(19)国家知识产权局

(12)发明专利

(10)授权公告号 CN 113637694 B
(45)授权公告日 2024.11.12

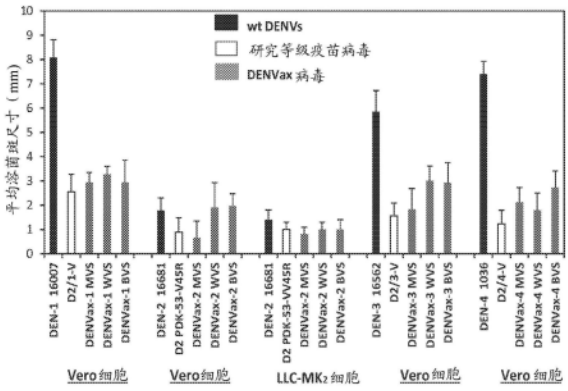
(21)申请号 202110718703.8
(22)申请日 2014.03.12
(65)同一申请的已公布的文献号
申请公布号 CN 113637694 A
(43)申请公布日 2021.11.12
(30)优先权数据
61/800,204 2013.03.15 US
(62)分案原申请数据
201480028001.5 2014.03.12
(73)专利权人 武田疫苗股份有限公司
地址 美国麻萨诸塞州
专利权人 美国政府健康及人类服务部
(72)发明人 丹.T.斯廷奇科姆 克莱尔.凯尼
理查德.M.凯尼 吉尔.A.利文格德
(74)专利代理机构 北京市柳沈律师事务所 11105
专利代理师 易方方
(51)Int.Cl.
C12N 15/62(2006.01)
C07K 19/00(2006.01)
A61K 39/295(2006.01)
A61K 39/12(2006.01)
A61P 31/14(2006.01)
A61P 37/04(2006.01)
C12N 15/85(2006.01)
C12N 5/10(2006.01)
(56)对比文件
TW 200740458 A,2007.11.01
CN 101657463 A,2010.02.24
审查员 朱晓乐
权利要求书1页 说明书60页
序列表123页 附图9页

(54)发明名称

用于疫苗中的登革热病毒嵌合式构建物的组合物及方法

(57)摘要

本文的实施方案报告了登革热病毒构建物和活减毒登革热病毒的组合物、用途及制造。一些实施方案涉及这样的组合物,其包括但不限于四价登革热病毒组合物。在某些实施方案中,组合物可包含登革热病毒的一种或多种血清型的构建物,诸如登革热-1(DEN-1)病毒、登革热-2(DEN-2)病毒、登革热-3(DEN-3)病毒或登革热-4(DEN-4)病毒的构建物。在其它实施方案中,本文所公开的构建物可组合于组合物中以产生对抗多于一种或多种登革热病毒构建物的疫苗,该构建物可以或可以不接续地在哺乳动物细胞内传代。



CN 113637694 B

1.由全基因组长度登革热-4/登革热-2核酸嵌合体表示的登革热-4/登革热-2嵌合病毒,所述登革热-4/登革热-2核酸嵌合体包含编码来自修饰的活减毒登革热-2病毒株PDK-53-V的非结构蛋白质NS1、NS2A、NS2B、NS3、NS4A、NS4B和NS5以及衣壳蛋白(C)的第一核苷酸序列,和编码来自登革热-4 1036的前膜/膜蛋白(prM)和被膜蛋白(E)的第二核苷酸序列,其中所述登革热-4/登革热-2核酸嵌合体编码由SEQ ID NO: 11或SEQ ID NO: 12所示的多肽分子。

2.权利要求1所述的登革热-4/登革热-2嵌合病毒,其中所述全基因组长度登革热-4/登革热-2核酸嵌合体由SEQ ID NO: 10或SEQ ID NO: 16所示。

3.由SEQ ID NO: 11或SEQ ID NO: 12所示的多肽分子。

4.根据权利要求1或权利要求2所述的登革热-4/登革热-2嵌合病毒,其包含一种或多种根据权利要求3所述的多肽分子。

5.药物组合物,其包含根据权利要求3所述的多肽分子或根据权利要求1、2或4中任一项所述的登革热-4/登革热-2嵌合病毒,以及药学上可接受的赋形剂。

6.药学上可接受量的权利要求5所述的药物组合物在制备药物中的用途,所述药物用于在受试者中诱导对登革热病毒的免疫应答。

7.载体,其包含全基因组长度登革热-4/登革热-2核酸嵌合体,所述全基因组长度登革热-4/登革热-2核酸嵌合体编码由SEQ ID NO: 11或SEQ ID NO: 12所示的多肽分子。

8.根据权利要求7所述的载体,其中所述载体是质粒载体。

9.根据权利要求7所述的载体,其中所述载体是cDNA感染性克隆。

10.细胞,其包含全基因组长度登革热-4/登革热-2核酸嵌合体,所述全基因组长度登革热-4/登革热-2核酸嵌合体编码由SEQ ID NO: 11或SEQ ID NO: 12所示的多肽分子。

11.免疫原性组合物,其包含由根据权利要求1或权利要求2所述的登革热-4/登革热-2嵌合病毒,以及药学上可接受的载剂。

12.权利要求11所述的免疫原性组合物,其还包含修饰的活减毒登革热-2病毒株PDK-53-V,所述修饰的活减毒登革热-2病毒株PDK-53-V由编码修饰的活减毒登革热-2病毒株PDK-53-V多肽分子的全基因组长度多核苷酸序列所示,其中所述多核苷酸由SEQ ID NO: 4所示。

13.权利要求12所述的免疫原性组合物,其中所述组合物是四价组合物。

14.权利要求12或13所述的免疫原性组合物,其与针对选自以下的黄病毒的免疫原性组合物组合:黄热病毒、蜱媒脑炎病毒、日本脑炎病毒、西尼罗病毒、丙型肝炎病毒、及其中两种或更多种的组合。

15.包含全部四种登革热病毒血清型的组合物,其中所述组合物包含一种或多种根据权利要求4所述的登革热-4/登革热-2嵌合病毒和药学上可接受的载剂。

16.权利要求15所述的组合物在制备药物中的用途,所述药物用于在受试者中诱导针对全部四种登革热病毒血清型的免疫应答。

17.试剂盒,其包括至少一种根据权利要求1或权利要求2所述的登革热-4/登革热-2嵌合病毒或至少一种根据权利要求5所述的药物组合物或至少一种根据权利要求11-14中任一项所述的免疫原性组合物或至少一种根据权利要求15所述的组合物,以及容器。

用于疫苗中的登革热病毒嵌合式构建物的组合物及方法

[0001] 本申请是基于申请日为2014年3月12日,优先权日为2013年3月15日,申请号为201480028001.5,发明名称为:“用于疫苗中的登革热病毒嵌合式构建物的组合物及方法”的专利申请的分案申请。

[0002] 优先权

[0003] 本申请要求于2013年3月15日提交的第61/800,204号美国临时申请的优先权。该申请通过援引以其整体并入本文以用于全部目的。

[0004] 联邦资助研发

[0005] 本文公开的一些实施方案以资助号R43 AI08429-01获得美国国家卫生研究院的部分支持。美国政府对实施本发明拥有某些权利。

技术领域

[0006] 本文的实施方案报告了登革热病毒构建物的组合物、方法、用途和制造程序及其疫苗组合物。一些实施方案涉及这样的组合物,其包括但不限于嵌合式黄病毒构建物,该构建物单独地或组合其它构建物可用于疫苗组合物。在某些实施方案中,组合物可包含多于一种登革热病毒血清型的构建物,诸如登革热-1(DEN-1)病毒、登革热-2(DEN-2)病毒、登革热-3(DEN-3)病毒和/或登革热-4(DEN-4)病毒的构建物。在其它实施方案中,制造策略可改善重组活减毒嵌合式登革热疫苗(DENVax)病毒的安全性和遗传稳定性。某些实施方案包括至少一种活减毒登革热病毒与被确定在疫苗组合物中是安全且有效的登革热病毒嵌合式构建物的组合,其中该构建物已经在细胞培养中经历额外的传代。

背景技术

[0007] 感染登革热病毒可能导致不同严重程度的疼痛发烧。迄今为止,已经鉴定四种登革热病毒血清型:登革热-1(DEN-1)、登革热-2(DEN-2)、登革热-3(DEN-3)和登革热-4(DEN-4)。登革热由登革热病毒感染而引起。未来可能找到其它血清型(例如DEN-5)。登革热病毒血清型1-4也可能引发出血性登革热(DHF)和登革热休克综合征(DSS)。感染的最严重后果(DHF和DSS)可能威胁生命。登革热病毒每年引发5千万至1亿例病弱型登革热病毒、500,000例DHF/DSS,以及多于20,000例死亡。迄今为止,没有有效的疫苗来抵御登革热,且没有药物来治疗该病。蚊虫防治努力未能有效地预防登革热在病区的爆发,或防止该病的进一步地理扩散。估计有35亿人受登革热病毒感染的威胁。此外,登革热病毒乃是病区(诸如亚洲、中南美洲及加勒比海地区)的旅行者发烧的主要病因。

[0008] 全部四种登革热病毒血清型在全球热带地区均为地方性的,且构成全球热带地区对人类有最大威胁的蚊媒病毒。登革热病毒主要由埃及伊蚊(Aedes aegypti)蚊子传播给人类。感染一种登革热病毒血清型导致终生免于再受该血清型的重复感染,但无法免于另外三种登革热病毒血清型之一的二次感染。实际上,先前感染一种登革热病毒血清型导致当二次感染不同血清型时重症(DHF/DSS)的风险增高。有效疫苗的开发代表了此全球性疾病的预防和控制的重要方法。多重免疫接种使得对登革热病毒地方性国家中的公共卫生努

力以及旅行者两者进行完整疫苗覆盖变得困难。

发明内容

[0009] 本文的实施方案涉及嵌合式登革热病毒构建物的组合物、方法及用途。在一些实施方案中,组合物可包含具有减毒登革热病毒骨架的嵌合式登革热病毒构建物,所述构建物带有来自至少另一个登革热病毒血清型的结构基因。其它实施方案涉及至少一种活减毒病毒与一种或多种嵌合式登革热病毒的组合。其它实施方案可包括嵌合式登革热病毒的组合物,其具有修饰的DEN-2骨架(例如PDK-53作为P1(1-代)的起始骨架以及传代变异性(在许可细胞系上体外传代和生长之后)如针对P2、P3、...、P8、...P10等所指示的)以及DEN-1、DEN-2、DEN-3或DEN-4的一种或多种结构组分。在其它实施方案中,生成免疫原性组合物,当引入个体时,该组合物在个体内产生针对一种或多种登革热病毒的免疫应答。因此,本文预期的构建物可在体外生成并传代,以及每一代各自提供预期用于药学上可接受的疫苗组合物的减毒登革热病毒。在某些实施方案中,活减毒病毒可为单独的活减毒登革热-2病毒或其与一种或多种嵌合式登革热病毒的组合。

[0010] 在某些实施方案中,登革热病毒血清型的嵌合式登革热病毒构建物可包含7-代(P7)活减毒病毒或嵌合式病毒,其具有由SEQ ID NO:1、4、7及10确定的核酸序列或由SEQ ID NO:2、3、5、6、8、9、11及12指示的多肽序列。本文预期了本文所述的任何活减毒病毒的任何传代可用于免疫原性组合物以诱导针对呈示的登革热病毒(例如血清型1-4)的免疫应答。依据这些实施方案,根据所选的构建物,包含P-8分离的活减毒病毒的免疫原性组合物可被给予个体以诱导对抗一种或多种登革热病毒血清型的免疫原性应答。此外,活减毒病毒可与这些嵌合式病毒中的一种或多种相组合。针对在各次接续细胞传代(例如非洲绿猴肾Vero细胞产生,后文称:Vero细胞)中分离/产生的每一活减毒病毒,预期了上述情况。本文预期了能够产生登革热病毒的任何细胞系(例如GMP产生的细胞存库、经FDA或EMA批准的)以制造规模用于使该病毒构建物中任一种传代,或视情况,本文预期了随后用于对抗登革热病毒的疫苗或免疫原性组合物。

[0011] 在其它实施方案中,本文预期的组合物可与对抗其它黄病毒的其它免疫原性组合物如西尼罗病毒、日本脑炎病毒或任何其它黄病毒嵌合式构建物和/或活减毒病毒相组合。在某些实施方案中,单一组合物可用以对抗多种黄病毒。

[0012] 在某些实施方案中,本发明的免疫原性组合物可包含对抗DEN-1、DEN-2、DEN-3、和/或DEN-4中的一个或多个的单独的嵌合式登革热病毒,或其与活减毒登革热病毒组合物的组合。

[0013] 在其它实施方案中,构建物可包括在病毒的结构区或非结构区具有适应性突变的构建物,该突变使生长或生产得到提高而不影响引入个体时病毒的减毒或安全性。在某些实施方案中,预期的嵌合式登革热病毒构建物中的任一种可包括具有特定突变的活减毒DEN-2病毒用作为骨架,其中活减毒DEN-2PDK病毒还包含其它登革热病毒血清型的prM(前膜)和E(被膜)结构蛋白质中的一种或多种的结构蛋白质。此外,DEN-2骨架可包括额外的突变,从而当给药时在个体中使对预定组合物的免疫应答的产生得到提高,或增强该免疫应答(例如嵌合式登革热病毒2/1、2/3或2/4)。

[0014] 在一些实施方案中,结构蛋白质基因可包括在DEN-2骨架上的DEN-1、DEN-2、DEN-3

或DEN-4的prM和E基因,所述DEN-2骨架具有一个或两个作为活减毒登革热病毒的一部分的突变。举例而言,在某些实施方案中,登革热构建物可包括称为DENVax-1-A、DENVax-2-F、DENVax-3-F和DENVax-4-F(参见实施例部分)的那些构建物,其中DEN-2骨架具有来自DEN-2活减毒病毒的一个或多个突变(例如,在P1或其它先前传代的病毒或PDK-53中未找到的),所述DEN-2活减毒病毒先前验证为安全有效地诱导免疫应答。本申请的DEN-2活减毒病毒是原先使用的DEN-2活减毒病毒的改良版本。本发明的嵌合式构建物可包括修饰的减毒DEN-2PDK-53骨架,其具有第二登革热病毒血清型的一种或多种结构蛋白质,其中所述结构蛋白质可包括额外的突变以增加对嵌合式构建物的免疫原性应答。在一些实施方案中,由减毒DEN-2PDK-53获得的某些突变在与P1构建物不同的构建物中可以产生或可以不产生保守性氨基酸变化,这可导致期望的产生特征等。

[0015] 在其它实施方案中,活减毒DEN-2基因组可用以生成登革热病毒血清型1(DEN-1)、登革热病毒血清型3(DEN-3)、及登革热病毒血清型4(DEN-4)的构建物,其中DEN-2病毒基因组的一种或多种结构蛋白质基因可分别被DEN-1、DEN-3或DEN-4的一种或多种结构蛋白质基因替换。在一些实施方案中,结构蛋白质可为第二登革热病毒的C、prM或E蛋白。在某些实施方案中,结构蛋白质基因包括DEN-1、DEN-3或DEN-4的prM和E基因。这些杂交病毒表达DEN-1、DEN-3或DEN-4的表面抗原,同时保留亲代减毒DEN-2的减毒表现型。

[0016] 本文公开的构建物可包括使用减毒DEN-2病毒作为骨架的表达DEN-1、DEN-3或DEN-4的表面抗原的DEN-4、DEN-2、DEN-1及DEN-3的嵌合式构建物。

[0017] 在某些实施方案中,本发明的组合物可以包括这样的组合物,其包含本文公开的单一嵌合式登革热病毒构建物和药学上可接受的载剂或赋形剂。或者,本发明的组合物可以包括这样的组合物,其包含两种或更多种、或三种或更多种的本文公开的嵌合式登革热病毒构建物和药学上可接受的载剂或赋形剂。依据这些实施方案,本文预期的一种或多种登革热病毒嵌合式构建物可与一种或多种活减毒登革热病毒相组合。在某些实施方案中,活减毒病毒可为活减毒DEN-2病毒,其中在NCR、NS1区或其它区中的额外的突变可增强免疫应答,增加改良的活减毒登革热病毒的病毒生长或其它改善。

[0018] 在某些实施方案中,DENV-2疫苗的减毒基因座(即核苷酸5'NCR-57-T、NS1-53-Asp及NS3-250-Val)先前已经确定,而全部这些变化均由四种DENVax病毒的共用PDK-53病毒特异性遗传背景所分享。针对cGMP制造的DENVax种,小心地监控三个减毒基因座的基因序列以及这些疫苗候选物先前建立的体外和活体内减毒表现型。本报告描述了用以生成主病毒种(MVS)的策略以及其用于制造登革热病毒疫苗组合物的基因表征和表现型表征。这些MVS可用以制造临床材料并最终供应商业疫苗。

附图说明

[0019] 下列附图形成本说明书的一部分,且包括该附图以进一步展示某些实施方案。一些实施方案可以通过单独参考这些附图中的一张或多张或者与所呈示的特定实施方案的详细说明的组合而得到更好地理解。

[0020] 图1示出示例性图表,其反映出与先前生成的构建物和野生型登革热病毒相比较的本发明的示例性嵌合式构建物DEN-2/DEN-4。

[0021] 图2示出示例性直方图,其比较了使用活减毒DEN-2骨架(带有额外的突变)和第二

登革热病毒血清型作为结构组分替代登革热-2结构组分(例如DENVax-1 MVS)的各种反应。该图例示DENVax MVS的溶菌斑尺寸。野生型登革热病毒及先前公开的研究级疫苗候选物病毒被包括在内以用于对照和比较。该图例示与对照登革热病毒嵌合式构建物相比,登革热病毒构建物的改善的产生。

[0022] 图3示出示例性直方图,其示出DENVax MVS(主病毒种)的温度敏感性。野生型登革热病毒及先前公开的研究级疫苗候选物病毒被包括在内以用于与MVS级比较。

[0023] 图4示出示例性直方图,其示出与对照相比,在C6/36细胞中DENVax MVS的病毒生长。野生型登革热病毒及先前公开的研究级疫苗候选物病毒被包括在内以用于与DENVax MVS比较。

[0024] 图5A-5C示出在新生小鼠中的神经毒力的示例性图。多个实验的汇集结果总结了野生型(wt)DENV-2 16681病毒在使用10^4pfu病毒(A)ic激发的CDC-ICR(n=72)和Taconic-ICR(n=32)新生小鼠中的神经毒力。以10^4pfu(B)或10^3pfu(C)剂量在Taconic-ICR小鼠中测试DENVax MVS的神经毒力。指出在一个实验(n=16)或两个汇集实验(n=31或32)中每组测试的动物数。

[0025] 图6示出示例性直方图,其例示DENVax MVS、WVS和BVS的溶菌斑尺寸。在感染后第9天测量在琼脂糖覆盖层下方的Vero细胞或LLC-MK_2细胞中的病毒溶菌斑的平均溶菌斑直径±SD(误差柱)。野生型DENV及先前公开的研究级疫苗候选物病毒被包括在内以用于对照和比较。

[0026] 图7示出示例性直方图,其例示在两个培养温度下于C6/36细胞中DENVax MVS、WVS和BVS的生长以证实在大规模制造之后保留这种体外减毒标记。

[0027] 图8示出示例性直方图,其例示在C6/36细胞中DENVax MVS、WVS和BVS的受限制的生长。感染后七天在C6/36细胞中复制的病毒的平均滴度±SD(误差柱)。野生型登革热病毒及先前公开的研究级疫苗候选物病毒被包括在内以用于比较。

[0028] 图9A-9B示出DENVax MVS在新生ICR小鼠中神经毒力的示例性数据图。(A)10^4pfu剂量的病毒的IC接种。(B)10^3pfu剂量的病毒的IC接种。

[0029] 图10示出示例性图表,其比较了新活减毒病毒与先前生成的活减毒登革热病毒。

[0030] 定义

[0031] 如本文所用,“一(a)”或“一(an)”可表示一项或多于一项。

[0032] 如本文所用,“一个个体”或“多个个体”可包括但不限于,哺乳动物,诸如人类或哺乳动物(驯养的或野生的),例如犬、猫、其它居家宠物(例如仓鼠、豚鼠、小鼠、大鼠)、雪貂、兔、猪、马、牛、土拨鼠、野生啮齿类、或动物园动物。

[0033] 如本文所用,术语“病毒嵌合体”、“嵌合式病毒”、“黄病毒嵌合体”及“嵌合式黄病毒”可表示这样的构建物,其包含登革热-2病毒的核苷酸序列的一部分且还包含非来自登革热-2病毒的核苷酸序列或来自不同黄病毒的核苷酸序列。“登革热嵌合体”包含至少两种不同的登革热病毒血清型,但非不同的黄病毒。因此,其它登革热病毒或黄病毒的实例包括但不限于,来自登革热-1病毒、登革热-3病毒、登革热-4病毒、西尼罗病毒、日本脑炎病毒、圣路易脑炎病毒、蜱媒脑炎病毒、黄热病毒、及其任何组合。

[0034] 如本文所用,“核酸嵌合体”可表示本发明的构建物,其包含登革热-2病毒的核苷酸序列的一部分且进一步包含与登革热-2病毒的核苷酸序列不同来源的核苷酸序列。相应

地,本文公开的任何嵌合式黄病毒或黄病毒嵌合体可认为是核酸嵌合体的实例。

[0035] 如本文所用,“活减毒病毒”可表示野生型病毒,其经突变或选择而具有用于疫苗或其它免疫原性组合物的特征,其中一些特征可包括毒力降低、安全性、功效、或改善的生长等。

[0036] 描述

[0037] 于下列部分中,描述各种示例性组合物和方法以详细说明各种实施方案。对本领域技术人员显而易见的是,实施各种实施方案并不要求采用本文概述的全部或甚至某些特定细节,而可以通过常规实验修正浓度、时间及其它特定细节。在一些情况下,公知的方法或组分不包括于该描述中。

[0038] 依据本发明的实施方案,可采用在本领域的技能范围之内的常规的分子生物学、蛋白质化学、微生物学及重组DNA技术。此类技术完整地阐述于参考文献中。参见,例如,Sambrook,Fritsch&Maniatis,Molecular Cloning:A Laboratory Manual,第二版,1989,Cold Spring Harbor Laboraoty Press,Cold Spring Harbor,N.Y.;Animal Cell Culture,R.I.Freshney编辑,1986。

[0039] 本文的实施方案涉及个别地或同时地于个体中诱导对抗一种或多种登革热病毒血清型的免疫应答的组合物、方法及用途。依据这些实施方案,生成减毒登革热病毒及核酸嵌合体,并用于本文公开的疫苗组合物。一些实施方案涉及修饰或突变的登革热构建物或嵌合体。其它实施方案涉及引入突变以修饰登革热病毒的结构蛋白质的氨基酸序列,其中该突变提高对病毒的免疫原性。

[0040] 已经由在细胞培养中传代野生型病毒而发展出全部四种血清型的活减毒登革热病毒。这些是用于对抗黄病毒和特定的登革热病毒感染和/或疾病的免疫接种的最有希望的活减毒疫苗候选物种的一些候选物。这些疫苗候选物已经由其登革热血清型的组合、其传代的细胞系及其传代次数加以标示。因此,在PDK细胞中传代13次的登革热血清型1野生型病毒标示为DEN-1 PDK-13病毒。其它疫苗候选物为DEN-2 PDK-53、DEN-3 PGMK-30/FRhL-3(例如于初代绿猴肾细胞传代30次,接着于胎儿恒河猴肺细胞传代3次)和DEN-4 PDK-48。这四种候选物疫苗病毒分别由野生型亲代DEN-1 16007、DEN-2 16681、DEN-3 16562及DEN-4 1036病毒的组织培养传代而衍生。

[0041] 在某些实施方案中,活减毒登革热-2PDK-53疫苗病毒含有病毒混合物,并且群体含有各种核苷酸差异。在减毒突变的基因表征之后,某些减毒特性被概括出并被改造进cDNA传染性克隆。从此种传染性克隆转录RNA并引入Vero细胞作为新表征且衍生的PDK-53-Vero-DEN-2-P 1病毒的1-代(例如参考表1)。针对各个DEN血清型产生此类减毒病毒,但针对DEN-1、DEN-3及DEN-4,prM和E基因被改造进3种单独的cDNA传染性克隆,由此生成四种单独的PDK-53-Vero病毒(本文分别称为:PDK-53-Vero-DEN-2-P 1、PDK-53-Vero-DEN-1-P 1、PDK-53-Vero-DEN-3-P 1、以及PDK-53-Vero-DEN-4-P 1)。这些减毒疫苗病毒株于Vero细胞中传代10次(表1),并且各个单独的世系当其适应于Vero细胞中生长时获得突变(表3)。本文某些实施方案涉及这些活减毒登革热病毒的衍生及用途。

[0042] 先前使用这些减毒病毒的人类临床试验已经指出DEN-2 PDK-53在人类中具有最低感染剂量(50%溶菌斑形成单位或PFU的50%最低感染剂量),具有强免疫原性,并且未引起明显的安全性担忧。DEN-1 PDK-13、DEN-3 PGMK-30/FRhL-3及DEN-4 PDK-48疫苗病毒候

选物在人类中分别具有10,000、3500及150PFU的较高50％最低感染剂量。虽然使用一价DEN-2 PDK-53病毒或DEN-4 PDK-48病毒只需要一次免疫接种即可在人类个体中实现100％血清转化,但针对具有用于人类的两个最高感染剂量的DEN-1 PDK-13和DEN-3 PGMK-30/FRhL-3病毒,仍需要加强接种(booster)才能实现相同的血清转化率。

[0043] DEN-2PDK-53病毒疫苗候选物也缩写为PDK-53,其具有与减毒相关的多种可测量的生物标记,包括温度敏感性、小溶菌斑尺寸、在蚊C6136细胞培养中的复制减少,在完好蚊体内的复制降低,对乳小鼠的神经毒力丧失以及在猴中的病毒血症发生率降低。候选物PDK-53疫苗的临床试验已经证实其在人类中的安全性和免疫原性。此外,PDK-53疫苗在人类疫苗接受者中诱导登革热病毒特异性T-细胞记忆反应。本文的一些实施方案描述了对在本文公开的嵌合式构建物中使用的DEN-2 PDK-53的改良。

[0044] 具有登革热-2病毒骨架以及至少一个另一种登革热病毒血清型的结构蛋白质的免疫原性黄病毒嵌合体可用于制备登革热病毒嵌合体,并描述了用于产生登革热病毒嵌合体的方法。在药学上可接受的载剂中单独地或组合地提供了免疫原性登革热病毒嵌合体作为免疫原性组合物,从而最小化、抑制或使个体免疫于单独或组合的一种或多种血清型(例如登革热病毒血清型DEN-1、DEN-2、DEN-3及DEN-4)的感染。当组合时,免疫原性登革热病毒嵌合体可用作多价疫苗(例如二价、三价及四价)以赋予同时对抗多于一种的黄病毒物种或病毒株的感染的保护作用。在某些实施方案中,登革热病毒嵌合体组合于可用作对抗已知登革热病毒血清型的二价、三价或四价疫苗的免疫原性组合物,或通过包含编码一种或多种来自不同黄病毒的蛋白质的核酸而赋予对其它病原性黄病毒的免疫力。

[0045] 在一些实施方案中,本文提供的无毒力免疫原性登革热病毒嵌合体含有:减毒登革热-2病毒(例如PDK-53)的非结构蛋白质基因,或其等同物;以及将要在个体内诱导对抗黄病毒的免疫原性的该黄病毒的结构蛋白质基因或其免疫原性部分中的一种或多种。例如,一些实施方案涉及这样的嵌合体,其具有:作为病毒骨架的减毒登革热-2病毒PDK-53基因组;以及PDK-53基因组的编码衣壳、前膜/膜、或被膜的一种或多种结构蛋白质基因或其组合,所述结构蛋白质基因或其组合被将要经保护以对抗诸如不同黄病毒或不同登革热病毒血清型的来自DEN-1、DEN-3或DEN-4或其它黄病毒的一种或多种相对应的结构蛋白质基因替换。依据这些实施方案,本文公开的核酸嵌合体可具有减毒登革热-2病毒的功能性质且为无毒力的,但表达DEN-1、DEN-3或DEN-4以及其它黄病毒的结构基因产物的抗原表位,并且为免疫原性的(例如在个体中诱导对基因产物的免疫应答)。然后,这些DNA构建物用于从传染性克隆转录RNA,此种RNA被引入Vero细胞内,再次产生处于P1的新后代。这些新的后代可与PDK-53区别(参见,例如P1-P10)。

[0046] 在另一实施方案中,核酸嵌合体可为这样的核酸嵌合体,其具有(但不限于)编码来自减毒登革热-2病毒的非结构蛋白质的第一核苷酸序列以及编码来自单独登革热-4病毒或来自登革热-4病毒与另一种黄病毒组合的结构蛋白质的第二核苷酸序列。在其它实施方案中,减毒登革热-2病毒可为具有一种或多种突变氨基酸的疫苗株PDK-53(参见实施例)。这些额外的突变赋予了用作活减毒登革热-2或本文所述的嵌合式构建物的期望特性。一些实施方案包括第二登革热病毒的C、prM或E蛋白中的一种或多种的结构蛋白质。

[0047] 其它方面包括嵌合式病毒可包括例如在对照PDK-53登革热-2基因组中的核苷酸和氨基酸取代、删除或插入以减少对靶标登革热病毒血清型的免疫原性应答的干扰。这些

修饰可在结构蛋白质及非结构蛋白质中单独进行,或与本文公开的示例性修饰组合地进行,并且可通过使减毒病毒传代且获得用以诱导对抗一种或多种登革热病毒血清型的免疫应答的改良组合物而生成。

[0048] 本文公开的某些实施方案提供了通过将所需的取代插入适当的骨架基因组中而使用重组技术制造本发明的嵌合式病毒的方法。本文的其它实施方案涉及使经确认的(例如安全且有效的)活减毒嵌合式病毒传代以获得额外的改良。在某些实施方案中,本文使用的登革热-2骨架可包括表3呈现的一个或多个突变。在其它实施方案中,本申请的登革热-登革热嵌合体可包括表3呈现的一个或多个突变。在其它实施方案中,登革热-登革热嵌合体可包括针对Den-2/Den-1、Den-2/Den-3或Den-2/Den-4的表3呈现的各种嵌合体的全部突变。预期了包括表3的构建物表示的活减毒病毒的药物组合物。例如,本文预期了使用表3呈现的嵌合体和活减毒登革热-2病毒的一-、二-、三-或四价组合物的用途。

[0049] 在某些实施方案中,本文预期的活减毒DEN-2变异体可配制成药物组合物,其中该药物组合物可单独给予或与登革热-登革热嵌合体或登革热-黄病毒嵌合体组合地给予。在某些实施方案中,二价、三价或四价组合物可以单次施用或多次施用的形式给予至个体。

[0050] 黄病毒嵌合体

[0051] 登革热型1-4(DEN-1至DEN-4)为蚊媒黄病毒病原体。黄病毒基因组含有5’-非编码区(5’-NC),接着为衣壳蛋白(C)编码区,接着为前膜/膜蛋白(prM)编码区,接着为被膜蛋白(E)编码区,接着为编码非结构蛋白(NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5)的区域及最后为3’非编码区(3’NC)。病毒结构蛋白质为C、prM及E,并且非结构蛋白质为NS1-NS5。结构蛋白质和非结构蛋白质翻译为单一多蛋白并由细胞和病毒蛋白酶处理。

[0052] 黄病毒嵌合体可为通过融合来自登革热或黄病毒科病毒种的一种类型或血清型的非结构蛋白质基因与来自登革热病毒或黄病毒科病毒种的不同类型或血清型的蛋白质基因例如结构蛋白质基因而形成的构建物。或者,本发明的黄病毒嵌合体为通过如下方式而形成的构建物,即,融合来自登革热病毒或黄病毒科病毒种的一种类型或血清型的非结构蛋白质基因与指导选自其它登革热病毒血清型或其它黄病毒科病毒的多肽或蛋白质的合成的其它核苷酸序列。

[0053] 在其它实施方案中,本文提供的无毒力免疫原性黄病毒嵌合体含有减毒登革热-2病毒的非结构蛋白质基因或其等同物,以及将要被赋予的免疫原性所针对的黄病毒的结构蛋白质基因中的一种或多种或其抗原部分。适当的黄病毒包括但不限于表1列举的那些。

[0054] 用于构建嵌合体的其它适当的登革热病毒可为野生型毒力DEN-1 16007、DEN-2 16681、DEN-3 16562及DEN-4 1036以及减毒疫苗株DEN-1 PDK-13、DEN-2 PDK-53、DEN-3 PMK-30/FRhL-3及DEN-4 PDK-48。预期了DEN-1、DEN-2、DEN-3及DEN-4野生型/减毒病毒对之间的基因差异,以及由病毒基因组编码的氨基酸序列的变化。

[0055] DEN-2 PDK-53的序列列表对应于DEN-2PDK-53-V变异体,其中基因组核苷酸位置5270从A突变为T,并且多蛋白的氨基酸位置1725或NS3蛋白的氨基酸位置250含有缬氨酸残基。不含此种核苷酸突变的DEN-2 PDK-53,即DEN-2PDK-53-E,与PDK-53-V的差异只在于这一个位置。DEN-2PDK-53-E在核苷酸位置5270处具有A且在多蛋白氨基酸位置1725(即NS3蛋白氨基酸位置250)处具有谷氨酸根。应理解本文的实施方案包括修饰的PDK 53,其包括在单独的宿主细胞(例如Vero细胞,参考表1)中的一次或多次传代,其中生成本文预期的用于

疫苗组合物的所需特性。

[0056] 在某些实施方案中,嵌合体的标示可基于DEN-2病毒特异性传染性克隆修饰骨架及其它登革热病毒或其它黄病毒的结构基因(prM-E或C-prM-E)插入物。DEN-2为登革热-2骨架,接着是插入结构基因所来自的株。一个DEN-2骨架变异体在数字标示后的下个字母中得到反映。从中构建嵌合体的一个特定DEN-2骨架变异体由置于连字符后方的字母指示,亲代16681(P),PDK-53-E(E)或PDK-53-V(V);最末字母指示来自亲代(P)株或其疫苗衍生物(V)的C-prM-E结构基因或来自亲代(P)或其疫苗衍生物(V1)的prM-E结构基因。例如,DEN-2/1-VP表示该嵌合体包含减毒DEN-2 PDK-53V骨架(在NS3-250处包含缬氨酸)和来自野生型DEN-1 16007的C-prM-E基因;DEN-2/1-VV表示DEN-2 PDK-53V骨架具有登革热-1、DEN-1PDK-13的疫苗株;DEN-2/1-VP1表示DEN-2 PDK-53V骨架和来自野生型DEN-1 16007的prM-E基因;DEN-2/3-VP1表示DEN-2 PDK-53V骨架和来自野生型DEN-3 16562的prM-E基因;DEN-2/4VP1表示DEN-2 PDK-53V骨架和来自野生型DEN-4 1036的prM-E基因。本文公开的其它嵌合体以相同方式指示。

[0057] 在一个实施方案中,本文公开的嵌合体含有减毒登革热-2病毒PDK-53基因组作为病毒骨架,其中PDK-53基因组的编码C、prM及E蛋白的结构蛋白质基因或其组合可以被来自登革热-1、登革热-3或登革热-4病毒以及任选地待被抵御的另一种黄病毒(诸如不同的黄病毒或不同的登革热病毒株)的相对应的结构蛋白质基因替代。

[0058] 在非结构蛋白质区域,在非结构蛋白质NS1-53(基因组核苷酸位置2579)处发现Gly-至-Asp(野生型至PDK-53)突变;在非结构蛋白质NS2A-181(基因组核苷酸位置4018)处发现Leu-至-Phe(野生型-至-PDK-53)突变;在非结构蛋白质NS3-250(基因组核苷酸位置5270)处发现Glu-至-Val(野生型-至-PDK-53)突变;以及在非结构蛋白质NS4A-75(基因组核苷酸位置6599)处发现Gly-至-Ala(野生型-至-PDK-53)突变。本发明的活减毒DEN-2病毒还包括如表3的任何嵌合体或活减毒登革热-2病毒所呈现的突变。

[0059] PDK-53病毒株在基因组核苷酸5270处具有混合基因型。相当一部分(约29%)的病毒群体编码存在于野生型DEN-2 16681病毒的非突变NS3-250-Glu,而非NS3-250-Val突变。因两种基因变异体均为无毒力的,故此种突变在无毒力嵌合体中可为非必要的。

[0060] 先前,发现减毒PDK-53病毒株的无毒力可促成在编码非结构蛋白质的核苷酸序列中以及在5'非编码区中的突变。例如,在NS1-53的单一突变、在NS1-53和5'NC-57的双突变,在NS1-53和NS3-250的双突变、以及在NS1-53、5'NC-57和NS3-250的三突变,导致DEN-2病毒的减毒。因此,在这些基因座处含有此类非保守氨基酸取代或核苷酸取代的任何登革热-2病毒的基因组可用作基础序列以衍生本文公开的修饰PDK-53病毒。根据需要,在5'非编码区的茎/环结构的茎中的另一突变会提供额外的无毒力表现型稳定性。对该区域的突变破坏对于病毒复制的重要的潜在二级结构。在DEN和委内瑞拉马脑炎病毒两者的这种短(长度只有6个核苷酸残基)茎结构中的单一突变破坏发夹结构的形成。在此茎结构的进一步突变降低了在此基因座反转的可能性,同时维持病毒活力。

[0061] 本文公开的突变可通过本领域已知的任何种方法实现,包括但不限于,具有额外特征的天然存在或所选的克隆在感兴趣的细胞系(例如Vero细胞)中传代一次。本领域技术人员应理解如本文所述且本领域公知的毒力筛检试验可用于区别毒力的与无毒力的骨架结构。

[0062] 黄病毒嵌合体的构建

[0063] 本文所述的黄病毒嵌合体可通过如下制备,通过期望免疫力所针对的黄病毒的结构蛋白质基因中的一种或多种剪接入PDK-53登革热病毒基因组骨架;使用重组工程或通过本领域已知的其它方法来去除相对应的PDK-53基因并用登革热-1、登革热-3或登革热-4病毒基因或本领域已知的其它基因对其进行替换。

[0064] 或者,使用序列表中提供的序列,使用已知的核酸合成技术可合成编码黄病毒蛋白质的核酸分子,并将其插入适当的载体中。因此,使用本领域技术人员已知的重组工程技术产生无毒力免疫原性病毒。

[0065] 靶标基因可插入骨架中,其编码DEN-1、DEN-3、DEN-4或其它黄病毒的感兴趣的黄病毒结构蛋白质。将要插入的黄病毒基因可为编码C蛋白、PrM蛋白和/或E蛋白的基因。插入登革热-2骨架的序列可编码PrM和E结构蛋白质。插入登革热-2骨架的序列可编码C、prM及E结构蛋白质中的全部或一种。

[0066] 可通过以下来评估含有编码其它黄病毒或登革热病毒血清型的结构蛋白质的核苷酸序列的适当嵌合体病毒或核酸嵌合体作为疫苗的有用性,根据指示无毒力的前述减毒表现型标记对其进行筛选,以及根据免疫原性对其进行筛选。可使用本领域技术人员已知的常规筛选程序,利用与黄病毒抗体或免疫反应性血清的体外或活体内反应性来评估抗原性和免疫原性。

[0067] 登革热病毒疫苗

[0068] 在某些实施方案中,嵌合体病毒和核酸嵌合体可提供可用作为免疫原或疫苗的活减毒病毒。一些实施方案包括展现对登革热-4病毒高免疫原性、同时不产生危险的致病或致命效应的嵌合体。

[0069] 为了减少在个体中出现DHF/DSS,需要四价疫苗来提供对全部四种病毒血清型同时的免疫力。通过将本发明的活减毒登革热-2病毒与上述登革热-2/1、登革热-2/3及登革热-2/4嵌合体在适当的药学载剂内组合而制备四价疫苗,从而以多价疫苗形式给药。

[0070] 本发明的嵌合式病毒或核酸嵌合体可包括在毒力或减毒DEN-2病毒骨架中的野生型或活减毒病毒的结构基因。例如,嵌合体可在任一DEN-2背景下表达野生型DEN-4 1036病毒的结构蛋白质基因、其候选物疫苗衍生物。

[0071] 本文所述的嵌合体中使用的病毒可使用本领域已知的方式生长。然后,进行病毒溶菌斑滴定并计数溶菌斑以评估生长培养物的活力和表现型特性。野生型病毒可通过培养的细胞系来传代,从而衍生减毒候选物起始材料。

[0072] 嵌合式传染性克隆可由可用的各种登革热血清型克隆构建。若需要,也可完成病毒特异性cDNA片段的克隆。通过逆转录酶-聚合酶链式反应(RT-PCR)使用各种引物从登革热病毒RNA扩增含有结构蛋白质或非结构蛋白质基因的cDNA片段。扩增的片段被克隆入其它中间克隆的裂解位置。然后,中间嵌合式登革热病毒克隆经测序以证实所插入的登革热病毒特异性cDNA的准确性。

[0073] 通过将登革热血清型病毒的结构蛋白质和/或非结构蛋白质基因区插入载体内而构建的全基因组长度嵌合式质粒可使用本领域技术人员公知的重组技术获得。

[0074] 核苷酸及氨基酸分析

[0075] 在DEN-2PDK-53疫苗病毒中的NS1-53突变对此种病毒的减毒表现型为重要的,因

为DEN-2 16681病毒的NS1-53-Gly在至今为止已测序的几乎全部的黄病毒,包括蜱媒病毒,中保守。DEN-4疫苗病毒也可含有在NS1蛋白的位置253处的氨基酸突变。在DEN-4PDK-48疫苗病毒中的Gln-至-His突变的这种基因座在全部四种野生登革热病毒血清型中均为Gln。此种Gln残基为黄病毒属内的登革热病毒所独有的。NS1蛋白为从黄病毒感染的细胞分泌的糖蛋白。其存在于感染的细胞的表面,并且NS1-特异性抗体存在于病毒感染的个体的血清中。已经报告用NS1蛋白免疫接种或用NS1特异性抗体被动免疫接种来保护动物。NS1蛋白可能参与早期病毒RNA复制。

[0076] 出现于DEN-1、-2、-3及-4减毒株的NS2A、NS2B、NS4A及NS4B蛋白中的突变本质上为保守的。DEN-2和DEN-4疫苗病毒分别的NS4A-75和NS4A-95突变出现在登革热病毒中氨基酸保守的位点,但通常不出现在黄病毒中。

[0077] 黄病毒NS3蛋白具有至少两种已认知的功能:病毒性蛋白酶以及RNA螺旋酶/NTPase。698-aa长度(DEN-2病毒)NS3蛋白含有氨基末端的丝氨酸蛋白酶结构域(NS3-51-His、-75-Asp、-135-Ser催化三联体),接着为RNA螺旋酶/NTPase功能的序列基序(NS3-196-GAGKT(SEQ ID NO:147)、-284-DEAH、-459-GRIGR)。在DEN-1、DEN-2或DEN-3病毒的NS3蛋白中无一突变出现在已认知的基序中。在DEN-1 PDK-13病毒中的NS-510Tyr-至-Phe突变为保守的。因为野生型DEN-2、-3及-4病毒在此位置含有Phe,所以Tyr-至-Phe突变在DEN-1病毒的减毒方面不可能发挥作用。在DEN-1 PDK-13病毒中的NS3-182 Glu-至-Lys突变出现在大部分蚊媒黄病毒中保守为Asp或Glu的位置,并且在减毒方面可发挥一些作用。此种突变位于GAGKT螺旋酶基序上游15个氨基酸残基处。如先前报告所记,在DEN-2 16681病毒中的NS3-250-Glu在除黄热病病毒之外的全部蚊媒黄病毒中保守。

[0078] 核酸探针与编码DEN-1、DEN-3及DEN-4病毒的核酸分子或其互补序列选择性地杂交。“选择性的”或“选择性地”表示序列不与其它核酸杂交以防止登革热病毒的充足检测。因此,在杂交核酸的设计中,选择性将取决于样本内存在的其它组分。杂交核酸应具有与其所杂交至的核酸片段至少70%的互补性。如本文用于描述核酸那样,术语“选择性地杂交”排除偶尔随机杂交的核酸,因而具有与“特异性杂交”相同的定义。本发明的选择性杂交核酸可具有与其所杂交至的序列片段至少70%、80%、85%、90%、95%、97%、98%及99%的互补性,优选85%或更高。

[0079] 预期了选择性杂交至编码核酸或该核酸的互补链或相反链的序列、探针或引物。与核酸的特异性杂交可在核酸中的微小修饰或取代的情况下发生,只要保持功能性种类特异性杂交能力即可。“探针”表示可用作与互补核酸序列选择性杂交以用于其检测或扩增的探针或引物的核酸序列,所述探针的长度可由约5个核苷酸变化至100个核苷酸,或优选约10个核苷酸至50个核苷酸,或约18个核苷酸至24个核苷酸。

[0080] 若用作引物,则该组合物优选包含至少两个杂交至靶标分子的不同区的核酸分子,以扩增期望的区。根据探针或引物的长度,靶标区可为70%互补碱基至完全互补之间,而仍在严格条件下杂交。例如,为了检测登革热病毒的存在,杂交核酸(探针或引物)与其所杂交的序列之间的互补程度至少足够区分与来自其它有机体的核酸的杂交。

[0081] 编码DEN-4、DEN-3或DEN-1病毒的核酸序列(例如结构元件)可插入载体(诸如质粒)内,并在活有机体内重组表达(例如在登革热-2骨架内),从而制造重组登革热病毒肽和/或多肽和/或病毒。

[0082] 核酸检测方法

[0083] 本发明提供了快速基因测试,其可诊断本文所述的各种疫苗病毒。本发明的该实施方案提高了从出现病毒血症的疫苗接种的人类的血清分离的病毒的分析,以及增加对使用候选物疫苗病毒免疫接种的非人灵长类动物中的病毒血症的表征。

[0084] 这些序列包括诊断性TaqMan探针,其用于报告通过使用逆转录酶/聚合酶链式反应(RT/PCR)从病毒基因组RNA模板扩增的cDNA扩增子的检测,以及正向和反向扩增引物,所述扩增引物经设计以扩增cDNA扩增子,如下文所述。在某些情况下,扩增引物之一已经被设计成在扩增引物3'-末端处含有疫苗病毒特异性突变,这有效使得该测试对疫苗株甚至更具有特异性,因为只要病毒RNA模板含有该特异性突变,即可发生在靶标位点的引物延长以及随后的扩增。

[0085] 可使用自动化的基于PCR的核酸序列检测系统,或用于核酸检测的其它已知技术。TaqMan测定是高度特异性且敏感的测定,其允许对来自样本核酸模板的PCR生成的扩增子的自动化实时可视化和定量。TaqMan可测定特定序列是否存在。在此测定中,正向和反向引物经设计而分别退火靶标突变位置的上游和下游。特异性检测子探针经设计而具有比任一扩增引物高约10℃的熔化温度,并且含有疫苗病毒特异性核苷酸突变或其补体(这取决于被检测的RT/PCR扩增子的链),构成此测定的第三引物组分。

[0086] 设计为特异性检测在疫苗病毒基因组之一中的突变基因座的探针将在探针中部含有疫苗特异性核苷酸。若病毒RNA模板为疫苗病毒特异性的,则此探针将在TaqMan测定中产生可检测的荧光。然而,来自野生型DEN病毒的基因组RNA模板将具有降低的探针杂交效率,原因在于单一核苷酸错配(在亲代病毒DEN病毒的情况下),或可能多于一个错配(可能发生于其它野生型DEN病毒中)将不会产生显著的荧光。DNA聚合酶更可能从RT/PCR扩增子模板替换错配的探针,而非裂解错配的探针以释放报告子染料(TaqMan等位基因分型测定,Applied Biosystems)。

[0087] 诊断性基因测试的一种策略是使用分子信标。分子信标策略也利用用于扩增子RT/PCR扩增的引物,并通过在探针末端含报告子和淬灭剂染料的探针来检测扩增子内部的特定序列。在此测定中,探针形成茎-环结构。分子信标测定采用与TaqMan测定所使用的不同淬灭剂和报告子染料。

[0088] 药物组合物

[0089] 本文的实施方案提供向个体给予化合物,所述化合物以适于活体内药学给药的生物相容形式。"适于活体内给药的生物相容形式"表示将要给予的活性剂(例如实施方案的药物化学品、蛋白质、基因)的形式,其中活性剂的治疗效果超过任何毒性效应。给予治疗上活性量的治疗组合物被定义为在实现期望结果所需的剂量和时间段方面有效的量。例如,治疗上活性量的化合物可依据多项因素而改变,诸如个体的疾病状态、年龄、性别及体重,以及抗体在个体中引发期望应答的能力。剂量方案可经调整以提供最佳治疗反应。

[0090] 在一个实施方案中,可以常规方式给予化合物(例如所述实施方案的药物化学品、蛋白质、肽等),例如皮下、静脉内、经口、吸入、皮内、经皮施用、阴道内施用、局部施用、鼻内或直肠给药。根据给药途径,活性化合物可含于保护缓冲剂(例如FTA、F127/海藻糖/白蛋白)中。在一个实施方案中,组合物可经口给予。在另一个实施方案中,组合物可静脉内给予。在一个实施方案中,组合物可于鼻内(诸如吸入)给予。在又一个实施方案中,组合物可

使用无针系统(例如Pharmajet®)或其它皮内给药系统而皮内给予。

[0091] 组合物可于适当载剂或稀释剂中与酶抑制剂共同给予施用于个体,或于适当载剂(诸如脂质体)中施用于个体。如本文所用的术语“药学上可接受的载剂”旨在包括稀释剂,诸如盐水和水性缓冲溶液。可能需要使用材料包被该化合物或与该化合物共同给予以防止其失活。活性剂也可经肠胃外或经腹膜内给予。分散液剂可在甘油、液体聚乙二醇及其混合物中以及在油中制备。在储存和使用的常见条件下,这些制剂可含有防腐剂(用于防止微生物的生长)或其它稳定配制剂(例如FTA)。

[0092] 适于注射用途的药物组合物可利用本领域已知的手段给予。例如,可使用用于临时制备无菌注射溶液剂或分散液的无菌水性溶液(当为水溶性时)或分散液以及无菌粉末。在所有情况下,该组合物可为无菌的,且可为流体(其程度使得存在易于注射性(syringability))。其在制造和储存条件下可为稳定的,且可经保存而不受微生物(诸如细菌和真菌)的污染。药学上可接受的载剂可为溶剂或分散介质,包括例如水、乙醇、多元醇(例如甘油、丙二醇及液体聚乙二醇等)及其适当的混合物。可以例如通过使用包衣(诸如卵磷脂),在分散液的情况下通过保持所需的粒径,以及通过使用界面活性剂,从而保持适当的流动性。微生物的预防可通过加热、将药剂暴露于清洁剂、辐照或添加多种抗菌剂或抗真菌剂而实现。

[0093] 无菌注射溶液均可如下制备,通过将需要量的活性化合物(例如诱导对一种或多种登革热病毒血清型的免疫应答的化合物)与上文列举的成分之一或其组合(根据需要)并入适当的溶剂中,接着过滤灭菌。

[0094] 当配制时,溶液将以与剂量配制剂相兼容的方式及以治疗有效量来给予。配制剂容易以多种剂型给予,诸如上述注射溶液类型。预期组合物尤其适用于肌肉内、皮下、皮内、鼻内及腹膜内给药。可寻求特定比例如1:1、1:2或其它比例(例如给定登革热病毒血清型的PFU)。

[0095] 活性治疗剂可在混合物内以预定比例配制。可以针对给定情况(例如旅行前、登革热爆发时)以适当进度表给予单次剂量或多次剂量。

[0096] 在另一实施方案中,鼻用溶液或喷雾剂、气溶胶或吸入剂可用于递送感兴趣的化合物。适用于其它给药方式的其它配制剂包括栓剂和阴道栓。

[0097] 某些配制剂可包括赋形剂,例如药学等级的甘露糖醇、乳糖、淀粉、硬脂酸镁、糖精钠、纤维素、碳酸镁等。

[0098] 药物组合物可使用保护活性成分免于从体内快速消除的载剂制备,诸如延时释放配制剂或包衣。此类载剂包括控释配制剂,诸如但不限于微胶囊递送系统、以及可生物降解、生物相容性聚合物,如乙烯乙酸乙烯酯、聚酐、聚乙醇酸、聚原酸酯、聚乳酸以及已知的其它物质。

[0099] 药物组合物以有效抑制或缓解植入物的副作用和/或减少或预防排斥的量和频率给予。精确的治疗剂量和治疗持续时间可使用已知的测试方案或通过在本领域已知的模型系统中测试该组合物并由此外推而经验地确定。剂量也可随病况的严重程度而改变。药物组合物通常经配制和给予而发挥治疗有用的效果,同时最小化非期望的副作用。一般而言,约10^2至10^6PFU的剂量范围可初步给予,任选地随后根据情况在30天内或至多180天后进行第二次给药。在某些实施方案中,个体可接受本文公开的一价、二价、三价或四价组合物的双重给药,其中该组合物为单一组成混合物或具有不同登革热病毒血清型的预定组成。在

一些实施方案中,DEN2/4嵌合体可以比其它登革热血清型(诸如活减毒登革热-1)更高的浓度存在。

[0100] 对于任何特定个体,显然可根据个别需要随时间调整特定剂量方案。

[0101] 在一个实施方案中,本文公开的组合物可经皮下或皮内给予于个体。

[0102] 含有活减毒登革热病毒的药物组合物可给予至个体,特别是人类,例如通过皮下、肌肉内、鼻内、经口、局部、经皮、肠胃外、经胃肠、经支气管及经肺泡。局部给药经由包含治疗有效量的丝氨酸蛋白酶抑制剂的局部施用的乳膏、凝胶、洗剂等而实现。经皮给药通过施用能够使丝氨酸蛋白酶抑制剂穿透皮肤并进入血流的乳膏、洗剂、凝胶等而实现。此外,渗透泵可用于给药。所需剂量将随正在治疗的特定病况、给药方法及该分子从体内的清除速率而改变。

[0103] 在本发明方法的某些实施方案中,个体可为哺乳动物,诸如人类或兽医动物和/或家畜或牲口或野生动物。

[0104] 治疗方法

[0105] 在本发明的一个实施方案中,提供了使用本文预期的活减毒和/或嵌合式病毒构建物的一价、二价、三价或四价配制剂,诱导对登革热病毒血清型的免疫应答的方法。

[0106] 本发明的实施方案通过下列非限制性实施例而例示,所述实施例绝非视为对本发明的范围施加限制。相反地,显然应理解,在阅读本文的描述之后,本领域技术人员可以在不背离本发明的主旨或随附权利要求的范围的情况下,联想到可以采取多种其它实施方案、修改、及其等同物。

实施例

[0107] 包括下列实施例以验证本文呈示的某些实施方案。本领域技术人员应理解下列实施例中公开的技术呈示了发现在本文公开的实施中运行良好的技术,因此可视为构成其实施的优选模式。然而,本领域技术人员鉴于本公开内容应认识到在不背离本文的主旨和范围的情况下可在所公开的特定实施方案中进行诸多变化,并且仍获得相同或类似的结果。

[0108] 实施例1

[0109] 在一些示例性方法中,公开了用于产生本文称为“主代病毒种(MVS)”的组合物。这些组合物可衍生自一种或多种活减毒登革热病毒,诸如DEN-1、DEN-2、DEN-3及DEN-4。在某些方法中,组合物可衍生自一种或多种活减毒登革热病毒,包括但不限于,本文公开的称为DENVax-1、DENVax-2、DENVax-3及DENVax-4的特定构建物。在其它示例性方法中,提供了用于生成和表征这些组合物的策略。在其它实施方案中,提供了四价登革热病毒配制剂以及这些配制剂的遗传学和表现型表征。

[0110] 前主代DENVax病毒的制造及分析

[0111] 进行某些程序以生成前主代登革热病毒种,诸如登革热病毒(例如DENVax)的一系列扩增和纯化。首先,通过将从全长重组DENVax cDNA转录的病毒RNA转染入核准生产的细胞(例如Vero细胞)而再衍生DENVax病毒,获得P1(1代)病毒种。来自登革热-1至登革热-4中每一种的四种P1病毒随后经扩增和溶菌斑纯化以获得候选前主代疫苗P7种(参见表1)。进行某些测试以分析登革热病毒的传代。例如,全长基因组测序证实全部四种P2(2代)种病毒在遗传学上与其同源祖先(经研究衍生的研究等级候选疫苗病毒)相同。原始溶菌斑表现型

也保留在P2病毒中。从P2种分离登革热各个血清型(例如DENVax 1-4)的六种溶菌斑纯化病毒(P3 A-F),并且每一分离的溶菌斑直接再进行溶菌斑纯化两次。每一病毒的第三次溶菌斑纯化(P5)于Vero细胞中扩增两次(P6 A-F和P7 A-F),从而制造潜在前主代P7 DENVax种(表1)。

[0112] 表1.DENVax病毒于WCB-Vero细胞中的cGMP再衍生的实例

[0113]

传代	种产生/纯化	表征
P1	用转录的病毒 RNA 转染 WCB-Vero	溶菌斑滴定
P2	扩增 P1 病毒	全基因组序列
P3	取来自 P2 溶菌斑测定的 6 个溶菌斑(A-F)/血清型	溶菌斑纯化
P4	取来自 P3 溶菌斑测定的溶菌斑 A-F	溶菌斑纯化
P5	取来自 P4 溶菌斑测定的溶菌斑 A-F	溶菌斑纯化
P6	扩增 P5 A-F 溶菌斑	溶菌斑滴定
P7	前主代种: 扩增 P6 A-F	全基因组序列，TaqMAMA，溶菌斑表现型
P8*	MVS: 扩增所选的 P7 病毒种	全基因和表现型表征
P9	WVS: 扩增 P8 主代种病毒	全基因组序列，TaqMAMA
P10	BVS: 扩增 P9 工作种病毒	全基因组序列，TaqMAMA
* 基于基因和溶菌斑分析来选择一种最佳的 P7 种(A、B、C、D、E 或 F)以制备 P8 MVS		

[0114] 进一步进行一些试验以表征P7 DENVax种,诸如分析P7种的基因组序列和溶菌斑表现型,并与P2种进行比较(表2)。P7病毒的溶菌斑表现型大致于类似P2种的溶菌斑表现型。在一些示例性实验中,监测病毒滴度。大部分P7种的病毒滴度超过6.0log pfu/ml,但5种病毒除外。在Vero细胞中经10次以上连续传代后,超过60种候选物疫苗病毒种的基因组测序确定在DEN-2PDK-53基因载体的三个主要减毒决定子在NS1-53和NS3-250处并无回复事件,表明这2个基因座在候选物疫苗病毒种中是相当稳定的。这两个位点的从正测序和反测序生成的24种候选物株的全部序列色谱图均为同源的,而在NS1-53和NS3-250遗传基因座处明显没有任何微小核苷酸群体。与NS1和NS3位点相反,从多个连续传代的研究等级的疫苗病毒确定在5'NCR-57减毒基因座处的不同程度的回复,表明该基因座在细胞培养中经多次传代后可能不如NS-1和NS3稳定。因此,开发了敏感性错配扩增测定(TaqMAMA)以通过实时RT-PCR准确地测量5'NCR57基因座处的回复率。在一些研究中,通过TaqMAMA测量全部24种P7种的5'NCR57回复率。根据该测定中对每一病毒的输入病毒RNA浓度,TaqMAMA的敏感性极限为0.01％至0.07％的回复,这比通过共有基因组序列分析可检测的10-30％回复敏感性极限更加敏感。所得数据表明24种P7病毒中15种具有极少或无法检测的回复(<0.07％),一种病毒(DENVax-3-D)具有几乎100％的回复,以及8种病毒(1种DENVax-1、1种DENVax-2、2种DENVax-3以及4种DENVax-4)具有0.08％至12.85％的部分回复(表2)。对于24

种P7病毒中的16种进行全长基因组测序,并且如TaqMAMA所测量的,5'NCR57回复的水平低。全部测序的病毒保持另两种DENVax减毒决定子(NS1-53、NS3-250),并且均具有在原始改造重组cDNA克隆中所不存在的额外突变(表2)。在一个示例性靶标疫苗组合物中,选择DENVax-1-A、DENVax-2-F、DENVax-3-F及DENVax-4-F作为每一血清型的靶标前主代种,因为其基因型和溶菌斑表现型最类似于原始设计的疫苗重组体。DENVax-1-A、DENVax-2-F及DENVax-4-F具有两种非同义突变,而DENVax-3-F则具有一种。证据表明在这4种前主代种中观察到的这些额外突变不会造成所述病毒的安全性忧虑或免疫原性改变。这些前主代种被进一步扩增以生成MVS(主代种,标示为P7,表1)。

[0115] 本文提供的示例性方法使用来自克隆cDNA质粒的纯化体外转录病毒RNA作为纯来源以转染核准用于疫苗(vaccine-certified)的Vero细胞,从而生成疫苗病毒。将连续溶菌斑纯化和全基因组序列分析并入制造程序中以确保所制造的疫苗种具有最佳纯度和遗传稳定性。对DENVax的每一血清型制备六种克隆病毒作为潜在前主代种。通过基因组分析,包括TaqMAMA和完整基因组测序以及病毒溶菌斑表现型的表征,前主代种经选择以用于每一血清型(血清型1-4)的主代病毒种制备。所选的前主代种在5'NCR-57基因座具有无法检测的回复(<0.01%或<0.07%),在其基因组中具有1种或2种氨基酸取代,以及保留先前观察到的小型溶菌斑表现型。

[0116] 表2.前主代(P7)种的表征

[0117]

病毒	克隆[a]	TaqMAMA[b]	Log_{10} pfu/ml	溶菌斑[c]	在基因组中确定的突变[d]
DENVax-I	**A**	**	6.85	P2	NS2A-116 I-L, NS2B-92 E-D, 一个沉默
	B	*	6.93	P2	nd[e]
	C	*	6.93	D	nd
	D	**	7.02	D	C-67 K-A; 一个沉默
	E	0.57%	7.28	P2	nd
	F	**	7.18	P2	E473 T-M; 一个沉默
DENVax-2	A	0.03%	6.33	P2	NS I-341 K-N
	B	*	6.33	P2	E-305 K-T, 两个沉默
	C	*	5.84	L	NS4A-18 T-A, 四个沉默
	D	0.08%	6.20	P2	NS2B-99 I-L, 一个 3'NCR
	E	0.03%	6.31	P2	prM-52 K-E, NS5-412 I-V, 两个沉默
	F	**	6.15	P2	prM-52 K-E, NS5-412I-V
DENVax-3	A	*	6.00	P2	NS5-200 K-N, 一个沉默, 一个 3'NCR
	B	0.05%	6.27	P2	NS2A-33 I-T, NS2A-59 M-T
	C	0.30%	6.25	P2	nd
	D	100.00%	6.27	P2	nd
	E	0.31%	6.00	P2	nd
	F	**	6.30	P2	E-223 T-S, 一个沉默
DENVax-4	A	0.47%	5.60	P2	E323 K-R/K, NS2B-21 L-F/L, NS2B-39 T-S, 一个沉默
	B	*	5.65	D	NS2A-126 A-V; NS4A-5 N-D; NS5-383 K-R, 一个沉默
	C	4.50%	5.90	P2	nd
	D	12.85%	5.97	D	nd

[0118]

	E	0.52%	6.85	S	prM-85 E-D, NS2B-45 T-A, NS5-320 M-T, NS5-551 E-G, 两个沉默
	F	0.02%	6.93	S	NS2A-66 D-G, NS4A-21 A-V, 四个沉默

[a] 为进一步开发 MVS 而选择的克隆病毒(通过连续溶菌斑纯化)标示为粗体。

[b]*: 回复率 <0.07% (检测极限)。**: 回复率 <0.01% (检测极限)

[c] 溶菌斑表现型: P2: 类似于 P2 病毒; L= 大于 P2 病毒, D= 相近大小, 但有时溶菌斑透明度表现不同; S= 小于 P2。

[d] 与改造的 DENVax cDNA 克隆不同的取代。氨基酸突变以病毒蛋白质的残基位置及改变(wt-突变)而列举。列出在每一种的结构和非结构基因中的沉默突变的总数。也注释出非编码区域(NCR)的突变。

[e] nd= 未进行。这些克隆与其它克隆相比具有更高的 5'NCR-57 回复率(由 TaqMAMA), 因此从进一步序列分析中排除。

[0119] 实施例2

[0120] 在一些示例性方法中,描述了主代病毒种、工作病毒种及散装病毒种(bulk virus seeds)的组合物及其遗传学和表现型表征。提供这些组合物用于临床材料的制造及最终商业疫苗供应。连续溶菌斑纯化及全基因组序列分析被并入制造过程中以确保疫苗种的组合物具有用于制造临床试验材料的最佳安全性和遗传稳定性。

[0121] MVS、WVS及BVS的产生及制造质量控制

[0122] 在一些研究中,通过将前主代P7种于核准的Vero细胞中扩增而产生4种DENVax的MVS。在其它研究中,MVS用于细胞培养器中制备大量的WVS。此外,从WVS扩增DENVax的BVS原料,并配制成用于人类临床试验的四价药品混合物。产物释放的质量控制以一些示例性方法进行,包括但不限于,测试全部MVS、WVS及BVS的身份、感染滴度、无菌性、支原体以及于体外和活体内的外源因子。使用血清型特异性RT-PCR测定,全部的种均通过病毒身份测试,其显示对应其血清型的阳性扩增以及对于非同源血清型的阴性扩增(数据未显示)。在MVS、WVS或BVS原料中未检测到可检测的支原体或外源因子。

[0123] MVS、WVS及BVS的遗传分析

[0124] 在某些示例性方法中,在从所选的前MVS(P7)生成MVS后,产生如上所选的株并对各病毒RNA再次测序。全长基因组测序显示DENVax-1的MVS与其前主代种相同,而WVS及随后的BVS获得在E-483和NS4B-108处的2个额外的取代(参见表2和3)。在E-483处的Ala取代表示在MVS中的部分基因型,但变成BVS中的主要基因型。DENVax-2和DENVax-3与其各自得前主代种相同(表2和3)。DENVax-2 MVS与其前主代种相同,以及WVS和BVS具有在NS4A-36和NS4B-111处的两种额外的突变。两种突变在WVS中均为部分基因型,并且在BVS中为主要基因型。DENVax-3的MVS再度与前主代种相同,但WVS和BVS含有在NS4A-23处的额外的氨基酸取代。DENVax-4 MVS在产生MVS期间获得在基因座NS2A-99处的额外的氨基酸突变(Lys至Lys/Arg混合基因型)(表3)。其WVS和BVS保留NS2A-99Lys/Arg混合基因型,并且BVS具有额外的NS4B-238Ser/Phe混合基因型。共有序列结果也证实MVS、WVS及BV保留在5'NCR-57、

NS1-53及NS3-250基因座处的三种减毒基因决定子。通过TaqMAMA分析最不稳定的减毒基因座证实5'NCR-57回复率在MVS中<0.7％至0.13％,在WVS中≤0.07％,以及在BVS中<0.07％至0.21％。在5'NCR-57基因座处的3％回复被视为疫苗批次可接受的最大容许回复率(表3)。

[0125] 表3.DENVax种中的核苷酸和氨基酸取代

[0126]

DENVax	核苷酸	氨基酸	前主代	MVS[a]	WVS[a]	BVS[a]
DENVax-I	2384G-C	E-483 Gly-Ala	-	-	**Gly/Ala**	**Ala**
	3823A-C	NS2A-116 Ile-Leu	Leu	Leu	Leu	Leu
	4407A-T	NS2B-92 Glu-Asp	Asp	Asp	Asp	Asp
	7148 C-T	NS4B-108 Thr-Ile	-	-	**Ile**	**Ile**
	7311A-G	沉默	G	G	G	G

[0127]

	TaqMAMA 5'NCR-57 回复%[b]		--	-	-	-
DENVax-2	592 A-G	prM-52 Lys-Glu	Glu	Glu	Glu	Glu
	6481G-C	NS4A-36 Ala-Pro	-	-	**Ala/Pro**	**Pro**
	7156 C-T	NS4B-111 Leu-Phe	-	-	**Leu/Phe**	**Phe**
	8803 A-G	NS5-412 Ile-Val	Val	Val	Val	Val
	TaqMAMA 5'NCR-57 回复%[b]		--	-	0.07%	0.21%
DENVax-3	1603 A-T	E-223 Thr-Ser	Ser	Ser	Ser	Ser
	6436 G-A	NS4A-23 Asp-Asn	-	-	**Asn**	**Asn**
	7620 A-G	沉默	G	G	G	G
	TaqMAMA 5'NCR-57 回复%[b]		--	-	-	-
DENVax-4	225 A-T	沉默	T	T	T	T
	3674A-G	NS2A-66 Asp-Gly	Gly	Gly	Gly	Gly
	3773 A-A/G	NS2A-99 Lys-Lys/Arg	-	**Lys/Arg**	**Lys/Arg**	**Lys/Arg**
	5391C-T	沉默	T	T	T	T
	6437 C-T	NS4A-21 Ala-Val	Val	Val	Val	Val
	7026 T-C	沉默	T/C	T/C	T/C	T/C
	7538 C-C/T	NS4B-238 Ser- Ser/Phe	-	-	**Ser/Phe**	**Ser/Phe**
	9750A-C	沉默	C	C	C	C
	TaqMAMA 5'NCR-57 回复%[b]		-	0.13%	-	-
[a] 粗体：于 MVS 原料开始的改变。						
[b]"--"表示回复率 <0.01% (检测极限), "-"表示回复率 <0.07%(检测极限)						

[0128] 全基因组序列分析显示在DENVax-4 MVS中发展出额外的氨基酸突变，而另外三个DENVax MVS批次保留其前主代种的共有基因组序列。总而言之，从P1种衍生至前主代(P7)种，在给定种中只出现1或2种非同义突变。从P1至MVS(P8)种，在任何给定DENVax种中鉴定2至7种核苷酸取代，这些取代中只有2至3种导致氨基酸改变。因此，出现微小改变。RNA病毒在其基因组复制中有出错趋势，因此在细胞传代期间黄病毒基因组的基因取代并非出乎意料的。在MSV中没有沉默突变在可能影响病毒复制的5'或3'NCR内。只有在DENVax-2中的prM-52Lys-Glu的改变以及在DENVax-4中的NS2A-66Asp-Gly的取代是非保守性改变。DENVax-4的NS2A-66突变在DENV-2PDK-53的非结构骨架部分中。虽然NS2A-66基因座在DENV-2的各种株中通常为Asp，但对DENV-4通常为Gly。可能的是，在DENVax-4中Asp至Gly的改变与DENVax-4在Vero细胞中的适应度相关。DENVax-2prM-52突变位于prM的C端部分，该部分从成熟病毒颗粒剪接掉。在一些示例性方法中，进行表现型表征以证实在MVS种中的突

变均未显著改变疫苗的减毒表现型。

[0129] DENVax病毒证明在制造过程中的高遗传稳定性。位于5'NCR、NS1-53及NS3-250中的三种经定义的DENV-2PDK-53减毒基因座在当DENVax从前主代株连续传代至散装疫苗制剂时于共有基因组序列中保持稳定。5'NCR-57基因座的高度敏感的TaqMAMA证明在登革热病毒血清型的MVS、WVS(P9/工作)以及BVS(疫苗的散装病毒种)中极少或无法检测的回复。DENVax BVS制剂(P10-等同物)的5'NCR57回复率显著低于出现在研究等级疫苗候选物在Vero细胞中经10次连续传代后的5'NCR57回复率(4-74%回复)。本文提供的DENVax种的大规模制造的策略产生遗传上稳定的疫苗病毒种,其保留候选物疫苗病毒中的减毒标记。

[0130] DENVax MVS的溶菌斑表现型

[0131] 在一个示例性方法中,对DENVax MVS与野生型登革热病毒及其同源研究级嵌合式病毒于Vero细胞中的溶菌斑表现型进行比较(图2)。在Vero细胞中,DENVax-1、-2及-3的MVS所产生的溶菌斑均显著小于其野生型同源物,且极为类似于(在0.4mm差值内)其同源研究级病毒。DENVax-4 MVS也显著小于野生型DENV-4,但稍微大于(0.9mm差值)原始实验室衍生的D2/4-V嵌合体。

[0132] 图2示出示例性直方图,其例示DENVax MVS比较对照野生型病毒及研究级疫苗候选物病毒的溶菌斑尺寸。在感染后第9天测量在琼脂糖覆盖层下方的Vero细胞中的病毒溶菌斑的平均溶菌斑直径(mm)±SD(误差柱)。包括以黑柱表示的野生型DEN病毒,以及以白柱表示的先前公开的研究级疫苗候选物病毒,以作为对照并与灰柱表示的DENVax主代疫苗种进行比较。

[0133] DENVax MVS的温度敏感性

[0134] 在另一示例性方法中,在Vero细胞中对DENVax MVS测试温度敏感性且与其同源野生型和原始研究级嵌合式疫苗病毒进行比较。野生型(wt)DENV-3 16562并非温度敏感的。野生型登革热病毒血清型1和登革热血清型4在39℃为中等温度敏感的(在39℃的滴度比37℃低约1.0$\log_{10}$ pfu/ml,图3)。野生型登革热病毒血清型-2 16681为所测试的野生型登革热病毒中温度敏感性最高的,导致在39℃的滴度降低100倍。DENVax-1、2及3与其原始同源研究级嵌合式疫苗病毒是同样温度敏感的(图2)。这些DENVax株在39℃的滴度降低2.0至3.0$\log_{10}$ pfu/ml。DENVax-4也为温度敏感的,表现滴度降低5倍。然而,原始研究级D2/4-V表现滴度降低约10倍。最终稳定化DENVax-4 MVS含有F127(及其它已知使这些配制剂稳定的试剂(FTA)),F127已显示提升登革热病毒的热稳定性。在DENVax-4 MVS中存在F127可能促成Vero培养测定中病毒较不明显的温度敏感性。在单独的实验中,进一步评估在不存在F127的情况下MVS衍生的DENVax-4株的温度敏感性。为了从该株去除F127,从DENVax-4散装病毒制剂分离病毒RNA,并转染于Vero细胞中。在不存在F127的情况下于感染后第3天,此种DENVax-4病毒表现与D2/4V研究株具有相同的温度敏感性(滴度降低1.5$\log_{10}$ pfu/ml)(图3)。

[0135] 图3示出示例性直方图,其例示DENVax MVS的温度敏感性。包括了野生型登革热病毒及先前公开的研究级疫苗候选物病毒,以进行比较。DENVax-4 MVS含有额外的F-127,其可掩盖此测定中病毒的温度敏感性结果。也包括了单独的实验,以分析在不存在F127的情况下的替代DENVax-4。在37℃或39℃于Vero细胞中复制的病毒的平均滴度±SD(误差柱)。

[0136] 蚊C6/36细胞中的DENVax MVS复制

[0137] 在一些示例性方法中,使DENVax MVS于C6/36细胞中生长以证实其体外减毒表现型的保留性,已知研究级嵌合式疫苗病毒保留了骨架DENV-2 PDK53病毒在这些蚊细胞中的减毒表现型。与野生型登革热病毒相比,在感染后第6天,DENVax-1、DENVax-2及DENVax-4MVS显示于C6/36细胞中显著的生长降低(至少3$\log_{10}$ pfu/ml降低)(图4)。与野生型DENVax-3 16562相比,DENVax-3 MSV也显示生长降低,但降低较不显著(1-2$\log_{10}$ pfu/ml降低)。然而,DENVax-3种批次的C6/36滴度类似于(在1$\log_{10}$ pfu/ml差值内)原始研究级嵌合式D2/3-V疫苗病毒的C6/36滴度。

[0138] 图4示出示例性直方图,其绘制DENVax MVS(灰柱)于C6/36细胞中与野生型登革热(黑柱)和研究级疫苗病毒(白柱)相比的受限生长。感染后第6天,在C6/36细胞中复制的病毒的平均滴度±SD(误差柱)。

[0139] 于全蚊的病毒感染、散播及传播率

[0140] 在一些示例性方法中,将DENVax的感染率及散播率与其亲代野生型登革热病毒相比较。在某些示例性实验中,在埃及伊蚊(Ae.aegypti)中进行经口感染实验。感染血粉经反向滴定以测量病毒滴度,并且在表4中只包括了针对每一血清型的亲代登革热病毒与DENVax之间的在血粉中具有类似病毒滴度(小于1$\log_{10}$ pfu/ml差值)的实验,以进行比较。DENVax-1、DENVax-2及研究级D2 PDK-53-VV45R不会通过经口进食而使蚊子感染,这与其亲代病毒DENV-1 16007(44%感染)和DENV-2 16681(43.3%感染)有显著差异($p<0.0001$)。因没有蚊子受DENVax-1和-2感染,故这两种疫苗病毒极少有或没有散播忧虑。尽管DENVax-4确实通过经口进食而感染一些蚊子(55只中的2只),但感染率显著比其亲代野生型病毒DENV-4 1036(50只中的8只)更低($p<0.05$)。在其中血粉病毒滴度为5.2±0.02$\log_{10}$ pfu/ml的两次实验中DENVax-3不感染任何蚊子(表4),而在血粉病毒滴度为6.0$\log_{10}$ pfu/ml的单独的实验中,30只蚊子中只有一只被感染(数据未显示)。然而,野生型登革热病毒-3 16562在5.2$\log_{10}$ pfu/ml下也具有极低的感染率(8%),而在使用6.2$\log_{10}$ pfu/ml的较高血粉病毒滴度的单独的实验中,感染率不增加(3%,30只蚊子中1只呈阳性,数据未显示)。虽然野生型(wt)登革热病毒-3和登革热病毒-4具有比野生型登革热病毒-1和登革热病毒-2显著更低的感染率,但在感染的蚊子中的平均病毒滴度相近(3.1至3.9$\log_{10}$ pfu/蚊)。相反,来自两种感染的蚊子的DENVax-4滴度均为最低的(0.7$\log_{10}$ pfu/蚊),这比来自由野生型登革热血清型-4 1036感染的蚊子的滴度(3.9±1.5pfu/蚊)低1,000倍。

[0141] 针对那些感染的蚊子,可以通过测定病毒是否存在于腿部来评估从中肠散播出。四种亲代DENV产生36.3%至62.5%的散播率,来自腿部的平均病毒滴度(以$\log_{10}$ pfu计)为0.9±0.3至2.2±0.7(排除阴性样本)。两种DENVax-4感染的蚊子均未产生向腿部的病毒散播(表4)。虽然在腿部中可检测到散播的病毒,但在经口感染的蚊子的唾液中并未检测到四种野生型登革热病毒,表明经口进食条件可能不足以敏感地测量这些DENV的传播率。因此,在其它示例性方法中,随后进行通过直接IT接种的高度严格的人工蚊子感染(表4)。除了DENVax-4之外,全部病毒(野生型和DENVax)均实现IT接种的埃及伊蚊的100%感染。DENVax-4接种物具有比另外三种病毒接种物略低的病毒滴度,但仍然成功地感染70%的接种的蚊子。尽管通过IT接种实现高的身体感染率,但全部四种DENVax病毒与野生型登革热病毒(43-87%,表4)相比表现出显著较低($p<0.005$)或无法检测的传播率(0-10%)。DENVax病毒于经口进食后显示有极少至没有感染和散播,高度严格的IT结果证实这些DENVax病毒

在埃及伊蚊中的低传播能力。

[0142] 表4:于全蚊中的病毒感染、散播及传播率

[0143]

病毒	经口进食					IT 接种				
	血粉[a]	感染[b]	身体滴度[c]		散播[e]	接种物	感染[b]	身体滴度[c]	唾液[f]	
	平均值±SD	% (P/N)	平均值±SD	p^d	% (P/N)[f]	pfu/剂量	% (P/N)	平均值±SD	% (P/N)	p^d
DENV-I 16007	6.6	44.0% (11/25)	3.6 ± 1.5		36.3% (4/11)	53.9	100% (30/30)	4.7 ± 0.48	43% (13/30)	

[0144]

DENVax-I	6.9	0% (0/30)	NA	<0.0001	NA	67.8	100% (30/30)	3.4 ± 0.39	10% (3/30)	<0.005
DENV-2 16681	6.6	43.3% (13/30)	3.1 ± 1.5		38.5% (5/13)	67.8	100% (30/30)	5.2 ± 0.34	87% (26/30)	
D2 PDK53-W45R	6.4	0% (0/30)	NA	<0.0001	NA	56.4	100% (30/30)	4.0 ± 0.20	0% (0/30)	<0.0001
DENVax-2	6.4	0% (0/30)	NA	<0.0001	NA	52.7	100% (30/30)	3.5 ± 0.27	7% (2/30)	<0.0001
DENV-3 16562	5.2	8% (2/25)	3.8 ± 0.2		50% (1/23)	34.0	100% (30/30)	4.2 ± 0.50	67% (20/30)	
DENVax-3	5.2 ± 0.02	0% (0/50)	NA	0.108	NA	37.3	100% (30/30)	3.3 ± 0.36	3% (1/30)	<0.0001
DENV-4 1036	5.8 ± 0.5	16% (8/50)	3.9 ± 1.5		62.5% (5/8)	69.4	100% (30/30)	5.2 ± 0.45	70% (21/30)	
DENVax-4	5.4 ± 0.4	3.6% (2/55)	0.7 ± 0.0	0.033	0% (0/2)	11.8	70% (21/30)	1.1 ± 0.46	0% (0/21)	<0.0001

[a] 如果通过反滴定得自血粉中的多于一次的实验(log_{10} pfu/ml)，则为病毒滴度或平均值±标准偏差。

[b] 在蚊体中检测到的病毒率。P/N = 阳性/全蚊

[c] 在蚊体内的平均病毒滴度±标准偏差(log_{10} pfu/蚊)，只包括了阳性样品以用于计算

[d] 通过 Fisher 确切概率的 wt DENV 与 DENVax 之间的差异的统计分析

[e] 在阳性感染的蚊子的腿部中检测到的病毒率

[f] 在阳性感染的蚊子的唾液中检测到的病毒率。用于测量传播效率

[0145] 载体胜任性是活减毒黄病毒疫苗病毒的重要安全性要素。先前,将研究级DENV-2PDK-53-VV45R病毒及野生型衍生物在埃及伊蚊中测试,并发现NS1-53-Asp减毒突变是受损的蚊复制的主要决定子。DENV-2 PDK-53疫苗的其它两个主要减毒基因座,即核苷酸5'NCR-57-T和NS3-250-Val,也表现出对在蚊中复制的一些抑制效应,由此对蚊载体胜任性提供了额外的冗余限制。本文描述的一些示例性方法用于测试全部四种DENVax株的蚊子经口和IT感染和复制。DENVax-1、-2和-3不会通过经口感染而感染任何埃及伊蚊(表4)。DENVax-4只感染3.6%的经口暴露的蚊子,该水平显著低于野生型DENV-4,在蚊体中的复制平均滴度低于野生型DENV-4感染的蚊子。出乎意料地,在感染的蚊子的腿部中检测到DENVax-4,表明DENVax-4无法在经口感染后从蚊子中肠散布。DENVax-1、-2及-4的感染率全部显著低于其野生型配对物,但DENVax-3与野生型DENV-3 16562之间的差异不显著,原因在于两种病

毒的感染率极低。与在同样收集自泰国美索省的埃及伊蚊中评估的DENV的其它野生株相比,用于改造DENVax的亲代野生型登革热病毒株表现具有经口感染的较低的感染率和散播率。用于改造基于黄热病(YF)17D疫苗的ChimeriVax-DEN疫苗的野生型DENV-1 PUO359、DENV-2 PUO218、DENV-3 PaH881/88及DENV-4 1288具有47-77%的感染率。相反地,YF 17D疫苗无法感染埃及伊蚊。虽然ChimeriVax株含有来自这些高度传染性的野生型DENV的prM-E,但ChimeriVax保留其YF 17D复制骨架的蚊减毒表现型。本文提供的结果也表明DENV-2PDK-53骨架的蚊减毒在DENVax株中得以保持。此外,在本文所述的组合物中所包括的构建物中使用具有较低蚊感染性的野生型登革热病毒株,提供了额外的安全性特征。

[0146] 经口感染结果表明DENVax具有最低蚊感染性和散播能力。此外,进行更敏感且更严格的IT感染实验以进一步分析DENVax由埃及伊蚊传播的潜力。IT结果证明全部四种DENVax病毒与其野生型配对物相比均具有无法检测的或最低的蚊传播潜力。DENVax传播在理论上可能发生,条件是(1)载体在具有足够病毒血症滴度的疫苗上供应以感染蚊中肠,(2)病毒能够在中肠上皮中复制且能够随后散播出中肠,以及(3)散播的病毒可在唾液腺中复制且吐出的唾液中有足量病毒以用于传播。尚未充分地建立感染蚊子所需要的人病毒血症的阀值,但在自然野生型DENV感染后人病毒血症可为10^6-10^8蚊感染剂量$_{50}$(MID_{50})/ml。此种MID_{50}基于使用稀释的人血浆直接IT接种蚊子。在非人灵长类中的DENVax分析表明DENVax免疫接种后,病毒血症滴度极低(低于2.4log_{10} pfu/ml)并持续2-7日。考虑到DENVax的低病毒血症水平和低的蚊感染、散播及传播能力,这些疫苗病毒在自然界中不可能由蚊子传播或导致病毒血症。

[0147] 因此,建议任何血清型的任一代(P1-P10)可用于组合物以生成针对1、2、3或全部4种登革热病毒血清型的安全有效疫苗。

[0148] 在乳鼠中的神经毒力

[0149] 原始研究级疫苗病毒在保持于DVBD/CDC内部的新生ICR小鼠中针对神经毒力进行高度减毒。所有这些小鼠均存活于使用10^4pfu的每一疫苗病毒的ic(脑内)攻击。另一方面,野生型登革热病毒血清型-2 16681病毒在各种实验中导致这些CDC-ICR小鼠的62.5%-100%死亡率。在一些实验中,得自Taconic Labs的商用ICR小鼠(Taconic-ICR)用于研究在新生小鼠中的神经毒力。观察到新生Taconic-ICR小鼠比先前CDC-ICR小鼠对登革热病毒血清型2感染显著地更敏感。图5A总结使用10^4pfu病毒ic攻击的野生型登革热病毒血清型-2 16681对CDC-ICR克隆和Taconic-ICR新生小鼠的神经毒力。Taconic-ICR小鼠(32只小鼠中100%死亡率,平均存活时间为8.3±0.5天)比先前CDC-ICR小鼠(72只小鼠中91%死亡率,平均存活时间14.6±2.3天)对脑内登革热病毒血清型-2 11681攻击更敏感。

[0150] 在其它示例性方法中,为了评估DENVax MVS的神经毒力,Taconic-ICR小鼠最初在一次(n=16)或两次(n=31-32)实验中被约10^4pfu剂量的野生型登革热病毒血清型-2 16681、D2 PDK-53VV45R、D2/3-V或DENVax 1-4病毒ic(脑内)攻击(图5B)。在此剂量,D2/3-V研究级病毒,以及DENVax-1和DENVax-3 MVS,表现出完全减毒神经毒力表现型(未发病或致死)。如所预期,发现野生型登革热病毒血清型-2为"致命的",平均小鼠存活时间(AST)为8.3±0.8天。在这些登革热病毒血清型-2-敏感Taconic-ICR小鼠中,D2 PDK-53-VV45R研究级病毒导致81.3%死亡率。DENVax-2 MVS和DENVax-4 MVS于Taconic-ICR中的致命性一致,分别显示9.8±1.7、10.2±1.4及11.3±0.4天的AST值。

[0151] 在一些示例性方法中,在低10倍的剂量(10^3pfu,图5C)下,将野生型登革热病毒血清型-2 16681病毒的神经毒力与D2 PDK-53 VV45R、DENVax-2 MVS和DENVax-4 MVS以及D2/4-V研究级病毒进行比较。在此较低攻击剂量下,野生型登革热病毒血清型-2保留一致的致命神经毒力表现型,AST为9.0±1.4天。其它4种病毒表现出中间神经毒力表现型,神经毒力程度为血清型特异性的。D2 PDK-53-VV45R病毒及其DENVax-2 MVS同源物显示显著的减毒(分别为32.3%存活且AST为13.1±3.8天,以及31.2%存活且AST为10.5±3.4天)。DENVax-4 MVS和研究级D2/4-V病毒针对神经毒力为高度减毒的(分别为81.3%存活且AST为18.8±5.8天,以及100%存活率)。结果表明DENVax-1和-3的MVS表现出神经毒力的完全减毒,而DENVax-2和-4MVS批次保留了十分类似于其同源研究级病毒疫苗候选物的减毒表现型。

[0152] 图5A-5C示出示例性图,其例示使用包括野生型登革热病毒血清型-2和不同减毒登革热病毒的各种组合物于新生小鼠中测试的神经毒力。诸多实验的汇集总结了在使用10^4pfu病毒(A)脑内攻击的CDC-ICR(n=72)和Taconic-ICR(n=32)新生小鼠中野生型登革热病毒血清型-2 16681的神经毒力。使用10^4pfu(B)或10^3pfu(C)剂量在Taconic-ICR小鼠中测试DENVax MVS的神经毒力。指出了一次实验(n=16)或两次汇集实验(n=31或32)中每组测试动物的数量。

[0153] WVS和BVS的溶菌斑表现型

[0154] 进行某些研究来比较WVS和BVS与MVS、野生型登革热病毒及其同源实验室衍生的研究级嵌合体在Vero细胞中的溶菌斑表现型(图6)。针对每一疫苗病毒从10个溶菌斑算出平均溶菌斑尺寸,但野生型DENV-1、-3和-4的数目减少。在Vero细胞中,DENVax-1、-2和-3的MVS病毒均产生显著小于其野生型同源物的溶菌斑,而十分类似(在0.4毫米差值内)于其同源研究级病毒。DENVax-4 MVS也显著小于野生型DENV-4,但略微(0.9毫米)大于原始实验室衍生的D2/4-V嵌合体。除了DENVax-2之外,DENVax-1、-3、-4的WVS和BVS与从其野生型同源物产生的溶菌斑尺寸相比保留了显著更小的溶菌斑尺寸。在Vero细胞中,DENVax-2 WVS和BVS产生的溶菌斑与野生型DENV-2病毒的溶菌斑类似,但当在LLC-MK_2细胞中测试时,所有DENVax-2制造的种所产生的溶菌斑均略小于野生型DENV-2(1.4±0.4)的溶菌斑且类似于实验室衍生的D2 PDK-53-VV45R(1.0±0.3)(图6)。

[0155] 病毒减毒的表现型标记(包括小溶菌斑表现型、温度敏感性、于蚊细胞中复制减少、由蚊子感染/散播/传播减少、以及于新生ICR小鼠中神经毒力降低)的评估是针对MVS原料的组合物进行评价的。结果表明全部DENVax保留与原始研究级疫苗病毒类似的预期减毒表现型。考虑到负责减毒的突变均在全部MVS、WVS和BV中保守,可预期减毒表现型保留于针对人临床试验制造的材料中。

[0156] 图6示出示例性直方图,其例示DENVax MVS、WVS及BVS的溶菌斑尺寸。在感染后第9天测量在琼脂糖覆盖层下方的Vero细胞或LLC-MK_2细胞中的病毒溶菌斑的平均溶菌斑直径±SD(误差柱)。包括野生型DENV及先前公开的研究级疫苗候选物病毒以用于对照和比较。

[0157] 在蚊C6/36细胞中的病毒复制

[0158] 先前研究证实研究级的基于PDK-53的嵌合式疫苗病毒保留骨架DENV-2PDK53病毒在C6/36细胞中的减毒表现型。在一些示例性方法中,使DENVax MSV、WVS及BVS于C6/36细胞中生长以证实在大规模制造后其保留此种体外减毒标记。与野生型登革热病毒相比,除了DENVax-3之外,所制造的种在感染后第6天于C6/36细胞中显示显著的生长降低(至少3$\log_{10}$

pfu/ml降低)(图7)。DENV-3种与野生型DENV-3 16562相比也显示生长降低,但降低较不显著(1-2log_{10}PFU/ml降低)。然而,DENVax-3种批次的滴度类似(在1log_{10} PFU/ml差值内)于原始研究级嵌合式D2/3-V疫苗病毒。

[0159] 图8示出示例性直方图,其绘制DENVax MVS、WVS及BVS于C6/36细胞中的受限的生长。病毒在感染后第7天于C6/36细胞中复制的平均滴度±SD(误差柱)。包括野生型登革热病毒及先前公开的研究级疫苗候选物病毒以进行比较。

[0160] 在乳鼠中的神经毒力

[0161] 进行额外的实验以分析在新生ICR小鼠中的神经毒力。在10^4PFU的颅内剂量下,对于野生型DENV-2 16681和D2 PDK-53-VV45R,ICR小鼠的存活率分别为0%和18.8%(图9A),但CDC ICR小鼠对于野生型DENV-2 16681的存活率为约20%以及对于D2 PDK-53-VV45R的存活率为100%。在此研究中,DENVax-1和DENVax-3 MVS在10^4PFU剂量下对于小鼠为减毒的(100%存活率),但DENVax-2和DENVax-4的MVS于超过10^4PFU的剂量下造成100%死亡率(图5A)。然而,当在10^3PFU病毒的剂量下测试时,DENVax-2(31.3%存活)和DENVax-4(81.3%存活)显示相对于野生型登革热病毒血清型-2 16681(0%存活)的神经毒力降低,并且其存活率分别类似于研究级疫苗病毒D2 PDK-53-VV45R(32.3%)和D2/4-V(100%)(图9B)。虽然本研究不包括野生型DENV-1、-3或-4用于比较,但先前研究工作证实通过脑内途径野生型DENV-1 16007于CDC-ICR小鼠中为减毒的,而野生型DENV-3 16562和DENV-4 1036对CDC-ICR小鼠有高毒力(0%存活)。可能的是,这3种野生型DENV在较为敏感的Taconic ICR小鼠中会表现出相似的或较高的毒力。因此,包括这些野生型登革热病毒以与其同源DENVax MVS比较被视为信息不足。此研究表明全部4种DENVax MVS和原始实验室衍生的候选物疫苗病毒相对于野生型DENV-2 16681表现出相当的小鼠减毒表现型。

[0162] 图9A-9B示出DENVax MVS于新生ICR小鼠中的神经毒力的数据的示例性图。(A)病毒于10^4PFU剂量下的IC接种。(B)病毒于10^3PFU的剂量下的IC接种。

[0163] 测试全部DENVax种批次的身份、无菌性及不含不期望的试剂。全基因组序列分析显示一种额外的氨基酸突变出现在DENVax-4 MVS中,而其它3种DENVax MVS保留其前主代种的共有基因组序列。在WVS批次中,相对于其前主代种,DENVax-3获得额外的氨基酸突变以及其它三种血清型积累两种额外的氨基酸取代。全部4个BVS批次的基因组序列均与WVS批次相同。整体而言,从P2种至前主代(P7)种,在给定的种中只出现1或2种非沉默突变。前主代种与BCS(P10)种之间,只观察到1至2种核苷酸取代,均出现于NS2A、4A、或4B,除了导致残基E-483处的保守甘氨酸和丙氨酸的单一核苷酸改变之外。从P2至BVS(P10)种,在任何给定的DENVax种中确定共3至8种核苷酸取代,并且这些取代中只有2至4种导致氨基酸改变。在BVS中的沉默突变无一在5'-或3'-NCR区内,该区域可能影响病毒复制。这些结果表明DENVax病毒在制造期间是遗传上高度稳定的。位于5'NCR、NS1-53及NS3-250的三种定义的DENV-2PDK-53减毒基因座在DENVax连续传代而生成BVS原料之后于共有基因组序列中保持不变。5'-NCR-57基因座的高度敏感性TaqMAMA显示在DENVax的MVS、WVS及BVS中的极少或无法检测的回复。在DENVax-2 BVS中鉴定0.21%的最高回复率。P10-等同BVS的回复率(<0.07%至0.21%)显著低于在于Vero细胞连续传代后于其它疫苗候选物中出现的回复率(P10的4-74%回复)。这表明,用于DENVax种的大规模制造的此种策略在候选物疫苗病毒中保持遗传稳定性和减毒标记的保留方面是成功的。

[0164] 因为本文公开的MVS原料将用于进一步制造WVS和BVS批次,故对全部MVS或其等同代用原料进行全组的病毒减毒表现型评估,包括小溶菌斑表现型、温度敏感性、于蚊细胞中复制减少、于全蚊中感染/散播/传播降低、以及于新生ICR小鼠中神经毒力降低。对WVS和BVS原料,也进行溶菌斑尺寸、于蚊细胞中的感染力以验证其减毒。结果表示DENVax的4种血清型的全部MVS原料保留了预期的减毒表现型,诸如小溶菌斑、于C6/36细胞中复制减少、以及小鼠神经毒力降低,与原始实验室衍生的疫苗病毒相似(图6、8及9)。如图3和图7所示,除了DENVax-4之外,DENVax的所有其它3种MVS原料在39℃均为TS。

[0165] 针对WVS和BVS原料,分析和证实两个减毒表现型,即小溶菌斑和于C6/36细胞中的受限复制。由于MVS与BVS之间极少有遗传变化,因此预期其会保留如同MVS一样的减毒表现型。除了本报告中描述的实验之外,已经测试所制造的DENVax于Ag129小鼠及非人灵长类动物中的安全性和免疫原性。

[0166] 本文提供示例性方法以展示在cGMP下DENVax MVS、WVS及BVS原料的制造。BVS原料用于配制目前在人类临床试验评估中的四价DENVax。一些示例性方法中提供了独特的制造策略以优化所制造的MVS的遗传稳定性和安全性。由于DENVax的主减毒基因座先前已经良好表征,并开发高度敏感且可量化的SNP测定TaqMAMA以整合基因组序列及TaqMAMA以鉴定用于制造MVS的最佳前主代种。完整分析MVS的遗传学及表现型特性,以证实这些病毒保留疫苗安全性所期望的减毒。其可能是由前主代一路制造成BVS原料期间可有效分析全部主要减毒基因座的唯一活减毒病毒疫苗。本文提供的结果例示出策略上设计的活减毒疫苗在疫苗安全性方面的优点。

[0167] 图10示出示例性表格,其比较新的活减毒疫苗与先前生成的活减毒登革热病毒。指出突变与对照病毒(例如16681)或其它活减毒登革热-2病毒不同。

[0168] 材料及方法

[0169] 病毒及细胞

[0170] DENV-1 16007、DENV-2 16681、DENV-3 16562及DENV-4 1034用作野生型(wt)DENV对照,其为四种重组DENVax疫苗候选物的亲代基因型病毒。先前制备并表征DENVax祖先研究级病毒,标示为D2/1-V、D2 PDK-53-VV45R、D2/3-V及D2/4-V。用于制备主代的Vero(非洲绿猴肾)细胞和用于疫苗生产的工作细胞库源自于美国典型菌种保藏中心(ATCC)CCL81细胞系,其已由世界卫生组织(WHO)表征用于疫苗制造(WCB-Vero细胞)。

[0171] 从cDNA克隆衍生活重组DENVax病毒

[0172] 为了在cGMP制造条件下再度衍生候选物疫苗病毒,使用先前改造的DENV传染性cDNA克隆,即pD2 PDK-53-VV45R、pD2/1-V、pD2/4-V、以及体外接合的含全基因组长度病毒cDNA的pD2/3-V,通过如前所述的体外转录来制备新鲜的病毒RNA转录本。简言之,经XbaI-线性化的DENV基因组cDNA经蛋白酶K处理,使用酚/氯仿萃取,以及在乙醇中沉淀以去除任何残余蛋白质,然后于转录之前悬浮于不含RNAase的Tris-EDTA缓冲液。遵照制造商推荐的方案,使用AmpliScribe T7高产率转录试剂盒(Epicentre Technologies)进行体外转录。在2小时转录反应期间将RNA A-帽类似物,即m7G(5')ppp(5')A(New England BioLabs)并入以将5'-端A-帽添加至RNA转录本。然后,使用DNase I处理样本以消化模板cDNA,接着是低pH酚/氯仿萃取以及乙醇沉积以去除残余DNA和蛋白质。将悬浮于不含RNase的水中的纯化RNA转录本分散于20μl等分部分内,并于-80℃储存,直至准备用于细胞转染。通过琼脂糖

凝胶电泳分析RNA转录本的完整性和浓度。估计各20μl等分部分含有足量基因组长度病毒RNA来允许通过电穿孔而感染0.4-1×10^7生产核准的Vero细胞。

[0173] 在Shantha Biotechnics的cGMP培养器中进行每一RNA转录本转染入WCB-Vero细胞。DENVax RNA转录本经解冻,与400μl Vero细胞悬浮液(1×10^7细胞/ml)混合,并转移到预先冷冻的无菌电穿孔试管(4mm间隙)以用于由Gene Pulser Xcell系统(BioRad Laboratories)进行电穿孔。每一样本以250V/∞Ohms/500μF施加脉冲一次,在室温孵育10-15分钟,转移至含30ml细胞生长培养基(含10％FBS的MEM)的75cm^2烧瓶,并在36℃±1℃,5％CO_2孵育6至11天。收获培养基,离心澄清、稳定化、并以小等分部分于低于-60℃储存。由转染所得的候选物疫苗原料(传代级别1称为P1)的病毒滴度通过在Vero细胞中的溶菌斑滴定测定来测定,并用于DENVax种的进一步繁殖。

[0174] DENVax病毒种的制造

[0175] P1病毒种用于通过设计用于确保制造批次的最佳遗传稳定性和安全性的策略来繁殖DENVax前主代、主代、工作及散装病毒批次。此策略包括三次连续溶菌斑纯化,以及于各种传代水平下的遗传分析,从而选择用于连续种生产的最佳克隆病毒群体(表1)。简言之,从转染的细胞收获的P1种通过以0.001的MOI感染Vero细胞而扩增一次,从而生成P2种。通过溶菌斑形态和完整病毒基因组测序来评估P2种原料的等分部分。遗传上证实的P2原料涂覆于如下溶菌斑滴定部分所描述的具有覆盖培养基(overlay medium)的Vero细胞单层上,从而生成完全分离的溶菌斑。在使用中性红可视化之后,分离4种血清型疫苗病毒各自的6个个别溶菌斑(溶菌斑克隆A至F)并混合入0.5ml培养基内(P3代)。6个溶菌斑悬浮液各自进行另两轮的溶菌斑纯化,导致在P4和P5代的两次和三次溶菌斑纯化病毒种。P5病毒通过两次连续Vero传代而扩增,以产生P7种原料。

[0176] 进行使用如先前所公开的斑点测序和/或基于Taqman的错配扩增突变测定(TaqMAMA)的三种主要DENVax减毒基因座的遗传分析,以及进行溶菌斑表现型分析,从而筛检全部24种P7种。然后通过完整基因组测序进一步表征具有适当初始特性的种。作为这些分析的结果,每一DENVax血清型的6种(克隆A-F)P7种之一基于DENV-2PDK-53减毒突变、最低基因组序列变化及预期溶菌斑表现型的存在而被选用为前主代种。每一所选的前主代种通过在多个175cm^2烧瓶的Vero细胞内以0.001MOI进行一次病毒传代而扩展成主代病毒种(MVS或P8)。除了DENVax-4 MVS之外,在感染后(pi)第8至10天收获主代病毒种。于感染后(pi)第6至10天收获MVS原料,离心澄清,通过添加蔗糖/磷酸盐/谷氨酸盐溶液(最终浓度分别为7.5％蔗糖,3.4mM磷酸二氢钾,7.2mM磷酸氢二钾,5.4mM谷氨酸一钠)以及0.95至1.90％FBS(最终浓度)而稳定化。DENVax-4 MVS以不同方式制备来优化其产率。简言之,多个烧瓶的细胞在0.1％已经验证可增加DENV病毒之热稳定性的F-127™泊洛沙姆407的存在下(其它EO-PO嵌段共聚物已经经过评估且可于此处替换,参见公布的专利),以0.001的MOI感染DENVax-4前主代种。于感染后6至10日收获感染培养基,使用17％FBS(终浓度)稳定化,汇集及冷冻。全部四种DENVax MVS原料以1ml液分储存于低于-60℃。

[0177] 通过在0.001MOI下,在MVS的Vero细胞培养中一次传代来制备DENVax工作病毒种(WVS)。程序类似于MVS的产生,但在多层细胞培养器(6360cm^2)中培养。WVS原料通过10μM和0.45μM过滤器过滤,使用用于MVS的相同稳定剂稳定化,等分入30ml PETG瓶或2.0ml冷冻小瓶内,并低于-60℃储存。

[0178] 在某些方法中,通过使用90mL稀释WVS以实现0.001MOI感染融合Vero细胞的多个细胞培养器(各为6360cm^2)而产生散装病毒种(BVS)。用于稀释MVS接种物的培养基含有0.1%F-127™且不含血清。经1.5小时吸附后,用PBS洗涤细胞3次,将800ml的不含血清的DMEM培养基添加至每一细胞培养器,并将培养器于36(±1)℃于5(±0.5)%CO_2孵育。孵育4天之后,收集培养基的小等分部分以进行无菌性测试。在感染后第5天至第10天之间收获病毒,即刻通过0.45μm孔径过滤器过滤,1L的每一澄清病毒汇集物通过添加500ml的3倍FTA缓冲液(最终浓度为15%海藻糖,1.0%Pluronic®F-127TM泊洛沙姆407、于PBS中的0.1%人白蛋白USP,pH 7.4)而稳定化。将稳定化的病毒分配于1-L PETG瓶内,在低于-60℃冷冻储存,以用于随后的汇集和质量控制测试。具有高于10^{5}PFU/ml的病毒滴度和可接受水平的残余DNA的全部稳定化病毒收获物于32℃水浴中快速解冻,然后以无菌方式汇集并混合。全部汇集的单层BVS被分配于加标签的PETG容器内,并低于-60℃储存,直至进一步使用。

[0179] 制造产品质量控制

[0180] 测试MVS、WVS及BVS种的身份、无菌性及可检测的外源因子。每一疫苗原料的身份通过RT-PCR使用DENVax血清型特异性引物而证实。扩增的cDNA片段含有E/NS1嵌合式接合位点以允许鉴定四种DENVax血清型中的每一种。每一种(seed)于全部4种血清型特异性RT-PCR反应中测试以证实病毒身份和免于异源DENVax血清型的交叉污染。根据USP 71(美国药典第71节)进行无菌性测试。进行支原体测试。

[0181] 全部使用在种制造期间收集的未经澄清的未经稳定化的DENVax收获物进行下列针对病毒污染的体外及活体内测试。收获的感染性培养基首先于36±1℃下使用DENV兔多克隆抗血清(Inviragen)中和以使DENV失活。针对体外试验,已中和的种接种在25cm^{2}烧瓶内的三种指示剂细胞系(MRC5、VERO及MA104)中。埃可病毒(CPE对照)或腮腺炎病毒(血细胞吸附对照)分别用作阳性CPE或血细胞吸附对照。每天监测全部细胞的CPE,共计14天。14天结束后,移除培养上清液,以10ml豚鼠红血细胞(RBC)溶液(3mL的含0.5%豚鼠RBC的磷酸盐缓冲盐水,使用细胞培养基补充至10ml)置换。然后烧瓶于5±3℃孵育30分钟,接着于室温孵育30分钟。用PBS洗涤单层,并在10倍放大下观察任何星形RBC簇的存在,用于血细胞吸附。

[0182] 在乳鼠、断奶后小鼠及豚鼠中进行外源因子的活体内测试。乳鼠经由腹膜内(ip)注射接种0.1ml或0.01ml(每一剂量组中有10只小鼠)DENV-抗血清中和种样本。类似地,10只断奶后小鼠腹膜内接种0.5ml或0.03ml样本。豚鼠(5只/组)各自腹膜内接种5.0ml。每天观察乳鼠的发病率及死亡率,总计接种后14天。在接种后,观察断奶后小鼠共28天,并且观察豚鼠共42天。若≥80%的接种动物于整个观察期保持健康,则该试验组满足可接受的标准。

[0183] 还在鸡胚蛋中实施污染物的活体内测试。针对每一样本,10颗鸡胚蛋(9日龄)各自通过0.5mL的DENV抗血清中和样本接种至尿囊液内,并于35℃孵育3天。从这10颗蛋收获尿囊液,汇集,传代入10颗新鲜鸡胚蛋(10-11日龄;0.5ml/蛋)的尿囊液内,并于35℃再孵育3天。类似地,针对每一样本,10颗鸡胚蛋(6-7日龄)通过注射入卵黄囊内而各自接种0.5ml/蛋(DENVax-2一价BVS)或0.25ml/蛋(DENVax-1、DENVax-3及DENVax-4 BVS),并于35℃孵育9天。得自这10颗蛋的卵黄囊经收获和汇集,并将10%悬浮液传代入10颗新鲜鸡胚蛋(6-7日龄;0.5ml/蛋)的卵黄囊内并于35℃再孵育9天。在3天孵育后观察在尿囊液中接种的蛋(包

括初次接种及传代接种)的存活率。在4℃和25℃下使用鸡、豚鼠及人O型红细胞测试尿囊液的两种汇集物的红细胞凝集活性。在9天孵育后观察在卵黄囊内接种的蛋(初次接种及传代接种二者)的存活率。

[0184] 病毒溶菌斑测定及免疫焦点测定

[0185] 使用Vero细胞通过溶菌斑测定或免疫焦点测定而测量病毒滴度。如先前所述,在融合Vero细胞的6孔板内于双琼脂糖覆盖层中进行溶菌斑测定,并且其也用于评估DENVax种的溶菌斑表现型。为了精确比较,在同一实验中测量全部病毒的溶菌斑尺寸并比较。在感染后第9天使用中性红可视化后,测量每一病毒的多达10个完全分离的溶菌斑,以用于平均溶菌斑尺寸计算。对野生型DENV-1、-3及-4测量较少溶菌斑,其较大的溶菌斑尺寸通常不允许测量10个完全分离的溶菌斑。

[0186] 因四价DENVax含有全部四种DENV血清型,故开发DENV血清型特异性免疫焦点测定来对四价配制剂中的每一DENVax组分进行定量。每一个别DENVax MVS的免疫焦点测定与溶菌斑测定进行比较以确保病毒滴定结果在两种测定之间相当。在感染连续稀释的病毒的融合Vero细胞的6孔板内进行免疫焦点测定。细胞上方覆盖有含0.7%高粘度羧甲基纤维素(Sigma)的平衡盐培养基(BSS/YE-LAH培养基),并于37℃使用5%CO_2孵育7天。去除覆盖层后,使用PBS洗涤三次细胞层,于-20℃使用80%冷丙酮固定30分钟,使用PBS洗涤一次,并于37℃使用含2.5%(w/v)非脂奶粉、0.5%Triton X-100、含0.05%Tween-20的PBS的封闭缓冲液封闭30分钟。封闭的细胞与稀释DENV血清型-特异性MAb、1F1(DENV-1)、3H5(DENV-2)、8A-1(DENV-3)、或1H10(DENV-4)在封闭缓冲液中于37℃一起孵育1小时或于4℃一起孵育过夜,用洗涤缓冲液(含0.05%Tween-20的PBS)洗涤三次,并于37℃与碱性磷酸镁-或辣根过氧化酶(HRP)-结合亲和力-纯山羊抗小鼠IgG(Jackson Immuno Research Laboratories)一起孵育45-60分钟。将板洗涤三次,然后添加适当底物(1-步NBT/BCIP)加碱性磷酸酶的抑制物(Pierce)或用于HRP的载体-VIP试剂盒(Vector Labs)以显色。当斑点完全显现后用水冲洗以中止显色。在光箱上直接可视化并计数染色免疫斑点。

[0187] 基因序列

[0188] 对MVS和WVS的全长基因组进行测序(参见下文)。简言之,通过使用QIAamp病毒RNA试剂盒(Qiagen)从DENVax种提取病毒RNA,并使用Titan One Tube RT-PCR试剂盒(Roche Applied Science,Inc.)扩增覆盖整个基因组的重迭cDNA片段。扩增的cDNA片段被凝胶纯化,然后使用BigDye Terminator v3.1循环测序试剂盒(Applied Biosystems)使用正向引物和反向引物测序。使用BigDye XTerminator纯化试剂盒(Applied Biosystems)清洁测序反应,并在DVBD/CDC下于3130x1Genetic分析仪(Applied Biosystems)上运行。使用Lasergene SeqMan软件(DNAStar Inc.)进行基因组分析及比较。

[0189] 基于Taqman的错配扩增突变测定(TaqMAMA)

[0190] TaqMAMA为敏感定量单一核苷酸多形性测定,其开发以用于更精细地评估于减毒5'NC-57基因座的回复水平,并针对此研究而进一步优化。通过使用对野生型或疫苗5'NC-57区有特异性的两组引物/Taqman探针的TaqMAMA来分析来自MVS和WVS的经提取的病毒RNA。用来检测DENV-2野生型和疫苗序列的正向引物分别为D2-41-GC和D2-40-TT。每一正向引物的3'-端核苷酸匹配各病毒的特异性5'NCR-57核苷酸,而在每一引物中与3'-端核苷酸相邻的核苷酸与DENV-2病毒基因组序列不同,以增加错配效应。用于野生型组和疫苗组的

反向引物CD-207和Taqman探针CD-169F是相同的。先前描述了引物和探针的序列以及循环条件。在含5μl病毒RNA模板、0.4μM每一引物以及0.2μM探针的25μl反应中,使用BioRad iScript RT-PCR(用于探针)试剂盒,以iQ5或CFX-95系统(BioRad)进行实时RT-PCR。针对每一样本进行各野生型特异性测定和疫苗特异性测定的重复三次反应。相对于针对每一病毒基因型准备的标准曲线来确定基因组拷贝数,其中RNA标准为从含每一基因型特异性cDNA的nt 1-2670的质粒衍生的转录本。此外,通过使用异源基因型引物/探针组测试每一RNA标准而证实测定的特异性,以确保于每个实验中最低的交叉反应性。结果报告为表现出回复的病毒基因组的百分比。先前,由于较高交叉反应背景(其限制此测定的输入RNA水平),原始检测敏感性为约0.1%回复(辨别能力)。此后,测定进一步使用改良的实时PCR设备和反应试剂盒而优化,并且交叉反应性背景在显著更高的RNA模板输入水平(7-8$\log_{10}$拷贝)下显著降低。此种优化导致检测敏感性显著改善,低至0.01-0.07%回复。

[0191] 在蚊C6/36细胞中的病毒复制及在哺乳动物Vero细胞中的温度敏感性

[0192] 在C6/36蚊细胞(白纹伊蚊(Aedes albopictus))中评估四个DENVax MVS原料及野生型DENV-1、-2、-3和-4病毒的复制表现型。生长于6孔板的C6/36细胞以0.001MOI一式两份感染每一病毒,并于5%CO_2孵育器内于28℃与含2%FBS的4ml/孔DMEM培养基一起孵育。在感染后第6天收集每一病毒的培养上清液的小等分部分,与含40%FBS的等体积培养基混合,并于-80℃储存,直至准备用于病毒溶菌斑滴定。

[0193] 在6孔板中于Vero细胞感染后第5天,通过比较39℃的病毒生长与37℃病毒的生长而进行温度敏感性。细胞在37℃细胞用每一病毒于0.001MOI一式四份感染。在病毒吸附后,感染的培养物与含2%FBS的4ml/孔的DMEM培养基在两个单独的5%CO_2孵育器内一起孵育,一个设定(一式两份的板)于37℃,而另一个设定于39℃。感染后第5天收集培养物上清液的等分部分(50μl),与含40%FBS的等体积DMEM混合,并于-80℃储存,直到准备用于病毒溶菌斑滴定。使用NIST-示踪培养器校准温度计(-1至51℃;ERTCO)校准孵育器温度。

[0194] 蚊感染、散播及传播

[0195] 用于研究的埃及伊蚊得自源于靠近泰国美索(16'N,33'E)的村庄的于2002年建立的集落。从幼虫蜕变之后,成蚊被保持在28℃和16:8(亮:暗)光周期下,并自由地供给10%蔗糖溶液。5至7日龄的雌蚊用于感染血粉进食或胸内(IT)接种。收获后即刻(未经任何冷冻-解冻周期)使用新鲜培养的DENVax和野生型DENV的等分部分来制备用于经口感染的如下指示的病毒血粉。向剩余的病毒上清液添加FBS,至最终浓度为20%,并且等分部分储存于-80℃以用于未来病毒溶菌斑滴定和IT接种物实验。用于这些实验的新鲜制备的DENVax种在Vero细胞中从前主代种扩增,并被视为DENVax MVS等同物。

[0196] 在经口感染当天以1:1比例混合新鲜病毒与去纤维蛋白化的鸡血(Colorado Serum Company)以制备感染血粉。蚊子被糖缺乏过夜,然后使用Hemotek膜进食系统(Discovery Workshops)提供病毒:血液混合物,历时1小时。50μl等分部分的血粉保持在-80℃,以用于病毒剂量的回滴定。完全饱食的雌蚊在冷麻醉下分类并置于纸箱内,自由提供10%蔗糖溶液。纸箱置于28℃和16:8小时(亮:暗)光周期下。14天后,得自每一病毒组的25至30只蚊子经由暴露于三乙胺(Flynap®,Carolina Biological Supply Company)而麻醉,并取一只后腿置于含10%FBS和5%青霉素/链霉素(分别为100U/ml和100μg/ml)的0.5ml DMEM中。将麻醉的蚊子的喙插入含2.5%FBS和25%蔗糖溶液的毛细管内,从而收集

唾液。允许蚊子分泌唾液至少15分钟,然后将毛细管和蚊体置于含DMEM的单独的试管内。蚊体、腿部及唾液储存于-80℃,直到其被磨碎并测定传染性病毒。对于IT接种,蚊子被冷麻醉并于0.34μl接种物内与约50pfu病毒一起孵育。接种的蚊子在与前述相同的条件下保持7天。然后将蚊子麻醉,如前述那样收集唾液和蚊体。样本储存于-80℃,直到进一步处理。

[0197] 为了处理样本以进行病毒滴定,将蚊体和腿部样本使用混合磨以24周期/秒历时4分钟与铜包BB(Crossman Corporation,NY)一起均化,然后以3,000×g离心3分钟而澄清。唾液样本于3,000×g离心3分钟以从毛细管中排出流体。通过溶菌斑测定检测蚊体和腿部均化物和唾液样本的10倍稀释液的传染性病毒的存在。从蚊体、腿部及唾液所得的结果分别用于测定感染率、散播率及传播率。

[0198] 小鼠神经毒力

[0199] 定时妊娠雌ICR小鼠得自Taconic Labs,并每天监测数次以确定胎鼠(pup litters)的大致出生时间。在给定的实验中,出生后约12-24小时,每种病毒使用两窝八头胎鼠(n=16),使用30号针头通过颅内(ic)接种含10^3至10^4pfu病毒的20μl稀释液进行攻击。攻击后每日至少3次监测动物,至少历时32天。在疾病的第一迹象(毛皮粗糙、驼背、体重减轻、活动异常、瘫痪或嗜睡)时,使用异氟醚气体通过致命性麻醉,接着颈椎脱位,从而使动物安乐死。安乐死的感染后天数表示动物的"生病/发病的时间"或"存活时间"。动物实验遵照DVBD/CDC IACUC-核准的动物方案进行。

[0200] 主代种病毒的衍生

[0201] DENVax-1主代病毒种(MVS)

[0202] 本文提供了嵌合式病毒基因组的核苷酸序列及翻译蛋白质的推定氨基酸序列。大部分prM-E基因(nt 457至-2379,下画线)为野生型(wt)DEN-1 16007病毒特异性的;剩余基因组为DEN-2PDK-53病毒特异性的。标出与野生型病毒(D1 16007或D2 16681)不同的全部改造的取代物,以及在MVS中检测的额外突变(从改造的cDNA克隆的改变)。

[0203] 基因组及蛋白质中包括的取代:

[0204] D1(prM-E)与D2骨架之间的接合位点:

[0205] a.MluI(nt 451-456):改造的沉默突变,nt-453A-至-G

[0206] b.NgoMIV(nt 2380-2385):改造的突变,nt-2381/2382TG-至-CC(导致E-482Val-至-Ala改变)

[0207] D2 PDK-53病毒骨架(从野生型D2 16681的改变):全部为粗体

[0208] a.5'-非编码区(NCR)-57(nt-57C-至-T):主要减毒基因座(红色)

[0209] b.NS1-53 Gly-至-Asp(nt-2579G-至-A):主要减毒基因座(红色)

[0210] c.NS2A-181Leu-至-Phe(nt-4018C-至-T)

[0211] d.NS3-250 Glu-至-Val(nt-5270A-至-T):主要减毒基因座(红色)

[0212] e.nt-5547(NS3基因)T-至-C沉默突变

[0213] f.NS4A-75Gly-至-Ala(nt-6599G-至-C)

[0214] *PDK-53的nt-8571C-至-T沉默突变未在疫苗病毒中被改造

[0215] DEN-1prM-E(从野生型D1 16007的改变)

[0216] a.改造的nt-1575T-至-C沉默突变用于去除天然XbaI位点

[0217] 在疫苗种中发现的额外取代(与原始克隆有0.03%nt不同)

[0218] a.NS2A-116Ile-至-Leu(nt-3823A-至-C,粗体)

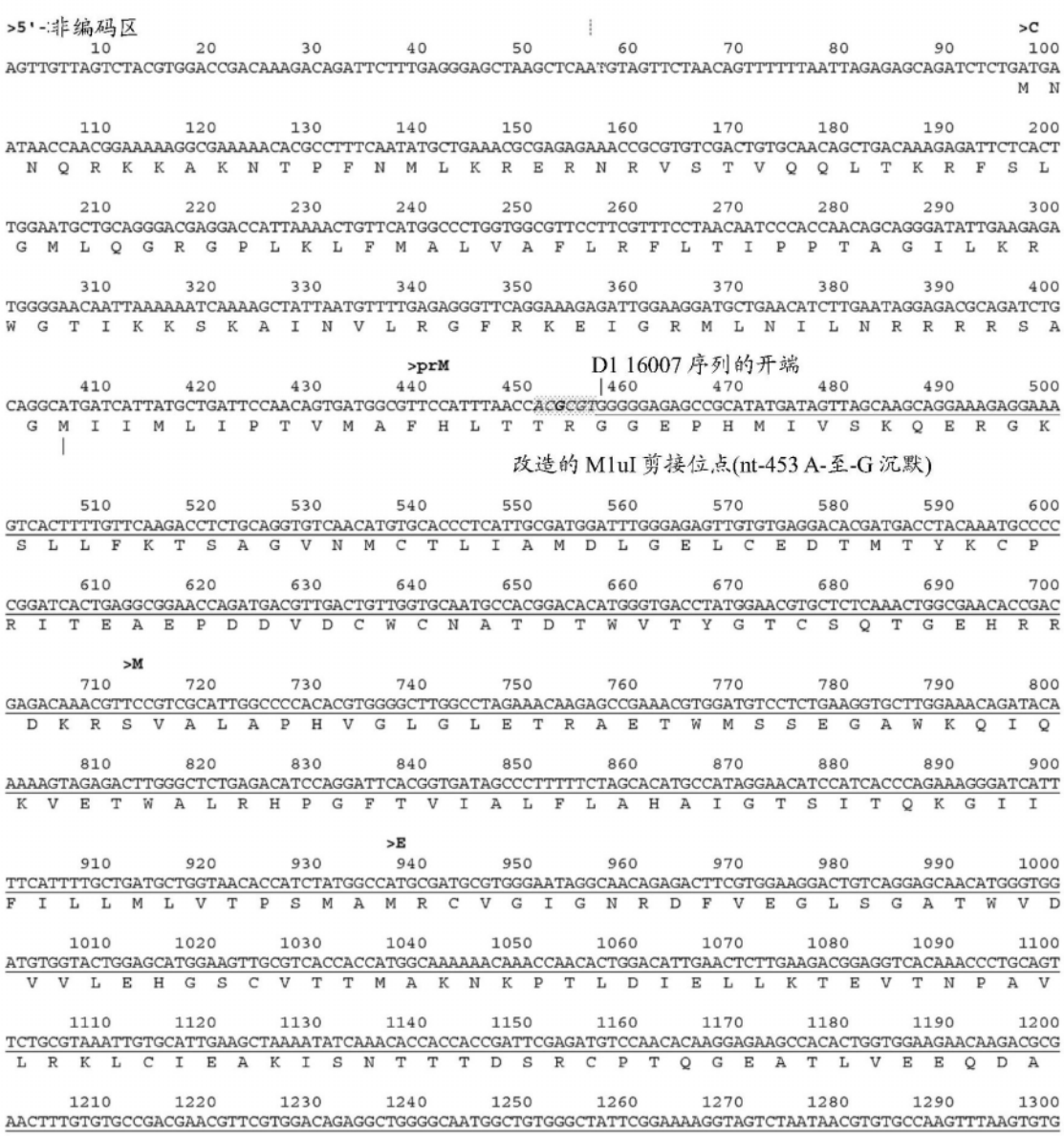
[0219] b.NS2B-92Glu-至-Asp(nt-4407A-至-T,粗体)

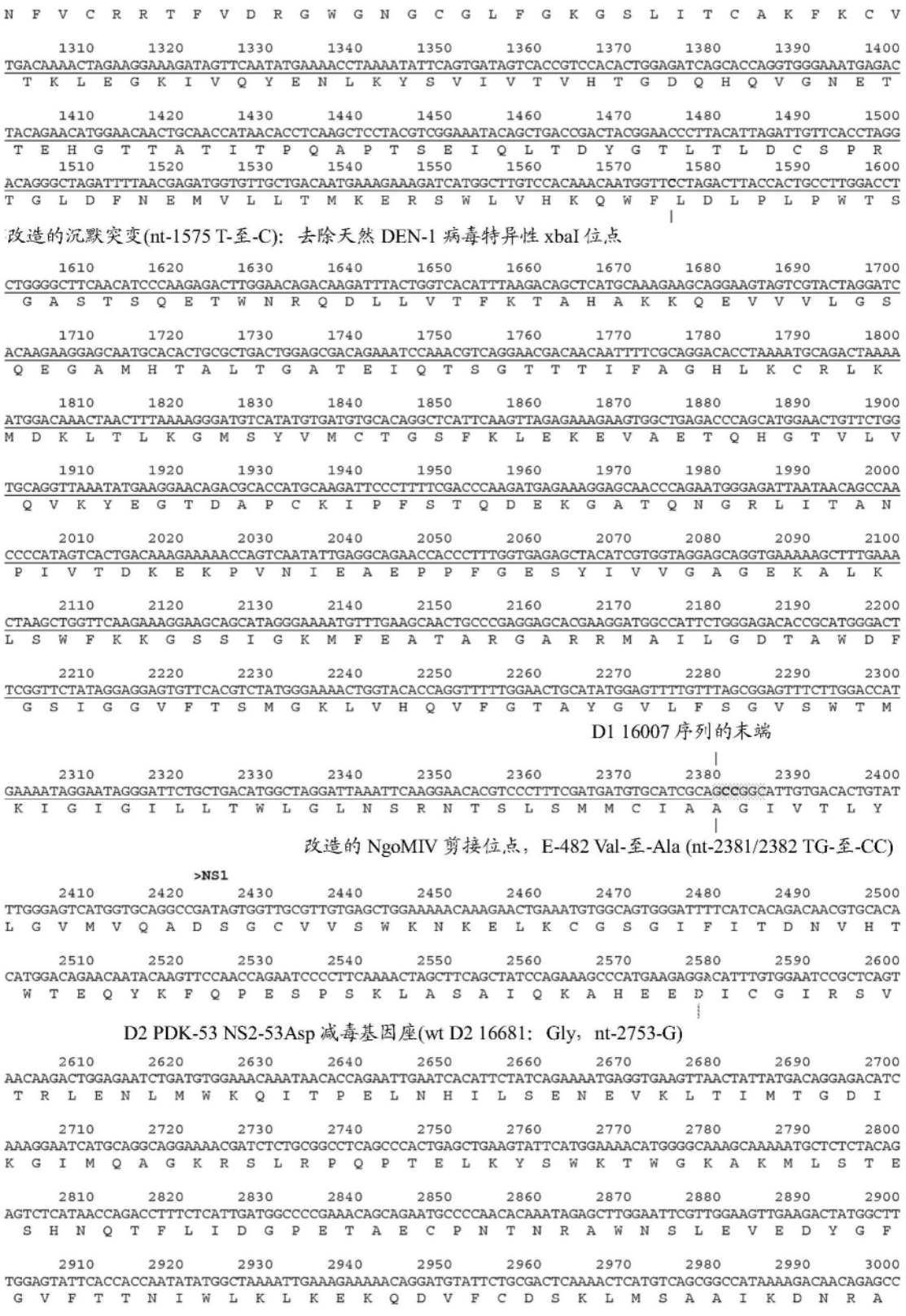
[0220] c.nt-7311A-至-G沉默突变(粗体)

[0221] DENVax-1 MVS的核苷酸序列(SEQ ID NO:13)

NCR-57-T，D2 PDK-53 减毒基因座(wt D216681: C)

[0222]




N F V C R R T F V D R G W G N G C G L F G K G S L I T C A K F K C V
1310 1320 1330 1340 1350 1360 1370 1380 1390 1400
TGACAAAACTAGAAGGAAAGATAGTTCAATATGAAAACCTAAAATATTCAGTGATAGTCACCGTCCACACTGGAGATCAGCACCAGGTGGGAAATGAGAC
T K L E G K I V Q Y E N L K Y S V I V T V H T G D Q H Q V G N E T
1410 1420 1430 1440 1450 1460 1470 1480 1490 1500
TACAGAACATGGAACAACTGCAACCATAACACCTCAAGCTCCTACGTCGGAAATACAGCTGACCGACTACGGAACCCTTACATTAGATTGTTCACCTAGG
T E H G T T A T I T P Q A P T S E I Q L T D Y G T L T L D C S P R
1510 1520 1530 1540 1550 1560 1570 1580 1590 1600
ACAGGGCTAGATTTTAACGAGATGGTGTTGCTGACAATGAAAGAAAGATCATGGCTTGTCCACAAACAATGGTTCCTAGACTTACCACTGCCTTGGACCT
T G L D F N E M V L L T M K E R S W L V H K Q W F L D L P L P W T S
改造的沉默突变(nt-1575 T-至-C): 去除天然 DEN-1 病毒特异性 xbaI 位点
1610 1620 1630 1640 1650 1660 1670 1680 1690 1700
CTGGGGCTTCAACATCCCAAGAGACTTGGAACAGACAAGATTTACTGGTCACATTTAAGACAGCTCATGCAAAGAAGCAGGAAGTAGTCGTACTAGGATC
G A S T S Q E T W N R Q D L L V T F K T A H A K K Q E V V V L G S
1710 1720 1730 1740 1750 1760 1770 1780 1790 1800
ACAAGAAGGAGCAATGCACACTGCGCTGACTGGAGCGACAGAAATCCAAACGTCAGGAACGACAACAATTTTCGCAGGACACCTAAAATGCAGACTAAAA
Q E G A M H T A L T G A T E I Q T S G T T T I F A G H L K C R L K
1810 1820 1830 1840 1850 1860 1870 1880 1890 1900
ATGGACAAACTAACTTTAAAAGGGATGTCATATGTGATGTGCACAGGCTCATTCAAGTTAGAGAAAGAAGTGGCTGAGACCCAGCATGGAACTGTTCTGG
M D K L T L K G M S Y V M C T G S F K L E K E V A E T Q H G T V L V
1910 1920 1930 1940 1950 1960 1970 1980 1990 2000
TGCAGGTTAAATATGAAGGAACAGACGCACCATGCAAGATTCCCTTTTCGACCCAAGATGAGAAAGGAGCAACCCAGAATGGGAGATTAATAACAGCCAA
Q V K Y E G T D A P C K I P F S T Q D E K G A T Q N G R L I T A N
2010 2020 2030 2040 2050 2060 2070 2080 2090 2100
CCCCATAGTCACTGACAAAGAAAAACCAGTCAATATTGAGGCAGAACCACCCTTTGGTGAGAGCTACATCGTGGTAGGAGCAGGTGAAAAAGCTTTGAAA
P I V T D K E K P V N I E A E P P F G E S Y I V V G A G E K A L K
2110 2120 2130 2140 2150 2160 2170 2180 2190 2200
CTAAGCTGGTTCAAGAAAGGAAGCAGCATAGGGAAAATGTTTGAAGCAACTGCCCGAGGAGCACGAAGGATGGCCATTCTGGGAGACACCGCATGGGACT
L S W F K K G S S I G K M F E A T A R G A R R M A I L G D T A W D F
2210 2220 2230 2240 2250 2260 2270 2280 2290 2300
TCGGTTCTATAGGAGGAGTGTTCACGTCTATGGGAAAACTGGTACACCAGGTTTTTGGAACTGCATATGGAGTTTTGTTTAGCGGAGTTTCTTGGACCAT
G S I G G V F T S M G K L V H Q V F G T A Y G V L F S G V S W T M
D1 16007 序列的末端
2310 2320 2330 2340 2350 2360 2370 2380 2390 2400
GAAAATAGGAATAGGGATTCTGCTGACATGGCTAGGATTAAATTCAAGGAACACGTCCCTTTCGATGATGTGCATCGCAGCCGGCATTGTGACACTGTAT
K I G I G I L L T W L G L N S R N T S L S M M C I A A G I V T L Y
改造的 NgoMIV 剪接位点，E-482 Val-至-Ala (nt-2381/2382 TG-至-CC)
>NS1
2410 2420 2430 2440 2450 2460 2470 2480 2490 2500
TTGGGAGTCATGGTGCAGGCCGATAGTGGTTGCGTTGTGAGCTGGAAAAACAAAGAACTGAAATGTGGCAGTGGGATTTTCATCACAGACAACGTGCACA
L G V M V Q A D S G C V V S W K N K E L K C G S G I F I T D N V H T
2510 2520 2530 2540 2550 2560 2570 2580 2590 2600
CATGGACAGAACAATACAAGTTCCAACCAGAATCCCCTTCAAAACTAGCTTCAGCTATCCAGAAAGCCCATGAAGAGGACATTTGTGGAATCCGCTCAGT
W T E Q Y K F Q P E S P S K L A S A I Q K A H E E D I C G I R S V
D2 PDK-53 NS2-53Asp 减毒基因座(wt D2 16681: Gly，nt-2753-G)
2610 2620 2630 2640 2650 2660 2670 2680 2690 2700
AACAAGACTGGAGAATCTGATGTGGAAACAAATAACACCAGAATTGAATCACATTCTATCAGAAAATGAGGTGAAGTTAACTATTATGACAGGAGACATC
T R L E N L M W K Q I T P E L N H I L S E N E V K L T I M T G D I
2710 2720 2730 2740 2750 2760 2770 2780 2790 2800
AAAGGAATCATGCAGGCAGGAAAACGATCTCTGCGGCCTCAGCCCACTGAGCTGAAGTATTCATGGAAAACATGGGGCAAAGCAAAAATGCTCTCTACAG
K G I M Q A G K R S L R P Q P T E L K Y S W K T W G K A K M L S T E
2810 2820 2830 2840 2850 2860 2870 2880 2890 2900
AGTCTCATAACCAGACCTTTCTCATTGATGGCCCCGAAACAGCAGAATGCCCCAACACAAATAGAGCTTGGAATTCGTTGGAAGTTGAAGACTATGGCTT
S H N Q T F L I D G P E T A E C P N T N R A W N S L E V E D Y G F
2910 2920 2930 2940 2950 2960 2970 2980 2990 3000
TGGAGTATTCACCACCAATATATGGCTAAAATTGAAAGAAAAACAGGATGTATTCTGCGACTCAAAACTCATGTCAGCGGCCATAAAAGACAACAGAGCC
G V F T T N I W L K L K E K Q D V F C D S K L M S A A I K D N R A

[0223]

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      3010       3020       3030       3040       3050       3060       3070       3080       3090       3100
GTCCATGCCGATATGGGTTATTGGATAGAAAGTGCACTCAATGACACATGGAAGATAGAGAAAGCCTCTTTCATTGAAGTTAAAAACTGCCACTGGCCAA
V  H  A  D  M  G  Y  W  I  E  S  A  L  N  D  T  W  K  I  E  K  A  S  F  I  E  V  K  N  C  H  W  P  K

      3110       3120       3130       3140       3150       3160       3170       3180       3190       3200
AATCACACACCCTCTGGAGCAATGGAGTGCTAGAAAGTGAGATGATAATTCCAAAGAATCTCGCTGGACCAGTGTCTCAACACAACTATAGACCAGGCTA
  S  H  T  L  W  S  N  G  V  L  E  S  E  M  I  I  P  K  N  L  A  G  P  V  S  Q  H  N  Y  R  P  G  Y

      3210       3220       3230       3240       3250       3260       3270       3280       3290       3300
CCATACACAAATAACAGGACCATGGCATCTAGGTAAGCTTGAGATGGACTTTGATTTCTGTGATGGAACAACAGTGGTAGTGACTGAGGACTGCGGAAAT
 H  T  Q  I  T  G  P  W  H  L  G  K  L  E  M  D  F  D  F  C  D  G  T  T  V  V  V  T  E  D  C  G  N

      3310       3320       3330       3340       3350       3360       3370       3380       3390       3400
AGAGGACCCTCTTTGAGAACAACCACTGCCTCTGGAAAACTCATAACAGAATGGTGCTGCCGATCTTGCACATTACCACCGCTAAGATACAGAGGTGAGG
R  G  P  S  L  R  T  T  T  A  S  G  K  L  I  T  E  W  C  C  R  S  C  T  L  P  P  L  R  Y  R  G  E  D

                                                                                  >NS2A
      3410       3420       3430       3440       3450       3460       3470       3480       3490       3500
ATGGGTGCTGGTACGGGATGGAAATCAGACCATTGAAGGAGAAAGAAGAGAATTTGGTCAACTCCTTGGTCACAGCTGGACATGGGCAGGTCGACAACTT
  G  C  W  Y  G  M  E  I  R  P  L  K  E  K  E  E  N  L  V  N  S  L  V  T  A  G  H  G  Q  V  D  N  F

      3510       3520       3530       3540       3550       3560       3570       3580       3590       3600
TTCACTAGGAGTCTTGGGAATGGCATTGTTCCTGGAGGAAATGCTTAGGACCCGAGTAGGAACGAAACATGCAATACTACTAGTTGCAGTTTCTTTTGTG
 S  L  G  V  L  G  M  A  L  F  L  E  E  M  L  R  T  R  V  G  T  K  H  A  I  L  L  V  A  V  S  F  V

      3610       3620       3630       3640       3650       3660       3670       3680       3690       3700
ACATTGATCACAGGGAACATGTCCTTTAGAGACCTGGGAAGAGTGATGGTTATGGTAGGCGCCACTATGACGGATGACATAGGTATGGGCGTGACTTATC
T  L  I  T  G  N  M  S  F  R  D  L  G  R  V  M  V  M  V  G  A  T  M  T  D  D  I  G  M  G  V  T  Y  L

      3710       3720       3730       3740       3750       3760       3770       3780       3790       3800
TTGCCCTACTAGCAGCCTTCAAAGTCAGACCAACTTTTGCAGCTGGACTACTCTTGAGAAAGCTGACCTCCAAGGAATTGATGATGACTACTATAGGAAT
  A  L  L  A  A  F  K  V  R  P  T  F  A  A  G  L  L  L  R  K  L  T  S  K  E  L  M  M  T  T  I  G  I

      3810       3820       3830       3840       3850       3860       3870       3880       3890       3900
TGTACTCCTCTCCCAGAGCACCCTACCAGAGACCATTCTTGAGTTGACTGATGCGTTAGCCTTAGGCATGATGGTCCTCAAAATGGTGAGAAATATGGAA
 V  L  L  S  Q  S  T  L  P  E  T  I  L  E  L  T  D  A  L  A  L  G  M  M  V  L  K  M  V  R  N  M  E
```

[0224] 在主代种和前主代种中的额外的 NS2A-116 Ile-至-Leu (nt3823 A-至-C)突变

```
      3910       3920       3930       3940       3950       3960       3970       3980       3990       4000
AAGTATCAATTGGCAGTGACTATCATGGCTATCTTGTGCGTCCCAAACGCAGTGATATTACAAAACGCATGGAAAGTGAGTTGCACAATATTGGCAGTGG
K  Y  Q  L  A  V  T  I  M  A  I  L  C  V  P  N  A  V  I  L  Q  N  A  W  K  V  S  C  T  I  L  A  V  V

      4010       4020       4030       4040       4050       4060       4070       4080       4090       4100
TGTCCGTTTCCCCACTGTTCTTAACATCCTCACAGCAAAAAACAGATTGGATACCATTAGCATTGACGATCAAAGGTCTCAATCCAACAGCTATTTTTCT
  S  V  S  P  L  F  L  T  S  S  Q  Q  K  T  D  W  I  P  L  A  L  T  I  K  G  L  N  P  T  A  I  F  L
```

D2 PDK-53 特异性 NS2A-181-Phe (wt D2 16681: Leu, nt-4018-C)

```
                                                >NS2B
      4110       4120       4130       4140       4150       4160       4170       4180       4190       4200
AACAACCCTCTCAAGAACCAGCAAGAAAAGGAGCTGGCCATTAAATGAGGCTATCATGGCAGTCGGGATGGTGAGCATTTTAGCCAGTTCTCTCCTAAAA
 T  T  L  S  R  T  S  K  K  R  S  W  P  L  N  E  A  I  M  A  V  G  M  V  S  I  L  A  S  S  L  L  K

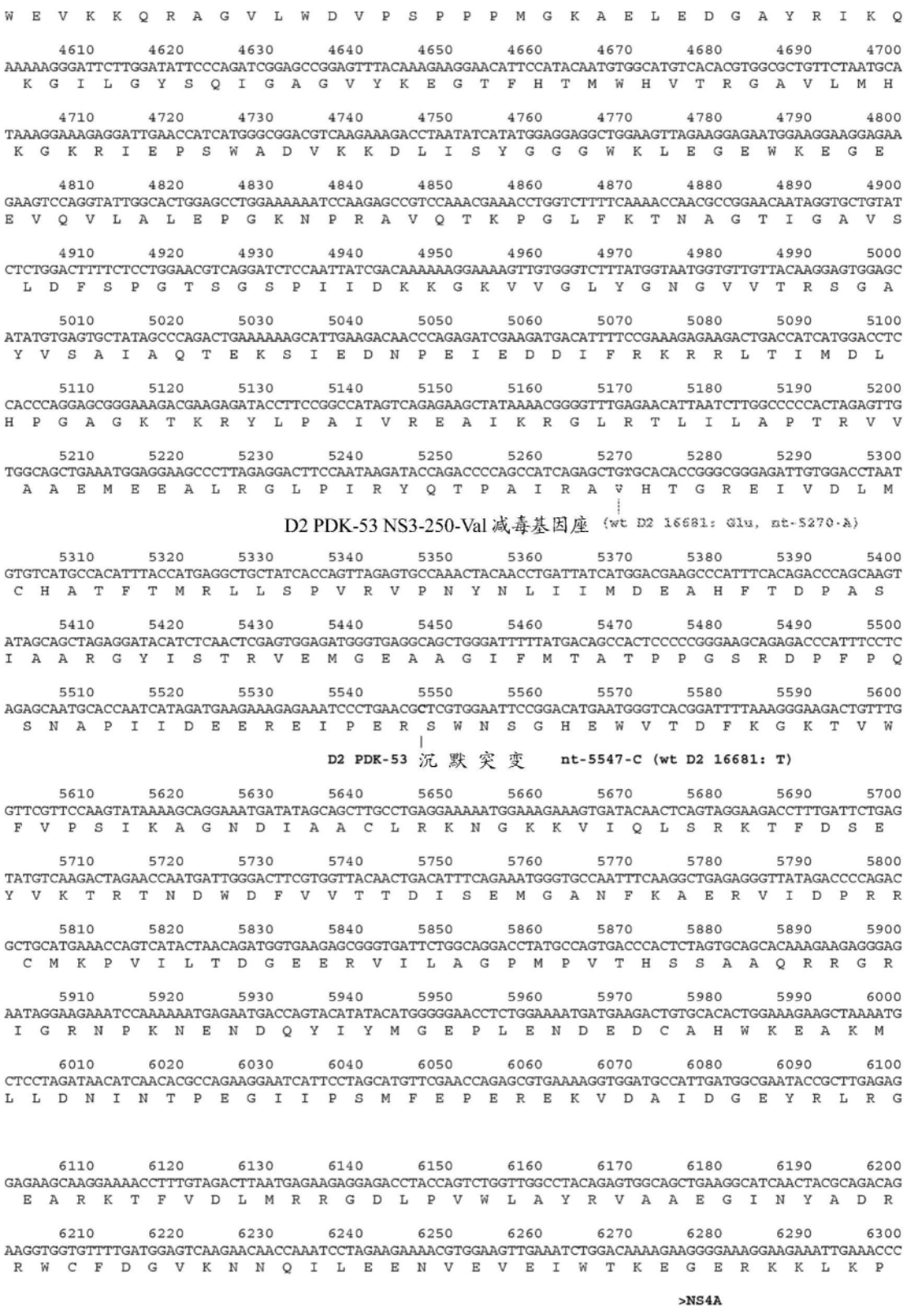
      4210       4220       4230       4240       4250       4260       4270       4280       4290       4300
AATGATATTCCCATGACAGGACCATTAGTGGCTGGAGGGCTCCTCACTGTGTGCTACGTGCTCACTGGACGATCGGCCGATTTGGAACTGGAGAGAGCAG
N  D  I  P  M  T  G  P  L  V  A  G  G  L  L  T  V  C  Y  V  L  T  G  R  S  A  D  L  E  L  E  R  A  A

      4310       4320       4330       4340       4350       4360       4370       4380       4390       4400
CCGATGTCAAATGGGAAGACCAGGCAGAGATATCAGGAAGCAGTCCAATCCTGTCAATAACAATATCAGAAGATGGTAGCATGTCGATAAAAAATGAAGA
  D  V  K  W  E  D  Q  A  E  I  S  G  S  S  P  I  L  S  I  T  I  S  E  D  G  S  M  S  I  K  N  E  E

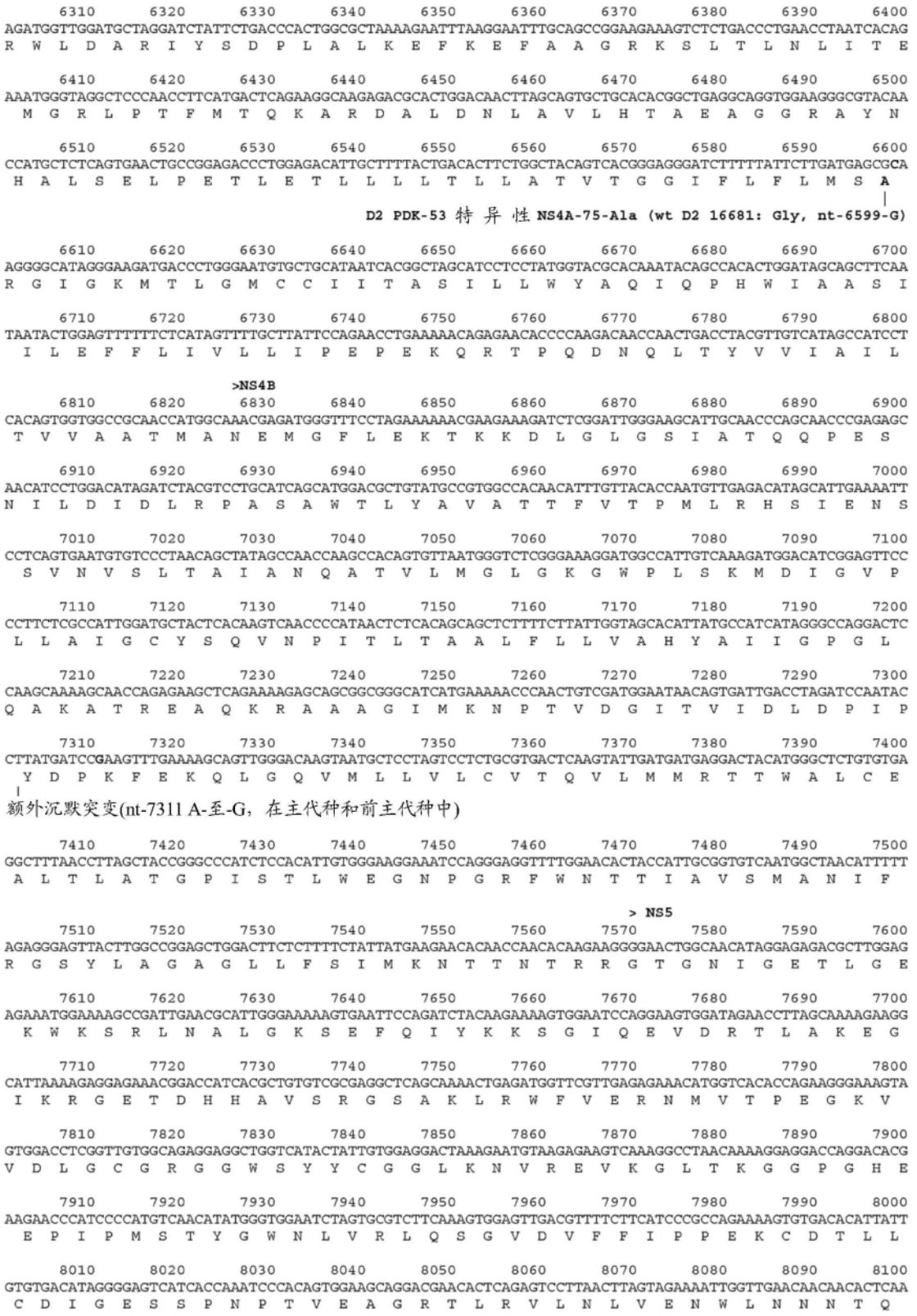
      4410       4420       4430       4440       4450       4460       4470       4480       4490       4500
GGAAGATCAAACACTGACCATACTCATTAGAACAGGATTGCTGGTGATCTCAGGACTTTTTCCTGTATCAATACCAATCACGGCAGCAGCATGGTACCTG
 E  D  Q  T  L  T  I  L  I  R  T  G  L  L  V  I  S  G  L  F  P  V  S  I  P  I  T  A  A  A  W  Y  L
```

额外的 NS2B-92 Glu-至-Asp (nt-4407 A-至-T)突变(在主代种和前主代种中)

```
                        >NS3
      4510       4520       4530       4540       4550       4560       4570       4580       4590       4600
TGGGAAGTGAAGAAACAACGGGCCGGAGTATTGTGGGATGTTCCTTCACCCCCACCCATGGGAAAGGCTGAACTGGAAGATGGAGCCTATAGAATTAAGC
```


W E V K K Q R A G V L W D V P S P P P M G K A E L E D G A Y R I K Q
4610 4620 4630 4640 4650 4660 4670 4680 4690 4700
AAAAAGGGATTCTTGGATATTCCCAGATCGGAGCCGGAGTTTACAAAGAAGGAACATTCCATACAATGTGGCATGTCACACGTGGCGCTGTTCTAATGCA
K G I L G Y S Q I G A G V Y K E G T F H T M W H V T R G A V L M H
4710 4720 4730 4740 4750 4760 4770 4780 4790 4800
TAAAGGAAAGAGGATTGAACCATCATGGGCGGACGTCAAGAAAGACCTAATATCATATGGAGGAGGCTGGAAGTTAGAAGGAGAATGGAAGGAAGGAGAA
K G K R I E P S W A D V K K D L I S Y G G G W K L E G E W K E G E
4810 4820 4830 4840 4850 4860 4870 4880 4890 4900
GAAGTCCAGGTATTGGCACTGGAGCCTGGAAAAAATCCAAGAGCCGTCCAAACGAAACCTGGTCTTTTCAAAACCAACGCCGGAACAATAGGTGCTGTAT
E V Q V L A L E P G K N P R A V Q T K P G L F K T N A G T I G A V S
4910 4920 4930 4940 4950 4960 4970 4980 4990 5000
CTCTGGACTTTTCTCCTGGAACGTCAGGATCTCCAATTATCGACAAAAAAGGAAAAGTTGTGGGTCTTTATGGTAATGGTGTTGTTACAAGGAGTGGAGC
L D F S P G T S G S P I I D K K G K V V G L Y G N G V V T R S G A
5010 5020 5030 5040 5050 5060 5070 5080 5090 5100
ATATGTGAGTGCTATAGCCCAGACTGAAAAAAGCATTGAAGACAACCCAGAGATCGAAGATGACATTTTCCGAAAGAGAAGACTGACCATCATGGACCTC
Y V S A I A Q T E K S I E D N P E I E D D I F R K R R L T I M D L
5110 5120 5130 5140 5150 5160 5170 5180 5190 5200
CACCCAGGAGCGGGAAAGACGAAGAGATACCTTCCGGCCATAGTCAGAGAAGCTATAAAACGGGGTTTGAGAACATTAATCTTGGCCCCCACTAGAGTTG
H P G A G K T K R Y L P A I V R E A I K R G L R T L I L A P T R V V
5210 5220 5230 5240 5250 5260 5270 5280 5290 5300
TGGCAGCTGAAATGGAGGAAGCCCTTAGAGGACTTCCAATAAGATACCAGACCCCAGCCATCAGAGCTGTGCACACCGGGCGGGAGATTGTGGACCTAAT
A A E M E E A L R G L P I R Y Q T P A I R A V H T G R E I V D L M
D2 PDK-53 NS3-250-Val 减毒基因座 (wt D2 16681: Glu, nt-5270-A)
5310 5320 5330 5340 5350 5360 5370 5380 5390 5400
GTGTCATGCCACATTTACCATGAGGCTGCTATCACCAGTTAGAGTGCCAAACTACAACCTGATTATCATGGACGAAGCCCATTTCACAGACCCAGCAAGT
C H A T F T M R L L S P V R V P N Y N L I I M D E A H F T D P A S
5410 5420 5430 5440 5450 5460 5470 5480 5490 5500
ATAGCAGCTAGAGGATACATCTCAACTCGAGTGGAGATGGGTGAGGCAGCTGGGATTTTTATGACAGCCACTCCCCCGGGAAGCAGAGACCCATTTCCTC
I A A R G Y I S T R V E M G E A A G I F M T A T P P G S R D P F P Q
5510 5520 5530 5540 5550 5560 5570 5580 5590 5600
AGAGCAATGCACCAATCATAGATGAAGAAAGAGAAATCCCTGAACGCTCGTGGAATTCCGGACATGAATGGGTCACGGATTTTAAAGGGAAGACTGTTTG
S N A P I I D E E R E I P E R S W N S G H E W V T D F K G K T V W
D2 PDK-53 沉 默 突 变 nt-5547-C (wt D2 16681: T)
5610 5620 5630 5640 5650 5660 5670 5680 5690 5700
GTTCGTTCCAAGTATAAAAGCAGGAAATGATATAGCAGCTTGCCTGAGGAAAAATGGAAAGAAAGTGATACAACTCAGTAGGAAGACCTTTGATTCTGAG
F V P S I K A G N D I A A C L R K N G K K V I Q L S R K T F D S E
5710 5720 5730 5740 5750 5760 5770 5780 5790 5800
TATGTCAAGACTAGAACCAATGATTGGGACTTCGTGGTTACAACTGACATTTCAGAAATGGGTGCCAATTTCAAGGCTGAGAGGGTTATAGACCCCAGAC
Y V K T R T N D W D F V V T T D I S E M G A N F K A E R V I D P R R
5810 5820 5830 5840 5850 5860 5870 5880 5890 5900
GCTGCATGAAACCAGTCATACTAACAGATGGTGAAGAGCGGGTGATTCTGGCAGGACCTATGCCAGTGACCCACTCTAGTGCAGCACAAAGAAGAGGGAG
C M K P V I L T D G E E R V I L A G P M P V T H S S A A Q R R G R
5910 5920 5930 5940 5950 5960 5970 5980 5990 6000
AATAGGAAGAAATCCAAAAAATGAGAATGACCAGTACATATACATGGGGGAACCTCTGGAAAATGATGAAGACTGTGCACACTGGAAAGAAGCTAAAATG
I G R N P K N E N D Q Y I Y M G E P L E N D E D C A H W K E A K M
6010 6020 6030 6040 6050 6060 6070 6080 6090 6100
CTCCTAGATAACATCAACACGCCAGAAGGAATCATTCCTAGCATGTTCGAACCAGAGCGTGAAAAGGTGGATGCCATTGATGGCGAATACCGCTTGAGAG
L L D N I N T P E G I I P S M F E P E R E K V D A I D G E Y R L R G
6110 6120 6130 6140 6150 6160 6170 6180 6190 6200
GAGAAGCAAGGAAAACCTTTGTAGACTTAATGAGAAGAGGAGACCTACCAGTCTGGTTGGCCTACAGAGTGGCAGCTGAAGGCATCAACTACGCAGACAG
E A R K T F V D L M R R G D L P V W L A Y R V A A E G I N Y A D R
6210 6220 6230 6240 6250 6260 6270 6280 6290 6300
AAGGTGGTGTTTTGATGGAGTCAAGAACAACCAAATCCTAGAAGAAAACGTGGAAGTTGAAATCTGGACAAAAGAAGGGGAAAGGAAGAAATTGAAACCC
R W C F D G V K N N Q I L E E N V E V E I W T K E G E R K K L K P
>NS4A

[0225]


6310 6320 6330 6340 6350 6360 6370 6380 6390 6400
AGATGGTTGGATGCTAGGATCTATTCTGACCCACTGGCGCTAAAAGAATTTAAGGAATTTGCAGCCGGAAGAAAGTCTCTGACCCTGAACCTAATCACAG
R W L D A R I Y S D P L A L K E F K E F A A G R K S L T L N L I T E
6410 6420 6430 6440 6450 6460 6470 6480 6490 6500
AAATGGGTAGGCTCCCAACCTTCATGACTCAGAAGGCAAGAGACGCACTGGACAACTTAGCAGTGCTGCACACGGCTGAGGCAGGTGGAAGGGCGTACAA
M G R L P T F M T Q K A R D A L D N L A V L H T A E A G G R A Y N
6510 6520 6530 6540 6550 6560 6570 6580 6590 6600
CCATGCTCTCAGTGAACTGCCGGAGACCCTGGAGACATTGCTTTTACTGACACTTCTGGCTACAGTCACGGGAGGGATCTTTTTATTCTTGATGAGCGCA
H A L S E L P E T L E T L L L L T L L A T V T G G I F L F L M S A
D2 PDK-53 特 异 性 NS4A-75-Ala (wt D2 16681: Gly, nt-6599-G)
6610 6620 6630 6640 6650 6660 6670 6680 6690 6700
AGGGGCATAGGGAAGATGACCCTGGGAATGTGCTGCATAATCACGGCTAGCATCCTCCTATGGTACGCACAAATACAGCCACACTGGATAGCAGCTTCAA
R G I G K M T L G M C C I I T A S I L L W Y A Q I Q P H W I A A S I
6710 6720 6730 6740 6750 6760 6770 6780 6790 6800
TAATACTGGAGTTTTTTCTCATAGTTTTGCTTATTCCAGAACCTGAAAAACAGAGAACACCCCAAGACAACCAACTGACCTACGTTGTCATAGCCATCCT
I L E F F L I V L L I P E P E K Q R T P Q D N Q L T Y V V I A I L
>NS4B
6810 6820 6830 6840 6850 6860 6870 6880 6890 6900
CACAGTGGTGGCCGCAACCATGGCAAACGAGATGGGTTTCCTAGAAAAAACGAAGAAAGATCTCGGATTGGGAAGCATTGCAACCCAGCAACCCGAGAGC
T V V A A T M A N E M G F L E K T K K D L G L G S I A T Q Q P E S
6910 6920 6930 6940 6950 6960 6970 6980 6990 7000
AACATCCTGGACATAGATCTACGTCCTGCATCAGCATGGACGCTGTATGCCGTGGCCACAACATTTGTTACACCAATGTTGAGACATAGCATTGAAAATT
N I L D I D L R P A S A W T L Y A V A T T F V T P M L R H S I E N S
7010 7020 7030 7040 7050 7060 7070 7080 7090 7100
CCTCAGTGAATGTGTCCCTAACAGCTATAGCCAACCAAGCCACAGTGTTAATGGGTCTCGGGAAAGGATGGCCATTGTCAAAGATGGACATCGGAGTTCC
S V N V S L T A I A N Q A T V L M G L G K G W P L S K M D I G V P
7110 7120 7130 7140 7150 7160 7170 7180 7190 7200
CCTTCTCGCCATTGGATGCTACTCACAAGTCAACCCCATAACTCTCACAGCAGCTCTTTTCTTATTGGTAGCACATTATGCCATCATAGGGCCAGGACTC
L L A I G C Y S Q V N P I T L T A A L F L L V A H Y A I I G P G L
[0226]
7210 7220 7230 7240 7250 7260 7270 7280 7290 7300
CAAGCAAAAGCAACCAGAGAAGCTCAGAAAAGAGCAGCGGCGGGCATCATGAAAAACCCAACTGTCGATGGAATAACAGTGATTGACCTAGATCCAATAC
Q A K A T R E A Q K R A A A G I M K N P T V D G I T V I D L D P I P
7310 7320 7330 7340 7350 7360 7370 7380 7390 7400
CTTATGATCCGAAGTTTGAAAAGCAGTTGGGACAAGTAATGCTCCTAGTCCTCTGCGTGACTCAAGTATTGATGATGAGGACTACATGGGCTCTGTGTGA
Y D P K F E K Q L G Q V M L L V L C V T Q V L M M R T T W A L C E
额外沉默突变(nt-7311 A-至-G，在主代种和前主代种中)
7410 7420 7430 7440 7450 7460 7470 7480 7490 7500
GGCTTTAACCTTAGCTACCGGGCCCATCTCCACATTGTGGGAAGGAAATCCAGGGAGGTTTTGGAACACTACCATTGCGGTGTCAATGGCTAACATTTTT
A L T L A T G P I S T L W E G N P G R F W N T T I A V S M A N I F
> NS5
7510 7520 7530 7540 7550 7560 7570 7580 7590 7600
AGAGGGAGTTACTTGGCCGGAGCTGGACTTCTCTTTTCTATTATGAAGAACACAACCAACACAAGAAGGGGAACTGGCAACATAGGAGAGACGCTTGGAG
R G S Y L A G A G L L F S I M K N T T N T R R G T G N I G E T L G E
7610 7620 7630 7640 7650 7660 7670 7680 7690 7700
AGAAATGGAAAAGCCGATTGAACGCATTGGGAAAAAGTGAATTCCAGATCTACAAGAAAAGTGGAATCCAGGAAGTGGATAGAACCTTAGCAAAAGAAGG
K W K S R L N A L G K S E F Q I Y K K S G I Q E V D R T L A K E G
7710 7720 7730 7740 7750 7760 7770 7780 7790 7800
CATTAAAAGAGGAGAAACGGACCATCACGCTGTGTCGCGAGGCTCAGCAAAACTGAGATGGTTCGTTGAGAGAAACATGGTCACACCAGAAGGGAAAGTA
I K R G E T D H H A V S R G S A K L R W F V E R N M V T P E G K V
7810 7820 7830 7840 7850 7860 7870 7880 7890 7900
GTGGACCTCGGTTGTGGCAGAGGAGGCTGGTCATACTATTGTGGAGGACTAAAGAATGTAAGAGAAGTCAAAGGCCTAACAAAAGGAGGACCAGGACACG
V D L G C G R G G W S Y Y C G G L K N V R E V K G L T K G G P G H E
7910 7920 7930 7940 7950 7960 7970 7980 7990 8000
AAGAACCCATCCCCATGTCAACATATGGGTGGAATCTAGTGCGTCTTCAAAGTGGAGTTGACGTTTTCTTCATCCCGCCAGAAAAGTGTGACACATTATT
E P I P M S T Y G W N L V R L Q S G V D V F F I P P E K C D T L L
8010 8020 8030 8040 8050 8060 8070 8080 8090 8100
GTGTGACATAGGGGAGTCATCACCAAATCCCACAGTGGAAGCAGGACGAACACTCAGAGTCCTTAACTTAGTAGAAAATTGGTTGAACAACAACACTCAA
C D I G E S S P N P T V E A G R T L R V L N L V E N W L N N N T Q

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      8110      8120      8130      8140      8150      8160      8170      8180      8190      8200
TTTTGCATAAAGGTTCTCAACCCATATATGCCCTCAGTCATAGAAAAAATGGAAGCACTACAAAGGAAATATGGAGGAGCCTTAGTGAGGAATCCACTCT
F  C  I  K  V  L  N  P  Y  M  P  S  V  I  E  K  M  E  A  L  Q  R  K  Y  G  G  A  L  V  R  N  P  L  S

      8210      8220      8230      8240      8250      8260      8270      8280      8290      8300
CACGAAACTCCACACATGAGATGTACTGGGTATCCAATGCTTCCGGGAACATAGTGTCATCAGTGAACATGATTTCAAGGATGTTGATCAACAGATTTAC
  R  N  S  T  H  E  M  Y  W  V  S  N  A  S  G  N  I  V  S  S  V  N  M  I  S  R  M  L  I  N  R  F  T

      8310      8320      8330      8340      8350      8360      8370      8380      8390      8400
AATGAGATACAAGAAAGCCACTTACGAGCCGGATGTTGACCTCGGAAGCGGAACCCGTAACATCGGGATTGAAAGTGAGATACCAAACCTAGATATAATT
 M  R  Y  K  K  A  T  Y  E  P  D  V  D  L  G  S  G  T  R  N  I  G  I  E  S  E  I  P  N  L  D  I  I

      8410      8420      8430      8440      8450      8460      8470      8480      8490      8500
GGGAAAAGAATAGAAAAAATAAAGCAAGAGCATGAAACATCATGGCACTATGACCAAGACCACCCATACAAAACGTGGGCATACCATGGTAGCTATGAAA
G  K  R  I  E  K  I  K  Q  E  H  E  T  S  W  H  Y  D  Q  D  H  P  Y  K  T  W  A  Y  H  G  S  Y  E  T

      8510      8520      8530      8540      8550      8560      8570      8580      8590      8600
CAAAACAGACTGGATCAGCATCATCCATGGTCAACGGAGTGGTCAGGCTGCTGACAAAACCTTGGGACGTCGTCCCCATGGTGACACAGATGGCAATGAC
  K  Q  T  G  S  A  S  S  M  V  N  G  V  V  R  L  L  T  K  P  W  D  V  V  P  M  V  T  Q  M  A  M  T

      8610      8620      8630      8640      8650      8660      8670      8680      8690      8700
AGACACGACTCCATTTGGACAACAGCGCGTTTTTAAAGAGAAAGTGGACACGAGAACCCAAGAACCGAAAGAAGGCACGAAGAAACTAATGAAAATAACA
 D  T  T  P  F  G  Q  Q  R  V  F  K  E  K  V  D  T  R  T  Q  E  P  K  E  G  T  K  K  L  M  K  I  T

      8710      8720      8730      8740      8750      8760      8770      8780      8790      8800
GCAGAGTGGCTTTGGAAAGAATTAGGGAAGAAAAAGACACCCAGGATGTGCACCAGAGAAGAATTCACAAGAAAGGTGAGAAGCAATGCAGCCTTGGGGG
A  E  W  L  W  K  E  L  G  K  K  K  T  P  R  M  C  T  R  E  E  F  T  R  K  V  R  S  N  A  A  L  G  A

      8810      8820      8830      8840      8850      8860      8870      8880      8890      8900
CCATATTCACTGATGAGAACAAGTGGAAGTCGGCACGTGAGGCTGTTGAAGATAGTAGGTTTTGGGAGCTGGTTGACAAGGAAAGGAATCTCCATCTTGA
  I  F  T  D  E  N  K  W  K  S  A  R  E  A  V  E  D  S  R  F  W  E  L  V  D  K  E  R  N  L  H  L  E

      8910      8920      8930      8940      8950      8960      8970      8980      8990      9000
AGGAAAGTGTGAAACATGTGTGTACAACATGATGGGAAAAAGAGAGAAGAAGCTAGGGGAATTCGGCAAGGCAAAAGGCAGCAGAGCCATATGGTACATG
 G  K  C  E  T  C  V  Y  N  M  M  G  K  R  E  K  K  L  G  E  F  G  K  A  K  G  S  R  A  I  W  Y  M

      9010      9020      9030      9040      9050      9060      9070      9080      9090      9100
TGGCTTGGAGCACGCTTCTTAGAGTTTGAAGCCCTAGGATTCTTAAATGAAGATCACTGGTTCTCCAGAGAGAACTCCCTGAGTGGAGTGGAAGGAGAAG
W  L  G  A  R  F  L  E  F  E  A  L  G  F  L  N  E  D  H  W  F  S  R  E  N  S  L  S  G  V  E  G  E  G

      9110      9120      9130      9140      9150      9160      9170      9180      9190      9200
GGCTGCACAAGCTAGGTTACATTCTAAGAGACGTGAGCAAGAAAGAGGGAGGAGCAATGTATGCCGATGACACCGCAGGATGGGATACAAGAATCACACT
  L  H  K  L  G  Y  I  L  R  D  V  S  K  K  E  G  G  A  M  Y  A  D  D  T  A  G  W  D  T  R  I  T  L

      9210      9220      9230      9240      9250      9260      9270      9280      9290      9300
AGAAGACCTAAAAAATGAAGAAATGGTAACAAACCACATGGAAGGAGAACACAAGAAACTAGCCGAGGCCATTTTCAAACTAACGTACCAAAACAAGGTG
 E  D  L  K  N  E  E  M  V  T  N  H  M  E  G  E  H  K  K  L  A  E  A  I  F  K  L  T  Y  Q  N  K  V

      9310      9320      9330      9340      9350      9360      9370      9380      9390      9400
GTGCGTGTGCAAAGACCAACACCAAGAGGCACAGTAATGGACATCATATCGAGAAGAGACCAAAGAGGTAGTGGACAAGTTGGCACCTATGGACTCAATA
V  R  V  Q  R  P  T  P  R  G  T  V  M  D  I  I  S  R  R  D  Q  R  G  S  G  Q  V  G  T  Y  G  L  N  T

      9410      9420      9430      9440      9450      9460      9470      9480      9490      9500
CTTTCACCAATATGGAAGCCCAACTAATCAGACAGATGGAGGGAGAAGGAGTCTTTAAAAGCATTCAGCACCTAACAATCACAGAAGAAATCGCTGTGCA
  F  T  N  M  E  A  Q  L  I  R  Q  M  E  G  E  G  V  F  K  S  I  Q  H  L  T  I  T  E  E  I  A  V  Q
      9510      9520      9530      9540      9550      9560      9570      9580      9590      9600
AAACTGGTTAGCAAGAGTGGGGCGCGAAAGGTTATCAAGAATGGCCATCAGTGGAGATGATTGTGTTGTGAAACCTTTAGATGACAGGTTCGCAAGCGCT
 N  W  L  A  R  V  G  R  E  R  L  S  R  M  A  I  S  G  D  D  C  V  V  K  P  L  D  D  R  F  A  S  A

      9610      9620      9630      9640      9650      9660      9670      9680      9690      9700
TTAACAGCTCTAAATGACATGGGAAAGATTAGGAAAGACATACAACAATGGGAACCTTCAAGAGGATGGAATGATTGGACACAAGTGCCCTTCTGTTCAC
L  T  A  L  N  D  M  G  K  I  R  K  D  I  Q  Q  W  E  P  S  R  G  W  N  D  W  T  Q  V  P  F  C  S  H

      9710      9720      9730      9740      9750      9760      9770      9780      9790      9800
ACCATTTCCATGAGTTAATCATGAAAGACGGTCGCGTACTCGTTGTTCCATGTAGAAACCAAGATGAACTGATTGGCAGAGCCCGAATCTCCCAAGGAGC
  H  F  H  E  L  I  M  K  D  G  R  V  L  V  V  P  C  R  N  Q  D  E  L  I  G  R  A  R  I  S  Q  G  A

      9810      9820      9830      9840      9850      9860      9870      9880      9890      9900
AGGGTGGTCTTTGCGGGAGACGGCCTGTTTGGGGAAGTCTTACGCCCAAATGTGGAGCTTGATGTACTTCCACAGACGCGACCTCAGGCTGGCGGCAAAT
 G  W  S  L  R  E  T  A  C  L  G  K  S  Y  A  Q  M  W  S  L  M  Y  F  H  R  R  D  L  R  L  A  A  N

      9910      9920      9930      9940      9950      9960      9970      9980      9990     10000
GCTATTTGCTCGGCAGTACCATCACATTGGGTTCCAACAAGTCGAACAACCTGGTCCATACATGCTAAACATGAATGGATGACAACGGAAGACATGCTGA
A  I  C  S  A  V  P  S  H  W  V  P  T  S  R  T  T  W  S  I  H  A  K  H  E  W  M  T  T  E  D  M  L  T

     10010     10020     10030     10040     10050     10060     10070     10080     10090     10100
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[0227]

[0228]

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CAGTCTGGAACAGGGTGTGGATTCAAGAAAACCCATGGATGGAAGACAAAACTCCAGTGGAATCATGGGAGGAAATCCCATACTTGGGGAAAAGAGAAGA
  V  W  N  R  V  W  I  Q  E  N  P  W  M  E  D  K  T  P  V  E  S  W  E  E  I  P  Y  L  G  K  R  E  D

     10110     10120     10130     10140     10150     10160     10170     10180     10190     10200
CCAATGGTGCGGCTCATTGATTGGGTTAACAAGCAGGGCCACCTGGGCAAAGAACATCCAAGCAGCAATAAATCAAGTTAGATCCCTTATAGGCAATGAA
 Q  W  C  G  S  L  I  G  L  T  S  R  A  T  W  A  K  N  I  Q  A  A  I  N  Q  V  R  S  L  I  G  N  E

                                                                                    >3'-非编码区
     10210     10220     10230     10240     10250     10260     10270     10280     10290     10300
GAATACACAGATTACATGCCATCCATGAAAAGATTCAGAAGAGAAGAGGAAGAAGCAGGAGTTCTGTGGTAGAAAGCAAAACTAACATGAAACAAGGCTA
E  Y  T  D  Y  M  P  S  M  K  R  F  R  R  E  E  E  E  A  G  V  L  W  *

     10310     10320     10330     10340     10350     10360     10370     10380     10390     10400
GAAGTCAGGTCGGATTAAGCCATAGTACGGAAAAAACTATGCTACCTGTGAGCCCCGTCCAAGGACGTTAAAAGAAGTCAGGCCATCATAAATGCCATAG

     10410     10420     10430     10440     10450     10460     10470     10480     10490     10500
CTTGAGTAAACTATGCAGCCTGTAGCTCCACCTGAGAAGGTGTAAAAAATCCGGGAGGCCACAAACCATGGAAGCTGTACGCATGGCGTAGTGGACTAGC

     10510     10520     10530     10540     10550     10560     10570     10580     10590     10600
GGTTAGAGGAGACCCCTCCCTTACAAATCGCAGCAACAATGGGGGCCCAAGGCGAGATGAAGCTGTAGTCTCGCTGGAAGGACTAGAGGTTAGAGGAGAC

     10610     10620     10630     10640     10650     10660     10670     10680     10690     10700
CCCCCCGAAACAAAAAACAGCATATTGACGCTGGGAAAGACCAGAGATCCTGCTGTCTCCTCAGCATCATTCCAGGCACAGAACGCCAGAAAATGGAATG

     10710     10720
GTGCTGTTGAATCAACAGGTTCT
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[0229] DENVax-2主代病毒种(MVS)

[0230] 本文提供重组病毒基因组的核苷酸序列及翻译蛋白质的推定氨基酸序列。改造的病毒基于D2 PDK-53病毒。标示出与野生型DEN-216681病毒(也是PDK-53的亲代病毒)不同的全部改造取代,以及于MVS中检测到的额外突变(从改造的cDNA克隆的改变)。

[0231] 基因组和蛋白质中包括的取代:

[0232] D2 PDK-53病毒骨架(从野生型D2 16681的改变):均为粗体

[0233] a.5'-非编码区(NCR)-57(nt-57C-至-T):主要减毒基因座(红色)

[0234] b.prM-29Asp-至-Val(nt-524A-至-T)

[0235] c.nt-2055C-至-T(E基因)沉默突变

[0236] d.NS1-53 Gly-至-Asp(nt-2579G-至-A):主要减毒基因座(红色)

[0237] e.NS2A-181Leu-至-Phe(nt-4018C-至-T)

[0238] f.NS3-250 Glu-至-Val(nt-5270A-至-T):主要减毒基因座(红色)

[0239] g.nt-5547(NS3基因)T-至-C沉默突变

[0240] h.NS4A-75Gly-至-Ala(nt-6599G-至-C)

[0241] *在疫苗病毒中的PDK-53的nt-8571C-至-T沉默突变未改造。

[0242] 改造的克隆标记(沉默突变):

[0243] a.nt-900T-至-C沉默突变:感染克隆标记

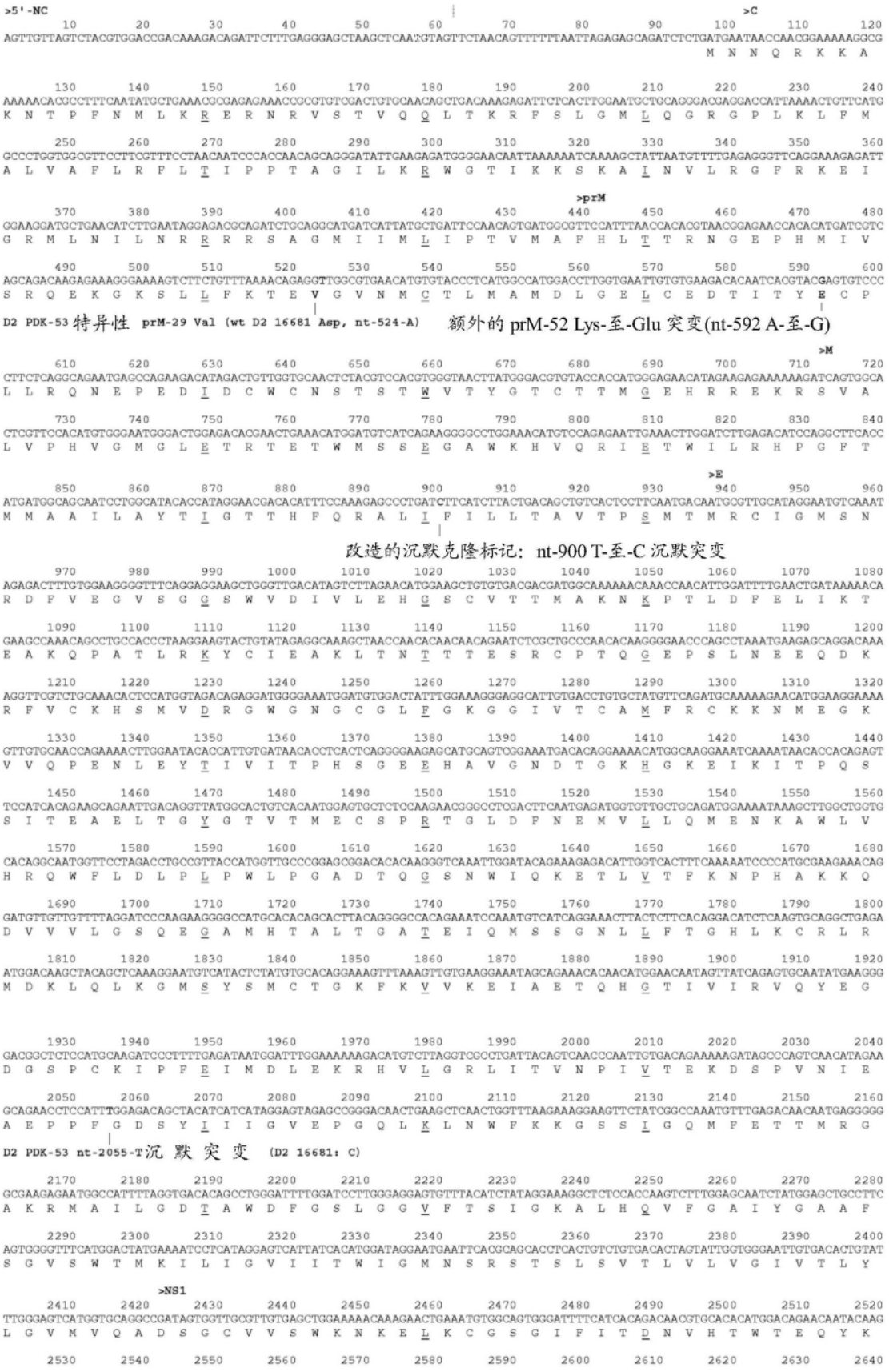
[0244] 在疫苗种中发现的额外取代(与原始克隆差异0.02%nt)

[0245] a.prM-52Lys-至-Glu(nt-592A-至-G),粗体

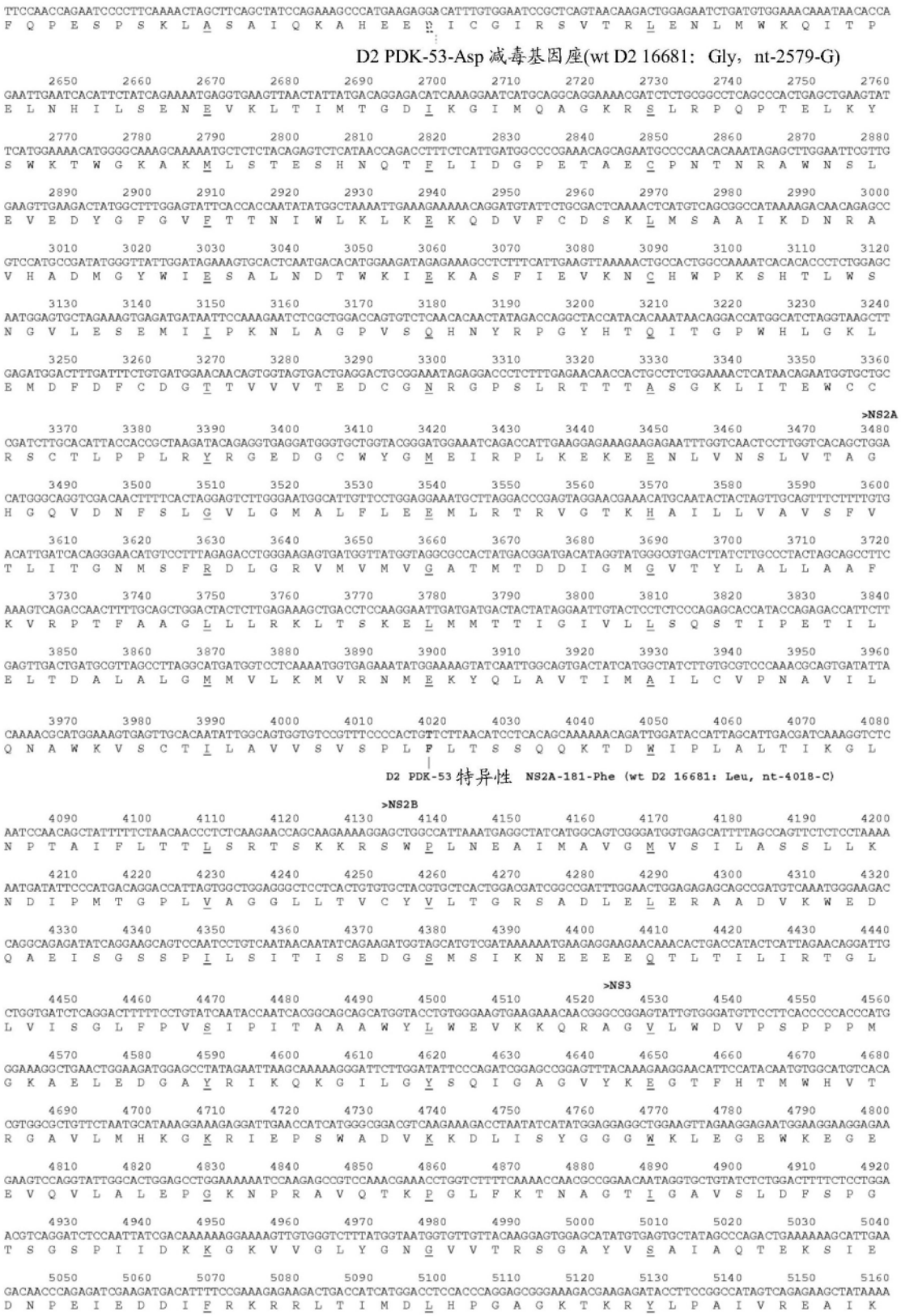
[0246] b.NS5-412 Ile-至-Val(nt-8803A-至-G),粗体

[0247] DENVax-2 MVS的核苷酸序列(SEQ ID NO:14)

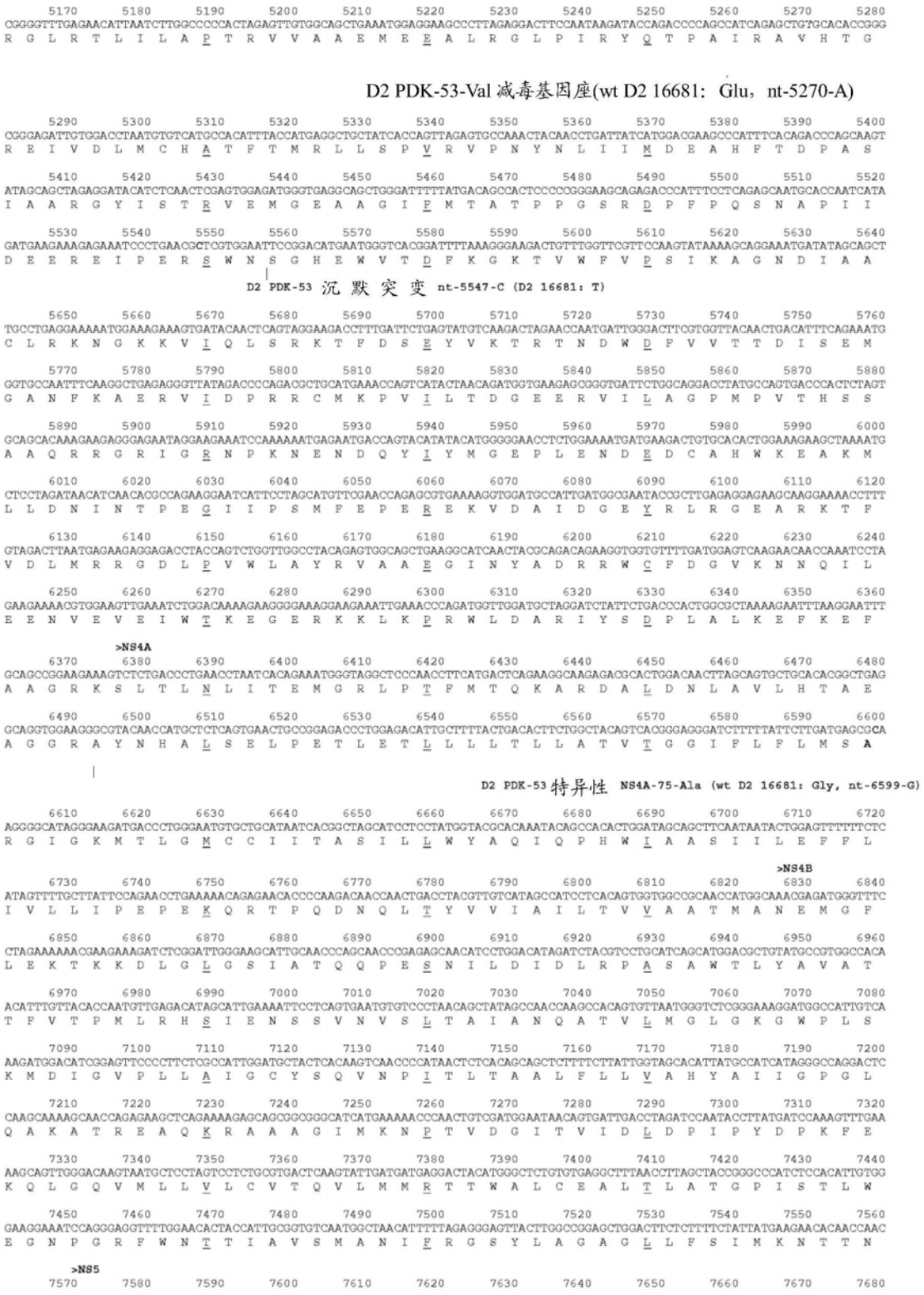
NCR-57-T，D2 PDK-53 减毒基因座(wt D2 16681: C)



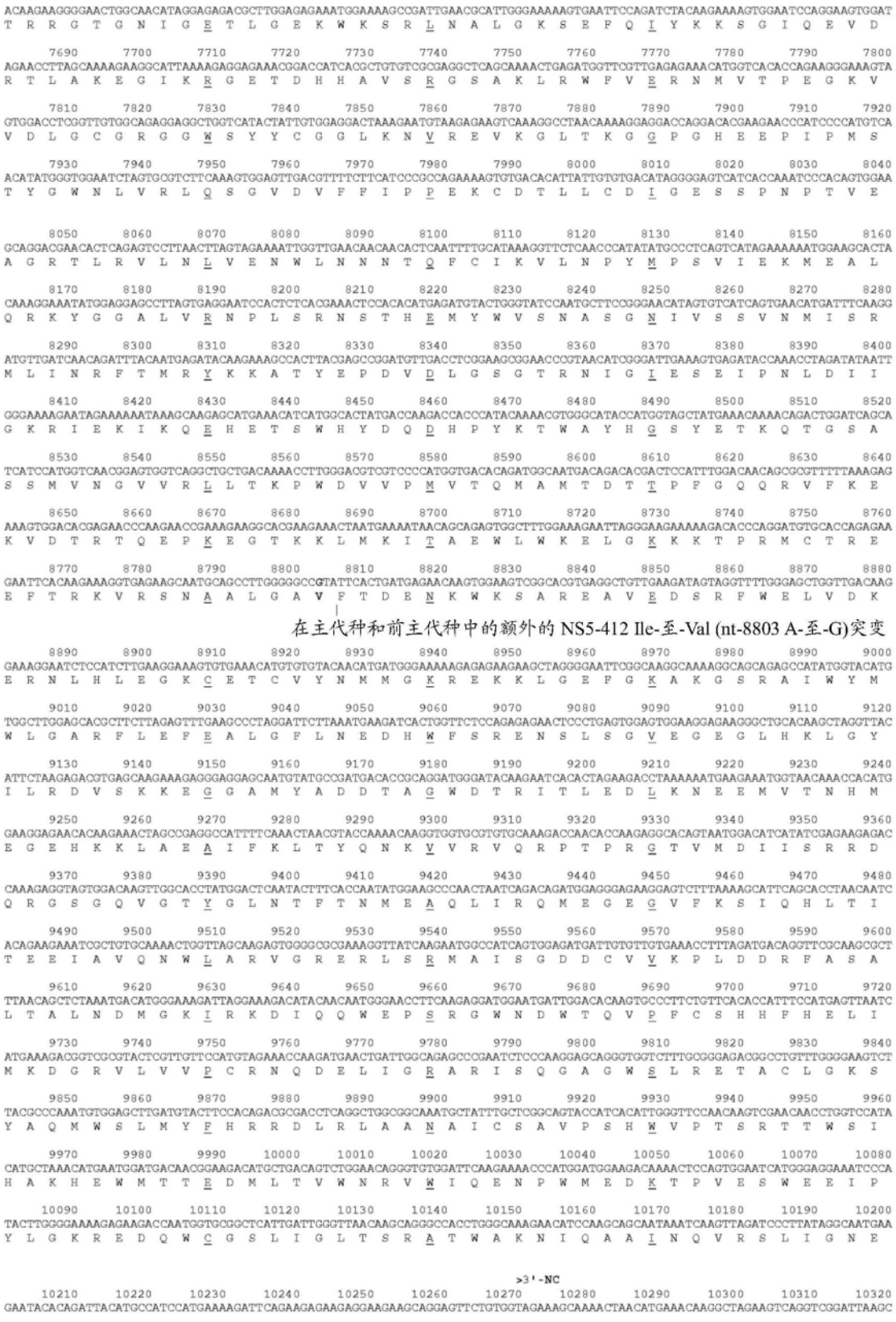
[0248]


D2 PDK-53-Asp 减毒基因座(wt D2 16681: Gly，nt-2579-G)
>NS2A
>NS2B
>NS3
D2 PDK-53 特异性 NS2A-181-Phe (wt D2 16681: Leu, nt-4018-C)

[0249]

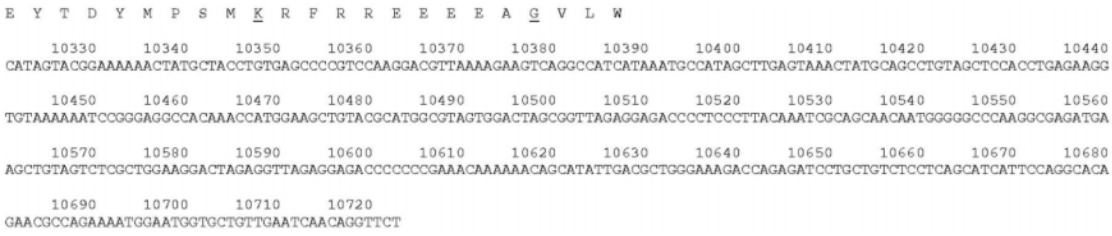

D2 PDK-53-Val 减毒基因座(wt D2 16681: Glu，nt-5270-A)
D2 PDK-53 沉 默 突 变 nt-5547-C (D2 16681: T)
>NS4A
D2 PDK-53 特异性 NS4A-75-Ala (wt D2 16681: Gly, nt-6599-G)
>NS4B
>NS5

[0250]



[0251]

[0252]



[0253] DENVax-3主代病毒种(MVS)

[0254] 本文提供嵌合式病毒基因组的核苷酸序列及翻译蛋白质的推定氨基酸序列。大部分prM-E基因(nt-457至-2373,下画线)为野生型(wt)DEN-3 16562病毒特异性的;剩余核苷酸序列为DEN-2PDK-53病毒特异性的。DEN-3病毒的E蛋白比DEN-2的E蛋白少两个氨基酸。因此,从NgoMIV起始的nt位置比原始DEN-2PDK-53nt位置少6nt。标记出与野生型病毒(DEN-3 16562或DEN-2 16681)不同的全部改造取代以及额外的突变(从改造cDNA克隆的改变)。

[0255] 基因组和蛋白质中包括的取代:

[0256] 接合位点:

[0257] a.MluI(nt 451-456):改造的沉默突变,nt-453A-至-G

[0258] b.NgoMIV(nt 2374-2379):改造的突变,nt-2375/2376TG-至-CC(导致E-480Val-至-Ala改变)

[0259] D2 PDK-53病毒骨架(从野生型D2 16681的改变):粗体

[0260] a.5'-非编码区(NCR)-57(nt-57C-至-T):主要减毒基因座(红色)

[0261] b.NS1-53 Gly-至-Asp(nt-2573G-至-A):主要减毒基因座(红色)

[0262] c.NS2A-181Leu-至-Phe(nt-4012C-至-T)

[0263] d.NS3-250 Glu-至-Val(nt-5264A-至-T):主要减毒基因座(红色)

[0264] e.nt-5541(NS3基因)T-至-C沉默突变

[0265] f.NS4A-75Gly-至-Ala(nt-6593G-至-C)

[0266] *PDK-53的nt-8565C-至-T沉默突变在疫苗病毒中未经改造

[0267] 在DEN-3prM-E中的改造突变(从野生型D3 16562的改变)

[0268] a.改造的nt-552C-至-T沉默突变:克隆标记

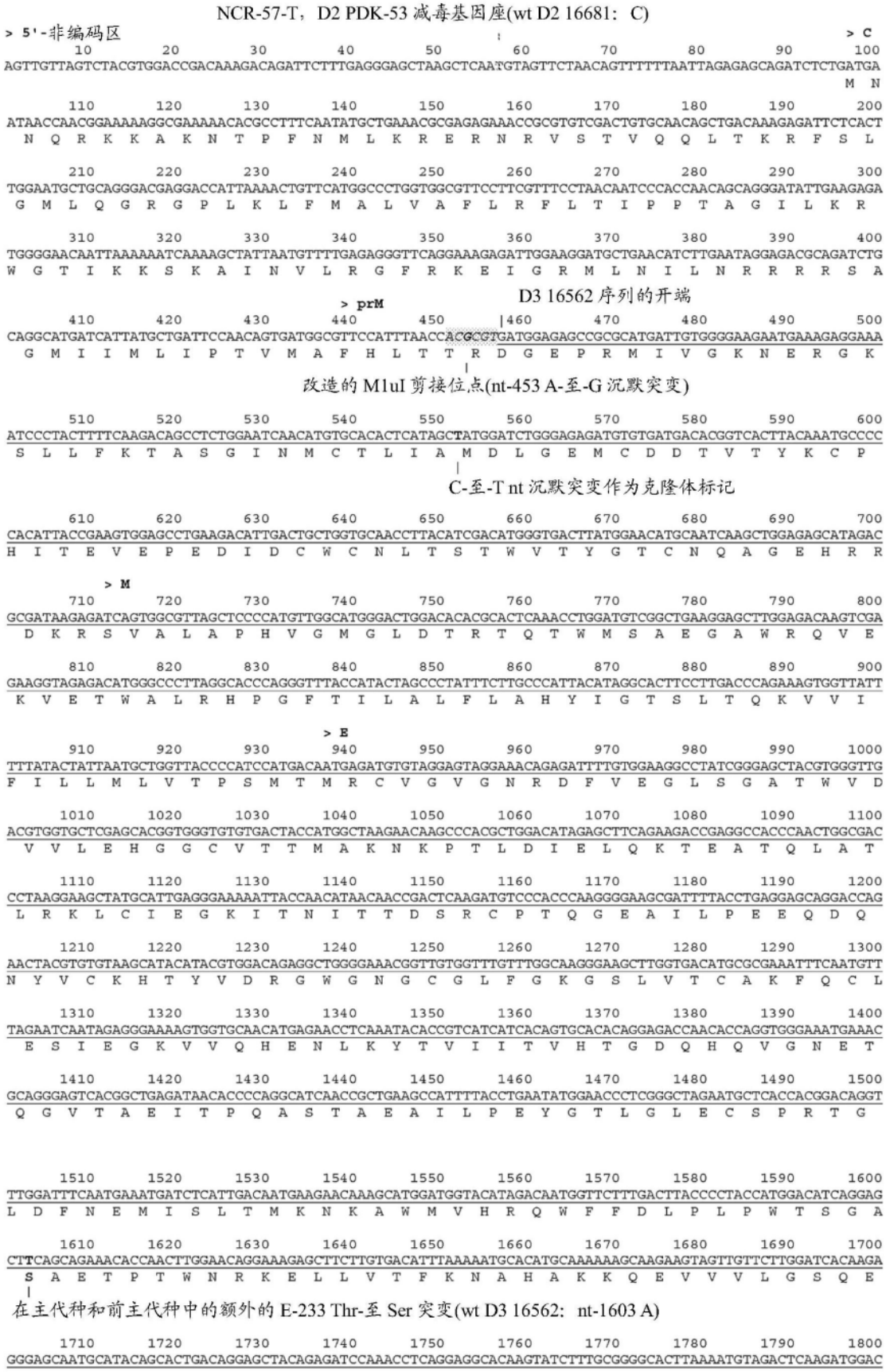
[0269] b.改造的E-345His-至-Leu(nt-1970A-至-T)用于在培养物中有效复制

[0270] 在疫苗种中发现的额外的取代(与原始克隆差异0.02%nt)

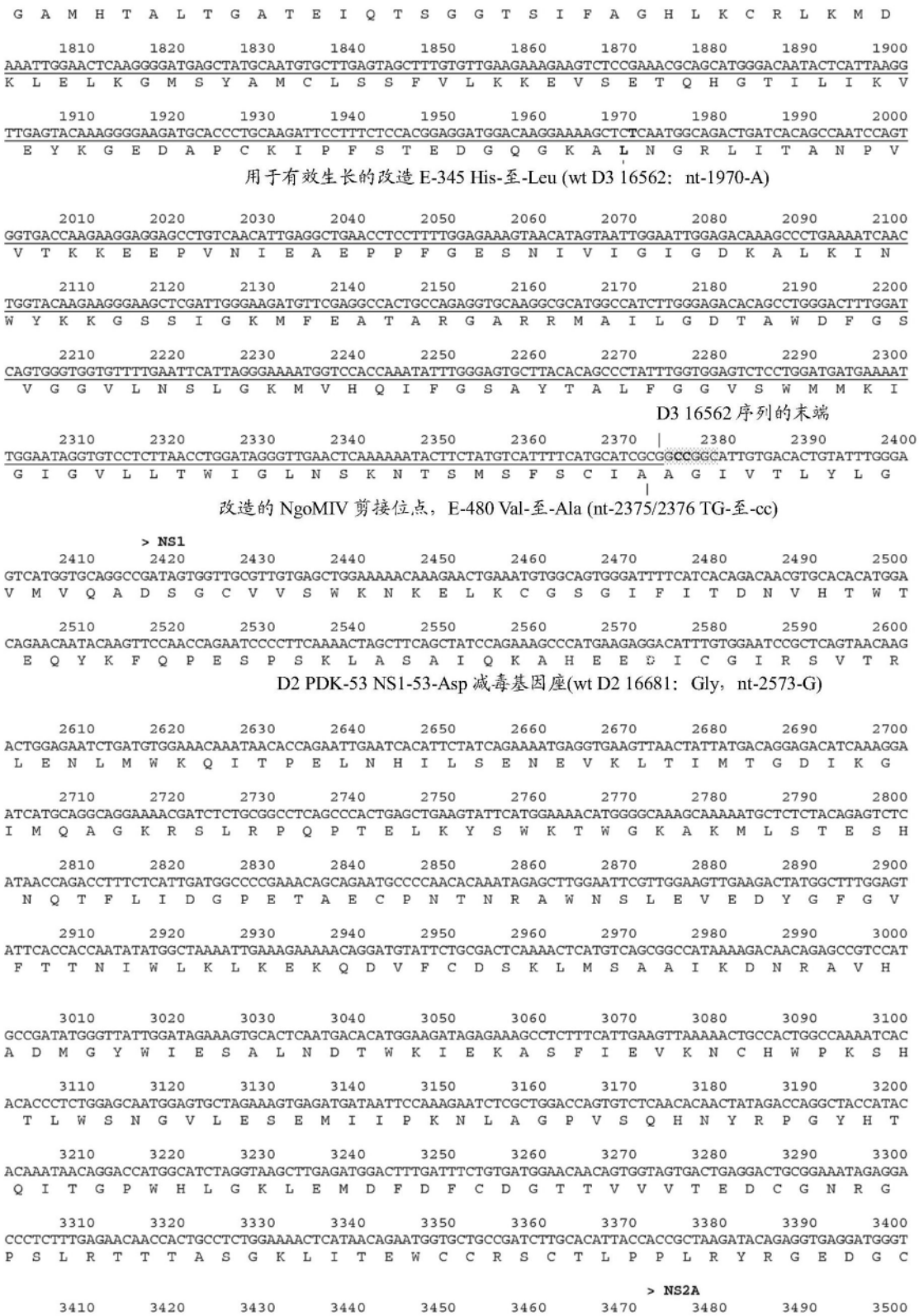
[0271] a.E-223Thr-至-Ser突变(nt1603 A-至-T,粗体)

[0272] b.nt-7620A-至-G沉默突变(粗体)

[0273] DENVax-3 MVS的核苷酸序列(SEQ ID NO:15)


NCR-57-T，D2 PDK-53 减毒基因座(wt D2 16681：C)
> 5'-非编码区
> C
M N
D3 16562 序列的开端
> prM
改造的 M1uI 剪接位点(nt-453 A-至-G 沉默突变)
C-至-T nt 沉默突变作为克隆体标记
> M
> E
在主代种和前主代种中的额外的 E-233 Thr-至 Ser 突变(wt D3 16562：nt-1603 A)

[0274]


用于有效生长的改造 E-345 His-至-Leu (wt D3 16562: nt-1970-A)
D3 16562 序列的末端
改造的 NgoMIV 剪接位点，E-480 Val-至-Ala (nt-2375/2376 TG-至-cc)
> NS1
D2 PDK-53 NS1-53-Asp 减毒基因座(wt D2 16681: Gly，nt-2573-G)
> NS2A

[0275]

```
GCTGGTACGGGATGGAAATCAGACCATTGAAGGAGAAAGAAGAGAATTTGGTCAACTCCTTGGTCACAGCTGGACATGGGCAGGTCGACAACTTTTCACT
  W  Y  G  M  E  I  R  P  L  K  E  K  E  E  N  L  V  N  S  L  V  T  A  G  H  G  Q  V  D  N  F  S  L

      3510       3520       3530       3540       3550       3560       3570       3580       3590       3600
AGGAGTCTTGGGAATGGCATTGTTCCTGGAGGAAATGCTTAGGACCCGAGTAGGAACGAAACATGCAATACTACTAGTTGCAGTTTCTTTTGTGACATTG
 G  V  L  G  M  A  L  F  L  E  E  M  L  R  T  R  V  G  T  K  H  A  I  L  L  V  A  V  S  F  V  T  L

      3610       3620       3630       3640       3650       3660       3670       3680       3690       3700
ATCACAGGGAACATGTCCTTTAGAGACCTGGGAAGAGTGATGGTTATGGTAGGCGCCACTATGACGGATGACATAGGTATGGGCGTGACTTATCTTGCCC
I  T  G  N  M  S  F  R  D  L  G  R  V  M  V  M  V  G  A  T  M  T  D  D  I  G  M  G  V  T  Y  L  A  L

      3710       3720       3730       3740       3750       3760       3770       3780       3790       3800
TACTAGCAGCCTTCAAAGTCAGACCAACTTTTGCAGCTGGACTACTCTTGAGAAAGCTGACCTCCAAGGAATTGATGATGACTACTATAGGAATTGTACT
  L  A  A  A  F  K  V  R  P  T  F  A  A  G  L  L  L  R  K  L  T  S  K  E  L  M  M  T  T  I  G  I  V  L

      3810       3820       3830       3840       3850       3860       3870       3880       3890       3900
CCTCTCCCAGAGCACCATACCAGAGACCATTCTTGAGTTGACTGATGCGTTAGCCTTAGGCATGATGGTCCTCAAAATGGTGAGAAATATGGAAAAGTAT
 L  S  Q  S  T  I  P  E  T  I  L  E  L  T  D  A  L  A  L  G  M  M  V  L  K  M  V  R  N  M  E  K  Y

      3910       3920       3930       3940       3950       3960       3970       3980       3990       4000
CAATTGGCAGTGACTATCATGGCTATCTTGTGCGTCCCAAACGCAGTGATATTACAAAACGCATGGAAAGTGAGTTGCACAATATTGGCAGTGGTGTCCG
Q  L  A  V  T  I  M  A  I  L  C  V  P  N  A  V  I  L  Q  N  A  W  K  V  S  C  T  I  L  A  V  V  S  V

      4010       4020       4030       4040       4050       4060       4070       4080       4090       4100
TTTCCCCACTGTTCTTAACATCCTCACAGCAAAAAACAGATTGGATACCATTAGCATTGACGATCAAAGGTCTCAATCCAACAGCTATTTTTCTAACAAC
  S  P  L  F  L  T  S  S  Q  Q  K  T  D  W  I  P  L  A  L  T  I  K  G  L  N  P  T  A  I  F  L  T  T
            |
      D2 PDK-53特 异 性 NS2A-181-Phe (wt D2 16681: Leu, nt-4012-C)

                          > NS2B
      4110       4120       4130       4140       4150       4160       4170       4180       4190       4200
CCTCTCAAGAACCAGCAAGAAAAGGAGCTGGCCATTAAATGAGGCTATCATGGCAGTCGGGATGGTGAGCATTTTAGCCAGTTCTCTCCTAAAAAATGAT
 L  S  R  T  S  K  K  R  S  W  P  L  N  E  A  I  M  A  V  G  M  V  S  I  L  A  S  S  L  L  K  N  D

      4210       4220       4230       4240       4250       4260       4270       4280       4290       4300
ATTCCCATGACAGGACCATTAGTGGCTGGAGGGCTCCTCACTGTGTGCTACGTGCTCACTGGACGATCGGCCGATTTGGAACTGGAGAGAGCAGCCGATG
I  P  M  T  G  P  L  V  A  G  G  L  L  T  V  C  Y  V  L  T  G  R  S  A  D  L  E  L  E  R  A  A  D  V

[0276]
      4310       4320       4330       4340       4350       4360       4370       4380       4390       4400
TCAAATGGGAAGACCAGGCAGAGATATCAGGAAGCAGTCCAATCCTGTCAATAACAATATCAGAAGATGGTAGCATGTCGATAAAAAATGAAGAGGAAGA
  K  W  E  D  Q  A  E  I  S  G  S  S  P  I  L  S  I  T  I  S  E  D  G  S  M  S  I  K  N  E  E  E  E

      4410       4420       4430       4440       4450       4460       4470       4480       4490       4500
ACAAACACTGACCATACTCATTAGAACAGGATTGCTGGTGATCTCAGGACTTTTTCCTGTATCAATACCAATCACGGCAGCAGCATGGTACCTGTGGGAA
 Q  T  L  T  I  L  I  R  T  G  L  L  V  I  S  G  L  F  P  V  S  I  P  I  T  A  A  A  W  Y  L  W  E

                    > NS3
      4510       4520       4530       4540       4550       4560       4570       4580       4590       4600
GTGAAGAAACAACGGGCCGGAGTATTGTGGGATGTTCCTTCACCCCCACCCATGGGAAAGGCTGAACTGGAAGATGGAGCCTATAGAATTAAGCAAAAAG
V  K  K  Q  R  A  G  V  L  W  D  V  P  S  P  P  P  M  G  K  A  E  L  E  D  G  A  Y  R  I  K  Q  K  G


      4610       4620       4630       4640       4650       4660       4670       4680       4690       4700
GGATTCTTGGATATTCCCAGATCGGAGCCGGAGTTTACAAAGAAGGAACATTCCATACAATGTGGCATGTCACACGTGGCGCTGTTCTAATGCATAAAGG
  I  L  G  Y  S  Q  I  G  A  G  V  Y  K  E  G  T  F  H  T  M  W  H  V  T  R  G  A  V  L  M  H  K  G

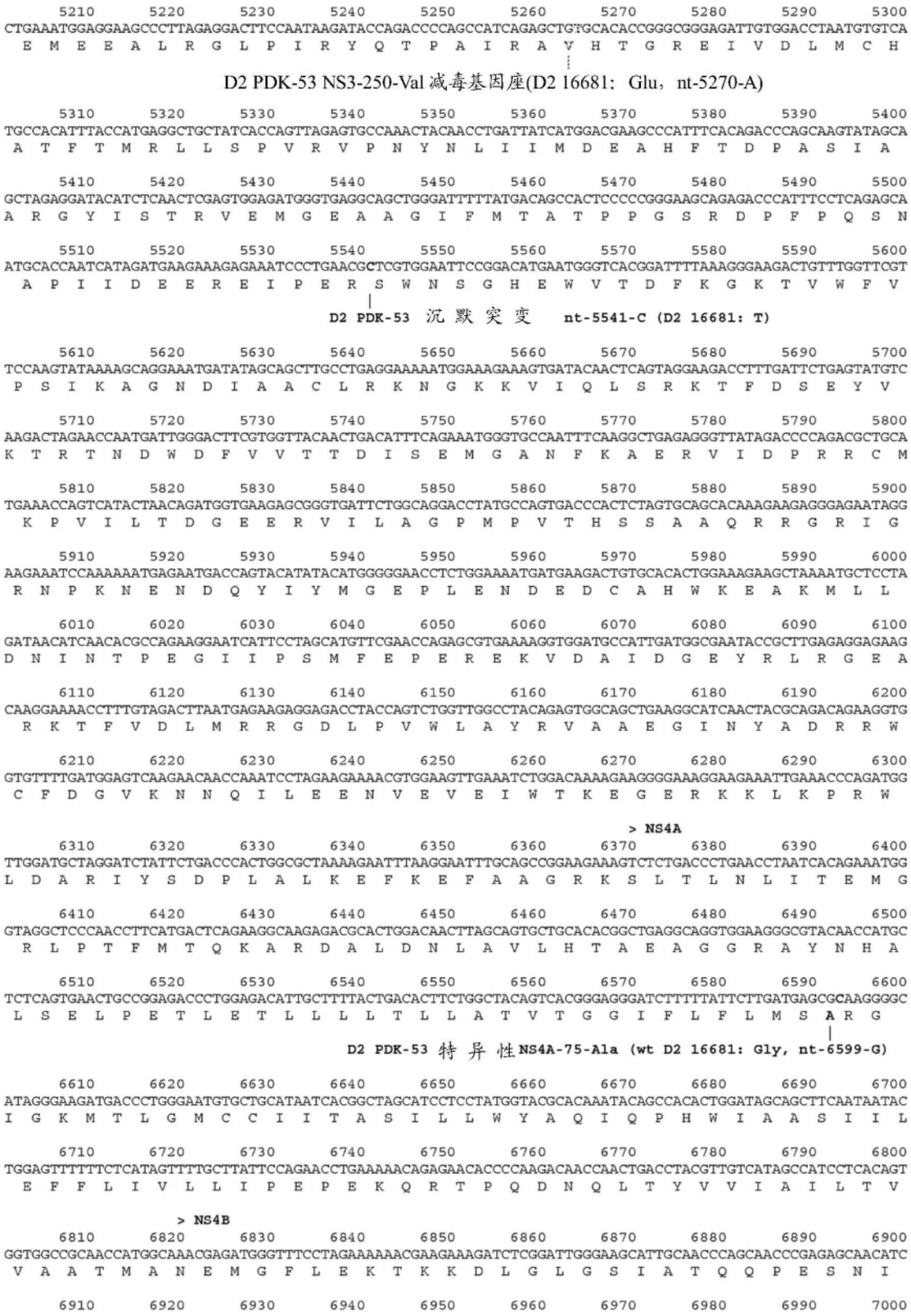
      4710       4720       4730       4740       4750       4760       4770       4780       4790       4800
AAAGAGGATTGAACCATCATGGGCGGACGTCAAGAAAGACCTAATATCATATGGAGGAGGCTGGAAGTTAGAAGGAGAATGGAAGGAAGGAGAAGAAGTC
 K  R  I  E  P  S  W  A  D  V  K  K  D  L  I  S  Y  G  G  G  W  K  L  E  G  E  W  K  E  G  E  E  V

      4810       4820       4830       4840       4850       4860       4870       4880       4890       4900
CAGGTATTGGCACTGGAGCCTGGAAAAAATCCAAGAGCCGTCCAAACGAAACCTGGTCTTTTCAAAACCAACGCCGGAACAATAGGTGCTGTATCTCTGG
Q  V  L  A  L  E  P  G  K  N  P  R  A  V  Q  T  K  P  G  L  F  K  T  N  A  G  T  I  G  A  V  S  L  D

      4910       4920       4930       4940       4950       4960       4970       4980       4990       5000
ACTTTTCTCCTGGAACGTCAGGATCTCCAATTATCGACAAAAAAGGAAAAGTTGTGGGTCTTTATGGTAATGGTGTTGTTACAAGGAGTGGAGCATATGT
  F  S  P  G  T  S  G  S  P  I  I  D  K  K  G  K  V  V  G  L  Y  G  N  G  V  V  T  R  S  G  A  Y  V

      5010       5020       5030       5040       5050       5060       5070       5080       5090       5100
GAGTGCTATAGCCCAGACTGAAAAAAGCATTGAAGACAACCCAGAGATCGAAGATGACATTTTCCGAAAGAGAAGACTGACCATCATGGACCTCCACCCA
 S  A  I  A  Q  T  E  K  S  I  E  D  N  P  E  I  E  D  D  I  F  R  K  R  R  L  T  I  M  D  L  H  P

      5110       5120       5130       5140       5150       5160       5170       5180       5190       5200
GGAGCGGGAAAGACGAAGAGATACCTTCCGGCCATAGTCAGAGAAGCTATAAAACGGGGTTTGAGAACATTAATCTTGGCCCCCACTAGAGTTGTGGCAG
G  A  G  K  T  K  R  Y  L  P  A  I  V  R  E  A  I  K  R  G  L  R  T  L  I  L  A  P  T  R  V  V  A  A
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D2 PDK-53 NS3-250-Val 减毒基因座(D2 16681: Glu，nt-5270-A)
D2 PDK-53 沉 默 突 变 nt-5541-C (D2 16681: T)
> NS4A
D2 PDK-53 特 异 性NS4A-75-Ala (wt D2 16681: Gly, nt-6599-G)
> NS4B

[0277]

```
CTGGACATAGATCTACGTCCTGCATCAGCATGGACGCTGTATGCCGTGGCCACAACATTTGTTACACCAATGTTGAGACATAGCATTGAAAATTCCTCAG
L  D  I  D  L  R  P  A  S  A  W  T  L  Y  A  V  A  T  T  F  V  T  P  M  L  R  H  S  I  E  N  S  S  V

      7010       7020       7030       7040       7050       7060       7070       7080       7090       7100
TGAATGTGTCCCTAACAGCTATAGCCAACCAAGCCACAGTGTTAATGGGTCTCGGGAAAGGATGGCCATTGTCAAAGATGGACATCGGAGTTCCCCTTCT
  N  V  S  L  T  A  I  A  N  Q  A  T  V  L  M  G  L  G  K  G  W  P  L  S  K  M  D  I  G  V  P  L  L

      7110       7120       7130       7140       7150       7160       7170       7180       7190       7200
CGCCATTGGATGCTACTCACAAGTCAACCCCATAACTCTCACAGCAGCTCTTTTCTTATTGGTAGCACATTATGCCATCATAGGGCCAGGACTCCAAGCA
 A  I  G  C  Y  S  Q  V  N  P  I  T  L  T  A  A  L  F  L  L  V  A  H  Y  A  I  I  G  P  G  L  Q  A

      7210       7220       7230       7240       7250       7260       7270       7280       7290       7300
AAAGCAACCAGAGAAGCTCAGAAAAGAGCAGCGGCGGGCATCATGAAAAACCCAACTGTCGATGGAATAACAGTGATTGACCTAGATCCAATACCTTATG
K  A  T  R  E  A  Q  K  R  A  A  A  G  I  M  K  N  P  T  V  D  G  I  T  V  I  D  L  D  P  I  P  Y  D

      7310       7320       7330       7340       7350       7360       7370       7380       7390       7400
ATCCAAAGTTTGAAAAGCAGTTGGGACAAGTAATGCTCCTAGTCCTCTGCGTGACTCAAGTATTGATGATGAGGACTACATGGGCTCTGTGTGAGGCTTT
  P  K  F  E  K  Q  L  G  Q  V  M  L  L  V  L  C  V  T  Q  V  L  M  M  R  T  T  W  A  L  C  E  A  L

      7410       7420       7430       7440       7450       7460       7470       7480       7490       7500
AACCTTAGCTACCGGGCCCATCTCCACATTGTGGGAAGGAAATCCAGGGAGGTTTTGGAACACTACCATTGCGGTGTCAATGGCTAACATTTTTAGAGGG
 T  L  A  T  G  P  I  S  T  L  W  E  G  N  P  G  R  F  W  N  T  T  I  A  V  S  M  A  N  I  F  R  G

                                                                                  > NS5
      7510       7520       7530       7540       7550       7560       7570       7580       7590       7600
AGTTACTTGGCCGGAGCTGGACTTCTCTTTTCTATTATGAAGAACACAACCAACACAAGAAGGGGAACTGGCAACATAGGAGAGACGCTTGGAGAGAAAT
S  Y  L  A  G  A  G  L  L  F  S  I  M  K  N  T  T  N  T  R  R  G  T  G  N  I  G  E  T  L  G  E  K  W

      7610       7620       7630       7640       7650       7660       7670       7680       7690       7700
GGAAAAGCCGATTGAACGCGTTGGGAAAAAGTGAATTCCAGATCTACAAGAAAAGTGGAATCCAGGAAGTGGATAGAACCTTAGCAAAAGAAGGCATTAA
  K  S  R  L  N  A  L  G  K  S  E  F  Q  I  Y  K  K  S  G  I  Q  E  V  D  R  T  L  A  K  E  G  I  K
                  |
                  在主代种和前主代种中的额外的 nt-7260 A-至-G 沉默突变

      7710       7720       7730       7740       7750       7760       7770       7780       7790       7800
AAGAGGAGAAACGGACCATCACGCTGTGTCGCGAGGCTCAGCAAAACTGAGATGGTTCGTTGAGAGAAACATGGTCACACCAGAAGGGAAAGTAGTGGAC
 R  G  E  T  D  H  H  A  V  S  R  G  S  A  K  L  R  W  F  V  E  R  N  M  V  T  P  E  G  K  V  V  D

[0278]
      7810       7820       7830       7840       7850       7860       7870       7880       7890       7900
CTCGGTTGTGGCAGAGGAGGCTGGTCATACTATTGTGGAGGACTAAAGAATGTAAGAGAAGTCAAAGGCCTAACAAAAGGAGGACCAGGACACGAAGAAC
L  G  C  G  R  G  G  W  S  Y  Y  C  G  G  L  K  N  V  R  E  V  K  G  L  T  K  G  G  P  G  H  E  E  P

      7910       7920       7930       7940       7950       7960       7970       7980       7990       8000
CCATCCCCATGTCAACATATGGGTGGAATCTAGTGCGTCTTCAAAGTGGAGTTGACGTTTTCTTCATCCCGCCAGAAAAGTGTGACACATTATTGTGTGA
  I  P  M  S  T  Y  G  W  N  L  V  R  L  Q  S  G  V  D  V  F  F  I  P  P  E  K  C  D  T  L  L  C  D

      8010       8020       8030       8040       8050       8060       8070       8080       8090       8100
CATAGGGGAGTCATCACCAAATCCCACAGTGGAAGCAGGACGAACACTCAGAGTCCTTAACTTAGTAGAAAATTGGTTGAACAACAACACTCAATTTTGC
 I  G  E  S  S  P  N  P  T  V  E  A  G  R  T  L  R  V  L  N  L  V  E  N  W  L  N  N  N  T  Q  F  C

      8110       8120       8130       8140       8150       8160       8170       8180       8190       8200
ATAAAGGTTCTCAACCCATATATGCCCTCAGTCATAGAAAAAATGGAAGCACTACAAAGGAAATATGGAGGAGCCTTAGTGAGGAATCCACTCTCACGAA
I  K  V  L  N  P  Y  M  P  S  V  I  E  K  M  E  A  L  Q  R  K  Y  G  G  A  L  V  R  N  P  L  S  R  N

      8210       8220       8230       8240       8250       8260       8270       8280       8290       8300
ACTCCACACATGAGATGTACTGGGTATCCAATGCTTCCGGGAACATAGTGTCATCAGTGAACATGATTTCAAGGATGTTGATCAACAGATTTACAATGAG
  S  T  H  E  M  Y  W  V  S  N  A  S  G  N  I  V  S  S  V  N  M  I  S  R  M  L  I  N  R  F  T  M  R

      8310       8320       8330       8340       8350       8360       8370       8380       8390       8400
ATACAAGAAAGCCACTTACGAGCCGGATGTTGACCTCGGAAGCGGAACCCGTAACATCGGGATTGAAAGTGAGATACCAAACCTAGATATAATTGGGAAA
 Y  K  K  A  T  Y  E  P  D  V  D  L  G  S  G  T  R  N  I  G  I  E  S  E  I  P  N  L  D  I  I  G  K

      8410       8420       8430       8440       8450       8460       8470       8480       8490       8500
AGAATAGAAAAAATAAAGCAAGAGCATGAAACATCATGGCACTATGACCAAGACCACCCATACAAAACGTGGGCATACCATGGTAGCTATGAAACAAAAC
R  I  E  K  I  K  Q  E  H  E  T  S  W  H  Y  D  Q  D  H  P  Y  K  T  W  A  Y  H  G  S  Y  E  T  K  Q

      8510       8520       8530       8540       8550       8560       8570       8580       8590       8600
AGACTGGATCAGCATCATCCATGGTCAACGGAGTGGTCAGGCTGCTGACAAAACCTTGGGACGTCGTCCCCATGGTGACACAGATGGCAATGACAGACAC
  T  G  S  A  S  S  M  V  N  G  V  V  R  L  L  T  K  P  W  D  V  V  P  M  V  T  Q  M  A  M  T  D  T

      8610       8620       8630       8640       8650       8660       8670       8680       8690       8700
GACTCCATTTGGACAACAGCGCGTTTTTAAAGAGAAAGTGGACACGAGAACCCAAGAACCGAAAGAAGGCACGAAGAAACTAATGAAAATAACAGCAGAG
 T  P  F  G  Q  Q  R  V  F  K  E  K  V  D  T  R  T  Q  E  P  K  E  G  T  K  K  L  M  K  I  T  A  E

      8710       8720       8730       8740       8750       8760       8770       8780       8790       8800
TGGCTTTGGAAAGAATTAGGGAAGAAAAAGACACCCAGGATGTGCACCAGAGAAGAATTCACAAGAAAGGTGAGAAGCAATGCAGCCTTGGGGGCCATAT
W  L  W  K  E  L  G  K  K  K  T  P  R  M  C  T  R  E  E  F  T  R  K  V  R  S  N  A  A  L  G  A  I  F
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      8810      8820      8830      8840      8850      8860      8870      8880      8890      8900
TCACTGATGAGAACAAGTGGAAGTCGGCACGTGAGGCTGTTGAAGATAGTAGGTTTTGGGAGCTGGTTGACAAGGAAAGGAATCTCCATCTTGAAGGAAA
  T  D  E  N  K  W  K  S  A  R  E  A  V  E  D  S  R  F  W  E  L  V  D  K  E  R  N  L  H  L  E  G  K

      8910      8920      8930      8940      8950      8960      8970      8980      8990      9000
GTGTGAAACATGTGTGTACAACATGATGGGAAAAAGAGAGAAGAAGCTAGGGGAATTCGGCAAGGCAAAAGGCAGCAGAGCCATATGGTACATGTGGCTT
  C  E  T  C  V  Y  N  M  M  G  K  R  E  K  K  L  G  E  F  G  K  A  K  G  S  R  A  I  W  Y  M  W  L

      9010      9020      9030      9040      9050      9060      9070      9080      9090      9100
GGAGCACGCTTCTTAGAGTTTGAAGCCCTAGGATTCTTAAATGAAGATCACTGGTTCTCCAGAGAGAACTCCCTGAGTGGAGTGGAAGGAGAAGGGCTGC
  G  A  R  F  L  E  F  E  A  L  G  F  L  N  E  D  H  W  F  S  R  E  N  S  L  S  G  V  E  G  E  G  L  H

      9110      9120      9130      9140      9150      9160      9170      9180      9190      9200
ACAAGCTAGGTTACATTCTAAGAGACGTGAGCAAGAAAGAGGGAGGAGCAATGTATGCCGATGACACCGCAGGATGGGATACAAGAATCACACTAGAAGA
  K  L  G  Y  I  L  R  D  V  S  K  K  E  G  G  A  M  Y  A  D  D  T  A  G  W  D  T  R  I  T  L  E  D

      9210      9220      9230      9240      9250      9260      9270      9280      9290      9300
CCTAAAAAATGAAGAAATGGTAACAAACCACATGGAAGGAGAACACAAGAAACTAGCCGAGGCCATTTTCAAACTAACGTACCAAAACAAGGTGGTGCGT
  L  K  N  E  E  M  V  T  N  H  M  E  G  E  H  K  K  L  A  E  A  I  F  K  L  T  Y  Q  N  K  V  V  R

      9310      9320      9330      9340      9350      9360      9370      9380      9390      9400
GTGCAAAGACCAACACCAAGAGGCACAGTAATGGACATCATATCGAGAAGAGACCAAAGAGGTAGTGGACAAGTTGGCACCTATGGACTCAATACTTTCA
V  Q  R  P  T  P  R  G  T  V  M  D  I  I  S  R  R  D  Q  R  G  S  G  Q  V  G  T  Y  G  L  N  T  F  T

      9410      9420      9430      9440      9450      9460      9470      9480      9490      9500
CCAATATGGAAGCCCAACTAATCAGACAGATGGAGGGAGAAGGAGTCTTTAAAAGCATTCAGCACCTAACAATCACAGAAGAAATCGCTGTGCAAAACTG
  N  M  E  A  Q  L  I  R  Q  M  E  G  E  G  V  F  K  S  I  Q  H  L  T  I  T  E  E  I  A  V  Q  N  W

      9510      9520      9530      9540      9550      9560      9570      9580      9590      9600
GTTAGCAAGAGTGGGGCGCGAAAGGTTATCAAGAATGGCCATCAGTGGAGATGATTGTGTTGTGAAACCTTTAGATGACAGGTTCGCAAGCGCTTTAACA
  L  A  R  V  G  R  E  R  L  S  R  M  A  I  S  G  D  D  C  V  V  K  P  L  D  D  R  F  A  S  A  L  T
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[0279]

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      9610      9620      9630      9640      9650      9660      9670      9680      9690      9700
GCTCTAAATGACATGGGAAAGATTAGGAAAGACATACAACAATGGGAACCTTCAAGAGGATGGAATGATTGGACACAAGTGCCCTTCTGTTCACACCATT
A  L  N  D  M  G  K  I  R  K  D  I  Q  Q  W  E  P  S  R  G  W  N  D  W  T  Q  V  P  F  C  S  H  H  F

      9710      9720      9730      9740      9750      9760      9770      9780      9790      9800
TCCATGAGTTAATCATGAAAGACGGTCGCGTACTCGTTGTTCCATGTAGAAACCAAGATGAACTGATTGGCAGAGCCCGAATCTCCCAAGGAGCAGGGTG
  H  E  L  I  M  K  D  G  R  V  L  V  V  P  C  R  N  Q  D  E  L  I  G  R  A  R  I  S  Q  G  A  G  W

      9810      9820      9830      9840      9850      9860      9870      9880      9890      9900
GTCTTTGCGGGAGACGGCCTGTTTGGGGAAGTCTTACGCCCAAATGTGGAGCTTGATGTACTTCCACAGACGCGACCTCAGGCTGGCGGCAAATGCTATT
  S  L  R  E  T  A  C  L  G  K  S  Y  A  Q  M  W  S  L  M  Y  F  H  R  R  D  L  R  L  A  A  N  A  I

      9910      9920      9930      9940      9950      9960      9970      9980      9990     10000
TGCTCGGCAGTACCATCACATTGGGTTCCAACAAGTCGAACAACCTGGTCCATACATGCTAAACATGAATGGATGACAACGGAAGACATGCTGACAGTCT
C  S  A  V  P  S  H  W  V  P  T  S  R  T  T  W  S  I  H  A  K  H  E  W  M  T  T  E  D  M  L  T  V  W

     10010     10020     10030     10040     10050     10060     10070     10080     10090     10100
GGAACAGGGTGTGGATTCAAGAAAACCCATGGATGGAAGACAAAACTCCAGTGGAATCATGGGAGGAAATCCCATACTTGGGGAAAAGAGAAGACCAATG
  N  R  V  W  I  Q  E  N  P  W  M  E  D  K  T  P  V  E  S  W  E  E  I  P  Y  L  G  K  R  E  D  Q  W

     10110     10120     10130     10140     10150     10160     10170     10180     10190     10200
GTGCGGCTCATTGATTGGGTTAACAAGCAGGGCCACCTGGGCAAAGAACATCCAAGCAGCAATAAATCAAGTTAGATCCCTTATAGGCAATGAAGAATAC
  C  G  S  L  I  G  L  T  S  R  A  T  W  A  K  N  I  Q  A  A  I  N  Q  V  R  S  L  I  G  N  E  E  Y

                                                                    > 3'-非编码区
     10210     10220     10230     10240     10250     10260     10270     10280     10290     10300
ACAGATTACATGCCATCCATGAAAAGATTCAGAAGAGAAGAGGAAGAAGCAGGAGTTCTGTGGTAGAAAGCAAAACTAACATGAAACAAGGCTAGAAGTC
T  D  Y  M  P  S  M  K  R  F  R  R  E  E  E  E  A  G  V  L  W  *

     10310     10320     10330     10340     10350     10360     10370     10380     10390     10400
AGGTCGGATTAAGCCATAGTACGGAAAAAACTATGCTACCTGTGAGCCCCGTCCAAGGACGTTAAAAGAAGTCAGGCCATCATAAATGCCATAGCTTGAG

     10410     10420     10430     10440     10450     10460     10470     10480     10490     10500
TAAACTATGCAGCCTGTAGCTCCACCTGAGAAGGTGTAAAAAATCCGGGAGGCCACAAACCATGGAAGCTGTACGCATGGCGTAGTGGACTAGCGGTTAG

     10510     10520     10530     10540     10550     10560     10570     10580     10590     10600
AGGAGACCCCTCCCTTACAAATCGCAGCAACAATGGGGGCCCAAGGCGAGATGAAGCTGTAGTCTCGCTGGAAGGACTAGAGGTTAGAGGAGACCCCCCC

     10610     10620     10630     10640     10650     10660     10670     10680     10690     10700
GAAACAAAAAACAGCATATTGACGCTGGGAAAGACCAGAGATCCTGCTGTCTCCTCAGCATCATTCCAGGCACAGAACGCCAGAAAATGGAATGGTGCTG

     10710
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[0280] DENVax-4主代病毒种(MVS)

[0281] 嵌合式病毒基因组的核苷酸序列及翻译蛋白质的推定氨基酸序列。大部分prM-E基因(nt-457至-2379,下画线)为野生型(wt)DEN-41036病毒特异性的;剩余核苷酸序列为DEN-2PDK-53病毒特异性的。标记出与野生型病毒(DEN-3 16562或DEN-2 16681)不同的全部改造取代,以及额外的突变(从改造cDNA克隆的改变)。

[0282] 基因组和蛋白质中包括的取代:

[0283] 接合位点:

[0284] a.MluI(nt 451-456):改造的沉默突变,nt-453A-至-G

[0285] b.NgoMIV(nt 2380-2385):改造的突变,nt-2381/2382TG-至-CC(导致E-482Val-至-Ala改变)

[0286] D2 PDK-53病毒骨架(从野生型D2 16681的改变)

[0287] a.5'-非编码区(NCR)-57(nt-57C-至-T):主要减毒基因座(红色)

[0288] b.NS1-53 Gly-至-Asp(nt-2579G-至-A):主要减毒基因座(红色)

[0289] c.NS2A-181Leu-至-Phe(nt-4018C-至-T,粗体)

[0290] d.NS3-250 Glu-至-Val(nt-5270A-至-T):主要减毒基因座(红色)

[0291] e.nt-5547(NS3基因)T-至-C沉默突变(粗体)

[0292] f.NS4A-75Gly-至-Ala(nt-6599G-至-C,粗体)

[0293] *PDK-53的nt-8571C-至-T沉默突变在疫苗病毒中未经改造

[0294] 在cDNA克隆中的改造的取代

[0295] a.改造的C-100Arg-至-Ser(nt-396A-至-C):可改善于培养物中的病毒复制

[0296] b.改造的nt-1401A-至-G沉默突变

[0297] c.改造的E-364Ala-至-Val(nt-2027C-至-T):可改善于培养物中的病毒复制

[0298] d.改造的E-447Met-至-Leu(nt-2275A-至-C):可改善于培养物中的病毒复制

[0299] 在疫苗种中发现的额外的取代(与原始克隆差异0.06%nt)

[0300] a.nt-225(C基因)A-至-T沉默突变(粗体)

[0301] b.NS2A-66Asp-至-Gly(nt-3674A-至-G)突变(粗体)

[0302] c.NS2A-99Lys-至-Lys/Arg混合物(nt-3773A-至-A/G混合,粗体)

[0303] d.nt-5391C-至-T(NS3基因)沉默突变(粗体)

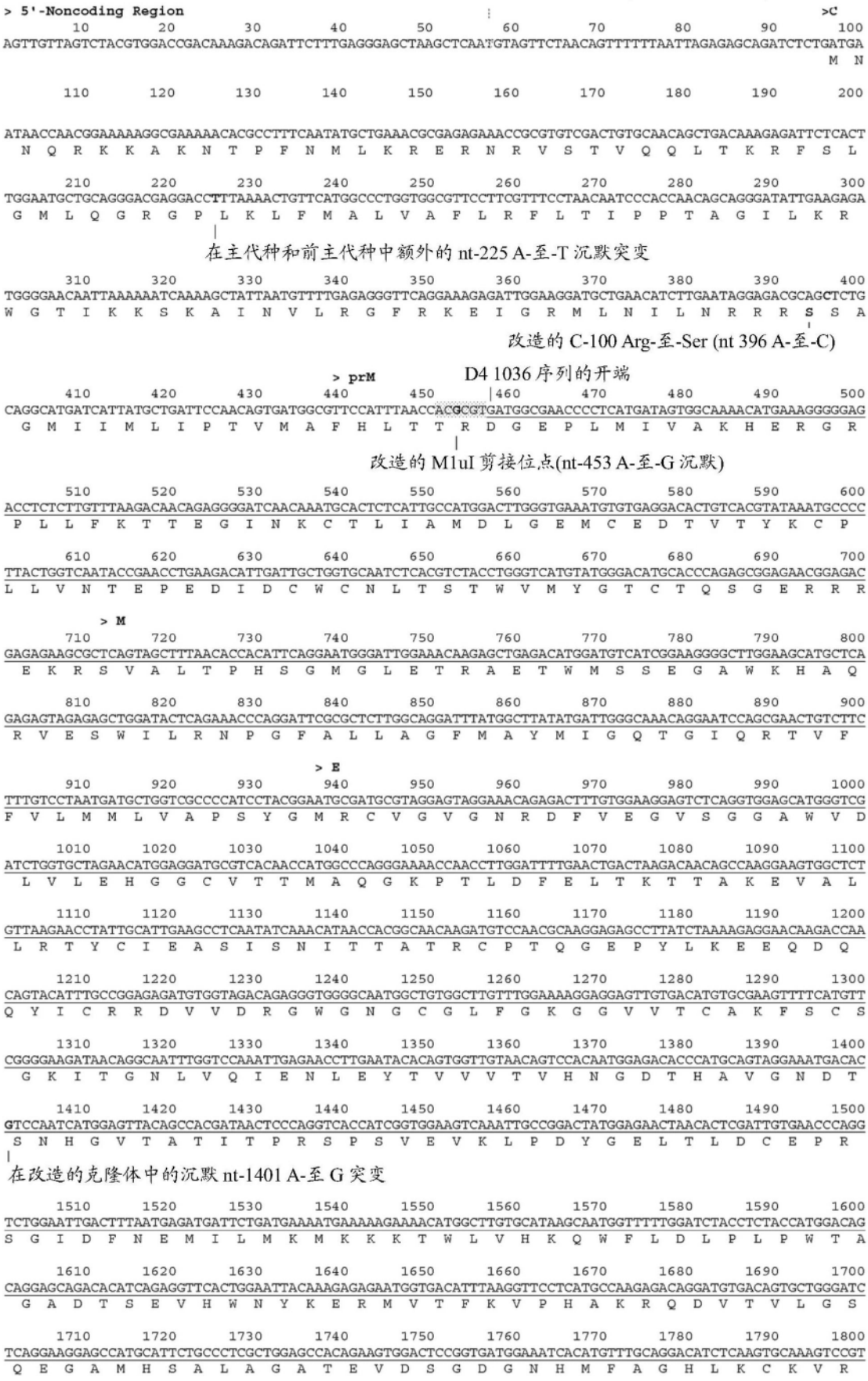
[0304] e.NS4A-21Ala-至-Val(nt-6437C-至-T,粗体)

[0305] f.nt-7026T-至-C/T混合沉默突变(粗体)

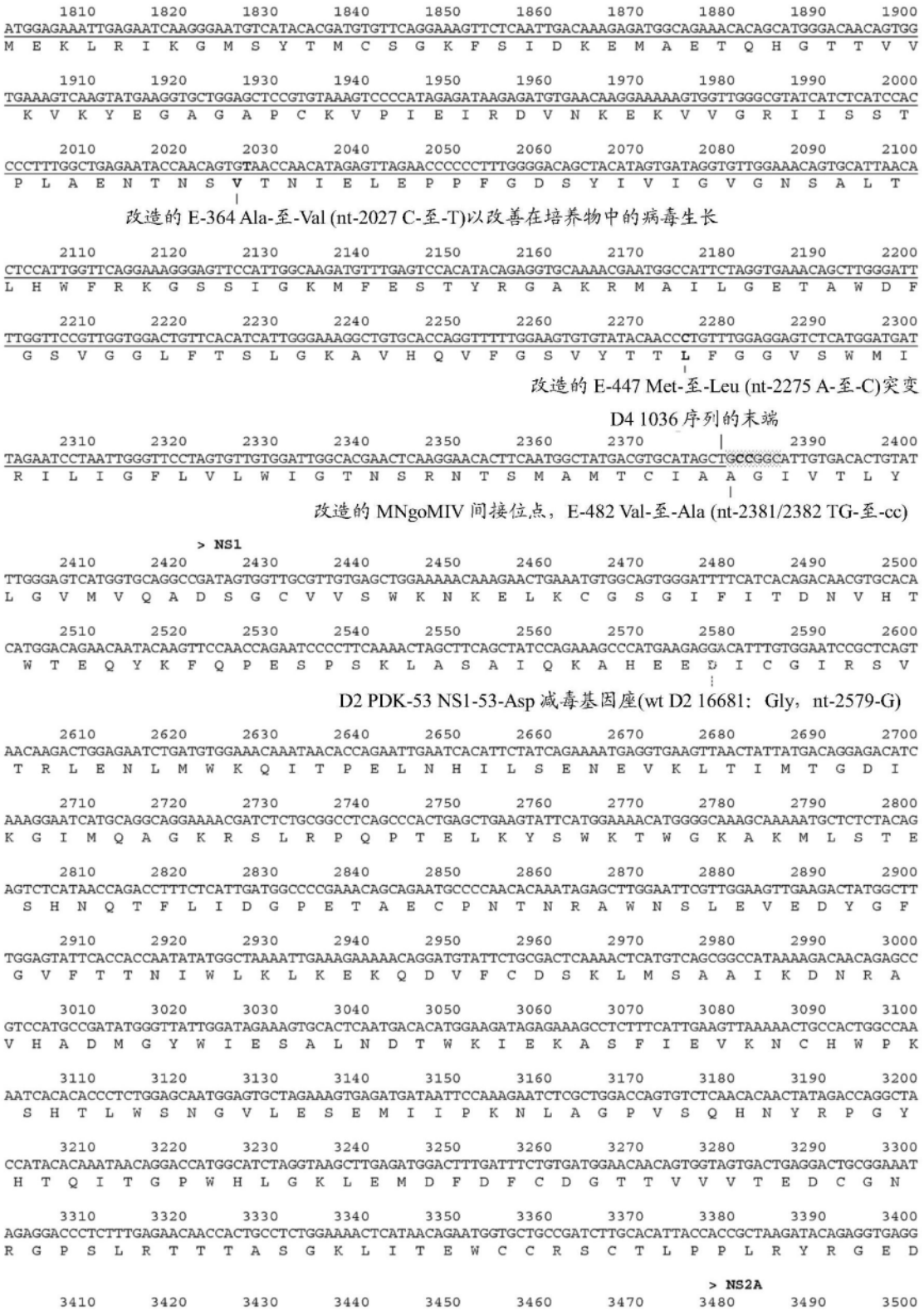
[0306] g.nt-9750A-至-C沉默突变(粗体)

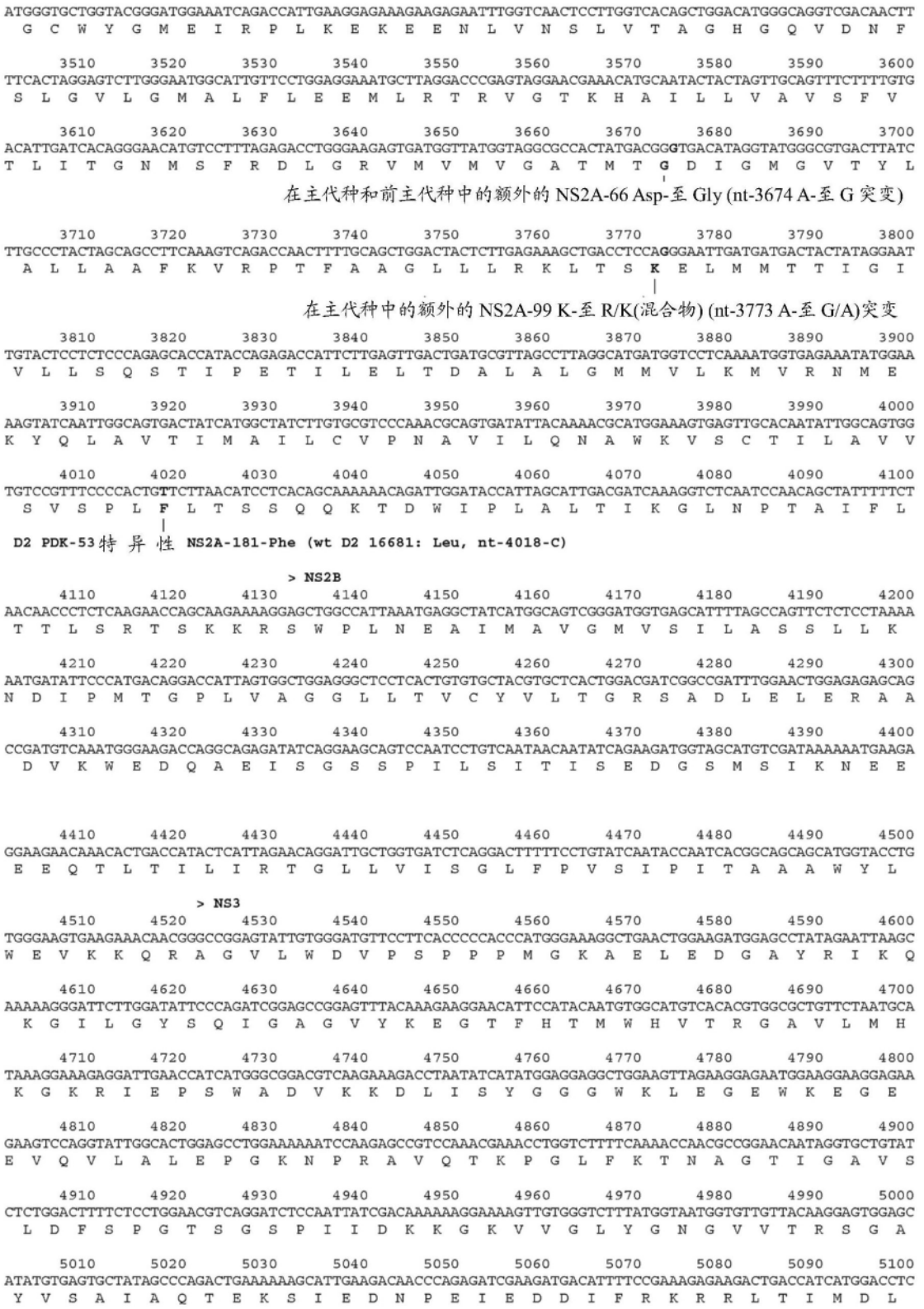
[0307] DENVax-4 MVS的核苷酸序列(SEQ ID NO:16)

NCR-57-T，D2 PDK-53 减毒基因座(wt D2 16681： C)

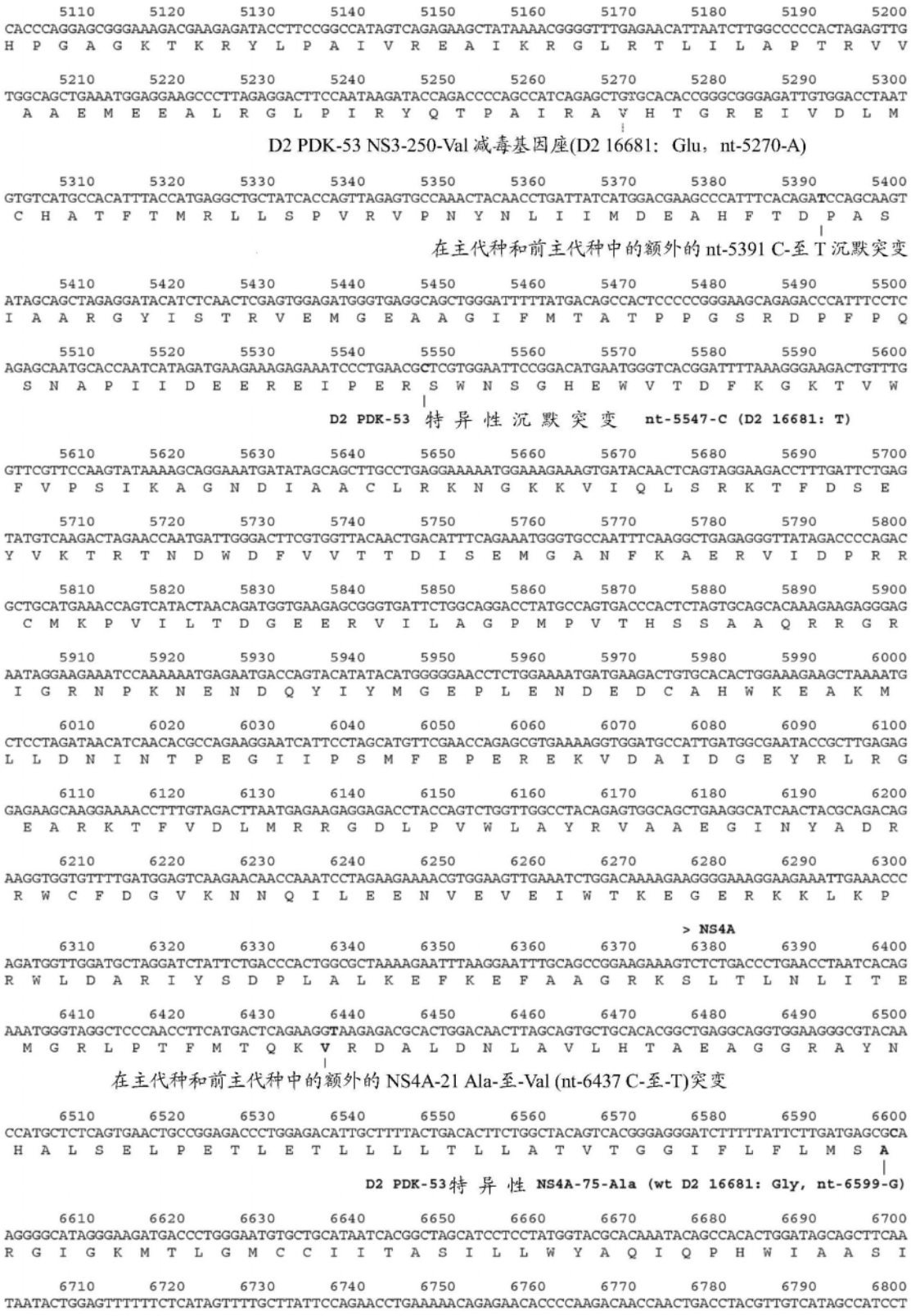


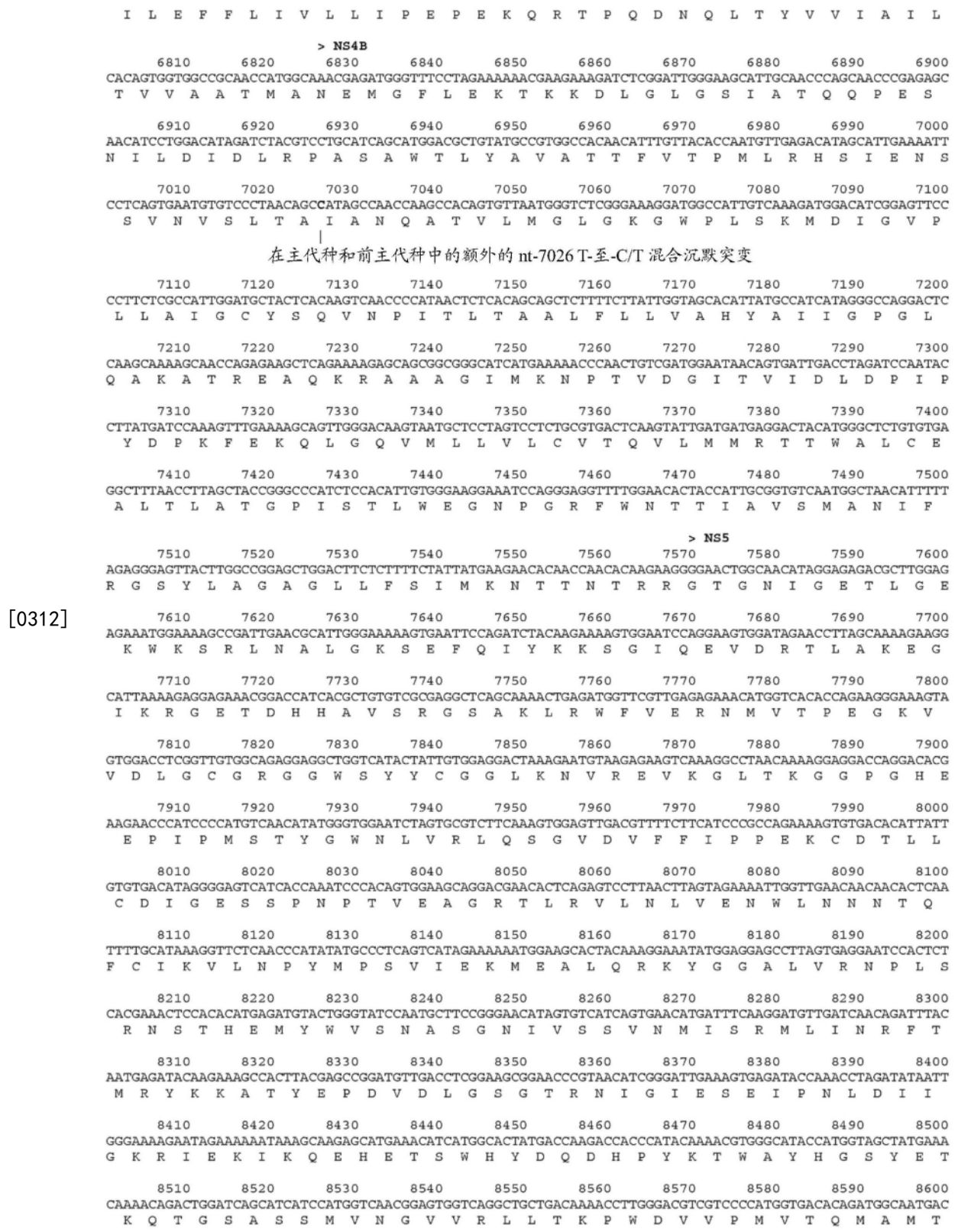
[0308]


1810 1820 1830 1840 1850 1860 1870 1880 1890 1900
ATGGAGAAATTGAGAATCAAGGGAATGTCATACACGATGTGTTCAGGAAAGTTCTCAATTGACAAAGAGATGGCAGAAACACAGCATGGGACAACAGTGG
M E K L R I K G M S Y T M C S G K F S I D K E M A E T Q H G T T V V
1910 1920 1930 1940 1950 1960 1970 1980 1990 2000
TGAAAGTCAAGTATGAAGGTGCTGGAGCTCCGTGTAAAGTCCCCATAGAGATAAGAGATGTGAACAAGGAAAAAGTGGTTGGGCGTATCATCTCATCCAC
K V K Y E G A G A P C K V P I E I R D V N K E K V V G R I I S S T
2010 2020 2030 2040 2050 2060 2070 2080 2090 2100
CCCTTTGGCTGAGAATACCAACAGTGTAACCAACATAGAGTTAGAACCCCCCTTTGGGGACAGCTACATAGTGATAGGTGTTGGAAACAGTGCATTAACA
P L A E N T N S V T N I E L E P P F G D S Y I V I G V G N S A L T
改造的 E-364 Ala-至-Val (nt-2027 C-至-T)以改善在培养物中的病毒生长
2110 2120 2130 2140 2150 2160 2170 2180 2190 2200
CTCCATTGGTTCAGGAAAGGGAGTTCCATTGGCAAGATGTTTGAGTCCACATACAGAGGTGCAAAACGAATGGCCATTCTAGGTGAAACAGCTTGGGATT
L H W F R K G S S I G K M F E S T Y R G A K R M A I L G E T A W D F
2210 2220 2230 2240 2250 2260 2270 2280 2290 2300
TTGGTTCCGTTGGTGGACTGTTCACATCATTGGGAAAGGCTGTGCACCAGGTTTTTGGAAGTGTGTATACAACCCTGTTTGGAGGAGTCTCATGGATGAT
G S V G G L F T S L G K A V H Q V F G S V Y T T L F G G V S W M I
改造的 E-447 Met-至-Leu (nt-2275 A-至-C)突变
D4 1036 序列的末端
2310 2320 2330 2340 2350 2360 2370 2390 2400
TAGAATCCTAATTGGGTTCCTAGTGTTGTGGATTGGCACGAACTCAAGGAACACTTCAATGGCTATGACGTGCATAGCTGCCGGCATTGTGACACTGTAT
R I L I G F L V L W I G T N S R N T S M A M T C I A A G I V T L Y
改造的 MNgoMIV 间接位点，E-482 Val-至-Ala (nt-2381/2382 TG-至-cc)
> NS1
2410 2420 2430 2440 2450 2460 2470 2480 2490 2500
TTGGGAGTCATGGTGCAGGCCGATAGTGGTTGCGTTGTGAGCTGGAAAAACAAAGAACTGAAATGTGGCAGTGGGATTTTCATCACAGACAACGTGCACA
L G V M V Q A D S G C V V S W K N K E L K C G S G I F I T D N V H T
2510 2520 2530 2540 2550 2560 2570 2580 2590 2600
CATGGACAGAACAATACAAGTTCCAACCAGAATCCCCTTCAAAACTAGCTTCAGCTATCCAGAAAGCCCATGAAGAGGACATTTGTGGAATCCGCTCAGT
W T E Q Y K F Q P E S P S K L A S A I Q K A H E E D I C G I R S V
[0309]
D2 PDK-53 NS1-53-Asp 减毒基因座(wt D2 16681: Gly，nt-2579-G)
2610 2620 2630 2640 2650 2660 2670 2680 2690 2700
AACAAGACTGGAGAATCTGATGTGGAAACAAATAACACCAGAATTGAATCACATTCTATCAGAAAATGAGGTGAAGTTAACTATTATGACAGGAGACATC
T R L E N L M W K Q I T P E L N H I L S E N E V K L T I M T G D I
2710 2720 2730 2740 2750 2760 2770 2780 2790 2800
AAAGGAATCATGCAGGCAGGAAAACGATCTCTGCGGCCTCAGCCCACTGAGCTGAAGTATTCATGGAAAACATGGGGCAAAGCAAAATGCTCTCTACAG
K G I M Q A G K R S L R P Q P T E L K Y S W K T W G K A K M L S T E
2810 2820 2830 2840 2850 2860 2870 2880 2890 2900
AGTCTCATAACCAGACCTTTCTCATTGATGGCCCCGAAACAGCAGAATGCCCCAACACAAATAGAGCTTGGAATTCGTTGGAAGTTGAAGACTATGGCTT
S H N Q T F L I D G P E T A E C P N T N R A W N S L E V E D Y G F
2910 2920 2930 2940 2950 2960 2970 2980 2990 3000
TGGAGTATTCACCACCAATATATGGCTAAAATTGAAAGAAAAACAGGATGTATTCTGCGACTCAAAACTCATGTCAGCGGCCATAAAAGACAACAGAGCC
G V F T T N I W L K L K E K Q D V F C D S K L M S A A I K D N R A
3010 3020 3030 3040 3050 3060 3070 3080 3090 3100
GTCCATGCCGATATGGGTTATTGGATAGAAAGTGCACTCAATGACACATGGAAGATAGAGAAAGCCTCTTTCATTGAAGTTAAAAACTGCCACTGGCCAA
V H A D M G Y W I E S A L N D T W K I E K A S F I E V K N C H W P K
3110 3120 3130 3140 3150 3160 3170 3180 3190 3200
AATCACACACCCTCTGGAGCAATGGAGTGCTAGAAAGTGAGATGATAATTCCAAAGAATCTCGCTGGACCAGTGTCTCAACACAACTATAGACCAGGCTA
S H T L W S N G V L E S E M I I P K N L A G P V S Q H N Y R P G Y
3210 3220 3230 3240 3250 3260 3270 3280 3290 3300
CCATACACAAATAACAGGACCATGGCATCTAGGTAAGCTTGAGATGGACTTTGATTTCTGTGATGGAACAACAGTGGTAGTGACTGAGGACTGCGGAAAT
H T Q I T G P W H L G K L E M D F D F C D G T T V V V T E D C G N
3310 3320 3330 3340 3350 3360 3370 3380 3390 3400
AGAGGACCCTCTTTGAGAACAACCACTGCCTCTGGAAAACTCATAACAGAATGGTGCTGCCGATCTTGCACATTACCACCGCTAAGATACAGAGGTGAGG
R G P S L R T T T A S G K L I T E W C C R S C T L P P L R Y R G E D
> NS2A
3410 3420 3430 3440 3450 3460 3470 3480 3490 3500


在主代种和前主代种中的额外的 NS2A-66 Asp-至 Gly (nt-3674 A-至 G 突变)
在主代种中的额外的 NS2A-99 K-至 R/K(混合物) (nt-3773 A-至 G/A)突变
D2 PDK-53特 异 性 NS2A-181-Phe (wt D2 16681: Leu, nt-4018-C)
> NS2B
> NS3

[0310]


5110 5120 5130 5140 5150 5160 5170 5180 5190 5200
CACCCAGGAGCGGGAAAGACGAAGAGATACCTTCCGGCCATAGTCAGAGAAGCTATAAAACGGGGTTTGAGAACATTAATCTTGGCCCCCACTAGAGTTG
H P G A G K T K R Y L P A I V R E A I K R G L R T L I L A P T R V V
5210 5220 5230 5240 5250 5260 5270 5280 5290 5300
TGGCAGCTGAAATGGAGGAAGCCCTTAGAGGACTTCCAATAAGATACCAGACCCCAGCCATCAGAGCTGTGCACACCGGGCGGGAGATTGTGGACCTAAT
A A E M E E A L R G L P I R Y Q T P A I R A V H T G R E I V D L M
D2 PDK-53 NS3-250-Val 减毒基因座(D2 16681: Glu，nt-5270-A)
5310 5320 5330 5340 5350 5360 5370 5380 5390 5400
GTGTCATGCCACATTTACCATGAGGCTGCTATCACCAGTTAGAGTGCCAAACTACAACCTGATTATCATGGACGAAGCCCATTTCACAGATCCAGCAAGT
C H A T F T M R L L S P V R V P N Y N L I I M D E A H F T D P A S
在主代种和前主代种中的额外的nt-5391 C-至T沉默突变
5410 5420 5430 5440 5450 5460 5470 5480 5490 5500
ATAGCAGCTAGAGGATACATCTCAACTCGAGTGGAGATGGGTGAGGCAGCTGGGATTTTTATGACAGCCACTCCCCCGGGAAGCAGAGACCCATTTCCTC
I A A R G Y I S T R V E M G E A A G I F M T A T P P G S R D P F P Q
5510 5520 5530 5540 5550 5560 5570 5580 5590 5600
AGAGCAATGCACCAATCATAGATGAAGAAAGAGAAATCCCTGAACGCTCGTGGAATTCCGGACATGAATGGGTCACGGATTTTAAAGGGAAGACTGTTTG
S N A P I I D E E R E I P E R S W N S G H E W V T D F K G K T V W
D2 PDK-53 特异性沉默突变 nt-5547-C (D2 16681: T)
5610 5620 5630 5640 5650 5660 5670 5680 5690 5700
GTTCGTTCCAAGTATAAAAGCAGGAAATGATATAGCAGCTTGCCTGAGGAAAAATGGAAAGAAAGTGATACAACTCAGTAGGAAGACCTTTGATTCTGAG
F V P S I K A G N D I A A C L R K N G K K V I Q L S R K T F D S E
5710 5720 5730 5740 5750 5760 5770 5780 5790 5800
TATGTCAAGACTAGAACCAATGATTGGGACTTCGTGGTTACAACTGACATTTCAGAAATGGGTGCCAATTTCAAGGCTGAGAGGGTTATAGACCCCAGAC
Y V K T R T N D W D F V V T T D I S E M G A N F K A E R V I D P R R
5810 5820 5830 5840 5850 5860 5870 5880 5890 5900
GCTGCATGAAACCAGTCATACTAACAGATGGTGAAGAGCGGGTGATTCTGGCAGGACCTATGCCAGTGACCCACTCTAGTGCAGCACAAAGAAGAGGGAG
C M K P V I L T D G E E R V I L A G P M P V T H S S A A Q R R G R
[0311]
5910 5920 5930 5940 5950 5960 5970 5980 5990 6000
AATAGGAAGAAATCCAAAAAATGAGAATGACCAGTACATATACATGGGGGAACCTCTGGAAAATGATGAAGACTGTGCACACTGGAAAGAAGCTAAAATG
I G R N P K N E N D Q Y I Y M G E P L E N D E D C A H W K E A K M
6010 6020 6030 6040 6050 6060 6070 6080 6090 6100
CTCCTAGATAACATCAACACGCCAGAAGGAATCATTCCTAGCATGTTCGAACCAGAGCGTGAAAAGGTGGATGCCATTGATGGCGAATACCGCTTGAGAG
L L D N I N T P E G I I P S M F E P E R E K V D A I D G E Y R L R G
6110 6120 6130 6140 6150 6160 6170 6180 6190 6200
GAGAAGCAAGGAAAACCTTTGTAGACTTAATGAGAAGAGGAGACCTACCAGTCTGGTTGGCCTACAGAGTGGCAGCTGAAGGCATCAACTACGCAGACAG
E A R K T F V D L M R R G D L P V W L A Y R V A A E G I N Y A D R
6210 6220 6230 6240 6250 6260 6270 6280 6290 6300
AAGGTGGTGTTTTGATGGAGTCAAGAACAACCAAATCCTAGAAGAAAACGTGGAAGTTGAAATCTGGACAAAAGAAGGGGAAAGGAAGAAATTGAAACCC
R W C F D G V K N N Q I L E E N V E V E I W T K E G E R K K L K P
> NS4A
6310 6320 6330 6340 6350 6360 6370 6380 6390 6400
AGATGGTTGGATGCTAGGATCTATTCTGACCCACTGGCGCTAAAAGAATTTAAGGAATTTGCAGCCGGAAGAAAGTCTCTGACCCTGAACCTAATCACAG
R W L D A R I Y S D P L A L K E F K E F A A G R K S L T L N L I T E
6410 6420 6430 6440 6450 6460 6470 6480 6490 6500
AAATGGGTAGGCTCCCAACCTTCATGACTCAGAAGGTAAGAGACGCACTGGACAACTTAGCAGTGCTGCACACGGCTGAGGCAGGTGGAAGGGCGTACAA
M G R L P T F M T Q K V R D A L D N L A V L H T A E A G G R A Y N
在主代种和前主代种中的额外的NS4A-21 Ala-至-Val (nt-6437 C-至-T)突变
6510 6520 6530 6540 6550 6560 6570 6580 6590 6600
CCATGCTCTCAGTGAACTGCCGGAGACCCTGGAGACATTGCTTTTACTGACACTTCTGGCTACAGTCACGGGAGGGATCTTTTTATTCTTGATGAGCGCA
H A L S E L P E T L E T L L L L T L L A T V T G G I F L F L M S A
D2 PDK-53特异性 NS4A-75-Ala (wt D2 16681: Gly, nt-6599-G)
6610 6620 6630 6640 6650 6660 6670 6680 6690 6700
AGGGGCATAGGGAAGATGACCCTGGGAATGTGCTGCATAATCACGGCTAGCATCCTCCTATGGTACGCACAAATACAGCCACACTGGATAGCAGCTTCAA
R G I G K M T L G M C C I I T A S I L L W Y A Q I Q P H W I A A S I
6710 6720 6730 6740 6750 6760 6770 6780 6790 6800
TAATACTGGAGTTTTTTCTCATAGTTTTGCTTATTCCAGAACCTGAAAAACAGAGAACACCCCAAGACAACCAACTGACCTACGTTGTCATAGCCATCCT


I L E F F L I V L L I P E P E K Q R T P Q D N Q L T Y V V I A I L
> NS4B
6810 6820 6830 6840 6850 6860 6870 6880 6890 6900
CACAGTGGTGGCCGCAACCATGGCAAACGAGATGGGTTTCCTAGAAAAAACGAAGAAAGATCTCGGATTGGGAAGCATTGCAACCCAGCAACCCGAGAGC
T V V A A T M A N E M G F L E K T K K D L G L G S I A T Q Q P E S
6910 6920 6930 6940 6950 6960 6970 6980 6990 7000
AACATCCTGGACATAGATCTACGTCCTGCATCAGCATGGACGCTGTATGCCGTGGCCACAACATTTGTTACACCAATGTTGAGACATAGCATTGAAAATT
N I L D I D L R P A S A W T L Y A V A T T F V T P M L R H S I E N S
7010 7020 7030 7040 7050 7060 7070 7080 7090 7100
CCTCAGTGAATGTGTCCCTAACAGCCATAGCCAACCAAGCCACAGTGTTAATGGGTCTCGGGAAAGGATGGCCATTGTCAAAGATGGACATCGGAGTTCC
S V N V S L T A I A N Q A T V L M G L G K G W P L S K M D I G V P
在主代种和前主代种中的额外的 nt-7026 T-至-C/T 混合沉默突变
7110 7120 7130 7140 7150 7160 7170 7180 7190 7200
CCTTCTCGCCATTGGATGCTACTCACAAGTCAACCCCATAACTCTCACAGCAGCTCTTTTCTTATTGGTAGCACATTATGCCATCATAGGGCCAGGACTC
L L A I G C Y S Q V N P I T L T A A L F L L V A H Y A I I G P G L
7210 7220 7230 7240 7250 7260 7270 7280 7290 7300
CAAGCAAAAGCAACCAGAGAAGCTCAGAAAAGAGCAGCGGCGGGCATCATGAAAAACCCAACTGTCGATGGAATAACAGTGATTGACCTAGATCCAATAC
Q A K A T R E A Q K R A A A G I M K N P T V D G I T V I D L D P I P
7310 7320 7330 7340 7350 7360 7370 7380 7390 7400
CTTATGATCCAAAGTTTGAAAAGCAGTTGGGACAAGTAATGCTCCTAGTCCTCTGCGTGACTCAAGTATTGATGATGAGGACTACATGGGCTCTGTGTGA
Y D P K F E K Q L G Q V M L L V L C V T Q V L M M R T T W A L C E
7410 7420 7430 7440 7450 7460 7470 7480 7490 7500
GGCTTTAACCTTAGCTACCGGGCCCATCTCCACATTGTGGGAAGGAAATCCAGGGAGGTTTTGGAACACTACCATTGCGGTGTCAATGGCTAACATTTTT
A L T L A T G P I S T L W E G N P G R F W N T T I A V S M A N I F
> NS5
7510 7520 7530 7540 7550 7560 7570 7580 7590 7600
AGAGGGAGTTACTTGGCCGGAGCTGGACTTCTCTTTTCTATTATGAAGAACACAACCAACACAAGAAGGGGAACTGGCAACATAGGAGAGACGCTTGGAG
R G S Y L A G A G L L F S I M K N T T N T R R G T G N I G E T L G E
[0312]
7610 7620 7630 7640 7650 7660 7670 7680 7690 7700
AGAAATGGAAAAGCCGATTGAACGCATTGGGAAAAAGTGAATTCCAGATCTACAAGAAAAGTGGAATCCAGGAAGTGGATAGAACCTTAGCAAAAGAAGG
K W K S R L N A L G K S E F Q I Y K K S G I Q E V D R T L A K E G
7710 7720 7730 7740 7750 7760 7770 7780 7790 7800
CATTAAAAGAGGAGAAACGGACCATCACGCTGTGTCGCGAGGCTCAGCAAAACTGAGATGGTTCGTTGAGAGAAACATGGTCACACCAGAAGGGAAAGTA
I K R G E T D H H A V S R G S A K L R W F V E R N M V T P E G K V
7810 7820 7830 7840 7850 7860 7870 7880 7890 7900
GTGGACCTCGGTTGTGGCAGAGGAGGCTGGTCATACTATTGTGGAGGACTAAAGAATGTAAGAGAAGTCAAAGGCCTAACAAAAGGAGGACCAGGACACG
V D L G C G R G G W S Y Y C G G L K N V R E V K G L T K G G P G H E
7910 7920 7930 7940 7950 7960 7970 7980 7990 8000
AAGAACCCATCCCCATGTCAACATATGGGTGGAATCTAGTGCGTCTTCAAAGTGGAGTTGACGTTTTCTTCATCCCGCCAGAAAAGTGTGACACATTATT
E P I P M S T Y G W N L V R L Q S G V D V F F I P P E K C D T L L
8010 8020 8030 8040 8050 8060 8070 8080 8090 8100
GTGTGACATAGGGGAGTCATCACCAAATCCCACAGTGGAAGCAGGACGAACACTCAGAGTCCTTAACTTAGTAGAAAATTGGTTGAACAACAACACTCAA
C D I G E S S P N P T V E A G R T L R V L N L V E N W L N N N T Q
8110 8120 8130 8140 8150 8160 8170 8180 8190 8200
TTTTGCATAAAGGTTCTCAACCCATATATGCCCTCAGTCATAGAAAAAATGGAAGCACTACAAAGGAAATATGGAGGAGCCTTAGTGAGGAATCCACTCT
F C I K V L N P Y M P S V I E K M E A L Q R K Y G G A L V R N P L S
8210 8220 8230 8240 8250 8260 8270 8280 8290 8300
CACGAAACTCCACACATGAGATGTACTGGGTATCCAATGCTTCCGGGAACATAGTGTCATCAGTGAACATGATTTCAAGGATGTTGATCAACAGATTTAC
R N S T H E M Y W V S N A S G N I V S S V N M I S R M L I N R F T
8310 8320 8330 8340 8350 8360 8370 8380 8390 8400
AATGAGATACAAGAAAGCCACTTACGAGCCGGATGTTGACCTCGGAAGCGGAACCCGTAACATCGGGATTGAAAGTGAGATACCAAACCTAGATATAATT
M R Y K K A T Y E P D V D L G S G T R N I G I E S E I P N L D I I
8410 8420 8430 8440 8450 8460 8470 8480 8490 8500
GGGAAAAGAATAGAAAAAATAAAGCAAGAGCATGAAACATCATGGCACTATGACCAAGACCACCCATACAAAACGTGGGCATACCATGGTAGCTATGAAA
G K R I E K I K Q E H E T S W H Y D Q D H P Y K T W A Y H G S Y E T
8510 8520 8530 8540 8550 8560 8570 8580 8590 8600
CAAAACAGACTGGATCAGCATCATCCATGGTCAACGGAGTGGTCAGGCTGCTGACAAAACCTTGGGACGTCGTCCCCATGGTGACACAGATGGCAATGAC
K Q T G S A S S M V N G V V R L L T K P W D V V P M V T Q M A M T

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      8610      8620      8630      8640      8650      8660      8670      8680      8690      8700
AGACACGACTCCATTTGGACAACAGCGCGTTTTTAAAGAGAAAGTGGACACGAGAACCCAAGAACCGAAAGAAGGCACGAAGAAACTAATGAAAATAACA
 D  T  T  P  F  G  Q  Q  R  V  F  K  E  K  V  D  T  R  T  Q  E  P  K  E  G  T  K  K  L  M  K  I  T

      8710      8720      8730      8740      8750      8760      8770      8780      8790      8800
GCAGAGTGGCTTTGGAAAGAATTAGGGAAGAAAAAGACACCCAGGATGTGCACCAGAGAAGAATTCACAAGAAAGGTGAGAAGCAATGCAGCCTTGGGGG
 A  E  W  L  W  K  E  L  G  K  K  K  T  P  R  M  C  T  R  E  E  F  T  R  K  V  R  S  N  A  A  L  G  A

      8810      8820      8830      8840      8850      8860      8870      8880      8890      8900
CCATATTCACTGATGAGAACAAGTGGAAGTCGGCACGTGAGGCTGTTGAAGATAGTAGGTTTTGGGAGCTGGTTGACAAGGAAAGGAATCTCCATCTTGA
  I  F  T  D  E  N  K  W  K  S  A  R  E  A  V  E  D  S  R  F  W  E  L  V  D  K  E  R  N  L  H  L  E

      8910      8920      8930      8940      8950      8960      8970      8980      8990      9000
AGGAAAGTGTGAAACATGTGTGTACAACATGATGGGAAAAAGAGAGAAGAAGCTAGGGGAATTCGGCAAGGCAAAAGGCAGCAGAGCCATATGGTACATG
 G  K  C  E  T  C  V  Y  N  M  M  G  K  R  E  K  K  L  G  E  F  G  K  A  K  G  S  R  A  I  W  Y  M

  9010      9020      9030      9040      9050      9060      9070      9080      9090      9100
TGGCTTGGAGCACGCTTCTTAGAGTTTGAAGCCCTAGGATTCTTAAATGAAGATCACTGGTTCTCCAGAGAGAACTCCCTGAGTGGAGTGGAAGGAGAAG
 W  L  G  A  R  F  L  E  F  E  A  L  G  F  L  N  E  D  H  W  F  S  R  E  N  S  L  S  G  V  E  G  E  G

      9110      9120      9130      9140      9150      9160      9170      9180      9190      9200
GGCTGCACAAGCTAGGTTACATTCTAAGAGACGTGAGCAAGAAAGAGGGAGGAGCAATGTATGCCGATGACACCGCAGGATGGGATACAAGAATCACACT
  L  H  K  L  G  Y  I  L  R  D  V  S  K  K  E  G  G  A  M  Y  A  D  D  T  A  G  W  D  T  R  I  T  L

      9210      9220      9230      9240      9250      9260      9270      9280      9290      9300
AGAAGACCTAAAAAATGAAGAAATGGTAACAAACCACATGGAAGGAGAACACAAGAAACTAGCCGAGGCCATTTTCAAACTAACGTACCAAAACAAGGTG
 E  D  L  K  N  E  E  M  V  T  N  H  M  E  G  E  H  K  K  L  A  E  A  I  F  K  L  T  Y  Q  N  K  V

      9310      9320      9330      9340      9350      9360      9370      9380      9390      9400
GTGCGTGTGCAAAGACCAACACCAAGAGGCACAGTAATGGACATCATATCGAGAAGAGACCAAAGAGGTAGTGGACAAGTTGGCACCTATGGACTCAATA
V  R  V  Q  R  P  T  P  R  G  T  V  M  D  I  I  S  R  R  D  Q  R  G  S  G  Q  V  G  T  Y  G  L  N  T

      9410      9420      9430      9440      9450      9460      9470      9480      9490      9500
CTTTCACCAATATGGAAGCCCAACTAATCAGACAGATGGAGGGAGAAGGAGTCTTTAAAAGCATTCAGCACCTAACAATCACAGAAGAAATCGCTGTGCA
  F  T  N  M  E  A  Q  L  I  R  Q  M  E  G  E  G  V  F  K  S  I  Q  H  L  T  I  T  E  E  I  A  V  Q
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[0313]

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      9510      9520      9530      9540      9550      9560      9570      9580      9590      9600
AAACTGGTTAGCAAGAGTGGGGCGCGAAAGGTTATCAAGAATGGCCATCAGTGGAGATGATTGTGTTGTGAAACCTTTAGATGACAGGTTCGCAAGCGCT
 N  W  L  A  R  V  G  R  E  R  L  S  R  M  A  I  S  G  D  D  C  V  V  K  P  L  D  D  R  F  A  S  A

      9610      9620      9630      9640      9650      9660      9670      9680      9690      9700
TTAACAGCTCTAAATGACATGGGAAAGATTAGGAAAGACATACAACAATGGGAACCTTCAAGAGGATGGAATGATTGGACACAAGTGCCCTTCTGTTCAC
L  T  A  L  N  D  M  G  K  I  R  K  D  I  Q  Q  W  E  P  S  R  G  W  N  D  W  T  Q  V  P  F  C  S  H

      9710      9720      9730      9740      9750      9760      9770      9780      9790      9800
ACCATTTCCATGAGTTAATCATGAAAGACGGTCGCGTACTCGTTGTTCCCTGTAGAAACCAAGATGAACTGATTGGCAGAGCCCGAATCTCCCAAGGAGC
  H  F  H  E  L  I  M  K  D  G  R  V  L  V  V  P  C  R  N  Q  D  E  L  I  G  R  A  R  I  S  Q  G  A
                                                 |
                                  在主代种和前主代种中的额外的 nt-9750 A-至-C 沉默突变

      9810      9820      9830      9840      9850      9860      9870      9880      9890      9900
AGGGTGGTCTTTGCGGGAGACGGCCTGTTTGGGGAAGTCTTACGCCCAAATGTGGAGCTTGATGTACTTCCACAGACGCGACCTCAGGCTGGCGGCAAAT
 G  W  S  L  R  E  T  A  C  L  G  K  S  Y  A  Q  M  W  S  L  M  Y  F  H  R  R  D  L  R  L  A  A  N

      9910      9920      9930      9940      9950      9960      9970      9980      9990     10000
GCTATTTGCTCGGCAGTACCATCACATTGGGTTCCAACAAGTCGAACAACCTGGTCCATACATGCTAAACATGAATGGATGACAACGGAAGACATGCTGA
A  I  C  S  A  V  P  S  H  W  V  P  T  S  R  T  T  W  S  I  H  A  K  H  E  W  M  T  T  E  D  M  L  T

     10010     10020     10030     10040     10050     10060     10070     10080     10090     10100
CAGTCTGGAACAGGGTGTGGATTCAAGAAAACCCATGGATGGAAGACAAAACTCCAGTGGAATCATGGGAGGAAATCCCATACTTGGGGAAAAGAGAAGA
  V  W  N  R  V  W  I  Q  E  N  P  W  M  E  D  K  T  P  V  E  S  W  E  E  I  P  Y  L  G  K  R  E  D

     10110     10120     10130     10140     10150     10160     10170     10180     10190     10200
CCAATGGTGCGGCTCATTGATTGGGTTAACAAGCAGGGCCACCTGGGCAAAGAACATCCAAGCAGCAATAAATCAAGTTAGATCCCTTATAGGCAATGAA
 Q  W  C  G  S  L  I  G  L  T  S  R  A  T  W  A  K  N  I  Q  A  A  I  N  Q  V  R  S  L  I  G  N  E

                                                                                  > 3'-非编码区
     10210     10220     10230     10240     10250     10260     10270     10280     10290     10300
GAATACACAGATTACATGCCATCCATGAAAAGATTCAGAAGAGAAGAGGAAGAAGCAGGAGTTCTGTGGTAGAAAGCAAAACTAACATGAAACAAGGCTA
E  Y  T  D  Y  M  P  S  M  K  R  F  R  R  E  E  E  E  A  G  V  L  W  *

     10310     10320     10330     10340     10350     10360     10370     10380     10390     10400
GAAGTCAGGTCGGATTAAGCCATAGTACGGAAAAAACTATGCTACCTGTGAGCCCCGTCCAAGGACGTTAAAAGAAGTCAGGCCATCATAAATGCCATAG

     10410     10420     10430     10440     10450     10460     10470     10480     10490     10500
CTTGAGTAAACTATGCAGCCTGTAGCTCCACCTGAGAAGGTGTAAAAAATCCGGGAGGCCACAAACCATGGAAGCTGTACGCATGGCGTAGTGGACTAGC

     10510     10520     10530     10540     10550     10560     10570     10580     10590     10600
GGTTAGAGGAGACCCCTCCCTTACAAATCGCAGCAACAATGGGGGCCCAAGGCGAGATGAAGCTGTAGTCTCGCTGGAAGGACTAGAGGTTAGAGGAGAC
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[0314]

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     10610     10620     10630     10640     10650     10660     10670     10680     10690     10700
CCCCCCGAAACAAAAAACAGCATATTGACGCTGGGAAAGACCAGAGATCCTGCTGTCTCCTCAGCATCATTCCAGGCACAGAACGCCAGAAAATGGAATG

     10710     10720
GTGCTGTTGAATCAACAGGTTCT
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[0315] 本发明包括以下内容：

[0316] 项目1.核酸嵌合体,包含编码来自修饰的活减毒登革热-2病毒株PDK-53的非结构蛋白质的第一核苷酸序列,和编码至少一种来自登革热-1的结构蛋白质的第二核苷酸序列,其中所述活减毒登革热-2病毒还包含至少一种额外的突变,所述额外的突变包括核酸位置3823处的突变,其中NS2A基因的氨基酸位置116为亮氨酸替代异亮氨酸。

[0317] 项目2.如项目1所述的核酸嵌合体,其中所述活减毒登革热-2病毒还包括位置4407处的突变,其中NS2B的氨基酸位置92为天冬氨酸替代谷氨酸。

[0318] 项目3.如项目1所述的核酸嵌合体,其中所述活减毒登革热-2病毒还包括位置7148处的突变,其中NS4B的氨基酸位置108为异亮氨酸替代苏氨酸。

[0319] 项目4.如项目1所述的核酸嵌合体,其中所述活减毒登革热-2病毒还包括位置7311处的突变。

[0320] 项目5.如项目1所述的核酸嵌合体,其中所述第二核苷酸序列编码来自登革热-1的E蛋白,所述登革热-1还包含位置2384处的突变,其中所述E蛋白的氨基酸位置483为丙氨酸替代甘氨酸。

[0321] 项目6.药物组合物,包含项目1至5中任一项所述的核酸嵌合体,以及药学上可接受的赋形剂。

[0322] 项目7.药物组合物,包含由项目1至5中任一项所述的核酸嵌合体编码的多肽,以及药学上可接受的赋形剂。

[0323] 项目8.在个体内诱导免疫应答的方法,包括给予药学上可接受量的项目6和7所述的组合物中的任一种,其中所述组合物在所述个体内诱导对登革热病毒的免疫应答。

[0324] 项目9.载体,其编码项目1至5中任一项所述的核酸序列。

[0325] 项目10.核酸序列,其包含编码修饰的活减毒登革热-2病毒株PDK-53的核酸序列,其中所述活减毒登革热-2病毒还包含至少一种额外的突变,所述额外的突变包括核酸位置6481处的突变,其中NS4A基因的氨基酸位置36为脯氨酸替代丙氨酸。

[0326] 项目11.如项目10所述的核酸序列,其中所述活减毒登革热-2病毒还包括位置7156处的突变,其中NS4B的氨基酸位置111为苯丙氨酸替代亮氨酸。

[0327] 项目12.如项目10所述的核酸序列,其中所述活减毒登革热-2病毒还包括位置8803处的突变,其中NS5的氨基酸位置412为缬氨酸替代异亮氨酸。

[0328] 项目13.如项目1所述的核酸序列,其中所述活减毒登革热-2病毒还包括位置592处的突变,其中prM的氨基酸位置52为谷氨酸替代赖氨酸。

[0329] 项目14.药物组合物,包含项目10至13中任一项所述的核酸嵌合体,以及药学上可接受的赋形剂。

[0330] 项目15.药物组合物,包含由项目10至13中任一项所述的核酸嵌合体编码的多肽,以及药学上可接受的赋形剂。

[0331] 项目16.在个体内诱导免疫应答的方法,包括给予药学上可接受量的项目14和15所述的组合物中的任一种,其中所述组合物在所述个体内诱导对登革热病毒的免疫应答。

[0332] 项目17.载体,其编码项目10至13中任一项所述的核酸序列。

[0333] 项目18.核酸嵌合体,包含编码来自修饰的活减毒登革热-2病毒株PDK-53的非结构蛋白质的第一核苷酸序列,和编码至少一种来自登革热-3的结构蛋白质的第二核苷酸序

列,其中所述活减毒登革热-2病毒还包含至少一种额外的突变,所述额外的突变包括核酸位置6436处的突变,其中N42A基因的氨基酸位置23为天冬酰胺替代天冬氨酸。

[0334] 项目19.如项目16所述的核酸嵌合体,其中所述活减毒登革热-2病毒还包括位置7620处的突变。

[0335] 项目20.如项目16所述的核酸嵌合体,其中所述第二核苷酸序列编码来自登革热-3的E蛋白,所述登革热-3还包含位置1603处的突变,其中所述E蛋白的氨基酸位置223为丝氨酸替代苏氨酸。

[0336] 项目21.药物组合物,包含项目18至20中任一项所述的核酸嵌合体,以及药学上可接受的赋形剂。

[0337] 项目22.药物组合物,包含由项目18至20中任一项所述的核酸嵌合体编码的多肽,以及药学上可接受的赋形剂。

[0338] 项目23.在个体内诱导免疫应答的方法,包括给予药学上可接受量项目21和22所述的组合物中的任一种,其中所述组合物在所述个体内诱导对登革热病毒的免疫应答。

[0339] 项目24.载体,其编码项目18至20中任一项所述的核酸序列。

[0340] 项目25.核酸嵌合体,包含编码来自修饰的活减毒登革热-2病毒株PDK-53的非结构蛋白质的第一核苷酸序列,和编码至少一种来自登革热-4的结构蛋白质的第二核苷酸序列,其中所述活减毒登革热-2病毒还包含至少一种额外的突变,所述额外的突变包括核酸位置3674处的突变,其中NS2A基因的氨基酸位置66为甘氨酸替代天冬氨酸。

[0341] 项目26.如项目22所述的核酸嵌合体,其中所述活减毒登革热-2病毒还包括位置3773处的突变,其中NS2A的氨基酸位置99为精氨酸替代赖氨酸。

[0342] 项目27.如项目22所述的核酸嵌合体,其中所述活减毒登革热-2病毒还包括位置5391处的突变。

[0343] 项目28.如项目22所述的核酸嵌合体,其中所述活减毒登革热-2病毒还包括位置6437处的突变,其中NS4A的氨基酸位置21为缬氨酸替代丙氨酸。

[0344] 项目29.如项目22所述的核酸嵌合体,其中所述活减毒登革热-2病毒还包括位置7026处的突变。

[0345] 项目30.如项目22所述的核酸嵌合体,其中所述活减毒登革热-2病毒还包括位置7538处的突变,其中NS4B的氨基酸位置238为苯丙氨酸替代丝氨酸。

[0346] 项目31.如项目22所述的核酸嵌合体,其中所述活减毒登革热-2病毒还包括位置9750处的突变。

[0347] 项目32.如项目22所述的核酸嵌合体,其中所述活减毒登革热-2病毒还包括位置225处的突变。

[0348] 项目33.药物组合物,包含项目25至32中任一项所述的核酸嵌合体,以及药学上可接受的赋形剂。

[0349] 项目34.药物组合物,包含由项目25至32中任一项所述的核酸嵌合体编码的多肽,以及药学上可接受的赋形剂。

[0350] 项目35.在个体内诱导免疫应答的方法,包括给予药学上可接受量的项目33和34所述的组合物中的任一种,其中所述组合物在所述个体内诱导对登革热病毒的免疫应答。

[0351] 项目36.载体,其编码项目25至32中任一项所述的核酸序列。

[0352] 项目37.核酸序列,其包含以SEQ ID NO.1、7和10确定的核酸序列中的一种或多种。

[0353] 项目38.如项目33所述的核酸,其中所述核酸嵌合体编码由SEQ ID NO.2、3、8、9、11或12表示的多肽。

[0354] 项目39.免疫原性组合物,包含项目37所述的核酸序列或项目38所述的多肽中的一种或多种,以及药学上可接受的载剂。

[0355] 项目40.如项目39所述的组合物,其还包含活减毒登革热-2病毒。

[0356] 项目41.如项目40所述的组合物,其中所述活减毒登革热-2病毒以SEQ ID NO.4的核酸序列或SEQ ID NO.5和6中的一个或多个的氨基酸序列表示。

[0357] 项目42.如项目40所述的组合物,其中所述组合物含有全部四种登革热病毒血清型四价组合物。

[0358] 项目43.如项目39所述的组合物,还包含针对选自以下的黄病毒的免疫原性组合物:黄热病毒、蜱媒脑炎病毒、日本脑炎病毒、西尼罗病毒、丙型肝炎病毒、及其中两种或更多种的组合。

[0359] 项目44.试剂盒,包括项目1至5、10至13、18至20或25至32中任一项所述的核酸序列中的至少一种;或项目6、7、14、15、21、22、33或34中任一项所述组合物中的至少一种,以及容器。

[0360] 项目45.活减毒病毒,包含项目1至5、10至13、18至20或25至32中任一项所述的核酸序列中的一种或多种。

[0361] 项目46.包括表3的核酸序列的核酸序列,或由包括表3的核酸序列的一种或多种核酸序列编码的多肽。

[0362] 项目47.包括DENVax-1-A、DENVax-2-F、DENVax-3-F和DENVax-4-F中的一个或多个的核酸序列,或由包括DENVax-1-A、DENVax-2-F、DENVax-3-F和DENVax-4-F中的一个或多个的一种或多种核酸序列编码的多肽。

[0363] 项目48.组合物,包含项目求47所述的核酸序列中的一种或多种或由项目47所述核酸序列编码的多肽中的一种或多种,以及药学上可接受的载剂或赋形剂。

[0364] 项目49.如项目48所述的组合物,其还包含药学上可接受的佐剂。

[0365] 项目50.组合物,包含项目45所述的活减毒病毒中的一种或多种,以及药学上可接受的载剂。

[0366] 项目51.如项目50所述的组合物,其中所述组合物包含能够在个体内诱导对抗全部四种登革热病毒血清型的免疫应答的四价登革热病毒组合物。

[0001] 序列表

[0002] <110> 武田疫苗股份有限公司

[0003] 美国政府健康及人类服务部

[0004] <120> 用于疫苗中的登革热病毒嵌合式构建物的组合物及方法

[0005] <130> T08239WOCND4

[0006] <150> US 61/800,204

[0007] <151> 2013-03-15

[0008] <150> PCT/US2014/024603

[0009] <151> 2014-03-12

[0010] <150> 201480028001.5

[0011] <151> 2014-03-12

[0012] <160> 16

[0013] <170> PatentIn version 3.5

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[0015] <211> 10723

[0016] <212> DNA

[0017] <213> 人工序列

[0018] <220>

[0019] <223> 登革热病毒血清型1, BVS

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[2624] 1865 1870 1875
[2625] Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys Ala Glu
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[2693] Asp Gly Ile Thr Val Ile Asp Leu Asp Pro Ile Pro Tyr Asp Pro
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[2739] Met Arg Tyr Lys Lys Ala Thr Tyr Glu Pro Asp Val Asp Leu Gly

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[2747] Tyr His Gly Ser Tyr Glu Thr Lys Gln Thr Gly Ser Ala Ser Ser

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[2781] Glu His Lys Lys Leu Ala Glu Ala Ile Phe Lys Leu Thr Tyr Gln

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[2783] Asn Lys Val Val Arg Val Gln Arg Pro Thr Pro Arg Gly Thr Val

[2784] 3065 3070 3075

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[2797] Ala Leu Asn Asp Met Gly Lys Ile Arg Lys Asp Ile Gln Gln Trp

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[2809] Arg Asp Leu Arg Leu Ala Ala Asn Ala Ile Cys Ser Ala Val Pro

[2810] 3260 3265 3270

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[3682] 1490 1495 1500

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[5089] acaagaaggg gaactggcaa cataggagag acgcttggag agaaatggaa aagccgattg 7620
[5090] aacgcattgg gaaaaagtga attccagatc tacaagaaaa gtggaatcca ggaagtggat 7680
[5091] agaaccttag caaaagaagg cattaaaaga ggagaaacgg accatcacgc tgtgtcgcga 7740
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D2/4嵌合体之间的遗传变异(相较于wtD2 16681和D4-1036)

基因组	D2				D4				Junction	D2													
基因	5'UTR		C		junction prM	E				NS1		NS2A			NS3			NS4A		2K4B		NS5	
变异类型	种		种	Eng	MluI	种	标记	Eng	Eng	NgenMV	种/NS3	种	PDK-53	种/NS3	种	PDK-53	种	PDK-53	种	种	PDK53	种
基因组NT position 蛋白质AA位置	C57T NC5	A225T C-silent	A896C C-R180S	A4536G prM-silent	C2647G/C prM-T799A/T	A2402G E-silent	C3027T E-A364V	A2275 E-M447X	T2238G/ICC E-V485A	G2579A NS1-E53D	A3873A/G NS2A-D666	C4018T NS2A-L121F	A5220T NS3-E250V	C5391T NS3-沉默	T5547C NS3-沉默	C6437T NS4A-A21V	C6598C NS4A-G75A	T7026C/T NS4B-沉默	C8571T**	A9750C NS5-沉默	NS5-沉默
D2-16681 D2-PDK-53 D4-1036	C T -	A - A (G)	A - G (T)	A	A	C (A)	A (G)		T (C)	A (G) - G (G)	A (G) - A/G (R/R)	T (T) T (T)	T (T) T (T)	- -	C T	T C	C (A) -	C (G) C (A)	T -	C T	A -	
Clone:D2/4-V1 (D2/4-VP1) DENVax-4 (DV4)	T	-	C (C)	C	-	C	T (T)	C (C)	C (A)	A (G)	-	T (T)	T (T)	-	C	T (T)	-	C (A)	-	-	-	

"-": 与wt D2 16681或D4 1036相同；小nt标记：在开放阅读区内的沉默突变

*：PDK-53：D2-PDK-53特异性基因型(相较于16681)；红色：主要减毒PDK-53基因座；种：突变只发生于特定病毒后不再原始克隆体中；Eng：D2/4克隆体的改造突变；MluI和NgmMV：D2/4嵌合改造RE位点

**：CB571T (PDK-53沉默突变)不被包括在大部分D2/4嵌合式克隆体中

图1

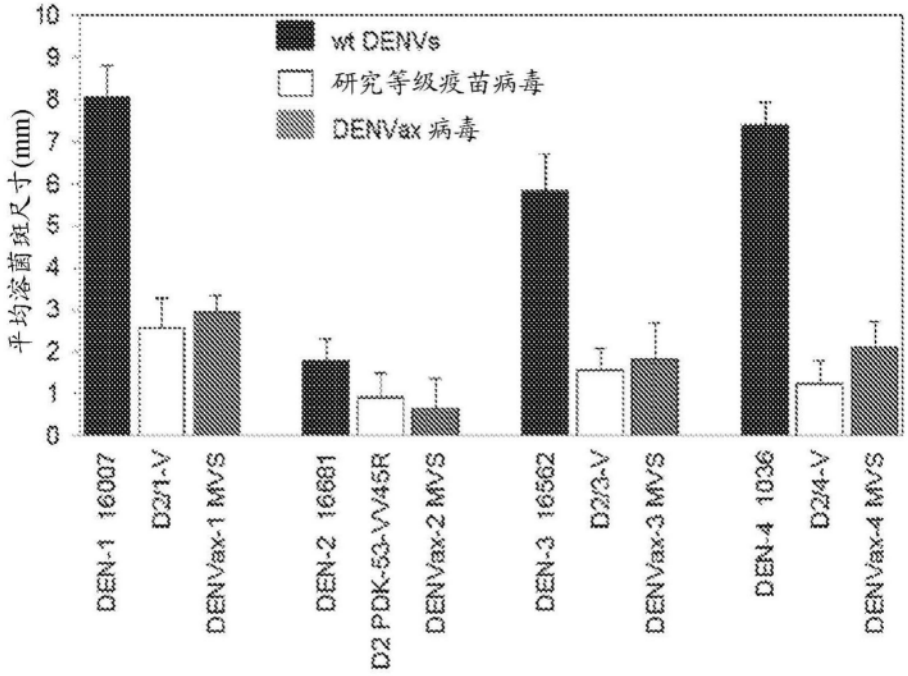

wt DENVs
研究等级疫苗病毒
DENVax 病毒
平均溶菌斑尺寸(mm)
0
1
2
3
4
5
6
7
8
9
10
DEN-1 16007
D2/1-V
DENVax-1 MVS
DEN-2 16681
D2 PDK-53-VV45R
DENVax-2 MVS
DEN-3 16562
D2/3-V
DENVax-3 MVS
DEN-4 1036
D2/4-V
DENVax-4 MVS

图2

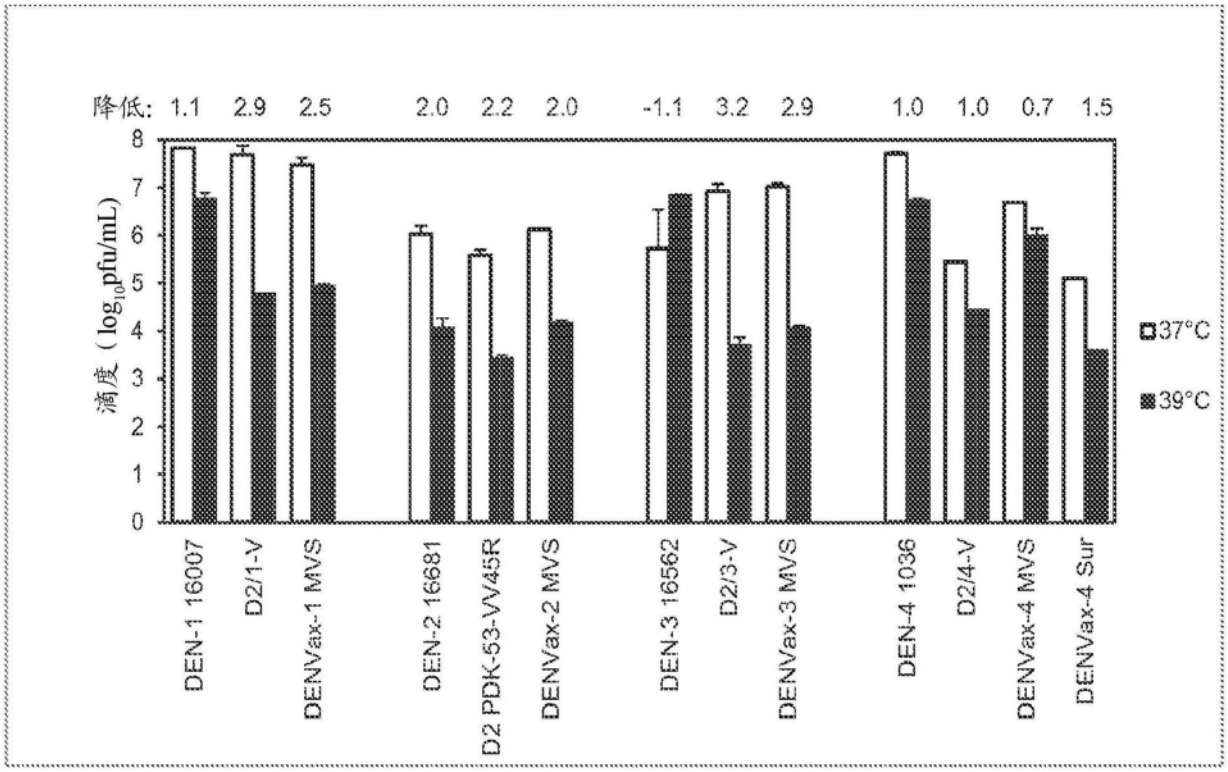

降低: 1.1 2.9 2.5 2.0 2.2 2.0 -1.1 3.2 2.9 1.0 1.0 0.7 1.5
滴度 (log10pfu/mL)
0
1
2
3
4
5
6
7
8
37°C
39°C
DEN-1 16007
D2/1-V
DENVax-1 MVS
DEN-2 16681
D2 PDK-53-VV45R
DENVax-2 MVS
DEN-3 16562
D2/3-V
DENVax-3 MVS
DEN-4 1036
D2/4-V
DENVax-4 MVS
DENVax-4 Sur

图3

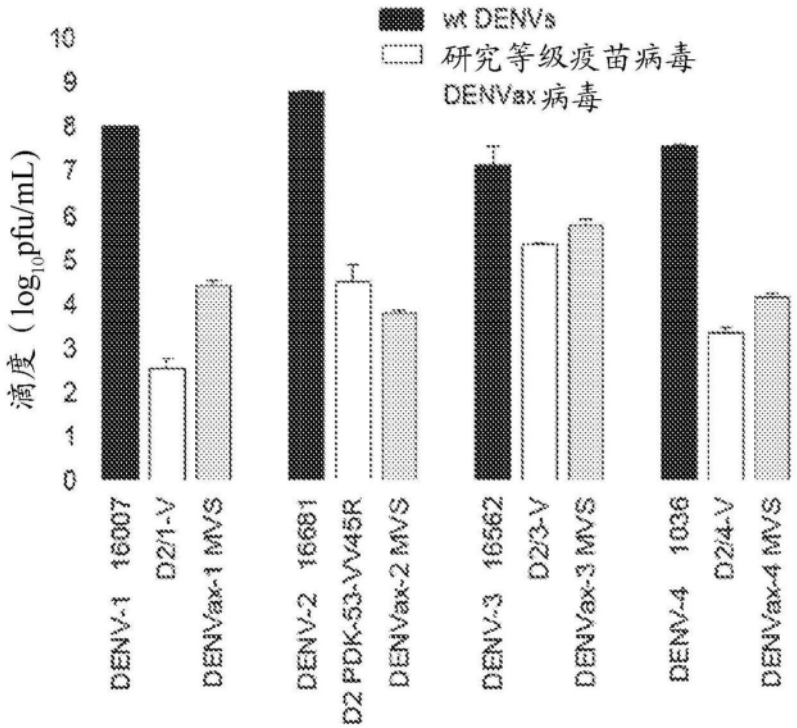

wt DENVs
研究等级疫苗病毒
DENVax病毒
滴度（log10pfu/mL）
0
1
2
3
4
5
6
7
8
9
10
DENV-1 16007
D2/1-V
DENVax-1 MVS
DENV-2 16681
D2 PDK-53-VV45R
DENVax-2 MVS
DENV-3 16562
D2/3-V
DENVax-3 MVS
DENV-4 1036
D2/4-V
DENVax-4 MVS

图4

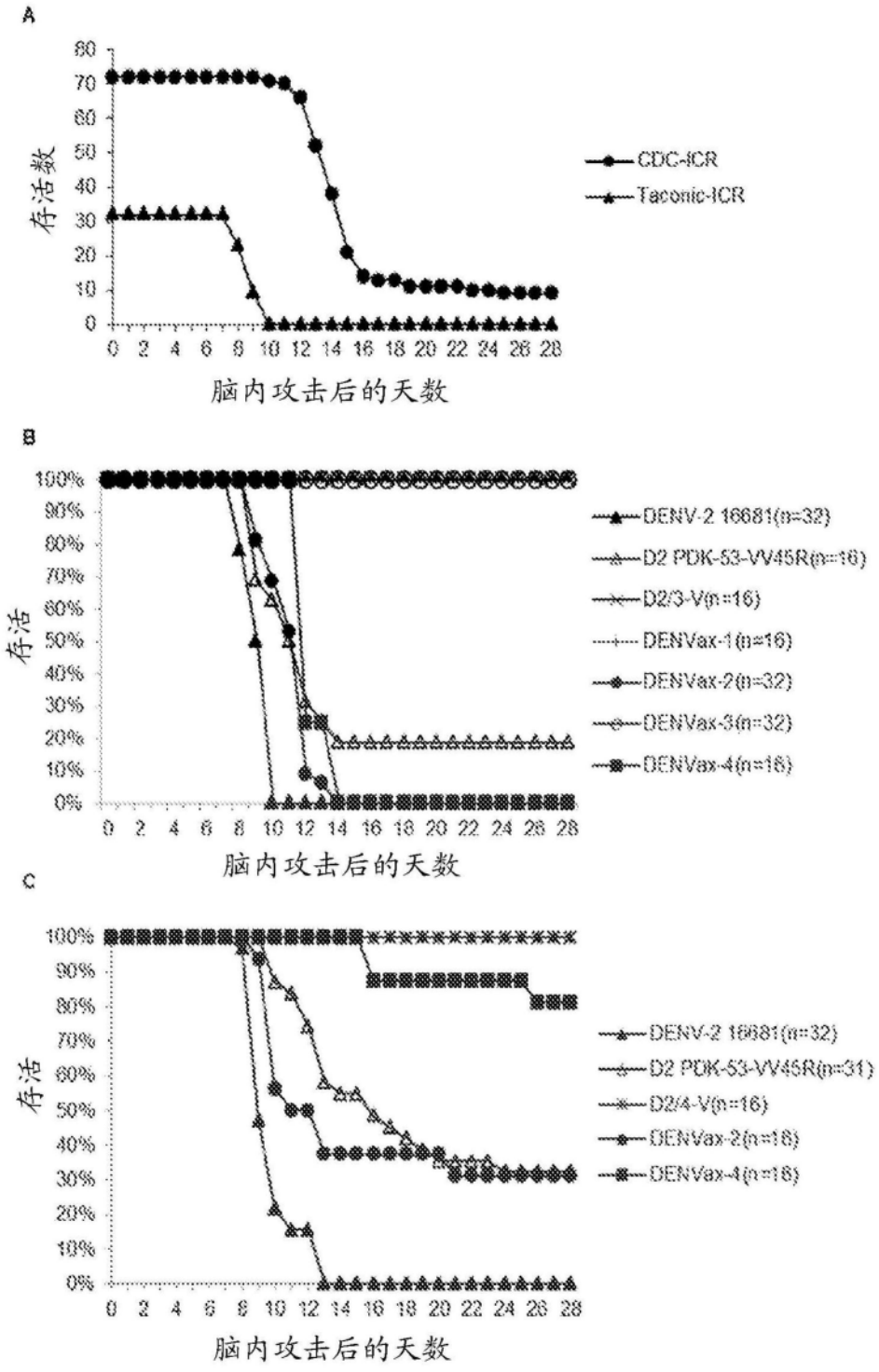

A
存活数
脑内攻击后的天数
CDC-ICR
Taconic-ICR
B
存活
脑内攻击后的天数
DENV-2 16681(n=32)
D2 PDK-53-VV45R(n=16)
D2/3-V(n=16)
DENVax-1(n=16)
DENVax-2(n=32)
DENVax-3(n=32)
DENVax-4(n=16)
C
存活
脑内攻击后的天数
DENV-2 16681(n=32)
D2 PDK-53-VV45R(n=31)
D2/4-V(n=16)
DENVax-2(n=16)
DENVax-4(n=16)

图5

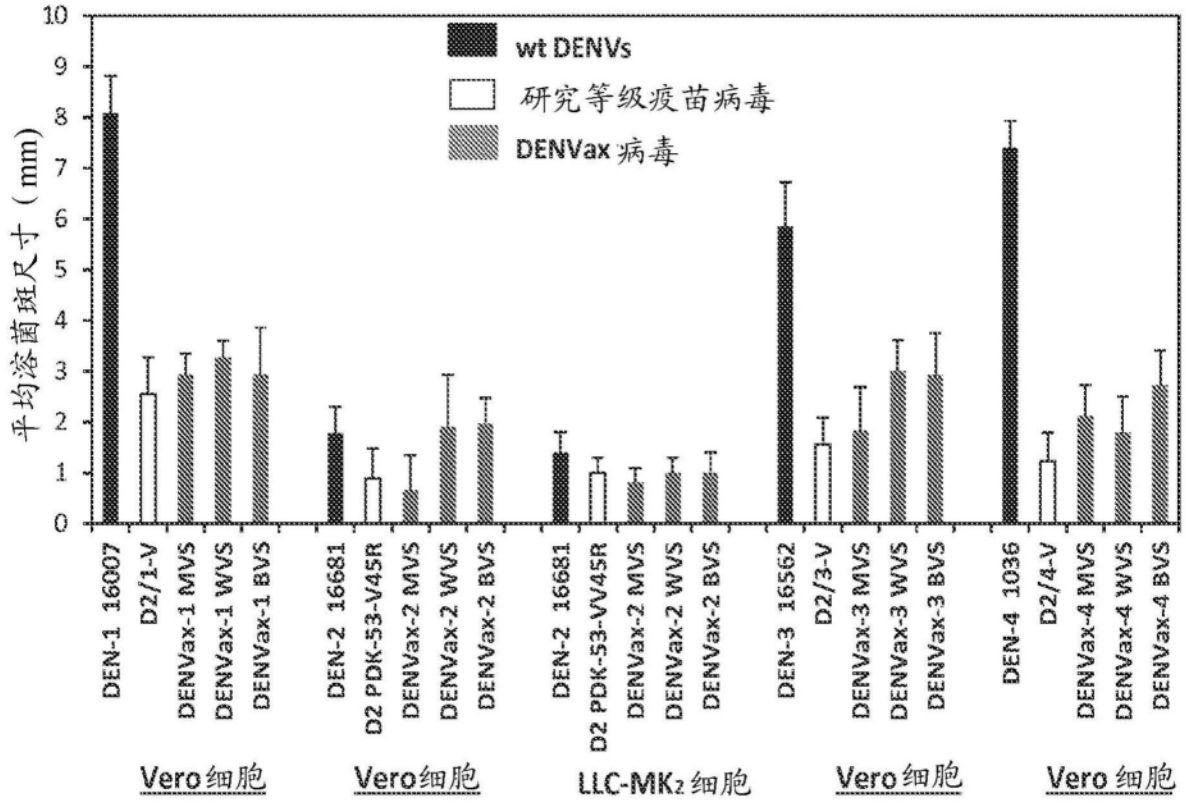

平均溶菌斑尺寸（mm）
wt DENVs
研究等级疫苗病毒
DENVax 病毒
DEN-1 16007
D2/1-V
DENVax-1 MVS
DENVax-1 WVS
DENVax-1 BVS
DEN-2 16681
D2 PDK-53-V45R
DENVax-2 MVS
DENVax-2 WVS
DENVax-2 BVS
DEN-2 16681
D2 PDK-53-VV45R
DENVax-2 MVS
DENVax-2 WVS
DENVax-2 BVS
DEN-3 16562
D2/3-V
DENVax-3 MVS
DENVax-3 WVS
DENVax-3 BVS
DEN-4 1036
D2/4-V
DENVax-4 MVS
DENVax-4 WVS
DENVax-4 BVS
Vero细胞
Vero细胞
LLC-MK2细胞
Vero细胞
Vero细胞

图6

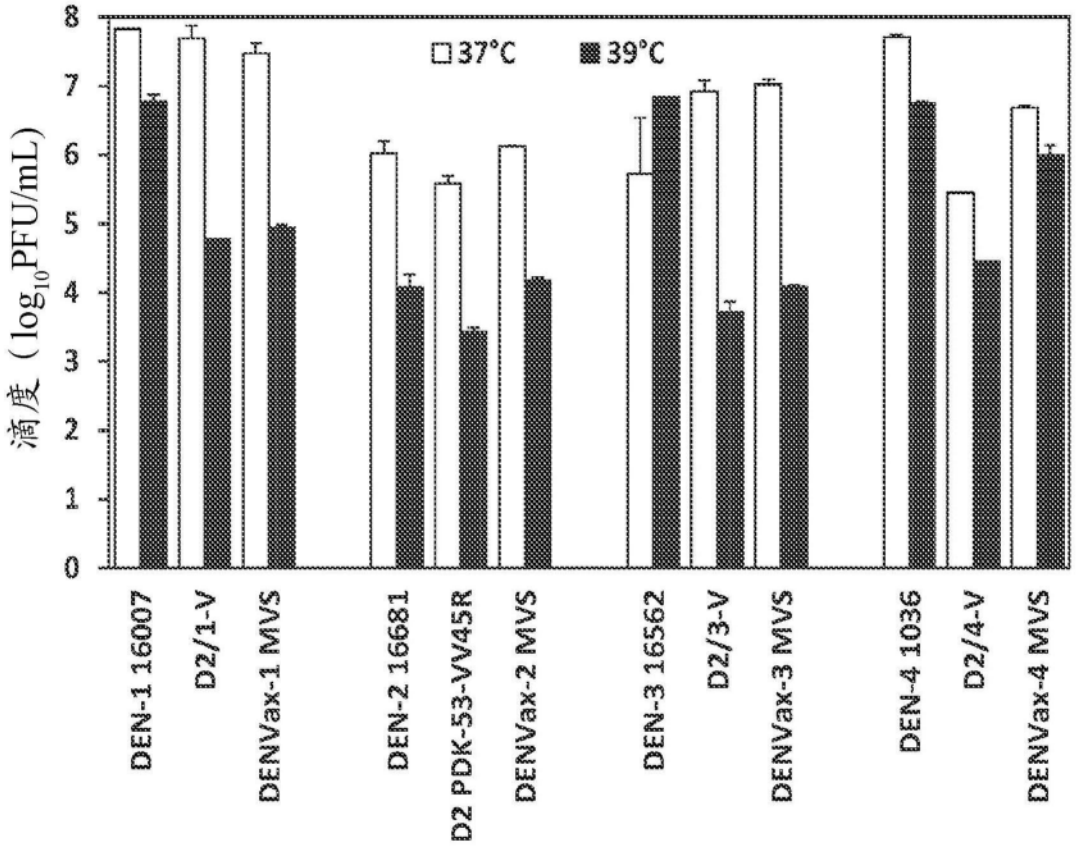

滴度（log10PFU/mL）
37°C
39°C
0
1
2
3
4
5
6
7
8
DEN-1 16007
D2/1-V
DENVax-1 MVS
DEN-2 16681
D2 PDK-53-VV45R
DENVax-2 MVS
DEN-3 16562
D2/3-V
DENVax-3 MVS
DEN-4 1036
D2/4-V
DENVax-4 MVS

图7

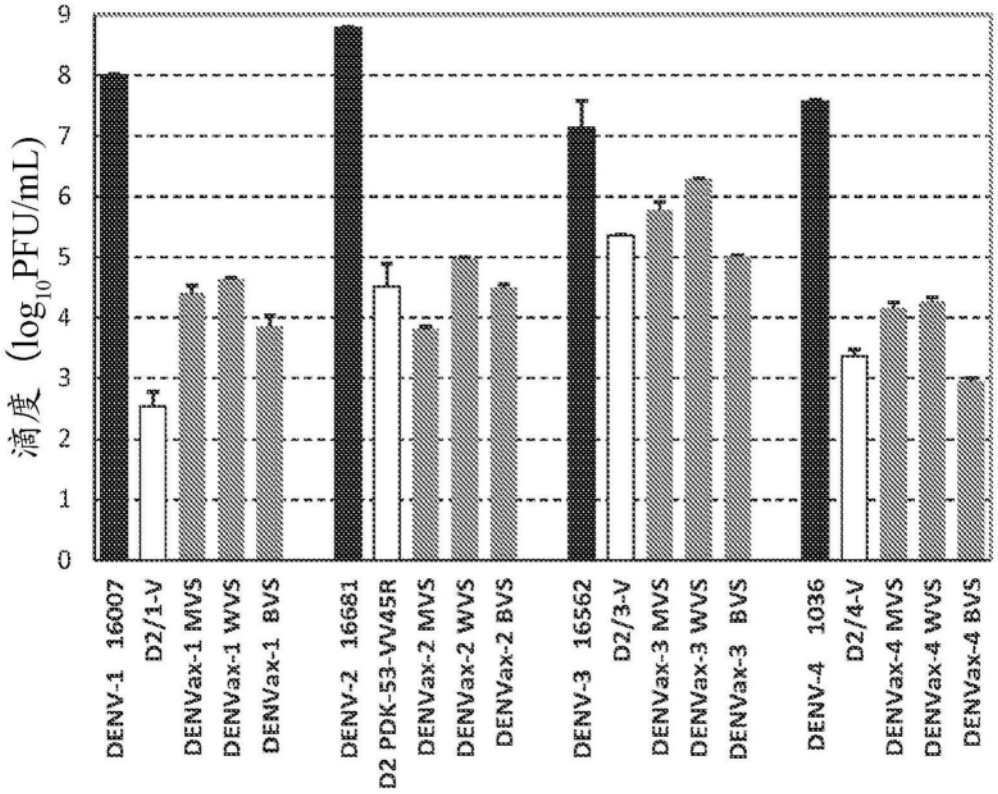

滴度 (log_{10}PFU/mL)
0
1
2
3
4
5
6
7
8
9
DENV-1 16007
D2/1-V
DENVax-1 MVS
DENVax-1 WVS
DENVax-1 BVS
DENV-2 16681
D2 PDK-53-VV45R
DENVax-2 MVS
DENVax-2 WVS
DENVax-2 BVS
DENV-3 16562
D2/3-V
DENVax-3 MVS
DENVax-3 WVS
DENVax-3 BVS
DENV-4 1036
D2/4-V
DENVax-4 MVS
DENVax-4 WVS
DENVax-4 BVS

图8

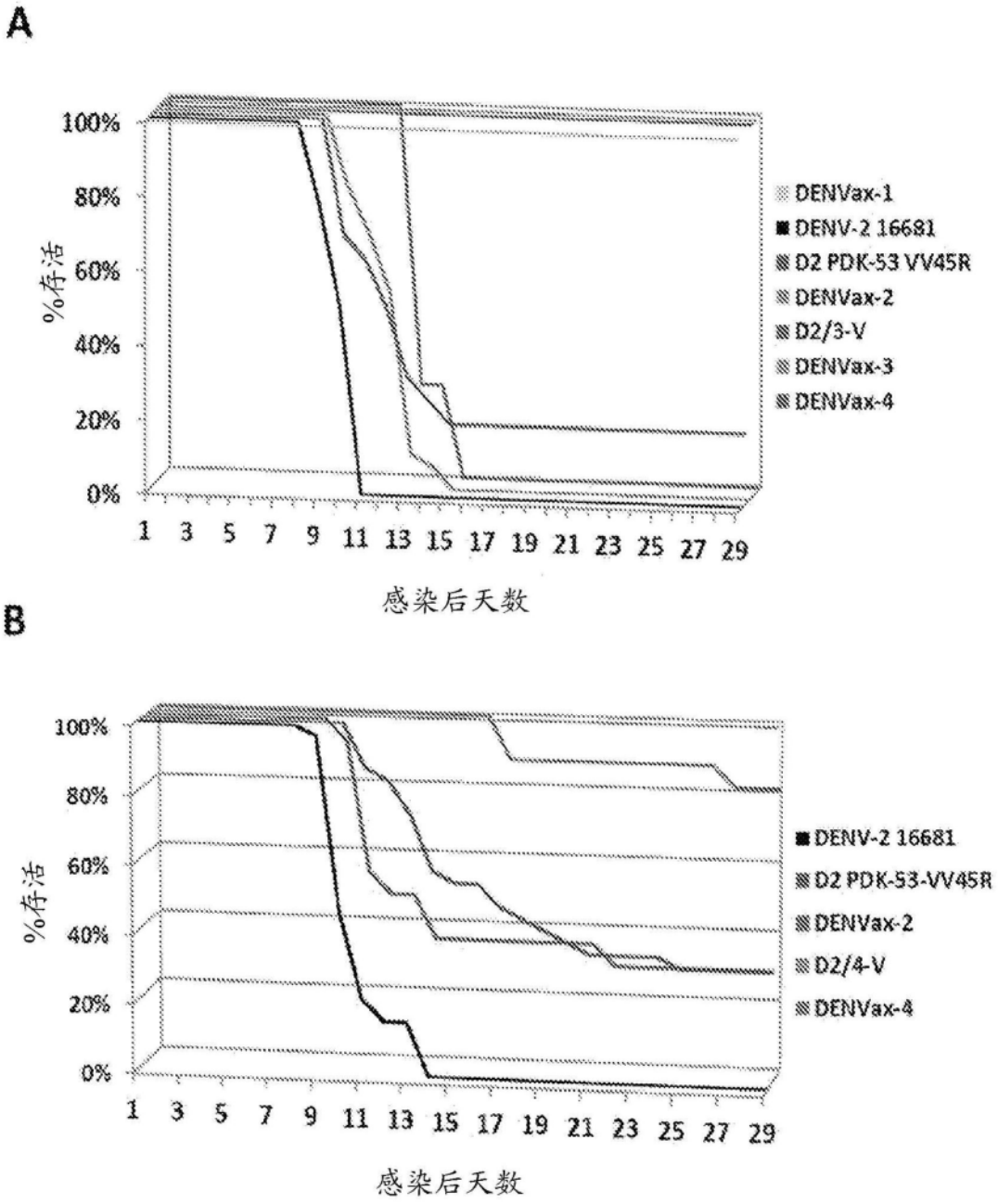
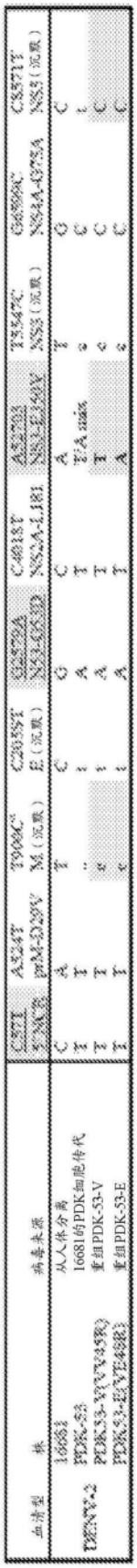

A
100%
80%
60%
40%
20%
0%
%存活
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29
感染后天数
DENVax-1
DENV-2 16681
D2 PDK-53 VV45R
DENVax-2
D2/3-V
DENVax-3
DENVax-4
B
100%
80%
60%
40%
20%
0%
%存活
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29
感染后天数
DENV-2 16681
D2 PDK-53-VV45R
DENVax-2
D2/4-V
DENVax-4

图9



血清型	株	病毒来源	C3771T NS3-G1053D	A3244T pr/M-S329V	T9004C M/(沉默)	C2835T E/(沉默)	G5475A NS3-G1553D	C4018T NS3A-L1031	A5270G NS3-E1540V	T5347C NS3/(沉默)	G6599C NS4A-G1753A	C8577T NS5/(沉默)
DEN2V2	16681	从人体分离	C	A	T	C	G	C	A	T	G	C
	PDK-53	16681的PDK细胞传代	T	T	..	i	A	T	T:A zizzk	a	C	i
	PDK-53-V(V1545K)	重组PDK-53-V	T	T	a	i	A	T	T	c	C	C
	PDK-53-E(V1546E)	重组PDK-53-E	T	T	c	i	A	T	A	c	C	C

下方划线的突变：PDK-53的三个最重要的减毒基因座
红色：PDK-53特异性序列(从16681变化)
粗体：PDK-53乳腺体衍生的V或E病毒之间的不同核苷酸序列
*用于区别原始PDK-53与重组(乳腺体衍生)的病毒后改造的沉默乳腺体标记

图10