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(71)申请人 安进公司
地址 美国加利福尼亚州
(72)发明人 J·麦考密克 A·麦考利
(74)专利代理机构 北京世峰知识产权代理有限公司 11713
专利代理师 王建秀 刘小立
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制备冻干蛋白配制品的加速方法

(57)摘要

本文披露了制备冻干配制品的加速方法,这些配制品包含表现出改善的储存稳定性的蛋白质,如抗体或双特异性抗原结合分子。

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1.一种制备冻干配制品的方法,该方法包括:

(a)冷却含有包含蛋白质、糖以及表面活性剂的液体配制品的冻干室至约-35℃至约-50℃的温度范围以产生冷冻配制品,并且将该室在约-40℃至约-50℃的温度范围下保持约1.5小时至约5.0小时的时间段;

(b)加热该室至约-30℃至约-20℃的温度范围和约75毫托至约125毫托的压力范围以产生初次干燥配制品,并且将该室在约-30℃至约-20℃的温度范围下和约75毫托至约125毫托的压力范围下保持约12小时至约24小时的时间段;

(c)加热该室至约20℃至约30℃的温度范围以产生二次干燥配制品,并且将该室在约20℃至约30℃的温度范围下和约50毫托至约100毫托的压力范围下保持约5小时至约12小时的时间段,以产生该冻干配制品;

其中该液体配制品具有约3-7的pH,并且不含有甘露糖醇;并且该方法缺少退火步骤。

2.如权利要求1所述的方法,其中该步骤(a)的冷却进行至约-45℃的温度。

3.如权利要求1或2所述的方法,其中该步骤(a)的冷却以约0.3℃/min至约1℃/min的速率范围进行。

4.如权利要求3所述的方法,其中该步骤(a)的冷却以约0.5℃/min的速率进行。

5.如权利要求1-4中任一项所述的方法,其中该步骤(a)的保持在约-45℃的温度下进行。

6.如权利要求1-5中任一项所述的方法,其中该步骤(a)的保持进行约1.5小时至约5小时的时间段。

7.如权利要求6所述的方法,其中该步骤(a)的保持进行约2至3小时。

8.如权利要求1-7中任一项所述的方法,其中该步骤(b)的加热进行至约-25℃至-30℃的温度。

9.如权利要求1-8中任一项所述的方法,其中该步骤(b)的加热以约0.1℃/min至约1℃/min的速率范围进行。

10.如权利要求9所述的方法,其中该步骤(b)的加热以约0.1℃/min至约0.5℃/min的速率范围进行。

11.如权利要求10所述的方法,其中该步骤(b)的加热以约0.3℃/min的速率进行。

12.如权利要求1-11中任一项所述的方法,其中该步骤(b)的加热在约75毫托至约125毫托的压力范围下进行。

13.如权利要求12所述的方法,其中该步骤(b)的加热在约100毫托的压力下进行。

14.如权利要求1-13中任一项所述的方法,其中该步骤(b)的保持在约-25℃至约-30℃的温度下进行。

15.如权利要求1-14中任一项所述的方法,其中该步骤(b)的保持在约75毫托至约125毫托的压力范围下进行。

16.如权利要求15所述的方法,其中该步骤(b)的保持在约100毫托的压力下进行。

17.如权利要求1-16中任一项所述的方法,其中该步骤(b)的保持进行约10小时至约25小时的时间段。

18.如权利要求17所述的方法,其中该步骤(b)的保持进行约17小时。

19.如权利要求1-18中任一项所述的方法,其中该步骤(c)的加热进行至约25℃的温

度。

20.如权利要求1-19中任一项所述的方法,其中该步骤(c)的加热升温速率以高达约0.5℃/min的速率范围进行。

21.如权利要求20所述的方法,其中该步骤(c)的加热升温速率以约0.1℃/min至约0.5℃/min的速率范围进行。

22.如权利要求21所述的方法,其中该步骤(c)的加热以约0.4℃/min的速率进行。

23.如权利要求1-22中任一项所述的方法,其中该步骤(c)的保持在约25℃的温度下进行。

24.如权利要求1-23中任一项所述的方法,其中该步骤(c)的保持在约50毫托至约100毫托的压力范围下进行。

25.如权利要求24所述的方法,其中该步骤(c)的保持在约70毫托的压力下进行。

26.如权利要求1-25中任一项所述的方法,其中,该步骤(c)的保持进行约8小时。

27.如权利要求1-26中任一项所述的方法,其中该蛋白质是抗体。

28.如权利要求1-26中任一项所述的方法,其中该蛋白质是双特异性抗原结合分子。

29.如权利要求28所述的方法,其中该双特异性抗原结合分子是半衰期延长的(HLE)双特异性抗原结合分子。

30.如权利要求29所述的方法,其中该HLE双特异性抗原结合分子包含以下列出的氨基酸序列:SEQ ID NO:20、SEQ ID NO:21、SEQ ID NO:22、SEQ ID NO:23、SEQ ID NO:33、SEQ ID NO:43、SEQ ID NO:44、SEQ ID NO:45、SEQ ID NO:55、SEQ ID NO:65、SEQ ID NO:66、SEQ ID NO:55、SEQ ID NO:76、SEQ ID NO:77、SEQ ID NO:87、SEQ ID NO:97、SEQ ID NO:98、SEQ ID NO:99、SEQ ID NO:109、SEQ ID NO:110、SEQ ID NO:111、SEQ ID NO:121、SEQ ID NO:122、SEQ ID NO:131、SEQ ID NO:141、SEQ ID NO:142、SEQ ID NO:146、SEQ ID NO:147、SEQ ID NO:156、SEQ ID NO:165、SEQ ID NO:174、SEQ ID NO:183、SEQ ID NO:184、SEQ ID NO:185、SEQ ID NO:186、SEQ ID NO:187、或SEQ ID NO:188。

31.如权利要求30所述的方法,其中该HLE双特异性抗原结合分子包含以下列出的氨基酸序列:SEQ ID NO:22、SEQ ID NO:77、SEQ ID NO:87、或SEQ ID NO:97。

32.如权利要求1-31中任一项所述的方法,其中该蛋白质以约0.1mg/mL至约100mg/mL的浓度范围存在于该液体配制品中。

33.如权利要求32所述的方法,其中该蛋白质以约0.1mg/mL至约70mg/mL的浓度范围存在。

34.如权利要求33所述的方法,其中该蛋白质以约0.5mg/mL至约30mg/mL的浓度范围存在。

35.如权利要求34所述的方法,其中该蛋白质以约1mg/ml至约20mg/mL的浓度范围存在。

36.如权利要求35所述的方法,其中该蛋白质以约1mg/mL的浓度存在。

37.如权利要求1-36中任一项所述的方法,其中该步骤(a)的液体配制品具有约4-6的pH。

38.如权利要求1-37中任一项所述的方法,其中该步骤(a)的液体配制品进一步包含缓冲液。

39.如权利要求38所述的方法,其中该缓冲液是乙酸盐缓冲液、谷氨酸盐缓冲液、柠檬酸盐缓冲液、乳酸盐缓冲液、琥珀酸盐缓冲液、酒石酸盐缓冲液、富马酸盐缓冲液、马来酸盐缓冲液、组氨酸缓冲液、磷酸盐缓冲液、2-(N-吗啉代)乙磺酸盐缓冲液、或其任何组合。

40.如权利要求39所述的方法,其中该缓冲液包含谷氨酸。

41.如权利要求38-40中任一项所述的方法,其中该缓冲液以约5mM至约200mM的浓度范围存在。

42.如权利要求41所述的方法,其中该缓冲液以约10mM至约50mM的浓度范围存在。

43.如权利要求42所述的方法,其中该缓冲液以约10mM的浓度存在。

44.如权利要求1-43中任一项所述的方法,其中该糖是单糖或二糖。

45.如权利要求44所述的方法,其中该糖是葡萄糖、半乳糖、果糖、木糖、蔗糖、乳糖、麦芽糖、海藻糖或其任何组合。

46.如权利要求45所述的方法,其中该糖是蔗糖。

47.如权利要求1-46中任一项所述的方法,其中该糖以约1%至约15%(w/v)的浓度范围存在于该液体配制品中。

48.如权利要求47所述的方法,其中该糖以约6%至12%(w/v)的浓度范围存在。

49.如权利要求48所述的方法,其中该糖以约9%(w/v)的浓度存在。

50.如权利要求1-49中任一项所述的方法,其中该表面活性剂是聚山梨醇酯20、聚山梨醇酯40、聚山梨醇酯60、聚山梨醇酯80、泊洛沙姆188、泊洛沙姆407、曲拉通X-100、聚氧乙烯、PEG 3350、PEG 4000或其组合。

51.如权利要求50所述的方法,其中该表面活性剂是聚山梨醇酯80。

52.如权利要求1-51中任一项所述的方法,其中该表面活性剂以约0.001%至0.5%(w/v)的浓度范围存在于该液体配制品中。

53.如权利要求52所述的方法,其中该表面活性剂以约0.001%至0.01%(w/v)的浓度范围存在。

54.如权利要求53所述的方法,其中该表面活性剂以约0.01%(w/v)的浓度存在。

55.如权利要求1-54中任一项所述的方法,其中该步骤(a)的液体配制品具有约4至约5的pH。

56.如权利要求1-55中任一项所述的方法,其中该步骤(a)的液体配制品具有约4.2的pH,并且包含约10mM L-谷氨酸、约9.0%(w/v)蔗糖以及约0.010%(w/v)聚山梨醇酯80。

57.如权利要求1-56中任一项所述的方法,其中该冻干配制品在重构后在40℃下储存一个月后表现出高分子量物质的百分比增加0.5%或更少。

58.如权利要求57所述的方法,其中该冻干配制品在重构后在40℃下储存一个月后表现出高分子量物质的百分比增加0.3%或更少。

59.一种冻干蛋白配制品,该冻干蛋白配制品通过如权利要求1-58中任一项所述的方法制备。

制备冻干蛋白配制品的加速方法

技术领域

[0001] 本披露提供了用于制备冻干配制品的加速方法,这些配制品包含表现出改善的储存稳定性的蛋白质,如抗体或双特异性抗原结合分子。

[0002] 通过引用并入以电子方式提交的材料

[0003] 通过引用整体并入的是与本文同时提交的计算机可读核苷酸/氨基酸序列表,其鉴定如下:文件名:I-56846_Seqlisting.txt;大小:345,286字节;创建于:2022年5月12日。

背景技术

[0004] 基于蛋白质的药物(如含有抗体、抗体片段以及双特异性抗原结合分子的药物)对于治疗各种疾病和病症变得日益重要。然而,蛋白质仅临界稳定(marginally stable)并且极易受到化学和物理降解二者的影响。化学降解是指涉及共价键的修饰,如脱酰胺化、氧化、裂解、剪切/片段化、形成新的二硫桥键、水解、异构化或去糖基化。物理降解包括蛋白质去折叠、对表面的不希望的吸附、和聚集。处理这些物理和化学不稳定性是蛋白质药物开发中最具挑战性的任务之一(Chi等人,Pharm Res[药物研究],第20卷,第9期,2003年9月,第1325-1336页,Roberts,Trends Biotechnol.[生物技术趋势]2014年7月;32(7):372-80)。

[0005] 特别地,需要保护半衰期延长的抗原结合分子(例如,包含半衰期延长模式的双特异性T细胞接合剂(BiTE®),如Fc分子),以防止蛋白质聚集和/或其他降解事件。BiTE®分子的蛋白质聚集是有问题的,因为它会损害治疗性蛋白的生物活性和质量(规格)。此外,由于从最终产物中去除聚集体所需的复杂的纯化步骤,BiTE®分子的聚集可能降低了产物产率。最近,人们还越来越关注并且有越来越多的证据证明聚集蛋白(甚至是人源化或全人源蛋白质)的存在可以显著增加患者对活性蛋白质单体产生免疫应答的风险,导致形成中和抗体和抗药性,或其他不良副作用(Mahler JPharm Sci.[药物科学杂志]2009年9月;98(9):2909-34)。

[0006] 通常将基于蛋白质的药物配制品冻干,并且以固态储存以帮助在储存过程中保持配制品中蛋白质(如抗体或双特异性抗原结合分子)的完整性。然而,许多当前的冻干蛋白配制品的方法与已知方法相比不能更快产生随时间变化表现出合适的稳定性的固态配制品。因此,需要新的加速方法,该方法产生表现出改善的储存稳定性的冻干蛋白配制品。

发明内容

[0007] 在一方面,本披露提供了制备冻干配制品的快速方法,该方法包括(a)冷却含有包含蛋白质、糖以及表面活性剂的液体配制品的冻干室至约-35℃至约-50℃的温度范围以产生冷冻配制品,并且将该室在约-40℃至约-50℃的温度范围下保持约1.0小时至约3.0小时的时间段;(b)加热该室至约-35℃至约-20℃的温度范围和约75毫托至约125毫托的压力范围以产生初次干燥配制品,并且将该室在约-35℃至约-20℃的温度范围下和约75毫托至约125毫托的压力范围下保持约12小时至约24小时的时间段;(c)加热该室至约20℃至约30℃的温度范围以产生二次干燥配制品,并且将该室在约20℃至约30℃的温度范围下和约50毫

托至约100毫托的压力范围下保持约5小时至约12小时的时间段,以产生该冻干配制品;其中该液体配制品具有约3-7的pH,并且不含有甘露糖醇;并且该方法缺少退火步骤。

[0008] 在另一方面,本披露提供了通过本披露的方法制备的冻干蛋白配制品。

[0009] 通过阅读以下详细说明,其他方面和优点对于本领域普通技术人员将显而易见。尽管本文披露的方法易于应用于各种形式的实施例,但在理解本披露为说明性的而不旨在将本发明限于本文所述的特定实施例的情况下,以下描述包括特定实施例。

附图说明

[0010] 图1显示出,通过视觉检查对完成循环后的干燥产物饼的宏观塌陷的任何迹象和总体质量进行评估。BITE B的产物饼被确定为可接受,并且显示了从几个角度拍摄的照片。

[0011] 图2显示出高分子量(HMW)物质的相对面积%的值随时间变化的作图。数据表明在研究过程中没有聚集不稳定性。

具体实施方式

[0012] 本文披露了制备冻干配制品的加速方法,这些配制品包含表现出改善的稳定性的蛋白质,如抗体或双特异性抗原结合分子(例如,半衰期延长的双特异性抗原结合分子)。本披露的加速冻干方法有利地导致降低的物理降解(如聚集),以及降低的化学降解(如降低的剪切和脱酰胺化)。此外,本文披露的加速冻干方法能够稳定低浓度和高浓度蛋白配制品,如含有抗体和双特异性抗原结合分子的配制品。

[0013] 定义

[0014] 如本文所用,术语“药物配制品”涉及适于向有需要的受试者施用的配制品。术语“受试者”或“个体”或“动物”或“患者”在本文中可互换地使用,是指任何希望施用本披露的药物配制品的受试者,特别是哺乳动物受试者。哺乳动物受试者包括人、非人灵长类动物、狗、猫、豚鼠、兔、大鼠、小鼠、马、牛、母牛等,优选人。本披露的药物配制品是稳定的和药学上可接受的,即能够引发所希望的治疗效果,而不会在施用药物配制品的受试者中引起显著不希望的局部或全身性作用。本披露的药学上可接受的配制品可以是无菌的。具体地,术语“药学上可接受的”可以意指由管理机构或其他受普遍承认的药典批准在动物中使用,并且更特别地在人中使用,但不限于由管理机构批准的那些。

[0015] 术语“稳定性”或“稳定化”涉及药物配制品的整体稳定性,并且特别地涉及活性成分(例如,蛋白质,如双特异性抗原结合分子)本身的稳定性,特别是在配制、填充、运输、储存以及施用期间。“稳定的配制品”是其中的蛋白质(例如,抗体或双特异性抗原结合分子)在储存后和加工过程(例如冷冻/解冻、机械混合和冻干)中基本上保持其物理和/或化学完整性和生物活性的配制品。蛋白质稳定性可以通过形成高分子量(HMW)物质、失去酶活性、产生肽片段以及改变电荷特征来测量。

[0016] 如本文所用,术语“聚集”是指分子之间的直接相互吸引,例如经由范德华力或化学键合。特别地,聚集被理解为蛋白质积聚和凝聚在一起。聚集体可包括无定形聚集体、寡聚体,并且典型地称为高分子量(HMW)物质,即,具有比非聚集分子的产物分子更高分子量的分子。

[0017] 本文使用的术语“(蛋白质)聚集体”通常涵盖较高分子量的蛋白质物质,如“寡聚

体”或“多聚体”,而不是所希望的确定物质(例如单体)。该术语在本文中可与术语“高分子量”物质和“HMW”互换地使用。蛋白质聚集体的大小(从小(二聚体)到大组件(亚可见或甚至可见颗粒)以及直径范围从纳米到微米)、形态(近似球状到针状)、蛋白质结构(天然相比于非天然/变性)、分子间键合的类型(共价相比于非共价)、可逆性和溶解性通常不同。可溶性聚集体覆盖约1至100nm的大小范围,并且蛋白质颗粒覆盖亚可见(约0.1-100nm)和可见(>100nm)范围。所有上述类型的蛋白质聚集体通常涵盖在该术语中。因此,术语“(蛋白质)聚集体”是指两种或更多种蛋白质单体的所有种类物理缔合或化学连接的非天然种类。

[0018] 如本文所用,术语“低分子量(LMW)”物质是指蛋白质的片段,如双特异性抗原结合分子。

[0019] 如本文所用,术语“冻干的加速方法”是指冻干方法比在冻干装置中使用不同温度和压力的已知方法快至少25%,同时保持如本文所述的冻干蛋白配制品的稳定性。

[0020] 方法

[0021] 本披露的一方面,提供了制备冻干配制品的加速方法,其中该方法缺少退火步骤。该方法包括:(a)冷却含有具有约3-7的pH并且包含蛋白质、糖以及表面活性剂,并且缺少甘露糖醇的液体配制品的冻干室,至约-40℃至约-50℃的温度范围,以产生冷冻配制品,并且将该室在约-40℃至约-50℃的温度范围保持约1至约3小时的时间段;(b)加热该室至约-30℃至约-20℃的温度范围和约75毫托至约125毫托的压力范围以产生初次干燥配制品,并且将该室在约-35℃至约-20℃的温度范围下和约75毫托至约125毫托的压力范围下保持约12小时至约24小时的时间段;以及(c)加热该室至约20℃至约35℃的温度范围以产生二次干燥配制品,并且将该室在约20℃至约30℃的温度范围下和约50毫托至约100毫托的压力范围下保持约5小时至约10小时的时间段,以产生该冻干配制品。

[0022] 如本文所用,术语“温度”是指冻干室内部的温度(冻干室的内部温度(“内部温度”),精确地说是在循环期间的冷冻干燥器的受控“温度”,经由硅油(通过室架泵入)的入口温度来测量。换句话说,该内部温度是泵入与样品瓶底部接触的室的金属架的液体温度)。同样地,如本文所用,术语“压力”是指冻干室内部的压力(即,冻干室的内部压力,“内部压力”)。

[0023] 步骤(a).在步骤(a)中,将含有液体配制品的冻干室冷却至约-35℃至约-50℃的温度(例如,内部温度)范围,以产生冷冻配制品,并且在约-40℃至约-50℃的温度(例如,内部温度)范围下保持约2小时至约24小时的时间段。在一些实施例中,冷却进行至约-40℃至约-50℃(例如,约-40℃、-41℃、-42℃、-43℃、-44℃、-45℃、-46℃、-47℃、-48℃、-49℃、或-50℃)的温度范围。在各种情况下,冷却可以进行至约-45℃的温度。在一些情况下,室的冷却以约0.1℃/min至约1℃/min的速率范围进行。在多个实施例中,冷却以约0.5℃/min至约0.8℃/min的速率进行。在一些实施例中,冷却以约0.5℃/min、0.6℃/min、0.7℃/min、0.8℃/min、0.9℃/min、或1℃/min的速率进行。在一些情况下,冷却以约0.5℃/min的速率进行。在一些实施例中,室的保持可以在约-40℃、-41℃、-42℃、-43℃、-44℃、-45℃、-46℃、-47℃、-48℃、-49℃、或-50℃的温度下进行。在一些实施例中,保持在约-45℃的温度下进行。在一些实施例中,冻干室冷却达到的温度和保持温度是相同的。在多个实施例中,保持进行约1小时至约3小时(例如,约1小时、1.5小时、2小时、2.5小时、或3小时)的时间段。在一些情况下,保持进行约2小时。

[0024] 步骤(b).在步骤(b)中,加热冻干室至约-35℃至约-20℃的温度(例如,内部温度)范围和约75毫托至约125毫托的压力(例如,内部压力)范围,以产生初次干燥配制品,并且在约-35℃至约-20℃的温度(例如,内部温度)范围和约75毫托至约125毫托的压力(例如,内部压力)范围保持约12小时至约24小时的时间段。在一些实施例中,加热进行至约-35℃、-34℃、-33℃、-32℃、-31℃、-30℃、-29℃、-28℃、-27℃、-26℃、-25℃、-24℃、-23℃、-22℃、-21℃、或-20℃的温度。在各种情况下,加热进行至约-27℃的温度。在一些情况下,加热以约0.1℃/min至约1℃/min的速率范围进行。在多个实施例中,加热以约0.1℃/min至约0.5℃/min(例如,0.1℃/min、0.2℃/min、0.3℃/min、0.4℃/min、或0.5℃/min)的速率进行。在一些情况下,加热以约0.3℃/min的速率进行。在各种情况下,加热在约75毫托至约125毫托、或约80毫托至约120毫托、或约85毫托至约115毫托、或约90毫托至约110毫托的压力范围下进行。在一些情况下,加热在约95毫托、96毫托、97毫托、98毫托、99毫托、100毫托、101毫托、102毫托、103毫托、104毫托、或105毫托的压力下进行。在多个实施例中,加热在约100毫托的压力下进行。在一些实施例中,室的保持在约-35℃、-34℃、-33℃、-32℃、-31℃、-30℃、-29℃、-28℃、-27℃、-26℃、-25℃、-24℃、-23℃、-22℃、-21℃、或-20℃的温度下进行。在各种情况下,保持在约-27℃的温度下进行。在多个实施例中,保持在约75毫托至约125毫托、或约80毫托至约120毫托、或约85毫托至约115毫托、或约90毫托至约110毫托的压力范围下进行。在一些情况下,加热在约95毫托、96毫托、97毫托、98毫托、99毫托、100毫托、101毫托、102毫托、103毫托、104毫托、或105毫托的压力下进行。在多个实施例中,加热在约100毫托的压力下进行。在一些实施例中,冻干室加热达到的温度和保持温度是相同的。在一些实施例中,加热冻干室所处的压力和保持压力是相同的。在一些实施例中,冻干室加热达到的温度和保持温度是相同的,并且加热冻干室所处的压力和保持压力是相同的。在一些情况下,保持进行约12小时至约24小时(例如,约12小时、13小时、14小时、15小时、16小时、17小时、或18小时)的时间段。在各种情况下,保持进行约16至17小时,例如进行16.7小时的时间段。

[0025] 步骤(c).在步骤(c)中,加热该室至约20℃至约35℃的温度(例如,内部温度)范围以产生二次干燥配制品,并且在约20℃至约35℃的温度(例如,内部温度)范围和约50毫托至约100毫托的压力(例如,内部压力)范围下保持约5小时至约12小时的时间段以产生冻干配制品。在一些实施例中,加热进行至约20℃、21℃、22℃、23℃、24℃、25℃、26℃、27℃、28℃、29℃、30℃、31℃、32℃、33℃、34℃、或35℃的温度。在各种情况下,加热进行至约25℃的温度。在多个实施例中,加热以高达约0.3至0.5℃/min速率范围进行以产生二次干燥配制品。在一些情况下,加热以约0.05℃/min至约0.5℃/min的速率进行。在各种情况下,加热以约0.05℃/min、0.1℃/min、0.15℃/min、0.2℃/min、0.25℃/min、0.3℃/min、0.35℃/min、0.4℃/min、0.45℃/min、或0.5℃/min的速率进行。在一些实施例中,加热以约0.4℃/min的速率进行。在一些实施例中,保持在约20℃、21℃、22℃、23℃、24℃、25℃、26℃、27℃、28℃、29℃、或30℃的温度下进行。在各种情况下,保持在约25℃的温度下进行。在一些实施例中,冻干室加热达到的温度和保持温度是相同的。在一些实施例中,保持在约50毫托至约100毫托、或约70毫托至约100毫托、或约65毫托至约75毫托的压力范围下进行。在一些情况下,保持在约65毫托、66毫托、67毫托、68毫托、69毫托、70毫托、71毫托、72毫托、73毫托、74毫托、或75毫托的压力下进行。在多个实施例中,保持在约70毫托的压力下进行。在一些情况下,

保持进行约5小时、6小时、7小时、8小时、9小时、或10小时的时间段。在各种情况下,保持进行约8.1小时、8.2小时、8.3小时、8.4小时、8.5小时的时间段,在一种情况下,保持进行约8.3小时的时间段。

[0026] 在本文披露的任一方法(含有或不含有退火步骤)的实施例中,该方法可以进一步包括(d)冷却包含步骤(c)的冻干配制品的室至约1℃至约10℃(或至约2℃至约7℃、或至约5℃)的温度范围,并且在约250毫托至约750毫托(或至约300毫托至约600毫托、或至约500毫托)的压力下,用惰性气体对冻干配制品充气。在一些情况下,惰性气体选自氩气、氦气、氮气以及其任何组合。在各种情况下,惰性气体是氮气。在实施例中,步骤(d)可促进塞住含有冻干配制品的容器(例如小瓶)。在实施例中,该方法进一步包括将冻干配制品在约2℃至约8℃的温度范围下储存。在实施例中,该方法进一步包括用水重构冻干配制品。

[0027] 在又另一方面,本披露提供了通过本文披露的方法制备的冻干蛋白配制品。在一些实施例中,通过本文披露的方法制备蛋白配制品,该方法缺少退火步骤。

[0028] 冻干蛋白配制品

[0029] 本文所述的冻干蛋白配制品包括蛋白质、糖、表面活性剂以及任选地缓冲液,并且具有约3至约7(或约3.5、4、4.5、5、5.5、6、6.5、或7)的pH。在一些情况下,pH为约4至约6。在一些情况下,配制品的pH为约4、或约4.2。在各种情况下,配制品的pH为约5。在一些实施例中,配制品的pH为约6。在实施例中,本文披露的冻干配制品不含有糖醇。如本文所用,"糖醇"是指其中每个碳原子附接一个羟基基团的线性多元醇。如本文所用的糖醇的实例包括木糖醇、赤藓糖醇、甘露糖醇以及山梨糖醇。在实施例中,冻干配制品不含有甘露糖醇。

[0030] 蛋白质

[0031] 在一些实施例中,冻干配制品的蛋白质是抗原结合蛋白。"抗原结合蛋白"是包含结构域的蛋白质,该结构域与特定的靶抗原(如CD3和/或CDH19、MSLN、DLL3、FLT3、EGFRvlll、BCMA、PSMA、CD33、CD19、CD70、CLDN18.2、或MUC17)结合。抗原结合蛋白包含支架或框架部分,其允许抗原结合结构域采用促进抗原结合蛋白与抗原结合的构象。

[0032] 在一些实施例中,冻干配制品的抗原结合蛋白是抗体或免疫球蛋白、或抗原结合抗体片段。在一些情况下,抗原结合蛋白是抗体。术语"抗体"是指完整的抗原结合免疫球蛋白。"抗体"是一种抗原结合蛋白。抗体可以是IgA、IgD、IgE、IgG、或IgM抗体,包括IgG1、IgG2、IgG3或IgG4中的任一种。在多个实施例中,完整抗体包含两条全长重链和两条全长轻链。抗体具有可变区和恒定区。在IgG形式中,可变区通常为约100-110或更多个氨基酸,包含三个互补决定区(CDR),主要负责抗原识别,并且与结合不同抗原的其他抗体差异很大。可变区典型地包含至少三个重链CDR或三个轻链CDR(Kabat等人,1991,Sequences of Proteins of Immunological Interest[免疫相关蛋白质序列],Public Health Service[公共卫生署]N.I.H.,贝塞斯达,马里兰州;还参见Chothia和Lesk,1987,J.Mol.Biol.[分子生物学杂志]196:901-917;Chothia等人,1989,Nature[自然]342:877-883),位于框架区内(由Kabat等人,1991指定框架区1-4、FR1、FR2、FR3、和FR4;还参见Chothia和Lesk,1987,同上)。恒定区允许抗体募集免疫系统的细胞和分子。

[0033] 在一些实施例中,配制品的抗体是双特异性抗原结合分子,即与两种不同靶(例如,CD3和不同第二靶)结合的抗原结合分子。如本文所用,术语"双特异性"是指与两种不同靶抗原结合的抗原结合分子或构建体,即,其包含第一结合结构域和第二结合结构域,其中

该第一结合结构域与一种抗原或靶(例如,靶细胞表面抗原)结合,并且该第二结合结构域与另一种抗原或靶(例如,CD3)结合。因此,根据本披露的抗原结合分子包含对两种不同的抗原或靶的特异性。术语"靶细胞表面抗原"是指由细胞表达的抗原结构,其存在于细胞表面,使得其可接近如本文所述的抗原结合分子或抗原结合构建体。靶细胞表面抗原可以是蛋白质,如蛋白质的细胞外部分,或碳水化合物结构,如蛋白质的碳水化合物结构,如糖蛋白。靶细胞表面抗原可以是肿瘤抗原。本披露还涵盖多特异性抗原结合分子或构建体,如三特异性抗原结合分子或构建体,后者包括三个结合结构域,或具有多于三种(例如,四种、五种……)特异性的构建体。

[0034] 如本文所理解的双特异性抗体和/或抗原结合分子或构建体包括但不限于传统的双特异性免疫球蛋白(例如,BsIgG)、包含附加的抗原结合结构域的IgG(例如,轻链或重链的氨基或羧基末端与另外的抗原结合结构域连接,如单结构域抗体或成对抗体可变结构域(例如,Fv或scFv))、BsAb片段(例如,双特异性单链抗体)、双特异性融合蛋白(例如,与效应子部分融合的抗原结合结构域)、以及BsAb缀合物。参见,例如,Spiess等人,Molecular Immunology[分子免疫学]67(2)部分A:97-106(2015),其描述了各种双特异性形式并通过引用并入文中。双特异性构建体的实例包括但不限于双抗体、单链双抗体、串联scFv、双特异性T细胞接合剂(BiTE®)形式(由通过接头连接的两个单链可变片段(scFv)组成的融合蛋白)、和Fab2双特异性抗体、以及包含全长抗体的工程化构建体。参见,例如,Chames和Baty,2009,mAbs[单克隆抗体]1[6]:1-9;和Holliger和Hudson,2005,Nature Biotechnology[自然生物技术]23[9]:1126-1136;Wu等人,2007,Nature Biotechnology[自然生物技术]25[11]:1290-1297;Michaelson等人,2009,mAbs[单克隆抗体]1[2]:128-141;国际专利公开号2009032782和2006020258;Zuo等人,2000,Protein Engineering[蛋白质工程]13[5]:361-367;美国专利申请公开号20020103345;Shen等人,2006,J Biol Chem[生物化学杂志]281[16]:10706-10714;Lu等人,2005,J Biol Chem[生物化学杂志]280[20]:19665-19672;以及Kontermann,2012MAbs[单克隆抗体]4(2):182,所有这些都明确地并入本文。

[0035] 在一些实施例中,本文所述的冻干配制品包含双特异性抗原结合分子或构建体,该双特异性抗原结合分子或构建体包含与靶细胞表面抗原结合的第一结合结构域、与T细胞表面上的人CD3结合的第二结合结构域,以及任选地按氨基到羧基的顺序包含铰链-CH2结构域-CH3结构域-接头-铰链-CH2结构域-CH3结构域的第三结构域。在一些实施例中,第一结合结构域和第二结合结构域中的每一者包含VH区和VL区。

[0036] 如本文所用,术语"结合结构域"是指(特异性地)结合至靶分子(抗原)上的给定靶表位或给定靶位点/与该靶表位或靶位点相互作用/识别该靶表位或靶位点的结构域,这些靶分子(抗原)例如分别为CDH19、MSLN、DLL3、FLT3、EGFRvlll、BCMA、PSMA、CD33、CD19、CD70、CLDN6、CLDN18.2或MUC17以及CD3。

[0037] 第一结合结构域(识别例如CDH19、MSLN、DLL3、FLT3、EGFRvlll、BCMA、PSMA、CD33、CD19、CD70、CLDN6、CLDN18.2或MUC17)的结构和功能,以及还有第二结合结构域(识别CD3)的结构和/或功能是基于抗体,例如全长或完整免疫球蛋白分子的结构和/或功能,和/或是从抗体或其片段的可变重链(VH)和/或可变轻链(VL)结构域中提取。在实施例中,第一结合结构域的特征在于存在三个轻链CDR(即VL区的CDR1、CDR2和CDR3)和/或三个重链CDR(即VH

区的CDR1、CDR2和CDR3)。在实施例中,第二结合结构域还包含允许靶结合的抗体的最小结构要求。在实施例中,第二结合结构域包含至少三个轻链CDR(即VL区的CDR1、CDR2和CDR3)和/或三个重链CDR(即VH区的CDR1、CDR2和CDR3)。设想第一结合结构域和/或第二结合结构域是通过噬菌体展示或文库筛选方法产生或可获得的,而不是通过将CDR序列从预先存在的(单克隆)抗体移植到支架中产生或可获得的。

[0038] 在一些实施例中,与靶细胞表面抗原结合的第一结合结构域和/或与CD3ε结合的第二结合结构域是人结合结构域。包含至少一种人结合结构域的抗体和抗原结合分子或构建体避免了与具有非人如啮齿动物(例如鼠、大鼠、仓鼠或兔)可变区和/或恒定区的抗体或抗体构建体相关的一些问题。这种啮齿动物来源的蛋白质的存在可以导致抗体或抗原结合分子或构建体的快速清除,或者可以导致患者生成针对抗体或抗原结合分子或构建体的免疫应答。为了避免使用啮齿动物来源的抗体或抗原结合分子或构建体,可以通过将人抗体功能引入到啮齿动物中以使啮齿动物产生完全人抗体来产生人或完全人抗体/抗原结合分子。

[0039] 在一些实施例中,抗原结合蛋白包含单链抗原结合分子。scFv包含可变重链、scFv接头和可变轻链结构域。任选地,可变轻链的C末端附接至scFv接头的N末端,该接头的C末端附接至可变重链的N末端(N-vh-接头-vl-C),虽然可以转换构型(N-vl-接头-vh-C)。可替代地,可变重链的C末端附接至scFv接头的N末端,该接头的C末端附接至可变轻链的N末端(N-vl-接头-vh-C),虽然可以转换构型(N-vh-接头-v-C)。因此,scFv的描绘和说明中特别包括的是任一取向的scFv。

[0040] 本披露的抗原结合分子的至少两种结合结构域和可变结构域(VH/VL)可以包含或可以不包含肽接头(间隔肽)。根据本披露,术语“肽接头”包含氨基酸序列,本披露的抗原结合分子的一个(可变和/或结合)结构域和另一个(可变和/或结合)结构域的氨基酸序列通过该氨基酸序列彼此连接。肽接头也可用于将第三结构域与本披露的抗原结合分子的其他结构域融合。这样的肽接头的特征在于它不包含任何聚合活性。合适的肽接头是在美国专利4,751,180和4,935,233或WO 88/09344中描述的那些,将其披露内容通过引用以其整体并入本文。肽接头也可用于将其他结构域或模块或区(如半衰期延长的结构域)附接到本文所述的双特异性抗原结合分子。

[0041] 在一些实施例中,第三结构域包含“Fc”或“Fc区”或“Fc结构域”,该“Fc”或“Fc区”或“Fc结构域”是指包含除第一恒定区免疫球蛋白结构域之外的抗体的恒定区的多肽。因此,“Fc结构域”是指IgA、IgD和IgG的最后两个恒定区免疫球蛋白结构域、IgE和IgM的最后三个恒定区免疫球蛋白结构域、和在这些结构域的N末端的柔性铰链。对于IgA和IgM,Fc可以包括J链。对于IgG,Fc结构域包含免疫球蛋白结构域Cγ2和Cγ3(Cγ2和Cγ3)以及Cγ1(Cγ1)和Cγ2(Cγ2)之间的下铰链区。在一些实施例中,双特异性抗原结合分子是IgG抗体(其包括几个亚类,包括但不限于IgG1、IgG2、IgG3以及IgG4)。尽管Fc区的边界可以变化,人IgG重链Fc区通常定义为在其羧基末端包括残基C226或P230,其中根据如在Kabat中的EU索引进行编号。在一些实施例中,对Fc区进行氨基酸修饰,例如,以改变与一种或多种FcγR受体或FcRn受体的结合。

[0042] 在一些实施例中,本文所述的配制品包含双特异性抗原结合分子,该双特异性抗原结合分子与人CD3和人CDH19、或人CD3和人MSLN、或人CD3和人DLL3、或人CD3和人FLT3、或

人CD3和人EGFRvIII、或人CD3和人BCMA、或人CD3和PSMA、或人CD3和人CD33、或人CD3和人CD19、人CD3和人CD70、或人CD3和人MUC17、或人CD3和人CLDN18.2、或人CD3和人CLDN6结合。

[0043] 在一些实施例中,双特异性抗原结合分子的第一结合结构域包含以下列出的一组6个CDR:(a)SEQ ID NO:24-29,(b)SEQ ID NO:34-39,(c)SEQ ID NO:78-83,(d)SEQ ID NO:10-15,(e)SEQ ID NO:46-51,(f)SEQ ID NO:88-93,(g)SEQ ID NO:67-72,(h)SEQ ID NO:56-61,(i)SEQ ID NO:112-117,(j)SEQ ID NO:100-105,(k)SEQ IDNO:148-153、SEQ ID NO:157-162、或SEQ ID NO:166-171、或SEQ ID NO:175-180,(l)SEQ ID NO:132-137,或(m)SEQ ID NO:123-128。

[0044] 在一些实施例中,双特异性抗原结合分子的第一结合结构域包含VH区,该VH区包含与SEQ ID NO:30、40、84、16、17、52、94、73、62、118、154、163、172、181、106、138、143、或129中列出的氨基酸序列具有至少90%同一性(例如,91%、92%、93%、94%、95%、96%、97%、98%、99%、或100%同一性)的氨基酸序列。在一些实施例中,双特异性抗原结合分子的第一结合结构域包含VH,该VH包含SEQ ID NO:30、40、84、16、17、52、94、73、62、118、154、163、172、181、106、138、143、或129中列出的氨基酸序列。

[0045] 在一些实施例中,双特异性抗原结合分子的第一结合结构域包含VL区,该VL区包含与SEQ ID NO:31、41、85、18、19、53、95、74、63、119、155、164、173、182、107、139、144、或130中列出的氨基酸序列具有至少90%同一性(例如,91%、92%、93%、94%、95%、96%、97%、98%、99%、或100%同一性)的氨基酸序列。在一些实施例中,双特异性抗原结合分子的第一结合结构域包含VL,该VL包含SEQ ID NO:31、41、85、18、19、53、95、74、63、119、155、164、173、182、107、139、144、或130中列出的氨基酸序列。

[0046] 在一些实施例中,其中第一结合结构域包含(a)VH区,该VH区包含SEQ ID NO:30中列出的氨基酸序列,以及VL区,该VL区包含SEQ ID NO:31中列出的氨基酸序列;(b)VH区,该VH区包含SEQ ID NO:40中列出的氨基酸序列,以及VL区,该VL区包含SEQ ID NO:41中列出的氨基酸序列;(c)VH区,该VH区包含SEQ IDNO:84中列出的氨基酸序列,以及VL区,该VL区包含SEQ ID NO:85中列出的氨基酸序列;(d)VH区,该VH区包含SEQ ID NO:16或17中列出的氨基酸序列,以及VL区,该VL区包含SEQ ID NO:18或19中列出的氨基酸序列;(e)VH区,该VH区包含SEQ ID NO:52中列出的氨基酸序列,以及VL区,该VL区包含SEQ ID NO:53中列出的氨基酸序列;(f)VH区,该VH区包含SEQ ID NO:94中列出的氨基酸序列,以及VL区,该VL区包含SEQ ID NO:95中列出的氨基酸序列;(g)VH区,该VH区包含SEQ ID NO:73中列出的氨基酸序列,以及VL区,该VL区包含SEQ ID NO:74中列出的氨基酸序列;(h)VH区,该VH区包含SEQ ID NO:62中列出的氨基酸序列,以及VL区,该VL区包含SEQ ID NO:63中列出的氨基酸序列;(i)VH区,该VH区包含SEQ ID NO:118中列出的氨基酸序列,以及VL区,该VL区包含SEQ IDNO:119中列出的氨基酸序列;(j)VH区,该VH区包含SEQ ID NO:154、163、172、或181中列出的氨基酸序列,以及VL区,该VL区包含SEQ ID NO:155、164、173、或182中列出的氨基酸序列;(k)VH区,该VH区包含SEQ ID NO:106中列出的氨基酸序列,以及VL区,该VL区包含SEQ ID NO:107中列出的氨基酸序列;(l)VH区,该VH区包含SEQ ID NO:138或143中列出的氨基酸序列,以及VL区,该VL区包含SEQ ID NO:139或144中列出的氨基酸序列;或(m)VH区,该VH区包含SEQ ID NO:129中列出的氨基酸序列,以及VL区,该VL区包含SEQ ID NO:130中列出的氨基酸序列。

[0047] 在一些实施例中,双特异性抗原结合分子的第二结合结构域包含SEQ ID NO:1-6中列出的一组6个CDR。

[0048] 在一些实施例中,双特异性抗原结合分子的第二结合结构域包含VH区,该VH区包含与SEQ ID NO:7中列出的氨基酸序列具有至少90%同一性(例如,91%、92%、93%、94%、95%、96%、97%、98%、99%、或100%同一性)的氨基酸序列。在一些实施例中,双特异性抗原结合分子的第二结合结构域包含VH,该VH包含SEQ IDNO:7中列出的氨基酸序列。

[0049] 在一些实施例中,双特异性抗原结合分子的第二结合结构域包含VL区,该VL区包含与SEQ ID NO:8中列出的氨基酸序列具有至少90%同一性(例如,91%、92%、93%、94%、95%、96%、97%、98%、99%、或100%同一性)的氨基酸序列。在一些实施例中,双特异性抗原结合分子的第二结合结构域包含VL,该VL包含SEQ IDNO:8中列出的氨基酸序列。

[0050] 在一些实施例中,其中第二结合结构域包含(a)VH区,该VH区包含SEQ ID NO:7中列出的氨基酸序列,以及VL区,该VL区包含SEQ ID NO:8中列出的氨基酸序列。

[0051] 在一些实施例中,双特异性抗原结合分子包含与CD19结合的第一结合结构域,该第一结合结构域包含含有SEQ ID NO:85的氨基酸序列的抗CD19可变轻链结构域以及含有SEQ ID NO:84的氨基酸序列的抗CD19可变重链结构域,和第二结合结构域,该第二结合结构域包含含有SEQ ID NO:7的氨基酸序列的抗CD3可变重链结构域以及含有SEQ ID NO:8的氨基酸序列的抗CD3可变轻链结构域。例如,在一个实施例中,双特异性抗原结合分子包含第一结合结构域,该第一结合结构域包含SEQ IDNO:86的氨基酸序列,和第二结合结构域,该第二结合结构域包含SEQ ID NO:9的氨基酸序列。在一些实施例中,双特异性抗原结合分子包含SEQ ID NO:87中列出的氨基酸序列。

[0052] 在一些实施例中,双特异性抗原结合分子包含与MSLN结合的第一结合结构域,该第一结合结构域包含含有SEQ ID NO:41的氨基酸序列的抗MSLN可变轻链结构域以及含有SEQ ID NO:40的氨基酸序列的抗MSLN可变重链结构域,和第二结合结构域,该第二结合结构域包含含有SEQ ID NO:7的氨基酸序列的抗CD3可变重链结构域以及含有SEQ ID NO:8的氨基酸序列的抗CD3可变轻链结构域。例如,在一个实施例中,双特异性抗原结合分子包含第一结合结构域,该第一结合结构域包含SEQ IDNO:42的氨基酸序列,和第二结合结构域,该第二结合结构域包含SEQ ID NO:9的氨基酸序列。在一些实施例中,双特异性抗原结合分子包含SEQ ID NO:43、44或45中列出的氨基酸序列。

[0053] 在一些实施例中,双特异性抗原结合分子包含与DLL3结合的第一结合结构域,该第一结合结构域包含含有SEQ ID NO:74的氨基酸序列的抗DLL3可变轻链结构域以及含有SEQ ID NO:73的氨基酸序列的抗DLL3可变重链结构域,和第二结合结构域,该第二结合结构域包含含有SEQ ID NO:7的氨基酸序列的抗CD3可变重链结构域以及含有SEQ ID NO:8的氨基酸序列的抗CD3可变轻链结构域。例如,在一个实施例中,双特异性抗原结合分子包含第一结合结构域,该第一结合结构域包含SEQ IDNO:75的氨基酸序列,和第二结合结构域,该第二结合结构域包含SEQ ID NO:9的氨基酸序列。在一些实施例中,双特异性抗原结合分子包含SEQ ID NO:76或77中列出的氨基酸序列。

[0054] 在一些实施例中,双特异性抗原结合分子包含与FLT3结合的第一结合结构域,该第一结合结构域包含含有SEQ ID NO:63的氨基酸序列的抗FLT3可变轻链结构域以及含有SEQ ID NO:62的氨基酸序列的抗FLT3可变重链结构域,和第二结合结构域,该第二结合结

构域包含含有SEQ ID NO:7的氨基酸序列的抗CD3可变重链结构域以及含有SEQ ID NO:8的氨基酸序列的抗CD3可变轻链结构域。例如,在一个实施例中,双特异性抗原结合分子包含第一结合结构域,该第一结合结构域包含SEQ IDNO:64的氨基酸序列,和第二结合结构域,该第二结合结构域包含SEQ ID NO:9的氨基酸序列。在一些实施例中,双特异性抗原结合分子包含SEQ ID NO:65或66中列出的氨基酸序列。

[0055] 在一些实施例中,双特异性抗原结合分子包含与EGFRvIII结合的第一结合结构域,该第一结合结构域包含含有SEQ ID NO:31的氨基酸序列的抗EGFRvIII可变轻链结构域以及含有SEQ ID NO:30的氨基酸序列的抗EGFRvIII可变重链结构域,和第二结合结构域,该第二结合结构域包含含有SEQ ID NO:7的氨基酸序列的抗CD3可变重链结构域以及含有SEQ ID NO:8的氨基酸序列的抗CD3可变轻链结构域。例如,在一个实施例中,双特异性抗原结合分子包含第一结合结构域,该第一结合结构域包含SEQ ID NO:32的氨基酸序列,和第二结合结构域,该第二结合结构域包含SEQ ID NO:9的氨基酸序列。在一些实施例中,双特异性抗原结合分子包含SEQ ID NO:33中列出的氨基酸序列。

[0056] 在一些实施例中,双特异性抗原结合分子包含与BCMA结合的第一结合结构域,该第一结合结构域包含含有SEQ ID NO:95的氨基酸序列的抗BCMA可变轻链结构域以及含有SEQ ID NO:94的氨基酸序列的抗BCMA可变重链结构域,和第二结合结构域,该第二结合结构域包含含有SEQ ID NO:7的氨基酸序列的抗CD3可变重链结构域以及含有SEQ ID NO:8的氨基酸序列的抗CD3可变轻链结构域。例如,在一个实施例中,双特异性抗原结合分子包含第一结合结构域,该第一结合结构域包含SEQ ID NO:96的氨基酸序列,和第二结合结构域,该第二结合结构域包含SEQ ID NO:9的氨基酸序列。在一些实施例中,双特异性抗原结合分子包含SEQ ID NO:98或SEQ ID NO:97中列出的氨基酸序列。

[0057] 在一些实施例中,双特异性抗原结合分子包含与PSMA结合的第一结合结构域,该第一结合结构域包含含有SEQ ID NO:119或107的氨基酸序列的抗PSMA可变轻链结构域以及含有SEQ ID NO:118或106的氨基酸序列的抗PSMA可变重链结构域,和第二结合结构域,该第二结合结构域包含含有SEQ ID NO:7的氨基酸序列的抗CD3可变重链结构域以及含有SEQ ID NO:8的氨基酸序列的抗CD3可变轻链结构域。例如,在一个实施例中,双特异性抗原结合分子包含第一结合结构域,该第一结合结构域包含SEQ ID NO:120或108的氨基酸序列,和第二结合结构域,该第二结合结构域包含SEQ ID NO:9的氨基酸序列。在一些实施例中,双特异性抗原结合分子包含SEQ ID NO:121、122、109、110或111中列出的氨基酸序列。

[0058] 在一些实施例中,双特异性抗原结合分子包含与CD33结合的第一结合结构域,该第一结合结构域包含含有SEQ ID NO:18或19的氨基酸序列的抗CD33可变轻链结构域以及含有SEQ ID NO:16或17的氨基酸序列的抗CD33可变重链结构域,和第二结合结构域,该第二结合结构域包含含有SEQ ID NO:7的氨基酸序列的抗CD3可变重链结构域以及含有SEQ ID NO:8的氨基酸序列的抗CD3可变轻链结构域。例如,在一个实施例中,双特异性抗原结合分子包含第一结合结构域,该第一结合结构域包含SEQ ID NO:189或190的氨基酸序列,和第二结合结构域,该第二结合结构域包含SEQ ID NO:9的氨基酸序列。在一些实施例中,双特异性抗原结合分子包含SEQ ID NO:20、21、22或23中列出的氨基酸序列。

[0059] 在一些实施例中,双特异性抗原结合分子包含与CDH19结合的第一结合结构域,该第一结合结构域包含含有SEQ ID NO:53的氨基酸序列的抗CDH19可变轻链结构域以及含有

SEQ ID NO:52的氨基酸序列的抗CDH19可变重链结构域,和第二结合结构域,该第二结合结构域包含含有SEQ ID NO:7的氨基酸序列的抗CD3可变重链结构域以及含有SEQ ID NO:8的氨基酸序列的抗CD3可变轻链结构域。例如,在一个实施例中,双特异性抗原结合分子包含第一结合结构域,该第一结合结构域包含SEQ ID NO:54的氨基酸序列,和第二结合结构域,该第二结合结构域包含SEQ ID NO:9的氨基酸序列。在一些实施例中,双特异性抗原结合分子包含SEQ ID NO:55中列出的氨基酸序列。

[0060] 在一些实施例中,双特异性抗原结合分子包含与MUC17结合的第一结合结构域,该第一结合结构域包含含有SEQ ID NO:155、164、173、或182的氨基酸序列的抗MUC17可变轻链结构域以及含有SEQ ID NO:154、163、172、或181的氨基酸序列的抗MUC17可变重链结构域,和第二结合结构域,该第二结合结构域包含含有SEQ ID NO:7的氨基酸序列的抗CD3可变重链结构域以及含有SEQ ID NO:8的氨基酸序列的抗CD3可变轻链结构域。在一些实施例中,双特异性抗原结合分子包含SEQ IDNO:156、165、174或183中列出的氨基酸序列。

[0061] 在一些实施例中,双特异性抗原结合分子包含与cldn18.2结合的第一结合结构域,该第一结合结构域包含含有SEQ ID NO:139或144的氨基酸序列的抗cldn18.2可变轻链结构域以及含有SEQ ID NO:138或143的氨基酸序列的抗cldn18.2可变重链结构域,和第二结合结构域,该第二结合结构域包含含有SEQ ID NO:7的氨基酸序列的抗CD3可变重链结构域以及含有SEQ ID NO:8的氨基酸序列的抗CD3可变轻链结构域。例如,在一个实施例中,双特异性抗原结合分子包含第一结合结构域,该第一结合结构域包含SEQ ID NO:140或145的氨基酸序列,和第二结合结构域,该第二结合结构域包含SEQ ID NO:9的氨基酸序列。在一些实施例中,双特异性抗原结合分子包含SEQ ID NO:141、142、146或147中列出的氨基酸序列。

[0062] 在一些实施例中,双特异性抗原结合分子包含与CD70结合的第一结合结构域,该第一结合结构域包含含有SEQ ID NO:130的氨基酸序列的抗CD70可变轻链结构域以及含有SEQ ID NO:129的氨基酸序列的抗CD70可变重链结构域,和第二结合结构域,该第二结合结构域包含含有SEQ ID NO:7的氨基酸序列的抗CD3可变重链结构域以及含有SEQ ID NO:8的氨基酸序列的抗CD3可变轻链结构域。在一些实施例中,双特异性抗原结合分子包含SEQ ID NO:131中列出的氨基酸序列。

[0063] 在一些实施例中,配制品的蛋白质是抗体。在多个实施例中,配制品的蛋白质是双特异性抗原结合分子。在一些情况下,配制品的蛋白质是半衰期延长的双特异性抗原结合分子。半衰期延长的双特异性抗原结合分子先前已在本文中描述。在一些实施例中,本披露的蛋白配制品包含SEQ ID NO:1-190中列出的氨基酸序列。在多个实施例中,本披露的蛋白配制品包含以下列出的氨基酸序列:SEQ ID NO:20、SEQ IDNO:21、SEQ ID NO:22、SEQ ID NO:23、SEQ ID NO:33、SEQ ID NO:43、SEQ IDNO:44、SEQ ID NO:45、SEQ ID NO:55、SEQ ID NO:65、SEQ ID NO:66、SEQ IDNO:55、SEQ ID NO:76、SEQ ID NO:77、SEQ ID NO:87、SEQ ID NO:97、SEQ IDNO:98、SEQ ID NO:99、SEQ ID NO:109、SEQ ID NO:110、SEQ ID NO:111、SEQ ID NO:121、SEQ ID NO:122、SEQ ID NO:131、SEQ ID NO:141、SEQ ID NO:142、SEQ ID NO:146、SEQ ID NO:147、SEQ ID NO:156、SEQ ID NO:165、SEQ ID NO:174、SEQ ID NO:183、SEQ ID NO:184、SEQ ID NO:185、SEQ ID NO:186、SEQ IDNO:187、或SEQ ID NO:188。在一些情况下,本披露的蛋白配制品包含以下列出的氨基酸序列:SEQ ID NO:22(BiTE A)、SEQ ID NO:

77(BiTE B)、SEQ ID NO:87(BiTE C)、或SEQ ID NO:97(BiTE D)。

[0064] 在一些实施例中,蛋白质,如抗体或双特异性的(例如HLE双特异性抗体构建体)以约0.1mg/mL至约100mg/mL(或约0.1mg/mL、0.5mg/mL、1mg/mL、5mg/mL、10mg/mL、15mg/mL、20mg/mL、25mg/mL、30mg/mL、35mg/mL、40mg/mL、45mg/mL、50mg/mL、55mg/mL、60mg/mL、65mg/mL、70mg/mL、75mg/mL、80mg/mL、85mg/mL、90mg/mL、95mg/mL、或100mg/mL)的量的范围存在于液体配制品(冻干前)。在多个实施例中,蛋白质以约0.1mg/mL至约70mg/mL的量的范围存在于液体配制品中。在一些情况下,蛋白质以约0.5mg/mL至约30mg/mL(或约0.5mg/mL、0.6mg/mL、0.7mg/mL、0.8mg/mL、0.9mg/mL、1mg/mL、2mg/mL、3mg/mL、4mg/mL、5mg/mL、6mg/mL、7mg/mL、8mg/mL、9mg/mL、10mg/mL、11mg/mL、12mg/mL、13mg/mL、14mg/mL、15mg/mL、16mg/mL、17mg/mL、18mg/mL、19mg/mL、20mg/mL、21mg/mL、22mg/mL、23mg/mL、24mg/mL、25mg/mL、26mg/mL、27mg/mL、28mg/mL、29mg/mL、或30mg/mL)的量范围存在于液体配制品中。在各种情况下,蛋白质以约1mg/mL至约20mg/mL(或约1mg/mL、1.5mg/mL、2mg/mL、2.5mg/mL、3mg/mL、3.5mg/mL、4mg/mL、4.5mg/mL、5mg/mL、5.5mg/mL、6mg/mL、6.5mg/mL、7mg/mL、7.5mg/mL、8mg/mL、8.5mg/mL、9mg/mL、9.5mg/mL、10mg/mL、10.5mg/mL、11mg/mL、11.5mg/mL、12mg/mL、12.5mg/mL、13mg/mL、13.5mg/mL、14mg/mL、14.5mg/mL、15mg/mL、15.5mg/mL、16mg/mL、16.5mg/mL、17mg/mL、17.5mg/mL、18mg/mL、18.5mg/mL、19mg/mL、19.5mg/mL、或20mg/mL)的量的范围存在于液体配制品中。在一些实施例中,蛋白质以约1mg/mL的量存在于液体配制品中。

[0065] 糖

[0066] 本披露的蛋白配制品包含糖。在一些实施例中,糖是单糖或二糖。合适的糖包括,例如葡萄糖、半乳糖、果糖、木糖、蔗糖、乳糖、麦芽糖、海藻糖或其任何组合。在一些情况下,糖包含蔗糖。

[0067] 在一些实施例中,液体配制品(冻干前)包含浓度为约1%至约15%w/v、或约4%至约13%w/v、或约6%至约12%w/v的糖。在一些实施例中,液体配制品包含浓度为至少1%、至少2%、至少3%、至少4%、至少5%、至少6%、至少7%、至少8%、至少9%、至少10%、至少11%、至少12%、至少13%、或至少14%w/v的糖。在一些实施例中,液体配制品包含浓度为约1%、约2%、约3%、约4%、约5%、约6%、约7%、约8%、约9%、约10%、约11%、约12%、约13%、约14%、或约15%w/v的糖。在一些实施例中,液体配制品包含浓度为约7%、约7.5%、约8%、约8.5%、约9%、约9.5%、约10%、约10.5%、约11%、约11.5%、或约12%w/v的糖。在一些实施例中,液体配制品包含浓度为约7%至约12%w/v的糖。在一些实施例中,液体配制品包含浓度为约9%w/v的糖。在一些实施例中,糖是蔗糖,并且以约6%至约12%w/v的浓度范围存在于液体配制品中。在一些情况下,糖是蔗糖,并且以约9%w/v的浓度存在于液体配制品中。

[0068] 表面活性剂

[0069] 本披露的蛋白配制品包含表面活性剂。合适的表面活性剂包括聚山梨醇酯、泊洛沙姆、聚氧乙烯、或其任何组合。预期的表面活性剂包括聚山梨醇酯20、聚山梨醇酯40、聚山梨醇酯60、聚山梨醇酯80、泊洛沙姆188、泊洛沙姆407、曲拉通X-100、聚氧乙烯、PEG 3350、PEG 4000、以及其任何组合。在一些实施例中,表面活性剂包含聚山梨醇酯。在一些情况下,表面活性剂是聚山梨醇酯80。

[0070] 本文所述的蛋白配制品可以包含一种表面活性剂或表面活性剂的混合物。在一些实施例中,液体配制品(冻干前)包含浓度为约0.001%至约5%w/v(或约0.001%至约0.5%、或约0.004%至约0.5%w/v、或约0.001%至约0.01%w/v或约0.004%至约0.01%w/v)的表面活性剂。在一些实施例中,液体配制品包含浓度为至少0.001%、至少0.002%、至少0.003%、至少0.004%、至少0.005%、至少0.007%、至少0.01%、至少0.05%、至少0.1%、至少0.2%、至少0.3%、至少0.4%、至少0.5%、至少0.6%、至少0.7%、至少0.8%、至少0.9%、至少1.0%、至少1.5%、至少2.0%、至少2.5%、至少3.0%、至少3.5%、至少4.0%、或至少4.5%w/v的表面活性剂。在一些实施例中,液体配制品包含浓度为约0.001%至约0.5%w/v的表面活性剂。在一些实施例中,液体配制品包含浓度为约0.001%至约0.01%w/v的表面活性剂。在一些实施例中,液体配制品包含浓度为约0.001%至约0.01%w/v的表面活性剂。在一些实施例中,液体配制品包含浓度为约0.001%、约0.002%、约0.003%、约0.004%、约0.005%、约0.006%、约0.007%、约0.008%、约0.009%、约0.01%、约0.05%、约0.1%、约0.2%、约0.3%、约0.4%至约0.5%w/v的表面活性剂。在一些实施例中,液体配制品包含浓度为约0.001%至约0.01%w/v的表面活性剂。在一些实施例中,表面活性剂是聚山梨醇酯80,聚山梨醇酯80以约0.01%w/v的浓度存在。

[0071] 缓冲液

[0072] 本披露的蛋白配制品任选地包含缓冲液。合适的缓冲液包括乙酸盐缓冲液、谷氨酸盐缓冲液、柠檬酸盐缓冲液、乳酸盐缓冲液、琥珀酸盐缓冲液、酒石酸盐缓冲液、富马酸盐缓冲液、马来酸盐缓冲液、组氨酸缓冲液、磷酸盐缓冲液、2-(N-吗啉代)乙磺酸盐缓冲液、或其任何组合。在一些情况下,缓冲液包含谷氨酸。

[0073] 通常采用缓冲剂来控制配制品中的pH。在一些实施例中,以一定浓度添加缓冲液使液体配制品的pH保持在约3至约7、或约4至约6、约4至5、或约4.2。pH对配制品的影响可以使用几种途径中的任何一种或多种来表征,如加速稳定性研究和量热筛选研究(Remmele R.L.Jr.,等人,Biochemistry[生物化学],38(16):5241-7(1999))。

[0074] 选择蛋白配制品中存在的缓冲液系统以在生理学上相容并保持所希望的pH。缓冲液可以按约0.1mM和约1000mM(1M)之间、或约5mM和约200mM之间、或约5mM至约100mM之间、或约10mM和约50mM之间的浓度存在于液体配制品(冻干前)中。合适的缓冲液浓度涵盖约200mM或更低的浓度。在一些实施例中,液体蛋白配制品(冻干前)中的缓冲液以约190mM、约180mM、约170mM、约160mM、约150mM、约140mM、约130mM、约120mM、约110mM、约100mM、约80mM、约70mM、约60mM、约50mM、约40mM、约30mM、约20mM、约10mM或约5mM的浓度存在。在一些实施例中,缓冲液的浓度为至少0.1、0.5、0.7、0.8、0.9、1.0、1.2、1.5、1.7、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、30、40、50、60、70、80、90、100、200、500、700、或900mM。在一些实施例中,缓冲液的浓度为在1、1.2、1.5、1.7、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、30、40、50、60、70、80、或90mM和100mM之间。在一些实施例中,缓冲液的浓度为在5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、30、或40mM和50mM之间。在一些实施例中,缓冲液的浓度为约10mM。

[0075] 在一些实施例中,液体蛋白配制品(冻干前)具有约4.2的pH,并且包含约10mM L-谷氨酸、约9.0%(w/v)蔗糖以及约0.01%(w/v)聚山梨醇酯80。

[0076] 冻干蛋白配制品的稳定性

[0077] 本文披露的方法有利地产生冻干蛋白配制品,该冻干蛋白配制品在用液体重构后表现出蛋白质的降低的物理降解(如聚集),以及降低的化学降解(如降低的剪切和脱酰胺化)。用于重构冻干蛋白配制品的液体可以是本领域已知的任何合适的液体。在实施例中,冻干蛋白配制品可以用水重构。此外,本文披露的冻干方法能够稳定低浓度和高浓度蛋白配制品,如含有抗体和双特异性抗原结合分子(例如,半衰期延长的双特异性抗体构建体)的配制品。

[0078] 如含有抗体或双特异性抗原结合分子(例如,HLE双特异性抗原结合分子)的配制品的蛋白配制品的稳定性可以以几种方式进行定量。在一些实施例中,蛋白配制品的稳定性通过尺寸排阻高效液相色谱(SE-HPLC)、尺寸排阻超高效液相色谱(SE-UHPLC)、阳离子交换高效液相色谱(CE-HPLC)、动态光散射(DLS)、分析超离心(AUC)、场流分离(FFF)、等电聚焦以及离子交换色谱(IEX)来表征。在一些实施例中,蛋白配制品(如抗体配制品)的稳定性通过部分解离来表征,如通过十二烷基硫酸钠的毛细管电泳(CE-SDS)和/或十二烷基硫酸钠-聚丙烯酰胺凝胶电泳(SDS-PAGE)测量的。在一些实施例中,配制品的稳定性通过还原型毛细管电泳-十二烷基硫酸钠(rCE-SDS)评估。rCE-SDS方法在还原条件下分离出重链(HC)、轻链(LC)、非糖基化的HC(NGHC)和其他次要的峰物质和基团。

[0079] 在一些实施例中,配制品的稳定性特征在于在不同时间点的储存条件后蛋白质如抗体或双特异性抗原结合分子(例如,HLE双特异性抗原结合分子)的高分子量(HMW)物质的量,或在于蛋白质的HMW物质的量的增加速率。在一些实施例中,在重构后在大约4℃或40℃下储存一周、两周、一个月、三个月、六个月或十二个月后确定蛋白质的HMW物质的量。在一些实施例中,在重构后在大约4℃或40℃下储存一周、两周、一个月、三个月、六个月或十二个月后确定蛋白质的HMW物质的增加速率。在一些实施例中,通过SE-UHPLC来测量重构冻干配制品中的蛋白质,如抗体或双特异性抗原结合分子(例如,HLE双特异性抗原结合分子)的HMW物质。

[0080] 蛋白质(如抗体或双特异性抗原结合分子(例如,HLE双特异性抗原结合分子))的稳定性和配制品保持蛋白质的稳定性的能力,可以在延长的时间段(例如,数周或数月)内评估。在配制品的上下文中,稳定的配制品是其中的蛋白质如抗体或双特异性抗原结合分子(例如,HLE双特异性抗原结合分子)在储存后和加工过程(例如冷冻/解冻、机械混合和冻干)中基本上保持其物理和/或化学完整性和生物活性的配制品。例如,可以通过测量高分子量(HMW)聚集体形成、电荷特征的改变以及颗粒大小的变化的水平和/或速率来评估蛋白质稳定性。

[0081] 在一些实施例中,蛋白质的任何特定物质,如完整BiTE®分子或主要物质、或高分子量(HMW)物质(即,聚集体)、或低分子量(LMW)物质(即,片段)的相对值是相对于总产物的各自的值来表示的。例如,在一些实施例中,2.5%或更少(例如,2.5%、或2%、或1.9%、或1.8%、或1.7%、或1.6%、或1.5%、或1.4%、或1.3%、或1.2%、或1.1%、或1%、或0.5%)的蛋白质(如抗体或双特异性抗原结合分子),在重构冻干配制品中作为HMW物质存在。在一些实施例中,在4℃下储存一个月或更久(例如,持续一个月、持续三个月、或持续六个月)后,HMW物质的量在重构冻干配制品中增加少于1%(例如,0.9%、0.8%、0.7%、0.6%、0.5%、0.4%、0.3%、0.2%、0.1%)。在一些实施例中,在4℃下储存一个月或更久(例如,持续一个月、持续三个月、或持续六个月)后,HMW物质的量在重构冻干配制品中增加大约

0.1%和0.4%(例如,0.1%、0.2%、0.3%、或0.4%)之间。在一些实施例中,在40℃下储存一周或更久(例如,持续一周、持续两周、持续一个月或持续三个月)后,HMW物质的量在重构冻干配制品中增加小于1%(例如,0.9%、0.8%、0.7%、0.6%、0.5%、0.4%、0.3%、0.2%、0.1%)。在一些实施例中,在40℃下储存一周或更久(例如,持续一周、持续两周、持续一个月或持续三个月)后,HMW物质的量在重构冻干配制品中增加小于0.5%(例如,0.5%、0.4%、0.3%、0.2%、0.1%)。在一些实施例中,在40℃下储存一个月或更久(例如,持续一个月、持续三个月、持续六个月、持续九个月、或持续十二个月)后,HMW物质的量在重构冻干配制品中增加小于0.5%(例如,0.5%、0.4%、0.3%、0.2%、0.1%)。在一些实施例中,在40℃下储存一个月后,HMW物质的量在重构冻干配制品中增加小于0.5%。在一些实施例中,在40℃下储存一个月后,HMW物质的量在重构冻干配制品中增加小于0.3%。在一些实施例中,在40℃下储存一周或更久(例如,持续一周、持续两周、持续一个月、或持续三个月)后,HMW物质的量在重构冻干配制品中增加大约0.1%和0.7%(例如,0.1%、0.2%、0.3%、0.4%、0.5%、0.6%、或0.7%)之间。在一些实施例中,在40℃下储存一周或更久(例如,持续一周、持续两周、持续一个月、或持续三个月)后,HMW物质的量在重构冻干配制品中增加大约0.1%和0.5%(例如,0.1%、0.2%、0.3%、0.4%以及0.5%)之间。在一些实施例中,在40℃下储存一个月或更久(例如,持续一个月、持续三个月、持续六个月、持续九个月或持续十二个月)后,HMW物质的量在重构冻干配制品中增加大约0.1%和0.5%(例如,0.1%、0.2%、0.3%、0.4%以及0.5%)之间。在一些实施例中,通过SE-UHPLC来测量重构冻干配制品中的双特异性抗原结合分子的HMW物质。

[0082] 在一些实施例中,配制品的稳定性特征在于在不同时间点的储存条件下蛋白质如抗体或双特异性抗原结合分子(HLE双特异性抗原结合分子)的低分子量(LMW)物质的量,或在于蛋白质的LMW物质的量的增加速率。在一些实施例中,在大约4℃或40℃下储存一周、两周、一个月、三个月、六个月或十二个月来确定LMW物质的量。在一些实施例中,在大约4℃或40℃下储存一周、两周、一个月、三个月、六个月或十二个月来确定LMW物质的增加速率。在一些实施例中,通过还原型毛细管电泳-十二烷基硫酸钠(rCE-SDS)来测量配制品中的蛋白质,如抗体或双特异性抗原结合分子(HLE双特异性抗原结合分子)的LMW物质。在一些实施例中,通过尺寸排阻色谱(SEC)来测量配制品中的双特异性抗原结合分子的LMW物质。

[0083] 在一些实施例中,少于2%(例如,1.9%、1.8%、1.7%、1.6%、1.5%、1.4%、1.3%、1.2%、1.1%、1%、或0.5%)的蛋白质,如抗体或双特异性抗原结合分子(HLE双特异性抗原结合分子),在重构冻干配制品中作为低分子量(LMW)物质存在。在一些实施例中,在4℃下储存一个月或更久(例如,持续一个月、持续三个月、或持续六个月)后,LMW物质的量在重构冻干配制品中增加少于2%(例如,1.9%、1.8%、1.7%、1.6%、1.5%、1.4%、1.3%、1.2%、1.1%、1%、或0.5%)。在一些实施例中,在4℃下储存一个月或更久(例如,持续一个月、持续三个月、或持续六个月)后,LMW物质的量在重构冻干配制品中增加大约0.1%和0.7%(例如,0.1%、0.2%、0.3%、0.4%、0.5%、0.6%或0.7%)之间。在一些实施例中,在40℃下储存一周或更久(例如,持续一周、持续两周、持续一个月或持续三个月)后,LMW物质的量在重构冻干配制品中增加小于1%(例如,0.9%、0.8%、0.7%、0.6%、0.5%、0.4%、0.3%、0.2%、0.1%)。在一些实施例中,在40℃下储存一周或更久(例如,持续一周、持续两周、持续一个月、或持续三个月)后,LMW物质的量在重构冻干配制品中增加大约0.1%和

0.7%(例如,0.1%、0.2%、0.3%、0.4%、0.5%、0.6%或0.7%)之间。在一些实施例中,通过尺寸排阻色谱(SEC)来测量重构冻干配制品中的双特异性抗原结合分子的LMW物质。在一些实施例中,通过还原型毛细管电泳-十二烷基硫酸钠(rCE-SDS)来测量重构冻干配制品中的双特异性抗原结合分子的LMW物质。

[0084] 在一些实施例中,蛋白质如抗体或双特异性抗原结合分子(HLE双特异性抗原结合分子)(即,主峰物质)在重构冻干配制品中的百分比大于配制品中总蛋白质含量的95%。

[0085] 在一些实施例中,配制品在约4℃下储存一个月后是稳定的,并且当储存至少一个月时,HMW物质的量在重构冻干配制品中增加大约0.1%至0.7%(例如,0.1%、或0.2%、或0.3%、或0.4%、或0.5%、或0.6%、或0.7%)之间。在一些实施例中,配制品在约4℃下储存三个月后是稳定的,并且当储存至少三个月时,HMW物质的量在重构冻干配制品中增加大约0.0%至0.2%(例如,0%、或0.1%、或0.2%)之间。在一些实施例中,配制品在约4℃下储存六个月后是稳定的,并且当储存至少六个月时,HMW物质的量在重构冻干配制品中增加大约0.0%至0.4%(例如,0%、或0.1%、或0.2%、或0.3%、或0.4%)之间。在一些实施例中,通过SE-UHPLC来测量重构冻干配制品中的双特异性抗原结合分子的HMW物质。

[0086] 在一些实施例中,配制品在约4℃下储存一个月、三个月以及六个月后是稳定的,并且蛋白质,如抗体或双特异性抗原结合分子(HLE双特异性抗原结合分子)的百分比高于总蛋白质含量的95%。在一些实施例中,配制品在约4℃下储存一个月、三个月、六个月、十二个月以及48个月后是稳定的,并且重构后蛋白质,如抗体或双特异性抗原结合分子(HLE双特异性抗原结合分子)的百分比高于总蛋白质含量的96%。

[0087] 本文所述配制品的稳定性还可以通过电荷分布,例如蛋白质,如抗体或双特异性抗原结合分子(HLE双特异性抗原结合分子)的电荷变体峰的量的变化来表征。例如,在一些实施例中,当在4℃下储存至少一个月(例如,持续一个月、三个月、六个月或十二个月)时,重构冻干配制品中的酸性峰(例如,脱酰胺化,具有相对较低的等电点(pI)的电荷变体)的量增加少于2%(例如,2%、1.9%、1.8%、1.7%、1.6%、1.5%、1.4%、1.3%、1.2%、1.1%、1.0%、0.9%、0.8%、0.7%、0.6%、0.5%、或更少)。在一些实施例中,当在4℃下储存至少一个月(例如,持续一个月、三个月、六个月或十二个月)时,重构冻干配制品中的碱性峰(例如,具有相对较高的pI的电荷变体)的量增加小于6%(例如,6%、5%、4%、3%、2%或1%)。在一些实施例中,当在4℃下储存至少一个月时,重构冻干配制品中的主峰的量降低少于4%(例如,4%、3.5%、3%、2.5%、2%、1%或更少)。在一些实施例中,当在4℃下储存至少三个月时,重构冻干配制品中的主峰的量降低小于6%(例如,6%、5%、4%、3.5%、3%、2.5%、2%或更少)。在一些实施例中,当在4℃下储存至少六个月时,重构冻干配制品中的主峰的量降低少于9%(例如,9%、8%、7%、6%、5%、4%、3.5%、3%、2.5%、2%或更少)。在一些实施例中,当在4℃下储存至少十二个月时,重构冻干配制品中的主峰的量降低少于9%(例如,9%、8%、7%、6%、5%、4%、3.5%、3%、2.5%、2%或更少)。

[0088] 在一些实施例中,当在40℃下储存至少一周(例如,持续一周、两周、一个月或三个月)时,重构冻干配制品中的酸性峰的量增加少于30%(例如,30%、25%、20%、15%、10%、9%、8%、7%、6%、4%、4%、3%、2%、1%或更少)。在一些实施例中,当在40℃下储存至少一周(例如,持续一周、两周、一个月或三个月)时,重构冻干配制品中的碱性峰(例如,具有相对较高的pI的电荷变体)的量增加少于15%(例如,15%、10%、9%、8%、7%、6%、4%、

4%、3%、2%、1%或更少)。在一些实施例中,当在4℃下储存至少一个月时,重构配制品中的主峰的量降低少于4%(例如,4%、3.5%、3%、2.5%、2%、1%或更少)。在一些实施例中,当在4℃下储存至少三个月时,重构冻干配制品中的主峰的量降低少于6%(例如,6%、5%、4%、3.5%、3%、2.5%、2%或更少)。

[0089] 与可比较的液体蛋白配制品相比,通过本披露的方法冻干的蛋白配制品表现出更优越的稳定性。例如,对根据本披露使用退火步骤冻干并且然后重构的蛋白配制品(含有1mg/mL的本披露的双特异性抗原结合分子、10mM L-谷氨酸、9%(w/v)蔗糖、以及0.01%(w/v)聚山梨醇酯80,pH 4.2)的稳定性进行具有十二烷基硫酸钠的还原型毛细管电泳(rCE-SDS)以确定在25℃和在40℃下储存一个月后的剪切程度。

[0090] 本披露的冻干方法还有利地稳定低浓度和高浓度的蛋白配制品。例如,使用退火步骤冻干并且然后重构的本披露的蛋白配制品(含有1mg/mL、5mg/mL、13mg/mL以及23mg/mL的本披露的双特异性抗原结合分子、10mM L-谷氨酸、9%(w/v)蔗糖、以及0.01%(w/v)聚山梨醇酯80,pH 4.2)在40℃下储存一个月后进行SEC-UHPLC以通过高分子量物质的百分比(%HMW)确定在配制品中的聚集程度。

[0091] 令人惊讶地发现,与包括退火步骤的冻干方法相比,缺少退火步骤的本披露的冻干方法导致蛋白配制品的更优越的稳定性。例如,使用和不使用退火步骤进行冻干的蛋白配制品(含有15mg/mL、20mg/mL、或23mg/mL的本披露双特异性抗原结合分子、10mM L-谷氨酸、9%(w/v)蔗糖、以及0.01%(w/v)聚山梨醇酯80,pH 4.2)在重构后进行SE-UHPLC以确定每个样品中的聚集量。

[0092] 提供以下实例用于说明而不旨在限制本发明的范围。

[0093] 实例

[0094] 通用程序

[0095] 具有十二烷基硫酸钠的还原型毛细管电泳(rCE-SDS)基于蛋白质在还原和变性条件下的流体动力学大小差异来分离蛋白质。蛋白质物质与SDS(阴离子洗涤剂)结合,并通过电动力学注射到填充有SDS凝胶缓冲液的裸露熔融石英毛细管中。在毛细管上施加电压,在此电压下,SDS包被的蛋白质由于在基于亲水聚合物的溶液中的迁移不同而被分离。蛋白质通过UV检测窗口时,通过光电二极管阵列(PDA)检测器检测。通过确定到达组分(reach component)的校正峰面积百分比来评估纯度。rCE-SDS方法在还原条件下分离出重链(HC)、轻链(LC)、非糖基化的HC(NGHC)和其他次要的峰物质和基团。通过将样品在SDS-MW还原凝胶中在70C+/-10下孵育10分钟(因此为60和80C之间孵育10分钟)然后允许冷却至室温来进行具有十二烷基硫酸钠的还原型毛细管电泳(rCE-SDS)。孵育后,将样品离心,并且然后使用电动力学注射将样品电动力学注射至具有50μm内径的67-cm裸露熔融石英毛细管。毛细管的有效长度为30.2cm。使用CE-SDS凝胶(贝克曼库尔特公司(Beckman Coulter),贝瑞阿,加利福尼亚州)和30kV有效电压进行分离。通过UV吸光度在220nm下进行检测。

[0096] 冻干饼的视觉检查.完成循环后,通过视觉检查对干燥的产物饼的宏观塌陷的任何迹象和总体质量进行评估。BITE B的产物饼被确定为可接受,并且在图1中显示了从几个角度拍摄的照片。将完整的视觉饼结构用作循环参数允许样品瓶充分干燥和均质性的初步指示。

[0097] 尺寸排阻超高效液相色谱(SE-UHPLC).SEC-UHPLC基于蛋白质流体动力学体积的

差异分离蛋白质。具有较高流体动力学体积的分子比具有较小体积的分子更先洗脱。将样品加载到SE-UHPLC柱(BEH200,4.6x 150mm,(沃特斯公司(Waters Corporation),186005226))上,等度分离并通过UV吸光度监测洗脱液。通过计算每个分离的组分与总积分面积相比的百分比来确定纯度。SE-UHPLC设置如下:流速:0.4mL/min,运行时间:9min,UV检测:220nm(280nm为蛋白质(包括抗体)所选择的常见波长,而大多数双特异性分子在220nm处检测)。柱温度:环境,靶蛋白质加载:10μg,蛋白质相容流动细胞:5mm。在确定使用该循环可达到可接受的水分含量后,将BiTE B的干燥产品小瓶在5℃、25℃和40℃下放置保持稳定性,总共持续四周。在此期间,在两周和四周时取出样品瓶,并且通过SE-UHPLC评估其聚集。将样品重构,通过涡旋混合,并且纯净地注射。图2中绘制了高分子量(HMW)物质的相对面积%值随时间的变化,并且该数据表明在研究过程中没有聚集不稳定性,支持了使用拟定循环没有引入聚集的结论。

[0098] 卡尔费歇尔滴定法(水分含量).为了更准确地评估拟定循环的干燥效率,通过卡尔费歇尔滴定法评估了产物饼的水分含量。虽然接受准则允许水分含量高达5%w/w,但是水分含量低于2%是高度优选的。将使用本发明的循环干燥的BITE B产物饼与先前使用最先进的BiTE生产的饼进行比较,并且发现水分含量为可接受的且具有竞争性,如表1所示。

[0099] 表1.在以下两种冻干条件下的BiTE B的水分含量.

[0100] 循环类型水分含量(%w/w)

[0101] 双特异性抗原结合分子的前一代循环 0.56±0.07

[0102] 双特异性抗原结合分子的减少的循环 0.33

[0103] 蛋白配制品.制备蛋白配制品,其包含浓度为1mg/mL、5mg/mL、13mg/mL、或23mg/mL的完整双特异性抗原结合分子,10mM L-谷氨酸、9%(w/v)蔗糖、0.01%(w/v)聚山梨醇酯80,pH 4.2。将蛋白配制品引入小瓶中用于冻干(不使用退火步骤)。

[0104] 实例1

[0105] 不使用退火步骤的双特异性抗原结合分子配制品的冻干

[0106] 将满足FIH BiTE平台条件的填充的小瓶(由Schott ISO 6R玻璃小瓶组成)用1.3mL的溶液填充,并且用D-777 20mm弹性氟聚合物塞住。出于循环开发和分析控制目的,始终使用配制品缓冲液,称为G42SuT(10mM谷氨酸、9.0%w/w蔗糖、0.01%聚山梨醇酯80,pH 4.2)。含有BITE B药物产品的样品瓶也在G42SuT中配制,其中蛋白质浓度为1mg/mL。对于SE-UHPLC方法,将BITE B用于系统适用性目的。将1%和5%水分含量标准用作卡尔费歇尔滴定法的标准。

[0107] 加速的冻干循环

[0108] 最终时间为约32.7小时,这表示与常规冻干循环相比,时间降低了大约67%。此外,该循环去除了称为退火的可选阶段,该阶段被认为更好地促进干燥均质性,但最近与冻干的BiTE样分子中的产物聚集相关。

[0109] 如上所述制备液体蛋白配制品,并且引入冻干室。以0.5℃/min的速率将室从5℃的加载温度冷却至-45℃,并且在-45℃下保持2小时。随后,以0.3℃/min进行升温,并且初次干燥在约-27℃的温度下和100毫托的室压力下进行16.7小时。以0.4℃/min的速率升温后在25℃下并且在70毫托压力下持续8.3小时,进行二次干燥。为了能够塞住小瓶,将室的温度降低至5℃,并且在500毫托下用氮气对冻干室充气。从冻干室移除含有冻干蛋白配制

品的小瓶,并且在2-8℃下储存直至进一步处理和分析。与使用先前循环条件的循环时间为超过70小时(精确地:72.7小时)相比,使用本发明循环的总循环时间持续32.7小时。表2显示出加速的和建立的冻干循环的参数。

[0110] 表2

循环阶段	循环步骤	前一代循环	加速的循环
		参数	
冷冻	加载温度	5°C	5°C
	冷冻升温速率	0.5°C/min	0.5°C/min
	冷冻温度	-45°C	-45°C
	冷冻时间	2 h	2 h
	退火的加热升温	0.5°C/min	-
	退火温度	-12°C	-
	退火时间	5 h	-
	退火后冷冻温度	-45°C	-
	退火后冷冻时间	2 h	-
初次干燥	加热升温进入初次干燥	0.33°C/min	0.3°C/min
	初次干燥温度	-25°C	-27°C
	初次干燥室压力	70 毫托	100 毫托
	初次干燥时间	42 h	16.7 h
二次干燥	进入二次干燥的加热升温速率	0.1°C/min	0.4°C/min
	二次干燥温度	30°C	25°C
	二次干燥室压力	70 毫托	70 毫托
	二次干燥时间	8 h	8.3 h
储存条件	储存温度	5°C	5°C
	加塞的室压力	500 托	500 托
	总循环时间	72.7 h	32.7 h

[0111]

[0112] 提供以上描述仅为了清楚理解,而不应理解为无必要的限制,因为本发明范畴内的修改方案对本领域普通技术人员是显而易见的。

[0113] 贯穿本说明书及其后的权利要求书,除非上下文另有要求,否则词语“包含(comprise)”以及变型如“包含(comprises)”或“包含(comprising)”应当被理解成隐含包

括所述整数或步骤或者整数或步骤的组,但不排除任何其他整数或步骤或者整数或步骤的组。

[0114] 应理解,当描述值范围时,所描述的特征可以是在该范围内找到的单个值。例如,“从约pH 4至约pH 6的pH”可以是但不限于,pH 4、4.2、4.6、5.1、5.5等,以及这些值之间的任何值。另外,“从约pH 4至约pH 6的pH”不应被解释为意指所考虑配制品的pH在储存期间在pH 4至pH 6的范围内变化2个pH单位,而是指溶液的pH可以在该范围内挑选值,并且pH在约该pH下保持缓冲。

[0115] 当使用术语“约”时,其意指所列举数字加上或减去所列举数字的5%、10%、15%或更多。预期的实际变化可从上下文确定。

[0116] 贯穿本说明书,在组合物描述为包括组分或材料时,除非另外描述,否则预期这些组合物也可基本上由或由所叙述的组分或材料的任何组合组成。同样,在方法描述为包括特定步骤时,除非另外描述,否则预期这些方法也可基本上由或由所叙述的步骤的任何组合组成。本文中说明性地披露的本发明可在不存在本文中未明确披露的任何要素或步骤的情况下适当地实践。

[0117] 本文中所披露的方法及其单个步骤的实践可人工和/或在电子设备辅助或由其提供的自动化下进行。虽然已参考特定实施例描述了诸多方法,但本领域普通技术人员应容易了解到,可使用执行与这些方法相关的动作的其他方式。例如,除非另外描述,否则可在不背离该方法的范畴或精神的情况下改变各步骤的顺序。此外,一些单个步骤可组合、省略或进一步再分成另外的步骤。

[0118] 本文中所引用的所有专利、出版物及参考文献均通过引用以其全文并入本文中。在本披露与所并入的专利、出版物及参考文献出现矛盾的情况下,应以本披露为主。

序列表

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Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
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Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
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Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe
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Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
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Met Glu Ile Arg Asn Leu Gly Gly Asp Asp Thr Ala Val Tyr Tyr Cys
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Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe
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Asp Lys Phe Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser
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Thr Ala Tyr Met Glu Ile Arg Asn Leu Gly Gly Asp Asp Thr Ala Val
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Tyr Tyr Cys Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe
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Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
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305 310 315 320
Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
325 330 335
Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
340 345 350
Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
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Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
370 375 380
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400
Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415
Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
420 425 430
Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
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Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460
Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
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Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe

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Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
660 665 670
Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
675 680 685
Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
690 695 700
Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
705 710 715 720
Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
725 730 735
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
740 745 750
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys
755 760 765
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
770 775 780
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
785 790 795 800

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
805 810 815
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
820 825 830
Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys
835 840 845
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
850 855 860
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
865 870 875 880
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
885 890 895
Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
900 905 910
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
915 920 925
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
930 935 940
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
945 950 955 960
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
965 970 975
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
980 985 990
Lys

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<211> 511
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<213> 人工序列
<220>
<223> 合成多肽
<400> 23

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

50 55 60

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

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

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<211> 16
<212> PRT
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<400> 24
Arg Ser Ser Gln Ser Leu Val His Ser Asp Gly Asn Thr Tyr Leu Ser
1 5 10 15

<210> 25
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 25
Arg Ile Ser Arg Arg Phe Ser
1 5

<210> 26
<211> 9
<212> PRT

<213> 人工序列
<220>
<223> 合成多肽
<400> 26
Met Gln Ser Thr His Val Pro Arg Thr
1 5
<210> 27
<211> 5
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 27
Asn Tyr Gly Met His
1 5
<210> 28
<211> 17
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 28
Val Ile Trp Tyr Asp Gly Ser Asp Lys Tyr Tyr Ala Asp Ser Val Arg
1 5 10 15
Gly
<210> 29
<211> 15
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 29
Asp Gly Tyr Asp Ile Leu Thr Gly Asn Pro Arg Asp Phe Asp Tyr
1 5 10 15
<210> 30
<211> 124
<212> PRT
<213> 人工序列
<220>

<223> 合成多肽
<400> 30

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

<210> 31
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 31

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

<210> 32
<211> 251
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 32

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

<210> 33
<211> 506
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 33

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

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

<210> 34
<211> 5
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 34

Asp Tyr Tyr Met Thr
1 5
<210> 35
<211> 17
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 35
Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15
Gly
<210> 36
<211> 8
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 36
Asp Arg Asn Ser His Phe Asp Tyr
1 5
<210> 37
<211> 11
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 37
Arg Ala Ser Gln Gly Ile Asn Thr Trp Leu Ala
1 5 10
<210> 38
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 38
Gly Ala Ser Gly Leu Gln Ser
1 5

<210> 39
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 39
Gln Gln Ala Lys Ser Phe Pro Arg Thr
1 5
<210> 40
<211> 117
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 40
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30
Tyr Met Thr Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45
Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Arg Asn Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115
<210> 41
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 41

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

<210> 42
<211> 239
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 42

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

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145 150 155 160
Ile Asn Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
165 170 175
Lys Leu Leu Ile Tyr Gly Ala Ser Gly Leu Gln Ser Gly Val Pro Ser
180 185 190
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
195 200 205
Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Lys
210 215 220
Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
225 230 235

<210> 43
<211> 494
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 43

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

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

465 470 475 480
Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
485 490

<210> 44
<211> 982
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 44

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

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

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

850 855 860

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
865 870 875 880

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
885 890 895

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
900 905 910

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
915 920 925

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
930 935 940

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
945 950 955 960

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
965 970 975

Ser Leu Ser Pro Gly Lys
980

<210> 45
<211> 982
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 45

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Tyr Met Thr Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Asn Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly

115 120 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser

130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly

145 150 155 160

Ile Asn Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro

165 170 175

Lys Leu Leu Ile Tyr Gly Ala Ser Gly Leu Gln Ser Gly Val Pro Ser

180 185 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser

195 200 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Lys

210 215 220

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Ser

225 230 235 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu

245 250 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe

260 265 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys

275 280 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala

290 295 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp

305 310 315 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu

325 330 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser

340 345 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val

355 360 365

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

370 375 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly

385 390 395 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser

405 410 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg

420 425 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
435 440 445
Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
450 455 460
Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser
465 470 475 480
Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
485 490 495
Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
500 505 510
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
515 520 525
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
530 535 540
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545 550 555 560
Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
565 570 575
Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
580 585 590
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
595 600 605
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
610 615 620
Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625 630 635 640
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
645 650 655
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
660 665 670
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
675 680 685
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
690 695 700
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705 710 715 720
Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
725 730 735
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly

740 745 750

Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu

755 760 765

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp

770 775 780

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp

785 790 795 800

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly

805 810 815

Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly

820 825 830

Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp

835 840 845

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro

850 855 860

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

865 870 875 880

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

885 890 895

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile

900 905 910

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr

915 920 925

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys

930 935 940

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys

945 950 955 960

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965 970 975

Ser Leu Ser Pro Gly Lys

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<400> 46

Ser Tyr Gly Met His

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<211> 17

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<220>

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Asp

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<211> 16

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<220>

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<210> 49

<211> 11

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 49

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<211> 7

<212> PRT

<213> 人工序列

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<223> 合成多肽

<400> 50

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<211> 9
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<211> 125
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1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Phe Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Glu Ser Val
50 55 60
Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Arg Ala Gly Ile Ile Gly Thr Ile Gly Tyr Tyr Tyr Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125
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1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Arg Leu Gly Glu Lys Tyr Thr
20 25 30
Ser Trp Tyr Gln Gln Arg Pro Gly Gln Ser Pro Leu Leu Val Ile Tyr
35 40 45
Gln Asp Thr Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Glu Ser Ser Thr Val Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Ser
100 105

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

145 150 155 160
Thr Cys Ser Gly Asp Arg Leu Gly Glu Lys Tyr Thr Ser Trp Tyr Gln
165 170 175
Gln Arg Pro Gly Gln Ser Pro Leu Leu Val Ile Tyr Gln Asp Thr Lys
180 185 190
Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn
195 200 205
Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met Asp Glu Ala Asp
210 215 220
Tyr Tyr Cys Gln Ala Trp Glu Ser Ser Thr Val Val Phe Gly Gly Gly
225 230 235 240
Thr Lys Leu Thr Val Leu Ser
245

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

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

Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr
465 470 475 480
Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr
485 490 495
Lys Leu Thr Val Leu His His His His His His
500 505

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1 5

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His Ile Phe Ser Asn Asp Glu Lys Ser Tyr Ser Thr Ser Leu Lys Asn
1 5 10 15

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<211> 14
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<400> 58
Ile Val Gly Tyr Gly Ser Gly Trp Tyr Gly Phe Phe Asp Tyr
1 5 10

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<211> 11
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<400> 59
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1 5 10
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<211> 7
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1 5
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<211> 9
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Leu Gln His Asn Ser Tyr Pro Leu Thr
1 5
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<211> 124
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20 25 30
Arg Met Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu Glu
35 40 45
Trp Leu Ala His Ile Phe Ser Asn Asp Glu Lys Ser Tyr Ser Thr Ser
50 55 60
Leu Lys Asn Arg Leu Thr Ile Ser Lys Asp Ser Ser Lys Thr Gln Val
65 70 75 80
Val Leu Thr Met Thr Asn Val Asp Pro Val Asp Thr Ala Thr Tyr Tyr

85 90 95
Cys Ala Arg Ile Val Gly Tyr Gly Ser Gly Trp Tyr Gly Phe Phe Asp
100 105 110
Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

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<212> PRT
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<400> 63

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

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

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

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

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

355 360 365

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly

370 375 380

Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro

385 390 395 400

Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser

405 410 415

Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln

420 425 430

Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu

435 440 445

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

450 455 460

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

465 470 475 480

Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr

485 490 495

Lys Leu Thr Val Leu

500

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<400> 66

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1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Leu Ser Gly Phe Ser Leu Asn Asn Ala

20 25 30

Arg Met Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu Glu

35 40 45

Trp Leu Ala His Ile Phe Ser Asn Asp Glu Lys Ser Tyr Ser Thr Ser

50 55 60

Leu Lys Asn Arg Leu Thr Ile Ser Lys Asp Ser Ser Lys Thr Gln Val

65 70 75 80

Val Leu Thr Met Thr Asn Val Asp Pro Val Asp Thr Ala Thr Tyr Tyr

85 90 95

Cys Ala Arg Ile Val Gly Tyr Gly Ser Gly Trp Tyr Gly Phe Phe Asp

100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly

115 120 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr

130 135 140

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

145 150 155 160

Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly Trp Tyr Gln

165 170 175

Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Thr

180 185 190

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

195 200 205

Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr

210 215 220

Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu Thr Phe Gly Cys Gly

225 230 235 240

Thr Lys Val Glu Ile Lys Ser Gly Gly Gly Gly Ser Glu Val Gln Leu

245 250 255

Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu

260 265 270

Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp

275 280 285

Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg

290 295 300

Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp

305 310 315 320

Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln

325 330 335

Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg

340 345 350

His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly

355 360 365

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly

370 375 380

Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro

385 390 395 400

Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser

405 410 415

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

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

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Gly Ala Ser Ser Arg Ala Thr
1 5

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Gln Gln Tyr Asp Arg Ser Pro Leu Thr
1 5
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<211> 118
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<400> 73
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu Glu Trp Ile
35 40 45
Gly Tyr Val Tyr Tyr Ser Gly Thr Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Ser Ile Ala Val Thr Gly Phe Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115
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<211> 108
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<400> 74

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

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<400> 75

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

Ser Leu Ser Pro Gly Glu Arg Val Thr Leu Ser Cys Arg Ala Ser Gln
145 150 155 160
Arg Val Asn Asn Asn Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln
165 170 175
Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile
180 185 190
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
195 200 205
Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
210 215 220
Tyr Asp Arg Ser Pro Leu Thr Phe Gly Cys Gly Thr Lys Leu Glu Ile
225 230 235 240
Lys

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<400> 76

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

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

Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp
465 470 475 480
Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
485 490 495

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<400> 77

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

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

530 535 540

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
545 550 555 560

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr
565 570 575

Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp
580 585 590

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
595 600 605

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
610 615 620

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
625 630 635 640

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
645 650 655

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
660 665 670

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
675 680 685

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
690 695 700

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
705 710 715 720

Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
725 730 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
740 745 750

Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
755 760 765

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
770 775 780

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
785 790 795 800

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
805 810 815

Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly
820 825 830

Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp
835 840 845

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

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<400> 78
Ser Tyr Gly Met His
1 5

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<211> 17
<212> PRT
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<400> 79
Val Ile Ser Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Glu Ser Val Lys
1 5 10 15
Gly

<210> 80
<211> 13

<212> PRT
<213> 人工序列
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<400> 80
Asp Arg Gly Thr Ile Phe Gly Asn Tyr Gly Leu Glu Val
1 5 10
<210> 81
<211> 16
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 81
Arg Ser Ser Gln Ser Leu Leu His Lys Asn Ala Phe Asn Tyr Leu Asp
1 5 10 15
<210> 82
<211> 7
<212> PRT
<213> 人工序列
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<400> 82
Leu Gly Ser Asn Arg Ala Ser
1 5
<210> 83
<211> 9
<212> PRT
<213> 人工序列
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<400> 83
Met Gln Ala Leu Gln Thr Pro Phe Thr
1 5
<210> 84
<211> 122
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 84

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

<210> 85
<211> 112
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 85

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

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<211> 503
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<223> 合成多肽
<400> 86

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

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

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<211> 991
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 87

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

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

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

930 935 940

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
945 950 955 960
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
965 970 975
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
980 985 990

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Asn His Ile Ile His
1 5
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<211> 17
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<400> 89
Tyr Ile Asn Pro Tyr Pro Gly Tyr His Ala Tyr Asn Glu Lys Phe Gln
1 5 10 15
Gly
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<211> 12
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<400> 90
Asp Gly Tyr Tyr Arg Asp Thr Asp Val Leu Asp Tyr
1 5 10
<210> 91
<211> 11
<212> PRT
<213> 人工序列

<220>
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<400> 91
Gln Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1 5 10
<210> 92
<211> 7
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<400> 92
Tyr Thr Ser Arg Leu His Thr
1 5
<210> 93
<211> 9
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<400> 93
Gln Gln Gly Asn Thr Leu Pro Trp Thr
1 5
<210> 94
<211> 121
<212> PRT
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<400> 94
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn His
20 25 30
Ile Ile His Trp Val Arg Gln Ala Pro Gly Gln Cys Leu Glu Trp Met
35 40 45
Gly Tyr Ile Asn Pro Tyr Pro Gly Tyr His Ala Tyr Asn Glu Lys Phe
50 55 60
Gln Gly Arg Ala Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Val Tyr

65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Gly Tyr Tyr Arg Asp Thr Asp Val Leu Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 95
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 95

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

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<211> 243
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<400> 96

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn His
20 25 30

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

<210> 97
<211> 986
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<400> 97

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

35 40 45

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

Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr
355 360 365
Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
370 375 380
Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr
385 390 395 400
Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly
405 410 415
Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly
420 425 430
Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly
435 440 445
Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu
450 455 460
Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val
465 470 475 480
Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr
485 490 495
Val Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro
500 505 510
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
515 520 525
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
530 535 540
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
545 550 555 560
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu
565 570 575
Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His
580 585 590
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
595 600 605
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
610 615 620
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
625 630 635 640
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
645 650 655
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn

660 665 670

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu

675 680 685

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val

690 695 700

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln

705 710 715 720

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly

725 730 735

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

740 745 750

Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys

755 760 765

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro

770 775 780

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys

785 790 795 800

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp

805 810 815

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu

820 825 830

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

835 840 845

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn

850 855 860

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

865 870 875 880

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

885 890 895

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr

900 905 910

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn

915 920 925

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe

930 935 940

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn

945 950 955 960

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr

965 970 975

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
980 985

<210> 98
<211> 504
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<400> 98

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

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

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<223> 合成多肽

<400> 99

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

290 295 300

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

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
610 615 620
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
625 630 635 640
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
645 650 655
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
660 665 670
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
675 680 685
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
690 695 700
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
705 710 715 720
Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly
725 730 735
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
740 745 750
Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys
755 760 765
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
770 775 780
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
785 790 795 800
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
805 810 815
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
820 825 830
Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu
835 840 845
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
850 855 860
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
865 870 875 880
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
885 890 895
Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
900 905 910
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn

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

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<400> 100
Asp Tyr Tyr Met Tyr
1 5

<210> 101
<211> 17
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 101
Ile Ile Ser Asp Ala Gly Tyr Tyr Thr Tyr Tyr Ser Asp Ile Ile Lys
1 5 10 15
Gly

<210> 102
<211> 12
<212> PRT
<213> 人工序列
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<400> 102
Gly Phe Pro Leu Leu Arg His Gly Ala Met Asp Tyr
1 5 10

<210> 103
<211> 11

<212> PRT
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<400> 103
Lys Ala Ser Gln Asn Val Asp Ala Asn Val Ala
1 5 10
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<211> 7
<212> PRT
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<223> 合成多肽
<400> 104
Ser Ala Ser Tyr Val Tyr Trp
1 5
<210> 105
<211> 9
<212> PRT
<213> 人工序列
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<400> 105
Gln Gln Tyr Asp Gln Gln Leu Ile Thr
1 5
<210> 106
<211> 121
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 106
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Glu
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30
Tyr Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Cys Leu Glu Trp Val
35 40 45
Ala Ile Ile Ser Asp Ala Gly Tyr Tyr Thr Tyr Tyr Ser Asp Ile Ile

50 55 60

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

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<211> 107
<212> PRT
<213> 人工序列
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<400> 107

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

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<211> 243
<212> PRT
<213> 人工序列
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<400> 108

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Glu
1 5 10 15

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

<210> 109
<211> 498
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 109

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Glu
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr

20 25 30

Tyr Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Ile Ile Ser Asp Gly Gly Tyr Tyr Thr Tyr Tyr Ser Asp Ile Ile
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Phe Pro Leu Leu Arg His Gly Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro
130 135 140

Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys
145 150 155 160

Ala Ser Gln Asn Val Asp Thr Asn Val Ala Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Gln Ala Pro Lys Ser Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Ser
180 185 190

Asp Val Pro Ser Arg Phe Ser Gly Ser Ala Ser Gly Thr Asp Phe Thr
195 200 205

Leu Thr Ile Ser Ser Val Gln Ser Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Gln Gln Tyr Asp Ser Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu
225 230 235 240

Glu Ile Lys Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser
245 250 255

Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala
260 265 270

Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln
275 280 285

Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr
290 295 300

Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr
305 310 315 320

Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn
325 330 335

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

<210> 110
<211> 986
<212> PRT
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<223> 合成多肽
<400> 110

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

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

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

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

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<211> 984
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<220>

<223> 合成多肽

<400> 111

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

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

595 600 605

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln

610 615 620

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

625 630 635 640

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro

645 650 655

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn

660 665 670

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu

675 680 685

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val

690 695 700

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln

705 710 715 720

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly

725 730 735

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

740 745 750

Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala

755 760 765

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro

770 775 780

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val

785 790 795 800

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val

805 810 815

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln

820 825 830

Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln

835 840 845

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala

850 855 860

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro

865 870 875 880

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

885 890 895

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser

900 905 910

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

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<211> 5
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<213> 人工序列
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<223> 合成多肽
<400> 112
Asp Tyr Tyr Met Tyr
1 5

<210> 113
<211> 17
<212> PRT
<213> 人工序列
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<400> 113
Ile Ile Ser Asp Gly Gly Tyr Tyr Thr Tyr Tyr Ser Asp Ile Ile Lys
1 5 10 15
Gly

<210> 114
<211> 12
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 114
Gly Phe Pro Leu Leu Arg His Gly Ala Met Asp Tyr
1 5 10

<210> 115

<211> 11
<212> PRT
<213> 人工序列
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<400> 115
Lys Ala Ser Gln Asn Val Asp Thr Asn Val Ala
1 5 10
<210> 116
<211> 7
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 116
Ser Ala Ser Tyr Val Tyr Trp
1 5
<210> 117
<211> 9
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 117
Gln Gln Tyr Asp Gln Gln Leu Ile Thr
1 5
<210> 118
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 118
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Glu
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30
Tyr Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

<210> 119
<211> 107
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 119

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

<210> 120
<211> 243
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 120

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Glu

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

<210> 121
<211> 498
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 121

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Glu
1 5 10 15

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

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

<210> 122
<211> 986
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 122

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

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

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

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

<210> 123
<211> 5
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<213> 人工序列
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<223> 合成多肽
<400> 123
Thr Tyr Ala Met Ser
1 5
<210> 124
<211> 17
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 124
Ala Ile Ser Gly Ser Gly Gly Arg Thr Phe Tyr Ala Glu Ser Val Glu
1 5 10 15
Gly
<210> 125
<211> 11
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 125
His Asp Tyr Ser Asn Tyr Pro Tyr Phe Asp Tyr
1 5 10
<210> 126
<211> 12
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 126
Arg Ala Ser Gln Ser Val Arg Ser Thr Tyr Leu Ala
1 5 10
<210> 127
<211> 7
<212> PRT
<213> 人工序列
<220>

<223> 合成多肽
<400> 127
Gly Ala Ser Ser Arg Ala Thr
1 5
<210> 128
<211> 9
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 128
Gln Gln Tyr Gly Asp Leu Pro Phe Thr
1 5
<210> 129
<211> 120
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 129
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Met Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Cys Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Arg Thr Phe Tyr Ala Glu Ser Val
50 55 60
Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys His Asp Tyr Ser Asn Tyr Pro Tyr Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120
<210> 130
<211> 108
<212> PRT

<213> 人工序列
<220>
<223> 合成多肽
<400> 130

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

<210> 131
<211> 986
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 131

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

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

420 425 430

Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly
435 440 445

Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu
450 455 460

Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val
465 470 475 480

Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr
485 490 495

Val Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro
500 505 510

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
515 520 525

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
530 535 540

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
545 550 555 560

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu
565 570 575

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

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
595 600 605

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
610 615 620

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
625 630 635 640

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
645 650 655

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
660 665 670

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
675 680 685

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
690 695 700

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
705 710 715 720

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly
725 730 735

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

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Gly Tyr Tyr Met His
1 5
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Trp Ile Asn Pro Asn Ser Gly Gly Thr Lys Tyr Ala Gln Lys Phe Gln
1 5 10 15
Gly
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Asp Arg Ile Thr Val Ala Gly Thr Tyr Tyr Tyr Tyr Gly Met Asp Val
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<400> 135
Arg Ala Ser Gln Gly Val Asn Asn Trp Leu Ala
1 5 10
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Thr Ala Ser Ser Leu Gln Ser
1 5

<210> 137
<211> 9
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<400> 137
Gln Gln Ala Asn Ser Phe Pro Ile Thr
1 5
<210> 138
<211> 125
<212> PRT
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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Cys Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Lys Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Arg Ile Thr Val Ala Gly Thr Tyr Tyr Tyr Tyr Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125
<210> 139
<211> 107
<212> PRT
<213> 人工序列
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<400> 139

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

<210> 140
<211> 247
<212> PRT
<213> 人工序列
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<400> 140

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

Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly Asp Arg Val Thr
145 150 155 160
Ile Thr Cys Arg Ala Ser Gln Gly Val Asn Asn Trp Leu Ala Trp Tyr
165 170 175
Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Thr Ala Ser
180 185 190
Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
195 200 205
Thr Asp Phe Thr Leu Thr Ile Arg Ser Leu Gln Pro Glu Asp Phe Ala
210 215 220
Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Ile Thr Phe Gly Cys
225 230 235 240
Gly Thr Arg Leu Glu Ile Lys
245

<210> 141
<211> 502
<212> PRT
<213> 人工序列
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<400> 141

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

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

450 455 460

Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu
465 470 475 480

Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly
485 490 495

Thr Lys Leu Thr Val Leu
500

<210> 142
<211> 990
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 142

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Cys Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Lys Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Ile Thr Val Ala Gly Thr Tyr Tyr Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met
130 135 140

Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly Asp Arg Val Thr
145 150 155 160

Ile Thr Cys Arg Ala Ser Gln Gly Val Asn Asn Trp Leu Ala Trp Tyr
165 170 175

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Thr Ala Ser
180 185 190

Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly

195 200 205

Thr Asp Phe Thr Leu Thr Ile Arg Ser Leu Gln Pro Glu Asp Phe Ala
210 215 220

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

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

Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys
260 265 270

Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn
275 280 285

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile
290 295 300

Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys
305 310 315 320

Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu
325 330 335

Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val
340 345 350

Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp
355 360 365

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
370 375 380

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu
385 390 395 400

Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly
405 410 415

Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln
420 425 430

Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe
435 440 445

Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly
450 455 460

Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu
465 470 475 480

Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly
485 490 495

Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys
500 505 510

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

820 825 830

Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val
835 840 845

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
850 855 860

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
865 870 875 880

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
885 890 895

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
900 905 910

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
915 920 925

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
930 935 940

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
945 950 955 960

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
965 970 975

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
980 985 990

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<211> 125
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<223> 合成多肽
<400> 143

Gln Val Gln Met Val Gln Ser Gly Ala Glu Val Lys Lys His Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Cys Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Lys Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

85 90 95
Ala Arg Asp Arg Ile Thr Val Ala Gly Thr Tyr Tyr Tyr Tyr Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125
<210> 144
<211> 107
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 144
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Val Asn Asn Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Thr Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Arg Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Ile
85 90 95
Thr Phe Gly Cys Gly Thr Arg Leu Glu Ile Lys
100 105
<210> 145
<211> 247
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 145
Gln Val Gln Met Val Gln Ser Gly Ala Glu Val Lys Lys His Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Cys Leu Glu Trp Met
35 40 45

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

<210> 146
<211> 502
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 146

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

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

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

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

100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly

115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met

130 135 140

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

145 150 155 160

Ile Thr Cys Arg Ala Ser Gln Gly Val Asn Asn Trp Leu Ala Trp Tyr

165 170 175

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Thr Ala Ser

180 185 190

Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly

195 200 205

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

210 215 220

Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Ile Thr Phe Gly Cys

225 230 235 240

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

245 250 255

Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys

260 265 270

Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn

275 280 285

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile

290 295 300

Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys

305 310 315 320

Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu

325 330 335

Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val

340 345 350

Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp

355 360 365

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly

370 375 380

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu

385 390 395 400

Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly

405 410 415

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

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

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Asn His Gly Met His
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Gly
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Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala Ser
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<211> 7
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Gln Asp Ala Lys Arg Pro Ser

1 5

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<211> 9

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<211> 121

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<400> 154

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

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<211> 106

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<400> 155

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

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

130 135 140

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

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

755 760 765

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
770 775 780

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

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
805 810 815

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu
820 825 830

Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His
835 840 845

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
850 855 860

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
865 870 875 880

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
885 890 895

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
900 905 910

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
915 920 925

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
930 935 940

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
945 950 955 960

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
965 970 975

Lys Ser Leu Ser Leu Ser Pro Gly Lys
980 985

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Asn His Ala Met His
1 5

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1 5 10 15
Gly
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Ala Thr Tyr Thr Thr Gly Trp Ser Tyr Phe Asp Tyr
1 5 10
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Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala Ser
1 5 10
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Gln Asp Arg Lys Arg Pro Ser
1 5
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Gln Ala Tyr Asp Ala Ser Thr Trp Val
1 5
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<211> 121
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn His
20 25 30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Cys Leu Glu Trp Val
35 40 45
Ala Gly Ile Trp Ser Glu Gly Ser Asn Lys Tyr Tyr Ala Glu Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ala Thr Tyr Thr Thr Gly Trp Ser Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120
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<400> 164
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala

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

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

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

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

785 790 795 800
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
805 810 815
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu
820 825 830
Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His
835 840 845
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
850 855 860
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
865 870 875 880
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
885 890 895
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
900 905 910
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
915 920 925
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
930 935 940
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
945 950 955 960
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
965 970 975
Lys Ser Leu Ser Leu Ser Pro Gly Lys
980 985

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<400> 166
Gly Tyr Tyr Trp Ser
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<211> 16
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<223> 合成多肽
<400> 167
Asp Ile Asp Ala Ser Gly Ser Thr Lys Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15
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<211> 12
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<400> 168
Lys Lys Tyr Ser Thr Val Trp Ser Tyr Phe Asp Asn
1 5 10
<210> 169
<211> 11
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<400> 169
Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala Ser
1 5 10
<210> 170
<211> 7
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<223> 合成多肽
<400> 170
Gln Asp Arg Lys Arg Pro Ser
1 5
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<211> 9
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<400> 171
Gln Ala Trp Gly Ser Ser Thr Ala Val

1 5

<210> 172
<211> 120
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<223> 合成多肽
<400> 172

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

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<211> 106
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<400> 173

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

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Gly Ser Ser Thr Ala Val
85 90 95
Phe Gly Cys Gly Thr Lys Leu Thr Val Leu
100 105

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

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

515 520 525

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val

530 535 540

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp

545 550 555 560

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr

565 570 575

Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp

580 585 590

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu

595 600 605

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

610 615 620

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys

625 630 635 640

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp

645 650 655

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys

660 665 670

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser

675 680 685

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser

690 695 700

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser

705 710 715 720

Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly

725 730 735

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

740 745 750

Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala

755 760 765

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro

770 775 780

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val

785 790 795 800

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val

805 810 815

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln

820 825 830

Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln
835 840 845
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
850 855 860
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
865 870 875 880
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
885 890 895
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
900 905 910
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
915 920 925
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
930 935 940
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
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Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
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Ser Leu Ser Leu Ser Pro Gly Lys
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Gly Tyr Tyr Trp Ser
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Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala Asn
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Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
20 25 30
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu Glu Trp Ile
35 40 45
Gly Asp Ile Asp Tyr Ser Gly Ser Thr Lys Tyr Asn Pro Ser Leu Lys
50 55 60
Ser Arg Val Thr Ile Ser Leu Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80
Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95
Arg Lys Lys Tyr Ser Thr Val Trp Ser Tyr Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

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

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

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

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

865 870 875 880
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
885 890 895
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
900 905 910
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
915 920 925
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
930 935 940
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
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Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
965 970 975
Ser Leu Ser Leu Ser Pro Gly Lys
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Phe Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Glu Ser Val
50 55 60
Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Arg Ala Gly Ile Ile Gly Thr Ile Gly Tyr Tyr Tyr Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly
115 120 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Glu Leu

130 135 140

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

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

755 760 765

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
770 775 780

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
785 790 795 800

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
805 810 815

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
820 825 830

Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu
835 840 845

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
850 855 860

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
865 870 875 880

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
885 890 895

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
900 905 910

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
915 920 925

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
930 935 940

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
945 950 955 960

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
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His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
980 985

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr

20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

35 40 45

Ala Phe Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Glu Ser Val

50 55 60

Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

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

85 90 95

Ala Arg Arg Ala Gly Ile Ile Gly Thr Ile Gly Tyr Tyr Tyr Gly Met

100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly

115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Glu Leu

130 135 140

Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln Thr Ala Ser Ile

145 150 155 160

Thr Cys Ser Gly Asp Arg Leu Gly Glu Lys Tyr Thr Ser Trp Tyr Gln

165 170 175

Gln Arg Pro Gly Gln Ser Pro Leu Leu Val Ile Tyr Gln Asp Thr Lys

180 185 190

Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn

195 200 205

Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met Asp Glu Ala Asp

210 215 220

Tyr Tyr Cys Gln Ala Trp Glu Ser Ser Thr Val Val Phe Gly Gly Gly

225 230 235 240

Thr Lys Leu Thr Val Leu Ser Gly Gly Gly Gly Ser Glu Val Gln Leu

245 250 255

Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu

260 265 270

Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp

275 280 285

Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg

290 295 300

Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp

305 310 315 320

Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln

325 330 335

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

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

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
965 970 975
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
980 985

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

Tyr Tyr Cys Gln Ala Trp Glu Ser Ser Thr Val Val Phe Gly Cys Gly
225 230 235 240
Thr Lys Leu Thr Val Leu Ser Gly Gly Gly Gly Ser Glu Val Gln Leu
245 250 255
Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu
260 265 270
Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp
275 280 285
Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg
290 295 300
Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
305 310 315 320
Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
325 330 335
Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
340 345 350
His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly
355 360 365
Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
370 375 380
Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro
385 390 395 400
Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser
405 410 415
Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln
420 425 430
Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu
435 440 445
Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys
450 455 460
Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr
465 470 475 480
Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr
485 490 495
Lys Leu Thr Val Leu
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<223> 合成多肽

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

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Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val

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

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Thr Cys Ser Gly Asp Arg Leu Gly Glu Lys Tyr Thr Ser Trp Tyr Gln

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His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly
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Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Gly
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Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
770 775 780
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr

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

50 55 60

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

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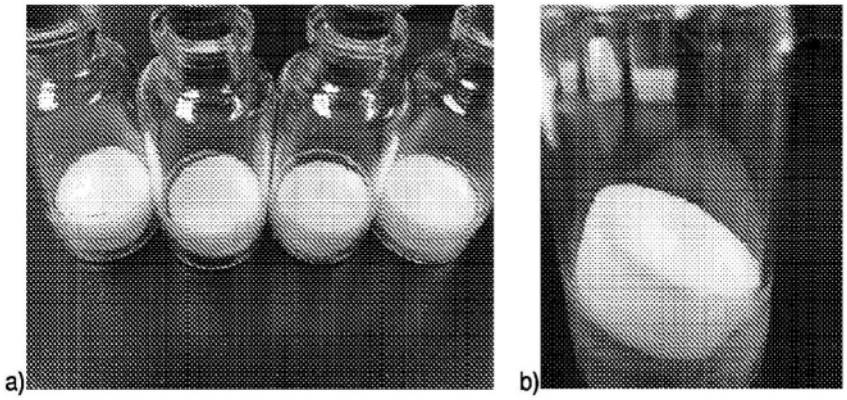


图1.使用加速循环的宏观的产物饼质量。

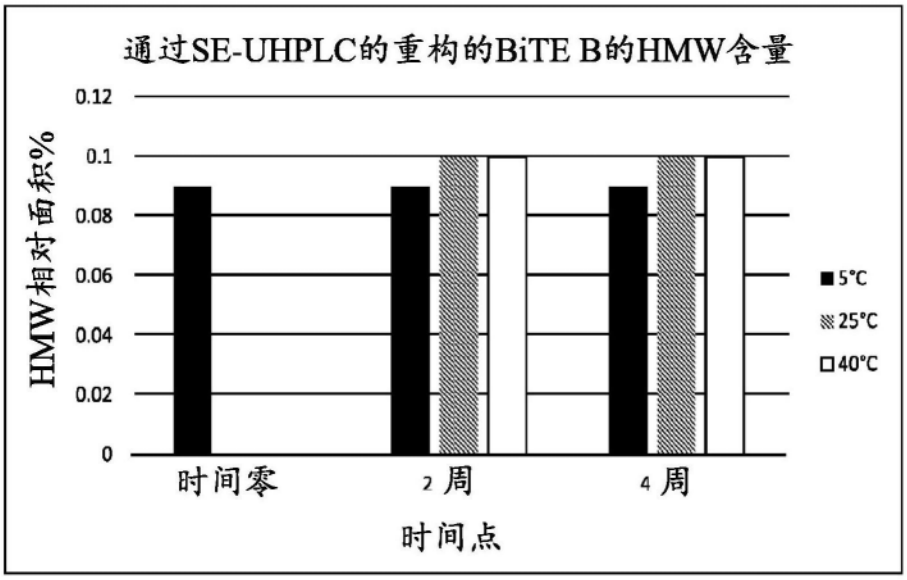


图2.通过SE-UHPLC的干燥产物饼的聚集体物质。