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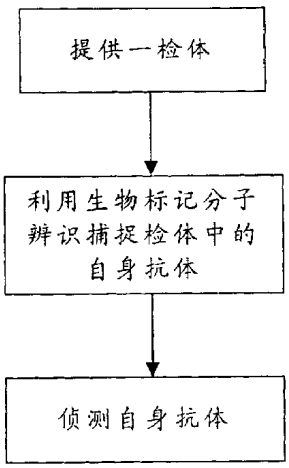
[54] 发明名称 肝脏疾病的生物标记分子及其检测方法

[57] 摘要

本发明涉及肝脏疾病的生物标记分子及其检测方法，所述生物标记分子，为选自 SEQ ID NO：1 至 SEQ NO：24 所示的任一氨基酸序列或其衍生物或其片段或其变异体或其组合物或其对应的自身抗体；利用这些生物标记分子发展为检测套组，藉筛选检体中自身抗体或自身抗原的存在判断是否罹患肝脏疾病，可有效提高准确度与灵敏度。



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1. 一种用于检测肝脏疾病的生物标记分子，其选自 SEQ ID NO:1 至 SEQ ID NO:24 所示的任一氨基酸序列或其衍生物或其片段或其变异体或其组合物及其对应的自身抗体。

2. 如权利要求 1 所述的检测肝脏疾病的生物标记分子，其中所述肝脏疾病为肝硬化或肝癌。

3. 如权利要求 1 所述的检测肝脏疾病的生物标记分子，其中所述变异体与所述 SEQ ID NO:1 至 SEQ ID NO:24 所示的任一氨基酸序列具有大于 80%的序列同源性。

4. 一种肝脏疾病的检测套组，包含：生物标记分子，其选自 SEQ ID NO:1 至 SEQ ID NO:24 所示的任一氨基酸序列或其衍生物或其片段或其变异体或其组合物。

5. 如权利要求 4 所述的肝脏疾病的检测套组，其中所述肝脏疾病为肝硬化或肝癌。

6. 如权利要求 4 所述的肝脏疾病的检测套组，其中所述检测套组进一步包含可辨识 SEQ ID NO:1 至 SEQ ID NO:24 所示的任一氨基酸序列或其衍生物或其片段或其组合物的自身抗体的二级抗体。

7. 一种肝脏疾病的体外筛检方法，包含下列步骤:

提供一检体;

利用 SEQ ID NO:1 至 SEQ ID NO:24 所示的任一氨基酸序列或其衍生物或其片段或其变异体或其组合物的生物标记分子辨识捕捉检体中的自身抗体；及

侦测自身抗体。

8. 如权利要求 7 所述的体外筛检方法，其中所述检体包含全血或血清。

9. 如权利要求 8 所述的体外筛检方法，其中所述检体为血清。

10. 如权利要求 7 所述的体外筛检方法，其中所述生物标记分子可制成检

测套组。

11. 如权利要求 7 所述的体外筛检方法，其中所述生物标记分子可进一步先行固定于基材上。

12. 如权利要求 11 所述的体外筛检方法，其中所述基材为免疫分析盘或生物芯片。

13. 如权利要求 7 所述的体外筛检方法，其中所述检体进一步先行以萤光标记进行标示。

14. 如权利要求 7 所述的体外筛检方法，其中可增加一利用二级抗体辨识吸附自身抗体的步骤。

15. 如权利要求 14 所述的体外筛检方法，其中所述二级抗体经修饰具有特殊官能团可进行显色反应、放射性侦测或萤光侦测。

16. 如权利要求 7 所述的体外筛检方法，其中所述侦测自身抗体是利用萤光扫瞄分析侦测具有萤光标记的自身抗体。

17. 如权利要求 7 所述的体外筛检方法，其中所述侦测自身抗体是利用酶联免疫检测、放射免疫分析或免疫萤光分析侦测二级抗体。

18. 一种肝脏疾病的检测套组，包含一组可辨识具有 SEQ ID NO: 1 至 SEQ ID NO: 24 所示的任一氨基酸序列的抗体。

19. 如权利要求 18 所述的肝脏疾病的检测套组，其中所述肝脏疾病为肝硬化或肝癌。

20. 一种肝脏疾病的体外筛检方法，包含下列步骤:

提供一检体;

利用 SEQ ID NO: 1 至 SEQ ID NO: 24 所示的任一氨基酸序列对应的抗体辨识捕捉检体中的抗原; 及

侦测抗体与抗原的复合物。

21. 如权利要求 20 所述的体外筛检方法，其中所述检体为全血或血清。

22. 如权利要求 21 所述的体外筛检方法，其中所述检体为血清。

肝脏疾病的生物标记分子及其检测方法

技术领域

本发明涉及肝脏疾病的生物标记分子及其检测方法，其是利用自身抗原筛选方法筛选出可用于检测肝脏疾病的生物标记分子，并利用这些生物标记分子发展为检测套组，藉筛选检体中自身抗体或自身抗原的存在判断是否罹患肝脏疾病。

背景技术

免疫系统若功能不健全，便会产生免疫性疾病，我们身体许多疾病的根本原因通常可追究于免疫系统的功能不健全。一般可分为三种情况。第一种是抵抗力降低，身体的免疫细胞活力下降，或生产的数量不足以抵抗入侵的细菌、病毒或霉菌，因此易被感染流行病，伤风、感冒、肺炎、肠炎甚至肝炎、爱滋病等，都属于这一类。第二种的免疫不全是免疫系统反应过度，这种情况是因为入侵的物质并不是细菌而只是小花粉或是食物中大分子蛋白质，免疫系统就释出大量的抗体加以对抗，而攻势就发生在我们的细胞中，如此引起一连串的反应，也被称为过敏症，而这时候若有细菌、病毒或霉菌之类真的病原来侵犯时，免疫系统已无余力抵抗了。第三种情况是免疫细胞攻击自身的正常细胞，也就是自身免疫疾病，例如：类风湿性关节炎、红斑性狼疮或疱疹等等，这种免疫系统疾病起因于患者本身免疫辨识系统发生问题，患者的免疫系统对本身的某些物质会产生自身抗体（或称自体抗体，autoantibody），进而破坏身体组织造成病痛。

目前已知并非是只有自身免疫疾病才有自身抗体的存在，越来越多的相关研究指出人类对癌症所发生的免疫反应，部分存在着肿瘤自身抗原

（autoantigen）与人类自身抗体的情形，因此对于发现这些可以引起人体反应的肿瘤自身抗原在癌症检测、诊断或建立预后上有一定的方向和应用性，进而应用于疾病的免疫治疗上。

在美国专利 6631330、5137807、5830667、6264949、5985542 等五篇中，揭露了使用生物标记分子诊断肝硬化（cirrhosis）、纤维化（fibrosis）或自身免疫性肝炎（autoimmune hepatitis, AIH）；而在美国专利 4994374、5175084 等两篇中则使用生物标记分子诊断肝癌（hepatcellular carcinoma）；另外在美国专利 6410724 则使用和肝癌相关的 DNA 引物(DNA primer)组成一检测套组，但这些生物标记分子多少都存在准确性不高或易被干扰的缺点。

在美国专利 5891436 及公开专利 20030138860 中，揭露了使用生物标记分子检测人体血清中其自身抗体的存在，以做为硬化（primary biliary cirrhosis）、癌症的判断，这说明在癌症病人中会有自身抗体（autoantibody）的产生，确立应用于筛选癌症相关的生物标记分子（biomarker）的合理性。

自 1982 年以来，癌症即跃居台湾地区十大死亡原因首位。其中肝癌不分男性或女性都名列前茅，这对人们的健康造成极大威胁，为有效筛检罹患肝脏疾病的患者，能够早期治疗而降低死亡率，发现高准确性及不被干扰的生物标记分子，以作为检测肝硬化及肝癌的检测套组，便成为重要的课题。

发明内容

有鉴于现有技术的缺失，本发明揭示了一种肝脏疾病的生物标记分子，由于确知其自身抗体的存在，因而可据此设计成检测套组，用于肝硬化或肝癌的诊断。

本发明的目的在于提供一种用于检测肝脏疾病的生物标记分子，其是

选自 SEQ ID NO:1 至 SEQ ID NO:24 所示的任一氨基酸序列或其衍生物或其片段或其变异体或其组合物或其对应的自身抗体。

其中，所述肝脏疾病是肝硬化或肝癌疾病。

所述变异体是将生物标记分子的氨基酸序列中的氨基酸以一个或多个氨基酸取代、删除、插入及/或添加；变异体的氨基酸序列与生物标记分子的氨基酸序列具有大于80%的序列同源性。

本发明的另一目的是提供一种肝脏疾病的检测套组，包含一组生物标记分子，其选自 SEQ ID NO:1 至 SEQ ID NO:24 所示的任一氨基酸序列或其衍生物或其片段或其变异体或其组合物。

其中，所述肝脏疾病为肝硬化或肝癌。

所述检测套组还可进一步包含可辨识 SEQ ID NO:1 至 SEQ ID NO:24 所示的任一氨基酸序列或其衍生物或其片段或其变异体的抗体的二级抗体。

本发明的再一目的是提供一种肝脏疾病的体外筛检方法，包含下列步骤：提供一检体；利用 SEQ ID NO:1 至 SEQ ID NO:24 所示的任一氨基酸序列或其衍生物或其片段或其变异体或其组合物的生物标记分子辨识捕捉检体中的自身抗体；及侦测自身抗体。

其中，所述肝脏疾病为肝硬化或肝癌。

所述检体为全血或血清，优选为血清。

所述生物标记分子可为各种型式，包括但不限于，检测套组、或先行固定于基材上，其中所述基材为免疫分析盘或生物芯片。

所述检体可进一步先行利用萤光标记进行标示。

所述筛检方法可增加利用二级抗体辨识吸附自身抗体的步骤。

所述二级抗体经修饰具有特殊官能团可进行显色反应、放射性侦测或萤光侦测。

所述侦测自身抗体是利用酶联免疫检测（Enzyme-linked

Immunosorbent Assay，ELISA）、放射免疫鉴定（Radioimmunoassay，RIA）或免疫萤光分析（Immunofluorescence）侦测二级抗体，或直接利用萤光扫描侦测被萤光标记标示的自身抗体。

本发明的再一目的是提供一种肝脏疾病的检测套组，包含一组可辨识具有 SEQ ID NO:1 至 SEQ ID NO:24 所示的任一氨基酸序列对应的抗体。

其中，所述肝脏疾病为肝硬化或肝癌。

本发明的再一目的是提供一种利用前述检测套组筛检肝脏疾病的方法，其包含下列步骤：提供一检体；利用 SEQ ID NO:1 至 SEQ ID NO:24 所示的任一氨基酸序列对应的抗体辨识捕捉检体中的抗原；及侦测抗体与抗原的复合物。

其中，所述肝脏疾病为肝硬化或肝癌。

所述检体为全血或血清，优选为血清。

本发明的基础是利用自身抗原筛选方法，先纯化出正常人和肝硬化、肝癌病人的抗体并分别固定于不同管柱中，再将人肝疾病相关的细胞株（HepG2 C3A&SNU-387）的细胞萃取物依序通入正常人及病人的管柱，以得到和肝硬化、肝癌等肝脏疾病相关的自身抗原，再以这些自身抗原做为检测肝硬化及肝癌的生物标记套组，结合酶联免疫检测（Enzyme-linked Immunosorbent Assay，ELISA）、放射免疫鉴定（Radioimmunoassay，RIA）或免疫萤光分析法（Immunofluorescence）等，藉检测人体血清中是否有该自身抗原（autoantigen）所相对应的自身抗体（autoantibody）的存在来判断是否罹患肝癌或肝硬化等肝脏疾病。由于这些生物标记分子都是以已存在的自身抗体筛选出来的，所以在诊断上可设计为检测套组，藉生物标记分子相对应的自身抗体是否存在，作为是否罹患该疾病的判断，这比直接筛检抗原的困难度要降低许多，并且还可有效提高准确度与灵敏度。

附图说明

图 1 为本发明中利用自身抗原筛选方法的流程示意图。

图 2 为本发明中利用生物标记分子筛选自身抗体的流程示意图。

具体实施方式

本发明提供了利用自身抗原筛选方法，筛选出可用于检测肝硬化或肝癌等肝脏疾病的生物标记分子，该自身抗原筛选方法如图 1 所示，包含以下步骤：首先取得正常人及患者的血清样品，分别利用可捕捉抗体的亲和力管柱纯化出血清样品中所含的抗体；接着将正常人的抗体与患者的抗体分别填充入管柱中，以制得含正常人抗体的管柱及含患者抗体的管柱。抗体填充固定于管柱之中的方法，是将由血清样品纯化出来的抗体与管柱中的化学官能团形成化学键结固定于管柱中。然后取一样品，该样品可为（癌）细胞株或者病理组织的萃取物；前述患者的血清样品可为单一患者的血清样品或多数患者的血清混合样品。

将来自（癌）细胞株或病理组织萃取物的样品通入正常人抗体管柱时，可藉由正常人抗体的专一亲和力将非专一性的抗原捕捉而滞留于管柱中，通过管柱的样品将不含非专一性抗原，这个程序其实可视为利用患者抗体管柱筛选检体中自身抗原的样品前处理。经移除样品中非专一性的抗原，样品组成便剩下特有的抗原，此时再将样品通入含患者抗体的管柱中，藉由患者所具有的自身抗体来进一步筛选疾病相关的自身抗原。由于已先藉由正常人的血清抗体去除非专一性的抗原，所以利用患者的自身抗体筛选所得到的自身抗原会具有较高的专一性。

由患者抗体管柱中置换而出的自身抗原，利用质谱技术进行鉴定；所述鉴定是将质谱讯号通过数据库比较对照，以取得自身抗原的信息。

将人类肝脏疾病相关的细胞株利用上述方法进行自身抗原的纯化与鉴定，由于这些自身抗原是利用患者血清中的抗体筛选出来的，所以可利用

这些自身抗原作为生物标记分子发展为检测套组，该检测套组是选自前述自身抗原筛选方法筛选出的自身抗原或其衍生物或其片段或其变异体或其组合物。藉筛选检体中自身抗体的存在，判断是否罹患肝硬化或肝癌疾病。检测套组中除生物标记分子外，还可进一步包含可辨识该生物标记分子的自身抗体的二级抗体，以利应用于相关检测方法。

运用前述检测套组筛检的方法如图 2 所示，包含下列步骤：首先提供一检体；接着利用生物标记分子辨识捕捉检体中的自身抗体，然后侦测自身抗体。其中，所述生物标记分子选自自身抗原筛选方法筛选出的自身抗原或其衍生物或其片段或其变异体或其组合物。

其中，所述检体为全血或血清，其中优选为血清。

为有利于检测的进行，所述生物标记分子可先行固定于基材上，常见的固定基材为免疫分析盘或生物芯片。当生物标记分子捕捉检体中的自身抗体后，可利用二级抗体辨识吸附自身抗体，这些二级抗体经修饰具有特殊官能团，以进行显色反应、放射性侦测或萤光侦测。

利用二级抗体辨识吸附自身抗体后，即可加入特殊试剂进行显色反应，然后利用酶联免疫检测进行二级抗体存在的判断，进而得知自身抗体是否存在，或通过放射免疫鉴定或免疫萤光分析，同样可以得知藉由二级抗体的反应判断自身抗体是否存在，以作为是否罹患肝癌或肝硬化的依据。

若不使用二级抗体，也可将检体在与生物标记分子反应前，先利用萤光标记（例如 Cy3 或 Cy5）标示，然后通过生物标记分子筛选自身抗体，由于自身抗体已先被萤光标记标示，所以在无须使用二级抗体情况下即可进行萤光扫瞄分析。

除了侦测自身抗体的存在作为判断，侦测抗原的存在也可作为是否罹患肝硬化或肝癌的依据，为达此目的，本发明设计了一种包含可辨识具有自身抗原筛选方法筛选出的自身抗原的抗体的检测套组，也可用于检测肝

脏疾病。

利用前述检测套组筛检肝癌及肝硬化的方法包含下列步骤：提供血清检体；利用所述抗体辨识捕捉血清中的抗原；及侦测抗体与抗原的复合物。

以下实施例用于进一步了解本发明的优点，但并非用于限制本发明的保护范围。

实施例 1. 利用肝脏疾病患者血清中的自身抗体筛选自身抗原

由血清纯化自身抗体:

首先取肝硬化或肝癌患者的血清，将血清用键结缓冲液（binding buffer: 20 mM PBS, pH 7.0）以 1:10 的比例稀释后，以 0.45μm 孔径的滤膜过滤，避免后续层析步骤造成管柱堵塞；接着以 10 倍管柱体积的键结缓冲液，在 1 ml/min 的流速下清洗 Protein G 亲和力管柱，之后将前述经滤膜过滤的血清样本以 0.2 ml/min 的流速通入 Protein G 亲和力管柱中，使抗体得以藉由与管柱的亲和力滞留于管柱中；再取 5-10 倍管柱体积的键结缓冲液以 1 ml/min 的流速清洗 Protein G 亲和力管柱，移除血清样品中不与管柱发生亲和力键结的物质，然后取 2-5 倍管柱体积的洗脱缓冲液（elution buffer: 0.1 M Glycine-HCl, pH 2.7）以 1 ml/min 的流速将抗体自管柱中洗脱出来并收集，收集抗体的试管中需预先加入 60-200μl 的 Tris-HCl 溶液（1 M, pH 9.0），最后将样品置换于耦合缓冲液（coupling buffer: 0.2 M $NaHCO_3$, 0.5 M NaCl, pH 8.3）中，即完成血清中自身抗体（IgG）的纯化。

由于本发明需要分别填充有正常人 IgG 及患者 IgG 的管柱各一只，所以需要取正常人及患者血清分别进行前述纯化步骤。

制备含有自身抗体的管柱:

取 NHS-activated 管柱一只，移除上端盖子后滴一滴酸化溶液（acidification solution: 1 mM HCl（需冰浴））以避免气泡生成。接着将此管柱上端与注射器（syringe）或泵（pump）连接后移除下端扭转

处，再以 2 倍管柱体积的酸化溶液将管柱中的异丙醇清洗出来，重复此清洗步骤 3 次后，将含有自身抗体的样品注入管柱中。前述的含有自身抗体的样品是由 Protein-G 亲和力管柱纯化血清得到的含有自身抗体的耦合缓冲液，经配制后成为总体积为 1 倍管柱体积，浓度为 0.5-10 mg/ml。将前述含有自身抗体的样品通入管柱后则将管柱密封，在 25℃中反应 15-30 分钟，或者在 4℃中反应 4 小时，使抗体得以与管柱产生化学键联固定于管柱中。

自身抗体与管柱完成键联反应后，先利用 2 倍管柱体积的封阻缓冲液（blocking buffer: 0.5 M 乙醇胺，0.5 M NaCl，pH 8.3）洗脱管柱，重复此步骤 3 次，再利用 2 倍管柱体积的清洗缓冲液（washing buffer: 0.1 M 醋酸盐，0.5 M NaCl，pH 4）清洗管柱，同样重复 3 次，接着再换回封阻缓冲液以 2 倍管柱体积洗脱管柱 3 次后，让管柱反应 15-30 分钟，使管柱中未键联自身抗体的官能团被封阻而失去活性，待封阻反应完成后以 2 倍管柱体积的清洗缓冲液清洗管柱，重复 3 次，接着以 2 倍管柱体积的封阻缓冲液洗脱管柱，重复 3 次，确保所有未键联自身抗体的官能团都能被封阻，再以 2 倍管柱体积的清洗缓冲液清洗管柱，重复 3 次后，最后以 2-5 倍管柱体积的一般中性 pH 缓冲液洗脱管柱后，完成含有自身抗体的管柱的制备。

由肝脏疾病相关的细胞株萃取物中纯化鉴定自身抗原:

首先将移除培养基的 HepG2 C3A cells（细胞株） 2.68 mg 以冰浴的 Tris saline溶液(50 mM Tris pH 7.5,150 mM NaCl,1.5 mM PMSF,Phosphatase inhibitors）清洗两次后，加入 Triton Extraction 溶液 1ml （15 Mm Tris pH 7.5，120 mM NaCl，25 mM KCl，2 mM EGTA，0.1 mM DTT，0.5% Triton X-100，10μg/ml leupeptin，0.5 Mm PMSF，Phosphatase inhibitors），置于 4℃、30 分钟，此时细胞开始分解释出蛋白质，然后利用台式离心机于 4℃以 14,000 rpm 的转速离心 15 分钟，移除固态不溶的细胞结构，收

集上层液进行后续的免疫亲和层析。

经收集得到的细胞萃取液与键结缓冲液（binding buffer）以 1:10 的比例稀释后，利用 0.45μm 孔径的滤膜过滤，以避免后续通入管柱后造成管柱的阻塞，而在将样品注入具有抗体（IgG）的管柱前，需先以 10 倍管柱体积的键结缓冲液，在 1 ml/min 的流速下清洗正常人及患者的抗体管柱，之后将前述经滤膜过滤的细胞萃取液以 0.2 ml/min 的流速通入正常人抗体管柱中，再取 5-10 倍管柱体积的键结缓冲液以 1 ml/min 的流速洗脱正常人抗体管柱，此时细胞萃取液中所含有的正常人抗体具有辨识捕捉的抗原会滞留其中，这一步骤的目的在于捕捉移除细胞株中非专一性的抗原，所以经管柱层析后的细胞萃取液中将不含非专一性的抗原；将此细胞萃取液收集导入患者抗体管柱，取 5-10 倍管柱体积的键结缓冲液以 1 ml/min 的流速洗脱患者抗体管柱，此时细胞萃取液中所具有的自身抗原将被管柱中患者的自身抗体所捕捉而滞留于管柱之中，当细胞萃取液通过正常人抗体管柱时，一般正常人抗体可辨识捕捉的抗原将被滞留于管柱中，而将不含前述正常人抗体可辨识捕捉的抗原的细胞萃取液导入患者抗体管柱时，只有患者抗体管柱可辨识捕捉的抗原被滞留于管柱之中，这些滞留于患者抗体管柱中的抗原，藉由 2-5 倍管柱体积的洗脱缓冲液（elution buffer）以 1 ml/min 的流速将自身抗原由患者抗体管柱中洗脱出并收集，接着使用胰蛋白酶（Trypsin）进行蛋白质水解反应，将被水解的自身抗原的多肽以质谱技术进行分析，所得的图谱可藉由数据库比较对照获知蛋白质的信息。

利用肝硬化或肝癌患者血清中的自身抗体筛选肝脏疾病相关细胞株，可得下列的自身抗原：

1. 二磷酸核苷激酶（Nucleoside diphosphate kinase, gi|1421609, SEQ ID NO.1）

2. NM23 protein（gi|35068, SEQ ID NO.2）

3. ATP 合成酶 beta chain（ATP synthase beta chain, mitochondrial [precursor], gi|28940, SEQ ID NO.3）

4. 14-3-3 蛋白 zeta（14-3-3 zeta protein, tyrosine 3/tryptophan 5 -monooxygenase activation protein)（gi|4507953, SEQ ID NO.4）

5. 14-3-3 蛋白 epsilon（14-3-3 epsilon protein, tyrosine 3/tryptophan 5 -monooxygenase activation protein)（gi|4507953, SEQ ID NO.5）

6. 蛋白质二硫异构酶相关蛋白-5（Protein disulfide isomerase-related protein 5, gi|1710248, SEQ ID NO.6）

7. unnamed protein product（gi|21750187, SEQ ID NO.7）

8. 水不溶性肌蛋白 alpha 3（Tropomyosin alpha 3, gi|37403, SEQ ID NO.8）

9. 水不溶性肌蛋白 alpha 4（Trypomyosin alpha 4, gi|10435300, SEQ ID NO.9）

10. Calreticulin precursor（gi|4757900, SEQ ID NO.10）

11. 人类 pre-mRNA 剪接因子 SF2p32(Human pre-mRNA splicing factor SF2p32, gi|338043, SEQ ID NO.11）

12. 肿瘤坏死因子第一型受体的相关蛋白（Tumor necrosis factor type 1 receptor associated protein TRAP-1, gi|1082886, SEQ ID NO.12）

13. 肿瘤排斥抗原（gp96）（Tumor rejection antigen（gp96）1; glucose regulated protein, gi|4507677, SEQ ID NO.13）

14. 热休克蛋白 90-beta（Heat shock protein 90-beta, gi|72222, SEQ ID NO.14）

15. 热休克蛋白 90-alpha（Heat shock 90-alpha, gi|123678, SEQ ID NO.15）

16. 热休克蛋白-60（Heat shock 60kDa protein 1, gi|31542947,

SEQ ID NO.16)

17. HMG-1蛋白质(HMG-1, gi|968888, SEQ ID NO.17)

18. KIAA0144 gene product (NICE-4 protein) (gi|13111995, SEQ ID NO.18)

19. Valosin-containing protein (p97); transitional endoplasmic reciculum ATPase (gi|6005942, SEQ ID NO.19)

20. 甘油醛三磷酸脱氢酶(Glyceraldehyde 3-phosphate dehydrogenase, liver, gi|30157565, SEQ ID NO.20)

21. 细胞角质蛋白(Cytokeratin, gi|1419564, SEQ ID NO.21)

22. 胰岛素生长因子II的mRNA结合蛋白(IGF-II mRNA-binding protein 1, gi|4191608, SEQ ID NO.22)

23. 醌还原酶(NADPH: quinone reductase, gi|13236495, SEQ ID NO.23)

24. 热休克蛋白90的协同伴随蛋白P23(Crystal Structure Of The Human Co-Chaperone P23, hsp-90 co-chaperone) (gi|9257073, SEQ ID NO.24)

上列由肝脏疾病相关的细胞株筛选的自身抗原如表一所示，其中左侧为蛋白质的GI编号(gi number)及名称，右侧为利用肝硬化或肝癌患者的血清在肝脏疾病相关细胞株中可被筛选出来的自身抗原，由表中显示，这些自身抗原并不局限于单一的肝脏疾病中才会被筛选出来，利用不同来源血清中的自身抗体针对不同细胞株也会重复筛选出来，显示这些抗原与肝脏疾病的相关性极为密切。表一中部分蛋白质具有两个GI编号，其是由于蛋白质及其变异体在质谱鉴定时具有近似的判别结果。

表一、由肝脏疾病相关的细胞株筛选的自身抗原

GI number	蛋白质名称	肝硬化血清 vs. HepG2 C3A	肝癌血清 vs. HepG2 C3A	肝硬化血清 vs. SNU-387	肝癌血清 vs. SNU-387
1421609	二磷酸核苷激酶(= NM23 protein)	●	●	●	●
28940	ATP 合成酶 beta chain, mitochondrial [Precursor]	●		●	
4507953, 5803225	14-3-3 蛋白	●		●	
1710248	蛋白质二硫异构酶相关蛋白-5		●		●
21750187	Gi|21750187 Unname protein product (RNA_rec_mot.)		●		
37403, 10435300	水不溶性肌蛋白			●	●
4757900	Calreticulin precursor	●	●		
338043	人类 pre-mRNA 剪接因子 SF2p32, complete sequence	●	●		
1082886	肿瘤坏死因子第一型受体的相关蛋白	●	●		
4507677	肿瘤排斥抗原 (gp96) 1; glucose regulated protein	●	●		
72222, 123678	热休克蛋白 90	●	●		
31542947	热休克蛋白 60(chaperonin); mitochondrial matrix protein P1	●			
968888	HMG-1 蛋白质(high-mobility group-1)	●			
13111995	KIAA0144 gene product (NICE-4 protein)	●			
6005942	Valosin-containing protein(p97); transitional endoplasmic reticulum ATPase	●			
30157565	甘油醛三磷酸脱氢酶	●			
1419564	细胞角质蛋白	●			
4191608	胰岛素生长因子 II 的 mRNA 结合蛋白	●			
13236495	醌还原酶		●		
9257073	热休克蛋白 90 的协同伴随蛋白 P23		●		

实施例 2. 鉴定利用自身抗原筛选方法筛选出来的自身抗原的可利用性

为进一步证实实施例 1. 筛选出的 24 个自身抗原的可利用性，需进一步使用免疫分析方法（ELISA、RIA、免疫萤光法等）搭配上述 24 个生物标记分子，分别对正常人、肝硬化患者及肝癌患者的血清样品做进一步检测，其检测方法依循图 2，首先提供一检体，然后利用 SEQ ID NO: 1 至 SEQ ID NO: 24 所示的任一氨基酸序列或其衍生物或其片段或其组合物的生物标记分子辨识捕捉检体中的自身抗体，最后侦测自身抗体。

以酶联免疫吸附分析（Enzyme-linked Immunosorbent Assay, ELISA）为例，其详细检测步骤如下：首先将生物标记分子以披覆缓冲液（coating buffer，可有三种选择为 a. 50mM Na_2HCO_3，pH=9.6 或 b. 20mM Tris-HCl，pH=8.5 或 c. 10mM PBS，pH=7.4）稀释成浓度 0.5～10μg/ml，披覆缓冲液依据生物标记分子的 pI 值选择，优选大于 pI 值 1-2 pH 值的缓冲液。在 ELISA plate 中加入 100μl/well 的生物标记分子溶液，置于 4℃中反应隔夜进行固定化。

接着移除未固定化的生物标记分子，以 PBST buffer 清洗两次（PBST buffer: PBS buffer + 0.05% Tween-20），然后加入 200μl/well 的封阻缓冲液（blocking buffer: 可有三种选择 a. Gelatin-NET: 0.5% Gelatin, 0.15M NaCl, 5mM EDTA 2Na, 0.05% Tween-20, 50mM Tris base 或 b. 1% BSA-PBS, pH=7.4 或 c. 5%Non-fat milk-PBS, pH=7.4）在室温下反应最少 2 小时进行封阻反应；反应完成后利用 PBST 缓冲液清洗 3 次，然后加入 100μl/well 待反应的血清溶液（血清溶液为使用封阻缓冲液稀释 1000 倍），此时血清中的自身抗体将与被固定化的生物标记分子进行辨识吸附，此反应在室温下至少进行 2 小时后，利用 PBST 缓冲液清洗 4 次，再加入 100μl/well 的二级抗体（二级抗体是利用封阻缓冲液稀释 5000 倍），此时二级抗体将会与自身抗体进行辨识吸附，此反应在室温下至少进行 1 小时后，以 PBST 缓冲液清洗 5 次，接着加入 100μl/well 的 TMB 进行 30 分钟显色

反应，然后加入 100μl/well 的 0.5M H_2SO_4 后，侦测 450nm 的吸收度。

为确认自身抗体的表现量确实可作为肝硬化及/或肝癌的检测，可分别利用 ELISA 分析各自身抗原筛选正常人、肝硬化患者及肝癌患者血清中的自身抗体的吸光值数据后，以生物统计学进行分析以 GADPH、NADPH、HMG-1、NM23 及 Cytokeratin 等五个蛋白质为例，利用 Wilcoxon-Mann-Whitney 进行检定，在 95%的信赖水准下所得结果如表二:

表二

	GADPH	NADPH	HMG-1	NM23	Cytokeratin
正常人 VS. 肝硬化患者	P=0.001	p=0.001	p=0.00006	p=0.0001	p=0.001
正常人 VS. 肝癌患者	P=0.017	p=0.016	p=0.015	p=0.002	p=0.016
肝硬化患者 VS. 肝癌患者	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05

正常人:N=10、肝硬化患者: N=15、肝癌患者: N=21（$p<0.05$ 假设成立）

假设各生物标记分子的自身抗体于正常人、肝硬化患者及肝癌患者中表现量具有差异性，则由表中显示这样的假设在正常人与肝硬化患者的比较，以及正常人与肝癌患者的比较的假设成立，意即各生物标记分子的自身抗体的表现量在正常人与肝硬化患者及肝癌患者中的差异，具有生物统计上的意义存在。

经由生物统计可知蛋白质 GADPH 的自身抗体在正常人与肝硬化患者中的表现量差异达 8.375 倍，在正常人与肝癌患者中的表现量差异达 4.86 倍；蛋白质 HMG-1 的自身抗体在正常人与肝硬化患者中的表现量差异达 74 倍；蛋白质 NM23 的自身抗体在正常人与肝硬化患者中的表现量达 24 倍，在正常人与肝癌患者中的表现量达 8.545 倍。这些结果证实在肝硬化及肝癌病人的血清中，本发明的24个自身抗原的相关自身抗体(autoantibodies)

的表现量高于正常人，因此将所述 24 个自身抗原搭配免疫分析方法组合成一套检测套组，藉此筛选检体中自身抗体表现量，确实可以应用于肝硬化及肝癌的检测。

上述优选实施例，并非用以限定本发明，任何熟悉此领域的技术人员，在不脱离本发明的精神和范围内，当可作各种的更动与润饰，因此，本发明的保护范围，应以权利要求书为准。

序列表

<110> 财团法人工业技术研究院

<120> 肝脏疾病的生物标记分子及其检测方法

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Arg Gly Leu Val Gly Glu Ile Ile Lys Arg Phe Glu Gln Lys Gly Phe
            20                  25                  30

Arg Leu Val Ala Met Lys Phe Leu Arg Ala Ser Glu Glu His Leu Lys
        35                  40                  45

Gln His Tyr Ile Asp Leu Lys Asp Arg Pro Phe Phe Pro Gly Leu Val
    50                  55                  60

Lys Tyr Met Asn Ser Gly Pro Val Val Ala Met Val Trp Glu Gly Leu
65                  70                  75                  80

Asn Val Val Lys Thr Gly Arg Val Met Leu Gly Glu Thr Asn Pro Ala
                85                  90                  95

Asp Ser Lys Pro Gly Thr Ile Arg Gly Asp Phe Cys Ile Gln Val Gly
            100                 105                 110

Arg Asn Ile Ile His Gly Ser Asp Ser Val Lys Ser Ala Glu Lys Glu
        115                 120                 125

Ile Ser Leu Trp Phe Lys Pro Glu Glu Leu Val Asp Tyr Lys Ser Cys
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Ala His Asp Trp Val Tyr Glu
145                 150
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1               5                  10                  15

Gln Pro Glu Phe Lys Pro Lys Gln Leu Glu Gly Thr Met Ala Asn Cys
            20                  25                  30

Glu Arg Thr Phe Ile Ala Ile Lys Pro Asp Gly Val Gln Arg Gly Leu
        35                  40                  45

Val Gly Glu Ile Ile Lys Arg Phe Glu Gln Lys Gly Phe Arg Leu Val
    50                  55                  60

Gly Leu Lys Phe Met Gln Ala Ser Glu Asp Leu Leu Lys Glu His Tyr
65                  70                  75                  80

Val Asp Leu Lys Asp Arg Pro Phe Phe Ala Gly Leu Val Lys Tyr Met
                85                  90                  95

His Ser Gly Pro Val Val Ala Met Val Trp Glu Gly Leu Asn Val Val
            100                 105                 110

Lys Thr Gly Arg Val Met Leu Gly Glu Thr Asn Pro Ala Asp Ser Lys
        115                 120                 125

Pro Gly Thr Ile Arg Gly Asp Phe Cys Ile Gln Val Gly Arg Asn Ile
    130                 135                 140

Ile His Gly Ser Asp Ser Val Glu Ser Ala Glu Lys Glu Ile Gly Leu
145                 150                 155                 160

Trp Phe His Pro Glu Glu Leu Val Asp Tyr Thr Ser Cys Ala Gln Asn
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Trp Ile Tyr Glu
            180
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            20                  25                  30

Ser Ala Ser Leu Pro Pro Ala Gln Leu Leu Leu Arg Ala Val Arg Arg
        35                  40                  45

Arg Ser His Pro Val Arg Asp Tyr Ala Ala Gln Thr Ser Pro Ser Pro
    50                  55                  60
```

```
Lys Ala Gly Ala Ala Thr Gly Arg Ile Val Ala Val Ile Gly Ala Val
65                  70                  75                  80

Val Asp Val Gln Phe Asp Glu Gly Leu Pro Pro Ile Leu Asn Ala Leu
                85                  90                  95

Glu Val Gln Gly Arg Glu Thr Arg Leu Val Leu Glu Val Ala Gln His
            100                 105                 110

Leu Gly Glu Ser Thr Val Arg Thr Ile Ala Met Asp Gly Thr Glu Gly
        115                 120                 125

Leu Val Arg Gly Gln Lys Val Leu Asp Ser Gly Ala Pro Ile Lys Ile
    130                 135                 140

Pro Val Gly Pro Glu Thr Leu Gly Arg Ile Met Asn Val Ile Gly Glu
145                 150                 155                 160

Pro Ile Asp Glu Arg Gly Pro Ile Lys Thr Lys Gln Phe Ala Pro Ile
                165                 170                 175

His Ala Glu Ala Pro Glu Phe Met Glu Met Ser Val Glu Gln Glu Ile
            180                 185                 190

Leu Val Thr Gly Ile Lys Val Val Asp Leu Leu Ala Pro Tyr Ala Lys
        195                 200                 205

Gly Gly Lys Ile Gly Leu Phe Gly Gly Ala Gly Val Gly Lys Thr Val
    210                 215                 220

Leu Ile Met Glu Leu Ile Asn Asn Val Ala Lys Ala His Gly Gly Tyr
225                 230                 235                 240

Ser Val Phe Ala Gly Val Gly Glu Arg Thr Arg Glu Gly Asn Asp Leu
                245                 250                 255

Tyr His Glu Met Ile Glu Ser Gly Val Ile Asn Leu Lys Asp Ala Thr
            260                 265                 270

Ser Lys Val Ala Leu Val Tyr Gly Gln Met Asn Gln Pro Pro Gly Ala
        275                 280                 285

Arg Ala Arg Val Ala Leu Thr Gly Leu Thr Val Ala Glu Tyr Phe Arg
    290                 295                 300

Asp Gln Glu Gly Gln Asp Val Leu Leu Phe Ile Asp Asn Ile Phe Arg
305                 310                 315                 320

Phe Thr Gln Ala Gly Ser Glu Val Ser Ala Leu Leu Gly Arg Ile Pro
                325                 330                 335

Ser Ala Val Gly Tyr Gln Pro Thr Leu Ala Thr Asp Met Gly Thr Met
            340                 345                 350

Gln Glu Arg Ile Thr Thr Thr Lys Lys Gly Ser Ile Thr Ser Val Gln
        355                 360                 365
```

```
Ala Ile Tyr Val Pro Ala Asp Asp Leu Thr Asp Pro Ala Pro Ala Thr
    370                 375                 380

Thr Phe Ala His Leu Asp Ala Thr Thr Val Leu Ser Arg Ala Ile Ala
385                 390                 395                 400

Glu Leu Gly Ile Tyr Pro Ala Val Asp Pro Leu Asp Ser Thr Ser Arg
                405                 410                 415

Ile Met Asp Pro Asn Ile Val Gly Ser Glu His Tyr Asp Val Ala Arg
            420                 425                 430

Gly Val Gln Lys Ile Leu Gln Asp Tyr Lys Ser Leu Gln Asp Ile Ile
        435                 440                 445

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

Ser Arg Ala Arg Lys Ile Gln Arg Phe Leu Ser Gln Pro Phe Gln Val
465                 470                 475                 480

Ala Glu Val Phe Thr Gly His Met Gly Lys Leu Val Pro Leu Lys Glu
                485                 490                 495

Thr Ile Lys Gly Phe Gln Gln Ile Leu Ala Gly Glu Tyr Asp His Leu
            500                 505                 510

Pro Glu Gln Ala Phe Tyr Met Val Gly Pro Ile Glu Glu Ala Val Ala
        515                 520                 525

Lys Ala Asp Lys Leu Ala Glu Glu His Ser Ser
    530                 535
```

<210> 4
<211> 245
<212> PRT
<213> 人属、人种

<400> 4

```
Met Asp Lys Asn Glu Leu Val Gln Lys Ala Lys Leu Ala Glu Gln Ala
1               5                   10                  15

Glu Arg Tyr Asp Asp Met Ala Ala Cys Met Lys Ser Val Thr Glu Gln
            20                  25                  30

Gly Ala Glu Leu Ser Asn Glu Glu Arg Asn Leu Leu Ser Val Ala Tyr
        35                  40                  45

Lys Asn Val Val Gly Ala Arg Arg Ser Ser Trp Arg Val Val Ser Ser
    50                  55                  60

Ile Glu Gln Lys Thr Glu Gly Ala Glu Lys Lys Gln Gln Met Ala Arg
65                  70                  75                  80
```

Glu Tyr Arg Glu Lys Ile Glu Thr Glu Leu Arg Asp Ile Cys Asn Asp
85 90 95

Val Leu Ser Leu Leu Glu Lys Phe Leu Ile Pro Asn Ala Ser Gln Ala
100 105 110

Glu Ser Lys Val Phe Tyr Leu Lys Met Lys Gly Asp Tyr Tyr Arg Tyr
115 120 125

Leu Ala Glu Val Ala Ala Gly Asp Asp Lys Lys Gly Ile Val Asp Gln
130 135 140

Ser Gln Gln Ala Tyr Gln Glu Ala Phe Glu Ile Ser Lys Lys Glu Met
145 150 155 160

Gln Pro Thr His Pro Ile Arg Leu Gly Leu Ala Leu Asn Phe Ser Val
165 170 175

Phe Tyr Tyr Glu Ile Leu Asn Ser Pro Glu Lys Ala Cys Ser Leu Ala
180 185 190

Lys Thr Ala Phe Asp Glu Ala Ile Ala Glu Leu Asp Thr Leu Ser Glu
195 200 205

Glu Ser Tyr Lys Asp Ser Thr Leu Ile Met Gln Leu Leu Arg Asp Asn
210 215 220

Leu Thr Leu Trp Thr Ser Asp Thr Gln Gly Asp Glu Ala Glu Ala Gly
225 230 235 240

Glu Gly Gly Glu Asn
245

<210> 5
<211> 255
<212> PRT
<213> 人属、人种

<400> 5

Met Asp Asp Arg Glu Asp Leu Val Tyr Gln Ala Lys Leu Ala Glu Gln
1 5 10 15

Ala Glu Arg Tyr Asp Glu Met Val Glu Ser Met Lys Lys Val Ala Gly
20 25 30

Met Asp Val Glu Leu Thr Val Glu Glu Arg Asn Leu Leu Ser Val Ala
35 40 45

Tyr Lys Asn Val Ile Gly Ala Arg Arg Ala Ser Trp Arg Ile Ile Ser
50 55 60

Ser Ile Glu Gln Lys Glu Glu Asn Lys Gly Gly Glu Asp Lys Leu Lys
65 70 75 80

Met Ile Arg Glu Tyr Arg Gln Met Val Glu Thr Glu Leu Lys Leu Ile

85 90 95

Cys Cys Asp Ile Leu Asp Val Leu Asp Lys His Leu Ile Pro Ala Ala
100 105 110

Asn Thr Gly Glu Ser Lys Val Phe Tyr Tyr Lys Met Lys Gly Asp Tyr
115 120 125

His Arg Tyr Leu Ala Glu Phe Ala Thr Gly Asn Asp Arg Lys Glu Ala
130 135 140

Ala Glu Asn Ser Leu Val Ala Tyr Lys Ala Ala Ser Asp Ile Ala Met
145 150 155 160

Thr Glu Leu Pro Pro Thr His Pro Ile Arg Leu Gly Leu Ala Leu Asn
165 170 175

Phe Ser Val Phe Tyr Tyr Glu Ile Leu Asn Ser Pro Asp Arg Ala Cys
180 185 190

Arg Leu Ala Lys Ala Ala Phe Asp Asp Ala Ile Ala Glu Leu Asp Thr
195 200 205

Leu Ser Glu Glu Ser Tyr Lys Asp Ser Thr Leu Ile Met Gln Leu Leu
210 215 220

Arg Asp Asn Leu Thr Leu Trp Thr Ser Asp Met Gln Gly Asp Gly Glu
225 230 235 240

Glu Gln Asn Lys Glu Ala Leu Gln Asp Val Glu Asp Glu Asn Gln
245 250 255

<210> 6
<211> 421
<212> PRT
<213> 人属、人种

<400> 6

Leu Tyr Ser Ser Ser Asp Asp Val Ile Glu Leu Thr Pro Ser Asn Phe
1 5 10 15

Asn Arg Glu Val Ile Gln Ser Asp Ser Leu Trp Leu Val Glu Phe Tyr
20 25 30

Ala Pro Trp Cys Gly His Cys Gln Arg Leu Thr Pro Glu Trp Lys Lys
35 40 45

Ala Ala Thr Ala Leu Lys Asp Val Val Lys Val Gly Ala Val Asp Ala
50 55 60

Asp Lys His His Ser Leu Gly Gly Gln Tyr Gly Val Gln Gly Phe Pro
65 70 75 80

Thr Ile Lys Ile Phe Gly Ser Asn Lys Asn Arg Pro Glu Asp Tyr Gln
85 90 95

```
Gly Gly Arg Thr Gly Glu Ala Ile Val Asp Ala Ala Leu Ser Ala Leu
            100                 105                 110

Arg Gln Leu Val Lys Asp Arg Leu Gly Gly Arg Ser Gly Gly Tyr Ser
        115                 120                 125

Ser Gly Lys Gln Gly Arg Ser Asp Ser Ser Ser Lys Lys Asp Val Ile
    130                 135                 140

Glu Leu Thr Asp Asp Ser Phe Asp Lys Asn Val Leu Asp Ser Glu Asp
145                 150                 155                 160

Val Trp Met Val Glu Phe Tyr Ala Pro Trp Cys Gly His Cys Lys Asn
                165                 170                 175

Leu Glu Pro Glu Trp Ala Ala Ala Ala Ser Glu Val Lys Glu Gln Thr
            180                 185                 190

Lys Gly Arg Val Lys Leu Ala Ala Val Asp Ala Thr Val Asn Gln Val
        195                 200                 205

Leu Ala Ser Arg Tyr Gly Ile Arg Gly Phe Pro Thr Ile Lys Ile Phe
    210                 215                 220

Gln Lys Gly Glu Ser Pro Val Asp Tyr Asp Gly Gly Arg Thr Arg Ser
225                 230                 235                 240

Asp Ile Val Ser Arg Ala Leu Asp Leu Phe Ser Asp Asn Ala Pro Pro
                245                 250                 255

Pro Glu Leu Leu Glu Ile Ile Asn Glu Asp Ile Ala Lys Arg Thr Cys
            260                 265                 270

Glu Glu His Gln Leu Cys Val Val Ala Val Leu Pro His Ile Leu Asp
        275                 280                 285

Thr Gly Ala Ala Gly Arg Asn Ser Tyr Leu Glu Val Leu Leu Lys Leu
    290                 295                 300

Ala Asp Lys Tyr Lys Lys Lys Met Trp Gly Trp Leu Trp Thr Glu Ala
305                 310                 315                 320

Gly Ala Gln Ser Glu Leu Glu Thr Ala Leu Gly Ile Gly Gly Phe Gly
                325                 330                 335

Tyr Pro Ala Met Ala Ala Ile Asn Ala Arg Lys Met Lys Phe Ala Leu
            340                 345                 350

Leu Lys Gly Ser Phe Ser Glu Gln Gly Ile Asn Glu Phe Leu Arg Glu
        355                 360                 365

Leu Ser Phe Gly Arg Gly Ser Thr Ala Pro Val Gly Gly Gly Ala Phe
    370                 375                 380

Pro Thr Ile Val Glu Arg Glu Pro Trp Asp Gly Arg Asp Gly Glu Leu
```

385 390 395 400

Pro Val Glu Asp Asp Ile Asp Leu Ser Asp Val Glu Leu Asp Asp Leu
405 410 415

Gly Lys Asp Glu Leu
420

<210> 7
<211> 687
<212> PRT
<213> 人属、人种

<400> 7

Met Val Lys Leu Ala Lys Ala Gly Lys Asn Gln Gly Asp Pro Lys Lys
1 5 10 15

Met Ala Pro Pro Pro Lys Glu Val Glu Glu Asp Ser Glu Asp Glu Glu
20 25 30

Met Ser Glu Asp Glu Glu Asp Asp Ser Ser Gly Glu Glu Val Val Ile
35 40 45

Pro Gln Lys Lys Gly Lys Lys Ala Ala Ala Thr Ser Ala Lys Lys Val
50 55 60

Val Val Ser Pro Thr Lys Lys Val Ala Val Ala Thr Pro Ala Lys Ala
65 70 75 80

Val Thr Thr Pro Gly Lys Lys Gly Ala Thr Pro Gly Lys Ala Leu Val
85 90 95

Ala Thr Pro Gly Lys Lys Gly Ala Ala Ile Pro Ala Lys Gly Ala Lys
100 105 110

Asn Gly Lys Asn Ala Lys Lys Glu Asp Ser Asp Glu Glu Glu Asp Asp
115 120 125

Asp Ser Glu Glu Asp Glu Glu Asp Asp Glu Asp Glu Asp Glu Asp Glu
130 135 140

Asp Glu Ile Glu Pro Ala Ala Met Lys Ala Ala Ala Ala Ala Pro Ala
145 150 155 160

Ser Glu Asp Glu Asp Asp Glu Asp Asp Glu Asp Asp Glu Asp Asp Asp
165 170 175

Asp Asp Glu Glu Asp Asp Ser Glu Glu Glu Ala Met Glu Thr Thr Pro
180 185 190

Ala Lys Gly Lys Lys Ala Ala Lys Val Val Pro Val Lys Ala Lys Asn
195 200 205

Val Ala Glu Asp Glu Asp Glu Glu Glu Asp Asp Glu Asp Glu Asp Asp
210 215 220

```
Asp Asp Asp Glu Asp Asp Glu Asp Asp Asp Asp Glu Asp Asp Glu Glu
225                 230                 235                 240

Glu Glu Glu Glu Glu Glu Glu Glu Pro Val Lys Glu Ala Pro Gly Lys
                245                 250                 255

Arg Lys Lys Glu Met Ala Lys Gln Lys Ala Ala Pro Glu Ala Lys Lys
            260                 265                 270

Gln Lys Val Glu Gly Thr Glu Pro Thr Thr Ala Phe Asn Leu Phe Val
        275                 280                 285

Gly Asn Leu Asn Phe Asn Lys Ser Ala Pro Glu Leu Lys Thr Gly Ile
    290                 295                 300

Ser Asp Val Phe Ala Lys Asn Asp Leu Ala Val Val Asp Val Arg Ile
305                 310                 315                 320

Gly Met Thr Arg Lys Phe Gly Tyr Val Asp Phe Glu Ser Ala Glu Asp
                325                 330                 335

Leu Glu Lys Ala Leu Glu Leu Thr Gly Leu Lys Val Phe Gly Asn Glu
            340                 345                 350

Ile Lys Leu Glu Lys Pro Lys Gly Lys Asp Ser Lys Lys Glu Arg Asp
        355                 360                 365

Ala Arg Thr Leu Leu Ala Lys Asn Leu Pro Tyr Lys Val Thr Gln Asp
    370                 375                 380

Glu Leu Lys Glu Val Phe Glu Asp Ala Ala Glu Ile Arg Leu Val Ser
385                 390                 395                 400

Lys Asp Gly Lys Ser Lys Gly Ile Ala Tyr Ile Glu Phe Lys Thr Glu
                405                 410                 415

Ala Asp Ala Glu Lys Thr Phe Glu Glu Lys Gln Gly Thr Glu Ile Asp
            420                 425                 430

Gly Arg Ser Ile Ser Leu Tyr Tyr Thr Gly Glu Lys Gly Gln Asn Gln
        435                 440                 445

Asp Tyr Arg Gly Gly Lys Asn Ser Thr Trp Ser Gly Glu Ser Lys Thr
    450                 455                 460

Leu Val Leu Ser Asn Leu Ser Tyr Ser Ala Thr Glu Glu Thr Leu Gln
465                 470                 475                 480

Glu Val Phe Glu Lys Ala Thr Phe Ile Lys Val Pro Gln Asn Gln Asn
                485                 490                 495

Gly Lys Ser Lys Gly Tyr Ala Phe Ile Glu Phe Ala Ser Phe Glu Asp
            500                 505                 510

Ala Lys Glu Ala Leu Asn Ser Cys Asn Lys Arg Glu Ile Gly Gly Arg
```

515 520 525

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

Ser Gln Pro Ser Lys Thr Leu Phe Val Lys Gly Leu Ser Glu Asp Thr
545 550 555 560

Thr Glu Glu Thr Leu Lys Glu Ser Phe Asp Gly Ser Val Arg Ala Arg
565 570 575

Ile Val Thr Asp Arg Glu Thr Gly Ser Ser Lys Gly Phe Gly Phe Val
580 585 590

Asp Phe Asn Ser Glu Glu Asp Ala Lys Ala Ala Lys Glu Ala Met Glu
595 600 605

Asp Gly Glu Ile Asp Gly Asn Lys Val Thr Leu Asp Trp Ala Lys Pro
610 615 620

Lys Gly Glu Gly Gly Phe Gly Gly Arg Gly Gly Gly Arg Gly Gly Phe
625 630 635 640

Gly Gly Arg Gly Gly Gly Arg Gly Gly Arg Gly Gly Phe Gly Gly Arg
645 650 655

Gly Arg Gly Gly Phe Gly Gly Arg Gly Gly Phe Arg Gly Gly Arg Gly
660 665 670

Gly Gly Gly Asp His Lys Pro Gln Gly Lys Lys Thr Lys Phe Glu
675 680 685

<210> 8
<211> 641
<212> PRT
<213> 人属、人种

<400> 8

Met Ala Gly Ile Thr Thr Ile Glu Ala Val Lys Arg Lys Ile Gln Val
1 5 10 15

Leu Gln Gln Gln Ala Asp Asp Ala Glu Glu Arg Ala Glu Arg Leu Gln
20 25 30

Arg Glu Val Glu Gly Glu Arg Arg Ala Arg Glu Gln Ala Glu Ala Glu
35 40 45

Val Ala Ser Leu Asn Arg Arg Ile Gln Leu Val Glu Glu Glu Leu Asp
50 55 60

Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys Leu Glu Glu Ala
65 70 75 80

Glu Lys Ala Ala Asp Glu Ser Glu Arg Gly Met Lys Val Ile Glu Asn
85 90 95

```
Arg Ala Leu Lys Asp Glu Glu Lys Met Glu Leu Gln Glu Ile Gln Leu
            100                 105                 110

Glu Glu Ala Lys His Ile Ala Glu Glu Ala Asp Arg Lys Tyr Glu Glu
        115                 120                 125

Val Ala Arg Lys Leu Val Ile Ile Glu Gly Asp Leu Glu Arg Thr Glu
    130                 135                 140

Glu Arg Ala Glu Leu Ala Glu Ser Arg Cys Arg Glu Met Asp Glu Gln
145                 150                 155                 160

Ile Arg Leu Met Asp Gln Asn Leu Lys Cys Leu Ser Ala Ala Glu Glu
                165                 170                 175

Lys Tyr Ser Gln Lys Glu Asp Lys Tyr Glu Glu Glu Ile Lys Ile Leu
            180                 185                 190

Thr Asp Lys Leu Lys Glu Ala Glu Thr Arg Ala Glu Phe Ala Glu Arg
        195                 200                 205

Ser Val Ala Lys Leu Glu Lys Thr Ile Asp Asp Leu Glu Asp Thr Asn
    210                 215                 220

Ser Thr Ser Gly Asp Pro Val Glu Lys Lys Asp Glu Thr Pro Phe Gly
225                 230                 235                 240

Val Ser Val Ala Val Gly Leu Ala Val Phe Ala Cys Leu Phe Leu Ser
                245                 250                 255

Thr Leu Leu Leu Val Leu Asn Lys Cys Gly Arg Arg Asn Lys Phe Gly
            260                 265                 270

Ile Asn Arg Pro Ala Val Leu Ala Pro Glu Asp Gly Leu Ala Met Ser
        275                 280                 285

Leu His Phe Met Thr Leu Gly Gly Ser Ser Leu Ser Pro Thr Glu Gly
    290                 295                 300

Lys Gly Ser Gly Leu Gln Gly His Ile Ile Glu Asn Pro Gln Tyr Phe
305                 310                 315                 320

Ser Asp Ala Cys Val His His Ile Lys Arg Arg Asp Ile Val Leu Lys
                325                 330                 335

Trp Glu Leu Gly Glu Gly Ala Phe Gly Lys Val Phe Leu Ala Glu Cys
            340                 345                 350

His Asn Leu Leu Pro Glu Gln Asp Lys Met Leu Val Ala Val Lys Ala
        355                 360                 365

Leu Lys Glu Ala Ser Glu Ser Ala Arg Gln Asp Phe Gln Arg Glu Ala
    370                 375                 380

Glu Leu Leu Thr Met Leu Gln His Gln His Ile Val Arg Phe Phe Gly
```

385 390 395 400

Val Cys Thr Glu Gly Arg Pro Leu Leu Met Val Phe Glu Tyr Met Arg
405 410 415

His Gly Asp Leu Asn Arg Phe Leu Arg Ser His Gly Pro Asp Ala Lys
420 425 430

Leu Leu Ala Gly Gly Glu Asp Val Ala Pro Gly Pro Leu Gly Leu Gly
435 440 445

Gln Leu Leu Ala Val Ala Ser Gln Val Ala Ala Gly Met Val Tyr Leu
450 455 460

Ala Gly Leu His Phe Val His Arg Asp Leu Ala Thr Arg Asn Cys Leu
465 470 475 480

Val Gly Gln Gly Leu Val Val Lys Ile Gly Asp Phe Gly Met Ser Arg
485 490 495

Asp Ile Tyr Ser Thr Asp Tyr Tyr Arg Val Gly Gly Arg Thr Met Leu
500 505 510

Pro Ile Arg Trp Met Pro Pro Glu Ser Ile Leu Tyr Arg Lys Phe Thr
515 520 525

Thr Glu Ser Asp Val Trp Ser Phe Gly Val Val Leu Trp Glu Ile Phe
530 535 540

Thr Tyr Gly Lys Gln Pro Trp Tyr Gln Leu Ser Asn Thr Glu Ala Ile
545 550 555 560

Asp Cys Ile Thr Gln Gly Arg Glu Leu Glu Arg Pro Arg Ala Cys Pro
565 570 575

Pro Glu Val Tyr Ala Ile Met Arg Gly Cys Trp Gln Arg Glu Pro Ser
580 585 590

Asn Ala Thr Ala Ser Arg Met Cys Thr Pro Gly Cys Lys Pro Trp Pro
595 600 605

Arg His Leu Leu Ser Thr Trp Met Ser Trp Ala Arg Gly Pro Ala Gln
610 615 620

Gly Leu Gly Val Val Ser Arg Asn Thr Gly Ala Cys Pro Gln His Pro
625 630 635 640

Pro

<210> 9
<211> 284
<212> PRT
<213> 人属、人种

<400> 9

```
Met Glu Ala Ile Lys Lys Lys Met Gln Met Leu Lys Leu Asp Lys Glu
1               5                  10                  15

Asn Ala Ile Asp Arg Ala Glu Gln Ala Glu Ala Asp Lys Lys Ala Ala
            20                  25                  30

Glu Asp Lys Cys Lys Gln Val Glu Glu Glu Leu Thr His Leu Gln Lys
        35                  40                  45

Lys Leu Lys Gly Thr Glu Asp Glu Leu Asp Lys Tyr Ser Glu Asp Leu
    50                  55                  60

Lys Asp Ala Gln Glu Lys Leu Glu Leu Thr Glu Lys Lys Ala Ser Asp
65                  70                  75                  80

Ala Glu Gly Asp Val Ala Ala Leu Asn Arg Arg Ile Gln Leu Val Glu
                85                  90                  95

Glu Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys
            100                 105                 110

Leu Glu Glu Ala Glu Lys Ala Ala Asp Glu Ser Glu Arg Gly Met Lys
        115                 120                 125

Val Ile Glu Asn Arg Ala Met Lys Asp Glu Glu Lys Met Glu Ile Gln
    130                 135                 140

Glu Met Gln Leu Lys Glu Ala Lys His Ile Ala Glu Glu Ala Asp Arg
145                 150                 155                 160

Lys Tyr Glu Glu Val Ala Arg Lys Leu Val Ile Leu Glu Gly Glu Leu
                165                 170                 175

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

Leu Glu Glu Glu Leu Lys Asn Val Thr Asn Asn Leu Lys Ser Leu Glu
        195                 200                 205

Ala Ala Ser Glu Lys Tyr Ser Glu Lys Glu Asp Lys Tyr Glu Glu Glu
    210                 215                 220

Ile Lys Leu Leu Ser Asp Lys Leu Lys Glu Ala Glu Thr Arg Ala Glu
225                 230                 235                 240

Phe Ala Glu Arg Thr Val Ala Lys Leu Glu Lys Thr Ile Asp Asp Leu
                245                 250                 255

Glu Glu Lys Leu Ala Gln Ala Lys Glu Glu Asn Val Gly Leu His Gln
            260                 265                 270

Thr Leu Asp Gln Thr Leu Asn Glu Leu Asn Cys Ile
        275                 280
```

<210> 10

<211> 417
<212> PRT
<213> 人属、人种

<400> 10

```
Met Leu Leu Ser Val Pro Leu Leu Leu Gly Leu Leu Gly Leu Ala Val
1               5                  10                  15

Ala Glu Pro Ala Val Tyr Phe Lys Glu Gln Phe Leu Asp Gly Asp Gly
            20                  25                  30

Trp Thr Ser Arg Trp Ile Glu Ser Lys His Lys Ser Asp Phe Gly Lys
        35                  40                  45

Phe Val Leu Ser Ser Gly Lys Phe Tyr Gly Asp Glu Glu Lys Asp Lys
    50                  55                  60

Gly Leu Gln Thr Ser Gln Asp Ala Arg Phe Tyr Ala Leu Ser Ala Ser
65                  70                  75                  80

Phe Glu Pro Phe Ser Asn Lys Gly Gln Thr Leu Val Val Gln Phe Thr
                85                  90                  95

Val Lys His Glu Gln Asn Ile Asp Cys Gly Gly Gly Tyr Val Lys Leu
            100                 105                 110

Phe Pro Asn Ser Leu Asp Gln Thr Asp Met His Gly Asp Ser Glu Tyr
        115                 120                 125

Asn Ile Met Phe Gly Pro Asp Ile Cys Gly Pro Gly Thr Lys Lys Val
    130                 135                 140

His Val Ile Phe Asn Tyr Lys Gly Lys Asn Val Leu Ile Asn Lys Asp
145                 150                 155                 160

Ile Arg Cys Lys Asp Asp Glu Phe Thr His Leu Tyr Thr Leu Ile Val
                165                 170                 175

Arg Pro Asp Asn Thr Tyr Glu Val Lys Ile Asp Asn Ser Gln Val Glu
            180                 185                 190

Ser Gly Ser Leu Glu Asp Asp Trp Asp Phe Leu Pro Pro Lys Lys Ile
        195                 200                 205

Lys Asp Pro Asp Ala Ser Lys Pro Glu Asp Trp Asp Glu Arg Ala Lys
    210                 215                 220

Ile Asp Asp Pro Thr Asp Ser Lys Pro Glu Asp Trp Asp Lys Pro Glu
225                 230                 235                 240

His Ile Pro Asp Pro Asp Ala Lys Lys Pro Glu Asp Trp Asp Glu Glu
                245                 250                 255

Met Asp Gly Glu Trp Glu Pro Pro Val Ile Gln Asn Pro Glu Tyr Lys
            260                 265                 270
```

```
Gly Glu Trp Lys Pro Arg Gln Ile Asp Asn Pro Asp Tyr Lys Gly Thr
        275                 280                 285

Trp Ile His Pro Glu Ile Asp Asn Pro Glu Tyr Ser Pro Asp Pro Ser
    290                 295                 300

Ile Tyr Ala Tyr Asp Asn Phe Gly Val Leu Gly Leu Asp Leu Trp Gln
305                 310                 315                 320

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

Ala Tyr Ala Glu Glu Phe Gly Asn Glu Thr Trp Gly Val Thr Lys Ala
            340                 345                 350

Ala Glu Lys Gln Met Lys Asp Lys Gln Asp Glu Glu Gln Arg Leu Lys
        355                 360                 365

Glu Glu Glu Glu Asp Lys Lys Arg Lys Glu Glu Glu Glu Ala Glu Asp
    370                 375                 380

Lys Glu Asp Asp Glu Asp Lys Asp Glu Asp Glu Glu Asp Glu Glu Asp
385                 390                 395                 400

Lys Glu Glu Asp Glu Glu Glu Asp Val Pro Gly Gln Ala Lys Asp Glu
                405                 410                 415

Leu
```

<210> 11
<211> 278
<212> PRT
<213> 人属、人种

<400> 11

```
Leu Arg Cys Val Pro Arg Val Leu Gly Ser Ser Val Ala Gly Leu Arg
1               5                   10                  15

Ala Ala Ala Pro Ala Ser Pro Phe Arg Gln Leu Leu Gln Pro Ala Pro
            20                  25                  30

Arg Leu Cys Thr Arg Pro Phe Gly Leu Leu Ser Val Arg Ala Gly Ser
        35                  40                  45

Glu Arg Arg Pro Gly Leu Leu Arg Pro Arg Gly Pro Cys Ala Cys Gly
    50                  55                  60

Cys Gly Cys Gly Ser Leu His Thr Asp Gly Asp Lys Ala Phe Val Asp
65                  70                  75                  80

Phe Leu Ser Asp Glu Ile Lys Glu Glu Arg Lys Ile Gln Lys His Lys
                85                  90                  95
```

```
Thr Leu Pro Lys Met Ser Gly Gly Trp Glu Leu Glu Leu Asn Gly Thr
            100                 105                 110

Glu Ala Lys Leu Val Arg Lys Val Ala Gly Glu Lys Ile Thr Val Thr
        115                 120                 125

Phe Asn Ile Asn Asn Ser Ile Pro Pro Thr Phe Asp Gly Glu Glu Glu
    130                 135                 140

Pro Ser Gln Gly Gln Lys Val Glu Glu Gln Glu Pro Glu Leu Thr Ser
145                 150                 155                 160

Thr Pro Asn Phe Val Val Glu Val Ile Lys Asn Asp Asp Gly Lys Lys
                165                 170                 175

Ala Leu Val Leu Asp Cys His Tyr Pro Glu Asp Glu Val Gly Gln Glu
            180                 185                 190

Asp Glu Ala Glu Ser Asp Ile Phe Ser Ile Arg Glu Val Ser Phe Gln
        195                 200                 205

Ser Thr Gly Glu Ser Glu Trp Lys Asp Thr Asn Tyr Thr Leu Asn Thr
    210                 215                 220

Asp Ser Leu Asp Trp Ala Leu Tyr Asp His Leu Met Asp Phe Leu Ala
225                 230                 235                 240

Asp Arg Gly Val Asp Asn Thr Phe Ala Asp Glu Leu Val Glu Leu Ser
                245                 250                 255

Thr Ala Leu Glu His Gln Glu Tyr Ile Thr Phe Leu Glu Asp Leu Lys
            260                 265                 270

Ser Phe Val Lys Ser Gln
        275
```

<210> 12
<211> 661
<212> PRT
<213> 人属、人种

<400> 12

```
Arg Ala Leu Arg Arg Ala Pro Ala Leu Ala Ala Val Pro Gly Gly Lys
1               5                   10                  15

Pro Ile Leu Cys Pro Arg Arg Thr Thr Ala Gln Leu Gly Pro Arg Arg
            20                  25                  30

Asn Pro Ala Trp Ser Leu Gln Ala Gly Arg Leu Phe Ser Thr Gln Thr
        35                  40                  45

Ala Glu Asp Lys Glu Glu Pro Leu His Ser Ile Ile Ser Ser Thr Glu
    50                  55                  60

Ser Val Gln Gly Ser Thr Ser Lys His Glu Phe Gln Ala Glu Thr Lys
```

65 70 75 80

Lys Leu Leu Asp Ile Val Ala Arg Ser Leu Tyr Ser Glu Lys Glu Val
85 90 95

Phe Ile Arg Glu Leu Ile Ser Asn Ala Ser Asp Ala Leu Glu Lys Leu
100 105 110

Arg His Lys Leu Val Ser Asp Gly Gln Ala Leu Pro Glu Met Glu Ile
115 120 125

His Leu Gln Thr Asn Ala Glu Lys Gly Thr Ile Thr Ile Gln Asp Thr
130 135 140

Gly Ile Gly Met Thr Gln Glu Glu Leu Val Ser Asn Leu Gly Thr Ile
145 150 155 160

Ala Arg Ser Gly Ser Lys Ala Phe Leu Asp Ala Leu Gln Asn Gln Ala
165 170 175

Glu Ala Ser Ser Lys Ile Ile Gly Gln Phe Gly Val Gly Phe Tyr Ser
180 185 190

Ala Phe Met Val Ala Asp Arg Val Glu Val Tyr Ser Arg Ser Ala Ala
195 200 205

Pro Gly Ser Leu Gly Tyr Gln Trp Leu Ser Asp Gly Ser Gly Val Phe
210 215 220

Glu Ile Ala Glu Ala Ser Gly Val Arg Thr Gly Thr Lys Ile Ile Ile
225 230 235 240

His Leu Lys Ser Asp Cys Lys Glu Phe Ser Ser Glu Ala Arg Val Arg
245 250 255

Asp Val Val Thr Lys Tyr Ser Asn Phe Val Ser Phe Pro Leu Tyr Leu
260 265 270

Asn Gly Arg Arg Met Asn Thr Leu Gln Ala Ile Trp Met Met Asp Pro
275 280 285

Lys Asp Val Gly Glu Trp Gln His Glu Glu Phe Tyr Arg Tyr Val Ala
290 295 300

Gln Ala His Asp Lys Pro Arg Tyr Thr Leu His Tyr Lys Thr Asp Ala
305 310 315 320

Pro Leu Asn Ile Arg Ser Ile Phe Tyr Val Pro Asp Met Lys Pro Ser
325 330 335

Met Phe Asp Val Ser Arg Glu Leu Gly Ser Ser Val Ala Leu Tyr Ser
340 345 350

Arg Lys Val Leu Ile Gln Thr Lys Ala Thr Asp Ile Leu Pro Lys Trp
355 360 365

Leu Arg Phe Ile Arg Gly Val Val Asp Ser Glu Asp Ile Pro Leu Asn
370 375 380

Leu Ser Arg Glu Leu Leu Gln Glu Ser Ala Leu Ile Arg Lys Leu Arg
385 390 395 400

Asp Val Leu Gln Gln Arg Leu Ile Lys Phe Phe Ile Asp Gln Ser Lys
405 410 415

Lys Asp Ala Glu Lys Tyr Ala Lys Phe Phe Glu Asp Tyr Gly Leu Phe
420 425 430

Met Arg Glu Gly Ile Val Thr Ala Thr Glu Gln Glu Val Lys Glu Asp
435 440 445

Ile Ala Lys Leu Leu Arg Tyr Glu Ser Ser Ala Leu Pro Ser Gly Gln
450 455 460

Leu Thr Ser Leu Ser Glu Tyr Ala Ser Arg Met Arg Ala Gly Thr Arg
465 470 475 480

Asn Ile Tyr Tyr Leu Cys Ala Pro Asn Arg His Leu Ala Glu His Ser
485 490 495

Pro Tyr Tyr Glu Ala Met Lys Lys Lys Asp Thr Glu Val Leu Phe Cys
500 505 510

Phe Glu Gln Phe Asp Glu Leu Thr Leu Leu His Leu Arg Glu Phe Asp
515 520 525

Lys Lys Lys Leu Ile Ser Val Glu Thr Asp Ile Val Val Asp His Tyr
530 535 540

Lys Glu Glu Lys Phe Glu Asp Arg Ser Pro Ala Ala Glu Cys Leu Ser
545 550 555 560

Glu Lys Glu Thr Glu Glu Leu Met Ala Trp Met Arg Asn Val Leu Gly
565 570 575

Ser Arg Val Thr Asn Val Lys Val Thr Leu Arg Leu Asp Thr His Pro
580 585 590

Ala Met Val Thr Val Leu Glu Met Gly Ala Ala Arg His Phe Leu Arg
595 600 605

Met Gln Gln Leu Ala Lys Thr Gln Glu Glu Arg Ala Gln Leu Leu Gln
610 615 620

Pro Thr Leu Glu Ile Asn Pro Arg His Ala Leu Ile Lys Lys Leu Asn
625 630 635 640

His Cys Ala Gln Ala Ser Leu Ala Trp Leu Ser Cys Trp Trp Ile Arg
645 650 655

Tyr Thr Arg Thr Pro
660

<210> 13
<211> 803
<212> PRT
<213> 人属、人种

<400> 13

Met Arg Ala Leu Trp Val Leu Gly Leu Cys Cys Val Leu Leu Thr Phe
1 5 10 15

Gly Ser Val Arg Ala Asp Asp Glu Val Asp Val Asp Gly Thr Val Glu
20 25 30

Glu Asp Leu Gly Lys Ser Arg Glu Gly Ser Arg Thr Asp Asp Glu Val
35 40 45

Val Gln Arg Glu Glu Glu Ala Ile Gln Leu Asp Gly Leu Asn Ala Ser
50 55 60

Gln Ile Arg Glu Leu Arg Glu Lys Ser Glu Lys Phe Ala Phe Gln Ala
65 70 75 80

Glu Val Asn Arg Met Met Lys Leu Ile Ile Asn Ser Leu Tyr Lys Asn
85 90 95

Lys Glu Ile Phe Leu Arg Glu Leu Ile Ser Asn Ala Ser Asp Ala Leu
100 105 110

Asp Lys Ile Arg Leu Ile Ser Leu Thr Asp Glu Asn Ala Leu Ser Gly
115 120 125

Asn Glu Glu Leu Thr Val Lys Ile Lys Cys Asp Lys Glu Lys Asn Leu
130 135 140

Leu His Val Thr Asp Thr Gly Val Gly Met Thr Arg Glu Glu Leu Val
145 150 155 160

Lys Asn Leu Gly Thr Ile Ala Lys Ser Gly Thr Ser Glu Phe Leu Asn
165 170 175

Lys Met Thr Glu Ala Gln Glu Asp Gly Gln Ser Thr Ser Glu Leu Ile
180 185 190

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

Val Ile Val Thr Ser Lys His Asn Asn Asp Thr Gln His Ile Trp Glu
210 215 220

Ser Asp Ser Asn Glu Phe Ser Val Ile Ala Asp Pro Arg Gly Asn Thr
225 230 235 240

Leu Gly Arg Gly Thr Thr Ile Thr Leu Val Leu Lys Glu Glu Ala Ser
245 250 255

```
Asp Tyr Leu Glu Leu Asp Thr Ile Lys Asn Leu Val Lys Lys Tyr Ser
            260                 265                 270

Gln Phe Ile Asn Phe Pro Ile Tyr Val Trp Ser Ser Lys Thr Glu Thr
        275                 280                 285

Val Glu Glu Pro Met Glu Glu Glu Glu Ala Ala Lys Glu Glu Lys Glu
    290                 295                 300

Glu Ser Asp Asp Glu Ala Ala Val Glu Glu Glu Glu Glu Glu Lys Lys
305                 310                 315                 320

Pro Lys Thr Lys Lys Val Glu Lys Thr Val Trp Asp Trp Glu Leu Met
                325                 330                 335

Asn Asp Ile Lys Pro Ile Trp Gln Arg Pro Ser Lys Glu Val Glu Glu
            340                 345                 350

Asp Glu Tyr Lys Ala Phe Tyr Lys Ser Phe Ser Lys Glu Ser Asp Asp
        355                 360                 365

Pro Met Ala Tyr Ile His Phe Thr Ala Glu Gly Glu Val Thr Phe Lys
    370                 375                 380

Ser Ile Leu Phe Val Pro Thr Ser Ala Pro Arg Gly Leu Phe Asp Glu
385                 390                 395                 400

Tyr Gly Ser Lys Lys Ser Asp Tyr Ile Lys Leu Tyr Val Arg Arg Val
                405                 410                 415

Phe Ile Thr Asp Asp Phe His Asp Met Met Pro Lys Tyr Leu Asn Phe
            420                 425                 430

Val Lys Gly Val Val Asp Ser Asp Asp Leu Pro Leu Asn Val Ser Arg
        435                 440                 445

Glu Thr Leu Gln Gln His Lys Leu Leu Lys Val Ile Arg Lys Lys Leu
    450                 455                 460

Val Arg Lys Thr Leu Asp Met Ile Lys Lys Ile Ala Asp Asp Lys Tyr
465                 470                 475                 480

Asn Asp Thr Phe Trp Lys Glu Phe Gly Thr Asn Ile Lys Leu Gly Val
                485                 490                 495

Ile Glu Asp His Ser Asn Arg Thr Arg Leu Ala Lys Leu Leu Arg Phe
            500                 505                 510

Gln Ser Ser His His Pro Thr Asp Ile Thr Ser Leu Asp Gln Tyr Val
        515                 520                 525

Glu Arg Met Lys Glu Lys Gln Asp Lys Ile Tyr Phe Met Ala Gly Ser
    530                 535                 540

Ser Arg Lys Glu Ala Glu Ser Ser Pro Phe Val Glu Arg Leu Leu Lys
545                 550                 555                 560
```

```
Lys Gly Tyr Glu Val Ile Tyr Leu Thr Glu Pro Val Asp Glu Tyr Cys
                565                 570                 575

Ile Gln Ala Leu Pro Glu Phe Asp Gly Lys Arg Phe Gln Asn Val Ala
            580                 585                 590

Lys Glu Gly Val Lys Phe Asp Glu Ser Glu Lys Thr Lys Glu Ser Arg
        595                 600                 605

Glu Ala Val Glu Lys Glu Phe Glu Pro Leu Leu Asn Trp Met Lys Asp
    610                 615                 620

Lys Ala Leu Lys Asp Lys Ile Glu Lys Ala Val Val Ser Gln Arg Leu
625                 630                 635                 640

Thr Glu Ser Pro Cys Ala Leu Val Ala Ser Gln Tyr Gly Trp Ser Gly
                645                 650                 655

Asn Met Glu Arg Ile Met Lys Ala Gln Ala Tyr Gln Thr Gly Lys Asp
            660                 665                 670

Ile Ser Thr Asn Tyr Tyr Ala Ser Gln Lys Lys Thr Phe Glu Ile Asn
        675                 680                 685

Pro Arg His Pro Leu Ile Arg Asp Met Leu Arg Arg Ile Lys Glu Asp
    690                 695                 700

Glu Asp Asp Lys Thr Val Leu Asp Leu Ala Val Val Leu Phe Glu Thr
705                 710                 715                 720

Ala Thr Leu Arg Ser Gly Tyr Leu Leu Pro Asp Thr Lys Ala Tyr Gly
                725                 730                 735

Asp Arg Ile Glu Arg Met Leu Arg Leu Ser Leu Asn Ile Asp Pro Asp
            740                 745                 750

Ala Lys Val Glu Glu Glu Pro Glu Glu Glu Pro Glu Glu Thr Ala Glu
        755                 760                 765

Asp Thr Thr Glu Asp Thr Glu Gln Asp Glu Asp Glu Glu Met Asp Val
    770                 775                 780

Gly Thr Asp Glu Glu Glu Glu Thr Ala Lys Glu Ser Thr Ala Glu Lys
785                 790                 795                 800

Asp Glu Leu
```

<210> 14
<211> 724
<212> PRT
<213> 人属、人种

<400> 14

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Met Pro Glu Glu Val His His Gly Glu Glu Glu Val Glu Thr Phe Ala
1               5                  10                  15

Phe Gln Ala Glu Ile Ala Gln Leu Met Ser Leu Ile Ile Asn Thr Phe
            20                  25                  30

Tyr Ser Asn Lys Glu Ile Phe Leu Arg Glu Leu Ile Ser Asn Ala Ser
        35                  40                  45

Asp Ala Leu Asp Lys Ile Arg Tyr Glu Ser Leu Thr Asp Pro Ser Lys
    50                  55                  60

Leu Asp Ser Gly Lys Glu Leu Lys Ile Asp Ile Ile Pro Asn Pro Gln
65                  70                  75                  80

Glu Arg Thr Leu Thr Leu Val Asp Thr Gly Ile Gly Met Thr Lys Ala
                85                  90                  95

Asp Leu Ile Asn Asn Leu Gly Thr Ile Ala Lys Ser Gly Thr Lys Ala
            100                 105                 110

Phe Met Glu Ala Leu Gln Ala Gly Ala Asp Ile Ser Met Ile Gly Gln
        115                 120                 125

Phe Gly Val Gly Phe Tyr Ser Ala Tyr Leu Val Ala Glu Lys Val Val
    130                 135                 140

Val Ile Arg Lys His Asn Asp Asp Glu Gln Tyr Ala Trp Glu Ser Ser
145                 150                 155                 160

Ala Gly Gly Ser Phe Thr Val Arg Ala Asp His Gly Glu Pro Ile Gly
                165                 170                 175

Met Gly Thr Lys Val Ile Leu His Leu Lys Glu Asp Gln Thr Glu Tyr
            180                 185                 190

Leu Glu Glu Arg Arg Val Lys Glu Val Val Lys Lys His Ser Gln Phe
        195                 200                 205

Ile Gly Tyr Pro Ile Thr Leu Tyr Leu Glu Lys Glu Arg Glu Lys Glu
    210                 215                 220

Ile Ser Asp Asp Glu Ala Glu Glu Glu Lys Gly Glu Lys Glu Glu Glu
225                 230                 235                 240

Asp Lys Asp Asp Glu Glu Lys Pro Lys Ile Glu Asp Val Gly Ser Asp
                245                 250                 255

Glu Glu Asp Asp Ser Gly Lys Asp Lys Lys Lys Lys Thr Lys Lys Ile
            260                 265                 270

Lys Glu Lys Tyr Ile Asp Gln Glu Glu Leu Asn Lys Thr Lys Pro Ile
        275                 280                 285

Trp Thr Arg Asn Pro Asp Asp Ile Thr Gln Glu Glu Tyr Gly Glu Phe
    290                 295                 300
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Tyr Lys Ser Leu Thr Asn Asp Trp Glu Asp His Leu Ala Val Lys His
305                 310                 315                 320

Phe Ser Val Glu Gly Gln Leu Glu Phe Arg Ala Leu Leu Phe Ile Pro
                325                 330                 335

Arg Arg Ala Pro Phe Asp Leu Phe Glu Asn Lys Lys Lys Lys Asn Asn
            340                 345                 350

Ile Lys Leu Tyr Val Arg Arg Val Phe Ile Met Asp Ser Cys Asp Glu
        355                 360                 365

Leu Ile Pro Glu Tyr Leu Asn Phe Ile Arg Gly Val Val Asp Ser Glu
    370                 375                 380

Asp Leu Pro Leu Asn Ile Ser Arg Glu Met Leu Gln Gln Ser Lys Ile
385                 390                 395                 400

Leu Lys Val Ile Arg Lys Asn Ile Val Lys Lys Cys Leu Glu Leu Phe
                405                 410                 415

Ser Glu Leu Ala Glu Asp Lys Glu Asn Tyr Lys Lys Phe Tyr Glu Ala
            420                 425                 430

Phe Ser Lys Asn Leu Lys Leu Gly Ile His Glu Asp Ser Thr Asn Arg
        435                 440                 445

Arg Arg Leu Ser Glu Leu Leu Arg Tyr His Thr Ser Gln Ser Gly Asp
    450                 455                 460

Glu Met Thr Ser Leu Ser Glu Tyr Val Ser Arg Met Lys Glu Thr Gln
465                 470                 475                 480

Lys Ser Ile Tyr Tyr Ile Thr Gly Glu Ser Lys Glu Gln Val Ala Asn
                485                 490                 495

Ser Ala Phe Val Glu Arg Val Arg Lys Arg Gly Phe Glu Val Val Tyr
            500                 505                 510

Met Thr Glu Pro Ile Asp Glu Tyr Cys Val Gln Gln Leu Lys Glu Phe
        515                 520                 525

Asp Gly Lys Ser Leu Val Ser Val Thr Lys Glu Gly Leu Glu Leu Pro
    530                 535                 540

Glu Asp Glu Glu Glu Lys Lys Lys Met Glu Glu Ser Lys Ala Lys Phe
545                 550                 555                 560

Glu Asn Leu Cys Lys Leu Met Lys Glu Ile Leu Asp Lys Lys Val Glu
                565                 570                 575

Lys Val Thr Ile Ser Asn Arg Leu Val Ser Ser Pro Cys Cys Ile Val
            580                 585                 590

Thr Ser Thr Tyr Gly Trp Thr Ala Asn Met Glu Arg Ile Met Lys Ala
```

595 600 605

Gln Ala Leu Arg Asp Asn Ser Thr Met Gly Tyr Met Met Ala Lys Lys
610 615 620

His Leu Glu Ile Asn Pro Asp His Pro Ile Val Glu Thr Leu Arg Gln
625 630 635 640

Lys Ala Glu Ala Asp Lys Asn Asp Lys Ala Val Lys Asp Leu Val Val
645 650 655

Leu Leu Phe Glu Thr Ala Leu Leu Ser Ser Gly Phe Ser Leu Glu Asp
660 665 670

Pro Gln Thr His Ser Asn Arg Ile Tyr Arg Met Ile Lys Leu Gly Leu
675 680 685

Gly Ile Asp Glu Asp Glu Val Ala Ala Glu Glu Pro Asn Ala Ala Val
690 695 700

Pro Asp Glu Ile Pro Pro Leu Glu Gly Asp Glu Asp Ala Ser Arg Met
705 710 715 720

Glu Glu Val Asp

<210> 15
<211> 732
<212> PRT
<213> 人属、人种

<400> 15

Met Pro Glu Glu Thr Gln Thr 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 Thr 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 Glu Asp Lys Pro
                245                 250                 255

Glu Ile Glu Asp Val Gly Ser Asp Glu Glu Glu Glu Lys Lys Asp Gly
            260                 265                 270

Asp Lys Lys Lys Lys Lys Lys Ile Lys Glu Lys Tyr Ile Asp Gln Glu
        275                 280                 285

Glu Leu Asn Lys Thr Lys Pro Ile Trp Thr Arg Asn Pro Asp Asp Ile
    290                 295                 300

Thr Asn Glu Glu Tyr Gly Glu Phe Tyr Lys Ser Leu Thr Asn Asp Trp
305                 310                 315                 320

Glu Asp His Leu Ala Val Lys His Phe Ser Val Glu Gly Gln Leu Glu
                325                 330                 335

Phe Arg Ala Leu Leu Phe Val Pro Arg Arg Ala Pro Phe Asp Leu Phe
            340                 345                 350

Glu Asn Arg Lys Lys Lys Asn Asn Ile Lys Leu Tyr Val Arg Arg Val
        355                 360                 365

Phe Ile Met Asp Asn Cys Glu Glu Leu Ile Pro Glu Tyr Leu Asn Phe
    370                 375                 380

Ile Arg Gly Val Val Asp Ser Glu Asp Leu Pro Leu Asn Ile Ser Arg
385                 390                 395                 400

Glu Met Leu Gln Gln Ser Lys Ile Leu Lys Val Ile Arg Lys Asn Leu
                405                 410                 415

Val Lys Lys Cys Leu Glu Leu Phe Thr Glu Leu Ala Glu Asp Lys Glu
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420 425 430

Asn Tyr Lys Lys Phe Tyr Glu Gln Phe Ser Lys Asn Ile Lys Leu Gly
435 440 445

Ile His Glu Asp Ser Gln Asn Arg Lys Lys Leu Ser Glu Leu Leu Arg
450 455 460

Tyr Tyr Thr Ser Ala Ser Gly Asp Glu Met Val Ser Leu Lys Asp Tyr
465 470 475 480

Cys Thr Arg Met Lys Glu Asn Gln Lys His Ile Tyr Tyr Ile Thr Gly
485 490 495

Glu Thr Lys Asp Gln Val Ala Asn Ser Ala Phe Val Glu Arg Leu Arg
500 505 510

Lys His Gly Leu Glu Val Ile Tyr Met Ile Glu Pro Ile Asp Glu Tyr
515 520 525

Cys Val Gln Gln Leu Lys Glu Phe Glu Gly Lys Thr Leu Val Ser Val
530 535 540

Thr Lys Glu Gly Leu Glu Leu Pro Glu Asp Glu Glu Glu Lys Lys Lys
545 550 555 560

Gln Glu Glu Lys Lys Thr Lys Phe Glu Asn Leu Cys Lys Ile Met Lys
565 570 575

Asp Ile Leu Glu Lys Lys Val Glu Lys Val Val Val Ser Asn Arg Leu
580 585 590

Val Thr Ser Pro Cys Cys Ile Val Thr Ser Thr Tyr Gly Trp Thr Ala
595 600 605

Asn Met Glu Arg Ile Met Lys Ala Gln Ala Leu Arg Asp Asn Ser Thr
610 615 620

Met Gly Tyr Met Ala Ala Lys Lys His Leu Glu Ile Asn Pro Asp His
625 630 635 640

Ser Ile Ile Glu Thr Leu Arg Gln Lys Ala Glu Ala Asp Lys Asn Asp
645 650 655

Lys Ser Val Lys Asp Leu Val Ile Leu Leu Tyr Glu Thr Ala Leu Leu
660 665 670

Ser Ser Gly Phe Ser Leu Glu Asp Pro Gln Thr His Ala Asn Arg Ile
675 680 685

Tyr Arg Met Ile Lys Leu Gly Leu Gly Ile Asp Glu Asp Asp Pro Thr
690 695 700

Ala Asp Asp Thr Ser Ala Ala Val Thr Glu Glu Met Pro Pro Leu Glu
705 710 715 720

Gly Asp Asp Asp Thr Ser Arg Met Glu Glu Val Asp
725 730

<210> 16
<211> 573
<212> PRT
<213> 人属、人种

<400> 16

Met Leu Arg Leu Pro Thr Val Phe Arg Gln Met Arg Pro Val Ser Arg
1 5 10 15

Val Leu Ala Pro His Leu Thr Arg Ala Tyr Ala Lys Asp Val Lys Phe
20 25 30

Gly Ala Asp Ala Arg Ala Leu Met Leu Gln Gly Val Asp Leu Leu Ala
35 40 45

Asp Ala Val Ala Val Thr Met Gly Pro Lys Gly Arg Thr Val Ile Ile
50 55 60

Glu Gln Ser Trp Gly Ser Pro Lys Val Thr Lys Asp Gly Val Thr Val
65 70 75 80

Ala Lys Ser Ile Asp Leu Lys Asp Lys Tyr Lys Asn Ile Gly Ala Lys
85 90 95

Leu Val Gln Asp Val Ala Asn Asn Thr Asn Glu Glu Ala Gly Asp Gly
100 105 110

Thr Thr Thr Ala Thr Val Leu Ala Arg Ser Ile Ala Lys Glu Gly Phe
115 120 125

Glu Lys Ile Ser Lys Gly Ala Asn Pro Val Glu Ile Arg Arg Gly Val
130 135 140

Met Leu Ala Val Asp Ala Val Ile Ala Glu Leu Lys Lys Gln Ser Lys
145 150 155 160

Pro Val Thr Thr Pro Glu Glu Ile Ala Gln Val Ala Thr Ile Ser Ala
165 170 175

Asn Gly Asp Lys Glu Ile Gly Asn Ile Ile Ser Asp Ala Met Lys Lys
180 185 190

Val Gly Arg Lys Gly Val Ile Thr Val Lys Asp Gly Lys Thr Leu Asn
195 200 205

Asp Glu Leu Glu Ile Ile Glu Gly Met Lys Phe Asp Arg Gly Tyr Ile
210 215 220

Ser Pro Tyr Phe Ile Asn Thr Ser Lys Gly Gln Lys Cys Glu Phe Gln
225 230 235 240

Asp Ala Tyr Val Leu Leu Ser Glu Lys Lys Ile Ser Ser Ile Gln Ser

245 250 255

Ile Val Pro Ala Leu Glu Ile Ala Asn Ala His Arg Lys Pro Leu Val
260 265 270

Ile Ile Ala Glu Asp Val Asp Gly Glu Ala Leu Ser Thr Leu Val Leu
275 280 285

Asn Arg Leu Lys Val Gly Leu Gln Val Val Ala Val Lys Ala Pro Gly
290 295 300

Phe Gly Asp Asn Arg Lys Asn Gln Leu Lys Asp Met Ala Ile Ala Thr
305 310 315 320

Gly Gly Ala Val Phe Gly Glu Glu Gly Leu Thr Leu Asn Leu Glu Asp
325 330 335

Val Gln Pro His Asp Leu Gly Lys Val Gly Glu Val Ile Val Thr Lys
340 345 350

Asp Asp Ala Met Leu Leu Lys Gly Lys Gly Asp Lys Ala Gln Ile Glu
355 360 365

Lys Arg Ile Gln Glu Ile Ile Glu Gln Leu Asp Val Thr Thr Ser Glu
370 375 380

Tyr Glu Lys Glu Lys Leu Asn Glu Arg Leu Ala Lys Leu Ser Asp Gly
385 390 395 400

Val Ala Val Leu Lys Val Gly Gly Thr Ser Asp Val Glu Val Asn Glu
405 410 415

Lys Lys Asp Arg Val Thr Asp Ala Leu Asn Ala Thr Arg Ala Ala Val
420 425 430

Glu Glu Gly Ile Val Leu Gly Gly Gly Cys Ala Leu Leu Arg Cys Ile
435 440 445

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

Ile Glu Ile Ile Lys Arg Thr Leu Lys Ile Pro Ala Met Thr Ile Ala
465 470 475 480

Lys Asn Ala Gly Val Glu Gly Ser Leu Ile Val Glu Lys Ile Met Gln
485 490 495

Ser Ser Ser Glu Val Gly Tyr Asp Ala Met Ala Gly Asp Phe Val Asn
500 505 510

Met Val Glu Lys Gly Ile Ile Asp Pro Thr Lys Val Val Arg Thr Ala
515 520 525

Leu Leu Asp Ala Ala Gly Val Ala Ser Leu Leu Thr Thr Ala Glu Val
530 535 540

Val Val Thr Glu Ile Pro Lys Glu Glu Lys Asp Pro Gly Met Gly Ala
545 550 555 560

Met Gly Gly Met Gly Gly Gly Met Gly Gly Gly Met Phe
565 570

<210> 17
<211> 215
<212> PRT
<213> 人属、人种

<400> 17

Met Gly Lys Gly Asp Pro Lys Lys Pro Arg Arg Lys Met Ser Ser Tyr
1 5 10 15

Ala Phe Phe Val Gln Thr Cys Arg Glu Glu His Lys Lys Lys His Pro
20 25 30

Asp Ala Ser Val Asn Phe Ser Glu Phe Ser Lys Lys Cys Ser Glu Arg
35 40 45

Trp Lys Thr Met Ser Ala Lys Glu Lys Gly Lys Phe Glu Asp Met Ala
50 55 60

Lys Ala Asp Lys Ala Arg Tyr Glu Arg Glu Met Lys Thr Tyr Ile Pro
65 70 75 80

Pro Lys Gly Glu Thr Lys Lys Lys Phe Lys Asp Pro Asn Ala Pro Lys
85 90 95

Arg Pro Pro Ser Ala Phe Phe Leu Phe Cys Ser Glu Tyr Arg Pro Lys
100 105 110

Ile Lys Gly Glu His Pro Gly Leu Ser Ile Gly Asp Val Ala Lys Lys
115 120 125

Leu Gly Glu Met Trp Asn Asn Thr Ala Ala Asp Asp Lys Gln Pro Tyr
130 135 140

Glu Lys Lys Ala Glu Lys Leu Lys Glu Lys Tyr Glu Lys Asp Ile Ala
145 150 155 160

Ala Tyr Arg Ala Lys Gly Lys Pro Asp Ala Ala Lys Lys Gly Val Val
165 170 175

Lys Ala Glu Lys Ser Lys Lys Lys Lys Glu Glu Glu Glu Gly Glu Glu
180 185 190

Asp Glu Glu Asp Glu Glu Glu Glu Glu Asp Glu Glu Asp Glu Asp Glu
195 200 205

Glu Glu Asp Asp Asp Asp Glu
210 215

<210> 18

<211> 1087
<212> PRT
<213> 人属、人种

<400> 18

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Met Met Thr Ser Val Gly Thr Asn Arg Ala Arg Gly Asn Trp Glu Gln
1               5                  10                  15

Pro Gln Asn Gln Asn Gln Thr Gln His Lys Gln Arg Pro Gln Ala Thr
            20                  25                  30

Ala Glu Gln Ile Arg Leu Ala Gln Met Ile Ser Asp His Asn Asp Ala
        35                  40                  45

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

Gln Asp Glu Cys Val Ile Ala Leu His Asp Cys Asn Gly Asp Val Asn
65                  70                  75                  80

Arg Ala Ile Asn Val Leu Leu Glu Gly Asn Pro Asp Thr His Ser Trp
                85                  90                  95

Glu Met Val Gly Lys Lys Lys Gly Val Ser Gly Gln Lys Asp Gly Gly
            100                 105                 110

Gln Thr Glu Ser Asn Glu Glu Gly Lys Glu Asn Arg Asp Arg Asp Arg
        115                 120                 125

Asp Tyr Ser Arg Arg Arg Gly Gly Pro Pro Arg Arg Gly Arg Gly Ala
    130                 135                 140

Ser Arg Gly Arg Glu Phe Arg Gly Gln Glu Asn Gly Leu Asp Gly Thr
145                 150                 155                 160

Lys Ser Gly Gly Pro Ser Gly Arg Gly Thr Glu Arg Gly Arg Arg Gly
                165                 170                 175

Arg Gly Arg Gly Arg Gly Gly Ser Gly Arg Arg Gly Gly Arg Phe Ser
            180                 185                 190

Ala Gln Gly Met Gly Thr Phe Asn Pro Ala Asp Tyr Ala Glu Pro Ala
        195                 200                 205

Asn Thr Asp Asp Asn Tyr Gly Asn Ser Ser Gly Asn Thr Trp Asn Asn
    210                 215                 220

Thr Gly His Phe Glu Pro Asp Asp Gly Thr Ser Ala Trp Arg Thr Ala
225                 230                 235                 240

Thr Glu Glu Trp Gly Thr Glu Asp Trp Asn Glu Asp Leu Ser Glu Thr
                245                 250                 255

Lys Ile Phe Thr Ala Ser Asn Val Ser Ser Val Pro Leu Pro Ala Glu
            260                 265                 270
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Asn Val Thr Ile Thr Ala Gly Gln Arg Ile Asp Leu Ala Val Leu Leu
        275                 280                 285

Gly Lys Thr Pro Ser Thr Met Glu Asn Asp Ser Ser Asn Leu Asp Pro
    290                 295                 300

Ser Gln Ala Pro Ser Leu Ala Gln Pro Leu Val Phe Ser Asn Ser Lys
305                 310                 315                 320

Gln Thr Ala Ile Ser Gln Pro Ala Ser Gly Asn Thr Phe Ser His His
                325                 330                 335

Ser Met Val Ser Met Leu Gly Lys Gly Phe Gly Asp Val Gly Glu Ala
            340                 345                 350

Lys Gly Gly Ser Thr Thr Gly Ser Gln Phe Leu Glu Gln Phe Lys Thr
        355                 360                 365

Ala Gln Ala Leu Ala Gln Leu Ala Ala Gln His Ser Gln Ser Gly Ser
    370                 375                 380

Thr Thr Thr Ser Ser Trp Asp Met Gly Ser Thr Thr Gln Ser Pro Ser
385                 390                 395                 400

Leu Val Gln Tyr Asp Leu Lys Asn Pro Ser Asp Ser Ala Val His Ser
                405                 410                 415

Pro Phe Thr Lys Arg Gln Ala Phe Thr Pro Ser Ser Thr Met Met Glu
            420                 425                 430

Val Phe Leu Gln Glu Lys Ser Pro Ala Val Ala Thr Ser Thr Ala Ala
        435                 440                 445

Pro Pro Pro Pro Ser Ser Pro Leu Pro Ser Lys Ser Thr Ser Ala Pro
    450                 455                 460

Gln Met Ser Pro Gly Ser Ser Asp Asn Gln Ser Ser Ser Pro Gln Pro
465                 470                 475                 480

Ala His Gln Lys Leu Lys Gln Gln Lys Lys Lys Ala Ser Leu Thr Ser
                485                 490                 495

Lys Ile Pro Ala Leu Ala Val Glu Met Pro Gly Ser Ala Asp Ile Ser
            500                 505                 510

Gly Leu Asn Leu Gln Phe Gly Ala Leu Gln Phe Gly Ser Glu Pro Val
        515                 520                 525

Leu Ser Asp Tyr Glu Ser Thr Pro Thr Thr Ser Ala Ser Ser Ser Gln
    530                 535                 540

Ala Pro Ser Ser Leu Tyr Thr Ser Thr Ala Ser Glu Ser Ser Ser Thr
545                 550                 555                 560

Ile Ser Ser Asn Gln Ser Gln Glu Ser Gly Tyr Gln Ser Gly Pro Ile
```

565 570 575

Gln Ser Thr Thr Tyr Thr Ser Gln Asn Asn Ala Gln Gly Pro Leu Tyr
580 585 590

Glu Gln Arg Ser Thr Gln Thr Arg Arg Tyr Pro Ser Ser Ile Ser Ser
595 600 605

Ser Pro Gln Lys Asp Leu Thr Gln Ala Lys Asn Gly Phe Ser Ser Val
610 615 620

Gln Ala Thr Gln Leu Gln Thr Thr Gln Ser Val Glu Gly Ala Thr Gly
625 630 635 640

Ser Ala Val Lys Ser Asp Ser Pro Ser Thr Ser Ser Ile Pro Pro Leu
645 650 655

Asn Glu Thr Val Ser Ala Ala Ser Leu Leu Thr Thr Thr Asn Gln His
660 665 670

Ser Ser Ser Leu Gly Gly Leu Ser His Ser Glu Glu Ile Pro Asn Thr
675 680 685

Thr Thr Thr Gln His Ser Ser Thr Leu Ser Thr Gln Gln Asn Thr Leu
690 695 700

Ser Ser Ser Thr Ser Ser Gly Arg Thr Ser Thr Ser Thr Leu Leu His
705 710 715 720

Thr Ser Val Glu Ser Glu Ala Asn Leu His Ser Ser Ser Ser Thr Phe
725 730 735

Ser Thr Thr Ser Ser Thr Val Ser Ala Pro Pro Pro Val Val Ser Val
740 745 750

Ser Ser Ser Leu Asn Ser Gly Ser Ser Leu Gly Leu Ser Leu Gly Ser
755 760 765

Asn Ser Thr Val Thr Ala Ser Thr Arg Ser Ser Val Ala Thr Thr Ser
770 775 780

Gly Lys Ala Pro Pro Asn Leu Pro Pro Gly Val Pro Pro Leu Leu Pro
785 790 795 800

Asn Pro Tyr Ile Met Ala Pro Gly Leu Leu His Ala Tyr Pro Pro Gln
805 810 815

Val Tyr Gly Tyr Asp Asp Leu Gln Met Leu Gln Thr Arg Phe Pro Leu
820 825 830

Asp Tyr Tyr Ser Ile Pro Phe Pro Thr Pro Thr Thr Pro Leu Thr Gly
835 840 845

Arg Asp Gly Ser Leu Ala Ser Asn Pro Tyr Ser Gly Asp Leu Thr Lys
850 855 860

Phe Gly Arg Gly Asp Ala Ser Ser Pro Ala Pro Ala Thr Thr Leu Ala
865 870 875 880

Gln Pro Gln Gln Asn Gln Thr Gln Thr His His Thr Thr Gln Gln Thr
885 890 895

Phe Leu Asn Pro Ala Leu Pro Pro Gly Tyr Ser Tyr Thr Ser Leu Pro
900 905 910

Tyr Tyr Thr Gly Val Pro Gly Leu Pro Ser Thr Phe Gln Tyr Gly Pro
915 920 925

Ala Val Phe Pro Val Ala Pro Thr Ser Ser Lys Gln His Gly Val Asn
930 935 940

Val Ser Val Asn Ala Ser Ala Thr Pro Phe Gln Gln Pro Ser Gly Tyr
945 950 955 960

Gly Ser His Gly Tyr Asn Thr Gly Val Ser Val Thr Ser Ser Asn Thr
965 970 975

Gly Val Pro Asp Ile Ser Gly Ser Val Tyr Ser Lys Thr Gln Gln Ser
980 985 990

Phe Glu Lys Gln Gly Phe His Ser Gly Thr Pro Ala Ala Ser Phe Asn
995 1000 1005

Leu Pro Ser Ala Leu Gly Ser Gly Gly Pro Ile Asn Pro Ala Thr
1010 1015 1020

Ala Ala Ala Tyr Pro Pro Ala Pro Phe Met His Ile Leu Thr Pro
1025 1030 1035

His Gln Gln Pro His Ser Gln Ile Leu His His His Leu Gln Gln
1040 1045 1050

Asp Gly Gln Thr Gly Ser Gly Gln Arg Ser Gln Thr Ser Ser Ile
1055 1060 1065

Pro Gln Lys Pro Gln Thr Asn Lys Ser Ala Tyr Asn Ser Tyr Ser
1070 1075 1080

Trp Gly Ala Asn
1085

<210> 19
<211> 806
<212> PRT
<213> 人属、人种

<400> 19

Met Ala Ser Gly Ala Asp Ser Lys Gly Asp Asp Leu Ser Thr Ala Ile
1 5 10 15

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

20 25 30

Asn Glu Asp Asn Ser Val Val Ser Leu Ser Gln Pro Lys Met Asp Glu
35 40 45

Leu Gln Leu Phe Arg Gly Asp Thr Val Leu Leu Lys Gly Lys Lys Arg
50 55 60

Arg Glu Ala Val Cys Ile Val Leu Ser Asp Asp Thr Cys Ser Asp Glu
65 70 75 80

Lys Ile Arg Met Asn Arg Val Val Arg Asn Asn Leu Arg Val Arg Leu
85 90 95

Gly Asp Val Ile Ser Ile Gln Pro Cys Pro Asp Val Lys Tyr Gly Lys
100 105 110

Arg Ile His Val Leu Pro Ile Asp Asp Thr Val Glu Gly Ile Thr Gly
115 120 125

Asn Leu Phe Glu Val Tyr Leu Lys Pro Tyr Phe Leu Glu Ala Tyr Arg
130 135 140

Pro Ile Arg Lys Gly Asp Ile Phe Leu Val Arg Gly Gly Met Arg Ala
145 150 155 160

Val Glu Phe Lys Val Val Glu Thr Asp Pro Ser Pro Tyr Cys Ile Val
165 170 175

Ala Pro Asp Thr Val Ile His Cys Glu Gly Glu Pro Ile Lys Arg Glu
180 185 190

Asp Glu Glu Glu Ser Leu Asn Glu Val Gly Tyr Asp Asp Ile Gly Gly
195 200 205

Cys Arg Lys Gln Leu Ala Gln Ile Lys Glu Met Val Glu Leu Pro Leu
210 215 220

Arg His Pro Ala Leu Phe Lys Ala Ile Gly Val Lys Pro Pro Arg Gly
225 230 235 240

Ile Leu Leu Tyr Gly Pro Pro Gly Thr Gly Lys Thr Leu Ile Ala Arg
245 250 255

Ala Val Ala Asn Glu Thr Gly Ala Phe Phe Phe Leu Ile Asn Gly Pro
260 265 270

Glu Ile Met Ser Lys Leu Ala Gly Glu Ser Glu Ser Asn Leu Arg Lys
275 280 285

Ala Phe Glu Glu Ala Glu Lys Asn Ala Pro Ala Ile Ile Phe Ile Asp
290 295 300

Glu Leu Asp Ala Ile Ala Pro Lys Arg Glu Lys Thr His Gly Glu Val
305 310 315 320

Glu Arg Arg Ile Val Ser Gln Leu Leu Thr Leu Met Asp Gly Leu Lys
325 330 335

Gln Arg Ala His Val Ile Val Met Ala Ala Thr Asn Arg Pro Asn Ser
340 345 350

Ile Asp Pro Ala Leu Arg Arg Phe Gly Arg Phe Asp Arg Glu Val Asp
355 360 365

Ile Gly Ile Pro Asp Ala Thr Gly Arg Leu Glu Ile Leu Gln Ile His
370 375 380

Thr Lys Asn Met Lys Leu Ala Asp Asp Val Asp Leu Glu Gln Val Ala
385 390 395 400

Asn Glu Thr His Gly His Val Gly Ala Asp Leu Ala Ala Leu Cys Ser
405 410 415

Glu Ala Ala Leu Gln Ala Ile Arg Lys Lys Met Asp Leu Ile Asp Leu
420 425 430

Glu Asp Glu Thr Ile Asp Ala Glu Val Met Asn Ser Leu Ala Val Thr
435 440 445

Met Asp Asp Phe Arg Trp Ala Leu Ser Gln Ser Asn Pro Ser Ala Leu
450 455 460

Arg Glu Thr Val Val Glu Val Pro Gln Val Thr Trp Glu Asp Ile Gly
465 470 475 480

Gly Leu Glu Asp Val Lys Arg Glu Leu Gln Glu Leu Val Gln Tyr Pro
485 490 495

Val Glu His Pro Asp Lys Phe Leu Lys Phe Gly Met Thr Pro Ser Lys
500 505 510

Gly Val Leu Phe Tyr Gly Pro Pro Gly Cys Gly Lys Thr Leu Leu Ala
515 520 525

Lys Ala Ile Ala Asn Glu Cys Gln Ala Asn Phe Ile Ser Ile Lys Gly
530 535 540

Pro Glu Leu Leu Thr Met Trp Phe Gly Glu Ser Glu Ala Asn Val Arg
545 550 555 560

Glu Ile Phe Asp Lys Ala Arg Gln Ala Ala Pro Cys Val Leu Phe Phe
565 570 575

Asp Glu Leu Asp Ser Ile Ala Lys Ala Arg Gly Gly Asn Ile Gly Asp
580 585 590

Gly Gly Gly Ala Ala Asp Arg Val Ile Asn Gln Ile Leu Thr Glu Met
595 600 605

Asp Gly Met Ser Thr Lys Lys Asn Val Phe Ile Ile Gly Ala Thr Asn
610 615 620

```
Arg Pro Asp Ile Ile Asp Pro Ala Ile Leu Arg Pro Gly Arg Leu Asp
625                 630                 635                 640

Gln Leu Ile Tyr Ile Pro Leu Pro Asp Glu Lys Ser Arg Val Ala Ile
                645                 650                 655

Leu Lys Ala Asn Leu Arg Lys Ser Pro Val Ala Lys Asp Val Asp Leu
            660                 665                 670

Glu Phe Leu Ala Lys Met Thr Asn Gly Phe Ser Gly Ala Asp Leu Thr
        675                 680                 685

Glu Ile Cys Gln Arg Ala Cys Lys Leu Ala Ile Arg Glu Ser Ile Glu
    690                 695                 700

Ser Glu Ile Arg Arg Glu Arg Glu Arg Gln Thr Asn Pro Ser Ala Met
705                 710                 715                 720

Glu Val Glu Glu Asp Asp Pro Val Pro Glu Ile Arg Arg Asp His Phe
                725                 730                 735

Glu Glu Ala Met Arg Phe Ala Arg Arg Ser Val Ser Asp Asn Asp Ile
            740                 745                 750

Arg Lys Tyr Glu Met Phe Ala Gln Thr Leu Gln Gln Ser Arg Gly Phe
        755                 760                 765

Gly Ser Phe Arg Phe Pro Ser Gly Asn Gln Gly Gly Ala Gly Pro Ser
    770                 775                 780

Gln Gly Ser Gly Gly Gly Thr Gly Gly Ser Val Tyr Thr Glu Asp Asn
785                 790                 795                 800

Asp Asp Asp Leu Tyr Gly
                805
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<210> 20
<211> 260
<212> PRT
<213> 人属、人种

<400> 20

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Met Val Lys Val Lys Val Glu Val Asn Gly Phe Gly His Thr Gly Arg
1               5                   10                  15

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

Ile Asn Asp Pro Phe Ile Asp Leu Asn Tyr Pro Phe Ile Asp Leu Asn
        35                  40                  45

Tyr Met Ile Tyr Met Phe Gln Tyr Asp Ser Met Ala Asn Ser Met Ala
    50                  55                  60
```

Pro Ser Arg Leu Arg Met Gly Ser Leu Ser Ser Arg Glu Ile Pro Ser
65 70 75 80

Pro Ser Ser Arg Ser Glu Ile Pro Pro Lys Ser Asn Gly Gly Glu Ala
85 90 95

Lys Arg Ile Ile Ile Ser Ala Pro Ser Ala Asp Ala Pro Met Phe Met
100 105 110

Met Gly Ile Asn Arg Glu Lys Tyr Asp Asn Ser Leu Glu Ile Ile Ser
115 120 125

Asn Ala Ser Cys Thr Thr Asn Cys Leu Ala Pro Leu Ala Lys Val Ile
130 135 140

His Asp Asn Phe Gly Ile Met Glu Gly Leu Met Thr Thr Val His Ala
145 150 155 160

Ile Ala Ala Thr Gln Lys Thr Val Asp Ser Pro Ser Gly Lys Leu Trp
165 170 175

Cys Asp Gly Cys Arg Ala Leu Gln Asn Ile Ile Pro Ala Ser Thr Gly
180 185 190

Ser Ser Leu Ala Lys Pro Ser Val Val Pro Thr Thr Asn Val Ser Val
195 200 205

Val Asp Leu Thr Cys His Leu Glu Lys Pro Ala Lys Tyr Asp Asp Ile
210 215 220

Lys Lys Trp Cys Ser Arg His Gln Lys Ala Pro Ser Arg Ala Ser Trp
225 230 235 240

Ala Thr Leu Ser Thr Cys Asn Arg Val Val Asp Leu Met Ala His Met
245 250 255

Ala Ser Lys Glu
260

<210> 21
<211> 279
<212> PRT
<213> 人属、人种

<400> 21

Met Asn Lys Val Glu Leu Glu Ser Arg Leu Glu Gly Leu Thr Asp Glu
1 5 10 15

Ile Asn Phe Leu Arg Gln Leu Tyr Glu Glu Glu Leu Arg Glu Leu Gln
20 25 30

Ser Gln Ile Ser Asp Thr Ser Val Val Leu Ser Met Asp Asn Ser Arg
35 40 45

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

50 55 60

Asp Ile Ala Asn Arg Ser Arg Ala Glu Ala Glu Ser Met Tyr Gln Ile
65 70 75 80

Lys Tyr Glu Glu Leu Gln Ser Leu Ala Gly Lys His Gly Asp Asp Leu
85 90 95

Arg Arg Thr Lys Thr Glu Ile Ser Glu Met Asn Arg Asn Ile Ser Arg
100 105 110

Leu Gln Ala Glu Ile Glu Gly Leu Lys Gly Gln Arg Ala Ser Leu Glu
115 120 125

Ala Ala Ile Ala Asp Ala Glu Gln Arg Gly Glu Leu Ala Ile Lys Asp
130 135 140

Ala Asn Ala Lys Leu Ser Glu Leu Glu Ala Ala Leu Gln Arg Ala Lys
145 150 155 160

Gln Asp Met Ala Arg Gln Leu Arg Glu Tyr Gln Glu Leu Met Asn Val
165 170 175

Lys Leu Ala Met Asp Ile Glu Ile Ala Thr Tyr Arg Lys Leu Leu Glu
180 185 190

Gly Glu Glu Ser Arg Leu Glu Ser Gly Met Gln Asn Met Ser Ile His
195 200 205

Thr Lys Thr Thr Gly Gly Tyr Ala Gly Gly Leu Ser Ser Ala Tyr Gly
210 215 220

Gly Leu Ala Ser Pro Gly Leu Ser Tyr Ser Leu Gly Ser Ser Phe Gly
225 230 235 240

Ser Gly Ala Gly Ser Ser Ser Phe Ser Arg Thr Ser Ser Ser Arg Ala
245 250 255

Val Val Val Lys Lys Ile Glu Thr Arg Asp Gly Lys Leu Val Ser Glu
260 265 270

Ser Ser Asp Val Leu Pro Lys
275

<210> 22
<211> 577
<212> PRT
<213> 人属、人种

<400> 22

Met Asn Lys Leu Tyr Ile Gly Asn Leu Asn Glu Ser Val Thr Pro Ala
1 5 10 15

Asp Leu Glu Lys Val Phe Ala Glu His Lys Ile Ser Tyr Ser Gly Gln
20 25 30

```
Phe Leu Val Lys Ser Gly Tyr Ala Phe Val Asp Cys Pro Asp Glu His
        35                  40                  45

Trp Ala Met Lys Ala Ile Glu Thr Phe Ser Gly Lys Val Glu Leu Gln
    50                  55                  60

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

Arg Lys Ile Gln Ile Arg Asn Ile Pro Pro Gln Leu Arg Trp Glu Val
                85                  90                  95

Leu Asp Ser Leu Leu Ala Gln Tyr Gly Thr Val Glu Asn Cys Glu Gln
            100                 105                 110

Val Asn Thr Glu Ser Glu Thr Ala Val Val Asn Val Thr Tyr Ser Asn
        115                 120                 125

Arg Glu Gln Thr Arg Gln Ala Ile Met Lys Leu Asn Gly His Gln Leu
    130                 135                 140

Glu Asn His Ala Leu Lys Val Ser Tyr Ile Pro Asp Glu Gln Ile Ala
145                 150                 155                 160

Gln Gly Pro Glu Asn Gly Arg Arg Gly Gly Phe Gly Ser Arg Gly Gln
                165                 170                 175

Pro Arg Gln Gly Ser Pro Val Ala Ala Gly Ala Pro Ala Lys Gln Gln
            180                 185                 190

Gln Val Asp Ile Pro Leu Arg Leu Leu Val Pro Thr Gln Tyr Val Gly
        195                 200                 205

Ala Ile Ile Gly Lys Glu Gly Ala Thr Ile Arg Asn Ile Thr Lys Gln
    210                 215                 220

Thr Gln Ser Lys Ile Asp Val His Arg Lys Glu Asn Ala Gly Ala Ala
225                 230                 235                 240

Glu Lys Ala Ile Ser Val His Ser Thr Pro Glu Gly Cys Ser Ser Ala
                245                 250                 255

Cys Lys Met Ile Leu Glu Ile Met His Lys Glu Ala Lys Asp Thr Lys
            260                 265                 270

Thr Ala Asp Glu Val Pro Leu Lys Ile Leu Ala His Asn Asn Phe Val
        275                 280                 285

Gly Arg Leu Ile Gly Lys Glu Gly Arg Asn Leu Lys Lys Val Glu Gln
    290                 295                 300

Asp Thr Glu Thr Lys Ile Thr Ile Ser Ser Leu Gln Asp Leu Thr Leu
305                 310                 315                 320

Tyr Asn Pro Glu Arg Thr Ile Thr Val Lys Gly Ala Ile Glu Asn Cys
```

325 330 335

Cys Arg Ala Glu Gln Glu Ile Met Lys Lys Val Arg Glu Ala Tyr Glu
340 345 350

Asn Asp Val Ala Ala Met Ser Leu Gln Ser His Leu Ile Pro Gly Leu
355 360 365

Asn Leu Ala Ala Val Gly Leu Phe Pro Ala Ser Ser Ser Ala Val Pro
370 375 380

Pro Pro Pro Ser Ser Val Thr Gly Ala Ala Pro Tyr Ser Ser Phe Met
385 390 395 400

Gln Ala Pro Glu Gln Glu Met Val Gln Val Phe Ile Pro Ala Gln Ala
405 410 415

Val Gly Ala Ile Ile Gly Lys Lys Gly Gln His Ile Lys Gln Leu Ser
420 425 430

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

Ser Lys Val Arg Met Val Ile Ile Thr Gly Pro Pro Glu Ala Gln Phe
450 455 460

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

Gly Pro Lys Glu Glu Val Lys Leu Glu Thr His Ile Arg Val Pro Ala
485 490 495

Ser Ala Ala Gly Arg Val Ile Gly Lys Gly Gly Lys Thr Val Asn Glu
500 505 510

Leu Gln Asn Leu Thr Ala Ala Glu Val Val Val Pro Arg Asp Gln Thr
515 520 525

Pro Asp Glu Asn Asp Gln Val Ile Val Lys Ile Ile Gly His Phe Tyr
530 535 540

Ala Ser Gln Met Ala Gln Arg Lys Ile Arg Asp Ile Leu Ala Gln Val
545 550 555 560

Lys Gln Gln His Gln Lys Gly Gln Ser Asn Gln Ala Gln Ala Arg Arg
565 570 575

Lys

<210> 23
<211> 329
<212> PRT
<213> 人属、人种

<400> 23

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Met Ala Thr Gly Gln Lys Leu Met Arg Ala Val Arg Val Phe Glu Phe
1               5                  10                  15

Gly Gly Pro Glu Val Leu Lys Leu Arg Ser Asp Ile Ala Val Pro Ile
            20                  25                  30

Pro Lys Asp His Gln Val Leu Ile Lys Val His Ala Cys Gly Val Asn
        35                  40                  45

Pro Val Glu Thr Tyr Ile Arg Ser Gly Thr Tyr Ser Arg Lys Pro Leu
    50                  55                  60

Leu Pro Tyr Thr Pro Gly Ser Asp Val Ala Gly Val Ile Glu Ala Val
65                  70                  75                  80

Gly Asp Asn Ala Ser Ala Phe Lys Lys Gly Asp Arg Val Phe Thr Ser
                85                  90                  95

Ser Thr Ile Ser Gly Gly Tyr Ala Glu Tyr Ala Leu Ala Ala Asp His
            100                 105                 110

Thr Val Tyr Lys Leu Pro Glu Lys Leu Asp Phe Lys Gln Gly Ala Ala
        115                 120                 125

Ile Gly Ile Pro Tyr Phe Thr Ala Tyr Arg Ala Leu Ile His Ser Ala
    130                 135                 140

Cys Val Lys Ala Gly Glu Ser Val Leu Val His Gly Ala Ser Gly Gly
145                 150                 155                 160

Val Gly Leu Ala Ala Cys Gln Ile Ala Arg Ala Tyr Gly Leu Lys Ile
                165                 170                 175

Leu Gly Thr Ala Gly Thr Glu Glu Gly Gln Lys Ile Val Leu Gln Asn
            180                 185                 190

Gly Ala His Glu Val Phe Asn His Arg Glu Val Asn Tyr Ile Asp Lys
        195                 200                 205

Ile Lys Lys Tyr Val Gly Glu Lys Gly Ile Asp Ile Ile Ile Glu Met
    210                 215                 220

Leu Ala Asn Val Asn Leu Ser Lys Asp Leu Ser Leu Leu Ser His Gly
225                 230                 235                 240

Gly Arg Val Ile Val Val Gly Ser Arg Gly Thr Ile Glu Ile Asn Pro
                245                 250                 255

Arg Asp Thr Met Ala Lys Glu Ser Ser Ile Ile Gly Val Thr Leu Phe
            260                 265                 270

Ser Ser Thr Lys Glu Glu Phe Gln Gln Tyr Ala Ala Ala Leu Gln Ala
        275                 280                 285

Gly Met Glu Ile Gly Trp Leu Lys Pro Val Ile Gly Ser Gln Tyr Pro
```

290 295 300

Leu Glu Lys Val Ala Glu Ala His Glu Asn Ile Ile His Gly Ser Gly
305 310 315 320

Ala Thr Gly Lys Met Ile Leu Leu Leu
325

<210> 24
<211> 125
<212> PRT
<213> 人属、人种

<400> 24

Met Gln Pro Ala Ser Ala Lys Trp Tyr Asp Arg Arg Asp Tyr Val Phe
1 5 10 15

Ile Glu Phe Cys Val Glu Asp Ser Lys Asp Val Asn Val Asn Phe Glu
20 25 30

Lys Ser Lys Leu Thr Phe Ser Cys Leu Gly Gly Ser Asp Asn Phe Lys
35 40 45

His Leu Asn Glu Ile Asp Leu Phe His Cys Ile Asp Pro Asn Asp Ser
50 55 60

Lys His Lys Arg Thr Asp Arg Ser Ile Leu Cys Cys Leu Arg Lys Gly
65 70 75 80

Glu Ser Gly Gln Ser Trp Pro Arg Leu Thr Lys Glu Arg Ala Lys Leu
85 90 95

Asn Trp Leu Ser Val Asp Phe Asn Asn Trp Lys Asp Trp Glu Asp Asp
100 105 110

Ser Asp Glu Asp Met Ser Asn Phe Asp Arg Phe Ser Glu
115 120 125

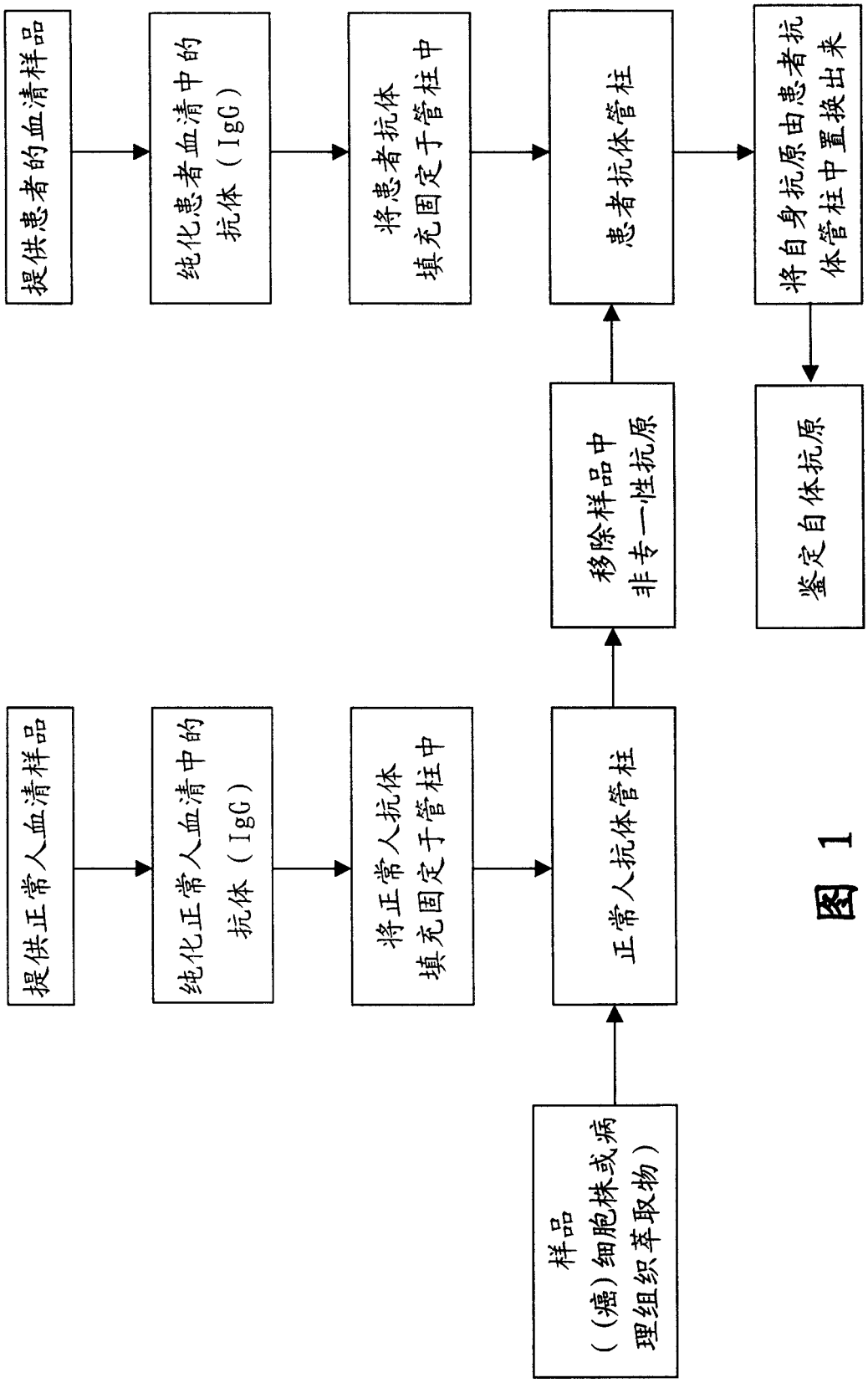
提供患者的血清样品
纯化患者血清中的抗体（IgG）
将患者抗体填充固定于管柱中
患者抗体管柱
将自身抗原由患者抗体管柱中置换出来
鉴定自体抗原
移除样品中非专一性抗原
提供正常人血清样品
纯化正常人血清中的抗体（IgG）
将正常人抗体填充固定于管柱中
正常人抗体管柱
样品（（癌）细胞株或病理组织萃取物）

图 1

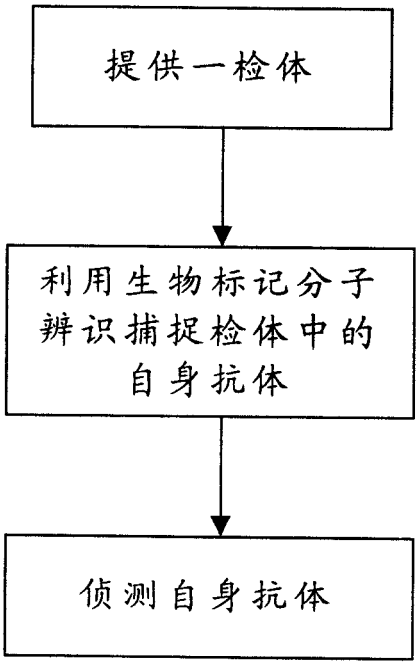

图 2

专利名称(译)	肝脏疾病的生物标记分子及其检测方法		
公开(公告)号	CN1632589A	公开(公告)日	2005-06-29
申请号	CN200310121792.X	申请日	2003-12-24
[标]申请(专利权)人(译)	财团法人工业技术研究院		
申请(专利权)人(译)	财团法人工业技术研究院		
当前申请(专利权)人(译)	工业技术研究院		
[标]发明人	曾锱翎 郑平福		
发明人	曾锱翎 郑平福		
IPC分类号	G01N33/53 G01N33/574 G01N33/68 G01N33/96		
代理人(译)	黄健		
外部链接	Espacenet SIPO		

摘要(译)

本发明涉及肝脏疾病的生物标记分子及其检测方法，所述生物标记分子，为选自SEQ ID NO：1至SEQ NO：24所示的任一氨基酸序列或其衍生物或其片段或其变异体或其组合物或其对应的自身抗体；利用这些生物标记分子发展为检测套组，藉筛选检体中自身抗体或自身抗原的存在判断是否罹患肝脏疾病，可有效提高准确度与灵敏度。