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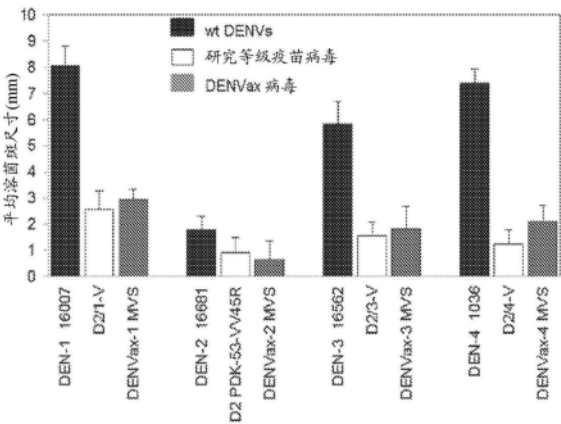
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(54) 发明名称

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,该构建物可以或不连续地在哺乳动物细胞内传代。



1. 修饰的活减毒登革热-2病毒株PDK-53-V, 其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表示, 其中所述多肽分子的氨基酸序列如SEQ ID NO:5或6所示。

2. 根据权利要求1所述的修饰的活减毒登革热-2病毒株PDK-53-V, 其中所述多核苷酸序列如SEQ ID NO:14所示。

3. 修饰的活减毒登革热-2病毒株PDK-53-V, 其包含氨基酸序列如SEQ ID NO:6所示的多肽分子。

4. 药物组合物, 其包含根据权利要求1-3中任一项所述的登革热-2病毒株PDK-53-V以及药学上可接受的赋形剂。

5. 药学上可接受量的权利要求4所述的组合物在制备用于在个体中诱导免疫应答的药物中的用途, 其中所述组合物在个体中针对登革热病毒诱导免疫应答。

6. 载体, 其包含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, 其中所述多肽分子的氨基酸序列如SEQ ID NO:5或6所示。

7. 根据权利要求6所述的载体, 其中所述载体是质粒载体。

8. 根据权利要求6所述的载体, 其中所述载体是cDNA传染性克隆。

9. 细胞, 其包含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, 其中所述多肽分子的氨基酸序列如SEQ ID NO:5或6所示。

10. 免疫原性组合物, 其包含至少一种根据权利要求1-2中任一项所述的修饰的活减毒登革热-2病毒株PDK-53-V以及药学上可接受的载剂。

11. 权利要求10所述的免疫原性组合物, 其进一步包含由全基因组长度核酸嵌合体表示的登革热-1/登革热-2嵌合体, 所述全基因组长度核酸嵌合体包含第一核苷酸序列和第二核苷酸序列, 所述第一核苷酸序列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, 所述第二核苷酸序列编码来自登革热-1 16007的前膜/膜蛋白和包膜蛋白, 其中所述核酸嵌合体编码氨基酸序列如SEQ ID NO:2或3所示的多肽。

12. 权利要求11所述的免疫原性组合物, 其中所述核酸嵌合体的核苷酸序列如SEQ ID NO:1或13所示。

13. 权利要求10所述的免疫原性组合物, 其进一步包含由全基因组长度核酸嵌合体表示的登革热-3/登革热-2嵌合体, 所述全基因组长度核酸嵌合体包含第一核苷酸序列和第二核苷酸序列, 所述第一核苷酸序列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, 所述第二核苷酸序列编码来自登革热-3 16562的前膜/膜蛋白和包膜蛋白, 其中所述核酸嵌合体编码氨基酸序列如SEQ ID NO:8或9所示的多肽。

14. 权利要求13所述的免疫原性组合物, 其中所述核酸嵌合体的核苷酸序列如SEQ ID NO:7或15所示。

15. 权利要求10所述的免疫原性组合物, 其进一步包含由全基因组长度核酸嵌合体表示的登革热-4/登革热-2嵌合体, 所述全基因组长度核酸嵌合体包含第一核苷酸序列和第二核苷酸序列, 所述第一核苷酸序列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, 所述第二核苷酸序列编码

来自登革热-4 1036的前膜/膜蛋白和包膜蛋白,其中所述核酸嵌合体编码氨基酸序列如SEQ ID NO:11或12所示的多肽。

16.根据权利要求15所述的免疫原性组合物,其中所述核酸嵌合体的核苷酸序列如SEQ ID NO:10或16所示。

17.权利要求15所述的免疫原性组合物,其中所述组合物包含全部四种登革热病毒血清型,其为四价组合物。

18.权利要求15所述的免疫原性组合物,其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、日本脑炎病毒和西尼罗病毒。

19.试剂盒,其包含至少一种根据权利要求1-2中任一项所述的修饰的活减毒登革热-2病毒株PDK-53-V或至少一种根据权利要求4和10-18中任一项所述的组合物以及容器。

20.组合物,其包含一种或多种权利要求3所述的修饰的活减毒登革热-2病毒株PDK-53-V和药学上可接受的载剂。

21.权利要求20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。

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] 本申请是申请日为2014年3月12日的PCT国际专利申请PCT/US2014/024603进入中国国家阶段的中国专利申请号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”的分案申请。

[0002] 优先权

[0003] 本PCT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,但无法免于另外减毒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-2 PDK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-2 PDK-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-2 PDK-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现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 10^4 pfu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 10^4 pfu(B)或 10^3 pfu(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-MK₂细胞中的病毒溶菌斑的平均溶菌斑直径 $\pm$ 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 $\pm$ 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) 10^4 pfu剂量的病毒的IC接种。(B) 10^3 pfu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。

具体实施方式

[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,公开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 Laboratory 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-2 PDK-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(boosters)才能实现相同的血清转化率。

[0043] DEN-2 PDK-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体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-2 PDK-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-2 PDK-53-E,与PDK-53-V的差异只在于这一个位置。DEN-2 PDK-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-1 PDK-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效用性,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-2 PDK-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-4 PDK-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°C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 10^6 PFU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] 以下是本发明的一些具体实施方案。

[0107] 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。

[0108] 2.如上述方面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。

[0109] 3.如上述方面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。

[0110] 4.如上述方面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。

[0111] 5.如上述方面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。

[0112] 6.药物组合物,包含上述方面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。

[0113] 7.药物组合物,包含由上述方面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。

[0114] 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上述方面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。

[0115] 9.载体,其编码上述方面1至5中任一项所述的核酸序列。

[0116] 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病毒还包含至少一个额外的突变, 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。

[0117] 11. 如上述方面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。

[0118] 12. 如上述方面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。

[0119] 13. 如上述方面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592处的突变, 其中prM的氨基酸位置52为谷氨酸替代赖氨酸。

[0120] 14. 药物组合物, 包含上述方面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。

[0121] 15. 药物组合物, 包含由上述方面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。

[0122] 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上述方面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。

[0123] 17. 载体, 其编码上述方面10至13中任一项所述的核酸序列。

[0124] 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。

[0125] 19. 如上述方面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。

[0126] 20. 如上述方面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。

[0127] 21. 药物组合物, 包含上述方面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。

[0128] 22. 药物组合物, 包含由上述方面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。

[0129] 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的上述方面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。

[0130] 24. 载体, 其编码上述方面18至20中任一项所述的核酸序列。

[0131] 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病毒还包含至少一个额外的突变, 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。

[0132] 26. 如上述方面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。

[0133] 27. 如上述方面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。

[0134] 28. 如上述方面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。

[0135] 29. 如上述方面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。

[0136] 30. 如上述方面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。

[0137] 31. 如上述方面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。

[0138] 32. 如上述方面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。

[0139] 33. 药物组合物,包含上述方面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。

[0140] 34. 药物组合物,包含由上述方面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。

[0141] 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上述方面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。

[0142] 36. 载体,其编码上述方面25至32中任一项所述的核酸序列。

[0143] 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。

[0144] 38. 如上述方面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。

[0145] 39. 免疫原性组合物,包含上述方面37所述的核酸序列或上述方面38所述的多肽中的一种或多种,以及药学上可接受的载剂。

[0146] 40. 如上述方面39所述的组合物,其还包含活减毒登革热-2病毒。

[0147] 41. 如上述方面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。

[0148] 42. 如上述方面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。

[0149] 43. 如上述方面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。

[0150] 44. 试剂盒,包括上述方面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;或上述方面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。

[0151] 45. 活减毒病毒,包含上述方面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。

[0152] 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。

[0153] 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。

[0154] 48.组合物,包含上述方面47所述的核酸序列中的一种或多种或由上述方面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。

[0155] 49.如上述方面48所述的组合物,其还包含药学上可接受的佐剂。

[0156] 50.组合物,包含上述方面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。

[0157] 51.如上述方面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。

[0158] 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。

[0159] 实施例

[0160] 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例中运行良好的技术,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。

[0161] 实施例1

[0162] 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。

[0163] 前主代DENVax病毒的制造及分析

[0164] 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)。

[0165] 表1.DENVax病毒于WCB-Vero细胞中的cGMP再衍生的实例

	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
[0166]	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
[0167]	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			

[0168] 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 $6.0 \log$ 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-2 PDK-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)。

[0169] 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。

[0170] 表2. 前主代(P7) 种的表征

[0171]

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-1	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

[0172]

	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
	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。

[0173] 实施例2

[0174] 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。

[0175] MVS、WVS及BVS的产生及制造质量控制

[0176] 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。

[0177] MVS、WVS及BVS的遗传分析

[0178] 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)。

[0179] 表3.DENVax种中的核苷酸和氨基酸取代

[0180]

DENVax	核苷酸	氨基酸	前主代	MVS ^a	WVS ^a	BVS ^a
DENVax-1	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
	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

[0181]

	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)						

[0182] 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-66 Asp-Gly的取代是非保守性改变。DENVax-4的NS2A-66突变在DENV-2 PDK-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。

[0183] 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-2 PDK-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。

[0184] DENVax MVS的溶菌斑表现型

[0185] 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。

[0186] 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) $\pm$ 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。

[0187] DENVax MVS的温度敏感性

[0188] 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°C为中等温度敏感的(在39°C的滴度比37°C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°C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°C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)。

[0189] 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°C或39°C于Vero细胞中复制的病毒的平均滴度 $\pm$ SD(误差柱)。

[0190] 蚊C6/36细胞中的DENVax MVS复制

[0191] 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-4 MVS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。

[0192] 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 $\pm$ SD(误差柱)。

[0193] 于全蚊的病毒感染、散播及传播率

[0194] 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 $5.2\pm 0.02\log_{10}$ 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),这比来自野生型登革热血清型-4 1036感染的蚊子的滴度(3.9 ± 1.5 pfu/蚊)低1,000倍。

[0195] 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。

[0196] 表4: 于全蚊中的病毒感染、散播及传播率

[0197]

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)	
DENVax-I	6.9	0% (0/30)	NA	<0.001	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	<0.001	NA	56.4	100% (30/30)	4.0 ± 0.20	0% (0/30)	<0.001
DENVax-2	6.4	0% (0/30)	NA	<0.001	NA	52.7	100% (30/30)	3.5 ± 0.27	7% (2/30)	<0.001
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)	<0.001
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)	<0.001

[0198]

- ^a 如果通过反滴定得自血粉中的多于一次的实验(log₁₀ 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(log₁₀ 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

[0199] 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-2

PDK-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疫苗的其他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的其他野生株相比,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 PU0359、DENV-2 PU0218、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-2 PDK-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。

[0200] 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阈值,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(MID₅₀)/ml。此种MID₅₀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 $2.4 \log_{10}$ 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。

[0201] 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。

[0202] 在乳鼠中的神经毒力

[0203] 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 10^4 pfu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 10^4 pfu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。

[0204] 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 10^4 pfu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。

[0205] 在一些示例性方法中,在低10倍的剂量(10^3 pfu,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。

[0206] 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 10^4 pfu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 10^4 pfu(B)或 10^3 pfu(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。

[0207] WVS和BVS的溶菌斑表现型

[0208] 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-MK₂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)。

[0209] 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。

[0210] 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-MK₂细胞中的病毒溶菌斑的平均溶菌斑直径 $\pm$ 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。

[0211] 在蚊C6/36细胞中的病毒复制

[0212] 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-2 PDK53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($1-2\log_{10}$ PFU/ml降低)。然而,DENVax-3种批次的滴度类似(在 $1\log_{10}$ PFU/ml差值内)于原始研究级嵌合式D2/3-V疫苗病毒。

[0213] 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 $\pm$ 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。

[0214] 在乳鼠中的神经毒力

[0215] 进行额外的实验以分析在新生ICR小鼠中的神经毒力。在 10^4 PFU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 10^4 PFU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 10^4 PFU的剂量下造成100%死亡率(图5A)。然而,当在 10^3 PFU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。

[0216] 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 10^4 PFU剂量下的IC接种。(B)病毒于 10^3 PFU的剂量下的IC接种。

[0217] 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-2 PDK-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。

[0218] 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°C均为TS。

[0219] 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。

[0220] 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。

[0221] 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。

[0222] 材料及方法

[0223] 病毒及细胞

[0224] 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)。

[0225] 从cDNA克隆衍生活重组DENVax病毒

[0226] 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20 μ l等分部分内,并于-80 $^{\circ}$ C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20 μ l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 $0.4-1 \times 10^7$ 生产核准的Vero细胞。

[0227] 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400 μ l 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/500 μ F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75cm²烧瓶,并在36 $^{\circ}$ C $\pm$ 1 $^{\circ}$ C, 5%CO₂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 $^{\circ}$ C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。

[0228] DENVax病毒种的制造

[0229] 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。

[0230] 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,从而筛选全部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-2 PDK-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175cm²烧瓶的Vero细胞内以0.001 MOI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-127TM泊洛沙姆407的存在下(其它E0-P0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°C。

[0231] 通过在0.001 MOI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(6360cm²)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°C储存。

[0232] 在某些方法中,通过使用90mL稀释WVS以实现0.001 MOI感染融合Vero细胞的多个细胞培养器(各为6360cm²)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-127TM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)°C于5(±0.5)%CO₂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°C冷冻储存,以用于随后的汇集和质量控制测试。具有高于10⁵PFU/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°C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°C储存,直至进一步使用。

[0233] 制造产品质量控制

[0234] 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。

[0235] 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°C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25cm²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°C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。

[0236] 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 $\geq 80\%$ 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。

[0237] 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°C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°C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°C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°C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°C和25°C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。

[0238] 病毒溶菌斑测定及免疫焦点测定

[0239] 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。

[0240] 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°C使用5%CO₂孵育7天。去除覆盖层后,使用PBS洗涤三次细胞层,于-20°C使用80%冷丙酮固定30分钟,使用PBS洗涤一次,并于37°C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°C一起孵育1小时或于4°C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°C与碱性磷酸酶-或辣根过氧化物酶(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剂(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。

[0241] 基因序列

[0242] 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。

[0243] 基于Taqman的错配扩增突变测定(TaqMAMA)

[0244] 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5 μ l病毒RNA模板、0.4 μ M每一引物以及0.2 μ M探针的25 μ l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(7-8log₁₀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。

[0245] 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

[0246] 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0.001 MOI一式两份感染每一病毒,并于5%CO₂孵育器内于28°C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°C储存,直至准备用于病毒溶菌斑滴定。

[0247] 在6孔板中于Vero细胞感染后第5天,通过比较39°C的病毒生长与37°C病毒的生长而进行温度敏感性。细胞在37°C细胞用每一病毒于0.001 MOI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%CO₂孵育器内一起孵育,一个设定(一式两份的板)于37°C,而另一个设定于39°C。感染后第5天收集培养物上清液的等分部分(50 μ l),与含40%FBS的等体积DMEM混合,并于-80°C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°C;ERTCO)校准孵育器温度。

[0248] 蚊感染、散播及传播

[0249] 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°C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°C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。

[0250] 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。50 μ l等分部分的血粉保持在-80 $^{\circ}$ C,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 $^{\circ}$ C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100 μ g/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 $^{\circ}$ C,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0.34 μ l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 $^{\circ}$ C,直到进一步处理。

[0251] 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 $\times$ g离心3分钟而澄清。唾液样本于3,000 $\times$ 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。

[0252] 小鼠神经毒力

[0253] 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10³至10⁴pfu病毒的20 μ l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。

[0254] 主代种病毒的衍生

[0255] DENVax-1主代病毒种(MVS)

[0256] 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-116007病毒特异性的;剩余基因组为DEN-2 PDK-53病毒特异性的。标出与野生型病毒(D116007或D216681)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)。

[0257] 基因组及蛋白质中包括的取代:

[0258] D1(prM-E)与D2骨架之间的接合位点:

[0259] a.MluI(nt 451-456):改造的沉默突变,nt-453A-至-G

[0260] b.NgoMIV(nt 2380-2385):改造的突变,nt-2381/2382TG-至-CC(导致E-482Val-至-Ala改变)

[0261] D2 PDK-53病毒骨架(从野生型D2 16681的改变):全部为粗体

[0262] a.5'-非编码区(NCR)-57(nt-57C-至-T):主要减毒基因座(红色)

- [0263] b.NS1-53 Gly-至-Asp(nt-2579G-至-A):主要减毒基因座(红色)
- [0264] c.NS2A-181Leu-至-Phe(nt-4018C-至-T)
- [0265] d.NS3-250 Glu-至-Val(nt-5270A-至-T):主要减毒基因座(红色)
- [0266] e.nt-5547(NS3基因)T-至-C沉默突变
- [0267] f.NS4A-75Gly-至-Ala(nt-6599G-至-C)
- [0268] *PDK-53的nt-8571C-至-T沉默突变未在疫苗病毒中被改造
- [0269] DEN-1prM-E(从野生型D1 16007的改变)
- [0270] a.改造的nt-1575T-至-C沉默突变用于去除天然XbaI位点
- [0271] 在疫苗种中发现的额外取代(与原始克隆有0.03%nt不同)
- [0272] a.NS2A-116Ile-至-Leu(nt-3823A-至-C,粗体)
- [0273] b.NS2B-92Glu-至-Asp(nt-4407A-至-T,粗体)
- [0274] c.nt-7311A-至-G沉默突变(粗体)
- [0275] DENVax-1 MV5的核酸序列(SEQ ID NO:13):

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

>5'-非编码区

10 20 30 40 50 60 70 80 90 100

AGTTGTTAGTCTACGTGGACCGACAAAGACAGATTCTTTGAGGGAGCTAAGCTCAATGTAGTTCTAACAGTTTTTTAATTAGAGAGCAGATCTCTGATGA

>C

M N

110 120 130 140 150 160 170 180 190 200

ATAACCAACGGAAGGCGAAAAACACGCCTTTCAATATGCTGAAACGCGAGAGAAACCGCGTGTGCAACAGCTGACAAAGAGATTCTCACT

N Q R K K A K N T P F N M L K R E R N R V S T V Q Q L T K R F S L

210 220 230 240 250 260 270 280 290 300

TGGAAATGCTGCGAGGACGAGGACCATTAATACTGTTTCATGGCCCTGTTGGCGCTTCCTTCGTTTCCTAACATCCCAACAGCAGGGATATTGAAGAGA

G M L Q G R G P L K L F M A L V A F L R F L T I P P T A G I L K R

310 320 330 340 350 360 370 380 390 400

TGGGGAACCAATTAATAATCAAAAGCTATTAATGTTTGGAGGGGTTTCAGGAAAGAGATTGGAAGGATGCTGAACATCTTGAATAGGAGACGAGATCTG

W G T I K K S K A I N V L R G F R K E I G R M L N I L N R R R R S A

>prM D1 16007 序列的开端

410 420 430 440 450 460 470 480 490 500

CAGGCATGATCATTATGCTGATTCCAACAGTGATGGCGTTCCATTTAACCAACCGCGTGGGGAGAGCCGCATATGATGTTAGCAAGCAGGAAAGAGGAA

G M I I M L I P T V M A F H L T T R G G E P H M I V S K Q E R G K

|

改造的 MluI 剪接位点(nt-453 A-至-G 沉默)

510 520 530 540 550 560 570 580 590 600

GTCACTTTTGTTCAGACCTCTGCAGGTGTCAACATGTGCACCTCAITTCGATGGATTGGGAGAGTTGTGTGAGGACAGATGACCTACAAATGCCCC

S L L F K T S A G V N M C T L I A M D L G E L C E D T M T Y K C P

610 620 630 640 650 660 670 680 690 700

CGGATCACTGAGGCGGAACAGATGACGTTGACTGTTGGTGCATGCCACGGACACATGGGTGACCTATGGAACGTGCTCTCAAATGGCGAACACCGAC

R I T E A E P D D V D C W C N A T D T W V T Y G T C S Q T G E H R R

>M

710 720 730 740 750 760 770 780 790 800

GAGACAAACGTTCCGTCGATTGGCCCCACAGTGGGGCTTGGCCTAGAAACAAGAGCCGAAACGTTGATGTCCTCTGAAGGTGCTTGGAAACAGATACA

D K R S V A L A P H V G L G L E T R A E T W M S S E G A W K Q I Q

810 820 830 840 850 860 870 880 890 900

AAAAGTAGAGACTTGGGCTCTGAGACATCCAGGATTCACGGTGATAGCCCTTTTCTAGCACATGCCATAGGAACATCCATCACCAGAAAGGGATCATT

K V E T W A L R H P G F T V I A L F L A H A I G T S I T Q K G I I

>E

910 920 930 940 950 960 970 980 990 1000

TTCACTTTGCTGATGCTGGTAACACCATCTATGGCCATGCGATGCGTGGGAATAGGCAACAGAGACTTCGTGGAAGGACTGTGAGGAGCAACATGGGTGG

F I L L M L V T P S M A M R C V G I G N R D F V E G L S G A T W V D

1010 1020 1030 1040 1050 1060 1070 1080 1090 1100

ATGTGTTACTGGAGCATGGAAGTTGCGTCAACCATGGCAAAAAACAACCAACATGGACATTGAACTCTTGAAGACGGAGGTCACAAACCCCTGCAGT

V V L E H G S C V T T M A K N K P T L D I E L L K T E V T N P A V

1110 1120 1130 1140 1150 1160 1170 1180 1190 1200

TCTGCGTAAATTGTGCAATTGAAGCTAAAAATATCAACACCAACCGATTTCGAGATGTCCAACACAAGGAGAAGCCACTGGTGGAGAACAAGACGCG

L R K L C I E A K I S N T T T D S R C P T Q G E A T L V E E Q D A

1210 1220 1230 1240 1250 1260 1270 1280 1290 1300

AACTTTGTGTGCCGACGAACGTTCTGTGGACAGAGGCTGGGGCAATGGCTGTGGGCTATTTCGGAAGGTAGTCTAATAACGTGTGCCAAGTTTAAGTGTG

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
TGACAAACTAGAAAGAAAGATAGTTCAATATGAAACCTAAAAATTTCAGTGATAGTCACCGTCCACACTGGAGATCAGCACCAGGTGGGAAATGAGAC
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
TACAGAACATGGAACTGCAACCATACACCTCAAGCTCCTACGTCGGAATACAGCTGACCGACTACGGAACCTTACATTAGATTGTTACCTAGG
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
ACAGGGCTAGATTTTAAACGAGATGGTGTGCTGACAATGAAAGAAAGATCATGGCTTGTCACAAACAATGGTTCCTAGACTTACCACTGCCTTGGACCT
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
CTGGGGCTTCAACATCCCAGAGACTTGAACAGACAAGATTACTGGTCACATTTAAGCAGCTCATGCAAAGAAGCAGGAAGTAGTCGTAAGTACTAGGATC
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
ACAAGAAGGAGCAATGCACACTGCGCTGACTGGAGCGACAGAAATCCAAACGTCAGGAACGACAAACAATTTTCGAGGACACCTAAAAATGCAGACTAAAA
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
ATGGACAACTAACTTTAAAGGGATGTCTATGTGTGTGACAGGCTCATTCAAGTTAGAGAAAGAAAGTGGCTGAGACCCAGCATGGAAGTGTCTGG
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
TGCAAGTTAAATGAAGGAACAGACGACCATGCAAGATTCCCTTTTCGACCCCAAGATGAGAAAGGAGCAACCCAGAAATGGGAGATTAAATAACAGCCAA
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
CCCCATAGTCACTGACAAAGAAAAACAGTCAATATTGAGGCAGAACACCCCTTTGGTGAGAGCTACATCGTGTAGGAGCAGGTGAAAAGCTTTGAA
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
CTAAGCTGGTTCAAGAAAGGAAGCAGCATAGGGAATGTTTGAAGCACTGCCGAGGAGCAGCAAGGATGGCCATTCTGGGAGACACCGCATGGGACT
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
TCGGTCTTATAGGAGGAGTGTTCACGTCTATGGGAAACTGGTACACCAAGTGTGGAAGTGCATATGGAGTTTGTGTTAGCGGAGTTTCTTGGACCAT
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
GAAATAGGAATAGGAGATTCTGCTGACATGGCTAGGATTAAATTCAAGGAACACGTCCTTTTCGATGATGTGCATCGCAGCCGGCATTGTGACACTGTAT
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
TTGGGAGTCATGGTGAGGCGGATAGTGGTTGCGTTGTGAGCTGGAAACAAAGAACTGAAATGTGCAGTGGGATTTCATCACAGACAACTGCACA
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
CATGGACAGAACATCAAGTTCACACCAAGATCCCTTCAAACTAGCTTCAGCTATCCAGAAAGCCATGAAGAGGACATTGTGGAATCCGCTCAGT
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
AACAAAGACTGGAGAATCTGATGTGGAACAAATAACACCAGAAATTGAATCACAATCTATCAGAAATGAGGTGAAGTTAACTATTATGACAGGAGACATC
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
AAAGGAATCATGCAGGAGGAAACGATCTCTGCGGCTCAGCCCACTGAGCTGAAGTATTCATGGAACATGGGCAAGCAAAATGCTCTCTACAG
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
AGTCTCATAACAGACCTTTCTCATTGATGGCCCCGAAACAGCAGAATGCCCAACACAAATAGAGCTTGAATTCGTTGGAAGTTGAAGACTATGGCTT
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
TGGAGTATTACACCAATATATGGCTAAAATTGAAAGAAAAACAGGATGTATTCTGCGACTCAAACTCATGTGACGGCCATAAAGACAAACAGAGCC
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

[0277]

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3010      3020      3030      3040      3050      3060      3070      3080      3090      3100
GTCCATGCCGATATGGGTTATTGGATAGAAAAGTGCACTCAATGACACATGGGAAGATAGAGAAAAGCCTCTTTTCATTGAAAGTTAAAACTGCCACTGGCCAA
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
AATCACACACCCTCTGGAGCAATGGAGTGCTAGAAAAGTGAGATGATAAATCCAAAGAAATCTCGCTGGACCAAGTGCTCAACACAACATATAGACCAGGCTA
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
CCATACACAAATAACAGGACCATGGCATCTAGGTAAGCTTGAGATGGACTTTGATTTCTGTGATGGAAACAAGTGGTAGTACTGAGGACTGCGGAAAT
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
AGAGGACCCCTCTTTGAGAACAACTGCTCTGGAAAACATCAACAGAATGGTGCTGCCGATCTTGACATTACCACCGCTAAGATACAGAGGTGAGG
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
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>NS2A

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3410      3420      3430      3440      3450      3460      3470      3480      3490      3500
ATGGGTGCTGGTACGGGATGGAAATCAGACCATTGAAGGAGAAAGAGAATTTGGTCAACTCCTTGCTCACAGCTGGACATGGGCAGGTCGACAACCTT
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
TTCAGTAGGAGTCTTGGGAATGGCATTGTCTCTGGAGGAAATGCTTAGGACCCGAGTAGGAACGAAACATGCAATACTACTAGTTGCAAGTTTCTTTTGTG
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
ACATTGATCAGGGAACATGTCTTTAGAGACCTGGGAAGAGTGATGGTTATGGTAGCGCCACTATGACGGATGACATAGGTATGGCGGTGACTTATC
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
TTGCCCTACTAGCAGCTTCAAAGTCAGACCAACTTTTGCACTGGAAGTACTCTTGAGAAAAGCTGACCTCCAAGGAATTGATGATGACTACTATAGGAAT
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
TGTACTCCTCTCCAGAGCACCCTACCAGAGACCACTTTGAGTTGACTGATGCGTTAGCCTTAGGCATGATGGTCTCAAATGGTGAGAAATATGGAA
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
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[0278]

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

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3910      3920      3930      3940      3950      3960      3970      3980      3990      4000
AAGTATCAATTTGGCAGTGACTATCATGGCTATCTTGTCGTCCCAACGAGTGATATTACAAAACGATGGAAAGTGAGTTGCACAATATTGGCAGTGG
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
TGTCCGTTTCCCCACTGTTCTTAACATCTCACAGCAAAAAACAGATTGGATACCATTAGCATTGACGATCAAAGGTCTCAATCCAACAGCTATTTTCT
S V S P L F L T S S 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
AACAAACCCTCTCAAGAACAGCAAGAAAAGGAGCTGGCCATTAAATGAGGCTATCATGGCAGTCGGGATGGTGAGCATTTTAGCCAGTTCTCTCCTAAAA
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
AATGATATTCCCATGACAGGACCATTAGTGGCTGGAGGGCTCCTCACTGTGTGCTACGTGCTCACTGGACGATCGGCCGATTGGAACTGGAGAGAGCAG
N D I P M T G P L V A G G 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
CCGATGTCAAATGGGAAGACAGGCAGAGATATCAGGAAGCAGTCCAATCCTGTCAATAACAATATCAGAAGATGGTAGCATGTGATAAAAAATGAAGA
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
GGAAGATCAAACACTGACCATACTCATTAGAACAGGATTGCTGGTGATCTCAGGACTTTTCTCTGTATCAATACCAATCACGGCAGCAGCATGGTACCTG
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
TGGGAAGTGAAGAAACAACGGGCCGAGTATTGTGGGATGTTCTTCACCCCCACCCATGGGAAGGCTGAACTGGAAGATGGAGCCTATAGAATTAAAGC
```

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
AAAAAGGATTCTTGGATATTTCCAGATCGGAGCCGAGTTTACAAAGAAGGAACATTCATACAATGTGGCATGTACACGTGGCGCTGTTCTAATGCA
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
TAAAGGAAAGAGGATTGAACCATCATGGGCGGACGTCAAGAAAGACCTTAATATCATATGGAGGAGGCTGGAAGTTAGAAGGAGAATGGAAGGAAGGAGAA
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
GAAGTCCAGGTATTGGCACTGGAGCCTGGAAAAATCCAAGAGCCGTCCAACGAAACCTGGTCTTTTCAAAACCAACGCGGAACAAATAGGTGCTGTAT
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
CTCTGACATTTTCTCTGGAACGTGAGGATCTCCAATTATCGACAAAAAGGAAAGTTGTGGGTCTTTATGGTAATGGTGTGTACAAGGAGTGGAGC
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
ATATGTGAGTGTATAGCCAGACTGAAAAAGCATTGAAGACAACCCAGAGATCGAAGATGACATTTCCGAAAGAGAAGACTGACCATCATGGACCTC
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
CACCCAGGAGCGGGAAGACGAAGAGATACCTTCCGGCCATAGTCAGAGAAGCTATAAAACGGGGTTTGAGAACATTAACTTGGCCCCACTAGAGTTG
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
TGGCAGCTGAAATGGAGGAAGCCCTTAGAGGACTTCCAATAAGATACAGACCCAGCCATCAGAGCTG*GCACACCGGGCGGAGATTGTGGACCTAAT
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
GTGTGATGCCACATTTACCATGAGGCTGCTATCACCAGTTAGAGTGCCAACTACAACTGATTATCATGGACGAAGCCCATTTACACAGCCAGCAAGT
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
ATAGCAGCTAGAGGATACATCTCAACTCGAGTGGAGATGGGTGAGGCAGCTGGGATTTTATGACAGCCACTCCCCGGGAAGCAGAGACCCATTTCTCTC
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
AGAGCAATGCACCAATCATAGATGAAGAAAGAGAAATCCCTGAACGCTCGTGGAAATCCGGACATGAATGGGTACCGGATTTTAAAGGGAAGACTGTTTG
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
GTTCTGTTCCAAGTATAAAGCAGGAATGATATAGCAGCTTGCCTGAGGAAAAATGGAAGAAAGTGATACAACCTCAGTAGGAAGACCTTTGATTCTGAG
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
TATGTCAAGACTAGAACCAATGATTGGGACTTCGTGGTTACAACCTGACATTTTCAGAAATGGGTGCCAATTTCAAGGCTGAGAGGGTTATAGACCCAGAC
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
GCTGCATGAACACAGTCATACTAACAGATGGTGAAGAGCGGGTGATTCTGCGAGGACCTATGCCAGTGACCCACTCTAGTGCAGCACAAGAGAGGGAG
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
AATAGGAAGAAATCCAAAAATGAGAATGACAGTACATATACATGGGGGAACTCTGGAAAAATGATGAAGACTGTGCACACTGGAAAGAAAGCTAAAATG
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
CTCTAGATAACATCAACACGCGCAGAAGGAATCATCTAGCATGTTGGAACAGAGCGTGAAAGGTGGATGCCATTGATGGCGAATACCGCTTGAGAG
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
GAGAAGCAAGGAAAACTTTGTAGACTTAATGAGAAGAGGAGACCTACAGTCTGGTGGCTACAGAGTGGCAGCTGAAGGCATCAACTACGCAGACAG
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
AAGGTGGTGGTTTGTATGGAGTCAAGAACAACCAATCCTAGAAGAAAACGTGGAAGTTGAAATCTGGACAAAAGAAGGGGAAGGAATGAAACCC
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
AGATGGTTGGATGCTAGGATCTATTCTGACCCACTGGCGCTAAAAGAATTTAAGGAATTTGCAGCCGGAAGAAAGTCTCTGACCCCTGAACCTAATCACAG
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
AAATGGGTAGGCTCCCAACCTTCATGACTCAGAAGCAAGAGACGCACCTAGCAACTTAGCAGTGTGCACACGGCTGAGGCAGTGGAAAGGGCGTACAA
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
CCATGCTCTCAGTGAAGTCCCGAGACCTGGAGACATTGCTTTTACTGACACTTCTGGCTACAGTACCGGAGGGATCTTTTATTCTTGATGAGCGCA
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
AGGGGCATAGGGAAGATGACCTGGGAATGTGCTGCATAATCAGCGCTAGCATCTCTATGGTACGCACAAATACAGCCACACTGGATAGCAGCTTCAA
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
TAATACTGGAGTTTTTCTCATAGTTTTGCTTATTCCAGAACCCTGAAACAGAGAACACCCCAAGACAACCAACTGACCTACGTTGTCATAGCCATCTT
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
CACAGTGGTGGCGCAACCATGGCAACGAGATGGGTTTCCTAGAAAAACGAAGAAAGATCTCGGATTGGGAAGCATTGCAACCCAGCAACCCGAGAGC
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
AACATCTGGACATAGATCTACGTCCTGCATCAGCATGGACGCTGTATGGCCGTCGCAACATTGTGTACACCAATGTGAGACATGACATTGAAATTT
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
CCTCAGTGAATGTGTCCCTAACAGCTATAGCCAACCAAGCCACAGTGTATGATGGGTCTCGGGAAGGATGGCCATTGTCAAAGATGGACATCGGAGTTCC
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
CCTTCTCGCCATTGGATGCTACTCACAAGTCAACCCATACTCTCACAGCAGCTCTTTTCTTATTGGTAGCACATTATGCCATCATAGGGCCAGGACTC
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
CAAGCAAAAGCAACCGAGAGCTCAGAAAAGAGCAGCGCGGGCATCATGAAAAACCAACTGTGCGATGGAATAACAGTGATTGACCTAGATCCAATAC
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
CTTATGATCCGAAGTTTGAAGAGCAGTTGGGACAAGTATGCTCCTAGTCTCTGCGTGAAGTATTGATGATGAGGACTACATGGGCTCTGTGTGA
Y D P K F E K Q L G Q V M 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
GGCTTTAACCCTTAGCTACCGGGCCCATCTCCACATTGTGGGAAGGAAATCCAGGGAGGTTTTGGAACTACTACCATTCGCGGTGTCAATGGCTAACATTTTT
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
AGAGGGAGTTACTTGGCCGAGCTGGACTTCTCTTTTCTATTATGAAGAACAACAACCAACAAGAAGGGGAACCTGGCAACATAGGAGAGACGCTTGGAG
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
AGAAATGGAAAAGCCGATTGAACGCATTGGGAAAAAGTGAATTCAGATCTACAAGAAAAGTGAATCCAGGAAGTGGATAGAACCCTTAGCAAAAAGAGG
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
CATTAAAAGAGGAGAAACGGACCATCACGCTGTGTGCGAGGCTCAGCAAACTGAGATGGTTGTTGAGAGAAACATGGTCCACACCAGAGGGGAAAGTA
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
GTGGACCTCGGTTGTGGCAGAGGAGGCTGGTCATACTATTGTGGAGGACTAAAGAATGTAAGAGAAGTCAAAGGCCTAACAAAAGGAGGACCAGGACAG
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
AAGAACCCTCCCATGTCAACATATGGGTGGAATCTAGTGCCTCTCAAAGTGGAGTTGACGTTTTCTTCATCCCGCCAGAAAAGTGTGACACATTATT
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
GTGTGACATAGGGGAGTCAACCAATCCCAAGTGAAGCAGGACGAACACTCAGAGTCTTAACTTAGTAGAAAATGGTTGAACAACAACACTCAA
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

[0280]

[0281]

8110 8120 8130 8140 8150 8160 8170 8180 8190 8200
TTTTGCATAAAGTTCTCAACCCATATATGCGCTCAGTCATAGAAAAATGGAAGCACTACAAAGGAAATATGGAGGAGCCCTAGTGAGGAATCCACTCT
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
CACGAACTCCACACATGAGATGTACTGGGTATCCAATGCTTCCGGGAACATAGTGTCACTCAGTGAACATGATTCAAGGATGTTGATCAACAGATTAC
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
AATGAGATACAAGAAAGCCACTTACGAGCCGGATGTTGACCTCGGAAGCGGAACCCGTAACATCGGGATTGAAAGTGAGATACCAACCTAGATATAATT
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
GGGAAAGAATAGAAAAATAAGCAAGAGCATGAAACATCATGGCACTATGACCAAGACCACCCATACAAAACGTGGGCATACCATGGTAGCTATGAAA
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
CAAAACAGACTGGATCAGCATCATCCATGGTCAACGGAGTGGTCAGGCTGCTGACAAAACCTTGGGACGTCGTCGCCATGGTGACACAGATGGCAATGAC
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
AGACAGACTCCATTGGACAACAGCGCTTTTAAAGAGAAAGTGGACACGAGAACCCAGAAACCGAAAGAGGACGAAGAACTAATGAAAATAACA
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
GCAGATGGCTTTGGAAAGAAATTAGGGAAGAAAAAGACACCCAGGATGTGCACAGAGAAGAAATTCACAAGAAAGGTGAGAGCAATGCAGCCTTGGGGG
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
CCATATTCTACTGATGAGAAAGTGAAGTCCGACGTCGAGCTGTTGAAGATAGTAGGTTTGGGAGCTGGTTGACAGGAAAGGAATCTCCATCTTGA
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
AGGAAAGTGTGAAACATGTGTACACATGATGGGAAAAAGAGAGAAGCTAGGGGAATTCGGCAAGGCAAAAGGCAGCAGGCCATATGGTACATG
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
TGGCTTGGAGCACGCTTCTTAGAGTTTGAAGCCCTAGGATTCTTAAATGAAGATCACTGGTTCTCCAGAGAGAACTCCCTGAGTGGAGTGAAGGAGAAG
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
GGCTGCACAGCTAGGTTACATTCTAAGAGACGTGAGCAAGAAAGAGGAGGAGCAATGTATGCCGATGACACCCGAGGATGGGATACAAGAAATCACACT
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
AGAAGACCTAAAAAATGAAGAAATGGTAACAAACCATGGAAGGAGAACACAAGAAACTAGCCGAGGCCATTTTCAAACCTAACGTACCAAAACAAGGTG
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
GTGCGTGTGCAAGACCAACCAAGAGGACAGTAAATGGACATCATATCGAGAAGAGACCAAGAGGTAGTGGACAAGTTGGCACCTATGGACTCAATA
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
CTTTCACCAATATGGAAGCCCAACTAATCAGACAGATGGAGGAGAGGAGTCTTTAAAGCATTTCAGCACCTAACATCACAGAAGAAATCGCTGTGCA
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
AAACTGGTTAGCAAGAGTGGGCGCGAAAGGTTATCAAGAATGGCCATCAGTGAGATGATTGTGTTGTGAAACCTTTAGATGACAGGTTTCGCAAGCGCT
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
TTAACAGCTCTAAATGACATGGGAAGATTAGGAAAGACATACAACATGGGAACCTTCAAGAGGATGGAATGATTGGACACAAGTGCCCTTCTGTTTCAC
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
ACCATTTCCATGAGTTAATCATGAAGACGGTCGCGTACTCGTTGTTCCATGTAGAAAACCAAGATGAAGTATTGGCAGAGCCCCGAATCTCCCAAGGAGC
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
AGGGTGGTCTTTGCGGAGACGGCTGTTTGGGGAAGTCTTACGCCCAATGTGGAGCTTGATGTACTTCCACAGACGCGACCTCAGGCTGGCGGCAAAAT
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
GCTATTGCTCGGCAGTACCATCACATTGGGTCCAACAAGTCGAACAACCTGGTCCATACATGCTAAACATGAATGGATGACAACGGAAGACATGCTGA
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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CAGTCTGGAACAGGGTGTGGATTCAAGAAAACCCATGGATGGAAGACAAAACCTCCAGTGGAATCATGGGAGGAAATCCCATACTTGGGGAAAAGAGAAGA
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
CCAATGGTGGCTCATTTGATTGGGTTAAACAAGCAGGGCCACCTGGGCAAAGAATCCAAGCAGCAATAAATCAAGTTAGATCCCTTATAGGCAATGAA
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

10210 10220 10230 10240 10250 10260 10270 10280 10290 10300
>3'-非编码区
GAATACACAGATTACATGCCATCCATGAAAAGATTGAGAAGAGAAGAGGAAGAAGCAGGAGTTCTGTGGTAGAAAGCAAACTAACATGAAACAAGGCTA
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
GAAGTCAGGTCGGATTAAAGCCATAGTACGGAATAAACTATGCTACCTGTGAGCCCCGTCCTCAAGGACGTTAAAGAAGTCAGGCCATCATAAATGCCATAG

10410 10420 10430 10440 10450 10460 10470 10480 10490 10500
CTTGAGTAAACTATGCAGCCTGTAGCTCCACCTGAGAAGGTGTAAAAAATCCGGAGGCCCAAAACCATGGAAGCTGTACGCATGGCGTAGTGGACTAGC

10510 10520 10530 10540 10550 10560 10570 10580 10590 10600
GGTTAGAGGAGACCCCTCCCTTACAAATCGCAGCAACAATGGGGGCCCAAGGCGAGATGAAGCTGTAGTCTCGCTGGAAGGACTAGAGGTTAGAGGAGAC

10610 10620 10630 10640 10650 10660 10670 10680 10690 10700
CCCCCGAAACAAAAACAGCATATTGACGCTGGGAAAGACCAGAGATCCTGCTGTCTCCTCAGCATCATTCCAGGCACAGAACGCCAGAAATGGAATG

10710 10720
GTGCTGTTGAATCAACAGGTTCT
```

[0282] DENVax-2主代病毒种(MVS)

[0284] 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-2 16681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)。

[0285] 基因组和蛋白质中包括的取代:

[0286] D2 PDK-53病毒骨架(从野生型D2 16681的改变):均为粗体

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

[0288] b.prM-29Asp-至-Val(nt-524A-至-T)

[0289] c.nt-2055C-至-T(E基因)沉默突变

[0290] d.NS1-53 Gly-至-Asp(nt-2579G-至-A):主要减毒基因座(红色)

[0291] e.NS2A-181Leu-至-Phe(nt-4018C-至-T)

[0292] f.NS3-250 Glu-至-Val(nt-5270A-至-T):主要减毒基因座(红色)

[0293] g.nt-5547(NS3基因)T-至-C沉默突变

[0294] h.NS4A-75Gly-至-Ala(nt-6599G-至-C)

[0295] *在疫苗病毒中的PDK-53的nt-8571C-至-T沉默突变未改造。

[0296] 改造的克隆标记(沉默突变):

[0297] a.nt-900T-至-C沉默突变:感染克隆标记

[0298] 在疫苗种中发现的额外取代(与原始克隆差异0.02%nt)

[0299] a.prM-52Lys-至-Glu(nt-592A-至-G),粗体

[0300] b.NS5-412 Ile-至-Val(nt-8803A-至-G),粗体

[0301] DENVax-2 MVS的核酸序列(SEQ ID NO:14):

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

>5'-NC 10 20 30 40 50 60 70 80 90 100 110 120 >C
AGTTGTTAGTCTACGTGGACGACAAAGACAGATTCTTTGAGGAGCTAAGCTCAAAGTAGTTCTAAACAGTTTTTAAATTAGAGAGCAGATCTCTGATGAATAACCAACGGAAAAAGCGG
M N N Q R K K A

130 140 150 160 170 180 190 200 210 220 230 240
AAAAACACGCTTTCAATATGCTGAAAAGGAGAGAAACCGCGTGTGACTGTGCAACAGCTGACAAAGAGATTCTCACTTGAATGCTGACGGGACGAGGACCATTTAAACTGTTTCATG
K N T P F N M L K E E R N R V S T V Q Q L T K R F S L G M L Q G R G P L K L F M

250 260 270 280 290 300 310 320 330 340 350 360
GCCCTGGTGGCGTTCTTCTGTTTCTTAACAATCCCAACAGCAGGGATATTGAAGAGATGGGGAACAATTTAAAAATCAAAAGCTATTATGTTTTGAGAGGGTTGAGGAAAGAGATT
A L V A F L R F L T I P P T A G I L K R W G T I K K S K A I N V L R G F R K E I

370 380 390 400 410 420 430 440 450 460 470 480
GGAAGGATGCTGAACATCTTGAATAGGAGACGAGATCTGAGGCTGATCATTATGCTGATTCCAAAGTGTGAGGCTTCCATTAAACCAACGTAGAGGAGAAACACATGATCGTC
G R M L N I L N R R R R S A G M I I M L I P T V M A F H L T T R N G E P H M I V

490 500 510 520 530 540 550 560 570 580 590 600
AGCAGACAAGAGAAAGGAAAAGTCTTCTGTTTAAACAGAGGTTGGCGTGAACATGTGTACCTCATGGCCATGGACCTTGGTGAATGTGTGAAGAACAATCACGATGACGAGTGTCC
S R Q E K G K S L L F K T E V G V N M C T L M A M D L G E L C E D T I T Y E C P

D2 PDK-53 特异性 prM-29 Val (wt D2 16681 Asp, nt-524-A) 额外的 prM-52 Lys-至-Glu 突变(nt-592 A-至-G)

610 620 630 640 650 660 670 680 690 700 710 720
CTTCTCAGGAGAAATCTGAGAGACATAGACTGTGCGAACTCTACGTCCACGTGGGTAACCTTGGGAGCGTGTACCCATGGAGAGAAACATAGAGAGAAAGATCAGTGGCA
L L R Q N E P E D I D C W C N S T S T W V T Y G T C T T M G E H R R E K R S V A

730 740 750 760 770 780 790 800 810 820 830 840
CTCGTTCCACATGTGGAGTGGGAGACGAGAACTGAAATGTCATCAGAGGGGCTGGAAACATGTCCAGAGAAATGGAACCTTGGATCTTGAGATCTCAGGCTTCACCC
L V P H V G M G L E T R T E T W M S S E G A W K H V Q R I E T W I L R H P G F T

850 860 870 880 890 900 910 920 930 940 950 960
ATGATGCGAGCAATCTGCGATACACATAGGAAAGACACATTTCCAAAGAGCGCTGATCTTCACTCTTACTGACAGCTGTCACTCTCTCAATGACAAATCGGTTCATAGGAATGTCAAAT
M M A A I L A Y T I G T T H F Q R A L I F I L L T A V T P S M T M R C I G M S N

改造的沉默克隆标记: nt-900 T-至-C 沉默突变

970 980 990 1000 1010 1020 1030 1040 1050 1060 1070 1080
AGAGACTTTGTGGAAGGGTTTCAGGAGGAGCTGGGTTGACATAGTCTTAGAACATGGAAGCTGTGTGACGACGATGGCAAAAAACAAACCAATTTGAACTGATAAAAACA
R D F V E G V S G G S W V D I V L E H G S C V T T M A K N K P T L D F E L I K T

1090 1100 1110 1120 1130 1140 1150 1160 1170 1180 1190 1200
GAAGCCAAACAGCCTGCCACCCCTAAGGAAGTACTGTATAGAGGCAAGCTAACCAACACAAACAGAAATCTGCTGCGCCACACAAGGGGAAACCAGCCTAAATGAAGAGCAGGACAAA
E A K Q P A T L R K Y C I E A K L T N T T E S R C P T Q G E P S L N E E Q D K

1210 1220 1230 1240 1250 1260 1270 1280 1290 1300 1310 1320
AGGTTGCTCTGCAAACTCTCCATGTTAGACAGAGGATGGGGAATGATGTGGACTATTGGAAGGGAGGCAATGTGACCTGTCTATGTTGAGATGCAAAAAGAAATGGAAGGAAAA
R F V C K H S M V D R G W G N G C G L E G K G I V T C A M F R C K K N M E G K

1330 1340 1350 1360 1370 1380 1390 1400 1410 1420 1430 1440
GTTGTGCAACAGAAAACTTGAATACACCATTTGTGATAACACCTCACTCAGGGGAGAGCATGCACTGCGAAATGACACAGGAAACATGGCAAGGAAATCAAAATACACACAGAGT
V V Q P E N L E Y T I V I T P H S G E E H A V G N D T G K H H G K E I K I T P Q S

1450 1460 1470 1480 1490 1500 1510 1520 1530 1540 1550 1560
TCCATCACAGAAGCAGAAATGACAGGTTATGGCACTGTCAATGGAGTGTCTCCAAGAACGGGCTCGACTTCAATGAGATGGTGTGCTGACAGATGAAAAATAAGCTTGGCTGGTG
S I T E A E L T G Y G T V T M E C S P R T G L D F N E M V L L Q M E N K A W L V

1570 1580 1590 1600 1610 1620 1630 1640 1650 1660 1670 1680
CACAGGCAATGGTTCCTAGACTGCGCTTACCATGTTGCGCGGAGCGGACACACAGAGGCTCAATTTGATACAGAAAGAGACATTTGGTCACTTTCAAAAATCCCCATGGCAAGAAACAG
H R Q W F L D L P L P W L P G A D T Q G S N W I Q K E T L V T F K N P H A K K Q

1690 1700 1710 1720 1730 1740 1750 1760 1770 1780 1790 1800
GATGTTGTTGTTTGGATCCCAAGAGGGGCGATGACACAGCACTTACAGGGGCAAGAAATCCAAATGTCATCAGGAACTTACTCTTCAAGGACATCTCAAGTGCGAGGCTGAGA
D V V V L G S Q E G A M H T A L T G A T E I Q M S S G N L L F T G H L K C R L R

1810 1820 1830 1840 1850 1860 1870 1880 1890 1900 1910 1920
ATGGACAAGCTACAGCTCAAGGAATGTCATCTATGTGCACAGGAAAGTTTAAAGTTTGAAGGAAATAGCAGAAACACAACATGGAAACAATAGTTATCAGATGCAATATGAAGGG
M D K L Q L K G M S Y S M C T G K F K V V K E I A E T Q H Q T I V I R V Q Y E G

1930 1940 1950 1960 1970 1980 1990 2000 2010 2020 2030 2040
GACGGCTCTCCATGCAAGATCCCTTTTGAATAATGGATTGGAAAAAGACATGCTTAGGTGCGCTGATTACAGTCAACCCAATTTGACAGAAAAAGATAGCCCAAGTCAACATAGAA
D G S P C K I P F E I M D L E K R H V L G R L I T V N P I V T E K D S P V N I E

2050 2060 2070 2080 2090 2100 2110 2120 2130 2140 2150 2160
GCAGAACCTCCATTGGAGACAGCTACATCATAGGAGTAGAGCGGGCAACTGAAGCTCACTGGTTTAAAGAAAGGAGTTCTATCGGCCAAATGTTTGAAGCAACATGAGGGGG
A E P P F G D S Y I I I G V E P G Q L K L N W F K K G S S I G Q M F E T T M R G

D2 PDK-53 nt-2055-T 沉默突变 (D2 16681: C)

2170 2180 2190 2200 2210 2220 2230 2240 2250 2260 2270 2280
GCGAAGAGAAATGGCCATTTAGGTGACACAGCCTGGGATTTTGGATCTTGGGAGGAGTGTTCATCTATAGGAAAGGCTCTCCCAAGTCTTTGGAGCAATCTATGGAGCTGCCTTC
A K R M A I L G D T A W D F G S L G G V F T S I G K A L H Q V F G A I Y G A A F

2290 2300 2310 2320 2330 2340 2350 2360 2370 2380 2390 2400
AGTGGGTTTCATGGACTATGAAAACTCTCATAGGAGTCATTATCATGGATAGGAATTCACGACGACCTCACTGTCTGTGACACTAGTATGGTGGGAATTTGACACTGTAT
S G V S W T M K I L I G V I I T W I G M N S R S T S L S V T L V L V G I V T L Y

>NS1

2410 2420 2430 2440 2450 2460 2470 2480 2490 2500 2510 2520
TTGGGAGTCATGGTCAGGCGGATAGTGGTTGGTGTGTAGCTGAAAAACAAAGAACTGAAATGTGGCAGTGGGATTTTCATCACAGACAACTGTCACACATGGACAGAAACATACAG
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 W T E Q Y K

2530 2540 2550 2560 2570 2580 2590 2600 2610 2620 2630 2640

[0302]

TTCCAACCAAGATCCCTTCAAACTAGCTTCAGCTATCCAGAAAGCCATGAAGAGGACATTTGTGGAATCCGCTCAGTAACAAGACTGGAGAATCTGATGTGGAAACAAATAACACCA
F Q P E S P S K L A S A I Q K A H E E E I C G I R S V T R L E N L M W K Q I T P

D2 PDK-53-Asp 减毒基因座(wt D2 16681: Gly, nt-2579-G)

2650 2660 2670 2680 2690 2700 2710 2720 2730 2740 2750 2760
GAATTGAATCACATTCTATCAGAAATGAGGTGAAGTAACTATTATGACAGGAGACATCAAGGAATCATGCGAGGAGGAAACGATCTCTGGGCTCAGCCACCTGAGCTGAAGTAT
E L N H I L S E N E V K L T I M T G D I K G I M Q A G K R S L R P Q P T E L K Y

2770 2780 2790 2800 2810 2820 2830 2840 2850 2860 2870 2880
TCATGGAAAAATGGGCAAGCAAAATGCTCTCTACAGACTCTCATAACAGACCTTTCTCATTGATGGCCCGAAACAGCAGAAATCCCCAACAAATAGAGCTTGGAAATTCGTTG
S W K T W G K A K M L S T E 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

2890 2900 2910 2920 2930 2940 2950 2960 2970 2980 2990 3000
GAAGTGAAGACTATGGCTTTGGAGTATTCAACCACATATATGGCTAAATTTGAAAGAAAAAGGAGTATTCTGCGACTCAAAACTCATGTCAGCGGCCATAAAAGACCAACAGAGCC
E V E D Y G F G V E 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 3110 3120
GTCCATCGGATATGGGTATTGGATGAAAGTGCCTCAATGACACATGGAAGATAGAGAAAGCCTCTTTCATTGAAGTTAAAACTGCCATCGGCCAAATACACACCCCTCTGGAGC
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 S H T L W S

3130 3140 3150 3160 3170 3180 3190 3200 3210 3220 3230 3240
AATGGAGTGTGAAGAGTGAAGTAAATTCACAAAGATCTCGTGGACAGTGTCTCAACACAACTATAGACAGGCTACCATACACAAATACAGGACCATGGACTCTAGGTAGCTT
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 H T Q I T G P W H L G K L

3250 3260 3270 3280 3290 3300 3310 3320 3330 3340 3350 3360
GAGATGGACTTTGATTTCTGTGATGGAACAAAGTGGTGTGACTGAGGAGCTGCGGAAATAGAGACCTCTTTGAGAACACCACTGCGCTCGGAAACTCTAATACAGAAATGGTGTGCT
E M D F D F C D G T T V V V T E D C G N R G P S L R T T T A S G K L I T E W C C

3370 3380 3390 3400 3410 3420 3430 3440 3450 3460 3470 3480
CGATCTTGACATTACCAACCGCTAAGATACAGAGGTGAGGATGGGTGCTGGTAACGGGATGGAAATCAGACCATTAAGGAGAGAAAGAGAAATTTGGTCAACTCCTTGGTCAAGCTGGA
R S C T L P P L R Y R G E D 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

3490 3500 3510 3520 3530 3540 3550 3560 3570 3580 3590 3600
CATGGGCGAGTCGAACCTTTTCACTAGGAGTCTTGGAAATGGCATTTGCTCTGGAGAAATGCTTAGGACCGAGTAGGAACGAAACATCAATCTACTAGTTGACAGTTCTTTTGTG
H G Q V D N F 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 3710 3720
ACATTGATCAGAGGAACATGTCCTTTAGAGACCTGGGAAGAGTGTATGTTATGTTAGGCGCCACTATGACGGATGACATAGGTATGGCGGTGACTTATCTTGGCCCTACTAGCAGCTTC
T L I T G N M S F E D L G R V M V M V Q A T M T D D I G M Q V T Y L A L L A A F

3730 3740 3750 3760 3770 3780 3790 3800 3810 3820 3830 3840
AAAGTCAGACCAACTTTTGCAGCTGACTCTCTGAGAAAGTGAACCTCCAAAGAAATTTGATGATGACTACTATAGGAATTTGACTCTCTCCAGAGCACCATTACAGAGACCAATCTT
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 L S Q S T I P E T I L

3850 3860 3870 3880 3890 3900 3910 3920 3930 3940 3950 3960
GAGTTGATGATCGGTTAGCCTTAGGCATGATGGTCTCTCAAAATGGTGAGAAATATGGAAGATCAATTGGCAGTACTATCATGGCTATCTGTGCTCCCAACGCGAGTGAATTA
E L T D A L A L G M M V L K M V R N M E K Y Q L A V T I M A I L C V P N A V I L

3970 3980 3990 4000 4010 4020 4030 4040 4050 4060 4070 4080
CAAAAGCAGTGAAGTGAAGTGCACAAATATGGCAGTGTGTCCTGTTCCCACTGTTCTTAACTCCTCAGCAAAACAGATTGGATACATTAGCATTGACGATCAAGGCTCTC
Q N A W K V S C T I L A V V 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

[0303]

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

4090 4100 4110 4120 4130 4140 4150 4160 4170 4180 4190 4200
AATCAACAGCTATTTTCTAAACACCCCTCTCAAGAACCAAGAAAGAGGCTGGCCATTAAATGAGGCTATCATGGCAGTGGGATGGTGAAGCATTTTATGCGAGTCTCTCTCAAA
N P T A I F L 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 4310 4320
AATGATATTTCCATGACAGGACCATTAAGTGGCTGGAGGGCTCTCACTGTGTGCTACGCTGCTCACTGGACGATCGGCCGATTGGAACTGGAGAGAGCAGCCGATGTCAATGGGAGAC
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 D V K W E D

4330 4340 4350 4360 4370 4380 4390 4400 4410 4420 4430 4440
CAGGCAGAGATATCAGGAAGCAGTCCAATCCTGTCAATAACAATATCAGAAGATGTTAGCATGTCGATAAAAAATGAAGAGGAAGAACAACTGACCATCTACTAGAACAGGATTG
Q A E I S G S S P L L S I T I S E D G S M S I K N E E E E Q T L T I L I R T G L

4450 4460 4470 4480 4490 4500 4510 4520 4530 4540 4550 4560
CTGGTATCTCAGGACTTTTCTGTATCAATACCAATCAACGAGCAGCAGCATGGTACCTGTGGGAAGTGAAGAAACAAACGGGCGGAGTATTGTGGGATGTTCTTCAACCCCAACCATG
L V I S G L F P V S I P I T A A A W Y L W E V K K Q R A G V L W D V P S P P M

4570 4580 4590 4600 4610 4620 4630 4640 4650 4660 4670 4680
GGAAAGCTGAACCTGAAGATGGAGCCTATAGAATTAAAGCAAAAGGGATCTTGGATATTTCCAGATCGGAGCGGAGTTTACAAAGAAAGAACATTCCATACATGTGGCATGTCA
G K A E L E D G A Y R I K Q 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

4690 4700 4710 4720 4730 4740 4750 4760 4770 4780 4790 4800
CGTGGCGCTGTTCTAATGCATAAAGGAAAGAGGATTGAACCATCATGGCGGAGCTCAAGAAAGCCTAATATCATATGAGGAGGCTGGAGTTAGAAGGAGAAATGGAAGGAAGAGAA
R G A V L M H 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 4910 4920
GAAGTCCAGGTATTGGCAGCTGGAGCTGGAAAAATCCAAAGAGCGTCCAAACGAAACCTGGTCTTTTCAAAACCAACGCGGAAACAAATAGGTGCTGTATCTCTGACCTTTCTCTGGA
E V Q V L A L E P Q 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 F S P G

4930 4940 4950 4960 4970 4980 4990 5000 5010 5020 5030 5040
ACGTCAAGGATCTCCAATATCGACAAAAAGGAAAGTTGTGGTCTTTATGGTAAATGGTGTGTTACAAGGAGTGGAGCATATGTGAGTGTATAGCCAGACTGAAAAAGCATTGAA
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 S A I A Q T E K S I E

5050 5060 5070 5080 5090 5100 5110 5120 5130 5140 5150 5160
GACAAACAGAGATCGAAGATGACATTTTCCGAAAGAGAACTGACCATCATGGACCTCCACCCAGGAGCGGAAAGACGAAGAGATACCTCCGGCCATAGTCAGAGAGCTATAAAA
D N P E I E D D I F R K R R L T I M D L H P G A G K T K R Y L P A I V R E A I K

5170 5180 5190 5200 5210 5220 5230 5240 5250 5260 5270 5280
CGGGTTTGGAACATTAACTTTGGCCGCCCTAGAGTTGTGGCAGCTGAAATGGAGGAAGCCCTTAGAGGACTTCCAATAAGATACCGAGACCCCGCCATCAGAGCTGTGACACCGGG
R G L R T L I L A E T R V V 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

D2 PDK-53-Val 减毒基因座(wt D2 16681: Glu, nt-5270-A)

5290 5300 5310 5320 5330 5340 5350 5360 5370 5380 5390 5400
CGGAGATTGTGGACCTAATGTGTCTATGCCACATTTACCATGAGGCTGCTATCACCCAGTTAGAGTGCCAACTACAACTGATTATCATGGACGAAGCCCATTTCAAGACCCAGCAAGT
R E I V D L M C H A T P T M R L L S P V R V P N Y N L I I M D E A H P T D P A S
5410 5420 5430 5440 5450 5460 5470 5480 5490 5500 5510 5520
ATAGCAGCTAGAGGATACATCTCAACTCGAGTGGAGATGGGTGAGGCTGGGATTTTATGACAGCACTCCCGCGGAAGCAGAGACCCATTCTCTCAGAGCAATGCACCAATCAT
I A A R G Y I S T R V E M G E A A G I E M T A T P P G S R D P F P Q S N A P I I
5530 5540 5550 5560 5570 5580 5590 5600 5610 5620 5630 5640
GATGAAGAAAGAGAAATCCCTGAAAGCTCGTGAATTCGGACATGAATGGGTCAAGGATTTTAAAGGGAAGACTGTGTGGTTCGTCCAAGTATAAAAGCAGGAAATGATATAGCAGCT
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 F V D S I K A G N D I A A

D2 PDK-53 沉默突变 nt-5547-C (D2 16681: T)

5650 5660 5670 5680 5690 5700 5710 5720 5730 5740 5750 5760
TGCTGAGGAAAAATGGAAAGAAAGTATACAACTCAGTAGGAAGACCTTTGATTCTGAGTATGTCAAGACTAGAACCAATGATTGGGACTTCGTGGTTACAACTGACATTTTCAGAAATG
C L R K N G K K V I Q L S R K T P D S E Y V K T R T N D W D F V V T T D I S E M
5770 5780 5790 5800 5810 5820 5830 5840 5850 5860 5870 5880
GGTGCCATTTCAAGCTGAGAGGTTATAGACCCAGACGCTGATGAAACCACTCATCTAACAGATGGTGAAGAGCGGGTATTCTGGCAGGACCTATGCCAGTACCCACTCTAGT
G A N F K A E R V I D P R R 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
5890 5900 5910 5920 5930 5940 5950 5960 5970 5980 5990 6000
GCAGCAGAAAGAGAGGAGAGTATGGAAGAAATCCAAAAATGAGATGACCATGACATATACATGGGGGAACTCTGGAAGATGATGAAGCTGTGCACACTGGAAGAGCTAAATG
A A Q R R G R 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 6110 6120
CTCCTAGATAACATCAACAGCCAGAGACCTACAGTCTGGTTGGCTACAGAGTGGCAGCTGAAGGCATCAACTACGAGACAGAGGTGGTGTGTTTGTAGTGAAGCAACCAATCTTA
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 E A R K T F
6130 6140 6150 6160 6170 6180 6190 6200 6210 6220 6230 6240
GTAGACTTAATGAGAGAGGAGACCTACAGTCTGGTTGGCTACAGAGTGGCAGCTGAAGGCATCAACTACGAGACAGAGGTGGTGTGTTTGTAGTGAAGCAACCAATCTTA
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 R W C F D G V K N N Q I L
6250 6260 6270 6280 6290 6300 6310 6320 6330 6340 6350 6360
GAAGAAATCCGGAAGTGAATCTGGACAAAGAGAGGAGAAATGGAACCCAGATGGTTGGATGCTAGGATCTATTCTGACCCACTGGCGCTAAAGAAATTTAAGGAATTT
E E N V E V E I W T K E G E R K K L K P R W L D A R I Y S D P L A L K E F K E F

[0304]

>NS4A

6370 6380 6390 6400 6410 6420 6430 6440 6450 6460 6470 6480
GCAGCGGAAAGAAAGTCTCTGACCTGAACCTAATACAGAAATGGTAGGCTCCCAACCTTCATGACTCAGAAAGCAGAGAGCAGCTGGAACCTTAGCAGTGTGTCACACGGCTGAG
A A G R K S L T L N L I T E 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
6490 6500 6510 6520 6530 6540 6550 6560 6570 6580 6590 6600
GCAGGTGGAAGGGCGTACCAACCATGCTCTGAGTGAACCTGGAGAGCCCTGGAGACATGCTTTTATCTGACACTTCTGGCTACAGTCAAGGAGGATCTTTTATTCTTGATGAGCGCA
A G G R A Y N 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 6710 6720
AGGGCATAGGGAAGTACCCCTGGGAATGTGCTGCATAATCAAGGATGAGTCTCCCTATGGTACGACAAATACAGCCACTGGATGACAGCTTCAATTAATCTGGATTTTCTC
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 I L E F F L
6730 6740 6750 6760 6770 6780 6790 6800 6810 6820 6830 6840
ATAGTTTTCCTTATTCAGAACTGAAACACAGAGAACCCCAAGACAACTGACCTGCTGATAGCCATCTCAGTGGTGGCGCAACCATGGCAACAGAGATGGGTTTC
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 T V V A A T M A N E M G F
6850 6860 6870 6880 6890 6900 6910 6920 6930 6940 6950 6960
CTAGAAAAAAGAAAGATCTCGGATTGGGAAGCATTGCAACCCAGCAACCCGAGGCAACATCCTGGACATAGATCTACGCTCGCATCAGCATGGACGCTGTATGCCGTGGCCACA
L E K T K K D L G L G S I A T Q Q P E S N I L D I D L R P A S A W T L Y A V A T
6970 6980 6990 7000 7010 7020 7030 7040 7050 7060 7070 7080
ACATTGTGACCAATGTTGAGACATAGCATTGAAATTCCTCAGTGAATGTGCTTAAACAGCTATAGCCAAACCAAGCCACAGTGTATATGGGTCTCGGGAAGGATGGCCATTGTCA
T F V T P M L R H S I E N S 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
7090 7100 7110 7120 7130 7140 7150 7160 7170 7180 7190 7200
AAGATGACATCGGAGTTCCTCTGCGCATTTGGATGCTACTCAAGTCAACCCCATAACTCTCAAGCAGCTCTTTTCTTATTTGGTACACATTATGCCATCATAGGCCAGGACTC
K M D I G V P 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 7310 7320
CAAGCAAAAGCAACAGAGAGCTCAGAAAAGAGCAGCGGGGATCATGAAAAACCCCACTGCGATGGAATAACAGTGATGACCTAGATCCAATACCTTATGATCCAAAGTTTGAA
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 Y D P K F E
7330 7340 7350 7360 7370 7380 7390 7400 7410 7420 7430 7440
AAGCAGTTGGGACAGTAATGCTCCTAGTCTGCGTGAATCAAGTATGATGAGGACTACATGGGCTCTGTGTGAGGCTTAACTTAGCTACCGGCCCCATCTCCACATTGTG
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 T L A T G G P I S T L W
7450 7460 7470 7480 7490 7500 7510 7520 7530 7540 7550 7560
GAAGAAATCCAGGAGGTTTGGAACTACCATTTGGGTGTCAATGGCTAAATTTTAAAGGGAGTTACTTGGCGGAGCTGAGCTTCTCTTTCTATTATGAAGAACACAAACAC
E G N P G R F W N T T I A V S M A N I F R G S Y L A G A G L L F S I M K N T T N
>NS5
7570 7580 7590 7600 7610 7620 7630 7640 7650 7660 7670 7680

ACAAGAAGGGGAACCTGGCAACATAGGAGAGACGCTTGGAGAGAAATGAAAGACCGATTGAACGCATTTGGGAAAAAGTGAATTCAGATCTACAAGAAAAGTGAATCCAGGAAGTGGAT
T R R G T G N I G E T L G E K W K S R L N A L G K S E P Q I Y K K S G I Q E V D

7690 7700 7710 7720 7730 7740 7750 7760 7770 7780 7790 7800
AGAACCCTTAGCAAAAGAGGCAATTAAGAGGAGAAACGACCATCAAGCTGTGTGCGGAGGCTCAGCAAACTGAGATGGTTCGTTGAGAGAAACATGGTCAACCAAGGAGGAAAGTA
R T L A K E G 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 7910 7920
GTGGACCTCGGTTGTGGCAGAGGAGGCTCATCTATTGTGGAGGACTAAAGAAATGTAAGAGAAAGTCAAAGGCTTAACAAAGGAGGACAGGACAGAAACCATCCCATATGTC
V D L G C G R G G N S Y Y C G G L K N V R E V K G L T K G Q P G H E E P I P M S

7930 7940 7950 7960 7970 7980 7990 8000 8010 8020 8030 8040
ACATATGGGTGAATCTAGTCGCTCTCAAAGTGGAGTTGACGTTTTCTTCATCCCGCCAGAAAGTGTGACACATATTGTGTGACATAGGGGAGTCATCCCAAATCCACAGTGGAA
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 I G E S S P N P T V E

8050 8060 8070 8080 8090 8100 8110 8120 8130 8140 8150 8160
GCAGGACGAACACTCAGAGTCCTTAACCTAGTAGAAAATGGTTGAACAAACACTCAATTTTGCATAAAGGTTCTCAACCCATATATGCCCTCATAGAAAATGGAAGCACTA
A G R T L R V L N L V E N W L N N N T Q F C I K V L N P Y M P S V I E K M E A L

8170 8180 8190 8200 8210 8220 8230 8240 8250 8260 8270 8280
CAAAGGAAATATGGAGGAGCCTTAGTGAGGAATCCACTCTCAGAACTCCACATAGATGTACTGGGTTCCAATGCTTCGGGAACATAGTGTCATCAGTGAACATGATTTCAGAGG
Q R K Y G G A L V R N P L S 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

8290 8300 8310 8320 8330 8340 8350 8360 8370 8380 8390 8400
ATGTTGATCAACAGATTACAATGAGATACAAGAAAGCCACTAGCGCCGATGTTGACCTCGGAGCGGAACCCGTAACATCGGGATTGAAAGTGAGATACCAACCTAGATATAATT
M L I N R F T 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 8510 8520
GGGAAAAGATAGAAAAATAAGCAAGCATGAAACATCATGTCATGACCAAGACCAACCAACCAAAAGCTGGGCATACCATGGTAGCTATGAAACAAAACAGACTGGATCAGCA
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 K Q T G S A

8530 8540 8550 8560 8570 8580 8590 8600 8610 8620 8630 8640
TCATCCATGGTCAACAGAGTGGTCAGGCTGCTGACAAAACCTTGGGACGTCGTCCTCATGGTGACACAGATGGCAATGACAGACGACCTCCATTGGCAACAGCGGCTTTTAAAGAG
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 T P F G Q Q R V F K E

8650 8660 8670 8680 8690 8700 8710 8720 8730 8740 8750 8760
AAAGTGGACAGGAAACCAAGAAACCGAAGAGAGGACGAAAGAACTAATGAAAATAACAGCAGAGTGGCTTTGGAAAGAAATAGGGAAGAAAGACCCAGGATGTGCACAGAGAA
K V D T R T Q E P K E G T K K L M K I T A E W L W K E L G K K K T P R M C T R E

8770 8780 8790 8800 8810 8820 8830 8840 8850 8860 8870 8880
GAATTCACAAAGGTGAGAGCAATGAGCCCTTGGGGGCCGATTCTCATGTAGAGAAACAGTGAAGTGGCACTGGAGGCTGTGAAGATAGTAGTTTGGGAGCTGGTTGACAAAG
E F T R K V R S N A A L G A V 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

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在主代种和前主代种中的额外的 NS5-412 Ile-至-Val (nt-8803 A-至-G) 突变

[0305]

8890 8900 8910 8920 8930 8940 8950 8960 8970 8980 8990 9000
GAAAGCAATCTCCATCTTGAAGAAAGTGTGAAACATGTGTGTACCACTATGGGAAAGAGAGAGAAAGCTAGGGCAATTTCGGCAAGGCAAGGCAAGCCATATGGTACATG
E R N L H L E 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 9110 9120
TGGCTTGGAGCACGCTTCTTAGAGTTTGAAGCCCTAGGATTCTTAATGAAGATCACTGGTTTCCAGAGAGAACTCCCTGAGTGGAGTGAAGGAGGAGGCTGCACAGCTAGGTATAC
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 L H K L G Y

9130 9140 9150 9160 9170 9180 9190 9200 9210 9220 9230 9240
ATTCTAAGAGACGTGAGCAAGAAAGAGGAGGCAATGTATGCGCATGACACCGCAGGATGGGATACAAGAAATCAACATAGAAAGCTTAAAGAAATGGAACAAACACATG
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 L K N E E M V T N H M

9250 9260 9270 9280 9290 9300 9310 9320 9330 9340 9350 9360
GAAGGAGAACACAAGAACTAGCCGAGGCCATTTTCAAACTAACCTACCAAAACAGGTGTGTGCTGTGCAAGACCAACCAAGAGGACACAGTAAATGGACATCATATCAGAAAGAGAC
E G E H K K L A E A I F K L T Y Q N K V V R V Q R P T P R Q T V M D I I S R R D

9370 9380 9390 9400 9410 9420 9430 9440 9450 9460 9470 9480
CAAAGAGGTAGTGGACAGTTGGCACCTATGGACTCAATCTTCACTCAATATGGAAGCCCACTAATCAGACAGATGGAGGAGAGGAGTCTTTAAAGCATTGAGCACTTAAACATC
Q R G S G Q V G T Y G L N T F T N M E A Q L I R Q M E G E Q V F K S I Q H L T I

9490 9500 9510 9520 9530 9540 9550 9560 9570 9580 9590 9600
ACAGAAGAAATCGCTGTGCAAACTGGTCAAGAGTGGGCGCGAAAGTTATCAAGAAATGGCCATCAGTGGAGATGATTGTGTGAAACCTTTAGATGACAGGTTCCGAAGCGCT
T E E I A V Q 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 9710 9720
TTAAGCCTCTAAATGACATGGGAAAGATTAGGAAGACATACAACATGGGAACCTTCAAGAGGATGGAATGATGGACAAAGTGCCTTCTGTTCACACCATTTCCATGAGTTAATC
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 H F H E L I

9730 9740 9750 9760 9770 9780 9790 9800 9810 9820 9830 9840
ATGAAGAGCGTTCGCTACTCGTTGTTCCATGTAGAAACCAAGATGAACCTGATGGCAGAGCCGAACTCTCCCAAGGAGCAGGCTGTCTTTGGCGGAGACGGCTGTTTGGGGAAGTCT
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 S L R E T A C L G K S

9850 9860 9870 9880 9890 9900 9910 9920 9930 9940 9950 9960
TACGCCCAATGTGGAGCTTGATGTACTTCCACAGACGCGACTCAGGCTGGCGGCAAAATGCTATTGTCTGGCAGTACCATCACATTTGGGTTCCAAAGTGAACCAACCTGGTCCATA
Y A Q M W S L M Y F H R R D L R L A N A I C S A V P S H W V P T S R T T W S I

9970 9980 9990 10000 10010 10020 10030 10040 10050 10060 10070 10080
CATGCTAAACATGAATGATGACAAACGAGACATGCTGACAGTCTGGAACAGGCTGTGATTCAGAGAAACCCATGGATGGAAGACAAACCTCCAGTGAATCATGGAGGAAATCCCA
H A K H E W M T T E D M L T 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

10090 10100 10110 10120 10130 10140 10150 10160 10170 10180 10190 10200
TACTTGGGAAAGAGAGCAATGGTGGCGCTCATTGATTGGGTAAACAGCAGGGCCACCTGGGCAAGAAACATCCAGCAGCAATAAATCAAGTTAGATCCCTTATAGGCAATGAA
Y L G K R E D 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'-NC

10210 10220 10230 10240 10250 10260 10270 10280 10290 10300 10310 10320
GAAATACACAGATTACATGCCATCCATGAAAGATTGAGAAGAGAGAGGAAGAGCAGGAGTTCTGTGTAGAAAGCAAACTAACATGAAACAGAGGCTAGAACTCAGGTCCGATTAAAGC

E Y T D Y M P S M K R F R R E E E E A G V L W

10330 10340 10350 10360 10370 10380 10390 10400 10410 10420 10430 10440
CATAGTACGGAAAACTATGCTACCTGTGAGCCCCGTCCAAGGACGTTAAAAGAACTCAGGCCATCATAATGCCATAGCTTGAGTAACTATGCAGCCTGTAGCTCCACCTGAGAAGG

[0306] 10450 10460 10470 10480 10490 10500 10510 10520 10530 10540 10550 10560
TGTAAAAAATCCGGGAGGCCAAACCATGGAAGCTGTACGCATGGCGTAGTGACTAGCGTTAGAGGAGACCCCTCCCTTACAAATCGCAGCAACAATGGGGGCCCAAGGCGAGATGA

10570 10580 10590 10600 10610 10620 10630 10640 10650 10660 10670 10680
AGCTGTAGTCTCGCTGGAAGGACTAGAGGTTAGAGGAGACCCCCGAAACAAAAACAGCATATTGACGCTGGGAAAGACCAGAGATCCTGCTGTCTCTCAGCATCATTCAGGCACA

10690 10700 10710 10720
GAACGCCAGAAAATGGAATGGTGTGCTGTGAATCAACAGGTTCT

[0307] DENVax-3主代病毒种(MVS)

[0308] 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-2 PDK-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-2 PDK-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)。

[0309] 基因组和蛋白质中包括的取代:

[0310] 接合位点:

[0311] a.MluI(nt 451-456):改造的沉默突变,nt-453A-至-G

[0312] b.NgoMIV(nt 2374-2379):改造的突变,nt-2375/2376TG-至-CC(导致E-480Val-至-Ala改变)

[0313] D2 PDK-53病毒骨架(从野生型D2 16681的改变):粗体

[0314] a.5'-非编码区(NCR)-57(nt-57C-至-T):主要减毒基因座(红色)

[0315] b.NS1-53 Gly-至-Asp(nt-2573G-至-A):主要减毒基因座(红色)

[0316] c.NS2A-181Leu-至-Phe(nt-4012C-至-T)

[0317] d.NS3-250 Glu-至-Val(nt-5264A-至-T):主要减毒基因座(红色)

[0318] e.nt-5541(NS3基因)T-至-C沉默突变

[0319] f.NS4A-75Gly-至-Ala(nt-6593G-至-C)

[0320] *PDK-53的nt-8565C-至-T沉默突变在疫苗病毒中未经改造

[0321] 在DEN-3prM-E中的改造突变(从野生型D3 16562的改变)

[0322] a.改造的nt-552C-至-T沉默突变:克隆标记

[0323] b.改造的E-345His-至-Leu(nt-1970A-至-T)用于在培养物中有效复制

[0324] 在疫苗种中发现的额外的取代(与原始克隆差异0.02%nt)

[0325] a.E-223Thr-至-Ser突变(nt1603 A-至-T,粗体)

[0326] b.nt-7620A-至-G沉默突变(粗体)

[0327] DENVax-3 MVS的核酸序列(SEQ ID NO:15):

> 5'-非编码区 NCR-57-T, D2 PDK-53 减毒基因座(wt D2 16681: C) > C

10 20 30 40 50 60 70 80 90 100
AGTTGTTAGTCTACGTGGACCGACAAAGACAGATTCTTTGAGGGAGCTAAGCTCAATGTAGTTCTAACAGTTTTTTAATTAGAGAGCAGATCTCTGATGA
M N

110 120 130 140 150 160 170 180 190 200
ATAACCAACGGAAGGCGAAAAACACGCTTTCAATATGCTGAACCGGAGAGAAACCGCGTGTGACTGTGCAACAGCTGACAAAGAGATTCTCACT
N Q R K K A K N T P F N M L K R E R N R V S T V Q Q L T K R F S L

210 220 230 240 250 260 270 280 290 300
TGGAATGCTGCAGGGACGAGGACCATTAAACTGTTTCATGGCCCTGGTGGCGTTCTTCTGTTTCTTAAACATCCCACCAACAGCAGGATATTGAAGAGA
G M L Q G R G P L K L F M A L V A F L R F L T I P P T A G I L K R

310 320 330 340 350 360 370 380 390 400
TGGGGAACAATTAATAAATCAAAAGCTATTAAATGTTTGTAGAGGGTTTCAAGAAAGAGATTGGAAGGATGCTGAACATCTTGAATAGGAGACGCAGATCTG
W G T I K K S K A I N V L R G F R K E I G R M L N I L N R R R R S A

> prM D3 16562 序列的开端

410 420 430 440 450 460 470 480 490 500
CAGGCATGATCATTATGCTGATTCCAACAGTGATGGCGTTCCATTAAACCAACGCGTGATGGAGAGCCGCGCATGATTGTGGGAAGAATGAAAGAGGAAA
G M I I M L I P T V M A F H L T T R D G E P R M I V G K N E R G K

改造的 MluI 剪接位点(nt-453 A-至-G 沉默突变)

510 520 530 540 550 560 570 580 590 600
ATCCCTACTTTTCAAGACAGCCTCTGGAATCAACATGTGCACACTCATAGCTATGGATCTGGGAGAGATGTGTGATGACACGGTCACTTACAAATGCCCC
S L L F K T A S G I N M C T L I A M D L G E M C D D T V T Y K C P

C-至-T nt 沉默突变作为克隆体标记

610 620 630 640 650 660 670 680 690 700
CACATTACCGAAGTGGAGCCTGAAGACATTGACTGCTGGTGCACCTTACATCGACATGGGTGACTTATGGAACATGCAATCAAGCTGGAGAGCATAGAC
H I T E V E P E D I D C W C N L T S T W V T Y G T C N Q A G E H R R

> M

710 720 730 740 750 760 770 780 790 800
GCGATAAGAGATCAGTGGCGTTAGCTCCCCATGTGGCATGGGACTGGACACACGCACTCAAACCTGGATGTCGGCTGAAGGAGCTTGGAGACAAGTCSA
D K R S V A L A P H V G M G L D T R T Q T W M S A E G A W R Q V E

810 820 830 840 850 860 870 880 890 900
GAAGGTAGAGACATGGGCCCTTAGGCACCCAGGGTTTACCATACTAGCCCTATTCTTGCCCATACATAGGCATTCCTTGACCCAGAAAGTGGTTATT
K V E T W A L R H P G F T I L A L F L A H Y I G T S L T Q K V V I

[0328]

> E

910 920 930 940 950 960 970 980 990 1000
TTTATACATTAATGCTGGTTACCCCATCCATGACAATGAGATGTGTAGGAGTAGGAAACAGAGATTTTGTGGAAGGCCTATCGGGAGCTACGTGGGTTG
F I L L M L V T P S M T M R C V G V G N R D F V E G L S G A T W V D

1010 1020 1030 1040 1050 1060 1070 1080 1090 1100
ACGTGGTGTCTGAGCAGCGTGGGTGTGTGACTACCATGGCTAAGAAACAAGCCACGCTGGACATAGAGCTTCAGAAGACCGAGGCCACCCAACTGGCGAC
V V L E H G C V T T M A K N K P T L D I E L Q K T E A T Q L A C T

1110 1120 1130 1140 1150 1160 1170 1180 1190 1200
CCTAAGGAAGCTATGCATTGAGGGAAAAATTACCAACATAACAACCGACTCAAGATGTCCCAACCAAGGGGAAGCGATTTTACCTGAGGAGCAGGACCAG
L R K L C I E G K I T N I T T D S R C P T Q G E A I L P E E Q D Q

1210 1220 1230 1240 1250 1260 1270 1280 1290 1300
AACTACGTGTGAAGCATACATACGTGGACAGAGGCTGGGGAAACGGTTGTGGTTTGTGGCAAGGGAAGCTTGGTGACATGCGCGAAATTTCAATGTT
N Y V C K H T Y V D R G W G N G C G L F G K G S L V T C A K F Q C L

1310 1320 1330 1340 1350 1360 1370 1380 1390 1400
TAGAATCAATAGAGGGAAAGTGGTGCAACATGAGAACCTCAAATACACCGTCAATCATCAGTGACACAGGAGACCAACACCAGGTGGGAAATGAAAC
E S I E G K V V Q H E N L K Y T V I I T V H T G D Q H Q V G N E T

1410 1420 1430 1440 1450 1460 1470 1480 1490 1500
GCAGGGAGTCACGGCTGAGATAACACCCAGGCATCAACCGCTGAAGCCATTTTACCTGAATATGGAACCCCTCGGGCTAGAATGCTCACCACGGACAGGT
Q G V T A E I T P Q A S T A E A I L P E Y G T L G L E C S P R T G

1510 1520 1530 1540 1550 1560 1570 1580 1590 1600
TTGGATTTCAATGAAATGATCTCATTGACAATGAAGAACAAGCATGGATGGTACATAGACAATGGTTCTTTGACTTACCCCTACCATGGACATCAGGAG
L D F N E M I S L T M K N K A W M V H R Q W F F D L P L P W T S G A

1610 1620 1630 1640 1650 1660 1670 1680 1690 1700
CTTCAGCAGAAAACCAACTTGGAAACAGGAAAGAGCTTCTTGTGACATTTAAAAATGCACATGCAAAAAAGCAAGAAGTAGTTGTTCTTGGATCACAAGA
S A E T P T W N R K E L L V T F K N A H A K K Q E V V V L G S Q 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)

1710 1720 1730 1740 1750 1760 1770 1780 1790 1800
GGGAGCAATGCATACAGCACTGACAGGAGCTACAGAGATCCAAACCTCAGGAGGCACAAGTATCTTTGCGGGGCACTTAAATGTAGACTCAAGATGGAC

G A M H T A L T G A T E I Q T S G G T S I F A G H L K C R L K M D
1810 1820 1830 1840 1850 1860 1870 1880 1890 1900
AAATTGGAACCTCAAGGGGATGAGCTATGCAATGTGCTTGTAGTAGCTTTGTGTTGAAGAAAGAGTCTCCGAAACGCAGCATGGGACAATACTCATTAAAGG
K L E L K G M S Y A M C L S S F V L K K E V S E T Q H G T I L I K V
1910 1920 1930 1940 1950 1960 1970 1980 1990 2000
TTGAGTACAAAGGGGAAGATGCACCTGCAAGATTCTCTTCTCCACGGAGGATGGACAAGGAAAGCTCTCAATGGCAGACTGATCACAGCCAATCCAGT
E Y K G E D A P C K I P F S T E D G Q G K A L N G R L I T A N P V

用于有效生长的改造 E-345 His-至-Leu (wt D3 16562: nt-1970-A)

2010 2020 2030 2040 2050 2060 2070 2080 2090 2100
GGTGACCAAGAAGGAGGAGCTGTCAACATTGAGGCTGAACCTCTCTTTGGAGAAAGTAACATAGTAATTGGAATTGGAGACAAGCCCTGAAAATCAAC
V T K K E E P V N I E A E P P F G E S N I V I G I G D K A L K I N
2110 2120 2130 2140 2150 2160 2170 2180 2190 2200
TGGTACAAGAAGGGAAGCTCGATTGGGAAGATGTTTCGAGGCCACTGCCAGAGGTGCAAGGCGCATGGCCATCTTGGGAGACACAGCCTGGGACTTTGGAT
W Y 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 G S
2210 2220 2230 2240 2250 2260 2270 2280 2290 2300
CAGTGGGTGGTGTCTTGAATTCAATAGGGAAAATGGTCCACCAATATTTGGGAGTGCTTACACAGCCCTATTGTTGGAGTCTCTGGATGATGAAAAT
V G G V L N S L G K M V H Q I F G S A Y T A L F G V S W M M K I

D3 16562 序列的末端

2310 2320 2330 2340 2350 2360 2370 2380 2390 2400
TGGAATAGGTGTCCTCTTAACCTGGATAGGGTTGAACTCAAAAAATCTTCTATGTCTATTTTCATGCATCGCGGCCGCGCATTGTGACACTGTATTGGGA
G I G V L L T W I G L N S K N T S M S F S C I A A G I V T L Y L G

改造的 NgoMIV 剪接位点, E-480 Val-至-Ala (nt-2375/2376 TG-至-cc)

> NS1
2410 2420 2430 2440 2450 2460 2470 2480 2490 2500
GTCATGGTGCAGGCCGATGTTGCGTTGTGAGCTGGAAAAACAAGAACTGAAATGTGGCAGTGGGATTTTCATCACAGACAAGTGCACACATGGA
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 W T
2510 2520 2530 2540 2550 2560 2570 2580 2590 2600
CAGAAACATCAAGTTCCAAACAGAAATCCCTTCAAACTAGCTTCAGCTATCCAGAAAGCCCATGAAGAGGACATTGTGGAATCCGCTCAGTAACAG
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 T R

[0329]

D2 PDK-53 NS1-53-Asp 减毒基因座(wt D2 16681: Gly, nt-2573-G)

2610 2620 2630 2640 2650 2660 2670 2680 2690 2700
ACTGGAGAATCTGATGTGGAACAAATAACACCAGAATTGAATCACATTCTATCAGAAAATGAGGTGAAGTTAACTATTATGACAGGAGACATCAAGGA
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 K G
2710 2720 2730 2740 2750 2760 2770 2780 2790 2800
ATCATGCAGGCAGGAAACGATCTCTGCGGCTCAGCCCACTGAGCTGAAGTATTCATGGAAAACATGGGGCAAGCAAAATGCTCTCTACAGAGTCTC
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 S H
2810 2820 2830 2840 2850 2860 2870 2880 2890 2900
ATAACAGACCTTTCTCATTGATGGCCCGAAACAGCAGAATGCCCAACAAATAGAGCTTGAATTCGTTGGAAGTTGAAGACTATGGCTTTGGAGT
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 G V
2910 2920 2930 2940 2950 2960 2970 2980 2990 3000
ATTACCACCAATATATGGCTAAAATTGAAAGAAAAACAGGATGTATTCTGCGACTCAAACTCATGTGAGCGGCCATAAAGACAAACAGAGCCGTCAT
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 V H
3010 3020 3030 3040 3050 3060 3070 3080 3090 3100
GCCGATATGGGTATTGGATAGAAAGTGCACTCAATGACACATGGAAGATAGAGAAAGCCTCTTTCATTGAAGTTAAAACTGCCACTGGCCAAAATCAC
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 S H
3110 3120 3130 3140 3150 3160 3170 3180 3190 3200
ACACCTCTGGAGCAATGGAGTGCTAGAAAAGTGAGATGATAATCCAAAGAATCTCGCTGGACCAAGTGTCTCAACAACTATAGACCAAGGCTACCATAC
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 H T
3210 3220 3230 3240 3250 3260 3270 3280 3290 3300
ACAAATAACAGGACCATGGCATCTAGGTAAGCTTGAGATGGACTTTGATTTCTGTGATGGAACAACAGTGGTAGTACTGAGGACTGCGGAAATAGAGGA
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 R G
3310 3320 3330 3340 3350 3360 3370 3380 3390 3400
CCCTCTTTGAGAACAAACCACTGCCTCTGGAAGAACTCATAACAGAAATGGTGGCGATCTTGACATTACCACCGCTAAGATACAGAGGTGAGGATGGGT
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 G C
> NS2A
3410 3420 3430 3440 3450 3460 3470 3480 3490 3500

GCTGGTACGGGATGGAAATCAGACCATTGAAGGAGAAAGAGAATTGGTCAACTCCTTGGTCACAGCTGGACATGGGCAGGTCGACAACCTTTTCACT
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
AGGAGTCTTGGGAATGGCATTGTTCTTGAGGAAATGCTTAGGACCCGAGTAGGAACGAAACATGCAATACTACTAGTTGCAGTTTCTTTGTGACATTG
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
TACTAGCAGCCTTCAAAGTCAGACCAACTTTTCAGCTGGACTACTCTTGAGAAAGCTGACCTCCAAGGAATTGATGATGACTACTATAGGAATTGTACT
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 V L

3810 3820 3830 3840 3850 3860 3870 3880 3890 3900
CCTCTCCCAGAGCACCATACCAGAGACCATTCTTGAGTTGACTGATGCGTTAGCCTTAGGCATGATGGTCCTCAAAATGGTGAGAAATATGGAAGATGAT
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
CAATTGGCAGTGACTATCATGGCTATCTTGTGCGTCCCAACGCGAGTGATATTACAAAACGCGATGGAAGTGAGTTGCACAATATTGGCAGTGGTGTCCG
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
TTTCCCACCTGTTCTTAACATCCTCAGCAAAAAACAGATTGGATACCATTAGCATTGACGATCAAAGGTCTCAATCCAACAGCTATTTTCTAACAAAC
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
CCTCTCAAGAACCAGCAAGAAAAGGAGCTGGCCATTAAATGAGGCTATCATGGCAGTCGGGATGGTGAGCATTTTAGCCAGTTCTCTCTAAAAAATGAT
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
ATTCCCATGACAGGACCATTAGTGGCTGGAGGGCTCCTCACTGTGTGCTACGTGCTCACTGGACGATCGGCCGATTTGGAATGGAGAGAGCAGCCGATG
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

4310 4320 4330 4340 4350 4360 4370 4380 4390 4400
TCAAATGGGAAGACCAGGCAGAGATATCAGGAAGCAGTCCAATCTGTCAATAACAATATCAGAAGATGGTAGCATGTTCGATAAAAAATGAAGAGGAAGA
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
ACAAACACTGACCATACTCATTAGAACAGGATTGCTGGTGATCTCAGGACTTTTCTCTGTATCAATACCAATCACGCGCAGCAGTGGTACCTGTGGGAA
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
GTGAAGAAACAACGGCCGAGTATTGTGGGATGTTCTTCAACCCCAACCCATGGGAAAGGCTGAACTGGAAGATGGAGCCTATAGAATTAAGCAAAAAG
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
GGATTCTTGATATTCCCAGATCGGAGCCGGAGTTTACAAAGAAGGAACATTCCATACAATGTGGCATGTACACGTTGGCTGTTCTAATGCATAAAGG
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
AAAGAGGATTGAACCATCATGGGCGGACGTCAAGAAAGACCTAATATCATATGGAGGAGGCTGGAAGTTAGAAGGAGAATGGAAGGAAGGAGAAGATC
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
CAGGTATTGGCACTGGAGCCTGAAAAAATCCAAGAGCCGTCCAACGAAACCTGGTCTTTTCAAAACCAACGCCGGAACAATAGGTGCTGTATCTCTGG
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
ACTTTTCTCTGGAACGTGAGGATCTCCAATTATCGACAAAAAAGGAAAGTTGTGGGTCTTTATGGTAATGGTGTGTACAAAGGAGTGGAGCATATGT
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
GAGTGTATAGCCCAGACTGAAAAAGCATTGAAGACAACCCAGAGATCGAAGATGACATTTTCCGAAAGAGAAGACTGACCATCATGGACCTCCACCCA
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
GGAGCGGGAAGACGAAGAGATACCTTCGGCCATAGTCAGAGAAGCTATAAAACGGGGTTTGAGAACATTAATCTTGGCCCCACTAGAGTTGTGGCAG
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

[0330]

5210 5220 5230 5240 5250 5260 5270 5280 5290 5300
CTGAAATGGAGGAAGCCCTTAGAGGACTTCCAATAAGATACCAGACCCAGCCATCAGAGCTGTGCACACCGGGGGGAGATTGTGGACCTAATGTGTCA
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 C H

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
TGCCACATTACCATGAGGCTGCTATCACCAGTTAGAGTGCCAACTACAACCTGATTATCATGGACGAAGCCCATTTTCACAGACCCAGCAAGTATAGCA
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 I A

5410 5420 5430 5440 5450 5460 5470 5480 5490 5500
GCTAGAGGATACATCTCAACTCGAGTGGAGATGGGTGAGGCAGCTGGGATTTTATGACAGCCACTCCCGGGGAAGCAGAGACCCATTTCTCAGAGCA
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 S N

5510 5520 5530 5540 5550 5560 5570 5580 5590 5600
ATGCACCAATCATAGATGAAGAAAGAGAAATCCCTGAACGCTCGTGGAATCCGGACATGAATGGGTACGGATTTTAAAGGGAAGACTGTTTGGTTCGT
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 F V

D2 PDK-53 沉默突变 nt-5541-C (D2 16681: T)

5610 5620 5630 5640 5650 5660 5670 5680 5690 5700
TCCAAGTATAAAGCAGGAAATGATATAGCAGCTTGCCTGAGGAAATGGAAGAAAGATGATCAACTCAGTAGGAAGACCTTTGATTCTGAGTATGTC
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 Y V

5710 5720 5730 5740 5750 5760 5770 5780 5790 5800
AAGACTAGAACCAATGATGGGACTTCGTGGTTACAACCTGACATTTCAAGAAATGGGTGCCAATTTCAAGGCTGAGAGGGTTATAGACCCAGACGCTGCA
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 C M

5810 5820 5830 5840 5850 5860 5870 5880 5890 5900
TGAAACCACTCATACTAACAGATGGTGAAGAGCGGTGATTCTGGCAGGACCTATGCCAGTGACCCACTCTAGTGCAGCACAAGAAGAGGGAGAATAGG
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 I G

5910 5920 5930 5940 5950 5960 5970 5980 5990 6000
AAGAAATCCAAAAATGAGAATGACCAGTACATATACATGGGGGAACCTCTGGAAAATGATGAAGACTGTGCACACTGGAAAGAAGCTAAATGCTCCTA
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 L L

6010 6020 6030 6040 6050 6060 6070 6080 6090 6100
GATAACATCAACACGCCAGAAGGAATCATTCTAGCATGTTTGAACACGAGCGTGAAAGGTGGATGCCATTGATGGCGAATACCGCTTGAGAGGAGAAG
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 E A

6110 6120 6130 6140 6150 6160 6170 6180 6190 6200
CAAGGAAAACCTTTGTAGACTTAATGAGAAGAGGAGACCTACAGTCTGGTTGGCTACAGAGTGGCAGCTGAAGGCATCAACTACGAGACAGAAAGGTG
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 R W

6210 6220 6230 6240 6250 6260 6270 6280 6290 6300
GTGTTTGTAGTCAAGAACAACCAATCTAGAGAAAACGTGGAAGTTGAAATCTGGACAAAAGAAGGGGAAGGAAGAAATGAAACCCAGATGG
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 R W

> NS4A

6310 6320 6330 6340 6350 6360 6370 6380 6390 6400
TTGGATGCTAGGATCTATTCTGACCCACTGGCGCTAAAAGAATTTAAGGAATTTGCAGCCGGAAGAAAGTCTCTGACCTGAACCTAATCAGAGAAATGG
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 M G

6410 6420 6430 6440 6450 6460 6470 6480 6490 6500
GTAGGCTCCCAACCTTCATGACTCAGAAGGCAAGAGACGCACTGGACAACCTTAGCAGTGCTGCACACGGCTGAGGCAAGTGAAGGGCGTACAACCATGC
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 H A

6510 6520 6530 6540 6550 6560 6570 6580 6590 6600
TCTCAGTGAAGTCCCGAGACCTGGAGACATTGCTTTTACTGACACTTCTGGCTACAGTCACGGGAGGGATCTTTTATTCTTGATGAGCGCAAGGGGC
L S E L P E T L E T L L L T L L A T V T G G I F L F L M S A R G

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
ATAGGGAAGATGACCTGGGAATGTGCTGCATAATCACGGCTAGCATCTCTCTATGGTACGCACAAATACAGCCCACTGGATAGCAGCTTCAATAATAC
I G K M T L G M C C I I T A S I L W Y A Q I Q P H W I A S I I L

6710 6720 6730 6740 6750 6760 6770 6780 6790 6800
TGGAGTTTTTCTCATAGTTTTGCTTATTCAGAACCTGAAAAACAGAGAACCCCAAGACAACCACTGACCTACGTTGTCATAGCCATCTCACAGT
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 T V

> NS4B

6810 6820 6830 6840 6850 6860 6870 6880 6890 6900
GGTGGCCGCAACCATGGCAAACGAGATGGGTTTCTAGAAAAACGAAGAAGATCTCGATTGGGAAGCATTGCAACCCAGCAACCCGAGAGCAACATC
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 N I

6910 6920 6930 6940 6950 6960 6970 6980 6990 7000

CTGGACATAGATCTACGTCTGCATCAGCATGGACGCTGTATGCCGTGGCCACAACATTTGTTACACCAATGTTGAGACATAGCATTGAAAATTCCTCAG
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
TGAATGTGTCCTAACAGCTATAGCCAACCAAGCCACAGTGTATGGGTCTCGGGAAGGATGGCCATTGTCAAAGATGGACATCGGAGTTCCCTTCT
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
CGCCATTGGATGCTACTCACAAGTCAACCCATAACTCTCACAGCAGCTCTTTCTTATTGGTAGCACATTATGCCATCATAGGGCCAGGACTCCAAGCA
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
AAAGCAACAGAGAGCTCAGAAAAGAGCAGCGGCGGCATCATGAAAAACCACTGTCGATGGAATAACAGTGATTGACCTAGATCCAATACCTTATG
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
ATCCAAAGTTTGAAGCAGTTGGGACAAGTAATGCTCCTAGTCTCTGCGTGACTCAAGTATTGATGATGAGGACTACATGGGCTCTGTGTGAGGCTTT
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
AACCTTAGCTACCGGGCCCATCTCCACATTGTGGGAAGGAAATCCAGGAGGTTTGGAACTACTACCTTGCCTGTCAATGGCTAACATTTTATAGAGG
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
AGTTACTTGGCGGAGCTGGACTTCTCTTTCTATTATGAAGAACACCAACCAAGGAGGAACTGGCAACATAGGAGAGACGCTTGGAGAGAAAT
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
GGAAAAGCCGATTGAACGCGTTGGGAAAAAGTAATCCAGATCTACAAGAAAAGTGAATCCAGGAAGTGGATAGAACCTTAGCAAAAGAGGCATTAA
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
AAGAGGAGAAACGGACCATCAGCTGTGTCGCGAGGCTCAGCAAACTGAGATGGTTCGTTGAGAGAAACATGGTCACACAGAGGGAAAGTAGTGGAC
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

7810 7820 7830 7840 7850 7860 7870 7880 7890 7900
CTCGGTTGTGGCAGAGGAGGCTGGTTCATATTGTGGAGGACTAAGAGATGTAAGAGAAGTCAAAGGCCCTAACAAAAGGAGGACCAGGACACGAGAAC
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
CCATCCCCATGTCAACATATGGGTGGAATCTAGTGCCTCTTCAAAGTGGAGTTGACGTTTCTTTCATCCCGCCAGAAAAGTGTGACACATTATTGTGTGA
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
CATAGGGGAGTCATCACCATAATCCACAGTGAAGCAGGACGAACACTCAGAGTCCTTAACCTTAGTAGAAAATTTGGTTGAACAACCAACTCAATTTTGC
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
ATAAAGTTCTCAACCCATATATGCCCTCAGTCATAGAAAAAATGGAAGCACTACAAAGGAAATATGGAGGAGCCTTAGTGAGGAATCCACTCTCACGAA
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
ACTCCACACATGAGATGTACTGGGTATCCAATGCTTCCGGGAACATAGTGTATCAGTGAACATGATTTCAGGATGTTGATCAACAGATTACAAATGAG
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
ATACAAGAAAGCCACTTACGAGCGGATGTTGACCTCGGAAGCGGAACCCGTAACATCGGGATTGAAAGTGAGATACCAACCTAGATATAATTGGGAAA
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
AGAATAGAAAAATAAAGCAAGAGCATGAAACATCATGGCACTATGACCAAGACCAACCCATACAAAACGTGGGCATACCATGGTAGCTATGAAACAAAC
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
AGACTGGATCAGCATCATCCATGGTCAACGGAGTGGTCAAGGCTGCTGACAAAACCTTGGGACGTCGTCCCATGGTGACAGATGGCAATGACAGAC
T G S A S S M V N G V R L L T K P W D V V P M V T Q M A M T D C T

8610 8620 8630 8640 8650 8660 8670 8680 8690 8700
GACTCCATTGGACACAGCGCGTTTTTAAAGAGAAAGTGGACACGAGAACCAAGAACCGAAAGGACGAGGAACTAATGAAAATAACAGCAGAG
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
TGGCTTTGGAAGAATTAGGGAAGAAAAAGACACCCAGGATGTGCACAGAGAAGAAATTCACAAAGAAAGGTGAGAAGCAATGCAGCCTTGGGGGCCATAT
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

[0332]

8810 8820 8830 8840 8850 8860 8870 8880 8890 8900
TCACTGATGAGAACAGTGGAGTTCGGCACGTGAGGCTGTTGAAGATAGTAGGTTTGGGAGCTGGTTGACAAGGAAAGGAATCTCCATCTTGAAGGAAA
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
GTGTGAAACATGTGTACAAATGATGGGAAAAAGAGAGAAGAAGCTAGGGGAATTCGGCAAGGCAAAAGGCAGCAGGCCATATGGTACATGTGGCTT
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
GGAGCAGCTTCTTAGAGTTTGAAGCCCTAGGATTCTTAAATGAAGATCACTGGTTCTCCAGAGAGAACTCCCTGAGTGGAGTGGGAAGAGAAGGGCTGC
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
ACAAGCTAGGTTACATTCTAAGAGACGTGAGCAAGAAAGAGGGAGGCAATGTATGCCGATGACACCGCAGGATGGGATACAAGAATCACACTAGAGA
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
CCTAAAAAATGAAGAAATGGTAACAAACCATGGAAGGAGAACACAAGAACTAGCCGAGGCCATTTTCAAACCTAACGTACCAAAACAAGGTGGTGGCT
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
GTGCAAGACCAACCAAGAGGCACAGTAATGGACATCATATCGAGAGAGACCAAGAGGATAGTGGACAAGTTGGCACCTATGGACTCAATACTTTCA
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
CCAATATGGAAGCCCAATTAACAGACAGATGGAGGAGAGAGTCTTTAAAGACATTCAGCACCTAACCAATCACAAGAAATCGCTGTGCAAAACTG
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
GTAGCAAGAGTGGGCGCGAAAGTTATCAAGATGGCCATCAGTGGAGATGATTGTGTTGTGAAACCTTTAGATGACAGGTTGCAAGCGCTTTAACA
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

9610 9620 9630 9640 9650 9660 9670 9680 9690 9700
GCTCTAAATGACATGGGAAAGATTAGGAAAGACATACAAATGGGAACCTTCAAGAGGATGGAATGATTGGACACAAGTGCCTTCTGTTACACCACTT
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
TCCATGAGTTAATCATGAAAGACGGTCGCTACTCGTTGTTCCATGTAGAAACCAAGATGAACTGATTGGCAGAGCCGGAATCTCCCAAGGAGCAGGGTG
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
GTCTTTGGGGAGACGGCTGTTTGGGGAAGTCTTACGCCCAATGTGGAGCTTGATGTACTTCCACAGACGCGACCTCAGGCTGGCGGCAATGCTATT
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
TGCTCGGCAGTACCATTCACATTGGGTTCCACAAGTCGAACAACCTGGTCCATACATGCTAAACATGAATGGATGACAAACGGAAGACATGCTGACAGTCT
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
GGAACAGGGTGTGGATTCAAGAAAACCCATGGATGGAAGACAAAACCTCCAGTGGAAATCATGGGAGGAAATCCCATACTTGGGAAAAGAGAAGACCAATG
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
GTGCGCTCATTGATTGGGTTAAACAGCAGGCGCCCTGGGCAAGAACATCCAAGCAGCAATAAATCAAGTTAGATCCCTTATAGGCAATGAAGAATAC
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
ACAGATTACATGCCATCCATGAAAAGATTGAGAAGAGAAGAGGAAGAAGCAGGAGTTCTGTGGTAGAAAAGCAAACTAACATGAACCAAGGCTAGAAGTC
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
AGGTCGGATTAAAGCCATAGTACGGAATAAATCTGCTACCTGTGAGCCCGTCCAGGACGTTAAAAGAAGTCAGGCCATCATAAATGCCATAGCTTGAG

10410 10420 10430 10440 10450 10460 10470 10480 10490 10500
TAAACTATGCAGCCTGTAGCTCCACCTGAGAAGGTGTAAAAAATCCGGAGGCCACAAACCATGGAAGCTGTACGCATGGCGTAGTGGACTAGCGGTTAG

10510 10520 10530 10540 10550 10560 10570 10580 10590 10600
AGGAGACCCCTCCCTTACAAATCGCAGCAACATGGGGGCCCAAGGCGAGATGAAGCTGTAGTCTCGCTGGAAGGACTAGAGGTTAGAGGAGACCCCCC

10610 10620 10630 10640 10650 10660 10670 10680 10690 10700
GAAACAAAAACAGCATATTGACGCTGGGAAAGACAGAGATCCTGCTGTCTCCTCAGCATCATTCAGGCACAGAAGCCAGAAAATGGAATGGTGGCTG

10710

[0334] DENVax-4主代病毒种(MVS)

[0335] 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-4 1036病毒特异性的;剩余核苷酸序列为DEN-2 PDK-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)。

- [0336] 基因组和蛋白质中包括的取代:
- [0337] 接合位点:
- [0338] a.MluI(nt 451-456):改造的沉默突变,nt-453A-至-G
- [0339] b.NgoMIV(nt 2380-2385):改造的突变,nt-2381/2382TG-至-CC(导致E-482Val-至-Ala改变)
- [0340] D2 PDK-53病毒骨架(从野生型D2 16681的改变)
- [0341] a.5'-非编码区(NCR)-57(nt-57C-至-T):主要减毒基因座(红色)
- [0342] b.NS1-53 Gly-至-Asp(nt-2579G-至-A):主要减毒基因座(红色)
- [0343] c.NS2A-181Leu-至-Phe(nt-4018C-至-T,粗体)
- [0344] d.NS3-250 Glu-至-Val(nt-5270A-至-T):主要减毒基因座(红色)
- [0345] e.nt-5547(NS3基因)T-至-C沉默突变(粗体)
- [0346] f.NS4A-75Gly-至-Ala(nt-6599G-至-C,粗体)
- [0347] *PDK-53的nt-8571C-至-T沉默突变在疫苗病毒中未经改造
- [0348] 在cDNA克隆中的改造的取代
- [0349] 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
- [0350] b.改造的nt-1401A-至-G沉默突变
- [0351] 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
- [0352] 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
- [0353] 在疫苗种中发现的额外的取代(与原始克隆差异0.06%nt)
- [0354] a.nt-225(C基因)A-至-T沉默突变(粗体)
- [0355] b.NS2A-66Asp-至-Gly(nt-3674A-至-G)突变(粗体)
- [0356] c.NS2A-99Lys-至-Lys/Arg混合物(nt-3773A-至-A/G混合,粗体)
- [0357] d.nt-5391C-至-T(NS3基因)沉默突变(粗体)
- [0358] e.NS4A-21Ala-至-Val(nt-6437C-至-T,粗体)
- [0359] f.nt-7026T-至-C/T混合沉默突变(粗体)
- [0360] g.nt-9750A-至-C沉默突变(粗体)
- [0361] DEN Vax-4 MVS的核酸序列(SEQID NO:16):

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

> 5'-非编码区'

10 20 30 40 50 60 70 80 90 100
AGTTGTTAGTCTACGTGGACCGACAAAGACAGATTCTTTGAGGGAGCTAAGCTCAATGTAGTTCTAACAGTTTTTTAATTAGAGAGCAGATCTCTGATGAM N
110 120 130 140 150 160 170 180 190 200

ATAACCAACGGAAAAAGCGAAAAACACGCCTTTCAATATGCTGAAACGCGAGAGAAACCGCGTGTGACTGTGCAACAGCTGACAAAGAGATTCTCACT
N Q R K K A K N T P F N M L K R E R N R V S T V Q Q L T K R F S L
210 220 230 240 250 260 270 280 290 300
TGGAAATGCTGCAGGGACGAGGACCTTTAAACTGTTTCATGGCCCTGGTGGCTTCTTCGTTTCCTAACATCCACCAACAGCAGGGATATTGAAGAGA
G M L Q G R G P L K L F M A L V A F L R F L T I P P T A G I L K R

在主代种和前主代种中额外的 nt-225 A-至-T 沉默突变

310 320 330 340 350 360 370 380 390 400
TGGGGAACAAATAAAAATCAAAAGCTATTAAATGTTTGTAGAGGGTTCAGGAAAGAGATTGGAAGGATGCTGAACATCTTGAATAGGAGACGCAGCTCTG
W G T I K K S K A I N V L R G F R K E I G R M L N I L N R R R S S A

改造的 C-100 Arg-至-Ser (nt 396 A-至-C)

410 420 430 440 450 460 470 480 490 500
CAGGCATGATCATTATGCTGATTCACACAGTGATGGCGTTCATTTAACCAACGCGTGATGGCGAACCCCTCATGATAGTGGCAAAACATGAAAGGGGGAG
G M I I M L I P T V M A F H L T T R D G E P L M I V A K H E R G R

改造的 MluI 剪接位点(nt-453 A-至-G 沉默)

510 520 530 540 550 560 570 580 590 600
ACCTCTCTTTTAAAGACAACAGAGGGGATCAACAAATGCACCTCTCATTTGCCATGGACTTGGGTGAAATGTGTGAGGACACTGTCACTATATAATGCCCC
P L L F K T T E G I N K C T L I A M D L G E M C E D T V T Y K C P

610 620 630 640 650 660 670 680 690 700
TTACTGGTCAATACCGAACCTGAAGACATTGATTGCTGGTGAATCTCACGTCTACCTGGGTCAATGTATGGGACATGACCCAGAGCGAGAAACGGAGAC
L L V N T E P E D I D C W C N L T S T W V M Y G T C T Q S G E R R R

> M

710 720 730 740 750 760 770 780 790 800
GAGAGAAACGCTCAGTAGCTTTAACACCCACATTGAGGAATGGGATTGGAAACAGAGCTGAGACATGGATGTATCGGAAGGGGCTTGGAAAGCATGCTCA
E K R S V A L T P H S G M G L E T R A E T W M S S E G A W K H A Q

810 820 830 840 850 860 870 880 890 900
GAGAGTAGAGAGCTGGATACTCAGAAACCCAGGATTGCGCGCTCTTGGCAGGATTTATGGCTTATATGATTGGGCAACAGGAATCCAGCGAACTGTCTTC
R V E S W I L R N P G F A L L A G F M A Y M I G Q T G I Q R T V F

> E

910 920 930 940 950 960 970 980 990 1000
TTTGTCTAATGATGCTGTCGCCCCATCCTACGGAATGCGATGCGTAGGAGTAGGAAACAGAGACTTTGTGGAAGGAGTCTCAGGTGGAGCATGGGTGCG
F V L M M L V A P S Y G M R C V G V G N R D F V E G V S G G A W V D

1010 1020 1030 1040 1050 1060 1070 1080 1090 1100
ATCTGGTGTAGAACATGGAGGATGCGTCACAACCATGGCCAGGAAACCAACCTTTGAACTGACTAAGACAACAGCCAGGAAGTGGCTCT
L V L E H G G C V T T M A Q G K P T L D F E L T K T T A K E V A L

1110 1120 1130 1140 1150 1160 1170 1180 1190 1200
GTTAAGAACCTATTGCAATTGAAGCCTCAATATCAAAACATAACACGGCAACAGATGTCCAACGCAAGGAGAGCCTTATCTAAAAGAGGAACAGACCAA
L R T Y C I E A S I S N I T T A T R C P T Q G E P Y L K E E Q D Q

1210 1220 1230 1240 1250 1260 1270 1280 1290 1300
CAGTACATTTGCCGGAGAGATGTGGTAGACAGAGGGTGGGGCAATGGCTGTGGCTTGTGGAAAAGGAGGAGTTGTGACATGTGCGAAGTTTTTCATGTT
Q Y I C R R D V V D R G W G N G C G L F G K G G V V T C A K F S C S

1310 1320 1330 1340 1350 1360 1370 1380 1390 1400
CGGGGAAGATAACAGGCAATTTGGTCCAAATTGAGAACCCTGAATACACAGTGGTTGTAACAGTCCACAATGGAGACACCCATGCAGTAGGAAATGACAC
G K I T G N L V Q I E N L E Y T V V V T V H N G D T H A V G N D T

1410 1420 1430 1440 1450 1460 1470 1480 1490 1500
GTCCAATCATGGAGTTACAGCCACGATAACTCCAGGTCACCATCGGTGGAAGTCAAATTGCCGACTATGGAGAACTAACACTCGATTGTGAACCCAGG
S N H G V T A T I T P R S P S V E V K L P D Y G E L T L D C E P R

在改造的克隆体中的沉默 nt-1401 A-至 G 突变

1510 1520 1530 1540 1550 1560 1570 1580 1590 1600
TCTGGAATTGACTTTAATGAGATGATTCTGATGAAAATGAAAAAGAAAACATGGCTTGTGCATAAGCAATGGTTTTTGGATCTACCTCTACCATGGACAG
S G I D F N E M I L M K M K K K T W L V H K Q W F L D L P L P W T A

1610 1620 1630 1640 1650 1660 1670 1680 1690 1700
CAGGAGCAGACACATCAGAGGTTCACTGGAATTACAAAGAGAGAATGGTGACATTTAAGGTTCTCATGCCAAGAGACAGGATGTGACAGTGTGGGATC
G A D T S E V H W N Y K E R M V T F K V P H A K R Q D V T V L G S

1710 1720 1730 1740 1750 1760 1770 1780 1790 1800
TCAGGAAGGAGCCATTTCTGCCCTCGCTGGAGCCACAGAAGTGGACTCCGGTGATGGAAATCACATGTTTGAGGACATCTCAAGTGCAAAGTCCGT
Q E G A M H S A L A G A T E V D S G D G N H M F A G H L K C K V R

[0362]

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1810      1820      1830      1840      1850      1860      1870      1880      1890      1900
ATGGAGAAATTGAGAATCAAGGGAATGTATACACGATGTGTTTCAGGAAAGTTCTCAATTGACAAAGAGATGGCAGAAACACAGCATGGGACAAACAGTGG
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
TGAAAGTCAAGTATGAAGGTGCTGGAGCTCCGTGTAAAGTCCCCATAGAGATAAGAGATGTGAACAAGGAAAAAGTTGGGCGTATCATCTCATCCAC
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
```

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
CTCCATTGGTTTCAGGAAAGGGAGTTCATTGGCAAGATGTTTGTAGTCCACATACAGAGGTGCAAAACGAATGGCCATTCTAGGTGAACAGCTTGGGATT
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
TTGGTTCGGTTGGTGGAGTTCACATCATTTGGGAAAGGCTGTGCACAGGTTTGGGAAGTGTGTATACAACTGTTGGAGGAGTCTCATGGATGAT
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

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2310      2320      2330      2340      2350      2360      2370      2390      2400
TAGAATCCTAATTGGGTTCTTAGTGTGTGGATTGGCAGCACTCAAGGAACACTTCAATGGCTATGACGTGCATAGCTGCCGGCATTGTGACACTGTAT
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
TTGGGAGTCATGGTGCAGGCCGATAGTGGTTGCGTTGTGAGCTGGAAAAACAAAGAACTGAAATGTGCGAGTGGGATTTCATCAGACAACTGTCACA
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
CATGGACAGAACAATACAAGTTCACCAAGTCCGCTTCAAACTAGCTTCAGCTATCCAGAAAGCCCATGAAGAGGACATTTGTGGAATCCGCTCAGT
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 E I C G I R S V
```

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
AACAGACTGGAGAATCTGATGTGGAACAAATAACACAGAAATGAAATCACATTCTATCAGAAAATGAGGTGAAGTTAACTATTATGACAGGAGACATC
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
AAAGGAATCATGCAGGCAGGAAAAACGATCTCTGCGGCTCAGCCCACTGAGCTGAAGTATTGAAACATGGGGCAAGCAAAATGCTCTCTACAG
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
AGTCTCATAACCAGACCTTTCTCATTGATGGCCCGAAACAGCAGAAATGCCCAACACAAATAGAGCTTGGAAATTCGTTGGAAGTTGAAGACTATGGCTT
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
TGGAGTATTACCAACCAATATATGGCTAAAATTGAAAGAAAAACAGGATGTATTCTGCGACTCAAACTCATGTCAGCGGCCATAAAAGACAACAGAGCC
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
GTCCATGCCGATATGGTTATTGGATAGAAAGTGCACTCAATGACACATGGAAGATAGAGAAAGCCTTTTCATTGAAGTTAAAACTGCCACTGGCCAA
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
AATCACACACCCCTCTGGAGCAATGGAGTGTCTAGAAAGTGAGATGATAATCCAAAGAATCTCGCTGGACCACTGCTCAACACAACCTATAGACAGGCTA
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
CCATACACAATAACAGGACCATGGCATCTAGGTAAGCTTGAGATGGACTTTGATTTCTGTGATGGAACAACAGTGGTAGTACTGAGGACTGCGGAAAT
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
AGAGGACCCCTCTTTGAGAACAAACACTGCCTCTGGAAGAACTCATAACAGAATGGTGTGCGGATCTTGACATTACCAACCGCTAAGATACAGAGGTGAGG
R G P S L R T T T A S G T 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
```

[0363]

ATGGGTGCTGGTACGGGATGGAATCAGACCATTGAAGGAGAAAGAGAATTTGGTCAACTCCTTGGTCACAGCTGGACATGGGCAGGTCGACAACCTT
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
TTCAC TAGGAGTCTTGGGAATGGCATTGTTCTTGGAGGAAATGCTTAGGACCCGAGTAGGAACGAAACATGCAATACTACTAGTTGACAGTTTCTTTTGTG
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
ACATTGATCACAGGGAACATGTCCTTTAGAGACCTGGGAAGAGTGATGGTTATGGTAGGCGCCACTATGACGGGTGACATAGGTATGGGCGTGACTTATC
T L I T G N M S F R D L G R V M V M V G A T M T G D I G M G V T Y L

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)

3710 3720 3730 3740 3750 3760 3770 3780 3790 3800
TTGCCCTACTAGCAGCCTTCAAAGTCAGACCAACTTTTGCAGCTGGACTACTCTTGAGAAAGCTGACCTCCAGGGAATTGATGATGACTACTATAGGAAT
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

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

3810 3820 3830 3840 3850 3860 3870 3880 3890 3900
TGTACTCCTCTCCAGAGCACCATACCCAGAGACCATCTTGAGTTGACTGATGCGTTAGCCTTAGGCATGATGGTCCTCAAATGGTGAGAAATATGGAA
V L 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

3910 3920 3930 3940 3950 3960 3970 3980 3990 4000
AAGTATCAATTGGCAGTGACTATCATGGCTATCTTGTGCGTCCCAACGACAGTGATATTACAAAACGATGGAAGTGAGTTGCACAAATATTGGCAGTGG
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
TGTCGCTTTCCCACTGTTCTTAACATCCTCACAGCAAAAAACAGATTGGATACCATTAGCATTGACGATCAAGGTCTCAATCCAACAGCTATTTTCT
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
AACAAACCTCTCAAGAACCAGCAAGAAAAGGAGCTGGCCATTAAATGAGGCTATCATGGCAGTCGGGATGGTGAGCATTTTAGCCAGTTCTCTCTCTAAAA
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
AATGATATTCCCATGACAGGACCATAGTGGCTGGAGGGCTCCTCACTGTGTGCTACGTGCTCACTGGACGATCGGCGGATTGGAACTGGAGAGAGCAG
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
CCGATGTCAAATGGGAAGACCAGGCAGAGATATCAGGAAGCAGTCCAATCTGTCAATAACAATATCAGAAGATGGTAGCATGTCGATAAAAAATGAAGA
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
GGAAGACAAACACTGACCATACTCATTAGAACAGGATTGCTGGTGATCTCAGGACTTTTCTCTGTATCAATACCAATCAGGCAGCAGCATGTGACCTG
E E 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

> NS3

4510 4520 4530 4540 4550 4560 4570 4580 4590 4600
TGGGAAGTGAAGAAACAACGGGCCGAGTATTGTGGGATGTTCTTCAACCCCAACCCATGGGAAAGGCTGAACTGGAAGATGGAGCCTATAGAATTAAAGC
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
AAAAAGGATTCTTGATATTCCAGATCGGAGCCGGAGTTTACAAAGAAGGAACATTCCATACAATGTGGCATGTCACAGTGGCGCTGTTCTAATGCA
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
TAAAGGAAAGAGGATTGAACCATCATGGGCGGACGTCAAGAAAGACCTAATATCATATGGAGGAGGCTGGAAGTTAGAAGGAGATGGAAGGAAGGAGAA
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
GAAGTCCAGTATTGGCACTGGAGCCTGGAATAATCCAAAGACCGTCCAAACGAAACCTGGTCTTTTCAAACCAACGCCGGAACAATAGGTGCTGTAT
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
CTCTGGACTTTTCTCTGGAACGTGAGGATCTCCAATTATCGACAAAAAGGAAAAGTTGTGGGTCTTTATGGTAATGGTGTGTTACAAGGAGTGGAGC
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
ATATGTGAGTGCTATAGCCGAGACTGAAAAAGCATTGAAGACAACCCAGAGATCGAAGATGACATTTTCCGAAAGAGAAGACTGACCATCATGGACCTC
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

[0364]

5110 5120 5130 5140 5150 5160 5170 5180 5190 5200
CACCCAGGAGCGGGAAGACGAAGAGATACCTTCCGGCCATAGTCAGAGAAGCTATAAACGGGGTTTGAGAACATTATCTTGGCCCCACTAGAGTTG
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
TGGCAGCTGAAATGGAGGAGCCCTTAGAGGACTTCCAATAAGATACCAGACCCAGCCATCAGAGCTGTGCACACCGGCGGAGATTGTGGACCTAAT
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
GTGTCATGCCACATTTACCATGAGGCTGCTATCACCAGTTAGAGTGCCAACTACAACCTGATTATCATGGACGAAGCCATTTCACAGATCCAGCAAGT
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
ATAGCAGCTAGAGGATACATCTCAACTCGAGTGAGATGGGTGAGGACGCTGGGATTTTATGACAGCCACTCCCCGGGAAGCAGAGACCCATTTCCTC
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
AGAGCAATGCACCAATCATAGATGAAGAAAGAGAAATCCCTGAACGCTCGTGGAATTCGGGACATGAATGGGTACGCGATTAAAGGGAAGACTGTTTG
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
GTTCTGTTCCAAGTATAAAAGCAGGAAATGATATAGCAGCTTGCCTGAGGAAAAATGGAAGAAAGTGATACAACCTCAGTAGGAAGACCTTTGATTCTGAG
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
TATGTCAAGACTAGAACCAATGATTGGGACTTCGTGGTTACAACCTGACATTTTCAGAAATGGGTGCCAATTTCAAGGCTGAGAGGGTTATAGACCCAGAC
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
GCTGCATGAAACCACTCACTAACAAGATGGTGAAGAGCGGGTGATTCTGGCAGGACCTATGCCAGTGACCCACTCTAGTGACAGCACAAAGAGAGGGGAG
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

[0365]

5910 5920 5930 5940 5950 5960 5970 5980 5990 6000
AATAGGAAGAAATCCAAAAATGAGAATGACCACTGATATACATGGGGAACTCTGGAAAATGATGAAGACTGTGCACACTGGAAAGAACTGAAATG
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
CTCCTAGATAACATCAACACGCGCAGAGGAATCATTCCTAGCATGTTTCGAACAGAGCGGTGAAAAGGTGGATGCCATTGATGGCGGAATACCGCTTGAGAG
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
GAGAAGCAAGGAAACCTTTGTAGACTTAATGAGAAGAGGAGACCTACCAGTCTGGTGGCTACAGAGTGGCAGCTGAAGGCATCAACTACGACAGACAG
E A R K T F 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
AAGGTGGTGTGTTTGTAGAGTCAAGAACAACCAATCCTAGAAAGAAACGTGGAAGTTGAAATCTGGACAAAAGAGGGGAAAGGAAGAAATTGAAACCC
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
AGATGGTTGGATGCTAGGATCTATTCTGACCCACTGGCGCTAAAAGAAATTTAAGGAATTTGCAGCCGGAAGAAAGTCTCTGACCTGAACTAATCACAG
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
AAATGGGTAGGCTCCCACTTCATGACTCAGAAGGTAAGAGACGCACTGGACAACTTAGCAGTGTGCACACGGCTGAGGCAGGTGGAAGGGCGTACAA
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
CCATGCTCTCAGTGAAGTCCCGGAGACCTGGAGACATGCTTTTACTGACACTTCTGGCTACAGTCACGGGAGGGATCTTTTATTCTTGATGAGCGCA
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
AGGGGATAGGGAAGATGACCCCTGGGAATGTGCTGCATAATCACGGCTAGCATCCTCTATGGTACGCACAAATACAGCCCACTGGATAGCAGCTTCAA
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
TAATACTGGAGTGTGTTTCTCATAGTTTGTCTTATTCAGAACCTGAAAAACAGAGAACACCCCAAGACAACCACTGACCTACGTTGTCATAGCCATCCT

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
CACAGTGGTGGCCGCAACCATGGCAAACGAGATGGGTTTCTAGAAAAACGAAGAAAGATCTCGGATTGGGAAGCATTGCAACCCAGCAACCCGAGAGC
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
AACATCCTGGACATAGATCTACGTCCTGCATCAGCATGGACGCTGTATGCCGTGGCCCAACATTGTTACACCAATTGTGAGACATAGCATTGAAATC
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
CCTCAGTGAATGTGTCCCTAACAGCCATAGCCAACCAAGCCACAGTGTAAATGGGTCTCGGGAAGGATGGCCATTGTCAAAGATGGACATCGGAGTTCC
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
CCTTCTCGCCATTTGGATGCTACTCACAAGTCAACCCCATAACTCTCACAGCAGCTCTTTCTTATTGGTAGCACATTATGCCATCATAGGCCAGGACTC
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
CAAGCAAAAGCAACAGAGAAGCTCAGAAAAGAGCAGCGCGGCATGAAAAACCAACTGTGATGGAATAACAGTGATTGACCTAGATCCAATAC
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
CTTATGATCCAAAGTTTGAAGCAGTTGGGACAAGTAATGCTCCTAGTCTCTGCGTGACTCAAGTATTGATGATGAGGACTACATGGGCTCTGTGTGA
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
GGCTTTAACTTAGCTACCGGGCCCATCTCCACATTGTGGGAAGGAAATCCAGGGAGGTTTTGGAACACTACCATTCGCGGTGTCAATGGCTAACATTTTT
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
AGAGGGAGTTACTTGGCCGAGCTGGACTTCTCTTTCTATTATGAAGAACACAACCAACAAGAAAGGGGAACCTGGCAACATAGGAGAGACGCTTGAG
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

[0366]

7610 7620 7630 7640 7650 7660 7670 7680 7690 7700
AGAAATGGAAAAGCCGATTGAACGCATTGGGAAAAAGTGAATTCAGATCTCAAGAAAAAGTGAATCCAGGAAGTGGATAGAACCCTTAGCAAAAAGAGG
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
CATTAAAGAGGAGAAACGGACCATCACGCTGTGTCGCGAGGCTCAGCAAACTGAGATGGTTGTTGAGAGAAACATGGTCACACCAGAGGGGAAAGTA
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
AAGAAACCATCCCCATGTCAACATATGGGTGGAATCTAGTGCCTCTCAAAGTGGAGTTGACGTTTTCTTCATCCCGCAGAAAAGTGTGACACATTATT
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
GTGTGACATAGGGGAGTCATCACCAAATCCACAGTGGGAAGCAGGACGAACTCAGAGTCTTAACTTAGTAGAAAATTGGTTGAACAACAACACTCAA
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
TTTTGCATAAAGTTCTCAACCATATATGCCCTCAGTCATAGAAAAATGGAAGCACTACAAAGGAAATATGGAGGAGCCCTTAGTGAGGAATCCACTCT
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
CACGAACTCCACACATGAGATGTACTGGGTATCCAATGCTTCCGGGAACATAGTGTCACTCAGTGAACATGATTTCAAGGATGTTGATCAACAGATTTC
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
AATGAGATACAAGAAAGCCACTTACGAGCCGATGTTGACCTCGGAAGCGGAACCCGTAACATCGGGATTGAAAGTGAGATACCAACCTAGATATAATT
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
GGGAAAAGAAATAGAAAAATAAAGCAAGAGCATGAAACATCATGGCACTATGACCAAGACCCACATACAAAACGTGGGCATACCATGGTAGCTATGAAA
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
CAAAACAGACTGGATCAGCATCATCCATGGTCAACGGAGTGGTCAGGCTGCTGACAAAACCTTGGGACGTCGTCCTCCCATGGTGACACAGATGGCAATGAC
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
AGACACGACTCCATTGGACAACAGCGCGTTTTTAAAGAGAAAGTGACACGAGAACCCAGAAACCGAAAGAGCAGAGAACTAATGAAAATAACA
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
GCAGAGTGGCTTTGGAAAGAAATAGGGAAGAAAAAGACACCCAGGATGTGCACGAGAGAATTCACAAGAAAGGTGAGAGCAATGCACCTTGGGGG
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
CCATATTCACTGATGAGAACAGTGAAGTCGCGACGTGAGGCTGTTGAAGATAGTAGGTTTGGGAGCTGGTTGACAAGGAAAGGAATCTCCATCTTGA
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
AGGAAAGTGTGAAACATGTGTACACATGATGGGAAAAAGAGAGAAGAGCTAGGGGAATTCGGCAAGGCAAAAGGCAGCAGAGCCATATGGTACATG
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
TGGCTTGGAGCAGCTTCTTAGAGTTTGAAGCCCTAGGATTCTTAATGAAGATCACTGGTTCTCCAGAGAGAACTCCCTGAGTGGAGTGAAGGAGAAG
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[0208]	1 5 10 15	
[0209]	Lys Arg Glu Arg Asn Arg Val Ser Thr Val Gln Gln Leu Thr Lys Arg	

[0210]	20	25	30
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[0212]	35	40	45
[0213]	Ala Leu Val Ala Phe Leu Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly		
[0214]	50	55	60
[0215]	Ile Leu Lys Arg Trp Gly Thr Ile Lys Lys Ser Lys Ala Ile Asn Val		
[0216]	65	70	75
[0217]	Leu Arg Gly Phe Arg Lys Glu Ile Gly Arg Met Leu Asn Ile Leu Asn		
[0218]	85	90	95
[0219]	Arg Arg Arg Arg Ser Ala Gly Met Ile Ile Met Leu Ile Pro Thr Val		
[0220]	100	105	110
[0221]	Met Ala Phe His Leu Thr Thr Arg Gly Gly Glu Pro His Met Ile Val		
[0222]	115	120	125
[0223]	Ser Lys Gln Glu Arg Gly Lys Ser Leu Leu Phe Lys Thr Ser Ala Gly		
[0224]	130	135	140
[0225]	Val Asn Met Cys Thr Leu Ile Ala Met Asp Leu Gly Glu Leu Cys Glu		
[0226]	145	150	155
[0227]	Asp Thr Met Thr Tyr Lys Cys Pro Arg Ile Thr Glu Ala Glu Pro Asp		
[0228]	165	170	175
[0229]	Asp Val Asp Cys Trp Cys Asn Ala Thr Asp Thr Trp Val Thr Tyr Gly		
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[0231]	Thr Cys Ser Gln Thr Gly Glu His Arg Arg Asp Lys Arg Ser Val Ala		
[0232]	195	200	205
[0233]	Leu Ala Pro His Val Gly Leu Gly Leu Glu Thr Arg Ala Glu Thr Trp		
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[0235]	Met Ser Ser Glu Gly Ala Trp Lys Gln Ile Gln Lys Val Glu Thr Trp		
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[0237]	Ala Leu Arg His Pro Gly Phe Thr Val Ile Ala Leu Phe Leu Ala His		
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[0239]	Ala Ile Gly Thr Ser Ile Thr Gln Lys Gly Ile Ile Phe Ile Leu Leu		
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[0245]	Leu Glu His Gly Ser Cys Val Thr Thr Met Ala Lys Asn Lys Pro Thr		
[0246]	305	310	315
[0247]	Leu Asp Ile Glu Leu Leu Lys Thr Glu Val Thr Asn Pro Ala Val Leu		
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[0249]	Arg Lys Leu Cys Ile Glu Ala Lys Ile Ser Asn Thr Thr Thr Asp Ser		
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[0257]	Cys Val Thr Lys Leu Glu Gly Lys Ile Val Gln Tyr Glu Asn Leu Lys		
[0258]	405	410	415
[0259]	Tyr Ser Val Ile Val Thr Val His Thr Gly Asp Gln His Gln Val Gly		
[0260]	420	425	430
[0261]	Asn Glu Thr Thr Glu His Gly Thr Thr Ala Thr Ile Thr Pro Gln Ala		
[0262]	435	440	445
[0263]	Pro Thr Ser Glu Ile Gln Leu Thr Asp Tyr Gly Thr Leu Thr Leu Asp		
[0264]	450	455	460
[0265]	Cys Ser Pro Arg Thr Gly Leu Asp Phe Asn Glu Met Val Leu Leu Thr		
[0266]	465	470	475
[0267]	Met Lys Glu Arg Ser Trp Leu Val His Lys Gln Trp Phe Leu Asp Leu		
[0268]	485	490	495
[0269]	Pro Leu Pro Trp Thr Ser Gly Ala Ser Thr Ser Gln Glu Thr Trp Asn		
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[0271]	Arg Gln Asp Leu Leu Val Thr Phe Lys Thr Ala His Ala Lys Lys Gln		
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[0273]	Glu Val Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu		
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[0275]	Thr Gly Ala Thr Glu Ile Gln Thr Ser Gly Thr Thr Thr Ile Phe Ala		
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[0277]	Gly His Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Thr Leu Lys Gly		
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[0279]	Met Ser Tyr Val Met Cys Thr Gly Ser Phe Lys Leu Glu Lys Glu Val		
[0280]	580	585	590
[0281]	Ala Glu Thr Gln His Gly Thr Val Leu Val Gln Val Lys Tyr Glu Gly		
[0282]	595	600	605
[0283]	Thr Asp Ala Pro Cys Lys Ile Pro Phe Ser Thr Gln Asp Glu Lys Gly		
[0284]	610	615	620
[0285]	Ala Thr Gln Asn Gly Arg Leu Ile Thr Ala Asn Pro Ile Val Thr Asp		
[0286]	625	630	635
[0287]	Lys Glu Lys Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Glu Ser		
[0288]	645	650	655
[0289]	Tyr Ile Val Val Gly Ala Gly Glu Lys Ala Leu Lys Leu Ser Trp Phe		
[0290]	660	665	670
[0291]	Lys Lys Gly Ser Ser Ile Gly Lys Met Phe Glu Ala Thr Ala Arg Gly		
[0292]	675	680	685
[0293]	Ala Arg Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser		

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[0295]	Ile Gly Gly Val Phe Thr Ser Met Gly Lys Leu Val His Gln Val Phe		
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[0297]	Gly Thr Ala Tyr Gly Val Leu Phe Ser Gly Val Ser Trp Thr Met Lys		
[0298]		725	730
[0299]	Ile Gly Ile Gly Ile Leu Leu Thr Trp Leu Gly Leu Asn Ser Arg Asn		735
[0300]		740	745
[0301]	Thr Ser Leu Ser Met Met Cys Ile Ala Ala Ala Ile Val Thr Leu Tyr		750
[0302]		755	760
[0303]	Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys		765
[0304]	770	775	780
[0305]	Asn Lys Glu Leu Lys Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val		
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[0307]	His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys		800
[0308]		805	810
[0309]	Leu Ala Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile		815
[0310]		820	825
[0311]	Arg Ser Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro		830
[0312]		835	840
[0313]	Glu Leu Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met		845
[0314]	850	855	860
[0315]	Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg		
[0316]	865	870	875
[0317]	Pro Gln Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala		880
[0318]		885	890
[0319]	Lys Met Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly		895
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[0321]	Pro Glu Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu		910
[0322]		915	920
[0323]	Glu Val Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu		925
[0324]	930	935	940
[0325]	Lys Leu Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser		
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[0327]	Ala Ala Ile Lys Asp Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp		960
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[0329]	Ile Glu Ser Ala Leu Asn Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe		975
[0330]		980	985
[0331]	Ile Glu Val Lys Asn Cys His Trp Pro Lys Ser His Thr Leu Trp Ser		990
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[0333]	Asn Gly Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala		1005
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[0335]	Gly Pro Val Ser Gln His Asn Tyr Arg Pro Gly Tyr His Thr Gln		

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[0337]	Ile Thr Gly Pro Trp His	Leu Gly Lys Leu Glu Met Asp Phe Asp	
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[0339]	Phe Cys Asp Gly Thr Thr	Val Val Val Thr Glu Asp Cys Gly Asn	
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[0341]	Arg Gly Pro Ser Leu Arg	Thr Thr Thr Ala Ser Gly Lys Leu Ile	
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[0343]	Thr Glu Trp Cys Cys Arg	Ser Cys Thr Leu Pro Pro Leu Arg Tyr	
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[0345]	Arg Gly Glu Asp Gly Cys	Trp Tyr Gly Met Glu Ile Arg Pro Leu	
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[0349]	His Gly Gln Val Asp Asn	Phe Ser Leu Gly Val Leu Gly Met Ala	
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[0351]	Leu Phe Leu Glu Glu Met	Leu Arg Thr Arg Val Gly Thr Lys His	
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[0353]	Ala Ile Leu Leu Val Ala	Val Ser Phe Val Thr Leu Ile Thr Gly	
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[0355]	Asn Met Ser Phe Arg Asp	Leu Gly Arg Val Met Val Met Val Gly	
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[0357]	Ala Thr Met Thr Asp Asp	Ile Gly Met Gly Val Thr Tyr Leu Ala	
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[0359]	Leu Leu Ala Ala Phe Lys	Val Arg Pro Thr Phe Ala Ala Gly Leu	
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[0361]	Leu Leu Arg Lys Leu Thr	Ser Lys Glu Leu Met Met Thr Thr Ile	
[0362]	1220	1225	1230
[0363]	Gly Ile Val Leu Leu Ser	Gln Ser Thr Leu Pro Glu Thr Ile Leu	
[0364]	1235	1240	1245
[0365]	Glu Leu Thr Asp Ala Leu	Ala Leu Gly Met Met Val Leu Lys Met	
[0366]	1250	1255	1260
[0367]	Val Arg Asn Met Glu Lys	Tyr Gln Leu Ala Val Thr Ile Met Ala	
[0368]	1265	1270	1275
[0369]	Ile Leu Cys Val Pro Asn	Ala Val Ile Leu Gln Asn Ala Trp Lys	
[0370]	1280	1285	1290
[0371]	Val Ser Cys Thr Ile Leu	Ala Val Val Ser Val Ser Pro Leu Phe	
[0372]	1295	1300	1305
[0373]	Leu Thr Ser Ser Gln Gln	Lys Thr Asp Trp Ile Pro Leu Ala Leu	
[0374]	1310	1315	1320
[0375]	Thr Ile Lys Gly Leu Asn	Pro Thr Ala Ile Phe Leu Thr Thr Leu	
[0376]	1325	1330	1335
[0377]	Ser Arg Thr Ser Lys Lys	Arg Ser Trp Pro Leu Asn Glu Ala Ile	

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[0379]	Met Ala Val Gly Met Val Ser Ile Leu Ala Ser Ser Leu Leu Lys		
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[0383]	Thr Val Cys Tyr Val Leu Thr Gly Arg Ser Ala Asp Leu Glu Leu		
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[0385]	Glu Arg Ala Ala Asp Val Lys Trp Glu Asp Gln Ala Glu Ile Ser		
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[0387]	Gly Ser Ser Pro Ile Leu Ser Ile Thr Ile Ser Glu Asp Gly Ser		
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[0389]	Met Ser Ile Lys Asn Glu Glu Glu Asp Gln Thr Leu Thr Ile Leu		
[0390]	1430	1435	1440
[0391]	Ile Arg Thr Gly Leu Leu Val Ile Ser Gly Leu Phe Pro Val Ser		
[0392]	1445	1450	1455
[0393]	Ile Pro Ile Thr Ala Ala Ala Trp Tyr Leu Trp Glu Val Lys Lys		
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[0395]	Gln Arg Ala Gly Val Leu Trp Asp Val Pro Ser Pro Pro Pro Met		
[0396]	1475	1480	1485
[0397]	Gly Lys Ala Glu Leu Glu Asp Gly Ala Tyr Arg Ile Lys Gln Lys		
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[0405]	Lys Asp Leu Ile Ser Tyr Gly Gly Gly Trp Lys Leu Glu Gly Glu		
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[0407]	Trp Lys Glu Gly Glu Glu Val Gln Val Leu Ala Leu Glu Pro Gly		
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[0409]	Lys Asn Pro Arg Ala Val Gln Thr Lys Pro Gly Leu Phe Lys Thr		
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[0411]	Asn Ala Gly Thr Ile Gly Ala Val Ser Leu Asp Phe Ser Pro Gly		
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[0413]	Thr Ser Gly Ser Pro Ile Ile Asp Lys Lys Gly Lys Val Val Gly		
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[0415]	Leu Tyr Gly Asn Gly Val Val Thr Arg Ser Gly Ala Tyr Val Ser		
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[0417]	Ala Ile Ala Gln Thr Glu Lys Ser Ile Glu Asp Asn Pro Glu Ile		
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[0419]	Glu Asp Asp Ile Phe Arg Lys Arg Arg Leu Thr Ile Met Asp Leu		

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[0423]	Arg Glu Ala Ile Lys Arg Gly Leu Arg Thr Leu Ile Leu Ala Pro		
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[0425]	Thr Arg Val Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu		
[0426]	1700	1705	1710
[0427]	Pro Ile Arg Tyr Gln Thr Pro Ala Ile Arg Ala Val His Thr Gly		
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[0429]	Arg Glu Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Met Arg		
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[0431]	Leu Leu Ser Pro Val Arg Val Pro Asn Tyr Asn Leu Ile Ile Met		
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[0433]	Asp Glu Ala His Phe Thr Asp Pro Ala Ser Ile Ala Ala Arg Gly		
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[0435]	Tyr Ile Ser Thr Arg Val Glu Met Gly Glu Ala Ala Gly Ile Phe		
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[0437]	Met Thr Ala Thr Pro Pro Gly Ser Arg Asp Pro Phe Pro Gln Ser		
[0438]	1790	1795	1800
[0439]	Asn Ala Pro Ile Ile Asp Glu Glu Arg Glu Ile Pro Glu Arg Ser		
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[0441]	Trp Asn Ser Gly His Glu Trp Val Thr Asp Phe Lys Gly Lys Thr		
[0442]	1820	1825	1830
[0443]	Val Trp Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile Ala Ala		
[0444]	1835	1840	1845
[0445]	Cys Leu Arg Lys Asn Gly Lys Lys Val Ile Gln Leu Ser Arg Lys		
[0446]	1850	1855	1860
[0447]	Thr Phe Asp Ser Glu Tyr Val Lys Thr Arg Thr Asn Asp Trp Asp		
[0448]	1865	1870	1875
[0449]	Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys		
[0450]	1880	1885	1890
[0451]	Ala Glu Arg Val Ile Asp Pro Arg Arg Cys Met Lys Pro Val Ile		
[0452]	1895	1900	1905
[0453]	Leu Thr Asp Gly Glu Glu Arg Val Ile Leu Ala Gly Pro Met Pro		
[0454]	1910	1915	1920
[0455]	Val Thr His Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg		
[0456]	1925	1930	1935
[0457]	Asn Pro Lys Asn Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu Pro		
[0458]	1940	1945	1950
[0459]	Leu Glu Asn Asp Glu Asp Cys Ala His Trp Lys Glu Ala Lys Met		
[0460]	1955	1960	1965
[0461]	Leu Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile Pro Ser Met		

[0462]	1970	1975	1980
[0463]	Phe Glu Pro Glu Arg Glu Lys Val Asp Ala Ile Asp Gly Glu Tyr		
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[0465]	Arg Leu Arg Gly Glu Ala Arg Lys Thr Phe Val Asp Leu Met Arg		
[0466]	2000	2005	2010
[0467]	Arg Gly Asp Leu Pro Val Trp Leu Ala Tyr Arg Val Ala Ala Glu		
[0468]	2015	2020	2025
[0469]	Gly Ile Asn Tyr Ala Asp Arg Arg Trp Cys Phe Asp Gly Val Lys		
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[0472]	2045	2050	2055
[0473]	Lys Glu Gly Glu Arg Lys Lys Leu Lys Pro Arg Trp Leu Asp Ala		
[0474]	2060	2065	2070
[0475]	Arg Ile Tyr Ser Asp Pro Leu Ala Leu Lys Glu Phe Lys Glu Phe		
[0476]	2075	2080	2085
[0477]	Ala Ala Gly Arg Lys Ser Leu Thr Leu Asn Leu Ile Thr Glu Met		
[0478]	2090	2095	2100
[0479]	Gly Arg Leu Pro Thr Phe Met Thr Gln Lys Ala Arg Asp Ala Leu		
[0480]	2105	2110	2115
[0481]	Asp Asn Leu Ala Val Leu His Thr Ala Glu Ala Gly Gly Arg Ala		
[0482]	2120	2125	2130
[0483]	Tyr Asn His Ala Leu Ser Glu Leu Pro Glu Thr Leu Glu Thr Leu		
[0484]	2135	2140	2145
[0485]	Leu Leu Leu Thr Leu Leu Ala Thr Val Thr Gly Gly Ile Phe Leu		
[0486]	2150	2155	2160
[0487]	Phe Leu Met Ser Ala Arg Gly Ile Gly Lys Met Thr Leu Gly Met		
[0488]	2165	2170	2175
[0489]	Cys Cys Ile Ile Thr Ala Ser Ile Leu Leu Trp Tyr Ala Gln Ile		
[0490]	2180	2185	2190
[0491]	Gln Pro His Trp Ile Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu		
[0492]	2195	2200	2205
[0493]	Ile Val Leu Leu Ile Pro Glu Pro Glu Lys Gln Arg Thr Pro Gln		
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[0495]	Asp Asn Gln Leu Thr Tyr Val Val Ile Ala Ile Leu Thr Val Val		
[0496]	2225	2230	2235
[0497]	Ala Ala Thr Met Ala Asn Glu Met Gly Phe Leu Glu Lys Thr Lys		
[0498]	2240	2245	2250
[0499]	Lys Asp Leu Gly Leu Gly Ser Ile Ala Thr Gln Gln Pro Glu Ser		
[0500]	2255	2260	2265
[0501]	Asn Ile Leu Asp Ile Asp Leu Arg Pro Ala Ser Ala Trp Thr Leu		
[0502]	2270	2275	2280
[0503]	Tyr Ala Val Ala Thr Thr Phe Val Thr Pro Met Leu Arg His Ser		

[0504]	2285	2290	2295
[0505]	Ile Glu Asn Ser Ser Val	Asn Val Ser Leu Thr	Ala Ile Ala Asn
[0506]	2300	2305	2310
[0507]	Gln Ala Thr Val Leu Met	Gly Leu Gly Lys Gly	Trp Pro Leu Ser
[0508]	2315	2320	2325
[0509]	Lys Met Asp Ile Gly Val	Pro Leu Leu Ala Ile	Gly Cys Tyr Ser
[0510]	2330	2335	2340
[0511]	Gln Val Asn Pro Ile Thr	Leu Ile Ala Ala Leu	Phe Leu Leu Val
[0512]	2345	2350	2355
[0513]	Ala His Tyr Ala Ile Ile	Gly Pro Gly Leu Gln	Ala Lys Ala Thr
[0514]	2360	2365	2370
[0515]	Arg Glu Ala Gln Lys Arg	Ala Ala Ala Gly Ile	Met Lys Asn Pro
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[0517]	Thr Val Asp Gly Ile Thr	Val Ile Asp Leu Asp	Pro Ile Pro Tyr
[0518]	2390	2395	2400
[0519]	Asp Pro Lys Phe Glu Lys	Gln Leu Gly Gln Val	Met Leu Leu Val
[0520]	2405	2410	2415
[0521]	Leu Cys Val Thr Gln Val	Leu Met Met Arg Thr	Thr Trp Ala Leu
[0522]	2420	2425	2430
[0523]	Cys Glu Ala Leu Thr Leu	Ala Thr Gly Pro Ile	Ser Thr Leu Trp
[0524]	2435	2440	2445
[0525]	Glu Gly Asn Pro Gly Arg	Phe Trp Asn Thr Thr	Ile Ala Val Ser
[0526]	2450	2455	2460
[0527]	Met Ala Asn Ile Phe Arg	Gly Ser Tyr Leu Ala	Gly Ala Gly Leu
[0528]	2465	2470	2475
[0529]	Leu Phe Ser Ile Met Lys	Asn Thr Thr Asn Thr	Arg Arg Gly Thr
[0530]	2480	2485	2490
[0531]	Gly Asn Ile Gly Glu Thr	Leu Gly Glu Lys Trp	Lys Ser Arg Leu
[0532]	2495	2500	2505
[0533]	Asn Ala Leu Gly Lys Ser	Glu Phe Gln Ile Tyr	Lys Lys Ser Gly
[0534]	2510	2515	2520
[0535]	Ile Gln Glu Val Asp Arg	Thr Leu Ala Lys Glu	Gly Ile Lys Arg
[0536]	2525	2530	2535
[0537]	Gly Glu Thr Asp His His	Ala Val Ser Arg Gly	Ser Ala Lys Leu
[0538]	2540	2545	2550
[0539]	Arg Trp Phe Val Glu Arg	Asn Met Val Thr Pro	Glu Gly Lys Val
[0540]	2555	2560	2565
[0541]	Val Asp Leu Gly Cys Gly	Arg Gly Gly Trp Ser	Tyr Tyr Cys Gly
[0542]	2570	2575	2580
[0543]	Gly Leu Lys Asn Val Arg	Glu Val Lys Gly Leu	Thr Lys Gly Gly
[0544]	2585	2590	2595
[0545]	Pro Gly His Glu Glu Pro	Ile Pro Met Ser Thr	Tyr Gly Trp Asn

[0546]	2600	2605	2610
[0547]	Leu Val Arg Leu Gln Ser Gly Val Asp Val Phe Phe Ile Pro Pro		
[0548]	2615	2620	2625
[0549]	Glu Lys Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Pro		
[0550]	2630	2635	2640
[0551]	Asn Pro Thr Val Glu Ala Gly Arg Thr Leu Arg Val Leu Asn Leu		
[0552]	2645	2650	2655
[0553]	Val Glu Asn Trp Leu Asn Asn Asn Thr Gln Phe Cys Ile Lys Val		
[0554]	2660	2665	2670
[0555]	Leu Asn Pro Tyr Met Pro Ser Val Ile Glu Lys Met Glu Ala Leu		
[0556]	2675	2680	2685
[0557]	Gln Arg Lys Tyr Gly Gly Ala Leu Val Arg Asn Pro Leu Ser Arg		
[0558]	2690	2695	2700
[0559]	Asn Ser Thr His Glu Met Tyr Trp Val Ser Asn Ala Ser Gly Asn		
[0560]	2705	2710	2715
[0561]	Ile Val Ser Ser Val Asn Met Ile Ser Arg Met Leu Ile Asn Arg		
[0562]	2720	2725	2730
[0563]	Phe Thr Met Arg Tyr Lys Lys Ala Thr Tyr Glu Pro Asp Val Asp		
[0564]	2735	2740	2745
[0565]	Leu Gly Ser Gly Thr Arg Asn Ile Gly Ile Glu Ser Glu Ile Pro		
[0566]	2750	2755	2760
[0567]	Asn Leu Asp Ile Ile Gly Lys Arg Ile Glu Lys Ile Lys Gln Glu		
[0568]	2765	2770	2775
[0569]	His Glu Thr Ser Trp His Tyr Asp Gln Asp His Pro Tyr Lys Thr		
[0570]	2780	2785	2790
[0571]	Trp Ala Tyr His Gly Ser Tyr Glu Thr Lys Gln Thr Gly Ser Ala		
[0572]	2795	2800	2805
[0573]	Ser Ser Met Val Asn Gly Val Val Arg Leu Leu Thr Lys Pro Trp		
[0574]	2810	2815	2820
[0575]	Asp Val Val Pro Met Val Thr Gln Met Ala Met Thr Asp Thr Thr		
[0576]	2825	2830	2835
[0577]	Pro Phe Gly Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg		
[0578]	2840	2845	2850
[0579]	Thr Gln Glu Pro Lys Glu Gly Thr Lys Lys Leu Met Lys Ile Thr		
[0580]	2855	2860	2865
[0581]	Ala Glu Trp Leu Trp Lys Glu Leu Gly Lys Lys Lys Thr Pro Arg		
[0582]	2870	2875	2880
[0583]	Met Cys Thr Arg Glu Glu Phe Thr Arg Lys Val Arg Ser Asn Ala		
[0584]	2885	2890	2895
[0585]	Ala Leu Gly Ala Ile Phe Thr Asp Glu Asn Lys Trp Lys Ser Ala		
[0586]	2900	2905	2910
[0587]	Arg Glu Ala Val Glu Asp Ser Arg Phe Trp Glu Leu Val Asp Lys		

[0588]	2915	2920	2925
[0589]	Glu Arg Asn Leu His Leu Glu Gly Lys Cys Glu Thr Cys Val Tyr		
[0590]	2930	2935	2940
[0591]	Asn Met Met Gly Lys Arg Glu Lys Lys Leu Gly Glu Phe Gly Lys		
[0592]	2945	2950	2955
[0593]	Ala Lys Gly Ser Arg Ala Ile Trp Tyr Met Trp Leu Gly Ala Arg		
[0594]	2960	2965	2970
[0595]	Phe Leu Glu Phe Glu Ala Leu Gly Phe Leu Asn Glu Asp His Trp		
[0596]	2975	2980	2985
[0597]	Phe Ser Arg Glu Asn Ser Leu Ser Gly Val Glu Gly Glu Gly Leu		
[0598]	2990	2995	3000
[0599]	His Lys Leu Gly Tyr Ile Leu Arg Asp Val Ser Lys Lys Glu Gly		
[0600]	3005	3010	3015
[0601]	Gly Ala Met Tyr Ala Asp Asp Thr Ala Gly Trp Asp Thr Arg Ile		
[0602]	3020	3025	3030
[0603]	Thr Leu Glu Asp Leu Lys Asn Glu Glu Met Val Thr Asn His Met		
[0604]	3035	3040	3045
[0605]	Glu Gly Glu His Lys Lys Leu Ala Glu Ala Ile Phe Lys Leu Thr		
[0606]	3050	3055	3060
[0607]	Tyr Gln Asn Lys Val Val Arg Val Gln Arg Pro Thr Pro Arg Gly		
[0608]	3065	3070	3075
[0609]	Thr Val Met Asp Ile Ile Ser Arg Arg Asp Gln Arg Gly Ser Gly		
[0610]	3080	3085	3090
[0611]	Gln Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Ala		
[0612]	3095	3100	3105
[0613]	Gln Leu Ile Arg Gln Met Glu Gly Glu Gly Val Phe Lys Ser Ile		
[0614]	3110	3115	3120
[0615]	Gln His Leu Thr Ile Thr Glu Glu Ile Ala Val Gln Asn Trp Leu		
[0616]	3125	3130	3135
[0617]	Ala Arg Val Gly Arg Glu Arg Leu Ser Arg Met Ala Ile Ser Gly		
[0618]	3140	3145	3150
[0619]	Asp Asp Cys Val Val Lys Pro Leu Asp Asp Arg Phe Ala Ser Ala		
[0620]	3155	3160	3165
[0621]	Leu Thr Ala Leu Asn Asp Met Gly Lys Ile Arg Lys Asp Ile Gln		
[0622]	3170	3175	3180
[0623]	Gln Trp Glu Pro Ser Arg Gly Trp Asn Asp Trp Thr Gln Val Pro		
[0624]	3185	3190	3195
[0625]	Phe Cys Ser His His Phe His Glu Leu Ile Met Lys Asp Gly Arg		
[0626]	3200	3205	3210
[0627]	Val Leu Val Val Pro Cys Arg Asn Gln Asp Glu Leu Ile Gly Arg		
[0628]	3215	3220	3225
[0629]	Ala Arg Ile Ser Gln Gly Ala Gly Trp Ser Leu Arg Glu Thr Ala		

[0630]	3230	3235	3240
[0631]	Cys Leu Gly Lys Ser Tyr	Ala Gln Met Trp Ser	Leu Met Tyr Phe
[0632]	3245	3250	3255
[0633]	His Arg Arg Asp Leu Arg	Leu Ala Ala Asn Ala	Ile Cys Ser Ala
[0634]	3260	3265	3270
[0635]	Val Pro Ser His Trp Val	Pro Thr Ser Arg Thr	Thr Trp Ser Ile
[0636]	3275	3280	3285
[0637]	His Ala Lys His Glu Trp	Met Thr Thr Glu Asp	Met Leu Thr Val
[0638]	3290	3295	3300
[0639]	Trp Asn Arg Val Trp Ile	Gln Glu Asn Pro Trp	Met Glu Asp Lys
[0640]	3305	3310	3315
[0641]	Thr Pro Val Glu Ser Trp	Glu Glu Ile Pro Tyr	Leu Gly Lys Arg
[0642]	3320	3325	3330
[0643]	Glu Asp Gln Trp Cys Gly	Ser Leu Ile Gly Leu	Thr Ser Arg Ala
[0644]	3335	3340	3345
[0645]	Thr Trp Ala Lys Asn Ile	Gln Ala Ala Ile Asn	Gln Val Arg Ser
[0646]	3350	3355	3360
[0647]	Leu Ile Gly Asn Glu Glu	Tyr Thr Asp Tyr Met	Pro Ser Met Lys
[0648]	3365	3370	3375
[0649]	Arg Phe Arg Arg Glu Glu	Glu Glu Ala Gly Val	Leu Trp
[0650]	3380	3385	3390
[0651]	<210> 3		
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[0654]	<213> 人工序列		
[0655]	<220>		
[0656]	<223> 登革热病毒血清型1, MVS		
[0657]	<400> 3		
[0658]	Met Asn Asn Gln Arg Lys	Lys Ala Lys Asn Thr	Pro Phe Asn Met Leu
[0659]	1	5	10 15
[0660]	Lys Arg Glu Arg Asn Arg	Val Ser Thr Val Gln	Gln Leu Thr Lys Arg
[0661]	20	25	30
[0662]	Phe Ser Leu Gly Met Leu	Gln Gly Arg Gly Pro	Leu Lys Leu Phe Met
[0663]	35	40	45
[0664]	Ala Leu Val Ala Phe Leu	Arg Phe Leu Thr Ile	Pro Pro Thr Ala Gly
[0665]	50	55	60
[0666]	Ile Leu Lys Arg Trp Gly	Thr Ile Lys Lys Ser	Lys Ala Ile Asn Val
[0667]	65	70	75 80
[0668]	Leu Arg Gly Phe Arg Lys	Glu Ile Gly Arg Met	Leu Asn Ile Leu Asn
[0669]	85	90	95
[0670]	Arg Arg Arg Arg Ser Ala	Gly Met Ile Ile Met	Leu Ile Pro Thr Val
[0671]	100	105	110

[0672]	Met Ala Phe His Leu Thr Thr Arg Gly Gly Glu Pro His Met Ile Val		
[0673]	115	120	125
[0674]	Ser Lys Gln Glu Arg Gly Lys Ser Leu Leu Phe Lys Thr Ser Ala Gly		
[0675]	130	135	140
[0676]	Val Asn Met Cys Thr Leu Ile Ala Met Asp Leu Gly Glu Leu Cys Glu		
[0677]	145	150	155
[0678]	Asp Thr Met Thr Tyr Lys Cys Pro Arg Ile Thr Glu Ala Glu Pro Asp		
[0679]	165	170	175
[0680]	Asp Val Asp Cys Trp Cys Asn Ala Thr Asp Thr Trp Val Thr Tyr Gly		
[0681]	180	185	190
[0682]	Thr Cys Ser Gln Thr Gly Glu His Arg Arg Asp Lys Arg Ser Val Ala		
[0683]	195	200	205
[0684]	Leu Ala Pro His Val Gly Leu Gly Leu Glu Thr Arg Ala Glu Thr Trp		
[0685]	210	215	220
[0686]	Met Ser Ser Glu Gly Ala Trp Lys Gln Ile Gln Lys Val Glu Thr Trp		
[0687]	225	230	235
[0688]	Ala Leu Arg His Pro Gly Phe Thr Val Ile Ala Leu Phe Leu Ala His		
[0689]	245	250	255
[0690]	Ala Ile Gly Thr Ser Ile Thr Gln Lys Gly Ile Ile Phe Ile Leu Leu		
[0691]	260	265	270
[0692]	Met Leu Val Thr Pro Ser Met Ala Met Arg Cys Val Gly Ile Gly Asn		
[0693]	275	280	285
[0694]	Arg Asp Phe Val Glu Gly Leu Ser Gly Ala Thr Trp Val Asp Val Val		
[0695]	290	295	300
[0696]	Leu Glu His Gly Ser Cys Val Thr Thr Met Ala Lys Asn Lys Pro Thr		
[0697]	305	310	315
[0698]	Leu Asp Ile Glu Leu Leu Lys Thr Glu Val Thr Asn Pro Ala Val Leu		
[0699]	325	330	335
[0700]	Arg Lys Leu Cys Ile Glu Ala Lys Ile Ser Asn Thr Thr Thr Asp Ser		
[0701]	340	345	350
[0702]	Arg Cys Pro Thr Gln Gly Glu Ala Thr Leu Val Glu Glu Gln Asp Ala		
[0703]	355	360	365
[0704]	Asn Phe Val Cys Arg Arg Thr Phe Val Asp Arg Gly Trp Gly Asn Gly		
[0705]	370	375	380
[0706]	Cys Gly Leu Phe Gly Lys Gly Ser Leu Ile Thr Cys Ala Lys Phe Lys		
[0707]	385	390	395
[0708]	Cys Val Thr Lys Leu Glu Gly Lys Ile Val Gln Tyr Glu Asn Leu Lys		
[0709]	405	410	415
[0710]	Tyr Ser Val Ile Val Thr Val His Thr Gly Asp Gln His Gln Val Gly		
[0711]	420	425	430
[0712]	Asn Glu Thr Thr Glu His Gly Thr Thr Ala Thr Ile Thr Pro Gln Ala		
[0713]	435	440	445

[0714]	Pro Thr Ser Glu Ile Gln Leu Thr Asp Tyr Gly Thr Leu Thr Leu Asp		
[0715]	450	455	460
[0716]	Cys Ser Pro Arg Thr Gly Leu Asp Phe Asn Glu Met Val Leu Leu Thr		
[0717]	465	470	475 480
[0718]	Met Lys Glu Arg Ser Trp Leu Val His Lys Gln Trp Phe Leu Asp Leu		
[0719]	485	490	495
[0720]	Pro Leu Pro Trp Thr Ser Gly Ala Ser Thr Ser Gln Glu Thr Trp Asn		
[0721]	500	505	510
[0722]	Arg Gln Asp Leu Leu Val Thr Phe Lys Thr Ala His Ala Lys Lys Gln		
[0723]	515	520	525
[0724]	Glu Val Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu		
[0725]	530	535	540
[0726]	Thr Gly Ala Thr Glu Ile Gln Thr Ser Gly Thr Thr Thr Ile Phe Ala		
[0727]	545	550	555 560
[0728]	Gly His Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Thr Leu Lys Gly		
[0729]	565	570	575
[0730]	Met Ser Tyr Val Met Cys Thr Gly Ser Phe Lys Leu Glu Lys Glu Val		
[0731]	580	585	590
[0732]	Ala Glu Thr Gln His Gly Thr Val Leu Val Gln Val Lys Tyr Glu Gly		
[0733]	595	600	605
[0734]	Thr Asp Ala Pro Cys Lys Ile Pro Phe Ser Thr Gln Asp Glu Lys Gly		
[0735]	610	615	620
[0736]	Ala Thr Gln Asn Gly Arg Leu Ile Thr Ala Asn Pro Ile Val Thr Asp		
[0737]	625	630	635 640
[0738]	Lys Glu Lys Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Glu Ser		
[0739]	645	650	655
[0740]	Tyr Ile Val Val Gly Ala Gly Glu Lys Ala Leu Lys Leu Ser Trp Phe		
[0741]	660	665	670
[0742]	Lys Lys Gly Ser Ser Ile Gly Lys Met Phe Glu Ala Thr Ala Arg Gly		
[0743]	675	680	685
[0744]	Ala Arg Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser		
[0745]	690	695	700
[0746]	Ile Gly Gly Val Phe Thr Ser Met Gly Lys Leu Val His Gln Val Phe		
[0747]	705	710	715 720
[0748]	Gly Thr Ala Tyr Gly Val Leu Phe Ser Gly Val Ser Trp Thr Met Lys		
[0749]	725	730	735
[0750]	Ile Gly Ile Gly Ile Leu Leu Thr Trp Leu Gly Leu Asn Ser Arg Asn		
[0751]	740	745	750
[0752]	Thr Ser Leu Ser Met Met Cys Ile Ala Ala Gly Ile Val Thr Leu Tyr		
[0753]	755	760	765
[0754]	Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys		
[0755]	770	775	780

[0756]	Asn Lys Glu Leu Lys Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val
[0757]	785 790 795 800
[0758]	His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys
[0759]	805 810 815
[0760]	Leu Ala Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile
[0761]	820 825 830
[0762]	Arg Ser Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro
[0763]	835 840 845
[0764]	Glu Leu Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met
[0765]	850 855 860
[0766]	Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg
[0767]	865 870 875 880
[0768]	Pro Gln Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala
[0769]	885 890 895
[0770]	Lys Met Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly
[0771]	900 905 910
[0772]	Pro Glu Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu
[0773]	915 920 925
[0774]	Glu Val Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu
[0775]	930 935 940
[0776]	Lys Leu Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser
[0777]	945 950 955 960
[0778]	Ala Ala Ile Lys Asp Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp
[0779]	965 970 975
[0780]	Ile Glu Ser Ala Leu Asn Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe
[0781]	980 985 990
[0782]	Ile Glu Val Lys Asn Cys His Trp Pro Lys Ser His Thr Leu Trp Ser
[0783]	995 1000 1005
[0784]	Asn Gly Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala
[0785]	1010 1015 1020
[0786]	Gly Pro Val Ser Gln His Asn Tyr Arg Pro Gly Tyr His Thr Gln
[0787]	1025 1030 1035
[0788]	Ile Thr Gly Pro Trp His Leu Gly Lys Leu Glu Met Asp Phe Asp
[0789]	1040 1045 1050
[0790]	Phe Cys Asp Gly Thr Thr Val Val Val Thr Glu Asp Cys Gly Asn
[0791]	1055 1060 1065
[0792]	Arg Gly Pro Ser Leu Arg Thr Thr Thr Ala Ser Gly Lys Leu Ile
[0793]	1070 1075 1080
[0794]	Thr Glu Trp Cys Cys Arg Ser Cys Thr Leu Pro Pro Leu Arg Tyr
[0795]	1085 1090 1095
[0796]	Arg Gly Glu Asp Gly Cys Trp Tyr Gly Met Glu Ile Arg Pro Leu
[0797]	1100 1105 1110

[0798]	Lys Glu Lys Glu Glu Asn Leu Val Asn Ser Leu Val Thr Ala Gly
[0799]	1115 1120 1125
[0800]	His Gly Gln Val Asp Asn Phe Ser Leu Gly Val Leu Gly Met Ala
[0801]	1130 1135 1140
[0802]	Leu Phe Leu Glu Glu Met Leu Arg Thr Arg Val Gly Thr Lys His
[0803]	1145 1150 1155
[0804]	Ala Ile Leu Leu Val Ala Val Ser Phe Val Thr Leu Ile Thr Gly
[0805]	1160 1165 1170
[0806]	Asn Met Ser Phe Arg Asp Leu Gly Arg Val Met Val Met Val Gly
[0807]	1175 1180 1185
[0808]	Ala Thr Met Thr Asp Asp Ile Gly Met Gly Val Thr Tyr Leu Ala
[0809]	1190 1195 1200
[0810]	Leu Leu Ala Ala Phe Lys Val Arg Pro Thr Phe Ala Ala Gly Leu
[0811]	1205 1210 1215
[0812]	Leu Leu Arg Lys Leu Thr Ser Lys Glu Leu Met Met Thr Thr Ile
[0813]	1220 1225 1230
[0814]	Gly Ile Val Leu Leu Ser Gln Ser Thr Leu Pro Glu Thr Ile Leu
[0815]	1235 1240 1245
[0816]	Glu Leu Thr Asp Ala Leu Ala Leu Gly Met Met Val Leu Lys Met
[0817]	1250 1255 1260
[0818]	Val Arg Asn Met Glu Lys Tyr Gln Leu Ala Val Thr Ile Met Ala
[0819]	1265 1270 1275
[0820]	Ile Leu Cys Val Pro Asn Ala Val Ile Leu Gln Asn Ala Trp Lys
[0821]	1280 1285 1290
[0822]	Val Ser Cys Thr Ile Leu Ala Val Val Ser Val Ser Pro Leu Phe
[0823]	1295 1300 1305
[0824]	Leu Thr Ser Ser Gln Gln Lys Thr Asp Trp Ile Pro Leu Ala Leu
[0825]	1310 1315 1320
[0826]	Thr Ile Lys Gly Leu Asn Pro Thr Ala Ile Phe Leu Thr Thr Leu
[0827]	1325 1330 1335
[0828]	Ser Arg Thr Ser Lys Lys Arg Ser Trp Pro Leu Asn Glu Ala Ile
[0829]	1340 1345 1350
[0830]	Met Ala Val Gly Met Val Ser Ile Leu Ala Ser Ser Leu Leu Lys
[0831]	1355 1360 1365
[0832]	Asn Asp Ile Pro Met Thr Gly Pro Leu Val Ala Gly Gly Leu Leu
[0833]	1370 1375 1380
[0834]	Thr Val Cys Tyr Val Leu Thr Gly Arg Ser Ala Asp Leu Glu Leu
[0835]	1385 1390 1395
[0836]	Glu Arg Ala Ala Asp Val Lys Trp Glu Asp Gln Ala Glu Ile Ser
[0837]	1400 1405 1410
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[0839]	1415 1420 1425

[0840]	Met Ser Ile Lys Asn Glu Glu Glu Asp Gln Thr Leu Thr Ile Leu
[0841]	1430 1435 1440
[0842]	Ile Arg Thr Gly Leu Leu Val Ile Ser Gly Leu Phe Pro Val Ser
[0843]	1445 1450 1455
[0844]	Ile Pro Ile Thr Ala Ala Ala Trp Tyr Leu Trp Glu Val Lys Lys
[0845]	1460 1465 1470
[0846]	Gln Arg Ala Gly Val Leu Trp Asp Val Pro Ser Pro Pro Pro Met
[0847]	1475 1480 1485
[0848]	Gly Lys Ala Glu Leu Glu Asp Gly Ala Tyr Arg Ile Lys Gln Lys
[0849]	1490 1495 1500
[0850]	Gly Ile Leu Gly Tyr Ser Gln Ile Gly Ala Gly Val Tyr Lys Glu
[0851]	1505 1510 1515
[0852]	Gly Thr Phe His Thr Met Trp His Val Thr Arg Gly Ala Val Leu
[0853]	1520 1525 1530
[0854]	Met His Lys Gly Lys Arg Ile Glu Pro Ser Trp Ala Asp Val Lys
[0855]	1535 1540 1545
[0856]	Lys Asp Leu Ile Ser Tyr Gly Gly Gly Trp Lys Leu Glu Gly Glu
[0857]	1550 1555 1560
[0858]	Trp Lys Glu Gly Glu Glu Val Gln Val Leu Ala Leu Glu Pro Gly
[0859]	1565 1570 1575
[0860]	Lys Asn Pro Arg Ala Val Gln Thr Lys Pro Gly Leu Phe Lys Thr
[0861]	1580 1585 1590
[0862]	Asn Ala Gly Thr Ile Gly Ala Val Ser Leu Asp Phe Ser Pro Gly
[0863]	1595 1600 1605
[0864]	Thr Ser Gly Ser Pro Ile Ile Asp Lys Lys Gly Lys Val Val Gly
[0865]	1610 1615 1620
[0866]	Leu Tyr Gly Asn Gly Val Val Thr Arg Ser Gly Ala Tyr Val Ser
[0867]	1625 1630 1635
[0868]	Ala Ile Ala Gln Thr Glu Lys Ser Ile Glu Asp Asn Pro Glu Ile
[0869]	1640 1645 1650
[0870]	Glu Asp Asp Ile Phe Arg Lys Arg Arg Leu Thr Ile Met Asp Leu
[0871]	1655 1660 1665
[0872]	His Pro Gly Ala Gly Lys Thr Lys Arg Tyr Leu Pro Ala Ile Val
[0873]	1670 1675 1680
[0874]	Arg Glu Ala Ile Lys Arg Gly Leu Arg Thr Leu Ile Leu Ala Pro
[0875]	1685 1690 1695
[0876]	Thr Arg Val Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu
[0877]	1700 1705 1710
[0878]	Pro Ile Arg Tyr Gln Thr Pro Ala Ile Arg Ala Val His Thr Gly
[0879]	1715 1720 1725
[0880]	Arg Glu Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Met Arg
[0881]	1730 1735 1740

[0882]	Leu Leu Ser Pro Val Arg Val Pro Asn Tyr Asn Leu Ile Ile Met
[0883]	1745 1750 1755
[0884]	Asp Glu Ala His Phe Thr Asp Pro Ala Ser Ile Ala Ala Arg Gly
[0885]	1760 1765 1770
[0886]	Tyr Ile Ser Thr Arg Val Glu Met Gly Glu Ala Ala Gly Ile Phe
[0887]	1775 1780 1785
[0888]	Met Thr Ala Thr Pro Pro Gly Ser Arg Asp Pro Phe Pro Gln Ser
[0889]	1790 1795 1800
[0890]	Asn Ala Pro Ile Ile Asp Glu Glu Arg Glu Ile Pro Glu Arg Ser
[0891]	1805 1810 1815
[0892]	Trp Asn Ser Gly His Glu Trp Val Thr Asp Phe Lys Gly Lys Thr
[0893]	1820 1825 1830
[0894]	Val Trp Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile Ala Ala
[0895]	1835 1840 1845
[0896]	Cys Leu Arg Lys Asn Gly Lys Lys Val Ile Gln Leu Ser Arg Lys
[0897]	1850 1855 1860
[0898]	Thr Phe Asp Ser Glu Tyr Val Lys Thr Arg Thr Asn Asp Trp Asp
[0899]	1865 1870 1875
[0900]	Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys
[0901]	1880 1885 1890
[0902]	Ala Glu Arg Val Ile Asp Pro Arg Arg Cys Met Lys Pro Val Ile
[0903]	1895 1900 1905
[0904]	Leu Thr Asp Gly Glu Glu Arg Val Ile Leu Ala Gly Pro Met Pro
[0905]	1910 1915 1920
[0906]	Val Thr His Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg
[0907]	1925 1930 1935
[0908]	Asn Pro Lys Asn Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu Pro
[0909]	1940 1945 1950
[0910]	Leu Glu Asn Asp Glu Asp Cys Ala His Trp Lys Glu Ala Lys Met
[0911]	1955 1960 1965
[0912]	Leu Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile Pro Ser Met
[0913]	1970 1975 1980
[0914]	Phe Glu Pro Glu Arg Glu Lys Val Asp Ala Ile Asp Gly Glu Tyr
[0915]	1985 1990 1995
[0916]	Arg Leu Arg Gly Glu Ala Arg Lys Thr Phe Val Asp Leu Met Arg
[0917]	2000 2005 2010
[0918]	Arg Gly Asp Leu Pro Val Trp Leu Ala Tyr Arg Val Ala Ala Glu
[0919]	2015 2020 2025
[0920]	Gly Ile Asn Tyr Ala Asp Arg Arg Trp Cys Phe Asp Gly Val Lys
[0921]	2030 2035 2040
[0922]	Asn Asn Gln Ile Leu Glu Glu Asn Val Glu Val Glu Ile Trp Thr
[0923]	2045 2050 2055

[0924]	Lys Glu Gly Glu Arg Lys Lys Leu Lys Pro Arg Trp Leu Asp Ala		
[0925]	2060	2065	2070
[0926]	Arg Ile Tyr Ser Asp Pro Leu Ala Leu Lys Glu Phe Lys Glu Phe		
[0927]	2075	2080	2085
[0928]	Ala Ala Gly Arg Lys Ser Leu Thr Leu Asn Leu Ile Thr Glu Met		
[0929]	2090	2095	2100
[0930]	Gly Arg Leu Pro Thr Phe Met Thr Gln Lys Ala Arg Asp Ala Leu		
[0931]	2105	2110	2115
[0932]	Asp Asn Leu Ala Val Leu His Thr Ala Glu Ala Gly Gly Arg Ala		
[0933]	2120	2125	2130
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[1305]	Leu Arg Gly Phe Arg Lys Glu Ile Gly Arg Met Leu Asn Ile Leu Asn		
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[1307]	Arg Arg Arg Arg Ser Ala Gly Met Ile Ile Met Leu Ile Pro Thr Val		
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[1309]	Met Ala Phe His Leu Thr Thr Arg Asn Gly Glu Pro His Met Ile Val		
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[1311]	Ser Arg Gln Glu Lys Gly Lys Ser Leu Leu Phe Lys Thr Glu Val Gly		
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[1313]	Val Asn Met Cys Thr Leu Met Ala Met Asp Leu Gly Glu Leu Cys Glu		
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[1315]	Asp Thr Ile Thr Tyr Glu Cys Pro Leu Leu Arg Gln Asn Glu Pro Glu		
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[1317]	Asp Ile Asp Cys Trp Cys Asn Ser Thr Ser Thr Trp Val Thr Tyr Gly		
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[1319]	Thr Cys Thr Thr Met Gly Glu His Arg Arg Glu Lys Arg Ser Val Ala		
[1320]	195	200	205
[1321]	Leu Val Pro His Val Gly Met Gly Leu Glu Thr Arg Thr Glu Thr Trp		
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[1323]	Met Ser Ser Glu Gly Ala Trp Lys His Val Gln Arg Ile Glu Thr Trp		
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[1325]	Ile Leu Arg His Pro Gly Phe Thr Met Met Ala Ala Ile Leu Ala Tyr		
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[1327]	Thr Ile Gly Thr Thr His Phe Gln Arg Ala Leu Ile Phe Ile Leu Leu		
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[1349]	Asn Asp Thr Gly Lys His Gly Lys Glu Ile Lys Ile Thr Pro Gln Ser			
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[1351]	Ser Ile Thr Glu Ala Glu Leu Thr Gly Tyr Gly Thr Val Thr Met Glu			
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[1353]	Cys Ser Pro Arg Thr Gly Leu Asp Phe Asn Glu Met Val Leu Leu Gln			
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[1355]	Met Glu Asn Lys Ala Trp Leu Val His Arg Gln Trp Phe Leu Asp Leu			
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[1357]	Pro Leu Pro Trp Leu Pro Gly Ala Asp Thr Gln Gly Ser Asn Trp Ile			
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[1359]	Gln Lys Glu Thr Leu Val Thr Phe Lys Asn Pro His Ala Lys Lys Gln			
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[1361]	Asp Val Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu			
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[1363]	Thr Gly Ala Thr Glu Ile Gln Met Ser Ser Gly Asn Leu Leu Phe Thr			
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[1365]	Gly His Leu Lys Cys Arg Leu Arg Met Asp Lys Leu Gln Leu Lys Gly			
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[1367]	Met Ser Tyr Ser Met Cys Thr Gly Lys Phe Lys Val Val Lys Glu Ile			
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[1369]	Ala Glu Thr Gln His Gly Thr Ile Val Ile Arg Val Gln Tyr Glu Gly			
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[1371]	Asp Gly Ser Pro Cys Lys Ile Pro Phe Glu Ile Met Asp Leu Glu Lys			
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[1373]	Arg His Val Leu Gly Arg Leu Ile Thr Val Asn Pro Ile Val Thr Glu			
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[1375]	Lys Asp Ser Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Asp Ser			
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[1377]	Tyr Ile Ile Ile Gly Val Glu Pro Gly Gln Leu Lys Leu Asn Trp Phe			
[1378]		660	665	670
[1379]	Lys Lys Gly Ser Ser Ile Gly Gln Met Phe Glu Thr Thr Met Arg Gly			
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[1381]	Ala Lys Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser			
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[1383]	Leu Gly Gly Val Phe Thr Ser Ile Gly Lys Ala Leu His Gln Val Phe			
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[1387]	Ile Leu Ile Gly Val Ile Ile Thr Trp Ile Gly Met Asn Ser Arg Ser					
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[1389]	Thr Ser Leu Ser Val Thr Leu Val Leu Val Gly Ile Val Thr Leu Tyr					
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[1391]	Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys					
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[1393]	Asn Lys Glu Leu Lys Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val					
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[1395]	His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys					
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[1397]	Leu Ala Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile					
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[1399]	Arg Ser Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro					
[1400]		835		840		845
[1401]	Glu Leu Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met					
[1402]		850		855		860
[1403]	Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg					
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[1405]	Pro Gln Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala					
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[1407]	Lys Met Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly					
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[1409]	Pro Glu Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu					
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[1421]	Asn Gly Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala					
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[1449]	Leu Leu Arg Lys Leu Thr Ser Lys Glu Leu Met Met Thr Thr Ile		
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[1459]	Val Ser Cys Thr Ile Leu Ala Val Val Ser Val Ser Pro Leu Phe		
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[1463]	Thr Ile Lys Gly Leu Asn Pro Thr Ala Ile Phe Leu Thr Thr Leu		
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[1475]	Gly Ser Ser Pro Ile Leu Ser Ile Thr Ile Ser Glu Asp Gly Ser		
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[1477]	Met Ser Ile Lys Asn Glu Glu Glu Glu Gln Thr Leu Thr Ile Leu		
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[1517]	Arg Glu Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Met Arg		
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[1523]	Tyr Ile Ser Thr Arg Val Glu Met Gly Glu Ala Ala Gly Ile Phe		
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[1525]	Met Thr Ala Thr Pro Pro Gly Ser Arg Asp Pro Phe Pro Gln Ser		
[1526]	1790	1795	1800
[1527]	Asn Ala Pro Ile Ile Asp Glu Glu Arg Glu Ile Pro Glu Arg Ser		
[1528]	1805	1810	1815
[1529]	Trp Asn Ser Gly His Glu Trp Val Thr Asp Phe Lys Gly Lys Thr		
[1530]	1820	1825	1830
[1531]	Val Trp Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile Ala Ala		
[1532]	1835	1840	1845
[1533]	Cys Leu Arg Lys Asn Gly Lys Lys Val Ile Gln Leu Ser Arg Lys		
[1534]	1850	1855	1860
[1535]	Thr Phe Asp Ser Glu Tyr Val Lys Thr Arg Thr Asn Asp Trp Asp		
[1536]	1865	1870	1875
[1537]	Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys		
[1538]	1880	1885	1890
[1539]	Ala Glu Arg Val Ile Asp Pro Arg Arg Cys Met Lys Pro Val Ile		
[1540]	1895	1900	1905
[1541]	Leu Thr Asp Gly Glu Glu Arg Val Ile Leu Ala Gly Pro Met Pro		
[1542]	1910	1915	1920
[1543]	Val Thr His Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg		
[1544]	1925	1930	1935
[1545]	Asn Pro Lys Asn Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu Pro		
[1546]	1940	1945	1950
[1547]	Leu Glu Asn Asp Glu Asp Cys Ala His Trp Lys Glu Ala Lys Met		
[1548]	1955	1960	1965
[1549]	Leu Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile Pro Ser Met		
[1550]	1970	1975	1980
[1551]	Phe Glu Pro Glu Arg Glu Lys Val Asp Ala Ile Asp Gly Glu Tyr		
[1552]	1985	1990	1995
[1553]	Arg Leu Arg Gly Glu Ala Arg Lys Thr Phe Val Asp Leu Met Arg		

[1554]	2000	2005	2010
[1555]	Arg Gly Asp Leu Pro Val	Trp Leu Ala Tyr Arg	Val Ala Ala Glu
[1556]	2015	2020	2025
[1557]	Gly Ile Asn Tyr Ala Asp	Arg Arg Trp Cys Phe	Asp Gly Val Lys
[1558]	2030	2035	2040
[1559]	Asn Asn Gln Ile Leu Glu	Glu Asn Val Glu Val	Glu Ile Trp Thr
[1560]	2045	2050	2055
[1561]	Lys Glu Gly Glu Arg Lys	Lys Leu Lys Pro Arg	Trp Leu Asp Ala
[1562]	2060	2065	2070
[1563]	Arg Ile Tyr Ser Asp Pro	Leu Ala Leu Lys Glu	Phe Lys Glu Phe
[1564]	2075	2080	2085
[1565]	Ala Ala Gly Arg Lys Ser	Leu Thr Leu Asn Leu	Ile Thr Glu Met
[1566]	2090	2095	2100
[1567]	Gly Arg Leu Pro Thr Phe	Met Thr Gln Lys Ala	Arg Asp Ala Leu
[1568]	2105	2110	2115
[1569]	Asp Asn Leu Ala Val Leu	His Thr Ala Glu Pro	Gly Gly Arg Ala
[1570]	2120	2125	2130
[1571]	Tyr Asn His Ala Leu Ser	Glu Leu Pro Glu Thr	Leu Glu Thr Leu
[1572]	2135	2140	2145
[1573]	Leu Leu Leu Thr Leu Leu	Ala Thr Val Thr Gly	Gly Ile Phe Leu
[1574]	2150	2155	2160
[1575]	Phe Leu Met Ser Ala Arg	Gly Ile Gly Lys Met	Thr Leu Gly Met
[1576]	2165	2170	2175
[1577]	Cys Cys Ile Ile Thr Ala	Ser Ile Leu Leu Trp	Tyr Ala Gln Ile
[1578]	2180	2185	2190
[1579]	Gln Pro His Trp Ile Ala	Ala Ser Ile Ile Leu	Glu Phe Phe Leu
[1580]	2195	2200	2205
[1581]	Ile Val Leu Leu Ile Pro	Glu Pro Glu Lys Gln	Arg Thr Pro Gln
[1582]	2210	2215	2220
[1583]	Asp Asn Gln Leu Thr Tyr	Val Val Ile Ala Ile	Leu Thr Val Val
[1584]	2225	2230	2235
[1585]	Ala Ala Thr Met Ala Asn	Glu Met Gly Phe Leu	Glu Lys Thr Lys
[1586]	2240	2245	2250
[1587]	Lys Asp Leu Gly Leu Gly	Ser Ile Ala Thr Gln	Gln Pro Glu Ser
[1588]	2255	2260	2265
[1589]	Asn Ile Leu Asp Ile Asp	Leu Arg Pro Ala Ser	Ala Trp Thr Leu
[1590]	2270	2275	2280
[1591]	Tyr Ala Val Ala Thr Thr	Phe Val Thr Pro Met	Leu Arg His Ser
[1592]	2285	2290	2295
[1593]	Ile Glu Asn Ser Ser Val	Asn Val Ser Leu Thr	Ala Ile Ala Asn
[1594]	2300	2305	2310
[1595]	Gln Ala Thr Val Leu Met	Gly Leu Gly Lys Gly	Trp Pro Leu Ser

[1596]	2315	2320	2325
[1597]	Lys Met Asp Ile Gly Val	Pro Leu Leu Ala Ile Gly Cys Tyr Ser	
[1598]	2330	2335	2340
[1599]	Gln Val Asn Pro Ile Thr	Leu Thr Ala Ala Phe Phe Leu Leu Val	
[1600]	2345	2350	2355
[1601]	Ala His Tyr Ala Ile Ile	Gly Pro Gly Leu Gln Ala Lys Ala Thr	
[1602]	2360	2365	2370
[1603]	Arg Glu Ala Gln Lys Arg	Ala Ala Ala Gly Ile Met Lys Asn Pro	
[1604]	2375	2380	2385
[1605]	Thr Val Asp Gly Ile Thr	Val Ile Asp Leu Asp Pro Ile Pro Tyr	
[1606]	2390	2395	2400
[1607]	Asp Pro Lys Phe Glu Lys	Gln Leu Gly Gln Val Met Leu Leu Val	
[1608]	2405	2410	2415
[1609]	Leu Cys Val Thr Gln Val	Leu Met Met Arg Thr Thr Trp Ala Leu	
[1610]	2420	2425	2430
[1611]	Cys Glu Ala Leu Thr Leu	Ala Thr Gly Pro Ile Ser Thr Leu Trp	
[1612]	2435	2440	2445
[1613]	Glu Gly Asn Pro Gly Arg	Phe Trp Asn Thr Thr Ile Ala Val Ser	
[1614]	2450	2455	2460
[1615]	Met Ala Asn Ile Phe Arg	Gly Ser Tyr Leu Ala Gly Ala Gly Leu	
[1616]	2465	2470	2475
[1617]	Leu Phe Ser Ile Met Lys	Asn Thr Thr Asn Thr Arg Arg Gly Thr	
[1618]	2480	2485	2490
[1619]	Gly Asn Ile Gly Glu Thr	Leu Gly Glu Lys Trp Lys Ser Arg Leu	
[1620]	2495	2500	2505
[1621]	Asn Ala Leu Gly Lys Ser	Glu Phe Gln Ile Tyr Lys Lys Ser Gly	
[1622]	2510	2515	2520
[1623]	Ile Gln Glu Val Asp Arg	Thr Leu Ala Lys Glu Gly Ile Lys Arg	
[1624]	2525	2530	2535
[1625]	Gly Glu Thr Asp His His	Ala Val Ser Arg Gly Ser Ala Lys Leu	
[1626]	2540	2545	2550
[1627]	Arg Trp Phe Val Glu Arg	Asn Met Val Thr Pro Glu Gly Lys Val	
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[1629]	Val Asp Leu Gly Cys Gly	Arg Gly Gly Trp Ser Tyr Tyr Cys Gly	
[1630]	2570	2575	2580
[1631]	Gly Leu Lys Asn Val Arg	Glu Val Lys Gly Leu Thr Lys Gly Gly	
[1632]	2585	2590	2595
[1633]	Pro Gly His Glu Glu Pro	Ile Pro Met Ser Thr Tyr Gly Trp Asn	
[1634]	2600	2605	2610
[1635]	Leu Val Arg Leu Gln Ser	Gly Val Asp Val Phe Phe Ile Pro Pro	
[1636]	2615	2620	2625
[1637]	Glu Lys Cys Asp Thr Leu	Leu Cys Asp Ile Gly Glu Ser Ser Pro	

[1638]	2630	2635	2640
[1639]	Asn Pro Thr Val Glu Ala Gly Arg Thr Leu Arg Val Leu Asn Leu		
[1640]	2645	2650	2655
[1641]	Val Glu Asn Trp Leu Asn Asn Asn Thr Gln Phe Cys Ile Lys Val		
[1642]	2660	2665	2670
[1643]	Leu Asn Pro Tyr Met Pro Ser Val Ile Glu Lys Met Glu Ala Leu		
[1644]	2675	2680	2685
[1645]	Gln Arg Lys Tyr Gly Gly Ala Leu Val Arg Asn Pro Leu Ser Arg		
[1646]	2690	2695	2700
[1647]	Asn Ser Thr His Glu Met Tyr Trp Val Ser Asn Ala Ser Gly Asn		
[1648]	2705	2710	2715
[1649]	Ile Val Ser Ser Val Asn Met Ile Ser Arg Met Leu Ile Asn Arg		
[1650]	2720	2725	2730
[1651]	Phe Thr Met Arg Tyr Lys Lys Ala Thr Tyr Glu Pro Asp Val Asp		
[1652]	2735	2740	2745
[1653]	Leu Gly Ser Gly Thr Arg Asn Ile Gly Ile Glu Ser Glu Ile Pro		
[1654]	2750	2755	2760
[1655]	Asn Leu Asp Ile Ile Gly Lys Arg Ile Glu Lys Ile Lys Gln Glu		
[1656]	2765	2770	2775
[1657]	His Glu Thr Ser Trp His Tyr Asp Gln Asp His Pro Tyr Lys Thr		
[1658]	2780	2785	2790
[1659]	Trp Ala Tyr His Gly Ser Tyr Glu Thr Lys Gln Thr Gly Ser Ala		
[1660]	2795	2800	2805
[1661]	Ser Ser Met Val Asn Gly Val Val Arg Leu Leu Thr Lys Pro Trp		
[1662]	2810	2815	2820
[1663]	Asp Val Val Pro Met Val Thr Gln Met Ala Met Thr Asp Thr Thr		
[1664]	2825	2830	2835
[1665]	Pro Phe Gly Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg		
[1666]	2840	2845	2850
[1667]	Thr Gln Glu Pro Lys Glu Gly Thr Lys Lys Leu Met Lys Ile Thr		
[1668]	2855	2860	2865
[1669]	Ala Glu Trp Leu Trp Lys Glu Leu Gly Lys Lys Lys Thr Pro Arg		
[1670]	2870	2875	2880
[1671]	Met Cys Thr Arg Glu Glu Phe Thr Arg Lys Val Arg Ser Asn Ala		
[1672]	2885	2890	2895
[1673]	Ala Leu Gly Ala Val Phe Thr Asp Glu Asn Lys Trp Lys Ser Ala		
[1674]	2900	2905	2910
[1675]	Arg Glu Ala Val Glu Asp Ser Arg Phe Trp Glu Leu Val Asp Lys		
[1676]	2915	2920	2925
[1677]	Glu Arg Asn Leu His Leu Glu Gly Lys Cys Glu Thr Cys Val Tyr		
[1678]	2930	2935	2940
[1679]	Asn Met Met Gly Lys Arg Glu Lys Lys Leu Gly Glu Phe Gly Lys		

[1680]	2945	2950	2955
[1681]	Ala Lys Gly Ser Arg Ala Ile Trp Tyr Met Trp Leu Gly Ala Arg		
[1682]	2960	2965	2970
[1683]	Phe Leu Glu Phe Glu Ala Leu Gly Phe Leu Asn Glu Asp His Trp		
[1684]	2975	2980	2985
[1685]	Phe Ser Arg Glu Asn Ser Leu Ser Gly Val Glu Gly Glu Gly Leu		
[1686]	2990	2995	3000
[1687]	His Lys Leu Gly Tyr Ile Leu Arg Asp Val Ser Lys Lys Glu Gly		
[1688]	3005	3010	3015
[1689]	Gly Ala Met Tyr Ala Asp Asp Thr Ala Gly Trp Asp Thr Arg Ile		
[1690]	3020	3025	3030
[1691]	Thr Leu Glu Asp Leu Lys Asn Glu Glu Met Val Thr Asn His Met		
[1692]	3035	3040	3045
[1693]	Glu Gly Glu His Lys Lys Leu Ala Glu Ala Ile Phe Lys Leu Thr		
[1694]	3050	3055	3060
[1695]	Tyr Gln Asn Lys Val Val Arg Val Gln Arg Pro Thr Pro Arg Gly		
[1696]	3065	3070	3075
[1697]	Thr Val Met Asp Ile Ile Ser Arg Arg Asp Gln Arg Gly Ser Gly		
[1698]	3080	3085	3090
[1699]	Gln Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Ala		
[1700]	3095	3100	3105
[1701]	Gln Leu Ile Arg Gln Met Glu Gly Glu Gly Val Phe Lys Ser Ile		
[1702]	3110	3115	3120
[1703]	Gln His Leu Thr Ile Thr Glu Glu Ile Ala Val Gln Asn Trp Leu		
[1704]	3125	3130	3135
[1705]	Ala Arg Val Gly Arg Glu Arg Leu Ser Arg Met Ala Ile Ser Gly		
[1706]	3140	3145	3150
[1707]	Asp Asp Cys Val Val Lys Pro Leu Asp Asp Arg Phe Ala Ser Ala		
[1708]	3155	3160	3165
[1709]	Leu Thr Ala Leu Asn Asp Met Gly Lys Ile Arg Lys Asp Ile Gln		
[1710]	3170	3175	3180
[1711]	Gln Trp Glu Pro Ser Arg Gly Trp Asn Asp Trp Thr Gln Val Pro		
[1712]	3185	3190	3195
[1713]	Phe Cys Ser His His Phe His Glu Leu Ile Met Lys Asp Gly Arg		
[1714]	3200	3205	3210
[1715]	Val Leu Val Val Pro Cys Arg Asn Gln Asp Glu Leu Ile Gly Arg		
[1716]	3215	3220	3225
[1717]	Ala Arg Ile Ser Gln Gly Ala Gly Trp Ser Leu Arg Glu Thr Ala		
[1718]	3230	3235	3240
[1719]	Cys Leu Gly Lys Ser Tyr Ala Gln Met Trp Ser Leu Met Tyr Phe		
[1720]	3245	3250	3255
[1721]	His Arg Arg Asp Leu Arg Leu Ala Ala Asn Ala Ile Cys Ser Ala		

[1722]	3260	3265	3270
[1723]	Val Pro Ser His Trp Val Pro Thr Ser Arg Thr Thr Trp Ser Ile		
[1724]	3275	3280	3285
[1725]	His Ala Lys His Glu Trp Met Thr Thr Glu Asp Met Leu Thr Val		
[1726]	3290	3295	3300
[1727]	Trp Asn Arg Val Trp Ile Gln Glu Asn Pro Trp Met Glu Asp Lys		
[1728]	3305	3310	3315
[1729]	Thr Pro Val Glu Ser Trp Glu Glu Ile Pro Tyr Leu Gly Lys Arg		
[1730]	3320	3325	3330
[1731]	Glu Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu Thr Ser Arg Ala		
[1732]	3335	3340	3345
[1733]	Thr Trp Ala Lys Asn Ile Gln Ala Ala Ile Asn Gln Val Arg Ser		
[1734]	3350	3355	3360
[1735]	Leu Ile Gly Asn Glu Glu Tyr Thr Asp Tyr Met Pro Ser Met Lys		
[1736]	3365	3370	3375
[1737]	Arg Phe Arg Arg Glu Glu Glu Glu Ala Gly Val Leu Trp		
[1738]	3380	3385	3390
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[1740]	<211> 3391		
[1741]	<212> PRT		
[1742]	<213> 人工序列		
[1743]	<220>		
[1744]	<223> 登革热病毒血清型2, MVS		
[1745]	<400> 6		
[1746]	Met Asn Asn Gln Arg Lys Lys Ala Lys Asn Thr Pro Phe Asn Met Leu		
[1747]	1 5 10 15		
[1748]	Lys Arg Glu Arg Asn Arg Val Ser Thr Val Gln Gln Leu Thr Lys Arg		
[1749]	20 25 30		
[1750]	Phe Ser Leu Gly Met Leu Gln Gly Arg Gly Pro Leu Lys Leu Phe Met		
[1751]	35 40 45		
[1752]	Ala Leu Val Ala Phe Leu Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly		
[1753]	50 55 60		
[1754]	Ile Leu Lys Arg Trp Gly Thr Ile Lys Lys Ser Lys Ala Ile Asn Val		
[1755]	65 70 75 80		
[1756]	Leu Arg Gly Phe Arg Lys Glu Ile Gly Arg Met Leu Asn Ile Leu Asn		
[1757]	85 90 95		
[1758]	Arg Arg Arg Arg Ser Ala Gly Met Ile Ile Met Leu Ile Pro Thr Val		
[1759]	100 105 110		
[1760]	Met Ala Phe His Leu Thr Thr Arg Asn Gly Glu Pro His Met Ile Val		
[1761]	115 120 125		
[1762]	Ser Arg Gln Glu Lys Gly Lys Ser Leu Leu Phe Lys Thr Glu Val Gly		
[1763]	130 135 140		

[1764]	Val Asn Met Cys Thr Leu Met Ala Met Asp Leu Gly Glu Leu Cys Glu		
[1765]	145	150	155 160
[1766]	Asp Thr Ile Thr Tyr Glu Cys Pro Leu Leu Arg Gln Asn Glu Pro Glu		
[1767]		165 170	175
[1768]	Asp Ile Asp Cys Trp Cys Asn Ser Thr Ser Thr Trp Val Thr Tyr Gly		
[1769]		180 185	190
[1770]	Thr Cys Thr Thr Met Gly Glu His Arg Arg Glu Lys Arg Ser Val Ala		
[1771]		195 200	205
[1772]	Leu Val Pro His Val Gly Met Gly Leu Glu Thr Arg Thr Glu Thr Trp		
[1773]		210 215	220
[1774]	Met Ser Ser Glu Gly Ala Trp Lys His Val Gln Arg Ile Glu Thr Trp		
[1775]		225 230	235 240
[1776]	Ile Leu Arg His Pro Gly Phe Thr Met Met Ala Ala Ile Leu Ala Tyr		
[1777]		245 250	255
[1778]	Thr Ile Gly Thr Thr His Phe Gln Arg Ala Leu Ile Phe Ile Leu Leu		
[1779]		260 265	270
[1780]	Thr Ala Val Thr Pro Ser Met Thr Met Arg Cys Ile Gly Met Ser Asn		
[1781]		275 280	285
[1782]	Arg Asp Phe Val Glu Gly Val Ser Gly Gly Ser Trp Val Asp Ile Val		
[1783]		290 295	300
[1784]	Leu Glu His Gly Ser Cys Val Thr Thr Met Ala Lys Asn Lys Pro Thr		
[1785]		305 310	315 320
[1786]	Leu Asp Phe Glu Leu Ile Lys Thr Glu Ala Lys Gln Pro Ala Thr Leu		
[1787]		325 330	335
[1788]	Arg Lys Tyr Cys Ile Glu Ala Lys Leu Thr Asn Thr Thr Thr Glu Ser		
[1789]		340 345	350
[1790]	Arg Cys Pro Thr Gln Gly Glu Pro Ser Leu Asn Glu Glu Gln Asp Lys		
[1791]		355 360	365
[1792]	Arg Phe Val Cys Lys His Ser Met Val Asp Arg Gly Trp Gly Asn Gly		
[1793]		370 375	380
[1794]	Cys Gly Leu Phe Gly Lys Gly Gly Ile Val Thr Cys Ala Met Phe Arg		
[1795]		385 390	395 400
[1796]	Cys Lys Lys Asn Met Glu Gly Lys Val Val Gln Pro Glu Asn Leu Glu		
[1797]		405 410	415
[1798]	Tyr Thr Ile Val Ile Thr Pro His Ser Gly Glu Glu His Ala Val Gly		
[1799]		420 425	430
[1800]	Asn Asp Thr Gly Lys His Gly Lys Glu Ile Lys Ile Thr Pro Gln Ser		
[1801]		435 440	445
[1802]	Ser Ile Thr Glu Ala Glu Leu Thr Gly Tyr Gly Thr Val Thr Met Glu		
[1803]		450 455	460
[1804]	Cys Ser Pro Arg Thr Gly Leu Asp Phe Asn Glu Met Val Leu Leu Gln		
[1805]		465 470	475 480

[1806]	Met Glu Asn Lys Ala Trp Leu Val His Arg Gln Trp Phe Leu Asp Leu		
[1807]		485	490
[1808]	Pro Leu Pro Trp Leu Pro Gly Ala Asp Thr Gln Gly Ser Asn Trp Ile		495
[1809]		500	505
[1810]	Gln Lys Glu Thr Leu Val Thr Phe Lys Asn Pro His Ala Lys Lys Gln		510
[1811]		515	520
[1812]	Asp Val Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu		525
[1813]		530	535
[1814]	Thr Gly Ala Thr Glu Ile Gln Met Ser Ser Gly Asn Leu Leu Phe Thr		540
[1815]		545	550
[1816]	Gly His Leu Lys Cys Arg Leu Arg Met Asp Lys Leu Gln Leu Lys Gly		555
[1817]		565	570
[1818]	Met Ser Tyr Ser Met Cys Thr Gly Lys Phe Lys Val Val Lys Glu Ile		575
[1819]		580	585
[1820]	Ala Glu Thr Gln His Gly Thr Ile Val Ile Arg Val Gln Tyr Glu Gly		590
[1821]		595	600
[1822]	Asp Gly Ser Pro Cys Lys Ile Pro Phe Glu Ile Met Asp Leu Glu Lys		605
[1823]		610	615
[1824]	Arg His Val Leu Gly Arg Leu Ile Thr Val Asn Pro Ile Val Thr Glu		620
[1825]		625	630
[1826]	Lys Asp Ser Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Asp Ser		635
[1827]		645	650
[1828]	Tyr Ile Ile Ile Gly Val Glu Pro Gly Gln Leu Lys Leu Asn Trp Phe		655
[1829]		660	665
[1830]	Lys Lys Gly Ser Ser Ile Gly Gln Met Phe Glu Thr Thr Met Arg Gly		670
[1831]		675	680
[1832]	Ala Lys Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser		685
[1833]		690	695
[1834]	Leu Gly Gly Val Phe Thr Ser Ile Gly Lys Ala Leu His Gln Val Phe		700
[1835]		705	710
[1836]	Gly Ala Ile Tyr Gly Ala Ala Phe Ser Gly Val Ser Trp Thr Met Lys		715
[1837]		725	730
[1838]	Ile Leu Ile Gly Val Ile Ile Thr Trp Ile Gly Met Asn Ser Arg Ser		735
[1839]		740	745
[1840]	Thr Ser Leu Ser Val Thr Leu Val Leu Val Gly Ile Val Thr Leu Tyr		750
[1841]		755	760
[1842]	Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys		765
[1843]		770	775
[1844]	Asn Lys Glu Leu Lys Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val		780
[1845]		785	790
[1846]	His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys		795
[1847]		805	810
			815

[1848]	Leu Ala Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile		
[1849]		820	825
[1850]	Arg Ser Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro		830
[1851]		835	840
[1852]	Glu Leu Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met		845
[1853]		850	855
[1854]	Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg		860
[1855]		865	870
[1856]	Pro Gln Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala		875
[1857]		885	890
[1858]	Lys Met Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly		895
[1859]		900	905
[1860]	Pro Glu Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu		910
[1861]		915	920
[1862]	Glu Val Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu		925
[1863]		930	935
[1864]	Lys Leu Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser		940
[1865]		945	950
[1866]	Ala Ala Ile Lys Asp Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp		955
[1867]		965	970
[1868]	Ile Glu Ser Ala Leu Asn Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe		975
[1869]		980	985
[1870]	Ile Glu Val Lys Asn Cys His Trp Pro Lys Ser His Thr Leu Trp Ser		990
[1871]		995	1000
[1872]	Asn Gly Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala		1005
[1873]		1010	1015
[1874]	Gly Pro Val Ser Gln His Asn Tyr Arg Pro Gly Tyr His Thr Gln		1020
[1875]		1025	1030
[1876]	Ile Thr Gly Pro Trp His Leu Gly Lys Leu Glu Met Asp Phe Asp		1035
[1877]		1040	1045
[1878]	Phe Cys Asp Gly Thr Thr Val Val Val Thr Glu Asp Cys Gly Asn		1050
[1879]		1055	1060
[1880]	Arg Gly Pro Ser Leu Arg Thr Thr Thr Ala Ser Gly Lys Leu Ile		1065
[1881]		1070	1075
[1882]	Thr Glu Trp Cys Cys Arg Ser Cys Thr Leu Pro Pro Leu Arg Tyr		1080
[1883]		1085	1090
[1884]	Arg Gly Glu Asp Gly Cys Trp Tyr Gly Met Glu Ile Arg Pro Leu		1095
[1885]		1100	1105
[1886]	Lys Glu Lys Glu Glu Asn Leu Val Asn Ser Leu Val Thr Ala Gly		1110
[1887]		1115	1120
[1888]	His Gly Gln Val Asp Asn Phe Ser Leu Gly Val Leu Gly Met Ala		1125
[1889]		1130	1135
			1140

[1890]	Leu Phe Leu Glu Glu Met Leu Arg Thr Arg Val Gly Thr Lys His
[1891]	1145 1150 1155
[1892]	Ala Ile Leu Leu Val Ala Val Ser Phe Val Thr Leu Ile Thr Gly
[1893]	1160 1165 1170
[1894]	Asn Met Ser Phe Arg Asp Leu Gly Arg Val Met Val Met Val Gly
[1895]	1175 1180 1185
[1896]	Ala Thr Met Thr Asp Asp Ile Gly Met Gly Val Thr Tyr Leu Ala
[1897]	1190 1195 1200
[1898]	Leu Leu Ala Ala Phe Lys Val Arg Pro Thr Phe Ala Ala Gly Leu
[1899]	1205 1210 1215
[1900]	Leu Leu Arg Lys Leu Thr Ser Lys Glu Leu Met Met Thr Thr Ile
[1901]	1220 1225 1230
[1902]	Gly Ile Val Leu Leu Ser Gln Ser Thr Ile Pro Glu Thr Ile Leu
[1903]	1235 1240 1245
[1904]	Glu Leu Thr Asp Ala Leu Ala Leu Gly Met Met Val Leu Lys Met
[1905]	1250 1255 1260
[1906]	Val Arg Asn Met Glu Lys Tyr Gln Leu Ala Val Thr Ile Met Ala
[1907]	1265 1270 1275
[1908]	Ile Leu Cys Val Pro Asn Ala Val Ile Leu Gln Asn Ala Trp Lys
[1909]	1280 1285 1290
[1910]	Val Ser Cys Thr Ile Leu Ala Val Val Ser Val Ser Pro Leu Phe
[1911]	1295 1300 1305
[1912]	Leu Thr Ser Ser Gln Gln Lys Thr Asp Trp Ile Pro Leu Ala Leu
[1913]	1310 1315 1320
[1914]	Thr Ile Lys Gly Leu Asn Pro Thr Ala Ile Phe Leu Thr Thr Leu
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[2511]	Val Ser Gln His Asn Tyr Arg Pro Gly Tyr His Thr Gln Ile Thr		
[2512]	1025	1030	1035
[2513]	Gly Pro Trp His Leu Gly Lys Leu Glu Met Asp Phe Asp Phe Cys		
[2514]	1040	1045	1050
[2515]	Asp Gly Thr Thr Val Val Val Thr Glu Asp Cys Gly Asn Arg Gly		
[2516]	1055	1060	1065
[2517]	Pro Ser Leu Arg Thr Thr Thr Ala Ser Gly Lys Leu Ile Thr Glu		
[2518]	1070	1075	1080
[2519]	Trp Cys Cys Arg Ser Cys Thr Leu Pro Pro Leu Arg Tyr Arg Gly		

[2520]	1085	1090	1095
[2521]	Glu Asp Gly Cys Trp Tyr Gly Met Glu Ile Arg Pro Leu Lys Glu		
[2522]	1100	1105	1110
[2523]	Lys Glu Glu Asn Leu Val Asn Ser Leu Val Thr Ala Gly His Gly		
[2524]	1115	1120	1125
[2525]	Gln Val Asp Asn Phe Ser Leu Gly Val Leu Gly Met Ala Leu Phe		
[2526]	1130	1135	1140
[2527]	Leu Glu Glu Met Leu Arg Thr Arg Val Gly Thr Lys His Ala Ile		
[2528]	1145	1150	1155
[2529]	Leu Leu Val Ala Val Ser Phe Val Thr Leu Ile Thr Gly Asn Met		
[2530]	1160	1165	1170
[2531]	Ser Phe Arg Asp Leu Gly Arg Val Met Val Met Val Gly Ala Thr		
[2532]	1175	1180	1185
[2533]	Met Thr Asp Asp Ile Gly Met Gly Val Thr Tyr Leu Ala Leu Leu		
[2534]	1190	1195	1200
[2535]	Ala Ala Phe Lys Val Arg Pro Thr Phe Ala Ala Gly Leu Leu Leu		
[2536]	1205	1210	1215
[2537]	Arg Lys Leu Thr Ser Lys Glu Leu Met Met Thr Thr Ile Gly Ile		
[2538]	1220	1225	1230
[2539]	Val Leu Leu Ser Gln Ser Thr Ile Pro Glu Thr Ile Leu Glu Leu		
[2540]	1235	1240	1245
[2541]	Thr Asp Ala Leu Ala Leu Gly Met Met Val Leu Lys Met Val Arg		
[2542]	1250	1255	1260
[2543]	Asn Met Glu Lys Tyr Gln Leu Ala Val Thr Ile Met Ala Ile Leu		
[2544]	1265	1270	1275
[2545]	Cys Val Pro Asn Ala Val Ile Leu Gln Asn Ala Trp Lys Val Ser		
[2546]	1280	1285	1290
[2547]	Cys Thr Ile Leu Ala Val Val Ser Val Ser Pro Leu Phe Leu Thr		
[2548]	1295	1300	1305
[2549]	Ser Ser Gln Gln Lys Thr Asp Trp Ile Pro Leu Ala Leu Thr Ile		
[2550]	1310	1315	1320
[2551]	Lys Gly Leu Asn Pro Thr Ala Ile Phe Leu Thr Thr Leu Ser Arg		
[2552]	1325	1330	1335
[2553]	Thr Ser Lys Lys Arg Ser Trp Pro Leu Asn Glu Ala Ile Met Ala		
[2554]	1340	1345	1350
[2555]	Val Gly Met Val Ser Ile Leu Ala Ser Ser Leu Leu Lys Asn Asp		
[2556]	1355	1360	1365
[2557]	Ile Pro Met Thr Gly Pro Leu Val Ala Gly Gly Leu Leu Thr Val		
[2558]	1370	1375	1380
[2559]	Cys Tyr Val Leu Thr Gly Arg Ser Ala Asp Leu Glu Leu Glu Arg		
[2560]	1385	1390	1395
[2561]	Ala Ala Asp Val Lys Trp Glu Asp Gln Ala Glu Ile Ser Gly Ser		

[2562]	1400	1405	1410
[2563]	Ser Pro Ile Leu Ser Ile Thr Ile Ser Glu Asp Gly Ser Met Ser		
[2564]	1415	1420	1425
[2565]	Ile Lys Asn Glu Glu Glu Glu Gln Thr Leu Thr Ile Leu Ile Arg		
[2566]	1430	1435	1440
[2567]	Thr Gly Leu Leu Val Ile Ser Gly Leu Phe Pro Val Ser Ile Pro		
[2568]	1445	1450	1455
[2569]	Ile Thr Ala Ala Ala Trp Tyr Leu Trp Glu Val Lys Lys Gln Arg		
[2570]	1460	1465	1470
[2571]	Ala Gly Val Leu Trp Asp Val Pro Ser Pro Pro Pro Met Gly Lys		
[2572]	1475	1480	1485
[2573]	Ala Glu Leu Glu Asp Gly Ala Tyr Arg Ile Lys Gln Lys Gly Ile		
[2574]	1490	1495	1500
[2575]	Leu Gly Tyr Ser Gln Ile Gly Ala Gly Val Tyr Lys Glu Gly Thr		
[2576]	1505	1510	1515
[2577]	Phe His Thr Met Trp His Val Thr Arg Gly Ala Val Leu Met His		
[2578]	1520	1525	1530
[2579]	Lys Gly Lys Arg Ile Glu Pro Ser Trp Ala Asp Val Lys Lys Asp		
[2580]	1535	1540	1545
[2581]	Leu Ile Ser Tyr Gly Gly Gly Trp Lys Leu Glu Gly Glu Trp Lys		
[2582]	1550	1555	1560
[2583]	Glu Gly Glu Glu Val Gln Val Leu Ala Leu Glu Pro Gly Lys Asn		
[2584]	1565	1570	1575
[2585]	Pro Arg Ala Val Gln Thr Lys Pro Gly Leu Phe Lys Thr Asn Ala		
[2586]	1580	1585	1590
[2587]	Gly Thr Ile Gly Ala Val Ser Leu Asp Phe Ser Pro Gly Thr Ser		
[2588]	1595	1600	1605
[2589]	Gly Ser Pro Ile Ile Asp Lys Lys Gly Lys Val Val Gly Leu Tyr		
[2590]	1610	1615	1620
[2591]	Gly Asn Gly Val Val Thr Arg Ser Gly Ala Tyr Val Ser Ala Ile		
[2592]	1625	1630	1635
[2593]	Ala Gln Thr Glu Lys Ser Ile Glu Asp Asn Pro Glu Ile Glu Asp		
[2594]	1640	1645	1650
[2595]	Asp Ile Phe Arg Lys Arg Arg Leu Thr Ile Met Asp Leu His Pro		
[2596]	1655	1660	1665
[2597]	Gly Ala Gly Lys Thr Lys Arg Tyr Leu Pro Ala Ile Val Arg Glu		
[2598]	1670	1675	1680
[2599]	Ala Ile Lys Arg Gly Leu Arg Thr Leu Ile Leu Ala Pro Thr Arg		
[2600]	1685	1690	1695
[2601]	Val Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu Pro Ile		
[2602]	1700	1705	1710
[2603]	Arg Tyr Gln Thr Pro Ala Ile Arg Ala Val His Thr Gly Arg Glu		

[2604]	1715	1720	1725
[2605]	Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Met Arg Leu Leu		
[2606]	1730	1735	1740
[2607]	Ser Pro Val Arg Val Pro Asn Tyr Asn Leu Ile Ile Met Asp Glu		
[2608]	1745	1750	1755
[2609]	Ala His Phe Thr Asp Pro Ala Ser Ile Ala Ala Arg Gly Tyr Ile		
[2610]	1760	1765	1770
[2611]	Ser Thr Arg Val Glu Met Gly Glu Ala Ala Gly Ile Phe Met Thr		
[2612]	1775	1780	1785
[2613]	Ala Thr Pro Pro Gly Ser Arg Asp Pro Phe Pro Gln Ser Asn Ala		
[2614]	1790	1795	1800
[2615]	Pro Ile Ile Asp Glu Glu Arg Glu Ile Pro Glu Arg Ser Trp Asn		
[2616]	1805	1810	1815
[2617]	Ser Gly His Glu Trp Val Thr Asp Phe Lys Gly Lys Thr Val Trp		
[2618]	1820	1825	1830
[2619]	Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile Ala Ala Cys Leu		
[2620]	1835	1840	1845
[2621]	Arg Lys Asn Gly Lys Lys Val Ile Gln Leu Ser Arg Lys Thr Phe		
[2622]	1850	1855	1860
[2623]	Asp Ser Glu Tyr Val Lys Thr Arg Thr Asn Asp Trp Asp Phe Val		
[2624]	1865	1870	1875
[2625]	Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys Ala Glu		
[2626]	1880	1885	1890
[2627]	Arg Val Ile Asp Pro Arg Arg Cys Met Lys Pro Val Ile Leu Thr		
[2628]	1895	1900	1905
[2629]	Asp Gly Glu Glu Arg Val Ile Leu Ala Gly Pro Met Pro Val Thr		
[2630]	1910	1915	1920
[2631]	His Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg Asn Pro		
[2632]	1925	1930	1935
[2633]	Lys Asn Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu Pro Leu Glu		
[2634]	1940	1945	1950
[2635]	Asn Asp Glu Asp Cys Ala His Trp Lys Glu Ala Lys Met Leu Leu		
[2636]	1955	1960	1965
[2637]	Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile Pro Ser Met Phe Glu		
[2638]	1970	1975	1980
[2639]	Pro Glu Arg Glu Lys Val Asp Ala Ile Asp Gly Glu Tyr Arg Leu		
[2640]	1985	1990	1995
[2641]	Arg Gly Glu Ala Arg Lys Thr Phe Val Asp Leu Met Arg Arg Gly		
[2642]	2000	2005	2010
[2643]	Asp Leu Pro Val Trp Leu Ala Tyr Arg Val Ala Ala Glu Gly Ile		
[2644]	2015	2020	2025
[2645]	Asn Tyr Ala Asp Arg Arg Trp Cys Phe Asp Gly Val Lys Asn Asn		

[2646]	2030	2035	2040
[2647]	Gln Ile Leu Glu Glu Asn Val Glu Val Glu Ile Trp Thr Lys Glu		
[2648]	2045	2050	2055
[2649]	Gly Glu Arg Lys Lys Leu Lys Pro Arg Trp Leu Asp Ala Arg Ile		
[2650]	2060	2065	2070
[2651]	Tyr Ser Asp Pro Leu Ala Leu Lys Glu Phe Lys Glu Phe Ala Ala		
[2652]	2075	2080	2085
[2653]	Gly Arg Lys Ser Leu Thr Leu Asn Leu Ile Thr Glu Met Gly Arg		
[2654]	2090	2095	2100
[2655]	Leu Pro Thr Phe Met Thr Gln Lys Ala Arg Asn Ala Leu Asp Asn		
[2656]	2105	2110	2115
[2657]	Leu Ala Val Leu His Thr Ala Glu Ala Gly Gly Arg Ala Tyr Asn		
[2658]	2120	2125	2130
[2659]	His Ala Leu Ser Glu Leu Pro Glu Thr Leu Glu Thr Leu Leu Leu		
[2660]	2135	2140	2145
[2661]	Leu Thr Leu Leu Ala Thr Val Thr Gly Gly Ile Phe Leu Phe Leu		
[2662]	2150	2155	2160
[2663]	Met Ser Ala Arg Gly Ile Gly Lys Met Thr Leu Gly Met Cys Cys		
[2664]	2165	2170	2175
[2665]	Ile Ile Thr Ala Ser Ile Leu Leu Trp Tyr Ala Gln Ile Gln Pro		
[2666]	2180	2185	2190
[2667]	His Trp Ile Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu Ile Val		
[2668]	2195	2200	2205
[2669]	Leu Leu Ile Pro Glu Pro Glu Lys Gln Arg Thr Pro Gln Asp Asn		
[2670]	2210	2215	2220
[2671]	Gln Leu Thr Tyr Val Val Ile Ala Ile Leu Thr Val Val Ala Ala		
[2672]	2225	2230	2235
[2673]	Thr Met Ala Asn Glu Met Gly Phe Leu Glu Lys Thr Lys Lys Asp		
[2674]	2240	2245	2250
[2675]	Leu Gly Leu Gly Ser Ile Ala Thr Gln Gln Pro Glu Ser Asn Ile		
[2676]	2255	2260	2265
[2677]	Leu Asp Ile Asp Leu Arg Pro Ala Ser Ala Trp Thr Leu Tyr Ala		
[2678]	2270	2275	2280
[2679]	Val Ala Thr Thr Phe Val Thr Pro Met Leu Arg His Ser Ile Glu		
[2680]	2285	2290	2295
[2681]	Asn Ser Ser Val Asn Val Ser Leu Thr Ala Ile Ala Asn Gln Ala		
[2682]	2300	2305	2310
[2683]	Thr Val Leu Met Gly Leu Gly Lys Gly Trp Pro Leu Ser Lys Met		
[2684]	2315	2320	2325
[2685]	Asp Ile Gly Val Pro Leu Leu Ala Ile Gly Cys Tyr Ser Gln Val		
[2686]	2330	2335	2340
[2687]	Asn Pro Ile Thr Leu Thr Ala Ala Leu Phe Leu Leu Val Ala His		

[2688]	2345	2350	2355
[2689]	Tyr Ala Ile Ile Gly Pro Gly Leu Gln Ala Lys Ala Thr Arg Glu		
[2690]	2360	2365	2370
[2691]	Ala Gln Lys Arg Ala Ala Ala Gly Ile Met Lys Asn Pro Thr Val		
[2692]	2375	2380	2385
[2693]	Asp Gly Ile Thr Val Ile Asp Leu Asp Pro Ile Pro Tyr Asp Pro		
[2694]	2390	2395	2400
[2695]	Lys Phe Glu Lys Gln Leu Gly Gln Val Met Leu Leu Val Leu Cys		
[2696]	2405	2410	2415
[2697]	Val Thr Gln Val Leu Met Met Arg Thr Thr Trp Ala Leu Cys Glu		
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[2699]	Ala Leu Thr Leu Ala Thr Gly Pro Ile Ser Thr Leu Trp Glu Gly		
[2700]	2435	2440	2445
[2701]	Asn Pro Gly Arg Phe Trp Asn Thr Thr Ile Ala Val Ser Met Ala		
[2702]	2450	2455	2460
[2703]	Asn Ile Phe Arg Gly Ser Tyr Leu Ala Gly Ala Gly Leu Leu Phe		
[2704]	2465	2470	2475
[2705]	Ser Ile Met Lys Asn Thr Thr Asn Thr Arg Arg Gly Thr Gly Asn		
[2706]	2480	2485	2490
[2707]	Ile Gly Glu Thr Leu Gly Glu Lys Trp Lys Ser Arg Leu Asn Ala		
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[2709]	Leu Gly Lys Ser Glu Phe Gln Ile Tyr Lys Lys Ser Gly Ile Gln		
[2710]	2510	2515	2520
[2711]	Glu Val Asp Arg Thr Leu Ala Lys Glu Gly Ile Lys Arg Gly Glu		
[2712]	2525	2530	2535
[2713]	Thr Asp His His Ala Val Ser Arg Gly Ser Ala Lys Leu Arg Trp		
[2714]	2540	2545	2550
[2715]	Phe Val Glu Arg Asn Met Val Thr Pro Glu Gly Lys Val Val Asp		
[2716]	2555	2560	2565
[2717]	Leu Gly Cys Gly Arg Gly Gly Trp Ser Tyr Tyr Cys Gly Gly Leu		
[2718]	2570	2575	2580
[2719]	Lys Asn Val Arg Glu Val Lys Gly Leu Thr Lys Gly Gly Pro Gly		
[2720]	2585	2590	2595
[2721]	His Glu Glu Pro Ile Pro Met Ser Thr Tyr Gly Trp Asn Leu Val		
[2722]	2600	2605	2610
[2723]	Arg Leu Gln Ser Gly Val Asp Val Phe Phe Ile Pro Pro Glu Lys		
[2724]	2615	2620	2625
[2725]	Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Pro Asn Pro		
[2726]	2630	2635	2640
[2727]	Thr Val Glu Ala Gly Arg Thr Leu Arg Val Leu Asn Leu Val Glu		
[2728]	2645	2650	2655
[2729]	Asn Trp Leu Asn Asn Asn Thr Gln Phe Cys Ile Lys Val Leu Asn		

[2730]	2660	2665	2670
[2731]	Pro Tyr Met Pro Ser Val	Ile Glu Lys Met Glu	Ala Leu Gln Arg
[2732]	2675	2680	2685
[2733]	Lys Tyr Gly Gly Ala Leu	Val Arg Asn Pro Leu	Ser Arg Asn Ser
[2734]	2690	2695	2700
[2735]	Thr His Glu Met Tyr Trp	Val Ser Asn Ala Ser	Gly Asn Ile Val
[2736]	2705	2710	2715
[2737]	Ser Ser Val Asn Met Ile	Ser Arg Met Leu Ile	Asn Arg Phe Thr
[2738]	2720	2725	2730
[2739]	Met Arg Tyr Lys Lys Ala	Thr Tyr Glu Pro Asp	Val Asp Leu Gly
[2740]	2735	2740	2745
[2741]	Ser Gly Thr Arg Asn Ile	Gly Ile Glu Ser Glu	Ile Pro Asn Leu
[2742]	2750	2755	2760
[2743]	Asp Ile Ile Gly Lys Arg	Ile Glu Lys Ile Lys	Gln Glu His Glu
[2744]	2765	2770	2775
[2745]	Thr Ser Trp His Tyr Asp	Gln Asp His Pro Tyr	Lys Thr Trp Ala
[2746]	2780	2785	2790
[2747]	Tyr His Gly Ser Tyr Glu	Thr Lys Gln Thr Gly	Ser Ala Ser Ser
[2748]	2795	2800	2805
[2749]	Met Val Asn Gly Val Val	Arg Leu Leu Thr Lys	Pro Trp Asp Val
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[2751]	Val Pro Met Val Thr Gln	Met Ala Met Thr Asp	Thr Thr Pro Phe
[2752]	2825	2830	2835
[2753]	Gly Gln Gln Arg Val Phe	Lys Glu Lys Val Asp	Thr Arg Thr Gln
[2754]	2840	2845	2850
[2755]	Glu Pro Lys Glu Gly Thr	Lys Lys Leu Met Lys	Ile Thr Ala Glu
[2756]	2855	2860	2865
[2757]	Trp Leu Trp Lys Glu Leu	Gly Lys Lys Lys Thr	Pro Arg Met Cys
[2758]	2870	2875	2880
[2759]	Thr Arg Glu Glu Phe Thr	Arg Lys Val Arg Ser	Asn Ala Ala Leu
[2760]	2885	2890	2895
[2761]	Gly Ala Ile Phe Thr Asp	Glu Asn Lys Trp Lys	Ser Ala Arg Glu
[2762]	2900	2905	2910
[2763]	Ala Val Glu Asp Ser Arg	Phe Trp Glu Leu Val	Asp Lys Glu Arg
[2764]	2915	2920	2925
[2765]	Asn Leu His Leu Glu Gly	Lys Cys Glu Thr Cys	Val Tyr Asn Met
[2766]	2930	2935	2940
[2767]	Met Gly Lys Arg Glu Lys	Lys Leu Gly Glu Phe	Gly Lys Ala Lys
[2768]	2945	2950	2955
[2769]	Gly Ser Arg Ala Ile Trp	Tyr Met Trp Leu Gly	Ala Arg Phe Leu
[2770]	2960	2965	2970
[2771]	Glu Phe Glu Ala Leu Gly	Phe Leu Asn Glu Asp	His Trp Phe Ser

[2772]	2975	2980	2985
[2773]	Arg Glu Asn Ser Leu Ser Gly Val Glu Gly Glu Gly Leu His Lys		
[2774]	2990	2995	3000
[2775]	Leu Gly Tyr Ile Leu Arg Asp Val Ser Lys Lys Glu Gly Gly Ala		
[2776]	3005	3010	3015
[2777]	Met Tyr Ala Asp Asp Thr Ala Gly Trp Asp Thr Arg Ile Thr Leu		
[2778]	3020	3025	3030
[2779]	Glu Asp Leu Lys Asn Glu Glu Met Val Thr Asn His Met Glu Gly		
[2780]	3035	3040	3045
[2781]	Glu His Lys Lys Leu Ala Glu Ala Ile Phe Lys Leu Thr Tyr Gln		
[2782]	3050	3055	3060
[2783]	Asn Lys Val Val Arg Val Gln Arg Pro Thr Pro Arg Gly Thr Val		
[2784]	3065	3070	3075
[2785]	Met Asp Ile Ile Ser Arg Arg Asp Gln Arg Gly Ser Gly Gln Val		
[2786]	3080	3085	3090
[2787]	Gly Thr Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Ala Gln Leu		
[2788]	3095	3100	3105
[2789]	Ile Arg Gln Met Glu Gly Glu Gly Val Phe Lys Ser Ile Gln His		
[2790]	3110	3115	3120
[2791]	Leu Thr Ile Thr Glu Glu Ile Ala Val Gln Asn Trp Leu Ala Arg		
[2792]	3125	3130	3135
[2793]	Val Gly Arg Glu Arg Leu Ser Arg Met Ala Ile Ser Gly Asp Asp		
[2794]	3140	3145	3150
[2795]	Cys Val Val Lys Pro Leu Asp Asp Arg Phe Ala Ser Ala Leu Thr		
[2796]	3155	3160	3165
[2797]	Ala Leu Asn Asp Met Gly Lys Ile Arg Lys Asp Ile Gln Gln Trp		
[2798]	3170	3175	3180
[2799]	Glu Pro Ser Arg Gly Trp Asn Asp Trp Thr Gln Val Pro Phe Cys		
[2800]	3185	3190	3195
[2801]	Ser His His Phe His Glu Leu Ile Met Lys Asp Gly Arg Val Leu		
[2802]	3200	3205	3210
[2803]	Val Val Pro Cys Arg Asn Gln Asp Glu Leu Ile Gly Arg Ala Arg		
[2804]	3215	3220	3225
[2805]	Ile Ser Gln Gly Ala Gly Trp Ser Leu Arg Glu Thr Ala Cys Leu		
[2806]	3230	3235	3240
[2807]	Gly Lys Ser Tyr Ala Gln Met Trp Ser Leu Met Tyr Phe His Arg		
[2808]	3245	3250	3255
[2809]	Arg Asp Leu Arg Leu Ala Ala Asn Ala Ile Cys Ser Ala Val Pro		
[2810]	3260	3265	3270
[2811]	Ser His Trp Val Pro Thr Ser Arg Thr Thr Trp Ser Ile His Ala		
[2812]	3275	3280	3285
[2813]	Lys His Glu Trp Met Thr Thr Glu Asp Met Leu Thr Val Trp Asn		

[2814]	3290	3295	3300
[2815]	Arg Val Trp Ile Gln Glu Asn Pro Trp Met Glu Asp Lys Thr Pro		
[2816]	3305	3310	3315
[2817]	Val Glu Ser Trp Glu Glu Ile Pro Tyr Leu Gly Lys Arg Glu Asp		
[2818]	3320	3325	3330
[2819]	Gln Trp Cys Gly Ser Leu Ile Gly Leu Thr Ser Arg Ala Thr Trp		
[2820]	3335	3340	3345
[2821]	Ala Lys Asn Ile Gln Ala Ala Ile Asn Gln Val Arg Ser Leu Ile		
[2822]	3350	3355	3360
[2823]	Gly Asn Glu Glu Tyr Thr Asp Tyr Met Pro Ser Met Lys Arg Phe		
[2824]	3365	3370	3375
[2825]	Arg Arg Glu Glu Glu Glu Ala Gly Val Leu Trp		
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[2830]	<213> 人工序列		
[2831]	<220>		
[2832]	<223> 登革热病毒血清型3, MVS		
[2833]	<400> 9		
[2834]	Met Asn Asn Gln Arg Lys Lys Ala Lys Asn Thr Pro Phe Asn Met Leu		
[2835]	1 5 10 15		
[2836]	Lys Arg Glu Arg Asn Arg Val Ser Thr Val Gln Gln Leu Thr Lys Arg		
[2837]	20 25 30		
[2838]	Phe Ser Leu Gly Met Leu Gln Gly Arg Gly Pro Leu Lys Leu Phe Met		
[2839]	35 40 45		
[2840]	Ala Leu Val Ala Phe Leu Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly		
[2841]	50 55 60		
[2842]	Ile Leu Lys Arg Trp Gly Thr Ile Lys Lys Ser Lys Ala Ile Asn Val		
[2843]	65 70 75 80		
[2844]	Leu Arg Gly Phe Arg Lys Glu Ile Gly Arg Met Leu Asn Ile Leu Asn		
[2845]	85 90 95		
[2846]	Arg Arg Arg Arg Ser Ala Gly Met Ile Ile Met Leu Ile Pro Thr Val		
[2847]	100 105 110		
[2848]	Met Ala Phe His Leu Thr Thr Arg Asp Gly Glu Pro Arg Met Ile Val		
[2849]	115 120 125		
[2850]	Gly Lys Asn Glu Arg Gly Lys Ser Leu Leu Phe Lys Thr Ala Ser Gly		
[2851]	130 135 140		
[2852]	Ile Asn Met Cys Thr Leu Ile Ala Met Asp Leu Gly Glu Met Cys Asp		
[2853]	145 150 155 160		
[2854]	Asp Thr Val Thr Tyr Lys Cys Pro His Ile Thr Glu Val Glu Pro Glu		
[2855]	165 170 175		

[2856]	Asp	Ile	Asp	Cys	Trp	Cys	Asn	Leu	Thr	Ser	Thr	Trp	Val	Thr	Tyr	Gly
[2857]				180					185						190	
[2858]	Thr	Cys	Asn	Gln	Ala	Gly	Glu	His	Arg	Arg	Asp	Lys	Arg	Ser	Val	Ala
[2859]				195				200					205			
[2860]	Leu	Ala	Pro	His	Val	Gly	Met	Gly	Leu	Asp	Thr	Arg	Thr	Gln	Thr	Trp
[2861]		210					215					220				
[2862]	Met	Ser	Ala	Glu	Gly	Ala	Trp	Arg	Gln	Val	Glu	Lys	Val	Glu	Thr	Trp
[2863]	225					230					235					240
[2864]	Ala	Leu	Arg	His	Pro	Gly	Phe	Thr	Ile	Leu	Ala	Leu	Phe	Leu	Ala	His
[2865]				245					250						255	
[2866]	Tyr	Ile	Gly	Thr	Ser	Leu	Thr	Gln	Lys	Val	Val	Ile	Phe	Ile	Leu	Leu
[2867]				260					265						270	
[2868]	Met	Leu	Val	Thr	Pro	Ser	Met	Thr	Met	Arg	Cys	Val	Gly	Val	Gly	Asn
[2869]				275					280				285			
[2870]	Arg	Asp	Phe	Val	Glu	Gly	Leu	Ser	Gly	Ala	Thr	Trp	Val	Asp	Val	Val
[2871]		290					295					300				
[2872]	Leu	Glu	His	Gly	Gly	Cys	Val	Thr	Thr	Met	Ala	Lys	Asn	Lys	Pro	Thr
[2873]	305					310					315					320
[2874]	Leu	Asp	Ile	Glu	Leu	Gln	Lys	Thr	Glu	Ala	Thr	Gln	Leu	Ala	Thr	Leu
[2875]				325						330					335	
[2876]	Arg	Lys	Leu	Cys	Ile	Glu	Gly	Lys	Ile	Thr	Asn	Ile	Thr	Thr	Asp	Ser
[2877]				340					345						350	
[2878]	Arg	Cys	Pro	Thr	Gln	Gly	Glu	Ala	Ile	Leu	Pro	Glu	Glu	Gln	Asp	Gln
[2879]			355				360						365			
[2880]	Asn	Tyr	Val	Cys	Lys	His	Thr	Tyr	Val	Asp	Arg	Gly	Trp	Gly	Asn	Gly
[2881]		370					375					380				
[2882]	Cys	Gly	Leu	Phe	Gly	Lys	Gly	Ser	Leu	Val	Thr	Cys	Ala	Lys	Phe	Gln
[2883]	385					390					395					400
[2884]	Cys	Leu	Glu	Ser	Ile	Glu	Gly	Lys	Val	Val	Gln	His	Glu	Asn	Leu	Lys
[2885]				405						410					415	
[2886]	Tyr	Thr	Val	Ile	Ile	Thr	Val	His	Thr	Gly	Asp	Gln	His	Gln	Val	Gly
[2887]				420					425						430	
[2888]	Asn	Glu	Thr	Gln	Gly	Val	Thr	Ala	Glu	Ile	Thr	Pro	Gln	Ala	Ser	Thr
[2889]			435					440					445			
[2890]	Ala	Glu	Ala	Ile	Leu	Pro	Glu	Tyr	Gly	Thr	Leu	Gly	Leu	Glu	Cys	Ser
[2891]		450					455					460				
[2892]	Pro	Arg	Thr	Gly	Leu	Asp	Phe	Asn	Glu	Met	Ile	Ser	Leu	Thr	Met	Lys
[2893]	465					470					475					480
[2894]	Asn	Lys	Ala	Trp	Met	Val	His	Arg	Gln	Trp	Phe	Phe	Asp	Leu	Pro	Leu
[2895]				485					490						495	
[2896]	Pro	Trp	Thr	Ser	Gly	Ala	Ser	Ala	Glu	Thr	Pro	Thr	Trp	Asn	Arg	Lys
[2897]				500					505						510	

[2898]	Glu Leu Leu Val Thr Phe Lys Asn Ala His Ala Lys Lys Gln Glu Val		
[2899]	515	520	525
[2900]	Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu Thr Gly		
[2901]	530	535	540
[2902]	Ala Thr Glu Ile Gln Thr Ser Gly Gly Thr Ser Ile Phe Ala Gly His		
[2903]	545	550	555 560
[2904]	Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Glu Leu Lys Gly Met Ser		
[2905]	565	570	575
[2906]	Tyr Ala Met Cys Leu Ser Ser Phe Val Leu Lys Lys Glu Val Ser Glu		
[2907]	580	585	590
[2908]	Thr Gln His Gly Thr Ile Leu Ile Lys Val Glu Tyr Lys Gly Glu Asp		
[2909]	595	600	605
[2910]	Ala Pro Cys Lys Ile Pro Phe Ser Thr Glu Asp Gly Gln Gly Lys Ala		
[2911]	610	615	620
[2912]	Leu Asn Gly Arg Leu Ile Thr Ala Asn Pro Val Val Thr Lys Lys Glu		
[2913]	625	630	635 640
[2914]	Glu Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Glu Ser Asn Ile		
[2915]	645	650	655
[2916]	Val Ile Gly Ile Gly Asp Lys Ala Leu Lys Ile Asn Trp Tyr Lys Lys		
[2917]	660	665	670
[2918]	Gly Ser Ser Ile Gly Lys Met Phe Glu Ala Thr Ala Arg Gly Ala Arg		
[2919]	675	680	685
[2920]	Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser Val Gly		
[2921]	690	695	700
[2922]	Gly Val Leu Asn Ser Leu Gly Lys Met Val His Gln Ile Phe Gly Ser		
[2923]	705	710	715 720
[2924]	Ala Tyr Thr Ala Leu Phe Gly Gly Val Ser Trp Met Met Lys Ile Gly		
[2925]	725	730	735
[2926]	Ile Gly Val Leu Leu Thr Trp Ile Gly Leu Asn Ser Lys Asn Thr Ser		
[2927]	740	745	750
[2928]	Met Ser Phe Ser Cys Ile Ala Ala Gly Ile Val Thr Leu Tyr Leu Gly		
[2929]	755	760	765
[2930]	Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys Asn Lys		
[2931]	770	775	780
[2932]	Glu Leu Lys Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val His Thr		
[2933]	785	790	795 800
[2934]	Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys Leu Ala		
[2935]	805	810	815
[2936]	Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile Arg Ser		
[2937]	820	825	830
[2938]	Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro Glu Leu		
[2939]	835	840	845

[2940]	Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met Thr Gly
[2941]	850 855 860
[2942]	Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg Pro Gln
[2943]	865 870 875 880
[2944]	Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala Lys Met
[2945]	885 890 895
[2946]	Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly Pro Glu
[2947]	900 905 910
[2948]	Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu Glu Val
[2949]	915 920 925
[2950]	Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu Lys Leu
[2951]	930 935 940
[2952]	Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser Ala Ala
[2953]	945 950 955 960
[2954]	Ile Lys Asp Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp Ile Glu
[2955]	965 970 975
[2956]	Ser Ala Leu Asn Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe Ile Glu
[2957]	980 985 990
[2958]	Val Lys Asn Cys His Trp Pro Lys Ser His Thr Leu Trp Ser Asn Gly
[2959]	995 1000 1005
[2960]	Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala Gly Pro
[2961]	1010 1015 1020
[2962]	Val Ser Gln His Asn Tyr Arg Pro Gly Tyr His Thr Gln Ile Thr
[2963]	1025 1030 1035
[2964]	Gly Pro Trp His Leu Gly Lys Leu Glu Met Asp Phe Asp Phe Cys
[2965]	1040 1045 1050
[2966]	Asp Gly Thr Thr Val Val Val Thr Glu Asp Cys Gly Asn Arg Gly
[2967]	1055 1060 1065
[2968]	Pro Ser Leu Arg Thr Thr Thr Ala Ser Gly Lys Leu Ile Thr Glu
[2969]	1070 1075 1080
[2970]	Trp Cys Cys Arg Ser Cys Thr Leu Pro Pro Leu Arg Tyr Arg Gly
[2971]	1085 1090 1095
[2972]	Glu Asp Gly Cys Trp Tyr Gly Met Glu Ile Arg Pro Leu Lys Glu
[2973]	1100 1105 1110
[2974]	Lys Glu Glu Asn Leu Val Asn Ser Leu Val Thr Ala Gly His Gly
[2975]	1115 1120 1125
[2976]	Gln Val Asp Asn Phe Ser Leu Gly Val Leu Gly Met Ala Leu Phe
[2977]	1130 1135 1140
[2978]	Leu Glu Glu Met Leu Arg Thr Arg Val Gly Thr Lys His Ala Ile
[2979]	1145 1150 1155
[2980]	Leu Leu Val Ala Val Ser Phe Val Thr Leu Ile Thr Gly Asn Met
[2981]	1160 1165 1170

[2982]	Ser Phe Arg Asp Leu Gly Arg Val Met Val Met Val Gly Ala Thr
[2983]	1175 1180 1185
[2984]	Met Thr Asp Asp Ile Gly Met Gly Val Thr Tyr Leu Ala Leu Leu
[2985]	1190 1195 1200
[2986]	Ala Ala Phe Lys Val Arg Pro Thr Phe Ala Ala Gly Leu Leu Leu
[2987]	1205 1210 1215
[2988]	Arg Lys Leu Thr Ser Lys Glu Leu Met Met Thr Thr Ile Gly Ile
[2989]	1220 1225 1230
[2990]	Val Leu Leu Ser Gln Ser Thr Ile Pro Glu Thr Ile Leu Glu Leu
[2991]	1235 1240 1245
[2992]	Thr Asp Ala Leu Ala Leu Gly Met Met Val Leu Lys Met Val Arg
[2993]	1250 1255 1260
[2994]	Asn Met Glu Lys Tyr Gln Leu Ala Val Thr Ile Met Ala Ile Leu
[2995]	1265 1270 1275
[2996]	Cys Val Pro Asn Ala Val Ile Leu Gln Asn Ala Trp Lys Val Ser
[2997]	1280 1285 1290
[2998]	Cys Thr Ile Leu Ala Val Val Ser Val Ser Pro Leu Phe Leu Thr
[2999]	1295 1300 1305
[3000]	Ser Ser Gln Gln Lys Thr Asp Trp Ile Pro Leu Ala Leu Thr Ile
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[3002]	Lys Gly Leu Asn Pro Thr Ala Ile Phe Leu Thr Thr Leu Ser Arg
[3003]	1325 1330 1335
[3004]	Thr Ser Lys Lys Arg Ser Trp Pro Leu Asn Glu Ala Ile Met Ala
[3005]	1340 1345 1350
[3006]	Val Gly Met Val Ser Ile Leu Ala Ser Ser Leu Leu Lys Asn Asp
[3007]	1355 1360 1365
[3008]	Ile Pro Met Thr Gly Pro Leu Val Ala Gly Gly Leu Leu Thr Val
[3009]	1370 1375 1380
[3010]	Cys Tyr Val Leu Thr Gly Arg Ser Ala Asp Leu Glu Leu Glu Arg
[3011]	1385 1390 1395
[3012]	Ala Ala Asp Val Lys Trp Glu Asp Gln Ala Glu Ile Ser Gly Ser
[3013]	1400 1405 1410
[3014]	Ser Pro Ile Leu Ser Ile Thr Ile Ser Glu Asp Gly Ser Met Ser
[3015]	1415 1420 1425
[3016]	Ile Lys Asn Glu Glu Glu Glu Gln Thr Leu Thr Ile Leu Ile Arg
[3017]	1430 1435 1440
[3018]	Thr Gly Leu Leu Val Ile Ser Gly Leu Phe Pro Val Ser Ile Pro
[3019]	1445 1450 1455
[3020]	Ile Thr Ala Ala Ala Trp Tyr Leu Trp Glu Val Lys Lys Gln Arg
[3021]	1460 1465 1470
[3022]	Ala Gly Val Leu Trp Asp Val Pro Ser Pro Pro Pro Met Gly Lys
[3023]	1475 1480 1485

[3024]	Ala Glu Leu Glu Asp Gly Ala Tyr Arg Ile Lys Gln Lys Gly Ile
[3025]	1490 1495 1500
[3026]	Leu Gly Tyr Ser Gln Ile Gly Ala Gly Val Tyr Lys Glu Gly Thr
[3027]	1505 1510 1515
[3028]	Phe His Thr Met Trp His Val Thr Arg Gly Ala Val Leu Met His
[3029]	1520 1525 1530
[3030]	Lys Gly Lys Arg Ile Glu Pro Ser Trp Ala Asp Val Lys Lys Asp
[3031]	1535 1540 1545
[3032]	Leu Ile Ser Tyr Gly Gly Gly Trp Lys Leu Glu Gly Glu Trp Lys
[3033]	1550 1555 1560
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[3036]	Pro Arg Ala Val Gln Thr Lys Pro Gly Leu Phe Lys Thr Asn Ala
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[3038]	Gly Thr Ile Gly Ala Val Ser Leu Asp Phe Ser Pro Gly Thr Ser
[3039]	1595 1600 1605
[3040]	Gly Ser Pro Ile Ile Asp Lys Lys Gly Lys Val Val Gly Leu Tyr
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[3043]	1625 1630 1635
[3044]	Ala Gln Thr Glu Lys Ser Ile Glu Asp Asn Pro Glu Ile Glu Asp
[3045]	1640 1645 1650
[3046]	Asp Ile Phe Arg Lys Arg Arg Leu Thr Ile Met Asp Leu His Pro
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[3050]	Ala Ile Lys Arg Gly Leu Arg Thr Leu Ile Leu Ala Pro Thr Arg
[3051]	1685 1690 1695
[3052]	Val Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu Pro Ile
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[3054]	Arg Tyr Gln Thr Pro Ala Ile Arg Ala Val His Thr Gly Arg Glu
[3055]	1715 1720 1725
[3056]	Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Met Arg Leu Leu
[3057]	1730 1735 1740
[3058]	Ser Pro Val Arg Val Pro Asn Tyr Asn Leu Ile Ile Met Asp Glu
[3059]	1745 1750 1755
[3060]	Ala His Phe Thr Asp Pro Ala Ser Ile Ala Ala Arg Gly Tyr Ile
[3061]	1760 1765 1770
[3062]	Ser Thr Arg Val Glu Met Gly Glu Ala Ala Gly Ile Phe Met Thr
[3063]	1775 1780 1785
[3064]	Ala Thr Pro Pro Gly Ser Arg Asp Pro Phe Pro Gln Ser Asn Ala
[3065]	1790 1795 1800

[3066]	Pro	Ile	Ile	Asp	Glu	Glu	Arg	Glu	Ile	Pro	Glu	Arg	Ser	Trp	Asn
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[3068]	Ser	Gly	His	Glu	Trp	Val	Thr	Asp	Phe	Lys	Gly	Lys	Thr	Val	Trp
[3069]	1820						1825							1830	
[3070]	Phe	Val	Pro	Ser	Ile	Lys	Ala	Gly	Asn	Asp	Ile	Ala	Ala	Cys	Leu
[3071]	1835						1840							1845	
[3072]	Arg	Lys	Asn	Gly	Lys	Lys	Val	Ile	Gln	Leu	Ser	Arg	Lys	Thr	Phe
[3073]	1850						1855							1860	
[3074]	Asp	Ser	Glu	Tyr	Val	Lys	Thr	Arg	Thr	Asn	Asp	Trp	Asp	Phe	Val
[3075]	1865						1870							1875	
[3076]	Val	Thr	Thr	Asp	Ile	Ser	Glu	Met	Gly	Ala	Asn	Phe	Lys	Ala	Glu
[3077]	1880						1885							1890	
[3078]	Arg	Val	Ile	Asp	Pro	Arg	Arg	Cys	Met	Lys	Pro	Val	Ile	Leu	Thr
[3079]	1895						1900							1905	
[3080]	Asp	Gly	Glu	Glu	Arg	Val	Ile	Leu	Ala	Gly	Pro	Met	Pro	Val	Thr
[3081]	1910						1915							1920	
[3082]	His	Ser	Ser	Ala	Ala	Gln	Arg	Arg	Gly	Arg	Ile	Gly	Arg	Asn	Pro
[3083]	1925						1930							1935	
[3084]	Lys	Asn	Glu	Asn	Asp	Gln	Tyr	Ile	Tyr	Met	Gly	Glu	Pro	Leu	Glu
[3085]	1940						1945							1950	
[3086]	Asn	Asp	Glu	Asp	Cys	Ala	His	Trp	Lys	Glu	Ala	Lys	Met	Leu	Leu
[3087]	1955						1960							1965	
[3088]	Asp	Asn	Ile	Asn	Thr	Pro	Glu	Gly	Ile	Ile	Pro	Ser	Met	Phe	Glu
[3089]	1970						1975							1980	
[3090]	Pro	Glu	Arg	Glu	Lys	Val	Asp	Ala	Ile	Asp	Gly	Glu	Tyr	Arg	Leu
[3091]	1985						1990							1995	
[3092]	Arg	Gly	Glu	Ala	Arg	Lys	Thr	Phe	Val	Asp	Leu	Met	Arg	Arg	Gly
[3093]	2000						2005							2010	
[3094]	Asp	Leu	Pro	Val	Trp	Leu	Ala	Tyr	Arg	Val	Ala	Ala	Glu	Gly	Ile
[3095]	2015						2020							2025	
[3096]	Asn	Tyr	Ala	Asp	Arg	Arg	Trp	Cys	Phe	Asp	Gly	Val	Lys	Asn	Asn
[3097]	2030						2035							2040	
[3098]	Gln	Ile	Leu	Glu	Glu	Asn	Val	Glu	Val	Glu	Ile	Trp	Thr	Lys	Glu
[3099]	2045						2050							2055	
[3100]	Gly	Glu	Arg	Lys	Lys	Leu	Lys	Pro	Arg	Trp	Leu	Asp	Ala	Arg	Ile
[3101]	2060						2065							2070	
[3102]	Tyr	Ser	Asp	Pro	Leu	Ala	Leu	Lys	Glu	Phe	Lys	Glu	Phe	Ala	Ala
[3103]	2075						2080							2085	
[3104]	Gly	Arg	Lys	Ser	Leu	Thr	Leu	Asn	Leu	Ile	Thr	Glu	Met	Gly	Arg
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[3107]	2105						2110							2115	

[3108]	Leu Ala Val Leu His Thr Ala Glu Ala Gly Gly Arg Ala Tyr Asn	
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[3110]	His Ala Leu Ser Glu Leu Pro Glu Thr Leu Glu Thr Leu Leu Leu	
[3111]	2135	2140 2145
[3112]	Leu Thr Leu Leu Ala Thr Val Thr Gly Gly Ile Phe Leu Phe Leu	
[3113]	2150	2155 2160
[3114]	Met Ser Ala Arg Gly Ile Gly Lys Met Thr Leu Gly Met Cys Cys	
[3115]	2165	2170 2175
[3116]	Ile Ile Thr Ala Ser Ile Leu Leu Trp Tyr Ala Gln Ile Gln Pro	
[3117]	2180	2185 2190
[3118]	His Trp Ile Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu Ile Val	
[3119]	2195	2200 2205
[3120]	Leu Leu Ile Pro Glu Pro Glu Lys Gln Arg Thr Pro Gln Asp Asn	
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[3122]	Gln Leu Thr Tyr Val Val Ile Ala Ile Leu Thr Val Val Ala Ala	
[3123]	2225	2230 2235
[3124]	Thr Met Ala Asn Glu Met Gly Phe Leu Glu Lys Thr Lys Lys Asp	
[3125]	2240	2245 2250
[3126]	Leu Gly Leu Gly Ser Ile Ala Thr Gln Gln Pro Glu Ser Asn Ile	
[3127]	2255	2260 2265
[3128]	Leu Asp Ile Asp Leu Arg Pro Ala Ser Ala Trp Thr Leu Tyr Ala	
[3129]	2270	2275 2280
[3130]	Val Ala Thr Thr Phe Val Thr Pro Met Leu Arg His Ser Ile Glu	
[3131]	2285	2290 2295
[3132]	Asn Ser Ser Val Asn Val Ser Leu Thr Ala Ile Ala Asn Gln Ala	
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[3134]	Thr Val Leu Met Gly Leu Gly Lys Gly Trp Pro Leu Ser Lys Met	
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[3137]	2330	2335 2340
[3138]	Asn Pro Ile Thr Leu Thr Ala Ala Leu Phe Leu Leu Val Ala His	
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[3140]	Tyr Ala Ile Ile Gly Pro Gly Leu Gln Ala Lys Ala Thr Arg Glu	
[3141]	2360	2365 2370
[3142]	Ala Gln Lys Arg Ala Ala Ala Gly Ile Met Lys Asn Pro Thr Val	
[3143]	2375	2380 2385
[3144]	Asp Gly Ile Thr Val Ile Asp Leu Asp Pro Ile Pro Tyr Asp Pro	
[3145]	2390	2395 2400
[3146]	Lys Phe Glu Lys Gln Leu Gly Gln Val Met Leu Leu Val Leu Cys	
[3147]	2405	2410 2415
[3148]	Val Thr Gln Val Leu Met Met Arg Thr Thr Trp Ala Leu Cys Glu	
[3149]	2420	2425 2430

[3150]	Ala Leu Thr Leu Ala Thr Gly Pro Ile Ser Thr Leu Trp Glu Gly
[3151]	2435 2440 2445
[3152]	Asn Pro Gly Arg Phe Trp Asn Thr Thr Ile Ala Val Ser Met Ala
[3153]	2450 2455 2460
[3154]	Asn Ile Phe Arg Gly Ser Tyr Leu Ala Gly Ala Gly Leu Leu Phe
[3155]	2465 2470 2475
[3156]	Ser Ile Met Lys Asn Thr Thr Asn Thr Arg Arg Gly Thr Gly Asn
[3157]	2480 2485 2490
[3158]	Ile Gly Glu Thr Leu Gly Glu Lys Trp Lys Ser Arg Leu Asn Ala
[3159]	2495 2500 2505
[3160]	Leu Gly Lys Ser Glu Phe Gln Ile Tyr Lys Lys Ser Gly Ile Gln
[3161]	2510 2515 2520
[3162]	Glu Val Asp Arg Thr Leu Ala Lys Glu Gly Ile Lys Arg Gly Glu
[3163]	2525 2530 2535
[3164]	Thr Asp His His Ala Val Ser Arg Gly Ser Ala Lys Leu Arg Trp
[3165]	2540 2545 2550
[3166]	Phe Val Glu Arg Asn Met Val Thr Pro Glu Gly Lys Val Val Asp
[3167]	2555 2560 2565
[3168]	Leu Gly Cys Gly Arg Gly Gly Trp Ser Tyr Tyr Cys Gly Gly Leu
[3169]	2570 2575 2580
[3170]	Lys Asn Val Arg Glu Val Lys Gly Leu Thr Lys Gly Gly Pro Gly
[3171]	2585 2590 2595
[3172]	His Glu Glu Pro Ile Pro Met Ser Thr Tyr Gly Trp Asn Leu Val
[3173]	2600 2605 2610
[3174]	Arg Leu Gln Ser Gly Val Asp Val Phe Phe Ile Pro Pro Glu Lys
[3175]	2615 2620 2625
[3176]	Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Pro Asn Pro
[3177]	2630 2635 2640
[3178]	Thr Val Glu Ala Gly Arg Thr Leu Arg Val Leu Asn Leu Val Glu
[3179]	2645 2650 2655
[3180]	Asn Trp Leu Asn Asn Asn Thr Gln Phe Cys Ile Lys Val Leu Asn
[3181]	2660 2665 2670
[3182]	Pro Tyr Met Pro Ser Val Ile Glu Lys Met Glu Ala Leu Gln Arg
[3183]	2675 2680 2685
[3184]	Lys Tyr Gly Gly Ala Leu Val Arg Asn Pro Leu Ser Arg Asn Ser
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[3186]	Thr His Glu Met Tyr Trp Val Ser Asn Ala Ser Gly Asn Ile Val
[3187]	2705 2710 2715
[3188]	Ser Ser Val Asn Met Ile Ser Arg Met Leu Ile Asn Arg Phe Thr
[3189]	2720 2725 2730
[3190]	Met Arg Tyr Lys Lys Ala Thr Tyr Glu Pro Asp Val Asp Leu Gly
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[3192]	Ser Gly Thr Arg Asn Ile Gly Ile Glu Ser Glu Ile Pro Asn Leu	
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[3194]	Asp Ile Ile Gly Lys Arg Ile Glu Lys Ile Lys Gln Glu His Glu	
[3195]	2765	2770 2775
[3196]	Thr Ser Trp His Tyr Asp Gln Asp His Pro Tyr Lys Thr Trp Ala	
[3197]	2780	2785 2790
[3198]	Tyr His Gly Ser Tyr Glu Thr Lys Gln Thr Gly Ser Ala Ser Ser	
[3199]	2795	2800 2805
[3200]	Met Val Asn Gly Val Val Arg Leu Leu Thr Lys Pro Trp Asp Val	
[3201]	2810	2815 2820
[3202]	Val Pro Met Val Thr Gln Met Ala Met Thr Asp Thr Thr Pro Phe	
[3203]	2825	2830 2835
[3204]	Gly Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg Thr Gln	
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[3206]	Glu Pro Lys Glu Gly Thr Lys Lys Leu Met Lys Ile Thr Ala Glu	
[3207]	2855	2860 2865
[3208]	Trp Leu Trp Lys Glu Leu Gly Lys Lys Lys Thr Pro Arg Met Cys	
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[3210]	Thr Arg Glu Glu Phe Thr Arg Lys Val Arg Ser Asn Ala Ala Leu	
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[3212]	Gly Ala Ile Phe Thr Asp Glu Asn Lys Trp Lys Ser Ala Arg Glu	
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[3214]	Ala Val Glu Asp Ser Arg Phe Trp Glu Leu Val Asp Lys Glu Arg	
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[3216]	Asn Leu His Leu Glu Gly Lys Cys Glu Thr Cys Val Tyr Asn Met	
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[3218]	Met Gly Lys Arg Glu Lys Lys Leu Gly Glu Phe Gly Lys Ala Lys	
[3219]	2945	2950 2955
[3220]	Gly Ser Arg Ala Ile Trp Tyr Met Trp Leu Gly Ala Arg Phe Leu	
[3221]	2960	2965 2970
[3222]	Glu Phe Glu Ala Leu Gly Phe Leu Asn Glu Asp His Trp Phe Ser	
[3223]	2975	2980 2985
[3224]	Arg Glu Asn Ser Leu Ser Gly Val Glu Gly Glu Gly Leu His Lys	
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[3226]	Leu Gly Tyr Ile Leu Arg Asp Val Ser Lys Lys Glu Gly Gly Ala	
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[3228]	Met Tyr Ala Asp Asp Thr Ala Gly Trp Asp Thr Arg Ile Thr Leu	
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[3230]	Glu Asp Leu Lys Asn Glu Glu Met Val Thr Asn His Met Glu Gly	
[3231]	3035	3040 3045
[3232]	Glu His Lys Lys Leu Ala Glu Ala Ile Phe Lys Leu Thr Tyr Gln	
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[3234]	Asn Lys Val Val Arg Val Gln Arg Pro Thr Pro Arg Gly Thr Val
[3235]	3065 3070 3075
[3236]	Met Asp Ile Ile Ser Arg Arg Asp Gln Arg Gly Ser Gly Gln Val
[3237]	3080 3085 3090
[3238]	Gly Thr Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Ala Gln Leu
[3239]	3095 3100 3105
[3240]	Ile Arg Gln Met Glu Gly Glu Gly Val Phe Lys Ser Ile Gln His
[3241]	3110 3115 3120
[3242]	Leu Thr Ile Thr Glu Glu Ile Ala Val Gln Asn Trp Leu Ala Arg
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[3244]	Val Gly Arg Glu Arg Leu Ser Arg Met Ala Ile Ser Gly Asp Asp
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[3246]	Cys Val Val Lys Pro Leu Asp Asp Arg Phe Ala Ser Ala Leu Thr
[3247]	3155 3160 3165
[3248]	Ala Leu Asn Asp Met Gly Lys Ile Arg Lys Asp Ile Gln Gln Trp
[3249]	3170 3175 3180
[3250]	Glu Pro Ser Arg Gly Trp Asn Asp Trp Thr Gln Val Pro Phe Cys
[3251]	3185 3190 3195
[3252]	Ser His His Phe His Glu Leu Ile Met Lys Asp Gly Arg Val Leu
[3253]	3200 3205 3210
[3254]	Val Val Pro Cys Arg Asn Gln Asp Glu Leu Ile Gly Arg Ala Arg
[3255]	3215 3220 3225
[3256]	Ile Ser Gln Gly Ala Gly Trp Ser Leu Arg Glu Thr Ala Cys Leu
[3257]	3230 3235 3240
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[3474]	20 25 30	
[3475]	Phe Ser Leu Gly Met Leu Gln Gly Arg Gly Pro Leu Lys Leu Phe Met	
[3476]	35 40 45	
[3477]	Ala Leu Val Ala Phe Leu Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly	
[3478]	50 55 60	
[3479]	Ile Leu Lys Arg Trp Gly Thr Ile Lys Lys Ser Lys Ala Ile Asn Val	
[3480]	65 70 75 80	
[3481]	Leu Arg Gly Phe Arg Lys Glu Ile Gly Arg Met Leu Asn Ile Leu Asn	
[3482]	85 90 95	
[3483]	Arg Arg Arg Ser Ser Ala Gly Met Ile Ile Met Leu Ile Pro Thr Val	
[3484]	100 105 110	
[3485]	Met Ala Phe His Leu Thr Thr Arg Asp Gly Glu Pro Leu Met Ile Val	

[3486]	115	120	125
[3487]	Ala Lys His Glu Arg Gly Arg Pro Leu Leu Phe Lys Thr Thr Glu Gly		
[3488]	130	135	140
[3489]	Ile Asn Lys Cys Thr Leu Ile Ala Met Asp Leu Gly Glu Met Cys Glu		
[3490]	145	150	155
[3491]	Asp Thr Val Thr Tyr Lys Cys Pro Leu Leu Val Asn Thr Glu Pro Glu		
[3492]	165	170	175
[3493]	Asp Ile Asp Cys Trp Cys Asn Leu Thr Ser Thr Trp Val Met Tyr Gly		
[3494]	180	185	190
[3495]	Thr Cys Thr Gln Ser Gly Glu Arg Arg Arg Glu Lys Arg Ser Val Ala		
[3496]	195	200	205
[3497]	Leu Thr Pro His Ser Gly Met Gly Leu Glu Thr Arg Ala Glu Thr Trp		
[3498]	210	215	220
[3499]	Met Ser Ser Glu Gly Ala Trp Lys His Ala Gln Arg Val Glu Ser Trp		
[3500]	225	230	235
[3501]	Ile Leu Arg Asn Pro Gly Phe Ala Leu Leu Ala Gly Phe Met Ala Tyr		
[3502]	245	250	255
[3503]	Met Ile Gly Gln Thr Gly Ile Gln Arg Thr Val Phe Phe Val Leu Met		
[3504]	260	265	270
[3505]	Met Leu Val Ala Pro Ser Tyr Gly Met Arg Cys Val Gly Val Gly Asn		
[3506]	275	280	285
[3507]	Arg Asp Phe Val Glu Gly Val Ser Gly Gly Ala Trp Val Asp Leu Val		
[3508]	290	295	300
[3509]	Leu Glu His Gly Gly Cys Val Thr Thr Met Ala Gln Gly Lys Pro Thr		
[3510]	305	310	315
[3511]	Leu Asp Phe Glu Leu Thr Lys Thr Thr Ala Lys Glu Val Ala Leu Leu		
[3512]	325	330	335
[3513]	Arg Thr Tyr Cys Ile Glu Ala Ser Ile Ser Asn Ile Thr Thr Ala Thr		
[3514]	340	345	350
[3515]	Arg Cys Pro Thr Gln Gly Glu Pro Tyr Leu Lys Glu Glu Gln Asp Gln		
[3516]	355	360	365
[3517]	Gln Tyr Ile Cys Arg Arg Asp Val Val Asp Arg Gly Trp Gly Asn Gly		
[3518]	370	375	380
[3519]	Cys Gly Leu Phe Gly Lys Gly Gly Val Val Thr Cys Ala Lys Phe Ser		
[3520]	385	390	395
[3521]	Cys Ser Gly Lys Ile Thr Gly Asn Leu Val Gln Ile Glu Asn Leu Glu		
[3522]	405	410	415
[3523]	Tyr Thr Val Val Val Thr Val His Asn Gly Asp Thr His Ala Val Gly		
[3524]	420	425	430
[3525]	Asn Asp Thr Ser Asn His Gly Val Thr Ala Thr Ile Thr Pro Arg Ser		
[3526]	435	440	445
[3527]	Pro Ser Val Glu Val Lys Leu Pro Asp Tyr Gly Glu Leu Thr Leu Asp		

[3528]	450	455	460
[3529]	Cys Glu Pro Arg Ser Gly Ile Asp Phe Asn Glu Met Ile Leu Met Lys		
[3530]	465	470	475 480
[3531]	Met Lys Lys Lys Thr Trp Leu Val His Lys Gln Trp Phe Leu Asp Leu		
[3532]	485	490	495
[3533]	Pro Leu Pro Trp Thr Ala Gly Ala Asp Thr Ser Glu Val His Trp Asn		
[3534]	500	505	510
[3535]	Tyr Lys Glu Arg Met Val Thr Phe Lys Val Pro His Ala Lys Arg Gln		
[3536]	515	520	525
[3537]	Asp Val Thr Val Leu Gly Ser Gln Glu Gly Ala Met His Ser Ala Leu		
[3538]	530	535	540
[3539]	Ala Gly Ala Thr Glu Val Asp Ser Gly Asp Gly Asn His Met Phe Ala		
[3540]	545	550	555 560
[3541]	Gly His Leu Lys Cys Lys Val Arg Met Glu Lys Leu Arg Ile Lys Gly		
[3542]	565	570	575
[3543]	Met Ser Tyr Thr Met Cys Ser Gly Lys Phe Ser Ile Asp Lys Glu Met		
[3544]	580	585	590
[3545]	Ala Glu Thr Gln His Gly Thr Thr Val Val Lys Val Lys Tyr Glu Gly		
[3546]	595	600	605
[3547]	Ala Gly Ala Pro Cys Lys Val Pro Ile Glu Ile Arg Asp Val Asn Lys		
[3548]	610	615	620
[3549]	Glu Lys Val Val Gly Arg Ile Ile Ser Ser Thr Pro Leu Ala Glu Asn		
[3550]	625	630	635 640
[3551]	Thr Asn Ser Val Thr Asn Ile Glu Leu Glu Pro Pro Phe Gly Asp Ser		
[3552]	645	650	655
[3553]	Tyr Ile Val Ile Gly Val Gly Asn Ser Ala Leu Thr Leu His Trp Phe		
[3554]	660	665	670
[3555]	Arg Lys Gly Ser Ser Ile Gly Lys Met Phe Glu Ser Thr Tyr Arg Gly		
[3556]	675	680	685
[3557]	Ala Lys Arg Met Ala Ile Leu Gly Glu Thr Ala Trp Asp Phe Gly Ser		
[3558]	690	695	700
[3559]	Val Gly Gly Leu Phe Thr Ser Leu Gly Lys Ala Val His Gln Val Phe		
[3560]	705	710	715 720
[3561]	Gly Ser Val Tyr Thr Thr Leu Phe Gly Gly Val Ser Trp Met Ile Arg		
[3562]	725	730	735
[3563]	Ile Leu Ile Gly Phe Leu Val Leu Trp Ile Gly Thr Asn Ser Arg Asn		
[3564]	740	745	750
[3565]	Thr Ser Met Ala Met Thr Cys Ile Ala Ala Gly Ile Val Thr Leu Tyr		
[3566]	755	760	765
[3567]	Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys		
[3568]	770	775	780
[3569]	Asn Lys Glu Leu Lys Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val		

[3570]	785	790	795	800
[3571]	His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys			
[3572]		805	810	815
[3573]	Leu Ala Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile			
[3574]		820	825	830
[3575]	Arg Ser Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro			
[3576]		835	840	845
[3577]	Glu Leu Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met			
[3578]		850	855	860
[3579]	Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg			
[3580]	865	870	875	880
[3581]	Pro Gln Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala			
[3582]		885	890	895
[3583]	Lys Met Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly			
[3584]		900	905	910
[3585]	Pro Glu Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu			
[3586]		915	920	925
[3587]	Glu Val Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu			
[3588]		930	935	940
[3589]	Lys Leu Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser			
[3590]	945	950	955	960
[3591]	Ala Ala Ile Lys Asp Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp			
[3592]		965	970	975
[3593]	Ile Glu Ser Ala Leu Asn Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe			
[3594]		980	985	990
[3595]	Ile Glu Val Lys Asn Cys His Trp Pro Lys Ser His Thr Leu Trp Ser			
[3596]		995	1000	1005
[3597]	Asn Gly Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala			
[3598]		1010	1015	1020
[3599]	Gly Pro Val Ser Gln His Asn Tyr Arg Pro Gly Tyr His Thr Gln			
[3600]		1025	1030	1035
[3601]	Ile Thr Gly Pro Trp His Leu Gly Lys Leu Glu Met Asp Phe Asp			
[3602]		1040	1045	1050
[3603]	Phe Cys Asp Gly Thr Thr Val Val Val Thr Glu Asp Cys Gly Asn			
[3604]		1055	1060	1065
[3605]	Arg Gly Pro Ser Leu Arg Thr Thr Thr Ala Ser Gly Lys Leu Ile			
[3606]		1070	1075	1080
[3607]	Thr Glu Trp Cys Cys Arg Ser Cys Thr Leu Pro Pro Leu Arg Tyr			
[3608]		1085	1090	1095
[3609]	Arg Gly Glu Asp Gly Cys Trp Tyr Gly Met Glu Ile Arg Pro Leu			
[3610]		1100	1105	1110
[3611]	Lys Glu Lys Glu Glu Asn Leu Val Asn Ser Leu Val Thr Ala Gly			

[3612]	1115	1120	1125
[3613]	His Gly Gln Val Asp Asn Phe Ser Leu Gly Val	Leu Gly Met Ala	
[3614]	1130	1135	1140
[3615]	Leu Phe Leu Glu Glu Met Leu Arg Thr Arg Val	Gly Thr Lys His	
[3616]	1145	1150	1155
[3617]	Ala Ile Leu Leu Val Ala Val Ser Phe Val Thr	Leu Ile Thr Gly	
[3618]	1160	1165	1170
[3619]	Asn Met Ser Phe Arg Asp Leu Gly Arg Val Met	Val Met Val Gly	
[3620]	1175	1180	1185
[3621]	Ala Thr Met Thr Gly Asp Ile Gly Met Gly Val	Thr Tyr Leu Ala	
[3622]	1190	1195	1200
[3623]	Leu Leu Ala Ala Phe Lys Val Arg Pro Thr Phe	Ala Ala Gly Leu	
[3624]	1205	1210	1215
[3625]	Leu Leu Arg Lys Leu Thr Ser Arg Glu Leu Met	Met Thr Thr Ile	
[3626]	1220	1225	1230
[3627]	Gly Ile Val Leu Leu Ser Gln Ser Thr Ile Pro	Glu Thr Ile Leu	
[3628]	1235	1240	1245
[3629]	Glu Leu Thr Asp Ala Leu Ala Leu Gly Met Met	Val Leu Lys Met	
[3630]	1250	1255	1260
[3631]	Val Arg Asn Met Glu Lys Tyr Gln Leu Ala Val	Thr Ile Met Ala	
[3632]	1265	1270	1275
[3633]	Ile Leu Cys Val Pro Asn Ala Val Ile Leu Gln	Asn Ala Trp Lys	
[3634]	1280	1285	1290
[3635]	Val Ser Cys Thr Ile Leu Ala Val Val Ser Val	Ser Pro Leu Phe	
[3636]	1295	1300	1305
[3637]	Leu Thr Ser Ser Gln Gln Lys Thr Asp Trp Ile	Pro Leu Ala Leu	
[3638]	1310	1315	1320
[3639]	Thr Ile Lys Gly Leu Asn Pro Thr Ala Ile Phe	Leu Thr Thr Leu	
[3640]	1325	1330	1335
[3641]	Ser Arg Thr Ser Lys Lys Arg Ser Trp Pro Leu	Asn Glu Ala Ile	
[3642]	1340	1345	1350
[3643]	Met Ala Val Gly Met Val Ser Ile Leu Ala Ser	Ser Leu Leu Lys	
[3644]	1355	1360	1365
[3645]	Asn Asp Ile Pro Met Thr Gly Pro Leu Val Ala	Gly Gly Leu Leu	
[3646]	1370	1375	1380
[3647]	Thr Val Cys Tyr Val Leu Thr Gly Arg Ser Ala	Asp Leu Glu Leu	
[3648]	1385	1390	1395
[3649]	Glu Arg Ala Ala Asp Val Lys Trp Glu Asp Gln	Ala Glu Ile Ser	
[3650]	1400	1405	1410
[3651]	Gly Ser Ser Pro Ile Leu Ser Ile Thr Ile Ser	Glu Asp Gly Ser	
[3652]	1415	1420	1425
[3653]	Met Ser Ile Lys Asn Glu Glu Glu Glu Gln Thr	Leu Thr Ile Leu	

[3654]	1430	1435	1440
[3655]	Ile Arg Thr Gly Leu Leu Val Ile Ser Gly Leu Phe Pro Val Ser		
[3656]	1445	1450	1455
[3657]	Ile Pro Ile Thr Ala Ala Ala Trp Tyr Leu Trp Glu Val Lys Lys		
[3658]	1460	1465	1470
[3659]	Gln Arg Ala Gly Val Leu Trp Asp Val Pro Ser Pro Pro Pro Met		
[3660]	1475	1480	1485
[3661]	Gly Lys Ala Glu Leu Glu Asp Gly Ala Tyr Arg Ile Lys Gln Lys		
[3662]	1490	1495	1500
[3663]	Gly Ile Leu Gly Tyr Ser Gln Ile Gly Ala Gly Val Tyr Lys Glu		
[3664]	1505	1510	1515
[3665]	Gly Thr Phe His Thr Met Trp His Val Thr Arg Gly Ala Val Leu		
[3666]	1520	1525	1530
[3667]	Met His Lys Gly Lys Arg Ile Glu Pro Ser Trp Ala Asp Val Lys		
[3668]	1535	1540	1545
[3669]	Lys Asp Leu Ile Ser Tyr Gly Gly Gly Trp Lys Leu Glu Gly Glu		
[3670]	1550	1555	1560
[3671]	Trp Lys Glu Gly Glu Glu Val Gln Val Leu Ala Leu Glu Pro Gly		
[3672]	1565	1570	1575
[3673]	Lys Asn Pro Arg Ala Val Gln Thr Lys Pro Gly Leu Phe Lys Thr		
[3674]	1580	1585	1590
[3675]	Asn Ala Gly Thr Ile Gly Ala Val Ser Leu Asp Phe Ser Pro Gly		
[3676]	1595	1600	1605
[3677]	Thr Ser Gly Ser Pro Ile Ile Asp Lys Lys Gly Lys Val Val Gly		
[3678]	1610	1615	1620
[3679]	Leu Tyr Gly Asn Gly Val Val Thr Arg Ser Gly Ala Tyr Val Ser		
[3680]	1625	1630	1635
[3681]	Ala Ile Ala Gln Thr Glu Lys Ser Ile Glu Asp Asn Pro Glu Ile		
[3682]	1640	1645	1650
[3683]	Glu Asp Asp Ile Phe Arg Lys Arg Arg Leu Thr Ile Met Asp Leu		
[3684]	1655	1660	1665
[3685]	His Pro Gly Ala Gly Lys Thr Lys Arg Tyr Leu Pro Ala Ile Val		
[3686]	1670	1675	1680
[3687]	Arg Glu Ala Ile Lys Arg Gly Leu Arg Thr Leu Ile Leu Ala Pro		
[3688]	1685	1690	1695
[3689]	Thr Arg Val Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu		
[3690]	1700	1705	1710
[3691]	Pro Ile Arg Tyr Gln Thr Pro Ala Ile Arg Ala Val His Thr Gly		
[3692]	1715	1720	1725
[3693]	Arg Glu Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Met Arg		
[3694]	1730	1735	1740
[3695]	Leu Leu Ser Pro Val Arg Val Pro Asn Tyr Asn Leu Ile Ile Met		

[3696]	1745	1750	1755
[3697]	Asp Glu Ala His Phe Thr Asp Pro Ala Ser Ile Ala Ala Arg Gly		
[3698]	1760	1765	1770
[3699]	Tyr Ile Ser Thr Arg Val Glu Met Gly Glu Ala Ala Gly Ile Phe		
[3700]	1775	1780	1785
[3701]	Met Thr Ala Thr Pro Pro Gly Ser Arg Asp Pro Phe Pro Gln Ser		
[3702]	1790	1795	1800
[3703]	Asn Ala Pro Ile Ile Asp Glu Glu Arg Glu Ile Pro Glu Arg Ser		
[3704]	1805	1810	1815
[3705]	Trp Asn Ser Gly His Glu Trp Val Thr Asp Phe Lys Gly Lys Thr		
[3706]	1820	1825	1830
[3707]	Val Trp Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile Ala Ala		
[3708]	1835	1840	1845
[3709]	Cys Leu Arg Lys Asn Gly Lys Lys Val Ile Gln Leu Ser Arg Lys		
[3710]	1850	1855	1860
[3711]	Thr Phe Asp Ser Glu Tyr Val Lys Thr Arg Thr Asn Asp Trp Asp		
[3712]	1865	1870	1875
[3713]	Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys		
[3714]	1880	1885	1890
[3715]	Ala Glu Arg Val Ile Asp Pro Arg Arg Cys Met Lys Pro Val Ile		
[3716]	1895	1900	1905
[3717]	Leu Thr Asp Gly Glu Glu Arg Val Ile Leu Ala Gly Pro Met Pro		
[3718]	1910	1915	1920
[3719]	Val Thr His Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg		
[3720]	1925	1930	1935
[3721]	Asn Pro Lys Asn Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu Pro		
[3722]	1940	1945	1950
[3723]	Leu Glu Asn Asp Glu Asp Cys Ala His Trp Lys Glu Ala Lys Met		
[3724]	1955	1960	1965
[3725]	Leu Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile Pro Ser Met		
[3726]	1970	1975	1980
[3727]	Phe Glu Pro Glu Arg Glu Lys Val Asp Ala Ile Asp Gly Glu Tyr		
[3728]	1985	1990	1995
[3729]	Arg Leu Arg Gly Glu Ala Arg Lys Thr Phe Val Asp Leu Met Arg		
[3730]	2000	2005	2010
[3731]	Arg Gly Asp Leu Pro Val Trp Leu Ala Tyr Arg Val Ala Ala Glu		
[3732]	2015	2020	2025
[3733]	Gly Ile Asn Tyr Ala Asp Arg Arg Trp Cys Phe Asp Gly Val Lys		
[3734]	2030	2035	2040
[3735]	Asn Asn Gln Ile Leu Glu Glu Asn Val Glu Val Glu Ile Trp Thr		
[3736]	2045	2050	2055
[3737]	Lys Glu Gly Glu Arg Lys Lys Leu Lys Pro Arg Trp Leu Asp Ala		

[3738]	2060	2065	2070
[3739]	Arg Ile Tyr Ser Asp Pro Leu Ala Leu Lys Glu Phe Lys Glu Phe		
[3740]	2075	2080	2085
[3741]	Ala Ala Gly Arg Lys Ser Leu Thr Leu Asn Leu Ile Thr Glu Met		
[3742]	2090	2095	2100
[3743]	Gly Arg Leu Pro Thr Phe Met Thr Gln Lys Val Arg Asp Ala Leu		
[3744]	2105	2110	2115
[3745]	Asp Asn Leu Ala Val Leu His Thr Ala Glu Ala Gly Gly Arg Ala		
[3746]	2120	2125	2130
[3747]	Tyr Asn His Ala Leu Ser Glu Leu Pro Glu Thr Leu Glu Thr Leu		
[3748]	2135	2140	2145
[3749]	Leu Leu Leu Thr Leu Leu Ala Thr Val Thr Gly Gly Ile Phe Leu		
[3750]	2150	2155	2160
[3751]	Phe Leu Met Ser Ala Arg Gly Ile Gly Lys Met Thr Leu Gly Met		
[3752]	2165	2170	2175
[3753]	Cys Cys Ile Ile Thr Ala Ser Ile Leu Leu Trp Tyr Ala Gln Ile		
[3754]	2180	2185	2190
[3755]	Gln Pro His Trp Ile Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu		
[3756]	2195	2200	2205
[3757]	Ile Val Leu Leu Ile Pro Glu Pro Glu Lys Gln Arg Thr Pro Gln		
[3758]	2210	2215	2220
[3759]	Asp Asn Gln Leu Thr Tyr Val Val Ile Ala Ile Leu Thr Val Val		
[3760]	2225	2230	2235
[3761]	Ala Ala Thr Met Ala Asn Glu Met Gly Phe Leu Glu Lys Thr Lys		
[3762]	2240	2245	2250
[3763]	Lys Asp Leu Gly Leu Gly Ser Ile Ala Thr Gln Gln Pro Glu Ser		
[3764]	2255	2260	2265
[3765]	Asn Ile Leu Asp Ile Asp Leu Arg Pro Ala Ser Ala Trp Thr Leu		
[3766]	2270	2275	2280
[3767]	Tyr Ala Val Ala Thr Thr Phe Val Thr Pro Met Leu Arg His Ser		
[3768]	2285	2290	2295
[3769]	Ile Glu Asn Ser Ser Val Asn Val Ser Leu Thr Ala Ile Ala Asn		
[3770]	2300	2305	2310
[3771]	Gln Ala Thr Val Leu Met Gly Leu Gly Lys Gly Trp Pro Leu Ser		
[3772]	2315	2320	2325
[3773]	Lys Met Asp Ile Gly Val Pro Leu Leu Ala Ile Gly Cys Tyr Ser		
[3774]	2330	2335	2340
[3775]	Gln Val Asn Pro Ile Thr Leu Thr Ala Ala Leu Phe Leu Leu Val		
[3776]	2345	2350	2355
[3777]	Ala His Tyr Ala Ile Ile Gly Pro Gly Leu Gln Ala Lys Ala Thr		
[3778]	2360	2365	2370
[3779]	Arg Glu Ala Gln Lys Arg Ala Ala Ala Gly Ile Met Lys Asn Pro		

[3780]	2375	2380	2385
[3781]	Thr Val Asp Gly Ile Thr	Val Ile Asp Leu Asp	Pro Ile Pro Tyr
[3782]	2390	2395	2400
[3783]	Asp Pro Lys Phe Glu Lys	Gln Leu Gly Gln Val	Met Leu Leu Val
[3784]	2405	2410	2415
[3785]	Leu Cys Val Thr Gln Val	Leu Met Met Arg Thr	Thr Trp Ala Leu
[3786]	2420	2425	2430
[3787]	Cys Glu Ala Leu Thr Leu	Ala Thr Gly Pro Ile	Ser Thr Leu Trp
[3788]	2435	2440	2445
[3789]	Glu Gly Asn Pro Gly Arg	Phe Trp Asn Thr Thr	Ile Ala Val Ser
[3790]	2450	2455	2460
[3791]	Met Ala Asn Ile Phe Arg	Gly Ser Tyr Leu Ala	Gly Ala Gly Leu
[3792]	2465	2470	2475
[3793]	Leu Phe Phe Ile Met Lys	Asn Thr Thr Asn Thr	Arg Arg Gly Thr
[3794]	2480	2485	2490
[3795]	Gly Asn Ile Gly Glu Thr	Leu Gly Glu Lys Trp	Lys Ser Arg Leu
[3796]	2495	2500	2505
[3797]	Asn Ala Leu Gly Lys Ser	Glu Phe Gln Ile Tyr	Lys Lys Ser Gly
[3798]	2510	2515	2520
[3799]	Ile Gln Glu Val Asp Arg	Thr Leu Ala Lys Glu	Gly Ile Lys Arg
[3800]	2525	2530	2535
[3801]	Gly Glu Thr Asp His His	Ala Val Ser Arg Gly	Ser Ala Lys Leu
[3802]	2540	2545	2550
[3803]	Arg Trp Phe Val Glu Arg	Asn Met Val Thr Pro	Glu Gly Lys Val
[3804]	2555	2560	2565
[3805]	Val Asp Leu Gly Cys Gly	Arg Gly Gly Trp Ser	Tyr Tyr Cys Gly
[3806]	2570	2575	2580
[3807]	Gly Leu Lys Asn Val Arg	Glu Val Lys Gly Leu	Thr Lys Gly Gly
[3808]	2585	2590	2595
[3809]	Pro Gly His Glu Glu Pro	Ile Pro Met Ser Thr	Tyr Gly Trp Asn
[3810]	2600	2605	2610
[3811]	Leu Val Arg Leu Gln Ser	Gly Val Asp Val Phe	Phe Ile Pro Pro
[3812]	2615	2620	2625
[3813]	Glu Lys Cys Asp Thr Leu	Leu Cys Asp Ile Gly	Glu Ser Ser Pro
[3814]	2630	2635	2640
[3815]	Asn Pro Thr Val Glu Ala	Gly Arg Thr Leu Arg	Val Leu Asn Leu
[3816]	2645	2650	2655
[3817]	Val Glu Asn Trp Leu Asn	Asn Asn Thr Gln Phe	Cys Ile Lys Val
[3818]	2660	2665	2670
[3819]	Leu Asn Pro Tyr Met Pro	Ser Val Ile Glu Lys	Met Glu Ala Leu
[3820]	2675	2680	2685
[3821]	Gln Arg Lys Tyr Gly Gly	Ala Leu Val Arg Asn	Pro Leu Ser Arg

[3822]	2690	2695	2700
[3823]	Asn Ser Thr His Glu Met Tyr Trp Val Ser Asn Ala Ser Gly Asn		
[3824]	2705	2710	2715
[3825]	Ile Val Ser Ser Val Asn Met Ile Ser Arg Met Leu Ile Asn Arg		
[3826]	2720	2725	2730
[3827]	Phe Thr Met Arg Tyr Lys Lys Ala Thr Tyr Glu Pro Asp Val Asp		
[3828]	2735	2740	2745
[3829]	Leu Gly Ser Gly Thr Arg Asn Ile Gly Ile Glu Ser Glu Ile Pro		
[3830]	2750	2755	2760
[3831]	Asn Leu Asp Ile Ile Gly Lys Arg Ile Glu Lys Ile Lys Gln Glu		
[3832]	2765	2770	2775
[3833]	His Glu Thr Ser Trp His Tyr Asp Gln Asp His Pro Tyr Lys Thr		
[3834]	2780	2785	2790
[3835]	Trp Ala Tyr His Gly Ser Tyr Glu Thr Lys Gln Thr Gly Ser Ala		
[3836]	2795	2800	2805
[3837]	Ser Ser Met Val Asn Gly Val Val Arg Leu Leu Thr Lys Pro Trp		
[3838]	2810	2815	2820
[3839]	Asp Val Val Pro Met Val Thr Gln Met Ala Met Thr Asp Thr Thr		
[3840]	2825	2830	2835
[3841]	Pro Phe Gly Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg		
[3842]	2840	2845	2850
[3843]	Thr Gln Glu Pro Lys Glu Gly Thr Lys Lys Leu Met Lys Ile Thr		
[3844]	2855	2860	2865
[3845]	Ala Glu Trp Leu Trp Lys Glu Leu Gly Lys Lys Lys Thr Pro Arg		
[3846]	2870	2875	2880
[3847]	Met Cys Thr Arg Glu Glu Phe Thr Arg Lys Val Arg Ser Asn Ala		
[3848]	2885	2890	2895
[3849]	Ala Leu Gly Ala Ile Phe Thr Asp Glu Asn Lys Trp Lys Ser Ala		
[3850]	2900	2905	2910
[3851]	Arg Glu Ala Val Glu Asp Ser Arg Phe Trp Glu Leu Val Asp Lys		
[3852]	2915	2920	2925
[3853]	Glu Arg Asn Leu His Leu Glu Gly Lys Cys Glu Thr Cys Val Tyr		
[3854]	2930	2935	2940
[3855]	Asn Met Met Gly Lys Arg Glu Lys Lys Leu Gly Glu Phe Gly Lys		
[3856]	2945	2950	2955
[3857]	Ala Lys Gly Ser Arg Ala Ile Trp Tyr Met Trp Leu Gly Ala Arg		
[3858]	2960	2965	2970
[3859]	Phe Leu Glu Phe Glu Ala Leu Gly Phe Leu Asn Glu Asp His Trp		
[3860]	2975	2980	2985
[3861]	Phe Ser Arg Glu Asn Ser Leu Ser Gly Val Glu Gly Glu Gly Leu		
[3862]	2990	2995	3000
[3863]	His Lys Leu Gly Tyr Ile Leu Arg Asp Val Ser Lys Lys Glu Gly		

[3864]	3005	3010	3015
[3865]	Gly Ala Met Tyr Ala Asp	Asp Thr Ala Gly Trp	Asp Thr Arg Ile
[3866]	3020	3025	3030
[3867]	Thr Leu Glu Asp Leu Lys	Asn Glu Glu Met Val	Thr Asn His Met
[3868]	3035	3040	3045
[3869]	Glu Gly Glu His Lys Lys	Leu Ala Glu Ala Ile	Phe Lys Leu Thr
[3870]	3050	3055	3060
[3871]	Tyr Gln Asn Lys Val Val	Arg Val Gln Arg Pro	Thr Pro Arg Gly
[3872]	3065	3070	3075
[3873]	Thr Val Met Asp Ile Ile	Ser Arg Arg Asp Gln	Arg Gly Ser Gly
[3874]	3080	3085	3090
[3875]	Gln Val Gly Thr Tyr Gly	Leu Asn Thr Phe Thr	Asn Met Glu Ala
[3876]	3095	3100	3105
[3877]	Gln Leu Ile Arg Gln Met	Glu Gly Glu Gly Val	Phe Lys Ser Ile
[3878]	3110	3115	3120
[3879]	Gln His Leu Thr Ile Thr	Glu Glu Ile Ala Val	Gln Asn Trp Leu
[3880]	3125	3130	3135
[3881]	Ala Arg Val Gly Arg Glu	Arg Leu Ser Arg Met	Ala Ile Ser Gly
[3882]	3140	3145	3150
[3883]	Asp Asp Cys Val Val Lys	Pro Leu Asp Asp Arg	Phe Ala Ser Ala
[3884]	3155	3160	3165
[3885]	Leu Thr Ala Leu Asn Asp	Met Gly Lys Ile Arg	Lys Asp Ile Gln
[3886]	3170	3175	3180
[3887]	Gln Trp Glu Pro Ser Arg	Gly Trp Asn Asp Trp	Thr Gln Val Pro
[3888]	3185	3190	3195
[3889]	Phe Cys Ser His His Phe	His Glu Leu Ile Met	Lys Asp Gly Arg
[3890]	3200	3205	3210
[3891]	Val Leu Val Val Pro Cys	Arg Asn Gln Asp Glu	Leu Ile Gly Arg
[3892]	3215	3220	3225
[3893]	Ala Arg Ile Ser Gln Gly	Ala Gly Trp Ser Leu	Arg Glu Thr Ala
[3894]	3230	3235	3240
[3895]	Cys Leu Gly Lys Ser Tyr	Ala Gln Met Trp Ser	Leu Met Tyr Phe
[3896]	3245	3250	3255
[3897]	His Arg Arg Asp Leu Arg	Leu Ala Ala Asn Ala	Ile Cys Ser Ala
[3898]	3260	3265	3270
[3899]	Val Pro Ser His Trp Val	Pro Thr Ser Arg Thr	Thr Trp Ser Ile
[3900]	3275	3280	3285
[3901]	His Ala Lys His Glu Trp	Met Thr Thr Glu Asp	Met Leu Thr Val
[3902]	3290	3295	3300
[3903]	Trp Asn Arg Val Trp Ile	Gln Glu Asn Pro Trp	Met Glu Asp Lys
[3904]	3305	3310	3315
[3905]	Thr Pro Val Glu Ser Trp	Glu Glu Ile Pro Tyr	Leu Gly Lys Arg

[3906]	3320	3325	3330
[3907]	Glu Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu Thr Ser Arg Ala		
[3908]	3335	3340	3345
[3909]	Thr Trp Ala Lys Asn Ile Gln Ala Ala Ile Asn Gln Val Arg Ser		
[3910]	3350	3355	3360
[3911]	Leu Ile Gly Asn Glu Glu Tyr Thr Asp Tyr Met Pro Ser Met Lys		
[3912]	3365	3370	3375
[3913]	Arg Phe Arg Arg Glu Glu Glu Glu Ala Gly Val Leu Trp		
[3914]	3380	3385	3390
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[3923]	1 5 10 15		
[3924]	Lys Arg Glu Arg Asn Arg Val Ser Thr Val Gln Gln Leu Thr Lys Arg		
[3925]	20 25 30		
[3926]	Phe Ser Leu Gly Met Leu Gln Gly Arg Gly Pro Leu Lys Leu Phe Met		
[3927]	35 40 45		
[3928]	Ala Leu Val Ala Phe Leu Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly		
[3929]	50 55 60		
[3930]	Ile Leu Lys Arg Trp Gly Thr Ile Lys Lys Ser Lys Ala Ile Asn Val		
[3931]	65 70 75 80		
[3932]	Leu Arg Gly Phe Arg Lys Glu Ile Gly Arg Met Leu Asn Ile Leu Asn		
[3933]	85 90 95		
[3934]	Arg Arg Arg Ser Ser Ala Gly Met Ile Ile Met Leu Ile Pro Thr Val		
[3935]	100 105 110		
[3936]	Met Ala Phe His Leu Thr Thr Arg Asp Gly Glu Pro Leu Met Ile Val		
[3937]	115 120 125		
[3938]	Ala Lys His Glu Arg Gly Arg Pro Leu Leu Phe Lys Thr Thr Glu Gly		
[3939]	130 135 140		
[3940]	Ile Asn Lys Cys Thr Leu Ile Ala Met Asp Leu Gly Glu Met Cys Glu		
[3941]	145 150 155 160		
[3942]	Asp Thr Val Thr Tyr Lys Cys Pro Leu Leu Val Asn Thr Glu Pro Glu		
[3943]	165 170 175		
[3944]	Asp Ile Asp Cys Trp Cys Asn Leu Thr Ser Thr Trp Val Met Tyr Gly		
[3945]	180 185 190		
[3946]	Thr Cys Thr Gln Ser Gly Glu Arg Arg Arg Glu Lys Arg Ser Val Ala		
[3947]	195 200 205		

[3948]	Leu Thr Pro His Ser Gly Met Gly Leu Glu Thr Arg Ala Glu Thr Trp
[3949]	210 215 220
[3950]	Met Ser Ser Glu Gly Ala Trp Lys His Ala Gln Arg Val Glu Ser Trp
[3951]	225 230 235 240
[3952]	Ile Leu Arg Asn Pro Gly Phe Ala Leu Leu Ala Gly Phe Met Ala Tyr
[3953]	245 250 255
[3954]	Met Ile Gly Gln Thr Gly Ile Gln Arg Thr Val Phe Phe Val Leu Met
[3955]	260 265 270
[3956]	Met Leu Val Ala Pro Ser Tyr Gly Met Arg Cys Val Gly Val Gly Asn
[3957]	275 280 285
[3958]	Arg Asp Phe Val Glu Gly Val Ser Gly Gly Ala Trp Val Asp Leu Val
[3959]	290 295 300
[3960]	Leu Glu His Gly Gly Cys Val Thr Thr Met Ala Gln Gly Lys Pro Thr
[3961]	305 310 315 320
[3962]	Leu Asp Phe Glu Leu Thr Lys Thr Thr Ala Lys Glu Val Ala Leu Leu
[3963]	325 330 335
[3964]	Arg Thr Tyr Cys Ile Glu Ala Ser Ile Ser Asn Ile Thr Thr Ala Thr
[3965]	340 345 350
[3966]	Arg Cys Pro Thr Gln Gly Glu Pro Tyr Leu Lys Glu Glu Gln Asp Gln
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[3968]	Gln Tyr Ile Cys Arg Arg Asp Val Val Asp Arg Gly Trp Gly Asn Gly
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[3972]	Cys Ser Gly Lys Ile Thr Gly Asn Leu Val Gln Ile Glu Asn Leu Glu
[3973]	405 410 415
[3974]	Tyr Thr Val Val Val Thr Val His Asn Gly Asp Thr His Ala Val Gly
[3975]	420 425 430
[3976]	Asn Asp Thr Ser Asn His Gly Val Thr Ala Thr Ile Thr Pro Arg Ser
[3977]	435 440 445
[3978]	Pro Ser Val Glu Val Lys Leu Pro Asp Tyr Gly Glu Leu Thr Leu Asp
[3979]	450 455 460
[3980]	Cys Glu Pro Arg Ser Gly Ile Asp Phe Asn Glu Met Ile Leu Met Lys
[3981]	465 470 475 480
[3982]	Met Lys Lys Lys Thr Trp Leu Val His Lys Gln Trp Phe Leu Asp Leu
[3983]	485 490 495
[3984]	Pro Leu Pro Trp Thr Ala Gly Ala Asp Thr Ser Glu Val His Trp Asn
[3985]	500 505 510
[3986]	Tyr Lys Glu Arg Met Val Thr Phe Lys Val Pro His Ala Lys Arg Gln
[3987]	515 520 525
[3988]	Asp Val Thr Val Leu Gly Ser Gln Glu Gly Ala Met His Ser Ala Leu
[3989]	530 535 540

[3990]	Ala Gly Ala Thr Glu Val Asp Ser Gly Asp Gly Asn His Met Phe Ala		
[3991]	545	550	555 560
[3992]	Gly His Leu Lys Cys Lys Val Arg Met Glu Lys Leu Arg Ile Lys Gly		
[3993]	565	570	575
[3994]	Met Ser Tyr Thr Met Cys Ser Gly Lys Phe Ser Ile Asp Lys Glu Met		
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[3996]	Ala Glu Thr Gln His Gly Thr Thr Val Val Lys Val Lys Tyr Glu Gly		
[3997]	595	600	605
[3998]	Ala Gly Ala Pro Cys Lys Val Pro Ile Glu Ile Arg Asp Val Asn Lys		
[3999]	610	615	620
[4000]	Glu Lys Val Val Gly Arg Ile Ile Ser Ser Thr Pro Leu Ala Glu Asn		
[4001]	625	630	635 640
[4002]	Thr Asn Ser Val Thr Asn Ile Glu Leu Glu Pro Pro Phe Gly Asp Ser		
[4003]	645	650	655
[4004]	Tyr Ile Val Ile Gly Val Gly Asn Ser Ala Leu Thr Leu His Trp Phe		
[4005]	660	665	670
[4006]	Arg Lys Gly Ser Ser Ile Gly Lys Met Phe Glu Ser Thr Tyr Arg Gly		
[4007]	675	680	685
[4008]	Ala Lys Arg Met Ala Ile Leu Gly Glu Thr Ala Trp Asp Phe Gly Ser		
[4009]	690	695	700
[4010]	Val Gly Gly Leu Phe Thr Ser Leu Gly Lys Ala Val His Gln Val Phe		
[4011]	705	710	715 720
[4012]	Gly Ser Val Tyr Thr Thr Leu Phe Gly Gly Val Ser Trp Met Ile Arg		
[4013]	725	730	735
[4014]	Ile Leu Ile Gly Phe Leu Val Leu Trp Ile Gly Thr Asn Ser Arg Asn		
[4015]	740	745	750
[4016]	Thr Ser Met Ala Met Thr Cys Ile Ala Ala Gly Ile Val Thr Leu Tyr		
[4017]	755	760	765
[4018]	Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys		
[4019]	770	775	780
[4020]	Asn Lys Glu Leu Lys Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val		
[4021]	785	790	795 800
[4022]	His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys		
[4023]	805	810	815
[4024]	Leu Ala Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile		
[4025]	820	825	830
[4026]	Arg Ser Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro		
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[4028]	Glu Leu Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met		
[4029]	850	855	860
[4030]	Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg		
[4031]	865	870	875 880

[4032]	Pro	Gln	Pro	Thr	Glu	Leu	Lys	Tyr	Ser	Trp	Lys	Thr	Trp	Gly	Lys	Ala
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[4035]						900				905					910	
[4036]	Pro	Glu	Thr	Ala	Glu	Cys	Pro	Asn	Thr	Asn	Arg	Ala	Trp	Asn	Ser	Leu
[4037]						915				920					925	
[4038]	Glu	Val	Glu	Asp	Tyr	Gly	Phe	Gly	Val	Phe	Thr	Thr	Asn	Ile	Trp	Leu
[4039]						930				935					940	
[4040]	Lys	Leu	Lys	Glu	Lys	Gln	Asp	Val	Phe	Cys	Asp	Ser	Lys	Leu	Met	Ser
[4041]	945					950				955					960	
[4042]	Ala	Ala	Ile	Lys	Asp	Asn	Arg	Ala	Val	His	Ala	Asp	Met	Gly	Tyr	Trp
[4043]						965				970					975	
[4044]	Ile	Glu	Ser	Ala	Leu	Asn	Asp	Thr	Trp	Lys	Ile	Glu	Lys	Ala	Ser	Phe
[4045]						980				985					990	
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[4047]						995				1000					1005	
[4048]	Asn	Gly	Val	Leu	Glu	Ser	Glu	Met	Ile	Ile	Pro	Lys	Asn	Leu	Ala	
[4049]						1010				1015					1020	
[4050]	Gly	Pro	Val	Ser	Gln	His	Asn	Tyr	Arg	Pro	Gly	Tyr	His	Thr	Gln	
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[4053]						1040				1045					1050	
[4054]	Phe	Cys	Asp	Gly	Thr	Thr	Val	Val	Val	Thr	Glu	Asp	Cys	Gly	Asn	
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[4062]	Lys	Glu	Lys	Glu	Glu	Asn	Leu	Val	Asn	Ser	Leu	Val	Thr	Ala	Gly	
[4063]						1115				1120					1125	
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[4067]						1145				1150					1155	
[4068]	Ala	Ile	Leu	Leu	Val	Ala	Val	Ser	Phe	Val	Thr	Leu	Ile	Thr	Gly	
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[4070]	Asn	Met	Ser	Phe	Arg	Asp	Leu	Gly	Arg	Val	Met	Val	Met	Val	Gly	
[4071]						1175				1180					1185	
[4072]	Ala	Thr	Met	Thr	Gly	Asp	Ile	Gly	Met	Gly	Val	Thr	Tyr	Leu	Ala	
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[4074]	Leu Leu Ala Ala Phe Lys Val Arg Pro Thr Phe Ala Ala Gly Leu
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[4076]	Leu Leu Arg Lys Leu Thr Ser Arg Glu Leu Met Met Thr Thr Ile
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[4079]	1235 1240 1245
[4080]	Glu Leu Thr Asp Ala Leu Ala Leu Gly Met Met Val Leu Lys Met
[4081]	1250 1255 1260
[4082]	Val Arg Asn Met Glu Lys Tyr Gln Leu Ala Val Thr Ile Met Ala
[4083]	1265 1270 1275
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[4085]	1280 1285 1290
[4086]	Val Ser Cys Thr Ile Leu Ala Val Val Ser Val Ser Pro Leu Phe
[4087]	1295 1300 1305
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[4092]	Ser Arg Thr Ser Lys Lys Arg Ser Trp Pro Leu Asn Glu Ala Ile
[4093]	1340 1345 1350
[4094]	Met Ala Val Gly Met Val Ser Ile Leu Ala Ser Ser Leu Leu Lys
[4095]	1355 1360 1365
[4096]	Asn Asp Ile Pro Met Thr Gly Pro Leu Val Ala Gly Gly Leu Leu
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[4098]	Thr Val Cys Tyr Val Leu Thr Gly Arg Ser Ala Asp Leu Glu Leu
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[4116]	Gly Thr Phe His Thr Met Trp His Val Thr Arg Gly Ala Val Leu		
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[4118]	Met His Lys Gly Lys Arg Ile Glu Pro Ser Trp Ala Asp Val Lys		
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[4120]	Lys Asp Leu Ile Ser Tyr Gly Gly Gly Trp Lys Leu Glu Gly Glu		
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[4122]	Trp Lys Glu Gly Glu Glu Val Gln Val Leu Ala Leu Glu Pro Gly		
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[4124]	Lys Asn Pro Arg Ala Val Gln Thr Lys Pro Gly Leu Phe Lys Thr		
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[4126]	Asn Ala Gly Thr Ile Gly Ala Val Ser Leu Asp Phe Ser Pro Gly		
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[4128]	Thr Ser Gly Ser Pro Ile Ile Asp Lys Lys Gly Lys Val Val Gly		
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[4130]	Leu Tyr Gly Asn Gly Val Val Thr Arg Ser Gly Ala Tyr Val Ser		
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[4132]	Ala Ile Ala Gln Thr Glu Lys Ser Ile Glu Asp Asn Pro Glu Ile		
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[4134]	Glu Asp Asp Ile Phe Arg Lys Arg Arg Leu Thr Ile Met Asp Leu		
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[4136]	His Pro Gly Ala Gly Lys Thr Lys Arg Tyr Leu Pro Ala Ile Val		
[4137]	1670	1675	1680
[4138]	Arg Glu Ala Ile Lys Arg Gly Leu Arg Thr Leu Ile Leu Ala Pro		
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[4140]	Thr Arg Val Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu		
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[4142]	Pro Ile Arg Tyr Gln Thr Pro Ala Ile Arg Ala Val His Thr Gly		
[4143]	1715	1720	1725
[4144]	Arg Glu Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Met Arg		
[4145]	1730	1735	1740
[4146]	Leu Leu Ser Pro Val Arg Val Pro Asn Tyr Asn Leu Ile Ile Met		
[4147]	1745	1750	1755
[4148]	Asp Glu Ala His Phe Thr Asp Pro Ala Ser Ile Ala Ala Arg Gly		
[4149]	1760	1765	1770
[4150]	Tyr Ile Ser Thr Arg Val Glu Met Gly Glu Ala Ala Gly Ile Phe		
[4151]	1775	1780	1785
[4152]	Met Thr Ala Thr Pro Pro Gly Ser Arg Asp Pro Phe Pro Gln Ser		
[4153]	1790	1795	1800
[4154]	Asn Ala Pro Ile Ile Asp Glu Glu Arg Glu Ile Pro Glu Arg Ser		
[4155]	1805	1810	1815
[4156]	Trp Asn Ser Gly His Glu Trp Val Thr Asp Phe Lys Gly Lys Thr		
[4157]	1820	1825	1830

[4158]	Val Trp Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile Ala Ala
[4159]	1835 1840 1845
[4160]	Cys Leu Arg Lys Asn Gly Lys Lys Val Ile Gln Leu Ser Arg Lys
[4161]	1850 1855 1860
[4162]	Thr Phe Asp Ser Glu Tyr Val Lys Thr Arg Thr Asn Asp Trp Asp
[4163]	1865 1870 1875
[4164]	Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys
[4165]	1880 1885 1890
[4166]	Ala Glu Arg Val Ile Asp Pro Arg Arg Cys Met Lys Pro Val Ile
[4167]	1895 1900 1905
[4168]	Leu Thr Asp Gly Glu Glu Arg Val Ile Leu Ala Gly Pro Met Pro
[4169]	1910 1915 1920
[4170]	Val Thr His Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg
[4171]	1925 1930 1935
[4172]	Asn Pro Lys Asn Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu Pro
[4173]	1940 1945 1950
[4174]	Leu Glu Asn Asp Glu Asp Cys Ala His Trp Lys Glu Ala Lys Met
[4175]	1955 1960 1965
[4176]	Leu Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile Pro Ser Met
[4177]	1970 1975 1980
[4178]	Phe Glu Pro Glu Arg Glu Lys Val Asp Ala Ile Asp Gly Glu Tyr
[4179]	1985 1990 1995
[4180]	Arg Leu Arg Gly Glu Ala Arg Lys Thr Phe Val Asp Leu Met Arg
[4181]	2000 2005 2010
[4182]	Arg Gly Asp Leu Pro Val Trp Leu Ala Tyr Arg Val Ala Ala Glu
[4183]	2015 2020 2025
[4184]	Gly Ile Asn Tyr Ala Asp Arg Arg Trp Cys Phe Asp Gly Val Lys
[4185]	2030 2035 2040
[4186]	Asn Asn Gln Ile Leu Glu Glu Asn Val Glu Val Glu Ile Trp Thr
[4187]	2045 2050 2055
[4188]	Lys Glu Gly Glu Arg Lys Lys Leu Lys Pro Arg Trp Leu Asp Ala
[4189]	2060 2065 2070
[4190]	Arg Ile Tyr Ser Asp Pro Leu Ala Leu Lys Glu Phe Lys Glu Phe
[4191]	2075 2080 2085
[4192]	Ala Ala Gly Arg Lys Ser Leu Thr Leu Asn Leu Ile Thr Glu Met
[4193]	2090 2095 2100
[4194]	Gly Arg Leu Pro Thr Phe Met Thr Gln Lys Val Arg Asp Ala Leu
[4195]	2105 2110 2115
[4196]	Asp Asn Leu Ala Val Leu His Thr Ala Glu Ala Gly Gly Arg Ala
[4197]	2120 2125 2130
[4198]	Tyr Asn His Ala Leu Ser Glu Leu Pro Glu Thr Leu Glu Thr Leu
[4199]	2135 2140 2145

[4200]	Leu Leu Leu Thr Leu Leu Ala Thr Val Thr Gly Gly Ile Phe Leu		
[4201]	2150	2155	2160
[4202]	Phe Leu Met Ser Ala Arg Gly Ile Gly Lys Met Thr Leu Gly Met		
[4203]	2165	2170	2175
[4204]	Cys Cys Ile Ile Thr Ala Ser Ile Leu Leu Trp Tyr Ala Gln Ile		
[4205]	2180	2185	2190
[4206]	Gln Pro His Trp Ile Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu		
[4207]	2195	2200	2205
[4208]	Ile Val Leu Leu Ile Pro Glu Pro Glu Lys Gln Arg Thr Pro Gln		
[4209]	2210	2215	2220
[4210]	Asp Asn Gln Leu Thr Tyr Val Val Ile Ala Ile Leu Thr Val Val		
[4211]	2225	2230	2235
[4212]	Ala Ala Thr Met Ala Asn Glu Met Gly Phe Leu Glu Lys Thr Lys		
[4213]	2240	2245	2250
[4214]	Lys Asp Leu Gly Leu Gly Ser Ile Ala Thr Gln Gln Pro Glu Ser		
[4215]	2255	2260	2265
[4216]	Asn Ile Leu Asp Ile Asp Leu Arg Pro Ala Ser Ala Trp Thr Leu		
[4217]	2270	2275	2280
[4218]	Tyr Ala Val Ala Thr Thr Phe Val Thr Pro Met Leu Arg His Ser		
[4219]	2285	2290	2295
[4220]	Ile Glu Asn Ser Ser Val Asn Val Ser Leu Thr Ala Ile Ala Asn		
[4221]	2300	2305	2310
[4222]	Gln Ala Thr Val Leu Met Gly Leu Gly Lys Gly Trp Pro Leu Ser		
[4223]	2315	2320	2325
[4224]	Lys Met Asp Ile Gly Val Pro Leu Leu Ala Ile Gly Cys Tyr Ser		
[4225]	2330	2335	2340
[4226]	Gln Val Asn Pro Ile Thr Leu Thr Ala Ala Leu Phe Leu Leu Val		
[4227]	2345	2350	2355
[4228]	Ala His Tyr Ala Ile Ile Gly Pro Gly Leu Gln Ala Lys Ala Thr		
[4229]	2360	2365	2370
[4230]	Arg Glu Ala Gln Lys Arg Ala Ala Ala Gly Ile Met Lys Asn Pro		
[4231]	2375	2380	2385
[4232]	Thr Val Asp Gly Ile Thr Val Ile Asp Leu Asp Pro Ile Pro Tyr		
[4233]	2390	2395	2400
[4234]	Asp Pro Lys Phe Glu Lys Gln Leu Gly Gln Val Met Leu Leu Val		
[4235]	2405	2410	2415
[4236]	Leu Cys Val Thr Gln Val Leu Met Met Arg Thr Thr Trp Ala Leu		
[4237]	2420	2425	2430
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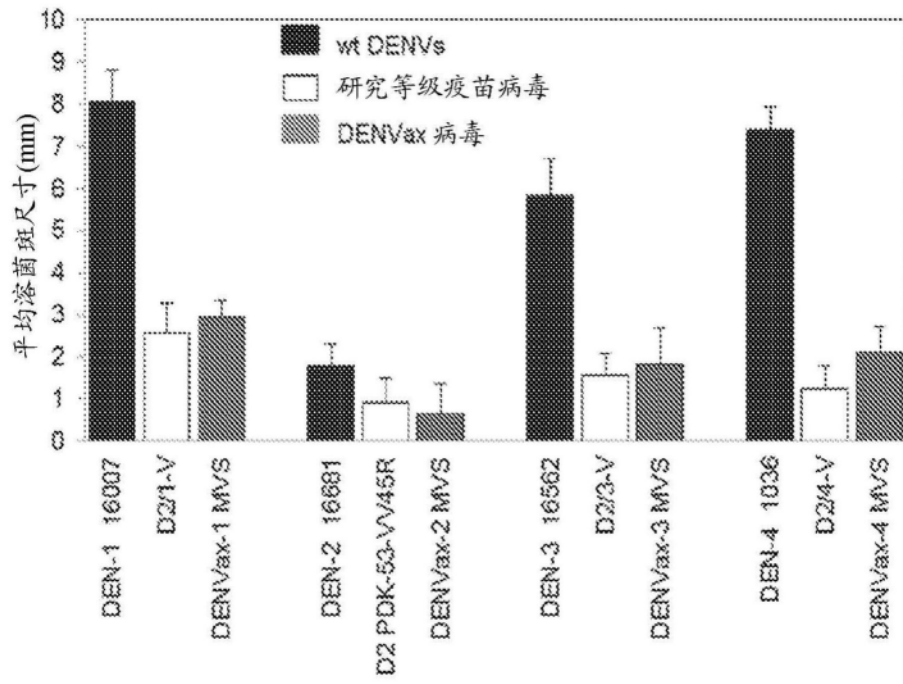


图2

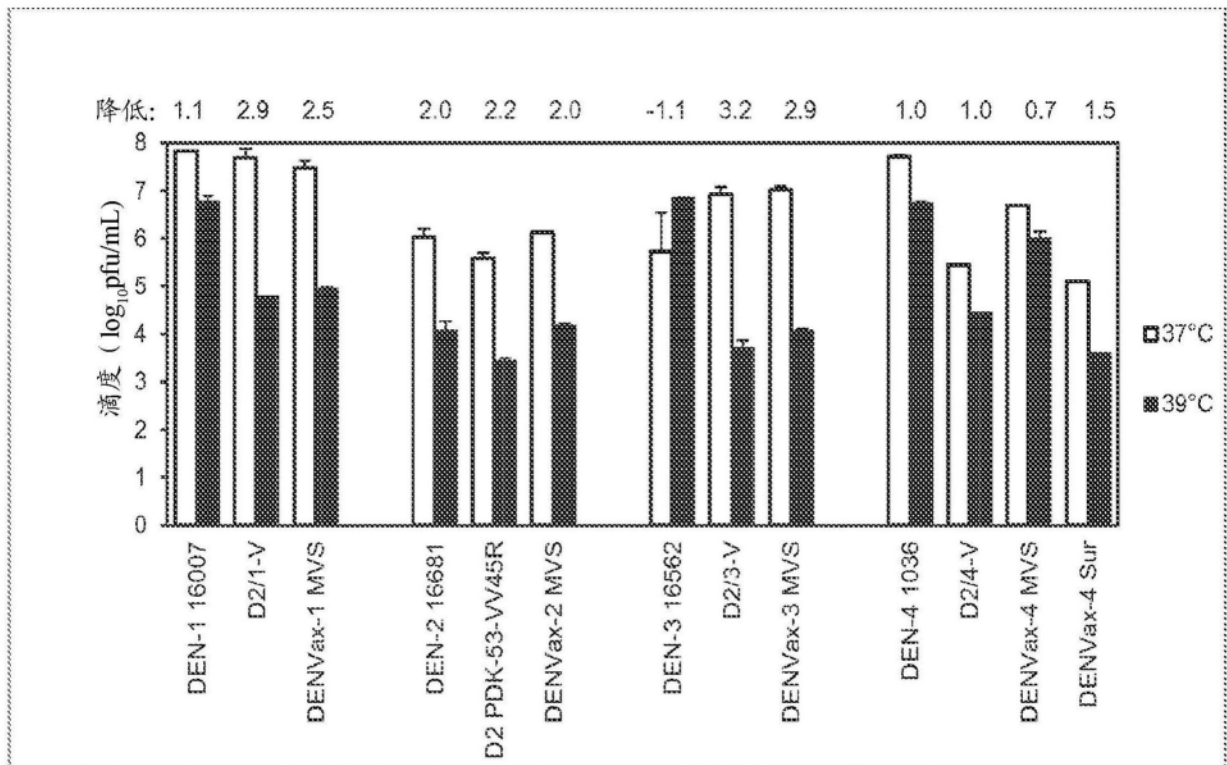


图3

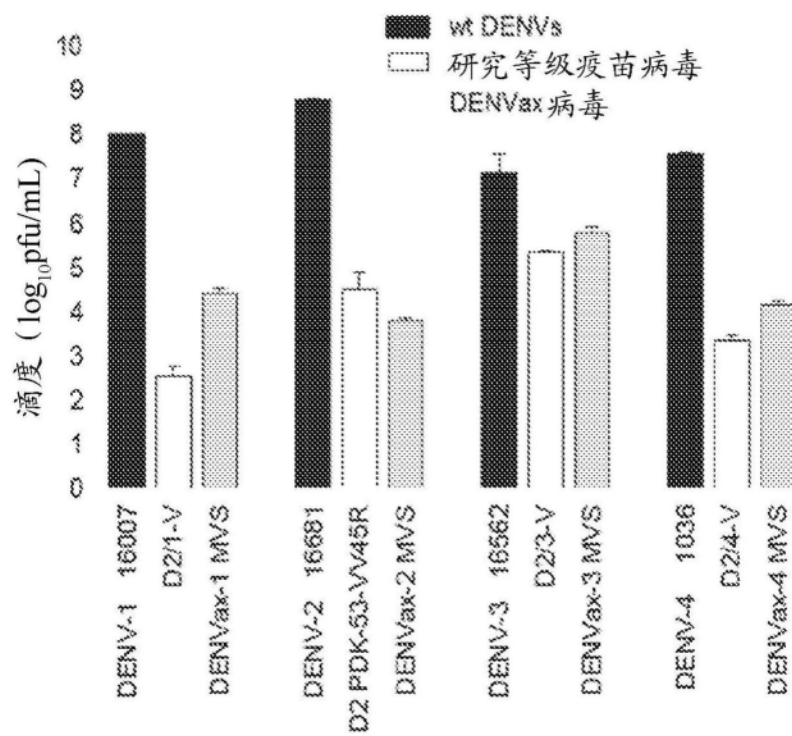


图4

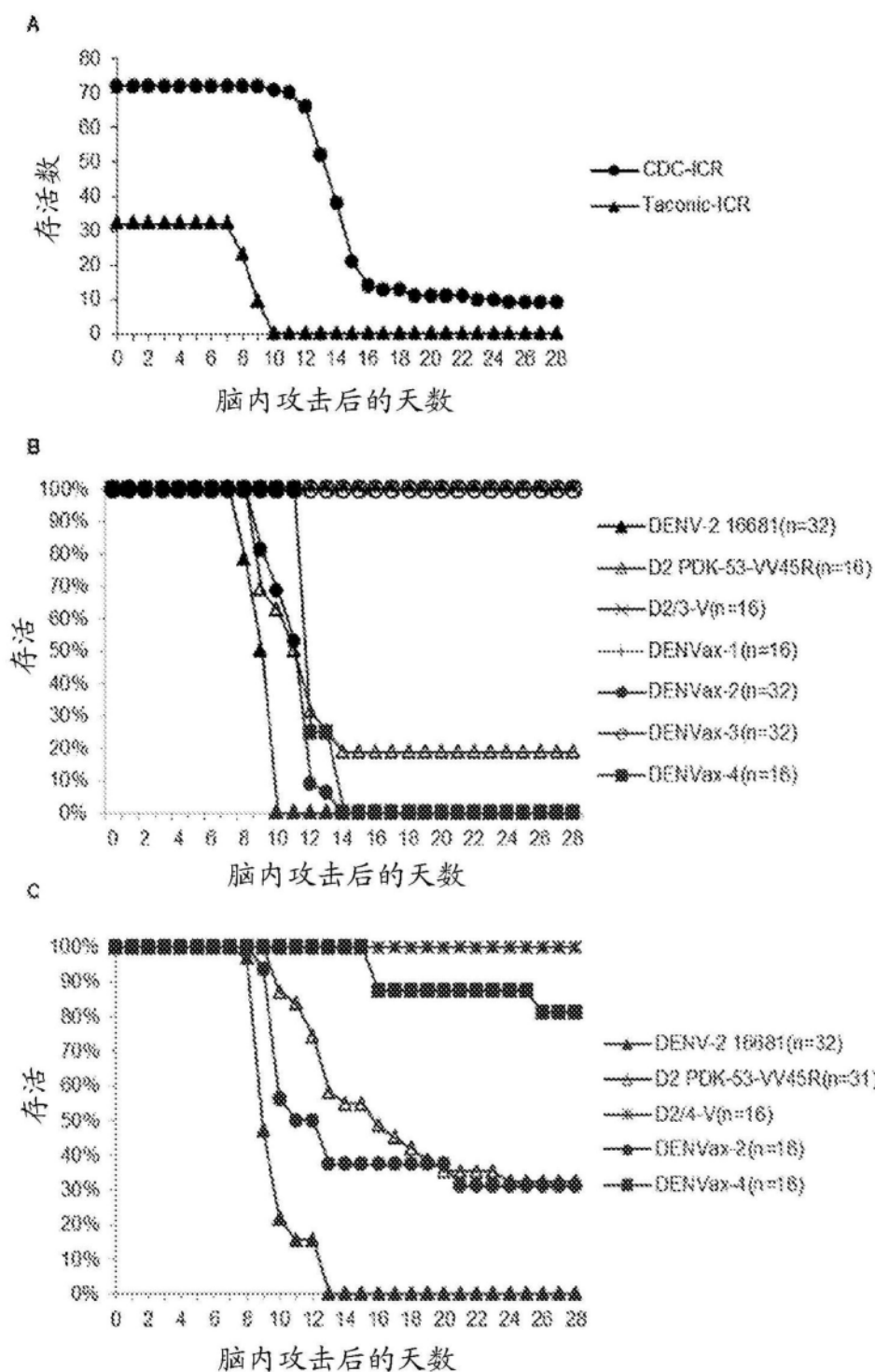


图5

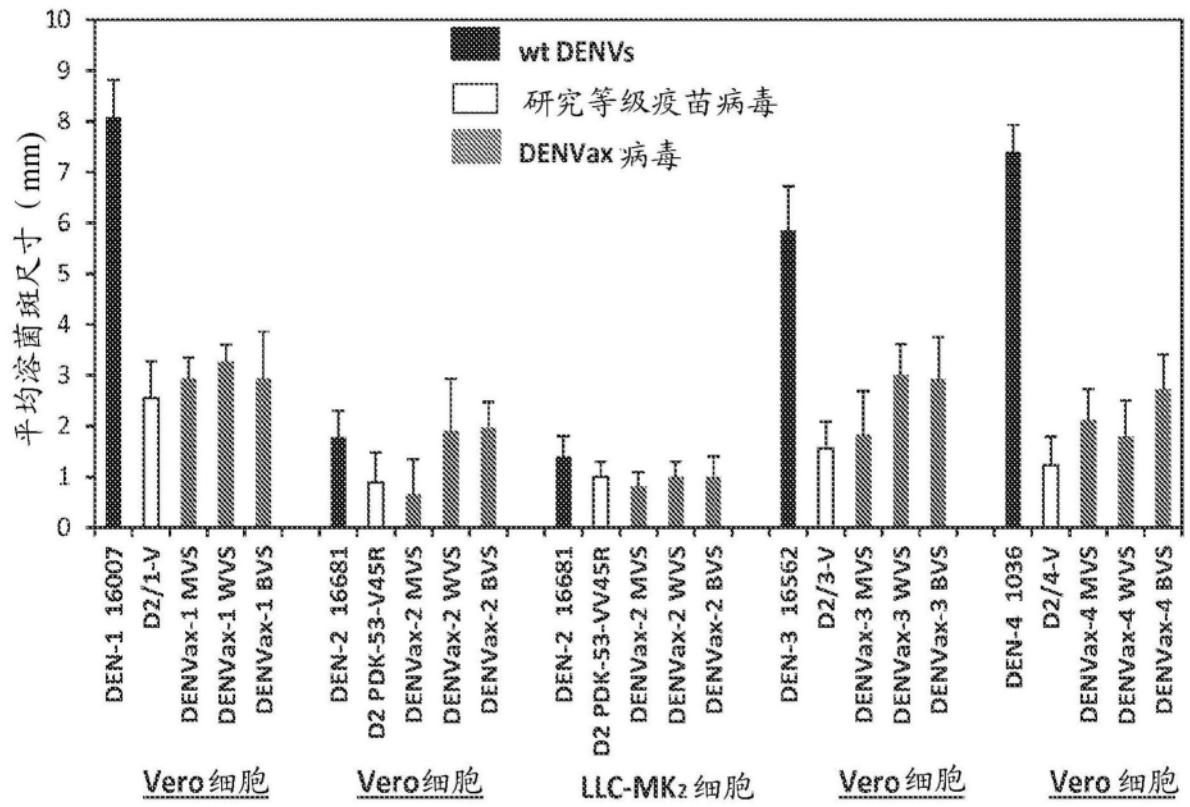


图6

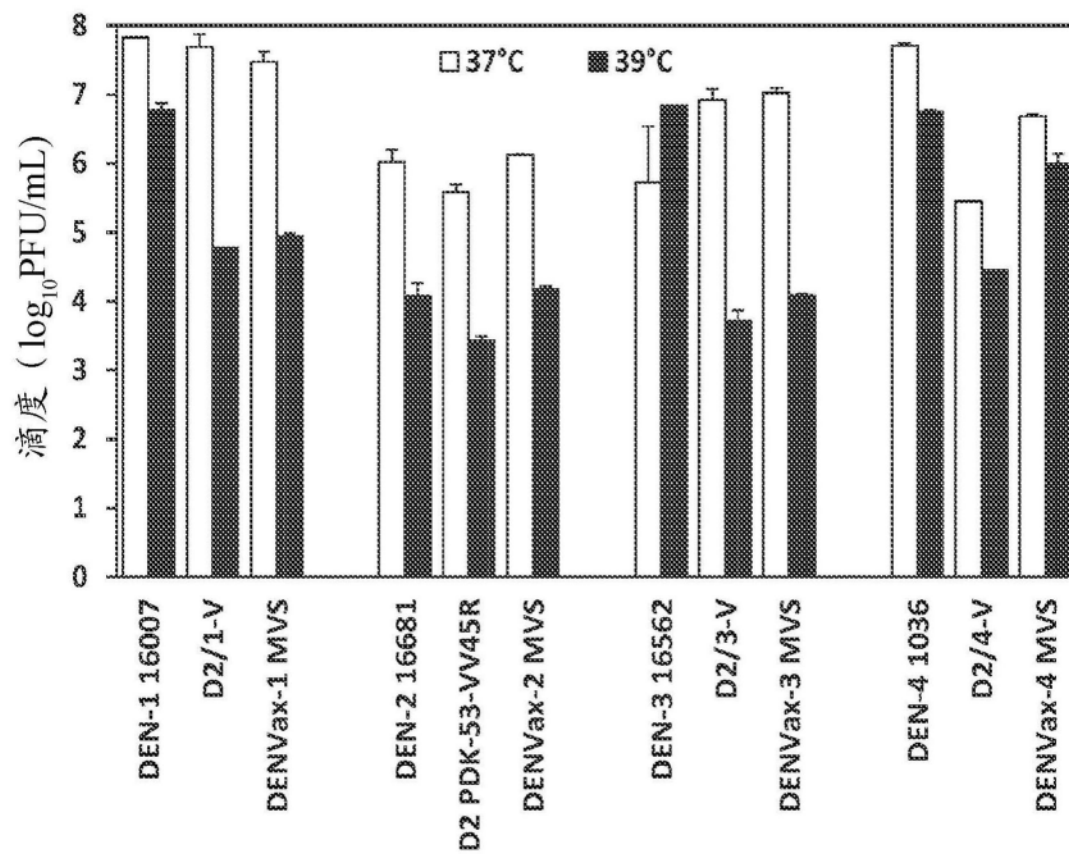


图7

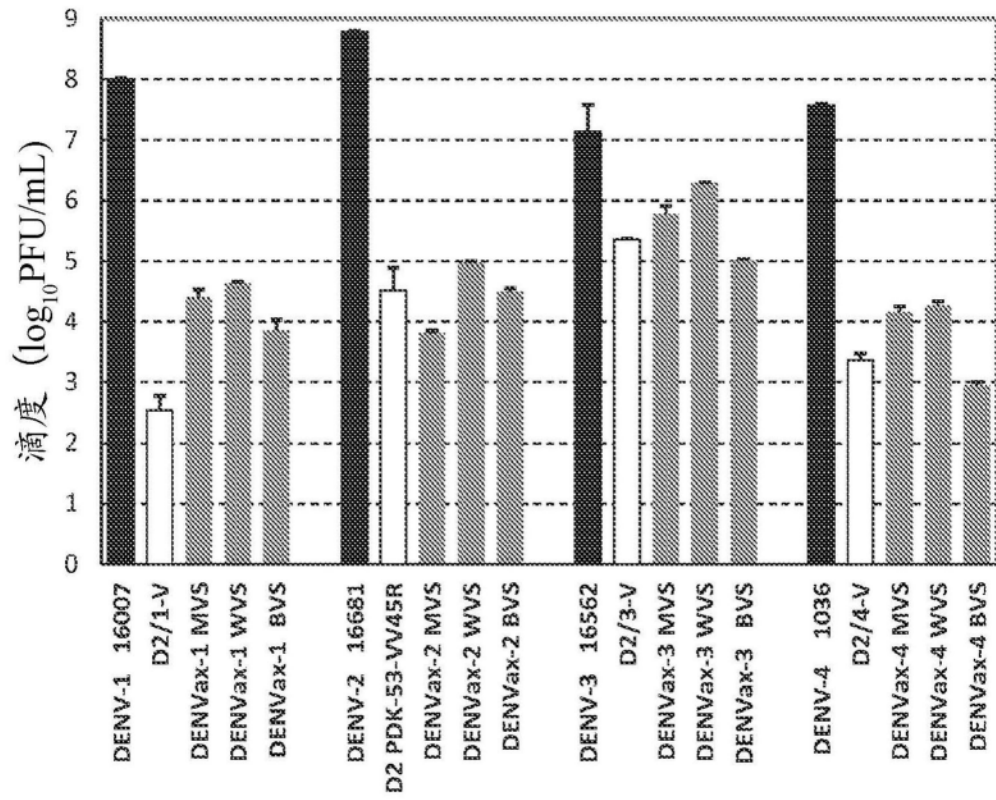


图8

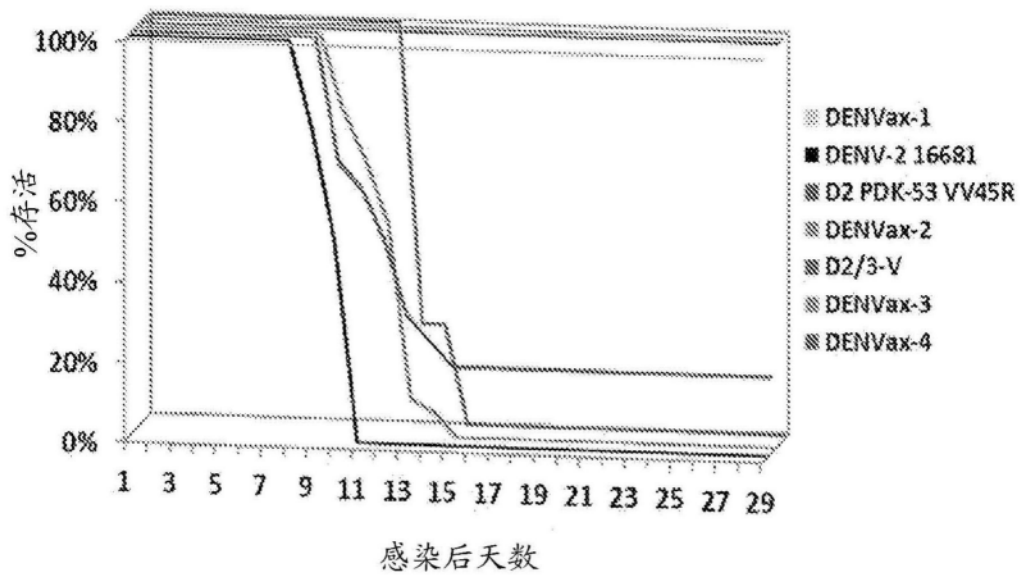
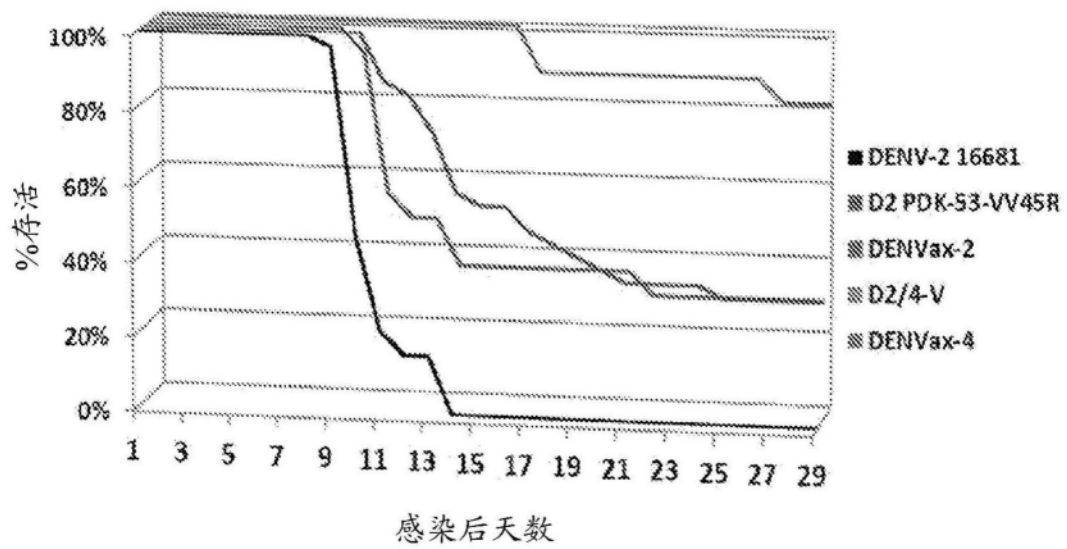
A**B**

图9

血清型	株	病毒来源	C571	A324T	3909G ^a	C205T	G2572A	C4018T	A32703	T3547C	G4896C	C5371T
			WT	WT	WT	E (沉默)	NS3-GS3D	NS2A-I181	NS3-E340V	NS3 (沉默)	NS2A-Q75A	NS3 (沉默)
16881		从人体分离	C	A	T	C	G	C	A	T	G	C
PDK-53		16881的PDK细胞传代	T	T	..	T	A	T	TAAG	T	C	T
PDK-53-V1V45R		重组PDK-53-V	T	T	G	T	A	T	T	C	C	C
PDK-53-E1VE45R		重组PDK-53-E	T	T	C	T	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16881变化)
粗体：PDK-53克隆体衍生的V或E病毒之间的不同核苷酸序列
^a用于区别原始PDK-53与重组 (克隆体衍生) 的病毒而改进的沉默克隆体标记

图10