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(71)申请人 Icosavax股份有限公司
地址 美国华盛顿

(72)发明人 A·L·费尔德豪斯
D·A·霍尔茨曼 C·B·沃尔夫

(74)专利代理机构 北京唐颂永信知识产权代理有限公司 11755
专利代理师 刘伟

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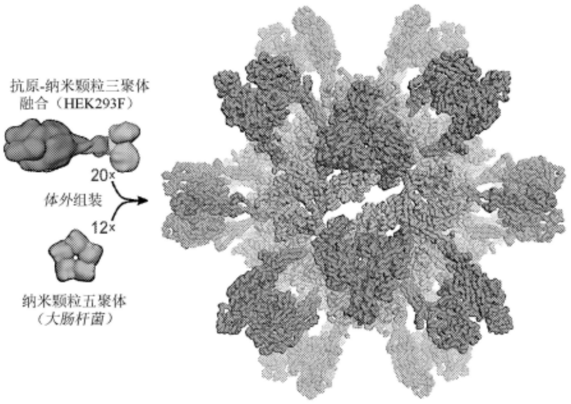
(54)发明名称

用于偏肺病毒的基于蛋白质的纳米颗粒疫苗

(57)摘要

提供了用于人偏肺病毒(hMPV)的病毒样颗粒疫苗,其中hMPV F蛋白的胞外结构域与对称的基于蛋白质的病毒样颗粒连接,并且由此显示在所述对称的基于蛋白质的病毒样颗粒上。例如,疫苗抗原可以是所述hMPV F蛋白的胞外结构域与具有单组分或双组分病毒样颗粒,如双组分二十面体病毒样颗粒的多聚化结构域的蛋白质的N末端融合体。进一步提供了疫苗组合物、制造方法和使用方法,例如使受试者免疫以产生针对hMPV的保护性免疫应答。



1.一种病毒样颗粒(VLP),其包括第一组分和任选地第二组分,

其中所述第一组分是融合蛋白,所述融合蛋白包括人偏肺病毒(hMPV)F蛋白胞外结构域或其抗原变体和第一多聚化结构域;并且

其中如果存在的话,所述第二组分是包括第二多聚化结构域的蛋白质。

2.根据权利要求1所述的VLP,其中所述第一多聚化结构域是三聚化结构域。

3.根据权利要求1或权利要求2所述的VLP,其中所述第一多聚化结构域选自SEQ ID NO:1、4、5、7、9、18、19、21、24、25、26、29、30、31、34、36、37、39、42、43、44、45、46、47、48、49、50、51、52、53、144、145或其功能变体。

4.根据权利要求1至3中任一项所述的VLP,其中所述第一多聚化结构域是I53-50A(SEQ ID NO:144)或其功能变体或变体。

5.根据权利要求1至3中任一项所述的VLP,其中所述第一多聚化结构域与以下共享至少70%、至少80%、至少90%、至少95%、至少98%、至少99%或100%同一性:

1 MEELFKKHKI VAVLRANSVE EAIEKAVAVF AGGVHLIEIT
41 FTVPDADTVI KALSVLKEKG AIIGAGTVTS VEQCRKAVES
81 GAEFIVSPHL DEEISQFCKE KGVFYMPGVM TPTELVKAMK
121 LGHTILKLFP GEVVGPQFVK AMKGPFPNVK FVPTGGVNLD
161 NVCEWFKAGV LAVGVGSALV KGTPDEVREK AKAFVEKIRG
201 CTE (SEQ ID NO: 144)

或

1 MEELFKKHKI VAVLRANSVE EAIEKAVAVF AGGVHLIEIT
41 FTVPDADTVI KALSVLKEKG AIIGAGTVTS VEQ**A**RKAVES
81 GAEFIVSPHL DEEISQF**A**KE KGVFYMPGVM TPTELVKAMK
121 LGHTILKLFP GEVVGPQFVK AMKGPFPNVK FVPTGGVNLD
161 NV**A**EWFKAGV LAVGVGSALV KGTPDEVREK AKAFVEKIRG
201 **A**TELE (SEQ ID NO: 145)。

6.根据权利要求5所述的VLP,其中所述第一多聚化结构域包括:

氨基酸取代C74A和C98A;

氨基酸取代C163A和C201A;或

相对于SEQ ID NO:144的氨基酸取代C74A、C98A、C163A和C201A。

7.根据权利要求1至3中任一项所述的VLP,其中所述第一多聚化结构域具有与SEQ ID NO:144相同的多肽序列。

8.根据权利要求1至3中任一项所述的VLP,其中所述第一多聚化结构域具有与SEQ ID NO:145相同的多肽序列。

9.根据权利要求1至9中任一项所述的VLP,其中所述第一多聚化结构域是VLP形成结构域。

10.根据权利要求1至9中任一项所述的VLP,其中所述第一多聚化结构域适于驱动二十面体颗粒或四面体颗粒的组装,任选地与第二多聚化结构域组装在一起。

11.根据权利要求1至10中任一项所述的VLP,其中所述第二多聚化结构域选自SEQ ID NO:2、3、6、8、10、11、12、13、14、15、16、17、20、22、23、27、28、32、33、35、38、40和41或其功能变体或片段。

12.根据权利要求1至11中任一项所述的VLP,其中所述第二多聚化结构域是I53-50B(SEQ ID NO:8)、I53-50B.4PosT1(SEQ ID NO:34)或其功能变体。

13.根据权利要求1至12中任一项所述的VLP,其中所述(hMPV)F蛋白胞外结构域或其抗原变体和所述第一多聚化结构域通过接头序列连接。

14.根据权利要求13所述的VLP,其中所述接头序列包括折叠子,其中折叠子序列是EKAAKAEEAARK(SEQ ID NO:125)。

15.根据权利要求13或14所述的VLP,其中所述接头序列包括GSGGSGSGSGGS(SEQ ID NO:126)。

16.根据权利要求1至15中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域含有一个或多个选自以下的取代或缺失:A185P、Q100R、S101R、T127C、N153C、V84C、A140C、A147C、A249C、N97G、P98G、R99G、Q100G、S101G、R102G、A63C、K188C、K450C、S470C、G106缺失、A113C、A120C、A339C、Q426C、T160F、Q100K、S101A、I177L、K450A、S470A、G294E、T365C、V463C、L219K、H368N和/或V231I。

17.根据权利要求1至15中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域含有一个或多个选自以下的取代或缺失:V84C、A140C、A147C、N97G、P98G、Q100G、S101G、R102G、A63C、K188C、K450C、S470C、R99G、A113C、A120C、A339C、Q426C、T160F、Q100K、S101A、Q100R、S101R、G106缺失、S101R、A185P、I177L和/或G294E。

18.根据权利要求1至15中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域含有两个或更多个选自以下的取代或缺失:V84C、A140C、A147C、N97G、P98G、Q100G、S101G、R102G、A63C、K188C、K450C、S470C、R99G、A113C、A120C、A339C、Q426C、T160F、Q100K、S101A、Q100R、S101R、G106缺失、S101R、A185P、I177L和/或G294E。

19.根据权利要求1至15中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域含有一个或多个选自以下的取代:A185P、Q100R、S101R、T127C、N153C、T365C、V463C、L219K、V231I、G294E、N153C、N97G、P98G、R99G、Q100G、S101G、H368N和/或R102G。

20.根据权利要求1至15中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域含有以下中的两个或更多个:A185P、Q100R、S101R、T127C、N153C、T365C、V463C、L219K、V231I、G294E、N153C、N97G、P98G、R99G、Q100G、S101G、H368N和/或R102G。

21.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括:

a.所述取代Q100R和S101R;

b.所述取代A185P、Q100R和S101R;

c.所述取代A185P、T127C、N153C、Q100R和S101R;

d.所述取代V84C、A140C、A147C、A249C、N97G、P98G、R99G、Q100G、S101G和R102G;

e.所述取代A63C、A140C、A147C、K188C、K450C、S470C、N97G、P98G、R99G、Q100G、S101G和R102G;

f.所述取代和缺失A63C、A140C、A147C、K188C、G106缺失、N97G、P98G、R99G、Q100G、S101G和R102G;

g.所述取代A113C、A120C、A339C、Q426C、T160F、I177L、Q100K和S101A;

h.所述取代V84C、A140C、A147C、A249C、Q100R和S101R;

i.所述取代A63C、A140C、A147C、K188C、K450C、S470C、Q100R和S101R;

j.所述取代和缺失A63C、A140C、A147C、K188C、G106缺失、Q100R和S101R;

k.取代A113C、A120C、A339C、Q426C、T160F、I177L、Q100R和S101R;

l.取代A185P、A113C、A339C、Q100R和S101R;

m.取代A185P、T160F、I177L、Q100R和S101R;

n.取代A185P、A113C、A339C、T160F、I177L、Q100R和S101R;

o.取代A63C、K188C、N97G、P98G、R99G、Q100G、S101G和R102G;

p.取代A63C、K188C、K450A、S470A、N97G、P98G、R99G、Q100G、S101G和R102G;

q.取代A63C、A140C、A147C、K188C、G294E、N97G、P98G、R99G、Q100G、S101G和R102G;

r.取代A63C、A140C、A147C、K188C、K450C、S470C、N97G、P98G、R99G、Q100G、S101G、R102G和G294E;

s.取代A63C、K188C、N97G、P98G、R99G、Q100G、S101G、R102G和G294E;

t.取代T127C、N153C、T365C、V463C、A185P、L219K、V231I、G294E、H368N、Q100R和S101R;

u.取代V84C、A140C、A147C、A249C、N97G、P98G、R99G、Q100G、S101G和R102G;或

v.取代T127C、N153C、T365C、V463C、A185P、L219K、V231I、G294E、N97G、P98G、R99G、Q100G、S101G、H368N和R102G。

22.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:58共享至少95%或至少99%同一性的序列。

23.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:59共享至少95%或至少99%同一性的序列。

24.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:60共享至少95%或至少99%同一性的序列。

25.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:61共享至少95%或至少99%同一性的序列。

26.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:62共享至少95%或至少99%同一性的序列。

27.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:63共享至少95%或至少99%同一性的序列。

28.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:64共享至少95%或至少99%同一性的序列。

29.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:65共享至少95%或至少99%同一性的序列。

30.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:66共享至少95%或至少99%同一性的序列。

31.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:67共享至少95%或至少99%同一性的序列。

32.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:68共享至少95%或至少99%同一性的序列。

33.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:69共享至少95%或至少99%同一性的序列。

34.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:70共享至少95%或至少99%同一性的序列。

35.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:71共享至少95%或至少99%同一性的序列。

36.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:72共享至少95%或至少99%同一性的序列。

37.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:73共享至少95%或至少99%同一性的序列。

38.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:74共享至少95%或至少99%同一性的序列。

39.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:75共享至少95%或至少99%同一性的序列。

40.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:76共享至少95%或至少99%同一性的序列。

41.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:77共享至少95%或至少99%同一性的序列。

42.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:78共享至少95%或至少99%同一性的序列。

43.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:79共享至少95%或至少99%同一性的序列。

44.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:80共享至少95%或至少99%同一性的序列。

45.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:81共享至少95%或至少99%同一性的序列。

46.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:82共享至少95%或至少99%同一性的序列。

47.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:83共享至少95%或至少99%同一性的序列。

48.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:84共享至少95%或至少99%同一性的序列。

49.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:85共享至少95%或至少99%同一性的序列。

50.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:86共享至少95%或至少99%同一性的序列。

51.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:87共享至少95%或至少99%同一性的序列。

52.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:88共享至少95%或至少99%同一性的序列。

53.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与

SEQ ID NO:89共享至少95％或至少99％同一性的序列。

54.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域包括与SEQ ID NO:90共享至少95％或至少99％同一性的序列。

55.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域与SEQ ID NO:58、60、61、77、78、86、87、88或89共享至少85％、至少90％、至少95％、至少99％或100％同一性。

56.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域与SEQ ID NO:59、62、63、64、71、76、81或83共享至少85％、至少90％、至少95％、至少99％或100％同一性。

57.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域与SEQ ID NO:72、79或80共享至少85％、至少90％、至少95％、至少99％或100％同一性。

58.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域与SEQ ID NO:65、66、82、84、85、90或91共享至少85％、至少90％、至少95％、至少99％或100％同一性。

59.根据权利要求1至20中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域与SEQ ID NO:65、79或80共享至少85％、至少90％、至少95％、至少99％或100％同一性。

60.根据权利要求1至59中任一项所述的VLP,其中所述第一组分与SEQ ID NO:92-124共享至少85％、至少90％、至少95％、至少99％或100％同一性。

61.根据权利要求1至59中任一项所述的VLP,其中所述第一组分与SEQ ID NO:97-116、119或122共享至少85％、至少90％、至少95％、至少99％或100％同一性。

62.根据权利要求1至59中任一项所述的VLP,其中所述第一组分与SEQ ID NO:92-94、96、117、118、120、121、123或124共享至少85％、至少90％、至少95％、至少99％或100％同一性。

63.根据权利要求1至59中任一项所述的VLP,其中所述第一组分与SEQ ID NO:99、112、117或118共享至少85％、至少90％、至少95％、至少99％或100％同一性。

64.根据权利要求1至63中任一项所述的VLP,其中所述VLP与一种或多种选自以下的hMPV F蛋白抗体结合:MF1、MF2、MF3、MF9、MF12、MF14、MF15、MF11、MF16、MF20、MF17、MF18、MF19、MF10或MPE8。

65.根据权利要求1至63中任一项所述的VLP,其中所述VLP与两种或更多种选自以下的抗体结合:MF1、MF2、MF3、MF9、MF12、MF14、MF15、MF11、MF16、MF20、MF17、MF18、MF19、MF10、MPE8。

66.根据权利要求1至63中任一项所述的VLP,其中所述VLP与三种或更多种选自以下的抗体结合:MF1、MF2、MF3、MF9、MF12、MF14、MF15、MF11、MF16、MF20、MF17、MF18、MF19、MF10、MPE8。

67.根据权利要求1至63中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域与优选与所述hMPV F蛋白胞外结构域的融合前形式结合的抗体结合。

68.根据权利要求64至67中任一项所述的VLP,其中所述第一组分与SEQ ID NO:42、45、58、61、63或64共享至少85％、至少90％、至少95％、至少99％或100％同一性。

69.根据权利要求1至63中任一项所述的VLP,其中所述hMPV F蛋白胞外结构域与优选

与所述hMPV F蛋白胞外结构域的融合后形式结合的抗体无结合或低结合。

70.根据权利要求69所述的VLP,其中VLP序列与SEQ ID NO:99、115、117或118共享至少85％、至少90％、至少95％、至少99％或100％同一性。

71.根据权利要求1所述的VLP,其中所述第一组分与SEQ ID NO:99共享至少85％、至少90％、至少95％、至少99％或100％同一性。

72.根据权利要求1所述的VLP,其中所述第一组分是单链。

73.根据权利要求37所述的VLP,其中所述单链与SEQ ID NO:123共享至少85％、至少90％、至少95％、至少99％或100％同一性。

74.根据权利要求1所述的VLP,其中所述第一组分与SEQ ID NO:117共享至少85％、至少90％、至少95％、至少99％或100％同一性。

75.一种多核苷酸,其编码根据权利要求1至74中任一项所述的VLP。

76.一种宿主细胞,其包括根据权利要求75所述的多核苷酸。

77.一种制造疫苗的方法,所述方法包括:在培养基中培养根据权利要求76所述的宿主细胞,使得所述宿主细胞将抗原分泌到所述培养基中;任选地从所述培养基中纯化所述抗原;将所述抗原与第二组分混合,其中所述第二组分与所述抗原多聚化以形成病毒样颗粒;以及任选地纯化所述病毒样颗粒。

78.一种疫苗,其包括根据权利要求1至74中任一项所述的VLP,其中所述疫苗任选地包括一种或多种药学上可接受的稀释剂、佐剂或赋形剂。

79.根据权利要求78所述的疫苗,其中所述疫苗是稳定乳液。

80.根据权利要求78或权利要求79所述的疫苗,其中所述疫苗包括一种或多种佐剂。

81.根据权利要求80所述的疫苗,其中所述一种或多种佐剂是角鲨烯、明矾、SLA、GLA、R848、IMQ、3M-052、CpG、皂苷(QS21)或其组合。

82.根据权利要求80所述的疫苗,其中所述佐剂是明矾。

83.根据权利要求80所述的疫苗,其中所述佐剂是基于角鲨烯的乳液。

84.根据权利要求83所述的疫苗,其中所述基于角鲨烯的乳液是MF59。

85.一种针对由人偏肺病毒引起的感染使受试者免疫的方法,所述方法包括施用根据权利要求78至84中任一项所述的疫苗。

86.根据权利要求85所述的方法,其中所述受试者同时针对由呼吸道合胞病毒(RSV)引起的感染进行免疫。

87.根据权利要求85所述的方法,其中所述疫苗是通过皮下注射施用的。

88.根据权利要求85所述的方法,其中所述疫苗是通过肌内注射施用的。

89.根据权利要求85所述的方法,其中所述疫苗是通过皮内注射施用的。

90.根据权利要求85所述的方法,其中所述疫苗是鼻内施用的。

91.一种预填充的注射器,其包括根据权利要求78至84中任一项所述的疫苗。

92.一种试剂盒,其包括根据权利要求78至84中任一项所述的疫苗或根据权利要求91所述的预填充的注射器。

93.根据权利要求77所述的方法,其中所述宿主细胞用编码弗林蛋白酶或其功能变体的多核苷酸转染。

用于偏肺病毒的基于蛋白质的纳米颗粒疫苗

[0001]　相关申请交叉引用

[0002]　本申请要求于2020年11月13日提交的美国临时专利申请第63/113,686号的权益，所述美国临时专利申请通过引用整体并入本文。

[0003]　通过引用并入序列表

[0004]　本申请含有已经以ASCII格式经由EFS-WEB递交的序列表并且所述序列表据此通过引用整体并入。创建于2021年11月5日的所述ASCII副本命名为ICVX-011_01WO_SeqList.txt并且大小为442,995字节。

背景技术

[0005]　人偏肺病毒(hMPV)会引起所有年龄段人群的上呼吸道和下呼吸道疾病。症状可以包含咳嗽、发烧、鼻塞和呼吸短促。在一些情况下，hMPV感染可以发展为如支气管炎或肺炎等严重疾病。

[0006]　hMPV是副粘病毒科的单链RNA病毒，所述副粘病毒科还包含麻疹、腮腺炎和如呼吸道合胞病毒(RSV)等其它呼吸道感染。hMPV可以有两种亚型:A和B，所述亚型通过对病毒基因组中的G和F基因进行基因分型来鉴定。F基因编码hMPV融合糖蛋白(hMPV F蛋白)，并且可以用作疫苗开发的靶标。然而，尽管有临床需要，但迄今为止还没有批准用于人的hMPV疫苗。

[0007]　因此需要针对hMPV的疫苗。

发明内容

[0008]　提供了用于人偏肺病毒的基于蛋白质的病毒样颗粒(VLP)疫苗，其中hMPV F蛋白胞外结构域与基于蛋白质的VLP连接，并且因此显示在所述基于蛋白质的VLP上。

[0009]　一方面，本公开提供了一种病毒样颗粒(VLP)，其包括第一组分和任选地第二组分，其中所述第一组分是融合蛋白，所述融合蛋白包括人偏肺病毒(hMPV)F蛋白胞外结构域或其抗原变体和第一多聚化结构域；并且其中如果存在的话，所述第二组分是包括第二多聚化结构域的蛋白质。

[0010]　在一些实施例中，第一多聚化结构域是三聚化结构域。在一些实施例中，多聚化结构域选自SEQ ID NO:1、4、5、7、9、18、19、21、24、25、26、29、30、31、34、36、37、39、42、43、44、45、46、47、48、49、50、51、52、53、144或145或其功能变体。在一些实施例中，多聚化结构域是I53-50A(SEQ ID NO:7或SEQ ID NO:144)或其功能变体或变体。在一些实施例中，第一多聚化结构域与SEQ ID NO:7、SEQ ID NO:53、SEQ ID NO:144或SEQ ID NO:145共享至少70％、至少80％、至少90％、至少95％、至少98％、至少99％或100％同一性。在一些实施例中，第一多聚化结构域包括:氨基酸取代C74A和C98A；氨基酸取代C163A和C201A；或相对于SEQ ID NO:144的氨基酸取代C74A、C98A、C163A和C201A。在一些实施例中，第一多聚化结构域具有与SEQ ID NO:7或SEQ ID NO:144相同的多肽序列。在一些实施例中，第一多聚化结构域具有与SEQ ID NO:53或SEQ ID NO:145相同的多肽序列。在一些实施例中，第一多聚化结构域

是VLP形成结构域。在一些实施例中,第一多聚化结构域适于驱动二十面体颗粒或四面体颗粒的组装,任选地与第二多聚化结构域组装在一起。

[0011] 在一些实施例中,第二多聚化结构域选自SEQ ID NO:2、3、6、8、10、11、12、13、14、15、16、17、20、22、23、27、28、32、33、35、38、40和41或其功能变体或片段。在一些实施例中,第二多聚化结构域是I53-50B(SEQ ID NO:8)、I53-50B.4PosT1(SEQ ID NO:34)或其功能变体。

[0012] 在一些实施例中,第一组分和第二组分通过接头序列连接。在一些实施例中,所述接头序列包括折叠子,其中折叠子序列是EKAAKAEEAARK(SEQ ID NO:125)。在一些实施例中,接头序列包括GSGGSGSGSGGS(SEQ ID NO:126)。

[0013] 在一些实施例中,所述hMPV F蛋白胞外结构域含有一个或多个选自以下的取代或缺失:A185P、Q100R、S101R、T127C、N153C、V84C、A140C、A147C、A249C、N97G、P98G、R99G、Q100G、S101G、R102G、A63C、K188C、K450C、S470C、G106缺失、A113C、A120C、A339C、Q426C、T160F、Q100K、S101A、I177L、K450A、S470A、G294E、T365C、V463C、L219K、H368N和/或V231I。在一些实施例中,所述hMPV F蛋白胞外结构域含有一个或多个选自以下的取代或缺失:V84C、A140C、A147C、N97G、P98G、Q100G、S101G、R102G、A63C、K188C、K450C、S470C、R99G、A113C、A120C、A339C、Q426C、T160F、Q100K、S101A、Q100R、S101R、G106缺失、S101R、A185P、I177L和/或G294E。

[0014] 在一些实施例中,所述hMPV F蛋白胞外结构域含有两个或更多个选自以下的取代或缺失:V84C、A140C、A147C、N97G、P98G、Q100G、S101G、R102G、A63C、K188C、K450C、S470C、R99G、A113C、A120C、A339C、Q426C、T160F、Q100K、S101A、Q100R、S101R、G106缺失、S101R、A185P、I177L和/或G294E。在一些实施例中,所述hMPV F蛋白胞外结构域含有一个或多个选自以下的取代:A185P、Q100R、S101R、T127C、N153C、T365C、V463C、L219K、V231I、G294E、N153C、N97G、P98G、R99G、Q100G、S101G、H368N和/或R102G。

[0015] 在一些实施例中,所述hMPV F蛋白胞外结构域含有以下中的两个或更多个:A185P、Q100R、S101R、T127C、N153C、T365C、V463C、L219K、V231I、G294E、N153C、N97G、P98G、R99G、Q100G、S101G、H368N和/或R102G。在一些实施例中,hMPV F蛋白胞外结构域包括:取代Q100R和S101R;取代A185P、Q100R和S101R;取代A185P、T127C、N153C、Q100R和S101R;取代V84C、A140C、A147C、A249C、N97G、P98G、R99G、Q100G、S101G和R102G;取代A63C、A140C、A147C、K188C、K450C、S470C、N97G、P98G、R99G、Q100G、S101G和R102G;取代和缺失A63C、A140C、A147C、K188C、G106缺失、N97G、P98G、R99G、Q100G、S101G和R102G;取代A113C、A120C、A339C、Q426C、T160F、I177L、Q100K和S101A;取代V84C、A140C、A147C、A249C、Q100R和S101R;取代A63C、A140C、A147C、K188C、K450C、S470C、Q100R和S101R;取代和缺失A63C、A140C、A147C、K188C、G106缺失、Q100R和S101R;取代A113C、A120C、A339C、Q426C、T160F、I177L、Q100R和S101R;取代A185P、A113C、A339C、Q100R和S101R;取代A185P、T160F、I177L、Q100R和S101R;取代A185P、A113C、A339C、T160F、I177L、Q100R和S101R;取代A63C、K188C、N97G、P98G、R99G、Q100G、S101G和R102G;取代A63C、K188C、K450A、S470A、N97G、P98G、R99G、Q100G、S101G和R102G;取代A63C、A140C、A147C、K188C、G294E、N97G、P98G、R99G、Q100G、S101G和R102G;取代A63C、A140C、A147C、K188C、K450C、S470C、N97G、P98G、R99G、Q100G、S101G、R102G和G294E;取代A63C、K188C、N97G、P98G、R99G、Q100G、S101G、R102G和G294E;取代T127C、

N153C、T365C、V463C、A185P、L219K、V231I、G294E、H368N、Q100R和S101R；取代A63C、A140C、A147C、K188C、K450C、S470C、N97G、P98G、R99G、Q100G、S101G和R102G；取代V84C、A140C、A147C、A249C、N97G、P98G、R99G、Q100G、S101G和R102G；取代T127C、N153C、T365C、V463C、A185P、L219K、V231I、G294E、H368N、N97G、P98G、R99G、Q100G、S101G和R102G。

[0016] 在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:58共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:59共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:60共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:61共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:62共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:63共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:64共享至少95％或至少99％同一性的序列。

[0017] 在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:65共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:66共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:67共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:68共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:69共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:70共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:71共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:72共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:73共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:74共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:75共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:76共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:77共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:78共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:79共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:80共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:81共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:82共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:83共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:84共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:85共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:86共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构

域包括与SEQ ID NO:87共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:88共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:89共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域包括与SEQ ID NO:90共享至少95％或至少99％同一性的序列。在一些实施例中，hMPV F蛋白胞外结构域与SEQ ID NO:58、60、61、77、78、86、87、88或89共享至少85％、至少90％、至少95％、至少99％或100％同一性。在一些实施例中，hMPV F蛋白胞外结构域与SEQ ID NO:59、62、63、64、71、76、81或83共享至少85％、至少90％、至少95％、至少99％或100％同一性。在一些实施例中，hMPV F蛋白胞外结构域与SEQ ID NO:72、79或80共享至少85％、至少90％、至少95％、至少99％或100％同一性。在一些实施例中，hMPV F蛋白胞外结构域与SEQ ID NO:65、66、82、84、85、90或91共享至少85％、至少90％、至少95％、至少99％或100％同一性。在一些实施例中，hMPV F蛋白胞外结构域与SEQ ID NO:65、79或80共享至少85％、至少90％、至少95％、至少99％或100％同一性。在一些实施例中，第一组分与SEQ ID NO:92-124共享至少85％、至少90％、至少95％、至少99％或100％同一性。在一些实施例中，第一组分与SEQ ID NO:97-116、119或122共享至少85％、至少90％、至少95％、至少99％或100％同一性。在一些实施例中，第一组分与SEQ ID NO:92-94、96、117、118、120、121、123或124共享至少85％、至少90％、至少95％、至少99％或100％同一性。在一些实施例中，第一组分与SEQ ID NO:99、112、117或118共享至少85％、至少90％、至少95％、至少99％或100％同一性。

[0018] 在一些实施例中，所述VLP与一种或多种选自以下的hMPV F蛋白抗体结合：MF1、MF2、MF3、MF9、MF12、MF14、MF15、MF11、MF16、MF20、MF17、MF18、MF19、MF10或MPE8。在一些实施例中，所述VLP与两种或更多种选自以下的抗体结合：MF1、MF2、MF3、MF9、MF12、MF14、MF15、MF11、MF16、MF20、MF17、MF18、MF19、MF10、MPE8。在一些实施例中，所述VLP与三种或更多种选自以下的抗体结合：MF1、MF2、MF3、MF9、MF12、MF14、MF15、MF11、MF16、MF20、MF17、MF18、MF19、MF10、MPE8。

[0019] 在一些实施例中，所述hMPV F蛋白胞外结构域与优选与所述hMPV F蛋白胞外结构域的融合前形式结合的抗体结合。在一些实施例中，第一组分与SEQ ID NO:42、45、58、61、63或64共享至少85％、至少90％、至少95％、至少99％或100％同一性。在一些实施例中，所述hMPV F蛋白胞外结构域与优选与所述hMPV F蛋白胞外结构域的融合后形式结合的抗体无结合或低结合。在一些实施例中，VLP序列与SEQ ID NO:99、115、117或118共享至少85％、至少90％、至少95％、至少99％或100％同一性。

[0020] 在一些实施例中，第一组分与SEQ ID NO:99共享至少85％、至少90％、至少95％、至少99％或100％同一性。

[0021] 在一些实施例中，第一组分是单链。在一些实施例中，所述单链与SEQ ID NO:123共享至少85％、至少90％、至少95％、至少99％或100％同一性。

[0022] 在一些实施例中，第一组分与SEQ ID NO:117共享至少85％、至少90％、至少95％、至少99％或100％同一性。

[0023] 一方面，本公开提供了一种编码本文所描述的VLP的多核苷酸。

[0024] 一方面，本公开提供了一种宿主细胞，其包括本文所描述的多核苷酸。

[0025] 一方面，本公开提供了一种制造疫苗的方法，所述方法包括在培养基中培养本文

所描述的宿主细胞,使得所述宿主细胞将抗原分泌到所述培养基中;任选地从所述培养基中纯化所述抗原;将所述抗原与第二组分混合,其中所述第二组分与所述抗原多聚化以形成病毒样颗粒;以及任选地纯化所述病毒样颗粒。

[0026] 一方面,本公开提供了一种疫苗,其包括本文所描述的VLP,其中所述疫苗任选地包括一种或多种药学上可接受的稀释剂、佐剂或赋形剂。在一些实施例中,疫苗是稳定乳液。在一些实施例中,疫苗包括一种或多种佐剂。在一些实施例中,所述一种或多种佐剂是角鲨烯、SLA、GLA、R848、IMQ、3M-052、CpG、皂苷(QS21)或其组合。在一些实施例中,佐剂是明矾。在一些实施例中,佐剂是基于角鲨烯的乳液。在一些实施例中,基于角鲨烯的乳液是MF59。

[0027] 一方面,本公开提供了一种针对由人偏肺病毒引起的感染使受试者免疫的方法,所述方法包括施用本文所描述的疫苗。在一些实施例中,所述受试者同时针对由呼吸道合胞病毒(RSV)引起的感染进行免疫。在一些实施例中,疫苗是通过皮下注射施用的。在一些实施例中,其中疫苗是通过肌内注射施用的。在一些实施例中,其中疫苗是通过皮内注射施用的。在一些实施例中,其中疫苗是鼻内施用的。一方面,本公开提供了一种预填充的注射器,其包括本文所描述的疫苗。一方面,本公开提供了一种试剂盒,其包括本文所描述的疫苗或本文所描述的预填充的注射器。

附图说明

[0028] 图1A示出了根据本公开的基于蛋白质的病毒样颗粒(VLP)的说明性实施例。

[0029] 图1B示出了VLP和VLP组分(G蛋白未示出)的另外的说明性实施例。

[0030] 图2示出了融合前构象中的hMPV F蛋白的二级结构图(PDB ID:5WB0;在www.rcsb.org处生成的图)。

[0031] 图3A-3C是示出了与本公开的说明性VLP的抗体结合概况的一系列图。抗体对各种形式的hMPV F蛋白具有特异性。MF14在位点II表位处与hMPV F蛋白的融合前形式和融合后形式结合(图3A)。MF16在位点IV表位处与hMPV F蛋白的融合前形式和融合后形式结合(图3B)。MPE8在位点III表位处与hMPV F蛋白的融合前形式结合(图3C)。

[0032] 图4是示出了响应于用佐剂配制的hMPV F蛋白VLP给药,小鼠中的中和抗体滴度的时程诱导的一系列图。

[0033] 图5A和5B示出了hMPV F蛋白突变体对2组分病毒样颗粒(VLP)的免疫原性。图示出了在第一次免疫后第35天收集的血清样品中针对hMPV/A(图5A)和hMPV/B(图5B)的中和抗体滴度。

[0034] 图6A和6B示出了hMPV008 VLP和对应的可溶性蛋白CompA-hMPV008的免疫原性。图示出了在第一次免疫后第35天收集的血清样品中针对hMPV/A(图6A)和hMPV/B(图6B)的中和抗体滴度。

[0035] 图7A和7B示出了显示hMPV F蛋白突变体hMPV008的VLP的免疫原性。在第一次免疫后第35天收集的血清样品中测定针对hMPV/A(图7A)和hMPV/B(图7B)的中和抗体滴度。

[0036] 图8A和8B示出了hMPV033的免疫原性。在第一次免疫后第35天收集的血清样品中测定针对hMPV/A(图8A)和hMPV/B(图8B)的中和抗体滴度。

[0037] 图9A-9C示出了hMPV033对棉鼠的hMPV感染的保护作用。在第一次免疫后第35天收

集的血清(图9C)、肺(图9B)和鼻(图9C)样品中测定针对hMPV/A的中和滴度。

具体实施方式

[0038] 提供了用于人偏肺病毒(hMPV)的基于蛋白质的病毒样颗粒(VLP)疫苗,其中hMPV F蛋白胞外结构域与基于蛋白质的VLP例如,设计的VLP,例如,对称VLP连接,并且因此显示在所述基于蛋白质的VLP上。例如,疫苗抗原可以是所述hMPV F蛋白的胞外结构域与具有如双组分二十面体VLP等单组分或双组分从头设计的VLP的多聚化结构域的蛋白质的N末端融合体。进一步提供了疫苗组合物、制造方法和使用方法,例如使受试者免疫以产生针对hMPV病毒的保护性免疫应答。

[0039] 定义

[0040] 本文中的所有出版物、专利和专利申请(包含任何附图和附录)出于所有目的以全文引用的方式并入,在程度上就像每个单独的出版物、专利或专利申请、附图或附录被特别地和单独地指出以出于所有目的以全文引用的方式并入相同。

[0041] 术语“病毒样颗粒”或“VLP”是指类似病毒但非传染性的分子组装,其显示病毒蛋白或糖蛋白的抗原蛋白或其抗原片段。“基于蛋白质的VLP”是指由蛋白质或糖蛋白形成且基本上不含其它组分(例如,脂质)的VLP。基于蛋白质的VLP可以包含翻译后修饰和化学修饰,但要与胶束VLP和通过从活的或活的灭活的病毒制剂中提取病毒蛋白质而形成的VLP区分开来。术语“设计的VLP”是指包括一种或多种通过计算蛋白质设计生成的多肽的VLP。说明性设计的VLP是包括图1B所描绘的纳米结构的VLP。术语“对称VLP”是指具有对称核的基于蛋白质的VLP,如图1B所示出的。这些包含但不限于设计的VLP。例如,蛋白质铁蛋白已用于使用天然存在的铁蛋白序列生成对称、基于蛋白质的VLP。基于铁蛋白的VLP与设计的VLP的区别在于,除了将病毒蛋白与铁蛋白分子融合之外,不需要蛋白质工程化来从铁蛋白形成对称VLP。蛋白质设计方法可以用于基于模板结构(例如,沉积在蛋白质数据库中的结构)或从头(即通过计算设计具有期望的结构但与天然存在的蛋白质几乎没有同源性的新蛋白质)生成类似的单组分和双组分纳米结构。此类单组分和双组分纳米结构然后可以用作设计的VLP的核。

[0042] 本公开的VLP显示能够引发针对人偏肺病毒或其它偏肺病毒的免疫应答的抗原。本公开的疫苗可用于预防和/或降低人偏肺病毒感染的严重程度。

[0043] 术语“二十面体颗粒”是指具有二十面体对称核的设计的VLP(例如,表1中标记为I53和I52的颗粒)。I53是指由五聚体和三聚体构建的二十面体颗粒。I52是指由五聚体和二聚体构建的二十面体颗粒。T33是指由两组三聚体构建的四面体颗粒。T32是指由三聚体和二聚体构建的四面体颗粒。

[0044] 抗原可以非共价或共价附接到基于蛋白质的VLP的核心,包含作为融合蛋白或通过本文所公开的其它方式。多聚体抗原可以任选地沿着VLP的对称轴显示。还提供了蛋白质和编码此类蛋白质的核酸分子、调配物和使用方法。

[0045] 术语“抗原”是指多肽或多肽复合物,包含至少一种被设计成引发免疫应答的组分。如本文所使用的,术语抗原不限于含有抗原表位的多肽或多肽复合物的部分。

[0046] 术语“多肽”是指通过肽键和任选地一种或多种翻译后修饰(例如,糖基化)和/或其它修饰(包含但不限于用作标志物(如荧光标签或佐剂)的多肽部分的缀合)连接的一系

列氨基酸残基。

[0047] 术语“感染”是指有症状和无症状感染。

[0048] 术语“胞外结构域”是指跨膜蛋白或糖蛋白的一部分,其在蛋白质的天然状态下位于细胞或病毒膜的外部上。

[0049] 术语“变体”是指相对于参考多肽具有一个或多个插入、缺失或氨基酸取代,但保留了参考蛋白的一种或多种特性的多肽。

[0050] 术语“抗原变体”是指具有一个或多个与参考多肽共有的表位和/或当作为参考多肽施用于受试者时产生相同或类似的免疫应答的变体。

[0051] 术语“功能变体”是指表现出与参考多肽相同或相似功能作用的变体。例如,多聚化结构域的功能变体能够以与参考多聚化结构域相同的程度或相似的程度促进多聚化,和/或能够与参考多聚化结构域相同的同源多聚化结构域进行多聚化。

[0052] 术语“接头”是指化学连接(即,共价键或一系列共价键与中间化学部分)或指通过肽键在N末端和C末端连接以产生融合蛋白的多肽。

[0053] 术语“结构域”是指采用三级结构的多肽的任何部分。

[0054] 术语“多聚化结构域”和“多聚化”是指多肽或多肽的结构域形成二聚体、三聚体、四聚体、五聚体或六聚体和/或与其它多聚化结构域形成异聚体的能力。

[0055] 术语“三聚化结构域”是指形成三聚体的多聚化结构域。

[0056] 术语“VLP形成结构域”是指单独或与其它多聚化结构域一起形成对称蛋白质复合物的多聚化结构域。

[0057] 术语“片段”是指与参考多肽相比具有一个或多个N末端或C末端截短的多肽。

[0058] 术语“功能片段”是指片段的功能变体。

[0059] 术语“氨基酸取代”是指用另一个氨基酸残基取代序列中的单个氨基酸。使用氨基酸取代的缩写的标准形式。例如,V94R是指用精氨酸(R)取代参考序列中的缬氨酸(V)。缩写Arg94是指相对于参考序列,其中第94个残基是精氨酸(Arg)的任何序列。

[0060] 术语“螺旋”(“helix”或“helical”)是指已知发生或预测要发生的多肽中的α-螺旋二级结构。例如,当计算建模表明序列可能采用螺旋构象时,序列可以被描述为螺旋。

[0061] 术语“组分”是指能够在适当条件下组装成病毒样颗粒的蛋白质或蛋白质复合物(例如,包括多三聚化结构域的抗原或多肽)。

[0062] 术语“疫苗”是指能够用于在受试者中产生免疫应答的药物组合物。

[0063] 术语“药学上可接受的赋形剂”意指对于在动物或人类体内使用是生物学或药理学上相容的赋形剂,并且可以意指被联邦或州政府的管理机构批准的或者在《美国药典(U.S.Pharmacopeia)》或其它普遍认可的药典中列出的用于动物并且更特别地用于人类的赋形剂。

[0064] 术语“佐剂”是指在与抗原共同施用时或在将抗原施用于受试者之前、期间或之后施用时增强对抗原的免疫应答的药学上可接受的物质。

[0065] 术语“TLR4免疫刺激剂”是指刺激受试者免疫细胞中的Toll样受体4(TLR4)以调节免疫应答的佐剂例如,单磷酰脂质A(MPL)、吡喃葡萄糖基脂质A(GLA)和/或可溶性利什曼原虫抗原(Soluble Leishmania Antigen,SLA)。

[0066] 术语“有效量”是指根据本发明的当施用于患者用于治疗状态、病症或病状时足以

实现此类治疗或当施用于患者用于产生免疫应答时足以产生此类免疫应答的调配物的量。“有效量”将根据活性成分、待治疗的状态、病症或病状和其严重程度,以及待治疗的受试者的年龄、体重、身体状况和应答性而变化。

[0067] 术语“免疫应答”是指在受试者中引发一种或多种免疫细胞类型的活性。免疫应答包含例如,T细胞和B细胞应答。

[0068] 术语“体液免疫应答”是指产生血浆或血清抗体(例如,IgG)的免疫应答。

[0069] 术语“保护性免疫应答”是指当受试者随后受到病原体激发时预防和/或降低病原体感染严重程度的免疫应答或产生与保护相关的免疫应答水平的免疫应答。例如,如果疫苗接种导致在受试者(例如,人、宠物或农业动物)的血浆或血清中产生保护受试者免受后续感染和/或用于赋予测试受试者(例如,新西兰白(NZW)兔)保护的以观察到的数量存在的中和抗体,则疫苗接种可能产生保护性免疫应答。

[0070] 术语“多克隆抗体应答”是指包括在其抗体序列中具有多于一种特异性和/或变异的抗体的抗体应答。

[0071] 术语“中和”(例如,“中和抗体应答”)是指防止病原体感染和/或降低病原体感染水平的抗体。中和抗体应答可以在体外测定(例如,在存在抗体的情况下通病原体感染培养物中细胞)或在体内测定(例如,通过在用感染剂量的病原体激发之前向受试者施用抗体来确定保护剂量的抗体)来测量。

[0072] 抗体与靶标(例如,人偏肺病毒或hMPV蛋白)“结合”或对其“具有特异性”或与其“特异性结合”(本文可互换使用)是本领域充分理解的术语,并且用于确定此类特异性或优先结合的方法也是本领域众所周知的。如果分子与特定细胞或物质比其与替代性细胞或物质更频繁地、更快速地、持续时间更长地和/或亲和力更大地反应或缔合,则所述分子被称为表现出“特异性结合”或“优先结合”。例如,与胸腺细胞特异性或优先结合的免疫球蛋白是与胸腺细胞以比其与其它细胞结合更大的亲和力、亲合力、更容易地和/或持续时间更长地结合的免疫球蛋白。与第一细胞或物质特异性结合的免疫球蛋白可以与或可以不与第二细胞或物质特异性或优先结合。如此,“特异性结合”不一定需要(但是其可以包含)排他性结合。通常,但不是必然地,提及结合是指特异性结合。

[0073] 术语“预定时间”是指选择适合于观察特定效果的时间间隔。可以在实验或程序之前或期间选择预定时间。

[0074] 术语“暴露后预防”是指向先前暴露于和/或感染病原体的受试者施用抗原组合物(例如,疫苗)以引发免疫应答,从而防止病原体感染和/或降低病原体感染的一种或多种症状的严重程度。

[0075] 术语“施用”是指以允许组合物具有其预期效果的方式向受试者提供组合物。用于疫苗接种或暴露后预防的施用可以通过肌内注射、静脉内注射、腹膜内注射或任何其它合适的途径进行。

[0076] 术语“免疫(immunization)”和“免疫(immunizing)”是指以足以在一个或多个施用步骤后引发期望的免疫应答(例如,针对VLP的体液免疫应答)的量向受试者施用组合物(例如,病毒样颗粒)。免疫可以包括一次至十次或更多次施用(例如注射)组合物,如1次、2次、3次、4次、5次、6次、7次、8次、9次、10次或更多次施用。首次施用可能不会引发可检测的免疫应答,因为通常每次后续施用将增强通过先前施用生成的免疫应答。如本文所使用的,

术语“免疫”包含暴露后预防。

[0077] 术语“受试者”是指为了疫苗接种、治疗或其它目的可以向其施用组合物的人或非人动物。在一些实施例中，非人动物是非人灵长类动物、兔、仓鼠、沙鼠、猪、牛、绵羊、山羊、豚鼠、大鼠、小鼠、松鼠、狼、狐狸、马、斑马、长颈鹿、大象、猫、狗、美洲驼或雪貂。

[0078] 术语“制造”是指以任何规模产生重组多肽或病毒样颗粒，包含至少25-mL、50-mL、1-L、1,000-L、50,000-L或更大规模。

[0079] 术语“培养”和“培养基”是指标准细胞培养和重组蛋白表达技术。

[0080] 术语“宿主细胞”是指能够用于表达重组多肽的任何细胞。

[0081] 术语“分泌”是指宿主细胞将多肽分泌到培养它们的培养基中的能力。

[0082] 术语“信号序列”是指通常位于在宿主细胞中表达的多肽的N末端处，将多肽引导到特定的细胞区室的多肽序列。信号序列可以是引起宿主细胞将多肽分泌到培养宿主细胞的培养基中的分泌信号。各种信号序列是已知的并且选择合适的信号序列在普通技术人员的技能范围内。

[0083] 术语“混合”是指将两种溶液接触以允许溶液混合。

[0084] 术语“纯化”是指将分子与组合物中存在的其它物质分离。多肽可以通过亲和性(例如，抗体或标签，例如，使用His标签捕获树脂)、通过电荷(例如，离子交换色谱法)、通过大小(例如，制备超速离心、尺寸排阻色谱法)或其它方式纯化。

[0085] 本文可互换使用的术语“多核苷酸”和“核酸”是指多于约100个核苷酸的(核糖核苷酸或脱氧核糖核苷酸)的核苷酸的聚合物形式。因此，此术语包含但不限于单链、双链或多链DNA或RNA、基因组DNA、cDNA、DNA-RNA杂交体或包括嘌呤和嘧啶碱基或其它天然的、经化学或生化修饰的、非天然的或衍生的核苷酸碱基的聚合物。“寡核苷酸”通常是指单链或双链DNA的约5至约100个核苷酸之间的多核苷酸。然而，出于本公开的目的，寡核苷酸的长度没有上限。寡核苷酸也称为“寡聚物(oligomer)”或“寡聚物(oligo)”，并且可以从基因中分离出来，或通过本领域已知的方法化学合成。应了解术语“多核苷酸”和“核酸”包含单链(例如有义或反义)和双链多核苷酸(如果所描述的实施例适用的话)。

[0086] 术语“同一性”、“同一”、“序列同一性”是指在两个多核苷酸或多肽序列之间相同且相对位置相同的碱基或氨基酸的百分比。因此，一个多核苷酸或多肽序列与另一多核苷酸或多肽序列相比具有一定百分比的序列同一性。为了进行序列比较，通常一个序列充当与测试序列进行比较的参考序列。术语“参考序列”是指与测试序列进行比较的分子。

[0087] 用于比较和确定序列同一性百分比的序列比对方法是本领域众所周知的。用于比较的序列的最佳比对可以例如分别通过以下进行：Needleman和Wunsch的同源性比对算法，(1970)《分子生物学杂志(J.Mol.Biol.)》48:443，通过Pearson和Lipman，(1988)《美国国家科学院院刊(Proc.Nat'l.Acad.Sci.USA)》85:2444的相似性搜索法；这些算法的计算机化实施例(威斯康星州麦迪逊科学大道575号遗传学计算机组(Genetics Computer Group，575Science Dr.，Madison，WI)的威斯康星遗传学软件包中的GAP、BESTFIT、FASTA和TFASTA)；手动比对和视觉检查(参见例如，Brent等人，(2003)《当代分子生物学实验指南(Current Protocols in Molecular Biology)》；通过使用本领域已知的算法，包含BLAST和BLAST 2.0算法，其分别描述于以下中：Altschul等人，(1977)《核酸研究(Nuc.Acids Res.)》25:3389-3402；以及Altschul等人，(1990)，《分子生物学杂志》215:403-410。用于执

行BLAST分析的软件可通过美国国家生物技术信息中心(National Center for Biotechnology Information)公开获得。

[0088] 术语“治疗”意指缓解、减轻、延迟、减少、逆转、改善或管理受试者病状的至少一种症状中的一种或多种。术语“治疗”还可以意指阻滞、延迟发作(即,在病状的临床表现之前的时期)或降低病状发生或恶化的风险中的一种或多种。

[0089] 术语“约”或“大约”意指在本领域普通技术人员确定的特定值的可接受误差范围内,这将部分取决于如何测量或确定值,例如,测量系统的局限性。例如,“约”可以意指在1个或多于1个标准偏差内。可替代地,“约”可以意指至多20%、至多10%或至多5%的正或负范围。

[0090] 除非另有说明,否则本文中引用的所有重量百分比(即“重量%”和“wt.%”和w/w)均相对于药物组合物的总重量进行测量。

[0091] 如本文所使用的,“基本上”或“基本”是指动作、特性、性质、状态、结构、项目或结果的完全或几乎完全的范围或程度。例如,“基本上”封闭的对象将会意味着对象被完全封闭或几乎完全封闭。在某些情况下,与绝对完全性的偏差的精确允许程度可以取决于具体的上下文。然而,一般而言,完成的接近度将是具有如获得了绝对且全部完成那样相同的总体结果。当以否定含义使用以指代动作、特性、性质、状态、结构、项目或结果的完全或几乎完全缺失时,“基本上”的使用同样适用。例如,“基本上不含”其它活性剂的组合物要么完全缺乏其它活性剂,要么几乎完全缺乏其它活性剂,其效果与完全缺乏其它活性剂的情况相同。换言之,“基本上不含”成分或元素或另一种活性剂的组合物仍然可以含有此类物质,只要其没有可测量效果。

[0092] 以下说明包含对理解本发明可能有用的信息。这并非承认本文所提供的任何信息是现有技术或与当前要求保护的发明相关,或并非承认任何具体或隐含引用的公开是现有技术。

[0093] 概述

[0094] 疫苗接种是一种治疗方式,用于预防或降低感染各种感染原(包含细菌、病毒和寄生虫)的严重程度。新疫苗的开发具有重要的商业和公共健康影响。具体地,莱姆病、百日咳、疱疹病毒、正粘病毒、副粘病毒、肺病毒、丝状病毒、黄病毒、呼肠孤病毒、逆转录病毒、冠状病毒和疟疾是已经存在、正在开发或可能期望疫苗的感染原。

[0095] 亚单位疫苗是由分离的抗原制成的疫苗,通常是在细菌、昆虫或哺乳动物细胞宿主中重组表达的蛋白质。典型地,亚单位疫苗的抗原组分选自观察到的在感染时引发天然免疫应答的感染原的蛋白质,尽管在某些情况下可以使用感染原的其它组分。用于亚单位疫苗的典型抗原包含在靶感染原表面上表达的蛋白质,如病毒表面表达的包膜糖蛋白。优选地,所述抗原是中和抗体的靶标。更优选地,所述抗原是广泛中和抗体的靶标,使得对所述抗原的免疫应答覆盖针对感染原的多种菌株的免疫。在一些情况下,通过对抗原表位的贡献或通过空间位阻引导对抗原上特定表位的免疫应答,与亚单位疫苗N连接或O连接的聚糖也可以在疫苗接种中发挥重要作用。响应于疫苗接种的免疫应答可以直接作用于蛋白质本身、聚糖或蛋白质和连接的聚糖两者。亚单位疫苗具有多种优点,包含其不含活病原体,这消除了有关患者被疫苗感染的担忧;其可以使用标准基因工程化技术来设计;其比其它形式的疫苗更同质;并且其可以在标准化的重组蛋白表达生产系统中使用充分表征的表达

系统制造。在一些情况下,抗原可以经过基因工程化,以利于生成期望的抗体,如中和或广泛中和抗体。具体地,通过X射线晶体学、电子显微镜或核磁共振实验获得的关于所关注的抗原的结构信息可以用于指导亚单位疫苗的合理设计。

[0096] 亚单位疫苗的已知限制是所引发的免疫应答有时可能弱于对其它类型疫苗(如全病毒、活疫苗或减毒活疫苗)的免疫应答。本发明人已经认识到并且在本文中公开了设计的和/或基于蛋白质的VLP疫苗有潜力利用亚单位疫苗的优点,同时通过以对称有序阵列显示抗原的多价来增加疫苗诱导的免疫应答的效力和广度。在本公开中,基于蛋白质的VLP与纳米颗粒疫苗不同,因为本领域中已使用术语“纳米颗粒疫苗”来指代基于蛋白质的或基于糖蛋白的疫苗(参见例如,专利第US 9,441,019号)、聚合脂质体(参见例如,美国专利第7,285,289号)、表面活性剂胶束(参见例如,美国专利公开第US 2004/0038406A1号)和合成可生物降解颗粒(参见例如美国专利第US 8,323,696号)。

[0097] 本公开的基于蛋白质的VLP与在含有表面活性剂(例如,NP-9)的胶束颗粒的表面上显示抗原的VLP是可区分的;或可替代地,通过从活病毒中提取抗原蛋白同时保留病毒包膜的脂质成分来制备。相比之下,本文所描述的基于蛋白质的VLP不含或基本上不含脂质和表面活性剂。此外,与其它VLP相比,hMPV F蛋白在本公开的基于蛋白质的VLP的一些实施例上的对称显示可以产生对F蛋白的优异免疫应答。

[0098] 实施例

[0099] 本公开涉及基于蛋白质的VLP和基于蛋白质的VLP疫苗。本公开的VLP显示能够引发针对hMPV的免疫应答的抗原。本公开的一些疫苗可用于预防或降低hMPV感染的严重程度。特别地,本公开的抗原显示hMPV F蛋白的胞外结构域。胞外结构域可以非共价或共价附接到VLP的核心,包含作为融合蛋白或通过本文所公开的其它方式。在一些实施例中,接头将胞外结构域连接到包括多聚化结构域的第一多肽。接头可以是任何化学连接,包含但不限于用于形成胞外结构域与第一多肽的N末端或C末端融合体的多肽。hMPV F蛋白可以任选地沿着VLP的对称轴显示。在一些实施例中,F蛋白在C末端连接到包括三聚化结构域和任选地另外的三聚化标签(例如,FoldOn标签)的第一多肽。还提供了蛋白质和编码此类蛋白质的核酸分子、调配物和使用方法。

[0100] 基于蛋白质的病毒样颗粒

[0101] 本发明的VLP可以包括适于显示hMPV F蛋白的胞外结构域或其抗原片段的多聚体蛋白组装体。本发明的VLP至少包括第一多个多肽。所述第一多个多肽(也称为“第一组分”)可以通过取代至少一个氨基酸残基或通过在N末端或C末端处添加一个或多个残基而源自天然存在的蛋白质序列。在一些情况下,第一组分包括通过计算方法确定的蛋白质序列。第一组分可以形成VLP的整个核心;或者VLP的核心可以包括一种或多种另外的多肽(也称为“第二组分”或第三、第四、第五组分等),使得VLP包括二、三、四、五、六、七或更多种多个多肽。在一些情况下,所述第一多个将形成通过3倍旋转对称性相关的三聚体并且所述第二多个将形成通过5倍旋转对称性相关的五聚体。在此类情况下,VLP形成具有I53对称性的“二十面体颗粒”。这些一种或多种多个多肽可以一起布置,使得每种多个多肽的成员通过对称性算子彼此相关。一种涉及蛋白质构建块在目标对称架构中的对称对接的用于设计自组装蛋白质材料的通用计算方法公开于专利公开第US2015/0356240 A1号中。

[0102] VLP的“核心”在本文中用于描述VLP的中心部分,所述中心部分将由VLP显示的

hMPV F蛋白胞外结构域或其抗原片段的若干个拷贝连接在一起。在一实施例中,第一组分包括包含hMPV F蛋白胞外结构域或其抗原变体的第一多肽、接头和包含多聚化结构域的第一多肽。因此,“抗原”是单一多肽,能够单独或此第二组分(第三、第四或第五等组分)自组装成VLP。将抗原本身设计成自组装的优点是整个VLP然后充当疫苗的抗原组分。在其它实施例中,胞外结构域或其抗原片段非共价或共价连接到包括多聚化结构域的第一多肽。例如,抗体或其抗原片段可以与第一多肽融合并且被配置成与第一多肽的一部分或第一多肽上的化学标签结合。可以采用链霉亲和素-生物素(或神经亲和素-生物素)接头。或者可以使用各种化学接头。将核心设计成通用平台的优点是可以提前设计和优化包括核心的所述一种或多种多个多肽,然后将其连续应用于胞外结构域以鉴定具有作为疫苗的优异功效的VLP。应当理解,在一些情况下,相同的多肽可以形成“核心”的一部分,然后向外延伸作为附接hMPV F蛋白胞外结构域的衔接子并包含胞外结构域(即,融合蛋白)。在本公开的各实施例中,除了hMPV F蛋白胞外结构域之外,抗原包括另外的多肽序列。在某些实施例中,胞外结构域被天然糖基化或使用替代寡糖(例如,对用于表达抗原的宿主细胞具有特异性的寡糖)糖基化。

[0103] 在一些情况下,胞外结构域的多聚化可以进一步促进自组装,即使在不存在胞外结构域的情况下,核心也能够独立地自组装。hMPV F蛋白在其天然状态下被检测为三聚体(Cseke等人《病毒学杂志(J.Virol.)》21(2):698-707(2007))。至少在一些实施例中,胞外结构域在VLP上的显示降低了组装的热力学屏障和/或组装与未组装的VLP组分的平衡比。在一些情况下,沿着VLP的3倍轴放置的三聚体胞外结构域促进了胞外结构域的适当折叠和构象稳定性,并且使VLP的自组装成为合作过程,因为胞外结构域被适当地三聚化,部分原因在于它显示在VLP核心的3倍轴上,并且VLP至少部分地通过三聚体单元之间的非共价或共价相互作用以其组装形式稳定。在一些情况下,向抗原或VLP组分引入突变可以任选地进一步使组装稳定,特别是如果半胱氨酸残基被定位成产生分子内二硫键。在一些实例中,二聚体、三聚体、四聚体、五聚体或六聚体抗原显示在设计成具有匹配的2倍、3倍、4倍、5倍或6倍对称轴的核心上,使得核心容纳具有抗原天然对称性的多聚体抗原的布置。

[0104] VLP的各种非限制性实例

[0105] 实施例的非限制性实例示出于图1A,所述图描绘了与VLP的组分(第一多个多肽)遗传融合的胞外结构域抗原,其任选地在宿主细胞(例如,293F细胞)中重组表达;连同任选地在相同或不同的宿主细胞(例如,大肠杆菌细胞(E.coli cell))中重组表达的五聚体蛋白质组装(第二多个多肽),这两种多个多肽自组装成在二十面体核心周围显示20个抗原三聚体的VLP。在此实施例中,核心具有通用设计。如下文所解释的,在其它实施例中,本公开的抗原与相同VLP中的另一种抗原蛋白混合,如来自第二病毒的蛋白胞外结构域或如来自另一种病毒的三聚体糖蛋白。在一些实施例中,除了hMPV F蛋白胞外结构域之外,VLP包括HIV-1、HIV-2、EBV、CMV、RSV、流感、埃博拉(Ebola)、马尔堡(Marburg)、登革热(Dengue)、SARS、MERS、汉塔(Hanta)或寨卡病毒(Zika virus)的三聚体糖蛋白。在一些实施例中,VLP包括与这些说明性病毒中的任何说明性病毒在进化上或序列同一性上相关的病毒的三聚体糖蛋白,包含但不限于疱疹病毒、正粘病毒、副粘病毒、肺病毒、丝状病毒、黄病毒、呼肠孤病毒或逆转录病毒。在一实施例中,VLP包括跨膜蛋白或糖蛋白的一个或多个胞外结构域或其抗原片段。在一些实施例中,VLP进一步连接到多肽或其它能够充当佐剂的药剂。在一些

实施例中,抗原(第一组分)和/或第二组分包括一个或多个T细胞表位,任选地异源来源的T细胞表位。

[0106] 可以与本公开的VLP一起使用以形成混合VLP的三聚体抗原在一些情况下是但不限于SARS-CoV-2、呼吸道合胞病毒、HIV gp140、流感HA、登革热E蛋白或埃博拉sGP。本公开的混合VLP包含包括hMPV F蛋白胞外结构域和来自水泡性口炎病毒、单纯疱疹病毒、杆状病毒、索戈托病毒(Thogotovirus)和玻那病毒科(Bornaviridae)中的一种或多种的抗原蛋白的那些。当使用其它三聚体抗原时,所述三聚体抗原可以任选地放置在VLP的3倍对称轴上。在一些情况下,所选择的抗原是单体的,并且仍然放置在3倍轴上。因此,描绘于图1A中的VLP能够显示20个三聚体抗原或60个单体抗原。另外或可替代地,VLP的五聚体复合物用于显示12个五聚体抗原或70个单体抗原。在一实施例中,VLP包括三聚体抗原的20个拷贝和五聚体抗原的12个拷贝。

[0107] VLP核心

[0108] 本公开的多肽的其它可能布置示出于图1B中。在一些实施例中,VLP适于显示至多8个三聚体;8个三聚体和12个二聚体;6个四聚体和12个二聚体;6个四聚体和8个三聚体;20个三聚体和30个二聚体;4个三聚体和6个二聚体;4个第一三聚体和4个第二三聚体或8个三聚体;12个五聚体和20个三聚体;或12个五聚体和30个二聚体;或4个三聚体。在一些情况下,对称轴之一不用于抗原显示,因此,在一些实施例中,VLP适于显示至多8个三聚体;12个二聚体;6个四聚体;20个三聚体;30个二聚体;4个三聚体;6个二聚体;8个三聚体;或12个五聚体。在一些情况下,显示单体抗原,并且因此,VLP适于显示至多12个、24个、60个或70个单体抗原。在一些情况下,VLP包括混合的多个多肽,使得VLP的核的相同多肽显示不同的抗原或不显示抗原。因此,取决于多肽的比率,VLP在一些情况下适于显示介于1个与130个之间的抗原(例如,在I52颗粒上),其中显示的每个抗原可以是相同的或可以是混合群体的不同成员,与所选择的任何比率成比例。抗原可以在重组表达系统中共表达,并且在纯化之前自组装。可替代地,抗原可以分别表达,然后在从表达宿主和相关污染物中纯化之前或之后混合在一起。在各种实施例中,显示1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29、30或更多个抗原。非限制性说明性VLP在以下中提供:Bale等人《科学(Science)》353:389-94(2016);Heinze等人《物理化学期刊(J.Phys.Chem B.)》120:5945-5952(2016);King等人《自然(Nature)》510:103-108(2014);以及King等人《科学》336:1171-71(2012)。

[0109] 混合VLP

[0110] 在一些情况下,VLP适于显示来自两种或更多种不同hMPV菌株的相同抗原。在非限制性实例中,相同VLP显示来自不同hMPV菌株的同源三聚体蛋白抗原的混合群体或蛋白抗原的混合异源三聚体。在一实施例中,VLP单独地或在混合VLP中显示在GenBank的通过用关键字“人偏肺病毒F”搜索蛋白质数据库找到的任何序列中公开的F蛋白或其抗原片段。

[0111] 制备混合VLP时,确保以菌株特异性方式形成同源多聚体而不是允许异源多聚化可能是有利的,使得例如,所有菌株1F蛋白都显示在T33颗粒的一个3倍轴上,而所有菌株2F蛋白都显示在T33颗粒的另一个3倍轴上。这可以通过使用包括两种或更多种多个多肽的VLP作为VLP的核心来实现,其中每种多个多肽附接到不同的抗原。可替代地,VLP可以被工程化成具有一个或多个对称性破坏突变,如杵臼突变(knob-in-hole mutation)或分子内

二硫键突变,所述突变具有防止不同抗原之间形成三聚体的作用。在所述情况下,VLP在VLP上的对称等同位置处显示来自不同菌株的多聚体抗原,但VLP上的每个位置都被来自同一菌株的同源多聚体占据,只有微不足道比例的菌株间异聚体抗原。在一些情况下,抗原本身可以被基因工程化成防止菌株间异源多聚化。在一实施例中,VLP被工程化成防止具有保守结构但抗原性不同的两种抗原蛋白的异源多聚化,例如菌株1F蛋白和菌株2F蛋白、或hMPV F蛋白和非hMPV抗原蛋白。此外,当制备混合VLP并将抗原显示为融合蛋白时,VLP将包括三种或更多种不同的蛋白质,因为融合蛋白将共享用于形成具有不同抗原结构域的VLP核心的相同(或等同)结构域,一个抗原结构域针对在VLP上显示的每种抗原。

[0112] 附接模式(接头)

[0113] 本公开的VLP以各种方式展示抗原蛋白,包含作为基因融合或通过本文所公开的其它方式。如本文所使用的,“连接到”或“附接到”表示本领域已知的用于引起两个多肽缔合的任何方式。缔和可以是直接的或间接的、可逆的或不可逆的、弱的或强的、共价的或非共价的、选择性的或非选择性的。

[0114] 在一些实施例中,附接是通过基因工程化成产生抗原与构成VLP的所述多个多肽之一的N末端或C末端融合来实现的。因此,VLP可以由或基本上由显示一、二、三、四、五、六、七、八、九或十种多个抗原的一、二、三、四、五、六、七、八、九或十种多个多肽组成,其中所述多个抗原中的至少一个抗原与所述多个多肽中的至少一个多肽基因融合。在一些情况下,VLP基本上由能够自组装并包括与其基因融合的所述多个抗原蛋白的一种多个多肽组成。在一些情况下,VLP基本上由以下组成:包括多个抗原的第一多个多肽;以及能够共组装成双组分VLP的第二多个多肽,一种多个多肽将抗原蛋白连接到VLP,并且另一种多个多肽促进VLP的自组装。

[0115] 在一些实施例中,附接是通过一种或多种多个多肽与一种或多种多个抗原蛋白之间的翻译后共价附接实现的。在一些情况下,化学交联用于将抗原非特异性地连接到VLP多肽。在一些情况下,化学交联用于将抗原蛋白特异性附接到VLP多肽(例如附接到第一多肽或第二多肽)。各种特异性和非特异性交联化学是本领域已知的,如点击化学和其它方法。通常,用于连接两种蛋白质的任何交联化学可以适于用于当前公开的VLP中。特别地,可以使用用于产生免疫缀合物或抗体药物缀合物的化学。在一些情况下,VLP是使用可切割或不可切割的接头产生的。用于将抗原与载体缀合的过程和方法由例如专利公开第US2008/0145373 A1号提供。

[0116] 在一实施例中,附接是通过一种或多种多个多肽与一种或多种多个抗原之间的非共价附接实现的。在一些情况下,抗原蛋白被工程化成在至少一个表面上带负电荷,并且核心多肽被工程化成在至少一个表面上带正电荷,或分别带正电荷和负电荷。这通过静电力促进了抗原蛋白与核心多肽之间的分子间缔和。在一些情况下,形状互补性用于引起抗原蛋白与核心的连接。形状互补性可以是预先存在的或合理设计的。在一些情况下,蛋白质-蛋白质界面的计算设计用于实现附接。在一实施例中,抗原是生物素标记的并且多肽包括链霉亲和素,反之亦然。在一实施例中,链霉亲和素通过基因融合或其它方式在核心的4倍轴上显示为四聚体,并且生物素标记的抗原是单体、二聚体或四聚体,允许以适合抗原天然多聚化的构型与核心缔和。在一些情况下,基于蛋白质的衔接子用于捕获抗原蛋白。在一些情况下,多肽与能够与互补蛋白结合的蛋白质融合,所述互补蛋白与抗原蛋白融合。

[0117] 可以通过改变胞外结构域相对于核心的定向来控制对hMPV F的免疫反应。根据抗原蛋白如何附接到VLP的核心,抗原蛋白可以以不同的定向显示。在一些实施例中,显示抗原蛋白,使得一个或多个已知表位定向在或朝向抗原蛋白的远端处,使得这些表位优选被免疫系统接近。在一些情况下,定向将概括病毒蛋白相对于病毒的定向。定向的选择可以将免疫系统引导到一个或另一个表位。

[0118] 在一些实施例中,表位偏好通过其它方式控制,如通过在多肽中的任何多肽的氨基酸序列中(包含在抗原蛋白的氨基酸序列中)的预定位置处添加或减去N连接的聚糖序列基序N-X-[T/S]来将聚糖定位在VLP上。

[0119] 在一些情况下,根据各种考虑,包含但不限于VLP的整体几何形状、表面疏水性、表面电荷和内源性存在于受试者中的蛋白质或疫苗组合物中外源性提供的蛋白质的竞争性结合,在从近端至远端的中间距离处发现的表位将优于更远定位的表位。本公开涵盖所有已知的蛋白质结构的合理设计方法并且前述内容不旨在限制。

[0120] VLP多肽序列

[0121] 本公开的多肽可以具有各种氨基酸序列中的任何氨基酸序列。专利公开第US 2015/0356240A1号描述了用于设计蛋白质组装的各种方法。如美国专利公开第US 2016/0122392A1号和国际专利公开第WO 2014/124301 A1号中所描述的,SEQ ID NO:1-51的分离的多肽被设计用于其成对自组装以形成VLP(如二十面体颗粒)的能力。所述设计涉及为多肽对的每个成员设计合适的界面残基,所述多肽对可以被组装以形成VLP。如此形成的VLP包含对称重复的、非天然的、非共价的多肽-多肽界面,所述界面将第一组装和第二组装定向到VLP中,如具有二十面体对称的一个。因此,在一个实施例中,第一多肽和第二多肽(即,VLP核的两个多肽)选自由以下组成的组:SEQ IDNO:1-51。在每种情况下,存在于全长蛋白中但可以被去除以进行融合的N-末端甲硫氨酸残基不包含在序列中。表1中鉴定的残基以N末端甲硫氨酸(未示出)开始编号。在各种实施例中,从N末端缺失一个或多个另外的残基和/或向N末端添加另外的残基(例如,以形成螺旋延伸)。

[0122] 表1

[0123]

名称	组分多聚体	氨基酸序列	鉴定的界面残基
I53-34A SEQ ID NO: 1	三聚体	EGMDPLAVLAESRLLPLLTVRGGEDLAGLATVLELMGVGALEITLRTEKGLEALKALRKSGLLLGAGTVRSPKEAEAALEAGAAFLVSPGLLEEVAALAQARGVPYLPGVLTPTEVERALALGLSALKFFPAEPFQGVRVLRAYAEVFPEVRFLPTGGIKEEHLPHYAALPNLLAVGGSWLLQGDLAAVMKKVKAAKALLSPQAPG	I53-34A：28、32、36、37、186、188、191、192、195
I53-34B SEQ ID NO: 2	五聚体	TKKVGIVDTTFARVDMAEAAIRTLKALSPNIKIIRKTVPGIKDLPVACKKLLEEEGCDIVMALGMPGKAEKDKVCAHEASLGLMLAQLMTNKHIIEVFVHEDEAKDDDELDILALVRAIEHAANVYYLLFKPEYLTRMAGKGLRQGREDAGPARE	I53-34B：19、20、23、24、27、109、113、116、117、120、124、148
I53-40A SEQ ID NO: 3	五聚体	TKKVGIVDTTFARVDMASAAILTLKMESPNIKIIRKTVPGIKDLPVACKKLLEEEGCDIVMALGMPGKAEKDKVCAHEASLGLMLAQLMTNKHIIEVFVHEDEAKDDAELKILAARRAIEHALNVYYLLFKPEYLTRMAGKGLRQGFEDAGPARE	I53-40A：20、23、24、27、28、109、112、113、116、120、124
I53-40B SEQ ID NO: 4	三聚体	STINNQLKALKVIPVIAIDNAEDIIPLGKVLAENGLPAAEITFRSSAAVKAIMLLRSAQPEMLIGAGTILNGVQALAAKEAGATFVVSPGFNPNTVRACQIIGIDIVPGVNNPSTVEAALEMGLTTLKFFPAEASGGISMVKSLVGPYGDIRLMPTGGITPSNIDNYLAIPQVLACGGTWMVDKKLVTNGEWDEIARLTREIVEQVNP	I53-40B：47、51、54、58、74、102
I53-47A SEQ ID NO: 5	三聚体	PIFTLNTNIKATDVPSDFLSLTSRLVGLILSKPGSYVAVHINTDQQLSFGGSTNPAAFGTLMSIGGIEPSKNRDHSAVLFDHLNAMLGIPKNRMYIHFVNLNGDDVGWNGTTF	I53-47A：22、25、29、72、79、86、87

[0124]

名称	组分多聚体	氨基酸序列	鉴定的界面残基
I53-47B SEQ ID NO: 6	五聚体	NQHSHKDYETVRIAVVRARWHADIVDACVEAFEIAMAAIGGDRFAVDVFDVPGAYEIPLHARTLAETGRYGAVLGTAFVVNGGIYRHEFVASAVIDGMMNVQLSTGVPVLSAVLTPHRYRDSAEHHRFFAAHFAVKGVEAARACIEILAAREKIAA	I53-47B: 28、31、35、36、39、131、132、135、139、146
I53-50A SEQ ID NO: 7	三聚体	EELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQCRKAVESGAEFIVSPHLDEEISQFCKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVCEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGCTE	I53-50A: 25、29、33、54、57
I53-50B SEQ ID NO: 8	五聚体	NQHSHKDYETVRIAVVRARWHAEIVDACVSAFEAAMADIGGDRFAVDVFDVPGAYEIPLHARTLAETGRYGAVLGTAFVVNGGIYRHEFVASAVIDGMMNVQLSTGVPVLSAVLTPHRYRDSDAHTLLFLALFAVKGMEAARACVEILAAREKIAA	I53-50B: 24、28、36、124、125、127、128、129、131、132、133、135、139
I53-51A SEQ ID NO: 9	三聚体	FTKSGDDGNTNVINKRVGKDSPLVNFLGDLDELNSFIGFAISKIPWEDMKKDLERVQVELFEIGEDLSTQSSKKKIDESYVLWLLAATAIYRIESGPVKLFVIPGGSEEASVLHVTRSVARRVERNAVKYTKELPEINRMIIVYLNRLSSLLFAMALVANKRRNQSEKIYEIGKSW	I53-51A: 80、83、86、87、88、90、91、94、166、172、176
I53-51B SEQ ID NO: 10	五聚体	NQHSHKDYETVRIAVVRARWHADIVDQCVRAFEEAMADAGGDRFAVDVFDVPGAYEIPLHARTLAETGRYGAVLGTAFVVNGGIYRHEFVASAVIDGMMNVQLSTGVPVLSAVLTPHRYRSSREHHEFFREHFMVKGVEAAAACITILAAREKIAA	I53-51B: 31、35、36、40、122、124、128、131、135、139、143、146、147

[0125]

名称	组分多聚体	氨基酸序列	鉴定的界面残基
I52-03A SEQ ID NO: 11	五聚体	GHTKGPTPQQHDGSALRIGIVHARWNKTIIMPLLIGTIAKLLECGVKASNIVVQSVPGSWELPIAVQRLYSASQLQTPSSGPSLSAGDLLGSSTTDLTALPTTTASSTGPFDALIAIGVLIKGETMHFEYIADSVSHGLMRVQLDTGVPVIFGVLTVLTDDQAKARAGVIEGSHNHGEDWGLAAVEMGVRRRDWAAGKTE	I52-03A: 28、32、36、39、44、49
I52-03B SEQ ID NO: 12	二聚体	YEVDHADVYDLFYLGRGKDYAAEASDIADLVRSRTPEASSLLDVACGTGTHLEHFTKEFGDTAGLELSEDMLTHARKRLPDATLHQGDMRDFQLGRKFSAVVSMFSSVGYLKTVAELGAAVASFAEHLEPGGVVVVEPWWFPETFADGWVSADVVRRDGRTVARVSHSVREGNATRMEVHFTVADPGKGVRHFSDVHLITLFHQREYEAAFMAAGLRVEYLEGGPSGRGLFVGVPA	I52-03B: 94、115、116、206、213
I52-32A SEQ ID NO: 13	二聚体	GMKEKFVLIITHGDFGKGLLSGAEVIIGKQENVHTVGLNLGDNIEKVAKEVMRIIIAKLAEDKEIIIVVDLFGGSPFNIALEMMKTFDVKVITGINMPMLVELLTSINVYDTTELLENISKIGKDGIKVIEKSSLKM	I52-32A: 47、49、53、54、57、58、61、83、87、88
I52-32B SEQ ID NO: 14	五聚体	KYDGSKLRIGILHARWNLEIIAALVAGAIKRLQEFGVKAENIIIETVPGSFELPYGSKLFVEKQKRLGKPLDAIIPIGVLIKGSTMHFEYICDSTTHQLMKLNFELGIPVIFGVLTCLTDEQAEARAGLIEGKMHNHGEDWGAAAVEMATKFN	I52-32B: 19、20、23、30、40
I52-33A SEQ ID NO: 15	五聚体	AVKGLGEVDQKYDGSKLRIGILHARWNRKIILALVAGAVLRLLEFGVKAENIIIETVPGSFELPYGSKLFVEKQKRLGKPLDAIIPIGVLIKGSTMHFEYICDSTTHQLMKLNFELGIPVIFGVLTCLTDEQAEARAGLIEGKMHNHGEDWGAAAVEMATKFN	I52-33A: 33、41、44、50
I52-33B SEQ ID NO: 16	二聚体	GANWYLDNESSRLSFTSTKNADIAEVHRFLVLHGKVDPKGLAEVEVETESISTGIPLRDMLLRVLVFQVSKFPVAQINAQLDMRPINNLAPGAQLELRLPLTVSLRGKSHSYNAELLATRLDERRFQVVTLEPLVIHAQDFDMVRAFNALRLVAGLSAVSLSVPVGAVLIFTAR	I52-33B: 61、63、66、67、72、147、148、154、155
I32-06A SEQ ID NO: 17	二聚体	TDYIRDGSAIKALSFAIILAEADLRHIPQDLQRLAVRVIHACGMVDVANDLAFSEGAGKAGRNALLAGAPILCDARMVAEGITRSRLPADNRVIYTLSDPSVPELAKKIGNTRSAAALDLWLPHIEGSIVAIGNAPTALFRLFELLDAGAPKPALIIGMPVGFVGAAESKDELAANSRGVPYVIVRGRRGGSAMTAAAVNALASERE	I32-06A: 9、12、13、14、20、30、33、34

[0126]

名称	组分多聚体	氨基酸序列	鉴定的界面残基
I32-06B SEQ ID NO: 18	三聚体	ITVFGLKSKLAPRREKLAEVIYSSLHLGLDIPKGKHAIRFLCLEKEDFYYPFDRSDDYTVIEINLMAGRSEETKMLLIFLLFIALERKLGIRAHDVEITIKEQPAHCWGFRGRTGDSARDLDYDIYV	I32-06B: 24、71、73、76、77、80、81、84、85、88、114、118
I32-19A SEQ ID NO: 19	三聚体	GSDLQKLQRFSTCDISDGLLNVYNIPTGGYFPNLTAISPPQNSSIVGTAYTVLFAPIDDPRPAVNYIDSVPPNSILVLALEPHLQSQFHPFIKITQAMYGGLMSTRAQYLKSNGTVVFGRIRDVDEHRTLNHPVFAYGVGSCAPKAVVKAVGTNVQLKILTSDGVTQTICPGDYIAGDNNGIVRIPVQETDISKLVTYIEKSIEVDRLVSEAIKNGLPAKAAQTARRMVLKDYI	I32-19A: 208、213、218、222、225、226、229、233
I32-19B SEQ ID NO: 20	二聚体	SGMRVYLGADHAGYELKQAIIAFLKMTGHEPIDCGALRYDADDDYPAFCIAAATRTVADPGSLGIVLGGSGNGEQIAANKVPGARCALAWSVQTAALAREHNNAQLIGIGGRMHTLEEALRIVKAFVTTPWSKAQRHQRRIDILAEYERTHEAPPVPGAPA	I32-19B: 20、23、24、27、117、118、122、125
I32-28A SEQ ID NO: 21	三聚体	GDDARIAAIGDVDELNSQIGVLLAEPLPDDVRAALSAIQHDLFDLGGELCIPGHAAITEDHLLRLALWLVHYNGQLPPLEEFILPGGARGAALAHVCRTVCRRAERSIKALGASEPLNIAPAAYVNLLSDLLFVLARVLNRAAGGADVLWDRTRAH	I32-28A: 60、61、64、67、68、71、110、120、123、124、128
I32-28B SEQ ID NO: 22	二聚体	ILSAEQSFTLRHPHGQAAALAFVREPAAALAGVQRLRGLDSDGEQVWGELLVRVPLLGEVDLPFRSEIVRTPQGAELRPLTLTGERAWVAVSGQATAAEGGEMAFAFQFQAHLATPEAEGEGGAAFEVMVQAAAGVTLLLVAMALPQGLAAGLPPA	I32-28B: 35、36、54、122、129、137、140、141、144、148

[0127]

名称	组分多聚体	氨基酸序列	鉴定的界面残基
I53-40A.1 SEQ ID NO: 23	五聚体	TKKVGIVDTTFARVDMASAAILTLKMESPNIKIIRKTVPGIKDLPVACKKLLEEEGCDIVMALGMPGKKEKDKVCAHEASLGLMLAQLMTNKHIIEVFVHEDEAKDDAELKILAARRAIEHALNVYYLLFKPEYLTRMAGKGLRQGFEDAGPARE	I53-40A: 20、23、24、27、28、109、112、113、116、120、124
I53-40B.1 SEQ ID NO: 24	三聚体	DDINNQLKRLKVIPVIAIDNAEDIIPLGKVLAENGLPAAEITFRSSAAVKAIMLLRSAQPEMLIGAGTILNGVQALAAKEAGADFVVSPGFNPNTVRACQIIGIDIVPGVNNPSTVEQALEMGLTTLKFFPAEASGGISMVKSLVGPYGDIRLMPTGGITPDNIDNYLAIPQVLACGGTWMVDKKLVRNGEWDEIARLTREIVEQVNP	I53-40B: 47、51、54、58、74、102
I53-47A.1 SEQ ID NO: 25	三聚体	PIFTLNTNIKADDVPSDFLSLTSRLVGLILSKPGSYVAVHINTDQQLSFGGSTNPAAFGTLMSIGGIEPDKNRDHSAVLFDHLNAMLGIPKNRMYIHFVNLNGDDVGWNGTTF	I53-47A: 22、25、29、72、79、86、87
I53-47A.1NegT2 SEQ ID NO: 26	三聚体	PIFTLNTNIKADDVPSDFLSLTSRLVGLILSEPGSYVAVHINTDQQLSFGGSTNPAAFGTLMSIGGIEPDKNEDHSAVLFDHLNAMLGIPKNRMYIHFVDLDGDDVGWNGTTF	I53-47A: 22、25、29、72、79、86、87
I53-47B.1 SEQ ID NO: 27	五聚体	NQHSHKDHETVRIAVVRARWHADIVDACVEAFEIAMAAIGGDRFAVDVFDVPGAYEIPLHARTLAETGRYGAVLGTAFVVNGGIYRHEFVASAVIDGMMNVQLDTGVPVLSAVLTPHRYRDSDEHHRFFAAHFAVKGVEAARACIEILNAREKIAA	I53-47B: 28、31、35、36、39、131、132、135、139、146
I53-47B.1NegT2 SEQ ID NO: 28	五聚体	NQHSHKDHETVRIAVVRARWHADIVDACVEAFEIAMAAIGGDRFAVDVFDVPGAYEIPLHARTLAETGRYGAVLGTAFVVDGGIYDHEFVASAVIDGMMNVQLDTGVPVLSAVLTPHEYEDSDEDHEFFAAHFAVKGVEAARACIEILNAREKIAA	I53-47B: 28、31、35、36、39、131、132、135、139、146

[0128]

名称	组分多聚体	氨基酸序列	鉴定的界面残基
I53-50A.1 SEQ ID NO: 29	三聚体	EELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQCRKAVESGAEFIVSPHLDEEISQFCKEKGVFYMPGVMTPTELVKAMKLGHDILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVCEWFKAGVLAVGVGDALVKGDPDEVREKAKKFVEKIRGCTE	I53-50A：25、29、33、54、57
I53-50A.1NegT2 SEQ ID NO: 30	三聚体	EELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQCRKAVESGAEFIVSPHLDEEISQFCKEKGVFYMPGVMTPTELVKAMKLGHDILKLFPGEVVGPEFVEAMKGPFPNVKFVPTGGVDLDDVCEWFDAGVLAVGVGDALVEGDPDEVREDAKEFVEEIRGCTE	I53-50A：25、29、33、54、57
I53-50A.1PosT1 SEQ ID NO: 31	三聚体	EELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQCRKAVESGAEFIVSPHLDEEISQFCKEKGVFYMPGVMTPTELVKAMKLGHDILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVCKWFKAGVLAVGVGKALVKGKPDEVREKAKKFVKKIRGCTE	I53-50A：25、29、33、54、57
I53-50B.1 SEQ ID NO: 32	五聚体	NQHSHKDHETVRIAVVRARWHAEIVDACVSAFEAAMRDIGGDRFAVDVFDVPGAYEIPLHARTLAETGRYGAVLGTAFVVNGGIYRHEFVASAVIDGMMNVQLDTGVPVLSAVLTPHRYRDSDAHTLLFLALFAVKGMEAARACVEILAAREKIAA	I53-50B：24、28、36、124、125、127、128、129、131、132、133、135、139
I53-50B.1NegT2 SEQ ID NO: 33	五聚体	NQHSHKDHETVRIAVVRARWHAEIVDACVSAFEAAMRDIGGDRFAVDVFDVPGAYEIPLHARTLAETGRYGAVLGTAFVVDGGIYDHEFVASAVIDGMMNVQLDTGVPVLSAVLTPHEYEDSDADTLLFLALFAVKGMEAARACVEILAAREKIAA	I53-50B：24、28、36、124、125、127、128、129、131、132、133、135、139

[0129]

名称	组分多聚体	氨基酸序列	鉴定的界面残基
I53-50B.4PosT1 SEQ ID NO: 34	三聚体	NQHSHKDHETVRIAVVRARWHAEIVDACVSAFEAAMRDIGGDRFAVDVFDVPGAYEIPLHARTLAETGRYGAVLGTAFVVNGGIYRHEFVASAVINGMMNVQLNTGVPVLSAVLTPHNYDKSKAHTLLFLALFAVKGMEAARACVEILAAREKIAA	I53-50B: 24、28、36、124、125、127、128、129、131、132、133、135、139
I53-40A属 SEQ ID NO: 35	五聚体	TKKVGIVDTTFARVDMASAAILTLKMESPNIKIIRKTVPGIKDLPVACKKLLEEEGCDIVMALGMPGK(A/K)EKDKVCAHEASLGLMLAQLMTNKHIIEVFVHEDEAKDDAELKILAARRAIEHALNVYYLLFKPEYLTRMAGKGLRQGFEDAGPARE	
I53-40B属 SEQ ID NO: 36	三聚体	(S/D)(T/D)INNQLK(A/R)LKVIPVIAIDNAEDIIPLGKVLAENGLPAAEITFRSSAAVKAIMLLRSAQPEMLIGAGTILNGVQALAAKEAGA(T/D)FVVSPGFNPNTVRACQIIGIDIVPGVNNPSTVE(A/Q)ALEMGLTTLKFFPAEASGGISMVKSLVGPYGDIRLMPTGGITP(S/D)NIDNYLAIPQVLACGGTWMVDKKLV(T/R)NGEWDEIARLTREIVEQVNP	
I53-47A属 SEQ ID NO: 37	三聚体	PIFTLNTNIKA(T/D)DVPSDFLSLTSRLVGLILS(K/E)PGSYVAVHINTDQQLSFGGSTNPAAFGTLMSIGGIEP(S/D)KN(R/E)DHSAVLFDHLNAMLGIPKNRMYIHFV(N/D)L(N/D)GDDVGWNGTTF	
I53-47B属 SEQ ID NO: 38	五聚体	NQHSHKD(Y/H)ETVRIAVVRARWHADIVDACVEAFEIAMAAIGGDRFAVDVFDVPGAYEIPLHARTLAETGRYGAVLGTAFVV(N/D)GGIY(R/D)HEFVASAVIDGMMNVQL(S/D)TGVPVLSAVLTPH(R/E)Y(R/E)DS(A/D)E(H/D)H(R/E)FFAAHFAVKGVEAARACIEIL(A/N)AREKIAA	
I53-50A属 SEQ ID NO: 39	三聚体	EELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQCRKAVESGAEFIVSPHLDEEISQFCKEKGVFYMPGVMTPTELVKAMKLGH(T/D)ILKLFPGEVVGP(Q/E)FV(K/E)AMKGPFPNVKFVPTGGV(N/D)LD(N/D)VC(E/K)WF(K/D)AGVLAVGVG(S/K/D)ALV(K/E)G(T/D/K)PDEVRE(K/D)AK(A/E/K)FV(E/K)(K/E)IRGCTE	

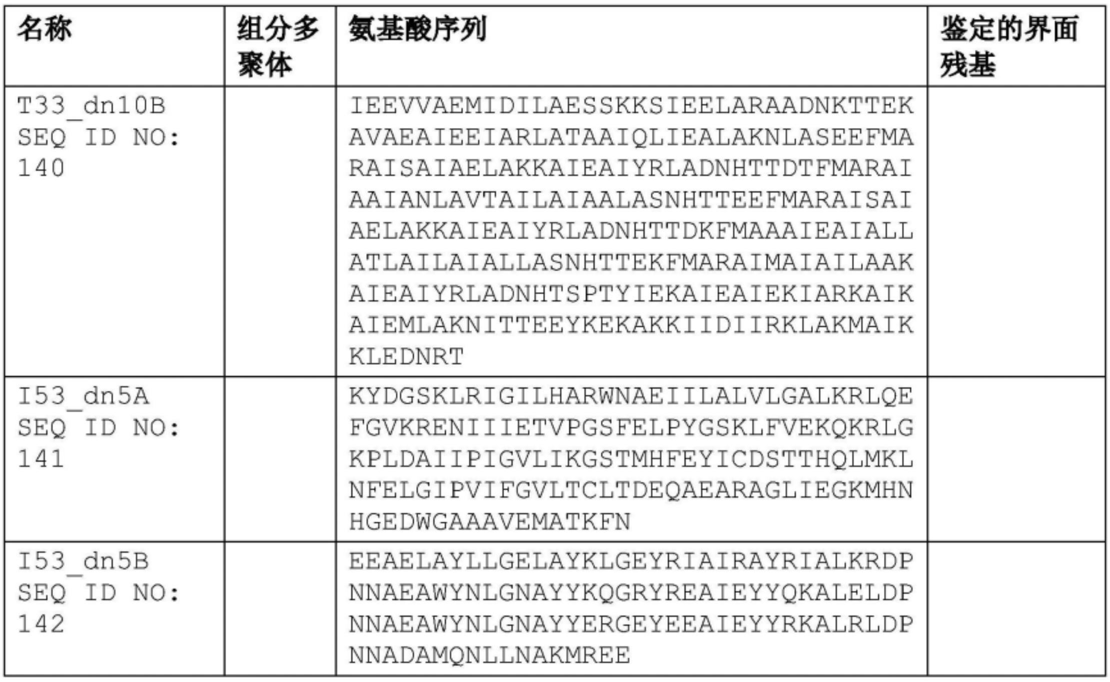
[0130]

名称	组分多聚体	氨基酸序列	鉴定的界面残基
I53-50B 属 SEQ ID NO: 40	五聚体	NQHSHKD(Y/H)ETVRIAVVRARWHAEIVDACVSAFEAAM(A/R)DIGGDRFAVDVFDVPGAYEIPLHARTLAETGRYGAVLGTAFVV(N/D)GGIY(R/D)HEFVASAVI(D/N)GMMNVQL(S/D/N)TGVPVLSAVLTPH(R/E/N)Y(R/D/E)(D/K)S(D/K)A(H/D)TLLFLALFAVKGMEAARACVEILAAREKIAA	
T32-28A SEQ ID NO: 41	二聚体	GEVPIGDPKELNGMEIAAVYLQPIEMEPRGIDLAASLADIHLEADIHALKNNPNGFPEGFWMPYLTIAYALANADTGAIKTGTLMPMVADDGPHYGANIAMEKDKKGGFGVGTYALTFLISNPEKQGFGRHVDEETGVGKWFEPFVVTYFFKYTGTPK	
T32-28B SEQ ID NO: 42	三聚体	SQAIGILELTSIAKGMELGDAMLKSANVDLLVSKTISPGKFLLMLGGDIGAIQQAIETGTSQAGEMLVDSLVLANIHPSVLPAISGLNSVDKRQAVGIVETWSVAACISAADLAVKGSNVTLVRVHMAFGIGGKCYMVVAGDVLDVAAAVATASLAAGAKGLLVYASIIPRPHEAMWRQMVEG	
T33-09A SEQ ID NO: 43	三聚体	EEVVLITVPSALVAVKIAHALVEERLAACVNIVPGLTSIYRWQGSVVSDHELLLLVKTTTHAFPKLKERVKALHPYTVPEIVALPIAEGNREYLDWLRENTG	
T33-09B SEQ ID NO: 44	三聚体	VRGIRGAITVEEDTPAAILAATIELLLKMLEANGIQSYEELAAVIFTVTEDLTSAFPAEAARLIGMHRVPLLSAREVPVPGSLPRVIRVLALWNTDTPQDRVRHVYLNEAVRLRPDLESAQ	
T33-15A SEQ ID NO: 45	三聚体	SKAKIGIVTVSDRASAGITADISGKAIILALNLYLTSEWEPIYQVIPDEQDVIETTLIKMADEQDCCLIVTTGGTGPAKRDVTPEATEAVCDRMMPGFGELMRAESLKEVPTAILSRQTAGLRGDSLIVNLPGDPASISDCLLAVFPAIPYCIDLMEGPYLECNEAMIKPFRPKAK	
T33-15B SEQ ID NO: 46	三聚体	VRGIRGAITVNSDTPTSIIIATILLLEKMLEANGIQSYEELAAVIFTVTEDLTSAFPAEAARQIGMHRVPLLSAREVPVPGSLPRVIRVLALWNTDTPQDRVRHVYLSEAVRLRPDLESAQ	
T33-21A SEQ ID NO: 47	三聚体	RITTKVGDKGSTRLFGGEEVWKDSPIIEANGTLDELTSFIGEAKHYVDEEMKGILEEIQNDIYKIMGEIGSKGKIEGISEERIAWLLKLILRYMEMVNLKSFVLPGGTLESAKLDVCRTIARRALRKVLTVTREFGIGAEAAAYLLALSDLLFLLARVIEIEKNKLKEVRS	
T33-21B SEQ ID NO: 48	三聚体	PHLVIEATANLRLETSPGELLEQANKALFASGQFGEADIKSRFVTLEAYRQGTAAVERAYLHACLSILDGRDIATRTLLGASLCAVLAEAVAGGGEEGVQVSVEVREMERLSYAKRVVARQR	

[0131]

名称	组分多聚体	氨基酸序列	鉴定的界面残基
T33-28A SEQ ID NO: 49	三聚体	ESVNTSFLSPSLVTIRDFDNGQFAVLRIGRTGFPADKGDIDLCLDKMIGVRAAQIFLGDDTEDGFKGPHIRIRCVDIDDKHTYNAMVYVDLIVGTGASEVERETAEEEAKLALRVALQVDIADEHSCVTQFEMKLREELLSSDSFHPDKDEYYKDFL	
T33-28B SEQ ID NO: 50	三聚体	PVIQTFVSTPLDHHKRLLLAIIYRIVTRVVLGKPEDLVMMTFHDSTPMHFFGSTDPVACVRVEALGGYGPSEPEKVTSIVTAAITAVCGIVADRIFVLYFSPLHCGWNGTNF	
T33-31A SEQ ID NO: 51	三聚体	EEVVLITVPSALVAVKIAHALVEERLAACVNIVPGLTSIYREEGSVVSDHELLLLVKTTTDAFPKLKERVKELHPYEVPEIVALPIAEGNREYLDWLRENTG	
I53-50A ΔCys SEQ ID NO: 53	三聚体	EELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQ**A**RKAVESGAEFIVSPHLDEEISQF**A**KEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNV**A**EWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRG**A**TE	
T33_dn2A SEQ ID NO: 135		NLAEKMYKAGNAMYRKGQYTIAIIAYTLALLKDPNNAEAWYNLGNAAYKKGEYDEAIEAYQKALELDPNNAEAWYNLGNAYYKQGDYDEAIEYYKKALRLDPRNVDAIENLIEAEEKQG	
T33_dn2B SEQ ID NO: 136		EEAELAYLLGELAYKLGEYRIAIRAYRIALKRDPNNAEAWYNLGNAYYKQGDYREAIRYYLRALKLDPENAEAWYNLGNALYKQGKYDLAIIAYQAALEEDPNNAEAKQNLGNAKQKQG	
T33_dn5A SEQ ID NO: 137		NSAEAMYKMGNAAYKQGDYILAIIAYLLALEKDPNNAEAWYNLGNAAYKQGDYDEAIEYYQKALELDPNNAEAWYNLGNAYYKQGDYDEAIEYYEKALELDPNNAEALKNLLEAIAEQD	
T33_dn5A SEQ ID NO: 138		TDPLAVILYIAILKAEKSIARAKAAEALGKIGDERAVEPLIKALKDEDALVRAAAADALGQIGDERAVEPLIKALKDEEGLVRASAAIALGQIGDERAVQPLIKALTDERDLVRVAAAVALGRIGDEKAVRPLIIVLKDEEGEVREAAAIALGSIGGERVRAAMEKLAERGTGFARKVAVNYLETHK	
T33_dn10A SEQ ID NO: 139		EEAELAYLLGELAYKLGEYRIAIRAYRIALKRDPNNAEAWYNLGNAYYKQGDYDEAIEYYQKALELDPNNAEAWYNLGNAYYKQGDYDEAIEYYEKALELDPENLEALQNLLNAMDKQG	

[0132]



名称	组分多聚体	氨基酸序列	鉴定的界面残基
T33_dn10B SEQ ID NO: 140		IEEVVAEMIDILAESSKKSIEELARAADNKTTEKAVAEAIEEIARLATAAIQLIEALAKNLASEEFMARAISAIAELAKKAIEAIYRLADNHTTDTFMARAIAAIANLAVTAILAIAALASNHTTEEFMARAISAIAELAKKAIEAIYRLADNHTTDKFMAAAIEAIALLATLAILAIALLASNHTTEKFMARAIMAIAILAAKAIEAIYRLADNHTSPTYIEKAIEAIEKIARKAIKAIEMLAKNITTEEYKEKAKKIIDIIRKLAKMAIKKLEDNRT	
I53_dn5A SEQ ID NO: 141		KYDGSKLRIGILHARWNAEIILALVLGALKRLQEFGVKRENIIIETVPGSFELPYGSKLFVEKQKRLGKPLDAIIPIGVLIKGSTMHFEYICDSTTHQLMKLNFELGIPVIFGVLTCLTDEQAEARAGLIEGKMHNHGEDWGAAAVEMATKFN	
I53_dn5B SEQ ID NO: 142		EEAELAYLLGELAYKLGEYRIAIRAYRIALKRDPNNAEAWYNLGNAYYKQGRYREAIEYYQKALELDPNNAEAWYNLGNAYYERGEYEEAIEYYRKALRLDPNNADAMQNLLNAKMREE	

[0133] 表1提供了本公开的实施例的第一多肽和第二多肽的氨基酸序列。在每种情况下，序列对一起形成具有二十面体对称的I53多聚体。表1中的右列鉴定了每个说明性多肽中的残基数量，所述说明性多肽被鉴定为存在于所得组装的病毒样颗粒的界面处(即：“鉴定的界面残基”)。可以看出，SEQ ID NO:1-34的说明性多肽的界面残基数量范围为4至13。在各种实施例中，第一多肽和第二多肽包括氨基酸序列，所述氨基酸序列与选自由以下组成的组的多肽的氨基酸序列在其长度上至少75％、80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％或99％相同，并且与至少1个、2个、3个、4个、5个、6个、7个、8个、9个、10个、11个、12个或13个鉴定的界面位置相同(取决于给定多肽的界面残基数量)：SEQ ID NO:1-34。SEQ ID NO:35-51表示来自本公开的实施例的第一多肽和第二多肽的其它氨基酸序列。在其它实施例中，第一多肽和/或第二多肽包括氨基酸序列，所述氨基酸与选自由以下组成的组的多肽的氨基酸序列在其长度上至少75％、80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％或99％相同的氨基酸序列，并且与鉴定的界面位置至少20％、25％、33％、40％、50％、60％、70％、75％、80％、90％或100％相同：SEQ ID NO:1-51。

[0134] 与一般蛋白质的情况一样，预期多肽能够容忍设计的序列中的一些变化，而不会破坏随后组装成病毒样颗粒的：特别是当此类变化包括保守氨基酸取代时。如本文所使用的，“保守氨基酸取代”意指：疏水性氨基酸(Ala、Cys、Gly、Pro、Met、Val、Ile、Leu)只能被其它疏水性氨基酸取代；具有庞大侧链的疏水性氨基酸(Phe、Tyr、Trp)只能被具有庞大侧链的其它疏水性氨基酸取代；带正电荷侧链的氨基酸(Arg、His、Lys)只能被带正电荷侧链的其它氨基酸取代；带负电荷侧链的氨基酸(Asp、Glu)只能被带负电荷侧链的其它氨基酸取代；并且具有极性不带电侧链(Ser、Thr、Asn、Gln)的氨基酸只能被具有极性不带电侧链的其它氨基酸取代。

[0135] 在本发明的VLP的各种实施例中，第一多肽和第二多肽，或反之亦然，包括具有选自以下对或其修饰的版本的氨基酸序列的多肽(即本发明的多肽所公开的允许的修饰：包括氨基酸序列的分离的多肽，所述氨基酸序列在其长度上与SEQ ID NO所示的氨基酸序列

至少有75％、至少80％、至少85％、至少90％、至少95％、至少99％、至少100％相同，和/或至少在一个鉴定的界面位置处相同)：

[0136] SEQ ID NO:1和SEQ ID NO:2(I53-34A和I53-34B)；

[0137] SEQ ID NO:3和SEQ ID NO:4(I53-40A和I53-40B)；

[0138] SEQ ID NO:3和SEQ ID NO:24(I53-40A和I53-40B.1)；

[0139] SEQ ID NO:23和SEQ ID NO:4(I53-40A.1和I53-40B)；

[0140] SEQ ID NO:35和SEQ ID NO:36(I53-40A属和I53-40B属)；

[0141] SEQ ID NO:5和SEQ ID NO:6(I53-47A和I53-47B)；

[0142] SEQ ID NO:5和SEQ ID NO:27(I53-47A和I53-47B.1)；

[0143] SEQ ID NO:5和SEQ ID NO:28(I53-47A和I53-47B.1NegT2)；

[0144] SEQ ID NO:25和SEQ ID NO:6(I53-47A.1和I53-47B)；

[0145] SEQ ID NO:25和SEQ ID NO:27(I53-47A.1和I53-47B.1)；

[0146] SEQ ID NO:25和SEQ ID NO:28(I53-47A.1和I53-47B.1NegT2)；

[0147] SEQ ID NO:26和SEQ ID NO:6(I53-47A.1NegT2和I53-47B)；

[0148] SEQ ID NO:26和SEQ ID NO:27(I53-47A.1NegT2和I53-47B.1)；

[0149] SEQ ID NO:26和SEQ ID NO:28(I53-47A.1NegT2和I53-47B.1NegT2)；

[0150] SEQ ID NO:37和SEQ ID NO:38(I53-47A属和I53-47B属)；

[0151] SEQ ID NO:7和SEQ ID NO:8(I53-50A和I53-50B)；

[0152] SEQ ID NO:7和SEQ ID NO:32(I53-50A和I53-50B.1)；

[0153] SEQ ID NO:7和SEQ ID NO:33(I53-50A和I53-50B.1NegT2)；

[0154] SEQ ID NO:7和SEQ ID NO:34(I53-50A和I53-50B.4PosT1)；

[0155] SEQ ID NO:29和SEQ ID NO:8(I53-50A.1和I53-50B)；

[0156] SEQ ID NO:29和SEQ ID NO:32(I53-50A.1和I53-50B.1)；

[0157] SEQ ID NO:29和SEQ ID NO:33(I53-50A.1和I53-50B.1NegT2)；

[0158] SEQ ID NO:29和SEQ ID NO:34(I53-50A.1和I53-50B.4PosT1)；

[0159] SEQ ID NO:30和SEQ ID NO:8(I53-50A.1NegT2和I53-50B)；

[0160] SEQ ID NO:30和SEQ ID NO:32(I53-50A.1NegT2和I53-50B.1)；

[0161] SEQ ID NO:30和SEQ ID NO:33(I53-50A.1NegT2和I53-50B.1NegT2)；

[0162] SEQ ID NO:30和SEQ ID NO:34(I53-50A.1NegT2和I53-50B.4PosT1)；

[0163] SEQ ID NO:31和SEQ ID NO:8(I53-50A.1PosT1和I53-50B)；

[0164] SEQ ID NO:31和SEQ ID NO:32(I53-50A.1PosT1和I53-50B.1)；

[0165] SEQ ID NO:31和SEQ ID NO:33(I53-50A.1PosT1和I53-50B.1NegT2)；

[0166] SEQ ID NO:31和SEQ ID NO:34(I53-50A.1PosT1和I53-50B.4PosT1)；

[0167] SEQ ID NO:39和SEQ ID NO:40(I53-50A属和I53-50B属)；

[0168] SEQ ID NO:9和SEQ ID NO:10(I53-51A和I53-51B)；

[0169] SEQ ID NO:11和SEQ ID NO:12(I52-03A和I52-03B)；

[0170] SEQ ID NO:13和SEQ ID NO:14(I52-32A和I52-32B)；

[0171] SEQ ID NO:15和SEQ ID NO:16(I52-33A和I52-33B)

[0172] SEQ ID NO:17和SEQ ID NO:18(I32-06A和I32-06B)；

[0173] SEQ ID NO:19和SEQ ID NO:20(I32-19A和I32-19B);

[0174] SEQ ID NO:21和SEQ ID NO:22(I32-28A和I32-28B);

[0175] SEQ ID NO:23和SEQ ID NO:24(I53-40A.1和I53-40B.1);

[0176] SEQ ID NO:41和SEQ ID NO:42(T32-28A和T32-28B);

[0177] SEQ ID NO:43和SEQ ID NO:44(T33-09A和T33-09B);

[0178] SEQ ID NO:45和SEQ ID NO:46(T33-15A和T33-15B);

[0179] SEQ ID NO:47和SEQ ID NO:48(T33-21A和T33-21B);

[0180] SEQ ID NO:49和SEQ ID NO:50(T33-28A和T32-28B);以及

[0181] SEQ ID NO:51和SEQ ID NO:44(T33-31A和T33-09B(也称为T33-31B))

[0182] 在一些实施例中,所述一种或多种hMPV F蛋白或其抗原片段表达为具有第一多聚化结构域的融合蛋白。在一些实施例中,第一多聚化结构域和hMPV F蛋白胞外结构域通过接头序列连接。在一些实施例中,所述接头序列包括折叠子,其中折叠子序列是EKAAKAEEAARK(SEQ ID NO:125)。

[0183] 在本公开的基于蛋白质的VLP中有用的设计的蛋白质复合物的非限制性实例包含以下中所公开的那些:美国专利第9,630,994号;国际专利公开第WO 2018187325A1号;美国专利公开第2018/0137234A1号;美国专利公开第2019/0155988A2号,所述专利中的每个专利均以其整体并入本文。

[0184] 在本公开的VLP的各种实施例中,多聚化结构域是具有选自以下对或其修饰的版本的氨基酸序列的多肽(即本发明的多肽所公开的允许的修饰:包括氨基酸序列的分离的多肽,所述氨基酸序列在其长度上与SEQ ID NO所示的氨基酸序列至少有75%、至少80%、至少85%、至少90%、至少95%、至少99%、至少100%相同,和/或至少在一个鉴定的界面位置处相同):

[0185] SEQ ID NO:135和SEQ ID NO:136(T33_dn2A和T33_dn2B);

[0186] SEQ ID NO:137和SEQ ID NO:138(T33_dn5A和T33_dn5B);

[0187] SEQ ID NO:139和SEQ ID NO:140(T33_dn10A和T33_dn10B);或

[0188] SEQ ID NO:141和SEQ ID NO:142(I53_dn5A和I53_dn5B)。

[0189] 抗原蛋白

[0190] 本公开提供了用于人或动物(特别是宠物、农业动物和与疾病传播相关的任何动物)中的hMPV的基于蛋白质的VLP疫苗。本公开涉及将hMPV F蛋白的抗原片段中的任何抗原片段——例如胞外结构域或其抗原片段——并入VLP疫苗中。指导尤其可从对感染或疫苗接种的免疫应答研究中获得,如结合或中和抗体的分离、F蛋白序列的遗传分析、抗原蛋白和抗体的结构研究,以及最特别的亚单位疫苗的临床和兽医经验。hMPV的亚单位疫苗可以通过采用上文提供的显示方式,适于与本公开的VLP一起使用。本公开涉及hMPV F的胞外结构域,但应理解可以包含跨膜结构域的各部分。

[0191] 术语“抗原片段”是指在体内对蛋白质产生免疫应答(体液或T细胞应答)的蛋白质的任何片段。抗原片段可以是线性表位、不连续表位或构象表位(例如,折叠的结构域)。抗原片段可保存全长蛋白的二级、三级和/或四级结构。在一些实施例中,抗原片段包括中和表位。在此类情况下,VLP可以生成中和抗体应答。抗原片段可以通过计算来设计,如通过预测二级结构并合理地去除N末端或C末端非结构化区域或内部环或整个结构元件(α螺旋和/

或β片层)。图2提供了说明性二级结构图。在一些实施例中,胞外结构域包括一些或全部N末端信号肽的截短或缺失(例如,MSWKVVIIFSLLITPQHGL(SEQ ID NO:133)或MSWKVMIIISLLITPQHGL(SEQ ID NO:134)。

[0192] 在一些实施例中,hMPV F蛋白胞外结构域是C末端截短。在一些实施例中,hMPV F蛋白胞外结构域序列在天然序列的残基470、471、472、473、474、475、476、477、478、479、480、481、482、483、484、485、486、487、488、489或490处终止。

[0193] A菌株hMPV F蛋白(GenBank AY145297)的天然序列如下文所示,其中信号序列加下划线和斜体,并且跨膜和胞内部分加下划线(SEQ ID NO:56):

[0194]
1 *MSWKVVIIFS LLITPQHGL*K ESYLEESCST ITEGYLSVLR
41 TGWYTNVFTL EVGDVENLTC SDGPSLIKTE LDLTKSALRE
81 LKTVSADQLA REEQIENPRQ SRFVLGAIAL GVATAAAVTA
121 GVAIAKTIRL ESEVTAIKNA LKTTNEAVST LGNGVRVLAT
161 AVRELKDFVS KNLTRAINKN KCDIDDLKMA VSFSQFNRRF
201 LNVVRQFSDN AGITPAISLD LMTDAELARA VSNMPTSAGQ
241 IKLMLENRAM VRRKGFGILI GVYGSSVIYM VQLPIFGVID
281 TPCWIVKAAP SCSGKKGNYA CLLREDQGWY CQNAGSTVYY
321 PNEKDCETRG DHVFCDTAAG INVAEQSKEC NINISTTNYP
361 CKVSTGRHPI SMVALSPLGA LVACYKGVSC SIGSNRVGII
401 KQLNKGCSYI TNQDADTVTI DNTVYQLSKV EGEQHVIKGR
441 PVSSSFDPIK FPEDQFNVAL DQVFENIENS QALVDQSNRI
481 LSSAEKGNTG FIIVIILIAV LGSSMILVSI FIIIKKTKKP
521 TGAPPELSGV TNNGFIPHS (SEQ ID NO: 56)

[0195] 当蛋白质被表达时,天然信号序列在翻译后被切割。天然信号序列可以用另一个信号序列代替以表达胞外结构域,或者在一些实施例中不使用信号序列。因此,在一些实施例中,hMPV F蛋白胞外结构域是SEQ ID NO:57或其变体:

[0196]
1 K ESYLEESCST ITEGYLSVLR
41 TGWYTNVFTL EVGDVENLTC SDGPSLIKTE LDLTKSALRE
81 LKTVSADQLA REEQIENPRQ SRFVLGAIAL GVATAAAVTA
121 GVAIAKTIRL ESEVTAIKNA LKTTNEAVST LGNGVRVLAT
161 AVRELKDFVS KNLTRAINKN KCDIDDLKMA VSFSQFNRRF
201 LNVVRQFSDN AGITPAISLD LMTDAELARA VSNMPTSAGQ
241 IKLMLENRAM VRRKGFGILI GVYGSSVIYM VQLPIFGVID
281 TPCWIVKAAP SCSGKKGNYA CLLREDQGWY CQNAGSTVYY
321 PNEKDCETRG DHVFCDTAAG INVAEQSKEC NINISTTNYP
361 CKVSTGRHPI SMVALSPLGA LVACYKGVSC SIGSNRVGII
401 KQLNKGCSYI TNQDADTVTI DNTVYQLSKV EGEQHVIKGR
441 PVSSSFDPIK FPEDQFNVAL DQVFENIENS QALVDQSNRI
481 LSSAEKGNTG F
521 (SEQ ID NO: 57)

[0197] 在一些实施例中,hMPV F蛋白胞外结构域与SEQ ID NO:57或其抗原片段共享至少90%、95%、96%、97%、98%、99%或100%序列同一性。

[0198] 表2提供了另外的hMPV F蛋白序列。在一些实施例中,hMPV F蛋白胞外结构域与表2中的胞外结构域或其抗原片段共享至少90%、95%、96%、97%、98%、99%或100%序列同一性。

[0199] 可以使用各种信号序列，与天然胞外结构域序列配对或在不同的hMPV序列之间交换。因此，在一些实施例中，抗原包括与表2中的信号序列共享至少90％、95％、96％、97％、98％、99％或100％序列同一性的序列。

[0200] hMPV F蛋白可以包括一个或多个取代。

[0201] 说明性取代包含相对于SEQ ID NO:57的A185P、Q100R、S101R、T127C、N153C、V84C、A140C、A147C、A249C、N97G、P98G、R99G、Q100G、S101G、R102G、A63C、K188C、K450C、S470C、G106缺失、A113C、A120C、A339C、Q426C、T160F、Q100K、S101A、I177L、K450A、S470A、G294E、T365C、V463C、L219K、H368N和/或V231I。因此，在各种实施例中，hMPV F蛋白胞外结构域包括选自此列表的一个或多个取代。

[0202] 说明性取代包含相对于SEQ ID NO:57的V84C、A140C、A147C、N97G、P98G、Q100G、S101G、R102G、A63C、K188C、K450C、S470C、R99G、A113C、A120C、A339C、Q426C、T160F、Q100K、S101A、Q100R、S101R、G106缺失、S101R、A185P、I177L和G294E。因此，在各种实施例中，hMPV F蛋白胞外结构域包括选自此列表的一个或多个取代。

[0203] 说明性取代包含V84C、A140C、A147C、N97G、P98G、Q100G、S101G、R102G、A63C、K188C、K450C、S470C、R99G、A113C、A120C、A339C、Q426C、T160F、Q100K、S101A、Q100R、S101R、G106缺失、S101R、A185P、I177L和G294E。因此，在各种实施例中，hMPV F蛋白胞外结构域包括选自此列表的两个或更多个取代。

[0204] 说明性取代包含A185P、Q100R、S101R、T127C、N153C、T365C、V463C、L219K、V231I、G294E、N153C、N97G、P98G、R99G、Q100G、S101G和R102G。因此，在各种实施例中，hMPV F蛋白胞外结构域包括选自此列表的一个或多个取代。

[0205] 说明性取代包含A185P、Q100R、S101R、T127C、N153C、T365C、V463C、L219K、V231I、G294E、N153C、N97G、P98G、R99G、Q100G、S101G和R102G。因此，在各种实施例中，hMPV F蛋白胞外结构域包括选自此列表的两个或更多个取代。

[0206] 在一些实施例中，hMPV F蛋白胞外结构域包括取代Q100R和S101R。在一些实施例中，hMPV F蛋白胞外结构域包括取代A185P、Q100R和S101R。在一些实施例中，hMPV F蛋白胞外结构域包括取代A185P、T127C、N153C、Q100R和S101R。在一些实施例中，hMPV F蛋白胞外结构域包括取代V84C、A140C、A147C、A249C、N97G、P98G、R99G、Q100G、S101G和R102G。在一些实施例中，hMPV F蛋白胞外结构域包括取代A63C、A140C、A147C、K188C、K450C、S470C、N97G、P98G、R99G、Q100G、S101G和R102G。在一些实施例中，hMPV F蛋白胞外结构域包括取代和缺失A63C、A140C、A147C、K188C、G106缺失、N97G、P98G、R99G、Q100G、S101G和R102G。在一些实施例中，hMPV F蛋白胞外结构域包括取代A113C、A120C、A339C、Q426C、T160F、I177L、Q100K和S101A。在一些实施例中，hMPV F蛋白胞外结构域包括取代V84C、A140C、A147C、A249C、Q100R和S101R。在一些实施例中，hMPV F蛋白胞外结构域包括取代A63C、A140C、A147C、K188C、K450C、S470C、Q100R和S101R。在一些实施例中，hMPV F蛋白胞外结构域包括取代和缺失A63C、A140C、A147C、K188C、G106缺失、Q100R和S101R。在一些实施例中，hMPV F蛋白胞外结构域包括取代A113C、A120C、A339C、Q426C、T160F、I177L、Q100R和S101R。在一些实施例中，hMPV F蛋白胞外结构域包括取代A185P、A113C、A339C、Q100R和S101R。在一些实施例中，hMPV F蛋白胞外结构域包括取代A185P、T160F、I177L、Q100R和S101R。在一些实施例中，hMPV F蛋白胞外结构域包括取代A185P、A113C、A339C、T160F、I177L、Q100R和S101R。在一些

实施例中,hMPV F蛋白胞外结构域包括取代A63C、K188C、N97G、P98G、R99G、Q100G、S101G和R102G。在一些实施例中,hMPV F蛋白胞外结构域包括取代A63C、K188C、K450A、S470A、N97G、P98G、R99G、Q100G、S101G和R102G。在一些实施例中,hMPV F蛋白胞外结构域包括取代A63C、A140C、A147C、K188C、G294E、N97G、P98G、R99G、Q100G、S101G和R102G。在一些实施例中,hMPV F蛋白胞外结构域包括取代A63C、A140C、A147C、K188C、K450C、S470C、N97G、P98G、R99G、Q100G、S101G、R102G和G294E。在一些实施例中,hMPV F蛋白胞外结构域包括取代A63C、K188C、N97G、P98G、R99G、Q100G、S101G、R102G和G294E。在一些实施例中,hMPV F蛋白胞外结构域包括取代T127C、N153C、T365C、V463C、A185P、L219K、V231I、G294E、H368N、Q100R和S101R。在一些实施例中,hMPV F蛋白胞外结构域包括取代A63C、A140C、A147C、K188C、K450C、S470C、N97G、P98G、R99G、Q100G、S101G和R102G。在一些实施例中,hMPV F蛋白胞外结构域包括取代V84C、A140C、A147C、A249C、N97G、P98G、R99G、Q100G、S101G和R102G。在一些实施例中,hMPV F蛋白胞外结构域包括取代T127C、N153C、T365C、V463C、A185P、L219K、V231I、G294E、N97G、P98G、R99G、Q100G、S101G、H368N和R102G。

[0207] 错误!未找到参考来源提供了另外的说明性氨基酸取代。在各种实施例中,胞外结构域包括一个或多个选自错误!未找到参考来源列出的取代和替代取代的取代。在一些实施例中,取代对VLP具有预期效果,应理解并非在具有所述取代的VLP的每个实施例中都达到预期效果。在一些实施例中,预期效果是产生细胞系中的表达增加(Mas等人《公共科学图书馆·病原学(PLoS Pathog.)》12:e1005859(2016))。在一些实施例中,预期效果使hMPV F蛋白胞外结构域的融合后或融合前形式稳定(Battles等人《自然通讯(Nat Commun.)》8:1528(2017))。在一些实施例中,预期效果是结合针对hMPV F蛋白的中和抗体。抗原可以进一步包括在N末端处的亮氨酸,如SEQ ID NO:146-178所示的。

[0208] 表2.说明性hMPV蛋白F胞外结构域抗原变体

[0209]

SEQ ID NO:	胞外结构域	hMPV 抗原突变	C 末端 F 蛋白终止残基
58	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQALVDQSNRIL	A185P、Q100R、S101R	481
59	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQA	A185P、Q100R、S101R	472
60	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQALVDQSNRILSSAEKGNT	A185P、Q100R、S101R	489

[0210]

SEQ ID NO:	胞外结构域	hMPV 抗原突变	C 末端 F 蛋白终止残基
61	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNGVRVLATAVRELKDFVSKNLTRAINKNKCDIADLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQA	Q100R、S101R	472
62	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKCIRLESEVTAIKNALKKTNEAVSTLGCGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRNPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQA	A185P、T127C、N153C、Q100R、S101R	472
63	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTCSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGCLKTTNECVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRCMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFESIENSQA	V84C、A140C、A147C、A249C、N97G、P98G、R99G、Q100G、S101G、R102G	472
64	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTCSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGCLKTTNECVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLKMAVSFSQFNRRFLNVVRQFSDNAGITPAI	V84C、A140C、A147C、A249C、N97G、P98G、	488

[0211]

SEQ ID NO:	胞外结构域	hMPV 抗原突变	C 末端 F 蛋白终止残基
	SLDLMTDAELARAVSYMPTSAGQIKLMLENRCMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFESIENSQALVDQSNKILNSAESAI	R99G、Q100G、S101G、R102G	
65	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDCPSLIKTELDLTKSALRELKTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGCLKTTNECVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPICFPEDQFNVALDQVFESIENCQA	A63C、A140C、A147C、K188C、K450C、S470C、N97G、P98G、R99G、Q100G、S101G、R102G	472
66	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDCPSLIKTELDLTKSALRELKTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGCLKTTNECVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPICFPEDQFNVALDQVFESIENCQALVDQSNKILNSAESAI	A63C、A140C、A147C、K188C、K450C、S470C、N97G、P98G、R99G、Q100G、S101G、R102G	488
67	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCSDCPSLIKTELDLTKSALRELKTVSADQLAREEQIEGGGGGGFVLAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNCLKTTNECVSTLGNGVRVLATAVRELKDFVSKNLTSAINKNKCDIDDLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKEC	A63C、A140C、A147C、K188C、缺失的G106、N97G、P98G、R99G、Q100G、S101G、R102G	472

[0212]

SEQ ID NO:	胞外结构域	hMPV 抗原突变	C 末端 F 蛋白终止残基
	NINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFENIENSQA		
68	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCSDCPSLIKTELDLTKSALRELKTVSADQLAREEQIEGGGGGGFVLAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNCLKTTNECVSTLGNGVRVLATAVRELKDFVSKNLTSAINKNKCDIDDLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFENIENSQALVDQSNRILSSAESAI	A63C、A140C、A147C、K188C、缺失的G106、N97G、P98G、R99G、Q100G、S101G、R102G	488
69	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPRKARFVLGAIALGVCTAAAVTCGIAIAKTIRLESEVNAIKGALKTTNEAVSTLGNGVRVLAFAVRELKEFVSKNLTSALNKNKCDIADLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTACGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYCLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFESIENSQA	A113C、A120C、A339C、Q426C、T160F、I17L、Q100K、S101A	472
70	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPRKARFVLGAIALGVCTAAAVTCGIAIAKTIRLESEVNAIKGALKTTNEAVSTLGNGVRVLAFAVRELKEFVSKNLTSALNKNKCDIADLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTACGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYCLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFESIENSQALVDQSNKILNSAESAI	A113C、A120C、A339C、Q426C、T160F、I177L、Q100K、S101A	488

[0213]

SEQ ID NO:	胞外结构域	hMPV 抗原突变	C 末端 F 蛋白终止残基
71	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTCSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGCLKTTNECVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRCMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFESIENSQA	V84C、 A140C、 A147C、 A249C、 Q100R、S101R	472
72	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDCPSLIKTELDLTKSALRELKTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGCLKTTNECVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPICFPEDQFNVALDQVFESIENCQA	A63C、 A140C、 A147C、 K188C、 K450C、 S470C、 Q100R、S101R	472
73	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCSDCPSLIKTELDLTKSALRELKTVSADQLAREEQIENPRRRRFVLAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNCLKTTNECVSTLGNGVRVLATAVRELKDFVSKNLTSAINKNKCDIDDLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFENIENSQA	A63C、 A140C、 A147C、 K188C、缺失的 G106、Q100R、 S101R	472
74	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPRRRRFVLGAIALGVCTAAAVTCGIAIAKTIRLESEVNAIKGALKTTNEAVSTLGNGVRVLAFAVRELKEFVSKNLTSALNKNKCDI	A113C、 A120C、 A339C、 Q426C、	472

[0214]

SEQ ID NO:	胞外结构域	hMPV 抗原突变	C 末端 F 蛋白终止残基
	ADLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTACGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYCLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFESIENSQA	T160F、I177L、Q100R、S101R	
75	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVCTAAAVTAGVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTACGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQA	A185P、 A113C、 A339C、 Q100R、S101R	472
76	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNGVRVLAFAVRELKDFVSKNLTRALNKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQA	A185P、 T160F、I177L、 Q100R、S101R	472
77	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVCTAAAVTAGVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNGVRVLAFAVRELKDFVSKNLTRALNKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTACGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALV	A185P、 A113C、 A339C、 T160F、I177L、 Q100R、S101R	472

[0215]

SEQ ID NO:	胞外结构域	hMPV 抗原突变	C 末端 F 蛋白终止残基
	ACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQA		
78	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDCPSLIKTELDLTKSALRELKTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGALKTTNEAVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFESIENSQA	A63C、K188C、N97G、P98G、R99G、Q100G、S101G、R102G	472
79	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDCPSLIKTELDLTKSALRELKTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGALKTTNEAVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIAFPEDQFNVALDQVFESIENAQA	A63C、K188C、K450A、S470A、N97G、P98G、R99G、Q100G、S101G、R102G	472
80	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCSDCPSLIKTELDLTKSALRELKTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNCLKTTNECVSTLGNGVRVLATAVRELKDFVSKNLTSAINKNKCDIDDLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFENIENSQA	A63C、A140C、A147C、K188C、G294E、N97G、P98G、R99G、Q100G、S101G、R102G	472
81	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADCPSLIKTELDLTKSALRELRTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAV	A63C、A140C、	472

[0216]

SEQ ID NO:	胞外结构域	hMPV 抗原突变	C 末端 F 蛋白终止残基
	TAGVAIAKTIRLESEVTAIKNCLKKTNECVSTLGNGVRVLATAVRELKDFVSKNLTRAINKNKCDIADLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVCFPEDQFNVALDQVFESIENCQA	A147C、K188C、K450C、S470C、N97G、P98G、R99G、Q100G、S101G、R102G、G294E	
82	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADCPSLIKTELDLTKSALRELRTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNGVRVLATAVRELKDFVSKNLTRAINKNKCDIADLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQA	A63C、K188C、N97G、P98G、R99G、Q100G、S101G、R102G、G294E	472
83	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKCIRLESEVTAIKNALKKTNEAVSTLGCGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISKDLMTDAELARAISNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSCGRNPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQCFESIENSQA	T127C、N153C、T365C、V463C、A185P、L219K、V231I、G294E、H368N、Q100R、S101R	472
84	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKCIRLESEVTAIKNALKKTNEAVSTLGCGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISKDLMTDAELARAISNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYCQNAGS	T127C、N153C、T365C、V463C、A185P、L219K、V231I、G294E、	490

[0217]

SEQ ID NO:	胞外结构域	hMPV 抗原突变	C 末端 F 蛋白终止残基
	TVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSCGRNPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQCFESIENSQALVDQSNRILSSAEKGNTG	H368N、Q100R、S101R	
85	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDCPSLIKTELDLTKSALRELKTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGCLKTTNECVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPICFPEDQFNVALDQVFESIENCQA	A63C、A140C、A147C、K188C、K450C、S470C、N97G、P98G、R99G、Q100G、S101G、R102G	472
86	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKCIRLESEVTAIKNALKKTNEAVSTLGCGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISKDLMTDAELARAISNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSCGRNPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQCFESIENSQA	T127C、N153C、T365C、V463C、A185P、L219K、V231I、G294E、Q100R、S101R	472
87	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKCIRLESEVTAIKNALKKTNEAVSTLGCGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISKDLMTDAELARAISNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSCGRNPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQCFESIENSQALVDQSNRIL	T127C、N153C、T365C、V463C、A185P、L219K、V231I、G294E、Q100R、S101R	490

[0218]

SEQ ID NO:	胞外结构域	hMPV 抗原突变	C 末端 F 蛋白终止残基
	SSAEKGNTG		
88	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEV GDVENLTCTDGPSLIKTELDLTKSALRELKTCS ADQLAREEQIEGGGGGGFVLGAIALGVATAAAV TAGIAIAKTIRLESEVNAIKGCLKTTNECVSTL GNGVRVLATAVRELKEFVSKNLTSAINKNKCDI ADLKMAVSFSQFNRRFLNVVRQFSDNAGITPAI SLDLMTDAELARAVSYMPTSAGQIKLMLENRCM VRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPC WIIKAAPSCSEKDGNYACLLREDQGWYCKNAGS TVYYPNDKDCETRGDHVFCDTAAGINVAEQSRE CNINISTTNYPCKVSTGRHPISMVALSPLGALV ACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDA DTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDP IKFPEDQFNVALDQVFESIENSQA	V84C、A140C、A147C、A249C、N97G、P98G、R99G、Q100G、S101G、R102G	472
89	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEV GDVENLTCADGPSLIKTELDLTKSALRELRTVS ADQLAREEQIEGGGGGGFVLGAIALGVATAAAV TAGVAIAKCIRLESEVTAIKNALKKTNEAVSTL GCGVRVLATAVRELKDFVSKNLTRAINKNKCDI PDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAI SKDLMTDAELARAISNMPTSAGQIKLMLENRAM VRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPC WIVKAAPSCSEKKGNYACLLREDQGWYCQNAGS TVYYPNEKDCETRGDHVFCDTAAGINVAEQSKE CNINISTTNYPCKVSCGRNPISMVALSPLGALV ACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDA DTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDP VKFPEDQFNVALDQCFESIENSQA	T127C、N153C、T365C、V463C、A185P、L219K、V231I、G294E、N97G、P98G、R99G、Q100G、S101G、H368N、R102G	472
90	KESYLEESCSTITEGYLSVLRTGWYTNVFTLEV GDVENLTCADGPSLIKTELDLTKSALRELRTVS ADQLAREEQIEGGGGGGFVLGAIALGVATAAAV TAGVAIAKCIRLESEVTAIKNALKKTNEAVSTL GCGVRVLATAVRELKDFVSKNLTRAINKNKCDI PDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAI SKDLMTDAELARAISNMPTSAGQIKLMLENRAM VRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPC WIVKAAPSCSEKKGNYACLLREDQGWYCQNAGS TVYYPNEKDCETRGDHVFCDTAAGINVAEQSKE CNINISTTNYPCKVSCGRNPISMVALSPLGALV ACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDA DTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDP VKFPEDQFNVALDQCFESIENSQALVDQSNRIL SSAEKGNTG	T127C、N153C、T365C、V463C、A185P、L219K、V231I、G294E、N97G、P98G、R99G、Q100G、S101G、H368N、R102G	490

[0219] 因此,在一些实施例中,hMPV F蛋白胞外结构域与SEQ ID NO:58-90或其抗原片段共享至少90％、95％、96％、97％、98％、99％或100％序列同一性。

[0220] 在一些实施例中,hMPV F蛋白包括一个或多个弗林蛋白酶切割位点,任选地Arg-X-X-Arg基序(SEQ ID NO:52)的一个或多个拷贝,如天然序列RQSR(SEQ ID NO:54)。在弗林蛋白酶切割位点存在于hMPV胞外结构域中的情况下,在一些情况下,可以通过从转染质粒或从宿主细胞中稳定整合的多核苷酸序列共表达弗林蛋白酶或其功能变体来增加表达产

量。在一些实施例中,hMPV F蛋白的弗林蛋白酶切割位点通过将RQSR(SEQ ID NO:54)基序突变为RRRR(SEQ ID NO:55)来修饰,或者通过取代Gly接头或通过进行其它氨基酸取代来去除。

[0221] hMPV中和活性由识别融合前和融合后F蛋白构象的抗体介导,并且体内免疫应答中产生的抗体可以选择性地识别融合前特异性或融合后特异性位点,或者可以识别F蛋白的融合前和融合后形式。Battles等人《自然通讯》8:1528(2017)。DS7、MPV196、MPV201和MPV314中和抗体与F蛋白的融合前和融合后形式中可访问的抗原位点结合,并且位于F蛋白的DI和DII头部结构域。Wen等人《自然结构与分子生物学(Nat Struct Mol Biol.)》19(4):461-463(2012);Bar-Peled等人《病毒学杂志》93:e00342-19(2019))。MPE8中和抗体与F蛋白上跨越DI、DII和DIII亚基的表位结合,形成依赖于融合前F构象的接触。Wen等人《自然微生物学(Nat Microbiol.)》2:16272(2017)。呼吸道合胞病毒(RSV)F蛋白共享若个抗原表位例如,以下中的位点III和位点IV表位:Huang等人《免疫学前沿(Front Immunol.)》10:2778(2019)。这些是针对hMPV F蛋白的中和抗体所描述的表位的实例而非详尽列表。

[0222] 中和表位通常是构象表位,因此对应于表位的肽不与抗体结合,因此不诱导中和滴度。中和抗体可以从对hMPV呈血清反应阳性的健康供体中分离,Battles等人,或者可以通过动物模型中的免疫产生,Gabriella等人《病毒学杂志》81(2):698-707(2007)。

[0223] 在一些实施例中,包括hMPV F蛋白胞外结构域的本公开的VLP可以与针对hMPV F蛋白的中和抗体(也称为抗hMPV F蛋白抗体)结合。在一些实施例中,本文所描述的VLP可以与抗hMPV F蛋白抗体结合,已知所述抗hMPV F蛋白抗体选择性地与hMPV F蛋白的融合前形式结合。选择性地与hMPV F蛋白的融合前形式结合的抗体的实例包含但不限于MF10和MPE8抗体。在一些实施例中,本文所描述的VLP与抗hMPV F蛋白抗体结合,已知所述抗hMPV F蛋白抗体选择性与hMPV F蛋白的融合后形式结合。选择性地与hMPV F蛋白的融合后形式结合的抗体实例包含但不限于MF1、MF2、MF3、MF11、MF17、MF18和MF19抗体。在一些实施例中,本文所描述的VLP可以与抗体结合,所述抗体与hMPV F蛋白的融合前和融合后形式结合。与hMPV F蛋白的融合前和融合后形式结合的抗体实例包含但不限于MF9、MF12、MF14、MF15、MF16和MF20抗体。在一些实施例中,本文所描述的VLP与一种或多种抗hMPV F蛋白抗体结合。在一些实施例中,本文所描述的VLP与两种或更多种抗hMPV F蛋白抗体结合。

[0224] 多聚化结构域和接头

[0225] 在一些实施例中,VLP包括抗原的三聚体组装,其包括包含第一多聚化结构域的第一多肽和包含第二多聚化结构域的第一多肽。第一多聚化结构域包括蛋白质-蛋白质界面,所述蛋白质-蛋白质界面诱导第一多肽的三个拷贝自缔合以形成三聚体构建块。在具有两个或更多个组分的VLP中,第一多聚化结构域的每个拷贝进一步包括与第二多聚化结构域上的互补表面暴露界面相互作用的表面暴露界面。类似地,第二多聚化结构域适于与(第一组分的第一多肽的)第一多聚化结构域多聚化。如King等人(《自然》510,103-108,2014);Bale等人(《科学》353,389-394,2016)以及专利公开WO 2014124301A1和US20160122392 A1所描述的,第一多聚化结构域与第二多聚化结构域之间的互补蛋白质-蛋白质界面驱动三聚体组装结构域和第二组装结构域的多个拷贝组装成靶VLP。在一些实施例中,VLP的三聚体组装结构域的每个拷贝携带与其连接的抗原蛋白或其抗原片段(例如,作为基因融合);这些VLP以全化合价显示蛋白质。在其它实施例中,本公开的VLP包括携带抗原蛋白或其抗

原片段(例如,作为基因融合)的第一多聚化结构域以及一个或多个不携带抗原蛋白的第一多聚化结构域的一个或多个拷贝;这些VLP以部分化合价显示G蛋白。第一多聚化结构域可以是形成三聚体并与第二多聚化结构域相互作用以驱动组装成靶VLP的任何多肽序列。在一些实施例中,VLP包括选自US20130274441 A1、US2015/0356240 A1、US2016/0122392 A1、WO 2018/187325A1中公开的那些的第一多肽和第二多肽,所述专利中的每个通过引用整体并入本文。

[0226] 在本公开的VLP的一些实施例中,抗原蛋白和VLP的核心可以遗传融合,使得其都存在于也称为单链多肽的单一多肽中。蛋白质与核心之间的连接允许抗原蛋白或其抗原片段显示在VLP的外部上。因此,与核心的连接点应该在形成的病毒样颗粒的核心外部上。多种多肽序列可以用于连接蛋白质或其抗原片段和病毒样颗粒的核心。在一些情况下,接头包括所述多肽序列。可以使用任何合适的接头多肽。在一些实施例中,接头施加了抗原蛋白(例如,胞外结构域)或其抗原片段相对于核心的刚性相对定向。在一些实施例中,接头将抗原蛋白(例如,胞外结构域)或其抗原片段柔性地连接到核心。在一些实施例中,接头包含另外的三聚化结构域(例如,T4纤维蛋白的折叠结构域)以帮助使F蛋白的三聚体形式稳定—例如,GYIPEAPRDGQAYVRKDGEWVLLSTFL(SEQ ID NO:91)或其功能变体。

[0227] 在一些实施例中,接头可以包括任何合适长度的Gly-Ser接头(即,由甘氨酸和丝氨酸残基组成的接头)。在一些实施例中,Gly-Ser接头的长度可以是3个、4个、5个、6个、7个、8个、9个、10个、11个、12个、13个、14个、15个、16个、17个、18个、19个、20个或更多个氨基酸。在一些实施例中,Gly-Ser接头可以包括或由以下的氨基酸序列组成:GSGGSGSGSGGSGSG(SEQ ID NO:127)、GGSGGSGS(SEQ ID NO:128)或GSGGSGSG(SEQ ID NO:129)。在一些实施例中,接头包括序列GSGSGSG(SEQ ID NO:130)。在一些实施例中,接头包括序列GSGSGSGSGSGSGSG(SEQ ID NO:131)。在一些实施例中,接头包括序列GSGGSGSGSGGS(SEQ ID NO:126)。

[0228] 在本公开的VLP的一些实施例中,第一组分可以任选地含有聚-His标签HHHHHH(SEQ ID NO:143)。

[0229] 表3示出了本文所描述的VLP序列的说明性实例。所述序列包括多聚化结构域、hMPV F蛋白胞外结构域、接头、聚-His标签和信号序列。信号和聚-His标签序列带有下划线并且任选地包含在序列中。

[0230] 表3.本公开的VLP的说明性氨基酸序列

[0231]

构建体名称	SEQ ID NO:	氨基酸序列
hMPV001	92	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQALVDQSNRILGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV002	93	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALS

[0232]

		PLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV003	94	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQALVDQSNRILSSAEKGNTGGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV004	95	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNGVRVLATAVRELKDFVSKNLTRAINKNKCDIADLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV005	96	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKCIRLESEVTAIKNALKKTNEAVSTLGCGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRNPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTV

[0233]

		TSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV006	97	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTCSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGCLKTTNECVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRCMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFESIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV007	98	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTCSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGCLKTTNECVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRCMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFESIENSQALVDQSNKILNSAESAIGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV008	99	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDCPSLIKTELDLTKSALRELKTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGCLKTTNECVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPICFPEDQFNVALDQVFESIENCQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH

[0234]

hMPV009	100	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDCPSLIKTELDLTKSALRELKTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGCLKTTNECVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPICFPEDQFNVALDQVFESIENCQALVDQSNKILNSAESAIGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV010	101	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCSDCPSLIKTELDLTKSALRELKTVSADQLAREEQIEGGGGGGFVLAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNCLKTTNECVSTLGNGVRVLATAVRELKDFVSKNLTSAINKNKCDIDDLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFENIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV011	102	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCSDCPSLIKTELDLTKSALRELKTVSADQLAREEQIEGGGGGGFVLAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNCLKTTNECVSTLGNGVRVLATAVRELKDFVSKNLTSAINKNKCDIDDLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFENIENSQALVDQSNRILSSAESAIGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV012	103	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPRKARFVLGAIALGVCTAAAVTCGIAIAKTIRLESEVNAIKGALKTTNEAVSTLGNGVRVLAFAVRELKEFVSKNLTSALNKNKCDIADLK

[0235]

		MAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTACGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYCLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFESIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV013	104	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPRKARFVLGAIALGVCTAAAVTCGIAIAKTIRLESEVNAIKGALKTTNEAVSTLGNGVRVLAFAVRELKEFVSKNLTSALNKNKCDIADLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTACGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYCLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFESIENSQALVDQSNKILNSAESAIGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV014	105	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTCSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGCLKTTNECVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRCMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFESIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV015	106	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDCPSLIKTELDLTKSALRELKTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGCLKTTNECVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALS

[0236]

		PLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPICFPEDQFNVALDQVFESIENCQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV016	107	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCSDCPSLIKTELDLTKSALRELKTVSADQLAREEQIENPRRRRFVLAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNCLKTTNECVSTLGNGVRVLATAVRELKDFVSKNLTSAINKNKCDIDDLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFENIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV017	108	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPRRRRFVLGAIALGVCTAAAVTCGIAIAKTIRLESEVNAIKGALKTTNEAVSTLGNGVRVLAFAVRELKEFVSKNLTSALNKNKCDIADLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTACGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYCLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFESIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV018	109	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVCTAAAVTAGVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTACGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTV

[0237]

		TSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV019	110	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNGVRVLAFAVRELKDFVSKNLTRALNKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV020	111	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVCTAAAVTAGVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNGVRVLAFAVRELKDFVSKNLTRALNKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSGKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTACGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV021	112	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDCPSLIKTELDLTKSALRELKTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGALKTTNEAVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFESIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH

[0238]

hMPV022	113	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDCPSLIKTELDLTKSALRELKTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGALKTTNEAVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIAFPEDQFNVALDQVFESIENAQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV023	114	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCSDCPSLIKTELDLTKSALRELKTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNCLKTTNECVSTLGNGVRVLATAVRELKDFVSKNLTSAINKNKCDIDDLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFENIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV024	115	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADCPSLIKTELDLTKSALRELRTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNCLKKTNECVSTLGNGVRVLATAVRELKDFVSKNLTRAINKNKCDIADLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVCFPEDQFNVALDQVFESIENCQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV025	116	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADCPSLIKTELDLTKSALRELRTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNGVRVLATAVRELKDFVSKNLTRAINKNKCDIADLC

[0239]

		MAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQIKLMLENRAMVRRKGFGFLIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQVFESIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV026	117	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKCIRLESEVTAIKNALKKTNEAVSTLGCGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISKDLMTDAELARAISNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSCGRNPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQCFESIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV027	118	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKCIRLESEVTAIKNALKKTNEAVSTLGCGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISKDLMTDAELARAISNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSCGRNPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQCFESIENSQALVDQSNRILSSAEKGNTGGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV028	119	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDCPSLIKTELDLTKSALRELKTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGCLKTTNECVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLCMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALS

[0240]

		PLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPICFPEDQFNVALDQVFESIENCQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQCRKAVESGAEFIVSPHLDEEISQFCKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVCEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGCTELEHHHHHH
hMPV029	120	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKCIRLESEVTAIKNALKKTNEAVSTLGCGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISKDLMTDAELARAISNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSCGRNPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQCFESIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQCRKAVESGAEFIVSPHLDEEISQFCKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVCEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGCTELEHHHHHH
hMPV030	121	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRRRRFVLGAIALGVATAAAVTAGVAIAKCIRLESEVTAIKNALKKTNEAVSTLGCGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISKDLMTDAELARAISNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSCGRNPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQCFESIENSQALVDQSNRILSSAEKGNTGGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQCRKAVESGAEFIVSPHLDEEISQFCKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVCEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGCTELEHHHHHH
hMPV031	122	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTCSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGIAIAKTIRLESEVNAIKGCLKTTNECVSTLGNGVRVLATAVRELKEFVSKNLTSAINKNKCDIADLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSYMPTSAGQIKLMLENRCMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCSEKDGNYACLLREDQGWYCKNAGSTVYYPNDKDCETRGDHVFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLPKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFESIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTV

[0241]

		TSVEQCRKAVESGAEFIVSPHLDEEISQFCKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVCEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGCTELEHHHHHH
hMPV033	123	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGVAIAKCIRLESEVTAIKNALKKTNEAVSTLGCGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISKDLMTDAELARAISNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSCGRNPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQCFESIENSQAGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH
hMPV034	124	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVGDVENLTCADGPSLIKTELDLTKSALRELRTVSADQLAREEQIEGGGGGGFVLGAIALGVATAAAVTAGVAIAKCIRLESEVTAIKNALKKTNEAVSTLGCGVRVLATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISKDLMTDAELARAISNMPTSAGQIKLMLENRAMVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCKVSCGRNPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQDADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPVKFPEDQFNVALDQCFESIENSQALVDQSNRILSSAEKGNTGGSGGSGSGSGGSEKAAKAEEAARKMEELFKKHKIVAVLRANSVEEAIEKAVAVFAGGVHLIEITFTVPDADTVIKALSVLKEKGAIIGAGTVTSVEQARKAVESGAEFIVSPHLDEEISQFAKEKGVFYMPGVMTPTELVKAMKLGHTILKLFPGEVVGPQFVKAMKGPFPNVKFVPTGGVNLDNVAEWFKAGVLAVGVGSALVKGTPDEVREKAKAFVEKIRGATELEHHHHHH

[0242] VLP的组装

[0243] 在一些实施例中,单个组分自组装到VLP中。在一些实施例中,用于形成VLP的第一和第二组分的一个或多个纯化的样品在水性条件下以大致等摩尔的摩尔比混合(例如,I53-50A/B二十面体VLP)。第一和第二组分(通过多聚化结构域和任选地通过胞外结构域)相互作用以驱动靶标VLP的组装。靶标VLP的成功组装可以通过使用常用的生物化学或生物物理方法分析体外组装反应来证实,所述方法用于评估蛋白质或蛋白质组装的物理尺寸,包含但不限于尺寸排阻色谱法、天然(非变性)凝胶电泳、动态光散射、多角度光散射、分析超速离心、负染色电子显微镜、冷冻电子显微镜或X射线晶体学。如果需要,组装的VLP可以使用通常用于通过其物理尺寸分离蛋白质的制备技术从体外组装反应中存在的其它物种或分子中纯化,包含但不限于尺寸排阻色谱法、制备超速离心、切向流过滤或制备凝胶电泳。VLP中抗原蛋白的存在可以通过通常用于确定水溶液中蛋白质分子的同一性的技术来评估,包含但不限于SDS-PAGE、质谱、蛋白质测序、ELISA、表面等离子体共振、生物层干涉或氨基酸分析。蛋白质在颗粒外部的可及性以及其构象或抗原性可以通过通常用于检测抗原的存在和构象的技术来评估,包含但不限于被单克隆抗体、构象特异性单克隆抗体、表面等

离子体共振、生物层干涉法或抗原特异性抗血清结合。

[0244] 在各种实施例中,本公开的VLP包括两种或更多种不同的第一多肽,所述第一多肽携带不同的抗原蛋白作为基因融合体;这些VLP在同一VLP上共显示多种不同的蛋白质。这些多抗原VLP是通过用两种或更多种抗原的混合物进行体外组装而产生的,每种所述抗原都包括多聚化结构域。混合物中每种抗原的级分决定了所得VLP中每种抗原蛋白的平均化合价。给定样品中每种抗原的存在和平均化合价可以通过使用上述用于评价全化合价VLP中抗原蛋白的存在的技术的定量分析来评估。

[0245] 在各种实施例中,VLP的直径介于约20纳米(nm)至约40纳米之间,内部内腔介于约15nm至约32nm之间,蛋白质壳中的孔径在其最长维度上介于约1nm至约14nm之间。

[0246] 在一些实施例中,VLP具有二十面体对称。在此类实施例中,VLP可以包括60个拷贝的第一组分和60个拷贝的第二组分。在一个此类实施例中,每个第一组装中相同的第一多肽的数量不同于每个第二组装中相同的第一多肽的数量。例如,在一些实施例中,VLP包括十二个第一组装和二十个第二组装;在此类实施例中,每个第一组装可以例如包括五个拷贝的相同的第一组分,并且每个第二组装可以例如包括三个拷贝的相同的第二组分。在其它实施例中,VLP包括十二个第一组装和三十个第二组装;在此类实施例中,每个第一组装可以例如包括五个拷贝的相同的第一组分,并且每个第二组装可以例如包括两个拷贝的相同的第二组分。在另外的实施例中,VLP包括二十个第一组装和三十个第二组装;在此实施例中,每个第一组装可以例如包括三个拷贝的相同的第一组分,并且每个第二组装可以例如包括两个拷贝的相同的第二组分。所有这些实施例都能够形成具有规则二十面体对称的基于蛋白质的VLP。

[0247] 在各种另外的实施例中,第一和第二多聚化结构域的低聚状态如下:

[0248] I53-34A:三聚体+I53-34B:五聚体;

[0249] I53-40A:五聚体+I53-40B:三聚体;

[0250] I53-47A:三聚体+I53-47B:五聚体;

[0251] I53-50A:三聚体+I53-50B:五聚体;

[0252] I53-51A:三聚体+I53-51B:五聚体;

[0253] I32-06A:二聚体+I32-06B:三聚体;

[0254] I32-19A:三聚体+I32-19B:二聚体;

[0255] I32-28A:三聚体+I32-28B:二聚体;

[0256] I52-03A:五聚体+I52-03B:二聚体;

[0257] I52-32A:二聚体+I52-32B:五聚体;以及

[0258] I52-33A:五聚体+I52-33B:二聚体

[0259] 在一些实施例中,第二多肽的第二多聚化结构域包括与I53-50A或其变体共享至少95%同一性的序列:

[0260] 153-50A

[0261]
1 MEELFKKHKI VAVLRANSVE EAIEKAVAVF AGGVHLIEIT
41 FTVPDADTVI KALSVLKEKG AIIGAGTVTS VEQCRKAVES
81 GAEFIVSPHL DEEISQFCKE KGVFYMPGVM TPTELVKAMK
121 LGHTILKLFP GEVVGPQFVK AMKGPFPNVK FVPTGGVNLD
161 NVCEWFKAGV LAVGVGSALV KGTPDEVREK AKAFVEKIRG
201 CTE (SEQ ID NO:
144)

[0262] 在一些实施例中，第二多聚化结构域与SEQ ID NO:7或SEQ ID NO:144或其抗原片段共享至少90％、95％、96％、97％、98％、99％或100％序列同一性。

[0263] I53-50A蛋白序列具有两个单体内二硫键。在一些实施例中，半胱氨酸残基突变为不含硫醇基团的残基(例如丙氨酸或丝氨酸)。去除硫醇基团可以促进正确的蛋白质折叠，同时不会损害多聚化。在一些实施例中，第一多肽的多聚化结构域包括相对于SEQ ID NO:144的在位置74、98、163和201中的一个或多个位置处的氨基酸取代，如在此示出的：

[0264] I53-50A

[0265]
1 MEELFKKHKI VAVLRANSVE EAIEKAVAVF AGGVHLIEIT
41 FTVPDADTVI KALSVLKEKG AIIGAGTVTS VEQ**C**RKAVES
81 GAEFIVSPHL DEEISQF**C**KE KGVFYMPGVM TPTELVKAMK
121 LGHTILKLFP GEVVGPQFVK AMKGPFPNVK FVPTGGVNLD
161 NV**C**EWFKAGV LAVGVGSALV KGTPDEVREK AKAFVEKIRG
201 **C**TE (SEQ ID NO:
144)

[0266] 在一些实施例中，第一多肽的多聚化结构域包括相对于SEQ ID NO:132的C74A、C98A、C163A和C201A中的一个或多个的氨基酸取代。在一些实施例中，第一多肽的多聚化结构域包括SEQ ID NO:132或其变体。

[0267] I53-50A-Δcys(无二硫形式)

[0268]
1 MEELFKKHKI VAVLRANSVE EAIEKAVAVF AGGVHLIEIT
41 FTVPDADTVI KALSVLKEKG AIIGAGTVTS VEQ**A**RKAVES
81 GAEFIVSPHL DEEISQF**A**KE KGVFYMPGVM TPTELVKAMK
121 LGHTILKLFP GEVVGPQFVK AMKGPFPNVK FVPTGGVNLD
161 NV**A**EWFKAGV LAVGVGSALV KGTPDEVREK AKAFVEKIRG
201 **A**TE (SEQ ID NO:
132)

[0269] 在一些实施例中，多聚化结构域与SEQ ID NO:144或SEQ ID NO:132或其抗原片段共享至少90％、95％、96％、97％、98％、99％或100％序列同一性，并且包括选自C74A、C98A、C163A和C201A的一个、两个、三个或四个氨基酸取代。可替代地，取代可以是C至A、T、S、L、I或除C之外的任何氨基酸。

[0270] 核酸

[0271] 另一方面，本公开提供了编码本公开的抗原、第一组分和/或第二组分的分离的核酸。分离的核酸序列可以包括RNA或DNA。如本文所使用的，“分离的核酸”是那些已经从基因组或cDNA序列中的其正常周围核酸序列中去除的核酸。此类分离的核酸序列可以包括可用

于促进编码的蛋白的表达和/或纯化的另外的序列，包含但不限于polyA序列、经修饰的Kozak序列和编码表位标签、输出信号和分泌信号、核定位信号和质膜定位信号的序列。基于本文的教导，本领域技术人员将清楚哪些核酸序列将编码本公开的蛋白质。

[0272] 在另外的方面，本公开提供重组表达载体，所述重组表达载体包括本公开的任何实施例或实施例的组合的分离的核酸，所述分离的核酸与合适的控制序列操作性地连接。“重组表达载体”包含将核酸编码区或基因与能够影响基因产物的表达的任何控制序列操作性地连接的载体。与本公开的核酸序列可操作地连接的“控制序列”是能够影响核酸分子表达的核酸序列。控制序列不需要与核酸序列邻接，只要其起到指导其表达的作用。因此，例如，中间的未翻译但仍被转录的序列可以存在于启动子序列与核酸序列之间，并且仍然可以认为启动子序列“可操作地连接”到编码序列。其它此类控制序列包含但不限于聚腺苷酸化信号、终止信号和核糖体结合位点。此类表达载体可以是本领域已知的任何类型，包含但不限于质粒和基于病毒的表达载体。用于驱动哺乳动物系统中公开的核酸序列的表达的控制序列可以是组成性的(由多种启动子中的任一种驱动，包含但不限于CMV、SV40、RSV、肌动蛋白、EF)或可诱导的(由多种可诱导启动子中的任一种驱动，包含但不限于四环素(tetracycline)、蜕皮激素、类固醇应答)。用于转染原核细胞的表达载体的构造也是本领域众所周知的，并且因此可以通过标准技术完成。(参见例如，Sambrook，Fritsch和Maniatis于以下中的描述:《分子克隆，实验室手册(Molecular Cloning，A Laboratory Manual)》，冷泉港实验室出版社(Cold Spring Harbor Laboratory Press)，1989;《基因转移和表达方案(Gene Transfer and Expression Protocols)》，第109-128页，编辑E.J.Murray，新泽西州克利夫顿的胡马纳出版社公司(The Humana Press Inc.，Clifton，N.J.)以及Ambion 1998目录(得克萨斯州奥斯汀的Ambion公司)。表达载体必须可以作为游离体或通过整合到宿主染色体DNA中在宿主生物体中复制。在优选的实施例中，表达载体包括质粒。然而，本公开旨在包含具有等效功能的其它表达载体，如病毒载体。

[0273] 另一方面，本公开提供了用本文所公开的重组表达载体转染或转导的宿主细胞，其中所述宿主细胞可以是原核或真核的。细胞可以瞬时或稳定地转染或转导。表达载体向原核细胞和真核细胞的此类转染或转导可以通过本领域已知的任何技术完成，包含但不限于标准细菌转化、磷酸钙共沉淀、电穿孔或脂质体介导的、DEAE葡聚糖介导的，聚阳离子介导的或病毒介导的转染。(参见例如，《分子克隆:实验室手册(Molecular Cloning:A Laboratory Manual)》(Sambrook等人，1989，冷泉港实验室出版社;《动物细胞培养:基础技术手册(Culture of Animal Cells:A Manual of Basic Technique)》，第2版(R.I.Freshney.1987.纽约州纽约市的Liss公司(Liss，Inc.New York，NY))。

[0274] 另一方面，本公开提供了产生根据本公开的抗原、组分或VLP的方法。在一些实施例中，所述方法包括以下步骤:(a)在有利于多肽表达的条件下培养根据本公开的此方面的宿主，以及(b)任选地回收所表达的多肽。

[0275] 在一些实施例中，本公开提供了一种制造疫苗的方法，所述方法包括在培养基中培养包括多核苷酸的宿主细胞，所述多核苷酸包括编码本公开的抗原的序列，使得所述宿主细胞将抗原分泌到培养基中;任选地从培养基中纯化抗原;将抗原与第二组分混合，其中所述第二组分与所述抗原多聚化以形成VLP;以及任选地纯化VLP。

[0276] 在一些实施例中，本公开提供了制造疫苗的方法，所述方法包括培养包括一种或

多种多核苷酸的宿主细胞,所述多核苷酸包括编码任一公开的VLP的两种组分的序列,使得宿主细胞将第一组分和第二组分分泌到培养基中;以及任选地从培养基中纯化VLP。

[0277] 说明性宿主细胞包含大肠杆菌细胞、293和293F细胞、HEK293细胞、Sf9细胞、中国仓鼠卵巢(CHO)细胞和用于生产重组蛋白的任何其它细胞系。

[0278] 在各种实施例中,第一组分在根据本公开的制造方法中以约0.5mg/mL、约1.0mg/mL、约1.5mg/mL、约2.5mg/mL、约5mg/mL、约10mg/mL、约25mg/mL、约50mg/mL、约75mg/mL、约100mg/mL或更大表达(例如悬浮液中生长的293F细胞)。在各种实施例中,第一组分在相同或类似表达系统中以至少50%、至少60%、至少70%、至少80%、至少90%或至少95%的hMPV F蛋白表达水平(任选地与VLP中相同的胞外结构域)表达。在各种实施例中,第一组分在相同或类似表达系统中以至少105%、至少110%、至少115%、至少120%、至少125%、至少150%、至少175%或至少200%的hMPV F蛋白表达水平(任选地与VLP中相同的胞外结构域)表达。

[0279] 在一些实施例中,第一组分的hMPV F蛋白胞外结构域处于融合前构象,或大部分hMPV F蛋白胞外结构域处于融合前构象。在各种实施例中,至少50%、至少60%、至少70%、至少80%、至少90%或至少95%的第一组分的hMPV F蛋白胞外结构域处于融合前构象。在一些实施例中,VLP的hMPV F蛋白胞外结构域处于融合前构象,或大部分hMPV F蛋白胞外结构域处于融合前构象。在各种实施例中,至少50%、至少60%、至少70%、至少80%、至少90%或至少95%的VLP的hMPV F蛋白胞外结构域处于融合前构象。

[0280] 在一些实施例中,处于融合前状态下的hMPV F蛋白胞外结构域的级分通过与构象特异性抗体(例如D1-25和1112-1)的结合来确定。在一些实施例中,处于融合前构象的第一组分中的hMPV F蛋白胞外结构域的级分比参考组分中的级分或未连接到多聚化结构域的参考蛋白中的级分大至少105%、至少110%、至少115%、至少120%、至少125%、至少150%、至少175%或至少200%。在一些实施例中,处于融合前构象的第一组分中的hMPV F蛋白胞外结构域的级分比VLP(例如,胶束VLP)中的级分大至少105%、至少110%、至少115%、至少120%、至少125%、至少150%、至少175%或至少200%。

[0281] 疫苗和施用

[0282] 本公开还提供了包括本文所描述的VLP的疫苗。此类组合物可以用于在哺乳动物(例如人)中产生抗体。本公开的疫苗组合物通常包含药学上可接受的载体,并且此类载体的详尽讨论可在《雷明顿:药学科学与实践(Remington:The Science and Practice of Pharmacy)》中获得。

[0283] 组合物的pH通常介于约4.5至约11之间,如介于约5至约11之间、介于约5.5至约11之间、介于约6至约11之间、介于约5至约10.5之间、介于约5.5至约10.5之间、介于约6至约10.5之间、介于约5至约10之间、介于约5.5至约10之间、介于约6至约10之间、介于约5至约9.5之间、介于约5.5至约9.5之间、介于约6至约9.5之间、介于约5至约9之间、介于约5.5至约9之间、介于约6至约9之间、介于约5至约8.5之间、介于约5.5至约8.5之间、介于约6至约8.5之间、介于约5至约8之间、介于约5.5至约8之间、介于约6至约8之间、约4.5、约5、约6.5、约6、约6.5、约7、约7.5、约8、约8.5、约9、约9.5、约10、约10.5、约11等。稳定的pH可以通过使用缓冲液来维持例如,Tris缓冲液、柠檬酸盐缓冲液、磷酸盐缓冲液或组氨酸缓冲液。因此组合物将通常包含缓冲液。

[0284] 组合物可以为无菌和/或无热原质的。组合物可以相对于人等渗。

[0285] 疫苗组合物包括免疫有效量的其抗原。“免疫有效量”或“有效量”是当施用于受试者时有效引发针对抗原的抗体应答的量。此量可能根据要治疗的个体的健康和身体状况、其年龄、个体免疫系统合成抗体的能力、期望的保护程度、疫苗的调配、主治医生对医疗状况的评估以及其它相关因素。预期所述量将落入可以通过常规试验确定的相对较宽的范围内。本公开的组合物的抗原含量将通常以每剂量的蛋白质质量表示。每种抗原10-500μg(例如50μg)的剂量可以是有用的。

[0286] 疫苗组合物可以包含免疫佐剂。说明性佐剂包含以下:1.含矿物质组合物;2.油乳液;3.皂苷调配物;4.病毒颗粒和病毒样颗粒;5.细菌或微生物衍生物;6.生物粘合剂和粘膜粘合剂;7.脂质体;8.聚氧乙烯醚和聚氧乙烯酯调配物;9.聚磷腈(pcpp);10.胞壁酰肽;11.咪唑喹诺酮化合物;12.缩氨基硫脲化合物;13.色氨酮化合物;14.人免疫调节剂;15.脂肽;16.苯并萘啶;17.微颗粒;18.免疫刺激性多核苷酸(如rna或dna;例如含cpg的寡核苷酸)。

[0287] 例如,组合物可以包含铝盐佐剂、水包油乳剂(例如包括角烯的水包油乳剂,如MF59或AS03)、TLR7激动剂(如咪唑喹啉或咪喹莫特(imiquimod))或其组合。合适的铝盐包含氢氧化物(例如羟基氧化物)、磷酸盐(例如,羟磷酸盐、正磷酸盐)(例如参见《疫苗设计(Vaccine Design.)》的第8和9章(1995)版.Powell和Newman.ISBN:030644867X.普莱南出版社(Plenum))和/或其混合物。盐可以采用任何合适的形式(例如凝胶、结晶、无定形等),例如抗原吸附到盐上。施用于患者的组合物中的Al^{+++}浓度可以小于5mg/ml例如,<4mg/ml、<3mg/ml、<2mg/ml、<1mg/ml等。优选的范围介于0.3与1mg/ml之间。优选最大0.85mg/剂量。氢氧化铝和磷酸铝佐剂适用于本公开。

[0288] 可以用于本文所提供的药物组合物的示例性佐剂包含但不限于3M-052、Adju-Phos^{TM}、Alhydrogel^{TM}、Adjumer^{TM}、白蛋白-肝素微粒,藻葡聚糖、阿伽目林(Algammulin)、明矾、抗原调配物、AS-2佐剂、AS01、AS03、自体树突状细胞、自体PBMC、Avridine^{TM}、B7-2、BAK、BAY R1005、BECC TLR-4激动剂、布比卡因(Bupivacaine)、布比卡因-HCl、BWZL、骨化三醇、磷酸钙凝胶、CCR5肽、CFA、霍乱海参毒素(Cholera holotoxin,CT)和霍乱毒素B亚基(CTB)、霍乱毒素A1-亚基-蛋白A D-片段融合蛋白、CpG、CPG-1018、CRL1005、含细胞因子的脂质体、D-莫拉帕米汀(D-Murapalmitine)、DDA、DHEA、白喉类毒素、DL-PGL、DMPC、DMPG、DOC/明矾复合物、禽痘、弗氏完全佐剂(Freund'sComplete Adjuvant)、γ菊粉、Gerbu佐剂、GM-CSF、GMDP、hGM-CSF、hIL-12(N222L)、hTNF-α、IFA、含IFN-γ的pcDNA3、IL-12DNA、IL-12质粒、IL-12/GMCSF质粒(赛克斯公司(Sykes))、含IL-2的pcDNA3、IL-2/Ig质粒、IL-2/Ig蛋白、IL-4、含IL-4的pcDNA3、Imiquimod^{TM}、ImmTher^{TM}、含有针对共刺激分子的抗体的免疫脂质体、干扰素-γ、白介素-1β、白介素-12、白介素-2、白介素-7、ISCOM(s)^{TM}、Iscoprep 7.0.3^{TM}、钥孔戚血蓝素、基于脂质的佐剂、脂质体、洛索立宾(Loxoribine)、LT(R192G)、LT-OA或LT口服佐剂、LT-R192G、LTK63、LTK72、Matrix-M^{TM}佐剂、MF59、MONTANIDE ISA 51、MONTANIDE ISA 720、MPL.^{TM}.、MPL-SE、MTP-PE、MTP-PE脂质体、莫拉美肽(Murametide)、莫拉帕米汀、NAGO、nCT天然霍乱毒素、非离子表面活性剂囊泡、霍乱毒素mCT-E112K的无毒突变体E112K、p-羟苯甲酸甲酯、pCIL-10、pCIL12、pCMVmCAT1、pCMVN、Peptomer-NP、Pleuran、PLG、PLGA、PGA和PLA、普朗尼克(Pluronic)L121、PMMA、PODDS^{TM}、Poly rA:Poly rU、聚山梨醇酯80、螺旋性蛋

白质、QS-21、Quadri A皂苷、Quil-A、Rehydragel HPA、Rehydragel LV、RIBI、Ribi样佐剂系统(MPL、TMD、CWS)、S-28463、SAF-1、Sclavo肽、仙台蛋白脂质体、含仙台的脂质基质、Span 85、Specol、角鲨烷1、角鲨烷2、硬脂酪氨酸、SWE、破伤风类毒素(TT)、Theramide™、苏胺酰基胞壁酰二肽(TMDP)、Ty颗粒和Walter Reed脂质体。

[0289] 在优选的实施例中,佐剂是氢氧化铝凝胶(例如Alhydrogel™)。在优选的实施例中,佐剂是SWE。在优选的实施例中,佐剂是MF59。

[0290] MF59是水包油乳液,所述水包油乳液含有含角鲨烯(4.3%)的柠檬酸缓冲液和稳定的非离子表面活性剂Tween 80(0.5%)和Span 85(0.5%)。MF59已被示出在人中具有良好的耐受性,并且用于针对季节性流感疫苗中(参见Ko和Kang,《人类疫苗和免疫疗法(Hum Vaccin Immunother.)》2018;14(12):3041-3045;美国专利第6,299,884号)。

[0291] 例如,组合物可以包含铝盐佐剂、水包油乳液(例如包括角烯的水包油乳液,如MF59、SWE或AS03)、TLR9激动剂(如CpG寡脱氧核苷酸)、TLR7激动剂(如咪唑喹啉或咪喹莫特)或其组合。在一些实施例中,佐剂是铝盐和CPG1018的组合。合适的铝盐包含氢氧化物(例如羟基氧化物)、磷酸盐(例如,羟磷酸盐、正磷酸盐)(例如参见《疫苗设计》的第8和9章(1995)版.Powell和Newman.ISBN:030644867X.普莱南出版社)和/或其混合物。盐可以采用任何合适的形式(例如凝胶、结晶、无定形等),例如抗原吸附到盐上。施用于患者的组合物中的Al+++浓度可以小于5mg/ml例如,<4mg/ml、<3mg/ml、<2mg/ml、<1mg/ml等。优选的范围介于0.3与1mg/ml之间。优选最大0.85mg/剂量。氢氧化铝和磷酸铝佐剂适用于本公开。在优选的实施例中,本文提供的药物组合物包括氢氧化铝作为佐剂。在一些实施例中,本文提供的药物组合物包括500μg氢氧化铝。

[0292] 佐剂的选择取决于要治疗的受试者。优选地,使用药学上可接受的佐剂。

[0293] 在一些实施例中,佐剂是角鲨烯乳液。

[0294] 在一些实施例中,佐剂是TLR4免疫刺激剂(例如SLA、GLA)例如,如Van Hoeven等人《公共科学图书馆综合(PLoS One.)》11(2):e0149610(2016)中所描述的。

[0295] 在一些实施例中,佐剂是TLR7/8免疫刺激剂(例如R848、IMQ、3M-052)例如,如Dowling D.《免疫视野(ImmunoHorizons)》(6):185-197(2018)中所描述的。

[0296] 在一些实施例中,佐剂是TLR9免疫刺激剂(CpG)例如,如Bode等人《疫苗专家评论(Expert Rev Vaccines.)》10(4):499-511(2011)中所描述的。

[0297] 在一些实施例中,佐剂是皂苷(QS21)例如,如Zhu等人《天然产物化学和研究(Nat Prod Chem Res.)》3(4):e113(2016)中所描述的。

[0298] 在一些实施例中,疫苗包括两种或多种佐剂的组合(例如角鲨烯乳液和明矾或TLR4免疫刺激剂)。

[0299] 一种合适的免疫佐剂包括如WO2011/027222中所定义的吸附到铝盐的式(I)的化合物或其药学上可接受的盐。可以使用许多另外的佐剂,包含Powell和Newman(1995)中公开的那些佐剂中的任何佐剂。

[0300] 组合物可以包含抗微生物剂,特别是当以多剂量形式包装时。疫苗中通常可见如硫柳汞和2-苯氧乙醇等抗微生物剂,但有时可能需要使用无汞防腐剂或根本不使用防腐剂。

[0301] 组合物可以包括洗涤剂例如,如聚山梨酯80等聚山梨酯。洗涤剂通常以例如<

0.01％的低水平存在。

[0302] 组合物可以包含钠盐(例如氯化钠)以提供张力。10±2mg/ml NaCl的浓度通常是例如约9mg/ml。

[0303] 在一些实施例中,疫苗组合物中的缓冲液是Tris缓冲液、组氨酸缓冲液、磷酸盐缓冲液、柠檬酸盐缓冲液或乙酸盐缓冲液。所述组合物还可以包含冻干保护剂,例如蔗糖、山梨醇或海藻糖。在某些实施例中,所述组合物包含防腐剂,例如苯扎氯铵、苄索铵、氯己定、苯酚、间甲酚、苄醇、对羟基苯甲酸甲酯、对羟基甲苯丙酯、氯丁醇、邻甲酚、对甲酚、氯甲酚、苯汞硝酸盐、硫柳汞、苯甲酸以及其各种混合物。在其它实施例中,所述组合物包含膨胀剂,如甘氨酸。在又其它实施例中,所述组合物包含表面活性剂,例如聚山梨醇酯-20、聚山梨醇酯-40、聚山梨醇酸酯-60、聚山梨醇酯-65、聚山梨醇酸酯-80、聚山梨醇酯-85、泊洛沙姆-188(poloxamer-188)、脱水山梨糖醇单月桂酸酯、脱水山梨糖醇单棕榈酸酯、脱水山梨糖醇单硬脂酸酯、脱水山梨糖醇三月桂酸酯、脱水山梨糖醇三硬脂酸酯、脱水山梨糖醇三油酸甘油酯或其组合。所述组合物还可包含张力调节剂,例如使所述调配物与人体血液基本上等张或等渗的化合物。说明性张力调节剂包含蔗糖、山梨醇、甘氨酸、甲硫氨酸、甘露醇、葡萄糖、肌醇、氯化钠、精氨酸和精氨酸盐酸盐。在其它实施例中,所述组合物另外包含稳定剂,例如基本上防止或减少冻干或液体形式的VLP的化学和/或物理不稳定性的分子。说明性稳定剂包含蔗糖、山梨醇、甘氨酸、肌醇、氯化钠、甲硫氨酸、精氨酸和精氨酸盐酸盐。

[0304] 在一些实施例中,本公开提供了包括一种或多种药学上可接受的赋形剂的疫苗(免疫原性组合物)。

[0305] 在一些实施例中,疫苗(免疫原性组合物)是稳定乳液。

[0306] 在一些实施例中,本公开提供了包括一种或多种佐剂的疫苗(免疫原性组合物)。在一些实施例中,所述一种或多种佐剂包括TLR4免疫刺激剂例如,单磷酰脂质A(MPL)、吡喃葡萄糖基脂质A(GLA)和/或可溶性利什曼原虫抗原(SLA)。

[0307] 另一方面,本公开提供了一种诱导针对hMPV的免疫应答的方法,所述方法包括向有需要的受试者施用免疫有效量的本文所描述的免疫原性组合物,其包括本文所描述的VLP。

[0308] 在某些实施例中,免疫应答包括产生针对感染原的中和抗体。在某些实施例中,中和抗体是补体依赖性的。

[0309] 免疫应答可以包括体液免疫应答、细胞介导的免疫应答或两者。在一些实施例中,针对每种递送的抗原蛋白诱导免疫应答。细胞介导的免疫应答可以包括辅助T细胞(Th)应答、CD8+细胞毒性T细胞(CTL)应答或两者。在一些实施例中,免疫应答包括体液免疫应答,并且抗体是中和抗体。中和抗体阻断细胞的病毒感染。病毒感染上皮细胞并且还感染成纤维细胞。在一些实施例中。免疫应答减少或防止两种细胞类型的感染。中和抗体应答可以是补体依赖性的或补体非依赖性的。在一些实施例中,中和抗体应答是补体依赖性的。在一些实施例中,中和抗体应答是交叉中和的;即,针对施用的组合物产生的抗体中和与组合物中使用的菌株不同的菌株的病毒。

[0310] 本领域中抗体效力的有用测量是“50％中和滴度”。为了确定50％中和滴度,将来自免疫动物的血清稀释,以评估稀释的血清如何仍能保持阻止50％的病毒进入细胞的能力。例如,700的滴度意指血清在稀释700倍后仍保留中和50％病毒的能力。因此,更高的滴

度表明更有效的中和抗体应答。在一些实施例中，此滴度在具有以下下限的范围内：约200、约400、约600、约800、约1000、约1500、约2000、约2500、约3000、约3500、约4000、约4500、约5000、约5500、约6000、约6500或约7000。50％中和滴度范围可以具有以下上限：约400、约600、约800、约1000、约1500、约2000、约2500、约3000、约3500、约4000、约4500、约5000、约5500、约6000、约6500、约7000、约8000、约9000、约10000、约11000、约12000、约13000、约14000、约15000、约16000、约17000、约18000、约19000、约20000、约21000、约22000、约23000、约24000、约25000、约26000、约27000、约28000、约29000或约30000。例如，50％中和滴度可以是约3000至约25000。“约”意指所列值的加或减10％。

[0311] 在一些实施例中，本公开的病毒样颗粒产生0.5IU/mL、1.0IU/mL、1.5IU/mL、2.0IU/mL、10IU/mL、25IU/mL、50IU/mL、100IU/mL或更大的免疫应答。在一些实施例中，本公开的病毒样颗粒产生0.5IU/mL或更大的免疫应答。

[0312] 本公开的组合物将通常直接施用于受试者。直接递送可以通过肠胃外注射(例如皮下、腹膜内、静脉内、肌内或组织间隙)、口服、鼻内或通过任何其它合适的途径来完成。例如，可以使用肌内施用例如到大腿或上臂。注射可以通过针(例如皮下注射针)进行，但可以可替代地使用无针注射。典型的肌内剂量体积为0.5ml。

[0313] 给药可以是通过单剂量方案或多剂量方案。在初次免疫方案中和/或在加强免疫方案中可以使用多个剂量。在多剂量方案中，各种剂量可以通过相同或不同的途径给予，例如胃肠外初免和粘膜加强、粘膜初免和胃肠外加强等。多个剂量通常将间隔至少1周(例如，约2周、约3周、约4周、约6周、约8周、约10周、约12周或约16周)施用。多个剂量可以间隔至少1个月(例如，约2个月、约3个月、约4个月、约6个月、约8个月、约10个月、约12个月、约16个月等)施用。可以在更长的间隔内施用第二次或后续剂量例如，在先前剂量后约1年或约2年。

[0314] 在疫苗用于预防性用途的情况下，人优选地是儿童(例如，幼儿或婴儿)、青少年或成人；在疫苗用于治疗用途时，人优选地是青少年或成年人。用于儿童的疫苗也可以施用于成人例如，以评估安全性、剂量、免疫原性等。

[0315] 本公开的疫苗可以是预防性的(即，用于预防疾病)或治疗性的(即，用于减少或消除疾病的症状)。术语预防性可以被视为降低特定病状的严重程度或预防其发作。为避免疑义，术语预防性疫苗还可以指改善未来感染影响的疫苗，例如通过降低此类感染的严重程度或持续时间。

[0316] 本文所描述的分离和/或纯化的VLP可以单独施用或作为混合模式方案中的初免或加强施用，如RNA初免或DNA引物，随后是蛋白质加强。与蛋白质初免/蛋白质加强策略相比，RNA初免/蛋白质加强策略的益处包含例如，抗体滴度增加、IgG1:IgG2a亚型谱更平衡、诱导与病毒颗粒的免疫应答类似的TH1型CD4+T细胞介导的免疫应答，并且减少了非中和抗体的产生。RNA初免可以增加组合物的免疫原性，无论所述组合物是否含有佐剂。

[0317] 在RNA初免/蛋白质加强策略中，RNA和蛋白质针对相同的靶抗原。合适的递送RNA模式的实例包含病毒样复制子颗粒(VRP)、甲病毒RNA、包封在脂质纳米颗粒(LNP)中的复制子或配制的RNA，如用阳离子纳米乳液(CNE)调配的复制子。合适的阳离子水包油纳米乳液公开于WO2012/006380中，例如包括油核(例如包括角鲨烯)和阳离子脂质(例如DOTAP、DMTAP、DSTAP、DC-胆固醇等)。

[0318] 可替代地，可以以预定间隔施用两个剂量的VLP以获得初免-加强效应。预定间隔

可以是1天、2天、3天、4天、6天、7天、10天或14天;或3-5天、7-10天或10-14天等。预定间隔可以是1周、2周、3周、4周或6周;或2-3周、3-4周或5-6周等。预定间隔可以是1个月、2个月、3个月或4个月。

[0319] 在一些实施例中,RNA分子被包封、结合或吸附在阳离子脂质、脂质体、螺旋体、病毒颗粒、免疫刺激复合物、微颗粒、微球、纳米球、单层囊泡、多层囊泡、水包油乳液、油包水乳液、乳脂体、聚阳离子肽、阳离子纳米乳液或其组合上。

[0320] 本公开进一步提供了组合疫苗。本公开的疫苗包含包括hMPV VLP和针对以下中的一种或多种的疫苗的疫苗:SARS-CoV-2、呼吸道合胞病毒、狂犬病、伤寒、甲型肝炎、脊髓灰质炎、流感、乙型肝炎、黄热病、日本脑炎(Japanese encephalitis)、细小病毒、瘟热、腺病毒、副流感病毒、流感、麻疹、莱姆病(Lyme disease)、冠状病毒、水疱性口炎病毒、单纯疱疹病毒、杆状病毒、索戈托病毒和玻那病毒科。

[0321] 本文还提供了用于施用本文所描述的核酸(例如,RNA)、纯化的蛋白质和纯化的VLP的试剂盒以及使用说明。本公开还提供了预填充有本文所公开的组合物或疫苗的递送装置。

[0322] 本文所描述的药物组合物可以与一种或多种另外的治疗剂组合施用。另外的治疗剂可以包含但不限于抗生素或抗菌剂、止吐剂、抗真菌剂、抗炎剂、抗病毒剂、免疫调节剂、细胞因子、抗抑郁药、激素、烷基化剂、抗代谢物、抗肿瘤抗生素、抗有丝分裂剂、拓扑异构酶抑制剂、细胞生长抑制剂、抗侵入剂、抗血管生成剂、生长因子功能的抑制剂、病毒复制抑制剂、病毒酶抑制剂、抗癌剂、α-干扰素、β-干扰素、利巴韦林、激素和其它toll样受体调节剂、免疫球蛋白(Ig)和调节Ig功能的抗体(如抗IgE((奥马珠单抗)omalizumab))。

[0323] 在某些实施例中,本文所公开的组合物可以用作药物例如,用于在如哺乳动物等有需要的受试者中诱导或增强免疫应答。

[0324] 在某些实施例中,本文所公开的组合物可以用于制造用于在如哺乳动物等有需要的受试者中诱导或增强免疫应答的药物。

[0325] 检查治疗性治疗的功效的一种方式涉及在施用本文所公开的组合物或疫苗后监测感染原的感染。检查预防性治疗的功效的一种方式涉及监测针对抗原的全身(如监测IgG1和IgG2a产生的水平)和/或粘膜(如监测IgA产生的水平)免疫应答。通常,抗原特异性血清抗体应答是在免疫后但激发前确定的,而抗原特异性粘膜抗体应答是在免疫后和激发后确定的。

[0326] 实例

[0327] 实例1

[0328] 此实例说明了双组分、二十面体VLP的产生,旨在用作hMPV病毒的疫苗。作为第一组分A,所述疫苗使用由hMPV F蛋白的胞外结构域组成的多肽抗原,所述hMPV F蛋白的胞外结构域在C末端与I53-50A蛋白(SEQ ID NO:144)融合。作为组分B,VLP使用I53-50B蛋白。已知I53-50A和I53-50B以3:5的比率自发组装形成具有二十面体(I53)对称性的VLP,如图1A和B所示出的。

[0329] 确定了与CompA融合的hMPV F蛋白的表达水平。人密码子优化的多核苷酸序列通过基因合成制备并且克隆到表达载体中。每个表达载体通过瞬时转染在Expi293细胞中单独表达。转染后四天收集上清液。

[0330] 为了确定重组表达的融合蛋白是否分泌到上清液中,进行了使用抗His6单克隆抗体的蛋白质印迹。将条件培养基在具有5%(v/v)β-巯基乙醇的2X莱姆利(Laemmli)上样缓冲液(伯乐公司(Bio-Rad))中稀释至少10倍,并且加热到95℃,持续10分钟,并且10μl在凝胶上运行。重组His标记的人血清白蛋白(HSA)的参考样品通过初始稀释到0.01mg/mL,随后进行2倍稀释系列制备,以在2X莱姆利上样缓冲液中的10μL上样体积中获得6.25至100ng的标准曲线。将样品上样到NuPAGE 4-12% Bis-Tris蛋白质凝胶上,并且在150V下运行45分钟。将蛋白质转移到免疫印迹PDVF膜(伯乐公司)上。转移后,将印迹用含3% BSA(w/v)的TBST在室温下通过振荡封闭1小时。将抗His、HRP缀合抗体(R&D系统公司(R&D Systems)MAB050H)在含3% BSA(w/v)的TBST中以1:8,000稀释,并且在室温下与膜温育1小时。然后使用TBST将膜洗涤三次,持续五分钟,然后使用鲁米诺化学发光底物(luminol chemiluminescent substrate)(VisiGlo,VWR)检测His标记的蛋白质,并且使用10-20秒的曝光时间在UVP Chemstudio(耶拿分析仪器公司(Analytik Jena))上捕获。

[0331] 表4示出了与CompA融合的hMPV F蛋白的表达水平。通过蛋白质印迹的视觉检查评估表达水平,并且指定为无表达(X)或低表达(*)至高表达(****)。hMPV008、hMPV009、hMPV024、hMPV026、hMPV027、hMPV033和hMPV034 CompA融合蛋白在此系统中示出最高的表达水平。

[0332] 表4.测试hMPV F-CompA融合蛋白在Expi293细胞中的表达。

[0333]

构建体名称	突变	hMPV 菌株(A 或 B)	CompA: Ala 或 Cys	C 末端截短	表达水平
hMPV001	A185P、Q100R、S101R	A	Ala	481	*
hMPV002	A185P、Q100R、S101R	A	Ala	472	**
hMPV003	A185P、Q100R、S101R	A	Ala	489	*
hMPV004	Q100R、S101R	A	Ala	472	*
hMPV005	A185P、T127C、N153C、Q100R、S101R	A	Ala	472	**
hMPV006	V84C、A140C、A147C、A249C、N97G、P98G、R99G、Q100G、S101G、R102G	B	Ala	472	**
hMPV007	V84C、A140C、A147C、A249C、N97G、P98G、R99G、Q100G、S101G、R102G	B	Ala	488	**
hMPV008	A63C、A140C、A147C、K188C、K450C、S470C、N97G、P98G、R99G、Q100G、S101G、R102G	B	Ala	472	****

[0334]

构建体名称	突变	hMPV 菌株（A 或 B）	CompA：Ala 或 Cys	C 末端截短	表达水平
hMPV009	A63C、A140C、A147C、K188C、K450C、S470C、N97G、P98G、R99G、Q100G、S101G、R102G	B	Ala	488	****
hMPV010	A63C、A140C、A147C、K188C、缺失的 G106、N97G、P98G、R99G、Q100G、S101G、R102G	A	Ala	472	X
hMPV011	A63C、A140C、A147C、K188C、缺失的 G106、N97G、P98G、R99G、Q100G、S101G、R102G	A	Ala	488	X
hMPV012	A113C、A120C、A339C、Q426C、T160F、I177L、Q100K、S101A	B	Ala	472	X
hMPV013	A113C、A120C、A339C、Q426C、T160F、I177L、Q100K、S101A	B	Ala	488	X
hMPV014	V84C、A140C、A147C、A249C、Q100R、S101R	B	Ala	472	**
hMPV015	A63C、A140C、A147C、K188C、K450C、S470C、Q100R、S101R	B	Ala	472	***
hMPV016	A63C、A140C、A147C、K188C、缺失的 G106、Q100R、S101R	A	Ala	472	X
hMPV017	A113C、A120C、A339C、Q426C、T160F、I177L、Q100R、S101R	B	Ala	472	X
hMPV018	A185P、A113C、A339C、Q100R、S101R	A	Ala	472	**
hMPV019	A185P、T160F、I177L、Q100R、S101R	A	Ala	472	*
hMPV020	A185P、A113C、A339C、T160F、I177L、Q100R、S101R	A	Ala	472	*

[0335]

构建体名称	突变	hMPV 菌株（A 或 B）	CompA：Ala 或 Cys	C 末端截短	表达水平
hMPV021	A63C、K188C、N97G、P98G、R99G、Q100G、S101G、R102G	B	Ala	472	***
hMPV022	A63C、K188C、K450A、S470A、N97G、P98G、R99G、Q100G、S101G、R102G	B	Ala	472	***
hMPV023	A63C、A140C、A147C、K188C、G294E、N97G、P98G、R99G、Q100G、S101G、R102G	A	Ala	472	**
hMPV024	A63C、A140C、A147C、K188C、K450C、S470C、N97G、P98G、R99G、Q100G、S101G、R102G、G294E	A	Ala	472	****
hMPV025	A63C、K188C、N97G、P98G、R99G、Q100G、S101G、R102G、G294E	A	Ala	472	**
hMPV026	T127C、N153C、T365C、V463C、A185P、L219K、V231I、G294E、H368N、Q100R、S101R	A	Ala	472	****
hMPV027	T127C、N153C、T365C、V463C、A185P、L219K、V231I、G294E、H368N、Q100R、S101R	A	Ala	490	****
hMPV028	A63C、A140C、A147C、K188C、K450C、S470C、N97G、P98G、R99G、Q100G、S101G、R102G	B	Cys	472	*
hMPV029	T127C、N153C、T365C、V463C、A185P、L219K、V231I、G294E、H368N、Q100R、S101R	A	Cys	472	*

[0336]

构建体名称	突变	hMPV 菌株（A 或 B）	CompA：Ala 或 Cys	C 末端截短	表达水平
hMPV030	T127C、N153C、T365C、V463C、A185P、L219K、V231I、G294E、H368N、Q100R、S101R	A	Cys	490	*
hMPV031	V84C、A140C、A147C、A249C、N97G、P98G、R99G、Q100G、S101G、R102G	B	Cys	472	*
hMPV033	T127C、N153C、T365C、V463C、A185P、L219K、V231I、G294E、N97G、P98G、R99G、Q100G、H368N、S101G、R102G	A	Ala	472	****
hMPV034	T127C、N153C、T365C、V463C、A185P、L219K、V231I、G294E、N97G、P98G、R99G、H368N、Q100G、S101G、R102G	A	Ala	490	****

[0337] 实例2

[0338] 在此实例中，含有hMPV F-CompA融合蛋白的条件培养基使用抗体结合活性来表征，以确定hMPV F蛋白的构象。评价融合蛋白hMPV005、hMPV008、hMPV021、hMPV024、hMPV026、hMPV027、hMPV027C和hMPV033(表5)。构建体hMPV026和hMPV027含有在Expi293瞬时转染中未被切割的弗林蛋白酶切割位点。在共转染人弗林蛋白酶后，表达的蛋白质被适当切割并且命名为hMPV026C或hMPV027C以表示切割形式。

[0339] 为了表征与CompA融合的重组表达的hMPV F蛋白的构象，使用与特定形式的hMPV F蛋白胞外结构域结合的15种单克隆抗体进行了ELISA。

[0340] 将96孔板的孔用pH 9.6的100μL 50mM碳酸钠-碳酸氢钠缓冲液中的200ng每种抗体或50ng MPE8在4℃下涂覆过夜。将板用300μl具有0.05％ Tween 20的PBS洗涤3次。在室温下用150μl具有1％ BSA的PBS封闭1小时后，通过在吸收垫上拍打来清空板。基于半定量蛋白质印迹，稀释来自每种构建体的Expi293转染的条件培养基上清液，使得抗原浓度将包含抗原的预期EC_{50}(来自Mas数据)。对于每种抗体，将每种构建体的三种稀释液以每孔100μL的浓度铺板，并且将板在室温下温育1小时。将板用300μl具有0.05％ Tween 20的PBS洗涤6次。将抗His单克隆抗体(R&D系统公司MAB050H)以1:15,000稀释，并且向每孔添加100μL，并且将板在室温下温育1小时。将板用300μl具有0.05％ Tween 20的PBS洗涤6次后，添加100μl TMB底物，并且将板在黑暗中显影10分钟。通过添加100μl 0.6N H_2SO_4来终止反应，并且在酶标仪上测量450nm处的吸光度。

[0341] 融合后特异性抗体与hMPV021结合，表明此构建体具有融合后构象。其它构建体不与融合后特异性Ab结合，并且与MPE8以及识别融合前和融合后构象的多种Ab结合。此数据

表明融合蛋白具有融合前构象特性。

[0342] 实例3

[0343] 用纯化的hMPV F-CompA融合蛋白观察到结合活性。图3A-3C示出了与已知浓度的纯化的组分A(CompA)融合体的结合——即,hMPV F蛋白胞外结构域在N末端与I53-50A(SEQ ID NO:144)或I53-50AΔCys(SEQ ID NO:145)融合。MF14、MPE8和MF16分别识别抗原位点II、III和IV,并且这些抗原位点是中和抗体识别的主要位点。另外,MPE8优先识别hMPV F蛋白的融合前形式。将96孔板的孔用pH 9.6的100μL50mM碳酸钠-碳酸氢钠缓冲液中的50ng MPE8以及100ng MF14和MF16在4℃下涂覆过夜。将板用300μl具有0.05% Tween 20的PBS洗涤3次。在室温下用150μl具有1%BSA的PBS封闭1小时后,通过在吸收垫上拍打来清空板。将每种构建体的纯化的样品稀释到40μg/mL(hMPV008、021、026和027)或4μg/mL(hMPV026C和033),随后分别在具有1% BSA的PBS中进行3倍或4倍稀释系列,并且以每孔100μL铺板,并将板在室温下温育1小时。将板用300μl具有0.05% Tween 20的PBS洗涤6次。将抗His单克隆抗体(R&D系统公司MAB050H)以1:15,000稀释,并且向每孔添加100μL,并且将板在室温下温育1小时。将板用300μl具有0.05% Tween 20的PBS洗涤6次后,添加100μl TMB底物,并且将板在黑暗中显影10分钟。通过添加100μl $0.6NH_2SO_4$来终止反应,并且在酶标仪上测量450nm处的吸光度。与MF14(位点II,图3A)和MF16(位点IV,图3B)结合是类似的,但与MPE8(位点III,图3C)结合比与hMPV008和hMPV021(表6)结合具有更高的EC_{50}。这表明位点III,即,中和抗体识别位点,在hMPV026、hMPV027和hMPV033中更保守,并且这些构建体比hMPV008和hMPV021更优先采用融合前构象。

[0344] 表6.中和抗体结合EC_{50}值

[0345]

	EC_{50}		
构建体:	**MPE8**	**MF14**	**MF16**
hMPV008	8.19E+00	1.78E-01	1.99E-01
hMPV021	1.28E+01	1.66E-01	1.86E-01
hMPV026	7.70E-02	9.57E-02	1.01E-01
hMPV026C	1.24E-01	1.36E-01	1.40E-01
hMPV027	7.96E-02	9.37E-02	9.65E-02
hMPV033	9.68E-02	1.08E-01	1.17E-01

[0346] 实例4

[0347] 在此实例中,在第0天和第21天,将组装的hMPV008 VLP或hMPV008 CompA单独肌内注射到雌性Balb/c小鼠的两条后腿中。表7中列出了每组的数量和调配物。在第0、24和35天收集抽血并加工成血清。第0天血清样品按组合并。所有血清样品都在hMPV中和抗体滴度测定中进行评价(图4)。具有佐剂Alhydrogel(明矾)或Addavax(角鲨烯水包油乳液)的hMPV008调配物在第24天和第35天时在所有剂量下诱导可测量的中和滴度,并且与健康成人血清的滴度相当(图4)。这些结果表明,hMPV008 VLP诱导与健康人对照血清的滴度相当的稳健中和滴度。

[0348] 表7.注射的VLP的数量和调配物

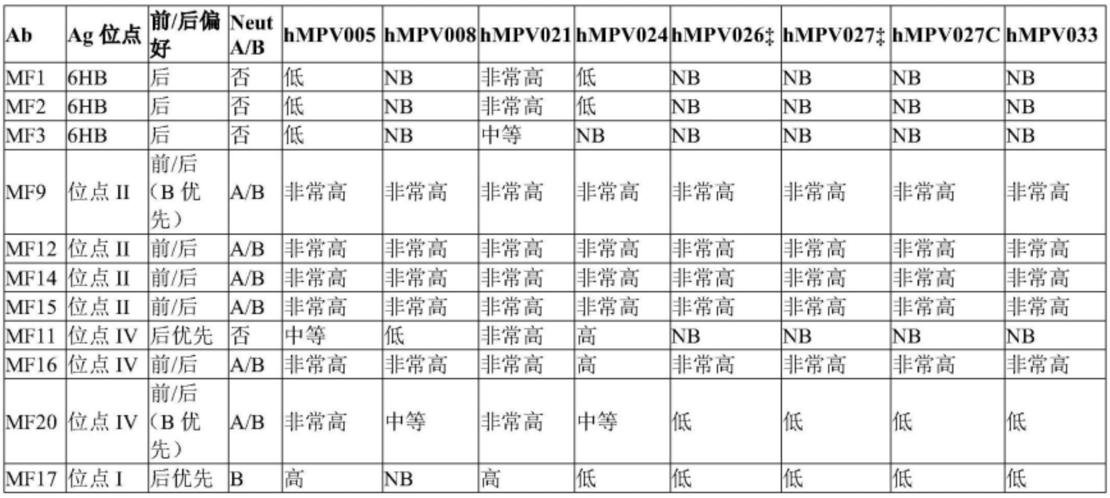
[0349]

抗原	剂量	调配物
hMPV008VLP	5μg	Addavax
hMPV008VLP	5μg	Alhydrogel

hMPV008VLP	0.25μg	Alhydrogel
hMPV008CompA	4.08μg	Alhydrogel
hMPV008CompA	0.2μg	Alhydrogel

[0350] 表5.与说明性CompA融合蛋白结合的抗体

[0351]



Ab	Ag 位点	前/后偏好	Neut A/B	hMPV005	hMPV008	hMPV021	hMPV024	hMPV026‡	hMPV027‡	hMPV027C	hMPV033
MF1	6HB	后	否	低	NB	非常高	低	NB	NB	NB	NB
MF2	6HB	后	否	低	NB	非常高	低	NB	NB	NB	NB
MF3	6HB	后	否	低	NB	中等	NB	NB	NB	NB	NB
MF9	位点 II	前/后（B 优先）	A/B	非常高	非常高	非常高	非常高	非常高	非常高	非常高	非常高
MF12	位点 II	前/后	A/B	非常高	非常高	非常高	非常高	非常高	非常高	非常高	非常高
MF14	位点 II	前/后	A/B	非常高	非常高	非常高	非常高	非常高	非常高	非常高	非常高
MF15	位点 II	前/后	A/B	非常高	非常高	非常高	非常高	非常高	非常高	非常高	非常高
MF11	位点 IV	后优先	否	中等	低	非常高	高	NB	NB	NB	NB
MF16	位点 IV	前/后	A/B	非常高	非常高	非常高	高	非常高	非常高	非常高	非常高
MF20	位点 IV	前/后（B 优先）	A/B	非常高	中等	非常高	中等	低	低	低	低
MF17	位点 I	后优先	B	高	NB	高	低	低	低	低	低

[0352]

MF18	位点 I	后优先	B	非常高	低	非常高	中等	低	低	低	低
MF19	位点 I	后优先	B	非常高	中等	非常高	中等	低	低	低	中等
MF10	位点 0	前（A 优先）	A	非常高	NB	NB	低	非常高	非常高	非常高	非常高
MPE8	位点 III	前	A/B	高	高	高	高	高	高	高	高

[0353] *非常高的应答表明OD450>2.0,高应答表明OD450>1.0但小于2.0,中等应答表明OD450>0.5但<1.0,并且低应答表明OD450>0.1但<0.5,并且NB(未结合)是<0.1。‡构建体保留了天然弗林蛋白酶切割位点。

[0354] 实例5

[0355] 在幼稚小鼠中进行了研究,以探索显示在2组分病毒样颗粒(VLP)上的免疫原性hMPV F蛋白突变体。测试了含有四种不同hMPV F蛋白突变体hMPV008、hMPV024、hMPV026C和hMPV033之一或对应于hMPV026C的可溶性蛋白的VLP。每组由8只雌性Balb/c小鼠组成。在第0天和第21天使小鼠免疫。所有测试物品均用Addavax,一种水包油佐剂,调配而成。施用两个剂量水平(1μg和0.25μg)或等效抗原含量的可溶性蛋白(表8)。针对抗hMPV/A和hMPV/B的中和抗体滴度由第35天的血清测定(分别地,图5A和5B)。结果表明,所有VLP均诱导了针对两种hMPV菌株的稳健中和滴度。可溶性蛋白还以低于VLP的水平诱导针对两种hMPV菌株的滴度。

[0356] 表8:注射的VLP的数量和调配物

[0357]

抗原	剂量	调配物
hMPV033VLP	1μg	Addavax
hMPV008VLP	1μg	Addavax
hMPV024VLP	1μg	Addavax
hMPV026C VLP	1μg	Addavax
hMPV033VLP	0.25μg	Addavax
hMPV008VLP	0.25μg	Addavax

hMPV024VLP	0.25μg	Addavax
hMPV026C VLP	0.25μg	Addavax
可溶性hMPV026C	0.64μg	Addavax
可溶性hMPV026C	0.16μg	Addavax
未处理	不适用	不适用

[0358] 实例6

[0359] 在幼稚小鼠中进行了研究，以探索hMPV008 VLP和对应的可溶性蛋白CompA-hMPV008的免疫原性。hMPV008 VLP和CompA-hMPV008在水性缓冲液、基于角鲨烯的佐剂(SE)或Alhydrogel中以两种剂量水平(1μg和0.1μg VLP以及CompA-hMPV008的等效抗原剂量)调制。另外，包含具有用SE调配的hMPV033 VLP(0.1μg)的一组(表9)。每组由8只雌性Balb/c小鼠组成。在第0天和第21天使小鼠免疫。针对抗hMPV/A和hMPV/B的中和抗体滴度由第35天的血清测定。结果表明，用SE调配的hMPV008 VLP引起比Alhydrogel或水性调配物的滴度更高的滴度(图6A和6B)。VLP用所有调配物诱导比可溶性蛋白CompA-hMPV008的中和滴度的更高的中和滴度(图6A和6B)。

[0360] 表9:注射的VLP的数量和调配物

[0361]

抗原	剂量	调配物
hMPV008VLP	1μg	SE
hMPV008VLP	1μg	Alhydrogel
hMPV08VLP	1μg	水溶液
hMPV008VLP	0.1μg	SE
hMPV008VLP	0.1μg	Alhydrogel
hMPV008VLP	0.1μg	水溶液
CompA-hMPV008	0.81μg	SE
CompA-hMPV008	0.81μg	Alhydrogel
CompA-hMPV008	0.81μg	水溶液
CompA-hMPV008	0.081μg	SE
CompA-hMPV008	0.081μg	Alhydrogel
CompA-hMPV008	0.081μg	水溶液
hMPV033	0.1μg	SE

[0362] 实例7

[0363] 在幼稚小鼠中进行了研究，以探索显示hMPV F蛋白突变体hMPV008的免疫原性VLP。每组由8只雌性Balb/c小鼠组成。使小鼠在第0天和第21天用通过Addavax，一种水包油佐剂，调配的hMPV008免疫。如表10所指示的，施用两种剂量水平(1ug和0.2ug)的VLP。由在第35天收集的血清样品测定hMPV/A和hMPV/B的中和抗体滴度。结果表明，具有两种剂量水平的hMPV008诱导了稳健的hMPV/A和hMPV/B中和滴度(图7A和7B)。

[0364] 表10:注射的VLP的数量和调配物

[0365]

抗原	剂量	调配物
hMPV008	1μg	Addavax
hMPV008	0.2μg	Addavax

[0366] 实例8

[0367] 在幼稚小鼠中进行了研究,以探索hMPV033的免疫原性。每组由8只雌性Balb/c小鼠组成。使小鼠在第0天和第21天用通过Addavax,一种水包油佐剂,在4种剂量水平(4、2、1和0.5μg)下调配的hMPV033免疫(表11)。由在第35天收集的血清样品测定hMPV/A和hMPV/B的中和抗体滴度。结果表明,具有所有剂量水平的hMPV033诱导了稳健的hMPV/A和hMPV/B中和滴度(图8A和8B)。

[0368] 表11:注射的VLP的数量和调配物

[0369]

抗原	剂量	调配物
hMPV033	4μg	Addavax
hMPV033	2μg	Addavax
hMPV033	1μg	Addavax
hMPV033	0.5μg	Addavax

[0370] 实例9

[0371] 在幼稚棉鼠中进行了研究,以评估和评价hMPV033保护棉鼠免受hMPV感染的能力。用Addavax调配的hMPV033在第0天和第21天以1μg的剂量水平施用(表12)。每组由8只雌性棉鼠组成。针对抗hMPV/A的中和滴度由第35天的血清样品测定(图9A)。各组在第35天用10^5pfu hMPV激发(表12),并且在第40天处死。在噬斑测定中由肺或鼻甲测定病毒滴度。结果证明hMPV033诱导了稳健的中和滴度(图9A)。对肺和鼻甲组织匀浆的噬斑测定证明,在对照动物的激发后,在肺和鼻甲中检测到高病毒滴度。相比之下,接种疫苗的棉鼠的病毒滴度低于肺和鼻甲样品的检测下限。(图9B和9C)。福尔马林灭活的hMPV疫苗接种不会防止随后的激发(图9B-9C)。

[0372] 表12:注射的VLP的数量和调配物

[0373]

抗原	剂量	调配物	hMPV激发
PBS	不适用	不适用	否
PBS	不适用	不适用	是
hMPV033	1μg	Addavax	是
福尔马林灭活的hMPV		不适用	是

[0374] ****

[0375] 虽然已经结合本发明提出的具体实施例描述了本发明,但应当理解,本发明能够进行进一步修改,并且本申请案旨在覆盖一般地遵循本发明的原理并且包含在本发明所属领域内的已知或惯常实践内出现的与本公开的这种偏离的任何变型、用途或改编,并且可以应用于上文阐述的基本特征和处于所附权利要求的范围内的以下内容。

序列表

<110> ICOSAVAX股份有限公司(ICOSAVAX, INC.)

<120> 用于偏肺病毒的基于蛋白质的纳米颗粒疫苗

<130> TPG03099A

<150> US 63/113,686

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

Ala Ser Ala Ala Ile Leu Thr Leu Lys Met Glu Ser Pro Asn Ile Lys
20 25 30
Ile Ile Arg Lys Thr Val Pro Gly Ile Lys Asp Leu Pro Val Ala Cys
35 40 45
Lys Lys Leu Leu Glu Glu Glu Gly Cys Asp Ile Val Met Ala Leu Gly
50 55 60
Met Pro Gly Lys Ala Glu Lys Asp Lys Val Cys Ala His Glu Ala Ser
65 70 75 80
Leu Gly Leu Met Leu Ala Gln Leu Met Thr Asn Lys His Ile Ile Glu
85 90 95
Val Phe Val His Glu Asp Glu Ala Lys Asp Asp Ala Glu Leu Lys Ile
100 105 110
Leu Ala Ala Arg Arg Ala Ile Glu His Ala Leu Asn Val Tyr Tyr Leu
115 120 125
Leu Phe Lys Pro Glu Tyr Leu Thr Arg Met Ala Gly Lys Gly Leu Arg
130 135 140
Gln Gly Phe Glu Asp Ala Gly Pro Ala Arg Glu
145 150 155
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<400> 4
Ser Thr Ile Asn Asn Gln Leu Lys Ala Leu Lys Val Ile Pro Val Ile
1 5 10 15
Ala Ile Asp Asn Ala Glu Asp Ile Ile Pro Leu Gly Lys Val Leu Ala
20 25 30
Glu Asn Gly Leu Pro Ala Ala Glu Ile Thr Phe Arg Ser Ser Ala Ala
35 40 45
Val Lys Ala Ile Met Leu Leu Arg Ser Ala Gln Pro Glu Met Leu Ile
50 55 60
Gly Ala Gly Thr Ile Leu Asn Gly Val Gln Ala Leu Ala Ala Lys Glu
65 70 75 80
Ala Gly Ala Thr Phe Val Val Ser Pro Gly Phe Asn Pro Asn Thr Val
85 90 95
Arg Ala Cys Gln Ile Ile Gly Ile Asp Ile Val Pro Gly Val Asn Asn
100 105 110

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

Phe Phe Pro Ala Glu Ala Ser Gly Gly Ile Ser Met Val Lys Ser Leu
130 135 140

Val Gly Pro Tyr Gly Asp Ile Arg Leu Met Pro Thr Gly Gly Ile Thr
145 150 155 160

Pro Ser Asn Ile Asp Asn Tyr Leu Ala Ile Pro Gln Val Leu Ala Cys
165 170 175

Gly Gly Thr Trp Met Val Asp Lys Lys Leu Val Thr Asn Gly Glu Trp
180 185 190

Asp Glu Ile Ala Arg Leu Thr Arg Glu Ile Val Glu Gln Val Asn Pro
195 200 205

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<400> 5

Pro Ile Phe Thr Leu Asn Thr Asn Ile Lys Ala Thr Asp Val Pro Ser
1 5 10 15

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

Pro Gly Ser Tyr Val Ala Val His Ile Asn Thr Asp Gln Gln Leu Ser
35 40 45

Phe Gly Gly Ser Thr Asn Pro Ala Ala Phe Gly Thr Leu Met Ser Ile
50 55 60

Gly Gly Ile Glu Pro Ser Lys Asn Arg Asp His Ser Ala Val Leu Phe
65 70 75 80

Asp His Leu Asn Ala Met Leu Gly Ile Pro Lys Asn Arg Met Tyr Ile
85 90 95

His Phe Val Asn Leu Asn Gly Asp Asp Val Gly Trp Asn Gly Thr Thr
100 105 110

Phe

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<223> 合成构建体

<400> 6

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

Arg Ala Arg Trp His Ala Asp Ile Val Asp Ala Cys Val Glu Ala Phe
20 25 30

Glu Ile Ala Met Ala Ala Ile Gly Gly Asp Arg Phe Ala Val Asp Val
35 40 45

Phe Asp Val Pro Gly Ala Tyr Glu Ile Pro Leu His Ala Arg Thr Leu
50 55 60

Ala Glu Thr Gly Arg Tyr Gly Ala Val Leu Gly Thr Ala Phe Val Val
65 70 75 80

Asn Gly Gly Ile Tyr Arg His Glu Phe Val Ala Ser Ala Val Ile Asp
85 90 95

Gly Met Met Asn Val Gln Leu Ser Thr Gly Val Pro Val Leu Ser Ala
100 105 110

Val Leu Thr Pro His Arg Tyr Arg Asp Ser Ala Glu His His Arg Phe
115 120 125

Phe Ala Ala His Phe Ala Val Lys Gly Val Glu Ala Ala Arg Ala Cys
130 135 140

Ile Glu Ile Leu Ala Ala Arg Glu Lys Ile Ala Ala
145 150 155

<210> 7

<211> 203

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 7

Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala
1 5 10 15

Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly
20 25 30

Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr
35 40 45

Val Ile Lys Ala Leu Ser Val Leu Lys Glu Lys Gly Ala Ile Ile Gly
50 55 60

Ala Gly Thr Val Thr Ser Val Glu Gln Cys Arg Lys Ala Val Glu Ser
65 70 75 80

Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
85 90 95
Phe Cys Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
100 105 110
Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
115 120 125
Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
130 135 140
Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
145 150 155 160
Asn Val Cys Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
165 170 175
Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
180 185 190
Ala Phe Val Glu Lys Ile Arg Gly Cys Thr Glu
195 200

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<211> 156
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<400> 8

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

Phe Leu Ala Leu Phe Ala Val Lys Gly Met Glu Ala Ala Arg Ala Cys
130 135 140

Val Glu Ile Leu Ala Ala Arg Glu Lys Ile Ala Ala
145 150 155

<210> 9

<211> 176

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 9

Phe Thr Lys Ser Gly Asp Asp Gly Asn Thr Asn Val Ile Asn Lys Arg
1 5 10 15

Val Gly Lys Asp Ser Pro Leu Val Asn Phe Leu Gly Asp Leu Asp Glu
20 25 30

Leu Asn Ser Phe Ile Gly Phe Ala Ile Ser Lys Ile Pro Trp Glu Asp
35 40 45

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

Glu Asp Leu Ser Thr Gln Ser Ser Lys Lys Lys Ile Asp Glu Ser Tyr
65 70 75 80

Val Leu Trp Leu Leu Ala Ala Thr Ala Ile Tyr Arg Ile Glu Ser Gly
85 90 95

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

Leu His Val Thr Arg Ser Val Ala Arg Arg Val Glu Arg Asn Ala Val
115 120 125

Lys Tyr Thr Lys Glu Leu Pro Glu Ile Asn Arg Met Ile Ile Val Tyr
130 135 140

Leu Asn Arg Leu Ser Ser Leu Leu Phe Ala Met Ala Leu Val Ala Asn
145 150 155 160

Lys Arg Arg Asn Gln Ser Glu Lys Ile Tyr Glu Ile Gly Lys Ser Trp
165 170 175

<210> 10

<211> 156

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 10

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

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<211> 200
<212> PRT
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<400> 11

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

85 90 95
Leu Thr Ala Leu Pro Thr Thr Thr Ala Ser Ser Thr Gly Pro Phe Asp
100 105 110
Ala Leu Ile Ala Ile Gly Val Leu Ile Lys Gly Glu Thr Met His Phe
115 120 125
Glu Tyr Ile Ala Asp Ser Val Ser His Gly Leu Met Arg Val Gln Leu
130 135 140
Asp Thr Gly Val Pro Val Ile Phe Gly Val Leu Thr Val Leu Thr Asp
145 150 155 160
Asp Gln Ala Lys Ala Arg Ala Gly Val Ile Glu Gly Ser His Asn His
165 170 175
Gly Glu Asp Trp Gly Leu Ala Ala Val Glu Met Gly Val Arg Arg Arg
180 185 190
Asp Trp Ala Ala Gly Lys Thr Glu
195 200

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<211> 236
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 12

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

130 135 140

Phe Ala Asp Gly Trp Val Ser Ala Asp Val Val Arg Arg Asp Gly Arg
145 150 155 160

Thr Val Ala Arg Val Ser His Ser Val Arg Glu Gly Asn Ala Thr Arg
165 170 175

Met Glu Val His Phe Thr Val Ala Asp Pro Gly Lys Gly Val Arg His
180 185 190

Phe Ser Asp Val His Leu Ile Thr Leu Phe His Gln Arg Glu Tyr Glu
195 200 205

Ala Ala Phe Met Ala Ala Gly Leu Arg Val Glu Tyr Leu Glu Gly Gly
210 215 220

Pro Ser Gly Arg Gly Leu Phe Val Gly Val Pro Ala
225 230 235

<210> 13
<211> 137
<212> PRT
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<223> 合成构建体
<400> 13

Gly Met Lys Glu Lys Phe Val Leu Ile Ile Thr His Gly Asp Phe Gly
1 5 10 15

Lys Gly Leu Leu Ser Gly Ala Glu Val Ile Ile Gly Lys Gln Glu Asn
20 25 30

Val His Thr Val Gly Leu Asn Leu Gly Asp Asn Ile Glu Lys Val Ala
35 40 45

Lys Glu Val Met Arg Ile Ile Ile Ala Lys Leu Ala Glu Asp Lys Glu
50 55 60

Ile Ile Ile Val Val Asp Leu Phe Gly Gly Ser Pro Phe Asn Ile Ala
65 70 75 80

Leu Glu Met Met Lys Thr Phe Asp Val Lys Val Ile Thr Gly Ile Asn
85 90 95

Met Pro Met Leu Val Glu Leu Leu Thr Ser Ile Asn Val Tyr Asp Thr
100 105 110

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

Val Ile Glu Lys Ser Ser Leu Lys Met
130 135

<210> 14

<211> 153

<212> PRT

<213> 人工序列

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<223> 合成构建体

<400> 14

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

<211> 163

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 15

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Ala Val Lys Gly Leu Gly Glu Val Asp Gln Lys Tyr Asp Gly Ser Lys
1               5                   10                  15
Leu Arg Ile Gly Ile Leu His Ala Arg Trp Asn Arg Lys Ile Ile Leu
            20                  25                  30
Ala Leu Val Ala Gly Ala Val Leu Arg Leu Leu Glu Phe Gly Val Lys
        35                  40                  45
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Ala Glu Asn Ile Ile Ile Glu Thr Val Pro Gly Ser Phe Glu Leu Pro
50 55 60
Tyr Gly Ser Lys Leu Phe Val Glu Lys Gln Lys Arg Leu Gly Lys Pro
65 70 75 80
Leu Asp Ala Ile Ile Pro Ile Gly Val Leu Ile Lys Gly Ser Thr Met
85 90 95
His Phe Glu Tyr Ile Cys Asp Ser Thr Thr His Gln Leu Met Lys Leu
100 105 110
Asn Phe Glu Leu Gly Ile Pro Val Ile Phe Gly Val Leu Thr Cys Leu
115 120 125
Thr Asp Glu Gln Ala Glu Ala Arg Ala Gly Leu Ile Glu Gly Lys Met
130 135 140
His Asn His Gly Glu Asp Trp Gly Ala Ala Ala Val Glu Met Ala Thr
145 150 155 160
Lys Phe Asn
<210> 16
<211> 174
<212> PRT
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<223> 合成构建体
<400> 16
Gly Ala Asn Trp Tyr Leu Asp Asn Glu Ser Ser Arg Leu Ser Phe Thr
1 5 10 15
Ser Thr Lys Asn Ala Asp Ile Ala Glu Val His Arg Phe Leu Val Leu
20 25 30
His Gly Lys Val Asp Pro Lys Gly Leu Ala Glu Val Glu Val Glu Thr
35 40 45
Glu Ser Ile Ser Thr Gly Ile Pro Leu Arg Asp Met Leu Leu Arg Val
50 55 60
Leu Val Phe Gln Val Ser Lys Phe Pro Val Ala Gln Ile Asn Ala Gln
65 70 75 80
Leu Asp Met Arg Pro Ile Asn Asn Leu Ala Pro Gly Ala Gln Leu Glu
85 90 95
Leu Arg Leu Pro Leu Thr Val Ser Leu Arg Gly Lys Ser His Ser Tyr
100 105 110
Asn Ala Glu Leu Leu Ala Thr Arg Leu Asp Glu Arg Arg Phe Gln Val
115 120 125
Val Thr Leu Glu Pro Leu Val Ile His Ala Gln Asp Phe Asp Met Val

130 135 140
Arg Ala Phe Asn Ala Leu Arg Leu Val Ala Gly Leu Ser Ala Val Ser
145 150 155 160
Leu Ser Val Pro Val Gly Ala Val Leu Ile Phe Thr Ala Arg
165 170

<210> 17
<211> 207
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 17

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

<210> 18

<211> 127
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 18
Ile Thr Val Phe Gly Leu Lys Ser Lys Leu Ala Pro Arg Arg Glu Lys
1 5 10 15
Leu Ala Glu Val Ile Tyr Ser Ser Leu His Leu Gly Leu Asp Ile Pro
20 25 30
Lys Gly Lys His Ala Ile Arg Phe Leu Cys Leu Glu Lys Glu Asp Phe
35 40 45
Tyr Tyr Pro Phe Asp Arg Ser Asp Asp Tyr Thr Val Ile Glu Ile Asn
50 55 60
Leu Met Ala Gly Arg Ser Glu Glu Thr Lys Met Leu Leu Ile Phe Leu
65 70 75 80
Leu Phe Ile Ala Leu Glu Arg Lys Leu Gly Ile Arg Ala His Asp Val
85 90 95
Glu Ile Thr Ile Lys Glu Gln Pro Ala His Cys Trp Gly Phe Arg Gly
100 105 110
Arg Thr Gly Asp Ser Ala Arg Asp Leu Asp Tyr Asp Ile Tyr Val
115 120 125
<210> 19
<211> 234
<212> PRT
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<223> 合成构建体
<400> 19
Gly Ser Asp Leu Gln Lys Leu Gln Arg Phe Ser Thr Cys Asp Ile Ser
1 5 10 15
Asp Gly Leu Leu Asn Val Tyr Asn Ile Pro Thr Gly Gly Tyr Phe Pro
20 25 30
Asn Leu Thr Ala Ile Ser Pro Pro Gln Asn Ser Ser Ile Val Gly Thr
35 40 45
Ala Tyr Thr Val Leu Phe Ala Pro Ile Asp Asp Pro Arg Pro Ala Val
50 55 60
Asn Tyr Ile Asp Ser Val Pro Pro Asn Ser Ile Leu Val Leu Ala Leu
65 70 75 80

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

<210> 20
<211> 161
<212> PRT
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<400> 20

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

Leu Ala Arg Glu His Asn Asn Ala Gln Leu Ile Gly Ile Gly Gly Arg
100 105 110
Met His Thr Leu Glu Glu Ala Leu Arg Ile Val Lys Ala Phe Val Thr
115 120 125
Thr Pro Trp Ser Lys Ala Gln Arg His Gln Arg Arg Ile Asp Ile Leu
130 135 140
Ala Glu Tyr Glu Arg Thr His Glu Ala Pro Pro Val Pro Gly Ala Pro
145 150 155 160
Ala
<210> 21
<211> 156
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 21
Gly Asp Asp Ala Arg Ile Ala Ala Ile Gly Asp Val Asp Glu Leu Asn
1 5 10 15
Ser Gln Ile Gly Val Leu Leu Ala Glu Pro Leu Pro Asp Asp Val Arg
20 25 30
Ala Ala Leu Ser Ala Ile Gln His Asp Leu Phe Asp Leu Gly Gly Glu
35 40 45
Leu Cys Ile Pro Gly His Ala Ala Ile Thr Glu Asp His Leu Leu Arg
50 55 60
Leu Ala Leu Trp Leu Val His Tyr Asn Gly Gln Leu Pro Pro Leu Glu
65 70 75 80
Glu Phe Ile Leu Pro Gly Gly Ala Arg Gly Ala Ala Leu Ala His Val
85 90 95
Cys Arg Thr Val Cys Arg Arg Ala Glu Arg Ser Ile Lys Ala Leu Gly
100 105 110
Ala Ser Glu Pro Leu Asn Ile Ala Pro Ala Ala Tyr Val Asn Leu Leu
115 120 125
Ser Asp Leu Leu Phe Val Leu Ala Arg Val Leu Asn Arg Ala Ala Gly
130 135 140
Gly Ala Asp Val Leu Trp Asp Arg Thr Arg Ala His
145 150 155
<210> 22
<211> 156
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<213> 人工序列
<220>
<223> 合成构建体
<400> 22
Ile Leu Ser Ala Glu Gln Ser Phe Thr Leu Arg His Pro His Gly Gln
1 5 10 15
Ala Ala Ala Leu Ala Phe Val Arg Glu Pro Ala Ala Ala Leu Ala Gly
20 25 30
Val Gln Arg Leu Arg Gly Leu Asp Ser Asp Gly Glu Gln Val Trp Gly
35 40 45
Glu Leu Leu Val Arg Val Pro Leu Leu Gly Glu Val Asp Leu Pro Phe
50 55 60
Arg Ser Glu Ile Val Arg Thr Pro Gln Gly Ala Glu Leu Arg Pro Leu
65 70 75 80
Thr Leu Thr Gly Glu Arg Ala Trp Val Ala Val Ser Gly Gln Ala Thr
85 90 95
Ala Ala Glu Gly Gly Glu Met Ala Phe Ala Phe Gln Phe Gln Ala His
100 105 110
Leu Ala Thr Pro Glu Ala Glu Gly Glu Gly Gly Ala Ala Phe Glu Val
115 120 125
Met Val Gln Ala Ala Ala Gly Val Thr Leu Leu Leu Val Ala Met Ala
130 135 140
Leu Pro Gln Gly Leu Ala Ala Gly Leu Pro Pro Ala
145 150 155
<210> 23
<211> 155
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<213> 人工序列
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<223> 合成构建体
<400> 23
Thr Lys Lys Val Gly Ile Val Asp Thr Thr Phe Ala Arg Val Asp Met
1 5 10 15
Ala Ser Ala Ala Ile Leu Thr Leu Lys Met Glu Ser Pro Asn Ile Lys
20 25 30
Ile Ile Arg Lys Thr Val Pro Gly Ile Lys Asp Leu Pro Val Ala Cys
35 40 45
Lys Lys Leu Leu Glu Glu Glu Gly Cys Asp Ile Val Met Ala Leu Gly
50 55 60

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

<210> 24
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<212> PRT
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<400> 24

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

Pro Asp Asn Ile Asp Asn Tyr Leu Ala Ile Pro Gln Val Leu Ala Cys
165 170 175

Gly Gly Thr Trp Met Val Asp Lys Lys Leu Val Arg Asn Gly Glu Trp
180 185 190

Asp Glu Ile Ala Arg Leu Thr Arg Glu Ile Val Glu Gln Val Asn Pro
195 200 205

<210> 25
<211> 113
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 25

Pro Ile Phe Thr Leu Asn Thr Asn Ile Lys Ala Asp Asp Val Pro Ser
1 5 10 15

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

Pro Gly Ser Tyr Val Ala Val His Ile Asn Thr Asp Gln Gln Leu Ser
35 40 45

Phe Gly Gly Ser Thr Asn Pro Ala Ala Phe Gly Thr Leu Met Ser Ile
50 55 60

Gly Gly Ile Glu Pro Asp Lys Asn Arg Asp His Ser Ala Val Leu Phe
65 70 75 80

Asp His Leu Asn Ala Met Leu Gly Ile Pro Lys Asn Arg Met Tyr Ile
85 90 95

His Phe Val Asn Leu Asn Gly Asp Asp Val Gly Trp Asn Gly Thr Thr
100 105 110

Phe

<210> 26
<211> 113
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 26

Pro Ile Phe Thr Leu Asn Thr Asn Ile Lys Ala Asp Asp Val Pro Ser
1 5 10 15

Asp Phe Leu Ser Leu Thr Ser Arg Leu Val Gly Leu Ile Leu Ser Glu
20 25 30

Pro Gly Ser Tyr Val Ala Val His Ile Asn Thr Asp Gln Gln Leu Ser
35 40 45
Phe Gly Gly Ser Thr Asn Pro Ala Ala Phe Gly Thr Leu Met Ser Ile
50 55 60
Gly Gly Ile Glu Pro Asp Lys Asn Glu Asp His Ser Ala Val Leu Phe
65 70 75 80
Asp His Leu Asn Ala Met Leu Gly Ile Pro Lys Asn Arg Met Tyr Ile
85 90 95
His Phe Val Asp Leu Asp Gly Asp Asp Val Gly Trp Asn Gly Thr Thr
100 105 110
Phe
<210> 27
<211> 156
<212> PRT
<213> 人工序列
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<400> 27
Asn Gln His Ser His Lys Asp His Glu Thr Val Arg Ile Ala Val Val
1 5 10 15
Arg Ala Arg Trp His Ala Asp Ile Val Asp Ala Cys Val Glu Ala Phe
20 25 30
Glu Ile Ala Met Ala Ala Ile Gly Gly Asp Arg Phe Ala Val Asp Val
35 40 45
Phe Asp Val Pro Gly Ala Tyr Glu Ile Pro Leu His Ala Arg Thr Leu
50 55 60
Ala Glu Thr Gly Arg Tyr Gly Ala Val Leu Gly Thr Ala Phe Val Val
65 70 75 80
Asn Gly Gly Ile Tyr Arg His Glu Phe Val Ala Ser Ala Val Ile Asp
85 90 95
Gly Met Met Asn Val Gln Leu Asp Thr Gly Val Pro Val Leu Ser Ala
100 105 110
Val Leu Thr Pro His Arg Tyr Arg Asp Ser Asp Glu His His Arg Phe
115 120 125
Phe Ala Ala His Phe Ala Val Lys Gly Val Glu Ala Ala Arg Ala Cys
130 135 140
Ile Glu Ile Leu Asn Ala Arg Glu Lys Ile Ala Ala
145 150 155
<210> 28

<211> 156
<212> PRT
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<400> 28
Asn Gln His Ser His Lys Asp His Glu Thr Val Arg Ile Ala Val Val
1 5 10 15
Arg Ala Arg Trp His Ala Asp Ile Val Asp Ala Cys Val Glu Ala Phe
20 25 30
Glu Ile Ala Met Ala Ala Ile Gly Gly Asp Arg Phe Ala Val Asp Val
35 40 45
Phe Asp Val Pro Gly Ala Tyr Glu Ile Pro Leu His Ala Arg Thr Leu
50 55 60
Ala Glu Thr Gly Arg Tyr Gly Ala Val Leu Gly Thr Ala Phe Val Val
65 70 75 80
Asp Gly Gly Ile Tyr Asp His Glu Phe Val Ala Ser Ala Val Ile Asp
85 90 95
Gly Met Met Asn Val Gln Leu Asp Thr Gly Val Pro Val Leu Ser Ala
100 105 110
Val Leu Thr Pro His Glu Tyr Glu Asp Ser Asp Glu Asp His Glu Phe
115 120 125
Phe Ala Ala His Phe Ala Val Lys Gly Val Glu Ala Ala Arg Ala Cys
130 135 140
Ile Glu Ile Leu Asn Ala Arg Glu Lys Ile Ala Ala
145 150 155
<210> 29
<211> 202
<212> PRT
<213> 人工序列
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<400> 29
Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala Asn
1 5 10 15
Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly Gly
20 25 30
Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr Val
35 40 45

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

<210> 30
<211> 202
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 30

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

Cys Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro Thr
100 105 110

Glu Leu Val Lys Ala Met Lys Leu Gly His Asp Ile Leu Lys Leu Phe
115 120 125

Pro Gly Glu Val Val Gly Pro Glu Phe Val Glu Ala Met Lys Gly Pro
130 135 140

Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asp Leu Asp Asp
145 150 155 160

Val Cys Glu Trp Phe Asp Ala Gly Val Leu Ala Val Gly Val Gly Asp
165 170 175

Ala Leu Val Glu Gly Asp Pro Asp Glu Val Arg Glu Asp Ala Lys Glu
180 185 190

Phe Val Glu Glu Ile Arg Gly Cys Thr Glu
195 200

<210> 31

<211> 202

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 31

Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala Asn
1 5 10 15

Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly Gly
20 25 30

Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr Val
35 40 45

Ile Lys Ala Leu Ser Val Leu Lys Glu Lys Gly Ala Ile Ile Gly Ala
50 55 60

Gly Thr Val Thr Ser Val Glu Gln Cys Arg Lys Ala Val Glu Ser Gly
65 70 75 80

Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln Phe
85 90 95

Cys Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro Thr
100 105 110

Glu Leu Val Lys Ala Met Lys Leu Gly His Asp Ile Leu Lys Leu Phe
115 120 125

Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly Pro
130 135 140

Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp Asn
145 150 155 160
Val Cys Lys Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly Lys
165 170 175
Ala Leu Val Lys Gly Lys Pro Asp Glu Val Arg Glu Lys Ala Lys Lys
180 185 190
Phe Val Lys Lys Ile Arg Gly Cys Thr Glu
195 200

<210> 32
<211> 156
<212> PRT
<213> 人工序列
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<400> 32

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

<210> 33
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<212> PRT
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<220>

<223> 合成构建体

<400> 33

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Asn Gln His Ser His Lys Asp His Glu Thr Val Arg Ile Ala Val Val
1               5                   10                  15
Arg Ala Arg Trp His Ala Glu Ile Val Asp Ala Cys Val Ser Ala Phe
            20                  25                  30
Glu Ala Ala Met Arg Asp Ile Gly Gly Asp Arg Phe Ala Val Asp Val
        35                  40                  45
Phe Asp Val Pro Gly Ala Tyr Glu Ile Pro Leu His Ala Arg Thr Leu
    50                  55                  60
Ala Glu Thr Gly Arg Tyr Gly Ala Val Leu Gly Thr Ala Phe Val Val
65                  70                  75                  80
Asp Gly Gly Ile Tyr Asp His Glu Phe Val Ala Ser Ala Val Ile Asp
                85                  90                  95
Gly Met Met Asn Val Gln Leu Asp Thr Gly Val Pro Val Leu Ser Ala
            100                 105                 110
Val Leu Thr Pro His Glu Tyr Glu Asp Ser Asp Ala Asp Thr Leu Leu
        115                 120                 125
Phe Leu Ala Leu Phe Ala Val Lys Gly Met Glu Ala Ala Arg Ala Cys
    130                 135                 140
Val Glu Ile Leu Ala Ala Arg Glu Lys Ile Ala Ala
145                 150                 155
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<210> 34

<211> 156

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 34

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

65 70 75 80
Asn Gly Gly Ile Tyr Arg His Glu Phe Val Ala Ser Ala Val Ile Asn
85 90 95
Gly Met Met Asn Val Gln Leu Asn Thr Gly Val Pro Val Leu Ser Ala
100 105 110
Val Leu Thr Pro His Asn Tyr Asp Lys Ser Lys Ala His Thr Leu Leu
115 120 125
Phe Leu Ala Leu Phe Ala Val Lys Gly Met Glu Ala Ala Arg Ala Cys
130 135 140
Val Glu Ile Leu Ala Ala Arg Glu Lys Ile Ala Ala
145 150 155
<210> 35
<211> 155
<212> PRT
<213> 人工序列
<220>
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<222> (69)..(69)
<223> Xaa是Ala或Lys
<400> 35
Thr Lys Lys Val Gly Ile Val Asp Thr Thr Phe Ala Arg Val Asp Met
1 5 10 15
Ala Ser Ala Ala Ile Leu Thr Leu Lys Met Glu Ser Pro Asn Ile Lys
20 25 30
Ile Ile Arg Lys Thr Val Pro Gly Ile Lys Asp Leu Pro Val Ala Cys
35 40 45
Lys Lys Leu Leu Glu Glu Glu Gly Cys Asp Ile Val Met Ala Leu Gly
50 55 60
Met Pro Gly Lys Xaa Glu Lys Asp Lys Val Cys Ala His Glu Ala Ser
65 70 75 80
Leu Gly Leu Met Leu Ala Gln Leu Met Thr Asn Lys His Ile Ile Glu
85 90 95
Val Phe Val His Glu Asp Glu Ala Lys Asp Asp Ala Glu Leu Lys Ile
100 105 110
Leu Ala Ala Arg Arg Ala Ile Glu His Ala Leu Asn Val Tyr Tyr Leu
115 120 125
Leu Phe Lys Pro Glu Tyr Leu Thr Arg Met Ala Gly Lys Gly Leu Arg

130 135 140

Gln Gly Phe Glu Asp Ala Gly Pro Ala Arg Glu

145 150 155

<210> 36

<211> 208

<212> PRT

<213> 人工序列

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<223> 合成构建体

<220>

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<222> (1)..(1)

<223> Xaa是Ser或Asp

<220>

<221> SITE

<222> (2)..(2)

<223> Xaa是Thr或Asp

<220>

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<222> (9)..(9)

<223> Xaa是Ala或Arg

<220>

<221> SITE

<222> (84)..(84)

<223> Xaa是Thr或Asp

<220>

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<222> (118)..(118)

<223> Xaa是Ala或Gln

<220>

<221> SITE

<222> (162)..(162)

<223> Xaa是Ser或Asp

<220>

<221> SITE

<222> (188)..(188)

<223> Xaa是Thr或Arg

<400> 36

Xaa Xaa Ile Asn Asn Gln Leu Lys Xaa Leu Lys Val Ile Pro Val Ile

1 5 10 15
Ala Ile Asp Asn Ala Glu Asp Ile Ile Pro Leu Gly Lys Val Leu Ala
20 25 30
Glu Asn Gly Leu Pro Ala Ala Glu Ile Thr Phe Arg Ser Ser Ala Ala
35 40 45
Val Lys Ala Ile Met Leu Leu Arg Ser Ala Gln Pro Glu Met Leu Ile
50 55 60
Gly Ala Gly Thr Ile Leu Asn Gly Val Gln Ala Leu Ala Ala Lys Glu
65 70 75 80
Ala Gly Ala Xaa Phe Val Val Ser Pro Gly Phe Asn Pro Asn Thr Val
85 90 95
Arg Ala Cys Gln Ile Ile Gly Ile Asp Ile Val Pro Gly Val Asn Asn
100 105 110
Pro Ser Thr Val Glu Xaa Ala Leu Glu Met Gly Leu Thr Thr Leu Lys
115 120 125
Phe Phe Pro Ala Glu Ala Ser Gly Gly Ile Ser Met Val Lys Ser Leu
130 135 140
Val Gly Pro Tyr Gly Asp Ile Arg Leu Met Pro Thr Gly Gly Ile Thr
145 150 155 160
Pro Xaa Asn Ile Asp Asn Tyr Leu Ala Ile Pro Gln Val Leu Ala Cys
165 170 175
Gly Gly Thr Trp Met Val Asp Lys Lys Leu Val Xaa Asn Gly Glu Trp
180 185 190
Asp Glu Ile Ala Arg Leu Thr Arg Glu Ile Val Glu Gln Val Asn Pro
195 200 205
<210> 37
<211> 113
<212> PRT
<213> 人工序列
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<222> (12)..(12)
<223> Xaa是Thr或Asp
<220>
<221> SITE
<222> (32)..(32)
<223> Xaa是Lys或Glu

<220>
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<222> (70)..(70)
<223> Xaa是Ser或Asp
<220>
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<222> (73)..(73)
<223> Xaa是Arg或Glu
<220>
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<222> (100)..(100)
<223> Xaa是Asn或Asp
<220>
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<222> (102)..(102)
<223> Xaa是Asn或Asp
<400> 37

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Pro Ile Phe Thr Leu Asn Thr Asn Ile Lys Ala Xaa Asp Val Pro Ser
1               5                   10                  15
Asp Phe Leu Ser Leu Thr Ser Arg Leu Val Gly Leu Ile Leu Ser Xaa
            20                  25                  30
Pro Gly Ser Tyr Val Ala Val His Ile Asn Thr Asp Gln Gln Leu Ser
        35                  40                  45
Phe Gly Gly Ser Thr Asn Pro Ala Ala Phe Gly Thr Leu Met Ser Ile
    50                  55                  60
Gly Gly Ile Glu Pro Xaa Lys Asn Xaa Asp His Ser Ala Val Leu Phe
65                  70                  75                  80
Asp His Leu Asn Ala Met Leu Gly Ile Pro Lys Asn Arg Met Tyr Ile
                85                  90                  95
His Phe Val Xaa Leu Xaa Gly Asp Asp Val Gly Trp Asn Gly Thr Thr
            100                 105                 110
Phe
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<210> 38
<211> 156
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<222> (8)..(8)
<223> Xaa是Tyr或His
<220>
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<222> (81)..(81)
<223> Xaa是Asn或Asp
<220>
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<222> (86)..(86)
<223> Xaa是Arg或Asp
<220>
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<222> (104)..(104)
<223> Xaa是Ser或Asp
<220>
<221> SITE
<222> (118)..(118)
<223> Xaa是Arg或Glu
<220>
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<222> (120)..(120)
<223> Xaa是Arg或Glu
<220>
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<222> (123)..(123)
<223> Xaa是Ala或Asp
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<222> (125)..(125)
<223> Xaa是His或Asp
<220>
<221> SITE
<222> (127)..(127)
<223> Xaa是Arg或Glu
<220>
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<222> (149)..(149)
<223> Xaa是Ala或Asn

<400> 38

Asn Gln His Ser His Lys Asp Xaa Glu Thr Val Arg Ile Ala Val Val
1 5 10 15

Arg Ala Arg Trp His Ala Asp Ile Val Asp Ala Cys Val Glu Ala Phe
20 25 30

Glu Ile Ala Met Ala Ala Ile Gly Gly Asp Arg Phe Ala Val Asp Val
35 40 45

Phe Asp Val Pro Gly Ala Tyr Glu Ile Pro Leu His Ala Arg Thr Leu
50 55 60

Ala Glu Thr Gly Arg Tyr Gly Ala Val Leu Gly Thr Ala Phe Val Val
65 70 75 80

Xaa Gly Gly Ile Tyr Xaa His Glu Phe Val Ala Ser Ala Val Ile Asp
85 90 95

Gly Met Met Asn Val Gln Leu Xaa Thr Gly Val Pro Val Leu Ser Ala
100 105 110

Val Leu Thr Pro His Xaa Tyr Xaa Asp Ser Xaa Glu Xaa His Xaa Phe
115 120 125

Phe Ala Ala His Phe Ala Val Lys Gly Val Glu Ala Ala Arg Ala Cys
130 135 140

Ile Glu Ile Leu Xaa Ala Arg Glu Lys Ile Ala Ala
145 150 155

<210> 39

<211> 202

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<220>

<221> SITE

<222> (123)..(123)

<223> Xaa是Thr或Asp

<220>

<221> SITE

<222> (136)..(136)

<223> Xaa是Gln或Glu

<220>

<221> SITE

<222> (139)..(139)

<223> Xaa是Lys或Glu

<220>
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<222> (157)..(157)
<223> Xaa是Asn或Asp
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<222> (160)..(160)
<223> Xaa是Asn或Asp
<220>
<221> SITE
<222> (163)..(163)
<223> Xaa是Glu或Lys
<220>
<221> SITE
<222> (166)..(166)
<223> Xaa是Lys或Asp
<220>
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<222> (176)..(176)
<223> Xaa是Ser、Lys或Asp
<220>
<221> SITE
<222> (180)..(180)
<223> Xaa是Lys或Glu
<220>
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<222> (182)..(182)
<223> Xaa是Thr、Asp或Lys
<220>
<221> SITE
<222> (189)..(189)
<223> Xaa是Lys或Asp
<220>
<221> SITE
<222> (192)..(192)
<223> Xaa是Ala、Glu或Lys
<220>
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<222> (195)..(195)

<223> Xaa是Glu或Lys
<220>
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<222> (196)..(196)
<223> Xaa是Lys或Glu
<400> 39

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

<210> 40
<211> 156
<212> PRT
<213> 人工序列
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<221> SITE
<222> (8)..(8)
<223> Xaa是Tyr或His
<220>
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<222> (37)..(37)
<223> Xaa是Ala或Arg
<220>
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<222> (81)..(81)
<223> Xaa是Asn或Asp
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<222> (86)..(86)
<223> Xaa是Arg或Asp
<220>
<221> SITE
<222> (96)..(96)
<223> Xaa是Asp或Asn
<220>
<221> SITE
<222> (104)..(104)
<223> Xaa是Ser、Asp或Asn
<220>
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<222> (118)..(118)
<223> Xaa是Arg、Glu或Asn
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<222> (120)..(121)
<223> Xaa是Arg、Asp或Glu
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<222> (123)..(123)
<223> Xaa是Asp或Lys

<220>
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<222> (125)..(125)
<223> Xaa是His或Asp
<400> 40
Asn Gln His Ser His Lys Asp Xaa Glu Thr Val Arg Ile Ala Val Val
1 5 10 15
Arg Ala Arg Trp His Ala Glu Ile Val Asp Ala Cys Val Ser Ala Phe
20 25 30
Glu Ala Ala Met Xaa Asp Ile Gly Gly Asp Arg Phe Ala Val Asp Val
35 40 45
Phe Asp Val Pro Gly Ala Tyr Glu Ile Pro Leu His Ala Arg Thr Leu
50 55 60
Ala Glu Thr Gly Arg Tyr Gly Ala Val Leu Gly Thr Ala Phe Val Val
65 70 75 80
Xaa Gly Gly Ile Tyr Xaa His Glu Phe Val Ala Ser Ala Val Ile Xaa
85 90 95
Gly Met Met Asn Val Gln Leu Xaa Thr Gly Val Pro Val Leu Ser Ala
100 105 110
Val Leu Thr Pro His Xaa Tyr Xaa Xaa Ser Xaa Ala Xaa Thr Leu Leu
115 120 125
Phe Leu Ala Leu Phe Ala Val Lys Gly Met Glu Ala Ala Arg Ala Cys
130 135 140
Val Glu Ile Leu Ala Ala Arg Glu Lys Ile Ala Ala
145 150 155
<210> 41
<211> 158
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 41
Gly Glu Val Pro Ile Gly Asp Pro Lys Glu Leu Asn Gly Met Glu Ile
1 5 10 15
Ala Ala Val Tyr Leu Gln Pro Ile Glu Met Glu Pro Arg Gly Ile Asp
20 25 30
Leu Ala Ala Ser Leu Ala Asp Ile His Leu Glu Ala Asp Ile His Ala
35 40 45
Leu Lys Asn Asn Pro Asn Gly Phe Pro Glu Gly Phe Trp Met Pro Tyr

50 55 60

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

Thr Gly Thr Leu Met Pro Met Val Ala Asp Asp Gly Pro His Tyr Gly
85 90 95

Ala Asn Ile Ala Met Glu Lys Asp Lys Lys Gly Gly Phe Gly Val Gly
100 105 110

Thr Tyr Ala Leu Thr Phe Leu Ile Ser Asn Pro Glu Lys Gln Gly Phe
115 120 125

Gly Arg His Val Asp Glu Glu Thr Gly Val Gly Lys Trp Phe Glu Pro
130 135 140

Phe Val Val Thr Tyr Phe Phe Lys Tyr Thr Gly Thr Pro Lys
145 150 155

<210> 42
<211> 183
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 42

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

Glu Leu Gly Asp Ala Met Leu Lys Ser Ala Asn Val Asp Leu Leu Val
20 25 30

Ser Lys Thr Ile Ser Pro Gly Lys Phe Leu Leu Met Leu Gly Gly Asp
35 40 45

Ile Gly Ala Ile Gln Gln Ala Ile Glu Thr Gly Thr Ser Gln Ala Gly
50 55 60

Glu Met Leu Val Asp Ser Leu Val Leu Ala Asn Ile His Pro Ser Val
65 70 75 80

Leu Pro Ala Ile Ser Gly Leu Asn Ser Val Asp Lys Arg Gln Ala Val
85 90 95

Gly Ile Val Glu Thr Trp Ser Val Ala Ala Cys Ile Ser Ala Ala Asp
100 105 110

Leu Ala Val Lys Gly Ser Asn Val Thr Leu Val Arg Val His Met Ala
115 120 125

Phe Gly Ile Gly Gly Lys Cys Tyr Met Val Val Ala Gly Asp Val Leu
130 135 140

Asp Val Ala Ala Ala Val Ala Thr Ala Ser Leu Ala Ala Gly Ala Lys

145 150 155 160
Gly Leu Leu Val Tyr Ala Ser Ile Ile Pro Arg Pro His Glu Ala Met
165 170 175
Trp Arg Gln Met Val Glu Gly
180

<210> 43
<211> 102
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 43

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

<210> 44
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 44

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

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

<210> 45
<211> 176
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 45

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

<210> 46
<211> 121
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 46

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

<210> 47
<211> 171
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 47

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

65 70 75 80

Glu Arg Ile Ala Trp Leu Leu Lys Leu Ile Leu Arg Tyr Met Glu Met

85 90 95

Val Asn Leu Lys Ser Phe Val Leu Pro Gly Gly Thr Leu Glu Ser Ala

100 105 110

Lys Leu Asp Val Cys Arg Thr Ile Ala Arg Arg Ala Leu Arg Lys Val

115 120 125

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

130 135 140

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

145 150 155 160

Ile Glu Lys Asn Lys Leu Lys Glu Val Arg Ser

165 170

<210> 48

<211> 122

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 48

Pro His Leu Val Ile Glu Ala Thr Ala Asn Leu Arg Leu Glu Thr Ser

1 5 10 15

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

20 25 30

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

35 40 45

Tyr Arg Gln Gly Thr Ala Ala Val Glu Arg Ala Tyr Leu His Ala Cys

50 55 60

Leu Ser Ile Leu Asp Gly Arg Asp Ile Ala Thr Arg Thr Leu Leu Gly

65 70 75 80

Ala Ser Leu Cys Ala Val Leu Ala Glu Ala Val Ala Gly Gly Gly Glu

85 90 95

Glu Gly Val Gln Val Ser Val Glu Val Arg Glu Met Glu Arg Leu Ser

100 105 110

Tyr Ala Lys Arg Val Val Ala Arg Gln Arg

115 120

<210> 49

<211> 157

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 49

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

<210> 50

<211> 112

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 50

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

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

<210> 51
<211> 102
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 51

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

<210> 52
<211> 4
<212> PRT
<213> 人工序列
<220>
<223> 弗林蛋白酶切割位点
<220>
<221> SITE
<222> (2)..(3)
<223> Xaa是任何氨基酸
<400> 52

Arg Xaa Xaa Arg

1
<210> 53
<211> 203
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 53
Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala
1 5 10 15
Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly
20 25 30
Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr
35 40 45
Val Ile Lys Ala Leu Ser Val Leu Lys Glu Lys Gly Ala Ile Ile Gly
50 55 60
Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser
65 70 75 80
Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
85 90 95
Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
100 105 110
Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
115 120 125
Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
130 135 140
Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
145 150 155 160
Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
165 170 175
Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
180 185 190
Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu
195 200
<210> 54
<211> 4
<212> PRT
<213> 人工序列
<220>

<223> 弗林蛋白酶切割位点

<400> 54

Arg Gln Ser Arg

1

<210> 55

<211> 4

<212> PRT

<213> 人工序列

<220>

<223> 弗林蛋白酶切割位点

<400> 55

Arg Arg Arg Arg

1

<210> 56

<211> 539

<212> PRT

<213> 人偏肺病毒

<400> 56

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln

1 5 10 15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr

20 25 30

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

35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro

50 55 60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu

65 70 75 80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu

85 90 95

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

100 105 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile

115 120 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Thr Thr

130 135 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr

145 150 155 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala

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

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
485 490 495
Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
500 505 510
Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
515 520 525
Gly Val Thr Asn Asn Gly Phe Ile Pro His Ser
530 535

<210> 57
<211> 472
<212> PRT
<213> 人偏肺病毒
<400> 57

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

Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
210 215 220
Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Ile Leu
225 230 235 240
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
245 250 255
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
260 265 270
Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
275 280 285
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
290 295 300
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
305 310 315 320
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
325 330 335
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
340 345 350
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
355 360 365
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
370 375 380
Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400
Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415
Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile Lys Phe
420 425 430
Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Asn Ile
435 440 445
Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile Leu Ser Ser
450 455 460
Ala Glu Lys Gly Asn Thr Gly Phe
465 470
<210> 58
<211> 462
<212> PRT
<213> 人工序列
<220>

<223> 合成构建体

<400> 58

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

290 295 300

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
305 310 315 320

Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
325 330 335

Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
340 345 350

Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
355 360 365

Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
370 375 380

Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400

Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415

Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Val Lys Phe
420 425 430

Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile
435 440 445

Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile Leu
450 455 460

<210> 59
<211> 453
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 59

Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15

Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30

Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro Ser Leu Ile
35 40 45

Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Arg Thr
50 55 60

Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Asn Pro Arg
65 70 75 80

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

85 90 95

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

100 105 110

Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr Asn Glu Ala

115 120 125

Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr Ala Val Arg

130 135 140

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

145 150 155 160

Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser Phe Ser Gln

165 170 175

Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala

180 185 190

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

195 200 205

Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln Ile Lys Leu

210 215 220

Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Phe Leu

225 230 235 240

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile

245 250 255

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser

260 265 270

Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln

275 280 285

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

290 295 300

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala

305 310 315 320

Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser

325 330 335

Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser

340 345 350

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

355 360 365

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

370 375 380

Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr

385 390 395 400

Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415
Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Val Lys Phe
420 425 430
Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile
435 440 445
Glu Asn Ser Gln Ala
450
<210> 60
<211> 470
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 60
Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15
Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30
Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro Ser Leu Ile
35 40 45
Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Arg Thr
50 55 60
Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Asn Pro Arg
65 70 75 80
Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val Ala Thr Ala
85 90 95
Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile Arg Leu Glu
100 105 110
Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr Asn Glu Ala
115 120 125
Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr Ala Val Arg
130 135 140
Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala Ile Asn Lys
145 150 155 160
Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser Phe Ser Gln
165 170 175
Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala
180 185 190

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

<210> 61

<211> 453

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 61

Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15

Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30

Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro Ser Leu Ile
35 40 45

Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Arg Thr
50 55 60

Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Asn Pro Arg
65 70 75 80

Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val Ala Thr Ala
85 90 95

Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile Arg Leu Glu
100 105 110

Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr Asn Glu Ala
115 120 125

Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr Ala Val Arg
130 135 140

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

Asn Lys Cys Asp Ile Ala Asp Leu Lys Met Ala Val Ser Phe Ser Gln
165 170 175

Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala
180 185 190

Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp Ala Glu Leu
195 200 205

Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
210 215 220

Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Phe Leu
225 230 235 240

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
245 250 255

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
260 265 270

Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln

275 280 285

Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
290 295 300

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
305 310 315 320

Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
325 330 335

Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
340 345 350

Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
355 360 365

Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
370 375 380

Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400

Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415

Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Val Lys Phe
420 425 430

Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile
435 440 445

Glu Asn Ser Gln Ala
450

<210> 62
<211> 453
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 62

Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15

Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30

Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro Ser Leu Ile
35 40 45

Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Arg Thr
50 55 60

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

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

Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400
Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415
Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Val Lys Phe
420 425 430
Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile
435 440 445
Glu Asn Ser Gln Ala
450

<210> 63
<211> 453
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 63

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

Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala
180 185 190
Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp Ala Glu Leu
195 200 205
Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
210 215 220
Met Leu Glu Asn Arg Cys Met Val Arg Arg Lys Gly Phe Gly Ile Leu
225 230 235 240
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
245 250 255
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
260 265 270
Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
275 280 285
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Asp
290 295 300
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
305 310 315 320
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
325 330 335
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
340 345 350
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
355 360 365
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
370 375 380
Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400
Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415
Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile Lys Phe
420 425 430
Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile
435 440 445
Glu Asn Ser Gln Ala
450
<210> 64
<211> 469
<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 64

Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1   5   10   15

Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
            20   25   30

Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro Ser Leu Ile
        35   40   45

Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Lys Thr
    50   55   60

Cys Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Gly Gly Gly
65   70   75   80

Gly Gly Gly Phe Val Leu Gly Ala Ile Ala Leu Gly Val Ala Thr Ala
                85   90   95

Ala Ala Val Thr Ala Gly Ile Ala Ile Ala Lys Thr Ile Arg Leu Glu
            100   105   110

Ser Glu Val Asn Ala Ile Lys Gly Cys Leu Lys Thr Thr Asn Glu Cys
        115   120   125

Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr Ala Val Arg
    130   135   140

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

Asn Lys Cys Asp Ile Ala Asp Leu Lys Met Ala Val Ser Phe Ser Gln
                165   170   175

Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala
            180   185   190

Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp Ala Glu Leu
        195   200   205

Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
    210   215   220

Met Leu Glu Asn Arg Cys Met Val Arg Arg Lys Gly Phe Gly Ile Leu
225   230   235   240

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
                245   250   255

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
            260   265   270

Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln

275 280 285

Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Asp
290 295 300

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
305 310 315 320

Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
325 330 335

Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
340 345 350

Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
355 360 365

Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
370 375 380

Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400

Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415

Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile Lys Phe
420 425 430

Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile
435 440 445

Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Lys Ile Leu Asn Ser
450 455 460

Ala Glu Ser Ala Ile
465

<210> 65
<211> 453
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 65

Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15

Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30

Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Cys Pro Ser Leu Ile
35 40 45

Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Lys Thr

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

Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
370 375 380
Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400
Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415
Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile Cys Phe
420 425 430
Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile
435 440 445
Glu Asn Cys Gln Ala
450
<210> 66
<211> 469
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 66
Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15
Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30
Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Cys Pro Ser Leu Ile
35 40 45
Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Lys Thr
50 55 60
Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Gly Gly Gly
65 70 75 80
Gly Gly Gly Phe Val Leu Gly Ala Ile Ala Leu Gly Val Ala Thr Ala
85 90 95
Ala Ala Val Thr Ala Gly Ile Ala Ile Ala Lys Thr Ile Arg Leu Glu
100 105 110
Ser Glu Val Asn Ala Ile Lys Gly Cys Leu Lys Thr Thr Asn Glu Cys
115 120 125
Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr Ala Val Arg
130 135 140
Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala Ile Asn Lys
145 150 155 160

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Asn Lys Cys Asp Ile Ala Asp Leu Cys Met Ala Val Ser Phe Ser Gln
                165                 170                 175
Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala
            180                 185                 190
Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp Ala Glu Leu
        195                 200                 205
Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
    210                 215                 220
Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Ile Leu
225                 230                 235                 240
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
                245                 250                 255
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
            260                 265                 270
Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
        275                 280                 285
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Asp
    290                 295                 300
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
305                 310                 315                 320
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
                325                 330                 335
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
            340                 345                 350
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
        355                 360                 365
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
    370                 375                 380
Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385                 390                 395                 400
Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
                405                 410                 415
Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile Cys Phe
            420                 425                 430
Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile
        435                 440                 445
Glu Asn Cys Gln Ala Leu Val Asp Gln Ser Asn Lys Ile Leu Asn Ser
    450                 455                 460
Ala Glu Ser Ala Ile
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465
<210> 67
<211> 452
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 67
Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15
Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30
Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Cys Pro Ser Leu Ile
35 40 45
Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Lys Thr
50 55 60
Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Gly Gly Gly
65 70 75 80
Gly Gly Gly Phe Val Leu Ala Ile Ala Leu Gly Val Ala Thr Ala Ala
85 90 95
Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile Arg Leu Glu Ser
100 105 110
Glu Val Thr Ala Ile Lys Asn Cys Leu Lys Thr Thr Asn Glu Cys Val
115 120 125
Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr Ala Val Arg Glu
130 135 140
Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Ser Ala Ile Asn Lys Asn
145 150 155 160
Lys Cys Asp Ile Asp Asp Leu Cys Met Ala Val Ser Phe Ser Gln Phe
165 170 175
Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala Gly
180 185 190
Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp Ala Glu Leu Ala
195 200 205
Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln Ile Lys Leu Met
210 215 220
Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Ile Leu Ile
225 230 235 240
Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile Phe

245 250 255

Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser Cys
260 265 270

Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln Gly
275 280 285

Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu Lys
290 295 300

Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala Gly
305 310 315 320

Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser Thr
325 330 335

Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser Met
340 345 350

Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly Val
355 360 365

Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu Asn
370 375 380

Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr Ile
385 390 395 400

Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His Val
405 410 415

Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile Lys Phe Pro
420 425 430

Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Asn Ile Glu
435 440 445

Asn Ser Gln Ala
450

<210> 68

<211> 468

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 68

Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15

Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30

Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Cys Pro Ser Leu Ile

35 40 45

Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Lys Thr

50 55 60

Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Gly Gly Gly

65 70 75 80

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

85 90 95

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

100 105 110

Glu Val Thr Ala Ile Lys Asn Cys Leu Lys Thr Thr Asn Glu Cys Val

115 120 125

Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr Ala Val Arg Glu

130 135 140

Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Ser Ala Ile Asn Lys Asn

145 150 155 160

Lys Cys Asp Ile Asp Asp Leu Cys Met Ala Val Ser Phe Ser Gln Phe

165 170 175

Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala Gly

180 185 190

Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp Ala Glu Leu Ala

195 200 205

Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln Ile Lys Leu Met

210 215 220

Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Ile Leu Ile

225 230 235 240

Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile Phe

245 250 255

Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser Cys

260 265 270

Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln Gly

275 280 285

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

290 295 300

Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala Gly

305 310 315 320

Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser Thr

325 330 335

Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser Met

340 345 350

Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly Val
355 360 365

Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu Asn
370 375 380

Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr Ile
385 390 395 400

Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His Val
405 410 415

Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile Lys Phe Pro
420 425 430

Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Asn Ile Glu
435 440 445

Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile Leu Ser Ser Ala
450 455 460

Glu Ser Ala Ile
465

<210> 69

<211> 453

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 69

Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15

Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30

Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro Ser Leu Ile
35 40 45

Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Lys Thr
50 55 60

Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Asn Pro Arg
65 70 75 80

Lys Ala Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val Cys Thr Ala
85 90 95

Ala Ala Val Thr Cys Gly Ile Ala Ile Ala Lys Thr Ile Arg Leu Glu
100 105 110

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

Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Phe Ala Val Arg
    130   135   140
Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala Leu Asn Lys
145   150   155   160
Asn Lys Cys Asp Ile Ala Asp Leu Lys Met Ala Val Ser Phe Ser Gln
                165   170   175
Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala
            180   185   190
Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp Ala Glu Leu
        195   200   205
Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
    210   215   220
Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Ile Leu
225   230   235   240
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
                245   250   255
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
            260   265   270
Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
        275   280   285
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Asp
    290   295   300
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Cys
305   310   315   320
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
                325   330   335
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
            340   345   350
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
        355   360   365
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
    370   375   380
Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385   390   395   400
Ile Asp Asn Thr Val Tyr Cys Leu Ser Lys Val Glu Gly Glu Gln His
                405   410   415
Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile Lys Phe
            420   425   430
Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile

435 440 445
Glu Asn Ser Gln Ala
450

<210> 70
<211> 469
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 70

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

225 230 235 240

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile

245 250 255

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser

260 265 270

Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln

275 280 285

Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Asp

290 295 300

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Cys

305 310 315 320

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

325 330 335

Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser

340 345 350

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

355 360 365

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

370 375 380

Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr

385 390 395 400

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

405 410 415

Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile Lys Phe

420 425 430

Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile

435 440 445

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

450 455 460

Ala Glu Ser Ala Ile

465

<210> 71

<211> 472

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 71

Met Ser Trp Lys Val Met Ile Ile Ile Ser Leu Leu Ile Thr Pro Gln

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

Pro Asn Asp Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335
Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile
340 345 350
Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
355 360 365
Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380
Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385 390 395 400
Lys Gln Leu Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
405 410 415
Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430
Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
435 440 445
Ile Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
450 455 460
Glu Ser Ile Glu Asn Ser Gln Ala
465 470
<210> 72
<211> 453
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 72
Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15
Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30
Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Cys Pro Ser Leu Ile
35 40 45
Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Lys Thr
50 55 60
Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Asn Pro Arg
65 70 75 80
Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val Ala Thr Ala
85 90 95

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

405 410 415

Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile Cys Phe

420 425 430

Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile

435 440 445

Glu Asn Cys Gln Ala

450

<210> 73

<211> 452

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 73

Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr

1 5 10 15

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

20 25 30

Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Cys Pro Ser Leu Ile

35 40 45

Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Lys Thr

50 55 60

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

65 70 75 80

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

85 90 95

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

100 105 110

Glu Val Thr Ala Ile Lys Asn Cys Leu Lys Thr Thr Asn Glu Cys Val

115 120 125

Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr Ala Val Arg Glu

130 135 140

Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Ser Ala Ile Asn Lys Asn

145 150 155 160

Lys Cys Asp Ile Asp Asp Leu Cys Met Ala Val Ser Phe Ser Gln Phe

165 170 175

Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala Gly

180 185 190

Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp Ala Glu Leu Ala

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

<210> 74
<211> 453
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体

<400> 74

Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr

1 5 10 15

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

20 25 30

Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro Ser Leu Ile

35 40 45

Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Lys Thr

50 55 60

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

65 70 75 80

Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val Cys Thr Ala

85 90 95

Ala Ala Val Thr Cys Gly Ile Ala Ile Ala Lys Thr Ile Arg Leu Glu

100 105 110

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

115 120 125

Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Phe Ala Val Arg

130 135 140

Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala Leu Asn Lys

145 150 155 160

Asn Lys Cys Asp Ile Ala Asp Leu Lys Met Ala Val Ser Phe Ser Gln

165 170 175

Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala

180 185 190

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

195 200 205

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

210 215 220

Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Ile Leu

225 230 235 240

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile

245 250 255

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser

260 265 270

Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln

275 280 285

Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Asp

290 295 300

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Cys
305 310 315 320
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
325 330 335
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
340 345 350
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
355 360 365
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
370 375 380
Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400
Ile Asp Asn Thr Val Tyr Cys Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415
Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile Lys Phe
420 425 430
Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile
435 440 445
Glu Asn Ser Gln Ala
450
<210> 75
<211> 453
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 75
Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15
Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30
Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro Ser Leu Ile
35 40 45
Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Arg Thr
50 55 60
Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Asn Pro Arg
65 70 75 80
Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val Cys Thr Ala
85 90 95

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Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile Arg Leu Glu
            100                 105                 110
Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr Asn Glu Ala
        115                 120                 125
Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr Ala Val Arg
    130                 135                 140
Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala Ile Asn Lys
145                 150                 155                 160
Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser Phe Ser Gln
                165                 170                 175
Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala
            180                 185                 190
Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp Ala Glu Leu
        195                 200                 205
Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
    210                 215                 220
Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Phe Leu
225                 230                 235                 240
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
                245                 250                 255
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
            260                 265                 270
Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
        275                 280                 285
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
    290                 295                 300
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Cys
305                 310                 315                 320
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
                325                 330                 335
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
            340                 345                 350
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
        355                 360                 365
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
    370                 375                 380
Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385                 390                 395                 400
Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
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405 410 415
Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Val Lys Phe
420 425 430
Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile
435 440 445
Glu Asn Ser Gln Ala
450

<210> 76
<211> 453
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 76

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

195 200 205

Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
210 215 220

Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Phe Leu
225 230 235 240

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
245 250 255

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
260 265 270

Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
275 280 285

Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
290 295 300

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
305 310 315 320

Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
325 330 335

Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
340 345 350

Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
355 360 365

Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
370 375 380

Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400

Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415

Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Val Lys Phe
420 425 430

Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile
435 440 445

Glu Asn Ser Gln Ala
450

<210> 77

<211> 453

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 77

Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15

Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30

Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro Ser Leu Ile
35 40 45

Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Arg Thr
50 55 60

Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Asn Pro Arg
65 70 75 80

Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val Cys Thr Ala
85 90 95

Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile Arg Leu Glu
100 105 110

Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr Asn Glu Ala
115 120 125

Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Phe Ala Val Arg
130 135 140

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

Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser Phe Ser Gln
165 170 175

Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala
180 185 190

Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp Ala Glu Leu
195 200 205

Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
210 215 220

Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Phe Leu
225 230 235 240

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
245 250 255

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
260 265 270

Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
275 280 285

Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
290 295 300

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

<210> 78
<211> 453
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 78

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

Ala Ala Val Thr Ala Gly Ile Ala Ile Ala Lys Thr Ile Arg Leu Glu
100 105 110

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

Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr Ala Val Arg
130 135 140

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

Asn Lys Cys Asp Ile Ala Asp Leu Cys Met Ala Val Ser Phe Ser Gln
165 170 175

Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala
180 185 190

Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp Ala Glu Leu
195 200 205

Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
210 215 220

Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Ile Leu
225 230 235 240

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
245 250 255

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
260 265 270

Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
275 280 285

Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Asp
290 295 300

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
305 310 315 320

Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
325 330 335

Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
340 345 350

Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
355 360 365

Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
370 375 380

Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400

Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His

405 410 415
Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile Lys Phe
420 425 430
Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile
435 440 445
Glu Asn Ser Gln Ala
450
<210> 79
<211> 453
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 79
Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15
Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30
Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Cys Pro Ser Leu Ile
35 40 45
Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Lys Thr
50 55 60
Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Gly Gly Gly
65 70 75 80
Gly Gly Gly Phe Val Leu Gly Ala Ile Ala Leu Gly Val Ala Thr Ala
85 90 95
Ala Ala Val Thr Ala Gly Ile Ala Ile Ala Lys Thr Ile Arg Leu Glu
100 105 110
Ser Glu Val Asn Ala Ile Lys Gly Ala Leu Lys Thr Thr Asn Glu Ala
115 120 125
Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr Ala Val Arg
130 135 140
Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala Ile Asn Lys
145 150 155 160
Asn Lys Cys Asp Ile Ala Asp Leu Cys Met Ala Val Ser Phe Ser Gln
165 170 175
Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala
180 185 190
Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp Ala Glu Leu

195 200 205

Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
210 215 220

Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Ile Leu
225 230 235 240

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
245 250 255

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
260 265 270

Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
275 280 285

Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Asp
290 295 300

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
305 310 315 320

Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
325 330 335

Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
340 345 350

Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
355 360 365

Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
370 375 380

Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400

Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415

Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile Ala Phe
420 425 430

Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile
435 440 445

Glu Asn Ala Gln Ala
450

<210> 80
<211> 453
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体

<400> 80
Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15
Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30
Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Cys Pro Ser Leu Ile
35 40 45
Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Lys Thr
50 55 60
Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Gly Gly Gly
65 70 75 80
Gly Gly Gly Phe Val Leu Gly Ala Ile Ala Leu Gly Val Ala Thr Ala
85 90 95
Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile Arg Leu Glu
100 105 110
Ser Glu Val Thr Ala Ile Lys Asn Cys Leu Lys Thr Thr Asn Glu Cys
115 120 125
Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr Ala Val Arg
130 135 140
Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Ser Ala Ile Asn Lys
145 150 155 160
Asn Lys Cys Asp Ile Asp Asp Leu Cys Met Ala Val Ser Phe Ser Gln
165 170 175
Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala
180 185 190
Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp Ala Glu Leu
195 200 205
Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
210 215 220
Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Ile Leu
225 230 235 240
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
245 250 255
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
260 265 270
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
275 280 285
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
290 295 300

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
305 310 315 320
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
325 330 335
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
340 345 350
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
355 360 365
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
370 375 380
Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400
Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415
Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile Lys Phe
420 425 430
Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Asn Ile
435 440 445
Glu Asn Ser Gln Ala
450
<210> 81
<211> 453
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 81
Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15
Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30
Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Cys Pro Ser Leu Ile
35 40 45
Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Arg Thr
50 55 60
Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Gly Gly Gly
65 70 75 80
Gly Gly Gly Phe Val Leu Gly Ala Ile Ala Leu Gly Val Ala Thr Ala
85 90 95

Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile Arg Leu Glu
100 105 110

Ser Glu Val Thr Ala Ile Lys Asn Cys Leu Lys Lys Thr Asn Glu Cys
115 120 125

Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr Ala Val Arg
130 135 140

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

Asn Lys Cys Asp Ile Ala Asp Leu Cys Met Ala Val Ser Phe Ser Gln
165 170 175

Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala
180 185 190

Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp Ala Glu Leu
195 200 205

Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
210 215 220

Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Phe Leu
225 230 235 240

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
245 250 255

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
260 265 270

Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
275 280 285

Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
290 295 300

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
305 310 315 320

Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
325 330 335

Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
340 345 350

Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
355 360 365

Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
370 375 380

Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400

Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His

405 410 415
Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Val Cys Phe
420 425 430
Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile
435 440 445
Glu Asn Cys Gln Ala
450

<210> 82
<211> 453
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 82

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

195 200 205

Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
210 215 220

Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Phe Leu
225 230 235 240

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
245 250 255

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
260 265 270

Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
275 280 285

Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
290 295 300

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
305 310 315 320

Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
325 330 335

Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
340 345 350

Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
355 360 365

Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
370 375 380

Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400

Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415

Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Val Lys Phe
420 425 430

Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile
435 440 445

Glu Asn Ser Gln Ala
450

<210> 83
<211> 453
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体

<400> 83
Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15
Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30
Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro Ser Leu Ile
35 40 45
Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Arg Thr
50 55 60
Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Asn Pro Arg
65 70 75 80
Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val Ala Thr Ala
85 90 95
Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Cys Ile Arg Leu Glu
100 105 110
Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr Asn Glu Ala
115 120 125
Val Ser Thr Leu Gly Cys Gly Val Arg Val Leu Ala Thr Ala Val Arg
130 135 140
Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala Ile Asn Lys
145 150 155 160
Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser Phe Ser Gln
165 170 175
Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala
180 185 190
Gly Ile Thr Pro Ala Ile Ser Lys Asp Leu Met Thr Asp Ala Glu Leu
195 200 205
Ala Arg Ala Ile Ser Asn Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
210 215 220
Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Ile Leu
225 230 235 240
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
245 250 255
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
260 265 270
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
275 280 285
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
290 295 300

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

<210> 84
<211> 471
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 84

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

Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Cys Ile Arg Leu Glu
100 105 110

Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr Asn Glu Ala
115 120 125

Val Ser Thr Leu Gly Cys Gly Val Arg Val Leu Ala Thr Ala Val Arg
130 135 140

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

Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser Phe Ser Gln
165 170 175

Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala
180 185 190

Gly Ile Thr Pro Ala Ile Ser Lys Asp Leu Met Thr Asp Ala Glu Leu
195 200 205

Ala Arg Ala Ile Ser Asn Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
210 215 220

Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Ile Leu
225 230 235 240

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
245 250 255

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
260 265 270

Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
275 280 285

Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
290 295 300

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
305 310 315 320

Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
325 330 335

Thr Thr Asn Tyr Pro Cys Lys Val Ser Cys Gly Arg Asn Pro Ile Ser
340 345 350

Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
355 360 365

Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
370 375 380

Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400

Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His

405 410 415
Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Val Lys Phe
420 425 430
Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Cys Phe Glu Ser Ile
435 440 445
Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile Leu Ser Ser
450 455 460
Ala Glu Lys Gly Asn Thr Gly
465 470

<210> 85
<211> 453
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 85

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

180 185 190

Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp Ala Glu Leu
195 200 205

Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
210 215 220

Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Ile Leu
225 230 235 240

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
245 250 255

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
260 265 270

Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
275 280 285

Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Asp
290 295 300

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
305 310 315 320

Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
325 330 335

Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
340 345 350

Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
355 360 365

Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
370 375 380

Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400

Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415

Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile Cys Phe
420 425 430

Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile
435 440 445

Glu Asn Cys Gln Ala
450

<210> 86
<211> 453
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体
<400> 86
Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15
Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30
Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro Ser Leu Ile
35 40 45
Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Arg Thr
50 55 60
Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Asn Pro Arg
65 70 75 80
Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val Ala Thr Ala
85 90 95
Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Cys Ile Arg Leu Glu
100 105 110
Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr Asn Glu Ala
115 120 125
Val Ser Thr Leu Gly Cys Gly Val Arg Val Leu Ala Thr Ala Val Arg
130 135 140
Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala Ile Asn Lys
145 150 155 160
Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser Phe Ser Gln
165 170 175
Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala
180 185 190
Gly Ile Thr Pro Ala Ile Ser Lys Asp Leu Met Thr Asp Ala Glu Leu
195 200 205
Ala Arg Ala Ile Ser Asn Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
210 215 220
Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Ile Leu
225 230 235 240
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
245 250 255
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
260 265 270
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
275 280 285

Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
290 295 300
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
305 310 315 320
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
325 330 335
Thr Thr Asn Tyr Pro Cys Lys Val Ser Cys Gly Arg Asn Pro Ile Ser
340 345 350
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
355 360 365
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
370 375 380
Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400
Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415
Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Val Lys Phe
420 425 430
Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Cys Phe Glu Ser Ile
435 440 445
Glu Asn Ser Gln Ala
450
<210> 87
<211> 471
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 87
Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15
Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30
Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro Ser Leu Ile
35 40 45
Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Arg Thr
50 55 60
Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Asn Pro Arg
65 70 75 80

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

85 90 95

Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Cys Ile Arg Leu Glu

100 105 110

Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr Asn Glu Ala

115 120 125

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

130 135 140

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

145 150 155 160

Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser Phe Ser Gln

165 170 175

Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala

180 185 190

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

195 200 205

Ala Arg Ala Ile Ser Asn Met Pro Thr Ser Ala Gly Gln Ile Lys Leu

210 215 220

Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Ile Leu

225 230 235 240

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile

245 250 255

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser

260 265 270

Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln

275 280 285

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

290 295 300

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala

305 310 315 320

Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser

325 330 335

Thr Thr Asn Tyr Pro Cys Lys Val Ser Cys Gly Arg Asn Pro Ile Ser

340 345 350

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

355 360 365

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

370 375 380

Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr

385 390 395 400
Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415
Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Val Lys Phe
420 425 430
Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Cys Phe Glu Ser Ile
435 440 445
Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile Leu Ser Ser
450 455 460
Ala Glu Lys Gly Asn Thr Gly
465 470
<210> 88
<211> 453
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 88
Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15
Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30
Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro Ser Leu Ile
35 40 45
Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Lys Thr
50 55 60
Cys Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Gly Gly Gly
65 70 75 80
Gly Gly Gly Phe Val Leu Gly Ala Ile Ala Leu Gly Val Ala Thr Ala
85 90 95
Ala Ala Val Thr Ala Gly Ile Ala Ile Ala Lys Thr Ile Arg Leu Glu
100 105 110
Ser Glu Val Asn Ala Ile Lys Gly Cys Leu Lys Thr Thr Asn Glu Cys
115 120 125
Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr Ala Val Arg
130 135 140
Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala Ile Asn Lys
145 150 155 160
Asn Lys Cys Asp Ile Ala Asp Leu Lys Met Ala Val Ser Phe Ser Gln

165 170 175

Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala

180 185 190

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

195 200 205

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

210 215 220

Met Leu Glu Asn Arg Cys Met Val Arg Arg Lys Gly Phe Gly Ile Leu

225 230 235 240

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile

245 250 255

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser

260 265 270

Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln

275 280 285

Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Asp

290 295 300

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala

305 310 315 320

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

325 330 335

Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser

340 345 350

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

355 360 365

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

370 375 380

Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr

385 390 395 400

Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His

405 410 415

Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile Lys Phe

420 425 430

Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu Ser Ile

435 440 445

Glu Asn Ser Gln Ala

450

<210> 89

<211> 453

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 89

Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15

Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30

Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro Ser Leu Ile
35 40 45

Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Arg Thr
50 55 60

Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu Gly Gly Gly
65 70 75 80

Gly Gly Gly Phe Val Leu Gly Ala Ile Ala Leu Gly Val Ala Thr Ala
85 90 95

Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Cys Ile Arg Leu Glu
100 105 110

Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr Asn Glu Ala
115 120 125

Val Ser Thr Leu Gly Cys Gly Val Arg Val Leu Ala Thr Ala Val Arg
130 135 140

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

Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser Phe Ser Gln
165 170 175

Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp Asn Ala
180 185 190

Gly Ile Thr Pro Ala Ile Ser Lys Asp Leu Met Thr Asp Ala Glu Leu
195 200 205

Ala Arg Ala Ile Ser Asn Met Pro Thr Ser Ala Gly Gln Ile Lys Leu
210 215 220

Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly Ile Leu
225 230 235 240

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
245 250 255

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
260 265 270

Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
275 280 285
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
290 295 300
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
305 310 315 320
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
325 330 335
Thr Thr Asn Tyr Pro Cys Lys Val Ser Cys Gly Arg Asn Pro Ile Ser
340 345 350
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
355 360 365
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
370 375 380
Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400
Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415
Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Val Lys Phe
420 425 430
Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Cys Phe Glu Ser Ile
435 440 445
Glu Asn Ser Gln Ala
450
<210> 90
<211> 471
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 90
Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr Glu Gly Tyr
1 5 10 15
Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe Thr Leu Glu
20 25 30
Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro Ser Leu Ile
35 40 45
Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu Leu Arg Thr
50 55 60

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

370 375 380

Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr Val Thr
385 390 395 400

Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu Gln His
405 410 415

Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Val Lys Phe
420 425 430

Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Cys Phe Glu Ser Ile
435 440 445

Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile Leu Ser Ser
450 455 460

Ala Glu Lys Gly Asn Thr Gly
465 470

<210> 91
<211> 27
<212> PRT
<213> 埃希氏杆菌属病毒T4(Escherichia virus T4)
<400> 91

Gly Tyr Ile Pro Glu Ala Pro Arg Asp Gly Gln Ala Tyr Val Arg Lys
1 5 10 15

Asp Gly Glu Trp Val Leu Leu Ser Thr Phe Leu
20 25

<210> 92
<211> 716
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 92

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1 5 10 15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro
50 55 60

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

Leu Arg Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95

Asn Pro Arg Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
115 120 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr
130 135 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145 150 155 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
165 170 175

Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220

Ala Glu Leu Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255

Gly Phe Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
275 280 285

Ala Pro Ser Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
340 345 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
355 360 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile

385 390 395 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp

405 410 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly

420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro

435 440 445

Val Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe

450 455 460

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

465 470 475 480

Leu Gly Ser Gly Gly Ser Gly Ser Gly Ser Gly Gly Ser Glu Lys Ala

485 490 495

Ala Lys Ala Glu Glu Ala Ala Arg Lys Met Glu Glu Leu Phe Lys Lys

500 505 510

His Lys Ile Val Ala Val Leu Arg Ala Asn Ser Val Glu Glu Ala Ile

515 520 525

Glu Lys Ala Val Ala Val Phe Ala Gly Gly Val His Leu Ile Glu Ile

530 535 540

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

545 550 555 560

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

565 570 575

Glu Gln Ala Arg Lys Ala Val Glu Ser Gly Ala Glu Phe Ile Val Ser

580 585 590

Pro His Leu Asp Glu Glu Ile Ser Gln Phe Ala Lys Glu Lys Gly Val

595 600 605

Phe Tyr Met Pro Gly Val Met Thr Pro Thr Glu Leu Val Lys Ala Met

610 615 620

Lys Leu Gly His Thr Ile Leu Lys Leu Phe Pro Gly Glu Val Val Gly

625 630 635 640

Pro Gln Phe Val Lys Ala Met Lys Gly Pro Phe Pro Asn Val Lys Phe

645 650 655

Val Pro Thr Gly Gly Val Asn Leu Asp Asn Val Ala Glu Trp Phe Lys

660 665 670

Ala Gly Val Leu Ala Val Gly Val Gly Ser Ala Leu Val Lys Gly Thr

675 680 685

Pro Asp Glu Val Arg Glu Lys Ala Lys Ala Phe Val Glu Lys Ile Arg

690 695 700

Gly Ala Thr Glu Leu Glu His His His His His His
705 710 715

<210> 93
<211> 707
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 93

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

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

Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser

565 570 575

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

580 585 590

Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro

595 600 605

Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu

610 615 620

Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly

625 630 635 640

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

645 650 655

Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly

660 665 670

Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys

675 680 685

Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His

690 695 700

His His His

705

<210> 94

<211> 725

<212> PRT

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<220>

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<400> 94

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln

1 5 10 15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr

20 25 30

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

35 40 45

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

50 55 60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu

65 70 75 80

Leu Arg Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu

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

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
405 410 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
435 440 445

Val Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
450 455 460

Glu Ser Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465 470 475 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Gly Ser Gly Gly Ser Gly
485 490 495

Ser Gly Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala
500 505 510

Arg Lys Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu
515 520 525

Arg Ala Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe
530 535 540

Ala Gly Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala
545 550 555 560

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

Ile Gly Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val
580 585 590

Glu Ser Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile
595 600 605

Ser Gln Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met
610 615 620

Thr Pro Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu
625 630 635 640

Lys Leu Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met
645 650 655

Lys Gly Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn
660 665 670

Leu Asp Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly
675 680 685

Val Gly Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys
690 695 700

Ala Lys Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His

705 710 715 720

His His His His His

725

<210> 95

<211> 707

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 95

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1 5 10 15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro
50 55 60

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

Leu Arg Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95

Asn Pro Arg Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
115 120 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr
130 135 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145 150 155 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
165 170 175

Ile Asn Lys Asn Lys Cys Asp Ile Ala Asp Leu Lys Met Ala Val Ser
180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220

Ala Glu Leu Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln

225 230 235 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255

Gly Phe Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
275 280 285

Ala Pro Ser Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
340 345 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
355 360 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385 390 395 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
405 410 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
435 440 445

Val Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
450 455 460

Glu Ser Ile Glu Asn Ser Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly
465 470 475 480

Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys
485 490 495

Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala
500 505 510

Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly
515 520 525

Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr
530 535 540

Val Ile Lys Ala Leu Ser Val Leu Lys Glu Lys Gly Ala Ile Ile Gly
545 550 555 560
Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser
565 570 575
Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
580 585 590
Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
595 600 605
Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
610 615 620
Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625 630 635 640
Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
645 650 655
Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
660 665 670
Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
675 680 685
Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His
690 695 700
His His His
705
<210> 96
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Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1 5 10 15
His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30
Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45
Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro
50 55 60
Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65 70 75 80

Leu Arg Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95

Asn Pro Arg Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Cys Ile
115 120 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr
130 135 140

Asn Glu Ala Val Ser Thr Leu Gly Cys Gly Val Arg Val Leu Ala Thr
145 150 155 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
165 170 175

Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220

Ala Glu Leu Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
275 280 285

Ala Pro Ser Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
340 345 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg Asn
355 360 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile

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385                 390                 395                 400
Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405                 410                 415
Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
            420                 425                 430
Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
        435                 440                 445
Val Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
    450                 455                 460
Glu Ser Ile Glu Asn Ser Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly
465                 470                 475                 480
Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys
                485                 490                 495
Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala
            500                 505                 510
Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly
        515                 520                 525
Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr
    530                 535                 540
Val Ile Lys Ala Leu Ser Val Leu Lys Glu Lys Gly Ala Ile Ile Gly
545                 550                 555                 560
Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser
                565                 570                 575
Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
            580                 585                 590
Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
        595                 600                 605
Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
    610                 615                 620
Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625                 630                 635                 640
Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
                645                 650                 655
Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
            660                 665                 670
Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
        675                 680                 685
Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His
    690                 695                 700
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His His His
705
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<212> PRT
<213> 人工序列
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<400> 97
Met Ser Trp Lys Val Met Ile Ile Ile Ser Leu Leu Ile Thr Pro Gln
1 5 10 15
His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30
Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45
Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro
50 55 60
Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65 70 75 80
Leu Lys Thr Cys Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95
Gly Gly Gly Gly Gly Gly Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110
Ala Thr Ala Ala Ala Val Thr Ala Gly Ile Ala Ile Ala Lys Thr Ile
115 120 125
Arg Leu Glu Ser Glu Val Asn Ala Ile Lys Gly Cys Leu Lys Thr Thr
130 135 140
Asn Glu Cys Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145 150 155 160
Ala Val Arg Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala
165 170 175
Ile Asn Lys Asn Lys Cys Asp Ile Ala Asp Leu Lys Met Ala Val Ser
180 185 190
Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205
Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220
Ala Glu Leu Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln
225 230 235 240

Ile Lys Leu Met Leu Glu Asn Arg Cys Met Val Arg Arg Lys Gly Phe
245 250 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala
275 280 285

Ala Pro Ser Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300

Glu Asp Gln Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320

Pro Asn Asp Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile
340 345 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
355 360 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385 390 395 400

Lys Gln Leu Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
405 410 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
435 440 445

Ile Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
450 455 460

Glu Ser Ile Glu Asn Ser Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly
465 470 475 480

Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys
485 490 495

Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala
500 505 510

Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly
515 520 525

Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr
530 535 540

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

545 550 555 560
Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser
565 570 575
Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
580 585 590
Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
595 600 605
Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
610 615 620
Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625 630 635 640
Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
645 650 655
Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
660 665 670
Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
675 680 685
Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His
690 695 700
His His His
705
<210> 98
<211> 723
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<223> 合成构建体
<400> 98
Met Ser Trp Lys Val Met Ile Ile Ile Ser Leu Leu Ile Thr Pro Gln
1 5 10 15
His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30
Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45
Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro
50 55 60
Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65 70 75 80
Leu Lys Thr Cys Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu

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

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

705 710 715 720

His His His

<210> 99

<211> 707

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 99

Met Ser Trp Lys Val Met Ile Ile Ile Ser Leu Leu Ile Thr Pro Gln
1 5 10 15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Cys Pro
50 55 60

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

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

Gly Gly Gly Gly Gly Gly Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Ile Ala Ile Ala Lys Thr Ile
115 120 125

Arg Leu Glu Ser Glu Val Asn Ala Ile Lys Gly Cys Leu Lys Thr Thr
130 135 140

Asn Glu Cys Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145 150 155 160

Ala Val Arg Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala
165 170 175

Ile Asn Lys Asn Lys Cys Asp Ile Ala Asp Leu Cys Met Ala Val Ser
180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220

Ala Glu Leu Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln
225 230 235 240

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

545 550 555 560
Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser
565 570 575
Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
580 585 590
Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
595 600 605
Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
610 615 620
Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625 630 635 640
Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
645 650 655
Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
660 665 670
Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
675 680 685
Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His
690 695 700
His His His
705
<210> 100
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<212> PRT
<213> 人工序列
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<400> 100
Met Ser Trp Lys Val Met Ile Ile Ile Ser Leu Leu Ile Thr Pro Gln
1 5 10 15
His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30
Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45
Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Cys Pro
50 55 60
Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65 70 75 80
Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu

85 90 95

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

100 105 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Ile Ala Ile Ala Lys Thr Ile

115 120 125

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

130 135 140

Asn Glu Cys Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr

145 150 155 160

Ala Val Arg Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala

165 170 175

Ile Asn Lys Asn Lys Cys Asp Ile Ala Asp Leu Cys Met Ala Val Ser

180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser

195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp

210 215 220

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

225 230 235 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe

245 250 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln

260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala

275 280 285

Ala Pro Ser Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg

290 295 300

Glu Asp Gln Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr

305 310 315 320

Pro Asn Asp Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp

325 330 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile

340 345 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His

355 360 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys

370 375 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile

385 390 395 400

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

His His His

<210> 101

<211> 706

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 101

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1 5 10 15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Cys Pro
50 55 60

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

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

Gly Gly Gly Gly Gly Gly Phe Val Leu Ala Ile Ala Leu Gly Val Ala
100 105 110

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

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

Glu Cys Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr Ala
145 150 155 160

Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Ser Ala Ile
165 170 175

Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Cys Met Ala Val Ser Phe
180 185 190

Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp
195 200 205

Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp Ala
210 215 220

Glu Leu Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln Ile
225 230 235 240

Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly
245 250 255

Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu
260 265 270

Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala
275 280 285

Pro Ser Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu
290 295 300

Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro
305 310 315 320

Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr
325 330 335

Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn
340 345 350

Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro
355 360 365

Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr
370 375 380

Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys
385 390 395 400

Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr
405 410 415

Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu
420 425 430

Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile
435 440 445

Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu
450 455 460

Asn Ile Glu Asn Ser Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly Ser
465 470 475 480

Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys Met
485 490 495

Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala Asn
500 505 510

Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly Gly
515 520 525

Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr Val
530 535 540

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

545 550 555 560

Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser Gly

565 570 575

Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln Phe

580 585 590

Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro Thr

595 600 605

Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu Phe

610 615 620

Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly Pro

625 630 635 640

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

645 650 655

Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly Ser

660 665 670

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

675 680 685

Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His His

690 695 700

His His

705

<210> 102

<211> 722

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 102

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln

1 5 10 15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr

20 25 30

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

35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Cys Pro

50 55 60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu

65 70 75 80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu

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                85                  90                  95
Gly Gly Gly Gly Gly Gly Phe Val Leu Ala Ile Ala Leu Gly Val Ala
            100                 105                 110
Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile Arg
        115                 120                 125
Leu Glu Ser Glu Val Thr Ala Ile Lys Asn Cys Leu Lys Thr Thr Asn
    130                 135                 140
Glu Cys Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr Ala
145                 150                 155                 160
Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Ser Ala Ile
                165                 170                 175
Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Cys Met Ala Val Ser Phe
            180                 185                 190
Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser Asp
        195                 200                 205
Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp Ala
    210                 215                 220
Glu Leu Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln Ile
225                 230                 235                 240
Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe Gly
                245                 250                 255
Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu
            260                 265                 270
Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala
        275                 280                 285
Pro Ser Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu
    290                 295                 300
Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro
305                 310                 315                 320
Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr
                325                 330                 335
Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn
            340                 345                 350
Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro
        355                 360                 365
Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr
    370                 375                 380
Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys
385                 390                 395                 400
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Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp Thr
405 410 415
Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly Glu
420 425 430
Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro Ile
435 440 445
Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe Glu
450 455 460
Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile Leu
465 470 475 480
Ser Ser Ala Glu Ser Ala Ile Gly Ser Gly Gly Ser Gly Ser Gly Ser
485 490 495
Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys Met
500 505 510
Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala Asn
515 520 525
Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly Gly
530 535 540
Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr Val
545 550 555 560
Ile Lys Ala Leu Ser Val Leu Lys Glu Lys Gly Ala Ile Ile Gly Ala
565 570 575
Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser Gly
580 585 590
Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln Phe
595 600 605
Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro Thr
610 615 620
Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu Phe
625 630 635 640
Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly Pro
645 650 655
Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp Asn
660 665 670
Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly Ser
675 680 685
Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys Ala
690 695 700
Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His His

705 710 715 720

His His

<210> 103

<211> 707

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 103

Met Ser Trp Lys Val Met Ile Ile Ile Ser Leu Leu Ile Thr Pro Gln
1 5 10 15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro
50 55 60

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

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

Asn Pro Arg Lys Ala Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Cys Thr Ala Ala Ala Val Thr Cys Gly Ile Ala Ile Ala Lys Thr Ile
115 120 125

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

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Phe
145 150 155 160

Ala Val Arg Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala
165 170 175

Leu Asn Lys Asn Lys Cys Asp Ile Ala Asp Leu Lys Met Ala Val Ser
180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220

Ala Glu Leu Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln
225 230 235 240

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

545 550 555 560

Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser

565 570 575

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

580 585 590

Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro

595 600 605

Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu

610 615 620

Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly

625 630 635 640

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

645 650 655

Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly

660 665 670

Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys

675 680 685

Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His

690 695 700

His His His

705

<210> 104

<211> 723

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 104

Met Ser Trp Lys Val Met Ile Ile Ile Ser Leu Leu Ile Thr Pro Gln

1 5 10 15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr

20 25 30

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

35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro

50 55 60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu

65 70 75 80

Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu

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

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

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35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro
50 55 60

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

Leu Lys Thr Cys Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95

Asn Pro Arg Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Ile Ala Ile Ala Lys Thr Ile
115 120 125

Arg Leu Glu Ser Glu Val Asn Ala Ile Lys Gly Cys Leu Lys Thr Thr
130 135 140

Asn Glu Cys Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145 150 155 160

Ala Val Arg Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala
165 170 175

Ile Asn Lys Asn Lys Cys Asp Ile Ala Asp Leu Lys Met Ala Val Ser
180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220

Ala Glu Leu Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln
225 230 235 240

Ile Lys Leu Met Leu Glu Asn Arg Cys Met Val Arg Arg Lys Gly Phe

245 250 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln

260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala

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290 295 300

Glu Asp Gln Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr

305 310 315 320

Pro Asn Asp Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp

325 330 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile

340 345 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His

355 360 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys

370 375 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile

385 390 395 400

Lys Gln Leu Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp

405 410 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly

420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro

435 440 445

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

450 455 460

Glu Ser Ile Glu Asn Ser Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly

465 470 475 480

Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys

485 490 495

Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala

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

515 520 525

Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr

530 535 540

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

545 550 555 560
Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser
565 570 575
Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
580 585 590
Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
595 600 605
Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
610 615 620
Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625 630 635 640
Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
645 650 655
Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
660 665 670
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675 680 685
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His His His
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35 40 45
Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Cys Pro
50 55 60
Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65 70 75 80
Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu

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

Lys Gln Leu Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
405 410 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
435 440 445

Ile Cys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
450 455 460

Glu Ser Ile Glu Asn Cys Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly
465 470 475 480

Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys
485 490 495

Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala
500 505 510

Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly
515 520 525

Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr
530 535 540

Val Ile Lys Ala Leu Ser Val Leu Lys Glu Lys Gly Ala Ile Ile Gly
545 550 555 560

Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser
565 570 575

Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
580 585 590

Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
595 600 605

Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
610 615 620

Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625 630 635 640

Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
645 650 655

Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
660 665 670

Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
675 680 685

Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His
690 695 700

His His His

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

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

Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser Gly
565 570 575

Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln Phe
580 585 590

Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro Thr
595 600 605

Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu Phe
610 615 620

Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly Pro
625 630 635 640

Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp Asn
645 650 655

Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly Ser
660 665 670

Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys Ala
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Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His His
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His His
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20 25 30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro
50 55 60

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

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

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

405 410 415
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420 425 430
Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
435 440 445
Ile Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
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Glu Ser Ile Glu Asn Ser Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly
465 470 475 480
Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys
485 490 495
Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala
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Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly
515 520 525
Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr
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545 550 555 560
Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser
565 570 575
Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
580 585 590
Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
595 600 605
Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
610 615 620
Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625 630 635 640
Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
645 650 655
Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
660 665 670
Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
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Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro
50 55 60

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

Leu Arg Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95

Asn Pro Arg Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Cys Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
115 120 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr
130 135 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145 150 155 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
165 170 175

Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220

Ala Glu Leu Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255

Gly Phe Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
275 280 285

Ala Pro Ser Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335

Thr Ala Cys Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
340 345 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
355 360 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385 390 395 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
405 410 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
435 440 445

Val Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
450 455 460

Glu Ser Ile Glu Asn Ser Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly
465 470 475 480

Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys
485 490 495

Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala
500 505 510

Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly
515 520 525

Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr
530 535 540

Val Ile Lys Ala Leu Ser Val Leu Lys Glu Lys Gly Ala Ile Ile Gly
545 550 555 560

Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser

565 570 575

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

580 585 590

Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro

595 600 605

Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu

610 615 620

Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly

625 630 635 640

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

645 650 655

Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly

660 665 670

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His His His

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35 40 45

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

50 55 60

Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu

65 70 75 80

Leu Arg Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu

85 90 95

Asn Pro Arg Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val

100 105 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
115 120 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr
130 135 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Phe
145 150 155 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
165 170 175

Leu Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220

Ala Glu Leu Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255

Gly Phe Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
275 280 285

Ala Pro Ser Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
340 345 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
355 360 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385 390 395 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
405 410 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
435 440 445

Val Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
450 455 460

Glu Ser Ile Glu Asn Ser Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly
465 470 475 480

Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys
485 490 495

Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala
500 505 510

Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly
515 520 525

Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr
530 535 540

Val Ile Lys Ala Leu Ser Val Leu Lys Glu Lys Gly Ala Ile Ile Gly
545 550 555 560

Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser
565 570 575

Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
580 585 590

Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
595 600 605

Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
610 615 620

Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625 630 635 640

Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
645 650 655

Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
660 665 670

Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
675 680 685

Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His
690 695 700

His His His
705

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

260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala

275 280 285

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

290 295 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr

305 310 315 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp

325 330 335

Thr Ala Cys Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile

340 345 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His

355 360 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys

370 375 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile

385 390 395 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp

405 410 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly

420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro

435 440 445

Val Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe

450 455 460

Glu Ser Ile Glu Asn Ser Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly

465 470 475 480

Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys

485 490 495

Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala

500 505 510

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

515 520 525

Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr

530 535 540

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

545 550 555 560

Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser

565 570 575

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Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
            580                 585                 590
Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
        595                 600                 605
Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
    610                 615                 620
Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625                 630                 635                 640
Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
                645                 650                 655
Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
            660                 665                 670
Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
        675                 680                 685
Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His
    690                 695                 700
His His His
705
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Met Ser Trp Lys Val Met Ile Ile Ile Ser Leu Leu Ile Thr Pro Gln
1               5                   10                  15
His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
            20                  25                  30
Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
        35                  40                  45
Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Cys Pro
    50                  55                  60
Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65                  70                  75                  80
Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
                85                  90                  95
Gly Gly Gly Gly Gly Gly Phe Val Leu Gly Ala Ile Ala Leu Gly Val
            100                 105                 110
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Ala Thr Ala Ala Ala Val Thr Ala Gly Ile Ala Ile Ala Lys Thr Ile
        115   120   125
Arg Leu Glu Ser Glu Val Asn Ala Ile Lys Gly Ala Leu Lys Thr Thr
    130   135   140
Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145   150   155   160
Ala Val Arg Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala
                165   170   175
Ile Asn Lys Asn Lys Cys Asp Ile Ala Asp Leu Cys Met Ala Val Ser
            180   185   190
Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
        195   200   205
Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
    210   215   220
Ala Glu Leu Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln
225   230   235   240
Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
                245   250   255
Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
            260   265   270
Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala
        275   280   285
Ala Pro Ser Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg
    290   295   300
Glu Asp Gln Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr
305   310   315   320
Pro Asn Asp Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
                325   330   335
Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile
            340   345   350
Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
        355   360   365
Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
    370   375   380
Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385   390   395   400
Lys Gln Leu Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
                405   410   415
Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly

420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro

435 440 445

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

450 455 460

Glu Ser Ile Glu Asn Ser Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly

465 470 475 480

Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys

485 490 495

Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala

500 505 510

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

515 520 525

Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr

530 535 540

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

545 550 555 560

Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser

565 570 575

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

580 585 590

Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro

595 600 605

Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu

610 615 620

Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly

625 630 635 640

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

645 650 655

Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly

660 665 670

Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys

675 680 685

Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His

690 695 700

His His His

705

<210> 113

<211> 707

<212> PRT

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<223> 合成构建体

<400> 113

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

Ala Pro Ser Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300

Glu Asp Gln Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320

Pro Asn Asp Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile
340 345 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
355 360 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385 390 395 400

Lys Gln Leu Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
405 410 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
435 440 445

Ile Ala Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
450 455 460

Glu Ser Ile Glu Asn Ala Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly
465 470 475 480

Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys
485 490 495

Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala
500 505 510

Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly
515 520 525

Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr
530 535 540

Val Ile Lys Ala Leu Ser Val Leu Lys Glu Lys Gly Ala Ile Ile Gly
545 550 555 560

Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser
565 570 575

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

580 585 590

Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
595 600 605

Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
610 615 620

Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625 630 635 640

Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
645 650 655

Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
660 665 670

Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
675 680 685

Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His
690 695 700

His His His
705

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Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
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His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Cys Pro
50 55 60

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

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

Gly Gly Gly Gly Gly Gly Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile

115 120 125
Arg Leu Glu Ser Glu Val Thr Ala Ile Lys Asn Cys Leu Lys Thr Thr
130 135 140
Asn Glu Cys Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145 150 155 160
Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Ser Ala
165 170 175
Ile Asn Lys Asn Lys Cys Asp Ile Asp Asp Leu Cys Met Ala Val Ser
180 185 190
Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205
Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220
Ala Glu Leu Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240
Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255
Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270
Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala
275 280 285
Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300
Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320
Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335
Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
340 345 350
Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
355 360 365
Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380
Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385 390 395 400
Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
405 410 415
Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
435 440 445
Ile Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
450 455 460
Glu Asn Ile Glu Asn Ser Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly
465 470 475 480
Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys
485 490 495
Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala
500 505 510
Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly
515 520 525
Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr
530 535 540
Val Ile Lys Ala Leu Ser Val Leu Lys Glu Lys Gly Ala Ile Ile Gly
545 550 555 560
Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser
565 570 575
Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
580 585 590
Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
595 600 605
Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
610 615 620
Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625 630 635 640
Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
645 650 655
Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
660 665 670
Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
675 680 685
Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His
690 695 700
His His His
705
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Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
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His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Cys Pro
50 55 60

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

Leu Arg Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95

Gly Gly Gly Gly Gly Gly Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
115 120 125

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

Asn Glu Cys Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145 150 155 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
165 170 175

Ile Asn Lys Asn Lys Cys Asp Ile Ala Asp Leu Cys Met Ala Val Ser
180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220

Ala Glu Leu Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255

Gly Phe Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala

275 280 285
Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300
Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320
Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335
Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
340 345 350
Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
355 360 365
Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380
Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385 390 395 400
Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
405 410 415
Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430
Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
435 440 445
Val Cys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
450 455 460
Glu Ser Ile Glu Asn Cys Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly
465 470 475 480
Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys
485 490 495
Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala
500 505 510
Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly
515 520 525
Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr
530 535 540
Val Ile Lys Ala Leu Ser Val Leu Lys Glu Lys Gly Ala Ile Ile Gly
545 550 555 560
Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser
565 570 575
Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
580 585 590

Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
595 600 605

Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
610 615 620

Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625 630 635 640

Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
645 650 655

Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
660 665 670

Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
675 680 685

Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His
690 695 700

His His His
705

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Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
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His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Cys Pro
50 55 60

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

Leu Arg Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95

Gly Gly Gly Gly Gly Gly Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
115 120 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr
130 135 140

Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145 150 155 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
165 170 175

Ile Asn Lys Asn Lys Cys Asp Ile Ala Asp Leu Cys Met Ala Val Ser
180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220

Ala Glu Leu Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255

Gly Phe Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
275 280 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
340 345 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
355 360 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385 390 395 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
405 410 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro

435 440 445

Val Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
450 455 460

Glu Ser Ile Glu Asn Ser Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly
465 470 475 480

Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys
485 490 495

Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala
500 505 510

Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly
515 520 525

Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr
530 535 540

Val Ile Lys Ala Leu Ser Val Leu Lys Glu Lys Gly Ala Ile Ile Gly
545 550 555 560

Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser
565 570 575

Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
580 585 590

Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
595 600 605

Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
610 615 620

Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625 630 635 640

Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
645 650 655

Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
660 665 670

Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
675 680 685

Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His
690 695 700

His His His
705

<210> 117
<211> 707
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<223> 合成构建体

<400> 117

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
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His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro
50 55 60

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

Leu Arg Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95

Asn Pro Arg Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Cys Ile
115 120 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr
130 135 140

Asn Glu Ala Val Ser Thr Leu Gly Cys Gly Val Arg Val Leu Ala Thr
145 150 155 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
165 170 175

Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Lys Asp Leu Met Thr Asp
210 215 220

Ala Glu Leu Ala Arg Ala Ile Ser Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
275 280 285

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

595 600 605
Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
610 615 620
Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625 630 635 640
Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
645 650 655
Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
660 665 670
Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
675 680 685
Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His
690 695 700
His His His
705
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<400> 118
Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1 5 10 15
His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30
Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45
Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro
50 55 60
Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65 70 75 80
Leu Arg Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95
Asn Pro Arg Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110
Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Cys Ile
115 120 125
Arg Leu Glu Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr

130 135 140
Asn Glu Ala Val Ser Thr Leu Gly Cys Gly Val Arg Val Leu Ala Thr
145 150 155 160
Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
165 170 175
Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
180 185 190
Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205
Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Lys Asp Leu Met Thr Asp
210 215 220
Ala Glu Leu Ala Arg Ala Ile Ser Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240
Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255
Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270
Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
275 280 285
Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300
Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320
Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335
Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
340 345 350
Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Cys Gly Arg Asn
355 360 365
Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380
Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385 390 395 400
Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
405 410 415
Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430
Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
435 440 445

Val Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Cys Phe
    450   455   460

Glu Ser Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465   470   475   480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Gly Ser Gly Gly Ser Gly
                485   490   495

Ser Gly Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala
            500   505   510

Arg Lys Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu
        515   520   525

Arg Ala Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe
    530   535   540

Ala Gly Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala
545   550   555   560

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

Ile Gly Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val
            580   585   590

Glu Ser Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile
        595   600   605

Ser Gln Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met
    610   615   620

Thr Pro Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu
625   630   635   640

Lys Leu Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met
                645   650   655

Lys Gly Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn
            660   665   670

Leu Asp Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly
        675   680   685

Val Gly Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys
    690   695   700

Ala Lys Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His
705   710   715   720

His His His His His
                725

<210> 119

<211> 707

<212> PRT

<213> 人工序列

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<223> 合成构建体

<400> 119

Met Ser Trp Lys Val Met Ile Ile Ile Ser Leu Leu Ile Thr Pro Gln
1 5 10 15

His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Cys Pro
50 55 60

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

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

Gly Gly Gly Gly Gly Gly Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Ile Ala Ile Ala Lys Thr Ile
115 120 125

Arg Leu Glu Ser Glu Val Asn Ala Ile Lys Gly Cys Leu Lys Thr Thr
130 135 140

Asn Glu Cys Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145 150 155 160

Ala Val Arg Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala
165 170 175

Ile Asn Lys Asn Lys Cys Asp Ile Ala Asp Leu Cys Met Ala Val Ser
180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220

Ala Glu Leu Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln
225 230 235 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala

275 280 285

Ala Pro Ser Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300

Glu Asp Gln Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320

Pro Asn Asp Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile
340 345 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
355 360 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385 390 395 400

Lys Gln Leu Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
405 410 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
435 440 445

Ile Cys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
450 455 460

Glu Ser Ile Glu Asn Cys Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly
465 470 475 480

Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys
485 490 495

Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala
500 505 510

Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly
515 520 525

Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr
530 535 540

Val Ile Lys Ala Leu Ser Val Leu Lys Glu Lys Gly Ala Ile Ile Gly
545 550 555 560

Ala Gly Thr Val Thr Ser Val Glu Gln Cys Arg Lys Ala Val Glu Ser
565 570 575

Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
580 585 590

Phe Cys Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
595 600 605

Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
610 615 620

Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625 630 635 640

Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
645 650 655

Asn Val Cys Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
660 665 670

Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
675 680 685

Ala Phe Val Glu Lys Ile Arg Gly Cys Thr Glu Leu Glu His His His
690 695 700

His His His
705

<210> 120
<211> 707
<212> PRT
<213> 人工序列
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<400> 120

Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
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His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30

Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro
50 55 60

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

Leu Arg Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95

Asn Pro Arg Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Cys Ile
115 120 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr
130 135 140
Asn Glu Ala Val Ser Thr Leu Gly Cys Gly Val Arg Val Leu Ala Thr
145 150 155 160
Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
165 170 175
Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
180 185 190
Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205
Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Lys Asp Leu Met Thr Asp
210 215 220
Ala Glu Leu Ala Arg Ala Ile Ser Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240
Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255
Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270
Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
275 280 285
Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300
Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320
Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335
Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
340 345 350
Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Cys Gly Arg Asn
355 360 365
Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380
Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385 390 395 400
Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
405 410 415
Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430
Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro

435 440 445

Val Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Cys Phe
450 455 460

Glu Ser Ile Glu Asn Ser Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly
465 470 475 480

Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys
485 490 495

Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala
500 505 510

Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly
515 520 525

Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr
530 535 540

Val Ile Lys Ala Leu Ser Val Leu Lys Glu Lys Gly Ala Ile Ile Gly
545 550 555 560

Ala Gly Thr Val Thr Ser Val Glu Gln Cys Arg Lys Ala Val Glu Ser
565 570 575

Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
580 585 590

Phe Cys Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
595 600 605

Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
610 615 620

Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625 630 635 640

Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
645 650 655

Asn Val Cys Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
660 665 670

Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
675 680 685

Ala Phe Val Glu Lys Ile Arg Gly Cys Thr Glu Leu Glu His His His
690 695 700

His His His
705

<210> 121

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<212> PRT

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<400> 121
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20 25 30
Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45
Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro
50 55 60
Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65 70 75 80
Leu Arg Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95
Asn Pro Arg Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110
Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Cys Ile
115 120 125
Arg Leu Glu Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr
130 135 140
Asn Glu Ala Val Ser Thr Leu Gly Cys Gly Val Arg Val Leu Ala Thr
145 150 155 160
Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
165 170 175
Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
180 185 190
Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205
Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Lys Asp Leu Met Thr Asp
210 215 220
Ala Glu Leu Ala Arg Ala Ile Ser Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240
Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255
Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270
Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
275 280 285

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

595 600 605
Ser Gln Phe Cys Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met
610 615 620
Thr Pro Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu
625 630 635 640
Lys Leu Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met
645 650 655
Lys Gly Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn
660 665 670
Leu Asp Asn Val Cys Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly
675 680 685
Val Gly Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys
690 695 700
Ala Lys Ala Phe Val Glu Lys Ile Arg Gly Cys Thr Glu Leu Glu His
705 710 715 720
His His His His His
725

<210> 122
<211> 707
<212> PRT
<213> 人工序列
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<223> 合成构建体
<400> 122

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

115 120 125
Arg Leu Glu Ser Glu Val Asn Ala Ile Lys Gly Cys Leu Lys Thr Thr
130 135 140
Asn Glu Cys Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145 150 155 160
Ala Val Arg Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala
165 170 175
Ile Asn Lys Asn Lys Cys Asp Ile Ala Asp Leu Lys Met Ala Val Ser
180 185 190
Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205
Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220
Ala Glu Leu Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln
225 230 235 240
Ile Lys Leu Met Leu Glu Asn Arg Cys Met Val Arg Arg Lys Gly Phe
245 250 255
Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270
Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala
275 280 285
Ala Pro Ser Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300
Glu Asp Gln Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320
Pro Asn Asp Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335
Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile
340 345 350
Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
355 360 365
Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380
Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385 390 395 400
Lys Gln Leu Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
405 410 415
Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
435 440 445

Ile Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
450 455 460

Glu Ser Ile Glu Asn Ser Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly
465 470 475 480

Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys
485 490 495

Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala
500 505 510

Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly
515 520 525

Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr
530 535 540

Val Ile Lys Ala Leu Ser Val Leu Lys Glu Lys Gly Ala Ile Ile Gly
545 550 555 560

Ala Gly Thr Val Thr Ser Val Glu Gln Cys Arg Lys Ala Val Glu Ser
565 570 575

Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
580 585 590

Phe Cys Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
595 600 605

Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
610 615 620

Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625 630 635 640

Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
645 650 655

Asn Val Cys Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
660 665 670

Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
675 680 685

Ala Phe Val Glu Lys Ile Arg Gly Cys Thr Glu Leu Glu His His His
690 695 700

His His His
705

<210> 123

<211> 707

<212> PRT

<213> 人工序列
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<223> 合成构建体
<400> 123
Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1 5 10 15
His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30
Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45
Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro
50 55 60
Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65 70 75 80
Leu Arg Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95
Gly Gly Gly Gly Gly Gly Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110
Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Cys Ile
115 120 125
Arg Leu Glu Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr
130 135 140
Asn Glu Ala Val Ser Thr Leu Gly Cys Gly Val Arg Val Leu Ala Thr
145 150 155 160
Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
165 170 175
Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
180 185 190
Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205
Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Lys Asp Leu Met Thr Asp
210 215 220
Ala Glu Leu Ala Arg Ala Ile Ser Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240
Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255
Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270
Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala

275 280 285

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

290 295 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr

305 310 315 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp

325 330 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile

340 345 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Cys Gly Arg Asn

355 360 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys

370 375 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile

385 390 395 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp

405 410 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly

420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro

435 440 445

Val Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Cys Phe

450 455 460

Glu Ser Ile Glu Asn Ser Gln Ala Gly Ser Gly Gly Ser Gly Ser Gly

465 470 475 480

Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys

485 490 495

Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala

500 505 510

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

515 520 525

Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr

530 535 540

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

545 550 555 560

Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser

565 570 575

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

580 585 590

Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
595 600 605
Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
610 615 620
Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
625 630 635 640
Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
645 650 655
Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
660 665 670
Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
675 680 685
Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His His His
690 695 700
His His His
705
<210> 124
<211> 725
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 124
Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1 5 10 15
His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
20 25 30
Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45
Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro
50 55 60
Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65 70 75 80
Leu Arg Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95
Gly Gly Gly Gly Gly Gly Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110
Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Cys Ile
115 120 125

Arg Leu Glu Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr
130 135 140

Asn Glu Ala Val Ser Thr Leu Gly Cys Gly Val Arg Val Leu Ala Thr
145 150 155 160

Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
165 170 175

Ile Asn Lys Asn Lys Cys Asp Ile Pro Asp Leu Lys Met Ala Val Ser
180 185 190

Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205

Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Lys Asp Leu Met Thr Asp
210 215 220

Ala Glu Leu Ala Arg Ala Ile Ser Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240

Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255

Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
275 280 285

Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300

Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320

Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335

Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
340 345 350

Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Cys Gly Arg Asn
355 360 365

Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385 390 395 400

Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
405 410 415

Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430

Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro

435 440 445

Val Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Cys Phe
450 455 460

Glu Ser Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
465 470 475 480

Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Gly Ser Gly Gly Ser Gly
485 490 495

Ser Gly Ser Gly Gly Ser Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala
500 505 510

Arg Lys Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu
515 520 525

Arg Ala Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe
530 535 540

Ala Gly Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala
545 550 555 560

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

Ile Gly Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val
580 585 590

Glu Ser Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile
595 600 605

Ser Gln Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met
610 615 620

Thr Pro Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu
625 630 635 640

Lys Leu Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met
645 650 655

Lys Gly Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn
660 665 670

Leu Asp Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly
675 680 685

Val Gly Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys
690 695 700

Ala Lys Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu Leu Glu His
705 710 715 720

His His His His His
725

<210> 125

<211> 12

<212> PRT
<213> 人工序列
<220>
<223> 折叠子序列
<400> 125
Glu Lys Ala Ala Lys Ala Glu Glu Ala Ala Arg Lys
1 5 10
<210> 126
<211> 12
<212> PRT
<213> 人工序列
<220>
<223> 接头序列
<400> 126
Gly Ser Gly Gly Ser Gly Ser Gly Ser Gly Gly Ser
1 5 10
<210> 127
<211> 15
<212> PRT
<213> 人工序列
<220>
<223> 接头序列
<400> 127
Gly Ser Gly Gly Ser Gly Ser Gly Ser Gly Gly Ser Gly Ser Gly
1 5 10 15
<210> 128
<211> 8
<212> PRT
<213> 人工序列
<220>
<223> 接头序列
<400> 128
Gly Gly Ser Gly Gly Ser Gly Ser
1 5
<210> 129
<211> 8
<212> PRT
<213> 人工序列
<220>

<223> 接头序列

<400> 129

Gly Ser Gly Gly Ser Gly Ser Gly
1 5

<210> 130

<211> 7

<212> PRT

<213> 人工序列

<220>

<223> 接头序列

<400> 130

Gly Ser Gly Ser Gly Ser Gly
1 5

<210> 131

<211> 15

<212> PRT

<213> 人工序列

<220>

<223> 接头序列

<400> 131

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

<210> 132

<211> 203

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 132

Met Glu Glu Leu Phe Lys Lys His Lys Ile Val Ala Val Leu Arg Ala
1 5 10 15

Asn Ser Val Glu Glu Ala Ile Glu Lys Ala Val Ala Val Phe Ala Gly
20 25 30

Gly Val His Leu Ile Glu Ile Thr Phe Thr Val Pro Asp Ala Asp Thr
35 40 45

Val Ile Lys Ala Leu Ser Val Leu Lys Glu Lys Gly Ala Ile Ile Gly
50 55 60

Ala Gly Thr Val Thr Ser Val Glu Gln Ala Arg Lys Ala Val Glu Ser
65 70 75 80

Gly Ala Glu Phe Ile Val Ser Pro His Leu Asp Glu Glu Ile Ser Gln
85 90 95
Phe Ala Lys Glu Lys Gly Val Phe Tyr Met Pro Gly Val Met Thr Pro
100 105 110
Thr Glu Leu Val Lys Ala Met Lys Leu Gly His Thr Ile Leu Lys Leu
115 120 125
Phe Pro Gly Glu Val Val Gly Pro Gln Phe Val Lys Ala Met Lys Gly
130 135 140
Pro Phe Pro Asn Val Lys Phe Val Pro Thr Gly Gly Val Asn Leu Asp
145 150 155 160
Asn Val Ala Glu Trp Phe Lys Ala Gly Val Leu Ala Val Gly Val Gly
165 170 175
Ser Ala Leu Val Lys Gly Thr Pro Asp Glu Val Arg Glu Lys Ala Lys
180 185 190
Ala Phe Val Glu Lys Ile Arg Gly Ala Thr Glu
195 200
<210> 133
<211> 19
<212> PRT
<213> 人工序列
<220>
<223> 信号肽
<400> 133
Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1 5 10 15
His Gly Leu
<210> 134
<211> 19
<212> PRT
<213> 人工序列
<220>
<223> 信号肽
<400> 134
Met Ser Trp Lys Val Met Ile Ile Ile Ser Leu Leu Ile Thr Pro Gln
1 5 10 15
His Gly Leu
<210> 135
<211> 119
<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 135

Asn Leu Ala Glu Lys Met Tyr Lys Ala Gly Asn Ala Met Tyr Arg Lys
1 5 10 15

Gly Gln Tyr Thr Ile Ala Ile Ile Ala Tyr Thr Leu Ala Leu Leu Lys
20 25 30

Asp Pro Asn Asn Ala Glu Ala Trp Tyr Asn Leu Gly Asn Ala Ala Tyr
35 40 45

Lys Lys Gly Glu Tyr Asp Glu Ala Ile Glu Ala Tyr Gln Lys Ala Leu
50 55 60

Glu Leu Asp Pro Asn Asn Ala Glu Ala Trp Tyr Asn Leu Gly Asn Ala
65 70 75 80

Tyr Tyr Lys Gln Gly Asp Tyr Asp Glu Ala Ile Glu Tyr Tyr Lys Lys
85 90 95

Ala Leu Arg Leu Asp Pro Arg Asn Val Asp Ala Ile Glu Asn Leu Ile
100 105 110

Glu Ala Glu Glu Lys Gln Gly
115

<210> 136

<211> 119

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 136

Glu Glu Ala Glu Leu Ala Tyr Leu Leu Gly Glu Leu Ala Tyr Lys Leu
1 5 10 15

Gly Glu Tyr Arg Ile Ala Ile Arg Ala Tyr Arg Ile Ala Leu Lys Arg
20 25 30

Asp Pro Asn Asn Ala Glu Ala Trp Tyr Asn Leu Gly Asn Ala Tyr Tyr
35 40 45

Lys Gln Gly Asp Tyr Arg Glu Ala Ile Arg Tyr Tyr Leu Arg Ala Leu
50 55 60

Lys Leu Asp Pro Glu Asn Ala Glu Ala Trp Tyr Asn Leu Gly Asn Ala
65 70 75 80

Leu Tyr Lys Gln Gly Lys Tyr Asp Leu Ala Ile Ile Ala Tyr Gln Ala
85 90 95

Ala Leu Glu Glu Asp Pro Asn Asn Ala Glu Ala Lys Gln Asn Leu Gly
100 105 110
Asn Ala Lys Gln Lys Gln Gly
115

<210> 137
<211> 119
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 137

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

<210> 138
<211> 187
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 138

Thr Asp Pro Leu Ala Val Ile Leu Tyr Ile Ala Ile Leu Lys Ala Glu
1 5 10 15
Lys Ser Ile Ala Arg Ala Lys Ala Ala Glu Ala Leu Gly Lys Ile Gly
20 25 30
Asp Glu Arg Ala Val Glu Pro Leu Ile Lys Ala Leu Lys Asp Glu Asp

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

<210> 139
<211> 119
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 139

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

100 105 110

Asn Ala Met Asp Lys Gln Gly

115

<210> 140

<211> 279

<212> PRT

<213> 人工序列

<220>

<223> 合成构建体

<400> 140

Ile Glu Glu Val Val Ala Glu Met Ile Asp Ile Leu Ala Glu Ser Ser

1 5 10 15

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

20 25 30

Glu Lys Ala Val Ala Glu Ala Ile Glu Glu Ile Ala Arg Leu Ala Thr

35 40 45

Ala Ala Ile Gln Leu Ile Glu Ala Leu Ala Lys Asn Leu Ala Ser Glu

50 55 60

Glu Phe Met Ala Arg Ala Ile Ser Ala Ile Ala Glu Leu Ala Lys Lys

65 70 75 80

Ala Ile Glu Ala Ile Tyr Arg Leu Ala Asp Asn His Thr Thr Asp Thr

85 90 95

Phe Met Ala Arg Ala Ile Ala Ala Ile Ala Asn Leu Ala Val Thr Ala

100 105 110

Ile Leu Ala Ile Ala Ala Leu Ala Ser Asn His Thr Thr Glu Glu Phe

115 120 125

Met Ala Arg Ala Ile Ser Ala Ile Ala Glu Leu Ala Lys Lys Ala Ile

130 135 140

Glu Ala Ile Tyr Arg Leu Ala Asp Asn His Thr Thr Asp Lys Phe Met

145 150 155 160

Ala Ala Ala Ile Glu Ala Ile Ala Leu Leu Ala Thr Leu Ala Ile Leu

165 170 175

Ala Ile Ala Leu Leu Ala Ser Asn His Thr Thr Glu Lys Phe Met Ala

180 185 190

Arg Ala Ile Met Ala Ile Ala Ile Leu Ala Ala Lys Ala Ile Glu Ala

195 200 205

Ile Tyr Arg Leu Ala Asp Asn His Thr Ser Pro Thr Tyr Ile Glu Lys

210 215 220

Ala Ile Glu Ala Ile Glu Lys Ile Ala Arg Lys Ala Ile Lys Ala Ile

225 230 235 240
Glu Met Leu Ala Lys Asn Ile Thr Thr Glu Glu Tyr Lys Glu Lys Ala
245 250 255
Lys Lys Ile Ile Asp Ile Ile Arg Lys Leu Ala Lys Met Ala Ile Lys
260 265 270
Lys Leu Glu Asp Asn Arg Thr
275
<210> 141
<211> 153
<212> PRT
<213> 人工序列
<220>
<223> 合成构建体
<400> 141
Lys Tyr Asp Gly Ser Lys Leu Arg Ile Gly Ile Leu His Ala Arg Trp
1 5 10 15
Asn Ala Glu Ile Ile Leu Ala Leu Val Leu Gly Ala Leu Lys Arg Leu
20 25 30
Gln Glu Phe Gly Val Lys Arg Glu Asn Ile Ile Ile Glu Thr Val Pro
35 40 45
Gly Ser Phe Glu Leu Pro Tyr Gly Ser Lys Leu Phe Val Glu Lys Gln
50 55 60
Lys Arg Leu Gly Lys Pro Leu Asp Ala Ile Ile Pro Ile Gly Val Leu
65 70 75 80
Ile Lys Gly Ser Thr Met His Phe Glu Tyr Ile Cys Asp Ser Thr Thr
85 90 95
His Gln Leu Met Lys Leu Asn Phe Glu Leu Gly Ile Pro Val Ile Phe
100 105 110
Gly Val Leu Thr Cys Leu Thr Asp Glu Gln Ala Glu Ala Arg Ala Gly
115 120 125
Leu Ile Glu Gly Lys Met His Asn His Gly Glu Asp Trp Gly Ala Ala
130 135 140
Ala Val Glu Met Ala Thr Lys Phe Asn
145 150
<210> 142
<211> 119
<212> PRT
<213> 人工序列
<220>

<223> 合成构建体
<400> 142
Glu Glu Ala Glu Leu Ala Tyr Leu Leu Gly Glu Leu Ala Tyr Lys Leu
1   5   10   15
Gly Glu Tyr Arg Ile Ala Ile Arg Ala Tyr Arg Ile Ala Leu Lys Arg
            20   25   30
Asp Pro Asn Asn Ala Glu Ala Trp Tyr Asn Leu Gly Asn Ala Tyr Tyr
        35   40   45
Lys Gln Gly Arg Tyr Arg Glu Ala Ile Glu Tyr Tyr Gln Lys Ala Leu
    50   55   60
Glu Leu Asp Pro Asn Asn Ala Glu Ala Trp Tyr Asn Leu Gly Asn Ala
65   70   75   80
Tyr Tyr Glu Arg Gly Glu Tyr Glu Glu Ala Ile Glu Tyr Tyr Arg Lys
                85   90   95
Ala Leu Arg Leu Asp Pro Asn Asn Ala Asp Ala Met Gln Asn Leu Leu
            100   105   110
Asn Ala Lys Met Arg Glu Glu
        115
<210> 143
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> 聚-His标签
<400> 143
His His His His His His
1   5

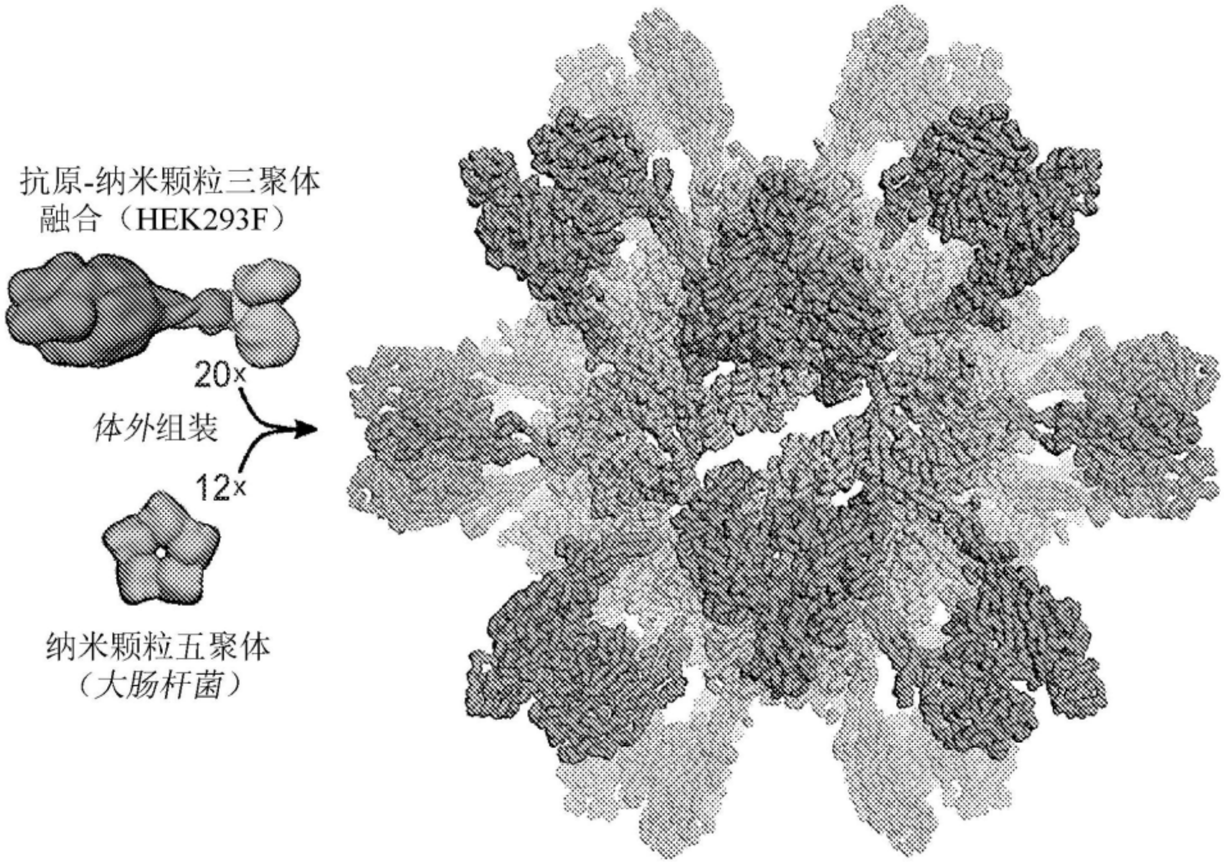

图1A

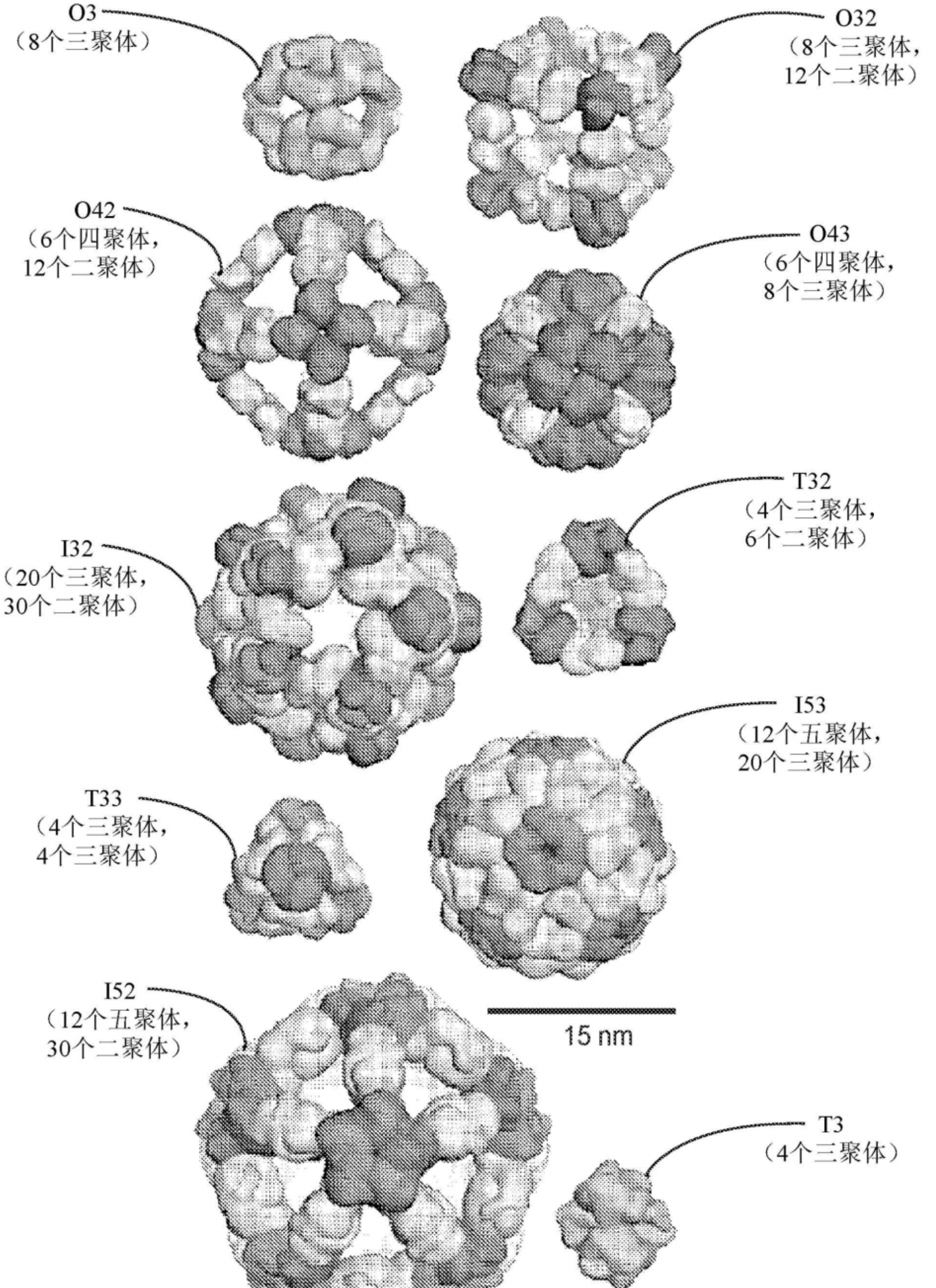
O3
（8个三聚体）
O32
（8个三聚体，
12个二聚体）
O42
（6个四聚体，
12个二聚体）
O43
（6个四聚体，
8个三聚体）
I32
（20个三聚体，
30个二聚体）
T32
（4个三聚体，
6个二聚体）
I53
（12个五聚体，
20个三聚体）
T33
（4个三聚体，
4个三聚体）
I52
（12个五聚体，
30个二聚体）
15 nm
T3
（4个三聚体）

图1B

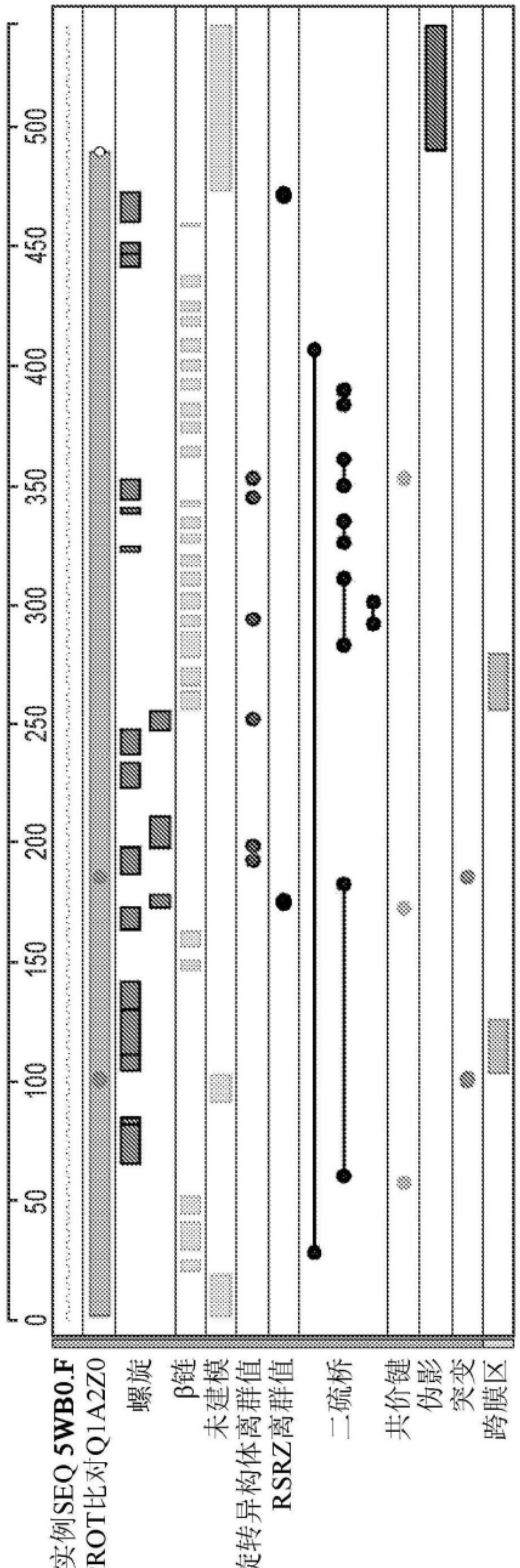
PDB实例SEQ 5WB0.F
UNIPROT比对Q1A2Z0
螺旋
β链
未建模
旋转异构体离群值
RSRZ离群值
二硫桥
共价键
伪影
突变
跨膜区
0
50
100
150
200
250
300
350
400
450
500

图2

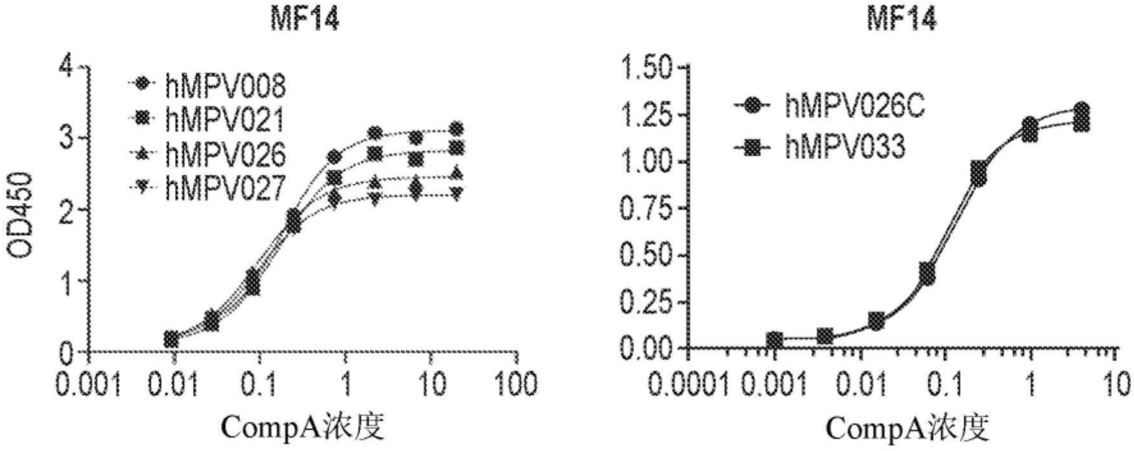
MF14
OD450
hMPV008
hMPV021
hMPV026
hMPV027
0
1
2
3
4
0.001
0.01
0.1
1
10
100
CompA浓度
MF14
hMPV026C
hMPV033
0.00
0.25
0.50
0.75
1.00
1.25
1.50
0.0001
0.001
0.01
0.1
1
10
CompA浓度

图3A

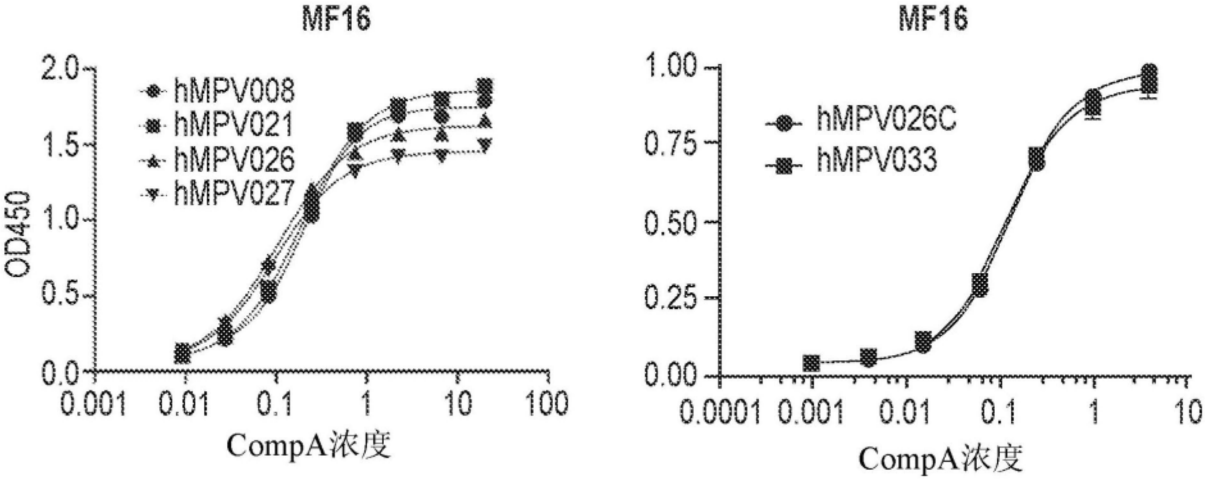
MF16
OD450
hMPV008
hMPV021
hMPV026
hMPV027
0.0
0.5
1.0
1.5
2.0
0.001
0.01
0.1
1
10
100
CompA浓度
MF16
hMPV026C
hMPV033
0.00
0.25
0.50
0.75
1.00
0.0001
0.001
0.01
0.1
1
10
CompA浓度

图3B

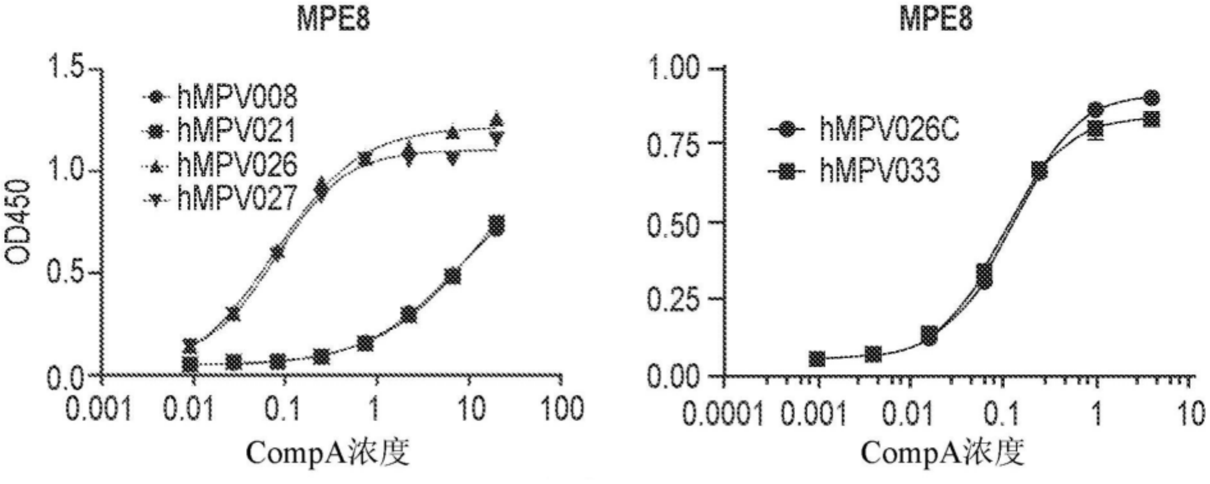
MPE8
OD450
hMPV008
hMPV021
hMPV026
hMPV027
0.0
0.5
1.0
1.5
0.001
0.01
0.1
1
10
100
CompA浓度
MPE8
hMPV026C
hMPV033
0.00
0.25
0.50
0.75
1.00
0.0001
0.001
0.01
0.1
1
10
CompA浓度

图3C

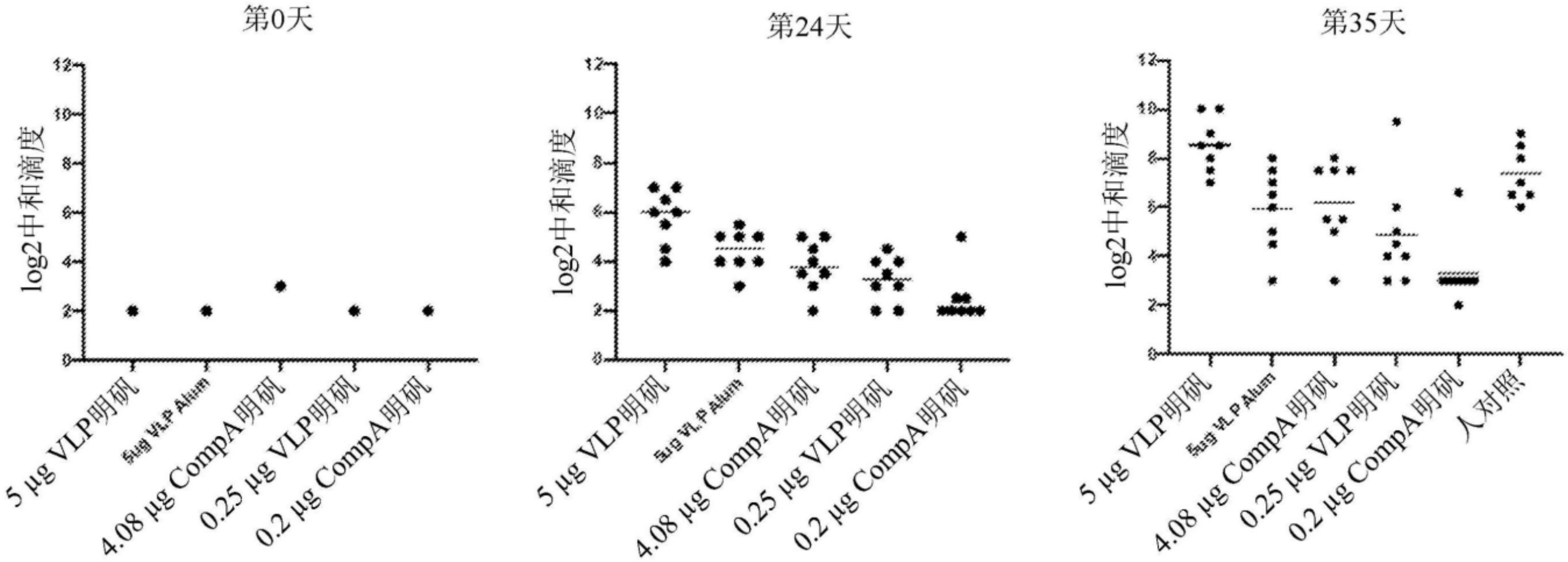
第0天
第24天
第35天
log2中和滴度
0
2
4
6
8
10
12
5 μg VLP明矾
5μg VLP Alum
4.08 μg CompA明矾
0.25 μg VLP明矾
0.2 μg CompA明矾
人对照

图4

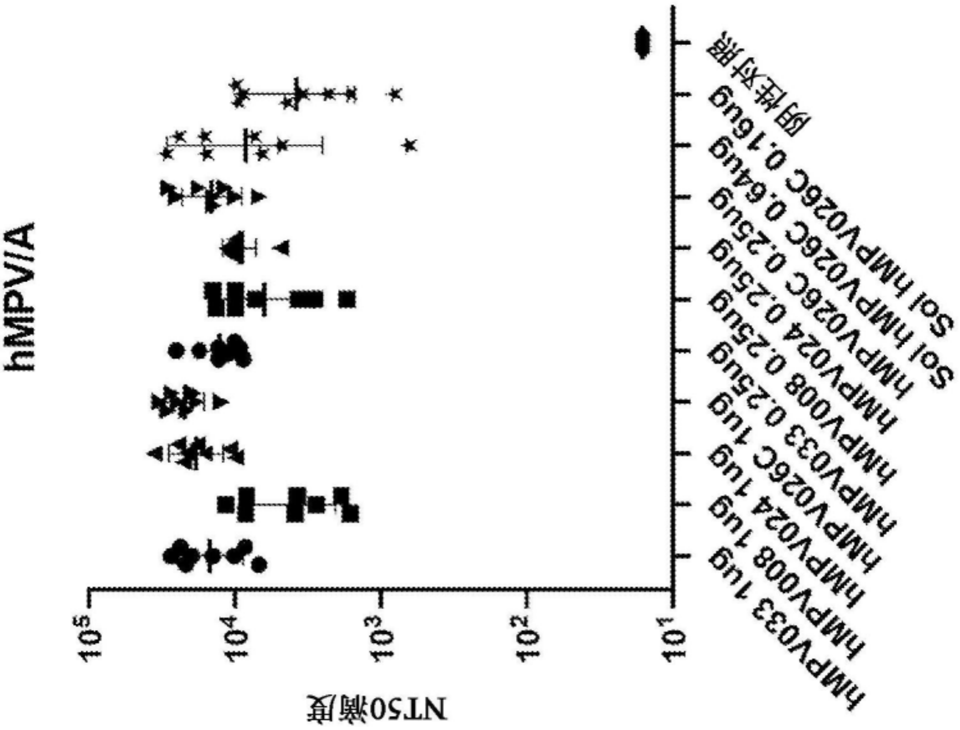
hMPV/A
NT50滴度
10^5
10^4
10^3
10^2
10^1
hMPV033 1ug
hMPV008 1ug
hMPV024 1ug
hMPV026C 1ug
hMPV033 0.25ug
hMPV008 0.25ug
hMPV024 0.25ug
hMPV026C 0.25ug
Sol hMPV026C 0.64ug
Sol hMPV026C 0.16ug
阴性对照

图5A

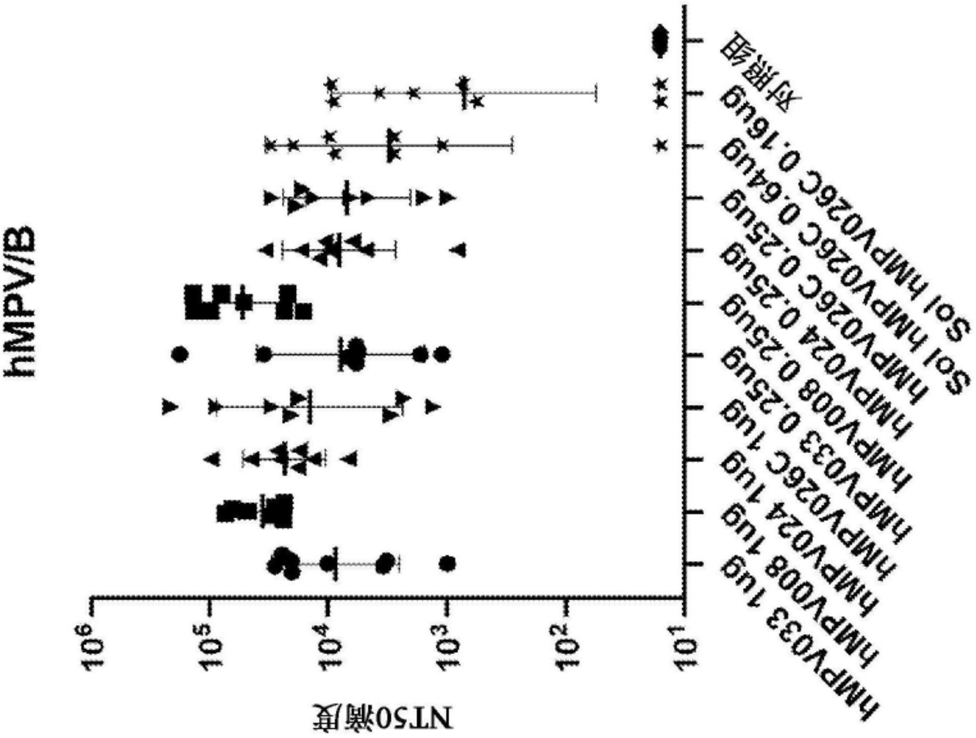
hMPV/B
NT50滴度
10^6
10^5
10^4
10^3
10^2
10^1
hMPV033 1ug
hMPV008 1ug
hMPV024 1ug
hMPV026C 1ug
hMPV033 0.25ug
hMPV008 0.25ug
hMPV024 0.25ug
hMPV026C 0.25ug
Sol hMPV026C 0.64ug
Sol hMPV026C 0.16ug
对照组

图5B

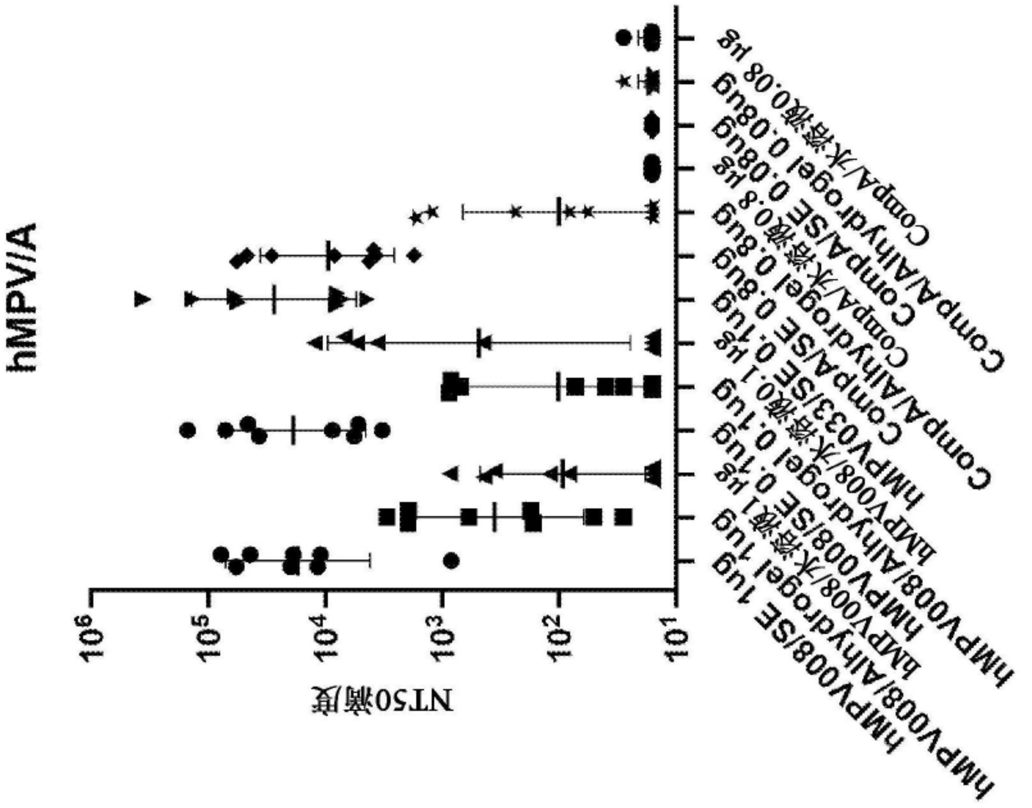
hMPV/A
NT50滴度
10^1
10^2
10^3
10^4
10^5
10^6
hMPV008/SE 1ug
hMPV008/Alhydrogel 1ug
hMPV008/水溶液1 μg
hMPV008/SE 0.1ug
hMPV008/Alhydrogel 0.1ug
hMPV008/水溶液0.1 μg
hMPV033/SE 0.1ug
CompA/SE 0.8ug
CompA/Alhydrogel 0.8ug
CompA/水溶液0.8 μg
CompA/SE 0.08ug
CompA/Alhydrogel 0.08ug
CompA/水溶液0.08 μg

图6A

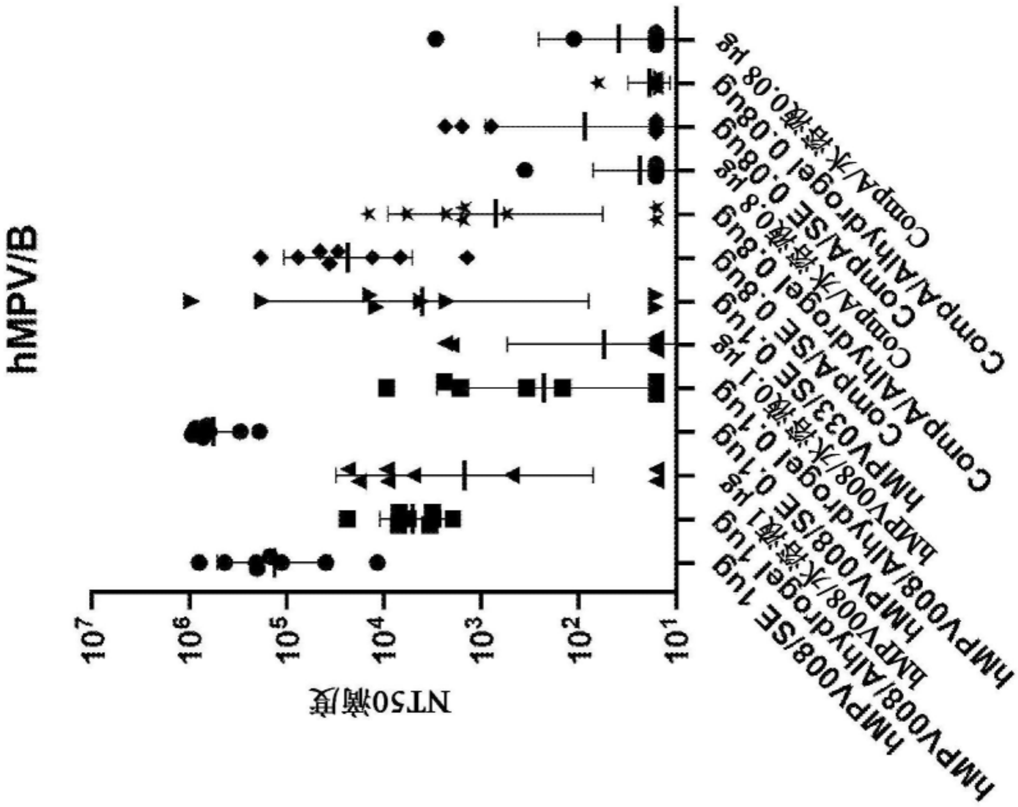
hMPV/B
NT50滴度
10^1
10^2
10^3
10^4
10^5
10^6
10^7
CompA/水溶液0.08 μg
CompA/Alhydrogel 0.08ug
CompA/SE 0.08ug
CompA/水溶液0.8 μg
CompA/Alhydrogel 0.8ug
CompA/SE 0.8ug
hMPV033/SE 0.1ug
hMPV008/水溶液0.1 μg
hMPV008/Alhydrogel 0.1ug
hMPV008/SE 0.1ug
hMPV008/水溶液1 μg
hMPV008/Alhydrogel 1ug
hMPV008/SE 1ug

图6B

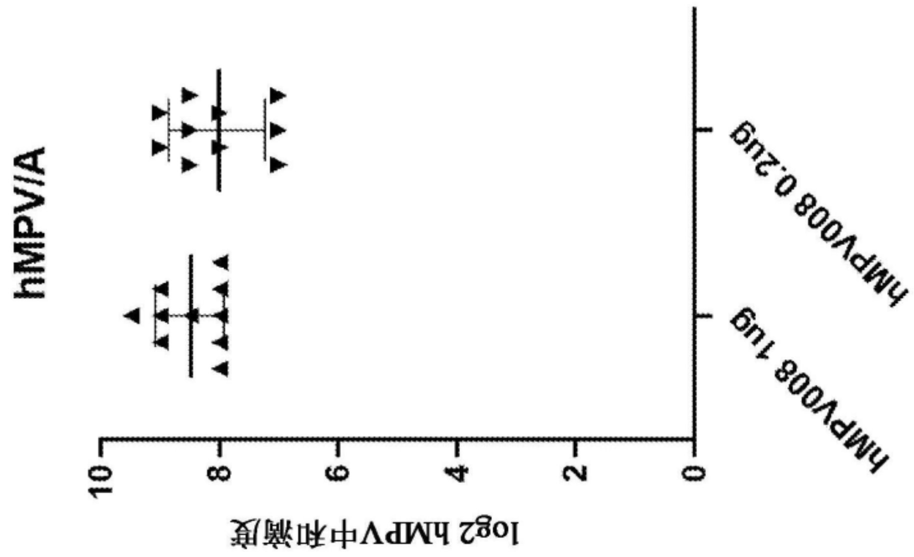
hMPV/A
log2 hMPV中和滴度
0
2
4
6
8
10
hMPV008 1ug
hMPV008 0.2ug

图7A

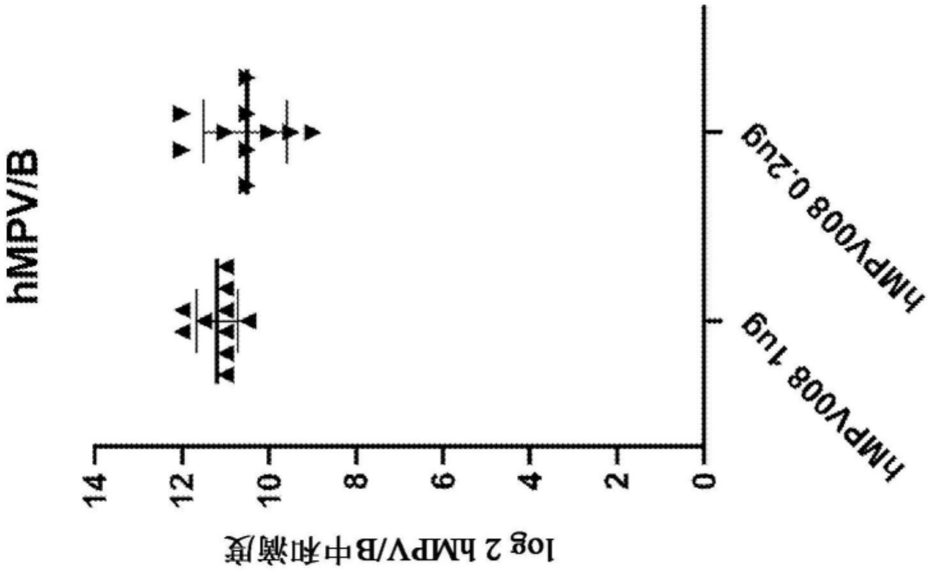
hMPV/B
log 2 hMPV/B中和滴度
14
12
10
8
6
4
2
0
hMPV008 1ug
hMPV008 0.2ug

图7B

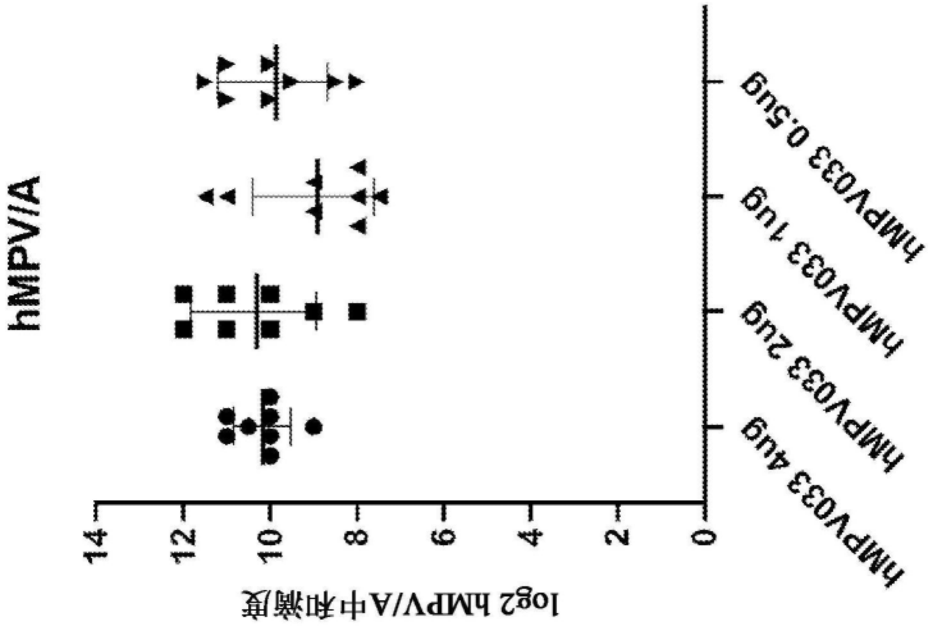
hMPV/A
log2 hMPV/A中和滴度
14
12
10
8
6
4
2
0
hMPV033 4ug
hMPV033 2ug
hMPV033 1ug
hMPV033 0.5ug

图8A

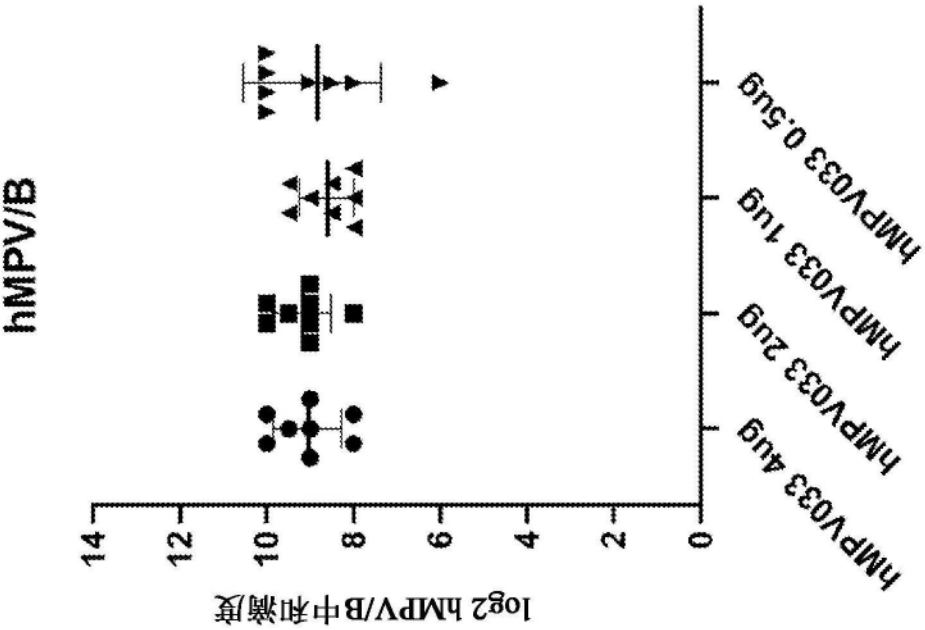
hMPV/B
log2 hMPV/B中和滴度
14
12
10
8
6
4
2
0
hMPV033 4ug
hMPV033 2ug
hMPV033 1ug
hMPV033 0.5ug

图8B

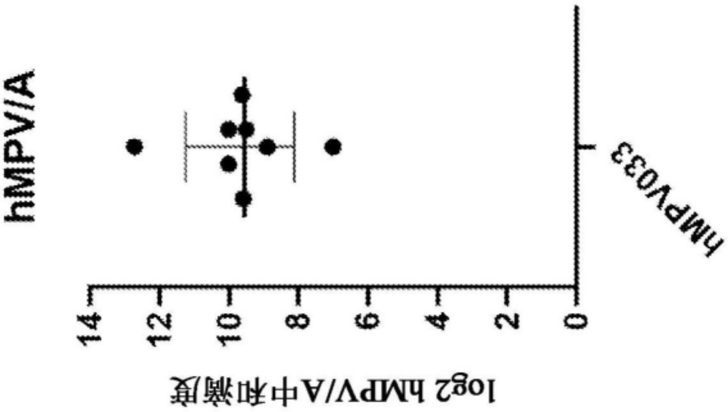
hMPV/A
log2 hMPV/A中和滴度
14
12
10
8
6
4
2
0
hMPV033

图9A

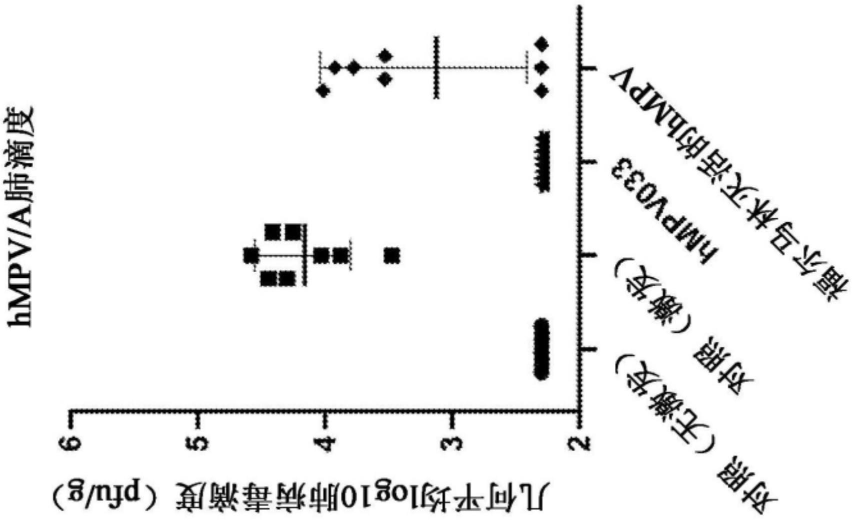
hMPV/A肺滴度
几何平均log10肺病毒滴度（pfu/g）
6
5
4
3
2
对照（无感染）
对照（感染）
hMPV033
福尔马林灭活的hMPV

图9B

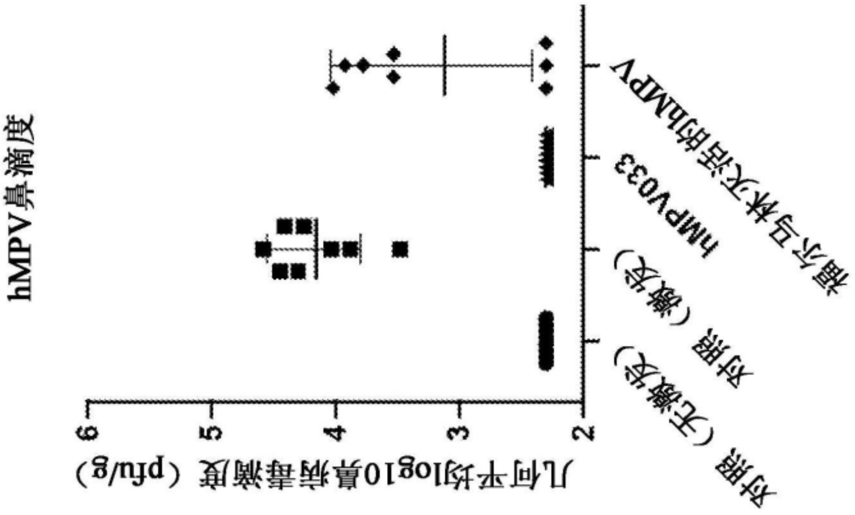
hMPV鼻滴度
几何平均log10鼻病毒滴度（pfu/g）
6
5
4
3
2
对照（无感染）
对照（感染）
hMPV033
福尔马林灭活的hMPV

图9C