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(54)发明名称

表达RSV G的重组嵌合牛/人副流感病毒3及其用途

(57)摘要

提供了表达呼吸道合胞病毒(RSV)G蛋白或重组RSV G蛋白的重组嵌合牛/人副流感病毒3(rB/HPIV3)载体、以及使用和制备它们的方法。所述rB/HPIV3载体包含如下基因组,所述基因组包含编码所述RSV G蛋白或所述重组RSV G蛋白的异源基因。还提供了包含所公开的rB/HPIV3载体的基因组或反基因组的序列的核酸分子。所公开的rB/HPIV3载体可以用于例如在受试者中诱导对RSV和HPIV3的免疫应答。

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1.一种重组嵌合牛/人副流感病毒3(rB/HPIV3),其包含:

以3'至5'顺序包含3'前导区、BPIV3 N基因、异源基因、BPIV3 P和M基因、HPIV3 F和HN基因、BPIV3 L基因和5'尾随区的基因组;

其中所述异源基因编码以下之一:

(a)RSV G蛋白,所述RSV G蛋白包含RSV G胞外结构域、跨膜结构域和胞质尾;

(b)重组RSV G蛋白,所述重组RSV G蛋白包含RSV G胞外结构域、BPIV3 HN跨膜结构域和BPIV3 HN胞质尾;

(c)重组RSV G蛋白,所述重组RSV G蛋白包含RSV G胞外结构域、HPIV3 HN跨膜结构域和HPIV3 HN胞质尾;或

(d)重组RSV G蛋白,所述重组RSV G蛋白包含RSV G胞外结构域、HPIV1 HN跨膜结构域和HPIV1 HN胞质尾;

其中所述HPIV3 HN基因编码在位置263和370处包含苏氨酸和脯氨酸残基的HPIV3 HN蛋白;并且

其中所述重组B/HPIV3是感染性的、减毒的和自我复制的。

2.根据权利要求1所述的rB/HPIV3,其中所述RSV G胞外结构域包含SEQ ID NO:23、48、50、52或54中任一个所阐述的氨基酸序列或与其至少90%相同的氨基酸序列,或者由所述氨基酸序列组成。

3.根据权利要求1或权利要求2所述的rB/HPIV3,其中所述BPIV3 HN跨膜结构域和胞质尾包含SEQ ID NO:29所阐述的氨基酸序列或与其至少90%相同的氨基酸序列,或者由所述氨基酸序列组成。

4.根据权利要求1或权利要求2所述的rB/HPIV3,其中所述HPIV3 HN跨膜结构域和胞质尾包含SEQ ID NO:57所阐述的氨基酸序列或与其至少90%相同的氨基酸序列,或者由所述氨基酸序列组成。

5.根据权利要求1或权利要求2所述的rB/HPIV3,其中所述HPIV1 HN跨膜结构域和胞质尾包含SEQ ID NO:60所阐述的氨基酸序列或与其至少90%相同的氨基酸序列,或者由所述氨基酸序列组成。

6.根据权利要求1所述的rB/HPIV3,其中所述RSV G蛋白包含SEQ ID NO:22、47、49、51、53中任一个所阐述的氨基酸序列或与其至少90%相同的氨基酸序列,或者由所述氨基酸序列组成。

7.根据权利要求1所述的rB/HPIV3,其中包含所述RSV G胞外结构域、所述BPIV3 HN跨膜结构域和所述BPIV3 HN胞质尾的重组RSV G蛋白包含SEQ ID NO:31、62、64、66或68中任一个所阐述的氨基酸序列或与其至少90%相同的氨基酸序列,或者由所述氨基酸序列组成。

8.根据权利要求1所述的rB/HPIV3,其中包含所述RSV G胞外结构域、所述HPIV3 HN跨膜结构域和所述HPIV3 HN胞质尾的重组RSV G蛋白包含SEQ ID NO:70、72、74、76或78中任一个所阐述的氨基酸序列或与其至少90%相同的氨基酸序列,或者由所述氨基酸序列组成。

9.根据权利要求1所述的rB/HPIV3,其中包含所述RSV G胞外结构域、所述HPIV1 HN跨膜结构域和所述HPIV1 HN胞质尾的重组RSV G蛋白包含SEQ ID NO:80、82、84、86或88中任

一个所阐述的氨基酸序列或与其至少90％相同的氨基酸序列，或者由所述氨基酸序列组成。

10.根据前述权利要求中任一项所述的rB/HPIV3，其中所述RSV G胞外结构域来自人A亚型RSV或人B亚型RSV。

11.根据前述权利要求中任一项所述的rB/HPIV3，其中所述RSV G蛋白是来自人A亚型RSV或人B亚型RSV的野生型RSV G蛋白。

12.根据前述权利要求中任一项所述的rB/HPIV3，其中：

所述BPIV3 N基因编码N蛋白，所述N蛋白包含SEQ ID NO:1所阐述的氨基酸序列或与其至少90％相同的氨基酸序列，或者由所述氨基酸序列组成；

所述BPIV3 P基因编码P、C和V蛋白，所述P、C和V蛋白分别包含SEQ ID NO:2、3和4所阐述的氨基酸序列或与其至少90％相同的氨基酸序列，或者由所述氨基酸序列组成；

所述BPIV3 M基因编码M蛋白，所述M蛋白包含SEQ ID NO:5所阐述的氨基酸序列或与其至少90％相同的氨基酸序列，或者由所述氨基酸序列组成；

所述HPIV3 F基因编码F蛋白，所述F蛋白包含SEQ ID NO:6所阐述的氨基酸序列或与其至少90％相同的氨基酸序列，或者由所述氨基酸序列组成；

所述HPIV3 HN基因编码HN蛋白，所述HN蛋白包含SEQ ID NO:7所阐述的氨基酸序列或与SEQ ID NO:7至少90％相同的氨基酸序列，或者由所述氨基酸序列组成;和/或

所述BPIV3 L基因编码L蛋白，所述L蛋白包含SEQ ID NO:10所阐述的氨基酸序列或与其至少90％相同的氨基酸序列，或者由所述氨基酸序列组成。

13.根据前述权利要求中任一项所述的rB/HPIV3，其中所述异源基因经密码子优化以在人类细胞中表达。

14.根据权利要求13所述的rB/HPIV3，其中经密码子优化以在人类中表达的所述异源基因包含SEQ ID NO:89、90或95所阐述的反基因组cDNA序列。

15.根据权利要求1所述的rB/HPIV3，其中所述基因组包含SEQ ID NO:91-94中任一个所阐述的反基因组cDNA序列。

16.根据前述权利要求中任一项所述的rB/HPIV3，其中所述rB/HPIV3诱导对RSV G蛋白、HPIV3 F蛋白和HPIV3 HN蛋白的免疫应答。

17.根据前述权利要求中任一项所述的rB/HPIV3，其中所述rB/HPIV3诱导中和RSV和HPIV3的免疫应答。

18.一种核酸分子，其包含根据前述权利要求中任一项所述的rB/HPIV3的基因组的核苷酸序列、或所述基因组的反基因组cDNA或RNA序列。

19.一种载体，其包含根据权利要求18所述的分离的核酸分子。

20.一种宿主细胞，其包含根据权利要求18或权利要求19所述的核酸分子或载体。

21.一种产生rB/HPIV3的方法，其包括：

用根据权利要求19所述的载体转染容许细胞培养物；

将所述细胞培养物温育足够的时间段以允许病毒复制;以及

纯化所复制的病毒以产生所述rB/HPIV3。

22.一种通过根据权利要求21所述的方法产生的rB/HPIV3。

23.一种免疫原性组合物，其包含根据权利要求1-17或22中任一项所述的rB/HPIV3以

及药学上可接受的载体。

24.一种在受试者中引发对呼吸道合胞病毒和人副流感病毒3的免疫应答的方法，其包括对所述受试者给予根据权利要求23所述的免疫原性组合物以产生所述免疫应答。

25.根据权利要求24所述的方法，其包括鼻内给予所述免疫原性组合物。

26.根据权利要求24或权利要求25所述的方法，其中所述受试者是人。

27.根据权利要求24-26中任一项所述的方法，其中所述受试者小于一岁。

28.根据权利要求24-27中任一项所述的方法，其中所述免疫应答是保护性免疫应答。

29.根据权利要求1-17或22中任一项所述的rB/HPIV3用以在受试者中引发对RSV和HPIV3的免疫应答的用途。

表达RSV G的重组嵌合牛/人副流感病毒3及其用途

[0001] 相关申请的交叉引用

[0002] 本申请要求2017年5月29日提交的美国临时申请号62/512,111的权益，其通过引用以整体并入本文。

技术领域

[0003] 本公开文本涉及表达呼吸道合胞病毒(RSV)G蛋白或重组RSV G蛋白的重组嵌合牛/人副流感病毒3(rB/HPIV3)载体，以及所述rB/HPIV3载体的用途，例如，用于在受试者中诱导对RSV和HPIV3的免疫应答。

[0004] 联合研究协议各方

[0005] 本发明是根据美国国立卫生研究院国家过敏症和传染病研究所和赛诺菲巴斯德公司(Sanofi Pasteur,Inc)之间的公共卫生服务合作研究与开发协议(PHS-CRADA)第2013-0810号完成的。

背景技术

[0006] RSV是肺泡病毒科(Pneumoviridae)正肺炎病毒属(Orthopneumovirus) 的一种有包膜的不分节段负链RNA病毒。它是一岁以下儿童毛细支气管炎和肺炎的最常见病因。RSV还会导致反复感染(包括严重的下呼吸道疾病)，其可能发生在任何年龄，尤其是在老年人或心脏、肺或免疫系统受损的人中。当前，被动免疫接种用于预防由RSV感染引起的严重疾病，尤其是在早产、支气管肺发育不良或先天性心脏病的婴儿中。尽管在某些人群中存在RSV感染的负担，但是有效的RSV疫苗的开发仍然遥遥无期。

[0007] 副流感病毒(PIV)是密切相关的有包膜的不分节段负链RNA病毒，其属于密切相关的副粘液病毒科。PIV包括呼吸道病毒属(Respirovirus)(包括 PIV1、PIV3、仙台病毒)和腮腺炎病毒属(Rubulavirus)(包括PIV2、PIV4、 PIV5)的成员。人副流感病毒(HPIV，血清型1、2和3)在引起全世界婴儿和儿童的严重呼吸道感染方面仅次于RSV，就疾病影响而言，HPIV3是相关性最高的HPIV。HPIV3基因组为约15.5kb，基因顺序为3'-N-P-M-F-HN-L。每个基因编码单独的mRNA，所述mRNA编码主要蛋白质:N，核蛋白;P，磷蛋白;M，基质蛋白;F，融合糖蛋白;HN，血凝素-神经氨酸酶糖蛋白； L，大聚合酶蛋白，其中P基因含有编码辅助C蛋白和V蛋白的其他开放阅读框。与RSV相似，有效的HPIV疫苗的开发仍然遥遥无期。

[0008] 开发针对RSV和HPIV3的儿科疫苗的主要挑战包括婴儿期免疫系统的不成熟、母体抗体的免疫抑制、呼吸道浅表上皮的免疫保护效率低下以及在对初次感染病毒的受者使用灭活或亚单位的RSV和HPIV3疫苗进行的研究中已观察到的疫苗诱导的疾病增强。此外，先前对表达RSV抗原(RSV F蛋白) 的减毒活rB/HPIV3载体的研究揭示，对RSV的被认为不足以用于疫苗使用的免疫原性令人失望。

[0009] 因此，尽管付出了巨大的努力，但是仍然需要诱导对RSV和HPIV3的保护性免疫应答(特别是在儿科受试者中)的安全且有效的免疫原。

发明内容

[0010] 本文提供了表达RSV G或其变体的重组嵌合牛/人副流感病毒3 (rB/HPIV3)载体(“rB/HPIV3-RSV G”载体)。所公开的rB/HPIV3-RSV G 载体包含基因组,所述基因组以3’至5’顺序包含3’前导区、BPIV3 N基因、异源基因、BPIV3 P和M基因、HPIV3 F和HN基因、BPIV3 L基因和5’尾随区。所述异源基因编码以下之一:(a)包含RSV G胞外结构域、跨膜结构域和胞质尾的RSV G蛋白;(b)包含RSV G胞外结构域、BPIV3 HN跨膜结构域和 BPIV3 HN胞质尾的重组RSV G蛋白;(c)包含RSV G胞外结构域、HPIV3 HN 跨膜结构域和HPIV3 HN胞质尾的重组RSV G蛋白;或(d)包含RSV G胞外结构域、HPIV1 HN跨膜结构域和HPIV1 HN胞质尾的重组RSV G蛋白。所述 HPIV3 HN基因编码包含263T和370P氨基酸分配的HPIV3 HN蛋白。本文公开的rB/HPIV3载体是感染性的、减毒的和自我复制的载体,并且可用于诱导对 RSV和HPIV3的免疫应答。

[0011] 在一些实施方案中,可以对编码野生型(wt)RSV G蛋白或重组RSV G 蛋白的异源基因进行密码子优化以在人类细胞中表达。

[0012] 本文还提供了与所公开的病毒的表达有关的方法和组合物。例如,公开了分离的多核苷酸分子,其包括编码所述病毒的基因组或反基因组的核酸序列。

[0013] 还提供了包括rB/HPIV3-RSV G的免疫原性组合物。所述组合物可以进一步包含佐剂。还公开了通过向受试者给予有效量的所公开的 rB/HPIV3-RSV G来在受试者中引发免疫应答的方法。在一些实施方案中,所述受试者是人类受试者,例如,年龄在1月龄与6月龄之间,或1月龄与12 月龄之间,或1月龄与18月龄之间或年龄更大的人类受试者。

[0014] 本公开文本的上述和其他特征和优点将从以下参照附图对若干实施方案的详细描述中变得更清楚。

附图说明

[0015] 图1A-1C.rB/HPIV3-RSV G载体的rB/HPIV3基因组和添加的RSV G基因的图谱,以及载体中包含的经修饰RSV G蛋白的示意图和特征。(图1A) rB/HPIV3基因图谱和G蛋白示意图。所述rB/HPIV3基因图谱显示在顶部,第二行显示了使用所示的AscI位点(加了下划线)在载体N和P基因之间第二基因位置插入的RSV病毒株A2 G基因侧翼的序列的详细信息。N GE:来自 BPIV3 N基因的基因终止信号;P GS:来自BPIV3 P基因的基因起始信号; M48:可以用作替代的翻译起始位点的RSV G开放阅读框(ORF)的AUG密码子48;CX3C(G氨基酸182-186):在RSV病毒株中保守的曲动蛋白 (fractalkine)基序;G ORF的TGA终止密码子加粗并加了下划线。额外的TAG 终止密码子用***划下划线,并包括在用***示出的那些G蛋白插入片段中:所述三核苷酸在当需要调整序列长度以符合“六位规则”时添加(参见Kolakofsky Virology 498:94-98,2016)。显示了RSV G蛋白结构的几个示意图,包括:(i)wt G,未经修饰的野生型RSV G;(ii)mG,由于消除了分泌G(sG) 表达的M48I突变,仅表达RSV G的跨膜形式(mG);(iii)sG,由于前47个密码子的缺失而仅表达sG,因此所述ORF以M48密码子开始;(iv)G_B3CT, RSV G的胞质尾(CT)被BPIV3 HN的CT替代;(v)G_B3TMCT,RSV G的跨膜结构域(TM)和CT被BPIV3 HN的TM和CT替代;(vi)G_dCX3C,具有 C186R突变,其消除CX3C基序(产生CX3R);(vii)G_wCX4C,添加有A186 以消除CX3C基序(产生CX3AC);(viii)G_dCX3C_B3CT,具有C186R突变,其消除CX3C基序,并带有BPIV3 HN的CT;(ix)G_dCX3C_

B3TMCT，具有 C186R突变，其消除CX3C基序，并带有BPIV3 HN的TM和CT；(x)wt G/GS-opt，GenScript密码子优化的wt G。(图1B)wt RSV G蛋白的TM和CT 结构域的氨基酸序列(顶部)；以及RSV G的以下经修饰版本：mG、sG、G_B3CT和G_B3TMCT；以及wt BPIV3 HN(Kansas株)和wt HPIV3 HN(JS 株)。所述序列根据氨基酸66处的所述G胞外结构域起点进行比对。假定的 CT、TM和胞外结构域用虚线标定，而BPIV3 HN序列则加了方框。注意，sG 的N末端是初级翻译产物的N末端，其随后经过蛋白水解修剪以产生N66处的主要N末端或I75处的次要N末端。(图1C)wt G蛋白的未经修饰的CX3C基序的序列(顶行，显示蛋白质(SEQ ID NO:41)和核苷酸(SEQ ID NO:42) 序列)；dCX3C版本的序列，其中所述CX3C基序被C186R错义突变破坏(中间行，显示蛋白质(SEQ ID NO:43)和核苷酸(SEQ ID NO:44)序列)；以及wCX4C版本的序列，其中所述CX3C基序通过在密码子185后添加丙氨酸密码子被破坏(底行，显示蛋白质(SEQ ID NO:45)和核苷酸(SEQ ID NO: 46)序列)。保守的半胱氨酸残基加粗；dCX3C和wCX4C中的突变核苷酸加了下划线。

[0016] 图2A-2D.来自rB/HPIV3-RSV G载体在Vero细胞中表达的经修饰RSV G蛋白的Western印迹分析。用所示的rB/HPIV3-RSV G载体或wt RSV分别以每个细胞10TCID$_{50}$或3PFU的MOI将Vero细胞感染。感染后24小时(h.p.i.)，收获所述细胞用于分析，并且在48h.p.i.，收获来自重复培养的上层细胞培养基上清液用于分析。通过在变性和还原条件下的凝胶电泳分别分析所述细胞和培养基上清液，随后通过使用分别针对RSV和HPIV3产生的抗血清并随后使用与红外荧光染料缀合的二抗进行Western印迹，并使用Odyssey成像系统 (LiCor)进行的光密度分析来定量完全糖基化的90-120kDa RSV G蛋白的大优势条带的相对水平。(图2A)来自感染细胞的蛋白质的Western印迹。顶图：左侧的条表示RSV G的完全糖基化和部分糖基化形式(分别为上部和下部条)，泳道11另外显示了由wt RSV表达的RSV N、P、M蛋白。中图：BPIV3 N 蛋白。底图：用作上样对照的GAPDH蛋白。(图2B)使用LiCor Image Studio 软件通过密度测量法从A部分中的实验中定量得到的完全糖基化(90-120 kDa)RSV G的相对水平，其中所述LiCor Image Studio软件使用GAPDH信号进行了校准并相对于设置为1.0的wt G(泳道2)归一化。(图2C)细胞培养基上清液中G蛋白的Western印迹。(图2D)来自图2C的完全糖基化的G蛋白的相对水平，相对于wt G归一化。

[0017] 图3A和3B.在LLC-MK2细胞中来自rB/HPIV3-RSV G载体的RSV G表达的Western印迹分析。如图2A所述，用所示的rB/HPIV3-RSV G构建体或wt RSV感染LLC-MK2细胞。在24h.p.i.收获细胞进行处理并使用分别针对RSV 和HPIV3产生的抗血清进行Western印迹分析，如图2A和2B中所述。(图3A) Western印迹显示RSV G(顶图)、BPIV3 N(中图)和作为上样对照的GAPDH (底图)的表达。(图3B)从图3A中定量并相对于为1.0的wt G(泳道2)归一化的的完全糖基化(90-120kDa)RSV G的相对水平。

[0018] 图4A和4B.表征来自rB/HPIV3-RSV G的经修饰形式的RSV G蛋白的表达的双重染色噬斑测定。将表达所示经修饰G蛋白的rB/HPIV3构建体以10倍稀释系列接种在24孔板的Vero细胞单层上，并在甲基纤维素覆盖下温育6天。用80％甲醇固定所述单层，并用所示的一抗进行分析，随后用缀合至红外染料的二抗进行分析。(图4A)用分别针对HPIV3和RSV产生的兔抗血清和针对RSV的山羊超免疫血清(ab20531，Abcam)探测的噬斑图像：单独的HPIV3 抗原可视化为绿色，单独的RSV G蛋白可视化为红色，并且共表达可视化为黄色。(图4B)用相同的HPIV3特异性兔超免疫血清和对CX3C结构域具有特异性的RSV G mAb 131-2G

探测的噬斑图像:单独的HPIV3抗原可视化为绿色,含有所述131-2G表位的RSV G蛋白可视化为红色,并且共表达可视化为黄色。

[0019] 图5A和5B.通过经纯化rB/HPIV3-RSV G颗粒的Western印迹分析进行的 RSV G封装效率的定量。将LLC-MK2和Vero细胞分别用0.01$TCID_{50}$的所示 rB/HPIV3-RSV G构建体或0.1PFU的wt RSV感染。在第4天收获培养物,并将澄清化的细胞培养基上清液以不连续的30%/60%w/v蔗糖梯度进行离心。从蔗糖界面收获经纯化的病毒体,并通过离心沉淀。在变性和还原条件下,将约4μg的每种病毒进行凝胶电泳。制备Western印迹并用分别针对RSV和HPIV3产生的抗血清进行分析。(图5A)空rB/HPIV3载体(泳道1)、表达wt RSV G的载体(泳道2)、表达所示经修饰形式的RSV G的载体(泳道3-5)和 wt RSV(泳道6)的Western印迹。上图用多克隆RSV抗体探测,显示泳道5 中明显的G的完全糖基化90-120kDa形式,以及RSV结构蛋白N、P、M和G 蛋白,包括先前所述(Corry等J.Virol.90:1311-1320,2015)的在Vero细胞的情况下通常观察到的G的较小的宽条带(约48-62kDa)(泳道6)。底图显示了BPIV3 N蛋白。(图5B)基于图5A的定量并相对于为1.0的wt G(泳道2) 归一化的RSV G封装效率。

[0020] 图6A-6L.通过使用免疫金标记的透射电子显微镜检查(TEM)对病毒体中封装的RSV G的成像。将来自图5中描述的制剂的经纯化病毒体与G特异性小鼠MAb 131-2G(对CX3C结构域具有特异性)和与10nm金颗粒缀合的多克隆山羊抗小鼠二抗一起温育。显示了以下的所选代表性病毒体图像:wt RSV(图6A和6B)、表达wt RSV G的rB/HPIV3载体(图6C和6D)、仅表达sG 的rB/HPIV3载体(图6E和6F)、表达带有BPIV3 HN的CT的嵌合RSV G的 rB/HPIV3载体(图6G和6H)、表达带有BPIV3 HN的TM和CT的嵌合RSV G 的rBHPIV3载体(图6I和6J)以及空rB/HPIV3载体(图6K和6L)。

[0021] 图7A和7B.rB/HPIV3-RSV G载体在仓鼠上呼吸道和下呼吸道中的复制。将六只一组的仓鼠用$10^5$$TCID_{50}$的载体或$10^6$PFU的wt RSV进行鼻内(IN) 感染。免疫接种后第5天收集鼻甲和肺,并进行均质化处理。通过对LLC-MK2 细胞进行$TCID_{50}$血细胞吸附测定确定鼻甲(图7A)和肺(图7B)中载体的滴度。$TCID_{50}$的检测限以虚线表示。平均滴度和平均值的标准误差(SEM) 显示为带有误差条的水平线。使用单向方差分析,随后采用Tukey-Kramer检验分析了本研究中所有组之间平均滴度差异的统计学显著性。用相同字母(A 或B)表示的任意两组的平均滴度没有统计学差异。

[0022] 图8A-8E.在免疫接种的仓鼠中,由rB/HPIV3-RSV G载体和wt RSV诱导的RSV和HPIV3中和血清抗体滴度。将六只一组的仓鼠用$10^5$$TCID_{50}$的所示 rB/HPIV3-RSV G载体或$10^6$PFU的wt RSV进行鼻内(IN)感染。在免疫接种后第28天收集血清。通过对Vero细胞单层进行60%噬斑减少中和测定 ($PRNT_{60}$)确定血清中和滴度。为了进行比较,RSV中和测定中包括用相同剂量表达未经修饰的wt RSV F的载体免疫接种的一组仓鼠的血清(来自以基本相同的方式进行的单独实验)。显示了针对以下的中和滴度:有补体的wt RSV(图8A)、有补体的HPIV3(图8B)、有补体的B亚组RSV B1(图8C)、有补体的RSV CX3C突变体(CWAIS)(图8D)和没有补体的wt RSV(图8E)。检测限用虚线表示。每个点代表单个动物的滴度。条表示各组的平均滴度;并且误差条代表SEM。使用单向方差分析,随后采用Tukey-Kramer检验分析了每个测定中所有组之间平均滴度差异的统计学显著性。用相同字母(A、B、C或D)表示的平均滴度没有统计学差异。在图8A中,在两个所示的组(2 和12)之间进行了学生t检验,差异的显著性显示为P值。

[0023] 图9A-9D.免疫接种的仓鼠针对wt RSV A2激发的保护。如图8所述，将六只一组的仓鼠用10^5TCID$_{50}$的所示rB/HPIV3-RSV G载体或10^6PFU的wt RSV 进行鼻内免疫接种，并且在31天后，用10^6PFU的wt RSV进行鼻内激发。激发后第3天，处死动物并通过Vero细胞中的噬斑测定确定鼻甲(NT)匀浆(图 9A)和肺匀浆(图9B)中的病毒滴度。检测限用虚线表示。每个点代表单个动物的滴度。平均滴度表示为短水平条。使用单向方差分析，随后采用Tukey-Kramer检验分析了所有组之间平均滴度差异的统计学显著性。用相同字母(A、B、C或D)表示的各组的平均滴度没有统计学差异。在图9C和9D 中，绘制了单个动物的鼻甲(图9C)和肺(图9D)中RSV激发病毒滴度与载体免疫接种后28天收集的补体依赖性血清RSV中和抗体的相应滴度(来自图8A)的关系的曲线。使用Pearson线性回归模型(统计软件Prism 7.0)显示中和滴度(Log2PRNT60)和病毒滴度(Log10PFU/g)的相关性，以实线显示。NT的R平方值为0.45，肺为0.51:R平方值表示数据对模型的拟合程度(值范围为0到1，值越大表明拟合度越高)。虚线表示95％置信区间。

[0024] 图10A-10D.来自带有G ORF的B/HPIV3载体的G蛋白表达，其中G ORF 经密码子优化以用于人类翻译(图1A中的构建体(x)，或wt G/GS-opt)。通过Western印迹分析评估在用表达wt G或wt G/GS-opt的rB/HPIV3载体感染的 LLC-MK2和Vero细胞中G蛋白的积累(图10A和10B)。用所示的 rB/HPIV3-RSV-G G载体或wt RSV分别以每个细胞10TCID$_{50}$或3PFU的MOI 将所述LLC-MK2(10A)和Vero(10B)细胞感染。感染后24小时，收获所述细胞，并制备裂解物并在变性和还原条件下通过凝胶电泳进行分析，随后用针对RSV产生的抗血清并随后用与红外荧光染料缀合的二抗进行Western 印迹，并使用Odyssey成像系统(LiCor)可视化结合的抗体。Western印迹分析中条带强度的定量表明，通过密码子优化，LLC-MK2细胞中的RSV G表达增加了2.3倍(图10C)，而在Vero细胞中增加了2.2倍(图10D)。

[0025] 图11由在免疫接种的仓鼠中表达经密码子优化或未经优化的G ORF的 rB/HPIV3-RSV-G载体诱导的RSV中和血清抗体滴度。将九只一组的仓鼠用 10^4TCID$_{50}$的所示rB/HPIV3-RSV G载体(泳道1-4)或10^6PFU的wt RSV(泳道5)进行鼻内感染。在免疫接种后第28天收集血清。通过在添加补体存在下对Vero细胞单层进行60％噬斑减少中和测定(PRNT$_{60}$)确定血清中和滴度。显示了在有添加补体的情况下，针对wt RSV的中和滴度。泳道1，空rB/HPIV3载体;泳道2，wt F，未经修饰的野生型RSV F，特别是专利申请(PCT/US2016/014154)和先前的出版物(Liang等，J.Virol.89:9499-9510, 2015)中所述的“非HEK/非opt”构建体;泳道3，wt G，A2株的野生型RSV G;泳道4，wt G/GS-opt，GenScript优化的A2株的野生型G，具有与泳道3中 wt G构建体相同的氨基酸序列;泳道5，wt RSV，作为对照的野生型RSV A2。检测限用虚线表示。每个点代表单个动物的滴度。水平线表示各组的平均滴度。使用非配对双尾学生t检验分析了每个测定中所有组之间平均滴度差异的统计学显著性:*表示$P<0.05$;ns＝不显著。

[0026] 图12A-12B在先前用所示rB/HPIV3-RSV-G或RSV-F载体或wt RSV感染的仓鼠中wt RSV激发的复制。对图11中感染的仓鼠在30天后在两个鼻孔中用总体积为100ul的10^6PFU的wt RSV进行鼻内激发。激发后第3天收集鼻甲 (NT)和肺，并进行均质化处理。通过在Vero单层中的噬斑测定确定鼻甲(图 12A)和肺(图12B)中RSV的滴度。水平线表示该组中滴度的平均值。检测限用虚线显示。

[0027] 图13.原代分化的粘膜纤毛人气道上皮(HAE)组织的体外模型中血清 RSV中和抗

体的RSV-GFP感染阻断能力的评估。将RSV-GFP的等分试样用来自图7和图8中所示实验的不存在添加补体的所示仓鼠血清在37℃下温育30 分钟,然后将其接种到HAE培养物上(每个样品一个孔)。在37℃下60分钟后,取出接种物,并将培养物温育48小时。对感染细胞的GFP灶成像并定量,并计算每组重复的平均值。通过非配对t检验鉴定出显著差异:**表示P<0.01;ns=不显著。

[0028] 序列表

[0029] 如37C.F.R.1.822所定义,使用核苷酸碱基的标准字母缩写和氨基酸的三字母代码显示所附序列表中列出的核酸和氨基酸序列。每个核酸序列仅显示一条链,但应理解为提及的任何显示的链包括互补链。序列表以ASCII文本文件的形式提交,文件名为“Sequence.txt”(约256kb),其创建于2018年 5月5日,并且通过引用并入本文。

具体实施方式

[0030] 开发针对RSV和HPIV3的儿科疫苗的主要挑战包括婴儿期免疫系统的不成熟、母体抗体的免疫抑制、呼吸道浅表上皮的免疫保护效率低下以及在对初次感染病毒的受者使用灭活或亚单位的RSV和HPIV3疫苗进行的研究中已观察到的疫苗诱导的疾病增强(Kim等,Amer.J.Epidemiol.89:422-434,1969; Ottolini等,Viral Immunol.13:231-236,2000;Schneider-Ohrum等,J.Virol. 91:e02180-16,2017)。此外,尽管用表达RSV抗原(未经修饰的RSV F蛋白) 的减活rB/HPIV3载体进行的免疫接种未引发疫苗诱导的疾病增强,但临床试验评估揭示了令人失望的RSV免疫原性(Bernstein等2012.Pediatric Infectious Disease Journal 31:109-114)。因此,尽管付出了巨大的努力,仍然需要一种诱导对RSV和/或HPIV3的保护性免疫应答的有效免疫原。

[0031] 本公开文本提供了满足上述需求的表达RSV G或其变体的重组嵌合牛/ 人副流感病毒3(rB/HPIV3)载体(“rB/HPIV3-RSV G”载体)。例如,如实施例中所述,在九种不同的rB/HPIV3-RSV G载体中,一种载体(包含编码 wt RSV G的异源基因的rB/HPIV3)在动物模型中产生了对RSV的免疫应答,其提供了在补体存在下测定的与由wt RSV感染诱导的显著不同的血清RSV 中和抗体滴度,即使所述RSV以高于10倍的剂量给予,未经减毒,并且同时带有F和G中和抗原。

[0032] I.术语概述

[0033] 除非另有说明外,技术术语根据常规用法使用。分子生物学中常用术语的定义可以在Benjamin Lewin,Genes X,Jones&Bartlett Publishers出版, 2009;和Meyers等(编),The Encyclopedia of Cell Biology and Molecular Medicine,Wiley-VCH出版,共16卷,2008;以及其他类似参考文献中找到。

[0034] 如本文所用,术语“包含”意指“包括”。尽管可以使用与本文描述的那些相似或等同的许多方法和材料,但是本文描述了特定的合适的方法和材料。在存在冲突的情况下,以本说明书(包括术语解释)为准。此外,材料、方法以及实施例仅仅是说明性的并不意在是限制性的。为了便于查阅各实施方案,提供了以下术语解释:

[0035] 佐剂:一种用于增强抗原性的媒介物。佐剂包括矿物质(铝、氢氧化铝或磷酸盐)的悬浮液,其上吸附有抗原;或油包水乳液,例如,将抗原溶液在矿物油中乳化的油包水乳液(弗氏不完全佐剂),有时包含杀死的分枝杆菌(弗氏完全佐剂)以进一步增强抗原性(抑制

抗原的降解和/或导致巨噬细胞流入)。免疫刺激性寡核苷酸(如包括CpG基序的那些)也可以用作佐剂。佐剂包括生物分子("生物佐剂"),如共刺激分子。示例性佐剂包括IL-2、RANTES、GM-CSF、TNF-α、IFN-γ、G-CSF、LFA-3、CD72、B7-1、B7-2、OX-40L、4-1BBL、免疫刺激复合物(ISCOM)基质和Toll样受体(TLR)激动剂,例如TLR-9激动剂、Poly I:C或PolyICLC。佐剂描述于例如Singh(编) Vaccine Adjuvants and Delivery Systems.Wiley-Interscience,2007。

[0036] 给药:通过选择的途径将组合物引入受试者体内。给予可为局部或全身的。例如,如果选择的途径是鼻内,则通过将组合物引入受试者的鼻道中来给予所述组合物(如包括公开的rB/HPIV3-RSV G载体的组合物)。示例性的给药途径包括但不限于口服、注射(例如皮下、肌内、真皮内、腹膜内和静脉内)、舌下、直肠、透皮(例如,局部)、鼻内、阴道和吸入途径。

[0037] 氨基酸取代:多肽中的一钟氨基酸被一种不同的氨基酸替代。

[0038] 减毒:"减毒"的或具有"减毒表型"的病毒是指在相似的感染条件下与参考病毒相比病毒性降低的病毒。与参考野生型病毒在相似感染条件下的复制相比,减毒通常与病毒复制减少相关联,因此,通常将"减毒"和"受限的复制"作为同义词使用。在一些宿主(典型地是非天然宿主,包括实验动物)中,在上述参考病毒感染的过程中疾病不明显,病毒复制的限制可以用作减毒的替代标记。在一些实施方案中,所公开的减毒的rB/HPIV3-RSV G 载体表现出的哺乳动物上呼吸道或下呼吸道中病毒滴度分别与相同感染条件下相同物种哺乳动物的上呼吸道或下呼吸道中未减毒野生型病毒滴度相比至少约10倍或更大的降低,如至少约100倍或更大的降低。哺乳动物的例子包括但不限于人、小鼠、兔子、大鼠、仓鼠,例如金黄仓鼠(Mesocricetus auratus),以及非人类的灵长类动物,例如非洲绿猴(Ceropithiecus aethiops)。减毒的rB/HPIV3-RSV G载体可能表现出不同的表型,包括但不限于改变的生长、温度敏感性生长、宿主范围受限制的生长或噬斑大小改变。

[0039] 胞质尾(CT):跨膜蛋白的连续区域,其包括所述蛋白的一个末端(N 或C末端),并从细胞膜的胞质表面或病毒包膜延伸到细胞的细胞质或包膜病毒中。对于I型跨膜蛋白,所述CT包括所述蛋白的C端。对于II型跨膜蛋白,所述CT包括所述蛋白的N端。

[0040] 简并变体:在本公开文本的上下文中,"简并变体"是指编码一种多肽的多核苷酸,所述多肽包含由于遗传密码而简并的序列。天然氨基酸有20种,其中大多数由一个以上的密码子指定。因此,编码肽的所有简并核苷酸序列均包括在内,只要由所述核苷酸序列编码的肽的氨基酸序列不变即可。

[0041] 基因:一种核酸序列,其包含RNA(无论是mRNA还是其他)转录所必需的控制和编码序列。例如,基因可以包含启动子、一个或多个增强子或沉默子、编码RNA和/或多肽的核酸序列、下游调控序列以及可能地,参与调控mRNA表达的其他核酸序列。

[0042] 如本文所述,rB/HPIV3载体的"基因"指编码mRNA的rB/HPIV3基因组的一部分,并且典型地在上游(3')末端以基因起始(GS)信号开始,并在下游(5')末端以基因末端(GE)信号结束。在这种背景下,术语基因还包括所谓的"翻译开放阅读框"或ORF,特别是在蛋白质(如C蛋白)是从其他ORF而非独有的mRNA表达的情况下。为了构建所公开的rB/HPIV3载体,可以全部或部分缺失、插入或取代一个或多个基因或基因组片段。

[0043] 异源:源自不同的遗传来源。重组基因组中包含的异源基因是非源自所述基因组

的基因。在一个具体的非限制性例子中，编码RSV G蛋白的胞外结构域的异源基因包含在本文所述的rB/HPIV3载体的基因组中。

[0044] 宿主细胞：可在其中繁殖载体并表达其核酸的细胞。所述细胞可以是原核细胞或真核细胞。所述术语还包括受试者宿主细胞的任何子代。应当理解，所有子代可能与亲代细胞并不相同，因为在复制过程中可能会发生突变。然而，当使用术语“宿主细胞”时，包括了此类子代。

[0045] 感染性和自我复制型病毒：一种能够进入培养细胞或动物或人类宿主的细胞中并在其中复制以产生具有相同活性的子代病毒的病毒。

[0046] 免疫应答：免疫系统细胞(如B细胞、T细胞或单核细胞)对刺激的应答。在一个实施方案中，所述应答对特定抗原具有特异性(“抗原特异性应答”)。在一个实施方案中，免疫应答是T细胞应答，如CD4+应答或CD8+应答。在另一个实施方案中，所述应答是B细胞应答，并导致特异性抗体的产生。

[0047] 免疫原性组合物：能够刺激免疫应答的免疫原性材料的制剂，在一些例子中，其可以被给予用于预防、改善或治疗感染性或其他类型的疾病。所述免疫原性材料可以包括减毒或杀死的微生物(如细菌或病毒)，或衍生自它们的抗原蛋白、肽或DNA。免疫原性组合物包含抗原(如病毒)，其诱导针对所述抗原的可测量的T细胞应答，或诱导针对所述抗原的可测量的B细胞应答(如抗体的产生)。在一个例子中，一种免疫原性组合物包含所公开的 rB/HPIV3-RSV G，当其被给予至受试者时，会诱导针对RSV和HPIV3的可测量的CTL应答，或诱导针对RSV和HPIV3的可测量的B细胞应答(如抗体的产生)。对于体内使用，所述免疫原性组合物典型地包括在药学上可接受的载体中的重组病毒，并且还可以包括其他试剂，如佐剂。

[0048] 分离的：“分离的”生物组分已与其他生物组分(如其中天然存在所述组分的其他生物组分，如其他染色体和染色体外DNA、RNA和蛋白质)基本分离或从其中纯化出来。已“分离”的蛋白质、肽、核酸和病毒包括通过标准纯化方法纯化的那些蛋白质、肽、核酸和病毒。分离的蛋白质、肽、核酸和病毒不需要绝对的纯度，并且可以包括纯度至少为50％(如至少75％、80％、90％、95％、98％、99％或者甚至99.9％的纯度)的蛋白质、肽、核酸或病毒分子。

[0049] 接头：一种双功能分子，其可用于将两个分子连接成一个连续分子。肽接头的非限制性例子包括甘氨酸-丝氨酸接头。

[0050] 核酸分子：核苷酸的一种聚合形式，其可包括RNA、cDNA、基因组DNA 的正义链和反义链以及以上的合成形式和混合聚合物。核苷酸是指核糖核苷酸、脱氧核苷酸或任一类型核苷酸的经修饰形式。如本文所用的术语“核酸分子”与“多核苷酸”同义。除非另外指明，否则核酸分子的长度通常是至少10个碱基。该术语包括单链-和双链-形式的DNA。核酸分子可以包括通过天然存在的和/或非天然存在的核苷酸连接而连接在一起的天然存在的和经修饰的核苷酸。

[0051] 可操作地连接：当第一核酸序列与第二核酸序列处于功能关系中时，第一核酸序列与第二核酸序列可操作地连接。例如，如果启动子影响编码序列的转录或表达，则该启动子与该编码序列可操作地连接。通常，可操作地连接的核酸序列是连续的，且在必要时将两个蛋白质编码区结合在同一阅读框内。

[0052] 副流感病毒(PIV)：描述性地分组在一起的一系列来自副粘液病毒科的有包膜的不分节段单股负链RNA病毒。这包括呼吸道病毒属的所有成员(例如，HPIV1、HPIV3)和腮腺

炎病毒属的许多成员(例如,HPIV2、HPIV4、PIV5)。PIV由两个结构模块组成:(1)包含病毒基因组的内部核糖核蛋白核心或核衣壳,以及(2)外部的、大致呈球形的脂蛋白包膜。PIV基因组的长度为约15,000个核苷酸,并且编码至少八种多肽。这些蛋白质包括核衣壳结构蛋白(NP、NC或N,取决于属类)、磷蛋白(P)、基质蛋白(M)、融合糖蛋白(F)、血凝素-神经氨酸酶糖蛋白(HN)、大型聚合酶蛋白(L)以及 C蛋白和D蛋白。基因顺序为3'-N-P-M-F-HN-L-5',并且每个基因编码一个单独的编码mRNA的蛋白质,P基因包含一个或多个编码辅助蛋白的其他开放阅读框(ORF)。

[0053] 药学上可接受的载体:有用的药学上可接受的载体是常规载体。Remington's Pharmaceutical Sciences,E.W.Martin著,Mack Publishing Co., Easton,PA,第19版,1995描述了适合用于所公开的免疫原的药物递送的组合物和配制品。

[0054] 通常,所述载体的性质将取决于所采用的特定给予方式。例如,肠胃外配制品通常包含注射液,所述注射液包括药学上和生理学上可接受的流体,如作为媒介物的水、生理盐水、平衡盐溶液、右旋糖水溶液、甘油等。对于固体组合物(例如,粉末、丸剂、片剂或胶囊形式),常规的无毒固体载体可包括,例如,药用级的甘露醇、乳糖、淀粉或硬脂酸镁。除生物中性载体外,待给予的药物组合物可包含少量的无毒辅助物质,如润湿剂或乳化剂、防腐剂和pH缓冲剂等,例如乙酸钠或脱水山梨糖醇单月桂酸酯。在特定的实施方案中,适合给予至受试者的载体可以是无菌的,和/或悬浮于或以其他方式包含在单位剂型中,所述单位剂型包含一种或多种测量剂量的适合用于诱导所需免疫应答的组合物。它也可伴随药物治疗用于治疗目的。所述单位剂型可以,例如,包装在包含无菌内容物的密封小瓶中或用于注射到受试者中的注射器中,或者冻干以便随后溶解和给予,或者以固体或控释剂量给予。

[0055] 多肽:任何氨基酸链,无论长度多少或是否有翻译后修饰(例如糖基化或磷酸化)。"多肽"适用于氨基酸聚合物,包括天然存在的氨基酸聚合物和非天然存在的氨基酸聚合物,以及其中一个或多个氨基酸残基是非天然氨基酸的氨基酸聚合物,例如天然存在的氨基酸相应的人造化学模拟物。"残基"是指通过酰胺键或酰胺键模拟物掺入多肽中的氨基酸或氨基酸模拟物。多肽具有氨基末端(N末端)和羧基末端(C末端)。"多肽"与肽或蛋白质可互换使用,并且在本文中用于指氨基酸残基的聚合物。

[0056] 重组:重组核酸分子或蛋白质是具有非天然存在的序列的核酸分子或蛋白质:例如,包含一个或多个核酸取代、缺失或插入,和/或具有通过将两个原本分开的序列片段人工组合而形成的序列。这种人工组合可以,例如,通过化学合成、天然存在的核酸分子或蛋白质的靶向突变或,例如,通过遗传工程技术人工操作分离的核酸片段来实现。重组病毒是包括包含重组核酸分子的基因组的病毒。

[0057] 重组嵌合牛/人副流感病毒3(rB/HPIV3):包含如下基因组的嵌合PIV3,所述基因组包含共同构成PIV3基因组中PIV3基因(N、P、M、F、HN和L基因)的完整补体的BPIV3和HPIV3基因的组合。所公开的rB/HPIV3载体基于 BPIV3基因组,该基因组的F和HN基因被来自HPIV3的相应基因替代(其一个例子在Schmidt AC等,J.Virol.74:8922-8929,2000中讨论)。控制基因表达的结构和功能遗传元件(如基因起始和基因终止序列以及基因组和抗基因组启动子)为BPIV3结构和功能遗传元件。本文所述的rB/HPIV3载体是感染性、自我复制的和减毒的载体。

[0058] 在一些实施方案中,将编码RSV G蛋白或其变体的异源基因插入 rB/HPIV3基因组

的N和P基因之间，以产生“rB/HPIV3-RSV G”载体。所公开的rB/HPIV3-RSV G载体是感染性、自我复制的和减毒的，并且可以用于在受试者中诱导对RSV和HPIV3的二价免疫应答。

[0059] 呼吸道合胞病毒(RSV)：肺泡病毒科正肺炎病毒属的一种有包膜的不分节段单股负链RNA病毒。RSV基因组的长度为约15,000个核苷酸，包括10 个基因，编码11种蛋白质，包括糖蛋白SH、G和F。F蛋白介导融合，允许病毒进入细胞质并促进合胞体的形成。主要基于所述G糖蛋白的抗原性差异，已经描述了人RSV病毒株的两个抗原亚组，A亚组和B亚组。用于其他物种的RSV病毒株也是已知的，包括牛RSV。可找到几种人类RSV感染的动物模型以及与之密切相关的动物对应模型，包括感染人类RSV的模型生物体以及感染物种特异性RSV的模型生物体，如在牛中使用bRSV感染(参见，例如，Bern等，Am J，Physiol.Lung Cell Mol.Physiol.，301:L148-L156，2011；Nam和 Kun(编).Respiratory Syncytial Virus: Prevention，Diagnosis and Treatment. Nova Biomedical Nova Science Publisher，2011；以及Cane(编)Respiratory Syncytial Virus.Elsevier Science，2007.)。

[0060] RSV G蛋白：一种RSV包膜糖蛋白，其是一种II型膜蛋白，可促进RSV 向宿主细胞膜的附着。

[0061] 所述RSV G蛋白在RSV感染期间以两种形式表达。一种是全长跨膜形式 (mG)，其在细胞表面表达并封装到病毒颗粒中。另一种形式是N末端截短的分泌形式sG。全长G蛋白(mG)是一种II型蛋白，其具有N端胞质尾(CT，预计在株A2中包含氨基酸1-37，见图1B)、疏水跨膜结构域(TM，包含约38-65 位氨基酸，见图1B)和胞外结构域(包含约66-298位氨基酸)。所述sG形式在RSV感染的细胞培养物中相对丰富，并且通过在ORF中第二个AUG密码子(M48)处的交替翻译起始产生，其在所述蛋白质中的相应位置位于TM结构域内(见图1B)。然后对所述N末端进行细胞内蛋白水解修剪，在N66处产生新的N末端(图1B)。

[0062] RSV G蛋白的胞外结构域包含两个大的发散结构域，其侧翼为氨基酸 164-186处的短中央保守区。所述发散结构域具有较高含量的脯氨酸、丙氨酸、苏氨酸和丝氨酸氨基酸，并且(对于株A2)估计有四个N-连接和24-25 个O-连接的碳水化合物侧链。所述中央保守结构域包含半胱氨酸套索(即，通过两个二硫键稳定的急弯)，其带有保守的CX3C基序(CWAIC，A2株的氨基酸182-186)。就糖基化和蛋白质结构而言，mG和sG形式被认为基本相同，只是mG形成很可能为三聚体或四聚体的多聚体，而sG仍为单体。

[0063] 本文提供的示例性RSV G蛋白序列为SEQ ID NO:22。

[0064] 序列同一性：氨基酸序列之间的相似性以所述序列之间的相似性表示，除此以外也被称为序列同一性。序列同一性经常用百分比同一性(或相似性或同源性)来测量；百分比越高，两个序列越相似。当使用标准方法比对时，多肽的同系物、直系同源物或变体将具有相对较高程度的序列同一性。

[0065] 当确定两个序列之间的序列同一性时，典型地一个序列充当参考序列，将其与测试序列进行比较。使用序列比较算法时，将测试序列和参考序列输入计算机，必要时指定子序列坐标，并指定序列算法程序参数。用于比较的序列的最佳比对可以，例如，通过Smith&Waterman，Adv.Appl.Math.2:482， 1981的局部同源性算法进行，通过Needleman&Wunsch，J.Mol.Biol.48:443， 1970的同源性比对算法进行，通过Pearson&Lipman，Proc.Nat’l.Acad.Sci. USA 85:2444，1988的相似性搜索法进行，通过这些算法的计算机化实现(Wisconsin Genetics软件包中的GAP、BESTFIT、FASTA和TFASTA，Genetics Computer

Group,575Science Dr.,Madison,WI)进行,或者通过人工比对和目视检查(参见,例如,Sambrook等(Molecular Cloning:A Laboratory Manual,第4版,Cold Spring Harbor,New York,2012)和Ausubel等(In Current Protocols in Molecular Biology,John Wiley& Sons,New York,增刊 104,2013)进行。

[0066] 适合用于确定序列同一性和序列相似性百分比的算法的另一个例子是 BLAST和BLAST 2.0算法,其描述于Altschul等,J.Mol.Biol.215:403-410,1990 和Altschul等,Nucleic Acids Res.25:3389-3402,1977。用于进行BLAST分析的软件是可通过国家生物技术信息中心(National Center for Biotechnology Information)公开获得的(ncbi.nlm.nih.gov)。BLASTN程序(用于核苷酸序列) 使用以下默认参数:字长(W)为11,比对次数(B)为50,期望(E)为10, M=5,N=-4,以及两条链的比较。BLASTP程序(用于氨基酸序列)使用默认,字长(W)为3,期望(E)为10,并且使用BLOSUM62评分矩阵(参见 Henikoff和Henikoff,Proc.Natl.Acad.Sci.USA 89:10915,1989)。

[0067] 在一个例子中,比对后,通过对两个序列中存在相同核苷酸或氨基酸残基的位置的数目进行计数来确定匹配数。序列同一性百分比是通过将匹配数除以已鉴定序列中阐述的序列的长度或被铰接的长度(如来自已鉴定序列中列出的序列的100个连续核苷酸或氨基酸残基)来确定的,随后将得到的值乘以100。例如,当与具有1554个氨基酸的测试序列比对时,具有1166个匹配的肽序列与该测试序列75.0%相同(1166÷1554*100=75.0)。序列同一性百分比值四舍五入到最接近的十分之一。例如,将75.11、75.12、75.13 和75.14向下舍入为75.1,而将75.15、75.16、75.17、75.18和75.19向上舍入为 75.2。长度值将始终为整数。

[0068] 多肽(如RSV G胞外结构域)的同系物和变体的特征典型地在于具有在与目的氨基酸序列的全长比对上计算出的至少约75%,例如至少约80%、 85%、90%、91%、92%、93%、94%、95%、96%、97%、98%或99%的序列同一性。如本文所用,提及的“至少90%同一性”或类似用语是指与指定参考序列的“至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或甚至100%同一性”。

[0069] 受试者:活的多细胞脊椎动物,包括人类和非人类哺乳动物的类别。在一个例子中,受试者是人。在一个特定的例子中,所述受试者是新生婴儿。在另一个例子中,选择需要抑制RSV感染和/或HPIV3感染的受试者。例如,受试者未感染并且有RSV感染和/或HPIV3感染的风险,或者被感染需要治疗。

[0070] 跨膜结构域(TM):跨脂质双层(如细胞或病毒或病毒样颗粒的脂质双层)的氨基酸序列。

[0071] 疫苗:能够刺激免疫应答的免疫原性材料的制剂,用于预防、改善或治疗感染性或其他类型的疾病而给予。所述免疫原性材料可以包括减毒或杀死的微生物(如细菌或病毒),或衍生自它们的抗原蛋白、肽或DNA。减毒疫苗是一种有毒生物体,其已经修饰以产生低病毒性形式,但仍保留了引发抗体和针对该病毒形式的细胞介导的免疫力的能力。灭活(杀死)疫苗是一种先前有毒的生物体,其已通过化学、加热或其他处理灭活,但会引发针对该生物体的抗体。疫苗可能引发预防性(预防性或保护性)和治疗性应答。给予方法根据疫苗而有所不同,但可能包括接种、摄入、吸入或其他给予形式。疫苗可与佐剂一起给予以增强免疫应答。

[0072] 载体:包含带有一个或多个启动子的DNA或RNA分子的实体,其可操作地连接至一个或多个目的抗原的编码序列,并且可以表达所述编码序列。非限制性例子包括裸露的或封装的(脂质和/或蛋白质)DNA、裸露的或封装的RNA、病毒或细菌或其他可能不具有复制能力的微生物的亚成分、或者病毒或细菌或其他可能具有复制能力的微生物。载体有时称为构建体。重组 DNA载体是具有重组DNA的载体。载体可包括容许其在宿主细胞中复制的核酸序列,如复制起点。载体还可以包括一个或多个选择性标记基因以及本领域中已知的其他遗传元件。病毒载体是具有至少一些衍生自一种或多种病毒的核酸序列的重组核酸载体。

[0073] II.rB/HPIV3-RSV G载体

[0074] 本文提供了重组嵌合病毒载体,其包含BPIV3 HN和F基因的编码序列被相应的HPIV3 HN和F基因的编码序列替代的BPIV3基因组,并且还包含编码 RSV G蛋白(如野生型RSV G蛋白)的异源基因或其变体。这些重组嵌合病毒载体被称为"rB/HPIV3-RSV G"载体。

[0075] 所述rB/HPIV3-RSV G基因组包含PIV3基因的完整补体。因此,所述 rB/HPIV3-RSV G载体具有感染性和复制能力,但由于所述BPIV3主链和异源基因的存在,在恒河猴和人中是减毒的。

[0076] 所述rB/HPIV3-RSV G载体的基因组包含编码RSV G或其变体的异源基因、HPIV3 F和HN基因、BPIV3 N、P、M和L基因以及BPIV3基因组启动子 (3'前导区)和5'尾随区,其顺序为3'-前导区-BPIV3 N、异源基因、BPIV3 P、 BPIV3 M、HPIV3 F、HPIV3 HN、BPIV3 L-5'尾随区。本文提供了这些基因的示例性核酸序列和由其编码的蛋白质,以及控制基因表达的结构和功能遗传元件,如基因起始序列和基因结束序列以及基因组和反基因组启动子。

[0077] 一个示例性的BPIV3基因组序列(Kansas染色)作为GenBank登记号 AF178654.1提供,其通过引用以整体并入本文。一个示例性的HPIV3 JS株基因组序列作为GenBank登记号Z11575.1提供,其通过引用以整体并入本文。在一些实施方案中,来自这些株的序列可以用于构建所述rB/HPIV3-RSV G 载体的rB/HPIV3方面,例如,如Schmidt等(J.Virol.74:8922-8929,2000)所述。在一些此类实施方案中,由所述HPIV3 HN基因编码的HN蛋白可以被修饰以分别在263和370位置具有苏氨酸和脯氨酸残基。

[0078] 在一些实施方案中,所述rB/HPIV3-RSV G载体包含的基因组包含编码如下所阐述的HPIV3 F和HN蛋白以及BPIV3 N、P、C、V、M、或L蛋白的 HPIV3 F和HN基因以及BPIV3 N、P、M和L基因,或编码HPIV3 F和HN蛋白以及BPIV3 N、P、C、V、M和L蛋白,其各自与如下所阐述相应的HPIV3 F 和HN蛋白以及BPIV3 N、P、C、V、M、或L蛋白分别具有至少90%(如至少95%或至少98%)的序列同一性:

[0079] BPIV3 N(GenBank登记号:AAF28254.1,由GenBank编号AF178654.1的核苷酸111-1658编码)

[0080] MLSLFDTFSARRQENITKSAGGAVIPGQKNTVSIFALGPSITDDNDKMTLALLFLSHSLDNEKQHAQRAGFLVSLL SMAYANPELYLTSNGSNADVKYVIYMIEKDPGRQKYGGFVVKTREMVYEKTTDWMFGSDLEYDQDNMLQNGRSTST IEDLVHTFGYPSCLGALIIQVWIILVKAITSISGLRKGFFTRLEAFRQDGTVKSSLVLSGDAVEQIGSIMRSQQSL VTLMVETLITMNTGRNDLTTIEKNIQIVGNYIRDAGLASFFNTIRYGIETRMAALTLSTLRPDINRLKALIELYLS KGPRAPFICILRDPVHGEFAPGNYPALWSYAMGVAVVQNKAMQQYVTGRSYLDIEMFQLGQAVARDAESQMSSILE DELGVTQEAKQSLKKHMKNISSSDTTFHKPTGGSAIEMAIDEEAGQPESRGDQDQGDEPRSSIVPYAWADETGNDN QTESTTEIDSIKTEQRNIRDRLNKRLNEKRKQSDPRSTDITNNTNQTEIDDLFSAFGSN(SEQ

ID NO:1)

[0081] BPIV3 P(GenBank登记号:AAF28255,由GenBank编号AF178654的核苷酸1784-3574编码)

[0082] MEDNVQNNQIMDSWEEGSGDKSSDISSALDIIEFILSTDSQENTADSNEINTGTTRLSTTIYQPESKTTETSKENSGPA NKNRQFGASHERATETKDRNVNQETVQGGYRRGSSPDSRTETMVTRRISRSSPDPNNGTQIQEDIDYNEVGEMDKDSTK REMRQFKDVPVKVSGSDAIPPTKQDGDGDDGRGLESISTFDSGYTSIVTAATLDDEEELLMKNNRPRKYQSTPQNSDKG IKKGVGRPKDTDKQSSILDYELNFKGSKKSQKILKASTNTGEPTRPQNGSQGKRITSWNILNSESGNRTESTNQTHQTS TSGQNHTMGPSRTTSEPRIKTQKTDGKEREDTEESTRFTERAITLLQNLGVIQSAAKLDLYQDKRVVCVANVLNNADTA SKIDFLAGLMIGVSMDHDTKLNQIQNEILSLKTDLKKMDESHRRLIENQKEQLSLITSLISNLKIMTERGGKKDQPEPS GRTSMIKTKAKEEKIKKVRFDPLMETQGIEKNIPDLYRSIEKTPENDTQIKSEINRLNDESNATRLVPRRISSTMRSLI IIINNSNLSSKAKQSYINELKLCKSDEEVSELMDMFNEDVSSQ(SEQ ID NO:2)

[0083] BPIV3 C(由GenBank编号AF178654的核苷酸1794-2399编码)

[0084] MFKTIKSWILGKRDQEINHLTSHRPSTSLNSYSAPTPKRTRQTAMKSTQEPQDLARQSTNLNPKQQKQARKIVDQL TKIDSLGHHTNVPQRQKIEMLIRRLYREDIGEEAAQIVELRLWSLEESPEAAQILTMEPKSRKILITMKLERWIRT LLRGKCDNLKMFQSRYQEVMPFLQQNKMETVMMEEAWNLSVHLIQDIPV(SEQ ID NO:3)

[0085] BPIV3 V(由GenBank编号AF178654的核苷酸1784-3018编码,在位于核苷酸2500-2507的基因编辑位点的核苷酸2505-2506之间插入有核苷酸g)

[0086] MEDNVQNNQIMDSWEEGSGDKSSDISSALDIIEFILSTDSQENTADSNEINTGTTRLSTTIYQPESKTTETSKENS GPANKNRQFGASHERATETKDRNVNQETVQGGYRRGSSPDSRTETMVTRRISRSSPDPNNGTQIQEDIDYNEVGEM DKDSTKREMRQFKDVPVKVSGSDAIPPTKQDGDGDDGRGLESISTFDSGYTSIVTAATLDDEEELLMKNNRPRKYQ STPQNSDKGIKKGGWKAKRHRQTIINIGLRTQLQRIEEEPENPQSQHEYRRTNKTTEWIPGEENHILEHPQQRERQ SNRINKPNPSDINLGTEPHNGTKQNNLRTKDQDTKDGWKGKRGHRREHSIYRKGDYIITESWCNPICSKIRPIPRQ ESCVCGECPKQCRYCIKDRLPSRFDDRSVNGS(SEQ ID NO:4)

[0087] BPIV3 M(GenBank登记号:AAF28256,由GenBank编号AF178654的核苷酸3735-4790编码)

[0088] MSITNSTIYTFPESSFSENGNIEPLPLKVNEQRKAIPHIRVVKIGDPPKHGSRYLDVFLLGFFEMERSKDRYGSIS DLDDDPSYKVCGSGSLPLGLARYTGNDQELLQAATKLDIEVRRTVKATEMIVYTVQNIKPELYPWSSRLRKGMLFD ANKVALAPQCLPLDRGIKFRVIFVNCTAIGSITLFKIPKSMALLSLPNTISINLQVHIKTGVQTDSKGVVQILDEK GEKSLNFMVHLGLIKRKMGRMYSVEYCKQKIEKMRLLFSLGLVGGISFHVNATGSISKTLASQLAFKREICYPLMD LNPHLNSVIWASSVEITRVDAVLQPSLPGEFRYYPNIIAKGVGKIRQ(SEQ ID NO:5)

[0089] HPIV3 F(由GenBank编号Z11575的核苷酸5072-6691编码)

[0090] MPTSILLIITTMIMASFCQIDITKLQHVGVLVNSPKGMKISQNFETRYLILSLIPKIEDSNSCGDQQIKQYKKLLD RLIIPLYDGLRLQKDVIVTNQESNENTDPRTKRFFGGVIGTIALGVATSAQITAAVALVEAKQARSDIEKLKEAIR DTNKAVQSVQSSIGNLIVAIKSVQDYVNKEIVPSIARLGCEAAGLQLGIALTQHYSELTNIFGDNIGSLQEKGIKL QGIASLYRTNITEIFTTSTVDKYDIYDLLFTESIKVRVIDVDLNDYSITLQVRLPLLTRLLNTQIYKVDSISYNIQ NREWYIPLPSHIMTKGAFLGGADVKECIEAFSSYICPSDPGFVLNHEIESCLSGNISQCPRTTVTSDIVPRYAFVN GGVVANCITTTCTCNGIGNRINQPPDQGVKIITHKECSTIGINGMLFNTNKEGTLAFYTPNDITLNNSVALDPIDI SIELNKAKSDLEESKEWIRRSNQKLDSIGNWHQSSTTIIIILIMIIILFIINITIITIAIKY

YRIQKRNRVDQNDK PYVLTNK(SEQ ID NO:6)

[0091] HPIV3 wt HN(由GenBank编号Z11575的核苷酸6806-8524编码)

[0092] MEYWKHTNHGKDAGNELETSMATHGNKLTNKIIYILWTIILVLLSIVFIIVLINSIKSEKAHESLLQD INNEFMEI TEKIQMASDNTNDLIQSGVNTRLLTIQSHVQNYIPISLTQQMSDLRKFISEITIRNDNQEVLPQRIT HDVGIKPLN PDDFWRCTSGLPSLMKTPKIRLMPGPGLLAMPTTVDGCVRTPSLVINDLIYAYTSNLITRGCQDIG KSYQVLQIGI ITVNSDLVPDLNPRISHTFNINDNRKSCSLALLNTDVYQLCSTPKVDERSDYASSGIEDIVLDIV NYDGSISTTRF KNNNISFDQPYAALYPSVGPGIYYKGKIIFLGYGGLEHPINENVICNTTGCPGKTQRDCNQASH SPWFSDRRMVNS IIVVDKGLNSIPKLKVWTISMRQNYWGSEGRLLLLGNKIYIYTRSTSWHSKLQLGIIDITDYS DIRIKWTWHNVLS RPGNNECPWGHSCPDGCITGVYTDAYPLNPTGSIVSSVILDSQKSRVNPVITYSTATERVNE LAILNRTLSAGYTT TSCITHYNKGYCFHIVEINHKSLNTFQPMLFKTEIPKSCS(SEQ ID NO:7)

[0093] 在一些实施方案中,rB/HPIV3载体中的HPIV3 HN基因编码包含如下阐述的氨基酸序列的HPIV3 HN蛋白:

[0094] MEYWKHTNHGKDAGNELETSMATHGNKLTNKIIYILWTIILVLLSIVFIIVLINSIKSEKAHESLLQD INNEFMEI TEKIQMASDNTNDLIQSGVNTRLLTIQSHVQNYIPISLTQQMSDLRKFISEITIRNDNQEVLPQRIT HDVGIKPLN PDDFWRCTSGLPSLMKTPKIRLMPGPGLLAMPTTVDGCVRTPSLVINDLIYAYTSNLITRGCQDIG KSYQVLQIGI ITVNSDLVPDLNPRISHTFNINDNRKSCSLALLNIDVYQLCSTPKVDERSDYASSGIEDIVLDIV NYDGSISTTRF KNNNISFDQPYAALYPSVGPGIYYKGKIIFLGYGGLEHPINENVICNTTGCPGKTQRDCNQASH STWFSDRRMVNS IIVVDKGLNSIPKLKVWTISMRQNYWGSEGRLLLLGNKIYIYTRSTSWHSKLQLGIIDITDYS DIRIKWTWHNVLS RPGNNECPWGHSCPDGCITGVYTDAYPLNPTGSIVSSVILDSQKSRVNPVITYSTATERVNE LAILNRTLSAGYTT TSCITHYNKGYCFHIVEINHKSLNTFQPMLFKTEIPKSCS(SEQ ID NO:8)

[0095] SEQ ID NO:7所示的HN蛋白包含263T和370P氨基酸分配。如实施例中所讨论的,可将包括具有263T和370P氨基酸分配的HN蛋白的rB/HPIV3-RSV G回收和传代,显著减少不定突变的发生,从而提高了病毒生产、分析和制备的效率。本文提供的任何rB/HPIV3-RSV G载体可以包含HPIV3 HN基因,所述HPIV3 HN基因编码具有263T和370P氨基酸分配的HN蛋白(例如,通过 I263T和T370P氨基酸取代引入HN蛋白中)。编码SEQ ID NO:7的示例性DNA 序列如下提供:

[0096] atggaatactggaagcataccaatcacggaaaggatgctggtaatgagctggagacgtctatggctac tcatggca acaagctcactaataagataatatacatattatggacaataatcctggtgttattatcaatagtctt catcatagt gctaattaattccatcaaaagtgaaaaggcccacgaatcattgctgcaagacataaataatgagtt tatggaaatt acagaaaagatccaaatggcatcggataataccaatgatctaatacagtcaggagtgaatacaag gcttcttacaa ttcagagtcatgtccagaattacataccaatatcattgacacaacagatgtcagatcttaggaa attcattagtga aattacaattagaaatgataatcaagaagtgctgccacaaagaataacacatgatgtaggtat aaaaacctttaaat ccagatgatttttggagatgcacgtctggtcttccatctttaatgaaaactccaaaaataag gttaatgccagggc cgggattattagctatgccaacgactgttgatggctgtgttagaactccgtctttagttat aaatgatctgattta tgcttatacctcaaatctaattactcgaggttgtcaggatataggaaaatcatatcaagt cttacagatagggata ataactgtaaactcagacttggtacctgacttaaatcctaggatctctcatacctttaa cataaatgacaatagga agtcatgttctctagcactcctaaatatagatgtatatcaactgtgttcaactcccaa agttgatgaaagatcaga ttatgcatcatcaggcatagaagatattgtacttgatattgtcaattatgatggttc aatctcaacaacaagattt aagaataataacataagctttgatcaaccatatgctgcactatacccatctgttgg

accagggatatactacaaag gcaaaataatatttctcgggtatggaggtcttgaacatccaataaatgagaatgt
aatctgcaacacaactgggtg ccccgggaaaacacagagagactgtaatcaagcatctcatagtacttggttttc
agataggaggatggtcaactcc atcattgttgttgacaaaggcttaaactcaattccaaaattgaaagtatggac
gatatctatgcgacaaaattact gggggtcagaaggaaggttacttctactaggtaacaagatctatatatatac
aagatctacaagttggcatagcaa gttacaattaggaataattgatattactgattacagtgatataaggataaa
atggacatggcataatgtgctatca agaccaggaaacaatgaatgtccatggggacattcatgtccagatggatg
tataacaggagtatatactgatgcat atccactcaatcccacagggagcattgtgtcatctgtcatattagactc
acaaaaatcgagagtgaacccagtcat aacttactcaacagcaaccgaaagagtaaacgagctggccatcctaaa
cagaacactctcagctggatatacaaca acaagctgcattacacactataacaaaggatattgttttcatatagt
agaaataaatcataaaagcttaaacacat ttcaacccatgttgttcaaaacagagattccaaaaagctgcagttaa
(SEQ ID NO:9)

[0097] BPIV3 L(GenBank登记号:AAF28259,由GenBank编号AF178654的核苷酸8640-15341编码)

[0098] MDTESHSGTTSDILYPECHLNSPIVKGKIAQLHTIMSLPQPYDMDDDSILIITRQKIKLNKLDKRQRS
IRKLRSVL MERVSDLGKYTFIRYPEMSSEMFQLCIPGINNKINELLSKASKTYNQMTDGLRDLWVTILSKLASKN
DGSNYDINE DISNISNVHMTYQSDKWYNPFKTWFTIKYDMRRLQKAKNEITFNRHKDYNLLEDQKNILLIHPELV
LILDKQNYNG YIMTPELVLMYCDVVEGRWNISSCAKLDPKLQSMYYKGNNLWEIIDGLFSTLGERTFDIISLLEP
LALSLIQTYDP VKQLRGAFLNHVLSEMELIFAAECTTEEIPNVDYIDKILDVFKESTIDEIAEIFSFFRTFGHPP
LEASIAAEKVRK YMYTEKCLKFDTINKCHAIFCTIIINGYRERHGGQWPPVTLPVHAHEFIINAYGSNSAISYEN
AVDYYKSFIGIKF DKFIEPQLDEDLTIYMKDKALSPKKSNWDTVYPASNLLYRTNVSHDSRRLVEVFIADSKFDP
HQVLDYVESGYWLD DPEFNISYSLKEKEIKQEGRLFAKMTYKMRATQVLSETLLANNIGKFFQENGMVKGEIELL
KRLTTISMSGVPRYN EVYNNSKSHTEELQAYNAISSSNLSSNQKSKKFEFKSTDIYNDGYETVSCFLTTDLKKYC
LNWRYESTALFGDTCN QIFGLKELFNWLHPRLEKSTIYVGDPYCPPSDIEHLPLDDHPDSGFYVHNPKGGIEGFC
QKLWTLISISAIHLAAV KIGVRVTAMVQGDNQAIAVTTRVPNNYDYKVKKEIVYKDVVRFFDSLREVMDDLGHEL
KLNETIISSKMFIYSKRI YYDGRILPQALKALSRCVFWSETIIDETRSASSNLATSFAKAIENGYSPVLGYVCSI
FKNIQQLYIALGMNINPTI TQNIKDQYFRNIHWMQYASLIPASVGGFNYMAMSRCFVRNIGDPTVAALADIKRFI
KANLLDRGVLYRIMNQEPGE SSFLDWASDPYSCNLPQSQNITTMIKNITARNVLQDSPNPLLSGLFTSTMIEEDE
ELAEFLMDRRIILPRVAHDIL DNSLTGIRNAIAGMLDTTKSLIRVGISRGGLTYNLLRKISNYDLVQYETLSKTL
RLIVSDKIKYEDMCSVDLAISL RQKMWMHLSGGRMINGLETPDPLELLSGVIITGSEHCRICYSTEGESPYTWMY
LPGNLNIGSAETGIASLRVPYFG SVTDERSEAQLGYIKNLSKPAKAAIRIAMIYTWAFGNDEISWMEASQIAQTR
ANFTLDSLKILTPVTTSTNLSHRL KDTATQMKFSSTSLIRVSRFITISNDNMSIKEANETKDTNLIYQQVMLTGL
SVFEYLFRLEESTGHNPMVMHLHIE DGCCIKESYNDEHINPESTLELIKYPESNEFIYDKDPLKDIDLSKLMVIR
DHSYTIDMNYWDDTDIVHAISICTAV TIADTMSQLDRDNLKELVVIANDDDINSLITEFLTLDILVFLKTFGGLL
VNQFAYTLYGLKIEGRDPIWDYIMRTL KDTSHSVLKVLSNALSHPKVFKRFWDCGVLNPIYGPNTASQDQVKLAL
SICEYSLDLFMREWLNGASLEIYICDSD MEIANDRRQAFLSRHLAFVCCLAEIASFGPNLLNLTYLERLDELKQY
LDLNIKEDPTLKYVQVSGLLIKSFPSTVT YVRKTAIKYLRIRGINPPETIEDWDPIEDENILDNIVKTVNDNCSD
NQKRNKSSYFWGLALKNYQVVKIRSITSDS EVNEASNVTTHGMTLPQGGSYLSHQLRLFGVNSTSCLKALELSQI
LMREVKKDKDRLFLGEGAGAMLACYDATLGP AINYYNSGLNITDVIGQRELKIFPSEVSLVGKKLGNVTQILNRV
RVLFNGNPNSTWIGNMECESLIWSELNDKSIG LVHCDMEGAIGKSEETVLHEHYSIIRITYLIGDDDVVLVSKII

PTITPNWSKILYLYKLYWKDVSVVSLKTSNPAS TELYLISKDAYCTVMEPSNLVLSKLKRISSIEENNLLKWIIL SKRKNNEWLQHEIKEGERDYGIMRPYHTALQIFG FQINLNHLAREFLSTPDLTNINNIIQSFTRTIKDVMFEWVN ITHDNKRHKLGGRYNLFPLKNKGKLRLLSRRLVLS WISLSLSTRLLTGRFPDEKFENRAQTGYVSLADIDLESLK LLSRNIVKNYKEHIGLISYWFLTKEVKILMKLIGGV KLLGIPKQYKELEDRSSQGYEYDNEFDID(SEQ ID NO:10)

[0099] 所述rB/HPIV3-RSV G载体中HPIV3 F和HN基因以及BPIV3 N、P、M和L 基因的编码序列侧翼为适当的基因起始和基因结束序列，以利于从病毒基因组表达。例如，在一些实施方案中，所述HPIV3 F和HN基因以及所述BPIV3 N、P、M和L基因的编码序列的侧翼可为如下BPIV3基因起始和基因结束序列：

[0100]

基因	基因起始	SEQ ID	基因结束	SEQ ID
N	aggattaaagac	11	aaataagaaaaa	16
P	aggattaaag	12	aaataagaaaaa	17
M	aggattaaag	12	aaataaaggataatcaaaaa	18
F	aggacaaaag	13	aattataaaaaa	19
HN	aggagtaaag	14	aaatataaaaaa	20
L	aggagcaaag	15	aaagtaagaaaaa	21

[0101] 此外，所述rB/HPIV3-RSV G载体包含合适的基因组和抗基因组启动子，如GenBank登记号AF178654中所阐述的BPIV3 Kansas株的那些，其提供作为核苷酸1-96的基因组启动子和作为核苷酸15361-15456的反基因组启动子。

[0102] 所述rB/HPIV3-RSV G的基因组包含编码天然RSV G蛋白或其变体的异源基因，如包含代替天然RSV G跨膜和/或胞质尾序列的BPIV3 HN跨膜和/或胞质尾序列的重组RSV G蛋白。人类RSV可以分为两组：A组和B组。A组和 B组主要基于附着蛋白(G)和融合蛋白(F)的序列变异性而包括亚组A1、A2、B1和B2。所述rB/HPIV3-RSV G的基因组中包含的异源基因可以编码 RSV G蛋白和/或RSV G胞外结构域，该RSV G蛋白和/或RSV G胞外结构域来自(或衍生自)任何人类RSV组(如A组或B组)或人类RSV亚组(如亚组 A1、A2、B1或B2)。

[0103] 来自亚组A2的示例性人RSV G蛋白序列如下所阐述：

[0104] MSKNKDQRTAKTLERTWDTLNHLLFISSCLYKLNLKSVAQITLSILAMIISTSLIIAAIIFIASANHK VTPTTAII QDATSQIKNTTPTYLTQNPQLGISPSNPSEITSQITTILASTTPGVKSTLQSTTVKTKNTTTTQTQP SKPTTKQRQ NKPPSKPNNDFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGKKTTTKPTKKPTLKTTKKDPKPQ TTKSKEVPTT KPTEEPTINTTKTNIITTLLTSNTTGNPELTSQMETFHSTSSEGNPSPSQVSTTSEYPSQPSSPP NTPRQ(SEQ ID NO:22)

[0105] 在一些实施方案中，包含在所述rB/HPIV3-RSV G的基因组中的所述异源基因编码RSV G蛋白，所述RSV G蛋白包含SEQ ID NO:22所阐述的氨基酸序列或与SEQ ID NO:22至少90％(如至少95％或至少98％)相同的氨基酸序列，或者由所述氨基酸序列组成

[0106] 来自亚组A2的示例性人RSV G胞外结构域序列如下所阐述：

[0107] NHKVTPTTAIIQDATSQIKNTTPTYLTQNPQLGISPSNPSEITSQITTILASTTPGVKSTLQSTTVKT KNTTTTQT QPSKPTTKQRQNKPPSKPNNDFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGKKTTTKPTKKPTL KTTKKDPKP QTTKSKEVPTTKPTEEPTINTTKTNIITTLLTSNTTGNPELTSQMETFHSTSSEGNPSPSQVSTTS EYPSQPSSPP NTPRQ(SEQ ID NO:23)

[0108] 在一些实施方案中,所述异源基因编码重组RSV G胞外结构域,所述重组RSV G胞外结构域包含SEQ ID NO:23所阐述的氨基酸序列或与SEQ ID NO:23至少90%(如至少95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。所述胞外结构域与合适的跨膜结构域和胞质尾序列连接,如本文所阐述的那些。

[0109] 来自RSV A/马里兰/001/11的示例性人RSV G蛋白序列如下所阐述:

[0110] MSKTKDQRTAKTLERTWDTLNHLLFISSCLYKLNLKSIAQITLSILAMIISTSLIIAAIIFIASANHKVTLTTAII QDATNQIKNTTPTYLTQNPQLGISLSNLSETTSKPTTILALTTPNAESTPQSTTVKTKNTTTTQIQPSKPTTKQRQ NKPQNKPNNDFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGRKTTTKPTKQPAIKTTKKDPKPQTTKPKEVLTT KPTEKPTINTTKTNIRTTLLTSNITENQEHTSQKETLHSTTSEGNPSPSQVYTTSEYLSQSLSPSNTTRW(SEQ ID NO:47)

[0111] 在一些实施方案中,包含在所述rB/HPIV3-RSV G的基因组中的所述异源基因编码RSV G蛋白,所述RSV G蛋白包含SEQ ID NO:47所阐述的氨基酸序列或与SEQ ID NO:47至少90%(如至少95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0112] 来自RSV A/马里兰/001/11的示例性人RSV G胞外结构域序列如下所阐述:

[0113] NHKVTLTTAIIQDATNQIKNTTPTYLTQNPQLGISLSNLSETTSKPTTILALTTPNAESTPQSTTVKTKNTTTTQI QPSKPTTKQRQNKPQNKPNNDFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGRKTTTKPTKQPAIKTTKKDPKP QTTKPKEVLTTKPTEKPTINTTKTNIRTTLLTSNITENQEHTSQKETLHSTTSEGNPSPSQVYTTSEYLSQSLSPS NTTRW(SEQ ID NO:48)

[0114] 在一些实施方案中,所述异源基因编码重组RSV G胞外结构域,所述重组RSV G胞外结构域包含SEQ ID NO:48所阐述的氨基酸序列或与SEQ ID NO:48至少90%(如至少95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。所述胞外结构域与合适的跨膜结构域和胞质尾序列连接,如本文所阐述的那些。

[0115] 来自亚组B(B1,AAB82435.1,参见Karron等,Proc.Natl.Acad.Sci.U.S.A. 94,13961-6,1997)的示例性人RSV G蛋白序列如下所阐述:

[0116] MSKHKNQRTARTLEKTWDTLNHLIVISSCLYRLNLKSIAQIALSVLAMIISTSLIIAAIIFIISANHKVTLTTVTV QTIKNHTEKNITTYLTQVPPERVSSSKQPTTTSPIHTNSATTSPNTKSETHHTTAQTKGRTTTSTQTNKPSTKPRL KNPPKKPKDDYHFEVFNFVPCSICGNNQLCKSICKTIPSNKPKKKPTIKPTNKPTTKTTNKRDPKTPAKTTKKETT TNPTKKPTLTTTERDTSTSQSTVLDTTTLEHTIQQQSLHSTTPENTPNSTQTPTASEPSTSNSTQNTQSHA(SEQ ID NO:49)

[0117] 在一些实施方案中,包含在所述rB/HPIV3-RSV G的基因组中的所述异源基因编码RSV G蛋白,所述RSV G蛋白包含SEQ ID NO:49所阐述的氨基酸序列或与SEQ ID NO:49至少90%(如至少95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0118] 来自亚组B(B1,AAB82435.1)的示例性人RSV G胞外结构域序列如下所阐述:

[0119] NHKVTLTTVTVQTIKNHTEKNITTYLTQVPPERVSSSKQPTTTSPIHTNSATTSPNTKSETHHTTAQTKGRTTTST QTNKPSTKPRLKNPPKKPKDDYHFEVFNFVPCSICGNNQLCKSICKTIPSNKPKKKPTIKPTNKPTTKTTNKRDPK TPAKTTKKETTTNPTKKPTLTTTERDTSTSQSTVLDTTTLEHTIQQQSLHSTTPENTPNSTQTPTASEPSTSNSTQ NTQSHA(SEQ ID NO:50)

[0120] 在一些实施方案中,所述异源基因编码重组RSV G胞外结构域,所述重组RSV G胞外结构域包含SEQ ID NO:50所阐述的氨基酸序列或与SEQ ID NO:50至少90%(如至少95%

或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。所述胞外结构域与合适的跨膜结构域和胞质尾序列连接,如本文所阐述的那些。

[0121] 来自亚组A(基因型ON1;ON67-1210A,AEQ98758.1,Eshagi A.等,Plos One 7(3):e32807,2012)的示例性人RSV G蛋白序列如下所阐述:

[0122] MSKTKDQRTAKTLERTWDTLNHLLFISSCLYKLNLKSIAQITLSILAMIISTSLIIAAIIFIASANHK VTLTTAII QDATNQIKNTTPTYLTQNPQLGISFSNLSGTTSQSTTILASTTPSAESTPQSTTVKIKNTTTTQILP SKPTTKQRQ NKPQNKPNNDFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGKKTTTKPTKKPTLKTTKKDPKPQ TTKPKEVLTT KPTGKPTINTTKTNIRTTLLTSNTKGNPEHTSQEETLHSTTSEGYLSPSQVYTTSGQEETLHSTT SEGYLSPSQVY TTSEYLSQSLSSSNTTK(SEQ ID NO:51)

[0123] 在一些实施方案中,包含在所述rB/HPIV3-RSV G的基因组中的所述异源基因编码RSV G蛋白,所述RSV G蛋白包含SEQ ID NO:51所阐述的氨基酸序列或与SEQ ID NO:51至少90%(如至少95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0124] 来自亚组A(基因型ON1;ON67-1210A,AEQ98758.1,Eshagi A.等,Plos One 7(3):e32807,2012)的示例性人RSV G胞外结构域序列如下所阐述:

[0125] NHKVTLTTAIIQDATNQIKNTTPTYLTQNPQLGISFSNLSGTTSQSTTILASTTPSAESTPQSTTVKI KNTTTTQI LPSKPTTKQRQNKPQNKPNNDFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGKKTTTKPTKKPTL KTTKKDPKP QTTKPKEVLTTKPTGKPTINTTKTNIRTTLLTSNTKGNPEHTSQEETLHSTTSEGYLSPSQVYTTS GQEETLHSTT SEGYLSPSQVYTTSEYLSQSLSSSNTTK(SEQ ID NO:52)

[0126] 在一些实施方案中,所述异源基因编码重组RSV G胞外结构域,所述重组RSV G胞外结构域包含SEQ ID NO:52所阐述的氨基酸序列或与SEQ ID NO:52至少90%(如至少95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。所述胞外结构域与合适的跨膜结构域和胞质尾序列连接,如本文所阐述的那些。

[0127] 来自亚组B(基因型BA1;BA4128/99B,AAQ16179.1,Trento A.等,J.Gen.Virol.84,3115-3120,2003)的示例性人RSV G蛋白序列如下所阐述:

[0128] MSKNKNQRTARTLEKTWDTLNHLIVISSCLYKLNLKSIAQIALSVLAMIISTSLIIAAIIFIISANHK VTLTTVTV QTIKNHTEKNITTYLTQVSPERVSPSKQLTTTPPIYTNSATISPNTKSETHHTTAQTKGRTTTPTQN NKPSTKPRP KNPPKKPKDDYHFEVFNFVPCSICGNNQLCKSICKTIPSNKPKKKPTIKPTNKPPTKTTNKRDPKK LAKTLKKETT INPTKKPTPKTTERDTSTSQSTVLDTTTSKHTERDTSTSQSTVLDTTTSKHTIQQQSLHSTTPEN TPNSTQTPTAS EPSTSNSTQKL(SEQ ID NO:53)

[0129] 在一些实施方案中,包含在所述rB/HPIV3-RSV G的基因组中的所述异源基因编码RSV G蛋白,所述RSV G蛋白包含SEQ ID NO:53所阐述的氨基酸序列或与SEQ ID NO:53至少90%(如至少95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0130] 来自亚组B(基因型BA1;BA4128/99B,AAQ16179.1,Trento A.等,J.Gen.Virol.84,3115—20,2003)的示例性人RSV G胞外结构域序列如下所阐述:NHKVTLTTVTVQ TIKNHTEKNITTYLTQVSPERVSPSKQLTTTPPIYTNSATISPNTKSETHHTTAQTKGRTTTPT QNNKPSTKPRP KNPPKKPKDDYHFEVFNFVPCSICGNNQLCKSICKTIPSNKPKKKPTIKPTNKPPTKTTNKRDPK KLAKTLKKET TINPTKKPTPKTTERDTSTSQSTVLDTTTSKHTERDTSTSQSTVLDTTTSKHTIQQQSLHSTTPEN TPNSTQTPTASEPSTSNSTQKL(SEQ ID NO:54)

[0131] 在一些实施方案中,所述异源基因编码重组RSV G胞外结构域,所述重组RSV G胞

外结构域包含SEQ ID NO:54所阐述的氨基酸序列或与SEQ ID NO:54至少90%(如至少95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。所述胞外结构域与合适的跨膜结构域和胞质尾序列连接,如本文所阐述的那些。

[0132] 在一些实施方案中,所述异源基因编码重组RSV G蛋白,所述重组RSV G蛋白包含连接至BPIV3 HN蛋白、HPIV3 HN蛋白或HPIV1 HN蛋白的胞质尾的RSV G胞外结构域和跨膜结构域。在一些实施方案中,所述异源基因编码重组RSV G蛋白,所述重组RSV G蛋白包含连接至BPIV3 HN蛋白、HPIV3 HN 蛋白或HPIV1 HN蛋白的跨膜结构域和胞质尾的RSV G胞外结构域。如实施例中所讨论的,将PIV HN跨膜和胞质尾蛋白序列与RSV G跨膜和胞质尾蛋白序列交换,可促进膜插入和将II型膜蛋白封装到病毒体包膜中。据信,暴露在病毒体包膜表面上的RSV G胞外结构域的量的增加导致对RSV G胞外结构域的免疫应答的相应增加。

[0133] 来自RSV A2的示例性RSV G序列的跨膜结构域和胞质尾如下所阐述:

[0134] RSV G CT:MSKNKDQRTAKTLERTWDTLNHLLFISSCLYKLNLKS,SEQ ID NO:24

[0135] RSV G TM:VAQITLSILAMIISTSLIIAAIIFIASA.SEQ ID NO:25

[0136] RSV G TM+CT:MSKNKDQRTAKTLERTWDTLNHLLFISSCLYKLNLKSVAQITLSILAMIISTSLIIAAIIFIASA, SEQ ID NO:26

[0137] 此外,示例性BPIV3 HN蛋白的胞质尾和跨膜结构域如下所阐述:

[0138] BPIV3 HN CT:MEYWKHTNSINNTNNETETARGKHSSKVTN,SEQ ID NO:27

[0139] BPIV3 HN TM:IIMYTFWTITLTILSVIFIMILTNLI,SEQ ID NO:28

[0140] BPIV3 HN TM+CT:MEYWKHTNSINNTNNETETARGKHSSKVTNIIMYTFWTITLTILSVIFIMILTNLI,SEQ ID NO:29

[0141] 此外,示例性HPIV3 HN蛋白的胞质尾和跨膜结构域如下所阐述:

[0142] HPIV3 HN CT:MEYWKHTNHGKDAGNELETSMATHGNKLTNK,SEQ ID NO:55

[0143] HPIV3 HN TM:IIYILWTIILVLLSIVFIIVLINSI,SEQ ID NO:56

[0144] HPIV3 HN TM+CT:MEYWKHTNHGKDAGNELETSMATHGNKLTNKIIYILWTIILVLLSIVFIIVLINSI,SEQ ID NO:57

[0145] 此外,示例性HPIV1 HN蛋白的胞质尾和跨膜结构域如下所阐述:

[0146] HPIV1 HN CT:MAEKGKTNSSYWSTTRNDNSTVNTHINTPAGRTHW,SEQ ID NO:58

[0147] HPIV1 HN TM:ILLIATTMHTVLSFIIMILCIDLII,SEQ ID NO:59

[0148] HPIV1 HN TM+CT:MAEKGKTNSSYWSTTRNDNSTVNTHINTPAGRTHWILLIATTMHTVLSFIIMILCIDLII, SEQ ID NO:60

[0149] 人RSV G、BPIV3 HN、HPIV3 HN和HPIV1 HN蛋白在相应的病毒亚组中表现出显著的序列保守性。因此,当构建rB/HPIV3-RSV G载体中包含的异源基因时,可以根据需要容易地鉴定出RSV G蛋白的胞质尾和跨膜结构域序列,并交换为BPIV3、HPIV3或HPIV1 HN蛋白的相应序列。

[0150] 下面提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自RSV A2的RSV G胞外结构域和跨膜结构域,以及BPIV3 HN胞质尾:

[0151] MEYWKHTNSINNTNNETETARGKHSSKVTNVAQITLSILAMIISTSLIIAAIIFIASANHKVTPTTAIIQDATSQIK NTTPTYLTQNPQLGISPSNPSEITSQITTILASTTPGVKSTLQSTTVKTKNTTTTQTQPSKPTTKQRQNKPPSKPNN DFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGKKTTTKPTKKPTLKTTKKDPKPQTTKSKEV

PTTKPTEEPTINT TKTNIITTLLTSNTTGNPELTSQMETFHSTSSEGNPSPSQVSTTSEYPSQPSSPPNTPRQ (SEQ ID NO:30)

[0152] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:30所阐述的氨基酸序列或与SEQ ID NO:30至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0153] 以下提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV A2的RSV G胞外结构域以及BPIV3 HN跨膜结构域和胞质尾:

[0154] MEYWKHTNSINNTNNETETARGKHSSKVTNIIMYTFWTITLTILSVIFIMILTNLINHKVTPTTAIIQ DATSQIKN TTPTYLTQNPQLGISPSNPSEITSQITTILASTTPGVKSTLQSTTVKTKNTTTTQTQPSKPTTKQRQ NKPPSKPNN DFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGKKTTTKPTKKPTLKTTKKDPKPQTTKSKEVPT TKPTEEPTIN TTKTNIITTLLTSNTTGNPELTSQMETFHSTSSEGNPSPSQVSTTSEYPSQPSSPPNTPRQ(SEQ ID NO:31)

[0155] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:31所阐述的氨基酸序列或与SEQ ID NO:31至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0156] 下面提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV B(B1,GenBank AAB82435.1)的RSV G胞外结构域和跨膜结构域,以及BPIV3 HN胞质尾:

[0157] MEYWKHTNSINNTNNETETARGKHSSKVTNIAQIALSVLAMIISTSLIIAAIIFIISANHKVTLTTVT VQTIKNHT EKNITTYLTQVPPERVSSSKQPTTTSPIHTNSATTSPNTKSETHHTTAQTKGRTTTSTQTNKPSTKP RLKNPPKKP KDDYHFEVFNFVPCSICGNNQLCKSICKTIPSNKPKKKPTIKPTNKPTTKTTNKRDPKTPAKTTKK ETTTNPTKKP TLTTTERDTSTSQSTVLDTTTLEHTIQQQSLHSTTPENTPNSTQTPTASEPSTSNSTQNTQSHA (SEQ ID NO: 61)

[0158] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:61所阐述的氨基酸序列或与SEQ ID NO:61至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0159] 以下提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV B(B1,GenBank AAB82435.1)的RSV G胞外结构域以及BPIV3 HN跨膜结构域和胞质尾:

[0160] MEYWKHTNSINNTNNETETARGKHSSKVTNIIMYTFWTITLTILSVIFIMILTNLINHKVTLTTVTVQ TIKNHTEK NITTYLTQVPPERVSSSKQPTTTSPIHTNSATTSPNTKSETHHTTAQTKGRTTTSTQTNKPSTKPRL KNPPKKPKD DYHFEVFNFVPCSICGNNQLCKSICKTIPSNKPKKKPTIKPTNKPTTKTTNKRDPKTPAKTTKKET TTNPTKKPTL TTTERDTSTSQSTVLDTTTLEHTIQQQSLHSTTPENTPNSTQTPTASEPSTSNSTQNTQSHA(SEQ ID NO:62)

[0161] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:62所阐述的氨基酸序列或与SEQ ID NO:62至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0162] 下面提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV A/马里兰/001/11的RSV G胞外结构域和跨膜结构域,以及BPIV3 HN胞质尾:

[0163] MEYWKHTNSINNTNNETETARGKHSSKVTNIAQITLSILAMIISTSLIIAAIIFIASANHKVTLTTAI IQDATNQIK NTTPTYLTQNPQLGISLSNLSETTSKPTTILALTTPNAESTPQSTTVKTKNTTTTQIQPSKPTTKQ

RQNKPQNKPNN DFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGRKTTTKPTKQPAIKTTKKDPKPQTTKPKEV LTTKPTEKPTINT TKTNIRTTLLTSNITENQEHTSQKETLHSTTSEGNPSPSQVYTTSEYLSQSLSPSNTTRW (SEQ ID NO:63)

[0164] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:63所阐述的氨基酸序列或与SEQ ID NO:63至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0165] 以下提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV A/马里兰/001/11的RSV G胞外结构域以及BPIV3 HN跨膜结构域和胞质尾:

[0166] MEYWKHTNSINNTNNETETARGKHSSKVTNIIMYTFWTITLTILSVIFIMILTNLINHKVTLTTAIIQ DATNQIKN TTPTYLTQNPQLGISLSNLSETTSKPTTILALTTPNAESTPQSTTVKTKNTTTTQIQPSKPTTKQRQ NKPQNKPNN DFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGRKTTTKPTKQPAIKTTKKDPKPQTTKPKEVLT TKPTEKPTIN TTKTNIRTTLLTSNITENQEHTSQKETLHSTTSEGNPSPSQVYTTSEYLSQSLSPSNTTRW(SEQ ID NO:64)

[0167] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:64所阐述的氨基酸序列或与SEQ ID NO:64至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0168] 下面提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV ON1的RSV G胞外结构域和跨膜结构域,以及BPIV3 HN胞质尾:

[0169] MEYWKHTNSINNTNNETETARGKHSSKVTNIAQITLSILAMIISTSLIIAAIIFIASANHKVTLTTAI IQDATNQI KNTTPTYLTQNPQLGISFSNLSGTTSQSTTILASTTPSAESTPQSTTVKIKNTTTTQILPSKPTTKQ RQNKPQNKP NNDFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGKKTTTKPTKKPTLKTTKKDPKPQTTKPKEV LTTKPTGKPT INTTKTNIRTTLLTSNTKGNPEHTSQEETLHSTTSEGYLSPSQVYTTSGQEETLHSTTSEGYLSP SQVYTTSEYLS QSLSSSNTTK(SEQ ID NO:65)

[0170] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:65所阐述的氨基酸序列或与SEQ ID NO:65至少90%(如至少95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0171] 以下提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV ON1的RSV G胞外结构域以及BPIV3 HN跨膜结构域和胞质尾:

[0172] MEYWKHTNSINNTNNETETARGKHSSKVTNIIMYTFWTITLTILSVIFIMILTNLINHKVTLTTAIIQ DATNQIKN TTPTYLTQNPQLGISFSNLSGTTSQSTTILASTTPSAESTPQSTTVKIKNTTTTQILPSKPTTKQRQ NKPQNKPNN DFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGKKTTTKPTKKPTLKTTKKDPKPQTTKPKEVLT TKPTGKPTIN TTKTNIRTTLLTSNTKGNPEHTSQEETLHSTTSEGYLSPSQVYTTSGQEETLHSTTSEGYLSPSQ VYTTSEYLSQS LSSSNTTK(SEQ ID NO:66)

[0173] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:66所阐述的氨基酸序列或与SEQ ID NO:66至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0174] 下面提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV BA1的RSV G胞外结构域和跨膜结构域,以及BPIV3 HN胞质尾:

[0175] MEYWKHTNSINNTNNETETARGKHSSKVTNIAQIALSVLAMIISTSLIIAAIIFIISANHKVTLTTVT

VQTIKNHT EKNITTYLTQVSPERVSPSKQLTTTPPIYTNSATISPNTKSETHHTTAQTKGRTTTPTQNNKPSTKP RPKNPPKKP KDDYHFEVFNFVPCSICGNNQLCKSICKTIPSNKPKKKPTIKPTNKPPTKTTNKRDPKKLAKTLKK ETTINPTKKP TPKTTERDTSTSQSTVLDTTTSKHTERDTSTSQSTVLDTTTSKHTIQQQSLHSTTPENTPNSTQT PTASEPSTSNS TQKL(SEQ ID NO:67)

[0176] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:67所阐述的氨基酸序列或与SEQ ID NO:67至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0177] 以下提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV BA1的RSV G胞外结构域以及BPIV3 HN跨膜结构域和胞质尾:

[0178] MEYWKHTNSINNTNNETETARGKHSSKVTNIIMYTFWTITLTILSVIFIMILTNLINHKVTLTTVTVQ TIKNHTEK NITTYLTQVSPERVSPSKQLTTTPPIYTNSATISPNTKSETHHTTAQTKGRTTTPTQNNKPSTKPRP KNPPKKPKD DYHFEVFNFVPCSICGNNQLCKSICKTIPSNKPKKKPTIKPTNKPPTKTTNKRDPKKLAKTLKKET TINPTKKPTP KTTERDTSTSQSTVLDTTTSKHTERDTSTSQSTVLDTTTSKHTIQQQSLHSTTPENTPNSTQTPT ASEPSTSNSTQ KL(SEQ ID NO:68)

[0179] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:68所阐述的氨基酸序列或与SEQ ID NO:68至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0180] 下面提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV A2的RSV G胞外结构域和跨膜结构域,以及HPIV3 HN胞质尾:

[0181] MEYWKHTNHGKDAGNELETSMATHGNKLTNKVAQITLSILAMIISTSLIIAAIIFIASANHKVTPTTA IIQDATSQI KNTTPTYLTQNPQLGISPSNPSEITSQITTILASTTPGVKSTLQSTTVKTKNTTTTQTQPSKPTTK QRQNKPPSKPN NDFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGKKTTTKPTKKPTLKTTKKDPKPQTTKSKE VPTTKPTEEPTIN TTKTNIITTLLTSNTTGNPELTSQMETFHSTSSEGNPSPSQVSTTSEYPSQPSSPPNTPRQ (SEQ ID NO:69)

[0182] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:69所阐述的氨基酸序列或与SEQ ID NO:69至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0183] 以下提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV A2的RSV G胞外结构域以及HPIV3 HN跨膜结构域和胞质尾:

[0184] MEYWKHTNHGKDAGNELETSMATHGNKLTNKIIYILWTIILVLLSIVFIIVLINSINHKVTPTTAIIQ DATSQIKN TTPTYLTQNPQLGISPSNPSEITSQITTILASTTPGVKSTLQSTTVKTKNTTTTQTQPSKPTTKQRQ NKPPSKPNN DFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGKKTTTKPTKKPTLKTTKKDPKPQTTKSKEVPT TKPTEEPTIN TTKTNIITTLLTSNTTGNPELTSQMETFHSTSSEGNPSPSQVSTTSEYPSQPSSPPNTPRQ(SEQ ID NO:70)

[0185] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:70所阐述的氨基酸序列或与SEQ ID NO:70至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0186] 下面提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV B(B1,GenBank AAB82435.1)的RSV G胞外结构域和跨膜结构域,以及HPIV3 HN胞质尾:

[0187] MEYWKHTNHGKDAGNELETSMATHGNKLTNKIAQIALSVLAMIISTSLIIAAIIFIISANHKVTLTTVTVQTIKNHT EKNITTYLTQVPPERVSSSKQPTTTSPIHTNSATTSPNTKSETHHTTAQTKGRTTTSTQTNKPSTKPRLKNPPKKPK DDYHFEVFNFVPCSICGNNQLCKSICKTIPSNKPKKKPTIKPTNKPTTKTTNKRDPKTPAKTTKKETTTNPTKKPTL TTTERDTSTSQSTVLDTTTLEHTIQQQSLHSTTPENTPNSTQTPTASEPSTSNSTQNTQSHA (SEQ ID NO:71)

[0188] 在一些实施方案中，所述异源基因编码重组RSV G，所述重组RSV G包含SEQ ID NO:71所阐述的氨基酸序列或与SEQ ID NO:71至少90％(如至少 95％或至少98％)相同的氨基酸序列，或者由所述氨基酸序列组成。

[0189] 以下提供了重组RSV G的示例性氨基酸序列，所述重组RSV G包含来自 RSV B(B1，GenBank AAB82435.1)的RSV G胞外结构域以及HPIV3 HN跨膜结构域和胞质尾：

[0190] MEYWKHTNHGKDAGNELETSMATHGNKLTNKIIYILWTIILVLLSIVFIIVLINSINHKVTLTTVTVQTIKNHTEK NITTYLTQVPPERVSSSKQPTTTSPIHTNSATTSPNTKSETHHTTAQTKGRTTTSTQTNKPSTKPRLKNPPKKPKD DYHFEVFNFVPCSICGNNQLCKSICKTIPSNKPKKKPTIKPTNKPTTKTTNKRDPKTPAKTTKKETTTNPTKKPTL TTTERDTSTSQSTVLDTTTLEHTIQQQSLHSTTPENTPNSTQTPTASEPSTSNSTQNTQSHA(SEQ ID NO:72)

[0191] 在一些实施方案中，所述异源基因编码重组RSV G，所述重组RSV G包含SEQ ID NO:72所阐述的氨基酸序列或与SEQ ID NO:72至少90％(如至少 95％或至少98％)相同的氨基酸序列，或者由所述氨基酸序列组成。

[0192] 下面提供了重组RSV G的示例性氨基酸序列，所述重组RSV G包含来自 RSV A/马里兰/001/11的RSV G胞外结构域和跨膜结构域，以及HPIV3 HN胞质尾：

[0193] MEYWKHTNHGKDAGNELETSMATHGNKLTNKIAQITLSILAMIISTSLIIAAIIFIASANHKVTLTTAIIQDATNQI KNTTPTYLTQNPQLGISLSNLSETTSKPTTILALTTPNAESTPQSTTVKTKNTTTTQIQPSKPTTKQRQNKPQNKPN NDFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGRKTTTKPTKQPAIKTTKKDPKPQTTKPKEVLTTKPTEKPTIN TTKTNIRTTLLTSNITENQEHTSQKETLHSTTSEGNPSPSQVYTTSEYLSQSLSPSNTTRW (SEQ ID NO:73)

[0194] 在一些实施方案中，所述异源基因编码重组RSV G，所述重组RSV G包含SEQ ID NO:73所阐述的氨基酸序列或与SEQ ID NO:73至少90％(如至少 95％或至少98％)相同的氨基酸序列，或者由所述氨基酸序列组成。

[0195] 以下提供了重组RSV G的示例性氨基酸序列，所述重组RSV G包含来自 RSV A/马里兰/001/11的RSV G胞外结构域以及HPIV3 HN跨膜结构域和胞质尾：

[0196] MEYWKHTNHGKDAGNELETSMATHGNKLTNKIIYILWTIILVLLSIVFIIVLINSINHKVTLTTAIIQDATNQIKN TTPTYLTQNPQLGISLSNLSETTSKPTTILALTTPNAESTPQSTTVKTKNTTTTQIQPSKPTTKQRQNKPQNKPNN DFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGRKTTTKPTKQPAIKTTKKDPKPQTTKPKEVLTTKPTEKPTIN TTKTNIRTTLLTSNITENQEHTSQKETLHSTTSEGNPSPSQVYTTSEYLSQSLSPSNTTRW(SEQ ID NO:74)

[0197] 在一些实施方案中，所述异源基因编码重组RSV G，所述重组RSV G包含SEQ ID NO:74所阐述的氨基酸序列或与SEQ ID NO:74至少90％(如至少 95％或至少98％)相同的氨基酸序列，或者由所述氨基酸序列组成。

[0198] 下面提供了重组RSV G的示例性氨基酸序列，所述重组RSV G包含来自 RSV ON1的

RSV G胞外结构域和跨膜结构域,以及HPIV3 HN胞质尾:

[0199] MEYWKHTNHGKDAGNELETSMATHGNKLTNKIAQITLSILAMIISTSLIIAAIIFIASANHKVTLTTAIIQDATNQ IKNTTPTYLTQNPQLGISFSNLSGTTSQSTTILASTTPSAESTPQSTTVKIKNTTTTQILPSKPTTKQRQNKPQNK PNNDFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGKKTTTKPTKKPTLKTTKKDPKPQTTKPKEVLTTKPTGKP TINTTKTNIRTTLLTSNTKGNPEHTSQEETLHSTTSEGYLSPSQVYTTSGQEETLHSTTSEGYLSPSQVYTTSEYL SQSLSSSNTTK(SEQ ID NO:75)

[0200] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:75所阐述的氨基酸序列或与SEQ ID NO:75至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0201] 以下提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV ON1的RSV G胞外结构域以及HPIV3 HN跨膜结构域和胞质尾:

[0202] MEYWKHTNHGKDAGNELETSMATHGNKLTNKIIYILWTIILVLLSIVFIIVLINSINHKVTLTTAIIQDATNQIKN TTPTYLTQNPQLGISFSNLSGTTSQSTTILASTTPSAESTPQSTTVKIKNTTTTQILPSKPTTKQRQNKPQNKPNN DFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGKKTTTKPTKKPTLKTTKKDPKPQTTKPKEVLTTKPTGKPTIN TTKTNIRTTLLTSNTKGNPEHTSQEETLHSTTSEGYLSPSQVYTTSGQEETLHSTTSEGYLSPSQVYTTSEYLSQS LSSSNTTK(SEQ ID NO:76)

[0203] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:76所阐述的氨基酸序列或与SEQ ID NO:76至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0204] 下面提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV BA1的RSV G胞外结构域和跨膜结构域,以及HPIV3 HN胞质尾:MEYWKHTNHGKDAGNELETSMATHGNKLTNKIAQIALSVLAMIISTSLIIAAIIFIISANHKVTLTTVTVQTIKNH TEKNITTYLTQVSPERVSPSKQLTTTPPIYTNSATISPNTKSETHHTTAQTKGRTTTPTQNNKPSTKPRPKNPPKK PKDDYHFEVFNFVPCSICGNNQLCKSICKTIPSNKPKKKPTIKPTNKPPTKTTNKRDPKKLAKTLKKETTINPTKK PTPKTTERDTSTSQSTVLDTTTSKHTERDTSTSQSTVLDTTTSKHTIQQQSLHSTTPENTPNSTQTPTASEPSTSN STQKL(SEQ ID NO:77)

[0205] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:77所阐述的氨基酸序列或与SEQ ID NO:77至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0206] 以下提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV BA1的RSV G胞外结构域以及HPIV3 HN跨膜结构域和胞质尾:

[0207] MEYWKHTNHGKDAGNELETSMATHGNKLTNKIIYILWTIILVLLSIVFIIVLINSINHKVTLTTVTVQTIKNHTEK NITTYLTQVSPERVSPSKQLTTTPPIYTNSATISPNTKSETHHTTAQTKGRTTTPTQNNKPSTKPRPKNPPKKPKD DYHFEVFNFVPCSICGNNQLCKSICKTIPSNKPKKKPTIKPTNKPPTKTTNKRDPKKLAKTLKKETTINPTKKPTP KTTERDTSTSQSTVLDTTTSKHTERDTSTSQSTVLDTTTSKHTIQQQSLHSTTPENTPNSTQTPTASEPSTSNSTQ KL(SEQ ID NO:78)

[0208] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:78所阐述的氨基酸序列或与SEQ ID NO:78至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0209] 下面提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV A2的

RSV G胞外结构域和跨膜结构域,以及HPIV1 HN胞质尾:

[0210] MAEKGKTNSSYWSTTRNDNSTVNTHINTPAGRTHWVAQITLSILAMIISTSLIIAAIIFIASANHKVTPTTAIIQD ATSQIKNTTPTYLTQNPQLGISPSNPSEITSQITTILASTTPGVKSTLQSTTVKTKNTTTTQTQPSKPTTKQRQNK PPSKPNNDFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGKKTTTKPTKKPTLKTTKKDPKPQTTKSKEVPTTKP TEEPTINTTKTNIITTLLTSNTTGNPELTSQMETFHSTSSEGNPSPSQVSTTSEYPSQPSSPPNTPRQ(SEQ ID NO:79)

[0211] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:79所阐述的氨基酸序列或与SEQ ID NO:79至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0212] 下面提供了重组RSV G的示例性氨基酸序列,其包含来自RSV A2的RSV G胞外结构域和HPIV1 HN跨膜结构域以及胞质尾:

[0213] MAEKGKTNSSYWSTTRNDNSTVNTHINTPAGRTHWILLIATTMHTVLSFIIMILCIDLIINHKVTPTTAIIQDATSQ IKNTTPTYLTQNPQLGISPSNPSEITSQITTILASTTPGVKSTLQSTTVKTKNTTTTQTQPSKPTTKQRQNKPPSKP NNDFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGKKTTTKPTKKPTLKTTKKDPKPQTTKSKEVPTTKPTEEPTI NTTKTNIITTLLTSNTTGNPELTSQMETFHSTSSEGNPSPSQVSTTSEYPSQPSSPPNTPRQ(SEQ ID NO:80)

[0214] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:80所阐述的氨基酸序列或与SEQ ID NO:80至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0215] 下面提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV B(B1,GenBank AAB82435.1)的RSV G胞外结构域和跨膜结构域,以及HPIV1 HN胞质尾:

[0216] MAEKGKTNSSYWSTTRNDNSTVNTHINTPAGRTHWIAQIALSVLAMIISTSLIIAAIIFIISANHKVTLTTVTVQT IKNHTEKNITTYLTQVPPERVSSSKQPTTTSPIHTNSATTSPNTKSETHHTTAQTKGRTTTSTQTNKPSTKPRLKN PPKKPKDDYHFEVFNFVPCSICGNNQLCKSICKTIPSNKPKKKPTIKPTNKPTTKTTNKRDPKTPAKTTKKETTTN PTKKPTLTTTERDTSTSQSTVLDTTTLEHTIQQQSLHSTTPENTPNSTQTPTASEPSTSNSTQNTQSHA(SEQ ID NO:81)

[0217] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:81所阐述的氨基酸序列或与SEQ ID NO:81至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0218] 以下提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV B(B1,GenBank AAB82435.1)的RSV G胞外结构域以及HPIV1 HN跨膜结构域和胞质尾:

[0219] MAEKGKTNSSYWSTTRNDNSTVNTHINTPAGRTHWILLIATTMHTVLSFIIMILCIDLIINHKVTLTTVTVQTIKNH TEKNITTYLTQVPPERVSSSKQPTTTSPIHTNSATTSPNTKSETHHTTAQTKGRTTTSTQTNKPSTKPRLKNPPKKP KDDYHFEVFNFVPCSICGNNQLCKSICKTIPSNKPKKKPTIKPTNKPTTKTTNKRDPKTPAKTTKKETTTNPTKKPT LTTTERDTSTSQSTVLDTTTLEHTIQQQSLHSTTPENTPNSTQTPTASEPSTSNSTQNTQSHA(SEQ ID NO:82)

[0220] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:82所阐述的氨基酸序列或与SEQ ID NO:82至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0221] 下面提供了重组RSV G的示例性氨基酸序列，所述重组RSV G包含来自 RSV A/马里兰/001/11的RSV G胞外结构域和跨膜结构域，以及HPIV1 HN胞质尾：

[0222] MAEKGKTNSSYWSTTRNDNSTVNTHINTPAGRTHWIAQITLSILAMIISTSLIIAAIIFIASANHKVTLTTAIIQD ATNQIKNTTPTYLTQNPQLGISLSNLSETTSKPTTILALTTPNAESTPQSTTVKTKNTTTTQIQPSKPTTKQRQNK PQNKPNNDFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGRKTTTKPTKQPAIKTTKKDPKPQTTKPKEVLTTKP TEKPTINTTKTNIRTTLLTSNITENQEHTSQKETLHSTTSEGNPSPSQVYTTSEYLSQSLSPSNTTRW(SEQ ID NO:83)

[0223] 在一些实施方案中，所述异源基因编码重组RSV G，所述重组RSV G包含SEQ ID NO:83所阐述的氨基酸序列或与SEQ ID NO:83至少90％(如至少 95％或至少98％)相同的氨基酸序列，或者由所述氨基酸序列组成。

[0224] 以下提供了重组RSV G的示例性氨基酸序列，所述重组RSV G包含来自 RSV A/马里兰/001/11的RSV G胞外结构域以及HPIV1 HN跨膜结构域和胞质尾：

[0225] MAEKGKTNSSYWSTTRNDNSTVNTHINTPAGRTHWILLIATTMHTVLSFIIMILCIDLIINHKVTLTTAIIQDATNQ IKNTTPTYLTQNPQLGISLSNLSETTSKPTTILALTTPNAESTPQSTTVKTKNTTTTQIQPSKPTTKQRQNKPQNKP NNDFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGRKTTTKPTKQPAIKTTKKDPKPQTTKPKEVLTTKPTEKPTI NTTKTNIRTTLLTSNITENQEHTSQKETLHSTTSEGNPSPSQVYTTSEYLSQSLSPSNTTRW(SEQ ID NO:84)

[0226] 在一些实施方案中，所述异源基因编码重组RSV G，所述重组RSV G包含SEQ ID NO:84所阐述的氨基酸序列或与SEQ ID NO:84至少90％(如至少 95％或至少98％)相同的氨基酸序列，或者由所述氨基酸序列组成。

[0227] 下面提供了重组RSV G的示例性氨基酸序列，所述重组RSV G包含来自 RSV ON1的RSV G胞外结构域和跨膜结构域，以及HPIV1 HN胞质尾：

[0228] MAEKGKTNSSYWSTTRNDNSTVNTHINTPAGRTHWIAQITLSILAMIISTSLIIAAIIFIASANHKVTLTTAIIQD ATNQIKNTTPTYLTQNPQLGISFSNLSGTTSQSTTILASTTPSAESTPQSTTVKIKNTTTTQILPSKPTTKQRQNK PQNKPNNDFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGKKTTTKPTKKPTLKTTKKDPKPQTTKPKEVLTTKP TGKPTINTTKTNIRTTLLTSNTKGNPEHTSQEETLHSTTSEGYLSPSQVYTTSGQEETLHSTTSEGYLSPSQVYTT SEYLSQSLSSSNTTK(SEQ ID NO:85)

[0229] 在一些实施方案中，所述异源基因编码重组RSV G，所述重组RSV G包含SEQ ID NO:85所阐述的氨基酸序列或与SEQ ID NO:85至少90％(如至少 95％或至少98％)相同的氨基酸序列，或者由所述氨基酸序列组成。

[0230] 以下提供了重组RSV G的示例性氨基酸序列，所述重组RSV G包含来自 RSV ON1的RSV G胞外结构域以及HPIV1 HN跨膜结构域和胞质尾：

[0231] MAEKGKTNSSYWSTTRNDNSTVNTHINTPAGRTHWILLIATTMHTVLSFIIMILCIDLIINHKVTLTTAIIQDATN QIKNTTPTYLTQNPQLGISFSNLSGTTSQSTTILASTTPSAESTPQSTTVKIKNTTTTQILPSKPTTKQRQNKPQN KPNNDFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGKKTTTKPTKKPTLKTTKKDPKPQTTKPKEVLTTKPTGK PTINTTKTNIRTTLLTSNTKGNPEHTSQEETLHSTTSEGYLSPSQVYTTSGQEETLHSTTSEGYLSPSQVYTTSEY LSQSLSSSNTTK(SEQ ID NO:86)

[0232] 在一些实施方案中，所述异源基因编码重组RSV G，所述重组RSV G包含SEQ ID NO:86所阐述的氨基酸序列或与SEQ ID NO:86至少90％(如至少 95％或至少98％)相同的

氨基酸序列,或者由所述氨基酸序列组成。

[0233] 下面提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV BA1的RSV G胞外结构域和跨膜结构域,以及HPIV1 HN胞质尾:

[0234] MAEKGKTNSSYWSTTRNDNSTVNTHINTPAGRTHWIAQIALSVLAMIISTSLIIAAIIFIISANHKVTLTTVTVQT IKNHTEKNITTYLTQVSPERVSPSKQLTTTPPIYTNSATISPNTKSETHHTTAQTKGRTTTPTQNNKPSTKPRPKN PPKKPKDDYHFEVFNFVPCSICGNNQLCKSICKTIPSNKPKKKPTIKPTNKPPTKTTNKRDPKKLAKTLKKETTIN PTKKPTPKTTERDTSTSQSTVLDTTTSKHTERDTSTSQSTVLDTTTSKHTIQQQSLHSTTPENTPNSTQTPTASEP STSNSTQKL(SEQ ID NO:87)

[0235] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:87所阐述的氨基酸序列或与SEQ ID NO:87至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列其组成。

[0236] 以下提供了重组RSV G的示例性氨基酸序列,所述重组RSV G包含来自 RSV BA1的RSV G胞外结构域以及HPIV1 HN跨膜结构域和胞质尾:

[0237] MAEKGKTNSSYWSTTRNDNSTVNTHINTPAGRTHWILLIATTMHTVLSFIIMILCIDLIINHKVTLTTVTVQTIKN HTEKNITTYLTQVSPERVSPSKQLTTTPPIYTNSATISPNTKSETHHTTAQTKGRTTTPTQNNKPSTKPRPKNPPK KPKDDYHFEVFNFVPCSICGNNQLCKSICKTIPSNKPKKKPTIKPTNKPPTKTTNKRDPKKLAKTLKKETTINPTK KPTPKTTERDTSTSQSTVLDTTTSKHTERDTSTSQSTVLDTTTSKHTIQQQSLHSTTPENTPNSTQTPTASEPSTS NSTQKL(SEQ ID NO:88)

[0238] 在一些实施方案中,所述异源基因编码重组RSV G,所述重组RSV G包含SEQ ID NO:88所阐述的氨基酸序列或与SEQ ID NO:88至少90%(如至少 95%或至少98%)相同的氨基酸序列,或者由所述氨基酸序列组成。

[0239] 在另外的实施方案中,所述rB/HPIV3-RSV G的异源基因包含编码野生型RSV G或其变体的序列,所述序列已经密码子优化以在人类细胞中表达。例如,可以使用GeneArt(GA)、DNA2.0(D2)或GenScript(GS)优化算法对所述异源基因的编码序列进行密码子优化以实现在人类中表达。以下提供了经密码子优化以在人类细胞中表达的RSV G蛋白编码核酸序列的非限制性例子:

[0240] 来自RSV A2的wt G的“GS”密码子优化的DNA编码序列:

[0241] atgtcaaagaacaaggatcagagaactgccaagaccctggaaagaacctgggacaccctgaaccacctgctgttta tctcaagctgcctgtacaagctgaatctgaaaagtgtggcccagatcaccctgtcaattctggctatgatcatttc aacaagcctgatcattgccgctatcattttcatcgcaagcgccaaccacaaggtcacccccaccacagctatcatt caggacgcaacatcccagattaagaacactacccccacctatctgacacagaatcctcagctgggaatctccccat ctaacccctcagagattaccagccagatcacaactattctggcctccaccacacctggcgtgaagtccactctgca gtctactaccgtcaagaccaaaaatacaactaccacacagacacagccttctaagccaactaccaaacagcggcag aataagccccctagtaaaccaaacaatgacttccattttgaggtgttcaactttgtcccatgcagcatctgttcca acaatcccacctgctgggccatctgtaagagaattccaaacaagaaacccggcaagaagaccactaccaaacctac taagaaaccaaccctgaagacaactaagaaagatcctaaaccacagaccacaaagtctaaagaagtgcccactacc aagcctacagaggaaccaactatcaacacaactaagactaacatcatcaccacactgctgacaagcaacactaccg gcaatcccgagctgaccagccagatggaaacctttcactccacaagctccgaggggaatcccagtccttcacaggt gtctacaactagtgaataccccagccagccttctagtccacccaacacccctaggca gtga(SEQ ID NO:89)

[0242] 来自RSV A/马里兰/001/11的wt G的密码子优化(Biobasic)DNA编码序列：

[0243] atgtctaagacaaaggatcagcggacagccaaaacactggaacggacatgggataccctgaatcacct cctcttca tcagcagttgcctgtacaagctcaatctgaagtccatcgcccagatcactctctccatccttgccat gatcatctc tacaagcctcatcattgccgcaattatcttcatcgccagcgctaaccacaaggtcaccccttaccac agccattatt caggatgccaccaaccagatcaagaacacaaccccctacctacctgacacagaaccctcagcttgg aatttcactga gcaacctgtccgaaaccacatctaaacctacaaccatcttggctctgaccacaccaaacgccga gtccaccccaca aagtaccacagtgaagaccaaaaacaccacaaccacacagattcagccaagcaagcctacaac taagcaaaggcag aacaagccacagaacaaacccaacaacgactttcactttgaggtgttcaactttgtgccctg ctccatttgctcca acaaccctacctgttgggctatctgcaagaggatccccaacaagaagcccggcaggaagac tactactaagcctac taaacagccagccattaagaccactaagaaggacccaaagccacagacaaccaagccaaa ggaggtgctcactacc aagcccactgagaagcccaccattaacaccactaaaaccaacatccgcacaacattgct gacatcaaacattacag agaaccaggagcacacaagccagaaggagacactgcatagcactacatccgaaggcaa tcccagcccaagccaggt ctatactacctcagagtacctgtcccagagcctgagccctagcaacactactagatg gtag(SEQ ID NO:95)

[0244] 来自RSV B1的wt G的密码子优化(Biobasic)DNA编码序列：

[0245] agtctaaacacaagaatcagcggaccgcccggaccttggaaaagacttgggataccccttaaccacctt atcgtgatt tcctcctgcctgtaccgcctcaacctcaagagcattgctcagatcgcgctctcagtgctggccatg ataatctccac ttccttgataattgccgccattatcttcattatttctgcaaaccacaaagtcaccctgaccacc gttaccgtgcaaa ccattaaaaaccacacggagaagaacatcactacatacctgactcaggttcccccggagcga gtgagcagctccaag cagcccacaacaacaagccctatccatacaaattcagcaacaacaagtccaaacacaaag tctgaaacgcatcacac aaccgctcagacgaaaggcaggaccacaacatccacccagactaataaacccagtact aagcctagactgaagaacc ctcccaagaaacctaaggacgactatcatttcgaggtgtttaattttgtaccttgc agcatctgtggcaacaatcag ctctgcaaaagcatctgtaagaccatcccgtctaataagccaaagaagaagccc acgataaaaccaacaaataaacc aactaccaagacaacaaataagagggacccaaagacccccgctaaaactacc aagaaggagactaccaccaacccga caaagaaacccaccctgacgactactgagagagatacttcaacttcacaa agcaccgtcctggatacaactaccctg gagcacacaatccagcaacagagcctgcatagtactacgcctgaaaac actccaaactctacccagacgcccacagc ctcagaaccttctacctccaatagtacccaaaatacccagagtcat gcatag(SEQ ID NO:90)

[0246] 在一些实施方案中，所述rB/HPIV3-RSV G载体的基因组包含SEQ ID NO: 85-88中任一个所阐述的反基因组cDNA序列。

[0247] 产生包括异源基因的重组副流感病毒(如rB/HPIV3)的方法的非限制性例子、减毒病毒的方法(例如，通过重组或化学手段)以及用于此类方法的病毒序列和试剂在美国专利公开2012/0045471、2010/0119547、2009/0263883、2009/0017517，7632508、7622123、7250171、7208161、7201907、7192593，PCT公开号WO 2016/118642，Liang等(J.Virol,88(8):4237-4250,2014)，以及Tang等(J Virol,77(20):10819-10828,2003)中提供，其每一个通过引用并入本文。在一些实施方案中，可以使用本文提供的描述根据需要修改这些方法，以构建所公开的rB/HPIV3-RSV G载体。

[0248] 所述rB/HPIV3-RSV G载体的基因组可以包含一个或多个变异(例如，导致氨基酸

缺失、取代或插入的突变),只要所得到的rB/HPIV3-RSV G保留所需的生物学功能(如减毒或免疫原性水平)即可。序列中的这些变异可以是天然存在的变异,或者它们可以是使用基因工程技术工程化的。

[0249] 其他突变涉及将基因组的3'末端用反基因组的对应物替代,这与RNA复制和转录的变化有关。此外,基因间区(Collins等,Proc.Natl.Acad.Sci.USA 83:4594-4598(1986))可以缩短或延长或改变序列内容,并且天然存在的基因重叠(Collins等,Proc.Natl.Acad.Sci.USA 84:5134-5138(1987))可以通过本文所述的方法移除或改变为不同的基因间区。

[0250] 在另一个实施方案中,对所选病毒基因的翻译起始位点周围的序列(优选地包含-3位置的核苷酸)单独或与上游起始密码子的引入组合进行修饰,以通过指定翻译的向上或向下调控来调节基因表达。

[0251] 可替代地,或与本文公开的其他修饰组合,可以通过改变所述病毒的一个或多个所选基因的转录GS信号来调节基因表达。在另外的实施方案中,可以将对转录GE信号的修饰掺入病毒基因组中。

[0252] 除了上述对rB/HPIV3-RSV G的修饰之外,还可以对基因组进行不同的或其他的修饰以便于操作,如在各个基因间区(例如,N和P基因之间的独有 Asc I位点)或其他位置插入独有的限制性位点。可以去除未翻译的基因序列以增加插入外来序列的容量。

[0253] 可以通过多种众所周知的方法将前述修饰引入rB/HPIV3-RSV G中。此类技术的例子可见于,例如,Sambrook等(Molecular Cloning:A Laboratory Manual,第4版,Cold Spring Harbor,New York,2012)和Ausubel等(Current Protocols in Molecular Biology,John Wiley&Sons,New York,增刊104, 2013)。从而,可以通过常规技术(例如,定点诱变)将确定的突变引入所述基因组或反基因组的cDNA拷贝中。使用反基因组或基因组cDNA亚片段组装完整的反基因组或基因组cDNA的优点是,每个区域可以分别进行操作(较小的cDNA比较大的cDNA更易于操作),然后可容易地将其组装成完整的 cDNA。因此,完整的反基因组或基因组cDNA或其任何亚片段可以用作寡核苷酸定向诱变的模板。然后可以将突变的亚片段组装成完整的反基因组或基因组cDNA。突变的范围可能从单核苷酸变化到包含一个或多个基因或基因组区域的大段cDNA的替代。

[0254] 所公开的rB/HPIV3-RSV G的实施方案是自我复制的,也就是说,它们能够在感染合适的宿主细胞后复制,并且具有减毒的表型,例如当给予人类受试者时。优选地,与对照HPIV3相比,在哺乳动物中,所述rB/HPIV3-RSV G在上呼吸道中减少约3至500倍或更多,而在下呼吸道中减少约100至5000 倍或更多。在一些实施方案中,优选的是,体外病毒复制的水平足以提供用于广泛传播规模使用的病毒生产。在一些实施方案中,优选的是,减毒副粘液病毒的体外病毒复制水平为每ml至少10^6,更优选地至少10^7,最优选地至少10^8。

[0255] 在一些实施方案中,可以使用基于反向遗传学重组DNA的技术来产生所述rB/HPIV3-RSV G载体(Collins等1995.Proc Natl Acad Sci USA 92:11563-11567)。该系统允许在限定条件下从合格细胞底物中的cDNA重新恢复感染性病毒。逆向遗传学提供了一种通过cDNA中间体将预定的突变引入rB/HPIV3-RSV G基因组中的方法。在临床前研究中对特定的减毒突变进行了表征,并将其组合以达到所需的减毒水平。从cDNA衍生疫苗病毒可最大程度地减少不定因子(adventitious agent)污染的风险,并且有助于使传代史保持简短并

有据可查。一旦恢复后,工程化的病毒株就以与生物学衍生病毒相同的方式繁殖。作为传代和扩增的结果,所述病毒不包含最初恢复的重组DNA。

[0256] 为了繁殖用于免疫接种和其他目的的rB/HPIV3-RSV G载体,可以使用允许病毒生长的多种细胞系。副流感病毒在各种人类和动物细胞中生长。用于传播减毒的rB/HPIV3-RSV G病毒以进行免疫接种的优选细胞系包括 HEp-2细胞、FRhL-DBS2细胞、LLC-MK2细胞、MRC-5细胞和Vero细胞。通常使用上皮细胞系(如Vero细胞)可获得最高的病毒产量。典型地以约0.001 至1.0或更高的感染复数向细胞接种病毒,并在容许病毒复制的条件下培养这些细胞,例如,在约30℃-37℃的温度下培养约3-10天或病毒达到足够的滴度所需要的时间。温度敏感性病毒通常使用32℃作为"容许温度"进行生长。典型地通过标准澄清化程序,例如离心,从细胞培养物中去除病毒,并从细胞成分中分离病毒,并且可以根据需要使用已知程序进一步纯化这些病毒。

[0257] 可以在各种众所周知且普遍接受的体外和体内模型中测试所述 rB/HPIV3-RSV G载体,以确认适当的减毒、对表型逆转的抗性和免疫原性。在体外测定中,测试了修饰病毒的病毒复制或"ts表型"的温度敏感性以及小噬斑表型。经修饰的病毒也可以在体外人气道上皮(HAE)模型中进行评估,该模型显现提供了一种在非人灵长类动物和人类中按病毒相对衰减的顺序对病毒进行排名的方法(Zhang等,2002J Virol 76:5654-5666;Schaap-Nutt等,2010 Vaccine 28:2788-2798;Ilyushina等,2012J Virol 86:11725-11734)。在 HPIV3或RSV感染的动物模型中进一步测试了经修饰的病毒。可以使用多种动物模型(例如,鼠科动物、棉鼠和灵长类动物)。

[0258] 可以在动物模型(如非人灵长类动物,例如非洲绿猴)中评估 rB/HPIV3-RSV G载体的免疫原性,例如,通过确定一次免疫接种和二次免疫接种后形成针对RSV和HPIV3抗体的动物数量,并通过测量该应答的强度。在一些实施方案中,如果约60%至80%的动物在第一次免疫接种后产生抗体并且约80%至100%的动物在第二次免疫接种后产生抗体,则rB/HPIV3-RSV G具有足够的免疫原性。优选地,所述免疫应答可防范RSV和HPIV3的感染。

[0259] 还提供了分离的多核苷酸,其包含所公开的rB/HPIV3-RSV G载体、包含所述多核苷酸的载体以及包含所述多核苷酸或载体的宿主细胞的基因组或反基因组,或者由所述氨基酸序列组成。

[0260] IV.免疫原性组合物

[0261] 还提供了包含所公开的rB/HPIV3-RSV G载体和药学上可接受的载体的免疫原性组合物。可以通过多种方式,例如通过鼻内途径,将此类组合物给予至受试者。用于制备可给予的免疫原性组合物的标准方法描述于例如以下出版物,Remingtons Pharmaceutical Sciences,第19版,Mack Publishing Company,Easton,Pennsylvania,1995。

[0262] 潜在的载体包括但不限于,生理平衡的培养基、磷酸盐缓冲盐水溶液、水、乳剂(例如,油/水或水/油乳剂)、各种类型的润湿剂、防冻添加剂或稳定剂如蛋白质、肽或水解产物(例如,白蛋白、明胶)、糖(例如,蔗糖、乳糖、山梨糖醇)、氨基酸(例如,谷氨酸钠)或其他保护剂。所得到的水溶液可以封装供原样使用或冻干。冻干的制剂在给予前与无菌溶液混合以用于单次或多次给药。

[0263] 所述免疫原性组合物可包含抑菌剂以防止或最大限度减少在储存过程中的降解,包括但不限于有效浓度(通常为≦1%w/v)的苯甲醇、苯酚、间甲酚、氯丁醇、对羟基苯甲酸

甲酯和/或对羟基苯甲酸丙酯。一些患者可能禁忌使用抑菌剂;因此,冻干配制品可以在含有或不含此组分的溶液中复原。

[0264] 所述免疫原性组合物可包含近似生理条件所需的药学上可接受的媒介物物质,例如pH调节剂和缓冲剂、张力调节剂、润湿剂等,例如,乙酸钠、乳酸钠、氯化钠、氯化钾、氯化钙、脱水山梨糖醇单月桂酸酯和油酸三乙醇胺。

[0265] 所述免疫原性组合物可任选地包含佐剂以增强宿主的免疫应答。合适的佐剂是,例如,Toll样受体激动剂、明矾、AlPO4、铝胶、脂质A及其衍生物或变体、油乳剂、皂苷、中性脂质体、含有重组病毒的脂质体以及细胞因子、非离子型嵌段聚合物和趋化因子。包含聚氧乙烯(POE)和聚氧丙烯(POP) 的非离子型嵌段聚合物,如POE-POP-POE™嵌段共聚物、MPL(3-O-脱酰基单磷酰脂质A;Corixa,印第安纳州哈密尔顿)和IL-12(Genetics Institute,马萨诸塞州坎布里奇),以及本领域众所周知的许多其他合适的佐剂,可以用作佐剂(Newman等,1998,Critical Reviews in Therapeutic Drug Carrier Systems 15:89-142)。这些佐剂的优点在于它们有助于以非特异性方式刺激免疫系统,从而增强了对药物产品的免疫应答。

[0266] 在一些实施方案中,所述免疫原性组合物可包含编码来自一个特定RSV 亚组或株的RSV G胞外结构域的rB/HPIV3-RSV G,以及编码来自一个不同的 RSV亚组或株的RSV G胞外结构域的重组rB/HPIV3-RSV G。例如,所述组合物可以包含rB/HPIV3-RSV G,其包含来自A亚型和B亚型RSV的重组RSV G蛋白。不同的病毒可以混合使用,并且可以同时给予或分开给予。由于某些RSV 株之间的交叉保护现象,用来自第一株的编码RSV G胞外结构域的一个rB/HPIV3-RSV G进行免疫接种可以防范相同或不同亚组的几种不同病毒株。

[0267] 在一些情况下,将包括所述rB/HPIV3-RSV G的免疫原性组合物与诱导对其他病毒试剂,特别是对引起其他儿童疾病的保护性应答的其他药物产品 (例如疫苗)相组合可能是理想的。例如,本文所述的包含rB/HPIV3-RSV G 的组合物还可以包含免疫实践咨询委员会(ACIP;cdc.gov/vaccines/acip/index.html)推荐的针对目标年龄段(例如,大约1到6月龄的婴儿)的其他疫苗。这些其他的疫苗包括但不限于鼻内给予的疫苗。因此,本文所述的rB/HPIV3-RSV G可与针对例如乙型肝炎(HepB)、白喉、破伤风和百日咳(DTaP)、肺炎双球菌(PCV)、乙型流感嗜血杆菌(Hib)、小儿麻痹症、流感和轮状病毒的疫苗同时给予。

[0268] 在一些实施方案中,所述免疫原性组合物可以以单位剂型提供,以用于在受试者中诱导免疫应答,例如,预防受试者中的HPIV3和/或RSV感染。单位剂型包含用于给予至受试者的合适的单一预选剂量,或两个或更多个预选单位剂量的合适的标记或测量倍数,和/或用于给予单位剂量或其倍数的计量机制。

[0269] V.引发免疫应答的方法

[0270] 本文提供了通过向受试者给予包含所公开的rB/HPIV3-RSV G的免疫原性组合物在受试者中引发免疫应答的方法。免疫接种后,受试者通过产生对 RSV G蛋白和HPIV3 HN和F蛋白中的一种或多种具有特异性的抗体来产生应答。另外,诱导了先天的和细胞介导的免疫应答,其可以提供抗病毒效应子并调节所述免疫应答。所述免疫接种的结果是宿主对HPIV3和/或RSV感染至少部分或完全免疫,或对发展成中度或重度HPIV3和/或RSV疾病(特别是下呼吸道)具有抗性。

[0271] 由于到5岁时几乎所有人都感染了RSV和HPIV3,因此整个出生队列都作为相关人

群进行免疫接种。这可以例如通过在以下的任何时间开始免疫接种方案来进行:从出生至6月龄,从6月龄至5岁,在孕妇(或育龄妇女)中通过被动转移抗体保护她们的婴儿、新生婴儿或仍在子宫内的婴儿家庭成员,以及年龄大于50岁的受试者。本公开文本的范围意在包括孕产妇免疫接种。在若干实施方案中,所述受试者是对RSV、HPIV3和/或HPIV1特异性抗体呈血清阴性的人类受试者。在另外的实施方案中,所述受试者不超过一岁,如不超过6个月、不超过3个月或不超过1个月。

[0272] 有严重症状(例如需要住院)的RSV和/或HPIV感染风险最高的受试者包括早产、支气管肺发育不良和先天性心脏病的儿童,这些受试者最容易患上严重疾病。在儿童期和成年期,疾病较轻,但可能伴随下呼吸道疾病,并且通常并发鼻窦炎。福利机构收容的老年人(例如,65岁以上的人)的疾病严重程度会增加。在患有严重的合并免疫缺陷疾病或在骨髓或肺移植后的人中也会发生严重的疾病。在一些实施方案中,可以选择这些受试者给予所公开的rB/HPIV3-RSV G。

[0273] 将含有所述rB/HPIV3-RSV G的免疫原性组合物以足以诱导或增强个体针对RSV和/或HPIV3的免疫应答能力的“有效量”给予易受RSV和/或HPIV3 感染或者有RSV和/或HPIV3感染风险的受试者。所述免疫原性组合物可以通过任何合适的方法来给予,包括但不限于通过注射、气雾剂递送、鼻喷雾剂、鼻滴剂、口服接种或局部施用。在一个优选的实施方案中,根据既有的人鼻内给予方案(例如,如Karron等JID 191:1093-104,2005所讨论的)给予所述减毒病毒。简而言之,通过液滴向成人或儿童鼻内接种有效量的典型地在0.5 ml体积的生理上可接受的稀释剂或载体中的rB/HPIV3-RSV G。与用非复制型病毒进行肠胃外免疫接种相比,它具有简单和安全的优势。它还可以直接刺激局部呼吸道免疫,这在抵抗RSV和HPIV3中起主要作用。此外,这种疫苗接种模式有效地绕过了HPIV3和RSV特异性母体衍生的血清抗体的免疫抑制作用,所述血清抗体典型地在年龄很小的人中发现。同样,尽管RSV抗原的肠胃外给予有时可能伴随免疫病理并发症,但这在活病毒的情况下尚未观察到。

[0274] 在所有受试者中,给予的免疫原的精确量以及给予的时机和重复次数将取决于各种因素,包括患者的健康状况和体重、给予方式、配制品的性质等。剂量通常在每位患者约3.0$\log_{10}$至约6.0$\log_{10}$噬斑形成单位(“PFU”)或更多病毒的范围内,更常见的是每位患者约4.0$\log_{10}$至5.0$\log_{10}$ PFU病毒。在一个实施方案中,可在婴儿期(如1月龄与6月龄之间)给予每位患者约5.0$\log_{10}$至6.0$\log_{10}$ PFU,并且可在2-6个月或更长时间后给予一次或多次额外的加强剂量。在另一个实施方案中,在大约2、4和6月龄时,可向小婴儿给予约5.0 $\log_{10}$至6.0$\log_{10}$ PFU/个患者的剂量,这是多种其他儿童疫苗的建议给予时间。在又另一个实施方案中,可在大约10-15月龄时给予额外的加强剂量。

[0275] 将本文所述的rB/HPIV3-RSV G的实施方案及其免疫原性组合物以诱导或增强受试者中针对HPIV3和RSV抗原的免疫应答的有效量给予至受试者,其中所述HPIV3和RSV抗原包含在所述rB/HPIV3-RSV G中。有效量将允许所述病毒一定程度的生长和增殖,以产生所需的免疫应答,但不会产生病毒相关的症状或疾病。基于本文提供的指导和本领域的知识,可确定用于免疫接种的rB/HPIV3-RSV G的合适量。

[0276] 所需要的免疫应答是抑制随后的RSV和/或HPIV3感染。不需要完全抑制 RSV和/或HPIV3感染以使所述方法有效。例如,给予有效量的所公开的 rB/HPIV3-RSV G可将随后的RSV和/或HPIV3感染(例如,如通过细胞感染或通过RSV和/或HPIV3感染的受试者的数量或

百分比来测量)与合适的对照相比减少所需的量,例如减少至少10%、至少20%、至少50%、至少60%、至少70%、至少80%、至少90%、至少95%、至少98%或甚至是至少100%(预防可检测的RSV和/或HPIV3感染)。

[0277] 有效剂量的确定典型地基于动物模型研究,随后进行人类临床试验,并以可显著减少受试者中靶标疾病症状或病症的发生率或严重程度或在受试者中诱导所需应答(例如中和免疫应答)的给药方案为指导。在这方面,合适的模型包括,例如鼠科动物、大鼠、仓鼠、棉鼠、牛、绵羊、猪、猫、白鼬、非人灵长类动物以及本领域已知的其他可接受的动物模型受试者。可替代地,可以使用体外模型(例如,免疫学和组织病理学测定)确定有效剂量。使用此类模型,仅需常规计算和调整即可确定以给予治疗有效量的组合物所需的合适浓度和剂量(例如,可有效引发所需免疫应答或缓解靶标疾病的一种或多种症状的量)。

[0278] 向受试者给予rB/HPIV3-RSV G可以引发免疫应答的产生,所述免疫应答可在受试者随后感染或再感染野生型RSV或HPIV3时防止出现严重的下呼吸道疾病,如肺炎和细支气管炎,或者是格鲁布性喉头炎(croup)。尽管自然循环的病毒仍然能够引起感染,特别是在上呼吸道,但由于所述免疫接种导致鼻炎的可能性降低,并且由于随后被野生型病毒感染而增强了抗性。免疫接种后,存在可检测水平的宿主产生的血清和分泌抗体,它们能够在体内和体外中和(同一亚组的)同源野生型病毒。在许多情况下,所述宿主抗体还将中和不同的非疫苗亚组的野生型病毒。为了实现更高水平的交叉保护,例如,针对另一亚组的异源株的保护,可以用多种免疫原性组合物对受试者进行免疫接种,所述免疫原性组合物一起包含rB/HPIV3-RSV G,其基因组编码来自RSV亚组A和B的至少一种优势株的RSV G蛋白。

[0279] 包括一种或多种所公开的rB/HPIV3-RSV G病毒的免疫原性组合物可用于协调(或初免-加强)免疫接种方案或组合配制品中。预期可有几次加强免疫接种,并且每个加强免疫接种可为不同的所公开的免疫原。在一些例子中还考虑加强免疫接种可为与另一加强免疫接种或初免相同的免疫原。在某些实施方案中,新颖的组合免疫原性组合物和协调免疫接种方案采用单独的免疫原或配制品,每个都旨在引发抗病毒免疫应答,如对RSV和HPIV3蛋白的免疫应答。可将引发抗病毒免疫应答的单独的免疫原性组合物与在单一免疫接种步骤中给予至受试者的多价免疫原性组合物中合并使用,也可在协调(或初免-加强)免疫接种方案中将它们(以单价免疫原性组合物)分别给予。

[0280] 可以通过多种方法表征所产生的免疫应答。这些方法包括采集鼻洗液或血清样品以分析RSV特异性抗体,可通过测试进行检测,包括但不限于补体固定、噬斑中和、酶联免疫吸附测定、萤光素酶免疫沉淀测定和流式细胞术。此外,可以通过以下方法检测免疫应答:测定鼻腔清洗液或血清中的细胞因子、任一来源的免疫细胞的ELISPOT、鼻腔冲洗液或血清样品的定量RT-PCR 或微阵列分析、以及通过重新体外暴露于病毒抗原进行的来自鼻腔清洗液或血清的免疫细胞的再刺激、以及通过流式细胞术分析细胞因子、表面标志物或其他免疫相关性指标的产生或展示、或者分析对展示RSV抗原的指示靶标细胞的细胞毒活性。在这方面,还监测个体的上呼吸道疾病的体征和症状。

[0281] 实施例

[0282] 提供以下实施例以说明某些实施方案的特定特征,但是各权利要求的范围不应限于所例示的那些特征。

[0283] 实施例1

[0284] 表达诱导对RSV和HPIV3的保护性免疫应答的RSV G或其变体的 rB/HPIV3载体的鉴定

[0285] 本实施例描述了rB/HPIV3载体的开发、生产和评估，以从载体N和P基因之间的第二基因位置表达RSV A2株的wt G蛋白及其变体。

[0286] 在本实施例中使用的载体主链是牛PIV3(Kansas株)和人PIV3(JS株) 的嵌合体，称为rB/HPIV3(Schmidt等,2000,J.Virol.74:8922-8929)。该载体由BPIV3组成，其中编码所述F和HN糖蛋白(两个PIV3中和抗原和主要保护性抗原)的基因已被其来自HPIV3的对应物替代。HPIV3和BPIV3是密切相关的病毒，并且所述rB/HPIV3嵌合体包含所有PIV3基因并具有完全复制能力，但由于BPIV3骨架而在恒河猴和人类中减毒(Karron等,2012,Vaccine 30:3975-3981)。

[0287] 所述rB/HPIV3的一种版本，其野生型(wt)RSV F基因插入第二个基因位置(N-P)，称为MEDI-534,之前曾在HPIV3和RSV血清阴性的婴儿和儿童中进行过评估(Bernstein等,Ped.Infect.Dis.,J.31:109-114,2012)。MEDI-534 被减毒并具有良好的耐受性(在血清阴性儿童中进行的另一项研究中，空 rB/HPIV3载体也是如此，Karron等,2012,Vaccine 30:3975-3981)。但是，尽管所有疫苗接种者都针对HPIV3产生了血清转化，但只有一半的人在没有添加补体的情况下通过微量中和测定分析产生了可检测的血清RSV中和抗体。还损失了来自疫苗接种者的鼻腔清洗液中回收的相当大比例的载体表达的 RSV F蛋白表达(Yang等,Vaccine 31:2822-2827,2013)。所述rB/HPIV3载体系统的优势在于，由于如上所述，表达RSV wt F蛋白的rB/HPIV3在血清阴性儿童中被证明是安全且耐受性良好的(Bernstein等,2012,Pediatr.Infect.Dis.J. 31:109-114)，具有改进的RSV插入的版本有望具有类似的良好耐受性，从而将它们带入临床开发的快速通道。

[0288] 所述rB/HPIV3-RSV G载体的设计使所述RSV G基因的侧翼为BPIV3转录调控元件，包括从N基因拷贝的基因结束(GE)信号、从P基因拷贝的基因起始(GS)信号和CTT三核苷酸基因间区(图1A)。另外，所述rB/HPIV3 的HN基因包含263T和370P氨基酸分配，这使得病毒可以被回收和传代，而不定突变的出现大大减少，从而提高了病毒生产、分析和制造的效率。

[0289] RSV G和RSV G变体

[0290] 所述RSV G蛋白在RSV感染期间以两种形式表达。一种是全长跨膜形式 (mG)，其在细胞表面表达并封装到病毒颗粒中。另一种形式是N末端截短的分泌形式sG。全长G蛋白(mG)是一种II型蛋白，其具有N端胞质尾(CT，预计在株A2中包含氨基酸1-37，见图1B)、疏水跨膜结构域(TM,包含约38-65 位氨基酸，见图1B)和胞外结构域(包含约66-298位氨基酸)。所述sG形式通过在ORF中第二个AUG密码子(M48)处的交替翻译起始产生，其在所述蛋白质中的相应位置位于TM结构域内(见图1B)。然后对所述N末端进行细胞内蛋白水解修剪，在N66处产生新的N末端(图1B)。

[0291] G的胞外结构域由两个大的发散结构域组成，所述发散结构域侧翼为氨基酸164-186处的短中央保守区。所述发散结构域具有较高含量的脯氨酸、丙氨酸、苏氨酸和丝氨酸氨基酸，并且(对于株A2)估计有四个N-连接和24-25 个O-连接的碳水化合物侧链。所述中央保守结构域包含半胱氨酸套索(即，通过两个二硫键稳定的急弯)，其带有保守的CX3C基序(CWAIC,A2株的182-186aa)。就糖基化和蛋白质结构而言，mG和sG形式被认为基本相同，

只是mG形成很可能为三聚体或四聚体的多聚体，而sG仍为单体。

[0292] CX3C结构域也出现在称为曲动蛋白的趋化因子中(图1C)，并且RSV G 和曲动蛋白中CX3C结构域侧翼的序列也具有序列相关性(Tripp等,Nature Immunol.2:732-738m 2001)。所述G蛋白已被证明在体外诱导白细胞趋化性的能力方面可模仿曲动蛋白(Tripp等,2001,Nature Immunol 2:732-738)，并且还与曲动蛋白受体CX3CR1结合，后者可引发RSV感染(Tripp等,2001, Nature Immunol 2:732-738;Johnson等,2015,PLoS Pathog.11:e1005318)。像所述G蛋白一样，曲动蛋白以全长跨膜形式和截短的分泌形式表达。对于曲动蛋白，所述全长跨膜形式充当粘附分子，与T细胞、NK细胞和单核细胞上表达的曲动蛋白受体CX3CR1相互作用，并且所述分泌形式可充当所述相同细胞类型的化学引诱物。所述CX3C结构域在RSV附着中的作用似乎很直接 (即，允许所述病毒与表达CX3CR1的细胞结合)，但是所述CX3C结构域和 sG对宿主免疫的影响尚不清楚。原则上，所述CX3C结构域和/或sG的表达的消除预期会减少免疫细胞的趋化性流入并可能减少疾病，这在若干关于突变 RSV的研究中得到了支持(例如，Maher等,2004,Microbes Infect. 6:1049-1055;Boyoglu-Barnum等,2017,J.Virol.,91(10):e02059-16)，但是也有矛盾的数据(例如Harcourt等,2006,J.Immunol.176:1600-1608)。还描述了 G的其他作用:例如，sG已显示出可作为抗原诱饵来减少抗体的中和作用，并且显现还可以干扰巨噬细胞和补体对RSV的清除(Bukreyev等,J.Virol., 86(19):10880-4,2012)。作为另一个例子，在体外，所述G蛋白干扰人类树突细胞激活(Johnson等,2012,J.Virol.86:1339-1347)。此外，RSV与在人类新生儿调节B细胞上表达的CX3CR1的结合导致Th2极化的应答(Zhivaki等, 2017,Immunity 46:301-314)。因此，所述G蛋白，包括其sG形式和CX3C基序，对宿主免疫的作用尚不完全清楚，且可能很复杂。

[0293] RSV G及其九种衍生物在图1A(构建体(i)-(x))中显示，如下所描述：

[0294] 构建体(i)是wt RSV G。在本实施例中使用的wt RSV G来自亚组A2，且其氨基酸序列如下所阐述：

[0295] MSKNKDQRTAKTLERTWDTLNHLLFISSCLYKLNLKSVAQITLSILAMIISTSLIIAAIIFIASANHK VTPTTAII QDATSQIKNTTPTYLTQNPQLGISPSNPSEITSQITTILASTTPGVKSTLQSTTVKTKNTTTTQTQP SKPTTKQRQ NKPPSKPNNDFHFEVFNFVPCSICSNNPTCWAICKRIPNKKPGKKTTTKPTKKPTLKTTKKDPKPQ TTKSKEVPTT KPTEEPTINTTKTNIITTLLTSNTTGNPELTSQMETFHSTSSEGNPSPSQVSTTSEYPSQPSSPP NTPRQ(SEQ ID NO:22)

[0296] 图1A中的构建体(ii)和(iii)编码G蛋白的mG和sG形式。通过用M48I 突变消除sG的表达来制备mG构建体(图1B)，并且通过缺失G ORF的前47 个密码子来制备所述sG构建体，从而密码子M48启动了ORF(图1B)；如前所述，所述蛋白随后在细胞内被修剪为具有N66的N末端的主要产物(Roberts 等,J.Virol.,68(7):4538-4546,1994,Teng等,J.Virol.289:283-296,2001)。

[0297] 图1A中的构建体(iv)和(v)(G_B3CT和G_B3TMCT)为嵌合蛋白，其 wt G的CT和TMCT被载体BPIV3 HN蛋白的那些(参见图1B)所替代，以提高RSV G封装到载体颗粒中的效率。据信，来自所述载体HN蛋白的CT或 TMCT结构域在RSV G中的存在将促进与内部载体蛋白(如M和N)的同源相互作用，以促进RSV G掺入病毒颗粒中。通过检查和与HPIV3 HN的比对来确定BPIV3 HN的TM和CT的序列边界的鉴定(图1B)。

[0298] 图1A中的构建体(vi)和(vii)(G_dCX3C和G_wCX4C)具有消除G蛋白中CX3C基序的突变:具体而言,G_dCX3C具有C186R突变,该突变改变了CX3C基序中第二半胱氨酸残基的分配(图1C),并且G_wCX4C在位置185 和186之间插入了丙氨酸残基,该丙氨酸残基破坏了所述基序的间隔(图1C)。

[0299] 图1A中的构建体(viii)和(ix)中,所述C186R突变也与B3CT和 B3TMCT取代(G_dCX3C_B3CT和G_dCX3C_B3TMCT)组合进行。

[0300] 另外,通过GenScript对编码wt G的构建体进行密码子优化以用于在人类中表达(wt G/GS-opt,图1A,形式x)。

[0301] RSV G变体的范围允许评估sG、所述CX3C基序、所述CT和TMCT突变以及密码子优化对RSV G蛋白免疫原性的影响。此外,还可以评估对所述 rB/HPIV3载体的免疫应答的可能影响。在这种背景下,PIV3是RSV的合适替代品,因为它是一种相关的呼吸道病毒,在流行病学、组织嗜性和疾病方面具有普遍相似性。此外,所述PIV载体的复制不需要RSV G插入片段,从而消除了这一混杂因素。因此,评估了对载体免疫原性的影响以及载体复制的免疫学限制的可能变化。

[0302] rB/HPIV3-RSV wtG(构建体(i))、rB/HPIV3-RSV wt G/GS-opt(构建体 (x))\rB/HPIV3-RSV G_B3TMCT(构建体(v))、rB/HPIV3-RSV G_B3CT(构建体(iv))的完整反基因组cDNA序列在下面的示例性序列部分中提供。

[0303] 病毒复制和RSV G表达

[0304] 表达各种形式的RSV G的rB/HPIV3载体在LLC-MK2细胞(7.6-8.6 $\log_{10}TCID_{50}/ml$)中高效地复制。在任何构建体的情况下均未观察到生长缺陷。

[0305] 通过Western印迹分析在Vero(图2A和2B)和LLC-MK2(图3)细胞中评估了各种构建体的RSV G细胞内表达。每种载体以每个细胞10$TCID_{50}$ (50%组织培养感染剂量)的感染复数(MOI)感染细胞,或以每个细胞3 个噬斑形成单位(PFU)的MOI通过wt RSV感染细胞。在感染后(p.i.)24 小时收获细胞,并制备细胞裂解物,在变性和还原条件下进行凝胶电泳,并使用针对RSV和HPIV3的多克隆抗体通过Western印迹法进行分析。

[0306] 检测到由表达wt RSV G的rB/HPIV3载体(图2A,泳道2)和wt RSV(泳道11)表达的细胞内RSV G为90-120kD的主要扩散条带(图2A),其对应于完全糖基化的形式,以及35-50kD的较不丰富的条带,这些条带代表具有不完全O-糖基化的G蛋白的加工中间体。通过mG构建体,上述各种G蛋白种类的表达与wt G基本相同(图2A和2B,泳道4与2)。相反,所述sG构建体仅具有痕量的大扩散带,与高效分泌一致。所述sG构建体还具有由于N末端截短而尺寸减小的G蛋白的不完全糖基化条带的版本。所述CT和TMCT取代使大 G条带的表达增加了50%-80%,这一作用尚无法解释(图2A和2B,泳道5和6 与2)。相反,CX3C消除使所述大G带的积累减少了20%-50%,这显现至少部分是由于35-50kD不完全糖基化形式的积累增加(图2A和图2B,泳道7和8 与2)。当与B3CT和B3TMCT取代组合时,补偿了与CX3C突变相关的大G带积累的减少(图2A和2B,泳道9和10)。在包括所述空载体(图2A)在内的构建体之间,所述BPIV3 N蛋白的表达没有显著差异,表明所述RSV G的所有形式均未对体外载体基因表达产生太大影响。所述RSV G和BPIV3 N蛋白在LLC-MK2细胞中的细胞内表达(图3A和3B)遵循与在Vero细胞中表达相似的模式。

[0307] 从Vero细胞培养物中评估RSV G的分泌,所述Vero细胞培养物如上所述被平行感

染并温育48小时(图2C、2D)。收集上层培养基,并通过以10,000 x g离心60分钟进行澄清化,以去除碎屑以及rB/HPIV3病毒体。然后将澄清化的上清液用针对RSV和HPIV3的多克隆抗体进行Western印迹分析。对于感染了表达wt G的rB/HPIV3(图2C,泳道2)的细胞或感染了RSV(泳道11)的细胞,在澄清化、病毒耗尽的培养基中检测到的G蛋白的唯一形式是大的扩散90-120kD种类,表明仅G的完全糖基化形式被分泌到培养基中(图2C,泳道2和11)。如预期的那样,在培养基中从mG构建体感染的细胞中检测到很少的G蛋白(图2C和2D,第4道),而sG构建体产生的sG蛋白较所述wt G构建体丰富70%(图2C和2D,泳道3与2)。通过任一突变消除CX3C显现会稍微减少sG蛋白的表达(图2C和2D,泳道7和8),这可能是由于总体表达降低(图 2A和2B,泳道7和8)所致。所述B3CT和B3TMCT取代完全消除了sG蛋白的表达(图2C和2D,泳道5-6和9-10)。对于B3TMCT,这也许不足为奇,因为通常用于启动sG蛋白合成的天然M48密码子位于G的TM结构域中,该结构域已被HPIV3 HN蛋白的TM结构域替代(尽管另外两个AUG密码子存在于 HPIV3 HN TM域中,但它们显然未被利用,图1B)。在B3CT取代的情况下,存在带有其M48密码子的天然TM,并且尚不清楚其为什么没有被利用。一种可能性是该区域上游的核苷酸序列会影响M48密码子处的起始。

[0308] rB/HPIV3构建体在体外传代后RSV G表达的稳定性通过双重染色噬斑测定确定(图4A),类似于先前描述的针对表达RSV F蛋白的rB/HPIV3构建体的测定(Liang等,J.Virol.,89(18):9499-9510,2015)。简而言之,用10倍连续稀释的病毒原液感染Vero细胞,并在甲基纤维素覆盖下温育直至形成噬斑。将噬斑固定,并先用兔抗HPIV3或山羊抗RSV一抗染色,随后用与红外染料缀合的物种特异性二抗染色(PIV3,绿色;RSV,红色)(图4A)。单个 PFU的HPIV3抗原和RSV G共表达可视化为黄色。发现表达RSV G的所有载体原液都含有几乎100%的表达RSV G的PFU,但对于sG构建体则无法确定,因为G迅速分泌到培养基中而阻止了针对该蛋白的噬斑染色(图4A,第3栏)。

[0309] 另外,使用对所述CX3C结构域具有特异性的RSV G MAb(131-2G)进行双噬斑测定(图4B)。该抗体与所有G版本(其中所述CX3C基序是完整的 (图4B泳道2、4、5、6),sG除外(泳道3))的噬斑结合,但不与具有所述 CX3C基序突变的版本结合(图4B,泳道7-10)。这表明CX3C基序的消除破坏了RSV G上的131-2G结合表位,并证实了这些突变体中不存在完整的CX3C基序。

[0310] RSV G封装

[0311] 为了评估将RSV G封装到rB/HPIV3病毒体中的封装效率,在LLC-MK2 中繁殖空载体和表达RSV G的各种载体,并在Vero细胞中繁殖wt RSV。收获覆盖于细胞上的培养基,通过低速离心进行澄清化,并以30%-60%的不连续蔗糖梯度进行离心。对于每个构建体,通过Western印迹分析四微克纯化的病毒(图5A),并相对于为1.0的wt G进行定量和归一化。这显示未经修饰的wt G在载体病毒体中可检测到非常微弱的条带(图5A,泳道2),并且其封装效率低于wt RSV的5%(按每μg病毒体蛋白计)(图5A和5B,泳道2和6)。请注意,封装在Vero细胞中生长的RSV病毒体中的大多数G蛋白的分子量(50-60 kD)低于正常情况下主导的90-120kD形式。先前显示这种情况的出现是由于在该特定细胞系中长时间温育期间所述细胞蛋白酶组织蛋白酶L的裂解所致(Corry等,2015,J.Virol.90:1311-1320)。在图5B所示的定量中,定量了两种形式的wt RSV。所述BPIV3 HN蛋白的TMCT取代使RSV G的封装效率提高了8.3倍(图5A和5B,泳道2和5),并且对于G_dCX3C_B3TMCT构建体也观察到了相同程度的

作用。单独的BPIV3 HN CT取代仅略微增加了RSV G往载体病毒体中的封装(图5A和5B,泳道2和4)。正如所预期的,sG蛋白没有封装在所述载体中(图5A,泳道3)。

[0312] RSV G的封装也可以通过免疫金标记和透射电子显微镜检查(TEM,图 6)可视化。通过用MAb 131-2G随后用与金颗粒缀合的抗小鼠IgG温育来标记如上所述制备的经纯化病毒体(图5)。如先前所述(Liang等,J.Virol.,90(21): 10022-10038,2016)通过TEM对样本进行成像。结果显示,wt RSV病毒体具有广泛的抗体染色,表明了所述RSV G蛋白的封装的高密度(图6A和6B)。相比之下,rB/HPIV3-wt G的病毒体只有零星的标记(图6C和6D),许多病毒体没有可检测到的G。基本上没有抗体与表达所述sG蛋白的载体的病毒体结合(图6E和图6F)。所述B3CT取代显现稍微增加了抗体结合(图6G和6H),而所述B3TMCT取代极大地改进了抗体结合的效率(图6I和6J)。空载体病毒体没有被所述免疫金颗粒标记(图6K和6L)。因此,在TEM分析中显示的RSV G的密度与通过Western印迹定量的G封装的效率一致。

[0313] 体内复制、免疫原性和保护

[0314] 在仓鼠模型中评估了所述载体的复制、免疫原性和保护效力(分别见图 7-9)。为了评估复制,将六只一组的仓鼠用10^5TCID$_{50}$的所示载体或10^6PFU 的wt RSV进行鼻内免疫接种。免疫接种后第5天收集肺和鼻甲,通过对 LLC-MK2细胞单层进行的TCID$_{50}$血细胞吸附测定来确定所述rB/HPIV3载体的滴度,而RSV滴度则通过对Vero单层的噬斑测定确定。在所述鼻甲中,所有带有RSV G插入片段的载体都复制到与空rB/HPIV3载体相似的滴度(图7A),而在肺中,带有RSV G插入片段的载体均比空载体减毒略多,尽管差异并不明显(图7B)。表达各种形式的RSV G的各种载体的复制之间没有显著差异。因此,例如,sG的表达,或sG的表达的缺失,或所述CX3C基序的存在或该基序的不存在,不会对仓鼠肺的免疫生物学环境产生足以影响所述 rB/HPIV3载体复制的影响,所述载体具有与RSV相同的组织嗜性(Zhang等, J.Virol.76:5654-5666,2002;Zhang等,J.Virol.79:1113-1124,2005),并且在生物学上有许多相似之处。

[0315] 为了评估免疫原性,如上所述,将仓鼠用载体和wt RSV免疫接种,并在免疫接种后第0和28天收集血清,进行体外60％噬斑减少中和测定以定量血清RSV和HPIV3中和抗体滴度(图8)。

[0316] 使用表达绿色荧光蛋白的重组RSV(RSV-GFP,Munir等,J.Virol. 82:8780-8796,2008),通过60％噬斑减少中和滴度(PRNT$_{60}$)测定对Vero细胞体外测定血清RSV中和抗体滴度。在存在或不存在补体的情况下进行测定。补体的存在可以赋予病毒裂解和空间阻滞能力,这些能力给予了原本非中和抗体的中和活性,并且可以增强中和效果较差的抗体的中和活性,而不存在补体的情况下中和则取决于所述抗体的直接能力。(Yoder等2004,J.Med.Virol.72:688-694)。因此,在没有补体的情况下进行的测定提供了更严格的评估,并且仅检测能够直接中和RSV的那些抗体(Liang等,J.Virol., 89(18):9499-9510,2015)。

[0317] 通过添加补体进行的中和测定评估血清RSV中和抗体的滴度时,表达wt G、mG、G_B3CT和G_B3TMCT的载体被证明诱导同样高的滴度(>1:1024),与由高出10倍(10^6PFU)的wt(即未减毒)RSV诱导的滴度无统计学差异 (图8A,泳道2、4-6与11)。相比之下,尽管sG构建体具有稳健的分泌表达 (图2C,泳道3),但它没有诱导可检测到的血清RSV中和抗体(图8A,泳道3)。有趣的是,CX3C消除极大地降低了所述RSV血清中和滴度(图8A,泳道7-10),表明所述CX3C基序在RSV中和抗体的诱导中的作用。因此,消除sG的表达或消除所述CX3C基序并没

有增加所述G蛋白的免疫原性,正如如果这些特征显著干扰宿主免疫时所期望的那样。相反,所述CX3C基序在很大程度上促进诱导强烈的RSV中和抗体应答。为了比较G与F诱导的中和活性,对先前研究(Liang等,J.Virol.,89(18):9499-9510,2015)中相同剂量的表达未经修饰的野生型(wt)RSV F的rB/HPIV3免疫接种的仓鼠的血清进行平行测定(图8A,泳道12)。所述wt G诱导的RSV血清中和抗体的滴度略低于wt F,但差异无统计学显著性(图8A,泳道2和12)。

[0318] 当通过有添加补体的测定评估血清HPIV3中和抗体滴度(即,针对所述载体)时,所有表达各种形式RSV G的载体均具有类似的免疫原性(图8B,泳道2-10),G_B3TMCT构建体除外,所述G_B3TMCT构建体诱导的血清 HPIV3中和抗体水平与空载体相比稍微但显著更低(图8B,泳道1和6)。由 G_B3TMCT构建体诱导的较低滴度表明RSV G通过其TMCT取代而增强的封装可能会通过减少载体HN蛋白的封装来干扰体内的载体复制效率。因此,在表达的G蛋白中是否存在所述sG蛋白或CX3C基序对针对载体的抗体应答没有显著影响。

[0319] 还测定了仓鼠血清中针对RSV的B亚组株的中和血清抗体(B1)。尽管对于wt RSV和wt F血清,针对所述B1株的中和活性保持相似的高水平(图8C,泳道11-12),但由RSV G构建体诱导的B1交叉中和活性却大大降低了(图8C,泳道2和4-6),并且所述CX3C基序的破坏几乎完全消除了中和活性(图8C,泳道7-10)。这表明RSV G A2的G蛋白诱导了中等滴度的交叉亚组中和抗体;此外,这高度依赖于CX3C基序的存在。

[0320] 为了进一步表征所述CX3C基序在RSV中和抗体的诱导中的作用,在添加补体存在下,使用带有G的突变CX3C(CWAIS)的A2 RSV株来分析血清 RSV中和滴度(图8D)。虽然与wt RSV和表达wt F的载体(图8D,泳道11和 12)相比,由四个CX3C消除突变体诱导的针对CX3C突变的RSV的血清中和活性(图8D,泳道7-10)仍然相对较低,但wt G、mG、G_B3CT和G_B3TMCT在血清中针对该CWAIS突变体的中和活性同样低(图8D,泳道2和4-6)。这进一步证实了所述CX3C结构域是G蛋白的主要中和表位。

[0321] 表1中显示了在补体存在下测得的针对wt RSV A2(来自图8A)、wt RSV B1(来自图8C)和RSV A2 CWAIS(来自图8D)的血清中和抗体的滴度。这进一步说明sG的消除(产生mG)不会导致增加的免疫原性;将G封装到载体颗粒中不会增加免疫原性;所述CX3C基序的消除强烈降低了免疫原性。

[0322] 表1.仓鼠中由10^5TCID$_{50}$载体诱导的相对平均RSV血清中和滴度与由 10^6PFU wt RSV A2诱导的滴度相比较。在补体存在下测定所有滴度。

[0323]

免疫接种病毒	用于中和测定的RSV株		
	RSV A2	RSV B1	RSV A2 CWAIS
空载体	< 4	< 4	< 4

[0324]

sG	< 4	< 4	< 4
wtG	3040	226	52
mG	2077	152	16
G_B3CT	1746	125	25
G_B3TMCT	1911	70	25
G_dCX3C	40	< 4	21
G_wCX4C	58	4	35
G_dCX3C_B3CT	83	6	42
G_dCX3C_B3TMCT	54	< 4	36
wt RSV A2	6339	2521	4640
RSV F	6889	3040	6654

[0325] 还通过在不存在添加补体的情况下进行的中和测定来评估血清RSV中和抗体的滴度(图8E),这提供了更严格的中和活性评估。不依赖补体的测定表明,尽管wt RSV和载体表达的wt F均诱导中等滴度的补体依赖性血清RSV中和抗体(图8E,泳道11和12),但G构建体诱导了相对较低滴度的血清抗体,这些血清抗体在体外在不存在补体的情况下能够中和RSV(图8E,泳道2-10)。对于提供的这一结果需要注意的是,Vero细胞缺乏CX3CR1受体,而所述CX3CR1受体可能在体内附着中起重要作用(Johnson SM等,2015, PLoS Pathog.,11:e1005318),因此这一基于Vero的测定可能无法检测到G特异性中和抗体。这可以通过使用表达所述CX3CR1受体的黏膜纤毛人气道上皮 (HAE)的体外模型进行中和测定来解决(Johnson SM等,2015,PLoS Pathog., 11:e1005318),尽管HAE培养物不太适合体外中和测定。

[0326] 为了测量保护效力,在图8的实验中将仓鼠进行免疫接种,在免疫接种后第31天,用10^6PFU的wt RSV对这些仓鼠进行IN激发。3天后处死仓鼠。收集鼻甲和肺,并进行均质化处理以用于RSV噬斑测定滴定(图9)。在所述鼻甲中,表达wt G的载体(图9A,泳道2)比任何其他G构建体(泳道3-10)明显更具保护性。相比之下,所述sG构建体不具有保护性(图9A,泳道3),与其不能诱导RSV中和抗体有关(图9A,泳道3)。构建体mG、G_B3CT和 G_B3TMCT诱导了实质性的保护(图9A,泳道4-6);而CX3C消除(泳道7 和8)与未经修饰的wt G(泳道2)相比大大降低了保护,降至与sG和所述空载体(泳道1和3)没有统计学差异的水平。通过B3CT和B3TMCT增强所述 dCX3C突变体的封装(图9A,泳道9和10)显现将保护效力稍微改进到明显优于sG和所述空载体的水平(泳道1和3)。仅wt RSV接种在鼻甲中实现了完全的保护(图9A,泳道11)。用wt RSV实现更佳的保护并不是意料之外的,因为它以高10倍的剂量给予,未经减毒,它同时带有F和G中和抗原,并且它表达所有病毒抗原并因此可以诱导更广泛的细胞免疫应答。在仓鼠中使用 PIV进行的研究中,嵌合病毒中的内部蛋白已显示出可在短期(1-2个月)激发中诱导保护作用,但这种作用到四个月时减弱(Tao T等,2000,Vaccine 18:1359-1366)。

[0327] 载体诱导的针对RSV的保护在肺部比在鼻甲中要好得多。表达wt G、mG、G_B3CT和B_B3TMCT的载体赋予了几乎完全的保护(图9B,泳道2和4-6)。但是表达所述四种CXC3消除突变体中的任一种的载体的保护性较差,每组 1-3只仓鼠没有被完全保护(图9B,泳道7-

10)。如在鼻甲中所观察到的,TMCT 取代显示出对所述dCX3C构建体的保护作用的一些改进(图9B,泳道10)。

[0328] 绘制了初次免疫接种后第28天的血清RSV中和抗体的滴度(在添加补体存在下对单个动物进行测量,来自图8A)与相同个体的鼻甲(来自图9A) 和肺(来自图9B)中激发RSV滴度的关系的曲线,得出分别如图9C和9D所示的绘图。这表明针对鼻甲或肺中的激发RSV复制的保护(通过激发病毒滴度的降低表明)与血清补体依赖性RSV中和抗体的滴度密切相关(分别为图 9C和9D)。

[0329] 密码子优化的G ORF(wtG/GS-opt)

[0330] 表达RSV G ORF的rB/HPIV3构建体经过了密码子优化以在人类中表达(GenScript),氨基酸编码没有变化(wtG/GS-opt,图1A中的构建体(x)),在Vero和LLCMK-2细胞中以与其他载体相似的高效率水平复制。通过 Western印迹分析评估了构建体wtG/GS-opt在LLC-MK2细胞和Vero细胞中G 蛋白的细胞内表达。将所述LLC-MK2和Vero细胞以每个细胞10TCID$_{50}$的MOI用表达wtG/GS-opt或wtG的rB/HPIV3感染,或者以每个细胞3PFU的MOI用wt RSV感染。在感染后24小时收获细胞,并制备细胞裂解物,在变性和还原条件下进行凝胶电泳,并使用针对RSV的多克隆抗体通过Western印迹法进行分析(图10A和B)。这表明密码子优化的版本比未优化的wt ORF表达效率高约2.2-2.3倍(图10C和10D)。

[0331] 与表达未经修饰的wt G ORF的rB/HPIV3平行评估了表达密码子优化的 G ORF的rB/HPIV3的体内复制和免疫原性。按照图7中描述的方法,将九只一组的仓鼠用10^{4}TCID$_{50}$的所示载体或10^{6}PFU的RSV进行鼻内免疫接种。在免疫接种后第28天收集血清。在第30天,用10^{6}PFU的wt RSV对仓鼠进行鼻内激发。激发后第3天收集肺和鼻甲。通过对Vero单层进行的噬斑测定来确定激发RSV复制的滴度。在补体存在下通过噬斑减少中和评估血清RSV中和抗体滴度(图11)。由野生型G(wt G)诱导的血清RSV中和抗体滴度略高于由野生型F(wt F)诱导的血清中和抗体滴度,但差异不显著(图11,泳道2 和3)。但是经密码子优化的野生型G(wtG/GS-opt)诱导的血清RSV中和抗体的滴度比wt F高2倍,这在统计学上是显著的(图11,泳道2和4)。这表明 RSV G的GS密码子优化增强了所述rB/HPIV3-RSV G载体的免疫原性。与它们诱导血清RSV中和抗体的趋势相似,wt G和wt G/GS-opt与wt F相比在鼻甲中赋予了针对RSV激发的增加的保护作用(图12A)。在肺中,wt G和 wtG/GS-opt赋予了完全保护,如同wt RSV(图12B,泳道3-5)一样,而wt F 仅是部分保护(图12B,泳道2)。这些结果表明,在仓鼠中,表达wt G的 rB/HPIV3比表达wt F的rB/HPIV3更具免疫原性和保护性,并且RSV G的GenScript密码子优化增强了其免疫原性和保护效力。

[0332] RSV G诱导的血清抗体阻断纤毛气道上皮细胞的RSV感染

[0333] 已知Vero细胞缺乏CX3CR1表面蛋白,所述表面蛋白已被鉴定为体内G 介导的附着的主要受体(Johnson SM等,2015,PLoS Pathog.,11:e1005318)。因此,Vero细胞中的中和测定可能会漏掉G诱导抗体的病毒中和的重要组成部分。为了更好地评估G诱导的血清抗体的中和活性,我们使用分化的粘膜纤毛人气道上皮(HAE)的体外模型进行了血清中和测定,所述体外模型已被证明与体内HAE非常相像,并且其表达CX3CR1(Johnson SM等,2015,PLoS Pathog.,11:e1005318)。

[0334] 使HAE细胞在培养中在气液界面处分化。通过纤毛细胞的形成和共聚焦显微镜成像的紧密连接验证完全分化。测试了来自图8所示实验的免疫接种仓鼠的血清在HAE模型中

阻断RSV感染的能力。在不存在添加补体的情况下，将RSV-GFP(A2株)的同等等分试样与仓鼠血清一起预温育，然后用于感染HAE培养物。感染后取出接种物，并在气液界面处培养细胞。在感染后 48小时，将被感染细胞的GFP灶可视化并定量(图13)。在未感染的培养物中，每个培养插入片段有大约6个灶的背景(图13，泳道1)，可能是由于自体荧光细胞引起的。在RSV-GFP感染的培养物中，平均检测到约200个(范围从53至518个)GFP荧光灶(图13，泳道2)。RSV-GFP与使用空载体感染的仓鼠的血清一起预温育对HAE细胞中RSV感染没有影响(图13，泳道3)。值得注意的是，用wt G或wt RSV免疫接种的仓鼠血清几乎完全防止了感染 (图13，泳道4和6)。令人惊讶的是，在该模型中，由表达wt RSV F的载体免疫接种的仓鼠的血清显示出极低的抑制活性；但是用表达稳定化的预融合 F的载体免疫接种的仓鼠的血清(来自先前的研究，在此用作高质量中和抗体应答的阳性对照)完全阻断了RSV感染(图13，泳道8)。有趣的是，与用 wt G感染的血清相比，用G_dCX3C构建体感染的仓鼠的血清仅具有部分保护性(图13，泳道4和5)。这些结果表明，所述wt RSV G诱导了高质量中和抗体，这些抗体可以在不存在添加补体的情况下有效预防HAE中的RSV感染。此外，所述CX3C基序的完整性对于RSV G的血清中和抗体诱导很重要。出乎意料的是，在该测定中，针对wt G产生的血清的中和活性大于wt F，这可能反映了对附着的影响。这些结果表明，在与真实HAE非常相似的HAE体外模型中，针对RSV G的抗体在RSV中和方面特别有效，并且因此所述G蛋白可能是要包含在RSV疫苗中的有效抗原。

[0335] 结论

[0336] 大量研究提供的数据表明，所述RSV G蛋白中的CX3C基序和RSV G (sG)可溶性形式的表达对于宿主对RSV感染的免疫应答具有多种有害作用。据报道，这包括减少的树突细胞激活(Johnson等，2012，J.Virol. 86:1339-1347)、增强的炎性反应(Johnson等，1998，J.Virol.72:2871-2880)、先天免疫的抑制(Shingai等，Int.Immunol.20:1169-1180；Polack等2005，Proc. Natl.Acad.Sci.USA102:8996-9001)以及免疫细胞应答的抑制(Chirkova等， J.Virol.87:13466-13479)以及其他活性。基于这些研究，预期所述CX3C基序和/或sG的消除应当可以制备更安全、更具免疫原性的疫苗(例如，Boyoglu-Barnum等，“Mutating the CX3C Motif in the G Protein Should Make a Live Respiratory Syncytial Virus Vaccine Safer and More Effective”，J.Virol.， 91(10):e02059-16，2017；Chirskova等，2013，J.Virol.87:13466-13479)。

[0337] 令人惊讶的是，本实施例中提供的数据表明，当从所述rB/HPIV3载体表达sG时，消除了sG表达的所述mG构建体(构建体(ii)，图1A)的免疫原性和保护性适度地低于wt G蛋白。sG蛋白表达的消除不会增加免疫原性和保护作用的这一发现与sG在削弱免疫应答中的假定作用相反。此外，sG表达增强本身并不影响载体复制或载体免疫原性。这在比较wtG(表达sG)和mG(不表达sG)以及评估单独sG蛋白表达的作用(构建体(iii)，图1A)时很明显，其中没有一个影响载体复制或免疫原性。因此，没有证据表明sG以显著影响RSV G免疫原性和保护效力或载体复制和免疫原性的方式影响宿主免疫应答。

[0338] 此外，所述CX3C基序的消除大大降低了RSV G的免疫原性(无论用或不用补体进行测定)和针对RSV的保护效力。因此，与上述讨论的研究相反， RSV G的这一区域提供对RSV免疫原性和保护效力的积极作用。消除CX3C 结构域也不会显著影响载体复制或免疫原性。因此，该基序对肺部免疫环境的改变不足以影响载体复制或免疫原性。

[0339] 本实施例证明，所述RSV G蛋白(如sG蛋白)和所述CX3C基序的特征不会损害从rB/HPIV3载体表达的G蛋白的免疫原性和保护效力。经鉴定，表达wt G胞外结构域的基于rB/HPIV3的免疫原对于诱导对RSV G的免疫应答是优选的。令人惊讶的是，在补体存在下测定的wt G构建体诱导的血清RSV 中和抗体滴度与wt RSV诱导的抗体滴度无显著差异，即使RSV以高于10倍的剂量给予，未经减毒，并且同时带有F和G中和抗原。另外，所述HAE测定(图13)显示，在高度模仿体内HAE(体内RSV复制的主要位点)的模型中，由wt G诱导的抗体完全阻断了感染，而由wt F诱导的抗体则没有。与F相比，RSV G蛋白通常被认为是次要中和和保护性抗原。目前的数据修正了这种观点，并且表明所述G蛋白可以改进中和作用(以及可能的保护作用)。这表明将表达RSV G的载体包含到RSV免疫接种方案中改进了中和和保护作用，这是不涉及RSV的CX3CR受体的常规中和测定未重视的一个贡献。

[0340] 示例性反基因组cDNA序列：

[0341] rB/HPIV3-RSV wt G(SEQ ID NO:91)：

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tatgtgcaagtatcaggactgttaattaaatcattcccctcaactgttacgtatgtaaggaaaactgcgattaagtatctgaggattcgtggtattaatccgcctgaaacgattgaagattgggatcccatagaagatgagaatatcttagacaatattgttaaaactgtaaatgacaattgcagtgataatcaaaagagaaataaaagtagttatttctggggattagctctaaagaattatcaagtcgtgaaaataagatccataacgagtgattctgaagttaatgaagcttcgaatgttactacacatggaatgacacttcctcagggaggaagttatctatcacatcagctgaggttatttggagtaaacagtacaagttgtcttaaagctcttgaattatcacaaatcttaatgagggaagttaaaaaagataaagatagactcttttttaggagaaggagcaggagctatgttagcatgttatgatgctacactcggtcctgcaataaattattataattctggtttaaatattacagatgtaattggtcaacgggaattaaaaatcttcccatcagaagtatcattagtaggtaaaaaactaggaaatgtaacacagattcttaatcgggtgagggtgttatttaatgggaatcccaattcaacatggataggaaatatggaatgtgagagtttaatatggagtgaattaaatgataagtcaattggtttagtacattgtgacatggagggagcgataggcaaatcagaagaaactgttctacatgaacattatagtattattaggattacatatttaatcggggatgatgatgttgtcctagtatcaaaaattataccaactattactccgaattggtctaaaatactctatctatacaagttgtattggaaggatgtaagtgtagtgtcccttaaaacatccaatcctgcctcaacagagctttatttaatttcaaaagatgcttactgtactgtaatggaacccagtaatcttgttttatcaaaacttaaaaggatatcatcaatagaagaaaataatctattaaagtggataatcttatcaaaaaggaagaataacgagtggttacagcatgaaatcaaagaaggagaaagggattatggataatgaggccatatcatacagcactgcaaattttggattccaaattaacttaaatcacttagctagagaattttttatcaactcctgatttaaccaacattaataatataattcaaagttttacaagaacaattaaagatgttatgttcgaatgggtcaatatcactcatgacaataaaagacataaattaggaggaagatataatctattcccgcttaaaaataaggggaaattaagattattatcacgaagattagtactaagctggatatcattatccttatcaaccagattactgacgggccgttttccagatgaaaaatttgaaaatagggcacagaccggatatgtatcattggctgatattgatttagaatccttaaagttattatcaagaaatattgtcaaaaattacaaagaacacataggattaatatcatactggtttttgaccaaagaggtcaaaatactaatgaagcttataggaggagtcaaactactaggaattcctaaacagtacaaagagttagaggatcgatcatctcagggttatgaatatgataatgaatttgatattgattaatacataaaacataaaataaaacacctattcctcacccattcacttccaacaaaatgaaaagtaagaaaaacatgtaatatatatataccaaacagagtttttctcttgtttggt

[0349] 显而易见的是，在不脱离所描述的实施方案的精神的情况下，可以改变或修改所描述的方法或组合物的精确细节。我们要求所有此类修改或改变落入以下权利要求书的范围和精神内。

序列表

<110> 美利坚合众国- 由健康及人类服务部部长代表(The United States of America, as represented by the Secretary, Department of Health and Human Services)

<120> 表达RSV G的重组嵌合牛/人副流感病毒3及其用途

<130> 9668-99001-02

<150> US 62/512,111

<151> 2017-05-29

<160> 95

<170> PatentIn 3.5版

<210> 1

<211> 515

<212> PRT

<213> 牛副流感病毒3

<400> 1

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

Thr Leu Ala Leu Leu Phe Leu Ser His Ser Leu Asp Asn Glu Lys Gln
    50   55   60

His Ala Gln Arg Ala Gly Phe Leu Val Ser Leu Leu Ser Met Ala Tyr
65   70   75   80

Ala Asn Pro Glu Leu Tyr Leu Thr Ser Asn Gly Ser Asn Ala Asp Val
                85   90   95

Lys Tyr Val Ile Tyr Met Ile Glu Lys Asp Pro Gly Arg Gln Lys Tyr
            100   105   110

Gly Gly Phe Val Val Lys Thr Arg Glu Met Val Tyr Glu Lys Thr Thr
        115   120   125

Asp Trp Met Phe Gly Ser Asp Leu Glu Tyr Asp Gln Asp Asn Met Leu
    130   135   140

Gln Asn Gly Arg Ser Thr Ser Thr Ile Glu Asp Leu Val His Thr Phe
145   150   155   160

Gly Tyr Pro Ser Cys Leu Gly Ala Leu Ile Ile Gln Val Trp Ile Ile
                165   170   175

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

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

Thr Asn Asn Thr Asn Gln Thr Glu Ile Asp Asp Leu Phe Ser Ala Phe
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Gly Ser Asn
515

<210> 2

<211> 596

<212> PRT

<213> 牛副流感病毒3

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Glu Phe Ile Leu Ser Thr Asp Ser Gln Glu Asn Thr Ala Asp Ser Asn
35 40 45

Glu Ile Asn Thr Gly Thr Thr Arg Leu Ser Thr Thr Ile Tyr Gln Pro
50 55 60

Glu Ser Lys Thr Thr Glu Thr Ser Lys Glu Asn Ser Gly Pro Ala Asn
65 70 75 80

Lys Asn Arg Gln Phe Gly Ala Ser His Glu Arg Ala Thr Glu Thr Lys
85 90 95

Asp Arg Asn Val Asn Gln Glu Thr Val Gln Gly Gly Tyr Arg Arg Gly
100 105 110

Ser Ser Pro Asp Ser Arg Thr Glu Thr Met Val Thr Arg Arg Ile Ser
115 120 125

Arg Ser Ser Pro Asp Pro Asn Asn Gly Thr Gln Ile Gln Glu Asp Ile
130 135 140

Asp Tyr Asn Glu Val Gly Glu Met Asp Lys Asp Ser Thr Lys Arg Glu
145 150 155 160

Met Arg Gln Phe Lys Asp Val Pro Val Lys Val Ser Gly Ser Asp Ala
165 170 175

Ile Pro Pro Thr Lys Gln Asp Gly Asp Gly Asp Asp Gly Arg Gly Leu
180 185 190

Glu Ser Ile Ser Thr Phe Asp Ser Gly Tyr Thr Ser Ile Val Thr Ala
195 200 205

Ala Thr Leu Asp Asp Glu Glu Glu Leu Leu Met Lys Asn Asn Arg Pro
210 215 220

Arg Lys Tyr Gln Ser Thr Pro Gln Asn Ser Asp Lys Gly Ile Lys Lys
225 230 235 240

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

545 550 555 560
Leu Ser Ser Lys Ala Lys Gln Ser Tyr Ile Asn Glu Leu Lys Leu Cys
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Lys Ser Asp Glu Glu Val Ser Glu Leu Met Asp Met Phe Asn Glu Asp
580 585 590
Val Ser Ser Gln
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<212> PRT
<213> 牛副流感病毒3
<400> 3
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20 25 30
Ser Ala Pro Thr Pro Lys Arg Thr Arg Gln Thr Ala Met Lys Ser Thr
35 40 45
Gln Glu Pro Gln Asp Leu Ala Arg Gln Ser Thr Asn Leu Asn Pro Lys
50 55 60
Gln Gln Lys Gln Ala Arg Lys Ile Val Asp Gln Leu Thr Lys Ile Asp
65 70 75 80
Ser Leu Gly His His Thr Asn Val Pro Gln Arg Gln Lys Ile Glu Met
85 90 95
Leu Ile Arg Arg Leu Tyr Arg Glu Asp Ile Gly Glu Glu Ala Ala Gln
100 105 110
Ile Val Glu Leu Arg Leu Trp Ser Leu Glu Glu Ser Pro Glu Ala Ala
115 120 125
Gln Ile Leu Thr Met Glu Pro Lys Ser Arg Lys Ile Leu Ile Thr Met
130 135 140
Lys Leu Glu Arg Trp Ile Arg Thr Leu Leu Arg Gly Lys Cys Asp Asn
145 150 155 160
Leu Lys Met Phe Gln Ser Arg Tyr Gln Glu Val Met Pro Phe Leu Gln
165 170 175
Gln Asn Lys Met Glu Thr Val Met Met Glu Glu Ala Trp Asn Leu Ser
180 185 190
Val His Leu Ile Gln Asp Ile Pro Val
195 200
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35 40 45
Glu Ile Asn Thr Gly Thr Thr Arg Leu Ser Thr Thr Ile Tyr Gln Pro
50 55 60
Glu Ser Lys Thr Thr Glu Thr Ser Lys Glu Asn Ser Gly Pro Ala Asn
65 70 75 80
Lys Asn Arg Gln Phe Gly Ala Ser His Glu Arg Ala Thr Glu Thr Lys
85 90 95
Asp Arg Asn Val Asn Gln Glu Thr Val Gln Gly Gly Tyr Arg Arg Gly
100 105 110
Ser Ser Pro Asp Ser Arg Thr Glu Thr Met Val Thr Arg Arg Ile Ser
115 120 125
Arg Ser Ser Pro Asp Pro Asn Asn Gly Thr Gln Ile Gln Glu Asp Ile
130 135 140
Asp Tyr Asn Glu Val Gly Glu Met Asp Lys Asp Ser Thr Lys Arg Glu
145 150 155 160
Met Arg Gln Phe Lys Asp Val Pro Val Lys Val Ser Gly Ser Asp Ala
165 170 175
Ile Pro Pro Thr Lys Gln Asp Gly Asp Gly Asp Asp Gly Arg Gly Leu
180 185 190
Glu Ser Ile Ser Thr Phe Asp Ser Gly Tyr Thr Ser Ile Val Thr Ala
195 200 205
Ala Thr Leu Asp Asp Glu Glu Glu Leu Leu Met Lys Asn Asn Arg Pro
210 215 220
Arg Lys Tyr Gln Ser Thr Pro Gln Asn Ser Asp Lys Gly Ile Lys Lys
225 230 235 240
Gly Gly Trp Lys Ala Lys Arg His Arg Gln Thr Ile Ile Asn Ile Gly
245 250 255
Leu Arg Thr Gln Leu Gln Arg Ile Glu Glu Glu Pro Glu Asn Pro Gln
260 265 270
Ser Gln His Glu Tyr Arg Arg Thr Asn Lys Thr Thr Glu Trp Ile Pro

275 280 285

Gly Glu Glu Asn His Ile Leu Glu His Pro Gln Gln Arg Glu Arg Gln

290 295 300

Ser Asn Arg Ile Asn Lys Pro Asn Pro Ser Asp Ile Asn Leu Gly Thr

305 310 315 320

Glu Pro His Asn Gly Thr Lys Gln Asn Asn Leu Arg Thr Lys Asp Gln

325 330 335

Asp Thr Lys Asp Gly Trp Lys Gly Lys Arg Gly His Arg Arg Glu His

340 345 350

Ser Ile Tyr Arg Lys Gly Asp Tyr Ile Ile Thr Glu Ser Trp Cys Asn

355 360 365

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

370 375 380

Cys Gly Glu Cys Pro Lys Gln Cys Arg Tyr Cys Ile Lys Asp Arg Leu

385 390 395 400

Pro Ser Arg Phe Asp Asp Arg Ser Val Asn Gly Ser

405 410

<210> 5

<211> 351

<212> PRT

<213> 牛副流感病毒3

<400> 5

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

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Arg Lys Ala Ile Pro His Ile Arg Val Val Lys Ile Gly Asp Pro Pro

35 40 45

Lys His Gly Ser Arg Tyr Leu Asp Val Phe Leu Leu Gly Phe Phe Glu

50 55 60

Met Glu Arg Ser Lys Asp Arg Tyr Gly Ser Ile Ser Asp Leu Asp Asp

65 70 75 80

Asp Pro Ser Tyr Lys Val Cys Gly Ser Gly Ser Leu Pro Leu Gly Leu

85 90 95

Ala Arg Tyr Thr Gly Asn Asp Gln Glu Leu Leu Gln Ala Ala Thr Lys

100 105 110

Leu Asp Ile Glu Val Arg Arg Thr Val Lys Ala Thr Glu Met Ile Val

115 120 125

Tyr Thr Val Gln Asn Ile Lys Pro Glu Leu Tyr Pro Trp Ser Ser Arg

130 135 140
Leu Arg Lys Gly Met Leu Phe Asp Ala Asn Lys Val Ala Leu Ala Pro
145 150 155 160
Gln Cys Leu Pro Leu Asp Arg Gly Ile Lys Phe Arg Val Ile Phe Val
165 170 175
Asn Cys Thr Ala Ile Gly Ser Ile Thr Leu Phe Lys Ile Pro Lys Ser
180 185 190
Met Ala Leu Leu Ser Leu Pro Asn Thr Ile Ser Ile Asn Leu Gln Val
195 200 205
His Ile Lys Thr Gly Val Gln Thr Asp Ser Lys Gly Val Val Gln Ile
210 215 220
Leu Asp Glu Lys Gly Glu Lys Ser Leu Asn Phe Met Val His Leu Gly
225 230 235 240
Leu Ile Lys Arg Lys Met Gly Arg Met Tyr Ser Val Glu Tyr Cys Lys
245 250 255
Gln Lys Ile Glu Lys Met Arg Leu Leu Phe Ser Leu Gly Leu Val Gly
260 265 270
Gly Ile Ser Phe His Val Asn Ala Thr Gly Ser Ile Ser Lys Thr Leu
275 280 285
Ala Ser Gln Leu Ala Phe Lys Arg Glu Ile Cys Tyr Pro Leu Met Asp
290 295 300
Leu Asn Pro His Leu Asn Ser Val Ile Trp Ala Ser Ser Val Glu Ile
305 310 315 320
Thr Arg Val Asp Ala Val Leu Gln Pro Ser Leu Pro Gly Glu Phe Arg
325 330 335
Tyr Tyr Pro Asn Ile Ile Ala Lys Gly Val Gly Lys Ile Arg Gln
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<213> 人副流感病毒3
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20 25 30
Asn Ser Pro Lys Gly Met Lys Ile Ser Gln Asn Phe Glu Thr Arg Tyr
35 40 45
Leu Ile Leu Ser Leu Ile Pro Lys Ile Glu Asp Ser Asn Ser Cys Gly

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

Thr Ser Asp Ile Val Pro Arg Tyr Ala Phe Val Asn Gly Gly Val Val
370 375 380
Ala Asn Cys Ile Thr Thr Thr Cys Thr Cys Asn Gly Ile Gly Asn Arg
385 390 395 400
Ile Asn Gln Pro Pro Asp Gln Gly Val Lys Ile Ile Thr His Lys Glu
405 410 415
Cys Ser Thr Ile Gly Ile Asn Gly Met Leu Phe Asn Thr Asn Lys Glu
420 425 430
Gly Thr Leu Ala Phe Tyr Thr Pro Asn Asp Ile Thr Leu Asn Asn Ser
435 440 445
Val Ala Leu Asp Pro Ile Asp Ile Ser Ile Glu Leu Asn Lys Ala Lys
450 455 460
Ser Asp Leu Glu Glu Ser Lys Glu Trp Ile Arg Arg Ser Asn Gln Lys
465 470 475 480
Leu Asp Ser Ile Gly Asn Trp His Gln Ser Ser Thr Thr Ile Ile Ile
485 490 495
Ile Leu Ile Met Ile Ile Ile Leu Phe Ile Ile Asn Ile Thr Ile Ile
500 505 510
Thr Ile Ala Ile Lys Tyr Tyr Arg Ile Gln Lys Arg Asn Arg Val Asp
515 520 525
Gln Asn Asp Lys Pro Tyr Val Leu Thr Asn Lys
530 535

<210> 7
<211> 572
<212> PRT
<213> 人副流感病毒3
<400> 7

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

Thr Arg Leu Leu Thr Ile Gln Ser His Val Gln Asn Tyr Ile Pro Ile
100 105 110

Ser Leu Thr Gln Gln Met Ser Asp Leu Arg Lys Phe Ile Ser Glu Ile
115 120 125

Thr Ile Arg Asn Asp Asn Gln Glu Val Leu Pro Gln Arg Ile Thr His
130 135 140

Asp Val Gly Ile Lys Pro Leu Asn Pro Asp Asp Phe Trp Arg Cys Thr
145 150 155 160

Ser Gly Leu Pro Ser Leu Met Lys Thr Pro Lys Ile Arg Leu Met Pro
165 170 175

Gly Pro Gly Leu Leu Ala Met Pro Thr Thr Val Asp Gly Cys Val Arg
180 185 190

Thr Pro Ser Leu Val Ile Asn Asp Leu Ile Tyr Ala Tyr Thr Ser Asn
195 200 205

Leu Ile Thr Arg Gly Cys Gln Asp Ile Gly Lys Ser Tyr Gln Val Leu
210 215 220

Gln Ile Gly Ile Ile Thr Val Asn Ser Asp Leu Val Pro Asp Leu Asn
225 230 235 240

Pro Arg Ile Ser His Thr Phe Asn Ile Asn Asp Asn Arg Lys Ser Cys
245 250 255

Ser Leu Ala Leu Leu Asn Thr Asp Val Tyr Gln Leu Cys Ser Thr Pro
260 265 270

Lys Val Asp Glu Arg Ser Asp Tyr Ala Ser Ser Gly Ile Glu Asp Ile
275 280 285

Val Leu Asp Ile Val Asn Tyr Asp Gly Ser Ile Ser Thr Thr Arg Phe
290 295 300

Lys Asn Asn Asn Ile Ser Phe Asp Gln Pro Tyr Ala Ala Leu Tyr Pro
305 310 315 320

Ser Val Gly Pro Gly Ile Tyr Tyr Lys Gly Lys Ile Ile Phe Leu Gly
325 330 335

Tyr Gly Gly Leu Glu His Pro Ile Asn Glu Asn Val Ile Cys Asn Thr
340 345 350

Thr Gly Cys Pro Gly Lys Thr Gln Arg Asp Cys Asn Gln Ala Ser His
355 360 365

Ser Pro Trp Phe Ser Asp Arg Arg Met Val Asn Ser Ile Ile Val Val
370 375 380

Asp Lys Gly Leu Asn Ser Ile Pro Lys Leu Lys Val Trp Thr Ile Ser
385 390 395 400

Met Arg Gln Asn Tyr Trp Gly Ser Glu Gly Arg Leu Leu Leu Leu Gly

405 410 415
Asn Lys Ile Tyr Ile Tyr Thr Arg Ser Thr Ser Trp His Ser Lys Leu
420 425 430
Gln Leu Gly Ile Ile Asp Ile Thr Asp Tyr Ser Asp Ile Arg Ile Lys
435 440 445
Trp Thr Trp His Asn Val Leu Ser Arg Pro Gly Asn Asn Glu Cys Pro
450 455 460
Trp Gly His Ser Cys Pro Asp Gly Cys Ile Thr Gly Val Tyr Thr Asp
465 470 475 480
Ala Tyr Pro Leu Asn Pro Thr Gly Ser Ile Val Ser Ser Val Ile Leu
485 490 495
Asp Ser Gln Lys Ser Arg Val Asn Pro Val Ile Thr Tyr Ser Thr Ala
500 505 510
Thr Glu Arg Val Asn Glu Leu Ala Ile Leu Asn Arg Thr Leu Ser Ala
515 520 525
Gly Tyr Thr Thr Thr Ser Cys Ile Thr His Tyr Asn Lys Gly Tyr Cys
530 535 540
Phe His Ile Val Glu Ile Asn His Lys Ser Leu Asn Thr Phe Gln Pro
545 550 555 560
Met Leu Phe Lys Thr Glu Ile Pro Lys Ser Cys Ser
565 570
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<213> 人副流感病毒3
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Leu Glu Thr Ser Met Ala Thr His Gly Asn Lys Leu Thr Asn Lys Ile
20 25 30
Ile Tyr Ile Leu Trp Thr Ile Ile Leu Val Leu Leu Ser Ile Val Phe
35 40 45
Ile Ile Val Leu Ile Asn Ser Ile Lys Ser Glu Lys Ala His Glu Ser
50 55 60
Leu Leu Gln Asp Ile Asn Asn Glu Phe Met Glu Ile Thr Glu Lys Ile
65 70 75 80
Gln Met Ala Ser Asp Asn Thr Asn Asp Leu Ile Gln Ser Gly Val Asn
85 90 95
Thr Arg Leu Leu Thr Ile Gln Ser His Val Gln Asn Tyr Ile Pro Ile

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

Asn Lys Ile Tyr Ile Tyr Thr Arg Ser Thr Ser Trp His Ser Lys Leu
420 425 430
Gln Leu Gly Ile Ile Asp Ile Thr Asp Tyr Ser Asp Ile Arg Ile Lys
435 440 445
Trp Thr Trp His Asn Val Leu Ser Arg Pro Gly Asn Asn Glu Cys Pro
450 455 460
Trp Gly His Ser Cys Pro Asp Gly Cys Ile Thr Gly Val Tyr Thr Asp
465 470 475 480
Ala Tyr Pro Leu Asn Pro Thr Gly Ser Ile Val Ser Ser Val Ile Leu
485 490 495
Asp Ser Gln Lys Ser Arg Val Asn Pro Val Ile Thr Tyr Ser Thr Ala
500 505 510
Thr Glu Arg Val Asn Glu Leu Ala Ile Leu Asn Arg Thr Leu Ser Ala
515 520 525
Gly Tyr Thr Thr Thr Ser Cys Ile Thr His Tyr Asn Lys Gly Tyr Cys
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Phe His Ile Val Glu Ile Asn His Lys Ser Leu Asn Thr Phe Gln Pro
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Met Leu Phe Lys Thr Glu Ile Pro Lys Ser Cys Ser
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gcccacgaat cattgctgca agacataaat aatgagttta tggaaattac agaaaagatc 240
caaatggcat cggataatac caatgatcta atacagtcag gagtgaatac aaggcttctt 300
acaattcaga gtcatgtcca gaattacata ccaatatcat tgacacaaca gatgtcagat 360
cttaggaaat tcattagtga aattacaatt agaaatgata atcaagaagt gctgccacaa 420
agaataacac atgatgtagg tataaaacct ttaaatccag atgatttttg gagatgcacg 480
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35 40 45
Ile Leu Ile Ile Thr Arg Gln Lys Ile Lys Leu Asn Lys Leu Asp Lys
50 55 60
Arg Gln Arg Ser Ile Arg Lys Leu Arg Ser Val Leu Met Glu Arg Val
65 70 75 80
Ser Asp Leu Gly Lys Tyr Thr Phe Ile Arg Tyr Pro Glu Met Ser Ser
85 90 95
Glu Met Phe Gln Leu Cys Ile Pro Gly Ile Asn Asn Lys Ile Asn Glu
100 105 110
Leu Leu Ser Lys Ala Ser Lys Thr Tyr Asn Gln Met Thr Asp Gly Leu
115 120 125
Arg Asp Leu Trp Val Thr Ile Leu Ser Lys Leu Ala Ser Lys Asn Asp
130 135 140
Gly Ser Asn Tyr Asp Ile Asn Glu Asp Ile Ser Asn Ile Ser Asn Val

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

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

770 775 780

Asn Asn Tyr Asp Tyr Lys Val Lys Lys Glu Ile Val Tyr Lys Asp Val
785 790 795 800

Val Arg Phe Phe Asp Ser Leu Arg Glu Val Met Asp Asp Leu Gly His
805 810 815

Glu Leu Lys Leu Asn Glu Thr Ile Ile Ser Ser Lys Met Phe Ile Tyr
820 825 830

Ser Lys Arg Ile Tyr Tyr Asp Gly Arg Ile Leu Pro Gln Ala Leu Lys
835 840 845

Ala Leu Ser Arg Cys Val Phe Trp Ser Glu Thr Ile Ile Asp Glu Thr
850 855 860

Arg Ser Ala Ser Ser Asn Leu Ala Thr Ser Phe Ala Lys Ala Ile Glu
865 870 875 880

Asn Gly Tyr Ser Pro Val Leu Gly Tyr Val Cys Ser Ile Phe Lys Asn
885 890 895

Ile Gln Gln Leu Tyr Ile Ala Leu Gly Met Asn Ile Asn Pro Thr Ile
900 905 910

Thr Gln Asn Ile Lys Asp Gln Tyr Phe Arg Asn Ile His Trp Met Gln
915 920 925

Tyr Ala Ser Leu Ile Pro Ala Ser Val Gly Gly Phe Asn Tyr Met Ala
930 935 940

Met Ser Arg Cys Phe Val Arg Asn Ile Gly Asp Pro Thr Val Ala Ala
945 950 955 960

Leu Ala Asp Ile Lys Arg Phe Ile Lys Ala Asn Leu Leu Asp Arg Gly
965 970 975

Val Leu Tyr Arg Ile Met Asn Gln Glu Pro Gly Glu Ser Ser Phe Leu
980 985 990

Asp Trp Ala Ser Asp Pro Tyr Ser Cys Asn Leu Pro Gln Ser Gln Asn
995 1000 1005

Ile Thr Thr Met Ile Lys Asn Ile Thr Ala Arg Asn Val Leu Gln
1010 1015 1020

Asp Ser Pro Asn Pro Leu Leu Ser Gly Leu Phe Thr Ser Thr Met
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Ile Glu Glu Asp Glu Glu Leu Ala Glu Phe Leu Met Asp Arg Arg
1040 1045 1050

Ile Ile Leu Pro Arg Val Ala His Asp Ile Leu Asp Asn Ser Leu
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Thr Gly Ile Arg Asn Ala Ile Ala Gly Met Leu Asp Thr Thr Lys
1070 1075 1080

Ser Leu Ile Arg Val Gly Ile Ser Arg Gly Gly Leu Thr Tyr Asn
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Leu Leu Arg Lys Ile Ser Asn Tyr Asp Leu Val Gln Tyr Glu Thr
1100 1105 1110
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1115 1120 1125
Glu Asp Met Cys Ser Val Asp Leu Ala Ile Ser Leu Arg Gln Lys
1130 1135 1140
Met Trp Met His Leu Ser Gly Gly Arg Met Ile Asn Gly Leu Glu
1145 1150 1155
Thr Pro Asp Pro Leu Glu Leu Leu Ser Gly Val Ile Ile Thr Gly
1160 1165 1170
Ser Glu His Cys Arg Ile Cys Tyr Ser Thr Glu Gly Glu Ser Pro
1175 1180 1185
Tyr Thr Trp Met Tyr Leu Pro Gly Asn Leu Asn Ile Gly Ser Ala
1190 1195 1200
Glu Thr Gly Ile Ala Ser Leu Arg Val Pro Tyr Phe Gly Ser Val
1205 1210 1215
Thr Asp Glu Arg Ser Glu Ala Gln Leu Gly Tyr Ile Lys Asn Leu
1220 1225 1230
Ser Lys Pro Ala Lys Ala Ala Ile Arg Ile Ala Met Ile Tyr Thr
1235 1240 1245
Trp Ala Phe Gly Asn Asp Glu Ile Ser Trp Met Glu Ala Ser Gln
1250 1255 1260
Ile Ala Gln Thr Arg Ala Asn Phe Thr Leu Asp Ser Leu Lys Ile
1265 1270 1275
Leu Thr Pro Val Thr Thr Ser Thr Asn Leu Ser His Arg Leu Lys
1280 1285 1290
Asp Thr Ala Thr Gln Met Lys Phe Ser Ser Thr Ser Leu Ile Arg
1295 1300 1305
Val Ser Arg Phe Ile Thr Ile Ser Asn Asp Asn Met Ser Ile Lys
1310 1315 1320
Glu Ala Asn Glu Thr Lys Asp Thr Asn Leu Ile Tyr Gln Gln Val
1325 1330 1335
Met Leu Thr Gly Leu Ser Val Phe Glu Tyr Leu Phe Arg Leu Glu
1340 1345 1350
Glu Ser Thr Gly His Asn Pro Met Val Met His Leu His Ile Glu
1355 1360 1365
Asp Gly Cys Cys Ile Lys Glu Ser Tyr Asn Asp Glu His Ile Asn

1370 1375 1380
Pro Glu Ser Thr Leu Glu Leu Ile Lys Tyr Pro Glu Ser Asn Glu
1385 1390 1395
Phe Ile Tyr Asp Lys Asp Pro Leu Lys Asp Ile Asp Leu Ser Lys
1400 1405 1410
Leu Met Val Ile Arg Asp His Ser Tyr Thr Ile Asp Met Asn Tyr
1415 1420 1425
Trp Asp Asp Thr Asp Ile Val His Ala Ile Ser Ile Cys Thr Ala
1430 1435 1440
Val Thr Ile Ala Asp Thr Met Ser Gln Leu Asp Arg Asp Asn Leu
1445 1450 1455
Lys Glu Leu Val Val Ile Ala Asn Asp Asp Asp Ile Asn Ser Leu
1460 1465 1470
Ile Thr Glu Phe Leu Thr Leu Asp Ile Leu Val Phe Leu Lys Thr
1475 1480 1485
Phe Gly Gly Leu Leu Val Asn Gln Phe Ala Tyr Thr Leu Tyr Gly
1490 1495 1500
Leu Lys Ile Glu Gly Arg Asp Pro Ile Trp Asp Tyr Ile Met Arg
1505 1510 1515
Thr Leu Lys Asp Thr Ser His Ser Val Leu Lys Val Leu Ser Asn
1520 1525 1530
Ala Leu Ser His Pro Lys Val Phe Lys Arg Phe Trp Asp Cys Gly
1535 1540 1545
Val Leu Asn Pro Ile Tyr Gly Pro Asn Thr Ala Ser Gln Asp Gln
1550 1555 1560
Val Lys Leu Ala Leu Ser Ile Cys Glu Tyr Ser Leu Asp Leu Phe
1565 1570 1575
Met Arg Glu Trp Leu Asn Gly Ala Ser Leu Glu Ile Tyr Ile Cys
1580 1585 1590
Asp Ser Asp Met Glu Ile Ala Asn Asp Arg Arg Gln Ala Phe Leu
1595 1600 1605
Ser Arg His Leu Ala Phe Val Cys Cys Leu Ala Glu Ile Ala Ser
1610 1615 1620
Phe Gly Pro Asn Leu Leu Asn Leu Thr Tyr Leu Glu Arg Leu Asp
1625 1630 1635
Glu Leu Lys Gln Tyr Leu Asp Leu Asn Ile Lys Glu Asp Pro Thr
1640 1645 1650
Leu Lys Tyr Val Gln Val Ser Gly Leu Leu Ile Lys Ser Phe Pro
1655 1660 1665

Ser Thr Val Thr Tyr Val Arg Lys Thr Ala Ile Lys Tyr Leu Arg
1670 1675 1680
Ile Arg Gly Ile Asn Pro Pro Glu Thr Ile Glu Asp Trp Asp Pro
1685 1690 1695
Ile Glu Asp Glu Asn Ile Leu Asp Asn Ile Val Lys Thr Val Asn
1700 1705 1710
Asp Asn Cys Ser Asp Asn Gln Lys Arg Asn Lys Ser Ser Tyr Phe
1715 1720 1725
Trp Gly Leu Ala Leu Lys Asn Tyr Gln Val Val Lys Ile Arg Ser
1730 1735 1740
Ile Thr Ser Asp Ser Glu Val Asn Glu Ala Ser Asn Val Thr Thr
1745 1750 1755
His Gly Met Thr Leu Pro Gln Gly Gly Ser Tyr Leu Ser His Gln
1760 1765 1770
Leu Arg Leu Phe Gly Val Asn Ser Thr Ser Cys Leu Lys Ala Leu
1775 1780 1785
Glu Leu Ser Gln Ile Leu Met Arg Glu Val Lys Lys Asp Lys Asp
1790 1795 1800
Arg Leu Phe Leu Gly Glu Gly Ala Gly Ala Met Leu Ala Cys Tyr
1805 1810 1815
Asp Ala Thr Leu Gly Pro Ala Ile Asn Tyr Tyr Asn Ser Gly Leu
1820 1825 1830
Asn Ile Thr Asp Val Ile Gly Gln Arg Glu Leu Lys Ile Phe Pro
1835 1840 1845
Ser Glu Val Ser Leu Val Gly Lys Lys Leu Gly Asn Val Thr Gln
1850 1855 1860
Ile Leu Asn Arg Val Arg Val Leu Phe Asn Gly Asn Pro Asn Ser
1865 1870 1875
Thr Trp Ile Gly Asn Met Glu Cys Glu Ser Leu Ile Trp Ser Glu
1880 1885 1890
Leu Asn Asp Lys Ser Ile Gly Leu Val His Cys Asp Met Glu Gly
1895 1900 1905
Ala Ile Gly Lys Ser Glu Glu Thr Val Leu His Glu His Tyr Ser
1910 1915 1920
Ile Ile Arg Ile Thr Tyr Leu Ile Gly Asp Asp Asp Val Val Leu
1925 1930 1935
Val Ser Lys Ile Ile Pro Thr Ile Thr Pro Asn Trp Ser Lys Ile
1940 1945 1950
Leu Tyr Leu Tyr Lys Leu Tyr Trp Lys Asp Val Ser Val Val Ser

1955 1960 1965

Leu Lys Thr Ser Asn Pro Ala Ser Thr Glu Leu Tyr Leu Ile Ser

1970 1975 1980

Lys Asp Ala Tyr Cys Thr Val Met Glu Pro Ser Asn Leu Val Leu

1985 1990 1995

Ser Lys Leu Lys Arg Ile Ser Ser Ile Glu Glu Asn Asn Leu Leu

2000 2005 2010

Lys Trp Ile Ile Leu Ser Lys Arg Lys Asn Asn Glu Trp Leu Gln

2015 2020 2025

His Glu Ile Lys Glu Gly Glu Arg Asp Tyr Gly Ile Met Arg Pro

2030 2035 2040

Tyr His Thr Ala Leu Gln Ile Phe Gly Phe Gln Ile Asn Leu Asn

2045 2050 2055

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

2060 2065 2070

Asn Asn Ile Ile Gln Ser Phe Thr Arg Thr Ile Lys Asp Val Met

2075 2080 2085

Phe Glu Trp Val Asn Ile Thr His Asp Asn Lys Arg His Lys Leu

2090 2095 2100

Gly Gly Arg Tyr Asn Leu Phe Pro Leu Lys Asn Lys Gly Lys Leu

2105 2110 2115

Arg Leu Leu Ser Arg Arg Leu Val Leu Ser Trp Ile Ser Leu Ser

2120 2125 2130

Leu Ser Thr Arg Leu Leu Thr Gly Arg Phe Pro Asp Glu Lys Phe

2135 2140 2145

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

2150 2155 2160

Leu Glu Ser Leu Lys Leu Leu Ser Arg Asn Ile Val Lys Asn Tyr

2165 2170 2175

Lys Glu His Ile Gly Leu Ile Ser Tyr Trp Phe Leu Thr Lys Glu

2180 2185 2190

Val Lys Ile Leu Met Lys Leu Ile Gly Gly Val Lys Leu Leu Gly

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Ile Pro Lys Gln Tyr Lys Glu Leu Glu Asp Arg Ser Ser Gln Gly

2210 2215 2220

Tyr Glu Tyr Asp Asn Glu Phe Asp Ile Asp

2225 2230

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<213> 呼吸道合胞病毒
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Trp Asp Thr Leu Asn His Leu Leu Phe Ile Ser Ser Cys Leu Tyr Lys
20 25 30
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35 40 45
Ile Ile Ser Thr Ser Leu Ile Ile Ala Ala Ile Ile Phe Ile Ala Ser
50 55 60
Ala Asn His Lys Val Thr Pro Thr Thr Ala Ile Ile Gln Asp Ala Thr

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

<210> 23
<211> 233
<212> PRT
<213> 呼吸道合胞病毒
<400> 23

Asn His Lys Val Thr Pro Thr Thr Ala Ile Ile Gln Asp Ala Thr Ser
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Gln Ile Lys Asn Thr Thr Pro Thr Tyr Leu Thr Gln Asn Pro Gln Leu
20 25 30
Gly Ile Ser Pro Ser Asn Pro Ser Glu Ile Thr Ser Gln Ile Thr Thr

35 40 45
Ile Leu Ala Ser Thr Thr Pro Gly Val Lys Ser Thr Leu Gln Ser Thr
50 55 60
Thr Val Lys Thr Lys Asn Thr Thr Thr Thr Gln Thr Gln Pro Ser Lys
65 70 75 80
Pro Thr Thr Lys Gln Arg Gln Asn Lys Pro Pro Ser Lys Pro Asn Asn
85 90 95
Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Ser
100 105 110
Asn Asn Pro Thr Cys Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys Lys
115 120 125
Pro Gly Lys Lys Thr Thr Thr Lys Pro Thr Lys Lys Pro Thr Leu Lys
130 135 140
Thr Thr Lys Lys Asp Pro Lys Pro Gln Thr Thr Lys Ser Lys Glu Val
145 150 155 160
Pro Thr Thr Lys Pro Thr Glu Glu Pro Thr Ile Asn Thr Thr Lys Thr
165 170 175
Asn Ile Ile Thr Thr Leu Leu Thr Ser Asn Thr Thr Gly Asn Pro Glu
180 185 190
Leu Thr Ser Gln Met Glu Thr Phe His Ser Thr Ser Ser Glu Gly Asn
195 200 205
Pro Ser Pro Ser Gln Val Ser Thr Thr Ser Glu Tyr Pro Ser Gln Pro
210 215 220
Ser Ser Pro Pro Asn Thr Pro Arg Gln
225 230
<210> 24
<211> 37
<212> PRT
<213> 呼吸道合胞病毒
<400> 24
Met Ser Lys Asn Lys Asp Gln Arg Thr Ala Lys Thr Leu Glu Arg Thr
1 5 10 15
Trp Asp Thr Leu Asn His Leu Leu Phe Ile Ser Ser Cys Leu Tyr Lys
20 25 30
Leu Asn Leu Lys Ser
35
<210> 25
<211> 28
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<213> 呼吸道合胞病毒

<400> 25

Val Ala Gln Ile Thr Leu Ser Ile Leu Ala Met Ile Ile Ser Thr Ser
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Leu Ile Ile Ala Ala Ile Ile Phe Ile Ala Ser Ala
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<210> 26

<211> 65

<212> PRT

<213> 呼吸道合胞病毒

<400> 26

Met Ser Lys Asn Lys Asp Gln Arg Thr Ala Lys Thr Leu Glu Arg Thr
1 5 10 15

Trp Asp Thr Leu Asn His Leu Leu Phe Ile Ser Ser Cys Leu Tyr Lys
20 25 30

Leu Asn Leu Lys Ser Val Ala Gln Ile Thr Leu Ser Ile Leu Ala Met
35 40 45

Ile Ile Ser Thr Ser Leu Ile Ile Ala Ala Ile Ile Phe Ile Ala Ser
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Ala
65

<210> 27

<211> 30

<212> PRT

<213> 牛副流感病毒3

<400> 27

Met Glu Tyr Trp Lys His Thr Asn Ser Ile Asn Asn Thr Asn Asn Glu
1 5 10 15

Thr Glu Thr Ala Arg Gly Lys His Ser Ser Lys Val Thr Asn
20 25 30

<210> 28

<211> 26

<212> PRT

<213> 牛副流感病毒3

<400> 28

Ile Ile Met Tyr Thr Phe Trp Thr Ile Thr Leu Thr Ile Leu Ser Val
1 5 10 15

Ile Phe Ile Met Ile Leu Thr Asn Leu Ile
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<210> 29
<211> 56
<212> PRT
<213> 牛副流感病毒3
<400> 29
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1 5 10 15
Thr Glu Thr Ala Arg Gly Lys His Ser Ser Lys Val Thr Asn Ile Ile
20 25 30
Met Tyr Thr Phe Trp Thr Ile Thr Leu Thr Ile Leu Ser Val Ile Phe
35 40 45
Ile Met Ile Leu Thr Asn Leu Ile
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<400> 30
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1 5 10 15
Thr Glu Thr Ala Arg Gly Lys His Ser Ser Lys Val Thr Asn Val Ala
20 25 30
Gln Ile Thr Leu Ser Ile Leu Ala Met Ile Ile Ser Thr Ser Leu Ile
35 40 45
Ile Ala Ala Ile Ile Phe Ile Ala Ser Ala Asn His Lys Val Thr Pro
50 55 60
Thr Thr Ala Ile Ile Gln Asp Ala Thr Ser Gln Ile Lys Asn Thr Thr
65 70 75 80
Pro Thr Tyr Leu Thr Gln Asn Pro Gln Leu Gly Ile Ser Pro Ser Asn
85 90 95
Pro Ser Glu Ile Thr Ser Gln Ile Thr Thr Ile Leu Ala Ser Thr Thr
100 105 110
Pro Gly Val Lys Ser Thr Leu Gln Ser Thr Thr Val Lys Thr Lys Asn
115 120 125
Thr Thr Thr Thr Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg
130 135 140
Gln Asn Lys Pro Pro Ser Lys Pro Asn Asn Asp Phe His Phe Glu Val

145 150 155 160
Phe Asn Phe Val Pro Cys Ser Ile Cys Ser Asn Asn Pro Thr Cys Trp
165 170 175
Ala Ile Cys Lys Arg Ile Pro Asn Lys Lys Pro Gly Lys Lys Thr Thr
180 185 190
Thr Lys Pro Thr Lys Lys Pro Thr Leu Lys Thr Thr Lys Lys Asp Pro
195 200 205
Lys Pro Gln Thr Thr Lys Ser Lys Glu Val Pro Thr Thr Lys Pro Thr
210 215 220
Glu Glu Pro Thr Ile Asn Thr Thr Lys Thr Asn Ile Ile Thr Thr Leu
225 230 235 240
Leu Thr Ser Asn Thr Thr Gly Asn Pro Glu Leu Thr Ser Gln Met Glu
245 250 255
Thr Phe His Ser Thr Ser Ser Glu Gly Asn Pro Ser Pro Ser Gln Val
260 265 270
Ser Thr Thr Ser Glu Tyr Pro Ser Gln Pro Ser Ser Pro Pro Asn Thr
275 280 285
Pro Arg Gln
290
<210> 31
<211> 289
<212> PRT
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 31
Met Glu Tyr Trp Lys His Thr Asn Ser Ile Asn Asn Thr Asn Asn Glu
1 5 10 15
Thr Glu Thr Ala Arg Gly Lys His Ser Ser Lys Val Thr Asn Ile Ile
20 25 30
Met Tyr Thr Phe Trp Thr Ile Thr Leu Thr Ile Leu Ser Val Ile Phe
35 40 45
Ile Met Ile Leu Thr Asn Leu Ile Asn His Lys Val Thr Pro Thr Thr
50 55 60
Ala Ile Ile Gln Asp Ala Thr Ser Gln Ile Lys Asn Thr Thr Pro Thr
65 70 75 80
Tyr Leu Thr Gln Asn Pro Gln Leu Gly Ile Ser Pro Ser Asn Pro Ser
85 90 95
Glu Ile Thr Ser Gln Ile Thr Thr Ile Leu Ala Ser Thr Thr Pro Gly

100 105 110
Val Lys Ser Thr Leu Gln Ser Thr Thr Val Lys Thr Lys Asn Thr Thr
115 120 125
Thr Thr Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg Gln Asn
130 135 140
Lys Pro Pro Ser Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn
145 150 155 160
Phe Val Pro Cys Ser Ile Cys Ser Asn Asn Pro Thr Cys Trp Ala Ile
165 170 175
Cys Lys Arg Ile Pro Asn Lys Lys Pro Gly Lys Lys Thr Thr Thr Lys
180 185 190
Pro Thr Lys Lys Pro Thr Leu Lys Thr Thr Lys Lys Asp Pro Lys Pro
195 200 205
Gln Thr Thr Lys Ser Lys Glu Val Pro Thr Thr Lys Pro Thr Glu Glu
210 215 220
Pro Thr Ile Asn Thr Thr Lys Thr Asn Ile Ile Thr Thr Leu Leu Thr
225 230 235 240
Ser Asn Thr Thr Gly Asn Pro Glu Leu Thr Ser Gln Met Glu Thr Phe
245 250 255
His Ser Thr Ser Ser Glu Gly Asn Pro Ser Pro Ser Gln Val Ser Thr
260 265 270
Thr Ser Glu Tyr Pro Ser Gln Pro Ser Ser Pro Pro Asn Thr Pro Arg
275 280 285
Gln
<210> 32
<211> 46
<212> DNA
<213> 人工序列
<220>
<223> 重组载体序列
<400> 32
ggcgcgccaa gtaagaaaaa cttaggatta atggacctgc aggatg 46
<210> 33
<211> 55
<212> DNA
<213> 人工序列
<220>
<223> 重组载体序列
<400> 33

tagtgatagc tagcggcgcg ccagcaacaa gtaagaaaaa cttaggatta atgga 55

<210> 34

<211> 77

<212> PRT

<213> 呼吸道合胞病毒

<400> 34

Met Ser Lys Asn Lys Asp Gln Arg Thr Ala Lys Thr Leu Glu Arg Thr
1 5 10 15

Trp Asp Thr Leu Asn His Leu Leu Phe Ile Ser Ser Cys Leu Tyr Lys
20 25 30

Leu Asn Leu Lys Ser Val Ala Gln Ile Thr Leu Ser Ile Leu Ala Met
35 40 45

Ile Ile Ser Thr Ser Leu Ile Ile Ala Ala Ile Ile Phe Ile Ala Ser
50 55 60

Ala Asn His Lys Val Thr Pro Thr Thr Ala Ile Ile Gln
65 70 75

<210> 35

<211> 77

<212> PRT

<213> 呼吸道合胞病毒

<400> 35

Met Ser Lys Asn Lys Asp Gln Arg Thr Ala Lys Thr Leu Glu Arg Thr
1 5 10 15

Trp Asp Thr Leu Asn His Leu Leu Phe Ile Ser Ser Cys Leu Tyr Lys
20 25 30

Leu Asn Leu Lys Ser Val Ala Gln Ile Thr Leu Ser Ile Leu Ala Ile
35 40 45

Val Ile Ser Thr Ser Leu Ile Ile Ala Ala Ile Ile Phe Ile Ala Ser
50 55 60

Ala Asn His Lys Val Thr Pro Thr Thr Ala Ile Ile Gln
65 70 75

<210> 36

<211> 30

<212> PRT

<213> 呼吸道合胞病毒

<400> 36

Met Ile Ile Ser Thr Ser Leu Ile Ile Ala Ala Ile Ile Phe Ile Ala
1 5 10 15

Ser Ala Asn His Lys Val Thr Pro Thr Thr Ala Ile Ile Gln

20 25 30

<210> 37

<211> 70

<212> PRT

<213> 人工序列

<220>

<223> 重组RSV G蛋白

<400> 37

Met Glu Tyr Trp Lys His Thr Asn Ser Ile Asn Asn Thr Asn Asn Glu
1 5 10 15

Thr Glu Thr Ala Arg Gly Lys His Ser Ser Lys Val Thr Asn Val Ala
20 25 30

Gln Ile Thr Leu Ser Ile Leu Ala Met Ile Ile Ser Thr Ser Leu Ile
35 40 45

Ile Ala Ala Ile Ile Phe Ile Ala Ser Ala Asn His Lys Val Thr Pro
50 55 60

Thr Thr Ala Ile Ile Gln
65 70

<210> 38

<211> 68

<212> PRT

<213> 人工序列

<220>

<223> 重组RSV G蛋白

<400> 38

Met Glu Tyr Trp Lys His Thr Asn Ser Ile Asn Asn Thr Asn Asn Glu
1 5 10 15

Thr Glu Thr Ala Arg Gly Lys His Ser Ser Lys Val Thr Asn Ile Ile
20 25 30

Met Tyr Thr Phe Trp Thr Ile Thr Leu Thr Ile Leu Ser Val Ile Phe
35 40 45

Ile Met Ile Leu Thr Asn Leu Ile Asn His Lys Val Thr Pro Thr Thr
50 55 60

Ala Ile Ile Gln
65

<210> 39

<211> 71

<212> PRT

<213> 牛副流感病毒3

<400> 39
Met Glu Tyr Trp Lys His Thr Asn Ser Ile Asn Asn Thr Asn Asn Glu
1 5 10 15
Thr Glu Thr Ala Arg Gly Lys His Ser Ser Lys Val Thr Asn Ile Ile
20 25 30
Met Tyr Thr Phe Trp Thr Ile Thr Leu Thr Ile Leu Ser Val Ile Phe
35 40 45
Ile Met Ile Leu Thr Asn Leu Ile Gln Glu Asn Asn His Asn Lys Leu
50 55 60
Met Leu Gln Glu Ile Arg Lys
65 70
<210> 40
<211> 70
<212> PRT
<213> 人副流感病毒3
<400> 40
Met Glu Tyr Trp Lys His Thr Asn His Gly Lys Asp Ala Gly Asn Glu
1 5 10 15
Leu Glu Thr Ser Met Ala Thr His Gly Asn Lys Leu Thr Asn Lys Ile
20 25 30
Ile Tyr Ile Leu Trp Thr Ile Ile Leu Val Leu Leu Ser Ile Val Phe
35 40 45
Ile Ile Val Leu Ile Asn Ser Ile Lys Ser Glu Lys Ala His Glu Ser
50 55 60
Leu Leu Gln Asp Ile Asn
65 70
<210> 41
<211> 5
<212> PRT
<213> 呼吸道合胞病毒
<400> 41
Cys Trp Ala Ile Cys
1 5
<210> 42
<211> 15
<212> DNA
<213> 呼吸道合胞病毒
<400> 42
tgctgggcta tctgc 15

<210> 43
<211> 5
<212> PRT
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 43
Cys Trp Ala Ile Arg
1 5
<210> 44
<211> 15
<212> DNA
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 44
tgctgggcta tccgc 15
<210> 45
<211> 6
<212> PRT
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 45
Cys Trp Ala Ile Ala Cys
1 5
<210> 46
<211> 18
<212> DNA
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 46
tgctgggcta tcgcatgc 18
<210> 47
<211> 298
<212> PRT
<213> 呼吸道合胞病毒
<400> 47

Met Ser Lys Thr Lys Asp Gln Arg Thr Ala Lys Thr Leu Glu Arg Thr
1 5 10 15
Trp Asp Thr Leu Asn His Leu Leu Phe Ile Ser Ser Cys Leu Tyr Lys
20 25 30
Leu Asn Leu Lys Ser Ile Ala Gln Ile Thr Leu Ser Ile Leu Ala Met
35 40 45
Ile Ile Ser Thr Ser Leu Ile Ile Ala Ala Ile Ile Phe Ile Ala Ser
50 55 60
Ala Asn His Lys Val Thr Leu Thr Thr Ala Ile Ile Gln Asp Ala Thr
65 70 75 80
Asn Gln Ile Lys Asn Thr Thr Pro Thr Tyr Leu Thr Gln Asn Pro Gln
85 90 95
Leu Gly Ile Ser Leu Ser Asn Leu Ser Glu Thr Thr Ser Lys Pro Thr
100 105 110
Thr Ile Leu Ala Leu Thr Thr Pro Asn Ala Glu Ser Thr Pro Gln Ser
115 120 125
Thr Thr Val Lys Thr Lys Asn Thr Thr Thr Thr Gln Ile Gln Pro Ser
130 135 140
Lys Pro Thr Thr Lys Gln Arg Gln Asn Lys Pro Gln Asn Lys Pro Asn
145 150 155 160
Asn Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys
165 170 175
Ser Asn Asn Pro Thr Cys Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys
180 185 190
Lys Pro Gly Arg Lys Thr Thr Thr Lys Pro Thr Lys Gln Pro Ala Ile
195 200 205
Lys Thr Thr Lys Lys Asp Pro Lys Pro Gln Thr Thr Lys Pro Lys Glu
210 215 220
Val Leu Thr Thr Lys Pro Thr Glu Lys Pro Thr Ile Asn Thr Thr Lys
225 230 235 240
Thr Asn Ile Arg Thr Thr Leu Leu Thr Ser Asn Ile Thr Glu Asn Gln
245 250 255
Glu His Thr Ser Gln Lys Glu Thr Leu His Ser Thr Thr Ser Glu Gly
260 265 270
Asn Pro Ser Pro Ser Gln Val Tyr Thr Thr Ser Glu Tyr Leu Ser Gln
275 280 285
Ser Leu Ser Pro Ser Asn Thr Thr Arg Trp
290 295
<210> 48

<211> 233
<212> PRT
<213> 呼吸道合胞病毒
<400> 48
Asn His Lys Val Thr Leu Thr Thr Ala Ile Ile Gln Asp Ala Thr Asn
1 5 10 15
Gln Ile Lys Asn Thr Thr Pro Thr Tyr Leu Thr Gln Asn Pro Gln Leu
20 25 30
Gly Ile Ser Leu Ser Asn Leu Ser Glu Thr Thr Ser Lys Pro Thr Thr
35 40 45
Ile Leu Ala Leu Thr Thr Pro Asn Ala Glu Ser Thr Pro Gln Ser Thr
50 55 60
Thr Val Lys Thr Lys Asn Thr Thr Thr Thr Gln Ile Gln Pro Ser Lys
65 70 75 80
Pro Thr Thr Lys Gln Arg Gln Asn Lys Pro Gln Asn Lys Pro Asn Asn
85 90 95
Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Ser
100 105 110
Asn Asn Pro Thr Cys Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys Lys
115 120 125
Pro Gly Arg Lys Thr Thr Thr Lys Pro Thr Lys Gln Pro Ala Ile Lys
130 135 140
Thr Thr Lys Lys Asp Pro Lys Pro Gln Thr Thr Lys Pro Lys Glu Val
145 150 155 160
Leu Thr Thr Lys Pro Thr Glu Lys Pro Thr Ile Asn Thr Thr Lys Thr
165 170 175
Asn Ile Arg Thr Thr Leu Leu Thr Ser Asn Ile Thr Glu Asn Gln Glu
180 185 190
His Thr Ser Gln Lys Glu Thr Leu His Ser Thr Thr Ser Glu Gly Asn
195 200 205
Pro Ser Pro Ser Gln Val Tyr Thr Thr Ser Glu Tyr Leu Ser Gln Ser
210 215 220
Leu Ser Pro Ser Asn Thr Thr Arg Trp
225 230
<210> 49
<211> 299
<212> PRT
<213> 呼吸道合胞病毒
<400> 49

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

<210> 50

<211> 234
<212> PRT
<213> 呼吸道合胞病毒
<400> 50
Asn His Lys Val Thr Leu Thr Thr Val Thr Val Gln Thr Ile Lys Asn
1 5 10 15
His Thr Glu Lys Asn Ile Thr Thr Tyr Leu Thr Gln Val Pro Pro Glu
20 25 30
Arg Val Ser Ser Ser Lys Gln Pro Thr Thr Thr Ser Pro Ile His Thr
35 40 45
Asn Ser Ala Thr Thr Ser Pro Asn Thr Lys Ser Glu Thr His His Thr
50 55 60
Thr Ala Gln Thr Lys Gly Arg Thr Thr Thr Ser Thr Gln Thr Asn Lys
65 70 75 80
Pro Ser Thr Lys Pro Arg Leu Lys Asn Pro Pro Lys Lys Pro Lys Asp
85 90 95
Asp Tyr His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Gly
100 105 110
Asn Asn Gln Leu Cys Lys Ser Ile Cys Lys Thr Ile Pro Ser Asn Lys
115 120 125
Pro Lys Lys Lys Pro Thr Ile Lys Pro Thr Asn Lys Pro Thr Thr Lys
130 135 140
Thr Thr Asn Lys Arg Asp Pro Lys Thr Pro Ala Lys Thr Thr Lys Lys
145 150 155 160
Glu Thr Thr Thr Asn Pro Thr Lys Lys Pro Thr Leu Thr Thr Thr Glu
165 170 175
Arg Asp Thr Ser Thr Ser Gln Ser Thr Val Leu Asp Thr Thr Thr Leu
180 185 190
Glu His Thr Ile Gln Gln Gln Ser Leu His Ser Thr Thr Pro Glu Asn
195 200 205
Thr Pro Asn Ser Thr Gln Thr Pro Thr Ala Ser Glu Pro Ser Thr Ser
210 215 220
Asn Ser Thr Gln Asn Thr Gln Ser His Ala
225 230
<210> 51
<211> 321
<212> PRT
<213> 呼吸道合胞病毒
<400> 51

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

305 310 315 320

Lys

<210> 52

<211> 256

<212> PRT

<213> 呼吸道合胞病毒

<400> 52

Asn His Lys Val Thr Leu Thr Thr Ala Ile Ile Gln Asp Ala Thr Asn
1 5 10 15

Gln Ile Lys Asn Thr Thr Pro Thr Tyr Leu Thr Gln Asn Pro Gln Leu
20 25 30

Gly Ile Ser Phe Ser Asn Leu Ser Gly Thr Thr Ser Gln Ser Thr Thr
35 40 45

Ile Leu Ala Ser Thr Thr Pro Ser Ala Glu Ser Thr Pro Gln Ser Thr
50 55 60

Thr Val Lys Ile Lys Asn Thr Thr Thr Thr Gln Ile Leu Pro Ser Lys
65 70 75 80

Pro Thr Thr Lys Gln Arg Gln Asn Lys Pro Gln Asn Lys Pro Asn Asn
85 90 95

Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Ser
100 105 110

Asn Asn Pro Thr Cys Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys Lys
115 120 125

Pro Gly Lys Lys Thr Thr Thr Lys Pro Thr Lys Lys Pro Thr Leu Lys
130 135 140

Thr Thr Lys Lys Asp Pro Lys Pro Gln Thr Thr Lys Pro Lys Glu Val
145 150 155 160

Leu Thr Thr Lys Pro Thr Gly Lys Pro Thr Ile Asn Thr Thr Lys Thr
165 170 175

Asn Ile Arg Thr Thr Leu Leu Thr Ser Asn Thr Lys Gly Asn Pro Glu
180 185 190

His Thr Ser Gln Glu Glu Thr Leu His Ser Thr Thr Ser Glu Gly Tyr
195 200 205

Leu Ser Pro Ser Gln Val Tyr Thr Thr Ser Gly Gln Glu Glu Thr Leu
210 215 220

His Ser Thr Thr Ser Glu Gly Tyr Leu Ser Pro Ser Gln Val Tyr Thr
225 230 235 240

Thr Ser Glu Tyr Leu Ser Gln Ser Leu Ser Ser Ser Asn Thr Thr Lys
245 250 255

<210> 53
<211> 315
<212> PRT
<213> 呼吸道合胞病毒
<400> 53
Met Ser Lys Asn Lys Asn Gln Arg Thr Ala Arg Thr Leu Glu Lys Thr
1 5 10 15
Trp Asp Thr Leu Asn His Leu Ile Val Ile Ser Ser Cys Leu Tyr Lys
20 25 30
Leu Asn Leu Lys Ser Ile Ala Gln Ile Ala Leu Ser Val Leu Ala Met
35 40 45
Ile Ile Ser Thr Ser Leu Ile Ile Ala Ala Ile Ile Phe Ile Ile Ser
50 55 60
Ala Asn His Lys Val Thr Leu Thr Thr Val Thr Val Gln Thr Ile Lys
65 70 75 80
Asn His Thr Glu Lys Asn Ile Thr Thr Tyr Leu Thr Gln Val Ser Pro
85 90 95
Glu Arg Val Ser Pro Ser Lys Gln Leu Thr Thr Thr Pro Pro Ile Tyr
100 105 110
Thr Asn Ser Ala Thr Ile Ser Pro Asn Thr Lys Ser Glu Thr His His
115 120 125
Thr Thr Ala Gln Thr Lys Gly Arg Thr Thr Thr Pro Thr Gln Asn Asn
130 135 140
Lys Pro Ser Thr Lys Pro Arg Pro Lys Asn Pro Pro Lys Lys Pro Lys
145 150 155 160
Asp Asp Tyr His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys
165 170 175
Gly Asn Asn Gln Leu Cys Lys Ser Ile Cys Lys Thr Ile Pro Ser Asn
180 185 190
Lys Pro Lys Lys Lys Pro Thr Ile Lys Pro Thr Asn Lys Pro Pro Thr
195 200 205
Lys Thr Thr Asn Lys Arg Asp Pro Lys Lys Leu Ala Lys Thr Leu Lys
210 215 220
Lys Glu Thr Thr Ile Asn Pro Thr Lys Lys Pro Thr Pro Lys Thr Thr
225 230 235 240
Glu Arg Asp Thr Ser Thr Ser Gln Ser Thr Val Leu Asp Thr Thr Thr
245 250 255
Ser Lys His Thr Glu Arg Asp Thr Ser Thr Ser Gln Ser Thr Val Leu
260 265 270

Asp Thr Thr Thr Ser Lys His Thr Ile Gln Gln Gln Ser Leu His Ser
275 280 285
Thr Thr Pro Glu Asn Thr Pro Asn Ser Thr Gln Thr Pro Thr Ala Ser
290 295 300
Glu Pro Ser Thr Ser Asn Ser Thr Gln Lys Leu
305 310 315
<210> 54
<211> 250
<212> PRT
<213> 呼吸道合胞病毒
<400> 54
Asn His Lys Val Thr Leu Thr Thr Val Thr Val Gln Thr Ile Lys Asn
1 5 10 15
His Thr Glu Lys Asn Ile Thr Thr Tyr Leu Thr Gln Val Ser Pro Glu
20 25 30
Arg Val Ser Pro Ser Lys Gln Leu Thr Thr Thr Pro Pro Ile Tyr Thr
35 40 45
Asn Ser Ala Thr Ile Ser Pro Asn Thr Lys Ser Glu Thr His His Thr
50 55 60
Thr Ala Gln Thr Lys Gly Arg Thr Thr Thr Pro Thr Gln Asn Asn Lys
65 70 75 80
Pro Ser Thr Lys Pro Arg Pro Lys Asn Pro Pro Lys Lys Pro Lys Asp
85 90 95
Asp Tyr His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Gly
100 105 110
Asn Asn Gln Leu Cys Lys Ser Ile Cys Lys Thr Ile Pro Ser Asn Lys
115 120 125
Pro Lys Lys Lys Pro Thr Ile Lys Pro Thr Asn Lys Pro Pro Thr Lys
130 135 140
Thr Thr Asn Lys Arg Asp Pro Lys Lys Leu Ala Lys Thr Leu Lys Lys
145 150 155 160
Glu Thr Thr Ile Asn Pro Thr Lys Lys Pro Thr Pro Lys Thr Thr Glu
165 170 175
Arg Asp Thr Ser Thr Ser Gln Ser Thr Val Leu Asp Thr Thr Thr Ser
180 185 190
Lys His Thr Glu Arg Asp Thr Ser Thr Ser Gln Ser Thr Val Leu Asp
195 200 205
Thr Thr Thr Ser Lys His Thr Ile Gln Gln Gln Ser Leu His Ser Thr
210 215 220

Thr Pro Glu Asn Thr Pro Asn Ser Thr Gln Thr Pro Thr Ala Ser Glu
225 230 235 240
Pro Ser Thr Ser Asn Ser Thr Gln Lys Leu
245 250
<210> 55
<211> 31
<212> PRT
<213> 人副流感病毒3
<400> 55
Met Glu Tyr Trp Lys His Thr Asn His Gly Lys Asp Ala Gly Asn Glu
1 5 10 15
Leu Glu Thr Ser Met Ala Thr His Gly Asn Lys Leu Thr Asn Lys
20 25 30
<210> 56
<211> 25
<212> PRT
<213> 人副流感病毒3
<400> 56
Ile Ile Tyr Ile Leu Trp Thr Ile Ile Leu Val Leu Leu Ser Ile Val
1 5 10 15
Phe Ile Ile Val Leu Ile Asn Ser Ile
20 25
<210> 57
<211> 56
<212> PRT
<213> 人副流感病毒3
<400> 57
Met Glu Tyr Trp Lys His Thr Asn His Gly Lys Asp Ala Gly Asn Glu
1 5 10 15
Leu Glu Thr Ser Met Ala Thr His Gly Asn Lys Leu Thr Asn Lys Ile
20 25 30
Ile Tyr Ile Leu Trp Thr Ile Ile Leu Val Leu Leu Ser Ile Val Phe
35 40 45
Ile Ile Val Leu Ile Asn Ser Ile
50 55
<210> 58
<211> 35
<212> PRT
<213> 人副流感病毒1

<400> 58
Met Ala Glu Lys Gly Lys Thr Asn Ser Ser Tyr Trp Ser Thr Thr Arg
1 5 10 15
Asn Asp Asn Ser Thr Val Asn Thr His Ile Asn Thr Pro Ala Gly Arg
20 25 30
Thr His Trp
35
<210> 59
<211> 25
<212> PRT
<213> 人副流感病毒1
<400> 59
Ile Leu Leu Ile Ala Thr Thr Met His Thr Val Leu Ser Phe Ile Ile
1 5 10 15
Met Ile Leu Cys Ile Asp Leu Ile Ile
20 25
<210> 60
<211> 60
<212> PRT
<213> 人副流感病毒1
<400> 60
Met Ala Glu Lys Gly Lys Thr Asn Ser Ser Tyr Trp Ser Thr Thr Arg
1 5 10 15
Asn Asp Asn Ser Thr Val Asn Thr His Ile Asn Thr Pro Ala Gly Arg
20 25 30
Thr His Trp Ile Leu Leu Ile Ala Thr Thr Met His Thr Val Leu Ser
35 40 45
Phe Ile Ile Met Ile Leu Cys Ile Asp Leu Ile Ile
50 55 60
<210> 61
<211> 292
<212> PRT
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 61
Met Glu Tyr Trp Lys His Thr Asn Ser Ile Asn Asn Thr Asn Asn Glu
1 5 10 15
Thr Glu Thr Ala Arg Gly Lys His Ser Ser Lys Val Thr Asn Ile Ala

20 25 30
Gln Ile Ala Leu Ser Val Leu Ala Met Ile Ile Ser Thr Ser Leu Ile
35 40 45
Ile Ala Ala Ile Ile Phe Ile Ile Ser Ala Asn His Lys Val Thr Leu
50 55 60
Thr Thr Val Thr Val Gln Thr Ile Lys Asn His Thr Glu Lys Asn Ile
65 70 75 80
Thr Thr Tyr Leu Thr Gln Val Pro Pro Glu Arg Val Ser Ser Ser Lys
85 90 95
Gln Pro Thr Thr Thr Ser Pro Ile His Thr Asn Ser Ala Thr Thr Ser
100 105 110
Pro Asn Thr Lys Ser Glu Thr His His Thr Thr Ala Gln Thr Lys Gly
115 120 125
Arg Thr Thr Thr Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys Pro Arg
130 135 140
Leu Lys Asn Pro Pro Lys Lys Pro Lys Asp Asp Tyr His Phe Glu Val
145 150 155 160
Phe Asn Phe Val Pro Cys Ser Ile Cys Gly Asn Asn Gln Leu Cys Lys
165 170 175
Ser Ile Cys Lys Thr Ile Pro Ser Asn Lys Pro Lys Lys Lys Pro Thr
180 185 190
Ile Lys Pro Thr Asn Lys Pro Thr Thr Lys Thr Thr Asn Lys Arg Asp
195 200 205
Pro Lys Thr Pro Ala Lys Thr Thr Lys Lys Glu Thr Thr Thr Asn Pro
210 215 220
Thr Lys Lys Pro Thr Leu Thr Thr Thr Glu Arg Asp Thr Ser Thr Ser
225 230 235 240
Gln Ser Thr Val Leu Asp Thr Thr Thr Leu Glu His Thr Ile Gln Gln
245 250 255
Gln Ser Leu His Ser Thr Thr Pro Glu Asn Thr Pro Asn Ser Thr Gln
260 265 270
Thr Pro Thr Ala Ser Glu Pro Ser Thr Ser Asn Ser Thr Gln Asn Thr
275 280 285
Gln Ser His Ala
290
<210> 62
<211> 290
<212> PRT
<213> 人工序列

<220>
<223> 重组RSV G蛋白
<400> 62
Met Glu Tyr Trp Lys His Thr Asn Ser Ile Asn Asn Thr Asn Asn Glu
1 5 10 15
Thr Glu Thr Ala Arg Gly Lys His Ser Ser Lys Val Thr Asn Ile Ile
20 25 30
Met Tyr Thr Phe Trp Thr Ile Thr Leu Thr Ile Leu Ser Val Ile Phe
35 40 45
Ile Met Ile Leu Thr Asn Leu Ile Asn His Lys Val Thr Leu Thr Thr
50 55 60
Val Thr Val Gln Thr Ile Lys Asn His Thr Glu Lys Asn Ile Thr Thr
65 70 75 80
Tyr Leu Thr Gln Val Pro Pro Glu Arg Val Ser Ser Ser Lys Gln Pro
85 90 95
Thr Thr Thr Ser Pro Ile His Thr Asn Ser Ala Thr Thr Ser Pro Asn
100 105 110
Thr Lys Ser Glu Thr His His Thr Thr Ala Gln Thr Lys Gly Arg Thr
115 120 125
Thr Thr Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys Pro Arg Leu Lys
130 135 140
Asn Pro Pro Lys Lys Pro Lys Asp Asp Tyr His Phe Glu Val Phe Asn
145 150 155 160
Phe Val Pro Cys Ser Ile Cys Gly Asn Asn Gln Leu Cys Lys Ser Ile
165 170 175
Cys Lys Thr Ile Pro Ser Asn Lys Pro Lys Lys Lys Pro Thr Ile Lys
180 185 190
Pro Thr Asn Lys Pro Thr Thr Lys Thr Thr Asn Lys Arg Asp Pro Lys
195 200 205
Thr Pro Ala Lys Thr Thr Lys Lys Glu Thr Thr Thr Asn Pro Thr Lys
210 215 220
Lys Pro Thr Leu Thr Thr Thr Glu Arg Asp Thr Ser Thr Ser Gln Ser
225 230 235 240
Thr Val Leu Asp Thr Thr Thr Leu Glu His Thr Ile Gln Gln Gln Ser
245 250 255
Leu His Ser Thr Thr Pro Glu Asn Thr Pro Asn Ser Thr Gln Thr Pro
260 265 270
Thr Ala Ser Glu Pro Ser Thr Ser Asn Ser Thr Gln Asn Thr Gln Ser
275 280 285

His Ala
290

<210> 63
<211> 291
<212> PRT
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 63

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

Leu Thr Ser Asn Ile Thr Glu Asn Gln Glu His Thr Ser Gln Lys Glu
245 250 255
Thr Leu His Ser Thr Thr Ser Glu Gly Asn Pro Ser Pro Ser Gln Val
260 265 270
Tyr Thr Thr Ser Glu Tyr Leu Ser Gln Ser Leu Ser Pro Ser Asn Thr
275 280 285
Thr Arg Trp
290
<210> 64
<211> 289
<212> PRT
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 64
Met Glu Tyr Trp Lys His Thr Asn Ser Ile Asn Asn Thr Asn Asn Glu
1 5 10 15
Thr Glu Thr Ala Arg Gly Lys His Ser Ser Lys Val Thr Asn Ile Ile
20 25 30
Met Tyr Thr Phe Trp Thr Ile Thr Leu Thr Ile Leu Ser Val Ile Phe
35 40 45
Ile Met Ile Leu Thr Asn Leu Ile Asn His Lys Val Thr Leu Thr Thr
50 55 60
Ala Ile Ile Gln Asp Ala Thr Asn Gln Ile Lys Asn Thr Thr Pro Thr
65 70 75 80
Tyr Leu Thr Gln Asn Pro Gln Leu Gly Ile Ser Leu Ser Asn Leu Ser
85 90 95
Glu Thr Thr Ser Lys Pro Thr Thr Ile Leu Ala Leu Thr Thr Pro Asn
100 105 110
Ala Glu Ser Thr Pro Gln Ser Thr Thr Val Lys Thr Lys Asn Thr Thr
115 120 125
Thr Thr Gln Ile Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg Gln Asn
130 135 140
Lys Pro Gln Asn Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn
145 150 155 160
Phe Val Pro Cys Ser Ile Cys Ser Asn Asn Pro Thr Cys Trp Ala Ile
165 170 175
Cys Lys Arg Ile Pro Asn Lys Lys Pro Gly Arg Lys Thr Thr Thr Lys
180 185 190

Pro Thr Lys Gln Pro Ala Ile Lys Thr Thr Lys Lys Asp Pro Lys Pro
195 200 205
Gln Thr Thr Lys Pro Lys Glu Val Leu Thr Thr Lys Pro Thr Glu Lys
210 215 220
Pro Thr Ile Asn Thr Thr Lys Thr Asn Ile Arg Thr Thr Leu Leu Thr
225 230 235 240
Ser Asn Ile Thr Glu Asn Gln Glu His Thr Ser Gln Lys Glu Thr Leu
245 250 255
His Ser Thr Thr Ser Glu Gly Asn Pro Ser Pro Ser Gln Val Tyr Thr
260 265 270
Thr Ser Glu Tyr Leu Ser Gln Ser Leu Ser Pro Ser Asn Thr Thr Arg
275 280 285
Trp
<210> 65
<211> 314
<212> PRT
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 65
Met Glu Tyr Trp Lys His Thr Asn Ser Ile Asn Asn Thr Asn Asn Glu
1 5 10 15
Thr Glu Thr Ala Arg Gly Lys His Ser Ser Lys Val Thr Asn Ile Ala
20 25 30
Gln Ile Thr Leu Ser Ile Leu Ala Met Ile Ile Ser Thr Ser Leu Ile
35 40 45
Ile Ala Ala Ile Ile Phe Ile Ala Ser Ala Asn His Lys Val Thr Leu
50 55 60
Thr Thr Ala Ile Ile Gln Asp Ala Thr Asn Gln Ile Lys Asn Thr Thr
65 70 75 80
Pro Thr Tyr Leu Thr Gln Asn Pro Gln Leu Gly Ile Ser Phe Ser Asn
85 90 95
Leu Ser Gly Thr Thr Ser Gln Ser Thr Thr Ile Leu Ala Ser Thr Thr
100 105 110
Pro Ser Ala Glu Ser Thr Pro Gln Ser Thr Thr Val Lys Ile Lys Asn
115 120 125
Thr Thr Thr Thr Gln Ile Leu Pro Ser Lys Pro Thr Thr Lys Gln Arg
130 135 140
Gln Asn Lys Pro Gln Asn Lys Pro Asn Asn Asp Phe His Phe Glu Val

145 150 155 160
Phe Asn Phe Val Pro Cys Ser Ile Cys Ser Asn Asn Pro Thr Cys Trp
165 170 175
Ala Ile Cys Lys Arg Ile Pro Asn Lys Lys Pro Gly Lys Lys Thr Thr
180 185 190
Thr Lys Pro Thr Lys Lys Pro Thr Leu Lys Thr Thr Lys Lys Asp Pro
195 200 205
Lys Pro Gln Thr Thr Lys Pro Lys Glu Val Leu Thr Thr Lys Pro Thr
210 215 220
Gly Lys Pro Thr Ile Asn Thr Thr Lys Thr Asn Ile Arg Thr Thr Leu
225 230 235 240
Leu Thr Ser Asn Thr Lys Gly Asn Pro Glu His Thr Ser Gln Glu Glu
245 250 255
Thr Leu His Ser Thr Thr Ser Glu Gly Tyr Leu Ser Pro Ser Gln Val
260 265 270
Tyr Thr Thr Ser Gly Gln Glu Glu Thr Leu His Ser Thr Thr Ser Glu
275 280 285
Gly Tyr Leu Ser Pro Ser Gln Val Tyr Thr Thr Ser Glu Tyr Leu Ser
290 295 300
Gln Ser Leu Ser Ser Ser Asn Thr Thr Lys
305 310
<210> 66
<211> 312
<212> PRT
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 66
Met Glu Tyr Trp Lys His Thr Asn Ser Ile Asn Asn Thr Asn Asn Glu
1 5 10 15
Thr Glu Thr Ala Arg Gly Lys His Ser Ser Lys Val Thr Asn Ile Ile
20 25 30
Met Tyr Thr Phe Trp Thr Ile Thr Leu Thr Ile Leu Ser Val Ile Phe
35 40 45
Ile Met Ile Leu Thr Asn Leu Ile Asn His Lys Val Thr Leu Thr Thr
50 55 60
Ala Ile Ile Gln Asp Ala Thr Asn Gln Ile Lys Asn Thr Thr Pro Thr
65 70 75 80
Tyr Leu Thr Gln Asn Pro Gln Leu Gly Ile Ser Phe Ser Asn Leu Ser

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

<210> 67
<211> 308
<212> PRT
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 67

Met Glu Tyr Trp Lys His Thr Asn Ser Ile Asn Asn Thr Asn Asn Glu
1 5 10 15
Thr Glu Thr Ala Arg Gly Lys His Ser Ser Lys Val Thr Asn Ile Ala

20 25 30

Gln Ile Ala Leu Ser Val Leu Ala Met Ile Ile Ser Thr Ser Leu Ile
35 40 45

Ile Ala Ala Ile Ile Phe Ile Ile Ser Ala Asn His Lys Val Thr Leu
50 55 60

Thr Thr Val Thr Val Gln Thr Ile Lys Asn His Thr Glu Lys Asn Ile
65 70 75 80

Thr Thr Tyr Leu Thr Gln Val Ser Pro Glu Arg Val Ser Pro Ser Lys
85 90 95

Gln Leu Thr Thr Thr Pro Pro Ile Tyr Thr Asn Ser Ala Thr Ile Ser
100 105 110

Pro Asn Thr Lys Ser Glu Thr His His Thr Thr Ala Gln Thr Lys Gly
115 120 125

Arg Thr Thr Thr Pro Thr Gln Asn Asn Lys Pro Ser Thr Lys Pro Arg
130 135 140

Pro Lys Asn Pro Pro Lys Lys Pro Lys Asp Asp Tyr His Phe Glu Val
145 150 155 160

Phe Asn Phe Val Pro Cys Ser Ile Cys Gly Asn Asn Gln Leu Cys Lys
165 170 175

Ser Ile Cys Lys Thr Ile Pro Ser Asn Lys Pro Lys Lys Lys Pro Thr
180 185 190

Ile Lys Pro Thr Asn Lys Pro Pro Thr Lys Thr Thr Asn Lys Arg Asp
195 200 205

Pro Lys Lys Leu Ala Lys Thr Leu Lys Lys Glu Thr Thr Ile Asn Pro
210 215 220

Thr Lys Lys Pro Thr Pro Lys Thr Thr Glu Arg Asp Thr Ser Thr Ser
225 230 235 240

Gln Ser Thr Val Leu Asp Thr Thr Thr Ser Lys His Thr Glu Arg Asp
245 250 255

Thr Ser Thr Ser Gln Ser Thr Val Leu Asp Thr Thr Thr Ser Lys His
260 265 270

Thr Ile Gln Gln Gln Ser Leu His Ser Thr Thr Pro Glu Asn Thr Pro
275 280 285

Asn Ser Thr Gln Thr Pro Thr Ala Ser Glu Pro Ser Thr Ser Asn Ser
290 295 300

Thr Gln Lys Leu
305

<210> 68

<211> 306

<212> PRT
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 68

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

Gln Gln Gln Ser Leu His Ser Thr Thr Pro Glu Asn Thr Pro Asn Ser
275 280 285
Thr Gln Thr Pro Thr Ala Ser Glu Pro Ser Thr Ser Asn Ser Thr Gln
290 295 300
Lys Leu
305
<210> 69
<211> 292
<212> PRT
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 69
Met Glu Tyr Trp Lys His Thr Asn His Gly Lys Asp Ala Gly Asn Glu
1 5 10 15
Leu Glu Thr Ser Met Ala Thr His Gly Asn Lys Leu Thr Asn Lys Val
20 25 30
Ala Gln Ile Thr Leu Ser Ile Leu Ala Met Ile Ile Ser Thr Ser Leu
35 40 45
Ile Ile Ala Ala Ile Ile Phe Ile Ala Ser Ala Asn His Lys Val Thr
50 55 60
Pro Thr Thr Ala Ile Ile Gln Asp Ala Thr Ser Gln Ile Lys Asn Thr
65 70 75 80
Thr Pro Thr Tyr Leu Thr Gln Asn Pro Gln Leu Gly Ile Ser Pro Ser
85 90 95
Asn Pro Ser Glu Ile Thr Ser Gln Ile Thr Thr Ile Leu Ala Ser Thr
100 105 110
Thr Pro Gly Val Lys Ser Thr Leu Gln Ser Thr Thr Val Lys Thr Lys
115 120 125
Asn Thr Thr Thr Thr Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys Gln
130 135 140
Arg Gln Asn Lys Pro Pro Ser Lys Pro Asn Asn Asp Phe His Phe Glu
145 150 155 160
Val Phe Asn Phe Val Pro Cys Ser Ile Cys Ser Asn Asn Pro Thr Cys
165 170 175
Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys Lys Pro Gly Lys Lys Thr
180 185 190
Thr Thr Lys Pro Thr Lys Lys Pro Thr Leu Lys Thr Thr Lys Lys Asp
195 200 205

Pro Lys Pro Gln Thr Thr Lys Ser Lys Glu Val Pro Thr Thr Lys Pro
210 215 220
Thr Glu Glu Pro Thr Ile Asn Thr Thr Lys Thr Asn Ile Ile Thr Thr
225 230 235 240
Leu Leu Thr Ser Asn Thr Thr Gly Asn Pro Glu Leu Thr Ser Gln Met
245 250 255
Glu Thr Phe His Ser Thr Ser Ser Glu Gly Asn Pro Ser Pro Ser Gln
260 265 270
Val Ser Thr Thr Ser Glu Tyr Pro Ser Gln Pro Ser Ser Pro Pro Asn
275 280 285
Thr Pro Arg Gln
290
<210> 70
<211> 289
<212> PRT
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 70
Met Glu Tyr Trp Lys His Thr Asn His Gly Lys Asp Ala Gly Asn Glu
1 5 10 15
Leu Glu Thr Ser Met Ala Thr His Gly Asn Lys Leu Thr Asn Lys Ile
20 25 30
Ile Tyr Ile Leu Trp Thr Ile Ile Leu Val Leu Leu Ser Ile Val Phe
35 40 45
Ile Ile Val Leu Ile Asn Ser Ile Asn His Lys Val Thr Pro Thr Thr
50 55 60
Ala Ile Ile Gln Asp Ala Thr Ser Gln Ile Lys Asn Thr Thr Pro Thr
65 70 75 80
Tyr Leu Thr Gln Asn Pro Gln Leu Gly Ile Ser Pro Ser Asn Pro Ser
85 90 95
Glu Ile Thr Ser Gln Ile Thr Thr Ile Leu Ala Ser Thr Thr Pro Gly
100 105 110
Val Lys Ser Thr Leu Gln Ser Thr Thr Val Lys Thr Lys Asn Thr Thr
115 120 125
Thr Thr Gln Thr Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg Gln Asn
130 135 140
Lys Pro Pro Ser Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn
145 150 155 160

Phe Val Pro Cys Ser Ile Cys Ser Asn Asn Pro Thr Cys Trp Ala Ile
165 170 175
Cys Lys Arg Ile Pro Asn Lys Lys Pro Gly Lys Lys Thr Thr Thr Lys
180 185 190
Pro Thr Lys Lys Pro Thr Leu Lys Thr Thr Lys Lys Asp Pro Lys Pro
195 200 205
Gln Thr Thr Lys Ser Lys Glu Val Pro Thr Thr Lys Pro Thr Glu Glu
210 215 220
Pro Thr Ile Asn Thr Thr Lys Thr Asn Ile Ile Thr Thr Leu Leu Thr
225 230 235 240
Ser Asn Thr Thr Gly Asn Pro Glu Leu Thr Ser Gln Met Glu Thr Phe
245 250 255
His Ser Thr Ser Ser Glu Gly Asn Pro Ser Pro Ser Gln Val Ser Thr
260 265 270
Thr Ser Glu Tyr Pro Ser Gln Pro Ser Ser Pro Pro Asn Thr Pro Arg
275 280 285
Gln

<210> 71
<211> 293
<212> PRT
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 71

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

115 120 125
Gly Arg Thr Thr Thr Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys Pro
130 135 140
Arg Leu Lys Asn Pro Pro Lys Lys Pro Lys Asp Asp Tyr His Phe Glu
145 150 155 160
Val Phe Asn Phe Val Pro Cys Ser Ile Cys Gly Asn Asn Gln Leu Cys
165 170 175
Lys Ser Ile Cys Lys Thr Ile Pro Ser Asn Lys Pro Lys Lys Lys Pro
180 185 190
Thr Ile Lys Pro Thr Asn Lys Pro Thr Thr Lys Thr Thr Asn Lys Arg
195 200 205
Asp Pro Lys Thr Pro Ala Lys Thr Thr Lys Lys Glu Thr Thr Thr Asn
210 215 220
Pro Thr Lys Lys Pro Thr Leu Thr Thr Thr Glu Arg Asp Thr Ser Thr
225 230 235 240
Ser Gln Ser Thr Val Leu Asp Thr Thr Thr Leu Glu His Thr Ile Gln
245 250 255
Gln Gln Ser Leu His Ser Thr Thr Pro Glu Asn Thr Pro Asn Ser Thr
260 265 270
Gln Thr Pro Thr Ala Ser Glu Pro Ser Thr Ser Asn Ser Thr Gln Asn
275 280 285
Thr Gln Ser His Ala
290
<210> 72
<211> 290
<212> PRT
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 72
Met Glu Tyr Trp Lys His Thr Asn His Gly Lys Asp Ala Gly Asn Glu
1 5 10 15
Leu Glu Thr Ser Met Ala Thr His Gly Asn Lys Leu Thr Asn Lys Ile
20 25 30
Ile Tyr Ile Leu Trp Thr Ile Ile Leu Val Leu Leu Ser Ile Val Phe
35 40 45
Ile Ile Val Leu Ile Asn Ser Ile Asn His Lys Val Thr Leu Thr Thr
50 55 60
Val Thr Val Gln Thr Ile Lys Asn His Thr Glu Lys Asn Ile Thr Thr

65 70 75 80
Tyr Leu Thr Gln Val Pro Pro Glu Arg Val Ser Ser Ser Lys Gln Pro
85 90 95
Thr Thr Thr Ser Pro Ile His Thr Asn Ser Ala Thr Thr Ser Pro Asn
100 105 110
Thr Lys Ser Glu Thr His His Thr Thr Ala Gln Thr Lys Gly Arg Thr
115 120 125
Thr Thr Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys Pro Arg Leu Lys
130 135 140
Asn Pro Pro Lys Lys Pro Lys Asp Asp Tyr His Phe Glu Val Phe Asn
145 150 155 160
Phe Val Pro Cys Ser Ile Cys Gly Asn Asn Gln Leu Cys Lys Ser Ile
165 170 175
Cys Lys Thr Ile Pro Ser Asn Lys Pro Lys Lys Lys Pro Thr Ile Lys
180 185 190
Pro Thr Asn Lys Pro Thr Thr Lys Thr Thr Asn Lys Arg Asp Pro Lys
195 200 205
Thr Pro Ala Lys Thr Thr Lys Lys Glu Thr Thr Thr Asn Pro Thr Lys
210 215 220
Lys Pro Thr Leu Thr Thr Thr Glu Arg Asp Thr Ser Thr Ser Gln Ser
225 230 235 240
Thr Val Leu Asp Thr Thr Thr Leu Glu His Thr Ile Gln Gln Gln Ser
245 250 255
Leu His Ser Thr Thr Pro Glu Asn Thr Pro Asn Ser Thr Gln Thr Pro
260 265 270
Thr Ala Ser Glu Pro Ser Thr Ser Asn Ser Thr Gln Asn Thr Gln Ser
275 280 285
His Ala
290
<210> 73
<211> 292
<212> PRT
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 73
Met Glu Tyr Trp Lys His Thr Asn His Gly Lys Asp Ala Gly Asn Glu
1 5 10 15
Leu Glu Thr Ser Met Ala Thr His Gly Asn Lys Leu Thr Asn Lys Ile

20 25 30

Ala Gln Ile Thr Leu Ser Ile Leu Ala Met Ile Ile Ser Thr Ser Leu
35 40 45

Ile Ile Ala Ala Ile Ile Phe Ile Ala Ser Ala Asn His Lys Val Thr
50 55 60

Leu Thr Thr Ala Ile Ile Gln Asp Ala Thr Asn Gln Ile Lys Asn Thr
65 70 75 80

Thr Pro Thr Tyr Leu Thr Gln Asn Pro Gln Leu Gly Ile Ser Leu Ser
85 90 95

Asn Leu Ser Glu Thr Thr Ser Lys Pro Thr Thr Ile Leu Ala Leu Thr
100 105 110

Thr Pro Asn Ala Glu Ser Thr Pro Gln Ser Thr Thr Val Lys Thr Lys
115 120 125

Asn Thr Thr Thr Thr Gln Ile Gln Pro Ser Lys Pro Thr Thr Lys Gln
130 135 140

Arg Gln Asn Lys Pro Gln Asn Lys Pro Asn Asn Asp Phe His Phe Glu
145 150 155 160

Val Phe Asn Phe Val Pro Cys Ser Ile Cys Ser Asn Asn Pro Thr Cys
165 170 175

Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys Lys Pro Gly Arg Lys Thr
180 185 190

Thr Thr Lys Pro Thr Lys Gln Pro Ala Ile Lys Thr Thr Lys Lys Asp
195 200 205

Pro Lys Pro Gln Thr Thr Lys Pro Lys Glu Val Leu Thr Thr Lys Pro
210 215 220

Thr Glu Lys Pro Thr Ile Asn Thr Thr Lys Thr Asn Ile Arg Thr Thr
225 230 235 240

Leu Leu Thr Ser Asn Ile Thr Glu Asn Gln Glu His Thr Ser Gln Lys
245 250 255

Glu Thr Leu His Ser Thr Thr Ser Glu Gly Asn Pro Ser Pro Ser Gln
260 265 270

Val Tyr Thr Thr Ser Glu Tyr Leu Ser Gln Ser Leu Ser Pro Ser Asn
275 280 285

Thr Thr Arg Trp
290

<210> 74

<211> 289

<212> PRT

<213> 人工序列

<220>
<223> 重组RSV G蛋白
<400> 74
Met Glu Tyr Trp Lys His Thr Asn His Gly Lys Asp Ala Gly Asn Glu
1 5 10 15
Leu Glu Thr Ser Met Ala Thr His Gly Asn Lys Leu Thr Asn Lys Ile
20 25 30
Ile Tyr Ile Leu Trp Thr Ile Ile Leu Val Leu Leu Ser Ile Val Phe
35 40 45
Ile Ile Val Leu Ile Asn Ser Ile Asn His Lys Val Thr Leu Thr Thr
50 55 60
Ala Ile Ile Gln Asp Ala Thr Asn Gln Ile Lys Asn Thr Thr Pro Thr
65 70 75 80
Tyr Leu Thr Gln Asn Pro Gln Leu Gly Ile Ser Leu Ser Asn Leu Ser
85 90 95
Glu Thr Thr Ser Lys Pro Thr Thr Ile Leu Ala Leu Thr Thr Pro Asn
100 105 110
Ala Glu Ser Thr Pro Gln Ser Thr Thr Val Lys Thr Lys Asn Thr Thr
115 120 125
Thr Thr Gln Ile Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg Gln Asn
130 135 140
Lys Pro Gln Asn Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn
145 150 155 160
Phe Val Pro Cys Ser Ile Cys Ser Asn Asn Pro Thr Cys Trp Ala Ile
165 170 175
Cys Lys Arg Ile Pro Asn Lys Lys Pro Gly Arg Lys Thr Thr Thr Lys
180 185 190
Pro Thr Lys Gln Pro Ala Ile Lys Thr Thr Lys Lys Asp Pro Lys Pro
195 200 205
Gln Thr Thr Lys Pro Lys Glu Val Leu Thr Thr Lys Pro Thr Glu Lys
210 215 220
Pro Thr Ile Asn Thr Thr Lys Thr Asn Ile Arg Thr Thr Leu Leu Thr
225 230 235 240
Ser Asn Ile Thr Glu Asn Gln Glu His Thr Ser Gln Lys Glu Thr Leu
245 250 255
His Ser Thr Thr Ser Glu Gly Asn Pro Ser Pro Ser Gln Val Tyr Thr
260 265 270
Thr Ser Glu Tyr Leu Ser Gln Ser Leu Ser Pro Ser Asn Thr Thr Arg
275 280 285

Trp
<210> 75
<211> 315
<212> PRT
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 75
Met Glu Tyr Trp Lys His Thr Asn His Gly Lys Asp Ala Gly Asn Glu
1 5 10 15
Leu Glu Thr Ser Met Ala Thr His Gly Asn Lys Leu Thr Asn Lys Ile
20 25 30
Ala Gln Ile Thr Leu Ser Ile Leu Ala Met Ile Ile Ser Thr Ser Leu
35 40 45
Ile Ile Ala Ala Ile Ile Phe Ile Ala Ser Ala Asn His Lys Val Thr
50 55 60
Leu Thr Thr Ala Ile Ile Gln Asp Ala Thr Asn Gln Ile Lys Asn Thr
65 70 75 80
Thr Pro Thr Tyr Leu Thr Gln Asn Pro Gln Leu Gly Ile Ser Phe Ser
85 90 95
Asn Leu Ser Gly Thr Thr Ser Gln Ser Thr Thr Ile Leu Ala Ser Thr
100 105 110
Thr Pro Ser Ala Glu Ser Thr Pro Gln Ser Thr Thr Val Lys Ile Lys
115 120 125
Asn Thr Thr Thr Thr Gln Ile Leu Pro Ser Lys Pro Thr Thr Lys Gln
130 135 140
Arg Gln Asn Lys Pro Gln Asn Lys Pro Asn Asn Asp Phe His Phe Glu
145 150 155 160
Val Phe Asn Phe Val Pro Cys Ser Ile Cys Ser Asn Asn Pro Thr Cys
165 170 175
Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys Lys Pro Gly Lys Lys Thr
180 185 190
Thr Thr Lys Pro Thr Lys Lys Pro Thr Leu Lys Thr Thr Lys Lys Asp
195 200 205
Pro Lys Pro Gln Thr Thr Lys Pro Lys Glu Val Leu Thr Thr Lys Pro
210 215 220
Thr Gly Lys Pro Thr Ile Asn Thr Thr Lys Thr Asn Ile Arg Thr Thr
225 230 235 240
Leu Leu Thr Ser Asn Thr Lys Gly Asn Pro Glu His Thr Ser Gln Glu

245 250 255
Glu Thr Leu His Ser Thr Thr Ser Glu Gly Tyr Leu Ser Pro Ser Gln
260 265 270
Val Tyr Thr Thr Ser Gly Gln Glu Glu Thr Leu His Ser Thr Thr Ser
275 280 285
Glu Gly Tyr Leu Ser Pro Ser Gln Val Tyr Thr Thr Ser Glu Tyr Leu
290 295 300
Ser Gln Ser Leu Ser Ser Ser Asn Thr Thr Lys
305 310 315
<210> 76
<211> 312
<212> PRT
<213> 人工序列
<220>
<223> 重组RSV G蛋白
<400> 76
Met Glu Tyr Trp Lys His Thr Asn His Gly Lys Asp Ala Gly Asn Glu
1 5 10 15
Leu Glu Thr Ser Met Ala Thr His Gly Asn Lys Leu Thr Asn Lys Ile
20 25 30
Ile Tyr Ile Leu Trp Thr Ile Ile Leu Val Leu Leu Ser Ile Val Phe
35 40 45
Ile Ile Val Leu Ile Asn Ser Ile Asn His Lys Val Thr Leu Thr Thr
50 55 60
Ala Ile Ile Gln Asp Ala Thr Asn Gln Ile Lys Asn Thr Thr Pro Thr
65 70 75 80
Tyr Leu Thr Gln Asn Pro Gln Leu Gly Ile Ser Phe Ser Asn Leu Ser
85 90 95
Gly Thr Thr Ser Gln Ser Thr Thr Ile Leu Ala Ser Thr Thr Pro Ser
100 105 110
Ala Glu Ser Thr Pro Gln Ser Thr Thr Val Lys Ile Lys Asn Thr Thr
115 120 125
Thr Thr Gln Ile Leu Pro Ser Lys Pro Thr Thr Lys Gln Arg Gln Asn
130 135 140
Lys Pro Gln Asn Lys Pro Asn Asn Asp Phe His Phe Glu Val Phe Asn
145 150 155 160
Phe Val Pro Cys Ser Ile Cys Ser Asn Asn Pro Thr Cys Trp Ala Ile
165 170 175
Cys Lys Arg Ile Pro Asn Lys Lys Pro Gly Lys Lys Thr Thr Thr Lys

180 185 190
Pro Thr Lys Lys Pro Thr Leu Lys Thr Thr Lys Lys Asp Pro Lys Pro
195 200 205
Gln Thr Thr Lys Pro Lys Glu Val Leu Thr Thr Lys Pro Thr Gly Lys
210 215 220
Pro Thr Ile Asn Thr Thr Lys Thr Asn Ile Arg Thr Thr Leu Leu Thr
225 230 235 240
Ser Asn Thr Lys Gly Asn Pro Glu His Thr Ser Gln Glu Glu Thr Leu
245 250 255
His Ser Thr Thr Ser Glu Gly Tyr Leu Ser Pro Ser Gln Val Tyr Thr
260 265 270
Thr Ser Gly Gln Glu Glu Thr Leu His Ser Thr Thr Ser Glu Gly Tyr
275 280 285
Leu Ser Pro Ser Gln Val Tyr Thr Thr Ser Glu Tyr Leu Ser Gln Ser
290 295 300
Leu Ser Ser Ser Asn Thr Thr Lys
305 310
<210> 77
<211> 309
<212> PRT
<213> 人工序列
<220>
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<400> 77
Met Glu Tyr Trp Lys His Thr Asn His Gly Lys Asp Ala Gly Asn Glu
1 5 10 15
Leu Glu Thr Ser Met Ala Thr His Gly Asn Lys Leu Thr Asn Lys Ile
20 25 30
Ala Gln Ile Ala Leu Ser Val Leu Ala Met Ile Ile Ser Thr Ser Leu
35 40 45
Ile Ile Ala Ala Ile Ile Phe Ile Ile Ser Ala Asn His Lys Val Thr
50 55 60
Leu Thr Thr Val Thr Val Gln Thr Ile Lys Asn His Thr Glu Lys Asn
65 70 75 80
Ile Thr Thr Tyr Leu Thr Gln Val Ser Pro Glu Arg Val Ser Pro Ser
85 90 95
Lys Gln Leu Thr Thr Thr Pro Pro Ile Tyr Thr Asn Ser Ala Thr Ile
100 105 110
Ser Pro Asn Thr Lys Ser Glu Thr His His Thr Thr Ala Gln Thr Lys

115 120 125

Gly Arg Thr Thr Thr Pro Thr Gln Asn Asn Lys Pro Ser Thr Lys Pro

130 135 140

Arg Pro Lys Asn Pro Pro Lys Lys Pro Lys Asp Asp Tyr His Phe Glu

145 150 155 160

Val Phe Asn Phe Val Pro Cys Ser Ile Cys Gly Asn Asn Gln Leu Cys

165 170 175

Lys Ser Ile Cys Lys Thr Ile Pro Ser Asn Lys Pro Lys Lys Lys Pro

180 185 190

Thr Ile Lys Pro Thr Asn Lys Pro Pro Thr Lys Thr Thr Asn Lys Arg

195 200 205

Asp Pro Lys Lys Leu Ala Lys Thr Leu Lys Lys Glu Thr Thr Ile Asn

210 215 220

Pro Thr Lys Lys Pro Thr Pro Lys Thr Thr Glu Arg Asp Thr Ser Thr

225 230 235 240

Ser Gln Ser Thr Val Leu Asp Thr Thr Thr Ser Lys His Thr Glu Arg

245 250 255

Asp Thr Ser Thr Ser Gln Ser Thr Val Leu Asp Thr Thr Thr Ser Lys

260 265 270

His Thr Ile Gln Gln Gln Ser Leu His Ser Thr Thr Pro Glu Asn Thr

275 280 285

Pro Asn Ser Thr Gln Thr Pro Thr Ala Ser Glu Pro Ser Thr Ser Asn

290 295 300

Ser Thr Gln Lys Leu

305

<210> 78

<211> 306

<212> PRT

<213> 人工序列

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<223> 重组RSV G蛋白

<400> 78

Met Glu Tyr Trp Lys His Thr Asn His Gly Lys Asp Ala Gly Asn Glu

1 5 10 15

Leu Glu Thr Ser Met Ala Thr His Gly Asn Lys Leu Thr Asn Lys Ile

20 25 30

Ile Tyr Ile Leu Trp Thr Ile Ile Leu Val Leu Leu Ser Ile Val Phe

35 40 45

Ile Ile Val Leu Ile Asn Ser Ile Asn His Lys Val Thr Leu Thr Thr

50 55 60
Val Thr Val Gln Thr Ile Lys Asn His Thr Glu Lys Asn Ile Thr Thr
65 70 75 80
Tyr Leu Thr Gln Val Ser Pro Glu Arg Val Ser Pro Ser Lys Gln Leu
85 90 95
Thr Thr Thr Pro Pro Ile Tyr Thr Asn Ser Ala Thr Ile Ser Pro Asn
100 105 110
Thr Lys Ser Glu Thr His His Thr Thr Ala Gln Thr Lys Gly Arg Thr
115 120 125
Thr Thr Pro Thr Gln Asn Asn Lys Pro Ser Thr Lys Pro Arg Pro Lys
130 135 140
Asn Pro Pro Lys Lys Pro Lys Asp Asp Tyr His Phe Glu Val Phe Asn
145 150 155 160
Phe Val Pro Cys Ser Ile Cys Gly Asn Asn Gln Leu Cys Lys Ser Ile
165 170 175
Cys Lys Thr Ile Pro Ser Asn Lys Pro Lys Lys Lys Pro Thr Ile Lys
180 185 190
Pro Thr Asn Lys Pro Pro Thr Lys Thr Thr Asn Lys Arg Asp Pro Lys
195 200 205
Lys Leu Ala Lys Thr Leu Lys Lys Glu Thr Thr Ile Asn Pro Thr Lys
210 215 220
Lys Pro Thr Pro Lys Thr Thr Glu Arg Asp Thr Ser Thr Ser Gln Ser
225 230 235 240
Thr Val Leu Asp Thr Thr Thr Ser Lys His Thr Glu Arg Asp Thr Ser
245 250 255
Thr Ser Gln Ser Thr Val Leu Asp Thr Thr Thr Ser Lys His Thr Ile
260 265 270
Gln Gln Gln Ser Leu His Ser Thr Thr Pro Glu Asn Thr Pro Asn Ser
275 280 285
Thr Gln Thr Pro Thr Ala Ser Glu Pro Ser Thr Ser Asn Ser Thr Gln
290 295 300
Lys Leu
305
<210> 79
<211> 296
<212> PRT
<213> 人工序列
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<223> 重组RSV G蛋白

<400> 79

Met Ala Glu Lys Gly Lys Thr Asn Ser Ser Tyr Trp Ser Thr Thr Arg
1 5 10 15

Asn Asp Asn Ser Thr Val Asn Thr His Ile Asn Thr Pro Ala Gly Arg
20 25 30

Thr His Trp Val Ala Gln Ile Thr Leu Ser Ile Leu Ala Met Ile Ile
35 40 45

Ser Thr Ser Leu Ile Ile Ala Ala Ile Ile Phe Ile Ala Ser Ala Asn
50 55 60

His Lys Val Thr Pro Thr Thr Ala Ile Ile Gln Asp Ala Thr Ser Gln
65 70 75 80

Ile Lys Asn Thr Thr Pro Thr Tyr Leu Thr Gln Asn Pro Gln Leu Gly
85 90 95

Ile Ser Pro Ser Asn Pro Ser Glu Ile Thr Ser Gln Ile Thr Thr Ile
100 105 110

Leu Ala Ser Thr Thr Pro Gly Val Lys Ser Thr Leu Gln Ser Thr Thr
115 120 125

Val Lys Thr Lys Asn Thr Thr Thr Thr Gln Thr Gln Pro Ser Lys Pro
130 135 140

Thr Thr Lys Gln Arg Gln Asn Lys Pro Pro Ser Lys Pro Asn Asn Asp
145 150 155 160

Phe His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Ser Asn
165 170 175

Asn Pro Thr Cys Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys Lys Pro
180 185 190

Gly Lys Lys Thr Thr Thr Lys Pro Thr Lys Lys Pro Thr Leu Lys Thr
195 200 205

Thr Lys Lys Asp Pro Lys Pro Gln Thr Thr Lys Ser Lys Glu Val Pro
210 215 220

Thr Thr Lys Pro Thr Glu Glu Pro Thr Ile Asn Thr Thr Lys Thr Asn
225 230 235 240

Ile Ile Thr Thr Leu Leu Thr Ser Asn Thr Thr Gly Asn Pro Glu Leu
245 250 255

Thr Ser Gln Met Glu Thr Phe His Ser Thr Ser Ser Glu Gly Asn Pro
260 265 270

Ser Pro Ser Gln Val Ser Thr Thr Ser Glu Tyr Pro Ser Gln Pro Ser
275 280 285

Ser Pro Pro Asn Thr Pro Arg Gln
290 295

<210> 80
<211> 293
<212> PRT
<213> 人工序列
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<223> 重组RSV G蛋白
<400> 80

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

Met Glu Thr Phe His Ser Thr Ser Ser Glu Gly Asn Pro Ser Pro Ser
260 265 270

Gln Val Ser Thr Thr Ser Glu Tyr Pro Ser Gln Pro Ser Ser Pro Pro
275 280 285

Asn Thr Pro Arg Gln
290

<210> 81

<211> 297

<212> PRT

<213> 人工序列

<220>

<223> 重组RSV G蛋白

<400> 81

Met Ala Glu Lys Gly Lys Thr Asn Ser Ser Tyr Trp Ser Thr Thr Arg
1 5 10 15

Asn Asp Asn Ser Thr Val Asn Thr His Ile Asn Thr Pro Ala Gly Arg
20 25 30

Thr His Trp Ile Ala Gln Ile Ala Leu Ser Val Leu Ala Met Ile Ile
35 40 45

Ser Thr Ser Leu Ile Ile Ala Ala Ile Ile Phe Ile Ile Ser Ala Asn
50 55 60

His Lys Val Thr Leu Thr Thr Val Thr Val Gln Thr Ile Lys Asn His
65 70 75 80

Thr Glu Lys Asn Ile Thr Thr Tyr Leu Thr Gln Val Pro Pro Glu Arg
85 90 95

Val Ser Ser Ser Lys Gln Pro Thr Thr Thr Ser Pro Ile His Thr Asn
100 105 110

Ser Ala Thr Thr Ser Pro Asn Thr Lys Ser Glu Thr His His Thr Thr
115 120 125

Ala Gln Thr Lys Gly Arg Thr Thr Thr Ser Thr Gln Thr Asn Lys Pro
130 135 140

Ser Thr Lys Pro Arg Leu Lys Asn Pro Pro Lys Lys Pro Lys Asp Asp
145 150 155 160

Tyr His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Gly Asn
165 170 175

Asn Gln Leu Cys Lys Ser Ile Cys Lys Thr Ile Pro Ser Asn Lys Pro
180 185 190

Lys Lys Lys Pro Thr Ile Lys Pro Thr Asn Lys Pro Thr Thr Lys Thr
195 200 205

Thr Asn Lys Arg Asp Pro Lys Thr Pro Ala Lys Thr Thr Lys Lys Glu
210 215 220
Thr Thr Thr Asn Pro Thr Lys Lys Pro Thr Leu Thr Thr Thr Glu Arg
225 230 235 240
Asp Thr Ser Thr Ser Gln Ser Thr Val Leu Asp Thr Thr Thr Leu Glu
245 250 255
His Thr Ile Gln Gln Gln Ser Leu His Ser Thr Thr Pro Glu Asn Thr
260 265 270
Pro Asn Ser Thr Gln Thr Pro Thr Ala Ser Glu Pro Ser Thr Ser Asn
275 280 285
Ser Thr Gln Asn Thr Gln Ser His Ala
290 295
<210> 82
<211> 294
<212> PRT
<213> 人工序列
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<223> 重组RSV G蛋白
<400> 82
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1 5 10 15
Asn Asp Asn Ser Thr Val Asn Thr His Ile Asn Thr Pro Ala Gly Arg
20 25 30
Thr His Trp Ile Leu Leu Ile Ala Thr Thr Met His Thr Val Leu Ser
35 40 45
Phe Ile Ile Met Ile Leu Cys Ile Asp Leu Ile Ile Asn His Lys Val
50 55 60
Thr Leu Thr Thr Val Thr Val Gln Thr Ile Lys Asn His Thr Glu Lys
65 70 75 80
Asn Ile Thr Thr Tyr Leu Thr Gln Val Pro Pro Glu Arg Val Ser Ser
85 90 95
Ser Lys Gln Pro Thr Thr Thr Ser Pro Ile His Thr Asn Ser Ala Thr
100 105 110
Thr Ser Pro Asn Thr Lys Ser Glu Thr His His Thr Thr Ala Gln Thr
115 120 125
Lys Gly Arg Thr Thr Thr Ser Thr Gln Thr Asn Lys Pro Ser Thr Lys
130 135 140
Pro Arg Leu Lys Asn Pro Pro Lys Lys Pro Lys Asp Asp Tyr His Phe
145 150 155 160

Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Gly Asn Asn Gln Leu
165 170 175
Cys Lys Ser Ile Cys Lys Thr Ile Pro Ser Asn Lys Pro Lys Lys Lys
180 185 190
Pro Thr Ile Lys Pro Thr Asn Lys Pro Thr Thr Lys Thr Thr Asn Lys
195 200 205
Arg Asp Pro Lys Thr Pro Ala Lys Thr Thr Lys Lys Glu Thr Thr Thr
210 215 220
Asn Pro Thr Lys Lys Pro Thr Leu Thr Thr Thr Glu Arg Asp Thr Ser
225 230 235 240
Thr Ser Gln Ser Thr Val Leu Asp Thr Thr Thr Leu Glu His Thr Ile
245 250 255
Gln Gln Gln Ser Leu His Ser Thr Thr Pro Glu Asn Thr Pro Asn Ser
260 265 270
Thr Gln Thr Pro Thr Ala Ser Glu Pro Ser Thr Ser Asn Ser Thr Gln
275 280 285
Asn Thr Gln Ser His Ala
290

<210> 83
<211> 296
<212> PRT
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<223> 重组RSV G蛋白
<400> 83

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

Leu Ala Leu Thr Thr Pro Asn Ala Glu Ser Thr Pro Gln Ser Thr Thr
115 120 125
Val Lys Thr Lys Asn Thr Thr Thr Thr Gln Ile Gln Pro Ser Lys Pro
130 135 140
Thr Thr Lys Gln Arg Gln Asn Lys Pro Gln Asn Lys Pro Asn Asn Asp
145 150 155 160
Phe His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Ser Asn
165 170 175
Asn Pro Thr Cys Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys Lys Pro
180 185 190
Gly Arg Lys Thr Thr Thr Lys Pro Thr Lys Gln Pro Ala Ile Lys Thr
195 200 205
Thr Lys Lys Asp Pro Lys Pro Gln Thr Thr Lys Pro Lys Glu Val Leu
210 215 220
Thr Thr Lys Pro Thr Glu Lys Pro Thr Ile Asn Thr Thr Lys Thr Asn
225 230 235 240
Ile Arg Thr Thr Leu Leu Thr Ser Asn Ile Thr Glu Asn Gln Glu His
245 250 255
Thr Ser Gln Lys Glu Thr Leu His Ser Thr Thr Ser Glu Gly Asn Pro
260 265 270
Ser Pro Ser Gln Val Tyr Thr Thr Ser Glu Tyr Leu Ser Gln Ser Leu
275 280 285
Ser Pro Ser Asn Thr Thr Arg Trp
290 295
<210> 84
<211> 293
<212> PRT
<213> 人工序列
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<223> 重组RSV G蛋白
<400> 84
Met Ala Glu Lys Gly Lys Thr Asn Ser Ser Tyr Trp Ser Thr Thr Arg
1 5 10 15
Asn Asp Asn Ser Thr Val Asn Thr His Ile Asn Thr Pro Ala Gly Arg
20 25 30
Thr His Trp Ile Leu Leu Ile Ala Thr Thr Met His Thr Val Leu Ser
35 40 45
Phe Ile Ile Met Ile Leu Cys Ile Asp Leu Ile Ile Asn His Lys Val
50 55 60

Thr Leu Thr Thr Ala Ile Ile Gln Asp Ala Thr Asn Gln Ile Lys Asn
65 70 75 80
Thr Thr Pro Thr Tyr Leu Thr Gln Asn Pro Gln Leu Gly Ile Ser Leu
85 90 95
Ser Asn Leu Ser Glu Thr Thr Ser Lys Pro Thr Thr Ile Leu Ala Leu
100 105 110
Thr Thr Pro Asn Ala Glu Ser Thr Pro Gln Ser Thr Thr Val Lys Thr
115 120 125
Lys Asn Thr Thr Thr Thr Gln Ile Gln Pro Ser Lys Pro Thr Thr Lys
130 135 140
Gln Arg Gln Asn Lys Pro Gln Asn Lys Pro Asn Asn Asp Phe His Phe
145 150 155 160
Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Ser Asn Asn Pro Thr
165 170 175
Cys Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys Lys Pro Gly Arg Lys
180 185 190
Thr Thr Thr Lys Pro Thr Lys Gln Pro Ala Ile Lys Thr Thr Lys Lys
195 200 205
Asp Pro Lys Pro Gln Thr Thr Lys Pro Lys Glu Val Leu Thr Thr Lys
210 215 220
Pro Thr Glu Lys Pro Thr Ile Asn Thr Thr Lys Thr Asn Ile Arg Thr
225 230 235 240
Thr Leu Leu Thr Ser Asn Ile Thr Glu Asn Gln Glu His Thr Ser Gln
245 250 255
Lys Glu Thr Leu His Ser Thr Thr Ser Glu Gly Asn Pro Ser Pro Ser
260 265 270
Gln Val Tyr Thr Thr Ser Glu Tyr Leu Ser Gln Ser Leu Ser Pro Ser
275 280 285
Asn Thr Thr Arg Trp
290
<210> 85
<211> 319
<212> PRT
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<400> 85
Met Ala Glu Lys Gly Lys Thr Asn Ser Ser Tyr Trp Ser Thr Thr Arg
1 5 10 15

Asn Asp Asn Ser Thr Val Asn Thr His Ile Asn Thr Pro Ala Gly Arg
20 25 30
Thr His Trp Ile Ala Gln Ile Thr Leu Ser Ile Leu Ala Met Ile Ile
35 40 45
Ser Thr Ser Leu Ile Ile Ala Ala Ile Ile Phe Ile Ala Ser Ala Asn
50 55 60
His Lys Val Thr Leu Thr Thr Ala Ile Ile Gln Asp Ala Thr Asn Gln
65 70 75 80
Ile Lys Asn Thr Thr Pro Thr Tyr Leu Thr Gln Asn Pro Gln Leu Gly
85 90 95
Ile Ser Phe Ser Asn Leu Ser Gly Thr Thr Ser Gln Ser Thr Thr Ile
100 105 110
Leu Ala Ser Thr Thr Pro Ser Ala Glu Ser Thr Pro Gln Ser Thr Thr
115 120 125
Val Lys Ile Lys Asn Thr Thr Thr Thr Gln Ile Leu Pro Ser Lys Pro
130 135 140
Thr Thr Lys Gln Arg Gln Asn Lys Pro Gln Asn Lys Pro Asn Asn Asp
145 150 155 160
Phe His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Ser Asn
165 170 175
Asn Pro Thr Cys Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys Lys Pro
180 185 190
Gly Lys Lys Thr Thr Thr Lys Pro Thr Lys Lys Pro Thr Leu Lys Thr
195 200 205
Thr Lys Lys Asp Pro Lys Pro Gln Thr Thr Lys Pro Lys Glu Val Leu
210 215 220
Thr Thr Lys Pro Thr Gly Lys Pro Thr Ile Asn Thr Thr Lys Thr Asn
225 230 235 240
Ile Arg Thr Thr Leu Leu Thr Ser Asn Thr Lys Gly Asn Pro Glu His
245 250 255
Thr Ser Gln Glu Glu Thr Leu His Ser Thr Thr Ser Glu Gly Tyr Leu
260 265 270
Ser Pro Ser Gln Val Tyr Thr Thr Ser Gly Gln Glu Glu Thr Leu His
275 280 285
Ser Thr Thr Ser Glu Gly Tyr Leu Ser Pro Ser Gln Val Tyr Thr Thr
290 295 300
Ser Glu Tyr Leu Ser Gln Ser Leu Ser Ser Ser Asn Thr Thr Lys
305 310 315
<210> 86

<211> 316

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<400> 86

Met Ala Glu Lys Gly Lys Thr Asn Ser Ser Tyr Trp Ser Thr Thr Arg
1 5 10 15

Asn Asp Asn Ser Thr Val Asn Thr His Ile Asn Thr Pro Ala Gly Arg
20 25 30

Thr His Trp Ile Leu Leu Ile Ala Thr Thr Met His Thr Val Leu Ser
35 40 45

Phe Ile Ile Met Ile Leu Cys Ile Asp Leu Ile Ile Asn His Lys Val
50 55 60

Thr Leu Thr Thr Ala Ile Ile Gln Asp Ala Thr Asn Gln Ile Lys Asn
65 70 75 80

Thr Thr Pro Thr Tyr Leu Thr Gln Asn Pro Gln Leu Gly Ile Ser Phe
85 90 95

Ser Asn Leu Ser Gly Thr Thr Ser Gln Ser Thr Thr Ile Leu Ala Ser
100 105 110

Thr Thr Pro Ser Ala Glu Ser Thr Pro Gln Ser Thr Thr Val Lys Ile
115 120 125

Lys Asn Thr Thr Thr Thr Gln Ile Leu Pro Ser Lys Pro Thr Thr Lys
130 135 140

Gln Arg Gln Asn Lys Pro Gln Asn Lys Pro Asn Asn Asp Phe His Phe
145 150 155 160

Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Ser Asn Asn Pro Thr
165 170 175

Cys Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys Lys Pro Gly Lys Lys
180 185 190

Thr Thr Thr Lys Pro Thr Lys Lys Pro Thr Leu Lys Thr Thr Lys Lys
195 200 205

Asp Pro Lys Pro Gln Thr Thr Lys Pro Lys Glu Val Leu Thr Thr Lys
210 215 220

Pro Thr Gly Lys Pro Thr Ile Asn Thr Thr Lys Thr Asn Ile Arg Thr
225 230 235 240

Thr Leu Leu Thr Ser Asn Thr Lys Gly Asn Pro Glu His Thr Ser Gln
245 250 255

Glu Glu Thr Leu His Ser Thr Thr Ser Glu Gly Tyr Leu Ser Pro Ser

260 265 270
Gln Val Tyr Thr Thr Ser Gly Gln Glu Glu Thr Leu His Ser Thr Thr
275 280 285
Ser Glu Gly Tyr Leu Ser Pro Ser Gln Val Tyr Thr Thr Ser Glu Tyr
290 295 300
Leu Ser Gln Ser Leu Ser Ser Ser Asn Thr Thr Lys
305 310 315
<210> 87
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<400> 87
Met Ala Glu Lys Gly Lys Thr Asn Ser Ser Tyr Trp Ser Thr Thr Arg
1 5 10 15
Asn Asp Asn Ser Thr Val Asn Thr His Ile Asn Thr Pro Ala Gly Arg
20 25 30
Thr His Trp Ile Ala Gln Ile Ala Leu Ser Val Leu Ala Met Ile Ile
35 40 45
Ser Thr Ser Leu Ile Ile Ala Ala Ile Ile Phe Ile Ile Ser Ala Asn
50 55 60
His Lys Val Thr Leu Thr Thr Val Thr Val Gln Thr Ile Lys Asn His
65 70 75 80
Thr Glu Lys Asn Ile Thr Thr Tyr Leu Thr Gln Val Ser Pro Glu Arg
85 90 95
Val Ser Pro Ser Lys Gln Leu Thr Thr Thr Pro Pro Ile Tyr Thr Asn
100 105 110
Ser Ala Thr Ile Ser Pro Asn Thr Lys Ser Glu Thr His His Thr Thr
115 120 125
Ala Gln Thr Lys Gly Arg Thr Thr Thr Pro Thr Gln Asn Asn Lys Pro
130 135 140
Ser Thr Lys Pro Arg Pro Lys Asn Pro Pro Lys Lys Pro Lys Asp Asp
145 150 155 160
Tyr His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Gly Asn
165 170 175
Asn Gln Leu Cys Lys Ser Ile Cys Lys Thr Ile Pro Ser Asn Lys Pro
180 185 190
Lys Lys Lys Pro Thr Ile Lys Pro Thr Asn Lys Pro Pro Thr Lys Thr

195 200 205
Thr Asn Lys Arg Asp Pro Lys Lys Leu Ala Lys Thr Leu Lys Lys Glu
210 215 220
Thr Thr Ile Asn Pro Thr Lys Lys Pro Thr Pro Lys Thr Thr Glu Arg
225 230 235 240
Asp Thr Ser Thr Ser Gln Ser Thr Val Leu Asp Thr Thr Thr Ser Lys
245 250 255
His Thr Glu Arg Asp Thr Ser Thr Ser Gln Ser Thr Val Leu Asp Thr
260 265 270
Thr Thr Ser Lys His Thr Ile Gln Gln Gln Ser Leu His Ser Thr Thr
275 280 285
Pro Glu Asn Thr Pro Asn Ser Thr Gln Thr Pro Thr Ala Ser Glu Pro
290 295 300
Ser Thr Ser Asn Ser Thr Gln Lys Leu
305 310
<210> 88
<211> 310
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<400> 88
Met Ala Glu Lys Gly Lys Thr Asn Ser Ser Tyr Trp Ser Thr Thr Arg
1 5 10 15
Asn Asp Asn Ser Thr Val Asn Thr His Ile Asn Thr Pro Ala Gly Arg
20 25 30
Thr His Trp Ile Leu Leu Ile Ala Thr Thr Met His Thr Val Leu Ser
35 40 45
Phe Ile Ile Met Ile Leu Cys Ile Asp Leu Ile Ile Asn His Lys Val
50 55 60
Thr Leu Thr Thr Val Thr Val Gln Thr Ile Lys Asn His Thr Glu Lys
65 70 75 80
Asn Ile Thr Thr Tyr Leu Thr Gln Val Ser Pro Glu Arg Val Ser Pro
85 90 95
Ser Lys Gln Leu Thr Thr Thr Pro Pro Ile Tyr Thr Asn Ser Ala Thr
100 105 110
Ile Ser Pro Asn Thr Lys Ser Glu Thr His His Thr Thr Ala Gln Thr
115 120 125
Lys Gly Arg Thr Thr Thr Pro Thr Gln Asn Asn Lys Pro Ser Thr Lys

130 135 140
Pro Arg Pro Lys Asn Pro Pro Lys Lys Pro Lys Asp Asp Tyr His Phe
145 150 155 160
Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys Gly Asn Asn Gln Leu
165 170 175
Cys Lys Ser Ile Cys Lys Thr Ile Pro Ser Asn Lys Pro Lys Lys Lys
180 185 190
Pro Thr Ile Lys Pro Thr Asn Lys Pro Pro Thr Lys Thr Thr Asn Lys
195 200 205
Arg Asp Pro Lys Lys Leu Ala Lys Thr Leu Lys Lys Glu Thr Thr Ile
210 215 220
Asn Pro Thr Lys Lys Pro Thr Pro Lys Thr Thr Glu Arg Asp Thr Ser
225 230 235 240
Thr Ser Gln Ser Thr Val Leu Asp Thr Thr Thr Ser Lys His Thr Glu
245 250 255
Arg Asp Thr Ser Thr Ser Gln Ser Thr Val Leu Asp Thr Thr Thr Ser
260 265 270
Lys His Thr Ile Gln Gln Gln Ser Leu His Ser Thr Thr Pro Glu Asn
275 280 285
Thr Pro Asn Ser Thr Gln Thr Pro Thr Ala Ser Glu Pro Ser Thr Ser
290 295 300
Asn Ser Thr Gln Lys Leu
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atcaccctgt caattctggc tatgatcatt tcaacaagcc tgatcattgc cgctatcatt 180
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ccatctaacc cctcagagat taccagccag atcacaacta ttctggcctc caccacacct 360
ggcgtgaagt ccactctgca gtctactacc gtcaagacca aaaatacaac taccacacag 420
acacagcctt ctaagccaac taccaaacag cggcagaata agccccctag taaaccaaac 480
aatgacttcc attttgaggt gttcaacttt gtcccatgca gcatctgttc caacaatccc 540

acctgctggg ccatctgtaa gagaattcca aacaagaaac ccggcaagaa gaccactacc 600
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aagtctaaag aagtgcccac taccaagcct acagaggaac caactatcaa cacaactaag 720
actaacatca tcaccacact gctgacaagc aacactaccg gcaatcccga gctgaccagc 780
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<210> 90
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<212> DNA
<213> 人工序列
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<400> 90
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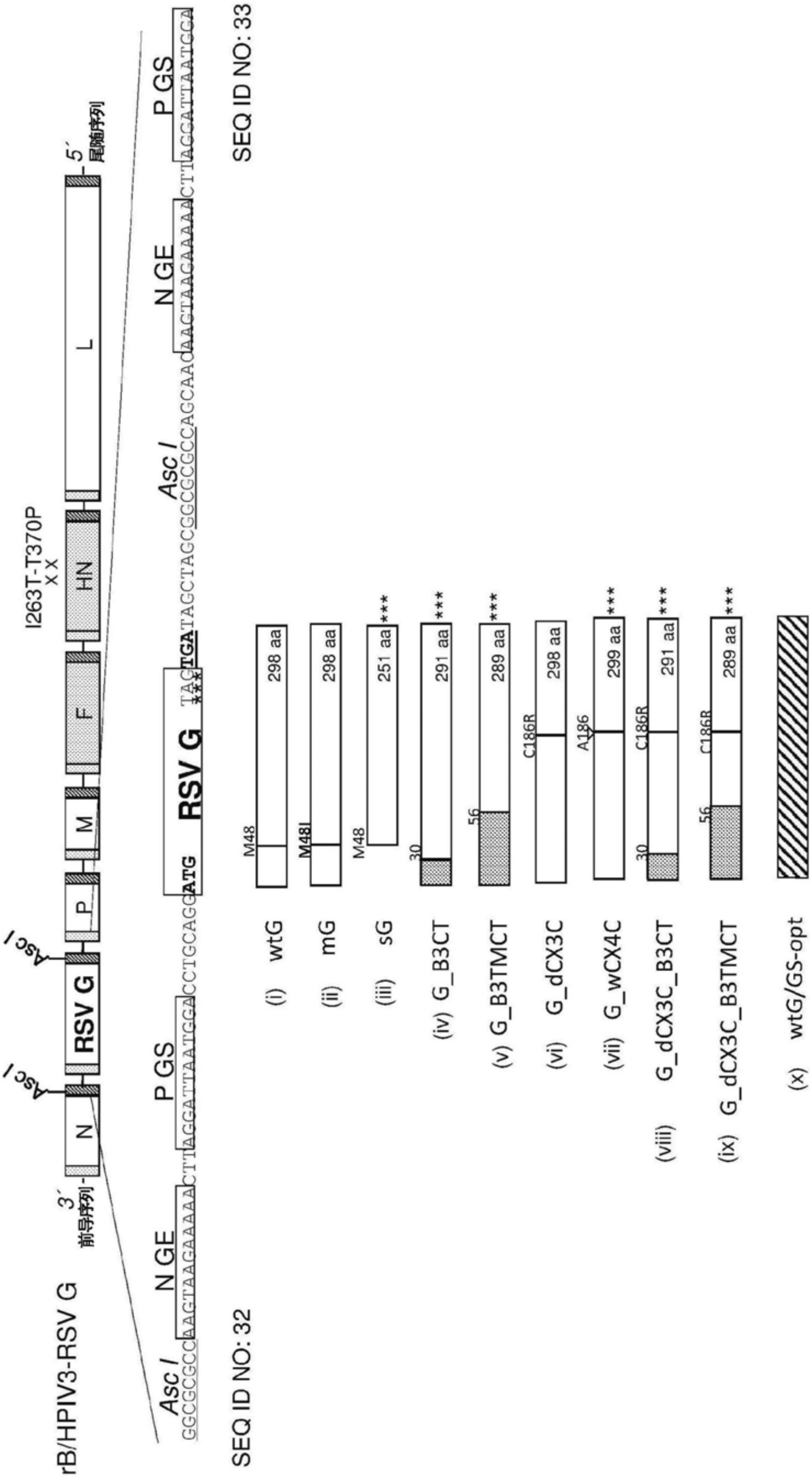
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L
5′
尾随序列
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图1A

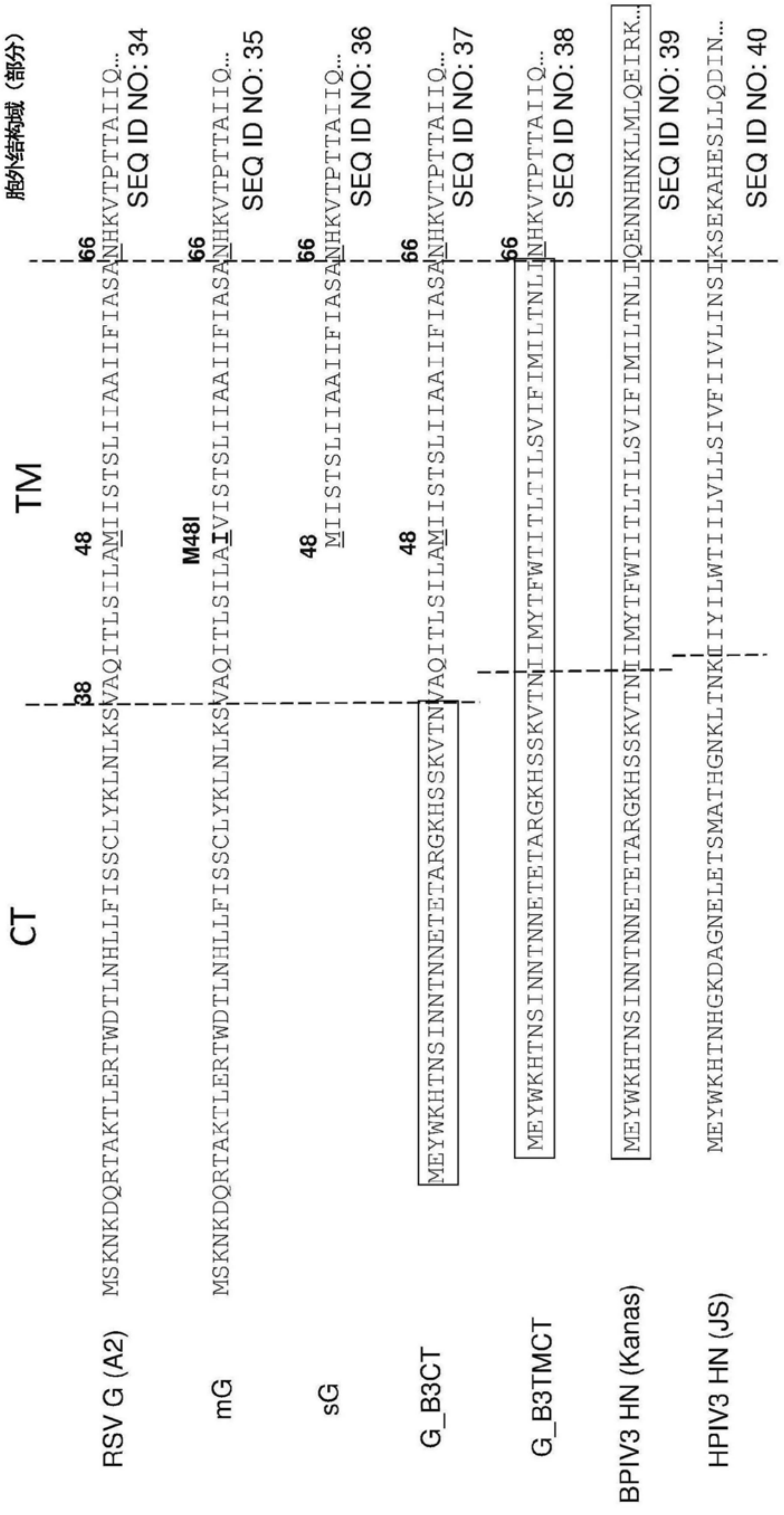
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图1B

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未经修饰的CX3C	**C** TGC	W TGG	A GCT	I ATC	**C** TGC	
dCX3C	**C** TGC	W TGG	A GCT	I ATC	R CGC	
wCX4C	**C** TGC	W TGG	A GCT	I ATC	A GCA	**C** TGC

图1C

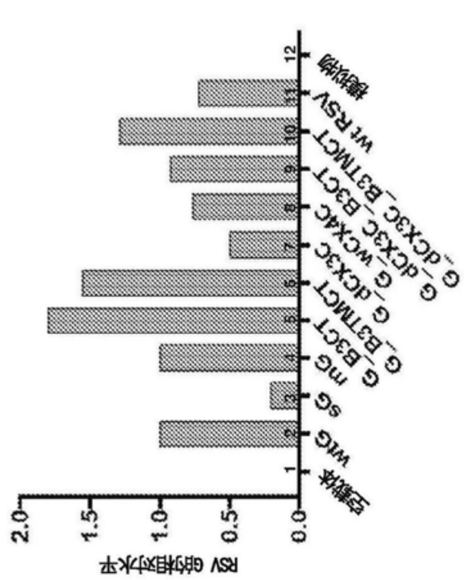


图2B

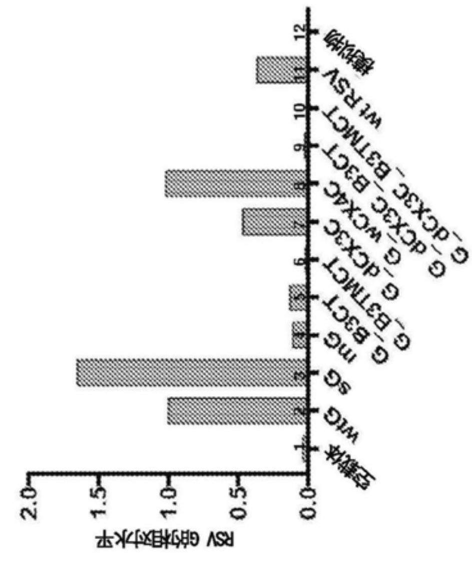


图2D

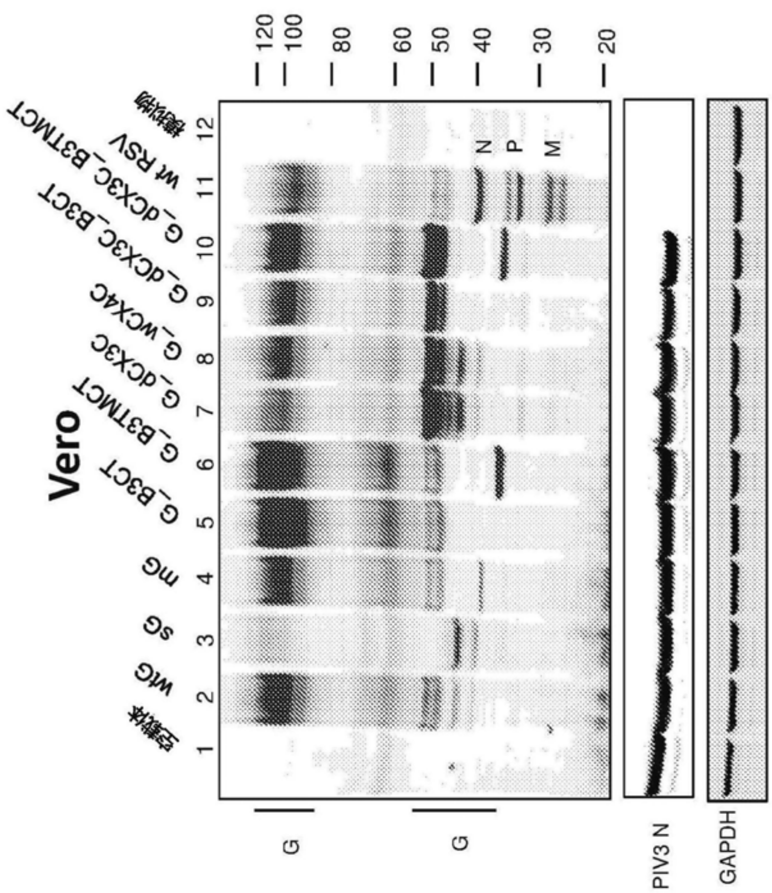


图2A

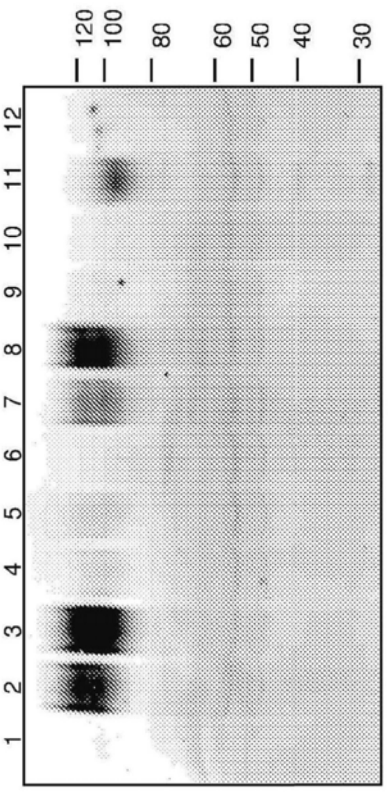
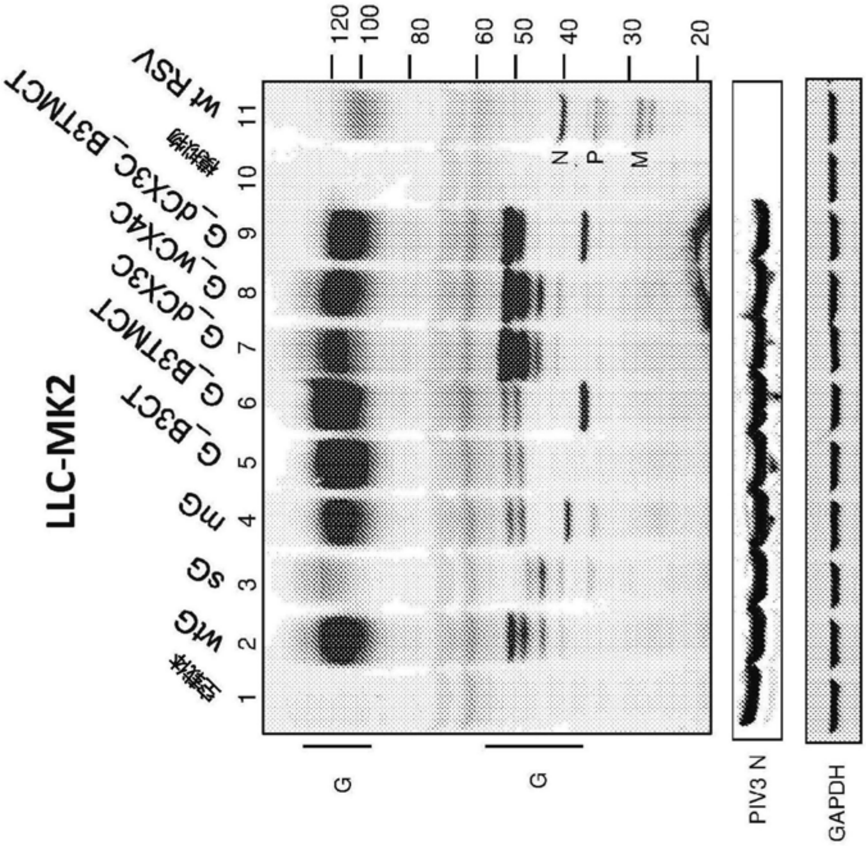


图2C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10
11
wtG
sG
mG
G_B3CT
G_B3TMCT
G_dCX3C
G_wCX4C
G_dCX3C_B3TMCT
wt RSV
120
100
80
60
50
40
30
20
N
P
M
G
G
PIV3 N
GAPDH

图3A

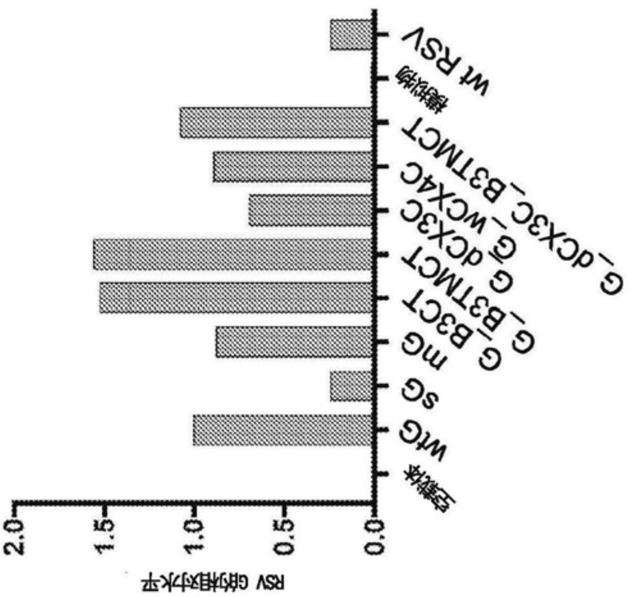

RSV G的相对水平
0.0
0.5
1.0
1.5
2.0
wtG
sG
mG
G_B3CT
G_B3TMCT
G_dCX3C
G_wCX4C
G_dCX3C_B3TMCT
wt RSV

图3B

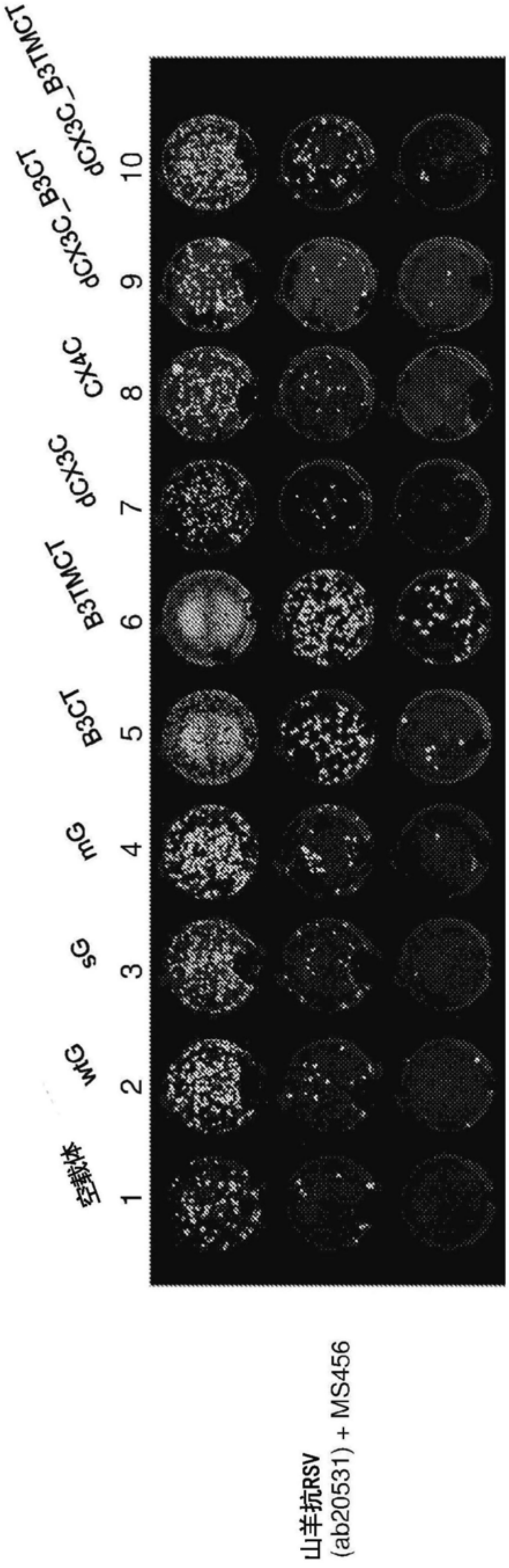

1 空载体
2 wtG
3 sG
4 mG
5 B3CT
6 B3TMCT
7 dCX3C
8 CX4C
9 dCX3C_B3CT
10 dCX3C_B3TMCT
山羊抗RSV
(ab20531) + MS456

图4A

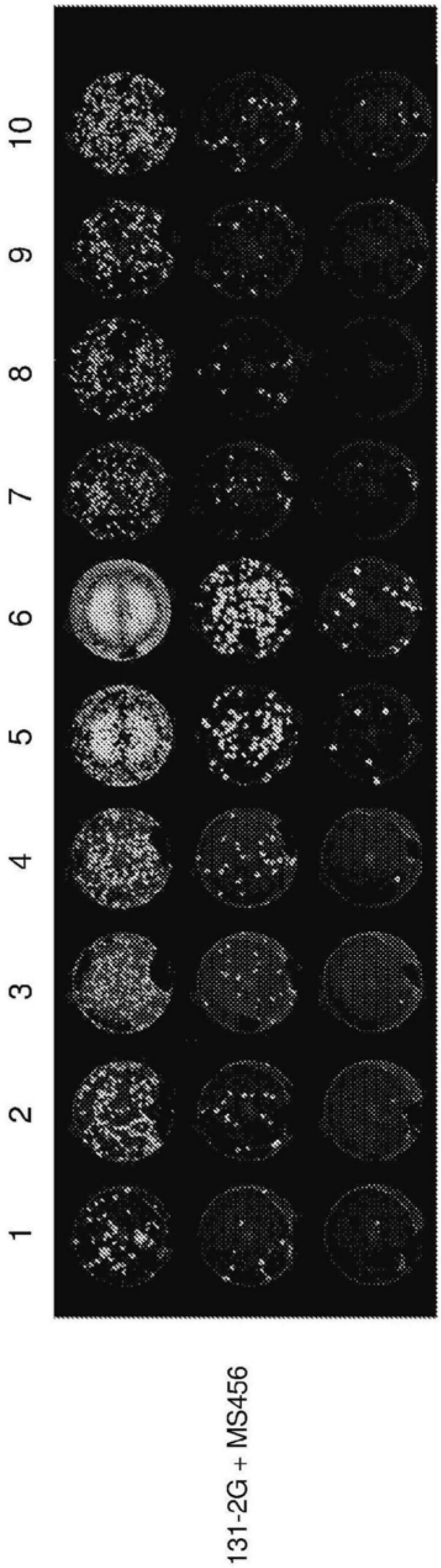
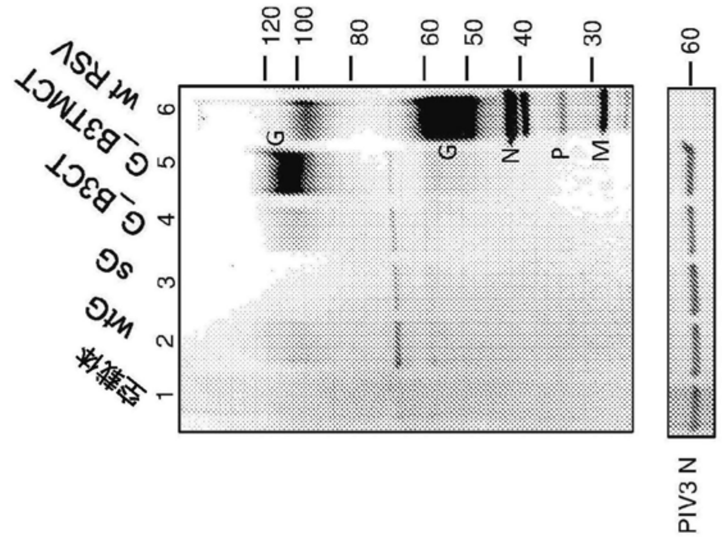
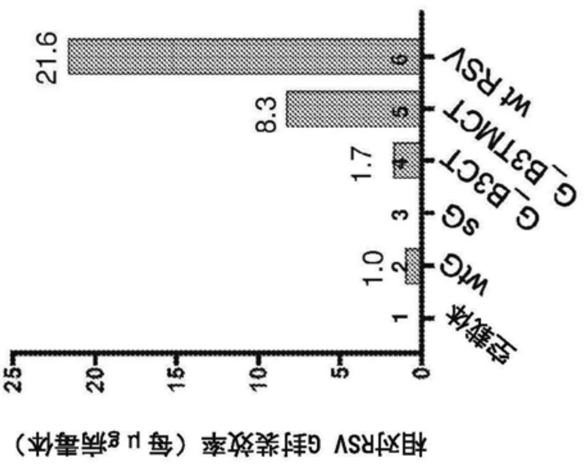


图4B



空载体
wtG
sG
G_B3CT
G_B3TMCT
wt RSV
1 2 3 4 5 6
120
100
80
60
50
40
30
G
G
N
P
M
60
PIV3 N

图5A



相对RSV G封装效率（每μg病毒体）
0 5 10 15 20 25
空载体
wtG
sG
G_B3CT
G_B3TMCT
wt RSV
1.0
1.7
8.3
21.6

图5B

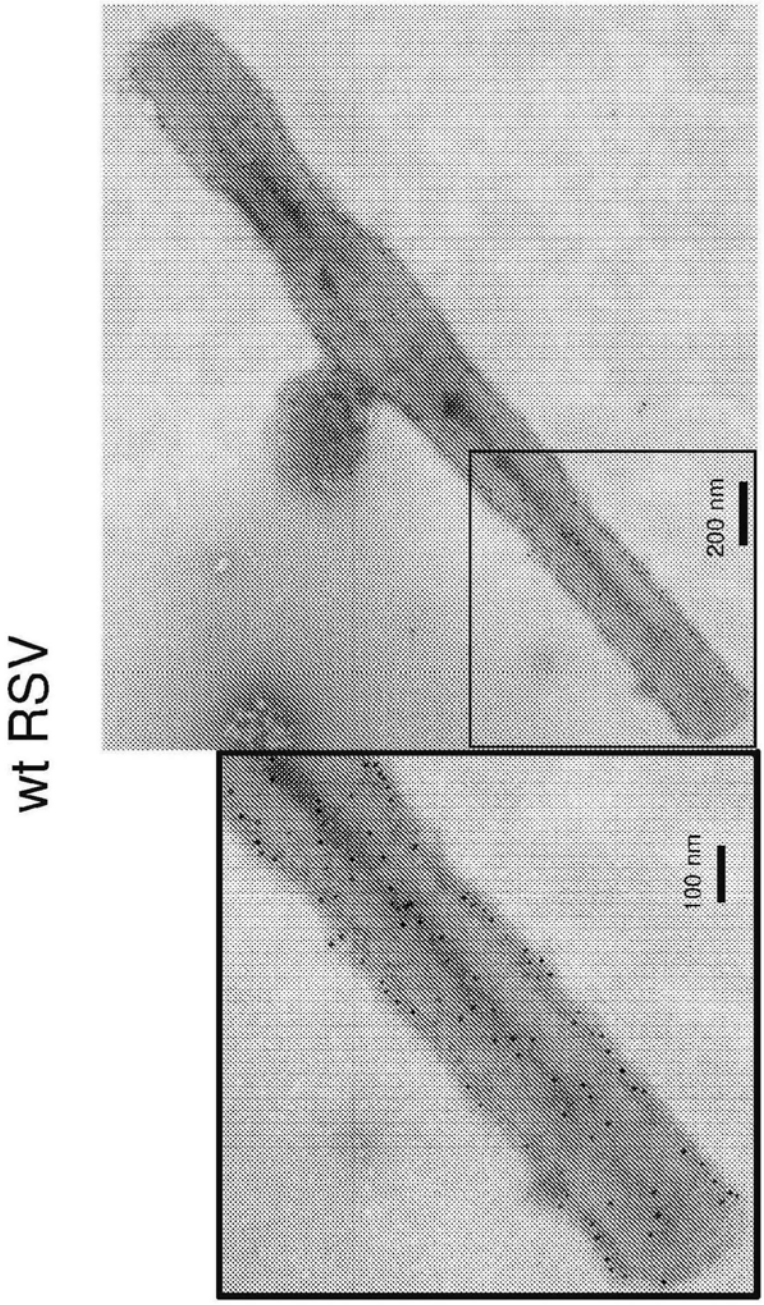


图6A

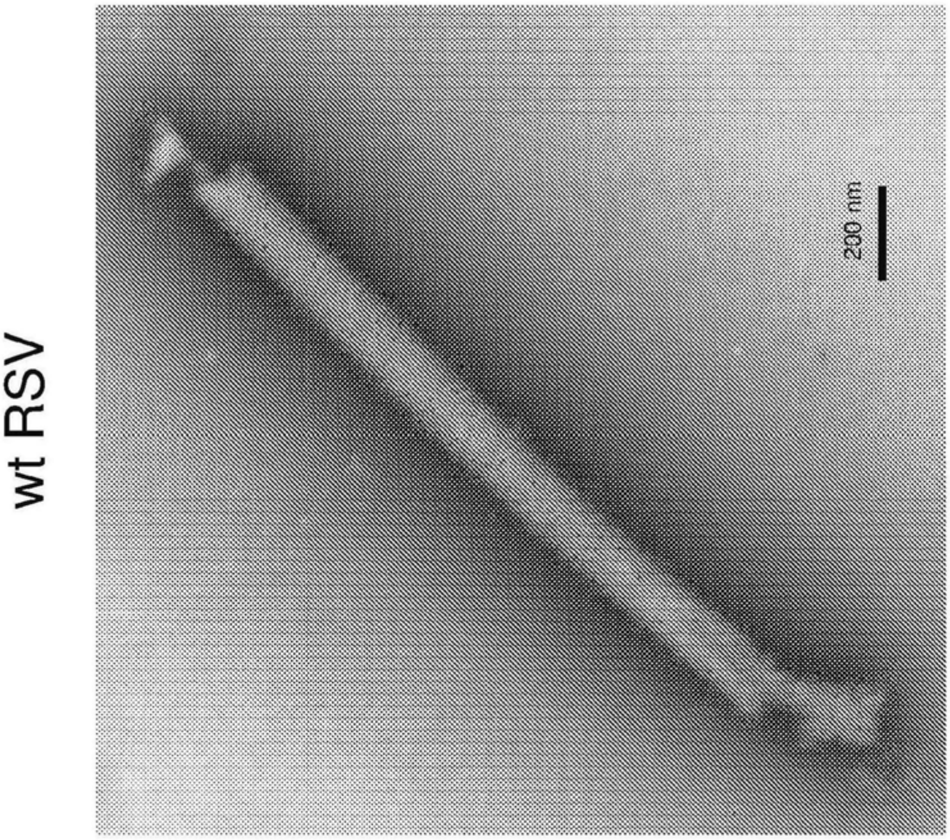


图6B

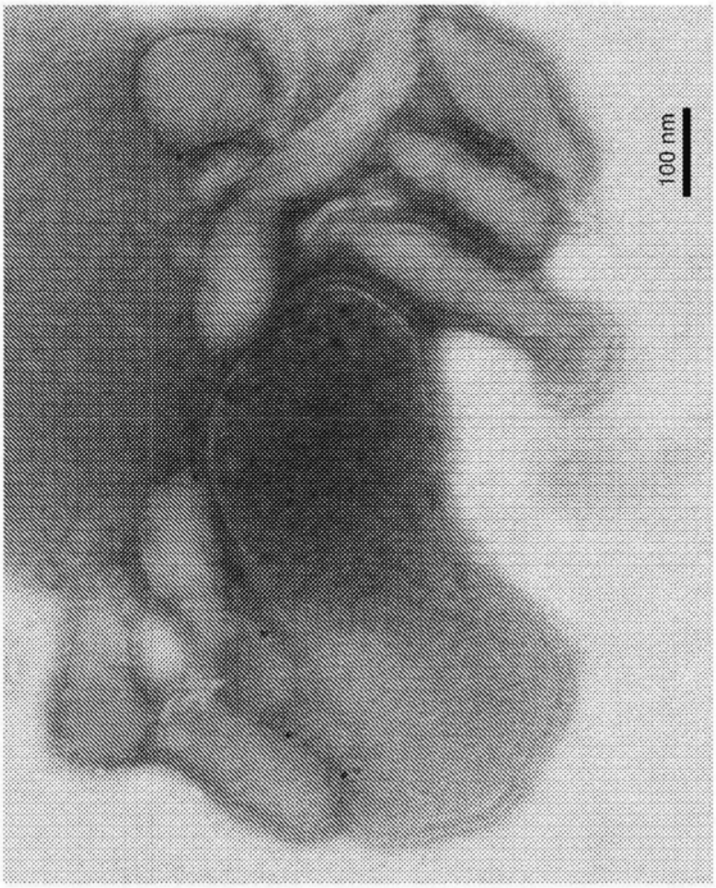


图6D

rB/HPIV3-wt G

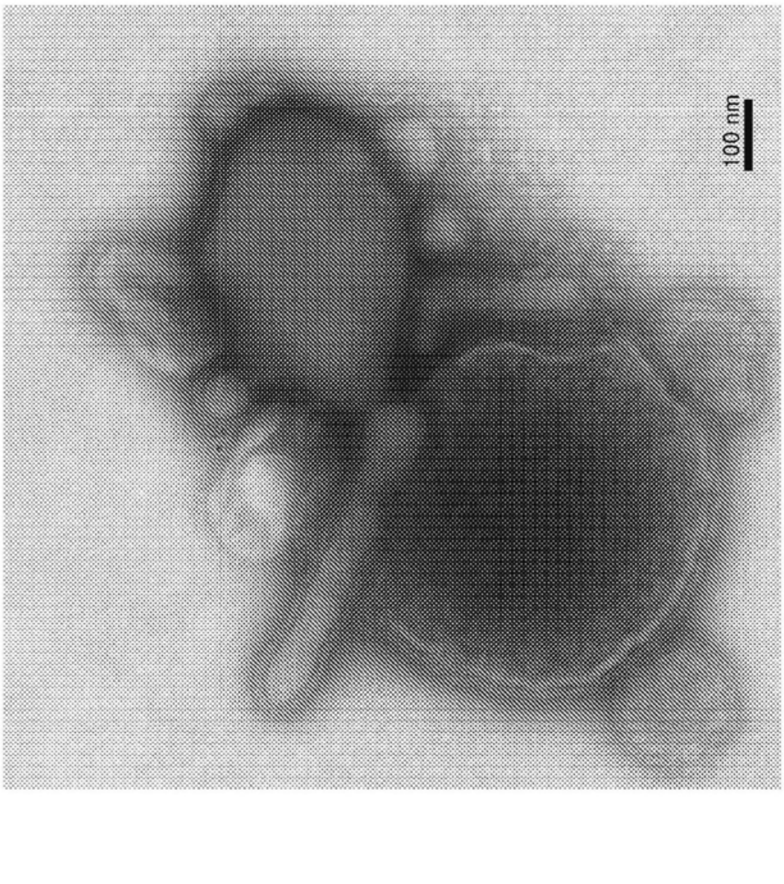


图6C

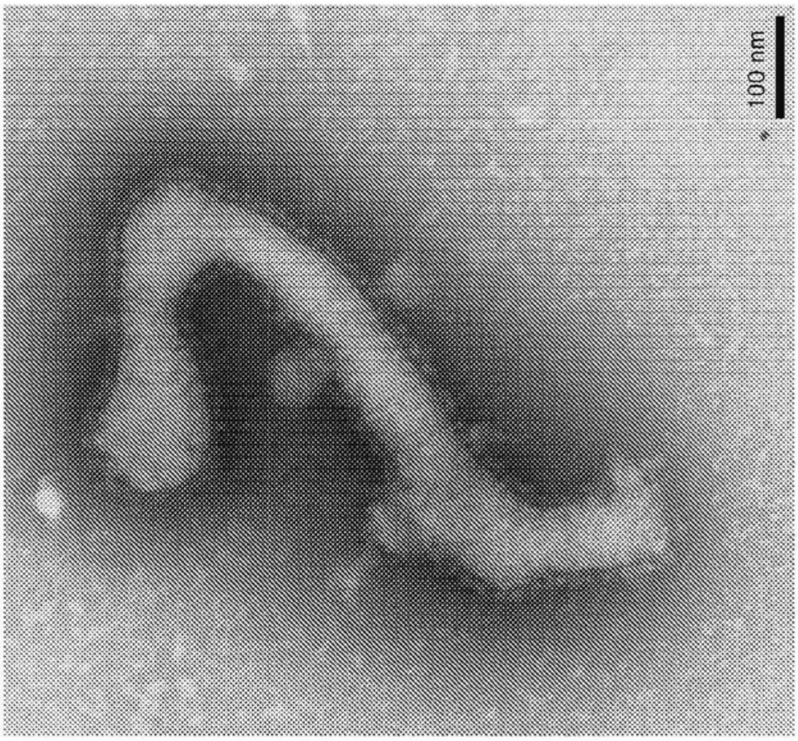


图6E

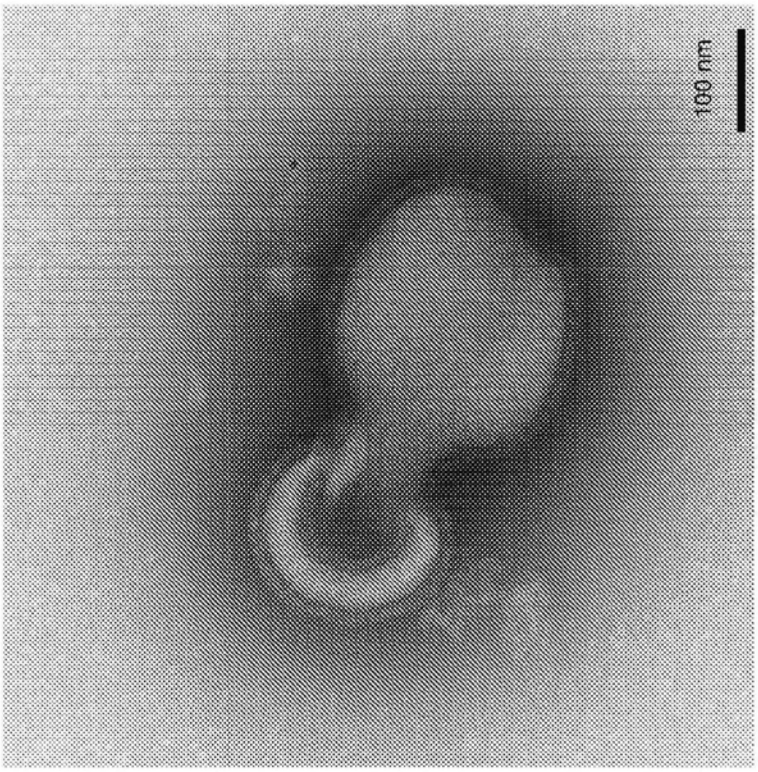


图6F

rB/HPIV3-sG

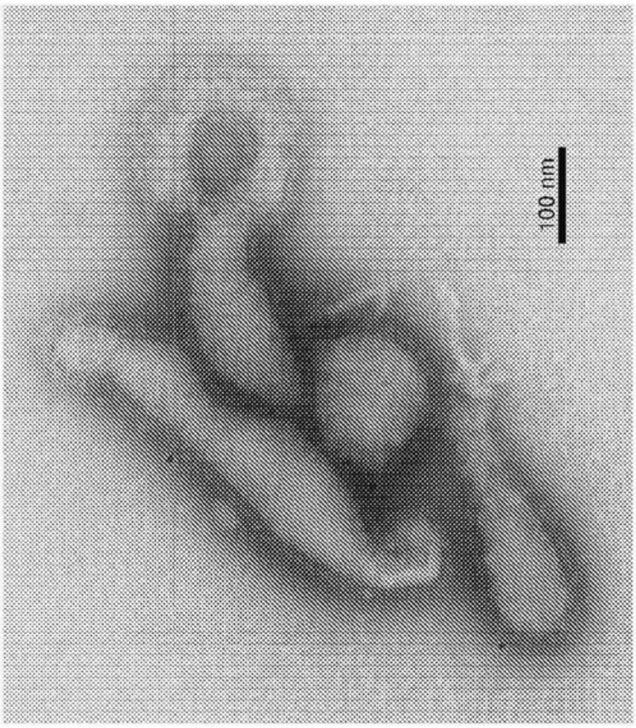


图6G

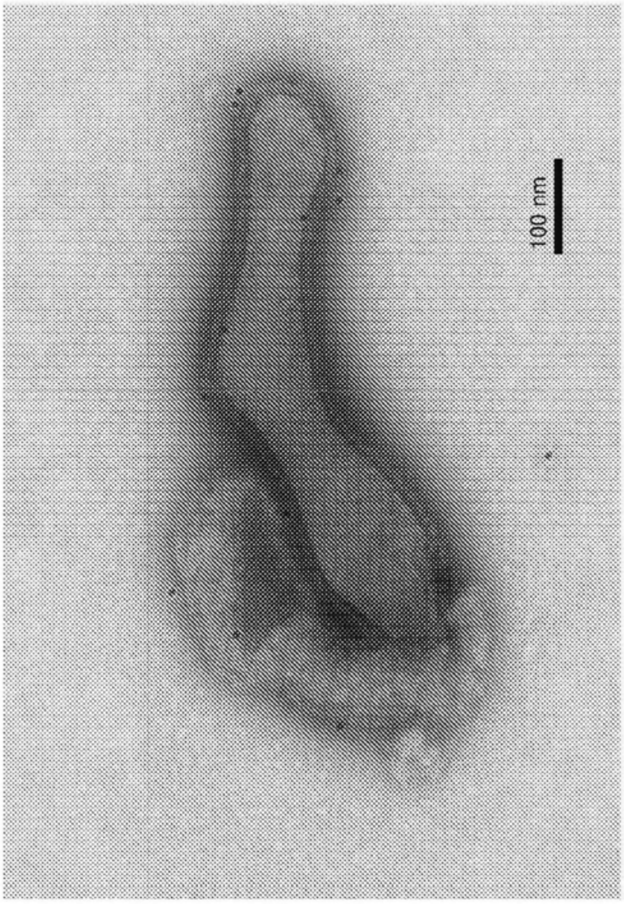


图6H

rB/HPIV3-G_B3CT

rB/HPIV3-G_B3TMCT

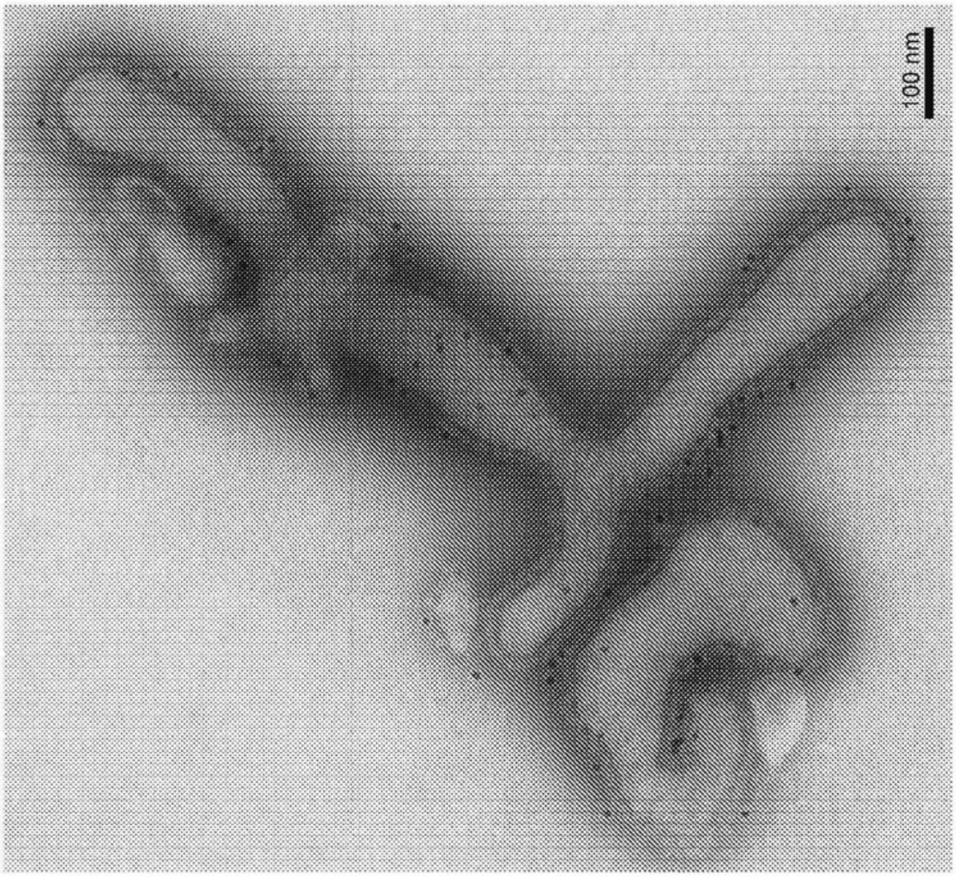


图6I

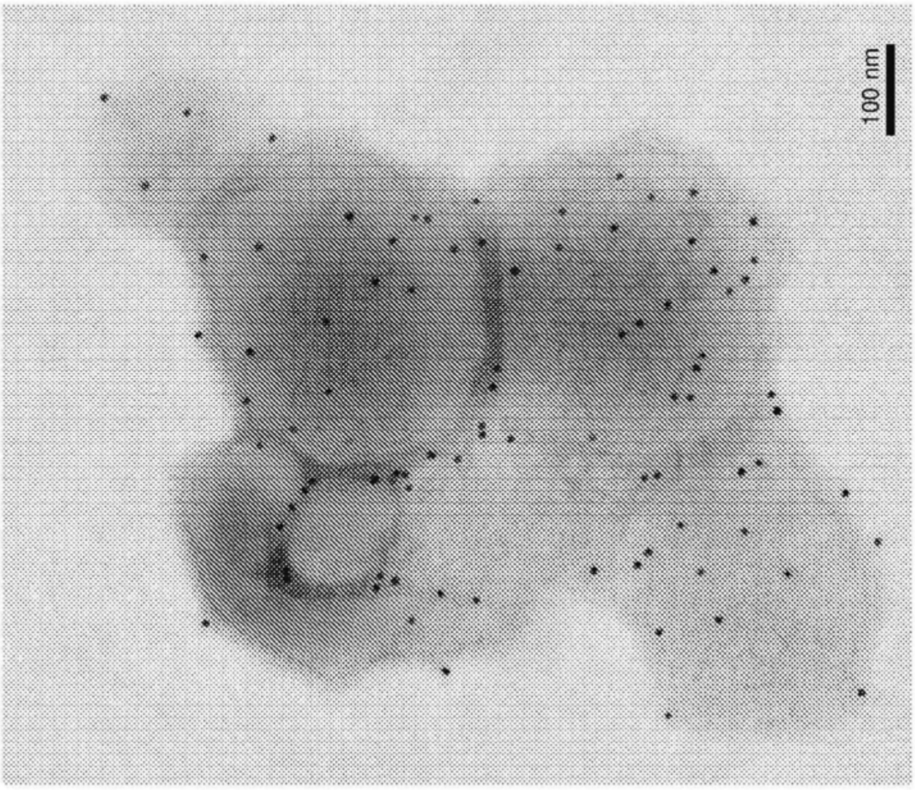


图6J

rB/HPIV3-Empty vector

图6K

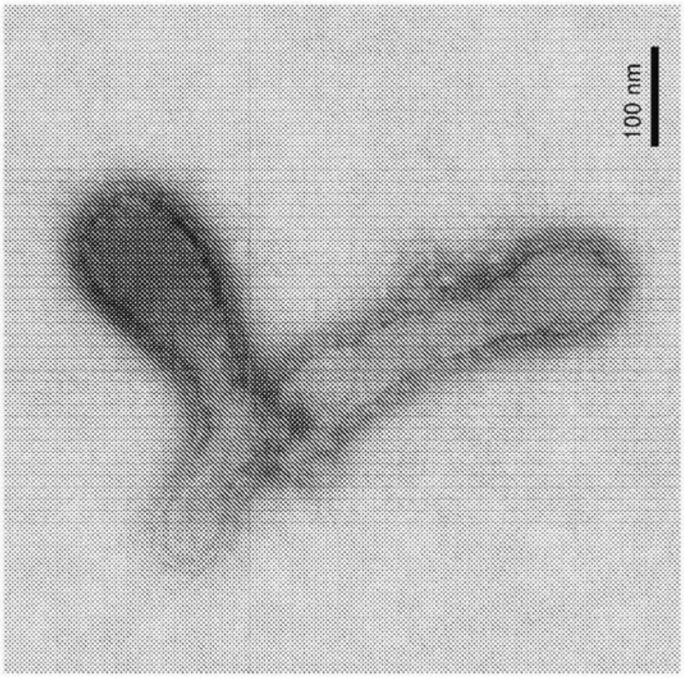


图6L

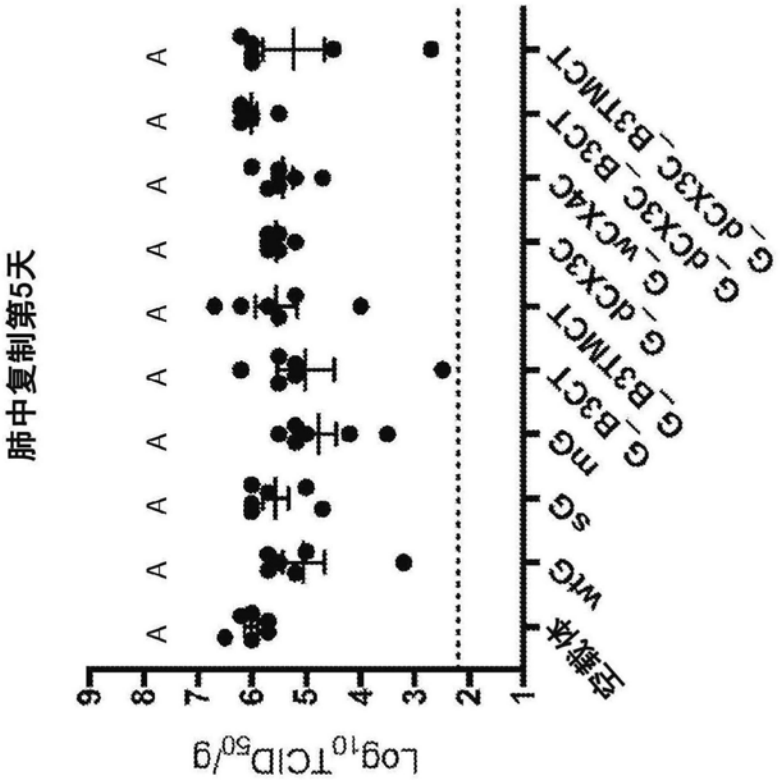

肺中复制第5天
Log10TCID50/g
空载体
wtG
sG
mG
G_B3CT
G_B3TMCT
G_dCX3C
G_wCX4C
G_dCX3C_B3CT
G_dCX3C_B3TMCT

图7B

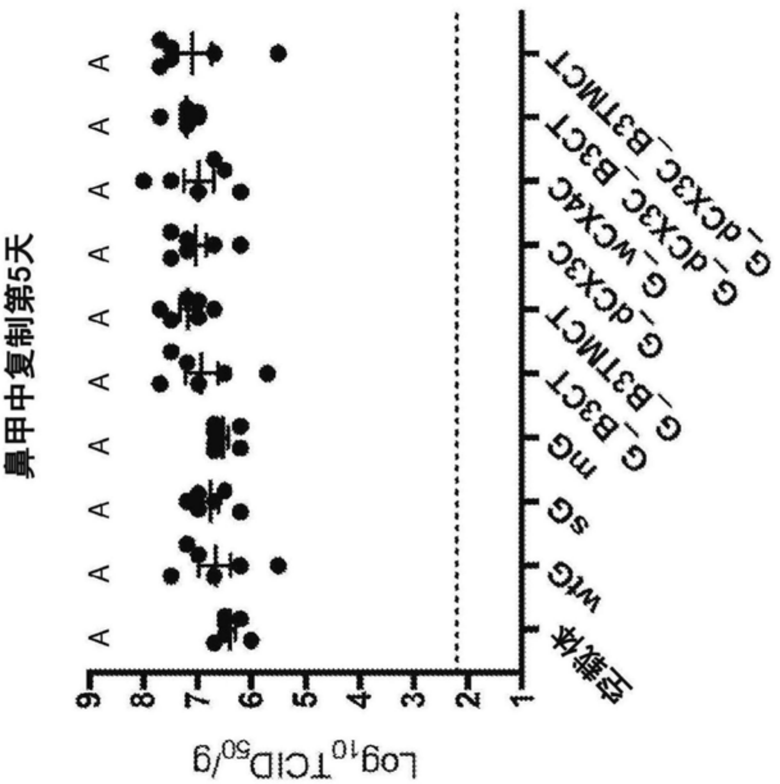

鼻甲中复制第5天
Log10TCID50/g
空载体
wtG
sG
mG
G_B3CT
G_B3TMCT
G_dCX3C
G_wCX4C
G_dCX3C_B3CT
G_dCX3C_B3TMCT

图7A

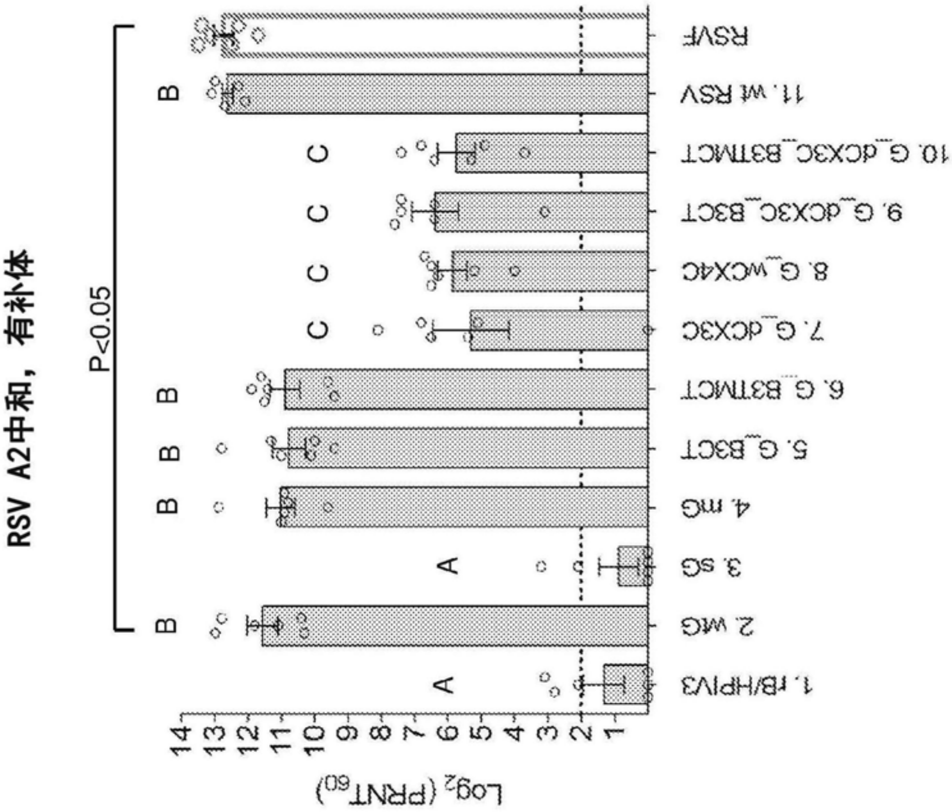

RSV A2中和，有补体
P<0.05
Log2 (PRNT60)
1. rB/HPIV3
2. wG
3. sG
4. mG
5. G_B3CT
6. G_B3TMCT
7. G_dCX3C
8. G_wCX4C
9. G_dCX3C_B3CT
10. G_dCX3C_B3TMCT
11. wt RSV
RSVF
A
B
A
B
B
B
C
C
C
C
B

图8A

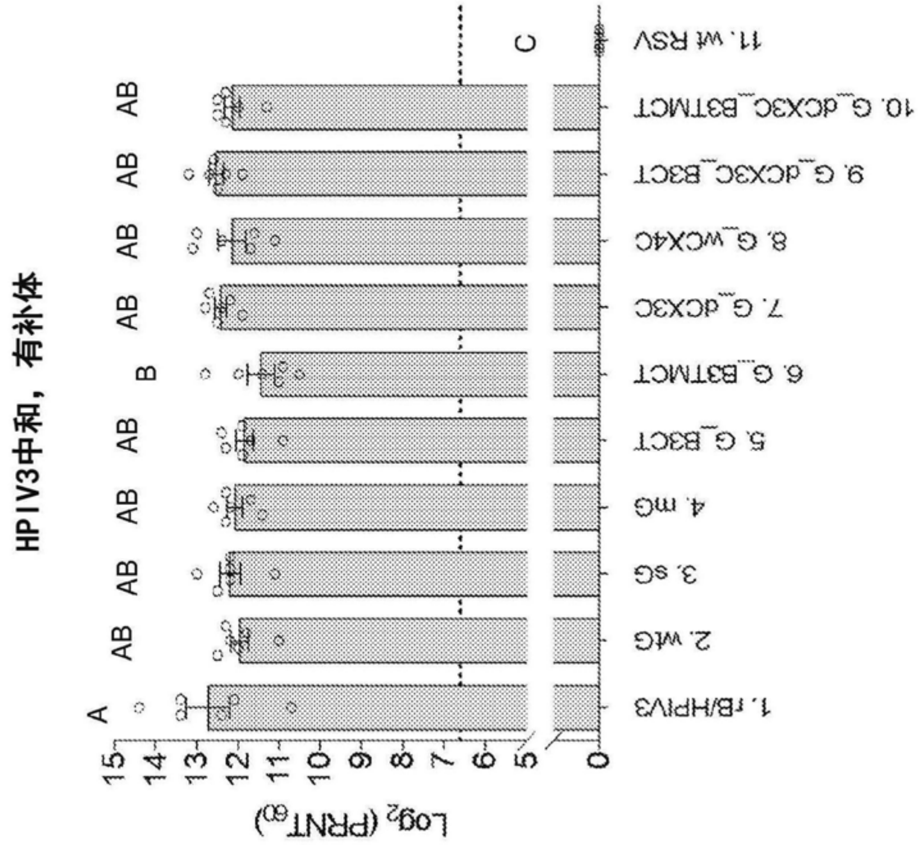

HPIV3中和，有补体
Log2 (PRNT60)
15
14
13
12
11
10
9
8
7
6
5
0
A
AB
AB
AB
AB
B
AB
AB
AB
AB
C
1. rB/HPIV3
2. wtG
3. sG
4. mG
5. G_B3CT
6. G_B3TMCT
7. G_dCX3C
8. G_wCX4C
9. G_dCX3C_B3CT
10. G_dCX3C_B3TMCT
11. wt RSV

图8B

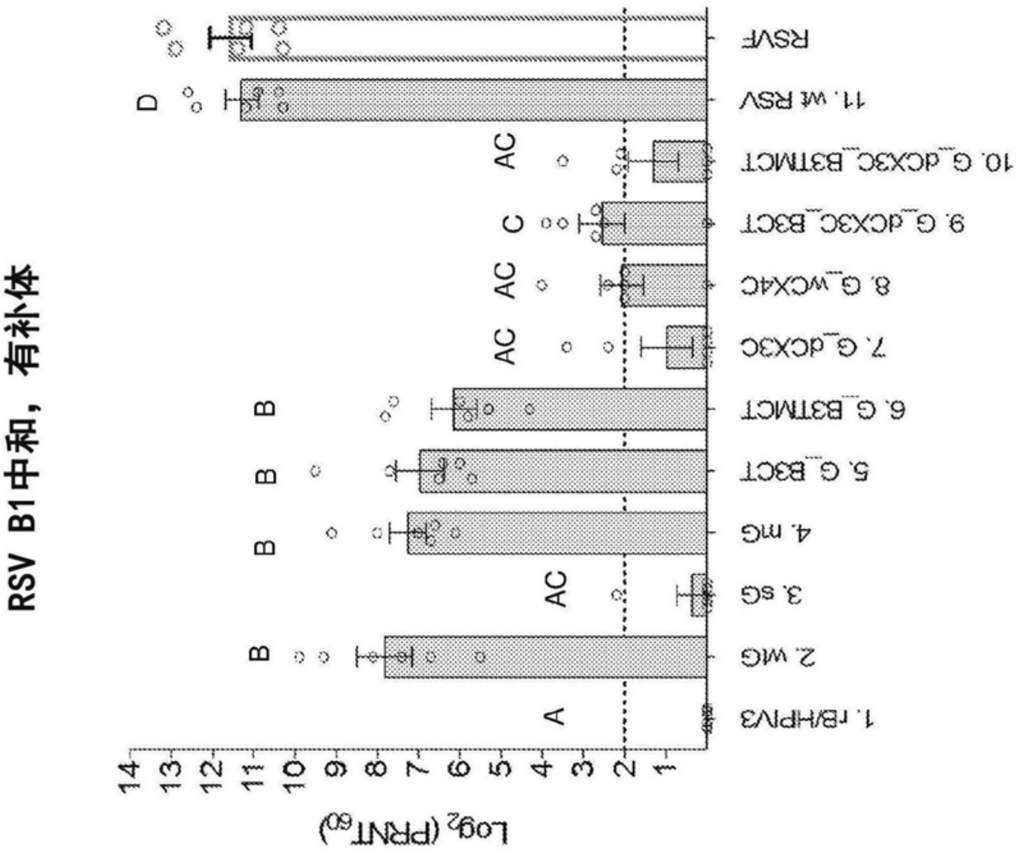

RSV B1中和，有补体
Log2 (PRNT60)
1 2 3 4 5 6 7 8 9 10 11 12 13 14
1. rB/HPIV3
2. wG
3. sG
4. mG
5. G_B3CT
6. G_B3TMCT
7. G_dCX3C
8. G_wCX4C
9. G_dCX3C_B3CT
10. G_dCX3C_B3TMCT
11. wt RSV
RSVF
A
B
AC
B
B
B
AC
AC
C
AC
D

图8C

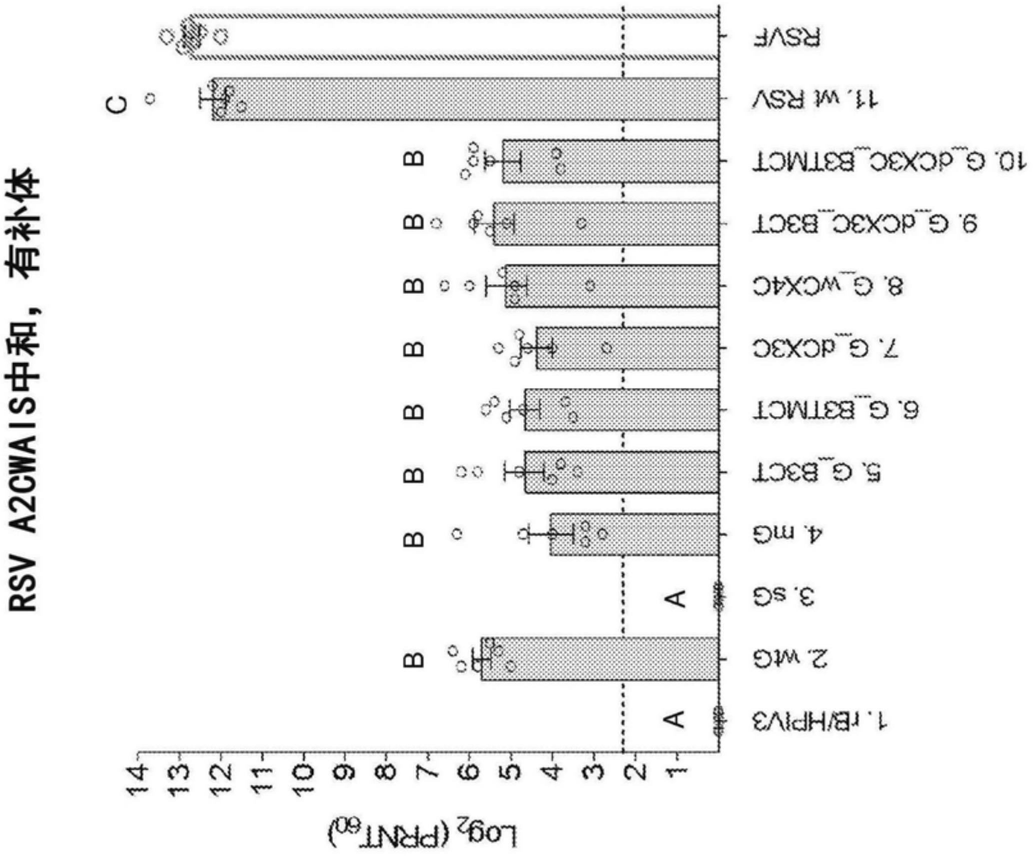

RSV A2CWAIS中和，有补体
Log2 (PRNT60)
14
13
12
11
10
9
8
7
6
5
4
3
2
1
1. rB/HPIV3
2. wtG
3. sG
4. mG
5. G_B3CT
6. G_B3TMCT
7. G_dCX3C
8. G_wCX4C
9. G_dCX3C_B3CT
10. G_dCX3C_B3TMCT
11. wt RSV
RSVF
A
B
A
B
B
B
B
B
B
B
C

图8D

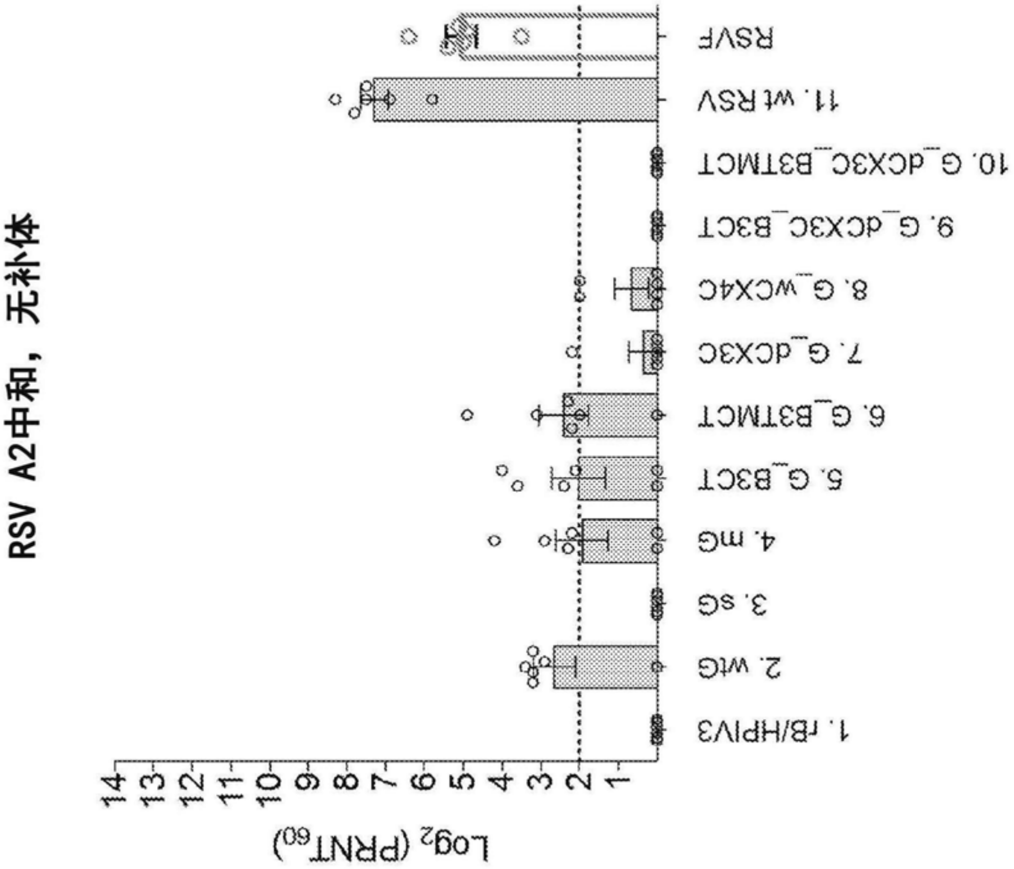

RSV A2中和，无补体
Log2 (PRNT60)
14
13
12
11
10
9
8
7
6
5
4
3
2
1
1. rB/HPIV3
2. wtG
3. sG
4. mG
5. G_B3CT
6. G_B3TMCT
7. G_dCX3C
8. G_wCX4C
9. G_dCX3C_B3CT
10. G_dCX3C_B3TMCT
11. wtRSV
RSVF

图8E

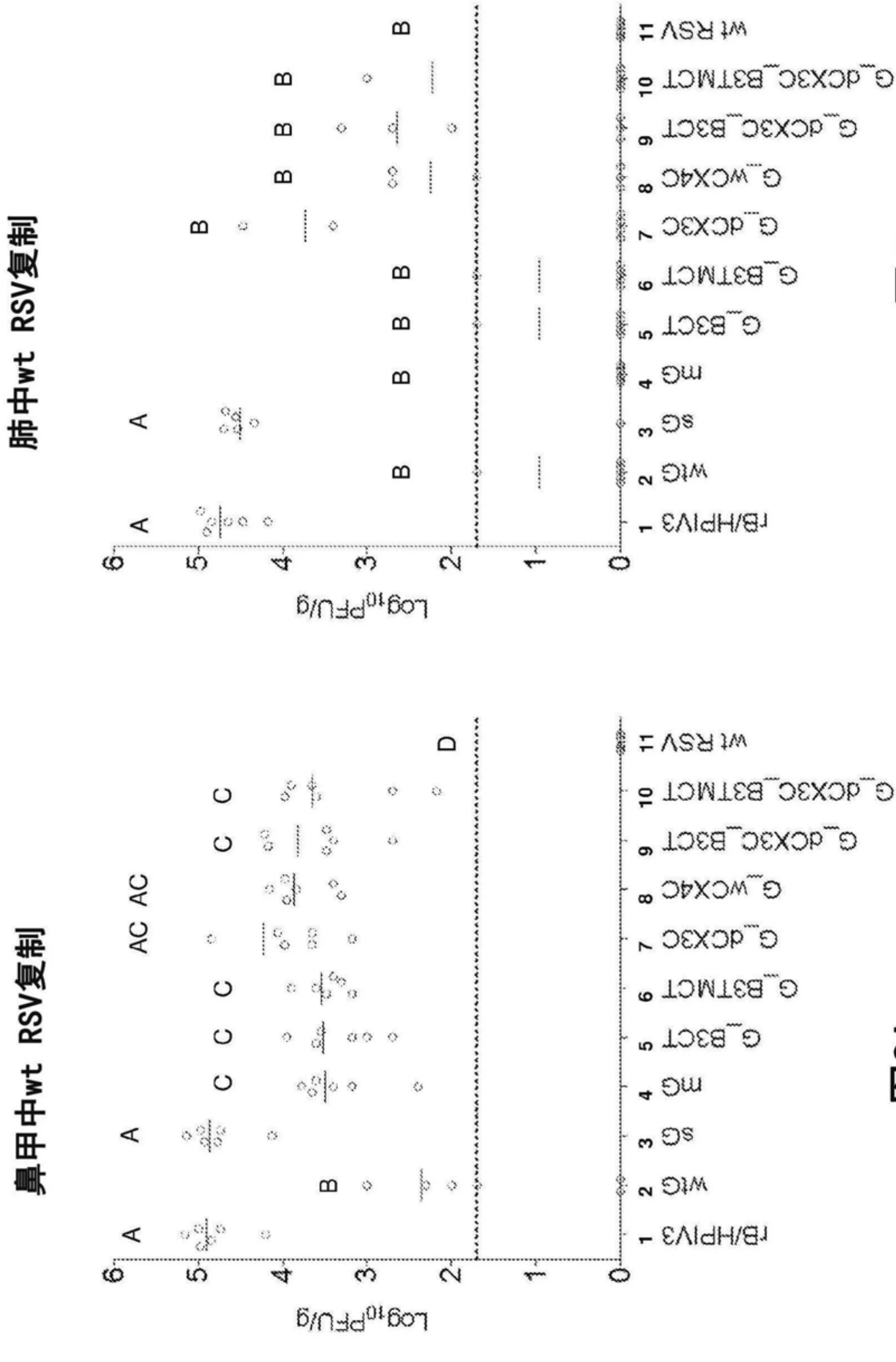


图9A

图9B

针对wt RSV A2激发的保护

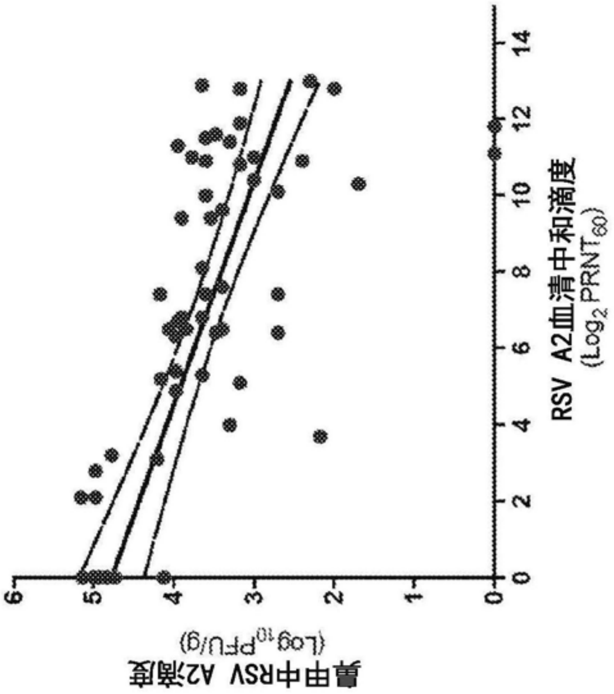

鼻甲中RSV A2滴度
(Log10PFU/g)
RSV A2血清中和滴度
(Log2 PRNT60)

图9C

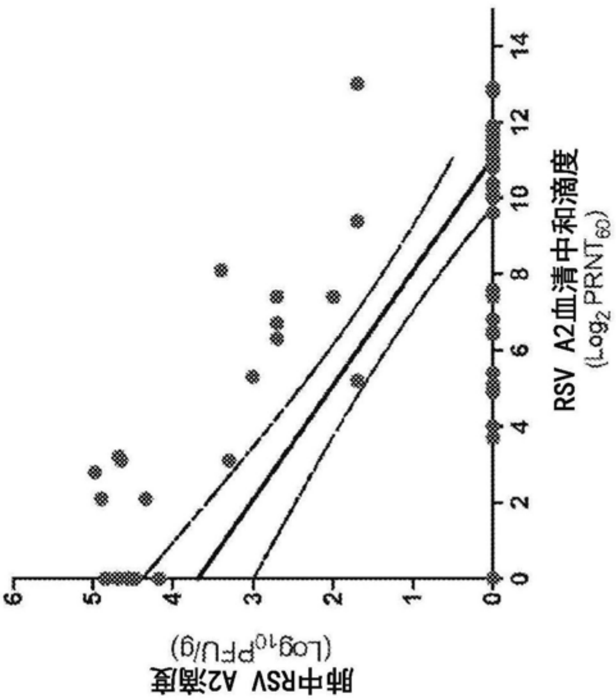

肺中RSV A2滴度
(Log10PFU/g)
RSV A2血清中和滴度
(Log2 PRNT60)

图9D

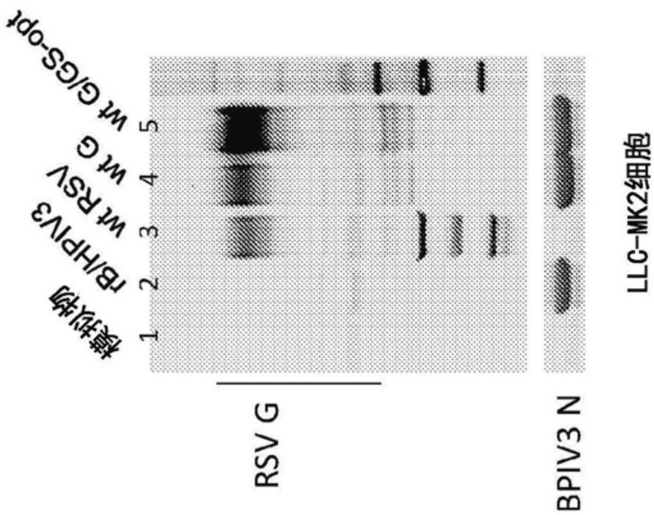

模拟物
rB/HPIV3
wt RSV
wt G
wt G/GS-opt
1
2
3
4
5
RSV G
BPIV3 N
LLC-MK2细胞

图10A

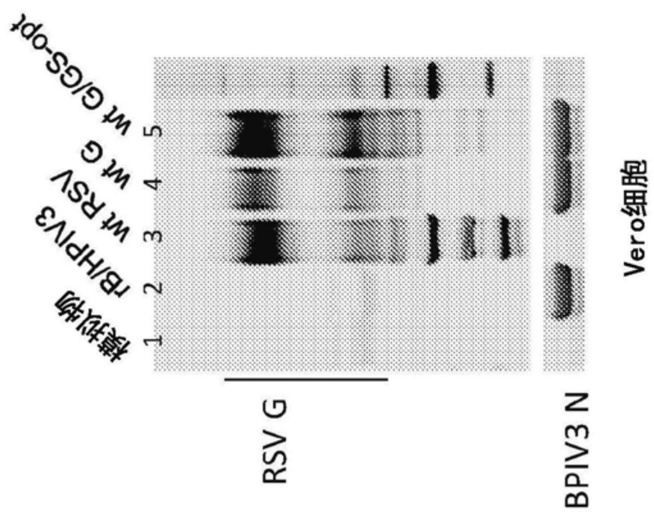

模拟物
rB/HPIV3
wt RSV
wt G
wt G/GS-opt
1
2
3
4
5
RSV G
BPIV3 N
Vero细胞

图10B

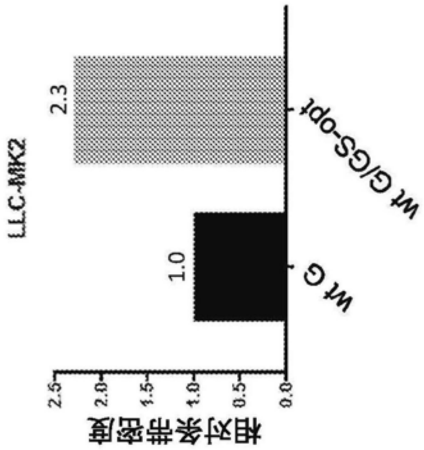

LLC-MK2
2.3
1.0
wt G
wt G/GS-opt
相对条带密度
0.0
0.5
1.0
1.5
2.0
2.5

图10C

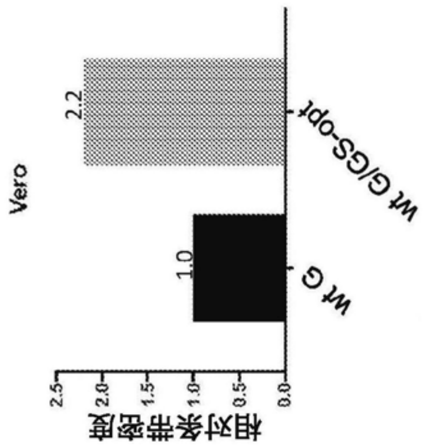

Vero
2.2
1.0
wt G
wt G/GS-opt
相对条带密度
0.0
0.5
1.0
1.5
2.0
2.5

图10D

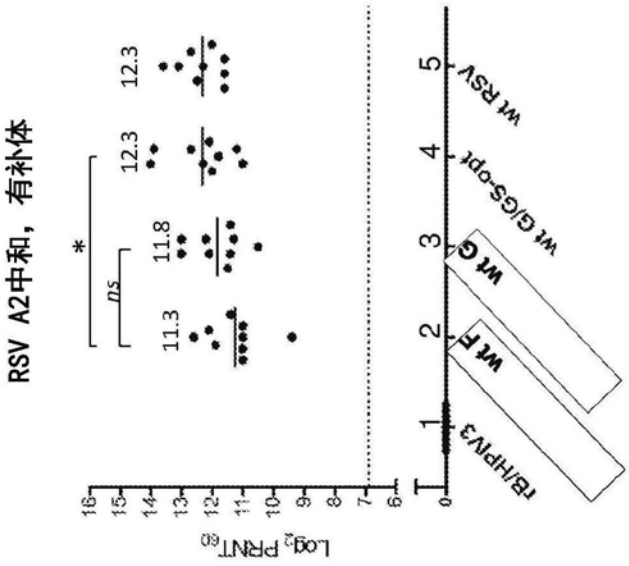

RSV A2中和，有补体
*
ns
11.3
11.8
12.3
12.3
Log2 PRNT60
rB/HPIV3
wt F
wt G
wt G/GS-opt
wt RSV

图11

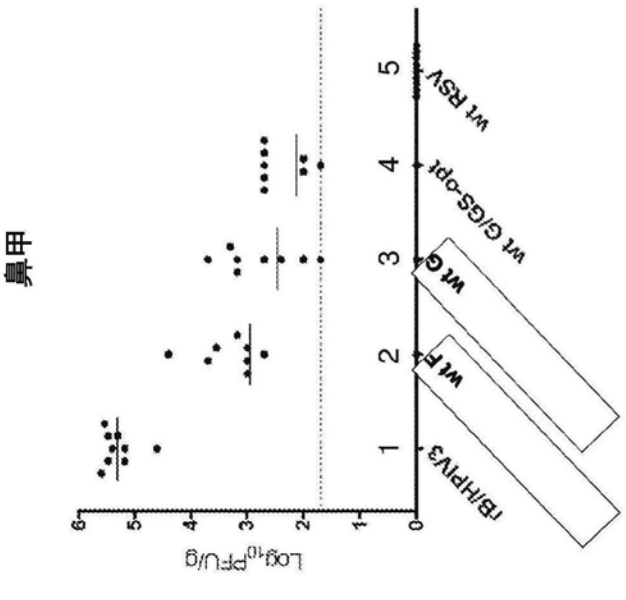

鼻甲
Log10 PFU/g
rB/HPIV3
wt F
wt G
wt G/GS-opt
wt RSV

图12A

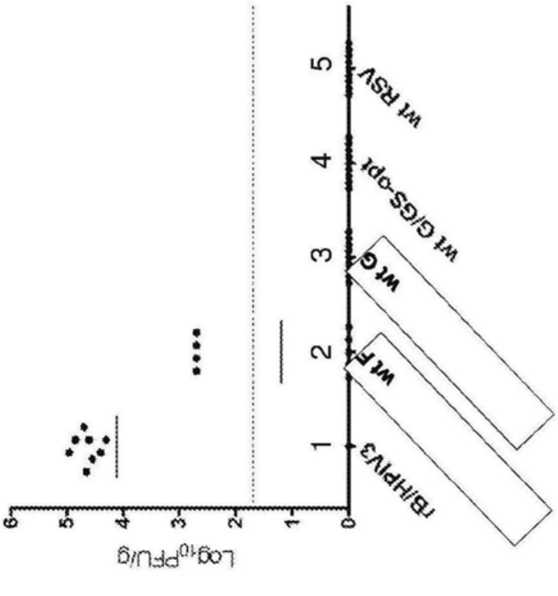

肺
Log10PFU/g
0
1
2
3
4
5
6
rB/HPIV3
wt F
wt G
wt G/GS-opt
wt RSV

图12B

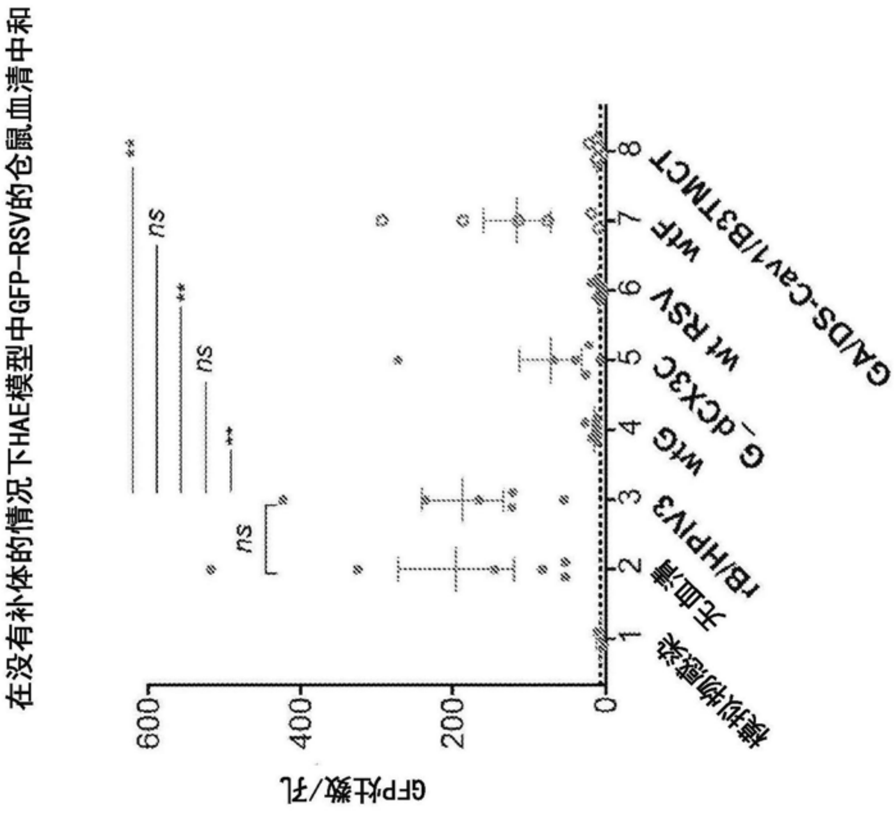

在没有补体的情况下HAE模型中GFP-RSV的仓鼠血清中和
GFP灶数/孔
0
200
400
600
模拟物感染
无血清
rB/HPIV3
wtG
G_dCX3C
wt RSV
wtF
GA/DS-Cav1/B3TMCT
ns
***
ns
**
ns
**

图13