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(54) 发明名称

抗原性爱泼斯坦-巴尔病毒多肽

(57) 摘要

本公开文本涉及抗原性EBV多肽及其在引发针对EBV的抗体中的用途。还公开了包含EBV多肽和铁蛋白蛋白的抗原性多肽。

1. 一种抗原性EBV多肽,所述抗原性EBV多肽包含爱泼斯坦-巴尔病毒(EBV) gL多肽和EBV gH多肽,其中具有至少15个氨基酸的长度的接头将所述EBV gL多肽和所述EBV gH多肽分开。

2. 一种抗原性EBV多肽,所述抗原性EBV多肽包含爱泼斯坦-巴尔病毒(EBV) gL多肽、EBV gH多肽和EBV gp42多肽,其中具有至少15个氨基酸的长度的接头将所述EBV gL多肽和所述EBV gH多肽分开。

3. 根据权利要求1或权利要求2所述的抗原性EBV多肽,所述抗原性EBV多肽进一步包含铁蛋白。

4. 一种抗原性EBV多肽,所述抗原性EBV多肽包含EBV多肽和铁蛋白蛋白,其中所述铁蛋白蛋白包含用半胱氨酸置换表面暴露的氨基酸的突变。

5. 根据权利要求4所述的抗原性EBV多肽,其中所述EBV多肽包含EBV gL多肽、EBV gH多肽或EBV gp220多肽。

6. 根据权利要求5所述的抗原性EBV多肽,其中所述EBV多肽包含gL多肽,并且所述多肽进一步包含EBV gH多肽。

7. 根据权利要求1或3-6中任一项所述的抗原性EBV多肽,其中所述多肽进一步包含EBV gp42多肽。

8. 一种组合物,所述组合物包含第一抗原性EBV多肽和第二抗原性EBV多肽,其中所述第一抗原性EBV多肽包含铁蛋白重链和第一EBV多肽,所述第二抗原性EBV多肽包含铁蛋白轻链和第二EBV多肽,并且所述第一EBV多肽和所述第二EBV多肽是不同的。

9. 根据权利要求8所述的组合物,其中所述第一EBV多肽或所述第二EBV多肽包括gp220多肽。

10. 根据权利要求8至9中任一项所述的组合物,其中(i)所述第一抗原性EBV多肽包含gL多肽和gH多肽中的一者或二者,并且所述第二抗原性EBV多肽包含gp220多肽,或(ii)所述第一抗原性EBV多肽包含gp220多肽,并且所述第二抗原性EBV多肽包含gL多肽和gH多肽中的一者或二者。

11. 根据权利要求8至10中任一项所述的组合物,其中所述第一抗原性EBV多肽包含gL多肽和gH多肽;或者所述第二抗原性EBV多肽包含gL多肽和EBV gH多肽。

12. 根据权利要求10或11所述的组合物,其中所述包含gL多肽和/或gH多肽的抗原性EBV多肽进一步包含gp42多肽。

13. 根据权利要求1-12中任一项所述的抗原性EBV多肽或组合物,所述抗原性EBV多肽或组合物包含gH和gL多肽,其中所述gH多肽在所述gL多肽的C末端,所述抗原性EBV多肽或组合物任选地包含gp42多肽,其中所述gp42多肽在所述gH多肽的C末端。

14. 根据权利要求1-13中任一项所述的抗原性EBV多肽或组合物,所述抗原性EBV多肽或组合物包含gp42多肽,其中所述gp42多肽包含与SEQ ID NO:239或240具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。

15. 根据权利要求1-14中任一项所述的抗原性EBV多肽或组合物,所述抗原性EBV多肽或组合物包含EBV gH多肽和EBV gp42多肽,其中具有至少15个氨基酸的长度的接头将所述EBV gH多肽与所述EBV gp42多肽分开,任选地其中所述接头具有15至60个氨基酸、20至60个氨基酸、30至60个氨基酸、40至60个氨基酸、30至50个氨基酸或40至50个氨基酸的长度,

进一步任选地其中所述接头包含与SEQ ID NO:234具有至少80%、85%、90%、95%、97%、98%、99%、或100%同一性的氨基酸序列。

16. 根据前述权利要求中任一项所述的抗原性EBV多肽或组合物,所述抗原性EBV多肽或组合物包含接头,其中所述接头具有至少15个氨基酸的长度,任选地其中所述接头将第一EBV多肽与第二EBV多肽分开。

17. 根据权利要求16所述的抗原性EBV多肽或组合物,其中所述接头具有15至60个氨基酸、20至60个氨基酸、30至60个氨基酸、40至60个氨基酸、30至50个氨基酸或40至50个氨基酸的长度。

18. 根据前述权利要求中任一项所述的抗原性EBV多肽或组合物,其中所述EBV多肽包含与SEQ ID NO:36具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。

19. 根据前述权利要求中任一项所述的抗原性EBV多肽或组合物,其中所述EBV多肽包含与SEQ ID NO:37具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。

20. 根据前述权利要求中任一项所述的抗原性EBV多肽或组合物,其中所述多肽包含接头,所述接头包含与SEQ ID NO:30具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列,任选地其中所述接头将第一EBV多肽和第二EBV多肽分开。

21. 根据前述权利要求中任一项所述的抗原性EBV多肽或组合物,其中所述EBV多肽包含与SEQ ID NO:38具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。

22. 根据权利要求3-21中任一项所述的抗原性EBV多肽或组合物,所述抗原性EBV多肽或组合物进一步包含将所述EBV多肽和所述铁蛋白分开的另外接头。

23. 根据权利要求3-22中任一项所述的抗原性EBV多肽或组合物,所述抗原性EBV多肽或组合物包含EBV gp42多肽,所述EBV gp42多肽位于所述铁蛋白的N末端并且位于所述gH多肽的C末端,其中接头将所述EBVgp42多肽与所述铁蛋白分开,任选地其中所述接头具有至少15个氨基酸的长度或具有15至60个氨基酸、20至60个氨基酸、30至60个氨基酸、40至60个氨基酸、30至50个氨基酸或40至50个氨基酸的长度,进一步任选地其中所述接头包含与SEQ ID NO:233、234、235、236、237或238中的任一个具有至少80%、85%、90%、95%、97%、98%、99%、或100%同一性的氨基酸序列。

24. 根据权利要求22或23所述的抗原性EBV多肽或组合物,其中所述接头包含半胱氨酸。

25. 根据权利要求22-24中任一项所述的抗原性EBV多肽或组合物,其中所述接头包含与SEQ ID NO:33具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。

26. 根据权利要求24-25所述的抗原性EBV多肽或组合物,其中所述半胱氨酸缀合至免疫刺激部分,任选地其中所述免疫刺激部分是TLR2、TLR7/8、TLR9或STING的激动剂。

27. 根据权利要求3-26中任一项所述的抗原性EBV多肽或组合物,其中所述铁蛋白包含幽门螺杆菌铁蛋白的E12C、S26C、S72C、A75C、K79C、S100C和S111C突变中的一种或多种或如通过成对或结构比对确定的非幽门螺杆菌铁蛋白中的一种或多种相应突变。

28. 根据权利要求3-27中任一项所述的抗原性EBV多肽或组合物,其中所述铁蛋白包含用非天冬酰胺氨基酸置换表面暴露的天冬酰胺的突变,任选地其中所述天冬酰胺是在幽门螺杆菌铁蛋白的位置19处,或如通过成对或结构比对确定的非幽门螺杆菌铁蛋白中的类似位置处。

29. 根据权利要求3-28中任一项所述的抗原性EBV多肽或组合物,其中所述铁蛋白包含用非半胱氨酸氨基酸置换内部半胱氨酸的突变,任选地其中所述内部半胱氨酸是在幽门螺杆菌铁蛋白的位置31处,或如通过成对或结构比对确定的对应于幽门螺杆菌铁蛋白的位置31的位置处。

30. 根据权利要求3-29中任一项所述的抗原性EBV多肽或组合物,其中所述铁蛋白包含与SEQ ID NO:201-207或211-215中的任一个具有80%、85%、90%、95%、98%或99%同一性的氨基酸序列。

31. 根据权利要求1-31中任一项所述的抗原性EBV多肽或组合物,其中所述抗原性EBV多肽包含与SEQ ID NO:226的氨基酸23-1078具有至少80%、85%、90%、95%、98%或99%同一性的序列。

32. 根据权利要求1-31中任一项所述的抗原性EBV多肽或组合物,其中所述抗原性EBV多肽包含与SEQ ID NO:226-231或241-242中的任一个具有至少80%、85%、90%、95%、98%或99%同一性的序列,任选地缺乏前导序列。

33. 一种铁蛋白颗粒,所述铁蛋白颗粒包含根据权利要求3-32中任一项所述的抗原性EBV多肽或所述第一多肽和所述第二多肽。

34. 一种组合物,所述组合物包含根据前述权利要求中任一项所述的一种或多种抗原性EBV多肽或铁蛋白颗粒和药学上可接受的载体。

35. 根据权利要求34所述的组合物,其中所述铁蛋白颗粒包含EBV gL多肽和EBV gH多肽,并且所述组合物进一步包含含有gp220多肽的第二铁蛋白颗粒。

36. 根据前述权利要求中任一项所述的抗原性EBV多肽、铁蛋白颗粒或组合物,用于在引发对流感的免疫应答或保护受试者免受EBV感染的方法中使用。

37. 一种引发对EBV的免疫应答或保护受试者免受EBV感染的方法,所述方法包括向受试者给予根据前述权利要求中任一项所述的任何一种或多种抗原性EBV多肽、铁蛋白颗粒或组合物。

38. 根据权利要求36-37中任一项所述的抗原性EBV多肽、铁蛋白颗粒、组合物或方法,其中所述受试者是人。

39. 一种核酸,所述核酸编码根据权利要求1-32中任一项所述的抗原性EBV多肽,任选地其中所述核酸是mRNA。

抗原性爱泼斯坦-巴尔病毒多肽

[0001] 本申请要求2018年4月3日提交的美国临时专利申请号62/652,201的优先权权益,所述临时专利申请通过引用以其整体并入本文。

[0002] 本申请含有已经以ASCII格式电子提交并且通过引用以其整体特此并入的序列表。2019年3月27日创建的所述ASCII副本被命名为2019-03-27_01121-0032-00PCT_SL-ST25.txt,并且大小为377,803字节。

[0003] 即使在疫苗学领域取得了许多成功,仍需要新的突破来保护人类免受许多威胁生命的传染性疾病的影响。当前许多已获许可的疫苗都依赖十年前的技术来产生活的减毒病原体或灭活的杀死病原体,所述病原体具有固有的安全性问题,并且在许多情况下,仅刺激短暂的弱免疫应答,从而需要给予多个剂量。虽然遗传学和生物化学工程学的进步使得开发针对具有挑战性的疾病靶标的治疗剂成为可能,但在疫苗学领域的这些应用尚未完全实现。重组蛋白技术现在允许设计最佳抗原。另外,纳米颗粒已越来越多地展示出用于最佳抗原呈递和靶向药物递送的潜力。已经显示具有多个附接抗原的纳米颗粒具有增加的结合亲合力,所述增加的结合亲合力凭借其分子货物的多价展示和由于其纳米尺寸而更有效地跨过生物屏障的能力而提供。与流感病毒血凝素(HA)蛋白融合的幽门螺杆菌(*Helicobacter pylori* (H.pylori))铁蛋白纳米颗粒可以改善抗原稳定性并增加在小鼠流感模型中的免疫原性(参见Kanekiyo等人,Nature 499:102-106 (2013))。此融合蛋白自组装成八面体对称性纳米颗粒并呈递8个三聚体HA刺突,从而在与佐剂一起使用时在各种临床前模型中产生稳健的免疫应答。

[0004] 爱泼斯坦-巴尔病毒(EBV)感染全世界约95%的成年人口,并且已经已知与两种B细胞淋巴瘤,即伯基特淋巴瘤和霍奇金淋巴瘤相关。病毒还可以感染上皮细胞并与鼻咽癌有相关。此外,EBV导致发达国家的大多数传染性单核细胞增多症病例,主要影响儿童和年轻成人。传染性单核细胞增多症可导致长达一个月的长恢复期。目前市场上没有批准的疫苗,因此强烈需要预防性疫苗。

[0005] 在此,提出了一组涉及EBV多肽的新多肽、纳米颗粒、组合物、方法和用途。产生了新型EBV单链gL和gH(有时描绘为gL/gH或gH/gL)多肽,也产生了包含这些新型EBV多肽和铁蛋白的抗原性多肽。包含单链gL和gH多肽的抗原性多肽和纳米颗粒可以在gL序列与gH序列之间包含相对较长的接头,据观察,所述接头提供免疫原性的增加。还产生了包含EBV gp220多肽的抗原性铁蛋白多肽和纳米颗粒。此外,开发了包含所述EBV多肽和铁蛋白的自佐剂化抗原性多肽,其中免疫刺激部分(如佐剂)直接化学附接至抗原性多肽。将免疫刺激部分直接缀合至抗原性多肽允许在单一大分子实体中靶向共递送免疫刺激部分和EBV多肽,这可以大大降低全身性毒性的可能性,所述全身性毒性是在包含作为单独分子的抗原和免疫刺激分子(如佐剂)的传统的疫苗的情况下所担忧的。免疫刺激部分与EBV多肽在大分子实体中的共递送以及它们的多价呈递也可以减少引发保护所需的总剂量,从而减少生产负担和成本。

发明内容

[0006] 本公开文本的目的是提供可以提供以上讨论的一个或多个优点,或者至少为公众提供有用选择的组合物、试剂盒、方法和用途。因此,本文公开了以下实施方案。

[0007] 实施方案1是一种抗原性EBV多肽,所述抗原性EBV多肽包含爱泼斯坦-巴尔病毒(EBV) gL多肽和EBV gH多肽,其中具有至少15个氨基酸的长度的接头将所述EBV gL多肽和所述EBV gH多肽分开。

[0008] 实施方案2是一种抗原性EBV多肽,所述抗原性EBV多肽包含爱泼斯坦-巴尔病毒(EBV) gL多肽、EBV gH多肽和EBV gp42多肽,其中具有至少15个氨基酸的长度的接头将所述EBV gL多肽和所述EBV gH多肽分开。

[0009] 实施方案3是根据权利要求1或权利要求2所述的抗原性EBV多肽,所述抗原性EBV多肽进一步包含铁蛋白。

[0010] 实施方案4是一种抗原性EBV多肽,所述抗原性EBV多肽包含EBV多肽和铁蛋白蛋白,其中所述铁蛋白蛋白包含用半胱氨酸置换表面暴露的氨基酸的突变。

[0011] 实施方案5是根据权利要求4所述的抗原性EBV多肽,其中所述EBV多肽包含EBV gL多肽、EBV gH多肽或EBV gp220多肽。

[0012] 实施方案6是根据权利要求5所述的抗原性EBV多肽,其中所述EBV多肽包含gL多肽,并且所述多肽进一步包含EBV gH多肽。

[0013] 实施方案7是根据权利要求1或3-6中任一项所述的抗原性EBV多肽,其中所述多肽进一步包含EBV gp42多肽。

[0014] 实施方案8是一种组合物,所述组合物包含第一抗原性EBV多肽和第二抗原性EBV多肽,其中所述第一抗原性EBV多肽包含铁蛋白重链和第一EBV多肽,所述第二抗原性EBV多肽包含铁蛋白轻链和第二EBV多肽,并且所述第一EBV多肽和所述第二EBV多肽是不同的。

[0015] 实施方案9是根据权利要求8所述的组合物,其中所述第一EBV多肽或所述第二EBV多肽包括gp220多肽。

[0016] 实施方案10是根据权利要求8至9中任一项所述的组合物,其中(i)所述第一抗原性EBV多肽包含gL多肽和gH多肽中的一者或二者,并且所述第二抗原性EBV多肽包含gp220多肽,或(ii)所述第一抗原性EBV多肽包含gp220多肽,并且所述第二抗原性EBV多肽包含gL多肽和gH多肽中的一者或二者。

[0017] 实施方案11是根据权利要求8至10中任一项所述的组合物,其中所述第一抗原性EBV多肽包含gL多肽和gH多肽;或者所述第二抗原性EBV多肽包含gL多肽和EBV gH多肽。

[0018] 实施方案12是根据权利要求10或11所述的组合物,其中所述包含gL多肽和/或gH多肽的抗原性EBV多肽进一步包含gp42多肽。

[0019] 实施方案13是根据权利要求1-12中任一项所述的抗原性EBV多肽或组合物,所述抗原性EBV多肽或组合物包含gH和gL多肽,其中所述gH多肽在所述gL多肽的C末端,所述抗原性EBV多肽或组合物任选地包含gp42多肽,其中所述gp42多肽在所述gH多肽的C末端。

[0020] 实施方案14是根据权利要求1-13中任一项所述的抗原性EBV多肽或组合物,所述抗原性EBV多肽或组合物包含gp42多肽,其中所述gp42多肽包含与SEQ ID NO:239或240具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。

[0021] 实施方案15是根据权利要求1-14中任一项所述的抗原性EBV多肽或组合物,所述

抗原性EBV多肽或组合物包含EBV gH多肽和EBV gp42多肽,其中具有至少15个氨基酸的长度的接头将所述EBV gH多肽与所述EBV gp42多肽分开,任选地其中所述接头具有15至60个氨基酸、20至60个氨基酸、30至60个氨基酸、40至60个氨基酸、30至50个氨基酸或40至50个氨基酸的长度,进一步任选地其中所述接头包含与SEQ ID NO:234具有至少80%、85%、90%、95%、97%、98%、99%、或100%同一性的氨基酸序列。

[0022] 实施方案16是根据前述权利要求中任一项所述的抗原性EBV多肽或组合物,所述抗原性EBV多肽或组合物包含接头,其中所述接头具有至少15个氨基酸的长度,任选地其中所述接头将第一EBV多肽与第二EBV多肽分开。

[0023] 实施方案17是根据权利要求16所述的抗原性EBV多肽或组合物,其中所述接头具有15至60个氨基酸、20至60个氨基酸、30至60个氨基酸、40至60个氨基酸、30至50个氨基酸或40至50个氨基酸的长度。

[0024] 实施方案18是根据前述权利要求中任一项所述的抗原性EBV多肽或组合物,其中所述EBV多肽包含与SEQ ID NO:36具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。

[0025] 实施方案19是根据前述权利要求中任一项所述的抗原性EBV多肽或组合物,其中所述EBV多肽包含与SEQ ID NO:37具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。

[0026] 实施方案20是根据前述权利要求中任一项所述的抗原性EBV多肽或组合物,其中所述多肽包含接头,所述接头包含与SEQ ID NO:30具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列,任选地其中所述接头将第一EBV多肽和第二EBV多肽分开。

[0027] 实施方案21是根据前述权利要求中任一项所述的抗原性EBV多肽或组合物,其中所述EBV多肽包含与SEQ ID NO:38具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。

[0028] 实施方案22是根据权利要求3-21中任一项所述的抗原性EBV多肽或组合物,所述抗原性EBV多肽或组合物进一步包含将所述EBV多肽和所述铁蛋白分开的另外接头。

[0029] 实施方案23是根据权利要求3-22中任一项所述的抗原性EBV多肽或组合物,所述抗原性EBV多肽或组合物包含EBV gp42多肽,所述EBV gp42多肽位于所述铁蛋白的N末端并且位于所述gH多肽的C末端,其中接头将所述EBV gp42多肽与所述铁蛋白分开,任选地其中所述接头具有至少15个氨基酸的长度或具有15至60个氨基酸、20至60个氨基酸、30至60个氨基酸、40至60个氨基酸、30至50个氨基酸或40至50个氨基酸的长度,进一步任选地其中所述接头包含与SEQ ID NO:233、234、235、236、237或238中的任一个具有至少80%、85%、90%、95%、97%、98%、99%、或100%同一性的氨基酸序列。

[0030] 实施方案24是根据权利要求22或23所述的抗原性EBV多肽或组合物,其中所述接头包含半胱氨酸。

[0031] 实施方案25是根据权利要求22-24中任一项所述的抗原性EBV多肽或组合物,其中所述接头包含与SEQ ID NO:33具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。

[0032] 实施方案26是根据权利要求24-25所述的抗原性EBV多肽或组合物,其中所述半胱

氨酸缀合至免疫刺激部分,任选地其中所述免疫刺激部分是TLR2、TLR7/8、TLR9或STING的激动剂。

[0033] 实施方案27是根据权利要求3-26中任一项所述的抗原性EBV多肽或组合物,其中所述铁蛋白包含幽门螺杆菌铁蛋白的E12C、S26C、S72C、A75C、K79C、S100C和S111C突变中的一种或多种或如通过成对或结构比对确定的非幽门螺杆菌铁蛋白中的一种或多种相应突变。

[0034] 实施方案28是根据权利要求3-27中任一项所述的抗原性EBV多肽或组合物,其中所述铁蛋白包含用非天冬酰胺氨基酸置换表面暴露的天冬酰胺的突变,任选地其中所述天冬酰胺是在幽门螺杆菌铁蛋白的位置19处,或如通过成对或结构比对确定的非幽门螺杆菌铁蛋白中的类似位置处。

[0035] 实施方案29是根据权利要求3-28中任一项所述的抗原性EBV多肽或组合物,其中所述铁蛋白包含用非半胱氨酸氨基酸置换内部半胱氨酸的突变,任选地其中所述内部半胱氨酸是在幽门螺杆菌铁蛋白的位置31处,或如通过成对或结构比对确定的对应于幽门螺杆菌铁蛋白的位置31的位置处。

[0036] 实施方案30是根据权利要求3-29中任一项所述的抗原性EBV多肽或组合物,其中所述铁蛋白包含与SEQ ID NO:201-207或211-215中的任一个具有80%、85%、90%、95%、98%或99%同一性的氨基酸序列。

[0037] 实施方案31是根据权利要求1-31中任一项所述的抗原性EBV多肽或组合物,其中所述抗原性EBV多肽包含与SEQ ID NO:226的氨基酸23-1078具有至少80%、85%、90%、95%、98%或99%同一性的序列。

[0038] 实施方案32是根据权利要求1-31中任一项所述的抗原性EBV多肽或组合物,其中所述抗原性EBV多肽包含与SEQ ID NO:226-231或241-242中的任一个具有至少80%、85%、90%、95%、98%或99%同一性的序列,任选地缺乏前导序列。

[0039] 实施方案33是一种铁蛋白颗粒,所述铁蛋白颗粒包含根据权利要求3-32中任一项所述的抗原性EBV多肽或所述第一多肽和所述第二多肽。

[0040] 实施方案34是一种组合物,所述组合物包含根据前述权利要求中任一项所述的一种或多种抗原性EBV多肽或铁蛋白颗粒和药学上可接受的载体。

[0041] 实施方案35是根据权利要求34所述的组合物,其中所述铁蛋白颗粒包含EBV gL多肽和EBV gH多肽,并且所述组合物进一步包含含有gp220多肽的第二铁蛋白颗粒。

[0042] 实施方案36是根据前述权利要求中任一项所述的抗原性EBV多肽、铁蛋白颗粒或组合物,用于在引发对流感的免疫应答或保护受试者免受EBV感染的方法中使用。

[0043] 实施方案37是一种引发对EBV的免疫应答或保护受试者免受EBV感染的方法,所述方法包括向受试者给予根据前述权利要求中任一项所述的任何一种或多种抗原性EBV多肽、铁蛋白颗粒或组合物。

[0044] 实施方案38是根据权利要求36-37中任一项所述的抗原性EBV多肽、铁蛋白颗粒、组合物或方法,其中所述受试者是人。

[0045] 实施方案39是一种核酸,所述核酸编码根据权利要求1-32中任一项所述的抗原性EBV多肽,任选地其中所述核酸是mRNA。

[0046] 其他目的和优点将阐述于随后的描述中,并且/或者将从所述描述中明显看出,或

者可以通过实践获知。所述目的和优点将借助所附权利要求中特别指出的要素和组合来实现和获得。

[0047] 应了解,上文的一般说明与下文的详细说明均仅是示例性和解释性的,并且对权利要求无限制性。

[0048] 并入本说明书并且构成本说明书的一部分的附图展示了某些实施方案,并且附图连同本说明一起用于解释本文所述的原理。

附图说明

[0049] 图1A至图1B通过考马斯和蛋白质印迹分析示出了去除或未去除His标签的纯化的单链gL和gH单体(图1A)(SEQ ID NO:6)和三聚体(图1B)(SEQ ID NO:11)。图1B还呈现了来自尺寸排阻柱(**Superose®6**)纯化的级分的UV吸收迹线。

[0050] 图2A至图2E示出了对单链gL/gH-铁蛋白纳米颗粒(SEQ ID NO:14)的纯化和表征。示出了**Superose®6**纯化级分的UV吸收迹线(图2A),以及对从纯化中选择的级分的考马斯(图2B)和蛋白质印迹(图2C)分析(L指示分子量梯状标志;150kDa和250kDa条带的位置在图2B中在右边指示出)。还呈现了单链纳米颗粒的动态光散射(图2D)和电子显微镜(图2E)分析。

[0051] 图3示出了不同的代表性单链gL/gH-铁蛋白构建体。

[0052] 图4示出了用掺合有AF03佐剂(其是基于角鲨烯乳剂的佐剂)的单链gL/gH三聚体或纳米颗粒(NP)对小鼠进行免疫后的抗体效价。当将NP构建体与其对应的三聚体构建体进行比较时,*p-值=<0.05。从左至右,构建体是SEQ ID NO:16、10、11、13、12和14。

[0053] 图5A至图5B示出了与单链gL/gH纳米颗粒和阴性对照裸铁蛋白(即,未与任何非铁蛋白多肽或免疫刺激部分缀合的铁蛋白)相比,小鼠中对包含gp220纳米颗粒(SEQ ID NO:1)和单链gL/gH纳米颗粒("gL_gH_C5 NP",SEQ ID NO:19)二者的二价组合物的抗gL/gH抗体应答。结果表明,相对于在单链gL/gH与阴性对照裸铁蛋白的情况下的结果,使用二价组合物不会导致对抗gL/gH抗体应答的干扰。两种组合物均包含AF03佐剂。示出了在各个稀释度(图5A)和结合效价(图5B)下的ELISA结果。

[0054] 图6A至图6B示出了对如对于图5A-B所述的包含gp220纳米颗粒和单链gL/gH纳米颗粒的二价组合物的抗gp220抗体应答。结果表明,相对于在gp220纳米颗粒与阴性对照裸铁蛋白的情况下的结果,使用二价组合物不会导致对抗gp220抗体应答的干扰。两种组合物均包含AF03佐剂。示出了在各个稀释度(图6A)和结合效价(图6B)下的ELISA结果。

[0055] 图7A示出了包含EBV多肽和铁蛋白的纳米颗粒的设计,所述铁蛋白包含用半胱氨酸置换表面暴露的氨基酸以用于与免疫刺激部分(如toll样受体(TLR)激动剂)缀合的突变。对于对应于该设计的示例性序列,参见SEQ ID NO:14,其中单链gL/gH抗原通过柔性的46个氨基酸接头与铁蛋白连接。图7B示出了适合于与根据图7A的构建体缀合的代表性toll样受体(TLR)激动剂(具有PEG4-马来酰亚胺接头的SM7/8a)。图7C示出了具有SM7/8a的gL/gH纳米颗粒的电子显微照片(EM)图像,所述SM7/8a经由铁蛋白表面上的半胱氨酸和PEG4-马来酰亚胺接头与所述gL/gH纳米颗粒缀合。

[0056] 图8A示出了包含用半胱氨酸置换表面暴露的氨基酸的突变的铁蛋白的部分结构,其中指出了半胱氨酸的位置。图8B说明了通过并置铁蛋白、接头和CpG佐剂来将CpG佐剂

(SEQ ID NO:247) 缀合至铁蛋白,所述缀合被取向成显示每个部分的彼此邻近地附接的部分。

[0057] 图9A至图9B示出了gL/gH-铁蛋白的未缀合形式(图9A)和SM7/8a缀合形式(图9B)的质谱(MS)光谱。主峰质量的差异为711Da,这大约相当于来自将SM7/8a与接头缀合的预测差异。

[0058] 图10A至图10B示出了gp220-铁蛋白的未缀合形式(图10A)和SM7/8a缀合形式(图10B)的质谱(MS)光谱。主峰质量的差异为714.7Da,这大约相当于来自将SM7/8a与接头缀合的预测差异。

[0059] 图11A至图11D示出了未缀合的(图11A、C)和缀合的(图11B、D)单链gL/gH(图11A、B)和gp220(图11C、D)铁蛋白纳米颗粒的电子显微镜(EM)图像,其表明SM7/8a与这些纳米颗粒的缀合没有破坏纳米颗粒结构。

[0060] 图12A至图12B示出了用包含不伴有缀合的SM7/8a或其他佐剂、伴有作为单独分子的AF03佐剂或伴有缀合的SM7/8a的单链gL/gH的铁蛋白纳米颗粒治疗后小鼠中的抗体应答。ELISA结果显示为各个稀释度(图12A)和结合效价(图12B)。

[0061] 图13A至图13B示出了用包含单独的、伴有作为单独分子的AF03佐剂或伴有缀合的SM7/8a的gp220的纳米颗粒治疗后小鼠中的抗体应答。ELISA结果显示为各个稀释度(图13A)和结合效价(图13B)。

[0062] 图14A至图14B示出了如通过ELISA所测量的,与用与SM7/8a缀合的单链gL/gH铁蛋白纳米颗粒和裸铁蛋白的治疗相比,用与SM7/8a缀合的gp220纳米颗粒和与SM7/8a缀合的单链gL/gH铁蛋白纳米颗粒治疗后小鼠中的抗gL/gH抗体应答。示出了对于不伴有(图14A)或伴有(图14B)掺合的AF03的实验的结果。

[0063] 图15A至图15B示出了如通过ELISA所测量的,与用与SM7/8a缀合的gp220纳米颗粒和裸铁蛋白的治疗相比,用与SM7/8a缀合的gp220纳米颗粒和与SM7/8a缀合的单链gL/gH纳米颗粒治疗后小鼠中的抗gp220抗体应答。示出了对于不伴有(图15A)或伴有(图15B)掺合的AF03的实验的结果。

[0064] 图16示出了如通过ELISA终点效价所测量的,在伴有或不伴有掺合的AF03佐剂和/或与单链gL/gH纳米颗粒缀合的SM7/8a中的任一种或二者的情况下,用单链gL/gH纳米颗粒(gL/gH_C5;SEQ ID NO:19)和裸铁蛋白治疗后小鼠中的抗gL/gH抗体应答。

[0065] 图17示出了在伴有或不伴有掺合的AF03佐剂和/或与gp220纳米颗粒缀合的SM7/8a中的任一种或二者的情况下,用gp220纳米颗粒和裸铁蛋白治疗后小鼠中的抗gp220抗体应答。

[0066] 图18示出了用包含gp220纳米颗粒和单链gL/gH纳米颗粒的二价组合物治疗后小鼠中的抗gL/gH抗体应答。如图例中所指示,一些纳米颗粒与SM7/8a缀合,并且一些纳米颗粒与AF03掺合。图例中从上到下的符号顺序与图中从左到右的符号顺序匹配。

[0067] 图19示出了用包含单链gL/gH纳米颗粒和gp220纳米颗粒和/或裸铁蛋白的二价组合物治疗后小鼠中的抗gp220抗体应答。如图例中所指示,一些纳米颗粒与SM7/8a缀合,并且一些纳米颗粒与AF03掺合。图例中从上到下的符号顺序与图中从左到右的符号顺序匹配。

[0068] 图20A至图20D示出了在伴有或不伴有掺合的AF03佐剂和/或与SM7/8a(图20A、图

20C或图20D)或CpG寡脱氧核苷酸(图20B)的缀合的情况下,用gL_gH_C7纳米颗粒(SEQ ID N0:20)治疗后小鼠中的抗体应答。示出了通过ELISA测量的来自初免取血的终点效价(图20A)、来自加强免疫取血的单独稀释度下的ELISA结果(图20B),以及通过ELISA测量的来自加强免疫取血(图20C)和终末期取血(图20D)的终点效价。

[0069] 图21以通过ELISA测量的来自初免、加强免疫和终末期取血的终点效价示出了在伴有或不伴有掺合的AF03佐剂和/或与SM7/8a的缀合的情况下,用gL_gH_C5纳米颗粒(SEQ ID N0:19)治疗后小鼠中的抗体应答。

[0070] 图22以通过ELISA测量的来自初免、加强免疫和终末期取血的终点效价示出了在伴有或不伴有掺合的AF03佐剂和/或与SM7/8a的缀合的情况下,用gp220纳米颗粒治疗后小鼠中的抗体应答。

[0071] 图23A示出了通过考马斯染色可视化的粉纹夜蛾(T.ni)铁蛋白的伴有或不伴有与gp220或gL/gH的融合的轻链和重链(图23A)。标记了图23A最右边泳道中的20、25、75、100和150kDa标记。图23B提供了包含粉纹夜蛾铁蛋白的伴有或不伴有与gp220或gL/gH的融合的轻链和重链的构建体的说明。

[0072] 图24A至图24D展示了gp220-粉纹夜蛾铁蛋白的离子交换(Q柱)色谱纯化和尺寸排阻色谱(SEC)纯化。示出了来自在pH 7下的Q柱(图24A)和SEC Superose® 6, 16/600(图24B)的吸光度迹线;来自pH 7下的Q柱的级分的考马斯染色(图24C)(从左边开始的泳道是输入(“In”)、流通液(“FT”)、分子量梯状标志(大小以kD标记在左侧)和选择的级分);并且来自SEC Superose® 6, 16/600的级分的考马斯染色(图24D)(从左边开始的泳道是分子量梯状标志(大小以kD标记在左侧)和选择的级分)。图24E示出了构建体的说明。

[0073] 图25A至图25D展示了gL/gH(轻)/gp220(重)-粉纹夜蛾铁蛋白的离子交换(Q柱)色谱纯化和尺寸排阻色谱(SEC)纯化。示出了来自在pH 7下的Q柱(图25A)和SEC Superose® 6, 16/600(图25B)的吸光度迹线;来自pH 7下的Q柱的级分的考马斯染色(图25C)(从左边开始的泳道是输入(“In”)、流通液(“FT”)、分子量梯状标志(大小以kD标记在左侧)和选择的级分);并且来自SEC Superose® 6, 16/600的级分的考马斯染色(图25D)(从左边开始的泳道是分子量梯状标志(大小以kD标记在左侧)和选择的级分)。图25E示出了构建体的说明。

[0074] 图26A至图26H示出了通过考马斯染色考马斯可视化的(图26A和图26E)、示意性地说明的(图26B和图26F)、通过动态光散射(DLS)表征的(图26D和图26H)和在电子显微照片中可视化的(图26C和图26G) gp220-粉纹夜蛾铁蛋白或gL/gH(轻链)/gp220(重链)-粉纹夜蛾铁蛋白构建体。图26A至图26D呈现出在与轻链和重链融合的gp220(图26B中的图)的情况下的数据。图26E至图26H呈现出在与重链融合的gp220和与轻链融合的gL/gH(图26F中的图)的情况下的数据。

[0075] 图27A至图27C示出了通过考马斯染色可视化的(图27A)、在电子显微照片中可视化的(图27B)和通过DLS表征的(图27C)裸粉纹夜蛾铁蛋白颗粒(即,未与非铁蛋白多肽融合)。

[0076] 图28A示出了在纯化的gL/gH/gp42 NP构建体(SEQ ID N0:227)(其在293expi细胞中表达)的情况下的SDS变性考马斯染色凝胶(在左侧),和(在右侧)gL/gH/gp42 NP的尺寸排阻色谱(SEC)峰。SEC色谱图的水平轴线的单位是mL。图28B示出了从CHO池中纯化的gL/

gL/gp42 NP,其具有约26.2nm的动态光散射半径。

[0077] 图29A-B示出了由单价gH/gL/gp42纳米颗粒组合物与裸铁蛋白纳米颗粒的组合或二价组合物(gH/gL/gp42纳米颗粒与gp220的组合)引发的免疫应答的评估。图29A示出了B细胞中和。图29B示出了上皮细胞中和。

[0078] 图30A-E示出了针对所指示抗原的终点结合效价。图30F-G示出了来自如所指示那样进行疫苗接种的雪貂的血清的(分别在B细胞和上皮细胞中)EBV病毒中和测定。初免=Inj.1并且加强免疫=Inj.2。

[0079] 图31A-B:图31A示出了使用Superose 6尺寸排阻色谱对gH/gL/gp42_NP_C12(SEQ ID NO:228)的纯化。箭头描绘了通过变性考马斯凝胶分析和使用抗铁蛋白抗体的蛋白质印迹分析从峰中收集的级分。图31B是图31A中样品的动态光散射分析,其显示出20.6nm的颗粒大小半径。

[0080] 图32A-B:图32A示出了使用Superose 6尺寸排阻色谱对gH/gL/gp42_NP_C13(SEQ ID NO:229)的纯化。箭头描绘了通过变性考马斯凝胶分析和使用抗铁蛋白抗体的蛋白质印迹分析从峰中收集的级分。图32B是图32A中样品的动态光散射分析,其显示出17.1nm的颗粒大小半径。

[0081] 图33A-B:图33A示出了使用Superose 6尺寸排阻色谱对gH/gL/gp42_NP_C14(SEQ ID NO:230)的纯化。箭头描绘了通过变性考马斯凝胶分析和使用抗铁蛋白抗体的蛋白质印迹分析从峰中收集的级分。图33B是图33A中样品的动态光散射分析,其显示出16.9nm的颗粒大小半径。

[0082] 图34:左侧的SDS还原考马斯凝胶示出了纯化的单链gH/gL/gp42-His产物(SEQ ID NO:226)。使用镍亲和色谱纯化蛋白质。右侧是单链gH/gL/gp42-His产物(SEQ ID NO:226)的2.9埃晶体结构。Gp42(为深灰色并用箭头指示)与gH/gL异二聚体相互作用。

[0083] 图35A-E:在图35A中示出了与铁蛋白融合的gH/gL/gp42的单链构建体(如在SEQ ID NO:227-231中的每一种中)的图片。每种蛋白质之间的融合是经由上文指定的柔性氨基酸接头或刚性氨基酸接头进行的。单链gH/gL/gp42分子将确保纳米颗粒上1:1:1比率的异三聚体形成。已解析出此异三聚体的晶体结构显示单链gH/gL/gp42可采用类似于自然界中发现的野生型gH、gL和gp42蛋白的异三聚体形态(图35B;也参见图34)。图35C是此单链gH/gL/gp42异三聚体如何通过与铁蛋白融合而在纳米颗粒上展示的模式。在单一纳米颗粒上展示二十四个拷贝的单链gH/gL/gp42。图35D示出了在293Expi细胞中表达SEQ ID NO:227后的纯化。变性SDS考马斯凝胶显示,与铁蛋白融合的gH/gL/gp42在糖基化的情况下高于150kD。图35E示出了纯化产物的负染色电子显微镜分析,其表明与铁蛋白融合的单链gH/gL/gp42可以成功地形成在表面上展示gH/gL/gp42抗原的纳米颗粒。

具体实施方式

[0084] 提供了EBV多肽,EBV多肽在单独给予、与作为单独分子的佐剂一起给予和/或作为可以自佐剂化的纳米颗粒(例如,铁蛋白颗粒或2,4-二氧四氢嘧啶合酶颗粒)的一部分给予时可以是抗原性的。此类多肽和包含此类多肽的组合物可以用于引发针对爱泼斯坦-巴尔病毒(EBV)的抗体应答。EBV多肽可以包含gL、gH、gL/gH、gp220或gp42多肽或其组合,以及多聚化结构域(如铁蛋白)。铁蛋白可以包含用半胱氨酸置换表面暴露的氨基酸的突变,所述

突变可有利于经由半胱氨酸将免疫刺激部分缀合至铁蛋白。这种缀合可以消除或减少对单独给予的佐剂的需要,并且还可以潜在地减少引发对EBV多肽的免疫应答所需的佐剂/免疫刺激部分的量。在一些实施方案中,提供了抗原性EBV多肽,所述抗原性EBV多肽包含(i)EBV多肽,和(ii-a)包含表面暴露的半胱氨酸的铁蛋白,或(ii-b)铁蛋白和包含半胱氨酸的N或C末端接头。本文所述的任何EBV多肽可以与下文所述的任何铁蛋白组合。还提供了编码本文所述多肽的核酸。

A. 定义

[0085] 如本文所用,“EBV多肽”是指包含由EBV编码的全部或部分氨基酸序列的多肽。类似地,gL、gH、gp42和gp220多肽是指分别包含由EBV编码的全部或部分gL、gH、gp42或gp220氨基酸序列的多肽。与EBV编码的多肽具有例如至少80%同一性的多肽将必定包含EBV编码的多肽的一部分。术语“gL多肽”、“gH多肽”、“gp42多肽”和“gp220多肽”可分别与“EBV gL多肽”、“EBV gH多肽”、“EBV gp42多肽”和“EBV gp220多肽”互换使用。用作为抗原性多肽的一部分或全部的EBV多肽进行免疫可以赋予保护以免受EBV感染。除非上下文另有指示,否则本文公开的包含EBV多肽的任何多肽均可以包含由EBV编码的多种序列的全部或一部分(例如,EBV的gL和gH的全部或一部分,或EBV的gL、gH和gp42的全部或一部分)。

[0086] 如本文所用,“单体”或“单体构建体”是指表达为单链蛋白质的构建体。单体可以包含以单链表达的EBV的gL和gH,或以单链表达的EBV的gL、gH和gp42。

[0087] 如本文所用,“三聚体”或“三聚体构建体”是指包含EBV的gL和/或gH以及三聚化结构域(如源自T4噬菌体次要纤维蛋白(fibritin)的折叠子三聚化结构域)的构建体。其他三聚化结构域,如人胶原蛋白XVIII三聚化结构域(参见,例如Alvarez-Cienfuegos等人,Scientific Reports 2016;6:28643)和L10RF1p三聚化结构域(参见,例如Khazina等人,Proc Natl Acad Sci U S A 2009年1月12日;106(3):731-36)也是本领域已知的,并且可以用于三聚体构建体中。

[0088] 如本文所用,“铁蛋白”或“铁蛋白蛋白”是指与幽门螺杆菌铁蛋白(SEQ ID NO:208或209)或本文所讨论的另一种铁蛋白(如激烈火球菌(*P. furiosus*)铁蛋白、粉纹夜蛾(*Trichoplusia ni*)铁蛋白或人铁蛋白)具有可检测的序列同一性的蛋白质,其用于例如在细胞内或组织中存储铁或在血流中携带铁。在下文详细讨论了此类示例性铁蛋白,包括以两条多肽链(称为重链和轻链)出现的那些(例如,粉纹夜蛾和人铁蛋白)。在一些实施方案中,铁蛋白包含与本文例如在表2(序列表)中公开的铁蛋白序列具有至少15%、20%、30%、40%、50%、60%、70%、75%、80%、85%、90%、95%、97%、98%、99%或99.5%同一性的序列。铁蛋白可以是全长天然存在的序列的片段。

[0089] 如本文所用,“野生型铁蛋白”是指其序列由天然存在的序列组成的铁蛋白。铁蛋白还包括其氨基酸序列与野生型铁蛋白有一个或多个差异的全长铁蛋白或铁蛋白片段。

[0090] 如本文所用,“铁蛋白单体”是指未与其他铁蛋白分子组装的单一铁蛋白分子(或,在适用时,单一铁蛋白重链或轻链)。“铁蛋白多聚体”包含多个缔合的铁蛋白单体。“铁蛋白蛋白”包括单体铁蛋白和多聚体铁蛋白。

[0091] 如本文所用,“铁蛋白颗粒”是指已经自组装成球状形式的铁蛋白。铁蛋白颗粒有时被称为“铁蛋白纳米颗粒”或简称为“纳米颗粒”。在一些实施方案中,铁蛋白颗粒包含24个铁蛋白单体(或,在适用时,总共24个重链和轻链)。

[0092] 如本文所用,“杂合铁蛋白”是指包含幽门螺杆菌铁蛋白与牛蛙铁蛋白的氨基末端延伸区的铁蛋白。用作牛蛙铁蛋白的氨基末端延伸区的示例性序列呈现为SEQ ID NO:217。在杂合铁蛋白中,可以将牛蛙铁蛋白的氨基末端延伸区与幽门螺杆菌铁蛋白融合,由此使得免疫刺激部分附接位点均匀分布在铁蛋白颗粒表面。如本文所用,“牛蛙接头”是包含序列SEQ ID NO:217的接头。杂合铁蛋白有时也称为“bfpFerr”或“bfp铁蛋白”。可以在没有牛蛙序列的情况下,例如像在没有接头或在具有替代性接头的情况下提供包含牛蛙序列的任何构建体。示例性牛蛙接头序列提供于表2中。在表2示出牛蛙接头的情况下,可以在没有接头或具有替代性接头的情况下制造相同的构建体。

[0093] 如本文所用,“N-聚糖”是指在蛋白质的N(天冬酰胺)残基的酰胺氮处附接至蛋白质的糖链。这样,通过N-糖基化过程形成N-聚糖。此聚糖可以是多糖。

[0094] 如本文所用,“糖基化”是指将糖单元添加至蛋白质。

[0095] 如本文所用,“免疫应答”是指免疫系统的细胞(如B细胞、T细胞、树突细胞、巨噬细胞或多形核细胞)对刺激物(如抗原或疫苗)的应答。免疫应答可以包括参与宿主防御应答的身体的任何细胞,例如包括分泌干扰素或细胞因子的上皮细胞。免疫应答包括但不限于先天性和/或适应性免疫应答。如本文所用,“保护性免疫应答”是指保护受试者免受感染(例如,预防感染或预防与感染相关的疾病的发生)的免疫应答。测量免疫应答的方法在本领域中是熟知的,并且包括例如通过测量淋巴细胞(如B或T细胞)的增殖和/或活性、细胞因子或趋化因子的分泌、炎症、抗体产生等。“抗体应答”是其中产生抗体的免疫应答。

[0096] 如本文所用,“抗原”是指引发免疫应答的因子;和/或当暴露或给予至生物体时由T细胞受体结合的因子(例如,当由MHC分子呈递时)或与抗体(例如,由B细胞产生)结合的因子。在一些实施方案中,抗原在生物体中引发体液应答(例如,包括产生抗原特异性抗体)。可替代地或另外,在一些实施方案中,抗原在生物体中引发细胞应答(例如,涉及其受体与抗原特异性相互作用的T细胞)。特定抗原可以在靶标生物体(例如,小鼠、兔、灵长类动物、人)的一个或若干成员中引发免疫应答,但不能在靶标生物体物种的所有成员中引发免疫应答。在一些实施方案中,抗原在靶标生物体物种的至少约25%、30%、35%、40%、45%、50%、55%、60%、65%、70%、75%、80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%的成员中引发免疫应答。在一些实施方案中,抗原结合抗体和/或T细胞受体,并且在生物体中可能诱导或可能不诱导特定生理应答。在一些实施方案中,例如,抗原可以在体外结合抗体和/或T细胞受体,无论在体内是否发生这种相互作用。在一些实施方案中,抗原与特定体液或细胞免疫的产物(包括由异源免疫原诱导的那些)反应。抗原包括如本文所述的抗原性铁蛋白蛋白,其包含铁蛋白(例如,包含一个或多个突变)和非铁蛋白多肽。

[0097] 如本文所用,“免疫刺激部分”是指共价附接至铁蛋白或抗原性铁蛋白多肽并可以激活免疫系统的组分(单独或当附接至铁蛋白或抗原性铁蛋白多肽时)的部分。示例性免疫刺激部分包括toll样受体(TLR)例如TLR4、7、8或9的激动剂。在一些实施方案中,免疫刺激部分是佐剂。

[0098] 如本文所用,“佐剂”是指非特异性增强对抗原的免疫应答的物质或媒介物。佐剂可以包括而限于其上吸附有抗原的矿物质(明矾、氢氧化铝或磷酸盐)的悬浮液;其中抗原溶液乳化在矿物油中或水中的油包水或水包油乳剂(例如,弗氏不完全佐剂)。有时包括

杀死的分枝杆菌(例如,弗氏完全佐剂)以进一步增强抗原性。免疫刺激寡核苷酸(例如,CpG基序)也可用作佐剂(例如,参见美国专利号6,194,388;6,207,646;6,214,806;6,218,371;6,239,116;6,339,068;6,406,705;和6,429,199)。佐剂还可以包括生物分子,如Toll样受体(TLR)激动剂和共刺激分子。佐剂可以作为单独分子在组合物中给予或与铁蛋白或抗原性铁蛋白多肽共价结合(缀合)。

[0099] “抗原性EBV多肽”在本文中用于指包含全部或部分EBV氨基酸序列的多肽,所述EBV氨基酸序列的长度足以使所述分子具有关于EBV的抗原性。抗原性可以是作为进一步包含异源序列(如铁蛋白或2,4-二氧四氢嘧啶合酶蛋白和/或免疫刺激部分)的构建体的一部分的EBV序列的特征。即,如果EBV序列是进一步包含异源序列的构建体的一部分,则所述构建体可以充当产生抗EBV抗体的抗原就足够了,而不管不伴有异源序列的EBV序列是否可以如此。

[0100] “抗原性铁蛋白多肽”和“抗原性铁蛋白蛋白”在本文中可互换用于指包含铁蛋白和非铁蛋白多肽(例如,EBV多肽)的多肽,所述非铁蛋白多肽的长度足以使所述分子具有关于非铁蛋白多肽的抗原性。抗原性铁蛋白多肽可以进一步包含免疫刺激部分。抗原性可以是作为较大构建体的一部分的非铁蛋白序列的特征。即,所述构建体可以充当针对非铁蛋白多肽的抗原就足够了,而不管不伴有铁蛋白(如果适用,和免疫刺激部分)的非铁蛋白多肽是否可以如此。在一些实施方案中,非铁蛋白多肽是EBV多肽,在这种情况下,抗原性铁蛋白多肽也是“抗原性EBV多肽”。然而,要清楚的是,抗原性EBV多肽不需要包含铁蛋白。“抗原性多肽”在本文中用于指为抗原性铁蛋白多肽和抗原性EBV多肽中的任一者或两者的多肽。

[0101] 如本文所用,“自佐剂化”是指组合物或多肽包含铁蛋白和直接缀合至铁蛋白的免疫刺激部分,使得铁蛋白和免疫刺激部分在同一分子实体中。可以将包含非铁蛋白多肽的抗原性铁蛋白多肽与免疫刺激部分缀合以产生自佐剂化多肽。

[0102] 如本文所用,“表面暴露的”氨基酸是指蛋白质(例如,铁蛋白)中具有侧链的氨基酸残基,当所述蛋白质在多聚化后(如果适用)处于其天然的三维构象时,所述侧链可以被溶剂分子接触。因此,例如,在形成24聚体的铁蛋白的情况下,当铁蛋白组装为24聚体,例如组装为铁蛋白多聚体或铁蛋白颗粒时,表面暴露的氨基酸残基是其侧链可以被溶剂接触的氨基酸残基。

[0103] 如本文所用,“受试者”是指动物界的任何成员。在一些实施方案中,“受试者”是指人。在一些实施方案中,“受试者”是指非人动物。在一些实施方案中,受试者包括但不限于哺乳动物、鸟、爬行动物、两栖动物、鱼、昆虫和/或蠕虫。在某些实施方案中,非人受试者是哺乳动物(例如,啮齿动物、小鼠、大鼠、兔、猴、犬、猫、绵羊、牛、灵长类动物和/或猪)。在一些实施方案中,受试者可以是转基因动物、基因工程化动物和/或克隆。在本发明的某些实施方案中,受试者是成人、青少年或婴儿。在一些实施方案中,术语“个体”或“患者”被使用并且旨在与“受试者”可互换。

[0104] 如本文所用,术语“疫苗接种(vaccination或vaccinate)”是指给予旨在例如对致病因子产生免疫应答的组合物。疫苗接种可以在暴露于致病因子和/或发生一种或多种症状之前、期间和/或之后给予,并且在一些实施方案中,在暴露于所述因子之前、期间和/或之后不久给予。在一些实施方案中,疫苗接种包括间隔适当时间的疫苗接种组合物的多次给予。

[0105] 本公开文本描述了分别与给定核酸序列或氨基酸序列(参考序列)具有一定同一性程度的核酸序列和氨基酸序列。

[0106] 两个核酸序列之间的“序列同一性”指示序列之间相同的核苷酸的百分比。两个氨基酸序列之间的“序列同一性”指示序列之间相同的氨基酸的百分比。

[0107] 术语“相同%”、“同一性%”或类似术语旨在具体是指在待比较的序列之间的最佳比对中相同的核苷酸或氨基酸的百分比。所述百分比是纯粹统计学的,并且两个序列之间的差异可以但不一定随机分布在待比较的序列的整个长度上。两个序列的比较通常通过以下方式进行:在最佳比对之后,关于区段或“比较窗口”比较所述序列,以鉴定相应序列的局部区域。用于比较的最佳比对可以手动地进行或借助于Smith和Waterman,1981,Ads App.Math.2,482的局部同源性算法、借助于Needleman和Wunsch,1970,J.Mol.Biol.48,443的局部同源性算法、借助于Pearson和Lipman,1988,Proc.Natl Acad.Sci.USA88,2444的相似性搜索算法、或借助于使用所述算法的计算机程序(在Wisconsin序列分析包(Genetics Computer Group,575Science Drive,威斯康星州麦迪逊)中的GAP、BESTFIT、FASTA、BLAST P、BLASTN和TFASTA)进行。

[0108] 百分比同一性通过以下方式获得:确定待比较的序列对应的相同位置的数目,用此数目除以比较的位置的数目(例如,参考序列中的位置的数目),并且然后将此结果乘以100。

[0109] 在一些实施方案中,同一性程度是针对区域给出的,所述区域是参考序列的整个长度的至少约50%、至少约60%、至少约70%、至少约80%、至少约90%或约100%。例如,如果参考核酸序列由200个核苷酸组成,则针对至少约100、至少约120、至少约140、至少约160、至少约180或约200个核苷酸(在一些实施方案中为连续核苷酸)给出同一性程度。在一些实施方案中,针对参考序列的整个长度给出同一性程度。

[0110] 分别与给定核酸序列或氨基酸序列具有特定同一性程度的核酸序列或氨基酸序列可具有所述给定序列的至少一种功能特性,例如并且在一些情况下,在功能上等同于所述给定序列。一个重要的特性包括充当细胞因子的能力,特别是当给予受试者时。在一些实施方案中,与给定核酸序列或氨基酸序列具有一定同一性程度的核酸序列和氨基酸序列在功能上等同于所述给定序列。

[0111] 如本文所用,术语“试剂盒”是指一组经包装的相关组分,如一种或多种化合物或组合物和一种或多种相关材料,如溶剂、溶液、缓冲液、说明书或干燥剂。

B. 包含gL和gH多肽的抗原性EBV多肽

[0112] EBV具有三种糖蛋白,即糖蛋白B(gB)、gH和gL,它们形成了核心膜融合机构以允许病毒穿透进入细胞。gL和gH先前已经在例如Matsuura等人,Proc Natl Acad Sci U S A.2010年12月28日;107(52):22641-6中进行了描述。用作疫苗的gL和gH的单体和三聚体已经例如在Cui等人,Vaccine.2016年7月25日;34(34):4050-5中进行了描述。gH和gL蛋白缔合形成异二聚体复合物,所述异二聚体复合物被认为是病毒进入所需的高效膜融合和与上皮细胞受体结合所必需的。

[0113] 本文公开了包含EBV gL和EBV gH的抗原性多肽。在一些实施方案中,多肽以单链存在。在一些实施方案中,多肽形成三聚体,例如通过三聚化结构域(如T4噬菌体次要纤维蛋白三聚化结构域)的三聚化形成。在一些实施方案中,多肽例如通过铁蛋白或2,4-二氧四

氢喋啶合酶的多聚化形成纳米颗粒(例如铁蛋白或2,4-二氧四氢喋啶合酶颗粒)。在一些实施方案中,根据本公开文本的抗原性EBV多肽包含EBV gL多肽和EBV gH多肽,以及将EBV gL多肽和EBV gH多肽分开、具有至少15个氨基酸的长度的接头。已经发现相对长的接头可以提供诸如改善的表达和/或免疫原性的益处。

[0114] 在一些实施方案中,EBV gH和/或gL多肽是全长gH和/或gL(对于示例性全长序列,分别参见GenBank登录号CEQ35765.1和YP_001129472.1)。在一些实施方案中,EBV gH和/或gL多肽是gH和/或gL的片段。在一些实施方案中,gL多肽是在gL C末端的末端具有7个氨基酸缺失的gL(D7)构建体。在一些实施方案中,gH多肽包含在C137处的突变,如C137A突变。在一些实施方案中,C137突变去除天然的不成对半胱氨酸以避免非特异性缀合。在一些实施方案中,gH多肽包含用以去除与SEQ ID NO:37的半胱氨酸137对应的半胱氨酸的突变,如C137A突变。在一些实施方案中,C137突变去除天然的不成对半胱氨酸以避免非特异性缀合。

[0115] 在一些实施方案中,EBV gL多肽包含与SEQ ID NO:36具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。在一些实施方案中,EBV gH多肽包含与SEQ ID NO:37具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。

[0116] 在一些实施方案中,哺乳动物前导序列(也称为信号序列)附加至EBV多肽(如gH或gL多肽)的N末端,例如在所述多肽的N末端。在一些实施方案中,哺乳动物前导序列当在哺乳动物细胞中表达时导致蛋白质的分泌。

[0117] 天然EBV gH和/或gL序列在GenBank登录号NC_009334.1(人疱疹病毒4,完整基因组,日期为2010年3月26日)中示出。对于本文公开的一些构建体,将NC_009334.1中gL氨基酸序列的氨基酸23-137用作gL多肽,并且将天然信号肽(NCBI序列的氨基酸1-22)替换为IgGκ前导序列。对于一些构建体,将NC_009334.1中gH氨基酸序列的氨基酸19-678用作gH多肽。在一些实施方案中,gL和gH经由如本文序列表中所示的接头连接。

[0118] 在一些实施方案中,gL和gH多肽表达为单链单体。在一些实施方案中,单体组合物包含在序列表中示出并且在说明书中表示为“单体”的序列或由所述序列组成。包含gL和gH多肽的单链可以称为“gL/gH”,其可以与“gH_gL”、“gL_gH”或“gL/gH”互换使用。

[0119] 在一些实施方案中,gL和gH被提供为三聚体。在一些实施方案中,将三聚化结构域置于gH序列之后(在其C末端),并且在一些实施方案中,这之后是His₆(SEQ ID NO:243)序列。折叠子三聚化结构域是示例性的,因为可以使用本领域已知的任何三聚化结构域,如本文引用的胶原蛋白或L1ORF1p三聚化结构域。已显示,使用外周血人幼稚B细胞,相对于gL和gH单体,gL和gH三聚体诱导更高的血清中和效价(参见例如Cui等人,Vaccine.2016年7月25日;34(34):4050-5)。

[0120] 在一些实施方案中,gL/gH三聚体具有这样的氨基酸序列,所述氨基酸序列包含在序列表中示出并且在说明书中表示为“三聚体”的序列或由所述序列组成。

[0121] gL/gH多肽可以与本文所讨论的铁蛋白或2,4-二氧四氢喋啶合酶中的任一种组合。例如,在一些实施方案中,抗原性EBV多肽包含单体或三聚体gL/gH多肽(+/-gp42和/或gp220),以及i)重链或轻链铁蛋白(例如粉纹夜蛾重链或轻链铁蛋白);或ii)铁蛋白,所述铁蛋白任选地包含表面暴露的半胱氨酸。

[0122] 另外,在一些实施方案中,包含EBV gL/gH多肽和铁蛋白的任何抗原性EBV多肽可以存在于包含本文公开的另一多肽的组合物中。

C. 包含gp220多肽的抗原性EBV多肽

[0123] 在一些实施方案中,抗原性EBV多肽包含gp220多肽。gp220-杂合牛蛙/幽门螺杆菌铁蛋白纳米颗粒先前已经在Kanekiyo Cell.2015年8月27日;162(5):1090-100中进行了描述。除了与本文所述的某些铁蛋白的其他差异之外,此纳米颗粒不包含提供表面暴露的半胱氨酸的突变或包含半胱氨酸的接头。

[0124] 在一些实施方案中,gp220多肽包含与SEQ ID NO:38具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。

[0125] 在一些实施方案中,哺乳动物前导序列(也称为信号序列)附加至gp220多肽的N末端。在一些实施方案中,哺乳动物前导序列当在哺乳动物细胞中表达时导致蛋白质的分泌。

[0126] gp220多肽可以与本文所讨论的铁蛋白或2,4-二氧四氢喋呤合酶中的任一种组合。例如,在一些实施方案中,抗原性EBV多肽包含gp220多肽(+/-gL/gH和/或gp42),以及i)重链或轻链铁蛋白(例如粉纹夜蛾重链或轻链铁蛋白);或ii)铁蛋白,所述铁蛋白任选地包含如本文所述的表面暴露的半胱氨酸。

[0127] 另外,在一些实施方案中,包含gp220多肽和铁蛋白的任何抗原性EBV多肽可以存在于包含本文公开的另一多肽的组合物中。

D. 包含gp42多肽的抗原性EBV多肽

[0128] 在一些实施方案中,抗原性EBV多肽包含gp42多肽。示例性gp42序列提供为SEQ ID NO:34。适合于包含在例如具有gL和gH多肽的融合体中的另外的示例性gp42序列提供为SEQ ID NO:239。适合于包含在例如具有gL和gH多肽的融合体中的另一种示例性gp42序列提供为SEQ ID NO:240。

[0129] 在一些实施方案中,gp42多肽包含与SEQ ID NO:34具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。在一些实施方案中,gp42多肽包含与SEQ ID NO:239具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。在一些实施方案中,gp42多肽包含与SEQ ID NO:240具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。

[0130] 在一些实施方案中,哺乳动物前导序列(也称为信号序列)附加至gp42多肽的N末端。在一些实施方案中,哺乳动物前导序列当在哺乳动物细胞中表达时导致蛋白质的分泌。示例性前导序列是SEQ ID NO:226的氨基酸1-22。

[0131] 在一些实施方案中,包含gH和/或gL多肽的抗原性EBV多肽进一步包含gp42多肽。上述的包含gH和/或gL多肽的任何EBV多肽可以进一步包含gp42多肽。在一些实施方案中,gp42多肽位于gH和/或gL多肽的C末端,如SEQ ID NO:21和226-231中例示的。在一些实施方案中,gp42多肽位于铁蛋白的N末端,也如SEQ ID NO:21和227-231中例示的。因此,例如,抗原性EBV多肽可以在N末端至C末端取向上包含gL多肽、gH多肽、gp42多肽和任选的铁蛋白。如本文所述的那些的接头可以将gp42多肽与位于其N末端和/或C末端的EBV多肽和/或铁蛋白分开。在一些实施方案中,接头将抗原性铁蛋白多肽中的每个EBV多肽(例如,gL多肽、gH多肽和gp42多肽)分开,并且在存在时的铁蛋白和与其接近的EBV多肽(例如,gp42多肽)之间可以存在另外的接头。

[0132] 在一些实施方案中,具有至少15个氨基酸的长度的接头将EBV gH多肽与EBV gp42多肽分开。这种接头可以具有15至60个氨基酸、20至60个氨基酸、30至60个氨基酸、40至60个氨基酸、30至50个氨基酸或40至50个氨基酸的长度。在一些实施方案中,接头包含与SEQ ID NO:234具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。

[0133] 在一些实施方案中,在gp42和铁蛋白存在于多肽中的情况下,接头将EBV gp42多肽和铁蛋白分开。这种接头可以具有至少15个氨基酸的长度或具有15至60个氨基酸、20至60个氨基酸、30至60个氨基酸、40至60个氨基酸、30至50个氨基酸或40至50个氨基酸的长度。在一些实施方案中,这种接头包含与SEQ ID NO:233、234、235、236、237或238中的任一个具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。

[0134] gp42多肽可以与本文所讨论的铁蛋白或2,4-二氧四氢嘧啶合酶中的任一种组合。例如,在一些实施方案中,多肽包含gp42多肽(+/-gL/gH和/或gp220),以及重链或轻链铁蛋白(例如粉纹夜蛾重链或轻链铁蛋白);或ii)铁蛋白,所述铁蛋白任选地包含如本文所述的表面暴露的半胱氨酸。

[0135] 在一些实施方案中,抗原性EBV多肽包含与SEQ ID NO:226的氨基酸23-1078具有至少80%、85%、90%、95%、98%或99%同一性的序列。在一些实施方案中,抗原性EBV多肽包含与SEQ ID NO:226的氨基酸1-1078具有80%、85%、90%、95%、98%或99%同一性的序列。在一些实施方案中,抗原性EBV多肽包含与SEQ ID NO:226、227、228、229、230或231中的任一个具有80%、85%、90%、95%、98%或99%同一性的序列,任选地缺乏前导序列(例如,缺乏这些序列中的氨基酸1-22的任一个或全部)。

[0136] 另外,在一些实施方案中,包含gp42多肽和铁蛋白的任何抗原性EBV多肽可以存在于包含本文公开的另一多肽的组合物中。

E. 接头

[0137] 在一些实施方案中,抗原性EBV多肽包含在gL与gH多肽之间的接头。在一些实施方案中,抗原性EBV多肽包含在EBV多肽与铁蛋白或2,4-二氧四氢嘧啶合酶之间的接头。关于此类接头中的任一种描述了以下特征,但是本发明提供了在gL与gH序列之间的相对较长的接头可以提供免疫原性的增加。可以使用任何接头,例如,在一些实施方案中,接头的长度为2、3、4、5、6、7、8、9或10个氨基酸。在一些实施方案中,接头的长度为约2-4、2-6、2-8、2-10、2-12或2-14个氨基酸。在一些实施方案中,接头是肽接头,其可以有利于抗原性铁蛋白多肽作为融合蛋白的表达(例如,从单一开放阅读框)。在一些实施方案中,接头是甘氨酸-丝氨酸接头。在一些实施方案中,甘氨酸-丝氨酸接头是GS、GGGS (SEQ ID NO:244)、2XGGGS (即,GGGSGGGS) (SEQ ID NO:245)或5XGGGS (SEQ ID NO:246)。在一些实施方案中,EBV多肽与铁蛋白之间的接头是GS、GGGS (SEQ ID NO:244)、2XGGGS (即,GGGSGGGS) (SEQ ID NO:245)或5XGGGS (SEQ ID NO:246)。

[0138] 在一些实施方案中,接头的长度为至少15个氨基酸。在一些实施方案中,接头的长度为至少25个氨基酸。在一些实施方案中,接头的长度为至少30个氨基酸。在一些实施方案中,接头的长度为至少35个氨基酸。在一些实施方案中,接头的长度为至少40个氨基酸。在一些实施方案中,接头的长度小于或等于60个氨基酸。在一些实施方案中,接头的长度小于或等于50个氨基酸。在一些实施方案中,接头的长度为约16、28、40、46或47个氨基酸。在一些实施方案中,接头是柔性的。在一些实施方案中,接头包含半胱氨酸,例如以用于缀

合免疫刺激部分(例如,佐剂)的位点;包含半胱氨酸的示例性接头提供为SEQ ID NO:225。在一些实施方案中,接头包含与SEQ ID NO:225具有至少75%、80%、85%、90%或95%同一性的序列,并且进一步包含对应于SEQ ID NO:225中的半胱氨酸的半胱氨酸。在一些实施方案中,接头包含至少25个氨基酸(例如,25至60个氨基酸),其中半胱氨酸位于在自N末端的第8个氨基酸到自C末端的第8个氨基酸范围内的位置处,或位于接头的中心残基或键的10个氨基酸之内。

[0139] 在一些实施方案中,接头包含甘氨酸(G)和/或丝氨酸(S)氨基酸。在一些实施方案中,接头包含以下项或由以下项组成:甘氨酸(G)、丝氨酸(S)、天冬酰胺(N)和/或丙氨酸(A)氨基酸以及任选的如上所讨论的半胱氨酸。在一些实施方案中,接头包含与SEQ ID NO:222具有至少80%、85%、90%、95%、97%、98%、99%或100%同一性的氨基酸序列。在一些实施方案中,接头包含GGGGSGGGSGGGSGG(SEQ ID NO:28)、GGSGSGSNSSASSGASSGGASGGSGSGG(SEQ ID NO:29)、GGSGSASS GASASGSSNGSGSGSGSNSSASSGASSGGASGGSGSGG(SEQ ID NO:30)或GS。在一些实施方案中,接头包含FR1(SEQ ID NO:31)或FR2(SEQ ID NO:32)。在一些实施方案中,接头包含SEQ ID NO:233-238。

[0140]

[0141] 在一些实施方案中,将包含半胱氨酸作为免疫刺激部分(如佐剂)的缀合位点的接头用于包含缺乏不成对的表面暴露的半胱氨酸的铁蛋白分子的构建体中,或用于包含含有不成对的表面暴露的半胱氨酸的铁蛋白分子的构建体中。

[0142] 在一些实施方案中,接头是半胱氨酸-凝血酶-组氨酸接头。在一些实施方案中,此接头用于经由点击化学将EBV多肽直接缀合至铁蛋白。包含半胱氨酸-凝血酶-组氨酸接头的示例性序列是SEQ ID NO:39。本文讨论了适合于涉及半胱氨酸-凝血酶-组氨酸接头的缀合反应的点击化学。

[0143] 在一些实施方案中,构建体不包含接头。在一些实施方案中,构建体包含一个接头。在一些实施方案中,构建体包含两个或多于两个的接头。

[0144] 在一些实施方案中,构建体包含在gH与gL之间的接头但不包含在多肽与铁蛋白之间的接头,或反之亦然。在一些实施方案中,构建体仅包含在多肽与铁蛋白之间的接头。

F. 包含EBV多肽和铁蛋白或2,4-二氧四氢喋啶合酶的抗原性EBV多肽

[0145] 在一些实施方案中,提供了抗原性EBV多肽,所述抗原性EBV多肽包含EBV多肽和铁蛋白。EBV多肽可以是本文所述的任何EBV多肽,如gL、gH、gL/gH、gp220、gp42多肽或其组合。多肽的铁蛋白组分可以是来自任何物种的铁蛋白,并且可以具有或不具有突变,如本文所述的用半胱氨酸置换表面暴露的氨基酸的突变。在一些实施方案中,多肽包含SEQ ID NO:1-27中任一个的氨基酸。

[0146] 在一些实施方案中,多肽中的铁蛋白是野生型铁蛋白。在一些实施方案中,铁蛋白是细菌、昆虫、真菌、鸟类或哺乳动物的。在一些实施方案中,铁蛋白是人的。在一些实施方案中,铁蛋白是细菌的。

[0147] 在一些实施方案中,铁蛋白是轻链和/或重链铁蛋白。在一些实施方案中,铁蛋白是昆虫铁蛋白,如粉纹夜蛾重链铁蛋白(SEQ ID NO:211)或粉纹夜蛾轻链铁蛋白(SEQ ID NO:212)。在一些实施方案中,铁蛋白是人铁蛋白,如人重链铁蛋白(SEQ ID NO:214或FTH1, GENE ID No:2495)或人轻链铁蛋白(SEQ ID NO:215或FTL, GENE ID No:2512)。在一些实施

方案中,铁蛋白纳米颗粒包含重链铁蛋白和轻链铁蛋白的总共24个亚基,如在人或粉纹夜蛾铁蛋白纳米颗粒中。粉纹夜蛾铁蛋白纳米颗粒可以包含12个重链铁蛋白亚基和12个轻链铁蛋白亚基。

[0148] 在一些实施方案中,抗原性EBV多肽包含轻链铁蛋白和EBV多肽。在一些实施方案中,抗原性EBV多肽包含重链铁蛋白和EBV多肽。在一些实施方案中,可以将包含轻链铁蛋白和EBV多肽的抗原性EBV多肽与未与EBV多肽连接的重链铁蛋白组装。在一些实施方案中,可以将包含重链铁蛋白和EBV多肽的抗原性EBV多肽与未与EBV多肽连接的轻链铁蛋白组装。未与EBV多肽(或更一般地,非铁蛋白多肽)连接的铁蛋白可以称为“裸铁蛋白”。

[0149] 在一些实施方案中,可以将包含重链铁蛋白和多肽的抗原性多肽与包含轻链铁蛋白和EBV多肽的抗原性多肽组装,以允许在单一铁蛋白纳米颗粒上呈递两种相同或不同的非铁蛋白多肽。在一些实施方案中,两种不同的非铁蛋白多肽是EBV多肽。在一些实施方案中,两种不同的非铁蛋白多肽由EBV和不同的感染原编码。在一些实施方案中,来自不同感染原的不同非铁蛋白多肽来自病毒或细菌。

[0150] 在一些实施方案中,可以将包含重链铁蛋白和非铁蛋白多肽的抗原性多肽与包含轻链铁蛋白和非铁蛋白多肽的多肽组装,以产生二价组合物。

[0151] 在一些实施方案中,抗原性多肽包含轻链铁蛋白和gp220和/或gp42多肽。在一些实施方案中,抗原性多肽包含重链铁蛋白和gp220和/或gp42多肽。

[0152] 在一些实施方案中,抗原性多肽包含轻链铁蛋白和单链gL和gH多肽。在一些实施方案中,抗原性多肽包含重链铁蛋白和单链gL和gH多肽。

[0153] 在一些实施方案中,可以将包含轻链铁蛋白和gp220和/或gp42多肽的抗原性多肽与包含重链铁蛋白和单链gL和gH多肽的抗原性多肽组装。

[0154] 在一些实施方案中,可以将包含重链铁蛋白和gp220和/或gp42多肽的抗原性多肽与包含轻链铁蛋白和单链gL和gH多肽的抗原性多肽组装。在一些实施方案中,在组装的铁蛋白纳米颗粒中包含十二(12)个gp220和/或gp42多肽以及十二(12)个单链gL和gH多肽,如在组装的粉纹夜蛾铁蛋白纳米颗粒的情况下。

[0155] 包含gp220和/或gp42以及单链gL和gH多肽二者的任何类型的一种或多种铁蛋白纳米颗粒可以称为“二价”或“二价EBV”颗粒或构建体。包含gL和gH三聚体以及含有gp220和/或gp42的铁蛋白的组合物也将是二价EBV组合物。

[0156] 在一些实施方案中,铁蛋白是任选地具有一个或多个突变(如本文所述的那些)的幽门螺杆菌铁蛋白(对于示例性幽门螺杆菌铁蛋白序列,参见SEQ ID NO:208或209)。在一些实施方案中,幽门螺杆菌铁蛋白(或其他细菌铁蛋白)与人铁蛋白之间较低的序列同源性在用作疫苗平台时可降低自身免疫的潜力(参见Kanekiyo等人,Cell 162,1090-1100(2015))。

[0157] 在一些实施方案中,提供了纳米颗粒,所述纳米颗粒包含如本文公开的含有EBV多肽和铁蛋白的抗原性EBV多肽。

1. 铁蛋白突变

[0158] 在一些实施方案中,本文公开了包含一个或多个突变的铁蛋白。在一些实施方案中,一个或多个突变包括野生型铁蛋白的氨基酸序列的改变和/或例如在N或C末端的插入。在一些实施方案中,与野生型铁蛋白相比,(在一些实施方案中,除了任何N末端插入),铁蛋

白中的一个、两个、三个、四个、五个或更多个不同的氨基酸被突变。一个或多个突变可以改变铁蛋白的功能特性,例如,如下文详细讨论的。通常,突变简单地是指相对于相应的野生型铁蛋白的序列差异(如取代、添加或缺失的一个或多个氨基酸残基)。

2. 用于缀合的半胱氨酸

[0159] 在一些实施方案中,铁蛋白被突变以提供用于缀合免疫刺激部分和/或EBV多肽的化学处理。这可以通过用半胱氨酸置换表面暴露的非半胱氨酸氨基酸的突变来实现。为了避免疑问,如“用半胱氨酸置换表面暴露的氨基酸”的语言必定意味着野生型或突变前序列中的表面暴露的氨基酸不是半胱氨酸。提供用于缀合免疫刺激部分或EBV多肽的化学处理的另一种方法是包括在铁蛋白的N或C末端的氨基酸区段(如接头),其中所述氨基酸区段包含半胱氨酸。在一些实施方案中,此半胱氨酸(无论是置换表面暴露的氨基酸还是在N或C末端接头中)是不成对的,这意指它没有合适的伴侣半胱氨酸来形成二硫键。在一些实施方案中,此半胱氨酸不改变铁蛋白的二级结构。在一些实施方案中,此半胱氨酸不改变铁蛋白的三级结构。

[0160] 在一些实施方案中,此半胱氨酸可以用于将药剂(如免疫刺激部分)与铁蛋白缀合。在一些实施方案中,此半胱氨酸提供了反应性的游离硫醇基团。在一些实施方案中,与铁蛋白上的此半胱氨酸缀合的药剂暴露在组装的铁蛋白颗粒的表面上。在一些实施方案中,在组装铁蛋白颗粒的同时,此半胱氨酸可以在给予后与受试者的分子和细胞相互作用。

[0161] 在一些实施方案中,此半胱氨酸的存在允许缀合一个或多个免疫刺激部分,例如佐剂。在一些实施方案中,在不存在此半胱氨酸的情况下不会发生免疫刺激部分的缀合。

[0162] 在一些实施方案中,被半胱氨酸置换的非半胱氨酸氨基酸选自幽门螺杆菌铁蛋白的E12、S72、A75、K79、S100和S111。因此,在一些实施方案中,被置换为半胱氨酸的表面暴露的氨基酸是对应于幽门螺杆菌铁蛋白的E12、S26、S72、A75、K79、S100或S111的氨基酸残基。通过成对或结构比对可以在非幽门螺杆菌铁蛋白中找到类似的氨基酸。在一些实施方案中,被半胱氨酸置换的非半胱氨酸氨基酸可以选自对应于人轻链铁蛋白的S3、S19、S33、I82、A86、A102和A120的氨基酸。在一些实施方案中,基于以下理解来选择要被半胱氨酸置换的表面暴露的氨基酸:如果天然氨基酸被半胱氨酸置换,它将在组装的铁蛋白多聚体或颗粒中是反应性的和/或此半胱氨酸不会破坏铁蛋白多聚体或颗粒的稳定性和/或此半胱氨酸不会导致铁蛋白表达水平降低。

[0163] 在一些实施方案中,铁蛋白包含E12C突变。在一些实施方案中,E12C残基可以用于将药剂(例如,免疫刺激部分和/或EBV多肽)与铁蛋白缀合。在一些实施方案中,E12C残基提供了反应性的游离硫醇基团。在一些实施方案中,与铁蛋白单体上的E12C残基缀合的药剂在组装的铁蛋白多聚体或颗粒的表面上表达。在一些实施方案中,铁蛋白多聚体或颗粒的表面上存在二十四个E12C残基(每个单体中一个)。

[0164] 在一些实施方案中,铁蛋白包含S26C突变。在一些实施方案中,S26C残基可以用于将药剂(例如,免疫刺激部分和/或EBV多肽)与铁蛋白缀合。在一些实施方案中,S26C残基提供了反应性的游离硫醇基团。在一些实施方案中,与铁蛋白单体上的S26C残基缀合的药剂在组装的铁蛋白多聚体或颗粒的表面上表达。在一些实施方案中,铁蛋白多聚体或颗粒的表面上存在二十四个S26C残基(每个单体中一个)。

[0165] 在一些实施方案中,铁蛋白包含S72C突变。在一些实施方案中,S72C残基可以用于

将药剂(例如,免疫刺激部分和/或EBV多肽)与铁蛋白缀合。在一些实施方案中,S72C残基提供了反应性的游离硫醇基团。在一些实施方案中,与铁蛋白单体上的S72C残基缀合的药剂在组装的铁蛋白多聚体或颗粒的表面上表达。在一些实施方案中,铁蛋白多聚体或颗粒的表面上存在二十四个S72C残基(每个单体中一个)。

[0166] 在一些实施方案中,铁蛋白包含A75C突变。在一些实施方案中,A75C残基可以用于将药剂(例如,免疫刺激部分和/或EBV多肽)与铁蛋白缀合。在一些实施方案中,A75C残基提供了反应性的游离硫醇基团。在一些实施方案中,与铁蛋白单体上的A75C残基缀合的药剂在组装的铁蛋白多聚体或颗粒的表面上表达。在一些实施方案中,铁蛋白多聚体或颗粒的表面上存在二十四个A75C残基(每个单体中一个)。

[0167] 在一些实施方案中,铁蛋白包含K79C突变。在一些实施方案中,K79C残基可以用于将药剂(例如,免疫刺激部分和/或EBV多肽)与铁蛋白缀合。在一些实施方案中,K79C残基提供了反应性的游离硫醇基团。在一些实施方案中,与铁蛋白单体上的K79C残基缀合的药剂在组装的铁蛋白多聚体或颗粒的表面上表达。在一些实施方案中,铁蛋白多聚体或颗粒的表面上存在二十四个K79C残基(每个单体中一个)。

[0168] 在一些实施方案中,铁蛋白包含S100C突变。在一些实施方案中,S100C残基可以用于将药剂(例如,免疫刺激部分和/或EBV多肽)与铁蛋白缀合。在一些实施方案中,S100C残基提供了反应性的游离硫醇基团。在一些实施方案中,与铁蛋白单体上的S100C残基缀合的药剂在组装的铁蛋白多聚体或颗粒的表面上表达。在一些实施方案中,铁蛋白多聚体或颗粒的表面上存在二十四个S100C残基(每个单体中一个)。

[0169] 在一些实施方案中,铁蛋白包含S111C突变。在一些实施方案中,S111C残基可以用于将药剂(例如,免疫刺激部分和/或EBV多肽)与铁蛋白缀合。在一些实施方案中,S111C残基提供了反应性的游离硫醇基团。在一些实施方案中,与铁蛋白单体上的S111C残基缀合的药剂在组装的铁蛋白多聚体或颗粒的表面上表达。在一些实施方案中,铁蛋白多聚体或颗粒的表面上存在二十四个S111C残基(每个单体中一个)。

3. 内部半胱氨酸的去除

[0170] 在一些实施方案中,铁蛋白包含用非半胱氨酸氨基酸置换内部半胱氨酸的突变。去除天然内部半胱氨酸残基可以确保每个铁蛋白单体只有一个未配对的半胱氨酸,并且避免了不希望的反应(如二硫化物形成),并且可以导致更稳定且高效的结果(例如,佐剂呈递)。在一些实施方案中,幽门螺杆菌铁蛋白的C31被非半胱氨酸氨基酸置换。在一些实施方案中,用丝氨酸(C31S)置换幽门螺杆菌铁蛋白的C31,但是可以使用任何非半胱氨酸残基,例如丙氨酸、甘氨酸、苏氨酸或天冬酰胺。通过成对或结构比对可以在非幽门螺杆菌铁蛋白中找到类似的氨基酸。因此,在一些实施方案中,被置换为非半胱氨酸的内部半胱氨酸是与幽门螺杆菌铁蛋白的C31对齐的氨基酸残基。显示C31S突变的示例性铁蛋白序列在SEQ ID NO:201-207中示出。在一些实施方案中,当铁蛋白中存在多于一个内部半胱氨酸时,两个或更多个(例如,每个)内部半胱氨酸被非半胱氨酸氨基酸置换,所述非半胱氨酸氨基酸如丝氨酸或选自丝氨酸、丙氨酸、甘氨酸、苏氨酸或天冬酰胺的氨基酸。

4. 糖基化

[0171] 人相容性糖基化可有助于重组药物产品的安全性和功效。监管批准可能取决于证明适当的糖基化是关键的质量属性(参见Zhang等人,Drug Discovery Today 21(5):740-

765 (2016))。N-聚糖可以由天冬酰胺侧链的糖基化产生,并且在人与其他生物体(如细菌和酵母)之间的结构可能不同。因此,可能期望减少或消除根据本公开文本的铁蛋白中的非人糖基化和/或N-聚糖形成。在一些实施方案中,控制铁蛋白的糖基化改善了组合物的功效和/或安全性,尤其是当用于人疫苗接种时。

[0172] 在一些实施方案中,铁蛋白被突变以抑制N-聚糖的形成。在一些实施方案中,与其相应的野生型铁蛋白相比,突变的铁蛋白具有降低的糖基化。

[0173] 在一些实施方案中,铁蛋白包含用非天冬酰胺氨基酸置换表面暴露的天冬酰胺的突变。在一些实施方案中,表面暴露的天冬酰胺是幽门螺杆菌铁蛋白的N19或如通过成对或结构比对确定的对应于幽门螺杆菌铁蛋白的位置31的位置。在一些实施方案中,使这种天冬酰胺(例如幽门螺杆菌铁蛋白的N19)突变降低了铁蛋白的糖基化。在一些实施方案中,突变是用谷氨酰胺置换了天冬酰胺。在一些实施方案中,铁蛋白是包含N19Q突变的幽门螺杆菌铁蛋白。SEQ ID NO:201-207是包含N19Q突变的示例性铁蛋白序列。

[0174] 暴露于细菌或酵母中产生的糖基化蛋白的哺乳动物可能会对糖基化蛋白产生免疫应答,因为细菌或酵母中给定蛋白的糖基化模式可能与哺乳动物中相同蛋白的糖基化模式不同。因此,一些糖基化的治疗性蛋白质可能不适合在细菌或酵母中生产。

[0175] 在一些实施方案中,通过氨基酸突变进行的铁蛋白糖基化减少有利于蛋白质在细菌或酵母中的产生。在一些实施方案中,减少的铁蛋白糖基化降低了在给予在细菌或酵母中表达的突变铁蛋白后在哺乳动物中产生不利影响的可能性。在一些实施方案中,因为糖基化减少,所以在细菌或酵母中产生的突变铁蛋白在人受试者中的反应原性降低。在一些实施方案中,与野生型铁蛋白相比,用具有减少的糖基化的突变铁蛋白治疗后,人受试者中超敏反应的发生率较低。

[0176] 在一些实施方案中,与包含野生型铁蛋白的组合物或包含具有野生型糖基化的相应铁蛋白的组合物相比,包含具有减少的糖基化的突变铁蛋白的组合物在受试者中的降解较慢。在一些实施方案中,与包含野生型铁蛋白的组合物或包含具有野生型糖基化的相应铁蛋白的组合物相比,包含具有减少的糖基化的突变铁蛋白的组合物在受试者中具有降低的清除率。在一些实施方案中,与野生型铁蛋白或包含具有野生型糖基化的相应铁蛋白的组合物相比,包含具有减少的糖基化的突变铁蛋白的组合物具有更长的血清半衰期。

5. 突变的组合

[0177] 在一些实施方案中,铁蛋白包含本文所述的多于一种类型的突变。在一些实施方案中,铁蛋白包含一种或多种独立地选自以下项的突变:减少糖基化的突变、去除内部半胱氨酸的突变和产生表面暴露的半胱氨酸的突变。在一些实施方案中,铁蛋白包含减少糖基化的突变、去除内部半胱氨酸的突变和产生表面暴露的半胱氨酸的突变。

[0178] 在一些实施方案中,铁蛋白包含N19Q突变、C31S突变和产生表面暴露的半胱氨酸的突变。在一些实施方案中,铁蛋白包含N19Q突变、C31S突变和E12C突变。在一些实施方案中,铁蛋白包含N19Q突变、C31S突变和S72C突变。在一些实施方案中,铁蛋白包含N19Q突变、C31S突变和A75C突变。在一些实施方案中,铁蛋白包含N19Q突变、C31S突变和K79C突变。在一些实施方案中,铁蛋白包含N19Q突变、C31S突变和S100C突变。在一些实施方案中,铁蛋白包含N19Q突变、C31S突变和S111C突变。在一些实施方案中,铁蛋白包含对应于前述突变组中的任一种的突变,其中相应的突变在通过铁蛋白氨基酸序列与幽门螺杆菌铁蛋白氨基酸

序列 (SEQ ID NO:208或209) 的成对比对确定的位置处将N改变为Q、将C改变为S,并且将非半胱氨酸表面暴露的氨基酸改变为半胱氨酸。

[0179] 包含多于一种类型的突变的示例性铁蛋白提供于SEQ ID NO:201-207中。

6. 结构比对

[0180] 如本文所讨论,可以通过成对或结构比对来鉴定对应于关于给定多肽(例如,幽门螺杆菌铁蛋白)描述的那些的突变位置。结构比对与大型蛋白质家族(如铁蛋白)有关,在大型蛋白质家族中,尽管有相当大的序列变异,但蛋白质共享相似的结构并且家族的许多成员已在结构上进行了表征;并且还可以用于鉴定本文所述的其他多肽(如EBV多肽(例如, gL、gH、gp220或gp42))的不同形式中的相应位置。蛋白质数据库(PDB)包括许多铁蛋白的3D结构,包括下文用其登录号列出的那些。

[0181] 2jd6、2jd7-PfFR-激烈火球菌。2jd8-PfFR+Zn。3a68-来自基因SferH4的soFR-大豆。3a9q-来自基因SferH4的soFR(突变体)。3egm、3bvf、3bvi、3bvk、3bvl-HpFR-幽门螺杆菌。5c6f-HpFR(突变体)+Fe。1z4a、1vlg-FR-海栖热袍菌(*Thermotoga maritime*)。1s3q、1sq3、3kx9-FR-闪烁古生球菌(*Archaeoglobus fulgidus*)。1krq-FR-空肠弯曲菌(*Campylobacter jejuni*)。1eum-EcFR-大肠杆菌。4reu-EcFR+Fe。4xgs-EcFR(突变体)+Fe202。4ztt-EcFR(突变体)+Fe20+Fe2+Fe+O2。1qgh-LiFR-英诺克李斯特菌(*Listeria innocua*)。3qz3-VcFR-霍乱弧菌(*Vibrio cholerae*)。3vnx-FR-孔石莼(*Ulva pertusa*)。4ism、4isp、4itt、4itw、4iwj、4iwk、4ixk、3e6s-PnmFR-多列拟菱形藻(*Pseudo-nitzschia multiseriata*)。4zkh、4zkw、4zky、4zl5、4zl6、4zlw、4zmc-PnmFR(突变体)+Fe。1z6o-FR-粉纹夜蛾。4cmy-FR+Fe-花柱绿杆菌(*Chlorobaculum tepidum*)。铁蛋白轻链(FTL)。1lb3、1h96-mFTL-小鼠。1rcc、1rce、1rci-bFTL+酒石酸盐+Mg。1rce、1rcg-bFTL+酒石酸盐+Mn。3noz、3np0、3np2、3o7r-hoFTL(突变体)-马。3o7s、3u90-hoFTL。4v1w-hoFTL-低温EM。3rav、3rd0-hoFTL+巴比妥酸盐。铁蛋白轻+重链:5gn8-hFTL+Ca。

[0182] 结构比对涉及通过以下方式鉴定两个(或更多个)多肽序列中的相应残基:(i)使用第二序列的已知结构对第一序列的结构建模或(ii)比较两者均已知的第一序列和第二序列的结构,并且鉴定第一序列中与第二序列中的目的残基最相似定位的残基。在一些算法中,基于叠加结构中的 α -碳距离最小化(例如,哪组成对 α 碳为比对提供最小的均方根偏差)鉴定出相应的残基。当鉴定非幽门螺杆菌铁蛋白中的对应于关于幽门螺杆菌铁蛋白描述的位置的位置时,幽门螺杆菌铁蛋白可以是“第二”序列。在目的幽门螺杆菌铁蛋白没有已知的可用结构,但相比于幽门螺杆菌铁蛋白与另一种具有已知结构的非幽门螺杆菌铁蛋白紧密相关的情况下,可能最有效的是使用紧密相关的非幽门螺杆菌铁蛋白的已知结构来对目的非幽门螺杆菌铁蛋白建模,然后将该模型与幽门螺杆菌铁蛋白结构进行比较,以鉴定目的铁蛋白中的期望的相应残基。关于结构建模和比对有大量文献,代表性的披露文本包括US 6859736;US 8738343;以及Aslam等人,Electronic Journal of Biotechnology 20(2016)9-13中引用的内容。对于基于已知的一种或多种相关结构对结构建模的讨论,参见例如Bordoli等人,Nature Protocols 4(2009)1-13及其中引用的参考文献。

7. 2,4-二氧四氢喋啶合酶

[0183] 在一些实施方案中,抗原性多肽包含2,4-二氧四氢喋啶合酶蛋白。2,4-二氧四氢喋啶合酶可以形成更高级的结构,例如60个亚基的2,4-二氧四氢喋啶合酶颗粒。示例性2,

4-二氧四氢喋啶合酶是风产液菌(*aquifex aeolicus*) 2,4-二氧四氢喋啶合酶(SEQ ID NO: 40)和大肠杆菌2,4-二氧四氢喋啶合酶(SEQ ID NO: 41)。在一些实施方案中,2,4-二氧四氢喋啶合酶与序列SEQ ID NO: 40或41具有至少85%、90%、95%、97%、98%、99%或100%同一性。2,4-二氧四氢喋啶合酶可以位于EBV多肽的C末端并且可以通过如本文所讨论的接头与EBV多肽分开。

G.gL、gH、gp42、接头和/或铁蛋白序列中的突变以消除潜在的氧化、脱酰胺或异天冬氨酸形成位点

[0184] 在一些实施方案中,抗原性EBV多肽包含一个或多个突变以消除潜在的氧化、脱酰胺或异天冬氨酸形成位点,如下表1中所示的示例性突变。

[0185] 例如,在一些实施方案中,gL序列包含一个或多个突变以消除潜在的琥珀酰亚胺/异天冬氨酸或脱酰胺位点。例如,gL序列可以包含在对应于SEQ ID NO: 227的位置36的位置处的G至A突变;在对应于SEQ ID NO: 227的位置47的位置处的N至Q突变;或在对应于SEQ ID NO: 227的位置105的位置处的N至Q突变。如果根据标准序列比对算法(如使用默认参数的Smith-Waterman算法),氨基酸序列中的位置与SEQ ID NO: 227中的给定位置对齐,则所述氨基酸序列中的位置“对应于”SEQ ID NO: 227中的所述给定位置。

[0186] 在一些实施方案中,接头包含一个或多个突变以消除潜在的脱酰胺位点。例如,接头序列可以包含在对应于SEQ ID NO: 227的位置132或141的位置处的N至G突变。

[0187] 在一些实施方案中,gH序列包含一个或多个突变以消除潜在的琥珀酰亚胺/异天冬氨酸或氧化位点。例如,gH序列可以包含在对应于SEQ ID NO: 227的位置189、401或729的位置处的M至L突变;在对应于SEQ ID NO: 227的位置368的位置处的D至E突变;在对应于SEQ ID NO: 227的位置499或639的位置处的M至I突变;或在对应于SEQ ID NO: 227的位置653的位置处的N至Q突变。

[0188] 在一些实施方案中,gp42序列包含一个或多个突变以消除潜在的脱酰胺位点。例如,gp42序列可以包含在对应于SEQ ID NO: 227的位置959或990的位置处的N至Q突变;或在对应于SEQ ID NO: 227的位置988的位置处的N至S突变。

[0189] 在一些实施方案中,铁蛋白序列包含一个或多个突变以消除潜在的脱酰胺、氧化或异天冬氨酸形成位点。例如,铁蛋白序列可以包含在对应于SEQ ID NO: 227的位置1150的位置处的Q至S突变;在对应于SEQ ID NO: 227的位置1168的位置处的M至I突变;在对应于SEQ ID NO: 227的位置1177的位置处的M至L突变;在对应于SEQ ID NO: 227的位置1188的位置处的G至A突变;或在对应于SEQ ID NO: 227的位置1253或1296的位置处的N至Q突变。

[0190] 示例性突变在下表1中示出。位置编号对应于SEQ ID NO: 227。

[00191] 表 1. 示例性突变。

位置	修饰	起始	结束	基序	溶剂暴露	突变
gL	琥珀酰亚胺/异天冬氨酸	35	36	DG	暴露的	G36A
gL	脱酰胺	47	47	N	很可能暴露的	N47Q
gL	脱酰胺	105	105	N	暴露的	N105Q
接头	脱酰胺	132	132	N	暴露的	N132G
接头	脱酰胺	141	141	N	暴露的	N141G
gH	氧化	189	189	M	暴露的	M189L
gH	琥珀酰亚胺/异天冬氨酸	368	369	DY	暴露的	D368E
gH	氧化	401	401	M	包埋的	M401L
gH	琥珀酰亚胺/异天冬氨酸	429	430	DT	暴露的	D429E
gH	氧化	499	499	M	暴露的	M499I
gH	氧化	639	639	M	暴露的	M639I
gH	氧化	653	653	N	暴露的	N653Q
gH	氧化	729	729	M	暴露的	M729L
gp42	脱酰胺	959	959	N	暴露的	N959Q
gp42	脱酰胺	988	988	N	暴露的	N988S
gp42	脱酰胺	990	990	N	暴露的	N990Q
铁蛋白	脱酰胺	1150	1150	Q	暴露的	Q1150S
铁蛋白	氧化	1168	1168	M	包埋的	M1168I
铁蛋白	脱酰胺	1177	1177	M	包埋的	M1177L
铁蛋白	异天冬氨酸	1187	1188	DG	包埋的	G1188A
铁蛋白	脱酰胺	1253	1253	N	暴露的	N1253Q
铁蛋白	脱酰胺	1296	1296	N	暴露的	N1296Q

H. 免疫刺激部分；佐剂；缀合的EBV多肽

[0192] 在一些实施方案中，将EBV多肽和/或免疫刺激部分（如佐剂）附接至表面暴露的氨

氨基酸。在一些实施方案中,表面暴露的氨基酸是半胱氨酸,例如,由上文讨论的突变产生的半胱氨酸。在一些实施方案中,表面暴露的氨基酸是赖氨酸、天冬氨酸或谷氨酸。使用戊二醛(用于将赖氨酸与带氨基的接头或部分缀合)或碳二亚胺(例如用于将天冬氨酸或谷氨酸与带氨基的接头或部分或将赖氨酸与带羧基的接头或部分缀合的1-环己基-3-(2-吗啉-4-基-乙基)碳二亚胺或1-乙基-3-(3-二甲基-氨基丙基)碳二亚胺(EDC;EDAC))的缀合程序例如描述于可从www.springer.com获得的Holtzhauer, M., Basic Methods for the Biochemical Lab, Springer 2006, ISBN978-3-540-32785-1的第四章中。

[0193] 在一些实施方案中,将免疫刺激部分(如佐剂)附接至铁蛋白的表面暴露的氨基酸。在一些实施方案中,将多于一个免疫刺激部分(如佐剂)附接至铁蛋白的表面暴露的氨基酸。在一些实施方案中,将二十四个免疫刺激部分附接至铁蛋白多聚体或颗粒(例如,幽门螺杆菌铁蛋白颗粒中每个单体有一个部分)。在具有多个附接至铁蛋白纳米颗粒的免疫刺激部分的实施方案中,所有的免疫刺激部分是相同的。在具有多个附接至铁蛋白纳米颗粒的免疫刺激部分的实施方案中,所有的免疫刺激部分是不相同的。

1. 免疫刺激部分的类型;佐剂

[0194] 可以附接至表面暴露的氨基酸(例如半胱氨酸)的任何免疫刺激部分都可以用于根据本公开文本的铁蛋白中。在一些实施方案中,免疫刺激部分是B细胞激动剂。

[0195] 在一些实施方案中,免疫刺激部分不是疏水性的。在一些实施方案中,免疫刺激部分是亲水性的。在一些实施方案中,免疫刺激部分是极性的。在一些实施方案中,免疫刺激部分能够进行氢键结合或离子键结合,例如包含氢键供体、氢键受体、阳离子部分或阴离子部分。如果部分在生理上相关的pH(如pH 6、7、7.4或8)下在水性溶液中将被离子化,则可以认为所述部分是阳离子或阴离子的。

[0196] 在一些实施方案中,免疫刺激部分是佐剂。在一些实施方案中,佐剂包括病原体相关分子模式(PAMP)。在一些实施方案中,佐剂是Toll样受体(TLR)激动剂,或干扰素基因刺激物(STING)激动剂。在一些实施方案中,佐剂激活B和/或T细胞中的TLR信号传导。在一些实施方案中,佐剂调节适应性免疫应答。

a) TLR2激动剂

[0197] 在一些实施方案中,免疫刺激部分是TLR2激动剂。在一些实施方案中,免疫刺激部分刺激TLR2信号传导。在一些实施方案中,免疫刺激部分是TLR2的合成小分子配体。在一些实施方案中,免疫刺激部分是TLR2信号传导的合成小分子激动剂。

[0198] 在一些实施方案中,TLR2激动剂是PAM2CSK4、FSL-1或PAM3CSK4。

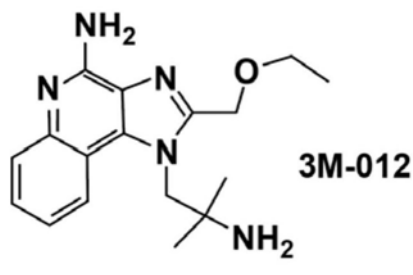
b) TLR7/8激动剂

[0199] 在一些实施方案中,免疫刺激部分是TLR7和/或TLR8激动剂(即,TLR7和TLR8中至少一者的激动剂)。在一些实施方案中,免疫刺激部分刺激TLR7和/或TLR8信号传导。在一些实施方案中,免疫刺激部分是TLR7和/或TLR8的合成小分子配体。在一些实施方案中,免疫刺激部分是TLR7和/或TLR8信号传导的合成小分子激动剂。

[0200] 在一些实施方案中,TLR7和/或TLR8激动剂是单链的(ssRNA)。在一些实施方案中,TLR7和/或TLR8激动剂是咪唑并喹啉。在一些实施方案中,TLR7和/或TLR8激动剂是核苷类似物。

[0201] 在一些实施方案中,TLR7和/或TLR8激动剂是咪唑并喹啉胺Toll样受体(TLR)激动

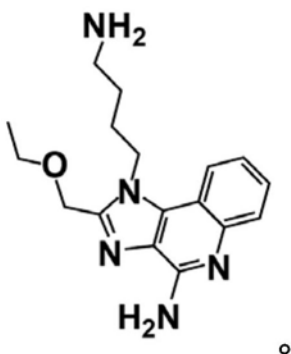
剂, 如 3M-012 (3M Pharmaceuticals)。游离 3M-012 的结构是:



应当理解的是, 可以通过以下方式将免疫刺激部分 (如 3M-

012) 或本文所讨论的任何部分缀合至铁蛋白: 用与本文所述的铁蛋白例如在表面暴露的半胱氨酸的硫处的键或与附接至这个硫的接头的键取代所述部分的适当的外围原子 (例如氢)。因此, 当缀合至铁蛋白时, 免疫刺激部分的结构将与游离分子的结构略有不同。

[0202] 在一些实施方案中, TLR7 和/或 TLR8 激动剂是 SM 7/8a。游离 SM 7/8a 的结构是:



[0203] 参见, 例如 Nat Biotechnol. 2015 年 11 月; 33 (11): 1201-10. doi:10.1038/nbt.3371。

c) TLR9 激动剂

[0204] 在一些实施方案中, 免疫刺激部分是 TLR9 激动剂。在一些实施方案中, 免疫刺激部分刺激 TLR9 信号传导。在一些实施方案中, 免疫刺激部分是 TLR9 的合成小分子配体。在一些实施方案中, 免疫刺激部分是 TLR9 信号传导的合成小分子激动剂。

[0205] 在一些实施方案中, TLR9 激动剂是 CpG 寡脱氧核苷酸 (ODN)。在一些实施方案中, TLR9 激动剂是未甲基化的 CpG ODN。在一些实施方案中, CpG ODN 包含部分或完整的硫代磷酸酯 (PS) 主链, 而不是普通 DNA 中发现的天然磷酸二酯 (PO) 主链。

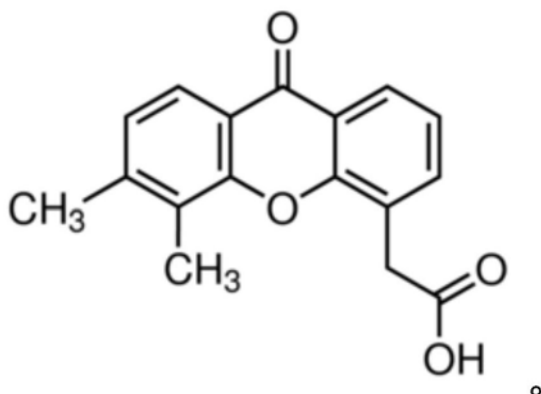
[0206] 在一些实施方案中, CpG ODN 是 B 类 ODN, 其包含一个或多个含有 5' 嘌呤 (Pu) - 嘧啶 (Py) - C-G-Py-Pu 3' 的 6 聚体 CpG 基序; 具有完全硫代磷酸化 (即 PS 改性) 的主链; 并且长度为 18-28 个核苷酸。在一些实施方案中, CpG ODN 包含 SEQ ID NO: 210 的序列, 任选地包含在主链中的硫代磷酸酯连接。

[0207] 在一些实施方案中, TLR9 激动剂包含免疫刺激序列 (ISS)。在一些实施方案中, TLR9 激动剂是 ISS-1018 (Dynavax) (SEQ ID NO: 210)。

d) STING 激动剂

[0208] 在一些实施方案中, 免疫刺激部分是 STING (干扰素基因蛋白的刺激物, 也称为内质网 IFN 刺激物) 激动剂。在一些实施方案中, 免疫刺激部分刺激 STING 信号传导。在一些实施方案中, 免疫刺激部分是 STING 的合成小分子配体。在一些实施方案中, 免疫刺激部分是 STING 信号传导的合成小分子激动剂。

[0209] 在一些实施方案中,STING激动剂是环状二核苷酸(CDN)。参见,例如Danilchanka等人,Cell 154:962-970 (2013)。示例性CDN包括cdA、cdG、cAMP-cGMP和2'-5',3'-5'cGAMP (对于结构,参见Danilchanka等人)。STING激动剂还包括合成激动剂,如DMXAA



2. 缀合的EBV多肽

[0210] 在一些实施方案中,EBV多肽缀合至铁蛋白的表面暴露的氨基酸。在一些实施方案中,EBV多肽使铁蛋白具有抗原性。在一些实施方案中,EBV多肽单独地具有抗原性,而在一些实施方案中,EBV多肽由于其与铁蛋白的缔合而具有抗原性。在一些实施方案中,EBV多肽是本文所述的任一种EBV多肽。

3. 缀合

[0211] 在一些实施方案中,表面暴露的半胱氨酸(例如,由本文所述的突变产生)或附接至铁蛋白(例如,在铁蛋白的N末端)的肽接头中的半胱氨酸用于将免疫刺激部分(如佐剂)或EBV多肽缀合至铁蛋白。在一些实施方案中,接头与这种半胱氨酸缀合,可以随后将所述接头缀合至免疫刺激部分(如佐剂)或EBV多肽。在一些实施方案中,这种半胱氨酸产生用于缀合反应以附接佐剂、接头或EBV多肽的化学处理。在一些实施方案中,产生了生物缀合物,其中在还原这种半胱氨酸后将免疫刺激部分(如佐剂)或EBV多肽连接至铁蛋白。在一些实施方案中,半胱氨酸是不成对的表面暴露的半胱氨酸,即所述半胱氨酸缺乏适当位置的伴侣半胱氨酸来形成二硫键。在一些实施方案中,半胱氨酸是包含游离硫醇侧链的不成对半胱氨酸。

a) 缀合化学的类型

[0212] 可以使用任何类型的化学,例如经由表面暴露的氨基酸(如半胱氨酸)或另一种氨基酸(如Lys、Glu或Asp)的反应,来将免疫刺激部分(如佐剂)或EBV多肽缀合至铁蛋白。

[0213] 在一些实施方案中,使用点击化学进行缀合。如本文所用,“点击化学”是指彼此快速且选择性地反应(即,“点击”)的一对官能团之间的反应。在一些实施方案中,点击化学可以在温和的水性条件下进行。在一些实施方案中,点击化学反应利用铁蛋白表面上的半胱氨酸(如由表面暴露的氨基酸突变产生的半胱氨酸)来使用可与所述半胱氨酸反应的官能团进行点击化学。

[0214] 满足点击化学标准的多种反应在本领域中是已知的,并且本领域技术人员可以使用许多公布的方法中的任何一种(参见,例如Hein等人,Pharm Res 25 (10):2216-2230 (2008))。可以使用众多种可商购的点击化学试剂,如来自Sigma Aldrich、Jena Bioscience或Lumiprobe的那些。在一些实施方案中,如以下实施例所述那样使用点击化

学进行缀合。

[0215] 在一些实施方案中,点击化学反应在铁蛋白还原之后发生。

[0216] 在一些实施方案中,点击化学可以是1步式点击反应。在一些实施方案中,点击化学可以是2步式点击反应。

[0217] 在一些实施方案中,一个或多个反应包括无金属点击化学。在一些实施方案中,一个或多个反应包括硫醇-马来酰亚胺和/或二硫化物交换。

无金属点击化学

[0218] 可以将无金属点击化学用于缀合反应以避免蛋白质的潜在氧化。无金属点击化学已被用于形成抗体缀合物(参见van Geel等人,Bioconjugate Chem.2015,26,2233-2242)。

[0219] 在一些实施方案中,在反应中使用无金属点击化学以将佐剂附接至铁蛋白。在一些实施方案中,在反应中使用无铜缀合以将佐剂附接至铁蛋白。在一些实施方案中,无金属点击化学使用双环[6.1.0]壬炔(BCN)。在一些实施方案中,无金属点击化学使用二苯并氮杂环辛炔(DBCO)。在一些实施方案中,BCN或DBCO与叠氮化物基团反应。

[0220] DBCO在不存在催化剂的情况下经由应变促进的点击反应对叠氮化物基团具有高特异性,从而产生高产率的稳定三唑。在一些实施方案中,DBCO在不存在铜催化剂的情况下与叠氮化物反应。

[0221] 在一些实施方案中,在1步式点击反应中使用无金属点击化学。在一些实施方案中,在2步式点击反应中使用无金属点击化学。

硫醇-马来酰亚胺和二硫化物交换

[0222] 本文所述的铁蛋白可以包含含有硫醇(也称为巯基)的半胱氨酸,其可用于与巯基反应性化学基团反应(或其可通过还原而变为可用的)。因此,半胱氨酸允许化学选择性修饰以将免疫刺激部分(如佐剂)添加至铁蛋白。在碱性条件下,半胱氨酸将被去质子化以产生硫醇盐亲核体,所述硫醇盐亲核体可以与软亲电体(如马来酰亚胺和碘乙酰胺)反应。半胱氨酸与马来酰亚胺或碘乙酰胺的反应产生碳-硫键。

[0223] 在一些实施方案中,巯基反应性化学基团与铁蛋白的表面暴露的半胱氨酸或铁蛋白接头中的半胱氨酸反应。在一些实施方案中,巯基反应性化学基团是卤代乙酰基、马来酰亚胺、氮丙啶、丙烯酰基、芳基化剂、乙烯基砜、吡啶基二硫化物或TNB-硫醇。

[0224] 在一些实施方案中,巯基反应性化学基团通过烷基化(即形成硫醚键)与半胱氨酸的巯基缀合。在一些实施方案中,巯基反应性化学基团通过二硫化物交换(即形成二硫键)与半胱氨酸的巯基缀合。

[0225] 在一些实施方案中,将免疫刺激部分(如佐剂)缀合至铁蛋白的反应是硫醇-马来酰亚胺反应。

[0226] 在一些实施方案中,巯基反应性化学基团是马来酰亚胺。在一些实施方案中,马来酰亚胺与半胱氨酸的反应导致形成稳定的硫酯连接,例如不可逆的硫酯连接。在一些实施方案中,马来酰亚胺不与铁蛋白中的酪氨酸、组氨酸或甲硫氨酸反应。在一些实施方案中,未反应的马来酰亚胺在反应结束时通过添加例如过量的游离硫醇来淬灭。

[0227] 在一些实施方案中,使免疫刺激部分(如佐剂)与铁蛋白缀合的反应是硫醇-二硫化物交换,也称为二硫化物互换。在一些实施方案中,反应涉及形成包含一部分原始二硫化物的混合二硫化物。在一些实施方案中,原始二硫化物是通过表面暴露的氨基酸的突变或N

末端接头的添加而在铁蛋白中引入的半胱氨酸。

[0228] 在一些实施方案中, 巯基反应性化学基团是吡啶基二硫醇。在一些实施方案中, 巯基反应性化学基团是TNB-硫醇基团。

b) 接头

[0229] 在一些实施方案中, 免疫刺激部分 (如佐剂) 或EBV多肽经由与表面暴露的氨基酸 (如半胱氨酸) 共价结合的接头附接至铁蛋白。在一些实施方案中, 接头包含聚乙二醇, 例如PEG接头。在一些实施方案中, 聚乙二醇 (例如PEG) 接头增加了与免疫刺激部分 (如佐剂) 连接的铁蛋白的水溶性和连接效率。PEG接头的长度在2至18个PEG之间, 例如PEG4、PEG5、PEG6、PEG7、PEG8、PEG9、PEG10、PEG11、PEG12、PEG13、PEG14、PEG15、PEG16、PEG17和PEG18。

[0230] 在一些实施方案中, 接头包含马来酰亚胺。在一些实施方案中, 接头包含免疫刺激部分 (ISM) - 接头 - 马来酰亚胺的组分。在一些实施方案中, 通过马来酰亚胺与铁蛋白的半胱氨酸的反应, 以1步式点击化学反应将ISM-接头-马来酰亚胺缀合至铁蛋白。在一些实施方案中, 佐剂-接头-马来酰亚胺的ISM是SM7/8a。在一些实施方案中, ISM-接头-马来酰亚胺的接头是PEG4。在一些实施方案中, ISM-接头-马来酰亚胺是SM7/8a-PEG4-马来酰亚胺。

[0231] 在一些实施方案中, 用下述接头使用2步式点击化学方案, 所述接头在一端包含巯基反应性化学基团, 并且在另一端包含胺反应性基团。在这种2步式点击化学方案中, 巯基反应性化学基团与铁蛋白的半胱氨酸反应, 而胺反应性基团与附接至ISM的试剂反应。以这种方式, ISM经由一组2种点击化学试剂缀合至铁蛋白。

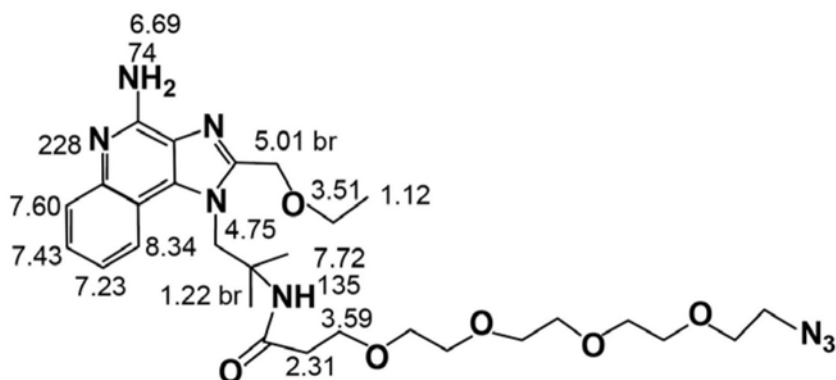
[0232] 在2步式点击化学方案的一些实施方案中, 巯基反应性化学基团是马来酰亚胺。在2步式点击化学方案的一些实施方案中, 马来酰亚胺与通过表面暴露的氨基酸的突变或N末端接头的添加而引入铁蛋白中的半胱氨酸反应。

[0233] 在2步式点击化学方案的一些实施方案中, 胺反应性基团是DBC0。在2步式点击化学方案的一些实施方案中, DBC0与附接至ISM的叠氮化物基团反应。

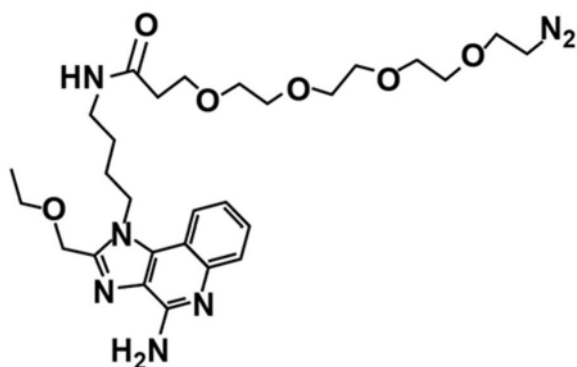
[0234] 在一些实施方案中, 使用马来酰亚胺-接头-DBC0。在一些实施方案中, 在铁蛋白还原后, 将马来酰亚胺-接头-DBC0缀合至铁蛋白。在一些实施方案中, 通过在这第一步中马来酰亚胺与铁蛋白的半胱氨酸的反应, 将马来酰亚胺-接头-试剂缀合至铁蛋白。在一些实施方案中, DBC0用于与附接至叠氮化物的ISM连接。在一些实施方案中, 偶联至叠氮化物的ISM是ISS-1018。在一些实施方案中, 偶联至叠氮化物的佐剂是3M-012或CpG。

[0235] 在一些实施方案中, 将具有反应性基团的接头添加至ISM。在一些实施方案中, 接头是PEG4-叠氮化物接头或PEG4-马来酰亚胺接头。

[0236] 在一些实施方案中, PEG4-叠氮化物接头缀合至3M-012。缀合至PEG4-叠氮化物接头的3M-012的示例性结构为:

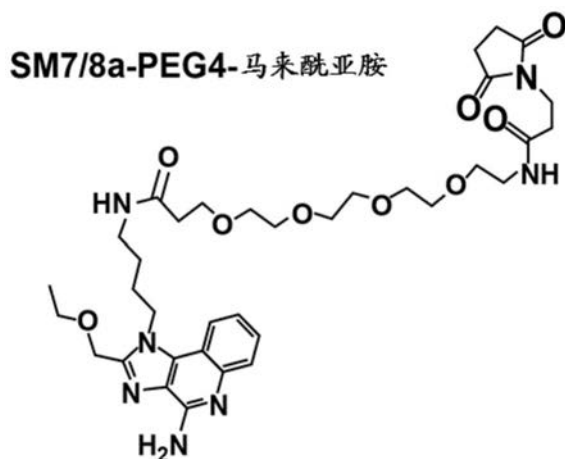


[0237] 在一些实施方案中,PEG4-叠氮化物接头缀合至SM7/8a。缀合至PEG4-叠氮化物接头的SM7/8a的示例性结构为:



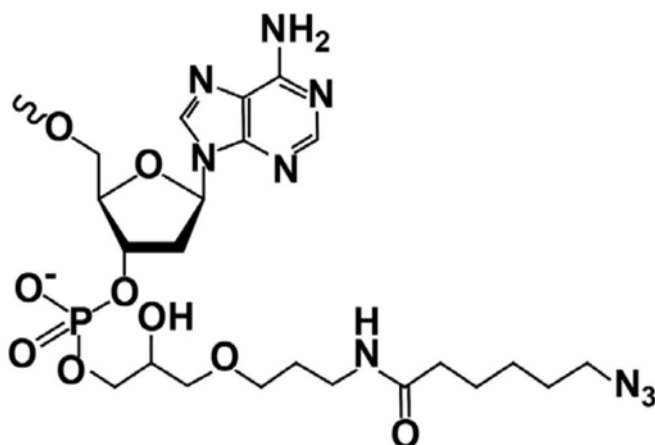
SM7/8a-PEG4-叠氮化物

[0238] 在一些实施方案中,PEG4-马来酰亚胺接头缀合至SM7/8a。缀合至PEG4-马来酰亚胺接头的SM7/8a的示例性结构为:



SM7/8a-PEG4-马来酰亚胺

[0239] 在一些实施方案中,叠氮化物基团缀合至ISS-1018。缀合至NHS酯-叠氮化物接头的ISS-1018的示例性结构为:



I. 示例性组合物、试剂盒、核酸、用途和方法

[0240] 在一些实施方案中,本发明提供了针对EBV感染免疫受试者的方法。本发明进一步提供了在受试者中引发针对EBV的免疫应答的方法。在一些实施方案中,本方法包括向受试者给予有效量的本文所述的药物组合物。在一些实施方案中,本方法包括向受试者给予有效量的本文所述的抗原性EBV多肽或纳米颗粒。

[0241] 在一些实施方案中,提供了组合物,所述组合物包含本文所述的抗原性EBV多肽中的任何一种或多种和药学上可接受的媒介物、佐剂或赋形剂。

[0242] 在一些实施方案中,将本文所述的抗原性EBV多肽、纳米颗粒或组合物给予至受试者(如人或下文所讨论的任一种受试者),以针对由EBV引起的感染进行免疫。在一些实施方案中,将本文所述的抗原性EBV多肽或纳米颗粒给予至受试者(如人),以产生针对将来的EBV感染的保护性免疫应答。在一些实施方案中,给予了抗原性EBV多肽。在一些实施方案中,给予了包含EBV多肽和铁蛋白的抗原性EBV多肽,其中铁蛋白可以具有本文所述的一个或多个突变。在一些实施方案中,给予了包含SEQ ID NO:1-27中任一个的抗原性EBV多肽或纳米颗粒。

[0243] 在一些实施方案中,保护性免疫应答降低了住院的发生率。在一些实施方案中,保护性免疫应答降低了EBV感染、单核细胞增多症、由单核细胞增多症引起的并发症(例如肝炎、脑炎、重度溶血性贫血或脾肿大)、鼻咽癌、胃癌或B淋巴瘤(例如伯基特淋巴瘤或霍奇金淋巴瘤)的发生率。

[0244] 在一些实施方案中,组合物包含一种抗原性EBV多肽(例如,单价组合物)。在一些实施方案中,组合物包含含有gH多肽的抗原性EBV多肽。在一些实施方案中,组合物包含含有gL多肽的抗原性EBV多肽。在一些实施方案中,组合物包含含有gp220多肽的抗原性EBV多肽。

[0245] 在一些实施方案中,组合物包含多于一种抗原性EBV多肽。在一些实施方案中,组合物包含含有多于一种由EBV编码的多肽的一种或多种抗原性EBV多肽(即,多价组合物)。在一些实施方案中,EBV疫苗包含含有gp220多肽的纳米颗粒,以及单独的含有gH和gL多肽的纳米颗粒。

[0246] 在一些实施方案中,提供了本文所述的抗原性EBV多肽、纳米颗粒或组合物中的任何一种或多种,用于在针对由EBV引起的感染免疫中使用。在一些实施方案中,提供了本文所述的多肽、纳米颗粒或组合物中的任何一种或多种,用于在产生针对将来的EBV感染的保

护性免疫应答中使用。

1. 受试者

[0247] 在一些实施方案中,受试者是哺乳动物。在一些实施方案中,受试者是人。

[0248] 在一些实施方案中,受试者是成人(大于或等于18岁)。在一些实施方案中,受试者是儿童或青少年(小于18岁)。在一些实施方案中,受试者是老年人(大于60岁)。在一些实施方案中,受试者是非老年人(大于或等于18岁且小于或等于60岁)。

[0249] 在一些实施方案中,将组合物适当地配制用于预期的给予途径。合适的给予途径的例子包括肌内、经皮、皮下、鼻内、口服或透皮。

[0250] 在一些实施方案中,向受试者给予多于一次的组合物给予。在一些实施方案中,加强免疫给予改善了免疫应答。

[0251] 在一些实施方案中,本文所述的抗原性多肽或组合物中的任何一种或多种用于在哺乳动物,如灵长类动物(例如,非人灵长类动物,如猴子(例如,猕猴,如恒河猴或食蟹猴)或猿)、啮齿动物(例如,小鼠或大鼠)或驯养的哺乳动物(例如,犬、兔、猫、马、绵羊、牛、山羊、骆驼或驴)中使用。

2. 佐剂

[0252] 可以将佐剂与本文所述的抗原性EBV多肽和/或纳米颗粒一起给予至受试者,其中与在不伴有佐剂的情况下的一种或多种EBV多肽给予相比,这种组合的给予可以在受试者中产生更高效价的针对一种或多种EBV多肽的抗体。佐剂可以促进对一种或多种EBV多肽的更早、更强效或更持久的免疫应答。

[0253] 在一些实施方案中,组合物包含一种佐剂。在一些实施方案中,组合物包含多于一种佐剂。在一些实施方案中,组合物不包含佐剂。

[0254] 在一些实施方案中,佐剂包含铝。在一些实施方案中,佐剂是磷酸铝。在一些实施方案中,佐剂是明矾(Alyhydrogel' 85 2%;Brenntag-目录号21645-51-2)。

[0255] 在一些实施方案中,佐剂是有机佐剂。在一些实施方案中,佐剂是油基佐剂。在一些实施方案中,佐剂是水包油纳米乳剂。

[0256] 在一些实施方案中,佐剂包含角鲨烯。在一些实施方案中,包含角鲨烯的佐剂是Ribi(Sigma adjuvant system目录号S6322-1vl)、AddavaxTM MF59、AS03或AF03(参见US9703095)。在一些实施方案中,包含角鲨烯的佐剂是纳米乳剂。

[0257] 在一些实施方案中,佐剂包含聚丙烯酸聚合物(PAA)。在一些实施方案中,包含PAA的佐剂是SPA09(参见WO 2017218819)。

[0258] 在一些实施方案中,佐剂包含非可代谢油。在一些实施方案中,佐剂是不完全弗氏佐剂(IFA)。

[0259] 在一些实施方案中,佐剂包含非可代谢油和杀死的结核分枝杆菌。在一些实施方案中,佐剂是完全弗氏佐剂(CFA)。

[0260] 在一些实施方案中,佐剂是脂多糖。在一些实施方案中,佐剂是单磷酸A(MPL或MPLA)。

3. 药物组合物

[0262] 在各种实施方案中,提供了药物组合物,所述药物组合物包含本文所述的抗原性EBV多肽和/或相关实体。在一些实施方案中,药物组合物是能够引发免疫应答(如针对病原

体的保护性免疫应答)的免疫原性组合物(例如,疫苗)。

[0263] 例如,在一些实施方案中,药物组合物可以包含以下项中的一种或多种:(1)抗原性EBV多肽,所述抗原性EBV多肽包含EBV多肽和铁蛋白,所述铁蛋白含有用半胱氨酸置换表面暴露的氨基酸的突变;(2)抗原性EBV多肽,所述抗原性EBV多肽包含EBV多肽和铁蛋白,所述铁蛋白含有用半胱氨酸置换表面暴露的氨基酸的突变和连接至所述半胱氨酸的免疫刺激部分;(3)抗原性EBV多肽,所述抗原性EBV多肽包含EBV多肽和铁蛋白,所述铁蛋白含有(i)表面暴露的半胱氨酸,(ii)在铁蛋白蛋白的N末端的肽接头,其中EBV多肽在肽接头的N末端;(4)抗原性EBV多肽,所述抗原性EBV多肽包含EBV多肽和铁蛋白,所述铁蛋白含有(i)用半胱氨酸置换表面暴露的氨基酸的突变和连接至所述半胱氨酸的免疫刺激部分,(ii)用非半胱氨酸氨基酸置换在幽门螺杆菌铁蛋白的位置31处的内部半胱氨酸的突变,或用非半胱氨酸氨基酸置换如通过成对或结构比对确定的非幽门螺杆菌铁蛋白中与位置31类似的位置处的内部半胱氨酸的突变,和(iii)用非天冬酰胺氨基酸置换表面暴露的天冬酰胺的突变;或(5)包含前述多肽中的任一种的铁蛋白颗粒。在一些实施方案中,药物组合物可以包含抗原性EBV gL/gH多肽,例如,其中多肽在gL与gH多肽序列之间包含至少15个氨基酸的接头。

[0264] 在一些实施方案中,本发明提供了药物组合物,所述药物组合物包含与本文所述的抗原性多肽相关的抗体或其他药剂。在一个实施方案中,药物组合物包含与本文所述的抗原性多肽结合和/或竞争的抗体。可替代地,抗体可以识别包含本文所述的抗原性多肽的非铁蛋白多肽组分的病毒颗粒或细菌。

[0265] 在一些实施方案中,将如本文所述的药物组合物单独给予或与一种或多种增强免疫应答的药剂(例如,以上所述的佐剂)组合给予。在一些实施方案中,药物组合物进一步包含如上所述的佐剂。

[0266] 在一些实施方案中,药物组合物进一步包含药学上可接受的载体或赋形剂。如本文所用,术语“载体”是指与药物组合物一起给予的稀释剂、佐剂、赋形剂或媒介物。在示例性实施方案中,载体可以包括无菌液体,例如像水和油,包括石油、动物、植物或合成起源的油,例如像花生油、大豆油、矿物油、芝麻油等。在一些实施方案中,载体是或包括一种或多种固体组分。药学上可接受的载体还可包括但不限于盐水、缓冲盐水、右旋糖、甘油、乙醇及其组合。如本文所用,赋形剂是可以包含在药物组合物中例如以提供或有助于所希望的稠度或稳定作用的任何非治疗剂。合适的药物赋形剂包括但不限于淀粉、葡萄糖、乳糖、蔗糖、明胶、麦芽、稻、面粉、白垩、硅胶、硬脂酸钠、单硬脂酸甘油酯、滑石、氯化钠、脱脂乳粉、甘油、丙烯、二醇、水、乙醇等。在各种实施方案中,药物组合物是无菌的。

[0267] 在一些实施方案中,药物组合物含有少量的润湿剂或乳化剂、或pH缓冲剂。在一些实施方案中,药物组合物可以包含多种添加剂(如稳定剂、缓冲液或防腐剂)中的任何一种。此外,可以包含辅助剂、稳定剂、增稠剂、润滑剂和着色剂。

[0268] 在各种实施方案中,可以将药物组合物配制成适合任何所期望的给予方式。例如,药物组合物可以采取以下形式:溶液、悬浮液、乳剂、滴剂、片剂、丸剂、球剂、胶囊、含有液体的胶囊、明胶胶囊、粉末、缓释配制品、栓剂、乳剂、气雾剂、喷雾剂、悬浮液、冻干粉、冷冻悬浮液、干燥粉或任何其他适合使用的形式。在药剂的配制和生产中的一般考虑可以见于例如Remington's Pharmaceutical Sciences,第19版,Mack Publishing Co.,宾夕法尼亚州

伊斯顿,1995(通过引用并入本文)中。

[0269] 可以经由任何给予途径来给予药物组合物。给予途径包括例如口服、皮内、肌内、腹膜内、静脉内、皮下、鼻内、粘膜、硬膜外、舌下、鼻内、脑内、阴道内、透皮、经直肠、通过气管内滴注、支气管滴注、吸入、或局部方式。给予可为局部或全身的。在一些实施方案中,给予是口服进行的。在另一个实施方案中,给予是通过肠胃外注射。在一些情况下,给予导致本文所述的抗原性铁蛋白多肽释放到血流中。给予方式可以由从业者决定。

[0270] 在一些实施方案中,药物组合物适合于肠胃外给予(例如静脉内、肌内、腹膜内和皮下)。可以将此类组合物配制成例如溶液、悬浮液、分散体、乳剂等。它们也可以以无菌固体组合物(例如冻干的组合物)的形式生产,所述无菌固体组合物可以在临使用前溶解或悬浮于无菌可注射介质中。例如,肠胃外给予可以通过注射来实现。在此类实施方案中,注射剂以常规形式制备,即作为液体溶液或悬浮液、适合于在注射前溶解或悬浮于液体中的固体形式、或作为乳剂。在一些实施方案中,注射溶液和悬浮液由无菌粉末、冻干粉末或颗粒制备。

[0271] 在另一个实施方案中,将药物组合物配制成用于通过吸入递送(例如,用于直接递送至肺和呼吸系统)。例如,组合物可以采取鼻喷雾剂或任何其他已知的气雾剂配制品的形式。在一些实施方案中,用于吸入或气雾剂递送的制剂包含多个颗粒。在一些实施方案中,此类制剂可以具有约1、约2、约3、约4、约5、约6、约7、约8、约9、约10、约11、约12或约13微米的平均粒度。在一些实施方案中,用于吸入或气雾剂递送的制剂被配制为干粉。在一些实施方案中,用于吸入或气雾剂递送的制剂例如通过包含润湿剂而被配制为湿粉。在一些实施方案中,润湿剂选自水、盐水或其他处于生理pH的液体。

[0272] 在一些实施方案中,将根据本发明的药物组合物以滴剂的形式给予至鼻腔或颊腔。在一些实施方案中,剂量可以包含多滴(例如1-100、1-50、1-20、1-10、1-5滴等)。

[0273] 可以将本发明的药物组合物以适合于实现所期望结果的任何剂量给予。在一些实施方案中,所期望的结果是诱导针对病原体的持久的适应性免疫应答,所述病原体如存在于组合物中的抗原性铁蛋白多肽中的非铁蛋白多肽的来源。在一些实施方案中,所期望的结果是降低一种或多种感染症状的强度、严重程度、频率和/或延迟一种或多种感染症状的发作。在一些实施方案中,所期望的结果是抑制或预防感染。所需的剂量将根据以下而在受试者之间有所不同:受试者的物种、年龄、体重和一般状况,被预防或治疗的感染的严重程度,所使用的特定组合物及其给予方式。

[0274] 在一些实施方案中,将根据本发明的药物组合物以单一剂量或多个剂量给予。在一些实施方案中,将药物组合物在不同日期以多个剂量给予(例如初免-加强免疫疫苗接种策略)。在一些实施方案中,将药物组合物作为加强免疫方案的一部分给予。

[0275] 在各种实施方案中,将药物组合物与一种或多种另外的治疗剂共同给予。如果治疗剂的给予的时间安排使得另外的治疗剂和药物组合物中的一种或多种活性成分的药理活性在时间上重叠,从而发挥组合的治疗作用,则共同给予不需要同时给予治疗剂。通常,每种药剂将以针对所述药剂确定的剂量和时间表来给予。

4. 核酸/mRNA

[0276] 还提供了核酸,所述核酸编码本文所述的抗原性EBV多肽。在一些实施方案中,核酸是mRNA。出于本公开文本的目的,任何能够经历翻译而产生多肽的核酸被认为是mRNA。

5. 试剂盒

[0277] 本文还提供了试剂盒,所述试剂盒包括本文所述的一种或多种抗原性EBV多肽、核酸、抗原性铁蛋白颗粒、抗原性2,4-二氧四氢嘧啶合酶颗粒、组合物或药物组合物。在一些实施方案中,试剂盒进一步包括溶剂、溶液、缓冲液、说明书或干燥剂中的一种或多种。

[0278] ***

[0279] 此描述和示例性实施方案不应被视为是限制性的。为了本说明书和所附权利要求的目的,除非另有指示,否则在说明书和权利要求中使用的所有表达数量、百分比或比例的数字和其他数值应被理解为在所有情况下被术语“约”修饰至已无法将其如此修饰的程度。“约”指示实质上不影响所述主题的特性的变化程度,例如在10%、5%、2%或1%之内。因此,除非有相反的指示,否则以下说明书和所附权利要求中阐述的数值参数是近似值,所述近似值可以根据试图获得的所需特性而变化。在最低限度并且不试图限制对权利要求范围的等价范围的原则的应用,每个数值参数均应当至少考虑报告的有效数字的数量和通过应用普通四舍五入技术来解读。

[0280] 注意,如本说明书和所附权利要求所用,单数形式“一个/种(a、an)”和“所述(the)”以及任何词语的任何单数使用包括复数个指示物,除非明确地并且清楚地限于一个/种指示物。如本文所用,术语“包括”及其语法变体旨在是非限制性的,使得列表中项目的详述不排除可以取代或添加到所列项目的其他类似项目。除非上下文另有指示,否则术语“或”以包括性含义使用,即等同于“和/或”。

SIB 7379 前导序列 gL(D7) ₋ 接头_gH 三聚体	<u>KCSQAVAGEPRQIPKI QNFTRTKSCIFCGFALLSYDEKEGLETTT</u><u>YTSQEQVNSILSNFYDFDNLHVHVL</u><u>LLTTNGTVMIEIAGLYEERA</u><u>SGGSGSGS</u> <u>GGSGSGSGSGS</u><u>QVRQFSDIEKLNEQVNKEMQSNLYMSMSWSYTHSLDGAGLFLDHAABEYEHAKKLIIFLNENNVPVQLTISISAPHEKTEGLT</u> <u>QIFQKAYEHEQHS</u><u>ENINIVDHAIKCKDHATNFWLQWYFAQHEEEVLFDKILDKIELIGNENHGLYLADQYVKGI</u><u>AKSRKS</u> <u>MRVGVFLAI</u><u>CLVTIFVLTPTWGNWAYPCCHVTQLRQAQHLALALENISDIYLVSNQTCDFGSLASLNSPKNGSNQLVIRSANGLN</u><u>VVSVFFSILKRSSS</u><u>ALTG</u> <u>HLRELLTTLETLYGFSFVEDLFGANLN</u><u>RGGSGSGS</u><u>ASGASGASGSGSGSGS</u><u>AAASLSEVKHLHIDIEGHASHYTIPTWTELM</u> <u>AKVPGLSPEAL</u><u>REANVTEDLASMLNRYKLIYKTS</u><u>GTGLGIALAEPVDIPAVSEGS</u><u>QMVDAKSVHPGVI</u><u>SGLNSPACML</u><u>SAPLEKQLFYI</u><u>GTML</u><u>ENTRPHSY</u> <u>VFYQLRCHLSYVALS</u><u>INGDKFYQTGAMTSKFLMGTVKRVT</u><u>EGDEHVL</u><u>SLVFGTKDLPDLRGPFSY</u><u>PSLTS</u><u>QAQSGDY</u><u>SLVITVTFVHYANFHN</u><u>FVFNPKD</u> <u>MF</u><u>SRAMVT</u><u>TAAS</u><u>YARYVLQKLVILEMKG</u><u>CCREPELDTETL</u><u>TMFEV</u><u>SVAFFKVG</u><u>HAVGETGNCVDLRWLAKS</u><u>FFELTVLKD</u><u>IIGICYGATV</u><u>KGMQSYGLER</u> <u>LAAMIMATV</u><u>KMEELGHL</u><u>LTTEKQEYALRLATVGY</u><u>PKAGVY</u><u>SLIGGATSVLLSAYNRHPLFQPLH</u><u>IVMRETLF</u><u>IGSHVVL</u><u>RELRLNVTTCQPNL</u><u>YQLLS</u><u>TA</u> <u>IC</u><u>SALET</u><u>IGEV</u><u>LRGLALG</u><u>TESGLF</u><u>SPCYLSIR</u><u>FDLTRDKLL</u><u>SMAPQEA</u><u>TLDOAAV</u><u>SN</u><u>AVDGF</u><u>GLRLSLEREDRD</u><u>AHMLPAYK</u><u>CDVRDL</u><u>KVIMI</u><u>IPLIN</u><u>VTFI</u> <u>SSDREVRG</u><u>SALYEASTTYLSS</u><u>SLFSPVIMNKCSQ</u><u>QAVAGEPRQIPKI QNFTRTKSCIFCGFALLSYDEKEGLETTT</u><u>YTSQEQVNSILSNFYDFDNLHV</u> <u>HYLLLTNGTVMIEIAGLYEERA</u><u>SGSGYI</u><u>PEAPRDQ</u><u>AYVRKDG</u><u>EWLLSTFLGSGSGSLVPRGSGAGGGHHHHH</u>	4
SIB 7380 前导序列 gL(D7) ₋ 接头_gH 三聚体	<u>METD</u><u>TLLWL</u><u>VL</u><u>LLW</u><u>VP</u><u>GS</u><u>TGNWAYPCCHVTQLRQAQHLALALENISDIYLVSNQTCDFGSLASLNSPKNGSNQLVIRSANGLN</u><u>VVSVFFSILKRSSS</u><u>ALTGHL</u> <u>RELLTTLETLYGFSFVEDLFGANLN</u><u>RGGSGSGS</u><u>ASGASGASGSGSGSGS</u><u>AAASLSEVKHLHIDIEGHASHYTIPTWTELM</u><u>AKVPGLSPEAL</u><u>REANVTEDLASMLNRYKLI</u> <u>YKTS</u><u>GTGLGIALAEPVDIPAVSEGS</u><u>QMVDAKSVHPGVI</u><u>SGLNSPACML</u><u>SAPLEKQLFYI</u><u>GTML</u><u>ENTRPHSY</u><u>VFYQLRCHLSYVALS</u><u>INGDKFYQTGAMTSK</u> <u>FMGT</u><u>YKRVT</u><u>EGDEHVL</u><u>SLVFGTKDLPDLRGPFSY</u><u>PSLTS</u><u>QAQSGDY</u><u>SLVITVTFVHYANFHN</u><u>FVFNPKD</u><u>MF</u><u>SRAMVT</u><u>TAAS</u><u>YARYVLQKLVILEMKG</u> <u>CCREPELDTETL</u><u>TMFEV</u><u>SVAFFKVG</u><u>HAVGETGNCVDLRWLAKS</u><u>FFELTVLKD</u><u>IIGICYGATV</u><u>KGMQSYGLER</u><u>LAAMIMATV</u><u>KMEELGHL</u><u>LTTEKQEYALRLATV</u> <u>GYPKAGVY</u><u>SLIGGATSVLLSAYNRHPLFQPLH</u><u>IVMRETLF</u><u>IGSHVVL</u><u>RELRLNVTTCQPNL</u><u>YQLLS</u><u>TA</u> <u>IC</u><u>SALET</u><u>IGEV</u><u>LRGLALG</u><u>TESGLF</u><u>SPCYLSIR</u><u>FDLTRDKLL</u><u>SMAPQEA</u><u>TLDOAAV</u><u>SN</u><u>AVDGF</u><u>GLRLSLEREDRD</u><u>AHMLPAYK</u><u>CDVRDL</u><u>KVIMI</u><u>IPLIN</u><u>VTFI</u> <u>SSDREVRG</u><u>SALYEASTTYLSS</u><u>SLFSPVIMNKCSQ</u><u>QAVAGEPRQIPKI QNFTRTKSCIFCGFALLSYDEKEGLETTT</u><u>YTSQEQVNSILSNFYDFDNLHV</u> <u>HYLLLTNGTVMIEIAGLYEERA</u><u>SGSGYI</u><u>PEAPRDQ</u><u>AYVRKDG</u><u>EWLLSTFLGSGSGSLVPRGSGAGGGHHHHH</u>	5
SIB 7381 前导序列 gL(D7) ₋ 接头_gH 单体	<u>MRVGVFLAI</u><u>CLVTIFVLTPTWGNWAYPCCHVTQLRQAQHLALALENISDIYLVSNQTCDFGSLASLNSPKNGSNQLVIRSANGLN</u><u>VVSVFFSILKRSSS</u><u>ALTG</u> <u>HLRELLTTLETLYGFSFVEDLFGANLN</u><u>RGGSGSGS</u><u>ASGASGASGSGSGSGS</u><u>AAASLSEVKHLHIDIEGHASHYTIPTWTELM</u> <u>AKVPGLSPEAL</u><u>REANVTEDLASMLNRYKLIYKTS</u><u>GTGLGIALAEPVDIPAVSEGS</u><u>QMVDAKSVHPGVI</u><u>SGLNSPACML</u><u>SAPLEKQLFYI</u><u>GTML</u><u>ENTRPHSY</u> <u>VFYQLRCHLSYVALS</u><u>INGDKFYQTGAMTSKFLMGTVKRVT</u><u>EGDEHVL</u><u>SLVFGTKDLPDLRGPFSY</u><u>PSLTS</u><u>QAQSGDY</u><u>SLVITVTFVHYANFHN</u><u>FVFNPKD</u> <u>MF</u><u>SRAMVT</u><u>TAAS</u><u>YARYVLQKLVILEMKG</u><u>CCREPELDTETL</u><u>TMFEV</u><u>SVAFFKVG</u><u>HAVGETGNCVDLRWLAKS</u><u>FFELTVLKD</u><u>IIGICYGATV</u><u>KGMQSYGLER</u> <u>LAAMIMATV</u><u>KMEELGHL</u><u>LTTEKQEYALRLATVGY</u><u>PKAGVY</u><u>SLIGGATSVLLSAYNRHPLFQPLH</u><u>IVMRETLF</u><u>IGSHVVL</u><u>RELRLNVTTCQPNL</u><u>YQLLS</u><u>TA</u> <u>IC</u><u>SALET</u><u>IGEV</u><u>LRGLALG</u><u>TESGLF</u><u>SPCYLSIR</u><u>FDLTRDKLL</u><u>SMAPQEA</u><u>TLDOAAV</u><u>SN</u><u>AVDGF</u><u>GLRLSLEREDRD</u><u>AHMLPAYK</u><u>CDVRDL</u><u>KVIMI</u><u>IPLIN</u><u>VTFI</u> <u>SSDREVRG</u><u>SALYEASTTYLSS</u><u>SLFSPVIMNKCSQ</u><u>QAVAGEPRQIPKI QNFTRTKSCIFCGFALLSYDEKEGLETTT</u><u>YTSQEQVNSILSNFYDFDNLHV</u> <u>HYLLLTNGTVMIEIAGLYEERA</u><u>SGSGSGSLVPRGSGAGGGHHHHH</u>	6
SIB 7382 前导序列 gL(D7) ₋ 接头_gH 单体	<u>METD</u><u>TLLWL</u><u>VL</u><u>LLW</u><u>VP</u><u>GS</u><u>TGNWAYPCCHVTQLRQAQHLALALENISDIYLVSNQTCDFGSLASLNSPKNGSNQLVIRSANGLN</u><u>VVSVFFSILKRSSS</u><u>ALTGHL</u> <u>RELLTTLETLYGFSFVEDLFGANLN</u><u>RGGSGSGS</u><u>ASGASGASGSGSGSGS</u><u>AAASLSEVKHLHIDIEGHASHYTIPTWTELM</u><u>AKVPGLSPEAL</u><u>REANVTEDLASMLNRYKLI</u> <u>YKTS</u><u>GTGLGIALAEPVDIPAVSEGS</u><u>QMVDAKSVHPGVI</u><u>SGLNSPACML</u><u>SAPLEKQLFYI</u><u>GTML</u><u>ENTRPHSY</u><u>VFYQLRCHLSYVALS</u><u>INGDKFYQTGAMTSK</u> <u>FMGT</u><u>YKRVT</u><u>EGDEHVL</u><u>SLVFGTKDLPDLRGPFSY</u><u>PSLTS</u><u>QAQSGDY</u><u>SLVITVTFVHYANFHN</u><u>FVFNPKD</u><u>MF</u><u>SRAMVT</u><u>TAAS</u><u>YARYVLQKLVILEMKG</u> <u>CCREPELDTETL</u><u>TMFEV</u><u>SVAFFKVG</u><u>HAVGETGNCVDLRWLAKS</u><u>FFELTVLKD</u><u>IIGICYGATV</u><u>KGMQSYGLER</u><u>LAAMIMATV</u><u>KMEELGHL</u><u>LTTEKQEYALRLATV</u> <u>GYPKAGVY</u><u>SLIGGATSVLLSAYNRHPLFQPLH</u><u>IVMRETLF</u><u>IGSHVVL</u><u>RELRLNVTTCQPNL</u><u>YQLLS</u><u>TA</u> <u>IC</u><u>SALET</u><u>IGEV</u><u>LRGLALG</u><u>TESGLF</u><u>SPCYLSIR</u><u>FDLTRDKLL</u><u>SMAPQEA</u><u>TLDOAAV</u><u>SN</u><u>AVDGF</u><u>GLRLSLEREDRD</u><u>AHMLPAYK</u><u>CDVRDL</u><u>KVIMI</u><u>IPLIN</u><u>VTFI</u> <u>SSDREVRG</u><u>SALYEASTTYLSS</u><u>SLFSPVIMNKCSQ</u><u>QAVAGEPRQIPKI QNFTRTKSCIFCGFALLSYDEKEGLETTT</u><u>YTSQEQVNSILSNFYDFDNLHV</u> <u>HYLLLTNGTVMIEIAGLYEERA</u><u>SGSGSGSLVPRGSGAGGGHHHHH</u>	7
SIB 7392 前导序列 gL(D7) ₋ 接头_gH 单体	<u>MRVGVFLAI</u><u>CLVTIFVLTPTWGNWAYPCCHVTQLRQAQHLALALENISDIYLVSNQTCDFGSLASLNSPKNGSNQLVIRSANGLN</u><u>VVSVFFSILKRSSS</u><u>ALTG</u> <u>HLRELLTTLETLYGFSFVEDLFGANLN</u><u>R</u><u>YAMHRRGGSGSGS</u><u>ASGASGASGSGSGS</u><u>NSASGASGSGSGSGS</u><u>GAASLSEVKHLHIDIEGHASHYTIPTWTE</u>	8

[illegible]

SIB 7404 前导序列 g _L -接头 g _H bfpFerr 纳米颗粒 N19Q/C31S/SI11C	D F D N L H V H Y L I L T T G T V M E I A G L Y E A R S G S G Y I P E A P R D Q A Y V R K D G E W L L S T F L G S G S G S G L V P R G S G A G G G H H H H H H M R A V G F L A I C L V T I F V L P T W G N W A Y P C C H V T Q L R A Q H L L A L E N I S D I Y L V S N Q T C D G F S L A S L N S P K N G S N Q L V I S R C A N G L N V V S F F I S I L K R S S S A L T G H L R E L L T T L E T L Y G S F S V E D L F G A N L N R Y A W H R G G G S G S A S S C A S G S G S G S G A A S L S E V K L H L D I E G H A S H Y T I P W T E L M A K V P G L S P E A L W R W R E A N V T D L A S M N R Y K L I Y K T S G T L G I A L A E P V D I P A V S E G S M Q V D A S K V H P G V I S G L N S P A C M L S A P L E K Q L F Y Y I G T M L P N T R P H S Y V F Y Q L R C H L S Y V A L S I N G D K F Q Y T G A M T S K F I M G T K R V T E K G D E H V L S V F G K T K O L P D L R G P F S Y P S L T S A Q S G D Y S L V I T F V H Y A N F H N Y F V P N L K D M F S R A V T M T A A S Y A R Y V L Q K L V L E M K G C R E P E L D T E T L T M F E V S V A F F K V G H A V E T G N G C V D L R W L A K S F F E L T V L K D I I G I C Y G A T V K G M Q S Y G L E R L A A M L M A T V K M E E L G H L T T E K Q E Y A I R L A T V G Y P K A G V Y S G L I G G A T S V L L S A Y N R H P L F Q P L H T V M R E T L F I G S H V V L R E L N V T T Q G P N L A Y Q L L S T A L C S A L E I G E V L R G L A L G T E S G L F S P C Y L S I R F D L T R D K L L S M A P Q E A T L D Q A A V S N A V D G F L G R L S L E R E D R D A W H L P A Y K C V D R L D K V I M I P L I N V T F I I S S D R E V R G S A L Y E A S T T Y L S S L F S P V I M N K C S Q A V A G E P R Q I P K I Q N F T R T Q K S C I F C G F A L L S Y D E K E G L E T T T Y I T S Q E V Q N S I L S S N Y F D F D N L H V H Y L I L T T N G T V M E I A G L Y E A R S G S G S G S G S G S G S Q V R Q Q F S K D I E K L I N E Q V N K M Q S N L Y M S M S W S Y T H S L D G A G L F L F D H A A E E Y E H A K K L I I F L N E N N V P V Q L T S I S A P E H K F E G L T Q I F O K A Y E H E Q H I S E S I N N I V D H A I K C K D H A T F N F L Q W T V A E Q H E E E V L F K D I L D K I E L I G N E N H G L Y L A D Q Y V K G I A K S R K S	13
SIB 7406 前导序列 g _L -接头 g _H bfpFerr 纳米颗粒 N19Q/C31S/SI11C	M R A V G F L A I C L V T I F V L P T W G N W A Y P C C H V T Q L R A Q H L L A L E N I S D I Y L V S N Q T C D G F S L A S L N S P K N G S N Q L V I S R C A N G L N V V S F F I S I L K R S S S A L T G H L R E L L T T L E T L Y G S F S V E D L F G A N L N R Y A W H R G G G S G S A S S G A S G S S N G S G S G S S A S S G A S S G S G S G A A S L S E V K L H L D I E G H A S H Y T I P W T E L M A K V P G L S P E A L W R E A N V T D L A S M N R Y K L I Y K T S G T L G I A L A E P V D I P A V S E G S M Q V D A S K V H P G V I S G L N S P A C M L S A P L E K Q L F Y Y I G T M L P N T R P H S Y V F Y Q L R C H L S Y V A L S I N G D K F Q Y T G A M T S K F I M G T K R V T E K G D E H V L S V F G K T K O L P D L R G P F S Y P S L T S A Q S G D Y S L V I T F V H Y A N F H N Y F V P N L K D M F S R A V T M T A A S Y A R Y V L Q K L V L E M K G C R E P E L D T E T L T M F E V S V A F F K V G H A V E T G N G C V D L R W L A K S F F E L T V L K D I I G I C Y G A T V K G M Q S Y G L E R L A A M L M A T V M E E L G H L T T E K Q E Y A I R L A T V G Y P K A G V Y S G L I G G A T S V L L S A Y N R H P L F Q P L H T V M R E T L F I G S H V V L R E L N V T T Q G P N L A Y Q L L S T A L C S A L E I G E V L R G L A L G T E S G L F S P C Y L S I R F D L T R D K L L S M A P Q E A T L D Q A A V S N A V D G F L G R L S L E R E D R D A W H L P A Y K C V D R L D K V I M I P L I N V T F I I S S D R E V R G S A L Y E A S T T Y L S S S L F S P V I M N K C S Q A V A G E P R Q I P K I Q N F T R T Q K S C I F C G F A L L S Y D E K E G L E T T T Y I T S Q E V Q N S I L S S N Y F D F D N L H V H Y L I L T T G T V M E I A G L Y E A R S G S G S G S G S G S G S Q V R Q Q F S K D I E K L I N E Q V N K M Q S N L Y M S M S W S Y T H S L D G A G L F L F D H A A E E Y E H A K K L I I F L N E N N V P V Q L T S I S A P E H K F E G L T Q I F O K A Y E H E Q H I S E S I N N I V D H A I K C K D H A T F N F L Q W T V A E Q H E E E V L F K D I L D K I E L I G N E N H G L Y L A D Q Y V K G I A K S R K S	14
SIB 7414 前导序列 g _L -接头 g _H 单体	M E T D T L L W L L V L L W P G S T W A Y P C C H V T Q L R A Q H L L A L E N I S D I Y L V S N Q T C D G F S L A S L N S P K N G S N Q L V I S R C A N G L N V V S F F I S I L K R S S S A L T G H L R E L L T T L E T L Y G S F S V E D L F G A N L N R Y A W H R G G G S G S G S G S G S G A A S L S E V K L H L D I E G H A S H Y T I P W T E L M A K V P G L S P E A L W R E A N V T D L A S M L N R Y K L I Y K T S G T L G I A L A E P V D I P A V S E G S M Q V D A S K V H P G V I S G L N S P A C M L S A P L E K Q L F Y Y I G T M L P N T R P H S Y V F Y Q L R C H L S Y V A L S I N G D K F Q Y T G A M T S K F I M G T K R V T E K G D E H V L S V F G K T K O L P D L R G P F S Y P S L T S A Q S G D Y S L V I T F V H Y A N F H N Y F V P N L K D M F S R A V T M T A A S Y A R Y V L Q K L V L L E K M G G C R E P E L D T E T L T M F E V S V A F F K V G H A V E T G N G C V D L R W L A K S F F E L T V L K D I I G I C Y G A T V K G M Q S Y G L E R L A A M L M A T V M E E L G H L T T E K Q E Y A L R L A T V G Y P K A G V Y S G L I G G A T S V L L S A Y N R H P L F Q P L H T V M R E T L F I G S H V V L R E L N V T T Q G P N L A Y Q L L S T A L C S A L E I G E V L R G L A L G T E S G L F S P C Y L S I R F D L T R D K L L S M A P Q E A T L D Q A A V S N A V D G F L G R L S L E R E D R D A W H L P A Y K C V D R L D K V I M I P L I N V T F I I S S D R E V R G S A L Y E A S T T Y L S S S L F L S P V I M N K C S Q A V A G E P R Q I P K I Q N F T R T Q K S C I F C G F A L L S Y D E K E G L E T T T Y I T S Q E V Q N S I L S S N Y F D F D N L H V H Y L I L T T N G T V M E I A G L Y E A R S G S G S G S G L V P R G S G A G G G H H H H H H	15
SIB 7429 前导序列 g _L -接头 g _H -三聚体	M E T D T L L W L L V L L W P G S T W A Y P C C H V T Q L R A Q H L L A L E N I S D I Y L V S N Q T C D G F S L A S L N S P K N G S N Q L V I S R C A N G L N V V S F F I S I L K R S S S A L T G H L R E L L T T L E T L Y G S F S V E D L F G A N L N R Y A W H R G G G S G S G S G S G S G A A S L S E V K L H L D I E G H A S H Y T I P W T E L M A K V P G L S P E A L W R E A N V T D L A S M L N R Y K L I Y K T S G T L G I A L A E P V D I P A V S E G S M Q V D A S K V H P G V I S G L N S P A C M L S A P L E K Q L F Y Y I G T M L P N T R P H S Y V F Y Q L R C H L S Y V A L S I N G D K F Q Y T G A M T S K F I M G T K R V T E K G D E H V L S V F G K T K O L P D L R G P F S Y P S L T S A Q S G D Y S L V I T F V H Y A N F H N Y F V P N L K D M F S R A V T M T A A S Y A R Y V L Q K L V L L E K M G G C R E P E L D T E T L T M F E V S V A F F K V G H A V E T G N G C V D L R W L A K S F F E L T V L K D I I G I C Y G A T V K G M Q S Y G L E R L A A M L M A T V M E E L G H L T T E K Q E Y A L R L A T V G Y P K A G V Y S G L I G G A T S V L L S A Y N R H P L F Q P L H T V M R E T L F I G S H V V L R E L N V T T Q G P N L A Y Q L L S T A L C S A L E I G E V L R G L A L G T E S G L F S P C Y L S I R F D L T R D K L L S M A P Q E A T L D Q A A V S N A V D G F L G R L S L E R E D R D A W H L P A Y K C V D R L D K V I M I P L I N V T F I I S S D R E V R G S A L Y E A S T T Y L S S S L F L S P V I M N K C S Q A V A G E P R Q I P K I Q N F T R T Q K S C I F C G F A L L S Y D E K E G L E T T T Y I T S Q E V Q N S I L S S N Y F D F D N L H V H Y L I L T T N G T V M E I A G L Y E A R S G S G S G S G L V P R G S G A G G G H H H H H H	16
SIB 15000 前导序列 g _L -接头 g _H -三聚体	G Y I P E A P R D Q A Y V R K D G E W L L S T F L G S G S G S G L V P R G S G A G G G H H H H H H M R A V G F L A I C L V T I F V L P T W G N W A Y P C C H V T Q L R A Q H L L A L E N I S D I Y L V S N Q T C D G F S L A S L N S P K N G S N Q L V I S R C A N G L N V V S F F I S I L K R S S S A L T G H L R E L L T T L E T L Y G S F S V E D L F G A N L N R Y A W H R G G G S G S A E A A A A A A K A G S G S G S G A A S L S E V K L H L D I E G H A S H Y T I P W T E L M A K V P G L S P E A L W R	17

[illegible]

[illegible]

[illegible]

示例性 gH 多肽	GANLNRYAWHRGG AASLSEVKLHLDIEGHASHYTIPTWTELMKAVPGLSPEALWREANVTEDLASMLNRYKLIYKTSCTGLIALAEPVDIPAVSEGSQVMDASKVHPGVI SGLNSP ACMLSAPLEKQLFYIYGTMLPNTRPHSVFYQURCHLSVVALSINGDKFQGTGAMTSKFLMGTYKRVTEKGDHVLVLVFGTKTKDLPDLRGPFSPYSLTSAQ SGDYSIVITVTFVHYANFHNYPVNLKDMFSRAVTMTAAS YARYVLQKVLLEMKGCCREPELDTETLTMTFEVSVAFFKVGHAVGETGNGCVDLRWLAKSF FELTVLKDIIIGICYGATVKGMSYGLERLAAMLMATVMEELGHILTTEKQYALRAVGYPKAGVSYGLIGGATSVLLSAYNNRHPLFQPLHTVMRETILFIG SHVVLRELNVTTQGNLALYQLLSTALCSALEIGEVLRLGALGTESGLSPCYLSLRFDLTRDKLLSMAPQEAETLDQAAVSNVAVDGLFGLRLSLEREDRDA WHLPAYKCVDRDLKVLMI I PLINVTFIISSDREVRGSALYEASTYLSLSSFLSPVIMNKCSQCAVAGEPRQIPKI QNFTRTQKSCIFCGFALLSYDEKEGL ETTYIITSQEVQNSILSSNYFDFDNLHVHYLLLTNGTMEIAGLYEERA	37
示例性 gp220 多肽	EAALLVCQYTIQSLIHLTGEDPGFFNVVEIPEFFPYPTCNVCTADVNTINFDVGGKKHQLDLDFGQLTPHTKAVYQPRGAFGGSENATNLFLELLGAGELA LTMRSKKLPINVTGEEQQVSLSESDVYFQDVFGTMMCHHAEMQNVPYLI PETVPYIKWDCNCSNTITAVVRAQGLDVTPLSLPTSAQDSNFSVKTEMLGN EIDIECIMEDGEISQVLPQDNKENITCSGYESHVPSGGILTSTSPVATPIPGTGAYLSRLTRPVPVSRFLGNNLSILYVFGNGPKASGGDYICIQSNIVFSD EIPASQDMPTNTTIDITYVGDNATYSVPMVTSSEDANS PNVTVTAFWAWPNNTETDFKCKWLTSTGTPSGCENISGAFASNRTFDITVSGLGTAPKTLIIITRTA TNATTTTHKVIFSKAPE	38
半胱氨酸-凝血酶- His 接头	CLVPRGSLHHHHHH	39
风产液菌(株系 VF5) 的 2,4-二氧四氮嘧啶 合酶	MQIYEGKLTAEGLRFGIVASRFNHALVDRLEGAIDCIVRHGGREDDITLVRVPSGWEIPVAAGELARKEDIDAVIAIGVLIRGATPHFDYIASEVSKGLAN LSLELRKPITFGVITADTLEQAIERAGTKHGNKGWEAALSAIEMANLFKSLR	40
大肠杆菌 6,7-二甲基 -8-核糖基 2,4-二氧四 氮嘧啶合酶	MNIIEANVATPDARVAITIARFNNFINDSLLEGAIDLAKRIGQVKDENITVWVPGAYELPLAAGALAKTGKYDAVIALGTVIRGGTAHFEYVAGGASNGLA HVAQDSEIPVAFGLVTESIEQAIERAGTKAGNKGAEEALTALEMINVLKAIKA	41
	Not Used	42-200
bfp 铁蛋白 - N19Q/C31S/S26C	ESQVRQQFSKDIKLLNEQVNMKQSNLYMCSWSYTHSLDAGLFLFDHAAEYEHAKKLIIFLNENNVVQVLTSSIAPEHKFEGLTQIFQKAYEHEQH ISESINNIVDHAIKSKDHATFNFLQWYVAEQHEEEVLFDKILDKIELIGNENHGLYLADQYVKGIAKSRKS	201
bfp 铁蛋白 - N19Q/C31S/S72C	ESQVRQQFSKDIKLLNEQVNMKQSNLYMCSWSYTHSLDAGLFLFDHAAEYEHAKKLIIFLNENNVVQVLTSSIAPEHKFEGLTQIFQKAYEHEQH ISESINNIVDHAIKSKDHATFNFLQWYVAEQHEEEVLFDKILDKIELIGNENHGLYLADQYVKGIAKSRKS	202
bfp 铁蛋白 - N19Q/C31S/A75C	ESQVRQQFSKDIKLLNEQVNMKQSNLYMCSWSYTHSLDAGLFLFDHAAEYEHAKKLIIFLNENNVVQVLTSSIAPEHKFEGLTQIFQKAYEHEQH ISESINNIVDHAIKSKDHATFNFLQWYVAEQHEEEVLFDKILDKIELIGNENHGLYLADQYVKGIAKSRKS	203
bfp 铁蛋白 - N19Q/C31S/K79C	ESQVRQQFSKDIKLLNEQVNMKQSNLYMCSWSYTHSLDAGLFLFDHAAEYEHAKKLIIFLNENNVVQVLTSSIAPEHKFEGLTQIFQKAYEHEQH ISESINNIVDHAIKSKDHATFNFLQWYVAEQHEEEVLFDKILDKIELIGNENHGLYLADQYVKGIAKSRKS	204
bfp 铁蛋白 - N19Q/C31S/S100C	ESQVRQQFSKDIKLLNEQVNMKQSNLYMCSWSYTHSLDAGLFLFDHAAEYEHAKKLIIFLNENNVVQVLTSSIAPEHKFEGLTQIFQKAYEHEQH ISESINNIVDHAIKSKDHATFNFLQWYVAEQHEEEVLFDKILDKIELIGNENHGLYLADQYVKGIAKSRKS	205
bfp 铁蛋白 - N19Q/C31S/S111C	ESQVRQQFSKDIKLLNEQVNMKQSNLYMCSWSYTHSLDAGLFLFDHAAEYEHAKKLIIFLNENNVVQVLTSSIAPEHKFEGLTQIFQKAYEHEQH ISESINNIVDHAIKSKDHATFNFLQWYVAEQHEEEVLFDKILDKIELIGNENHGLYLADQYVKGIAKSRKS	206
bfp 铁蛋白 - N19Q/C31S/E12C	ESQVRQQFSKDIKLLNEQVNMKQSNLYMCSWSYTHSLDAGLFLFDHAAEYEHAKKLIIFLNENNVVQVLTSSIAPEHKFEGLTQIFQKAYEHEQH ISESINNIVDHAIKSKDHATFNFLQWYVAEQHEEEVLFDKILDKIELIGNENHGLYLADQYVKGIAKSRKS	207
具有牛痘接头的示例 性幽门螺杆菌铁蛋白	ESQVRQQFSKDIKLLNEQVNMKQSNLYMCSWSYTHSLDAGLFLFDHAAEYEHAKKLIIFLNENNVVQVLTSSIAPEHKFEGLTQIFQKAYEHEQH ISESINNIVDHAIKSKDHATFNFLQWYVAEQHEEEVLFDKILDKIELIGNENHGLYLADQYVKGIAKSRKS	208
示例性野生型幽门螺 杆菌铁蛋白	LSKDIIKLLNEQVNMKQSNLYMCSWSYTHSLDAGLFLFDHAAEYEHAKKLIIFLNENNVVQVLTSSIAPEHKFEGLTQIFQKAYEHEQHISESINN IVDHAIKSKDHATFNFLQWYVAEQHEEEVLFDKILDKIELIGNENHGLYLADQYVKGIAKSRKS	209

(GenBank 登录号 AAD06160.1)(没有牛蛙接头或 N 末端 Met)		
CpG(1SS-1018)	TGACTGTGAACGTTCCGAGATGA	210
粉纹夜蛾重链铁蛋白	TQCNVNPVQIPKDWITMHRSCNRMRQQIQMEVGRSLQYLAMGAHFSKDVNPPGFAQLFFDAASEEREHAMKLI EYLLMRGELTNDVSSLLQVRPPTRSSW KGGVEALEHALSMESDVTKSIRNVIKACEDDSEFN DYHLVDYLTGTDFLEEQYKQORDLAGKASTIKKLMRHEALGEF IFDKLLGIDV	211
粉纹夜蛾轻链铁蛋白	ADTCYNDVALDCGITSNSIALPRCNAVYGEYSGHGNVATELQAYAKLHLERSYDYLLSAAFYNNYQTNRAGFSKLFKKLSDEAWSKTIDI IKHVTKRGDQMN FDQHSTMKTERKNYTAENHELEALAKALDTQKELAPAFYIHTREATNSQHLHDPEIAQYLEEEFIEDHAEKIRTLAGHTSDLKFFTANNGHDL SLALYVF DEYLQKTV	212
激烈火球菌铁蛋白	MLSERMLKALNDQLNRELYSAYLYFAMAAYFEDLGLGEGFANWKAQAE EEEIGHALRFYNY IYDRNGRVELDEIPKPKEWESPLKAFEAAYEHKFI SKSYELAAEAEEKDYSTRAFL EWFINEQVEEEASVKI LDKLFAKDSQI LFM LDKELSARAPKLPGLIMQGG E	213
人重链铁蛋白	MTTASTSQVRQNYHQDSEAAINRQINLELYASYVYLSMSYYFDRDDVALKNFAKYFLHQSHEEREHAEKLMKLQNRGGRIFLQDIKKPDCCDDWESGLNAME CALHLEKNVQSSLLLELHKLATDKNDPHLCDFIETHYLNEQVKAIKELGDHVTNLRKMGAPESGLAEYLFDKHTLGDSDQES	214
人轻链铁蛋白(信号肽以下划线表示)	MDSKGSQKGSRLLLLVVSNLLLPQGVLA SSI RQNYSTDVEAAVNSLVNLYLQASYTSLGFFYFDRDDVALEGVSHFFRELAEEKREGYERLLKMQNQR GGRALFQDIKKPAEDEWGTTPDAMKAAMALEKKLNQALLDLHALGSARTDPLCLDFLETHFLDEEVKLIKMGDHLTNLHRLGGPEAGLGEYLFERLTLLKHD	215
来自风产液菌(Aquifex aeolicus)的2,4-二氧四氮嘧啶合酶	MQIYEGKLTAEGLRFGIVASRFNHALVDRIVEGAIDCIVRHGGREEDITLVRVPGSWEIPVAAGELARKEDI DAVIAIGVLIRGATPHFDYIASEVSKGLAN LSLELRKPITFGVITADTLEQAIERAGTKHGNKGWEAALS AIEMANLFKSLR	216
牛蛙接头	ESQVRQQF	217
半胱氨酸-凝血酶-His 接头	CLVPRGSLEHHHHH	218
大肠杆菌 6,7-二甲基-8-核糖基 2,4-二氧四氮嘧啶合酶	MNII EANVATPDARVAIT IARFNNFINDSLLEGAIDALKRIGQVKDENITVVVWPGAYELPLAAGALAKTGKYDAVIALGTVIRGGTAHFYVAGGASNGLA HVAQDSEI PVAFGVLTTESIEQAIERAGTKAGNKGAFAALTALEMINVLKAIKA	219
16 个氨基酸的接头	GGGGSGGGSGGGSGG	220
28 个氨基酸的接头	GGSGSGSNSSASSGASGGASGGSGGGSG	221
46 个氨基酸的接头	GGSGSASGASASGSGSGSGSGSNSSASSGASGGASGGSGGGSG	222
FR1	GGSGSASAEAAAKEAAAKAGAGGGSGG	223
FR2	GGSGSASAEAAAKEAAAKEAAKASGGSGGGSG	224
47 个氨基酸的接头, 其包含用于缀合的 C	SGGGSGSASGASASGSSCSGSGSGSSSASSGASGGASGGSGGGSG	225
SIB 15007 gL/gH/gp42-His	MRVGVFLAICLVITFVLPTWGNWAYPCCHVTQLRAQHLLALENISDIYLVSNQTCDFGFSLASLNSPKNGSNQLVTSRCANGINVVSPFISILKRSSSALTG HLRELLTTLETTYGSFSVEDLFGANLNRVYAWHRGGSGSGSASGASGSGSNSSASSGASGGASGGSGGGSGAASLSEVKLHLIDIEGHASHYT	226

[illegible]

SIB 15011 gH/gL_gp42_NP_ C14	DFDNLHVHYLLLTNGTVMEIAGLYEERASGGSGSGSASSGASGSGSGSGSGSSASSGLAYFLPVRVGRGRVAAAAITWVPKPNVEVWPDVPPPVNF NKTAEQYEGDKEVKLPHTPTLHTFOVPQNYKANTCTNTREYTFYKGCFFYTKKHTWNGCFOACAEIYPCYTFYGPPTDILPVVTRNLNAIESLWVG VYRVGEGNWTSLDGGTFKVIYQIFGSHCTYVSKFSTVPVSHHESFLKPKCLCVSQRNSSEPEPEPEPGGSQVRQFSKDI EKLNEQVNKEMQSSNLVMS MSWSYTHSIDGAGLFLFDHAAEEYEHAKKLIIFLNENNVPVQLTISAPHEKFEGLTQIFQKAYEHEQHISESINNIVDHAICKDHATFNFLOWYVAEQH EEVLFKDILDKIELIGNENHGLYLADQYVKGIAKSRKS MRVGVFLAICLVITFVLPWGNWAYPCCHVTQLRAQHLLALENISDIYLVSNQTCDFSLASLNSPKNGSNQLVSRACANGLNVVVFFSILKRSSSALTG HLRELLTTLETLYGFSFVEDLFGANLNRYAMHRRGGSGSGSASSGASGSGSGSGSGSSASSGLAYFLPVRVGRGRVAAAAITWVPKPNVEVWPDVPPPVNF IPWTELMKVPGLSPEALMREANVTEDLASMLNRYKLIYKTSGLTGLIALAEPVDIPAVSEGSMDVASKVHPGVI SGLNSPACMLSAPLEKQIFYIIGTMLP NTRPHSYVYQLRAHLSYVALSINGDKFYQTGAMTSKFLMGTYKRVTEKGDHVL SVFGTKDLPDLRGPFSYPSLTSQAQSDYSIVITVTFVHYANFHN FVNLKDMFSRAVTMTAASYARYVLQKLVLEMKGGCREPELDTETLTMFEVSVAFFKVGHAVEGTNGCVDLRLWLAKSFFELTVLKDIIGICYGATVKG QSYGLERLAAMIMATVMEELGHLTTEKQYALRLATVGYPKAGVYSGLI GGATSVLLSAYNRHPLFQPLHTVMRETLFIGSHVVLRELRLNVTTOGPNLAL YQLLSTALCSALEIGEVLRGIALGTESGLFSPCYLSLRFDLTRDKLMSAPQEAATLDQAVSNVDFGLGRLSLEREDRDADHLPAYKCVDRDKVIMI IPL INVTFIISDREVRGSALYEASTTYLSSSLFSPVIMNKC SQAVAGEPROI PKI ONFTQKSCIFCGFALLSYDEKEGLETTITYITSOEQVNSILSSNYF DFDNLHVHYLLLTNGTVMEIAGLYEERASGGSGSGSASSGASGSGSGSGSGSSASSGLAYFLPVRVGRGRVAAAAITWVPKPNVEVWPDVPPPVNF NKTAEQYEGDKEVKLPHTPTLHTFOVPQNYKANTCTNTREYTFYKGCFFYTKKHTWNGCFOACAEIYPCYTFYGPPTDILPVVTRNLNAIESLWVG VYRVGEGNWTSLDGGTFKVIYQIFGSHCTYVSKFSTVPVSHHESFLKPKCLCVSQRNSSEPEPEPEPGGSQVRQFSKDI EKLNEQVNKEMQSSNLVMSMSWSYTH SLDGAGLFLFDHAAEEYEHAKKLIIFLNENNVPVQLTISAPHEKFEGLTQIFQKAYEHEQHISESINNIVDHAICKDHATFNFLOWYVAEQHEEEVLFKD ILDKIELIGNENHGLYLADQYVKGIAKSRKS	230
SIB 15012 gH/gL_gp42_NP_ C16	MDSKGSSQKSRLLILLVSNLLPQGVLAAMWAYPCCHVTQLRAQHLLALENISDIYLVSNQTCDFSLASLNSPKNGSNQLVSRACANGLNVVVFFSILK RSSSALTGHLRELLTTLETLYGFSFVEDLFGALNRYAMHRRGGSGSGSASSGASGSGSGSGSGSSASSGLAYFLPVRVGRGRVAAAAITWVPKPNVEVWPDVPPPVNF EGHASHYTPWTELLAKVPGLSPEALMREANVTEDLASMLNRYKLIYKTSGLTGLIALAEPVDIPAVSEGSMDVASKVHPGVI SGLNSPACMLSAPLEKQIFYIIGTMLP YYIGTMLPNTRPHSYVYQLRCHLSYVALSINGDKFYQTGAMTSKFLMGTYKRVTEKGDHVL SVFGTKDLPDLRGPFSYPSLTSQAQSDYSIVITVTFV HYANFHNYPVNLKDMFSRAVTMTAASYARYVLQKLVLEMKGGCREPELDTETLTMFEVSVAFFKVGHAVEGTNGCVDLRLWLAKSFFELTVLKDIIGICY YGATVKGMSYGLERLAAMIMATVMEELGHLTTEKQYALRLATVGYPKAGVYSGLI GGATSVLLSAYNRHPLFQPLHTVMRETLFIGSHVVLRELRLNVT TOGPNLALYQLLSTALCSALEIGEVLRGIALGTESGLFSPCYLSLRFDLTRDKLMSAPQEAATLDQAVSNVDFGLGRLSLEREDRDADHLPAYKCVDRDL KVIMI IPLINVTFIISDREVRGSALYEASTTYLSSSLFSPVIMNKC SQAVAGEPROI PKI ONFTQKSCIFCGFALLSYDEKEGLETTITYITSOEQV SILSSNYFDFDNLHVHYLLLTNGTVMEIAGLYEERASGGSGSGSASSGASGSGSGSGSGSSASSGLAYFLPVRVGRGRVAAAAITWVPKPNVEVWPDVPPPVNF KEVKLPHTPTLHTFOVPQNYKANTCTNTREYTFYKGCFFYTKKHTWNGCFOACAEIYPCYTFYGPPTDILPVVTRNLNAIESLWVG SLDGGTFKVIYQIFGSHCTYVSKFSTVPVSHHESFLKPKCLCVSQRNSSEPEPEPEPGGSQVRQFSKDI EKLNEQVNKEMQSSNLVMSMSWSYTH SASGSGSGSGSGSGSSASSGASGSGSGSGSGSGSSASSGLAYFLPVRVGRGRVAAAAITWVPKPNVEVWPDVPPPVNF ENNVVQLTISAPHEKFEGLTQIFQKAYEHEQHISESINNIVDHAICKDHATFNFLOWYVAEQHEEEVLFKDILDKIELIGNENHGLYLADQYVKGIAKSRKS	231
SIB 15013 gH/gL_例性_NP	MRVGVFLAICLVITFVLPWGNWAYPCCHVTQLRAQHLLALENISDIYLVSNQTCDFSLASLNSPKNGSNQLVSRACANGLNVVVFFSILKRSSSALTG HLRELLTTLETLYGFSFVEDLFGANLNRYAMHRRGGSGSGSASSGASGSGSGSGSGSSASSGLAYFLPVRVGRGRVAAAAITWVPKPNVEVWPDVPPPVNF IPWTELMKVPGLSPEALMREANVTEDLASMLNRYKLIYKTSGLTGLIALAEPVDIPAVSEGSMDVASKVHPGVI SGLNSPACMLSAPLEKQIFYIIGTMLP NTRPHSYVYQLRAHLSYVALSINGDKFYQTGAMTSKFLMGTYKRVTEKGDHVL SVFGTKDLPDLRGPFSYPSLTSQAQSDYSIVITVTFVHYANFHN FVNLKDMFSRAVTMTAASYARYVLQKLVLEMKGGCREPELDTETLTMFEVSVAFFKVGHAVEGTNGCVDLRLWLAKSFFELTVLKDIIGICYGATVKG QSYGLERLAAMIMATVMEELGHLTTEKQYALRLATVGYPKAGVYSGLI GGATSVLLSAYNRHPLFQPLHTVMRETLFIGSHVVLRELRLNVTTOGPNLAL YQLLSTALCSALEIGEVLRGIALGTESGLFSPCYLSLRFDLTRDKLMSAPQEAATLDQAVSNVDFGLGRLSLEREDRDADHLPAYKCVDRDKVIMI IPL INVTFIISDREVRGSALYEASTTYLSSSLFSPVIMNKC SQAVAGEPROI PKI ONFTQKSCIFCGFALLSYDEKEGLETTITYITSOEQVNSILSSNYF DFDNLHVHYLLLTNGTVMEIAGLYEERASGGSGSGSASSGASGSGSGSGSGSSASSGLAYFLPVRVGRGRVAAAAITWVPKPNVEVWPDVPPPVNF SSNLVMSMSWSYTHSLDGAGLFLFDHAAEEYEHAKKLIIFLNENNVPVQLTISAPHEKFEGLTQIFQKAYEHEQHISESINNIVDHAICKDHATFNFLOWYVAEQHEEEVLFKDILDKIELIGNENHGLYLADQYVKGIAKSRKS	232

[illegible]

实施例

[0281] 提供以下实施例以说明某些公开的实施方案,并且不应解释为以任何方式限制本

公开文本的范围。

1. 引发针对EBV的抗体的抗原性EBV多肽

[0282] 开发了引发针对EBV的抗体的抗原性多肽。开发了以单链展示EBV gL和gH多肽的自组装铁蛋白纳米颗粒,并评价了这些纳米颗粒在小鼠中的免疫原性。

[0283] 表达和纯化单体和三聚体gL/gH构建体。图1A示出了通过考马斯和蛋白质印迹(抗His)分析得出的单链gL和gH单体(SEQ ID NO:6)+/-His标签切割。图1B示出了以吸光度迹线并通过考马斯得出的gL和gH三聚体(SEQ ID NO:11)在Superose® SEC柱上的分级分离,以及确认由凝血酶蛋白酶进行的His标签切割的蛋白质印迹。对于SEQ ID NO:6构建体,样品的最终浓度为1mg/mL,总体积为15mL,并且内毒素水平为1.48EU/mL。

[0284] 表达和纯化了单链gL/gH铁蛋白纳米颗粒(SEQ ID NO:14)。图2A至2E示出了对其通过Superose® 6 SEC分级分离(2A)、SEC级分的考马斯(2B)、用抗铁蛋白一级Ab对SEC级分进行的蛋白质印迹(2C)、动态光散射(DLS, 2D)和电子显微镜(2E)进行的纯化和表征。

[0285] 融合至铁蛋白的单链EBV gL和gH的示例性构建体示出在图3中。用于免疫刺激部分(如tol1样受体7/8激动剂(TLR7/8a))的缀合位点可以存在于铁蛋白上或接头中(对于示例性序列,参见例如SEQ ID NO:14、19、22、20、23和33)。

[0286] 将具有不同接头的gL/gH三聚体或纳米颗粒注射至小鼠内,并评估免疫血清(图4)。在伴有佐剂AF03(一种基于角鲨烯乳剂的佐剂)的情况下,向小鼠给予两次2-μg注射液,在剂量之间间隔3周。在第6周通过ELISA测量抗gL/gH抗体终点效价。对于gH₁₆gL₁₆纳米颗粒(SEQ ID NO:10)优于三聚体构建体(SEQ ID NO:16)。gL₂₈gH₂₈纳米颗粒(SEQ ID NO:13)的表现与三聚体构建体(SEQ ID NO:11)没有显著不同。gL₄₆gH₄₆纳米颗粒(SEQ ID NO:14)优于gL₄₆gH₄₆三聚体(SEQ ID NO:12)。

[0287] 这些数据表明,单链gL/gH纳米颗粒可以引发针对EBV的稳健免疫应答。

2. 针对gL/gH和gp220的二价免疫

[0288] 使用包含单链gL/gH纳米颗粒和gp220纳米颗粒的组合物进行二价免疫。如通过使用来自如上所述进行疫苗接种的小鼠的血清进行ELISA结合测定所测量的,包括gp220纳米颗粒(SEQ ID NO:1)对由单链gL/gH纳米颗粒(gL-gH_{C5} NP[SEQ ID NO:19])引发的免疫应答无显著干扰作用。(图5A至5B,分别示出了在各个稀释度和结合效价下的测量值)。类似地,如通过ELISA所测量的,当与单链gL/gH纳米颗粒组合给予时,在对gp220纳米颗粒的免疫应答中没有观察到干扰(图6A至图6B,分别示出了在各个稀释度和结合效价下的测量值)。

[0289] 因此,用单链gL/gH纳米颗粒和gp220纳米颗粒二者免疫均不会降低对任一多肽的免疫应答。

3. 佐剂与铁蛋白纳米颗粒的缀合

[0290] 接下来,评估佐剂与铁蛋白纳米颗粒的缀合。图7A说明了构建体,其中铁蛋白包含用半胱氨酸置换表面暴露的氨基酸的突变,所述半胱氨酸可用于缀合。图7B示出了连接至PEG4接头和马来酰亚胺的示例性免疫刺激部分(SM7/8a, TLR-7/8激动剂)。此马来酰亚胺可用于将接头(自身附接至SM7/8a)共价缀合至铁蛋白的表面暴露的半胱氨酸。在图7C的电子显微照片中示出了包含融合至与SM7/8a缀合的铁蛋白的单链gL/gH多肽的多肽。

[0291] 在图8A中的铁蛋白分子结构中说明了由表面暴露的氨基酸突变产生的半胱氨酸。

在图8B中说明了通过并置铁蛋白、接头和CpG佐剂来将CpG佐剂 (SEQ ID NO:230) 缀合至铁蛋白,所述缀合被取向成显示每个部分的彼此邻近地附接的部分。

[0292] 使用2mM TCEP还原gL/gH纳米颗粒 (SEQ ID NO:19),然后经由添加1X PBS和使用100kD微旋柱去除TCEP来将其氧化。然后将SM7/8a与gL/gH纳米颗粒一起孵育以进行缀合。通过100kD微旋柱从反应中去除过量的SM7/8a。质谱 (MS) 数据表明,基于主MS峰相对于未缀合多肽的光谱的移位 (图9A),约100%的包含单链gL/gH和铁蛋白的多肽 (SEQ ID NO:19) 与SM7/8a缀合 (图9B)。缀合多肽与未缀合多肽的质量之差对应于SM7/8a-接头-马来酰亚胺加合物的分子量 (711Da)。

[0293] 使用2mM TCEP还原gp220纳米颗粒 (SEQ ID NO:1),然后经由添加1X PBS和使用100kD微旋柱去除TCEP来将所述纳米颗粒氧化。然后将SM7/8a与gL/gH纳米颗粒一起孵育以进行缀合。通过100kD微旋柱从反应中去除过量的SM7/8a。MS数据表明,基于主MS峰相对于未缀合多肽的光谱的移位 (图10A),约100%的包含gp220和铁蛋白的缀合多肽 (SEQ ID NO:1) 与SM7/8a缀合 (图10B)。

[0294] 电子显微镜 (EM) 数据还确认,SM7/8a与包含单链gL/gH和铁蛋白 (图11B,与图11A中的未缀合样品相比) 或包含gp220和铁蛋白 (图11D,与图11C中的未缀合样品相比) 的多肽的缀合未破坏纳米颗粒组装。

[0295] 在用1 μ g包含单链gL/gH的纳米颗粒 (gL_gH_C5 NP,图12A和图12B) 或包含gp220的纳米颗粒 (图13A和图13B) 免疫后,通过ELISA测定抗体应答。将纳米颗粒与1 μ g裸铁蛋白组合并且不缀合至或缀合至SM7/8a。在伴有或不伴有掺合的AF03佐剂的情况下给予未缀合的纳米颗粒。使每只小鼠接受100 μ L的如上所述的纳米颗粒组合物。对于接受AF03佐剂的小鼠,将1:1体积的AF03与纳米颗粒混合。将BALB/c小鼠 (n=5/组) 免疫两次,在剂量之间间隔3周。在第5周进行取血以用于ELISA分析。对于在AF03佐剂中给予的纳米颗粒,看到最稳健的ELISA应答。与不伴有佐剂的未缀合的纳米颗粒相比,与SM7/8a缀合产生更稳健的ELISA应答。

[0296] 与图14A至14B和图15A至15B中的伴有裸铁蛋白纳米颗粒的任一纳米颗粒的单一给予相比,还评估了各自1 μ g的与SM7/8a缀合的gL_gH_C5纳米颗粒和与SM7/8a缀合的gp220纳米颗粒的共同给予的作用。没有观察到对于对单链gL/gH (图14A至图14B,分别在不伴有和伴有AF03的情况下) 或gp220 (图15A至图15B,分别在不伴有和伴有AF03的情况下) 的免疫应答的干扰。

4. 长期免疫原性研究

[0297] 进行研究以评估在用包含单链gL/gH的纳米颗粒 (gL/gH_C5,SEQ ID NO:19) 给药后3个月时的免疫原性。将BALB/c小鼠 (n=5/组) 免疫两次,在剂量之间间隔3周。将裸铁蛋白 (即未与任何多肽或佐剂缀合的铁蛋白) 以1 μ g与1 μ g包含单链gL/gH的纳米颗粒一起给予,并在存在或不存在掺合的AF03佐剂的情况下配制纳米颗粒。在第13周进行取血以用于ELISA分析。对于接受AF03佐剂的小鼠,将1:1体积的AF03与纳米颗粒组合物混合。使每只小鼠接受100 μ L的上文所述的纳米颗粒组合物。使一些小鼠接受其中铁蛋白与SM7/8a (图16至图17中的“7/8a”) 缀合的包含单链gL/gH的纳米颗粒。

[0298] 如图16中所示,与SM7/8a缀合的包含单链gL/gH的纳米颗粒在AF03中配制时产生最大的免疫应答。对于不伴有AF03的这些纳米颗粒,也看到了稳健的免疫应答。

[0299] 使用gp220纳米颗粒 (SEQ ID NO:1) (伴有或不伴有与SM7/8a的缀合) 代替包含单链gL/gH的纳米颗粒进行了平行实验。对于这些纳米颗粒观察到相似的结果,其中包含掺合的AF03的配制品产生最稳健的应答,并且对于不伴有AF03的这些纳米颗粒也看到稳健的免疫应答 (图17)。

[0300] 评估了由包含含有单链gL/gH的纳米颗粒 (gL/gH_C5;SEQ ID NO:19) 和包含gp220的纳米颗粒 (SEQ ID NO:1) 的二价组合物引发的免疫应答。对BALB/c小鼠 (n=5/组) 进行免疫,在剂量之间间隔3周。给予100 μ L的含有1 μ g的每种纳米颗粒的纳米颗粒组合物。对于接受AF03佐剂的小鼠,将1:1体积的AF03与疫苗混合。进行终末期第13周取血以用于ELISA分析。对于针对单链gL/gH (图18) 和gp220 (图19) 二者的免疫应答,与任一纳米颗粒与裸铁蛋白的组合物相比,未看到由于纳米颗粒组合的给予而引起的干扰。

[0301] 使用gL/gH_C5纳米颗粒 (SEQ ID NO:19) 进行的进一步实验确认,当将纳米颗粒与SM7/8a (7/8a) 缀合时或在AF03中配制纳米颗粒时,可以看到长期免疫应答 (图21)。对BALB/c小鼠 (n=5/组) 进行免疫,在剂量之间间隔3周。给予100 μ L的含有1 μ g纳米颗粒的纳米颗粒组合物。对于接受AF03佐剂的小鼠,将1:1体积的AF03与疫苗混合。进行第2周 (初免)、第5周 (加强免疫) 和第13周 (终末期) 取血以用于ELISA分析。使用gp220纳米颗粒 (SEQ ID NO:1) 进行了平行实验,并且对于gp220纳米颗粒也看到了类似的长期应答 (图22)。

[0302] 还评估了包含单链gL/gH的不同纳米颗粒 (gL_gH_C7;SEQ ID NO:20)。gL_gH_C7构建体包含在gH多肽与铁蛋白之间的柔性接头,所述柔性接头具有半胱氨酸以作为免疫刺激部分的缀合位点。接头可以与缺乏表面暴露的半胱氨酸的铁蛋白 (如SEQ ID NO:20中所示) 一起使用。通过以下方式将SM7/8a缀合至gL_gH_C7:使用2mM TCEP还原蛋白质,然后通过添加1X PBS并使用100kD微旋柱去除TCEP来进行氧化。然后将SM7/8a与gL/gH纳米颗粒一起孵育。缀合后,通过100kD微旋柱从反应中去除过量的SM7/8a。

[0303] 使小鼠接受1 μ g的这些gL/gH纳米颗粒 (缀合至7/8a或未缀合) 加上1 μ g裸铁蛋白。给予100 μ L的含有1 μ g纳米颗粒的纳米颗粒组合物。对BALB/c小鼠 (n=5/组) 进行免疫,在剂量之间间隔3周。对于接受AF03佐剂的小鼠,将1:1体积的AF03与纳米颗粒组合物混合。进行第2周 (初免)、第5周 (加强免疫) 和第13周 (终末期) 取血以用于ELISA分析。如在初免取血时通过ELISA终点效价所测量的,这些纳米颗粒在AF03中配制时或在与SM7/8a缀合时引发免疫应答 (图20A)。关于加强免疫取血 (图20C) 或终末期取血 (图20D) 样品看到了相似的结果。还将这些纳米颗粒与CpG寡脱氧核苷酸缀合,并以相同方式给予。在第5周时,对于CpG缀合物的结果类似于未缀合的纳米颗粒 (图20B)。

5. 对包含粉纹夜蛾铁蛋白的纳米颗粒的表征

[0304] 还开发了包含粉纹夜蛾铁蛋白和gp220和/或gL/gH多肽的纳米颗粒。粉纹夜蛾铁蛋白纳米颗粒含有以1:1比率自组装的重链和轻链。发现将具有轻链的一种非铁蛋白多肽与在重链上的另一种非铁蛋白多肽组合允许在单独纳米颗粒的表面上呈递两种不同的多肽。因此,例如,自组装的粉纹夜蛾铁蛋白纳米颗粒可以呈递gp220和gL/gH二者。

[0305] 产生并纯化了粉纹夜蛾铁蛋白纳米颗粒,所述纳米颗粒具有与gp220 (SEQ ID NO:24) 或单链gL/gH (SEQ ID NO:25) 融合的重链和与gp220 (SEQ ID NO:26) 或单链gL/gH (SEQ ID NO:27) 融合的轻链 (构建体展示于图23B中,并且通过图23A中的考马斯凝胶染色可视化,示出了相对于单独的轻链和重链的预期分子量增加)。分别与gL/gH和gp220融合的轻链

和重链或反之亦然的组合产生了可以呈递两种不同EBV多肽的单个多价纳米颗粒。

[0306] 还产生了在重链和轻链二者中均仅具有gp220(如图24E中所示)或在重链中具有gp220并且在轻链中具有gH_gL(如图25E中所示)的两种粉纹夜蛾铁蛋白纳米颗粒。纯化遵循两个步骤:第一纯化步骤是离子交换色谱步骤(Q柱,参见图24A和在图24C中的考马斯结果以及图25A和示于图25C中的考马斯结果)。此步骤之后进行尺寸排阻色谱(参见图24B和在图24D中的考马斯结果以及图25B和在图25D中的考马斯结果)。

[0307] 基于考马斯染色(图26A)、相对于裸粉纹夜蛾铁蛋白(图27C)的DLS半径增加(图26D)、和EM分析(图26C)(其中相对于裸纳米颗粒(图27B)显现出在纳米颗粒核心周围的附加周边密度),包含与gp220融合的粉纹夜蛾轻链和重链的纳米颗粒(SEQ ID NO:24和26;展示于图26B中)显示出与包含异源gp220多肽的纳米颗粒的形成一致的概况。对于SEQ ID NO:24和27(具有gL/gH多肽的粉纹夜蛾轻链和具有gp220多肽的重链;对于通过考马斯染色进行的可视化、构建体的展示、电子显微照片和通过DLS进行的表征,分别参见图26E至26H),观察到表明纳米颗粒中存在异源gL/gH和gp220多肽的相似结果。为了进行比较,图27A至图27C示出了裸粉纹夜蛾铁蛋白(即未与任何多肽缀合)的考马斯染色(图27A)、DLS半径(图27B)和EM分析(图27C)。

[0308] 因此,粉纹夜蛾铁蛋白的使用允许在单个纳米颗粒上呈递2种多肽。

6. gH/gL/gp42构建体

[0309] 在图35A中示出了与铁蛋白融合的gH/gL/gp42的单链构建体(如在SEQ ID NO:227-231和241-242中的每一种中)的图片。每种蛋白质之间的融合是经由柔性氨基酸接头或刚性氨基酸接头进行的。单链gH/gL/gp42分子提供了在纳米颗粒上1:1:1比率的异三聚体形成。

[0310] 已解析出gH/gL/gp42带有His标签的融合体(SEQ ID NO:226)的晶体结构显示单链gH/gL/gp42可采用类似于自然界中发现的野生型gH、gL和gp42蛋白的异三聚体构象(图34和图35B)。在图34和图35B中,Gp42(在图34中为深灰色并用箭头指示)与gH/gL异二聚体相互作用。图35C是显示与铁蛋白融合的此单链gH/gL/gp42异三聚体如何展示在纳米颗粒上的模型。存在将在单一纳米颗粒上展示的二十四个拷贝的单链gH/gL/gp42。

[0311] 将gH/gL/gp42 NP构建体(SEQ ID NO:227)在293expi细胞中表达并纯化(图28A)。从CHO池中纯化的gH/gL/gp42 NP具有约26.2nm的动态光散射半径(图28B)。

[0312] 评估了由单价(gH/gL/gp42 NP+裸铁蛋白纳米颗粒)或二价(gH/gL/gp42 NP+gp220 NP)组合物引发的免疫应答。gH/gL/gp42 NP具有序列SEQ ID NO:227,并且gp220 NP具有SEQ ID NO:1的序列。对BALB/c小鼠(n=5/组)进行免疫,在剂量之间间隔3周。在伴有AF03佐剂(1:1体积的AF03与疫苗混合)的情况下,给予100μL的含有1μg的每种纳米颗粒的纳米颗粒组合物。加强免疫指示在第二次免疫后第5周收集血清。使用在第5周从小鼠收集的血清进行B细胞(图29A)和上皮细胞(图29B)中的EBV病毒中和测定分析。与单价形式(gH/gL/gp42与裸铁蛋白)的给予相比,未看到由于以二价配制品给予纳米颗粒而引起的干扰。

[0313] 使用包含在佐剂AF03的存在下的单链gL/gH纳米颗粒(gL_gH_C137A_bfpFerr纳米颗粒N19Q/C31S/S111C[SEQ ID NO:22])和gp220纳米颗粒(SEQ ID NO:1)(图30A至30B)或在佐剂AF03的存在下的gL/gH/gp42 NP(SEQ ID NO:227)和gp220纳米颗粒(SEQ ID NO:1)(图30C至30E)的组合物对雪貂进行二价免疫。Inj.1=注射1(在注射1后2周从6只雪貂收集

血清)。Inj.2=注射2(在注射2后2周从6只雪貂收集血清)。ELISA结合测定测量了针对图30A至图30E中所指示的抗原的终点结合效价。图30F-G示出了来自接受在佐剂AF03的存在下的gL/gH/gp42 NP (SEQ ID NO:227) 和gp220纳米颗粒 (SEQ ID NO:1) 的二价疫苗接种的雪貂的血清的EBV病毒中和测定(分别在B细胞和上皮细胞中)。初免=Inj.1并且加强免疫=Inj.2。

[0314] 表达gL/gL/gp42_NP_C12 (SEQ ID NO:228) 并且使用Superose6尺寸排阻色谱将其纯化(图31A)。图31A中样品的动态光散射分析显示出20.6nm的颗粒大小半径(图31B)。

[0315] 表达gL/gL/gp42_NP_C13 (SEQ ID NO:229) 并且使用Superose6尺寸排阻色谱将其纯化(图32A)。图32A中样品的动态光散射分析显示出17.1nm的颗粒大小半径(图32B)。

[0316] 表达gL/gL/gp42_NP_C14 (SEQ ID NO:230) 并且使用Superose6尺寸排阻色谱将其纯化(图33A)。图33A中样品的动态光散射分析显示出16.9nm的颗粒大小半径(图33B)。

[0317] 图35D示出了对在293Expi细胞中表达后的SEQ ID NO:227的纯化。变性SDS考马斯凝胶显示,与铁蛋白融合的gL/gL/gp42在糖基化的情况下高于150kD。纯化产物的负染色电子显微镜分析显示,与铁蛋白融合的单链gL/gL/gp42可以成功地形成在表面上展示gL/gL/gp42抗原的纳米颗粒(图35E)。通过在第0、3、7或14天的温度、氧化和/或脱酰胺应激测试,已经由序列分析或质谱鉴定了SEQ ID NO:227的单链gL/gL/gp42纳米颗粒的潜在不稳定序列。为了改善此疫苗构建体的疫苗稳定性、表达和/或免疫原性,将以不同组合,特别是在表1中所列位点对SEQ ID NO:227进行保守氨基酸取代突变。还将在SEQ ID NO:228-230中测试在特定基因中对应位置处的保守氨基酸突变,所述SEQ ID NO:228-230与SEQ ID NO.227的不同之处仅在于使gp42的C末端与铁蛋白序列的N末端融合的接头序列。

序列表

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<151> 2018-04-03

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Gly Glu Asp Pro Gly Phe Phe Asn Val Glu Ile Pro Glu Phe Pro Phe
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Tyr Pro Thr Cys Asn Val Cys Thr Ala Asp Val Asn Val Thr Ile Asn
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Phe Asp Val Gly Gly Lys Lys His Gln Leu Asp Leu Asp Phe Gly Gln
          85           90           95
Leu Thr Pro His Thr Lys Ala Val Tyr Gln Pro Arg Gly Ala Phe Gly
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Gly Glu Leu Ala Leu Thr Met Arg Ser Lys Lys Leu Pro Ile Asn Val
          130          135          140
Thr Thr Gly Glu Glu Gln Gln Val Ser Leu Glu Ser Val Asp Val Tyr
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Tyr Ala Tyr Ser Leu Arg Leu Thr Pro Arg Pro Val Ser Arg Phe Leu					
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Val Ser Asn Gln Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu Asn Ser
50           55           60
Pro Lys Asn Gly Ser Asn Gln Leu Val Ile Ser Arg Cys Ala Asn Gly
65           70           75           80
Leu Asn Val Val Ser Phe Phe Ile Ser Ile Leu Lys Arg Ser Ser Ser
85           90           95
Ala Leu Thr Gly His Leu Arg Glu Leu Leu Thr Thr Leu Glu Thr Leu
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Tyr Gly Ser Phe Ser Val Glu Asp Leu Phe Gly Ala Asn Leu Asn Arg
115          120          125
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130          135          140
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145          150          155          160
His Ala Ser His Tyr Thr Ile Pro Trp Thr Glu Leu Met Ala Lys Val
165          170          175
Pro Gly Leu Ser Pro Glu Ala Leu Trp Arg Glu Ala Asn Val Thr Glu
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Gly Thr Leu Gly Ile Ala Leu Ala Glu Pro Val Asp Ile Pro Ala Val
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Ser Glu Gly Ser Met Gln Val Asp Ala Ser Lys Val His Pro Gly Val
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Lys Gln Leu Phe Tyr Tyr Ile Gly Thr Met Leu Pro Asn Thr Arg Pro

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

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

	885		890		895
Glu Asn Asn Val Pro Val Gln Leu Thr Ser Ile Ser Ala Pro Glu His					
900		905		910	
Lys Phe Glu Gly Leu Thr Gln Ile Phe Gln Lys Ala Tyr Glu His Glu					
915		920		925	
Gln His Ile Ser Glu Ser Ile Asn Asn Ile Val Asp His Ala Ile Lys					
930		935		940	
Cys Lys Asp His Ala Thr Phe Asn Phe Leu Gln Trp Tyr Val Ala Glu					
945		950		955	
Gln His Glu Glu Glu Val Leu Phe Lys Asp Ile Leu Asp Lys Ile Glu					
965		970		975	
Leu Ile Gly Asn Glu Asn His Gly Leu Tyr Leu Ala Asp Gln Tyr Val					
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Lys Gly Ile Ala Lys Ser Arg Lys Ser					
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Val Leu Pro Thr Trp Gly Asn Trp Ala Tyr Pro Cys Cys His Val Thr					
20		25		30	
Gln Leu Arg Ala Gln His Leu Leu Ala Leu Glu Asn Ile Ser Asp Ile					
35		40		45	
Tyr Leu Val Ser Asn Gln Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu					
50		55		60	
Asn Ser Pro Lys Asn Gly Ser Asn Gln Leu Val Ile Ser Arg Cys Ala					
65		70		75	
Asn Gly Leu Asn Val Val Ser Phe Phe Ile Ser Ile Leu Lys Arg Ser					
85		90		95	
Ser Ser Ala Leu Thr Gly His Leu Arg Glu Leu Leu Thr Thr Leu Glu					
100		105		110	
Thr Leu Tyr Gly Ser Phe Ser Val Glu Asp Leu Phe Gly Ala Asn Leu					
115		120		125	
Asn Arg Gly Gly Ser Gly Ser Ala Ser Ser Gly Ala Ser Ala Ser Gly					

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

Thr	Thr	Met	Phe	Glu	Val	Ser	Val	Ala	Phe	Phe	Lys	Val	Gly	His	Ala
450						455					460				
Val	Gly	Glu	Thr	Gly	Asn	Gly	Cys	Val	Asp	Leu	Arg	Trp	Leu	Ala	Lys
465					470					475					480
Ser	Phe	Phe	Glu	Leu	Thr	Val	Leu	Lys	Asp	Ile	Ile	Gly	Ile	Cys	Tyr
			485						490					495	
Gly	Ala	Thr	Val	Lys	Gly	Met	Gln	Ser	Tyr	Gly	Leu	Glu	Arg	Leu	Ala
			500					505						510	
Ala	Met	Leu	Met	Ala	Thr	Val	Lys	Met	Glu	Glu	Leu	Gly	His	Leu	Thr
			515					520					525		
Thr	Glu	Lys	Gln	Glu	Tyr	Ala	Leu	Arg	Leu	Ala	Thr	Val	Gly	Tyr	Pro
			530					535					540		
Lys	Ala	Gly	Val	Tyr	Ser	Gly	Leu	Ile	Gly	Gly	Ala	Thr	Ser	Val	Leu
545					550					555					560
Leu	Ser	Ala	Tyr	Asn	Arg	His	Pro	Leu	Phe	Gln	Pro	Leu	His	Thr	Val
			565						570					575	
Met	Arg	Glu	Thr	Leu	Phe	Ile	Gly	Ser	His	Val	Val	Leu	Arg	Glu	Leu
			580						585					590	
Arg	Leu	Asn	Val	Thr	Thr	Gln	Gly	Pro	Asn	Leu	Ala	Leu	Tyr	Gln	Leu
			595						600					605	
Leu	Ser	Thr	Ala	Leu	Cys	Ser	Ala	Leu	Glu	Ile	Gly	Glu	Val	Leu	Arg
			610						615					620	
Gly	Leu	Ala	Leu	Gly	Thr	Glu	Ser	Gly	Leu	Phe	Ser	Pro	Cys	Tyr	Leu
625					630					635					640
Ser	Leu	Arg	Phe	Asp	Leu	Thr	Arg	Asp	Lys	Leu	Leu	Ser	Met	Ala	Pro
			645						650					655	
Gln	Glu	Ala	Thr	Leu	Asp	Gln	Ala	Ala	Val	Ser	Asn	Ala	Val	Asp	Gly
			660						665					670	
Phe	Leu	Gly	Arg	Leu	Ser	Leu	Glu	Arg	Glu	Asp	Arg	Asp	Ala	Trp	His
			675						680					685	
Leu	Pro	Ala	Tyr	Lys	Cys	Val	Asp	Arg	Leu	Asp	Lys	Val	Leu	Met	Ile
			690						695					700	
Ile	Pro	Leu	Ile	Asn	Val	Thr	Phe	Ile	Ile	Ser	Ser	Asp	Arg	Glu	Val
705					710					715					720
Arg	Gly	Ser	Ala	Leu	Tyr	Glu	Ala	Ser	Thr	Thr	Tyr	Leu	Ser	Ser	Ser
			725						730					735	
Leu	Phe	Leu	Ser	Pro	Val	Ile	Met	Asn	Lys	Cys	Ser	Gln	Gly	Ala	Val
			740						745					750	
Ala	Gly	Glu	Pro	Arg	Gln	Ile	Pro	Lys	Ile	Gln	Asn	Phe	Thr	Arg	Thr

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

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

115	120	125
Gly Gly Gly Ser Gly Gly Gly	Ser Gly Gly Gly Ser Gly Gly Gly	Ser Gly Gly Gly Ser
130	135	140
Gly Ala Ala Ser Leu Ser Glu Val Lys Leu His Leu Asp Ile Glu Gly		
145	150	155
His Ala Ser His Tyr Thr Ile Pro Trp Thr Glu Leu Met Ala Lys Val		
165	170	175
Pro Gly Leu Ser Pro Glu Ala Leu Trp Arg Glu Ala Asn Val Thr Glu		
180	185	190
Asp Leu Ala Ser Met Leu Asn Arg Tyr Lys Leu Ile Tyr Lys Thr Ser		
195	200	205
Gly Thr Leu Gly Ile Ala Leu Ala Glu Pro Val Asp Ile Pro Ala Val		
210	215	220
Ser Glu Gly Ser Met Gln Val Asp Ala Ser Lys Val His Pro Gly Val		
225	230	235
Ile Ser Gly Leu Asn Ser Pro Ala Cys Met Leu Ser Ala Pro Leu Glu		
245	250	255
Lys Gln Leu Phe Tyr Tyr Ile Gly Thr Met Leu Pro Asn Thr Arg Pro		
260	265	270
His Ser Tyr Val Phe Tyr Gln Leu Arg Cys His Leu Ser Tyr Val Ala		
275	280	285
Leu Ser Ile Asn Gly Asp Lys Phe Gln Tyr Thr Gly Ala Met Thr Ser		
290	295	300
Lys Phe Leu Met Gly Thr Tyr Lys Arg Val Thr Glu Lys Gly Asp Glu		
305	310	315
His Val Leu Ser Leu Val Phe Gly Lys Thr Lys Asp Leu Pro Asp Leu		
325	330	335
Arg Gly Pro Phe Ser Tyr Pro Ser Leu Thr Ser Ala Gln Ser Gly Asp		
340	345	350
Tyr Ser Leu Val Ile Val Thr Thr Phe Val His Tyr Ala Asn Phe His		
355	360	365
Asn Tyr Phe Val Pro Asn Leu Lys Asp Met Phe Ser Arg Ala Val Thr		
370	375	380
Met Thr Ala Ala Ser Tyr Ala Arg Tyr Val Leu Gln Lys Leu Val Leu		
385	390	395
Leu Glu Met Lys Gly Gly Cys Arg Glu Pro Glu Leu Asp Thr Glu Thr		
405	410	415
Leu Thr Thr Met Phe Glu Val Ser Val Ala Phe Phe Lys Val Gly His		
420	425	430

Ala Val Gly Glu Thr Gly Asn Gly Cys Val Asp Leu Arg Trp Leu Ala		
435	440	445
Lys Ser Phe Phe Glu Leu Thr Val Leu Lys Asp Ile Ile Gly Ile Cys		
450	455	460
Tyr Gly Ala Thr Val Lys Gly Met Gln Ser Tyr Gly Leu Glu Arg Leu		
465	470	475
Ala Ala Met Leu Met Ala Thr Val Lys Met Glu Glu Leu Gly His Leu		
	485	490
Thr Thr Glu Lys Gln Glu Tyr Ala Leu Arg Leu Ala Thr Val Gly Tyr		
	500	505
Pro Lys Ala Gly Val Tyr Ser Gly Leu Ile Gly Gly Ala Thr Ser Val		
	515	520
Leu Leu Ser Ala Tyr Asn Arg His Pro Leu Phe Gln Pro Leu His Thr		
	530	535
Val Met Arg Glu Thr Leu Phe Ile Gly Ser His Val Val Leu Arg Glu		
	545	550
Leu Arg Leu Asn Val Thr Thr Gln Gly Pro Asn Leu Ala Leu Tyr Gln		
	565	570
Leu Leu Ser Thr Ala Leu Cys Ser Ala Leu Glu Ile Gly Glu Val Leu		
	580	585
Arg Gly Leu Ala Leu Gly Thr Glu Ser Gly Leu Phe Ser Pro Cys Tyr		
	595	600
Leu Ser Leu Arg Phe Asp Leu Thr Arg Asp Lys Leu Leu Ser Met Ala		
	610	615
Pro Gln Glu Ala Thr Leu Asp Gln Ala Ala Val Ser Asn Ala Val Asp		
	625	630
Gly Phe Leu Gly Arg Leu Ser Leu Glu Arg Glu Asp Arg Asp Ala Trp		
	645	650
His Leu Pro Ala Tyr Lys Cys Val Asp Arg Leu Asp Lys Val Leu Met		
	660	665
Ile Ile Pro Leu Ile Asn Val Thr Phe Ile Ile Ser Ser Asp Arg Glu		
	675	680
Val Arg Gly Ser Ala Leu Tyr Glu Ala Ser Thr Thr Tyr Leu Ser Ser		
	690	695
Ser Leu Phe Leu Ser Pro Val Ile Met Asn Lys Cys Ser Gln Gly Ala		
	705	710
Val Ala Gly Glu Pro Arg Gln Ile Pro Lys Ile Gln Asn Phe Thr Arg		
	725	730
Thr Gln Lys Ser Cys Ile Phe Cys Gly Phe Ala Leu Leu Ser Tyr Asp		

740	745	750
Glu Lys Glu Gly Leu Glu Thr Thr Thr Tyr Ile Thr Ser Gln Glu Val		
755	760	765
Gln Asn Ser Ile Leu Ser Ser Asn Tyr Phe Asp Phe Asp Asn Leu His		
770	775	780
Val His Tyr Leu Leu Leu Thr Thr Asn Gly Thr Val Met Glu Ile Ala		
785	790	795
Gly Leu Tyr Glu Glu Arg Ala Ser Gly Ser Gly Tyr Ile Pro Glu Ala		800
805	810	815
Pro Arg Asp Gly Gln Ala Tyr Val Arg Lys Asp Gly Glu Trp Val Leu		
820	825	830
Leu Ser Thr Phe Leu Gly Ser Gly Ser Gly Ser Gly Leu Val Pro Arg		
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Gly Ser Gly Ala Gly Gly Gly His His His His His His		
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Val Leu Pro Thr Trp Gly Asn Trp Ala Tyr Pro Cys Cys His Val Thr		15
20	25	30
Gln Leu Arg Ala Gln His Leu Leu Ala Leu Glu Asn Ile Ser Asp Ile		
35	40	45
Tyr Leu Val Ser Asn Gln Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu		
50	55	60
Asn Ser Pro Lys Asn Gly Ser Asn Gln Leu Val Ile Ser Arg Cys Ala		
65	70	75
Asn Gly Leu Asn Val Val Ser Phe Phe Ile Ser Ile Leu Lys Arg Ser		
85	90	95
Ser Ser Ala Leu Thr Gly His Leu Arg Glu Leu Leu Thr Thr Leu Glu		
100	105	110
Thr Leu Tyr Gly Ser Phe Ser Val Glu Asp Leu Phe Gly Ala Asn Leu		
115	120	125
Asn Arg Gly Gly Ser Gly Ser Ala Ser Ser Gly Ala Ser Ala Ser Gly		

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

Thr Thr Met Phe Glu Val Ser Val Ala Phe Phe Lys Val Gly His Ala		
450	455	460
Val Gly Glu Thr Gly Asn Gly Cys Val Asp Leu Arg Trp Leu Ala Lys		
465	470	475 480
Ser Phe Phe Glu Leu Thr Val Leu Lys Asp Ile Ile Gly Ile Cys Tyr		
485	490	495
Gly Ala Thr Val Lys Gly Met Gln Ser Tyr Gly Leu Glu Arg Leu Ala		
500	505	510
Ala Met Leu Met Ala Thr Val Lys Met Glu Glu Leu Gly His Leu Thr		
515	520	525
Thr Glu Lys Gln Glu Tyr Ala Leu Arg Leu Ala Thr Val Gly Tyr Pro		
530	535	540
Lys Ala Gly Val Tyr Ser Gly Leu Ile Gly Gly Ala Thr Ser Val Leu		
545	550	555 560
Leu Ser Ala Tyr Asn Arg His Pro Leu Phe Gln Pro Leu His Thr Val		
565	570	575
Met Arg Glu Thr Leu Phe Ile Gly Ser His Val Val Leu Arg Glu Leu		
580	585	590
Arg Leu Asn Val Thr Thr Gln Gly Pro Asn Leu Ala Leu Tyr Gln Leu		
595	600	605
Leu Ser Thr Ala Leu Cys Ser Ala Leu Glu Ile Gly Glu Val Leu Arg		
610	615	620
Gly Leu Ala Leu Gly Thr Glu Ser Gly Leu Phe Ser Pro Cys Tyr Leu		
625	630	635 640
Ser Leu Arg Phe Asp Leu Thr Arg Asp Lys Leu Leu Ser Met Ala Pro		
645	650	655
Gln Glu Ala Thr Leu Asp Gln Ala Ala Val Ser Asn Ala Val Asp Gly		
660	665	670
Phe Leu Gly Arg Leu Ser Leu Glu Arg Glu Asp Arg Asp Ala Trp His		
675	680	685
Leu Pro Ala Tyr Lys Cys Val Asp Arg Leu Asp Lys Val Leu Met Ile		
690	695	700
Ile Pro Leu Ile Asn Val Thr Phe Ile Ile Ser Ser Asp Arg Glu Val		
705	710	715 720
Arg Gly Ser Ala Leu Tyr Glu Ala Ser Thr Thr Tyr Leu Ser Ser Ser		
725	730	735
Leu Phe Leu Ser Pro Val Ile Met Asn Lys Cys Ser Gln Gly Ala Val		
740	745	750
Ala Gly Glu Pro Arg Gln Ile Pro Lys Ile Gln Asn Phe Thr Arg Thr		

755	760	765
Gln Lys Ser Cys Ile Phe Cys Gly Phe Ala Leu Leu Ser Tyr Asp Glu		
770	775	780
Lys Glu Gly Leu Glu Thr Thr Thr Tyr Ile Thr Ser Gln Glu Val Gln		
785	790	795
Asn Ser Ile Leu Ser Ser Asn Tyr Phe Asp Phe Asp Asn Leu His Val		
805	810	815
His Tyr Leu Leu Leu Thr Thr Asn Gly Thr Val Met Glu Ile Ala Gly		
820	825	830
Leu Tyr Glu Glu Arg Ala Ser Gly Ser Gly Ser Gly Ser Gly Leu Val		
835	840	845
Pro Arg Gly Ser Gly Ala Gly Gly Gly His His His His His His		
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Gly Ser Thr Gly Asn Trp Ala Tyr Pro Cys Cys His Val Thr Gln Leu		
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Arg Ala Gln His Leu Leu Ala Leu Glu Asn Ile Ser Asp Ile Tyr Leu		
35	40	45
Val Ser Asn Gln Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu Asn Ser		
50	55	60
Pro Lys Asn Gly Ser Asn Gln Leu Val Ile Ser Arg Cys Ala Asn Gly		
65	70	75
Leu Asn Val Val Ser Phe Phe Ile Ser Ile Leu Lys Arg Ser Ser Ser		
85	90	95
Ala Leu Thr Gly His Leu Arg Glu Leu Leu Thr Thr Leu Glu Thr Leu		
100	105	110
Tyr Gly Ser Phe Ser Val Glu Asp Leu Phe Gly Ala Asn Leu Asn Arg		
115	120	125
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser		
130	135	140
Gly Ala Ala Ser Leu Ser Glu Val Lys Leu His Leu Asp Ile Glu Gly		

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

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

770	775	780
Val His Tyr Leu Leu Leu Thr Thr Asn Gly Thr Val Met Glu Ile Ala		
785	790	795
Gly Leu Tyr Glu Glu Arg Ala Ser Gly Ser Gly Ser Gly Ser Gly Leu		800
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Val Pro Arg Gly Ser Gly Ala Gly Gly Gly His His His His His His		815
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		30
Gln Leu Arg Ala Gln His Leu Leu Ala Leu Glu Asn Ile Ser Asp Ile		
	35	40
		45
Tyr Leu Val Ser Asn Gln Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu		
	50	55
		60
Asn Ser Pro Lys Asn Gly Ser Asn Gln Leu Val Ile Ser Arg Cys Ala		
65	70	75
		80
Asn Gly Leu Asn Val Val Ser Phe Phe Ile Ser Ile Leu Lys Arg Ser		
	85	90
		95
Ser Ser Ala Leu Thr Gly His Leu Arg Glu Leu Leu Thr Thr Leu Glu		
	100	105
		110
Thr Leu Tyr Gly Ser Phe Ser Val Glu Asp Leu Phe Gly Ala Asn Leu		
	115	120
		125
Asn Arg Tyr Ala Trp His Arg Gly Gly Gly Gly Ser Gly Ser Ala Ser		
	130	135
		140
Ser Gly Ala Ser Ala Ser Gly Ser Ser Asn Gly Ser Gly Ser Gly Ser		
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		160
Gly Ser Asn Ser Ser Ala Ser Ser Gly Ala Ser Ser Gly Gly Ala Ser		
	165	170
		175
Gly Gly Ser Gly Gly Ser Gly Ala Ala Ser Leu Ser Glu Val Lys Leu		
	180	185
		190
His Leu Asp Ile Glu Gly His Ala Ser His Tyr Thr Ile Pro Trp Thr		

195	200	205
Glu Leu Met Ala Lys Val Pro Gly Leu Ser Pro Glu Ala Leu Trp Arg		
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Glu Ala Asn Val Thr Glu Asp Leu Ala Ser Met Leu Asn Arg Tyr Lys		
225	230	235
Leu Ile Tyr Lys Thr Ser Gly Thr Leu Gly Ile Ala Leu Ala Glu Pro		
245	250	255
Val Asp Ile Pro Ala Val Ser Glu Gly Ser Met Gln Val Asp Ala Ser		
260	265	270
Lys Val His Pro Gly Val Ile Ser Gly Leu Asn Ser Pro Ala Cys Met		
275	280	285
Leu Ser Ala Pro Leu Glu Lys Gln Leu Phe Tyr Tyr Ile Gly Thr Met		
290	295	300
Leu Pro Asn Thr Arg Pro His Ser Tyr Val Phe Tyr Gln Leu Arg Cys		
305	310	315
His Leu Ser Tyr Val Ala Leu Ser Ile Asn Gly Asp Lys Phe Gln Tyr		
325	330	335
Thr Gly Ala Met Thr Ser Lys Phe Leu Met Gly Thr Tyr Lys Arg Val		
340	345	350
Thr Glu Lys Gly Asp Glu His Val Leu Ser Leu Val Phe Gly Lys Thr		
355	360	365
Lys Asp Leu Pro Asp Leu Arg Gly Pro Phe Ser Tyr Pro Ser Leu Thr		
370	375	380
Ser Ala Gln Ser Gly Asp Tyr Ser Leu Val Ile Val Thr Thr Phe Val		
385	390	395
His Tyr Ala Asn Phe His Asn Tyr Phe Val Pro Asn Leu Lys Asp Met		
405	410	415
Phe Ser Arg Ala Val Thr Met Thr Ala Ala Ser Tyr Ala Arg Tyr Val		
420	425	430
Leu Gln Lys Leu Val Leu Leu Glu Met Lys Gly Gly Cys Arg Glu Pro		
435	440	445
Glu Leu Asp Thr Glu Thr Leu Thr Thr Met Phe Glu Val Ser Val Ala		
450	455	460
Phe Phe Lys Val Gly His Ala Val Gly Glu Thr Gly Asn Gly Cys Val		
465	470	475
Asp Leu Arg Trp Leu Ala Lys Ser Phe Phe Glu Leu Thr Val Leu Lys		
485	490	495
Asp Ile Ile Gly Ile Cys Tyr Gly Ala Thr Val Lys Gly Met Gln Ser		
500	505	510

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

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Thr	Val	Met	Glu	Ile	Ala	Gly	Leu	Tyr	Glu	Glu	Arg	Ala	Ser	Gly	Ser
	835					840					845				
Gly	Ser	Gly	Ser	Gly	Leu	Val	Pro	Arg	Gly	Ser	Gly	Ala	Gly	Gly	Gly
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	20					25					30				
Gln	Leu	Arg	Ala	Gln	His	Leu	Leu	Ala	Leu	Glu	Asn	Ile	Ser	Asp	Ile
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Tyr	Leu	Val	Ser	Asn	Gln	Thr	Cys	Asp	Gly	Phe	Ser	Leu	Ala	Ser	Leu
	50					55					60				
Asn	Ser	Pro	Lys	Asn	Gly	Ser	Asn	Gln	Leu	Val	Ile	Ser	Arg	Cys	Ala
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Asn	Gly	Leu	Asn	Val	Val	Ser	Phe	Phe	Ile	Ser	Ile	Leu	Lys	Arg	Ser
	85					90					95				
Ser	Ser	Ala	Leu	Thr	Gly	His	Leu	Arg	Glu	Leu	Leu	Thr	Thr	Leu	Glu
	100					105					110				
Thr	Leu	Tyr	Gly	Ser	Phe	Ser	Val	Glu	Asp	Leu	Phe	Gly	Ala	Asn	Leu
	115					120					125				
Asn	Arg	Tyr	Ala	Trp	His	Arg	Gly	Gly	Gly	Gly	Ser	Gly	Ser	Gly	Ser
	130					135					140				
Asn	Ser	Ser	Ala	Ser	Ser	Gly	Ala	Ser	Ser	Gly	Gly	Ala	Ser	Gly	Gly
145				150					155					160	
Ser	Gly	Gly	Ser	Gly	Ala	Ala	Ser	Leu	Ser	Glu	Val	Lys	Leu	His	Leu
	165					170					175				
Asp	Ile	Glu	Gly	His	Ala	Ser	His	Tyr	Thr	Ile	Pro	Trp	Thr	Glu	Leu
	180					185					190				
Met	Ala	Lys	Val	Pro	Gly	Leu	Ser	Pro	Glu	Ala	Leu	Trp	Arg	Glu	Ala

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Asn Val Thr Glu Asp Leu Ala Ser Met Leu Asn Arg Tyr Lys Leu Ile		
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Tyr Lys Thr Ser Gly Thr Leu Gly Ile Ala Leu Ala Glu Pro Val Asp		
225	230	235
Ile Pro Ala Val Ser Glu Gly Ser Met Gln Val Asp Ala Ser Lys Val		
245	250	255
His Pro Gly Val Ile Ser Gly Leu Asn Ser Pro Ala Cys Met Leu Ser		
260	265	270
Ala Pro Leu Glu Lys Gln Leu Phe Tyr Tyr Ile Gly Thr Met Leu Pro		
275	280	285
Asn Thr Arg Pro His Ser Tyr Val Phe Tyr Gln Leu Arg Cys His Leu		
290	295	300
Ser Tyr Val Ala Leu Ser Ile Asn Gly Asp Lys Phe Gln Tyr Thr Gly		
305	310	315
Ala Met Thr Ser Lys Phe Leu Met Gly Thr Tyr Lys Arg Val Thr Glu		
325	330	335
Lys Gly Asp Glu His Val Leu Ser Leu Val Phe Gly Lys Thr Lys Asp		
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Leu Pro Asp Leu Arg Gly Pro Phe Ser Tyr Pro Ser Leu Thr Ser Ala		
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Gln Ser Gly Asp Tyr Ser Leu Val Ile Val Thr Thr Phe Val His Tyr		
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Ala Asn Phe His Asn Tyr Phe Val Pro Asn Leu Lys Asp Met Phe Ser		
385	390	395
Arg Ala Val Thr Met Thr Ala Ala Ser Tyr Ala Arg Tyr Val Leu Gln		
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Lys Leu Val Leu Leu Glu Met Lys Gly Gly Cys Arg Glu Pro Glu Leu		
420	425	430
Asp Thr Glu Thr Leu Thr Thr Met Phe Glu Val Ser Val Ala Phe Phe		
435	440	445
Lys Val Gly His Ala Val Gly Glu Thr Gly Asn Gly Cys Val Asp Leu		
450	455	460
Arg Trp Leu Ala Lys Ser Phe Phe Glu Leu Thr Val Leu Lys Asp Ile		
465	470	475
Ile Gly Ile Cys Tyr Gly Ala Thr Val Lys Gly Met Gln Ser Tyr Gly		
485	490	495
Leu Glu Arg Leu Ala Ala Met Leu Met Ala Thr Val Lys Met Glu Glu		
500	505	510

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

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

210	215	220
Val Asp Ile Pro Ala	Val Ser Glu Gly Ser Met	Gln Val Asp Ala Ser
225	230	235
Lys Val His Pro Gly	Val Ile Ser Gly Leu Asn	Ser Pro Ala Cys Met
245	250	255
Leu Ser Ala Pro Leu	Glu Lys Gln Leu Phe	Tyr Tyr Ile Gly Thr Met
260	265	270
Leu Pro Asn Thr Arg	Pro His Ser Tyr Val	Phe Tyr Gln Leu Arg Cys
275	280	285
His Leu Ser Tyr Val	Ala Leu Ser Ile Asn	Gly Asp Lys Phe Gln Tyr
290	295	300
Thr Gly Ala Met Thr	Ser Lys Phe Leu Met	Gly Thr Tyr Lys Arg Val
305	310	315
Thr Glu Lys Gly Asp	Glu His Val Leu Ser	Leu Val Phe Gly Lys Thr
325	330	335
Lys Asp Leu Pro Asp	Leu Arg Gly Pro Phe	Ser Tyr Pro Ser Leu Thr
340	345	350
Ser Ala Gln Ser Gly	Asp Tyr Ser Leu Val	Ile Val Thr Thr Phe Val
355	360	365
His Tyr Ala Asn Phe	His Asn Tyr Phe Val	Pro Asn Leu Lys Asp Met
370	375	380
Phe Ser Arg Ala Val	Thr Met Thr Ala Ala	Ser Tyr Ala Arg Tyr Val
385	390	395
Leu Gln Lys Leu Val	Leu Leu Glu Met Lys	Gly Gly Cys Arg Glu Pro
405	410	415
Glu Leu Asp Thr Glu	Thr Leu Thr Thr Met	Phe Glu Val Ser Val Ala
420	425	430
Phe Phe Lys Val Gly	His Ala Val Gly Glu	Thr Gly Asn Gly Cys Val
435	440	445
Asp Leu Arg Trp Leu	Ala Lys Ser Phe Phe	Glu Leu Thr Val Leu Lys
450	455	460
Asp Ile Ile Gly Ile	Cys Tyr Gly Ala Thr	Val Lys Gly Met Gln Ser
465	470	475
Tyr Gly Leu Glu Arg	Leu Ala Ala Met Leu	Met Ala Thr Val Lys Met
485	490	495
Glu Glu Leu Gly His	Leu Thr Thr Glu Lys	Gln Glu Tyr Ala Leu Arg
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Leu Ala Thr Val Gly	Tyr Pro Lys Ala Gly	Val Tyr Ser Gly Leu Ile
515	520	525

Gly Gly Ala Thr Ser Val Leu Leu Ser Ala Tyr Asn Arg His Pro Leu		
530	535	540
Phe Gln Pro Leu His Thr Val Met Arg Glu Thr Leu Phe Ile Gly Ser		
545	550	555 560
His Val Val Leu Arg Glu Leu Arg Leu Asn Val Thr Thr Gln Gly Pro		
	565	570 575
Asn Leu Ala Leu Tyr Gln Leu Leu Ser Thr Ala Leu Cys Ser Ala Leu		
	580	585 590
Glu Ile Gly Glu Val Leu Arg Gly Leu Ala Leu Gly Thr Glu Ser Gly		
	595	600 605
Leu Phe Ser Pro Cys Tyr Leu Ser Leu Arg Phe Asp Leu Thr Arg Asp		
	610	615 620
Lys Leu Leu Ser Met Ala Pro Gln Glu Ala Thr Leu Asp Gln Ala Ala		
625	630	635 640
Val Ser Asn Ala Val Asp Gly Phe Leu Gly Arg Leu Ser Leu Glu Arg		
	645	650 655
Glu Asp Arg Asp Ala Trp His Leu Pro Ala Tyr Lys Cys Val Asp Arg		
	660	665 670
Leu Asp Lys Val Leu Met Ile Ile Pro Leu Ile Asn Val Thr Phe Ile		
	675	680 685
Ile Ser Ser Asp Arg Glu Val Arg Gly Ser Ala Leu Tyr Glu Ala Ser		
	690	695 700
Thr Thr Tyr Leu Ser Ser Ser Leu Phe Leu Ser Pro Val Ile Met Asn		
705	710	715 720
Lys Cys Ser Gln Gly Ala Val Ala Gly Glu Pro Arg Gln Ile Pro Lys		
	725	730 735
Ile Gln Asn Phe Thr Arg Thr Gln Lys Ser Cys Ile Phe Cys Gly Phe		
	740	745 750
Ala Leu Leu Ser Tyr Asp Glu Lys Glu Gly Leu Glu Thr Thr Thr Tyr		
	755	760 765
Ile Thr Ser Gln Glu Val Gln Asn Ser Ile Leu Ser Ser Asn Tyr Phe		
	770	775 780
Asp Phe Asp Asn Leu His Val His Tyr Leu Leu Leu Thr Thr Asn Gly		
785	790	795 800
Thr Val Met Glu Ile Ala Gly Leu Tyr Glu Glu Arg Ala Ser Gly Gly		
	805	810 815
Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly		
	820	825 830
Gly Ser Glu Ser Gln Val Arg Gln Gln Phe Ser Lys Asp Ile Glu Lys		

835	840	845
Leu Leu Asn Glu Gln Val Asn Lys Glu Met Gln Ser Ser Asn Leu Tyr		
850	855	860
Met Ser Met Ser Ser Trp Ser Tyr Thr His Ser Leu Asp Gly Ala Gly		
865	870	875
Leu Phe Leu Phe Asp His Ala Ala Glu Glu Tyr Glu His Ala Lys Lys		880
885	890	895
Leu Ile Ile Phe Leu Asn Glu Asn Asn Val Pro Val Gln Leu Thr Ser		
900	905	910
Ile Ser Ala Pro Glu His Lys Phe Glu Gly Leu Thr Gln Ile Phe Gln		
915	920	925
Lys Ala Tyr Glu His Glu Gln His Ile Ser Glu Ser Ile Asn Asn Ile		
930	935	940
Val Asp His Ala Ile Lys Cys Lys Asp His Ala Thr Phe Asn Phe Leu		
945	950	955
Gln Trp Tyr Val Ala Glu Gln His Glu Glu Glu Val Leu Phe Lys Asp		
965	970	975
Ile Leu Asp Lys Ile Glu Leu Ile Gly Asn Glu Asn His Gly Leu Tyr		
980	985	990
Leu Ala Asp Gln Tyr Val Lys Gly Ile Ala Lys Ser Arg Lys Ser		
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Val Leu Pro Thr Trp Gly Asn Trp Ala Tyr Pro Cys Cys His Val Thr		
20	25	30
Gln Leu Arg Ala Gln His Leu Leu Ala Leu Glu Asn Ile Ser Asp Ile		
35	40	45
Tyr Leu Val Ser Asn Gln Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu		
50	55	60
Asn Ser Pro Lys Asn Gly Ser Asn Gln Leu Val Ile Ser Arg Cys Ala		
65	70	75
Asn Gly Leu Asn Val Val Ser Phe Phe Ile Ser Ile Leu Lys Arg Ser		80

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Ser	Ser	Ala	Leu	Thr	Gly	His	Leu	Arg	Glu	Leu	Leu	Thr	Thr	Leu	Glu		
				100					105					110			
Thr	Leu	Tyr	Gly	Ser	Phe	Ser	Val	Glu	Asp	Leu	Phe	Gly	Ala	Asn	Leu		
				115					120					125			
Asn	Arg	Tyr	Ala	Trp	His	Arg	Gly	Gly	Gly	Gly	Ser	Gly	Ser	Gly	Ser		
				130					135					140			
Asn	Ser	Ser	Ala	Ser	Ser	Gly	Ala	Ser	Ser	Gly	Gly	Ala	Ser	Gly	Gly		
145						150					155				160		
Ser	Gly	Gly	Ser	Gly	Ala	Ala	Ser	Leu	Ser	Glu	Val	Lys	Leu	His	Leu		
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Asp	Ile	Glu	Gly	His	Ala	Ser	His	Tyr	Thr	Ile	Pro	Trp	Thr	Glu	Leu		
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Met	Ala	Lys	Val	Pro	Gly	Leu	Ser	Pro	Glu	Ala	Leu	Trp	Arg	Glu	Ala		
				195					200					205			
Asn	Val	Thr	Glu	Asp	Leu	Ala	Ser	Met	Leu	Asn	Arg	Tyr	Lys	Leu	Ile		
				210					215					220			
Tyr	Lys	Thr	Ser	Gly	Thr	Leu	Gly	Ile	Ala	Leu	Ala	Glu	Pro	Val	Asp		
225						230					235				240		
Ile	Pro	Ala	Val	Ser	Glu	Gly	Ser	Met	Gln	Val	Asp	Ala	Ser	Lys	Val		
				245							250				255		
His	Pro	Gly	Val	Ile	Ser	Gly	Leu	Asn	Ser	Pro	Ala	Cys	Met	Leu	Ser		
				260							265				270		
Ala	Pro	Leu	Glu	Lys	Gln	Leu	Phe	Tyr	Tyr	Ile	Gly	Thr	Met	Leu	Pro		
				275							280				285		
Asn	Thr	Arg	Pro	His	Ser	Tyr	Val	Phe	Tyr	Gln	Leu	Arg	Cys	His	Leu		
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Ser	Tyr	Val	Ala	Leu	Ser	Ile	Asn	Gly	Asp	Lys	Phe	Gln	Tyr	Thr	Gly		
305						310					315				320		
Ala	Met	Thr	Ser	Lys	Phe	Leu	Met	Gly	Thr	Tyr	Lys	Arg	Val	Thr	Glu		
				325							330				335		
Lys	Gly	Asp	Glu	His	Val	Leu	Ser	Leu	Val	Phe	Gly	Lys	Thr	Lys	Asp		
				340							345				350		
Leu	Pro	Asp	Leu	Arg	Gly	Pro	Phe	Ser	Tyr	Pro	Ser	Leu	Thr	Ser	Ala		
				355							360				365		
Gln	Ser	Gly	Asp	Tyr	Ser	Leu	Val	Ile	Val	Thr	Thr	Phe	Val	His	Tyr		
				370								380					
Ala	Asn	Phe	His	Asn	Tyr	Phe	Val	Pro	Asn	Leu	Lys	Asp	Met	Phe	Ser		
385						390					395				400		

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

705	710	715	720
Tyr Leu Ser Ser Ser	Leu Phe Leu Ser Pro	Val Ile Met Asn Lys Cys	
	725	730	735
Ser Gln Gly Ala Val	Ala Gly Glu Pro Arg	Gln Ile Pro Lys Ile Gln	
	740	745	750
Asn Phe Thr Arg Thr	Gln Lys Ser Cys Ile Phe	Cys Gly Phe Ala Leu	
	755	760	765
Leu Ser Tyr Asp Glu	Lys Glu Gly Leu Glu	Thr Thr Thr Tyr Ile Thr	
	770	775	780
Ser Gln Glu Val Gln	Asn Ser Ile Leu Ser	Ser Asn Tyr Phe Asp Phe	
785	790	795	800
Asp Asn Leu His Val	His Tyr Leu Leu Leu	Thr Thr Asn Gly Thr Val	
	805	810	815
Met Glu Ile Ala Gly	Leu Tyr Glu Glu Arg	Ala Ser Gly Ser Gly Tyr	
	820	825	830
Ile Pro Glu Ala Pro	Arg Asp Gly Gln Ala	Tyr Val Arg Lys Asp Gly	
	835	840	845
Glu Trp Val Leu Leu	Ser Thr Phe Leu Gly	Ser Gly Ser Gly Ser Gly	
	850	855	860
Leu Val Pro Arg Gly	Ser Gly Ala Gly Gly	Gly His His His His	
865	870	875	880
His			
<210> 12			
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<212> PRT			
<213> 人工序列			
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<223> 合成多肽			
<400> 12			
Met Arg Ala Val Gly	Val Phe Leu Ala Ile	Cys Leu Val Thr Ile Phe	
1	5	10	15
Val Leu Pro Thr Trp	Gly Asn Trp Ala Tyr	Pro Cys Cys His Val Thr	
	20	25	30
Gln Leu Arg Ala Gln	His Leu Leu Ala Leu	Glu Asn Ile Ser Asp Ile	
	35	40	45
Tyr Leu Val Ser Asn	Gln Thr Cys Asp Gly	Phe Ser Leu Ala Ser Leu	
	50	55	60
Asn Ser Pro Lys Asn	Gly Ser Asn Gln Leu	Val Ile Ser Arg Cys Ala	
65	70	75	80

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

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

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

His His His

<210> 13

<211> 1021

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 13

Met Arg Ala Val Gly Val Phe Leu Ala Ile Cys Leu Val Thr Ile Phe			
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Val Leu Pro Thr Trp Gly Asn Trp Ala Tyr Pro Cys Cys His Val Thr			
	20	25	30
Gln Leu Arg Ala Gln His Leu Leu Ala Leu Glu Asn Ile Ser Asp Ile			
	35	40	45
Tyr Leu Val Ser Asn Gln Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu			

50	55	60
Asn Ser Pro Lys Asn Gly Ser Asn Gln Leu Val Ile Ser Arg Cys Ala		
65	70	75
Asn Gly Leu Asn Val Val Ser Phe Phe Ile Ser Ile Leu Lys Arg Ser		80
	85	90
Ser Ser Ala Leu Thr Gly His Leu Arg Glu Leu Leu Thr Thr Leu Glu		95
	100	105
Thr Leu Tyr Gly Ser Phe Ser Val Glu Asp Leu Phe Gly Ala Asn Leu		110
	115	120
Asn Arg Tyr Ala Trp His Arg Gly Gly Gly Gly Ser Gly Ser Gly Ser		125
	130	135
Asn Ser Ser Ala Ser Ser Gly Ala Ser Ser Gly Gly Ala Ser Gly Gly		140
145	150	155
Ser Gly Gly Ser Gly Ala Ala Ser Leu Ser Glu Val Lys Leu His Leu		160
	165	170
Asp Ile Glu Gly His Ala Ser His Tyr Thr Ile Pro Trp Thr Glu Leu		175
	180	185
Met Ala Lys Val Pro Gly Leu Ser Pro Glu Ala Leu Trp Arg Glu Ala		190
	195	200
Asn Val Thr Glu Asp Leu Ala Ser Met Leu Asn Arg Tyr Lys Leu Ile		205
	210	215
Tyr Lys Thr Ser Gly Thr Leu Gly Ile Ala Leu Ala Glu Pro Val Asp		220
225	230	235
Ile Pro Ala Val Ser Glu Gly Ser Met Gln Val Asp Ala Ser Lys Val		240
	245	250
His Pro Gly Val Ile Ser Gly Leu Asn Ser Pro Ala Cys Met Leu Ser		255
	260	265
Ala Pro Leu Glu Lys Gln Leu Phe Tyr Tyr Ile Gly Thr Met Leu Pro		270
	275	280
Asn Thr Arg Pro His Ser Tyr Val Phe Tyr Gln Leu Arg Cys His Leu		285
	290	295
Ser Tyr Val Ala Leu Ser Ile Asn Gly Asp Lys Phe Gln Tyr Thr Gly		300
305	310	315
Ala Met Thr Ser Lys Phe Leu Met Gly Thr Tyr Lys Arg Val Thr Glu		320
	325	330
Lys Gly Asp Glu His Val Leu Ser Leu Val Phe Gly Lys Thr Lys Asp		335
	340	345
Leu Pro Asp Leu Arg Gly Pro Phe Ser Tyr Pro Ser Leu Thr Ser Ala		350
	355	360
		365

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

675	680	685
Lys Val Leu Met Ile Ile Pro	Leu Ile Asn Val Thr Phe Ile Ile Ser	
690	695	700
Ser Asp Arg Glu Val Arg Gly Ser Ala Leu Tyr Glu Ala Ser Thr Thr		
705	710	715
Tyr Leu Ser Ser Ser Leu Phe Leu Ser Pro Val Ile Met Asn Lys Cys		
725	730	735
Ser Gln Gly Ala Val Ala Gly Glu Pro Arg Gln Ile Pro Lys Ile Gln		
740	745	750
Asn Phe Thr Arg Thr Gln Lys Ser Cys Ile Phe Cys Gly Phe Ala Leu		
755	760	765
Leu Ser Tyr Asp Glu Lys Glu Gly Leu Glu Thr Thr Thr Tyr Ile Thr		
770	775	780
Ser Gln Glu Val Gln Asn Ser Ile Leu Ser Ser Asn Tyr Phe Asp Phe		
785	790	795
Asp Asn Leu His Val His Tyr Leu Leu Leu Thr Thr Asn Gly Thr Val		
805	810	815
Met Glu Ile Ala Gly Leu Tyr Glu Glu Arg Ala Ser Gly Gly Gly Ser		
820	825	830
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser		
835	840	845
Glu Ser Gln Val Arg Gln Gln Phe Ser Lys Asp Ile Glu Lys Leu Leu		
850	855	860
Asn Glu Gln Val Asn Lys Glu Met Gln Ser Ser Asn Leu Tyr Met Ser		
865	870	875
Met Ser Ser Trp Ser Tyr Thr His Ser Leu Asp Gly Ala Gly Leu Phe		
885	890	895
Leu Phe Asp His Ala Ala Glu Glu Tyr Glu His Ala Lys Lys Leu Ile		
900	905	910
Ile Phe Leu Asn Glu Asn Asn Val Pro Val Gln Leu Thr Ser Ile Ser		
915	920	925
Ala Pro Glu His Lys Phe Glu Gly Leu Thr Gln Ile Phe Gln Lys Ala		
930	935	940
Tyr Glu His Glu Gln His Ile Ser Glu Ser Ile Asn Asn Ile Val Asp		
945	950	955
His Ala Ile Lys Cys Lys Asp His Ala Thr Phe Asn Phe Leu Gln Trp		
965	970	975
Tyr Val Ala Glu Gln His Glu Glu Glu Val Leu Phe Lys Asp Ile Leu		
980	985	990

Asp Lys Ile Glu Leu Ile Gly Asn Glu Asn His Gly Leu Tyr Leu Ala
 995 1000 1005
 Asp Gln Tyr Val Lys Gly Ile Ala Lys Ser Arg Lys Ser
 1010 1015 1020
 <210> 14
 <211> 1039
 <212> PRT
 <213> 人工序列
 <220>
 <223> 合成多肽
 <400> 14
 Met Arg Ala Val Gly Val Phe Leu Ala Ile Cys Leu Val Thr Ile Phe
 1 5 10 15
 Val Leu Pro Thr Trp Gly Asn Trp Ala Tyr Pro Cys Cys His Val Thr
 20 25 30
 Gln Leu Arg Ala Gln His Leu Leu Ala Leu Glu Asn Ile Ser Asp Ile
 35 40 45
 Tyr Leu Val Ser Asn Gln Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu
 50 55 60
 Asn Ser Pro Lys Asn Gly Ser Asn Gln Leu Val Ile Ser Arg Cys Ala
 65 70 75 80
 Asn Gly Leu Asn Val Val Ser Phe Phe Ile Ser Ile Leu Lys Arg Ser
 85 90 95
 Ser Ser Ala Leu Thr Gly His Leu Arg Glu Leu Leu Thr Thr Leu Glu
 100 105 110
 Thr Leu Tyr Gly Ser Phe Ser Val Glu Asp Leu Phe Gly Ala Asn Leu
 115 120 125
 Asn Arg Tyr Ala Trp His Arg Gly Gly Gly Gly Ser Gly Ser Ala Ser
 130 135 140
 Ser Gly Ala Ser Ala Ser Gly Ser Ser Asn Gly Ser Gly Ser Gly Ser
 145 150 155 160
 Gly Ser Asn Ser Ser Ala Ser Ser Gly Ala Ser Ser Gly Gly Ala Ser
 165 170 175
 Gly Gly Ser Gly Gly Ser Gly Ala Ala Ser Leu Ser Glu Val Lys Leu
 180 185 190
 His Leu Asp Ile Glu Gly His Ala Ser His Tyr Thr Ile Pro Trp Thr
 195 200 205
 Glu Leu Met Ala Lys Val Pro Gly Leu Ser Pro Glu Ala Leu Trp Arg
 210 215 220

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

530	535	540
Leu Ala Thr Val Gly Tyr Pro Lys Ala Gly Val Tyr Ser Gly Leu Ile		
545	550	555
Gly Gly Ala Thr Ser Val Leu Leu Ser Ala Tyr Asn Arg His Pro Leu		
565	570	575
Phe Gln Pro Leu His Thr Val Met Arg Glu Thr Leu Phe Ile Gly Ser		
580	585	590
His Val Val Leu Arg Glu Leu Arg Leu Asn Val Thr Thr Gln Gly Pro		
595	600	605
Asn Leu Ala Leu Tyr Gln Leu Leu Ser Thr Ala Leu Cys Ser Ala Leu		
610	615	620
Glu Ile Gly Glu Val Leu Arg Gly Leu Ala Leu Gly Thr Glu Ser Gly		
625	630	635
Leu Phe Ser Pro Cys Tyr Leu Ser Leu Arg Phe Asp Leu Thr Arg Asp		
645	650	655
Lys Leu Leu Ser Met Ala Pro Gln Glu Ala Thr Leu Asp Gln Ala Ala		
660	665	670
Val Ser Asn Ala Val Asp Gly Phe Leu Gly Arg Leu Ser Leu Glu Arg		
675	680	685
Glu Asp Arg Asp Ala Trp His Leu Pro Ala Tyr Lys Cys Val Asp Arg		
690	695	700
Leu Asp Lys Val Leu Met Ile Ile Pro Leu Ile Asn Val Thr Phe Ile		
705	710	715
Ile Ser Ser Asp Arg Glu Val Arg Gly Ser Ala Leu Tyr Glu Ala Ser		
725	730	735
Thr Thr Tyr Leu Ser Ser Ser Leu Phe Leu Ser Pro Val Ile Met Asn		
740	745	750
Lys Cys Ser Gln Gly Ala Val Ala Gly Glu Pro Arg Gln Ile Pro Lys		
755	760	765
Ile Gln Asn Phe Thr Arg Thr Gln Lys Ser Cys Ile Phe Cys Gly Phe		
770	775	780
Ala Leu Leu Ser Tyr Asp Glu Lys Glu Gly Leu Glu Thr Thr Thr Tyr		
785	790	795
Ile Thr Ser Gln Glu Val Gln Asn Ser Ile Leu Ser Ser Asn Tyr Phe		
805	810	815
Asp Phe Asp Asn Leu His Val His Tyr Leu Leu Leu Thr Thr Asn Gly		
820	825	830
Thr Val Met Glu Ile Ala Gly Leu Tyr Glu Glu Arg Ala Ser Gly Gly		
835	840	845

Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly		
850	855	860
Gly Ser Glu Ser Gln Val Arg Gln Gln Phe Ser Lys Asp Ile Glu Lys		
865	870	875 880
Leu Leu Asn Glu Gln Val Asn Lys Glu Met Gln Ser Ser Asn Leu Tyr		
	885 890	895
Met Ser Met Ser Ser Trp Ser Tyr Thr His Ser Leu Asp Gly Ala Gly		
	900 905	910
Leu Phe Leu Phe Asp His Ala Ala Glu Glu Tyr Glu His Ala Lys Lys		
	915 920	925
Leu Ile Ile Phe Leu Asn Glu Asn Asn Val Pro Val Gln Leu Thr Ser		
	930 935	940
Ile Ser Ala Pro Glu His Lys Phe Glu Gly Leu Thr Gln Ile Phe Gln		
945	950 955	960
Lys Ala Tyr Glu His Glu Gln His Ile Ser Glu Ser Ile Asn Asn Ile		
	965 970	975
Val Asp His Ala Ile Lys Cys Lys Asp His Ala Thr Phe Asn Phe Leu		
	980 985	990
Gln Trp Tyr Val Ala Glu Gln His Glu Glu Glu Val Leu Phe Lys Asp		
	995 1000	1005
Ile Leu Asp Lys Ile Glu Leu Ile Gly Asn Glu Asn His Gly Leu		
	1010 1015	1020
Tyr Leu Ala Asp Gln Tyr Val Lys Gly Ile Ala Lys Ser Arg Lys		
	1025 1030	1035

Ser

<210> 15

<211> 838

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 15

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro		
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Gly Ser Thr Gly Asn Trp Ala Tyr Pro Cys Cys His Val Thr Gln Leu		
	20 25	30
Arg Ala Gln His Leu Leu Ala Leu Glu Asn Ile Ser Asp Ile Tyr Leu		
	35 40	45
Val Ser Asn Gln Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu Asn Ser		

50	55	60
Pro Lys Asn Gly Ser	Asn Gln Leu Val Ile Ser	Arg Cys Ala Asn Gly
65	70	75
Leu Asn Val Val Ser	Phe Phe Ile Ser Ile Leu Lys Arg Ser Ser Ser	
85	90	95
Ala Leu Thr Gly His	Leu Arg Glu Leu Leu Thr Thr Leu Glu Thr Leu	
100	105	110
Tyr Gly Ser Phe Ser	Val Glu Asp Leu Phe Gly Ala Asn Leu Asn Arg	
115	120	125
Tyr Ala Trp His Arg	Gly Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly	
130	135	140
Ser Gly Gly Gly Gly	Ser Gly Ala Ala Ser Leu Ser Glu Val Lys Leu	
145	150	155
His Leu Asp Ile Glu	Gly His Ala Ser His Tyr Thr Ile Pro Trp Thr	
165	170	175
Glu Leu Met Ala Lys	Val Pro Gly Leu Ser Pro Glu Ala Leu Trp Arg	
180	185	190
Glu Ala Asn Val Thr	Glu Asp Leu Ala Ser Met Leu Asn Arg Tyr Lys	
195	200	205
Leu Ile Tyr Lys Thr	Ser Gly Thr Leu Gly Ile Ala Leu Ala Glu Pro	
210	215	220
Val Asp Ile Pro Ala	Val Ser Glu Gly Ser Met Gln Val Asp Ala Ser	
225	230	235
Lys Val His Pro Gly	Val Ile Ser Gly Leu Asn Ser Pro Ala Cys Met	
245	250	255
Leu Ser Ala Pro Leu	Glu Lys Gln Leu Phe Tyr Tyr Ile Gly Thr Met	
260	265	270
Leu Pro Asn Thr Arg	Pro His Ser Tyr Val Phe Tyr Gln Leu Arg Cys	
275	280	285
His Leu Ser Tyr Val	Ala Leu Ser Ile Asn Gly Asp Lys Phe Gln Tyr	
290	295	300
Thr Gly Ala Met Thr	Ser Lys Phe Leu Met Gly Thr Tyr Lys Arg Val	
305	310	315
Thr Glu Lys Gly Asp	Glu His Val Leu Ser Leu Val Phe Gly Lys Thr	
325	330	335
Lys Asp Leu Pro Asp	Leu Arg Gly Pro Phe Ser Tyr Pro Ser Leu Thr	
340	345	350
Ser Ala Gln Ser Gly	Asp Tyr Ser Leu Val Ile Val Thr Thr Phe Val	
355	360	365

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

675	680	685
Ile Ser Ser Asp Arg Glu Val Arg Gly Ser Ala Leu Tyr Glu Ala Ser		
690	695	700
Thr Thr Tyr Leu Ser Ser Ser Leu Phe Leu Ser Pro Val Ile Met Asn		
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Lys Cys Ser Gln Gly Ala Val Ala Gly Glu Pro Arg Gln Ile Pro Lys		
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Ile Gln Asn Phe Thr Arg Thr Gln Lys Ser Cys Ile Phe Cys Gly Phe		
740	745	750
Ala Leu Leu Ser Tyr Asp Glu Lys Glu Gly Leu Glu Thr Thr Thr Tyr		
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Ile Thr Ser Gln Glu Val Gln Asn Ser Ile Leu Ser Ser Asn Tyr Phe		
770	775	780
Asp Phe Asp Asn Leu His Val His Tyr Leu Leu Leu Thr Thr Asn Gly		
785	790	795
Thr Val Met Glu Ile Ala Gly Leu Tyr Glu Glu Arg Ala Ser Gly Ser		
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Arg Ala Gln His Leu Leu Ala Leu Glu Asn Ile Ser Asp Ile Tyr Leu		
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Val Ser Asn Gln Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu Asn Ser		
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Pro Lys Asn Gly Ser Asn Gln Leu Val Ile Ser Arg Cys Ala Asn Gly		
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Leu Asn Val Val Ser Phe Phe Ile Ser Ile Leu Lys Arg Ser Ser Ser		

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

Leu	Gln	Lys	Leu	Val	Leu	Leu	Glu	Met	Lys	Gly	Gly	Cys	Arg	Glu	Pro	
				405					410					415		
Glu	Leu	Asp	Thr	Glu	Thr	Leu	Thr	Thr	Met	Phe	Glu	Val	Ser	Val	Ala	
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Phe	Phe	Lys	Val	Gly	His	Ala	Val	Gly	Glu	Thr	Gly	Asn	Gly	Cys	Val	
				435					440					445		
Asp	Leu	Arg	Trp	Leu	Ala	Lys	Ser	Phe	Phe	Glu	Leu	Thr	Val	Leu	Lys	
				450					455					460		
Asp	Ile	Ile	Gly	Ile	Cys	Tyr	Gly	Ala	Thr	Val	Lys	Gly	Met	Gln	Ser	
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Tyr	Gly	Leu	Glu	Arg	Leu	Ala	Ala	Met	Leu	Met	Ala	Thr	Val	Lys	Met	
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Glu	Glu	Leu	Gly	His	Leu	Thr	Thr	Glu	Lys	Gln	Glu	Tyr	Ala	Leu	Arg	
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Leu	Ala	Thr	Val	Gly	Tyr	Pro	Lys	Ala	Gly	Val	Tyr	Ser	Gly	Leu	Ile	
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Gly	Gly	Ala	Thr	Ser	Val	Leu	Leu	Ser	Ala	Tyr	Asn	Arg	His	Pro	Leu	
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Phe	Gln	Pro	Leu	His	Thr	Val	Met	Arg	Glu	Thr	Leu	Phe	Ile	Gly	Ser	
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His	Val	Val	Leu	Arg	Glu	Leu	Arg	Leu	Asn	Val	Thr	Thr	Gln	Gly	Pro	
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Asn	Leu	Ala	Leu	Tyr	Gln	Leu	Leu	Ser	Thr	Ala	Leu	Cys	Ser	Ala	Leu	
				580					585					590		
Glu	Ile	Gly	Glu	Val	Leu	Arg	Gly	Leu	Ala	Leu	Gly	Thr	Glu	Ser	Gly	
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Leu	Phe	Ser	Pro	Cys	Tyr	Leu	Ser	Leu	Arg	Phe	Asp	Leu	Thr	Arg	Asp	
				610					615					620		
Lys	Leu	Leu	Ser	Met	Ala	Pro	Gln	Glu	Ala	Thr	Leu	Asp	Gln	Ala	Ala	
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Val	Ser	Asn	Ala	Val	Asp	Gly	Phe	Leu	Gly	Arg	Leu	Ser	Leu	Glu	Arg	
				645					650					655		
Glu	Asp	Arg	Asp	Ala	Trp	His	Leu	Pro	Ala	Tyr	Lys	Cys	Val	Asp	Arg	
				660					665					670		
Leu	Asp	Lys	Val	Leu	Met	Ile	Ile	Pro	Leu	Ile	Asn	Val	Thr	Phe	Ile	
				675					680					685		
Ile	Ser	Ser	Asp	Arg	Glu	Val	Arg	Gly	Ser	Ala	Leu	Tyr	Glu	Ala	Ser	
				690					695					700		
Thr	Thr	Tyr	Leu	Ser	Ser	Ser	Leu	Phe	Leu	Ser	Pro	Val	Ile	Met	Asn	

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Lys Cys Ser Gln Gly Ala Val Ala Gly Glu Pro Arg Gln Ile Pro Lys			
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Ile Gln Asn Phe Thr Arg Thr Gln Lys Ser Cys Ile Phe Cys Gly Phe			
	740	745	750
Ala Leu Leu Ser Tyr Asp Glu Lys Glu Gly Leu Glu Thr Thr Thr Tyr			
	755	760	765
Ile Thr Ser Gln Glu Val Gln Asn Ser Ile Leu Ser Ser Asn Tyr Phe			
	770	775	780
Asp Phe Asp Asn Leu His Val His Tyr Leu Leu Leu Thr Thr Asn Gly			
785	790	795	800
Thr Val Met Glu Ile Ala Gly Leu Tyr Glu Glu Arg Ala Ser Gly Ser			
	805	810	815
Gly Tyr Ile Pro Glu Ala Pro Arg Asp Gly Gln Ala Tyr Val Arg Lys			
	820	825	830
Asp Gly Glu Trp Val Leu Leu Ser Thr Phe Leu Gly Ser Gly Ser Gly			
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Val Leu Pro Thr Trp Gly Asn Trp Ala Tyr Pro Cys Cys His Val Thr			
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Gln Leu Arg Ala Gln His Leu Leu Ala Leu Glu Asn Ile Ser Asp Ile			
	35	40	45
Tyr Leu Val Ser Asn Gln Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu			
	50	55	60
Asn Ser Pro Lys Asn Gly Ser Asn Gln Leu Val Ile Ser Arg Cys Ala			
65	70	75	80
Asn Gly Leu Asn Val Val Ser Phe Phe Ile Ser Ile Leu Lys Arg Ser			

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Ser	Ser	Ala	Leu	Thr	Gly	His	Leu	Arg	Glu	Leu	Leu	Thr	Thr	Leu	Glu		
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Thr	Leu	Tyr	Gly	Ser	Phe	Ser	Val	Glu	Asp	Leu	Phe	Gly	Ala	Asn	Leu		
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Asn	Arg	Tyr	Ala	Trp	His	Arg	Gly	Gly	Gly	Gly	Ser	Gly	Ser	Ala	Ser		
			130				135					140					
Ala	Glu	Ala	Ala	Ala	Lys	Glu	Ala	Ala	Ala	Lys	Ala	Gly	Gly	Ser	Gly		
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Gly	Ser	Gly	Ala	Ala	Ser	Leu	Ser	Glu	Val	Lys	Leu	His	Leu	Asp	Ile		
			165				170					175					
Glu	Gly	His	Ala	Ser	His	Tyr	Thr	Ile	Pro	Trp	Thr	Glu	Leu	Met	Ala		
			180				185					190					
Lys	Val	Pro	Gly	Leu	Ser	Pro	Glu	Ala	Leu	Trp	Arg	Glu	Ala	Asn	Val		
			195				200					205					
Thr	Glu	Asp	Leu	Ala	Ser	Met	Leu	Asn	Arg	Tyr	Lys	Leu	Ile	Tyr	Lys		
			210				215					220					
Thr	Ser	Gly	Thr	Leu	Gly	Ile	Ala	Leu	Ala	Glu	Pro	Val	Asp	Ile	Pro		
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Leu	Glu	Lys	Gln	Leu	Phe	Tyr	Tyr	Ile	Gly	Thr	Met	Leu	Pro	Asn	Thr		
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Val	Ala	Leu	Ser	Ile	Asn	Gly	Asp	Lys	Phe	Gln	Tyr	Thr	Gly	Ala	Met		
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Thr	Ser	Lys	Phe	Leu	Met	Gly	Thr	Tyr	Lys	Arg	Val	Thr	Glu	Lys	Gly		
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Asp	Glu	His	Val	Leu	Ser	Leu	Val	Phe	Gly	Lys	Thr	Lys	Asp	Leu	Pro		
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Gly	Asp	Tyr	Ser	Leu	Val	Ile	Val	Thr	Thr	Phe	Val	His	Tyr	Ala	Asn		
			370				375					380					
Phe	His	Asn	Tyr	Phe	Val	Pro	Asn	Leu	Lys	Asp	Met	Phe	Ser	Arg	Ala		
385				390						395				400			

Val Thr Met Thr Ala Ala Ser Tyr Ala Arg Tyr Val Leu Gln Lys Leu		
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Val Leu Leu Glu Met Lys Gly Gly Cys Arg Glu Pro Glu Leu Asp Thr		
420	425	430
Glu Thr Leu Thr Thr Met Phe Glu Val Ser Val Ala Phe Phe Lys Val		
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Gly His Ala Val Gly Glu Thr Gly Asn Gly Cys Val Asp Leu Arg Trp		
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Leu Ala Lys Ser Phe Phe Glu Leu Thr Val Leu Lys Asp Ile Ile Gly		
465	470	475
Ile Cys Tyr Gly Ala Thr Val Lys Gly Met Gln Ser Tyr Gly Leu Glu		
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Arg Leu Ala Ala Met Leu Met Ala Thr Val Lys Met Glu Glu Leu Gly		
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His Leu Thr Thr Glu Lys Gln Glu Tyr Ala Leu Arg Leu Ala Thr Val		
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Gly Tyr Pro Lys Ala Gly Val Tyr Ser Gly Leu Ile Gly Gly Ala Thr		
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Ser Val Leu Leu Ser Ala Tyr Asn Arg His Pro Leu Phe Gln Pro Leu		
545	550	555
His Thr Val Met Arg Glu Thr Leu Phe Ile Gly Ser His Val Val Leu		
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Arg Glu Leu Arg Leu Asn Val Thr Thr Gln Gly Pro Asn Leu Ala Leu		
580	585	590
Tyr Gln Leu Leu Ser Thr Ala Leu Cys Ser Ala Leu Glu Ile Gly Glu		
595	600	605
Val Leu Arg Gly Leu Ala Leu Gly Thr Glu Ser Gly Leu Phe Ser Pro		
610	615	620
Cys Tyr Leu Ser Leu Arg Phe Asp Leu Thr Arg Asp Lys Leu Leu Ser		
625	630	635
Met Ala Pro Gln Glu Ala Thr Leu Asp Gln Ala Ala Val Ser Asn Ala		
645	650	655
Val Asp Gly Phe Leu Gly Arg Leu Ser Leu Glu Arg Glu Asp Arg Asp		
660	665	670
Ala Trp His Leu Pro Ala Tyr Lys Cys Val Asp Arg Leu Asp Lys Val		
675	680	685
Leu Met Ile Ile Pro Leu Ile Asn Val Thr Phe Ile Ile Ser Ser Asp		
690	695	700
Arg Glu Val Arg Gly Ser Ala Leu Tyr Glu Ala Ser Thr Thr Tyr Leu		

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Ser Ser Ser Leu Phe	Leu Ser Pro Val	Ile Met Asn Lys Cys	Ser Gln
	725	730	735
Gly Ala Val Ala Gly	Glu Pro Arg Gln	Ile Pro Lys Ile	Gln Asn Phe
	740	745	750
Thr Arg Thr Gln Lys	Ser Cys Ile Phe	Cys Gly Phe Ala	Leu Leu Ser
	755	760	765
Tyr Asp Glu Lys Glu	Gly Leu Glu Thr Thr	Thr Tyr Ile Thr	Ser Gln
	770	775	780
Glu Val Gln Asn Ser	Ile Leu Ser Ser Asn	Tyr Phe Asp Phe	Asp Asn
785	790	795	800
Leu His Val His Tyr	Leu Leu Leu Thr Thr	Asn Gly Thr Val	Met Glu
	805	810	815
Ile Ala Gly Leu Tyr	Glu Glu Arg Ala Ser	Gly Gly Gly Ser	Gly Gly
	820	825	830
Gly Ser Gly Gly Gly	Ser Gly Gly Gly Ser	Gly Gly Gly Ser	Glu Ser
	835	840	845
Gln Val Arg Gln Gln	Phe Ser Lys Asp Ile	Glu Lys Leu Leu	Asn Glu
	850	855	860
Gln Val Asn Lys Glu	Met Gln Ser Ser Asn	Leu Tyr Met Ser	Met Ser
865	870	875	880
Ser Trp Ser Tyr Thr	His Ser Leu Asp Gly	Ala Gly Leu Phe	Leu Phe
	885	890	895
Asp His Ala Ala Glu	Glu Tyr Glu His Ala	Lys Lys Leu Ile	Ile Phe
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Leu Asn Glu Asn Asn	Val Pro Val Gln Leu	Thr Ser Ile Ser	Ala Pro
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Glu His Lys Phe Glu	Gly Leu Thr Gln Ile	Phe Gln Lys Ala	Tyr Glu
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His Glu Gln His Ile	Ser Glu Ser Ile Asn	Asn Ile Val Asp	His Ala
945	950	955	960
Ile Lys Cys Lys Asp	His Ala Thr Phe Asn	Phe Leu Gln Trp	Tyr Val
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Ala Glu Gln His Glu	Glu Glu Val Leu Phe	Lys Asp Ile Leu	Asp Lys
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Gln Leu Arg Ala Gln His Leu Leu Ala Leu Glu Asn Ile Ser Asp Ile
          35           40           45
Tyr Leu Val Ser Asn Gln Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu
          50           55           60
Asn Ser Pro Lys Asn Gly Ser Asn Gln Leu Val Ile Ser Arg Cys Ala
65           70           75           80
Asn Gly Leu Asn Val Val Ser Phe Phe Ile Ser Ile Leu Lys Arg Ser
          85           90           95
Ser Ser Ala Leu Thr Gly His Leu Arg Glu Leu Leu Thr Thr Leu Glu
          100          105          110
Thr Leu Tyr Gly Ser Phe Ser Val Glu Asp Leu Phe Gly Ala Asn Leu
          115          120          125
Asn Arg Tyr Ala Trp His Arg Gly Gly Gly Gly Ser Gly Ser Ala Ser
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Ala Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys
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Ala Ser Gly Gly Ser Gly Gly Ser Gly Ala Ala Ser Leu Ser Glu Val
          165          170          175
Lys Leu His Leu Asp Ile Glu Gly His Ala Ser His Tyr Thr Ile Pro
          180          185          190
Trp Thr Glu Leu Met Ala Lys Val Pro Gly Leu Ser Pro Glu Ala Leu
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Trp Arg Glu Ala Asn Val Thr Glu Asp Leu Ala Ser Met Leu Asn Arg
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Tyr Lys Leu Ile Tyr Lys Thr Ser Gly Thr Leu Gly Ile Ala Leu Ala
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Glu Pro Val Asp Ile Pro Ala Val Ser Glu Gly Ser Met Gln Val Asp
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Cys Met Leu Ser Ala Pro Leu Glu Lys Gln Leu Phe Tyr Tyr Ile Gly		
275	280	285
Thr Met Leu Pro Asn Thr Arg Pro His Ser Tyr Val Phe Tyr Gln Leu		
290	295	300
Arg Cys His Leu Ser Tyr Val Ala Leu Ser Ile Asn Gly Asp Lys Phe		
305	310	315
Gln Tyr Thr Gly Ala Met Thr Ser Lys Phe Leu Met Gly Thr Tyr Lys		
325	330	335
Arg Val Thr Glu Lys Gly Asp Glu His Val Leu Ser Leu Val Phe Gly		
340	345	350
Lys Thr Lys Asp Leu Pro Asp Leu Arg Gly Pro Phe Ser Tyr Pro Ser		
355	360	365
Leu Thr Ser Ala Gln Ser Gly Asp Tyr Ser Leu Val Ile Val Thr Thr		
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Phe Val His Tyr Ala Asn Phe His Asn Tyr Phe Val Pro Asn Leu Lys		
385	390	395
Asp Met Phe Ser Arg Ala Val Thr Met Thr Ala Ala Ser Tyr Ala Arg		
405	410	415
Tyr Val Leu Gln Lys Leu Val Leu Leu Glu Met Lys Gly Gly Cys Arg		
420	425	430
Glu Pro Glu Leu Asp Thr Glu Thr Leu Thr Thr Met Phe Glu Val Ser		
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Val Ala Phe Phe Lys Val Gly His Ala Val Gly Glu Thr Gly Asn Gly		
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Cys Val Asp Leu Arg Trp Leu Ala Lys Ser Phe Phe Glu Leu Thr Val		
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Leu Lys Asp Ile Ile Gly Ile Cys Tyr Gly Ala Thr Val Lys Gly Met		
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Gln Ser Tyr Gly Leu Glu Arg Leu Ala Ala Met Leu Met Ala Thr Val		
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Lys Met Glu Glu Leu Gly His Leu Thr Thr Glu Lys Gln Glu Tyr Ala		
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Leu Arg Leu Ala Thr Val Gly Tyr Pro Lys Ala Gly Val Tyr Ser Gly		
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Leu Ile Gly Gly Ala Thr Ser Val Leu Leu Ser Ala Tyr Asn Arg His		
545	550	555
Pro Leu Phe Gln Pro Leu His Thr Val Met Arg Glu Thr Leu Phe Ile		

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Gly	Pro	Asn	Leu	Ala	Leu	Tyr	Gln	Leu	Leu	Ser	Thr	Ala	Leu	Cys	Ser		
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Ala	Leu	Glu	Ile	Gly	Glu	Val	Leu	Arg	Gly	Leu	Ala	Leu	Gly	Thr	Glu		
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Arg	Asp	Lys	Leu	Leu	Ser	Met	Ala	Pro	Gln	Glu	Ala	Thr	Leu	Asp	Gln		
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Glu	Arg	Glu	Asp	Arg	Asp	Ala	Trp	His	Leu	Pro	Ala	Tyr	Lys	Cys	Val		
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Asp	Arg	Leu	Asp	Lys	Val	Leu	Met	Ile	Ile	Pro	Leu	Ile	Asn	Val	Thr		
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Phe	Ile	Ile	Ser	Ser	Asp	Arg	Glu	Val	Arg	Gly	Ser	Ala	Leu	Tyr	Glu		
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Ala	Ser	Thr	Thr	Tyr	Leu	Ser	Ser	Ser	Leu	Phe	Leu	Ser	Pro	Val	Ile		
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Met	Asn	Lys	Cys	Ser	Gln	Gly	Ala	Val	Ala	Gly	Glu	Pro	Arg	Gln	Ile		
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Pro	Lys	Ile	Gln	Asn	Phe	Thr	Arg	Thr	Gln	Lys	Ser	Cys	Ile	Phe	Cys		
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785																	
				790					795					800			
Tyr	Phe	Asp	Phe	Asp	Asn	Leu	His	Val	His	Tyr	Leu	Leu	Leu	Thr	Thr		
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Leu Tyr Met Ser Met Ser Ser Trp Ser Tyr Thr His Ser Leu Asp Gly																			
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Lys Lys Leu Ile Ile Phe Leu Asn Glu Asn Asn Val Pro Val Gln Leu																			
Thr Ser Ile Ser Ala Pro Glu His Lys Phe Glu Gly Leu Thr Gln Ile																			
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Gln Leu Arg Ala Gln His Leu Leu Ala Leu Glu Asn Ile Ser Asp Ile																			
Tyr Leu Val Ser Asn Gln Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu																			
Asn Ser Pro Lys Asn Gly Ser Asn Gln Leu Val Ile Ser Arg Cys Ala																			
65																			
Asn Gly Leu Asn Val Val Ser Phe Phe Ile Ser Ile Leu Lys Arg Ser																			

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

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Phe Ser Arg Ala Val Thr Met Thr Ala Ala Ser Tyr Ala Arg Tyr Val					
	420		425		430
Leu Gln Lys Leu Val Leu Leu Glu Met Lys Gly Gly Cys Arg Glu Pro					
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Glu Leu Asp Thr Glu Thr Leu Thr Thr Met Phe Glu Val Ser Val Ala					
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Phe Phe Lys Val Gly His Ala Val Gly Glu Thr Gly Asn Gly Cys Val					
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Asp Leu Arg Trp Leu Ala Lys Ser Phe Phe Glu Leu Thr Val Leu Lys					
	485		490		495
Asp Ile Ile Gly Ile Cys Tyr Gly Ala Thr Val Lys Gly Met Gln Ser					
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Tyr Gly Leu Glu Arg Leu Ala Ala Met Leu Met Ala Thr Val Lys Met					
	515		520		525
Glu Glu Leu Gly His Leu Thr Thr Glu Lys Gln Glu Tyr Ala Leu Arg					
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Leu Ala Thr Val Gly Tyr Pro Lys Ala Gly Val Tyr Ser Gly Leu Ile					
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Gly Gly Ala Thr Ser Val Leu Leu Ser Ala Tyr Asn Arg His Pro Leu					
	565		570		575
Phe Gln Pro Leu His Thr Val Met Arg Glu Thr Leu Phe Ile Gly Ser					
	580		585		590
His Val Val Leu Arg Glu Leu Arg Leu Asn Val Thr Thr Gln Gly Pro					
	595		600		605
Asn Leu Ala Leu Tyr Gln Leu Leu Ser Thr Ala Leu Cys Ser Ala Leu					
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Glu Ile Gly Glu Val Leu Arg Gly Leu Ala Leu Gly Thr Glu Ser Gly					
625		630		635	640
Leu Phe Ser Pro Cys Tyr Leu Ser Leu Arg Phe Asp Leu Thr Arg Asp					
	645		650		655
Lys Leu Leu Ser Met Ala Pro Gln Glu Ala Thr Leu Asp Gln Ala Ala					
	660		665		670
Val Ser Asn Ala Val Asp Gly Phe Leu Gly Arg Leu Ser Leu Glu Arg					
	675		680		685
Glu Asp Arg Asp Ala Trp His Leu Pro Ala Tyr Lys Cys Val Asp Arg					
	690		695		700
Leu Asp Lys Val Leu Met Ile Ile Pro Leu Ile Asn Val Thr Phe Ile					
705		710		715	720

Ile Ser Ser Asp Arg Glu Val Arg Gly Ser Ala Leu Tyr Glu Ala Ser		
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Thr Thr Tyr Leu Ser Ser Ser Leu Phe Leu Ser Pro Val Ile Met Asn		
740	745	750
Lys Cys Ser Gln Gly Ala Val Ala Gly Glu Pro Arg Gln Ile Pro Lys		
755	760	765
Ile Gln Asn Phe Thr Arg Thr Gln Lys Ser Cys Ile Phe Cys Gly Phe		
770	775	780
Ala Leu Leu Ser Tyr Asp Glu Lys Glu Gly Leu Glu Thr Thr Thr Tyr		
785	790	795
Ile Thr Ser Gln Glu Val Gln Asn Ser Ile Leu Ser Ser Asn Tyr Phe		
805	810	815
Asp Phe Asp Asn Leu His Val His Tyr Leu Leu Leu Thr Thr Asn Gly		
820	825	830
Thr Val Met Glu Ile Ala Gly Leu Tyr Glu Glu Arg Ala Ser Gly Gly		
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Gly Ser Gly Ser Ala Ser Ser Gly Ala Ser Ala Ser Gly Ser Ser Gly		
850	855	860
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885	890	895
Arg Gln Gln Phe Ser Lys Asp Ile Glu Lys Leu Leu Asn Glu Gln Val		
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Asn Lys Glu Met Gln Ser Ser Asn Leu Tyr Met Ser Met Ser Ser Trp		
915	920	925
Ser Tyr Thr His Ser Leu Asp Gly Ala Gly Leu Phe Leu Phe Asp His		
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Ala Ala Glu Glu Tyr Glu His Ala Lys Lys Leu Ile Ile Phe Leu Asn		
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Glu Asn Asn Val Pro Val Gln Leu Thr Ser Ile Ser Ala Pro Glu His		
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Lys Phe Glu Gly Leu Thr Gln Ile Phe Gln Lys Ala Tyr Glu His Glu		
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Gln His Ile Ser Glu Ser Ile Asn Asn Ile Val Asp His Ala Ile Lys		
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Cys Lys Asp His Ala Thr Phe Asn Phe Leu Gln Trp Tyr Val Ala		
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Glu Gln His Glu Glu Glu Val Leu Phe Lys Asp Ile Leu Asp Lys		

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Ile Glu Leu Ile Gly Asn	Glu Asn His Gly Leu	Tyr Leu Ala Asp
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Tyr Leu Val Ser Asn Gln Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu		
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Asn Ser Pro Lys Asn Gly Ser Asn Gln Leu Val Ile Ser Arg Cys Ala		
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Asn Gly Leu Asn Val Val Ser Phe Phe Ile Ser Ile Leu Lys Arg Ser		
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Ser Ser Ala Leu Thr Gly His Leu Arg Glu Leu Leu Thr Thr Leu Glu		
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Thr Leu Tyr Gly Ser Phe Ser Val Glu Asp Leu Phe Gly Ala Asn Leu		
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Asn Arg Tyr Ala Trp His Arg Gly Gly Gly Gly Ser Gly Ser Ala Ser		
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Ser Gly Ala Ser Ala Ser Gly Ser Ser Asn Gly Ser Gly Ser Gly Ser		
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Gly Ser Asn Ser Ser Ala Ser Ser Gly Ala Ser Ser Gly Gly Ala Ser		
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Gly Gly Ser Gly Gly Ser Gly Ala Ala Ser Leu Ser Glu Val Lys Leu		
180	185	190
His Leu Asp Ile Glu Gly His Ala Ser His Tyr Thr Ile Pro Trp Thr		
195	200	205
Glu Leu Met Ala Lys Val Pro Gly Leu Ser Pro Glu Ala Leu Trp Arg		

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

Glu	Glu	Leu	Gly	His	Leu	Thr	Thr	Glu	Lys	Gln	Glu	Tyr	Ala	Leu	Arg
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Leu	Ala	Thr	Val	Gly	Tyr	Pro	Lys	Ala	Gly	Val	Tyr	Ser	Gly	Leu	Ile
545				550					555					560	
Gly	Gly	Ala	Thr	Ser	Val	Leu	Leu	Ser	Ala	Tyr	Asn	Arg	His	Pro	Leu
			565					570					575		
Phe	Gln	Pro	Leu	His	Thr	Val	Met	Arg	Glu	Thr	Leu	Phe	Ile	Gly	Ser
		580						585					590		
His	Val	Val	Leu	Arg	Glu	Leu	Arg	Leu	Asn	Val	Thr	Thr	Gln	Gly	Pro
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Leu	Phe	Ser	Pro	Cys	Tyr	Leu	Ser	Leu	Arg	Phe	Asp	Leu	Thr	Arg	Asp
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Lys	Leu	Leu	Ser	Met	Ala	Pro	Gln	Glu	Ala	Thr	Leu	Asp	Gln	Ala	Ala
			660					665					670		
Val	Ser	Asn	Ala	Val	Asp	Gly	Phe	Leu	Gly	Arg	Leu	Ser	Leu	Glu	Arg
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Ile	Ser	Ser	Asp	Arg	Glu	Val	Arg	Gly	Ser	Ala	Leu	Tyr	Glu	Ala	Ser
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Thr	Thr	Tyr	Leu	Ser	Ser	Ser	Leu	Phe	Leu	Ser	Pro	Val	Ile	Met	Asn
		740						745					750		
Lys	Cys	Ser	Gln	Gly	Ala	Val	Ala	Gly	Glu	Pro	Arg	Gln	Ile	Pro	Lys
	755						760						765		
Ile	Gln	Asn	Phe	Thr	Arg	Thr	Gln	Lys	Ser	Cys	Ile	Phe	Cys	Gly	Phe
770						775					780				
Ala	Leu	Leu	Ser	Tyr	Asp	Glu	Lys	Glu	Gly	Leu	Glu	Thr	Thr	Thr	Tyr
785					790					795					800
Ile	Thr	Ser	Gln	Glu	Val	Gln	Asn	Ser	Ile	Leu	Ser	Ser	Asn	Tyr	Phe
			805						810				815		
Asp	Phe	Asp	Asn	Leu	His	Val	His	Tyr	Leu	Leu	Leu	Thr	Thr	Asn	Gly
		820						825					830		
Thr	Val	Met	Glu	Ile	Ala	Gly	Leu	Tyr	Glu	Glu	Arg	Ala	Ser	Gly	Gly

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Ser Gly Ser Gly Ser Gly Ser Ser Ser Ala Ser Ser Gly Ala Ser Ser		
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Gly Gly Ala Ser Gly Gly Gly Ser Gly Gly Ser Gly Glu Ser Gln Val		
885	890	895
Arg Gln Gln Phe Ser Lys Asp Ile Glu Lys Leu Leu Asn Glu Gln Val		
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Asn Lys Glu Met Gln Ser Ser Asn Leu Tyr Met Ser Met Ser Ser Trp		
915	920	925
Ser Tyr Thr His Ser Leu Asp Gly Ala Gly Leu Phe Leu Phe Asp His		
930	935	940
Ala Ala Glu Glu Tyr Glu His Ala Lys Lys Leu Ile Ile Phe Leu Asn		
945	950	955
Glu Asn Asn Val Pro Val Gln Leu Thr Ser Ile Ser Ala Pro Glu His		
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Lys Phe Glu Gly Leu Thr Gln Ile Phe Gln Lys Ala Tyr Glu His Glu		
980	985	990
Gln His Ile Ser Glu Ser Ile Asn Asn Ile Val Asp His Ala Ile Lys		
995	1000	1005
Ser Lys Asp His Ala Thr Phe Asn Phe Leu Gln Trp Tyr Val Ala		
1010	1015	1020
Glu Gln His Glu Glu Glu Val Leu Phe Lys Asp Ile Leu Asp Lys		
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Ile Glu Leu Ile Gly Asn Glu Asn His Gly Leu Tyr Leu Ala Asp		
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Gln Leu Arg Ala Gln His Leu	Leu Ala Leu Glu Asn Ile Ser Asp Ile	
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Tyr Leu Val Ser Asn Gln Thr	Cys Asp Gly Phe Ser Leu Ala Ser Leu	
50	55	60
Asn Ser Pro Lys Asn Gly Ser	Asn Gln Leu Val Ile Ser Arg Cys Ala	
65	70	75
Asn Gly Leu Asn Val Val Ser	Phe Phe Ile Ser Ile Leu Lys Arg Ser	
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Ser Ser Ala Leu Thr Gly His	Leu Arg Glu Leu Leu Thr Thr Leu Glu	
100	105	110
Thr Leu Tyr Gly Ser Phe Ser	Val Glu Asp Leu Phe Gly Ala Asn Leu	
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Asn Arg Tyr Ala Trp His Arg	Gly Gly Gly Gly Ser Gly Ser Ala Ser	
130	135	140
Ser Gly Ala Ser Ala Ser Gly	Ser Ser Asn Gly Ser Gly Ser Gly Ser	
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Gly Ser Asn Ser Ser Ala Ser	Ser Ser Gly Ala Ser Ser Gly Gly Ala Ser	
165	170	175
Gly Gly Ser Gly Gly Ser Gly	Ala Ala Ser Leu Ser Glu Val Lys Leu	
180	185	190
His Leu Asp Ile Glu Gly His	Ala Ser His Tyr Thr Ile Pro Trp Thr	
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Glu Leu Met Ala Lys Val Pro	Gly Leu Ser Pro Glu Ala Leu Trp Arg	
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Glu Ala Asn Val Thr Glu Asp	Leu Ala Ser Met Leu Asn Arg Tyr Lys	
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Leu Ile Tyr Lys Thr Ser Gly	Thr Leu Gly Ile Ala Leu Ala Glu Pro	
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Val Asp Ile Pro Ala Val Ser	Glu Gly Ser Met Gln Val Asp Ala Ser	
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Lys Val His Pro Gly Val Ile	Ser Gly Leu Asn Ser Pro Ala Cys Met	
275	280	285
Leu Ser Ala Pro Leu Glu Lys	Gln Leu Phe Tyr Tyr Ile Gly Thr Met	
290	295	300
Leu Pro Asn Thr Arg Pro His	Ser Tyr Val Phe Tyr Gln Leu Arg Cys	
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His Leu Ser Tyr Val Ala Leu	Ser Ile Asn Gly Asp Lys Phe Gln Tyr	
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Thr Gly Ala Met Thr Ser Lys Phe Leu Met Gly Thr Tyr Lys Arg Val			
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Thr Glu Lys Gly Asp Glu His Val Leu Ser Leu Val Phe Gly Lys Thr			
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Lys Asp Leu Pro Asp Leu Arg Gly Pro Phe Ser Tyr Pro Ser Leu Thr			
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Ser Ala Gln Ser Gly Asp Tyr Ser Leu Val Ile Val Thr Thr Phe Val			
385	390	395	400
His Tyr Ala Asn Phe His Asn Tyr Phe Val Pro Asn Leu Lys Asp Met			
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Phe Ser Arg Ala Val Thr Met Thr Ala Ala Ser Tyr Ala Arg Tyr Val			
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Leu Gln Lys Leu Val Leu Leu Glu Met Lys Gly Gly Cys Arg Glu Pro			
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Glu Leu Asp Thr Glu Thr Leu Thr Thr Met Phe Glu Val Ser Val Ala			
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Asp Leu Arg Trp Leu Ala Lys Ser Phe Phe Glu Leu Thr Val Leu Lys			
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Glu Glu Leu Gly His Leu Thr Thr Glu Lys Gln Glu Tyr Ala Leu Arg			
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Leu Ala Thr Val Gly Tyr Pro Lys Ala Gly Val Tyr Ser Gly Leu Ile			
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Gly Gly Ala Thr Ser Val Leu Leu Ser Ala Tyr Asn Arg His Pro Leu			
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Asn Leu Ala Leu Tyr Gln Leu Leu Ser Thr Ala Leu Cys Ser Ala Leu			
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Leu Phe Ser Pro Cys Tyr Leu Ser Leu Arg Phe Asp Leu Thr Arg Asp			

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

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

Glu Leu Asp Thr Glu Thr Leu Thr Thr Met Phe Glu Val Ser Val Ala		
450	455	460
Phe Phe Lys Val Gly His Ala Val Gly Glu Thr Gly Asn Gly Cys Val		
465	470	475 480
Asp Leu Arg Trp Leu Ala Lys Ser Phe Phe Glu Leu Thr Val Leu Lys		
	485	490 495
Asp Ile Ile Gly Ile Cys Tyr Gly Ala Thr Val Lys Gly Met Gln Ser		
	500	505 510
Tyr Gly Leu Glu Arg Leu Ala Ala Met Leu Met Ala Thr Val Lys Met		
	515	520 525
Glu Glu Leu Gly His Leu Thr Thr Glu Lys Gln Glu Tyr Ala Leu Arg		
	530	535 540
Leu Ala Thr Val Gly Tyr Pro Lys Ala Gly Val Tyr Ser Gly Leu Ile		
545	550	555 560
Gly Gly Ala Thr Ser Val Leu Leu Ser Ala Tyr Asn Arg His Pro Leu		
	565	570 575
Phe Gln Pro Leu His Thr Val Met Arg Glu Thr Leu Phe Ile Gly Ser		
	580	585 590
His Val Val Leu Arg Glu Leu Arg Leu Asn Val Thr Thr Gln Gly Pro		
	595	600 605
Asn Leu Ala Leu Tyr Gln Leu Leu Ser Thr Ala Leu Cys Ser Ala Leu		
	610	615 620
Glu Ile Gly Glu Val Leu Arg Gly Leu Ala Leu Gly Thr Glu Ser Gly		
625	630	635 640
Leu Phe Ser Pro Cys Tyr Leu Ser Leu Arg Phe Asp Leu Thr Arg Asp		
	645	650 655
Lys Leu Leu Ser Met Ala Pro Gln Glu Ala Thr Leu Asp Gln Ala Ala		
	660	665 670
Val Ser Asn Ala Val Asp Gly Phe Leu Gly Arg Leu Ser Leu Glu Arg		
	675	680 685
Glu Asp Arg Asp Ala Trp His Leu Pro Ala Tyr Lys Cys Val Asp Arg		
	690	695 700
Leu Asp Lys Val Leu Met Ile Ile Pro Leu Ile Asn Val Thr Phe Ile		
705	710	715 720
Ile Ser Ser Asp Arg Glu Val Arg Gly Ser Ala Leu Tyr Glu Ala Ser		
	725	730 735
Thr Thr Tyr Leu Ser Ser Ser Leu Phe Leu Ser Pro Val Ile Met Asn		
	740	745 750
Lys Cys Ser Gln Gly Ala Val Ala Gly Glu Pro Arg Gln Ile Pro Lys		

755	760	765
Ile Gln Asn Phe Thr Arg Thr Gln Lys Ser Cys	Ile Phe Cys Gly Phe	
770	775	780
Ala Leu Leu Ser Tyr Asp Glu Lys Glu Gly Leu Glu Thr Thr Thr Tyr		
785	790	795
Ile Thr Ser Gln Glu Val Gln Asn Ser Ile Leu Ser Ser Asn Tyr Phe		800
805	810	815
Asp Phe Asp Asn Leu His Val His Tyr Leu Leu Leu Thr Thr Asn Gly		
820	825	830
Thr Val Met Glu Ile Ala Gly Leu Tyr Glu Glu Arg Ala Ser Gly Gly		
835	840	845
Gly Ser Gly Ser Ala Ser Ser Gly Ala Ser Ala Ser Gly Ser Ser Gly		
850	855	860
Ser Gly Ser Gly Ser Gly Ser Ser Ser Ala Ser Ser Gly Ala Ser Ser		
865	870	875
Gly Gly Ala Ser Gly Gly Gly Ser Gly Gly Ser Gly Glu Ser Gln Val		
885	890	895
Arg Gln Gln Phe Ser Lys Asp Ile Glu Lys Leu Leu Asn Glu Gln Val		
900	905	910
Asn Lys Glu Met Gln Ser Ser Asn Leu Tyr Met Ser Met Ser Ser Trp		
915	920	925
Ser Tyr Thr His Ser Leu Asp Gly Ala Gly Leu Phe Leu Phe Asp His		
930	935	940
Ala Ala Glu Glu Tyr Glu His Ala Lys Lys Leu Ile Ile Phe Leu Asn		
945	950	955
Glu Asn Asn Val Pro Val Gln Leu Thr Ser Ile Ser Ala Pro Glu His		
965	970	975
Lys Phe Glu Gly Leu Thr Gln Ile Phe Gln Lys Ala Tyr Glu His Glu		
980	985	990
Gln His Ile Ser Glu Ser Ile Asn Asn Ile Val Asp His Ala Ile Lys		
995	1000	1005
Cys Lys Asp His Ala Thr Phe Asn Phe Leu Gln Trp Tyr Val Ala		
1010	1015	1020
Glu Gln His Glu Glu Glu Val Leu Phe Lys Asp Ile Leu Asp Lys		
1025	1030	1035
Ile Glu Leu Ile Gly Asn Glu Asn His Gly Leu Tyr Leu Ala Asp		
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Gln Tyr Val Lys Gly Ile Ala Lys Ser Arg Lys Ser		
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<212> PRT

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<223> 合成多肽

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

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

				565					570					575			
Phe	Gln	Pro	Leu	His	Thr	Val	Met	Arg	Glu	Thr	Leu	Phe	Ile	Gly	Ser		
				580					585					590			
His	Val	Val	Leu	Arg	Glu	Leu	Arg	Leu	Asn	Val	Thr	Thr	Gln	Gly	Pro		
				595					600					605			
Asn	Leu	Ala	Leu	Tyr	Gln	Leu	Leu	Ser	Thr	Ala	Leu	Cys	Ser	Ala	Leu		
				610					615					620			
Glu	Ile	Gly	Glu	Val	Leu	Arg	Gly	Leu	Ala	Leu	Gly	Thr	Glu	Ser	Gly		
625						630					635				640		
Leu	Phe	Ser	Pro	Cys	Tyr	Leu	Ser	Leu	Arg	Phe	Asp	Leu	Thr	Arg	Asp		
				645					650					655			
Lys	Leu	Leu	Ser	Met	Ala	Pro	Gln	Glu	Ala	Thr	Leu	Asp	Gln	Ala	Ala		
				660					665					670			
Val	Ser	Asn	Ala	Val	Asp	Gly	Phe	Leu	Gly	Arg	Leu	Ser	Leu	Glu	Arg		
				675					680					685			
Glu	Asp	Arg	Asp	Ala	Trp	His	Leu	Pro	Ala	Tyr	Lys	Cys	Val	Asp	Arg		
				690					695					700			
Leu	Asp	Lys	Val	Leu	Met	Ile	Ile	Pro	Leu	Ile	Asn	Val	Thr	Phe	Ile		
705						710					715				720		
Ile	Ser	Ser	Asp	Arg	Glu	Val	Arg	Gly	Ser	Ala	Leu	Tyr	Glu	Ala	Ser		
				725					730					735			
Thr	Thr	Tyr	Leu	Ser	Ser	Ser	Leu	Phe	Leu	Ser	Pro	Val	Ile	Met	Asn		
				740					745					750			
Lys	Cys	Ser	Gln	Gly	Ala	Val	Ala	Gly	Glu	Pro	Arg	Gln	Ile	Pro	Lys		
				755					760					765			
Ile	Gln	Asn	Phe	Thr	Arg	Thr	Gln	Lys	Ser	Cys	Ile	Phe	Cys	Gly	Phe		
				770					775					780			
Ala	Leu	Leu	Ser	Tyr	Asp	Glu	Lys	Glu	Gly	Leu	Glu	Thr	Thr	Thr	Tyr		
785						790					795				800		
Ile	Thr	Ser	Gln	Glu	Val	Gln	Asn	Ser	Ile	Leu	Ser	Ser	Asn	Tyr	Phe		
				805					810					815			
Asp	Phe	Asp	Asn	Leu	His	Val	His	Tyr	Leu	Leu	Leu	Thr	Thr	Asn	Gly		
				820					825					830			
Thr	Val	Met	Glu	Ile	Ala	Gly	Leu	Tyr	Glu	Glu	Arg	Ala	Ser	Gly	Gly		
				835					840					845			
Gly	Ser	Gly	Ser	Ala	Ser	Ser	Gly	Ala	Ser	Ala	Ser	Gly	Ser	Ser	Cys		
				850					855					860			
Ser	Gly	Ser	Gly	Ser	Gly	Ser	Ser	Ser	Ala	Ser	Ser	Gly	Ala	Ser	Ser		
865						870					875				880		

Gly Gly Ala Ser Gly Gly Gly Ser Gly Gly Ser Gly Glu Ser Gln Val		
	885	890 895
Arg Gln Gln Phe Ser Lys Asp Ile Glu Lys Leu Leu Asn Glu Gln Val		
	900	905 910
Asn Lys Glu Met Gln Ser Ser Asn Leu Tyr Met Ser Met Ser Ser Trp		
	915	920 925
Ser Tyr Thr His Ser Leu Asp Gly Ala Gly Leu Phe Leu Phe Asp His		
	930	935 940
Ala Ala Glu Glu Tyr Glu His Ala Lys Lys Leu Ile Ile Phe Leu Asn		
945	950	955 960
Glu Asn Asn Val Pro Val Gln Leu Thr Ser Ile Ser Ala Pro Glu His		
	965	970 975
Lys Phe Glu Gly Leu Thr Gln Ile Phe Gln Lys Ala Tyr Glu His Glu		
	980	985 990
Gln His Ile Ser Glu Ser Ile Asn Asn Ile Val Asp His Ala Ile Lys		
	995	1000 1005
Ser Lys Asp His Ala Thr Phe Asn Phe Leu Gln Trp Tyr Val Ala		
	1010	1015 1020
Glu Gln His Glu Glu Glu Val Leu Phe Lys Asp Ile Leu Asp Lys		
	1025	1030 1035
Ile Glu Leu Ile Gly Asn Glu Asn His Gly Leu Tyr Leu Ala Asp		
	1040	1045 1050
Gln Tyr Val Lys Gly Ile Ala Lys Ser Arg Lys Ser		
	1055	1060 1065
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Leu Val Val Ser Asn Leu Leu Leu Pro Gln Gly Val Leu Ala Glu Ala		
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Ala Leu Leu Val Cys Gln Tyr Thr Ile Gln Ser Leu Ile His Leu Thr		
	35	40 45
Gly Glu Asp Pro Gly Phe Phe Asn Val Glu Ile Pro Glu Phe Pro Phe		
	50	55 60

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

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

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<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 25

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

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

595	600	605
Asn Leu Ala Leu Tyr Gln Leu Leu Ser Thr Ala Leu Cys Ser Ala Leu		
610	615	620
Glu Ile Gly Glu Val Leu Arg Gly Leu Ala Leu Gly Thr Glu Ser Gly		
625	630	635
Leu Phe Ser Pro Cys Tyr Leu Ser Leu Arg Phe Asp Leu Thr Arg Asp		
645	650	655
Lys Leu Leu Ser Met Ala Pro Gln Glu Ala Thr Leu Asp Gln Ala Ala		
660	665	670
Val Ser Asn Ala Val Asp Gly Phe Leu Gly Arg Leu Ser Leu Glu Arg		
675	680	685
Glu Asp Arg Asp Ala Trp His Leu Pro Ala Tyr Lys Cys Val Asp Arg		
690	695	700
Leu Asp Lys Val Leu Met Ile Ile Pro Leu Ile Asn Val Thr Phe Ile		
705	710	715
Ile Ser Ser Asp Arg Glu Val Arg Gly Ser Ala Leu Tyr Glu Ala Ser		
725	730	735
Thr Thr Tyr Leu Ser Ser Ser Leu Phe Leu Ser Pro Val Ile Met Asn		
740	745	750
Lys Cys Ser Gln Gly Ala Val Ala Gly Glu Pro Arg Gln Ile Pro Lys		
755	760	765
Ile Gln Asn Phe Thr Arg Thr Gln Lys Ser Cys Ile Phe Cys Gly Phe		
770	775	780
Ala Leu Leu Ser Tyr Asp Glu Lys Glu Gly Leu Glu Thr Thr Thr Tyr		
785	790	795
Ile Thr Ser Gln Glu Val Gln Asn Ser Ile Leu Ser Ser Asn Tyr Phe		
805	810	815
Asp Phe Asp Asn Leu His Val His Tyr Leu Leu Leu Thr Thr Asn Gly		
820	825	830
Thr Val Met Glu Ile Ala Gly Leu Tyr Glu Glu Arg Ala Ser Gly Ser		
835	840	845
Thr Gln Cys Asn Val Asn Pro Val Gln Ile Pro Lys Asp Trp Ile Thr		
850	855	860
Met His Arg Ser Cys Arg Asn Ser Met Arg Gln Gln Ile Gln Met Glu		
865	870	875
Val Gly Ala Ser Leu Gln Tyr Leu Ala Met Gly Ala His Phe Ser Lys		
885	890	895
Asp Val Val Asn Arg Pro Gly Phe Ala Gln Leu Phe Phe Asp Ala Ala		
900	905	910

Ser Glu Glu Arg Glu His Ala Met Lys Leu Ile Glu Tyr Leu Leu Met
 915 920 925
 Arg Gly Glu Leu Thr Asn Asp Val Ser Ser Leu Leu Gln Val Arg Pro
 930 935 940
 Pro Thr Arg Ser Ser Trp Lys Gly Gly Val Glu Ala Leu Glu His Ala
 945 950 955 960
 Leu Ser Met Glu Ser Asp Val Thr Lys Ser Ile Arg Asn Val Ile Lys
 965 970 975
 Ala Cys Glu Asp Asp Ser Glu Phe Asn Asp Tyr His Leu Val Asp Tyr
 980 985 990
 Leu Thr Gly Asp Phe Leu Glu Glu Gln Tyr Lys Gly Gln Arg Asp Leu
 995 1000 1005
 Ala Gly Lys Ala Ser Thr Leu Lys Lys Leu Met Asp Arg His Glu
 1010 1015 1020
 Ala Leu Gly Glu Phe Ile Phe Asp Lys Lys Leu Leu Gly Ile Asp
 1025 1030 1035
 Val
 <210> 26
 <211> 669
 <212> PRT
 <213> 人工序列
 <220>
 <223> 合成多肽
 <400> 26
 Met Asp Ser Lys Gly Ser Ser Gln Lys Gly Ser Arg Leu Leu Leu Leu
 1 5 10 15
 Leu Val Val Ser Asn Leu Leu Leu Pro Gln Gly Val Leu Ala Glu Ala
 20 25 30
 Ala Leu Leu Val Cys Gln Tyr Thr Ile Gln Ser Leu Ile His Leu Thr
 35 40 45
 Gly Glu Asp Pro Gly Phe Phe Asn Val Glu Ile Pro Glu Phe Pro Phe
 50 55 60
 Tyr Pro Thr Cys Asn Val Cys Thr Ala Asp Val Asn Val Thr Ile Asn
 65 70 75 80
 Phe Asp Val Gly Gly Lys Lys His Gln Leu Asp Leu Asp Phe Gly Gln
 85 90 95
 Leu Thr Pro His Thr Lys Ala Val Tyr Gln Pro Arg Gly Ala Phe Gly
 100 105 110
 Gly Ser Glu Asn Ala Thr Asn Leu Phe Leu Leu Glu Leu Leu Gly Ala

115	120	125
Gly Glu Leu Ala Leu Thr Met Arg Ser Lys Lys Leu Pro Ile Asn Val		
130	135	140
Thr Thr Gly Glu Glu Gln Gln Val Ser Leu Glu Ser Val Asp Val Tyr		
145	150	155
Phe Gln Asp Val Phe Gly Thr Met Trp Cys His His Ala Glu Met Gln		
165	170	175
Asn Pro Val Tyr Leu Ile Pro Glu Thr Val Pro Tyr Ile Lys Trp Asp		
180	185	190
Asn Cys Asn Ser Thr Asn Ile Thr Ala Val Val Arg Ala Gln Gly Leu		
195	200	205
Asp Val Thr Leu Pro Leu Ser Leu Pro Thr Ser Ala Gln Asp Ser Asn		
210	215	220
Phe Ser Val Lys Thr Glu Met Leu Gly Asn Glu Ile Asp Ile Glu Cys		
225	230	235
Ile Met Glu Asp Gly Glu Ile Ser Gln Val Leu Pro Gly Asp Asn Lys		
245	250	255
Phe Asn Ile Thr Cys Ser Gly Tyr Glu Ser His Val Pro Ser Gly Gly		
260	265	270
Ile Leu Thr Ser Thr Ser Pro Val Ala Thr Pro Ile Pro Gly Thr Gly		
275	280	285
Tyr Ala Tyr Ser Leu Arg Leu Thr Pro Arg Pro Val Ser Arg Phe Leu		
290	295	300
Gly Asn Asn Ser Ile Leu Tyr Val Phe Tyr Ser Gly Asn Gly Pro Lys		
305	310	315
Ala Ser Gly Gly Asp Tyr Cys Ile Gln Ser Asn Ile Val Phe Ser Asp		
325	330	335
Glu Ile Pro Ala Ser Gln Asp Met Pro Thr Asn Thr Thr Asp Ile Thr		
340	345	350
Tyr Val Gly Asp Asn Ala Thr Tyr Ser Val Pro Met Val Thr Ser Glu		
355	360	365
Asp Ala Asn Ser Pro Asn Val Thr Val Thr Ala Phe Trp Ala Trp Pro		
370	375	380
Asn Asn Thr Glu Thr Asp Phe Lys Cys Lys Trp Thr Leu Thr Ser Gly		
385	390	395
Thr Pro Ser Gly Cys Glu Asn Ile Ser Gly Ala Phe Ala Ser Asn Arg		
405	410	415
Thr Phe Asp Ile Thr Val Ser Gly Leu Gly Thr Ala Pro Lys Thr Leu		
420	425	430

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

<210> 27

<211> 1060

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 27

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

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

	325		330		335
Thr Gly Ala Met Thr Ser Lys Phe Leu Met Gly Thr Tyr Lys Arg Val					
	340		345		350
Thr Glu Lys Gly Asp Glu His Val Leu Ser Leu Val Phe Gly Lys Thr					
	355		360		365
Lys Asp Leu Pro Asp Leu Arg Gly Pro Phe Ser Tyr Pro Ser Leu Thr					
	370		375		380
Ser Ala Gln Ser Gly Asp Tyr Ser Leu Val Ile Val Thr Thr Phe Val					
385		390		395	400
His Tyr Ala Asn Phe His Asn Tyr Phe Val Pro Asn Leu Lys Asp Met					
	405		410		415
Phe Ser Arg Ala Val Thr Met Thr Ala Ala Ser Tyr Ala Arg Tyr Val					
	420		425		430
Leu Gln Lys Leu Val Leu Leu Glu Met Lys Gly Gly Cys Arg Glu Pro					
	435		440		445
Glu Leu Asp Thr Glu Thr Leu Thr Thr Met Phe Glu Val Ser Val Ala					
450		455		460	
Phe Phe Lys Val Gly His Ala Val Gly Glu Thr Gly Asn Gly Cys Val					
465		470		475	480
Asp Leu Arg Trp Leu Ala Lys Ser Phe Phe Glu Leu Thr Val Leu Lys					
	485		490		495
Asp Ile Ile Gly Ile Cys Tyr Gly Ala Thr Val Lys Gly Met Gln Ser					
	500		505		510
Tyr Gly Leu Glu Arg Leu Ala Ala Met Leu Met Ala Thr Val Lys Met					
	515		520		525
Glu Glu Leu Gly His Leu Thr Thr Glu Lys Gln Glu Tyr Ala Leu Arg					
	530		535		540
Leu Ala Thr Val Gly Tyr Pro Lys Ala Gly Val Tyr Ser Gly Leu Ile					
545		550		555	560
Gly Gly Ala Thr Ser Val Leu Leu Ser Ala Tyr Asn Arg His Pro Leu					
	565		570		575
Phe Gln Pro Leu His Thr Val Met Arg Glu Thr Leu Phe Ile Gly Ser					
	580		585		590
His Val Val Leu Arg Glu Leu Arg Leu Asn Val Thr Thr Gln Gly Pro					
	595		600		605
Asn Leu Ala Leu Tyr Gln Leu Leu Ser Thr Ala Leu Cys Ser Ala Leu					
	610		615		620
Glu Ile Gly Glu Val Leu Arg Gly Leu Ala Leu Gly Thr Glu Ser Gly					
625		630		635	640

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

945	950	955	960
Arg Lys Asn Tyr Thr	Ala Glu Asn His Glu	Leu Glu Ala Leu	Ala Lys
	965	970	975
Ala Leu Asp Thr Gln	Lys Glu Leu Ala Glu	Arg Ala Phe Tyr	Ile His
	980	985	990
Arg Glu Ala Thr Arg	Asn Ser Gln His Leu	His Asp Pro Glu	Ile Ala
	995	1000	1005
Gln Tyr Leu Glu Glu	Glu Phe Ile Glu Asp	His Ala Glu Lys	Ile
	1010	1015	1020
Arg Thr Leu Ala Gly	His Thr Ser Asp Leu	Lys Lys Phe Ile	Thr
	1025	1030	1035
Ala Asn Asn Gly His	Asp Leu Ser Leu Ala	Leu Tyr Val Phe	Asp
	1040	1045	1050
Glu Tyr Leu Gln Lys	Thr Val		
	1055	1060	
<210>	28		
<211>	16		
<212>	PRT		
<213>	人工序列		
<220>			
<223>	合成多肽		
<400>	28		
Gly Gly Gly Gly Ser	Gly Gly Gly Gly Ser	Gly Gly Gly Gly Ser	Gly
1	5	10	15
<210>	29		
<211>	28		
<212>	PRT		
<213>	人工序列		
<220>			
<223>	合成多肽		
<400>	29		
Gly Gly Ser Gly Ser	Gly Ser Asn Ser Ser	Ala Ser Ser Gly	Ala Ser
1	5	10	15
Ser Gly Gly Ala Ser	Gly Gly Ser Gly Gly	Ser Gly	
	20	25	
<210>	30		
<211>	46		
<212>	PRT		
<213>	人工序列		

<220>

<223> 合成多肽

<400> 30

Gly	Gly	Ser	Gly	Ser	Ala	Ser	Ser	Gly	Ala	Ser	Ala	Ser	Gly	Ser	Ser
1				5					10					15	
Asn	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Asn	Ser	Ser	Ala	Ser	Ser	Gly
			20					25					30		
Ala	Ser	Ser	Gly	Gly	Ala	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly		
			35				40						45		

<210> 31

<211> 26

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 31

Gly	Gly	Ser	Gly	Ser	Ala	Ser	Ala	Glu	Ala	Ala	Ala	Lys	Glu	Ala	Ala
1				5					10					15	
Ala	Lys	Ala	Gly	Gly	Ser	Gly	Gly	Ser	Gly						
			20				25								

<210> 32

<211> 32

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 32

Gly	Gly	Ser	Gly	Ser	Ala	Ser	Ala	Glu	Ala	Ala	Ala	Lys	Glu	Ala	Ala
1				5					10					15	
Ala	Lys	Glu	Ala	Ala	Ala	Lys	Ala	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly
			20				25					30			

<210> 33

<211> 47

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 33

Ser	Gly	Gly	Gly	Ser	Gly	Ser	Ala	Ser	Ser	Gly	Ala	Ser	Ala	Ser	Gly
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

1	5	10	15
Ser Ser Cys Ser Gly Ser Gly Ser Gly Ser Ser Ser Ala Ser Ser Gly			
20	25	30	
Ala Ser Ser Gly Gly Ala Ser Gly Gly Gly Ser Gly Gly Ser Gly			
35	40	45	
<210> 34			
<211> 228			
<212> PRT			
<213> 爱泼斯坦-巴尔病毒			
<400> 34			
Asp Ser Lys Gly Ser Ser Gln Lys Gly Ser Arg Leu Leu Leu Leu Leu			
1	5	10	15
Val Val Ser Asn Leu Leu Leu Pro Gln Gly Val Leu Ala Tyr Phe Leu			
20	25	30	
Pro Pro Arg Val Arg Gly Gly Gly Arg Val Ala Ala Ala Ala Ile Thr			
35	40	45	
Trp Val Pro Lys Pro Asn Val Glu Val Trp Pro Val Asp Pro Pro Pro			
50	55	60	
Pro Val Asn Phe Asn Lys Thr Ala Glu Gln Glu Tyr Gly Asp Lys Glu			
65	70	75	80
Val Lys Leu Pro His Trp Thr Pro Thr Leu His Thr Phe Gln Val Pro			
85	90	95	
Gln Asn Tyr Thr Lys Ala Asn Cys Thr Tyr Cys Asn Thr Arg Glu Tyr			
100	105	110	
Thr Phe Ser Tyr Lys Gly Cys Cys Phe Tyr Phe Thr Lys Lys Lys His			
115	120	125	
Thr Trp Asn Gly Cys Phe Gln Ala Cys Ala Glu Leu Tyr Pro Cys Thr			
130	135	140	
Tyr Phe Tyr Gly Pro Thr Pro Asp Ile Leu Pro Val Val Thr Arg Asn			
145	150	155	160
Leu Asn Ala Ile Glu Ser Leu Trp Val Gly Val Tyr Arg Val Gly Glu			
165	170	175	
Gly Asn Trp Thr Ser Leu Asp Gly Gly Thr Phe Lys Val Tyr Gln Ile			
180	185	190	
Phe Gly Ser His Cys Thr Tyr Val Ser Lys Phe Ser Thr Val Pro Val			
195	200	205	
Ser His His Glu Cys Ser Phe Leu Lys Pro Cys Leu Cys Val Ser Gln			
210	215	220	
Arg Ser Asn Ser			

225

<210> 35

<211> 22

<212> DNA

<213> 人工序列

<220>

<223> 合成寡核苷酸

<400> 35

tgactgtgaa cgttcgagat ga 22

<210> 36

<211> 115

<212> PRT

<213> 爱泼斯坦-巴尔病毒

<400> 36

Asn Trp Ala Tyr Pro Cys Cys His Val Thr Gln Leu Arg Ala Gln His

1 5 10 15

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

20 25 30

Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu Asn Ser Pro Lys Asn Gly

35 40 45

Ser Asn Gln Leu Val Ile Ser Arg Cys Ala Asn Gly Leu Asn Val Val

50 55 60

Ser Phe Phe Ile Ser Ile Leu Lys Arg Ser Ser Ser Ala Leu Thr Gly

65 70 75 80

His Leu Arg Glu Leu Leu Thr Thr Leu Glu Thr Leu Tyr Gly Ser Phe

85 90 95

Ser Val Glu Asp Leu Phe Gly Ala Asn Leu Asn Arg Tyr Ala Trp His

100 105 110

Arg Gly Gly

115

<210> 37

<211> 662

<212> PRT

<213> 爱泼斯坦-巴尔病毒

<400> 37

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

1 5 10 15

Ala Ser His Tyr Thr Ile Pro Trp Thr Glu Leu Met Ala Lys Val Pro

20 25 30

Gly	Leu	Ser	Pro	Glu	Ala	Leu	Trp	Arg	Glu	Ala	Asn	Val	Thr	Glu	Asp
35				40				45							
Leu	Ala	Ser	Met	Leu	Asn	Arg	Tyr	Lys	Leu	Ile	Tyr	Lys	Thr	Ser	Gly
50				55				60							
Thr	Leu	Gly	Ile	Ala	Leu	Ala	Glu	Pro	Val	Asp	Ile	Pro	Ala	Val	Ser
65				70				75				80			
Glu	Gly	Ser	Met	Gln	Val	Asp	Ala	Ser	Lys	Val	His	Pro	Gly	Val	Ile
				85				90				95			
Ser	Gly	Leu	Asn	Ser	Pro	Ala	Cys	Met	Leu	Ser	Ala	Pro	Leu	Glu	Lys
				100				105				110			
Gln	Leu	Phe	Tyr	Tyr	Ile	Gly	Thr	Met	Leu	Pro	Asn	Thr	Arg	Pro	His
115				120				125							
Ser	Tyr	Val	Phe	Tyr	Gln	Leu	Arg	Cys	His	Leu	Ser	Tyr	Val	Ala	Leu
130				135				140							
Ser	Ile	Asn	Gly	Asp	Lys	Phe	Gln	Tyr	Thr	Gly	Ala	Met	Thr	Ser	Lys
145				150				155				160			
Phe	Leu	Met	Gly	Thr	Tyr	Lys	Arg	Val	Thr	Glu	Lys	Gly	Asp	Glu	His
				165				170				175			
Val	Leu	Ser	Leu	Val	Phe	Gly	Lys	Thr	Lys	Asp	Leu	Pro	Asp	Leu	Arg
180				185				190							
Gly	Pro	Phe	Ser	Tyr	Pro	Ser	Leu	Thr	Ser	Ala	Gln	Ser	Gly	Asp	Tyr
195				200				205							
Ser	Leu	Val	Ile	Val	Thr	Thr	Phe	Val	His	Tyr	Ala	Asn	Phe	His	Asn
210				215				220							
Tyr	Phe	Val	Pro	Asn	Leu	Lys	Asp	Met	Phe	Ser	Arg	Ala	Val	Thr	Met
225				230				235				240			
Thr	Ala	Ala	Ser	Tyr	Ala	Arg	Tyr	Val	Leu	Gln	Lys	Leu	Val	Leu	Leu
				245				250				255			
Glu	Met	Lys	Gly	Gly	Cys	Arg	Glu	Pro	Glu	Leu	Asp	Thr	Glu	Thr	Leu
260				265				270							
Thr	Thr	Met	Phe	Glu	Val	Ser	Val	Ala	Phe	Phe	Lys	Val	Gly	His	Ala
275				280				285							
Val	Gly	Glu	Thr	Gly	Asn	Gly	Cys	Val	Asp	Leu	Arg	Trp	Leu	Ala	Lys
290				295				300							
Ser	Phe	Phe	Glu	Leu	Thr	Val	Leu	Lys	Asp	Ile	Ile	Gly	Ile	Cys	Tyr
305				310				315				320			
Gly	Ala	Thr	Val	Lys	Gly	Met	Gln	Ser	Tyr	Gly	Leu	Glu	Arg	Leu	Ala
				325				330				335			
Ala	Met	Leu	Met	Ala	Thr	Val	Lys	Met	Glu	Glu	Leu	Gly	His	Leu	Thr

340	345	350
Thr Glu Lys Gln Glu Tyr Ala Leu Arg Leu Ala Thr Val Gly Tyr Pro		
355	360	365
Lys Ala Gly Val Tyr Ser Gly Leu Ile Gly Gly Ala Thr Ser Val Leu		
370	375	380
Leu Ser Ala Tyr Asn Arg His Pro Leu Phe Gln Pro Leu His Thr Val		
385	390	395
Met Arg Glu Thr Leu Phe Ile Gly Ser His Val Val Leu Arg Glu Leu		
405	410	415
Arg Leu Asn Val Thr Thr Gln Gly Pro Asn Leu Ala Leu Tyr Gln Leu		
420	425	430
Leu Ser Thr Ala Leu Cys Ser Ala Leu Glu Ile Gly Glu Val Leu Arg		
435	440	445
Gly Leu Ala Leu Gly Thr Glu Ser Gly Leu Phe Ser Pro Cys Tyr Leu		
450	455	460
Ser Leu Arg Phe Asp Leu Thr Arg Asp Lys Leu Leu Ser Met Ala Pro		
465	470	475
Gln Glu Ala Thr Leu Asp Gln Ala Ala Val Ser Asn Ala Val Asp Gly		
485	490	495
Phe Leu Gly Arg Leu Ser Leu Glu Arg Glu Asp Arg Asp Ala Trp His		
500	505	510
Leu Pro Ala Tyr Lys Cys Val Asp Arg Leu Asp Lys Val Leu Met Ile		
515	520	525
Ile Pro Leu Ile Asn Val Thr Phe Ile Ile Ser Ser Asp Arg Glu Val		
530	535	540
Arg Gly Ser Ala Leu Tyr Glu Ala Ser Thr Thr Tyr Leu Ser Ser Ser		
545	550	555
Leu Phe Leu Ser Pro Val Ile Met Asn Lys Cys Ser Gln Gly Ala Val		
565	570	575
Ala Gly Glu Pro Arg Gln Ile Pro Lys Ile Gln Asn Phe Thr Arg Thr		
580	585	590
Gln Lys Ser Cys Ile Phe Cys Gly Phe Ala Leu Leu Ser Tyr Asp Glu		
595	600	605
Lys Glu Gly Leu Glu Thr Thr Thr Tyr Ile Thr Ser Gln Glu Val Gln		
610	615	620
Asn Ser Ile Leu Ser Ser Asn Tyr Phe Asp Phe Asp Asn Leu His Val		
625	630	635
His Tyr Leu Leu Leu Thr Thr Asn Gly Thr Val Met Glu Ile Ala Gly		
645	650	655

Leu Tyr Glu Glu Arg Ala

660

<210> 38

<211> 425

<212> PRT

<213> 爱泼斯坦-巴尔病毒

<400> 38

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

1 5 10 15

Leu Thr Gly Glu Asp Pro Gly Phe Phe Asn Val Glu Ile Pro Glu Phe

20 25 30

Pro Phe Tyr Pro Thr Cys Asn Val Cys Thr Ala Asp Val Asn Val Thr

35 40 45

Ile Asn Phe Asp Val Gly Gly Lys Lys His Gln Leu Asp Leu Asp Phe

50 55 60

Gly Gln Leu Thr Pro His Thr Lys Ala Val Tyr Gln Pro Arg Gly Ala

65 70 75 80

Phe Gly Gly Ser Glu Asn Ala Thr Asn Leu Phe Leu Leu Glu Leu Leu

85 90 95

Gly Ala Gly Glu Leu Ala Leu Thr Met Arg Ser Lys Lys Leu Pro Ile

100 105 110

Asn Val Thr Thr Gly Glu Glu Gln Gln Val Ser Leu Glu Ser Val Asp

115 120 125

Val Tyr Phe Gln Asp Val Phe Gly Thr Met Trp Cys His His Ala Glu

130 135 140

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

145 150 155 160

Trp Asp Asn Cys Asn Ser Thr Asn Ile Thr Ala Val Val Arg Ala Gln

165 170 175

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

180 185 190

Ser Asn Phe Ser Val Lys Thr Glu Met Leu Gly Asn Glu Ile Asp Ile

195 200 205

Glu Cys Ile Met Glu Asp Gly Glu Ile Ser Gln Val Leu Pro Gly Asp

210 215 220

Asn Lys Phe Asn Ile Thr Cys Ser Gly Tyr Glu Ser His Val Pro Ser

225 230 235 240

Gly Gly Ile Leu Thr Ser Thr Ser Pro Val Ala Thr Pro Ile Pro Gly

245 250 255

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

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<212> PRT

<213> 人工序列

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<223> 合成多肽

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Cys Leu Val Pro Arg Gly Ser Leu Glu His His His His His His
 1 5 10 15

<210> 40

<211> 154

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<213> 风产液菌 (Aquifex aeolicus)

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

Ile Val Ala Ser Arg Phe Asn His Ala Leu Val Asp Arg Leu Val Glu

20	25	30
Gly Ala Ile Asp Cys Ile Val Arg His Gly Gly Arg Glu Glu Asp Ile		
35	40	45
Thr Leu Val Arg Val Pro Gly Ser Trp Glu Ile Pro Val Ala Ala Gly		
50	55	60
Glu Leu Ala Arg Lys Glu Asp Ile Asp Ala Val Ile Ala Ile Gly Val		
65	70	75
Leu Ile Arg Gly Ala Thr Pro His Phe Asp Tyr Ile Ala Ser Glu Val		
85	90	95
Ser Lys Gly Leu Ala Asn Leu Ser Leu Glu Leu Arg Lys Pro Ile Thr		
100	105	110
Phe Gly Val Ile Thr Ala Asp Thr Leu Glu Gln Ala Ile Glu Arg Ala		
115	120	125
Gly Thr Lys His Gly Asn Lys Gly Trp Glu Ala Ala Leu Ser Ala Ile		
130	135	140
Glu Met Ala Asn Leu Phe Lys Ser Leu Arg		
145	150	
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<213> 大肠杆菌 (Escherichia coli)		
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Met Asn Ile Ile Glu Ala Asn Val Ala Thr Pro Asp Ala Arg Val Ala		
1	5	10
Ile Thr Ile Ala Arg Phe Asn Asn Phe Ile Asn Asp Ser Leu Leu Glu		
20	25	30
Gly Ala Ile Asp Ala Leu Lys Arg Ile Gly Gln Val Lys Asp Glu Asn		
35	40	45
Ile Thr Val Val Trp Val Pro Gly Ala Tyr Glu Leu Pro Leu Ala Ala		
50	55	60
Gly Ala Leu Ala Lys Thr Gly Lys Tyr Asp Ala Val Ile Ala Leu Gly		
65	70	75
Thr Val Ile Arg Gly Gly Thr Ala His Phe Glu Tyr Val Ala Gly Gly		
85	90	95
Ala Ser Asn Gly Leu Ala His Val Ala Gln Asp Ser Glu Ile Pro Val		
100	105	110
Ala Phe Gly Val Leu Thr Thr Glu Ser Ile Glu Gln Ala Ile Glu Arg		
115	120	125
Ala Gly Thr Lys Ala Gly Asn Lys Gly Ala Glu Ala Ala Leu Thr Ala		

130	135	140
Leu Glu Met Ile Asn Val	Leu Lys Ala Ile Lys Ala	
145	150	155
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<211> 173

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 201

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

1 5 10 15

Asn Glu Gln Val Asn Lys Glu Met Gln Ser Ser Asn Leu Tyr Met Cys

20 25 30

Met Ser Ser Trp Ser Tyr Thr His Ser Leu Asp Gly Ala Gly Leu Phe

35 40 45

Leu Phe Asp His Ala Ala Glu Glu Tyr Glu His Ala Lys Lys Leu Ile

50 55 60

Ile Phe Leu Asn Glu Asn Asn Val Pro Val Gln Leu Thr Ser Ile Ser

65 70 75 80

Ala Pro Glu His Lys Phe Glu Gly Leu Thr Gln Ile Phe Gln Lys Ala

85 90 95

Tyr Glu His Glu Gln His Ile Ser Glu Ser Ile Asn Asn Ile Val Asp

100 105 110

His Ala Ile Lys Ser Lys Asp His Ala Thr Phe Asn Phe Leu Gln Trp

115 120 125

Tyr Val Ala Glu Gln His Glu Glu Glu Val Leu Phe Lys Asp Ile Leu

130 135 140

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

145 150 155 160

Asp Gln Tyr Val Lys Gly Ile Ala Lys Ser Arg Lys Ser
165 170

<210> 202

<211> 173

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 202

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

<210> 203

<211> 173

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 203

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

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

<210> 204

<211> 173

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 204

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

	85		90		95										
Tyr	Glu	His	Glu	Gln	His	Ile	Ser	Glu	Ser	Ile	Asn	Asn	Ile	Val	Asp
	100		105		110										
His	Ala	Ile	Lys	Ser	Lys	Asp	His	Ala	Thr	Phe	Asn	Phe	Leu	Gln	Trp
	115		120		125										
Tyr	Val	Ala	Glu	Gln	His	Glu	Glu	Glu	Val	Leu	Phe	Lys	Asp	Ile	Leu
	130		135		140										
Asp	Lys	Ile	Glu	Leu	Ile	Gly	Asn	Glu	Asn	His	Gly	Leu	Tyr	Leu	Ala
145			150		155										160
Asp	Gln	Tyr	Val	Lys	Gly	Ile	Ala	Lys	Ser	Arg	Lys	Ser			
	165		170												

<210> 205

<211> 173

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 205

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

165	170
<210> 206	
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<212> PRT	
<213> 人工序列	
<220>	
<223> 合成多肽	
<400> 206	
Glu Ser Gln Val Arg Gln Gln Phe Ser Lys Asp Ile Glu Lys Leu Leu	
1 5 10 15	
Asn Glu Gln Val Asn Lys Glu Met Gln Ser Ser Asn Leu Tyr Met Ser	
20 25 30	
Met Ser Ser Trp Ser Tyr Thr His Ser Leu Asp Gly Ala Gly Leu Phe	
35 40 45	
Leu Phe Asp His Ala Ala Glu Glu Tyr Glu His Ala Lys Lys Leu Ile	
50 55 60	
Ile Phe Leu Asn Glu Asn Asn Val Pro Val Gln Leu Thr Ser Ile Ser	
65 70 75 80	
Ala Pro Glu His Lys Phe Glu Gly Leu Thr Gln Ile Phe Gln Lys Ala	
85 90 95	
Tyr Glu His Glu Gln His Ile Ser Glu Ser Ile Asn Asn Ile Val Asp	
100 105 110	
His Ala Ile Lys Cys Lys Asp His Ala Thr Phe Asn Phe Leu Gln Trp	
115 120 125	
Tyr Val Ala Glu Gln His Glu Glu Glu Val Leu Phe Lys Asp Ile Leu	
130 135 140	
Asp Lys Ile Glu Leu Ile Gly Asn Glu Asn His Gly Leu Tyr Leu Ala	
145 150 155 160	
Asp Gln Tyr Val Lys Gly Ile Ala Lys Ser Arg Lys Ser	

165	170
<210> 207	
<211> 173	
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<213> 人工序列	
<220>	
<223> 合成多肽	
<400> 207	
Glu Ser Gln Val Arg Gln Gln Phe Ser Lys Asp Ile Glu Lys Leu Leu	
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Asn	Cys	Gln	Val	Asn	Lys	Glu	Met	Gln	Ser	Ser	Asn	Leu	Tyr	Met	Ser
20				25				30							
Met	Ser	Ser	Trp	Ser	Tyr	Thr	His	Ser	Leu	Asp	Gly	Ala	Gly	Leu	Phe
35				40				45							
Leu	Phe	Asp	His	Ala	Ala	Glu	Glu	Tyr	Glu	His	Ala	Lys	Lys	Leu	Ile
50				55				60							
Ile	Phe	Leu	Asn	Glu	Asn	Asn	Val	Pro	Val	Gln	Leu	Thr	Ser	Ile	Ser
65				70				75				80			
Ala	Pro	Glu	His	Lys	Phe	Glu	Gly	Leu	Thr	Gln	Ile	Phe	Gln	Lys	Ala
85				90				95							
Tyr	Glu	His	Glu	Gln	His	Ile	Ser	Glu	Ser	Ile	Asn	Asn	Ile	Val	Asp
100				105				110							
His	Ala	Ile	Lys	Ser	Lys	Asp	His	Ala	Thr	Phe	Asn	Phe	Leu	Gln	Trp
115				120				125							
Tyr	Val	Ala	Glu	Gln	His	Glu	Glu	Glu	Val	Leu	Phe	Lys	Asp	Ile	Leu
130				135				140							
Asp	Lys	Ile	Glu	Leu	Ile	Gly	Asn	Glu	Asn	His	Gly	Leu	Tyr	Leu	Ala
145				150				155				160			
Asp	Gln	Tyr	Val	Lys	Gly	Ile	Ala	Lys	Ser	Arg	Lys	Ser			
165				170											

<210> 208

<211> 173

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 208

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

Tyr Glu His Glu Gln His Ile Ser Glu Ser Ile Asn Asn Ile Val Asp
100 105 110
His Ala Ile Lys Ser Lys Asp His Ala Thr Phe Asn Phe Leu Gln Trp
115 120 125
Tyr Val Ala Glu Gln His Glu Glu Glu Val Leu Phe Lys Asp Ile Leu
130 135 140
Asp Lys Ile Glu Leu Ile Gly Asn Glu Asn His Gly Leu Tyr Leu Ala
145 150 155 160
Asp Gln Tyr Val Lys Gly Ile Ala Lys Ser Arg Lys Ser
165 170

<210> 209

<211> 166

<212> PRT

<213> 幽门螺杆菌 (Helicobacter pylori)

<400> 209

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

<211> 22

<212> DNA

<213> 人工序列

<220>

<223> 合成寡核苷酸

<400> 210

tgactgtgaa cgttcgagat ga 22

<210> 211

<211> 191

<212> PRT

<213> 粉纹夜蛾 (Trichoplusia ni)

<400> 211

Thr Gln Cys Asn Val Asn Pro Val Gln Ile Pro Lys Asp Trp Ile Thr
1 5 10 15

Met His Arg Ser Cys Arg Asn Ser Met Arg Gln Gln Ile Gln Met Glu
20 25 30

Val Gly Ala Ser Leu Gln Tyr Leu Ala Met Gly Ala His Phe Ser Lys
35 40 45

Asp Val Val Asn Arg Pro Gly Phe Ala Gln Leu Phe Phe Asp Ala Ala
50 55 60

Ser Glu Glu Arg Glu His Ala Met Lys Leu Ile Glu Tyr Leu Leu Met
65 70 75 80

Arg Gly Glu Leu Thr Asn Asp Val Ser Ser Leu Leu Gln Val Arg Pro
85 90 95

Pro Thr Arg Ser Ser Trp Lys Gly Gly Val Glu Ala Leu Glu His Ala
100 105 110

Leu Ser Met Glu Ser Asp Val Thr Lys Ser Ile Arg Asn Val Ile Lys
115 120 125

Ala Cys Glu Asp Asp Ser Glu Phe Asn Asp Tyr His Leu Val Asp Tyr
130 135 140

Leu Thr Gly Asp Phe Leu Glu Glu Gln Tyr Lys Gly Gln Arg Asp Leu
145 150 155 160

Ala Gly Lys Ala Ser Thr Leu Lys Lys Leu Met Asp Arg His Glu Ala
165 170 175

Leu Gly Glu Phe Ile Phe Asp Lys Lys Leu Leu Gly Ile Asp Val
180 185 190

<210> 212

<211> 212

<212> PRT

<213> 粉纹夜蛾 (Trichoplusia ni)

<400> 212

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

<210> 213

<211> 174

<212> PRT

<213> 激烈火球菌 (Pyrococcus furiosus)

<400> 213

Met Leu Ser Glu Arg Met Leu Lys Ala Leu Asn Asp Gln Leu Asn Arg
 1 5 10 15
 Glu Leu Tyr Ser Ala Tyr Leu Tyr Phe Ala Met Ala Ala Tyr Phe Glu
 20 25 30
 Asp Leu Gly Leu Glu Gly Phe Ala Asn Trp Met Lys Ala Gln Ala Glu

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

<210> 214

<211> 183

<212> PRT

<213> 智人(Homo sapeins)

<400> 214

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

130	135	140
Ala Ile Lys Glu Leu Gly Asp His Val Thr Asn Leu Arg Lys Met Gly		
145	150	155
Ala Pro Glu Ser Gly Leu Ala Glu Tyr Leu Phe Asp Lys His Thr Leu		
	165	170
Gly Asp Ser Asp Gln Glu Ser		175
180		
<210> 215		
<211> 204		
<212> PRT		
<213> 智人 (Homo sapeins)		
<400> 215		
Met Asp Ser Lys Gly Ser Ser Gln Lys Gly Ser Arg Leu Leu Leu Leu		
1	5	10
Leu Val Val Ser Asn Leu Leu Leu Pro Gln Gly Val Leu Ala Ser Ser		15
	20	25
Gln Ile Arg Gln Asn Tyr Ser Thr Asp Val Glu Ala Ala Val Asn Ser		30
	35	40
Leu Val Asn Leu Tyr Leu Gln Ala Ser Tyr Thr Tyr Leu Ser Leu Gly		45
	50	55
Phe Tyr Phe Asp Arg Asp Asp Val Ala Leu Glu Gly Val Ser His Phe		60
65	70	75
Phe Arg Glu Leu Ala Glu Glu Lys Arg Glu Gly Tyr Glu Arg Leu Leu		80
	85	90
Lys Met Gln Asn Gln Arg Gly Gly Arg Ala Leu Phe Gln Asp Ile Lys		95
	100	105
Lys Pro Ala Glu Asp Glu Trp Gly Lys Thr Pro Asp Ala Met Lys Ala		110
	115	120
Ala Met Ala Leu Glu Lys Lys Leu Asn Gln Ala Leu Leu Asp Leu His		125
	130	135
Ala Leu Gly Ser Ala Arg Thr Asp Pro His Leu Cys Asp Phe Leu Glu		140
145	150	155
Thr His Phe Leu Asp Glu Glu Val Lys Leu Ile Lys Lys Met Gly Asp		160
	165	170
His Leu Thr Asn Leu His Arg Leu Gly Gly Pro Glu Ala Gly Leu Gly		175
	180	185
Glu Tyr Leu Phe Glu Arg Leu Thr Leu Lys His Asp		190
	195	200
<210> 216		

<211> 154

<212> PRT

<213> 风产液菌(Aquifex aeolicus)

<400> 216

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

<210> 217

<211> 8

<212> PRT

<213> 未知

<220>

<223> 牛蛙接头序列

<400> 217

Glu Ser Gln Val Arg Gln Gln Phe
1 5

<210> 218

<211> 15

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 218

Cys Leu Val Pro Arg Gly Ser Leu Glu His His His His His His

1 5 10 15

<210> 219

<211> 156

<212> PRT

<213> 大肠杆菌 (Escherichia coli)

<400> 219

Met Asn Ile Ile Glu Ala Asn Val Ala Thr Pro Asp Ala Arg Val Ala

1 5 10 15

Ile Thr Ile Ala Arg Phe Asn Asn Phe Ile Asn Asp Ser Leu Leu Glu

20 25 30

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

35 40 45

Ile Thr Val Val Trp Val Pro Gly Ala Tyr Glu Leu Pro Leu Ala Ala

50 55 60

Gly Ala Leu Ala Lys Thr Gly Lys Tyr Asp Ala Val Ile Ala Leu Gly

65 70 75 80

Thr Val Ile Arg Gly Gly Thr Ala His Phe Glu Tyr Val Ala Gly Gly

85 90 95

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

100 105 110

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

115 120 125

Ala Gly Thr Lys Ala Gly Asn Lys Gly Ala Glu Ala Ala Leu Thr Ala

130 135 140

Leu Glu Met Ile Asn Val Leu Lys Ala Ile Lys Ala

145 150 155

<210> 220

<211> 16

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 220

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly

1 5 10 15

<210> 221

<211> 28

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 221

Gly	Gly	Ser	Gly	Ser	Gly	Ser	Asn	Ser	Ser	Ala	Ser	Ser	Gly	Ala	Ser
1				5				10					15		
Ser	Gly	Gly	Ala	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly				
			20					25							

<210> 222

<211> 46

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 222

Gly	Gly	Ser	Gly	Ser	Ala	Ser	Ser	Gly	Ala	Ser	Ala	Ser	Gly	Ser	Ser
1				5				10					15		
Asn	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Asn	Ser	Ser	Ala	Ser	Ser	Gly
			20					25					30		
Ala	Ser	Ser	Gly	Gly	Ala	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly		
			35				40					45			

<210> 223

<211> 26

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 223

Gly	Gly	Ser	Gly	Ser	Ala	Ser	Ala	Glu	Ala	Ala	Ala	Lys	Glu	Ala	Ala
1				5				10					15		
Ala	Lys	Ala	Gly	Gly	Ser	Gly	Gly	Ser	Gly						
			20					25							

<210> 224

<211> 32

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

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

420	425	430
Leu Gln Lys Leu Val Leu Leu Glu Met Lys Gly Gly Cys Arg Glu Pro		
435	440	445
Glu Leu Asp Thr Glu Thr Leu Thr Thr Met Phe Glu Val Ser Val Ala		
450	455	460
Phe Phe Lys Val Gly His Ala Val Gly Glu Thr Gly Asn Gly Cys Val		
465	470	475
Asp Leu Arg Trp Leu Ala Lys Ser Phe Phe Glu Leu Thr Val Leu Lys		
485	490	495
Asp Ile Ile Gly Ile Cys Tyr Gly Ala Thr Val Lys Gly Met Gln Ser		
500	505	510
Tyr Gly Leu Glu Arg Leu Ala Ala Met Leu Met Ala Thr Val Lys Met		
515	520	525
Glu Glu Leu Gly His Leu Thr Thr Glu Lys Gln Glu Tyr Ala Leu Arg		
530	535	540
Leu Ala Thr Val Gly Tyr Pro Lys Ala Gly Val Tyr Ser Gly Leu Ile		
545	550	555
Gly Gly Ala Thr Ser Val Leu Leu Ser Ala Tyr Asn Arg His Pro Leu		
565	570	575
Phe Gln Pro Leu His Thr Val Met Arg Glu Thr Leu Phe Ile Gly Ser		
580	585	590
His Val Val Leu Arg Glu Leu Arg Leu Asn Val Thr Thr Gln Gly Pro		
595	600	605
Asn Leu Ala Leu Tyr Gln Leu Leu Ser Thr Ala Leu Cys Ser Ala Leu		
610	615	620
Glu Ile Gly Glu Val Leu Arg Gly Leu Ala Leu Gly Thr Glu Ser Gly		
625	630	635
Leu Phe Ser Pro Cys Tyr Leu Ser Leu Arg Phe Asp Leu Thr Arg Asp		
645	650	655
Lys Leu Leu Ser Met Ala Pro Gln Glu Ala Thr Leu Asp Gln Ala Ala		
660	665	670
Val Ser Asn Ala Val Asp Gly Phe Leu Gly Arg Leu Ser Leu Glu Arg		
675	680	685
Glu Asp Arg Asp Ala Trp His Leu Pro Ala Tyr Lys Cys Val Asp Arg		
690	695	700
Leu Asp Lys Val Leu Met Ile Ile Pro Leu Ile Asn Val Thr Phe Ile		
705	710	715
Ile Ser Ser Asp Arg Glu Val Arg Gly Ser Ala Leu Tyr Glu Ala Ser		
725	730	735

Thr Thr Tyr Leu Ser Ser Ser Leu Phe Leu Ser Pro Val Ile Met Asn		
740	745	750
Lys Cys Ser Gln Gly Ala Val Ala Gly Glu Pro Arg Gln Ile Pro Lys		
755	760	765
Ile Gln Asn Phe Thr Arg Thr Gln Lys Ser Cys Ile Phe Cys Gly Phe		
770	775	780
Ala Leu Leu Ser Tyr Asp Glu Lys Glu Gly Leu Glu Thr Thr Thr Tyr		
785	790	795
Ile Thr Ser Gln Glu Val Gln Asn Ser Ile Leu Ser Ser Asn Tyr Phe		
805	810	815
Asp Phe Asp Asn Leu His Val His Tyr Leu Leu Leu Thr Thr Asn Gly		
820	825	830
Thr Val Met Glu Ile Ala Gly Leu Tyr Glu Glu Arg Ala Ser Gly Gly		
835	840	845
Gly Ser Gly Ser Ala Ser Ser Gly Ala Ser Ala Ser Gly Ser Ser Gly		
850	855	860
Ser Gly Ser Gly Ser Gly Ser Ser Ser Ala Ser Ser Gly Leu Ala Tyr		
865	870	875
Phe Leu Pro Pro Arg Val Arg Gly Gly Gly Arg Val Ala Ala Ala Ala		
885	890	895
Ile Thr Trp Val Pro Lys Pro Asn Val Glu Val Trp Pro Val Asp Pro		
900	905	910
Pro Pro Pro Val Asn Phe Asn Lys Thr Ala Glu Gln Glu Tyr Gly Asp		
915	920	925
Lys Glu Val Lys Leu Pro His Trp Thr Pro Thr Leu His Thr Phe Gln		
930	935	940
Val Pro Gln Asn Tyr Thr Lys Ala Asn Cys Thr Tyr Cys Asn Thr Arg		
945	950	955
Glu Tyr Thr Phe Ser Tyr Lys Gly Cys Cys Phe Tyr Phe Thr Lys Lys		
965	970	975
Lys His Thr Trp Asn Gly Cys Phe Gln Ala Cys Ala Glu Leu Tyr Pro		
980	985	990
Cys Thr Tyr Phe Tyr Gly Pro Thr Pro Asp Ile Leu Pro Val Val Thr		
995	1000	1005
Arg Asn Leu Asn Ala Ile Glu Ser Leu Trp Val Gly Val Tyr Arg		
1010	1015	1020
Val Gly Glu Gly Asn Trp Thr Ser Leu Asp Gly Gly Thr Phe Lys		
1025	1030	1035
Val Tyr Gln Ile Phe Gly Ser His Cys Thr Tyr Val Ser Lys Phe		

1040	1045	1050
Ser Thr Val Pro Val Ser	His His Glu Cys Ser	Phe Leu Lys Pro
1055	1060	1065
Cys Leu Cys Val Ser Gln	Arg Ser Asn Ser Gly	Ser His His His
1070	1075	1080
His His His		
1085		
<210> 227		
<211> 1339		
<212> PRT		
<213> 人工序列		
<220>		
<223> 合成多肽		
<400> 227		
Met Arg Ala Val Gly Val Phe Leu Ala Ile Cys Leu Val Thr Ile Phe		
1 5 10 15		
Val Leu Pro Thr Trp Gly Asn Trp Ala Tyr Pro Cys Cys His Val Thr		
20 25 30		
Gln Leu Arg Ala Gln His Leu Leu Ala Leu Glu Asn Ile Ser Asp Ile		
35 40 45		
Tyr Leu Val Ser Asn Gln Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu		
50 55 60		
Asn Ser Pro Lys Asn Gly Ser Asn Gln Leu Val Ile Ser Arg Cys Ala		
65 70 75 80		
Asn Gly Leu Asn Val Val Ser Phe Phe Ile Ser Ile Leu Lys Arg Ser		
85 90 95		
Ser Ser Ala Leu Thr Gly His Leu Arg Glu Leu Leu Thr Thr Leu Glu		
100 105 110		
Thr Leu Tyr Gly Ser Phe Ser Val Glu Asp Leu Phe Gly Ala Asn Leu		
115 120 125		
Asn Arg Tyr Ala Trp His Arg Gly Gly Gly Gly Ser Gly Ser Ala Ser		
130 135 140		
Ser Gly Ala Ser Ala Ser Gly Ser Ser Asn Gly Ser Gly Ser Gly Ser		
145 150 155 160		
Gly Ser Asn Ser Ser Ala Ser Ser Gly Ala Ser Ser Gly Gly Ala Ser		
165 170 175		
Gly Gly Ser Gly Gly Ser Gly Ala Ala Ser Leu Ser Glu Val Lys Leu		
180 185 190		
His Leu Asp Ile Glu Gly His Ala Ser His Tyr Thr Ile Pro Trp Thr		

195	200	205
Glu Leu Met Ala Lys Val Pro	Gly Leu Ser Pro	Glu Ala Leu Trp Arg
210	215	220
Glu Ala Asn Val Thr Glu Asp	Leu Ala Ser Met	Leu Asn Arg Tyr Lys
225	230	235
240	245	250
Leu Ile Tyr Lys Thr Ser Gly	Thr Leu Gly Ile Ala Leu Ala Glu Pro	
255	260	265
Val Asp Ile Pro Ala Val Ser	Glu Gly Ser Met Gln Val Asp Ala Ser	
270	275	280
Lys Val His Pro Gly Val Ile	Ser Gly Leu Asn Ser Pro Ala Cys Met	
285	290	295
Leu Ser Ala Pro Leu Glu Lys	Gln Leu Phe Tyr Tyr Ile Gly Thr Met	
300	305	310
Leu Pro Asn Thr Arg Pro His	Ser Tyr Val Phe Tyr Gln Leu Arg Ala	
315	320	325
His Leu Ser Tyr Val Ala Leu	Ser Ile Asn Gly Asp Lys Phe Gln Tyr	
330	335	340
Thr Gly Ala Met Thr Ser Lys	Phe Leu Met Gly Thr Tyr Lys Arg Val	
345	350	355
Thr Glu Lys Gly Asp Glu His	Val Leu Ser Leu Val Phe Gly Lys Thr	
360	365	370
Lys Asp Leu Pro Asp Leu Arg	Gly Pro Phe Ser Tyr Pro Ser Leu Thr	
375	380	385
Ser Ala Gln Ser Gly Asp Tyr	Ser Leu Val Ile Val Thr Thr Phe Val	
390	395	400
His Tyr Ala Asn Phe His Asn	Tyr Phe Val Pro Asn Leu Lys Asp Met	
405	410	415
Phe Ser Arg Ala Val Thr Met	Thr Ala Ala Ser Tyr Ala Arg Tyr Val	
420	425	430
Leu Gln Lys Leu Val Leu Leu	Glu Met Lys Gly Gly Cys Arg Glu Pro	
435	440	445
Glu Leu Asp Thr Glu Thr Leu	Thr Thr Met Phe Glu Val Ser Val Ala	
450	455	460
Phe Phe Lys Val Gly His Ala	Val Gly Glu Thr Gly Asn Gly Cys Val	
465	470	475
480	485	490
Asp Leu Arg Trp Leu Ala Lys	Ser Phe Phe Glu Leu Thr Val Leu Lys	
495	500	505
Asp Ile Ile Gly Ile Cys Tyr	Gly Ala Thr Val Lys Gly Met Gln Ser	
510	515	520

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

820	825	830
Thr Val Met Glu Ile Ala Gly Leu Tyr Glu Glu Arg Ala Ser Gly Gly		
835	840	845
Gly Ser Gly Ser Ala Ser Ser Gly Ala Ser Ala Ser Gly Ser Ser Gly		
850	855	860
Ser Gly Ser Gly Ser Gly Ser Ser Ser Ala Ser Ser Gly Leu Ala Tyr		
865	870	875
Phe Leu Pro Pro Arg Val Arg Gly Gly Gly Arg Val Ala Ala Ala Ala		
885	890	895
Ile Thr Trp Val Pro Lys Pro Asn Val Glu Val Trp Pro Val Asp Pro		
900	905	910
Pro Pro Pro Val Asn Phe Asn Lys Thr Ala Glu Gln Glu Tyr Gly Asp		
915	920	925
Lys Glu Val Lys Leu Pro His Trp Thr Pro Thr Leu His Thr Phe Gln		
930	935	940
Val Pro Gln Asn Tyr Thr Lys Ala Asn Cys Thr Tyr Cys Asn Thr Arg		
945	950	955
Glu Tyr Thr Phe Ser Tyr Lys Gly Cys Cys Phe Tyr Phe Thr Lys Lys		
965	970	975
Lys His Thr Trp Asn Gly Cys Phe Gln Ala Cys Ala Glu Leu Tyr Pro		
980	985	990
Cys Thr Tyr Phe Tyr Gly Pro Thr Pro Asp Ile Leu Pro Val Val Thr		
995	1000	1005
Arg Asn Leu Asn Ala Ile Glu Ser Leu Trp Val Gly Val Tyr Arg		
1010	1015	1020
Val Gly Glu Gly Asn Trp Thr Ser Leu Asp Gly Gly Thr Phe Lys		
1025	1030	1035
Val Tyr Gln Ile Phe Gly Ser His Cys Thr Tyr Val Ser Lys Phe		
1040	1045	1050
Ser Thr Val Pro Val Ser His His Glu Cys Ser Phe Leu Lys Pro		
1055	1060	1065
Cys Leu Cys Val Ser Gln Arg Ser Asn Ser Gly Gly Ser Gly Ser		
1070	1075	1080
Ala Ser Ser Gly Ala Ser Ala Ser Gly Ser Ser Gly Ser Gly Ser		
1085	1090	1095
Gly Ser Gly Ser Ser Ser Ala Ser Ser Gly Ala Ser Ser Gly Gly		
1100	1105	1110
Ala Ser Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Gly Ser Ala		
1115	1120	1125

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

Ser

<210> 228

⟨211⟩ 1295

<212> PRT

〈213〉 人工序列

 $\langle 220 \rangle$

〈223〉 合成多肽

<400> 228

Met Arg Ala Val Gly Val Phe Leu Ala Ile Cys Leu Val Thr Ile Phe
1 5 10 15
Val Leu Pro Thr Trp Gly Asn Trp Ala Tyr Pro Cys Cys His Val Thr

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Gln Leu Arg Ala Gln His Leu	Leu Ala Leu Glu Asn Ile Ser Asp Ile	
35	40	45
Tyr Leu Val Ser Asn Gln Thr	Cys Asp Gly Phe Ser Leu Ala Ser Leu	
50	55	60
Asn Ser Pro Lys Asn Gly Ser	Asn Gln Leu Val Ile Ser Arg Cys Ala	
65	70	75
Asn Gly Leu Asn Val Val Ser	Phe Phe Ile Ser Ile Leu Lys Arg Ser	
85	90	95
Ser Ser Ala Leu Thr Gly His	Leu Arg Glu Leu Leu Thr Thr Leu Glu	
100	105	110
Thr Leu Tyr Gly Ser Phe Ser	Val Glu Asp Leu Phe Gly Ala Asn Leu	
115	120	125
Asn Arg Tyr Ala Trp His Arg	Gly Gly Gly Gly Ser Gly Ser Ala Ser	
130	135	140
Ser Gly Ala Ser Ala Ser Gly	Ser Ser Asn Gly Ser Gly Ser Gly Ser	
145	150	155
Gly Ser Asn Ser Ser Ala Ser	Ser Ser Gly Ala Ser Ser Gly Gly Ala Ser	
165	170	175
Gly Gly Ser Gly Gly Ser Gly	Ala Ala Ser Leu Ser Glu Val Lys Leu	
180	185	190
His Leu Asp Ile Glu Gly His	Ala Ser His Tyr Thr Ile Pro Trp Thr	
195	200	205
Glu Leu Met Ala Lys Val Pro	Gly Leu Ser Pro Glu Ala Leu Trp Arg	
210	215	220
Glu Ala Asn Val Thr Glu Asp	Leu Ala Ser Met Leu Asn Arg Tyr Lys	
225	230	235
Leu Ile Tyr Lys Thr Ser Gly	Thr Leu Gly Ile Ala Leu Ala Glu Pro	
245	250	255
Val Asp Ile Pro Ala Val Ser	Glu Gly Ser Met Gln Val Asp Ala Ser	
260	265	270
Lys Val His Pro Gly Val Ile	Ser Gly Leu Asn Ser Pro Ala Cys Met	
275	280	285
Leu Ser Ala Pro Leu Glu Lys	Gln Leu Phe Tyr Tyr Ile Gly Thr Met	
290	295	300
Leu Pro Asn Thr Arg Pro His	Ser Tyr Val Phe Tyr Gln Leu Arg Ala	
305	310	315
His Leu Ser Tyr Val Ala Leu	Ser Ile Asn Gly Asp Lys Phe Gln Tyr	
325	330	335

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

			645					650					655				
Lys	Leu	Leu	Ser	Met	Ala	Pro	Gln	Glu	Ala	Thr	Leu	Asp	Gln	Ala	Ala		
			660					665					670				
Val	Ser	Asn	Ala	Val	Asp	Gly	Phe	Leu	Gly	Arg	Leu	Ser	Leu	Glu	Arg		
			675					680					685				
Glu	Asp	Arg	Asp	Ala	Trp	His	Leu	Pro	Ala	Tyr	Lys	Cys	Val	Asp	Arg		
			690					695					700				
Leu	Asp	Lys	Val	Leu	Met	Ile	Ile	Pro	Leu	Ile	Asn	Val	Thr	Phe	Ile		
705			710					715					720				
Ile	Ser	Ser	Asp	Arg	Glu	Val	Arg	Gly	Ser	Ala	Leu	Tyr	Glu	Ala	Ser		
			725					730					735				
Thr	Thr	Tyr	Leu	Ser	Ser	Ser	Leu	Phe	Leu	Ser	Pro	Val	Ile	Met	Asn		
			740					745					750				
Lys	Cys	Ser	Gln	Gly	Ala	Val	Ala	Gly	Glu	Pro	Arg	Gln	Ile	Pro	Lys		
			755					760					765				
Ile	Gln	Asn	Phe	Thr	Arg	Thr	Gln	Lys	Ser	Cys	Ile	Phe	Cys	Gly	Phe		
770			775					780									
Ala	Leu	Leu	Ser	Tyr	Asp	Glu	Lys	Glu	Gly	Leu	Glu	Thr	Thr	Thr	Tyr		
785			790					795					800				
Ile	Thr	Ser	Gln	Glu	Val	Gln	Asn	Ser	Ile	Leu	Ser	Ser	Asn	Tyr	Phe		
			805					810					815				
Asp	Phe	Asp	Asn	Leu	His	Val	His	Tyr	Leu	Leu	Leu	Thr	Thr	Asn	Gly		
			820					825					830				
Thr	Val	Met	Glu	Ile	Ala	Gly	Leu	Tyr	Glu	Glu	Arg	Ala	Ser	Gly	Gly		
			835					840					845				
Gly	Ser	Gly	Ser	Ala	Ser	Ser	Gly	Ala	Ser	Ala	Ser	Gly	Ser	Ser	Gly		
850			855					860									
Ser	Gly	Ser	Gly	Ser	Gly	Ser	Ser	Ser	Ala	Ser	Ser	Gly	Leu	Ala	Tyr		
865			870					875					880				
Phe	Leu	Pro	Pro	Arg	Val	Arg	Gly	Gly	Gly	Arg	Val	Ala	Ala	Ala	Ala		
			885					890					895				
Ile	Thr	Trp	Val	Pro	Lys	Pro	Asn	Val	Glu	Val	Trp	Pro	Val	Asp	Pro		
			900					905					910				
Pro	Pro	Pro	Val	Asn	Phe	Asn	Lys	Thr	Ala	Glu	Gln	Glu	Tyr	Gly	Asp		
			915					920					925				
Lys	Glu	Val	Lys	Leu	Pro	His	Trp	Thr	Pro	Thr	Leu	His	Thr	Phe	Gln		
930			935					940									
Val	Pro	Gln	Asn	Tyr	Thr	Lys	Ala	Asn	Cys	Thr	Tyr	Cys	Asn	Thr	Arg		
945			950					955					960				

Glu Tyr Thr Phe Ser Tyr Lys Gly Cys Cys Phe Tyr Phe Thr Lys Lys		
	965	970 975
Lys His Thr Trp Asn Gly Cys Phe Gln Ala Cys Ala Glu Leu Tyr Pro		
	980	985 990
Cys Thr Tyr Phe Tyr Gly Pro Thr Pro Asp Ile Leu Pro Val Val Thr		
	995	1000 1005
Arg Asn Leu Asn Ala Ile Glu Ser Leu Trp Val Gly Val Tyr Arg		
	1010	1015 1020
Val Gly Glu Gly Asn Trp Thr Ser Leu Asp Gly Gly Thr Phe Lys		
	1025	1030 1035
Val Tyr Gln Ile Phe Gly Ser His Cys Thr Tyr Val Ser Lys Phe		
	1040	1045 1050
Ser Thr Val Pro Val Ser His His Glu Cys Ser Phe Leu Lys Pro		
	1055	1060 1065
Cys Leu Cys Val Ser Gln Arg Ser Asn Ser Gly Gly Ser Gly Ser		
	1070	1075 1080
Ala Ser Ser Gly Ala Ser Ala Ser Gly Ser Ser Gly Ser Gly Ser		
	1085	1090 1095
Gly Ser Gly Ser Ser Ser Ala Ser Ser Gly Ala Ser Ser Gly Gly		
	1100	1105 1110
Ala Ser Gly Gly Ser Gly Gly Ser Gly Glu Ser Gln Val Arg Gln		
	1115	1120 1125
Gln Phe Ser Lys Asp Ile Glu Lys Leu Leu Asn Glu Gln Val Asn		
	1130	1135 1140
Lys Glu Met Gln Ser Ser Asn Leu Tyr Met Ser Met Ser Ser Trp		
	1145	1150 1155
Ser Tyr Thr His Ser Leu Asp Gly Ala Gly Leu Phe Leu Phe Asp		
	1160	1165 1170
His Ala Ala Glu Glu Tyr Glu His Ala Lys Lys Leu Ile Ile Phe		
	1175	1180 1185
Leu Asn Glu Asn Asn Val Pro Val Gln Leu Thr Ser Ile Ser Ala		
	1190	1195 1200
Pro Glu His Lys Phe Glu Gly Leu Thr Gln Ile Phe Gln Lys Ala		
	1205	1210 1215
Tyr Glu His Glu Gln His Ile Ser Glu Ser Ile Asn Asn Ile Val		
	1220	1225 1230
Asp His Ala Ile Lys Cys Lys Asp His Ala Thr Phe Asn Phe Leu		
	1235	1240 1245
Gln Trp Tyr Val Ala Glu Gln His Glu Glu Glu Val Leu Phe Lys		

1250					1255					1260					
Asp	Ile	Leu	Asp	Lys	Ile	Glu	Leu	Ile	Gly	Asn	Glu	Asn	His	Gly	
1265					1270					1275					
Leu	Tyr	Leu	Ala	Asp	Gln	Tyr	Val	Lys	Gly	Ile	Ala	Lys	Ser	Arg	
1280					1285					1290					
Lys	Ser														
1295															
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<211> 1263															
<212> PRT															
<213> 人工序列															
<220>															
<223> 合成多肽															
<400> 229															
Met	Arg	Ala	Val	Gly	Val	Phe	Leu	Ala	Ile	Cys	Leu	Val	Thr	Ile	Phe
1				5					10					15	
Val	Leu	Pro	Thr	Trp	Gly	Asn	Trp	Ala	Tyr	Pro	Cys	Cys	His	Val	Thr
			20					25					30		
Gln	Leu	Arg	Ala	Gln	His	Leu	Leu	Ala	Leu	Glu	Asn	Ile	Ser	Asp	Ile
		35					40					45			
Tyr	Leu	Val	Ser	Asn	Gln	Thr	Cys	Asp	Gly	Phe	Ser	Leu	Ala	Ser	Leu
	50					55					60				
Asn	Ser	Pro	Lys	Asn	Gly	Ser	Asn	Gln	Leu	Val	Ile	Ser	Arg	Cys	Ala
65					70					75					80
Asn	Gly	Leu	Asn	Val	Val	Ser	Phe	Phe	Ile	Ser	Ile	Leu	Lys	Arg	Ser
				85					90					95	
Ser	Ser	Ala	Leu	Thr	Gly	His	Leu	Arg	Glu	Leu	Leu	Thr	Thr	Leu	Glu
		100						105					110		
Thr	Leu	Tyr	Gly	Ser	Phe	Ser	Val	Glu	Asp	Leu	Phe	Gly	Ala	Asn	Leu
		115					120					125			
Asn	Arg	Tyr	Ala	Trp	His	Arg	Gly	Gly	Gly	Gly	Ser	Gly	Ser	Ala	Ser
	130					135					140				
Ser	Gly	Ala	Ser	Ala	Ser	Gly	Ser	Ser	Asn	Gly	Ser	Gly	Ser	Gly	Ser
145					150				155						160
Gly	Ser	Asn	Ser	Ser	Ala	Ser	Ser	Gly	Ala	Ser	Ser	Gly	Gly	Ala	Ser
				165					170					175	
Gly	Gly	Ser	Gly	Gly	Ser	Gly	Ala	Ala	Ser	Leu	Ser	Glu	Val	Lys	Leu
			180					185					190		
His	Leu	Asp	Ile	Glu	Gly	His	Ala	Ser	His	Tyr	Thr	Ile	Pro	Trp	Thr

195	200	205
Glu Leu Met Ala Lys Val Pro Gly Leu Ser Pro Glu Ala Leu Trp Arg		
210	215	220
Glu Ala Asn Val Thr Glu Asp Leu Ala Ser Met Leu Asn Arg Tyr Lys		
225	230	235
Leu Ile Tyr Lys Thr Ser Gly Thr Leu Gly Ile Ala Leu Ala Glu Pro		
245	250	255
Val Asp Ile Pro Ala Val Ser Glu Gly Ser Met Gln Val Asp Ala Ser		
260	265	270
Lys Val His Pro Gly Val Ile Ser Gly Leu Asn Ser Pro Ala Cys Met		
275	280	285
Leu Ser Ala Pro Leu Glu Lys Gln Leu Phe Tyr Tyr Ile Gly Thr Met		
290	295	300
Leu Pro Asn Thr Arg Pro His Ser Tyr Val Phe Tyr Gln Leu Arg Ala		
305	310	315
His Leu Ser Tyr Val Ala Leu Ser Ile Asn Gly Asp Lys Phe Gln Tyr		
325	330	335
Thr Gly Ala Met Thr Ser Lys Phe Leu Met Gly Thr Tyr Lys Arg Val		
340	345	350
Thr Glu Lys Gly Asp Glu His Val Leu Ser Leu Val Phe Gly Lys Thr		
355	360	365
Lys Asp Leu Pro Asp Leu Arg Gly Pro Phe Ser Tyr Pro Ser Leu Thr		
370	375	380
Ser Ala Gln Ser Gly Asp Tyr Ser Leu Val Ile Val Thr Thr Phe Val		
385	390	395
His Tyr Ala Asn Phe His Asn Tyr Phe Val Pro Asn Leu Lys Asp Met		
405	410	415
Phe Ser Arg Ala Val Thr Met Thr Ala Ala Ser Tyr Ala Arg Tyr Val		
420	425	430
Leu Gln Lys Leu Val Leu Leu Glu Met Lys Gly Gly Cys Arg Glu Pro		
435	440	445
Glu Leu Asp Thr Glu Thr Leu Thr Thr Met Phe Glu Val Ser Val Ala		
450	455	460
Phe Phe Lys Val Gly His Ala Val Gly Glu Thr Gly Asn Gly Cys Val		
465	470	475
Asp Leu Arg Trp Leu Ala Lys Ser Phe Phe Glu Leu Thr Val Leu Lys		
485	490	495
Asp Ile Ile Gly Ile Cys Tyr Gly Ala Thr Val Lys Gly Met Gln Ser		
500	505	510

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

820	825	830
Thr Val Met Glu Ile Ala Gly Leu Tyr Glu Glu Arg Ala Ser Gly Gly		
835	840	845
Gly Ser Gly Ser Ala Ser Ser Gly Ala Ser Ala Ser Gly Ser Ser Gly		
850	855	860
Ser Gly Ser Gly Ser Gly Ser Ser Ser Ala Ser Ser Gly Leu Ala Tyr		
865	870	875
Phe Leu Pro Pro Arg Val Arg Gly Gly Gly Arg Val Ala Ala Ala Ala		
885	890	895
Ile Thr Trp Val Pro Lys Pro Asn Val Glu Val Trp Pro Val Asp Pro		
900	905	910
Pro Pro Pro Val Asn Phe Asn Lys Thr Ala Glu Gln Glu Tyr Gly Asp		
915	920	925
Lys Glu Val Lys Leu Pro His Trp Thr Pro Thr Leu His Thr Phe Gln		
930	935	940
Val Pro Gln Asn Tyr Thr Lys Ala Asn Cys Thr Tyr Cys Asn Thr Arg		
945	950	955
Glu Tyr Thr Phe Ser Tyr Lys Gly Cys Cys Phe Tyr Phe Thr Lys Lys		
965	970	975
Lys His Thr Trp Asn Gly Cys Phe Gln Ala Cys Ala Glu Leu Tyr Pro		
980	985	990
Cys Thr Tyr Phe Tyr Gly Pro Thr Pro Asp Ile Leu Pro Val Val Thr		
995	1000	1005
Arg Asn Leu Asn Ala Ile Glu Ser Leu Trp Val Gly Val Tyr Arg		
1010	1015	1020
Val Gly Glu Gly Asn Trp Thr Ser Leu Asp Gly Gly Thr Phe Lys		
1025	1030	1035
Val Tyr Gln Ile Phe Gly Ser His Cys Thr Tyr Val Ser Lys Phe		
1040	1045	1050
Ser Thr Val Pro Val Ser His His Glu Cys Ser Phe Leu Lys Pro		
1055	1060	1065
Cys Leu Cys Val Ser Gln Arg Ser Asn Ser Glu Pro Glu Pro Glu		
1070	1075	1080
Pro Glu Pro Glu Pro Gly Gly Glu Ser Gln Val Arg Gln Gln Phe		
1085	1090	1095
Ser Lys Asp Ile Glu Lys Leu Leu Asn Glu Gln Val Asn Lys Glu		
1100	1105	1110
Met Gln Ser Ser Asn Leu Tyr Met Ser Met Ser Ser Trp Ser Tyr		
1115	1120	1125

Thr His Ser Leu Asp Gly Ala Gly Leu Phe Leu Phe Asp His Ala		
1130	1135	1140
Ala Glu Glu Tyr Glu His Ala Lys Lys Leu Ile Ile Phe Leu Asn		
1145	1150	1155
Glu Asn Asn Val Pro Val Gln Leu Thr Ser Ile Ser Ala Pro Glu		
1160	1165	1170
His Lys Phe Glu Gly Leu Thr Gln Ile Phe Gln Lys Ala Tyr Glu		
1175	1180	1185
His Glu Gln His Ile Ser Glu Ser Ile Asn Asn Ile Val Asp His		
1190	1195	1200
Ala Ile Lys Cys Lys Asp His Ala Thr Phe Asn Phe Leu Gln Trp		
1205	1210	1215
Tyr Val Ala Glu Gln His Glu Glu Glu Val Leu Phe Lys Asp Ile		
1220	1225	1230
Leu Asp Lys Ile Glu Leu Ile Gly Asn Glu Asn His Gly Leu Tyr		
1235	1240	1245
Leu Ala Asp Gln Tyr Val Lys Gly Ile Ala Lys Ser Arg Lys Ser		
1250	1255	1260

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<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

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Val Leu Pro Thr Trp Gly Asn Trp Ala Tyr Pro Cys Cys His Val Thr		
	20	25
Gln Leu Arg Ala Gln His Leu Leu Ala Leu Glu Asn Ile Ser Asp Ile		
	35	40
Tyr Leu Val Ser Asn Gln Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu		
	50	55
Asn Ser Pro Lys Asn Gly Ser Asn Gln Leu Val Ile Ser Arg Cys Ala		
65	70	75
Asn Gly Leu Asn Val Val Ser Phe Phe Ile Ser Ile Leu Lys Arg Ser		
	85	90
Ser Ser Ala Leu Thr Gly His Leu Arg Glu Leu Leu Thr Thr Leu Glu		
	100	105
		110

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

420	425	430
Leu Gln Lys Leu Val Leu Leu Glu Met Lys Gly Gly Cys Arg Glu Pro		
435	440	445
Glu Leu Asp Thr Glu Thr Leu Thr Thr Met Phe Glu Val Ser Val Ala		
450	455	460
Phe Phe Lys Val Gly His Ala Val Gly Glu Thr Gly Asn Gly Cys Val		
465	470	475
Asp Leu Arg Trp Leu Ala Lys Ser Phe Phe Glu Leu Thr Val Leu Lys		
485	490	495
Asp Ile Ile Gly Ile Cys Tyr Gly Ala Thr Val Lys Gly Met Gln Ser		
500	505	510
Tyr Gly Leu Glu Arg Leu Ala Ala Met Leu Met Ala Thr Val Lys Met		
515	520	525
Glu Glu Leu Gly His Leu Thr Thr Glu Lys Gln Glu Tyr Ala Leu Arg		
530	535	540
Leu Ala Thr Val Gly Tyr Pro Lys Ala Gly Val Tyr Ser Gly Leu Ile		
545	550	555
Gly Gly Ala Thr Ser Val Leu Leu Ser Ala Tyr Asn Arg His Pro Leu		
565	570	575
Phe Gln Pro Leu His Thr Val Met Arg Glu Thr Leu Phe Ile Gly Ser		
580	585	590
His Val Val Leu Arg Glu Leu Arg Leu Asn Val Thr Thr Gln Gly Pro		
595	600	605
Asn Leu Ala Leu Tyr Gln Leu Leu Ser Thr Ala Leu Cys Ser Ala Leu		
610	615	620
Glu Ile Gly Glu Val Leu Arg Gly Leu Ala Leu Gly Thr Glu Ser Gly		
625	630	635
Leu Phe Ser Pro Cys Tyr Leu Ser Leu Arg Phe Asp Leu Thr Arg Asp		
645	650	655
Lys Leu Leu Ser Met Ala Pro Gln Glu Ala Thr Leu Asp Gln Ala Ala		
660	665	670
Val Ser Asn Ala Val Asp Gly Phe Leu Gly Arg Leu Ser Leu Glu Arg		
675	680	685
Glu Asp Arg Asp Ala Trp His Leu Pro Ala Tyr Lys Cys Val Asp Arg		
690	695	700
Leu Asp Lys Val Leu Met Ile Ile Pro Leu Ile Asn Val Thr Phe Ile		
705	710	715
Ile Ser Ser Asp Arg Glu Val Arg Gly Ser Ala Leu Tyr Glu Ala Ser		
725	730	735

Thr Thr Tyr Leu Ser Ser Ser Leu Phe Leu Ser Pro Val Ile Met Asn		
740	745	750
Lys Cys Ser Gln Gly Ala Val Ala Gly Glu Pro Arg Gln Ile Pro Lys		
755	760	765
Ile Gln Asn Phe Thr Arg Thr Gln Lys Ser Cys Ile Phe Cys Gly Phe		
770	775	780
Ala Leu Leu Ser Tyr Asp Glu Lys Glu Gly Leu Glu Thr Thr Thr Tyr		
785	790	795
Ile Thr Ser Gln Glu Val Gln Asn Ser Ile Leu Ser Ser Asn Tyr Phe		
805	810	815
Asp Phe Asp Asn Leu His Val His Tyr Leu Leu Leu Thr Thr Asn Gly		
820	825	830
Thr Val Met Glu Ile Ala Gly Leu Tyr Glu Glu Arg Ala Ser Gly Gly		
835	840	845
Gly Ser Gly Ser Ala Ser Ser Gly Ala Ser Ala Ser Gly Ser Ser Gly		
850	855	860
Ser Gly Ser Gly Ser Gly Ser Ser Ser Ala Ser Ser Gly Leu Ala Tyr		
865	870	875
Phe Leu Pro Pro Arg Val Arg Gly Gly Gly Arg Val Ala Ala Ala Ala		
885	890	895
Ile Thr Trp Val Pro Lys Pro Asn Val Glu Val Trp Pro Val Asp Pro		
900	905	910
Pro Pro Pro Val Asn Phe Asn Lys Thr Ala Glu Gln Glu Tyr Gly Asp		
915	920	925
Lys Glu Val Lys Leu Pro His Trp Thr Pro Thr Leu His Thr Phe Gln		
930	935	940
Val Pro Gln Asn Tyr Thr Lys Ala Asn Cys Thr Tyr Cys Asn Thr Arg		
945	950	955
Glu Tyr Thr Phe Ser Tyr Lys Gly Cys Cys Phe Tyr Phe Thr Lys Lys		
965	970	975
Lys His Thr Trp Asn Gly Cys Phe Gln Ala Cys Ala Glu Leu Tyr Pro		
980	985	990
Cys Thr Tyr Phe Tyr Gly Pro Thr Pro Asp Ile Leu Pro Val Val Thr		
995	1000	1005
Arg Asn Leu Asn Ala Ile Glu Ser Leu Trp Val Gly Val Tyr Arg		
1010	1015	1020
Val Gly Glu Gly Asn Trp Thr Ser Leu Asp Gly Gly Thr Phe Lys		
1025	1030	1035
Val Tyr Gln Ile Phe Gly Ser His Cys Thr Tyr Val Ser Lys Phe		

1040	1045	1050
Ser Thr Val Pro Val Ser	His His Glu Cys Ser	Phe Leu Lys Pro
1055	1060	1065
Cys Leu Cys Val Ser Gln	Arg Ser Asn Ser Gly	Gly Ser Gly Glu
1070	1075	1080
Ser Gln Val Arg Gln Gln	Phe Ser Lys Asp Ile	Glu Lys Leu Leu
1085	1090	1095
Asn Glu Gln Val Asn Lys	Glu Met Gln Ser Ser	Asn Leu Tyr Met
1100	1105	1110
Ser Met Ser Ser Trp Ser	Tyr Thr His Ser Leu	Asp Gly Ala Gly
1115	1120	1125
Leu Phe Leu Phe Asp His	Ala Ala Glu Glu Tyr	Glu His Ala Lys
1130	1135	1140
Lys Leu Ile Ile Phe Leu	Asn Glu Asn Asn Val	Pro Val Gln Leu
1145	1150	1155
Thr Ser Ile Ser Ala Pro	Glu His Lys Phe Glu	Gly Leu Thr Gln
1160	1165	1170
Ile Phe Gln Lys Ala Tyr	Glu His Glu Gln His	Ile Ser Glu Ser
1175	1180	1185
Ile Asn Asn Ile Val Asp	His Ala Ile Lys Cys	Lys Asp His Ala
1190	1195	1200
Thr Phe Asn Phe Leu Gln	Trp Tyr Val Ala Glu	Gln His Glu Glu
1205	1210	1215
Glu Val Leu Phe Lys Asp	Ile Leu Asp Lys Ile	Glu Leu Ile Gly
1220	1225	1230
Asn Glu Asn His Gly Leu	Tyr Leu Ala Asp Gln	Tyr Val Lys Gly
1235	1240	1245
Ile Ala Lys Ser Arg Lys	Ser	
1250	1255	
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<400> 231		
Met Asp Ser Lys Gly Ser	Ser Gln Lys Gly Ser	Arg Leu Leu Leu Leu
1	5	10
Leu Val Val Ser Asn Leu	Leu Leu Pro Gln Gly	Val Leu Ala Asn Trp

20	25	30
Ala Tyr Pro Cys Cys His Val Thr Gln Leu Arg Ala Gln His Leu Leu		
35	40	45
Ala Leu Glu Asn Ile Ser Asp Ile Tyr Leu Val Ser Asn Gln Thr Cys		
50	55	60
Asp Ala Phe Ser Leu Ala Ser Leu Asn Ser Pro Lys Gln Gly Ser Asn		
65	70	75
Gln Leu Val Ile Ser Arg Cys Ala Asn Gly Leu Asn Val Val Ser Phe		
85	90	95
Phe Ile Ser Ile Leu Lys Arg Ser Ser Ser Ala Leu Thr Gly His Leu		
100	105	110
Arg Glu Leu Leu Thr Thr Leu Glu Thr Leu Tyr Gly Ser Phe Ser Val		
115	120	125
Glu Asp Leu Phe Gly Ala Gln Leu Asn Arg Tyr Ala Trp His Arg Gly		
130	135	140
Gly Gly Gly Ser Gly Ser Ala Ser Ser Gly Ala Ser Ala Ser Gly Ser		
145	150	155
Ser Gly Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Ser Ala Ser Ser		
165	170	175
Gly Ala Ser Ser Gly Gly Ala Ser Gly Gly Ser Gly Gly Ser Gly Ala		
180	185	190
Ala Ser Leu Ser Glu Val Lys Leu His Leu Asp Ile Glu Gly His Ala		
195	200	205
Ser His Tyr Thr Ile Pro Trp Thr Glu Leu Leu Ala Lys Val Pro Gly		
210	215	220
Leu Ser Pro Glu Ala Leu Trp Arg Glu Ala Asn Val Thr Glu Asp Leu		
225	230	235
Ala Ser Met Leu Asn Arg Tyr Lys Leu Ile Tyr Lys Thr Ser Gly Thr		
245	250	255
Leu Gly Ile Ala Leu Ala Glu Pro Val Asp Ile Pro Ala Val Ser Glu		
260	265	270
Gly Ser Met Gln Val Asp Ala Ser Lys Val His Pro Gly Val Ile Ser		
275	280	285
Gly Leu Asn Ser Pro Ala Cys Met Leu Ser Ala Pro Leu Glu Lys Gln		
290	295	300
Leu Phe Tyr Tyr Ile Gly Thr Met Leu Pro Asn Thr Arg Pro His Ser		
305	310	315
Tyr Val Phe Tyr Gln Leu Arg Cys His Leu Ser Tyr Val Ala Leu Ser		
325	330	335

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

				645					650					655			
Leu	Arg	Phe	Asp	Leu	Thr	Arg	Asp	Lys	Leu	Leu	Ser	Ile	Ala	Pro	Gln		
				660					665					670			
Glu	Ala	Thr	Leu	Asp	Gln	Ala	Ala	Val	Ser	Gln	Ala	Val	Asp	Gly	Phe		
				675					680					685			
Leu	Gly	Arg	Leu	Ser	Leu	Glu	Arg	Glu	Asp	Arg	Asp	Ala	Trp	His	Leu		
				690					695					700			
Pro	Ala	Tyr	Lys	Cys	Val	Asp	Arg	Leu	Asp	Lys	Val	Leu	Met	Ile	Ile		
705																	
Pro	Leu	Ile	Asn	Val	Thr	Phe	Ile	Ile	Ser	Ser	Asp	Arg	Glu	Val	Arg		
				725					730					735			
Gly	Ser	Ala	Leu	Tyr	Glu	Ala	Ser	Thr	Thr	Tyr	Leu	Ser	Ser	Ser	Leu		
				740					745					750			
Phe	Leu	Ser	Pro	Val	Ile	Leu	Asn	Lys	Cys	Ser	Gln	Gly	Ala	Val	Ala		
				755					760					765			
Gly	Glu	Pro	Arg	Gln	Ile	Pro	Lys	Ile	Gln	Asn	Phe	Thr	Arg	Thr	Gln		
				770					775					780			
Lys	Ser	Cys	Ile	Phe	Cys	Gly	Phe	Ala	Leu	Leu	Ser	Tyr	Asp	Glu	Lys		
785																	
Glu	Gly	Leu	Glu	Thr	Thr	Thr	Tyr	Ile	Thr	Ser	Gln	Glu	Val	Gln	Asn		
				805					810					815			
Ser	Ile	Leu	Ser	Ser	Asn	Tyr	Phe	Asp	Phe	Asp	Asn	Leu	His	Val	His		
				820					825					830			
Tyr	Leu	Leu	Leu	Thr	Thr	Asn	Gly	Thr	Val	Met	Glu	Ile	Ala	Gly	Leu		
				835					840					845			
Tyr	Glu	Glu	Arg	Ala	Ser	Gly	Gly	Gly	Ser	Gly	Ser	Ala	Ser	Ser	Gly		
				850					855					860			
Ala	Ser	Ala	Ser	Gly	Ser	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Ser		
865																	
				870					875					880			
Ser	Ala	Ser	Ser	Gly	Ala	Ile	Thr	Trp	Val	Pro	Lys	Pro	Asn	Val	Glu		
				885					890					895			
Val	Trp	Pro	Val	Asp	Pro	Pro	Pro	Pro	Val	Asn	Phe	Asn	Lys	Thr	Ala		
				900					905					910			
Glu	Gln	Glu	Tyr	Gly	Asp	Lys	Glu	Val	Lys	Leu	Pro	His	Trp	Thr	Pro		
				915					920					925			
Thr	Leu	His	Thr	Phe	Gln	Val	Pro	Gln	Asn	Tyr	Thr	Lys	Ala	Asn	Cys		
				930					935					940			
Thr	Tyr	Cys	Asn	Thr	Arg	Glu	Tyr	Thr	Phe	Ser	Tyr	Lys	Gly	Cys	Cys		
945																	
				950					955					960			

Phe Tyr Phe Thr Lys Lys Lys His Thr Trp Gln Gly Cys Phe Gln Ala		
965	970	975
Cys Ala Glu Leu Tyr Pro Cys Thr Tyr Phe Tyr Gly Pro Thr Pro Asp		
980	985	990
Ile Leu Pro Val Val Thr Arg Ser Leu Gln Ala Ile Glu Ser Leu Trp		
995	1000	1005
Val Gly Val Tyr Arg Val Gly Glu Gly Asn Trp Thr Ser Leu Asp		
1010	1015	1020
Gly Gly Thr Phe Lys Val Tyr Gln Ile Phe Gly Ser His Cys Thr		
1025	1030	1035
Tyr Val Ser Lys Phe Ser Thr Val Pro Val Ser His His Glu Cys		
1040	1045	1050
Ser Phe Leu Lys Pro Cys Leu Cys Val Ser Gln Arg Ser Asn Ser		
1055	1060	1065
Gly Gly Ser Gly Ser Ala Ser Ser Gly Ala Ser Ala Ser Gly Ser		
1070	1075	1080
Ser Gly Ser Gly Ser Gly Ser Gly Ser Ser Ser Ala Ser Ser Gly		
1085	1090	1095
Ala Ser Ser Gly Gly Ala Ser Gly Gly Ser Gly Gly Ser Gly Gly		
1100	1105	1110
Gly Ser Gly Ser Ala Ser Ser Gly Ala Ser Ala Ser Gly Ser Ser		
1115	1120	1125
Gly Ser Gly Ser Gly Ser Gly Ser Ser Ser Ala Ser Ser Gly Ala		
1130	1135	1140
Ser Ser Gly Gly Ala Ser Gly Gly Ser Gly Gly Ser Gly Glu Ser		
1145	1150	1155
Gln Val Arg Ser Gln Phe Ser Lys Asp Ile Glu Lys Leu Leu Asn		
1160	1165	1170
Glu Gln Val Asn Lys Glu Met Gln Ser Ser Asn Leu Tyr Met Ser		
1175	1180	1185
Met Ser Ser Trp Ser Tyr Thr His Ser Leu Asp Gly Ala Gly Leu		
1190	1195	1200
Phe Leu Phe Asp His Ala Ala Glu Glu Tyr Glu His Ala Lys Lys		
1205	1210	1215
Leu Ile Ile Phe Leu Asn Glu Asn Asn Val Pro Val Gln Leu Thr		
1220	1225	1230
Ser Ile Ser Ala Pro Glu His Lys Phe Glu Gly Leu Thr Gln Ile		
1235	1240	1245
Phe Gln Lys Ala Tyr Glu His Glu Gln His Ile Ser Glu Ser Ile		

1250	1255	1260
Asn Gln Ile Val Asp His	Ala Ile Lys Cys Lys	Asp His Ala Thr
1265	1270	1275
Phe Asn Phe Leu Gln Trp	Tyr Val Ala Glu Gln	His Glu Glu Glu
1280	1285	1290
Val Leu Phe Lys Asp Ile	Leu Asp Lys Ile Glu	Leu Ile Gly Gln
1295	1300	1305
Glu Asn His Gly Leu Tyr	Leu Ala Asp Gln Tyr	Val Lys Gly Ile
1310	1315	1320
Ala Lys Ser Arg Lys Ser		
1325		
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Met Arg Ala Val Gly Val Phe Leu Ala Ile Cys Leu Val Thr Ile Phe		
1	5	10
Val Leu Pro Thr Trp Gly Asn Trp Ala Tyr Pro Cys Cys His Val Thr		
20	25	30
Gln Leu Arg Ala Gln His Leu Leu Ala Leu Glu Asn Ile Ser Asp Ile		
35	40	45
Tyr Leu Val Ser Asn Gln Thr Cys Asp Gly Phe Ser Leu Ala Ser Leu		
50	55	60
Asn Ser Pro Lys Asn Gly Ser Asn Gln Leu Val Ile Ser Arg Cys Ala		
65	70	75
Asn Gly Leu Asn Val Val Ser Phe Phe Ile Ser Ile Leu Lys Arg Ser		
85	90	95
Ser Ser Ala Leu Thr Gly His Leu Arg Glu Leu Leu Thr Thr Leu Glu		
100	105	110
Thr Leu Tyr Gly Ser Phe Ser Val Glu Asp Leu Phe Gly Ala Asn Leu		
115	120	125
Asn Arg Tyr Ala Trp His Arg Gly Gly Gly Gly Ser Gly Ser Ala Ser		
130	135	140
Ser Gly Ala Ser Ala Ser Gly Ser Ser Asn Gly Ser Gly Ser Gly Ser		
145	150	155
Gly Ser Asn Ser Ser Ala Ser Ser Gly Ala Ser Ser Gly Gly Ala Ser		
160		

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

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

785	790	795	800
Ile Thr Ser Gln Glu Val Gln Asn Ser Ile Leu Ser Ser Asn Tyr Phe			
	805	810	815
Asp Phe Asp Asn Leu His Val His Tyr Leu Leu Leu Thr Thr Asn Gly			
	820	825	830
Thr Val Met Glu Ile Ala Gly Leu Tyr Glu Glu Arg Ala Ser Gly Glu			
	835	840	845
Pro Glu Pro Glu Pro Glu Pro Glu Pro Glu Pro Glu Pro Glu Pro Glu			
	850	855	860
Pro Glu Pro Glu Pro Glu Pro Glu Pro Glu Pro Glu Pro Glu Pro Glu			
865	870	875	880
Pro Glu Pro Glu Pro Glu Pro Glu Pro Glu Pro Glu Pro Glu Ser Gln			
	885	890	895
Val Arg Gln Gln Phe Ser Lys Asp Ile Glu Lys Leu Leu Asn Glu Gln			
	900	905	910
Val Asn Lys Glu Met Gln Ser Ser Asn Leu Tyr Met Ser Met Ser Ser			
	915	920	925
Trp Ser Tyr Thr His Ser Leu Asp Gly Ala Gly Leu Phe Leu Phe Asp			
	930	935	940
His Ala Ala Glu Glu Tyr Glu His Ala Lys Lys Leu Ile Ile Phe Leu			
945	950	955	960
Asn Glu Asn Asn Val Pro Val Gln Leu Thr Ser Ile Ser Ala Pro Glu			
	965	970	975
His Lys Phe Glu Gly Leu Thr Gln Ile Phe Gln Lys Ala Tyr Glu His			
	980	985	990
Glu Gln His Ile Ser Glu Ser Ile Asn Asn Ile Val Asp His Ala Ile			
	995	1000	1005
Lys Cys Lys Asp His Ala Thr Phe Asn Phe Leu Gln Trp Tyr Val			
	1010	1015	1020
Ala Glu Gln His Glu Glu Glu Val Leu Phe Lys Asp Ile Leu Asp			
	1025	1030	1035
Lys Ile Glu Leu Ile Gly Asn Glu Asn His Gly Leu Tyr Leu Ala			
	1040	1045	1050
Asp Gln Tyr Val Lys Gly Ile Ala Lys Ser Arg Lys Ser			
	1055	1060	1065
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<211> 46			
<212> PRT			
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<220>

<223> 合成多肽

<400> 233

Gly	Gly	Ser	Gly	Ser	Ala	Ser	Ser	Gly	Ala	Ser	Ala	Ser	Gly	Ser	Ser
1				5					10					15	
Gly	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Ser	Ala	Ser	Ser	Gly
			20					25					30		
Ala	Ser	Ser	Gly	Gly	Ala	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly		
			35				40						45		

<210> 234

<211> 32

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 234

Ser	Gly	Gly	Gly	Ser	Gly	Ser	Ala	Ser	Ser	Gly	Ala	Ser	Ala	Ser	Gly
1				5					10					15	
Ser	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Ser	Ser	Ala	Ser	Ser	Gly
			20					25					30		

<210> 235

<211> 88

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 235

Gly	Gly	Ser	Gly	Ser	Ala	Ser	Ser	Gly	Ala	Ser	Ala	Ser	Gly	Ser	Ser
1				5					10					15	
Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Ser	Ser	Ala	Ser	Ser	Gly	Ala	Ser
			20					25					30		
Ser	Gly	Gly	Ala	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly	Gly	Gly	Ser	Gly
			35				40						45		
Ser	Ala	Ser	Ser	Gly	Ala	Ser	Ala	Ser	Gly	Ser	Ser	Gly	Ser	Gly	Ser
			50				55				60				
Gly	Ser	Gly	Ser	Ser	Ser	Ala	Ser	Ser	Gly	Ala	Ser	Ser	Gly	Gly	Ala
65					70					75					80
Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly								
				85											

<210> 236

<211> 44

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 236

Gly	Gly	Ser	Gly	Ser	Ala	Ser	Ser	Gly	Ala	Ser	Ala	Ser	Gly	Ser	Ser
1				5				10					15		
Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Ser	Ser	Ala	Ser	Ser	Gly	Ala	Ser
				20				25					30		
Ser	Gly	Gly	Ala	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly				
				35				40							

<210> 237

<211> 12

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 237

Glu	Pro	Glu	Pro	Glu	Pro	Glu	Pro	Glu	Pro	Gly	Gly
1				5				10			

<210> 238

<211> 48

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 238

Ser	Gly	Glu	Pro	Glu	Pro	Glu	Pro	Glu	Pro	Glu	Pro	Glu	Pro	Glu	Pro
1				5				10				15			
Glu	Pro	Glu	Pro	Glu	Pro	Glu	Pro	Glu	Pro	Glu	Pro	Glu	Pro	Glu	Pro
				20				25				30			
Glu	Pro	Glu	Pro	Glu	Pro	Glu	Pro	Glu	Pro	Glu	Pro	Glu	Pro	Glu	Pro
				35				40				45			

<210> 239

<211> 201

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 239

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

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<213> 人工序列

<220>

<223> 合成多肽

<400> 240

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1           5           10           15
Pro Pro Pro Pro Val Asn Phe Asn Lys Thr Ala Glu Gln Glu Tyr Gly

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

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

				85					90					95			
Phe	Ile	Ser	Ile	Leu	Lys	Arg	Ser	Ser	Ser	Ala	Leu	Thr	Gly	His	Leu		
				100					105					110			
Arg	Glu	Leu	Leu	Thr	Thr	Leu	Glu	Thr	Leu	Tyr	Gly	Ser	Phe	Ser	Val		
				115					120					125			
Glu	Asp	Leu	Phe	Gly	Ala	Gln	Leu	Asn	Arg	Tyr	Ala	Trp	His	Arg	Gly		
				130					135					140			
Gly	Gly	Gly	Ser	Gly	Ser	Ala	Ser	Ser	Gly	Ala	Ser	Ala	Ser	Gly	Ser		
145						150				155					160		
Ser	Gly	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Ser	Ala	Ser	Ser		
				165					170					175			
Gly	Ala	Ser	Ser	Gly	Gly	Ala	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly	Ala		
				180					185					190			
Ala	Ser	Leu	Ser	Glu	Val	Lys	Leu	His	Leu	Asp	Ile	Glu	Gly	His	Ala		
				195					200					205			
Ser	His	Tyr	Thr	Ile	Pro	Trp	Thr	Glu	Leu	Leu	Ala	Lys	Val	Pro	Gly		
				210					215					220			
Leu	Ser	Pro	Glu	Ala	Leu	Trp	Arg	Glu	Ala	Asn	Val	Thr	Glu	Asp	Leu		
225						230				235					240		
Ala	Ser	Met	Leu	Asn	Arg	Tyr	Lys	Leu	Ile	Tyr	Lys	Thr	Ser	Gly	Thr		
				245					250					255			
Leu	Gly	Ile	Ala	Leu	Ala	Glu	Pro	Val	Asp	Ile	Pro	Ala	Val	Ser	Glu		
				260					265					270			
Gly	Ser	Met	Gln	Val	Asp	Ala	Ser	Lys	Val	His	Pro	Gly	Val	Ile	Ser		
				275					280					285			
Gly	Leu	Asn	Ser	Pro	Ala	Cys	Met	Leu	Ser	Ala	Pro	Leu	Glu	Lys	Gln		
				290					295					300			
Leu	Phe	Tyr	Tyr	Ile	Gly	Thr	Met	Leu	Pro	Asn	Thr	Arg	Pro	His	Ser		
305					310					315					320		
Tyr	Val	Phe	Tyr	Gln	Leu	Arg	Cys	His	Leu	Ser	Tyr	Val	Ala	Leu	Ser		
				325					330					335			
Ile	Asn	Gly	Asp	Lys	Phe	Gln	Tyr	Thr	Gly	Ala	Met	Thr	Ser	Lys	Phe		
				340					345					350			
Leu	Met	Gly	Thr	Tyr	Lys	Arg	Val	Thr	Glu	Lys	Gly	Asp	Glu	His	Val		
				355					360					365			
Leu	Ser	Leu	Val	Phe	Gly	Lys	Thr	Lys	Asp	Leu	Pro	Asp	Leu	Arg	Gly		
				370					375					380			
Pro	Phe	Ser	Tyr	Pro	Ser	Leu	Thr	Ser	Ala	Gln	Ser	Gly	Glu	Tyr	Ser		
385						390				395					400		

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

705	710	715	720
Pro Leu Ile Asn Val Thr Phe Ile Ile Ser Ser Asp Arg Glu Val Arg			
	725	730	735
Gly Ser Ala Leu Tyr Glu Ala Ser Thr Thr Tyr Leu Ser Ser Ser Leu			
	740	745	750
Phe Leu Ser Pro Val Ile Met Asn Lys Cys Ser Gln Gly Ala Val Ala			
	755	760	765
Gly Glu Pro Arg Gln Ile Pro Lys Ile Gln Asn Phe Thr Arg Thr Gln			
	770	775	780
Lys Ser Cys Ile Phe Cys Gly Phe Ala Leu Leu Ser Tyr Asp Glu Lys			
785	790	795	800
Glu Gly Leu Glu Thr Thr Thr Tyr Ile Thr Ser Gln Glu Val Gln Asn			
	805	810	815
Ser Ile Leu Ser Ser Asn Tyr Phe Asp Phe Asp Asn Leu His Val His			
	820	825	830
Tyr Leu Leu Leu Thr Thr Asn Gly Thr Val Met Glu Ile Ala Gly Leu			
	835	840	845
Tyr Glu Glu Arg Ala Ser Gly Gly Gly Ser Gly Ser Ala Ser Ser Gly			
	850	855	860
Ala Ser Ala Ser Gly Ser Ser Gly Ser Gly Ser Gly Ser Gly Ser Ser			
865	870	875	880
Ser Ala Ser Ser Gly Ala Ile Thr Trp Val Pro Lys Pro Asn Val Glu			
	885	890	895
Val Trp Pro Val Asp Pro Pro Pro Pro Val Asn Phe Asn Lys Thr Ala			
	900	905	910
Glu Gln Glu Tyr Gly Asp Lys Glu Val Lys Leu Pro His Trp Thr Pro			
	915	920	925
Thr Leu His Thr Phe Gln Val Pro Gln Asn Tyr Thr Lys Ala Asn Cys			
	930	935	940
Thr Tyr Cys Asn Thr Arg Glu Tyr Thr Phe Ser Tyr Lys Gly Cys Cys			
945	950	955	960
Phe Tyr Phe Thr Lys Lys Lys His Thr Trp Gln Gly Cys Phe Gln Ala			
	965	970	975
Cys Ala Glu Leu Tyr Pro Cys Thr Tyr Phe Tyr Gly Pro Thr Pro Asp			
	980	985	990
Ile Leu Pro Val Val Thr Arg Asn Leu Asn Ala Ile Glu Ser Leu Trp			
	995	1000	1005
Val Gly Val Tyr Arg Val Gly Glu Gly Asn Trp Thr Ser Leu Asp			
	1010	1015	1020

Gly Gly Thr Phe Lys Val Tyr Gln Ile Phe Gly Ser His Cys Thr		
1025	1030	1035
Tyr Val Ser Lys Phe Ser Thr Val Pro Val Ser His His Glu Cys		
1040	1045	1050
Ser Phe Leu Lys Pro Cys Leu Cys Val Ser Gln Arg Ser Asn Ser		
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Gly Gly Ser Gly Ser Ala Ser Ser Gly Ala Ser Ala Ser Gly Ser		
1070	1075	1080
Ser Gly Ser Gly Ser Gly Ser Gly Ser Ser Ser Ala Ser Ser Gly		
1085	1090	1095
Ala Ser Ser Gly Gly Ala Ser Gly Gly Ser Gly Gly Ser Gly Gly		
1100	1105	1110
Gly Ser Gly Ser Ala Ser Ser Gly Ala Ser Ala Ser Gly Ser Ser		
1115	1120	1125
Gly Ser Gly Ser Gly Ser Gly Ser Ser Ser Ala Ser Ser Gly Ala		
1130	1135	1140
Ser Ser Gly Gly Ala Ser Gly Gly Ser Gly Gly Ser Gly Glu Ser		
1145	1150	1155
Gln Val Arg Ser Gln Phe Ser Lys Asp Ile Glu Lys Leu Leu Asn		
1160	1165	1170
Glu Gln Val Asn Lys Glu Met Gln Ser Ser Asn Leu Tyr Met Ser		
1175	1180	1185
Met Ser Ser Trp Ser Tyr Thr His Ser Leu Asp Gly Ala Gly Leu		
1190	1195	1200
Phe Leu Phe Asp His Ala Ala Glu Glu Tyr Glu His Ala Lys Lys		
1205	1210	1215
Leu Ile Ile Phe Leu Asn Glu Asn Asn Val Pro Val Gln Leu Thr		
1220	1225	1230
Ser Ile Ser Ala Pro Glu His Lys Phe Glu Gly Leu Thr Gln Ile		
1235	1240	1245
Phe Gln Lys Ala Tyr Glu His Glu Gln His Ile Ser Glu Ser Ile		
1250	1255	1260
Asn Gln Ile Val Asp His Ala Ile Lys Cys Lys Asp His Ala Thr		
1265	1270	1275
Phe Asn Phe Leu Gln Trp Tyr Val Ala Glu Gln His Glu Glu Glu		
1280	1285	1290
Val Leu Phe Lys Asp Ile Leu Asp Lys Ile Glu Leu Ile Gly Gln		
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Glu Asn His Gly Leu Tyr Leu Ala Asp Gln Tyr Val Lys Gly Ile		

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

225	230	235	240
Ala Ser Met Leu Asn Arg Tyr Lys Leu Ile Tyr Lys Thr Ser Gly Thr			
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Leu Gly Ile Ala Leu Ala Glu Pro Val Asp Ile Pro Ala Val Ser Glu			
	260	265	270
Gly Ser Met Gln Val Asp Ala Ser Lys Val His Pro Gly Val Ile Ser			
	275	280	285
Gly Leu Asn Ser Pro Ala Cys Met Leu Ser Ala Pro Leu Glu Lys Gln			
	290	295	300
Leu Phe Tyr Tyr Ile Gly Thr Met Leu Pro Asn Thr Arg Pro His Ser			
305	310	315	320
Tyr Val Phe Tyr Gln Leu Arg Cys His Leu Ser Tyr Val Ala Leu Ser			
	325	330	335
Ile Asn Gly Asp Lys Phe Gln Tyr Thr Gly Ala Met Thr Ser Lys Phe			
	340	345	350
Leu Met Gly Thr Tyr Lys Arg Val Thr Glu Lys Gly Asp Glu His Val			
	355	360	365
Leu Ser Leu Val Phe Gly Lys Thr Lys Asp Leu Pro Asp Leu Arg Gly			
	370	375	380
Pro Phe Ser Tyr Pro Ser Leu Thr Ser Ala Gln Ser Gly Glu Tyr Ser			
385	390	395	400
Leu Val Ile Val Thr Thr Phe Val His Tyr Ala Asn Phe His Asn Tyr			
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Phe Val Pro Asn Leu Lys Asp Met Phe Ser Arg Ala Val Thr Met Thr			
	420	425	430
Ala Ala Ser Tyr Ala Arg Tyr Val Leu Gln Lys Leu Val Leu Leu Glu			
	435	440	445
Met Lys Gly Gly Cys Arg Glu Pro Glu Leu Glu Thr Glu Thr Leu Thr			
	450	455	460
Thr Met Phe Glu Val Ser Val Ala Phe Phe Lys Val Gly His Ala Val			
465	470	475	480
Gly Glu Thr Gly Asn Gly Cys Val Asp Leu Arg Trp Leu Ala Lys Ser			
	485	490	495
Phe Phe Glu Leu Thr Val Leu Lys Asp Ile Ile Gly Ile Cys Tyr Gly			
	500	505	510
Ala Thr Val Lys Gly Met Gln Ser Tyr Gly Leu Glu Arg Leu Ala Ala			
	515	520	525
Met Leu Met Ala Thr Val Lys Met Glu Glu Leu Gly His Leu Thr Thr			
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Ser	Ala	Tyr	Asn	Arg	His	Pro	Leu	Phe	Gln	Pro	Leu	His	Thr	Val	Met
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Leu	Asn	Val	Thr	Thr	Gln	Gly	Pro	Asn	Leu	Ala	Leu	Tyr	Gln	Leu	Leu
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Glu	Ala	Thr	Leu	Asp	Gln	Ala	Ala	Val	Ser	Asn	Ala	Val	Asp	Gly	Phe
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Leu	Gly	Arg	Leu	Ser	Leu	Glu	Arg	Glu	Asp	Arg	Asp	Ala	Trp	His	Leu
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Pro	Ala	Tyr	Lys	Cys	Val	Asp	Arg	Leu	Asp	Lys	Val	Leu	Met	Ile	Ile
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Pro	Leu	Ile	Asn	Val	Thr	Phe	Ile	Ile	Ser	Ser	Asp	Arg	Glu	Val	Arg
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Gly	Ser	Ala	Leu	Tyr	Glu	Ala	Ser	Thr	Thr	Tyr	Leu	Ser	Ser	Ser	Leu
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Phe	Leu	Ser	Pro	Val	Ile	Met	Asn	Lys	Cys	Ser	Gln	Gly	Ala	Val	Ala
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Gly	Glu	Pro	Arg	Gln	Ile	Pro	Lys	Ile	Gln	Asn	Phe	Thr	Arg	Thr	Gln
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Lys	Ser	Cys	Ile	Phe	Cys	Gly	Phe	Ala	Leu	Leu	Ser	Tyr	Asp	Glu	Lys
785						790				795					800
Glu	Gly	Leu	Glu	Thr	Thr	Thr	Tyr	Ile	Thr	Ser	Gln	Glu	Val	Gln	Asn
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Ser	Ile	Leu	Ser	Ser	Asn	Tyr	Phe	Asp	Phe	Asp	Asn	Leu	His	Val	His
					820				825						830
Tyr	Leu	Leu	Leu	Thr	Thr	Asn	Gly	Thr	Val	Met	Glu	Ile	Ala	Gly	Leu
					835				840						845
Tyr	Glu	Glu	Arg	Ala	Ser	Gly	Gly	Gly	Ser	Gly	Ser	Ala	Ser	Ser	Gly

850	855	860
Ala Ser Ala Ser Gly Ser Ser Gly Ser Gly Ser Gly Ser Gly Ser Ser		
865	870	875
Ser Ala Ser Ser Gly Ala Ile Thr Trp Val Pro Lys Pro Asn Val Glu		880
885	890	895
Val Trp Pro Val Asp Pro Pro Pro Pro Val Asn Phe Asn Lys Thr Ala		
900	905	910
Glu Gln Glu Tyr Gly Asp Lys Glu Val Lys Leu Pro His Trp Thr Pro		
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Thr Leu His Thr Phe Gln Val Pro Gln Asn Tyr Thr Lys Ala Asn Cys		
930	935	940
Thr Tyr Cys Asn Thr Arg Glu Tyr Thr Phe Ser Tyr Lys Gly Cys Cys		
945	950	955
Phe Tyr Phe Thr Lys Lys Lys His Thr Trp Asn Gly Cys Phe Gln Ala		960
965	970	975
Cys Ala Glu Leu Tyr Pro Cys Thr Tyr Phe Tyr Gly Pro Thr Pro Asp		
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Ile Leu Pro Val Val Thr Arg Asn Leu Asn Ala Ile Glu Ser Leu Trp		
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Val Gly Val Tyr Arg Val Gly Glu Gly Asn Trp Thr Ser Leu Asp		
1010	1015	1020
Gly Gly Thr Phe Lys Val Tyr Gln Ile Phe Gly Ser His Cys Thr		
1025	1030	1035
Tyr Val Ser Lys Phe Ser Thr Val Pro Val Ser His His Glu Cys		
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Ser Gly Ser Gly Ser Gly Ser Gly Ser Ser Ser Ala Ser Ser Gly		
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1115	1120	1125
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1130	1135	1140
Ser Ser Gly Gly Ala Ser Gly Gly Ser Gly Gly Ser Gly Glu Ser		
1145	1150	1155

Gln Val Arg Ser Gln Phe Ser Lys Asp Ile Glu Lys Leu Leu Asn		
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Glu Gln Val Asn Lys Glu Met Gln Ser Ser Asn Leu Tyr Met Ser		
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Met Ser Ser Trp Ser Tyr Thr His Ser Leu Asp Gly Ala Gly Leu		
1190	1195	1200
Phe Leu Phe Asp His Ala Ala Glu Glu Tyr Glu His Ala Lys Lys		
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Leu Ile Ile Phe Leu Asn Glu Asn Asn Val Pro Val Gln Leu Thr		
1220	1225	1230
Ser Ile Ser Ala Pro Glu His Lys Phe Glu Gly Leu Thr Gln Ile		
1235	1240	1245
Phe Gln Lys Ala Tyr Glu His Glu Gln His Ile Ser Glu Ser Ile		
1250	1255	1260
Asn Gln Ile Val Asp His Ala Ile Lys Cys Lys Asp His Ala Thr		
1265	1270	1275
Phe Asn Phe Leu Gln Trp Tyr Val Ala Glu Gln His Glu Glu Glu		
1280	1285	1290
Val Leu Phe Lys Asp Ile Leu Asp Lys Ile Glu Leu Ile Gly Gln		
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Glu Asn His Gly Leu Tyr Leu Ala Asp Gln Tyr Val Lys Gly Ile		
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Ala Lys Ser Arg Lys Ser		
1325		

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His His His His His His

1 5

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Gly Gly Gly Ser

1

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<211> 8

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Gly Gly Gly Ser Gly Gly Gly Ser

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5

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5

10

15

Gly Gly Gly Ser

20

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tccatgacgt tcctgacgtt 20

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考马斯 蛋白质印迹 抗His

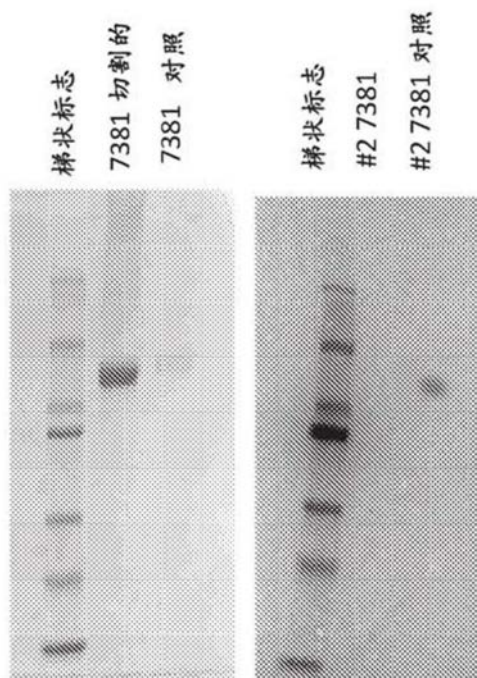


图1A

构建体: SEQ ID NO: 11三聚体

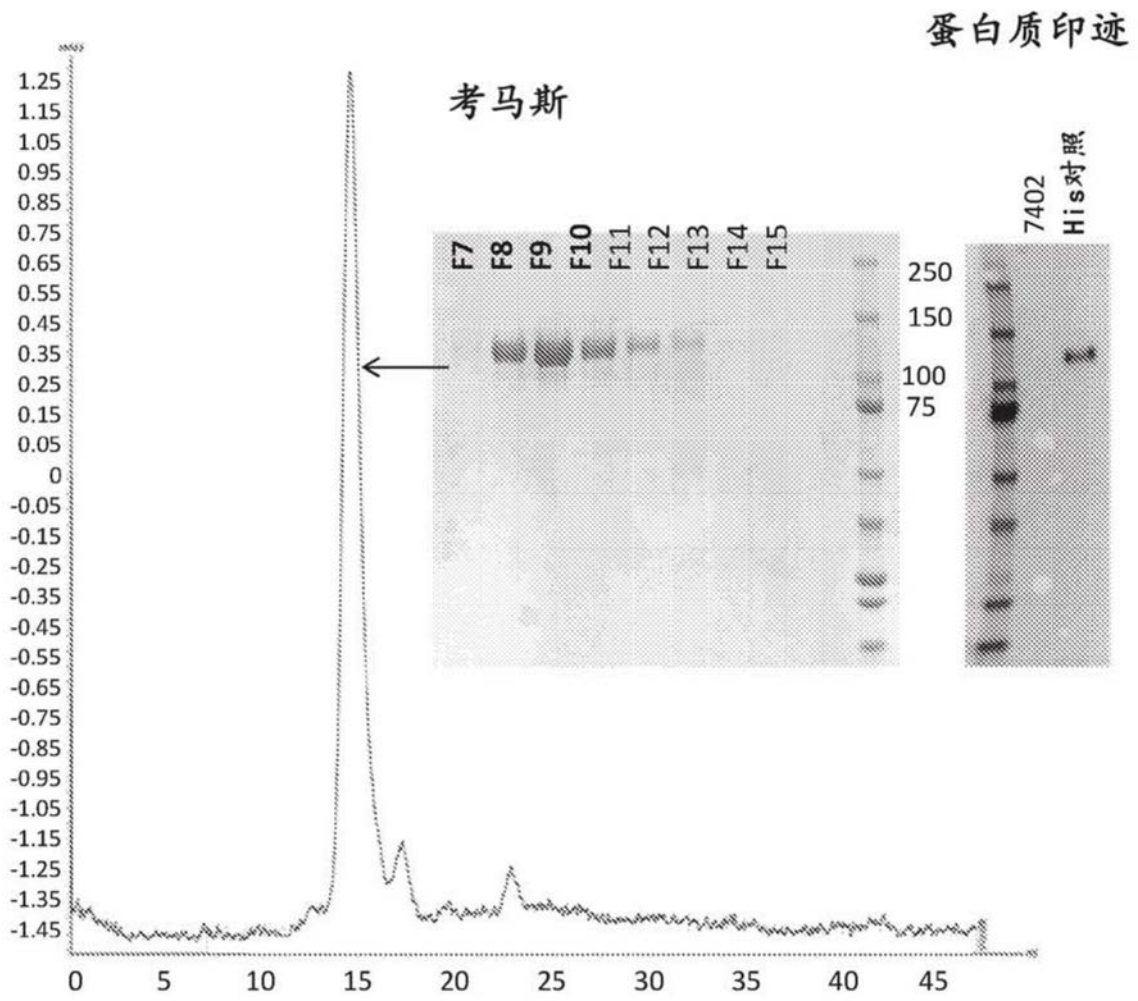


图1B

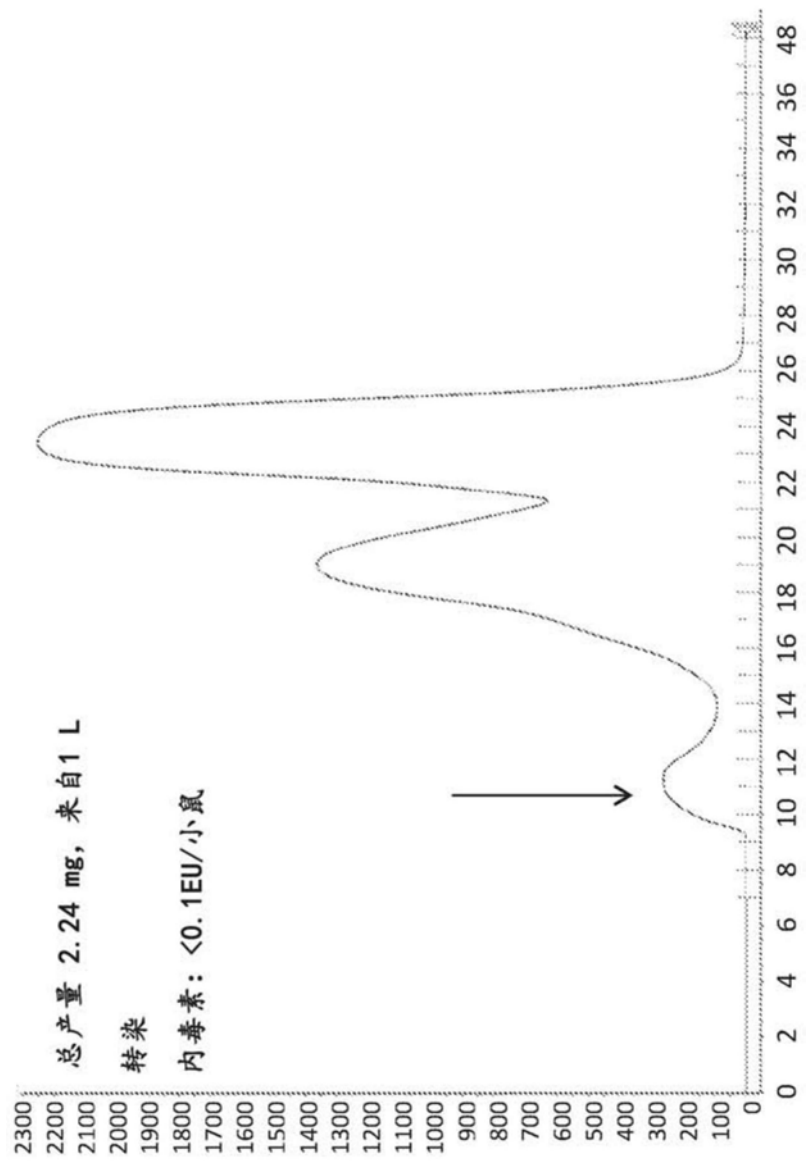


图2A

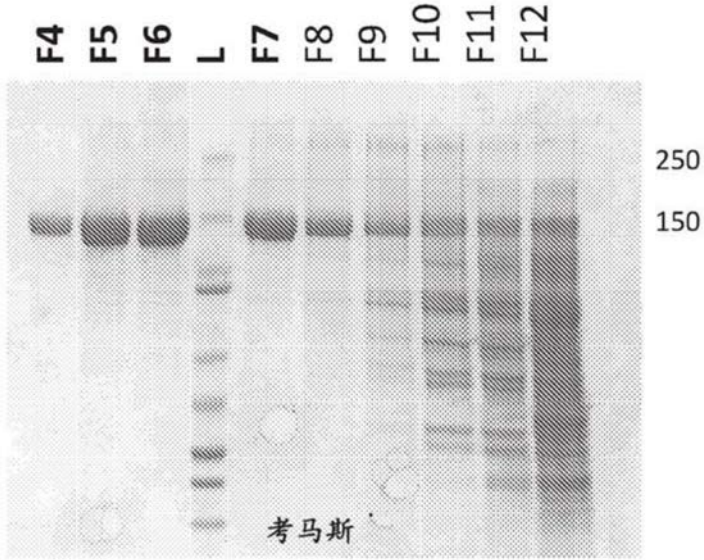


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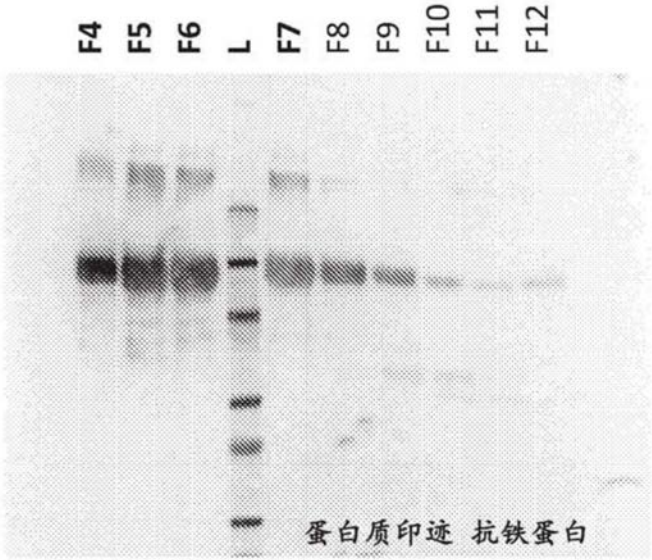


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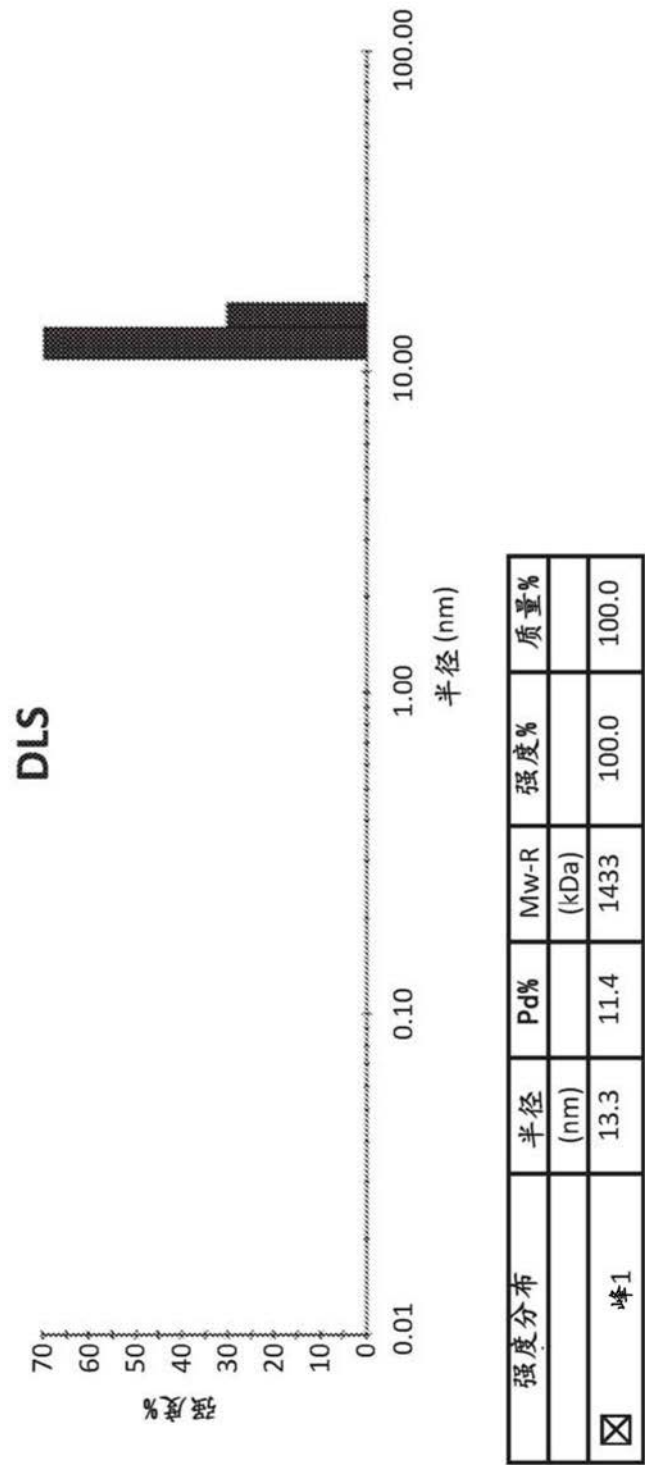


图2D

gL 和 gH 纳米颗粒的负染色 EM 图像

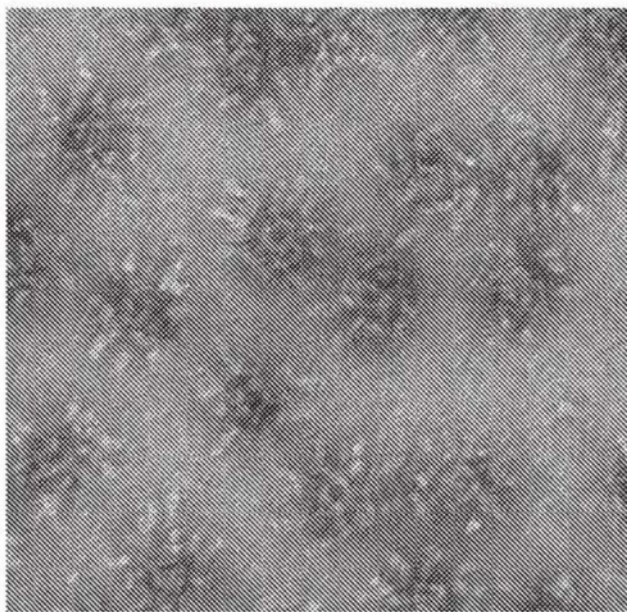


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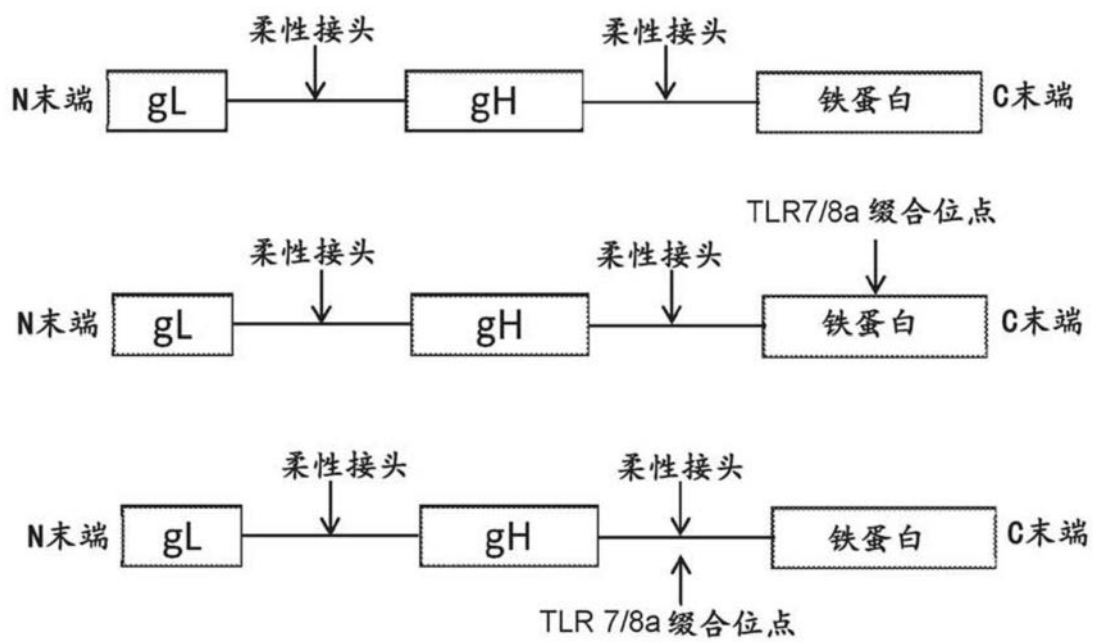


图3

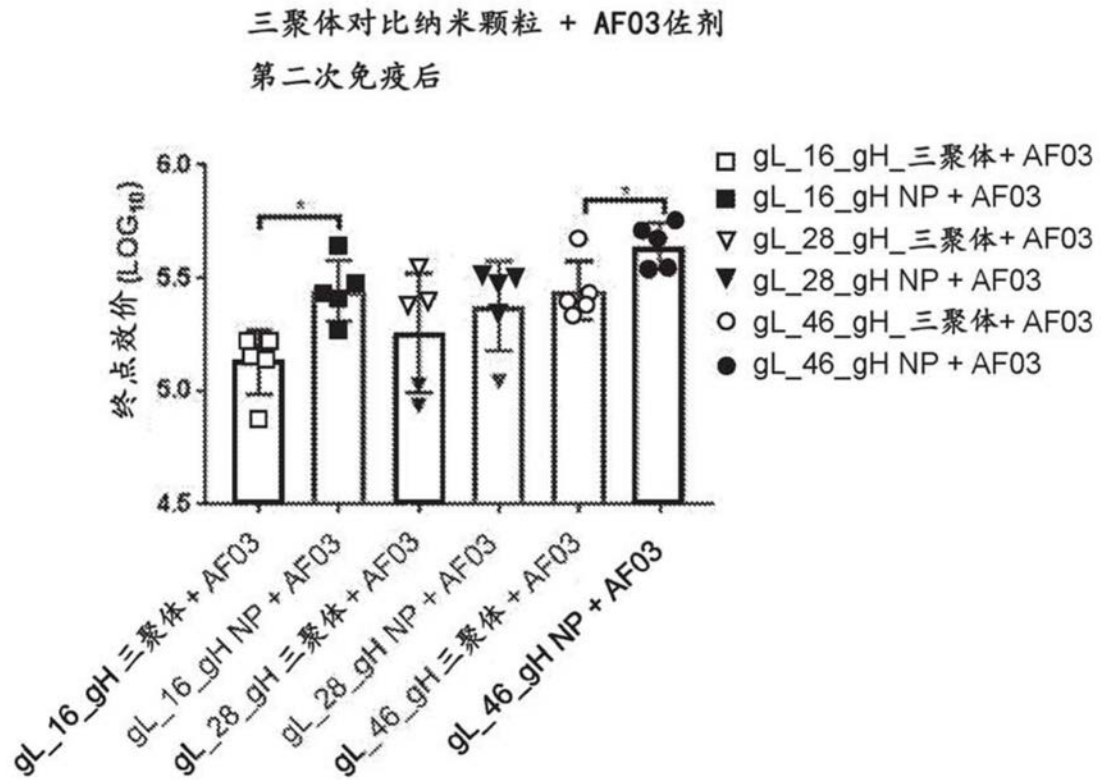


图4

针对单体单链gL/gH的ELISA结合测定

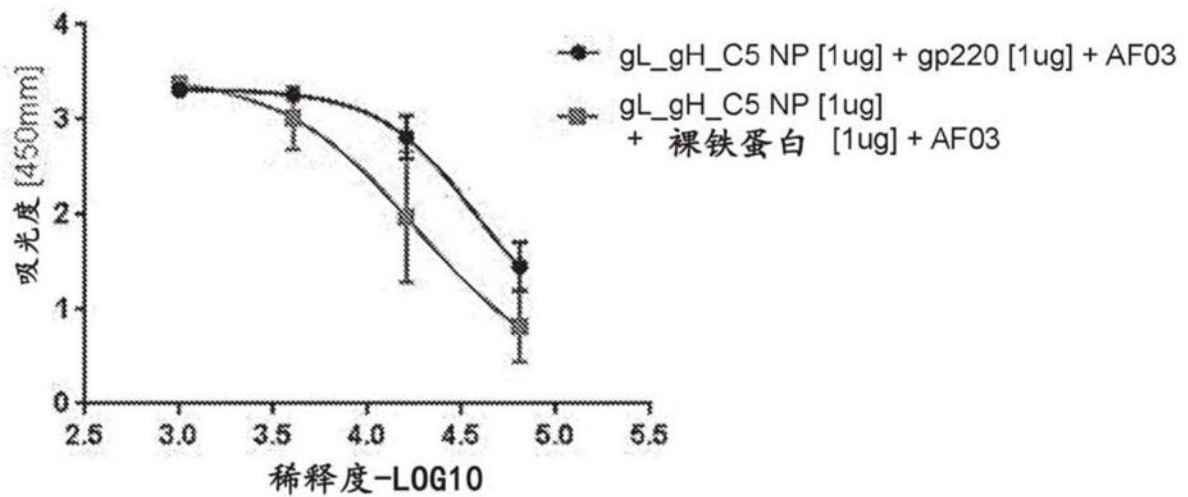


图5A

针对单体单链gLgH的ELISA结合测定

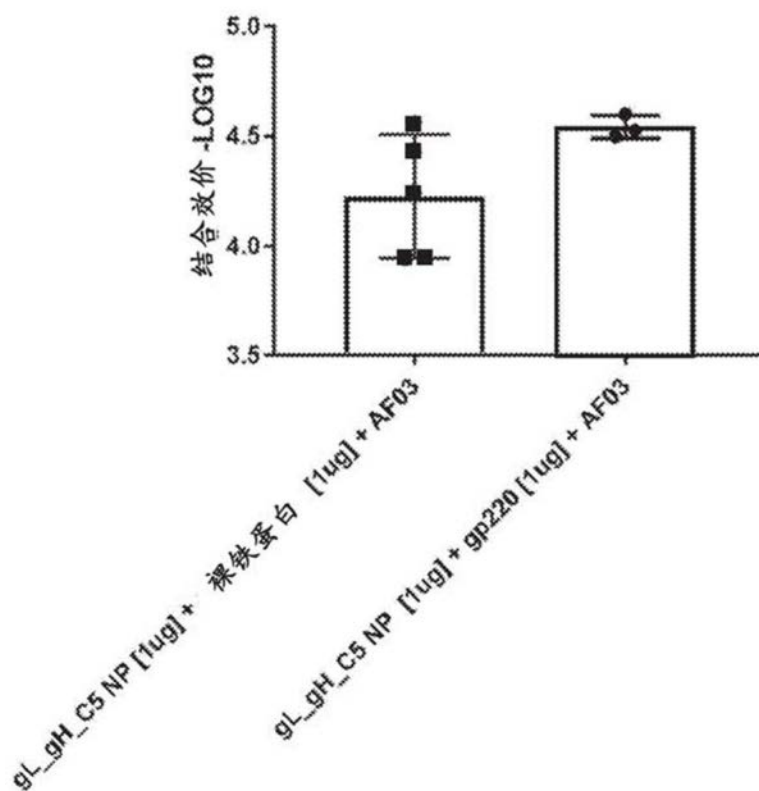


图5B

针对gp220的ELISA结合测定

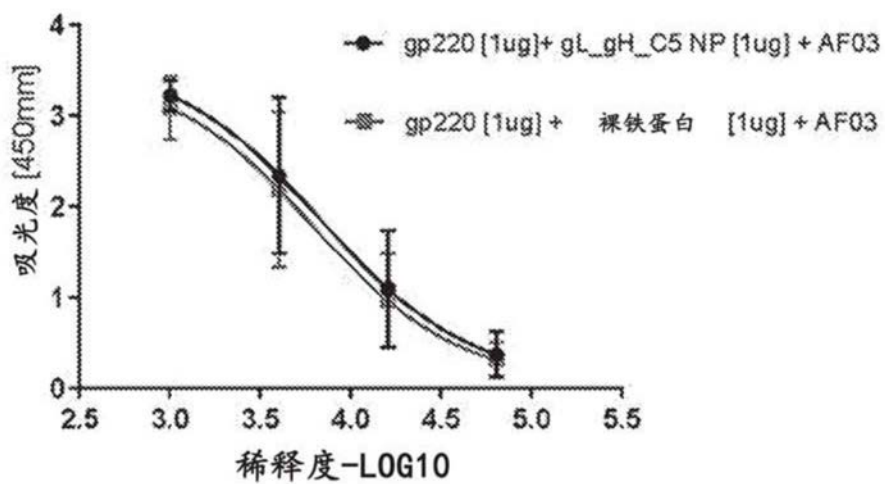


图6A

针对gp220的ELISA结合测定

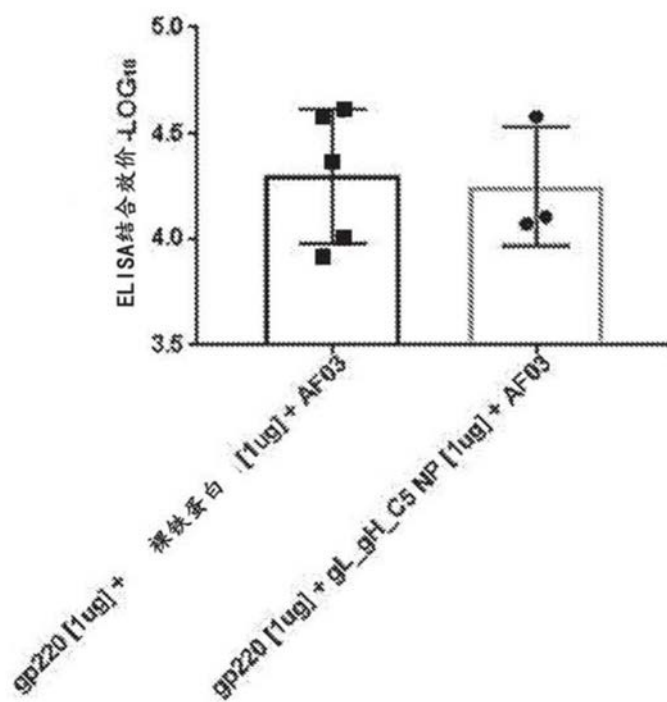


图6B

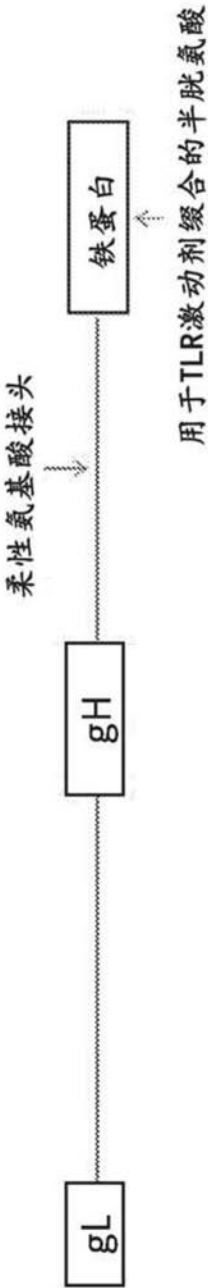


图7A

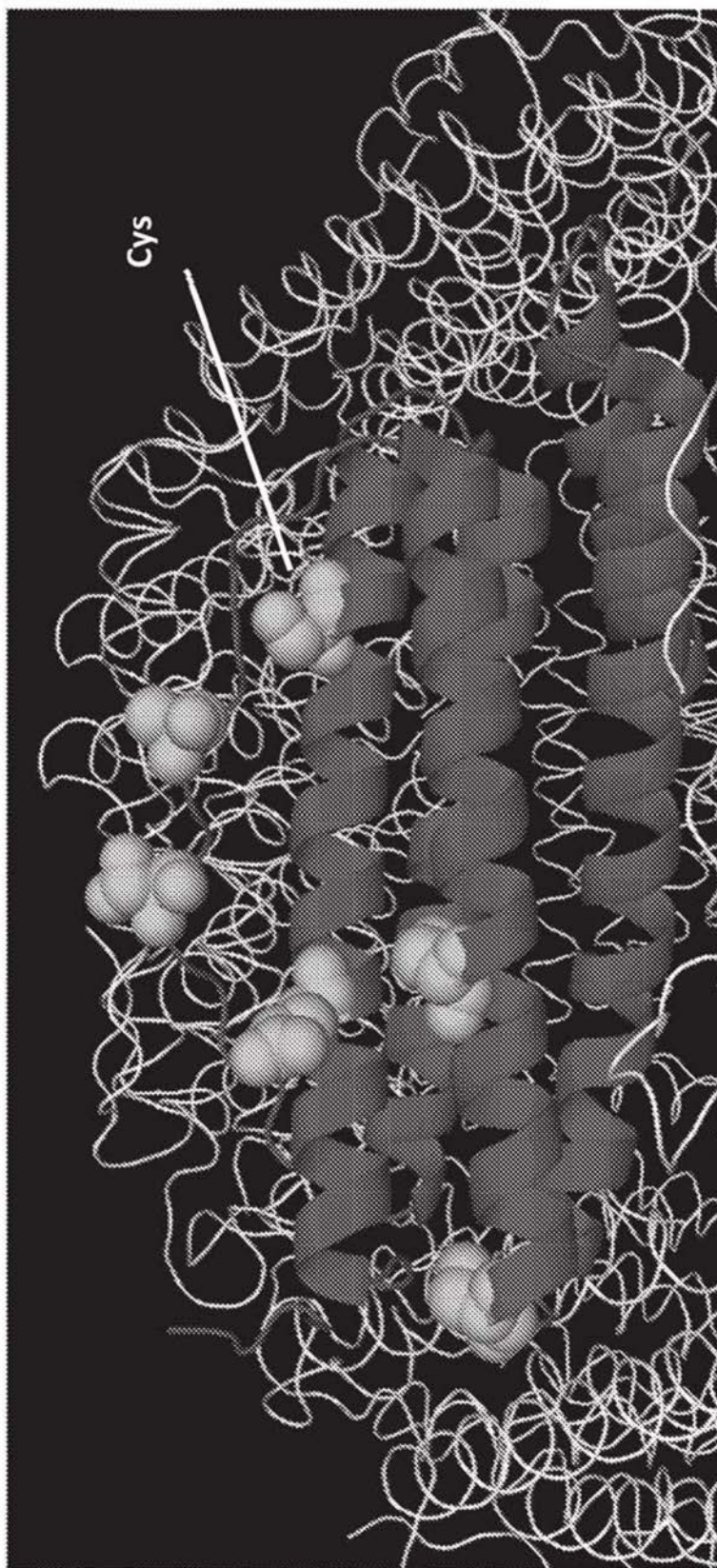


图8A

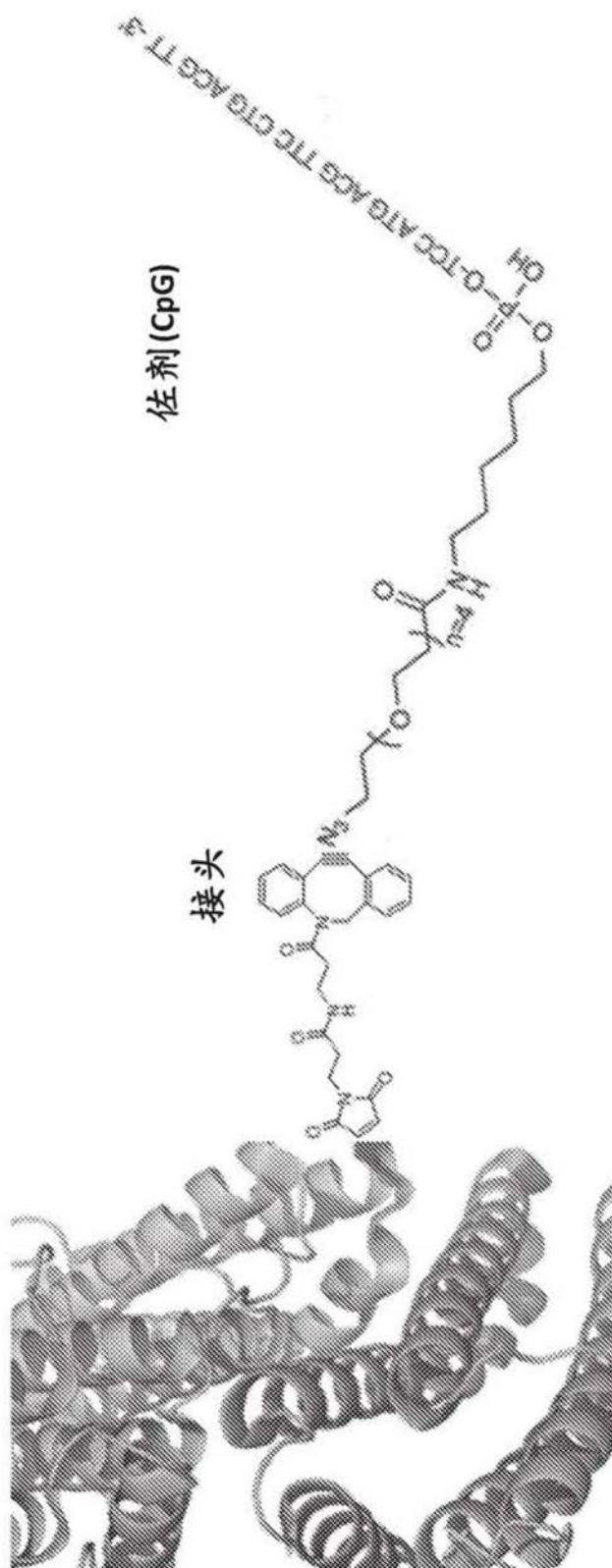


图8B



图9A

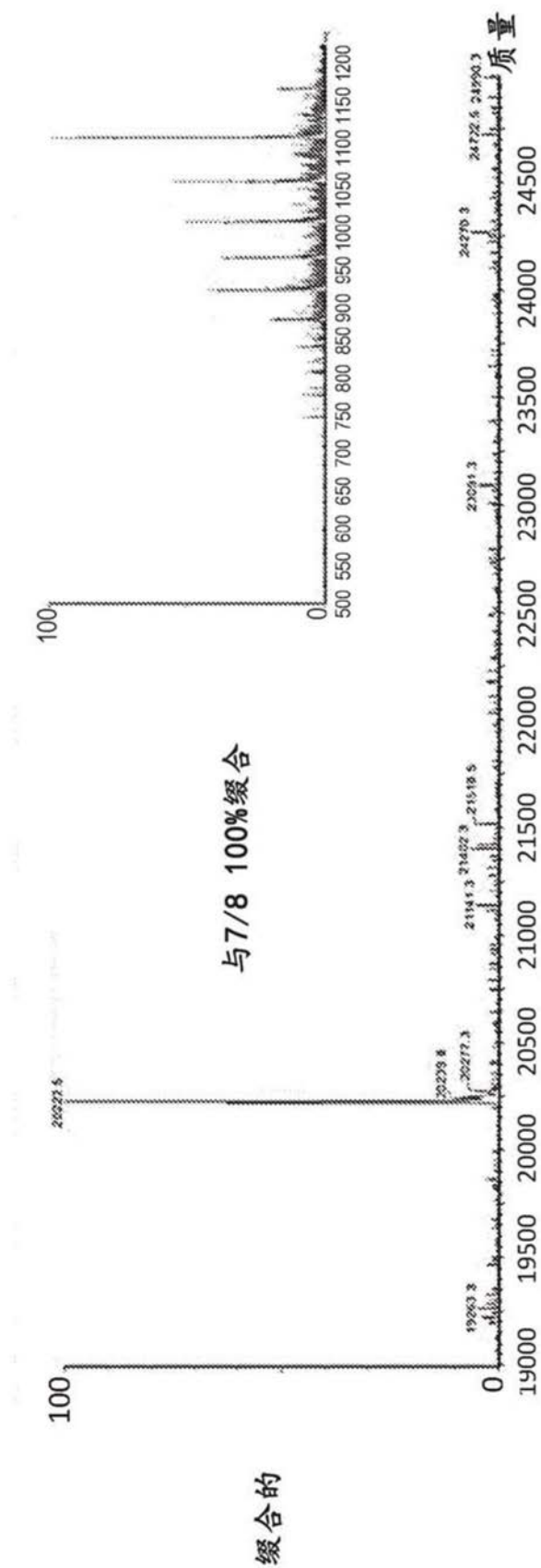


图9B

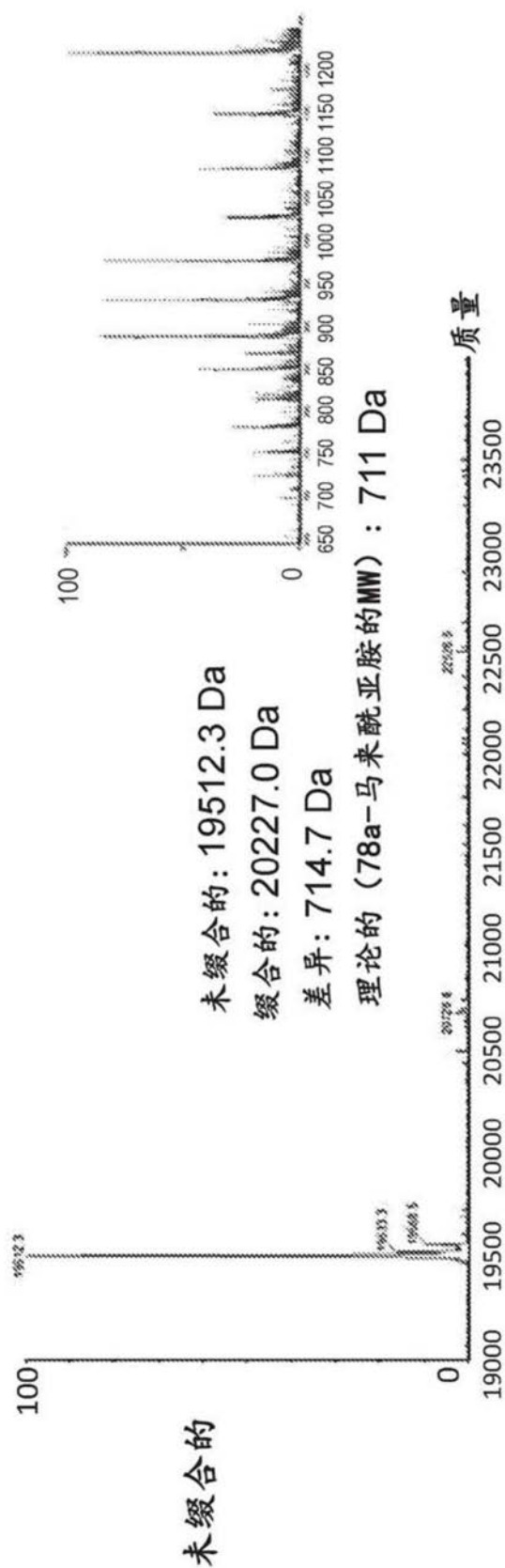


图10A

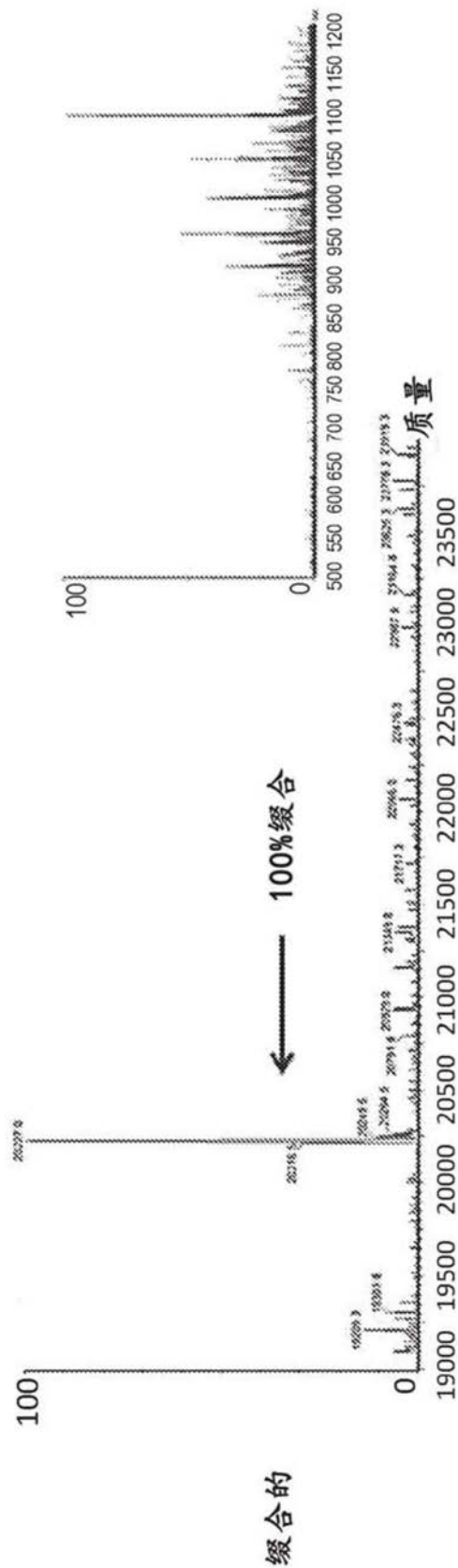


图10B

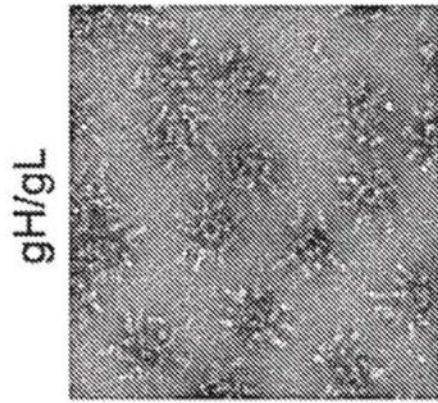


图11A

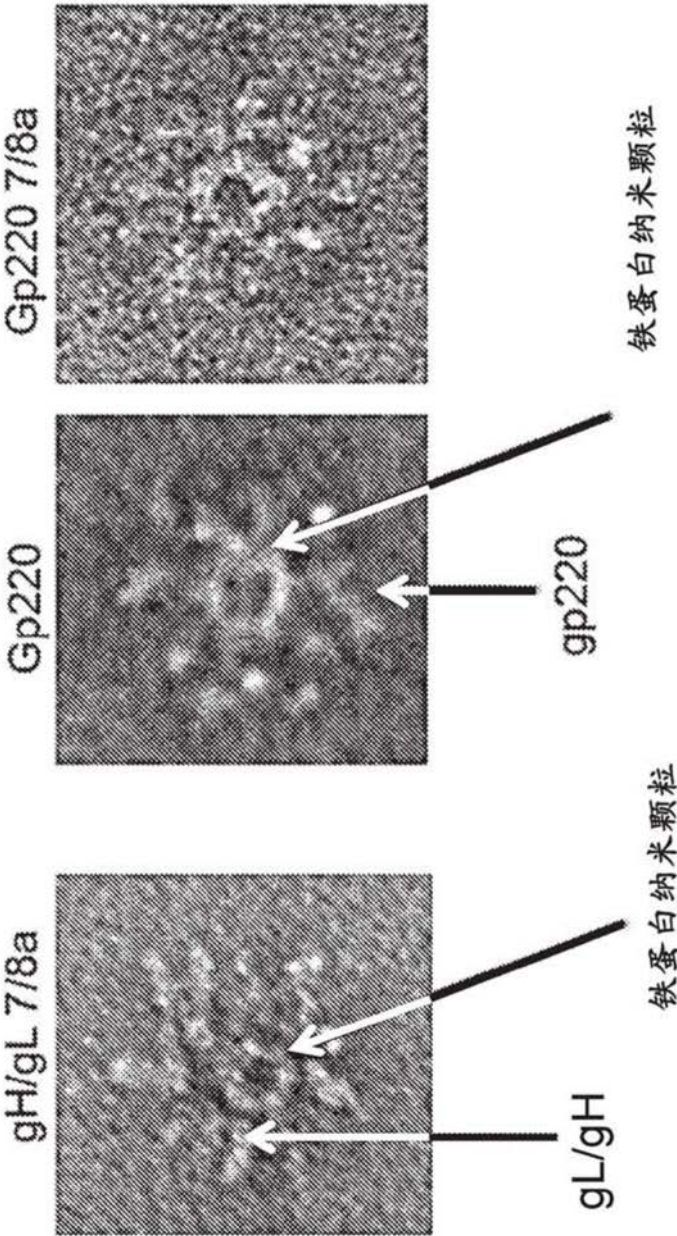


图11B

图11C

图11D

针对单体单链gL/gH的ELISA结合测定

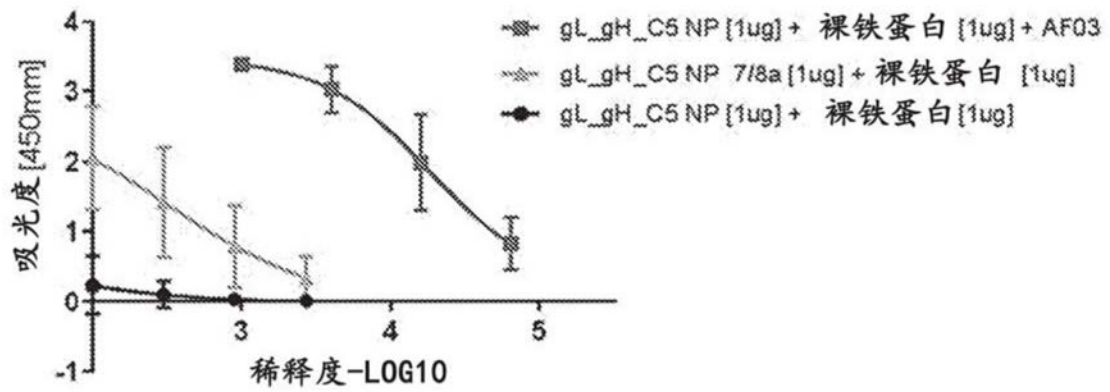


图12A

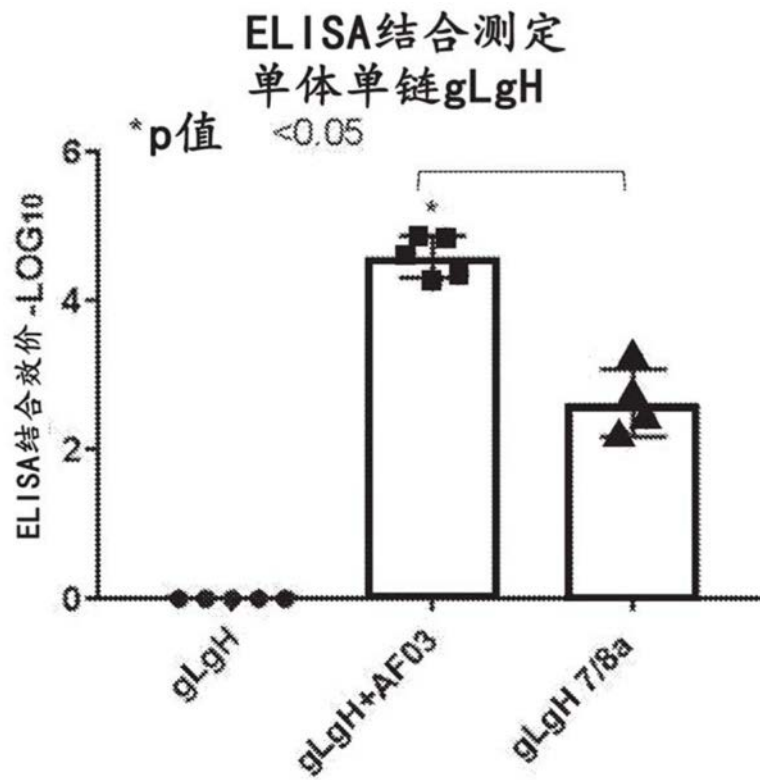


图12B

针对gp220的ELISA结合测定

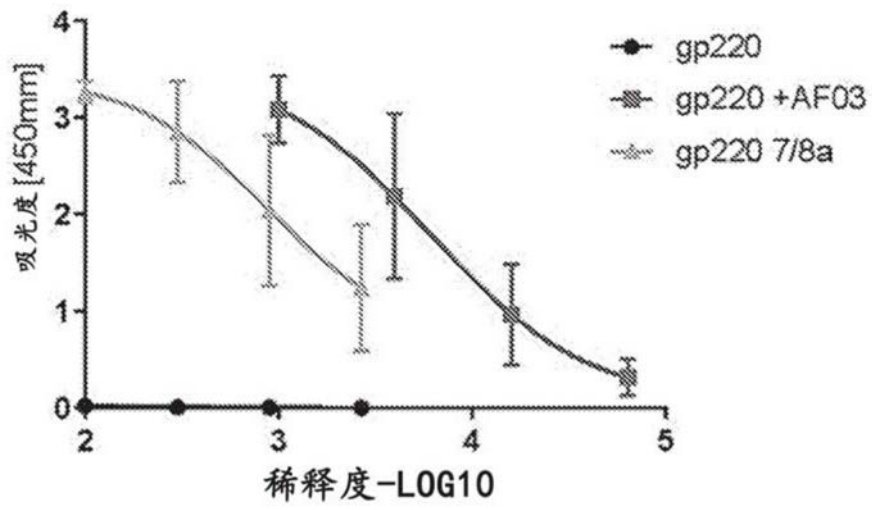


图13A

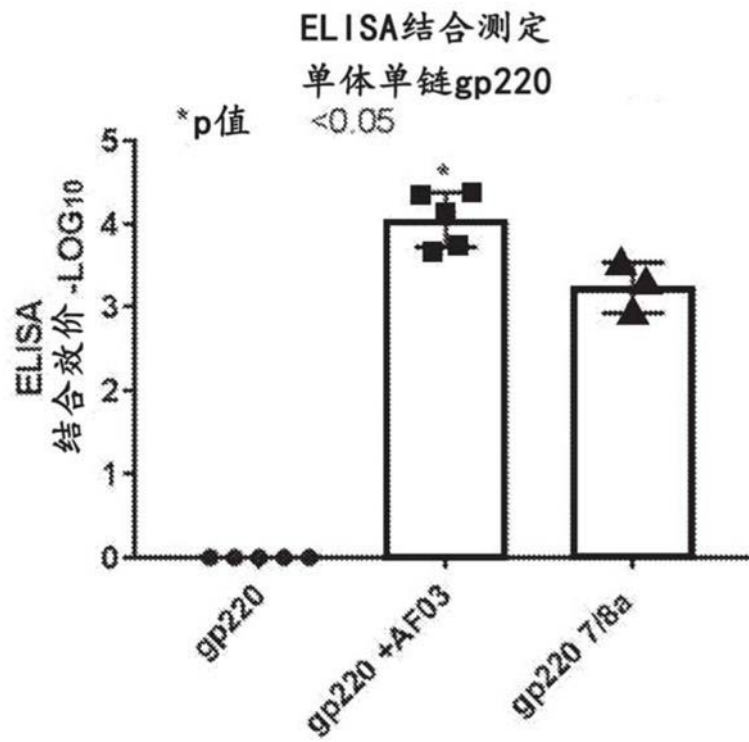


图13B

针对单体单链gL/gH的ELISA结合测定

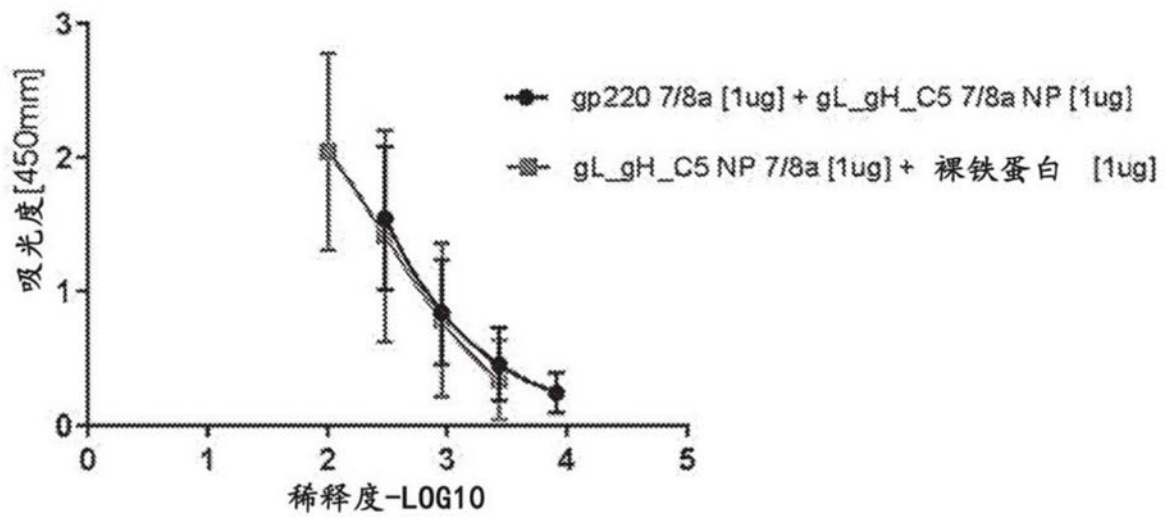


图14A

针对单体单链gL/gH的ELISA结合测定

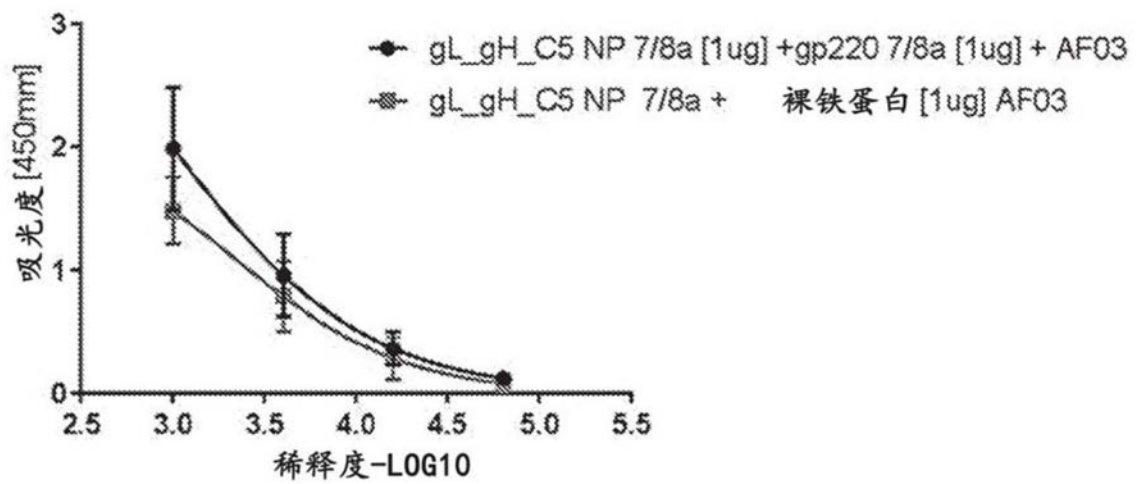


图14B

针对gp220的ELISA结合测定

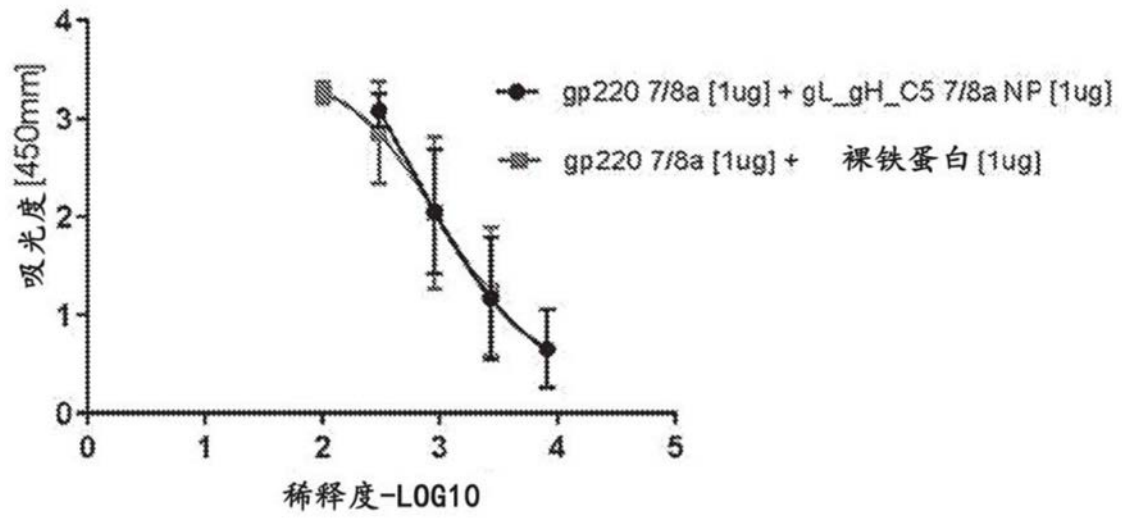


图15A

针对gp220的ELISA结合测定

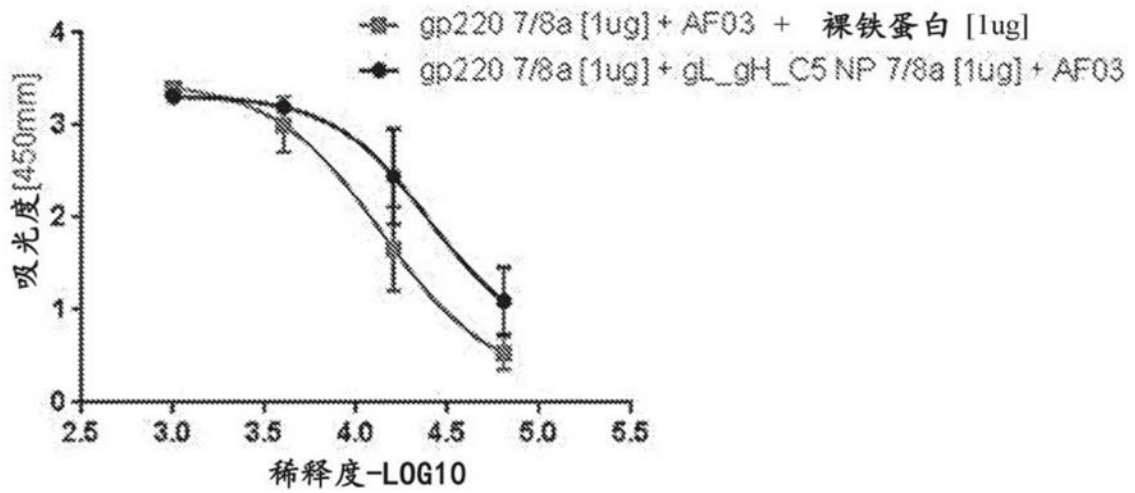


图15B

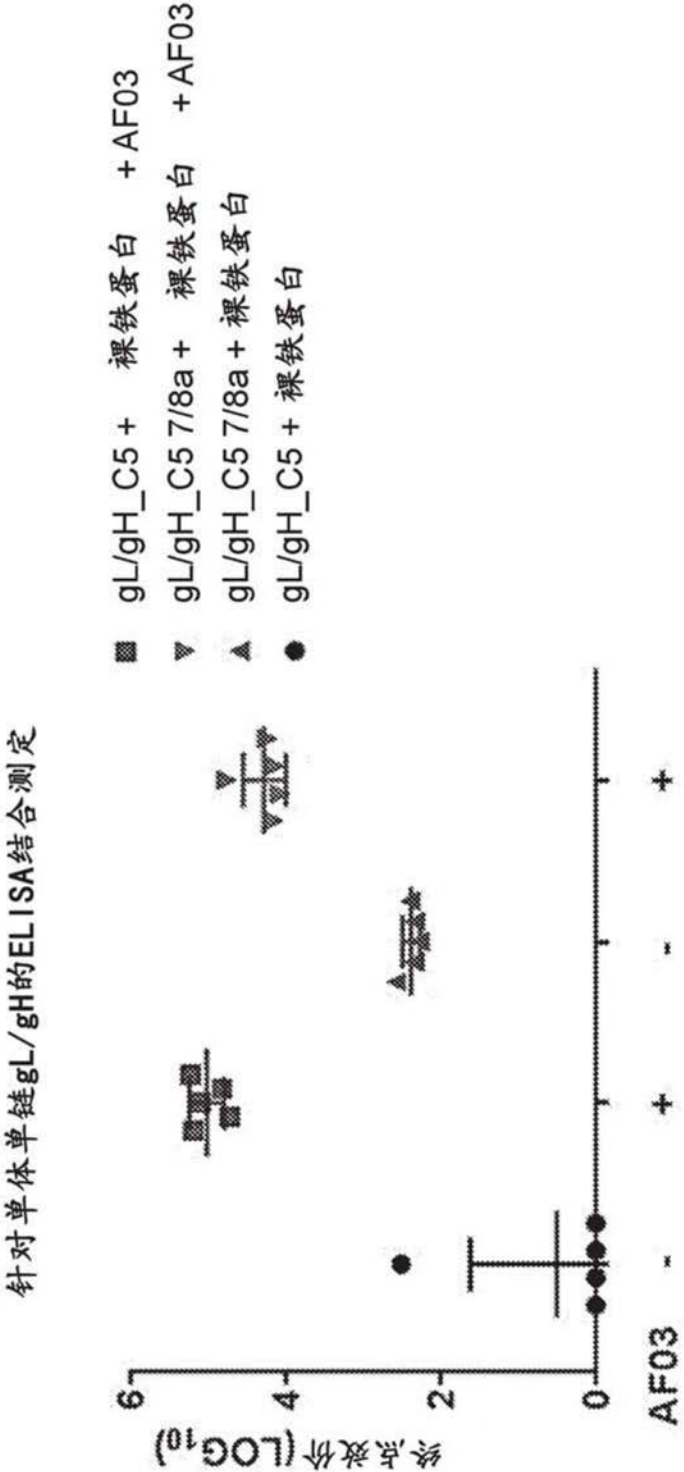


图16

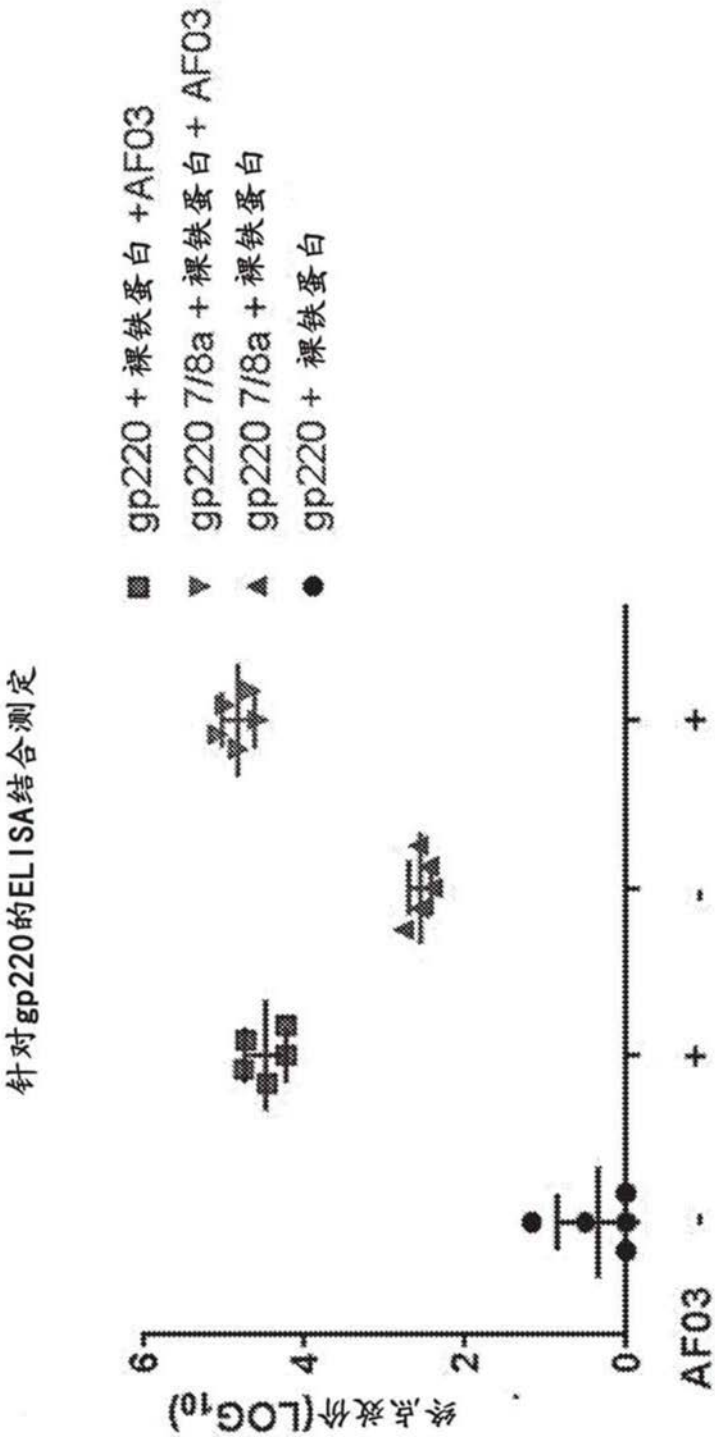


图17

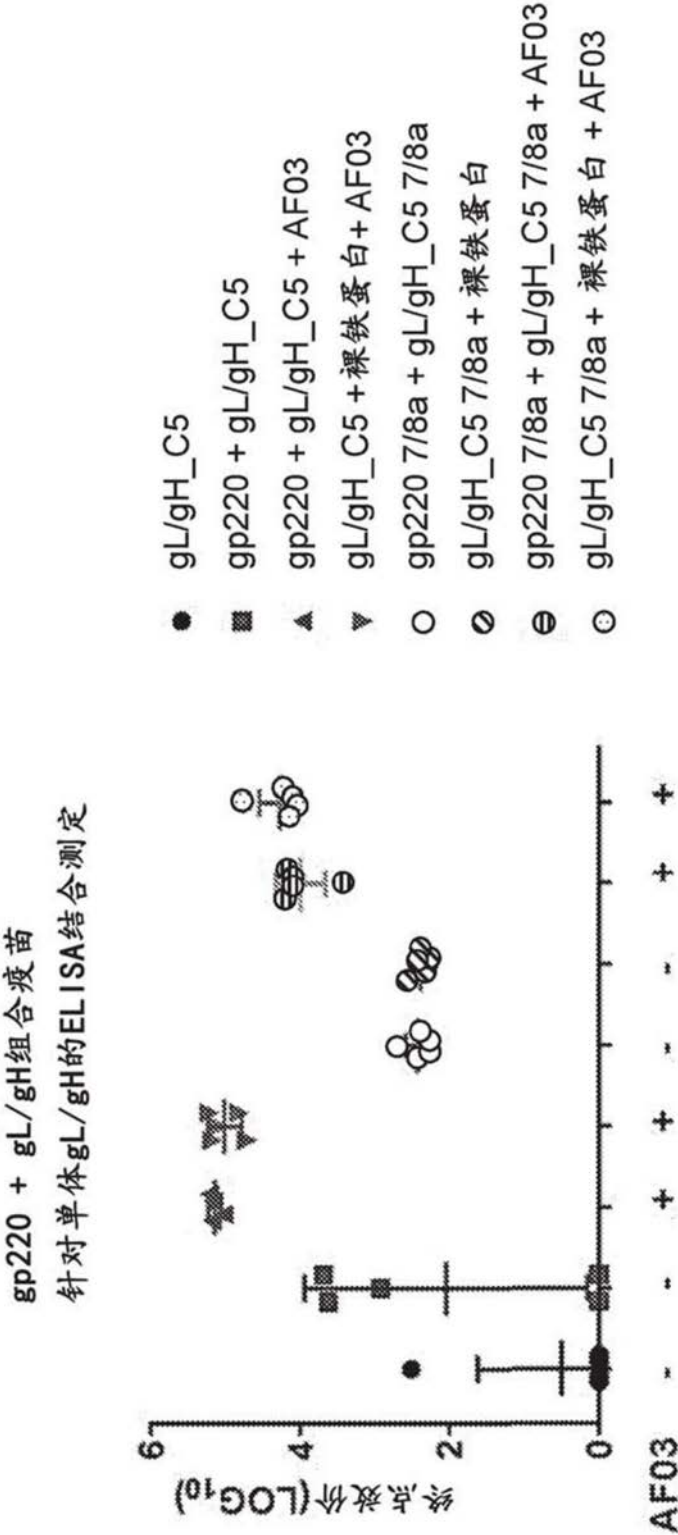


图18

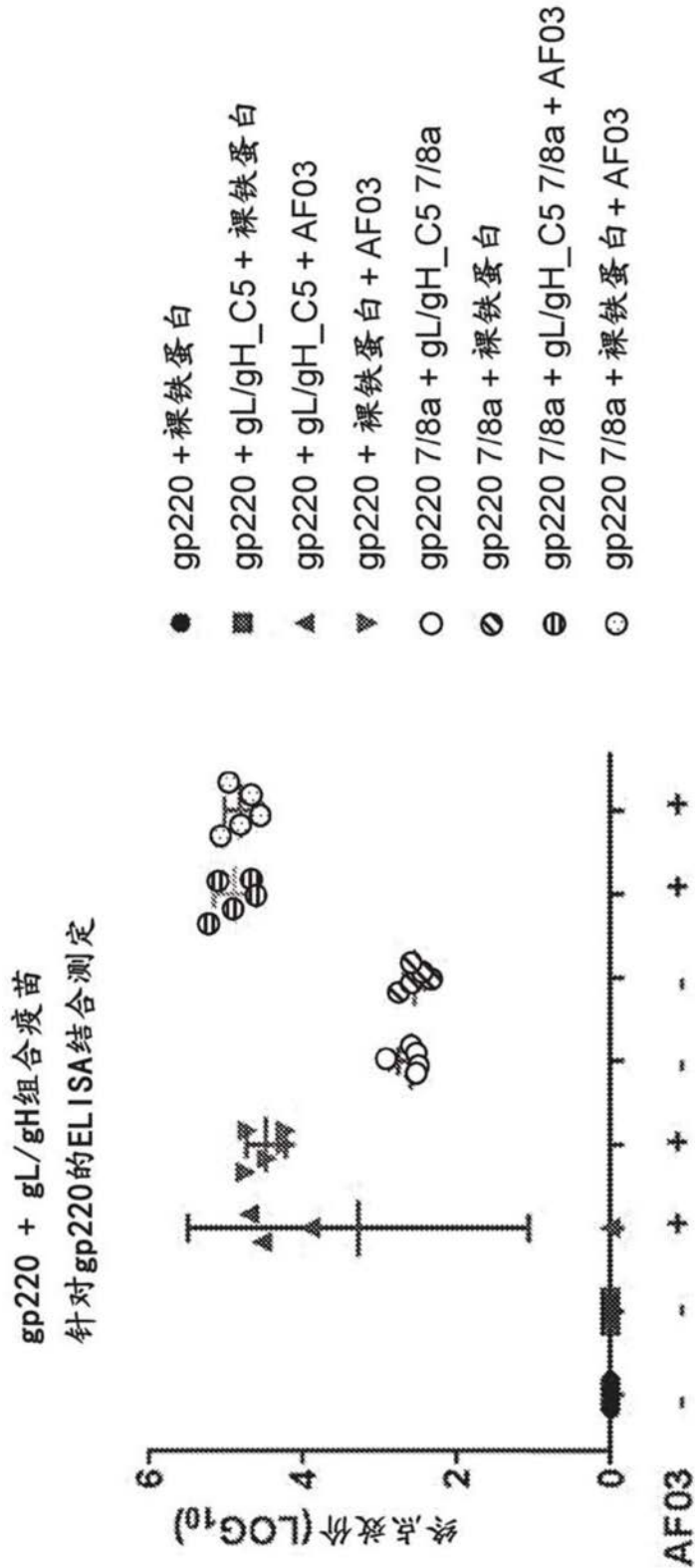


图19

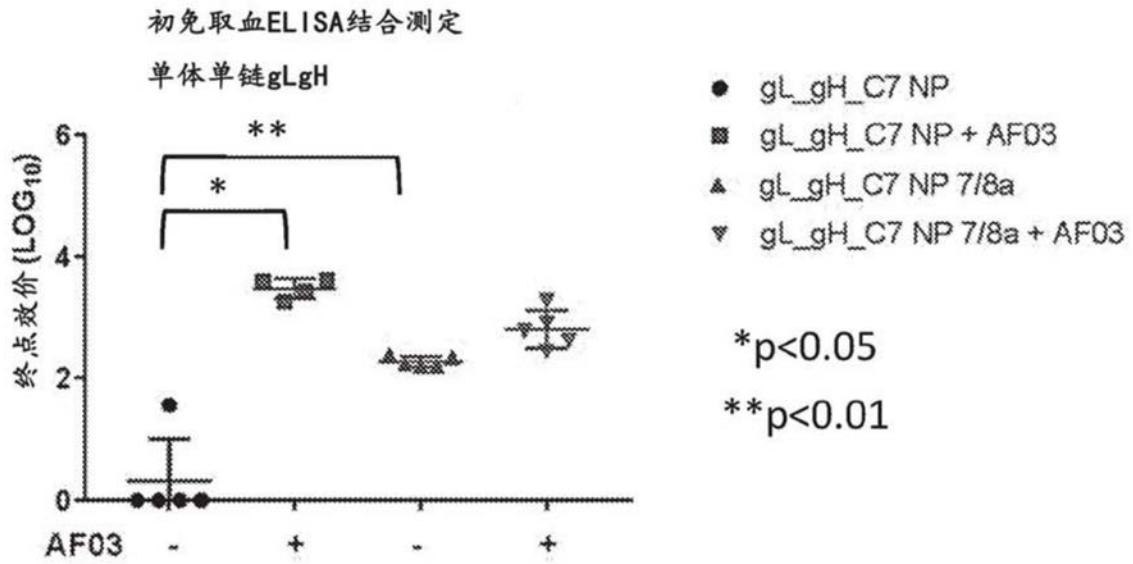


图20A

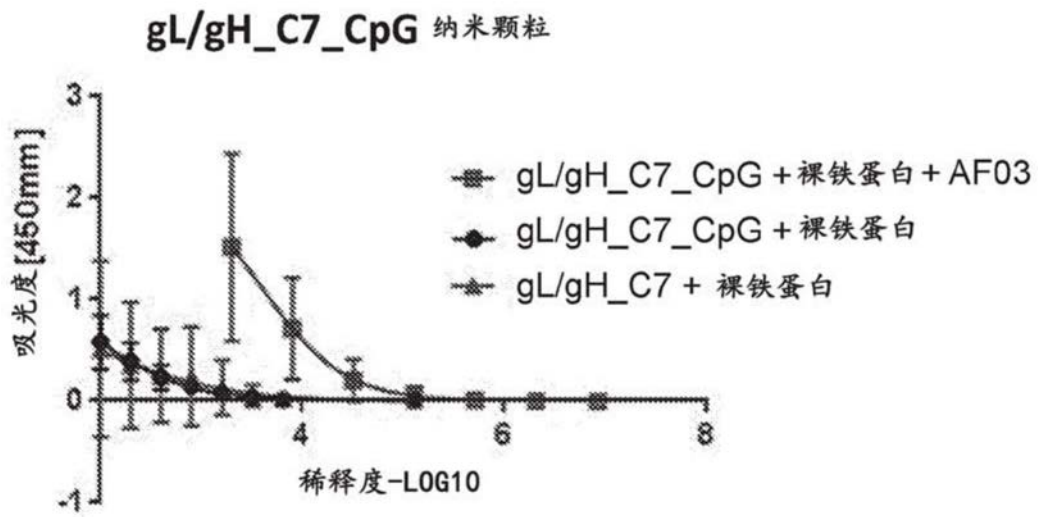


图20B

针对单体单链gL/gH的加强免疫取血ELISA结合测定

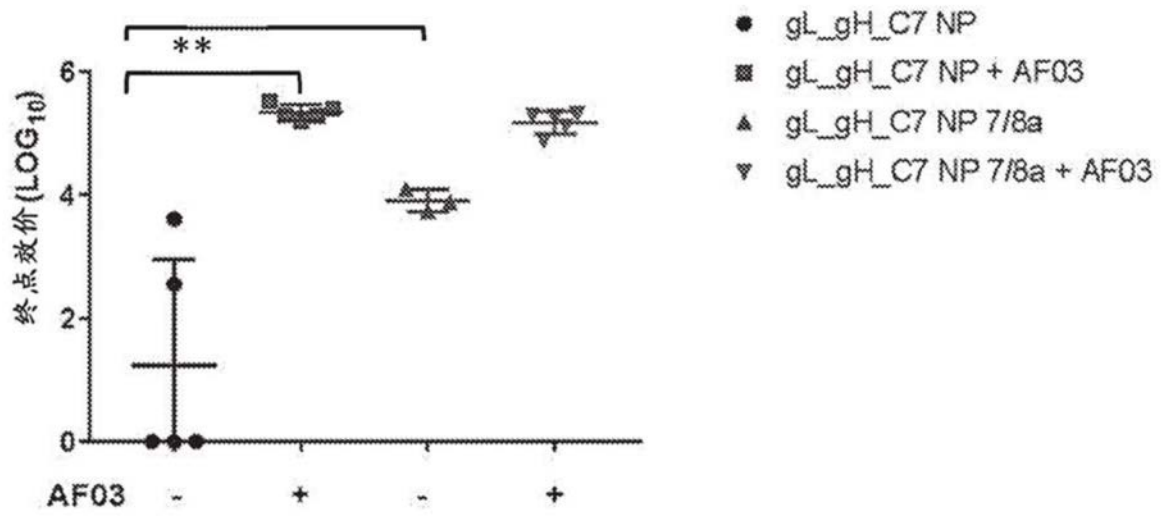


图20C

针对单体单链gL/gH的终末期取血ELISA结合测定

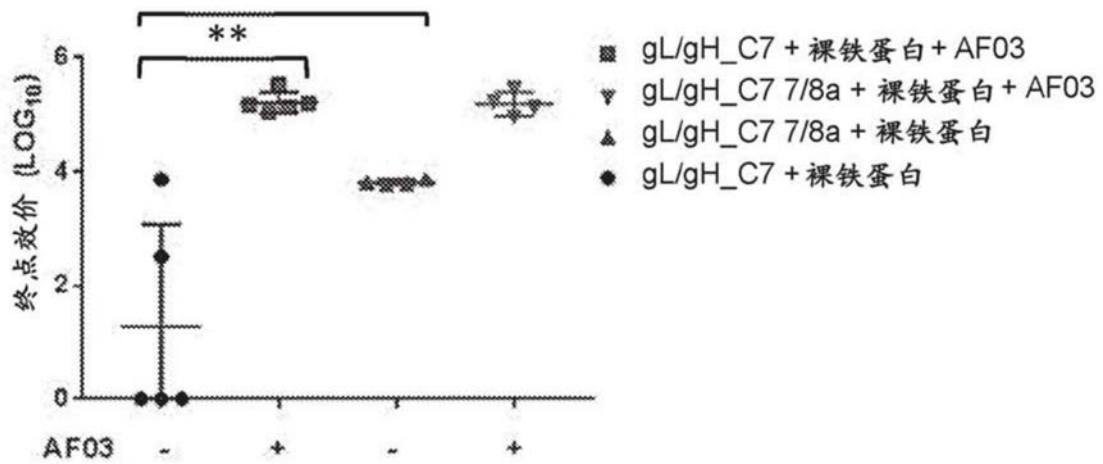


图20D

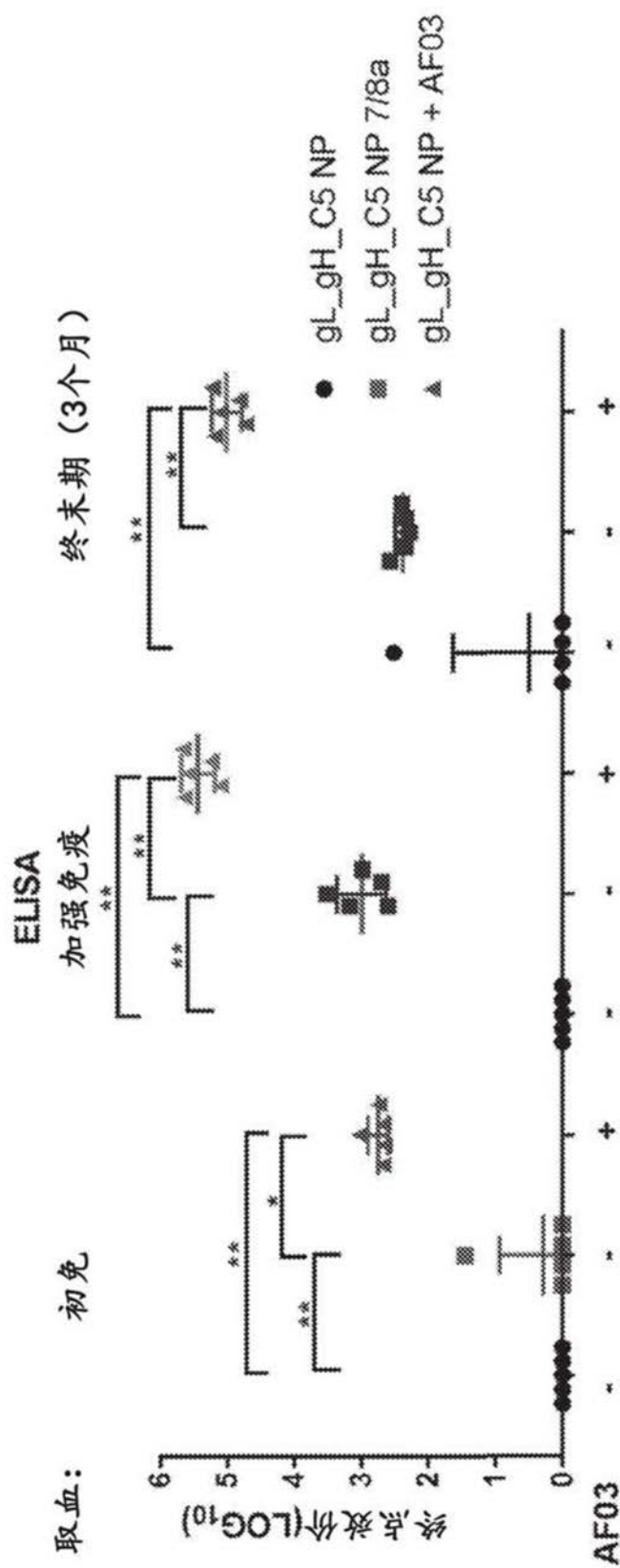


图21

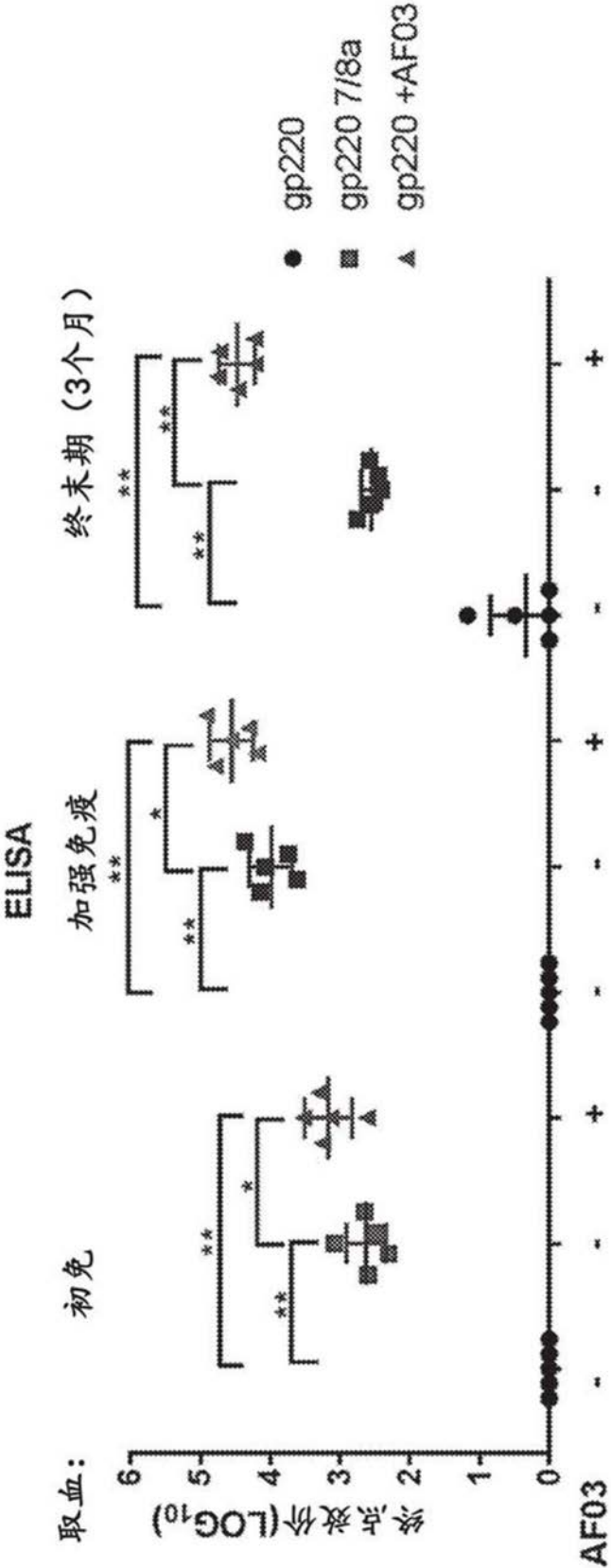


图22

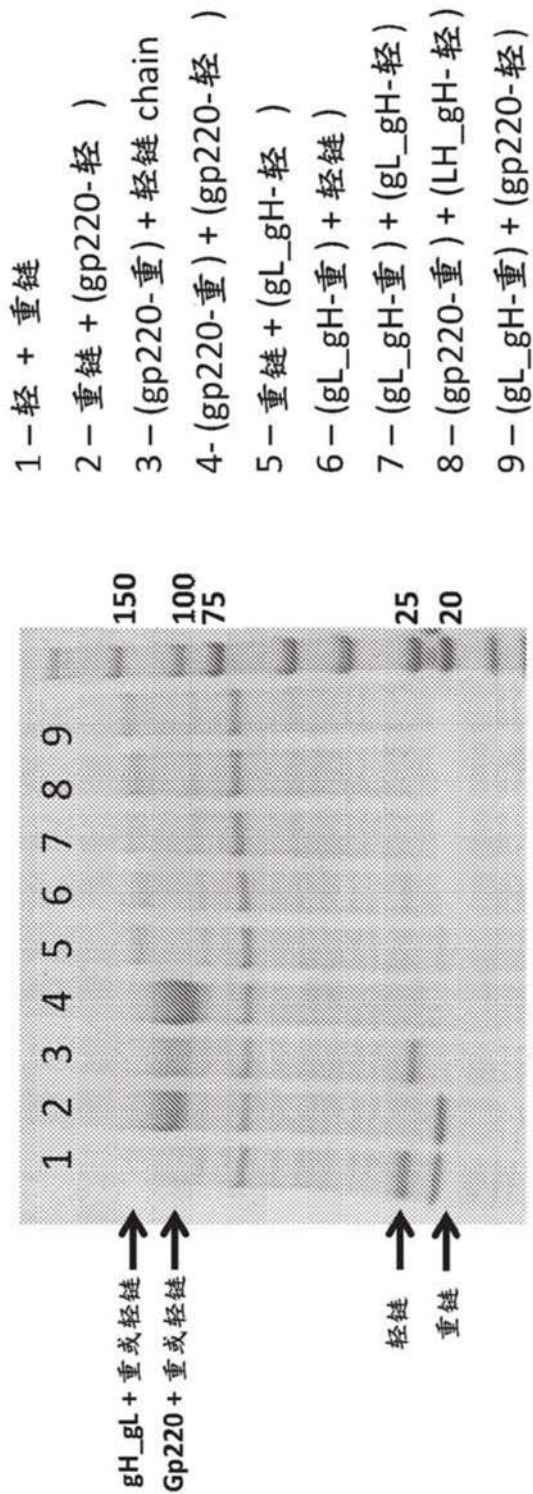


图23A

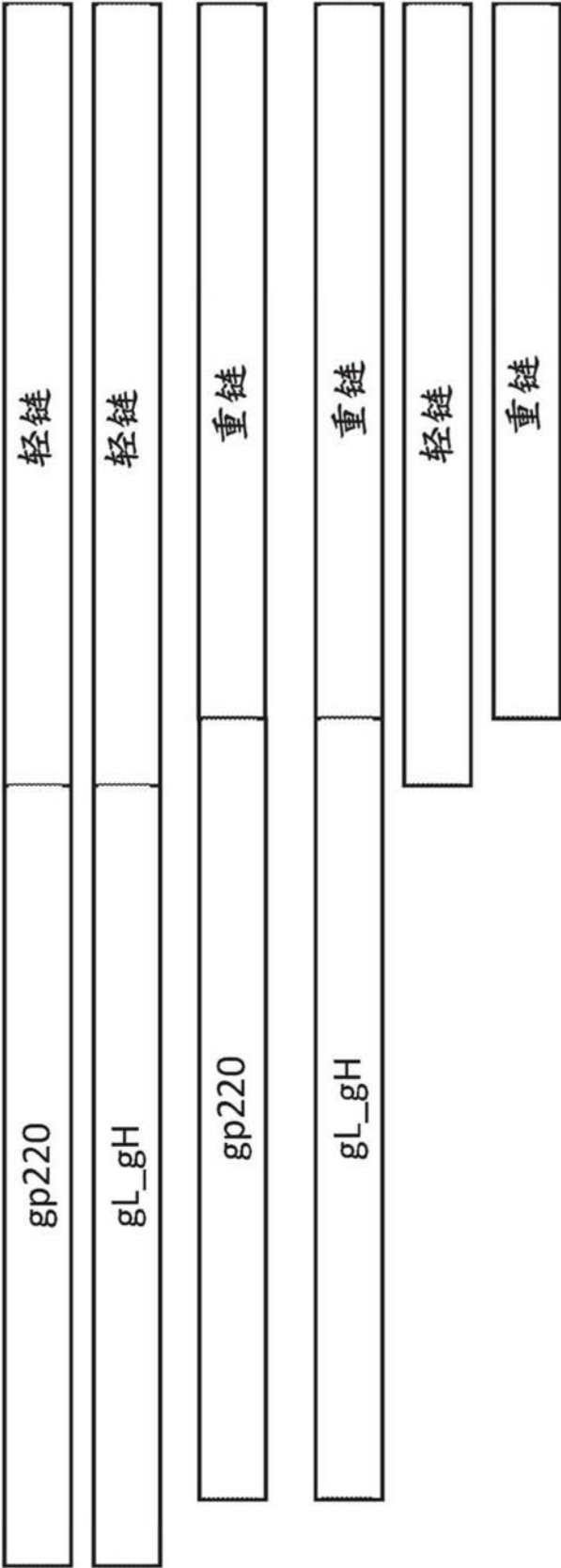


图23B

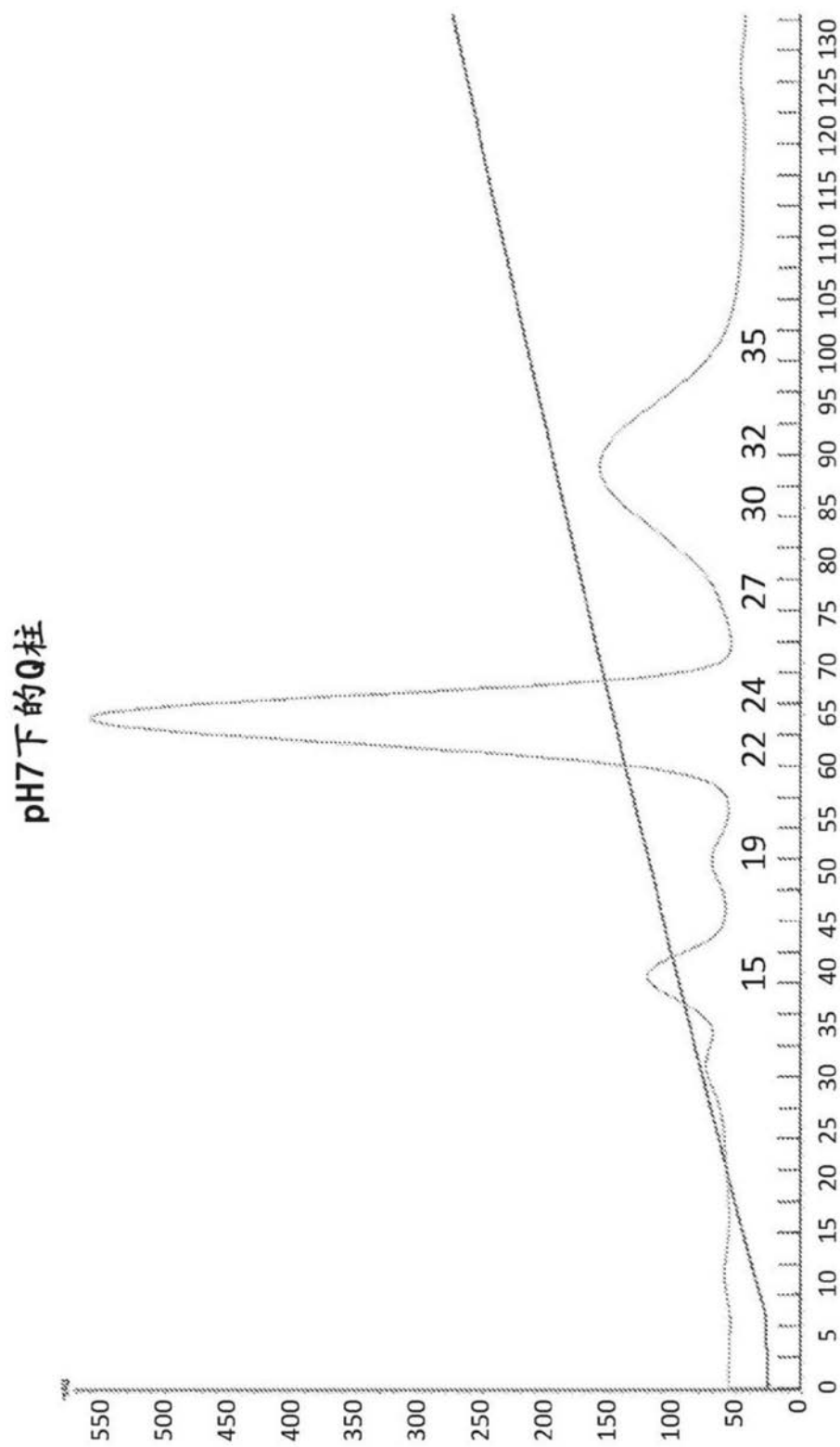


图24A

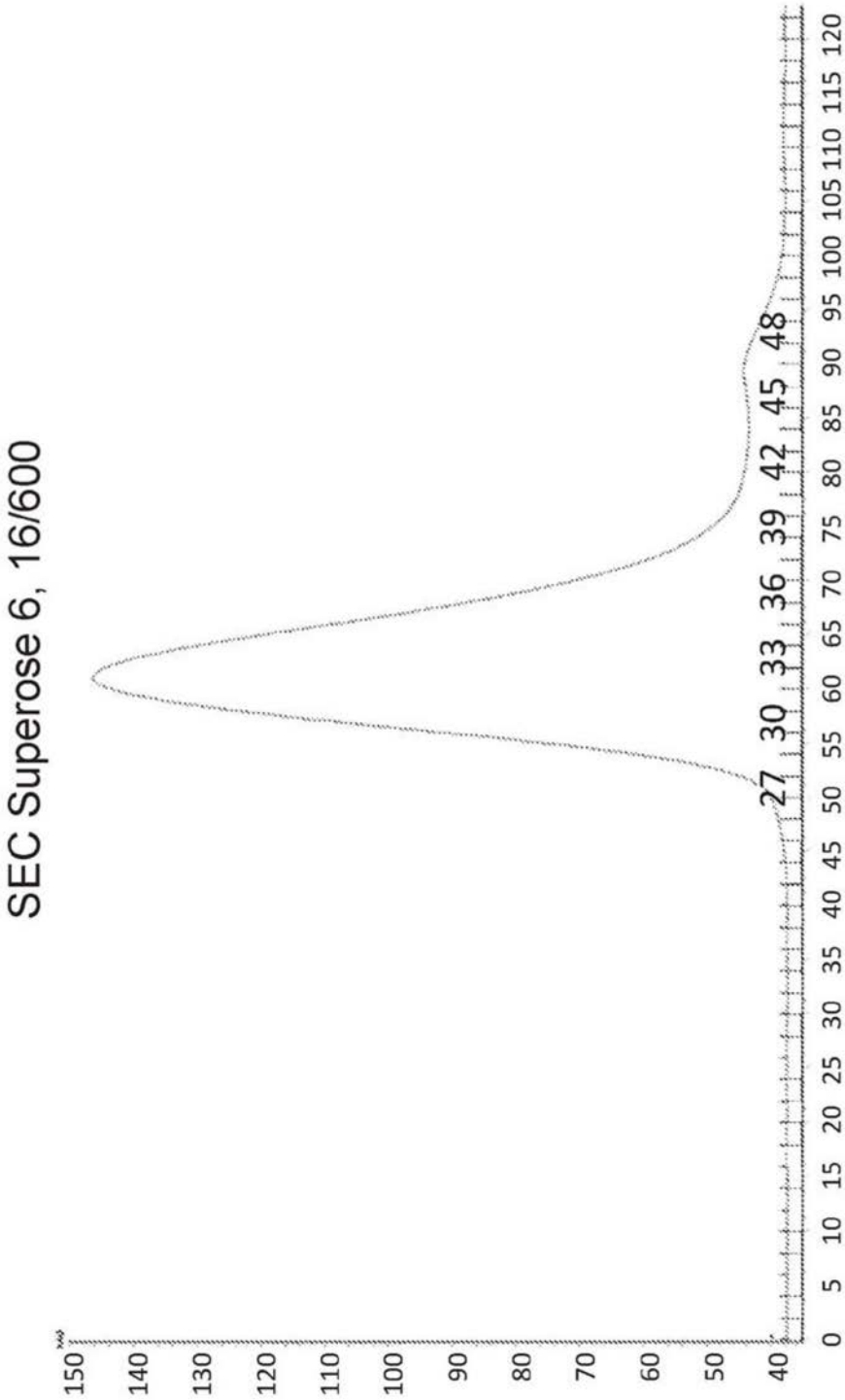


图24B

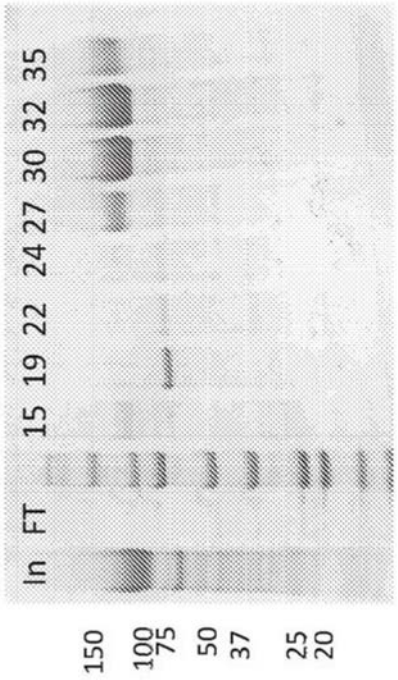


图24C

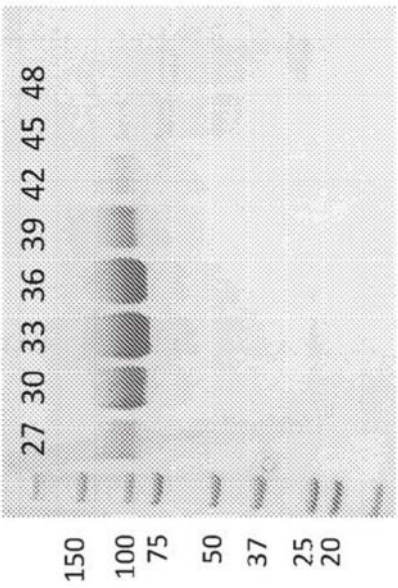


图24D

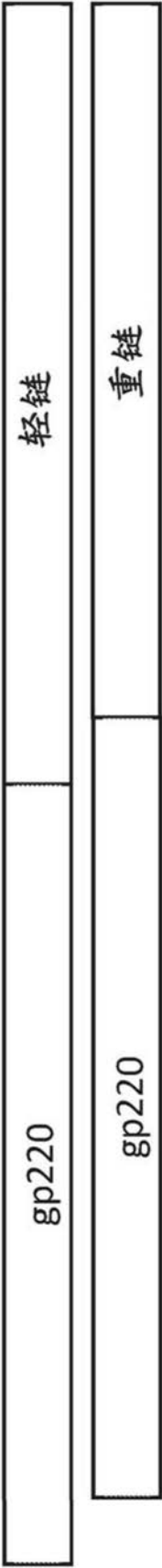


图24E

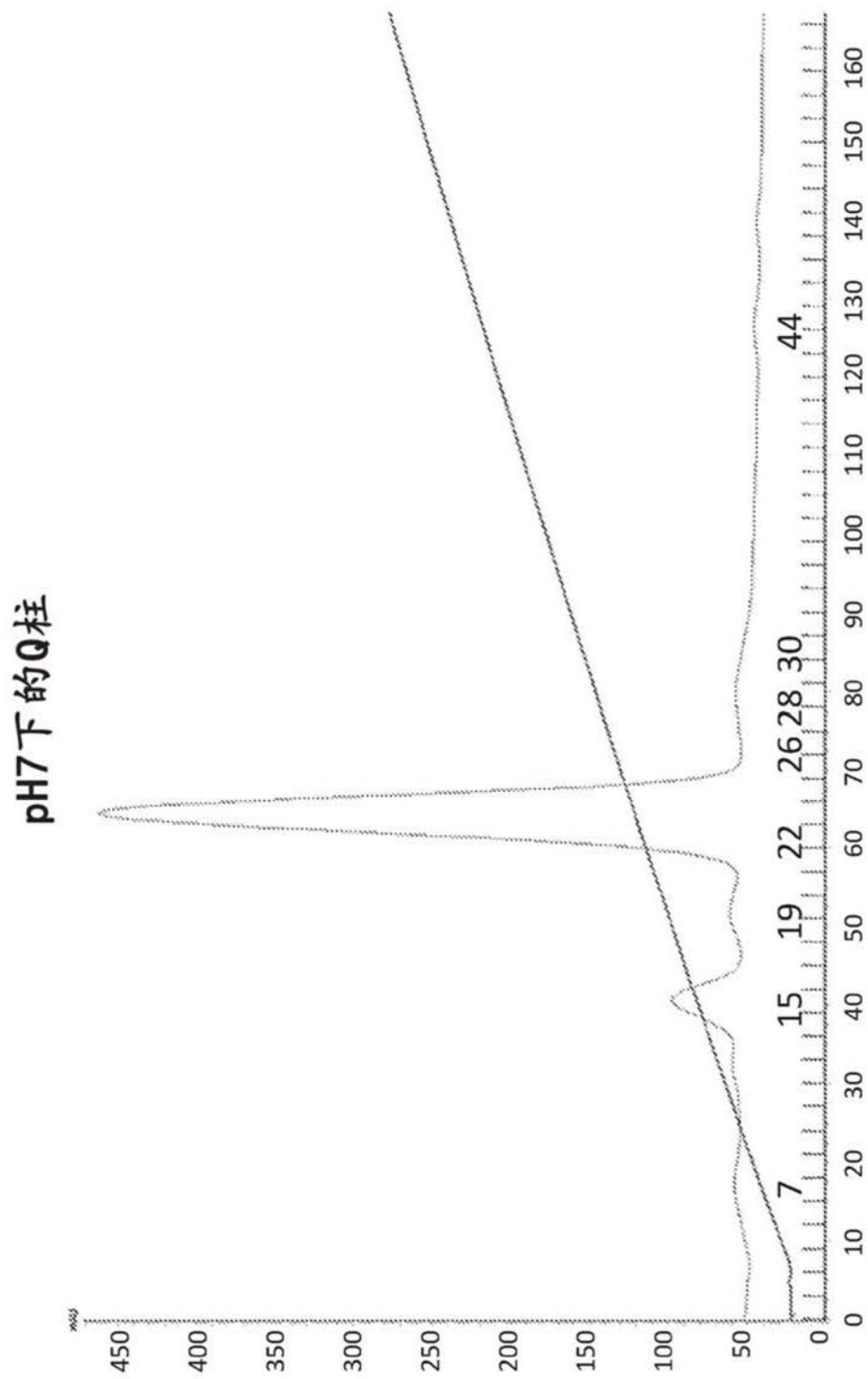


图25A

SEC Superose 6, 16/600

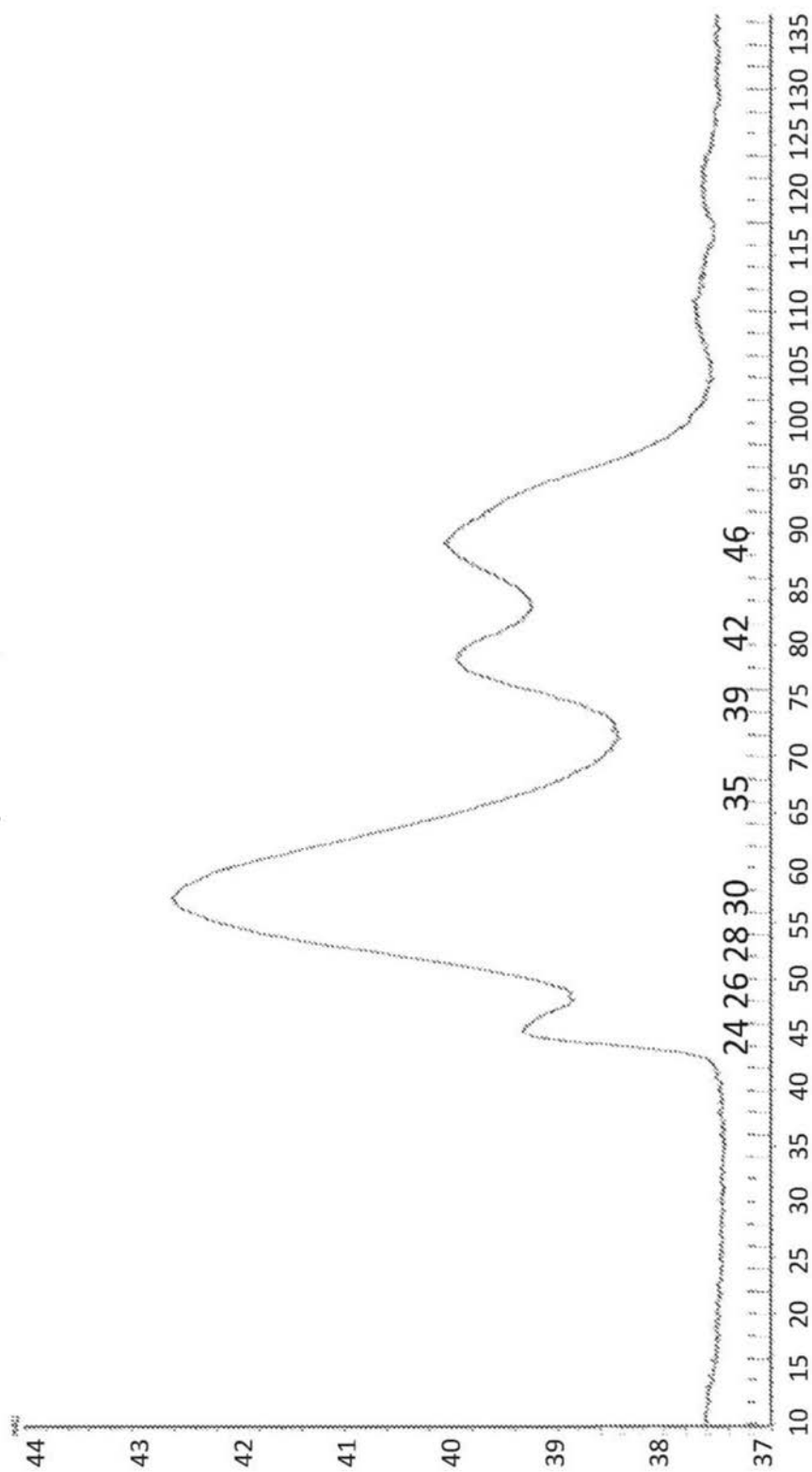


图25B

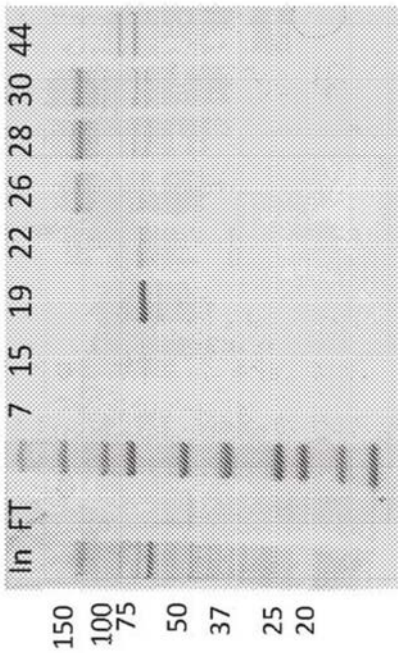


图25C

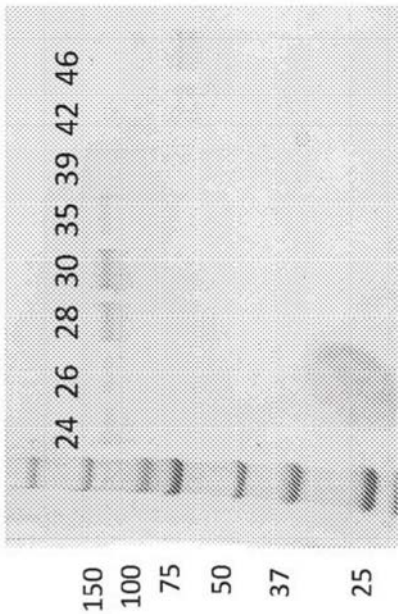


图25D

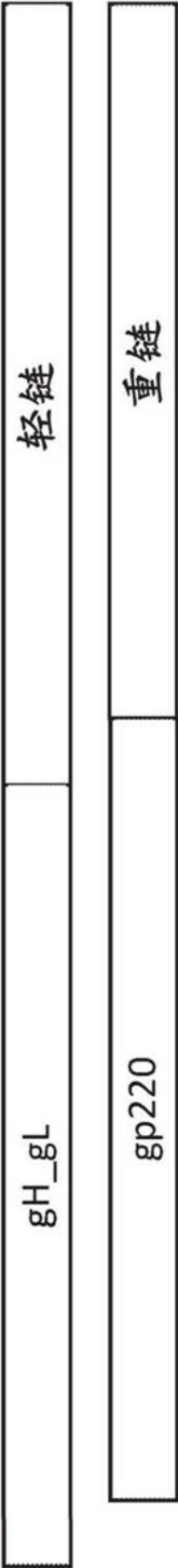


图25E

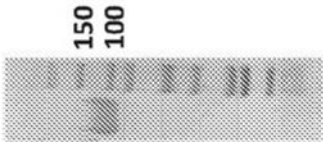


图26A



图26B

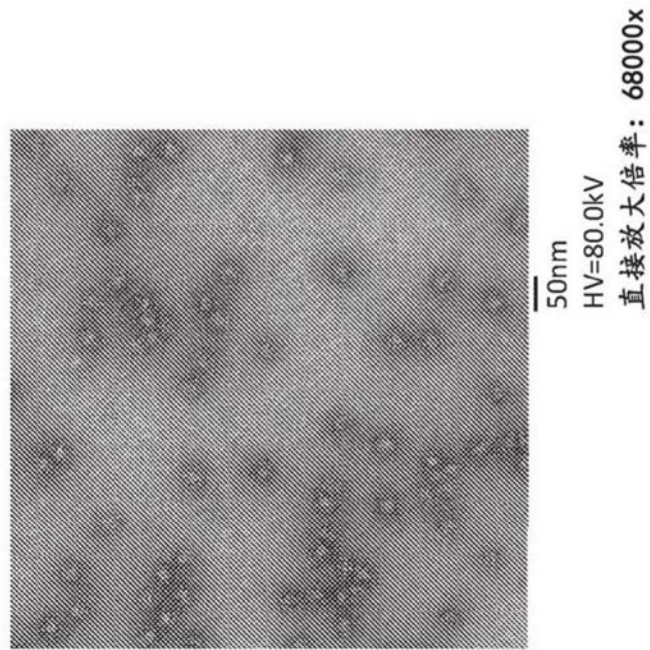


图26C

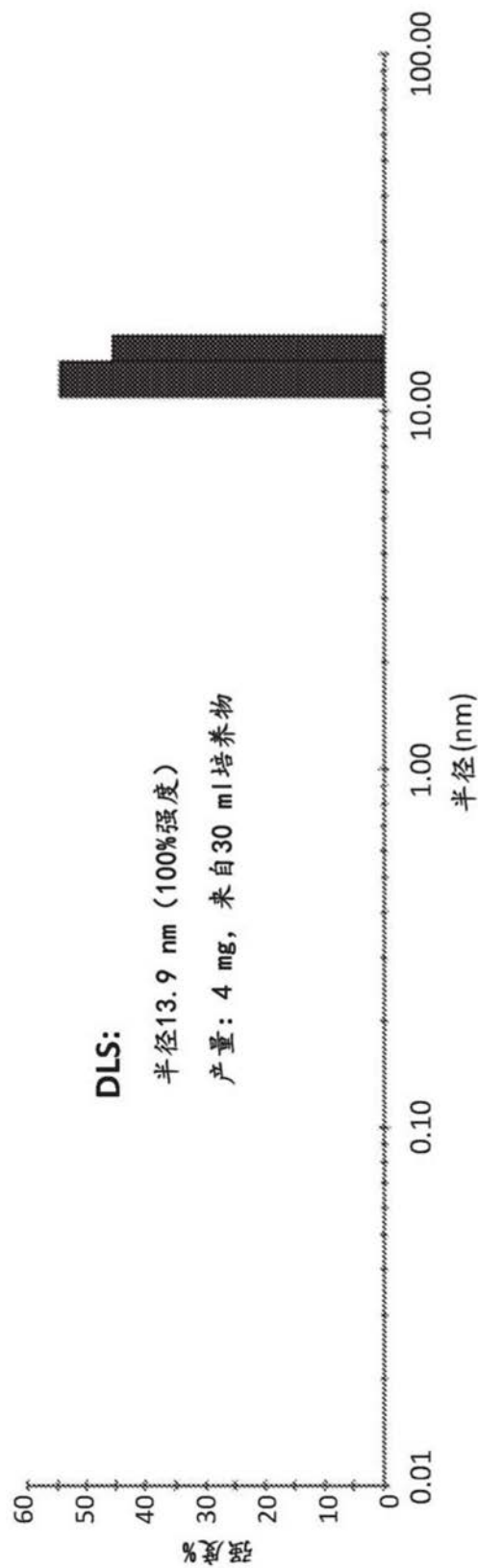


图26D

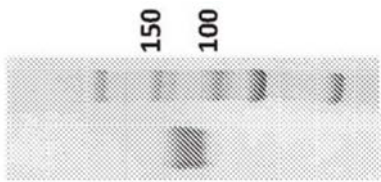


图26E



图26F

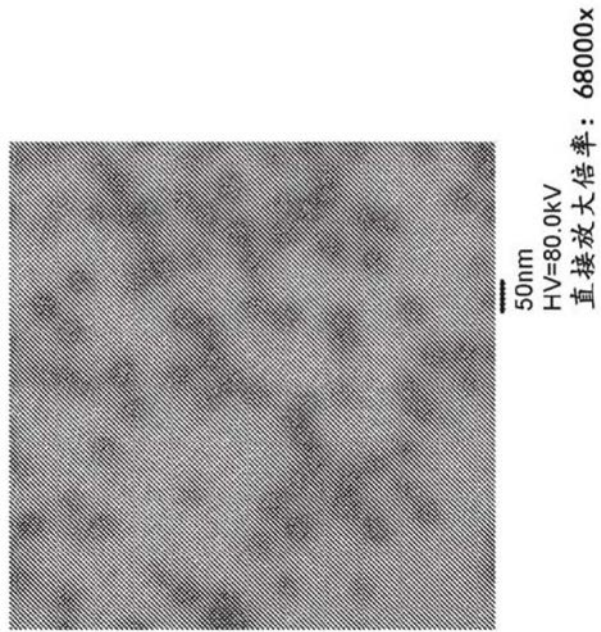


图26G

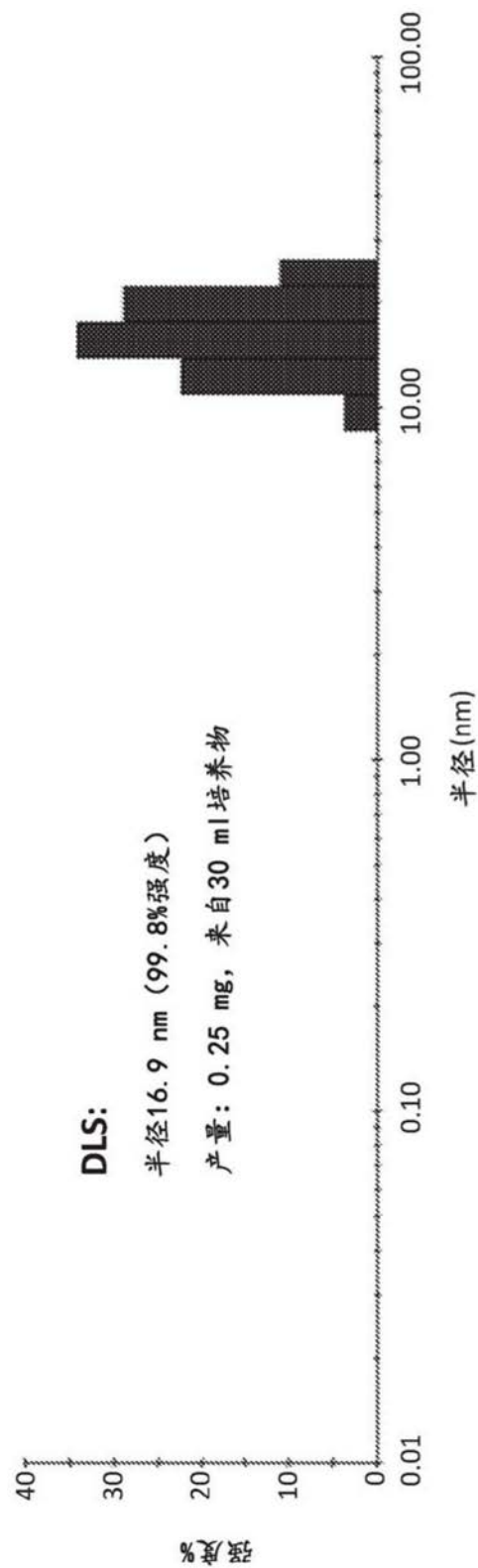


图26H

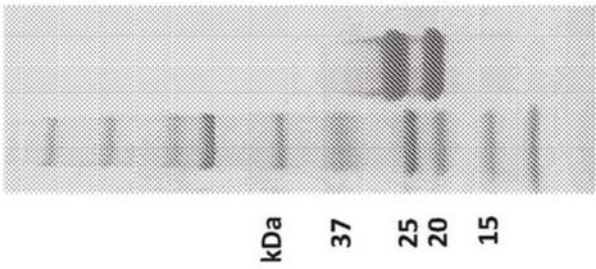
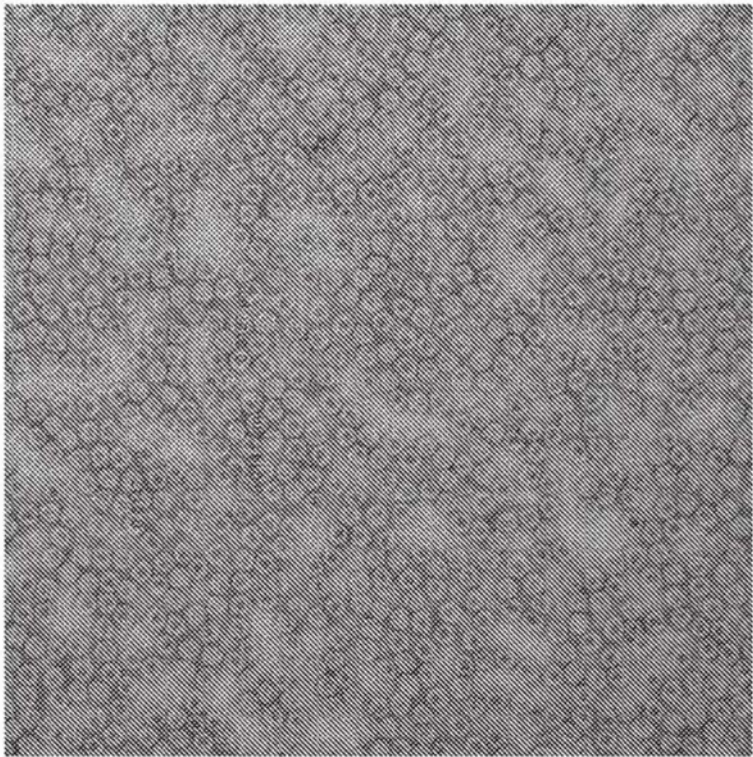


图27A



50nm
HV=80.0kV
直接放大倍率: 98000x
裸粉纹夜蛾铁蛋白颗粒

图27B

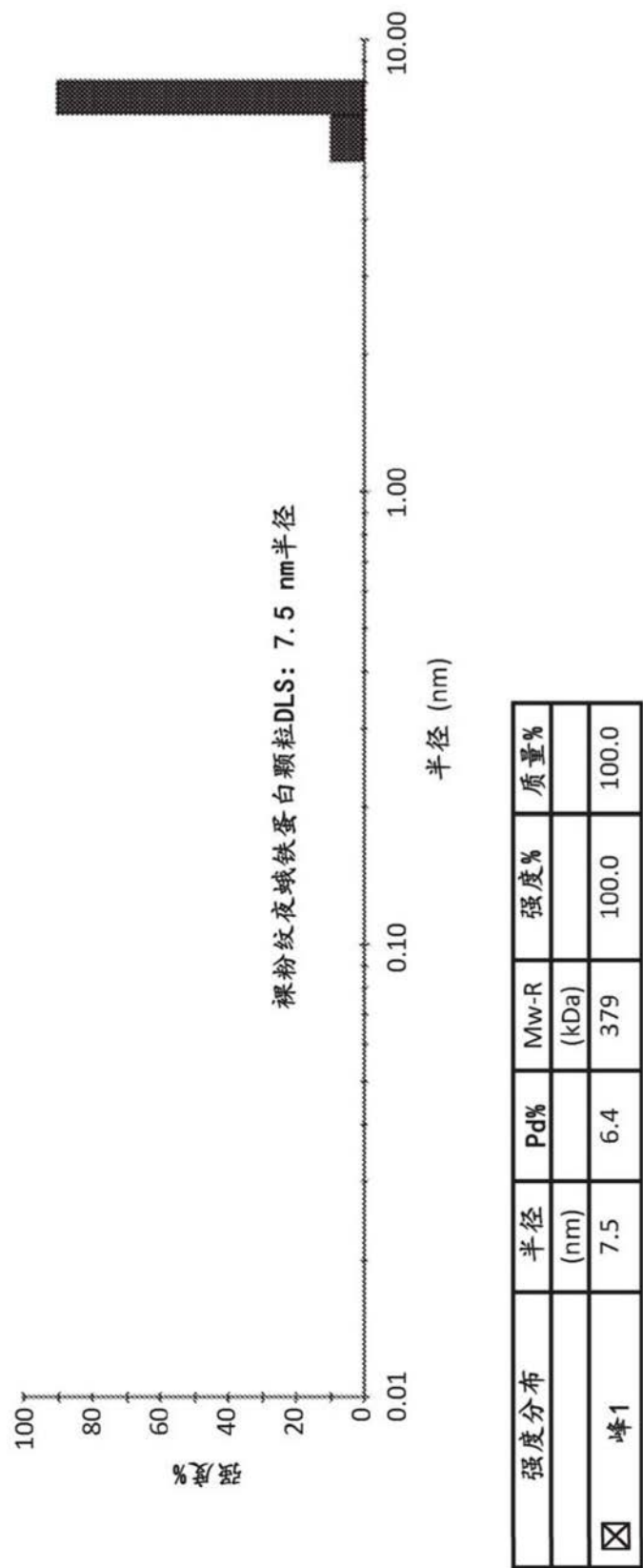


图27C

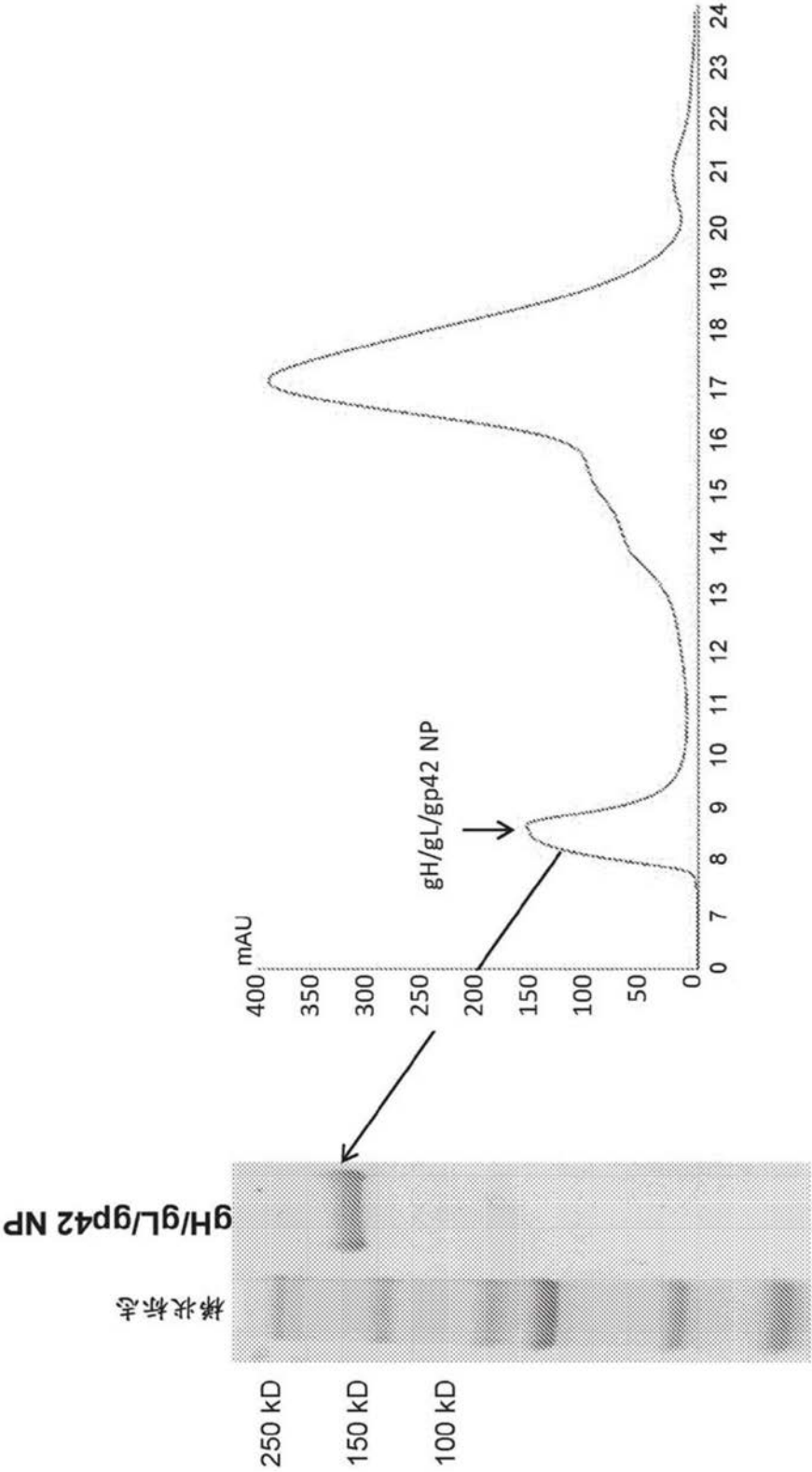


图28A

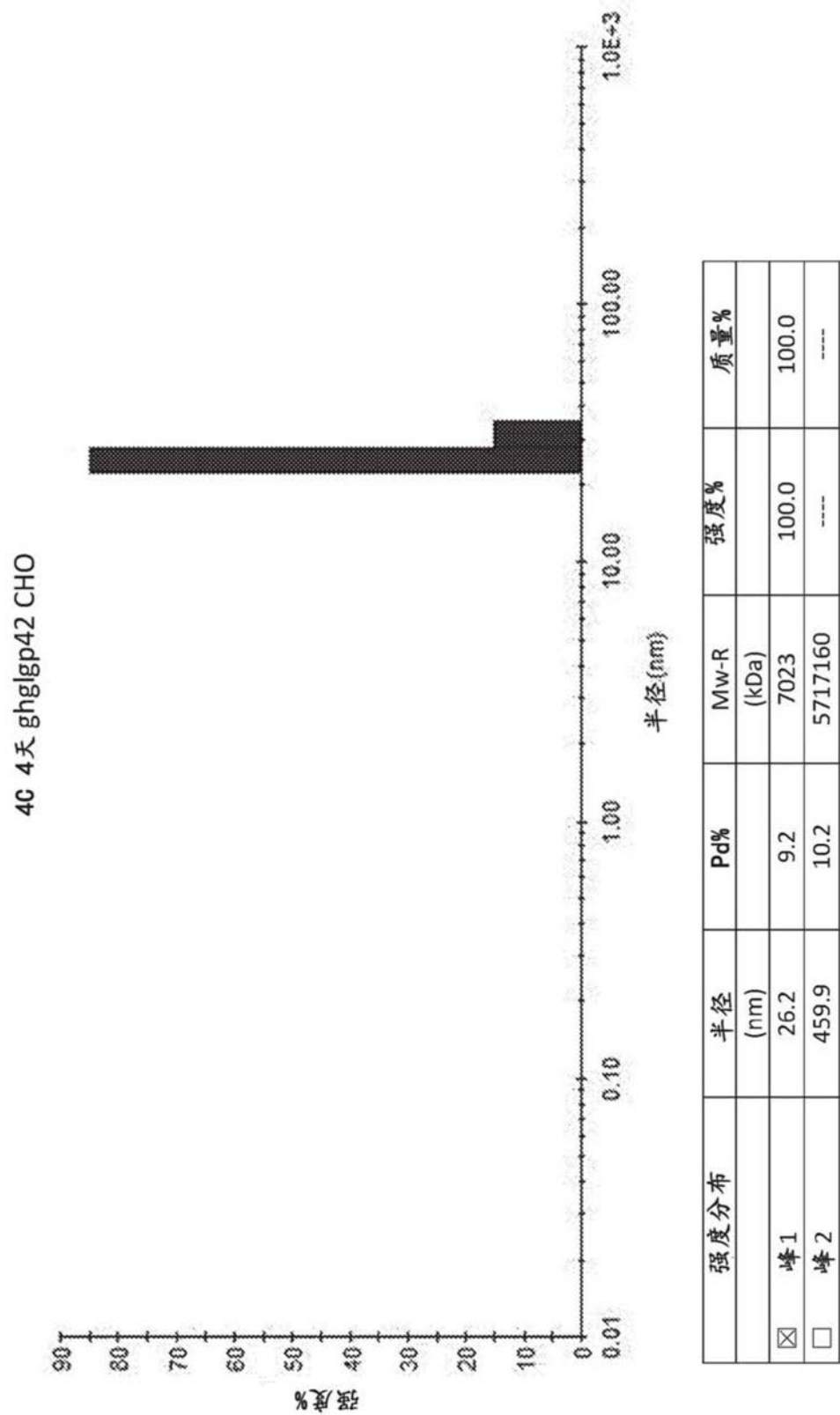


图28B

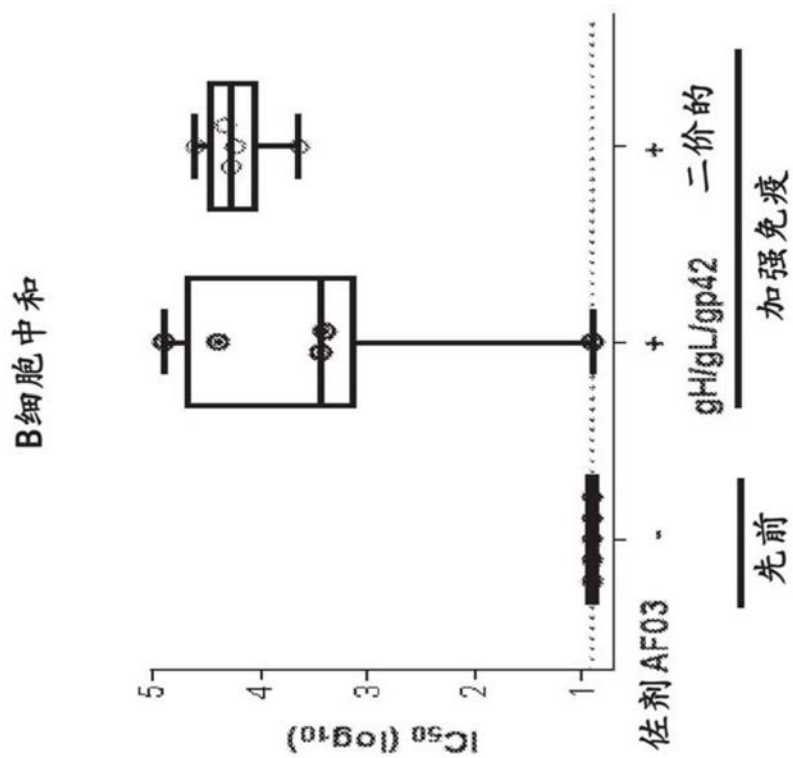


图29A

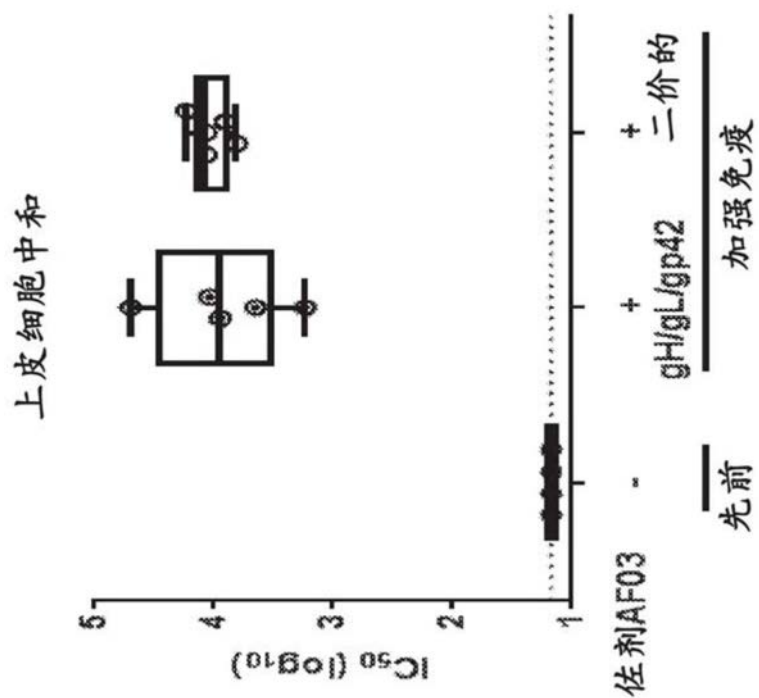


图29B

与gHgL单体的铁蛋白血清结合

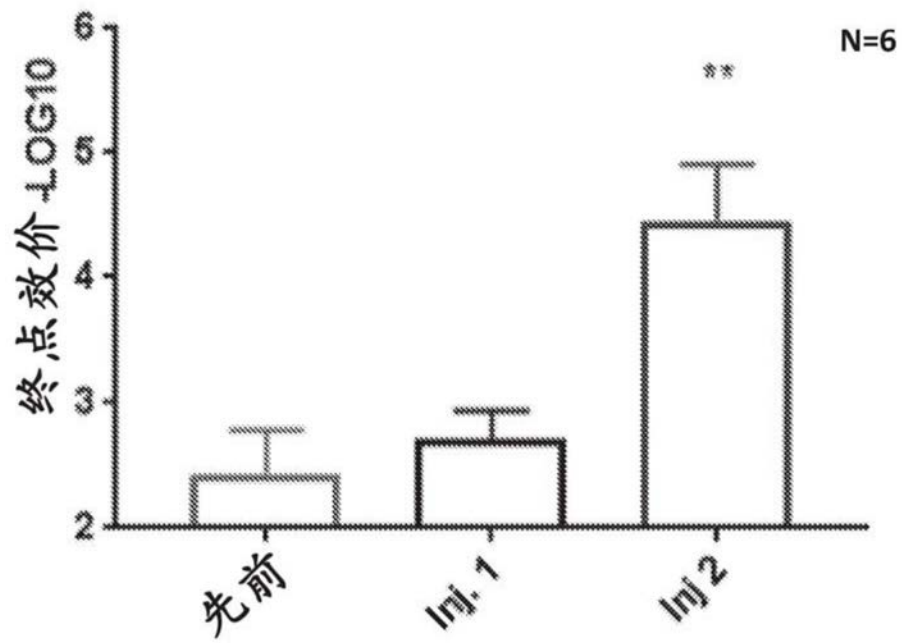


图30A

与gp220单体的铁蛋白血清结合

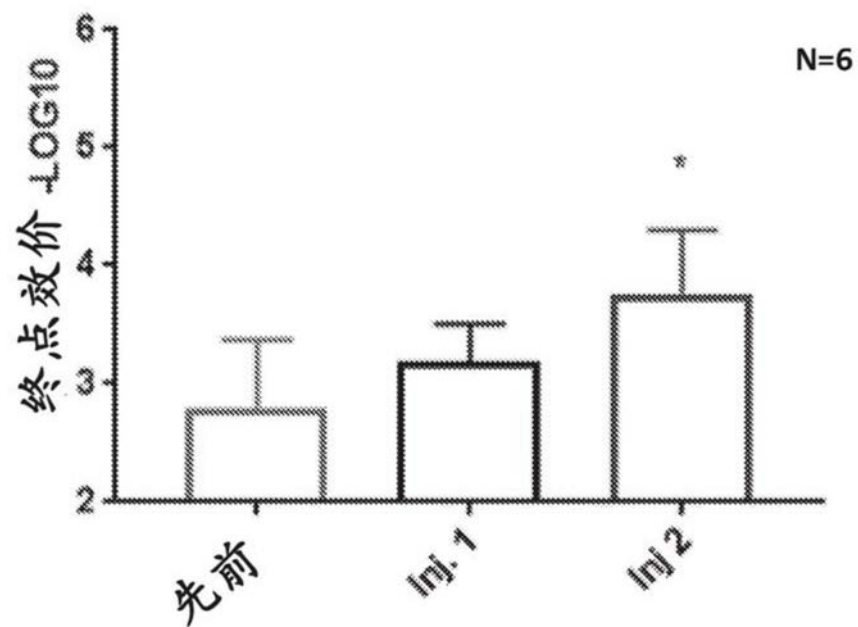


图30B

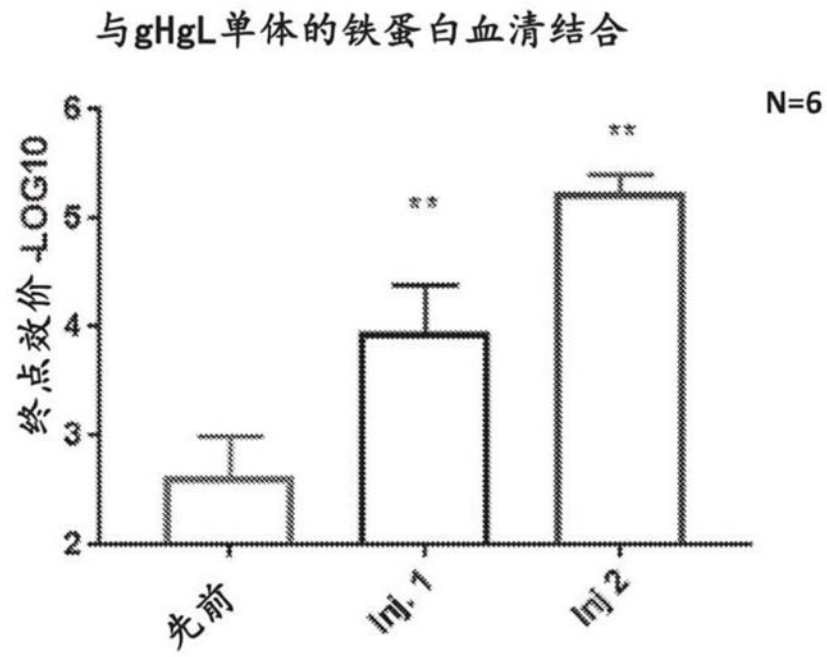


图30C

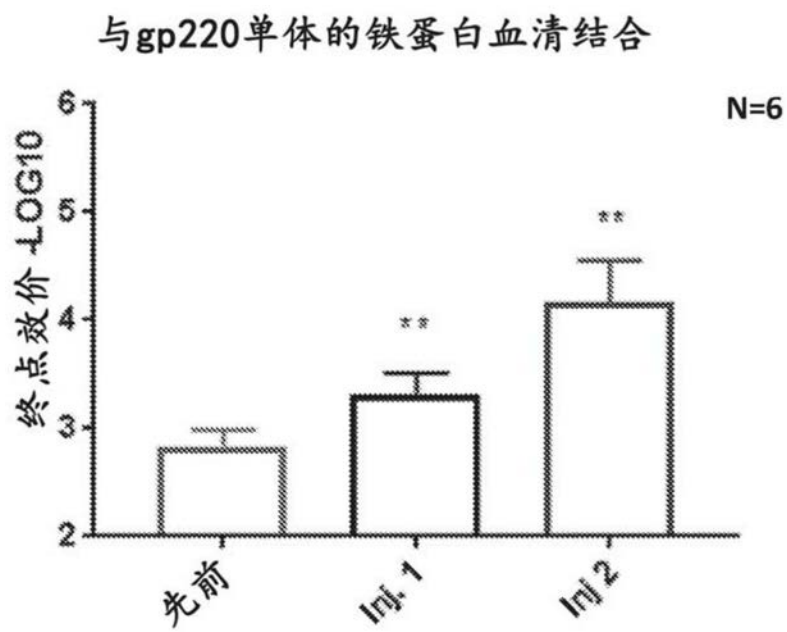


图30D

与gp42单体的铁蛋白血清结合

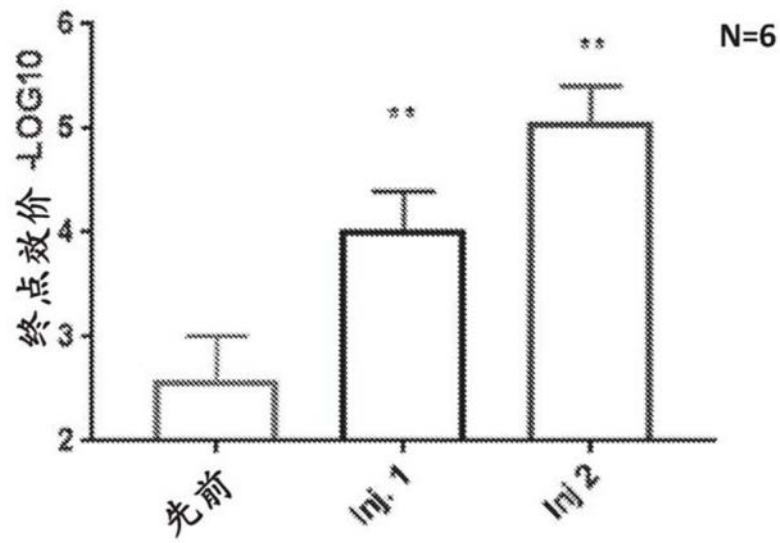


图30E

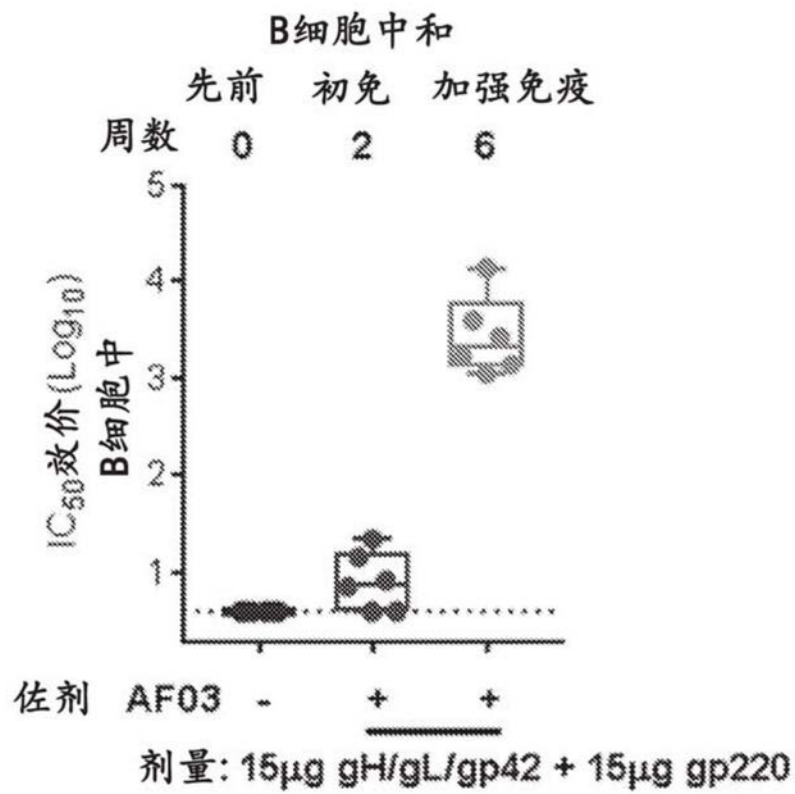


图30F

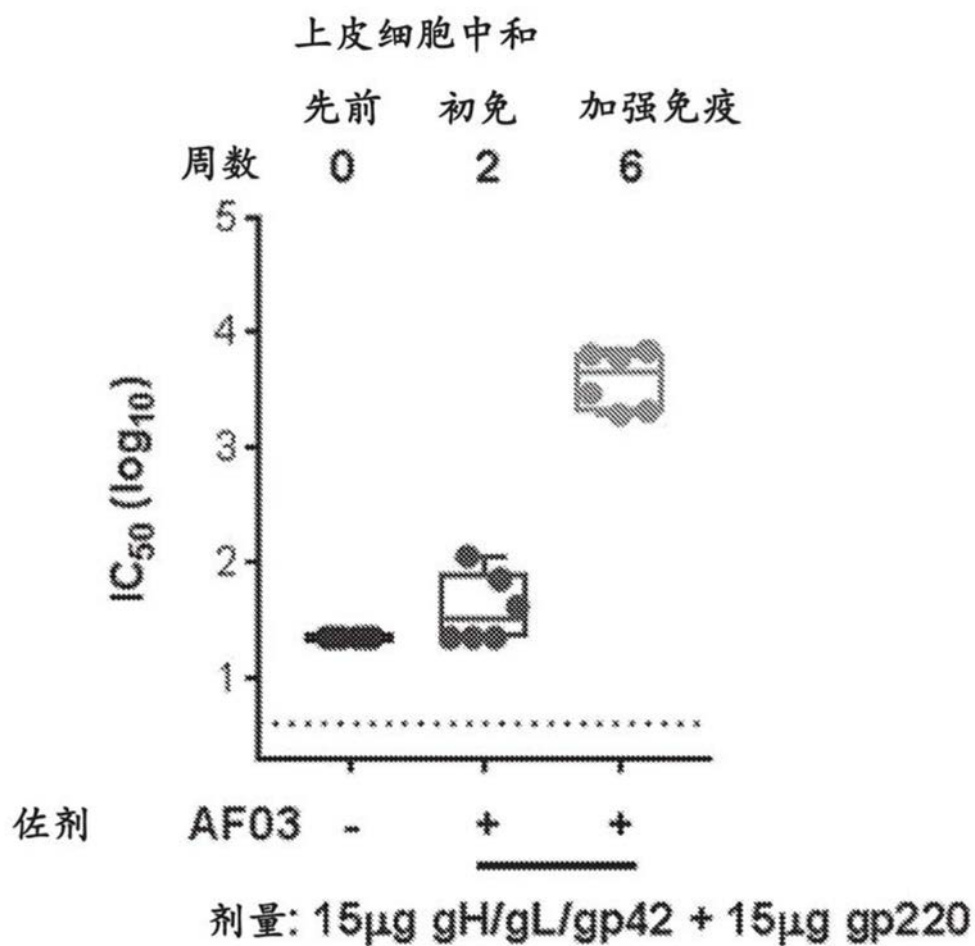


图30G

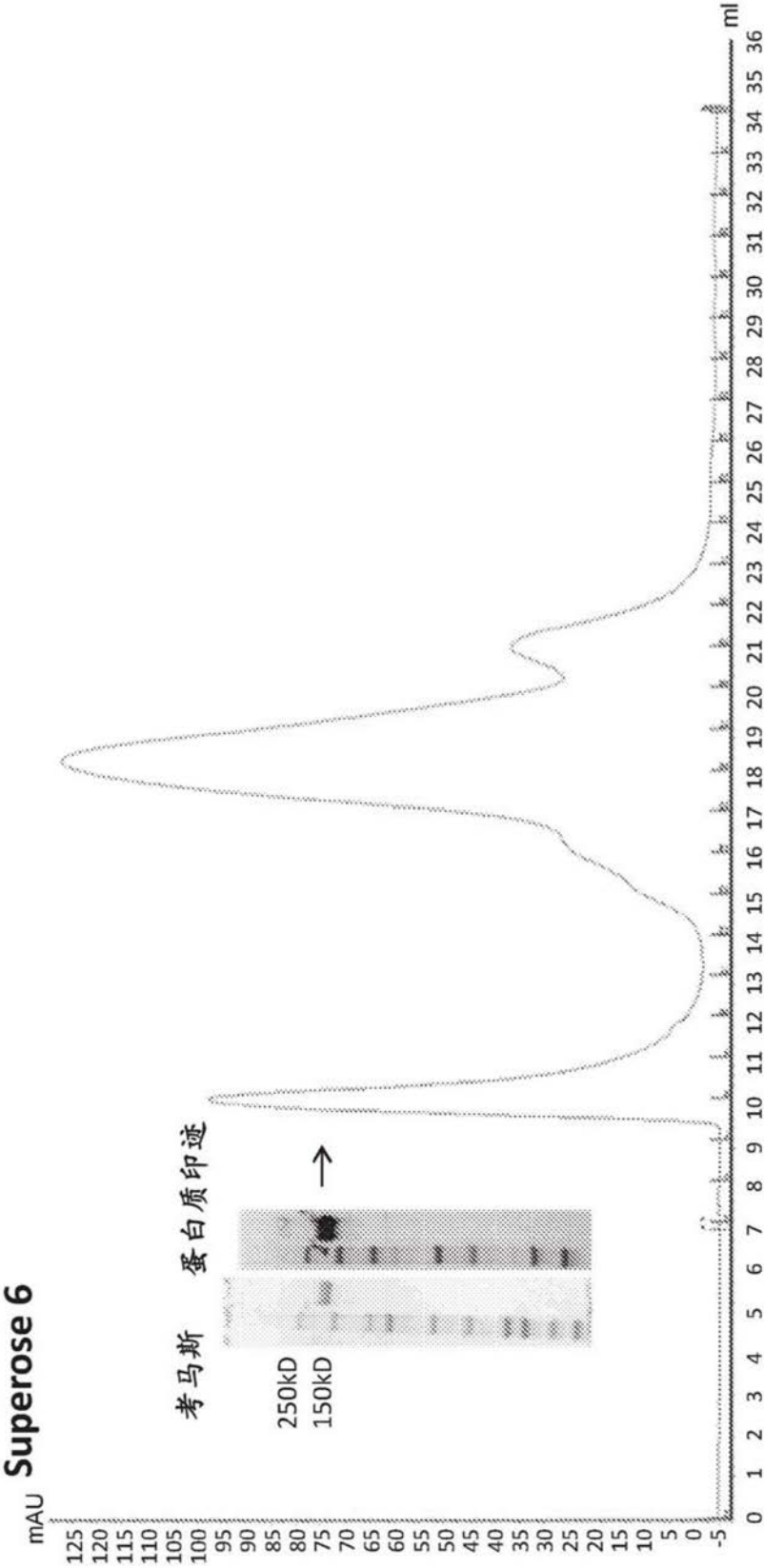


图31A

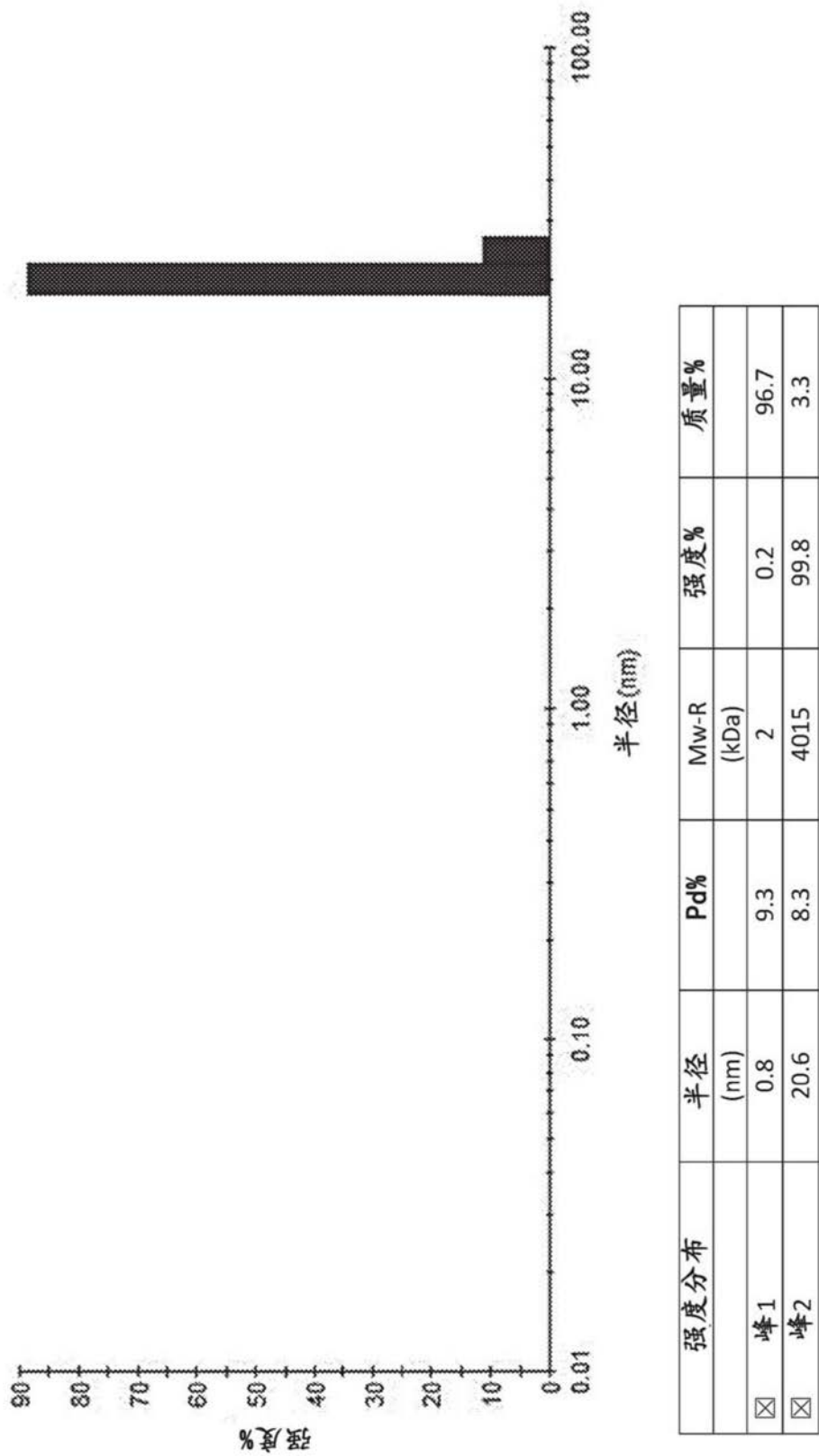


图31B

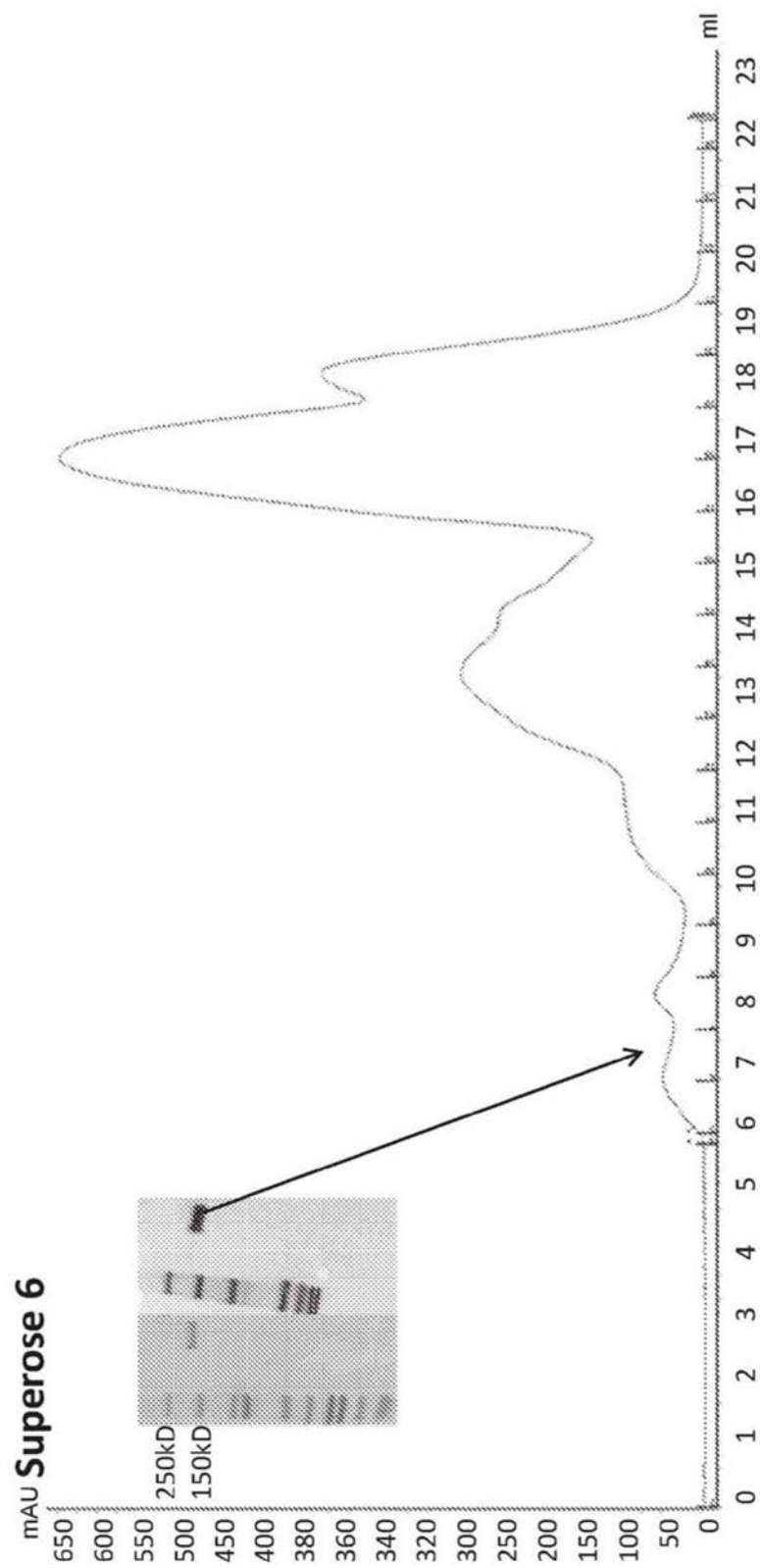


图32A

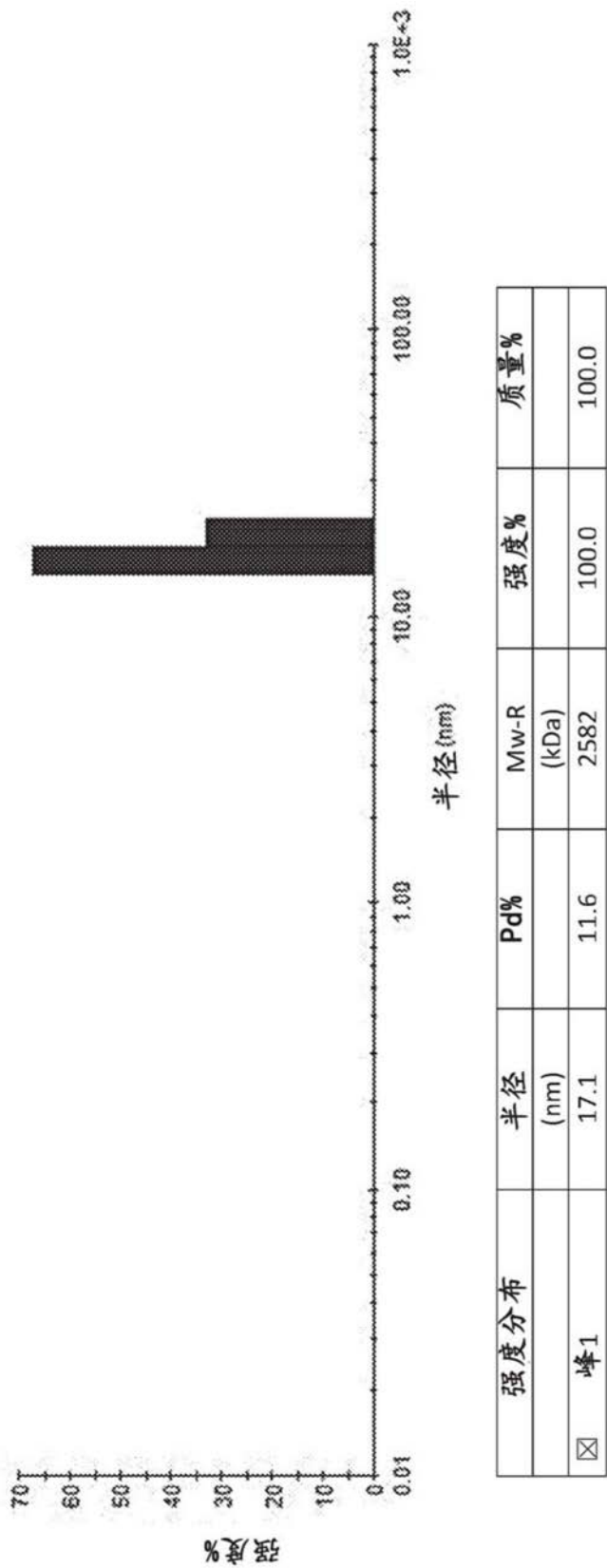


图32B

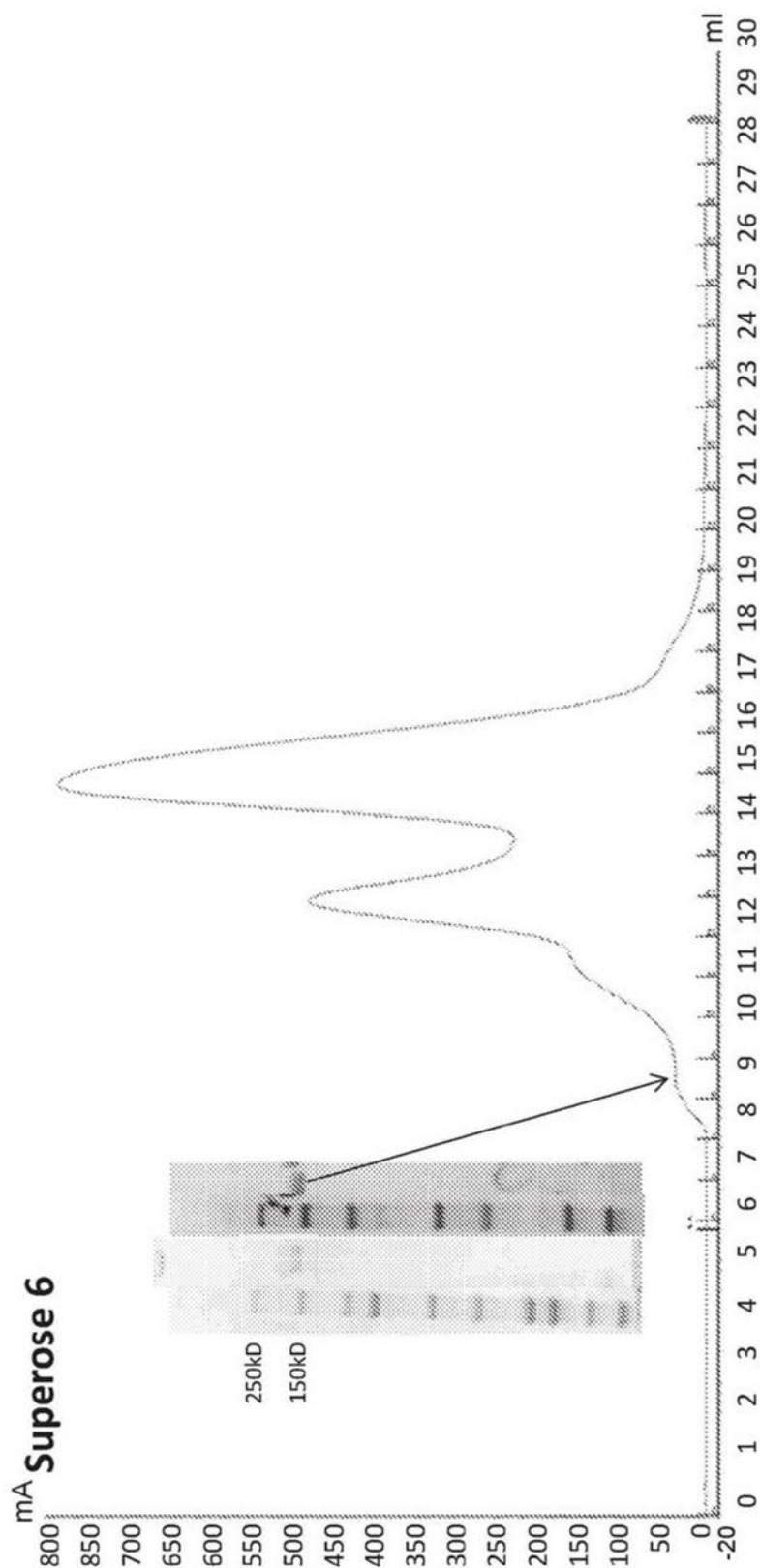


图33A

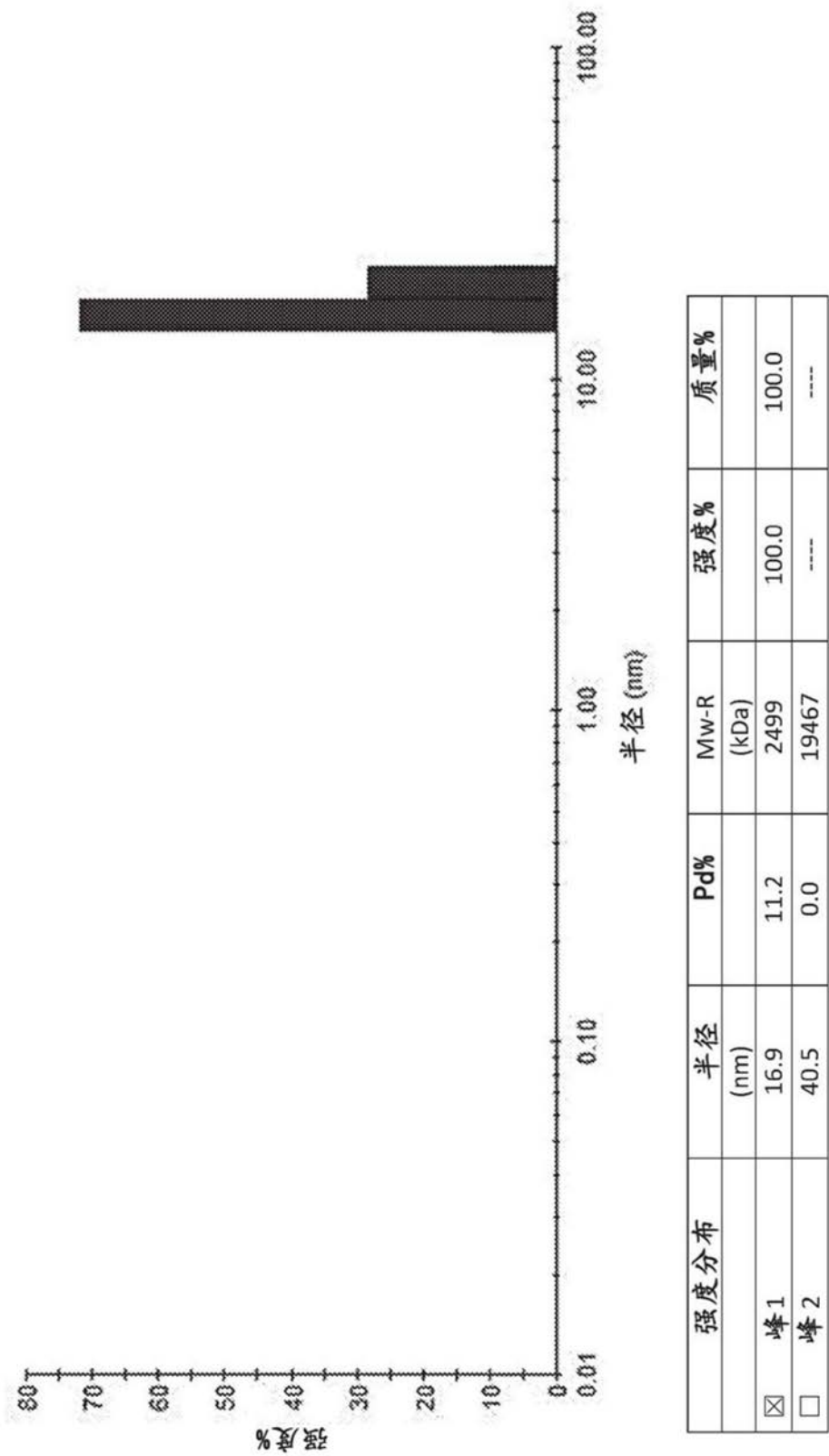


图33B

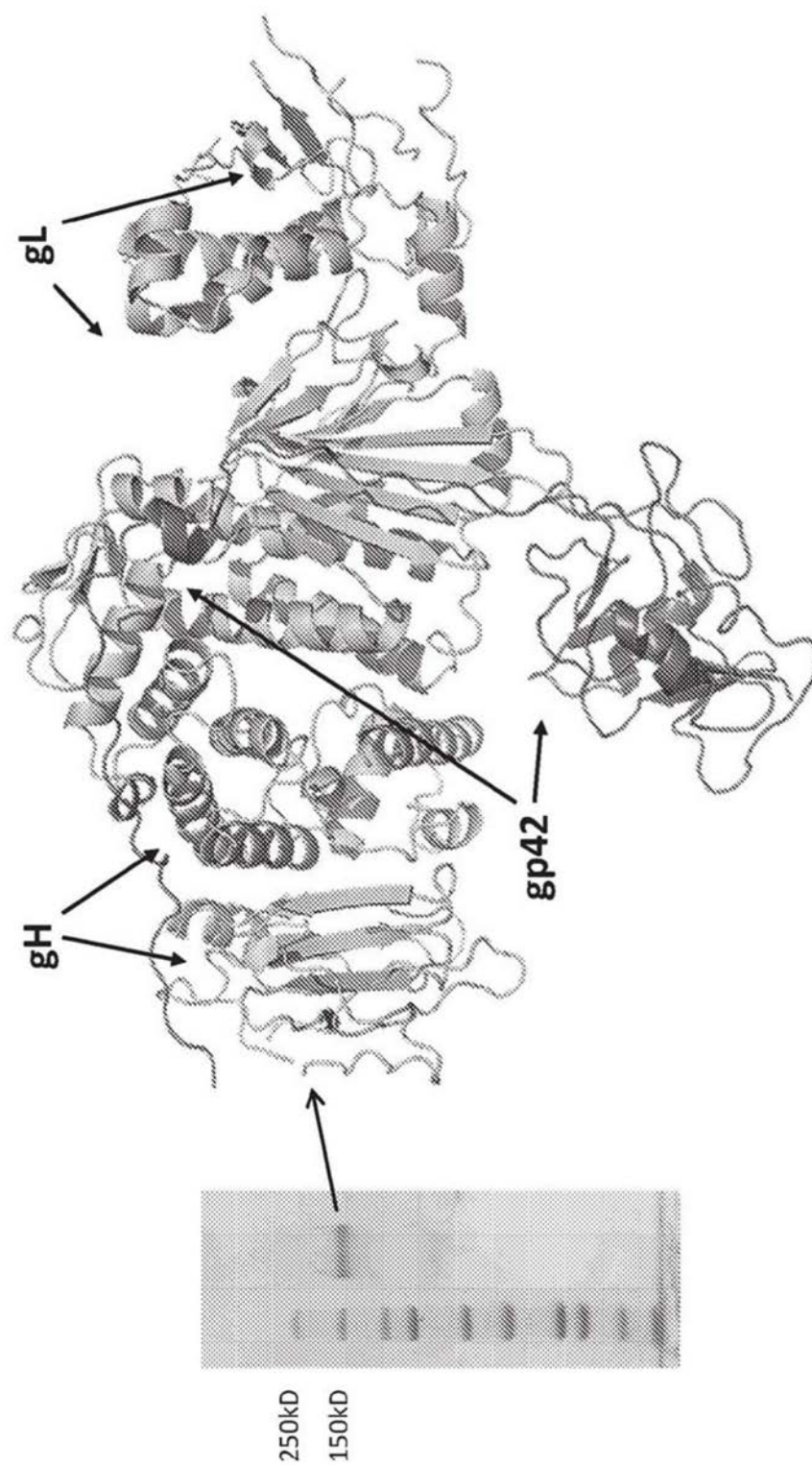


图34



图35A

