(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 111334530 A
(43)申请公布日 2020.06.26

(21)申请号 202010070674.4

(22)申请日 2014.03.13

(30)优先权数据
61/779,888 2013.03.13 US

(62)分案原申请数据
201480027225.4 2014.03.13

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(51)Int.Cl.
C12N 15/86(2006.01)
C12N 7/00(2006.01)
C12N 5/10(2006.01)
A61K 39/145(2006.01)
A61P 31/16(2006.01)

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(54)发明名称

乙型流感病毒重配

(57)摘要

提供了用于生产重配乙型流感病毒的新的流感供体毒株。

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1.一种制备重配乙型流感病毒的方法,所述方法包括以下步骤:

(i)将一种或多种编码生产乙型流感病毒所需的病毒区段的表达构建体导入培养宿主,所述表达构建体编码来自第一乙型流感病毒的HA区段和来自第二乙型流感病毒的NP和/或PB2区段,所述第二乙型流感病毒是B/Victoria/2/87样毒株;以及

(ii)培养所述培养宿主以生产重配乙型流感病毒。

2.一种制备重配乙型流感病毒的方法,所述方法包括以下步骤:

(i)将一种或多种编码生产乙型流感病毒所需的病毒区段的表达构建体导入培养宿主,所述表达构建体编码来自第一乙型流感病毒的HA区段和来自第二乙型流感病毒的NP区段,所述第二乙型流感病毒不是B/Lee/40或B/Ann Arbor/1/66或B/Panama/45/90;以及

(ii)培养所述培养宿主以生产重配乙型流感病毒。

3.一种制备重配乙型流感病毒的方法,所述方法包括以下步骤:

(i)将一种或多种编码生产乙型流感病毒所需的病毒区段的表达构建体导入培养宿主,所述乙型流感病毒包含来自B/Yamagata/16/88样毒株的HA区段和至少一个来自B/Victoria/2/87样毒株的主链区段;以及

(ii)培养所述培养宿主以生产重配乙型流感病毒。

4.一种制备重配乙型流感病毒的方法,所述方法包括以下步骤:

(i)将一种或多种编码生产乙型流感病毒所需的病毒区段的表达构建体导入培养宿主,所述乙型流感病毒包含来自B/Victoria/2/87样毒株和B/Yamagata/16/88样毒株的病毒区段,来自所述B/Victoria/2/87样毒株和所述B/Yamagata/16/88样毒株的区段的比例是1:7、2:6、3:5、4:4、5:3、6:2或7:1;以及

(ii)培养所述培养宿主以生产重配乙型流感病毒。

5.一种制备重配乙型流感病毒的方法,所述方法包括以下步骤:

(i)将一种或多种编码生产乙型流感病毒所需的病毒区段的表达构建体导入培养宿主,所述乙型流感病毒包含:

a)SEQ ID NO:11的PA区段、SEQ ID NO:12的PB1区段、SEQ ID NO:13的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:16的NS区段和SEQ ID NO:15的M区段;或

b)SEQ ID NO:11的PA区段、SEQ ID NO:31的PB1区段、SEQ ID NO:13的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:35的NS区段和SEQ ID NO:34的M区段;或

c)SEQ ID NO:11的PA区段、SEQ ID NO:31的PB1区段、SEQ ID NO:32的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:16的NS区段和SEQ ID NO:15的M区段;或

d)SEQ ID NO:30的PA区段、SEQ ID NO:12的PB1区段、SEQ ID NO:13的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:16的NS区段和SEQ ID NO:15的M区段,或

e)SEQ ID NO:11的PA区段、SEQ ID NO:12的PB1区段、SEQ ID NO:13的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:35的NS区段和SEQ ID NO:34的M区段;

f)SEQ ID NO:30的PA区段、SEQ ID NO:31的PB1区段、SEQ ID NO:13的PB2区段、SEQ ID NO:33的NP区段、SEQ ID NO:35的NS区段和SEQ ID NO:34的M区段,或

g)SEQ ID NO:30的PA区段、SEQ ID NO:31的PB1区段、SEQ ID NO:32的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:35的NS区段和SEQ ID NO:34的M区段,或

h)SEQ ID NO:11的PA区段、SEQ ID NO:12的PB1区段、SEQ ID NO:13的PB2区段、SEQ ID

NO:33的NP区段、SEQ ID NO:35的NS区段和SEQ ID NO:34的M区段，或

i)SEQ ID NO:11的PA区段、SEQ ID NO:12的PB1区段、SEQ ID NO:32的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:35的NS区段和SEQ ID NO:34的M区段，或

j)SEQ ID NO:30的PA区段、SEQ ID NO:12的PB1区段、SEQ ID NO:13的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:35的NS区段和SEQ ID NO:34的M区段，或

k)SEQ ID NO:30的PA区段、SEQ ID NO:31的PB1区段、SEQ ID NO:13的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:35的NS区段和SEQ ID NO:34的M区段；以及

(ii)培养所述培养宿主以生产重配乙型流感病毒。

6.可通过权利要求1-5中任一项所述方法获得重配乙型流感病毒。

7.一种制备疫苗的方法，所述方法包括以下步骤：(a)通过权利要求1-5中任一项所述的方法制备病毒以及(b)从所述病毒制备疫苗。

8.一种制备疫苗的方法，包括从权利要求6所述的病毒制备疫苗的步骤。

9.一种包含一种或多种表达构建体的表达系统，所述表达构建体包含权利要求6所述乙型流感病毒的vRNA编码区段。

10.一种包含权利要求9所述表达系统的宿主细胞。

乙型流感病毒重配

[0001] 本申请部分是在生物医学高级研究和开发机构(BARDA)授予的基金号HHSO10020100061C的政府支持下完成。政府对本发明享有某些权利。

[0002] 本申请要求2013年3月13日提交的美国临时申请61/779,888的优先权,其全部内容通过引用纳入本文。

技术领域

[0003] 本发明属于乙型流感病毒重配领域。此外,其涉及生产用于保护抵御乙型流感病毒的疫苗。

背景技术

[0004] 针对流感感染的最有效保护是抗流行株的疫苗接种,且尽快生成用于疫苗生产的流感病毒是重要的。

[0005] 野生型流感病毒通常在鸡蛋和细胞培养物内生长达到低效价。为了获得生长更好的毒株用于疫苗生产,可以使用快速生长的高产供体毒株重配流行疫苗株。这可以通过以下方法完成:用流行流感毒株和高产供体毒株共同感染培养宿主,并选择含有来自疫苗毒株的血凝素(HA)和神经氨酸酶(NA)区段和来自供体毒株的其它病毒区段(即,编码PB1、PB2、PA、NP、M_1、M_2、NS_1和NS_2的那些)的重配病毒。另一个方法是通过反向遗传重配流感病毒(参见,例如参考文献1和2)。

[0006] 虽然常见做法是在疫苗生产中使用重配甲型流感毒株,但通常不使用重配乙型流感毒株,因为野生型乙型流感病毒通常就能在鸡蛋中提供合适的产率。此外,野生型乙型流感病毒已被报道具有优于重配乙型流感病毒的生长优势(参见,例如,参考文献3)。因此,仅生成高生长乙型流感重配株用于少量目前的乙型流感病毒。这些重配株通常含有来自B/Lee/40、B/Brisbane/60/08和B/Panama/45/90的主链基因区段的混合物(4,5)。

[0007] 迄今为止,只有两种重配乙型流感病毒(BX-35和BX-39)被用于商业化疫苗制造。BX-35含有来自B/Brisbane/60/08毒株的HA、NA、PA、PB1和NS区段、来自B/Panama/45/90的PB2和M区段,以及来自B/Lee/40的NP区段。BX-39含有来自B/Hubei-Wujiagang/159/08毒株的HA、NA、PB1和M区段、来自B/Panama/45/90的PA和NS区段,以及来自B/Lee/40的PB2和NP区段(6,7)。

[0008] 目前仅存在有限数目的用于疫苗制造的重配乙型流感病毒的供体毒株且已知的重配乙型流感病毒不总是比亲本毒株生长的更好。因此,本领域需要提供进一步和改善的供体毒株用于乙型流感病毒重配。

具体实施方式

[0009] 本发明因此提供了与作为HA区段来源的相应野生型乙型流感病毒相比,在培养宿主中(特别是在细胞培养物中)生长速度相同或更快的重配乙型流感病毒。例如,发明人出乎意料地发现,该方法可用于生产包含来自第一乙型流感病毒的HA区段和来自第二乙型流

感病毒的NP和/或PB2区段的重配乙型流感毒株，该第二乙型流感病毒是在细胞培养物和鸡蛋中生长特别好的B/Victoria/2/87样毒株。该B/Victoria/2/87样毒株可以是B/Brisbane/60/08。

[0010] 发明人还提供了包含来自第一乙型流感病毒的HA区段和来自第二乙型流感病毒的NP区段的重配乙型流感病毒，该第二乙型流感病毒不是B/Lee/40或B/Ann Arbor/1/66或B/Panama/45/90。例如，该重配乙型流感病毒可具有不具有SEQ ID NO:33、38、39或43的序列的NP区段。该重配乙型流感病毒还可具有不编码SEQ ID NO:19、23、44或45的蛋白的NP区段。发明人发现，包含来自除B/Lee/40或B/Ann Arbor/1/66或B/Panama/45/90以外的乙型流感病毒的NP区段的重配乙型流感病毒可在培养宿主中生长得非常好。该重配乙型流感病毒可包含来自第二乙型流感病毒的NP和PB2区段。该第二乙型流感病毒优选是B/Victoria/2/87样毒株。该B/Victoria/2/87样毒株可以是B/Brisbane/60/08。

[0011] 发明人还发现，包含来自B/Yamagata/16/88样毒株的HA区段和来自B/Victoria/2/87样毒株的至少一个主链区段的重配乙型流感病毒可以在培养宿主中良好生长。该重配乙型流感病毒可包含两个、三个、四个、五个或六个来自B/Victoria/2/87样毒株的主链区段。在优选的实施方式中，该重配乙型流感病毒包含所有来自B/Victoria/2/87样毒株的主链区段。该B/Victoria/2/87样毒株可以是B/Brisbane/60/08。

[0012] 本发明还提供了一种包含来自B/Victoria/2/87样毒株和B/Yamagata/16/88样毒株的病毒区段的重配乙型流感病毒，其中来自B/Victoria/2/87样毒株和B/Yamagata/16/88样毒株的区段的比例是1:7、2:6、4:4、5:3、6:2或7:1。7:1、6:2、4:4、3:5或1:7的比例(特别是4:4的比例)是优选的，因为这类重配乙型流感病毒在培养宿主中生长得特别好。该B/Victoria/2/87样毒株可以是B/Brisbane/60/08。该B/Yamagata/16/88样毒株可以是B/Panama/45/90。在这些实施方式中，该重配乙型流感病毒通常不包含所有来自相同乙型流感供体毒株的主链区段。

[0013] 还提供了包含以下区段的重配乙型流感病毒：

[0014] a)SEQ ID NO:11的PA区段、SEQ ID NO:12的PB1区段、SEQ ID NO:13的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:16的NS区段和SEQ ID NO:15的M区段；或

[0015] b)SEQ ID NO:11的PA区段、SEQ ID NO:31的PB1区段、SEQ ID NO:13的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:35的NS区段和SEQ ID NO:34的M区段；或

[0016] c)SEQ ID NO:11的PA区段、SEQ ID NO:31的PB1区段、SEQ ID NO:32的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:16的NS区段和SEQ ID NO:15的M区段；或

[0017] d)SEQ ID NO:30的PA区段、SEQ ID NO:12的PB1区段、SEQ ID NO:13的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:16的NS区段和SEQ ID NO:15的M区段；或

[0018] e)SEQ ID NO:11的PA区段、SEQ ID NO:12的PB1区段、SEQ ID NO:13的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:35的NS区段和SEQ ID NO:34的M区段；或

[0019] f)SEQ ID NO:30的PA区段、SEQ ID NO:31的PB1区段、SEQ ID NO:13的PB2区段、SEQ ID NO:33的NP区段、SEQ ID NO:35的NS区段和SEQ ID NO:34的M区段；或

[0020] g)SEQ ID NO:30的PA区段、SEQ ID NO:31的PB1区段、SEQ ID NO:32的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:35的NS区段和SEQ ID NO:34的M区段；或

[0021] h)SEQ ID NO:11的PA区段、SEQ ID NO:12的PB1区段、SEQ ID NO:13的PB2区段、

SEQ ID NO:33的NP区段、SEQ ID NO:35的NS区段和SEQ ID NO:34的M区段;或

[0022] i)SEQ ID NO:11的PA区段、SEQ ID NO:12的PB1区段、SEQ ID NO:32的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:35的NS区段和SEQ ID NO:34的M区段;或

[0023] j)SEQ ID NO:30的PA区段、SEQ ID NO:12的PB1区段、SEQ ID NO:13的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:35的NS区段和SEQ ID NO:34的M区段;或

[0024] k)SEQ ID NO:30的PA区段、SEQ ID NO:31的PB1区段、SEQ ID NO:13的PB2区段、SEQ ID NO:14的NP区段、SEQ ID NO:35的NS区段和SEQ ID NO:34的M区段。

[0025] 在这些重配乙型流感病毒中,HA和NA区段可来自任何乙型流感毒株。

[0026] 具有上文(a)至(k)段所述区段组合的重配乙型流感病毒是优选的,因为发明人已证明其在培养宿主中生长得特别好。(a)、(b)和(e)的重配乙型流感毒株在培养宿主中生长得特别好且因此是特别优选的。

[0027] 本发明还提供了上文(a)至(k)段中鉴定的重配乙型流感病毒的变体,其包含与这些段中鉴定的病毒区段至少97%相同、至少98%相同或至少99%相同的病毒区段。这类变体可优选地在培养宿主中生长至病毒效价,其是相同时间内且相同生长条件下使用作为这些变体来源的重配乙型流感毒株所达到的病毒效价的3%内。

[0028] 本发明提供了制备本发明的重配乙型流感病毒的方法。这些方法包括以下步骤:(i)将一种或多种表达构建体引入培养宿主,所述表达构建体编码产生本发明的重配乙型流感病毒所需的病毒区段;以及(ii)培养所述培养宿主以产生重配病毒;和可选地(iii)纯化步骤(ii)中获得的病毒。

[0029] 这些方法还可包括以下步骤:(iv)用步骤(ii)或步骤(iii)中获得的病毒感染培养宿主;(v)培养来自步骤(iv)的培养宿主以生成其它病毒;和可选地(vi)纯化步骤(v)中获得的病毒。

[0030] 还提供可用于本发明的方法的表达构建体。

[0031] 例如,该表达构建体可编码的重配乙型流感病毒包含来自第一乙型流感病毒的HA区段和来自第二乙型流感病毒的NP和/或PB2区段,该第二乙型流感病毒是B/Victoria/2/87样毒株。NP和PB2区段都可来自B/Victoria/2/87样毒株。该B/Victoria/2/87样毒株优选是B/Brisbane/60/08。

[0032] 该表达构建体可编码的重配乙型流感病毒还包含来自第一乙型流感病毒的HA区段和来自第二乙型流感病毒的NP区段,该第二乙型流感病毒不是B/Lee/40或B/Ann Arbor/1/66或B/Panama/45/90。例如,该表达构建体不编码具有SEQ ID NO:19、23、44或45的序列的NP区段。NP和PB2区段都可来自第二乙型流感病毒。该第二乙型流感病毒可以是B/Victoria/2/87样毒株且优选是B/Brisbane/60/08。

[0033] “第一流感病毒”和“第二流感病毒”彼此不同。

[0034] 该表达构建体可编码的重配乙型流感病毒包含来自B/Victoria/2/87样毒株和B/Yamagata/16/88样毒株的病毒区段,其中来自B/Victoria/2/87样毒株和B/Yamagata/16/88样毒株的区段的比例是1:7、2:6、4:4、5:3、6:2或7:1。优选的比例是7:1、6:2、4:4、3:5或1:7,特别优选4:4。该B/Victoria/2/87样毒株可以是B/Brisbane/60/08。该B/Yamagata/16/88样毒株可以是B/Panama/45/90。

[0035] 还提供了编码上文所述重配乙型流感病毒的表达构建体。

[0036] 本发明提供了包含本发明的一种或多种表达构建体的表达系统。本发明还提供一种包含本发明的表达系统的宿主细胞。这些宿主细胞能由所述表达系统中的表达构建体表达乙型流感病毒。

[0037] 本发明还提供一种用于产生流感病毒的方法，所述方法包括以下步骤：(a)用本发明的重配病毒感染培养宿主；(b)培养来自步骤(a)的宿主以产生所述病毒；和可选地(c)纯化步骤(b)中获得的病毒。

[0038] 本发明还提供一种制备疫苗的方法，所述方法包括以下步骤：(a)通过上述实施方式中任何一种的方法制备病毒和(b)从所述病毒制备疫苗。

[0039] 还提供了一种从本发明的重配乙型流感病毒制备疫苗的方法。

[0040] 本发明还提供了可通过本发明的方法获得的疫苗。

[0041] 重配病毒

[0042] 本发明的重配乙型流感病毒含有来自疫苗毒株和一种或多种供体毒株的病毒区段。该疫苗毒株是提供重配流感毒株的HA区段的乙型流感毒株。该疫苗毒株可以是任何毒株并可随季节变化。

[0043] 供体毒株是提供乙型流感毒株的一种或多种主链区段(即编码PB1、PB2、PA、NP、M_1、M_2、NS_1和NS_2的那些)的乙型流感毒株。NA区段还可由供体毒株提供或者其可由疫苗毒株提供。本发明的重配乙型流感病毒还可包含一种或多种(但不是全部)来自疫苗毒株的主链区段。由于重配乙型流感病毒含有总共八个区段，其因此含有x个(其中x为1-7)来自疫苗毒株的病毒区段和8-x个来自一种或多种供体毒株的病毒区段。

[0044] 如上文所述，本发明的目的是提供以下重配乙型流感病毒，其一旦拯救即可在培养宿主中生长至较高或类似的病毒效价。因此，与野生型疫苗毒株相比，在相同的时间(例如12小时、24小时、48小时或72小时)内且在相同生长条件下，本发明的重配乙型流感病毒毒株可在细胞培养物和/或鸡蛋中生长至较高或类似的病毒效价。具体而言，与野生型疫苗毒株相比，在相同的时间内且在相同生长条件下，其可在MDCK细胞(如MDCK 33016)中生长至较高或类似的病毒效价。可通过本领域技术人员已知的标准方法测定病毒效价。有用地，在相同时间框内且在相同条件下，本发明的重配乙型流感病毒能达到的病毒效价比野生型疫苗毒株的病毒效价高出至少5％、至少10％、至少20％、至少50％、至少100％、至少200％或至少500％。与野生型疫苗毒株相比，在相同的时间内且在相同生长条件下，该重配乙型流感病毒还可生长至类似病毒效价。此时类似效价指重配乙型流感病毒所生长至的效价是在相同时间内且在相同生长条件下野生型疫苗毒株所能达到的病毒效价的3％以内(即野生型效价±3％)。

[0045] 乙型流感病毒目前不显示不同的HA亚型，但乙型流感病毒毒株属于两种不同的谱系。这些谱系出现于1980年代晚期，并且具有在抗原/遗传上可彼此区分的HA[8]。当前的乙型流感病毒毒株是B/Victoria/2/87样或B/Yamagata/16/88样。通常可从抗原性区分这些毒株，但氨基酸序列的差异也可以区分这两种谱系，例如B/Yamagata/16/88样毒株常常(但并非总是)具有氨基酸残基164缺失(相对'Lee40'HA序列进行编号)的HA蛋白[9]。在一些实施方式中，本发明的重配乙型流感病毒包含所有来自B/Victoria/2/87样毒株的病毒区段。它们可包含来自B/Yamagata/16/88样毒株的病毒区段。或者，它们可包含来自B/Victoria/2/87样毒株和B/Yamagata/16/88样毒株的病毒区段。

[0046] 当该重配乙型流感病毒包含来自两种或多种乙型流感病毒毒株的病毒区段时，这些病毒区段可源自具有相关神经氨酸酶的乙型流感毒株。例如，提供病毒区段的乙型流感毒株可以都具有B/Victoria/2/87样神经氨酸酶[10]或可都具有B/Yamagata/16/88样神经氨酸酶。例如，两种B/Victoria/2/87样神经氨酸酶可都具有一种或多种以下序列特性：(1)在残基27处不是丝氨酸，但优选亮氨酸；(2)在残基44处不是谷氨酸，但优选赖氨酸；(3)在残基46处不是苏氨酸，但优选异亮氨酸；(4)在残基51处不是脯氨酸，但优选丝氨酸；(5)在残基65处不是精氨酸，但优选组氨酸；(6)在残基70处不是甘氨酸，但优选谷氨酸；(7)在残基73处不是亮氨酸，但优选苯丙氨酸；和/或(8)在残基88处不是脯氨酸，但优选谷氨酸。类似地，在一些实施方式中，神经氨酸酶可在残基43处有缺失，或可以是苏氨酸；在残基43处有缺失，由NA基因中的三核苷缺失引起，其已被报道为B/Victoria/2/87样毒株特征，但近来的毒株重新获得了Thr-43[10]。相反地，当然，两种B/Yamagata/16/88样神经氨酸酶也可具有相反性质，例如S27、E44、T46、P51、R65、G70、L73和/或P88。这些氨基酸相对于‘Lee40’神经氨酸酶序列进行编号[11]。该重配乙型流感病毒可包含具有上述特性的NA区段。或者，或此外，该重配乙型流感病毒可包含来自特定乙型流感毒株的病毒区段(不是NA)，该乙型流感毒株包含具有上述特性的NA区段。

[0047] 是B/Victoria/2/87样毒株的乙型流感病毒的主链病毒区段与来自B/Victoria/2/87的相应病毒区段的相同性水平高于其与B/Yamagata/16/88的相应病毒区段的相同性水平，且反之亦然。例如，B/Panama/45/90(其是B/Yamagata/16/88样毒株)的NP区段与B/Yamagata/16/88的NP区段具有99％相同性而与B/Victoria/2/87的NP区段仅具有96％相同性。

[0048] 当本发明的重配乙型流感病毒包含来自B/Victoria/2/87样毒株的主链病毒区段时，该病毒区段可编码具有以下序列的蛋白。PA蛋白可与SEQ ID NO:1的序列至少97％相同、至少98％相同、至少99％相同或100％相同。PB1蛋白可与SEQ ID NO:2的序列至少97％相同、至少98％相同、至少99％相同或100％相同。PB2蛋白可与SEQ ID NO:3的序列至少97％相同、至少98％相同、至少99％相同或100％相同。NP蛋白可与SEQ ID NO:4的序列至少97％相同、至少98％相同、至少99％相同或100％相同。M_1蛋白可与SEQ ID NO:5的序列至少97％相同、至少98％相同、至少99％相同或100％相同。M_2蛋白可与SEQ ID NO:6的序列至少97％相同、至少98％相同、至少99％相同或100％相同。NS_1蛋白可与SEQ ID NO:7的序列至少97％相同、至少98％相同、至少99％相同或100％相同。NS_2蛋白可与SEQ ID NO:8的序列至少97％相同、至少98％相同、至少99％相同或100％相同。在一些实施方式中，该重配乙型流感病毒还可包含所用这些主链区段。

[0049] 当本发明的重配乙型流感病毒包含来自B/Yamagata/16/88样毒株的主链病毒区段时，该病毒区段可编码具有以下序列的蛋白。PA蛋白可与SEQ ID NO:20的序列至少97％相同、至少98％相同、至少99％相同或100％相同。PB1蛋白可与SEQ ID NO:21的序列至少97％相同、至少98％相同、至少99％相同或100％相同。PB2蛋白可与SEQ ID NO:22的序列至少97％相同、至少98％相同、至少99％相同或100％相同。NP蛋白可与SEQ ID NO:23的序列至少97％相同、至少98％相同、至少99％相同或100％相同。M_1蛋白可与SEQ ID NO:24的序列至少97％相同、至少98％相同、至少99％相同或100％相同。M_2蛋白可与SEQ ID NO:25的序列至少97％相同、至少98％相同、至少99％相同或100％相同。NS_1蛋白可与SEQ ID NO:26

的序列至少97％相同、至少98％相同、至少99％相同或100％相同。NS_2蛋白可与SEQ ID NO:27的序列至少97％相同、至少98％相同、至少99％相同或100％相同。

[0050] 本发明还可用与SEQ ID NO 11-16或30-35序列具有至少约70％、至少约75％、至少约80％、至少约85％、至少约90％、至少约95％或至少约99％或100％相同性的病毒区段的供体毒株实施。由于遗传密码的简并性，具有不同序列的若干核酸编码相同多肽是可能的。例如，SEQ ID NO:40和41的核苷酸序列仅有73％相同性，但其编码相同的病毒蛋白。因此，本发明可用编码与序列SEQ ID NO 11-16或30-35相同的多肽的病毒区段实施。

[0051] 通常，重配流感病毒会仅包含各主链区段之一。例如，当流感病毒包含来自B/Brisbane/60/08的NP区段时，其不会同时包含来自另一流感毒株的NP区段。

[0052] 在一些实施方式中，本发明的重配乙型流感病毒可包含来自同一乙型流感供体毒株的所有主链区段。或者，其可包含来自超过一种流感供体毒株(例如两种、三种、四种或五种供体毒株)的主链区段。当该重配乙型流感病毒包含来自两种或三种供体毒株的主链区段时，各供体毒株可提供超过一种的重配乙型流感病毒主链区段，但该供体毒株中的一或两种也可仅提供单一的主链区段。优选地，至少一种主链区段是来自B/Yamagata/16/88样毒株，因为发明人发现这类重配流感病毒在细胞培养物中生长良好。在本发明的上下文中，优选的B/Yamagata/16/88样毒株是B/Panama/45/90。通常，重配乙型流感病毒不可包含超过六种主链区段。因此，例如，若这些供体毒株之一提供五种病毒区段，则该重配乙型流感病毒仅能包含来自总共两种不同流感毒株(例如两种供体毒株或者一种供体毒株和一种疫苗毒株)的主链区段。

[0053] 当所述重配乙型流感病毒包含来自单一供体毒株的主链区段时，这些重配病毒包含的供体毒株与疫苗毒株的区段比通常是1:7、2:6、3:5、4:4、5:3、6:2或7:1。当该重配病毒包含来自两种供体毒株的主链区段时，该重配病毒包含的来自第一种供体毒株、来自第二种供体毒株和来自疫苗毒株的区段比通常是1:1:6、1:2:5、1:3:4、1:4:3、1:5:2、1:6:1、2:1:5、2:2:4、2:3:3、2:4:2、2:5:1、3:1:4、3:2:3、3:3:2、3:4:1、4:1:3、4:2:2、4:3:1、5:1:2、5:2:1或6:1:1。

[0054] 这些重配乙型流感病毒含有来自疫苗毒株的HA区段，其编码流感病毒的主要疫苗抗原并因此来自于疫苗毒株。本发明的重配病毒还优选具有来自疫苗毒株的NA区段，但本发明还包括含有来自不同毒株的HA和NA区段的重配病毒。

[0055] 可用作疫苗毒株的毒株包括对抗病毒治疗有抗性(例如对奥塞米韦[12]和/或扎那米韦有抗性)的毒株，包括抗性大流行毒株[13]。

[0056] 包含不编码功能性NS蛋白的NS区段的重配病毒也在本发明的范围内。参考文献14描述了NS1敲除突变。这些NS1突变病毒株尤其适于制备活减毒流感疫苗。

[0057] 病毒传代过程中能出现的自发性突变可产生DNA和氨基酸序列内的变异。这类变体流感毒株也可用于本发明。

[0058] 反向遗传学

[0059] 本发明特别适合于通过反向遗传学技术生产重配乙型流感病毒株。在这些技术中，使用一种或多种表达系统在培养宿主中生产病毒。该表达系统可编码生成本发明的重配乙型流感病毒所必需的所有区段。

[0060] 流感病毒的反向遗传学可用表达起始复制与转录所需4种蛋白(PB1、PB2、PA和NP)

的12种质粒以及所有八种病毒基因组区段来实施。然而为减少所需的构建体数量，多个RNA聚合酶I转录盒(用于合成病毒RNA)可包含在单一质粒(如编码1、2、3、4、5、6、7或所有8种流感vRNA片段的序列)上，并且将多个蛋白编码区与RNA聚合酶II启动子包含在另一个质粒(如编码1、2、3、4、5、6、7或8种流感mRNA转录物的序列)上[15]。也可将一种或多种流感vRNA区段纳入pol I启动子的控制下并将一种或多种流感蛋白编码区纳入同一质粒的另一启动子控制下，特别是pol II启动子。优选使用双向质粒实现这点。

[0061] 参考文献15方法的优选方面涉及：(a)单一表达构建体上的PB1、PB2、NP和PA mRNA编码区域；和(b)单一表达构建体上的所有8种vRNA编码区段。特别优选在一种表达构建体上包括神经氨酸酶(NA)和血凝素(HA)区段并在另一表达构建体上包括六种其他病毒区段，因为新出现的流感病毒株通常在所述NA和/或HA区段具有突变。因此，在独立的表达构建体上具有HA和/或NA区段的优势是仅需替换包含HA和NA序列的载体。因此，在本发明的一个方面中，所述疫苗毒株的NA和/或HA区段可包含在一个表达构建体上，而来自一种或多种本发明供体毒株的HA和/或NA区段以外的vRNA编码区段包含在不同的表达构建体上。因此，本发明提供包含编码本发明供体毒株中主链病毒区段的一种、两种、三种、四种、五种或六种vRNA的表达构建体。该表达构建体可包含生成功能性HA和/或NA蛋白的HA和/或NA病毒区段。

[0062] 已知的反向遗传系统涉及用pol I启动子、细菌RNA聚合酶启动子、噬菌体聚合酶启动子等表达编码所需病毒RNA(vRNA)分子的DNA分子。由于流感病毒需要病毒聚合酶存在以起始生命周期，系统还可提供这些蛋白，例如，所述系统还包括编码病毒聚合酶蛋白的DNA分子从而表达两种类型DNA引起完全感染性病毒的装配。还可以蛋白形式提供病毒聚合酶。

[0063] 当反向遗传学用于流感vRNA表达时，本领域技术人员清楚序列元件彼此的精确间隔对于聚合酶启动复制是重要的。因此编码所述病毒RNA的DNA分子在所述pol I启动子和所述终止序列之间的正确定位很重要，但该定位在反向遗传学系统操作人员的能力范围内。

[0064] 为了生产重组病毒，细胞必须表达组装病毒粒子所需病毒基因组的所有区段。克隆到本发明表达构建体内的DNA优选提供所有病毒RNA和蛋白，但也可使用辅助病毒以提供一些RNA和蛋白，但优选不使用辅助病毒的系统。由于所述流感病毒是分区段病毒，本发明的方法中所述病毒基因组通常使用多于一种表达构建体来表达。然而，还考虑在单一表达构建体上组合所述病毒基因组的一种或多种区段或甚至所有区段。

[0065] 一些实施方式中，也可包括导致宿主细胞内辅助蛋白表达的表达构建体。例如，作为反向遗传学系统一部分，表达非病毒丝氨酸蛋白酶(如胰蛋白酶)可具有优势。

[0066] 表达构建体

[0067] 用于本发明的表达系统的表达构建体可以是单向或双向表达构建体。所述方法中使用多于一种转基因时(不论在相同或不同表达构建体上)，可以使用单向和/或双向表达。

[0068] 由于流感病毒的传染性需要蛋白质，通常优选使用双向表达构建体，因为这能减少所述宿主细胞需要的表达构建体总数。因此，本发明的方法可利用至少一种双向表达构建体，其中基因或cDNA位于上游pol II启动子和下游非内源pol I启动子之间。从所述pol II启动子转录所述基因或cDNA产生可翻译为蛋白质的加帽正义病毒mRNA，而从所述非内源

pol I启动子转录产生负义vRNA。所述双向表达构建体可以是双向表达载体。

[0069] 双向表达构建体含有从同一构建体中的不同方向(即5'到3'和3'到5')驱动表达的至少两种启动子。这两种启动子可操作连接同一双链DNA的不同链。优选该启动子之一是pol I启动子且至少一种其他启动子为pol II启动子。这是有利的,因为该pol I启动子可用于表达非加帽的vRNA而该pol II启动子可用于转录随后翻译为蛋白质的mRNA,因此能从同一构建体同时表达RNA和蛋白质。当表达系统中使用超过一种表达构建体时,该启动子可以是内源性和非内源性启动子的混合物。

[0070] 表达构建体中使用的pol I和pol II启动子对于与宿主细胞来源具有相同分类学目的生物而言可以是内源的。或者,该启动子可来源于具有不同于宿主细胞的分类学目的生物体。术语"目"指常规分类学分级,目的示例为灵长目、啮齿目、食肉目、有袋目、鲸目等。人和黑猩猩在同一分类学目中(灵长目),但人和狗在不同的目中(灵长目与食肉目)。例如,可以使用人pol I启动子在犬细胞(如MDCK细胞)中表达病毒区段[16]。

[0071] 该表达构建体通常包括RNA转录终止序列。该终止序列可为内源终止序列或对所述宿主细胞非内源的终止序列。合适的终止序列对本领域技术人员而言是显而易见的且包括但不限于RNA聚合酶I转录终止序列、RNA聚合酶II转录终止序列和核酶。此外,该表达构建体可含有mRNA的一种或多种聚腺苷酸化信号,尤其在表达受pol II启动子控制的基因末端。

[0072] 表达系统可包括至少2种、至少3种、至少4种、至少5种、至少6种、至少7种、至少8种、至少9种、至少10种、至少11种或至少12种表达构建体。

[0073] 表达构建体可为载体,如质粒或其他游离构建体。此类载体通常包括至少一个细菌和/或真核的复制起点。此外,该载体可包括能在原核和/或真核细胞中筛选的选择标记。此类选择标记的示例为赋予抗生素抗性的基因,如氨苄青霉素或卡那霉素。该载体还可包含一个或多个多克隆位点以促进DNA序列克隆。

[0074] 或者,表达构建体可为线性表达构建体。这类线性表达构建体通常不含任何扩增和/或选择序列。但是,包含所述扩增和/或选择序列的线性构建体也在本发明的范围内。参考文献17描述了各病毒区段的单个线性表达构建体。也可能在相同线性表达构建体上包含多于一种,例如两种、三种、四种、五种或六种病毒区段。例如,参考文献18中描述了这类系统。还可以使用以下表达系统,其中一些病毒区段(例如HA和/或NA区段)在线性构建体上编码且剩余的病毒区段(例如主链区段)在非线性构建体(如载体、质粒或其他游离构建体)上编码。

[0075] 表达构建体可用本领域已知方法产生。例如,参考文献19中描述了此类方法。当该表达构建体为线性表达构建体时,可在引入宿主细胞前利用单个限制性酶位点使之线性化。或者,可用至少两种限制性酶位点从载体中切下该表达构建体。此外,也可通过用核酸扩增技术(如用PCR)扩增获得线性表达构建体。

[0076] 用于本发明的系统的表达构建体可以是非病毒表达构建体。这表示所述构建体可在真核细胞中驱动其内所编码病毒RNA区段的表达,但其不包括所述构建体在细菌中增殖所需的组分。因此所述构建体不含细菌复制起点(ori),且通常不含细菌选择标记(如抗生素抗性标记)。这类表达构建体描述于参考文献20。

[0077] 这些表达构建体可通过化学合成制备。这些表达构建体可完全或部分通过化学合

成制备。例如,参考文献20中描述了用于通过化学合成制备表达构建体的合适方法。

[0078] 可利用本领域技术人员已知的任何技术将本发明的表达构建体引入宿主细胞。例如,可通过使用电穿孔、DEAE-右旋糖苷、磷酸钙沉淀、脂质体、微注射或微粒轰击将表达构建体引入宿主细胞。可将表达构建体引入与随后用于重配乙型流感病毒的增殖的细胞类型相同的细胞类型。或者,其中引入表达构建体的细胞和用于增殖重配乙型流感病毒的细胞可以是不同的。在一些实施方式中,可将相同或不同细胞类型的未转染细胞添加至宿主细胞,随后使用表达构建体转染这些宿主细胞,如参考文献21中所述。

[0079] 常规重配

[0080] 传统上,通过用供体毒株和疫苗毒株共同感染培养宿主(通常是鸡蛋)来重配流感病毒。通过添加对所述供体毒株HA和/或NA蛋白特异的抗体来选择重配病毒,从而选择包含所述疫苗毒株的HA和/或NA蛋白的重配病毒。经过该处理的数次传代,可以选择包含所述疫苗毒株HA和/或NA区段的快速生长重配病毒。

[0081] 还可通过添加抑制剂来选择重配流感病毒,所述抑制剂优先降低所需重配流感病毒中不存在的病毒区段的转录和/或翻译,如WO2011/145081中教导的那样。

[0082] 本发明适于这些方法中的应用。相较于供体毒株,来自不同乙型流感谱系的疫苗毒株更易使用,因为这有利于重配病毒的选择。然而,也可能使用来自相同乙型流感谱系的疫苗毒株作为供体毒株,而这在本发明的一些方面中优选。在这种情况下,对所述供体毒株的HA和/或NA蛋白具有优先特异性的抗体或抑制剂应该是可获得的。

[0083] 培养宿主

[0084] 本发明所用的培养宿主可以是能产生感兴趣病毒的任何真核细胞。本发明通常使用细胞系,尽管例如原代细胞可用作替代。所述细胞通常是哺乳动物或鸟类。合适的哺乳动物细胞包括但不限于仓鼠、牛、灵长类(包括人类和猴)以及犬细胞。可以使用多种细胞类型,如肾细胞、成纤维细胞、视网膜细胞、肺细胞等。合适的仓鼠细胞的示例是名为BHK21或HKCC的细胞系。合适的猴细胞是例如非洲绿猴细胞,例如肾细胞,如Vero细胞系[22-24]。合适的犬细胞是(例如)肾细胞,例如CLDK和MDCK细胞系中。合适的禽胚胎干细胞包括来源于鸡胚胎干细胞的Ebx细胞系,EB45、EB14和EB14-074[25]。也可使用鸡胚成纤维细胞(CEF)。

[0085] 其他合适的细胞包括但不限于:CHO;293T;BHK;MRC 5;PER.C6[26];FRhL2;WI-38;等。合适的细胞系可由各种来源获得,例如美国典型培养物保藏中心(ATCC)[27]、Coriell细胞库[28]或欧洲细胞培养物保藏中心(ECACC)。例如,ATCC提供各种不同Vero细胞,目录号为CCL81、CCL81.2、CRL1586和CRL-1587;并提供MDCK细胞,目录号为CCL34。PER.C6可获自ECACC,保藏号为96022940。

[0086] 本发明使用的细胞优选源自马达二氏(Madin Darby)犬肾的MDCK细胞[29-31]。原始MDCK细胞可以CCL 34获自ATCC。优选地,使用MDCK细胞的衍生物。这类衍生物描述于例如参考文献29中,其公开了适合悬浮培养的MDCK细胞('MDCK 33016'或'33016-PF',保藏号DSM ACC 2219)。此外,参考文献32公开了在无血清培养基中悬浮培养的MDCK衍生细胞('B-702',保藏号FERM BP-7449)。在一些实施方式中,所用MDCK细胞系可为致瘤性的。也考虑使用非致瘤性MDCK细胞。例如,参考文献33公开了非致瘤性MDCK细胞,包括'MDCK-S'(ATCC PTA-6500)、'MDCK-SF101'(ATCC PTA-6501)、'MDCK-SF102'(ATCC PTA-6502)和'MDCK-SF103'(PTA-6503)。参考文献34公开了对感染有高度易感性的MDCK细胞,包括'MDCK.5F1'

细胞(ATCC CRL 12042)。

[0087] 可使用多于一种细胞类型的混合物来实施本发明的方法。但本发明的方法优选用单一细胞类型如用单克隆细胞实施。本发明方法所用细胞优选来自单一细胞系。此外,同一细胞系可用于重配所述病毒和所述病毒的任何后续繁殖。

[0088] 该细胞优选在无血清情况下培养以避免常见污染源。本领域技术人员已知用于真核细胞培养的各种无血清培养基(如伊可夫氏(Iscove's)培养基、超CHO培养基(BW公司(BioWhittaker))、EX-CELL(JRH生物科学公司(JRH Biosciences)))。此外,可用无蛋白培养基(如PF-CHO(JRH生物科学公司))。另外,用于复制的细胞也可在常规含血清培养基中(如含0.5%-10%胎牛血清的MEM或DMEM培养基)培养。

[0089] 该细胞可贴壁培养或悬浮培养。

[0090] 还可使用鸡蛋作为培养宿主来对本发明的重配乙型流感病毒进行增殖。目前培养流感病毒用于疫苗的标准方法采用含胚鸡蛋,从鸡蛋内容物(尿囊液)纯化病毒。也可通过鸡蛋对病毒传代并随后在细胞培养物中繁殖,反之亦然。

[0091] 病毒制备

[0092] 在一个实施方式中,本发明提供一种生产流感病毒的方法,所述方法包括以下步骤:(a)用本发明的重配病毒感染培养宿主;(b)培养来自步骤(a)的宿主以生产所述病毒;和可选地(c)纯化步骤(b)中生产的病毒。

[0093] 步骤(b)中的培养宿主可以是细胞(如上文所述)或含胚鸡蛋。本发明此方面中用细胞作培养宿主时,已知细胞培养条件(如温度、细胞密度、pH值等)根据所用细胞系和病毒在较宽的范围内变化且可根据应用需求调整。因此下述信息仅代表指南。

[0094] 细胞优选在无血清或无蛋白的培养基中培养。

[0095] 细胞的繁殖可按照本领域技术人员已知的方法进行。例如,可在使用常规支持方法如离心或过滤的灌注系统中培养细胞。此外,可根据本发明于感染前在分批进料系统中繁殖细胞。在本发明的内容中,培养系统指分批进料系统,其中该细胞初始培养于分批系统中且通过控制浓缩营养的进料来补偿培养基中营养物(或部分营养物)的消耗。在感染前的细胞繁殖期间将培养基的pH值值调节为pH 6.6-pH 7.8,特别是pH 7.2-pH 7.3是有利的。细胞培养优选在30-40℃的温度进行。在培养受感染细胞(步骤b)时,所述细胞优选在30℃-36℃或32℃-34℃或33℃的温度下培养。这是特别优选的,因为已显示在该温度范围内孵育受感染细胞能生产配入疫苗时功效改善的病毒[35]。

[0096] 感染前培养中的氧分压优选调节为25%-95%且特别为35%-60%的值。本发明内容中的氧分压值基于空气饱和度。在分批系统中细胞密度优选约8-25x10^5细胞/mL时或在灌注系统中优选约5-20x10^6细胞/mL时进行细胞感染。该细胞可用10^{-8}至10,优选0.0001-0.5的病毒剂量(MOI值,"感染复数",相当于感染时每细胞的病毒单位数量)感染。

[0097] 可以在贴壁或悬浮培养的细胞中培养病毒。可采用微载体培养。在一些实施方式中,这些细胞可适用于悬浮培养。

[0098] 本发明所述方法还包括收获和分离病毒或其产生的蛋白。分离病毒或蛋白期间,通过标准方法如分离、过滤或超滤从所述培养基中分离细胞。之后按照本领域技术人员充分已知的方法如梯度离心、过滤、沉淀、色谱等浓缩病毒或蛋白,然后纯化。根据本发明,优选在纯化期间或之后对病毒进行灭活。可在纯化过程中任何点用例如β-丙内酯或甲醛进行

病毒灭活。

[0099] 疫苗

[0100] 疫苗(特别针对流感病毒)通常基于活病毒或灭活病毒。灭活疫苗可基于完整病毒颗粒、'裂解'病毒颗粒或基于纯化的表面抗原。抗原也可以病毒体形式存在。可使用本发明制造任意这些类型的疫苗,但优选灭活疫苗。

[0101] 采用灭活病毒时,该疫苗可包含完整的病毒颗粒、分裂病毒颗粒或纯化的表面抗原(对于流感,包括血凝素,通常也包括神经氨酸酶)。灭活病毒的化学方法包括用有效量的以下一种或多种试剂处理:去污剂、甲醛、β-丙内酯、亚甲基蓝、亚甲蓝、补骨脂素、羧基富勒烯(C60)、二元乙胺、乙酰基乙烯亚胺或其组合。本领域已知病毒灭活的非化学方法,例如UV射线或γ射线辐射。

[0102] 可通过各种方法由含病毒液体(如尿囊液或细胞培养物上清)收获病毒颗粒。例如,纯化方法可包括用含有去污剂以破坏病毒颗粒的线性蔗糖梯度溶液进行区带离心。任选稀释后,可通过渗滤纯化抗原。

[0103] 用去污剂(如乙醚、聚山梨醇酯80、脱氧胆酸盐、三正丁基磷酸盐、曲通X100、曲通N101、溴化十六烷基三甲铵、特吉托NP9等)处理纯化的病毒颗粒以获得裂解病毒颗粒,从而产生亚病毒颗粒制品,包括'吐温-醚'裂解方法。裂解流感病毒的方法为本领域熟知,例如参见参考文献36-41等。一般使用破坏浓度的裂解剂破坏或片段化全病毒来裂解该病毒,无论该病毒有无感染性。这种破坏导致病毒蛋白的完全或部分溶解,改变病毒的完整性。优选的裂解剂是非离子型和离子型(例如阳离子)表面活性剂,如烷基糖苷、烷基硫苷、酰基糖、磺基甜菜碱、甜菜碱、聚氧乙烯烷基醚、N,N-二烷基-葡糖酰胺、6-O-(N-庚甲酰)-甲基-á-D-葡萄糖苷(Hecameg)、烷基苯氧基-聚乙氧基乙醇、NP9、季铵化合物、肌氨酰、CTAB(溴化十六烷基三甲铵)、三正丁基磷酸酯、塞弗伦(Cetavlon)、十四烷基三甲铵盐、脂质转染试剂(Lipofectin)、脂质体转染试剂(lipofectamine)和DOT-MA、辛基-或壬基苯氧基聚氧乙醇(如曲通表面活性剂,如曲通X100或曲通N101)、聚氧乙烯去水山梨糖醇酯(吐温表面活性剂)、聚氧乙烯醚、聚氧乙烯酯等。一种有用的裂解方法利用脱氧胆酸钠和甲醛的连续作用,并且裂解可在病毒颗粒初始纯化期间进行(例如在蔗糖密度梯度溶液中)。因此,裂解过程可包括:澄清含病毒颗粒的材料(以去除非病毒颗粒物质),浓缩收获的病毒颗粒(例如使用吸附方法,如$CaHPO_4$吸附),从非病毒颗粒材料中分离全病毒颗粒,用裂解剂在密度梯度离心步骤中裂解病毒颗粒(例如,用含有裂解剂如脱氧胆酸钠的蔗糖梯度),然后过滤(例如超滤)以去除不需要的物质。可将裂解病毒颗粒重悬于磷酸钠缓冲的等渗氯化钠溶液中。裂解流感疫苗的示例是BEGRIVAC™、FLUARIX™、FLUZONE™和FLUSHIELD™产品。

[0104] 纯化的流感病毒表面抗原疫苗包含表面抗原血凝素,一般还包含神经氨酸酶。制备这些纯化形式的蛋白质的方法是本领域熟知的。FLUVIRIN™、AGRIPPAL™和INFLUVAC™产品是流感亚基疫苗。

[0105] 另一种形式的灭活抗原是病毒体[42](不含核酸的病毒样脂质体颗粒)。其可通过使用去污剂溶解病毒,然后去除核衣壳和重建含病毒糖蛋白的膜来制备。一种用于制备病毒体的替代性方法包括将病毒膜糖蛋白加入过量磷脂中,得到膜中具有病毒蛋白质的脂质体。

[0106] 本发明的方法还可用于生产活疫苗。通常通过从含病毒颗粒的流体中纯化病毒颗

粒来制备这类疫苗。例如，该流体可通过离心澄清并用缓冲液(例如含蔗糖、磷酸钾和谷氨酸单钠)稳定。目前可以获得各种形式的流感病毒疫苗(例如参见参考文献43的第17和18章)。活病毒疫苗包括米迪缪尼公司(MedImmune)的FLUMIST™产品。

[0107] 该病毒可以是减毒的。该病毒可以是温度敏感型的。该病毒可以是冷适应性的。使用活病毒作为抗原时这三种特征特别有用。

[0108] HA是现有灭活流感疫苗中的主要免疫原，且参照一般由SRID测定的HA水平来标准化疫苗剂量。现有的疫苗一般含有约15μg HA/毒株，但也可使用更低的剂量，例如用于儿童或大流行情况下，或者是使用佐剂时。分数剂量如1/2(即7.5μg HA/毒株)、1/4和1/8已有应用，更高剂量的(如3x或9x剂量也有使用[44,45])。因此，疫苗可包含0.1-150μg HA/流感毒株，优选0.1-50μg，例如0.1-20μg、0.1-15μg、0.1-10μg、0.1-7.5μg、0.5-5μg等。具体剂量包括例如，约45、约30、约15、约10、约7.5、约5、约3.8、约3.75、约1.9、约1.5等/株。

[0109] 对于活疫苗，利用组织培养感染剂量中值($TCID_{50}$)而非HA含量来衡量剂量，且$TCID_{50}$一般为10^6至10^8(优选为$10^{6.5}$-$10^{7.5}$)/株。

[0110] 本发明所用的流感株可以具有野生型病毒中的天然HA，或具有修饰HA。例如，已知修饰HA以去除使病毒在禽类物种中具有高致病性的决定簇(如HA1/HA2切割位点周围的超碱性区域(hyper-basic region))。反向遗传学的使用促进了这类修饰。

[0111] 除了适于针对大流行间期株系的免疫，本发明的疫苗特别适用于免疫抵御大流行或潜在大流行株系。本发明适用于免疫人以及非人动物。

[0112] 本发明的疫苗可包含来自一种或多种(如1、2、3、4或更多)流感病毒株的抗原，包括甲型流感病毒和/或乙型流感病毒，前提是至少一种流感病毒是本发明的重配流感病毒。还考虑包括以下疫苗，其中两种抗原来自本发明的重配流感毒株。当疫苗包含超过一种流感的毒株时，一般单独培养不同毒株，收获病毒后将它们混合在一起，然后制备抗原。因此，本发明方法可包括混合超过一种流感毒株的抗原的步骤。三价疫苗是典型的，其包含来自两种甲型流感病毒株和一种乙型流感病毒株的抗原。也可用四价疫苗[46]，其包含来自两种甲型流感病毒毒株和两种乙型流感病毒毒株(优选不同谱系的两种乙型流感毒株)、或者三种甲型流感病毒毒株和一种乙型流感病毒毒株的抗原。当流感疫苗包含来自超过一种乙型流感毒株的抗原时，其中一种或多种可来源于本发明的重配乙型流感病毒。

[0113] 本发明的疫苗优选为药学上可接受的组合物。它们通常还包含抗原外的其它组分，例如它们一般包含一种或多种药物载体和/或赋形剂。如下所述，也可包含佐剂。对这类组分的充分讨论参见参考文献47。

[0114] 疫苗通常是水性形式。然而，一些疫苗可为干燥形式，如可注射固体或贴片上的干燥或聚合制品的形式。

[0115] 疫苗可含有防腐剂，如硫柳汞或2-苯氧乙醇。然而，疫苗优选应基本不含(即小于5μg/ml)含汞物质，如不含硫柳汞[40,48]。更优选无汞的疫苗。可包含琥珀酸α-生育酚以替代含汞化合物[40]。特别优选不含防腐剂的疫苗。

[0116] 为了控制张力，优选包含生理盐(如钠盐)。优选氯化钠(NaCl)，其浓度可以是1-20mg/ml。可以存在的其它盐，包括氯化钾、磷酸二氢钾、无水合磷酸氢二钠、氯化镁、氯化钙等。

[0117] 疫苗的渗透压通常为200mOsm/kg-400mOsm/kg，优选为240-360mOsm/kg，更优选为

290-310mOsm/kg。虽然以前报道过渗透压对疫苗接种引起的疼痛无影响[49]，但优选将渗透压保持在此范围内。

[0118] 疫苗可含有一种或多种缓冲剂。典型的缓冲剂包括：磷酸盐缓冲剂；Tris缓冲剂；硼酸盐缓冲剂；琥珀酸盐缓冲剂；组氨酸缓冲剂(尤其是含氢氧化铝佐剂时)；或柠檬酸盐缓冲剂。包含的缓冲剂的浓度一般为5至20mM的范围。

[0119] 疫苗的pH通常为5.0-8.1，更一般为6.0-8.0，例如6.5-7.5，或者7.0-7.8。因此，本发明方法可包括在包装前调整散装疫苗pH的步骤。

[0120] 该疫苗优选是无菌的。该疫苗优选无热原，如小于1EU/剂量(内毒素单位，标准量度)，优选小于0.1EU/剂量。该疫苗优选不含谷蛋白。

[0121] 本发明的疫苗可包含去污剂，如聚氧乙烯去水山梨糖醇酯表面活性剂(称为'吐温')、辛苯聚糖(如辛苯聚糖-9(曲通X100)或叔辛基苯氧基聚乙氧基乙醇)、溴化十六烷基三甲铵('CTAB')或脱氧胆酸钠，特别用于裂解疫苗或表面抗原疫苗。去污剂可仅以痕量存在。因此，疫苗中可包含各自的含量小于1mg/ml的辛苯聚醇-10和聚山梨醇酯80。其它痕量残留组分可以是抗生素(如新霉素、卡那霉素、多粘菌素B)。

[0122] 疫苗可含有一次免疫的物质，或者可含有多次免疫的物质(即'多剂量'药盒)。多剂量配置优选含有防腐剂。作为多剂量疫苗中包含防腐剂的替代方案(或补充方案)，这些疫苗可包含在装有无菌接头以取出物质的容器中。

[0123] 流感疫苗的给药剂量体积一般为约0.5ml，但可将一半剂量(即约0.25ml)给予儿童。

[0124] 疫苗和药盒优选储存于2℃-8℃。其不应冷冻。理想情况下应避直射光保存。

[0125] 宿主细胞DNA

[0126] 由细胞系分离和/或培养病毒时，标准实践是使最终疫苗中残留的细胞系DNA含量最小化，以最小化该DNA的潜在致癌活性。

[0127] 因此，本发明的疫苗优选含有每剂量低于10ng(优选低于1ng，更优选低于100pg)的残留宿主细胞DNA，但可能存在痕量宿主细胞DNA。

[0128] 任何残留宿主细胞DNA的平均长度优选小于500bp，例如小于400bp、小于300bp、小于200bp、小于100bp等。

[0129] 在疫苗制备过程中可采用标准纯化方法，如色谱法等去除污染的DNA。可通过核酸酶处理，例如DNA酶处理来提高对残留宿主细胞DNA的去除。参考文献58和59公开了一种减少宿主细胞DNA污染的方便方法，该方法包括两步处理，先使用DNA酶(如Benzonase)处理，这一步可以在病毒生长过程中使用，然后使用阳离子去污剂(如CTAB)处理，这一步可以在病毒颗粒破坏过程中使用。也可利用烷化剂(如β-丙内酯)处理来去除宿主细胞DNA，该方法也宜用于灭活病毒颗粒[52]。

[0130] 佐剂

[0131] 本发明的疫苗宜包含佐剂，其作用是增强在接受疫苗的患者中引起的免疫应答(体液免疫和/或细胞免疫)。优选的佐剂包含水包油乳液。已知多种这类佐剂，它们通常包含至少一种油和至少一种表面活性剂，所述油和表面活性剂是可生物降解(可代谢)和生物相容的。乳液中的油滴直径通常小于5μm，理想情况下具有亚微米直径，通过微流化床实现这种小尺寸以提供稳定的乳液。优选尺寸小于220nm的液滴，因为其可进行过滤灭菌。

[0132] 所述乳液可以包含如动物(如鱼)或植物来源的油。植物油的来源包括坚果、种籽和谷物。最常见的坚果油的示例有花生油、大豆油、椰子油和橄榄油。可以采用例如获自霍霍巴豆的霍霍巴油。种籽油包括红花油、棉花籽油、葵花籽油、芝麻籽油等。在谷物油中,最常见的是玉米油,但也可以使用其它谷类的油,如小麦、燕麦、黑麦、稻、画眉草、黑小麦等。甘油和1,2-丙二醇的6-10碳脂肪酸酯虽然不天然存在于种籽油中,但可从坚果和种籽油开始,通过水解、分离和酯化合适物质来制备。来源于哺乳动物乳汁的脂肪和油类是可代谢的,因此可以用于实施本发明。获得动物来源的纯油所必需的分离、纯化、皂化和其它方法的过程是本领域中熟知的。大多数鱼类含有容易回收的可代谢油。例如,可用于本文的鱼油的几种示例有鳕鱼肝油、鲨鱼肝油和鲸油(诸如鲸蜡)。通过生化途径以5-碳异戊二烯单位合成许多支链油,其总称为萜类。鲨鱼肝油含有称为角鲨烯的支链不饱和萜类化合物,2,6,10,15,19,23-六甲基-2,6,10,14,18,22-二十四碳六烯,其是本文特别优选的。角鲨烯的饱和类似物角鲨烷也是优选的油。包括角鲨烯和角鲨烷在内的鱼油易于从市售来源获得,或可以通过本领域已知的方法获得。另一种优选的油是α-生育酚(参见下文)。

[0133] 可以使用油的混合物。

[0134] 表面活性剂可以按其“HLB”(亲水/亲脂平衡)分类。本发明优选的表面活性剂的HLB值为至少10,优选至少15,更优选至少16。可用于本发明的表面活性剂包括但不限于:聚氧乙烯脱水山梨糖醇酯表面活性剂(通常称为吐温),特别是聚山梨酯20和聚山梨酯80;以商品名DOWFAX™出售的环氧乙烷(EO)、环氧丙烷(PO)和/或环氧丁烷(BO)的共聚物,如直链EP/PO嵌段共聚物;重复的乙氧基(氧-1,2-乙二基)数量不同的辛苯聚醇,特别感兴趣的是辛苯聚醇9(曲通X-100,或叔辛基苯氧基聚乙氧基乙醇);(辛基苯氧基)聚乙氧基乙醇(IGEPAL CA-630/NP-40);磷脂,如磷脂酰胆碱(卵磷脂);壬酚乙醇酯,如Tergitol™ NP系列;衍生自月桂醇、鲸蜡醇、硬脂醇和油醇的聚氧乙烯脂肪醚(称为苄泽(Brij)表面活性剂),如三甘醇单月桂基醚(苄泽30);以及脱水山梨糖醇酯(通常称为司盘(SPAN)),如脱水山梨糖醇三油酸酯(司盘85)和脱水山梨糖醇单月桂酸酯。优选非离子型表面活性剂。乳液中包含的表面活性剂优选吐温80(聚氧乙烯去水山梨糖醇单油酸酯)、司盘85(去水山梨糖醇三油酸酯)、卵磷脂和曲通X-100。

[0135] 可使用表面活性剂的混合物,如吐温80/司盘85混合物。聚氧乙烯脱水山梨糖醇酯(如聚氧乙烯去水山梨糖醇单油酸酯(吐温80))和辛苯聚醇(如叔辛基苯氧基聚乙氧基乙醇(曲通X-100))的组合也是有用的。另一种有用的组合包括月桂醇聚醚-9加聚氧乙烯山梨糖醇酯和/或辛苯聚醇。

[0136] 优选的表面活性剂含量(重量百分比)为:聚氧乙烯去水山梨糖醇酯(如吐温80)0.01-1%,特别是约0.1%;辛基-或壬基苯氧基聚氧乙醇(如曲通X-100或曲通系列的其它去污剂)0.001-0.1%,特别是0.005-0.02%;聚氧乙烯醚(如月桂醇聚醚9)0.1-20%,优选0.1-10%,特别是0.1-1%或约0.5%。

[0137] 该疫苗含裂解病毒时,优选在水相中含有游离的表面活性剂。这是有利的,因为游离表面活性剂可在所述抗原上产生‘裂解效果’,因此破坏否则可能存在的任何未裂解病毒颗粒和/或病毒颗粒聚集体。这可改善裂解病毒疫苗的安全性[53]。

[0138] 优选的乳液的平均液滴大小为小于1μm,例如小于等于750nm、小于等于500nm、小于等于400nm、小于等于300nm、小于等于250nm、小于等于220nm、小于等于200nm或更小。可

通过某些技术(如微流化)方便地获得这些液滴尺寸。

[0139] 本发明所用的具体水包油乳剂佐剂包括但不限于：

[0140] 角鲨烯、吐温80和司盘85的亚微米乳液。所述乳液的体积组成可以是约5％角鲨烯、约0.5％聚山梨酯80和约0.5％司盘85。以重量计，这些比例为4.3％角鲨烯、0.5％聚山梨酯80和0.48％司盘85。这种佐剂称为‘MF59’[54-56]，参考文献57的第10章和参考文献58的第12章更详细地描述了该佐剂。.MF59乳液优选包含柠檬酸根离子，例如10mM柠檬酸钠缓冲液。

[0141] 包含角鲨烯、α-生育酚和聚山梨酯80的乳液。该乳液可包含磷酸盐缓冲盐水。这些乳剂可含有(以体积计)2-10％角鲨烯、2-10％生育酚和0.3-3％聚山梨酯80，且角鲨烯:生育酚的重量比优选小于等于1(例如0.90)，因为这能提供更稳定的乳剂。角鲨烯和聚山梨酯80的体积比可以约为5:2，或者重量比约为11:5。因此这三种组分(角鲨烯、生育酚、聚山梨酯80)可以1068:1186:485或约55:61:25的重量比存在。可通过以下方法制备一种这样的乳液(“AS03”)：将吐温80溶解于PBS产生2％溶液，然后将90ml该溶液与5g DL-α-生育酚和5ml角鲨烯的混合物混合，然后使该混合物微流体化。所得乳液可含有如平均直径为100-250nm，优选约180nm的亚微米油滴。该乳液也可含有3-脱-O-酰化单磷酰脂质A(3d-MPL)。此种类型的另一有用乳液可包含(每人剂量)0.5-10mg角鲨烯、0.5-11mg生育酚和0.1-4mg聚山梨酯80[59]，例如，以上述比例。

[0142] 角鲨烯、生育酚和曲通去污剂(如曲通X-100)的乳液。该乳液也可包含3d-MPL(见下文)。该乳液可包含磷酸盐缓冲液。

[0143] 含有聚山梨酯(如聚山梨酯80)、曲通去污剂(如曲通X-100)和生育酚(如琥珀酸α-生育酚)的乳液。该乳液可包含这三种组分，其质量比约为75:11:10(例如，750μg/ml聚山梨酯80、110μg/ml曲通X-100和100μg/ml琥珀酸α-生育酚)，且这些浓度应包括来自抗原的这些组分的任何贡献。该乳液还可包含角鲨烯。该乳液也可包含3d-MPL(见下文)。水相可包含磷酸盐缓冲液。

[0144] 角鲨烷、聚山梨酯80和泊洛沙姆401(“Pluronic™ L121”)的乳液。该乳液可用pH 7.4的磷酸盐缓冲盐水配制。该乳液是一种有用的胞壁酰二肽递送载体，已与苏氨酰基-MDP一起用于“SAF-I”佐剂中[60](0.05-1％Thr-MDP、5％角鲨烷、2.5％Pluronic L121和0.2％聚山梨酸酯80)。也可不与Thr-MDP一起使用，例如在“AF”佐剂中[61](5％角鲨烷、1.25％Pluronic L121和0.2％聚山梨酸酯80)。优选微流体化。

[0145] 含有角鲨烯、水溶剂、聚氧乙烯烷基醚亲水性非离子型表面活性剂(如聚氧乙烯(12)十六十八醚)和疏水性非离子型表面活性剂(如去水山梨糖醇酯或二缩甘露醇酯，如去水山梨糖醇单油酸酯或‘司盘80’)的乳液。所述乳液优选为热可逆的和/或其中至少90％油滴(以体积计)小于200nm[62]。该乳液也可含有一种或多种以下物质：糖醇；低温保护剂(例如糖，如十二烷基麦芽苷和/或蔗糖)；和/或烷基聚糖苷。所述乳液可包含TLR4激动剂[63]。可将这类乳液冻干。

[0146] 角鲨烯、泊洛沙姆-105和Abil-Care的乳液[64]。含佐剂化疫苗中这些组分的终浓度(重量)是5％角鲨烯、4％泊洛沙姆-105(普流罗尼克多元醇)和2％Abil-Care 85(双-PEG/PPG-16/16PEG/PPG-16/16二甲硅油；辛酸/癸酸甘油三酯)。

[0147] 含有0.5-50％油、0.1-10％磷脂和0.05-5％非离子型表面活性剂的乳液。如参考

文献65所述，优选的磷脂组分是磷脂酰胆碱、磷脂酰乙醇胺、磷脂酰丝氨酸、磷脂酰肌醇、磷脂酰甘油、磷脂酸、鞘磷脂和心磷脂。优选亚微米液滴尺寸。

[0148] 不可代谢油(如轻质矿物油)和至少一种表面活性剂(如卵磷脂、吐温80或司盘80)的亚微米水包油乳液。可包含添加剂，例如QuilA皂苷、胆固醇、皂苷-亲脂体偶联物(如通过葡糖醛酸的羧基将脂族胺加到脱酰基皂苷上而产生的GPI-0100，如参考文献66所述)、二甲基二-十八烷基溴化铵和/或N,N-二-十八烷基-N,N-双(2-羟乙基)丙二胺。

[0149] 皂苷(如QuilA或QS21)和固醇(如胆固醇)结合成螺旋胶束的乳液[67]。

[0150] 包含矿物油、非离子亲脂性乙氧基化脂肪醇和非离子亲水性表面活性剂(例如，乙氧基化脂肪醇和/或聚氧乙烯-聚氧丙烯嵌段共聚物)的乳液[68]。

[0151] 包含矿物油、非离子亲脂水性乙氧基化脂肪醇和非离子亲脂性表面活性剂(例如，乙氧基化脂肪醇和/或聚氧乙烯-聚氧丙烯嵌段共聚物)的乳液[68]。

[0152] 在一些实施方式中，可在递送时临时将乳液与抗原混合，因此所述佐剂和抗原可单独地保存在包装或分销的疫苗中，以便在使用时配制成最终制剂。在其它实施方式中，在生产过程中将乳液与抗原混合，因此组合物以液体含佐剂形式包装。该抗原通常采用水性形式，从而最终通过混合两种液体来制备疫苗。待混合的两种液体的体积比可变(例如5:1-1:5)，但一般是约1:1。在上述具体乳液说明中给出组分浓度时，这些浓度通常用于非稀释组合物，因此所述浓度在混合抗原溶液后会降低。

[0153] 疫苗的包装

[0154] 适用于本发明的疫苗(或药盒组分)的容器包括药瓶、注射器(如一次性注射器)、鼻喷雾等。这些容器应无菌。

[0155] 组合物/组分装在药瓶中时，药瓶优选由玻璃或塑料材料制成。在加入组合物之前，摇瓶优选已灭菌。为了避免胶乳过敏患者的问题，药瓶优选用无胶乳塞子密封，且优选所有包装材料均不含胶乳。该药瓶可包含单一剂量的疫苗，或者可以包含一个以上剂量('多剂量'药瓶)，如10个剂量。优选地，药瓶由无色玻璃制成。药瓶，特别是多剂量药瓶可装有允许无菌取出其内含物的瓶帽。

[0156] 将某一组分包装到注射器中时，该注射器可连有针头。如果未连接针头，可随注射器提供单独的针头以便组装和使用。这种针头可装在护罩中。优选安全针头。一般是1-英寸23号、1-英寸25号和5/8-英寸25号针头。可提供有剥离标签的注射器，该标签上可打印上内含物的批号、流感季节和过期日期，以帮助记录保存。注射器中的活塞优选带有防脱装置，以防止活塞在吸出时意外脱出。注射器可以具有胶乳橡胶帽和/或活塞。一次性注射器含有单一剂量的疫苗。注射器通常带有顶帽，以在连接针头前密封顶端，且该顶帽优选由丁基橡胶制成。如果注射器和针头分开包装，则针头优选地装有丁基橡胶护罩。优选的注射器是以商品名"Tip-Lok"™销售的注射器。

[0157] 容器可标注显示半剂量体积，例如以利于递送给儿童。例如，含有0.5ml剂量的注射器可有显示0.25ml体积的标记。

[0158] 在使用玻璃容器(如注射器或药瓶)时，优选采用由硼硅酸盐玻璃，而非钠钙玻璃制成的容器。

[0159] 可将药盒或组合物与单页宣传品包装在一起(在同一个盒子中)，所述单页宣传品包括疫苗的详细情况如给药说明书、疫苗内所含抗原的详情等。说明书也可包含警示，例如

准备好肾上腺素溶液以防疫苗接种后发生过敏反应等。

[0160] 治疗方法和疫苗的给药

[0161] 本发明提供了一种根据本发明生产的疫苗。这些疫苗适合给予人类或非人动物对象如猪或鸟类，且本发明提供了在对象中产生免疫应答的方法，该方法包括将本发明的疫苗给予所述对象的步骤。本发明还提供用作药物的本发明的疫苗，并提供本发明的疫苗在生产在对象中产生免疫应答的药物中的应用。

[0162] 这些方法和应用产生的免疫应答通常包括抗体应答，优选保护性抗体应答。评价接种流感病毒疫苗后抗体应答、中和能力和保护水平的方法为本领域熟知。人类研究表明，对人流感病毒血凝素的抗体效价与保护作用相关联(约30-40的血清样品血凝反应-抑制效价给出对同源病毒感染产生约50％保护作用)[69]。一般通过血凝反应抑制、微量中和、单径向免疫扩散(SRID)和/或单径向溶血(SRH)来测定抗体应答。本领域熟知这些测定技术。

[0163] 可以各种方式给予本发明的疫苗。最优选的免疫途径是肌肉内注射(如注射到上肢或下肢)，但其它可用的途径包括皮下注射、鼻内[70-72]、口服[73]、皮内[74,75]、经皮、透皮[76]等。

[0164] 根据本发明制备的疫苗可用于治疗儿童和成人。目前，推荐将流感疫苗用于年龄大于6个月的儿童和成年人免疫。因此，人类对象可以小于1岁、1～5岁、5～15岁、15～55岁或至少55岁。接受该疫苗的优选对象是老年人(例如大于等于50岁、大于等于60岁，优选大于等于65岁)、年轻人(如小于等于5岁)、住院对象、健康护理工作人员、军队服务人员和军人、妊娠妇女、慢性疾病对象、免疫缺陷对象、在接受该疫苗7天前接受过抗病毒化合物(如奥塞米韦或扎那米韦化合物；见下)的对象、对鸡蛋过敏的人和出国旅行者。然而该疫苗不仅适用于这些人群，还可用于更广泛的群体。对于大流行毒株，优选给予所有年龄组。

[0165] 本发明的优选疫苗满足1、2或3个CPMP功效标准。在成年人(18-60岁)中，这些标准是：(1)大于等于70％血清保护；(2)大于等于40％血清转化；和/或(3)GMT增加大于等于2.5倍。在老年人(大于60岁)中，这些标准是：(1)大于等于60％血清保护；(2)大于等于30％血清转化；和/或(3)GMT增加大于等于2倍。这些标准基于至少50位患者的开放标记研究。

[0166] 可通过单剂量方案或多剂量方案进行治疗。多剂量可用于初次免疫方案和/或加强免疫方案。在多剂量方案中，可通过相同或不同的途径(如肠胃外初次和粘膜加强，粘膜初次和肠胃外加强等)给予多个剂量。给予一个以上剂量(一般是两个剂量)特别用于免疫未曾免疫接触的患者，例如从未接受过流感疫苗的人，或者用于免疫接种抵御新的HA亚型(如大流行爆发中的亚型)。一般以至少1周(例如约2周、约3周、约4周、约6周、约8周、约10周、约12周、约16周等)的间隔给予多个剂量。

[0167] 可将本发明产生的疫苗与其它疫苗基本上同时(在健康护理专业人员或疫苗接种中心的同一医学咨询或就诊期间)给予患者，例如与麻疹疫苗、腮腺炎疫苗、风疹疫苗、MMR疫苗、水痘疫苗、MMRV疫苗、白喉疫苗、破伤风疫苗、百日咳疫苗、DTP疫苗、偶联的B型流感嗜血杆菌(H.influenzae)疫苗、脊髓灰质炎病毒灭活疫苗、乙型肝炎病毒疫苗、脑膜炎球菌偶联疫苗(如四价A-C-W135-Y疫苗)、呼吸道合胞病毒疫苗、肺炎球菌偶联疫苗等基本同时给药。在老年患者中特别有用的是与肺炎球菌疫苗和/或脑膜炎球菌疫苗基本同时给药。

[0168] 相似地，可将本发明疫苗与抗病毒化合物，具体是对流感病毒有活性的抗病毒化合物(如奥塞米韦和/或扎那米韦)基本上同时给予患者(在对健康护理专业人员进行的同

一用药咨询或就诊期间)。这些抗病毒化合物包括神经氨酸酶抑制剂,如(3R,4R,5S)-4-乙酰基氨基-5-氨基-3(1-乙基丙氧基)-1-环己烯-1-羧酸或5-(乙酰基氨基)-4-[(氨基亚氨基甲基)-氨基]-2,6-脱水-3,4,5-三脱氧-D-甘油-D-半乳糖壬-2-烯酮酸,包括它们的酯(如乙酯)和盐(如磷酸盐)。优选的抗病毒药物是(3R,4R,5S)-4-乙酰基氨基-5-氨基-3(1-乙基丙氧基)-1-环己烯-1-羧酸,乙酯和磷酸盐(1:1),也称为磷酸奥塞米韦(达菲(TAMIFLU)™)。

[0169] 概述

[0170] 术语“包括”涵盖“包含”以及“由……组成”,例如,“包括”X的组合物可以仅由X组成或可以包括其它物质,例如X+Y。

[0171] 词语“基本上”不排除“完全”,如“基本上不含”Y的组合物可能完全不含Y。需要时,词语“基本上”可从本发明的定义中略去。

[0172] 与数值x相关的术语“约”是可任选的,并且表示,例如x±10%。

[0173] 除非另有明确说明,包括混合两种或更多种组分的步骤的工艺不要求任何特定的混合顺序。因此,组分可以任何顺序混合。在有三种组分时,可将两种组分相互合并,然后可将组合与第三种组分合并等。

[0174] 本方法的各步骤可在相同或不同时间、相同或不同地理位置如国家以及由相同或不同人或实体进行。

[0175] 将动物(且特别是牛)材料用于培养细胞时,其应获自未患传染性海绵状脑病(TSE),特别是未患牛海绵状脑病(BSE)的来源。总之,优选在完全不含动物来源物质的条件下培养细胞。

[0176] 将化合物作为组合物的一部分给予机体时,该化合物或可由合适的前药替代。

[0177] 两个氨基酸序列间的序列相同性百分数表示进行比对时所比较的两条序列中相同氨基酸的百分数。利用本领域所知软件程序,例如参考文献77的7.7.18部分所描述的软件程序,可进行比对并确定同源性百分数或序列相同性百分数。优选的比对通过史密斯-沃特曼(Smith-Waterman)同源性搜索算法使用仿射缺口搜索确定,其中缺口开放罚12分,缺口延伸罚2分,BLOSUM矩阵计62分。参考文献78中公开了史密斯-沃特曼同源性搜索算法。

[0178] 两个核酸序列间的序列相同性百分数表示进行比对时所比较的两条序列中相同碱基的百分数。利用本领域所知软件程序,例如参考文献77的7.7.18部分所描述的软件程序,可进行比对并确定同源性百分数或序列相同性百分数。优选的比对程序是GCG Gap(威斯康星州的遗传计算机组(Genetics Computer Group),套件版本10.1),优选使用以下默认参数:开放缺口=3;延伸缺口=1。

附图说明

[0179] 图1比较相对于野生型(WT)或反向遗传学来源的(RG)B/Brisbane/60/08毒株,MDCK细胞中不同重配乙型流感毒株的HA产率。测试的乙型流感病毒的病毒区段示于表1。y轴显示HA产率(单位为μg/mL)。

[0180] 图2比较相对于野生型(WT)或反向遗传学来源的(RG)B/Panama/45/90毒株,MDCK细胞中不同重配乙型流感毒株的HA产率。测试的乙型流感病毒的病毒区段示于表1。y轴显示HA产率(单位为μg/mL)。

[0181] 图3比较包含B/Panama/45/90或B/Brisbane/60/08主链的重配乙型流感病毒的HA产率和使用相应野生型毒株获得的HA产率。使用以下区段进行不同的实验:B/Brisbane/60/08HA和NA区段(A)、B/Panama/45/90HA和NA区段(B)、B/Florida/4/06HA和NA区段(C)或者B/Lee/40HA和NA区段(D)。白色柱显示使用野生型毒株的结果,阴影线柱显示使用B/Panama/45/90主链的结果且格子花纹柱显示使用B/Brisbane/60/08主链的结果。图3(A)、3(B)和3(C)的y轴显示ELISA测定的HA产率(单位为μg/mL)且图3(D)的y轴显示HA试验测定的HA效价。

[0182] 图4比较包含#2、#9、#32或#34杂交主链(如表1所示)的重配乙型流感病毒的HA产率和使用BX-35、B/Panama/45/90或B/Brisbane/60/08主链或者相应野生型病毒获得的HA产率。使用以下区段进行不同的实验:B/Brisbane/60/08HA和NA区段(A)、B/Panama/45/90HA和NA区段(B)、BX-35HA和NA区段(C)或者B/Florida/4/06HA和NA区段(D)。y轴显示HA产率(单位为μg/mL)。

[0183] 图5比较包含#34或B/Brisbane/60/08主链的重配乙型流感病毒的HA产率和使用相应野生型毒株获得的HA产率。使用以下区段进行不同的实验:B/Panama/45/90HA和NA区段(A)、B/Brisbane/60/08HA和NA区段(B)、B/Florida/4/06HA和NA区段(C)、B/Brisbane/03/07HA和NA区段(D)、B/Brisbane/32/02HA和NA区段(E)、BX-35HA和NA区段(F)、B/Malaysia/2506/04HA和NA区段(G),或B/Hubei-Wujiagang/159/08HA和NA区段(H)。白色柱显示使用B/Brisbane/60/08主链的结果,阴影线柱显示使用#34主链的结果且格子花纹柱显示使用野生型毒株的结果。y轴显示HA产率(单位为μg/mL)。

[0184] 图6比较以下病毒在含胚鸡蛋中生长后的HA效价(A)和病毒生长(B):包含来自B/Brisbane/60/08(#35)的所有主链区段和来自B/Wisconsin/1/10的HA和NA区段的反向遗传学衍生的重配乙型流感病毒,(b)包含来自B/Lee/40的PB2、NP和M区段和来自B/Wisconsin/1/10(#41)的所有其他基因的重配乙型流感病毒,以及(c)野生型B/Wisconsin/1/10毒株(WT)。各三角形代表单个鸡蛋且横线代表平均值。“280”和“2800”表示对这些鸡蛋接种的感染剂量(IU)。(A)中的y轴代表HA产率且(B)中的y轴代表IU/mL。

[0185] 具体实施方式

[0186] 新供体毒株的开发

[0187] 为提供高生长供体毒株,发明人发现,包含来自B/Brisbane/60/08和B/Panama/45/90的主链区段的重配乙型流感病毒在鸡蛋和细胞(如MDCK细胞)中生长的特别好。为此,生产了包含来自这些病毒的主链区段的重配乙型流感病毒并使所得乙型流感病毒在MDCK细胞中生长。通过本领域已知的ELISA(如PCT/IB2012/057235所述)或HA试验测定病毒产率。

[0188] 重配乙型流感病毒的生长特性

[0189] 通过反向遗传学生产重配乙型流感病毒,其含有来自多种流感毒株的HA和NA蛋白以及来自B/Brisbane/60/08和/或B/Panama/45/90的其他病毒区段。作为对照,使用了相应的野生型乙型流感毒株。在含胚鸡蛋或MDCK细胞中培养这些病毒。使用了以下乙型流感毒株:

[0190] 表1

[0191]

	主链区段						抗原决定簇	
组合编号	PA	PB1	PB2	NP	NS	M	HA	NA
1 (WT)	Brisbane	Brisbane	Brisbane	Brisbane	Brisbane	Brisbane	Brisbane	Brisbane
2	Panama	Brisbane	Brisbane	Brisbane	Brisbane	Brisbane	Brisbane	Brisbane
3	Brisbane	Panama	Brisbane	Brisbane	Brisbane	Brisbane	Brisbane	Brisbane
4	Brisbane	Brisbane	Panama	Brisbane	Brisbane	Brisbane	Brisbane	Brisbane
5	Brisbane	Brisbane	Brisbane	Panama	Brisbane	Brisbane	Brisbane	Brisbane
6	Panama	Panama	Brisbane	Brisbane	Brisbane	Brisbane	Brisbane	Brisbane
7	Panama	Brisbane	Panama	Brisbane	Brisbane	Brisbane	Brisbane	Brisbane
8	Panama	Brisbane	Brisbane	Panama	Brisbane	Brisbane	Brisbane	Brisbane
9	Brisbane	Panama	Panama	Brisbane	Brisbane	Brisbane	Brisbane	Brisbane
10	Brisbane	Panama	Brisbane	Panama	Brisbane	Brisbane	Brisbane	Brisbane
11	Brisbane	Brisbane	Panama	Panama	Brisbane	Brisbane	Brisbane	Brisbane
12	Panama	Panama	Panama	Brisbane	Brisbane	Brisbane	Brisbane	Brisbane
13	Panama	Panama	Brisbane	Panama	Brisbane	Brisbane	Brisbane	Brisbane
14	Panama	Brisbane	Panama	Panama	Brisbane	Brisbane	Brisbane	Brisbane
15	Brisbane	Panama	Panama	Panama	Brisbane	Brisbane	Brisbane	Brisbane
16	Panama	Panama	Panama	Panama	Brisbane	Brisbane	Brisbane	Brisbane
17	Panama	Panama	Panama	Panama	Panama	Panama	Brisbane	Brisbane
20	Brisbane	Panama	Panama	Panama	Panama	Panama	Panama	Panama
21	Panama	Brisbane	Panama	Panama	Panama	Panama	Panama	Panama
22	Panama	Panama	Brisbane	Panama	Panama	Panama	Panama	Panama
23	Panama	Panama	Panama	Brisbane	Panama	Panama	Panama	Panama
24	Brisbane	Brisbane	Panama	Panama	Panama	Panama	Panama	Panama
25	Brisbane	Panama	Brisbane	Panama	Panama	Panama	Panama	Panama
26	Brisbane	Panama	Panama	Brisbane	Panama	Panama	Panama	Panama
27	Panama	Brisbane	Brisbane	Panama	Panama	Panama	Panama	Panama
28	Panama	Brisbane	Panama	Brisbane	Panama	Panama	Panama	Panama
29	Panama	Panama	Brisbane	Brisbane	Panama	Panama	Panama	Panama
30	Brisbane	Brisbane	Brisbane	Panama	Panama	Panama	Panama	Panama
31	Brisbane	Brisbane	Panama	Brisbane	Panama	Panama	Panama	Panama
32	Brisbane	Panama	Brisbane	Brisbane	Panama	Panama	Panama	Panama
33	Panama	Brisbane	Brisbane	Brisbane	Panama	Panama	Panama	Panama
34	Brisbane	Brisbane	Brisbane	Brisbane	Panama	Panama	Panama	Panama
35	Brisbane	Brisbane	Brisbane	Brisbane	Brisbane	Brisbane	Panama	Panama

[0192] 结果显示，与相应的野生型毒株相比，重配病毒#2、#9、#22、#23、#29、#30、#31、#32、#33、#34和#35在培养宿主中生长的一样好或甚至更好(参见图1和2)。这些毒株中的大多数包含来自B/Brisbane/60/08的NP区段且一些(特别是生长得最好的那些)还含有来自B/Brisbane/60/08的PB2区段。所有这些病毒还以7:1、6:2、4:4、3:4或1:7的比例含有来自B/Victoria/2/87样毒株和B/Yamagata/16/88样毒株的病毒区段。

[0193] 包含来自B/Brisbane/60/08的主链区段的重配乙型流感病毒的生长特性

[0194] 为测试本发明的重配乙型流感病毒是否与来自不同毒株的HA和NA区段联用，生产

了包含来自B/Panama/45/90、B/Lee/40或B/Florida/04/06的HA和NA区段以及来自B/Brisbane/60/08的主链区段的重配乙型流感病毒。将重配流感病毒在MDCK细胞中生长60小时并通过ELISA或HA试验测定HA产率。数据(参见图3)显示,与野生型乙型流感病毒相比,所有重配乙型流感病毒都生长至较高效价,这表明本发明的重配乙型流感病毒可用于多种不同的HA和NA区段。

[0195] 包含杂交主链区段的重配乙型流感病毒的生长特性

[0196] 还相对于野生型乙型流感病毒和已知的乙型流感病毒BX35(其包含来自B/Brisbane/60/08的HA、NA、PA、PBI和NS区段、来自B/Panama/45/90的PB2和M区段以及来自B/Lee/40的NP区段)测定包含本发明的主链区段的重配乙型流感病毒的生长特性。使用B/Brisbane/60/08、B/Panama/45/90、BX-35和B/Florida/04/06的HA和NA蛋白测试各主链。将重配流感病毒在MDCK细胞中生长60小时并通过ELISA或RP-HPLC试验测定HA产率。数据(参见图4)显示,与包含已知BX35主链的重配乙型流感病毒和野生型相比,包含本发明的主链的重配乙型流感病毒可生长至较高效价。

[0197] 还使用了多种不同的HA和NA区段测试了使用#34和#35获得的HA产率。使用重配乙型流感病毒和相应的野生型乙型流感病毒感染MDCK细胞。数据(参见图5)显示,与相应的野生型毒株相比,所有包含本发明的主链的重配乙型流感病毒都生长得一样好或更好。

[0198] 鸡蛋中重配乙型流感病毒的生长特性

[0199] 使用以下病毒的280或2800感染性剂量(IU)接种含胚鸡蛋:包含来自B/Brisbane/60/08(#35主链)的所有主链区段和来自B/Wisconsin/1/10的HA和NA区段的反向遗传学衍生的重配乙型流感病毒,(b)包含来自B/Lee/40的PB2、NP和M区段和来自B/Wisconsin/1/10(BX-41)的所有其他基因的重配乙型流感病毒,以及(c)野生型B/Wisconsin/1/10毒株。在感染后72小时收获鸡蛋尿囊液,并通过HA试验测定HA效价或通过病灶形成试验测定病毒生长。数据(参见图6)显示,与对照毒株相比,本发明的重配乙型流感病毒可生长得一样好或更好。

[0200] 应理解,仅以举例的方式描述了本发明,可对之进行修改而仍在本发明的范围和构思内。

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[0278] 序列

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ATCAGAGGGTTTGTATTAGTAGTTGAAAACTTGGCTAAAAATATATGTGAAAATCTAGAACAAAGTGGTTTACCAGT
AGGTGGAAACGAGAAGAAAGCCAAACTGTCAAACGCAGTGGCCAAAATGCTCAGTAACTGCCCACCAGGAGGGATTA
GCATGACAGTAACAGGAGACAATACAAAATGGAATGAATGTTTAAACCCAAGAATCTTTTTGGCTATGACTGAAAGA
ATAACCAGAGACAGCCCAGTTTGGTTCAGGGATTTTTGTAGTATAGCACCGGTCCTGTTCTCCAATAAGATAGCAAG
ATTGGGGAAAGGGTTTATGATAACAAGCAAAACAAAAAGACTGAAGGCTCAAATACCTTGTCCTGATCTGTTTAGTA
TACCGTTAGAAAGATATAATGAAGAAACAAGGGCAAAATTGAAAAAGCTAAAACCATTCTTCAATGAAGAAGGAACT
GCATCTTTGTCGCCTGGGATGATGATGGGAATGTTTAATATGCTATCTACCGTGTTGGGAGTAGCTGCACTAGGTAT
CAAGAACATTGGAAACAAAGAATACTTATGGGATGGACTGCAATCTTCTGATGATTTTGCTCTGTTTGTTAATGCAA
AGGATGAAGAAACATGTATGGAAGGAATAAACGACTTTTACCGAACATGTAAATTATTGGGAGTAAACATGAGCAAA
AAGAAAAGTTACTGTAATGAGACTGGAATGTTTGAATTTACAAGCATGTTCTACAGAGATGGATTTGTATCTAATTT
TGCAATGGAACTCCCTTCGTTTGGGGTTGCTGGAGTAAATGAATCAGCAGATATGGCAATAGGAATGACAATAATAA
AGAACAACATGATCAACAATGGAATGGGTCCGGCAACAGCACAAACAGCCATACAGTTATTCATAGCTGATTATAGA
TACACCTACAAATGCCACAGGGGAGATTCCAAAGTAGAAGGAAAGAGAATGAAAATCATAAAGGAGTTATGGGAAAA
CACTAAAGGAAGAGATGGTCTATTAGTAGCAGATGGTGGGCCCAACATTTACAATTTGAGAAACCTGCATATCCCAG
AAATAGTATTAAAGTATAATCTAATGGACCCTGAATACAAAGGGCGGTTACTTCATCCTCAAAATCCCTTTGTGGGA
CATTTGTCTATTGAGGGCATCAAAGAGGCAGACATAACCCCAGCACATGGTCCAGTAAAGAAAATGGACTACGATGC
GGTGTCTGGAACTCATAGTTGGAGAACCAAAAGAAACAGATCTATACTAAACACTGATCAGAGGAACATGATTCTTG
AGGAACAATGCTACGCTAAATGTTGCAACCTATTTGAGGCCTGTTTTAACAGTGCATCATACAGGAAGCCAGTGGGT
CAACATAGCATGCTTGAGGCTATGGCCCACAGATTAAGAATGGATGCACGATTAGATTATGAATCAGGGAGAATGTC
AAAGGATGATTTTGAGAAAGCAATGGCTCACCTTGGTGAGATTGGGTACATATAAGCTTCGAAGATGTTTATGGGGT
TATTGGTCATCATTGAATACATGCGATACACAAATGATTAAAATGAAAAAAGGCTCGTGTTTCTACT

[0303] SEQ ID NO:13(PB2,B/Brisbane/60/08)

[0304] AGCAGAAGCGGAGCGTTTTCAAGATGACATTGGCCAAAATTGAATTGTTAAAACAACTGCTAAGGGACA
ATGAAGCCAAAACAGTTTTGAAGCAAACAACGGTAGACCAATATAACATAATAAGAAAATTCAATACATCAAGGATT
GAAAAGAATCCTTCACTAAGGATGAAGTGGGCCATGTGTTCTAATTTTCCCTTGGCTCTAACCAAGGGCGATATGGC
AAACAGAATCCCCTTGGAATACAAAGGGATACAACTTAAAACAAATGCTGAAGACATAGGAACCAAAGGCCAAATGT
GCTCAATAGCAGCAGTTACTTGGTGGAATACATATGGACCAATAGGAGATACTGAAGGTTTCGAAAGGGTCTACGAA
AGCTTTTTTCTCAGAAAAATGAGACTTGACAACGCCACTTGGGGCCGAATAACTTTTGGCCCAGTTGAAAGAGTGAG
AAAAAGGGTACTGCTAAACCCTCTCACCAAGGAAATGCCTCCGGATGAGGCGAGCAATGTGATAATGGAAATATTGT
TCCCTAAAGAAGCAGGAATACCAAGAGAATCCACTTGGATACATAGGGAACTGATAAAAGAAAAAAGAGAAAAATTG
AAAGGAACAATGATAACTCCAATCGTACTGGCATACATGCTTGAAAGAGAACTGGTTGCTCGAAGAAGATTCTTGCC
AGTGGCAGGAGCAACATCAGCTGAGTTCATAGAAATGCTACACTGCTTACAAGGTGAAAATTGGAGACAAATATATC
ACCCAGGAGGGAATAAATTAACTGAGTCCAGGTCTCAATCAATGATAGTAGCTTGTAGAAAAATAATCAGAAGATCA
ATAGTCGCTTCAAACCCACTGGAGCTAGCTGTAGAAATTGCAAACAAGACTGTGATAGATACTGAACCTTTAAAGTC
ATGTCTGGCAGCCATAGACGGAGGTGATGTAGCTTGTGACATAATAAGAGCTGCATTAGGACTAAAGATCAGACAAA
GACAAAGATTTGGACGGCTTGAGCTAAAAAGAATATCAGGAAGAGGATTCAAAAATGATGAAGAAATATTAATAGGG
AACGGAACAATACAGAAGATTGGAATATGGGACGGGGAAGAGGAGTTCCATGTAAGATGTGGTGAATGCAGGGGAAT
ATTAAAAAAGAGTAAAATGAAACTGGAAAAACTACTGATAAATTCAGCCAAAAAGGAGGATATGAGAGATTTAATAA
TCTTATGCATGGTATTTTCTCAAGACACTAGGATGTTCCAAGGAGTGAGAGGAGAAATAAATTTTCTTAATCGAGCA

GGCCAACTTTTATCTCCAATGTACCAACTCCAACGATATTTTTTGAATAGAAGCAACGACCTTTTTGATCAATGGGG
GTATGAGGAATCACCCAAAGCAAGTGAACTACATGGGATAAATGAATCAATGAATGCATCTGACTATACATTGAAAG
GGATTGTAGTGACAAGAAATGTAATTGACGACTTTAGCTCTATTGAAACAGAAAAAGTATCCATAACAAAAAATCTT
AGTTTAATAAAAAGGACTGGGGAAGTCATAATGGGAGCTAATGACGTGAGTGAATTAGAATCACAAGCACAGCTGAT
GATAACATATGATACACCTAAAATGTGGGAAATGGGAACAACCAAAGAACTGGTGCAAAACACTTATCAATGGGTGC
TAAAAAACTTGGTGACACTGAAGGCTCAGTTTCTTCTAGGAAAAGAGGACATGTTCCAATGGGATGCATTTGAAGCA
TTTGAGAGCATAATTCCTCAGAAGATGGCTGGTCAGTACAGTGGATTTGCAAGAGCAGTGCTCAAACAAATGAGAGA
CCAGGAGGTTATGAAAACTGACCAGTTCATAAAGTTGTTGCCTTTTTGTTTCTCACCACCAAAATTAAGGAGCAATG
GGGAGCCTTATCAATTCTTAAAACTTGTGTTGAAAGGAGGAGGGGAAAATTTCATCGAAGTAAGGAAAGGGTCCCCT
CTATTTTCCTATAATCCACAAACAGAAGTCCTAACTATATGCGGCAGAATGATGTCATTAAAAGGGAAAATTGAAGA
TGAAGAAAGGAATAGATCAATGGGTAATGCAGTATTAGCAGGCTTTCTCGTTAGTGGCAAGTATGACCCAGATCTTG
GAGATTTCAAAACTATTGAAGAACTTGAAAAGCTGAAACCGGGGGAAAAGGCAAACATCTTACTTTATCAAGGAAAA
CCAGTTAAAGTAGTTAAAAGGAAAAGGTATAGTGCTTTGTCCAATGACATTTCACAAGGAATTAAGAGACAAAGAAT
GACAGTTGAGTCTATGGGGTGGGCCTTGAGCTAATATAAATTTATCCATTAATTCAATGAACGCAATTGAGTGAAAA
ATGCTCGTGTTTCTACT

[0305] SEQ ID NO:14(NP,B/Brisbane/60/08)

[0306] AGCAGAAGCACAGCATTTTCTTGTGAACTTCAAGCACCAGTAAAAGAACTGAAAATCAAAATGTCCAAC
ATGGATATTGACGGTATAAACACTGGGACAATTGACAAAACACCGGAAGAAATAACTTCTGGAACCAGTGGGACAAC
CAGACCAATCATTAGACCAGCAACCCTTGCCCCACCAAGCAACAAACGAACCCGTAACCCATCCCCGGAAAGAGCAA
CCACAAGCAGTGAAGATGATGTCGGAAGGAAAACCCAAAAGAAACAGACCCCGACAGAGATAAAGAAGAGCGTCTAC
AACATGGTGGTGAAACTGGGCGAATTCTATAACCAGATGATGGTCAAAGCTGGACTCAATGATGACATGGAGAGAAA
TCTAATCCAAAATGCGCATGCCGTGGAAAGAATTCTATTGGCTGCCACTGATGACAAGAAAACCGAGTTCCAGAAGA
AAAAGAATGCCAGAGATGTCAAAGAAGGGAAAGAAGAAATAGATCACAACAAAACAGGAGGCACCTTTTACAAGATG
GTAAGAGATGATAAAACCATCTACTTCAGCCCTATAAGAATTACCTTTTTAAAAGAAGAGGTGAAAACAATGTACAA
AACCACCATGGGGAGTGATGGCTTCAGTGGACTAAATCACATAATGATTGGGCATTCACAGATGAATGATGTCTGTT
TCCAAAGATCAAAGGCACTAAAAAGAGTTGGACTTGATCCTTCATTAATCAGTACCTTTGCGGGAAGCACAGTCCCC
AGAAGATCAGGTGCGACTGGTGTTGCAATCAAAGGAGGTGGAACCTTAGTGGCTGAAGCCATTCGATTTATAGGAAG
AGCAATGGCAGACAGAGGGCTATTGAGAGACATCAAAGCCAAGACTGCCTATGAAAAGATTCTTCTGAATCTAAAAA
ACAAATGCTCTGCGCCCCAACAAAAGGCTCTAGTTGATCAAGTGATCGGAAGCAGAAATCCGGGGATTGCAGACATT
GAAGATCTAACCCTGCTTGCTCGTAGTATGGTCGTTGTTAGGCCCTCTGTGGCAAGCAAAGTGGTGCTTCCCATAAG
CATTTACGCCAAAATACCTCAACTAGGGTTCAATGTTGAAGAGTACTCTATGGTTGGGTACGAAGCCATGGCTCTTT
ACAATATGGCAACACCTGTGTCCATATTAAGAATGGGAGATGATGCAAAAGATAAATCGCAATTATTCTTCATGTCT
TGCTTCGGAGCTGCCTATGAAGACCTGAGAGTTTTGTCTGCATTAACAGGCACAGAATTCAAGCCTAGATCAGCATT
AAAATGCAAGGGTTTCCATGTTCCAGCAAAGGAACAGGTAGAAGGAATGGGAGCAGCTCTGATGTCCATCAAGCTCC
AGTTTTGGGCTCCGATGACCAGATCTGGGGGGAACGAAGTAGGTGGAGACGGAGGGTCTGGCCAAATAAGCTGCAGC
CCAGTGTTTGCAGTGGAAAGACCTATTGCTCTAAGCAAGCAAGCTGTAAGAAGAATGCTGTCAATGAATATTGAGGG
ACGTGATGCAGATGTCAAAGGAAATCTACTCAAGATGATGAATGACTCAATGGCTAAGAAAACCAGTGGAAATGCTT
TCATTGGGAAGAAAATGTTTCAAATATCAGACAAAAACAAAACCAATCCCATTGAAATTCCAATTAAGCAGACCATC
CCCAATTTCTTCTTTGGGAGGGACACAGCAGAGGATTATGATGACCTCGATTATTAAGGCAACAAAATAGACACTAT

GACTGTGATTGTTTCAATACGTTTGGAATGTGGGTGTTTATTCTTATTAAAATAAATATAAAAAATGCTGTTGTTTC
TACT

[0307] SEQ ID NO:15(M,B/Brisbane/60/08)

[0308] AGCAGAAGCACGCACTTTCTTAAAATGTCGCTGTTTGGAGACACAATTGCCTACCTGCTTTCATTGACA
GAAGATGGAGAAGGCAAAGCAGAACTAGCAGAAAAATTACACTGTTGGTTTGGTGGGAAAGAATTTGACCTAGACTC
TGCCTTGGAATGGATAAAAAACAAAAGATGCTTAACTGATATACAAAAAGCACTAATTGGTGCCTCTATATGCTTTT
TAAAACCCAAAGACCAGGAAAGAAAAAGAAGATTCATCACAGAGCCCTTATCAGGAATGGGAACAACAGCAACAAAA
AAGAAAGGCCTGATTCTGGCTGAGAGAAAAATGAGAAGATGTGTGAGCTTTCATGAAGCATTTGAAATAGCAGAAGG
CCATGAAAGCTCAGCGCTACTATACTGTCTCATGGTCATGTACCTGAATCCTGGAAATTATTCAATGCAAGTAAAAC
TAGGAACGCTCTGTGCTTTATGCGAGAAACAAGCATCACATTCACACAGGGCTCATAGCAGAGCAGCGAGATCTTCA
GTGCCTGGAGTGAGACGAGAAATGCAGATGGTCTCAGCTATGAACACAGCAAAAACAATGAATGGAATGGGAAAAGG
AGAAGACGTCCAAAAGCTGGCAGAAGAGTTGCAAAGCAACATTGGAGTGCTGAGATCTCTTGGGGCAAGCCAAAAGA
ATGGGGAAGGGATTGCAAAGGATGTAATGGAAGTGCTAAAGCAGAGCTCCATGGGAAATTCAGCTCTTGTGAAGAAA
TATCTATAATGCTCGAACCATTTCAGATTCTTACAATTTGTTCTTTTATCTTATCAGCTCTCCATTTCATGGCTTGG
ACAATAGGGCATTTGAATCAAATAAAAAGAGGAATAAACATGAAAATACGAATAAAAGGTCCAAACAAAGAGACAAT
AAACAGAGAGGTATCAATTTTGAGACACAGTTACCAAAAAGAAATCCAGGCCAAAGAAACAATGAAGGAAGTACTCT
CTGACAACATGGAGGTATTGAATGACCACATAATAATTGAGGGGCTTTCTGCCGAAGAGATAATAAAAATGGGTGAA
ACAGTTTTGGAGATAGAAGAATTGCATTAAATTCAATTTTACTGTATTTCTTACTATGCATTTAAGCAAATTGTAAT
CAATGTCAGCAAATAAACTGGAAAAAGTGCGTTGTTTCTACT

[0309] SEQ ID NO:16(NS,B/Brisbane/60/08)

[0310] AGCAGAAGCAGAGGATTTGTTTAGTCACTGGCAAACAGGGAAAAATGGCGAACAACAACATGACCACAA
CACAAATTGAGGTGGGTCCGGGAGCAACCAATGCCACCATAAACTTTGAAGCAGGAATTCTAGAGTGCTATGAAAGG
CTTTCATGGCAAAGAGCCCTTGACTACCCTGGTCAAGACCGCCTAAACAGACTAAAGAGAAAATTAGAGTCAAGAAT
AAAGACTCACAACAAAAGTGAGCCTGAAAGTAAAAGGATGTCCCTTGAAGAGAGAAAAGCAATTGGAGTAAAAATGA
TGAAAGTACTCCTATTTATGAATCCGTCTGCTGGAATTGAAGGGTTTGAGCCATACTGTATGAAAAGTTCCTCAAAT
AGCAACTGTACGAAATACAATTGGACTGATTACCCTTCAACACCAGAGAGGTGCCTTGATGACATAGAGGAAGAACC
AGAGGATGTTGATGGCCCAACTGAAATAGTATTAAGGGACATGAACAACAAAGATGCAAGGCAAAAGATAAAGGAGG
AAGTAAACACTCAGAAAGAAGGGAAGTTCCGTTTGACAATAAAAAGGGATATGCGTAATGTATTGTCCTTGAGAGTG
TTGGTAAACGGAACATTCCTCAAACACCCCAATGGACACAAGTCCTTATCAACTCTGCATAGATTGAATGCATATGA
CCAGAGTGGAAGGCTTGTTGCTAAACTTGTTGCCACTGATGATCTTACAGTGGAGGATGAAGAAGATGGCCATCGGA
TCCTCAACTCACTCTTCGAGCGTCTTAATGAAGGACATTCAAAGCCAATTCGAGCAGCTGAAACTGCGGTGGGAGTC
TTATCCCAATTTGGTCAAGAGCACCGATTATCACCAGAAGAGGGAGACAATTAGACTGGTCACGGAAGAACTTTATC
TTTTAAGTAAAAGAATTGATGATAACATACTATTCCACAAAACAGTAATAGCTAACAGCTCCATAATAGCTGACATG
GTTGTATCATTATCATTATTAGAAACATTGTATGAAATGAAGGATGTGGTTGAAGTGTACAGCAGGCAGTGCTTGTG
AATTTAAAATAAAAATCCTCTTGTTACTACT

[0311] SEQ ID NO:17(HA,B/Brisbane/60/08)

[0312] AGCAGAAGCAGAGCATTTTCTAATATCCACAAAATGAAGGCAATAATTGTACTACTCATGGTAGTAACA
TCCAATGCAGATCGAATCTGCACTGGGATAACATCGTCAAACTCACCACATGTCGTCAAAACTGCTACTCAAGGGGA
GGTCAATGTGACTGGTGTAATACCACTGACAACAACACCCACCAAATCTCATTTTGCAAATCTCAAAGGAACAGAAA

CCAGGGGGAAACTATGCCCAAAATGCCTCAACTGCACAGATCTGGACGTAGCCTTGGGCAGACCAAAATGCACGGGG
AAAATACCCTCGGCAAGAGTTTCAATACTCCATGAAGTCAGACCTGTTACATCTGGGTGCTTTCCTATAATGCACGA
CAGAACAAAAATTAGACAGCTGCCTAACCTTCTCCGAGGATACGAACATATCAGGTTATCAACCCATAACGTTATCA
ATGCAGAAAATGCACCAGGAGGACCCTACAAAATTGGAACCTCAGGGTCTTGCCCTAACATTACCAATGGAAACGGA
TTTTTCGCAACAATGGCTTGGGCCGTCCCAAAAAACGACAAAAACAAAACAGCAACAAATCCATTAACAATAGAAGT
ACCATACATTTGTACAGAAGGAGAAGACCAAATTACCGTTTGGGGGTTCCACTCTGACAACGAGGCCCAAATGGCAA
AGCTCTATGGGGACTCAAAGCCCCAGAAGTTCACCTCATCTGCCAACGGAGTGACCACACATTACGTTTCACAGATT
GGTGGCTTCCCAAATCAAACAGAAGACGGAGGACTACCACAAAGTGGTAGAATTGTTGTTGATTACATGGTGCAAAA
ATCTGGGAAAACAGGAACAATTACCTATCAAAGGGGTATTTTATTGCCTCAAAAGGTGTGGTGCGCAAGTGGCAGGA
GCAAGGTAATAAAAGGATCCTTGCCTTTAATTGGAGAAGCAGATTGCCTCCACGAAAAATACGGTGGATTAAACAAA
AGCAAGCCTTACTACACAGGGGAACATGCAAAGGCCATAGGAAATTGCCCAATATGGGTGAAAACACCCTTGAAGCT
GGCCAATGGAACCAAATATAGACCTCCTGCAAAACTATTAAAGGAAAGGGGTTTCTTCGGAGCTATTGCTGGTTTCT
TAGAAGGAGGATGGGAAGGAATGATTGCAGGTTGGCACGGATACACATCCCATGGGGCACATGGAGTAGCGGTGGCA
GCAGACCTTAAGAGCACTCAAGAGGCCATAAACAAGATAACAAAAAATCTCAACTCTTTGAGTGAGCTGGAAGTAAA
GAATCTTCAAAGACTAAGCGGTGCCATGGATGAACTCCACAACGAAATACTAGAACTAGATGAGAAAGTGGATGATC
TCAGAGCTGATACAATAAGCTCACAAATAGAACTCGCAGTCCTGCTTTCCAATGAAGGAATAATAAACAGTGAAGAT
GAACATCTCTTGGCGCTTGAAAGAAAGCTGAAGAAAATGCTGGGCCCCTCTGCTGTAGAGATAGGGAATGGATGCTT
TGAAACCAAACACAAGTGCAACCAGACCTGTCTCGACAGAATAGCTGCTGGTACCTTTGATGCAGGAGAATTTTCTC
TCCCCACCTTTGATTCACTGAATATTACTGCTGCATCTTTAAATGACGATGGATTGGATAATCATACTATACTGCTT
TACTACTCAACTGCTGCCTCCAGTTTGGCTGTAACACTGATGATAGCTATCTTTGTTGTTTATATGGTCTCCAGAGA
CAATGTTTCTTGCTCCATCTGTCTATAAGGGAAGTTAAGCCCTGTATTTTCCTTTATTGTAGTGCTTGTTTACTTGT
TGTCATTACAAAGAAACGTTATTGAAAAATGCTCTTGTTACTACT

[0313] SEQ ID NO:18(NA,B/Brisbane/60/08)

[0314] AGCAGAAGCAGAGCATCTTCTCAAAACTGAAGCAAATAGGCCAAAAATGAACAATGCTACCTTCAACTA
TACAAACGTTAACCCTATTTCTCACATCAGGGGGAGTATTATTATCACTATATGTGTCAGCTTCATTATCATACTTA
CTATATTCGGATATATTGCTAAAATTCTCACCAACAGAAATAACTGCACCAACAATGCCATTGGATTGTGCAAACGC
ATCAAATGTTCAGGCTGTGAACCGTTCTGCAACAAAAGGGGTGACACTTCTTCTCCCAGAACCGGAGTGGACATACC
CGCGTTTATCTTGCCCGGGCTCAACCTTTCAGAAAGCACTCCTAATTAGCCCTCATAGATTCGGAGAAACCAAAGGA
AACTCAGCTCCCTTGATAATAAGGGAACCTTTTATTGCTTGTGGACCAAATGAATGCAAACACTTTGCTCTAACCCA
TTATGCAGCCCAACCAGGGGGATACTACAATGGAACAAGAGGAGACAGAAACAAGCTGAGGCATCTAATTTCAGTCA
AATTGGGCAAAATCCCAACAGTAGAAAACTCCATTTTCCACATGGCAGCATGGAGCGGGTCCGCGTGCCATGATGGT
AAGGAATGGACATATATCGGAGTTGATGGCCCTGACAATAATGCATTGCTCAAAGTAAAATATGGAGAAGCATATAC
TGACACATACCATTCCTATGCAAACAAAATCCTAAGAACACAAGAAAGTGCCTGCAATTGCATCGGGGGAAATTGTT
ATCTTATGATAACTGATGGCTCAGCTTCAGGTGTTAGTGAATGCAGATTTCTTAAGATTCGAGAGGGCCGAATAATA
AAAGAAATATTTCCAACAGGAAGAGTAAAACACACTGAGGAATGCACATGCGGATTTGCCAGCAATAAAACCATAGA
ATGTGCCTGTAGAGATAACAGTTACACAGCAAAAAGACCTTTTGTCAAATTAAACGTGGAGACTGATACAGCAGAAA
TAAGATTGATGTGCACAGATACTTATTTGGACACCCCCAGACCAAACGATGGAAGCATAACAGGCCCTTGTGAATCT
AATGGGGACAAAGGGAGTGGAGGCATCAAGGGAGGATTTGTTCATCAAAGAATGGAATCCAAGATTGGAAGGTGGTA
CTCTCGAACGATGTCTAAAACTGAAAGGATGGGGATGGGACTGTATGTCAAGTATGATGGAGACCCATGGGCTGACA

GTGATGCCCTAGCTTTTAGTGGAGTAATGGTTTCAATGAAAGAACCTGGTTGGTACTCCTTTGGCTTCGAAATAAAA
GATAAGAAATGCGATGTCCCCTGTATTGGGATAGAGATGGTACATGATGGTGGAAAAGAGACTTGGCACTCAGCAGC
AACAGCCATTTACTGTTTAATGGGCTCAGGACAGCTGCTGTGGGACACTGTCACAGGTGTTGACATGGCTCTGTAAT
GGAGGAATGGTTGAGTCTGTTCTAAACCCTTTGTTCCTGTTTTGTTTGAACAATTGTCCTTACTAAACTTAATTGTT
TCTGAAAAATGCTCTTGTTACTACT

[0315] SEQ ID NO:19(NP,B/Lee/40)

[0316] MSNMDIDSINTGTIDKKPEELTPGTSGATRPIIKPATLAPPSNKRTRNPSPERTTTSSETDIGRKIQKK
QTPTEIKKSVYNMVVKLGEFYNQMMVKAGLNDDMERNLIQNAQAVERILLAATDDKKTEYQKKRNARDVKEGKEEID
HNKTGGTFYKMVRDDKTIYFSPIKITFLKEEVKTMYKTTMGSDGFSGLNHIMIGHSQMNDVCFQRSKALKRVGLDPS
LISTFAGSTLPRRSGTTGVAIKGGGTLVAEAIRFIGRAMADRGLLRDIKAKTAYEKILLNLKNKCSAPQQKALVDQV
IGSRNPGIADIEDLTLLARSMIVVRPSVASKVVLPISIYAKIPQLGFNIEEYSMVGYEAMALYNMATPVSILRMGDD
AKDKSQLFFMSCFGAAYEDLRVLSALTGTEFKPRSALKCKGFHVPAKEQVEGMGAALMSIKLQFWAPMTRSGGNEVS
GEGGSGQISCSPVFAVERPIALSKQAVRRMLSMNVEGRDADVKGNLLKMMNDSMAKKTSGNAFIGKKMFQISDKNKV
NPIEIPIKQTIPSFFFGRDTAEDYDDLDY

[0317] SEQ ID NO:20(PA,B/Panama/45/90)

[0318] MDTFITRNFQTTIIQKAKNTMAEFSEDPELQPAMLFNICVHLEVCYVISDMNFLDEEGKSYTALEGQGK
EQNLRPQYEVIEGMPRTIAWMVQRSLAQEHGIETPKYLADLFDYKTKRFIEVGITKGLADDYFWKKKEKLGNSMELM
IFSYNQDYSLSNESSLDEEGKGRVLSRLTELQAELSLKNLWQVLIGEEDVEKGIDFKLGQTISRLRDISVPAGFSNF
EGMRSYIDNIDPKGAIERNLARMSPLVSATPKKLKWEDLRPIGPHIYNHELPEVPYNAFLLMSDELGLANMTEGKSK
KPKTLAKECLEKYSTLRDQTDPILIMKSEKANENFLWKLWRDCVNTISNEEMSNELQKTNYAKWATGDGLTYQKIMK
EVAIDDETMCQEEPKIPNKCRVAAWVQTEMNLLSTLTSKRALDLPEIGPDVAPVEHVGSERRKYFVNEINCCKASTV
MMKYVLFHTSLLNESNASMGKYKVIPITNRVVNEKGESFDMLYGLAVKGQSHLRGDTDVVTVVTFEFSGTDPRVDSG
KWPKYTVFRIGSLFVSGREKSVYLYCRVNGTNKIQMKWGMEARRCLLQSMQQMEAIVEQESSIQGYDMTKACFKGDR
VNSPKTFSIGTQEGKLVKGSFGKALRVIFTKCLMHYVFGNAQLEGFSAESRRLLLLIQALKDRKGPWVFDLEGMYSG
IEECISNNPWVIQSAYWFNEWLGFEKEGSKVLESVDEIMNE

[0319] SEQ ID NO:21(PB1,B/Panama/45/90)

[0320] MNINPYFLFIDVPIQAAISTTFPYTGVPPYSHGTGTGHTIDTVIRTHEYSNKGKQYVSDITGCTMVDPT
NGPLPEDNEPSAYAQLDCVLEALDRMDEEHPGLFQAASQNAMEALMVTTVDKLTQGRQTFDWTVCRNQPAATALNTT
ITSFRLNDLNGADKGGLVPFCQDIIDSLDKPEMTFFSVKNIKKKLPAKNRKGFLIKRIPMKVKDRITRVEYIKRALS
LNTMTKDAERGKLKRRAIATAGIQIRGFVLVVENLAKNICENLEQSGLPVGGNEKKAKLSNAVAKMLSNCPPGGISM
TVTGDNTKWNECLNPRIFLAMTERITRDSPIWFRDFCSIAPVLFSNKIARLGKGFMITSKTKRLKAQIPCPDLFSIP
LERYNEETRAKLKKLKPFFNEEGTASLSPGMMMGMFNMLSTVLGVAALGIKNIGNKEYLWDGLQSSDDFALFVNAKD
EETCMEGINDFYRTCKLLGINMSKKKSYCNETGMFEFTSMFYRDGFVSNFAMEIPSFGVAGVNESADMAIGMTIIKN
NMINNGMGPATAQTAIQLFIADYRYTYKCHRGDSKVEGKRMKIIKELWENTKGRDGLLVADGGPNIYNLRNLHIPEI
VLKYNLMDPEYKGRLLHPQNPFVGHLSIEGIKEADITPAHGPVKKMDYDAVSGTHSWRTKRNRSILNTDQRNMILEE
QCYAKCCNLFEACFNSASYRKPVGQHSMLEAMAHRLRVDARLDYESGRMSKDDFEKAMAHLGEIGYI

[0321] SEQ ID NO:22(PB2,B/Panama/45/90)

[0322] MTLAKIELLKQLLRDNEAKTVLKQTTVDQYNIIRKFNTSRIEKNPSLRMKWAMCSNFPLALTKGDMANR
IPLEYKGIQLKTNAEDIGTKGQMCSIAAVTWWNTYGPIGDTEGFEKVYESFFLRKMRLDNATWGRITFGPVERVRKR

VLLNPLTKEMPPDEASNVIMEILFPKEAGIPRESTWIHRELIKEKREKLKGTMITPIVLAYMLERELVARRRFLPVA
GATSAEFIEMLHCLQGENWRQIYHPGGNKLTESRSQSMIVACRKIIRRSIVASNPLELAVEIANKTVIDTEPLKSCL
TAIDGGDVACDIIRAALGLKIRQRQRFGRLELKRISGRGFKNDEEILIGNGTIQKIGIWDGEEEFHVRCGECRGILK
KSKMRMEKLLINSAKKEDMKDLIILCMVFSQDTRMFQGVRGEINFLNRAGQLLSPMYQLQRYFLNRSNDLFDQWGYE
ESPKASELHGINELMNASDYTLKGVVVTKNVIDDFSSTETEKVSITKNLSLIKRTGEVIMGANDVSELESQAQLMIT
YDTPKMWEMGTTKELVQNTYQWVLKNLVTLKAQFLLGKEDMFQWDAFEAFESIIPQKMAGQYSGFARAVLKQMRDQE
VMKTDQFIKLLPFCFSPPKLRRNGEPYQFLRLVLKGGGENFIEVRKGSPLFSYNPQTEVLTICGRMMSLKGKIEDEE
RNRSMGNAVLAGFLVSGKYDPDLGDFKTIEELEKLKPGEKANILLYQGKPVKVVKRKRYSALSNDISQGIKRQRMTV
ESMGWALS

[0323] SEQ ID NO:23(NP,B/Panama/45/90)

[0324] MSNMDIDGINTGTIDKTPEEITSGTSGTTRPIIRPATLAPPSNKRTRNPSPERATTSSEADVGRKTQKK
QTPTEIKKSVYNMVVKLGEFYNQMMVKAGLNDDMERNLIQNAHAVERILLAATDDKKTEFQRKKNARDVKEGKEEID
HNKTGGTFYKMVRDDKTIYFSPIRITFLKEEVKTMYKTTMGSDGFSGLNHIMIGHSQMNDVCFQRSKALKRVGLDPS
LISTFAGSTLPRRSGATGVAIKGGGTLVAEAIRFIGRAMADRGLLRDIKAKTAYEKILLNLKNKCSAPQQKALVDQV
IGSRNPGIADIEDLTLLARSMVVVRPSVASKVVLPISIYAKIPQLGFNVEEYSMVGYEAMALYNMATPVSILRMGDD
AKDKSQLFFMSCFGAAYEDLRVLSALTGIEFKPRSALKCKGFHVPAKEQVEGMGAALMSIKLQFWAPMTRSGGNEVG
GDGGSGQISCSPVFAVERPIALSKQAVRRMLSMNIEGRDADVKGNLLKMMNDSMAKKTNGNAFIGKKMFQISDKNKT
NPVEIPIKQTIPNFFFGRDTAEDYDDLDY

[0325] SEQ ID NO:24(M_1,B/Panama/45/90)

[0326] MSLFGDTIAYLLSLTEDGEGKAELAEKLHCWFGGKEFDLDSALEWIKNKRCLTDIQKALIGASICFLKP
KDQERKRRFITEPLSGMGTTATKKKGLILAERKMRRCVSFHEAFEIAEGHESSALLYCLMVMYLNPGNYSMQVKLGT
LCALCEKQASHSHRAHSRAARSSVPGVRREMQMVSAMNTAKTMNGMGKGEDVQKLAEELQSNIGVLRSLGASQKNGE
GIAKDVMEVLKQSSMGNSALVKKYL

[0327] SEQ ID NO:25(M_2,B/Panama/45/90)

[0328] MLEPFQILSICSFILSALHFMAWTIGHLNQIKRGVNMKIRIKNPNKETINREVSILRHSYQKEIQAKET
MKEVLSDNMEVLSDHIVIEGLSAEEIIKMGETVLEVEELH

[0329] SEQ ID NO:26(NS_1,B/Panama/45/90)

[0330] MADNMTTTQIEVGPGATNATINFEAGILECYERLSWQRALDYPGQDRLNKLKRKLESRIKTHNKSEPES
KRMSLEERKAIGVKMMKVLLFMNPSAGVEGFEPYCMKNPSNSNCPDCNWADYPPTPGKYLDGIEEEPENVGDSTEIV
LRDMNNKDARQKIKEEVNTQKEGKFRLTIKRDIRNVLSLRVLVNGTFIKHPNGYKSLSTLHRLNAYDQSGRLVAKLV
ATDDLTVEDEEDGHRILNSLFERLNEGHSKPIRAAETAVGVLSQFGQEHRLSPEERDN

[0331] SEQ ID NO:27(NS_2,B/Panama/45/90)

[0332] MADNMTTTQIEWRMKKMAIGSSTHSSSVLMKDIQSQFEQLKLRWESYPNLVKSTDYHQKRETIRLVTEE
LYLLSKRIDDNILFHKTVIANSSIIADMIVSLSLLETLYEMKDVVEVYSRQCL

[0333] SEQ ID NO:28(HA,B/Panama/45/90)

[0334] MKAIIVLLMVVTSNADRICTGITSSNSPHVVKTATQGEVNVTGVIPLTTTPTKSHFANLKGTKTRGKLC
PNCLNCTDLDVALGRPMCVGTTPSAKASILHEVRPVTSGCFPIMHDRTKIRQLPNLLRGYENIRLSTQNVINAERAP
GGPYRLGTSGSCPNVTSRDGFFATMAWAVPRDNKTATNPLTVEVPYICTKGEDQITVWGFHSDDKTQMKNLYGDSNP
QKFTSSANGVTTHYVSQIGGFPNQTEDGGLPQSGRIVVDYMVQKPGKTGTIVYQRGVLLPQKVWCASGRSKVIKGSL

PLIGEADCLHEKYGGLNKSKPYYTGEHAKAIGNCPIWVKTPLKLANGTKYRPPAKLLKERGFFGAIAGFLEGGWEGM
IAGWHGYTSHGAHGVAVAADLKSTQEAINKITKNLNSLSELEVKNLQRLSGAMDELHNEILELDEKVDDLRADTISS
QIELAVLLSNEGIINSEDEHLLALERKLKKMLGPSAVDIGNGCFETKHKCNQTCLDRIAAGTFNAGEFSLPTFDSLN
ITAASLNDDGLDNHTILLYYSTAASSLAVTLMIAIFIVYMVSRDNVSCSICL

[0335] SEQ ID NO:29(NA,B/Panama/45/90)

[0336] MLPSTIQTLTLFLTSGGVLLSLYVSASLSYLLYSDILLKFSPTEITAPTMPLDCANASNVQAVNRSATK
EMTLLLPEPEWTYPRLSCPGSTFQKALLISPHRFGETRGNSAPLTIREPFIACGPKECKHFALTHYAAQPGGYYNGT
REDRNKLRHLISVKLGKIPTVENSIFHMAAWSGSACHDGREWTYIGVDGPDSNALIKIKYGEAYTDTYHSYANNILR
TQESACNCIGGDCYLMITDGSASGISKCRFLKIREGRIIKEIFPTGRVEHTEECTCGFASNKTIECACRDNSYTAKR
PFVKLNVETDTAEIRLMCTETYLDTPRPDDGSITGPCESNGDKGRGGIKGGFVHQRMASKIGRWYSRTMSKTERMGM
ELYVKYDGDPWTDSEALAPSGVMVSMEEPGWYSFGFEIKDKKCDVPCIGIEMVHDGGKKTWHSAATAIYCLMGSGQL
LWDTVTGVDMAL

[0337] SEQ ID NO:30(PA,B/Panama/45/90)

[0338] AGCAGAAGCGGTGCGTTTGATTTGCCATAATGGATACTTTTATTACAAGAAACTTCCAGACTACAATAA
TACAAAAGGCCAAAAACACAATGGCAGAATTTAGTGAAGATCCTGAATTACAACCAGCAATGCTATTCAACATCTGC
GTCCATCTAGAGGTTTGCTATGTAATAAGTGACATGAATTTTCTTGACGAAGAAGGAAAATCATATACAGCATTAGA
AGGACAAGGAAAAGAACAAAACTTGAGACCACAATATGAAGTAATTGAGGGAATGCCAAGAACCATAGCATGGATGG
TCCAAAGATCCTTAGCTCAAGAGCATGGAATAGAGACTCCAAAGTATCTGGCTGATTTGTTTGATTATAAAACCAAG
AGATTTATAGAAGTTGGAATAACAAAAGGATTGGCTGATGATTACTTTTGGAAAAAGAAAGAAAAGCTGGGAAATAG
CATGGAACTGATGATATTCAGCTACAATCAAGACTATTCGTTAAGTAATGAATCCTCATTGGATGAGGAAGGGAAAG
GGAGAGTGCTAAGCAGACTCACAGAACTTCAGGCTGAATTAAGTCTGAAAAACCTATGGCAAGTTCTCATAGGAGAA
GAAGATGTTGAAAAGGGAATTGACTTTAAACTTGGACAAACAATATCTAGACTAAGGGATATATCTGTTCCAGCTGG
TTTCTCCAATTTTGAAGGAATGAGGAGCTACATAGACAATATAGATCCTAAAGGAGCAATAGAAAGAAATCTAGCAA
GGATGTCTCCCTTAGTATCAGCCACACCTAAAAAGTTGAAATGGGAGGACCTAAGACCAATAGGGCCTCACATTTAC
AACCATGAGTTACCAGAAGTTCCATATAATGCCTTTCTTCTAATGTCTGATGAATTGGGGCTGGCCAATATGACTGA
GGGAAAGTCCAAAAAACCGAAGACATTAGCCAAAGAATGTCTAGAAAAGTACTCAACACTACGGGATCAAACTGACC
CAATATTAATAATGAAAAGCGAAAAAGCTAACGAAAATTTCCTATGGAAGCTGTGGAGGGACTGTGTAAATACAATA
AGTAATGAGGAAATGAGTAACGAGTTACAGAAAACCAATTATGCCAAGTGGGCCACAGGAGATGGATTAACATACCA
GAAAATAATGAAAGAAGTAGCAATAGATGACGAAACAATGTGCCAAGAAGAGCCTAAAATCCCTAACAAATGTAGAG
TGGCTGCTTGGGTTCAAACAGAGATGAATTTATTGAGCACTCTGACAAGTAAAAGAGCTCTGGACCTACCAGAAATA
GGGCCAGACGTAGCACCCGTGGAGCATGTAGGGAGTGAAAGAAGGAAATACTTTGTTAATGAAATCAACTGCTGTAA
GGCCTCTACAGTTATGATGAAGTATGTGCTTTTTCACACTTCATTATTGAATGAAAGCAATGCCAGCATGGGAAAAT
ATAAAGTAATACCAATAACCAATAGAGTAGTAAATGAAAAAGGAGAAAGTTTCGACATGCTTTATGGTCTGGCGGTT
AAAGGACAATCTCATCTGAGGGGAGATACTGATGTTGTAACAGTTGTGACTTTCGAATTTAGTGGTACAGATCCCAG
AGTGGACTCAGGAAAGTGGCCAAAATATACTGTGTTTAGGATTGGCTCCCTATTTGTGAGTGGGAGGGAAAAATCTG
TGTACCTATATTGCCGAGTGAATGGCACAAATAAGATCCAAATGAAATGGGGAATGGAAGCTAGAAGATGTCTGCTT
CAATCAATGCAACAAATGGAAGCAATTGTTGAACAAGAATCATCGATACAAGGATATGACATGACCAAAGCTTGTTT
CAAGGGAGACAGAGTAAATAGCCCCAAAACTTTTAGTATTGGGACTCAAGAAGGAAAACTAGTAAAAGGATCCTTTG
GGAAAGCACTAAGAGTAATATTTACCAAATGTTTGATGCACTATGTATTTGGAAATGCCCAATTGGAGGGGTTTAGT

GCCGAGTCTAGGAGACTTCTACTGTTAATTCAAGCACTAAAGGACAGAAAGGGCCCTTGGGTGTTCGACTTAGAGGG
AATGTATTCTGGAATAGAAGAATGTATTAGTAACAACCCTTGGGTAATACAGAGTGCATACTGGTTCAATGAATGGT
TGGGCTTTGAAAAGGAGGGGAGTAAAGTATTAGAATCAGTAGATGAAATAATGAATGAATGAAAAAACATAGTACTC
AATTTGGTACTATTTTGTTCATTATGTATCTAAACATCCAATAAAAAGAATCGAGAATCAAAAATGCACGTGTTTCT
ACT

[0339] SEQ ID NO:31(PB1,B/Panama/45/90)

[0340] AGCAGAAGCGGAGCCTTTAAGATGAATATAAATCCTTATTTTCTCTTCATAGATGTACCCATACAGGCA
GCAATTTCAACAACATTCCCATACACCGGTGTTCCCCCTTACTCCCATGGAACGGGAACAGGCCACACAATAGACAC
CGTGATCAGAACACATGAGTACTCGAACAAGGGAAAACAGTATGTTTCTGACATCACAGGATGTACAATGGTAGATC
CAACAAATGGGCCATTACCCGAAGACAATGAGCCGAGTGCCTATGCACAATTAGATTGCGTTCTGGAGGCTTTGGAT
AGAATGGATGAAGAACATCCAGGTTTGTTTCAAGCAGCCTCACAGAATGCCATGGAGGCACTAATGGTCACAACTGT
AGACAAATTAACCCAGGGGAGACAGACTTTTGATTGGACAGTATGCAGAAACCAGCCTGCTGCAACGGCACTAAACA
CAACAATAACCTCCTTTAGGTTGAATGATTTGAATGGAGCTGACAAGGGTGGATTGGTACCCTTTTGCCAAGATATC
ATTGATTCATTGGACAAACCTGAAATGACTTTCTTCTCAGTAAAGAATATAAAGAAAAAATTGCCTGCTAAAAACAG
AAAGGGTTTCCTCATAAAGAGAATACCAATGAAAGTAAAAGACAGGATAACCAGAGTGGAATACATCAAAAGAGCAT
TATCATTAAACACAATGACAAAAGATGCTGAAAGGGGCAAACTAAAAAGAAGAGCGATTGCAACCGCTGGAATACAA
ATCAGAGGGTTTGTATTAGTAGTTGAAAACTTGGCTAAAAATATCTGTGAAAATCTAGAACAAAGTGGTTTGCCCGT
AGGTGGAAATGAAAAGAAGGCCAAACTGTCAAATGCAGTGGCCAAAATGCTCAGTAACTGCCCACCAGGAGGGATCA
GCATGACAGTAACAGGAGACAATACTAAATGGAATGAATGCTTAAATCCAAGAATCTTTTTGGCTATGACTGAAAGG
ATAACAAGAGACAGCCCAATTTGGTTCCGGGATTTTTGTAGTATAGCACCGGTCTTGTTCTCCAATAAAATAGCCAG
ATTGGGAAAAGGATTTATGATAACAAGCAAAACAAAAAGACTGAAGGCTCAAATACCTTGTCCAGATCTGTTTAGCA
TACCATTAGAAAGATATAATGAAGAAACAAGGGCAAAATTAAAAAAGCTGAAACCATTCTTCAATGAAGAAGGAACG
GCATCTTTGTCGCCTGGGATGATGATGGGAATGTTTAATATGCTATCTACCGTGTTGGGAGTAGCCGCACTAGGTAT
CAAAAACATTGGAAACAAAGAATATTTATGGGATGGACTGCAATCTTCTGATGATTTTGCTCTGTTTGTTAATGCAA
AAGATGAAGAGACATGTATGGAAGGAATAAACGACTTTTACCGAACATGTAAATTATTGGGAATAAACATGAGCAAA
AAGAAAAGTTACTGTAATGAAACTGGAATGTTTGAATTTACAAGCATGTTCTATAGAGATGGATTTGTATCTAATTT
TGCAATGGAAATTCCTTCATTTGGAGTTGCTGGAGTAAATGAATCAGCAGATATGGCAATAGGAATGACAATAATAA
AGAACAATATGATCAACAATGGGATGGGTCCAGCAACAGCACAAACAGCCATACAATTATTCATAGCTGATTATAGG
TACACCTACAAATGCCACAGGGGAGATTCCAAAGTGGAAGGAAAAAGAATGAAAATTATAAAGGAGCTATGGGAAAA
CACTAAAGGAAGAGATGGTCTGTTAGTGGCAGATGGTGGGCCCAACATTTACAATTTGAGAAACTTACATATCCCAG
AAATAGTATTGAAGTACAACCTAATGGACCCTGAATACAAAGGGCGGTTACTTCATCCTCAAAATCCATTTGTAGGA
CATTTATCTATTGAGGGCATCAAAGAAGCAGATATAACCCCAGCACATGGTCCCGTAAAGAAAATGGATTATGATGC
AGTATCTGGAACTCATAGTTGGAGAACCAAAAGGAACAGATCTATACTAAATACTGACCAGAGGAACATGATTCTTG
AGGAACAATGCTACGCTAAGTGTTGCAACCTTTTTGAGGCCTGTTTTAATAGTGCATCATACAGGAAACCAGTAGGT
CAGCACAGCATGCTTGAGGCTATGGCCCACAGATTAAGAGTGGATGCACGACTAGATTATGAATCAGGAAGAATGTC
AAAGGATGATTTTGAGAAAGCAATGGCTCACCTTGGTGAGATTGGGTACATATAAGCTCCGAAGATGTCTATGGGGT
TATTGGTCATCATTGAATACATGTGATAAACAAATGATTAAAATGAAAAAAGGCTCGTGTTTCTACT

[0341] SEQ ID NO:32(PB2,B/Panama/45/90)

[0342] AGCAGAAGCGGAGCGTTTTCAAGATGACATTGGCTAAAATTGAATTGTTAAAACAACTGTTAAGGGACA

ATGAAGCCAAAACAGTATTGAAACAAACAACGGTAGACCAATATAACATAATAAGAAAATTCAATACATCAAGAATT
GAAAAGAACCCTTCATTGAGGATGAAGTGGGCAATGTGTTCTAATTTTCCCTTGGCTCTGACCAAGGGTGATATGGC
AAACAGAATCCCCTTGGAATACAAGGGAATACAACTTAAAACAAATGCTGAAGACATAGGAACTAAAGGCCAAATGT
GCTCAATAGCAGCAGTTACCTGGTGGAATACATATGGACCAATAGGAGATACTGAAGGTTTCGAAAAGGTCTACGAA
AGCTTTTTTCTCAGAAAGATGAGACTTGACAATGCCACTTGGGGCCGAATAACTTTTGGCCCAGTTGAAAGAGTAAG
AAAAAGGGTACTGCTAAACCCTCTCACCAAGGAAATGCCTCCAGATGAAGCAAGTAATGTGATAATGGAAATATTGT
TCCCTAAGGAAGCAGGAATACCAAGAGAATCTACTTGGATACATAGGGAACTGATAAAAGAAAAAAGAGAAAAATTG
AAAGGAACAATGATAACTCCCATTGTACTGGCATACATGCTTGAGAGAGAATTGGTTGCCAGAAGAAGGTTCCTGCC
GGTGGCAGGAGCAACATCAGCTGAGTTCATAGAAATGCTACACTGCTTACAAGGTGAAAATTGGAGACAAATATATC
ACCCAGGAGGAAATAAACTAACTGAATCTAGGTCTCAATCGATGATTGTAGCTTGTAGAAAGATAATCAGAAGATCA
ATAGTCGCATCAAACCCATTAGAGCTAGCTGTAGAAATTGCAAACAAGACTGTGATAGATACTGAACCTTTAAAATC
ATGTCTGACAGCCATAGACGGAGGTGATGTAGCCTGTGACATAATAAGAGCTGCATTAGGACTAAAGATCAGACAAA
GACAAAGATTTGGACGACTTGAACTAAAGAGAATATCAGGAAGAGGATTCAAAAATGATGAAGAAATATTAATCGGG
AACGGAACAATACAGAAGATTGGAATATGGGACGGAGAAGAGGAGTTCCATGTAAGATGTGGTGAATGCAGGGGAAT
ATTAAAAAAGAGCAAAATGAGAATGGAAAAACTACTAATAAATTCAGCTAAAAAGGAAGACATGAAAGATTTAATAA
TCTTGTGCATGGTATTTTCTCAAGACACTAGGATGTTCCAAGGAGTGAGAGGAGAAATAAATTTTCTTAATAGAGCA
GGCCAACTTTTATCTCCAATGTACCAACTCCAAAGATATTTTTTGAATAGAAGCAACGATCTCTTTGATCAATGGGG
GTATGAGGAATCACCCAAAGCAAGTGAGCTACATGGAATAAATGAATTAATGAATGCATCTGACTACACTTTGAAAG
GGGTTGTAGTAACAAAAAATGTAATTGATGATTTTAGTTCTACTGAAACAGAAAAAGTATCTATAACAAAAAATCTT
AGTTTAATAAAAAGGACTGGGGAAGTCATAATGGGGGCTAATGACGTAAGTGAATTAGAATCACAAGCTCAGCTAAT
GATAACATATGATACACCTAAGATGTGGGAGATGGGAACAACCAAAGAACTGGTGCAAAACACCTACCAATGGGTGC
TGAAAAATTTGGTAACACTGAAGGCTCAGTTTCTTCTAGGAAAAGAAGACATGTTCCAATGGGATGCATTTGAAGCA
TTTGAAAGCATAATCCCCCAGAAGATGGCTGGCCAGTACAGTGGATTTGCAAGAGCAGTGCTCAAACAAATGAGAGA
CCAAGAGGTTATGAAAACTGACCAGTTCATAAAGTTGTTGCCCTTTTGTTTCTCACCACCAAAATTAAGGAGAAATG
GGGAGCCTTATCAGTTCTTGAGGCTTGTATTGAAGGGAGGAGGAGAAAATTTCATCGAAGTAAGGAAAGGGTCCCCT
CTATTCTCTTACAATCCACAAACAGAAGTCCTAACTATATGCGGCAGAATGATGTCATTAAAAGGGAAAATTGAAGA
TGAAGAAAGGAATAGATCAATGGGGAATGCAGTATTAGCGGGCTTTCTCGTTAGTGGCAAGTATGACCCAGATCTTG
GAGATTTCAAAACTATTGAAGAACTTGAAAAGCTGAAACCGGGGGAGAAAGCAAACATCTTACTTTATCAAGGAAAG
CCCGTTAAAGTAGTTAAAAGGAAAAGATATAGTGCTTTATCCAATGACATTTCACAAGGAATTAAGAGACAAAGAAT
GACAGTTGAGTCCATGGGGTGGGCCTTGAGCTAATATAAATTTATCCATTAATTCAATAAACACAATTGAGTGAAAA
ATGCTCGTGTTTCTACT

[0343] SEQ ID NO:33(NP,B/Panama/45/90)

[0344] AGCAGAAGCACAGCATTTTCTTATTAACTTCAAGTACCAACAAAAGAACTGAAAATCAAAATGTCCAAC
ATGGATATTGACGGTATCAACACTGGGACAATTGACAAAACACCGGAAGAAATAACTTCTGGAACCAGTGGGACAAC
CAGACCAATCATCAGACCAGCAACCCTTGCCCCACCAAGCAACAAACGAACCCGGAACCCATCCCCGGAAAGAGCAA
CCACAAGCAGTGAAGCTGATGTCGGAAGGAAAACCCAAAAGAAACAGACCCCGACAGAGATAAAGAAGAGCGTCTAC
AATATGGTAGTGAAACTGGGTGAATTCTATAACCAGATGATGGTCAAAGCTGGACTCAACGATGACATGGAGAGAAA
CCTAATCCAAAATGCGCATGCTGTGGAAAGAATTCTATTGGCTGCCACTGATGACAAGAAAACTGAATTCCAGAGGA
AAAAGAATGCCAGAGATGTCAAAGAAGGAAAAGAAGAAATAGACCACAACAAAACAGGAGGCACCTTTTACAAGATG

GTAAGAGATGATAAAACCATCTACTTCAGCCCTATAAGAATTACCTTTTTAAAAGAAGAGGTGAAAACAATGTACAA
AACCACCATGGGGAGTGATGGCTTCAGTGGACTAAATCACATAATGATTGGGCATTCACAGATGAATGATGTCTGTT
TCCAAAGATCAAAGGCCCTAAAAAGAGTTGGACTTGACCCTTCATTAATCAGTACCTTTGCAGGAAGCACACTCCCC
AGAAGATCAGGTGCAACTGGTGTTGCAATCAAAGGAGGTGGAACTTTAGTGGCTGAAGCCATTCGATTTATAGGAAG
AGCAATGGCAGACAGAGGGCTATTGAGAGACATCAAAGCCAAGACTGCCTATGAAAAGATTCTTCTGAATCTAAAAA
ACAAATGCTCTGCGCCCCAACAAAAGGCTCTAGTTGATCAAGTGATCGGAAGTAGAAATCCAGGGATTGCAGACATT
GAAGACCTAACCCTGCTTGCTCGTAGTATGGTCGTTGTTAGGCCCTCTGTGGCGAGCAAAGTAGTGCTTCCCATAAG
CATTTATGCTAAAATACCTCAACTAGGGTTCAATGTTGAAGAATACTCTATGGTTGGGTATGAAGCCATGGCTCTCT
ACAATATGGCAACACCTGTTTCCATATTAAGAATGGGAGATGATGCAAAAGATAAATCGCAATTATTCTTCATGTCT
TGCTTCGGAGCTGCCTATGAAGACCTGAGAGTTTTGTCTGCATTAACAGGCATAGAATTCAAGCCTAGATCAGCATT
AAAATGCAAGGGTTTCCATGTTCCAGCAAAGGAACAGGTGGAAGGAATGGGGGCAGCTCTGATGTCCATCAAGCTCC
AGTTTTGGGCTCCAATGACCAGATCTGGAGGGAACGAAGTAGGTGGAGACGGAGGGTCTGGCCAAATAAGTTGCAGC
CCAGTGTTTGCAGTAGAAAGACCTATTGCTCTAAGCAAGCAAGCTGTAAGAAGAATGCTTTCAATGAATATTGAGGG
ACGTGATGCAGATGTCAAAGGAAATCTACTCAAGATGATGAATGACTCAATGGCTAAGAAAACCAATGGAAATGCTT
TCATTGGGAAGAAAATGTTTCAAATATCAGACAAAAACAAAACCAATCCCGTTGAAATTCCAATTAAGCAGACCATC
CCCAATTTCTTCTTTGGGAGGGACACAGCAGAGGATTATGATGACCTCGATTATTAAAGCAACAAAATAGACACTAT
GACTGTGATTGTTTCAATACGTTTGGAATGTGGGTGTTTACTCTTATTGAAATAAATATAAAAAATGCTGTTGTTTC
TACT

[0345] SEQ ID NO:34(M,B/Panama/45/90)

[0346] AGCAGAAGCACGCACTTTCTTAAAATGTCGCTGTTTGGAGACACAATTGCCTACCTGCTTTCATTGACA
GAAGATGGAGAAGGCAAAGCAGAACTAGCAGAAAAATTACACTGTTGGTTCGGTGGGAAAGAATTTGACCTAGACTC
TGCCTTGGAATGGATAAAAAACAAAAGATGCTTAACTGATATACAGAAAGCACTAATTGGTGCCTCTATCTGCTTTT
TAAAACCAAAAGACCAAGAAAGAAAAAGAAGATTCATCACAGAGCCCCTATCAGGAATGGGAACAACAGCAACAAAA
AAGAAGGGCCTGATTCTAGCTGAGAGAAAAATGAGAAGATGTGTGAGTTTTCATGAAGCATTTGAAATAGCAGAAGG
CCATGAAAGCTCAGCGCTACTATATTGTCTCATGGTCATGTACCTGAACCCTGGAAATTATTCAATGCAAGTAAAAC
TAGGAACGCTCTGTGCTTTGTGCGAGAAACAAGCATCACATTCACACAGGGCTCATAGCAGAGCAGCAAGATCTTCA
GTGCCTGGAGTGAGGCGAGAAATGCAGATGGTCTCAGCTATGAACACAGCAAAAACAATGAATGGAATGGGAAAGGG
AGAAGACGTCCAAAAACTGGCAGAAGAGCTGCAAAGCAACATTGGAGTATTGAGATCTCTTGGGGCAAGTCAAAAGA
ATGGGGAAGGAATTGCAAAGGATGTGATGGAAGTGCTAAAGCAGAGCTCTATGGGAAATTCAGCTCTTGTGAAGAAA
TACCTATAATGCTCGAACCATTTCAGATTCTTTCAATTTGTTCTTTCATCTTATCAGCTCTCCATTTCATGGCTTGG
ACAATAGGGCATTTGAATCAAATAAAAAGAGGAGTAAACATGAAAATACGAATAAAAAATCCAAATAAAGAGACAAT
AAACAGAGAGGTATCAATTTTGAGACACAGTTACCAAAAAGAAATCCAGGCCAAAGAAACAATGAAGGAAGTACTCT
CTGACAACATGGAGGTATTGAGTGACCACATAGTAATTGAGGGGCTTTCTGCTGAAGAGATAATAAAAATGGGTGAA
ACAGTTTTGGAGGTAGAAGAATTGCATTAAATTCAATTTTTACTGTATTTCTTGCTATGCATTTAAGCAAATTGTAA
TCAATGTCAGCAAATAAACTGGAAAAAGTGCGTTGTTTCTACT

[0347] SEQ ID NO:35(NS,B/Panama/45/90)

[0348] AGCAGAAGCAGAGGATTTGTTTAGTCACTGGCAAACGAAAAAATGGCGGACAACATGACCACAACACAA
ATTGAGGTGGGTCCGGGAGCAACCAATGCCACCATAAACTTTGAAGCAGGAATTTTGGAGTGCTATGAAAGGCTTTC
ATGGCAAAGAGCCCTTGACTACCCTGGTCAAGACCGCCTAAACAAACTAAAGAGAAAATTGGAATCAAGAATAAAGA

CTCACAACAAAAGTGAGCCAGAAAGTAAAAGGATGTCTCTTGAAGAGAGAAAAGCTATTGGGGTAAAAATGATGAAA
GTGCTCCTATTTATGAACCCATCTGCTGGAGTTGAAGGGTTTGAGCCATATTGTATGAAAAATCCCTCCAATAGCAA
CTGTCCAGACTGCAATTGGGCTGATTACCCTCCAACACCAGGAAAGTACCTTGATGGCATAGAAGAAGAACCGGAGA
ATGTTGGTGACTCAACTGAAATAGTATTAAGGGACATGAACAACAAAGATGCAAGGCAAAAGATAAAAGAGGAAGTA
AACACTCAGAAAGAAGGGAAATTCCGTTTGACAATAAAAAGGGATATACGTAATGTGTTGTCCTTGAGAGTGTTGGT
AAACGGAACATTCATCAAGCACCCTAATGGATACAAGTCCTTATCAACTCTGCATAGATTGAATGCATATGACCAGA
GTGGAAGACTTGTTGCTAAACTTGTTGCTACTGATGATCTTACAGTGGAGGATGAAGAAGATGGCCATCGGATCCTC
AACTCACTCTTCGAGCGTCTTAATGAAGGACATTCAAAGCCAATTCGAGCAGCTGAAACTGCGGTGGGAGTCTTATC
CCAATTTGGTCAAGAGCACCGATTATCACCAGAAGAGAGAGACAATTAGACTGGTTACGGAAGAACTTTATCTTTTA
AGTAAAAGAATTGATGATAACATATTGTTCCACAAAACAGTAATAGCCAACAGCTCCATAATAGCTGACATGATTGT
ATCATTATCATTATTGGAAACATTGTATGAAATGAAGGATGTGGTTGAAGTGTACAGCAGGCAGTGCTTGTGAATTT
AAAATAAAAATCCTCTTGTTACTACT

[0349] SEQ ID NO:36(NA,B/Panama/45/90)

[0350] AGCAGAAGCAGAGCATCTTCTCAAAACTGAGGCAAATAGGCCAAAAATGAACAATGCTACCTTCAACTA
TACAAACGTTAACCCTATTTCTCACATCAGGGGGAGTGTTATTATCACTATATGTGTCAGCTTCACTATCATACTTA
CTGTATTCGGATATATTGCTAAAATTTTCACCAACAGAAATAACTGCACCAACAATGCCATTGGATTGTGCAAACGC
ATCAAATGTTCAGGCTGTGAACCGTTCTGCAACAAAAGAGATGACACTTCTTCTCCCAGAACCGGAGTGGACATACC
CTCGTTTATCTTGCCCGGGCTCAACCTTTCAGAAAGCACTCCTAATTAGCCCTCATAGATTCGGAGAAACCAGAGGA
AACTCAGCTCCCTTGACAATAAGGGAACCTTTTATTGCTTGTGGACCAAAGGAATGCAAACACTTTGCTCTAACCCA
TTATGCAGCTCAACCAGGGGGATACTACAATGGAACAAGAGAGGACAGAAACAAGCTGAGGCATCTGATTTCAGTCA
AATTGGGCAAAATACCAACAGTAGAAAACTCCATTTTCCACATGGCAGCTTGGAGCGGGTCCGCATGCCATGATGGT
AGAGAATGGACATATATCGGAGTTGATGGCCCTGACAGTAATGCATTGATCAAAATAAAATATGGAGAAGCATATAC
TGACACATACCATTCCTATGCAAACAACATCCTAAGAACACAAGAAAGTGCCTGCAATTGCATTGGGGGAGATTGTT
ATCTTATGATAACTGATGGCTCAGCTTCAGGAATTAGTAAATGCAGATTTCTTAAGATTCGAGAGGGTCGAATAATA
AAAGAAATATTTCCAACAGGAAGAGTAGAACATACTGAAGAATGCACATGCGGATTTGCCAGCAACAAAACCATAGA
ATGTGCCTGTAGAGATAACAGTTACACAGCAAAAAGACCCTTTGTCAAATTAAATGTGGAGACTGATACAGCTGAAA
TAAGATTGATGTGCACAGAGACTTATTTGGACACCCCCAGACCAGATGATGGAAGCATAACAGGGCCTTGCGAATCT
AATGGGGACAAAGGGCGTGGAGGCATCAAGGGAGGATTTGTTCATCAAAGAATGGCATCCAAGATTGGAAGATGGTA
CTCTCGAACGATGTCTAAAACTGAAAGAATGGGGATGGAACTGTATGTCAAGTATGATGGAGACCCATGGACTGACA
GTGAAGCCCTTGCTCCTAGTGGAGTAATGGTTTCAATGGAAGAACCTGGTTGGTATTCTTTTGGCTTCGAAATAAAA
GATAAGAAATGTGATGTCCCCTGTATTGGGATAGAGATGGTACACGATGGTGGAAAAAAGACTTGGCACTCAGCAGC
AACAGCCATTTACTGTTTAATGGGCTCAGGACAATTGCTATGGGACACTGTCACAGGTGTTGATATGGCTCTGTAAT
GGAGGAATGGTTGAGTCTGTTCTAAACCCTTTGTTCCTATTTTGTTTGAATAATTGTCCTTACTGAACTTAATTGTT
TCTGAAAAATGCTCTTGTTACTACT

[0351] SEQ ID NO:37(HA,B/Panama/45/90)

[0352] AGCAGAAGCAGAGCATTTTCTAATATCCACAAAATGAAGGCAATAATTGTACTACTCATGGTAGTAACA
TCCAACGCAGATCGAATCTGCACTGGGATAACATCTTCAAACTCACCTCATGTGGTCAAAACAGCTACTCAAGGGGA
AGTCAATGTGACTGGTGTGATACCACTGACAACAACACCAACAAAATCTCATTTTGCAAATCTAAAAGGAACAAAGA
CCAGAGGGAAACTATGCCCAAACTGTCTCAACTGCACAGATCTGGATGTGGCCTTGGGCAGACCAATGTGTGTGGGG

ACCACACCTTCGGCAAAAGCTTCAATACTCCACGAAGTCAGACCTGTTACATCCGGGTGCTTTCCTATAATGCACGA
CAGAACAAAAATCAGACAGCTACCCAATCTTCTCAGAGGATATGAAAATATCAGATTATCAACCCAAAACGTTATCA
ACGCAGAAAGAGCACCAGGAGGACCCTACAGACTTGGAACCTCAGGATCTTGCCCTAACGTTACCAGTAGAGACGGA
TTCTTCGCAACAATGGCTTGGGCTGTCCCAAGGGACAACAAAACAGCAACGAATCCACTAACAGTAGAAGTACCATA
CATTTGTACAAAAGGAGAAGACCAAATTACTGTTTGGGGGTTCCATTCTGATGACAAAACCCAAATGAAAAACCTCT
ATGGAGACTCAAATCCTCAAAAGTTCACCTCATCTGCCAATGGAGTAACCACACATTATGTTTCTCAGATTGGTGGC
TTCCCAAATCAAACAGAAGACGGAGGGCTACCACAAAGCGGCAGAATTGTTGTTGATTACATGGTGCAAAAACCTGG
GAAAACAGGAACAATTGTCTATCAAAGAGGTGTTTTGTTGCCTCAAAAGGTGTGGTGCGCAAGTGGCAGGAGCAAGG
TAATAAAAGGGTCCTTGCCTTTAATTGGTGAAGCAGATTGCCTTCACGAAAAATACGGTGGATTAAACAAAAGCAAG
CCTTACTACACAGGAGAACATGCAAAAGCCATAGGAAATTGCCCAATATGGGTGAAAACACCTTTGAAGCTTGCCAA
TGGAACCAAATATAGACCTCCTGCAAAACTATTAAAGGAAAGGGGTTTCTTCGGAGCTATTGCTGGTTTCTTAGAAG
GAGGATGGGAAGGAATGATTGCAGGTTGGCACGGATACACATCTCATGGAGCACATGGAGTGGCAGTGGCAGCAGAC
CTTAAGAGTACGCAAGAAGCCATAAACAAGATAACAAAAAATCTCAATTCTTTGAGTGAGCTAGAAGTAAAGAATCT
TCAAAGACTAAGTGGTGCCATGGATGAACTCCACAACGAAATACTCGAGCTGGATGAGAAAGTGGATGATCTCAGAG
CTGACACAATAAGCTCGCAAATAGAGCTTGCAGTCTTGCTTTCCAACGAAGGAATAATAAACAGTGAAGATGAGCAT
CTATTGGCACTTGAGAGAAAACTAAAGAAAATGCTGGGTCCCTCTGCTGTAGACATAGGGAATGGATGCTTCGAAAC
CAAACACAAGTGCAACCAGACCTGCTTAGACAGAATAGCTGCTGGCACCTTTAATGCAGGAGAATTTTCTCTTCCCA
CTTTTGATTCACTGAATATTACTGCTGCATCTTTAAATGATGATGGATTGGATAATCATACTATACTGCTCTACTAC
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[0353] SEQ ID NO:38(NP,B/Ann Arbor/1/66)

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[0355] SEQ ID NO:39(NP,B/Ann Arbor/1/66-替代序列)

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[0359] SEQ ID NO:41(编码与SEQ ID NO:40相同的氨基酸序列)

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[0361] SEQ ID NO:42(HA,BX-35)

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[0363] SEQ ID NO:43(NP,B/Lee/40)

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[0365] SEQ ID NO:44(NP,B/Ann Arbor/1/66)

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序列表

<110> 诺华股份有限公司 (Novartis AG)

合成基因组疫苗股份有限公司 (Synthetic Genomic Vaccines, Inc.)

<120> 流感病毒重配

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

210 215 220

Asn Thr Met Thr Lys Asp Ala Glu Arg Gly Lys Leu Lys Arg Arg Ala

225 230 235 240

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

245 250 255

Asn Leu Ala Lys Asn Ile Cys Glu Asn Leu Glu Gln Ser Gly Leu Pro

260 265 270

Val Gly Gly Asn Glu Lys Lys Ala Lys Leu Ser Asn Ala Val Ala Lys

275 280 285

Met Leu Ser Asn Cys Pro Pro Gly Gly Ile Ser Met Thr Val Thr Gly

290 295 300

Asp Asn Thr Lys Trp Asn Glu Cys Leu Asn Pro Arg Ile Phe Leu Ala

305 310 315 320

Met Thr Glu Arg Ile Thr Arg Asp Ser Pro Val Trp Phe Arg Asp Phe

325 330 335

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

645 650 655
Asp Ala Val Ser Gly Thr His Ser Trp Arg Thr Lys Arg Asn Arg Ser
660 665 670
Ile Leu Asn Thr Asp Gln Arg Asn Met Ile Leu Glu Glu Gln Cys Tyr
675 680 685
Ala Lys Cys Cys Asn Leu Phe Glu Ala Cys Phe Asn Ser Ala Ser Tyr
690 695 700
Arg Lys Pro Val Gly Gln His Ser Met Leu Glu Ala Met Ala His Arg
705 710 715 720
Leu Arg Met Asp Ala Arg Leu Asp Tyr Glu Ser Gly Arg Met Ser Lys
725 730 735
Asp Asp Phe Glu Lys Ala Met Ala His Leu Gly Glu Ile Gly Tyr Ile
740 745 750

<210> 3
<211> 770
<212> PRT
<213> 乙型流感
<400> 3

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

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

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

<210> 4

<211> 560
<212> PRT
<213> 乙型流感
<400> 4

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

Ser Ala Pro Gln Gln Lys Ala Leu Val Asp Gln Val Ile Gly Ser Arg
290 295 300

Asn Pro Gly Ile Ala Asp Ile Glu Asp Leu Thr Leu Leu Ala Arg Ser
305 310 315 320

Met Val Val Val Arg Pro Ser Val Ala Ser Lys Val Val Leu Pro Ile
325 330 335

Ser Ile Tyr Ala Lys Ile Pro Gln Leu Gly Phe Asn Val Glu Glu Tyr
340 345 350

Ser Met Val Gly Tyr Glu Ala Met Ala Leu Tyr Asn Met Ala Thr Pro
355 360 365

Val Ser Ile Leu Arg Met Gly Asp Asp Ala Lys Asp Lys Ser Gln Leu
370 375 380

Phe Phe Met Ser Cys Phe Gly Ala Ala Tyr Glu Asp Leu Arg Val Leu
385 390 395 400

Ser Ala Leu Thr Gly Thr Glu Phe Lys Pro Arg Ser Ala Leu Lys Cys
405 410 415

Lys Gly Phe His Val Pro Ala Lys Glu Gln Val Glu Gly Met Gly Ala
420 425 430

Ala Leu Met Ser Ile Lys Leu Gln Phe Trp Ala Pro Met Thr Arg Ser
435 440 445

Gly Gly Asn Glu Val Gly Gly Asp Gly Gly Ser Gly Gln Ile Ser Cys
450 455 460

Ser Pro Val Phe Ala Val Glu Arg Pro Ile Ala Leu Ser Lys Gln Ala
465 470 475 480

Val Arg Arg Met Leu Ser Met Asn Ile Glu Gly Arg Asp Ala Asp Val
485 490 495

Lys Gly Asn Leu Leu Lys Met Met Asn Asp Ser Met Ala Lys Lys Thr
500 505 510

Ser Gly Asn Ala Phe Ile Gly Lys Lys Met Phe Gln Ile Ser Asp Lys
515 520 525

Asn Lys Thr Asn Pro Ile Glu Ile Pro Ile Lys Gln Thr Ile Pro Asn
530 535 540

Phe Phe Phe Gly Arg Asp Thr Ala Glu Asp Tyr Asp Asp Leu Asp Tyr
545 550 555 560

<210> 5

<211> 248

<212> PRT

<213> 乙型流感

<400> 5

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

<210> 6

<211> 109

<212> PRT

<213> 乙型流感

<400> 6

Met Leu Glu Pro Phe Gln Ile Leu Thr Ile Cys Ser Phe Ile Leu Ser

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

<210> 7
<211> 282
<212> PRT
<213> 乙型流感
<400> 7
Met Ala Asn Asn Asn Met Thr Thr Thr Gln Ile Glu Val Gly Pro Gly
1 5 10 15
Ala Thr Asn Ala Thr Ile Asn Phe Glu Ala Gly Ile Leu Glu Cys Tyr
20 25 30
Glu Arg Leu Ser Trp Gln Arg Ala Leu Asp Tyr Pro Gly Gln Asp Arg
35 40 45
Leu Asn Arg Leu Lys Arg Lys Leu Glu Ser Arg Ile Lys Thr His Asn
50 55 60
Lys Ser Glu Pro Glu Ser Lys Arg Met Ser Leu Glu Glu Arg Lys Ala
65 70 75 80
Ile Gly Val Lys Met Met Lys Val Leu Leu Phe Met Asn Pro Ser Ala
85 90 95
Gly Ile Glu Gly Phe Glu Pro Tyr Cys Met Lys Ser Ser Ser Asn Ser
100 105 110
Asn Cys Thr Lys Tyr Asn Trp Thr Asp Tyr Pro Ser Thr Pro Glu Arg
115 120 125
Cys Leu Asp Asp Ile Glu Glu Glu Pro Glu Asp Val Asp Gly Pro Thr
130 135 140
Glu Ile Val Leu Arg Asp Met Asn Asn Lys Asp Ala Arg Gln Lys Ile
145 150 155 160
Lys Glu Glu Val Asn Thr Gln Lys Glu Gly Lys Phe Arg Leu Thr Ile

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

<210> 8
<211> 123
<212> PRT
<213> 乙型流感
<400> 8
Met Ala Asn Asn Asn Met Thr Thr Thr Gln Ile Glu Trp Arg Met Lys
1 5 10 15
Lys Met Ala Ile Gly Ser Ser Thr His Ser Ser Ser Val Leu Met Lys
20 25 30
Asp Ile Gln Ser Gln Phe Glu Gln Leu Lys Leu Arg Trp Glu Ser Tyr
35 40 45
Pro Asn Leu Val Lys Ser Thr Asp Tyr His Gln Lys Arg Glu Thr Ile
50 55 60
Arg Leu Val Thr Glu Glu Leu Tyr Leu Leu Ser Lys Arg Ile Asp Asp
65 70 75 80
Asn Ile Leu Phe His Lys Thr Val Ile Ala Asn Ser Ser Ile Ile Ala
85 90 95
Asp Met Val Val Ser Leu Ser Leu Leu Glu Thr Leu Tyr Glu Met Lys
100 105 110
Asp Val Val Glu Val Tyr Ser Arg Gln Cys Leu
115 120

<210> 9
<211> 585
<212> PRT

<213> 乙型流感

<400> 9

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

290 295 300

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

<210> 10

<211> 466

<212> PRT

<213> 乙型流感

<400> 10

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

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

<210> 11
<211> 2305
<212> DNA
<213> 乙型流感
<400> 11

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ctacaataat acaaaaggcc aaaaacacaa tggcagaatt tagtgaagat cctgaattgc 120
aaccagcaat gctattcaat atctgcgtcc atctagaggt ttgctatgta ataagtgaca 180
tgaattttct tgacgaagaa ggaaaagcat atacagcatt agaaggacaa gggaaagaac 240
aaaacttgag accacaatat gaagtaattg agggaatgcc aagaaccata gcatggatgg 300
tccagagatc cttagctcaa gagcatggaa tagagactcc caagtatctg gctgatttgt 360
ttgattataa aaccaaaaga tttatagaag ttggaataac aaagggattg gctgatgatt 420
acttttggaa aaagaaagaa aagttgggaa atagcatgga actgatgata ttcagctaca 480
atcaagacta ctcgttaagt aatgaatcct cattggatga ggaagggaaa gggagagtgc 540
taagcagact cacagaactt caggctgaat taagtctgaa aaatttatgg caagttctca 600

taggagaaga agatgttgaa aagggaattg attttaaact tggacaaaca atatctagac 660
taagggatat atctgttcca gctggtttct ccaattttga aggaatgagg agctacatag 720
acaatataga cccaaaagga gcaatagaga gaaatctagc aaggatgtct cccttagtat 780
cagtcacacc taaaaagtta acatgggagg acctaagacc aatagggcct cacatttacg 840
accatgagct accagaagtt ccatataatg cctttcttct aatgtctgat gaactgggat 900
tggccaatat gactgaggga aagtccaaaa aaccgaagac attagccaaa gaatgtctag 960
aaaagtactc aacactacgg gatcaaactg acccaatatt aataatgaaa agcgaaaaag 1020
ctaacgaaaa tttcctatgg aagctttgga gagactgtgt aaatacaata agtaatgagg 1080
aaacgagtaa cgagttacag aaaaccaatt atgccaaatg ggccacaggg gatggattaa 1140
cataccagaa aataatgaaa gaagtagcaa tagatgacga aacaatgtgc caagaagagc 1200
ctaaaatccc taacaaatgt agagtggctg cttgggttca aacagagatg aatctattga 1260
gcactctgac aagtaaaaga gctctggacc taccagaaat agggccagac atagcacccg 1320
tggagcatgt aggaagtgaa agaaggaaat actttgttaa tgaaatcaac tactgtaagg 1380
cctctacagt tatgatgaag tatgtgcttt ttcacacttc attgttgaat gaaagcaatg 1440
ccagcatggg aaaatacaaa gtaataccaa taaccaatag agtagtaaat gaaaaaggag 1500
aaagtttcga catgctttac ggtctggcgg ttaaaggaca atctcatctg aggggagata 1560
ctgatgttgt aacagttgta actttcgaat ttagtagtac agatccaaga gtggactcag 1620
gaaagtggcc aaaatatact gtgtttagga ttggctccct atttgtgagt gggagggaaa 1680
aatctgtgta cttgtattgc cgagtgaatg gcacaaataa gatccaaatg aaatggggaa 1740
tggaagctag aagatgtttg cttcaatcaa tgcaacaaat ggaggcaatt gttgaacagg 1800
aatcatcaat acaaggatat gacatgacca aagcctgttt caagggagac agagtaaata 1860
gccccaaaac tttcagtatt ggaactcaag aaggaaaact agtaaaagga tcctttggaa 1920
aagcactaag agtaatattt actaaatgct tgatgcacta tgtatttgga aatgcccaat 1980
tggaggggtt tagtgccgag tctaggagac ttctactgtt gattcaagca ttaaaggaca 2040
gaaagggccc ttgggtgttc gacttagagg gaatgtattc tggaatagaa gaatgtatta 2100
gcaacaaccc ttgggtaata cagagtgtat actggttcaa tgaatggttg ggctttgaaa 2160
aggaggggaa taaagtgttg gaatcagtgg atgaaataat ggatgaataa aaggaaatgg 2220
tactcaattt ggtactattt tgttcattat gtatctaaac atccaataaa aagaaccaag 2280
aatcaaaaat gcacgtgttt ctact 2305

<210> 12
<211> 2369
<212> DNA
<213> 乙型流感
<400> 12

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<210> 13
<211> 2396
<212> DNA
<213> 乙型流感

<400> 13

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taagaaaatt caatacatca aggattgaaa agaatccttc actaaggatg aagtgggcca 180
tgtgttctaa ttttcccttg gctctaacca agggcgatat ggcaaacaga atccccttgg 240
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<210> 14
<211> 1844
<212> DNA
<213> 乙型流感
<400> 14

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<210> 15

<211> 1189
<212> DNA
<213> 乙型流感
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<210> 16
<211> 1101
<212> DNA
<213> 乙型流感
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<210> 17
<211> 1885
<212> DNA
<213> 乙型流感
<400> 17

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<210> 18
<211> 1557
<212> DNA
<213> 乙型流感
<400> 18

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<210> 19

<211> 560
<212> PRT
<213> 乙型流感
<400> 19

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

275 280 285

Ser Ala Pro Gln Gln Lys Ala Leu Val Asp Gln Val Ile Gly Ser Arg
290 295 300

Asn Pro Gly Ile Ala Asp Ile Glu Asp Leu Thr Leu Leu Ala Arg Ser
305 310 315 320

Met Ile Val Val Arg Pro Ser Val Ala Ser Lys Val Val Leu Pro Ile
325 330 335

Ser Ile Tyr Ala Lys Ile Pro Gln Leu Gly Phe Asn Ile Glu Glu Tyr
340 345 350

Ser Met Val Gly Tyr Glu Ala Met Ala Leu Tyr Asn Met Ala Thr Pro
355 360 365

Val Ser Ile Leu Arg Met Gly Asp Asp Ala Lys Asp Lys Ser Gln Leu
370 375 380

Phe Phe Met Ser Cys Phe Gly Ala Ala Tyr Glu Asp Leu Arg Val Leu
385 390 395 400

Ser Ala Leu Thr Gly Thr Glu Phe Lys Pro Arg Ser Ala Leu Lys Cys
405 410 415

Lys Gly Phe His Val Pro Ala Lys Glu Gln Val Glu Gly Met Gly Ala
420 425 430

Ala Leu Met Ser Ile Lys Leu Gln Phe Trp Ala Pro Met Thr Arg Ser
435 440 445

Gly Gly Asn Glu Val Ser Gly Glu Gly Gly Ser Gly Gln Ile Ser Cys
450 455 460

Ser Pro Val Phe Ala Val Glu Arg Pro Ile Ala Leu Ser Lys Gln Ala
465 470 475 480

Val Arg Arg Met Leu Ser Met Asn Val Glu Gly Arg Asp Ala Asp Val
485 490 495

Lys Gly Asn Leu Leu Lys Met Met Asn Asp Ser Met Ala Lys Lys Thr
500 505 510

Ser Gly Asn Ala Phe Ile Gly Lys Lys Met Phe Gln Ile Ser Asp Lys
515 520 525

Asn Lys Val Asn Pro Ile Glu Ile Pro Ile Lys Gln Thr Ile Pro Ser
530 535 540

Phe Phe Phe Gly Arg Asp Thr Ala Glu Asp Tyr Asp Asp Leu Asp Tyr
545 550 555 560

<210> 20

<211> 726

<212> PRT

<213> 乙型流感

<400> 20

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

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

610 615 620
Val Lys Gly Ser Phe Gly Lys Ala Leu Arg Val Ile Phe Thr Lys Cys
625 630 635 640
Leu Met His Tyr Val Phe Gly Asn Ala Gln Leu Glu Gly Phe Ser Ala
645 650 655
Glu Ser Arg Arg Leu Leu Leu Leu Ile Gln Ala Leu Lys Asp Arg Lys
660 665 670
Gly Pro Trp Val Phe Asp Leu Glu Gly Met Tyr Ser Gly Ile Glu Glu
675 680 685
Cys Ile Ser Asn Asn Pro Trp Val Ile Gln Ser Ala Tyr Trp Phe Asn
690 695 700
Glu Trp Leu Gly Phe Glu Lys Glu Gly Ser Lys Val Leu Glu Ser Val
705 710 715 720
Asp Glu Ile Met Asn Glu
725

<210> 21
<211> 752
<212> PRT
<213> 乙型流感
<400> 21
Met Asn Ile Asn Pro Tyr Phe Leu Phe Ile Asp Val Pro Ile Gln Ala
1 5 10 15
Ala Ile Ser Thr Thr Phe Pro Tyr Thr Gly Val Pro Pro Tyr Ser His
20 25 30
Gly Thr Gly Thr Gly His Thr Ile Asp Thr Val Ile Arg Thr His Glu
35 40 45
Tyr Ser Asn Lys Gly Lys Gln Tyr Val Ser Asp Ile Thr Gly Cys Thr
50 55 60
Met Val Asp Pro Thr Asn Gly Pro Leu Pro Glu Asp Asn Glu Pro Ser
65 70 75 80
Ala Tyr Ala Gln Leu Asp Cys Val Leu Glu Ala Leu Asp Arg Met Asp
85 90 95
Glu Glu His Pro Gly Leu Phe Gln Ala Ala Ser Gln Asn Ala Met Glu
100 105 110
Ala Leu Met Val Thr Thr Val Asp Lys Leu Thr Gln Gly Arg Gln Thr
115 120 125
Phe Asp Trp Thr Val Cys Arg Asn Gln Pro Ala Ala Thr Ala Leu Asn
130 135 140
Thr Thr Ile Thr Ser Phe Arg Leu Asn Asp Leu Asn Gly Ala Asp Lys

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

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

<210> 22
<211> 770
<212> PRT

<213> 乙型流感

<400> 22

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

290 295 300
Gly Gly Asp Val Ala Cys Asp Ile Ile Arg Ala Ala Leu Gly Leu Lys
305 310 315 320
Ile Arg Gln Arg Gln Arg Phe Gly Arg Leu Glu Leu Lys Arg Ile Ser
325 330 335
Gly Arg Gly Phe Lys Asn Asp Glu Glu Ile Leu Ile Gly Asn Gly Thr
340 345 350
Ile Gln Lys Ile Gly Ile Trp Asp Gly Glu Glu Glu Phe His Val Arg
355 360 365
Cys Gly Glu Cys Arg Gly Ile Leu Lys Lys Ser Lys Met Arg Met Glu
370 375 380
Lys Leu Leu Ile Asn Ser Ala Lys Lys Glu Asp Met Lys Asp Leu Ile
385 390 395 400
Ile Leu Cys Met Val Phe Ser Gln Asp Thr Arg Met Phe Gln Gly Val
405 410 415
Arg Gly Glu Ile Asn Phe Leu Asn Arg Ala Gly Gln Leu Leu Ser Pro
420 425 430
Met Tyr Gln Leu Gln Arg Tyr Phe Leu Asn Arg Ser Asn Asp Leu Phe
435 440 445
Asp Gln Trp Gly Tyr Glu Glu Ser Pro Lys Ala Ser Glu Leu His Gly
450 455 460
Ile Asn Glu Leu Met Asn Ala Ser Asp Tyr Thr Leu Lys Gly Val Val
465 470 475 480
Val Thr Lys Asn Val Ile Asp Asp Phe Ser Ser Thr Glu Thr Glu Lys
485 490 495
Val Ser Ile Thr Lys Asn Leu Ser Leu Ile Lys Arg Thr Gly Glu Val
500 505 510
Ile Met Gly Ala Asn Asp Val Ser Glu Leu Glu Ser Gln Ala Gln Leu
515 520 525
Met Ile Thr Tyr Asp Thr Pro Lys Met Trp Glu Met Gly Thr Thr Lys
530 535 540
Glu Leu Val Gln Asn Thr Tyr Gln Trp Val Leu Lys Asn Leu Val Thr
545 550 555 560
Leu Lys Ala Gln Phe Leu Leu Gly Lys Glu Asp Met Phe Gln Trp Asp
565 570 575
Ala Phe Glu Ala Phe Glu Ser Ile Ile Pro Gln Lys Met Ala Gly Gln
580 585 590
Tyr Ser Gly Phe Ala Arg Ala Val Leu Lys Gln Met Arg Asp Gln Glu
595 600 605

Val Met Lys Thr Asp Gln Phe Ile Lys Leu Leu Pro Phe Cys Phe Ser
610 615 620
Pro Pro Lys Leu Arg Arg Asn Gly Glu Pro Tyr Gln Phe Leu Arg Leu
625 630 635 640
Val Leu Lys Gly Gly Gly Glu Asn Phe Ile Glu Val Arg Lys Gly Ser
645 650 655
Pro Leu Phe Ser Tyr Asn Pro Gln Thr Glu Val Leu Thr Ile Cys Gly
660 665 670
Arg Met Met Ser Leu Lys Gly Lys Ile Glu Asp Glu Glu Arg Asn Arg
675 680 685
Ser Met Gly Asn Ala Val Leu Ala Gly Phe Leu Val Ser Gly Lys Tyr
690 695 700
Asp Pro Asp Leu Gly Asp Phe Lys Thr Ile Glu Glu Leu Glu Lys Leu
705 710 715 720
Lys Pro Gly Glu Lys Ala Asn Ile Leu Leu Tyr Gln Gly Lys Pro Val
725 730 735
Lys Val Val Lys Arg Lys Arg Tyr Ser Ala Leu Ser Asn Asp Ile Ser
740 745 750
Gln Gly Ile Lys Arg Gln Arg Met Thr Val Glu Ser Met Gly Trp Ala
755 760 765
Leu Ser
770

<210> 23
<211> 560
<212> PRT
<213> 乙型流感
<400> 23

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

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

405 410 415
Lys Gly Phe His Val Pro Ala Lys Glu Gln Val Glu Gly Met Gly Ala
420 425 430
Ala Leu Met Ser Ile Lys Leu Gln Phe Trp Ala Pro Met Thr Arg Ser
435 440 445
Gly Gly Asn Glu Val Gly Gly Asp Gly Gly Ser Gly Gln Ile Ser Cys
450 455 460
Ser Pro Val Phe Ala Val Glu Arg Pro Ile Ala Leu Ser Lys Gln Ala
465 470 475 480
Val Arg Arg Met Leu Ser Met Asn Ile Glu Gly Arg Asp Ala Asp Val
485 490 495
Lys Gly Asn Leu Leu Lys Met Met Asn Asp Ser Met Ala Lys Lys Thr
500 505 510
Asn Gly Asn Ala Phe Ile Gly Lys Lys Met Phe Gln Ile Ser Asp Lys
515 520 525
Asn Lys Thr Asn Pro Val Glu Ile Pro Ile Lys Gln Thr Ile Pro Asn
530 535 540
Phe Phe Phe Gly Arg Asp Thr Ala Glu Asp Tyr Asp Asp Leu Asp Tyr
545 550 555 560

<210> 24
<211> 248
<212> PRT
<213> 乙型流感
<400> 24

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

115 120 125
Met Val Met Tyr Leu Asn Pro Gly Asn Tyr Ser Met Gln Val Lys Leu
130 135 140
Gly Thr Leu Cys Ala Leu Cys Glu Lys Gln Ala Ser His Ser His Arg
145 150 155 160
Ala His Ser Arg Ala Ala Arg Ser Ser Val Pro Gly Val Arg Arg Glu
165 170 175
Met Gln Met Val Ser Ala Met Asn Thr Ala Lys Thr Met Asn Gly Met
180 185 190
Gly Lys Gly Glu Asp Val Gln Lys Leu Ala Glu Glu Leu Gln Ser Asn
195 200 205
Ile Gly Val Leu Arg Ser Leu Gly Ala Ser Gln Lys Asn Gly Glu Gly
210 215 220
Ile Ala Lys Asp Val Met Glu Val Leu Lys Gln Ser Ser Met Gly Asn
225 230 235 240
Ser Ala Leu Val Lys Lys Tyr Leu
245

<210> 25
<211> 109
<212> PRT
<213> 乙型流感
<400> 25
Met Leu Glu Pro Phe Gln Ile Leu Ser Ile Cys Ser Phe Ile Leu Ser
1 5 10 15
Ala Leu His Phe Met Ala Trp Thr Ile Gly His Leu Asn Gln Ile Lys
20 25 30
Arg Gly Val Asn Met Lys Ile Arg Ile Lys Asn Pro Asn Lys Glu Thr
35 40 45
Ile Asn Arg Glu Val Ser Ile Leu Arg His Ser Tyr Gln Lys Glu Ile
50 55 60
Gln Ala Lys Glu Thr Met Lys Glu Val Leu Ser Asp Asn Met Glu Val
65 70 75 80
Leu Ser Asp His Ile Val Ile Glu Gly Leu Ser Ala Glu Glu Ile Ile
85 90 95
Lys Met Gly Glu Thr Val Leu Glu Val Glu Glu Leu His
100 105

<210> 26
<211> 281
<212> PRT

<213> 乙型流感

<400> 26

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

<210> 27

<211> 122
<212> PRT
<213> 乙型流感
<400> 27

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

<210> 28
<211> 583
<212> PRT
<213> 乙型流感
<400> 28

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

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

420 425 430

Leu His Asn Glu Ile Leu Glu Leu Asp Glu Lys Val Asp Asp Leu Arg

435 440 445

Ala Asp Thr Ile Ser Ser Gln Ile Glu Leu Ala Val Leu Leu Ser Asn

450 455 460

Glu Gly Ile Ile Asn Ser Glu Asp Glu His Leu Leu Ala Leu Glu Arg

465 470 475 480

Lys Leu Lys Lys Met Leu Gly Pro Ser Ala Val Asp Ile Gly Asn Gly

485 490 495

Cys Phe Glu Thr Lys His Lys Cys Asn Gln Thr Cys Leu Asp Arg Ile

500 505 510

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

515 520 525

Ser Leu Asn Ile Thr Ala Ala Ser Leu Asn Asp Asp Gly Leu Asp Asn

530 535 540

His Thr Ile Leu Leu Tyr Tyr Ser Thr Ala Ala Ser Ser Leu Ala Val

545 550 555 560

Thr Leu Met Ile Ala Ile Phe Ile Val Tyr Met Val Ser Arg Asp Asn

565 570 575

Val Ser Cys Ser Ile Cys Leu

580

<210> 29

<211> 466

<212> PRT

<213> 乙型流感

<400> 29

Met Leu Pro Ser Thr Ile Gln Thr Leu Thr Leu Phe Leu Thr Ser Gly

1 5 10 15

Gly Val Leu Leu Ser Leu Tyr Val Ser Ala Ser Leu Ser Tyr Leu Leu

20 25 30

Tyr Ser Asp Ile Leu Leu Lys Phe Ser Pro Thr Glu Ile Thr Ala Pro

35 40 45

Thr Met Pro Leu Asp Cys Ala Asn Ala Ser Asn Val Gln Ala Val Asn

50 55 60

Arg Ser Ala Thr Lys Glu Met Thr Leu Leu Leu Pro Glu Pro Glu Trp

65 70 75 80

Thr Tyr Pro Arg Leu Ser Cys Pro Gly Ser Thr Phe Gln Lys Ala Leu

85 90 95

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

100 105 110

Leu Thr Ile Arg Glu Pro Phe Ile Ala Cys Gly Pro Lys Glu Cys Lys

115 120 125

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

130 135 140

Gly Thr Arg Glu Asp Arg Asn Lys Leu Arg His Leu Ile Ser Val Lys

145 150 155 160

Leu Gly Lys Ile Pro Thr Val Glu Asn Ser Ile Phe His Met Ala Ala

165 170 175

Trp Ser Gly Ser Ala Cys His Asp Gly Arg Glu Trp Thr Tyr Ile Gly

180 185 190

Val Asp Gly Pro Asp Ser Asn Ala Leu Ile Lys Ile Lys Tyr Gly Glu

195 200 205

Ala Tyr Thr Asp Thr Tyr His Ser Tyr Ala Asn Asn Ile Leu Arg Thr

210 215 220

Gln Glu Ser Ala Cys Asn Cys Ile Gly Gly Asp Cys Tyr Leu Met Ile

225 230 235 240

Thr Asp Gly Ser Ala Ser Gly Ile Ser Lys Cys Arg Phe Leu Lys Ile

245 250 255

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

260 265 270

His Thr Glu Glu Cys Thr Cys Gly Phe Ala Ser Asn Lys Thr Ile Glu

275 280 285

Cys Ala Cys Arg Asp Asn Ser Tyr Thr Ala Lys Arg Pro Phe Val Lys

290 295 300

Leu Asn Val Glu Thr Asp Thr Ala Glu Ile Arg Leu Met Cys Thr Glu

305 310 315 320

Thr Tyr Leu Asp Thr Pro Arg Pro Asp Asp Gly Ser Ile Thr Gly Pro

325 330 335

Cys Glu Ser Asn Gly Asp Lys Gly Arg Gly Gly Ile Lys Gly Gly Phe

340 345 350

Val His Gln Arg Met Ala Ser Lys Ile Gly Arg Trp Tyr Ser Arg Thr

355 360 365

Met Ser Lys Thr Glu Arg Met Gly Met Glu Leu Tyr Val Lys Tyr Asp

370 375 380

Gly Asp Pro Trp Thr Asp Ser Glu Ala Leu Ala Pro Ser Gly Val Met

385 390 395 400

Val Ser Met Glu Glu Pro Gly Trp Tyr Ser Phe Gly Phe Glu Ile Lys

405 410 415

Asp Lys Lys Cys Asp Val Pro Cys Ile Gly Ile Glu Met Val His Asp
420 425 430
Gly Gly Lys Lys Thr Trp His Ser Ala Ala Thr Ala Ile Tyr Cys Leu
435 440 445
Met Gly Ser Gly Gln Leu Leu Trp Asp Thr Val Thr Gly Val Asp Met
450 455 460
Ala Leu
465

<210> 30
<211> 2305
<212> DNA
<213> 乙型流感
<400> 30

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aaccagcaat gctattcaac atctgcgtcc atctagaggt ttgctatgta ataagtgaca 180
tgaattttct tgacgaagaa ggaaaatcat atacagcatt agaaggacaa ggaaaagaac 240
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<210> 31
<211> 2369
<212> DNA
<213> 乙型流感
<400> 31

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acgggaacag gccacacaat agacaccgtg atcagaacac atgagtactc gaacaaggga 180
aaacagtatg tttctgacat cacaggatgt acaatggtag atccaacaaa tgggccatta 240
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ctaatggtca caactgtaga caaattaacc caggggagac agacttttga ttggacagta 420
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gatttgaatg gagctgacaa gggtggattg gtacccttttt gccaagatat cattgattca 540
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taaaatgaaa aaaggctcgt gtttctact 2369

<210> 32
<211> 2396
<212> DNA
<213> 乙型流感
<400> 32

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taagaaaatt caatacatca agaattgaaa agaacccttc attgaggatg aagtgggcaa 180
tgtgttctaa ttttcccttg gctctgacca agggtgatat ggcaaacaga atccccttgg 240
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gctcaatagc agcagttacc tggtggaata catatggacc aataggagat actgaaggtt 360
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gccgaataac ttttggccca gttgaaagag taagaaaaag ggtactgcta aaccctctca 480
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aaaaattgaa aggaacaatg ataactccca ttgtactggc atacatgctt gagagagaat 660
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<210> 33
<211> 1844
<212> DNA
<213> 乙型流感
<400> 33

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ataacttctg gaaccagtgg gacaaccaga ccaatcatca gaccagcaac ccttgcccca 180
ccaagcaaca aacgaacccg gaacccatcc ccggaaagag caaccacaag cagtgaagct 240
gatgtcggaa ggaaaaccca aaagaaacag accccgacag agataaagaa gagcgtctac 300
aatatggtag tgaaactggg tgaattctat aaccagatga tggtcaaagc tggactcaac 360
gatgacatgg agagaaacct aatccaaaat gcgcatgctg tggaaagaat tctattggct 420
gccactgatg acaagaaaac tgaattccag aggaaaaaga atgccagaga tgtcaaagaa 480
ggaaaagaag aaatagacca caacaaaaca ggaggcacct tttacaagat ggtaagagat 540

gataaaacca tctacttcag ccctataaga attacctttt taaaagaaga ggtgaaaaca 600
atgtacaaaa ccaccatggg gagtgatggc ttcagtggac taaatcacat aatgattggg 660
cattcacaga tgaatgatgt ctgtttccaa agatcaaagg ccctaaaaag agttggactt 720
gacccttcat taatcagtac ctttgcagga agcacactcc ccagaagatc aggtgcaact 780
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<210> 34
<211> 1190
<212> DNA
<213> 乙型流感
<400> 34

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gaaagaaaaa gaagattcat cacagagccc ctatcaggaa tgggaacaac agcaacaaaa 300
aagaagggcc tgattctagc tgagagaaaa atgagaagat gtgtgagttt tcatgaagca 360
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ctaaagcaga gctctatggg aaattcagct cttgtgaaga aatacctata atgctcgaac 780
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aggtagaaga attgcattaa attcaatttt tactgtattt cttgctatgc atttaagcaa 1140
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<211> 1096
<212> DNA
<213> 乙型流感
<400> 35

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attttggagt gctatgaaag gctttcatgg caaagagccc ttgactaccc tggtcaagac 180
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ccagaaagta aaaggatgtc tcttgaagag agaaaagcta ttggggtaaa aatgatgaaa 300
gtgctcctat ttatgaaccc atctgctgga gttgaagggt ttgagccata ttgtatgaaa 360
aatccctcca atagcaactg tccagactgc aattgggctg attaccctcc aacaccagga 420
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<210> 36
<211> 1557
<212> DNA
<213> 乙型流感
<400> 36

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<210> 37
<211> 1879
<212> DNA
<213> 乙型流感
<400> 37

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<211> 1842
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<213> 乙型流感
<400> 38

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aacttccgga accagtgggg caaccagacc aatcatcaag ccagcaaccc ttgccccacc 180
aagcaataaa cgaacccgaa acccatcccc agaaagggca accacaagca gcgaagcgat 240
tgtcggaagg agaacccaaa agaaacaaac cccgacagag ataaagaaga gcgtctacaa 300
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tgacatggag agaaacctaa tccaaaatgc acatgctgtg gaaagaattc tattggctgc 420
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gtacaagacc accatgggga gtgatggttt cagtggacta aatcacatca tgattgggca 660
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<210> 39
<211> 1842
<212> DNA
<213> 乙型流感
<400> 39

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<211> 2277
<212> DNA
<213> 乙型流感
<400> 40

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<210> 41
<211> 2277
<212> DNA
<213> 乙型流感
<400> 41

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<210> 42
<211> 585
<212> PRT
<213> 乙型流感
<400> 42

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20 25 30
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35 40 45
Thr Thr Pro Thr Lys Ser His Phe Ala Asn Leu Lys Gly Thr Glu Thr
50 55 60
Arg Gly Lys Leu Cys Pro Lys Cys Leu Asn Cys Thr Asp Leu Asp Val
65 70 75 80

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

385 390 395 400
Lys Ser Thr Gln Glu Ala Ile Asn Lys Ile Thr Lys Asn Leu Asn Ser
405 410 415
Leu Ser Glu Leu Glu Val Lys Asn Leu Gln Arg Leu Ser Gly Ala Met
420 425 430
Asp Glu Leu His Asn Glu Ile Leu Glu Leu Asp Glu Lys Val Asp Asp
435 440 445
Leu Arg Ala Asp Thr Ile Ser Ser Gln Ile Glu Leu Ala Val Leu Leu
450 455 460
Ser Asn Glu Gly Ile Ile Asn Ser Glu Asp Glu His Leu Leu Ala Leu
465 470 475 480
Glu Arg Lys Leu Lys Lys Met Leu Gly Pro Ser Ala Val Glu Ile Gly
485 490 495
Asn Gly Cys Phe Glu Thr Lys His Lys Cys Asn Gln Thr Cys Leu Asp
500 505 510
Arg Ile Ala Ala Gly Thr Phe Asp Ala Gly Glu Phe Ser Leu Pro Thr
515 520 525
Phe Asp Ser Leu Asn Ile Thr Ala Ala Ser Leu Asn Asp Asp Gly Leu
530 535 540
Asp Asn His Thr Ile Leu Leu Tyr Tyr Ser Thr Ala Ala Ser Ser Leu
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Ala Val Thr Leu Met Ile Ala Ile Phe Val Val Tyr Met Val Ser Arg
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<211> 560
<212> PRT
<213> 乙型流感
<400> 44

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

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

405 410 415
Lys Gly Phe His Val Pro Ala Lys Glu Gln Val Glu Gly Met Gly Ala
420 425 430
Ala Leu Met Ser Ile Lys Leu Gln Phe Trp Ala Pro Met Thr Arg Ser
435 440 445
Gly Gly Asn Glu Val Gly Gly Asp Gly Gly Ser Gly Gln Ile Ser Cys
450 455 460
Ser Pro Val Phe Ala Val Glu Arg Pro Ile Ala Leu Ser Lys Gln Ala
465 470 475 480
Val Arg Arg Met Leu Ser Met Asn Ile Glu Gly Arg Asp Ala Asp Val
485 490 495
Lys Gly Asn Leu Leu Lys Met Met Asn Asp Ser Met Ala Lys Lys Thr
500 505 510
Asn Gly Asn Ala Phe Ile Gly Lys Lys Met Phe Gln Ile Ser Asp Lys
515 520 525
Asn Lys Ile Asn Pro Val Asp Ile Pro Ile Lys Gln Thr Ile Pro Asn
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Phe Phe Phe Gly Arg Asp Thr Ala Glu Asp Tyr Asp Asp Leu Asp Tyr
545 550 555 560

<210> 45
<211> 560
<212> PRT
<213> 乙型流感
<400> 45

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

115 120 125

Phe Gln Lys Lys Lys Asn Ala Arg Asp Val Lys Glu Gly Lys Glu Glu
130 135 140

Ile Asp His Asn Lys Thr Gly Gly Thr Phe Tyr Lys Met Val Arg Asp
145 150 155 160

Asp Lys Thr Ile Tyr Phe Ser Pro Ile Arg Ile Thr Phe Leu Lys Glu
165 170 175

Glu Val Lys Thr Met Tyr Lys Thr Thr Met Gly Ser Asp Gly Phe Ser
180 185 190

Gly Leu Asn His Ile Met Ile Gly His Ser Gln Met Asn Asp Val Cys
195 200 205

Phe Gln Arg Ser Lys Ala Leu Lys Arg Val Gly Leu Asp Pro Ser Leu
210 215 220

Ile Ser Thr Phe Ala Gly Ser Thr Leu Pro Arg Arg Ser Gly Ala Thr
225 230 235 240

Gly Val Ala Ile Lys Gly Gly Gly Thr Leu Val Ala Glu Ala Ile Arg
245 250 255

Phe Ile Gly Arg Ala Met Ala Asp Arg Gly Leu Leu Arg Asp Ile Arg
260 265 270

Ala Lys Thr Ala Tyr Glu Lys Ile Leu Leu Asn Leu Lys Asn Lys Cys
275 280 285

Ser Ala Pro Gln Gln Lys Ala Leu Val Asp Gln Val Ile Gly Ser Arg
290 295 300

Asn Pro Gly Ile Ala Asp Ile Glu Asp Leu Thr Leu Leu Ala Arg Ser
305 310 315 320

Met Val Val Val Arg Pro Ser Val Ala Ser Lys Val Val Leu Pro Ile
325 330 335

Ser Ile Asn Ala Lys Ile Pro Gln Leu Gly Phe Asn Val Glu Glu Tyr
340 345 350

Ser Met Val Gly Tyr Glu Ala Met Ala Leu Tyr Asn Met Ala Thr Pro
355 360 365

Val Ser Ile Leu Arg Met Gly Asp Asp Ala Lys Asp Lys Ser Gln Leu
370 375 380

Phe Phe Met Ser Cys Phe Gly Ala Ala Tyr Glu Asp Gln Arg Val Leu
385 390 395 400

Ser Ala Leu Thr Gly Thr Glu Phe Lys His Arg Ser Ala Leu Lys Cys
405 410 415

Lys Gly Phe His Val Pro Ala Lys Glu Gln Val Glu Gly Met Gly Ala
420 425 430

Ala Leu Met Ser Ile Lys Leu Gln Phe Trp Ala Pro Met Thr Arg Ser
435 440 445
Gly Gly Asn Glu Val Gly Gly Asp Gly Gly Ser Gly Gln Ile Ser Cys
450 455 460
Ser Pro Val Phe Ala Val Glu Arg Pro Ile Ala Leu Ser Lys Gln Ala
465 470 475 480
Val Arg Arg Met Leu Ser Met Asn Ile Glu Gly Arg Asp Ala Asp Val
485 490 495
Lys Gly Asn Leu Leu Lys Met Met Asn Asp Ser Met Thr Lys Lys Thr
500 505 510
Asn Gly Asn Ala Phe Ile Gly Lys Lys Met Phe Gln Ile Ser Asp Lys
515 520 525
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530 535 540
Phe Phe Phe Gly Arg Asp Thr Ala Glu Asp Tyr Asp Asp Leu Asp Tyr
545 550 555 560

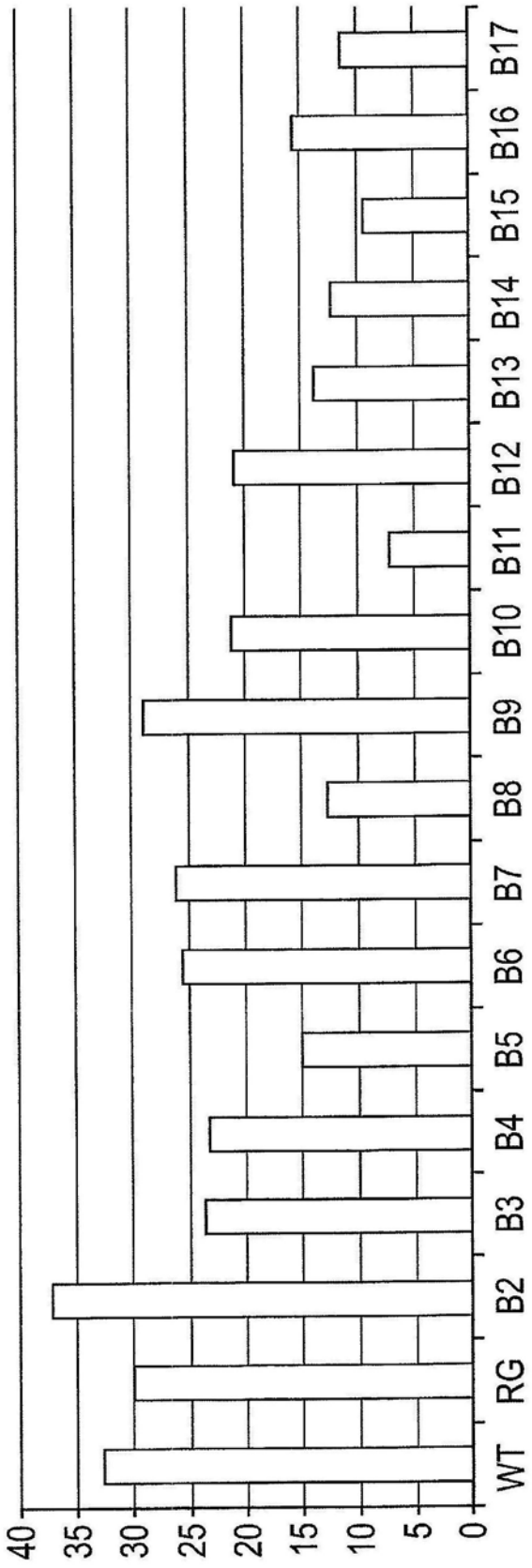

WT
RG
B2
B3
B4
B5
B6
B7
B8
B9
B10
B11
B12
B13
B14
B15
B16
B17
0
5
10
15
20
25
30
35
40

图1

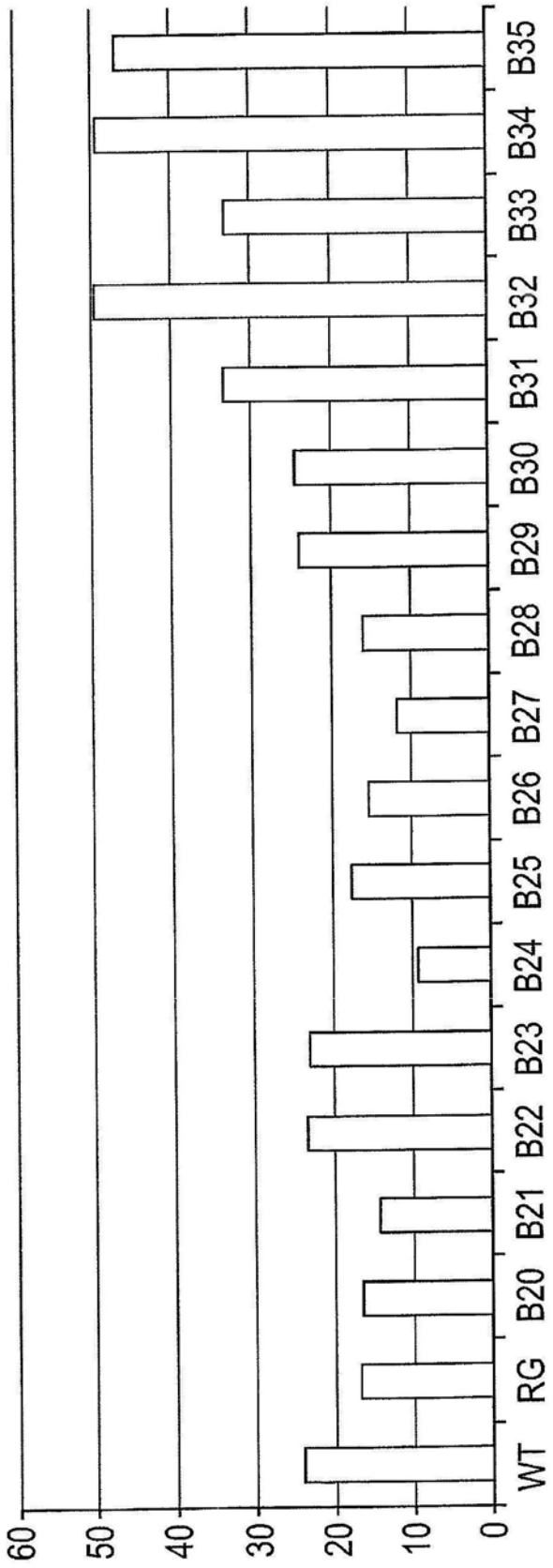
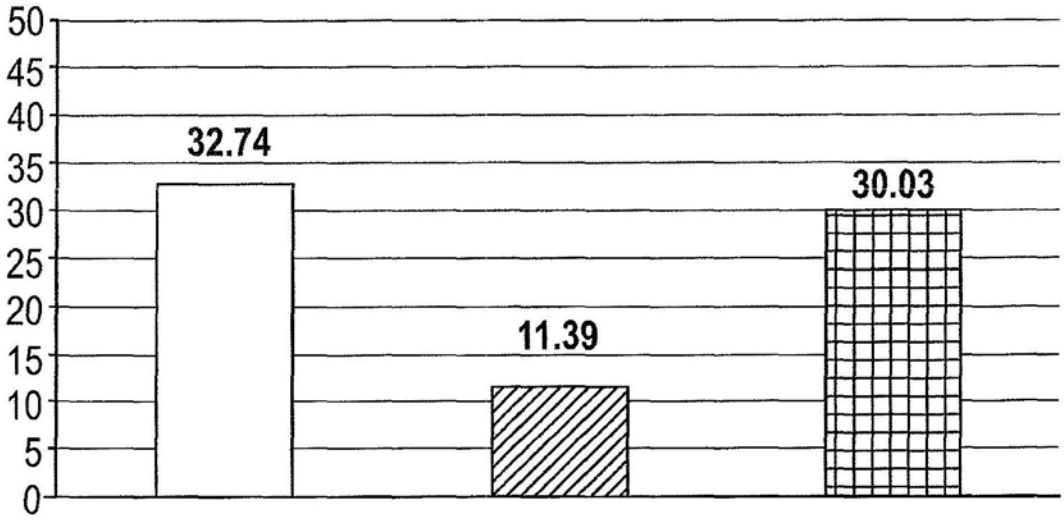

60
50
40
30
20
10
0
WT
RG
B20
B21
B22
B23
B24
B25
B26
B27
B28
B29
B30
B31
B32
B33
B34
B35

图2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45
40
35
30
25
20
15
10
5
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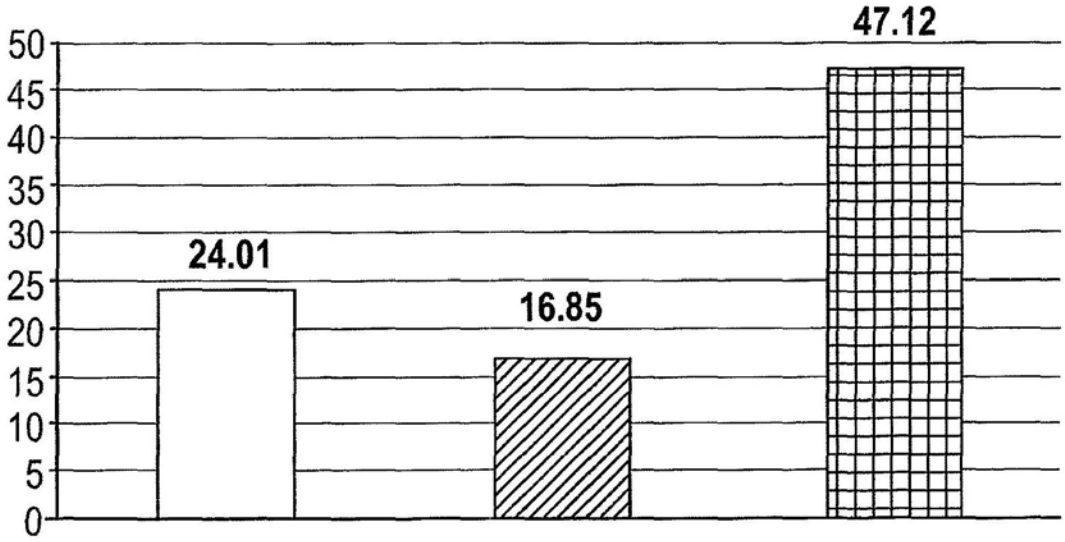
32.74
11.39
30.03

图3A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45
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35
30
25
20
15
10
5
0
24.01
16.85
47.12

图3B

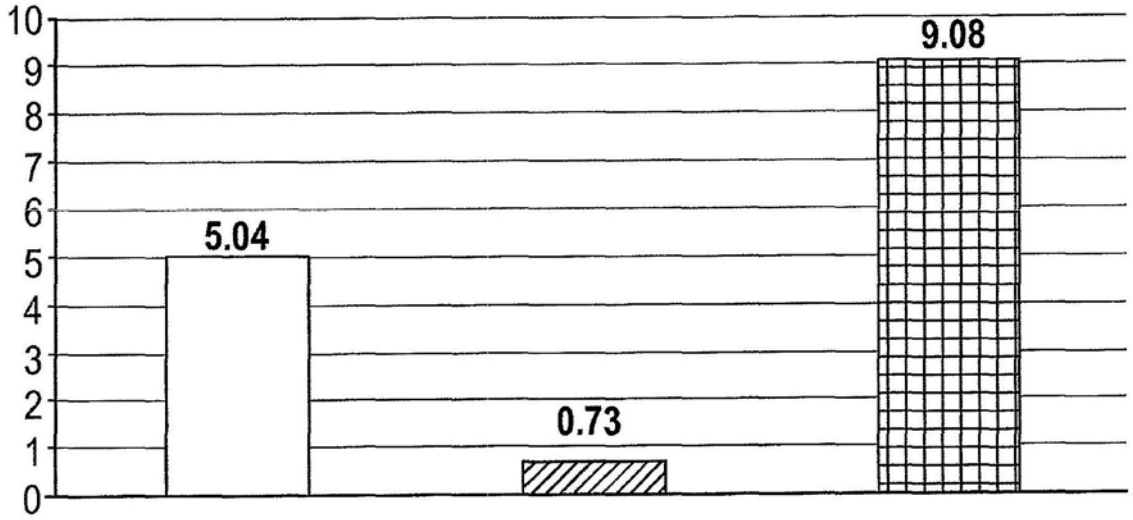


图3C

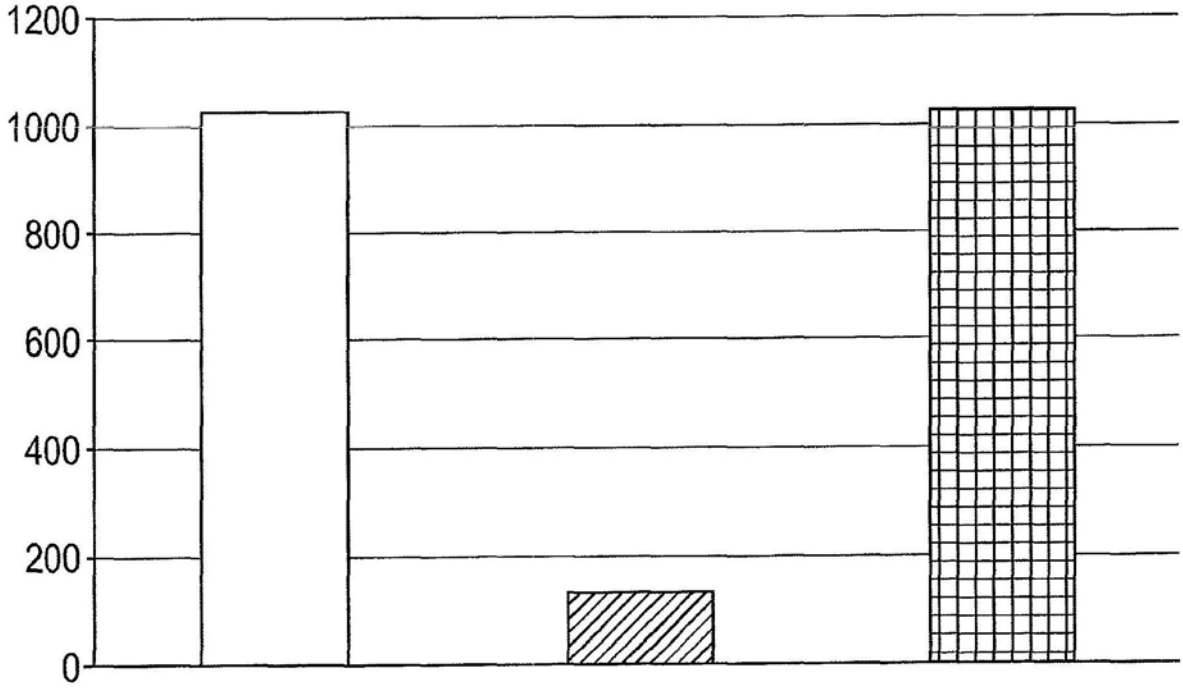


图3D

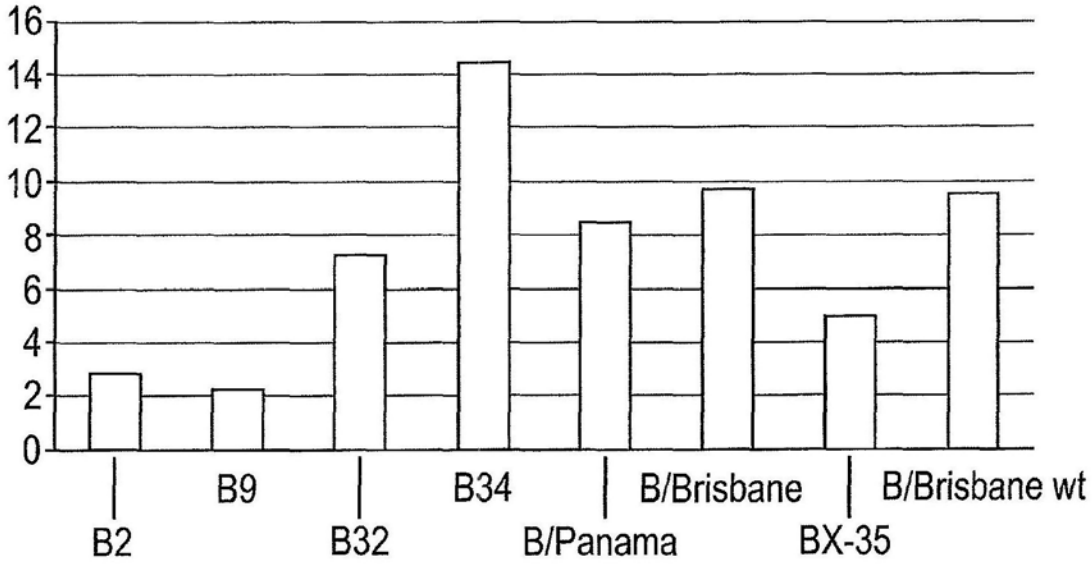

16
14
12
10
8
6
4
2
0
B2
B9
B32
B34
B/Panama
B/Brisbane
BX-35
B/Brisbane wt

图4A

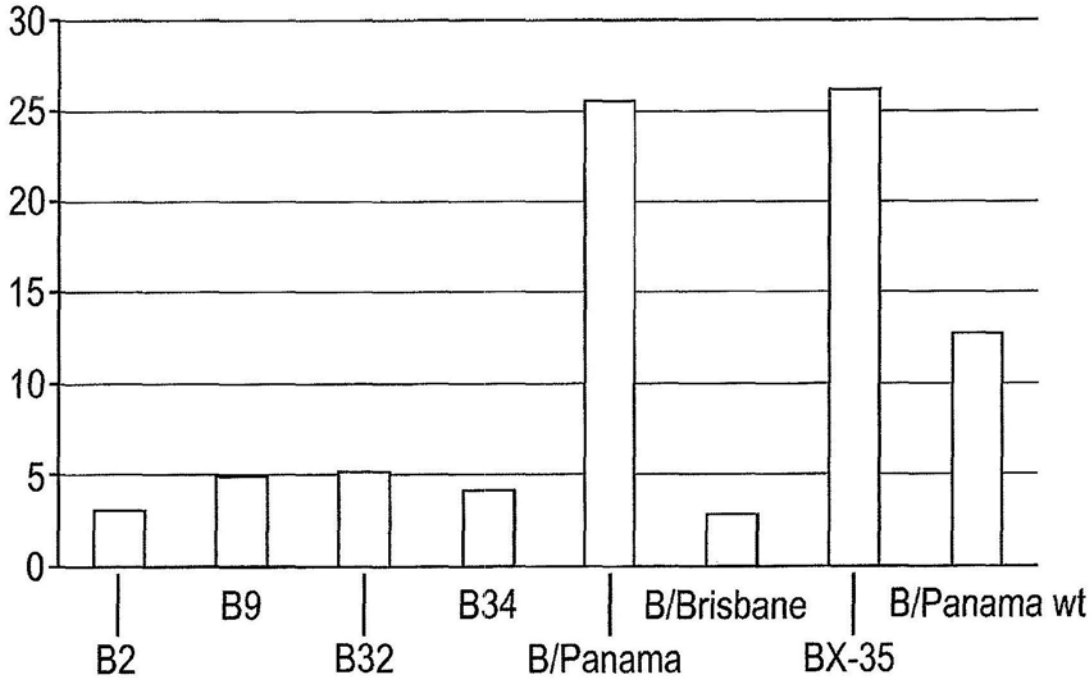

30
25
20
15
10
5
0
B2
B9
B32
B34
B/Panama
B/Brisbane
BX-35
B/Panama wt

图4B

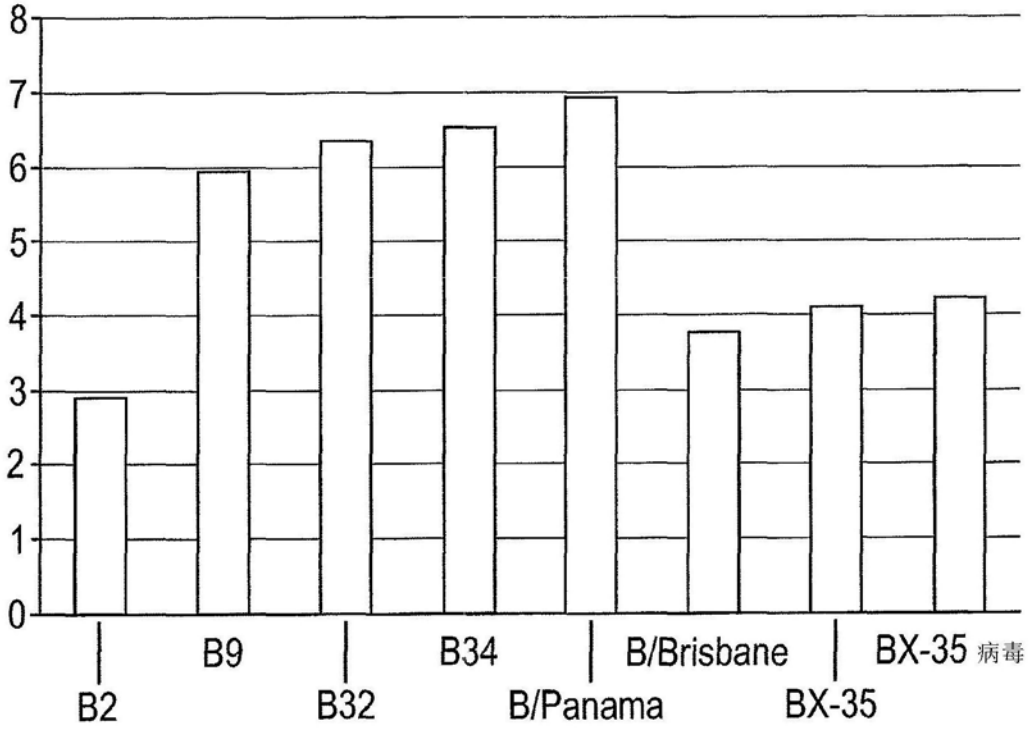
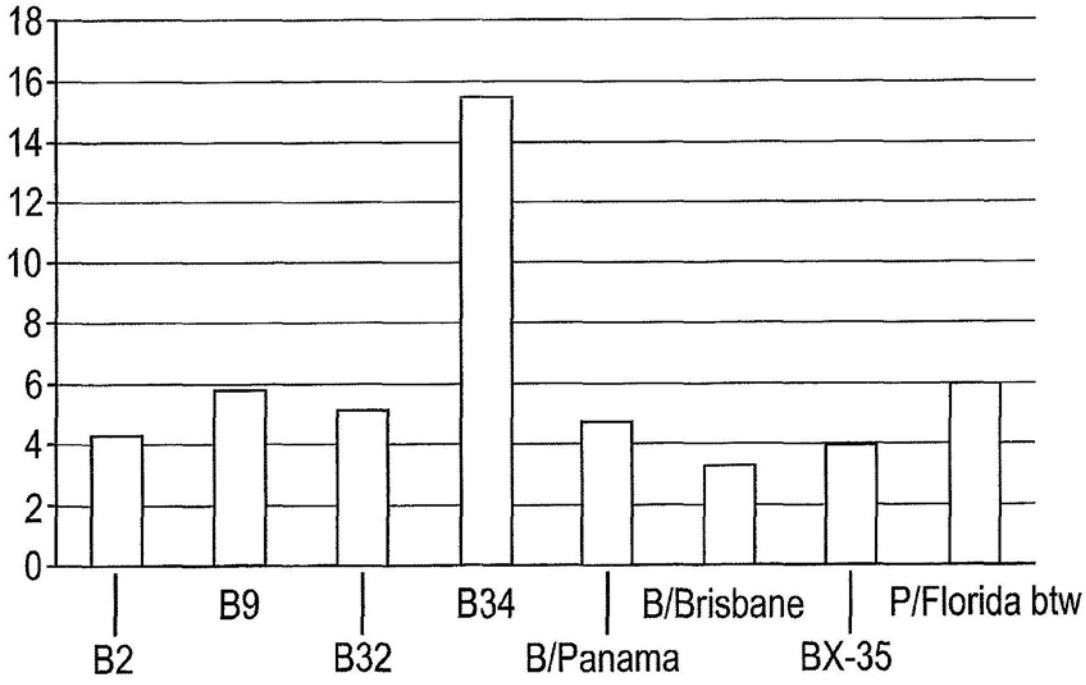

8
7
6
5
4
3
2
1
0
B2
B9
B32
B34
B/Panama
B/Brisbane
BX-35
BX-35 病毒

图4C


18
16
14
12
10
8
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B2
B9
B32
B34
B/Panama
B/Brisbane
BX-35
P/Florida btw

图4D

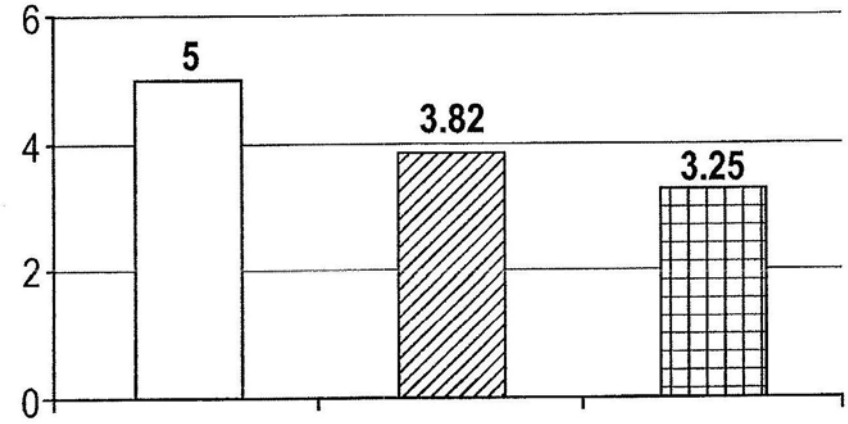

图5A

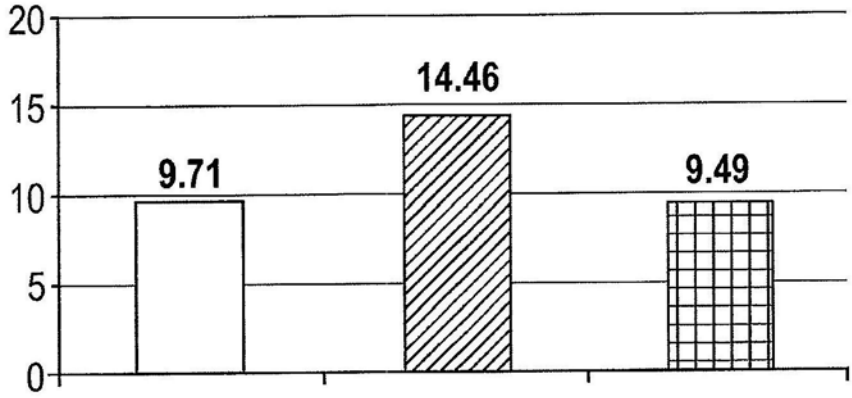

图5B

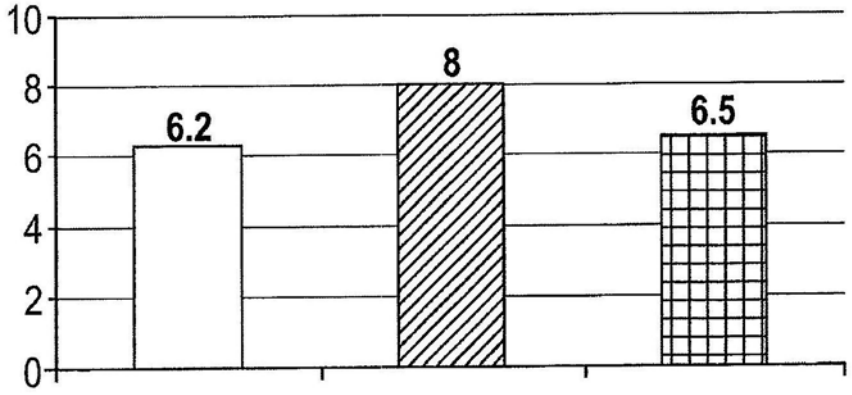

图5C

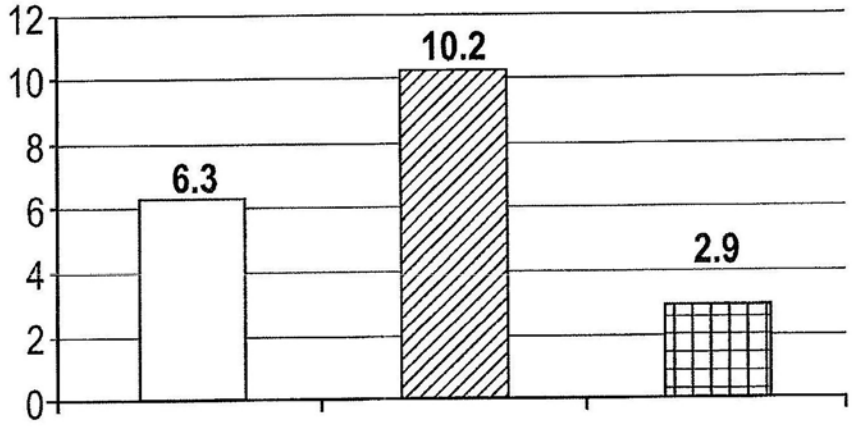

图5D

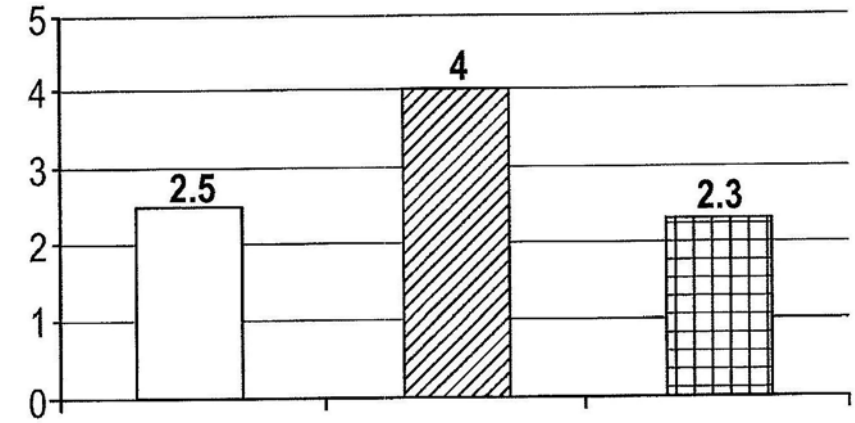

图5E

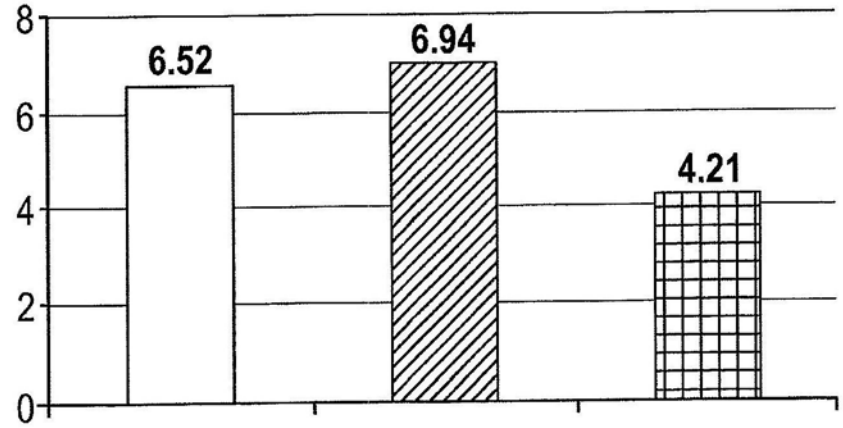

图5F

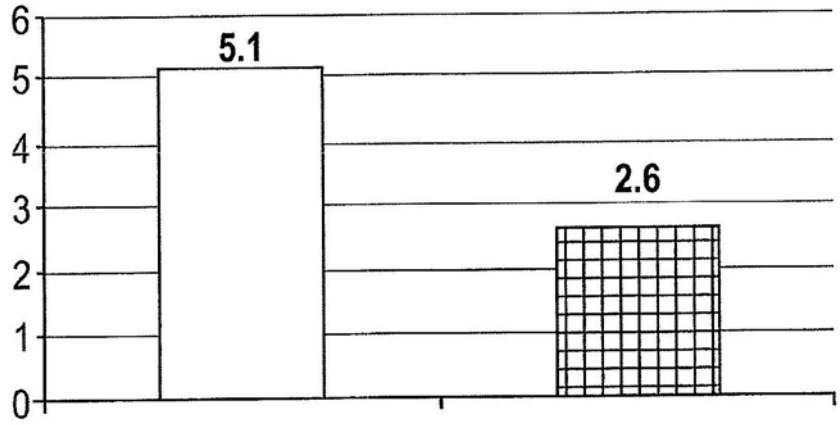

图5G

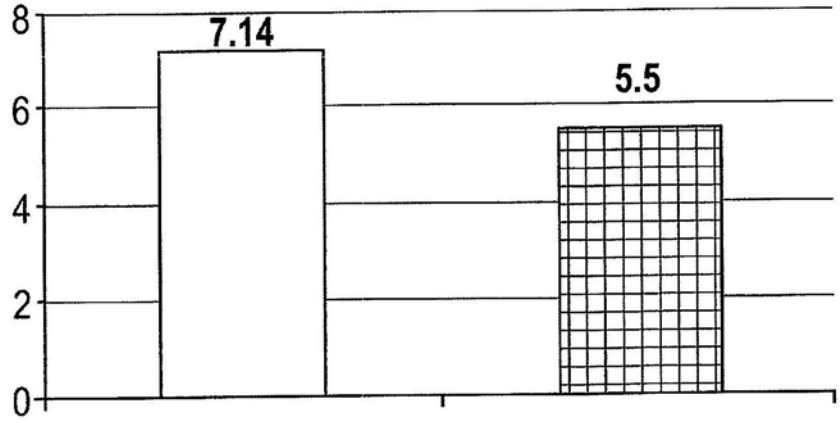

图5H

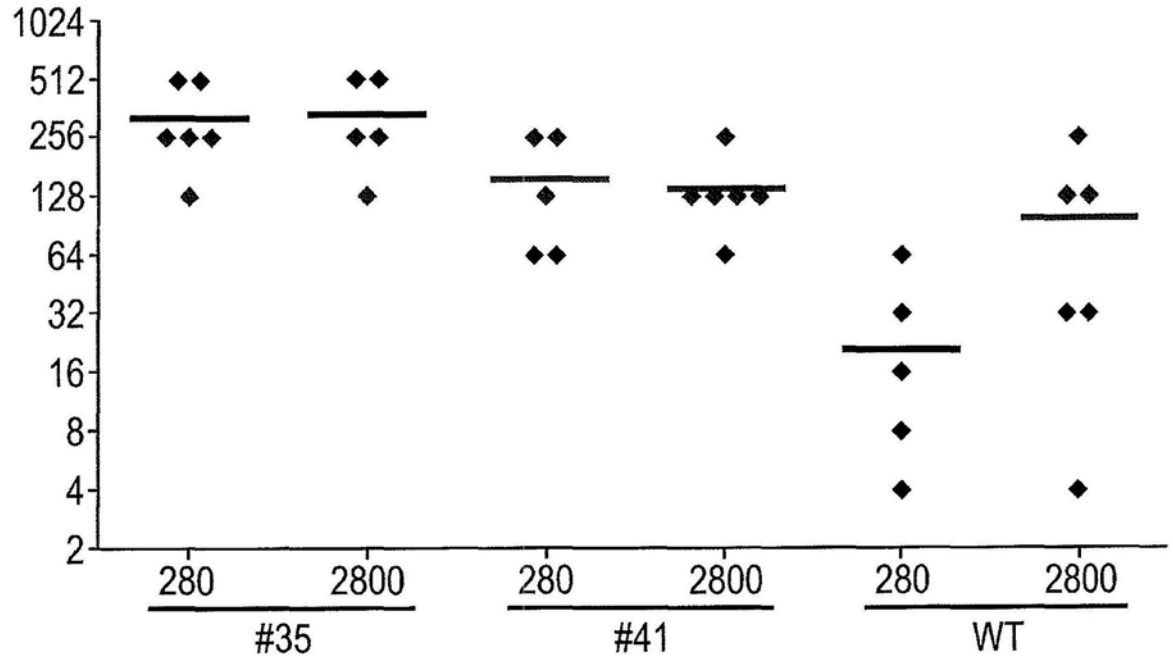
1024
512
256
128
64
32
16
8
4
2
280
2800
280
2800
280
2800
#35
#41
WT

图6A

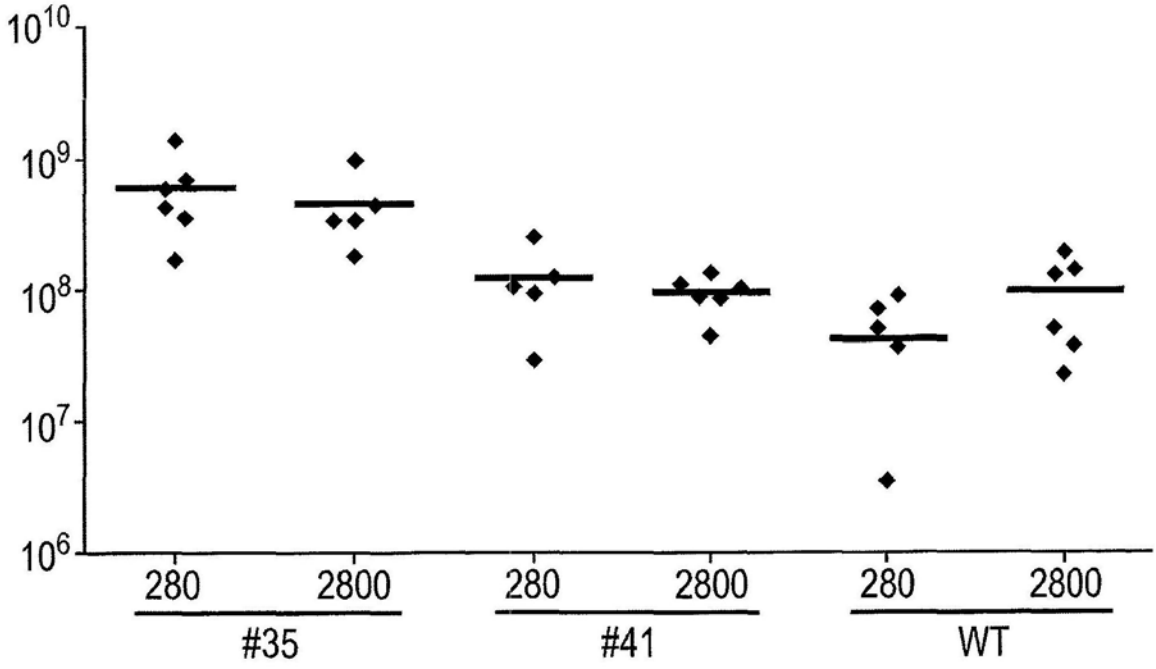
10^{10}
10^{9}
10^{8}
10^{7}
10^{6}
280
2800
280
2800
280
2800
#35
#41
WT

图6B