



(12)发明专利申请

(10)申请公布号 CN 111373031 A

(43)申请公布日 2020.07.03

(21)申请号 201880074245.5

(22)申请日 2018.11.10

(30)优先权数据

62/584,449 2017.11.10 US

(85)PCT国际申请进入国家阶段日

2020.05.15

(86)PCT国际申请的申请数据

PCT/US2018/060227 2018.11.10

(87)PCT国际申请的公布数据

W02019/094847 EN 2019.05.16

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(51)Int.Cl.

C12N 5/0783(2006.01)

A61K 38/17(2006.01)

C07K 16/28(2006.01)

A61K 39/395(2006.01)

权利要求书5页 说明书80页

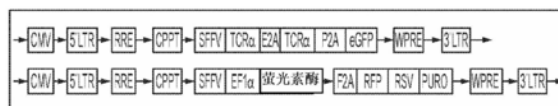
序列表209页 附图10页

(54)发明名称

基于主要组织相容性复合物的嵌合受体和其用于治疗自身免疫性疾病的用途

(57)摘要

用于靶向自身反应性免疫细胞的基于主要组织相容性复合物的嵌合受体(MHC-CAR)。由此还提供了表达MHC-CAR的遗传改造的免疫细胞，用于治疗自身免疫性疾病，例如多发性硬化。



1. 一种基于主要组织相容性复合物 (MHC) 的嵌合受体, 包含:
 - (i) 与来自参与自身免疫性疾病的抗原的抗原肽缀合的MHC分子的胞外结构域; 以及
 - (ii) 胞质信号传导结构域、至少一个共刺激结构域或其组合。
2. 根据权利要求1所述的基于MHC的嵌合受体, 其包含至少一个共刺激结构域。
3. 根据权利要求2所述的基于MHC的嵌合受体, 其中所述至少一个共刺激结构域是来自4-1BB (CD137) 的共刺激结构域、来自CD28的共刺激结构域或其组合。
4. 根据权利要求2或权利要求3所述的基于MHC的嵌合受体, 其中所述基于MHC的嵌合受体不含胞质信号传导结构域。
5. 根据权利要求1-4中任一项所述的基于MHC的嵌合受体, 其进一步包含位于(i) 和(ii) 之间的铰链结构域。
6. 根据权利要求1-5中任一项所述的基于MHC的嵌合受体, 其包含CD3 ζ 的胞质信号传导结构域。
7. 根据权利要求1-3中任一项所述的基于MHC的嵌合受体, 其中所述抗原肽来自髓磷脂碱性蛋白 (MBP)、髓磷脂少突胶质细胞糖蛋白 (MOG)、蛋白脂质蛋白质 (PLP)、胰岛素、谷氨酸脱羧酶或在表1中所描述。
8. 根据权利要求1-7中任一项所述的基于MHC的嵌合受体, 其中所述MHC分子是I类MHC。
9. 根据权利要求8所述的基于MHC的嵌合受体, 其中所述I类MHC是人I类MHC。
10. 根据权利要求8或权利要求9所述的基于MHC的嵌合受体, 其中所述嵌合受体的胞外结构域包含I类MHC的 α 链的胞外结构域, 其与所述抗原肽融合。
11. 根据权利要求10所述的基于MHC的嵌合受体, 其中所述嵌合受体是融合多肽, 其包含(i) I类MHC分子的胞外结构域和(ii) 胞质结构域、至少一个共刺激结构域或其组合。
12. 根据权利要求11所述的基于MHC的嵌合受体, 其中所述嵌合受体是融合多肽, 其从N末端至C末端包含信号肽、第一肽接头、抗原肽、第二肽接头、巨球蛋白的胞外结构域、第三肽接头、I类MHC分子、跨膜结构域、至少一个共刺激结构域和CD3 ζ 。
13. 根据权利要求1-7中任一项所述的基于MHC的嵌合受体, 其中所述MHC分子是II类MHC。
14. 根据权利要求13所述的基于MHC的嵌合受体, 其中所述II类MHC是人MHC II。
15. 根据权利要求13或权利要求14所述的基于MHC的嵌合受体, 其中所述嵌合受体包含第一多肽和第二多肽, 所述第一多肽包含第一MHC II类的胞外结构域, 所述第二多肽包含第二MHC II类的 β 链的胞外结构域, 以及其中所述抗原肽与第一多肽或第二多肽融合, 以及其中第一多肽或第二多肽进一步包含胞质信号传导结构域、至少一个共刺激结构域或其组合。
16. 根据权利要求13或权利要求14所述的基于MHC的嵌合受体, 其中所述嵌合受体是融合多肽, 其包含(i) 第一MHC II类分子的 α 链的胞外结构域, (ii) 第二MHC II类分子的 β 链的胞外结构域, (iii) 抗原肽和(iv) 胞质信号传导结构域、至少一个共刺激结构域或其组合。
17. 根据权利要求13-16中任一项所述的基于MHC的嵌合受体, 其中所述第一MHC II类是HLA-DRA*1010。
18. 根据权利要求13-17中任一项所述的基于MHC的嵌合受体, 其中所述第二MHC II类是HLA-DRB1*1501。

19. 一种核酸或核酸组,其共同编码权利要求1-18中任一项的基于MHC的嵌合受体。
20. 根据权利要求19所述的核酸或核酸组,其中所述核酸或核酸组位于病毒载体中。
21. 一种遗传修饰的免疫细胞,其表达权利要求1-18中任一项的基于MHC的嵌合受体。
22. 根据权利要求21所述的遗传修饰的免疫细胞,其是T细胞。
23. 根据权利要求22所述的遗传修饰的免疫细胞,其中内源性T细胞受体(TCR)的活性受到抑制。
24. 根据权利要求23所述的遗传修饰的免疫细胞,其中内源性TCR的 α 链、内源性TCR的 β 链或二者被突变或缺失,以破坏内源性TCR的表面表达。
25. 根据权利要求22-24中任一项所述的遗传修饰的免疫细胞,其中内源性CD52的表达受到破坏。
26. 根据权利要求21-25中任一项所述的遗传修饰的免疫细胞,进一步表达自杀基因、标记基因或二者。
27. 根据权利要求26所述的遗传修饰的免疫细胞,其中所述自杀基因是RQR8。
28. 根据权利要求26所述的遗传修饰的免疫细胞,其中所述标记基因是荧光蛋白基因。
29. 根据权利要求21-28中任一项所述的遗传修饰的免疫细胞,其中所述免疫细胞经进一步修饰以进行淋巴结递送和保留。
30. 根据权利要求29所述的遗传修饰的免疫细胞,其中所述免疫细胞经进一步改造以过表达VAP-1、L-选择蛋白、CCR7或其组合。
31. 根据权利要求29或权利要求30所述的遗传修饰的免疫细胞,其中内源性鞘氨醇-1-磷酸受体1的表达在免疫细胞中被破坏。
32. 根据权利要求21-28中任一项所述的遗传修饰的免疫细胞,其中所述免疫细胞经进一步修饰以表达一种或多种表面分子,以进行三级淋巴结或异位淋巴结递送和保留。
33. 根据权利要求21-32中任一项所述的遗传修饰的免疫细胞,其中所述免疫细胞经IL6ST敲除、IL6R敲除或二者修饰。
34. 根据权利要求21-33中任一项所述的遗传修饰的免疫细胞,其中所述免疫细胞经进一步修饰以表达或过度表达趋化因子受体。
35. 根据权利要求34所述的遗传修饰的免疫细胞,其中所述趋化因子受体参与病理细胞向发炎组织的迁移。
36. 根据权利要求35所述的遗传修饰的免疫细胞,其中所述趋化因子受体包含CCR5、CXCR3、CCR4、CCR3、CCR6、CXCR3、CXCR4、CXCR5或其组合。
37. 根据权利要求21-36中任一项所述的遗传修饰的免疫细胞,其中所述免疫细胞经进一步修饰以表达或过度表达粘附受体。
38. 根据权利要求37所述的遗传修饰的免疫细胞,其中所述粘附受体参与病理免疫细胞向发炎区域的运输。
39. 根据权利要求38所述的遗传修饰的免疫细胞,其中所述粘附受体包含VLA-4、 $\alpha_4\beta_1$ 、 $\alpha_4\beta_7$ 、 $\alpha_L\beta_2$ 或其组合。
40. 根据权利要求21-39中任一项所述的遗传修饰的免疫细胞,进一步包含导致PD-1信号传导的阻断的遗传修饰。
41. 根据权利要求40所述的遗传修饰的免疫细胞,其中所述修饰是PD-1敲除、PD-L1敲

除或其组合。

42. 根据权利要求21-41中任一项所述的遗传修饰的免疫细胞, 其是调节性T细胞, 其中所述调节性T细胞是CD25⁺。

43. 根据权利要求42所述的遗传修饰的免疫细胞, 其中所述调节性T细胞衍生自从外周血单核细胞分离的CD25⁺⁺CD45R⁺T细胞。

44. 根据权利要求42所述的遗传修饰的免疫细胞, 其中所述调节性T细胞包含编码CD25的转基因。

45. 根据权利要求42-44中任一项所述的遗传修饰的免疫细胞, 其中所述调节性T细胞包含编码FoxP3的转基因。

46. 根据权利要求42-45中任一项所述的遗传修饰的免疫细胞, 其中所述调节性T细胞进一步表达对CD19特异性的嵌合受体、对CS-1特异性的嵌合受体或二者。

47. 根据权利要求42-46中任一项所述的遗传修饰的免疫细胞, 其中所述调节性T细胞进一步表达CCR6、CXCR5、PD-1或其组合。

48. 根据权利要求42-47中任一项所述的遗传修饰的免疫细胞, 其中所述调节性T细胞是CD4⁺。

49. 根据权利要求42-48中任一项所述的遗传修饰的免疫细胞, 其中所述调节性T细胞展示对自身抗原特异性的抗体。

50. 根据权利要求49所述的遗传修饰的免疫细胞, 其中所述自身抗原是表1所列的自身抗原。

51. 根据权利要求50所述的遗传修饰的免疫细胞, 其中所述自身抗原是MOG。

52. 根据权利要求42-51中任一项所述的遗传修饰的免疫细胞, 其中所述细胞分泌抗炎性细胞因子。

53. 根据权利要求52所述的遗传修饰的免疫细胞, 其中所述抗炎性细胞因子包含IL-35、IL-10和/或TGF- β 。

54. 根据权利要求21-41中任一项所述的遗传修饰的免疫细胞, 其是细胞毒性淋巴细胞, 其中细胞毒性T细胞是CD8⁺。

55. 根据权利要求54所述的遗传修饰的免疫细胞, 其中所述细胞毒性T细胞衍生自从外周血单核细胞分离的CD8⁺T细胞。

56. 根据权利要求54或权利要求55所述的遗传修饰的免疫细胞, 其中所述细胞毒性T细胞进一步表达对CD19特异性的嵌合受体、对CS-1特异性的嵌合受体或二者。

57. 根据权利要求54-56中任一项所述的遗传修饰的免疫细胞, 其中所述细胞毒性T细胞进一步表达CCR6、CXCR5、PD-1或其组合。

58. 一种用于抑制具有自身免疫性疾病的受试者的自身反应性免疫细胞的方法, 包括给予所述受试者有效量的权利要求21-57中任一项所述的遗传修饰的免疫细胞。

59. 根据权利要求58所述的方法, 其中所述遗传修饰的免疫细胞是T细胞。

60. 根据权利要求58或权利要求59所述的方法, 其中所述自身免疫性疾病是多发性硬化。

61. 根据权利要求58-60中任一项所述的方法, 其中所述遗传修饰的免疫细胞是自体的。

62. 根据权利要求58-60中任一项所述的方法, 其中所述遗传修饰的免疫细胞是同种异体的。

63. 根据权利要求58-62中任一项所述的方法, 其中将所述遗传修饰的免疫细胞给予至受试者的淋巴结。

64. 根据权利要求58-63中任一项所述的方法, 其中所述受试者正经历包含对CD52特异性的抗体的疗法。

65. 根据权利要求58-64中任一项所述的方法, 其中所述受试者是具有多发性硬化或多发性硬化风险的人患者, 以及所述遗传修饰的T细胞是权利要求33-43中任一项所述的Treg细胞。

66. 根据权利要求65所述的方法, 其中所述人患者是早期MS患者, 以及所述Treg细胞表达MHC-CAR并具有的一种或多种以下遗传修饰:

- (i) PD-L1和/或PD-1敲除;
- (ii) CCR6和/或CXCR5的表面表达;
- (iii) 对MOG特异性的抗体或其抗原结合片段的表面展示; 以及
- (iv) 靶向CD19的嵌合受体的表面表达。

67. 根据权利要求66所述的方法, 其中所述人患者具有复发-缓解性MS或早期进行性MS, 以及所述Treg细胞表达MHC-CAR并具有的一种或多种以下修饰:

- (i) 靶向CD19的嵌合受体的表面表达; 以及
- (ii) CXCR5的表面表达。

68. 根据权利要求66所述的方法, 其中所述人患者具有复发-缓解性MS或早期进行性MS, 以及所述Treg细胞表达MHC-CAR并具有的一种或多种以下修饰:

- (i) 对MOG特异性的抗体或其抗原结合片段的表面展示; 以及
- (ii) CCR6的表面表达。

69. 根据权利要求66所述的方法, 其中所述人患者具有慢性进行性形式的MS, 以及所述Treg细胞表达MHC-CAR并具有的一种或多种以下修饰:

- (i) 靶向CS-1的嵌合受体的表面表达; 以及
- (ii) 靶向CXCR4和/或CXCR3的试剂的表面表达。

70. 根据权利要求66所述的方法, 其中所述人患者是早期MS患者, 以及所述细胞毒性CD8 T细胞表达MHC-CAR并具有的一种或多种以下遗传修饰:

- (i) PD-L1和/或PD-1敲除;
- (ii) CCR6和/或CXCR5的表面表达;
- (iii) 对MOG特异性的抗体或其抗原结合片段的表面展示; 以及
- (iv) 靶向CD19的嵌合受体的表面表达。

71. 根据权利要求58-67中任一项所述的方法, 其中所述受试者是具有多发性硬化或多发性硬化风险的人患者, 以及所述遗传修饰的T细胞是权利要求54-57中任一项所述的细胞毒性CD8+T细胞。

72. 根据权利要求71所述的方法, 其中所述人患者具有复发-缓解性MS或早期进行性MS, 以及所述细胞毒性CD8 T细胞表达MHC-CAR并具有的一种或多种以下修饰:

- (i) 靶向CD19的嵌合受体的表面表达; 以及

(ii) CXCR5的表面表达。

73. 根据权利要求71所述的方法, 其中所述人患者具有复发-缓解性MS或早期进行性MS, 以及所述细胞毒性CD8 T细胞表达MHC-CAR并具有以下一种或多种修饰:

(i) 对MOG特异性的抗体或其抗原结合片段的表面展示; 以及

(ii) CCR6的表面表达。

74. 根据权利要求71所述的方法, 其中所述人患者具有慢性进行性形式的MS, 以及所述细胞毒性CD8 T细胞表达MHC-CAR并具有以下一种或多种修饰:

(i) 靶向CS-1的嵌合受体的表面表达; 以及

(ii) 靶向CXCR4和/或CXCR3的试剂的表面表达。

75. 根据权利要求58-74中任一项所述的方法, 其中给予所述人患者权利要求33-43中任一项所述的Treg细胞和权利要求54-57中任一项所述的细胞毒性细胞二者。

76. 根据权利要求75所述的方法, 其中所述Treg细胞和所述细胞毒性细胞被同时或序贯给予。

基于主要组织相容性复合物的嵌合受体和其用于治疗自身免疫性疾病的用途

[0001] 相关申请

[0002] 本申请要求2017年11月10日提交的美国临时申请序列号62/584,449的申请日的权益。该参考申请的全部内容通过引用并入本文。

背景技术

[0003] 自身免疫性疾病的特征为针对自身抗原的异常免疫反应,导致组织的损害或破坏。多发性硬化(MS)是一种中枢神经系统自身免疫性疾病,其中活化的自身反应性T细胞侵袭血脑屏障,启动导致髓磷脂破坏和轴突丧失的炎性反应。尽管MS的病因、与其发病和进展有关的机制以及其后果的确定仍未阐明,但所有可用的证据表明特异性靶向负责MS的病理免疫细胞的疗法将具有在可获得的疗法中改进的治疗后果。Reinhard等人,Proceedings of the National Academy of Sciences (国家科学院院刊),101(suppl 2):14599-14606; 2004。该策略可延伸到具有类似机制的其它免疫病症,包括类风湿性关节炎。Carol等人, Nature Reviews Immunology (自然评论免疫学),2(2):85-95,2002。

[0004] 主要组织相容性复合物(MHC),在人类中称为人白细胞(HLA),是对于免疫系统识别外来试剂所必需的一组细胞表面蛋白。MHC复合物结合衍生自病原体的抗原并将其展示给T细胞,其然后被活化,导致消除展示外来抗原的细胞。MHC复合物也可展示完整(和在一些情况下错误折叠)的宿主来源的蛋白到B细胞,从而诱导自身免疫性病症典型的自身抗体反应。Jiang等人,International immunology (国际免疫学),25(4):235-246(2013)和 Busch等人,The EMBO journal (欧洲分子生物学杂志),15(2):418,(1996)。

发明内容

[0005] 在一方面,本公开的特征为基于主要组织相容性复合物(MHC)的嵌合受体(CAR),包含:(i)与来自参与自身免疫性疾病的抗原的抗原肽缀合的MHC分子的胞外结构域;以及(ii)胞质信号传导结构域、至少一个共刺激结构域或其组合。基于MHC的CAR可进一步包含位于(i)和(ii)之间的铰链结构域。抗原肽取决于自身免疫性病症,并且可来自髓磷脂碱性蛋白(MBP)、蛋白脂质蛋白质(PLP)、胰岛素、谷氨酸脱羧酶或表1所述的其它示例性自身抗原。

[0006] 在一些实例中,基于MHC的嵌合受体包含至少一个共刺激结构域,其可以是来自4-1BB(CD137)的共刺激结构域、来自CD28的共刺激结构域或其组合。在其它实例中,本文所述的基于MHC的嵌合受体可不含胞质信号传导结构域。备选地或另外,MHC-CAR包含CD3 ζ 的胞质信号传导结构域。

[0007] 在一些实施方案中,MHC-CAR中的MHC分子是I类MHC,例如人I类MHC。在一些情况下,嵌合受体的胞外结构域包含I类MHC的 α 链的胞外结构域,其与抗原肽融合。例如,嵌合受体可以是融合多肽,包含(i)I类MHC分子的胞外结构域,以及(ii)胞质结构域、至少一个共刺激结构域或其组合。在一个实例中,嵌合受体是融合多肽,其从N末端到C末端包含信号

肽、第一肽接头、抗原肽、第二肽接头、巨球蛋白的胞外结构域、第三肽接头、I类MHC分子、跨膜结构域、至少一个共刺激结构域和CD3 ζ 。

[0008] 在其它实施方案中,本文所述的基于MHC的嵌合受体包含II类MHC(例如,人MHC II)或其部分。这样的嵌合受体可包含第一多肽和第二多肽,第一多肽包含第一MHC II类的胞外结构域,第二多肽包含第二MHC II类的 β 链的胞外结构域,以及其中抗原肽与第一多肽或第二多肽融合,以及其中第一多肽或第二多肽进一步包含胞质信号传导结构域、至少一个共刺激结构域或其组合。在一些实例中,嵌合受体可以是融合多肽,包含(i)第一MHC II类分子的 α 链的胞外结构域、(ii)第二MHC II类分子的 β 链的胞外结构域、(iii)抗原肽、以及(iv)胞质信号传导结构域、至少一个共刺激结构域或其组合。在一些实例中抗原蛋白可不与MHC II类连接,而是可作为具有可选的信号肽(例如来自CD150,即MDPKGLLSLTFLFLSLAFG(SEQ ID NO:388))的单独的融合多肽而表达。在一些实例中,第一MHC II类是HLA-DRA*1010。备选地或另外,第二MHC II类是HLA-DRB1*1501。

[0009] 在另一方面,本公开的特征为核酸或核酸组,其共同编码任何本文所述的基于MHC的嵌合受体。在一些情况下,核酸或核酸组可位于一种或多种载体中,例如病毒载体。

[0010] 此外,本公开提供了遗传修饰的免疫细胞(例如,T细胞),其表达任何本文所述的基于MHC的嵌合受体。在一些情况下,内源性T细胞受体(TCR)的活性可受到抑制,这可通过突变或缺失内源性TCR的 α 链、内源性TCR的 β 链或二者以破坏内源性TCR的表面表达来实现。备选地或另外,内源性CD52的表达可受到破坏。

[0011] 在一些实施方案中,本文所述的遗传修饰的免疫细胞可进一步表达自杀基因(例如,RQR8)、标记基因(例如,GFP)或二者。当需要时,免疫细胞可经进一步修饰以进行淋巴结或三级淋巴器官递送和保留。例如,免疫细胞可经进一步改造以过表达VAP-1、L-选择蛋白、CCR7、CXCR5或其组合。在一些情况下,内源性鞘氨醇-1-磷酸受体1的表达可在遗传修饰的免疫细胞中被破坏。

[0012] 在一些实施方案中,免疫细胞可经改造以移动至炎症位点,例如使用趋化因子受体例如CCR6(例如,至Th17细胞的位点)、CXCR3或CXCR4(例如,至浆细胞的位点)或通过膜连接的抗原靶向抗体。备选地或另外,遗传修饰的免疫细胞可进一步包含导致PD-1信号传导的阻断的遗传修饰。如果需要并且病症是特别严重的,MHC-CAR细胞也可经设计以除去或失活旁观者B细胞(用CD19或CD20-CAR)或浆细胞(用CS1-CAR和/或CS1敲除)。

[0013] 在一些实施方案中,本文所述的遗传修饰的免疫细胞可以是调节性T细胞,其可以是CD25⁺和任选地CD4⁺。在一些情况下,调节性T细胞可衍生自从外周血单核细胞或从脐带血分离的CD25⁺CD45R⁺T细胞。在其它情况下,调节性T细胞可包含编码CD25的转基因。任何本文公开的Treg细胞可进一步表达对CD19特异性的嵌合受体、对CS-1特异性的嵌合受体或二者。备选地或另外,调节性T细胞可进一步表达CCR6、CXCR5、PD-1或其组合。在一些实例中,调节性T细胞可展示对MOG特异性的抗体。

[0014] 在又一方面,本公开提供了用于抑制具有自身免疫性疾病(例如,多发性硬化)的受试者的自身反应性免疫细胞的方法。所述方法可包括给予受试者有效量的本文所述的遗传修饰的免疫细胞,其可为T细胞。

[0015] 在一些实施方案中,遗传修饰的免疫细胞是自体的。在其它实施方案中,遗传修饰的免疫细胞是同种异体的。任何遗传修饰的免疫细胞可给予至受试者的淋巴结。在一些情

况下,受试者正经历包含对CD52特异性的抗体的疗法。

[0016] 在一些实施方案中,受试者是具有多发性硬化或有多发性硬化风险的人患者,以及遗传修饰的T细胞是本文所述的Treg细胞或细胞毒性淋巴细胞 (CTLs)。

[0017] 在一些实例中,人患者是早期MS患者,以及Treg细胞表达MHC-CAR并具有一种或多种以下遗传修饰:(i) PD-L1和/或PD-1敲除;(ii) CCR6和/或CXCR5的表面表达;(iii) 对MOG特异性的抗体或其抗原结合片段的表面展示;以及(iv) 靶向CD19的嵌合受体的表面表达。在一些实例中患者可首先、同时或可选地用具有相同类型的修饰的细胞毒性CTL治疗。

[0018] 在一些实例中,人患者具有复发-缓解性MS或早期进行性MS,以及Treg细胞表达MHC-CAR并具有一种或多种以下修饰:(i) 对MOG特异性的抗体或抗原结合片段的表面展示;以及(ii) CCR6的表面表达。在一些实例中患者可首先、同时或可选地用具有相同类型的修饰的细胞毒性CTL治疗。

[0019] 在一些实例中,人患者具有复发-缓解性MS或早期进行性MS,以及Treg细胞表达MHC-CAR并具有一种或多种以下修饰:(i) 靶向CD19的嵌合受体的表面表达;以及(ii) CXCR5的表面表达。在一些实例中患者可首先、同时或可选地用具有相同修饰的CTL治疗。

[0020] 在一些实例中,人患者具有慢性进行性形式的MS,以及Treg细胞表达MHC-CAR并具有一种或多种以下修饰:(i) 靶向CS-1的嵌合受体的表面表达;以及(ii) 试剂CXCR4、CCR6和/或CXCR5的表面表达。在一些实例中患者可首先、同时或可选地用具有相同修饰的CTL治疗。

[0021] 在一些实施方案中,受试者是具有或有风险发生系统性红斑狼疮、类风湿性关节炎、幼年特发性关节炎(亦称为幼年特发性关节炎)、斯耶格伦氏综合征、系统性硬化症、强直性脊柱炎、1型糖尿病、自身免疫性甲状腺病(格雷夫氏病和桥本氏病)、多发性硬化、重症肌无力、炎性肠病(克罗恩氏病或溃疡性结肠炎)、银屑病或表1中提及的疾病的人患者,以及遗传修饰的T细胞是本文所述的Treg细胞和/或CTL。

[0022] 在一些实例中,人患者是任何本文所述的自身免疫性病症(例如,表1所列的那些)的早期患者,以及Treg细胞表达MHC-CAR并具有一种或多种以下遗传修饰:(i) PD-L1和/或PD-1敲除;(ii) CCR6和/或CXCR5的表面表达;(iii) 抗体或其抗原结合片段的表面展示,其对表1中描述为自身免疫性病症的自身抗原的相关蛋白是特异性的;以及(iv) 靶向CD19的嵌合受体的表面表达。在一些实例中,患者可首先、同时或可选地用具有相同修饰的CTL治疗。

[0023] 在一些实例中,人患者具有任何本文所述的自身免疫性病症(例如,表1所列的那些)的中等严重疾病状态,以及Treg细胞表达MHC-CAR并具有一种或多种以下修饰:(i) 对表1中描述为对于自身免疫性病症的自身抗原的相关蛋白特异性的抗体或抗原结合片段的表面展示;以及(ii) CCR6的表面表达。在一些实例中,患者可首先、同时或可选地用具有相同修饰的CTL治疗。

[0024] 在一些实例中,人患者具有任何本文所述的自身免疫性病症(例如,表1所列的那些)的中等严重疾病状态,以及Treg细胞表达MHC-CAR并具有一种或多种以下修饰:(i) 靶向CD19的嵌合受体的表面表达;以及(ii) CXCR5的表面表达。在一些实例中,患者可首先、同时或可选地用具有相同修饰的CTL治疗。

[0025] 在一些实例中,人患者具有任何本文所述的自身免疫性病症(例如,表1所列的那

些)的严重疾病状态,以及Treg细胞表达MHC-CAR并具有一种或多种以下修饰:(i)靶向CS-1的嵌合受体的表面表达;以及(ii)靶向CXCR4、CCR6和/或CXCR5的试剂的表面表达。在一些实例中,患者可首先、同时或可选地用具有相同修饰的CTL治疗。

[0026] 还在本公开的范围内的的是用于治疗自身免疫性疾病的药物组合物,所述组合物包含本文所述的表达MHC-CAR的遗传修饰的免疫细胞,例如Treg细胞和药学上可接受的载体,以及这样的遗传修饰的免疫细胞在制备用于治疗目标自身免疫性疾病的药物的用途。

[0027] 本发明的一个或多个实施方案的细节在下面的描述中阐明。本发明的其它特征或优点根据以下附图和若干实施方案的详细描述以及随附的权利要求,将显而易见。

附图说明

[0028] 图1是用于表达抗原特异性T细胞受体(TCR)的慢病毒表达载体的示例性设计的示意图。mRNA和多顺反子mRNA设计是类似的。

[0029] 图2是MHC-CAR T细胞的示意图,其表达MHC-CAR的各种设计,如结合用于靶向参与多发性硬化(MS)的病理T细胞的髓磷脂碱性蛋白(MBP)肽所示。任选地,MHC-CAR T细胞可具有内源性TCR和/或CD52敲除。MHC-CAR T细胞可在细胞表面上进一步表达RQR8。

[0030] 图3是各种MHC-CAR构建体的示例性设计的示意图。示例性MHC-CAR构建体可具有两个亚单元:含有前导序列、DRA*1010结构域和胞质结构域的 α -链和包括来自HLA-DRB1*1501的前导序列、来自MBP的肽和来自HLA-DRB1*1501的结构域的 β -链。用于产生mRNA的DNA含有单链或者是多顺反子的,并被正交2A序列分开。RQR8和eBFP(或GFP)用于细胞对照和标记二者。

[0031] 图4是含有MBP肽的各种MHC-CAR构建体的表达盒的示例性设计的示意图,其可进一步包括eBFP(或GFP)或RQR8。

[0032] 图5是MHC-CAR和任选地标记蛋白例如eBFP和/或RQR8的慢病毒表达构建体的示例性设计的示意图。这样的表达盒将足够小以包括在一个慢病毒包装中。

[0033] 图6是MHC-CAR的示例性设计的示意图,其可包括许多标记用位点。位点1是对于天然HLA-DR不表达或由于CIITA编辑的情况的HLA-DR抗体结合位点。位点2和3是对于多组氨酸-标签基序的潜在的插入位点。位点4和5分别表示RQR和RQR8。

[0034] 图7是与抗原肽连接的MHC II类部分的示例性设计的示意图。“N”是指多肽的N末端。圆形黑点是指抗原肽。

[0035] 图8A和图8B是MHC I类示例性构建体的示意图。图8A描述与抗原肽连接的MHC I类部分的示例性设计。“N”是指多肽的N末端。圆形黑点是指抗原肽。图8B描述MHC I类CAR构建体的示例性表达盒。

[0036] 图9描述用于构建MHC-CAR的示例性共刺激结构域和其组合,以及对于细胞因子的共表达的考虑。

[0037] 图10描述示例性单链和多链MHC I类和II类MHC-CAR构建体,包括含有MHC I类和II类组分二者的多链MHC-CAR构建体。

[0038] 图11是显示在原代人刺激CD3+T细胞(TCELL-0028)上的CD3表达的图,所述细胞用编码Cas9(“仅仅Cas9”)的mRNA或编码Cas9(“仅仅Cas9”)的mRNA和靶向编码T细胞受体 α 结构域(TRAC)(“Cas9+TRAC gRNA”)的基因的sgRNA转染。

[0039] 图12是显示在杀伤测定中的相对细胞成活力的图。用构建体1、构建体2或构建体1和2二者转染的HEK-293细胞用仅仅培养基、利妥昔单抗、补体或利妥昔单抗和补体二者孵育。

具体实施方式

[0040] 自身反应性T细胞(例如,对于参与多发性硬化的髓磷脂组分的那些)存在于正常个体中。疾病诱导的大多数决定因素处于当这些自身反应性T细胞在自身免疫性患者(例如,MS患者)中触发时发生的免疫反应类别中。病理性自身反应性T细胞的产生由特定的主要组织相容性复合物(MHC)和非-MHC基因二者促进,它们决定个体对其反应的蛋白序列和免疫反应类别。

[0041] 一旦对初始自身抗原(例如,MS中的髓磷脂抗原)的免疫攻击开始,存在对其它自身抗原的反应性的扩展;也就是说,如果T细胞攻击一种自身抗原(例如,MS中的脑蛋白),在称为“表位-扩展”的过程中其它结构被破坏并且它们可敏化另外的T细胞以攻击其它目标,该过程被所有自身免疫性病症共享,并且通常对疾病反应是共同的。

[0042] B细胞也是由初始自身反应性攻击引起的早期疾病损伤(例如活性MS损伤)中免疫反应的普通组分。B细胞积聚作为包装的聚集体或异位B细胞滤泡发生。Serafini等人,Brain Pathol(大脑病理).14:164-144(2004);Wekerle,Autoimmunity(自身免疫),50:1,57-60(2017);以及Pröbstel等人,International journal of molecular sciences(国际分子科学杂志),16(7),pp.16576-16592(2015)。在MS中,据报道B细胞存在于RR-、SP-和P-阶段MS患者的脑和脊髓中。已证明直接或间接靶向B细胞的治疗性治疗有利于治疗自身免疫性疾病,例如MS。Wekerle,2017。

[0043] CD4+和CD8+T细胞二者存在于MS损伤中,并且被认为在疾病发展中起中心作用。与健康对照相比,在MS患者中发现增加频率的髓磷脂-活性(MBP、PLP和MOG)CD4和CD8细胞。Cao等人,Sci.Transl.Med.7(287),287ra74(2014);Martin等人,J.Exp.Med.173(1991年1月1日);Ota等人,Nature(自然)346,183(1990年7月12日);Pette等人,Neurology(神经病学)40,1770(1990);以及Raddassi等人,J.Immunol(免疫).187,1039(2011)。

[0044] 产生IFN- γ 的Th1细胞和Th17细胞是独特病原性的。促进Th1细胞发展的因子在MS患者中升高,并且也被病毒感染所触发: γ 干扰素;IL-12-在影响免疫系统和有助于MS的几乎所有治疗中,几乎全部降低Th1反应和增加Th2和Th3反应。Th17细胞存在于组织炎症的位点处,并且参与自身免疫性/慢性炎性病况。产生CD4和CD8细胞的Th17在患者的损伤、血液和CSF中增加。[Tzartos 2008;Matusevicius 1999;Bruchlacher-Waldert 2009]。Th17细胞上的CCR6和CD161被假设是发炎组织的归巢分子[Cosmi,2008]。

[0045] Th17细胞还参与许多其它自身免疫性疾病,例如系统性红斑狼疮、类风湿性关节炎、幼年特发性关节炎(亦称为幼年特发性关节炎)、斯耶格伦氏综合征、系统性硬化症、强直性脊柱炎、1型糖尿病、自身免疫性甲状腺病(格雷夫氏病和桥本氏病)、重症肌无力、炎性肠病(克罗恩氏病或溃疡性结肠炎)和银屑病。Tabarkiewicz等人,Archivum immunologiae et therapiae experimentalis(免疫学与实验治疗档案),63(6):435-449(2015)。

[0046] 自身免疫性疾病的任何治疗的最终目的是完全抑制病理。在多发性硬化和其它自身免疫性病症的情况下,预期病理性淋巴细胞(B和T细胞二者,以及如果需要,对于非常严

重的情况为浆细胞)被消除或被控制以停止疾病过程,并且在疾病进展的不同阶段的干预需要不同的细胞靶标以及因此治疗性细胞。

[0047] 本文公开了基于主要组织相容性复合物(MHC)的嵌合受体(MHC-CAR)以靶向自身反应性免疫细胞,例如自身反应性T细胞。本文所述的MHC-CAR包含一个或多个MHC多肽或其胞外结构域和一个或多个细胞信号传导结构域,例如胞质信号传导结构域(例如,来自CD3 ζ),至少一个共刺激结构域(例如,来自4-1BB或CD28)或二者。MHC-CAR可进一步包含抗原肽,其来自自身抗原或在引发自身免疫反应方面模拟自身抗原的外来抗原。本文还公开了编码MHC-CAR的核酸、携带其的载体和表达MHC-CAR的遗传改造的免疫细胞,例如T细胞和自然杀伤(NK)细胞。这样的遗传改造的免疫细胞可用于靶向自身反应性免疫细胞,从而有利于治疗包括自身反应性免疫细胞的自身免疫性疾病。

[0048] 本文还公开了表达基于MHC的嵌合受体的遗传修饰的调节性T(Treg)细胞,如本文所公开的。可用靶向T细胞和/或B细胞表面标志物的嵌合受体、以及用于例如靶向特定组织位点(例如,淋巴结或炎症位点)或调节免疫反应(例如,检查点调节)的另外的遗传改造,进一步修饰这样的Treg细胞。遗传修饰的Treg细胞可用于在目标疾病的早期抑制病原性,以在疾病中期(例如,复发或缓解性MS)控制疾病进展,或在疾病后期(例如,慢性进行性MS)通过例如诱导病理性CD8+T细胞的细胞毒性来抑制病理。

[0049] I. 基于主要组织相容性复合物(MHC)的嵌合受体(MHC-CAR)

[0050] 本文所述的基于MHC的嵌合受体(MHC-CAR)包含:MHC部分,其与抗原肽(例如,错误折叠的抗原肽)缀合,以及至少一个细胞信号传导部分,其可以是胞质信号传导结构域(例如,CD3 ζ 的胞质信号传导结构域)、一个或多个共刺激结构域(例如,4-1BB或CD28的共刺激结构域)或其组合。在一些情况下,抗原肽可以是MHC-CAR的融合多肽的一部分。在其它情况下,抗原肽不与MHC-CAR形成融合多肽,而是与MHC-CAR形成复合物。如本文使用的,术语“缀合”是指至少两个组分通过共价键或通过非共价相互作用物理缔合。

[0051] 在一些实例中,MHC-CAR可以是单一融合多肽,其含有MHC部分、抗原肽和至少一个细胞信号传导部分。这样的单一融合多肽当在合适的免疫细胞中表达时可与内源性细胞膜蛋白(例如, β -微球蛋白)形成复合物。

[0052] 在其它实例中,本文所述的MHC-CAR可以是多链蛋白复合物,例如异源二聚体,包含一个包含抗原肽的多肽。在一些情况下,抗原肽或多肽可作为单独的多肽表达,其可与MHC组分形成复合物(例如,三聚体)。抗原多肽可以是错误折叠的抗原蛋白,其与MHC结合。任选地,MHC-CAR可进一步包含:铰链结构域,其可邻近抗原肽和/或MHC部分,在N末端的信号肽,和/或一个或多个标记位点,例如组氨酸蛋白标签和/或另外用作杀伤-开关位点的RQR结构域。

[0053] (i) MHC-CAR的组分

[0054] (a) MHC部分

[0055] 本文公开的MHC-CAR构建体包含MHC部分,其可包含一个或多个MHC多肽或其胞外结构域。MHC部分可衍生自合适的来源,例如人或非-人哺乳动物(例如,猴、小鼠、大鼠、兔、猪等)。在一些情况下,MHC部分来自人MHC分子(亦称为HLA)。在一些情况下,与来自其它细胞的分子(TCR或BCR)相互作用的结构域来自人MHC分子。主要有两类MHC分子,MHC I类分子和MHC II类分子,这二者均可用于构建本文所述的MHC-CAR。各种物种(例如,人、非人灵长

类、犬、鱼、羊、牛、马、猪、鼠和鸡)的MHC I类和II类分子的序列可获自公共基因数据库,例如由EMBL-EBI提供的IPD-MHC数据库和IMGT/HLA数据库以及由National Center for Biotechnology Information(国家生物技术信息中心)(NCBI)提供的dbMHC数据库。

[0056] MHC I类分子是含有 α 链和 β -微球蛋白的异源二聚体。 α 链的胞外结构域包括三个子结构域, $\alpha 1$ 、 $\alpha 2$ 和 $\alpha 3$ 。在一些实施方案中,MHC部分可包括MHC I类分子的 α 链或其胞外结构域,例如 $\alpha 1$ 结构域、 $\alpha 2$ 结构域、 $\alpha 3$ 结构域或其组合。MHC I类分子可以是人HLA-A分子、人HLA-B分子或人HLA-C分子。在一些情况下,MHC I类分子的 α 链可与 β -微球蛋白融合以产生单链融合蛋白。在一些实例中,MHC I类部分来自HLA A3,其可与PLP肽共同使用。Honma等人,J.Neuroimmunol(神经免疫).73:7-14(1997)。在其它实例中,MHC I类来自HLA A2,其可与相同的PLP肽一起使用,以及展示病毒肽,例如TAX。TAX来自蛋白tax或p40(Genbank登录号BAB20130.1),其是人神经元蛋白的分子模拟物和来自HTLV-1病毒,该病毒参与疾病,例如类风湿性关节炎、系统性红斑狼疮和斯耶格伦氏综合征。Garboczi等人,The Journal of Immunology(免疫学杂志),157(12):5403-5410,1996。Quaresma等人,2015.Viruses(病毒),8(1):52015。I类蛋白和肽可另外含有能够进行更稳健的肽加载的修饰,例如用丙氨酸置换重链的84位的非变异酪氨酸;或可选地,84位的酪氨酸可用半胱氨酸置换,如肽- $\beta 2m$ 接头的第二位可能的情况,以产生二硫化物桥。Hansen等人,Trends in immunology(免疫学趋势),31(10):363(2010)。

[0057] 如同MHC I类分子,MHC II类分子也是由两个同源肽(α -链和 β -链)组成的异源二聚体。 α -链和 β -链每一个的胞外结构域含有两个子结构域 $\alpha 1/\alpha 2$ 和 $\beta 1/\beta 2$ 。当MHC II类分子用于构建MHC-CAR时,MHC部分可包括两个亚单元,一个包括 α -链或其一部分,例如其胞外结构域(例如, $\alpha 1$ 、 $\alpha 2$ 或二者),另一个包括 β -链或其一部分,例如其胞外结构域(例如, $\beta 1$ 、 $\beta 2$ 或二者)。在其中仅使用与其它细胞类型相互作用的区域的情况下(即, $\alpha 1$ 和 $\beta 1$),可能需要特定的氨基酸修饰以增强微小MHC的折叠,参见具有阴影区域的微小序列和Birnbaum等人。MHC II类分子可以是人HLA DP分子、人HLA DM分子、人HLA DOA分子、人HLA DOB分子、人HLA DQ分子或人HLA DR分子。在一些实例中,MHC II类分子是人HLA DR分子,例如HLA DR*1501。

[0058] (b) 抗原肽

[0059] 本文所述的MHC-CAR的抗原肽是可被参与自身免疫性疾病的病原性免疫细胞(例如,自身反应性T细胞或B细胞)识别的抗原肽。当由合适的MHC分子呈递时,这样的抗原肽将与病原性T细胞的抗原特异性T细胞受体相互作用,导致下游的免疫反应。

[0060] 在一些情况下,特定的抗原肽可使用本领域已知的方法设计用于特定的自身免疫性疾病患者,例如MS患者。程序例如NetMHC能够个性化设计对患者MHC特异性的抗原肽,并已用于开发个性化癌症疫苗。Hacohen等人,Cancer immunology research(癌症免疫学研究),1(1):11-15(2013)。用于自身免疫性病症的个性化CAR T和Treg疗法也在本公开的范围。对于具有非常强的MHC关联的病症(例如MS),个性化疗法可用于治疗在疾病不同阶段的大的患者种类。最近研究还已证明,II类MHC和特别是参与自身免疫性病症的HLA可展示整个抗原蛋白,而不是仅仅加工的肽。Jiang等人,International immunology(国际免疫学),25(4):235-246,(2013)。这些MHC-蛋白复合物似乎在自身免疫性病症中诱导自身抗体产生,包括不结合正确折叠的蛋白的抗体以及对特定自身免疫性病症的那些特异性的自身抗体。本发明人估计MHC-CAR中抗原蛋白的展示可提供除去或失活自身免疫性特异性B细胞

的特定途径,所述细胞例如在MS中产生寡克隆条带的那些,所述条带对蛋白的特异性尚未揭示,尽管有许多严格的尝试。Owens等人,Annals of neurology (神经学年鉴),65 (60): 639-649,2009;Chastre等人,New England Journal of Medicine (新英格兰医学杂志),374 (15):1495-1496,2016;Housley等人,Clinical Immunology (临床免疫学),161 (1):51-58,2015;Larman等人,2013.Journal of autoimmunity (自身免疫杂志),43:1-9,2013。如果抗原蛋白不结合MHC,然后特异性MHC-CAR将不表达,而是作为Treg或CTL,其仍可根据它的其它特征在修饰免疫反应中起到旁观者作用以及作为具有不同特异性的MHC-CAR T和Treg细胞的患者特异性群体的一部分。

[0061] 本文使用的抗原肽可以是参与自身免疫性疾病的自身抗原的片段,例如参与多发性硬化的髓磷脂碱性蛋白 (MBP)、髓磷脂少突胶质细胞糖蛋白 (MOG) 和蛋白脂质蛋白质 (PLP),参与I型糖尿病的胰岛素和谷氨酸脱羧酶 (GAD),参与类风湿性关节炎 (RA) 的类胰蛋白酶,以及下表1中包括的蛋白。或者,抗原肽可以是与参与自身免疫性疾病的自身抗原高度同源的病原体蛋白的片段,所述病原体蛋白例如病毒或细菌蛋白。这样的抗原肽也可靶向病原性T细胞。如果需要,抗原肽可以是(通常错误折叠的)抗原蛋白或蛋白片段,其可单独表达和直接结合本文所述的MHC-CAR的MHC部分。在它们的天然状态下(附接至MHC而不是MHC-CAR的MHC部分),这样的抗原蛋白/MHC复合物刺激病原性B细胞以产生自身抗体。对于蛋白例如类风湿性关节炎中的IgGH或类风湿性因子 (Jin等人,Proceedings of the National Academy of Sciences (国家科学院院刊),111 (10):3787-3792,2014)、抗磷脂综合征 (Tanimura等人,Blood (血液),125 (18):2835-2844,2015) 和复发性流产 (Tanimura等人,Placenta (胎盘),46:108,2016) 中的 β 2-糖蛋白I、自身免疫性肺泡蛋白质沉积症 (Hamano等,ALVEOLAR MACROPHAGE BIOLOGY (肺泡巨噬细胞生物学) B32:A3147-A3147,2016) 中的GM-CSF、白癜风中的酪氨酸酶 (Arase等人,Journal of Dermatological Science (皮肤科学杂志),84 (1):e87,2016) 和显微镜下多血管炎中的髓过氧化物酶 (Hiwa等人,Arthritis&Rheumatology (关节炎与风湿病),69 (10):2069-2080,2017),HLA介导的表面展示以及在一些情况下错误折叠的变体/HLA复合物的自身抗体结合可发生。

[0062] 用于本文所述的MHC-CAR的抗原肽可含有至多20个氨基酸残基,抗原蛋白的胞外结构域或全长抗原蛋白。当与MHC I类部分共同使用时,抗原肽可以是8-10个氨基酸长。这样的抗原肽将充分配合MHC I类分子的肽结合位点。与MHC II类部分共同使用的抗原肽可更长,例如含有15-24个氨基酸残基或至多抗原蛋白的全长,因为MHC II类分子的抗原-结合沟在两端均打开,而在I类分子上相应的抗原-结合沟通常在每一端关闭。参与自身免疫性病症的MHC II类分子的打开的抗原-结合沟还可经常展示完整(例如,仍错误折叠的)抗原蛋白或剪接变体。Jiang等人,International immunology (国际免疫学),25 (4):235-246,2013。

[0063] 在一些实例中,人MBP的片段用于构建本文所述的MHC-CAR。人MBP的示例性氨基酸序列在下面提供:

MASQKRPSQRHGSKYLATASTMDHARHGFLPRHRDTGILDSIGRFFGGDRGAPKRGSGKVPWLKXPGRSPL

[0064] PSHARSQPGLCNMYKDSHHPARTAHYGS L P Q K S H G R T Q D E N P V V H F F K N I V T P R T P P S Q G K G R G L S L S R

FSWGAEGQRPGFGYGGGRASDYKSAHKGFKGVDAQGTLSKIFKLGGGRDSRSGSPMARRHHHHHH (SEQ ID NO:

1)

[0065] 示例性MBP抗原肽包括但不限于:

GSKYLATASTMDHARHGFLPRHRDTGILDSIGRFFGGDRG (SEQ ID NO: 2),
KYLATASTMDHARHGFLPRH (SEQ ID NO: 3), ATASTMDHARHGFLPRHRDTGIL (SEQ ID NO: 4),
RDTGILDSIGRFFGGDRGAP (SEQ ID NO: 5), IGRFFGGDRGAPKRGSGKDSHHPARTAHY (SEQ ID
NO: 6), APKRGSGKDSHHAARTAHY (SEQ ID NO: 7), GSGKDSHHPARTAHYGSLPQ (SEQ ID NO:
8), HHPARTAHYGSLPQKSHGR (SEQ ID NO: 9), HAARTAHYGSLPQKSQGHR (SEQ ID NO: 10),
SLPQKSHGRQTQDENPVVHF (SEQ ID NO: 11), PQDENPVVHFFKNIVTPRTP (SEQ ID NO: 12),
TQDENPVVHFFKNIVTPRTP (SEQ ID NO: 13), QDENPVVHFFKNIVTPRTP (SEQ ID NO: 14),
DENPVVHFFKNIVTPRTP (SEQ ID NO: 15), ENPVVHFFKNIVTPR (SEQ ID NO: 16),
[0066] ENPVVHFFKNIVTPRTP (SEQ ID NO: 17), ENPVVHFFKNIVTP (SEQ ID NO: 18),
NPVVHFFKNIVTPRTPPSQ (SEQ ID NO: 19), VVHFFKNIVTPRT (SEQ ID NO: 20),
VVHFFKNIVTPRTPPSQ (SEQ ID NO: 21), KNIVTPRTPPSQKGRGL (SEQ ID NO: 22),
PSQKGRGLSLSRFSWGAE (SEQ ID NO: 23), GKGRGLSLSRFSWGAEQRP (SEQ ID NO: 24),
LSRFSWGAEQRPFGYGG (SEQ ID NO: 25), QRPFGYGGGRASDYKSAHK (SEQ ID NO: 26),
ASDYKSAHKGFKVDAQGT (SEQ ID NO: 27), FKVDAQGTLSKIFKLGR (SEQ ID NO: 28),
VDAQGTLSKIFKLGRDSRS (SEQ ID NO: 29), and SKIFKLGRDSRSGSPMARR (SEQ ID NO:
30).

[0067] 编码SEQ ID NO:15的MBP抗原肽的示例性核酸序列在下面提供:

[0068] GATGAGAAATCCCGTGGTTCATTTTTTAAGAACATCGTCACACCGCGCACCCACCTG (SEQ ID NO: 411)

[0069] 具体实例包括MBP13-32、MBP89-101、MBP83-99、MBP111-129或MBP146-170。

[0070] 人髓磷脂少突胶质细胞糖蛋白、蛋白脂质蛋白质和髓磷脂相关糖蛋白的示例性氨基酸序列在下面提供:

[0071] >CAA52617.1髓磷脂少突胶质细胞糖蛋白[智人]

MASLSRPSLPSCLCSFLLLLLLLVSSSYAGQFRVIGPRHPIRALVGDEVELPCRISP GK NATGMEVGWYRPPFSR
[0072] VVHLYRNGKDQDQDAPEYRGRTELLKDAIGEGKVTLRIRNVRFSDGGFTCFFRDHSYQEEAAAMELKVEDFFYW
VSPGVLVLLI AVLPLVLLQITVGLVFLCLQYRLRGKLR AEIENLHRTFDPHFLRVPCWKITLFVIVPVLGLPLVALI
ICYNWLHRRLAGQFLEELRNPF (SEQ ID NO: 31)

[0073] 示例性MOG抗原肽包括MOG1-20或MOG35-55。

[0074] >AAA60117.1蛋白脂质蛋白质[智人]

MGLLECCARCLVGAFFASLVATGLCFFGVALFCGCGHEALTGTE**KLIETYFSK**NYQDY EYLINVIHAFQYVIYGT
[0075] ASFFFLYGALLLAEGFYTTGAVRQIFGDYKTTICGKLSATVTGGQKGRGSRGQHQAHSLE R VCTCLGKWLGHDP
KEVGITYALT VVWLLVFACSAVPVYIYFNTWTTCQSIAFP SKTSASIGSLCADARMYGVL PWN AEPGKVCGSNLL
SICKTAEFQMTFHLFIAAFVGAAATLVSLLT F MIAATYNFAVLKLMGRGTFK (SEQ ID NO: 32)

[0076] PLP的示例性抗原片段用下划线和粗体强调。其它实例包括PLP139-151 (4) 或
PLP178-191。

[0077] >AAH93045.1髓磷脂相关糖蛋白[智人]

MIFLTALPLFWIMI SASRGGHWGAWMPSSISAFEGTCVSI PCRFDFPDEL RPAVVHGVWYFNSPYPKNYPPVVFK
SRTQVVHESFQGRSRL LGDLGLRNC TLLLSNVSP ELGGKYFRGDLGGYNQYTFSEHSVLDIVNTPNIVVPPEVV
AGTEVEVSCMVPDNCPELRPELSWLGHEGLGEP AVLGR LREDEGTWVQVSL LH FVPTREANGHRLGCQASFPNTT
[0078] LQFEGYASMDVKYPPVIVEMNSSVEAIEGSHVSLLCGADSNPPPLLTWMRDGT V LREAVAESL LLEEEVTPAED
GVYACLAENAYGQDNRTVGLSVMYAPWKPTVNGTMVAVEGETVSILCSTQSNPDPI LTIFKEKQILSTVIYESEL
QLELPAVSPEDDGEYWCVAENQYGRATAFNLSVEFAPVLLLESHCAAARDTVQCLCVVKS NPEPSVAFELPSRN
VTVNESEREFVYSERSGLVLT SILTLRQAQAPPRVICTARNLYGAKSLELPFQGAHRLMWAKIGFVGAVVAFAI
LIAIVCYITQTRKKNVTESPSFSAGDNPPVLFSSDFRISGAPEKYESKEVSTLESH (SEQ ID NO: 33)

[0079] 下表1提供了与其它自身免疫性疾病相关的另外的示例性自身抗原。

[0080] 表1.各种自身免疫性病症的自身抗原

自身抗原	GeneBank 登 录 号	相关的自身免疫性疾病
多巴色素互变异构酶	AAH28311.1	斑秃
黑素瘤抗原 gp100	AAC60634.1	斑秃
黑素细胞蛋白 pmel	NP_001186983.1	斑秃
黑素细胞刺激激素受体	NP_002377.4	斑秃
毛透明蛋白	AAA65582.1	斑秃
酪氨酸 3-单加氧酶	NP_954986.2	斑秃
淀粉样 β A4 蛋白	NP_000475.1	阿尔茨海默病
血管活性肠多肽受体 1	NP_004615.2	强直性脊柱炎
潜在膜蛋白 2	CAA57360.1	强直性脊柱炎
固氮酶铁蛋白	ART03999.1	强直性脊柱炎
聚集蛋白聚糖核心蛋白	NP_001126.3	强直性脊柱炎
β -2-糖蛋白 1	NP_000033.2	抗磷脂综合征
M 蛋白前体	AAA26918.1	抗磷脂综合征
大间层蛋白	ACL51127.1	抗磷脂综合征
类固醇 21-羟化酶	NP_000491.4	自身免疫性肾上腺炎
类固醇 17- α -羟化酶/17,20 裂解酶	NP_000093.1	自身免疫性肾上腺炎
钾运输 ATP 酶 α 链	AAB50172.1	自身免疫性胃炎
钾运输 ATP 酶 β 链	AAA35987.1	自身免疫性胃炎
细胞色素 P450 2D6	ABB77909.1	自身免疫性肝炎
基因组多蛋白	S35630	自身免疫性肝炎
O-磷酸丝氨酸-tRNA(Sec)硫转移酶	NP_058651.3	自身免疫性肝炎
去唾液酸糖蛋白受体	ABB58308.1	自身免疫性肝炎
谷胱甘肽 S-转移酶	CAA48637.1	自身免疫性肝炎
细胞角蛋白 8	AAB18966.1	自身免疫性肝炎
M 蛋白	AAA26918.1	自身免疫性心肌炎
肌球蛋白-7	NP_000248.2	自身免疫性心肌炎
心肌肌球蛋白轻链 1	AAF91089.1	自身免疫性心肌炎
心肌肌球蛋白轻链 2	AAA91832.1	自身免疫性心肌炎
心肌肌动蛋白	NP_005150.1	自身免疫性心肌炎
肌钙蛋白 I	AC14461.1	自身免疫性心肌炎
甲状腺过氧化物酶	AAA61217.2	自身免疫性甲状腺炎
促甲状腺素受体	AAB23390.2	自身免疫性甲状腺炎
甲状腺球蛋白	NP_003226.4	自身免疫性甲状腺炎

[0082]

S-视紫红质抑制蛋白	NP_000532.2	自身免疫性葡萄膜炎
LAMP2	AAB67314.1	自身免疫性血管炎
髓过氧化物酶	AAA59863.1	自身免疫性血管炎
成髓细胞素	NP_002768.3	自身免疫性血管炎
α -麦醇溶蛋白	AFX69628.1	腹部疾病
蛋白-谷氨酰胺 γ -谷氨酰基转移酶 2	NP_004604.2	腹部疾病
75k γ 黑麦醇溶蛋白	ADP95479.1	腹部疾病
γ 1 大麦醇溶蛋白	AFM77738.1	腹部疾病
燕麦蛋白-3-样	ADA62372.1	腹部疾病
糖基转移酶	ANR93567.1	克罗恩氏病
线粒体 60 kDa 热休克蛋白	NP_002147.2	克罗恩氏病
跨膜蛋白 UO-44D	NP_002147.2	克罗恩氏病
GM-CSF	AAA52578.1	克罗恩氏病
肠蔗糖酶-异麦芽糖酶	NP_001032.2	克罗恩氏病
谷胱甘肽过氧化物酶 2	NP_002074.2	克罗恩氏病
60 kDa 伴侣素 2	ARX70571.1	克罗恩氏病
胰腺分泌糖蛋白 2	NP_001493.2	克罗恩氏病
60 kDa 伴侣素 2	OMH58317.1	克罗恩氏病
细胞骨架相关蛋白 5	EAW67976.1	克罗恩氏病
AhpC	ETZ42359.1	克罗恩氏病
白三烯 B4 受体 2	NP_062813.2	克罗恩氏病
克罗莫结构域-螺旋酶-DNA 结合蛋白 4	NP_001264.2	皮炎
克罗莫结构域-螺旋酶-DNA 结合蛋白 3	NP_001005273.1	皮炎
β -1 肾上腺素能受体	NP_000675.1	扩张型心肌病
草毒碱乙酰胆碱受体 M2	NP_001006633.1	扩张型心肌病
胶原 α -3(IV)链	CAA56335.1	古德帕斯彻氏综合征
促甲状腺激素受体	AAB23390.2	格雷夫氏病
甲状腺过氧化物酶	AAA61217.2	格雷夫氏病
甲状腺球蛋白	CAA29104.1	格雷夫氏病
谷氨酸脱羧酶 2	NP_000809.1	格雷夫氏病
TSHR 蛋白	AAI27629.1	格雷夫氏病
甲状腺过氧化物酶	AAA61217.2	桥本甲状腺炎
甲状腺球蛋白	CAA29104.1	桥本甲状腺炎
甲状腺刺激激素受体	AAI41971.1	桥本甲状腺炎
胰岛素	AAA59172.1	低血糖症
胰岛素受体	AAA59452.1	低血糖症
整联蛋白 β -3	NP_000203.2	免疫性血小板减少性紫癜
整联蛋白 α -IIb	NP_000410.2	免疫性血小板减少性紫癜
血小板糖蛋白 Ib α 链	NP_000164.5	免疫性血小板减少性紫癜
血小板糖蛋白 IIIa	AAA52600.1	免疫性血小板减少性紫癜
血小板生成素	AAB03393.1	免疫性血小板减少性紫癜
胰岛素受体	AAA59452.1	胰岛素抵抗糖尿病
磷脂酶 A2	NP_000919.1	膜性肾炎
髓磷脂碱性蛋白	AAC41944.1	多发性硬化
髓磷脂蛋白脂质蛋白	AAA59656.1	多发性硬化
髓磷脂少突胶质细胞糖蛋白	CAA52617.1	多发性硬化
EB 病毒核抗原 1	Q1HVF7.1	多发性硬化

[0083]

DNA 聚合酶催化亚基	AMD82168.1	多发性硬化
2',3'-环状-核苷酸 3'-磷酸二酯酶	AAB24298.2	多发性硬化
少突胶质细胞髓磷脂糖蛋白	AAA59970.1	多发性硬化
水通道蛋白-4	AAH22286.1	多发性硬化
胞质肌动蛋白 1	NP_001092.1	多发性硬化
转座酶突变基因家族蛋白	EUA400986.1	多发性硬化
E4 基因产物	YP_002640224.1	多发性硬化
蛋白 BOLFI	AIE89051.1	多发性硬化
髓磷脂相关糖蛋白	AAH93045.1	多发性硬化
转醛醇酶	NP_006746.1	多发性硬化
可能的转座酶	CCP46656.1	多发性硬化
Claudin-11	NP_005593.2	多发性硬化
干扰素 β	AAC41702.1	多发性硬化
α -晶体蛋白 B 链	ACA05949.1	多发性硬化
载脂蛋白 E	AAB59518.1	多发性硬化
EB 病毒核抗原 6	AAA45895.1	多发性硬化
反式激活蛋白 BZLF1	BAP94413.1	多发性硬化
血凝素	ALB07770.1	多发性硬化
蛋白 S100-B	NP_006263.1	多发性硬化
DNA 聚合酶催化亚基	SCL76875.1	多发性硬化
三分末端酶亚基 UL15	SCL76864.1	多发性硬化
甘油醛-3-磷酸脱氢酶	CAA25833.1	多发性硬化
α -烯醇化酶	CAA34360.1	多发性硬化
神经丝轻多肽	NP_006149.2	多发性硬化
连接蛋白 43	AAA52131.1	多发性硬化
神经丝中多肽	NP_005373.2	多发性硬化
POTE 锚蛋白结构域家族成员 I	NP_001264335.1	多发性硬化
线粒体 60 kDa 热休克蛋白	NP_002147.2	多发性硬化
EB 病毒核抗原 3	BAP94411.1	多发性硬化
推定的 HTLV-1 相关内源序列	CAA34646.1	多发性硬化
胶原原纤维酸性蛋白	AAB22581.1	多发性硬化
磷酸甘露糖变位酶/磷酸葡萄糖变位酶	OPA62825.1	多发性硬化
小衣壳蛋白 L2	P36745.1	多发性硬化
N-乙酰基胞壁酰基-L-丙氨酸酰胺酶 CwlH	KIX84070.1	多发性硬化
ATP 敏感性内向整流钾通道 10	NP_002232.2	多发性硬化
mRNA 输出因子 ICP27 同系物	YP_401659.1	多发性硬化
乙酰胆碱受体亚基 α	NP_001034612.1	重症肌无力
乙酰胆碱受体亚基 γ	NP_005190.4	重症肌无力
乙酰胆碱受体亚基 δ	NP_000742.1	重症肌无力
乙酰胆碱受体亚基 ϵ	NP_000071.1	重症肌无力
毒蕈碱受体	AAB95158.1	重症肌无力-MUSC
水通道蛋白 4	AAH22286.1	视神经脊髓炎
α -突触核蛋白	NP_000336.1	帕金森氏病
DNA 聚合酶持续合成因子	SBO07788.1	帕金森氏病
桥粒核心糖蛋白-3	NP_001935.2	天疱疮
胶原 α -1(XVII)链	NP_000485.3	天疱疮

[0084]

桥粒核心糖蛋白-1	NP_001933.2	天疱疮
谷氨酸脱羧酶 2	NP_000809.1	前驱糖尿病
线粒体 60 kDa 热休克蛋白	NP_002147.2	前驱糖尿病
胰岛素	AAA59172.1	前驱糖尿病
胰岛素同种型 2	NP_001035835.1	前驱糖尿病
胰岛细胞抗原	NP_002837.1	前驱糖尿病
丙酮酸脱氢酶复合物的二氢硫辛酰赖氨酸残基乙酰转移酶组分	NP_001922.2	原发性胆汁性肝硬化
丙酮酸脱氢酶复合物的二氢硫辛酰赖氨酸残基乙酰转移酶组分	OAF98393.1	原发性胆汁性肝硬化
2-酮戊二酸脱氢酶复合物的二氢硫辛酰赖氨酸残基琥珀酰转移酶组分	WP_032229692.1	原发性胆汁性肝硬化
糖原磷酸化酶	AAC18079.1	原发性胆汁性肝硬化
核孔糖蛋白 210	NP_079199.2	原发性胆汁性肝硬化
肌氨酸脱羧酶	AAD32214.1	原发性胆汁性肝硬化
亚硫酸盐氧化酶	AAA74886.1	原发性胆汁性肝硬化
转谷氨酰胺酶	BAA14329.1	原发性胆汁性肝硬化
核自身抗原 Sp-100	NP_001073860.1	原发性胆汁性肝硬化
线粒体的 2-酮戊二酸脱氢酶复合物的二氢硫辛酰赖氨酸残基琥珀酰转移酶组分	NP_001924.2	原发性胆汁性肝硬化
核孔 p62	AAA59990.1	原发性胆汁性肝硬化
M 蛋白前体	AAA26918.1	银屑病
角蛋白 I 型细胞骨架 16	NP_005548.2	银屑病
角蛋白 I 型细胞骨架 17	NP_000413.1	银屑病
ADAMTS-样蛋白 5	NP_998769.2	银屑病
转录激活物	AHF70996.1	银屑病关节炎
血纤蛋白原 α 链	AAI01936.1	银屑病关节炎
波形蛋白	NP_003371.2	银屑病关节炎
伴肌动蛋白相关锚定蛋白	AI26408.1	银屑病关节炎
M 蛋白	CAM31002.1	风湿热
肌球蛋白-2	NP_060004.3	风湿热
血纤蛋白原 β 链	AAI06761.1	类风湿性关节炎
波形蛋白	NP_003371.2	类风湿性关节炎
类风湿因子(IgG)	AAH73766.1	类风湿性关节炎
葡萄糖-6-磷酸异构酶	ARJ36701.1	类风湿性关节炎
胶原 α -1(II)链	NP_001835.3	类风湿性关节炎
血纤蛋白原 α 链	AAI01936.1	类风湿性关节炎
α -烯醇化酶	CAA34360.1	类风湿性关节炎
类胰蛋白酶前体	AAA86934.1	类风湿性关节炎
中间丝相关蛋白	NP_002007.1	类风湿性关节炎
聚集蛋白聚糖核心蛋白	NP_001126.3	类风湿性关节炎
小核核糖核蛋白 Sm D1	NP_008869.1	类风湿性关节炎
核糖体蛋白 L23a	AAB17510.1	类风湿性关节炎
60 kDa 伴侣素 2	OMH58317.1	类风湿性关节炎
反式激活蛋白 BZLF1	BAP94413.1	类风湿性关节炎
EB 病毒核抗原 1	YP_401677.1	类风湿性关节炎
伴侣蛋白 DnaJ	EDV64758.1	类风湿性关节炎

[0085]

线粒体 60 kDa 热休克蛋白	NP_002147.2	类风湿性关节炎
甲壳酶-3-样蛋白 1	NP_001267.2	类风湿性关节炎
mRNA 输出因子 ICP27 同系物	YP_401659.1	类风湿性关节炎
视紫红质抑制蛋白	AAC50992.1	类风湿性关节炎, 虹膜炎
蛋白 BOLF1	AIE89051.1	类风湿性关节炎, 幼年
线粒体 60 kDa 热休克蛋白	NP_002147.2	类风湿性关节炎, 幼年
主要 DNA 结合蛋白	BAX36606.1	类风湿性关节炎, 幼年
角蛋白II型细胞骨架 3	NP_476429.2	类风湿性关节炎, 幼年
原纤维蛋白 1	BAD16739.1	类风湿性关节炎, 幼年
结合腕蛋白前体	NP_002151.2	类风湿性关节炎, 幼年
间充质溶解素-1 前原蛋白	NP_002413.1	类风湿性关节炎, 幼年
间质胶原酶	NP_002412.1	类风湿性关节炎, 幼年
Ospa	CAA32579.1	类风湿性关节炎, 莱姆病
整联蛋白 α -L	NP_002200.2	类风湿性关节炎, 莱姆病
DNA 拓扑异构酶 1	NP_003277.1	硬皮病/系统性硬化症
组蛋白 H3-样着丝粒蛋白 A	NP_001800.1	硬皮病/系统性硬化症
小核核糖核蛋白 Sm D1	NP_008869.1	硬皮病/系统性硬化症
主要着丝粒自身抗原 B	NP_001801.1	硬皮病/系统性硬化症
E3 泛素-蛋白连接酶 TRIM21	NP_003132.2	硬皮病/系统性硬化症
EB 病毒核抗原 1	YP_401677.1	硬皮病/系统性硬化症
U11/U12 snRNP	Q6IEG0	硬皮病/系统性硬化症
rRNA 2'-O-甲基转移酶纤维蛋白	NP_001427.2	硬皮病/系统性硬化症
核糖核酸酶 P 蛋白亚基 p25	NP_060263.2	硬皮病/系统性硬化症
60 kDa SS-A/Ro 核糖核蛋白	NP_001166995.1	斯耶格伦氏综合征
狼疮 La 蛋白	NP_003133.1	斯耶格伦氏综合征
E3 泛素-蛋白连接酶 TRIM21	NP_003132.2	斯耶格伦氏综合征
毒蕈碱乙酰胆碱受体 M3	NP_000731.1	斯耶格伦氏综合征
小核核糖核蛋白 Sm D1	NP_008869.1	斯耶格伦氏综合征
U1 小核核糖核蛋白 A	NP_004587.1	斯耶格伦氏综合征
推定的 HTLV-1 相关内源序列	CAA34646.1	斯耶格伦氏综合征
钙网织蛋白	AAB51176.1	斯耶格伦氏综合征
血影蛋白 α 链, 非红细胞 1	NP_001123910.1	斯耶格伦氏综合征
β -微管蛋白	AAB59507.1	西登哈姆氏舞蹈病
多巴胺受体 1	NP_000785.1	西登哈姆氏舞蹈病
多巴胺受体 2	NP_000786.1	西登哈姆氏舞蹈病
60 kDa SS-A/Ro 核糖核蛋白	NP_001166995.1	系统性红斑狼疮
小核核糖核蛋白 Sm D1	NP_008869.1	系统性红斑狼疮
U1 小核核糖核蛋白 70 kDa	NP_003080.2	系统性红斑狼疮
自然杀伤组蛋白 2-A	AAC17488.1	系统性红斑狼疮
小核核糖核蛋白相关蛋白 B 和 B'	NP_937859.1	系统性红斑狼疮
小核核糖核蛋白相关蛋白 N	NP_001336393.1	系统性红斑狼疮
E3 泛素-蛋白连接酶 TRIM21	NP_003132.2	系统性红斑狼疮
EB 病毒核抗原 1	YP_401677.1	系统性红斑狼疮
U1 小核核糖核蛋白 C	NP_003084.1	系统性红斑狼疮
NHP2-样蛋白 1	NP_001003796	系统性红斑狼疮
60S 酸性核糖体蛋白 P2	XP_805182.1	系统性红斑狼疮
组蛋白 H1.4	NP_005312.1	系统性红斑狼疮

[0086]

谷氨酸脱羧酶 2	NP_000809.1	1 型糖尿病
胰岛素	AAA59172.1	1 型糖尿病
胰岛细胞抗原	NP_002837.1	1 型糖尿病
葡萄糖 6-磷酸酶 2	NP_066999.1	1 型糖尿病
线粒体 60 kDa 热休克蛋白	AAH02676.1	1 型糖尿病
锌运输蛋白 8	AAP44332.1	1 型糖尿病
胰岛素同种型 2	NP_001035835.1	1 型糖尿病
基因组多蛋白	AAX23962.1	1 型糖尿病
胰岛淀粉样多肽	NP_000406.1	1 型糖尿病
血凝素	ALB07770.1	1 型糖尿病
胰岛淀粉样多肽	NP_000406.1	2 型糖尿病
锌运输蛋白 8	AAP44332.1	2 型糖尿病
胰腺分泌糖蛋白 2	NP_001493.2	溃疡性结肠炎
GM-CSF	AAA52578.1	溃疡性结肠炎
成髓细胞素	NP_002768.3	溃疡性结肠炎
VII 型胶原蛋白	AAA96439.1	溃疡性结肠炎
黑素细胞蛋白 PMEL	NP_001186983.1	白癜风
黑素浓缩激素受体 1	NP_005288.3	白癜风
酪氨酸 3-单加氧酶	NP_954986.2	白癜风
酪氨酸酶	NP_000363.1	白癜风
L-多巴色素互变异构酶	NP_001913.2	白癜风
TrpC1	NP_001238774.1	白癜风
成髓细胞素	NP_002768.3	韦格纳氏肉芽肿病
胶原 α -1(II)链	NP_001835.3	韦格纳氏肉芽肿病

[0087] 下表2提供了与自身免疫性病症通常相关的HLA和种类,尽管在示例性的情况下,HLA或HLA的一部分是患者特异性的和衍生自患有该病症或血清学等同病症的患者的分辨率序列。

[0088] 表2.通常与自身免疫性疾病相关的HLA类型和种类

[0089]

常见 HLA II类血清型	常见 II类变体	常见 HLA I类血清型	常见 I类变体	相关的自身免疫性疾病
DR4 (例如 DRB1*04); 和 DR5 (例如 DRB1*11 和 DRB1*12)	DRB1*04:01; DRB1*11; 和 DRB1*11:04	A2 (例如 A*02)	A*02; A*02:01; 和 B*07:02	斑秃
		A2		阿尔茨海默病
		B27 (例如 B*2701-2759);	B*27:02; B*27:05;	强直性脊柱炎

[0090]

		B40 (例如 B*40); B27-B40; 和 B7 (例如 B*07)	B*40:01; B*52; 和 B*38	
DR7 (例如 DRB1*0701-0705); DR4; DR5; 和 DR12 (例如 DRB1*1201-3 和 DRB1*1206)	DRB1*09; DRB1*09:01; DRB1*04; DRB1*04:05; 和 DRB1*14			抗磷脂综合征
DR17 (例如 DRB1*0301 和 DRB1*0304); DR4; DR4/DR3; DQ2 (例如 DQB1*02); 和 DQ8 (例如 DQB1*0302)	DRB1*03:01; DRB1*04; 和 DRB1*04:04			自身免疫性肾上腺炎
DR2 (例如 DRB1*15 和 DRB1 DR4; DR5; DR2/DR4; 和 DR4/DR5				自身免疫性胃炎
	DRB1*03:01; DRB3*01:01; DRB1*04:01; DRB1*04:05; DRB1*07; 和 DRB1*13:01			自身免疫性肝炎
DR7; DR4; DR11 (例如 DRB1*1101至 DRB1*1110); DR3 (例如 DRB1*03); 和 DR11-DQ7.5	DRB1*04:09; DRB1*07; 和 DRB1*04			自身免疫性心肌炎
		B27; A29 (例如 A*29); 和 B51 (例如 B*51)	A*29:02; 和 B*57:01	自身免疫性葡萄膜炎
DQ2; DQ8; DR12-DQ7.5; 和 DR7-DQ2.2	DQA1*05:01/ DQB1*02:01; DQA1*03/DQB1*03:02; 和 DQA1*0505/ DQBA1*0301			腹部疾病
DR1 (例如 DRB1*01); 和 DR3	DRB1*07; DRB1*01:03; DRB1*0301; DRB1*0302; 和 DRB3*0301/DRB1*1302	B27		克罗恩氏病

[0091]

	DRB1*0301; 和 DRB1*0302			皮炎
DR4	DRB1*0302			扩张型心肌病
DR2		B8 (例如 B*08)		古德帕斯彻氏综合征
DR17; DR52 (例如 DRB3*); 和 DR7	DRB1*03:01; DRB1*04:01; DRB3*01; 和 DRB3*0202			格雷夫氏病
DR3; 和 DR5				桥本甲状腺炎
DR4				免疫性血小板减少性紫癜
DR3; DR4; 和 DR3/DR4				胰岛素抵抗糖尿病
DR3	DRB1*01:02			膜性肾炎
DR2; DR15 (例如 DRB1*1505-5 和 DRB1*1507); 和 DR53 (DRB4*)	DRB1*15:01; DRB1*15:01/ DRB1*15:01; DRB1*15:01/ DRB5*01:01; DRB1*15; DRB5*01:01; DPw2; DRB1*04:01; DRB1*04:04; DPA1*01:03/ DPB1*02:01; DPA1*01:03/ DPB1*04:01; DQA1*01:02/ DQB1*05:02; DQB1*06; 和 DQB1*06:02	A3 (A*03); 和 B7		多发性硬化
DR17; DR3; 和 DR7	DRB1*03:01			重症肌无力
DR14-DQ5				重症肌无力-MUSC
DR3				视神经脊髓炎
DR 患者特异性				帕金森氏病
DR4; 和 DR6	DRB1*01:01; 和 DRB1*04:02			天疱疮
DR3; DR4; 和 DR3/DR4	DRB1*03:01; DRB1*04:01; 和 DRB1*03:01/* 04:01			前驱糖尿病
DR8 (例如 DRB1*0801-*0807 和 DRB1*0810- *0812)	DRB1*0801; 和 DRB1*0803			原发性胆汁性肝硬化

[0092]

DR7	DRB1*01:02	B27; 和 Cw6 (C*06:02 和 C*06:05)		银屑病
		B16 (例如 B38 和 B39); B17 (例如 B57 和 B58); B27; B39 (例如 B*39); 和 Cw6		银屑病关节炎
DR7				风湿热
DR4; DR4-DQ8; DR1; DR12; 和 DR18 (例如 DRB1*03:02 和 DRB1*03:03)	DRB1*01:01; DRB1*01:02; DRB1*04:01; DRB1*04:02; DRB1*04:03; DRB1*04:04; DRB1*04:05; DRB1*04:06; DRB1*04:07; DRB1*04:08; DRB1*04:09; DRB1*04:10; DRB1*04:11; DRB1*04:12; DRB1*04:13; 对于上述 是纯合的; DRB1*01:01/* 04:04; 和 DRB1*01:01/* 04:01			类风湿性关节炎
DR4; DR5; DR14 (例如 DRB1*14:01-*14:08 和 DRB1*14:10- *14:08); 和 DR15	DRB1*04:01; DRB1*04:04; DRB1*04:05; DRB1*14:02; 和 DRB1*12:01			类风湿性关节炎, 青少年
DR5; 和 DR11	DRB1*04:01; DRB1*10:01; 和 DRB1*11:02			类风湿性关节炎, 莱姆病
DR11; 和 DR8	DRB1*11:04			类风湿性关节炎, 少关节 (青少年)
DR5	DRB1*12:01	B35		类风湿性关节炎, 虹膜炎
DR5	DQB1*05:01; DRB1*11; DRB1*11:04; DRB1*15:02; DRB1*13:02; DRB1*04:06;			硬皮病/系统性硬化
	DRB1*03 DRB1*15;			斯耶格伦氏综合征

[0093]

	DRB1*03:01/ DRB1*15:01			
DR1		B49 (例如 B*49)		西登哈姆氏舞蹈病
DR11; 和 DR53- DR7	DRB1*03:01; DRB1*15:01; DRB1*04:02; DRB1*04:03; DRB1*04:06; DRB1*11:01; 和 DRB3*03:01			系统性红斑狼疮
DR3	DRB1*03:02; DRB1*04; DRB1*04:01; DRB1*04:02; DRB1*04:05; DRB1*03:01; 和 DRB1*03:01/ DRB1*04:01			1 型糖尿病
DR4				2 型糖尿病
DR1	DRB1*01:03; 和 DRB1*15:02	B27		溃疡性结肠炎
	DRB1*07:01		A*02:01	白癜风
	DPB1*04			韦格纳氏肉芽肿病

[0094] 在一些实施方案中,本文使用的抗原肽与HLA-DR*1501相关,例如GAD肽TYEIAPVFVLLFYVTLKKMR (SEQ ID NO: 34) (参与I型糖尿病)、上文列出的MBP肽、以下的MPP肽 (参与MS)

LLECCARCLVGAPFASLVATGLCFFGVALFC (SEQ ID NO: 35),

LVGAPFASLVATGLCFFGVA (SEQ ID NO: 36),

FGVALFCGCEVEALTGTEKLIETYFSKNYQD (SEQ ID NO: 37),

LFCGCGHEALTGTEKLIETY (SEQ ID NO: 38), TGTEKLIETYFSKNYQDYEY (SEQ ID

NO: 39), TGTEKLIETYFSKNYQDYEYL (SEQ ID NO: 40),

[0095] YFSKNYQDYEYLINVIHAFQYVIYGTASFFFL (SEQ ID NO: 41),

GTASFFFLYGALLLAYGFYTTGAVRQIFGDYK (SEQ ID NO: 42),

LYGALLLAEGFYTTGAVRQI (SEQ ID NO: 43), FYYTTGAVRQIFGDYKTTICG (SEQ

ID NO: 44), AVRQIFGDYKTTICGKGLSATV (SEQ ID NO: 45),

RQIFGDYKTTICGKGLSATVTGGQKGRGSRGQ (SEQ ID NO: 46),

KGLSATVTGGQKGRGYRGQH (SEQ ID NO: 47),

QKGRGSRGQHQAHSRLERVCH (SEQ ID NO: 48),
 KGRGSRGQHQAHSRLERVCHCLGCWLGHDPKFV (SEQ ID NO: 49),
 LGHPDKFVGITYALTVVWLLVFACSAVPVYIY (SEQ ID NO: 50),
 SAVPVYIYFNTWTTCQSIAAPCKTSASIGTLC (SEQ ID NO: 51),
 AVPVYIYFNTWTTCQSIAFP (SEQ ID NO: 52),
 [0096] WTTCQSIAFPSKTSASIGSL (SEQ ID NO: 53),
 SASIGTLCADARMYGVLPWNAFFGKVCGSNLL (SEQ ID NO: 54),
 KVCGSNLLSICKTAEFQMTFHLFIAAFVGAAA (SEQ ID NO: 55),
 AAFVGAAATLVSLTFMIAATYNFAVLKLMGR (SEQ ID NO: 56),
 MIAATYNFAVLKLMGRGTKF (SEQ ID NO: 57), 和
 MAATYNFAVLKLMGRFTKF (SEQ ID NO: 58)

[0097] 在一些实施方案中,抗原肽或抗原多肽是患者特异性的和设计成用于患者的MHC。例如,医生可诊断患者具有自身免疫性病症和确定疾病的严重性。患者的I类(HLA-A、B和C)和II类(HLA-DR、DQ、DP)区域可被分型,这现在可以高分辨率使用DNA测序进行并与参考数据库(www.ebi.ac.uk/ipd/imgt/hla/)比较。具有自身免疫性参与的最强证据的患者的I类和II类MHC可对该病症鉴定。已知与特定自身免疫性病症相关的那些可用作参考。参见例如,表1和2。基于最强证据的抗原对于该病症(iedb.org/)和表1进行鉴定。可鉴定预期结合患者参与自身免疫的MHC的一组个性化肽(cbs.dtu.dk/services/NetMHC/或cbs.dtu.dk/services/NetMHCII/)和蛋白靶标(对于II类)。

[0098] 个性化MHC-CAR慢病毒或mRNA可制备用于患者以能够靶向病原性免疫细胞。个性化慢病毒用于制备自体或同种异体的T细胞(CTL和/或Treg),其可与受体或细胞修饰组合以允许与另外的疗法共治疗,与病原性细胞的所需的相互作用,定向至所需位置(用于与病原性炎性或炎症产生细胞相互作用)或分泌细胞因子(以减少炎症)。

[0099] (c) 共刺激信号传导结构域

[0100] 除了抗原-特异性信号的刺激之外,许多免疫细胞还需要共刺激以促进细胞增殖、分化和存活,以及激活细胞的效应子作用。本文所述的MHC-CAR可包含一个或多个共刺激信号传导结构域。如本文使用的术语“共刺激信号传导结构域”是指在细胞内介导信号转导以诱导免疫反应例如效应子作用的蛋白的至少一部分。本文所述的MHC-CAR的共刺激信号传导结构域可以是来自共刺激蛋白的胞质信号传导结构域,其转导信号和调节由免疫细胞介导的反应,例如T细胞、NK细胞、巨噬细胞、中性粒细胞或嗜酸性细胞。

[0101] 宿主细胞(例如,免疫细胞)中共刺激信号传导结构域的活化可诱导细胞增加或降低细胞因子的产生和分泌、吞噬性质、增殖、分化、存活和/或细胞毒性。任何共刺激分子的共刺激信号传导结构域可以相容地用在本文所述的MHC-CAR中。用于嵌合受体的共刺激信号传导结构域的实例可以是共刺激蛋白的胞质信号传导结构域,所述共刺激蛋白包括但不限于:B7/CD28家族的成员(例如,B7-1/CD80、B7-2/CD86、B7-H1/PD-L1、B7-H2、CD28、CTLA-4、ICOS/CD278或PD-1);TNF超家族的成员(例如,4-1BB/TNFSF9/CD137、4-1BB配体/TNFSF9、CD40/TNFRSF5、CD40配体/TNFSF5、DR3/TNFRSF25、OX40/TNFRSF4、OX40配体/TNFSF4或TNF- α);以及其它分子,例如FRB和FKBF,其允许仅在存在特定药物分子的情况下诱导共刺激(但

此处与独特的异源二聚体MHC-CAR相关)。Wu等人, Science (科学), 350 (6258): aab4077, 2015。在一些实施方案中, 共刺激蛋白的任何胞质信号传导结构域可用于靶向失活的旁观者B细胞 (例如, 用CD19或CD20-CAR) 或浆细胞 (例如, 用CS1-CAR和/或CS1敲除) 的受体。

[0102] 在一些情况下, MHC-CAR可包含组合 (例如, 2或3个) 共刺激结构域, 其可来自相同的共刺激受体或来自不同的共刺激受体。实例包括: CD28+4-1BB、CD28+FRB、CD28+FKBF或4-1BB+FRB。亦参见图9。在一些实例中, MHC-CAR包含来自CD28的共刺激结构域、来自4-1BB的共刺激结构域或二者。在一些实施方案中, 共刺激结构域前面是短接头。例如, 对于II类MHC-CAR, 短接头可以是TS (即, MHC内部接头); 对于I类MHC-CAR, 短接头可以是PG。

[0103] 在一些情况下, 本文所述的MHC-CAR构建体可不包括共刺激结构域。或者, 其可含有非传统的元件, 例如TALEN核酸酶、活化剂或阻抑物, 其现在可使用含有TAL结构域的重编码或非重复序列 (non-repeat) 以临床可应用的慢病毒形式实施, 以及通过衍生自Notch的膜结构域与单链MHC-CAR连接。

[0104] 用于本文所述的MHC-CAR的示例性共刺激结构域包括但不限于:

[0105] 41BB胞内结构域:

[0106] KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEEGGCEL (SEQ ID NO: 59)

[0107] 41BB_e胞内结构域:

[0108] pgKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEEGGCELaha (SEQ ID NO: 60)

[0109] CD28胞内结构域:

[0110] RSKRSRGGHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRS (SEQ ID NO: 61)

[0111] CD28_e胞内结构域:

[0112] pgRSKRSRGGHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSaha (SEQ ID NO: 62)

[0113] FRB:

[0114] EMWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDLMEAQEWCRKYMKSGNVKD
LLQAWDLYYHVFRI (SEQ ID NO: 63)

[0115] FBP-含接头:

(GSSS)₄-

[0116] EMWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDLMEAQEWCRKYMKSGNV
KDLLQAWDLYYHVFRI-(GSSS)₃ (SEQ ID NO: 64)

[0117] FKRB:

[0118] GVQVETISPGDGRTFFPKRGQTCVVHYTGMLDGGKFDSSDRNKPFFKMLGKQEVIRGWEEGVAQMSVGQRAKLT
ISPDIYAYGATGHPGIIPPHATLVFDVELLKLE (SEQ ID NO: 65)

[0119] FKBP-含接头:

(GSSS)₄-

[0120] GVQVETISPGDGRTFFPKRGQTCVVHYTGMLDGGKFDSSDRNKPFFKMLGKQEVIRGWEEGVAQMSVG
QRAKLTISPDIYAYGATGHPGIIPPHATLVFDVELLKLE-(GSSS)₃ (SEQ ID NO: 66)

[0121] (d) 胞质信号传导结构域

[0122] 包含免疫受体酪氨酸激活基序 (ITAM) 的任何胞质信号传导结构域可用于构建本文所述的嵌合受体。如本文使用的“ITAM”是通常存在于在许多免疫细胞中表达的信号传导分子的尾部分的保守蛋白基序。该基序可包含由6-8个氨基酸分开的两个重复的氨基酸序列YxxL/I, 其中每个x独立地是任何氨基酸, 产生保守基序YxxL/I_x (6-8) YxxL/I。在一些实例中, 包含ITAM的胞质信号传导结构域是CD3ζ的胞质信号传导结构域。在一些实例中, MHC-

CAR不包含共刺激结构域,以及胞质信号传导结构域前面是短接头。例如,对于II类MHC-CAR,短接头可以是TS(即,MHC内部接头)。例如对于I类MHC-CAR,短接头可以是PG。在一些情况下,接头可以是AHA或不存在,例如当共刺激结构域在信号传导结构域之前存在的某些情况。

[0123] 在一些实施方案中,MHC-CAR可不包括胞质信号传导结构域,例如CD3 ζ 的胞质信号传导结构域。这样的无CD3 ζ MHC-CAR具有针对靶细胞的抑制效应或诱导靶细胞死亡。Moisini等人,The Journal of Immunology(免疫学杂志),180(5),pp.3601-3611。

[0124] 在下面提供了来自CD3 ζ 的示例性胞质信号传导结构域:

[0125] RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPFMGGKPRRKNPQEGLYNELQKDKMAE
AYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 67)

[0126] 在下面提供了编码来自CD3 ζ 的胞质信号传导结构域的示例性核酸序列:

AGAGTAAAGTTTTCCTCCGAAGTGCAGGACGCTCCCGCTATCAGCAAGGTCAAAACAGCTTTACAAACGAAGTGAAC
TTGGGACGACGCGAAGAGTACGATGTTCTTGATAAGCGGAGAGGGCGCGATCCCGAAATGGGGGAAAGCCTCGG
AGGAAGAACCACAAGAAGGCCCTTTATAATGAAGTGCAGAAGGACAAGATGGCGGAGGCGTATTCGAAATAGGC
ATGAAGGGTGACGAGGAGAGGAAAGGGACATGACGGACTTTATCAAGGATTGTCTACCGCAACTAAAGACACC
TATGACGCGTTGCACATGCAGGCTCTCCCTCCGAGA (SEQ ID NO: 410)

[0127] CCGGTCAAATTTAGCAGATCCGCTGACGCACCGGCCTACCAGCAGGGCCAGAACCAACTCTACAACGAGCTGAAT
CTCGGCCGACGGGAAGAGTATGACGTACTCGACAAGCGGAGAGGTCGAGACCTGAGATGGGCGGTAAACCGAGA
CGGAAAAATCCCCAAGAGGGTCTTTATAATGAAGTCCAGAAGGATAAGATGGCTGAAGCCTATCTGAGATAGGG
ATGAAAGGCGAGCGGCGGAGGGGTAAGGGCCATGATGGCCTTTACCAGGGACTCTCCACGGCAACCAAAGATACT
TACGACGCCCTTCACATGCAAGCCCTCCCGCCACGC (SEQ ID NO: 422)

[0128] (e) 其它组分

[0129] 本文所述的MHC-CAR可任选地进一步包括一种或多种以下组分:铰链结构域、跨膜结构域、信号(前导)肽和肽接头。

[0130] 在一些情况下,抗原肽可与铰链肽连接,以增强得到的MHC-CAR的免疫靶向活性和/或降低靶细胞对MHC-TCR复合物的抗体反应。在一些实例中,含有铰链肽的MHC-CAR可不包括胞质结构域(例如,不含CD3 ζ 结构域)。含有铰链肽的MHC-CAR构建体还可包括MHC I类部分。铰链结构域可含有约10-100个氨基酸,例如,15-75个氨基酸、20-50个氨基酸或30-60个氨基酸。在一些实施方案中,铰链结构域可具有10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29、30、35、40、45、50、55、60、65、70或75个氨基酸长度。

[0131] 在一些实例中,以下肽接头可用于I类MHC-CAR:

MHCI 接头1: GGGGSGGGSGGGGS (SEQ ID NO: 68)

MHCI 接头2: GGGGGSGGSGGSGG (SEQ ID NO: 69)

[0132] MHCI 接头3: GGGGSGGGSGGGSGGGGS (SEQ ID NO: 70)

MHCI 接头4: GGGGSGGGSGGGGS (SEQ ID NO: 68)

[0133] 对于II类MHC-CAR的示例性肽接头可以是GSGSGSGS(MHCIILinker1;SEQ ID NO: 72)、GGGGSGGGSGGGGS(MHC II LinkerII;SEQ ID NO:68)、GGGGSGGGSGGS(SEQ ID NO: 400)或本文称为MHCI Linker(即,MHCI Linker 1-4)的那些。对于II类MHC-CAR的示例性的前-肽接头可以是AS或GS、或AS或GS的一个或两个拷贝。

[0134] 编码SED ID NO:400提供的肽接头的示例性核酸序列在下面提供:

[0135] GGGGGAGGCGGATCTGGCGGAGGCGGGAGTGGAGGCTCA (SEQ ID NO:
401)

[0136] 用于本文所述的MHC-CAR的铰链肽可衍生自天然存在的受体。本领域已知的包含铰链结构域的任何蛋白的铰链结构域能相容地用在本文所述的嵌合受体中。在一些实施方案中,铰链结构域是CD8 α 的铰链结构域的一部分,例如,含有CD8 α 的铰链结构域的至少15(例如,20、25、30、35或40)个连续氨基酸的片段。或者,它可以是合成肽。

[0137] 示例性铰链结构域包括: IYIWAPLAGTCGVLLLSLVIT (SEQ ID NO: 73) 和 IWAPLAGICVALLSLIITLI (SEQ ID NO: 74)。另外的实例在下面提供:

[0138] FKBP/FRB-CD8铰链:

[0139] GVQVETISPGDGRTPFKRGQTCVVHYTGMLEDGKKKFDSSRDNRNPKFKMLGKQEVIRGWEEGVAQMSVQGAKLIT
ISPDYAYGATGHPGIIPPHATLVFDEVLLKLEEAAREAAAAEAAAAREAAARGRVAILWHEMWHEGLEEASRLYF
GERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDLMEAQEWCRKYMKSGNVKDLLQAWDLYYHVFRRITTTT
PAPRPPTPAPTIASOPLSLRPEACRPAAGGAVHTRGLDEACD (SEQ ID NO: 75)

[0140] GS短铰链:GGGSGGGG5GGGS (SEQ ID NO:68)

[0141] GS长铰链:

[0142] GGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS (SEO ID NO: 76)

[0143] H2-Kb铰链:LRWEPPPSTVSNM(SEQ ID NO:77)

[0144] HLA-A2铰链:LRWEPSSQPTIPI (SEQ ID NO:78)

[0145] HLA-A3铰链:LRWELSSQPTIPI (SEQ ID NO:79)

[0146] DAP10铰链:

[0147] QTTPGERSSLPAFYPGTSGSCSGCGSLSLP (SEQ ID NO: 80)

[0148] 含接头的DAP10铰链:

[0149] (GSSS)₄CTTPGERSSLPAFYPGTSGSCSGCGLSLP (SEQ ID NO: 81)

[0150] DAP12铰链:LRPVQAQAQSDCSCSTVSP (SEQ ID No:82)

[0151] 含接头的DAP12铰链: (GSSS)₄LRPVQAQAQSDCSCSTVSP (SEQ ID NO:83)

[0152] FcIgGIIIa铰链:GLAVSTISSFFPPGYQ (SEQ ID NO:84)

[0153] CD8α铰链:

[0154] TTTTAPRRPTTAPTIAISOPLSLRPEACRPAAGGAVHTRGLDFACD (SEQ ID NO: 85)

[0155] IgG1铰链:

[0156] EPKSPDKRTHTCPPCPAPPVAGPSVFLFPPPKPKDTLMIARTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTPPPVLDSGDSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNNHYTQKSL
SLSPGK (SEQ ID NO: 86)

[0157] DRA*0101铰链:EFDAPSPLPETTE (SEQ ID NO:87)

[0158] DRB1*1501铰链:VEWRARSESAQSK (SEQ ID NO:88)

[0159] 编码DRA*0101铰链的示例性核酸序列在下面提供:

[0160] GAGTTCGACGCCCCATCACCGCTTCCAGAAACGACTGAA (SEQ ID NO: 417)

[0161] 编码DRB1*1501铰链的示例性核酸序列在下面提供:

[0162] GTTGAGTGGAGGGCGCGGTCAGAGAGCGCACAAATCTAAA (SEQ ID NO: 404)

[1063] 在一些实施方案中,本文所述的MHC-CAR构建体进一步包含跨膜结构域。用于MHC-CAR的任何跨膜结构域可以是本领域已知的任何形式。如本文使用的,“跨膜结构域”是指在细胞膜(优选地真核细胞膜)中热力学上稳定的任何蛋白结构。可以相容地用在本文使用的嵌合受体中的跨膜结构域可获自天然存在的蛋白。或者,其可以是合成的、非天然存在的蛋白区段,例如,疏水蛋白区段,其在细胞膜中是热力学上稳定的。

[0164] 跨膜结构域根据跨膜结构域的三维结构分类。例如,跨膜结构域可形成 α 螺旋、超过一个 α 螺旋的复合物、 β -桶或能够跨越细胞的磷脂双层的任何其它稳定的结构。此外,跨膜结构域还可或可选地可以根据跨膜结构域拓扑进行分类,包括跨膜结构域跨越膜的通道数和蛋白方向。例如,单通道膜蛋白跨过细胞膜一次,以及多通道膜蛋白跨过细胞膜至少两次(例如,2、3、4、5、6、7或更多次)。

[0165] 可根据相对于细胞的内部和外部的它们的末端和跨膜区段的拓扑,定义膜蛋白为I型、II型或III型。I型膜蛋白具有单一跨膜区并被定向成使得蛋白的N末端存在于细胞脂质双层的胞外侧上,以及蛋白的C末端存在于胞质侧上。II型膜蛋白也具有单一跨膜区,但被定向成使得蛋白的C末端存在于细胞脂质双层的胞外侧上,以及蛋白的N末端存在于胞质侧上。III型膜蛋白具有多个跨膜区段,并且可根据跨膜区段的数量以及N末端和C末端的位置进一步细分类。

[0166] 在一些实施方案中,本文所述的MHC-CAR的跨膜结构域衍生自I型单通道膜蛋白,例如,CD8 α 、CD8 β 、4-1BB/CD137或CD28。来自多通道膜蛋白的跨膜结构域也可相容地用在本文所述的嵌合受体中。多通道膜蛋白可包含复合(至少2、3、4、5、6、7或更多个) α 螺旋或 β 片结构。优选地,多通道膜蛋白的N末端和C末端存在于脂质双层的相对侧,例如,蛋白的N末端存在于脂质双层的胞质侧上,以及蛋白的C末端存在于胞外侧上。来自多通道膜蛋白的一个或多个螺旋通道可用于构建本文所述的嵌合受体变体。

[0167] 用于构建本文所述的MHC-CAR构建体的示例性跨膜结构域在下面提供:

[0168] CD8 α 跨膜结构域: IYIWAPLAGTCGVLLLSLVITLYC (SEQ ID NO: 89)

[0169] HLA-A2跨膜结构域: VGIIAGLVLF GAVITGAVVAAVMW (SEQ ID NO: 90)

[0170] HLA-A3跨膜结构域: VGIIAGLVLL GAVITGAVVAAVMW (SEQ ID NO: 91)

[0171] CD3 ζ 跨膜结构域: LCYLLDGILFIYGVILTALFL (SEQ ID NO: 92)

[0172] DR*1501跨膜结构域:

[0173] MLSGVGGFVLGLLFLGAGLFI (SEQ ID NO: 93)

[0174] DR*1501e跨膜结构域: MLSGVGGFVLGLLFLGAGLFIYFRNQ (SEQ ID NO: 94)

[0175] DRA*0101跨膜结构域:

[0176] NVVCALGLTVGLVGIIIGTIFII (SEQ ID NO: 416)

[0177] DRA*0101e跨膜结构域:

[0178] NVVCALGLTVGLVGIIIGTIFIIRGL (SEQ ID NO: 418)

[0179] 编码DR*1501e跨膜结构域的示例性核酸序列在下面提供:

[0180] ATGCTGTCAGGAGTAGCGGATTTGTACTCGGACTCCTCTTTTGGGCGCTGGGTGTTTATCTACTTTAGAAAC
CAA (SEQ ID NO: 406)

[0181] 编码DRA*0101e跨膜结构域的示例性核酸序列在下面提供:

[0182] AACGTTGTCGCGCTCTTGGCCTGACAGTGGGCCTGGTAGGCATTATTATCGGGACCATCTTTATCATCAAAGGT
TTG (SEQ ID NO: 419)

[0183] Notch跨膜结构域:

[0184] ILDYSFTGGAGRDIPPPQIEEACELPECQVDAGNKVCNLQCNHACGWDGGDCSLNFNDPWKNCTQSLQ
CWKYFSDGHCDSCNSAGCLFDGFDCQLTEGQCNP LYDQYCKDHFSDGHCDQGCNSAECEWDGLDCAEH
VPERLAAGTLVLVLLPDPQLRNN SFHFLREL SHVLHTNVVFKRDAQGQQMIFPPYGHHEELRKHP IKR
STVGWATSSLLPGTSGGRQRRELDPM DIRGSI VYLEIDNRQCVQSSQCFQSATDVAAFLGALASLGSL
NIPYKIEAVKSEPVPPPLPSQLHLMYVAAA FVLLFFVGCGLLSRKR (SEQ ID NO: 95)

[0185] Notch 2跨膜结构域:

[0186]

PCVGSNPCYNQGTCEPTSENPFYRCLCPAKFNGLLCHILDYSFTGGAGRDIPPPQIEEACELPECQVDA
GNKVCNLCNNHACGWDGGDCSLNFNDPWKNCTQSLQCWKYFSDGHCDSDQNSAGCLFDGFDCLTEGQ
CNPLYDQYCKDHFSDGHCDQGCNSAECEWDGLDCAEHVPERLAAGTLVLVLLPPDQLRNNSFHFLREL
SHVLHTNVVFKRDAQQGQMI FPYYGHEEELRKHPKIRSTVGWATSSLLPGTSGGRQRRELDPMDIRGSI
VYLEIDNRQCQVSSSQCFQSATDVAAFLGALASLGSLNIPYKIEAVKSEPEVPEPLPSQLHLMYVAAAAF
VLLFFVGCGLLSRKRRR (SEQ ID NO: 96)

[0187] 在一些实施方案中,MHC-CAR还可在多肽的N末端包含信号肽(亦称为信号序列或前导肽)。通常,信号序列是将多肽靶向细胞中的所需位点的肽序列。在一些实施方案中,信号序列将MHC-CAR靶向细胞的分泌途径,以及将允许MHC-CAR整合和锚定到脂质双层中。信号序列,包括天然存在的蛋白的信号序列或合成的非-天然存在的信号序列,其能相容地用在本文所述的嵌合受体中,对本领域技术人员将是显而易见的。在一些实施方案中,信号序列来自CD8 α 。在一些实施方案中,信号序列来自CD28(例如,MLRLLALNLFPSIQVTG (SEQ ID NO:97))。

[0188] 示例性信号肽包括但不限于, β -2-微球蛋白信号肽(例如,MSRSVALAVLALLSLSGLEA (SEQ ID NO:98))、HLA A3信号肽(例如,MAVMAPRTLALLLSGALALTQTWA (SEQ ID NO:99))、DRA*0101信号肽(例如,MAISGVPVLGFFIIAVLMSAQESWA (SEQ ID NO:100))、DRB1*1501信号肽(例如,MVCLKLPGGSCMTALTVTLMVLSSPLAL (SEQ ID NO:101))和DRB5信号肽(例如,MVCLKLPGGSYMAKLTVTLMVLSSPLALA (SEQ ID NO:102))。示例性信号肽之后可以是柔性前-肽接头,例如AS、GS、ASAS、GSGS。在一些实施方案中,当信号肽是II类并且之后是引入的肽时使用柔性前-肽接头。编码本文所述的MHC-CAR的任何构建体可包含编码上述任何前-肽接头的核酸序列,例如AS可通过核酸序列GCATCT编码,TS可通过核酸序列ACAAGT编码。

[0189] 编码 β -2-微球蛋白信号肽的示例性核酸序列在下面提供:

ATGGTATGCTTGAAGCTCCCGGGCGGGTCTGCATGACCGCTCTCACTGTTACTCTTATGGTCCTTAGTTCACCG
CTTGCCCTG (SEQ ID NO: 397)

[0190]

ATGGCAATATCTGGTGTTCCTGTCCTCGGGTTTTTTATCATAGCCGTACTGATGTCAGCACAGGAATCATGGGCG
(SEQ ID NO: 414)

[0191] 在一些实施方案中,本文所述的MHC-CAR可包括在本文所述的其它组分之间的一个或多个肽接头。实例包括(Gly_xSer)_n接头,其中x和n独立地可以是3和12之间的整数,包括3、4、5、6、7、8、9、10、11、12或更大。在一些实例中,肽接头可以是(Gly₄Ser)_n (SEQ ID NO: 103),其中n可以是3和20之间的整数。具体实例包括(Gly₄Ser)₃ (SEQ ID NO:68)、(Gly₄Ser)₆ (SEQ ID NO:69)、(Gly₄Ser)₉ (SEQ ID NO:76)、(Gly₄Ser)₁₂ (SEQ ID NO:105)和(Gly₄Ser)₁₅ (SEQ ID NO:106)。

[0192] (ii) MHC-CAR的构造

[0193] 本文公开的MHC-CAR构建体,包含本文所述的一种或多种组分,可以任何合适的形式构造。示例性MHC I类构建体和MHC II类构建体在图7和8中提供。

[0194] 本文所述的含有MHC I类部分的MHC-CAR构建体可以是单一融合多肽,其包含MHC I类部分、抗原肽和信号传导结构域(例如,共刺激结构域、胞质信号传导结构域或其组合),以及任选地一种或多种本文所述的另外的组分。参见例如,图8。在一些实例中,MHC I类CAR构建体含有邻近抗原肽的铰链结构域。MHC I类CAR可不含有 β 2-微球蛋白(b2m)。当在细胞表面上表达时,这样的MHC-CAR可与内源性b2m形成异源二聚体。或者,MHC I类CAR也可包括b2m,其可与 α 链融合以产生单一多肽。在一些情况下,MHC I类CAR可含有两个亚单元,一个包括 α 链或其一部分(例如,胞外结构域),以及另一个包括b2m或其一部分(例如,胞外结构域)。

域)。在一些实例中,抗原肽可与 α 链融合。在其它实例中,抗原肽可与b2m融合。任选地,MHCI类CAR可含有两个组分之间的肽接头。一个实例在图8B中提供。

[0195] 在一些实例中,MHC-CAR包含I类分子或其一部分,例如HLA A3或HLA A2,以及合适由I类分子呈递的抗原肽(例如,PLP片段KLIETYFSK(SEQ ID NO:107)或TAX片段LLFGYPVYV(SEQ ID NO:108))。任选地,MHC-CAR可进一步包含b2m。或者,b2m分子可与I类MHC-CAR分开表达。I类分子和b2m序列的实例在下面提供:

HLA A2:

```
GSHSMRYFFTSVSRPGRGEPRIAVGYVDDTQFVRFSDAASQRMPEPRAPWIEQEGPEYWDGETRKVKASQTHR  
VDLGLTRGYYNQSEAGSHTVQRMYGCDVGS DWRFLRGYHQYAYDGKDYLKEDLRSWTAADMAAQITKRKWEAA  
HVAEQLRAYLEGTCVEWLRRLYLENGKETLQRTDAPKTHMTHHAVSDHEATLRCWALSFP AEITLTWQRDGEDQT  
QDTELVEPTRPAGDGTTFQKWA AVVVP SGEEQRYTCHVQH EGLPKPLT (SEQ ID NO: 109)
```

[0196]

HLA A3:

```
GSHSMRYFFTSVSRPGRGEPRIAVGYVDDTQFVRFSDAASQRMPEPRAPWIEQEGPEYWDGETRNVKAQSQTHR  
VDLGLTRGYYNQSEAGSHTIQIMYGCDVGS DGRFLRGYHQYAYDGKDYLKEDLRSWTAADMAAQITKRKWEAA  
HEAEQLRAYLDGTCVEWLRRLYLENGKETLQRTDPPKTHMTHHPI SDHEATLRCWALGFYPAEITLTWQRDGEDQT  
QDTELVEPTRPAGDGTTFQKWA AVVVP SGEEQRYTCHVQH EGLPKPLT (SEQ ID NO: 110)
```

[0197]

对于上述的微延伸序列(microextension):LRWE(SEQ ID NO:111)

[0198]

具有H-2K^b α 3结构域(下划线/斜体)的HLA A2

```
GSHSMRYFFTSVSRPGRGEPRIAVGYVDDTQFVRFSDAASQRMPEPRAPWIEQEGPEYWDGETRKVKASQTHR  
VDLGLTRGYYNQSEAGSHTVQRMYGCDVGS DGRFLRGYHQYAYDGKDYLKEDLRSWTAADMAAQITKRKWEAA  
HVAEQLRAYLEGTCVEWLRRLYLENGKETLQRTD DS PKAHVTHHSRPEDKVT LR CWALGFYPADITLTWQLNGEELI  
QDMELVETRPAGDGTTFQKWA SVVPLGKEQYYTCHVYHQGLPEPLT (SEQ ID NO: 112)
```

[0199]

[0200]

具有H-2K^b α 3结构域(下划线/斜体)的HLA A3

```
GSHSMRYFFTSVSRPGRGEPRIAVGYVDDTQFVRFSDAASQRMPEPRAPWIEQEGPEYWDGETRNVKAQSQTHR  
VDLGLTRGYYNQSEAGSHTIQIMYGCDVGS DGRFLRGYHQYAYDGKDYLKEDLRSWTAADMAAQITKRKWEAA  
HEAEQLRAYLDGTCVEWLRRLYLENGKETLQRTD DS PKAHVTHHSRPEDKVT LR CWALGFYPADITLTWQLNGEELI  
QDMELVETRPAGDGTTFQKWA SVVPLGKEQYYTCHVYHQGLPEPLT (SEQ ID NO: 113)
```

[0201]

[0202]

对于上述的微延伸序列:LRWE(SEQ ID NO:111)

[0203]

B2-微球蛋白(人):

```
IQRTPKIQVYSRHPAENGKSNFLNCYVSGFHPSDIEVDLLKNGERIEKVEHSDLSFSKDWSFYLLYYTEFTPTTEK  
DEYACRVNHVTLTSQPKIVKWDRDM (SEQ ID NO: 114)
```

[0204]

[0205]

B2-微球蛋白(小鼠):

```
IQKTPQIQVYSRHPPENGKPNILNCYVTQFHPHIEIQMLKNGKKIPKVEMSDMSFSKDWSFYILAHTTEFTPTTE  
DTYACRVKHASMAEPKTVYWDKDRDM (SEQ ID NO: 115)
```

[0206]

[0207] 图7提供了MHC II类CAR构建体的许多示例性设计。通常,MHC II类CAR构建体含有两个亚单元,一个包括 α 链或其一部分(例如,胞外结构域)以及另一个包括 β 链或其一部分(例如,胞外结构域)。抗原肽可与 α 链或 β 链融合。在一些情况下,MHC II类CAR也可呈单一融合多肽形式,其中 α 和 β 链融合形成单一多肽。MHC II类CAR的 α 链和 β 链可衍生自相同的MHC II类分子。或者,它们可来自不同的MHC II类分子。例如,MHC II类CAR可含有来自HLA DRA*1010的 α 链和来自HLA DRB1*1501的 β 链,其可与抗原肽融合,例如MBP肽。

[0208] 在一些实例中,MHC-CAR包含II类分子或其一部分,例如DRB1*1501或DRA*0101,以及合适由II类分子呈递的抗原肽(例如,MBP片段DENPVVHFFKNIVTPRTPP(SEQ ID NO:15))。II类分子序列的实例在下面提供:

DRB1*1501:

GDTRPRFLWQPKRECHFFNGTERVRLDRYFYNQEESVRFDSDVGEFRAVTELGRPDAEYWNQSQKDILEQARA
AVDTYCRHNYGVVESFTVQRRVQPKVTVPYPSKTQPLQHNNLLVCSVSGFYPGSIEVRWFLNGQEEKAGMVSTGLIQN
GDWTFQTLVLMLETVPERSGEVYTCQVEHPSVTSPLT (SEQ ID NO :117)

[0209]

DRA*0101

IKEEHVIIQAEFYLNPDQSGEFMFDFDGDDEIFHVDMAKKETVWRLEEFGRFASFEAQGALANIAVDKANLEIMTK
RSNYTPITNVPPEVTVLTNSPVLEPENVLICFIDKETPPVNVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHY
LPFLPSTEDVYDCRVEHWGLDEPLLKH (SEQ ID NO: 118)

[0210] DRB1*1501人/IA-D β 小鼠 (突变残基用粗体和下划线表示)

IKEEHVIIQAESYLNPDQSGEFKDFDGDDEIFHVDMAKKETVWRLEEFGRFASFEAQGALANIAVDKANLEIMTK
RSNYTPIEETEVPPLSLRLEQPNVAISLSRTEALNHHNTLVCSVTDIFYPAKIKVRWFRNGQEEVGVSSSTQLIRN
GDWTFQVLVLMLEMTPHQGEVYTCVHEHPSLXSPIT (SEQ ID NO: 119)

[0211]

[0212] DRA*0101人/IA-D α 小鼠 (突变残基用粗体和下划线表示)

IKEEHVIIQAESYLNPDQSGEFKDFDGDDEIFHVDMAKKETVWRLEEFGRFASFEAQGALANIAVDKANLEIMTK
RSNYTPITATNEAPQATVFPKSPVLLGQPHLLICFVDNIFPPVINITWLRNSKSVTDGVYETSFVLNDRHDSFHKLS
YLTFF
IPSDDDIYDCKVEHWGLEEPVLKHWEPEI (SEQ ID NO: 120)

[0213]

[0214] DR-2 β 小型 (突变残基用粗体和下划线表示)

RPRFLWQSKRECHFFNGTERVRLDRYFYNQEESVRFDSDVGEFRAVTELGRPDAEYWNQSQKDILEQARA
AVDTYCRHNYGVVESFTVQR (SEQ ID NO: 121)

[0215]

[0216] DR-2 α 小型

IKEEHVIIQAESYLNPDQSGEFKDFDGDDEIFHVDMAKKETVWRLEEFGRFASFEAQGALANIAVDKANLEIMTK
RSNYTPI (SEQ ID NO: 122)

[0217]

[0218] 编码DRB1*1501的示例性核酸序列在下面提供:

GGAGACACAAGACCCCGATTCTTGTTGGCAGCCCAAAAGGGAGTGCCATTTTTTCAATGGGACGGACGAGTTCGC
TTCCTTGATCGGTACTTTTACAACCAAGAAGAGAGTGTACGGTTCGACTCAGATGTCGGCGAGTTCGAGCGGTT
ACGGAATTGGGGCGACCTGACGCGGAGTACTGGAACCTCCCAAAAGGATATTTTGGAGCAGGCACGACGCTGTG
GACACCTIATTTGTCACATAAATTTATGGTGTGGTGGAAATCCTTTACAGTTTCAGCGGCGGGTGAACCTAAAGTGACC
GTGTATCCATCTAAACGCAACCCCTCCAACACCATAACCTCCTGGTGTGTTCGGTAAGCGGCTTCTATCCCGGG
TCAATTGAGGTTCAGGTGGTTCCTCAACGGTCAGGAGGAGAAGGCCGAATGGTAAGTACTGGTCTTATCCAGAAC
GGAGACTGGACCTTCCAAACTTTGGTAATGTTGGAAACGGTGCCGCGATCCGGGGAGGTGTATACATGCCAAGTT
GAACACCCGAGTGTACGAGCCCCCTGACG (SEQ ID NO: 402)

[0219]

[0220] 编码DRA*0101的示例性核酸序列在下面提供:

ATAAAAGAAGAGCACGTGATAATACAGGCGGAGTTTATTTGAACCCGGACAGAGCGGTGAGTTTCATGTTTCGAT
TTTGATGGCGACGAGATATTTACGTTGACATGGCAAAAAAGGAAACGGTGTGGAGACTTGAGGAGTTTGGACGA
TTCGCATCATTTGAGGCACAAGGAGCACTCGCCAATATCGCGGTGGACAAGGCCAACCTGGAGATCATGACAAAA
CGCTCCAATTATACGCTATCACTAATGTGCCCTGAGGTTACTGTGCTCACAAATCTCCCGTAGAACTTAGG
GAACCTAACGTCCTCATATGTTTCATCGACAAGTTCACTCCCTCCGGTGGTCAATGTAACGTGGCTTCGGAATGGT
AAGCCGGTCACCAAGGGTGTCTCAGAGACCGTATTTCTGCCAGAGAAGACCACCTCTCCGCAAAFTTCATTAC
CTTCCCTTTCTTCAACGGAAGACGTTTACGACTGCAGGGTCAACATTTGGGGCTTGACGAGCCACTTCTC
AAGCATTTGG (SEQ ID NO: 415)

[0221]

[0222] 本文所述的任何MHC I类和MHC II类构建体可进一步融合至一个或多个信号传导结构域和任选地一种或多种另外的组分。在一些情况下,本文所述的MHC-CAR构建体不含信号传导结构域。

[0223] 优选地,本文所述的MHC-CAR含有匹配的MHC部分和抗原肽,例如,呈递抗原肽或天然状态的同源类似物的MHC分子。在一些情况下,本文所述的MHC-CAR也可含有来自HLA DRB1*1501的 α 链或 β 链和与该HLA等位基因相关的抗原肽,例如本文所述的那些MBP肽等等。参与自身免疫性疾病的抗原肽和特定HLA等位基因之间的关联是本领域众所周知的,或可通过常规实践鉴定,例如文库筛选。

[0224] 一种示例性MHC-CAR可具有以下结构式(+/-表示该特定组分是任选的)：

[0225] 单链(MHC I类或II类+肽)(+/-铰链)+单链CD28/4-1BB(+/-二亮氨酸基序)(+/-cd3ζ)。(另外的短肽接头可加入组分之间,如之前所述)。

[0226] 其它示例性MHC-CAR设计(单链和多链)在图10中说明。在多链构建体的情况下,一个或多个短铰链可用于增强MHC-CAR的成功表达。此外,可能需要用来自小鼠结构域的保守结构域置换一部分结构以防止交叉反应性。注意在一些情况下,内部结构域可仅与一条链衔接。

[0227] MHC-CAR结合(其展示MBP)TCR的氨基酸序列在下面提供:

[0228] TCRαMBP

[0229] METLLGVSLVILWLQLARVNSQQGEEDPQALSIQEGENATMNC SYKTSINN LQWYRQNSGRGLVHLILIRS
NEREKHSGRLRVTLDTSKSSSLITASRAADTASYFCATAAVGGFKTIFGAGTRLFVKANIQNPDPAVYQ
LRDSKSSDKSVCLFTDFDSQTNVSQSKSDVYITDKTVLDMRSMDFKSNSAVAWSNKSDFACANAFNNSII
PEDTFFPSPRESSCDVKLVEKSFETDTNLFQNL SVIGFRILLKLVAGFNLLMTLRLWSS (SEQ ID NO:
123)

[0230] TCRβMBP

[0231] MLLLLLLLLLGLAGSGLGAVVSQHPSPWVLSKSGTSVKIECRSLDFQATTMFWRQFPKQSLMLMATSNEGSKA
TYEQGVEKDKFLINHASLTSLTLVTSAPHPEDSSFYICSAARDLTSGANNEQFFGPGTRLTVLEDLKNVFPF
EVAVFEPSEAEISHTQKATLVCLATGFYPDHVELSWVNGKEVHSGVSTDPQLKEQPALNDSRYLSRL
RVSATFWQNP RNHFRCQVQFYGLSENDEWTQDRAKPVQTQIVSAEAWGRADCGFTSESYQQGVLSATILYEI
LLGKATLYAVLV SALVLMAMVKRKDSRG (SEQ ID NO: 124)

[0232] TCRαI类

[0233] mamllgasvl ilwlqpdwvn sqgkndd
QQVKQNSPSSLVSQEGRISILNCDYTN SMFDYFLWYKKYPAEGPTFLISISSIKDKNADGR
FTVFLNKS AKHLSLHIVPSQPGDSAVYFCAAMEGAQKLVFGQGT RL TINPNIQNPDPAVY
QLRDSKSSDKSVCLFTDFDSQTNVSQSKSDVYITDKTVLDMRSMDFKSNSAVAWSNKSD
FACANAFNNSIIPEDTFFPSPRESS
Cdvklve ksfetdtlnln fqnlsvigfr illllkvagfn llmtlrlwss (SEQ ID NO: 125)

[0234] TCRβI类

[0235] msigllccaa lsllwagpv
NAGVTQTQPKFQVLKTGQSM TLQCAQDMNHEYMSWYRQDPGMGLRLIHYSGAGITDQGEV
PNGYNVSRSTTEDFPLRLLSAAPSQT SVYFCASSYPGGGFYEQYFGPGTRLTVTEDLKNV
FPPEVAVFEPSEAEISHTQKATLVCLATGFYPDHVELSWVNGKEVHSGVSTDPQLKEQ
PALNDSRYALSSRLRVSATFWQDPRNHFRCQVQFYGLSENDEWTQDRAKPVQTQIVSAEAW
GRAD
cgftse syqqgvlsat ilyeillgka tlyavlv sal vlmamvkrkd srg (SEQ ID NO: 126)

[0236] 示例性CD19靶向CAR构建体的氨基酸序列在下面提供(注意这些设计含有4-1BB结构域,其可被cd28结构域置换)：

[0237] 4G7-CAR版本1:

[0238] MALPVTALLLPLALLLHAARPEVQLQQSGPELIKPGASVKMSCKASGYFTTSYVMHWVKQKPGQGLEWIGYINPY
NDGTYNEKEFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARGTYYYGSRVFDYWGQTTTLTVSSGGGGSGGG
SGGGGSDIVMTQAAPSIPVTPGESVVISCRSSKSLNNGNGSGSGTAFTLRISRVEAEDVGYYCMQHLEYFPF
TAGTKLELKRSDPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLS
LVITLYCKRGRKKLLYIFKQPFMRPVQTQQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNL
GRREYDVLDKRRGRDPFMGGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRRRGKGDGLYQGLSTATKDTY
DALHMQALPPR (SEQ ID NO: 127)

[0239] 4G7-CAR版本2:

[0240]

METDTLLLWV	LLLWVPGSTG	EVQLQQSGPE	LIKPGASVKM	SCKASGYTFT	SYVMHWVKQK
PGQGLEWIGY	INPYNDGTKY	NEKFKGKATL	TSDKSSSTAY	MELSSLTSED	SAVYYCARGT
YYYGSRVFDY	WGQGTTLPVS	SGGGSGGGG	SGGGGSDIVM	TQAAPSIPVT	PGESVSI SCR
SSKSLNSNG	NTYLWFLQR	PGQSPQLLIY	RMSNLASGVP	DRFSGSGSGT	AFTLRISRVE
AEDVGVYYCM	QHLEYPTFTG	AGTKLELKR	DPTTTPAPRP	PTPAPTIASQ	PLSLRPEACR
PAAGGAVHTR	GLDFACDIYI	WAPLAGTCGV	LLLSLVITLY	CKRGRKKLLY	IFKQPFMRPV
QTTQEEDGCS	CRFPEEEEGG	CELRVKFSRS	ADAPAYQQGQ	NQLYNELNLG	RREEDVLDK
RRGRDPEMGG	KPRRKNPQEG	LYNELQKDKM	AEAYSEIGMK	GERRRGKGHD	GLYQGLSTAT
KDTYDALHMQ	ALPPR (SEQ	ID NO: 128)			

[0241] 示例性CD19靶向CAR构建体的核酸序列在下面提供。

[0242] 4G7-CAR版本2:

[0243]
atggagacagacactcttctctcttgggtcttctgtctgtggttcccggaagcacaggagaagtacagttgcaa
cagttctggggccagaactcatcaaacccggagcttctgtaaaaatgtcatgcaaagctagtggatatacatttact
tcttacgtgatgcactgggtaaaaacagaaacctgggtcaggggcttgagtggatcgggtacattaacctatataat
gacggcaccaaaataataacgagaaaattcaagggaagggtacgcttacatcagataaagtcagtagcacgcgttat
atggaacttagcagccttactctccgaagattccgcgggtgtattactgcgcgagagggacttactactacgggagt
caggtattcgattatttgggggtcaaggcacgacgctcacggtgagctcaggtggtggaggggtctgggggtggcggc
agtgggtgggggggggtcagacatcgtgatgacccaggcagcaccttctatcccggtaacccccaggcgagttctgta
tctatcagttgtcgggtccagcaagttctcttctcaacagtaattggcaatacatatcttcttactgggttcttccaaagg
cttggggcaagtcctcaacttcttataatcggatgttccaatcttgcgagtgggcgttaccgcagaggttttcagggt
cttggggagcgaaacgctctttacgttgagaatatccagggtagaagtcaggacgctcggtgtatattatttgcagt
caacatctcgaaatacccccttacccttcggcgctgggtacaaagctcgaattgaaacgcagcgatccaaaccaagc
ccagcgccacgaccaacctacgcccgtctcaactattgcctcccagccccaggtcttcggccagaagcgtgtaga
cctgctgcccggcggggcttccatacgcggggccttgacttgcagtgtgatctctatatatgggctcctttggcg
ggaaacttgcggagtgcttcttttgtcactcgtgataacggtgtattgtaaaaaggggtcgaaagaaactcctctat
atatttaagcagccctttatgaggcccggtgcaaacacacaagaagaggacgggatgctcttctgtcgattcccgga
gaggaggaggggggtgtgagcttagggtcaagtttctcgctctgcgcgacgcgccagcctatcaacagggccaa
aaccagctgtataacgaactcaacctcgggcgcggggaagagtatgacgtccttgacaaaacggcgcggtcgcgac
cctgaaatgggtggaaaaacgagggcgaaaagaaacccccaggagggactttacaaagaaattgcaaaaagacaagatg
gccgaagcctattccgaaattggaatgaaaggcgagcggagacgaggttaaggggcattgacggcctgtatcaagggt
ctctctacggccacgaaggatacttacgacgccccttcatatgcaagctcttccaccacgg (SEQ ID NO:
390)

[0244] 含有MHC-CAR1部分B (MHC-DRB CAR)-HLA DRB1*1501 (信号肽)、MBP肽、HLA DRB1*1501 (外部, 铰链, 跨膜) CD3 ζ (胞质信号传导结构域) 的MHC-CAR1在下面提供:

[0245] MVCLKLPGGSCMIALPTVTLMLVLSPLALASDENFVVHFFKNIVTPRTPPGGGGSGGGGSGGSDTRPRFLWQPKR
ECHFFNGTERVRFELDRFYFNQEEVSREDSVGEFRAVTELGPRDAEYWNSQKDILEQARAADVITYCRHNYGVVES
FTVQRRVQPKVTVPYPSKTQPLQHHNLLVCSVSGFYPGSIEVRWFLNGQEEKAGMVSTGLIQNGDWTFTQTLVMLET
VPRSGEVYTCQVEHPSVTSPLTVEWRARSESAQSKMLSGVGGFVLGLLFLGAGLFYIFRNQTSRVKFSRSADAPA
YQQGQNLRLNENLNGRREEVDLDRKRGRPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRRGKGD
GLYQGLSTATKDTYDALHMOALPPR (SEQ ID NO 412)

[0246] 编码含有MHC-CAR1部分B(MHC-DRB CAR)-HLA DRB1*1501(信号肽)、MBP肽、HLA DRB1*1501(外部, 铰链, 跨膜) CD3ζ(胞质信号传导结构域)的MHC_CAR1的示例性核酸序列在下面提供:

[0247]

ATGGGTATGCTTGAAGCTCCCGGGCGGGTCTGTCATGACCGCTCTCACTGTTACTCTTATGGTCCTTAGTTACCCG
CTTGCCCTGGCATCTGATGAGAATCCCGTGGTTTCATTTTTTAAGAACATCGTCACACCGCGCACCCACCTGGG
GGAGGCGGATCTGGCGGAGGCGGGAGTGGAGGCTCAGGAGACACAAGACCCGATTCTTGTGGCAGCCCAAAAGG
GAGTGCATTTTTTCAATGGGACGGAACGAGTTCCGTTCTTGATCGGTACTTTTACAACCAAGAAGAGAGTGT
CGGTTCGACTCAGATGTCGGCGAGTTCGAGCGGTTACGGAATTGGGGCGACCTGACGCGGAGTACTGGAATCC
CAAAAGGATATTTTGGAGCAGGCACGAGCAGCTGTGGACACCTATGTGCGACATAATTATGTTGTGGTGAATCC
TTTACAGTTTACGCGCGGGTGAACCTAAAGTGACCGTGTATCCATCTAAAACGCAACCCCTCCAACACCATAAC
CTCCTGGTGTGTTCCGTAAGCGGCTTCTATCCCGGGTCAATTGAGGTCAGGTGGTTCCTCAACGGTCAGGAGGAG
AAGGCCGGAATGGTAAGTACTGGTCTTATCCAGAACGGGAGACTGGACCTTCCAAACTTTGGTAATGTTGGAAACG
GTGCCGCGATCCGGGGAGGTGTATACATGCCAAGTTGAACACCCGAGTGTACGAGCCCCCTGACGGTTGAGTGG
AGGGCGCGGTGAGAGCGCACAACTTAAATGCTGTGAGGAGTAGGCGGATTTGTAAGTCTCGGACTCCTCTTTTGT
GGCGCTGGGTGTATCTACTTTAGAAACCAACAAGTAGAGTAAAGTTTCCCGAAGTGGCGACGCTCCCGCG
TATCAGCAAGGTCAAAACGAGCTTTACAACGAACTGAACCTGGGACGACGCGAAGAGTACGATGTTCTTGATAAG
CGGAGAGGGCGGATCCCGAAATGGGGGAAAGCCTCGGAGGAAGAACCCACAAGAAAGGCTTTATAATGAAGT
CAGAAGGACAAGATGGCGGAGGCGTATTCGAAATAGGCATGAAGGTGAACGGAGGAGAGGAAAGGGACATGAC
GGACTTTATCAAGGATTGCTTACCGCAACTAAAGACACCTATGACGCGTTGCACATGCAGGCTCTCCTCCGAGA
(SEQ ID NO: 413)

[0248] 含有MHC-CAR1部分A (MHC-DRA CAR) HLA-DRA*1010 (信号肽, 外部, 铰链, 跨膜)、CD3
ζ (胞质信号传导结构域) 的MHC-CAR在下面提供:

[0249]

MAISGVPVLGFFIIAVLMSAQESWAIKEEHVIIQAEFYLNPDQSGEFMFDFDGEIFHV
DMAKKETVWRLEEFGRFASFEAQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTV
LTNSPVELREPNVLICFIDKFTPPVVNVTWLRNGKPVTTGVSETVFLPREDFHFRKFH
YLPFLPSTEDVDYDCRVEHWGLDEPLLKHWEFDAPSPLPETTENVVVCALGLTVGLVGII
IGTIFIIKGLTSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDP
GGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT
YDALHMQALPPR (SEQ ID NO: 423)

[0250] 编码MHC-CAR1部分A (MHC-DRA CAR) HLA-DRA*1010 (信号肽, 外部, 铰链, 跨膜)、CD3
ζ (胞质信号传导结构域) 的示例性核酸序列在下面提供:

[0251]

ATGGCAATATCTGGTGTTCCTGTCCTCGGGTTTTTTATCATAGCCGTACTGATGTCAGCACAGGAATCATGGGCG
ATAAAAGAAGAGCACGTGATAATACAGGCGGAGTTTTTATTTGAACCCGGACCAGAGCGGTGAGTTTCATGTTTCGAT
TTTGATGGCGACGAGATATTTACGTTGACATGGCAAAAAGGAAACGGTGTGGAGACTTGAGGAGTTTGGACGA
TTCGCATCATTTGAGGCACAAGGAGCACTCGCCAATATCGCGGTGGACAAGGCCAACCTGGAGATCATGACAAAA
CGCTCCAATTATACGCCTATCACTAATGTGCCCCCTGAGGTTACTGTGCTCACAAATCTCCCGTAGAACTTAGG
GAACCTAACGTCCTCATATGTTTCATCGACAAGTTCACTCCTCCGGTGGTCAATGTAACGTGGCTTCGGAATGGT
AAGCCGGTCACCACGGGTGTCTCAGAGACCGTATTTCTGCCCAGAGAAGACCACCTCTTCCGCAAATTTTCATTAC
CTTCCCTTTCTTCTTCAACGGAAGACGTTTACGACTGCAGGGTCGAACATTGGGGGCTTGACGAGCCACTTCTC
AAGCATTTGGGAGTTCGACGCCCCATCACCGCTTCCAGAAACGACTGAAAACGTTGTCTGCGCTCTTGGCCTGACA
GTGGGCCTGGTAGGCATTATATCGGGACCATCTTTATCATCAAAGGTTTGACTTCCCGGGTCAAATTTAGCAGA
TCCGCTGACGCACCGGCCTACCAGCAGGGCCAGAACCAACTCTACAACGAGCTGAATCTCGGCCGACGGGAAGAG
TATGACGTAAGTTCGACAAGCGGAGAGGTTCGAGACCTGAGATGGCGGTAAACCGAGACGGAAAAATCCCCAAGAG
GGTCTTTATAATGAAGTCCAGAAGGATAAGATGGCTGAAGCCTATCTGAGATAGGGATGAAAGGCGAGCGGCGG
AGGGGTAAAGGCCATGATGGCTTTACCAGGCACTCTCCAGGCAACCAAGATACTTACGACGCCCTTCACATG
CAAGCCCTCCCGCCACGC (SEQ ID NO: 424)

[0252] 构建体1 (CD19 CAR和CCR6区) 在下面提供:

[0253]

METDTLLLLWVLLLVPGSTGEVQLQQSGPELIKPGASVKMSCKASGYTFTSYVMHWVKQKPGQGLEWIGYINPYN
DGTKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARGTYYYGSRVFDYWGQGTTLTVSSGGGSGGGG
SGGGGSDIVMTQAAPSIPTVTPGESVSISSCRSSKSLNNGNTYLYWFLQRPQGSPQLLIYRMSNLASGVPDRFSG
SGSGTAFTLRISRVEAEDVGVIYCMQHLEYPFTFGAGTKLELKRSDPTTTPAPRPPTPAPTIASQPLSLRPEACR
PAAGGAVHTRGLDFACDIYIWAFLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPE
EEEGGCELRLVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPGEGGKPRRKNPQEGLYNELQKDKM
AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRGSSSGSGEGRGSLLTCGDVEENPGPMGSGESM
NFSDFDSSSEDYFVSVNTSYYSVDSEMLLCSLQEVRFSLFVPIAYSLICVFGLLGNILVVITFAFYKKARSMT
DVYLLNMAIADILFVLTLFPFWAVSHATGAWVFSNATCKLLKGIYAINFNCGMLLLTCISMDRYIAIVQATKSFR
RSRTLPRSKIIICLVVWGLSVIISSSTFVFNQKYNTQGSQDVCEPKYQTVSEPIRWKLLMLGLELLFGFFIPLMFI
FCYTFIVKTLVQAQNSKRHKAIRVIIAVVLVFLACQIPHNMVLLVTAANLGKMNRSQCSEKLIQYTKTVTEVLAF
LHCCLNPVLYAFIQKFRNYFLKILKDLWCVRKRYKSSGFSACAGRYSENIQRQTSETADNDNASSFTM (SEQ
ID NO: 425)

[0254]

构建体1 (CD19 CAR,CCR6,GFP区) 在下面提供:

[0255]

METDTLLLLWVLLLVPGSTGEVQLQQSGPELIKPGASVKMSCKASGYTFTSYVMHWVKQKPGQGLEWIGYINPYN
DGTKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARGTYYYGSRVFDYWGQGTTLTVSSGGGSGGGG
SGGGGSDIVMTQAAPSIPTVTPGESVSISSCRSSKSLNNGNTYLYWFLQRPQGSPQLLIYRMSNLASGVPDRFSG
SGSGTAFTLRISRVEAEDVGVIYCMQHLEYPFTFGAGTKLELKRSDPTTTPAPRPPTPAPTIASQPLSLRPEACR
PAAGGAVHTRGLDFACDIYIWAFLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPE
EEEGGCELRLVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPGEGGKPRRKNPQEGLYNELQKDKM
AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRGSSSGSGEGRGSLLTCGDVEENPGPMGSGESM
NFSDFDSSSEDYFVSVNTSYYSVDSEMLLCSLQEVRFSLFVPIAYSLICVFGLLGNILVVITFAFYKKARSMT
DVYLLNMAIADILFVLTLFPFWAVSHATGAWVFSNATCKLLKGIYAINFNCGMLLLTCISMDRYIAIVQATKSFR
RSRTLPRSKIIICLVVWGLSVIISSSTFVFNQKYNTQGSQDVCEPKYQTVSEPIRWKLLMLGLELLFGFFIPLMFI
FCYTFIVKTLVQAQNSKRHKAIRVIIAVVLVFLACQIPHNMVLLVTAANLGKMNRSQCSEKLIQYTKTVTEVLAF
LHCCLNPVLYAFIQKFRNYFLKILKDLWCVRKRYKSSGFSACAGRYSENIQRQTSETADNDNASSFTMGSGATNF
SLLKQACDVEENPGPVSKGEELFTGVVPIILVELDGDVNGHKFSVSGEGDATYCKLTLKFICTTGKLPVPWPTL
VTTLTYGVQCFSRYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGN
ILGHKLEYNNYSHNVYIMADKQKNGIKANFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALS
KD PNEKRDMVLLFVTAAGITLGMDELYK (SEQ ID NO: 429)

[0256]

编码构建体1 (CD19 CAR,CCR6,GFP区) 的示例性核酸序列在下面提供:

[0257]

atggagacagacactcttctccttgggtcttctgctgctgtgggttcccggaagcaaggagaaagtacagttgcaa
cagtcctgggccagaaatcatcaaacccggagctctctgtaaaaaatgtcatgcaaaagctagtggatatacatttact
tcttacgtgatgcaactgggtaaaaacagaaacctgggtcaggggcttgagtgagatcggttacattaacccatataat
gacggcaccaaatataacgagaaattcaagggaaggctacgcttacatcagataagtcagtagcaccgcttat
atggaacttagcagccttacttccgaagattccgcggtgtattactgcgcgagagggacttactactacgggagt
cgagtatctcgattattgggggtcaaggcaagcagctcaggtgagctcaggtgggtggagggtctgggggtggcggc
agtgtgtggggggggtcagacatcgtgatgacccaggcagcaccttctatcccggtaacccaggcgagtcgtta
tctatcagttgtcggtccagcaagtccttctcaacagtaaatggcaatacatatcttactggttctccaaagg
cctgggcaaaagtctcaactctcttatatatcggtatgtccaatcttgcgagtgggcgtacccgacaggttttcaggg
tctgggagcggaacagcttttacgttgagaatatccagggtagaagctgaggacgctcggtgtatattattgcatg
caacatctcgaataacccctttaccttcggcgctggtacaaagctcgaattgaaacgcagcgatccaaccacgacg
ccagcgccacgaccactacgcccgtccaactattgcctcccagcccctgagtccttcggccagaagcgtgtaga
cctgctgcggcgggggcgttcatacgggggcttgactttgcatgtgatctatataatgggctcctttggcg
ggaaacttgaggagtgccttcttcttgctcactcgtgataacggtgtattgttaaaaggggtcgaaagaaactcctcat
atatattaagcagcctcttatgaggccccgtgcaaacacacaaagaggacggatgctcttgcgattcccgaa
gaggaggaggggggtgtgagcttagggtcaagtttctcgtctgcccagcgcgcagcctatcaacaggggccaa
aaccagctgtataacgaactcaacctcgggcgccgggaagagtgatgacgtccttgacaaacggcgcggtgcgcac
cctgaaatgggtggaaaacccgagggcgaagaacccccaggaggagctttacaaagaaattgcaaaaagacaaagt
gccgaagcctattccgaaattggaatgaaaggcgagcgagagcagggtaaggggcatgacggcctgtatcaaggg
ctctctacggccacgaaggatacttacgacgcccctcatatgcaagctcttccaccacgggggttcgagcggcagt
ggagagggcgagaggaagtctgctaacatcggtgacgtcgaggagaatcctggcccaatgagtggggaaagtatg
aacttcagcgatgtatttgactcctccgaagattactttgtatctgtgaatacagagctattactccgtcgatagt
gaaatgctgctctgtagtctccaagaagtcggccaattcagtcgcctcttctgctcccatcgcgtaactcccttatt
tgtgtttttggccttctgggttaacatcctggtgtgaatcacattcgctttctataaaaaagctcggagtatgact
gatgtttaccttcttaacatggctatagcggacattctttttgtgcttactctcccattctgggctgtgagccat
gcaacagggggcgtgggttttttcaaagtcacatgtaagctgcttaaagggtatctatgcaataaacttcaattgc
gggatgctcctgctgacatgcatcagtatggatcgatacatagctatagtagacaggcgactaagtccttccgctg
cgatcccgacactgcctaggagcaaaattatttgcctcgtcgatgggggctctcagtgatcatctcctccagt
acgtttgtcttttaaccagaaatataacacacaggggtctctgagtgtgtaaccaaagtatcagacagtgagtgaa
ccaatacgggtggaagtgtcttatggtgggcttgagctgctttttgggttttccatcccaactgatgttcagatt
ttctgttatacatttattgttaagacctggttcaggcgcaaaatagcaagagacataaggcaattcagagtcac
attgcggtggtgttggtcttcttggcctgtcagatccccataataatggttctgctcgtcacccgcgttaacttg
ggtaagatgaatcgatcttctcagtcagagaaagtgatcggtacacacaaaactgtgacagaagtgtggccttc
cttcaactgttctgaacccagtttctgtatgcttttataggacagaagtttcgaaattacttcttgaaatcctc
aaggacctctggtgtgttcgaagggaagtacaagagctctggctttagttgcgctggcgctacagtgagaatata
tcccgcgagacctccgagactgctgataatgacaacgcaagttccttcaactatgggatccggcgcaacaaacttc
tctctgctgaaacaagccggagatgtcgaaagagaatcctggaccggtgagcaagggcgaggagctgtccacggg
gtggtccccatcctggtcgagctggacggcgacgtaaaacggcccaagttcagcgtgtctggcgagggcgagggc
gatgccacctacggcaagctgacctgaagttcatctgcaaccacgggcaagctgcccgtgcccgtgcccacccctc
gtgaccacccctgacctacggcgtgcagtgtctcagccgctaccccgaccacatgaagcagcagcacttcttcaag
tccgccatgccgaaggctacgtccaggagcgccacatcttcttcaaggacgacggcaactacaagacccgcgcc
gaggtgaagttcgagggcgacacccctggtgaaccgcatcgagctgaagggcatcgacttcaaggaggacggcaac
atcctggggcacaagctggagtacaactacaacagccacaacgtcttatatcatggccgacaagcagaagaacggc
atcaaggcgcaacttcaagatccgcacacacatcgaggacggcagcgtgcagctcgccgacactaccagcagaac
accccatcggcgacggccccgtgctgctgccgacaaacactacctgagcacccagtcggcctgagcagaagac
cccaacgagaagcgcgatcacatggtcctgctggagtctgtgacggcgccgggatcactctcgccatggaagcag
ctgtacaagtaa (SEQ ID NO: 430)

[0258]

构建体2MHC CAR区 (MHC-CAR1部分B,MHC-CAR1部分A区) 在下面提供:

MVCLKLPGGSCMTALTVTLMVLSSPLALASDENPVVHFFKNIVTPRTPPGGGSGGGSGSGSDTRPFLWQPKR
ECHFFNGTERVRFELDRYFYNQEESVRFDSVGEFRAVTELGRPD AEYWN SQKDILEQARA AVDTYCRHNYGVVES
FTVQRRVQPKVTVPYSKTQPLQHNNLLVCSVSGFYPGSIEVRWFLNGQEEKAGMVSTGLIQNGDWTFTQTLVMLET
VPRSGEVYTCQVEHPSVTSPLTVEWRARSESAQSKMLSGVGGFVLGLLFLGAGLFIFYFRNQTSRVKFSRSADAPA
YQQGQNQLYNELNLGRREYDVLDRGRDPPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHD
GLYQGLSTATKDTYDALHMQUALPPRSGSSGSGEGRGSLTCCGDVEENPGPMALSGVPVLGFFIIAVLMSAQESWAI
KEEHVIIQAEFYLNPDQSGEFMFDFDGSDEIFHVDMAKKETVWRLEEFGRFASF EAQ GALANLAVDKANLEIMTKR
SNYTPITNPVPEVTVLNTPVELREPVLICFIDKFTPPVVNVTLWRNGKPVITGVSETVFLPREDHLFRKFHYL
PFLPSTEDVDYDCRVEHWGLDEPLLKHWEFDAPSPLETTENVVCALGLTVGLVGIIGTIFIIKGLTSRVKFSRS
ADAPAYQQGQNQLYNELNLGRREYDVLDRGRDPPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRR
GKGHDGLYQGLSTATKDTYDALHMQUALPPR (SEQ ID NO: 431)

[0259]

[0260]

编码构建体2MHC CAR区 (MHC-CAR1部分B,MHC-CAR1部分A) 的示例性核酸序列在下

面提供:

[0261]

```
atgggtatgcttgaagctcccgggcggtcctgcatgacgcctctcactgttactcttatggtccttagttcacccg
cttgccttgccatctgatgagaatcccggtggtcatttttttaagaacatcgccacacccgcgcacccccacctggg
ggagggcgatctggcgaggcgaggagtgagggtcaggagacacaaagaccccgattcttggcgagcccaaaagg
gagtgccatttttcaatgggacggaacgaggttcgcttcttgatcggtacttttacaccaagaagagagtgta
cggttcgactcagatgtcggcgaggttcggagcggttacggaaattggggcgacctgacgcggagtaactggaaactcc
caaaaggatattttggagcaggcagcagctgtggacacctaattgtcgacataattatgggtgtggtggaactcc
tttacagttcagcgggcggtgcaacctaaagtgaacgtgtatccatctaaaacgcaacccctccaaacaccataac
ctcctgggtgtgtccgtaagcggtcttatcccggtcaattgaggtcaggtggttccctcaacggtcaggaggag
aaggccggaatggttaagtactggtcttatccagaacggagactggaccttccaaaacttggtaagtgtggaacg
gtgcgcgcatccggggagggtgtatcatgccaaagttgaacacccgagtggttacgagcccccgaagggttgagtg
agggcgcggtcagagagcgcacaatctaaaatgctgtcaggagtaggcggtttgtactcggactcctctttttg
ggcgtgggttgtttatctacttttagaaaccaaagtagagtaaagttttccggaagtgcggacgctcccgcg
tatcagcaaggtcaaaaccagctttacaacgaactgaacttgggacgacggaagagtagatgttcttgataag
cggagagggcgcgatccgaaatggggggaaagcctcggaggaagaaccacacaagaaggcctttataatgaactg
cagaaggacaagatggcgaggcggtattccgaaataggcatgaagggtgaacggagagaggaaagggaacatgac
ggactttatcaaggattgtctaccgcaactaaagacacctatgacgcgttgacatgcagggtctcctctccgaga
ggttcgagcgcgagtgaggagggcagaggaagtctgctaacatgcggtgacgtcgaggagaatcctggcccaatg
gcaatatctggtgttctgtcctcgggttttttatcatagccgtaactgatgtcagcacaggaatcatgggcgata
aaagaagagcagctgataatacaggcgaggttttatttgaacccggaccagagcggtgaggttcagttcgatctt
gattggcgagcagatattttcaggttgacatggcaaaaaggaaacgggtgtggagacttgaggagtttggacgattc
gcatcatttgagggcacaaggagcactcgccaatatcgcggtggacaaggccaacctggagatcatgacaaaacgc
tccaattatagcctatcactaatgtgccccctgaggttactgtgctcacaattctcccgtagaacttagggaa
cctaacgtcctcatatgtttcatcgacaagttcactcctccggtggtcaatgtaacgtggcttcggaatggttaag
ccggtcaccacgggtgtctcagagacgttattctgcccagagaagaccacctcttccgcaatttcattacott
ccctttcttcttcaacggaagacgtttacgactgcagggtcgaacattgggggcttgacgagccacttctcaag
cattgggagttcgacgccccatcacgcttccagaaacgactgaaaacgttgtctgcgctcttggcctgacagtg
ggcctggtaggcattattatcgggaccatctttatcatcaaaaggtttgacttcccggtcacaatttagcagatcc
gctgacgcaccggcctaccagcagggccagaaccaactctacaacgagctgaatctcgggcgaagggaagagtat
gacgtactcgacaagcggagaggtcgagaccctgagatggcggttaaaccgagacggaaaaatccccaaaggggt
ctttataatgaactccagaaggataagatggctgaagcctattctgagatagggaagaaaggcgagcgggcgagg
ggttaaggccatgatggcctttaccaggaactctccacggcaaccaagatacttacgacgccccctcacatgcaa
gccccccgccaagc (SEQ ID NO: 71)
```

[0262] 构建体2杀伤开关和MHC CAR区(RQR8,MHC-CAR1部分B,MHC-CAR1部分A区)在下面提供:

[0263]

```
MGTSLLCWMALCLLGADHADACPYSNPSLCSGGGSELPTQGTFSNVSTNVSPAKPTTTACPYSNPSLCSGGGGS
PAPRPPTFAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAFLAGTCGVLLLSLVITLYCNHRNRRVC
KCPRPVVRSGSGQCTNYALLKLAGDVESNPGPPTGMVCLKLPGGSCMTALTVTLMVLSSPLALASDENPVVHFFK
NIVTPRTFPGGGSGGGSGSGDTRPRFLWQPKRECHFFNGTERVRFIDRYFYNQEESVRFSDVGEFRAVTEL
GRPDAEYWNQKDIIEQARAADTYCRHNYGVVESFTVQRRVQPKVTVYPSKTQPLQHHNLLVCSVSGFYPGSIE
VRWFLNGQEEKAGMVSTGLIQNGDWTFTQTLVMLETVPRSGEVYTCQVEHPSVTSPLTVEWRARSESAQSKMLSGV
GGFVLGLLFLGAGLFIYFRNQTSRVKFSRSADAPAYQQQNQLYNELNLGRREEYDVLDKRRGRDPMEGGKPRRK
NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGDGLYQGLSTATKDTYDALHMQALPPRGSSSGSGEGRGSLLTC
GDVEENPGPMASGVPLGFFIILAVLSAQESWAIKEEHVILQAEFYLNPDQSGEFMFDFDGEI FHVDMARKET
VWRLEEFGRFASFEAQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTVLNTPVELREPVLICFIDKFTFPV
VNVTWLRNGKPVTTGVSETVFLPREDFLFRKFHYLPFLFLESTEDVYDCRVEHWGLDEPLLKHWEFDAPSPLPETTE
NVVCALGLTVGLVGIIIGTIFIKGLTSRVKFSRSADAPAYQQQNQLYNELNLGRREEYDVLDKRRGRDPMEGG
KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID
NO: 211)
```

[0264] 编码构建体2杀伤开关和MHC CAR区(RQR8,MHC-CAR1部分B,MHC-CAR1部分A区)的示例性核酸序列在下面提供:

[0265]

atgggtacttcactgttgtgctggatggcactttgtcttttgggtgccgatcatgctgatgcatgtccgtactcc
aatcctagcctgtgctccgggggggagggagtgaaactccctacacagggaaacctctctaatgtctccaccaac
gtctcccttgcaaaaccgaccacaacagcttgccctatagtaacctctccctctgtagtggagggggggttca
cctgtctccacgcccctctacccccgcgcacacgatcgctgcacacccgctcagttcttaggcgggaagcctgtagg
ccagcggctggcgggtgcgggttcatacgcggggattggattttgctgacacatttatcttgggtcccgctggcc
ggtagctgtgggggtattgtgtgtgtctctgttattacgctttattgcaatcacagggaacaggcgacgagtatgc
aaatgcccgcggcccgctcgtgagatctgggtccggcccaatgtactaaactacgctttgttgaaactcgtggcgat
gttgaaagttaaccccggtcctccaacaggtatggatgctgaagctccggggcggtcctgcatgacggctctc
actgttactcttatgtgtccttagtccaccgcttgccctggcatctgatagagaatcccggtggttcatttttttaag
aacatcgtcacaccgcgcacccccacctgggggagggcggtctggcgaggcgggagtgagggtcaggagacaca
agaccccgattcttgtggcagcccaaaaggagtgccatttttcaatgggacggaaacgagttcgtctccttgat
cggtagctttttacaaccaagaagagagtgtagcgttcgactcagatgtcggcgagttccgagcgggttacggaattg
ggcgacacctgacgcggagtagtctggaaactcccaaaaggatattttggagcaggcacgagcagctgtggacacctat
tgtcgacataattatggtgtggtggaatcctttacagttcagcggcggtgcaacctaaagtgaacctgtatcca
tctaaaaacgaacccctccaacaccataacctcctggtgtgttccgtaagcggcttctatcccggtcaattgag
gtcaggtggttctcctcaacggtcaggaggagaagggcgggaatggtaagtaactggtcttctccagaacggagagtg
accttccaaactttggtaatgttggaacggtgcggcgatccggggaggtgtatacatgccaaagtgaacacccg
agtgttacgagccccctgacggttgagtgaggggcggtcagagagcgcaaatctaaaatgctcgtcaggagta
ggcggtattgtactcggactcctctttttggcgctgggtgtttatctacttttagaaaccaaacagtagagta
aagttttccgaagtgcggacgctcccgctatcagcaagggtcaaaaccagctttacaacgaactgaacttgga
cgacgcgaagagtagatggtcttgataagcggagagggcgcgatcccgaaatgggggaaagcctcggaggaag
aacccacaagaaggcctttataatgaactgcagaaggacaagatggcgaggcggtattccgaaataggcatgaag
ggtgaacggaggagaggaagggacatgacggactttatcaaggattgtctaccgcaactaaagacacctatgac
gcgttgacacatgcaggctctcctcccgagagggttcgagcggcagtgagagggcgaggaagtctgctaactgc
ggtgacgtcgaggagaatcctggcccaatggcaatatctggtgttctgtctcctcggttttttatcatagccgta
ctgatgtcagcacaggaatcatggcgataaaaagaagagcagtgataatacaggcgaggttttatttgaacccg
gaccagagcgggtgagttcatgttcgattttgatggcgacgagatattttacgttgacatggcaaaaaaggaaacg
gtgtggagacttgaggagtttgacgattcgcattttgaggcacaaggagcactcgccaatatcgcggtggac
aaggccaaacctggagatcatgacaaaacgctccaattatacgcctatcactaatgtgccccctgaggttaactgtg
ctcacaattctcccgtagaacttagggaaacctaaagtcctcatatgtttcatcgacaagttcactcctccggtg
gtcaatgtaacgtggcttcggaatggtaagccgggtcaccacgggtgtctcagagaccgtattttctgccagagaa
gaccacctcttcgcaatttcttacccttcccttcttccctcaacggaagacgtttacgactgcagggtcgaa
cattgggggcttgacgagccacttctcaagcattgggagttcgacgccccatcaccgcttcagaaacgactgaa
aacgtgtctgcgctcttgccctgacagtggtggttaggcattattatcgggaccatctttatcatcaaaggt
ttgacttcccggtcaaattagcagatccgctgacgcaccggcctaccagcagggccagaaccaactctacaac
gagctgaatctcgccgacgggaagagtagatgacgtactcgacaagcggagaggtcgagacctgagatggcggt
aaaccgagacggaaaaatccccaaagggtctttataatgaactccagaaggataagatggctgaagcctattct
gagatagggatgaaaggcgagcggcgagggttaaggccatgatggcctttaccagggaactctccacggcaacc
aaagatacttacgacgccccttcacatgcaagccctcccgccacgc (SEQ ID NO: 403)

[0266] 构建体2 (RQR8, MHC-CAR1 部分B, MHC-CAR1 部分A, GFP区) 在下面提供。

[0267]

MGTSLLCWMALCLLGADHADACPYSNPFLCSGGGGSELPTQGTFSNVSTNVSPAKPTTTACPYSNPFLCSGGGGG
PAPRPPTPAPTIASQFLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHRNRRRV
KCPRPVVRSGSGQCTNYALLKLADVESNPPTGMVCLKLPGGSCMTALTVTLMVLSSPLALASDENPVVHFFK
NIVTPRTPPGGGSGGGSGSGDTRPRFLWQPKRECHFFNGTERVRFLDRYFYNQESVRFDSVGEFRAVTE
GRPDAEYWNQKDIIEQARAADVTCRHNYGVVESFTVQRVQPKVTVPYPSKTQPLQHNLVCSVSQFYPGSIE
VRWFLNGQEEKAGMVSTGLIQNGDWTFTQLVMLETVPVRSGEVYTCQVEHPSVTSPLTVEWRARSESASQKMLS
GGFVLGLLEFLGAGLFIYFRNQTSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDP
NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKHGDLGYQLSTATKDTYDALHMQALPPRGSSGSGEGRGSL
GDVEENPGPMAISGVPVLGFFIIAVLMSAQESWAIKEEHVIIQAEFYLNPDQSGEFMFDFGDEIFHVDMAKKE
VWRLEEFGRFASFEGALANIAVDKANLEIMTKRSNYTPTNVPPEVTVLTNSPVELREPVLICFIDKFTPPV
VNVTLWRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVEHWGLDEPLKHWEDAPSPLPETTE
NVVCALGLTVGLVGIIIGTIFI IKGLTSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDP
KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKHGDLGYQLSTATKDTYDALHMQALPPRGSGATNFSLL
KQAGDVEENPGPVSKGEEFTGVVPII LVELDGDVNGHKFSVSSEGEEDATYCKLTFLKICTTGKLPVPWPTLVTT
LTYGVQCFSRYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGI DFEDGNI LG
HKLEYNYNSHNVYIMADKQKNGIKANFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALS
KDPNE
KRDHMLLEFVTAAGITLGMDELYK* (SEQ ID NO: 405)

[0268] 编码构建体2 (RQR8, MHC-CAR1 部分B, MHC-CAR1 部分A, GFP区) 的示例性核酸序列在

下面提供。

[0269]

```
atgggtacttcactgttgtgctggatggcactttgtcttttgggtgcccgatcatgctgatgcatgtccgtactcc
aatcctagcctgtgctccggggggggaggagtgaaactccctacacagggaaccttctctaatgtctccaccaac
gtctccctgcaaaaaccgaccacaacagcttgcctctatagtaaccttccctctgtagtggagggggggttca
cctgctccacgcctcctacccccgcgcacaacgatcgctcacaaacgctcagtccttaggcgggaagcctgtagg
ccagcggctggcggtgcggttcatacgcgggattggattttgctcgcgacatttacatttgggtccgctggcc
ggtacttgggggtattgctgttgtctcttgttattacgctttattgcaatcacagggaacaggcgacgagatgac
aaatgcccgcggccgctcgtgagatctgggtccggccaatgtactaaactacgctttgttgaaactcgctggcgat
gttgaagtaaccccggtcctccaacaggtatgggtatgcttgaagctcccgggcggttccgcatgaccgctctc
actgttactctttaggtccttagttcacgccttgcctggcatctgatgagaatcccgtggttcatttttttaag
aacatcgctcacacgcgcaccccacctgggggaggcggtatctggcgaggcgaggagtgagggtcaggagacaca
agaccccgattcttgggcagcccaaaaggagtgccatttttcaatgggacggaaacgagttcgcttcttctgat
cggtaacttttacaaccaagaagagagtgtaacgggtcgactcagatgtcggcgagttccgagcgggttacggaattg
ggcgacacctgacgcggagtagtggaactcccaaaaggatattttggagcaggcaacgagcagctgtggacacctat
```

[0270]

```
tgtcgacataattatgggtgtggtggaatcctttacagttcagcggcggtgcaacctaaagtgcacctgtatcca
tctaaaacgcaacccctccaacaccataacctcctggtgtgttccgtaaagcggcttctatcccggtcaattgag
gtcagggtggttctcacaacggtcaggaggagaaggccgggaatggtaagtactggtcttattccagaacgggagactgg
accttccaaactttggtaagtgttgaaacggtgcccgcgactccggggagggtgtatacatgccaaagtgaacacccg
agtgttacagacccctgacggttgagtgaggcgctcagagagcgcaaatctaaaatgctgtcaggagta
ggcggtatttgtactcggaactcctcttttgggcgctgggttgtttatctactttagaacccaacaagtagagta
aagttttccgaagtgcggacgctccgcgtatcagcaagggtcaaaaccagctttacaacgaactgaacttggga
cgacgcgaagagtagcatgttcttgataagcggagaggcgcgatcccgaatggggggaaagcctcggaggaaag
aaccacacaagaaggcctttataatgaactgcagaaggacaagatggcgaggcggtattccgaataggcatgaag
ggtgaacggaggagaggaaagggaatgacggaactttatcaaggattgtctaccgcaactaaagacacctatgac
gcgttgcaatgacggctctcctccgagagggttcgagcggcagtgagaggggcagagggaagtcgttaacatgc
ggtgacgtcgaggagaatcctggcccaatggcaatatctggtgttctgtctcctcggttttttatcatagccgta
ctgatgtcagcacaggaatcatgggcgataaaagaagagcagtgataatacaggcggagttttatttgaaacccg
gaccagagcggtaggttcatgttcgattttgatggcgacgagatatttcacgttgacatggcaaaaaaggaaacg
gtgtggagacttgaggagtttggacgattcgcatcatttgaggcacaaggagcactcgccaatatcgcggtggac
aaggccaacctggagatcatgacaaaacgctccaattatacgcctatcactaatgtgccccctgaggttactgtg
ctcacaattctcccgtagaacttagggaacctaaacgtcctcatatgtttcatcgacaagttcactcctccggtg
gtcaatgtaaacgtggcttcggaatggtgaacgggtcaccacgggtgtctcagagaccgtattttcggccagagaa
gaccacctcttcgcaaatctcattaccttccctttcttccctcaacgggaagacgtttacgactgcagggtcgaa
cattgggggcttgacgagccacttctcaagcattgggagttcgacgccccatcacgccttcagaaaaacgactgaa
aacgttgtctgcgctcttggcctgacagtgggctggttaggcattattatcgggaccatctttatcatcaagggt
ttgacttccgggtcaaattttagcagatccgctgacgcacccggcctaaccagcagggccagaaacccaactctacaac
gagctgaatctcggcgcgacgggaagagtagtgactactcgacaagcggagaggtcgagacccctgagatgggcggt
aaaacgagacgggaaaaatcccaagagggtctttataatgaactccagaaggataagatggctgaaagcctattct
gagatagggtatgaaaggcagcggcgaggggtaaggggccatgatggcctttaccagggaacttccacggcaacc
aaagataacttacgacgccttccatgcaagccctccggccacgcggatccggcgcaacaaacttctctctgctg
aaacaagcgggagatgtcgaagagaatcctggacgggtgagcaaggcgaggagctgttaccgggggtggtgcc
atcctggtcgagctggacggcgacgtaaacggccacaagttcagcgtgtctggcgaggggcgaggcgatgccacc
tacggcaagctgacctgaagtcatctgcaccacggcgaagctgcccgtgcccggccacctcgtgaccacc
ctgacctacggcgtgcagtgctcagccgctaccccgaccacatgaagcagcagcacttctcaagtcggccatg
cccgaaggctacgtccaggagcgcacccatcttcttcaaggacgacggcaactacaagaccccgccgaggtgaag
ttcgagggcgacacctggtgaacggcatcgagctgaagggtcactcgacttcaaggaggacggcaacatcctgggg
cacaagctggagtacaactacaacagccacaacgtctatatcatggcgcgaagcagaagaacggcatcaaggcg
aacttcaagatccgccacaacatcgaggacggcagcgtgcagctcgcgaccactaccagcagaacacccccatc
ggcgacggccccgtgctgctgcccgaacacactacctgagcaccagtcggcctgagcaaaagaccccaacgag
aagcgcgatcacatggctcctgctggagttcgtgacccgcgcgggatcactctcgccatggacgagctgtacaag
taa` (SEQ ID NO: 109)
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[0271] 示例性CS-1靶向CAR构建体的氨基酸序列在下面提供(注意这些设计含有4-1BB结构域,其可被CD28结构域置换):

[0272] 抗-CS1-CAR-v1 (Luc63-V1 CAR):

[0273] MALPVTALLLPLALLLHAARPEVKLLESGGGLVQPGGSLKLSAASGFDFSRWMSWVRQAPGKGLEWIGEINPD
SSTINYTPSLKDKFIIISRDNAKNTLYLQMSKVRSEDTALYYCARPDGNYWYFDVWGAGTTVTVSSGGGSGGGGS
GGGGSIDVMTQSHKEMSTSVGDRVSITCKASQDVGLAVAWYQQKPGQSPKLLIYWASTRHTGVPDRFTGSGSGTD
FTLTISNVQSEDLADYFCQQYSSYPYTFGGGTKEIKGLAVSTISSFFPPGYQKRGRKKLLYIFKQPFMRPVQTT
QEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPPEMGGKPRRKNPQ
EGLYNELQDKMAEAYSEIGMKGERRRRGKGDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 129)

[0274] 抗-CS1-CAR-v2 (Luc63-V2 CAR) :

[0275] MALPVTALLLPLALLLHAARPEVKLLESGGGLVQPGGSLKLSAASGFDFSRWMSWVRQAPGKGLEWIGEINPD
SSTINYTPSLKDKFIIISRDNAKNTLYLQMSKVRSEDTALYYCARPDGNYWYFDVWGAGTTVTVSSGGGSGGGGS
GGGGSIDVMTQSHKEMSTSVGDRVSITCKASQDVGLAVAWYQQKPGQSPKLLIYWASTRHTGVPDRFTGSGSGTD
FTLTISNVQSEDLADYFCQQYSSYPYTFGGGTKEIKTTPAPRPPTAPPTIASQPLSLRPEACRPAAGGAVHTR
GLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRV
KFSSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPPEMGGKPRRKNPQEGLYNELQDKMAEAYSEIGMK
GERRRRGKGDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 130)

[0276] 抗-CS1-CAR-v3 (Luc63-V3 CAR) :

[0277] MALPVTALLLPLALLLHAARPEVKLLESGGGLVQPGGSLKLSAASGFDFSRWMSWVRQAPGKGLEWIGEINPD
SSTINYTPSLKDKFIIISRDNAKNTLYLQMSKVRSEDTALYYCARPDGNYWYFDVWGAGTTVTVSSGGGSGGGGS
GGGGSIDVMTQSHKEMSTSVGDRVSITCKASQDVGLAVAWYQQKPGQSPKLLIYWASTRHTGVPDRFTGSGSGTD
FTLTISNVQSEDLADYFCQQYSSYPYTFGGGTKEIKPKSPDKTHTCPPCPAPPVAGPSVFLFPKPKDTLMIA
RTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQLDNLNGKEYCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSF
FLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRF
PEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPPEMGGKPRRKNPQEGLYNELQDK
MAEAYSEIGMKGERRRRGKGDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 131)

[0278] 抗-CS1-CAR-v4 (Luc90-V1 CAR) :

[0279] MALPVTALLLPLALLLHAARPQVQLQPGAEIVRPGASVKLSCKASGYSTFTTYWMNWVKQRPQGGLWIGIMHPS
DSEIRLNQKFQDKATLTVDKSSSTAYMQLSSPTSEDSAVYYCARSTMIATRAMDYWGQGTSTVTVSSGGGSGGGG
SGGGGSIDVMTQSQKSMSTSVGDRVSITCKASQDVITGVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGT
DFTFTISNVQAEIDLAVYYCQHYSTPLTFGAGTKLELKLGLAVSTISSFFPPGYQKRGRKKLLYIFKQPFMRPVQT
TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPPEMGGKPRRKNP
QEGLYNELQDKMAEAYSEIGMKGERRRRGKGDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 132)

[0280] 抗-CS1-CAR-v5 (Luc90-V2 CAR) :

[0281] MALPVTALLLPLALLLHAARPQVQLQPGAEIVRPGASVKLSCKASGYSTFTTYWMNWVKQRPQGGLWIGIMHPS
DSEIRLNQKFQDKATLTVDKSSSTAYMQLSSPTSEDSAVYYCARSTMIATRAMDYWGQGTSTVTVSSGGGSGGGG
SGGGGSIDVMTQSQKSMSTSVGDRVSITCKASQDVITGVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGT
DFTFTISNVQAEIDLAVYYCQHYSTPLTFGAGTKLELKTTPAPRPPTAPPTIASQPLSLRPEACRPAAGGAVHT
RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELR
VKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPPEMGGKPRRKNPQEGLYNELQDKMAEAYSEIGM
KGERRRRGKGDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 133)

[0282] 抗-CS1-CAR-v6 (Luc90-V3 CAR) :

[0283] MALPVTALLLPLALLLHAARPQVQLQPGAEIVRPGASVKLSCKASGYSTFTTYWMNWVKQRPQGGLWIGIMHPS
DSEIRLNQKFQDKATLTVDKSSSTAYMQLSSPTSEDSAVYYCARSTMIATRAMDYWGQGTSTVTVSSGGGSGGGG
SGGGGSIDVMTQSQKSMSTSVGDRVSITCKASQDVITGVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGT
DFTFTISNVQAEIDLAVYYCQHYSTPLTFGAGTKLELKEPKSPDKTHTCPPCPAPPVAGPSVFLFPKPKDTLMI
ARTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQLDNLNGKEYCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGS
FFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCR
FPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPPEMGGKPRRKNPQEGLYNELQDK
MAEAYSEIGMKGERRRRGKGDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 134)

[0284] 抗-CA1-CAR-v7 (Luc34-V1 CAR) :

- [0285] MALPVTALLLPLALLLHAARPQVQLQQSGAELARPGASVKLSCKASGYTFTSYWMQWVKQRPQGQGLEWIGAIYPG
DGDTRYTQKFKGKATLTADKSSSTAYMQLSSLASEDSAVYYCARGKVYYSNPFAYWGQGTLLTVTSAGGGGSGGG
GSGGGGSDIQMTQSSSYLSVSLGGRVTITCKASDHINNWLAWYQQKPGNAPRLISGATSLETGVPSRFSGSGSG
KDYTLISITSLQTEDVATYYCQQYWSTPWTFGGGTKLEIKGLAVSTISSFFPGYQKRGKKLLYIFKQPFMRPVQ
TTQEDGDCSCRFPEEEGGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPPEMGGKPRRKN
PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO:
135)
- [0286] 抗-CS1-CAR-v8 (Luc34-V2 CAR) :
- [0287] MALPVTALLLPLALLLHAARPQVQLQQSGAELARPGASVKLSCKASGYTFTSYWMQWVKQRPQGQGLEWIGAIYPG
DGDTRYTQKFKGKATLTADKSSSTAYMQLSSLASEDSAVYYCARGKVYYSNPFAYWGQGTLLTVTSAGGGGSGGG
GSGGGGSDIQMTQSSSYLSVSLGGRVTITCKASDHINNWLAWYQQKPGNAPRLISGATSLETGVPSRFSGSGSG
KDYTLISITSLQTEDVATYYCQQYWSTPWTFGGGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVH
TRGLDFACDIYIWAFLAGTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEDGDCSCRFPEEEGGGCEL
RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIG
MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 136)
- [0288] 抗-CS1-CAR-v9 (Luc34-V3 CAR) :
- [0289] MALPVTALLLPLALLLHAARPQVQLQQSGAELARPGASVKLSCKASGYTFTSYWMQWVKQRPQGQGLEWIGAIYPG
DGDTRYTQKFKGKATLTADKSSSTAYMQLSSLASEDSAVYYCARGKVYYSNPFAYWGQGTLLTVTSAGGGGSGGG
GSGGGGSDIQMTQSSSYLSVSLGGRVTITCKASDHINNWLAWYQQKPGNAPRLISGATSLETGVPSRFSGSGSG
KDYTLISITSLQTEDVATYYCQQYWSTPWTFGGGTKLEIKEPKSPDKTHTCPPCPAPPVAGPSVFLFPKPKDTLM
IARTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
SEFLYSLKLTVDKSRWQQGNVFSQSVMEALHNHYTQKSLSLSPGKKRGRKKLLYIFKQPFMRPVQTTQEDGDCSC
RFPEEEGGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPPEMGGKPRRKNPQEGLYNELQ
KDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 137)
- [0290] 抗-CS1-CAR-v10 (LucX1-V1 CAR) :
- [0291] MALPVTALLLPLALLLHAARPQVQLQQSGPELVKPGASVKISCKASGYAFSSSWMNWVKQRPQGQGLEWIGRIYPG
DGDTRYNGKFKGKATLTADKSSSTAYMQLSSLTSVDSAVYFCARSTMIATGAMDYWGQGTSTVTVSSGGGGSGGGG
SGGGGSETTVTQSPASLSMAIGEKVTIRCTSTDDIDDMNWWYQQKPGEPKLLISEGNTLRPGVPSRFSSSGYGT
DFVFTIENMLSEDAVYYCLOSDNLPITFGGGTKLEIKGLAVSTISSFFPGYQKRGKKLLYIFKQPFMRPVQTT
TQEDGDCSCRFPEEEGGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPPEMGGKPRRKNP
QEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 138)
- [0292] 抗-CS1-CAR-v11 (LucX1-V2 CAR) :
- [0293] MALPVTALLLPLALLLHAARPQVQLQQSGAELARPGASVKLSCKASGYTFTSYWMQWVKQRPQGQGLEWIGAIYPG
DGDTRYTQKFKGKATLTADKSSSTAYMQLSSLASEDSAVYYCARGKVYYSNPFAYWGQGTLLTVTSAGGGGSGGG
GSGGGGSDIQMTQSSSYLSVSLGGRVTITCKASDHINNWLAWYQQKPGNAPRLISGATSLETGVPSRFSGSGSG
KDYTLISITSLQTEDVATYYCQQYWSTPWTFGGGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVH
TRGLDFACDIYIWAFLAGTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEDGDCSCRFPEEEGGGCEL
RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIG
MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 139)
- [0294] 抗-CS1-CAR-v12 (LucX1-V3 CAR) :
- [0295] MALPVTALLLPLALLLHAARPQVQLQQSGPELVKPGASVKISCKASGYAFSSSWMNWVKQRPQGQGLEWIGRIYPG
DGDTRYNGKFKGKATLTADKSSSTAYMQLSSLTSVDSAVYFCARSTMIATGAMDYWGQGTSTVTVSSGGGGSGGGG
SGGGGSETTVTQSPASLSMAIGEKVTIRCTSTDDIDDMNWWYQQKPGEPKLLISEGNTLRPGVPSRFSSSGYGT
DFVFTIENMLSEDAVYYCLOSDNLPITFGGGTKLEIKEPKSPDKTHTCPPCPAPPVAGPSVFLFPKPKDTLMI
ARTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
SEFLYSLKLTVDKSRWQQGNVFSQSVMEALHNHYTQKSLSLSPGKKRGRKKLLYIFKQPFMRPVQTTQEDGDCSC
RFPEEEGGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPPEMGGKPRRKNPQEGLYNELQ
KDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 140)
- [0296] 抗-CS1-CAR-v13 (LucX2-V1 CAR) :

[0297] MALPVTALLLP LALLLHAARPQVQLQQSGPELVKPGASVKISCKASGYAFSSSWMNWVKQRPGQGLEWIGRIYPG
DGDITKYNKFKGKATLTADKSSSTAYMQLSSLTSVDSAVYFCARSTMIATGAMDYWGQGTSTVTVSSGGGSGGGG
SGGGSDIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGT
FTFTISSVQAEDLAVYYCQQHYSTPPYTFGGGTKEIKGLAVSTISSFFPPGYQKRGRKLLYIFKQPFMRPVQT
TQEDDGCCRFPEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPEMGGKPRRKNPQ
EGLYNELQKDKMAEAYSEIGMKGERRRRGKGDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 141)

[0298] 抗-CS1-CAR-v14 (LucX2-V2 CAR) :

[0299] MALPVTALLLP LALLLHAARPQVQLQQSGPELVKPGASVKISCKASGYAFSSSWMNWVKQRPGQGLEWIGRIYPG
DGDITKYNKFKGKATLTADKSSSTAYMQLSSLTSVDSAVYFCARSTMIATGAMDYWGQGTSTVTVSSGGGSGGGG
SGGGSDIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGT
DFTFTISSVQAEDLAVYYCQQHYSTPPYTFGGGTKEIKTTTPA2REPPTPA2TIASQPLSLRPEACRPAAGGAVH
TRGLDFADIYIWAFLAGTCGVLLLSLVITLYCKRGRKLLYIFKQPFMRPVQTTQEDDGCCRFPEEEGGCELR
VKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM
KGERRRRGKGDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 142)

[0300] 抗-CS1-CAR-v15 (LucX2-V3 CAR) :

[0301] MALPVTALLLP LALLLHAARPQVQLQQSGPELVKPGASVKISCKASGYAFSSSWMNWVKQRPGQGLEWIGRIYPG
DGDITKYNKFKGKATLTADKSSSTAYMQLSSLTSVDSAVYFCARSTMIATGAMDYWGQGTSTVTVSSGGGSGGGG
SGGGSDIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGT
DFTFTISSVQAEDLAVYYCQQHYSTPPYTFGGGTKEIKEPKSPDKTHTCPPCPAPPVAGPSVELEFPKPKDTLM
LARTPEVCCVVDVSHEDPEVKFNWYVDGVGVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPILEKTIISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGS
FTLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKRGKLLYIFKQPFMRPVQTTQEDDGCCRF
PEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPEMGGKPRRKNPQEGLYNELQK
DKMAEAYSEIGMKGERRRRGKGDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 143)

[0302] (iii) MHC-CAR的制备

[0303] 本文所述的任何MHC-CAR构建体可通过常规方法制备,例如重组技术。用于制备本文的嵌合受体的方法包括产生编码或共同编码MHC-CAR构建体(包括单一多肽或两个亚单元)的核酸或核酸组。在一些实施方案中,核酸还编码在MHC-CAR的两个亚单元的编码序列之间或在MHC-CAR的编码序列和与MHC-CAR在宿主细胞中共表达的其它基因的编码序列之间的自切割肽(例如,P2A、T2A或E2A肽)(见下文论述)。

[0304] MHC-CAR的各组分的序列可通过常规技术(例如PCR扩增)从本领域已知的多种来源的任何一种获得。在一些实施方案中,MHC-CAR的一种或多种组分的序列获自人细胞。或者,可合成MHC-CAR的一种或多种组分的序列。各组分(例如,结构域)的序列可使用例如PCR扩增或连接的方法直接或间接接合(例如,使用编码肽接头的核酸序列),以形成编码MHC-CAR的核酸序列。或者,可合成编码MHC-CAR的核酸。在一些实施方案中,核酸是DNA。在其它实施方案中,核酸是RNA。

[0305] MHC-CAR蛋白、编码其的核酸和携带这样的核酸的表达载体(全部在本公开的范围内的任何一种可与药学上可接受的载体混合以形成药物组合物,其也在本公开的范围内的。”可接受的”是指载体与组合物的活性成分(例如,核酸、载体、细胞或治疗性抗体)相容并且不负面影响组合物所给予的受试者。用于本方法的任何药物组合物可包含呈冻干制剂或水性溶液的形式的药学上可接受的载体、赋形剂或稳定剂。

[0306] 药学上可接受的载体,包括缓冲液,是本领域众所周知的,以及可包含:磷酸盐、柠檬酸盐和其它有机酸;抗氧化剂,包括抗坏血酸和甲硫氨酸;防腐剂;低分子量多肽;蛋白,例如血清白蛋白、明胶或免疫球蛋白;氨基酸;疏水性聚合物;单糖;二糖;以及其它碳水化合物;金属络合物;和/或非离子表面活性剂。参见例如Remington:The Science and Practice of Pharmacy 20th Ed.(药学科学与实践第20版)(2000)Lippincott Williams

和Wilkins,Ed.K E.Hoover。

[0307] II.表达MHC-CAR的遗传改造的免疫细胞

[0308] (i) 表达MHC-CAR的免疫细胞

[0309] 表达本文所述的MHC-CAR的免疫细胞提供特定细胞群,其可通过MHC/肽-TCR接合来识别参与自身免疫性疾病的病原性细胞(例如,自身反应性T细胞)。MHC-CAR的MHC-肽部分和病原性细胞上的同源TCR之间的相互作用将通过MHC-CAR的信号传导结构域(任选地通过募集免疫细胞的细胞膜信号传导分子)激活表达MHC-CAR的免疫细胞,导致表达MHC-CAR的免疫细胞的增殖和/或效应子作用,这进而消除病原性细胞。免疫细胞可以是T细胞、NK细胞、巨噬细胞、中性粒细胞、嗜酸性细胞或其任何组合。在一些实施方案中,免疫细胞是T细胞。在一些实施方案中,免疫细胞是NK细胞。具体实例在下文的实施例中提供。

[0310] 免疫细胞群可获自任何来源,例如外周血单核细胞(PBMC)、骨髓、组织例如脾、淋巴结、胸腺、肿瘤组织或建立的细胞系。适合获得所需免疫细胞类型的来源对于本领域技术人员而言是明显的。在一些实施方案中,免疫细胞群衍生自PBMC。所需免疫细胞的类型(例如,T细胞、NK细胞、巨噬细胞、中性粒细胞、嗜酸性细胞或其任何组合)可通过与刺激分子共培养细胞,在获得的细胞群内扩增,例如,抗-CD3和抗-CD28抗体可用于扩增T细胞。

[0311] 为了构建表达本文所述的任何MHC-CAR构建体的免疫细胞,用于稳定或瞬时表达嵌合受体构建体的表达载体可通过本文所述的常规方法构建和引入免疫宿主细胞中。例如,编码MHC-CAR的核酸可与合适的启动子可操作连接而克隆至合适的表达载体,例如病毒载体(例如,慢病毒载体)。核酸和载体可在合适的条件下与限制性酶接触以在各分子上产生互补末端,其可彼此配对和用连接酶连接。或者,合成的核酸接头可连接至编码嵌合受体的核酸的末端。合成的接头可含有对应于载体中特定限制位点的核酸序列。表达载体/质粒/病毒载体的选择将取决于用于表达嵌合受体的宿主细胞的类型,但应适合于在真核细胞中整合和复制。

[0312] 各种启动子可用于表达本文所述的MHC-CAR构建体,包括但不限于巨细胞病毒(CMV)中间早期启动子、病毒LTR例如劳斯肉瘤病毒LTR、HIV-LTR、HTLV-1LTR、猿猴病毒40(SV40)早期启动子、单纯疱疹tk病毒启动子。用于表达嵌合受体的另外的启动子包括免疫细胞中的任何组成型活性启动子。或者,可使用任何调节型启动子,使得其表达可在免疫细胞内调节。

[0313] 另外,载体可含有例如以下的一些或全部:可选择标记基因,例如新霉素基因,用于在宿主细胞中选择稳定或瞬时转染子;来自人CMV的立即早期基因的增强子/启动子序列,用于高水平转录;来自SV40的转录终止和RNA加工信号,用于mRNA稳定性;SV40多瘤病毒复制起点和ColE1,用于正确游离基因复制;内部核糖体结合位点(IRESes)、通用多克隆位点;T7和SP6 RNA启动子,用于体外转录有义和反义RNA;“自杀开关”或“自杀基因”,当触发时其导致携带载体的细胞死亡(例如,HSV胸腺嘧啶激酶、诱导型半胱天冬酶例如iCasp9);以及报告基因,用于评价MHC-CAR的表达。

[0314] 在一些实施方案中,用于本公开的标志物/分选/自杀分子可用于利妥昔单抗杀伤和/或QBEND分选。Philip等人,Blood(血液)124(8):1277-87;2014)。一个实例是RQR8,其含有利妥昔单抗模拟位点和QBEND-10表位。示例性序列在下面提供:

MGTSLLCWMALCCLLGADHADACPYSNPSLCSGGGGSELPTQGTFSNVSTNVSPAKPTTTACPYSNPSLC
SGGGGSPAPPPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHRN
RRRVCKCPRPVV (SEQ ID NO: 144)

[0315]

MGTSLLCWMALCCLLGADHADACPYSNPSLCSGGGGSELPTQGTFSNVSTNVSPAKPTTTACPYSNPSLC
SGGGGSPAPPPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHRN
NRRRVCKCPRPVV (SEQ ID NO: 394)

[0316] 编码RQR8的示例性核酸序列在下面提供。

ATGGGTACTTCACCTGTTGTGCTGGATGGCAGCTTTGTCTTTTGGGTGCCGATCATGCTGATGCATGTCCGTACTCC
AATCCTAGCCTGTGCTCCGGGGGGGGAGGGAGTGAACCTCCCTACACAGGGAACCTTCTCTAATGTCTCCACCAAC
GTCTCCCTGCAAAACCGACCAACAGCTTGCCCCATAGTAAACCTTCCCTCTGTAGTGGAGGGGGGGGTTC
CCTGCTCCACGCCCTCCTACCCCCGCGCAACGATCGCGTCACAACCGCTCAGTCTTAGGCCGGAAGCCTGTAGG
CCAGCGGCTGGCGGTGCGGTTCATACGCGGGGATTGGATTTTGCCTGCGACATTTACATTTGGGCTCCGCTGGCC
GGTACTTGTGGGTATTGCTGTGTCTCTTGTATTATACGCTTATTGCAATCACAGGAACAGCGACGAGTATGC
AAATGCCCGCGGCCCGCTCTG (SEQ ID NO: 395)

[0317] 在另一个实例中,以下示例性RQR序列标签可附加到本文公开的MHC-CAR构建体:

[0318] ACPYSNPSLCSGGGGSELPTQGTFSNVSTNVSPAKPTTTACPYSNPSLCSGGGG (SEQ ID NO: 145)

[0319] 粗体片段是利妥昔单抗模拟位和下划线/斜体片段是QBEND-10表位。

[0320] 合适的载体和用于产生含有转基因的载体的方法是本领域众所周知的和可获得的。包含编码本文所述的MHC-CAR构建体的核酸序列的任何载体也在本公开的范围内。这样的载体可通过合适的方法递送至宿主免疫细胞。递送载体至免疫细胞的方法是本领域众所周知的并可包括DNA电穿孔、RNA电穿孔、转染试剂例如脂质体、或病毒转导。在一些实施方案中,用于表达MHC-CAR的载体通过病毒转导递送至宿主细胞。示例性病毒递送方法包括但不限于,重组逆转录病毒(参见例如,PCT公开号W090/07936;W094/03622;W093/25698;W093/25234;W093/11230;W093/10218;W091/02805;美国专利号5,219,740和4,777,127;英国专利号2,200,651;以及欧洲专利号0 345 242)、基于 α 病毒的载体和腺相关病毒(AAV)载体(参见例如,PCT公开号W094/12649,W093/03769;W093/19191;W094/28938;W095/11984和W095/00655)。在一些实施方案中,用于表达嵌合受体的载体是逆转录病毒。在一些实施方案中,用于表达嵌合受体的载体是慢病毒。

[0321] 在其中使用病毒载体将编码嵌合受体的载体引入宿主细胞的实例中,能够感染免疫细胞和携带载体的病毒颗粒可通过本领域已知的任何方法产生,并可见于例如PCT申请公开号W01991/002805A2,W01998/009271A1和美国专利6,194,191。从细胞培养上清液收获病毒颗粒,并可经分离和/或纯化,然后使病毒颗粒与免疫细胞接触。

[0322] 在将编码本文提供的任何MHC-CAR的载体引入宿主细胞后,将细胞在允许表达嵌合受体的条件下培养。在其中编码MHC-CAR的核酸受调节型启动子调节的实例中,宿主细胞在其中调节型启动子被活化的条件中培养。在一些实施方案中,启动子是诱导型启动子且免疫细胞在诱导分子的存在下或在其中产生诱导分子的条件中培养。确定MHC-CAR是否表达对于本领域技术人员是显而易见的,并可通过任何已知的方法评价,例如通过定量逆转录酶PCR(qRT-PCR)检测编码嵌合受体的mRNA或通过包括蛋白质印迹、荧光显微术和流式细胞术的方法检测嵌合受体蛋白。亦参见下文的实施例。或者,MHC-CAR的表达可在将免疫细胞给予受试者后在体内发生。

[0323] 或者,在本文公开的任何免疫细胞中表达MHC-CAR构建体可通过引入编码MHC-CAR

构建体的RNA分子实现。这样的RNA分子可通过体外转录或通过化学合成制备。RNA分子可然后通过例如电穿孔引入合适的宿主细胞,例如免疫细胞(例如,T细胞、NK细胞、巨噬细胞、中性粒细胞、嗜酸性细胞或其任何组合)。例如,RNA分子可按照Rabinovich等人,Human Gene Therapy (人类基因疗法),17:1027-1035和WO 2013/040557中描述的方法合成和引入宿主免疫细胞。

[0325] 制备表达本文所述的任何MHC-CAR的宿主免疫细胞的方法可包括离体扩增宿主免疫细胞。扩增宿主免疫细胞可包括导致表达MHC-CAR的细胞的数量增加的任何方法,例如允许宿主细胞增殖或刺激宿主细胞增殖。用于刺激宿主细胞扩增的方法将取决于用于表达嵌合受体的宿主细胞的类型,并且对于本领域技术人员是显而易见的。在一些实施方案中,表达本文所述的任何MHC-CAR的宿主免疫细胞可离体扩增,然后给予受试者。

[0326] (ii) 另外的遗传修饰

[0327] 一种或多种另外的遗传修饰可在转染MHC-CAR构建体之前、同时或之后引入宿主免疫细胞。例如,一种或多种标志物和/或自杀基因可引入宿主免疫细胞。实例包括绿色荧光蛋白(GFP)、增强蓝色荧光蛋白(eBFP)和RQR基因,例如RQR8(组合来自CD34和CD20的靶表位的T细胞的紧密标志物/自杀基因。Philip等人,Blood(血液)124(8):1277-87;2014)。这样的标志物/自杀基因可在一个表达盒中与MHC-CAR组分一起构建。

[0328] GFP的氨基酸序列的实例在下面提供:

[0329] VSKGEELEFTGVVPIIVELDGDVNGHKFSVSSEGEEDATYGLTLKFICTTGKLPVPWPTLVTTLTLYGVQCFSRYPDHMKQHDFFSKAMPEGYVQERTIFFKDDGNKYTRAEVKFEGDTLVNRIELKGIIDFKEDGNILGHKLEYNNSHNVYIMADKQKNGIKANFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALS KDPNEKRDMVLLEFVT AAGITLGMDELYK (SEQ ID NO: 427)

[0330] 编码GFP的核酸序列的实例在下面提供:

[0331] gtgagcaaggcgagagctgttcaccggggtggtgccatcctggctcgagctggacggcgacgtaaacggccac
aagttcagcgtgtctggcgagggcgagggcgatgccacctacggcaagctgacctgaagttcatctgcaccacc
ggcaagctgcccgtgccctggcccacctctgtgaccacctgacctacggcgtgcagtgtctcagccgctacccc
gaccacatgaagcagcagcacttcttcaagtcgccatgccgaaggtacgtccaggagcgcaccatcttcttc
aaggacgacggcaactacaagaccgcgcgaggtgaagttcgagggcgacacctgggtgaaccgcatcgagctg
aaggcgcacgacttcaaggagcagcgaacatcctggggcacaagctggagtacaactacaacagccacaacgtc
tatatcatggccgacaagcagaagaacggcatcaaggcgaacttcaagatccgccacaacatcgaggacggcagc
gtgcagctcgccgaccactaccagcagaacacccccatcggcgacggccccgtgctgctgcccgaacaaccactac
ctgagcaccagtcgccttgagcaaaagaccccaacgagaagcgcgatcacatggtcctgctggaggttcgtgacc
gccgcgggatcactctcgccatggacgagctgtacaagtaa (SEQ ID NO: 428)

[0332] 在一些情况下,内源性TCR(α 链、 β 链或二者)可被破坏,使得宿主免疫细胞不表达内源性TCR。内源性TCR的缺乏可避免不需要的T细胞活化。备选地或另外,某些细胞表面受体可被敲除。这样的表面受体可以是用于疾病治疗的靶受体,例如CD52,其是MS治疗的靶标。从MHC-CAR免疫细胞敲除这样的靶受体允许共同使用MHC-CAR免疫细胞与对靶受体特异性的治疗剂(例如,抗-CD52抗体,例如阿仑单抗)。

[0333] 在一些实施方案中,宿主免疫细胞可用合成的表面蛋白修饰以增强它们在特定器官或组织中的保留,例如在淋巴结中、在三级淋巴器官中或在炎症位点处。如此进行将允许修饰的免疫细胞接近靶病原性细胞,同时最小化由于渗透血脑屏障或免疫细胞通过外周血自由移动导致的致命脱靶效应。在T细胞分化途径中早期的细胞(例如,幼稚、干细胞记忆和中央记忆T细胞)自由移动至淋巴结。随着分化进展,大多数效应T细胞离开淋巴结。病理免疫细胞也可移动和聚集至炎症位点。通过活化CAR-T细胞的治疗当它们与不需要的靶标反应时,具有许多不必要的作用。与心脏组织相互作用可能对心脏蛋白是致命的,以及渗透脑

可导致致命的脑水肿。最近已在使用比使用CD19 CAR T疗法的癌症全身治疗更低剂量的CAR T疗法治疗脑癌症胶质母细胞瘤方面取得了进展。Brown等人, *New England Journal of Medicine* (新英格兰医学杂志), 375 (26):2561-2569, 2016。炎症消除具有转换病理环境为保护性环境的潜力。Gagliani等人, *Nature* (自然), 523 (7559):221-225, 2015。

[0334] 将一种或多种淋巴结保留蛋白引入免疫细胞可增强免疫细胞在淋巴结中的保留, 其中免疫细胞仍接近靶病原性细胞, 同时上述不必要的作用可显著降低。幼稚淋巴细胞通过高内皮微静脉 (HEV) 进入淋巴结。因此, 表达或过表达参与HEV锚定和/或进入的蛋白可促进免疫细胞进入淋巴结。示例性淋巴结保留蛋白包括但不限于CCR7 (趋化因子受体)、MECA79 (周围淋巴结地址素)、血管粘附蛋白-1 (VAP-1) 和CD62 (选择蛋白, 细胞粘附分子家族)。Azzi等人, *Blood* (血液) 124 (4):476-477, 2016; Streeter等人, *J. Cell. Biol.* 107:1853-186; 1988; Michie等人, *Amer. J. Path.* 143:1688-1698; 1993; Berg等人, *J. Cell. Biol.* 114:343-349; 1991; Berg等人, *Nature* (自然) 366:695-698; 1993; 以及 Hemmerich等人, *J. Exp. Med.* 180:2219-2226; 1994。或者, 编码参与淋巴细胞从胸腺和淋巴器官流出的蛋白 (例如, 鞘氨醇-1-磷酸受体-1或S1P) 的基因可从免疫细胞敲除。

[0335] 促进运输至炎症位点的趋化因子受体和粘附受体也可使MHC-CAR免疫细胞与传播免疫疾病的病原性细胞接触 [Barreiro等人, *Cardiovascular research* (心血管研究), 86 (2):174-182, 2010], 参见表3和4。参与募集传播炎症的免疫细胞的受体包括募集至三级淋巴器官 (其中表达CXCL13、CCL19、CCL20、CCL21) 的受体 (即, CXCR5、CCR7、CCR6)。

[0336] 一个或多个编码参与靶向其它器官/组织 (例如脑/CNS、骨髓、胰腺、肠、肝、肺、脾和/或胸腺) 的蛋白的基因也可被引入免疫细胞或从免疫细胞敲除。

[0337] 通过在治疗性细胞中病毒诱导或临时RNA介导的表达 (可能与敲除内源性基因组), 基因 (在表3和4中) 可用于传递Treg或CTL细胞至所需的位置或处理/移动所需的细胞。Barreiro等人 *Cardiovascular research* (心血管研究), 86 (2):174-182, 2010。如果使用mRNA转染, 则其可允许表达趋化因子或粘附受体持续一周。Wang和Rivière. *Molecular Therapy-Oncolytics* (分子治疗-肿瘤学), 3:16015 2016。

[0338] 表3. 趋化因子受体和天然背景

[0339]

受体	通常在以下 上面表达	GeneBank 登录号	配体
CXCR1	中性粒细胞	AA21515.1	CXCL8, CXCL6
CXCR2	中性粒细胞	NP_001548.1	CXCL1, 2, 3, 4, 5, 7
CXCR3	T 细胞和一些 B 细胞	NP_001495.1	CXCL9, 10, 11
CXCR4	大多数成熟和未 成熟造血细胞	CAA12166.1	CXCL12
CXCR5	B 细胞和 T _H 细胞	NP_001707.1	CXCL13
CXCR6	炎症反应 T 细 胞，但弱趋化性	NP_006555.1	CXCL16
CXCR7	记忆 B 细胞、 T 细胞	NP_064707.1	CXCL12

[0340]

CCR1	外周淋巴细胞、 记忆 T 细胞	NP_001286.1	CCL4, CCL5, CCL6, CCL14, CCL15, CCL16, CCL23
CCR2	单核细胞、活化记 忆 T 细胞、B 细胞、 嗜碱性细胞	AAA19119.1	CCL11, CCL26, CCL7, CCL13, CCL15, CCL24 & CCL5, CCL28
CCR3	在过敏性反应中起 作用, B 和 T 细胞 至粘液、嗜酸性细 胞、嗜碱性细胞	NP_001828.1	CCL11, CCL26, CCL7, CCL13, CCL15, CCL24, CCL5
CCR4	Th2 淋巴细胞、树 突细胞	NP_005499.1	CCL3, CCL5, CCL17, CCL22
CCR5	外周血树突细胞、 CD34+造血 祖细胞、活化/ 记忆 Th1	NP_000570.1	CCL2, CCL3, CCL4, CCL5, CCL11, CCL13, CCL14, CCL16
CCR6	失活记忆 T 细胞、 树突细胞、Th17, 在活化 T 细胞上 下调	AAC51124.1	CCL20
CCR7	跨 HEV 运输 B、T 和树突细胞, 并 进入淋巴结的 T 细胞区	AAH35343.1	CCL19, CCL21
CCR8	Th2 细胞、胸腺、 淋巴结、脾、脑、 单核细胞	NP_005192.1	CCL1, CCL16
CCR9	胸腺、肠	NP_112477.1	CCL25
CCR10	皮肤、粘膜层、调 节性 T 细胞	NP_057686.2	CCL27, CCL28
XCR1		NP_005274.1	XCL1, XCL2
CX3CR1		NP_001164642.1	CX3CL1

[0341] 由AAC51124.1提供的CCR6的氨基酸序列在下面显示:

[0342]

MSGESMNFSDVFDSSSEDYFVSVNTSYYSVDSEMLLCSLQEVQRQFSRLEVPPIAYSLICVFGLLGNIILVVITFAFYK
 KARSMTDVYLLNMAIADILFVLTLPFWAVSHATGAWVFSNATCKLLKGIYAINFNCGMLLLTCISMTRYIAIVQA
 TKSFRLRSRTLPRSKIICLVVWGLSVIILSSSTFVENQKYNTQGSVDCEPKYQTVSEPIRWKLLMLGLELLFGFFI
 PLMFMIFCYTFIVKTLVQAQNSKRHKAIRVIIAVVLVFLACQIPHNMVLLVTAANLGKMNRSQCSEKLIGYTKTV
 TEVLAFLHCCLNPNVLYAFIQKFRNYFLKILKDLWCVRRKYKSSGFSCAGRYSENISRQTSETADNDNASSFTM
 (SEQ ID NO: 391)

[0343] CCR6的示例性核酸序列在下面显示:

atgagtggggaaagtatgaacttcagcgatgtatattgactccctccgaagattactttgtatctgtgaatacagagc
tattactccgtcgatagtgaaatgctgctctgtagtcctccaaagagtcggccaattcagtcgctctctgttccc
atcgcgtactcccttattttgtgtttttggccttctgtggtaacaacctggttgtaatacacattcgcctctctataaa
aaagctcggagatgatgactgagtgtttacctctttaacatggctatacgggacattctttttgtgcttactctccca
ttctgggctgtgagccatgcaacagggcggtgggttttttcaaatgccacatgtaagctgcttaagggaatctat
gcaataaaacttcaattgcgggatgctcctgctgacatgcacatcagtatggatcgatacatagctatagtaacagggc
actaagtccttccgctgcatcccgacactgcttaggagcaaaattatttgcctcgtcgtatgggggctctca
gtgatcatctcctccagtagctttgtcttcaaccagaaatataacacacagggttctgtagtatgtgaaccaaag
tatcagacagtgaagtgaaaccaatacgggtggaagttgcttatgttgggcttggaagctgctttttgggttttccatc
ccactgatgttcatgatattttcgttatacattttattgttaagaccttgggttcaggcgcaaaatagcaagagacat
aaggcaattcagagtcacatttgcgtgggtgttgggtctcttctggcctgacagatcccccataaatatgggtctgctc
gtcacgcgcgctaacttgggttaagatgaatcgatcttctgacgtccgagaagttgatcggtacacacaaactgtg
acagaagtgtggtctcttccactgttgcgtgaacccagttttgtatgcttttataggacagaagtttcgaaat
tactctctgaaaatcctcaaggacctctggtgtgttcgaaggaagtacaagagctctggctttagtcgctggg
cgctacagtgaagaatatatcccgccagacctccgagactgctgataatgacaacgcaagttccttccactatg
(SEQ ID NO: 392)

[0344]

ATGAGCGGGGAATCAATGAATTTTCAGCGATGTTTTTCGACTCCAGTGAAGATTATTTTGTG
TCAGTCAATACTTCATATTACTCAGTTGATTCTGAGATGTTACTGTGCTCCTTGCAGGAG
GTCAGGCAGTTCTCCAGGCTATTTGTACCGATTCCTACTCCTTGATCTGTGTCTTTGGC
CTCCTGGGGAATATTTCTGGTGGTGATCACCTTTGCTTTTATAAGAAGGCCAGGTCATG
ACAGACGTCTATCTCTTGAACATGGCCATTGCAGACATCCTCTTTGTTCTTACTCTCCCA
TTCTGGGCAGTGAAGTCATGCCACTGGTGGGTGTTTTTCAGCAATGCCAGTGCAGTTG
CTAAAAGGCATCTATGCCATCAACTTTAACTGCGGGATGCTGCTCCTGACTTGCATTAGC
ATGGACCGGTACATCGCCATTGTACAGGCGACTAAGTCATTCCGGCTCCGATCCAGAACA
CTACCGCGCACGAAAATCATCTGCCTTGTGTGTGGGGGCTGTCAGTCATCATCTCCAGC
TCAACTTTTGTCTTCAACCAAAAATACAACACCCCAAGGCAGCGATGTCGTGAACCCAAG
TACCAGACTGTCTCGGAGCCCATCAGGTGGAAGCTGCTGATGTTGGGGCTTGAGCTACTC
TTTGGTTTCTTTATCCCTTTGATGTTTATGATATTTTGTACACGTTTATTGTCAAACCC
TTGGTGCAAGCTCAGAATCTAAAAGGCACAAAGCCATCCGTGTAATCATAGCTGTGGTG
CTTGTGTTTCTGGCTTGTGAGATTCTCCTCATAACATGGTCTGCTTGTGACGGTGCAAAT
TTGGGTAAAATGAACCGATCTTGCAGAGCGAAAAGCTAAATTTGGCTATACGAAAACCTGTC
ACAGAAGTCCCTGGCTTTTCTGCACCTGCTGCCTGAACCCCTGTGCTCTACGCTTTTATTTGGG
CAGAAGTTCAGAACTACTTTCTGAAGATCTTGAAGGACCTGTGGTGTGTGAGAAGGAAG
TACAAGTCTCAGGCTTCTCTGTGCGGGAGGTACTCAGAAAACATTTCTCGGCAGACC
AGTGAGACCGCAGATAACGACAATGCGTCTGCTCCTTCACTATG (SEQ ID NO: 393)

[0345] 表4.粘附受体和天然背景

[0346]

受体	通常在以下上表达	登录号	配体
VLA-1 或 $\alpha_1\beta_1$	许多细胞类型	NP_852478.1, AAH20057.1	胶原蛋白、层粘连蛋白
VLA-2 或 $\alpha_2\beta_1$	许多细胞类型	NP_002194.2, AAH20057.1	胶原蛋白、层粘连蛋白
VLA-3 或 $\alpha_3\beta_1$	许多细胞类型	AAI50191.1, AAH20057.1	层粘连蛋白-5
VLA-4 或 $\alpha_4\beta_1$	造血细胞	NP_000876.3, AAH20057.1	纤连蛋白和蛋白酶
VLA-5 或 $\alpha_5\beta_1$	许多细胞类型	NP_002196.4, AAH20057.1	纤连蛋白、VCAM-1
VLA-6 或 $\alpha_6\beta_1$	许多细胞类型	AAI36456.1, AAH20057.1	层粘连蛋白
$\alpha_4\beta_7$	肠	NP_000876.3, NP_000880.1	MADCAM1
$\alpha_7\beta_1$	肌肉	AAQ89241.1, AAH20057.1	层粘连蛋白
$\alpha_L\beta_2$	T 淋巴细胞	NP_002200.2, NP_000202.3	I-CAM1, I-CAM2

[0347]

MAC-1 或 $\alpha_M\beta_2$	中性粒细胞和单核细胞	AAB24821.1, NP_000202.3	I-CAM1
$\alpha_{IIb}\beta_3$	血小板	AAI26443.1, AAI27668.1	血纤蛋白原、纤连蛋白
$\alpha_v\beta_1$	黑素细胞	AAA61631.1, AAH20057.1	玻连蛋白、血纤蛋白原
$\alpha_v\beta_3$	活化内皮细胞	AAA61631.1, AAI27668.1	玻连蛋白、纤连蛋白、血纤蛋白原、骨桥蛋白、Cyr61、甲状腺素、Tetrac
$\alpha_v\beta_5$	上皮细胞和成纤维细胞	AAA61631.1, NP_002204.2	玻连蛋白
$\alpha_v\beta_6$	肺、乳腺	AAA61631.1, NP_000879.2	纤连蛋白和 TGF- $\beta_{1,3}$
$\alpha_v\beta_8$	神经组织	AAA61631.1, NP_002205.1	纤连蛋白和 TGF- $\beta_{1,3}$
$\alpha_6\beta_4$	上皮细胞	AAA61631.1, CAB61345.1	层粘连蛋白

[0348] 备选地或另外,可增强免疫细胞功能(例如增殖、细胞毒性等)的基因也可引入免疫细胞或从免疫细胞敲除。实例包括:TNF/TNFR2过表达(对于短寿命但更有效的CD8 T细胞);gld(FasL突变体;用于淋巴增殖;CTL不通过Fas-FasL途径杀伤);lpr(Fas突变体;用于上调对FasL-介导的凋亡抵抗的FasL-靶细胞);粒酶B*缺乏(延迟靶细胞的核凋亡变化);粒酶A和B*缺乏(延迟靶细胞的核凋亡变化);穿孔素缺乏(完全缺少颗粒介导的凋亡);穿孔素和FasL缺乏(缺陷的颗粒介导和Fas介导的凋亡);组织蛋白酶C(二肽基-肽酶I)缺乏(不能产生活性粒酶和一些造血丝氨酸蛋白酶);FAS(CD95)表达不足;和/或FASL过表达。

[0349] 下表5列出了MHC-CAR T细胞的另外的遗传修饰或本文所述的共治疗以及从其产生的伴随优点。

[0350] 表5. 遗传修饰或共治疗及其益处

[0351]

遗传修饰	优点
-TCR 敲除 -CIITA 缺失(以除去内源性 MHC II类表达) -CS-1(CD319)缺失(其存在于 T 细胞上)	减少对 MHC-CAR 中的肽-MHC 具有亲和力的天然 CD8 ⁺ T 细胞对 MHC-CAR T 细胞的同胞杀伤,从而延长 MHC-CAR T 细胞的寿命。(没有遗传修饰时, MHC-CAR T 细胞将仍是细胞毒性的和有效的, 但具有短寿

[0352]	-Fas 缺失, 其任选地可与 FasL 过表达组合 -PD-1 缺失, 其任选地可与 PD-L1 和/或 PD-L2 过表达组合 -共表达 CS-1 CAR(具有对 CS-1 特异性的胞外结构域的常规 CAR 构建体) -共表达 CD19 CAR (具有对 CD19 特异性的胞外结构域的常规 CAR 构建体)	命) 增强活性以消除 CD8 细胞毒性 T 细胞、抗原呈递细胞(APC)和/或 B 细胞
	-PD-L1 过表达, 其可任选地与 PD-1 缺失组合 -PD-L1 + CTLA4-Ig, 其可任选地与 PD-1 缺失组合 -FasL 过表达, 其可任选地与 Fas 缺失组合 -半乳糖素 9 表达, 其可任选地与 Tim-3 缺失组合 -CS-1 缺失(当 CS-1 CAR 用于减少同胞杀伤时) -MHC-CAR 中包括铰链	减少 MHC-CAR T 细胞被其它免疫细胞消除的水平; 包括铰链可降低/防止细胞 TCR 杀伤, 例如通过降低其接合 CD4 或 CD8 的能力
	-TCR 敲除, 当使用同种异体细胞时(细胞可经分选以除去非编辑细胞)	降低移植物抗宿主病的风险
	-表达 MHC-CAR 的 Treg 细胞 -PD-1 和/或 PD-L1 敲除 -CXCR5 表达	减少对目的肽-MHC 的体液反应(例如抗体反应), 特别是 B 细胞反应
	-IL-35 表达 -靶向产生细胞因子的 B 细胞(例如靶向 CD10)和/或其它活化免疫细胞(例如靶向 CS-1)的抑制剂(例如抗体)	减少炎症和/或增强耐受性环境
	-相关趋化因子受体表达以指向相关器官(Schall 等人, Nature Reviews Immunology (自然评论免疫学), 11(5): 355-363, 2011)或与相关细胞类型相互作用(例如, 对于 B 细胞为 CXCR5, 对于 Th17 为 CCR6) -抗原靶向抗体 scFv, 其包含 CD8 铰链、跨膜结构域和任选的刺激和共刺激结构域(仅对于 Treg)。(例如, 抗-MOG 抗体)。可使用质谱测量从市售可得的人靶向单克隆变体的测序产生相关的抗体序列(对于表 1 中的抗原靶标的子集)。Tran 等人 Scientific reports (科学报告), 6:31730, 2016	定向发炎或抗原呈递或抗原靶向环境
	-遗传编码的杀伤开关	降低细胞因子危象

[0353] 在一些实施方案中, 导致PD阻断的遗传修饰可引入表达本文所述的MHC-CAR的免疫细胞中。这样的修饰包括PD-1敲除、PD-L1或L2过表达或PD-L1敲除中的一种或多种。PD阻断可与免疫-抑制剂(例如, 敲除CTLA-4、TIM-3、LAG3、TIGIT、IDO或精氨酸酶, 或CTLA-4Ig分泌)、免疫刺激剂(例如, 抗-OX40、抗-CD137、IL-2、TLR配体或STING) 和/或激酶抑制剂(例如, Braf抑制剂或MEK抑制剂) 组合。

[0354] 下表6提供了用于PD阻断、免疫抑制剂、死亡受体、免疫刺激剂、toll样受体、激酶抑制、主调节剂、细胞因子信号传导、细胞相互作用降低和药物相互作用相关编辑的示例性遗传修饰。该表还提供了在T细胞中使用Cas9用于指导RNA的靶序列以及可用于表达/过表

达的序列的Genbank登录号。使用gRNA的基因组编辑通过转导含有所需gRNA和酿脓链球菌Cas9核酸酶的慢病毒(lentiCRISPRv2)进行。这可作为在方案中递送TALEN RNA的备选方案进行。Sanjana等人Nature Methods(自然方法)(2014)11(8):783-784。

[0355] 表6. 用于遗传修饰和相应的Cas9-介导的编辑的示例性基因

PD 阻断相关编辑	Genbank 登录号	Cas9 靶向的基因组序列 (gRNA)
程序化细胞死亡蛋白 1(PDCD1)	NP_005009.2	TGACGTTACCTCGTGCGGCC (SEQ ID NO: 146), CACGAAGCTCTCCGATGTGT (SEQ ID NO: 147), GCGTGACTTCCACATGAGCG (SEQ ID NO: 148), TTGGAAGTGGCCGGCTGGCC (SEQ ID NO: 149), GTGGCATACTCCGTCTGCTC (SEQ ID NO: 150), GATGAGGTGCCCATTCGCT (SEQ ID NO: 151),
程序化细胞死亡 1 配体 1(CD274)	NP_005009.2	TACCGCTGCATGATCAGCTA (SEQ ID NO: 152), AGCTACTATGCTGAACCTTC (SEQ ID NO: 153), GGATGACCAATTCAGCTGTA (SEQ ID NO: 154), ACCCCAAGGCCGAAGTCATC (SEQ ID NO: 155), TCTTTATATTCATGACCTAC (SEQ ID NO: 156), ACCGTTCAGCAAATGCCAGT (SEQ ID NO: 157)
免疫抑制剂相关编辑	Genbank 登录号	Cas9 靶向的基因组序列 (gRNA)
细胞毒性 T-淋巴细胞蛋白 4(CTLA4)	NP_005205.2	GTACCCACCGCCATACTACC (SEQ ID NO: 158), TTGCCTATGCCAGGTAGTA (SEQ ID NO: 159), CCTTGTGCCGCTGAAATCCA (SEQ ID NO: 160), ACCCCGAACTAACTGCTGCA (SEQ ID NO: 161), ACATAGACCCCTGTTGTAAG (SEQ ID NO: 162), ATCCTTGCAGCAGTTAGTTC (SEQ ID NO: 163)

[0356]

[0357]

CTLA4-Ig (Orencia)	APZ76727.1	
丝氨酸/苏氨酸-蛋白磷酸酶 2A 催化亚基 α 同种型(PPP2CA)	NP_002706.1	ACATCGAACCTCTTGACAGT (SEQ ID NO: 164), TACAGCTCACCTTCTCGCAG (SEQ ID NO: 165), GGTATATCTCCTCGAGGAGC (SEQ ID NO: 166), TACACTGCTTGTAGCTCTTA (SEQ ID NO: 167), GAGCTCTAGACACCAACGTG (SEQ ID NO: 168), CAAGCAGCTGTCCGAGTCCC (SEQ ID NO: 169)
丝氨酸/苏氨酸-蛋白磷酸酶 2A 催化亚基 β 同种型(PPP2CB)	CAA31183.1	AATGTGTAGCCAGCACCACG (SEQ ID NO: 170), GAACTTCCTGTAAACGATCC (SEQ ID NO: 171), TACATACCTCCATTACAAGC (SEQ ID NO: 172), CCATCTACTAAAGCTGTAAG (SEQ ID NO: 173), CTCAATATTGTAATGCGTTC (SEQ ID NO: 174), CTCTCCATCCATAGACACAC (SEQ ID NO: 175)
蛋白酪氨酸磷酸酶, 非受体 6 型 (PTPN6)	AAA35963.1	TAAGACCTACATCGCCAGCC (SEQ ID NO: 176), GAAGAACTTGCACCAGCGTC (SEQ ID NO: 177), GTCAGCCGCATTACCCCTCG (SEQ ID NO: 178), CTGCCAGAAGTCATTGACCG (SEQ ID NO: 179), CCCAGCCGTACTATGCCACG (SEQ ID NO: 180), GCCGCTGCCCTTCCAGACGC (SEQ ID NO: 181)
酪氨酸蛋白磷酸酶非受体 22 型 (PTPN22)	AAD00904.1	GTAGCTGGAATCCTCATCAG (SEQ ID NO: 182), CAAAACCTATCCTACAACCTG (SEQ ID NO: 183), TTAGGGAGTTTATGGACCCA (SEQ ID NO: 184), CTCAGCCACAGTTGTAGGAT (SEQ ID NO: 185), TCACTGTACCTTAATGAAGT (SEQ ID NO: 186), TCCTTTATCTACAACCCCTCC (SEQ ID NO: 187)
淋巴细胞活化基因 3 蛋白(LAG3)	CAA36243.3	TCCATAGGTGCCCAACGCTC (SEQ ID NO: 188), GTTCCGGAACCAATGCACAG (SEQ ID NO: 189), GCGAGAAGTCCCCGCGCTGC (SEQ ID NO: 190), TGACCCCTGCTCTTCGCAGA (SEQ ID NO: 191), CGCCGGCGAGTACCGCGCCG (SEQ ID NO: 192), TGGGCGGTGAGGGCGGCTGA (SEQ ID NO: 193)

[0358]

甲型肝炎病毒细胞受体 2 (Tim3, HAVCR2)	AAM19100.1	CTAAATGGGGATTTCGCAA (SEQ ID NO: 194), ATCCCCATTAGCCAGTATC (SEQ ID NO: 195), GTGAAGTCTCTGCCCAGT (SEQ ID NO: 196), AGGTCACCCCTGCACCGACT (SEQ ID NO: 197), CTTACTGTTAGATTATATC (SEQ ID NO: 198), TATAGCAGAGACACAGACAC (SEQ ID NO: 199)
B 和 T 淋巴细胞弱化子(BTLA)	AAP44003.1	GTGACTTGGTGCAAGCTCAA (SEQ ID NO: 200), TCTGCTTGCCATTTCGTCCT (SEQ ID NO: 201), CTGTTAGCACAGTATTTAC (SEQ ID NO: 202), CCAAAGGAAGTAAACGATAC (SEQ ID NO: 203), ATGTTCCAGATGTCCAGATA (SEQ ID NO: 204), CTTCTTCTTAATCCCATATC (SEQ ID NO: 205)
CD160 抗原(CD160)	AAC72302.1	AGTTTAGTCGCGTTCCTTCC (SEQ ID NO: 206), CACTGTGCAACGGTGTGACT (SEQ ID NO: 207), GGATGTCCACAATTGCCAGC (SEQ ID NO: 208), AACTGAGAGTGCCTTCATTA (SEQ ID NO: 209), GACAGGGAACACTACACAGTGA (SEQ ID NO: 210), GACAGGGAACACTACACAGTGA (SEQ ID NO: 210), ATTGTGGACATCCAGTCTGG (SEQ ID NO: 212)
具有 Ig 和 ITIM 结构域的 T 细胞免疫受体(TIGIT)	BAC04973.1	TCGCTGACCGTGAACGATAC (SEQ ID NO: 213), TGGGGCCACTCGATCCTTGA (SEQ ID NO: 214), GCAGATGACCACCAGCGTCG (SEQ ID NO: 215), TCAGGCCTTACCTGAGGCGA (SEQ ID NO: 216), CATCTGCACAGCAGTCATCG (SEQ ID NO: 217), ATTGAAGTAGTCATGCAGCT (SEQ ID NO: 218)
T 细胞表面蛋白触觉(tactile) (CD96)	AAA36662.1	AGGCACAGTAGAAGCCGTAT (SEQ ID NO: 219), GCTGTCTATCATCCCCAATA (SEQ ID NO: 220), ACTTACCACCGACCATGCAT (SEQ ID NO: 221)
细胞毒性和调节性 T 细胞分子(CRTAM)	AAC80267.1	CACACTTTAGAGTGAGCGTC (SEQ ID NO: 222), CTCCAGTGGCTGACCCCTC (SEQ ID NO: 223), CCACAGCAGCCCACAGTAC (SEQ ID NO: 224)

[0359]

白细胞相关免疫球蛋白样受体 1(LAIR1)	AF013249.1	TTATAATAGATGCAGCGATA (SEQ ID NO: 225), TCATTGTGACTGTTGTCCGA (SEQ ID NO: 226), GCCAGGCACCGTGATCCCC (SEQ ID NO: 227)
唾液酸结合 Ig 样凝集素 7(SIGLEC7)	AF170485.1	CATCCTTATCCCCGGTACCC (SEQ ID NO: 228), CAGAGAGTTCTGAGCTCGAC (SEQ ID NO: 229), AGTGTTGCTGGGGGCGGTCCG (SEQ ID NO: 230)
唾液酸结合 Ig 样凝集素 9(SIGLEC9)	AF135027.1	GACGATGCAGAGTTCCGTGA (SEQ ID NO: 231), ACTCACAGGACACGTTGAGA (SEQ ID NO: 232), TACCCTGGCCCAGTAGTTCA (SEQ ID NO: 233)
自然杀伤细胞受体 2B4(CD244)	AF105261.1	ACCTTCGTCTGTATGCTGTT (SEQ ID NO: 234), ACCAAACAGCATACAGACGA (SEQ ID NO: 235), CTACTCTATGATCCAGTCCC (SEQ ID NO: 236)
死亡受体和途径编辑		
肿瘤坏死因子配体超家族成员 10(TRAIL)	AAC50332.1	ACTCCGTCAGCTCGTTAGAA (SEQ ID NO: 237), GTCATACTCTCTTCGTCAT (SEQ ID NO: 238), AGAGTAGCAGCTCACATAAC (SEQ ID NO: 239)
肿瘤坏死因子受体超家族成员 10B(TNFRSF10B)	AF018657.1	TTCCAGAGCTCACAACGACC (SEQ ID NO: 240), ATAGTCCTGTCCATATTTGC (SEQ ID NO: 241), AGATACTCACGATCTCATTG (SEQ ID NO: 242)
肿瘤坏死因子受体超家族成员 10A(TNFRSF10A)	AAC51226.1	AGGTCAAGGATTGTACGCC (SEQ ID NO: 243), GAAGTCCCTGCACCACGACC (SEQ ID NO: 244), TTTGGTTGTTCCGTTGCTGT (SEQ ID NO: 245)
半胱天冬酶-8(CASP8)	CAA66853.1	TGATCGACCCTCCGCCAGAA (SEQ ID NO: 246), GGGTCGATCATCTATTAATA (SEQ ID NO: 247), TCCTTTGCGGAATGTAGTCC (SEQ ID NO: 248)
半胱天冬酶-10(CASP10)	AAC50644.1	CTATGTATCCTTTTCGGCATG (SEQ ID NO: 249), TCTTCTGCCGTATGATATAG (SEQ ID NO: 250), GTGAGACATGATCTCCCGAA (SEQ ID NO: 251)
半胱天冬酶-3(CASP3)	AAA65015.1	ATGTCGATGCAGCAAACCTC (SEQ ID NO: 252), ATTATACATAAACCCATCTC (SEQ ID NO: 253), AATGGACTCTGGAATATCCC (SEQ ID NO: 254)

[0360]

半胱天冬酶-6(CASP6)	AAC50168.1	ATAGAGACAATCTTACCCGC (SEQ ID NO: 255), AAGATTGTCTCTATCTGCGC (SEQ ID NO: 256), AAATGTGATTGCCTTCGCCA (SEQ ID NO: 257)
半胱天冬酶-7(CASP7)	AAC50303.1	CGTTTGTACCGTCCCTCTC (SEQ ID NO: 258), TGCGATCCATCAAGACCACC (SEQ ID NO: 259), TTGATATTTAGGCTTGCCGA (SEQ ID NO: 260)
FAS 相关死亡结构域蛋白(FADD)	AAA86517.1	AGTCGTCGACGCGCCGACG (SEQ ID NO: 261), AGCGGCCCATCAGGACGCTT (SEQ ID NO: 262), GCGGCGCGTCGACGACTTCG (SEQ ID NO: 263)
肿瘤坏死因子受体超家族成员 6(FAS)	AAA63174.1	GTGTAACATACCTGGAGGAC (SEQ ID NO: 264), TACATCTGCACTTGGTATTC (SEQ ID NO: 265), CTAAAACTTACTTGGTGCAA (SEQ ID NO: 266)
IDO	AAA36081.1	TCTCAACTCTTCTCGAAGC (SEQ ID NO: 267), CTGCCTGATCTCATAGAGTC (SEQ ID NO: 268), CAGATACTTACTCATAAGTC (SEQ ID NO: 269)
精氨酸酶 EIF2AK4	AAH09350.2	CGCTGAGAAATGACTGCACG (SEQ ID NO: 270), CATATACTTCTTCACCAGTT (SEQ ID NO: 271), ATGTACTCACACATCTGGAT (SEQ ID NO: 272)
免疫刺激剂编辑		
OX40 (TRAF2)	BAA14259.1	ACCGAATGTCCCGCGTGCAA (SEQ ID NO: 273), GCCTTTGCACGCGGACATT (SEQ ID NO: 274), GGGGACCCTGAAAGAATACG (SEQ ID NO: 275)
CD137 (TNFRSF9)	TNFRSF9	CCTGCGCTGGAGAACTATT (SEQ ID NO: 276), CCTTGTAGTAACTGCCCAGC (SEQ ID NO: 277), CATAGTAGCCACTCTGTTGC (SEQ ID NO: 278)
IL2	CAA25292.1	CAATATCAACGTAATAGTTC (SEQ ID NO: 279), GACTTAGTGCAATGCAAGAC (SEQ ID NO: 280), GATATTGCTGATTAAGTCCC (SEQ ID NO: 281)
干扰素基因蛋白的刺激剂(STING 或 TMEM173)	ACI46648.1	GCGGGCCGACCGCATTTGGG (SEQ ID NO: 282), CATATTACATCGGATATCTG (SEQ ID NO: 283), ACTCTTCTGCCGGACACTTG (SEQ ID NO: 284)
Toll 样受体编辑		

[0361]

TLR1	AAC34137.1	TTATAGAGGAACCTACTAA (SEQ ID NO: 285), TTGTGGGCACCTTACTGAGT (SEQ ID NO: 286), CGAACACATCGCTGACAACT (SEQ ID NO: 287)
TLR2	AAC34377.1	GTTAACGTTTCCACTTTACC (SEQ ID NO: 288), TTCCCGCTGAGCCTCGTCCA (SEQ ID NO: 289), TATCTAATTTATCGTCTTCC (SEQ ID NO: 290)
TLR3	AAC34134.1	TTCGAGCATCAGTCGTTGA (SEQ ID NO: 291), TTCAACGACTGATGCTCCGA (SEQ ID NO: 292), CATGCACTCTGTTTGC GAAG (SEQ ID NO: 293)
TLR4	AAC80227.1	TTCTCCAGAACCAACGA (SEQ ID NO: 294), GATGATGTCTGCCTCGCGCC (SEQ ID NO: 295), ATGCCCCATCTTCAATTGTC (SEQ ID NO: 296)
TLR5	AAC34376.1	TATTCGGCCATCAAAGGAGC (SEQ ID NO: 297), GACTAAGCCTCAACTCCAAC (SEQ ID NO: 298), TATACAAGCTATTAGCTGCG (SEQ ID NO: 299)
TLR6	BAA78631.1	GAACATCATCGCTGAGCTTC (SEQ ID NO: 300), GCCATCCTATTGTGAGTTTC (SEQ ID NO: 301), TGTCTCCAATTAACTAACG (SEQ ID NO: 302)
TLR7	AAF60188.1	AAGGAATAGTCACCTCCGTA (SEQ ID NO: 303), AATGGGGCATTATAACAACG (SEQ ID NO: 304), GGTGAGGTTCGTGGTGTTCG (SEQ ID NO: 305)
TLR8	AAF64061.1	GTGCAGCAATCGTCGACTAC (SEQ ID NO: 306), AATCCCGGTATACAATCAAA (SEQ ID NO: 307), CTCGAGTTGCTTGACTTACG (SEQ ID NO: 308)
TLR9	AAF72189.1	GGCTCACGGCTATTCGGCCG (SEQ ID NO: 309), GCGTCTCCGTGACAATTACC (SEQ ID NO: 310), CCGACAGGTCCACGTAGCGC (SEQ ID NO: 311)
TLR10	AAK26744.1	CCCACATTTACGCCTATCCT (SEQ ID NO: 312), TAACATTAATAGCAGCTCGA (SEQ ID NO: 313), GACCCAGCCACAACGACAC (SEQ ID NO: 314)
激酶抑制编辑		

[0362]

丝氨酸/苏氨酸蛋白激酶 B-raf(BRAF)	AAA35609.2	CCCCACCAAATTTGTCCAAT (SEQ ID NO: 315), GAGGCCCTATTGGACAAATT (SEQ ID NO: 316), GTTGCTCCGTGCCACATCTG (SEQ ID NO: 317)
双特异性丝裂原活化蛋白激酶激酶 1(MAP2K 或 MEK)	AAA36318.1	CCATACTTACTCCGCAGAGC (SEQ ID NO: 318), TATGGTGCGTTCTACAGCGA (SEQ ID NO: 319), CCCGACGGCTCTGCAGTTAA (SEQ ID NO: 320)
主调节剂编辑		
FoxP3	AAG53607.1	
细胞因子信号传导编辑(这些编辑的 一种或两种的目的是防止或最小化治 疗性 Treg 由于内源性 IL-6 而转化为 Th17 细胞).		
Gagliani 等人, Nature (自然), 523(7559):221-225, 2015. Korn 等人 Proceedings of the National Academy of Sciences (国家科学院院 刊), 105(47):18460-18465, 2008。		
白介素 6 受体亚基 α (IL6R)	CAA31312.1	TCGGTGCGAGCTCCACGACTC (SEQ ID NO: 321), AACTATTTCATGCTACCGGGC (SEQ ID NO: 322), CGTGGTGCGAGCTTCGTGCCC (SEQ ID NO: 323)
白介素 6 受体亚基 β (IL6ST 或 GP130)	AAA59155.1	AGATGCCTCAACTTGGAGCC (SEQ ID NO: 324), TTTGAGTTGCATTGTGAACG (SEQ ID NO: 325), ATTGCTGTATGAAGGAAGA (SEQ ID NO: 326)
减少细胞相互作用的编辑		
TCR α (见优选的 talen 编辑)		
TCR β (见优选的 talen 编辑)		
CIITA	CAA52354.1	TTCTACACAATGCGTTGCC (SEQ ID NO: 327), GATATTGGCATAAGCCTCCC (SEQ ID NO: 328), TCAACTGCGACCAGTTCAGC (SEQ ID NO: 329)
B7-1 (CD80)	AAA36045.1	TCGTATGTGCCCTCGTCAGA (SEQ ID NO: 330), GAGTGAATCAGACCTTCAAC (SEQ ID NO: 331), TATGGCCCGAGTACAAGAAC (SEQ ID NO: 332)
B7-2 (CD86)	AAB03814.1	GTAACCGTGTATAGATGAGC (SEQ ID NO: 333), ATACTCGATAGTTGAATTCT (SEQ ID NO: 334), CATCAGATCTTTCAGGTATA (SEQ ID NO: 335)

[0363]

b2m	AAA51811.1	ACTCACGCTGGATAGCCTCC (SEQ ID NO: 336), GAGTAGCGCGAGCACAGCTA (SEQ ID NO: 337), CAGTAAGTCAACTTCAATGT (SEQ ID NO: 338)
UL18	CAA68399.1	
PDL2	AAK31105.1	
FasL	AAC50071.1	GGTTGTTGCAAGATTGACCC (SEQ ID NO: 339), GAGGAACTCTAAGTATCCCC (SEQ ID NO: 340), TCTGGTTGCCTTGGTAGGAT (SEQ ID NO: 341)
穿孔素(PRF1)	CAA31612.1	CGCAGCCACAAGTTCGTGCC (SEQ ID NO: 342), GGAGCTGGGTGGCCGCATAT (SEQ ID NO: 343), CCCGAACAGCAGGTCGTAA (SEQ ID NO: 344)
半乳凝素 9(LGALS9)	AA88922.1	
PVT/CD155	AAA36461.1	
药物相互作用相关编辑		
CD52	CAA44323.1	CTCTTACCTGTACCATAACC (SEQ ID NO: 345), AATGCCTCCGCTTATGTTGC (SEQ ID NO: 346), TGGCATTGGCCACGAAGAAA (SEQ ID NO: 347)
托西珠单抗-样重链(对于 scfv)	BAJ21229.1	
托西珠单抗-样轻链(对于 scfv)	BAJ21230.1	
整联蛋白 α -4(ITGA4)	CAA34852.1	CGACTACTTCGGTAGTATGC (SEQ ID NO: 348), CAGCATACTACCGAAGTAGT (SEQ ID NO: 349), GTGTTTGTGTACATCAACTC (SEQ ID NO: 350)

[0364] 下表提供了用于TALEN编辑的靶序列以及蛋白序列。

[0365] 表7. 主要TALEN介导的编辑

[0366]

相关的 CS1 编辑	序列或 Genbank 登录号
CS1	NP_067004.3
CS1v1TALEN 靶标	tgacttcagagag caataaggct ggtcccca catgctca (SEQ ID NO: 351)
CS1v1 左 TALEN 靶标	tgacttcagagagcaa (SEQ ID NO: 352)

[0367]

CS1v1 左 TALEN 蛋白	MDYKDHDGDYKDHDIDYKDDDDKMAPKKKKRVGIHGVPAAVDLRTLGYSSQQQKEKPK VRSTVAQHHEALVGHGFTHAHIVALSQHPPAALGTAVKYQDMIAALPEATHEAIVGVGKQ WSGARALEALLTVAGELRGPPQLQDGTGQLLKIAGRGVTAVEAVHAWRNALTGAPNLTP EQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLC QAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQ RLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGK QALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAI ASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLT PEQVVAIASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLC QAHGLTPEQVVAIASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQ RLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQ ALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIA CLGGRPALDAVKKGLPHAPALIKRTNRRIPERTSHR VAGSQLVKSELEKKSELRHKLKYVP HEYIELIEIARNSTQDRILEMKVMEFFMKVYGYRGKHLGGSRKPDGAIYTVGSPIDYGVIVDT KAYSGGYNLPIGQADEMQRYVEENQTRNKHINPNNEWKVPSSVTEFKFLFVSGHFKGNY KAQLTRLNHTNCNGAVLSVEELLIGGEMIKAGTLTLEEVRRKFNNGEINFRS (SEQ ID NO: 353)
CS1v1 右 TALEN 靶标	aacatgcctc accctca (SEQ ID NO: 354)
CS1v1 右 TALEN 蛋白	MDYKDHDGDYKDHDIDYKDDDDKMAPKKKKRVGIHGVPAAVDLRTLGYSSQQQKEKPK VRSTVAQHHEALVGHGFTHAHIVALSQHPPAALGTAVKYQDMIAALPEATHEAIVGVGKQ WSGARALEALLTVAGELRGPPQLQDGTGQLLKIAGRGVTAVEAVHAWRNALTGAPNLTP EQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQRLLPVLC QAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQ RLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGK QALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAI ASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLT PEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLC QAHGLTPEQVVAIASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETV QRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGG KQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAI LACLGGRPALDAVKKGLPHAPALIKRTNRRIPERTSHR VAGSQLVKSELEKKSELRHKLKY VPHEYIELIEIARNSTQDRILEMKVMEFFMKVYGYRGKHLGGSRKPDGAIYTVGSPIDYGVIV DTKAYSGGYNLPIGQADEMQRYVEENQTRNKHINPNNEWKVPSSVTEFKFLFVSGHFKG NYKAQLTRLNHTNCNGAVLSVEELLIGGEMIKAGTLTLEEVRRKFNNGEINFRS (SEQ ID NO: 355)
CS1v2TALEN 靶标	ttccagagag caatatggct gggtcccaaa catgcctcac cctcatcta (SEQ ID NO: 356)
CS1v2 左 TALEN 靶标	ttccagagag caatatg (SEQ ID NO: 357)
CS1v2 左 TALEN 蛋白	MDYKDHDGDYKDHDIDYKDDDDKMAPKKKKRVGIHGVPAAVDLRTLGYSSQQQKEKPK VRSTVAQHHEALVGHGFTHAHIVALSQHPPAALGTAVKYQDMIAALPEATHEAIVGVGKQ WSGARALEALLTVAGELRGPPQLQDGTGQLLKIAGRGVTAVEAVHAWRNALTGAPNLTP EQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLC QAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQ RLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQ ALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIA SNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLT EQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQRLLPVLC QAHGLTPEQVVAIASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQ RLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQ ALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIA CLGGRPALDAVKKGLPHAPALIKRTNRRIPERTSHR VAGSQLVKSELEKKSELRHKLKYVP HEYIELIEIARNSTQDRILEMKVMEFFMKVYGYRGKHLGGSRKPDGAIYTVGSPIDYGVIVDT KAYSGGYNLPIGQADEMQRYVEENQTRNKHINPNNEWKVPSSVTEFKFLFVSGHFKGNY KAQLTRLNHTNCNGAVLSVEELLIGGEMIKAGTLTLEEVRRKFNNGEINFRS (SEQ ID NO: 358)
CS1v2 右 TALEN 靶标	tgcctcaccc tcacta (SEQ ID NO: 359)
CS1v2 右 TALEN 蛋白	MDYKDHDGDYKDHDIDYKDDDDKMAPKKKKRVGIHGVPAAVDLRTLGYSSQQQKEKPK VRSTVAQHHEALVGHGFTHAHIVALSQHPPAALGTAVKYQDMIAALPEATHEAIVGVGKQ WSGARALEALLTVAGELRGPPQLQDGTGQLLKIAGRGVTAVEAVHAWRNALTGAPNLTP EQVVAIASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLC QAHGLTPEQVVAIASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQ RLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQ ALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIA SNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLT EQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLC QAHGLTPEQVVAIASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQ RLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGG KQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVA AIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQRLLPVLCQAHGLT TNDHLVALACLGGRPALDAVKKGLPHAPALIKRTNRRIPERTSHR VAGSQLVKSELEKKSE LRHKLKYVPHEYIELIEIARNSTQDRILEMKVMEFFMKVYGYRGKHLGGSRKPDGAIYTVGS PIDYGVIVDTKAYSGGYNLPIGQADEMQRYVEENQTRNKHINPNNEWKVPSSVTEFKFLF VSGHFKGNYKAQLTRLNHTNCNGAVLSVEELLIGGEMIKAGTLTLEEVRRKFNNGEINFRS (SEQ ID NO: 360)
CS1v3 靶标	ttgactctat tgtctggacc ttcaacacaa cccctctgtg caccataca (SEQ ID NO: 361)

[0368]

CSIv3 左 TALEN 靶标	ttgactctat tgcctgg (SEQ ID NO: 362)
CSIv3 左 TALEN 蛋白	MDYKDHDGDKDHDIDYKDDDDKMAPKKKRVGIHGVPAAVDLRTLGYSSQQQEEKIKPK VRSTVAQHHEALVGHGFTAHIVALSQHPAALGTAVKYQDMIAALPEATHEAIVGVGKQ WSGARALEALLTVAGELRGPPQLDGTGQLLKIAGRGVTAVEAVHAWRNALTGAPLNLT EQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLC QAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGKQALETVQ RLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGK QALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAI ASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLT PEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLC QAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGKQALETV QRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNG KQALETVQRLLPVLCQAHGLTPEQVVAIASNNGRPALESIVAQLSRPDPALAAALNDHLVA LACLGGRPALDAVKKGLPHAPALIKRTNRRIPERTSHRVAGSQLVKSELEKKSELHKLKY VPHEYIELIEIARNSTQDRILEMKVMEFFMKVYGYRGKHLGGSRKPDGAIYTVGSPIDYGVIV DTKAYSGGYNLPIGQADEMQRYVEENQTRNKHINPNEWWKVYSSVTEFKFLFVSGHFKG NYKAQLTRLNHTNCNGAVLSVEELLIGGEMIKAGTLTLEEVRKFNNGEINFRS (SEQ ID NO: 363)
CSIv3 右 TALEN 靶标	cctcttgca ccatata (SEQ ID NO: 364)
CSIv3 右 TALEN 蛋白	MDYKDHDGDKDHDIDYKDDDDKMAPKKKRVGIHGVPAAVDLRTLGYSSQQQEEKIKPK VRSTVAQHHEALVGHGFTAHIVALSQHPAALGTAVKYQDMIAALPEATHEAIVGVGKQ WSGARALEALLTVAGELRGPPQLDGTGQLLKIAGRGVTAVEAVHAWRNALTGAPLNLT EQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLC QAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQ RLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGK QALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAI ASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQRLLPVLCQAHGLT PEQVVAIASHDGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQRLLPVLC QAHGLTPEQVVAIASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQ RLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQ ALETVQRLLPVLCQAHGLTPEQVVAIASNNGRPALESIVAQLSRPDPALAAALNDHLVALA CLGGRPALDAVKKGLPHAPALIKRTNRRIPERTSHRVAGSQLVKSELEKKSELHKLKYVP HEYIELIEIARNSTQDRILEMKVMEFFMKVYGYRGKHLGGSRKPDGAIYTVGSPIDYGVIVDT KAYSGGYNLPIGQADEMQRYVEENQTRNKHINPNEWWKVYSSVTEFKFLFVSGHFKGNY KAQLTRLNHTNCNGAVLSVEELLIGGEMIKAGTLTLEEVRKFNNGEINFRS (SEQ ID NO: 365)
相关的 CIITA 编辑	序列或 Genbank 登录号
CIITA	NP_001273331.1
CIITA TALEN 靶标	TTCCCTCCCAGGCAGCTCacagtgtgccaccaTGGAGTTGGGGCCCCCT A (SEQ ID NO: 366)
CIITA 左 TALEN 靶标	TTCCCTCCCAGGCAGCTC (SEQ ID NO: 367)
CIITA 左 TALEN 蛋白	MDYKDHDGDKDHDIDYKDDDDKMAPKKKRVGIHGVPAAVDLRTLGYSSQQQEEKIKPK VRSTVAQHHEALVGHGFTAHIVALSQHPAALGTAVKYQDMIAALPEATHEAIVGVGKQ WSGARALEALLTVAGELRGPPQLDGTGQLLKIAGRGVTAVEAVHAWRNALTGAPLNLT EQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGKQALETVQRLLPVLC QAHGLTPEQVVAIASHDGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGKQALETVQ RLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGK QALETVQRLLPVLCQAHGLTPEQVVAIASHDGKQALETVQRLLPVLCQAHGLTPEQVVAI ASHDGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQRLLPVLCQAHGLT PEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLC QAHGLTPEQVVAIASHDGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETV QRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGK KQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVA IASHDGGRPALESIVAQLSRPDPALAAALNDHLVALACLGGRPALDAVKKGLPHAPALIKRT NRRIPERTSHRVAGSQLVKSELEKKSELHKLKYVPHEYIELIEIARNSTQDRILEMKVMEFF MKVYGYRGKHLGGSRKPDGAIYTVGSPIDYGVIVDTKAYSGGYNLPIGQADEMQRYVEEN QTRNKHINPNEWWKVYSSVTEFKFLFVSGHFKGNYKAQLTRLNHTNCNGAVLSVEELLIG GEMIKAGTLTLEEVRKFNNGEINFRS (SEQ ID NO: 368)
CIITA 右靶标	TGGAGTTGGGGCCCCCTA (SEQ ID NO: 369)
CIITA 右蛋白	MDYKDHDGDKDHDIDYKDDDDKMAPKKKRVGIHGVPAAVDLRTLGYSSQQQEEKIKPK VRSTVAQHHEALVGHGFTAHIVALSQHPAALGTAVKYQDMIAALPEATHEAIVGVGKQ WSGARALEALLTVAGELRGPPQLDGTGQLLKIAGRGVTAVEAVHAWRNALTGAPLNLT EQVVAIASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLC QAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQ RLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGK QALETVQRLLPVLCQAHGLTPEQVVAIASHDGKQALETVQRLLPVLCQAHGLTPEQVVAI ASHDGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGKQALETVQRLLPVLCQAHGLT PEQVVAIASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQRLLPVLC

[0369]

	QAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGRPALESIVAQLSRPDPALAAALTNDHLVALACLGGRPALDAVKKGLPHAPALIKRTNRRIPERTSHRVAGSQLVKSELEEKSELRHKLKYYV PHEYIELIEIARNSTQDRILEMKVMEFFMKVYGYRGKHLGGSRKPDGAIYTVGSPIDYGVIVDTKAYSGGYNLPIGQADEMQRYVEENQTRNKHINPNEWWKVYPSSVTEFKFLFVSGHFKGN YKAQLTRLNHTNCNGAVLSVEELLIGGEMIKAGTLTLEEVRKFNNGEINFRS (SEQ ID NO: 370)
相关的 CD52 编辑	序列或 Genbank 登录号
CD52	NP_001794.2
CD52 靶标	TTCCTCCTACTCACCATcagcctcctggttatGGTACAGGTAAGAGCAA (SEQ ID NO: 371)
CD52 左靶标	TTCCTCCTACTCACCAT (SEQ ID NO: 372)
CD52 左蛋白	MDYKDHDGDYKDHDIDYKDDDDKMAPKKRKVGHHGVPAAVDLRTLGYSSQQQEKIKPKVRSTVAQHHEALVGHGFTAHIVALSQHPAALGTAVKYQDMIAALPEATHEAIVGVGKQWSGARALEALLTVAGELRGPLQLDTGQLLKIAKRGGVTAVEAVHAWRNALTGAPLNLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGRPALESIVAQLSRPDPALAAALTNDHLVALACLGGRPALDAVKKGLPHAPALIKRTNRRIPERTSHRVAGSQLVKSELEEKSELRHKLKYYV PHEYIELIEIARNSTQDRILEMKVMEFFMKVYGYRGKHLGGSRKPDGAIYTVGSPIDYGVIVDTKAYSGGYNLPIGQADEMQRYVEENQTRNKHINPNEWWKVYPSSVTEFKFLFVSGHFKGN YKAQLTRLNHTNCNGAVLSVEELLIGGEMIKAGTLTLEEVRKFNNGEINFRS (SEQ ID NO: 373)
CD52 右靶标	GGTACAGGTAAGAGCAA (SEQ ID NO: 374)
CD52 右蛋白	MDYKDHDGDYKDHDIDYKDDDDKMAPKKRKVGHHGVPAAVDLRTLGYSSQQQEKIKPKVRSTVAQHHEALVGHGFTAHIVALSQHPAALGTAVKYQDMIAALPEATHEAIVGVGKQWSGARALEALLTVAGELRGPLQLDTGQLLKIAKRGGVTAVEAVHAWRNALTGAPLNLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGRPALESIVAQLSRPDPALAAALTNDHLVALACLGGRPALDAVKKGLPHAPALIKRTNRRIPERTSHRVAGSQLVKSELEEKSELRHKLKYYV PHEYIELIEIARNSTQDRILEMKVMEFFMKVYGYRGKHLGGSRKPDGAIYTVGSPIDYGVIVDTKAYSGGYNLPIGQADEMQRYVEENQTRNKHINPNEWWKVYPSSVTEFKFLFVSGHFKGN YKAQLTRLNHTNCNGAVLSVEELLIGGEMIKAGTLTLEEVRKFNNGEINFRS (SEQ ID NO: 375)
相关的 TRAC 编辑	序列或 Genbank 登录号
TRAC	CAA26435.1
TRAC TALEN 靶标	TTGTCCCACAGATATCCagaacctgacctgCCGTGTACCAGCTGAGA (SEQ ID NO: 376)
TRAC 左 TALEN 靶标	TTGTCCCACAGATATCC (SEQ ID NO: 377)

用能够例如在靶向核苷酸序列处切割基因组的核酸的内切核酸酶。基因组中双链断裂的修复可以是修复引入突变,和/或外源核酸可插入靶位点。

[0373] 基因组编辑方法通常根据参与产生靶核酸的双链断裂的内切核酸酶的类型来分类。这些方法包括使用锌指核酸酶 (ZFN)、基于转录激活物样效应物的核酸酶 (TALEN)、大范围核酸酶和CRISPR/Cas系统。

[0374] 在一些情况下,本文所述的免疫细胞的遗传修饰使用本领域已知的TALEN技术进行。TALEN是改造的限制性酶,其可特异性地结合和切割所需的靶DNA分子。TALEN通常含有与DNA切割结构域融合的转录激活物样效应物 (TALE) DNA-结合结构域。DNA结合结构域可含有高度保守的33-34个氨基酸序列,具有在位置12和13处的分叉2氨基酸RVD(重复可变二肽基序)。RVD基序决定对核酸序列的结合特异性,并且可根据本领域技术人员已知的方法改造以特异性地结合所需的DNA序列(参见例如,Juillerat等人(2015年1月).Scientific reports(科学报告),5;Miller等人(2011年2月).Nature Biotechnology(自然生物技术) 29(2):143-8;Zhang等人(2011年2月).Nature Biotechnology(自然生物技术) 29(2):149-53;Geißler等人,Boch,(2011),PLoS ONE 6(5):e19509;Boch(2011年2月).Nature Biotechnology(自然生物技术) 29(2):135-6;Boch等人(2009年12月).Science(科学) 326(5959):1509-12;以及Moscou等人(2009年12月).Science(科学) 326(5959):1501。DNA切割结构域可衍生自FokI内切核酸酶,其在许多不同的细胞类型中有活性。FokI结构域作为二聚体起作用,需要两个对于靶基因组中的位点具有独特DNA结合结构域的构建体,具有合适的取向和间距。TALE DNA结合结构域和FokI切割结构域之间的氨基酸残基数量和两个单独的TALEN结合位点之间的碱基数量似乎是实现高水平活性的重要参数。Miller等人(2011) Nature Biotech.(自然生物技术) 29:143-8。

[0375] 对目的靶基因中的序列特异性的TALEN(例如,本文所述的TCR、CD52、MHC等)可使用本领域已知的任何方法构建,包括使用模块组分和各种方案。Zhang等人(2011) Nature Biotech.(自然生物技术) 29:149-53;Geibler等人(2011) PLoS ONE 6:e19509。

[0376] 对目的靶基因特异性的TALEN可在细胞内使用以产生双链断裂(DSB)。如果修复机制通过非同源末端连接错误地修复断裂,可在断裂位点处引入突变。例如,错误修复可引入移码突变。或者,具有所需序列的外源DNA分子可与TALEN一起引入细胞。根据外源DNA序列和染色体序列,该方法可用于纠正缺陷或引入DNA片段至目的靶基因,或引入这样的缺陷至内源性基因,从而降低靶基因的表达。

[0377] 在一些情况下,本文所述的免疫细胞的遗传修饰使用本领域已知的CRISPR技术(CRISPR/Cas系统)进行。这样的修饰可包括缺失或突变目的靶基因中的序列,可使用CRISPR-Cas系统构建,其中规律成簇的间隔短回文重复(CRISPR)-Cas系统是一种改造的、非-天然存在的CRISPR-Cas系统。本公开使用CRISPR/Cas系统,其与目的靶基因中的靶序列杂交,其中CRISPR/Cas系统包含Cas内切核酸酶和改造的crRNA/tracrRNA(或单一指导RNA("sgRNA"))。在一些实施方案中,CRISPR/Cas系统包括crRNA并且不包括tracrRNA序列。CRISPR/Cas复合物可结合谱系特异性蛋白多核苷酸并允许切割蛋白多核苷酸,从而修饰多核苷酸。

[0378] 本公开的CRISPR Cas系统可结合和/或切割目的靶基因内的目的区,在基因内或附近,例如前导序列、尾序列或内含子,或在非转录区内,在编码区的上游或下游。用于本公

开的指导RNA (gRNA) 可被设计成使得gRNA指导Cas酶-gRNA复合物结合至基因组中预确定的切割位点(靶位点)。切割位点可经选择以释放含有未知序列的区、或含有SNP、核苷酸插入、核苷酸缺失、重排等的区的片段。基因区域的切割可包含在靶序列的位置通过Cas酶切割一条或两条链。在一个实施方案中,这样的切割可导致降低靶基因的转录。在另一个实施方案中,切割可进一步包含通过与外源模板多核苷酸同源重组修复切割的靶多核苷酸,其中修复导致插入、缺失或取代靶多核苷酸的一个或多个核苷酸。

[0379] 术语“gRNA”、“指导RNA”和“CRISPR指导序列”可在全文互换使用,并且是指包含决定CRISPR/Cas系统的Cas DNA结合蛋白的特异性的序列的核酸。gRNA与宿主细胞的基因组的靶核酸序列杂交(部分或完全互补)。杂交至靶核酸的gRNA或其部分可为15-25个核苷酸、18-22个核苷酸或19-21个核苷酸长。在一些实施方案中,杂交至靶核酸的gRNA序列是15、16、17、18、19、20、21、22、23、24或25个核苷酸长。在一些实施方案中,杂交至靶核酸的gRNA序列是10-30或15-25个核苷酸长。

[0380] 除了结合至靶核酸的序列之外,在一些实施方案中,gRNA还包含骨架序列。编码与靶核酸互补的序列和骨架序列二者的gRNA的表达具有结合(杂交)至靶核酸和募集内切核酸酶至靶核酸的双重功能,这可导致位点特异性CRISPR活性。在一些实施方案中,这样的嵌合gRNA可称为单一指导RNA (sgRNA)。

[0381] 如本文使用的,“骨架序列”也称为tracrRNA,是指募集Cas内切核酸酶至与互补gRNA序列结合(杂交)的靶核酸的核酸序列。包含至少一个茎环结构和募集内切核酸酶的任何骨架序列可用于本文所述的遗传元件和载体。示例性骨架序列对于本领域技术人员是显而易见的并且可见于例如Jinek等人Science (科学) (2012) 337 (6096):816-821,Ran等人Nature Protocols (自然实验手册) (2013) 8:2281-2308,PCT申请公开号W02014/093694和PCT申请公开号W02013/176772。在一些实施方案中,CRISPR-Cas系统不包括tracrRNA序列。

[0382] 在一些实施方案中,gRNA序列不包含骨架序列,并且骨架序列作为单独的转录物表达。在这样的实施方案中,gRNA序列进一步包含另外的序列,其与一部分骨架序列互补以及用于结合(杂交)骨架序列并募集内切核酸酶至靶核酸。

[0383] 在一些实施方案中,gRNA序列与靶核酸至少50%、55%、60%、65%、70%、75%、80%、85%、90%、95%、96%、97%、98%、99%或至少100%互补(亦参见美国专利8,697,359,其通过引用并入,以教导gRNA序列与靶多核苷酸序列的互补性)。已证实,在靶核酸3'末端附近CRISPR指导序列和靶核酸之间的错配可废除核酸酶切割活性(Upadhyay等人,Genes Genome Genetics (基因基因组遗传学) (2013) 3 (12):2233-2238)。在一些实施方案中,gRNA序列与靶核酸的3'末端(例如,靶核酸的3'末端的最后5、6、7、8、9或10个核苷酸)至少50%、55%、60%、65%、70%、75%、80%、85%、90%、95%、96%、97%、98%、99%或至少100%互补。

[0384] 本文提供了示例性sgRNA序列,包括修饰和未修饰的sgRNA,其靶向T细胞受体 α 恒定 (TRAC) 基因。如本领域普通技术人员显而易见的,sgRNA序列的选择可取决于这样的因素,例如预测的在靶和/或脱靶结合位点数量。在一些实施方案中,sgRNA序列被选择成以最大化潜在的在靶位点和最小化潜在的脱靶位点。

[0385] 在一些实施方案中,Cas内切核酸酶是Cas9核酸酶(或其变体)或Cpf1核酸酶(或其变体)。Cas9内切核酸酶切割靶核酸的双链DNA,导致平端,而用Cpf1核酸酶切割导致核酸的

交错末端。

[0386] 通常,靶核酸在3'侧或5'侧侧接前间隔序列邻近基序(PAM),其可与内切核酸酶相互作用并进一步参与将内切核酸酶活性靶向靶核酸。通常认为侧接靶核酸的PAM序列依赖于内切核酸酶和内切核酸酶所衍生的来源。例如,对于衍生自酿脓链球菌的Cas9内切核酸酶,PAM序列是NGG,尽管PAM序列NAG和NGA可以较低效率识别。对于衍生自金黄色葡萄球菌的Cas9内切核酸酶,PAM序列是NNGRRT。对于衍生自脑膜炎奈瑟氏菌的Cas9内切核酸酶,PAM序列是NNNGATT。衍生自嗜热链球菌的Cas9内切核酸酶,St1Cas9和dSt3Cas9,PAM序列分别是NNAGAAW和NGGNG。对于衍生自齿垢密螺旋体的Cas9内切核酸酶,PAM序列是NAAAAC。在一些实施方案中,Cas内切核酸酶是Cpf1核酸酶。与Cas9内切核酸酶相反,Cpf1内切核酸酶通常不需要tracrRNA序列并识别位于靶核酸的5'末端的PAM序列。对于Cpf1核酸酶,PAM序列是TTTN。在一些实施方案中,Cas内切核酸酶是MAD7(亦称为来自直肠真杆菌的Cpf1核酸酶),并且PAM序列是YTTTN。

[0387] 在一些实施方案中,遗传改造细胞还包括引入Cas内切核酸酶或编码其的核酸序列(例如,编码Cas内切核酸酶的mRNA)至细胞中。在一些实施方案中,Cas内切核酸酶和编码gRNA的核酸在同一核酸(例如,载体)上提供。在一些实施方案中,Cas内切核酸酶和编码gRNA的核酸在不同的核酸(例如,不同的载体)上提供。在一些实施方案中,Cas内切核酸酶作为编码Cas内切核酸酶的mRNA提供,以及gRNA作为修饰的gRNA分子提供。备选地或另外,Cas内切核酸酶可以蛋白形式提供或引入细胞中。

[0388] 在一些实施方案中,Cas内切核酸酶是Cas9酶或其变体。在一些实施方案中,Cas9内切核酸酶衍生自酿脓链球菌、金黄色葡萄球菌、脑膜炎奈瑟氏菌、嗜热链球菌或齿垢密螺旋体。在一些实施方案中,编码Cas内切核酸酶的核苷酸序列可经密码子优化以在宿主细胞中表达。在一些实施方案中,内切核酸酶是Cas9同系物或直向同源物。

[0389] 在一些实施方案中,编码Cas9内切核酸酶的核苷酸序列经进一步修饰以改变蛋白的活性。在一些实施方案中,Cas9内切核酸酶已被修饰以失活内切核酸酶的一个或多个催化残基。在一些实施方案中,Cas9内切核酸酶已被修饰以失活内切核酸酶的催化残基的其中一个,称为“切口酶”或“Cas9n”。Cas9切口酶内切核酸酶切割靶核酸的一条DNA链。在一些实施方案中,本文所述的方法包括两个不同的切割反应,其中一种Cas9切口酶针对切割靶核酸的一条DNA链,以及Cas9切口酶针对切割靶核酸的第二条DNA链。

[0390] (iv) MHC-CAR调节性T细胞(Treg)

[0391] 本文公开的任何表达MHC-CAR的T细胞可以是调节性T细胞(Treg),其可模拟滤泡调节性细胞的免疫调节活性。如本文使用的,调节性T细胞或Treg细胞,其亦称为抑制性T细胞,是指调节免疫系统、维持对自身抗原的耐受性和/或防止自身免疫性疾病的T细胞亚群。Treg细胞用作免疫抑制剂以抑制或下调效应T细胞(例如参与自身免疫性疾病的病理性CD4⁺和/或CD8⁺细胞)的诱导和/或增殖。

[0392] 本文公开的遗传修饰的Treg细胞表达在自然中与Treg细胞相关的一种或多种生物标志物,例如CD4、FOXP3、CD25、CD45R(例如,CD45RA或CD45RO)或其组合。Treg细胞可使用(衍生自)从合适的供体(例如,经治疗的人患者)分离的外周血单核细胞(PBMC)来制备。用于从PBMC分离Treg细胞亚群的方法是本领域众所周知的,例如细胞分选。合适的MHC-CAR构建体以及其它遗传修饰(例如,本文所述的那些)的表达载体可通过本文所述的方法或本

领域已知的其它方法引入Treg亚群。或者,遗传修饰的Treg细胞可通过引入编码CD25和/或其它Treg细胞标志物的转基因至合适的T细胞来制备,所述细胞可进一步被修饰以引入对于MHC-CAR和任选本文所述的其它遗传修饰的表达盒。

[0393] 在一些实施方案中,遗传修饰的Treg细胞可进一步被修饰,以展示(例如,表面表达或表面附着)靶向特定类型的病理细胞(例如,CD4⁺细胞或CD8⁺细胞)的分子,和/或展示靶向特定组织位点(例如,淋巴结或炎症位点)的分子。

[0394] 在一些实例中,遗传修饰的Treg细胞进一步表达嵌合受体(CAR),其包含胞外结构域,例如对B细胞表面标志物(例如CD19)特异性的单链抗体(scFv)。备选地或另外,Treg细胞可进一步表达嵌合受体,其包含对T细胞表面标志物(例如CS-1)特异性的胞外结构域(例如,scFv)。这样的嵌合受体可以是细胞-表面受体,其包含胞外结构域、跨膜结构域和胞质结构域(例如,包含共刺激结构域、例如CD3 ζ 的胞质信号传导结构域或其组合)的组合,其天然不一起存在于单一蛋白上。

[0395] Treg细胞可进一步展示靶向淋巴结和/或生发中心的分子,例如CXCR5,和/或展示靶向炎症位点的分子,例如CCR6。靶向生发中心B细胞(GC B细胞)可至少部分地通过专门的辅助T细胞子集,CXCR5^{high}PD-1^{high} T滤泡性辅助(TFH)细胞介导。Foxp3⁺Treg可通过表达Bcl6和SAP-介导的与B细胞的相互作用,而被转换为TFH抑制物。得到的滤泡性调节性T细胞(TFR)预期共享TFH和Treg细胞二者的特征,位于生发中心,以及体内调节TFH细胞群和生发中心的规模。

[0396] 此外,本文公开的Treg细胞可包括本文所述的一种或多种另外的遗传修饰,例如检查点分子敲除。

[0397] 表达B-细胞或T-细胞特异性CAR的Treg细胞可靶向参与自身免疫性疾病的病理性B细胞和/或T细胞。例如,本文所述的遗传修饰的Treg细胞将预期显示类似于滤泡性调节性细胞的功能,例如,靶向B细胞、T细胞和/或树突细胞,从而例如下调B细胞刺激,分泌可抑制生发中心活化的抑制性细胞因子(GCB细胞(例如IL-10和TGF- β),诱导Tfh(通过MHC CAR)和GC B(例如,通过CD19 CAR)的细胞溶解,和/或机械破坏至GC B细胞或T滤泡性辅助(Tfh)细胞的信号转导(例如,通过结合GC B和MHC-肽Tfh)。备选地或另外,Treg细胞可潜在地接合辅助T细胞、B细胞和/或抗原呈递细胞,或在一些情况下,物理阻断接合。

[0398] III. 表达MHC-CAR的免疫细胞在免疫疗法中的应用

[0399] 表达本文所述的MHC-CAR(编码核酸或包含其的载体)的宿主免疫细胞可用于靶向和消除参与自身免疫性疾病的病原性细胞,所述疾病例如MS、I型糖尿病、狼疮、类风湿性关节炎等。在一些实施方案中,受试者是哺乳动物,例如人、猴、小鼠、兔或驯养哺乳动物。在一些实施方案中,受试者是人,例如具有、疑似具有或有风险发生自身免疫性疾病(例如,MS)的人患者。

[0400] 表达MHC-CAR的免疫细胞可与药学上可接受的载体混合以形成药物组合物,其也在本公开的范围内。为了进行本文所述的方法,可给予需要治疗的受试者有效量的表达本文所述的任何MHC-CAR构建体的免疫细胞。免疫细胞可以对受试者是自体的,即免疫细胞获自需要治疗的受试者,经遗传改造以表达MHC-CAR构建体以及任选地含有本文所述的一种或多种另外的遗传修饰,然后给予同一受试者。与给予非自体细胞相比,给予自体细胞至受试者可导致减少免疫细胞的排斥。或者,免疫细胞是同种异体细胞,即细胞获自第一受试

者,经遗传改造以表达MHC-CAR构建体,并给予不同于第一受试者但是相同物种的第二受试者。例如,同种异体免疫细胞可衍生自人供体并给予不同于供体的人受体。

[0401] 在一些实施方案中,免疫细胞与目标免疫疾病的治疗剂(例如用于治疗MS的阿仑单抗)共同使用。这样的免疫疗法用于治疗、减轻或降低目标免疫疾病的症状,对于所述疾病,认为免疫疗法可用于受试者。

[0402] MHC-CAR免疫疗法的功效可通过本领域已知的任何方法评价并且对于医学专业技术人员将是显而易见的。例如,免疫疗法的功效可通过受试者的存活率和/或受试者中疾病症状的减轻来评价。

[0403] 在一些实施方案中,将表达本文公开的任何MHC-CAR的免疫细胞给予已用自身免疫性疾病的治疗剂治疗或正在用自身免疫性疾病的治疗剂治疗的受试者。表达本文公开的任何一种MHC-CAR的免疫细胞可与治疗剂共给予。例如,免疫细胞可与治疗剂同时给予人受试者。或者,免疫细胞可在包括治疗剂的治疗过程期间给予人受试者。在一些实例中,免疫细胞和治疗剂可以至少4小时间隔给予人受试者,例如,至少12小时间隔、至少1天间隔、至少3天间隔、至少1周间隔、至少2周间隔或至少1个月间隔。

[0404] 为了实施本文公开的方法,有效量的表达MHC-CAR的免疫细胞或其组合物可通过合适途径给予需要治疗的受试者(例如,人MS患者),例如静脉内给予。任何表达MHC-CAR的免疫细胞或其组合物可以有效量给予受试者。如本文使用的,有效量是指在给予时赋予受试者治疗效果的相应试剂(例如,表达MHC-CAR的免疫细胞或其组合物)的量。确定本文所述的细胞或组合物的量是否实现治疗效果,对于本领域技术人员是显而易见的。如本领域技术人员所认识到的,有效量在医疗从业人员的知识和专业内根据治疗的具体病况、病况的严重性、个体患者参数(包括年龄、身体情况、大小、性别和重量)、治疗持续时间、同时疗法(如果有的话)的性质、具体给予途径等因素而改变。在一些实施方案中,有效量在受试者中减轻、缓解、改善、改进、降低任何疾病或病症的症状,或延迟任何疾病或病症的进展。在一些实施方案中,受试者是人。在一些实施方案中,受试者是人癌症患者。

[0405] 在一些实施方案中,受试者是患有自身免疫性疾病的人患者,所述疾病的特征在于攻击正常身体部分的异常免疫反应。自身免疫性疾病的实例包括多发性硬化、系统性红斑狼疮、类风湿性关节炎、幼年特发性关节炎(亦称为幼年特发性关节炎)、斯耶格伦氏综合征、系统性硬化症、强直性脊柱炎、1型糖尿病、自身免疫性甲状腺病(格雷夫氏病和桥本氏病)、多发性硬化、重症肌无力、炎症肠病(克罗恩氏病或溃疡性结肠炎)、银屑病或表1中提及的疾病。

[0406] 免疫级联中存在许多阶段,其中通常可影响自身免疫性疾病。本文公开的方法包含的编辑组合可能进行连续干预。例如,除了MHC-CAR外还展示一组不同的表面分子的Treg细胞可用于治疗不同阶段的自身免疫性疾病。

[0407] 在许多免疫病症(包括MS)的早期阶段,调节机制存在无法解释的缺陷和/或MS中存在耐受性诱导,并且由T细胞开始重复攻击神经系统。表达合适的MHC-CAR和抗-CD19 CAR(任选地具有本文所述的其它遗传修饰)的Treg细胞可用于干预。

[0408] 自身反应性Treg细胞的益处是它们充当“旁观者”抑制剂,在响应由受影响组织局部表达的同源抗原时以位点特异性方式消除炎症的能力。调节性T细胞的诱导(通过自身抗原)可抑制疾病进展,甚至当存在各种自身抗原时(或者当启动/初始自身抗原未知时)。

Treg可相对自由地移动,以及抑制T细胞和B细胞并防止回到炎性环境。这些自身反应性Treg在其充当旁观者抑制剂和在响应由受影响组织局部表达的同源抗原时以位点特异性方式消除炎症的能力方面是有利的。

[0409] 因此,遗传修饰的Treg细胞可被设计成模拟自身反应性Treg细胞的抑制剂功能。这样的Treg细胞可被修饰成例如使PD-L1/PD-1敲除,展示CCR6和/或靶向MOG的scFv以传送到炎症位点,表达合适的MHC-CAR和/或抗-CD19-CAR。或者,Treg细胞可修饰成例如使PD-L1/PD-1敲除,展示CXCR5以传送到生发中心和/或异位淋巴结,表达合适的MHC-CAR和/或抗-CD19-CAR。这些类型的Treg细胞可与炎症位点的病原性细胞相互作用,阻断病原性相互作用和/或平静炎性环境。它们可在早期疾病阶段(以抑制病原性)或在细胞毒性疗法后(以防止返回炎性环境)使用。

[0410] 复发-缓解性MS(中期)自然调节本身,以及增强这些自然调节性机制的治疗将有助于控制疾病过程。在成功的疾病治疗中,存在从Th1细胞到Th2和Th3细胞的变化,以及其它调节性细胞的出现。在该阶段,治疗靶标将包括病原性B细胞和病原性T细胞二者。用于治疗这样的中期疾病的Treg细胞可表达本文所述的合适的MHC-CAR,以及靶向B细胞(例如,抗-CD19 CAR)或靶向例如CD8+细胞的T细胞的另外的CAR。Treg细胞可进一步展示CXCR5或不含CXCR5靶向。表达抗-CD19 CAR的Treg细胞可用于消除生发中心中的B细胞。

[0411] 当MS从复发缓解性向慢性进行性形式(后期)变化时,T细胞进入慢性活化状态和退化过程发生。针对细胞毒性CD8+T细胞的侵袭性治疗需要足够细胞毒性的CAR加强。在该点上,治疗可从主要由Treg细胞驱动的治疗变化为由MHC-CAR CD8+T细胞以及甚至MHC-CAR CS-1细胞驱动的治疗。最终目的仍相同:通过由旁观者效应增强的细胞毒性抑制病理。在该疾病阶段使用的遗传改造的T细胞可表达合适的MHC-CAR,以及另外的CAR,其靶向参与疾病后期的病理性T细胞,例如CD8+T细胞。在一些实例中,另外的CAR可靶向CS-1(亦称为SLAMF7),其为在CD8+T细胞上表达的糖蛋白。CS1是可用于靶向和杀死CD8+T细胞和浆细胞的有希望的抗原。CS1-CAR T细胞分泌更多IFN- γ 以及IL-2,表达更高水平的活化标志物CD69,更高的脱粒能力和展示增强的细胞毒性。抗-CS1 CAR将靶向CD8+T-细胞。遗传修饰的T细胞可进一步展示用于浆细胞的骨髓靶向的分子,例如CXCR4,以及它们用CXCR3靶向发炎组织。Hiepe等人,Nature Reviews Rheumatology(自然评论风湿病),7(3):170-178,2011。实例包括在狼疮中浆细胞的靶向。

[0412] IV. 治疗用途的试剂盒

[0413] 本公开还提供了使用表达MHC-CAR的免疫细胞的试剂盒,用于在自身免疫中抑制病原性免疫细胞,例如自身反应性T细胞。这样的试剂盒可包括一个或多个包含组合物的容器,所述组合物包含表达MAR-CAR的免疫细胞(例如本文所述的那些)和药学上可接受的载体。

[0414] 在一些实施方案中,试剂盒可包含本文所述的任何方法的用法说明。包括的用法说明可包含将表达MHC-CAR的免疫细胞给予需要治疗的受试者(例如MS患者)的描述。试剂盒可进一步包含根据鉴定受试者是否需要治疗来选择适合治疗的受试者的描述。在一些实施方案中,用法说明包含给予需要治疗的受试者免疫细胞的描述。

[0415] 涉及使用表达本文所述的MHC-CAR的免疫细胞的用法说明通常包括关于对预期治疗的剂量、给药方案和给予途径的信息。容器可以是单位剂量、散装包装(例如多剂量包装)

或亚单位剂量。本公开的试剂盒中提供的用法说明通常是在标签或包装插页上的书面用法说明。标签或包装插页指示药物组合物用于治疗受试者的疾病或病症、延迟其发作和/或减轻受试者的疾病或病症。

[0416] 本文提供的试剂盒在合适的包装中。合适的包装包括但不限于小瓶、瓶、罐、柔性包装等。还预期与特定装置组合使用的包装。试剂盒可具有无菌存取口(例如,容器可以是静脉内溶液袋或具有通过皮下注射针可穿刺的塞子的小瓶)。容器也可具有无菌存取口。药物组合物中至少一种活性剂是本文所述的表达MHC-CAR的免疫细胞。

[0417] 试剂盒任选地可提供另外的组分,例如缓冲液和解释信息。通常,试剂盒包含容器和在容器上或伴随容器的标签或包装插页。在一些实施方案中,本公开提供了包含上述试剂盒的内容物的制品。

[0418] 无需进一步确定,认为本领域技术人员根据上文描述可最充分程度地利用本发明。因此以下具体实施方案应解释为仅是说明性的,并且无论如何不以任何方式限制本公开的剩余部分。本文引用的所有出版物为本文提及的目的或主题通过引用并入。

[0419] 实施例

[0420] 本实施例关注利用嵌合受体以针对参与MS的髓磷脂碱性蛋白(MBP)特异性T淋巴细胞使治疗性T细胞选择性重定向,开发细胞免疫疗法[16]。该程序的结果可支持进一步开发能够抵消病理性的自特异性T淋巴细胞的重定向治疗性T细胞,以及特别地验证了人源化MBP-DR2-嵌合受体作为MS的治疗靶标[29]。

[0421] 实施例1:对髓磷脂碱性蛋白特异性的修饰的T-细胞的构建

[0422] 靶向MBP-加载的主要组织相容性复合物-嵌合抗原受体(MHC-CAR)的抗原特异性T-细胞受体(TCR)的构建体被设计成用于重新引入具有TCR敲除的细胞,以进行试验。TCR构建体的设计是基于具有公布的结构抗原特异性TCR和在细胞系中验证的TCR表达构建体[17,46,51,52]。绿色荧光蛋白(eGFP)或萤光素酶基因编码用于标记[28]。包含TCR构建体和报告基因的示例性慢病毒表达载体在图1中提供。

[0423] 选择若干个细胞系用于测试TCR表达和活性,包括Jurkat E6-1(表达TCR的对照株)、Jurkat J.RT3-T3.5(缺少TCR β 的细胞株)、SupT1(具有破坏的TCR α 的细胞株)和原代人T细胞(其含有TCR克隆型的各种群)。

[0424] Jurkat E6-1细胞是来自外周血的已建立的人T淋巴细胞细胞系。其用作表达TCR的对照细胞系[15,18]。

[0425] Jurkat RT3-T3.5由于排除TCR β -链的表达的突变而缺少TCR β 。它也不能表达表面CD3或产生T-细胞受体 α , β 异源二聚体。因此,其用于验证T-细胞受体基因转移[1,6,21,49]。

[0426] SupT1是表达多种T谱系标志物的人成淋巴细胞系,以及因为它编码无功能受体并且不能表达TCR α 而被使用[49]。

[0427] PMBC-衍生的原代人T细胞含有TCR克隆型的各种库。

[0428] 如图1所示的含有抗原特异性TCR的慢病毒载体用于转导缺少至少一条TCR链的癌细胞系,以及随后使用荧光-活化细胞分选(FACS)评价表达。在含有抗原特异性TCR的癌细胞系中,在成功稳定的表达后萤光素酶被加入细胞系以使其能够用于小鼠研究。

[0429] 通过根据遗传编码的eGFP和用抗-TCR或抗-CD3抗体标记进行筛选,用于mRNA、多

顺反子mRNA和慢病毒转导的TCR构建体直接继续进行[3,19]。

[0430] 实施例2:基于MHC的嵌合受体(MHC-CAR)和表达其的T-细胞的构建

[0431] (i) MHC-CAR构建体的设计

[0432] 产生用于继承性细胞疗法的受体,其将MBP 84-102表位遗传连锁至人白细胞抗原HLADR2,并且掺入或缺少嵌合细胞内信号传导结构域[29]。抗原-主要组织相容性复合物(Ag-MHC)结构域用作受体,结合MBP特异性靶细胞的TCR。按照[9,25]中提供的方法,Ag-MHC-CAR已在临床前小鼠模型中用CD3- ζ (即第一代信号传导结构域)验证,其可任选地与另外的共刺激信号传导结构域(即第二代或第三代信号传导结构域)组合用于在人中的功效。MHC-CAR的各种设计的示意图在图2中提供。

[0433] MHC-CAR根据HLA-DR的结构设计,并且与各种内部胞质共刺激结构域组合。MHC-CAR具有两个亚单元:(i)含有前导序列、DRA*1010结构域和胞质结构域的 α -链;以及(ii)含有前导序列(来自HLA-DRB1*1501)、肽(来自髓磷脂碱性蛋白的DENPVVHFFKNIVTPRTPP(SEQ ID NO:15))、结构域(来自HLA-DRB1*1501)和例如CD3 ζ 的胞质信号结构域的 β -链[29]。图3。用于产生mRNA的DNA含有单链(如图4的一个实施方案所示)或是多顺反子的并且由正交2A序列分开,如图5所示。遗传编码的eBFP或RQR8被引入至细胞中用于细胞标记或提供损耗机制[4,5,37,40]。图3和5。

[0434] 如图6所示,设计的MHC-CAR具有许多标记用位点。位点1是对于其中天然HLA-DR由于CIITA编辑而不表达的情况的HLA-DR抗体结合位点[26,38]。位点2和3是对于多组氨酸-标签基序的潜在插入位点[24]。位点4和5分别表示RQR和RQR8[37]。多发性硬化显示影响血脑屏障渗透性,因此为了增强治疗性MHC-CAR的安全性,遗传编码的RQR将允许在给予利妥昔单抗后快速损耗MHC-CAR T细胞,利妥昔单抗为在重度MS治疗中标签外使用的嵌合单克隆抗体治疗[42]。

[0435] (ii) 表达MHC-CAR的T细胞系的构建

[0436] 选择下面论述的许多细胞系,以测试MHC-CAR构建体。然后,在人T细胞中继续试验,以建立临床上可转移的方案。

[0437] K56细胞缺少I类和II类MHC,允许使用抗体进行HLA-DR表达的无标签验证(HLA-DR是MHC-CAR的组分)[45]。表达测定允许使用流式细胞术评价相对于RQR8表达的MHC-CAR表达,以及相同的慢病毒构建体然后被用于PMBC-衍生的T细胞[23]。

[0438] KM-H2是人霍奇金淋巴瘤细胞系,其可用作HLA-DR阳性对照系[34,44]。如上所述,在递送CIITA时,Jurkat E6-1有条件地表达HLA-DR,并且如果使用CIITA敲除,可用于评价CIITA TALEN[33]。

[0439] 此外,可使用原代人T细胞。PMBC-衍生的原代人T细胞从全血中纯化和富集,然后活化。转导允许富集。细胞用重组人白介素-2(和/或IL-7和/或IL-15)孵育[7,12,43]。根据临床前研究和预期的治疗过程,所需的细胞类型是CD8⁺T细胞,具有干细胞记忆TSCM、中央记忆TCM和幼稚细胞TN的分子和功能特征[11,22,32,35]。抗体染色允许细胞免疫分型[27]。

[0440] 使用mRNA、多顺反子mRNA和慢病毒策略在K562细胞中表达初始构建体,包括信号传导结构域(CD3 ζ ,41BB,CD28)的变更。细胞系缺少MHC I类和II类允许按照成功使用的策略,使用HLA-DR抗体无标签验证MHC-CAR表达[29]。在更加临床相关的细胞系(包括治疗性T

细胞)中表达效率的定量取决于构建体,并且将使用遗传编码的荧光报告子(BFP)或抗体染色RQR位点、多组氨酸-(HIS)-标签或MHCCAR(如果CIITA使用TALEN失活,用HLA-DR抗体)进行测量。标记位点在图6中指示。为了测试MHC-CAR作为潜在的治疗载体的递送速率,BFP被从构建体除去,而RQR被保留以提供损耗对照。临床相关构建体的表达速率使用抗体染色后-编辑进行测量。

[0441] 转录激活物样效应物技术(TALEN)也可用于制备表达MHC-CAR的T细胞。人T细胞系被活化,用TALEN转染和用MHC-CAR转染或转导。它们然后被染色和通过流式细胞术分析以评价TALEN基因失活和MHC-CAR表达。在所需的细胞系中验证构建体表达后,进行TALEN转导(TCR α 和CD52或CIITA,如下面所述)至人T细胞系。将TALEN引入活化的人T细胞系中,以及将MHC-CAR随后引入相同的T细胞系中,用于评价。可进行人T细胞的修饰,以防止由于天然TCR导致的MHC修饰细胞的偶然同族互杀[10]。将证实TALEN-编辑的MHC-CAR T-细胞的活性。

[0442] (iii) 表达MHC-CAR的T细胞通过转录激活物样效应物(TALEN)的修饰

[0443] 选择人T细胞以证实通过TALEN导致的TCR α 和CD52或CIITA基因的失活,接着与MHC-CAR组合使用TALEN进行评价。转录激活物样效应物(TALEN)以序列特异性方式结合DNA。DNA结合结构域含有高度保守的33-34个氨基酸序列,其中分叉2氨基酸RVD(重复可变二肽基序)赋予特异性核苷酸识别[23,31]。

[0444] TCR的 α 或 β 链的突变足以破坏表面TCR表达[15,36]。在通过不需要的易位没有引入增殖性优势的情况下,TALEN用于抑制在治疗性细胞中两个基因的表达[39][47]。通过TRAC-靶向的TALEN抑制TCR表达,以防止移植物抗宿主病(GvHD)并允许产生同种异体疗法[15,39,47]。

[0445] 为了阿仑单抗相容性,可进行CD52缺失。阿仑单抗是人源化抗-CD52 IgG1单克隆抗体,其靶向和损耗循环T和B淋巴细胞[41]。阿仑单抗可在重度发作MS中用作拯救疗法或第一线药物[50],并在人患者群中共给予。TALEN敲除使得MHC-CAR与患者中的同时治疗相容[14,39]。此外,可进行CIITA缺失以表征MHC-CAR中的HLA-DR。CIITA是对于HLA II类启动子的转录活性所必需的蛋白编码基因[26]。敲除将允许使用抗体直接测量HLA-DR,以表征MHC-CAR表达[38,53]。CD52表达的抑制允许与Lemtrada R(阿仑单抗)的同时治疗,Lemtrada R为FDA批准的用于多发性硬化的治疗[42]。阿仑单抗还用作淋巴-损耗/淋巴-抑制剂,其帮助CAR T疗法的移入[39]。用TRAC-和CD52-靶向的TALEN修饰的CAR T-细胞疗法目前正在临床试验中测试[38,40,43]。

[0446] 代替CD52,TALEN失活MHC II类反式激活蛋白(CIITA),因为失活CIITA预期抑制HLA-DR表达[26][38],从而允许通过HLA-DR抗体染色直接鉴定含有MHC-CAR的细胞。验证的TALEN(TRAC):

TTGTCCCACAGATATCCagaaccctgaccctgCCGTGTACCAGCTGAGA (SEQ ID NO: 376), CD52:TTCCTCCTACTCACCATcagcctcctggttatGGTACAGGTAAGAGCAA (SEQ ID NO: 371), CIITA: TTCCCTCCCAGGCAGCTCacagtgtgccaccaTGGAGTTGGGGCCCCTA (SEQ ID NO: 366)

[0448] 获自Cellestis或被设计成靶向之前验证的位点[38,43]。

[0449] 人T细胞被活化和用编码3种不同TALEN的变体的mRNA电穿孔:TCR- α 恒定链、CD52和CIITA。细胞用抗-CD3或抗-TCR(TCR- α 恒定链)、抗-CD52(CD52)或抗-HLA-DR(CIITA)进行

表面染色,然后通过流式细胞术分析。

[0450] 在TALEN表达试验中,之前验证的TALEN失活靶基因的能力被再次验证[39]。易位研究和脱靶研究被再次进行,并且若干个全基因组序列证实结果。GUIDE-seq可用作全基因组测序的备选方案,以证实在靶和脱靶编辑[8]。

[0451] 一个或多个以下内源性基因将被编辑,以降低与其它细胞的相互作用:TCR(通过TCR α 或 β 链;以减少靶向不需要的细胞)、CIITA(调节MHC II类基因的表达;用于尝试者缺失的靶细胞)、B7-1(CD80)和/或B7-2(CD86)敲除、以及b2m(调节MHC I类基因的表达)带有NKG2D配体或UL18。

[0452] 此外,一个或多个以下基因可被编辑以修饰相互作用细胞的功能:PD-L1+/-CTLA4-Ig过表达;PD-L1/2过表达+/-PD-1敲除;FasL过表达+/-Fas敲除;半乳凝素9过表达+/-TIM3敲除;和/或PVT/CD155过表达+/-TIGIT敲除。PD-1、Fas、TIM3、TIGIT的缺陷使患者易患自身免疫。一些药物可恢复功能(例如:Tim3、醋酸格列默和IFN- β)。如果使用来自患有自身免疫性疾病的患者的自体细胞,它们可能需要缺陷基因的患者特异性纠正,该缺陷基因影响CTL和Treg功能。它们的个人突变集也可确定CTL或Treg细胞是否是最治疗相关的,以及一些细胞修饰是否是有效的,如果使用自体或同种异体细胞的话。

[0453] 此外,以下编辑可修饰细胞的位置和/或功能(例如,使其更像滤泡性调节性细胞):

[0454] -MHC-CAR-(FOX3P)-(CS1或CD19 CAR)/(对于CS-1 CAR所需的CS-1敲除)

[0455] -MHC-CAR-(FOX3P)-(CCR7或CXCR5)

[0456] 此外,以下编辑可能使组合疗法用于自身免疫性疾病(例如,MS特异性疗法)

[0457] -RQR标签:改造的T细胞可用利妥昔单抗(杀伤开关)除去。可产生用于新批准的抗-CD20抗体Ocrevus的标签。

[0458] -雷帕霉素开关:CAR仅当患者用雷帕霉素(他克莫司)治疗时失活/激活(in/active)

[0459] -CD52敲除:允许用Lemtrada(阿仑单抗)预处理以降低存在的免疫细胞的数量

[0460] -VLA-4敲除:可用那他珠单抗(tysabri)治疗以移动病原性免疫细胞至周围,但改造的细胞被迫使留在那里(对于具有确立的MS的患者可能不是理想的,因为细胞粘附在脑脊髓中;然而,VLA-4的同时mRNA表达可提供临时接近那些位置)

[0461] -IL-6抗体(Tocilizumab)从改造的T细胞分泌:当改造的T细胞必须接近脑和脊髓时有帮助,但该药物由于BBB而不能接近该位置。

[0462] 实施例3:MHC-CAR活性的研究

[0463] (i) 表达MHC-CAR的原代T细胞的制备

[0464] 原代T细胞可如下制备。T细胞从外周血单核细胞分离(EasySep Human T Cell Enrichment Kit, Stemcell Technologies (EasySep人T细胞富集试剂盒, Stemcell技术公司))以及用(X-Vivo 15培养基, Lonza; 20mg/ml IL-2, Miltenyi; 5%人AB血清, Seralab)活化(Dynabeads Human T-Activator CD3/CD28, Life Technologies (Dynabeads人T激活剂CD3/CD28, 生命技术))。使用常规方法将含有MBP抗原肽的合适的MHC-CAR构建体引入原代T细胞中。MHC-CAR构建体的表面表达通过FACS和抗体染色验证。

[0465] (ii) MHC-CAR活性体外测试

[0466] 在验证构建体运输和表达(用mRNA、多顺反子mRNA、慢病毒)后,进行体外活性测试。以不同的效应物:靶(E:F)细胞浓度进行所有测试。体外测试提供了MHC-CAR信号传导结构域和T细胞子集的初始评价。

[0467] (iii) 通过IL-2产生评价信号传导结构域

[0468] 电穿孔后24小时,用MHC-CAR瞬时改造的人T细胞用板结合的HLA-DR抗体进行刺激,以确定MHC-CAR(含有各种信号传导结构域)是否具有功能。之后24小时使用StemCell IL-2ELISA试剂盒测量IL-2产生。该测试提供了关于变体应被再改造还是放弃的快速试验[29]。

[0469] (iv) 通过增殖试验的MHC-CAR细胞和病原性TCR细胞的相互作用

[0470] 电穿孔后24小时,瞬时表达TCR的靶细胞系经磁分选以进行TCR表达并经照射,以测试MHC-CAR与抗原特异性TCR的接合是否刺激含有MHC-CAR的T细胞的增殖。或者,稳定表达TCR的靶细胞系被照射。展示(+/-抗原特异性)TCR的照射的细胞用CFSE-标记的MHCCAR细胞孵育,并在以不同的T:E比率培养后,测量增殖[30]。

[0471] (v) 脱粒试验

[0472] CAR T-细胞通过RQR(其不在使用的靶细胞上表达)上的表位或eBFP代替T细胞标志物进行标记。对具有瞬时或稳定表达的细胞系进行试验(描述瞬时表达的实施例)。电穿孔后24小时,具有RQR8或BFP的MHC-CAR人T-细胞与靶(抗原特异性TCR SupT1或Jurkat)或对照(+/-TCR Jurkat或TCR-SupT1)细胞共培养6小时。瞬时表达(和随后稳定表达)的靶细胞用抗原特异性TCR电穿孔,以及电穿孔后用CD3磁珠分选。RQR+或BFP+MHC-CAR T-细胞(用抗-利妥昔单抗抗体,QBEnd10抗体鉴定)通过流式细胞术分析,以检测脱粒标志物CD107a在其表面上的表达[2]。

[0473] (vi) 细胞因子分泌试验

[0474] 对于具有瞬时或稳定表达的细胞系进行试验(描述瞬时表达)。电穿孔后24小时,在与靶细胞共培养后,评价瞬时表达MHC-CAR的人T细胞的细胞因子分泌。瞬时表达MHC-CAR的人T细胞与靶(含有抗原特异性TCR的Jurkat或SupT1细胞)或对照(+/-非抗原特异性Jurkat或SupT1)细胞共培养24小时。然后,通过照射杀死抗原特异性TCR,然后试验。收获上清液和使用TH1/TH2细胞因子细胞计数珠阵列试剂盒分析,以定量由T细胞产生的细胞因子[13]。在与表达抗原特异性TCR的靶细胞的共培养中但不在与对照细胞的共培养中,MHC-CAR T-细胞产生IFN和其它细胞因子。

[0475] (vii) IFN γ 释放试验

[0476] 转染后24小时,各种水平的表达MHC-CAR的细胞与照射的TCR T-细胞一起孵育。共培养维持24小时。孵育和离心后,通过ELISA以IFN γ 检测测试上清液。

[0477] (viii) 细胞毒性试验

[0478] TCR T-细胞与治疗性MHC-CAR以及对照细胞一起孵育。靶细胞和对照细胞用荧光细胞内染料(CFSE或Cell Trace Violet(细胞追踪紫))标记,然后与MHC-CAR T-细胞共培养。共培养孵育4小时。该孵育期之后,细胞用可固定成活力染料标记并通过流式细胞术分析。测定各细胞群(靶或阴性对照)的成活力,并计算特定细胞溶解的百分比。转导后48小时进行细胞毒性试验。

[0479] (ix) 抑制试验

[0480] PBMC与照射的或丝裂霉素处理的、表达MHC-CAR构建体的、改造的T细胞共培养。作为对照,PBMC与照射的或丝裂霉素处理的、不表达MHC-CAR构建体的、改造的T细胞共培养。7天后,来自人患者供体A的细胞增殖通过XTT比色测定或通过CFSE稀释(FACS分析)进行测量。尽管在对照中观察到细胞增殖,但当改造的T细胞表达分泌的FP时,预期没有细胞增殖或有限的细胞增殖。来自该实验的结果目的是显示当表达MHC-CAR的T细胞表达FP时,同种异体反应性T细胞增殖被抑制。

[0481] (x) 增殖

[0482] 为了测试MHC-CAR与抗原特异性TCR的接合是否刺激含有MHC-CAR的T细胞的增殖,电穿孔后24小时瞬时表达TCR的靶细胞系对TCR表达进行磁分选并被照射。或者,稳定表达TCR的靶细胞系被照射。展示(+/-抗原特异性)TCR的照射的细胞与CFSE-标记的MHC-CAR细胞一起孵育,并在以不同的T:E比率培养后,测量增殖。

[0483] (xi) 体内测试

[0484] 在小鼠T细胞中MHC-CAR(具有小鼠和人MHC)之前已经显示在实验性变应性脑脊髓炎(多发性硬化小鼠模型)中的治疗性功效[25,29]。这里,使用类似于在前的CAR T临床前研究的体内小鼠模型,测试人细胞中的MHC-CAR是否可靶向人T细胞系中的人TCR[39]。体内测试允许进一步评价MHC-CAR信号传导结构域和T细胞子集。

[0485] MHC-CAR-T细胞的体内活性可在小鼠异种移植物模型中验证,如图7所示。

[0486] 作为MS异种移植物小鼠模型,免疫缺陷NOG小鼠经静脉内注射表达抗原特异性TCR-萤光素酶的T-细胞。用肿瘤细胞系注射后2或7天,小鼠然后接受以不同剂量测试的静脉注射剂量的MHC-CAR T-细胞。静脉内注射未用CAR慢病毒载体转导的T-细胞用作对照。在T-细胞注射当天(D0)、T-细胞注射后D7、14、21、28和40,测定生物发光信号以跟踪在不同的动物中表达TCR-萤光素酶的细胞的扩增[39]。

[0487] 与此处显示的细胞具有类似背景修饰的CAR T-细胞(TALEN以失活天然TCR和最小化移植物抗宿主,TALEN以失活CD52并允许用阿仑单抗同时治疗,以及RQR8以允许损耗)之前已经在小鼠模型中验证,并且现在用于UCART19临床试验[39]。

[0488] (xii) 杀伤开关验证

[0489] 将转导的T细胞暴露于25%幼兔补体(AbD Serotec)4小时,包括或不包括药用补体(利妥昔单抗、tysabri或阿仑单抗),以检查补体依赖性细胞毒性(CDC)-介导的敏感性。Miltenyi CD34磁珠选择的转导RQR8 T-细胞与类似处理的Q8-转导T细胞群比较,以证实CDC-介导的缺失的特异性。使用与12.5、25、50和100mg/mL的药用补体孵育的RQR8-转导的T细胞,通过时程/剂量-滴定试验,以及范围为1-120分钟的时间点评价,进一步检查CDC试验参数。

[0490] 实施例4:表达MHC-CAR的调节性T细胞(Treg)

[0491] 与抗原-非特异性疗法相比,抗原特异性靶向病理性T淋巴细胞(负责多发性硬化和其它自身免疫性疾病)的疗法预期具有改进的治疗指数。该实施例提供了示例性细胞免疫疗法,其使用嵌合抗原受体以针对参与MS的髓磷脂碱性蛋白特异性T淋巴细胞选择性重定向治疗性T细胞。

[0492] Treg细胞分选、转导和扩增

[0493] CD4⁺T细胞通过RosetteSep(STEMCELL技术公司)从PBMC分离以及富集CD25⁺细胞

(Miltenyi生物技术公司),然后通过FACS分选为活的CD4+CD45RO-CD45RA+CD25+Treg和CD4+CD45RO-CD45RA+CD25-对照T细胞。分选的T细胞用加载有 α CD3 mAb的人工APC (aAPC) 在1,000U/ml或100U/ml的IL-2中进行刺激,分别用于Treg或非-reg对照T。之后一天,细胞用慢病毒转导。在第7天, Δ NGFR+细胞用磁选纯化(Miltenyi生物技术公司),然后用上述aAPC再次刺激和扩增6-7天。

[0494] 流式细胞术:

[0495] 对于表型分析,细胞用可固定成活力染料(FVD) (65-0865-14和65-0866-14, eBioscience) 染色,以及对于表面标志物在用FOXP3/转录因子染色缓冲液套盒(eBioscience)固定/渗透(perm)前,接着对细胞内蛋白染色。对于细胞因子产生的分析,用10ng/ml PMA和500ng/ml伊屋诺霉素,在布雷菲德菌素A(10 μ g ml) (全部Sigma-Aldrich)存在下,刺激细胞4小时。通过流式细胞术分析样品。

[0496] 显微术:

[0497] PBMC用PKH26或PKH67 (Sigma-Aldrich, PKH26GL-1KT和PKH67GL-1KT) 标记,以及Treg用细胞增殖染料(CPD) eFluor450 (eBiosciences, 65-0842-85) 标记,然后按照制造商的一般3D凝胶方案悬浮于由1 $\times$ DMEM和10%FCS组成的1.5%大鼠尾胶原蛋白I型(Ibidi)的3D凝胶中。将细胞悬浮液用移液管移到 μ -Slide Chemotaxis3D(μ -载玻片趋化作用3D)中,并允许在潮湿孵育箱中在35 $^{\circ}$ C和5%CO₂ (Tokai Hit) 下在Leica TCS SP8共焦显微镜上聚合30分钟。外室填充1 $\times$ DMEM以及使用 $\times$ 10/0.30物镜每2分钟记录图像,持续3小时。分别在405nm、488nm和561nm激发eFluor450、PKH67和PKH26,以及在415-470nm、495-525nm和570-650nm收集荧光发射。CAR-Treg和靶细胞或对照细胞之间的相互作用数量被每20分钟定量。不移动的细胞从分析中排除。每视野的各标记细胞类型的总数可使用ImageJ (imagej.nih.gov/ij/)的分析颗粒功能计算。

[0498] Treg特异性去甲基化区(TSDR)分析

[0499] 稳定的Foxp3的Treg稳定表达与在Foxp3基因座内TSDR的选择性去甲基化有关。为了测试稳定的表达,来自冷冻的T细胞团的DNA用DNeasy Blood and Tissue Kit (DNeasy血液和组织试剂盒) (QIAGEN) 分离,以及用EZ Direct Kit (EZ直接试剂盒) (Zymo Research) 进行亚硫酸氢盐转化。用Human FOXP3 Kit (人FOXP3试剂盒) (Epigen DX) 进行BisDNA的PCR并准备以使用PyroMark缓冲液(QIAGEN)进行焦磷酸测序,然后在Biotage PyroMark Q96 MD焦磷酸测序仪(QIAGEN)上测试。用Pyro Q-CpG软件(Biotage)计算结果。

[0500] 细胞因子产生

[0501] 为了测量细胞因子产生,T细胞系用K562细胞(1K562:2T细胞)刺激48小时。收集上清液和通过人Th1/Th2/Th17细胞因子试剂盒(BD Biosciences)测定细胞因子浓度并分析。

[0502] MHC CAR特异性增殖的抑制

[0503] 为了测试对靶标特异性的Treg是否也能够抑制CD4+T细胞增殖,分离了MHC CAR特异性CD4+T克隆。使用慢病毒用MHC-CAR转导EB病毒转化的B淋巴母细胞样细胞系。EBV细胞系生长过夜,以150Gy照射,以及在缺少或存在表达CAR的Treg或常规T细胞的情况下与CPD-标记的MHC CAR特异性CD4+T克隆共培养。4天后测定增殖,以及MHC CAR特异性克隆的抑制百分比使用增殖百分比如下计算: $(100 - [(\% \text{增殖的MHC CAR} + \text{测试}) / (\% \text{增殖的MHC CAR单独})] \times 100)$ 。

[0504] 在验证构建体运输和表达(用mRNA、多顺反子mRNA和/或慢病毒)后,活性测试在体外开始。以不同的效应物:靶(E:F)细胞浓度进行所有测试。体外测试预期提供MHC-CAR信号传导结构域和T细胞子集的初始评价。

[0505] T细胞中趋化因子和粘附受体的瞬时或慢病毒表达

[0506] 在单/多顺反子mRNA或慢病毒转导的电穿孔后,受体在人T细胞中表达。受体的表达使用流式细胞术分析。简言之:用抗CD3/CD28涂覆珠和IL2预活化数天(3-5)的 5×10^6 个T细胞被重悬于细胞化缓冲液(cytoporation buffer)T中,以及用45 μ g的mRNA电穿孔。电穿孔后24小时,用可固定成活力染料eFluor-780和特异性的PE-缀合的山羊抗小鼠IgG F(ab')₂片段,标记使用编码多链CAR的多顺反子mRNA改造的人T细胞,并通过流式细胞术分析。或者,受体在慢病毒中被加载(vectorized),表达和类似地分析。

[0507] 体外趋化试验

[0508] 在趋化试验中如之前所述使用转导的T细胞[Bürkle等人,Blood(血液),110(9):3316-3325,2007;Wu和Hwang,Journal of immunology(免疫学杂志),168(10):5096,2002;Singh等人,Journal of immunology(免疫学杂志),180(1):214-221,2008;Ryu等人,Molecules and Cells(分子和细胞),39.12:898-908,2016]。细胞(~20,000个细胞在培养基中,一百万个细胞, 5×10^6 mL)一式两份置于5- μ m孔径过滤器的上方,而含和不含趋化因子的培养基置于下室中。在37°C下,30min、1h、3h、5hr、24hr后,已掉落到板底部的迁移细胞:

[0509] A.使用4 $\times$ 物镜照相。来自两个孔的每一个的三个随机视野使用Image Pro Plus(Media Cybernetics,Silver Spring,MD)计数。进行三次独立实验,具有类似结果。

[0510] B.400 μ L的细胞悬浮液加入至100 μ L的含有 4×10^{-7} M FITC-标记的鬼笔环肽、0.5mg/mL 1- α -溶血磷脂酰胆碱(均来自Sigma,St Louis,MO)和7%甲醛/磷酸盐缓冲盐水(PBS)的溶液。固定的细胞通过流式细胞术在FACSCalibur上分析,以及所有时间点相对于在加入趋化因子之前样品的平均相对荧光作图。

[0511] C.下室中的细胞使用Countess II FL(Thermo Fisher Scientific,USA)进行计数,或450nm处的O.D.值使用Versamax微板阅读器(分子装置)进行测量。

[0512] 实施例5:在HEK293细胞中基于MHC的嵌合受体(MHC-CAR)的表达

[0513] 编码MHC-CAR的构建体如实施例2所述构建以及评价在HEK293细胞中的表达。简言之,构建体1包括EF1 α 短启动子、CD19 CAR(4G7-CAR)、CCR6和GFP(由SEQ ID NO:426提供);以及构建体2包括EF1 α 短启动子、RQR8、MHC-CAR1部分B、MHC-CAR1部分A和GFP(由SEQ ID NO:409提供)。

[0514] 将构建体1、2或培养基对照(未转染)转染至HEK293细胞中并培养。通过显微术根据GFP表达评价细胞的表达。在用构建体1或构建体2转染的组中,观察到GF-阳性细胞群。还通过流式细胞术评价细胞的由构建体编码的组分的表达。表8和9。

[0515] 构建体1表达

[0516] 对于检测CCR6,用缀合至APC的抗-CCR6单克隆抗体(17-1969-42,eBioscience)孵育细胞;以及对于检测CD19,用生物素化的CD19(Acro CD9-H8259,Acro Biosystems),接着通过链霉亲和素-PE(405203,BioLegend®)孵育细胞。

[0517] 表8:构建体1的表达

[0518]

CCR6表达	FITC (GFP)	APC (CCR6)	PE (CD19)
未染色	71.9	0.1	17.4
CCR6	71.3	81.9	16.9
CD19表达	FITC (GFP)	APC (CCR6)	PE (CD19)
未染色	71.9	0.1	17.4
CD19	71.3	0.1	33.3
仅链霉亲和素-PE	71.5	0.1	18.5

[0519] 构建体2表达

[0520] 对于检测来自RQR8中包括的表位的CD34表达,用抗-CD34 APC-缀合的单克隆抗体孵育细胞;以及对于检测MHC-CAR表达,用抗-HLA-DR抗体孵育细胞。

[0521] 表9:构建体2表达

[0522]

GFP 表达	FITC (GFP)	APC (CD34)	PE
未染色	62.3	0.1	2.4
RQR 表达	FITC (GFP)	APC (CD34)	PE
未染色	62.3	0.0	2.4
CD34	61.8	58.0	2.5
MHC CAR 表达	FITC (GFP)	APC (HLA-DR)	PE
未染色	62.3	0.0	2.4
HLA-DR	63.9	98.1	2.1

[0523] 构建体1的核酸序列 (SEQ ID NO:426)

[0524]

atggagacagacactcttctcctttgggtcttctgctgctgtgggttcccggaagcacaggagaagtacagttgcaa
cagtctggggccagaactcatcaaacccggagcttctgtaaaaatgtcatgcaaagctagtggatatacatttact
tcttacgtgatgcaactgggtaaaaacagaaacctgggtcaggggcttgagtggatcgggtacattaaacctatataat
gacggcaccataataacgagaaattcaagggaaggctacgcttacatcagataagtccagtagcacccgcttat
atggaacttagcagccttacttccgaagattccgcggtgtattactgcgcgagagggacttactactacgggagt
cgagtattcgattattgggggtcaaggcacgacgctcacggtgagctcaggtgggtggagggtctgggggtggcggc
agtgggtgggggggctcagacatcgtgatgacccaggcagcaccttctatcccggttaacccaggcgagctctgta
tctatcagttgtcgggtccagcaagtctcttctcaacagtaatggcaatacatatcttactgtggtcctccaaagg
cctgggcaaaagtctcacttcttatatatcggtgtccaatcttgcgagtggcgtaaccgacaggttttcagggt
tctgggagcggaacagcttttacgttgagaatatccagggtagaagctgaggacgtcgggtgtatattattgcatg
caacatctcgaataccccctttaccttcggcgctgggtacaaagctcgaattgaaacgcagcgatccaaccacgacg
ccagcgccacgacacctaagcggcctccaactattgctcccagccccctgagttctcggccagaagcggtgtaga
cctgctgcggcgggggcggttcatacgcggggccttgacttgcgcatgtgatcttatatatggggtcctttggcg
ggaacttgcggagtgccttctttgtcactcgtgataacgttgtattgtaaaaggggtcgaaagaaactcctctat
atatttaagcaagccctttatgagcgccgtgcaaaacacacaagaagaggacggatgctcctgtcgattcccgga
gaggaggagggggggtgtgagcttaggggtcaagtttctcgtctgcgcgacgcgcgcagcctatcaacaggggccaa
aacagctgtataacgaactcaacctcggggcgccgggaagagtatgacgtccttgacaaacggcgcggtgcgcac
cctgaaatgggtggaaaacaggagcgaaagaacccccaggagggactttacaacgaattgcaaaaagacaagatg
gccgaagcctattccgaaattggaatgaaaggcgagcggagacgaggttaaggggcatgacggcctgtatcaagg
ctctctacggccacgaaggatacttacgacgccttcatatgcaagctcttccaccacgggggttcgagcggcagt
ggagagggcgaggaagtctgctaactgcgggtgacgtcgaggagaatcctggcccaatgagtggggaaagtatg
aacttcagcgtatgtatttgactcctccgaagattactttgtatctgtgaatacagagctattactccgtcgatagt
gaaatgctgctctgtagtctccaagaagtcgcgaattcagtcgcctcttctgttcccatcgcgtaactccttatt
tgtgtttttggccttctgggttaacatcctgggtgtaatcacattcgccttctataaaaaagctcgaggtatgact
gatgtttaccttcttaacatggctatagcggacattctttttgtgcttactctccattctgggctgtgagccat
gcaacagggcggtgggttttttcaaatgccacatgtaagctgcttaaagggtatctatgcaataaaacttcaattgc
gggatgctcctgctgacatgcatcagtatggatcgatacatagctatagtaacaggcgactaagtcttccgcctg
cgatccgcacactgcctaggagcaaaattatttgcctcgtcgtatgggggctctcagtgatcatctcctccagt
acgtttgtcttttaaccagaaatataacacacagggttctgatgtatgtgaaccaaagtatcagacagtgagtgaa
ccaatacgggtggaagtgtcttatgttgggcttggagctgctttttgggtttttcatccactgatgttcattgatt
ttctgttatacatttattgttaagacottgggttcaggcgcaaaatagcaagagacataaggcaattcgagtcac
attgccgtgggtgttgggtcttcttggcctgtcagatccccataatatgggtctgctcgtcacccgcgctaacttg
ggtaagatgaatcgatcttgtcagtcgcgagaagttgatcggtacacccaaaactgtgacagaagtgtggccttc
cttcactgtgtgtgaacccagttttgtatgcttttataggacagaagtttcgaaattacttcttgaaaatcctc
aaggacctctgggtgtgttcgaagggaagtacaagagctctggcttttagttgcgctggggcgctacagtgagaatata
tcccggcagacctccgagactgctgataatgacaacgcaagttccttcactatg (SEQ ID NO: 426)

[0525] 构建体2的核酸序列 (SEQ ID NO:409)

[0526]

atgggtacttcaactgttgtgctggatggcaactttgtcttttgggtgccgatcatgctgatgcatgtccgtactcc
aatcctagcctgtgctccgggggggagggagtgaactccctacacagggaaaccttctctaagtctccaccaac
gtctccccctgcaaaaccgaccacaacagcttgccctatagtaaccttccctctgtagtggagggggggttca
cctgctccacgccttctacccccgcgcacaacgatcgctgcacaaccgctcagttcttaggcggaagcctgtagg
ccagcggctggcgggtgcggttcatacgcggggattggattttgcctgcgacatttacatttgggctccgctggcc
ggacttctgggggtattgctgttgtctcttgttattacgctttatttgcaatcacaggaacagggcgacgagtatgc
aaatgcccgcgcccgctcgtgagatctgggtccggccaatgtactaactacgctttgttgaactcgttggcgat
gttgaagtaaccccggtcctccaacaggtatggatgcttgaagctcccgggcggttctgcatgacgctctc
actgttactcttatggtccttagttcacgcttgccctggcatctgatgagaatcccggtggttcatttttttaag
aacatcgtcacacccgcgcaccccaacctgggggagggcggtctggcgaggcgaggagtggaggtcaggagacaca
agaccccgattcttgtggcagcccaaaaggagtgccatttttcaatgggacggaacgagttcgcttctcttgat
cggtaacttttacaaccaagaagagagtgtacggttcgactcagatgtcggcgagttccgagcgggttacggaattg
ggcgacctgacgcggagtaactggaaactccaaaaggataatttggagcaggcagcagcagctgtggacacctat
tgtcgacataattatgggtgtgtggaatcctttacagttcagcggcggtgcaacctaaagtgaacctgtatcca
tctaaaacgcaacccctccaacaccataacctctggtgtgttcctgtaagcggcttctatcccggtcaattgag
gtcaggtggttctcaacggtcaggaggagaaggccggaatggtaagtaactggtcttatccagaaaggagactgg
accttccaaaactttggtaatgttggaaaagggtgcccgatccggggagggtgatacatgccaaagtgaacacccg
agtgttacgagccccctgacggttgagtggaggcgcggtcagagagcgcaaatctaaaatgctgtcaggagta
ggcggattttgtaactcggactcctcttttggcgctgggttgtttatctacttttagaaaccaaacaagtagagta
aagttttccgaagtgcggacgctcccgctatcagcaagggtcaaaaccagctttacaacgaaactgaacttggga
cgacgcgaagagtaagatgttcttgataagcggagaggcgcgatcccgaaatggggggaaagcctcggaggaag
aaccacacaagaaggcctttataatgaactgcagaaggacaagatggcgaggcggtattccgaaataggcatgaag
ggtgaacggaggagaggaaaggacatgacggactttatcaaggattgtctaccgcaactaaagacacctatgac
gcgttgacatgcaggctctccctccgagagggtcgagcggcagtgagaggcgagaggaagtctgctaaccatgc
ggtgacgtcgaggagaatcctggcccaatggcaatatctgggtgttctgtcctcgggttttttatcatagccgta
ctgatgtcagcacaggaatcatggcgataaaaagaagacgctgataatacaggcgagggttttatttgaacccg
gaccagagcgggtgagttcatgttctgattttgatggcgacgagatatttcacgttgacatggcaaaaaggaaacg
gtgtggagacttgaggagtttggacgattcgcacatatttgaggcacaaggagcactcgccaatatcgcggtggac
aaggccaacctggagatcatgacaaaacgctccaattatacgcctatcactaatgtgccccctgagggttactgtg
ctcacaattctccgtagaacttagggaaacctaacgtcctcatatgttctatcgacaagttcactcctccggtg
gtcaatgtaacgtggcttcggaatggtaagccggtcaccacgggtgtctcagagaccgtatttctgccagagaa
gaccacctcttcgcaaatctcattaccttccctttcttcttcaacggaagacggtttacgactgcagggtcgaa
cattggggggttgacgagccacttctcaagcattgggagttcgacgccccatcacgcttccagaaacgactgaa
aacgttgtctgcgctcttggcctgacagtggtggcctgtaggcattattatcgggaccatctttatcatcaaagg
ttgacttcccggtcaaatttagcagatccgctgacgcacccggcctaccagcaggggccagaaccaactctacaac
gagctgaaatctcggccgacgggaagagtatgacgtactcgacaagcggagaggtcgagacccctgagatggcggt
aaaccgagacggaaaaatcccaagagggtctttataatgaactccagaaggataagatggctgaagcctattct
gagatagggatgaaaggcgagcggcgagggggtaaggggccatgatggcctttaccagggactctccacggcaacc
aaagatacttacgacgcccctcacatgcaagccctcccgccacgcgatccggcgcaacaaactctctctgctg
aaacaagccggagatgtcgaagagaatcctggaccgggtgagcaaggcgaggagctgttcacgggggtggtgcc
atcctggtcgagctggacggcgacgtaaacggccacaagttcagcgtgtctggcgaggcgaggcgatgccacc
tacggcaagctgacctgaagttcatctgaccaccggcaagctgcccgtgcccgtggccacctcgtgaccacc
ctgacctacggcgtgacgtgcttcagccgctaccccgaccacatgaagcagcagacttctcaagtccgcatg
cccgaaggctacgtccaggagcgaccatcttctcaaggacgacggcaactacaagaccgcgccgaggtgaag
ttcgaggcgacacccctgggtgaaccgcatcgagctgaagggtcatcgactcaaggaggacggcaacatcctgggg
cacaagctggagtacaactacaacagccacaacgtctatatcatggccgacaagcagaagaacggcatcaaggcg
aacttcaagatccggccacaacatcgaggacggcagcgtgcagctcgccgaccactaccagcagaacacccccatc
ggcgacggccccgtgctgctgccgacaaccactacctgagcaccagtcggccctgagcaaaagaccccaacgag
aagcgcgatcacatggtcctgctggagttcgtgaccgcgcggggtactctcgcatggacgagctgtacaag
taa` (SEQ ID NO: 409)

[0527] 实施例6:CD3的表达

[0528] 评价CD3的表达以确定靶向T细胞受体 α 恒定 (TRAC) 基因的CRISPR方法的功效。简言之,使用正向引物 (5'-AGCGCTCTCGTACAGAGTTGG-3' (SEQ ID NO:385)) 和反向引物 (5'-AAAAAAGCACCGACTCGGTGCC-3' (SEQ ID NO:386) 通过扩增靶位点产生靶向TRAC基因的sgRNA。

[0529] 未修饰的sgRNA通过以下核酸序列提供:

[0530] 5'- GAG AAU CAA AAU CGG UGA AUG UUU UAG AGC UAG AAA UAG CAA GUU AAA
AUA AGG CUA GUC CGU UAU CAA CUU GAA AAA GUG GCA CCG AGU CGG UGC UUU
U -3'. (SEQ ID NO: 384)

[0531] 修饰的sgRNA通过以下核酸序列提供:

[0532] 5'- 2'OMe(G(ps)A(ps)G(ps)) AAU CAA AAU CGG UGA AUG UUU UAG AGC UAG
AAA UAG CAA GUU AAA AUA AGG CUA GUC CGU UAU CAA CUU GAA AAA GUG GCA
CCG AGU CGG UGC 2'OMe(U(ps)U(ps)U(ps)) U -3' (SEQ ID NO: 387)

[0533] 2'OMe=2'O)-甲基RNA和ps=硫代磷酸酯

[0534] 用编码Cas9的mRNA (仅Cas9) 或编码Cas9的mRNA和靶向TRAC基因的sgRNA二者, 转染原代人刺激CD3+T-细胞。转染后7天后, 通过流式细胞术评价CD3的表达。用1:100稀释的抗-CD3-APC抗体(克隆OKT3; **BioLegend®** 目录号317318) 孵育细胞。如图11所示, 编码Cas9的mRNA和靶向TRAC基因的sgRNA的转染导致CD3表达的大幅降低。

[0535] 实施例7: 杀伤开关验证

[0536] 使用细胞成活力试验评价示例性构建体2中编码的RQR8杀伤开关的功效。简言之, 用仅仅培养基、构建体1 (SEQ ID NO:X)、构建体2 (其编码利妥昔单抗-介导的RQR8杀伤开关, SEQ ID NO:X) 或构建体1和构建体2二者转染HEK细胞。收获转染的HEK293细胞, 计数, 以及以 1×10^6 个细胞/mL重悬。将300uL的细胞悬浮液转移至48-孔组织培养板的4个孔的每一个中。将100uL的完全培养基和4uL的利妥昔单抗加入第二个孔, 以及100uL的新制备的幼兔补体和4uL的利妥昔单抗加入第四个孔。将板孵育2、4或24小时。通过加入1uL的冷冻的膜联蛋白V缓冲液 (150mM NaCl, 10mM HEPES, 10mM CaCl) 终止试验, 然后将样品转移至含有3mL的膜联蛋白V缓冲液的预准备的流式细胞术管中。

[0537] 通过离心收获样品, 并用纸巾吸掉任何残留缓冲液。然后, 样品用1uL的膜联蛋白V APC染色, 旋涡, 以及置于柔光中15分钟。然后, 用膜联蛋白V缓冲液洗涤样品, 并且补充5uL的碘化丙啶/mL缓冲液, 以及置于冰上, 直到最后悬浮后立即进行流式细胞术。

[0538] 定量GFP-阳性细胞的百分比, 以量化由RQR8杀伤开关诱导的杀伤。如图12所示, 用单独的补体孵育导致一些细胞死亡, 然而在所有细胞组中观察到这种成活力降低。在表达构建体2或构建体1和2二者的细胞中, 在存在利妥昔单抗和补体的组合的情况下, 观察到细胞死亡, 表明特异性RQR8-介导的细胞死亡。

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- [0624] 其它实施方案
- [0625] 本说明书中公开的所有特征可以任何组合进行组合。本说明书中公开的每个特征可被用于相同、等同或类似目的的备选特征替换。因此, 除非另外明确说明, 公开的每个特征仅是一系列通有的等同或类似特征的实例。
- [0626] 根据上文的描述, 本领域技术人员可容易确定本发明的基本特征, 并且在不脱离其精神和范围的情况下, 可对本发明进行各种变化和修改, 以使其适应各种用途和情况。因此, 其它实施方案也在权利要求内。

序列表

<110> Jura Bio, Inc.

〈120〉 基于主要组织相容性复合物的嵌合受体和其用于治疗自身免疫性疾病的用途

<130> .J0300.70000W000

〈140〉 尚未转让

<141> 2018-11-10

<150> US 62/584,449

<151> 2017-11-10

<160> 431

<170> PatentIn version 3.5

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⟨212⟩ PRT

〈213〉 智人

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

<210> 53

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<400> 53

Trp	Thr	Thr	Cys	Gln	Ser	Ile	Ala	Phe	Pro	Ser	Lys	Thr	Ser	Ala	Ser
1				5				10					15		
Ile	Gly	Ser	Leu												
			20												

<210> 54

<211> 32

<212> PRT

<213> 人工序列

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<223> 合成的

<400> 54

Ser Ala Ser Ile Gly Thr Leu Cys Ala Asp Ala Arg Met Tyr Gly Val

1 5 10 15

Leu Pro Trp Asn Ala Phe Phe Gly Lys Val Cys Gly Ser Asn Leu Leu

20 25 30

<210> 55

<211> 32

<212> PRT

<213> 人工序列

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<223> 合成的

<400> 55

Lys Val Cys Gly Ser Asn Leu Leu Ser Ile Cys Lys Thr Ala Glu Phe

1 5 10 15

Gln Met Thr Phe His Leu Phe Ile Ala Ala Phe Val Gly Ala Ala Ala

20 25 30

<210> 56

<211> 32

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<213> 人工序列

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<223> 合成的

<400> 56

Ala Ala Phe Val Gly Ala Ala Ala Thr Leu Val Ser Leu Leu Thr Phe

1 5 10 15

Met Ile Ala Ala Thr Tyr Asn Phe Ala Val Leu Lys Leu Met Gly Arg

20 25 30

<210> 57

<211> 20

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 57

Met Ile Ala Ala Thr Tyr Asn Phe Ala Val Leu Lys Leu Met Gly Arg
1 5 10 15
Gly Thr Lys Phe
20

<210> 58

<211> 19

<212> PRT

<213> 人工序列

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<223> 合成的

<400> 58

Met Ala Ala Thr Tyr Asn Phe Ala Val Leu Lys Leu Met Gly Arg Phe
1 5 10 15
Thr Lys Phe

<210> 59

<211> 42

<212> PRT

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<223> 合成的

<400> 59

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

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<211> 47

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<400> 60

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

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Ala His Ala
 35 40 45

<210> 61

<211> 41

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<400> 61

Arg Ser Lys Arg Ser Arg Gly Gly His Ser Asp Tyr Met Asn Met Thr
 1 5 10 15
 Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
 20 25 30
 Pro Arg Asp Phe Ala Ala Tyr Arg Ser
 35 40

<210> 62

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<400> 62

Pro Gly Arg Ser Lys Arg Ser Arg Gly Gly His Ser Asp Tyr Met Asn
 1 5 10 15
 Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr
 20 25 30
 Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Ala His Ala
 35 40 45

<210> 63

<211> 87

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

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

<210> 64

<211> 115

<212> PRT

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<223> 合成的

<400> 64

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

<210> 65

<211> 107

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<223> 合成的

<400> 65

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

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

<210> 66

<211> 135

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<223> 合成的

<400> 66

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

<210> 67

<211> 112

<212> PRT

<213> 人工序列

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<223> 合成的

<400> 67

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

<210> 68

<211> 15

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 68

Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser
1				5					10					15

<210> 69

<211> 15

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 69

Gly	Gly	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly	Gly
1				5					10					15

<210> 70

<211> 20

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 70

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

1 5 10 15

Gly Gly Gly Ser

20

<210> 71

<211> 2340

<212> DNA

<213> 人工序列

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<223> 合成的

<400> 71

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<213> 人工序列

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<400> 72

Gly Ser Gly Ser Gly Ser Gly Ser

1 5

<210> 73

<211> 21

<212> PRT

<213> 人工序列

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<400> 73

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

1 5 10 15

Ser Leu Val Ile Thr

20

<210> 74

<211> 21

Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala

180	185	190
Gln Glu Trp Cys Arg Lys Tyr Met	Lys Ser Gly Asn Val Lys Asp Leu	
195	200	205
Leu Gln Ala Trp Asp Leu Tyr Tyr	His Val Phe Arg Arg Ile Thr Thr	
210	215	220
Thr Pro Ala Pro Arg Pro Pro Thr	Pro Ala Pro Thr Ile Ala Ser Gln	
225	230	235
Pro Leu Ser Leu Arg Pro Glu Ala	Cys Arg Pro Ala Ala Gly Gly Ala	
245	250	255
Val His Thr Arg Gly Leu Asp Phe	Ala Cys Asp	
260	265	

<210> 76

<211> 45

<212> PRT

<213> 人工序列

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<223> 合成的

<400> 76

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

<210> 77

<211> 13

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<213> 人工序列

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<400> 77

Leu Arg Trp Glu Pro Pro Pro Ser	Thr Val Ser Asn Met
1	5 10

<210> 78

<211> 13

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<213> 人工序列

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<223> 合成的

<400> 78

Leu Arg Trp Glu Pro Ser Ser Gln Pro Thr Ile Pro Ile

1 5 10

<210> 79

<211> 13

<212> PRT

<213> 人工序列

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<223> 合成的

<400> 79

Leu Arg Trp Glu Leu Ser Ser Gln Pro Thr Ile Pro Ile

1 5 10

<210> 80

<211> 30

<212> PRT

<213> 人工序列

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<223> 合成的

<400> 80

Gln Thr Thr Pro Gly Glu Arg Ser Ser Leu Pro Ala Phe Tyr Pro Gly

1 5 10 15

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

20 25 30

<210> 81

<211> 46

<212> PRT

<213> 人工序列

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<223> 合成的

<400> 81

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

1 5 10 15

Gln Thr Thr Pro Gly Glu Arg Ser Ser Leu Pro Ala Phe Tyr Pro Gly

20 25 30

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

35 40 45

<210> 82

<211> 19

<212> PRT

<213> 人工序列

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<223> 合成的

<400> 82

Leu	Arg	Pro	Val	Gln	Ala	Gln	Ala	Gln	Ser	Asp	Cys	Ser	Cys	Ser	Thr
1				5					10					15	

Val Ser Pro

<210> 83

<211> 35

<212> PRT

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<223> 合成的

<400> 83

Gly	Ser	Ser	Ser	Gly	Ser	Ser	Ser	Gly	Ser	Ser	Ser	Gly	Ser	Ser	Ser
1				5					10					15	

Leu	Arg	Pro	Val	Gln	Ala	Gln	Ala	Gln	Ser	Asp	Cys	Ser	Cys	Ser	Thr
			20					25					30		

Val Ser Pro

35

<210> 84

<211> 16

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<213> 人工序列

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<400> 84

Gly	Leu	Ala	Val	Ser	Thr	Ile	Ser	Ser	Phe	Phe	Pro	Pro	Gly	Tyr	Gln
1				5					10					15	

<210> 85

<211> 45

<212> PRT

<213> 人工序列

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<223> 合成的

<400> 85

Thr	Thr	Thr	Pro	Ala	Pro	Arg	Pro	Pro	Thr	Pro	Ala	Pro	Thr	Ile	Ala
1				5					10					15	

Ser	Gln	Pro	Leu	Ser	Leu	Arg	Pro	Glu	Ala	Cys	Arg	Pro	Ala	Ala	Gly
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

	20				25				30						
Gly	Ala	Val	His	Thr	Arg	Gly	Leu	Asp	Phe	Ala	Cys	Asp			
	35				40				45						
<210>	86														
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<213>	人工序列														
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Glu	Pro	Lys	Ser	Pro	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala
1			5					10					15		
Pro	Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys
	20				25				30						
Asp	Thr	Leu	Met	Ile	Ala	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val
	35				40				45						
Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp
	50				55				60						
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr
65	70				75				80						
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp
	85				90				95						
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu
	100				105				110						
Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg
	115				120				125						
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys
	130				135				140						
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp
145	150				155				160						
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys
	165				170				175						
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser
	180				185				190						
Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser
	195				200				205						
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser
	210				215				220						
Leu	Ser	Leu	Ser	Pro	Gly	Lys									

225 230

<210> 87

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<213> 人工序列

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<223> 合成的

<400> 87

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

1 5 10

<210> 88

<211> 13

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<213> 人工序列

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<223> 合成的

<400> 88

Val Glu Trp Arg Ala Arg Ser Glu Ser Ala Gln Ser Lys

1 5 10

<210> 89

<211> 24

<212> PRT

<213> 人工序列

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<223> 合成的

<400> 89

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

1 5 10 15

Ser Leu Val Ile Thr Leu Tyr Cys

20

<210> 90

<211> 24

<212> PRT

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<223> 合成的

<400> 90

Val Gly Ile Ile Ala Gly Leu Val Leu Phe Gly Ala Val Ile Thr Gly

1 5 10 15

Ala Val Val Ala Ala Val Met Trp

20

<210> 91

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<212> PRT

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<400> 91

Val Gly Ile Ile Ala Gly Leu Val Leu Leu Gly Ala Val Ile Thr Gly

1

5

10

15

Ala Val Val Ala Ala Val Met Trp

20

<210> 92

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<212> PRT

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<223> 合成的

<400> 92

Leu Cys Tyr Leu Leu Asp Gly Ile Leu Phe Ile Tyr Gly Val Ile Leu

1

5

10

15

Thr Ala Leu Phe Leu

20

<210> 93

<211> 21

<212> PRT

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<223> 合成的

<400> 93

Met Leu Ser Gly Val Gly Gly Phe Val Leu Gly Leu Leu Phe Leu Gly

1

5

10

15

Ala Gly Leu Phe Ile

20

<210> 94

<211> 26

<212> PRT

<213> 人工序列

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<223> 合成的

<400> 94

Met	Leu	Ser	Gly	Val	Gly	Gly	Phe	Val	Leu	Gly	Leu	Leu	Phe	Leu	Gly
1				5					10					15	
Ala	Gly	Leu	Phe	Ile	Tyr	Phe	Arg	Asn	Gln						
				20				25							

<210> 95

<211> 326

<212> PRT

<213> 人工序列

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<223> 合成的

<400> 95

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

195	200	205
Thr Val Gly Trp Ala Thr Ser Ser Leu Leu Pro Gly Thr Ser Gly Gly		
210	215	220
Arg Gln Arg Arg Glu Leu Asp Pro Met Asp Ile Arg Gly Ser Ile Val		
225	230	235
Tyr Leu Glu Ile Asp Asn Arg Gln Cys Val Gln Ser Ser Ser Gln Cys		
245	250	255
Phe Gln Ser Ala Thr Asp Val Ala Ala Phe Leu Gly Ala Leu Ala Ser		
260	265	270
Leu Gly Ser Leu Asn Ile Pro Tyr Lys Ile Glu Ala Val Lys Ser Glu		
275	280	285
Pro Val Glu Pro Pro Leu Pro Ser Gln Leu His Leu Met Tyr Val Ala		
290	295	300
Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly Cys Gly Val Leu Leu		
305	310	315
Ser Arg Lys Arg Arg Arg		
325		

<210> 96

<211> 363

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 96

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

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

<210> 97

<211> 18

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 97

Met Leu Arg Leu Leu Leu Ala Leu Asn Leu Phe Pro Ser Ile Gln Val

1	5	10	15
Thr Gly			
<210> 98			
<211> 20			
<212> PRT			
<213> 人工序列			
<220>			
<223> 合成的			
<400> 98			
Met Ser Arg Ser Val Ala Leu Ala Val Leu Ala Leu Leu Ser Leu Ser			
1	5	10	15
Gly Leu Glu Ala			
20			
<210> 99			
<211> 24			
<212> PRT			
<213> 人工序列			
<220>			
<223> 合成的			
<400> 99			
Met Ala Val Met Ala Pro Arg Thr Leu Leu Leu Leu Leu Ser Gly Ala			
1	5	10	15
Leu Ala Leu Thr Gln Thr Trp Ala			
20			
<210> 100			
<211> 25			
<212> PRT			
<213> 人工序列			
<220>			
<223> 合成的			
<400> 100			
Met Ala Ile Ser Gly Val Pro Val Leu Gly Phe Phe Ile Ile Ala Val			
1	5	10	15
Leu Met Ser Ala Gln Glu Ser Trp Ala			
20	25		
<210> 101			
<211> 28			
<212> PRT			
<213> 人工序列			

<220>

<223> 合成的

<400> 101

Met	Val	Cys	Leu	Lys	Leu	Pro	Gly	Gly	Ser	Cys	Met	Thr	Ala	Leu	Thr
1				5					10					15	
Val	Thr	Leu	Met	Val	Leu	Ser	Ser	Pro	Leu	Ala	Leu				
			20					25							

<210> 102

<211> 29

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 102

Met	Val	Cys	Leu	Lys	Leu	Pro	Gly	Gly	Ser	Tyr	Met	Ala	Lys	Leu	Thr
1				5					10					15	
Val	Thr	Leu	Met	Val	Leu	Ser	Ser	Pro	Leu	Ala	Leu	Ala			
			20					25							

<210> 103

<211> 100

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<220>

<221> 其它特征

<222> (16) .. (100)

<223> 可以不存在

<400> 103

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

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
85 90 95

Gly Gly Gly Ser
100

<210> 104

<211> 30

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 104

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25 30

<210> 105

<211> 60

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 105

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
35 40 45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
50 55 60

<210> 106

<211> 75

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 106

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
 20 25 30
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 35 40 45
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 50 55 60
 Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
 65 70 75

<210> 107

<211> 9

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 107

Lys Leu Ile Glu Thr Tyr Phe Ser Lys
 1 5

<210> 108

<211> 9

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 108

Leu Leu Phe Gly Tyr Pro Val Tyr Val
 1 5

<210> 109

<211> 271

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 109

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

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

<210> 110

<211> 271

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 110

Gly Ser His Ser Met Arg Tyr Phe Phe Thr Ser Val Ser Arg Pro Gly		
1	5	10 15
Arg Gly Glu Pro Arg Phe Ile Ala Val Gly Tyr Val Asp Asp Thr Gln		
20	25	30

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

<210> 111

<211> 4

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 111

Leu Arg Trp Glu

1

<210> 112

<211> 271

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 112

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

Tyr Thr Cys His Val Tyr His Gln Gly Leu Pro Glu Pro Leu Thr
 260 265 270
 <210> 113
 <211> 271
 <212> PRT
 <213> 人工序列
 <220>
 <223> 合成的
 <400> 113
 Gly Ser His Ser Met Arg Tyr Phe Phe Thr Ser Val Ser Arg Pro Gly
 1 5 10 15
 Arg Gly Glu Pro Arg Phe Ile Ala Val Gly Tyr Val Asp Asp Thr Gln
 20 25 30
 Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln Arg Met Glu Pro Arg
 35 40 45
 Ala Pro Trp Ile Glu Gln Glu Gly Pro Glu Tyr Trp Asp Gln Glu Thr
 50 55 60
 Arg Asn Val Lys Ala Gln Ser Gln Thr Asp Arg Val Asp Leu Gly Thr
 65 70 75 80
 Leu Arg Gly Tyr Tyr Asn Gln Ser Glu Ala Gly Ser His Thr Ile Gln
 85 90 95
 Ile Met Tyr Gly Cys Asp Val Gly Ser Asp Gly Arg Phe Leu Arg Gly
 100 105 110
 Tyr Arg Gln Asp Ala Tyr Asp Gly Lys Asp Tyr Ile Ala Leu Asn Glu
 115 120 125
 Asp Leu Arg Ser Trp Thr Ala Ala Asp Met Ala Ala Gln Ile Thr Lys
 130 135 140
 Arg Lys Trp Glu Ala Ala His Glu Ala Glu Gln Leu Arg Ala Tyr Leu
 145 150 155 160
 Asp Gly Thr Cys Val Glu Trp Leu Arg Arg Tyr Leu Glu Asn Gly Lys
 165 170 175
 Glu Thr Leu Gln Arg Thr Asp Ser Pro Lys Ala His Val Thr His His
 180 185 190
 Ser Arg Pro Glu Asp Lys Val Thr Leu Arg Cys Trp Ala Leu Gly Phe
 195 200 205
 Tyr Pro Ala Asp Ile Thr Leu Thr Trp Gln Leu Asn Gly Glu Glu Leu
 210 215 220
 Ile Gln Asp Met Glu Leu Val Glu Thr Arg Pro Ala Gly Asp Gly Thr
 225 230 235 240

Phe Gln Lys Trp Ala Ser Val Val Val Pro Leu Gly Lys Glu Gln Tyr
 245 250 255

Tyr Thr Cys His Val Tyr His Gln Gly Leu Pro Glu Pro Leu Thr
 260 265 270

<210> 114

<211> 99

<212> PRT

<213> 智人

<400> 114

Ile Gln Arg Thr Pro Lys Ile Gln Val Tyr Ser Arg His Pro Ala Glu
 1 5 10 15

Asn Gly Lys Ser Asn Phe Leu Asn Cys Tyr Val Ser Gly Phe His Pro
 20 25 30

Ser Asp Ile Glu Val Asp Leu Leu Lys Asn Gly Glu Arg Ile Glu Lys
 35 40 45

Val Glu His Ser Asp Leu Ser Phe Ser Lys Asp Trp Ser Phe Tyr Leu
 50 55 60

Leu Tyr Tyr Thr Glu Phe Thr Pro Thr Glu Lys Asp Glu Tyr Ala Cys
 65 70 75 80

Arg Val Asn His Val Thr Leu Ser Gln Pro Lys Ile Val Lys Trp Asp
 85 90 95

Arg Asp Met

<210> 115

<211> 99

<212> PRT

<213> 小鼠

<400> 115

Ile Gln Lys Thr Pro Gln Ile Gln Val Tyr Ser Arg His Pro Pro Glu
 1 5 10 15

Asn Gly Lys Pro Asn Ile Leu Asn Cys Tyr Val Thr Gln Phe His Pro
 20 25 30

Pro His Ile Glu Ile Gln Met Leu Lys Asn Gly Lys Lys Ile Pro Lys
 35 40 45

Val Glu Met Ser Asp Met Ser Phe Ser Lys Asp Trp Ser Phe Tyr Ile
 50 55 60

Leu Ala His Thr Glu Phe Thr Pro Thr Glu Thr Asp Thr Tyr Ala Cys
 65 70 75 80

Arg Val Lys His Ala Ser Met Ala Glu Pro Lys Thr Val Tyr Trp Asp
 85 90 95

Arg Asp Met

<210> 116

<211> 149

<212> DNA

<213> 人工序列

<220>

<223> 合成的

<400> 116

agcgctctcg tacagagttg gcattataat acgactcact ataggggaga atcaaaatcg 60
gtgaatgttt tagagctaga aatagcaagt taaaataagg ctagtccgtt atcaacttga 120
aaaagtgga ccgagtcggt gcttttttt 149

<210> 117

<211> 185

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 117

Gly Asp Thr Arg Pro Arg Phe Leu Trp Gln Pro Lys Arg Glu Cys His

1 5 10 15

Phe Phe Asn Gly Thr Glu Arg Val Arg Phe Leu Asp Arg Tyr Phe Tyr

20 25 30

Asn Gln Glu Glu Ser Val Arg Phe Asp Ser Asp Val Gly Glu Phe Arg

35 40 45

Ala Val Thr Glu Leu Gly Arg Pro Asp Ala Glu Tyr Trp Asn Ser Gln

50 55 60

Lys Asp Ile Leu Glu Gln Ala Arg Ala Ala Val Asp Thr Tyr Cys Arg

65 70 75 80

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

85 90 95

Pro Lys Val Thr Val Tyr Pro Ser Lys Thr Gln Pro Leu Gln His His

100 105 110

Asn Leu Leu Val Cys Ser Val Ser Gly Phe Tyr Pro Gly Ser Ile Glu

115 120 125

Val Arg Trp Phe Leu Asn Gly Gln Glu Glu Lys Ala Gly Met Val Ser

130 135 140

Thr Gly Leu Ile Gln Asn Gly Asp Trp Thr Phe Gln Thr Leu Val Met

145 150 155 160

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

	165		170		175
His Pro Ser Val Thr Ser Pro Leu Thr					
	180		185		
<210> 118					
<211> 178					
<212> PRT					
<213> 人工序列					
<220>					
<223> 合成的					
<400> 118					
Ile Lys Glu Glu His Val Ile Ile Gln Ala Glu Phe Tyr Leu Asn Pro					
1	5		10		15
Asp Gln Ser Gly Glu Phe Met Phe Asp Phe Asp Gly Asp Glu Ile Phe					
	20		25		30
His Val Asp Met Ala Lys Lys Glu Thr Val Trp Arg Leu Glu Glu Phe					
	35		40		45
Gly Arg Phe Ala Ser Phe Glu Ala Gln Gly Ala Leu Ala Asn Ile Ala					
	50		55		60
Val Asp Lys Ala Asn Leu Glu Ile Met Thr Lys Arg Ser Asn Tyr Thr					
65	70		75		80
Pro Ile Thr Asn Val Pro Pro Glu Val Thr Val Leu Thr Asn Ser Pro					
	85		90		95
Val Glu Leu Arg Glu Pro Asn Val Leu Ile Cys Phe Ile Asp Lys Phe					
	100		105		110
Thr Pro Pro Val Val Asn Val Thr Trp Leu Arg Asn Gly Lys Pro Val					
	115		120		125
Thr Thr Gly Val Ser Glu Thr Val Phe Leu Pro Arg Glu Asp His Leu					
	130		135		140
Phe Arg Lys Phe His Tyr Leu Pro Phe Leu Pro Ser Thr Glu Asp Val					
145	150		155		160
Tyr Asp Cys Arg Val Glu His Trp Gly Leu Asp Glu Pro Leu Leu Lys					
	165		170		175
His Trp					
<210> 119					
<211> 185					
<212> PRT					
<213> 人工序列					
<220>					
<223> 合成的					

<400> 119

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

<210> 120

<211> 183

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 120

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

50	55	60
Val Asp Lys Ala Asn Leu Glu Ile Met Thr Lys Arg Ser Asn Tyr Thr		
65	70	75
Pro Ile Ala Thr Asn Glu Ala Pro Gln Ala Thr Val Phe Pro Lys Ser		80
	85	90
Pro Val Leu Leu Gly Gln Pro His Thr Leu Ile Cys Phe Val Asp Asn		95
	100	105
Ile Phe Pro Pro Val Ile Asn Ile Thr Trp Leu Arg Asn Ser Lys Ser		110
	115	120
Val Thr Asp Gly Val Tyr Glu Thr Ser Phe Leu Val Asn Arg Asp His		125
	130	135
Ser Phe His Lys Leu Ser Tyr Leu Thr Phe Ile Pro Ser Asp Asp Asp		140
145	150	155
Ile Tyr Asp Cys Lys Val Glu His Trp Gly Leu Glu Glu Pro Val Leu		160
	165	170
Lys His Trp Glu Pro Glu Ile		175
	180	

<210> 121

<211> 90

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 121

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

<210> 122

<211> 82

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 122

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

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<210> 123

<211> 272

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 123

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

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130	135	140
Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp		
145	150	155
Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr		
165	170	175
Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser		
180	185	190
Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe		
195	200	205
Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu Ser		
210	215	220
Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn		
225	230	235
Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Leu		
245	250	255
Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser		
260	265	270
<210> 124		
<211> 312		
<212> PRT		
<213> 人工序列		
<220>		
<223> 合成的		
<400> 124		
Met Leu Leu Leu Leu Leu Leu Leu Gly Leu Ala Gly Ser Gly Leu Gly		
1	5	10
Ala Val Val Ser Gln His Pro Ser Trp Val Ile Ser Lys Ser Gly Thr		
20	25	30
Ser Val Lys Ile Glu Cys Arg Ser Leu Asp Phe Gln Ala Thr Thr Met		
35	40	45
Phe Trp Tyr Arg Gln Phe Pro Lys Gln Ser Leu Met Leu Met Ala Thr		
50	55	60
Ser Asn Glu Gly Ser Lys Ala Thr Tyr Glu Gln Gly Val Glu Lys Asp		
65	70	75
Lys Phe Leu Ile Asn His Ala Ser Leu Thr Leu Ser Thr Leu Thr Val		
85	90	95
Thr Ser Ala His Pro Glu Asp Ser Ser Phe Tyr Ile Cys Ser Ala Arg		
100	105	110
Asp Leu Thr Ser Gly Ala Asn Asn Glu Gln Phe Phe Gly Pro Gly Thr		

115	120	125
Arg Leu Thr Val Leu Glu Asp	Leu Lys Asn Val Phe	Pro Pro Glu Val
130	135	140
Ala Val Phe Glu Pro Ser Glu	Ala Glu Ile Ser His Thr	Gln Lys Ala
145	150	155
Thr Leu Val Cys Leu Ala Thr	Gly Phe Tyr Pro Asp His	Val Glu Leu
165	170	175
Ser Trp Trp Val Asn Gly Lys	Glu Val His Ser Gly Val	Ser Thr Asp
180	185	190
Pro Gln Pro Leu Lys Glu Gln	Pro Ala Leu Asn Asp Ser	Arg Tyr Ser
195	200	205
Leu Ser Ser Arg Leu Arg Val	Ser Ala Thr Phe Trp Gln	Asn Pro Arg
210	215	220
Asn His Phe Arg Cys Gln Val	Gln Phe Tyr Gly Leu Ser	Glu Asn Asp
225	230	235
Glu Trp Thr Gln Asp Arg Ala	Lys Pro Val Thr Gln Ile	Val Ser Ala
245	250	255
Glu Ala Trp Gly Arg Ala Asp	Cys Gly Phe Thr Ser Glu	Ser Tyr Gln
260	265	270
Gln Gly Val Leu Ser Ala Thr	Ile Leu Tyr Glu Ile Leu	Leu Gly Lys
275	280	285
Ala Thr Leu Tyr Ala Val Leu	Val Ser Ala Leu Val Leu	Met Ala Met
290	295	300
Val Lys Arg Lys Asp Ser Arg	Gly	
305	310	
<210>	125	
<211>	278	
<212>	PRT	
<213>	人工序列	
<220>		
<223>	合成的	
<400>	125	
Met Ala Met Leu Leu Gly Ala	Ser Val Leu Ile Leu Trp	Leu Gln Pro
1	5	10
Asp Trp Val Asn Ser Gln Gln	Lys Asn Asp Asp Gln Gln	Val Lys Gln
20	25	30
Asn Ser Pro Ser Leu Ser Val	Gln Glu Gly Arg Ile Ser	Ile Leu Asn
35	40	45
Cys Asp Tyr Thr Asn Ser Met	Phe Asp Tyr Phe Leu Trp	Tyr Lys Lys

50	55	60													
Tyr	Pro	Ala	Glu	Gly	Pro	Thr	Phe	Leu	Ile	Ser	Ile	Ser	Ser	Ile	Lys
65					70					75					80
Asp	Lys	Asn	Ala	Asp	Gly	Arg	Phe	Thr	Val	Phe	Leu	Asn	Lys	Ser	Ala
				85						90					95
Lys	His	Leu	Ser	Leu	His	Ile	Val	Pro	Ser	Gln	Pro	Gly	Asp	Ser	Ala
				100						105					110
Val	Tyr	Phe	Cys	Ala	Ala	Met	Glu	Gly	Ala	Gln	Lys	Leu	Val	Phe	Gly
				115						120					125
Gln	Gly	Thr	Arg	Leu	Thr	Ile	Asn	Pro	Asn	Ile	Gln	Asn	Pro	Asp	Pro
				130						135					140
Ala	Val	Tyr	Gln	Leu	Arg	Asp	Ser	Lys	Ser	Ser	Asp	Lys	Ser	Val	Cys
145					150					155					160
Leu	Phe	Thr	Asp	Phe	Asp	Ser	Gln	Thr	Asn	Val	Ser	Gln	Ser	Lys	Asp
				165						170					175
Ser	Asp	Val	Tyr	Ile	Thr	Asp	Lys	Thr	Val	Leu	Asp	Met	Arg	Ser	Met
				180						185					190
Asp	Phe	Lys	Ser	Asn	Ser	Ala	Val	Ala	Trp	Ser	Asn	Lys	Ser	Asp	Phe
				195						200					205
Ala	Cys	Ala	Asn	Ala	Phe	Asn	Asn	Ser	Ile	Ile	Pro	Glu	Asp	Thr	Phe
				210						215					220
Phe	Pro	Ser	Pro	Glu	Ser	Ser	Cys	Asp	Val	Lys	Leu	Val	Glu	Lys	Ser
225					230					235					240
Phe	Glu	Thr	Asp	Thr	Asn	Leu	Asn	Phe	Gln	Asn	Leu	Ser	Val	Ile	Gly
				245						250					255
Phe	Arg	Ile	Leu	Leu	Leu	Lys	Val	Ala	Gly	Phe	Asn	Leu	Leu	Met	Thr
				260						265					270
Leu	Arg	Leu	Trp	Ser	Ser										
				275											
<210>	126														
<211>	312														
<212>	PRT														
<213>	人工序列														
<220>															
<223>	合成的														
<400>	126														
Met	Ser	Ile	Gly	Leu	Leu	Cys	Cys	Ala	Ala	Leu	Ser	Leu	Leu	Trp	Ala
1				5						10				15	
Gly	Pro	Val	Asn	Ala	Gly	Val	Thr	Gln	Thr	Pro	Lys	Phe	Gln	Val	Leu

461 <211>

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 127

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

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Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala																	
275																280	285
Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr																	
290																295	300
Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln																	
305																310	315 320
Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser																	
																325	330 335
Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys																	
																340	345 350
Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln																	
																355	360 365
Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu																	
																370	375 380
Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg																	
385																390	395 400
Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met																	
																405	410 415
Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly																	
																420	425 430
Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp																	
																435	440 445
Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg																	
																450	455 460
<210> 128																	
<211> 495																	
<212> PRT																	
<213> 人工序列																	
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<223> 合成的																	
<400> 128																	
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro																	
1																5	10 15
Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile																	
																20	25 30
Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr																	
																35	40 45
Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly																	
																50	55 60

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

370	375	380
Val Lys Phe Ser Arg	Ser Ala Asp Ala Pro	Ala Tyr Gln Gln Gly Gln
385	390	395
Asn Gln Leu Tyr Asn	Glu Leu Asn Leu Gly	Arg Arg Glu Glu Tyr Asp
405	410	415
Val Leu Asp Lys Arg	Arg Gly Arg Asp Pro	Glu Met Gly Gly Lys Pro
420	425	430
Arg Arg Lys Asn Pro	Gln Glu Gly Leu Tyr	Asn Glu Leu Gln Lys Asp
435	440	445
Lys Met Ala Glu Ala	Tyr Ser Glu Ile Gly	Met Lys Gly Glu Arg Arg
450	455	460
Arg Gly Lys Gly His	Asp Gly Leu Tyr Gln	Gly Leu Ser Thr Ala Thr
465	470	475
Lys Asp Thr Tyr Asp	Ala Leu His Met Gln	Ala Leu Pro Pro Arg
485	490	495
<210> 129		
<211> 432		
<212> PRT		
<213> 人工序列		
<220>		
<223> 合成的		
<400> 129		
Met Ala Leu Pro Val	Thr Ala Leu Leu Leu	Pro Leu Ala Leu Leu
1	5	10
His Ala Ala Arg Pro	Glu Val Lys Leu Leu	Glu Ser Gly Gly Gly Leu
20	25	30
Val Gln Pro Gly Gly	Ser Leu Lys Leu Ser	Cys Ala Ala Ser Gly Phe
35	40	45
Asp Phe Ser Arg Tyr	Trp Met Ser Trp Val	Arg Gln Ala Pro Gly Lys
50	55	60
Gly Leu Glu Trp Ile	Gly Glu Ile Asn Pro	Asp Ser Ser Thr Ile Asn
65	70	75
Tyr Thr Pro Ser Leu	Lys Asp Lys Phe Ile	Ile Ser Arg Asp Asn Ala
85	90	95
Lys Asn Thr Leu Tyr	Leu Gln Met Ser Lys	Val Arg Ser Glu Asp Thr
100	105	110
Ala Leu Tyr Tyr Cys	Ala Arg Pro Asp Gly	Asn Tyr Trp Tyr Phe Asp
115	120	125
Val Trp Gly Ala Gly	Thr Thr Val Thr Val	Ser Ser Gly Gly Gly Gly

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

<210> 130

<211> 485

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 130

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

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

<210> 131

<211> 647

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 131

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
 1 5 10 15
 His Ala Ala Arg Pro Glu Val Lys Leu Leu Glu Ser Gly Gly Gly Leu
 20 25 30

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

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

<210> 132

<211> 433

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 132

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

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

Arg

<210> 133

<211> 486

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 133

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

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

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

<210> 134

<211> 648

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 134

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

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

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

135

434 $\langle 211 \rangle$

<212> PRT

〈213〉 人工序列

 $\langle 220 \rangle$

〈223〉 合成的

<400> 135

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

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

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
 370 375 380
 Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
 385 390 395 400
 Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
 405 410 415
 Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
 420 425 430
 Pro Arg
 <210> 136
 <211> 487
 <212> PRT
 <213> 人工序列
 <220>
 <223> 合成的
 <400> 136
 Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
 1 5 10 15
 His Ala Ala Arg Pro Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu
 20 25 30
 Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr
 35 40 45
 Thr Phe Thr Ser Tyr Trp Met Gln Trp Val Lys Gln Arg Pro Gly Gln
 50 55 60
 Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asp Gly Asp Thr Arg
 65 70 75 80
 Tyr Thr Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser
 85 90 95
 Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser
 100 105 110
 Ala Val Tyr Tyr Cys Ala Arg Gly Lys Val Tyr Tyr Gly Ser Asn Pro
 115 120 125
 Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Gly Gly
 130 135 140
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln
 145 150 155 160
 Met Thr Gln Ser Ser Ser Tyr Leu Ser Val Ser Leu Gly Gly Arg Val
 165 170 175
 Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp Leu Ala Trp

180	185	190
Tyr Gln Gln Lys Pro Gly Asn Ala Pro Arg Leu Leu Ile Ser Gly Ala		
195	200	205
Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser		
210	215	220
Gly Lys Asp Tyr Thr Leu Ser Ile Thr Ser Leu Gln Thr Glu Asp Val		
225	230	235
Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Thr Pro Trp Thr Phe Gly		
245	250	255
Gly Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro		
260	265	270
Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro		
275	280	285
Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu		
290	295	300
Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys		
305	310	315
Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly		
325	330	335
Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val		
340	345	350
Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu		
355	360	365
Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp		
370	375	380
Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn		
385	390	395
Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg		
405	410	415
Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly		
420	425	430
Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu		
435	440	445
Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu		
450	455	460
Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His		
465	470	475
Met Gln Ala Leu Pro Pro Arg		480
485		

<210> 137

<211> 649

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 137

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

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

					565					570					575				
Gly	Arg	Asp	Pro	Glu	Met	Gly	Gly	Lys	Pro	Arg	Arg	Lys	Asn	Pro	Gln				
					580					585					590				
Glu	Gly	Leu	Tyr	Asn	Glu	Leu	Gln	Lys	Asp	Lys	Met	Ala	Glu	Ala	Tyr				
					595					600					605				
Ser	Glu	Ile	Gly	Met	Lys	Gly	Glu	Arg	Arg	Arg	Gly	Lys	Gly	His	Asp				
					610					615					620				
Gly	Leu	Tyr	Gln	Gly	Leu	Ser	Thr	Ala	Thr	Lys	Asp	Thr	Tyr	Asp	Ala				
					625					630					635				640
Leu	His	Met	Gln	Ala	Leu	Pro	Pro	Arg											
					645														
<210> 138																			
<211> 433																			
<212> PRT																			
<213> 人工序列																			
<220>																			
<223> 合成的																			
<400> 138																			
Met	Ala	Leu	Pro	Val	Thr	Ala	Leu	Leu	Leu	Pro	Leu	Ala	Leu	Leu	Leu				
1				5						10					15				
His	Ala	Ala	Arg	Pro	Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Pro	Glu	Leu				
				20						25					30				
Val	Lys	Pro	Gly	Ala	Ser	Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr				
				35						40					45				
Ala	Phe	Ser	Ser	Ser	Trp	Met	Asn	Trp	Val	Lys	Gln	Arg	Pro	Gly	Gln				
				50						55					60				
Gly	Leu	Glu	Trp	Ile	Gly	Arg	Ile	Tyr	Pro	Gly	Asp	Gly	Asp	Thr	Lys				
65					70					75					80				
Tyr	Asn	Gly	Lys	Phe	Lys	Gly	Lys	Ala	Thr	Leu	Thr	Ala	Asp	Lys	Ser				
				85						90					95				
Ser	Ser	Thr	Ala	Tyr	Met	Gln	Leu	Ser	Ser	Leu	Thr	Ser	Val	Asp	Ser				
				100						105					110				
Ala	Val	Tyr	Phe	Cys	Ala	Arg	Ser	Thr	Met	Ile	Ala	Thr	Gly	Ala	Met				
				115						120					125				
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Ser	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly				
				130						135					140				
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Glu	Thr	Thr	Val				
145					150					155					160				
Thr	Gln	Ser	Pro	Ala	Ser	Leu	Ser	Met	Ala	Ile	Gly	Glu	Lys	Val	Thr				

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

Arg

<210> 139

<211> 486

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 139

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

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

$\langle 210 \rangle$ 140

<211> 647

<212> PRT

〈213〉 人工序列

 $\langle 220 \rangle$

〈223〉 合成的

$\langle 400 \rangle$ 140

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

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

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

<210> 141

<211> 432

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 141

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

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275	280	285
Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu		
290	295	300
Asp Gly Cys Cys Arg Phe Pro Glu Glu Glu Gly Gly Cys Glu Leu		
305	310	315
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly		
325	330	335
Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr		
340	345	350
Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys		
355	360	365
Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys		
370	375	380
Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg		
385	390	395
Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala		
405	410	415
Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg		
420	425	430
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<400> 142		
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu		
1	5	10
His Ala Ala Arg Pro Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu		
20	25	30
Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr		
35	40	45
Ala Phe Ser Ser Ser Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln		
50	55	60
Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly Asp Gly Asp Thr Lys		
65	70	75
Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser		
85	90	95
Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Val Asp Ser		

	100		105		110
Ala Val Tyr Phe Cys Ala Arg Ser Thr Met Ile Ala Thr Gly Ala Met					
115		120		125	
Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly					
130		135		140	
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met					
145		150		155	160
Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly Asp Arg Val Ser					
	165		170		175
Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala Val Ala Trp Tyr					
180		185		190	
Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Ser Ala Ser					
195		200		205	
Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly					
210		215		220	
Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala					
225		230		235	240
Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Pro Tyr Thr Phe Gly					
	245		250		255
Gly Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro					
260		265		270	
Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro					
275		280		285	
Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu					
290		295		300	
Asp Phe Ala Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly					
305		310		315	320
Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg					
	325		330		335
Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln					
	340		345		350
Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu					
	355		360		365
Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala					
370		375		380	
Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu					
385		390		395	400
Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp					
	405		410		415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
 420 425 430
 Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
 435 440 445
 Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
 450 455 460
 Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
 465 470 475 480
 Gln Ala Leu Pro Pro Arg
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<210> 143

<211> 648

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 143

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

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

				485					490					495			
Gly	Arg	Lys	Lys	Leu	Leu	Tyr	Ile	Phe	Lys	Gln	Pro	Phe	Met	Arg	Pro		
				500					505					510			
Val	Gln	Thr	Thr	Gln	Glu	Glu	Asp	Gly	Cys	Ser	Cys	Arg	Phe	Pro	Glu		
				515					520					525			
Glu	Glu	Glu	Gly	Gly	Cys	Glu	Leu	Arg	Val	Lys	Phe	Ser	Arg	Ser	Ala		
				530					535					540			
Asp	Ala	Pro	Ala	Tyr	Gln	Gln	Gly	Gln	Asn	Gln	Leu	Tyr	Asn	Glu	Leu		
545					550					555					560		
Asn	Leu	Gly	Arg	Arg	Glu	Glu	Tyr	Asp	Val	Leu	Asp	Lys	Arg	Arg	Gly		
				565					570					575			
Arg	Asp	Pro	Glu	Met	Gly	Gly	Lys	Pro	Arg	Arg	Lys	Asn	Pro	Gln	Glu		
				580					585					590			
Gly	Leu	Tyr	Asn	Glu	Leu	Gln	Lys	Asp	Lys	Met	Ala	Glu	Ala	Tyr	Ser		
				595					600					605			
Glu	Ile	Gly	Met	Lys	Gly	Glu	Arg	Arg	Arg	Gly	Lys	Gly	His	Asp	Gly		
				610					615					620			
Leu	Tyr	Gln	Gly	Leu	Ser	Thr	Ala	Thr	Lys	Asp	Thr	Tyr	Asp	Ala	Leu		
625					630					635					640		
His	Met	Gln	Ala	Leu	Pro	Pro	Arg										
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<210> 144																	
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<223> 合成的																	
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Met	Gly	Thr	Ser	Leu	Leu	Cys	Trp	Met	Ala	Leu	Cys	Leu	Leu	Gly	Ala		
1				5				10						15			
Asp	His	Ala	Asp	Ala	Cys	Pro	Tyr	Ser	Asn	Pro	Ser	Leu	Cys	Ser	Gly		
				20				25						30			
Gly	Gly	Gly	Ser	Glu	Leu	Pro	Thr	Gln	Gly	Thr	Phe	Ser	Asn	Val	Ser		
				35				40						45			
Thr	Asn	Val	Ser	Pro	Ala	Lys	Pro	Thr	Thr	Thr	Ala	Cys	Pro	Tyr	Ser		
				50				55						60			
Asn	Pro	Ser	Leu	Cys	Ser	Gly	Gly	Gly	Gly	Ser	Pro	Ala	Pro	Pro	Pro		
65					70					75					80		
Thr	Pro	Ala	Pro	Thr	Ile	Ala	Ser	Gln	Pro	Leu	Ser	Leu	Arg	Pro	Glu		

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caagcagctg tccgagtccc 20
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20

25

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Gly Ile His Gly Val Pro Ala Ala Val Asp Leu Arg Thr Leu Gly Tyr

35

40

45

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

50

55

60

Ala Gln His His Glu Ala Leu Val Gly His Gly Phe Thr His Ala His

65

70

75

80

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

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Thr Val Gln Arg Leu	Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr		
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Pro Glu Gln Val Val Ala Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala			
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Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly			
435	440	445	
Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys			
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Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala			
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His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn Ile Gly			
485	490	495	
Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys			
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Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn			
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Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val			
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Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala			
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Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu			
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Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala			
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Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg			
595	600	605	
Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val			
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Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val			
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Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu			
645	650	655	
Gln Val Val Ala Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu			
660	665	670	
Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr			
675	680	685	
Pro Glu Gln Val Val Ala Ile Ala Ser Asn Ile Gly Gly Arg Pro Ala			
690	695	700	

Leu	Glu	Ser	Ile	Val	Ala	Gln	Leu	Ser	Arg	Pro	Asp	Pro	Ala	Leu	Ala
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Ala	Leu	Thr	Asn	Asp	His	Leu	Val	Ala	Leu	Ala	Cys	Leu	Gly	Gly	Arg
			725							730					735
Pro	Ala	Leu	Asp	Ala	Val	Lys	Lys	Gly	Leu	Pro	His	Ala	Pro	Ala	Leu
			740							745					750
Ile	Lys	Arg	Thr	Asn	Arg	Arg	Ile	Pro	Glu	Arg	Thr	Ser	His	Arg	Val
			755							760					765
Ala	Gly	Ser	Gln	Leu	Val	Lys	Ser	Glu	Leu	Glu	Glu	Lys	Lys	Ser	Glu
			770												780
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785						790									800
Glu	Ile	Ala	Arg	Asn	Ser	Thr	Gln	Asp	Arg	Ile	Leu	Glu	Met	Lys	Val
						805									815
Met	Glu	Phe	Phe	Met	Lys	Val	Tyr	Gly	Tyr	Arg	Gly	Lys	His	Leu	Gly
						820									830
Gly	Ser	Arg	Lys	Pro	Asp	Gly	Ala	Ile	Tyr	Thr	Val	Gly	Ser	Pro	Ile
						835									845
Asp	Tyr	Gly	Val	Ile	Val	Asp	Thr	Lys	Ala	Tyr	Ser	Gly	Gly	Tyr	Asn
						850									860
Leu	Pro	Ile	Gly	Gln	Ala	Asp	Glu	Met	Gln	Arg	Tyr	Val	Glu	Glu	Asn
865						870									880
Gln	Thr	Arg	Asn	Lys	His	Ile	Asn	Pro	Asn	Glu	Trp	Trp	Lys	Val	Tyr
						885									895
Pro	Ser	Ser	Val	Thr	Glu	Phe	Lys	Phe	Leu	Phe	Val	Ser	Gly	His	Phe
						900									910
Lys	Gly	Asn	Tyr	Lys	Ala	Gln	Leu	Thr	Arg	Leu	Asn	His	Ile	Thr	Asn
						915									925
Cys	Asn	Gly	Ala	Val	Leu	Ser	Val	Glu	Glu	Leu	Leu	Ile	Gly	Gly	Glu
						930									940
Met	Ile	Lys	Ala	Gly	Thr	Leu	Thr	Leu	Glu	Glu	Val	Arg	Arg	Lys	Phe
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Tyr Lys Asp Asp Asp Asp Lys Met Ala Pro Lys Lys Lys Arg Lys Val

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Gly Ile His Gly Val Pro Ala Ala Val Asp Leu Arg Thr Leu Gly Tyr

35 40 45

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

50 55 60

Ala Gln His His Glu Ala Leu Val Gly His Gly Phe Thr His Ala His

65 70 75 80

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

85 90 95

Lys Tyr Gln Asp Met Ile Ala Ala Leu Pro Glu Ala Thr His Glu Ala

100 105 110

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

115 120 125

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

130 135 140

Thr Gly Gln Leu Leu Lys Ile Ala Lys Arg Gly Gly Val Thr Ala Val

145 150 155 160

Glu Ala Val His Ala Trp Arg Asn Ala Leu Thr Gly Ala Pro Leu Asn

165 170 175

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

180 185 190

Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala

195 200 205

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

210 215 220

Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys

225 230 235 240

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

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

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

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Lys	Gly	Asn	Tyr	Lys	Ala	Gln	Leu	Thr	Arg	Leu	Asn	His	Ile	Thr	Asn				
				915					920					925					
Cys	Asn	Gly	Ala	Val	Leu	Ser	Val	Glu	Glu	Leu	Leu	Ile	Gly	Gly	Glu				
				930					935					940					
Met	Ile	Lys	Ala	Gly	Thr	Leu	Thr	Leu	Glu	Glu	Val	Arg	Arg	Lys	Phe				
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			20					25					30		
Gly	Ile	His	Gly	Val	Pro	Ala	Ala	Val	Asp	Leu	Arg	Thr	Leu	Gly	Tyr
		35					40					45			
Ser	Gln	Gln	Gln	Gln	Glu	Lys	Ile	Lys	Pro	Lys	Val	Arg	Ser	Thr	Val
		50				55					60				
Ala	Gln	His	His	Glu	Ala	Leu	Val	Gly	His	Gly	Phe	Thr	His	Ala	His
65					70				75					80	
Ile	Val	Ala	Leu	Ser	Gln	His	Pro	Ala	Ala	Leu	Gly	Thr	Val	Ala	Val

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

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

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

<210> 359

<211> 17

<212> DNA

<213> 智人

<400> 359

tgcctcaccc tcattcta 17

<210> 360

<211> 969

<212> PRT

<213> 智人

<400> 360

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

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Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala		
275	280	285
Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu		
290	295	300
Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala		
305	310	315
Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg		
	325	330
Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val		
	340	345
Val Ala Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu Thr Val		
	355	360
Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu		
	370	375
Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu		
385	390	395
Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr		
	405	410
Pro Glu Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala		
	420	425
Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly		
	435	440
Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys		
	450	455
Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala		
465	470	475
His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn Gly Gly		
	485	490
Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys		
	500	505
Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn		
	515	520
Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val		
	530	535
Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala		
545	550	555
Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu		
	565	570
Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala		

580	585	590
Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg		
595	600	605
Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val		
610	615	620
Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val		
625	630	635
Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu		
645	650	655
Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu		
660	665	670
Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr		
675	680	685
Pro Glu Gln Val Val Ala Ile Ala Ser Asn Ile Gly Gly Arg Pro Ala		
690	695	700
Leu Glu Ser Ile Val Ala Gln Leu Ser Arg Pro Asp Pro Ala Leu Ala		
705	710	715
Ala Leu Thr Asn Asp His Leu Val Ala Leu Ala Cys Leu Gly Gly Arg		
725	730	735
Pro Ala Leu Asp Ala Val Lys Lys Gly Leu Pro His Ala Pro Ala Leu		
740	745	750
Ile Lys Arg Thr Asn Arg Arg Ile Pro Glu Arg Thr Ser His Arg Val		
755	760	765
Ala Gly Ser Gln Leu Val Lys Ser Glu Leu Glu Glu Lys Lys Ser Glu		
770	775	780
Leu Arg His Lys Leu Lys Tyr Val Pro His Glu Tyr Ile Glu Leu Ile		
785	790	795
Glu Ile Ala Arg Asn Ser Thr Gln Asp Arg Ile Leu Glu Met Lys Val		
805	810	815
Met Glu Phe Phe Met Lys Val Tyr Gly Tyr Arg Gly Lys His Leu Gly		
820	825	830
Gly Ser Arg Lys Pro Asp Gly Ala Ile Tyr Thr Val Gly Ser Pro Ile		
835	840	845
Asp Tyr Gly Val Ile Val Asp Thr Lys Ala Tyr Ser Gly Gly Tyr Asn		
850	855	860
Leu Pro Ile Gly Gln Ala Asp Glu Met Gln Arg Tyr Val Glu Glu Asn		
865	870	875
Gln Thr Arg Asn Lys His Ile Asn Pro Asn Glu Trp Trp Lys Val Tyr		
885	890	895

Pro Ser Ser Val Thr Glu Phe Lys Phe Leu Phe Val Ser Gly His Phe
 900 905 910
 Lys Gly Asn Tyr Lys Ala Gln Leu Thr Arg Leu Asn His Ile Thr Asn
 915 920 925
 Cys Asn Gly Ala Val Leu Ser Val Glu Glu Leu Leu Ile Gly Gly Glu
 930 935 940
 Met Ile Lys Ala Gly Thr Leu Thr Leu Glu Glu Val Arg Arg Lys Phe
 945 950 955 960
 Asn Asn Gly Glu Ile Asn Phe Arg Ser
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<210> 361

<211> 49

<212> DNA

<213> 智人

<400> 361

ttgactctat tgtctggacc ttcaacacaa cccctcttgt caccataca 49

<210> 362

<211> 17

<212> DNA

<213> 智人

<400> 362

ttgactctat tgtctgg 17

<210> 363

<211> 969

<212> PRT

<213> 智人

<400> 363

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

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

405					410					415						
Pro	Glu	Gln	Val	Val	Ala	Ile	Ala	Ser	Asn	Ile	Gly	Gly	Lys	Gln	Ala	
420					425					430						
Leu	Glu	Thr	Val	Gln	Arg	Leu	Leu	Pro	Val	Leu	Cys	Gln	Ala	His	Gly	
435					440					445						
Leu	Thr	Pro	Glu	Gln	Val	Val	Ala	Ile	Ala	Ser	Asn	Gly	Gly	Gly	Lys	
450					455					460						
Gln	Ala	Leu	Glu	Thr	Val	Gln	Arg	Leu	Leu	Pro	Val	Leu	Cys	Gln	Ala	
465					470					475					480	
His	Gly	Leu	Thr	Pro	Glu	Gln	Val	Val	Ala	Ile	Ala	Ser	Asn	Gly	Gly	
485					490					495						
Gly	Lys	Gln	Ala	Leu	Glu	Thr	Val	Gln	Arg	Leu	Leu	Pro	Val	Leu	Cys	
500					505					510						
Gln	Ala	His	Gly	Leu	Thr	Pro	Glu	Gln	Val	Val	Ala	Ile	Ala	Ser	Asn	
515					520					525						
Asn	Gly	Gly	Lys	Gln	Ala	Leu	Glu	Thr	Val	Gln	Arg	Leu	Leu	Pro	Val	
530					535					540						
Leu	Cys	Gln	Ala	His	Gly	Leu	Thr	Pro	Glu	Gln	Val	Val	Ala	Ile	Ala	
545					550					555					560	
Ser	Asn	Gly	Gly	Gly	Lys	Gln	Ala	Leu	Glu	Thr	Val	Gln	Arg	Leu	Leu	
565					570					575						
Pro	Val	Leu	Cys	Gln	Ala	His	Gly	Leu	Thr	Pro	Glu	Gln	Val	Val	Ala	
580					585					590						
Ile	Ala	Ser	His	Asp	Gly	Gly	Lys	Gln	Ala	Leu	Glu	Thr	Val	Gln	Arg	
595					600					605						
Leu	Leu	Pro	Val	Leu	Cys	Gln	Ala	His	Gly	Leu	Thr	Pro	Glu	Gln	Val	
610					615					620						
Val	Ala	Ile	Ala	Ser	Asn	Gly	Gly	Gly	Lys	Gln	Ala	Leu	Glu	Thr	Val	
625					630					635					640	
Gln	Arg	Leu	Leu	Pro	Val	Leu	Cys	Gln	Ala	His	Gly	Leu	Thr	Pro	Glu	
645					650					655						
Gln	Val	Val	Ala	Ile	Ala	Ser	Asn	Asn	Gly	Gly	Lys	Gln	Ala	Leu	Glu	
660					665					670						
Thr	Val	Gln	Arg	Leu	Leu	Pro	Val	Leu	Cys	Gln	Ala	His	Gly	Leu	Thr	
675					680					685						
Pro	Glu	Gln	Val	Val	Ala	Ile	Ala	Ser	Asn	Asn	Gly	Gly	Arg	Pro	Ala	
690					695					700						
Leu	Glu	Ser	Ile	Val	Ala	Gln	Leu	Ser	Arg	Pro	Asp	Pro	Ala	Leu	Ala	
705					710					715					720	

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

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<211> 17

<212> DNA

<213> 智人

<400> 364

cctcttggtca ccataca 17

<210> 365

<211> 969

<212> PRT

<213> 智人

<400> 365

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

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275	280	285
Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu		
290	295	300
Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala		
305	310	315
Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg		
325	330	335
Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val		
340	345	350
Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val		
355	360	365
Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu		
370	375	380
Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu		
385	390	395
Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr		
405	410	415
Pro Glu Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala		
420	425	430
Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly		
435	440	445
Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn Ile Gly Gly Lys		
450	455	460
Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala		
465	470	475
His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly		
485	490	495
Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys		
500	505	510
Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn		
515	520	525
Ile Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val		
530	535	540
Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala		
545	550	555
Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu		
565	570	575
Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala		
580	585	590

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

900	905	910
Lys Gly Asn Tyr Lys Ala Gln Leu Thr Arg Leu Asn His Ile Thr Asn		
915	920	925
Cys Asn Gly Ala Val Leu Ser Val Glu Glu Leu Leu Ile Gly Gly Glu		
930	935	940
Met Ile Lys Ala Gly Thr Leu Thr Leu Glu Glu Val Arg Arg Lys Phe		
945	950	955
Asn Asn Gly Glu Ile Asn Phe Arg Ser		960
965		

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<212> DNA

<213> 智人

<400> 366

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<210> 367

<211> 18

<212> DNA

<213> 智人

<400> 367

ttccctccca ggcagctc 18

<210> 368

<211> 1003

<212> PRT

<213> 智人

<400> 368

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

100	105	110
Ile Val Gly Val Gly Lys Gln Trp Ser Gly Ala Arg Ala Leu Glu Ala		
115	120	125
Leu Leu Thr Val Ala Gly Glu Leu Arg Gly Pro Pro Leu Gln Leu Asp		
130	135	140
Thr Gly Gln Leu Leu Lys Ile Ala Lys Arg Gly Gly Val Thr Ala Val		
145	150	155
Glu Ala Val His Ala Trp Arg Asn Ala Leu Thr Gly Ala Pro Leu Asn		
165	170	175
Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys		
180	185	190
Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala		
195	200	205
His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly		
210	215	220
Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys		
225	230	235
Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His		
245	250	255
Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val		
260	265	270
Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala		
275	280	285
Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu		
290	295	300
Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala		
305	310	315
Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg		
325	330	335
Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val		
340	345	350
Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val		
355	360	365
Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu		
370	375	380
Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu		
385	390	395
Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr		
405	410	415

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

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

<210> 369

<211> 17

<212> DNA

<213> 智人

<400> 369

tggagttggg gccccta 17

<210> 370

<211> 969

<212> PRT

<213> 智人

<400> 370

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

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

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

Gln Thr Arg Asn Lys His Ile Asn Pro Asn Glu Trp Trp Lys Val Tyr
885 890 895
Pro Ser Ser Val Thr Glu Phe Lys Phe Leu Phe Val Ser Gly His Phe
900 905 910
Lys Gly Asn Tyr Lys Ala Gln Leu Thr Arg Leu Asn His Ile Thr Asn
915 920 925
Cys Asn Gly Ala Val Leu Ser Val Glu Glu Leu Leu Ile Gly Gly Glu
930 935 940
Met Ile Lys Ala Gly Thr Leu Thr Leu Glu Glu Val Arg Arg Lys Phe
945 950 955 960
Asn Asn Gly Glu Ile Asn Phe Arg Ser
965

<210> 371

<211> 49

<212> DNA

<213> 智人

<400> 371

ttcctcctac tcaccatcag cctcctggtt atggtacagg taagagcaa 49

<210> 372

<211> 17

<212> DNA

<213> 智人

<400> 372

ttcctcctac tcaccat 17

<210> 373

<211> 969

<212> PRT

<213> 智人

<400> 373

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

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

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

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

<210> 374

<211> 17

<212> DNA

<213> 智人

<400> 374

ggtacaggta agagcaa 17

<210> 375

<211> 969

<212> PRT

<213> 智人

<400> 375

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

260	265	270
Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala		
275	280	285
Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu		
290	295	300
Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala		
305	310	315
Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg		
325	330	335
Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val		
340	345	350
Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val		
355	360	365
Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu		
370	375	380
Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu		
385	390	395
Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr		
405	410	415
Pro Glu Gln Val Val Ala Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala		
420	425	430
Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly		
435	440	445
Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys		
450	455	460
Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala		
465	470	475
His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly		
485	490	495
Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys		
500	505	510
Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn		
515	520	525
Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val		
530	535	540
Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala		
545	550	555
Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu		
565	570	575

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

				885					890					895					
Pro	Ser	Ser	Val	Thr	Glu	Phe	Lys	Phe	Leu	Phe	Val	Ser	Gly	His	Phe				
				900					905					910					
Lys	Gly	Asn	Tyr	Lys	Ala	Gln	Leu	Thr	Arg	Leu	Asn	His	Ile	Thr	Asn				
				915					920					925					
Cys	Asn	Gly	Ala	Val	Leu	Ser	Val	Glu	Glu	Leu	Leu	Ile	Gly	Gly	Glu				
				930					935					940					
Met	Ile	Lys	Ala	Gly	Thr	Leu	Thr	Leu	Glu	Glu	Val	Arg	Arg	Lys	Phe				
945								950					955			960			
Asn	Asn	Gly	Glu	Ile	Asn	Phe	Arg	Ser											

965

<210> 376

<211> 49

<212> DNA

<213> 智人

<400> 376

ttgtcccaca gatattccaga accctgaccc tgccgtgtac cagctgaga 49

<210> 377

<211> 17

<212> DNA

<213> 智人

<400> 377

ttgtcccaca gatattcc 17

<210> 378

<211> 969

<212> PRT

<213> 智人

<400> 378

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

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

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

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

<210> 379

<211> 17

<212> DNA

<213> 智人

<400> 379

ccgtgtacca gctgaga 17

<210> 380

<211> 969

<212> PRT

<213> 智人

<400> 380

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

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Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala		
275	280	285
Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu		
290	295	300
Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala		
305	310	315
Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg		
	325	330
Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val		
	340	345
Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val		
	355	360
Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu		
	370	375
Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu		
385	390	395
Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr		
	405	410
Pro Glu Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala		
	420	425
Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly		
	435	440
Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys		
	450	455
Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala		
465	470	475
His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn Gly Gly		
	485	490
Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys		
	500	505
Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn		
	515	520
Ile Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val		
	530	535
Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala		
545	550	555
Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu		
	565	570
Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala		

580	585	590
Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg		
595	600	605
Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val		
610	615	620
Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val		
625	630	635
Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu		
645	650	655
Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu		
660	665	670
Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr		
675	680	685
Pro Glu Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Arg Pro Ala		
690	695	700
Leu Glu Ser Ile Val Ala Gln Leu Ser Arg Pro Asp Pro Ala Leu Ala		
705	710	715
Ala Leu Thr Asn Asp His Leu Val Ala Leu Ala Cys Leu Gly Gly Arg		
725	730	735
Pro Ala Leu Asp Ala Val Lys Lys Gly Leu Pro His Ala Pro Ala Leu		
740	745	750
Ile Lys Arg Thr Asn Arg Arg Ile Pro Glu Arg Thr Ser His Arg Val		
755	760	765
Ala Gly Ser Gln Leu Val Lys Ser Glu Leu Glu Glu Lys Lys Ser Glu		
770	775	780
Leu Arg His Lys Leu Lys Tyr Val Pro His Glu Tyr Ile Glu Leu Ile		
785	790	795
Glu Ile Ala Arg Asn Ser Thr Gln Asp Arg Ile Leu Glu Met Lys Val		
805	810	815
Met Glu Phe Phe Met Lys Val Tyr Gly Tyr Arg Gly Lys His Leu Gly		
820	825	830
Gly Ser Arg Lys Pro Asp Gly Ala Ile Tyr Thr Val Gly Ser Pro Ile		
835	840	845
Asp Tyr Gly Val Ile Val Asp Thr Lys Ala Tyr Ser Gly Gly Tyr Asn		
850	855	860
Leu Pro Ile Gly Gln Ala Asp Glu Met Gln Arg Tyr Val Glu Glu Asn		
865	870	875
Gln Thr Arg Asn Lys His Ile Asn Pro Asn Glu Trp Trp Lys Val Tyr		
885	890	895

Pro Ser Ser Val Thr Glu Phe Lys Phe Leu Phe Val Ser Gly His Phe
 900 905 910
 Lys Gly Asn Tyr Lys Ala Gln Leu Thr Arg Leu Asn His Ile Thr Asn
 915 920 925
 Cys Asn Gly Ala Val Leu Ser Val Glu Glu Leu Leu Ile Gly Gly Glu
 930 935 940
 Met Ile Lys Ala Gly Thr Leu Thr Leu Glu Glu Val Arg Arg Lys Phe
 945 950 955 960
 Asn Asn Gly Glu Ile Asn Phe Arg Ser
 965

<210> 381

<211> 49

<212> DNA

<213> 智人

<400> 381

ttctccccag ccctgctcgt ggtgaccgaa ggggacaacg ccaccttca 49

<210> 382

<211> 936

<212> PRT

<213> 智人

<400> 382

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

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

450	455	460
His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly		
465	470	475
Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys		
485	490	495
Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His		
500	505	510
Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val		
515	520	525
Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala		
530	535	540
Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu		
545	550	555
Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala		
565	570	575
Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg		
580	585	590
Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val		
595	600	605
Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val		
610	615	620
Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu		
625	630	635
Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu		
645	650	655
Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr		
660	665	670
Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Arg Pro Ala		
675	680	685
Leu Glu Ser Ile Val Ala Gln Leu Ser Arg Pro Asp Pro Ala Leu Ala		
690	695	700
Ala Leu Thr Asn Asp His Leu Val Ala Leu Ala Cys Leu Gly Gly Arg		
705	710	715
Pro Ala Leu Asp Ala Val Lys Lys Gly Leu Gly Asp Pro Ile Ser Arg		
725	730	735
Ser Gln Leu Val Lys Ser Glu Leu Glu Glu Lys Lys Ser Glu Leu Arg		
740	745	750
His Lys Leu Lys Tyr Val Pro His Glu Tyr Ile Glu Leu Ile Glu Ile		
755	760	765

Ala Arg Asn Ser Thr Gln Asp Arg Ile Leu Glu Met Lys Val Met Glu		
770	775	780
Phe Phe Met Lys Val Tyr Gly Tyr Arg Gly Lys His Leu Gly Gly Ser		
785	790	795 800
Arg Lys Pro Asp Gly Ala Ile Tyr Thr Val Gly Ser Pro Ile Asp Tyr		
805	810	815
Gly Val Ile Val Asp Thr Lys Ala Tyr Ser Gly Gly Tyr Asn Leu Pro		
820	825	830
Ile Gly Gln Ala Asp Glu Met Gln Arg Tyr Val Glu Glu Asn Gln Thr		
835	840	845
Arg Asn Lys His Ile Asn Pro Asn Glu Trp Trp Lys Val Tyr Pro Ser		
850	855	860
Ser Val Thr Glu Phe Lys Phe Leu Phe Val Ser Gly His Phe Lys Gly		
865	870	875 880
Asn Tyr Lys Ala Gln Leu Thr Arg Leu Asn His Ile Thr Asn Cys Asn		
885	890	895
Gly Ala Val Leu Ser Val Glu Glu Leu Leu Ile Gly Gly Glu Met Ile		
900	905	910
Lys Ala Gly Thr Leu Thr Leu Glu Glu Val Arg Arg Lys Phe Asn Asn		
915	920	925
Gly Glu Ile Asn Phe Ala Ala Asp		
930	935	
<210> 383		
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<213> 智人		
<400> 383		
Met Gly Asp Pro Lys Lys Lys Arg Lys Val Ile Asp Lys Glu Thr Ala		
1	5	10 15
Ala Ala Lys Phe Glu Arg Gln His Met Asp Ser Ile Asp Ile Ala Asp		
20	25	30
Leu Arg Thr Leu Gly Tyr Ser Gln Gln Gln Gln Glu Lys Ile Lys Pro		
35	40	45
Lys Val Arg Ser Thr Val Ala Gln His His Glu Ala Leu Val Gly His		
50	55	60
Gly Phe Thr His Ala His Ile Val Ala Leu Ser Gln His Pro Ala Ala		
65	70	75 80
Leu Gly Thr Val Ala Val Lys Tyr Gln Asp Met Ile Ala Ala Leu Pro		
85	90	95

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

	405		410		415
Ile Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Ala Leu Leu Pro Val					
	420		425		430
Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala					
	435		440		445
Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu					
	450		455		460
Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala					
465		470		475	480
Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg					
	485		490		495
Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val					
	500		505		510
Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val					
	515		520		525
Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln					
	530		535		540
Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu					
545		550		555	560
Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr					
	565		570		575
Pro Glu Gln Val Val Ala Ile Ala Ser Asn Gly Gly Lys Gln Ala Leu					
	580		585		590
Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu					
	595		600		605
Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln					
	610		615		620
Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His					
625		630		635	640
Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly Gly					
	645		650		655
Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln					
	660		665		670
Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly					
	675		680		685
Gly Gly Arg Pro Ala Leu Glu Ser Ile Val Ala Gln Leu Ser Arg Pro					
	690		695		700
Asp Pro Ala Leu Ala Ala Leu Thr Asn Asp His Leu Val Ala Leu Ala					
705		710		715	720

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

<210> 384

<211> 100

<212> RNA

<213> 人工序列

<220>

<223> 合成的

<400> 384

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 cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 385

<211> 21

<212> DNA
<213> 人工序列
<220>
<223> 合成的
<400> 385
agcgctctcg tacagagttg g 21
<210> 386
<211> 23
<212> DNA
<213> 人工序列
<220>
<223> 合成的
<400> 386
aaaaaaagca ccgactcggg gcc 23
<210> 387
<211> 100
<212> RNA
<213> 人工序列
<220>
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<223> 2'OMe
<220>
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<223> 硫代磷酸酯
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<223> 2'OMe

<220>

<221> 其它特征

<222> (97) .. (98)

<223> 硫代磷酸酯

<220>

<221> 其它特征

<222> (98) .. (99)

<223> 硫代磷酸酯

<220>

<221> 其它特征

<222> (99) .. (100)

<223> 硫代磷酸酯

<400> 387

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 388

<211> 20

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 388

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Leu Ala Phe Gly

20

<210> 389

<211> 495

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 389

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro

1 5 10 15

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

20 25 30

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr

35	40	45
Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly		
50	55	60
Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr		
65	70	75
Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser		
85	90	95
Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala		
100	105	110
Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe		
115	120	125
Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly		
130	135	140
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met		
145	150	155
Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser		
165	170	175
Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr		
180	185	190
Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu		
195	200	205
Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser		
210	215	220
Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu		
225	230	235
Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro		
245	250	255
Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro		
260	265	270
Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala		
275	280	285
Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly		
290	295	300
Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile		
305	310	315
Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val		
325	330	335
Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe		
340	345	350

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

<210> 390

<211> 1485

<212> DNA

<213> 人工序列

<220>

<223> 合成的

<400> 390

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tcattgcaaag ctagtggata tacatttact tcttacgtga tgcactgggt aaaacagaaa 180
cctgggtcagg ggcttgagtg gatcgggtac attaacccat ataatgacgg caccaaatat 240
aacgagaaat tcaagggaag ggctacgctt acatcagata agtccagtag caccgcttat 300
atggaactta gcagccttac ttccgaagat tccgcggtgt attactgctg gagagggact 360
tactactacg ggagtcgagt attcgattat tggggtcaag gcacgacgct cacggtgagc 420
tcaggtggtg gaggggtctgg ggggtggcggc agtggtgggg ggggctcaga catcgtgatg 480
accaggcag cacccttctat cccggttaacc ccaggcgagt ctgtatctat cagttgtcgg 540
tccagcaagt ctcttctcaa cagtaatggc aatacatatc ttacttggtt cctccaaagg 600
cctgggcaaa gtctctcaact tcttatatat cggtatgtcca atcttgcgag tggcgtaccc 660
gacaggtttt cagggtcttg gagcggaaca gcttttacgt tgagaatatc cagggtagaa 720
gctgaggacg tcggtgtata ttattgcatg caacatctcg aatacccctt taccttcggc 780
gctggtacaa agctcgaatt gaaacgcagc gatccaacca cgacgccagc gccacgacca 840

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cctacgccccg ctccaactat tgcctcccag cccctgagtc ttcggccaga agcgtgtaga 900
 cctgctgccg gcggggccgt tcatacgcg ggccttgact ttgcatgtga tatctatata 960
 tgggctcctt tggcggaac ttgcggagt cttcttttgt cactcgtgat aacgttgtat 1020
 tgtaaaaggg gtcgaaagaa actcctctat atatttaagc agccctttat gaggcccggtg 1080
 caaacaacac aagaagagga cggatgctct tgtcgattcc cggaagagga ggaggggggg 1140
 tgtgagctta gggcaagtt ttctcgtct ggcgacgcgc cagcctatca acagggccaa 1200
 aaccagctgt ataacgaact caacctcggg cgccgggaag agtatgacgt ccttgacaaa 1260
 cggcgcggtc gcgaccctga aatgggtgga aaaccgaggc gaaagaaccc ccaggaggga 1320
 ctttacaacg aattgcaaaa agacaagatg gccgaagcct attccgaaat tggaatgaaa 1380
 ggcgagcgga gacgaggtaa ggggcatgac ggctgtatc aagggtcttc tacggccacg 1440
 aaggatactt acgacgccct tcatatgcaa gctcttcac cacgg 1485

<210> 391

<211> 374

<212> PRT

<213> 智人

<400> 391

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

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

<210> 392

<211> 1122

<212> DNA

<213> 人工序列

<220>

<223> 合成的

<400> 392

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gtccgccaat tcagtcgcct cttcgttccc atcgcgatcc cccttatttg tgtttttggc 180
cttctgggta acatcctggt tgtaatcaca ttcgctttct ataaaaaagc tcggagtatg 240
actgatgttt accttcttaa catggctata gcggacattc tttttgtgct tactctccca 300
ttctgggctg tgagccatgc aacaggggcg tgggtttttt caaatgccac atgtaagctg 360
cttaaaggga tctatgcaat aaacttcaat tgcgggatgc tcctgctgac atgcatcagt 420

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atggatcgat acatagctat agtacaggcg actaagtcct tccgcctgcg atccccgaca 480
 ctgcctagga gcaaaattat ttgcctcgtc gtatgggggc tctcagtgat catctcctcc 540
 agtacgtttg tctttaacca gaaatataac acacagggtt ctgatgtatg tgaaccaaag 600
 tatcagacag tgagtgaacc aatacgggtg aagttgctta tgttgggctt ggagctgctt 660
 tttgggtttt tcatcccact gatgttcatt attttctgtt atacatttat tgttaagacc 720
 ttgggttcagg cgcaaaatag caagagacat aaggcaattc gagtcattcat tgccgtggtg 780
 ttgggtcttct tggcctgtca gatcccccat aatatgggtc tgctcgtcac cgccgctaac 840
 ttgggtaaga tgaatcgatc ttgtcagtcg gagaagttga tcggatacac caaaactgtg 900
 acagaagtgc tggccttcct tcaactgttg ctgaaccag ttttgtatgc ttttatagga 960
 cagaagtctt gaaattactt cttgaaaatc ctcaaggacc tctgggtgtg tcgaaggaag 1020
 tacaagagct ctggcttttag ttgcgtggg cgctacagtg agaatatatc ccggcagacc 1080
 tccgagactg ctgataatga caacgcaagt tccttcaacta tg 1122

<210> 393

<211> 1122

<212> DNA

<213> 智人

<400> 393

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 gtcaggcagt tctccaggct atttgtaccg attgcctact ccttgatctg tgtctttggc 180
 ctcttgggga atattctggt ggtgatcacc tttgcttttt ataagaaggc caggtctatg 240
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 ttctgggcag tgagtcattg cactgggtgc tgggttttca gcaatgccac gtgcaagttg 360
 ctaaaaggca tctatgccat caactttaac tgcgggatgc tgctcctgac ttgcattagc 420
 atggaccggt acatcgccat tgtacaggcg actaagtcatt tccggctccg atccagaaca 480
 ctaccgcgca cgaaaatcat ctgccttggt gtgtgggggc tgcagtcatt catctccagc 540
 tcaacttttg tcttcaacca aaaatacaac acccaaggca gcgatgtctg tgaacccaag 600
 taccagactg tctcggagcc catcaggtgg aagctgctga tgttggggct tgagctactc 660
 tttggtttct ttatcccttt gatgttcatt atttttgtt acacgttcat tgtcaaaacc 720
 ttggtgcaag ctcaagaattc taaaaggcac aaagccatcc gtgtaatcat agctgtggtg 780
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 acagaagtcc tggctttcct gcaactgtgc ctgaacctg tgctctacgc ttttattggg 960
 cagaagtcca gaaactactt tctgaagatc ttgaaggacc tgtggtgtgt gagaaggaag 1020
 tacaagtcct caggcttctc ctgtgccggg aggtactcag aaaacatttc tcggcagacc 1080
 agtgagaccg cagataacga caatgcgtcg tccttcaacta tg 1122

<210> 394

<211> 157

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 394

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

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<210> 395

<211> 471

<212> DNA

<213> 人工序列

<220>

<223> 合成的

<400> 395

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cagggaacct tctctaattg ctccaccaac gtctccctg caaaaccgac cacaacagct 180
tgcccctata gtaacccttc cctctgtagt ggaggggggg gttcacctgc tccacgcct 240
cctacccccg cgccaacgat cgcgtcacia ccgctcagtc ttaggccgga agcctgtagg 300
ccagcggctg gcggtgcggt tcatacgcg ggattggatt ttgcctgcga catttacatt 360
tgggctccgc tggccgttac ttgtgggta ttgctgttgt ctcttgttat tacgctttat 420
tgcaatcaca ggaacaggcg acgagtatgc aaatgccgc ggcccgtcgt g 471

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<210> 396

<211> 28

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 396

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

1 5 10 15

Val Thr Leu Met Val Leu Ser Ser Pro Leu Ala Leu

20 25

<210> 397

<211> 84

<212> DNA

<213> 人工序列

<220>

<223> 合成的

<400> 397

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gtccttagtt caccgcttgc cctg 84

<210> 398

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<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 398

Ala Ser

1

<210> 399

<211> 6

<212> DNA

<213> 人工序列

<220>

<223> 合成的

<400> 399

gcatct 6

<210> 400

<211> 13

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 400

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

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5

10

<210> 401

<211> 39

<212> DNA

<213> 人工序列

<220>

<223> 合成的

<400> 401

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<210> 402

<211> 555

<212> DNA

<213> 人工序列

<220>

<223> 合成的

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gactcagatg tcggcgagtt ccgagcgggt acggaattgg ggcgacctga cgcggagtac 180
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ggaatggtaa gtactggtct tatccagaac ggagactgga ccttccaaac tttggtaatg 480
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<211> 2895

<212> DNA

<213> 人工序列

<220>

<223> 合成的

<400> 403

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<210> 404

<211> 39

<212> DNA

<213> 人工序列

<220>

<223> 合成的

<400> 404

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<210> 405

<211> 1225

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 405

Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala

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

20 25 30

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

35 40 45

Thr Asn Val Ser Pro Ala Lys Pro Thr Thr Thr Ala Cys Pro Tyr Ser

50 55 60

Asn Pro Ser Leu Cys Ser Gly Gly Gly Gly Ser Pro Ala Pro Arg Pro

65 70 75 80

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

85 90 95

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu

100 105 110

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

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

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

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

<210> 406

<211> 78

<212> DNA

<213> 人工序列

<220>

<223> 合成的

<400> 406

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<210> 407

<211> 2

<212> PRT

<213> 人工序列

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<223> 合成的

<400> 407

Thr Ala

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<210> 408

<211> 6

<212> DNA

<213> 人工序列

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<223> 合成的

<400> 408

acaagt 6

<210> 409

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<212> DNA

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<210> 410

<211> 336

<212> DNA

<213> 人工序列

<220>

<223> 合成的

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 cgcgatccccg aaatgggggg aaagcctcgg aggaagaacc cacaagaagg cttttataat 180
 gaactgcaga aggacaagat ggcggaggcg tattccgaaa taggcatgaa gggatgaacgg 240
 aggagaggaa agggacatga cggactttat caaggattgt ctaccgcaac taaagacacc 300
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<210> 411

<211> 58

<212> DNA

<213> 人工序列

<220>

<223> 合成的

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<210> 412

<211> 400

<212> PRT

<213> 人工序列

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<223> 合成的

<400> 412

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				20				25					30		
Asn	Pro	Val	Val	His	Phe	Phe	Lys	Asn	Ile	Val	Thr	Pro	Arg	Thr	Pro
				35				40					45		
Pro	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Ser	Gly	Asp
				50				55					60		

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

370	375	380	
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385	390	395	400
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<212> DNA			
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aacatcgta caccgcgcac cccacctggg ggaggcggat ctggcggagg cgggagtgga	180		
ggctcaggag acacaagacc ccgattcttg tggcagccca aaagggagtg ccattttttc	240		
aatgggacgg aacgagttcg cttccttgat cggtactttt acaaccaaga agagagtgtg	300		
cggttcgact cagatgtcgg cgagttccga gcggttacgg aattggggcg acctgacgcg	360		
gagtactgga actcccaaaa ggatattttg gagcaggcac gagcagctgt ggacacctat	420		
tgtcgacata attatggtgt ggtggaatcc tttacagttc agcggcgggt gcaacctaaa	480		
gtgaccgtgt atccatctaa aacgcaaccc ctccaacacc ataacctcct ggtgtgttcc	540		
gtaagcggct tctatcccgg gtcaattgag gtcaggtggt tcctcaacgg tcaggaggag	600		
aaggccggaa tggtaagtac tggctctatc cagaacggag actggacctt ccaaactttg	660		
gtaatgttgg aaacggtgcc gcgatccggg gaggtgtata catgccaagt tgaacacccg	720		
agtgttacga gccccctgac ggttgagtgg agggcgcggt cagagagcgc acaatctaaa	780		
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tatcagcaag gtcaaaacca gctttacaac gaactgaact tgggacgacg cgaagagtac	960		
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gaaataggca tgaagggtga acggaggaga ggaaaggac atgacggact ttatcaagga	1140		
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<220>			
<223> 合成的			
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caggaatcat gggcg	75		

<210> 415

<211> 534

<212> DNA

<213> 人工序列

<220>

<223> 合成的

<400> 415

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acgggtgtgga gacttgagga gtttggacga ttcgcatcat ttgaggcaca aggagcactc 180
gccaatatcg cggtggacaa ggccaacctg gagatcatga caaacgctc caattatacg 240
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gaacctaacg tcctcatatg tttcatcgac aagttcactc ctccggtgggt caatgtaacg 360
tggttcgga atggttaagc ggtcaccacg ggtgtctcag agaccgtatt tctgcccaga 420
gaagaccacc tcttccgcaa atttcattac ctccctttc ttccttcaac ggaagacgtt 480
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<210> 416

<211> 23

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 416

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1           5           10           15
Ile Gly Thr Ile Phe Ile Ile
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<210> 417

<211> 39

<212> DNA

<213> 人工序列

<220>

<223> 合成的

<400> 417

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<211> 26

<212> PRT

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<220>

<223> 合成的

<400> 418

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1 5 10 15

Ile Gly Thr Ile Phe Ile Ile Lys Gly Leu

20 25

<210> 419

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<220>

<223> 合成的

<400> 419

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<211> 2

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 420

Thr Ser

1

<210> 421

<211> 6

<212> DNA

<213> 人工序列

<220>

<223> 合成的

<400> 421

acttcc 6

<210> 422

<211> 336

<212> DNA

<213> 人工序列

<220>

<223> 合成的

<400> 422

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 cgagaccctg agatgggscgg taaaccgaga cggaaaaatc cccaagaggg tctttataat 180
 gaactccaga aggataagat ggctgaagcc tattctgaga tagggatgaa aggcgagcgg 240
 cggaggggta agggccatga tggcctttac cagggactct ccacggcaac caagataact 300
 tacgacgccc ttcacatgca agccctcccg ccacgc 336

<210> 423

<211> 356

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 423

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

195	200	205
Ser Pro Leu Pro Glu Thr Thr Glu Asn Val Val Cys Ala Leu Gly Leu		
210	215	220
Thr Val Gly Leu Val Gly Ile Ile Ile Gly Thr Ile Phe Ile Ile Lys		
225	230	235
Gly Leu Thr Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala		
245	250	255
Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg		
260	265	270
Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu		
275	280	285
Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn		
290	295	300
Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met		
305	310	315
Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly		
325	330	335
Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala		
340	345	350

Leu Pro Pro Arg

355

<210> 424

<211> 1068

<212> DNA

<213> 人工序列

<220>

<223> 合成的

<400> 424

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ccggaccaga gcggtgagtt catgttcgat tttgatggcg acgagatatt tcacgttgac 180
atggcaaaaa aggaaacggt gtggagactt gaggagtttg gacgattcgc atcatttgag 240
gcacaaggag cactcgccaa tatcgcggtg gacaaggcca acctggagat catgacaaaa 300
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cccgtagaac ttagggaacc taacgtcttc atatgtttca tcgacaagtt cactcctccg 420
gtgggtcaatg taacgtggct tcggaatggt aagccggtca ccacgggtgt ctcagagacc 480
gtattttctgc ccagagaaga ccacctcttc cgcaaatttc attaccttcc cttttcttct 540
tcaacggaag acgtttacga ctgcagggtc gaacattggg ggcttgacga gccacttctc 600
aagcattggg agttcgacgc cccatcaccg cttccagaaa cgactgaaaa cgttgtctgc 660

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gctcttggcc tgacagtggg cctggtaggc attattatcg ggaccatctt tatcatcaaa 720
 ggtttgactt cccgggtcaa atttagcaga tccgctgacg caccggccta ccagcagggc 780
 cagaaccaac tctacaacga gctgaatctc ggccgacggg aagagtatga cgtactcgac 840
 aagcggagag gtcgagaccc tgagatgggc ggtaaaccga gacggaaaaa tccccaagag 900
 ggtctttata atgaactcca gaaggataag atggctgaag cctattctga gatagggatg 960
 aaaggcgagc ggccggagggg taagggccat gatggccttt accagggact ctccacggca 1020
 accaaagata cttacgacgc cttcacatg caagccctcc cgccacgc 1068

<210> 425

<211> 893

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 425

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

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

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

820	825	830
Val Leu Tyr Ala Phe Ile Gly Gln Lys Phe Arg Asn Tyr Phe Leu Lys		
835	840	845
Ile Leu Lys Asp Leu Trp Cys Val Arg Arg Lys Tyr Lys Ser Ser Gly		
850	855	860
Phe Ser Cys Ala Gly Arg Tyr Ser Glu Asn Ile Ser Arg Gln Thr Ser		
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Glu Thr Ala Asp Asn Asp Asn Ala Ser Ser Phe Thr Met		880
885	890	

<210> 426

<211> 2679

<212> DNA

<213> 人工序列

<220>

<223> 合成的

<400> 426

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<211> 238

<212> PRT

<213> 人工序列

<220>

<223> 合成的

<400> 427

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

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

				565					570					575			
Val	Phe	Gly	Leu	Leu	Gly	Asn	Ile	Leu	Val	Val	Ile	Thr	Phe	Ala	Phe		
				580					585					590			
Tyr	Lys	Lys	Ala	Arg	Ser	Met	Thr	Asp	Val	Tyr	Leu	Leu	Asn	Met	Ala		
				595					600					605			
Ile	Ala	Asp	Ile	Leu	Phe	Val	Leu	Thr	Leu	Pro	Phe	Trp	Ala	Val	Ser		
				610					615					620			
His	Ala	Thr	Gly	Ala	Trp	Val	Phe	Ser	Asn	Ala	Thr	Cys	Lys	Leu	Leu		
625						630					635				640		
Lys	Gly	Ile	Tyr	Ala	Ile	Asn	Phe	Asn	Cys	Gly	Met	Leu	Leu	Leu	Thr		
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Cys	Ile	Ser	Met	Asp	Arg	Tyr	Ile	Ala	Ile	Val	Gln	Ala	Thr	Lys	Ser		
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Phe	Arg	Leu	Arg	Ser	Arg	Thr	Leu	Pro	Arg	Ser	Lys	Ile	Ile	Cys	Leu		
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Val	Val	Trp	Gly	Leu	Ser	Val	Ile	Ile	Ser	Ser	Ser	Thr	Phe	Val	Phe		
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Asn	Gln	Lys	Tyr	Asn	Thr	Gln	Gly	Ser	Asp	Val	Cys	Glu	Pro	Lys	Tyr		
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Gln	Thr	Val	Ser	Glu	Pro	Ile	Arg	Trp	Lys	Leu	Leu	Met	Leu	Gly	Leu		
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Glu	Leu	Leu	Phe	Gly	Phe	Phe	Ile	Pro	Leu	Met	Phe	Met	Ile	Phe	Cys		
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Tyr	Thr	Phe	Ile	Val	Lys	Thr	Leu	Val	Gln	Ala	Gln	Asn	Ser	Lys	Arg		
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785						790					795				800		
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Val	Leu	Tyr	Ala	Phe	Ile	Gly	Gln	Lys	Phe	Arg	Asn	Tyr	Phe	Leu	Lys		
				835					840					845			
Ile	Leu	Lys	Asp	Leu	Trp	Cys	Val	Arg	Arg	Lys	Tyr	Lys	Ser	Ser	Gly		
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Phe	Ser	Cys	Ala	Gly	Arg	Tyr	Ser	Glu	Asn	Ile	Ser	Arg	Gln	Thr	Ser		
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Glu Thr Ala Asp Asn Asp Asn Ala Ser Ser Phe Thr Met Gly Ser Gly		
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Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn		
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Pro Gly Pro Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro		
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Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val		
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Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys		
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Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val		
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Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His		
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Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val		
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Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr		
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Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile		
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Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly		
1040	1045	1050
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Ala Asp Lys Gln Lys Asn Gly Ile Lys Ala Asn Phe Lys Ile Arg		
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His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln		
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Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn		
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His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu		
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<213> 人工序列

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<223> 合成的

<400> 430

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<212> PRT

<213> 人工序列

<220>

<223> 合成的

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

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

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Gly	Ser	Ser	Gly	Ser	Gly	Glu	Gly	Arg	Gly	Ser	Leu	Leu	Thr	Cys	Gly	
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Asp	Val	Glu	Glu	Asn	Pro	Gly	Pro	Met	Ala	Ile	Ser	Gly	Val	Pro	Val	
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Leu	Gly	Phe	Phe	Ile	Ile	Ala	Val	Leu	Met	Ser	Ala	Gln	Glu	Ser	Trp	
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Ala	Ile	Lys	Glu	Glu	His	Val	Ile	Ile	Gln	Ala	Glu	Phe	Tyr	Leu	Asn	
450						455					460					
Pro	Asp	Gln	Ser	Gly	Glu	Phe	Met	Phe	Asp	Phe	Asp	Gly	Asp	Glu	Ile	
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Pro	Val	Glu	Leu	Arg	Glu	Pro	Asn	Val	Leu	Ile	Cys	Phe	Ile	Asp	Lys	
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Val	Tyr	Asp	Cys	Arg	Val	Glu	His	Trp	Gly	Leu	Asp	Glu	Pro	Leu	Leu	
610					615				620							
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Asn	Val	Val	Cys	Ala	Leu	Gly	Leu	Thr	Val	Gly	Leu	Val	Gly	Ile	Ile	
					645			650					655			
Ile	Gly	Thr	Ile	Phe	Ile	Ile	Lys	Gly	Leu	Thr	Ser	Arg	Val	Lys	Phe	
		660				665						670				
Ser	Arg	Ser	Ala	Asp	Ala	Pro	Ala	Tyr	Gln	Gln	Gly	Gln	Asn	Gln	Leu	
		675				680					685					
Tyr	Asn	Glu	Leu	Asn	Leu	Gly	Arg	Arg	Glu	Glu	Tyr	Asp	Val	Leu	Asp	

690	695	700
Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys		
705	710	715
Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala		
	725	730
Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys		
	740	745
Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr		
	755	760
Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg		
770	775	780



图1

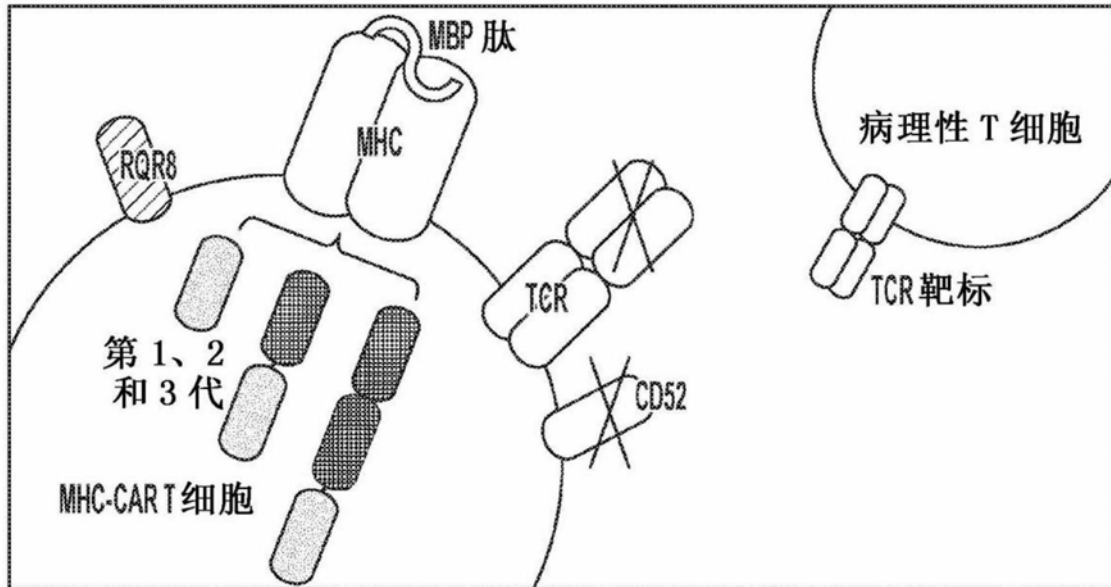


图2

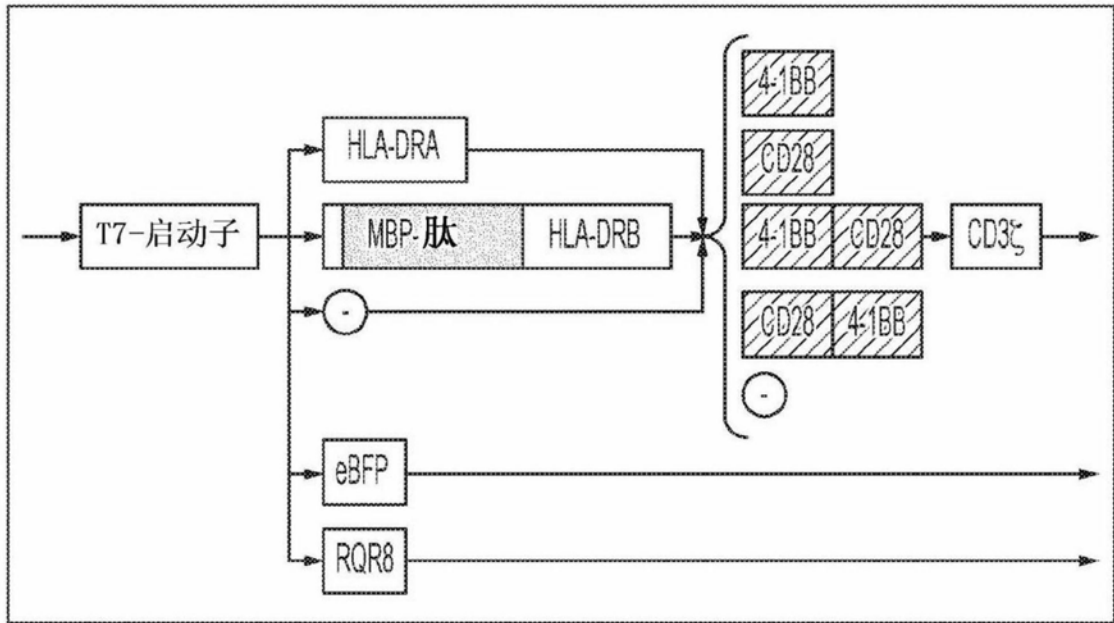


图3

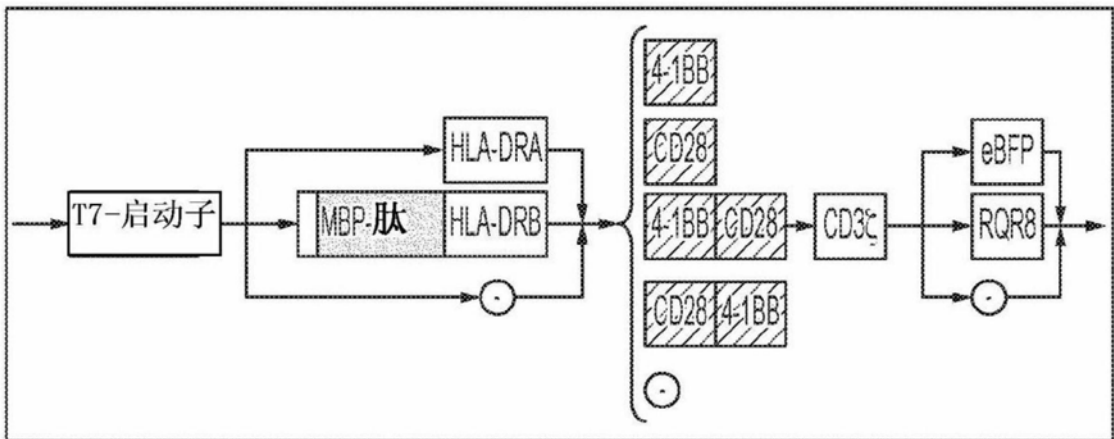


图4

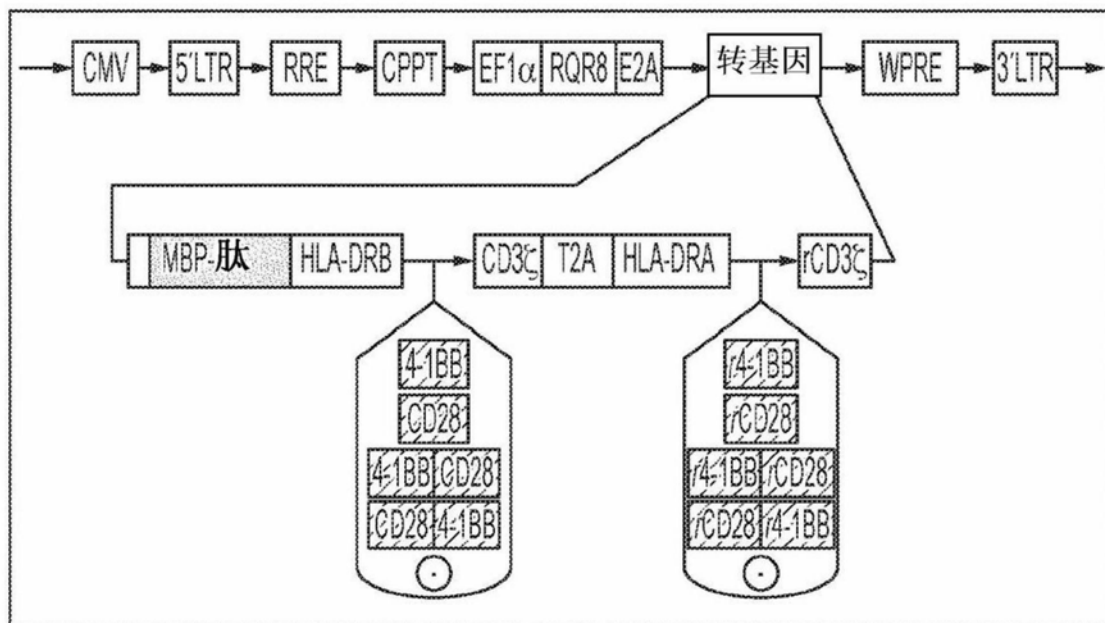


图5

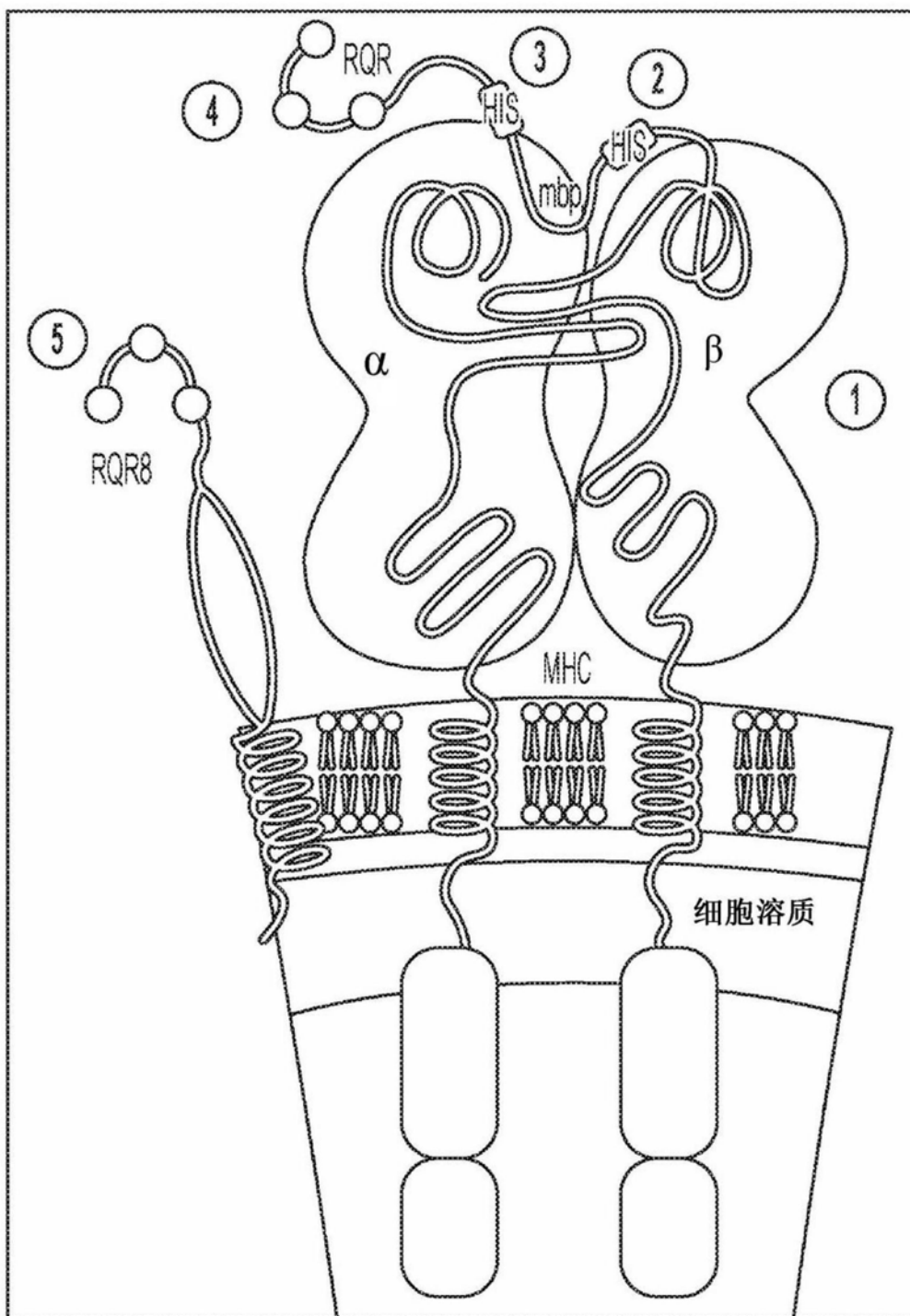
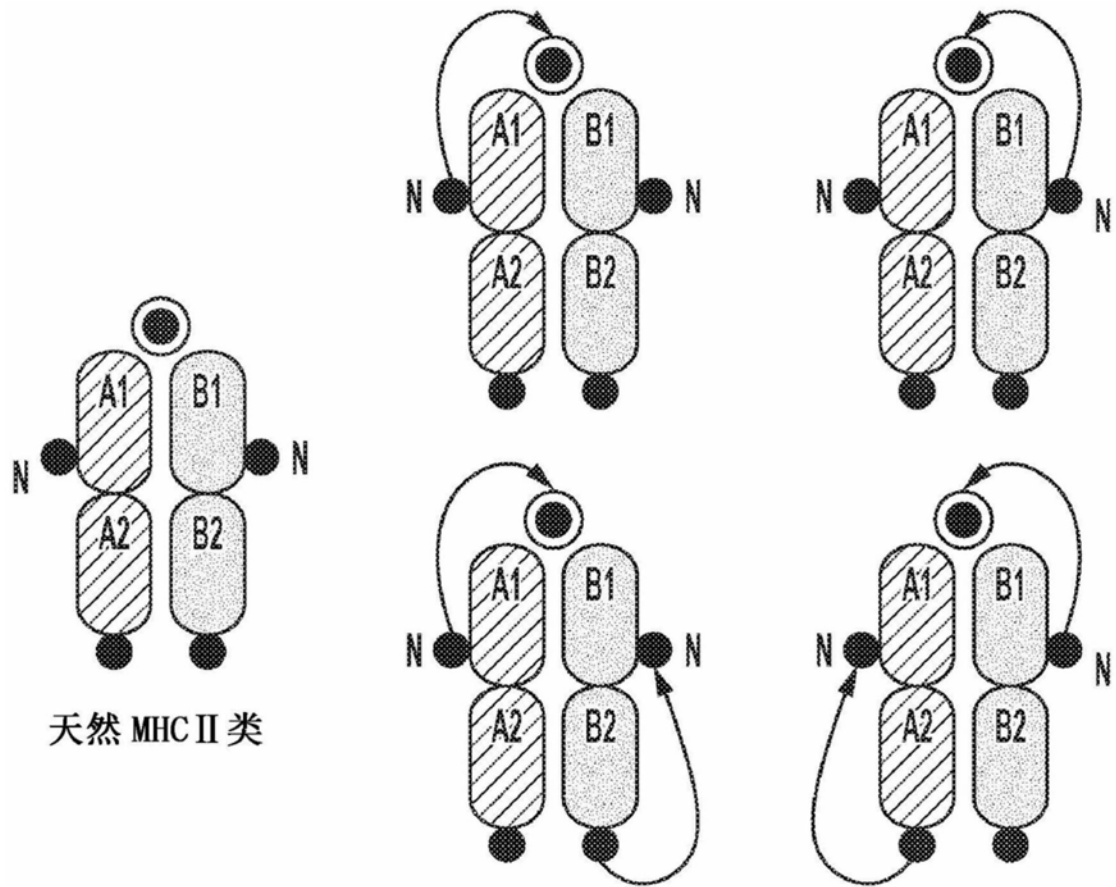


图6



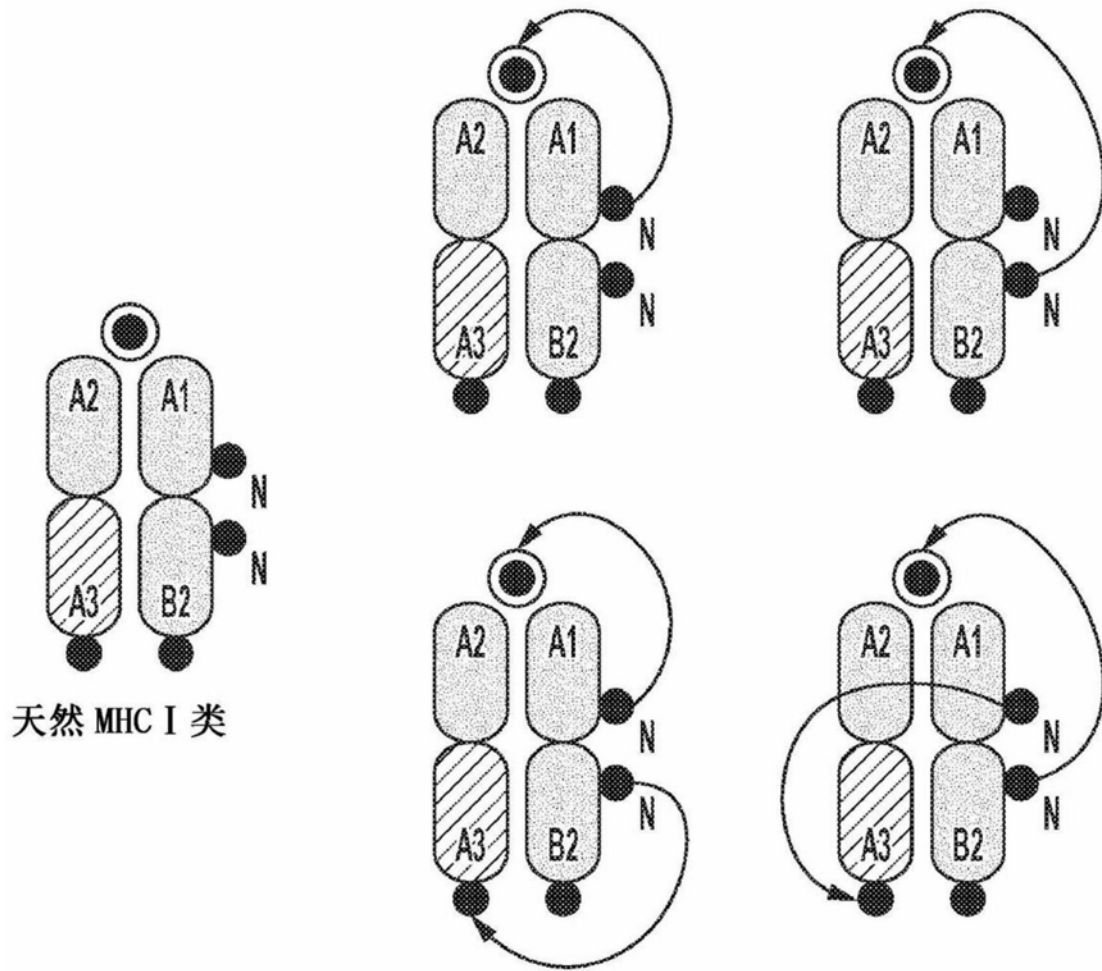


图8A

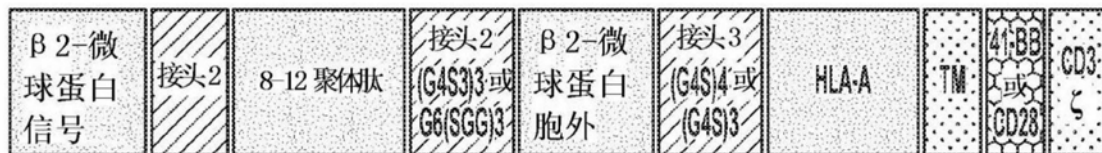


图8B

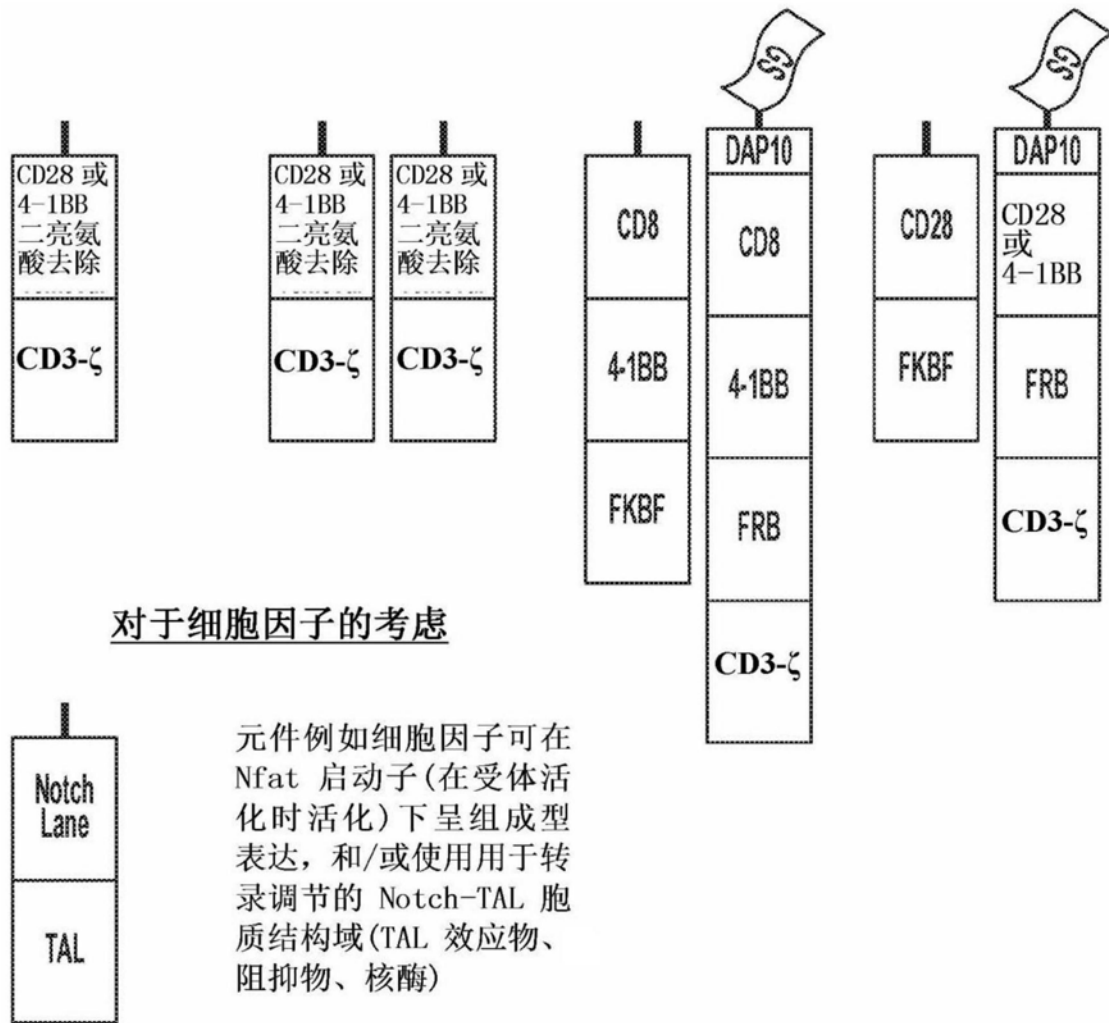
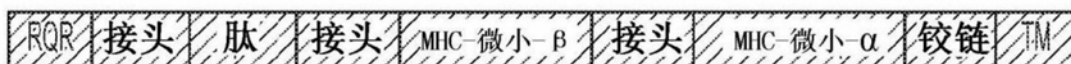
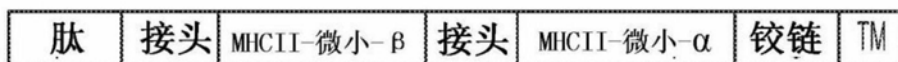
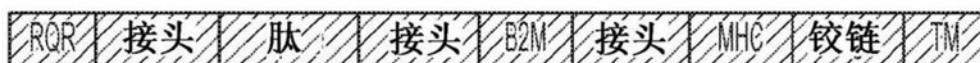
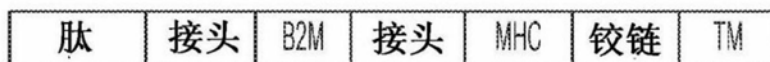


图9

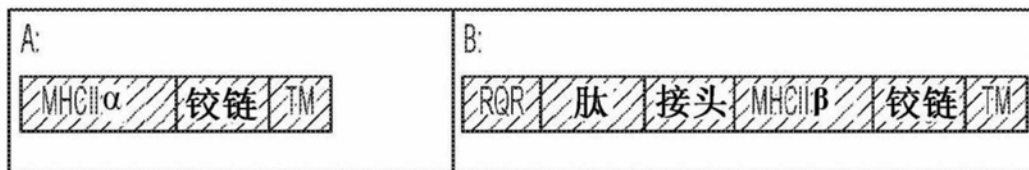
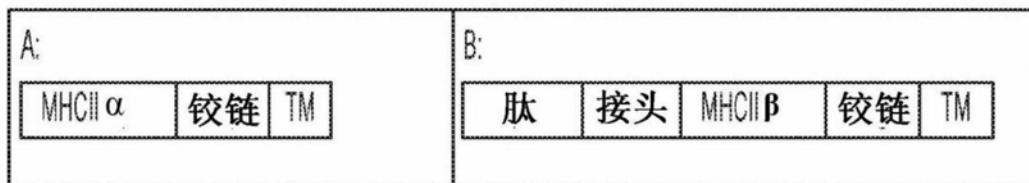
单链-II类



单链-I类



多链: II类



多链: I类

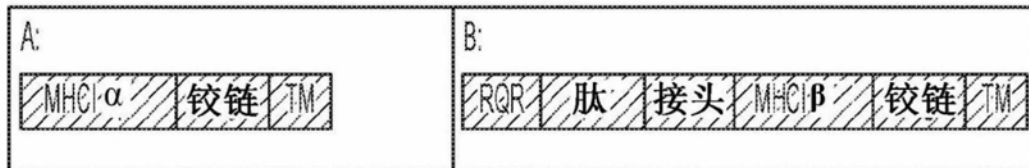
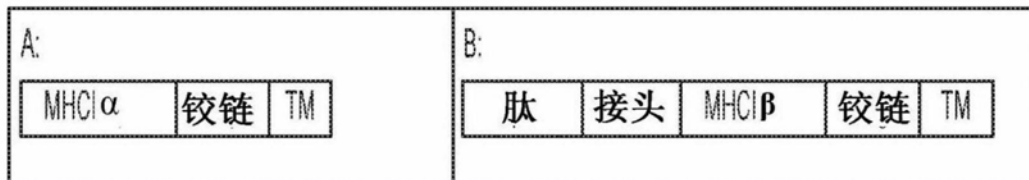


图10

多链：I / II 类

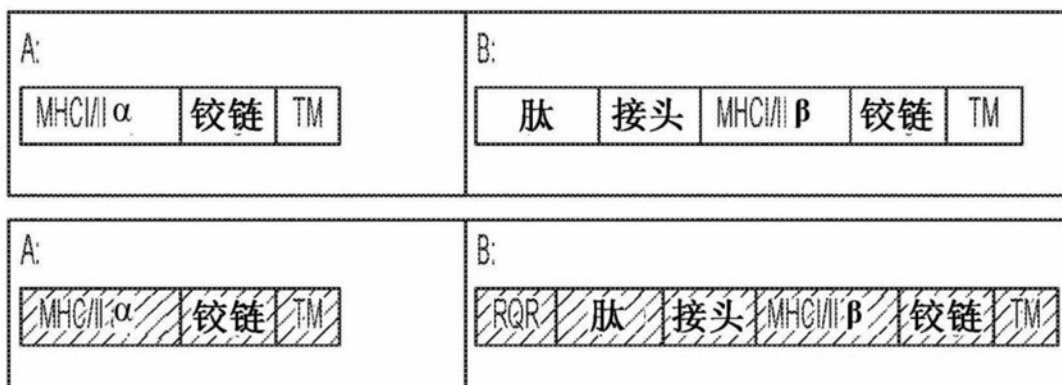


图10 (续)

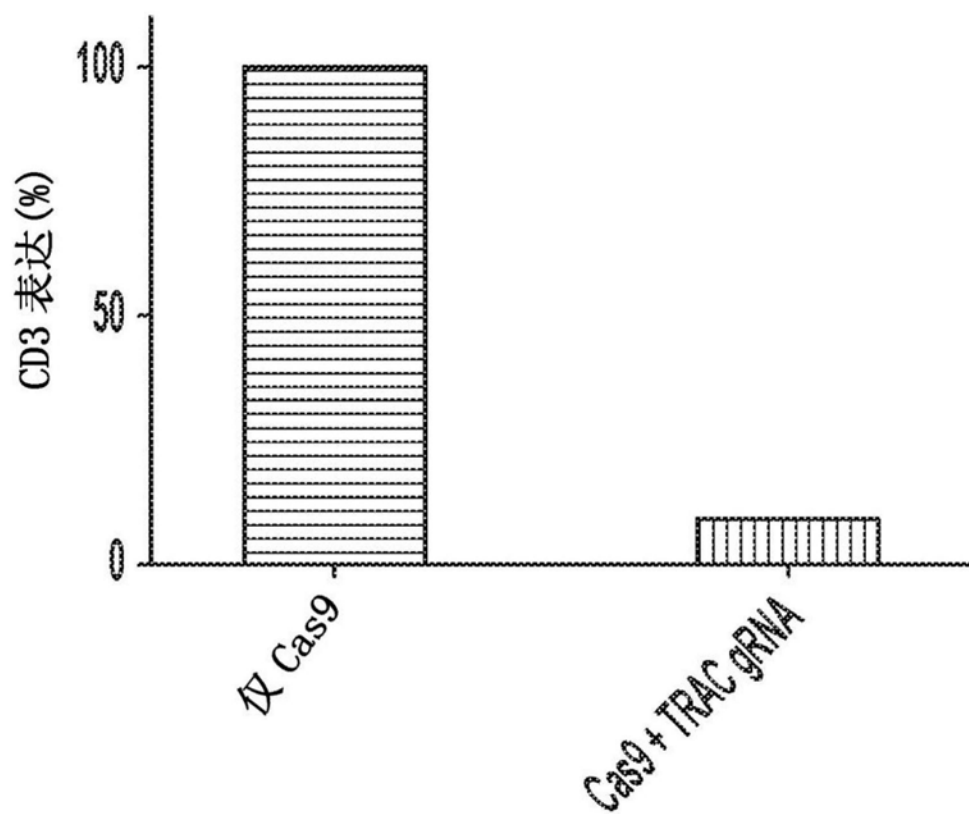


图11

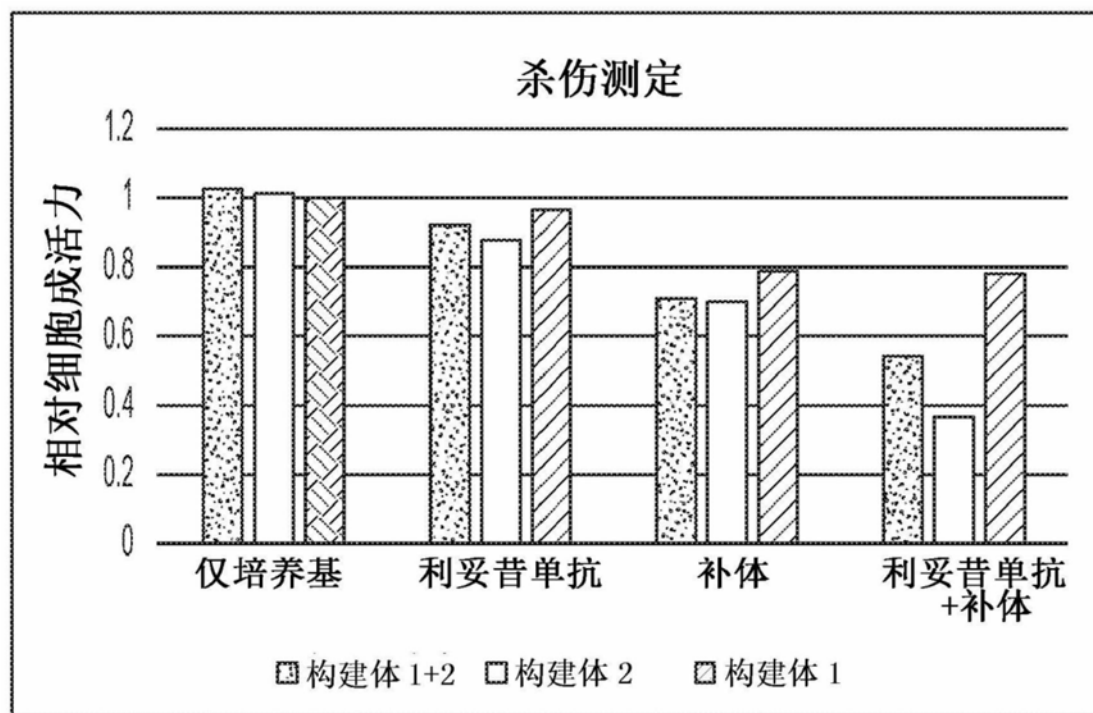


图12