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(54)发明名称

用于治疗高同型半胱氨酸血症和同型胱胺酸尿症患者的人类酶介导的同型半胱氨酸耗竭

(57)摘要

描述了与具有同型(半)胱氨酸酶活性的改良蛋白的工程化有关的方法和组合物。例如,公开了包含一个或多个氨基酸取代并且能够降解同型(半)胱氨酸的经修饰的胱硫醚-γ-裂解酶(CGL)。此外,提供了使用所公开的酶或核酸,利用同型(半)胱氨酸耗竭来治疗同型胱胺酸尿症或高同型半胱氨酸血症的组合物和方法。

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1.一种分离的经修饰的灵长类胱硫醚-γ-裂解酶(CGL),其至少包含以下相对于天然人CGL氨基酸序列(SEQ ID NO:1)的取代,其中所述经修饰的酶具有同型胱氨酸酶活性和同型半胱氨酸酶活性两者,所述取代选自由以下项组成的组:

(a)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的天冬氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸;

(b)59位的天冬酰胺、119位的亮氨酸、336位的天冬氨酸和339位的缬氨酸;

(c)59位的天冬酰胺、63位的亮氨酸、91位的蛋氨酸、119位的亮氨酸、268位的精氨酸、311位的甘氨酸、336位的天冬氨酸、339位的缬氨酸和353位的丝氨酸;

(d)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的亮氨酸、268位的精氨酸、311位的甘氨酸、336位的天冬氨酸、339位的缬氨酸和353位的丝氨酸;

(e)59位的天冬酰胺、63位的亮氨酸、91位的蛋氨酸、119位的丙氨酸、268位的精氨酸、311位的甘氨酸、336位的天冬氨酸、339位的缬氨酸和353位的丝氨酸;

(f)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的丙氨酸、268位的精氨酸、311位的甘氨酸、336位的天冬氨酸、339位的缬氨酸和353位的丝氨酸;

(g)59位的天冬酰胺、119位的亮氨酸、336位的谷氨酸和339位的缬氨酸;

(h)59位的天冬酰胺、63位的亮氨酸、91位的蛋氨酸、119位的亮氨酸、268位的精氨酸、311位的甘氨酸、336位的谷氨酸、339位的缬氨酸和353位的丝氨酸;

(i)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的亮氨酸、268位的精氨酸、311位的甘氨酸、336位的谷氨酸、339位的缬氨酸和353位的丝氨酸;

(j)59位的天冬酰胺、63位的亮氨酸、91位的蛋氨酸、119位的亮氨酸、268位的精氨酸、311位的甘氨酸、336位的谷氨酸、339位的缬氨酸和353位的丝氨酸;

(i)59位的天冬酰胺、63位的亮氨酸、91位的蛋氨酸、119位的丙氨酸、268位的精氨酸、311位的甘氨酸、336位的谷氨酸、339位的缬氨酸和353位的丝氨酸;

(k)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的丙氨酸、268位的精氨酸、311位的甘氨酸、336位的谷氨酸、339位的缬氨酸和353位的丝氨酸;

(l)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的组氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸;以及

(m)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的甘氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸。

2.如权利要求1所述的酶,其中所述取代包括59位的天冬酰胺、119位的亮氨酸、336位的天冬氨酸和339位的缬氨酸。

3.如权利要求2所述的酶,其中所述取代进一步包括63位的亮氨酸、91位的蛋氨酸、268位的精氨酸、311位的甘氨酸和353位的丝氨酸。

4.如权利要求1所述的酶,其中所述取代包括59位的天冬酰胺、119位的亮氨酸、336位的谷氨酸和339位的缬氨酸。

5.如权利要求4所述的酶,其中所述取代进一步包括63位的亮氨酸、91位的蛋氨酸、268位的精氨酸、311位的甘氨酸和353位的丝氨酸。

6.如权利要求1所述的酶,其中所述取代包括59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的天冬氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨

酸。

7.如权利要求1所述的酶，其中所述取代包括59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的组氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸。

8.如权利要求1所述的酶，其中所述取代包括59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的甘氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸。

9.如权利要求1所述的酶，其中所述经修饰的CGL酶是经修饰的苏门答腊猩猩CGL酶。

10.如权利要求9所述的酶，其中所述经修饰的苏门答腊猩猩CGL酶包含选自由以下项组成的组的取代：

(a)V59I、S63L、L91M、R119D、K268R、T311G、E339V和V353S；

(b)V59N、R119L、T336D和E339V；

(c)V59N、S63L、L91M、R119L、K268R、T311G、T336D、E339V和V353S；

(d)V59I、S63L、L91M、R119L、K268R、T311G、T336D、E339V和V353S；

(e)V59N、S63L、L91M、R119A、K268R、T311G、T336D、E339V和V353S；

(f)V59I、S63L、L91M、R119A、K268R、T311G、T336D、E339V和V353S；

(g)V59N、R119L、T336E和E339V；

(h)V59N、S63L、L91M、R119L、K268R、T311G、T336E、E339V和V353S；

(i)V59I、S63L、L91M、R119L、K268R、T311G、T336E、E339V和V353S；

(j)V59N、S63L、L91M、R119A、K268R、T311G、T336E、E339V和V353S；

(k)V59I、S63L、L91M、R119A、K268R、T311G、T336E、E339V和V353S；

(l)V59I、S63L、L91M、R119H、K268R、T311G、E339V和V353S；以及

(m)V59I、S63L、L91M、R119G、K268R、T311G、E339V和V353S。

11.如权利要求1所述的酶，其中所述经修饰的CGL酶是经修饰的人CGL酶、经修饰的食蟹猴CGL酶、经修饰的黑猩猩CGL酶或经修饰的倭黑猩猩CGL酶。

12.如权利要求11所述的酶，其中所述经修饰的人CGL酶、经修饰的食蟹猴CGL酶、经修饰的黑猩猩CGL酶或经修饰的倭黑猩猩CGL酶包含选自由以下项组成的组的取代：

(a)E59I、S63L、L91M、R119D、K268R、T311G、E339V和I353S；

(b)E59N、R119L、T336D和E339V；

(c)E59N、S63L、L91M、R119L、K268R、T311G、T336D、E339V和I353S；

(d)E59I、S63L、L91M、R119L、K268R、T311G、T336D、E339V和I353S；

(e)E59N、S63L、L91M、R119A、K268R、T311G、T336D、E339V和I353S；

(f)E59I、S63L、L91M、R119A、K268R、T311G、T336D、E339V和I353S；

(g)E59N、R119L、T336E和E339V；

(h)E59N、S63L、L91M、R119L、K268R、T311G、T336E、E339V和I353S；

(i)E59I、S63L、L91M、R119L、K268R、T311G、T336E、E339V和I353S；

(j)E59N、S63L、L91M、R119A、K268R、T311G、T336E、E339V和I353S；

(k)E59I、S63L、L91M、R119A、K268R、T311G、T336E、E339V和I353S；

(l)E59I、S63L、L91M、R119H、K268R、T311G、E339V和I353S；以及

(m)E59I、S63L、L91M、R119G、K268R、T311G、E339V和I353S。

13.如权利要求1至8中任一项所述的酶,其进一步包含异源肽片段或多糖。

14.如权利要求13所述的酶,其中所述异源肽片段是XTEN多肽、IgGFc、白蛋白或白蛋白结合肽。

15.如权利要求13所述的酶,其中所述多糖包括聚唾液酸聚合物。

16.如权利要求1-15中任一项所述的酶,其中所述酶与聚乙二醇(PEG)偶联。

17.如权利要求16所述的酶,其中所述酶经由一个或多个赖氨酸残基偶联至PEG。

18.一种核酸,其包含编码如权利要求1-14中任一项所述的酶的核苷酸序列。

19.如权利要求18所述的核酸,其中所述核酸经密码子优化,以在细菌、真菌、昆虫或哺乳动物中表达。

20.如权利要求19所述的核酸,其中所述细菌是大肠杆菌。

21.如权利要求20所述的核酸,其中所述核酸包含SEQ ID NO:64至SEQ ID NO:66中的一者。

22.一种表达载体,其包含如权利要求18或19所述的核酸。

23.一种包含如权利要求18或19所述的核酸的宿主细胞。

24.如权利要求23所述的宿主细胞,其中所述宿主细胞是细菌细胞、真菌细胞、昆虫细胞或哺乳动物细胞。

25.一种治疗制剂,其包含在药学上可接受的载体中的如权利要求1-17中任一项所述的酶或如权利要求18或19中任一项所述的核酸。

26.一种治疗患有同型胱氨酸尿症或高同型半胱氨酸血症或具有发展成同型胱氨酸尿症或高同型半胱氨酸血症风险的受试者的方法,其包括向所述受试者施用治疗有效量的如权利要求25所述的制剂。

27.一种治疗患有同型胱氨酸尿症或高同型半胱氨酸血症或具有发展成同型胱氨酸尿症或高同型半胱氨酸血症风险的受试者的方法,所述方法包括:

向所述受试者施用治疗有效量的如权利要求25所述的制剂,或包含分离的、经修饰的灵长类胱硫醚-γ-裂解酶(CGL)的制剂,所述酶具有相对于天然人CGL氨基酸序列(SEQ ID NO:1)的取代,或包含编码所述经修饰的酶的核苷酸序列的核酸,所述取代选自由以下项组成的组:

(a)59位的天冬酰胺、119位的亮氨酸和339位的缬氨酸;

(b)59位的缬氨酸、119位的亮氨酸和339位的缬氨酸;

(c)59位的天冬酰胺、63位的亮氨酸、91位的蛋氨酸、119位的亮氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸;

(d)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的亮氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸;

(e)59位的天冬酰胺、63位的亮氨酸、91位的蛋氨酸、119位的丙氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸;以及

(f)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的丙氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸。

28.如权利要求27所述的方法,其中所述经修饰的CGL酶是经修饰的苏门答腊猩猩CGL

酶。

29.如权利要求28所述的方法，其中所述经修饰的苏门答腊猩猩CGL酶包含选自由以下项组成的组的取代：

(a)V59N、R119L和E339V；

(b)R119L和E339V；

(c)V59N、S63L、L91M、R119L、K268R、T311G、E339V和V353S；

(d)V59I、S63L、L91M、R119L、K268R、T311G、E339V和V353S；

(e)V59N、S63L、L91M、R119A、K268R、T311G、E339V和V353S；以及

(f)V59I、S63L、L91M、R119A、K268R、T311G、E339V和V353S。

30.如权利要求27所述的方法，其中所述经修饰的CGL酶是经修饰的人CGL酶、经修饰的食蟹猴CGL酶、经修饰的黑猩猩CGL酶，或经修饰的倭黑猩猩CGL酶。

31.如权利要求30所述的方法，其中所述经修饰的人CGL酶、经修饰的食蟹猴CGL酶，经修饰的黑猩猩CGL酶或经修饰的倭黑猩猩CGL酶包含选自由以下项组成的组的取代：

(a)E59N、R119L和E339V；

(b)E59V、R119L和E339V；

(c)E59N、S63L、L91M、R119L、K268R、T311G、E339V和I353S；

(d)E59I、S63L、L91M、R119L、K268R、T311G、E339V和I353S；

(e)E59N、S63L、L91M、R119A、K268R、T311G、E339V和I353S；以及

(f)E59I、S63L、L91M、R119A、K268R、T311G、E339V和I353S。

32.如权利要求27-31中任一项所述的方法，其中所述酶进一步包含异源肽片段。

33.如权利要求32所述的方法，其中所述异源肽片段是XTEN多肽、IgG Fc、白蛋白、白蛋白结合肽，或聚唾液酸时间延长。

34.如权利要求27-31中任一项所述的方法，其中所述酶与聚乙二醇(PEG)偶联。

35.如权利要求34所述的方法，其中所述酶通过一个或多个赖氨酸或半胱氨酸残基偶联至PEG。

36.如权利要求27所述的方法，其中所述受试者维持蛋氨酸限制饮食。

37.如权利要求27所述的方法，其中所述受试者维持正常饮食。

38.如权利要求27所述的方法，其中所述受试者是人类患者。

39.如权利要求27所述的方法，其中所述制剂通过注射、输注、连续输注、直接局部灌注沐浴靶细胞或经由导管而在静脉内、动脉内、腹膜内、病变内、关节内、前列腺内、胸膜内、气管内、玻璃体内、肌内、囊泡内、脐带内施用。

40.如权利要求27所述的方法，其中所述受试者先前已进行同型胱氨酸尿症或高同型半胱氨酸血症治疗，并且所述酶被施用以预防所述同型胱氨酸尿症或高同型半胱氨酸血症的复发。

41.如权利要求27所述的方法，其进一步包括对所述受试者施用至少第二同型胱氨酸尿症或高同型半胱氨酸血症疗法。

42.如权利要求41所述的方法，其中所述第二同型胱氨酸尿症或高同型半胱氨酸血症疗法是高剂量维生素B6或甜菜碱(N,N,N-三甲基甘氨酸)疗法。

43.如权利要求25所述的治疗制剂，其用作治疗患有同型胱氨酸尿症或高同型半胱氨

酸血症的受试者的药物。

44.如权利要求1-14中任一项所述的酶,其用于治疗受试者的同型胱氨酸尿症或高同型半胱氨酸血症。

用于治疗高同型半胱氨酸血症和同型胱胺酸尿症患者的人类酶介导的同型半胱氨酸耗竭

[0001] 相关申请的交叉引用

[0002] 本申请要求2017年5月12日提交的美国临时申请号62/505,493的优先权权益，该申请的全部内容通过引用并入本申请。

[0003] 关于联邦政府赞助的研究的声明

[0004] 本发明是在美国国立卫生研究院授予的政府拨款号R01 CA139059的支持下完成的。政府对本发明享有一定的权利。

[0005] 序列表的参考

[0006] 本申请包含序列表，该序列表已通过EFS-Web以ASCII格式提交，并且在此以其全部内容通过引用并入。所述ASCII副本创建于2018年4月24日，命名为UTFBP1138WO_ST25.txt，大小为230KB。

技术领域

[0007] 公开了具有适用于人体治疗的同型半胱氨酸降解活性和稳定性的重组工程化的灵长类酶变体。还提供了用降解同型半胱氨酸和同型胱氨酸的酶治疗同型胱胺酸尿症和高同型半胱氨酸血症的组合物和方法。

背景技术

[0008] 相关技术说明

[0009] 同型胱胺酸尿症是一种罕见病，是由涉及硫氨基酸的先天性代谢缺陷引起的。典型的同型胱氨酸尿症，最常见形式是由胱硫醚β-合酶(CBS)的缺乏引起的(Mudd等人，1964)，而非经典的同型胱氨酸尿症通常与涉及叶酸代谢的多种酶(例如，MTHFR、MTRR或MTR)的缺乏有关(Kang等人，1987)。同型胱氨酸尿症患者经常表现出血栓栓塞、认知障碍、骨质疏松和晶状体脱位(Kruger等人，2003)。患者还患有高同型半胱氨酸血症，其中血清同型半胱氨酸(Hcy)浓度超过15μM的病况。患有典型同型胱氨酸尿症以及一些非典型形式的患者经常表现出升高的血清蛋氨酸(Met)水平，而胱硫醚(Cth)和半胱氨酸(Cys)却水平较低(Kruger等人，2003)。据估计，全球每344,000人中就有一人受到影响，但是，在某些国家中，它的发病率要高得多。与典型同型胱氨酸尿症有关的最常见医学病症是心血管并发症，包括增加的血凝块风险。其他症状包括骨骼畸变、眼内晶状体脱位以及发育和学习缺陷。

[0010] 当前可用于治疗典型同型胱氨酸尿症的方法包括蛋氨酸限制饮食以及高剂量的维生素B6和甜菜碱(N,N,N-三甲基甘氨酸)，后者降低同型半胱氨酸水平。这些治疗专注于防止Hcy的积累，并且显示出中等至有限的功效(Walter等人，1998)。尽管这些疗法对某些患者可能是有效的，但由于推动该疾病的基因突变的变化，反应明显波动。结果，就有机会开发一种通过降低血液中同型胱氨酸水平，使其回到正常范围来满足所有患者需求的疗法。因此，需要用于治疗这些患者的新方法和组合物。

发明内容

[0011] 公开了利用工程化人胱硫醚-γ-裂解酶(CGL)来有效降解同型(半)胱氨酸的方

法，使得通过降解过量的血清同型(半)胱氨酸并提供细胞内同型(半)胱氨酸的水槽来治疗同型胱胺酸尿症和高同型半胱氨酸血症患者的合适疗法。该方法可将血清同型半胱氨酸水平(tHcy)降低至小于25μM的水平。

[0012] 提供了包括在基因治疗载体中施用经修饰的CGL酶、编码经修饰的CGL酶的核酸或包含经修饰的CGL酶的制剂的治疗方法，特别是治疗同型胱氨酸尿症或高同型半胱氨酸血症的受试者的方法。受试者可以是任何动物，例如小鼠。例如，受试者可以是哺乳动物、啮齿动物、灵长类动物或人类患者。该方法可以包括选择患有同型胱氨酸尿症或高同型半胱氨酸血症的患者。可结合用所述的组合物治疗使受试者或患者保持蛋氨酸限制饮食或正常饮食。

[0013] 本文提供用于治疗方法的对同型(半)胱氨酸具有催化活性的人胱硫醚-γ-裂解酶(hCGL)突变体。例如，酶变体可以具有的氨基酸序列，该氨基酸序列选自由以下项组成的组：SEQ ID NO:2-6和37-39。特别地，该变体可以衍生自人体酶，例如人胱硫醚-γ-裂解酶(CGL)。提供了包含能够降解同型(半)胱氨酸的经修饰的人CGL的多肽。该多肽在生理条件下可能能够降解同型(半)胱氨酸。例如，该多肽可显示出对L-同型胱氨酸的催化活性，直至k_{cat}/K_M达到100、95、90、85、80、75、70、65、60、55、50、45、40、35、30、25、20、15、10、9、8、7、6、5、4、3、2、1、0.9、0.8、0.7、0.6、0.5、0.4、0.3、0.2、0.1、0.05、0.01、0.005、0.001$mM^{-1}s^{-1}$或其中导出的任何范围。

[0014] 通过在人体酶胱硫醚-γ-裂解酶(CGL)中引入氨基酸取代来改造这些酶。具有氨基酸取代的变体包括SEQ ID NO:2，hCGL-E59N-R119L-E339V(hCGL-NLV)；SEQ ID NO:3，hCGL-E59N-S63L-L91M-R119L-K268R-T311G-E339V-I353S(hCGL-8mut-1)；SEQ ID NO:4，hCGL-E59I-S63L-L91M-R119L-K268R-T311G-E339V-I353S(hCGL-8mut-2)；SEQ ID NO:5，hCGL-E59N-S63L-L91M-R119A-K268R-T311G-E339V-I353S(hCGL-8mut-3)；SEQ ID NO:6，hCGL-E59I-S63L-L91M-R119A-K268R-T311G-E339V-I353S(hCGL-8mut-4)；SEQ ID NO:27，hCGL-E59N-R119L-T336D-E339V(hCGL-NLDV)；SEQ ID NO:28，hCGL-E59N-S63L-L91M-R119L-K268R-T311G-T336D-E339V-I353S(hCGL-9mutD-1)；SEQ ID NO:29，hCGL-E59I-S63L-L91M-R119L-K268R-T311G-T336D-E339V-I353S(hCGL-9mutD-2)；SEQ ID NO:30，hCGL-E59N-S63L-L91M-R119A-K268R-T311G-T336D-E339V-I353S(hCGL-9mutD-3)；SEQ ID NO:31，hCGL-E59I-S63L-L91M-R119A-K268R-T311G-T336D-E339V-I353S(hCGL-9mutD-4)；SEQ ID NO:32，hCGL-E59N-R119L-T336E-E339V(hCGL-NLEV)；SEQ ID NO:33，hCGL-E59N-S63L-L91M-R119L-K268R-T311G-T336E-E339V-I353S(hCGL-9mutE-1)；SEQ ID NO:34，hCGL-E59I-S63L-L91M-R119L-K268R-T311G-T336E-E339V-I353S(hCGL-9mutE-2)；SEQ ID NO:35，hCGL-E59N-S63L-L91M-R119A-K268R-T311G-T336E-E339V-I353S(hCGL-9mutE-3)；SEQ ID NO:36，hCGL-E59I-S63L-L91M-R119A-K268R-T311G-T336E-E339V-I353S(hCGL-9mutE-4)；SEQ ID NO:37，hCGL-E59I-S63L-L91M-R119D-K268R-T311G-E339V-I353S(突变体3)；SEQ ID NO:38，hCGL-E59I-S63L-L91M-R119H-K268R-T311G-E339V-I353S(突变体4)；以及SEQ ID NO:39，hCGL-E59I-S63L-L91M-R119G-K268R-T311G-E339V-I353S(突变体5)。

[0015] 本文所讨论的经修饰的CGL酶可表征为与未经修饰的CGL酶(例如，天然CGL酶)相比具有一定百分比的同一性。例如，未经修饰的CGL酶可以是天然灵长类胱硫醚酶(即，胱硫醚-γ-裂解酶)。经修饰的CGL酶的未经修饰部分(即，经修饰的CGL酶的序列，不包括SEQ ID

NO:1的59位、63位、91位、119位、268位、311位、336位、339位和/或353位的氨基酸以及其SEQ ID No:7-10的同源位任何取代，参见图6)和天然CGL酶之间的同一性百分比可以是至少90％、95％、96％、97％、98％、99％或100％(或其中可导出的任何范围)。还考虑到，与相应天然酶的未经修饰区域相比，以上讨论的同一性百分比可涉及酶的特定修饰区域。例如，经修饰的CGL酶可以包含经修饰的或突变的底物识别位点，其可以基于经修饰的或突变的底物识别位点的氨基酸序列与来自相同物种或跨物种的未经修饰的或天然的CGL酶的氨基酸序列的同一性来表征。例如，特征为与未经修饰的人CGL酶具有至少90％同一性的经修饰的人CGL酶是指经修饰的人CGL酶中至少90％的氨基酸与未经修饰的人CGL酶中的氨基酸相同。

[0016] 未修饰的CGL酶可以是天然的CGL酶，特别是人同种型或其他灵长类同种型。例如，天然人CGL酶可以具有SEQ ID NO:1.其他天然灵长类CGL酶的非限制性实例包括苏门达腊猩猩CGL(基因库ID:NP_001124635.1;SEQ ID NO:7)，食蟹猴CGL(基因库ID:AAW71993.1;SEQ ID NO:8)，黑猩猩CGL(基因库ID:XP_513486.2;SEQ ID NO:9)和倭黑猩猩CGL(基因库ID:XP_003830652.1;SEQ ID NO:10)。示例性的天然CGL酶包括与SEQ ID NOs:1或7-10具有至少90％、95％、96％、97％、98％、99％或100％同一性(或其中可导出的任何范围)的序列。

[0017] 天然CGL可以通过一种或多种其他修饰来修饰，例如化学修饰、取代、插入、缺失和/或截短。修饰可以在天然酶的底物识别位点。可以通过取代来修饰天然CGL。例如，取代的数目可以是四个、五个、六个、七个或更多。天然CGL可以在底物识别位点或可能影响底物特异性的任何位置上被修饰。修饰的多肽可以在对应于SEQ ID NO:1的E59、S63、L91、R119、K268、T311、T336、E339和/或I353的氨基酸位置或灵长类CGL的59、63、91、119、268、311、336、339和/或353的氨基酸位置具有至少一个氨基酸取代。例如，灵长类动物可以是人、苏门答腊猩猩，食蟹猴、黑猩猩或倭黑猩猩。例如，在SEQ ID NO:1中用于对SEQ ID NO:7进行E59的等效取代将修饰如SEQ ID NO:1中的缬氨酸而不是谷氨酸1.SEQ ID NO:7的另一预期取代是V353，其为如图6所示的SEQ ID NO:1的等效位置处的异亮氨酸.

[0018] 经修饰的CGL酶中的取代可以在59、63、91、119、268、311、339和/或353位氨基酸处发生，并且可以是天冬氨酸(N)、缬氨酸(V)、亮氨酸(L)、蛋氨酸(M)、精氨酸(R)、甘氨酸(G)、丙氨酸(A)或丝氨酸(S)。修饰可以是选自由以下项组成的组：E/V59N、E59I、S63L、L91M、R119L、R119A、R119D、R119H、R119G、K268R、T311G、T336D、T336E、E339V和I/V353S的一个或多个取代。取代可包含S63L、L91M、K268R、T311G、E339V和I/V353S取代。取代可包含E/V59N或E/V59I的其他取代；R119L、R119A、R119D、R119H和R119G中的任何一个；和/或T336D或T336E。

[0019] 取代基可以是人CGL的E59N、S63L、L91M、R119L、K268R、T311G、I353S和E339V的组合(例如，具有SEQ ID NO:3的氨基酸序列的经修饰的多肽，其片段或同系物)、人CGL的E59I、S63L、L91M、R119L、K268R、T311G、E339V和I353S的组合(例如，具有SEQ ID NO:4的氨基酸序列的经修饰的多肽，其片段或同系物)、人CGL的E59N、S63L、L91M、R119A、K268R、T311G、E339V和I353S的组合(例如，具有SEQ ID NO:5的氨基酸序列的经修饰的多肽，其片段或同系物)，人CGL的E59I、S63L、L91M、R119A、K268R、T311G、E339V和I353S的组合(例如，具有SEQ ID NO:6的氨基酸序列的经修饰的多肽，其片段或其同源物)，E59I、S63L、L91M、R119D、K268R、T311G、E339V和I353S的组合(例如，具有SEQ ID NO:37的氨基酸序列的经修

饰的多肽,其片段或其同源物),E59I、S63L、L91M、R119H、K268R、T311G、E339V和I353S的组合(例如,具有SEQ ID NO:38的氨基酸序列的经修饰的多肽,其片段或其同源物),E59I、S63L、L91M、R119G、K268R、T311G、E339V和I353S的组合(例如,具有SEQ ID NO:39的氨基酸序列的经修饰的多肽,其片段或其同源物),或SEQ ID NO:2-6和37-39结合T336D或T336E的这些修饰中的任一个。经修饰的CGL酶可以是苏门答腊猩猩CGL-NLMLRGVS突变体(SEQ ID NO:11)、苏门答腊猩猩CGL-ILMLRGVS突变体(SEQ ID NO:12)、苏门答腊猩猩CGL-NLMARGVS突变体(SEQ ID NO:13)、苏门答腊猩猩CGL-ILMARGVS突变体(SEQ ID NO:14)、苏门答腊猩猩CGL-ILMARGVS突变体(SEQ ID NO:40)、苏门答腊猩猩CGL-ILMARGVS突变体(SEQ ID NO:41)、苏门答腊猩猩CGL-ILMARGVS突变体(SEQ ID NO:42)、苏门答腊猩猩CGL-NLMARGVS突变体(SEQ ID NO:52)、苏门答腊猩猩CGL-NLMARGVS突变体(SEQ ID NO:53)、苏门答腊猩猩CGL-NLMARGVS突变体(SEQ ID NO:54)、食蟹猴CGL-NLMLRGVS突变体(SEQ ID NO:15)、食蟹猴CGL-ILMARGVS突变体(SEQ ID NO:16)、食蟹猴CGL-NLMLRGVS突变体(SEQ ID NO:17)、食蟹猴CGL-ILMARGVS突变体(SEQ ID NO:18)、食蟹猴CGL-ILMARGVS突变体(SEQ ID NO:43)、食蟹猴CGL-ILMARGVS突变体(SEQ ID NO:44)、食蟹猴CGL-ILMARGVS突变体(SEQ ID NO:45)、食蟹猴CGL-NLMLRGVS突变体(SEQ ID NO:55)、食蟹猴CGL-NLMLRGVS突变体(SEQ ID NO:56)、食蟹猴CGL-NLMLRGVS突变体(SEQ ID NO:57)、黑猩猩CGL-NLMLRGVS突变体(SEQ ID NO:19)、黑猩猩CGL-ILMARGVS突变体(SEQ ID NO:20)、黑猩猩CGL-NLMLRGVS突变体(SEQ ID NO:21)、黑猩猩CGL-ILMARGVS突变体(SEQ ID NO:22)、黑猩猩CGL-ILMARGVS突变体(SEQ ID NO:46)、黑猩猩CGL-ILMARGVS突变体(SEQ ID NO:47)、黑猩猩CGL-ILMARGVS突变体(SEQ ID NO:48)、黑猩猩CGL-NLMLRGVS突变体(SEQ ID NO:58)、黑猩猩CGL-NLMLRGVS突变体(SEQ ID NO:59)、黑猩猩CGL-NLMLRGVS突变体(SEQ ID NO:60)、倭黑猩猩CGL-NLMLRGVS突变体(SEQ ID NO:23)、倭黑猩猩CGL-ILMARGVS突变体(SEQ ID NO:24)、倭黑猩猩CGL-NLMLRGVS突变体(SEQ ID NO:25)、倭黑猩猩CGL-ILMARGVS突变体(SEQ ID NO:26)、倭黑猩猩CGL-ILMARGVS突变体(SEQ ID NO:49)、倭黑猩猩CGL-ILMARGVS突变体(SEQ ID NO:50),或倭黑猩猩CGL-ILMGRGVS突变体(SEQ ID NO:51)、倭黑猩猩CGL-NLMDRGVS突变体(SEQ ID NO:61)、倭黑猩猩CGL-NLMDRGVS突变体(SEQ ID NO:62)、倭黑猩猩CGL-NLMDRGVS突变体(SEQ ID NO:63)。

[0020] 修饰的CGL酶可以与异源氨基酸序列连接。例如,经修饰的CGL酶可以作为融合蛋白与异源氨基酸序列连接。经修饰的CGL酶可以连接至氨基酸序列,例如IgG Fc、白蛋白、白蛋白结合肽、聚唾液酸时间延长或XTEN多肽,以增加体内半衰期。

[0021] 为了增加血清稳定性,可以将经修饰的CGL酶与一种或多种聚醚分子连接。聚醚可以是聚乙二醇(PEG)。经修饰的CGL酶可以通过特定的氨基酸残基例如赖氨酸或半胱氨酸与PEG连接。为了治疗性施用,可以将包含经修饰的CGL酶的这种多肽分散在药学上可接受的载体中。

[0022] 考虑了编码经修饰的CGL酶的核酸。可以对核酸进行密码子优化以在细菌中表达,例如在大肠杆菌(E.coli)中表达。经密码子优化以在大肠杆菌中表达SEQ ID NO:37-39中提供的经修饰的CGL酶的核酸分别在SEQ ID NO:64-66中提供。SED ID NO:64-66中提供的序列编码N端6x-组氨酸标签。因此,由SEQ ID NO:64-66编码的第十二个及以下氨基酸分别对应于SEQ ID No:37-39的第二个和以下氨基酸。或者,可以对核酸进行密码子优化以在真菌(例如,酵母)、昆虫或哺乳动物中表达。还考虑了包含此类核酸的载体,例如表达载体。编

码经修饰的CGL酶的核酸可与启动子可操作地连接，所述启动子包括但不限于异源启动子。经修饰的CGL酶可以通过载体(例如，基因治疗载体)递送至靶细胞。可以通过重组DNA技术修饰此类载体，以实现经修饰的CGL编码核酸在靶细胞中的表达。这些载体可以衍生自非病毒(例如，质粒)或病毒(例如，腺病毒、腺相关病毒、逆转录病毒、慢病毒、疱疹病毒或牛痘病毒)来源的载体。非病毒载体可以与试剂复合以促进DNA跨细胞膜进入。此类非病毒载体复合物的实例包括具有聚阳离子剂的制剂，其促进DNA的缩合，以及基于脂质的递送系统。基于脂质的递送系统包括基于脂质体的核酸的递送。

[0023] 提供了包含此类载体的宿主细胞。宿主细胞可以是细菌(例如，大肠杆菌)、真菌细胞(例如，酵母)、昆虫细胞或哺乳动物细胞。

[0024] 可以将载体引入宿主细胞以表达经修饰的CGL酶。蛋白质可以任何合适的方式表达。蛋白质可以在宿主细胞中表达，使得蛋白质被糖基化。或者，蛋白质可以在宿主细胞中表达，使得蛋白质被非糖基化。

[0025] 含有经修饰的CGL酶的治疗制剂可以静脉内、皮内、动脉内、腹膜内、肌内、皮下、通过输注、连续输注、经由导管在脂质组合物(例如，脂质体)中施用。该受试者先前可能已经接受过同型胱氨酸尿症或高同型半胱氨酸血症的治疗。施用该酶以治疗或改善同型胱氨酸尿症或高同型半胱氨酸血症的复发；本文所述化合物或组合物的施用可改善与同型胱氨酸尿症和高同型半胱氨酸血症相关的一种或多种病况和/或症状。同型胱氨酸尿症的已知症状包括眼内晶状体脱位、近视、异常血凝块、骨质疏松、学习障碍、发育问题、胸部畸形、脊柱侧弯、巨幼细胞性贫血和癫痫发作。高同型半胱氨酸血症的已知症状包括血凝块、血管内衬受损、痴呆(例如，阿尔茨海默氏病)和骨折。

[0026] 该方法还可包括对受试者施用至少第二种疗法，例如第二种同型胱氨酸尿症或高同型半胱氨酸血症疗法。第二种同型胱氨酸尿症或高同型半胱氨酸血症疗法可以是大剂量维生素B6或甜菜碱(N,N,N-三甲基甘氨酸)疗法。

[0027] 提供了包含经修饰的CGL酶或编码修饰的CGL酶的核酸的组合物，用于治疗受试者中的同型胱氨酸尿症或高同型半胱氨酸血症。提供了经修饰的CGL酶或编码经修饰的CGL酶的核酸在制备用于治疗同型胱氨酸尿症或高同型半胱氨酸血症的药物中的用途。经修饰的CGL酶可以是本文公开的任何经修饰的CGL酶。

[0028] 本文还提供了：

[0029] 1.一种分离的经修饰的灵长类胱硫醚-γ-裂解酶(CGL)，其至少包含以下相对于天然人CGL氨基酸序列(SEQ ID NO:1)的取代，其中所述经修饰的酶具有同型胱氨酸酶活性和同型半胱氨酸酶活性两者，所述取代选自由以下项组成的组：

[0030] (a)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的天冬氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸；

[0031] (b)59位的天冬酰胺、119位的亮氨酸、336位的天冬氨酸和339位的缬氨酸；

[0032] (c)59位的天冬酰胺、63位的亮氨酸、91位的蛋氨酸、119位的亮氨酸、268位的精氨酸、311位的甘氨酸、336位的天冬氨酸、339位的缬氨酸和353位的丝氨酸；

[0033] (d)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的亮氨酸、268位的精氨酸、311位的甘氨酸、336位的天冬氨酸、339位的缬氨酸和353位的丝氨酸；

[0034] (e)59位的天冬酰胺、63位的亮氨酸、91位的蛋氨酸、119位的丙氨酸、268位的精氨

酸、311位的甘氨酸、336位的天冬氨酸、339位的缬氨酸和353位的丝氨酸；

[0035] (f)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的丙氨酸、268位的精氨酸、311位的甘氨酸、336位的天冬氨酸、339位的缬氨酸和353位的丝氨酸；

[0036] (g)59位的天冬酰胺、119位的亮氨酸、336位的谷氨酸和339位的缬氨酸；

[0037] (h)59位的天冬酰胺、63位的亮氨酸、91位的蛋氨酸、119位的亮氨酸、268位的精氨酸、311位的甘氨酸、336位的谷氨酸、339位的缬氨酸和353位的丝氨酸；

[0038] (i)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的亮氨酸、268位的精氨酸、311位的甘氨酸、336位的谷氨酸、339位的缬氨酸和353位的丝氨酸；

[0039] (j)59位的天冬酰胺、63位的亮氨酸、91位的蛋氨酸、119位的亮氨酸、268位的精氨酸、311位的甘氨酸、336位的谷氨酸、339位的缬氨酸和353位的丝氨酸；

[0040] (i)59位的天冬酰胺、63位的亮氨酸、91位的蛋氨酸、119位的丙氨酸、268位的精氨酸、311位的甘氨酸、336位的谷氨酸、339位的缬氨酸和353位的丝氨酸；

[0041] (k)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的丙氨酸、268位的精氨酸、311位的甘氨酸、336位的谷氨酸、339位的缬氨酸和353位的丝氨酸；

[0042] (l)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的组氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸；以及

[0043] (m)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的甘氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸。

[0044] 2.如权利要求1所述的酶，其中所述取代包括59位的天冬酰胺、119位的亮氨酸、336位的天冬氨酸和339位的缬氨酸。

[0045] 3.如权利要求2所述的酶，其中所述取代进一步包括63位的亮氨酸、91位的蛋氨酸、268位的精氨酸、311位的甘氨酸和353位的丝氨酸。

[0046] 4.如权利要求1所述的酶，其中所述取代包括59位的天冬酰胺、119位的亮氨酸、336位的谷氨酸和339位的缬氨酸。

[0047] 5.如权利要求4所述的酶，其中所述取代进一步包括63位的亮氨酸、91位的蛋氨酸、268位的精氨酸、311位的甘氨酸和353位的丝氨酸。

[0048] 6.如权利要求1所述的酶，其中所述取代包括59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的天冬氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸。

[0049] 7.如权利要求1所述的酶，其中所述取代包括59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的组氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸。

[0050] 8.如权利要求1所述的酶，其中所述取代包括59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的甘氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸。

[0051] 9.如权利要求1所述的酶，其中所述经修饰的CGL酶是经修饰的苏门答腊猩猩CGL酶。

[0052] 10.如权利要求9所述的酶，其中所述经修饰的苏门答腊猩猩CGL酶包含选自由以下项组成的组的取代：

[0053] (a)V59I、S63L、L91M、R119D、K268R、T311G、E339V和V353S；

[0054] (b)V59N、R119L、T336D和E339V；

[0055] (c)V59N、S63L、L91M、R119L、K268R、T311G、T336D、E339V和V353S；

[0056] (d)V59I、S63L、L91M、R119L、K268R、T311G、T336D、E339V和V353S；

[0057] (e)V59N、S63L、L91M、R119A、K268R、T311G、T336D、E339V和V353S；

[0058] (f)V59I、S63L、L91M、R119A、K268R、T311G、T336D、E339V和V353S；

[0059] (g)V59N、R119L、T336E和E339V；

[0060] (h)V59N、S63L、L91M、R119L、K268R、T311G、T336E、E339V和V353S；

[0061] (i)V59I、S63L、L91M、R119L、K268R、T311G、T336E、E339V和V353S；

[0062] (j)V59N、S63L、L91M、R119A、K268R、T311G、T336E、E339V和V353S；

[0063] (k)V59I、S63L、L91M、R119A、K268R、T311G、T336E、E339V和V353S；

[0064] (l)V59I、S63L、L91M、R119H、K268R、T311G、E339V和V353S；以及

[0065] (m)V59I、S63L、L91M、R119G、K268R、T311G、E339V和V353S。

[0066] 11.如权利要求1所述的酶，其中所述经修饰的CGL酶是经修饰的人CGL酶、经修饰的食蟹猴CGL酶、经修饰的黑猩猩CGL酶或经修饰的倭黑猩猩CGL酶。

[0067] 12.如权利要求11所述的酶，其中所述经修饰的人CGL酶、经修饰的食蟹猴CGL酶、经修饰的黑猩猩CGL酶或经修饰的倭黑猩猩CGL酶包含选自由以下项组成的组的取代：

[0068] (a)E59I、S63L、L91M、R119D、K268R、T311G、E339V和I353S；

[0069] (b)E59N、R119L、T336D和E339V；

[0070] (c)E59N、S63L、L91M、R119L、K268R、T311G、T336D、E339V和I353S；

[0071] (d)E59I、S63L、L91M、R119L、K268R、T311G、T336D、E339V和I353S；

[0072] (e)E59N、S63L、L91M、R119A、K268R、T311G、T336D、E339V和I353S；

[0073] (f)E59I、S63L、L91M、R119A、K268R、T311G、T336D、E339V和I353S；

[0074] (g)E59N、R119L、T336E和E339V；

[0075] (h)E59N、S63L、L91M、R119L、K268R、T311G、T336E、E339V和I353S；

[0076] (i)E59I、S63L、L91M、R119L、K268R、T311G、T336E、E339V和I353S；

[0077] (j)E59N、S63L、L91M、R119A、K268R、T311G、T336E、E339V和I353S；

[0078] (k)E59I、S63L、L91M、R119A、K268R、T311G、T336E、E339V和I353S；

[0079] (l)E59I、S63L、L91M、R119H、K268R、T311G、E339V和I353S；以及

[0080] (m)E59I、S63L、L91M、R119G、K268R、T311G、E339V和I353S。

[0081] 13.如权利要求1至8中任一项所述的酶，其进一步包含异源肽片段或多糖。

[0082] 14.如权利要求13所述的酶，其中所述异源肽片段是XTEN多肽、IgGFc、白蛋白或白蛋白结合肽。

[0083] 15.如权利要求13所述的酶，其中所述多糖包括聚唾液酸聚合物。

[0084] 16.如权利要求1-15中任一项所述的酶，其中所述酶与聚乙二醇(PEG)偶联。

[0085] 17.如权利要求16所述的酶，其中所述酶经由一个或多个赖氨酸残基偶联至PEG。

[0086] 18.一种核酸，其包含编码如权利要求1-14中任一项所述的酶的核苷酸序列。

[0087] 19.如权利要求18所述的核酸，其中所述核酸经密码子优化，以在细菌、真菌、昆虫或哺乳动物中表达。

[0088] 20.如权利要求19所述的核酸,其中所述细菌是大肠杆菌。

[0089] 21.如权利要求20所述的核酸,其中所述核酸包含SEQ ID NO:64至SEQ ID NO:66中的一者。

[0090] 22.一种表达载体,其包含如权利要求18或19所述的核酸。

[0091] 23.一种包含如权利要求18或19所述的核酸的宿主细胞。

[0092] 24.如权利要求23所述的宿主细胞,其中所述宿主细胞是细菌细胞、真菌细胞、昆虫细胞或哺乳动物细胞。

[0093] 25.一种治疗制剂,其包含在药学上可接受的载体中的如权利要求1-17中任一项所述的酶或如权利要求18或19中任一项所述的核酸。

[0094] 26.一种治疗患有同型胱氨酸尿症或高同型半胱氨酸血症或具有发展成同型胱氨酸尿症或高同型半胱氨酸血症风险的受试者的方法,其包括向所述受试者施用治疗有效量的如权利要求25所述的制剂。

[0095] 27.一种治疗患有同型胱氨酸尿症或高同型半胱氨酸血症或具有发展成同型胱氨酸尿症或高同型半胱氨酸血症风险的受试者的方法,所述方法包括:

[0096] 向所述受试者施用治疗有效量的如权利要求25所述的制剂,或包含分离的、经修饰的灵长类胱硫醚-γ-裂解酶(CGL)的制剂,所述酶具有相对于天然人CGL氨基酸序列(SEQ ID NO:1)的取代,或包含编码所述经修饰的酶的核苷酸序列的核酸,所述取代选自由以下项组成的组:

[0097] (a)59位的天冬酰胺、119位的亮氨酸和339位的缬氨酸;

[0098] (b)59位的缬氨酸、119位的亮氨酸和339位的缬氨酸;

[0099] (c)59位的天冬酰胺、63位的亮氨酸、91位的蛋氨酸、119位的亮氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸;

[0100] (d)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的亮氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸;

[0101] (e)59位的天冬酰胺、63位的亮氨酸、91位的蛋氨酸、119位的丙氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸;以及

[0102] (f)59位的异亮氨酸、63位的亮氨酸、91位的蛋氨酸、119位的丙氨酸、268位的精氨酸、311位的甘氨酸、339位的缬氨酸和353位的丝氨酸。

[0103] 28.如权利要求27所述的方法,其中所述经修饰的CGL酶是经修饰的苏门答腊猩猩CGL酶。

[0104] 29.如权利要求28所述的方法,其中所述经修饰的苏门答腊猩猩CGL酶包含选自由以下项组成的组的取代:

[0105] (a)V59N、R119L和E339V;

[0106] (b)R119L和E339V;

[0107] (c)V59N、S63L、L91M、R119L、K268R、T311G、E339V和V353S;

[0108] (d)V59I、S63L、L91M、R119L、K268R、T311G、E339V和V353S;

[0109] (e)V59N、S63L、L91M、R119A、K268R、T311G、E339V和V353S;以及

[0110] (f)V59I、S63L、L91M、R119A、K268R、T311G、E339V和V353S。

[0111] 30.如权利要求27所述的方法,其中所述经修饰的CGL酶是经修饰的人CGL酶、经修

饰的食蟹猴CGL酶、经修饰的黑猩猩CGL酶，或经修饰的倭黑猩猩CGL酶。

[0112] 31.如权利要求30所述的方法，其中所述经修饰的人CGL酶、经修饰的食蟹猴CGL酶，经修饰的黑猩猩CGL酶或经修饰的倭黑猩猩CGL酶包含选自由以下项组成的组的取代：

[0113] (a)E59N、R119L和E339V；

[0114] (b)E59V、R119L和E339V；

[0115] (c)E59N、S63L、L91M、R119L、K268R、T311G、E339V和I353S；

[0116] (d)E59I、S63L、L91M、R119L、K268R、T311G、E339V和I353S；

[0117] (e)E59N、S63L、L91M、R119A、K268R、T311G、E339V和I353S；以及

[0118] (f)E59I、S63L、L91M、R119A、K268R、T311G、E339V和I353S。

[0119] 32.如权利要求27-31中任一项所述的方法，其中所述酶进一步包含异源肽片段。

[0120] 33.如权利要求32所述的方法，其中所述异源肽片段是XTEN多肽、IgG Fc、白蛋白、白蛋白结合肽，或聚唾液酸时间延长。

[0121] 34.如权利要求27-31中任一项所述的方法，其中所述酶与聚乙二醇(PEG)偶联。

[0122] 35.如权利要求34所述的方法，其中所述酶通过一个或多个赖氨酸或半胱氨酸残基偶联至PEG。

[0123] 36.如权利要求27所述的方法，其中所述受试者维持蛋氨酸限制饮食。

[0124] 37.如权利要求27所述的方法，其中所述受试者维持正常饮食。

[0125] 38.如权利要求27所述的方法，其中所述受试者是人类患者。

[0126] 39.如权利要求27所述的方法，其中所述制剂通过注射、输注、连续输注、直接局部灌注沐浴靶细胞或经由导管而在静脉内、动脉内、腹膜内、病变内、关节内、前列腺内、胸膜内、气管内、玻璃体内、肌内、囊泡内、脐带内施用。

[0127] 40.如权利要求27所述的方法，其中所述受试者先前已进行同型胱氨酸尿症或高同型半胱氨酸血症治疗，并且所述酶被施用以预防所述同型胱氨酸尿症或高同型半胱氨酸血症的复发。

[0128] 41.如权利要求27所述的方法，其进一步包括对所述受试者施用至少第二同型胱氨酸尿症或高同型半胱氨酸血症疗法。

[0129] 42.如权利要求41所述的方法，其中所述第二同型胱氨酸尿症或高同型半胱氨酸血症疗法是高剂量维生素B6或甜菜碱(N,N,N-三甲基甘氨酸)疗法。

[0130] 43.如权利要求25所述的治疗制剂，其用作治疗患有同型胱氨酸尿症或高同型半胱氨酸血症的受试者的药物。

[0131] 44.如权利要求1-14中任一项所述的酶，其用于治疗受试者的同型胱氨酸尿症或高同型半胱氨酸血症。

[0132] 如本文所用，关于核酸的术语“编码(encode)或(encoding)”用于使本领域技术人员容易理解本发明。然而，这些术语可以分别与“包含(comprise)或(comprising)”互换使用。

[0133] 如本文中所使用的，就特定组分而言，“基本上不含”在本文中被用于表示未将任何特定组分故意配制成组合物和/或仅作为污染物或微量存在。因此，由组合物的任何意外污染而产生的特定组分的总量远低于0.05％，优选低于0.01％。最优选的是使用标准分析方法无法检测特定组分的组合物。

[0134] 如本说明书所使用的，“a”或“an”可指一个或多个。如在一个或多个权利要求中所使用的，当与“包含”一词一起使用时，“a”或“an”可指一个或多个。

[0135] 尽管本公开支持仅提及替代品和“和/或”的定义，在权利要求书中使用的术语“或”是指“和/或”，除非明确指出仅提及替代品或替代品相互排斥。如本文中所使用的“另一个”可表示至少第二个或更多。

[0136] 如本文所用，术语“约”是本领域普通技术人员理解的，并且将在使用它的上下文中在一定程度上变化。通常，约包含参考值的加/减10％的值的范围。

[0137] 附图简要说明

[0138] 以下附图构成本说明书的一部分并被包括，以进一步说明所述方法、化合物和组合物。

[0139] 图1-体内经修饰CGL的评估。酶以50mg/kg(腹膜内)单次给药。突变体1对应于hCGL-NLV(SEQ ID NO:2)，且突变体2对应于hCGL-8mut-4(SEQ ID NO:6)。注射前和注射后每24小时收集血清一周。

[0140] 图2-多剂量药效学。酶(hCGL-8mut-4;SEQ ID NO:6)每5天以50mg/kg(腹膜内)给药。在每次注射前和注射后24小时收集血清。

[0141] 图3-经修饰的CGL的体内治疗作用。酶(hCGL-8mut-4;SEQ ID NO:6)从出生后第10天开始，每周注射两次。顶线代表经修改的CGL。底线代表无活性的酶。

[0142] 图4-体内突变体3的评估。酶(Mutant 3;SEQ ID NO:37)一次以50mg/kg(腹膜内)的剂量给药。注射前和注射后每24小时收集血清一周。顶线代表失活酶。底线代表突变体3(SEQ ID NO:37)。

[0143] 图5-突变体3的体内治疗作用。酶(Mutant 3;SEQ ID NO:37)从出生后第10天开始，每周注射两次。

[0144] 图6-SEQ ID NO:1和7-10的序列比对。星号表示各种经修饰的CGL酶中的工程化位置。

具体实施方式

[0145] 提供了使用降解同型半胱氨酸和同型胱氨酸的经修饰的治疗性酶来治疗疾病(例如同型胱氨酸尿症和高同型半胱氨酸血症)的方法。治疗性酶包括hCGL-NLV突变体(E59N、R119L、E339V)以及相对于hCGL-NLV突变体具有改良的同型(半)胱氨酸酶活性的重组工程化人胱硫醚-γ-裂解酶(hCGL)。显示出较高催化活性的突变体需要较低浓度的治疗剂以用于患者给药。

[0146] I.定义

[0147] 如本文所用，术语“酶”和“蛋白质”和“多肽”是指包含通过肽键连接的氨基酸的化合物，并且可以互换使用。

[0148] 如本文所用，术语“融合蛋白”是指包含以非天然方式可操作地连接的蛋白质或蛋白质片段的嵌合蛋白质。

[0149] 如本文所用，术语“半衰期”(1/2-寿命)是指例如，在哺乳动物中注射后，多肽的浓度在体外(例如，如在细胞培养基中所测量的)或体内(例如，如在血清中测量的)降低一半所需的时间。测量“半衰期”的方法包括使用ELISA(酶联免疫吸附测定)格式中使用的对CGL

或PEG特异的抗体，以便根据时间测量蛋白质的物理量。与测量半衰期密切相关的其他方法包括通过任何检测方法来确定酶药物的催化活性随时间的变化，该检测方法可检测由于同型(半)胱氨酸转化为产物(例如α-酮丁酸酯、甲硫醇和/或氨水)而导致的任何底物的产生。

[0150] 术语“以可操作的组合”、“以可操作的顺序”和“可操作地连接”是指一种连接，其中所述组分处于允许它们以其预期方式起作用的关系，例如核酸序列以能够指导给定基因的转录和/或所需蛋白质分子的合成的方式连接，或氨基酸序列以产生融合蛋白的方式连接。

[0151] 术语“接头”是指充当分子桥以可操作地连接两个不同分子的化合物或部分，其中该接头的一部分可操作地连接至第一分子，并且其中该接头的另一部分可操作地连接到第二分子。

[0152] 术语“PEG化”是指与聚乙二醇(PEG)的缀合，聚乙二醇由于其高度的生物相容性和易于修饰而被广泛用作药物载体。PEG可以通过化学方法借助PEG链末端的羟基偶联(例如，共价连接)至活性剂上；然而，PEG本身局限于每个分子最多只能有两种活性剂。在不同的方法中，已经研究了PEG和氨基酸的共聚物作为新型生物材料，该材料将保留PEG的生物相容性，但是每个分子具有许多附着点(从而提供更大的载药量)的额外优势，并且可被综合设计以适合各种应用。

[0153] 术语“基因”是指DNA序列，其包含产生多肽或其前体所必需的对照和编码序列。该多肽可以由全长编码序列或该编码序列的任何部分编码，以便保留所需的酶活性。

[0154] 术语“天然”是指当从天然存在的来源分离时的基因、基因产物的典型或野生型形式，或该基因或基因产物的特征。相反，术语“经修饰的”、“变体”、“突变蛋白”或“突变体”是指与天然基因或基因产物相比时显示出序列和功能特性(即，改变的特征)修饰的基因或基因产物，其中经修饰的基因或基因产物是经过基因工程改造的，并非天然存在的。

[0155] 术语“载体”用于指一种核酸序列可插入其中以引入细胞进行复制的载体核酸分子。核酸序列可以是“外源的”，这意味着所述序列对所述载体被引入的细胞是外来的或者所述序列与细胞中的序列是同源的但位于通常找不到该核酸序列的宿主细胞核酸中。载体包括质粒、黏粒、病毒(噬菌体、动物病毒和植物病毒)和人工染色体(例如，YACs)。本领域技术人员将装备精良以通过标准重组技术来构建载体(参见例如Maniatis等人，1988和Ausubel等人，1994，这两篇文献均以引用方式并入本文)。

[0156] 术语“表达载体”是指任何类型的遗传结构，包括编码可被转录的RNA的核酸。在一些情况下，RNA分子之后被翻译成蛋白质、多肽或肽。在其他情况下，例如，在反义分子或核糖酶的生成过程中，这些序列没有被翻译。表达载体可以包含多种“控制序列”，这些“控制序列”是指特定宿主细胞中可操作连接的编码序列的转录和可能的翻译所必需的核酸序列。除了控制转录和翻译的控制序列外，载体和表达载体还可包含具有其他功能的核酸序列。

[0157] 如在此使用的，术语“治疗有效量”是指治疗组合物(即，经修饰的CGL酶或编码这种酶的核酸)在达到治疗效果的方法(即，将患者血液循环中的同型(半)胱氨酸耗竭至正常参考值或低于正常参考值的水平)中使用的量。在本申请中通篇使用的术语“治疗益处”或“治疗有效的”是指促进或增强受试者在本条件的医疗方面的福祉的任何东西。这包括但不限于，疾病症状或体征的频率或严重程度的降低，比如升高的(例如，15μmol/L以上)总同型

半胱氨酸血清水平。治疗组合物的给药剂量范围应足够大,以产生减少同型胱胺酸尿症症状的预期效果。例如,治疗组合物的治疗有效量可以是这样一个量,即当施用在生理上容许组合物时所述量足以实现血管内(血浆)经修饰的CGL酶的浓度从约0.001到约100U/mL、优选地高于0.1U/mL、和更优选地高于1.0U/mL。典型剂量可根据体重施用,范围约为1-100U/kg/天、优选约为2-25U/kg/天、更优选约为2.0-8.0U/kg/天。一个典型的量可以是5.0U/kg/天或35U/kg/周。剂量不宜过大,以免引起超高粘度综合症、肺水肿、充血性心力衰竭等不良副作用。概括而言,本领域技术人员可以根据病人的年龄、症状、性别和病情的不同来确定剂量。在出现并发症时也可以由医生来调整剂量。剂量应引起受试者血清中tHcy含量在约12至24小时内至少降低50%、至少降低60%、和至少降低70%。剂量可引起受试者血清tHcy含量在6小时内至少降低50%至70%。产生有统计学意义的反应的剂量应引起受试者血清中的tHcy含量降低到与Nygard等人(1998)公布的参考水平相差两个标准偏差以内的水平。因此,该剂量可导致受试者血清中的tHcy含量减少到低于20-25μM的水平。

[0158] 如本文所用的术语"K_M"是指酶的Michaelis-Menten常数,定义为催化反应中给定酶产生其最大速度一半时特定底物的浓度。如本文所用的术语"k_{cat}"是指每个酶位点转换成单位时间产物的底物分子的周转数或数量,且其中酶以最高效率工作。如本文所用的术语"k_{cat}/K_M"是指特异性常数,它是一种衡量酶将底物转化为产物的效率的计量单位。

[0159] 术语"胱硫醚-γ-裂解酶"(CGL或胱硫醚酶)是指任何催化胱硫醚水解为半胱氨酸的酶。如本文所用的,所属术语也考虑到胱硫醚-γ-裂解酶的灵长类形式,包括胱硫醚-γ-裂解酶的人类形式。

[0160] "治疗(Treatment和treating)"是指为获得疾病或与健康有关的状况的治疗益处而对受试者施用或应用治疗剂,或对受试者执行手术或物理疗法。例如,治疗可包括施用治疗有效量的同型(半)胱氨酸酶。

[0161] "受试者"和"患者"是指人类或非人类,如灵长类动物、哺乳动物和脊椎动物。受试者可以是人。

[0162] II.胱硫醚-γ-裂解酶

[0163] 裂解酶是一种催化各种化学键断裂,通常从而形成新的双键或新的环状结构的酶。例如,催化该反应的酶应是裂解酶:ATP→cAMP+PPi。裂解酶与其他酶的不同之处在于,它们只需要一个底物进行单向反应,而需要两个底物进行反向反应。

[0164] 许多依赖于5'-磷酸吡哆醛(PLP)的酶参与半胱氨酸、同型半胱氨酸和蛋氨酸的代谢,这些酶形成进化相关家族,被称为Cys/Met代谢PLP依赖酶。这些酶是由约400个氨基酸组成的蛋白质,PLP基团与位于多肽中心位置的赖氨酸残基相连。该家族的成员包括胱硫醚-γ-裂解酶(CGL)、胱硫醚-γ-合成酶(CGS)、胱硫醚-β-裂解酶(CBL)、蛋氨酸-γ-裂解酶(MGL),以及O-乙酰高丝氨酸(OAH)/O-乙酰-丝氨酸(OAS)硫化氢解酶(OSHS)。它们中的所有的共同特点是形成米氏复合体,从而形成外底物醛亚胺。进一步的反应过程是由特定酶的底物特异性决定的。

[0165] 例如,本发明人引入特异性突变成PLP依赖性裂解酶家族成员(诸如人类胱硫醚-γ-裂解酶),以改变其底物特异性。以这种方式,本发明人生产了具有从头合成能力的新型变体,来以高于hGGL-NLV的催化活性降解作为底物的同型(半)胱氨酸。还可以考虑对其他PLP依赖性酶进行修饰,以产生新型同型(半)胱氨酸降解活性。

[0166] CGL是一种四聚体,其催化哺乳动物转硫作用途径的最后一步(Rao等人,1990)。CGL催化L-胱硫醚转化为L-半胱氨酸、α-酮丁酸和氨。磷酸吡哆醛是这种酶的辅基。利用蛋白质工程将仅具有对同型半胱氨酸和同型胱氨酸的弱降解活性的胱硫醚酶转化为能高速降解同型半胱氨酸和同型胱氨酸的酶(美国专利号9,481,877所述,该美国专利全文以引用方式并入本文)。

[0167] III.同型(半)胱氨酸酶工程

[0168] 因为人类不产生同型(半)胱氨酸酶,所以需要为人类治疗对同型(半)胱氨酸酶进行工程化,使其具有在生理条件下降解同型(半)胱氨酸的高活性和特异性,以及在生理体液(诸如血清)中的高稳定性,并且通常为非免疫原性的,因为它们是通常引起免疫耐受性的天然蛋白质。

[0169] 由于在用pMGL(来自恶臭假单孢菌(P.putida)的MGL)进行的动物研究中观察到不期望的免疫原性效应,因此需要对人酶的同型(半)胱氨酸降解活性进行工程化。对人类蛋白质的免疫耐受性使这种酶可能是非免疫原性的或最低免疫原性的,因此可被良好耐受。

[0170] 尽管哺乳动物不具有同型(半)胱氨酸酶,但是它们具有胱硫醚-γ-裂解酶(CGL)。CGL是一种四聚体,其催化哺乳动物转硫作用途径的最后一步(Rao等人,1990)。CGL催化L-胱硫醚转化为L-半胱氨酸、α-酮丁酸和氨。人类CGL(hCGL)cDNA先前已被克隆和表达,但产量相对较低(约5mg/L培养物)(Lu等人,1992;Steegborn等人,1999)。

[0171] 因此,提供了与经诱变修饰以高效水解同型(半)胱氨酸的灵长类动物(特别是人类)胱硫醚-γ-裂解酶(CGL或胱硫醚酶)相关的方法和组合物。

[0172] 描述了经修饰的CGL酶,其表现出至少一种与未经修饰的CGL酶相当的功能活性。经修饰的CGL酶可以进一步修饰以提高血清稳定性。与未经修饰的CGL酶相比,经修饰的CGL酶包括例如具有附加优势(诸如同型(半)胱氨酸酶活性)的蛋白质。未经修饰的蛋白质或多肽可以是天然的胱硫醚-γ-裂解酶,诸如人类胱硫醚-γ-裂解酶。

[0173] 活性测定,特别是关于酶活性的测定,可以本领域技术人员熟悉的检测方法来实现,并且出于比较目的可包括例如使用经修饰的或未经修饰酶的天然和/或重组形式。例如,同型(半)胱氨酸酶活性可以通过检测因同型(半)胱氨酸转化产生的任何底物(诸如α-酮丁酸、甲硫醇和/或氨)的任何测定来确定。

[0174] 经修饰的CGL酶,可以根据其增强的同型(半)胱氨酸降解活性来鉴定。例如,可以识别未经修饰的多肽的底物识别位点。这种识别可基于结构分析或同源性分析。可能产生包括对此类底物识别位点的修饰的突变体群体。具有增强的同型(半)胱氨酸降解活性的突变体可选自该突变体群体。所需突变体的选择可包括诸如检测来自同型(半)胱氨酸降解的副产物或产物等方法。

[0175] 经修饰的CGL酶可具有氨基酸的缺失和/或取代;因此,具有缺失的酶、具有取代的酶、具有缺失和取代的酶都是经修饰的CGL酶。这些经修饰的CGL酶可进一步包括插入或添加的氨基酸,诸如融合蛋白或接头蛋白。“经修饰的缺失CGL酶”缺乏一个或多个天然酶的残基,但可具有天然酶的特异性和/或活性。经修饰的缺失CGL酶也可降低免疫原性或抗原性。经修饰的缺失CGL酶的一个示例是具有一个从至少一个抗原活性区域中缺失的氨基酸残基的酶,所述抗原活性区域是在特定生物体(诸如可以施用修饰的CGL酶的生物体的类型)中被确定为抗原活性的酶的区域。

[0176] 取代或替代变体可包含蛋白质内一个或多个位点的一个氨基酸与另一个氨基酸的交换，可被设计成调节多肽的一个或多个特性，特别是其效应器功能和/或生物利用度。取代可能是保守的，也可能不是保守的，即一个氨基酸被一个形状和电荷相似的氨基酸取代。保守的取代是本领域众所周知的，包括，例如：丙氨酸变化为丝氨酸；精氨酸变化为赖氨酸；天冬酰胺变化为谷氨酰胺或组氨酸；天门冬氨酸变化为谷氨酸；半胱氨酸变化为丝氨酸；谷氨酰胺变化为天冬酰胺；谷氨酸变化为天门冬氨酸；甘氨酸变化为脯氨酸；组氨酸变化为天冬酰胺或谷氨酰胺；异亮氨酸变化为亮氨酸或缬氨酸；亮氨酸变化为缬氨酸或异亮氨酸；赖氨酸变化为精氨酸；蛋氨酸变化为亮氨酸或异亮氨酸；苯丙氨酸变化为酪氨酸、亮氨酸或蛋氨酸；丝氨酸变化为苏氨酸；苏氨酸变化为丝氨酸；色氨酸变化为酪氨酸；酪氨酸变化为色氨酸或苯丙氨酸；缬氨酸变化为异亮氨酸或亮氨酸。

[0177] 除了缺失或取代，经修饰的CGL酶可具有残基的插入，这通常涉及在酶中添加至少一个残基。这可包括靶向肽或多肽或简单的单一残基的插入。将在下面讨论末端添加物(也称为融合蛋白)。

[0178] 术语“生物功能当量”是本领域很好理解的，并在本文中有进一步的详细定义。因此，包括具有与SEQ ID NO:1约90％或更多序列同一性，或者与本文公开的经修饰的CGL酶的氨基酸甚至约91％至约99％(包括92％、93％、94％、95％、96％、97％、98％和99％)相同的或保守取代的氨基酸的CGL酶序列，在保持酶的生物活性的前提下，使得可测量的生物活性参数(例如，同型(半)胱氨酸转化为α-酮丁酸、甲硫醇和氨水)在本文公开的经修饰的CGL酶的约20％、约15％、约10％或约5％范围内。经修饰的CGL酶在生物学功能上可与未经修饰的CGL酶相同。

[0179] 还可以理解的是，氨基酸序列和核酸序列可包括额外的残基(比如额外的N-或C-末端氨基酸或5′和3′序列)，然而，只要序列符合上述标准规定，包括在蛋白质表达方面维持生物蛋白质活性，这些序列本质上仍然是如前所述的本文公开序列之一。末端序列的添加特别适用于核酸序列，这些核酸序列，例如，可包括编码区域的5’或3’部分侧翼的各种非编码序列，或者可包括已知的在基因中存在的各种内部序列，即，内含子。

[0180] 特别地，除了三个突变位点(即E59N-R119L-E339V)外，五个氨基酸位置被发现与hCGL-NLV(SEQ ID NO:2)。这些额外位位于hCGL(SEQ ID NO:1)残基63、91、268、311、353(见图6)。这些位中的一个或多个发生S63L、L91M、K268R、T311G和I353S的突变，结合59、119和339位的残基突变，与hCGL-NLV相比，活性提高。特别地，变体中包含对应于SEQ ID NO:3，hCGL-E59N-S63L-L91M-R119L-K268R-T311G-E339V-I353S(hCGL-8mut-1)；SEQ ID NO:4，hCGL-E59I-S63L-L91M-R119L-K268R-T311G-E339V-I353S(hCGL-8mut-2)；SEQ ID NO:5，hCGL-E59N-S63L-L91M-R119A-K268R-T311G-E339V-I353S(hCGL-8mut-3)；SEQ ID NO:6，hCGL-E59I-S63L-L91M-R119A-K268R-T311G-E339V-I353S(hCGL-8mut-4)；SEQ ID NO:27，hCGL-E59N-R119L-T336D-E339V(hCGL-NLDV)；SEQ ID NO:28，hCGL-E59N-S63L-L91M-R119L-K268R-T311G-T336D-E339V-I353S(hCGL-9mutD-1)；SEQ ID NO:29，hCGL-E59I-S63L-L91M-R119L-K268R-T311G-T336D-E339V-I353S(hCGL-9mutD-2)；SEQ ID NO:30，hCGL-E59N-S63L-L91M-R119A-K268R-T311G-T336D-E339V-I353S(hCGL-9mutD-3)；SEQ ID NO:31，hCGL-E59I-S63L-L91M-R119A-K268R-T311G-T336D-E339V-I353S(hCGL-9mutD-4)；SEQ ID NO:32，hCGL-E59N-R119L-T336E-E339V(hCGL-NLEV)；SEQ ID NO:33，hCGL-E59N-

S63L-L91M-R119L-K268R-T311G-T336E-E339V-I353S(hCGL-9mutE-1);SEQ ID NO:34,hCGL-E59I-S63L-L91M-R119L-K268R-T311G-T336E-E339V-I353S(hCGL-9mutE-2);SEQ ID NO:35,hCGL-E59N-S63L-L91M-R119A-K268R-T311G-T336E-E339V-I353S(hCGL-9mutE-3);SEQ ID NO:36,hCGL-E59I-S63L-L91M-R119A-K268R-T311G-T336E-E339V-I353S(hCGL-9mutE-4);SEQ ID NO:37,hCGL-E59I-S63L-L91M-R119D-K268R-T311G-E339V-I353S(突变体3);SEQ ID NO:38,hCGL-E59I-S63L-L91M-R119H-K268R-T311G-E339V-I353S(突变体4);以及SEQ ID NO:39,hCGL-E59I-S63L-L91M-R119G-K268R-T311G-E339V-I353S(突变体5)的氨基酸取代。

[0181] IV.用于治疗的酶促同型(半)胱氨酸耗竭

[0182] 通过耗竭同型胱氨酸和/或同型半胱氨酸的新型酶,该多肽可用于治疗疾病(诸如同型胱胺酸尿症)。公开了使用含有L-(半)胱氨酸降解活性的经修饰的CGL的治疗方法。提供了具有同型(半)胱氨酸降解活性的以提高治疗效果的酶。

[0183] 提供了具有同型(半)胱氨酸降解活性的用于治疗疾病(诸如同型胱胺酸尿症)的经修饰的CGL酶。特别地,该经修饰的多肽可具有人类多肽序列,因此,在施用于人类患者时,其可预防不良的免疫原性反应,允许重复给药,提高治疗效果。

[0184] 可在如下情况下进行耗竭:哺乳动物体内血液循环中、组织培养或其他生物培养基需要同型(半)胱氨酸缺乏的体外情况下、体外操纵生物体液、细胞或组织随后回到哺乳动物患者的体内的离体手术中。在血液循环、培养基、生物体液、或细胞中进行同型(半)胱氨酸的耗竭以减少被处理的材料可获得的同型(半)胱氨酸的量,因此其包括使待耗竭的材料与同型(半)胱氨酸耗竭量的工程化酶在同型(半)胱氨酸耗竭条件下接触,以降解被接触的材料中的环境同型(半)胱氨酸。

[0185] 同型(半)胱氨酸耗竭效率因应用的不同而有很大差异,一般取决于出现在材料中的同型(半)胱氨酸的量、所需的耗竭速率和材料对暴露于同型(半)胱氨酸的耐受性。可以很容易地通过本领域公知的各种化学和生物化学方法来监测一种材料中同型(半)胱氨酸的水平以及该材料的同型(半)胱氨酸的耗竭率。本文进一步描述了示例性的同型(半)胱氨酸耗竭量,其在每毫升(mL)待处理材料中的工程化酶范围可从0.001到100个单位(U)、优选在约0.01到10U之间、更优选在约0.1到5U之间。

[0186] 同型(半)胱氨酸耗竭条件是与同型(半)胱氨酸酶的生物活性相适应的缓冲和温度条件,包括与酶相适应的温和温度、盐和pH条件,比如生理条件。示例性的条件包括约4-40℃,离子强度约为0.05-0.2M NaCl,pH约为5-9,同时包括生理条件。

[0187] 可通过施用、静脉注射或腹腔注射来完成体内接触,治疗有效量的生理上可耐受的组合物包括施用于患者的经修饰的CGL酶,从而耗竭患者血液中循环的同型(半)胱氨酸。

[0188] 该经修饰的CGL酶可以通过注射或逐渐输注的方式进行非肠道施用。经修饰的CGL酶可经静脉内、腹膜内、肌内施用,可直接注射到含有肿瘤细胞的组织中,或也可通过连接到导管上的泵施用,该导管可能含有潜在的生物传感器或同型(半)胱氨酸。

[0189] 含有经修饰的CGL酶的治疗组合物通常通过静脉内施用,例如通过注射单位剂量。当用于治疗组合物时,术语"单位剂量"是指适用于受试者的作为单一剂量的物理上分离的单位,每一单位包含可引起所需的稀释液(即载体或媒介物)有关的预期的治疗效果的预定数量的活性物质。

[0190] 该组合物以与剂量配方相适应的方式并以治疗有效量来施用。施用的量取决于待治疗的受试者、受试者系统利用活性成分的能力以及所需的治疗效果的程度。需要施用的活性成分的精确量取决于医师的判断且为每个个体所特有。但是，本文还公开了适合全身使用的剂量范围，该剂量范围取决于施用途径。还考虑了适用于初次施用和加强注射的方案，其典型做法是先给药，然后每隔一小时或多小时重复给药，然后再注射或其他施用途径。本文描述了示例性的多次施用，特别推荐持续维持经修饰的CGL酶的高血清和组织水平，反之则保持低血清和组织水平的同型(半)胱氨酸。或者，可以考虑持续静脉输液，使血液中的浓度维持在体内治疗规定的范围内。值得注意的是，用于治疗同型胱胺酸尿症和高同型半胱氨酸血症的经修饰的CGL酶的周剂量约为癌症治疗所需的周剂量的四分之一。美国专利号9,481,877。

[0191] V.共轭物

[0192] 提供的组合物和方法涉及对经修饰的CGL酶进行进一步的修饰以改进，例如通过与异源肽片段或聚合物(比如聚乙二醇)形成共轭物。经修饰的CGL酶可与PEG连接，增加酶的流体力学半径，从而增加血清持久性。所公开的多肽可以偶联到任何靶向剂上，比如能够特异性、稳定地结合到肿瘤细胞的外部受体或结合位点上的配体(美国专利公开2009/0304666)。PEG的大小在约3,000到20,000道尔顿之间，示例性的大小为5,000道尔顿。

[0193] A.融合蛋白

[0194] 在融合蛋白中，经修饰的CGL酶可以在N-或C-末端连接到异源结构域。例如，融合还可使用来自其他物种的前导序列，以允许在异源宿主中重组表达蛋白。另一种有用的融合包括蛋白质亲和标签(诸如血清白蛋白亲和标签或六组氨酸残基)或免疫活性结构域(诸如抗体表位，优选可切割地)的添加，以促进融合蛋白的纯化。非限制性亲和标签包括多组氨酸、几丁质结合蛋白(CBP)、麦芽糖结合蛋白(MBP)和谷胱甘肽-s-转移酶(GST)。

[0195] 经修饰的CGL酶可能与增加体内半衰期的肽(诸如XTEN多肽(Schellenberger等人，2009)、IgG Fc域、白蛋白或白蛋白结合肽)相连。

[0196] 产生融合蛋白的方法是本领域技术人员所熟知的。可以通过如下方式产生这类蛋白，例如，完全融合蛋白的从头合成，或编码异源结构域的DNA序列的连接以及完整融合蛋白的表达。

[0197] 通过将基因与编码肽接头(该肽接头在串联连接的多肽之间剪接)的桥接DNA片段连接起来，可以促进恢复母体蛋白功能活性的融合蛋白的产生。该接头应该具有足够的长度以允许适当折叠所生成的融合蛋白。

[0198] B.接头

[0199] 经修饰的CGL酶可以用双功能交联试剂进行化学共轭，也可以在蛋白水平上与肽接头融合。双功能交联试剂已被广泛用于各种用途，包括亲和基质的制备、各种结构的修饰和稳定、配体和受体结合位点的识别、和结构研究。合适的肽接头(诸如Gly-Ser接头)也可用于连接经修饰的CGL酶。

[0200] 携带两个相同官能团的同源双官能试剂可引起相同或不同的大分子或大分子亚基之间的交联，并将多肽配体连接到其特定的结合位点。异源双官能试剂包含两个不同的官能团。利用两个不同官能团的不同反应活性，可以选择性地和顺序地控制交联。根据官能团的特异性，可将双功能交联试剂分为氨基-、巯基-、胍基、吲哚基、羧基特异性基团等。其

中，以游离氨基基团为导向的试剂因其商业上的可用性、易于合成以及适用的温和反应条件而受到欢迎。

[0201] 一些异源双官能交联试剂包含一个初级胺反应性基团和硫醇反应性基团。在另一个示例中，描述了异源双官能交联试剂和使用该交联试剂的方法(美国专利号5,889,155，更确切地说，该美国专利全文以引用方式并入本文)。该交联试剂将亲核酰肼残基与亲电马来酰亚胺残基结合，允许(比如)醛类与游离的硫醇的偶联。该交联试剂可被修饰成交联各种官能团。

[0202] 此外，本领域技术人员已知的任何其他连接/偶联剂和/或机制可以用来结合经修饰的CGL酶，比如，抗体-抗原相互作用、亲和素-生物素键、酰胺键、酯键、硫酯键、醚键、硫醚键、磷酸酯键、磷酰胺键、酸酐键、二硫化物键、离子和疏水性相互作用、双特异性抗体和抗体片段或它们的组合。

[0203] 优选使用具有合理血液稳定性的交联剂。已知有许多类型的含有二硫键的接头可成功地用于共轭靶向和治疗/预防剂。含有空间位阻的二硫键的接头在体内可更稳定。因此，这些接头是一组连接剂。

[0204] 除了受阻交联剂，也可以按照本文的规定使用非受阻交联剂。其他有用的(不被认为包含或产生受保护的二硫键)交联剂包括SATA、SPDP和2-亚氨基硫醚(Wawrzynczak和Thorpe，1987)。这种交联剂的使用是本领域很好理解的。也可以使用柔性接头。

[0205] 一旦被化学共轭，肽通常会被纯化以从非共轭剂和其他污染物中分离共轭物。大量的纯化技术可用于提供足够纯度的共轭物，使其在临床上有用。

[0206] 基于粒度分离的纯化方法(比如凝胶过滤、凝胶渗透或高效液相色谱)通常是最常用的。其他色谱技术(比如Blue-Sepharose分离)也是可以使用的。传统的从包涵体中纯化融合蛋白的方法可以是有用的，比如使用弱洗涤剂，比如十二烷基肌氨酸钠(SLS)。

[0207] C聚乙二醇化

[0208] 公开了涉及经修饰的CGL酶的聚乙二醇化的方法和组合物。例如，该经修饰的CGL酶可以按照本文公开的方法进行聚乙二醇化。

[0209] 聚乙二醇化是聚(乙二醇)聚合物链与另一分子(通常是药物或治疗蛋白)共价连接的过程。聚乙二醇化通常是通过将PEG的反应性衍生物与目标大分子孵育来实现的。PEG与药物或治疗蛋白的共价连接可以“掩蔽”该药剂以对抗宿主免疫系统(降低的免疫原性和抗原性)、提高药剂的流体力学大小(在溶液中的大小)，这可以通过降低肾清除而延长其循环时间。聚乙二醇化还可以给疏水性药物和蛋白质提供水溶性。

[0210] 聚乙二醇化的第一步是PEG聚合物在一个或两个末端处的合适官能化。每个末端均用相同反应性部分活化的PEG称为“同源双官能的”，而如果存在的官能团不同，则PEG衍生物称为“异源双官能的”或“异源官能的”。制备PEG聚合物的化学活性或活化衍生物，以将PEG连接至所需分子。

[0211] 用于PEG衍生物的合适官能团的选择基于将偶联至PEG的分子上的可用反应性基团的类型。对于蛋白质，典型反应性氨基酸包括赖氨酸、半胱氨酸、组氨酸、精氨酸、天冬氨酸、谷氨酸、丝氨酸、苏氨酸和酪氨酸。也可以使用N-末端氨基基团和C-末端羧酸。

[0212] 用于形成第一代PEG衍生物的技术通常使PEG聚合物与可与羟基反应的基团(通常为酸酐、酰氯、氯甲酸酯和碳酸酯)反应。在第二代聚乙二醇化化学中，更有效的官能团(比

如醛、酯、酰胺等)可用于共轭。

[0213] 由于聚乙二醇化的应用已经变得越来越先进和复杂,对于用于缀合的异源双官能PEG的需求已经增加。这些异源双官能PEG非常适用于连接其中需要亲水性、柔性和生物相容性间隔区的两个实体。用于异源双官能PEG的优选端基是顺丁烯二酰亚胺、乙烯基砜、二硫吡啶、胺、羧酸和NHS酯。

[0214] 最常见的修饰剂或接头基于甲氧基PEG(mPEG)分子。其活性取决于将蛋白质修饰基团添加至醇末端。在一些情况下,聚乙二醇(PEG二醇)用作前体分子。随后在两个末端处修饰二醇,以产生异源二聚或同源二聚PEG连接分子。

[0215] 蛋白质通常在亲核位点(诸如未质子化的硫醇(半胱氨酰残基)或氨基基团处)聚乙二醇化。半胱氨酰特异性修饰试剂的示例包括PEG顺丁烯二酰亚胺、PEG碘乙酸酯、PEG硫醇和PEG乙烯基砜。所有四者均在温和条件和中性至微碱性pH下具有强半胱氨酰特异性,但各自具有一些缺陷。通过顺丁烯二酰亚胺形成的硫醚可在碱性条件下稍微不稳定,因此使用这种接头的配制选择可能存在一些限制。通过碘PEG形成的硫代氨基甲酸酯键更稳定,但游离的碘可在一些条件下修饰酪氨酸残基。PEG硫醇与蛋白硫醇形成二硫键,但这种键也可在碱性条件下不稳定。PEG-乙烯基砜反应性与顺丁烯二酰亚胺和碘PEG相比相对缓慢;然而,所形成的硫醚键极稳定。其较慢反应速率也可使PEG-乙烯基砜反应更容易控制。

[0216] 在天然半胱氨酰残基处的位点特异性聚乙二醇化很少进行,因为这些残基通常为二硫键的形式或为生物学活性所需。在另一个方面,定点诱变可用于掺入用于硫醇特异性接头的半胱氨酰聚乙二醇化位点。必须设计半胱氨酸突变,以使其可接近聚乙二醇化试剂并且在聚乙二醇化后仍具有生物学活性。

[0217] 胺特异性修饰剂包括PEG NHS酯、PEG三氟乙基磺酸酯、PEG醛、PEG异硫氰酸酯等。其均在温和条件下反应并且对氨基极具特异性。PEG NHS酯可能是一种更具反应性的试剂;然而,其高反应性可使聚乙二醇化反应在大规模下难以控制。PEG醛与氨基基团形成亚胺,随后用氰基硼氢化钠将亚胺还原为仲胺。不同于硼氢化钠,氰基硼氢化钠将不会还原二硫键。然而,这种化学品具有高度毒性并且必须谨慎地处置,特别是在其具有挥发性的较低pH下。

[0218] 由于大多数蛋白质上的多个赖氨酸残基,位点特异性聚乙二醇化具有挑战性。幸运的是,因为这些试剂与未质子化的氨基基团发生反应,所以有可能通过在较低pH下进行反应而将聚乙二醇化引向较低pK氨基基团。一般来说,α-氨基基团的pK比赖氨酸残基的ε-氨基基团小1-2个pH单位。通过在pH7或更低下使分子聚乙二醇化,通常可获得对N-末端的高选择性。然而,这仅在蛋白质的N-末端部分不为生物学活性所需的情况下可行。另外,聚乙二醇化的药代动力学有益效果通常强于体外生物学活性的显著损失,得到具有更大体内生物学活性的产物,而与聚乙二醇化化学无关。

[0219] 开发聚乙二醇化程序时需要考虑多个参数。幸运的是,参数通常不超过四个或五个。优化聚乙二醇化条件的“实验设计”方法非常有用。对于硫醇特异性聚乙二醇化反应,需要考虑的参数包括:蛋白质浓度、PEG与蛋白质之比(以摩尔计)、温度、pH、反应时间以及在一些情况下除氧气。(氧气可有助于通过蛋白质实现分子间二硫化物形成,这将降低聚乙二醇化产物的产率。)关于胺特异性修饰应考虑相同的因素(除氧气外),pH甚至可能更关键,特别是当靶向N-末端氨基基团时。

[0220] 关于胺和硫醇特异性修饰，反应条件可影响蛋白质的稳定性。这可限制温度、蛋白质浓度和pH。另外，在开始聚乙二醇化反应之前应已知PEG接头的反应性。例如，如果聚乙二醇化试剂仅有70％活性，那么所用的PEG的量应确保仅有活性的PEG分子计算在蛋白质与PEG反应化学计量中。

[0221] Ⅵ.蛋白质和肽

[0222] 提供包含至少一种蛋白质或肽(比如经修饰的CGL酶)的组合物。这些肽可包含于融合蛋白中或共轭至上文所述的试剂。

[0223] 如本文所用，蛋白质或肽通常指但不限于大于约200个氨基酸直至从基因翻译的全长序列的蛋白质；大于约100个氨基酸的多肽；和/或约3至约100个氨基酸的肽。为了方便起见，术语“蛋白质”、“多肽”、和“肽”在本文中可互换使用。

[0224] 因此，术语“蛋白质或肽”涵盖包含自然存在的蛋白质中的20种常见氨基酸中的至少一种，或至少一种经修饰的或非自然的氨基酸。

[0225] 可通过本领域技术人员已知的任何技术制备蛋白质或肽，所述技术包括通过标准分子生物技术来表达蛋白质、多肽或肽，从自然来源分离蛋白质或肽，或者化学合成蛋白质或肽。可使用本文公开的或本领域普通技术人员已知的技术扩增和/或表达用于已知基因的编码区。或者，蛋白质、多肽和肽的各种商业化制剂是本领域技术人员已知的。

[0226] VII.核酸和载体

[0227] 公开了编码经修饰的CGL酶或含有经修饰的CGL酶的融合蛋白的核酸序列。根据所用的表达系统，可基于常规方法选择核酸序列。例如，如果经修饰的CGL酶来源于人类胱硫醚酶，并且含有大肠杆菌中很少使用的多个密码子，那么其可干扰表达。因此，可使用免费软件(参见Hoover&Lubkowski，2002)来设计不含稀有密码子的编码序列，以对个别基因或其变体针对大肠杆菌表达进行密码子优化。多种载体也可用于表达所关注的蛋白质，诸如经修饰的CGL酶。示例性载体包括但不限于质粒载体、病毒载体、转座子或基于脂质体的载体。

[0228] VIII.宿主细胞

[0229] 宿主细胞可以是可转化以允许经修饰的CGL酶及其共轭物的表达和分泌的任何细胞。宿主细胞可以是细菌、哺乳动物细胞、酵母或丝状真菌。各种细菌包括埃希氏菌属(Escherichia)和芽孢杆菌属(Bacillus)。属于酵母属(Saccharomyces)、克鲁维酵母属(Kiuyveromyces)、汉逊酵母属(Hansenula)或毕赤酵母属(Pichia)的酵母将可用作适当的宿主细胞。丝状真菌的各物种均可用作表达宿主，包括以下属：曲霉属(Aspergillus)、木霉菌属(Trichoderma)、脉孢菌属(Neurospora)、青霉菌属(Penicillium)、头孢霉属(Cephalosporium)、裸绵霉属(Achlya)、柄孢壳菌属(Podospora)、内座壳属(Endothia)、毛霉属(Mucor)、旋孢腔菌属(Cochliobolus)、和梨孢属(Pyricularia)。

[0230] 可用的宿主生物的示例包括细菌，例如大肠杆菌MC1061、枯草芽孢杆菌(Bacillus subtilis)BRB1的衍生物(Sibakov等人，1984)、金黄色葡萄球菌(Staphylococcus aureus)SAI123(Lordanescu，1975)或浅青紫链球菌(Streptococcus lividans)(Hopwood等人，1985)；酵母，例如酿酒酵母(Saccharomyces cerevisiae)AH 22(Mellor等人，1983)或粟酒裂殖酵母(Schizosaccharomyces pombe)；以及丝状真菌，例如构巢曲霉(Aspergillus nidulans)、泡盛曲霉(Aspergillus awamori)(Ward，1989)或里氏木霉(Trichoderma

reesei)(Penttila等人,1987;Harkki等人,1989)。

[0231] 哺乳动物宿主细胞的示例包括中国仓鼠卵巢细胞(CHO-K1;美国典型培养物保藏中心(ATCC)No.CCL61)、大鼠垂体细胞(GH1;ATCC No.CCL82)、海拉S3细胞(ATCC No.CCL2.2)、大鼠肝癌细胞(H-4-II-E;ATCC No.CRL-1548)、SV40转化猴肾细胞(COS-1;ATCC No.CRL-1650)和鼠类胚细胞(NIH-3T3;ATCC No.CRL-1658)。前述内容是说明性的,而非限制本领域已知的多种可能的宿主生物体。原则上,所有能够分泌的宿主均可使用,无论是原核生物还是真核生物。

[0232] 表达经修饰的CGL酶和/或其融合蛋白的哺乳动物宿主细胞在通常用于培养亲本细胞系的条件下培养。一般来说,细胞在含有生理盐和营养物的通常补充有5%-10%血清(比如胎牛血清)的标准培养基(比如标准RPMI、MEM、IMEM或DMEM)中培养。培养条件也是标准的,例如培养物在37℃下静置培养或旋转培养,直至实现所需的蛋白质水平。

[0233] IX.蛋白质纯化

[0234] 蛋白质纯化技术是本领域技术人员所熟知的。这些技术在一个层面上涉及细胞、组织或器官至多肽和非多肽部分的均质化和粗分离。除非另外规定,否则可使用色谱和电泳技术进一步纯化所关注的蛋白质或多肽,以实现部分或完全纯化(或纯化至均一性)。特别适用于制备纯肽的分析方法是离子交换色谱、凝胶排阻色谱、聚丙烯酰胺凝胶电泳、亲和色谱、免疫亲和色谱、和等电点聚焦。纯化肽的特别有效方法是快速高效液相色谱(FPLC)或甚至高效液相色谱(HPLC)。

[0235] 纯化的蛋白质或肽意指可与其他组分分离的组合物,其中蛋白质或肽相对于其自然获得状态纯化至任何程度。所以,分离的或纯化的蛋白质或肽还指从其可自然存在的环境中分离的蛋白质或肽。一般来说,“纯化的”将指已进行分级以除去各种其他组分的蛋白质或肽组合物,并且该组合物实质上保持其表达的生物学活性。在使用术语“实质上纯化的”的情况下,这个名称将指组合物,其中蛋白质或肽形成组合物的主要组分,比如构成组合物中的约50%、约60%、约70%、约80%、约90%、约95%或更多的蛋白质。

[0236] 适用于蛋白质纯化的各种技术是本领域的技术人员所熟知的。这些技术例如包括用硫酸铵、PEG、抗体等沉淀,或通过热变性,然后离心;色谱步骤,比如离子交换、凝胶过滤、反相、羟磷灰石和亲和色谱;等电点聚焦;凝胶电泳;以及这些和其他技术的组合。如本领域中通常所知,进行各种纯化步骤的顺序可以改变,或者某些步骤可以省略,并且仍然是用于制备实质上纯化的蛋白质或肽的合适方法。

[0237] 用于定量蛋白质或肽的纯化程度的各种方法是本领域的技术人员已知的。这些方法例如包括确定活性级分的比活性,或通过SDS/PAGE分析来评估级分内的多肽的量。用于分析级分的纯度的优选方法是计算级分的比活性,将其与初始提取物的比活性相比较,从而计算其中的纯度程度,所述纯度程度通过“纯化倍数”来评估。当然,用于表示活性的量的实际单位取决于被选为纯化之后的特定检测技术,以及所表达的蛋白质或肽是否表现出可检测的活性。

[0238] 一般不要求始终以其最纯状态提供蛋白质或肽。实际上,可以预期,实质上不太纯的产物可能具有实用性。部分纯化可通过组合使用较少的纯化步骤或通过利用相同的一般纯化方案的不同形式来实现。例如,需要理解的是,利用HPLC装置进行的阳离子交换柱色谱通常得到大于利用低压色谱系统的相同技术的纯化“倍数”。相对纯化度较低的方法可在蛋

白质产物的总回收方面、或在维持所表达的蛋白质的活性方面具有优势。

[0239] 蛋白质或肽可以是分离的或纯化的，例如经修饰的CGL酶、含有经修饰的CGL酶的融合蛋白或聚乙二醇化后的经修饰的CGL酶。例如，His标签或亲和表位可包含于这种经修饰的CGL酶中以促进纯化。亲和色谱是依赖于待分离的物质与其可特异性结合的分子之间的特异性亲和力的色谱程序。这是受体-配体的相互作用类型。通过将一种结合配偶体共价偶联至不溶性基质来合成柱材料。然后柱材料能够从溶液特异性吸附物质。通过将条件改为不发生结合的那些条件(例如，改变的pH、离子强度、温度等)来进行洗脱。基质应该是一种在很大程度上不吸附分子的物质，并且具有广泛的化学、物理和热稳定性。配体应以不会影响其结合性质的方式偶联。配体还应提供相对紧密的结合。应该可以在不破坏样品或配体的情况下洗脱物质。

[0240] 尺寸排阻色谱(SEC)是其中溶液中的分子基于其尺寸或以更具技术性的术语——流体动力学体积来分离的色谱方法。其通常适用于大分子或大分子复合物，诸如蛋白质和工业聚合物。通常，当使用水溶液通过柱输送样品时，该技术称为凝胶过滤色谱，而当使用有机溶剂作为流动相时，则称为凝胶渗透色谱法。

[0241] SEC的基本原理是不同尺寸的粒子以不同速率通过固定相洗脱(过滤)。这使粒子的溶液基于尺寸分离。如果所有粒子同时或几乎同时加载，相同尺寸的粒子应一起洗脱。各尺寸排阻柱具有可分离的分子量范围。排阻限将分子量限定在该范围的上端，并且是分子太大而不能捕获在固定相中的限制。渗透限将分子量限定在分离范围的下端，在这里尺寸足够小的分子可以完全穿透到固定相的孔中，并且小于该分子质量的所有分子均过小以致于不能作为单一条带洗脱。

[0242] 高效液相色谱(或高压液相色谱，HPLC)是通常用于生物化学和分析化学以分离、鉴定和定量化合物的柱色谱形式。HPLC利用容纳色谱填充材料(固定相)的柱、移动流动相通过柱的泵、以及显示分子的保留时间的检测器。保留时间取决于固定相、所分析的分子、以及所用溶剂之间的相互作用而变化。

[0243] X.治疗组合物

[0244] 人类胱硫醚-γ-裂解酶基因含有大肠杆菌中很少使用的并可干扰表达的多个密码子。因此，为了优化大肠杆菌的蛋白表达，可以使用DNA-Works软件设计的密码子优化寡核苷酸来组装相应的基因(Hoover等人，2002)。每个构建体可含有N-末端NcoI限制性位点、框内N-末端His6标签和C-末端EcoRI位点，以简化克隆。在克隆至pET28a载体(Novagen)之后，含有适当的胱硫醚酶表达载体的大肠杆菌(BL21)可在37℃的含有50μg/mL卡那霉素的(TBTerrific Broth,TB)培养基中、250rpm摇瓶培养直到达到OD_{600}＝～0.5-0.6。此时，培养物可以转到25℃的振荡器中，并且用0.5mM IPTG诱导，并再表达蛋白质12h。然后可通过离心收集细胞沉淀并重悬于IMAC缓冲液(10mM $NaPO_4$/10mM咪唑/300mM NaCl，pH8)中。在通过弗氏(French)细胞压碎器裂解之后，将裂解物在4℃20,000x g下离心20min，并将所得的上清液施用于镍IMAC柱，用含有0.1％TRITONTM 114的(90-100倍柱体积)IMAC缓冲剂广泛地洗涤，用10-20个柱体积的IMAC缓冲液洗涤，然后用IMAC洗脱缓冲剂(50mM $NaPO_4$/250mM咪唑/300mM NaCl，pH8)洗脱。可以使用10,000MWCO(截留分子量)过滤装置对纯化的蛋白质进行缓冲剂液交换至100mM $NaPO_4$缓冲剂pH8.3。然后可在25℃下使用10mM PLP孵育含有酶的级分1h。可以以80:1的摩尔比将甲氧基PEG琥珀酰亚胺基羧甲基酯5000MW(JenKem

Technology)加入CGL-8mut-1,并允许在25℃下恒定搅拌反应1h。使用100,000MWCO过滤装置(Amicon)对所得的混合物进行广泛地缓冲液交换(含10％甘油的PBS),并且用0.2微米注射器式过滤器(VWR)灭菌。可在液氮中速冻酶的等分试样,并储存在-80℃下。如通过SDS-PAGE和考马斯染色所评估的,以这种方式纯化的CGL或CGL变体的均一性可以>95％。可在最终缓冲液浓度为6M的盐酸胍盐,20mM磷酸盐缓冲剂,pH值6.5的条件下,基于计算得到的消光系数λ_{280}＝29870$M^{-1}cm^{-1}$计算产率(Gill和von Hippel,1989)。

[0245] 例如,通过在37℃的最终浓度10μM的收集的人类血清中孵化酶来测试聚乙二醇化的hCGL-8mut-1的血清稳定性。在不同的时间点,对等分试样进行提取并测试,该测试使用DTNB(Ellman试剂;5,5-二硫代-双-(2-硝基苯甲酸))的检测方法,如美国专利公开2011/0200576所述,该专利通过整体引用并入本文。计算得到的聚乙二醇化的hCGL-8mut-1的半衰期($T_{0.5}$)为101±4小时。

[0246] 不旨在限制治疗性制剂的特定性质。例如,此类组合物可与生理可耐受液体、凝胶或固体载剂、稀释剂和赋形剂一起在制剂中提供。这些治疗性制剂可施用于哺乳动物,用于诸如家畜的兽医用途,以及以类似于其他治疗剂的方式施用于人类,用于临床用途。一般来说,治疗功效所需的剂量将根据施用类型和施用模式以及个别受试者的特殊需求而变化。

[0247] 此类组合物通常制备成液体溶液或悬浮液,用作注射用。合适的稀释剂和赋形剂是例如水、盐水、葡萄糖、甘油等以及它们的组合。另外,如有需要,组合物可含有少量辅助物质,诸如湿润剂或乳化剂、稳定剂或pH缓冲剂。

[0248] 在考虑临床应用的情况下,可能需要以适用于预期应用的形式制备包含蛋白质、抗体和药物的治疗组合物。一般来说,药物组合物可包含有效量的溶解或分散于药学上可接受的载体中的一种或多种经修饰的CGL变体或附加药剂。术语“治疗上或治疗上可接受的”是指分子实体和组合物当视情况而定施用于动物(例如人)时不产生不利的、过敏的或其他不良反应。含有通过本文公开的方法分离的至少一种经修饰的CGL酶、或另外的活性成分的药物组合物的制备将是本领域的技术人员已知的,如《雷明顿药物科学》(Remington's Pharmaceutical Sciences),第18版,1990所示例,该文献以引用的方式并入本文。此外,对于动物(如人)施用,应理解制剂应符合FDA生物标准办公室要求的无菌性、热原性、一般安全性和纯度标准。

[0249] 如在此使用的和本领域的普通技术人员所已知的,“药学上可接受的载剂”包括任何和所有溶剂、分散介质、涂层、表面活性剂、抗氧化剂、防腐剂(例如,抗细菌剂、抗真菌剂)、等渗剂、吸收延迟剂、盐、防腐剂、药物、药物稳定剂、凝胶、粘合剂、赋形剂、此类类似材料及其组合(参见例如《雷明顿药物科学》,第18版,1990,该文献以引用的方式并入本文)。除非任何常规载体与活性成分不相容,否则考虑其在药物组合物中的用途。

[0250] 组合物可以皮下、静脉内、动脉内、腹膜内、肌内、通过注射、输注、连续输注、经由导管、在脂质组合物(例如,脂质体)中或通过如本领域的普通技术人员应已知的其他方法或前述的任何组合(参见例如Remington's Pharmaceutical Sciences,18th Ed.,1990,该文献以引用的方式并入本文)施用。

[0251] 经修饰的多肽可以配制成游离碱、中性或盐形式的组合物。治疗上可接受的盐包括酸加成盐,例如通过蛋白质组合物的游离氨基基团形成的那些,或通过无机酸(例如,盐酸或磷酸)或有机酸(诸如乙酸、草酸、酒石酸或扁桃酸)形成的那些。通过游离羧基基团形

成的盐也可以从无机碱(例如氢氧化钠、氢氧化钾、氢氧化铵、氢氧化钙或氢氧化铁);或有机碱(诸如异丙胺、三甲胺、组氨酸或普鲁卡因)衍生。在配制时,溶液将以与剂量制剂相容的方式并且以治疗有效的这种量施用。制剂可以多种剂型施用,诸如配制用于肠胃外施用,诸如注射溶液,或用于递送至肺的气雾剂,或配制用于饮食施用,诸如药物释放胶囊等。

[0252] 适用于施用的该披露的组合物可以提供于具有或不具有惰性稀释剂的药学上可接受的载体中。除非任何常规介质、试剂、稀释剂或载体对接受者或对其中所含的组合物的治疗有效性有害,否则其在用于实践方法的可施用组合物中的用途是适当的。载剂或稀释剂的示例包括脂肪、油、水、盐水溶液、脂质、脂质体等,或它们的组合。组合物也可包含各种抗氧化剂,以延迟一种或多种组分的氧化。另外,微生物作用的预防可通过防腐剂,诸如各种抗细菌剂和抗真菌剂,包括但不限于对羟基苯甲酸酯(例如,对羟基苯甲酸甲酯、对羟基苯甲酸丙酯)、氯丁醇、苯酚、山梨酸、硫柳汞或它们的组合来实现。

[0253] 该公开的组合物与载体以任何便利和实用的方式来组合,即通过溶液、悬浮液、乳化、掺合物、封装、吸收等。

[0254] 提供了包括CGL酶、一种或多种脂质、和水性溶剂的治疗脂质媒介物组合物的用途。如在此使用的,术语“脂质”将定义为包括特征在于不溶于水并且可使用有机溶剂萃取的广泛范围的物质中的任一者。这种广泛种类的化合物是本领域的技术人员熟知的,并且当本文使用术语“脂质”时,其不限于任何特定结构。示例包括含有长链脂族烃及其衍生物的化合物。脂质可以是自然存在的或合成的(即,人工设计或产生的)。然而,脂质通常是生物物质。生物脂质是本领域熟知的,并且包括例如中性脂肪、磷脂、磷酸甘油酯、类固醇、萜烯、溶血脂质、鞘糖脂、糖脂、硫酯、具有醚和酯连接脂肪酸的脂质、可聚合脂质以及它们的组合。当然,组合物和方法还涵盖本领域的技术人员理解为脂质的不同于本文特别描述的那些的化合物。

[0255] 本领域的普通技术人员应熟悉可用于将组合物分散于脂质媒介物中的技术的范围。例如,经修饰的CGL酶或其融合蛋白可以分散于含有脂质的溶液中、用脂质溶解、用脂质乳化、与脂质混合、与脂质组合、共价连接至脂质、以悬浮液包含于脂质中、包含于胶束或脂质体中或与胶束或脂质体复合或者通过本领域的普通技术人员已知的任何方式与脂质或脂质结构缔合。分散可以或不可以引起脂质体的形成。

[0256] 施用于动物患者的组合物的实际剂量由的物理和生理因素(诸如体重、病症的严重性、所治疗的疾病的类型、先前或并行治疗介入、患者的自发病和施用途径)确定。根据剂量和施用途径,优选的剂量和/或治疗有效量的施用次数可以根据受试者的反应而变化。在任何情况下,负责施用的执业者将针对个体受试者来确定组合物中活性成分的浓度和适当剂量。

[0257] 治疗组合物可包含例如至少约0.1%的活性化合物。活性化合物可以包含例如占单位重量的约2%至约75%之间,或约25%至约60%之间,以及可从其中推导的任何范围。当然,各治疗可用组合物中的活性化合物的量可以以在化合物的任何给定单位剂量中获得的合适剂量的这种方式准备。制备此类药物制剂的本领域的技术人员将设想诸如溶解度、生物可用性、生物半衰期、施用路线、产品保存期的因素以及其他药物考虑,因此多种剂量和治疗方案可以是所期望的。

[0258] 剂量也可包含每次施用约500微克/kg体重、约1微克/kg体重、约5微克/kg体重、约

10微克/kg体重、约50微克/kg体重、约100微克/kg体重、约750毫克/kg体重或更多，以及可从其中推导的任何范围。如果每周给药，剂量可以是5mg/kg体重，或者例如，一个70kg的受试者需要350mg的蛋白质。

[0259] XI.试剂盒

[0260] 可提供试剂盒，诸如治疗试剂盒。例如，试剂盒可包含一种或多种本文所述的治疗组合物以及任选地关于其使用的说明书。试剂盒还可包含一种或多种用于实现此类组合物的施用的装置。例如，受试者试剂盒可包含治疗组合物和用于实现向目标组织直接静脉内注射组合物的导管。试剂盒可包含任选地配制为治疗组合物或冻干的经修饰的CGL酶的预填充安瓿，它与递送装置一起使用。

[0261] 试剂盒可包含具有标签的容器。合适的容器例如包括瓶、小瓶、和试管。容器可由多种材料(诸如玻璃或塑料)形成。容器可容纳包括如上所述的有效用于治疗性或非治疗性应用的经修饰的CGL酶的组合物。容器上的标签可指示诸如上文所述的组合物用于特定疗法或非治疗性应用，并且还可指示关于体内或体外使用的指导。本发明的试剂盒将通常包含上文所述的容器和一个或多个包含从商业和使用者观点来说所需的材料的其他容器，包括缓冲剂、稀释剂、过滤器、针、注射器和具有使用说明书的包装插页。

[0262] XII.实施例：

[0263] 包括以下实施例以说明本发明的优选实施方案。本领域技术人员应该理解，以下实施例中公开的技术代表本发明人发现的在本发明的实践中发挥良好作用的技术，因此可以被视为构成本发明实践的优选模式。然而，根据本公开，本领域技术人员应当理解，在不脱离本发明的精神和范围的情况下，可以对所公开的特定实施方案进行许多改变并且仍可获得相同或相似的结果。

[0264] 实施例1-使用人类胱硫醚-γ-裂解酶的变体来治疗高同型半胱氨酸血症的小鼠模型

[0265] 传统的同型胱胺酸尿症是胱硫醚-β-合成酶基因遗传缺陷引起的。代谢途径的中断导致高同型半胱氨酸血症，这是一种血清总同型半胱氨酸(tHcy)水平严重升高的病症。高胱氨酸尿症的特征包括骨骼、眼部、血管和神经系统的问题。这些症状可能是血清和细胞内同型半胱氨酸积累的结果。

[0266] 这项工作的目的是开发一种能够降解多余的血清同型半胱氨酸的新型酶治疗方法，为细胞内的同型半胱氨酸提供一个池，并创造一种治疗同型半胱氨酸尿症的新方法。人类胱硫醚-γ-裂解酶(CGL)进行工程化以降解同型半胱氨酸和同型胱氨酸。使用随机的和理性的诱变，生成CGL变体库，和通过同型半胱氨酸降解成α-丁酮酸，以与大肠杆菌的工程化菌株相比具有生长优势的遗传选择进行克隆鉴定。对CGL变体进行了动力学测试，结果如表1所示。

[0267] 使用高蛋氨酸饮食(2.5％w/w蛋氨酸，而不是正常啮齿动物饮食中出现的0.6％w/w蛋氨酸)，在小鼠中诱导高同型半胱氨酸血症，创建小鼠模型，以评估开发的酶的疗效。对高蛋氨酸饮食小鼠模型施用一个单一剂量50mg/kg(腹膜内)的经修饰的CGL在24小时内使tHcy从380±13μM显著降低到44.7±4.8μM(图1)。注意，正常小鼠的tHcy水平约是4±0.5μM。每5天一次、每次给药量50mg/kg(腹膜内)、持续30天可引起tHcy持续降低(如图2.此外，长期、频繁的给药并没有导致体重下降或任何其他毒性迹象。在饮食诱导的小鼠模型中，施

用该酶成功地耗竭了tHcy,没有副作用。高蛋氨酸饮食是一种正常的啮齿动物饮食,但含有4倍的蛋氨酸。

[0268] 为了评估经修饰的CGL(hCGL-8mut-4;突变体2;SEQ ID NO:6)的治疗效果,使用$cbs^{-/-}$小鼠品系,可导致新生儿的致命性。从第10天开始注射经修饰的CGL和灭活酶(20mg/kg Ip,每周两次),到第50天结束。在接受治疗的小鼠中,预期存在生存优势。母鼠和幼鼠的饮食中都含有甜菜碱(一种被认为可以提高疾病存活率的食物添加剂)。如图3所示经修饰的CGL(突变体2)的处理提高了幼崽的存活率,暗示了控制Hcy水平对改善病情有重要意义。

[0269] 实施例2-高特异性同型半胱氨酸/同型胱氨酸降解变体的设计和动力学特征

[0270] 随着酶活性或对同型半胱氨酸或同型胱氨酸选择性的提高,使用突变体2酶的基因编码(SEQ ID NO:6)作为一个起点来产生更多的变体。选择假设协调底物结合的活性位点残基进行饱和诱变,然后通过重叠延伸PCR(聚合酶链反应)生成相应的文库。最后组装好的PCR产物经NcoI和EcoRI消化后,用T4DNA连接酶连接到pET28a载体上。所得到的连接直接转化为大肠杆菌(B121),并在LB-卡那霉素板上进行后续筛选(如美国专利号号9,481,877所述,该美国专利全文以引用方式并入本文)。筛选到的菌落是文库理论多样性的两倍。对表现出显著活性的克隆进行分离和测序,以识别具有改善活性的突变。在R119位点发现了三个突变体(突变体3:R119D,SEQ ID NO:37;突变体4:R119H,SEQ ID NO:38;突变体5:R119G,SEQ ID NO:39),纯化至经SDS-PAGE鉴定为95%以上同一性,并在37℃、pH 7.3(表1)的100mM PBS(磷酸盐缓冲盐水)缓冲液中对蛋氨酸、半胱氨酸、胱氨酸、同型半胱氨酸和同型胱氨酸的降解能力进行动力学表征(如美国专利号9,481,877所述,该美国专利全文以引用方式并入本文)。

[0271] 表1 CGL突变体的动力学

[0272]

	K_{cat}/k_M ($s^{-1}mM^{-1}$)				
	蛋氨酸	半胱氨酸	胱氨酸	同型半胱氨酸	同型胱氨酸
野生型	ND*	0.2	0.85	0.2	ND*
突变体1	0.75	2.7	2.6	8.0	7.6
突变体2	5.3	8.5	2.1	12	21.6
突变体3	1.1	3.6	2.3	11.9	18.8
突变体4	2.7	4.7	1.9	11.7	17.7
突变体5	1.7	5.4	2.1	13.1	20.7

[0273] *ND=无数据

[0274] 实施例3-使用高同型半胱氨酸血症的饮食诱导小鼠模型的小鼠中突变体3的同型半胱氨酸药效学

[0275] 高蛋氨酸饮食(2.5%w/w,而不是例1中所述的正常0.6%w/w)被用于诱导小鼠高同型半胱氨酸血症。这些小鼠分别以50mg/kg的动物体重(腹膜内)单一剂量给予突变体3(SEQ ID NO:37)或失活酶。高蛋氨酸饮食小鼠模型中的突变体3在48小时内使tHcy从335±37μM显著降低到42±20μM(图4)。

[0276] 实施例4-用突变体3治疗高同型半胱氨酸血症小鼠模型

[0277] 为了评价突变体3的疗效(R119D;SEQ ID NO:37)(相比其蛋氨酸、半胱氨酸、胱氨

酸降解活性，显示对同型半胱氨酸/同型胱氨酸的最高底物选择性)，使用突变体3或将样品放置在沸水浴10分钟热去活化的突变体3酶对$cbs^{-/-}$幼鼠进行治疗。在出生后第10天开始注射幼鼠，剂量为25mg/kg动物体重(腹膜内施用，每周两次)，直到第50天进行最后一次治疗。母鼠和幼鼠的饮食中都含有甜菜碱(一种被认为可以提高疾病存活率的食物添加剂)。如图5中所示，与施用等量失活酶的动物相比，用活性突变体3治疗完全降低了$cbs^{-/-}$幼鼠的新生儿死亡率。

[0278] **

[0279] 鉴于本公开，可以在不进行过度实验的情况下进行和执行本文所公开和要求保护的所有方法。尽管已经根据优选实施方案描述了本发明的组合物和方法，但是对于本领域技术人员而言将显而易见的是，在不脱离本发明的概念、精神和范围的情况下，可以对本文所述的方法和对本文所述方法的步骤或对本文所述方法的步骤顺序应用改变。更具体地，将显而易见的是，在化学和生理上均相关的某些药剂可以代替本文所述的药剂，同时将获得相同或相似的结果。对于本领域技术人员显而易见的所有此类类似替代和修改都被认为落入由所附权利要求所限定的本发明的精神、范围和概念内。

[0280] 参考文献

[0281] 以下参考文献在一定程度上提供了示例性的过程或其他细节，所述示例性的过程或其他细节是对本文所述的那些过程或细节的补充，所述参考文献以引用方式明确地并入本文。

[0282] 美国专利号4,870,287

[0283] 美国专利号5,739,169

[0284] 美国专利号5,760,395

[0285] 美国专利号5,801,005

[0286] 美国专利号5,824,344

[0287] 美国专利号5,830,880

[0288] 美国专利号5,846,945

[0289] 美国专利号5,889,155

[0290] 美国专利号8,709,407

[0291] 美国专利号9,481,877

[0292] 美国专利公开2009/0304666

[0293] 美国专利公开2011/0200576

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

<210> 10
<211> 405
<212> PRT
<213> 倭黑猩猩
<400> 10

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

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

355 360 365

Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380

Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400

Ser Gly Ser His Ser
405

<210> 11
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 11

Met Gln Glu Lys Glu Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15

His Phe Ala Thr Gln Ala Ile His Val Gly Gln Glu Pro Glu Gln Trp
20 25 30

Thr Ser Arg Ala Val Val Pro Pro Ile Ser Pro Ser Val Thr Phe Lys
35 40 45

Gln Gly Ala Pro Gly Gln His Ser Gly Phe Asn Tyr Ser Arg Leu Gly
50 55 60

Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly
65 70 75 80

Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Met Ala Ala Thr Val Thr
85 90 95

Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp
100 105 110

Val Tyr Ala Gly Thr Asn Leu Tyr Phe Arg Gln Val Ala Ser Glu Phe
115 120 125

Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu
130 135 140

Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr
145 150 155 160

Asn Pro Thr Gln Lys Met Thr Asp Ile Glu Ala Cys Ala His Ile Val
165 170 175

His Lys His Gly Asp Ile Ile Leu Val Val Asp Asn Thr Phe Met Ser
180 185 190

Pro Tyr Phe Gln Arg Pro Leu Ala Leu Gly Ala Asp Ile Cys Met Cys

195 200 205

Ser Ala Thr Lys Tyr Met Asn Gly His Ser Asp Val Val Met Gly Leu
210 215 220

Val Ser Val Asn Cys Glu Ser Leu Tyr Asn Arg Leu Arg Phe Leu Gln
225 230 235 240

Asn Ser Leu Gly Ala Val Pro Ser Pro Ile Asp Cys Tyr Leu Cys Asn
245 250 255

Arg Gly Leu Lys Thr Leu Gln Val Arg Met Glu Arg His Phe Lys Asn
260 265 270

Gly Met Ala Val Ala Gln Phe Leu Glu Ser Asn Pro Trp Val Glu Lys
275 280 285

Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Val Lys
290 295 300

Arg Gln Cys Thr Gly Cys Gly Gly Met Val Thr Phe Tyr Ile Lys Gly
305 310 315 320

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335

Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Val Glu Leu Pro Ala
340 345 350

Ser Met Thr His Ala Ser Val Leu Lys Lys Asp Arg Asp Val Leu Gly
355 360 365

Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380

Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400

Ser Gly Ser His Ser
405

<210> 12
<211> 405
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 12

Met Gln Glu Lys Glu Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15

His Phe Ala Thr Gln Ala Ile His Val Gly Gln Glu Pro Glu Gln Trp
20 25 30

Thr Ser Arg Ala Val Val Pro Pro Ile Ser Pro Ser Val Thr Phe Lys

35 40 45

Gln Gly Ala Pro Gly Gln His Ser Gly Phe Ile Tyr Ser Arg Leu Gly
50 55 60

Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly
65 70 75 80

Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Met Ala Ala Thr Val Thr
85 90 95

Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp
100 105 110

Val Tyr Ala Gly Thr Asn Leu Tyr Phe Arg Gln Val Ala Ser Glu Phe
115 120 125

Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu
130 135 140

Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr
145 150 155 160

Asn Pro Thr Gln Lys Met Thr Asp Ile Glu Ala Cys Ala His Ile Val
165 170 175

His Lys His Gly Asp Ile Ile Leu Val Val Asp Asn Thr Phe Met Ser
180 185 190

Pro Tyr Phe Gln Arg Pro Leu Ala Leu Gly Ala Asp Ile Cys Met Cys
195 200 205

Ser Ala Thr Lys Tyr Met Asn Gly His Ser Asp Val Val Met Gly Leu
210 215 220

Val Ser Val Asn Cys Glu Ser Leu Tyr Asn Arg Leu Arg Phe Leu Gln
225 230 235 240

Asn Ser Leu Gly Ala Val Pro Ser Pro Ile Asp Cys Tyr Leu Cys Asn
245 250 255

Arg Gly Leu Lys Thr Leu Gln Val Arg Met Glu Arg His Phe Lys Asn
260 265 270

Gly Met Ala Val Ala Gln Phe Leu Glu Ser Asn Pro Trp Val Glu Lys
275 280 285

Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Val Lys
290 295 300

Arg Gln Cys Thr Gly Cys Gly Gly Met Val Thr Phe Tyr Ile Lys Gly
305 310 315 320

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335

Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Val Glu Leu Pro Ala
340 345 350

Ser Met Thr His Ala Ser Val Leu Lys Lys Asp Arg Asp Val Leu Gly
355 360 365
Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380
Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400
Ser Gly Ser His Ser
405

<210> 13
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 13

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

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

<210> 14
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 14

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

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

340 345 350

Ser Met Thr His Ala Ser Val Leu Lys Lys Asp Arg Asp Val Leu Gly
355 360 365

Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380

Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400

Ser Gly Ser His Ser
405

<210> 15
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 15

Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15

His Phe Ala Thr Gln Ala Ile His Val Gly Gln Glu Pro Glu Gln Trp
20 25 30

Thr Ser Arg Ala Val Val Pro Leu Ile Ser Leu Ser Thr Thr Phe Lys
35 40 45

Gln Ala Ala Pro Gly Gln His Ser Gly Phe Asn Tyr Ser Arg Leu Gly
50 55 60

Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly
65 70 75 80

Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Met Ala Ala Thr Val Thr
85 90 95

Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp
100 105 110

Val Tyr Gly Gly Thr Asn Leu Tyr Phe Arg Gln Val Ala Ser Glu Phe
115 120 125

Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu
130 135 140

Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr
145 150 155 160

Asn Pro Val Leu Lys Met Ile Asp Ile Glu Ala Cys Ala His Ile Val
165 170 175

His Lys Arg Gly Asp Ile Ile Leu Val Val Asp Asn Thr Phe Met Ser

180 185 190

Pro Tyr Phe Gln Arg Pro Leu Ala Leu Gly Ala Asp Ile Cys Met Cys
195 200 205

Ser Ala Thr Lys Tyr Met Asn Gly His Ser Asp Val Val Met Gly Leu
210 215 220

Val Ser Val Asn Cys Glu Arg Leu His Asn Arg Leu Arg Phe Leu Gln
225 230 235 240

Asn Ser Leu Gly Ala Val Pro Ser Pro Leu Asp Cys Tyr Leu Cys Asn
245 250 255

Arg Gly Leu Lys Thr Leu His Val Arg Met Glu Arg His Phe Lys Asn
260 265 270

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

Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Ala Lys
290 295 300

Arg Gln Cys Thr Gly Cys Gly Gly Met Ile Thr Phe Tyr Ile Lys Gly
305 310 315 320

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335

Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Val Glu Leu Pro Ala
340 345 350

Ser Met Thr His Ala Ser Val Pro Lys Asn Asp Arg Asp Val Leu Gly
355 360 365

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

Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400

Ser Gly Ser His Asn
405

<210> 16

<211> 405

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 16

Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15

His Phe Ala Thr Gln Ala Ile His Val Gly Gln Glu Pro Glu Gln Trp

20 25 30

Thr Ser Arg Ala Val Val Pro Leu Ile Ser Leu Ser Thr Thr Phe Lys

35 40 45

Gln Ala Ala Pro Gly Gln His Ser Gly Phe Ile Tyr Ser Arg Leu Gly

50 55 60

Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly

65 70 75 80

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

85 90 95

Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp

100 105 110

Val Tyr Gly Gly Thr Asn Leu Tyr Phe Arg Gln Val Ala Ser Glu Phe

115 120 125

Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu

130 135 140

Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr

145 150 155 160

Asn Pro Val Leu Lys Met Ile Asp Ile Glu Ala Cys Ala His Ile Val

165 170 175

His Lys Arg Gly Asp Ile Ile Leu Val Val Asp Asn Thr Phe Met Ser

180 185 190

Pro Tyr Phe Gln Arg Pro Leu Ala Leu Gly Ala Asp Ile Cys Met Cys

195 200 205

Ser Ala Thr Lys Tyr Met Asn Gly His Ser Asp Val Val Met Gly Leu

210 215 220

Val Ser Val Asn Cys Glu Arg Leu His Asn Arg Leu Arg Phe Leu Gln

225 230 235 240

Asn Ser Leu Gly Ala Val Pro Ser Pro Leu Asp Cys Tyr Leu Cys Asn

245 250 255

Arg Gly Leu Lys Thr Leu His Val Arg Met Glu Arg His Phe Lys Asn

260 265 270

Gly Met Ala Val Ala Gln Phe Leu Glu Ser Asn Pro Gly Val Glu Lys

275 280 285

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

290 295 300

Arg Gln Cys Thr Gly Cys Gly Gly Met Ile Thr Phe Tyr Ile Lys Gly

305 310 315 320

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr

325 330 335

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

<210> 17
<211> 405
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 17

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

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

<210> 18
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 18
Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15

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

325 330 335
Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Val Glu Leu Pro Ala
340 345 350
Ser Met Thr His Ala Ser Val Pro Lys Asn Asp Arg Asp Val Leu Gly
355 360 365
Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Lys
370 375 380
Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400
Ser Gly Ser His Asn
405

<210> 19
<211> 405
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 19
Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15
His Phe Ala Thr Gln Ala Ile His Val Gly Gln Asp Pro Glu Gln Trp
20 25 30
Thr Ser Arg Ala Leu Val Pro Pro Ile Ser Leu Ser Thr Thr Phe Lys
35 40 45
Gln Gly Ala Pro Gly Gln His Ser Gly Phe Asn Tyr Ser Arg Leu Gly
50 55 60
Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly
65 70 75 80
Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Met Ala Ala Thr Val Thr
85 90 95
Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp
100 105 110
Val Tyr Gly Gly Thr Asn Leu Tyr Phe Arg Gln Val Ala Ser Glu Phe
115 120 125
Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu
130 135 140
Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr
145 150 155 160
Asn Pro Thr Gln Lys Val Ile Asp Ile Glu Ala Cys Ala His Ile Val

165 170 175

His Lys His Gly Asp Ile Ile Leu Val Val Asp Asn Thr Phe Met Ser
180 185 190

Pro Tyr Phe Gln Arg Pro Leu Ala Leu Gly Ala Asp Ile Cys Met Tyr
195 200 205

Ser Ala Thr Lys Tyr Met Asn Gly His Ser Asp Val Val Met Gly Leu
210 215 220

Val Ser Val Asn Cys Glu Ser Leu His Asn Arg Leu Arg Phe Leu Gln
225 230 235 240

Asn Ser Leu Gly Ala Val Pro Ser Pro Ile Asp Cys Tyr Leu Cys Asn
245 250 255

Arg Gly Leu Lys Thr Leu His Val Arg Met Glu Arg His Phe Lys Asn
260 265 270

Gly Met Ala Val Ala Gln Phe Leu Glu Ser Asn Pro Trp Val Glu Lys
275 280 285

Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Val Lys
290 295 300

Arg Gln Cys Thr Gly Cys Gly Gly Met Val Thr Phe Tyr Ile Lys Gly
305 310 315 320

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335

Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350

Ser Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365

Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380

Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400

Ser Gly Ser His Ser
405

<210> 20
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 20

Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln

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

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335
Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350
Ser Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365
Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380
Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400
Ser Gly Ser His Ser
405

<210> 21
<211> 405
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 21

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

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

<210> 22
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<212> PRT
<213> 人工序列
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<400> 22

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

305 310 315 320
Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335
Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350
Ser Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365
Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380
Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400
Ser Gly Ser His Ser
405

<210> 23
<211> 405
<212> PRT
<213> 人工序列
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<400> 23
Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15
His Phe Ala Thr Gln Ala Ile His Val Gly Gln Asp Pro Glu Gln Trp
20 25 30
Thr Ser Lys Ala Leu Val Pro Pro Ile Ser Leu Ser Thr Thr Phe Lys
35 40 45
Gln Gly Ala Pro Gly Gln His Ser Gly Phe Asn Tyr Ser Arg Leu Gly
50 55 60
Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly
65 70 75 80
Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Met Ala Ala Thr Val Thr
85 90 95
Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp
100 105 110
Val Tyr Gly Gly Thr Asn Leu Tyr Phe Arg Gln Val Ala Ser Glu Phe
115 120 125
Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu
130 135 140
Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr

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

<210> 24
<211> 405
<212> PRT
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<223> 合成多肽

<400> 24

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

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

<210> 25
<211> 405
<212> PRT
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<400> 25

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

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

<210> 26
<211> 405
<212> PRT
<213> 人工序列
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<223> 合成多肽

<400> 26

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

290 295 300

Arg Gln Cys Thr Gly Cys Gly Gly Met Val Thr Phe Tyr Ile Lys Gly
305 310 315 320

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335

Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350

Ser Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365

Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380

Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400

Ser Gly Ser His Ser
405

<210> 27
<211> 405
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 27

Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15

His Phe Ala Thr Gln Ala Ile His Val Gly Gln Asp Pro Glu Gln Trp
20 25 30

Thr Ser Arg Ala Val Val Pro Pro Ile Ser Leu Ser Thr Thr Phe Lys
35 40 45

Gln Gly Ala Pro Gly Gln His Ser Gly Phe Asn Tyr Ser Arg Ser Gly
50 55 60

Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly
65 70 75 80

Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Leu Ala Ala Thr Val Thr
85 90 95

Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp
100 105 110

Val Tyr Gly Gly Thr Asn Leu Tyr Phe Arg Gln Val Ala Ser Glu Phe
115 120 125

Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu

130 135 140

Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr
145 150 155 160

Asn Pro Thr Gln Lys Val Ile Asp Ile Glu Gly Cys Ala His Ile Val
165 170 175

His Lys His Gly Asp Ile Ile Leu Val Val Asp Asn Thr Phe Met Ser
180 185 190

Pro Tyr Phe Gln Arg Pro Leu Ala Leu Gly Ala Asp Ile Ser Met Tyr
195 200 205

Ser Ala Thr Lys Tyr Met Asn Gly His Ser Asp Val Val Met Gly Leu
210 215 220

Val Ser Val Asn Cys Glu Ser Leu His Asn Arg Leu Arg Phe Leu Gln
225 230 235 240

Asn Ser Leu Gly Ala Val Pro Ser Pro Ile Asp Cys Tyr Leu Cys Asn
245 250 255

Arg Gly Leu Lys Thr Leu His Val Arg Met Glu Lys His Phe Lys Asn
260 265 270

Gly Met Ala Val Ala Gln Phe Leu Glu Ser Asn Pro Trp Val Glu Lys
275 280 285

Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Val Lys
290 295 300

Arg Gln Cys Thr Gly Cys Thr Gly Met Val Thr Phe Tyr Ile Lys Gly
305 310 315 320

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Asp
325 330 335

Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350

Ile Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365

Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380

Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400

Ser Gly Ser His Ser
405

<210> 28

<211> 405

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 28

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

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

<210> 29
<211> 405
<212> PRT
<213> 人工序列
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<400> 29
Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15
His Phe Ala Thr Gln Ala Ile His Val Gly Gln Asp Pro Glu Gln Trp
20 25 30
Thr Ser Arg Ala Val Val Pro Pro Ile Ser Leu Ser Thr Thr Phe Lys
35 40 45
Gln Gly Ala Pro Gly Gln His Ser Gly Phe Ile Tyr Ser Arg Leu Gly
50 55 60
Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly
65 70 75 80
Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Met Ala Ala Thr Val Thr
85 90 95
Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp
100 105 110
Val Tyr Gly Gly Thr Asn Leu Tyr Phe Arg Gln Val Ala Ser Glu Phe
115 120 125

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

<210> 30
<211> 405
<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 30

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

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

<210> 31
<211> 405
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 31
Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15
His Phe Ala Thr Gln Ala Ile His Val Gly Gln Asp Pro Glu Gln Trp
20 25 30
Thr Ser Arg Ala Val Val Pro Pro Ile Ser Leu Ser Thr Thr Phe Lys
35 40 45
Gln Gly Ala Pro Gly Gln His Ser Gly Phe Ile Tyr Ser Arg Leu Gly
50 55 60
Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly
65 70 75 80
Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Met Ala Ala Thr Val Thr
85 90 95
Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp
100 105 110
Val Tyr Gly Gly Thr Asn Ala Tyr Phe Arg Gln Val Ala Ser Glu Phe

115 120 125

Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu
130 135 140

Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr
145 150 155 160

Asn Pro Thr Gln Lys Val Ile Asp Ile Glu Gly Cys Ala His Ile Val
165 170 175

His Lys His Gly Asp Ile Ile Leu Val Val Asp Asn Thr Phe Met Ser
180 185 190

Pro Tyr Phe Gln Arg Pro Leu Ala Leu Gly Ala Asp Ile Ser Met Tyr
195 200 205

Ser Ala Thr Lys Tyr Met Asn Gly His Ser Asp Val Val Met Gly Leu
210 215 220

Val Ser Val Asn Cys Glu Ser Leu His Asn Arg Leu Arg Phe Leu Gln
225 230 235 240

Asn Ser Leu Gly Ala Val Pro Ser Pro Ile Asp Cys Tyr Leu Cys Asn
245 250 255

Arg Gly Leu Lys Thr Leu His Val Arg Met Glu Arg His Phe Lys Asn
260 265 270

Gly Met Ala Val Ala Gln Phe Leu Glu Ser Asn Pro Trp Val Glu Lys
275 280 285

Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Val Lys
290 295 300

Arg Gln Cys Thr Gly Cys Gly Gly Met Val Thr Phe Tyr Ile Lys Gly
305 310 315 320

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Asp
325 330 335

Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350

Ser Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365

Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380

Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400

Ser Gly Ser His Ser
405

<210> 32

<211> 405

<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 32

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

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

<210> 33
<211> 405
<212> PRT
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<400> 33

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

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

<210> 34

<211> 405
<212> PRT
<213> 人工序列
<220>
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<400> 34

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

260 265 270

Gly Met Ala Val Ala Gln Phe Leu Glu Ser Asn Pro Trp Val Glu Lys
275 280 285

Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Val Lys
290 295 300

Arg Gln Cys Thr Gly Cys Gly Gly Met Val Thr Phe Tyr Ile Lys Gly
305 310 315 320

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Glu
325 330 335

Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350

Ser Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365

Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380

Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400

Ser Gly Ser His Ser
405

<210> 35
<211> 405
<212> PRT
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<400> 35

Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15

His Phe Ala Thr Gln Ala Ile His Val Gly Gln Asp Pro Glu Gln Trp
20 25 30

Thr Ser Arg Ala Val Val Pro Pro Ile Ser Leu Ser Thr Thr Phe Lys
35 40 45

Gln Gly Ala Pro Gly Gln His Ser Gly Phe Asn Tyr Ser Arg Leu Gly
50 55 60

Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly
65 70 75 80

Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Met Ala Ala Thr Val Thr
85 90 95

Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp

100 105 110

Val Tyr Gly Gly Thr Asn Ala Tyr Phe Arg Gln Val Ala Ser Glu Phe
115 120 125

Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu
130 135 140

Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr
145 150 155 160

Asn Pro Thr Gln Lys Val Ile Asp Ile Glu Gly Cys Ala His Ile Val
165 170 175

His Lys His Gly Asp Ile Ile Leu Val Val Asp Asn Thr Phe Met Ser
180 185 190

Pro Tyr Phe Gln Arg Pro Leu Ala Leu Gly Ala Asp Ile Ser Met Tyr
195 200 205

Ser Ala Thr Lys Tyr Met Asn Gly His Ser Asp Val Val Met Gly Leu
210 215 220

Val Ser Val Asn Cys Glu Ser Leu His Asn Arg Leu Arg Phe Leu Gln
225 230 235 240

Asn Ser Leu Gly Ala Val Pro Ser Pro Ile Asp Cys Tyr Leu Cys Asn
245 250 255

Arg Gly Leu Lys Thr Leu His Val Arg Met Glu Arg His Phe Lys Asn
260 265 270

Gly Met Ala Val Ala Gln Phe Leu Glu Ser Asn Pro Trp Val Glu Lys
275 280 285

Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Val Lys
290 295 300

Arg Gln Cys Thr Gly Cys Gly Gly Met Val Thr Phe Tyr Ile Lys Gly
305 310 315 320

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Glu
325 330 335

Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350

Ser Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365

Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380

Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400

Ser Gly Ser His Ser
405

<210> 36
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<223> 合成多肽
<400> 36

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

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

<210> 37
<211> 405
<212> PRT
<213> 人工序列
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<400> 37
Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15
His Phe Ala Thr Gln Ala Ile His Val Gly Gln Asp Pro Glu Gln Trp
20 25 30
Thr Ser Arg Ala Val Val Pro Pro Ile Ser Leu Ser Thr Thr Phe Lys
35 40 45
Gln Gly Ala Pro Gly Gln His Ser Gly Phe Ile Tyr Ser Arg Leu Gly
50 55 60
Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly
65 70 75 80
Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Met Ala Ala Thr Val Thr
85 90 95

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

405

<210> 38
<211> 405
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 38

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

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

<210> 39
<211> 405
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 39
Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15
His Phe Ala Thr Gln Ala Ile His Val Gly Gln Asp Pro Glu Gln Trp
20 25 30
Thr Ser Arg Ala Val Val Pro Pro Ile Ser Leu Ser Thr Thr Phe Lys
35 40 45
Gln Gly Ala Pro Gly Gln His Ser Gly Phe Ile Tyr Ser Arg Leu Gly
50 55 60
Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly
65 70 75 80
Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Met Ala Ala Thr Val Thr

85 90 95

Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp
100 105 110

Val Tyr Gly Gly Thr Asn Gly Tyr Phe Arg Gln Val Ala Ser Glu Phe
115 120 125

Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu
130 135 140

Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr
145 150 155 160

Asn Pro Thr Gln Lys Val Ile Asp Ile Glu Gly Cys Ala His Ile Val
165 170 175

His Lys His Gly Asp Ile Ile Leu Val Val Asp Asn Thr Phe Met Ser
180 185 190

Pro Tyr Phe Gln Arg Pro Leu Ala Leu Gly Ala Asp Ile Ser Met Tyr
195 200 205

Ser Ala Thr Lys Tyr Met Asn Gly His Ser Asp Val Val Met Gly Leu
210 215 220

Val Ser Val Asn Cys Glu Ser Leu His Asn Arg Leu Arg Phe Leu Gln
225 230 235 240

Asn Ser Leu Gly Ala Val Pro Ser Pro Ile Asp Cys Tyr Leu Cys Asn
245 250 255

Arg Gly Leu Lys Thr Leu His Val Arg Met Glu Arg His Phe Lys Asn
260 265 270

Gly Met Ala Val Ala Gln Phe Leu Glu Ser Asn Pro Trp Val Glu Lys
275 280 285

Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Val Lys
290 295 300

Arg Gln Cys Thr Gly Cys Gly Gly Met Val Thr Phe Tyr Ile Lys Gly
305 310 315 320

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335

Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350

Ser Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365

Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380

Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400

Ser Gly Ser His Ser
405

<210> 40
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 40

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

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

<210> 41
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 41

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

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

385 390 395 400
Ser Gly Ser His Ser
405

<210> 42
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 42

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

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

<210> 43
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 43
Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15
His Phe Ala Thr Gln Ala Ile His Val Gly Gln Glu Pro Glu Gln Trp
20 25 30
Thr Ser Arg Ala Val Val Pro Leu Ile Ser Leu Ser Thr Thr Phe Lys
35 40 45
Gln Ala Ala Pro Gly Gln His Ser Gly Phe Ile Tyr Ser Arg Leu Gly
50 55 60
Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly

65 70 75 80
Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Met Ala Ala Thr Val Thr
85 90 95
Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp
100 105 110
Val Tyr Gly Gly Thr Asn Asp Tyr Phe Arg Gln Val Ala Ser Glu Phe
115 120 125
Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu
130 135 140
Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr
145 150 155 160
Asn Pro Val Leu Lys Met Ile Asp Ile Glu Ala Cys Ala His Ile Val
165 170 175
His Lys Arg Gly Asp Ile Ile Leu Val Val Asp Asn Thr Phe Met Ser
180 185 190
Pro Tyr Phe Gln Arg Pro Leu Ala Leu Gly Ala Asp Ile Cys Met Cys
195 200 205
Ser Ala Thr Lys Tyr Met Asn Gly His Ser Asp Val Val Met Gly Leu
210 215 220
Val Ser Val Asn Cys Glu Arg Leu His Asn Arg Leu Arg Phe Leu Gln
225 230 235 240
Asn Ser Leu Gly Ala Val Pro Ser Pro Leu Asp Cys Tyr Leu Cys Asn
245 250 255
Arg Gly Leu Lys Thr Leu His Val Arg Met Glu Arg His Phe Lys Asn
260 265 270
Gly Met Ala Val Ala Gln Phe Leu Glu Ser Asn Pro Gly Val Glu Lys
275 280 285
Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Ala Lys
290 295 300
Arg Gln Cys Thr Gly Cys Gly Gly Met Ile Thr Phe Tyr Ile Lys Gly
305 310 315 320
Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335
Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Val Glu Leu Pro Ala
340 345 350
Ser Met Thr His Ala Ser Val Pro Lys Asn Asp Arg Asp Val Leu Gly
355 360 365
Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Lys
370 375 380

Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400
Ser Gly Ser His Asn
405

<210> 44
<211> 405
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 44

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

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

<210> 45
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 45

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

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

370 375 380
Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400
Ser Gly Ser His Asn
405

<210> 46
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 46

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

210 215 220
Val Ser Val Asn Cys Glu Ser Leu His Asn Arg Leu Arg Phe Leu Gln
225 230 235 240
Asn Ser Leu Gly Ala Val Pro Ser Pro Ile Asp Cys Tyr Leu Cys Asn
245 250 255
Arg Gly Leu Lys Thr Leu His Val Arg Met Glu Arg His Phe Lys Asn
260 265 270
Gly Met Ala Val Ala Gln Phe Leu Glu Ser Asn Pro Trp Val Glu Lys
275 280 285
Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Val Lys
290 295 300
Arg Gln Cys Thr Gly Cys Gly Gly Met Val Thr Phe Tyr Ile Lys Gly
305 310 315 320
Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335
Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350
Ser Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365
Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380
Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400
Ser Gly Ser His Ser
405

<210> 47
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 47
Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15
His Phe Ala Thr Gln Ala Ile His Val Gly Gln Asp Pro Glu Gln Trp
20 25 30
Thr Ser Arg Ala Leu Val Pro Pro Ile Ser Leu Ser Thr Thr Phe Lys
35 40 45
Gln Gly Ala Pro Gly Gln His Ser Gly Phe Ile Tyr Ser Arg Leu Gly

50 55 60

Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly
65 70 75 80

Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Met Ala Ala Thr Val Thr
85 90 95

Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp
100 105 110

Val Tyr Gly Gly Thr Asn His Tyr Phe Arg Gln Val Ala Ser Glu Phe
115 120 125

Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu
130 135 140

Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr
145 150 155 160

Asn Pro Thr Gln Lys Val Ile Asp Ile Glu Ala Cys Ala His Ile Val
165 170 175

His Lys His Gly Asp Ile Ile Leu Val Val Asp Asn Thr Phe Met Ser
180 185 190

Pro Tyr Phe Gln Arg Pro Leu Ala Leu Gly Ala Asp Ile Cys Met Tyr
195 200 205

Ser Ala Thr Lys Tyr Met Asn Gly His Ser Asp Val Val Met Gly Leu
210 215 220

Val Ser Val Asn Cys Glu Ser Leu His Asn Arg Leu Arg Phe Leu Gln
225 230 235 240

Asn Ser Leu Gly Ala Val Pro Ser Pro Ile Asp Cys Tyr Leu Cys Asn
245 250 255

Arg Gly Leu Lys Thr Leu His Val Arg Met Glu Arg His Phe Lys Asn
260 265 270

Gly Met Ala Val Ala Gln Phe Leu Glu Ser Asn Pro Trp Val Glu Lys
275 280 285

Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Val Lys
290 295 300

Arg Gln Cys Thr Gly Cys Gly Gly Met Val Thr Phe Tyr Ile Lys Gly
305 310 315 320

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335

Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350

Ser Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365

Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380
Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400
Ser Gly Ser His Ser
405

<210> 48
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 48

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

Ser Ala Thr Lys Tyr Met Asn Gly His Ser Asp Val Val Met Gly Leu
210 215 220
Val Ser Val Asn Cys Glu Ser Leu His Asn Arg Leu Arg Phe Leu Gln
225 230 235 240
Asn Ser Leu Gly Ala Val Pro Ser Pro Ile Asp Cys Tyr Leu Cys Asn
245 250 255
Arg Gly Leu Lys Thr Leu His Val Arg Met Glu Arg His Phe Lys Asn
260 265 270
Gly Met Ala Val Ala Gln Phe Leu Glu Ser Asn Pro Trp Val Glu Lys
275 280 285
Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Val Lys
290 295 300
Arg Gln Cys Thr Gly Cys Gly Gly Met Val Thr Phe Tyr Ile Lys Gly
305 310 315 320
Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335
Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350
Ser Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365
Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380
Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400
Ser Gly Ser His Ser
405

<210> 49
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 49

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

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

355 360 365

Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380

Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400

Ser Gly Ser His Ser
405

<210> 50
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 50

Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15

His Phe Ala Thr Gln Ala Ile His Val Gly Gln Asp Pro Glu Gln Trp
20 25 30

Thr Ser Lys Ala Leu Val Pro Pro Ile Ser Leu Ser Thr Thr Phe Lys
35 40 45

Gln Gly Ala Pro Gly Gln His Ser Gly Phe Ile Tyr Ser Arg Leu Gly
50 55 60

Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly
65 70 75 80

Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Met Ala Ala Thr Val Thr
85 90 95

Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp
100 105 110

Val Tyr Gly Gly Thr Asn His Tyr Phe Arg Gln Val Ala Ser Glu Phe
115 120 125

Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu
130 135 140

Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr
145 150 155 160

Asn Pro Thr Gln Lys Val Ile Asp Ile Glu Ala Cys Ala His Ile Val
165 170 175

His Lys His Gly Asp Ile Ile Leu Val Val Asp Asn Thr Phe Met Ser
180 185 190

Pro Tyr Phe Gln Arg Pro Leu Ala Leu Gly Ala Asp Ile Cys Met Tyr

195 200 205

Ser Ala Thr Lys Tyr Met Asn Gly His Ser Asp Val Val Ile Gly Leu
210 215 220

Val Ser Val Asn Cys Glu Ser Leu His Asn Arg Leu Arg Phe Leu Gln
225 230 235 240

Asn Ser Leu Gly Ala Val Pro Ser Pro Ile Asp Cys Tyr Leu Cys Asn
245 250 255

Arg Gly Leu Lys Thr Leu His Val Arg Met Glu Arg His Phe Lys Asn
260 265 270

Gly Met Ala Val Ala Gln Phe Leu Glu Ser Asn Pro Trp Val Glu Lys
275 280 285

Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Val Lys
290 295 300

Arg Gln Cys Thr Gly Cys Gly Gly Met Val Thr Phe Tyr Ile Lys Gly
305 310 315 320

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335

Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350

Ser Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365

Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380

Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400

Ser Gly Ser His Ser
405

<210> 51
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 51

Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15

His Phe Ala Thr Gln Ala Ile His Val Gly Gln Asp Pro Glu Gln Trp
20 25 30

Thr Ser Lys Ala Leu Val Pro Pro Ile Ser Leu Ser Thr Thr Phe Lys

35 40 45

Gln Gly Ala Pro Gly Gln His Ser Gly Phe Ile Tyr Ser Arg Leu Gly
50 55 60

Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly
65 70 75 80

Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Met Ala Ala Thr Val Thr
85 90 95

Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp
100 105 110

Val Tyr Gly Gly Thr Asn Gly Tyr Phe Arg Gln Val Ala Ser Glu Phe
115 120 125

Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu
130 135 140

Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr
145 150 155 160

Asn Pro Thr Gln Lys Val Ile Asp Ile Glu Ala Cys Ala His Ile Val
165 170 175

His Lys His Gly Asp Ile Ile Leu Val Val Asp Asn Thr Phe Met Ser
180 185 190

Pro Tyr Phe Gln Arg Pro Leu Ala Leu Gly Ala Asp Ile Cys Met Tyr
195 200 205

Ser Ala Thr Lys Tyr Met Asn Gly His Ser Asp Val Val Ile Gly Leu
210 215 220

Val Ser Val Asn Cys Glu Ser Leu His Asn Arg Leu Arg Phe Leu Gln
225 230 235 240

Asn Ser Leu Gly Ala Val Pro Ser Pro Ile Asp Cys Tyr Leu Cys Asn
245 250 255

Arg Gly Leu Lys Thr Leu His Val Arg Met Glu Arg His Phe Lys Asn
260 265 270

Gly Met Ala Val Ala Gln Phe Leu Glu Ser Asn Pro Trp Val Glu Lys
275 280 285

Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Val Lys
290 295 300

Arg Gln Cys Thr Gly Cys Gly Gly Met Val Thr Phe Tyr Ile Lys Gly
305 310 315 320

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335

Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350

Ser Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365
Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380
Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400
Ser Gly Ser His Ser
405

<210> 52
<211> 405
<212> PRT
<213> 人工序列
<220>
<223> 合成多肽
<400> 52

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

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

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<211> 405
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<213> 人工序列
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Met Gln Glu Lys Glu Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15
His Phe Ala Thr Gln Ala Ile His Val Gly Gln Glu Pro Glu Gln Trp
20 25 30

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

340 345 350

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

355 360 365

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

370 375 380

Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro

385 390 395 400

Ser Gly Ser His Ser

405

<210> 54

<211> 405

<212> PRT

<213> 人工序列

<220>

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<400> 54

Met Gln Glu Lys Glu Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln

1 5 10 15

His Phe Ala Thr Gln Ala Ile His Val Gly Gln Glu Pro Glu Gln Trp

20 25 30

Thr Ser Arg Ala Val Val Pro Pro Ile Ser Pro Ser Val Thr Phe Lys

35 40 45

Gln Gly Ala Pro Gly Gln His Ser Gly Phe Asn Tyr Ser Arg Leu Gly

50 55 60

Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly

65 70 75 80

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

85 90 95

Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp

100 105 110

Val Tyr Ala Gly Thr Asn Gly Tyr Phe Arg Gln Val Ala Ser Glu Phe

115 120 125

Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu

130 135 140

Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr

145 150 155 160

Asn Pro Thr Gln Lys Met Thr Asp Ile Glu Ala Cys Ala His Ile Val

165 170 175

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

180 185 190

Pro Tyr Phe Gln Arg Pro Leu Ala Leu Gly Ala Asp Ile Cys Met Cys
195 200 205

Ser Ala Thr Lys Tyr Met Asn Gly His Ser Asp Val Val Met Gly Leu
210 215 220

Val Ser Val Asn Cys Glu Ser Leu Tyr Asn Arg Leu Arg Phe Leu Gln
225 230 235 240

Asn Ser Leu Gly Ala Val Pro Ser Pro Ile Asp Cys Tyr Leu Cys Asn
245 250 255

Arg Gly Leu Lys Thr Leu Gln Val Arg Met Glu Arg His Phe Lys Asn
260 265 270

Gly Met Ala Val Ala Gln Phe Leu Glu Ser Asn Pro Trp Val Glu Lys
275 280 285

Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Val Lys
290 295 300

Arg Gln Cys Thr Gly Cys Gly Gly Met Val Thr Phe Tyr Ile Lys Gly
305 310 315 320

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335

Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Val Glu Leu Pro Ala
340 345 350

Ser Met Thr His Ala Ser Val Leu Lys Lys Asp Arg Asp Val Leu Gly
355 360 365

Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380

Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400

Ser Gly Ser His Ser
405

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<400> 55

Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15

His Phe Ala Thr Gln Ala Ile His Val Gly Gln Glu Pro Glu Gln Trp

20 25 30

Thr Ser Arg Ala Val Val Pro Leu Ile Ser Leu Ser Thr Thr Phe Lys
35 40 45

Gln Ala Ala Pro Gly Gln His Ser Gly Phe Asn Tyr Ser Arg Leu Gly
50 55 60

Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly
65 70 75 80

Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Met Ala Ala Thr Val Thr
85 90 95

Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp
100 105 110

Val Tyr Gly Gly Thr Asn Asp Tyr Phe Arg Gln Val Ala Ser Glu Phe
115 120 125

Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu
130 135 140

Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr
145 150 155 160

Asn Pro Val Leu Lys Met Ile Asp Ile Glu Ala Cys Ala His Ile Val
165 170 175

His Lys Arg Gly Asp Ile Ile Leu Val Val Asp Asn Thr Phe Met Ser
180 185 190

Pro Tyr Phe Gln Arg Pro Leu Ala Leu Gly Ala Asp Ile Cys Met Cys
195 200 205

Ser Ala Thr Lys Tyr Met Asn Gly His Ser Asp Val Val Met Gly Leu
210 215 220

Val Ser Val Asn Cys Glu Arg Leu His Asn Arg Leu Arg Phe Leu Gln
225 230 235 240

Asn Ser Leu Gly Ala Val Pro Ser Pro Leu Asp Cys Tyr Leu Cys Asn
245 250 255

Arg Gly Leu Lys Thr Leu His Val Arg Met Glu Arg His Phe Lys Asn
260 265 270

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

Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Ala Lys
290 295 300

Arg Gln Cys Thr Gly Cys Gly Gly Met Ile Thr Phe Tyr Ile Lys Gly
305 310 315 320

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335

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

<210> 56
<211> 405
<212> PRT
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<400> 56

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

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

<210> 57
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<400> 57
Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15

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

325 330 335
Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Val Glu Leu Pro Ala
340 345 350
Ser Met Thr His Ala Ser Val Pro Lys Asn Asp Arg Asp Val Leu Gly
355 360 365
Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Lys
370 375 380
Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400
Ser Gly Ser His Asn
405

<210> 58
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<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 58
Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15
His Phe Ala Thr Gln Ala Ile His Val Gly Gln Asp Pro Glu Gln Trp
20 25 30
Thr Ser Arg Ala Leu Val Pro Pro Ile Ser Leu Ser Thr Thr Phe Lys
35 40 45
Gln Gly Ala Pro Gly Gln His Ser Gly Phe Asn Tyr Ser Arg Leu Gly
50 55 60
Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly
65 70 75 80
Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Met Ala Ala Thr Val Thr
85 90 95
Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp
100 105 110
Val Tyr Gly Gly Thr Asn Asp Tyr Phe Arg Gln Val Ala Ser Glu Phe
115 120 125
Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu
130 135 140
Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr
145 150 155 160
Asn Pro Thr Gln Lys Val Ile Asp Ile Glu Ala Cys Ala His Ile Val

165 170 175

His Lys His Gly Asp Ile Ile Leu Val Val Asp Asn Thr Phe Met Ser
180 185 190

Pro Tyr Phe Gln Arg Pro Leu Ala Leu Gly Ala Asp Ile Cys Met Tyr
195 200 205

Ser Ala Thr Lys Tyr Met Asn Gly His Ser Asp Val Val Met Gly Leu
210 215 220

Val Ser Val Asn Cys Glu Ser Leu His Asn Arg Leu Arg Phe Leu Gln
225 230 235 240

Asn Ser Leu Gly Ala Val Pro Ser Pro Ile Asp Cys Tyr Leu Cys Asn
245 250 255

Arg Gly Leu Lys Thr Leu His Val Arg Met Glu Arg His Phe Lys Asn
260 265 270

Gly Met Ala Val Ala Gln Phe Leu Glu Ser Asn Pro Trp Val Glu Lys
275 280 285

Val Ile Tyr Pro Gly Leu Pro Ser His Pro Gln His Glu Leu Val Lys
290 295 300

Arg Gln Cys Thr Gly Cys Gly Gly Met Val Thr Phe Tyr Ile Lys Gly
305 310 315 320

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335

Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350

Ser Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365

Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380

Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400

Ser Gly Ser His Ser
405

<210> 59
<211> 405
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 59

Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln

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

Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335
Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350
Ser Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365
Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380
Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400
Ser Gly Ser His Ser
405

<210> 60
<211> 405
<212> PRT
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<223> 合成多肽
<400> 60

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

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

<210> 61
<211> 405
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 61

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

305 310 315 320
Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335
Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350
Ser Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365
Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
370 375 380
Asp Leu Leu Glu Asp Leu Asp Gln Ala Leu Lys Ala Ala His Pro Pro
385 390 395 400
Ser Gly Ser His Ser
405

<210> 62
<211> 405
<212> PRT
<213> 人工序列
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<223> 合成多肽
<400> 62
Met Gln Glu Lys Asp Ala Ser Ser Gln Gly Phe Leu Pro His Phe Gln
1 5 10 15
His Phe Ala Thr Gln Ala Ile His Val Gly Gln Asp Pro Glu Gln Trp
20 25 30
Thr Ser Lys Ala Leu Val Pro Pro Ile Ser Leu Ser Thr Thr Phe Lys
35 40 45
Gln Gly Ala Pro Gly Gln His Ser Gly Phe Asn Tyr Ser Arg Leu Gly
50 55 60
Asn Pro Thr Arg Asn Cys Leu Glu Lys Ala Val Ala Ala Leu Asp Gly
65 70 75 80
Ala Lys Tyr Cys Leu Ala Phe Ala Ser Gly Met Ala Ala Thr Val Thr
85 90 95
Ile Thr His Leu Leu Lys Ala Gly Asp Gln Ile Ile Cys Met Asp Asp
100 105 110
Val Tyr Gly Gly Thr Asn His Tyr Phe Arg Gln Val Ala Ser Glu Phe
115 120 125
Gly Leu Lys Ile Ser Phe Val Asp Cys Ser Lys Ile Lys Leu Leu Glu
130 135 140
Ala Ala Ile Thr Pro Glu Thr Lys Leu Val Trp Ile Glu Thr Pro Thr

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

<210> 63
<211> 405
<212> PRT
<213> 人工序列
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<223> 合成多肽

<400> 63

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

Arg Gln Cys Thr Gly Cys Gly Gly Met Val Thr Phe Tyr Ile Lys Gly
305 310 315 320
Thr Leu Gln His Ala Glu Ile Phe Leu Lys Asn Leu Lys Leu Phe Thr
325 330 335
Leu Ala Val Ser Leu Gly Gly Phe Glu Ser Leu Ala Glu Leu Pro Ala
340 345 350
Ser Met Thr His Ala Ser Val Leu Lys Asn Asp Arg Asp Val Leu Gly
355 360 365
Ile Ser Asp Thr Leu Ile Arg Leu Ser Val Gly Leu Glu Asp Glu Glu
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385 390 395 400
Ser Gly Ser His Ser
405

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<211> 1245
<212> DNA
<213> 人工序列
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cagtggacgt cgcgtgcggt tgtaccgccg attagcctga gcacgacctt taaacaaggt 180
gcgccgggcc agcatagcgg ttttatttat agccgtctgg gcaatcccac acggaattgc 240
ctggagaagg cggtggcggc tctggacggc gcgaagtatt gccttgcgtt tgcgagcgga 300
atggcggcca ccgtgaccat tacccacctg cttaaggctg gggaccagat tatttgcatg 360
gatgatgtgt atggtgggac caatgattat ttccgtcagg tggcgagcga gttcggcctg 420
aagatatcct ttgtcgactg ctcgaagatc aagctgttag aggcagcgat tacgccggaa 480
acaaaacttg tgtggataga aaccccgacg aacccgaccc agaaagtgat tgacattgaa 540
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gataccctga ttcgcctgtc cgtaggactg gaagatgaag aagatctgct ggaggatctg 1200
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cagtggacgt cgcgtgcggt tgtaccgccg attagcctga gcacgacctt taaacaaggt 180
gcgccgggcc agcatagcgg ttttatttat agccgtctgg gcaatcccac acggaattgc 240
ctggagaagg cggtggcggc tctggacggc gcgaagtatt gccttgcgtt tgcgagcgga 300
atggcggcca ccgtgaccat tacccacctg cttaaggctg gggaccagat tatttgcatg 360
gatgatgtgt atggtgggac caatcattat ttccgtcagg tggcgagcga gttcggcctg 420
aagatatcct ttgtcgactg ctcgaagatc aagctgttag aggcagcgat tacgccggaa 480
acaaaacttg tgtggataga aaccccgacg aacccgaccc agaaagtgat tgacattgaa 540
ggctgcgccc acattgtgca taaacacggc gatatcatcc tggtcgtgga taataccttc 600
atgagcccgt acttccagcg tccgctggcg cttggcgccg acattagcat gtattcggcg 660
accaagtata tgaacggcca tagcgacgtt gtcatgggcc tggtgagcgt gaattgcgag 720
agcctgcata atcgtctgcg ttttctgcaa aattcgcttg gagcggtgcc gagcccgatc 780
gattgctatc tgtgcaatcg tgggctgaag actctgcatg tgcggatgga gagacatttt 840
aagaatggca tggctgtggc gcagtttctg gaaagcaatc cgtgggtgga aaaagttatc 900
tacccgggac tgcccagcca cccgcagcat gaactggtca aacgtcagtg cacaggttgc 960
ggcggcatgg tgaccttcta tatcaagggc accctgcaac acgccgaaat ctttctgaaa 1020
aacctgaaac tgtttaccct ggcagtgagc ttgggcggct ttgaaagcct tgctgaactg 1080
ccggccagta tgactcatgc ctccgtgttg aaaaatgatc gtgatgttct gggcataagc 1140
gataccctga ttcgcctgtc cgtaggactg gaagatgaag aagatctgct ggaggatctg 1200
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<211> 1245
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<213> 人工序列
<220>
<223> 合成多肽
<400> 66

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cagtggacgt cgcgtgcggt tgtaccgccg attagcctga gcacgacctt taaacaaggt 180
gcgccgggcc agcatagcgg ttttatttat agccgtctgg gcaatcccac acggaattgc 240
ctggagaagg cggtggcggc tctggacggc gcgaagtatt gccttgcgtt tgcgagcgga 300
atggcggcca ccgtgaccat tacccacctg cttaaggctg gggaccagat tatttgcatg 360
gatgatgtgt atggtgggac caatggttat ttccgtcagg tggcgagcga gttcggcctg 420
aagatatcct ttgtcgactg ctcgaagatc aagctgttag aggcagcgat tacgccggaa 480
acaaaacttg tgtggataga aaccccgacg aacccgaccc agaaagtgat tgacattgaa 540
ggctgcgccc acattgtgca taaacacggc gatatcatcc tggtcgtgga taataccttc 600
atgagcccgt acttccagcg tccgctggcg cttggcgccg acattagcat gtattcggcg 660
accaagtata tgaacggcca tagcgacgtt gtcatgggcc tggtgagcgt gaattgcgag 720
agcctgcata atcgtctgcg ttttctgcaa aattcgcttg gagcggtgcc gagcccgatc 780
gattgctatc tgtgcaatcg tgggctgaag actctgcatg tgcggatgga gagacatttt 840
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tacccgggac tgcccagcca cccgcagcat gaactggtca aacgtcagtg cacaggttgc 960
ggcggcatgg tgaccttcta tatcaagggc accctgcaac acgccgaaat ctttctgaaa 1020
aacctgaaac tgtttaccct ggcagtgagc ttgggcggct ttgaaagcct tgctgaactg 1080
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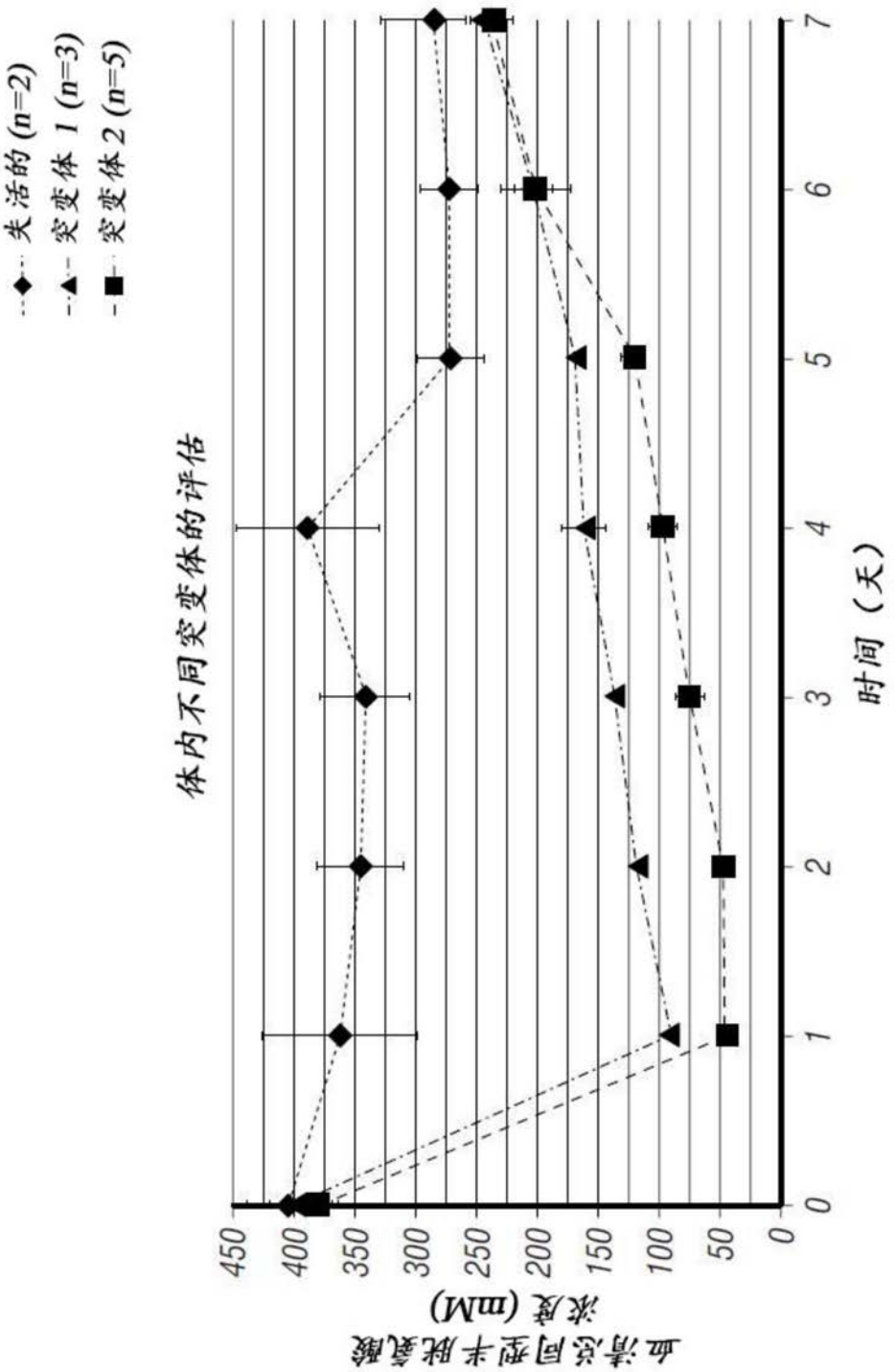
失活的 (n=2)
突变体 1 (n=3)
突变体 2 (n=5)
体内不同突变体的评估
血清总同型半胱氨酸
浓度 (mM)
时间（天）
0
50
100
150
200
250
300
350
400
450
0
1
2
3
4
5
6
7

图1

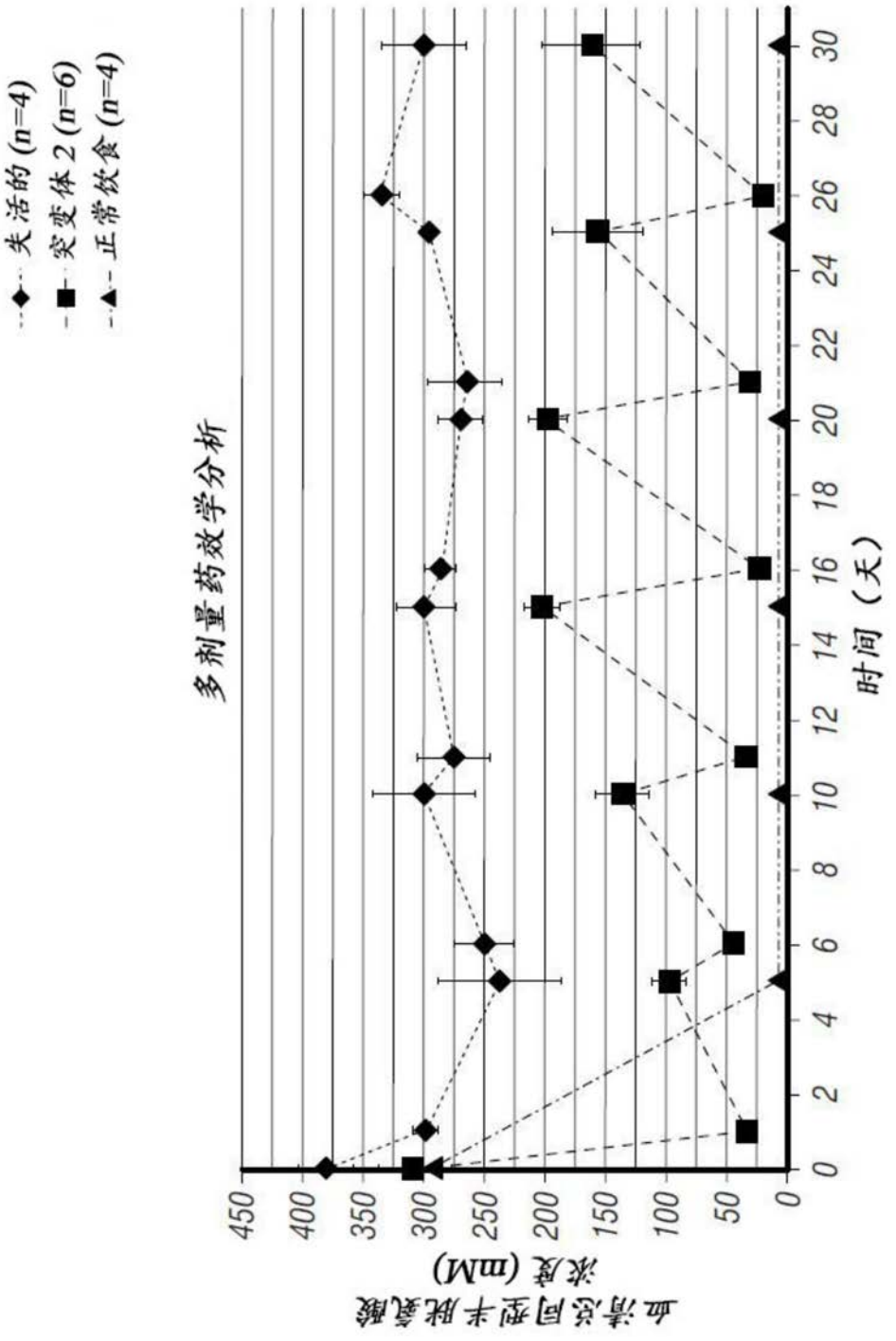
失活的 (n=4)
突变体 2 (n=6)
正常饮食 (n=4)
多剂量药效学分析
血清总同型半胱氨酸
浓度 (mM)
时间（天）
0
50
100
150
200
250
300
350
400
450
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30

图2

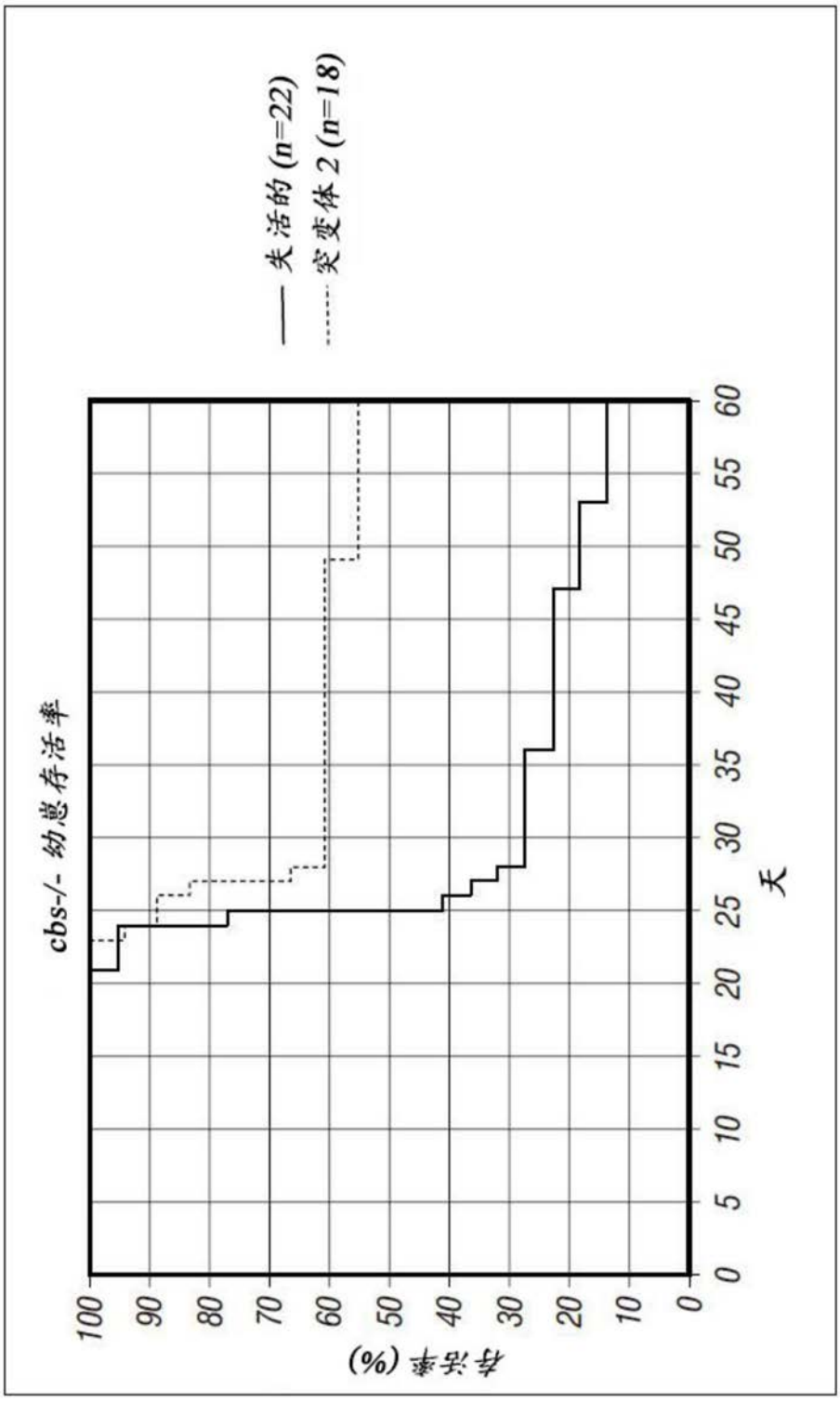
失活的 (n=22)
突变体 2 (n=18)
cbs-/- 幼崽存活率
存活率 (%)
天
0
10
20
30
40
50
60
70
80
90
100
0
5
10
15
20
25
30
35
40
45
50
55
60

图3

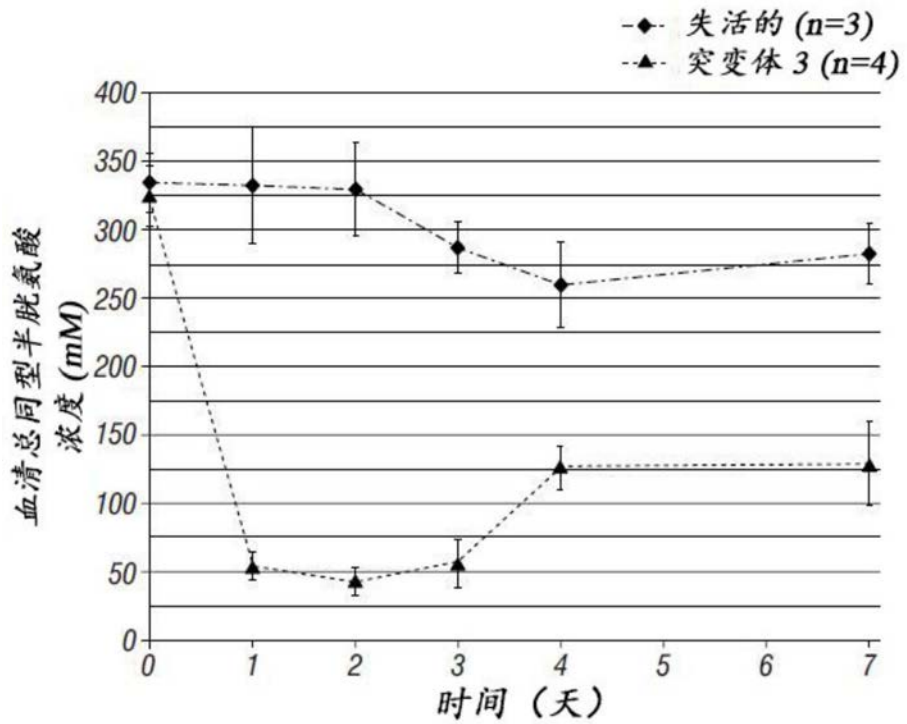
失活的 (n=3)
突变体 3 (n=4)
血清总同型半胱氨酸浓度 (mM)
400
350
300
250
200
150
100
50
0
0
1
2
3
4
5
6
7
时间（天）

图4

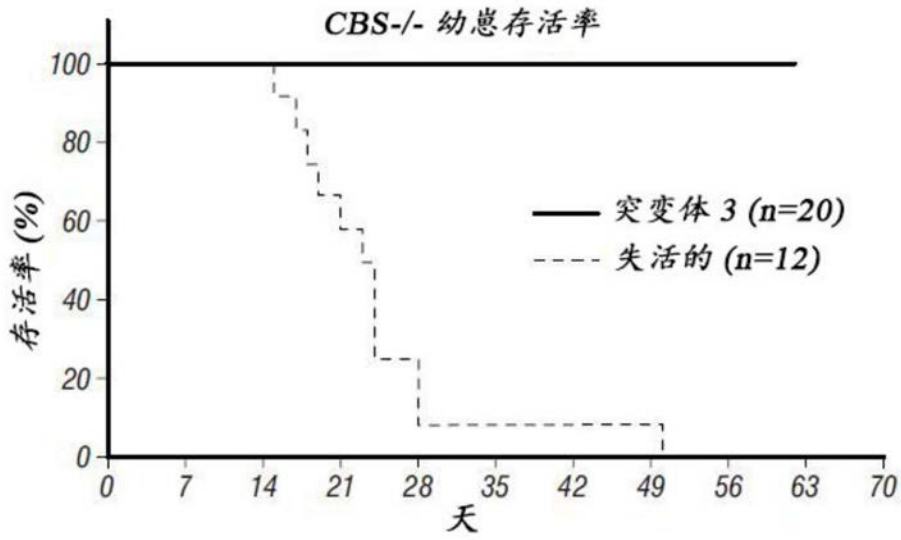
CBS-/- 幼崽存活率
存活率 (%)
100
80
60
40
20
0
0
7
14
21
28
35
42
49
56
63
70
天
突变体 3 (n=20)
失活的 (n=12)

图5

```
                                                  *   *
SEQ ID NO: 1    1   MQEKDASSQGFLPHFQHFATQAIHVGQDPEQWTSRAVVPPISLSTTFKQGAPGQHSGFEYSRSGNPTRNCLEKAVAALDG  80
SEQ ID NO: 7    1   MQEKEASSQGFLPHFQHFATQAIHVGQEPEQWTSRAVVPPISPSVTFKQGAPGQHSGFVYSRSGNPTRNCLEKAVAALDG  80
SEQ ID NO: 8    1   MQEKDASSQGFLPHFQHFATQAIHVGQEPEQWTSRAVVPLISLSTTFKQAAPGQHSGFEYSRSGNPTRNCLEKAVAALDG  80
SEQ ID NO: 9    1   MQEKDASSQGFLPHFQHFATQAIHVGQDPEQWTSRALVPPISLSTTFKQGAPGQHSGFEYSRSGNPTRNCLEKAVAALDG  80
SEQ ID NO: 10   1   MQEKDASSQGFLPHFQHFATQAIHVGQDPEQWTSKALVPPISLSTTFKQGAPGQHSGFEYSRSGNPTRNCLEKAVAALDG  80

                                        *                   *
SEQ ID NO: 1    81  AKYCLAFASGLAATVTITHLLKAGDQIICMDDVYGGTNRYFRQVASEFGLKISFVDCSKIKLLEAAITPETKLVWIETPT  160
SEQ ID NO: 7    81  AKYCLAFASGLAATVTITHLLKAGDQIICMDDVYAGTNRYFRQVASEFGLKISFVDCSKIKLLEAAITPETKLVWIETPT  160
SEQ ID NO: 8    81  AKYCLAFASGLAATVTITHLLKAGDQIICMDDVYGGTNRYFRQVASEFGLKISFVDCSKIKLLEAAITPETKLVWIETPT  160
SEQ ID NO: 9    81  AKYCLAFASGLAATVTITHLLKAGDQIICMDDVYGGTNRYFRQVASEFGLKISFVDCSKIKLLEAAITPETKLVWIETPT  160
SEQ ID NO: 10   81  AKYCLAFASGLAATVTITHLLKAGDQIICMDDVYGGTNRYFRQVASEFGLKISFVDCSKIKLLEAAITPETKLVWIETPT  160

SEQ ID NO: 1    161 NPTQKVIDIEGCAHIVHKHGDIILVVDNTFMSPYFQRPLALGADISMYSATKYMNGHSDVVMGLVSVNCESLHNRLRFLQ  240
SEQ ID NO: 7    161 NPTQKMTDIEACAHIVHKHGDIILVVDNTFMSPYFQRPLALGADICMCSATKYMNGHSDVVMGLVSVNCESLYNRLRFLQ  240
SEQ ID NO: 8    161 NPVLKMIDIEACAHIVHKRGDIILVVDNTFMSPYFQRPLALGADICMCSATKYMNGHSDVVMGLVSVNCERLHNRLRFLQ  240
SEQ ID NO: 9    161 NPTQKVIDIEACAHIVHKHGDIILVVDNTFMSPYFQRPLALGADICMYSATKYMNGHSDVVMGLVSVNCESLHNRLRFLQ  240
SEQ ID NO: 10   161 NPTQKVIDIEACAHIVHKHGDIILVVDNTFMSPYFQRPLALGADICMYSATKYMNGHSDVVIGLVSVNCESLHNRLRFLQ  240
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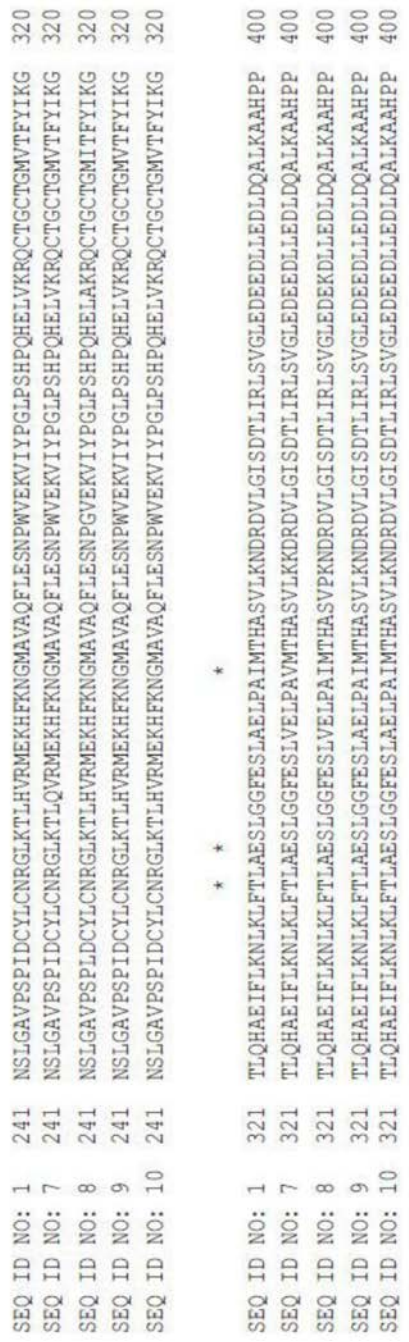
图6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SEQ ID NO: 7 241 NSLGAVPSPIDCYLCNRGLKTLQVRMEKHFKNGMAVAQFLESNPWVEKVIYPGLPSHPQHELVKRQCTGCTGMVTFYIKG 320
SEQ ID NO: 8 241 NSLGAVPSPLDCYLCNRGLKTLHVRMEKHFKNGMAVAQFLESNPGVEKVIYPGLPSHPQHELAKRQCTGCTGMITFYIKG 320
SEQ ID NO: 9 241 NSLGAVPSPIDCYLCNRGLKTLHVRMEKHFKNGMAVAQFLESNPWVEKVIYPGLPSHPQHELVKRQCTGCTGMVTFYIKG 320
SEQ ID NO: 10 241 NSLGAVPSPIDCYLCNRGLKTLHVRMEKHFKNGMAVAQFLESNPWVEKVIYPGLPSHPQHELVKRQCTGCTGMVTFYIKG 320
SEQ ID NO: 1 321 TLQHAEIFLKNLKLFTLAESLGGFESLAELPAIMTHASVLKNDRDVLGISDTLIRLSVGLEDEEDLLEDLDQALKAAHPP 400
SEQ ID NO: 7 321 TLQHAEIFLKNLKLFTLAESLGGFESLVELPAVMTHASVLKKDRDVLGISDTLIRLSVGLEDEEDLLEDLDQALKAAHPP 400
SEQ ID NO: 8 321 TLQHAEIFLKNLKLFTLAESLGGFESLVELPAIMTHASVPKNDRDVLGISDTLIRLSVGLEDEKDLLEDLDQALKAAHPP 400
SEQ ID NO: 9 321 TLQHAEIFLKNLKLFTLAESLGGFESLAELPAIMTHASVLKNDRDVLGISDTLIRLSVGLEDEEDLLEDLDQALKAAHPP 400
SEQ ID NO: 10 321 TLQHAEIFLKNLKLFTLAESLGGFESLAELPAIMTHASVLKNDRDVLGISDTLIRLSVGLEDEEDLLEDLDQALKAAHPP 400
SEQ ID NO: 1 401 SGSHS 405
SEQ ID NO: 7 401 SGSHS 405
SEQ ID NO: 8 401 SGSHN 405
SEQ ID NO: 9 401 SGSHS 405
SEQ ID NO: 10 401 SGSHS 405

图6(续)