ac-CILDSIG(Cit)FFGG-酰胺	5
MBP R50	Ac-FGGD(Cit)GAPKRGC-酰胺	6
MBP R92	Ac-CDSHHPA(Cit)TAHYG-酰胺	7
MBP R106	Ac-CQKSHG(Cit)TQDEN-酰胺	8
MBP R124	Ac-CFKNIVTP(Cit)TP-酰胺	9
MBP R149	Ac-GAEGQ(Cit)PGFGYC-酰胺	10
MBP R157	Ac-CGYGG(Cit)ASDYKS-酰胺	11
MBP R186, R189	Ac-CKLGG(Cit)DS(Cit)SG-酰胺	12
MBP R196, R197	Ac-C(Ahx)SGSPMA(Cit)(Cit)-OH	13
GFAP (胶质纤维酸性蛋白)	MERRRITSAARRSYVSSGEMMVGGLAPGRRLGPGTRLSLARMP PPLPTRVDFSLAGALNAGFKETRASER AEMMELNDRFASYIEKVRFLEQQNKALAAELNQLRAKEPTKLA DVYQAELRELRLRLDQLTANSARLEVE RDNLAQDLATVRQKLQDETNLRLEAENNLAAYRQEADEATLAR LDLERKIESLEEEIRFLRKIHEEEVRE LQEQLARQQVHVELDVAKPDLTAALKEIRTQYEAMASSNMHEA EEWYRSKFADLTDAAARNAELLRQAKH EANDYRRQLQSLTCDLESLRGTNESLERQMREQEERHVREAAS YQEALARLEEEGQSLKDEMARHLQEYQ	14

[0245]

	DLLNVKLALDIEIATYRKLLEGEENRITIPVQTFSNLQIRETS LDTKSVSEGHLKRNIVVKTVEMRDGEV TKESKQEHKDVM Calbiochem (345996)	
GFAP- 体外瓜氨酸化	Calbiochem 中一个或多个精氨酸的转译后瓜氨酸化(345996)	15
GFAP R30	Ac-LAPGR(Cit)LGPGTC-酰胺	16
GFAP R36	Ac-CLGPGT(Cit)LSLAR-酰胺	17
GFAP R270	Ac-AA(Cit)NAELLRQC-酰胺	18
GFAP R406	Ac-CEGHLK(Cit)NIVVK-酰胺	19
GFAP R416	Ac-CVKTVEM(Cit)DGEVI-酰胺	20
NRGN (神经颗粒素)	MDCCTENACSKPDDDILDIPLDDPGANAAAAKIQASFRGHMAR KKIKSGERGRKGPGPGGPGGAGVARGG AGGGPSGD	21
NRGN- 体外瓜氨酸化	NRGN 中一个或多个精氨酸的转译后瓜氨酸化	22
NRGN R51, R53	Ac-CKSGE(Cit)G(Cit)KGPG-酰胺	23
NRGN R68	Ac-CGGAGVA(Cit)GGAG-酰胺	24
ERMIN	MKTLSPDRIQPHIMTDVPATFTQAECNGDKPPENGQQTITKIS EELTDVDSPLPHYRVEPSLEGALTKGS QEERRKLQGNMLLNSSMEDKMLKENPEEKLFIVHKAITDLSLQ ETSADEMTFREGHIQWEKIPLSGSNQEI RRQKERITEQPLKEEEDEDRKNKGHQAAEIEWLGFRKPSQADM LHSKHDEEQKVWDEEIDDDDDDNCNND EDEVRVIEFKKKHEEVSQFKEEGDASEDSPLSSASSQAVTPDE QPTLGKKSDISRNAYSRYNTISYRKIR KGNTKQRIDEFESMMHL	25
ERMIN-体外瓜氨酸化	ERMIN 中一个或多个精氨酸的转译后瓜氨酸化	26
Ermin R57	Ac-DSPLPHY(Cit)VEPSLEC-酰胺	27

[0246]

ICAM5	MPGPSPGLRRALLGLWAALGLGLFGLSAVSQEPFWADLQPRVA FVERGGSLWLNCSTNCPRPERGGLETS LRRNGTQRGLRWLARQLVDIREPETQPVCFFRCARRTLQARGL IRTFQRPDRVELMPLPPWQPVGENFTL SCRVPGAGPRASLTLTLLRGAQELIRRSFAGEPPRARGAVLTA TVLARREDHGANFSCRAELDLRPHGLG LFENSSAPRELRTFSLSPDAPRLAAPRLLEVGSERPVSCTLDG LFPASEARVYLALGDQNLSPDVTLEGD AFVATATATASAEQEGARQLVCNVTLGGENRETRENVTIYSFP APLLTLSEPSVSEGQMVTVTCAAGAQA LVTLEGVPAAVPGQPAQLQLNATENDDRRSFFCDATLDVDGET LIKNRSAELRVLYAPRLDDSDCPRSWT WPEGPEQTLRCEARGNPEPSVHCARSDGGAVLALGLLGPVTRA LSGTYRCKAANDQGEAVKDVTLTVEYA PALDSVGCPERITWLEGTEASLSCVAHGVPPPDVICVRSGELG AVIEGLLRVAREHAGTYRCEATNPRGS AAKNVAVTVEYGPRFEEPSCPSNWTWVEGSGRLFSCEVDGKPQ PSVKCVGSGGATEGVLLPLAPPDPSPR APRIPRVLAPGIYVCNATNRHGSVAKTVVVSAESPPEMDESTC PSHQTWLEGAEASALACAARGRPSPGV RCSREGIPWPEQQRVSREDAGTYHCVATNAHGTDSRTVTVGVE YRPVVAELAASPPGGVRPGGNFTLTCR AEAWPPAQISWRAPPGALNIGLSSNNSTLSVAGAMGSHGGEYE CAATNAHGRHARRITVRVAGPWLWVAV GGAAGGAALLAAGAGLAFYVQSTACKKGEYNVQEAESSGEAVC LNGAGGGAGGAAGAEGGPEAAGGAAES PAEGEVFAIQLTSA R&D (1950-M5)	28
SNCB（β-突触核蛋白）	MDVFMKGLSMAKEGVVAAAEKTKQGVTEAAEKTKEGVLYVGSK TREGVVQGVASVAEKTKEQASHLGGAV FSGAGNIAAATGLVKREEFPTDLKPEEVAQEAAEEPLIEPLME PEGESYEDPPQEEYQEYEPEA OriGene (TP315165)	29
MT3（金属硫蛋白III）	MDPETCPCPSGGSCTCADSCKCEGCKCTSCKKSCCSCCPAECE KCAKDCVCKGGEAAEAEAEKCSCCQ	30
OMG（少突细胞髓	MEYQILKMSLCLFILLFLTPGILCICPLQCICTERHRHVDCSG RNLSTLPSGLQENIIHLNLSYNHFTDL	31

[0247]

糖蛋白)	HNQLTQYTNLRTLDISNNRLESLPAHLPRSLWNMSAANNNIKL LDKSDTAYQWNLKYLDVSKNMLEKVVL IKNTLRSLEVLNLSSNKLWTVPTNMPSKLHIVDLSNNSLTQIL PGTLINLTNLTHLYLHNNKFTFIPDQS FDQLFQLQEITLYNNRWSCDIIKQNITYLLKWMMETKAIIVIGTP CSTQISSLKEHNMYPTPSGFTSSLFTV SGMQTVDTINSLSVVTQPKVTKIPKQYRTKETTFGATLSKDTT FTSTDKAFVPYPEDTSTETINSHEAAA ATLTIHLQDGMVTNTSLTSSTKSSPTPMTLSITSGMPNNFSEM PQQSTTLNLWREETTTNVKTPLPSVAN AWKVNASFLLLLNVVVMLAV	
CNDP1 (肌肽二肽酶 1)		32
网状内皮素 1	MAAPGDPQDELLPLAGPGSQWLRIIRGEGENEAVTPKGATPAPQ AGEPSPGLGARAREAASREAGSGPARQ SPVAMETASTGVAGVSSAMDHTFSTTSKDGEGSCYTSLISDIC YPPQEDSTYFTGILQKENGHVTISESP EELGTPGPSLPDVPGIESRGLFSSDSGIEMTPAESTEVNKILA DPLDQMKAEAYKYIDITRPEEVKHQEQ HHPELEDKDLDFKNKDTDISIKPEGVREPDKPAPVEGKIIKDH LLEESTFAPYIDDLSEEQRRAPQITTP VKITLTEIEPSVETTTQEKTPEKQDICLKPSPDTVPTVTVSEP EDDSPGSITPPSSGTEPSAAESQGKGS ISEDELITAIKEAKGLSYETAENPRPVGQLADRPEVKARSGPP TIPSPLDHEASSAESGDSEIELVSEDP MAAEDALPSGYVSFGHVGGPPPSPASPSIQYSILREEREAELD SELITESCDASSASEESPKREQDSPPM KPSALDAIREETGVRAEERAPSRRGLAEPGSFLDYPSTEPQPG PELPPGDGALEPETPMLPRKPEEDSSS NQSPAATKGPGPLGPGAPPPLLFLNKQKAIDLLYWRDIKQTGI VFGSFLLLLFSLTQFSVVSVVAYLALA ALSATISFRIYKSVLQAVQKTDEGHPFKAYLELEITLSQEQIQ KYTDCLQFYVNSTLKELRRLFLVQDLV DSLKFAVLMWLLTYVGALFNGLTLLLMAVVSMFTLPVVYVKHQ AQIDQYLGLVRTHINAVVAKIQAKIPG AKRHAE	33
星形肌动	MALAGLCALLACCWGPAAVLATAAGDVDPSKELECKLKSITVS	34

[0248]

蛋白 1	ALPFLRENDLSIMHSPSASEPKLLFSV RNDFPGEMVVVDDLENTELPYFVLEISGNTEDIPLVRWRQQWL ENGTLLFHIHHQDGAPSLPGQDPTEEP QHESAEEELRILHISVMGGMIALLLSILCLVMILYTRRRWCKR RRVPQPQKSASAEAANEIHYIPSVLIG GHGRESLRNARVQGHNSSGTLSIRETPILDGYEYDITDLRHHL QRECMNGGEDFASQVTRTLDSLQGCNE KSGMDLTPGSDNAKLSLMNKYKDNIIATSPVDSNHQQATLLSH TSSSQRKRTNNKARAGSAFLNPEGDSG TEAENDPQLTFYTDPSRSRRRSRVGSPRSPVNKTTLTLISITS CVIGLVCSSHVNCPLVVKITLHVPEHL IADGSRFILLEGSQLDASDWLNPAQVVLFSQQNSSGPWAMDLC ARRLLDPCEHQCDPETGECLCYEGYMK DPVHKHLCIRNEWGTNQGPWPYTIFQRGFDLVLGEQPSDKIFR FTYTLGEGMWLPLSKSFVIPPAELAIN PSAKCKTDMTVMEDAVEVREELMTSSSFDSLEVLLDSFGPVRD CSKDNGGCSKNFRCISDRKLDSTGCVC PSGLSPMKDSSGCYDRIIIGVDCSDGFNGGCEQLCLQQMAPFPD DPTLYNILMFCGCIEDYKLGVDGRSCQ LITETCPEGSDCGESRELPMNQTLFGEMFFGYNNHSKEVAAGQ VLKGTFRQNNFARGLDQQLPDGLVVAT VPLENQCLEEISEPTPDPDFLTGMVNFSEVSGYPVLQHWKVRS VMYHIKLNQVAISQALSNALHSLDGAT SRADFVALLDQFGNHYIQEAIYGFEESCSIWYPNKQVQRRLWL EYEDISKGNSPSDESEERERDPKVLTF PEYITSLSDSGTKIIMAAGVRMECIISKGRCPSSCPLCIIVTSSPD TPAEPVLLEVTKAAPIYELVTNNQTQR LLQEATMSSLWCSGTGDVIEDWCRCDSTAFGADGLPTCAPLPQ PVLRLSTVHEPSSTLVVLEWEHSEPPI GVQIVDYLLRQEKVTDRMDHSKVETETVLSFVDDIISGAKSPC AMPSQVPDKQLTTISLIIRCLEPDTIY MFTLWGVDNTGRRSRPSDVIVKTPCPVVDDVKAQEIADKIYNL FNGYTSGKEQQTAYNTLLDLGSPTLHR VLYIIYNQIIYESFGEFTWRCEDELGPRKAGLILSQLGDLSSWCN GLLQEPKISLRRSSLKYLGCRYSEIKP YGLDWAELSRDLRKTCEEQTLSIPYNDYGDSKEI	
脑血管生成抑制因	uniprot# 060242	35

	子3		
	谷氨酸盐受体，代谢型 3	uniprot# Q14832	36
	类 Kelch 32	uniprot# Q96NJ5	37
	基质金属蛋白酶-9	uniprot# P14780	38
	黑色素瘤抗原家族 E，2	uniprot# Q8TD90	39
	神经调节蛋白 3	uniprot# P56975	40
	类 SLIT 和 NTRK 家族，成员 3	uniprot#O94933	41
[0249]	BDNF（脑源性神经营养因子）	MTILFLTMVISYFGCMKAAPMKEANIRGQGGLAYPGVRTHGTL ESVNGPKAGSRGLTSLADTFEHVIEEL LDEDQKVRPNEENNKDADLYTSRVMLSSQVPLEPPLLFLLEEY KNYLDAANMSMRVRRHSDPARRGELSV CDSISEWVTAADKKTAVDMSGGTVTVLEKVPVSKGQLKQYFYE TKCNPMGYTKEGCRGIDKRHWNSQCRT TQSYVRALTMDSKKRIGWRFIRIDTSCVCTLTIKRGR R&D (248BD005)	42
	UBIQUITIN CTERMINAL HYDROLASE L1	uniprot# P09936	43
	Oligo24	T16G1: TTT TTT TTT TTT TTT TG	44
	微管蛋白β-4B链，体外瓜氨酸化	uniprot# P68371	45
	微管蛋白β-4B链	(K)IREEYPDrIMNTF(S)	46

[0250]

微管蛋白α-1B链	uniprot# P68363	47
微管蛋白α-1B链，体外瓜氨酸化		48
微管蛋白α-1B链	(K)YMAccLLYrGDVVPK(D)	49
微管蛋白α-1B链	(E)VrTGTYrQLFHPE(Q)	50
突触结合蛋白	uniprot# P21579	51
AB1-42		52
CNPase	(K)STLArVIVDK(Y)	53
CNPase	(K)ITPGArGAFSEEYK(R)	54
层粘连蛋白	uniprot# Q13753	55
PPIA体外瓜氨酸化	uniprot# P62937	56
PPIA	(K)TAENFrALSTGEK(G)	57
S100A10	Uniprot# P60903	58
Septin-7，体外瓜氨酸化		59
Septin-7	(R)ILEQQNSSrTLEK(N)	60
脂肪酸结合蛋白(FABP-3)	Prospec (PRO-340)	61
延长因子1-α2，体外瓜氨酸化	Uniprot#Q05639	62
延长因子1-α2	(K)PLrLPLQDVYK(I)	63
延长因子1-α2	(D)VYKIGGIGTVPVGrVE(T)	64
ICNPase (2',3'-	uniprot# P09543	65

[0251]

环状核苷酸 3'-磷酸二酯酶)		
胶原蛋白 IV	uniprot# P02462	66
TPPP	(K)AISSPTVSrLTDTTK(F)	67
磷酸化-c-Jun	uniprot# P05412	68
TPPP3，体外瓜氨酸化	(K)TGGAVD(Cit)LTDTSrYTGSHK(E)	69
TPPP3	(K)TGGAVDRLTDTSrYTGSHK(E)	70
TPPP3	(K)GIAGrQDILDDSGYVSAYK(N)	71
多孔膜蛋白神经降压素-1 (p24)	uniprot# Q8IZ57	72
NDRG2，异构体 2，体外瓜氨酸化	uniprot# Q9UN36	73
NDRG2，异构体 2	(R)TASLTSAASVDGNrSR(S)	74
S100 钙结合蛋白 B(S100B)	MSELEKAMVALIDVFHQYSGREGDKHKLKKSELKELINNELSH FLEEIKEQEVVDKVMETLDNDGDGECD FQEFMAFVAMVTTACHEFFEHE Sigma (S6677)	75
NSE(神经元特异性烯醇化酶 ENO2)	MSIEKIWAREILDSRGNPTVEVDLYTAKGLFRAAVPSGASTGI YEALELRDGDKQRYLGKGVLKAVDHIN STIAPALISSGLSVVEQEKLDNLMLELDGTENKSKFGANAILG VSLAVCKAGAAERELPLYRHIAQLAGN SDLILPVPAFNVINGGSHAGNKLAMQEFMILPVGAESFRDAMR LGAEVYHTLKGVIKDKYGKDATNVGDE GGFAPNILENSEALELVKEAIDKAGYTEKIVIGMDVAASEFYR DGKYDLDFKSPTDPSRYITGDQLGALY QDFVRDYPVVSIEDPFDQDDWAAWSKFTANVGIQIVGDDLTVT NPKRIERAVEEKACNCLLLKVNQIGSV	76

[0252]

	TEAIQACKLAQENGWGVMVSHRSGETEDTFIADLVVGLCTGQI KTGAPCRSERLAKYNQLMRIEEELGDE ARFAGHNFRNPSVL Abnova (H00002026-P01)	
MCP1(单核细胞趋向蛋白-1)	Prospec (CHM-271)	77
θ，总	Sigma (T9392)	78
神经丝轻多肽		79
神经丝重多肽		80
γ-烯醇化酶		81
凝血酶原-因子 II		82
EXOSC10	uniprot# Q01780	83
血影蛋白，分解产物	Sigma (S3644)	84
髓过氧化物酶(MPO)	Sigma (M6908)	85
CMV	Prospec (CMV Pp150)	86
ICAM	uniprot# Q8N6I2	87
SLC39A11	uniprot# Q8N1S5	88
MAP2(微管相关蛋白2		89
MAPT (微管相关θ基因)		90
HTR1A(羟色胺受体 1A基因)		91
PLXNA4		92

[0253]

(丛蛋白A4)		
白介素-6	PVPPGEDSKD VAAPHRQPLT SSERIDKQIR YILDGISALR KETCNKSNMC ESSKEALAEN NLNLPKMAEK DGCFQSGFNE ETCLVKIITG LLEFEVYLEY LQNRFESSEE QARAVQMSTK VLIQFLQKKA KNLDAITTPD PTTNASLLTK LQAQNQWLQD MTTHLILRSF KEFLQSSLRA LRQM Peprotech (200-06)	93
白介素-12	p40 Subunit: IWELKK DVYVVELDWY PDAPGEMVVL TCDTPEEDGI TWTLDQSSEV LGSGKTLTIQ VKEFGDAGQY TCHKGGEVLS HSLLLLHKKE DGIWSTDILK DQKEPKNKTF LRCEAKNYSG RFTCWWLTTI STDLTFSVKS SRGSSDPQGV TCGAATLSAE RVRGDNKEYE YSVECQEDSA CPAAEESLPI EVMVDAVHKL KYENYTSSFF IRDIIKPDPP KNLQLKPLKN SRQVEVSWEY PDTWSTPHSY FSLTFCVQVQ GKSKREKKDR VFTDKTSATV ICRKNASISV RAQDRYYSSS WSEWASVPCS Peprotech (200-12)	94
白介素-15	MNWVNVISDL KKIEDLIQSM HIDATLYTES DVHPSCKVTA MKCFLLELQV ISLESGDASI HDTVENLIIL ANNSLSSNGN VTESGCKECE ELEEKNIKEF LQSFVHIVQM FINTS Peprotech (200-15)	95
白介素-17	MIVKAGITIP RNPGCPNSED KNFPRTVMVN LNIHNRNTNT NPKRSSDYYN RSTSPWNLHR NEDPERYPSV IWEAKCRHLG CINADGNVDY HMNSVPIQQE ILVLRREPPH CPNSFRLEKI LVSVGCTCVT PIVHHVA Peprotech (200-17)	96
白介素-1ra	MRPSGRKSSK MQAFRIWDVN QKTFYLRNNQ LVAGYLQGPN VNLEEKIDVV PIEPHALFLG IHGGKMCLSC VKSGDETRLQ LEAVNITDLS ENRKQDKRFA FIRSDSGPTT SFESAACPGW FLCTAMEADQ PVSLTNMPDE GVMVTKFYFQ EDE Peprotech (200-01RA)	97
TNFRI	MDSVCPQGKY IHPQNNSICC TKCHKGTYLY NDCPGPGQDT DCRECESGSF TASENHLRHC LSCSKCRKEM GQVEISSCTV DRDTVCGCRK NQYRHYWSEN LFQCFNCSLC LNGTVHLSCQ EKQNTVCTCH AGFFLRENEC VSCSNCKKSL ECTKLCLPQI EN Peprotech (310-07)	98
VEGF	APMAEGGGQN HHEVVKFMDV YQRSYCHPIE TLVDIFQEYP	99

[0254]

	DEIEYIFKPS CVPLMRCGGC CNDEGLECVP TEESNITMQI MRIKPHQGQH IGEMSFLQHN KCECRPKKDR ARQENPCGPC SERRKHLFVQ DPQTCKCSCK NTDSRCKARQ LELNERTCRC DKPRR Peprotech (100-20)	
VCAM1	FKIETTPESR YLAQIGDSVS LTCSTTGCES PFFSWRTQID SPLNGKVTNE GTTSTLTMNP VSFGNEHSYL CTATCESRKL EKGIQVEIYS FPKDPEIHLS GPLEAGKPIT VKCSVADVYP FDRLEIDLLK GDHLMKSQEF LEDADRKSLE TKSLEVTFTP VIEDIGKVLV CRAKLHIDEM DSVPTVRQAV KELQVYISPK NTVISVNPST KLQEGGSVTM TCSSEGLPAP EIFWSKKLDN GNLQHLSGNA TLTLIAMRME DSGIYVCEGV NLIGKNRKEV ELIVQEKPFT VEISPGPRIA AQIGDSVMLT CSVMGCESPS FSWRTQIDSP LSGKVRSEGT NSTLTLSPVS FENEHSYLCT VTCGHKKLEK GIQVELYSFP RDPEIEMSGG LVNGSSVTVS CKVPSVYPLD RLEIELLKGE TILENIEFLE DTDMKSLENK SLEMTFIPTI EDTGKALVCQ AKLHIDDMEF EPKQRQSTQT LYVNVAPRDT TVLVSPSSIL EEGSSVNMTC LSQGFPAPKI LWSRQLPNGE LQPLSENATL TLISTKMEDS GVYLCEGINQ AGRSRKEVEL IIQVTPKDIK LTAFPSESVK EGDTVIISCT CGNVPETWII LKKKAETGDT VLKSIDGAYT IRKAQLKDAG VYECESKNKV GSQLRSLTLD VQGRENNKDY FSP Peprotech (150-04)	100
因子VIIa	AKRONbiotech (AK9916)	101
胶原蛋白II		102
微球蛋白-b2	Sigma (M4890)	103
TNFRSF12A	EQAPGTAPCS RGSSWSADLD KCMDCASCRA RPHSDFCLGC AAAPPAPFRL LWP Peprotech (310-21)	104
TNFRII	MAPEPGSTCR LREYYDQTAQ MCCSKCSPGQ HAKVFCTKTS DTVCDSCEDS TYTQLWNWVP ECLSCGSRCS SDQVETQACT REQNRICTCR PGWYCALSKQ EGCRLCAPLR KCRPGFGVAR PGTETSDVVC KPCAPGTFSN TTSSTDICRP HQICNVVAIP GNASMDAVCT STSP Peprotech (310-12)	105
CRP	Sigma (C4063)	106

[0255]

BAFF-R	MRRGPRSLRG RDAPAPTPCV PAECFDLLVR HCVACGLLRT PRPKPAGASS PAPRTALQPQ ESVGAGAGEA ALPLPG Peprotech (310-13R)	107
BAFF	AVQGPEETVT QDCLQLIADS ETPTIQKGSY TFVPWLLSFK RGSALEEKEN KILVKETGYF FIYGQVLYTD KTYAMGHLIQ RKKVHVFGDE LSLVTLFRCI QNMPETLPNN SCYSAGIAKL EEGDELQLAI PRENAQISLD GDVTFFGALK LL Peprotech (310-13)	108
GLP1	HAEGTFTSDV SSYLEGQAAK EFIAWLVKGR G Peprotech (130-08)	109
HSP90	Sigma (H6774)	110
EGFP	Prospec (cyt-332)	111
C4	Sigma (C8195)	112
C3	Sigma (C2910)	113
C1q	Prospec (pro-554)	114
纤维素原	AKRONbiotech (AK9026)	115

[0256] 如图1中所示，与具有GOSE分数＝8的患者(圆点)相比，在损伤后第30天从格拉斯哥结局量表扩展(GOSE)分数<8的TBI患者(十字)的血清样本中抗脂肪酸结合蛋白质(FABP，SEQ ID No:61)IgM自身抗体的水平较低。

[0257] 如图2中所示，与具有GOSE分数＝8的患者(圆点)相比，在损伤后第30天从格拉斯哥结局量表扩展(GOSE)分数<8的TBI患者(十字)的血清样本中抗髓磷脂碱性蛋白(MBPR149，SEQ ID No:10，MBP衍生的BSA缀合肽)IgM自身抗体的水平较高。这些结果第一次表明，从TBI患者获取的血清样本中抗FABP IgM自身抗体水平的增加，是所述TBI患者从脑损伤恢复的指征。此外，从TBI患者获取的血清样本中抗MBPR149IgM自身抗体水平的下降，是所述TBI患者从脑损伤恢复的指征。因此，本发明揭露了可用于监控脑损伤及/或脑损伤预后的特异性抗原抗体反应性。

[0258] 实施例2：与健康对照相比，从TBI患者获取的血清样本中抗髓过氧化物酶(MPO，SEQ ID No:85)IgM自身抗体的水平提高

[0259] 如图3中所示，与健康对照(十字)相比，从TBI患者(圆点)获取的血清样本中抗MPO IgM自身抗体的水平较高。这些结果第一次表明，抗MPO自身抗体的水平增加是脑损伤的指征。

[0260] 实施例3：与健康对照相比，从TBI患者获取的血清样本中抗CMV(SEQ ID No:86)IgG自身抗体的水平下降

[0261] 如图4A中所示，与健康对照(十字)(N＝21)相比，在损伤后第30天和第90天从TBI患者(圆点)(N＝142)获取的血清样本中抗CMV(SEQ ID No:86)IgG自身抗体的水平较低。图4B通过抗CMV IgG自身抗体水平的受试者工作特征(ROC)曲线显示分离效能。

[0262] 实施例4：基于在损伤后第30天从TBI患者获取的血清样本中的抗TNFRSF12A(SEQ ID No:104)IgM自身抗体的水平，对TBI患者在损伤后第90天的临床状态的预测

[0263] 如图5A中所示，可使用在损伤后第30天从TBI患者获取的血清样本中的抗TNFRSF12A(SEQ ID No:104)IgM自身抗体的水平，来预测TBI患者在损伤后第90天的临床状态(GOSE<8或GOSE＝8)。图5B通过抗TNFRSF12A IgM自身抗体水平的受试者工作特征(ROC)曲线显示分离效能。

[0264] 实施例5：与健康对照相比，从TBI患者获取的血清样本中自身抗体与生物标记物的水平的组合测量

[0265] 为了确定能否区分TBI患者与健康对照血清样本中抗体和生物标记物水平的组合测量，进行组合分析。将在时间0(t0,N＝85)从TBI患者获取的血清样本与从健康对照(HC,N＝21)获取的血清样本比较。该分析基于464种iChip特征(232种抗原，IgM和IgG)和四种ELISA特征。iChip数据基于两种封闭复本的平均，之后进行校正过程。基于数据可用性而选择ELISA特征；仅使用具有可用于>80％的iChip样本的数据的特征。从该分析中移除具有缺失ELISA数据的样本。

[0266] 图6显示基于100次迭代的70:30交叉验证的六种分类方法(SVM、LR、QDA、CART、RF及LDA)的受试者工作特征(ROC)曲线下的面积。根据其中位数得分或模型内含物的频率，依据所使用的方法，将特征排名。

[0267] 使用LDA分类方法透露，随机背景水平之上最高的六种特征是生物标记物：GFAP及SNCB与下述自身抗体组合：体外瓜氨酸化的抗MBP(SEQ ID No:2)IgM、抗GFAP(SEQ ID No:14)IgM、抗ICAM5(SEQ ID No:28)IgM、及抗BDNF(SEQ ID No:42)IgM。

[0268] 使用QDA分类方法透露，随机背景水平之上最高的三种特征是生物标记物：GFAP及SNCB与自身抗体：体外瓜氨酸化的抗MBP(SEQ ID No:2)组合。

[0269] 实施例6：与具有正常CT的TBI患者相比，从头部CT具有颅内出血的TBI患者获取的血清样本中抗体与生物标记物水平的组合测量

[0270] 为了确定能否区分头部CT具有颅内出血的TBI患者与具有正常CT的TBI患者的血清样本中抗体和生物标记物水平的组合测量，进行组合分析。将在时间0(t0)从具有异常CT的TBI患者获取的血清样本与在时间0(t0)从具有正常CT的TBI患者获取的血清样本比较。该分析基于464种iChip特征(232种抗原，IgM和IgG)和四种ELISA特征。iChip数据基于两种封闭复本的平均，之后进行校正过程。基于数据可用性而选择ELISA特征；仅使用具有可用于>80％的iChip样本的数据的特征。从该分析中移除具有缺失ELISA数据的样本。

[0271] 图7显示基于100次迭代的70:30交叉验证的六种分类方法(SVM、LR、QDA、CART、RF及LDA)的ROC曲线下的面积。根据其中位数得分或模型内含物的频率，依据所使用的方法，将特征排名。

[0272] 使用LDA分类方法透露，随机背景水平之上最高的五种特征是生物标记物：SNCB与下述自身抗体组合：抗胶原IV(SEQ ID No:66)IgG、抗Oligo24(SEQ ID No:44)IgM、抗EBV IgM和抗胶原II(SEQ ID No:102)IgG。

[0273] 前述对特定具体实施例的说明将因此完全透露本发明的通常特性，通过应用当下的知识，其他人可轻易地修改此类特定具体实施例及/或令其适用于多种应用而不悖离通用概念，以及，因此，此类改动或修改应该且倾向于被理解为处于所揭露具体实施例等效的意义和范围内。应理解，本文中采用的措辞或术语用于说明而非限制。用于实施所揭露的功能的手段、材料和步骤可采取各种备选形式，而不悖离本发明。

序列表

<110> 美国免疫阵列公司(Immunarray)

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克伦,贾科比(Jakobi , Keren)

<120> 用于诊断脑损伤或神经退行性变的方法和组合物

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<151> 2015-02-04

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Ser Asn Leu Gln Ile Xaa Glu Thr Ser Leu Asp Thr Lys Ser Val Ser
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Glu Gly His Leu Lys Xaa Asn Ile Val Val Lys Thr Val Glu Met Xaa
405 410 415

Asp Gly Glu Val Ile Lys Glu Ser Lys Gln Glu His Lys Asp Val Met
420 425 430

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Leu Ala Pro Gly Arg Xaa Leu Gly Pro Gly Thr Cys
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Cys Leu Gly Pro Gly Thr Xaa Leu Ser Leu Ala Arg
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Ala Ala Xaa Asn Ala Glu Leu Leu Arg Gln Cys
1 5 10
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<222> (12)..(12)
<223> 酰胺化
<400> 19
Cys GIu GIy His Leu Lys Xaa Asn IIe VaI VaI Lys
1 5 10
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Cys VaI Lys Thr VaI GIu Met Xaa Asp GIy GIu VaI IIe

1 5 10

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<211> 78
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<400> 21

Met Asp Cys Cys Thr GIu Asn AIa Cys Ser Lys Pro Asp Asp Asp IIe
1 5 10 15
Leu Asp IIe Pro Leu Asp Asp Pro GIy AIa Asn AIa AIa AIa AIa Lys
20 25 30
IIe GIn AIa Ser Phe Arg GIy His Met AIa Arg Lys Lys IIe Lys Ser
35 40 45
GIy GIu Arg GIy Arg Lys GIy Pro GIy Pro GIy GIy Pro GIy GIy AIa
50 55 60
GIy VaI AIa Arg GIy GIy AIa GIy GIy GIy Pro Ser GIy Asp
65 70 75

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<400> 22

Met Asp Cys Cys Thr GIu Asn AIa Cys Ser Lys Pro Asp Asp Asp IIe
1 5 10 15
Leu Asp IIe Pro Leu Asp Asp Pro GIy AIa Asn AIa AIa AIa AIa Lys
20 25 30
IIe GIn AIa Ser Phe Xaa GIy His Met AIa Xaa Lys Lys IIe Lys Ser
35 40 45
GIy GIu Xaa GIy Xaa Lys GIy Pro GIy Pro GIy GIy Pro GIy GIy AIa
50 55 60
GIy VaI AIa Xaa GIy GIy AIa GIy GIy GIy Pro Ser GIy Asp
65 70 75

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Cys Lys Ser GIy GIu Xaa GIy Xaa Lys GIy Pro GIy
1 5 10

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<223> 瓜氨酸
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<223> 酰胺化
<400> 24
Cys Gly Gly Ala Gly Val Ala Xaa Gly Gly Ala Gly
1 5 10
<210> 25
<211> 297
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<400> 25
Met Lys Thr Leu Ser Pro Asp Arg Ile Gln Pro His Ile Met Thr Asp
1 5 10 15
Val Pro Ala Thr Phe Thr Gln Ala Glu Cys Asn Gly Asp Lys Pro Pro
20 25 30
Glu Asn Gly Gln Gln Thr Ile Thr Lys Ile Ser Glu Glu Leu Thr Asp
35 40 45
Val Asp Ser Pro Leu Pro His Tyr Arg Val Glu Pro Ser Leu Glu Gly
50 55 60
Ala Leu Thr Lys Gly Ser Gln Glu Glu Arg Arg Lys Leu Gln Gly Asn
65 70 75 80
Met Leu Leu Asn Ser Ser Met Glu Asp Lys Met Leu Lys Glu Asn Pro
85 90 95
Glu Glu Lys Leu Phe Ile Val His Lys Ala Ile Thr Asp Leu Ser Leu

100 105 110

GIn GIu Thr Ser AIa Asp GIu Met Thr Phe Arg GIu GIy His GIn Trp

115 120 125

GIu Lys IIe Pro Leu Ser GIy Ser Asn GIn GIu IIe Arg Arg GIn Lys

130 135 140

GIu Arg IIe Thr GIu GIn Pro Leu Lys GIu GIu GIu Asp GIu Asp Arg

145 150 155 160

Lys Asn Lys GIy His GIn AIa AIa GIu IIe GIu Trp Leu GIy Phe Arg

165 170 175

Lys Pro Ser GIn AIa Asp Met Leu His Ser Lys His Asp GIu GIu GIn

180 185 190

Lys VaI Trp Asp GIu GIu IIe Asp Asp Asp Asp Asp Asp Asn Cys Asn

195 200 205

Asn Asp GIu Asp GIu VaI Arg VaI IIe GIu Phe Lys Lys Lys His GIu

210 215 220

GIu VaI Ser GIn Phe Lys GIu GIu GIy Asp AIa Ser GIu Asp Ser Pro

225 230 235 240

Leu Ser Ser AIa Ser Ser GIn AIa VaI Thr Pro Asp GIu GIn Pro Thr

245 250 255

Leu GIy Lys Lys Ser Asp IIe Ser Arg Asn AIa Tyr Ser Arg Tyr Asn

260 265 270

Thr IIe Ser Tyr Arg Lys IIe Arg Lys GIy Asn Thr Lys GIn Arg IIe

275 280 285

Asp GIu Phe GIu Ser Met Met His Leu

290 295

<210> 26

<211> 297

<212> PRT

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

165 170 175

Lys Pro Ser GIn AIa Asp Met Leu His Ser Lys His Asp GIu GIu GIn

180 185 190

Lys VaI Trp Asp GIu GIu IIe Asp Asp Asp Asp Asp Asn Cys Asn

195 200 205

Asn Asp GIu Asp GIu VaI Xaa VaI IIe GIu Phe Lys Lys Lys His GIu

210 215 220

GIu VaI Ser GIn Phe Lys GIu GIu GIy Asp AIa Ser GIu Asp Ser Pro

225 230 235 240

Leu Ser Ser AIa Ser Ser GIn AIa VaI Thr Pro Asp GIu GIn Pro Thr

245 250 255

Leu GIy Lys Lys Ser Asp IIe Ser Xaa Asn AIa Tyr Ser Xaa Tyr Asn

260 265 270

Thr IIe Ser Tyr Xaa Lys IIe Xaa Lys GIy Asn Thr Lys GIn Xaa IIe

275 280 285

Asp GIu Phe GIu Ser Met Met His Leu

290 295

<210> 27

<211> 15

<212> PRT

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<222> (8)..(8)

<223> 瓜氨酸

<220>

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<222> (15)..(15)

<223> 酰胺化

<400> 27

Asp Ser Pro Leu Pro His Tyr Xaa VaI GIu Pro Ser Leu GIu Cys

1 5 10 15

<210> 28

<211> 924
<212> PRT
<213> 人
<400> 28

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

275 280 285

Thr Ala Ser Ala Glu Gln Glu Gly Ala Arg Gln Leu Val Cys Asn Val

290 295 300

Thr Leu Gly Gly Glu Asn Arg Glu Thr Arg Glu Asn Val Thr Ile Tyr

305 310 315 320

Ser Phe Pro Ala Pro Leu Leu Thr Leu Ser Glu Pro Ser Val Ser Glu

325 330 335

Gly Gln Met Val Thr Val Thr Cys Ala Ala Gly Ala Gln Ala Leu Val

340 345 350

Thr Leu Glu Gly Val Pro Ala Ala Val Pro Gly Gln Pro Ala Gln Leu

355 360 365

Gln Leu Asn Ala Thr Glu Asn Asp Asp Arg Arg Ser Phe Phe Cys Asp

370 375 380

Ala Thr Leu Asp Val Asp Gly Glu Thr Leu Ile Lys Asn Arg Ser Ala

385 390 395 400

Glu Leu Arg Val Leu Tyr Ala Pro Arg Leu Asp Asp Ser Asp Cys Pro

405 410 415

Arg Ser Trp Thr Trp Pro Glu Gly Pro Glu Gln Thr Leu Arg Cys Glu

420 425 430

Ala Arg Gly Asn Pro Glu Pro Ser Val His Cys Ala Arg Ser Asp Gly

435 440 445

Gly Ala Val Leu Ala Leu Gly Leu Leu Gly Pro Val Thr Arg Ala Leu

450 455 460

Ser Gly Thr Tyr Arg Cys Lys Ala Ala Asn Asp Gln Gly Glu Ala Val

465 470 475 480

Lys Asp Val Thr Leu Thr Val Glu Tyr Ala Pro Ala Leu Asp Ser Val

485 490 495

Gly Cys Pro Glu Arg Ile Thr Trp Leu Glu Gly Thr Glu Ala Ser Leu

500 505 510

Ser Cys Val Ala His Gly Val Pro Pro Pro Asp Val Ile Cys Val Arg

515 520 525

Ser Gly Glu Leu Gly Ala Val Ile Glu Gly Leu Leu Arg Val Ala Arg

530 535 540

Glu His Ala Gly Thr Tyr Arg Cys Glu Ala Thr Asn Pro Arg Gly Ser

545 550 555 560

Ala Ala Lys Asn Val Ala Val Thr Val Glu Tyr Gly Pro Arg Phe Glu

565 570 575

Glu Pro Ser Cys Pro Ser Asn Trp Thr Trp Val Glu Gly Ser Gly Arg

580 585 590

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

900 905 910

GIu GIy GIu VaI Phe AIa IIe GIn Leu Thr Ser AIa

915 920

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<211> 134

<212> PRT

<213> 人

<400> 29

Met Asp VaI Phe Met Lys GIy Leu Ser Met AIa Lys GIu GIy VaI VaI
1 5 10 15
AIa AIa AIa GIu Lys Thr Lys GIn GIy VaI Thr GIu AIa AIa GIu Lys
20 25 30
Thr Lys GIu GIy VaI Leu Tyr VaI GIy Ser Lys Thr Arg GIu GIy VaI
35 40 45
VaI GIn GIy VaI AIa Ser VaI AIa GIu Lys Thr Lys GIu GIn AIa Ser
50 55 60
His Leu GIy GIy AIa VaI Phe Ser GIy AIa GIy Asn IIe AIa AIa AIa
65 70 75 80
Thr GIy Leu VaI Lys Arg GIu GIu Phe Pro Thr Asp Leu Lys Pro GIu
85 90 95
GIu VaI AIa GIn GIu AIa AIa GIu GIu Pro Leu IIe GIu Pro Leu Met
100 105 110
GIu Pro GIu GIy GIu Ser Tyr GIu Asp Pro Pro GIn GIu GIu Tyr GIn
115 120 125
GIu Tyr GIu Pro GIu AIa
130

<210> 30

<211> 68

<212> PRT

<213> 人

<400> 30

Met Asp Pro GIu Thr Cys Pro Cys Pro Ser GIy GIy Ser Cys Thr Cys
1 5 10 15
AIa Asp Ser Cys Lys Cys GIu GIy Cys Lys Cys Thr Ser Cys Lys Lys
20 25 30
Ser Cys Cys Ser Cys Cys Pro AIa GIu Cys GIu Lys Cys AIa Lys Asp
35 40 45
Cys VaI Cys Lys GIy GIy GIu AIa AIa GIu AIa GIu AIa GIu Lys Cys
50 55 60

Ser Cys Cys GIn
65

<210> 31
<211> 440
<212> PRT
<213> 人
<400> 31

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

GIn IIe Ser Ser Leu Lys GIu His Asn Met Tyr Pro Thr Pro Ser GIy
260 265 270
Phe Thr Ser Ser Leu Phe Thr VaI Ser GIy Met GIn Thr VaI Asp Thr
275 280 285
IIe Asn Ser Leu Ser VaI VaI Thr GIn Pro Lys VaI Thr Lys IIe Pro
290 295 300
Lys GIn Tyr Arg Thr Lys GIu Thr Thr Phe GIy AIa Thr Leu Ser Lys
305 310 315 320
Asp Thr Thr Phe Thr Ser Thr Asp Lys AIa Phe VaI Pro Tyr Pro GIu
325 330 335
Asp Thr Ser Thr GIu Thr IIe Asn Ser His GIu AIa AIa AIa AIa Thr
340 345 350
Leu Thr IIe His Leu GIn Asp GIy Met VaI Thr Asn Thr Ser Leu Thr
355 360 365
Ser Ser Thr Lys Ser Ser Pro Thr Pro Met Thr Leu Ser IIe Thr Ser
370 375 380
GIy Met Pro Asn Asn Phe Ser GIu Met Pro GIn GIn Ser Thr Thr Leu
385 390 395 400
Asn Leu Trp Arg GIu GIu Thr Thr Thr Asn VaI Lys Thr Pro Leu Pro
405 410 415
Ser VaI AIa Asn AIa Trp Lys VaI Asn AIa Ser Phe Leu Leu Leu Leu
420 425 430
Asn VaI VaI VaI Met Leu AIa VaI
435 440

<210> 32
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<212> PRT
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<400> 32

Met Asp Pro Lys Leu GIy Arg Met AIa AIa Ser Leu Leu AIa VaI Leu
1 5 10 15
Leu Leu Leu Leu GIu Arg GIy Met Phe Ser Ser Pro Ser Pro Pro Pro
20 25 30
AIa Leu Leu GIu Lys VaI Phe GIn Tyr IIe Asp Leu His GIn Asp GIu
35 40 45
Phe VaI GIn Thr Leu Lys GIu Trp VaI AIa IIe GIu Ser Asp Ser VaI
50 55 60
GIn Pro VaI Pro Arg Phe Arg GIn GIu Leu Phe Arg Met Met AIa VaI
65 70 75 80

Ala Ala Asp Thr Leu Gln Arg Leu Gly Ala Arg Val Ala Ser Val Asp
85 90 95
Met Gly Pro Gln Gln Leu Pro Asp Gly Gln Ser Leu Pro Ile Pro Pro
100 105 110
Ile Ile Leu Ala Glu Leu Gly Ser Asp Pro Thr Lys Gly Thr Val Cys
115 120 125
Phe Tyr Gly His Leu Asp Val Gln Pro Ala Asp Arg Gly Asp Gly Trp
130 135 140
Leu Thr Asp Pro Tyr Val Leu Thr Glu Val Asp Gly Lys Leu Tyr Gly
145 150 155 160
Arg Gly Ala Thr Asp Asn Lys Gly Pro Val Leu Ala Trp Ile Asn Ala
165 170 175
Val Ser Ala Phe Arg Ala Leu Glu Gln Asp Leu Pro Val Asn Ile Lys
180 185 190
Phe Ile Ile Glu Gly Met Glu Glu Ala Gly Ser Val Ala Leu Glu Glu
195 200 205
Leu Val Glu Lys Glu Lys Asp Arg Phe Phe Ser Gly Val Asp Tyr Ile
210 215 220
Val Ile Ser Asp Asn Leu Trp Ile Ser Gln Arg Lys Pro Ala Ile Thr
225 230 235 240
Tyr Gly Thr Arg Gly Asn Ser Tyr Phe Met Val Glu Val Lys Cys Arg
245 250 255
Asp Gln Asp Phe His Ser Gly Thr Phe Gly Gly Ile Leu His Glu Pro
260 265 270
Met Ala Asp Leu Val Ala Leu Leu Gly Ser Leu Val Asp Ser Ser Gly
275 280 285
His Ile Leu Val Pro Gly Ile Tyr Asp Glu Val Val Pro Leu Thr Glu
290 295 300
Glu Glu Ile Asn Thr Tyr Lys Ala Ile His Leu Asp Leu Glu Glu Tyr
305 310 315 320
Arg Asn Ser Ser Arg Val Glu Lys Phe Leu Phe Asp Thr Lys Glu Glu
325 330 335
Ile Leu Met His Leu Trp Arg Tyr Pro Ser Leu Ser Ile His Gly Ile
340 345 350
Glu Gly Ala Phe Asp Glu Pro Gly Thr Lys Thr Val Ile Pro Gly Arg
355 360 365
Val Ile Gly Lys Phe Ser Ile Arg Leu Val Pro His Met Asn Val Ser
370 375 380
Ala Val Glu Lys Gln Val Thr Arg His Leu Glu Asp Val Phe Ser Lys

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

<210> 33
<211> 776
<212> PRT
<213> 人
<400> 33
Met Ala Ala Pro Gly Asp Pro Gln Asp Glu Leu Leu Pro Leu Ala Gly
1 5 10 15
Pro Gly Ser Gln Trp Leu Arg His Arg Gly Glu Gly Glu Asn Glu Ala
20 25 30
Val Thr Pro Lys Gly Ala Thr Pro Ala Pro Gln Ala Gly Glu Pro Ser
35 40 45
Pro Gly Leu Gly Ala Arg Ala Arg Glu Ala Ala Ser Arg Glu Ala Gly
50 55 60
Ser Gly Pro Ala Arg Gln Ser Pro Val Ala Met Glu Thr Ala Ser Thr
65 70 75 80
Gly Val Ala Gly Val Ser Ser Ala Met Asp His Thr Phe Ser Thr Thr
85 90 95
Ser Lys Asp Gly Glu Gly Ser Cys Tyr Thr Ser Leu Ile Ser Asp Ile
100 105 110
Cys Tyr Pro Pro Gln Glu Asp Ser Thr Tyr Phe Thr Gly Ile Leu Gln
115 120 125
Lys Glu Asn Gly His Val Thr Ile Ser Glu Ser Pro Glu Glu Leu Gly
130 135 140
Thr Pro Gly Pro Ser Leu Pro Asp Val Pro Gly Ile Glu Ser Arg Gly

145 150 155 160
Leu Phe Ser Ser Asp Ser Gly Ile Glu Met Thr Pro Ala Glu Ser Thr
165 170 175
Glu Val Asn Lys Ile Leu Ala Asp Pro Leu Asp Gln Met Lys Ala Glu
180 185 190
Ala Tyr Lys Tyr Ile Asp Ile Thr Arg Pro Glu Glu Val Lys His Gln
195 200 205
Glu Gln His His Pro Glu Leu Glu Asp Lys Asp Leu Asp Phe Lys Asn
210 215 220
Lys Asp Thr Asp Ile Ser Ile Lys Pro Glu Gly Val Arg Glu Pro Asp
225 230 235 240
Lys Pro Ala Pro Val Glu Gly Lys Ile Ile Lys Asp His Leu Leu Glu
245 250 255
Glu Ser Thr Phe Ala Pro Tyr Ile Asp Asp Leu Ser Glu Glu Gln Arg
260 265 270
Arg Ala Pro Gln Ile Thr Thr Pro Val Lys Ile Thr Leu Thr Glu Ile
275 280 285
Glu Pro Ser Val Glu Thr Thr Thr Gln Glu Lys Thr Pro Glu Lys Gln
290 295 300
Asp Ile Cys Leu Lys Pro Ser Pro Asp Thr Val Pro Thr Val Thr Val
305 310 315 320
Ser Glu Pro Glu Asp Asp Ser Pro Gly Ser Ile Thr Pro Pro Ser Ser
325 330 335
Gly Thr Glu Pro Ser Ala Ala Glu Ser Gln Gly Lys Gly Ser Ile Ser
340 345 350
Glu Asp Glu Leu Ile Thr Ala Ile Lys Glu Ala Lys Gly Leu Ser Tyr
355 360 365
Glu Thr Ala Glu Asn Pro Arg Pro Val Gly Gln Leu Ala Asp Arg Pro
370 375 380
Glu Val Lys Ala Arg Ser Gly Pro Pro Thr Ile Pro Ser Pro Leu Asp
385 390 395 400
His Glu Ala Ser Ser Ala Glu Ser Gly Asp Ser Glu Ile Glu Leu Val
405 410 415
Ser Glu Asp Pro Met Ala Ala Glu Asp Ala Leu Pro Ser Gly Tyr Val
420 425 430
Ser Phe Gly His Val Gly Gly Pro Pro Pro Ser Pro Ala Ser Pro Ser
435 440 445
Ile Gln Tyr Ser Ile Leu Arg Glu Glu Arg Glu Ala Glu Leu Asp Ser
450 455 460

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

770 775

<210> 34

<211> 1294

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<400> 34

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

260 265 270

Asp Ser Leu Gln Gly Cys Asn Glu Lys Ser Gly Met Asp Leu Thr Pro

275 280 285

Gly Ser Asp Asn Ala Lys Leu Ser Leu Met Asn Lys Tyr Lys Asp Asn

290 295 300

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

305 310 315 320

Leu Ser His Thr Ser Ser Ser Gln Arg Lys Arg Ile Asn Asn Lys Ala

325 330 335

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

340 345 350

Ala Glu Asn Asp Pro Gln Leu Thr Phe Tyr Thr Asp Pro Ser Arg Ser

355 360 365

Arg Arg Arg Ser Arg Val Gly Ser Pro Arg Ser Pro Val Asn Lys Thr

370 375 380

Thr Leu Thr Leu Ile Ser Ile Thr Ser Cys Val Ile Gly Leu Val Cys

385 390 395 400

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

405 410 415

Pro Glu His Leu Ile Ala Asp Gly Ser Arg Phe Ile Leu Leu Glu Gly

420 425 430

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

435 440 445

Phe Ser Gln Gln Asn Ser Ser Gly Pro Trp Ala Met Asp Leu Cys Ala

450 455 460

Arg Arg Leu Leu Asp Pro Cys Glu His Gln Cys Asp Pro Glu Thr Gly

465 470 475 480

Glu Cys Leu Cys Tyr Glu Gly Tyr Met Lys Asp Pro Val His Lys His

485 490 495

Leu Cys Ile Arg Asn Glu Trp Gly Thr Asn Gln Gly Pro Trp Pro Tyr

500 505 510

Thr Ile Phe Gln Arg Gly Phe Asp Leu Val Leu Gly Glu Gln Pro Ser

515 520 525

Asp Lys Ile Phe Arg Phe Thr Tyr Thr Leu Gly Glu Gly Met Trp Leu

530 535 540

Pro Leu Ser Lys Ser Phe Val Ile Pro Pro Ala Glu Leu Ala Ile Asn

545 550 555 560

Pro Ser Ala Lys Cys Lys Thr Asp Met Thr Val Met Glu Asp Ala Val

565 570 575

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

885 890 895
Glu Ser Glu Glu Arg Glu Arg Asp Pro Lys Val Leu Thr Phe Pro Glu
900 905 910
Tyr Ile Thr Ser Leu Ser Asp Ser Gly Thr Lys His Met Ala Ala Gly
915 920 925
Val Arg Met Glu Cys His Ser Lys Gly Arg Cys Pro Ser Ser Cys Pro
930 935 940
Leu Cys His Val Thr Ser Ser Pro Asp Thr Pro Ala Glu Pro Val Leu
945 950 955 960
Leu Glu Val Thr Lys Ala Ala Pro Ile Tyr Glu Leu Val Thr Asn Asn
965 970 975
Gln Thr Gln Arg Leu Leu Gln Glu Ala Thr Met Ser Ser Leu Trp Cys
980 985 990
Ser Gly Thr Gly Asp Val Ile Glu Asp Trp Cys Arg Cys Asp Ser Thr
995 1000 1005
Ala Phe Gly Ala Asp Gly Leu Pro Thr Cys Ala Pro Leu Pro Gln
1010 1015 1020
Pro Val Leu Arg Leu Ser Thr Val His Glu Pro Ser Ser Thr Leu
1025 1030 1035
Val Val Leu Glu Trp Glu His Ser Glu Pro Pro Ile Gly Val Gln
1040 1045 1050
Ile Val Asp Tyr Leu Leu Arg Gln Glu Lys Val Thr Asp Arg Met
1055 1060 1065
Asp His Ser Lys Val Glu Thr Glu Thr Val Leu Ser Phe Val Asp
1070 1075 1080
Asp Ile Ile Ser Gly Ala Lys Ser Pro Cys Ala Met Pro Ser Gln
1085 1090 1095
Val Pro Asp Lys Gln Leu Thr Thr Ile Ser Leu Ile Ile Arg Cys
1100 1105 1110
Leu Glu Pro Asp Thr Ile Tyr Met Phe Thr Leu Trp Gly Val Asp
1115 1120 1125
Asn Thr Gly Arg Arg Ser Arg Pro Ser Asp Val Ile Val Lys Thr
1130 1135 1140
Pro Cys Pro Val Val Asp Asp Val Lys Ala Gln Glu Ile Ala Asp
1145 1150 1155
Lys Ile Tyr Asn Leu Phe Asn Gly Tyr Thr Ser Gly Lys Glu Gln
1160 1165 1170
Gln Thr Ala Tyr Asn Thr Leu Leu Asp Leu Gly Ser Pro Thr Leu
1175 1180 1185

His Arg Val Leu Tyr His Tyr Asn Gln His Tyr Glu Ser Phe Gly
1190 1195 1200
Glu Phe Thr Trp Arg Cys Glu Asp Glu Leu Gly Pro Arg Lys Ala
1205 1210 1215
Gly Leu Ile Leu Ser Gln Leu Gly Asp Leu Ser Ser Trp Cys Asn
1220 1225 1230
Gly Leu Leu Gln Glu Pro Lys Ile Ser Leu Arg Arg Ser Ser Leu
1235 1240 1245
Lys Tyr Leu Gly Cys Arg Tyr Ser Glu Ile Lys Pro Tyr Gly Leu
1250 1255 1260
Asp Trp Ala Glu Leu Ser Arg Asp Leu Arg Lys Thr Cys Glu Glu
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Gln Thr Leu Ser Ile Pro Tyr Asn Asp Tyr Gly Asp Ser Lys Glu
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Ile

<210> 35
<211> 1522
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<400> 35

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

145 150 155 160
Val Ser Pro Ser Gln Phe Gly Cys His Val Leu Cys Thr Trp Leu Glu
165 170 175
Ser Cys Leu Lys Ser Glu Asn Gly Arg Thr Glu Ser Cys Gly Ile Met
180 185 190
Tyr Thr Lys Cys Thr Cys Pro Gln His Leu Gly Glu Trp Gly Ile Asp
195 200 205
Asp Gln Ser Leu Ile Leu Leu Asn Asn Val Val Leu Pro Leu Asn Glu
210 215 220
Gln Thr Glu Gly Cys Leu Thr Gln Glu Leu Gln Thr Thr Gln Val Cys
225 230 235 240
Asn Leu Thr Arg Glu Ala Lys Arg Pro Pro Lys Glu Glu Phe Gly Met
245 250 255
Met Gly Asp His Thr Ile Lys Ser Gln Arg Pro Arg Ser Val His Glu
260 265 270
Lys Arg Val Pro Gln Glu Gln Ala Asp Ala Ala Lys Phe Met Ala Gln
275 280 285
Thr Gly Glu Ser Gly Val Glu Glu Trp Ser Gln Trp Ser Thr Cys Ser
290 295 300
Val Thr Cys Gly Gln Gly Ser Gln Val Arg Thr Arg Thr Cys Val Ser
305 310 315 320
Pro Tyr Gly Thr His Cys Ser Gly Pro Leu Arg Glu Ser Arg Val Cys
325 330 335
Asn Asn Thr Ala Leu Cys Pro Val His Gly Val Trp Glu Glu Trp Ser
340 345 350
Pro Trp Ser Leu Cys Ser Phe Thr Cys Gly Arg Gly Gln Arg Thr Arg
355 360 365
Thr Arg Ser Cys Thr Pro Pro Gln Tyr Gly Gly Arg Pro Cys Glu Gly
370 375 380
Pro Glu Thr His His Lys Pro Cys Asn Ile Ala Leu Cys Pro Val Asp
385 390 395 400
Gly Gln Trp Gln Glu Trp Ser Ser Trp Ser Gln Cys Ser Val Thr Cys
405 410 415
Ser Asn Gly Thr Gln Gln Arg Ser Arg Gln Cys Thr Ala Ala Ala His
420 425 430
Gly Gly Ser Glu Cys Arg Gly Pro Trp Ala Glu Ser Arg Glu Cys Tyr
435 440 445
Asn Pro Glu Cys Thr Ala Asn Gly Gln Trp Asn Gln Trp Gly His Trp
450 455 460

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

770 775 780

Ser Lys Ile Ile Val Val Thr Ile Arg Pro Glu Pro Lys Thr Thr Asp
785 790 795 800

Ser Phe Leu Glu Ile Glu Leu Ala His Leu Ala Asn Gly Thr Leu Asn
805 810 815

Pro Tyr Cys Val Leu Trp Asp Asp Ser Lys Thr Asn Glu Ser Leu Gly
820 825 830

Thr Trp Ser Thr Gln Gly Cys Lys Thr Val Leu Thr Asp Ala Ser His
835 840 845

Thr Lys Cys Leu Cys Asp Arg Leu Ser Thr Phe Ala Ile Leu Ala Gln
850 855 860

Gln Pro Arg Glu Ile Ile Met Glu Ser Ser Gly Thr Pro Ser Val Thr
865 870 875 880

Leu Ile Val Gly Ser Gly Leu Ser Cys Leu Ala Leu Ile Thr Leu Ala
885 890 895

Val Val Tyr Ala Ala Leu Trp Arg Tyr Ile Arg Ser Glu Arg Ser Ile
900 905 910

Ile Leu Ile Asn Phe Cys Leu Ser Ile Ile Ser Ser Asn Ile Leu Ile
915 920 925

Leu Val Gly Gln Thr Gln Thr His Asn Lys Ser Ile Cys Thr Thr Thr
930 935 940

Thr Ala Phe Leu His Phe Phe Phe Leu Ala Ser Phe Cys Trp Val Leu
945 950 955 960

Thr Glu Ala Trp Gln Ser Tyr Met Ala Val Thr Gly Lys Ile Arg Thr
965 970 975

Arg Leu Ile Arg Lys Arg Phe Leu Cys Leu Gly Trp Gly Leu Pro Ala
980 985 990

Leu Val Val Ala Thr Ser Val Gly Phe Thr Arg Thr Lys Gly Tyr Gly
995 1000 1005

Thr Asp His Tyr Cys Trp Leu Ser Leu Glu Gly Gly Leu Leu Tyr
1010 1015 1020

Ala Phe Val Gly Pro Ala Ala Ala Val Val Leu Val Asn Met Val
1025 1030 1035

Ile Gly Ile Leu Val Phe Asn Lys Leu Val Ser Arg Asp Gly Ile
1040 1045 1050

Leu Asp Lys Lys Leu Lys His Arg Ala Gly Gln Met Ser Glu Pro
1055 1060 1065

His Ser Gly Leu Thr Leu Lys Cys Ala Lys Cys Gly Val Val Ser
1070 1075 1080

Thr Thr Ala Leu Ser Ala Thr Thr Ala Ser Asn Ala Met Ala Ser
1085 1090 1095
Leu Trp Ser Ser Cys Val Val Leu Pro Leu Leu Ala Leu Thr Trp
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Met Ser Ala Val Leu Ala Met Thr Asp Lys Arg Ser Ile Leu Phe
1115 1120 1125
Gln Ile Leu Phe Ala Val Phe Asp Ser Leu Gln Gly Phe Val Ile
1130 1135 1140
Val Met Val His Cys Ile Leu Arg Arg Glu Val Gln Asp Ala Phe
1145 1150 1155
Arg Cys Arg Leu Arg Asn Cys Gln Asp Pro Ile Asn Ala Asp Ser
1160 1165 1170
Ser Ser Ser Phe Pro Asn Gly His Ala Gln Ile Met Thr Asp Phe
1175 1180 1185
Glu Lys Asp Val Asp Ile Ala Cys Arg Ser Val Leu His Lys Asp
1190 1195 1200
Ile Gly Pro Cys Arg Ala Ala Thr Ile Thr Gly Thr Leu Ser Arg
1205 1210 1215
Ile Ser Leu Asn Asp Asp Glu Glu Glu Lys Gly Thr Asn Pro Glu
1220 1225 1230
Gly Leu Ser Tyr Ser Thr Leu Pro Gly Asn Val Ile Ser Lys Val
1235 1240 1245
Ile Ile Gln Gln Pro Thr Gly Leu His Met Pro Met Ser Met Asn
1250 1255 1260
Glu Leu Ser Asn Pro Cys Leu Lys Lys Glu Asn Ser Glu Leu Arg
1265 1270 1275
Arg Thr Val Tyr Leu Cys Thr Asp Asp Asn Leu Arg Gly Ala Asp
1280 1285 1290
Met Asp Ile Val His Pro Gln Glu Arg Met Met Glu Ser Asp Tyr
1295 1300 1305
Ile Val Met Pro Arg Ser Ser Val Asn Asn Gln Pro Ser Met Lys
1310 1315 1320
Glu Glu Ser Lys Met Asn Ile Gly Met Glu Thr Leu Pro His Glu
1325 1330 1335
Arg Leu Leu His Tyr Lys Val Asn Pro Glu Phe Asn Met Asn Pro
1340 1345 1350
Pro Val Met Asp Gln Phe Asn Met Asn Leu Glu Gln His Leu Ala
1355 1360 1365
Pro Gln Glu His Met Gln Asn Leu Pro Phe Glu Pro Arg Thr Ala

1370 1375 1380
Val Lys Asn Phe Met Ala Ser Glu Leu Asp Asp Asn Ala Gly Leu
1385 1390 1395
Ser Arg Ser Glu Thr Gly Ser Thr Ile Ser Met Ser Ser Leu Glu
1400 1405 1410
Arg Arg Lys Ser Arg Tyr Ser Asp Leu Asp Phe Glu Lys Val Met
1415 1420 1425
His Thr Arg Lys Arg His Met Glu Leu Phe Gln Glu Leu Asn Gln
1430 1435 1440
Lys Phe Gln Thr Leu Asp Arg Phe Arg Asp Ile Pro Asn Thr Ser
1445 1450 1455
Ser Met Glu Asn Pro Ala Pro Asn Lys Asn Pro Trp Asp Thr Phe
1460 1465 1470
Lys Asn Pro Ser Glu Tyr Pro His Tyr Thr Thr Ile Asn Val Leu
1475 1480 1485
Asp Thr Glu Ala Lys Asp Ala Leu Glu Leu Arg Pro Ala Glu Trp
1490 1495 1500
Glu Lys Cys Leu Asn Leu Pro Leu Asp Val Gln Glu Gly Asp Phe
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Gln Thr Glu Val
1520

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

100 105 110

Val Arg Ala Ser Leu Thr Lys Val Asp Glu Ala Glu Tyr Met Cys Pro

115 120 125

Asp Gly Ser Tyr Ala Ile Gln Glu Asn Ile Pro Leu Leu Ile Ala Gly

130 135 140

Val Ile Gly Gly Ser Tyr Ser Ser Val Ser Ile Gln Val Ala Asn Leu

145 150 155 160

Leu Arg Leu Phe Gln Ile Pro Gln Ile Ser Tyr Ala Ser Thr Ser Ala

165 170 175

Lys Leu Ser Asp Lys Ser Arg Tyr Asp Tyr Phe Ala Arg Thr Val Pro

180 185 190

Pro Asp Phe Tyr Gln Ala Lys Ala Met Ala Glu Ile Leu Arg Phe Phe

195 200 205

Asn Trp Thr Tyr Val Ser Thr Val Ala Ser Glu Gly Asp Tyr Gly Glu

210 215 220

Thr Gly Ile Glu Ala Phe Glu Gln Glu Ala Arg Leu Arg Asn Ile Cys

225 230 235 240

Ile Ala Thr Ala Glu Lys Val Gly Arg Ser Asn Ile Arg Lys Ser Tyr

245 250 255

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

260 265 270

Val Leu Phe Met Arg Ser Asp Asp Ser Arg Glu Leu Ile Ala Ala Ala

275 280 285

Ser Arg Ala Asn Ala Ser Phe Thr Trp Val Ala Ser Asp Gly Trp Gly

290 295 300

Ala Gln Glu Ser Ile Ile Lys Gly Ser Glu His Val Ala Tyr Gly Ala

305 310 315 320

Ile Thr Leu Glu Leu Ala Ser Gln Pro Val Arg Gln Phe Asp Arg Tyr

325 330 335

Phe Gln Ser Leu Asn Pro Tyr Asn Asn His Arg Asn Pro Trp Phe Arg

340 345 350

Asp Phe Trp Glu Gln Lys Phe Gln Cys Ser Leu Gln Asn Lys Arg Asn

355 360 365

His Arg Arg Val Cys Asp Lys His Leu Ala Ile Asp Ser Ser Asn Tyr

370 375 380

Glu Gln Glu Ser Lys Ile Met Phe Val Val Asn Ala Val Tyr Ala Met

385 390 395 400

Ala His Ala Leu His Lys Met Gln Arg Thr Leu Cys Pro Asn Thr Thr

405 410 415

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

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

<210> 37
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Met Pro Ser Glu Arg Cys Leu Ser Ile Gln Glu Met Leu Thr Gly Gln
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Arg Leu Cys His Ser Glu Ser His Asn Asp Ser Val Leu Ala Ala Leu
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Asn Gln Gln Arg Ser Asp Gly Ile Leu Cys Asp Ile Thr Leu Ile Ala
35 40 45
Glu Glu Gln Lys Phe His Ala His Lys Ala Val Leu Ala Ala Cys Ser
50 55 60
Asp Tyr Phe Arg Ala Met Phe Ser Leu Cys Met Val Glu Ser Gly Ala
65 70 75 80
Asp Glu Val Asn Leu His Gly Val Thr Ser Leu Gly Leu Lys Gln Ala
85 90 95
Leu Glu Phe Ala Tyr Thr Gly Gln Ile Leu Leu Glu Pro Gly Val Ile
100 105 110
Gln Asp Val Leu Ala Ala Gly Ser His Leu Gln Leu Leu Glu Leu Leu

115 120 125

Asn Leu Cys Ser His Tyr Leu Ile Gln Glu Leu Asn Ser Phe Asn Tyr

130 135 140

Leu Asp Leu Tyr Arg Leu Ala Asp Leu Phe Asn Leu Thr Leu Leu Glu

145 150 155 160

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

165 170 175

Ser Arg Pro Glu Glu Val Leu Thr Leu Pro Tyr Cys Leu Leu Gln Glu

180 185 190

Val Leu Lys Ser Asp Arg Leu Thr Ser Leu Ser Glu Glu Gln Ile Trp

195 200 205

Gln Leu Ala Val Arg Trp Leu Glu His Asn Cys His Tyr Gln Tyr Met

210 215 220

Asp Glu Leu Leu Gln Tyr Ile Arg Phe Gly Leu Met Asp Val Asp Thr

225 230 235 240

Leu His Thr Val Ala Leu Ser His Pro Leu Val Gln Ala Ser Glu Thr

245 250 255

Ala Thr Ala Leu Val Asn Glu Ala Leu Glu Tyr His Gln Ser Ile Tyr

260 265 270

Ala Gln Pro Val Trp Gln Thr Arg Arg Thr Lys Pro Arg Phe Gln Ser

275 280 285

Asp Thr Leu Tyr Ile Ile Gly Gly Lys Lys Arg Glu Val Cys Lys Val

290 295 300

Lys Glu Leu Arg Tyr Phe Asn Pro Val Asp Gln Glu Asn Ala Leu Ile

305 310 315 320

Ala Ala Ile Ala Asn Trp Ser Glu Leu Ala Pro Met Pro Val Gly Arg

325 330 335

Ser His His Cys Val Ala Val Met Gly Asp Phe Leu Phe Val Ala Gly

340 345 350

Gly Glu Val Glu His Ala Ser Gly Arg Thr Cys Ala Val Arg Thr Ala

355 360 365

Cys Arg Tyr Asp Pro Arg Ser Asn Ser Trp Ala Glu Ile Ala Pro Met

370 375 380

Lys Asn Cys Arg Glu His Phe Val Leu Gly Ala Met Glu Glu Tyr Leu

385 390 395 400

Tyr Ala Val Gly Gly Arg Asn Glu Leu Arg Gln Val Leu Pro Thr Val

405 410 415

Glu Arg Tyr Cys Pro Lys Lys Asn Lys Trp Thr Phe Val Gln Ser Phe

420 425 430

Asp Arg Ser Leu Ser Cys His Ala Gly Tyr Val Ala Asp Gly Leu Leu
435 440 445
Trp Ile Ser Gly Gly Val Thr Asn Thr Ala Gln Tyr Gln Asn Arg Leu
450 455 460
Met Val Tyr Glu Pro Asn Gln Asn Lys Trp Ile Ser Arg Ser Pro Met
465 470 475 480
Leu Gln Arg Arg Val Tyr His Ser Met Ala Ala Val Gln Arg Lys Leu
485 490 495
Tyr Val Leu Gly Gly Asn Asp Leu Asp Tyr Asn Asn Asp Arg Ile Leu
500 505 510
Val Arg His Ile Asp Ser Tyr Asn Ile Asp Thr Asp Gln Trp Thr Arg
515 520 525
Cys Asn Phe Asn Leu Leu Thr Gly Gln Asn Glu Ser Gly Val Ala Val
530 535 540
His Asn Gly Arg Ile Tyr Leu Val Gly Gly Tyr Ser Ile Trp Thr Asn
545 550 555 560
Glu Pro Leu Ala Cys Ile Gln Val Leu Asp Val Ser Arg Glu Gly Lys
565 570 575
Glu Glu Val Phe Tyr Gly Pro Thr Leu Pro Phe Ala Ser Asn Gly Ile
580 585 590
Ala Ala Cys Phe Leu Pro Ala Pro Tyr Phe Thr Cys Pro Asn Leu Gln
595 600 605
Thr Leu Gln Val Pro His His Arg Ile Gly Thr Ile
610 615 620

<210> 38
<211> 707
<212> PRT
<213> 人
<400> 38

Met Ser Leu Trp Gln Pro Leu Val Leu Val Leu Leu Val Leu Gly Cys
1 5 10 15
Cys Phe Ala Ala Pro Arg Gln Arg Gln Ser Thr Leu Val Leu Phe Pro
20 25 30
Gly Asp Leu Arg Thr Asn Leu Thr Asp Arg Gln Leu Ala Glu Glu Tyr
35 40 45
Leu Tyr Arg Tyr Gly Tyr Thr Arg Val Ala Glu Met Arg Gly Glu Ser
50 55 60
Lys Ser Leu Gly Pro Ala Leu Leu Leu Leu Gln Lys Gln Leu Ser Leu
65 70 75 80

Pro Glu Thr Gly Glu Leu Asp Ser Ala Thr Leu Lys Ala Met Arg Thr
85 90 95
Pro Arg Cys Gly Val Pro Asp Leu Gly Arg Phe Gln Thr Phe Glu Gly
100 105 110
Asp Leu Lys Trp His His His Asn Ile Thr Tyr Trp Ile Gln Asn Tyr
115 120 125
Ser Glu Asp Leu Pro Arg Ala Val Ile Asp Asp Ala Phe Ala Arg Ala
130 135 140
Phe Ala Leu Trp Ser Ala Val Thr Pro Leu Thr Phe Thr Arg Val Tyr
145 150 155 160
Ser Arg Asp Ala Asp Ile Val Ile Gln Phe Gly Val Ala Glu His Gly
165 170 175
Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala His Ala Phe
180 185 190
Pro Pro Gly Pro Gly Ile Gln Gly Asp Ala His Phe Asp Asp Asp Glu
195 200 205
Leu Trp Ser Leu Gly Lys Gly Val Val Val Pro Thr Arg Phe Gly Asn
210 215 220
Ala Asp Gly Ala Ala Cys His Phe Pro Phe Ile Phe Glu Gly Arg Ser
225 230 235 240
Tyr Ser Ala Cys Thr Thr Asp Gly Arg Ser Asp Gly Leu Pro Trp Cys
245 250 255
Ser Thr Thr Ala Asn Tyr Asp Thr Asp Asp Arg Phe Gly Phe Cys Pro
260 265 270
Ser Glu Arg Leu Tyr Thr Gln Asp Gly Asn Ala Asp Gly Lys Pro Cys
275 280 285
Gln Phe Pro Phe Ile Phe Gln Gly Gln Ser Tyr Ser Ala Cys Thr Thr
290 295 300
Asp Gly Arg Ser Asp Gly Tyr Arg Trp Cys Ala Thr Thr Ala Asn Tyr
305 310 315 320
Asp Arg Asp Lys Leu Phe Gly Phe Cys Pro Thr Arg Ala Asp Ser Thr
325 330 335
Val Met Gly Gly Asn Ser Ala Gly Glu Leu Cys Val Phe Pro Phe Thr
340 345 350
Phe Leu Gly Lys Glu Tyr Ser Thr Cys Thr Ser Glu Gly Arg Gly Asp
355 360 365
Gly Arg Leu Trp Cys Ala Thr Thr Ser Asn Phe Asp Ser Asp Lys Lys
370 375 380
Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val Ala Ala

385 390 395 400
His Glu Phe Gly His Ala Leu Gly Leu Asp His Ser Ser Val Pro Glu
405 410 415
Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro Pro Leu His
420 425 430
Lys Asp Asp Val Asn Gly Ile Arg His Leu Tyr Gly Pro Arg Pro Glu
435 440 445
Pro Glu Pro Arg Pro Pro Thr Thr Thr Thr Pro Gln Pro Thr Ala Pro
450 455 460
Pro Thr Val Cys Pro Thr Gly Pro Pro Thr Val His Pro Ser Glu Arg
465 470 475 480
Pro Thr Ala Gly Pro Thr Gly Pro Pro Ser Ala Gly Pro Thr Gly Pro
485 490 495
Pro Thr Ala Gly Pro Ser Thr Ala Thr Thr Val Pro Leu Ser Pro Val
500 505 510
Asp Asp Ala Cys Asn Val Asn Ile Phe Asp Ala Ile Ala Glu Ile Gly
515 520 525
Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg Phe Ser Glu
530 535 540
Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala Asp Lys Trp
545 550 555 560
Pro Ala Leu Pro Arg Lys Leu Asp Ser Val Phe Glu Glu Arg Leu Ser
565 570 575
Lys Lys Leu Phe Phe Phe Ser Gly Arg Gln Val Trp Val Tyr Thr Gly
580 585 590
Ala Ser Val Leu Gly Pro Arg Arg Leu Asp Lys Leu Gly Leu Gly Ala
595 600 605
Asp Val Ala Gln Val Thr Gly Ala Leu Arg Ser Gly Arg Gly Lys Met
610 615 620
Leu Leu Phe Ser Gly Arg Arg Leu Trp Arg Phe Asp Val Lys Ala Gln
625 630 635 640
Met Val Asp Pro Arg Ser Ala Ser Glu Val Asp Arg Met Phe Pro Gly
645 650 655
Val Pro Leu Asp Thr His Asp Val Phe Gln Tyr Arg Glu Lys Ala Tyr
660 665 670
Phe Cys Gln Asp Arg Phe Tyr Trp Arg Val Ser Ser Arg Ser Glu Leu
675 680 685
Asn Gln Val Asp Gln Val Gly Tyr Val Thr Tyr Asp Ile Leu Gln Cys
690 695 700

Pro Glu Asp
705
<210> 39
<211> 523
<212> PRT
<213> 人
<400> 39

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

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

<210> 40
<211> 720
<212> PRT
<213> 人
<400> 40

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

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

Cys Lys Asn Ser Tyr Ser Ala Asp Val Val Asn Val Ser Ile Pro Val
625 630 635 640
Ser Asp Cys Leu Ile Ala Glu Gln Gln Glu Val Lys Ile Leu Leu Glu
645 650 655
Thr Val Gln Glu Gln Ile Arg Ile Leu Thr Asp Ala Arg Arg Ser Glu
660 665 670
Asp Tyr Glu Leu Ala Ser Val Glu Thr Glu Asp Ser Ala Ser Glu Asn
675 680 685
Thr Ala Phe Leu Pro Leu Ser Pro Thr Ala Lys Ser Glu Arg Glu Ala
690 695 700
Gln Phe Val Leu Arg Asn Glu Ile Gln Arg Asp Ser Ala Leu Thr Lys
705 710 715 720

<210> 41
<211> 977
<212> PRT
<213> 人
<400> 41

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

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

485 490 495

Pro Ala Ala Phe Ser Leu Met Pro Asn Leu Lys Leu Leu Phe Leu Asn

500 505 510

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

515 520 525

Leu Ala Arg Leu Asn Leu Arg Lys Asn Tyr Phe Leu Tyr Leu Pro Val

530 535 540

Ala Gly Val Leu Glu His Leu Asn Ala Ile Val Gln Ile Asp Leu Asn

545 550 555 560

Glu Asn Pro Trp Asp Cys Thr Cys Asp Leu Val Pro Phe Lys Gln Trp

565 570 575

Ile Glu Thr Ile Ser Ser Val Ser Val Val Gly Asp Val Leu Cys Arg

580 585 590

Ser Pro Glu Asn Leu Thr His Arg Asp Val Arg Thr Ile Glu Leu Glu

595 600 605

Val Leu Cys Pro Glu Met Leu His Val Ala Pro Ala Gly Glu Ser Pro

610 615 620

Ala Gln Pro Gly Asp Ser His Leu Ile Gly Ala Pro Thr Ser Ala Ser

625 630 635 640

Pro Tyr Glu Phe Ser Pro Pro Gly Gly Pro Val Pro Leu Ser Val Leu

645 650 655

Ile Leu Ser Leu Leu Val Leu Phe Phe Ser Ala Val Phe Val Ala Ala

660 665 670

Gly Leu Phe Ala Tyr Val Leu Arg Arg Arg Arg Lys Lys Leu Pro Phe

675 680 685

Arg Ser Lys Arg Gln Glu Gly Val Asp Leu Thr Gly Ile Gln Met Gln

690 695 700

Cys His Arg Leu Phe Glu Asp Gly Gly Gly Gly Gly Gly Gly Gly Ser Gly

705 710 715 720

Gly Gly Gly Arg Pro Thr Leu Ser Ser Pro Glu Lys Ala Pro Pro Val

725 730 735

Gly His Val Tyr Glu Tyr Ile Pro His Pro Val Thr Gln Met Cys Asn

740 745 750

Asn Pro Ile Tyr Lys Pro Arg Glu Glu Glu Glu Val Ala Val Ser Ser

755 760 765

Ala Gln Glu Ala Gly Ser Ala Glu Arg Gly Gly Pro Gly Thr Gln Pro

770 775 780

Pro Gly Met Gly Glu Ala Leu Leu Gly Ser Glu Gln Phe Ala Glu Thr

785 790 795 800

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

<210> 42
<211> 247
<212> PRT
<213> 人
<400> 42

Met Thr Ile Leu Phe Leu Thr Met Val Ile Ser Tyr Phe Gly Cys Met
1 5 10 15
Lys Ala Ala Pro Met Lys Glu Ala Asn Ile Arg Gly Gln Gly Gly Leu
20 25 30
Ala Tyr Pro Gly Val Arg Thr His Gly Thr Leu Glu Ser Val Asn Gly
35 40 45
Pro Lys Ala Gly Ser Arg Gly Leu Thr Ser Leu Ala Asp Thr Phe Glu
50 55 60
His Val Ile Glu Glu Leu Leu Asp Glu Asp Gln Lys Val Arg Pro Asn
65 70 75 80
Glu Glu Asn Asn Lys Asp Ala Asp Leu Tyr Thr Ser Arg Val Met Leu

85 90 95

Ser Ser Gln Val Pro Leu Glu Pro Pro Leu Leu Phe Leu Leu Glu Glu
100 105 110

Tyr Lys Asn Tyr Leu Asp Ala Ala Asn Met Ser Met Arg Val Arg Arg
115 120 125

His Ser Asp Pro Ala Arg Arg Gly Glu Leu Ser Val Cys Asp Ser Ile
130 135 140

Ser Glu Trp Val Thr Ala Ala Asp Lys Lys Thr Ala Val Asp Met Ser
145 150 155 160

Gly Gly Thr Val Thr Val Leu Glu Lys Val Pro Val Ser Lys Gly Gln
165 170 175

Leu Lys Gln Tyr Phe Tyr Glu Thr Lys Cys Asn Pro Met Gly Tyr Thr
180 185 190

Lys Glu Gly Cys Arg Gly Ile Asp Lys Arg His Trp Asn Ser Gln Cys
195 200 205

Arg Thr Thr Gln Ser Tyr Val Arg Ala Leu Thr Met Asp Ser Lys Lys
210 215 220

Arg Ile Gly Trp Arg Phe Ile Arg Ile Asp Thr Ser Cys Val Cys Thr
225 230 235 240

Leu Thr Ile Lys Arg Gly Arg
245

<210> 43
<211> 223
<212> PRT
<213> 人
<400> 43

Met Gln Leu Lys Pro Met Glu Ile Asn Pro Glu Met Leu Asn Lys Val
1 5 10 15

Leu Ser Arg Leu Gly Val Ala Gly Gln Trp Arg Phe Val Asp Val Leu
20 25 30

Gly Leu Glu Glu Glu Ser Leu Gly Ser Val Pro Ala Pro Ala Cys Ala
35 40 45

Leu Leu Leu Leu Phe Pro Leu Thr Ala Gln His Glu Asn Phe Arg Lys
50 55 60

Lys Gln Ile Glu Glu Leu Lys Gly Gln Glu Val Ser Pro Lys Val Tyr
65 70 75 80

Phe Met Lys Gln Thr Ile Gly Asn Ser Cys Gly Thr Ile Gly Leu Ile
85 90 95

His Ala Val Ala Asn Asn Gln Asp Lys Leu Gly Phe Glu Asp Gly Ser

100 105 110

Val Leu Lys Gln Phe Leu Ser Glu Thr Glu Lys Met Ser Pro Glu Asp

115 120 125

Arg Ala Lys Cys Phe Glu Lys Asn Glu Ala Ile Gln Ala Ala His Asp

130 135 140

Ala Val Ala Gln Glu Gly Gln Cys Arg Val Asp Asp Lys Val Asn Phe

145 150 155 160

His Phe Ile Leu Phe Asn Asn Val Asp Gly His Leu Tyr Glu Leu Asp

165 170 175

Gly Arg Met Pro Phe Pro Val Asn His Gly Ala Ser Ser Glu Asp Thr

180 185 190

Leu Leu Lys Asp Ala Ala Lys Val Cys Arg Glu Phe Thr Glu Arg Glu

195 200 205

Gln Gly Glu Val Arg Phe Ser Ala Val Ala Leu Cys Lys Ala Ala

210 215 220

<210> 44

<211> 17

<212> DNA

<213> 人工序列

<220>

<223> 合成

<400> 44

ttttttttt ttttttg 17

<210> 45

<211> 445

<212> PRT

<213> 人工序列

<220>

<223> 合成

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> 瓜氨酸

<220>

<221> MISC_FEATURE

<222> (46)..(46)

<223> 瓜氨酸

<220>

<221> MISC_FEATURE

<222> (62)..(62)
<223> 瓜氨酸
<220>
<221> MISC_FEATURE
<222> (77)..(77)
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<220>
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<222> (156)..(156)
<223> 瓜氨酸
<220>
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<222> (162)..(162)
<223> 瓜氨酸
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<222> (213)..(213)
<223> 瓜氨酸
<220>
<221> MISC_FEATURE
<222> (241)..(241)
<223> 瓜氨酸
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<221> MISC_FEATURE
<222> (251)..(251)
<223> 瓜氨酸
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<221> MISC_FEATURE
<222> (262)..(262)
<223> 瓜氨酸
<220>

<221> MISC_FEATURE
<222> (276)..(276)
<223> 瓜氨酸
<220>
<221> MISC_FEATURE
<222> (282)..(282)
<223> 瓜氨酸
<220>
<221> MISC_FEATURE
<222> (306)..(306)
<223> 瓜氨酸
<220>
<221> MISC_FEATURE
<222> (309)..(309)
<223> 瓜氨酸
<220>
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<222> (318)..(318)
<223> 瓜氨酸
<220>
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<222> (320)..(320)
<223> 瓜氨酸
<220>
<221> MISC_FEATURE
<222> (359)..(359)
<223> 瓜氨酸
<220>
<221> MISC_FEATURE
<222> (380)..(380)
<223> 瓜氨酸
<220>
<221> MISC_FEATURE
<222> (390)..(390)
<223> 瓜氨酸
<220>
<221> MISC_FEATURE
<222> (391)..(391)
<223> 瓜氨酸

<400> 45

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

Pro Xaa His Gly Xaa Tyr Leu Thr Val Ala Ala Val Phe Xaa Gly Xaa
305 310 315 320
Met Ser Met Lys Glu Val Asp Glu Gln Met Leu Asn Val Gln Asn Lys
325 330 335
Asn Ser Ser Tyr Phe Val Glu Trp Ile Pro Asn Asn Val Lys Thr Ala
340 345 350
Val Cys Asp Ile Pro Pro Xaa Gly Leu Lys Met Ser Ala Thr Phe Ile
355 360 365
Gly Asn Ser Thr Ala Ile Gln Glu Leu Phe Lys Xaa Ile Ser Glu Gln
370 375 380
Phe Thr Ala Met Phe Xaa Xaa Lys Ala Phe Leu His Trp Tyr Thr Gly
385 390 395 400
Glu Gly Met Asp Glu Met Glu Phe Thr Glu Ala Glu Ser Asn Met Asn
405 410 415
Asp Leu Val Ser Glu Tyr Gln Gln Tyr Gln Asp Ala Thr Ala Glu Glu
420 425 430
Glu Gly Glu Phe Glu Glu Glu Ala Glu Glu Glu Val Ala
435 440 445

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<211> 451
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<213> 人

<400> 47

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

Cys Asp Pro Arg His Gly Lys Tyr Met Ala Cys Cys Leu Leu Tyr Arg
305 310 315 320
Gly Asp Val Val Pro Lys Asp Val Asn Ala Ala Ile Ala Thr Ile Lys
325 330 335
Thr Lys Arg Ser Ile Gln Phe Val Asp Trp Cys Pro Thr Gly Phe Lys
340 345 350
Val Gly Ile Asn Tyr Gln Pro Pro Thr Val Val Pro Gly Gly Asp Leu
355 360 365
Ala Lys Val Gln Arg Ala Val Cys Met Leu Ser Asn Thr Thr Ala Ile
370 375 380
Ala Glu Ala Trp Ala Arg Leu Asp His Lys Phe Asp Leu Met Tyr Ala
385 390 395 400
Lys Arg Ala Phe Val His Trp Tyr Val Gly Glu Gly Met Glu Glu Gly
405 410 415
Glu Phe Ser Glu Ala Arg Glu Asp Met Ala Ala Leu Glu Lys Asp Tyr
420 425 430
Glu Glu Val Gly Val Asp Ser Val Glu Gly Glu Gly Glu Glu Glu Gly
435 440 445
Glu Glu Tyr
450

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<211> 451
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Met Arg Glu Cys Ile Ser Ile His Val Gly Gln Ala Gly Val Gln Ile
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Gly Asn Ala Cys Trp Glu Leu Tyr Cys Leu Glu His Gly Ile Gln Pro
20 25 30
Asp Gly Gln Met Pro Ser Asp Lys Thr Ile Gly Gly Gly Asp Asp Ser
35 40 45
Phe Asn Thr Phe Phe Ser Glu Thr Gly Ala Gly Lys His Val Pro Arg
50 55 60
Ala Val Phe Val Asp Leu Glu Pro Thr Val Ile Asp Glu Val Arg Thr
65 70 75 80
Gly Thr Tyr Arg Gln Leu Phe His Pro Glu Gln Leu Ile Thr Gly Lys
85 90 95
Glu Asp Ala Ala Asn Asn Tyr Ala Arg Gly His Tyr Thr Ile Gly Lys
100 105 110

Glu Ile Ile Asp Leu Val Leu Asp Arg Ile Arg Lys Leu Ala Asp Gln
115 120 125
Cys Thr Gly Leu Gln Gly Phe Leu Val Phe His Ser Phe Gly Gly Gly
130 135 140
Thr Gly Ser Gly Phe Thr Ser Leu Leu Met Glu Arg Leu Ser Val Asp
145 150 155 160
Tyr Gly Lys Lys Ser Lys Leu Glu Phe Ser Ile Tyr Pro Ala Pro Gln
165 170 175
Val Ser Thr Ala Val Val Glu Pro Tyr Asn Ser Ile Leu Thr Thr His
180 185 190
Thr Thr Leu Glu His Ser Asp Cys Ala Phe Met Val Asp Asn Glu Ala
195 200 205
Ile Tyr Asp Ile Cys Arg Arg Asn Leu Asp Ile Glu Arg Pro Thr Tyr
210 215 220
Thr Asn Leu Asn Arg Leu Ile Ser Gln Ile Val Ser Ser Ile Thr Ala
225 230 235 240
Ser Leu Arg Phe Asp Gly Ala Leu Asn Val Asp Leu Thr Glu Phe Gln
245 250 255
Thr Asn Leu Val Pro Tyr Pro Arg Ile His Phe Pro Leu Ala Thr Tyr
260 265 270
Ala Pro Val Ile Ser Ala Glu Lys Ala Tyr His Glu Gln Leu Ser Val
275 280 285
Ala Glu Ile Thr Asn Ala Cys Phe Glu Pro Ala Asn Gln Met Val Lys
290 295 300
Cys Asp Pro Arg His Gly Lys Tyr Met Ala Cys Cys Leu Leu Tyr Arg
305 310 315 320
Gly Asp Val Val Pro Lys Asp Val Asn Ala Ala Ile Ala Thr Ile Lys
325 330 335
Thr Lys Arg Ser Ile Gln Phe Val Asp Trp Cys Pro Thr Gly Phe Lys
340 345 350
Val Gly Ile Asn Tyr Gln Pro Pro Thr Val Val Pro Gly Gly Asp Leu
355 360 365
Ala Lys Val Gln Arg Ala Val Cys Met Leu Ser Asn Thr Thr Ala Ile
370 375 380
Ala Glu Ala Trp Ala Arg Leu Asp His Lys Phe Asp Leu Met Tyr Ala
385 390 395 400
Lys Arg Ala Phe Val His Trp Tyr Val Gly Glu Gly Met Glu Glu Gly
405 410 415
Glu Phe Ser Glu Ala Arg Glu Asp Met Ala Ala Leu Glu Lys Asp Tyr

420 425 430

Glu Glu Val Gly Val Asp Ser Val Glu Gly Glu Gly Glu Glu Glu Gly

435 440 445

Glu Glu Tyr

450

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<220>

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<222> (17)..(17)

<223> 天冬氨酸或无氨基酸

<400> 49

Xaa Tyr Met Ala Cys Cys Leu Leu Tyr Arg Gly Asp Val Val Pro Lys

1 5 10 15

Xaa

<210> 50

<211> 15

<212> PRT

<213> 人工序列

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<223> 合成

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<222> (1)..(1)

<223> 谷氨酸或无氨基酸

<220>

<221> MISC_FEATURE

<222> (15)..(15)

<223> 谷氨酰胺或无氨基酸

<400> 50

Xaa Val Arg Thr Gly Thr Tyr Arg Gln Leu Phe His Pro Glu Xaa

1 5 10 15

<210> 51

<211> 422

<212> PRT

<213> 人

<400> 51

Met Val Ser Glu Ser His His Glu Ala Leu Ala Ala Pro Pro Val Thr
1 5 10 15

Thr Val Ala Thr Val Leu Pro Ser Asn Ala Thr Glu Pro Ala Ser Pro
20 25 30

Gly Glu Gly Lys Glu Asp Ala Phe Ser Lys Leu Lys Glu Lys Phe Met
35 40 45

Asn Glu Leu His Lys Ile Pro Leu Pro Pro Trp Ala Leu Ile Ala Ile
50 55 60

Ala Ile Val Ala Val Leu Leu Val Leu Thr Cys Cys Phe Cys Ile Cys
65 70 75 80

Lys Lys Cys Leu Phe Lys Lys Lys Asn Lys Lys Lys Gly Lys Glu Lys
85 90 95

Gly Gly Lys Asn Ala Ile Asn Met Lys Asp Val Lys Asp Leu Gly Lys
100 105 110

Thr Met Lys Asp Gln Ala Leu Lys Asp Asp Asp Ala Glu Thr Gly Leu
115 120 125

Thr Asp Gly Glu Glu Lys Glu Glu Pro Lys Glu Glu Glu Lys Leu Gly
130 135 140

Lys Leu Gln Tyr Ser Leu Asp Tyr Asp Phe Gln Asn Asn Gln Leu Leu
145 150 155 160

Val Gly Ile Ile Gln Ala Ala Glu Leu Pro Ala Leu Asp Met Gly Gly
165 170 175

Thr Ser Asp Pro Tyr Val Lys Val Phe Leu Leu Pro Asp Lys Lys Lys
180 185 190

Lys Phe Glu Thr Lys Val His Arg Lys Thr Leu Asn Pro Val Phe Asn
195 200 205

Glu Gln Phe Thr Phe Lys Val Pro Tyr Ser Glu Leu Gly Gly Lys Thr
210 215 220

Leu Val Met Ala Val Tyr Asp Phe Asp Arg Phe Ser Lys His Asp Ile
225 230 235 240

Ile Gly Glu Phe Lys Val Pro Met Asn Thr Val Asp Phe Gly His Val
245 250 255

Thr Glu Glu Trp Arg Asp Leu Gln Ser Ala Glu Lys Glu Glu Gln Glu

260 265 270

Lys Leu Gly Asp Ile Cys Phe Ser Leu Arg Tyr Val Pro Thr Ala Gly
275 280 285

Lys Leu Thr Val Val Ile Leu Glu Ala Lys Asn Leu Lys Lys Met Asp
290 295 300

Val Gly Gly Leu Ser Asp Pro Tyr Val Lys Ile His Leu Met Gln Asn
305 310 315 320

Gly Lys Arg Leu Lys Lys Lys Lys Thr Thr Ile Lys Lys Asn Thr Leu
325 330 335

Asn Pro Tyr Tyr Asn Glu Ser Phe Ser Phe Glu Val Pro Phe Glu Gln
340 345 350

Ile Gln Lys Val Gln Val Val Val Thr Val Leu Asp Tyr Asp Lys Ile
355 360 365

Gly Lys Asn Asp Ala Ile Gly Lys Val Phe Val Gly Tyr Asn Ser Thr
370 375 380

Gly Ala Glu Leu Arg His Trp Ser Asp Met Leu Ala Asn Pro Arg Arg
385 390 395 400

Pro Ile Ala Gln Trp His Thr Leu Gln Val Glu Glu Glu Val Asp Ala
405 410 415

Met Leu Ala Val Lys Lys
420

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<211> 42
<212> PRT
<213> 人
<400> 52

Asp Ala Glu Phe Arg His Asp Ser Gly Tyr Glu Val His His Gln Lys
1 5 10 15

Leu Val Phe Phe Ala Glu Asp Val Gly Ser Asn Lys Gly Ala Ile Ile
20 25 30

Gly Leu Met Val Gly Gly Val Val Ile Ala
35 40

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<223> 酪氨酸或无氨基酸
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Xaa Ser Thr Leu Ala Arg Val Ile Val Asp Lys Xaa
1 5 10
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<211> 16
<212> PRT
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<222> (16)..(16)
<223> 精氨酸或无氨基酸
<400> 54
Xaa Ile Thr Pro Gly Ala Arg Gly Ala Phe Ser Glu Glu Tyr Lys Xaa
1 5 10 15
<210> 55
<211> 1193
<212> PRT
<213> 人
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Met Pro Ala Leu Trp Leu Gly Cys Cys Leu Cys Phe Ser Leu Leu Leu
1 5 10 15
Pro Ala Ala Arg Ala Thr Ser Arg Arg Glu Val Cys Asp Cys Asn Gly
20 25 30
Lys Ser Arg Gln Cys Ile Phe Asp Arg Glu Leu His Arg Gln Thr Gly
35 40 45
Asn Gly Phe Arg Cys Leu Asn Cys Asn Asp Asn Thr Asp Gly Ile His

50 55 60

Cys Glu Lys Cys Lys Asn Gly Phe Tyr Arg His Arg Glu Arg Asp Arg
65 70 75 80

Cys Leu Pro Cys Asn Cys Asn Ser Lys Gly Ser Leu Ser Ala Arg Cys
85 90 95

Asp Asn Ser Gly Arg Cys Ser Cys Lys Pro Gly Val Thr Gly Ala Arg
100 105 110

Cys Asp Arg Cys Leu Pro Gly Phe His Met Leu Thr Asp Ala Gly Cys
115 120 125

Thr Gln Asp Gln Arg Leu Leu Asp Ser Lys Cys Asp Cys Asp Pro Ala
130 135 140

Gly Ile Ala Gly Pro Cys Asp Ala Gly Arg Cys Val Cys Lys Pro Ala
145 150 155 160

Val Thr Gly Glu Arg Cys Asp Arg Cys Arg Ser Gly Tyr Tyr Asn Leu
165 170 175

Asp Gly Gly Asn Pro Glu Gly Cys Thr Gln Cys Phe Cys Tyr Gly His
180 185 190

Ser Ala Ser Cys Arg Ser Ser Ala Glu Tyr Ser Val His Lys Ile Thr
195 200 205

Ser Thr Phe His Gln Asp Val Asp Gly Trp Lys Ala Val Gln Arg Asn
210 215 220

Gly Ser Pro Ala Lys Leu Gln Trp Ser Gln Arg His Gln Asp Val Phe
225 230 235 240

Ser Ser Ala Gln Arg Leu Asp Pro Val Tyr Phe Val Ala Pro Ala Lys
245 250 255

Phe Leu Gly Asn Gln Gln Val Ser Tyr Gly Gln Ser Leu Ser Phe Asp
260 265 270

Tyr Arg Val Asp Arg Gly Gly Arg His Pro Ser Ala His Asp Val Ile
275 280 285

Leu Glu Gly Ala Gly Leu Arg Ile Thr Ala Pro Leu Met Pro Leu Gly
290 295 300

Lys Thr Leu Pro Cys Gly Leu Thr Lys Thr Tyr Thr Phe Arg Leu Asn
305 310 315 320

Glu His Pro Ser Asn Asn Trp Ser Pro Gln Leu Ser Tyr Phe Glu Tyr
325 330 335

Arg Arg Leu Leu Arg Asn Leu Thr Ala Leu Arg Ile Arg Ala Thr Tyr
340 345 350

Gly Glu Tyr Ser Thr Gly Tyr Ile Asp Asn Val Thr Leu Ile Ser Ala
355 360 365

Arg Pro Val Ser Gly Ala Pro Ala Pro Trp Val Glu Gln Cys Ile Cys
370 375 380
Pro Val Gly Tyr Lys Gly Gln Phe Cys Gln Asp Cys Ala Ser Gly Tyr
385 390 395 400
Lys Arg Asp Ser Ala Arg Leu Gly Pro Phe Gly Thr Cys Ile Pro Cys
405 410 415
Asn Cys Gln Gly Gly Gly Ala Cys Asp Pro Asp Thr Gly Asp Cys Tyr
420 425 430
Ser Gly Asp Glu Asn Pro Asp Ile Glu Cys Ala Asp Cys Pro Ile Gly
435 440 445
Phe Tyr Asn Asp Pro His Asp Pro Arg Ser Cys Lys Pro Cys Pro Cys
450 455 460
His Asn Gly Phe Ser Cys Ser Val Met Pro Glu Thr Glu Glu Val Val
465 470 475 480
Cys Asn Asn Cys Pro Pro Gly Val Thr Gly Ala Arg Cys Glu Leu Cys
485 490 495
Ala Asp Gly Tyr Phe Gly Asp Pro Phe Gly Glu His Gly Pro Val Arg
500 505 510
Pro Cys Gln Pro Cys Gln Cys Asn Asn Asn Val Asp Pro Ser Ala Ser
515 520 525
Gly Asn Cys Asp Arg Leu Thr Gly Arg Cys Leu Lys Cys Ile His Asn
530 535 540
Thr Ala Gly Ile Tyr Cys Asp Gln Cys Lys Ala Gly Tyr Phe Gly Asp
545 550 555 560
Pro Leu Ala Pro Asn Pro Ala Asp Lys Cys Arg Ala Cys Asn Cys Asn
565 570 575
Pro Met Gly Ser Glu Pro Val Gly Cys Arg Ser Asp Gly Thr Cys Val
580 585 590
Cys Lys Pro Gly Phe Gly Gly Pro Asn Cys Glu His Gly Ala Phe Ser
595 600 605
Cys Pro Ala Cys Tyr Asn Gln Val Lys Ile Gln Met Asp Gln Phe Met
610 615 620
Gln Gln Leu Gln Arg Met Glu Ala Leu Ile Ser Lys Ala Gln Gly Gly
625 630 635 640
Asp Gly Val Val Pro Asp Thr Glu Leu Glu Gly Arg Met Gln Gln Ala
645 650 655
Glu Gln Ala Leu Gln Asp Ile Leu Arg Asp Ala Gln Ile Ser Glu Gly
660 665 670
Ala Ser Arg Ser Leu Gly Leu Gln Leu Ala Lys Val Arg Ser Gln Glu

675 680 685

Asn Ser Tyr Gln Ser Arg Leu Asp Asp Leu Lys Met Thr Val Glu Arg

690 695 700

Val Arg Ala Leu Gly Ser Gln Tyr Gln Asn Arg Val Arg Asp Thr His

705 710 715 720

Arg Leu Ile Thr Gln Met Gln Leu Ser Leu Ala Glu Ser Glu Ala Ser

725 730 735

Leu Gly Asn Thr Asn Ile Pro Ala Ser Asp His Tyr Val Gly Pro Asn

740 745 750

Gly Phe Lys Ser Leu Ala Gln Glu Ala Thr Arg Leu Ala Glu Ser His

755 760 765

Val Glu Ser Ala Ser Asn Met Glu Gln Leu Thr Arg Glu Thr Glu Asp

770 775 780

Tyr Ser Lys Gln Ala Leu Ser Leu Val Arg Lys Ala Leu His Glu Gly

785 790 795 800

Val Gly Ser Gly Ser Gly Ser Pro Asp Gly Ala Val Val Gln Gly Leu

805 810 815

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

820 825 830

Glu Ala Thr Gln Ala Glu Ile Glu Ala Asp Arg Ser Tyr Gln His Ser

835 840 845

Leu Arg Leu Leu Asp Ser Val Ser Arg Leu Gln Gly Val Ser Asp Gln

850 855 860

Ser Phe Gln Val Glu Glu Ala Lys Arg Ile Lys Gln Lys Ala Asp Ser

865 870 875 880

Leu Ser Ser Leu Val Thr Arg His Met Asp Glu Phe Lys Arg Thr Gln

885 890 895

Lys Asn Leu Gly Asn Trp Lys Glu Glu Ala Gln Gln Leu Leu Gln Asn

900 905 910

Gly Lys Ser Gly Arg Glu Lys Ser Asp Gln Leu Leu Ser Arg Ala Asn

915 920 925

Leu Ala Lys Ser Arg Ala Gln Glu Ala Leu Ser Met Gly Asn Ala Thr

930 935 940

Phe Tyr Glu Val Glu Ser Ile Leu Lys Asn Leu Arg Glu Phe Asp Leu

945 950 955 960

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

965 970 975

Ser Tyr Ile Ser Gln Lys Val Ser Asp Ala Ser Asp Lys Thr Gln Gln

980 985 990

Ala Glu Arg Ala Leu Gly Ser Ala Ala Ala Asp Ala Gln Arg Ala Lys
995 1000 1005
Asn Gly Ala Gly Glu Ala Leu Glu Ile Ser Ser Glu Ile Glu Gln
1010 1015 1020
Glu Ile Gly Ser Leu Asn Leu Glu Ala Asn Val Thr Ala Asp Gly
1025 1030 1035
Ala Leu Ala Met Glu Lys Gly Leu Ala Ser Leu Lys Ser Glu Met
1040 1045 1050
Arg Glu Val Glu Gly Glu Leu Glu Arg Lys Glu Leu Glu Phe Asp
1055 1060 1065
Thr Asn Met Asp Ala Val Gln Met Val Ile Thr Glu Ala Gln Lys
1070 1075 1080
Val Asp Thr Arg Ala Lys Asn Ala Gly Val Thr Ile Gln Asp Thr
1085 1090 1095
Leu Asn Thr Leu Asp Gly Leu Leu His Leu Met Asp Gln Pro Leu
1100 1105 1110
Ser Val Asp Glu Glu Gly Leu Val Leu Leu Glu Gln Lys Leu Ser
1115 1120 1125
Arg Ala Lys Thr Gln Ile Asn Ser Gln Leu Arg Pro Met Met Ser
1130 1135 1140
Glu Leu Glu Glu Arg Ala Arg Gln Gln Arg Gly His Leu His Leu
1145 1150 1155
Leu Glu Thr Ser Ile Asp Gly Ile Leu Ala Asp Val Lys Asn Leu
1160 1165 1170
Glu Asn Ile Arg Asp Asn Leu Pro Pro Gly Cys Tyr Asn Thr Gln
1175 1180 1185
Ala Leu Glu Gln Gln
1190

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<400> 56

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Met Val Asn Pro Thr Val Phe Phe Asp Ile Ala Val Asp Gly Glu Pro
1               5                  10                  15
Leu Gly Xaa Val Ser Phe Glu Leu Phe Ala Asp Lys Val Pro Lys Thr
            20                  25                  30
Ala Glu Asn Phe Xaa Ala Leu Ser Thr Gly Glu Lys Gly Phe Gly Tyr
        35                  40                  45
Lys Gly Ser Cys Phe His Xaa Ile Ile Pro Gly Phe Met Cys Gln Gly
    50                  55                  60
Gly Asp Phe Thr Xaa His Asn Gly Thr Gly Gly Lys Ser Ile Tyr Gly
65                  70                  75                  80
Glu Lys Phe Glu Asp Glu Asn Phe Ile Leu Lys His Thr Gly Pro Gly
                85                  90                  95
Ile Leu Ser Met Ala Asn Ala Gly Pro Asn Thr Asn Gly Ser Gln Phe
            100                 105                 110
Phe Ile Cys Thr Ala Lys Thr Glu Trp Leu Asp Gly Lys His Val Val
        115                 120                 125
Phe Gly Lys Val Lys Glu Gly Met Asn Ile Val Glu Ala Met Glu Xaa
    130                 135                 140
Phe Gly Ser Xaa Asn Gly Lys Thr Ser Lys Lys Ile Thr Ile Ala Asp
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145 150 155 160
Cys Gly Gln Leu Glu
165
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<222> (14)..(14)
<223> 甘氨酸或无氨基酸
<400> 57
Xaa Ala Glu Asn Phe Arg Ala Leu Ser Thr Gly Glu Lys Xaa
1 5 10
<210> 58
<211> 60
<212> PRT
<213> 人
<400> 58
Met Pro Ser Gln Met Glu His Ala Met Glu Thr Met Met Phe Thr Phe
1 5 10 15
His Lys Phe Ala Gly Asp Lys Gly Tyr Leu Thr Lys Glu Asp Leu Arg
20 25 30
Val Leu Met Glu Lys Glu Phe Pro Gly Phe Leu Glu Asn Gln Lys Asp
35 40 45
Pro Leu Ala Val Asp Lys Ile Met Lys Asp Leu Asp
50 55 60
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<211> 37
<212> PRT
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<222> (3)..(3)
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Gln Cys Xaa Asp Gly Lys Val Gly Phe Gln Ser Phe Phe Ser Leu Ile
1 5 10 15
Ala Gly Leu Thr Ile Ala Cys Asn Asp Tyr Phe Val Val His Met Lys
20 25 30
Gln Lys Gly Lys Lys
35
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<223> 最初为精氨酸或无氨基酸
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<222> (15)..(15)
<223> 天冬酰胺或无氨基酸
<400> 60
Xaa Ile Leu Glu Gln Gln Asn Ser Ser Arg Thr Leu Glu Lys Xaa
1 5 10 15
<210> 61
<211> 133
<212> PRT
<213> 人
<400> 61
Met Ala Asp Ala Phe Leu Gly Thr Trp Lys Leu Val Asp Ser Lys Asn
1 5 10 15
Phe Asp Asp Tyr Met Lys Ser Leu Gly Val Gly Phe Ala Thr Arg Gln
20 25 30
Val Ala Ser Met Thr Lys Pro Thr Thr Ile Ile Glu Lys Asn Gly Asp
35 40 45

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

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

Pro Trp Phe Lys Gly Trp Lys Val Glu Xaa Lys Glu Gly Asn Ala Ser
210 215 220
Gly Val Ser Leu Leu Glu Ala Leu Asp Thr Ile Leu Pro Pro Thr Xaa
225 230 235 240
Pro Thr Asp Lys Pro Leu Xaa Leu Pro Leu Gln Asp Val Tyr Lys Ile
245 250 255
Gly Gly Ile Gly Thr Val Pro Val Gly Xaa Val Glu Thr Gly Ile Leu
260 265 270
Xaa Pro Gly Met Val Val Thr Phe Ala Pro Val Asn Ile Thr Thr Glu
275 280 285
Val Lys Ser Val Glu Met His His Glu Ala Leu Ser Glu Ala Leu Pro
290 295 300
Gly Asp Asn Val Gly Phe Asn Val Lys Asn Val Ser Val Lys Asp Ile
305 310 315 320
Xaa Xaa Gly Asn Val Cys Gly Asp Ser Lys Ser Asp Pro Pro Gln Glu
325 330 335
Ala Ala Gln Phe Thr Ser Gln Val Ile Ile Leu Asn His Pro Gly Gln
340 345 350
Ile Ser Ala Gly Tyr Ser Pro Val Ile Asp Cys His Thr Ala His Ile
355 360 365
Ala Cys Lys Phe Ala Glu Leu Lys Glu Lys Ile Asp Xaa Xaa Ser Gly
370 375 380
Lys Lys Leu Glu Asp Asn Pro Lys Ser Leu Lys Ser Gly Asp Ala Ala
385 390 395 400
Ile Val Glu Met Val Pro Gly Lys Pro Met Cys Val Glu Ser Phe Ser
405 410 415
Gln Tyr Pro Pro Leu Gly Xaa Phe Ala Val Xaa Asp Met Xaa Gln Thr
420 425 430
Val Ala Val Gly Val Ile Lys Asn Val Glu Lys Lys Ser Gly Gly Ala
435 440 445
Gly Lys Val Thr Lys Ser Ala Gln Lys Ala Gln Lys Ala Gly Lys
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Xaa Pro Leu Arg Leu Pro Leu GIn Asp VaI Tyr Lys Xaa
1 5 10
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1 5 10 15
GIu Xaa
<210> 65
<211> 421
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<400> 65
Met Asn Arg GIy Phe Ser Arg Lys Ser His Thr Phe Leu Pro Lys IIe
1 5 10 15
Phe Phe Arg Lys Met Ser Ser Ser GIy AIa Lys Asp Lys Pro GIu Leu
20 25 30
GIn Phe Pro Phe Leu GIn Asp GIu Asp Thr VaI AIa Thr Leu Leu GIu
35 40 45

Cys Lys Thr Leu Phe Ile Leu Arg Gly Leu Pro Gly Ser Gly Lys Ser
50 55 60
Thr Leu Ala Arg Val Ile Val Asp Lys Tyr Arg Asp Gly Thr Lys Met
65 70 75 80
Val Ser Ala Asp Ala Tyr Lys Ile Thr Pro Gly Ala Arg Gly Ala Phe
85 90 95
Ser Glu Glu Tyr Lys Arg Leu Asp Glu Asp Leu Ala Ala Tyr Cys Arg
100 105 110
Arg Arg Asp Ile Arg Ile Leu Val Leu Asp Asp Thr Asn His Glu Arg
115 120 125
Glu Arg Leu Glu Gln Leu Phe Glu Met Ala Asp Gln Tyr Gln Tyr Gln
130 135 140
Val Val Leu Val Glu Pro Lys Thr Ala Trp Arg Leu Asp Cys Ala Gln
145 150 155 160
Leu Lys Glu Lys Asn Gln Trp Gln Leu Ser Ala Asp Asp Leu Lys Lys
165 170 175
Leu Lys Pro Gly Leu Glu Lys Asp Phe Leu Pro Leu Tyr Phe Gly Trp
180 185 190
Phe Leu Thr Lys Lys Ser Ser Glu Thr Leu Arg Lys Ala Gly Gln Val
195 200 205
Phe Leu Glu Glu Leu Gly Asn His Lys Ala Phe Lys Lys Glu Leu Arg
210 215 220
Gln Phe Val Pro Gly Asp Glu Pro Arg Glu Lys Met Asp Leu Val Thr
225 230 235 240
Tyr Phe Gly Lys Arg Pro Pro Gly Val Leu His Cys Thr Thr Lys Phe
245 250 255
Cys Asp Tyr Gly Lys Ala Pro Gly Ala Glu Glu Tyr Ala Gln Gln Asp
260 265 270
Val Leu Lys Lys Ser Tyr Ser Lys Ala Phe Thr Leu Thr Ile Ser Ala
275 280 285
Leu Phe Val Thr Pro Lys Thr Thr Gly Ala Arg Val Glu Leu Ser Glu
290 295 300
Gln Gln Leu Gln Leu Trp Pro Ser Asp Val Asp Lys Leu Ser Pro Thr
305 310 315 320
Asp Asn Leu Pro Arg Gly Ser Arg Ala His Ile Thr Leu Gly Cys Ala
325 330 335
Ala Asp Val Glu Ala Val Gln Thr Gly Leu Asp Leu Leu Glu Ile Leu
340 345 350
Arg Gln Glu Lys Gly Gly Ser Arg Gly Glu Glu Val Gly Glu Leu Ser

355 360 365

Arg GIy Lys Leu Tyr Ser Leu GIy Asn GIy Arg Trp Met Leu Thr Leu

370 375 380

AIa Lys Asn Met GIu VaI Arg AIa IIe Phe Thr GIy Tyr Tyr GIy Lys

385 390 395 400

GIy Lys Pro VaI Pro Thr GIn GIy Ser Arg Lys GIy GIy AIa Leu GIn

405 410 415

Ser Cys Thr IIe IIe

420

<210> 66

<211> 1669

<212> PRT

<213> 人

<400> 66

Met GIy Pro Arg Leu Ser VaI Trp Leu Leu Leu Leu Pro AIa AIa Leu

1 5 10 15

Leu Leu His GIu GIu His Ser Arg AIa AIa AIa Lys GIy GIy Cys AIa

20 25 30

GIy Ser GIy Cys GIy Lys Cys Asp Cys His GIy VaI Lys GIy GIn Lys

35 40 45

GIy GIu Arg GIy Leu Pro GIy Leu GIn GIy VaI IIe GIy Phe Pro GIy

50 55 60

Met GIn GIy Pro GIu GIy Pro GIn GIy Pro Pro GIy GIn Lys GIy Asp

65 70 75 80

Thr GIy GIu Pro GIy Leu Pro GIy Thr Lys GIy Thr Arg GIy Pro Pro

85 90 95

GIy AIa Ser GIy Tyr Pro GIy Asn Pro GIy Leu Pro GIy IIe Pro GIy

100 105 110

GIn Asp GIy Pro Pro GIy Pro Pro GIy IIe Pro GIy Cys Asn GIy Thr

115 120 125

Lys GIy GIu Arg GIy Pro Leu GIy Pro Pro GIy Leu Pro GIy Phe AIa

130 135 140

GIy Asn Pro GIy Pro Pro GIy Leu Pro GIy Met Lys GIy Asp Pro GIy

145 150 155 160

GIu IIe Leu GIy His VaI Pro GIy Met Leu Leu Lys GIy GIu Arg GIy

165 170 175

Phe Pro GIy IIe Pro GIy Thr Pro GIy Pro Pro GIy Leu Pro GIy Leu

180 185 190

GIn GIy Pro VaI GIy Pro Pro GIy Phe Thr GIy Pro Pro GIy Pro Pro

195 200 205

GIy Pro Pro GIy Pro Pro GIy GIu Lys GIy GIn Met GIy Leu Ser Phe

210 215 220

GIn GIy Pro Lys GIy Asp Lys GIy Asp GIn GIy VaI Ser GIy Pro Pro

225 230 235 240

GIy VaI Pro GIy GIn AIa GIn VaI GIn GIu Lys GIy Asp Phe AIa Thr

245 250 255

Lys GIy GIu Lys GIy GIn Lys GIy GIu Pro GIy Phe GIn GIy Met Pro

260 265 270

GIy VaI GIy GIu Lys GIy GIu Pro GIy Lys Pro GIy Pro Arg GIy Lys

275 280 285

Pro GIy Lys Asp GIy Asp Lys GIy GIu Lys GIy Ser Pro GIy Phe Pro

290 295 300

GIy GIu Pro GIy Tyr Pro GIy Leu IIe GIy Arg GIn GIy Pro GIn GIy

305 310 315 320

GIu Lys GIy GIu AIa GIy Pro Pro GIy Pro Pro GIy IIe VaI IIe GIy

325 330 335

Thr GIy Pro Leu GIy GIu Lys GIy GIu Arg GIy Tyr Pro GIy Thr Pro

340 345 350

GIy Pro Arg GIy GIu Pro GIy Pro Lys GIy Phe Pro GIy Leu Pro GIy

355 360 365

GIn Pro GIy Pro Pro GIy Leu Pro VaI Pro GIy GIn AIa GIy AIa Pro

370 375 380

GIy Phe Pro GIy GIu Arg GIy GIu Lys GIy Asp Arg GIy Phe Pro GIy

385 390 395 400

Thr Ser Leu Pro GIy Pro Ser GIy Arg Asp GIy Leu Pro GIy Pro Pro

405 410 415

GIy Ser Pro GIy Pro Pro GIy GIn Pro GIy Tyr Thr Asn GIy IIe VaI

420 425 430

GIu Cys GIn Pro GIy Pro Pro GIy Asp GIn GIy Pro Pro GIy IIe Pro

435 440 445

GIy GIn Pro GIy Phe IIe GIy GIu IIe GIy GIu Lys GIy GIn Lys GIy

450 455 460

GIu Ser Cys Leu IIe Cys Asp IIe Asp GIy Tyr Arg GIy Pro Pro GIy

465 470 475 480

Pro GIn GIy Pro Pro GIy GIu IIe GIy Phe Pro GIy GIn Pro GIy AIa

485 490 495

Lys GIy Asp Arg GIy Leu Pro GIy Arg Asp GIy VaI AIa GIy VaI Pro

500 505 510

Gly Pro Gln Gly Thr Pro Gly Leu Ile Gly Gln Pro Gly Ala Lys Gly
515 520 525
Glu Pro Gly Glu Phe Tyr Phe Asp Leu Arg Leu Lys Gly Asp Lys Gly
530 535 540
Asp Pro Gly Phe Pro Gly Gln Pro Gly Met Thr Gly Arg Ala Gly Ser
545 550 555 560
Pro Gly Arg Asp Gly His Pro Gly Leu Pro Gly Pro Lys Gly Ser Pro
565 570 575
Gly Ser Val Gly Leu Lys Gly Glu Arg Gly Pro Pro Gly Gly Val Gly
580 585 590
Phe Pro Gly Ser Arg Gly Asp Thr Gly Pro Pro Gly Pro Pro Gly Tyr
595 600 605
Gly Pro Ala Gly Pro Ile Gly Asp Lys Gly Gln Ala Gly Phe Pro Gly
610 615 620
Gly Pro Gly Ser Pro Gly Leu Pro Gly Pro Lys Gly Glu Pro Gly Lys
625 630 635 640
Ile Val Pro Leu Pro Gly Pro Pro Gly Ala Glu Gly Leu Pro Gly Ser
645 650 655
Pro Gly Phe Pro Gly Pro Gln Gly Asp Arg Gly Phe Pro Gly Thr Pro
660 665 670
Gly Arg Pro Gly Leu Pro Gly Glu Lys Gly Ala Val Gly Gln Pro Gly
675 680 685
Ile Gly Phe Pro Gly Pro Pro Gly Pro Lys Gly Val Asp Gly Leu Pro
690 695 700
Gly Asp Met Gly Pro Pro Gly Thr Pro Gly Arg Pro Gly Phe Asn Gly
705 710 715 720
Leu Pro Gly Asn Pro Gly Val Gln Gly Gln Lys Gly Glu Pro Gly Val
725 730 735
Gly Leu Pro Gly Leu Lys Gly Leu Pro Gly Leu Pro Gly Ile Pro Gly
740 745 750
Thr Pro Gly Glu Lys Gly Ser Ile Gly Val Pro Gly Val Pro Gly Glu
755 760 765
His Gly Ala Ile Gly Pro Pro Gly Leu Gln Gly Ile Arg Gly Glu Pro
770 775 780
Gly Pro Pro Gly Leu Pro Gly Ser Val Gly Ser Pro Gly Val Pro Gly
785 790 795 800
Ile Gly Pro Pro Gly Ala Arg Gly Pro Pro Gly Gly Gln Gly Pro Pro
805 810 815
Gly Leu Ser Gly Pro Pro Gly Ile Lys Gly Glu Lys Gly Phe Pro Gly

820 825 830

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

835 840 845

Gly Leu Pro Gly Ile Thr Gly Gln Ser Gly Leu Pro Gly Leu Pro Gly

850 855 860

Gln Gln Gly Ala Pro Gly Ile Pro Gly Phe Pro Gly Ser Lys Gly Glu

865 870 875 880

Met Gly Val Met Gly Thr Pro Gly Gln Pro Gly Ser Pro Gly Pro Val

885 890 895

Gly Ala Pro Gly Leu Pro Gly Glu Lys Gly Asp His Gly Phe Pro Gly

900 905 910

Ser Ser Gly Pro Arg Gly Asp Pro Gly Leu Lys Gly Asp Lys Gly Asp

915 920 925

Val Gly Leu Pro Gly Lys Pro Gly Ser Met Asp Lys Val Asp Met Gly

930 935 940

Ser Met Lys Gly Gln Lys Gly Asp Gln Gly Glu Lys Gly Gln Ile Gly

945 950 955 960

Pro Ile Gly Glu Lys Gly Ser Arg Gly Asp Pro Gly Thr Pro Gly Val

965 970 975

Pro Gly Lys Asp Gly Gln Ala Gly Gln Pro Gly Gln Pro Gly Pro Lys

980 985 990

Gly Asp Pro Gly Ile Ser Gly Thr Pro Gly Ala Pro Gly Leu Pro Gly

995 1000 1005

Pro Lys Gly Ser Val Gly Gly Met Gly Leu Pro Gly Thr Pro Gly

1010 1015 1020

Glu Lys Gly Val Pro Gly Ile Pro Gly Pro Gln Gly Ser Pro Gly

1025 1030 1035

Leu Pro Gly Asp Lys Gly Ala Lys Gly Glu Lys Gly Gln Ala Gly

1040 1045 1050

Pro Pro Gly Ile Gly Ile Pro Gly Leu Arg Gly Glu Lys Gly Asp

1055 1060 1065

Gln Gly Ile Ala Gly Phe Pro Gly Ser Pro Gly Glu Lys Gly Glu

1070 1075 1080

Lys Gly Ser Ile Gly Ile Pro Gly Met Pro Gly Ser Pro Gly Leu

1085 1090 1095

Lys Gly Ser Pro Gly Ser Val Gly Tyr Pro Gly Ser Pro Gly Leu

1100 1105 1110

Pro Gly Glu Lys Gly Asp Lys Gly Leu Pro Gly Leu Asp Gly Ile

1115 1120 1125

Pro Gly Val Lys Gly Glu Ala Gly Leu Pro Gly Thr Pro Gly Pro
1130 1135 1140
Thr Gly Pro Ala Gly Gln Lys Gly Glu Pro Gly Ser Asp Gly Ile
1145 1150 1155
Pro Gly Ser Ala Gly Glu Lys Gly Glu Pro Gly Leu Pro Gly Arg
1160 1165 1170
Gly Phe Pro Gly Phe Pro Gly Ala Lys Gly Asp Lys Gly Ser Lys
1175 1180 1185
Gly Glu Val Gly Phe Pro Gly Leu Ala Gly Ser Pro Gly Ile Pro
1190 1195 1200
Gly Ser Lys Gly Glu Gln Gly Phe Met Gly Pro Pro Gly Pro Gln
1205 1210 1215
Gly Gln Pro Gly Leu Pro Gly Ser Pro Gly His Ala Thr Glu Gly
1220 1225 1230
Pro Lys Gly Asp Arg Gly Pro Gln Gly Gln Pro Gly Leu Pro Gly
1235 1240 1245
Leu Pro Gly Pro Met Gly Pro Pro Gly Leu Pro Gly Ile Asp Gly
1250 1255 1260
Val Lys Gly Asp Lys Gly Asn Pro Gly Trp Pro Gly Ala Pro Gly
1265 1270 1275
Val Pro Gly Pro Lys Gly Asp Pro Gly Phe Gln Gly Met Pro Gly
1280 1285 1290
Ile Gly Gly Ser Pro Gly Ile Thr Gly Ser Lys Gly Asp Met Gly
1295 1300 1305
Pro Pro Gly Val Pro Gly Phe Gln Gly Pro Lys Gly Leu Pro Gly
1310 1315 1320
Leu Gln Gly Ile Lys Gly Asp Gln Gly Asp Gln Gly Val Pro Gly
1325 1330 1335
Ala Lys Gly Leu Pro Gly Pro Pro Gly Pro Pro Gly Pro Tyr Asp
1340 1345 1350
Ile Ile Lys Gly Glu Pro Gly Leu Pro Gly Pro Glu Gly Pro Pro
1355 1360 1365
Gly Leu Lys Gly Leu Gln Gly Leu Pro Gly Pro Lys Gly Gln Gln
1370 1375 1380
Gly Val Thr Gly Leu Val Gly Ile Pro Gly Pro Pro Gly Ile Pro
1385 1390 1395
Gly Phe Asp Gly Ala Pro Gly Gln Lys Gly Glu Met Gly Pro Ala
1400 1405 1410
Gly Pro Thr Gly Pro Arg Gly Phe Pro Gly Pro Pro Gly Pro Asp

1415 1420 1425

GIy Leu Pro GIy Ser Met GIy Pro Pro GIy Thr Pro Ser VaI Asp

1430 1435 1440

His GIy Phe Leu VaI Thr Arg His Ser GIn Thr IIe Asp Asp Pro

1445 1450 1455

GIn Cys Pro Ser GIy Thr Lys IIe Leu Tyr His GIy Tyr Ser Leu

1460 1465 1470

Leu Tyr VaI GIn GIy Asn GIu Arg AIa His GIy GIn Asp Leu GIy

1475 1480 1485

Thr AIa GIy Ser Cys Leu Arg Lys Phe Ser Thr Met Pro Phe Leu

1490 1495 1500

Phe Cys Asn IIe Asn Asn VaI Cys Asn Phe AIa Ser Arg Asn Asp

1505 1510 1515

Tyr Ser Tyr Trp Leu Ser Thr Pro GIu Pro Met Pro Met Ser Met

1520 1525 1530

AIa Pro IIe Thr GIy GIu Asn IIe Arg Pro Phe IIe Ser Arg Cys

1535 1540 1545

AIa VaI Cys GIu AIa Pro AIa Met VaI Met AIa VaI His Ser GIn

1550 1555 1560

Thr IIe GIn IIe Pro Pro Cys Pro Ser GIy Trp Ser Ser Leu Trp

1565 1570 1575

IIe GIy Tyr Ser Phe VaI Met His Thr Ser AIa GIy AIa GIu GIy

1580 1585 1590

Ser GIy GIn AIa Leu AIa Ser Pro GIy Ser Cys Leu GIu GIu Phe

1595 1600 1605

Arg Ser AIa Pro Phe IIe GIu Cys His GIy Arg GIy Thr Cys Asn

1610 1615 1620

Tyr Tyr AIa Asn AIa Tyr Ser Phe Trp Leu AIa Thr IIe GIu Arg

1625 1630 1635

Ser GIu Met Phe Lys Lys Pro Thr Pro Ser Thr Leu Lys AIa GIy

1640 1645 1650

GIu Leu Arg Thr His VaI Ser Arg Cys GIn VaI Cys Met Arg Arg

1655 1660 1665

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<223> 赖氨酸或无氨基酸
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<221> MISC_FEATURE
<222> (17)..(17)
<223> 苯丙氨酸或无氨基酸
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Xaa AIa IIe Ser Ser Pro Thr VaI Ser Arg Leu Thr Asp Thr Thr Lys
1               5                   10                  15
Xaa
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<210> 68
<211> 331
<212> PRT
<213> 人
<400> 68

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Met Thr AIa Lys Met GIu Thr Thr Phe Tyr Asp Asp AIa Leu Asn AIa
1               5                   10                  15
Ser Phe Leu Pro Ser GIu Ser GIy Pro Tyr GIy Tyr Ser Asn Pro Lys
            20                  25                  30
IIe Leu Lys GIn Ser Met Thr Leu Asn Leu AIa Asp Pro VaI GIy Ser
        35                  40                  45
Leu Lys Pro His Leu Arg AIa Lys Asn Ser Asp Leu Leu Thr Ser Pro
    50                  55                  60
Asp VaI GIy Leu Leu Lys Leu AIa Ser Pro GIu Leu GIu Arg Leu IIe
65                  70                  75                  80
IIe GIn Ser Ser Asn GIy His IIe Thr Thr Thr Pro Thr Pro Thr GIn
                85                  90                  95
Phe Leu Cys Pro Lys Asn VaI Thr Asp GIu GIn GIu GIy Phe AIa GIu
            100                 105                 110
GIy Phe VaI Arg AIa Leu AIa GIu Leu His Ser GIn Asn Thr Leu Pro
        115                 120                 125
Ser VaI Thr Ser AIa AIa GIn Pro VaI Asn GIy AIa GIy Met VaI AIa
    130                 135                 140
Pro AIa VaI AIa Ser VaI AIa GIy GIy Ser GIy Ser GIy GIy Phe Ser
145                 150                 155                 160
AIa Ser Leu His Ser GIu Pro Pro VaI Tyr AIa Asn Leu Ser Asn Phe
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165 170 175

Asn Pro GIy AIa Leu Ser Ser GIy GIy GIy AIa Pro Ser Tyr GIy AIa

180 185 190

AIa GIy Leu AIa Phe Pro AIa GIn Pro GIn GIn GIn GIn GIn Pro Pro

195 200 205

His His Leu Pro GIn GIn Met Pro VaI GIn His Pro Arg Leu GIn AIa

210 215 220

Leu Lys GIu GIu Pro GIn Thr VaI Pro GIu Met Pro GIy GIu Thr Pro

225 230 235 240

Pro Leu Ser Pro IIe Asp Met GIu Ser GIn GIu Arg IIe Lys AIa GIu

245 250 255

Arg Lys Arg Met Arg Asn Arg IIe AIa AIa Ser Lys Cys Arg Lys Arg

260 265 270

Lys Leu GIu Arg IIe AIa Arg Leu GIu GIu Lys VaI Lys Thr Leu Lys

275 280 285

AIa GIn Asn Ser GIu Leu AIa Ser Thr AIa Asn Met Leu Arg GIu GIn

290 295 300

VaI AIa GIn Leu Lys GIn Lys VaI Met Asn His VaI Asn Ser GIy Cys

305 310 315 320

GIn Leu Met Leu Thr GIn GIn Leu GIn Thr Phe

325 330

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<212> PRT

<213> 人工序列

<220>

<223> 合成

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<222> (1)..(1)

<223> 赖氨酸或无氨基酸

<220>

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<222> (8)..(8)

<223> 瓜氨酸

<220>

<221> MISC_FEATURE

<222> (21)..(21)

<223> 谷氨酸或无氨基酸

<400> 69

Xaa Thr GIy GIy AIa VaI Asp Xaa Leu Thr Asp Thr Ser Arg Tyr Thr
1 5 10 15

GIy Ser His Lys Xaa
20

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<211> 21

<212> PRT

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<222> (1)..(1)

<223> 赖氨酸或无氨基酸

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<223> 谷氨酸或无氨基酸

<400> 70

Xaa Thr GIy GIy AIa VaI Asp Arg Leu Thr Asp Thr Ser Arg Tyr Thr
1 5 10 15

GIy Ser His Lys Xaa
20

<210> 71

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<220>

<223> 合成

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<222> (1)..(1)

<223> 赖氨酸或无氨基酸

<220>

<221> MISC_FEATURE

<222> (21)..(21)

<223> 天冬酰胺或无氨基酸

<400> 71

Xaa Gly Ile Ala Gly Arg Gln Asp Ile Leu Asp Asp Ser Gly Tyr Val
1 5 10 15
Ser Ala Tyr Lys Xaa
20

<210> 72
<211> 195
<212> PRT
<213> 人
<400> 72

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

<210> 73
<211> 371
<212> PRT
<213> 人

<400> 73

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

Glu Ala Phe Lys Tyr Phe Leu Gln Gly Met Gly Tyr Met Ala Ser Ser
305 310 315 320
Cys Met Thr Arg Leu Ser Arg Ser Arg Thr Ala Ser Leu Thr Ser Ala
325 330 335
Ala Ser Val Asp Gly Asn Arg Ser Arg Ser Arg Thr Leu Ser Gln Ser
340 345 350
Ser Glu Ser Gly Thr Leu Ser Ser Gly Pro Pro Gly His Thr Met Glu
355 360 365
Val Ser Cys
370

<210> 74
<211> 18
<212> PRT
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<222> (18)..(18)
<223> 丝氨酸或无氨基酸
<400> 74
Xaa Thr Ala Ser Leu Thr Ser Ala Ala Ser Val Asp Gly Asn Arg Ser
1 5 10 15
Arg Xaa

<210> 75
<211> 92
<212> PRT
<213> 人
<400> 75
Met Ser Glu Leu Glu Lys Ala Met Val Ala Leu Ile Asp Val Phe His
1 5 10 15
Gln Tyr Ser Gly Arg Glu Gly Asp Lys His Lys Leu Lys Lys Ser Glu
20 25 30
Leu Lys Glu Leu Ile Asn Asn Glu Leu Ser His Phe Leu Glu Glu Ile
35 40 45

Lys Glu Gln Glu Val Val Asp Lys Val Met Glu Thr Leu Asp Asn Asp
50 55 60
Gly Asp Gly Glu Cys Asp Phe Gln Glu Phe Met Ala Phe Val Ala Met
65 70 75 80
Val Thr Thr Ala Cys His Glu Phe Phe Glu His Glu
85 90

<210> 76
<211> 434
<212> PRT
<213> 人
<400> 76

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

Glu Leu Val Lys Glu Ala Ile Asp Lys Ala Gly Tyr Thr Glu Lys Ile
225 230 235 240
Val Ile Gly Met Asp Val Ala Ala Ser Glu Phe Tyr Arg Asp Gly Lys
245 250 255
Tyr Asp Leu Asp Phe Lys Ser Pro Thr Asp Pro Ser Arg Tyr Ile Thr
260 265 270
Gly Asp Gln Leu Gly Ala Leu Tyr Gln Asp Phe Val Arg Asp Tyr Pro
275 280 285
Val Val Ser Ile Glu Asp Pro Phe Asp Gln Asp Asp Trp Ala Ala Trp
290 295 300
Ser Lys Phe Thr Ala Asn Val Gly Ile Gln Ile Val Gly Asp Asp Leu
305 310 315 320
Thr Val Thr Asn Pro Lys Arg Ile Glu Arg Ala Val Glu Glu Lys Ala
325 330 335
Cys Asn Cys Leu Leu Leu Lys Val Asn Gln Ile Gly Ser Val Thr Glu
340 345 350
Ala Ile Gln Ala Cys Lys Leu Ala Gln Glu Asn Gly Trp Gly Val Met
355 360 365
Val Ser His Arg Ser Gly Glu Thr Glu Asp Thr Phe Ile Ala Asp Leu
370 375 380
Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro Cys Arg
385 390 395 400
Ser Glu Arg Leu Ala Lys Tyr Asn Gln Leu Met Arg Ile Glu Glu Glu
405 410 415
Leu Gly Asp Glu Ala Arg Phe Ala Gly His Asn Phe Arg Asn Pro Ser
420 425 430
Val Leu

<210> 77
<211> 76
<212> PRT
<213> 人
<400> 77

Gln Pro Asp Ala Ile Asn Ala Pro Val Thr Cys Cys Tyr Asn Phe Thr
1 5 10 15
Asn Arg Lys Ile Ser Val Gln Arg Leu Ala Ser Tyr Arg Arg Ile Thr
20 25 30
Ser Ser Lys Cys Pro Lys Glu Ala Val Ile Phe Lys Thr Ile Val Ala
35 40 45
Lys Glu Ile Cys Ala Asp Pro Lys Gln Lys Trp Val Gln Asp Ser Met

50 55 60

Asp His Leu Asp Lys Gln Thr Gln Thr Pro Lys Thr
65 70 75

<210> 78

<211> 758

<212> PRT

<213> 人

<400> 78

Met Ala Glu Pro Arg Gln Glu Phe Glu Val Met Glu Asp His Ala Gly
1 5 10 15

Thr Tyr Gly Leu Gly Asp Arg Lys Asp Gln Gly Gly Tyr Thr Met His
20 25 30

Gln Asp Gln Glu Gly Asp Thr Asp Ala Gly Leu Lys Glu Ser Pro Leu
35 40 45

Gln Thr Pro Thr Glu Asp Gly Ser Glu Glu Pro Gly Ser Glu Thr Ser
50 55 60

Asp Ala Lys Ser Thr Pro Thr Ala Glu Asp Val Thr Ala Pro Leu Val
65 70 75 80

Asp Glu Gly Ala Pro Gly Lys Gln Ala Ala Ala Gln Pro His Thr Glu
85 90 95

Ile Pro Glu Gly Thr Thr Ala Glu Glu Ala Gly Ile Gly Asp Thr Pro
100 105 110

Ser Leu Glu Asp Glu Ala Ala Gly His Val Thr Gln Glu Pro Glu Ser
115 120 125

Gly Lys Val Val Gln Glu Gly Phe Leu Arg Glu Pro Gly Pro Pro Gly
130 135 140

Leu Ser His Gln Leu Met Ser Gly Met Pro Gly Ala Pro Leu Leu Pro
145 150 155 160

Glu Gly Pro Arg Glu Ala Thr Arg Gln Pro Ser Gly Thr Gly Pro Glu
165 170 175

Asp Thr Glu Gly Gly Arg His Ala Pro Glu Leu Leu Lys His Gln Leu
180 185 190

Leu Gly Asp Leu His Gln Glu Gly Pro Pro Leu Lys Gly Ala Gly Gly
195 200 205

Lys Glu Arg Pro Gly Ser Lys Glu Glu Val Asp Glu Asp Arg Asp Val
210 215 220

Asp Glu Ser Ser Pro Gln Asp Ser Pro Pro Ser Lys Ala Ser Pro Ala
225 230 235 240

Gln Asp Gly Arg Pro Pro Gln Thr Ala Ala Arg Glu Ala Thr Ser Ile

245 250 255

Pro Gly Phe Pro Ala Glu Gly Ala Ile Pro Leu Pro Val Asp Phe Leu
260 265 270

Ser Lys Val Ser Thr Glu Ile Pro Ala Ser Glu Pro Asp Gly Pro Ser
275 280 285

Val Gly Arg Ala Lys Gly Gln Asp Ala Pro Leu Glu Phe Thr Phe His
290 295 300

Val Glu Ile Thr Pro Asn Val Gln Lys Glu Gln Ala His Ser Glu Glu
305 310 315 320

His Leu Gly Arg Ala Ala Phe Pro Gly Ala Pro Gly Glu Gly Pro Glu
325 330 335

Ala Arg Gly Pro Ser Leu Gly Glu Asp Thr Lys Glu Ala Asp Leu Pro
340 345 350

Glu Pro Ser Glu Lys Gln Pro Ala Ala Ala Pro Arg Gly Lys Pro Val
355 360 365

Ser Arg Val Pro Gln Leu Lys Ala Arg Met Val Ser Lys Ser Lys Asp
370 375 380

Gly Thr Gly Ser Asp Asp Lys Lys Ala Lys Thr Ser Thr Arg Ser Ser
385 390 395 400

Ala Lys Thr Leu Lys Asn Arg Pro Cys Leu Ser Pro Lys His Pro Thr
405 410 415

Pro Gly Ser Ser Asp Pro Leu Ile Gln Pro Ser Ser Pro Ala Val Cys
420 425 430

Pro Glu Pro Pro Ser Ser Pro Lys Tyr Val Ser Ser Val Thr Ser Arg
435 440 445

Thr Gly Ser Ser Gly Ala Lys Glu Met Lys Leu Lys Gly Ala Asp Gly
450 455 460

Lys Thr Lys Ile Ala Thr Pro Arg Gly Ala Ala Pro Pro Gly Gln Lys
465 470 475 480

Gly Gln Ala Asn Ala Thr Arg Ile Pro Ala Lys Thr Pro Pro Ala Pro
485 490 495

Lys Thr Pro Pro Ser Ser Gly Glu Pro Pro Lys Ser Gly Asp Arg Ser
500 505 510

Gly Tyr Ser Ser Pro Gly Ser Pro Gly Thr Pro Gly Ser Arg Ser Arg
515 520 525

Thr Pro Ser Leu Pro Thr Pro Pro Thr Arg Glu Pro Lys Lys Val Ala
530 535 540

Val Val Arg Thr Pro Pro Lys Ser Pro Ser Ser Ala Lys Ser Arg Leu
545 550 555 560

Gln Thr Ala Pro Val Pro Met Pro Asp Leu Lys Asn Val Lys Ser Lys
565 570 575
Ile Gly Ser Thr Glu Asn Leu Lys His Gln Pro Gly Gly Gly Lys Val
580 585 590
Gln Ile Ile Asn Lys Lys Leu Asp Leu Ser Asn Val Gln Ser Lys Cys
595 600 605
Gly Ser Lys Asp Asn Ile Lys His Val Pro Gly Gly Gly Ser Val Gln
610 615 620
Ile Val Tyr Lys Pro Val Asp Leu Ser Lys Val Thr Ser Lys Cys Gly
625 630 635 640
Ser Leu Gly Asn Ile His His Lys Pro Gly Gly Gly Gln Val Glu Val
645 650 655
Lys Ser Glu Lys Leu Asp Phe Lys Asp Arg Val Gln Ser Lys Ile Gly
660 665 670
Ser Leu Asp Asn Ile Thr His Val Pro Gly Gly Gly Asn Lys Lys Ile
675 680 685
Glu Thr His Lys Leu Thr Phe Arg Glu Asn Ala Lys Ala Lys Thr Asp
690 695 700
His Gly Ala Glu Ile Val Tyr Lys Ser Pro Val Val Ser Gly Asp Thr
705 710 715 720
Ser Pro Arg His Leu Ser Asn Val Ser Ser Thr Gly Ser Ile Asp Met
725 730 735
Val Asp Ser Pro Gln Leu Ala Thr Leu Ala Asp Glu Val Ser Ala Ser
740 745 750
Leu Ala Lys Gln Gly Leu
755

<210> 79
<211> 543
<212> PRT
<213> 人
<400> 79

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

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

370 375 380
Glu Ile Ala Ala Tyr Arg Lys Leu Leu Glu Gly Glu Glu Thr Arg Leu
385 390 395 400
Ser Phe Thr Ser Val Gly Ser Ile Thr Ser Gly Tyr Ser Gln Ser Ser
405 410 415
Gln Val Phe Gly Arg Ser Ala Tyr Gly Gly Leu Gln Thr Ser Ser Tyr
420 425 430
Leu Met Ser Thr Arg Ser Phe Pro Ser Tyr Tyr Thr Ser His Val Gln
435 440 445
Glu Glu Gln Ile Glu Val Glu Glu Thr Ile Glu Ala Ala Lys Ala Glu
450 455 460
Glu Ala Lys Asp Glu Pro Pro Ser Glu Gly Glu Ala Glu Glu Glu Glu
465 470 475 480
Lys Asp Lys Glu Glu Ala Glu Glu Glu Glu Glu Ala Ala Glu Glu Glu Glu
485 490 495
Ala Ala Lys Glu Glu Ser Glu Glu Ala Lys Glu Glu Glu Glu Gly Gly
500 505 510
Glu Gly Glu Glu Gly Glu Glu Thr Lys Glu Ala Glu Glu Glu Glu Lys
515 520 525
Lys Val Glu Gly Ala Gly Glu Glu Gln Ala Ala Lys Lys Lys Asp
530 535 540

<210> 80
<211> 1026
<212> PRT
<213> 人
<400> 80

Met Met Ser Phe Gly Gly Ala Asp Ala Leu Leu Gly Ala Pro Phe Ala
1 5 10 15
Pro Leu His Gly Gly Gly Ser Leu His Tyr Ala Leu Ala Arg Lys Gly
20 25 30
Gly Ala Gly Gly Thr Arg Ser Ala Ala Gly Ser Ser Ser Gly Phe His
35 40 45
Ser Trp Thr Arg Thr Ser Val Ser Ser Val Ser Ala Ser Pro Ser Arg
50 55 60
Phe Arg Gly Ala Gly Ala Ala Ser Ser Thr Asp Ser Leu Asp Thr Leu
65 70 75 80
Ser Asn Gly Pro Glu Gly Cys Met Val Ala Val Ala Thr Ser Arg Ser
85 90 95
Glu Lys Glu Gln Leu Gln Ala Leu Asn Asp Arg Phe Ala Gly Tyr Ile

100 105 110

Asp Lys Val Arg Gln Leu Glu Ala His Asn Arg Ser Leu Glu Gly Glu

115 120 125

Ala Ala Ala Leu Arg Gln Gln Gln Ala Gly Arg Ser Ala Met Gly Glu

130 135 140

Leu Tyr Glu Arg Glu Val Arg Glu Met Arg Gly Ala Val Leu Arg Leu

145 150 155 160

Gly Ala Ala Arg Gly Gln Leu Arg Leu Glu Gln Glu His Leu Leu Glu

165 170 175

Asp Ile Ala His Val Arg Gln Arg Leu Asp Asp Glu Ala Arg Gln Arg

180 185 190

Glu Glu Ala Glu Ala Ala Ala Arg Ala Leu Ala Arg Phe Ala Gln Glu

195 200 205

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

210 215 220

Glu Glu Cys Gly Tyr Leu Arg Arg His His Gln Glu Glu Val Gly Glu

225 230 235 240

Leu Leu Gly Gln Ile Gln Gly Ser Gly Ala Ala Gln Ala Gln Met Gln

245 250 255

Ala Glu Thr Arg Asp Ala Leu Lys Cys Asp Val Thr Ser Ala Leu Arg

260 265 270

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

275 280 285

Ser Glu Glu Trp Phe Arg Val Arg Leu Asp Arg Leu Ser Glu Ala Ala

290 295 300

Lys Val Asn Thr Asp Ala Met Arg Ser Ala Gln Glu Glu Ile Thr Glu

305 310 315 320

Tyr Arg Arg Gln Leu Gln Ala Arg Thr Thr Glu Leu Glu Ala Leu Lys

325 330 335

Ser Thr Lys Asp Ser Leu Glu Arg Gln Arg Ser Glu Leu Glu Asp Arg

340 345 350

His Gln Ala Asp Ile Ala Ser Tyr Gln Glu Ala Ile Gln Gln Leu Asp

355 360 365

Ala Glu Leu Arg Asn Thr Lys Trp Glu Met Ala Ala Gln Leu Arg Glu

370 375 380

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

385 390 395 400

Ala Tyr Arg Lys Leu Leu Glu Gly Glu Glu Cys Arg Ile Gly Phe Gly

405 410 415

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

725 730 735
Lys Thr Pro Glu Lys Ala Lys Ser Pro Val Lys Glu Glu Ala Lys Ser
740 745 750
Pro Glu Lys Ala Lys Ser Pro Glu Lys Ala Lys Thr Leu Asp Val Lys
755 760 765
Ser Pro Glu Ala Lys Thr Pro Ala Lys Glu Glu Ala Arg Ser Pro Ala
770 775 780
Asp Lys Phe Pro Glu Lys Ala Lys Ser Pro Val Lys Glu Glu Val Lys
785 790 795 800
Ser Pro Glu Lys Ala Lys Ser Pro Leu Lys Glu Asp Ala Lys Ala Pro
805 810 815
Glu Lys Glu Ile Pro Lys Lys Glu Glu Val Lys Ser Pro Val Lys Glu
820 825 830
Glu Glu Lys Pro Gln Glu Val Lys Val Lys Glu Pro Pro Lys Lys Ala
835 840 845
Glu Glu Glu Lys Ala Pro Ala Thr Pro Lys Thr Glu Glu Lys Lys Asp
850 855 860
Ser Lys Lys Glu Glu Ala Pro Lys Lys Glu Ala Pro Lys Pro Lys Val
865 870 875 880
Glu Glu Lys Lys Glu Pro Ala Val Glu Lys Pro Lys Glu Ser Lys Val
885 890 895
Glu Ala Lys Lys Glu Glu Ala Glu Asp Lys Lys Lys Val Pro Thr Pro
900 905 910
Glu Lys Glu Ala Pro Ala Lys Val Glu Val Lys Glu Asp Ala Lys Pro
915 920 925
Lys Glu Lys Thr Glu Val Ala Lys Lys Glu Pro Asp Asp Ala Lys Ala
930 935 940
Lys Glu Pro Ser Lys Pro Ala Glu Lys Lys Glu Ala Ala Pro Glu Lys
945 950 955 960
Lys Asp Thr Lys Glu Glu Lys Ala Lys Lys Pro Glu Glu Lys Pro Lys
965 970 975
Thr Glu Ala Lys Ala Lys Glu Asp Asp Lys Thr Leu Ser Lys Glu Pro
980 985 990
Ser Lys Pro Lys Ala Glu Lys Ala Glu Lys Ser Ser Ser Thr Asp Gln
995 1000 1005
Lys Asp Ser Lys Pro Pro Glu Lys Ala Thr Glu Asp Lys Ala Ala
1010 1015 1020
Lys Gly Lys
1025

<210> 81
<211> 434
<212> PRT
<213> 人
<400> 81

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

Gly Asp Gln Leu Gly Ala Leu Tyr Gln Asp Phe Val Arg Asp Tyr Pro
275 280 285
Val Val Ser Ile Glu Asp Pro Phe Asp Gln Asp Asp Trp Ala Ala Trp
290 295 300
Ser Lys Phe Thr Ala Asn Val Gly Ile Gln Ile Val Gly Asp Asp Leu
305 310 315 320
Thr Val Thr Asn Pro Lys Arg Ile Glu Arg Ala Val Glu Glu Lys Ala
325 330 335
Cys Asn Cys Leu Leu Leu Lys Val Asn Gln Ile Gly Ser Val Thr Glu
340 345 350
Ala Ile Gln Ala Cys Lys Leu Ala Gln Glu Asn Gly Trp Gly Val Met
355 360 365
Val Ser His Arg Ser Gly Glu Thr Glu Asp Thr Phe Ile Ala Asp Leu
370 375 380
Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro Cys Arg
385 390 395 400
Ser Glu Arg Leu Ala Lys Tyr Asn Gln Leu Met Arg Ile Glu Glu Glu
405 410 415
Leu Gly Asp Glu Ala Arg Phe Ala Gly His Asn Phe Arg Asn Pro Ser
420 425 430
Val Leu

<210> 82
<211> 622
<212> PRT
<213> 人
<400> 82

Met Ala His Val Arg Gly Leu Gln Leu Pro Gly Cys Leu Ala Leu Ala
1 5 10 15
Ala Leu Cys Ser Leu Val His Ser Gln His Val Phe Leu Ala Pro Gln
20 25 30
Gln Ala Arg Ser Leu Leu Gln Arg Val Arg Arg Ala Asn Thr Phe Leu
35 40 45
Glu Glu Val Arg Lys Gly Asn Leu Glu Arg Glu Cys Val Glu Glu Thr
50 55 60
Cys Ser Tyr Glu Glu Ala Phe Glu Ala Leu Glu Ser Ser Thr Ala Thr
65 70 75 80
Asp Val Phe Trp Ala Lys Tyr Thr Ala Cys Glu Thr Ala Arg Thr Pro
85 90 95
Arg Asp Lys Leu Ala Ala Cys Leu Glu Gly Asn Cys Ala Glu Gly Leu

100 105 110

Gly Thr Asn Tyr Arg Gly His Val Asn Ile Thr Arg Ser Gly Ile Glu

115 120 125

Cys Gln Leu Trp Arg Ser Arg Tyr Pro His Lys Pro Glu Ile Asn Ser

130 135 140

Thr Thr His Pro Gly Ala Asp Leu Gln Glu Asn Phe Cys Arg Asn Pro

145 150 155 160

Asp Ser Ser Thr Thr Gly Pro Trp Cys Tyr Thr Thr Asp Pro Thr Val

165 170 175

Arg Arg Gln Glu Cys Ser Ile Pro Val Cys Gly Gln Asp Gln Val Thr

180 185 190

Val Ala Met Thr Pro Arg Ser Glu Gly Ser Ser Val Asn Leu Ser Pro

195 200 205

Pro Leu Glu Gln Cys Val Pro Asp Arg Gly Gln Gln Tyr Gln Gly Arg

210 215 220

Leu Ala Val Thr Thr His Gly Leu Pro Cys Leu Ala Trp Ala Ser Ala

225 230 235 240

Gln Ala Lys Ala Leu Ser Lys His Gln Asp Phe Asn Ser Ala Val Gln

245 250 255

Leu Val Glu Asn Phe Cys Arg Asn Pro Asp Gly Asp Glu Glu Gly Val

260 265 270

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

275 280 285

Asn Tyr Cys Glu Glu Ala Val Glu Glu Glu Thr Gly Asp Gly Leu Asp

290 295 300

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

305 310 315 320

Gln Thr Phe Phe Asn Pro Arg Thr Phe Gly Ser Gly Glu Ala Asp Cys

325 330 335

Gly Leu Arg Pro Leu Phe Glu Lys Lys Ser Leu Glu Asp Lys Thr Glu

340 345 350

Arg Glu Leu Leu Glu Ser Tyr Ile Asp Gly Arg Ile Val Glu Gly Ser

355 360 365

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

370 375 380

Ser Pro Gln Glu Leu Leu Cys Gly Ala Ser Leu Ile Ser Asp Arg Trp

385 390 395 400

Val Leu Thr Ala Ala His Cys Leu Leu Tyr Pro Pro Trp Asp Lys Asn

405 410 415

Phe Thr Glu Asn Asp Leu Leu Val Arg Ile Gly Lys His Ser Arg Thr
420 425 430
Arg Tyr Glu Arg Asn Ile Glu Lys Ile Ser Met Leu Glu Lys Ile Tyr
435 440 445
Ile His Pro Arg Tyr Asn Trp Arg Glu Asn Leu Asp Arg Asp Ile Ala
450 455 460
Leu Met Lys Leu Lys Lys Pro Val Ala Phe Ser Asp Tyr Ile His Pro
465 470 475 480
Val Cys Leu Pro Asp Arg Glu Thr Ala Ala Ser Leu Leu Gln Ala Gly
485 490 495
Tyr Lys Gly Arg Val Thr Gly Trp Gly Asn Leu Lys Glu Thr Trp Thr
500 505 510
Ala Asn Val Gly Lys Gly Gln Pro Ser Val Leu Gln Val Val Asn Leu
515 520 525
Pro Ile Val Glu Arg Pro Val Cys Lys Asp Ser Thr Arg Ile Arg Ile
530 535 540
Thr Asp Asn Met Phe Cys Ala Gly Tyr Lys Pro Asp Glu Gly Lys Arg
545 550 555 560
Gly Asp Ala Cys Glu Gly Asp Ser Gly Gly Pro Phe Val Met Lys Ser
565 570 575
Pro Phe Asn Asn Arg Trp Tyr Gln Met Gly Ile Val Ser Trp Gly Glu
580 585 590
Gly Cys Asp Arg Asp Gly Lys Tyr Gly Phe Tyr Thr His Val Phe Arg
595 600 605
Leu Lys Lys Trp Ile Gln Lys Val Ile Asp Gln Phe Gly Glu
610 615 620

<210> 83
<211> 885
<212> PRT
<213> 人
<400> 83

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

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

370 375 380
Asn Met Phe Asp Thr His Gln Ala Ala Arg Leu Leu Asn Leu Gly Arg
385 390 395 400
His Ser Leu Asp His Leu Leu Lys Leu Tyr Cys Asn Val Asp Ser Asn
405 410 415
Lys Gln Tyr Gln Leu Ala Asp Trp Arg Ile Arg Pro Leu Pro Glu Glu
420 425 430
Met Leu Ser Tyr Ala Arg Asp Asp Thr His Tyr Leu Leu Tyr Ile Tyr
435 440 445
Asp Lys Met Arg Leu Glu Met Trp Glu Arg Gly Asn Gly Gln Pro Val
450 455 460
Gln Leu Gln Val Val Trp Gln Arg Ser Arg Asp Ile Cys Leu Lys Lys
465 470 475 480
Phe Ile Lys Pro Ile Phe Thr Asp Glu Ser Tyr Leu Glu Leu Tyr Arg
485 490 495
Lys Gln Lys Lys His Leu Asn Thr Gln Gln Leu Thr Ala Phe Gln Leu
500 505 510
Leu Phe Ala Trp Arg Asp Lys Thr Ala Arg Arg Glu Asp Glu Ser Tyr
515 520 525
Gly Tyr Val Leu Pro Asn His Met Met Leu Lys Ile Ala Glu Glu Leu
530 535 540
Pro Lys Glu Pro Gln Gly Ile Ile Ala Cys Cys Asn Pro Val Pro Pro
545 550 555 560
Leu Val Arg Gln Gln Ile Asn Glu Met His Leu Leu Ile Gln Gln Ala
565 570 575
Arg Glu Met Pro Leu Leu Lys Ser Glu Val Ala Ala Gly Val Lys Lys
580 585 590
Ser Gly Pro Leu Pro Ser Ala Glu Arg Leu Glu Asn Val Leu Phe Gly
595 600 605
Pro His Asp Cys Ser His Ala Pro Pro Asp Gly Tyr Pro Ile Ile Pro
610 615 620
Thr Ser Gly Ser Val Pro Val Gln Lys Gln Ala Ser Leu Phe Pro Asp
625 630 635 640
Glu Lys Glu Asp Asn Leu Leu Gly Thr Thr Cys Leu Ile Ala Thr Ala
645 650 655
Val Ile Thr Leu Phe Asn Glu Pro Ser Ala Glu Asp Ser Lys Lys Gly
660 665 670
Pro Leu Thr Val Ala Gln Lys Lys Ala Gln Asn Ile Met Glu Ser Phe
675 680 685

Glu Asn Pro Phe Arg Met Phe Leu Pro Ser Leu Gly His Arg Ala Pro
690 695 700
Val Ser Gln Ala Ala Lys Phe Asp Pro Ser Thr Lys Ile Tyr Glu Ile
705 710 715 720
Ser Asn Arg Trp Lys Leu Ala Gln Val Gln Val Gln Lys Asp Ser Lys
725 730 735
Glu Ala Val Lys Lys Lys Ala Ala Glu Gln Thr Ala Ala Arg Glu Gln
740 745 750
Ala Lys Glu Ala Cys Lys Ala Ala Ala Glu Gln Ala Ile Ser Val Arg
755 760 765
Gln Gln Val Val Leu Glu Asn Ala Ala Lys Lys Arg Glu Arg Ala Thr
770 775 780
Ser Asp Pro Arg Thr Thr Glu Gln Lys Gln Glu Lys Lys Arg Leu Lys
785 790 795 800
Ile Ser Lys Lys Pro Lys Asp Pro Glu Pro Pro Glu Lys Glu Phe Thr
805 810 815
Pro Tyr Asp Tyr Ser Gln Ser Asp Phe Lys Ala Phe Ala Gly Asn Ser
820 825 830
Lys Ser Lys Val Ser Ser Gln Phe Asp Pro Asn Lys Gln Thr Pro Ser
835 840 845
Gly Lys Lys Cys Ile Ala Ala Lys Lys Ile Lys Gln Ser Val Gly Asn
850 855 860
Lys Ser Met Ser Phe Pro Thr Gly Lys Ser Asp Arg Gly Phe Arg Tyr
865 870 875 880
Asn Trp Pro Gln Arg
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<210> 84
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Val Leu Glu Thr Ala Glu Glu Ile Gln Glu Arg Arg Gln Glu Val Leu
20 25 30
Thr Arg Tyr Gln Ser Phe Lys Glu Arg Val Ala Glu Arg Gly Gln Lys
35 40 45
Leu Glu Asp Ser Tyr His Leu Gln Val Phe Lys Arg Asp Ala Asp Asp
50 55 60

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

370 375 380

Trp Met Asn Glu Lys Thr Ala Ala Ile Asn Ala Asp Glu Leu Pro Thr
385 390 395 400

Asp Val Ala Gly Gly Glu Val Leu Leu Asp Arg His Gln Gln His Lys
405 410 415

His Glu Ile Asp Ser Tyr Asp Asp Arg Phe Gln Ser Ala Asp Glu Thr
420 425 430

Gly Gln Asp Leu Val Asn Ala Asn His Glu Ala Ser Asp Glu Val Arg
435 440 445

Glu Lys Met Glu Ile Leu Asp Asn Asn Trp Thr Ala Leu Leu Glu Leu
450 455 460

Trp Asp Glu Arg His Arg Gln Tyr Glu Gln Cys Leu Asp Phe His Leu
465 470 475 480

Phe Tyr Arg Asp Ser Glu Gln Val Asp Ser Trp Met Ser Arg Gln Glu
485 490 495

Ala Phe Leu Glu Asn Glu Asp Leu Gly Asn Ser Leu Gly Ser Ala Glu
500 505 510

Ala Leu Leu Gln Lys His Glu Asp Phe Glu Glu Ala Phe Thr Ala Gln
515 520 525

Glu Glu Lys Ile Ile Thr Val Asp Lys Thr Ala Thr Lys Leu Ile Gly
530 535 540

Asp Asp His Tyr Asp Ser Glu Asn Ile Lys Ala Ile Arg Asp Gly Leu
545 550 555 560

Leu Ala Arg Arg Asp Ala Leu Arg Glu Lys Ala Ala Thr Arg Arg Arg
565 570 575

Leu Leu Lys Glu Ser Leu Leu Leu Gln Lys Leu Tyr Glu Asp Ser Asp
580 585 590

Asp Leu Lys Asn Trp Ile Asn Lys Lys Lys Lys Leu Ala Asp Asp Glu
595 600 605

Asp Tyr Lys Asp Ile Gln Asn Leu Lys Ser Arg Val Gln Lys Gln Gln
610 615 620

Val Phe Glu Lys Glu Leu Ala Val Asn Lys Thr Gln Leu Glu Asn Ile
625 630 635 640

Gln Lys Thr Gly Gln Glu Met Ile Glu Gly Gly His Tyr Ala Ser Asp
645 650 655

Asn Val Thr Thr Arg Leu Ser Glu Val Ala Ser Leu Trp Glu Glu Leu
660 665 670

Leu Glu Ala Thr Lys Gln Lys Gly Thr Gln Leu His Glu Ala Asn Gln
675 680 685

Gln Leu Gln Phe Glu Asn Asn Ala Glu Asp Leu Gln Arg Trp Leu Glu
690 695 700
Asp Val Glu Trp Gln Val Thr Ser Glu Asp Tyr Gly Lys Gly Leu Ala
705 710 715 720
Glu Val Gln Asn Arg Leu Arg Lys His Gly Leu Leu Glu Ser Ala Val
725 730 735
Ala Ala Arg Gln Asp Gln Val Asp Ile Leu Thr Asp Leu Ala Ala Tyr
740 745 750
Phe Glu Glu Ile Gly His Pro Asp Ser Lys Asp Ile Arg Ala Arg Gln
755 760 765
Glu Ser Leu Val Cys Arg Phe Glu Ala Leu Lys Glu Pro Leu Ala Thr
770 775 780
Arg Lys Lys Lys Leu Leu Asp Leu Leu His Leu Gln Leu Ile Cys Arg
785 790 795 800
Asp Thr Glu Asp Glu Glu Ala Trp Ile Gln Glu Thr Glu Pro Ser Ala
805 810 815
Thr Ser Thr Tyr Leu Gly Lys Asp Leu Ile Ala Ser Lys Lys Leu Leu
820 825 830
Asn Arg His Arg Val Ile Leu Glu Asn Ile Ala Ser His Glu Pro Arg
835 840 845
Ile Gln Glu Ile Thr Glu Arg Gly Asn Lys Met Val Glu Glu Gly His
850 855 860
Phe Ala Ala Glu Asp Val Ala Ser Arg Val Lys Ser Leu Asn Gln Asn
865 870 875 880
Met Glu Ser Leu Arg Ala Arg Ala Ala Arg Arg Gln Asn Asp Leu Glu
885 890 895
Ala Asn Val Gln Phe Gln Gln Tyr Leu Ala Asp Leu His Glu Ala Glu
900 905 910
Thr Trp Ile Arg Glu Lys Glu Pro Ile Val Asp Asn Thr Asn Tyr Gly
915 920 925
Ala Asp Glu Glu Ala Ala Gly Ala Leu Leu Lys Lys His Glu Ala Phe
930 935 940
Leu Leu Asp Leu Asn Ser Phe Gly Asp Ser Met Lys Ala Leu Arg Asn
945 950 955 960
Gln Ala Asn Ala Cys Gln Gln Gln Gln Ala Ala Pro Val Glu Gly Val
965 970 975
Ala Gly Glu Gln Arg Val Met Ala Leu Tyr Asp Phe Gln Ala Arg Ser
980 985 990
Pro Arg Glu Val Thr Met Lys Lys Gly Asp Val Leu Thr Leu Leu Ser

995 1000 1005

Ser Ile Asn Lys Asp Trp Trp Lys Val Glu Ala Ala Asp His Gln

1010 1015 1020

Gly Ile Val Pro Ala Val Tyr Val Arg Arg Leu Ala His Asp Glu

1025 1030 1035

Phe Pro Met Leu Pro Gln Arg Arg Arg Glu Glu Pro Gly Asn Ile

1040 1045 1050

Thr Gln Arg Gln Glu Gln Ile Glu Asn Gln Tyr Arg Ser Leu Leu

1055 1060 1065

Asp Arg Ala Glu Glu Arg Arg Arg Arg Leu Leu Gln Arg Tyr Asn

1070 1075 1080

Glu Phe Leu Leu Ala Tyr Glu Ala Gly Asp Met Leu Glu Trp Ile

1085 1090 1095

Gln Glu Lys Lys Ala Glu Asn Thr Gly Val Glu Leu Asp Asp Val

1100 1105 1110

Trp Glu Leu Gln Lys Lys Phe Asp Glu Phe Gln Lys Asp Leu Asn

1115 1120 1125

Thr Asn Glu Pro Arg Leu Arg Asp Ile Asn Lys Val Ala Asp Asp

1130 1135 1140

Leu Leu Phe Glu Gly Leu Leu Thr Pro Glu Gly Ala Gln Ile Arg

1145 1150 1155

Gln Glu Leu Asn Ser Arg Trp Gly Ser Leu Gln Arg Leu Ala Asp

1160 1165 1170

Glu Gln Arg Gln Leu Leu Gly Ser Ala His Ala Val Glu Val Phe

1175 1180 1185

His Arg Glu Ala Asp Asp Thr Lys Glu Gln Ile Glu Lys Lys Cys

1190 1195 1200

Gln Ala Leu Ser Ala Ala Asp Pro Gly Ser Asp Leu Phe Ser Val

1205 1210 1215

Gln Ala Leu Gln Arg Arg His Glu Gly Phe Glu Arg Asp Leu Val

1220 1225 1230

Pro Leu Gly Asp Lys Val Thr Ile Leu Gly Glu Thr Ala Glu Arg

1235 1240 1245

Leu Ser Glu Ser His Pro Asp Ala Thr Glu Asp Leu Gln Arg Gln

1250 1255 1260

Lys Met Glu Leu Asn Glu Ala Trp Glu Asp Leu Gln Gly Arg Thr

1265 1270 1275

Lys Asp Arg Lys Glu Ser Leu Asn Glu Ala Gln Lys Phe Tyr Leu

1280 1285 1290

Phe Leu Ser Lys Ala Arg Asp Leu Gln Asn Trp Ile Ser Ser Ile
1295 1300 1305
Gly Gly Met Val Ser Ser Gln Glu Leu Ala Glu Asp Leu Thr Gly
1310 1315 1320
Ile Glu Ile Leu Leu Glu Arg His Gln Glu His Arg Ala Asp Met
1325 1330 1335
Glu Ala Glu Ala Pro Thr Phe Gln Ala Leu Glu Asp Phe Ser Ala
1340 1345 1350
Glu Leu Ile Asp Ser Gly His His Ala Ser Pro Glu Ile Glu Lys
1355 1360 1365
Lys Leu Gln Ala Val Lys Leu Glu Arg Asp Asp Leu Glu Lys Ala
1370 1375 1380
Trp Glu Lys Arg Lys Lys Ile Leu Asp Gln Cys Leu Glu Leu Gln
1385 1390 1395
Met Phe Gln Gly Asn Cys Asp Gln Val Glu Ser Trp Met Val Ala
1400 1405 1410
Arg Glu Asn Ser Leu Arg Ser Asp Asp Lys Ser Ser Leu Asp Ser
1415 1420 1425
Leu Glu Ala Leu Met Lys Lys Arg Asp Asp Leu Asp Lys Ala Ile
1430 1435 1440
Thr Ala Gln Glu Gly Lys Ile Thr Asp Leu Glu His Phe Ala Glu
1445 1450 1455
Ser Leu Ile Ala Asp Glu His Tyr Ala Lys Glu Glu Ile Ala Thr
1460 1465 1470
Arg Leu Gln Arg Val Leu Asp Arg Trp Lys Ala Leu Lys Ala Gln
1475 1480 1485
Leu Ile Asp Glu Arg Thr Lys Leu Gly Asp Tyr Ala Asn Leu Lys
1490 1495 1500
Gln Phe Tyr Arg Asp Leu Glu Glu Leu Glu Glu Trp Ile Ser Glu
1505 1510 1515
Met Leu Pro Thr Ala Cys Asp Glu Ser Tyr Lys Asp Ala Thr Asn
1520 1525 1530
Ile Gln Arg Lys Tyr Leu Lys His Gln Thr Phe Ala His Glu Val
1535 1540 1545
Asp Gly Arg Ser Glu Gln Val His Gly Val Ile Asn Leu Gly Asn
1550 1555 1560
Ser Leu Ile Glu Cys Ser Ala Cys Asp Gly Asn Glu Glu Ala Met
1565 1570 1575
Lys Glu Gln Leu Glu Gln Leu Lys Glu His Trp Asp His Leu Leu

1580 1585 1590

Glu Arg Thr Asn Asp Lys Gly Lys Lys Leu Asn Glu Ala Ser Arg

1595 1600 1605

Gln Gln Arg Phe Asn Thr Ser Ile Arg Asp Phe Glu Phe Trp Leu

1610 1615 1620

Ser Glu Ala Glu Thr Leu Leu Ala Met Lys Asp Gln Ala Arg Asp

1625 1630 1635

Leu Ala Ser Ala Gly Asn Leu Leu Lys Lys His Gln Leu Leu Glu

1640 1645 1650

Arg Glu Met Leu Ala Arg Glu Asp Ala Leu Lys Asp Leu Asn Thr

1655 1660 1665

Leu Ala Glu Asp Leu Leu Ser Ser Gly Thr Phe Asn Val Asp Gln

1670 1675 1680

Ile Val Lys Lys Lys Asp Asn Val Asn Lys Arg Phe Leu Asn Val

1685 1690 1695

Gln Glu Leu Ala Ala Ala His His Glu Lys Leu Lys Glu Ala Tyr

1700 1705 1710

Ala Leu Phe Gln Phe Phe Gln Asp Leu Asp Asp Glu Glu Ser Trp

1715 1720 1725

Ile Glu Glu Lys Leu Ile Arg Val Ser Ser Gln Asp Tyr Gly Arg

1730 1735 1740

Asp Leu Gln Gly Val Gln Asn Leu Leu Lys Lys His Lys Arg Leu

1745 1750 1755

Glu Gly Glu Leu Val Ala His Glu Pro Ala Ile Gln Asn Val Leu

1760 1765 1770

Asp Met Ala Glu Lys Leu Lys Asp Lys Ala Ala Val Gly Gln Glu

1775 1780 1785

Glu Ile Gln Leu Arg Leu Ala Gln Phe Val Glu His Trp Glu Lys

1790 1795 1800

Leu Lys Glu Leu Ala Lys Ala Arg Gly Leu Lys Leu Glu Glu Ser

1805 1810 1815

Leu Glu Tyr Leu Gln Phe Met Gln Asn Ala Glu Glu Glu Glu Ala

1820 1825 1830

Trp Ile Asn Glu Lys Asn Ala Leu Ala Val Arg Gly Asp Cys Gly

1835 1840 1845

Asp Thr Leu Ala Ala Thr Gln Ser Leu Leu Met Lys His Glu Ala

1850 1855 1860

Leu Glu Asn Asp Phe Ala Val His Glu Thr Arg Val Gln Asn Val

1865 1870 1875

Cys Ala Gln Gly Glu Asp Ile Leu Asn Lys Val Leu Gln Glu Glu
1880 1885 1890
Ser Gln Asn Lys Glu Ile Ser Ser Lys Ile Glu Ala Leu Asn Glu
1895 1900 1905
Lys Thr Pro Ser Leu Ala Lys Ala Ile Ala Ala Trp Lys Leu Gln
1910 1915 1920
Leu Glu Asp Asp Tyr Ala Phe Gln Glu Phe Asn Trp Lys Ala Asp
1925 1930 1935
Val Val Glu Ala Trp Ile Ala Asp Lys Glu Thr Ser Leu Lys Thr
1940 1945 1950
Asn Gly Asn Gly Ala Asp Leu Gly Asp Phe Leu Thr Leu Leu Ala
1955 1960 1965
Lys Gln Asp Thr Leu Asp Ala Ser Leu Gln Ser Phe Gln Gln Glu
1970 1975 1980
Arg Leu Pro Glu Ile Thr Asp Leu Lys Asp Lys Leu Ile Ser Ala
1985 1990 1995
Gln His Asn Gln Ser Lys Ala Ile Glu Glu Arg Tyr Ala Ala Leu
2000 2005 2010
Leu Lys Arg Trp Glu Gln Leu Leu Glu Ala Ser Ala Val His Arg
2015 2020 2025
Gln Lys Leu Leu Glu Lys Gln Leu Pro Leu Gln Lys Ala Glu Asp
2030 2035 2040
Leu Phe Val Glu Phe Ala His Lys Ala Ser Ala Leu Asn Asn Trp
2045 2050 2055
Cys Glu Lys Met Glu Glu Asn Leu Ser Glu Pro Val His Cys Val
2060 2065 2070
Ser Leu Asn Glu Ile Arg Gln Leu Gln Lys Asp His Glu Asp Phe
2075 2080 2085
Leu Ala Ser Leu Ala Arg Ala Gln Ala Asp Phe Lys Cys Leu Leu
2090 2095 2100
Glu Leu Asp Gln Gln Ile Lys Ala Leu Gly Val Pro Ser Ser Pro
2105 2110 2115
Tyr Thr Trp Leu Thr Val Glu Val Leu Glu Arg Thr Trp Lys His
2120 2125 2130
Leu Ser Asp Ile Ile Glu Glu Arg Glu Gln Glu Leu Gln Lys Glu
2135 2140 2145
Glu Ala Arg Gln Val Lys Asn Phe Glu Met Cys Gln Glu Phe Glu
2150 2155 2160
Gln Asn Ala Ser Thr Phe Leu Gln Trp Ile Leu Glu Thr Arg Ala

2165 2170 2175

Tyr Phe Leu Asp Gly Ser Leu Leu Lys Glu Thr Gly Thr Leu Glu

2180 2185 2190

Ser Gln Leu Glu Ala Asn Lys Arg Lys Gln Lys Glu Ile Gln Ala

2195 2200 2205

Met Lys Arg Gln Leu Thr Lys Ile Val Asp Leu Gly Asp Asn Leu

2210 2215 2220

Glu Asp Ala Leu Ile Leu Asp Ile Lys Tyr Ser Thr Ile Gly Leu

2225 2230 2235

Ala Gln Gln Trp Asp Gln Leu Tyr Gln Leu Gly Leu Arg Met Gln

2240 2245 2250

His Asn Leu Glu Gln Gln Ile Gln Ala Lys Asp Ile Lys Gly Val

2255 2260 2265

Ser Glu Glu Thr Leu Lys Glu Phe Ser Thr Ile Tyr Lys His Phe

2270 2275 2280

Asp Glu Asn Leu Thr Gly Arg Leu Thr His Lys Glu Phe Arg Ser

2285 2290 2295

Cys Leu Arg Gly Leu Asn Tyr Tyr Leu Pro Met Val Glu Glu Asp

2300 2305 2310

Glu His Glu Pro Lys Phe Glu Lys Phe Leu Asp Ala Val Asp Pro

2315 2320 2325

Gly Arg Lys Gly Tyr Val Ser Leu Glu Asp Tyr Thr Ala Phe Leu

2330 2335 2340

Ile Asp Lys Glu Ser Glu Asn Ile Lys Ser Ser Asp Glu Ile Glu

2345 2350 2355

Asn Ala Phe Gln Ala Leu Ala Glu Gly Lys Ser Tyr Ile Thr Lys

2360 2365 2370

Glu Asp Met Lys Gln Ala Leu Thr Pro Glu Gln Val Ser Phe Cys

2375 2380 2385

Ala Thr His Met Gln Gln Tyr Met Asp Pro Arg Gly Arg Ser His

2390 2395 2400

Leu Ser Gly Tyr Asp Tyr Val Gly Phe Thr Asn Ser Tyr Phe Gly

2405 2410 2415

Asn

<210> 85

<211> 745

<212> PRT

<213> 人

<400> 85

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

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

Lys Leu Ala Arg Lys Leu Met Glu Gln Tyr Gly Thr Pro Asn Asn Ile
625 630 635 640
Asp Ile Trp Met Gly Gly Val Ser Glu Pro Leu Lys Arg Lys Gly Arg
645 650 655
Val Gly Pro Leu Leu Ala Cys Ile Ile Gly Thr Gln Phe Arg Lys Leu
660 665 670
Arg Asp Gly Asp Arg Phe Trp Trp Glu Asn Glu Gly Val Phe Ser Met
675 680 685
Gln Gln Arg Gln Ala Leu Ala Gln Ile Ser Leu Pro Arg Ile Ile Cys
690 695 700
Asp Asn Thr Gly Ile Thr Thr Val Ser Lys Asn Asn Ile Phe Met Ser
705 710 715 720
Asn Ser Tyr Pro Arg Asp Phe Val Asn Cys Ser Thr Leu Pro Ala Leu
725 730 735
Asn Leu Ala Ser Trp Arg Glu Ala Ser
740 745

<210> 86
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Met Ser Leu Gln Phe Ile Gly Leu Gln Arg Arg Asp Val Val Ala Leu
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Val Asn Phe Leu Arg His Leu Thr Gln Lys Pro Asp Val Asp Leu Glu
20 25 30
Ala His Pro Lys Ile Leu Lys Lys Cys Gly Glu Lys Arg Leu His Arg
35 40 45
Arg Thr Val Leu Phe Asn Glu Leu Met Leu Trp Leu Gly Tyr Tyr Arg
50 55 60
Glu Leu Arg Phe His Asn Pro Asp Leu Ser Ser Val Leu Glu Glu Phe
65 70 75 80
Glu Val Arg Cys Val Ala Val Ala Arg Arg Gly Tyr Thr Tyr Pro Phe
85 90 95
Gly Asp Arg Gly Lys Ala Arg Asp His Leu Ala Val Leu Asp Arg Thr
100 105 110
Glu Phe Asp Thr Asp Val Arg His Asp Ala Glu Ile Val Glu Arg Ala
115 120 125
Leu Val Ser Ala Val Ile Leu Ala Lys Met Ser Val Arg Glu Thr Leu
130 135 140

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

450 455 460

Phe Ser Gly Leu Leu Ser Ser Gly Ser Gln Lys Pro Thr Ser Gly Pro
465 470 475 480

Leu Asn Ile Pro Gln Gln Gln Gln Arg His Ala Ala Phe Ser Leu Val
485 490 495

Ser Pro Gln Val Thr Lys Ala Ser Pro Gly Arg Val Arg Arg Asp Ser
500 505 510

Ala Trp Asp Val Arg Pro Leu Thr Glu Thr Arg Gly Asp Leu Phe Ser
515 520 525

Gly Asp Glu Asp Ser Asp Ser Ser Asp Gly Tyr Pro Pro Asn Arg Gln
530 535 540

Asp Pro Arg Phe Thr Asp Thr Leu Val Asp Ile Thr Asp Thr Glu Thr
545 550 555 560

Ser Ala Lys Pro Pro Val Thr Thr Ala Tyr Lys Phe Glu Gln Pro Thr
565 570 575

Leu Thr Phe Gly Ala Gly Val Asn Val Pro Ala Gly Ala Gly Ala Ala
580 585 590

Ile Leu Thr Pro Thr Pro Val Asn Pro Ser Thr Ala Pro Ala Pro Ala
595 600 605

Pro Thr Pro Thr Phe Ala Gly Thr Gln Thr Pro Val Asn Gly Asn Ser
610 615 620

Pro Trp Ala Pro Thr Ala Pro Leu Pro Gly Asp Met Asn Pro Ala Asn
625 630 635 640

Trp Pro Arg Glu Arg Ala Trp Ala Leu Lys Asn Pro His Leu Ala Tyr
645 650 655

Asn Pro Phe Arg Met Pro Thr Thr Ser Thr Ala Ser Gln Asn Thr Val
660 665 670

Ser Thr Thr Pro Arg Arg Pro Ser Thr Pro Arg Ala Ala Val Thr Gln
675 680 685

Thr Ala Ser Arg Asp Ala Ala Asp Glu Val Trp Ala Leu Arg Asp Gln
690 695 700

Thr Ala Glu Ser Pro Val Glu Asp Ser Glu Glu Glu Asp Asp Asp Ser
705 710 715 720

Ser Asp Thr Gly Ser Val Val Ser Leu Gly His Thr Thr Pro Ser Ser
725 730 735

Asp Tyr Asn Asn Asp Val Ile Ser Pro Pro Ser Gln Thr Pro Glu Gln
740 745 750

Ser Thr Pro Ser Arg Ile Arg Lys Ala Lys Leu Ser Ser Pro Met Thr
755 760 765

Thr Thr Ser Thr Ser Gln Lys Pro Val Leu Gly Lys Arg Val Ala Thr
770 775 780
Pro His Ala Ser Ala Arg Ala Gln Thr Val Thr Ser Thr Pro Val Gln
785 790 795 800
Gly Arg Leu Glu Lys Gln Val Ser Gly Thr Pro Ser Thr Val Pro Ala
805 810 815
Thr Leu Leu Gln Pro Gln Pro Ala Ser Ser Lys Thr Thr Ser Ser Arg
820 825 830
Asn Val Thr Ser Gly Ala Gly Thr Ser Ser Ala Ser Ser Ala Arg Gln
835 840 845
Pro Ser Ala Ser Ala Ser Val Leu Ser Pro Thr Glu Asp Asp Val Val
850 855 860
Ser Pro Ala Thr Ser Pro Leu Ser Met Leu Ser Ser Ala Ser Pro Ser
865 870 875 880
Pro Ala Lys Ser Ala Pro Pro Ser Pro Val Lys Gly Arg Gly Ser Arg
885 890 895
Val Gly Val Pro Ser Leu Lys Pro Thr Leu Gly Gly Lys Ala Val Val
900 905 910
Gly Arg Pro Pro Ser Val Pro Val Ser Gly Ser Ala Pro Gly Arg Leu
915 920 925
Ser Gly Ser Ser Arg Ala Ala Ser Thr Thr Pro Thr Tyr Pro Ala Val
930 935 940
Thr Thr Val Tyr Pro Pro Ser Ser Thr Ala Lys Ser Ser Val Ser Asn
945 950 955 960
Ala Pro Pro Val Ala Ser Pro Ser Ile Leu Lys Pro Gly Ala Ser Ala
965 970 975
Ala Leu Gln Ser Arg Arg Ser Thr Gly Thr Ala Ala Val Gly Ser Pro
980 985 990
Val Lys Ser Thr Thr Gly Met Lys Thr Val Ala Phe Asp Leu Ser Ser
995 1000 1005
Pro Gln Lys Ser Gly Thr Gly Pro Gln Pro Gly Ser Ala Gly Met
1010 1015 1020
Gly Gly Ala Lys Thr Pro Ser Asp Ala Val Gln Asn Ile Leu Gln
1025 1030 1035
Lys Ile Glu Lys Ile Lys Asn Thr Glu Glu
1040 1045

<210> 87
<211> 812
<212> PRT

<213> 人

<400> 87

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

290 295 300

Arg Ser Trp Thr Trp Pro Glu Gly Pro Glu Gln Thr Leu Arg Cys Glu
305 310 315 320

Ala Arg Gly Asn Pro Glu Pro Ser Val His Cys Ala Arg Ser Asp Gly
325 330 335

Gly Ala Val Leu Ala Leu Gly Leu Leu Gly Pro Val Thr Arg Ala Leu
340 345 350

Ser Gly Thr Tyr Arg Cys Lys Ala Ala Asn Asp Gln Gly Glu Ala Val
355 360 365

Lys Asp Val Thr Leu Thr Val Glu Tyr Ala Pro Ala Leu Asp Ser Val
370 375 380

Gly Cys Pro Glu Arg Ile Thr Trp Leu Glu Gly Thr Glu Ala Ser Leu
385 390 395 400

Ser Cys Val Ala His Gly Val Pro Pro Pro Asp Val Ile Cys Val Arg
405 410 415

Ser Gly Glu Leu Gly Ala Val Ile Glu Gly Leu Leu Arg Val Ala Arg
420 425 430

Glu His Ala Gly Thr Tyr Arg Cys Glu Ala Thr Asn Pro Arg Gly Ser
435 440 445

Ala Ala Lys Asn Val Ala Val Thr Val Glu Tyr Gly Pro Arg Phe Glu
450 455 460

Glu Pro Ser Cys Pro Ser Asn Trp Thr Trp Val Glu Gly Ser Gly Arg
465 470 475 480

Leu Phe Ser Cys Glu Val Asp Gly Lys Pro Gln Pro Ser Val Lys Cys
485 490 495

Val Gly Ser Gly Gly Ala Thr Glu Gly Val Leu Leu Pro Leu Ala Pro
500 505 510

Pro Asp Pro Ser Pro Arg Ala Pro Arg Ile Pro Arg Val Leu Ala Pro
515 520 525

Gly Ile Tyr Val Cys Asn Ala Thr Asn Arg His Gly Ser Val Ala Lys
530 535 540

Thr Val Val Val Ser Ala Glu Ser Pro Pro Glu Met Asp Glu Ser Thr
545 550 555 560

Cys Pro Ser His Gln Thr Trp Leu Glu Gly Ala Glu Ala Ser Ala Leu
565 570 575

Ala Cys Ala Ala Arg Gly Arg Pro Ser Pro Gly Val Arg Cys Ser Arg
580 585 590

Glu Gly Ile Pro Trp Pro Glu Gln Gln Arg Val Ser Arg Glu Asp Ala
595 600 605

Gly Thr Tyr His Cys Val Ala Thr Asn Ala His Gly Thr Asp Ser Arg
610 615 620
Thr Val Thr Val Gly Val Glu Tyr Arg Pro Val Val Ala Glu Leu Ala
625 630 635 640
Ala Ser Pro Pro Gly Gly Val Arg Pro Gly Gly Asn Phe Thr Leu Thr
645 650 655
Cys Arg Ala Glu Ala Trp Pro Pro Ala Gln Ile Ser Trp Arg Ala Pro
660 665 670
Pro Gly Ala Leu Asn Ile Gly Leu Ser Ser Asn Asn Ser Thr Leu Ser
675 680 685
Val Ala Gly Ala Met Gly Ser His Gly Gly Glu Tyr Glu Cys Ala Ala
690 695 700
Thr Asn Ala His Gly Arg His Ala Arg Arg Ile Thr Val Arg Val Ala
705 710 715 720
Gly Pro Trp Leu Trp Val Ala Val Gly Gly Ala Ala Gly Gly Ala Ala
725 730 735
Leu Leu Ala Ala Gly Ala Gly Leu Ala Phe Tyr Val Gln Ser Thr Ala
740 745 750
Cys Lys Lys Gly Glu Tyr Asn Val Gln Glu Ala Glu Ser Ser Gly Glu
755 760 765
Ala Val Cys Leu Asn Gly Ala Gly Gly Gly Ala Gly Gly Ala Ala Gly
770 775 780
Ala Glu Gly Gly Pro Glu Ala Ala Gly Gly Ala Ala Glu Ser Pro Ala
785 790 795 800
Glu Gly Glu Val Phe Ala Ile Gln Leu Thr Ser Ala
805 810

<210> 88
<211> 342
<212> PRT
<213> 人
<400> 88

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

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

<210> 89
<211> 1827
<212> PRT

<213> 人

<400> 89

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

290 295 300

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

Met Ser Pro Met His Lys Asn Gly Asp Lys Glu Phe Gln Thr Gly Lys
610 615 620
Glu Ser Gln Pro Ser Pro Pro Ala Gln Glu Ala Gly Tyr Ser Thr Leu
625 630 635 640
Ala Gln Ser Tyr Pro Ser Asp Leu Pro Glu Glu Pro Ser Ser Pro Gln
645 650 655
Glu Arg Met Phe Thr Ile Asp Pro Lys Val Tyr Gly Glu Lys Arg Asp
660 665 670
Leu His Ser Lys Asn Lys Asp Asp Leu Thr Leu Ser Arg Ser Leu Gly
675 680 685
Leu Gly Gly Arg Ser Ala Ile Glu Gln Arg Ser Met Ser Ile Asn Leu
690 695 700
Pro Met Ser Cys Leu Asp Ser Ile Ala Leu Gly Phe Asn Phe Gly Arg
705 710 715 720
Gly His Asp Leu Ser Pro Leu Ala Ser Asp Ile Leu Thr Asn Thr Ser
725 730 735
Gly Ser Met Asp Glu Gly Asp Asp Tyr Leu Pro Ala Thr Thr Pro Ala
740 745 750
Leu Glu Lys Ala Pro Cys Phe Pro Val Glu Ser Lys Glu Glu Glu Gln
755 760 765
Ile Glu Lys Val Lys Ala Thr Gly Glu Glu Ser Thr Gln Ala Glu Ile
770 775 780
Ser Cys Glu Ser Pro Phe Leu Ala Lys Asp Phe Tyr Lys Asn Gly Thr
785 790 795 800
Val Met Ala Pro Asp Leu Pro Glu Met Leu Asp Leu Ala Gly Thr Arg
805 810 815
Ser Arg Leu Ala Ser Val Ser Ala Asp Ala Glu Val Ala Arg Arg Lys
820 825 830
Ser Val Pro Ser Glu Thr Val Val Glu Asp Ser Arg Thr Gly Leu Pro
835 840 845
Pro Val Thr Asp Glu Asn His Val Ile Val Lys Thr Asp Ser Gln Leu
850 855 860
Glu Asp Leu Gly Tyr Cys Val Phe Asn Lys Tyr Thr Val Pro Leu Pro
865 870 875 880
Ser Pro Val Gln Asp Ser Glu Asn Leu Ser Gly Glu Ser Gly Thr Phe
885 890 895
Tyr Glu Gly Thr Asp Asp Lys Val Arg Arg Asp Leu Ala Thr Asp Leu
900 905 910
Ser Leu Ile Glu Val Lys Leu Ala Ala Ala Gly Arg Val Lys Asp Glu

915 920 925

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

930 935 940

Gly Leu Ser Lys Glu Phe Asp Gln Glu Lys Lys Ala Asn Asp Arg Leu

945 950 955 960

Asp Thr Val Leu Glu Lys Ser Glu Glu His Ala Asp Ser Lys Glu His

965 970 975

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

980 985 990

Gly Val Thr Tyr Glu Gln Ala Leu Ala Lys Asp Leu Ser Ile Pro Thr

995 1000 1005

Asp Ala Ser Ser Glu Lys Ala Glu Lys Gly Leu Ser Ser Val Pro

1010 1015 1020

Glu Ile Ala Glu Val Glu Pro Ser Lys Lys Val Glu Gln Gly Leu

1025 1030 1035

Asp Phe Ala Val Gln Gly Gln Leu Asp Val Lys Ile Ser Asp Phe

1040 1045 1050

Gly Gln Met Ala Ser Gly Leu Asn Ile Asp Asp Arg Arg Ala Thr

1055 1060 1065

Glu Leu Lys Leu Glu Ala Thr Gln Asp Met Thr Pro Ser Ser Lys

1070 1075 1080

Ala Pro Gln Glu Ala Asp Ala Phe Met Gly Val Glu Ser Gly His

1085 1090 1095

Met Lys Glu Gly Thr Lys Val Ser Glu Thr Glu Val Lys Glu Lys

1100 1105 1110

Val Ala Lys Pro Asp Leu Val His Gln Glu Ala Val Asp Lys Glu

1115 1120 1125

Glu Ser Tyr Glu Ser Ser Gly Glu His Glu Ser Leu Thr Met Glu

1130 1135 1140

Ser Leu Lys Ala Asp Glu Gly Lys Lys Glu Thr Ser Pro Glu Ser

1145 1150 1155

Ser Leu Ile Gln Asp Glu Ile Ala Val Lys Leu Ser Val Glu Ile

1160 1165 1170

Pro Cys Pro Pro Ala Val Ser Glu Ala Asp Leu Ala Thr Asp Glu

1175 1180 1185

Arg Ala Asp Val Gln Met Glu Phe Ile Gln Gly Pro Lys Glu Glu

1190 1195 1200

Ser Lys Glu Thr Pro Asp Ile Ser Ile Thr Pro Ser Asp Val Ala

1205 1210 1215

Glu Pro Leu His Glu Thr Ile Val Ser Glu Pro Ala Glu Ile Gln
1220 1225 1230
Ser Glu Glu Glu Glu Ile Glu Ala Gln Gly Glu Tyr Asp Lys Leu
1235 1240 1245
Leu Phe Arg Ser Asp Thr Leu Gln Ile Thr Asp Leu Gly Val Ser
1250 1255 1260
Gly Ala Arg Glu Glu Phe Val Glu Thr Cys Pro Ser Glu His Lys
1265 1270 1275
Gly Val Ile Glu Ser Val Val Thr Ile Glu Asp Asp Phe Ile Thr
1280 1285 1290
Val Val Gln Thr Thr Thr Asp Glu Gly Glu Ser Gly Ser His Ser
1295 1300 1305
Val Arg Phe Ala Ala Leu Glu Gln Pro Glu Val Glu Arg Arg Pro
1310 1315 1320
Ser Pro His Asp Glu Glu Glu Phe Glu Val Glu Glu Ala Ala Glu
1325 1330 1335
Ala Gln Ala Glu Pro Lys Asp Gly Ser Pro Glu Ala Pro Ala Ser
1340 1345 1350
Pro Glu Arg Glu Glu Val Ala Leu Ser Glu Tyr Lys Thr Glu Thr
1355 1360 1365
Tyr Asp Asp Tyr Lys Asp Glu Thr Thr Ile Asp Asp Ser Ile Met
1370 1375 1380
Asp Ala Asp Ser Leu Trp Val Asp Thr Gln Asp Asp Asp Arg Ser
1385 1390 1395
Ile Met Thr Glu Gln Leu Glu Thr Ile Pro Lys Glu Glu Lys Ala
1400 1405 1410
Glu Lys Glu Ala Arg Arg Ser Ser Leu Glu Lys His Arg Lys Glu
1415 1420 1425
Lys Pro Phe Lys Thr Gly Arg Gly Arg Ile Ser Thr Pro Glu Arg
1430 1435 1440
Lys Val Ala Lys Lys Glu Pro Ser Thr Val Ser Arg Asp Glu Val
1445 1450 1455
Arg Arg Lys Lys Ala Val Tyr Lys Lys Ala Glu Leu Ala Lys Lys
1460 1465 1470
Thr Glu Val Gln Ala His Ser Pro Ser Arg Lys Phe Ile Leu Lys
1475 1480 1485
Pro Ala Ile Lys Tyr Thr Arg Pro Thr His Leu Ser Cys Val Lys
1490 1495 1500
Arg Lys Thr Thr Ala Ala Gly Gly Glu Ser Ala Leu Ala Pro Ser

1505 1510 1515

Val Phe Lys Gln Ala Lys Asp Lys Val Ser Asp Gly Val Thr Lys

1520 1525 1530

Ser Pro Glu Lys Arg Ser Ser Leu Pro Arg Pro Ser Ser Ile Leu

1535 1540 1545

Pro Pro Arg Arg Gly Val Ser Gly Asp Arg Asp Glu Asn Ser Phe

1550 1555 1560

Ser Leu Asn Ser Ser Ile Ser Ser Ser Ala Arg Arg Thr Thr Arg

1565 1570 1575

Ser Glu Pro Ile Arg Arg Ala Gly Lys Ser Gly Thr Ser Thr Pro

1580 1585 1590

Thr Thr Pro Gly Ser Thr Ala Ile Thr Pro Gly Thr Pro Pro Ser

1595 1600 1605

Tyr Ser Ser Arg Thr Pro Gly Thr Pro Gly Thr Pro Ser Tyr Pro

1610 1615 1620

Arg Thr Pro His Thr Pro Gly Thr Pro Lys Ser Ala Ile Leu Val

1625 1630 1635

Pro Ser Glu Lys Lys Val Ala Ile Ile Arg Thr Pro Pro Lys Ser

1640 1645 1650

Pro Ala Thr Pro Lys Gln Leu Arg Leu Ile Asn Gln Pro Leu Pro

1655 1660 1665

Asp Leu Lys Asn Val Lys Ser Lys Ile Gly Ser Thr Asp Asn Ile

1670 1675 1680

Lys Tyr Gln Pro Lys Gly Gly Gln Val Gln Ile Val Thr Lys Lys

1685 1690 1695

Ile Asp Leu Ser His Val Thr Ser Lys Cys Gly Ser Leu Lys Asn

1700 1705 1710

Ile Arg His Arg Pro Gly Gly Gly Arg Val Lys Ile Glu Ser Val

1715 1720 1725

Lys Leu Asp Phe Lys Glu Lys Ala Gln Ala Lys Val Gly Ser Leu

1730 1735 1740

Asp Asn Ala His His Val Pro Gly Gly Gly Asn Val Lys Ile Asp

1745 1750 1755

Ser Gln Lys Leu Asn Phe Arg Glu His Ala Lys Ala Arg Val Asp

1760 1765 1770

His Gly Ala Glu Ile Ile Thr Gln Ser Pro Gly Arg Ser Ser Val

1775 1780 1785

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

1790 1795 1800

Asn Leu Leu Glu Ser Pro Gln Leu Ala Thr Leu Ala Glu Asp Val
1805 1810 1815
Thr Ala Ala Leu Ala Lys Gln Gly Leu
1820 1825

<210> 90
<211> 758
<212> PRT
<213> 人
<400> 90

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

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

545 550 555 560
Gln Thr Ala Pro Val Pro Met Pro Asp Leu Lys Asn Val Lys Ser Lys
565 570 575
Ile Gly Ser Thr Glu Asn Leu Lys His Gln Pro Gly Gly Gly Lys Val
580 585 590
Gln Ile Ile Asn Lys Lys Leu Asp Leu Ser Asn Val Gln Ser Lys Cys
595 600 605
Gly Ser Lys Asp Asn Ile Lys His Val Pro Gly Gly Gly Ser Val Gln
610 615 620
Ile Val Tyr Lys Pro Val Asp Leu Ser Lys Val Thr Ser Lys Cys Gly
625 630 635 640
Ser Leu Gly Asn Ile His His Lys Pro Gly Gly Gly Gln Val Glu Val
645 650 655
Lys Ser Glu Lys Leu Asp Phe Lys Asp Arg Val Gln Ser Lys Ile Gly
660 665 670
Ser Leu Asp Asn Ile Thr His Val Pro Gly Gly Gly Asn Lys Lys Ile
675 680 685
Glu Thr His Lys Leu Thr Phe Arg Glu Asn Ala Lys Ala Lys Thr Asp
690 695 700
His Gly Ala Glu Ile Val Tyr Lys Ser Pro Val Val Ser Gly Asp Thr
705 710 715 720
Ser Pro Arg His Leu Ser Asn Val Ser Ser Thr Gly Ser Ile Asp Met
725 730 735
Val Asp Ser Pro Gln Leu Ala Thr Leu Ala Asp Glu Val Ser Ala Ser
740 745 750
Leu Ala Lys Gln Gly Leu
755

<210> 91
<211> 422
<212> PRT
<213> 人
<400> 91
Met Asp Val Leu Ser Pro Gly Gln Gly Asn Asn Thr Thr Ser Pro Pro
1 5 10 15
Ala Pro Phe Glu Thr Gly Gly Asn Thr Thr Gly Ile Ser Asp Val Thr
20 25 30
Val Ser Tyr Gln Val Ile Thr Ser Leu Leu Leu Gly Thr Leu Ile Phe
35 40 45
Cys Ala Val Leu Gly Asn Ala Cys Val Val Ala Ala Ile Ala Leu Glu

50 55 60

Arg Ser Leu Gln Asn Val Ala Asn Tyr Leu Ile Gly Ser Leu Ala Val
65 70 75 80

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

Gln Val Leu Asn Lys Trp Thr Leu Gly Gln Val Thr Cys Asp Leu Phe
100 105 110

Ile Ala Leu Asp Val Leu Cys Cys Thr Ser Ser Ile Leu His Leu Cys
115 120 125

Ala Ile Ala Leu Asp Arg Tyr Trp Ala Ile Thr Asp Pro Ile Asp Tyr
130 135 140

Val Asn Lys Arg Thr Pro Arg Arg Ala Ala Ala Leu Ile Ser Leu Thr
145 150 155 160

Trp Leu Ile Gly Phe Leu Ile Ser Ile Pro Pro Met Leu Gly Trp Arg
165 170 175

Thr Pro Glu Asp Arg Ser Asp Pro Asp Ala Cys Thr Ile Ser Lys Asp
180 185 190

His Gly Tyr Thr Ile Tyr Ser Thr Phe Gly Ala Phe Tyr Ile Pro Leu
195 200 205

Leu Leu Met Leu Val Leu Tyr Gly Arg Ile Phe Arg Ala Ala Arg Phe
210 215 220

Arg Ile Arg Lys Thr Val Lys Lys Val Glu Lys Thr Gly Ala Asp Thr
225 230 235 240

Arg His Gly Ala Ser Pro Ala Pro Gln Pro Lys Lys Ser Val Asn Gly
245 250 255

Glu Ser Gly Ser Arg Asn Trp Arg Leu Gly Val Glu Ser Lys Ala Gly
260 265 270

Gly Ala Leu Cys Ala Asn Gly Ala Val Arg Gln Gly Asp Asp Gly Ala
275 280 285

Ala Leu Glu Val Ile Glu Val His Arg Val Gly Asn Ser Lys Glu His
290 295 300

Leu Pro Leu Pro Ser Glu Ala Gly Pro Thr Pro Cys Ala Pro Ala Ser
305 310 315 320

Phe Glu Arg Lys Asn Glu Arg Asn Ala Glu Ala Lys Arg Lys Met Ala
325 330 335

Leu Ala Arg Glu Arg Lys Thr Val Lys Thr Leu Gly Ile Ile Met Gly
340 345 350

Thr Phe Ile Leu Cys Trp Leu Pro Phe Phe Ile Val Ala Leu Val Leu
355 360 365

Pro Phe Cys Glu Ser Ser Cys His Met Pro Thr Leu Leu Gly Ala Ile
370 375 380
Ile Asn Trp Leu Gly Tyr Ser Asn Ser Leu Leu Asn Pro Val Ile Tyr
385 390 395 400
Ala Tyr Phe Asn Lys Asp Phe Gln Asn Ala Phe Lys Lys Ile Ile Lys
405 410 415
Cys Lys Phe Cys Arg Gln
420

<210> 92
<211> 1894
<212> PRT
<213> 人
<400> 92

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

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

515 520 525

Trp Cys Val Leu His Asn Thr Cys Thr Arg Lys Glu Arg Cys Glu Arg

530 535 540

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

545 550 555 560

Leu Thr Val His Pro Asn Asn Ile Ser Val Ser Gln Tyr Asn Val Leu

565 570 575

Leu Val Leu Glu Thr Tyr Asn Val Pro Glu Leu Ser Ala Gly Val Asn

580 585 590

Cys Thr Phe Glu Asp Leu Ser Glu Met Asp Gly Leu Val Val Gly Asn

595 600 605

Gln Ile Gln Cys Tyr Ser Pro Ala Ala Lys Glu Val Pro Arg Ile Ile

610 615 620

Thr Glu Asn Gly Asp His His Val Val Gln Leu Gln Leu Lys Ser Lys

625 630 635 640

Glu Thr Gly Met Thr Phe Ala Ser Thr Ser Phe Val Phe Tyr Asn Cys

645 650 655

Ser Val His Asn Ser Cys Leu Ser Cys Val Glu Ser Pro Tyr Arg Cys

660 665 670

His Trp Cys Lys Tyr Arg His Val Cys Thr His Asp Pro Lys Thr Cys

675 680 685

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

690 695 700

Leu Arg Val Asp Lys Ile Leu Val Pro Val Glu Val Ile Lys Pro Ile

705 710 715 720

Thr Leu Lys Ala Lys Asn Leu Pro Gln Pro Gln Ser Gly Gln Arg Gly

725 730 735

Tyr Glu Cys Ile Leu Asn Ile Gln Gly Ser Glu Gln Arg Val Pro Ala

740 745 750

Leu Arg Phe Asn Ser Ser Ser Val Gln Cys Gln Asn Thr Ser Tyr Ser

755 760 765

Tyr Glu Gly Met Glu Ile Asn Asn Leu Pro Val Glu Leu Thr Val Val

770 775 780

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

785 790 795 800

Leu Tyr Lys Cys Gly Ala Met Arg Glu Ser Cys Gly Leu Cys Leu Lys

805 810 815

Ala Asp Pro Asp Phe Ala Cys Gly Trp Cys Gln Gly Pro Gly Gln Cys

820 825 830

Thr Leu Arg Gln His Cys Pro Ala Gln Glu Ser Gln Trp Leu Glu Leu
835 840 845
Ser Gly Ala Lys Ser Lys Cys Thr Asn Pro Arg Ile Thr Glu Ile Ile
850 855 860
Pro Val Thr Gly Pro Arg Glu Gly Gly Thr Lys Val Thr Ile Arg Gly
865 870 875 880
Glu Asn Leu Gly Leu Glu Phe Arg Asp Ile Ala Ser His Val Lys Val
885 890 895
Ala Gly Val Glu Cys Ser Pro Leu Val Asp Gly Tyr Ile Pro Ala Glu
900 905 910
Gln Ile Val Cys Glu Met Gly Glu Ala Lys Pro Ser Gln His Ala Gly
915 920 925
Phe Val Glu Ile Cys Val Ala Val Cys Arg Pro Glu Phe Met Ala Arg
930 935 940
Ser Ser Gln Leu Tyr Tyr Phe Met Thr Leu Thr Leu Ser Asp Leu Lys
945 950 955 960
Pro Ser Arg Gly Pro Met Ser Gly Gly Thr Gln Val Thr Ile Thr Gly
965 970 975
Thr Asn Leu Asn Ala Gly Ser Asn Val Val Val Met Phe Gly Lys Gln
980 985 990
Pro Cys Leu Phe His Arg Arg Ser Pro Ser Tyr Ile Val Cys Asn Thr
995 1000 1005
Thr Ser Ser Asp Glu Val Leu Glu Met Lys Val Ser Val Gln Val
1010 1015 1020
Asp Arg Ala Lys Ile His Gln Asp Leu Val Phe Gln Tyr Val Glu
1025 1030 1035
Asp Pro Thr Ile Val Arg Ile Glu Pro Glu Trp Ser Ile Val Ser
1040 1045 1050
Gly Asn Thr Pro Ile Ala Val Trp Gly Thr His Leu Asp Leu Ile
1055 1060 1065
Gln Asn Pro Gln Ile Arg Ala Lys His Gly Gly Lys Glu His Ile
1070 1075 1080
Asn Ile Cys Glu Val Leu Asn Ala Thr Glu Met Thr Cys Gln Ala
1085 1090 1095
Pro Ala Leu Ala Leu Gly Pro Asp His Gln Ser Asp Leu Thr Glu
1100 1105 1110
Arg Pro Glu Glu Phe Gly Phe Ile Leu Asp Asn Val Gln Ser Leu
1115 1120 1125
Leu Ile Leu Asn Lys Thr Asn Phe Thr Tyr Tyr Pro Asn Pro Val

1130 1135 1140

Phe Glu Ala Phe Gly Pro Ser Gly Ile Leu Glu Leu Lys Pro Gly
1145 1150 1155

Thr Pro Ile Ile Leu Lys Gly Lys Asn Leu Ile Pro Pro Val Ala
1160 1165 1170

Gly Gly Asn Val Lys Leu Asn Tyr Thr Val Leu Val Gly Glu Lys
1175 1180 1185

Pro Cys Thr Val Thr Val Ser Asp Val Gln Leu Leu Cys Glu Ser
1190 1195 1200

Pro Asn Leu Ile Gly Arg His Lys Val Met Ala Arg Val Gly Gly
1205 1210 1215

Met Glu Tyr Ser Pro Gly Met Val Tyr Ile Ala Pro Asp Ser Pro
1220 1225 1230

Leu Ser Leu Pro Ala Ile Val Ser Ile Ala Val Ala Gly Gly Leu
1235 1240 1245

Leu Ile Ile Phe Ile Val Ala Val Leu Ile Ala Tyr Lys Arg Lys
1250 1255 1260

Ser Arg Glu Ser Asp Leu Thr Leu Lys Arg Leu Gln Met Gln Met
1265 1270 1275

Asp Asn Leu Glu Ser Arg Val Ala Leu Glu Cys Lys Glu Ala Phe
1280 1285 1290

Ala Glu Leu Gln Thr Asp Ile His Glu Leu Thr Ser Asp Leu Asp
1295 1300 1305

Gly Ala Gly Ile Pro Phe Leu Asp Tyr Arg Thr Tyr Thr Met Arg
1310 1315 1320

Val Leu Phe Pro Gly Ile Glu Asp His Pro Val Leu Arg Asp Leu
1325 1330 1335

Glu Val Pro Gly Tyr Arg Gln Glu Arg Val Glu Lys Gly Leu Lys
1340 1345 1350

Leu Phe Ala Gln Leu Ile Asn Asn Lys Val Phe Leu Leu Ser Phe
1355 1360 1365

Ile Arg Thr Leu Glu Ser Gln Arg Ser Phe Ser Met Arg Asp Arg
1370 1375 1380

Gly Asn Val Ala Ser Leu Ile Met Thr Val Leu Gln Ser Lys Leu
1385 1390 1395

Glu Tyr Ala Thr Asp Val Leu Lys Gln Leu Leu Ala Asp Leu Ile
1400 1405 1410

Asp Lys Asn Leu Glu Ser Lys Asn His Pro Lys Leu Leu Leu Arg
1415 1420 1425

Arg Thr Glu Ser Val Ala Glu Lys Met Leu Thr Asn Trp Phe Thr
1430 1435 1440
Phe Leu Leu Tyr Lys Phe Leu Lys Glu Cys Ala Gly Glu Pro Leu
1445 1450 1455
Phe Ser Leu Phe Cys Ala Ile Lys Gln Gln Met Glu Lys Gly Pro
1460 1465 1470
Ile Asp Ala Ile Thr Gly Glu Ala Arg Tyr Ser Leu Ser Glu Asp
1475 1480 1485
Lys Leu Ile Arg Gln Gln Ile Asp Tyr Lys Thr Leu Val Leu Ser
1490 1495 1500
Cys Val Ser Pro Asp Asn Ala Asn Ser Pro Glu Val Pro Val Lys
1505 1510 1515
Ile Leu Asn Cys Asp Thr Ile Thr Gln Val Lys Glu Lys Ile Leu
1520 1525 1530
Asp Ala Ile Phe Lys Asn Val Pro Cys Ser His Arg Pro Lys Ala
1535 1540 1545
Ala Asp Met Asp Leu Glu Trp Arg Gln Gly Ser Gly Ala Arg Met
1550 1555 1560
Ile Leu Gln Asp Glu Asp Ile Thr Thr Lys Ile Glu Asn Asp Trp
1565 1570 1575
Lys Arg Leu Asn Thr Leu Ala His Tyr Gln Val Pro Asp Gly Ser
1580 1585 1590
Val Val Ala Leu Val Ser Lys Gln Val Thr Ala Tyr Asn Ala Val
1595 1600 1605
Asn Asn Ser Thr Val Ser Arg Thr Ser Ala Ser Lys Tyr Glu Asn
1610 1615 1620
Met Ile Arg Tyr Thr Gly Ser Pro Asp Ser Leu Arg Ser Arg Thr
1625 1630 1635
Pro Met Ile Thr Pro Asp Leu Glu Ser Gly Val Lys Met Trp His
1640 1645 1650
Leu Val Lys Asn His Glu His Gly Asp Gln Lys Glu Gly Asp Arg
1655 1660 1665
Gly Ser Lys Met Val Ser Glu Ile Tyr Leu Thr Arg Leu Leu Ala
1670 1675 1680
Thr Lys Gly Thr Leu Gln Lys Phe Val Asp Asp Leu Phe Glu Thr
1685 1690 1695
Ile Phe Ser Thr Ala His Arg Gly Ser Ala Leu Pro Leu Ala Ile
1700 1705 1710
Lys Tyr Met Phe Asp Phe Leu Asp Glu Gln Ala Asp Lys His Gly

1715 1720 1725
Ile His Asp Pro His Val Arg His Thr Trp Lys Ser Asn Cys Leu
1730 1735 1740
Pro Leu Arg Phe Trp Val Asn Met Ile Lys Asn Pro Gln Phe Val
1745 1750 1755
Phe Asp Ile His Lys Asn Ser Ile Thr Asp Ala Cys Leu Ser Val
1760 1765 1770
Val Ala Gln Thr Phe Met Asp Ser Cys Ser Thr Ser Glu His Arg
1775 1780 1785
Leu Gly Lys Asp Ser Pro Ser Asn Lys Leu Leu Tyr Ala Lys Asp
1790 1795 1800
Ile Pro Ser Tyr Lys Asn Trp Val Glu Arg Tyr Tyr Ser Asp Ile
1805 1810 1815
Gly Lys Met Pro Ala Ile Ser Asp Gln Asp Met Asn Ala Tyr Leu
1820 1825 1830
Ala Glu Gln Ser Arg Met His Met Asn Glu Phe Asn Thr Met Ser
1835 1840 1845
Ala Leu Ser Glu Ile Phe Ser Tyr Val Gly Lys Tyr Ser Glu Glu
1850 1855 1860
Ile Leu Gly Pro Leu Asp His Asp Asp Gln Cys Gly Lys Gln Lys
1865 1870 1875
Leu Ala Tyr Lys Leu Glu Gln Val Ile Thr Leu Met Ser Leu Asp
1880 1885 1890
Ser

<210> 93
<211> 184
<212> PRT
<213> 人
<400> 93
Pro Val Pro Pro Gly Glu Asp Ser Lys Asp Val Ala Ala Pro His Arg
1 5 10 15
Gln Pro Leu Thr Ser Ser Glu Arg Ile Asp Lys Gln Ile Arg Tyr Ile
20 25 30
Leu Asp Gly Ile Ser Ala Leu Arg Lys Glu Thr Cys Asn Lys Ser Asn
35 40 45
Met Cys Glu Ser Ser Lys Glu Ala Leu Ala Glu Asn Asn Leu Asn Leu
50 55 60
Pro Lys Met Ala Glu Lys Asp Gly Cys Phe Gln Ser Gly Phe Asn Glu
65 70 75 80

Glu Thr Cys Leu Val Lys Ile Ile Thr Gly Leu Leu Glu Phe Glu Val
85 90 95
Tyr Leu Glu Tyr Leu Gln Asn Arg Phe Glu Ser Ser Glu Glu Gln Ala
100 105 110
Arg Ala Val Gln Met Ser Thr Lys Val Leu Ile Gln Phe Leu Gln Lys
115 120 125
Lys Ala Lys Asn Leu Asp Ala Ile Thr Thr Pro Asp Pro Thr Thr Asn
130 135 140
Ala Ser Leu Leu Thr Lys Leu Gln Ala Gln Asn Gln Trp Leu Gln Asp
145 150 155 160
Met Thr Thr His Leu Ile Leu Arg Ser Phe Lys Glu Phe Leu Gln Ser
165 170 175
Ser Leu Arg Ala Leu Arg Gln Met
180

<210> 94
<211> 306
<212> PRT
<213> 人
<400> 94

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

Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu Cys Gln Glu Asp Ser Ala
165 170 175
Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile Glu Val Met Val Asp Ala
180 185 190
Val His Lys Leu Lys Tyr Glu Asn Tyr Thr Ser Ser Phe Phe Ile Arg
195 200 205
Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln Leu Lys Pro Leu
210 215 220
Lys Asn Ser Arg Gln Val Glu Val Ser Trp Glu Tyr Pro Asp Thr Trp
225 230 235 240
Ser Thr Pro His Ser Tyr Phe Ser Leu Thr Phe Cys Val Gln Val Gln
245 250 255
Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg Val Phe Thr Asp Lys Thr
260 265 270
Ser Ala Thr Val Ile Cys Arg Lys Asn Ala Ser Ile Ser Val Arg Ala
275 280 285
Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser Glu Trp Ala Ser Val Pro
290 295 300
Cys Ser
305

<210> 95
<211> 114
<212> PRT
<213> 人
<400> 95

Met Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
1 5 10 15
Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
20 25 30
His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
35 40 45
Gln Val Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60
Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80
Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
85 90 95
Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
100 105 110

Thr Ser

<210> 96

<211> 137

<212> PRT

<213> 人

<400> 96

Met Ile Val Lys Ala Gly Ile Thr Ile Pro Arg Asn Pro Gly Cys Pro
1 5 10 15

Asn Ser Glu Asp Lys Asn Phe Pro Arg Thr Val Met Val Asn Leu Asn
20 25 30

Ile His Asn Arg Asn Thr Asn Thr Asn Pro Lys Arg Ser Ser Asp Tyr
35 40 45

Tyr Asn Arg Ser Thr Ser Pro Trp Asn Leu His Arg Asn Glu Asp Pro
50 55 60

Glu Arg Tyr Pro Ser Val Ile Trp Glu Ala Lys Cys Arg His Leu Gly
65 70 75 80

Cys Ile Asn Ala Asp Gly Asn Val Asp Tyr His Met Asn Ser Val Pro
85 90 95

Ile Gln Gln Glu Ile Leu Val Leu Arg Arg Glu Pro Pro His Cys Pro
100 105 110

Asn Ser Phe Arg Leu Glu Lys Ile Leu Val Ser Val Gly Cys Thr Cys
115 120 125

Val Thr Pro Ile Val His His Val Ala
130 135

<210> 97

<211> 153

<212> PRT

<213> 人

<400> 97

Met Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
1 5 10 15

Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
20 25 30

Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
35 40 45

Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
50 55 60

Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
65 70 75 80

Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
85 90 95
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
100 105 110
Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
115 120 125
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
130 135 140
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 98
<211> 162
<212> PRT
<213> 人
<400> 98

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

<210> 99
<211> 165
<212> PRT

<213> 人

<400> 99

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

<210> 100

<211> 673

<212> PRT

<213> 人

<400> 100

Phe Lys Ile Glu Thr Thr Pro Glu Ser Arg Tyr Leu Ala Gln Ile Gly
1 5 10 15
Asp Ser Val Ser Leu Thr Cys Ser Thr Thr Gly Cys Glu Ser Pro Phe
20 25 30
Phe Ser Trp Arg Thr Gln Ile Asp Ser Pro Leu Asn Gly Lys Val Thr
35 40 45
Asn Glu Gly Thr Thr Ser Thr Leu Thr Met Asn Pro Val Ser Phe Gly
50 55 60
Asn Glu His Ser Tyr Leu Cys Thr Ala Thr Cys Glu Ser Arg Lys Leu
65 70 75 80

Glu Lys Gly Ile Gln Val Glu Ile Tyr Ser Phe Pro Lys Asp Pro Glu
85 90 95
Ile His Leu Ser Gly Pro Leu Glu Ala Gly Lys Pro Ile Thr Val Lys
100 105 110
Cys Ser Val Ala Asp Val Tyr Pro Phe Asp Arg Leu Glu Ile Asp Leu
115 120 125
Leu Lys Gly Asp His Leu Met Lys Ser Gln Glu Phe Leu Glu Asp Ala
130 135 140
Asp Arg Lys Ser Leu Glu Thr Lys Ser Leu Glu Val Thr Phe Thr Pro
145 150 155 160
Val Ile Glu Asp Ile Gly Lys Val Leu Val Cys Arg Ala Lys Leu His
165 170 175
Ile Asp Glu Met Asp Ser Val Pro Thr Val Arg Gln Ala Val Lys Glu
180 185 190
Leu Gln Val Tyr Ile Ser Pro Lys Asn Thr Val Ile Ser Val Asn Pro
195 200 205
Ser Thr Lys Leu Gln Glu Gly Gly Ser Val Thr Met Thr Cys Ser Ser
210 215 220
Glu Gly Leu Pro Ala Pro Glu Ile Phe Trp Ser Lys Lys Leu Asp Asn
225 230 235 240
Gly Asn Leu Gln His Leu Ser Gly Asn Ala Thr Leu Thr Leu Ile Ala
245 250 255
Met Arg Met Glu Asp Ser Gly Ile Tyr Val Cys Glu Gly Val Asn Leu
260 265 270
Ile Gly Lys Asn Arg Lys Glu Val Glu Leu Ile Val Gln Glu Lys Pro
275 280 285
Phe Thr Val Glu Ile Ser Pro Gly Pro Arg Ile Ala Ala Gln Ile Gly
290 295 300
Asp Ser Val Met Leu Thr Cys Ser Val Met Gly Cys Glu Ser Pro Ser
305 310 315 320
Phe Ser Trp Arg Thr Gln Ile Asp Ser Pro Leu Ser Gly Lys Val Arg
325 330 335
Ser Glu Gly Thr Asn Ser Thr Leu Thr Leu Ser Pro Val Ser Phe Glu
340 345 350
Asn Glu His Ser Tyr Leu Cys Thr Val Thr Cys Gly His Lys Lys Leu
355 360 365
Glu Lys Gly Ile Gln Val Glu Leu Tyr Ser Phe Pro Arg Asp Pro Glu
370 375 380
Ile Glu Met Ser Gly Gly Leu Val Asn Gly Ser Ser Val Thr Val Ser

385 390 395 400
Cys Lys Val Pro Ser Val Tyr Pro Leu Asp Arg Leu Glu Ile Glu Leu
405 410 415
Leu Lys Gly Glu Thr Ile Leu Glu Asn Ile Glu Phe Leu Glu Asp Thr
420 425 430
Asp Met Lys Ser Leu Glu Asn Lys Ser Leu Glu Met Thr Phe Ile Pro
435 440 445
Thr Ile Glu Asp Thr Gly Lys Ala Leu Val Cys Gln Ala Lys Leu His
450 455 460
Ile Asp Asp Met Glu Phe Glu Pro Lys Gln Arg Gln Ser Thr Gln Thr
465 470 475 480
Leu Tyr Val Asn Val Ala Pro Arg Asp Thr Thr Val Leu Val Ser Pro
485 490 495
Ser Ser Ile Leu Glu Glu Gly Ser Ser Val Asn Met Thr Cys Leu Ser
500 505 510
Gln Gly Phe Pro Ala Pro Lys Ile Leu Trp Ser Arg Gln Leu Pro Asn
515 520 525
Gly Glu Leu Gln Pro Leu Ser Glu Asn Ala Thr Leu Thr Leu Ile Ser
530 535 540
Thr Lys Met Glu Asp Ser Gly Val Tyr Leu Cys Glu Gly Ile Asn Gln
545 550 555 560
Ala Gly Arg Ser Arg Lys Glu Val Glu Leu Ile Ile Gln Val Thr Pro
565 570 575
Lys Asp Ile Lys Leu Thr Ala Phe Pro Ser Glu Ser Val Lys Glu Gly
580 585 590
Asp Thr Val Ile Ile Ser Cys Thr Cys Gly Asn Val Pro Glu Thr Trp
595 600 605
Ile Ile Leu Lys Lys Lys Ala Glu Thr Gly Asp Thr Val Leu Lys Ser
610 615 620
Ile Asp Gly Ala Tyr Thr Ile Arg Lys Ala Gln Leu Lys Asp Ala Gly
625 630 635 640
Val Tyr Glu Cys Glu Ser Lys Asn Lys Val Gly Ser Gln Leu Arg Ser
645 650 655
Leu Thr Leu Asp Val Gln Gly Arg Glu Asn Asn Lys Asp Tyr Phe Ser
660 665 670
Pro

<210> 101
<211> 466
<212> PRT

<213> 人

<400> 101

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

290 295 300

Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320
Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 102
<211> 1487
<212> PRT
<213> 人
<400> 102

Met Ile Arg Leu Gly Ala Pro Gln Thr Leu Val Leu Leu Thr Leu Leu
1 5 10 15
Val Ala Ala Val Leu Arg Cys Gln Gly Gln Asp Val Gln Glu Ala Gly
20 25 30
Ser Cys Val Gln Asp Gly Gln Arg Tyr Asn Asp Lys Asp Val Trp Lys
35 40 45
Pro Glu Pro Cys Arg Ile Cys Val Cys Asp Thr Gly Thr Val Leu Cys
50 55 60
Asp Asp Ile Ile Cys Glu Asp Val Lys Asp Cys Leu Ser Pro Glu Ile
65 70 75 80
Pro Phe Gly Glu Cys Cys Pro Ile Cys Pro Thr Asp Leu Ala Thr Ala

85 90 95

Ser Gly Gln Pro Gly Pro Lys Gly Gln Lys Gly Glu Pro Gly Asp Ile
100 105 110

Lys Asp Ile Val Gly Pro Lys Gly Pro Pro Gly Pro Gln Gly Pro Ala
115 120 125

Gly Glu Gln Gly Pro Arg Gly Asp Arg Gly Asp Lys Gly Glu Lys Gly
130 135 140

Ala Pro Gly Pro Arg Gly Arg Asp Gly Glu Pro Gly Thr Pro Gly Asn
145 150 155 160

Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Leu Gly
165 170 175

Gly Asn Phe Ala Ala Gln Met Ala Gly Gly Phe Asp Glu Lys Ala Gly
180 185 190

Gly Ala Gln Leu Gly Val Met Gln Gly Pro Met Gly Pro Met Gly Pro
195 200 205

Arg Gly Pro Pro Gly Pro Ala Gly Ala Pro Gly Pro Gln Gly Phe Gln
210 215 220

Gly Asn Pro Gly Glu Pro Gly Glu Pro Gly Val Ser Gly Pro Met Gly
225 230 235 240

Pro Arg Gly Pro Pro Gly Pro Pro Gly Lys Pro Gly Asp Asp Gly Glu
245 250 255

Ala Gly Lys Pro Gly Lys Ala Gly Glu Arg Gly Pro Pro Gly Pro Gln
260 265 270

Gly Ala Arg Gly Phe Pro Gly Thr Pro Gly Leu Pro Gly Val Lys Gly
275 280 285

His Arg Gly Tyr Pro Gly Leu Asp Gly Ala Lys Gly Glu Ala Gly Ala
290 295 300

Pro Gly Val Lys Gly Glu Ser Gly Ser Pro Gly Glu Asn Gly Ser Pro
305 310 315 320

Gly Pro Met Gly Pro Arg Gly Leu Pro Gly Glu Arg Gly Arg Thr Gly
325 330 335

Pro Ala Gly Ala Ala Gly Ala Arg Gly Asn Asp Gly Gln Pro Gly Pro
340 345 350

Ala Gly Pro Pro Gly Pro Val Gly Pro Ala Gly Gly Pro Gly Phe Pro
355 360 365

Gly Ala Pro Gly Ala Lys Gly Glu Ala Gly Pro Thr Gly Ala Arg Gly
370 375 380

Pro Glu Gly Ala Gln Gly Pro Arg Gly Glu Pro Gly Thr Pro Gly Ser
385 390 395 400

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

705 710 715 720
Leu Pro Gly Thr Pro Gly Thr Asp Gly Pro Lys Gly Ala Ser Gly Pro
725 730 735
Ala Gly Pro Pro Gly Ala Gln Gly Pro Pro Gly Leu Gln Gly Met Pro
740 745 750
Gly Glu Arg Gly Ala Ala Gly Ile Ala Gly Pro Lys Gly Asp Arg Gly
755 760 765
Asp Val Gly Glu Lys Gly Pro Glu Gly Ala Pro Gly Lys Asp Gly Gly
770 775 780
Arg Gly Leu Thr Gly Pro Ile Gly Pro Pro Gly Pro Ala Gly Ala Asn
785 790 795 800
Gly Glu Lys Gly Glu Val Gly Pro Pro Gly Pro Ala Gly Ser Ala Gly
805 810 815
Ala Arg Gly Ala Pro Gly Glu Arg Gly Glu Thr Gly Pro Pro Gly Pro
820 825 830
Ala Gly Phe Ala Gly Pro Pro Gly Ala Asp Gly Gln Pro Gly Ala Lys
835 840 845
Gly Glu Gln Gly Glu Ala Gly Gln Lys Gly Asp Ala Gly Ala Pro Gly
850 855 860
Pro Gln Gly Pro Ser Gly Ala Pro Gly Pro Gln Gly Pro Thr Gly Val
865 870 875 880
Thr Gly Pro Lys Gly Ala Arg Gly Ala Gln Gly Pro Pro Gly Ala Thr
885 890 895
Gly Phe Pro Gly Ala Ala Gly Arg Val Gly Pro Pro Gly Ser Asn Gly
900 905 910
Asn Pro Gly Pro Pro Gly Pro Pro Gly Pro Ser Gly Lys Asp Gly Pro
915 920 925
Lys Gly Ala Arg Gly Asp Ser Gly Pro Pro Gly Arg Ala Gly Glu Pro
930 935 940
Gly Leu Gln Gly Pro Ala Gly Pro Pro Gly Glu Lys Gly Glu Pro Gly
945 950 955 960
Asp Asp Gly Pro Ser Gly Ala Glu Gly Pro Pro Gly Pro Gln Gly Leu
965 970 975
Ala Gly Gln Arg Gly Ile Val Gly Leu Pro Gly Gln Arg Gly Glu Arg
980 985 990
Gly Phe Pro Gly Leu Pro Gly Pro Ser Gly Glu Pro Gly Lys Gln Gly
995 1000 1005
Ala Pro Gly Ala Ser Gly Asp Arg Gly Pro Pro Gly Pro Val Gly
1010 1015 1020

Pro Pro Gly Leu Thr Gly Pro Ala Gly Glu Pro Gly Arg Glu Gly
1025 1030 1035
Ser Pro Gly Ala Asp Gly Pro Pro Gly Arg Asp Gly Ala Ala Gly
1040 1045 1050
Val Lys Gly Asp Arg Gly Glu Thr Gly Ala Val Gly Ala Pro Gly
1055 1060 1065
Ala Pro Gly Pro Pro Gly Ser Pro Gly Pro Ala Gly Pro Thr Gly
1070 1075 1080
Lys Gln Gly Asp Arg Gly Glu Ala Gly Ala Gln Gly Pro Met Gly
1085 1090 1095
Pro Ser Gly Pro Ala Gly Ala Arg Gly lle Gln Gly Pro Gln Gly
1100 1105 1110
Pro Arg Gly Asp Lys Gly Glu Ala Gly Glu Pro Gly Glu Arg Gly
1115 1120 1125
Leu Lys Gly His Arg Gly Phe Thr Gly Leu Gln Gly Leu Pro Gly
1130 1135 1140
Pro Pro Gly Pro Ser Gly Asp Gln Gly Ala Ser Gly Pro Ala Gly
1145 1150 1155
Pro Ser Gly Pro Arg Gly Pro Pro Gly Pro Val Gly Pro Ser Gly
1160 1165 1170
Lys Asp Gly Ala Asn Gly lle Pro Gly Pro lle Gly Pro Pro Gly
1175 1180 1185
Pro Arg Gly Arg Ser Gly Glu Thr Gly Pro Ala Gly Pro Pro Gly
1190 1195 1200
Asn Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Gly lle
1205 1210 1215
Asp Met Ser Ala Phe Ala Gly Leu Gly Pro Arg Glu Lys Gly Pro
1220 1225 1230
Asp Pro Leu Gln Tyr Met Arg Ala Asp Gln Ala Ala Gly Gly Leu
1235 1240 1245
Arg Gln His Asp Ala Glu Val Asp Ala Thr Leu Lys Ser Leu Asn
1250 1255 1260
Asn Gln lle Glu Ser lle Arg Ser Pro Glu Gly Ser Arg Lys Asn
1265 1270 1275
Pro Ala Arg Thr Cys Arg Asp Leu Lys Leu Cys His Pro Glu Trp
1280 1285 1290
Lys Ser Gly Asp Tyr Trp lle Asp Pro Asn Gln Gly Cys Thr Leu
1295 1300 1305
Asp Ala Met Lys Val Phe Cys Asn Met Glu Thr Gly Glu Thr Cys

1310 1315 1320
Val Tyr Pro Asn Pro Ala Asn Val Pro Lys Lys Asn Trp Trp Ser
1325 1330 1335
Ser Lys Ser Lys Glu Lys Lys His Ile Trp Phe Gly Glu Thr Ile
1340 1345 1350
Asn Gly Gly Phe His Phe Ser Tyr Gly Asp Asp Asn Leu Ala Pro
1355 1360 1365
Asn Thr Ala Asn Val Gln Met Thr Phe Leu Arg Leu Leu Ser Thr
1370 1375 1380
Glu Gly Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile Ala
1385 1390 1395
Tyr Leu Asp Glu Ala Ala Gly Asn Leu Lys Lys Ala Leu Leu Ile
1400 1405 1410
Gln Gly Ser Asn Asp Val Glu Ile Arg Ala Glu Gly Asn Ser Arg
1415 1420 1425
Phe Thr Tyr Thr Ala Leu Lys Asp Gly Cys Thr Lys His Thr Gly
1430 1435 1440
Lys Trp Gly Lys Thr Val Ile Glu Tyr Arg Ser Gln Lys Thr Ser
1445 1450 1455
Arg Leu Pro Ile Ile Asp Ile Ala Pro Met Asp Ile Gly Gly Pro
1460 1465 1470
Glu Gln Glu Phe Gly Val Asp Ile Gly Pro Val Cys Phe Leu
1475 1480 1485

<210> 103
<211> 119
<212> PRT
<213> 人
<400> 103

Met Ser Arg Ser Val Ala Leu Ala Val Leu Ala Leu Leu Ser Leu Ser
1 5 10 15
Gly Leu Glu Ala Ile Gln Arg Thr Pro Lys Ile Gln Val Tyr Ser Arg
20 25 30
His Pro Ala Glu Asn Gly Lys Ser Asn Phe Leu Asn Cys Tyr Val Ser
35 40 45
Gly Phe His Pro Ser Asp Ile Glu Val Asp Leu Leu Lys Asn Gly Glu
50 55 60
Arg Ile Glu Lys Val Glu His Ser Asp Leu Ser Phe Ser Lys Asp Trp
65 70 75 80
Ser Phe Tyr Leu Leu Tyr Tyr Thr Glu Phe Thr Pro Thr Glu Lys Asp

85 90 95

Glu Tyr Ala Cys Arg Val Asn His Val Thr Leu Ser Gln Pro Lys Ile
100 105 110

Val Lys Trp Asp Arg Asp Met
115

<210> 104
<211> 53
<212> PRT
<213> 人
<400> 104

Glu Gln Ala Pro Gly Thr Ala Pro Cys Ser Arg Gly Ser Ser Trp Ser
1 5 10 15

Ala Asp Leu Asp Lys Cys Met Asp Cys Ala Ser Cys Arg Ala Arg Pro
20 25 30

His Ser Asp Phe Cys Leu Gly Cys Ala Ala Ala Pro Pro Ala Pro Phe
35 40 45

Arg Leu Leu Trp Pro
50

<210> 105
<211> 174
<212> PRT
<213> 人
<400> 105

Met Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Tyr Asp
1 5 10 15

Gln Thr Ala Gln Met Cys Cys Ser Lys Cys Ser Pro Gly Gln His Ala
20 25 30

Lys Val Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys Glu
35 40 45

Asp Ser Thr Tyr Thr Gln Leu Trp Asn Trp Val Pro Glu Cys Leu Ser
50 55 60

Cys Gly Ser Arg Cys Ser Ser Asp Gln Val Glu Thr Gln Ala Cys Thr
65 70 75 80

Arg Glu Gln Asn Arg Ile Cys Thr Cys Arg Pro Gly Trp Tyr Cys Ala
85 90 95

Leu Ser Lys Gln Glu Gly Cys Arg Leu Cys Ala Pro Leu Arg Lys Cys
100 105 110

Arg Pro Gly Phe Gly Val Ala Arg Pro Gly Thr Glu Thr Ser Asp Val
115 120 125

Val Cys Lys Pro Cys Ala Pro Gly Thr Phe Ser Asn Thr Thr Ser Ser
130 135 140
Thr Asp Ile Cys Arg Pro His Gln Ile Cys Asn Val Val Ala Ile Pro
145 150 155 160
Gly Asn Ala Ser Met Asp Ala Val Cys Thr Ser Thr Ser Pro
165 170

<210> 106
<211> 102
<212> PRT
<213> 人
<400> 106

Met Glu Lys Leu Leu Cys Phe Leu Val Leu Thr Ser Leu Ser His Ala
1 5 10 15
Phe Gly Gln Thr Asp Met Ser Arg Lys Ala Phe Val Phe Pro Lys Glu
20 25 30
Ser Asp Thr Ser Tyr Val Ser Leu Lys Ala Pro Leu Thr Lys Pro Leu
35 40 45
Lys Ala Phe Thr Val Cys Leu His Phe Tyr Thr Glu Leu Ser Ser Thr
50 55 60
His Glu Ile Asn Thr Ile Tyr Leu Gly Gly Pro Phe Ser Pro Asn Val
65 70 75 80
Leu Asn Trp Arg Ala Leu Lys Tyr Glu Val Gln Gly Glu Val Phe Thr
85 90 95
Lys Pro Gln Leu Trp Pro
100

<210> 107
<211> 76
<212> PRT
<213> 人
<400> 107

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

65 70 75

<210> 108
<211> 152
<212> PRT
<213> 人
<400> 108

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

<210> 109
<211> 31
<212> PRT
<213> 人
<400> 109

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
20 25 30

<210> 110
<211> 733
<212> PRT
<213> 人

<400> 110

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

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

610 615 620

Thr Met Gly Tyr Met Ala Ala Lys Lys His Leu Glu Ile Asn Pro Asp
625 630 635 640

His Ser Ile Ile Glu Thr Leu Arg Gln Lys Ala Glu Ala Asp Lys Asn
645 650 655

Asp Lys Ser Val Lys Asp Leu Val Ile Leu Leu Tyr Glu Thr Ala Leu
660 665 670

Leu Ser Ser Gly Phe Ser Leu Glu Asp Pro Gln Thr His Ala Asn Arg
675 680 685

Ile Tyr Arg Met Ile Lys Leu Gly Leu Gly Ile Asp Glu Asp Asp Pro
690 695 700

Thr Ala Asp Asp Ser Ser Ala Ala Val Thr Glu Glu Met Pro Pro Leu
705 710 715 720

Glu Gly Asp Asp Asp Thr Ser Arg Met Glu Glu Val Asp
725 730

<210> 111
<211> 53
<212> PRT
<213> 人
<400> 111

Asn Ser Asp Ser Glu Cys Pro Leu Ser His Asp Gly Tyr Cys Leu His
1 5 10 15

Asp Gly Val Cys Met Tyr Ile Glu Ala Leu Asp Lys Tyr Ala Cys Asn
20 25 30

Cys Val Val Gly Tyr Ile Gly Glu Arg Cys Gln Tyr Arg Asp Leu Lys
35 40 45

Trp Trp Glu Leu Arg
50

<210> 112
<211> 1744
<212> PRT
<213> 人
<400> 112

Met Arg Leu Leu Trp Gly Leu Ile Trp Ala Ser Ser Phe Phe Thr Leu
1 5 10 15

Ser Leu Gln Lys Pro Arg Leu Leu Leu Phe Ser Pro Ser Val Val His
20 25 30

Leu Gly Val Pro Leu Ser Val Gly Val Gln Leu Gln Asp Val Pro Arg
35 40 45

Gly Gln Val Val Lys Gly Ser Val Phe Leu Arg Asn Pro Ser Arg Asn
50 55 60
Asn Val Pro Cys Ser Pro Lys Val Asp Phe Thr Leu Ser Ser Glu Arg
65 70 75 80
Asp Phe Ala Leu Leu Ser Leu Gln Val Pro Leu Lys Asp Ala Lys Ser
85 90 95
Cys Gly Leu His Gln Leu Leu Arg Gly Pro Glu Val Gln Leu Val Ala
100 105 110
His Ser Pro Trp Leu Lys Asp Ser Leu Ser Arg Thr Thr Asn Ile Gln
115 120 125
Gly Ile Asn Leu Leu Phe Ser Ser Arg Arg Gly His Leu Phe Leu Gln
130 135 140
Thr Asp Gln Pro Ile Tyr Asn Pro Gly Gln Arg Val Arg Tyr Arg Val
145 150 155 160
Phe Ala Leu Asp Gln Lys Met Arg Pro Ser Thr Asp Thr Ile Thr Val
165 170 175
Met Val Glu Asn Ser His Gly Leu Arg Val Arg Lys Lys Glu Val Tyr
180 185 190
Met Pro Ser Ser Ile Phe Gln Asp Asp Phe Val Ile Pro Asp Ile Ser
195 200 205
Glu Pro Gly Thr Trp Lys Ile Ser Ala Arg Phe Ser Asp Gly Leu Glu
210 215 220
Ser Asn Ser Ser Thr Gln Phe Glu Val Lys Lys Tyr Val Leu Pro Asn
225 230 235 240
Phe Glu Val Lys Ile Thr Pro Gly Lys Pro Tyr Ile Leu Thr Val Pro
245 250 255
Gly His Leu Asp Glu Met Gln Leu Asp Ile Gln Ala Arg Tyr Ile Tyr
260 265 270
Gly Lys Pro Val Gln Gly Val Ala Tyr Val Arg Phe Gly Leu Leu Asp
275 280 285
Glu Asp Gly Lys Lys Thr Phe Phe Arg Gly Leu Glu Ser Gln Thr Lys
290 295 300
Leu Val Asn Gly Gln Ser His Ile Ser Leu Ser Lys Ala Glu Phe Gln
305 310 315 320
Asp Ala Leu Glu Lys Leu Asn Met Gly Ile Thr Asp Leu Gln Gly Leu
325 330 335
Arg Leu Tyr Val Ala Ala Ala Ile Ile Glu Ser Pro Gly Gly Glu Met
340 345 350
Glu Glu Ala Glu Leu Thr Ser Trp Tyr Phe Val Ser Ser Pro Phe Ser

355 360 365

Leu Asp Leu Ser Lys Thr Lys Arg His Leu Val Pro Gly Ala Pro Phe

370 375 380

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

385 390 395 400

Ile Pro Val Lys Val Ser Ala Thr Val Ser Ser Pro Gly Ser Val Pro

405 410 415

Glu Val Gln Asp Ile Gln Gln Asn Thr Asp Gly Ser Gly Gln Val Ser

420 425 430

Ile Pro Ile Ile Ile Pro Gln Thr Ile Ser Glu Leu Gln Leu Ser Val

435 440 445

Ser Ala Gly Ser Pro His Pro Ala Ile Ala Arg Leu Thr Val Ala Ala

450 455 460

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

465 470 475 480

Arg Pro Pro Arg Val Gly Asp Thr Leu Asn Leu Asn Leu Arg Ala Val

485 490 495

Gly Ser Gly Ala Thr Phe Ser His Tyr Tyr Tyr Met Ile Leu Ser Arg

500 505 510

Gly Gln Ile Val Phe Met Asn Arg Glu Pro Lys Arg Thr Leu Thr Ser

515 520 525

Val Ser Val Phe Val Asp His His Leu Ala Pro Ser Phe Tyr Phe Val

530 535 540

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

545 550 555 560

Asp Val Gln Ala Gly Ala Cys Glu Gly Lys Leu Glu Leu Ser Val Asp

565 570 575

Gly Ala Lys Gln Tyr Arg Asn Gly Glu Ser Val Lys Leu His Leu Glu

580 585 590

Thr Asp Ser Leu Ala Leu Val Ala Leu Gly Ala Leu Asp Thr Ala Leu

595 600 605

Tyr Ala Ala Gly Ser Lys Ser His Lys Pro Leu Asn Met Gly Lys Val

610 615 620

Phe Glu Ala Met Asn Ser Tyr Asp Leu Gly Cys Gly Pro Gly Gly Gly

625 630 635 640

Asp Ser Ala Leu Gln Val Phe Gln Ala Ala Gly Leu Ala Phe Ser Asp

645 650 655

Gly Asp Gln Trp Thr Leu Ser Arg Lys Arg Leu Ser Cys Pro Lys Glu

660 665 670

Lys Thr Thr Arg Lys Lys Arg Asn Val Asn Phe Gln Lys Ala Ile Asn
675 680 685
Glu Lys Leu Gly Gln Tyr Ala Ser Pro Thr Ala Lys Arg Cys Cys Gln
690 695 700
Asp Gly Val Thr Arg Leu Pro Met Met Arg Ser Cys Glu Gln Arg Ala
705 710 715 720
Ala Arg Val Gln Gln Pro Asp Cys Arg Glu Pro Phe Leu Ser Cys Cys
725 730 735
Gln Phe Ala Glu Ser Leu Arg Lys Lys Ser Arg Asp Lys Gly Gln Ala
740 745 750
Gly Leu Gln Arg Ala Leu Glu Ile Leu Gln Glu Glu Asp Leu Ile Asp
755 760 765
Glu Asp Asp Ile Pro Val Arg Ser Phe Phe Pro Glu Asn Trp Leu Trp
770 775 780
Arg Val Glu Thr Val Asp Arg Phe Gln Ile Leu Thr Leu Trp Leu Pro
785 790 795 800
Asp Ser Leu Thr Thr Trp Glu Ile His Gly Leu Ser Leu Ser Lys Thr
805 810 815
Lys Gly Leu Cys Val Ala Thr Pro Val Gln Leu Arg Val Phe Arg Glu
820 825 830
Phe His Leu His Leu Arg Leu Pro Met Ser Val Arg Arg Phe Glu Gln
835 840 845
Leu Glu Leu Arg Pro Val Leu Tyr Asn Tyr Leu Asp Lys Asn Leu Thr
850 855 860
Val Ser Val His Val Ser Pro Val Glu Gly Leu Cys Leu Ala Gly Gly
865 870 875 880
Gly Gly Leu Ala Gln Gln Val Leu Val Pro Ala Gly Ser Ala Arg Pro
885 890 895
Val Ala Phe Ser Val Val Pro Thr Ala Ala Ala Ala Val Ser Leu Lys
900 905 910
Val Val Ala Arg Gly Ser Phe Glu Phe Pro Val Gly Asp Ala Val Ser
915 920 925
Lys Val Leu Gln Ile Glu Lys Glu Gly Ala Ile His Arg Glu Glu Leu
930 935 940
Val Tyr Glu Leu Asn Pro Leu Asp His Arg Gly Arg Thr Leu Glu Ile
945 950 955 960
Pro Gly Asn Ser Asp Pro Asn Met Ile Pro Asp Gly Asp Phe Asn Ser
965 970 975
Tyr Val Arg Val Thr Ala Ser Asp Pro Leu Asp Thr Leu Gly Ser Glu

980 985 990

Gly Ala Leu Ser Pro Gly Gly Val Ala Ser Leu Leu Arg Leu Pro Arg

995 1000 1005

Gly Cys Gly Glu Gln Thr Met Ile Tyr Leu Ala Pro Thr Leu Ala

1010 1015 1020

Ala Ser Arg Tyr Leu Asp Lys Thr Glu Gln Trp Ser Thr Leu Pro

1025 1030 1035

Pro Glu Thr Lys Asp His Ala Val Asp Leu Ile Gln Lys Gly Tyr

1040 1045 1050

Met Arg Ile Gln Gln Phe Arg Lys Ala Asp Gly Ser Tyr Ala Ala

1055 1060 1065

Trp Leu Ser Arg Asp Ser Ser Thr Trp Leu Thr Ala Phe Val Leu

1070 1075 1080

Lys Val Leu Ser Leu Ala Gln Glu Gln Val Gly Gly Ser Pro Glu

1085 1090 1095

Lys Leu Gln Glu Thr Ser Asn Trp Leu Leu Ser Gln Gln Gln Ala

1100 1105 1110

Asp Gly Ser Phe Gln Asp Pro Cys Pro Val Leu Asp Arg Ser Met

1115 1120 1125

Gln Gly Gly Leu Val Gly Asn Asp Glu Thr Val Ala Leu Thr Ala

1130 1135 1140

Phe Val Thr Ile Ala Leu His His Gly Leu Ala Val Phe Gln Asp

1145 1150 1155

Glu Gly Ala Glu Pro Leu Lys Gln Arg Val Glu Ala Ser Ile Ser

1160 1165 1170

Lys Ala Asn Ser Phe Leu Gly Glu Lys Ala Ser Ala Gly Leu Leu

1175 1180 1185

Gly Ala His Ala Ala Ala Ile Thr Ala Tyr Ala Leu Thr Leu Thr

1190 1195 1200

Lys Ala Pro Val Asp Leu Leu Gly Val Ala His Asn Asn Leu Met

1205 1210 1215

Ala Met Ala Gln Glu Thr Gly Asp Asn Leu Tyr Trp Gly Ser Val

1220 1225 1230

Thr Gly Ser Gln Ser Asn Ala Val Ser Pro Thr Pro Ala Pro Arg

1235 1240 1245

Asn Pro Ser Asp Pro Met Pro Gln Ala Pro Ala Leu Trp Ile Glu

1250 1255 1260

Thr Thr Ala Tyr Ala Leu Leu His Leu Leu Leu His Glu Gly Lys

1265 1270 1275

Ala Glu Met Ala Asp Gln Ala Ser Ala Trp Leu Thr Arg Gln Gly
1280 1285 1290
Ser Phe Gln Gly Gly Phe Arg Ser Thr Gln Asp Thr Val Ile Ala
1295 1300 1305
Leu Asp Ala Leu Ser Ala Tyr Trp Ile Ala Ser His Thr Thr Glu
1310 1315 1320
Glu Arg Gly Leu Asn Val Thr Leu Ser Ser Thr Gly Arg Asn Gly
1325 1330 1335
Phe Lys Ser His Ala Leu Gln Leu Asn Asn Arg Gln Ile Arg Gly
1340 1345 1350
Leu Glu Glu Glu Leu Gln Phe Ser Leu Gly Ser Lys Ile Asn Val
1355 1360 1365
Lys Val Gly Gly Asn Ser Lys Gly Thr Leu Lys Val Leu Arg Thr
1370 1375 1380
Tyr Asn Val Leu Asp Met Lys Asn Thr Thr Cys Gln Asp Leu Gln
1385 1390 1395
Ile Glu Val Thr Val Lys Gly His Val Glu Tyr Thr Met Glu Ala
1400 1405 1410
Asn Glu Asp Tyr Glu Asp Tyr Glu Tyr Asp Glu Leu Pro Ala Lys
1415 1420 1425
Asp Asp Pro Asp Ala Pro Leu Gln Pro Val Thr Pro Leu Gln Leu
1430 1435 1440
Phe Glu Gly Arg Arg Asn Arg Arg Arg Arg Glu Ala Pro Lys Val
1445 1450 1455
Val Glu Glu Gln Glu Ser Arg Val His Tyr Thr Val Cys Ile Trp
1460 1465 1470
Arg Asn Gly Lys Val Gly Leu Ser Gly Met Ala Ile Ala Asp Val
1475 1480 1485
Thr Leu Leu Ser Gly Phe His Ala Leu Arg Ala Asp Leu Glu Lys
1490 1495 1500
Leu Thr Ser Leu Ser Asp Arg Tyr Val Ser His Phe Glu Thr Glu
1505 1510 1515
Gly Pro His Val Leu Leu Tyr Phe Asp Ser Val Pro Thr Ser Arg
1520 1525 1530
Glu Cys Val Gly Phe Glu Ala Val Gln Glu Val Pro Val Gly Leu
1535 1540 1545
Val Gln Pro Ala Ser Ala Thr Leu Tyr Asp Tyr Tyr Asn Pro Glu
1550 1555 1560
Arg Arg Cys Ser Val Phe Tyr Gly Ala Pro Ser Lys Ser Arg Leu

1565 1570 1575
Leu Ala Thr Leu Cys Ser Ala Glu Val Cys Gln Cys Ala Glu Gly
1580 1585 1590
Lys Cys Pro Arg Gln Arg Arg Ala Leu Glu Arg Gly Leu Gln Asp
1595 1600 1605
Glu Asp Gly Tyr Arg Met Lys Phe Ala Cys Tyr Tyr Pro Arg Val
1610 1615 1620
Glu Tyr Gly Phe Gln Val Lys Val Leu Arg Glu Asp Ser Arg Ala
1625 1630 1635
Ala Phe Arg Leu Phe Glu Thr Lys Ile Thr Gln Val Leu His Phe
1640 1645 1650
Thr Lys Asp Val Lys Ala Ala Ala Asn Gln Met Arg Asn Phe Leu
1655 1660 1665
Val Arg Ala Ser Cys Arg Leu Arg Leu Glu Pro Gly Lys Glu Tyr
1670 1675 1680
Leu Ile Met Gly Leu Asp Gly Ala Thr Tyr Asp Leu Glu Gly His
1685 1690 1695
Pro Gln Tyr Leu Leu Asp Ser Asn Ser Trp Ile Glu Glu Met Pro
1700 1705 1710
Ser Glu Arg Leu Cys Arg Ser Thr Arg Gln Arg Ala Ala Cys Ala
1715 1720 1725
Gln Leu Asn Asp Phe Leu Gln Glu Tyr Gly Thr Gln Gly Cys Gln
1730 1735 1740
Val

<210> 113
<211> 1663
<212> PRT
<213> 人
<400> 113

Met Gly Pro Thr Ser Gly Pro Ser Leu Leu Leu Leu Leu Leu Thr His
1 5 10 15
Leu Pro Leu Ala Leu Gly Ser Pro Met Tyr Ser Ile Ile Thr Pro Asn
20 25 30
Ile Leu Arg Leu Glu Ser Glu Glu Thr Met Val Leu Glu Ala His Asp
35 40 45
Ala Gln Gly Asp Val Pro Val Thr Val Thr Val His Asp Phe Pro Gly
50 55 60
Lys Lys Leu Val Leu Ser Ser Glu Lys Thr Val Leu Thr Pro Ala Thr
65 70 75 80

Asn His Met Gly Asn Val Thr Phe Thr Ile Pro Ala Asn Arg Glu Phe
85 90 95
Lys Ser Glu Lys Gly Arg Asn Lys Phe Val Thr Val Gln Ala Thr Phe
100 105 110
Gly Thr Gln Val Val Glu Lys Val Val Leu Val Ser Leu Gln Ser Gly
115 120 125
Tyr Leu Phe Ile Gln Thr Asp Lys Thr Ile Tyr Thr Pro Gly Ser Thr
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Val Leu Tyr Arg Ile Phe Thr Val Asn His Lys Leu Leu Pro Val Gly
145 150 155 160
Arg Thr Val Met Val Asn Ile Glu Asn Pro Glu Gly Ile Pro Val Lys
165 170 175
Gln Asp Ser Leu Ser Ser Gln Asn Gln Leu Gly Val Leu Pro Leu Ser
180 185 190
Trp Asp Ile Pro Glu Leu Val Asn Met Gly Gln Trp Lys Ile Arg Ala
195 200 205
Tyr Tyr Glu Asn Ser Pro Gln Gln Val Phe Ser Thr Glu Phe Glu Val
210 215 220
Lys Glu Tyr Val Leu Pro Ser Phe Glu Val Ile Val Glu Pro Thr Glu
225 230 235 240
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245 250 255
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Phe Gly Ile Gln Asp Gly Glu Gln Arg Ile Ser Leu Pro Glu Ser Leu
275 280 285
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Tyr Gln Ile His Phe Thr Lys Thr Pro Lys Tyr Phe Lys Pro Gly Met
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Pro Phe Asp Leu Met Val Phe Val Thr Asn Pro Asp Gly Ser Pro Ala
370 375 380
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Gln Lys Pro Leu Ser Ile Thr Val Arg Thr Lys Lys Gln Glu Leu Ser
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Glu Ala Glu Gln Ala Thr Arg Thr Met Gln Ala Leu Pro Tyr Ser Thr
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450 455 460
Leu Arg Pro Gly Glu Thr Leu Asn Val Asn Phe Leu Leu Arg Met Asp
465 470 475 480
Arg Ala His Glu Ala Lys Ile Arg Tyr Tyr Thr Tyr Leu Ile Met Asn
485 490 495
Lys Gly Arg Leu Leu Lys Ala Gly Arg Gln Val Arg Glu Pro Gly Gln
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Asp Leu Val Val Leu Pro Leu Ser Ile Thr Thr Asp Phe Ile Pro Ser
515 520 525
Phe Arg Leu Val Ala Tyr Tyr Thr Leu Ile Gly Ala Ser Gly Gln Arg
530 535 540
Glu Val Val Ala Asp Ser Val Trp Val Asp Val Lys Asp Ser Cys Val
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Gly Ser Leu Val Val Lys Ser Gly Gln Ser Glu Asp Arg Gln Pro Val
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Pro Gly Gln Gln Met Thr Leu Lys Ile Glu Gly Asp His Gly Ala Arg
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Val Val Leu Val Ala Val Asp Lys Gly Val Phe Val Leu Asn Lys Lys
595 600 605
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Ile Gly Cys Thr Pro Gly Ser Gly Lys Asp Tyr Ala Gly Val Phe Ser
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Asp Ala Gly Leu Thr Phe Thr Ser Ser Ser Gly Gln Gln Thr Ala Gln
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Arg Ala Glu Leu Gln Cys Pro Gln Pro Ala Ala Arg Arg Arg Arg Ser
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Val Gln Leu Thr Glu Lys Arg Met Asp Lys Val Gly Lys Tyr Pro Lys
675 680 685
Glu Leu Arg Lys Cys Cys Glu Asp Gly Met Arg Glu Asn Pro Met Arg
690 695 700

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Lys Lys Val Phe Leu Asp Cys Cys Asn Tyr Ile Thr Glu Leu Arg Arg
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Gln His Ala Arg Ala Ser His Leu Gly Leu Ala Arg Ser Asn Leu Asp
740 745 750
Glu Asp Ile Ile Ala Glu Glu Asn Ile Val Ser Arg Ser Glu Phe Pro
755 760 765
Glu Ser Trp Leu Trp Asn Val Glu Asp Leu Lys Glu Pro Pro Lys Asn
770 775 780
Gly Ile Ser Thr Lys Leu Met Asn Ile Phe Leu Lys Asp Ser Ile Thr
785 790 795 800
Thr Trp Glu Ile Leu Ala Val Ser Met Ser Asp Lys Lys Gly Ile Cys
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Val Ala Asp Pro Phe Glu Val Thr Val Met Gln Asp Phe Phe Ile Asp
820 825 830
Leu Arg Leu Pro Tyr Ser Val Val Arg Asn Glu Gln Val Glu Ile Arg
835 840 845
Ala Val Leu Tyr Asn Tyr Arg Gln Asn Gln Glu Leu Lys Val Arg Val
850 855 860
Glu Leu Leu His Asn Pro Ala Phe Cys Ser Leu Ala Thr Thr Lys Arg
865 870 875 880
Arg His Gln Gln Thr Val Thr Ile Pro Pro Lys Ser Ser Leu Ser Val
885 890 895
Pro Tyr Val Ile Val Pro Leu Lys Thr Gly Leu Gln Glu Val Glu Val
900 905 910
Lys Ala Ala Val Tyr His His Phe Ile Ser Asp Gly Val Arg Lys Ser
915 920 925
Leu Lys Val Val Pro Glu Gly Ile Arg Met Asn Lys Thr Val Ala Val
930 935 940
Arg Thr Leu Asp Pro Glu Arg Leu Gly Arg Glu Gly Val Gln Lys Glu
945 950 955 960
Asp Ile Pro Pro Ala Asp Leu Ser Asp Gln Val Pro Asp Thr Glu Ser
965 970 975
Glu Thr Arg Ile Leu Leu Gln Gly Thr Pro Val Ala Gln Met Thr Glu
980 985 990
Asp Ala Val Asp Ala Glu Arg Leu Lys His Leu Ile Val Thr Pro Ser
995 1000 1005
Gly Cys Gly Glu Gln Asn Met Ile Gly Met Thr Pro Thr Val Ile

1010 1015 1020

Ala Val His Tyr Leu Asp Glu Thr Glu Gln Trp Glu Lys Phe Gly
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Leu Glu Lys Arg Gln Gly Ala Leu Glu Leu Ile Lys Lys Gly Tyr
1040 1045 1050

Thr Gln Gln Leu Ala Phe Arg Gln Pro Ser Ser Ala Phe Ala Ala
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Phe Val Lys Arg Ala Pro Ser Thr Trp Leu Thr Ala Tyr Val Val
1070 1075 1080

Lys Val Phe Ser Leu Ala Val Asn Leu Ile Ala Ile Asp Ser Gln
1085 1090 1095

Val Leu Cys Gly Ala Val Lys Trp Leu Ile Leu Glu Lys Gln Lys
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Pro Asp Gly Val Phe Gln Glu Asp Ala Pro Val Ile His Gln Glu
1115 1120 1125

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Val Ala Ile Ala Gly Tyr Ala Leu Ala Gln Met Gly Arg Leu Lys
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Arg Trp Glu Asp Pro Gly Lys Gln Leu Tyr Asn Val Glu Ala Thr
1220 1225 1230

Ser Tyr Ala Leu Leu Ala Leu Leu Gln Leu Lys Asp Phe Asp Phe
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Val Pro Pro Val Val Arg Trp Leu Asn Glu Gln Arg Tyr Tyr Gly
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Gly Gly Tyr Gly Ser Thr Gln Ala Thr Phe Met Val Phe Gln Ala
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His Arg Ile His Trp Glu Ser Ala Ser Leu Leu Arg Ser Glu Glu
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Gln Gly Thr Leu Ser Val Val Thr Met Tyr His Ala Lys Ala Lys
1340 1345 1350
Asp Gln Leu Thr Cys Asn Lys Phe Asp Leu Lys Val Thr Ile Lys
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1430 1435 1440
Leu Ile Ile Tyr Leu Asp Lys Val Ser His Ser Glu Asp Asp Cys
1445 1450 1455
Leu Ala Phe Lys Val His Gln Tyr Phe Asn Val Glu Leu Ile Gln
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Pro Gly Ala Val Lys Val Tyr Ala Tyr Tyr Asn Leu Glu Glu Ser
1475 1480 1485
Cys Thr Arg Phe Tyr His Pro Glu Lys Glu Asp Gly Lys Leu Asn
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Phe Ile Gln Lys Ser Asp Asp Lys Val Thr Leu Glu Glu Arg Leu
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Asp Lys Ala Cys Glu Pro Gly Val Asp Tyr Val Tyr Lys Thr Arg
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1595 1600 1605

Ser Asp Phe Trp Gly Glu Lys Pro Asn Leu Ser Tyr Ile Ile Gly

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Lys Asp Thr Trp Val Glu His Trp Pro Glu Glu Asp Glu Cys Gln

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Glu Ser Met Val Val Phe Gly Cys Pro Asn

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35 40 45

Gly Glu Gln Gly Glu Pro Gly Ala Pro Gly Ile Arg Thr Gly Ile Gln

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Gly Leu Lys Gly Asp Gln Gly Glu Pro Gly Pro Ser Gly Asn Pro Gly

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Lys Val Gly Tyr Pro Gly Pro Ser Gly Pro Leu Gly Ala Arg Gly Ile

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Pro Gly Ile Lys Gly Thr Lys Gly Ser Pro Gly Asn Ile Lys Asp Gln

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Pro Arg Pro Ala Phe Ser Ala Ile Arg Arg Asn Pro Pro Met Gly Gly

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Asn Val Val Ile Phe Asp Thr Val Ile Thr Asn Gln Glu Glu Pro Tyr

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Gln Asn His Ser Gly Arg Phe Val Cys Thr Val Pro Gly Tyr Tyr Tyr

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Phe Thr Phe Gln Val Leu Ser Gln Trp Glu Ile Cys Leu Ser Ile Val

165 170 175

Ser Ser Ser Arg Gly Gln Val Arg Arg Ser Leu Gly Phe Cys Asp Thr

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Thr Asn Lys Gly Leu Phe Gln Val Val Ser Gly Gly Met Val Leu Gln

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

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Lys Met Lys Pro Val Pro Asp Leu Val Pro Gly Asn Phe Lys Ser Gln
225 230 235 240

Leu Gln Lys Val Pro Pro Glu Trp Lys Ala Leu Thr Asp Met Pro Gln
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Met Arg Met Glu Leu Glu Arg Pro Gly Gly Asn Glu Ile Thr Arg Gly
260 265 270

Gly Ser Thr Ser Tyr Gly Thr Gly Ser Glu Thr Glu Ser Pro Arg Asn
275 280 285

Pro Ser Ser Ala Gly Ser Trp Asn Ser Gly Ser Ser Gly Pro Gly Ser
290 295 300

Thr Gly Asn Arg Asn Pro Gly Ser Ser Gly Thr Gly Gly Thr Ala Thr
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Trp Lys Pro Gly Ser Ser Gly Pro Gly Ser Thr Gly Ser Trp Asn Ser
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Arg Pro Gly Ser Thr Gly Thr Trp Asn Pro Gly Ser Ser Glu Arg Gly
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Gln Trp His Ser Glu Ser Gly Ser Phe Arg Pro Asp Ser Pro Gly Ser
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Gly Asn Ala Arg Pro Asn Asn Pro Asp Trp Gly Thr Phe Glu Glu Val
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Ser Gly Asn Val Ser Pro Gly Thr Arg Arg Glu Tyr His Thr Glu Lys
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Leu Val Thr Ser Lys Gly Asp Lys Glu Leu Arg Thr Gly Lys Glu Lys
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Val Thr Ser Gly Ser Thr Thr Thr Thr Arg Arg Ser Cys Ser Lys Thr
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Val Thr Lys Thr Val Ile Gly Pro Asp Gly His Lys Glu Val Thr Lys
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Glu Val Val Thr Ser Glu Asp Gly Ser Asp Cys Pro Glu Ala Met Asp
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Leu Gly Thr Leu Ser Gly Ile Gly Thr Leu Asp Gly Phe Arg His Arg
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His Pro Asp Glu Ala Ala Phe Phe Asp Thr Ala Ser Thr Gly Lys Thr
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595 600 605
Ser Glu Ala Asp His Glu Gly Thr His Ser Thr Lys Arg Gly His Ala
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Lys Ser Arg Pro Val Arg Asp Cys Asp Asp Val Leu Gln Thr His Pro
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Lys Ile Phe Ser Val Tyr Cys Asp Gln Glu Thr Ser Leu Gly Gly Trp
660 665 670
Leu Leu Ile Gln Gln Arg Met Asp Gly Ser Leu Asn Phe Asn Arg Thr
675 680 685
Trp Gln Asp Tyr Lys Arg Gly Phe Gly Ser Leu Asn Asp Glu Gly Glu
690 695 700
Gly Glu Phe Trp Leu Gly Asn Asp Tyr Leu His Leu Leu Thr Gln Arg
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Gly Ser Val Leu Arg Val Glu Leu Glu Asp Trp Ala Gly Asn Glu Ala
725 730 735
Tyr Ala Glu Tyr His Phe Arg Val Gly Ser Glu Ala Glu Gly Tyr Ala
740 745 750
Leu Gln Val Ser Ser Tyr Glu Gly Thr Ala Gly Asp Ala Leu Ile Glu
755 760 765
Gly Ser Val Glu Glu Gly Ala Glu Tyr Thr Ser His Asn Asn Met Gln
770 775 780
Phe Ser Thr Phe Asp Arg Asp Ala Asp Gln Trp Glu Glu Asn Cys Ala
785 790 795 800
Glu Val Tyr Gly Gly Gly Trp Trp Tyr Asn Asn Cys Gln Ala Ala Asn
805 810 815
Leu Asn Gly Ile Tyr Tyr Pro Gly Gly Ser Tyr Asp Pro Arg Asn Asn
820 825 830
Ser Pro Tyr Glu Ile Glu Asn Gly Val Val Trp Val Ser Phe Arg Gly

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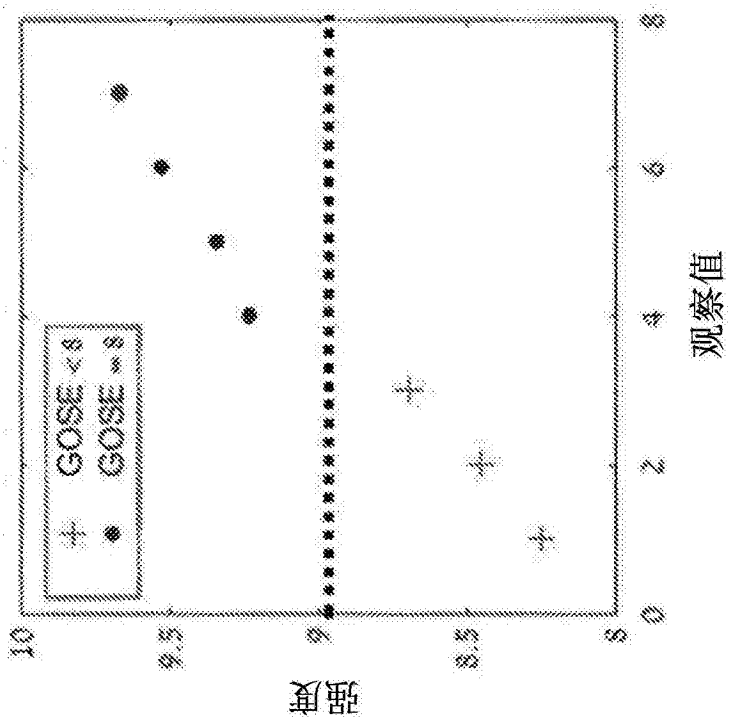

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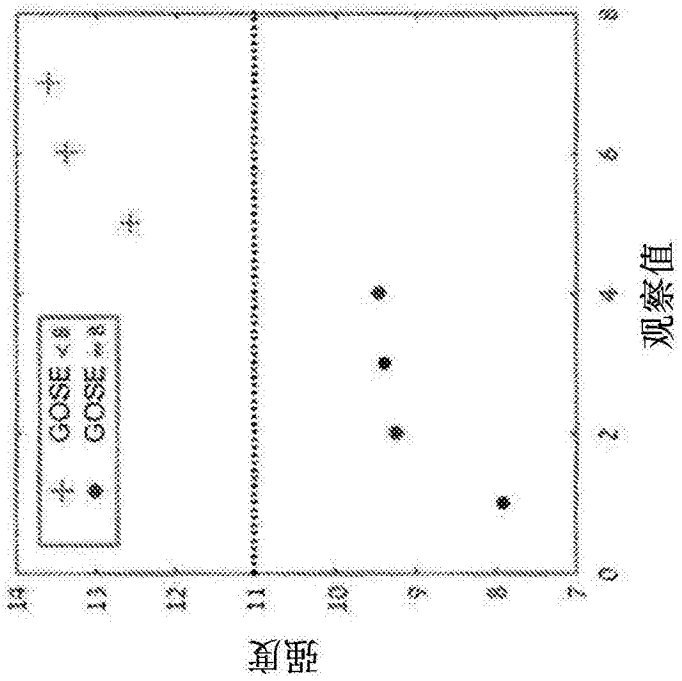

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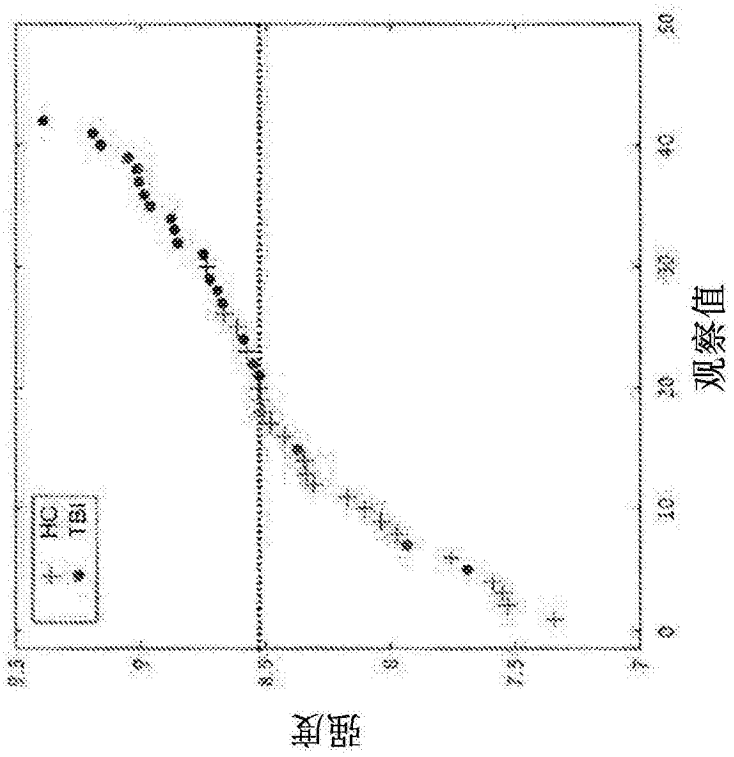

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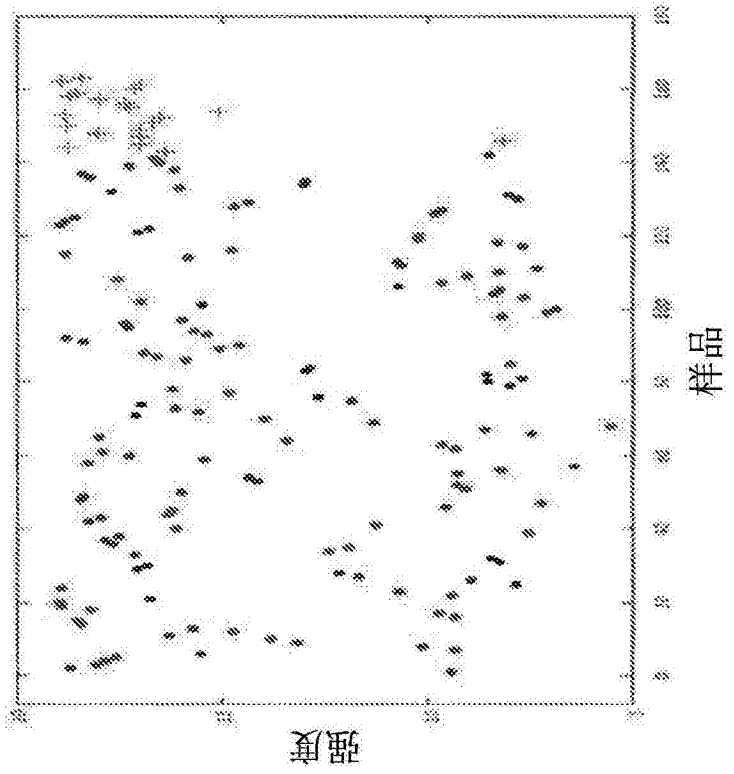
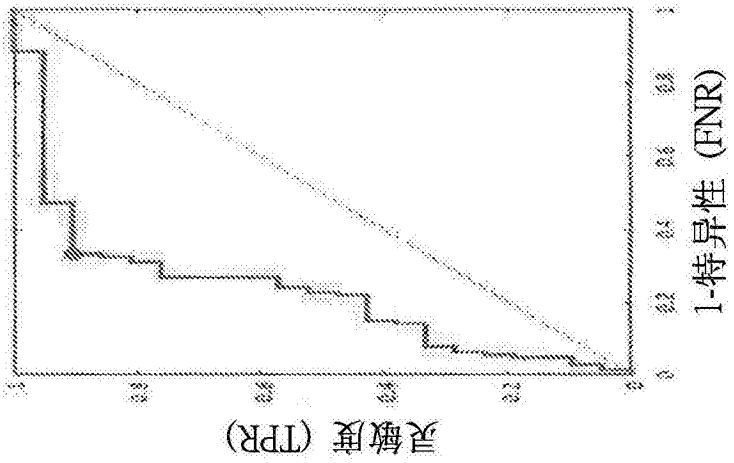


图4A



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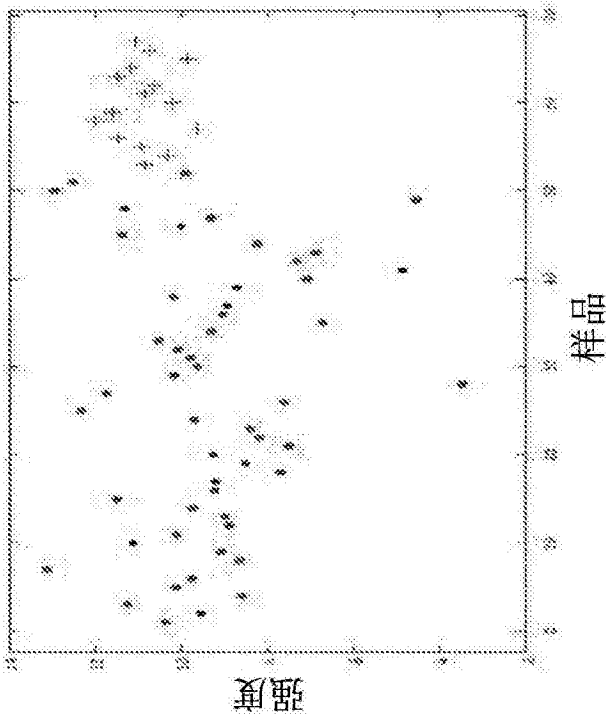


图5A

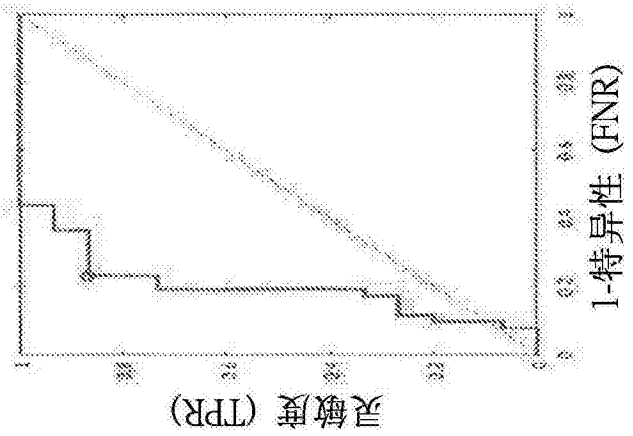
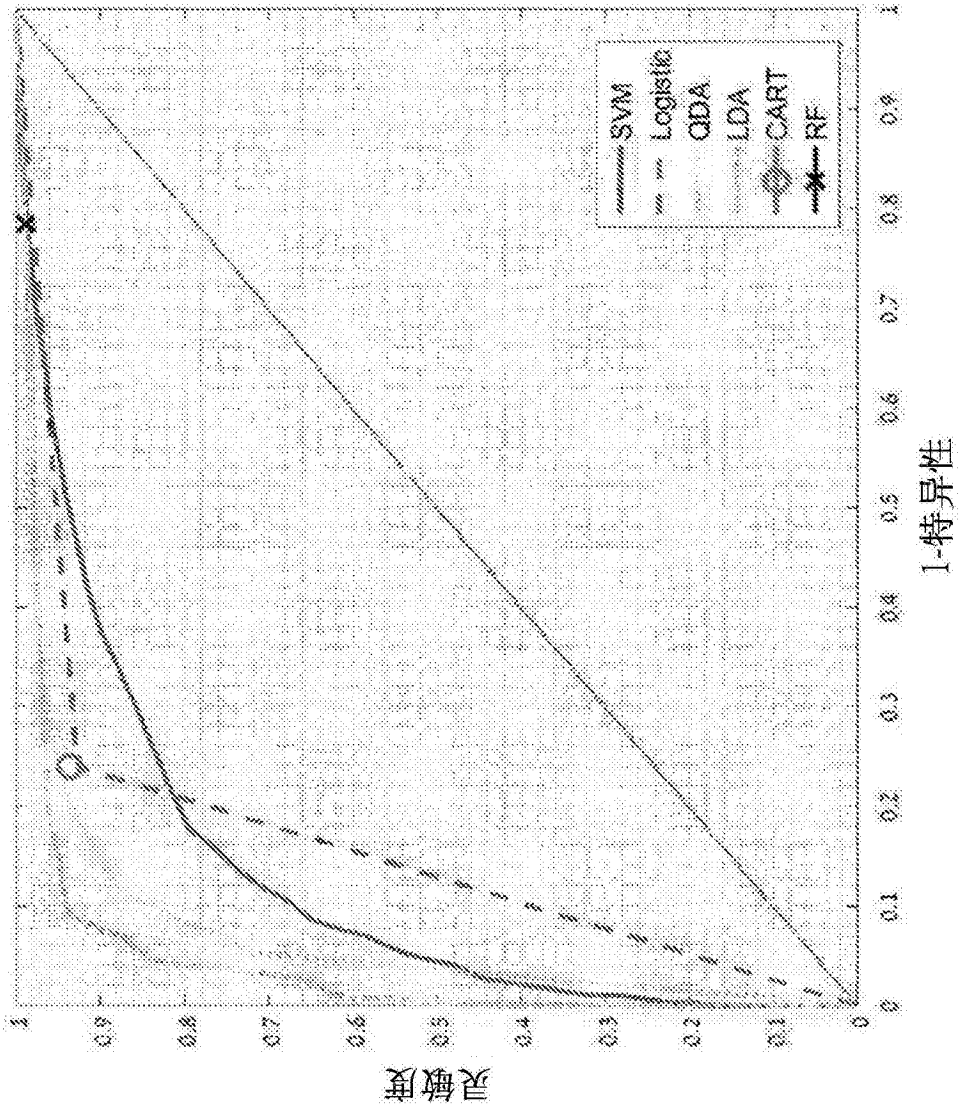


图5B



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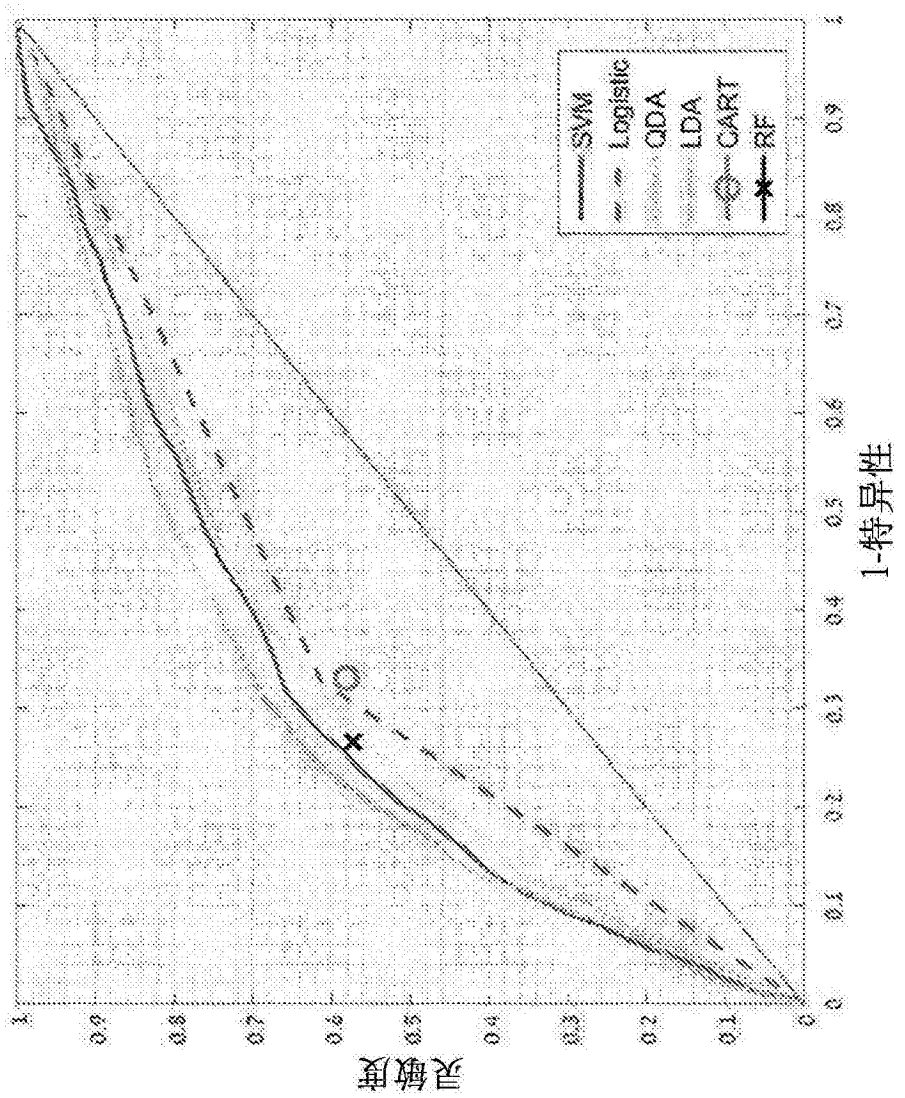

图7

专利名称(译)	用于诊断脑损伤或神经退行性变的方法和组合物		
公开(公告)号	CN107533048A	公开(公告)日	2018-01-02
申请号	CN201680020961.6	申请日	2016-02-01
[标]发明人	蕾切尔索莱克 克伦贾科比 唐娜埃德蒙兹		
发明人	蕾切尔·索莱克 克伦·贾科比 唐娜·埃德蒙兹		
IPC分类号	G01N33/50 G01N33/53 C07K14/46		
CPC分类号	G01N33/6896 C07K14/47 G01N33/54366 G01N33/96 G01N2800/28 G01N2800/52 G01N2800/56		
代理人(译)	程伟		
优先权	62/112189 2015-02-05 US		
外部链接	Espacenet SIPO		

摘要(译)

提供用于诊断对象的脑损伤、神经退行性变；或其倾向的方法和组合物。特别地，本发明涉及可用于诊断对象的脑损伤、神经退行性变；或其倾向的特异性抗原抗体反应性。

抗原	氨基酸序列或产品(产品目录号)	SEQ ID NO:
MBP（髓磷脂碱性蛋白）	MASQKRPSQRHGSKYLATASTMDHARHGFLPRHRDTGILDSTGRFFGGDRGAPKRGSGKVPWLKPGRSPL PSHARSQPGLCNMYKDSHHPARTAHYGSLPQKSHGRTQDENPVVHFFKNIVTPRTPPPSQGKGRGLSLSR FSWGAEGQRPGFGYGGRASDYKSAHKGFKGVDAQGTLSKIFKLGGRDSRSGSPMARR Enzo LS （ALX-200-606-M001）	1
MBP-体外瓜氨酸化	Enzo LS 中一个或多个精氨酸的转译后瓜氨酸化（ALX-200-606-M001）	2
MBP R26	Ac-TMDHA(Cit)HGFLPC-酰胺	3
MBP R32, R34	Ac-GFLP(Cit)H(Cit)DTGIC-酰胺	4
MBP R44	Ac-CILDSIG(Cit)FFGG-酰胺	5
MBP R50	Ac-FGGD(Cit)GAPKRGC-酰胺	6
MBP R92	Ac-CDSHHPA(Cit)TAHYG-酰胺	7
MBP R106	Ac-CQKSHG(Cit)TQDEN-酰胺	8
MBP R124	Ac-CFKNIVTP(Cit)TP-酰胺	9
MBP R149	Ac-GAEGQ(Cit)PGFGYC-酰胺	10
MBP R157	Ac-CGYGG(Cit)ASDYKS-酰胺	11
MBP R186, R189	Ac-CKLGG(Cit)DS(Cit)SG-酰胺	12
MBP R196, R197	Ac-C(Ahx)SGSPMA(Cit)(Cit)-OH	13
GFAP（胶质纤维酸性蛋白）	MERRRITSAARRSYVSSGEMMVGGLAPGRRLGPGTRLSLARMPPPLPTRVDFSLAGALNAGFKETRASER AEMMELNDRFASYIEKVRFLEQQNKALAAELNQLRAKEPTKLADVYQAELRELRLRLDQLTANSARLEVE RDNLAQDLATVRQKLQDETNLRLEAENNLAAYRQEADEATLARLDLERKIESLEEEIRFLRKTHEEEVRE LQEQLARQQVHVELDVAKPDLTAALKEIRTQYEAMASSNMHEAEEWYRSKFADLTDAAARNAELLRQAKH EANDYRRQLQSLTCDLESLRGTNESLERQMREQEERHVREAASYQEALARLEEEGQSLKDEMARHLQEYQ	14