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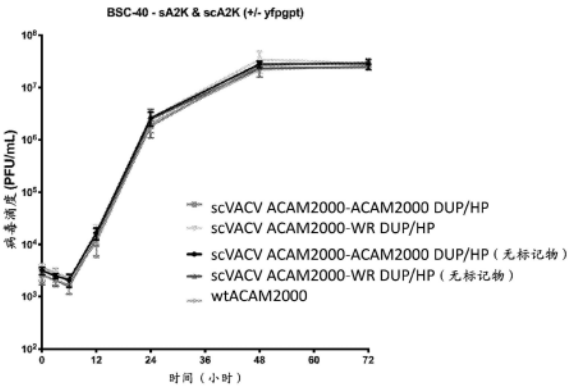
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(54)发明名称

合成嵌合痘苗病毒

(57)摘要

本发明在各个方面涉及合成嵌合痘苗病毒或包含该病毒的组合物,以及用于产生该合成嵌合痘苗病毒的系统和方法的开发与应用。该合成嵌合痘苗病毒尤其非常适合作为病毒疫苗或产生溶瘤反应和药物制剂。



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1.一种合成嵌合痘苗病毒(scVACV),所述scVACV是从源于化学合成的DNA的DNA复制和再激活的,所述scVACV的基因组不同于选自由以下各项组成的组的痘苗病毒(VACV)株的对应野生型基因组:Western Reserve(WR)、克隆3、Tian Tian、Tian Tian克隆TP5、Tian Tian克隆TP3、NYCBH、NYCBH克隆Acambis 2000、Wyeth、Copenhagen、Lister、Lister 107、Lister-LO、Lister GL-ONC1、Lister GL-ONC2、Lister GL-ONC3、Lister GL-ONC4、Lister CTC1、Lister IMG2 (Turbo FP635)、IHD-W、LC16m18、Lederle、Tashkent克隆TKT3、Tashkent克隆TKT4、USSR、Evans、Praha、L-IVP、V-VET1或LIVP 6.1.1、Ikeda、EM-63、Malbran、Duke、3737、CV-1、Connaught Laboratories、Serro 2、CM-01、NYCBH Dryvax、VACV-IOC、安卡拉绒毛膜尿囊痘苗病毒(CVA)、改良的安卡拉痘苗病毒(MVA)和MVA-BN,其中所述不同在于所述scVACV的特征在于左侧末端发夹环和右侧末端发夹环,所述左侧末端发夹环和右侧末端发夹环源于化学合成的DNA,与所述scVACV的对应野生型的末端发夹环相比,所述scVACV的末端发夹环中的一个或两个是异源的,所述环独立地来源于痘苗病毒,并且其中与对应的野生型末端发夹环相比,所述末端发夹环中的一个或两个包含不同的串联重复区或不同数量的串联重复区。

2.根据权利要求1所述的scVACV,其中所述scVACV还包含消除一个或多个独特的限制位点的一个或多个修饰。

3.根据权利要求1所述的scVACV,其中所述scVACV还包含添加或修复一个或多个独特的限制位点的一个或多个修饰。

4.根据权利要求2所述的scVACV,其中所述消除一个或多个独特的限制位点的一个或多个修饰包括消除一个或多个AarI限制位点。

5.根据权利要求2所述的scVACV,其中所述消除一个或多个独特的限制位点的一个或多个修饰包括消除一个或多个BsaI限制位点。

6.根据权利要求1所述的scVACV,其中异源末端发夹环中的一个或两个来源于选自由以下各项组成的组的痘苗病毒株:Western Reserve(WR)、克隆3、Tian Tian、Tian Tian克隆TP5、Tian Tian克隆TP3、NYCBH、NYCBH克隆Acambis 2000、Wyeth、Copenhagen、Lister、Lister 107、Lister-LO、Lister GL-ONC1、Lister GL-ONC2、Lister GL-ONC3、Lister GL-ONC4、Lister CTC1、Lister IMG2 (Turbo FP635)、IHD-W、LC16m18、Lederle、Tashkent克隆TKT3、Tashkent克隆TKT4、USSR、Evans、Praha、L-IVP、V-VET1或LIVP 6.1.1、Ikeda、EM-63、Malbran、Duke、3737、CV-1、Connaught Laboratories、Serro 2、CM-01、NYCBH Dryvax克隆DPP13、NYCBH Dryvax克隆DPP15、NYCBH Dryvax克隆DPP20、NYCBH Dryvax克隆DPP17、NYCBH Dryvax克隆DPP21、VACV-IOC、安卡拉绒毛膜尿囊痘苗病毒(CVA)、改良的安卡拉痘苗病毒(MVA)和MVA-BN。

7.根据权利要求6所述的scVACV,其中异源末端发夹环中的一个或两个来源于VACV Western Reserve(WR)株。

8.根据权利要求1所述的scVACV,其中所述VACV株的野生型基因组是NYCBH克隆Acambis 2000的基因组。

9.根据权利要求1所述的scVACV,其中所述NYCBH Dryvax选自由以下各项组成的组:NYCBH Dryvax克隆DPP13、NYCBH Dryvax克隆DPP15、NYCBH Dryvax克隆DPP20、NYCBH Dryvax克隆DPP17和NYCBH Dryvax克隆DPP21。

10.根据权利要求1所述的scVACV,其中所述VACV株的野生型基因组是V-VET1的基因组。

11.根据权利要求1所述的scVACV,其中所述VACV株的野生型基因组是改良的安卡拉痘苗病毒(MVA)的基因组。

12.根据权利要求1所述的scVACV,其中所述VACV株的野生型基因组是MVA-BN的基因组。

13.根据权利要求1所述的scVACV,其中所述VACV株的野生型基因组是VACV-IOC的基因组。

14.根据权利要求7所述的scVACV,其中异源末端发夹环中的一个或两个独立地选自痘苗病毒末端发夹环的慢速形式和快速形式。

15.根据权利要求14所述的scVACV,其中所述慢速形式包含与SEQ ID NO: 13的核苷酸序列至少85%相同的核苷酸序列,并且所述快速形式包含与SEQ ID NO: 14的核苷酸序列至少85%相同的核苷酸序列。

16.根据权利要求14所述的scVACV,其中所述慢速形式包含与SEQ ID NO: 13的序列至少90%相同的核苷酸序列,并且所述快速形式包含与SEQ ID NO: 14的核苷酸序列至少90%相同的核苷酸序列。

17.根据权利要求14所述的scVACV,其中所述慢速形式包含与SEQ ID NO: 13的核苷酸序列至少95%相同的核苷酸序列,并且所述快速形式包含与SEQ ID NO: 14的核苷酸序列至少95%相同的核苷酸序列。

18.根据权利要求14所述的scVACV,其中所述慢速形式由SEQ ID NO: 13的核苷酸序列组成,并且所述快速形式由SEQ ID NO: 14的核苷酸序列组成。

19.根据权利要求1至18中任一项所述的scVACV,其中所述scVACV是从源于重叠的化学合成的DNA片段的DNA和源于与左侧末端发夹环和右侧末端发夹环对应的化学合成的DNA的DNA复制和再激活的,所述重叠的化学合成的DNA片段与痘苗病毒的对应野生型基因组不同。

20.根据权利要求19所述的scVACV,其中所述重叠的化学合成的DNA片段包含2-14个重叠片段。

21.根据权利要求20所述的scVACV,其中所述重叠的化学合成的DNA片段包含6-12个重叠片段。

22.根据权利要求21所述的scVACV,其中所述重叠的化学合成的DNA片段包含9个重叠片段。

23.根据权利要求1所述的scVACV,其中使用野兔痘病毒催化的重组和再激活来再激活所述scVACV。

24.根据权利要求23所述的scVACV,其中所述野兔痘病毒选自由以下各项组成的组:休普氏纤维瘤病毒(SFV)、野兔纤维瘤病毒、家兔纤维瘤病毒、松鼠纤维瘤病毒和粘液瘤病毒。

25.一种制备合成嵌合痘苗病毒(scVACV)的方法,其包括以下步骤:

(i) 化学合成重叠DNA片段,所述重叠DNA片段对应于选自由以下各项组成的组的野生型痘苗病毒:Western Reserve(WR)、克隆3、Tian Tian、Tian Tian克隆TP5、Tian Tian克隆TP3、NYCBH、NYCBH克隆Acambis 2000、Wyeth、Copenhagen、Lister、Lister 107、Lister-LO、

Lister GL-ONC1、Lister GL-ONC2、Lister GL-ONC3、Lister GL-ONC4、Lister CTC1、Lister IMG2 (Turbo FP635)、IHD-W、LC16m18、Lederle、Tashkent克隆TKT3、Tashkent克隆TKT4、USSR、Evans、Praha、L-IVP、V-VET1或LIVP 6.1.1、Ikeda、EM-63、Malbran、Duke、3737、CV-1、Connaught Laboratories、Serro 2、CM-01、NYCBH Dryvax、VACV-IOC、安卡拉绒毛膜尿囊痘苗病毒(CVA)、改良的安卡拉痘苗病毒(MVA)和MVA-BN;

(ii) 化学合成DNA,所述DNA对应于:

(a) 痘苗病毒的左侧末端发夹环和痘苗病毒的右侧末端发夹环;或

(b) 痘苗病毒的左侧末端发夹环和痘苗病毒的右侧末端发夹环,其中与对应的野生型末端发夹环相比,所述末端发夹环中的一个或两个包含不同的串联重复区或不同数量的串联重复区,

其中与对应的野生型痘苗病毒的末端发夹环相比,(a)和(b)中的所述末端发夹环中的一个或两个是异源的,和

将源于(a)或(b)的化学合成的DNA的末端发夹环连接至源于步骤(i)的化学合成的DNA的重叠DNA片段的左侧末端和右侧末端;

(iii) 将来自步骤(ii)的所连接的DNA转染到辅助病毒感染的细胞中;

(iv) 培养所述细胞以在所述细胞中产生辅助病毒和scVACV颗粒的混合物;和

(v) 将混合物铺板在对所述scVACV具有特异性的宿主细胞上以回收scVACV。

26.根据权利要求25所述的方法,其中所述辅助病毒选自由以下各项组成的组:野兔痘病毒、禽痘病毒和补骨脂素灭活的辅助病毒。

27.根据权利要求26所述的方法,其中所述野兔痘病毒选自由以下各项组成的组:休普氏纤维瘤病毒(SFV)、野兔纤维瘤病毒、家兔纤维瘤病毒、松鼠纤维瘤病毒和粘液瘤病毒。

28.根据权利要求25所述的方法,其中所述辅助病毒感染的细胞是BGMK细胞。

29.根据权利要求25至28中任一项所述的方法,其中所述重叠DNA片段包含:

(i) 与SEQ ID NO: 1-9的序列至少85%相同的核苷酸序列;

(ii) 与SEQ ID NO: 1-9的序列至少90%相同的核苷酸序列;

(iii) 与SEQ ID NO: 1-9的序列至少95%相同的核苷酸序列;或

(iv) 由SEQ ID NO: 1-9的序列组成的核苷酸序列。

30.一种药物组合物,其包含权利要求1至24中任一项所述的scVACV和药学上可接受的载体。

31.根据权利要求30所述的药物组合物,其中所述scVACV是灭活的。

32.根据权利要求31所述的药物组合物,其中所述灭活是通过加热、UV或福尔马林进行的。

33.包含权利要求1至24中任一项所述的scVACV的组合物或权利要求30至32中任一项所述的药物组合物在制备药物中的用途,其中所述药物用于触发或增强针对痘苗病毒、天花病毒和猴痘病毒中一种或多种的免疫反应。

34.包含权利要求1至24中任一项所述的scVACV的组合物或权利要求30至32中任一项所述的药物组合物在制备药物中的用途,其中所述药物用于对人受试者免疫接种以保护所述受试者免于天花病毒感染、痘苗病毒感染和猴痘病毒感染中的一种或多种。

35.包含权利要求1至24中任一项所述的scVACV的组合物或权利要求30至32中任一项

所述的药物组合物在制备用药物中的用途,其中所述药物用于治疗天花病毒感染、痘苗病毒感染和猴痘病毒感染中的一种或多种。

36.根据权利要求33至35中任一项所述的用途,其中包含所述scVACV的组合物或所述药物组合物配制成用于皮肤划痕、肌内或静脉内施用。

合成嵌合痘苗病毒

背景技术

[0001] 与本申请相关的序列表通过EFS-Web以文本格式电子提交,并且由此通过引用完整地结合到说明书中。含有序列表的文本文件的名称为104545-0031-WO-SequenceListing.txt。文本文件在2019年5月2日创建,大小为288,652字节。

[0002] 痘病毒(痘病毒科(Poxviridae)的成员)是可感染人和动物两者的双链DNA病毒。痘病毒基于宿主范围分为两个亚科。感染脊椎动物宿主的脊椎动物痘病毒(Chordopoxviridae)亚科由八个属组成,已知其中的四个属(正痘病毒属(Orthopoxvirus)、副痘病毒属(Parapoxvirus)、软疣痘病毒属(Molluscipoxvirus)和亚塔痘病毒属(Yatapoxvirus))会感染人类。天花是由天花病毒(variola virus,VARV)感染引起,所述天花病毒是正痘病毒属(OPV)的成员。OPV属包括许多遗传上相关且形态上相同的病毒,包括骆驼痘病毒(camelpox virus,CMLV)、牛痘病毒(cowpox virus,CPXV)、鼠痘病毒(ectromelia virus,ECTV、“鼠痘试剂”)、马痘病毒(horsepox virus,HPXV)、猴痘病毒(monkeypox virus,MPXV)、兔痘病毒(rabbitpox virus,RPXV)、浣熊痘病毒(raccoonpox virus)、臭鼬痘病毒(skunkpox virus)、沙鼠痘病毒(Taterapox virus)、瓦辛吉舒病病毒(Uasin Gishu disease virus)、痘苗病毒(vaccinia virus,VACV)、天花病毒(variola virus,VARV)和田鼠痘病毒(volepox virus,VPV)。除了VARV以外,已知至少三种其他OPV(包括VACV、MPXV和CPXV)会感染人类。迄今,用“活”VACV疫苗接种是唯一经证实可以抵御天花的保护。一项积极的疫苗接种计划导致于1980年消灭了天花,停止了公众的常规天花疫苗接种。然而,仍然需要寻找针对VARV和其他OPV的新的安全且有效的个体疫苗接种的方法。

[0003] VACV的多种制剂已经用作天花疫苗。这些疫苗中的大多数由多种相关病毒组成(例如,Dryvax),并且一种包含单个分子克隆ACAM2000。然而,类似Dryvax和其他VACV疫苗,甚至ACAM2000也与包括心肌病和心包炎的严重副作用相关。为了降低风险,ACAM2000疫苗与其他活疫苗相似,具有许多禁忌,排除患有癌症、免疫缺陷症的个体、器官移植受者、患有特应性皮炎、湿疹、银屑病、心脏病的患者和服用免疫抑制剂的患者。据估计,15-50%的美国人群属于这些类别之一,证实需要开发更安全的疫苗或疫苗接种方案(Kennedy等,2007Kennedy R,Poland GA.2007.T-Cell epitope discovery for variola and vaccinia viruses.Rev Med Viroll7:93-113)。因此,需要开发一种功效类似于Dryvax或ACAM2000™但是更安全的疫苗。

[0004] 生产安全、纯净、强力和有效的疫苗需要品质保证程序以保证疫苗生产过程的一致性和连贯性。过去,含胚胎的鸡蛋或初级鸡胚胎成纤维细胞培养物已经用于培养病毒以制备抵御黄热病、流感、麻疹和腮腺炎的疫苗。这些基质被认为是可接受的,因为认为可感染鸡的外源因子将不感染人类且不对人类致病(FDA简报文件疫苗和相关生物产品咨询委员会会议(FDA Briefing Document Vaccines and Related Biological Products Advisory Committee Meeting),2012年9月19日)。然而,如果病毒嗜性变化,则可损害安全性。

[0005] 其他基质已经用于培养用于生产疫苗的病毒,诸如用于天花疫苗的小牛淋巴。在小牛接种天花后,提取含有白细胞的淋巴并将其保存在毛细管中。随后将这用于人的疫苗接种以预防天花。然而,存在被牛海绵状脑病或羊瘙痒病朊病毒污染的风险。尽管用于现代疫苗的规定和指南表明所有使用的材料必须来自无BSE的地区,但是没有关于无羊瘙痒病区域状态的任何规定和指南。特别关注的事实是在1980-1982年生产的Dryvax疫苗没有通过现代方法细察。具体地,这些储液没有进行关于外源因子的测试(Murphy和Osburn.Emerging Infectious Diseases.www.cdc.gov/eid.卷11,No.7,2005年7月)。

[0006] 因此,需要开发一种疫苗,其功效类似于现有的Dryvax或ACAM2000™疫苗,但是更安全、可复制并且不含残余细胞、残余DNA、朊病毒和外源因子。

[0007] 本申请提供从化学合成的DNA组装和复制的嵌合痘苗病毒,其是安全的、可复制的且不含污染物。因为化学基因组合成不依赖于天然模板,所以病毒基因组的多种结构和功能性修饰是可能的。当没有天然模板可用于遗传复制或通过常规分子生物学方法修饰时,化学基因组合成是尤其有用的。

[0008] 发明概述

[0009] 本发明的一个方面提供合成嵌合痘苗病毒、用于产生此类病毒的方法和该病毒例如作为免疫原、在免疫原性制剂中、在体外测定中、作为异源基因表达的载体或作为用于治疗癌症的溶瘤试剂的用途。本申请的合成嵌合痘苗病毒其特征在于相对于野生型痘苗病毒有一个或多个修饰。

[0010] 在一方面,本发明是基于可从化学合成的痘苗病毒基因组重叠片段产生合成嵌合痘苗病毒(例如,scVACV)的发现。

[0011] 因此,在一方面,本发明涉及合成嵌合痘苗病毒(例如scVACV),所述病毒是从源于合成DNA的DNA复制和再激活的,所述病毒的病毒基因组不同于所述病毒的野生型基因组的特征在于一个或多个修饰,所述修饰来源于包含化学合成的DNA、cDNA或基因组DNA的组。

[0012] 在另一方面,本发明涉及制备合成嵌合痘苗病毒(scVACV)的方法,其包括以下步骤:(i)化学合成对应于痘苗病毒的基本上全部病毒基因组的重叠DNA片段;(ii)将重叠DNA片段转染至辅助病毒感染的细胞中;(iii)培养所述细胞以在所述细胞中产生辅助病毒和合成嵌合痘苗颗粒的混合物;和(iv)将混合物铺板在对scVACV具有特异性的宿主细胞上以回收scVACV。

[0013] 在另一方面,本发明涉及通过本发明的方法产生的合成嵌合痘苗病毒(scVACV)。

[0014] 在另一方面,本发明涉及药物组合物,其包含本发明的合成嵌合痘苗病毒(scVACV)和药学上可接受的载体。

[0015] 在另一方面,本发明涉及一种在受试者中诱导溶瘤反应的方法,其包括向所述受试者施用包含本发明的scVACV的组合物。

[0016] 在另一方面,本发明涉及用于在宿主细胞中表达异源蛋白的方法,包括将异源核酸序列引入本发明的scVACV中,用scVACV感染宿主细胞,并在用于表达所述异源蛋白的条件下培养宿主细胞。

[0017] 在另一方面,本发明涉及一种触发或增强针对痘苗病毒的免疫反应的方法,其包括向有需要的受试者施用包含本发明的scVACV的组合物。

[0018] 在另一方面,本发明涉及一种触发或增强针对天花病毒感染的免疫反应的方法,

其包括向所述受试者施用包含本发明的scVACV的组合物。

[0019] 在另一方面,本发明涉及一种触发或增强针对猴痘病毒感染的免疫反应的方法,其包括向所述受试者施用包含本发明的scVACV的组合物。

[0020] 在另一方面,本发明涉及一种使人受试者免疫以保护所述受试者免受天花病毒感染的方法,其包括向所述受试者施用包含本发明的scVACV的组合物。

[0021] 在另一方面,本发明涉及一种治疗天花病毒感染的方法,其包括向所述受试者施用包含本发明的scVACV的组合物。

[0022] 在另一方面,本发明涉及一种在受试者中治疗癌症的方法,其包括向有需要的受试者施用包含本发明的scVACV的组合物。

[0023] 附图简述

[0024] 本专利申请含有至少一个彩色制图。本专利申请带有彩色附图的副本将由专利局在得到请求和支付必要费用之后提供。

[0025] 当结合附图阅读时,将更好地理解本发明的上述概述以及以下详述。为了阐明本发明的目的,在附图中显示了目前优选的实施方案。然而,应当理解本发明不限于所显示的精确配置和工具。

[0026] 图1A和1B.ACAM2000株的线性dsDNA VACV基因组(Genbank登录号AY313847)的图示。图1A阐明了VACV ACAM2000基因组的未修饰的基因组序列,其中示出了天然存在的AarI和BsaI限制位点。图1B描述修饰的VACV ACAM2000基因组,其用于化学合成大的ds DNA片段。重叠的scVACV ACAM2000基因组片段以蓝色描绘。也显示了在左侧反向末端重复序列(LITR)和右侧反向末端重复序列(RITR)中没有被沉默突变的改造的BsaI限制位点。

[0027] 图2A-2C.(A)VACV WR株和(B)VACV ACAM2000的公开的基因组的前~1500-3000bp的详细示意图。串联重复区用红色(70bp重复序列)、蓝色(125bp重复序列)和绿色(54bp重复序列)方框表示。对应于基因C23L的ORF也在每个基因组中标示出来。(C)VACV WR中含有70bp重复序列的直接重复区的示意图。合成该序列以含有5'末端的SapI限制位点和在3'末端的NheI限制位点,以分别连接发夹/双链体片段和VACV ACAM2000 ITR片段。

[0028] 图3A和3B.将痘苗病毒末端发夹环与双链体DNA组装至第一个70bp重复序列。(A)描绘产生WR双链体DNA的有序磷酸化寡核苷酸序列。(B)描绘WR株双链体DNA(泳道2)和单独发夹DNA(泳道3)和连接后(泳道4)的凝胶电泳。连接产物(箭头)随后从凝胶上切下并纯化,使得其能够连接至70bp重复序列以模拟wtVACV ACAM2000序列的序列。

[0029] 图4.SapI/NheI消化的70bp重复片段与WR株发夹/双链体DNA片段连接。将70bp重复片段用SapI和NheI消化,然后凝胶纯化,之后与发夹/双链体DNA片段以5:1的发夹/双链体DNA:70bp片段的摩尔比率连接。在泳道4和泳道5中约2300bp的条带中向上位移指示发夹/双链体片段的成功添加。随后从凝胶中凝胶提取这些条带,之后连接于消化的VACV ACAM2000 ITR片段。

[0030] 图5.scVACV ACAM2000片段的消化。ITR片段用NheI/I-SceI两者在37℃消化2小时,之后用碱性磷酸酶去磷酸化以去除磷酸酯基团和促进该片段更有效地连接于末端发夹环/双链体/70bp串联重复片段。其他scVACV ACAM2000 DNA质粒用I-SceI在37℃线性化2小时,接着用限制酶在65℃热灭活10分钟。

[0031] 图6.scVACV ACAM2000-WR DUP/HP的体外生长性质。在猴肾表皮细胞(BSC-40)中

测量多步骤生长动力学。以0.03的感染复数感染细胞,在指定时间收获病毒,并且将病毒在BSC-40细胞上滴定。数据表示三次独立实验。误差条表示平均值的标准误差(SEM)。

[0032] 图7.与其中YFP-gpt标记物已经用J2R基因序列(VAC_WRΔJ2R)替换的scVACV ACAM2000-WR DUP/HP和scVACV ACAM2000-ACAM2000 DUP/HP以及wtVACV ACAM2000相比,scVACV ACAM2000-WR DUP/HP和scVACV ACAM2000-ACAM2000DUP/HP的体外生长性质。在猴肾上皮细胞(BSC-40)中测量多步生长动力学。以0.03的感染复数感染细胞,在指定时间收获病毒,并且将病毒在BSC-40细胞上滴定。误差条表示平均值的标准误差(SEM)。

[0033] 图8.再激活的scVACV ACAM2000-WR DUP/HP克隆的限制性内切酶作图。脉冲场凝胶电泳分析。纯化两个独立的scVACV ACAM2000-WR DUP/HP克隆加上VACV WR对照(它们中的YFP-gpt标志物已经用J2R基因序列(VAC_WRΔJ2R)替换)和wtVACV ACAM2000对照(VAC_ACAM2000),然后保持不消化、用BsaI、HindIII、或NotI和PvuI消化。在scVACV ACAM2000克隆中几乎所有BsaI位点的预期缺失是明显的。观察到HindIII消化的scVACV ACAM2000基因组DNA与VAC_WRΔJ2R和VACV_ACAM2000相比有较小差异。用NotI和PvuI消化的基因组DNA切割在左侧ITR和右侧ITR序列处发现的70bp串联重复片段。在VAC_WRΔJ2R中,70bp重复序列的近似大小接近于3.6kbp。有趣的是,在两个独立的scVACV ACAM2000克隆中,观察到对应于70bp串联重复的两个不同大小的条带(用*标记),即使全长70bp串联重复元件连接于ITR片段。当将ACAM2000基因组DNA用NotI和PvuI消化时,观察到~4.7kbp处的条带,其可以指示ACAM2000中70bp重复序列的大小。

[0034] 图9.VACV株序列之间的核苷酸序列变化。图9A描绘在ITR(SEQ ID NO:15-18)中双链体区内的VACV核苷酸序列变化。图9B描绘了VACV ACAM2000二级发夹环,其共价连接至ACAM2000(S型SEQ ID NO:19和F型SEQ ID NO:20)的线性dsDNA基因组的末端。末端环序列用绿色突出显示。

[0035] 发明详述

[0036] 一般技术

[0037] 除非本文中另外定义,否则本申请中使用的科学和技术术语应当具有本领域普通技术人员通常理解的含义。通常,与本发明中描述的药理学、细胞和组织培养、分子生物学、细胞和癌症生物学、神经生物学、神经化学、病毒学、免疫学、微生物学、遗传学和蛋白和核酸化学结合使用的命名法以及其技术是本领域公知和常用的那些。在有冲突的情况下,以本说明书(包括定义)为准。

[0038] 除非另外指示,否则本发明的实施将采用在本领域技术人员技术之内的常规分子生物学(包括重组技术)、微生物学、细胞生物学、生物化学和免疫学的技术。这些技术在文献中充分解释,诸如Molecular Cloning:A Laboratory Manual,第二版(Sambrook等,1989)冷泉港出版社;Oligonucleotide Synthesis(M.J.Gait编辑,1984);Methods in Molecular Biology,Humana Press;Cell Biology:A Laboratory Notebook(J.E.Cellis编辑,1998)Academic Press;Animal Cell Culture(R.I.Freshney编辑,1987);Introduction to Cell and Tissue Culture(J.P.Mather和P.E.Roberts,1998)Plenum Press;Cell and Tissue Culture:Laboratory Procedures(A.Doyle,J.B.Griffiths和D.G.Newell编辑,1993-1998)J.Wiley&Sons;Methods in Enzymology(Academic Press、Inc.);Gene Transfer Vectors for Mammalian Cells(J.M.Miller和M.P.Calos编辑,

1987);Current Protocols in Molecular Biology(F.M.Ausubel等编辑,1987);PCR:The Polymerase Chain Reaction(Mullis等编辑,1994);Sambrook和Russell,Molecular Cloning:A Laboratory Manual,第3版,冷泉港Laboratory Press,冷泉港,NY(2001);Ausubel等,Current Protocols in Molecular Biology,John Wiley&Sons,NY(2002);Harlow和Lane,Using Antibodies:A Laboratory Manual、冷泉港Laboratory Press,冷泉港,NY(1998);Coligan等,Short Protocols in Protein Science,John Wiley&Sons,NY(2003);Short Protocols in Molecular Biology(Wiley&Sons,1999)。

[0039] 酶促反应和纯化技术根据制造商的说明书进行,如本领域通常完成或如本文所述。与本文所述的分析化学、生物化学、免疫学、分子生物学、合成有机化学和医学以及药理化学结合使用的命名法及其实验室程序和技术是本领域公知的和常用的。使用标准技术用于化学合成和化学分析。

[0040] 贯穿本说明书和实施例,词语“包含”或变体诸如“包含(comprises)”或“包含(comprising)”应理解为暗示包括所述整数或整数组,但是不排除任何其他整数或整数组。

[0041] 应当理解,在本文中使用语言“包含”描述实施方案的任何地方,还提供了以“由...组成”和/或“基本上由.....组成”描述的其他类似实施方案。

[0042] 术语“包括”用于意指“包括但不限于”。“包括”和“包括但不限于”可互换使用。

[0043] 在术语“例如”或“举例而言”之后的任何实例并不意味着是穷尽性的或限制性的。

[0044] 除非上下文另外要求,否则单数术语应当包括复数并且复数术语应该包括单数。

[0045] 冠词“一个/种(a/an)”和“所述(the)”在本文中是用于指代冠词的一个或多于一个(即至少一个)的语法对象。举例而言,“元素”是指一种元素或多于一种元素。本文中提及的“约”某一值或参数包括(且描述)涉及该值或参数本身的实施方案。例如,提及“约X”的描述包括“X”的描述。数值范围包括界定该范围的数字。

[0046] 尽管阐述本发明宽泛范围的数字范围和参数是近似值,但是尽可能精确地报道在特定实施例中阐述的数值。然而,任何数值均固有地含有由在其各自的测试测量中发现的标准差所必然引起的某些误差。然而,本文所公开的所有范围应理解为涵盖其中包含的任何和所有子范围。例如,“1至10”的所述范围应当考虑为包括在最小值1和最大值10之间的任何和所有子范围(并且包括端点值);即所有子范围以最小值1或更大(例如,1至6.1)开始并且以最大值10或更小(例如,5.5至10)结束。

[0047] 例举性方法和材料在本文中描述,但是类似或等效于本文所述的那些的方法和材料也可以在本申请的实施或测试中使用。所述材料、方法和实例是说明性的并且不意欲是限制性的。

[0048] 定义

[0049] 除非另外指出,否则以下术语应理解为具有以下含义:

[0050] 如本文所用,术语“野生型病毒”、“野生型基因组”、“野生型蛋白”或“野生型核酸”是指在某一群体(例如特定病毒种等)内天然存在的氨基酸或核酸的序列。

[0051] 术语“嵌合”或“工程化改造的”或“修饰的”(例如,嵌合痘苗病毒、工程化改造的多肽、修饰的多肽、工程化改造的核酸、修饰的核酸)或其语法变化形式在本文中可互换使用,以指代已经操作而相对于天然序列具有一个或多个变化的非天然序列。

[0052] 如本文所用,“合成病毒”是指最初源自合成DNA(例如化学合成的DNA、PCR扩增的

DNA、工程化改造的DNA、包含核苷酸类似物的多核苷酸等,或其组合)的病毒并且包括其后代,且由于天然、偶然或有意的突变,后代可以不一定与原始亲本合成病毒完全相同(在形态学或基因组DNA互补序列方面)。在一些实施方案中,合成病毒是指其中基本上所有病毒基因组最初来源于合成DNA(例如化学合成的DNA、PCR扩增的DNA、工程化改造的DNA、包含核苷酸类似物的多核苷酸等,或其组合)的病毒。在一个优选实施方案中,合成病毒来源于化学合成的DNA。

[0053] 如本文其他地方所概述,病毒基因组的某些位置可以改变。本文所用的"位置"是指基因组序列中的位置。对应位置一般通过与其他亲本序列比对来确定。

[0054] 如本文所用,在多肽情形中的术语"残基"是指直链多肽链中的氨基酸单元。这是在从α-氨基酸(即NH2-CHR-COOH)形成多肽中去除水后每个氨基酸的剩余物(即-NH-CHR-C-)。

[0055] 如本领域已知,在本文中可互换使用的"多核苷酸"或"核酸"是指任何长度的核苷酸链,并且包括DNA和RNA。核苷酸可以是脱氧核糖核苷酸、核糖核苷酸、修饰的核苷酸或碱基和/或它们的类似物,或可以通过DNA或RNA聚合酶掺入链中的任何基质。多核苷酸可以包含修饰的核苷酸,诸如甲基化核苷酸和它们的类似物。如果存在,可以在链组装之前或之后赋予对核苷酸结构的修饰。核苷酸序列可以被非核苷酸组分中断。在聚合后,多核苷酸可以进一步被修饰,诸如通过与标记组分缀合。其他类型的修饰包括例如"封端(caps)"、用类似物替换一个或多个天然存在的核苷酸;核苷酸间修饰,诸如例如具有不带电荷键(例如,膦酸甲酯,磷酸三酯,氨基磷酸酯,氨甲酸酯等)和具有带电荷键(例如,硫代磷酸酯,二硫代磷酸酯等)的那些;含有侧挂部分的那些,诸如例如蛋白质(例如,核酸酶、毒素、抗体、信号肽、聚-L-赖氨酸等);具有嵌入剂(例如,吖啶、补骨脂素等)的那些;含有螯合剂(例如,金属、放射性金属、硼、氧化金属等)的那些;含有烷基化剂的那些;具有修饰的键(例如,α异头(anomeric)核酸等)的那些;以及多核苷酸的未修饰形式。此外,一般存在于糖中的任何羟基可以例如通过膦酸酯基团、磷酸酯基团替换、通过标准保护基保护或经激活以制备与另外的核苷酸的另外的键联,或者可以缀合至固体支持物。5'和3'末端OH可以被磷酸化或者用1-20碳原子的胺或有机封端基团部分替代。其他羟基也可以衍生成标准保护基。多核苷酸也可以含有本领域通常已知的核糖或脱氧核糖的类似物形式,包括例如2'-O-甲基-、2'-O-烯丙基、2'-氟-或2'-叠氮基-核糖、碳环糖类似物、α-或β-异头糖、差向异构糖(如阿拉伯糖、木糖或来苏糖、吡喃糖、呋喃糖、景天庚酮糖)、无环类似物和无碱基核苷类似物诸如甲基核糖苷。一个或多个磷酸二酯键可以用替代性连接基团替换。这些替代性连接基团包括但不限于其中磷酸酯由P(O)S("硫代物")、P(S)S("二硫物")、(O)NR_2("酰胺酯")、P(O)R、P(O)OR'、CO或CH_2("甲缩醛")替换的实施方案,其中各个R或R'独立地是H取代或未取代的烷基(1-20C)(任选地含有醚(-O-)键)、芳基、烯基、环烷基、环烯基或芳醛基。多核苷酸中并非所有键是相同的。前述描述适用于本文所提及的所有多核苷酸,包括RNA和DNA。

[0056] 术语"多肽"、"寡肽"、"肽"和"蛋白质"在本文中可互换使用以指代任何长度的氨基酸链。该链可以是直链或支链的,其可以含有修饰的氨基酸和/或可以被非氨基酸中断。该术语还包括已经天然或通过干预修饰的氨基酸链;例如,二硫键形成、糖基化、脂质化、乙酰化、磷酸化或任何其他操作或修饰,诸如与标记组分缀合。定义内还包括例如含有一个或多个氨基酸类似物(包括例如非天然氨基酸等)以及本领域已知的其他修饰的多肽。应当理

解,多肽可以作为单一链或缔合的链存在。

[0057] “同源”以其所有语法形式和拼写变化指具有“共同进化起源”的两种蛋白质(包括来自相同生物体物种的超家族的蛋白质,以及来自不同生物体物种的同源蛋白质)之间的关系。这些蛋白质(和它们的编码核酸)具有序列同源性,如通过其序列相似性(无论通过同一性百分比还是通过特定残基或基序和保守位置的存在)反映。“同源的”也可以指对病毒而言为天然的核酸。

[0058] 然而,在通常用法和本申请中,当用诸如“高度”的副词修饰时,术语“同源”可以指序列相似性,且可以涉及或可以不涉及共同的进化起源。

[0059] “异源”以其所有语法形式和拼写变化可以指对于病毒而言非天然的核酸。其意指源自与核酸相对于其描述为异源的生物体的核酸不同的物种或不同的毒株。在非限制性实例中,scVACV的病毒基因组包含异源末端发夹环。所述异源末端发夹环可以源自不同的病毒物种或源自不同的VACV株。

[0060] 术语“序列相似性”以其所有语法形式指核酸或氨基酸序列之间的同一性或对应性的程度,其可以共有或可以不共有共同的进化起源。

[0061] 相对于参考多肽(或核苷酸)序列的“序列同一性百分比(%)”或“序列同一性%”定义为在比对序列并引入缺口(如有必要)以实现最大的序列同一性百分比后,并且在不考虑任何保守取代作为序列同一性的部分的情况下,候选序列中与参照多肽(核苷酸)序列中的氨基酸残基(或核酸)相同的氨基酸残基(或核酸)的百分比。出于确定氨基酸序列同一性百分比的目的的比对可以以本领域技术范围内的各种方式实现,例如使用可公开获得的计算机软件,诸如BLAST、BLAST-2、ALIGN或Megalign(DNASTAR)软件。本领域技术人员能够确定用于比对序列的适当参数,包括在比较的序列全长上实现最大比对所需的任何算法。

[0062] 如本文所用,“宿主细胞”包括可以是或已经是本发明病毒的接受者的单个细胞或细胞培养物。宿主细胞包括单个宿主细胞的后代,并且由于天然、偶然或有意突变,后代可能不一定与原始亲本细胞完全相同(在形态上或在基因组DNA互补序列方面)。宿主细胞包括用本发明的痘病毒体内转染和/或转化的细胞。

[0063] 如本文所用,“载体”是指能够在宿主细胞中递送且优选表达一个或多个目标基因或序列的构建体。载体的实例包括但不限于病毒载体、裸DNA或RNA表达载体、质粒、粘粒或噬菌体载体、与阳离子缩合剂结合的DNA或RNA表达载体、包封于脂质体中的DNA或RNA表达载体、和某些真核细胞,诸如生产者细胞。

[0064] 如本文所用,“分离的分子”(其中分子是例如多肽,多核苷酸或其片段)为以下分子:就其起源或衍生来源而言,(1)不与其天然状态中伴随其的一种或多种天然相关组分相关,(2)基本上不含来自相同物种的一种或多种其他分子,(3)由来自不同物种的细胞表达,或(4)在自然界中不存在。因此,化学合成的或在与其天然来源的细胞不同的细胞系统中表达的分子将从其天然相关组分“分离”。使用本领域公知的纯化技术,通过分离也可以使得分子基本上不含天然相关组分。可以通过本领域公知的许多方式测定分子纯度或同质性。例如,多肽样品的纯度可以使用聚丙烯酰胺凝胶电泳和凝胶染色以使用本领域公知的技术使多肽可视化来分析。为了某些目的,可通过使用HPLC或本领域熟知的用于纯化的其他方式来提供更高分辨率。

[0065] 如本文所用,在病毒情形中,术语“分离的”是指源自单一亲本病毒的病毒。病毒可

以使用本领域技术人员已知的常规方法分离,包括但不限于基于空斑纯化和限制稀释法的那些方法。

[0066] 如本文所用,短语“感染复数”或“MOI”是每个感染细胞的病毒平均数。MOI通过将加入的病毒数(添加的ml x空斑形成单位(PFU))除以加入的细胞数(加入的ml x细胞/ml)来确定。

[0067] 如本文所用,“纯化”及其语法变体是指从含有多肽和一种或多种杂质的混合物中去除(无论是完全地还是部分地)至少一种杂质,由此提高组合物中多肽的纯度水平(即,通过降低组合物中杂质的量(ppm))。如本文所用,病毒情形中的“纯化”是指基本上不含来自病毒所源自的细胞或组织来源的细胞材料和培养基的病毒。语言“基本上不含细胞材料”包括病毒制剂,其中所述病毒与从中分离或从其重组产生的细胞的细胞组分分离。因此,基本上不含细胞材料的病毒包括具有少于大约30%、20%、10%、或5%(以干重计)细胞蛋白(在本文中也称为“污染蛋白”)的蛋白制剂。病毒还基本上不含培养基,即培养基占病毒制剂体积的小于大约20%、10%或5%。可以使用本领域技术人员已知的常规方法(包括但不限于色谱法和离心)纯化病毒。

[0068] 如本文所用,“基本上纯”是指至少50%纯(即不含污染物)、更优选至少90%纯、更优选至少95%纯、还更优选至少98%纯和最优选至少99%纯的物质。

[0069] 术语“患者”、“受试者”或“个体”在本文中可互换使用并且是指人或非人动物。这些术语包括哺乳动物,诸如人、灵长类、家畜动物(包括牛、猪、骆驼等)、伴侣动物(例如,犬科动物、猫科动物等)和啮齿动物(例如,小鼠和大鼠)。

[0070] 如本文所用,术语“预防(prevent/preventing/prevention)”是指由于施用疗法(例如预防剂或治疗剂)在受试者中延迟疾病(例如痘病毒感染)的一个或多个症状的复发或发作或使一个或多个症状减轻。例如,在针对感染施用疗法于受试者的情况下,“预防”是指由于施用疗法(例如预防剂或治疗剂)或施用疗法组合(例如,预防剂或治疗剂的组合)在受试者中抑制或减轻感染(例如痘病毒感染或与其相关的病症)的发展或发作,或预防感染(例如痘病毒感染或与其相关的病症)的一个或多个症状的复发、发作或发展。

[0071] 如本文所用,术语“治疗(treat/treating/treatment)”是指治疗病症或患者,并且是指采取步骤以获得有益的或期望的结果,包括临床结果。关于感染(例如痘病毒感染或天花病毒感染),治疗是指由施用一种或多种疗法(包括但不限于施用一种或多种预防剂或治疗剂)导致的传染因子(例如痘病毒或天花病毒)复制的根除或控制、传染因子的数量(例如降低病毒滴度)的减少、感染(例如痘病毒/天花感染或与其相关的病症或症状)进展、严重性和/或持续时间的减轻或改善或一个或多个症状的改善。关于癌症,治疗是指由于施用本发明的一种或多种治疗剂导致的原发性、局部或转移性癌症组织的根除、去除、减轻或控制。在某些实施方案中,该术语是指由于向患有此种疾病的受试者施用本发明的一种或多种治疗剂导致的癌症扩散的最小化或延迟。在其他实施方案中,该术语是指消除引起疾病的细胞。

[0072] 可以使用本领域技术人员已知的各种方法之一进行向受试者“施用(administering/administration of)”物质、化合物或药剂。例如,可以通过舌下或鼻内、通过吸入肺或经直肠施用化合物或药剂。施用也可以例如一次、多次和/或历经一个或多个延长时期进行。在一些方面,施用包括直接施用(包括自我施用)和间接施用(包括开处方行

为)。例如,如本文所用,指导患者自我施用药物或通过另一人施用药物和/或向患者提供药物处方的医师将药物施用于患者。

[0073] 本文所述的每个实施方案可以单独地或与本文所述的任何其他实施方案组合地使用。

[0074] 概述

[0075] 痘病毒是在感染细胞的细胞质中复制的大(~200kbp)DNA病毒。正痘病毒(OPV)属包括许多痘病毒,所述痘病毒感染不同宿主的能力变化极大。例如,痘苗病毒(VACV)可以感染广泛宿主群,而天花的病原体天花病毒(VARV)仅感染人类。许多痘病毒(如果不是全部的话)的共同特征是它们在宿主内非遗传性“再激活”的能力。非遗传性再激活是指其中被一种痘病毒感染的细胞可以促进本身是非感染性的第二“死亡”病毒(例如热灭活的病毒)的恢复的过程。

[0076] 纯化的痘病毒DNA不具有传染性,因为病毒生命周期需要通过包装在病毒体中的病毒编码的RNA聚合酶转录早期基因。然而,如果将病毒DNA转染到先前用辅助痘病毒感染的细胞中,提供反式转录、复制和包装感染基因组所需的必需因子(Sam CK,Dumbell KR.Expression of poxvirus DNA in coinfected cells and marker rescue of thermosensitive mutants by subgenomic fragments of DNA.Ann Virol(Inst Past).1981;132:135-50),则可克服此缺陷。尽管这产生混合病毒后代,但是通过在支持两种病毒繁殖的细胞系中进行再激活反应,且随后通过将病毒混合物铺板在不支持辅助病毒生长的细胞上以消除辅助病毒(Scheiflinger F,Dorner F,Falkner FG.Construction of chimeric vaccinia viruses by molecular cloning and packaging.Proceedings of the National Academy of Sciences of the United States of America.1992;89(21):9977-81),可以克服该问题。

[0077] 先前,Yao和Evans描述了一种通过兔痘病毒、休普氏纤维瘤病毒(SFV)催化高频重组反应和复制反应可与SFV-催化的再激活反应偶联以使用病毒DNA的多个重叠片段来迅速地组装重组痘苗毒株的方法(Yao XD,Evans DH.High-frequency genetic recombination and reactivation of orthopoxviruses from DNA fragments transfected into leporipoxvirus-infected cells.Journal of Virology.2003;77(13):7281-90)。首次描述了使用化学合成的重叠双链DNA片段再激活和表征功能性的合成嵌合痘苗病毒[scVACV]。

[0078] 本发明的合成嵌合痘苗病毒

[0079] 在一方面,本发明提供了功能性合成嵌合痘苗病毒(scVACV),其最初由化学合成的DNA复制和组装。根据本发明的方法可以产生的病毒可以是基因组已经测序或可以大部分测序或可获得天然分离株的任何痘苗病毒。各种实施方案的scVACV可以基于天然存在的毒株、变体或突变体、诱变病毒或遗传工程化改造的病毒的基因组序列。在一些实施方案中,scVACV的病毒基因组包括相对于所述病毒的野生型基因组或基础基因组序列的一个或多个修饰。该修饰可以包括一个或多个缺失、插入、取代或其组合。在一个实施方案中,修饰可以包括插入一个或多个多克隆位点,使得可以插入外源DNA。应当理解,修饰可以以本领域公知的多种方式引入。基因组的修饰部分可以来源于化学合成的DNA、cDNA或基因组DNA。在另一个实施方案中,本发明的scVACV的病毒基因组包括一个或多个修饰以添加或修复一

个或多个独特的限制位点。添加或修复一个或多个限制位点的修饰可以在经消除以促进克隆选择的限制位点上进行。

[0080] 当天然模板不可用于通过常规分子生物学方法进行遗传修饰、扩增或复制时,化学基因组合成尤其有用。wtVACV(株NYCBH,克隆ACAM2000)的基因组序列已经描述和公开,尽管其不完整。未测定末端发夹环的序列,仅四个54bp重复序列被鉴定。在测序之后,在VACV ACAM2000的野生型分离株中证实70bp、125bp和54bp串联重复序列的存在,指示当前公布的ACAM2000序列是不完整的。本发明人产生了一种功能性的合成嵌合VACV(scVACV)。具体地,本发明人通过使用基于不同株的wtVACV端粒的末端发夹环代替VACV自身的末端发夹环序列,成功地产生了功能性scVACV株NYCBH,克隆ACAM2000。在一些实施方案中,VACV病毒的病毒基因组是选自下组的株:Western Reserve、克隆3、Tian Tian、Tian Tian克隆TP5、Tian Tian克隆TP3、NYCBH、NYCBH克隆Acambis 2000、Wyeth、Copenhagen、Lister、Lister 107、Lister-LO、Lister GL-ONC1、Lister GL-ONC2、Lister GL-ONC3、Lister GL-ONC4、Lister CTC1、Lister IMG2(Turbo FP635)、IHD-W、LC16m18、Lederle、Tashkent克隆TKT3、Tashkent克隆TKT4、USSR、Evans、Praha、L-IVP、V-VET1或LIVP 6.1.1、Ikeda、EM-63、Malbran、Duke、3737、CV-1、Connaught Laboratories、Serro 2、CM-01、NYCBH Dryvax克隆DPP13、NYCBH Dryvax克隆DPP15、NYCBH Dryvax克隆DPP20、NYCBH Dryvax克隆DPP17、NYCBH Dryvax克隆DPP21、VACV-IOC、安卡拉绒毛膜尿囊痘苗病毒(CVA)、改良的安卡拉痘苗病毒(MVA)和MVA-BN。在一个优选实施方案中,病毒基因组是基于NYCBH株。更优选地,病毒基因组来源于NYCBH株,克隆Acambis 2000或ACAM2000。仍不断地发现新VACV株。应当理解,本发明的scVACV可以基于此新发现的VACV株。

[0081] **Dryvax®**源自纽约市健康委员会痘苗病毒株(Wyeth Laboratories,Marietta,PA)并且培养在小牛皮肤上,然后基本上冷冻干燥用于储存。

[0082] 活的VACV ACAM2000株、天花(痘苗)疫苗是来源于**Dryvax®**的空斑纯化克隆的活痘苗病毒,并且培养在非洲绿猴肾脏(Vero)细胞中,并且经测试不含外源因子(Osborne JD等Vaccine.2007;25(52):8807-32)。

[0083] V-VET1或LIVP 6.1.1由Genelux开发。其分离自痘苗病毒的Lister株(Lister株,病毒制剂研究所(LIVP),莫斯科,俄罗斯)的野生型储液,并且代表“天然”病毒(没有进行遗传操作)。LIVP 6.1.1病毒的胸苷激酶(tk)基因是无活性的(Shvalov AN等,Genome Announc.2016年5月-6月;4(3):e00372-16)。

[0084] Genelux从Lister株开发了GLV-1h68(命名为GL-ONC1,生产用于临床研究),通过将编码海肾(Renilla)荧光素酶-水母绿色荧光蛋白融合物(Ruc-GFP)、LacZ和β-葡糖苷酸酶的三个表达盒分别插入病毒基因组的F14.5L、J2R(胸苷激酶)和A56R(血凝素)基因座(Zhang Q等,Cancer Res.2007;67(20):10038-46.)而进行。

[0085] 化学病毒基因组合成也开拓了向所得基因组或其特定部分引入大量有用修饰的可能性。修饰可提高克隆产生病毒的容易性,提供用于引入重组基因产物的位点,提高鉴定再激活病毒克隆的容易性和/或赋予多个其他有用特征(例如,引入所需抗原,生产溶瘤病毒等)。在一些实施方案中,修饰可以包括削弱或缺失一种或多种毒力因子。在一些实施方案中,修饰可以包括添加或插入一种或多种毒力调节基因或基因编码调节因子。

[0086] 传统上,痘病毒的末端发夹难以克隆和测序,因此一些公开的基因组序列(例如VACV、ACAM2000和HPXV MNR-76)不完整并不意外。具体地,已经描述和公开了wtVACV株NYCBH克隆ACAM2000的基因组序列,但是其并不完整。未测定末端发夹环的序列,仅四个54bp重复序列被鉴定出来。由于公开的wtVACV株NYCBH克隆ACAM2000的基因组序列不完整,所以不能精确复制发夹,并且在本申请之前,不知道VACV是否能够仅基于wtVACV基因组的已知部分从多核苷酸复制和组装。也不知道来自一种病毒株的发夹将在另一毒株中有效。本发明人产生了一种功能性的合成嵌合VACV(scVACV)ACAM2000,通过使用基于不同株的wtVACV端粒的末端发夹环代替VACV自身的末端发夹环序列而进行。在例举性实施方案中,使用公开的VACV WR株端粒序列作为引导而化学合成ssDNA片段,并将其连接至包含VACV株NYCBH的左侧末端和右侧末端的dsDNA片段上。在一些实施方案中,末端发夹是基于基因组已经完全测序或其天然分离株可用于基因组测序的任何VACV株的末端发夹。在一些实施方案中,末端发夹环是基于选自以下的组的株:Western Reserve、克隆3、Tian Tian、Tian Tian克隆TP5、Tian Tian克隆TP3、NYCBH、NYCBH克隆Acambis 2000、Wyeth、Copenhagen、Lister、Lister 107、Lister-LO、Lister GL-ONC1、Lister GL-ONC2、Lister GL-ONC3、Lister GL-ONC4、Lister CTC1、Lister IMG2(Turbo FP635)、IHD-W、LC16m18、Lederle、Tashkent克隆TKT3、Tashkent克隆TKT4、USSR、Evans、Praha、L-IVP、V-VET1或LIVP6.1.1、Ikeda、EM-63、Malbran、Duke、3737、CV-1、Connaught Laboratories、Serro 2、CM-01、NYCBH Dryvax克隆DPP13、NYCBH Dryvax克隆DPP15、NYCBH Dryvax克隆DPP20、NYCBH Dryvax克隆DPP17、NYCBH Dryvax克隆DPP21、VACV-IOC、安卡拉绒毛膜尿囊痘苗病毒(CVA)、改良的安卡拉痘苗病毒(MVA)和MVA-BN。在优选实施方案中,末端发夹环是基于VACV的Western Reserve株(WR株)。新VACV株仍然不断被发现。应当理解,本发明的scVACV可以基于此类新发现的VACV株。

[0087] 在另一个实施方案中,本发明的scVACV的病毒基因组包含同源或异源末端发夹环和位于发夹环下游的串联重复区(70bp、125bp和54bp串联重复),其中串联重复区包含与wtVACV(即,天然存在的病毒)不同数目的重复。VACV病毒(株WR)中发现的70bp、125bp和54bp串联重复的重复数目分别是22、2和8。在另一个实施方案中,串联重复区的数目在不同痘病毒、不同痘苗病毒和不同痘苗病毒株中可变。术语同源末端发夹环意指所述末端发夹环是来自相同病毒种/相同株,而术语异源末端发夹环意指所述末端发夹环是来自不同病毒种/不同株。

[0088] 在一些实施方案中,修饰可以包括缺失一个或多个限制位点。在一些实施方案中,修饰可以包括引入一个或多个限制位点。在一些实施方案中,要从基因组中缺失或添加至基因组的限制位点可以选自以下的一个或多个限制位点:诸如但不限于AanI、AarI、AasI、AatI、AatII、AbaSI、AbsI、Acc65I、AccI、AccII、AccIII、AciI、AclI、AcuI、AfeI、AflII、AflIII、AgeI、AhdI、AleI、AluI、AlwI、AlwNI、ApaI、ApaLI、ApeKI、ApoI、AscI、AseI、AsiSI、AvaI、AvaII、AvrII、BaeGI、BaeI、BamHI BanI、BanII、BbsI、BbvCI、BbvI、BccI、BceAI、BcgI、BciVI、BclI、BcoDI、BfaI、BfuAI、BfuCI、BglI、BglII、BlpI、BmgBI、BmrI、BmtI、BpmI、Bpu10I、BpuEI、BsaAI、BsaBI、BsaHI、BsaI、BsaJI、BsaWI、BsaXI、BseRI、BseYI、BsgI、BsiEI、BsiHKAI、BsiWI、BslI、BsmAI、BsmBI、BsmFI、BsmI、BsoBI、Bsp1286I、BspCNI、BspDI、BspEI、BspHI、BspMI、BspQI、BsrBI、BsrDI、BsrFαI、BsrGI、BsrI、BssHII、BssSαI、BstAPI、BstBI、

BstEII、BstNI、BstUI、BstXI、BstYI、BstZ17I、Bsu36I、BtgI、BtgZI、BtsαI、BtsCI、BtsIMutI、Cac8I、ClaI、CspCI、CviAII、CviKI-1、CviQI、DdeI、DpnI、DpnII、DraI、DrdI、EaeI、EagI、EarI、EciI、Eco53kI、EcoNI、Eco0109I、EcoP15I、EcoRI、EcoRV、FatI、FauI、Fnu4HI、FokI、FseI、FspEI、FspI、HaeII、HaeIII、HgaI、HhaI、HincII、HindIII、HinfI、HinP1I、HpaI、HpaII、HphI、Hpy166II、Hpy188I、Hpy188III、Hpy99I、HpyAV、HpyCH4III、HpyCH4IV、HpyCH4V、I-CeuI、I-SceI、KasI、KpnI、LpnPI、MboI、MboII、MfeI、MluCI、MluI、MlyI、MmeI、MnlI、MscI、MseI、MslI、MspA1I、MspI、MspJI、MwoI、NaeI、NarI、NciI、NcoI、NdeI、NgoMIV、NheI、NlaIII、NlaIV、NmeAIII、NotI、NruI、NsiI、NspI、PacI、PaeR7I、PciI、PflFI、PflMI、PleI、PluTI、PmeI、PmlI、PpuMI、PshAI、PsiI、PspGI、PspOMI、PspXI、PstI、PvuI、PvuII、RsaI、RsrII、SacI、SacII、SalI、SapI、Sau3AI、Sau96I、SbfI、ScrFI、SexAI、SfaNI、SfcI、SfiI、SfoI、SgrAI、SmaI、SmlI、SnaBI、SpeI、SphI、SrfI、SspI、StuI、StyD4I、StyI、SwaI、TaqαI、TfiI、TseI、Tsp45I、TspMI、TspRI、Tth111I、XbaI、XcmI、XhoI、XmaI、XmnI或ZraI。应当理解,可以将任何期望的限制位点或限制位点的组合插入基因组中或从基因组中突变和/或消除。在一些实施方案中,一个或多个AarI位点从病毒基因组中缺失。在一些实施方案中,一个或多个BsaI位点从病毒基因组中缺失。在一些实施方案中,一个或多个限制位点完全从基因组中消除(例如,可以消除病毒基因组中的所有AarI位点)。在一些实施方案中,将一个或多个AvaI限制位点引入病毒基因组。在一些实施方案中,将一个或多个StuI位点引入病毒基因组。在一些实施方案中,一个或多个修饰可以包括掺入重组工程靶标,包括但不限于loxP或FRT位点。

[0089] 在一些实施方案中,修饰可以包括引入荧光标记物,诸如但不限于绿色荧光蛋白(GFP)、增强的GFP、黄色荧光蛋白(YFP)、青色/蓝色荧光蛋白(BFP)、红色荧光蛋白(RFP)或其变体等;可选标记物,诸如但不限于耐药标记物(例如,大肠杆菌(E.coli)黄嘌呤-鸟嘌呤磷酸核糖基转移酶基因(gpt)、白黑链霉菌(Streptomyces alboniger)嘌呤乙酰转移酶基因(pac)、新霉素磷酸转移酶I基因(nptI)、新霉素磷酸转移酶基因II(nptII)、潮霉素磷酸转移酶(hpt)、sh ble基因等);蛋白或肽标签,诸如但不限于MBP(麦芽糖结合蛋白)、CBD(纤维素结合结构域)、GST(谷胱甘肽-S-转移酶)、聚(His)、FLAG、V5、c-Myc、HA(血凝素)、NE-标签、CAT(氯霉素乙酰转移酶)、DHFR(二氢叶酸还原酶)、HSV(单纯疱疹病毒)、VSV-G(水泡性口炎病毒糖蛋白)、荧光素酶、蛋白质A、蛋白质G、链霉抗生物素蛋白、T7、硫氧还蛋白、酵母双杂交标签诸如B42、GAL4、LexA或VP16;定位标签,诸如NLS-标签、SNAP-标签、Myr-标签等。应当理解,可以使用本领域已知的其他选择标记物和/或标签。在一些实施方案中,修饰包括一个或多个选择标记物以帮助选择再激活的克隆(例如荧光标记物,诸如YFP、药物选择标记物诸如gpt等),以帮助选择再激活的病毒克隆。在一些实施方案中,所述一个或多个选择标记物在选择步骤之后从再激活克隆中删除。

[0090] 在一方面,本发明的scVACV可以用作保护免受致病性痘病毒感染(例如VARV、MPXV、MCV、ORFV、Ausdyk病毒、BPSV、海豹痘病毒等)的疫苗,用作治疗或预防致病性痘病毒感染(例如VARV、MPXV、MCV、ORFV、Ausdyk病毒、BPSV、海豹痘病毒等)的治疗剂,用作异源基因表达的媒介物,或作为溶瘤剂。在一些实施方案中,scVACV可以用作疫苗以保护免受VARV感染。在一些实施方案中,scVACV可以用于治疗或预防VARV感染。

[0091] 产生合成嵌合VACV的方法

[0092] 在一方面,本发明提供用于从病毒基因组的化学合成的重叠双链DNA片段合成、再激活和分离功能性的合成嵌合VACV(scVACV)的系统和方法。在先前感染辅助病毒的细胞中进行病毒基因组的重叠DNA片段的重组和功能性scVACV的再激活。简而言之,涵盖scVACV的全部或基本上全部的病毒基因组的重叠DNA片段经化学合成并转染到辅助病毒感染的细胞中。培养转染的细胞以产生包含辅助病毒和再激活的scVACV的混合病毒后代。接下来,将混合的病毒后代铺板到不支持辅助病毒生长但是允许合成嵌合痘苗病毒生长的宿主细胞上,以便消除辅助病毒和回收合成嵌合痘苗病毒。在一些实施方案中,辅助病毒不感染宿主细胞。在一些实施方案中,辅助病毒可以感染宿主细胞,但是在宿主细胞中生长差。在一些实施方案中,与scVACV相比,辅助细胞在宿主细胞中生长更慢。

[0093] 在一些实施方案中,基本上全部合成嵌合痘苗病毒基因组是来源于化学合成的DNA。在一些实施方案中,约40%、约50%、约60%、约70%、约75%、约80%、约85%、约90%、约95%、约96%、约97%、约98%、约99%、超过99%或100%的合成嵌合痘苗病毒基因组来源于化学合成的DNA。在一些实施方案中,痘苗病毒基因组来源于化学合成DNA和天然存在DNA的组合。在一些实施方案中,所有包含痘苗病毒基因组的片段是化学合成的。在一些实施方案中,一个或多个所述片段是化学合成的并且一个或多个片段来源于天然存在的DNA(例如,通过PCR扩增或通过公认的重组DNA技术)。

[0094] 本发明方法中使用的重叠DNA片段的数目将取决于痘苗病毒基因组的大小。实际考虑因素,诸如一方面重组效率随着片段数目增加而降低,和另一方面随着片段数目减少合成极大DNA片段有困难,也将为本发明的方法中使用的重叠片段的数目提供信息。在一些实施方案中,合成嵌合痘苗病毒基因组可以合成为单个片段。在一些实施方案中,合成嵌合痘苗病毒基因组由2-14个重叠DNA片段组装。在一些实施方案中,合成嵌合痘苗病毒基因组由4-12个重叠DNA片段组装。在一些实施方案中,合成嵌合痘苗病毒基因组由6-12个重叠DNA片段组装。在一些实施方案中,合成嵌合痘苗病毒基因组由8-11个重叠DNA片段组装。在一些实施方案中,合成嵌合痘苗病毒基因组由8-10、10-12或10-14个重叠DNA片段组装。在一些实施方案中,合成嵌合痘苗病毒基因组由2、3、4、5、6、7、8、9、10、11、12、13、14或15个重叠DNA片段组装。在一个优选实施方案中,合成嵌合痘苗病毒基因组由9个重叠DNA片段组装。在本发明的例举性实施方案中,从9个化学合成的重叠双链DNA片段再激活合成的痘苗病毒(scVACV)。在一些实施方案中,末端发夹环单独地合成并且连接到包含痘苗病毒基因组的左侧末端和右侧末端的片段上。在一些实施方案中,末端发夹环可以来源于天然存在的模板。在一些实施方案中,scVACV的末端发夹来源于wtVACV。在一些实施方案中,末端发夹来源于不同株的wtVACV末端发夹,代替VACV自身末端发夹环序列。在一些实施方案中,末端发夹是基于其基因组已经完全测序或其天然分离株可用于基因组测序的任何wtVACV的末端发夹。

[0095] 本发明方法的各个方面中使用的重叠片段的大小将取决于痘苗病毒基因组的大小。应当理解,片段大小可以宽泛变化,并且各种实际考虑因素,诸如化学合成极大DNA片段的能力,将为片段大小的选择提供信息。在一些实施方案中,片段大小范围为约2,000bp至约50,000bp。在一些实施方案中,片段大小范围为约3,000bp至约45,000bp。在一些实施方案中,片段大小范围为约4,000bp至40,000bp。在一些实施方案中,片段大小范围为约5,000bp至35,000bp。在一些实施方案中,最大片段是约18,000bp,20,000bp,21,000bp,22,

000bp,23,000bp,24,000bp,25,000bp,26,000bp,27,000bp,28,000bp,29,000bp,30,000bp,31,000bp,32,000bp,33,000bp,34,000bp,35,000bp,36,000bp,37,000bp,38,000bp,39,000bp,40,000bp,41,000bp,42,000bp,43,000bp,44,000bp,45,000bp,46,000bp,47,000bp,48,000bp,49,000bp或50,000bp。在本发明的例举性实施方案中,从9个化学合成的大小范围为约10,000bp至约32,000bp(表1)的重叠双链DNA片段再激活scVACV。

[0096] 辅助病毒可以是能够提供从转染的DNA再激活痘病毒所需的反式作用酶促机制的任何痘病毒。辅助病毒可以具有与待产生的scVACV相比不同或更窄的宿主细胞范围(例如,与正痘病毒诸如痘苗病毒(VACV)或HPXV相比,休普氏纤维瘤病毒(SFV)具有极窄宿主范围)。与待产生的scVACV相比,辅助病毒可以具有不同的空斑表型。在一些实施方案中,辅助病毒是兔痘病毒。在一些实施方案中,兔痘病毒是SFV、野兔纤维瘤病毒、家兔纤维瘤病毒、松鼠纤维瘤病毒或粘液瘤病毒。在一个优选实施方案中,辅助病毒是SFV。在一些实施方案中,辅助病毒是正痘病毒。在一些实施方案中,正痘病毒是骆驼痘病毒(CMLV)、牛痘病毒(CPXV)、鼠痘病毒(ECTV、“鼠痘试剂”)、HPXV、猴痘病毒(MPXV)、兔痘病毒(RPXV)、浣熊痘病毒、臭鼬痘病毒、沙鼠痘病毒、瓦辛吉舒病病毒(Uasin Gishu disease virus)、VACV和田鼠痘病毒(VPV)。在一些实施方案中,辅助病毒是禽痘病毒、羊痘病毒、鹿痘病毒、鳄鱼痘病毒(Crocodylipoxvirus)、软疣痘病毒、副痘病毒、猪痘病毒或亚塔痘病毒。在一些实施方案中,辅助病毒是禽痘病毒。在一些实施方案中,辅助病毒是α昆虫痘病毒、β昆虫痘病毒或γ昆虫痘病毒。在一些实施方案中,辅助病毒是补骨脂素灭活的辅助病毒。在本发明的例举性实施方案中,从转染至SFV-感染的BGMK细胞中的重叠DNA片段再激活scVACV。随后通过将混合病毒后代铺板在BSC-40细胞上来消除SFV。

[0097] 本领域技术人员将理解,将适合的宿主细胞用于scVACV的再激活,并且scVACV的选择和/或分离将取决于辅助病毒和通过本发明方法的各个方面产生的嵌合痘病毒的特定组合。支持辅助病毒和scVACV两者生长的任何宿主细胞可以用于再激活步骤,并且不支持辅助病毒生长的任何宿主细胞将用于消除辅助病毒和选择和/或分离scVACV。在一些实施方案中,辅助细胞是兔痘病毒,并且用于再激活步骤的宿主细胞可以选自兔肾细胞(例如LLC-RK1、RK13等)、兔肺细胞(例如R9ab)、兔皮肤细胞(例如SF1Ep、DRS、RAB-9)、兔角膜细胞(例如SIRC)、兔癌细胞(例如Oc4T/cc)、兔皮肤/癌细胞(例如CTPS)、猴细胞(例如Vero、BGMK等)或仓鼠细胞(例如BHK-21等)。在一个优选实施方案中,宿主细胞是BGMK细胞。

[0098] 在一些实施方案中,scVACV可以在容许病毒生长至允许使用本文所述的scVACV的滴度的任何基质中繁殖。在一个实施方案中,该基质允许scVACV生长至与对于相应的野生型病毒测定的那些相当的滴度。在一些实施方案中,scVACV可以在易感染VACV的细胞(例如禽细胞、蝙蝠细胞、牛细胞、骆驼细胞、金丝雀细胞、猫细胞、鹿细胞、马细胞、家禽细胞、沙鼠细胞、山羊细胞、人细胞、猴细胞、猪细胞、兔细胞、浣熊细胞、海豹细胞、绵羊细胞、臭鼬细胞、田鼠细胞等)中生长。这些方法是本领域技术人员公知的。代表性的哺乳动物细胞包括但不限于BHK、BGMK、BRL3A、BSC-40、CEF、CEK、CHO、COS、CVI、HaCaT、HEL、HeLa细胞、HEK293、人骨骼骨肉瘤细胞系143B、MDCK、NIH/3T3和Vero细胞。对于病毒分离,通常通过公知的澄清程序(例如,诸如梯度离心和柱层析)将scVACV从细胞培养物中移出并且与细胞组分分离,并且根据需要使用本领域技术人员公知的程序(诸如空斑测定)进一步纯化。

[0099] 在本发明的另一方面,产生合成嵌合痘苗病毒(scVACV)的方法包括以下步骤:(i)

化学合成对应于痘苗病毒的基本上全部病毒基因组的重叠DNA片段,和化学合成来自另一痘苗病毒株的末端发夹环;(ii)将重叠DNA片段转染到辅助病毒感染的细胞中;(iii)培养所述细胞以在所述细胞中产生辅助病毒和合成嵌合痘苗病毒颗粒的混合物;和(iv)将混合物铺板在对scVACV具有特异性的宿主细胞上以回收scVACV。在一些实施方案中,本方法的scVACV来源于毒株NYCBH株克隆Acambis 2000并且末端发夹环来源于痘苗病毒Western Reserve株。

[0100] 本发明的多核苷酸

[0101] 一方面,本发明提供用于产生功能性的合成嵌合痘病毒(scVACV)的多核苷酸(例如双链DNA片段)。在一些实施方案中,本发明提供从合成DNA(例如化学合成的DNA、PCR扩增的DNA、工程化改造的DNA、包含核苷类似物的多核苷酸等)产生功能性scVACV的方法。在一些实施方案中,本发明提供从病毒基因组的化学合成的重叠双链DNA片段产生功能性scVACV的方法。本发明各方面的多核苷酸可以基于公开可获得的基因组序列进行设计。当容易获得痘苗病毒的天然分离株时,可以在选择和设计本发明的多核苷酸之前对病毒基因组测序。备选地,当痘苗病毒的部分DNA序列(例如,来自临床分离株,来自法医样品或来自与感染的人相关的材料的PCR扩增的DNA)可获得时,可以在选择和设计本发明的多核苷酸之前对部分病毒基因组测序。一方面,本发明的scVACV和因此本发明的多核苷酸,可以基于天然存在的株、变体或突变体、诱变的病毒或基因工程化改造的病毒的基因组序列。

[0102] 一方面,本发明提供了分离的多核苷酸,其包括与参考VACV基因组序列或其互补序列的全部或一部分至少90%相同(例如至少91%、92%、93%或94%相同)、至少95%相同(例如至少96%、97%、98%或99%相同)或100%相同的核苷酸序列。本发明的分离的多核苷酸可以包括参考多核苷酸分子(例如参考VACV基因组或其片段)的至少5、6、7、8、9、10、20、30、40、50、60、70、80、90、100、200、300、400、500、600、700、800、900、1000、2000、3000、4000、5000、6000、7000、8000、9000、10000、15000、20000、25000、30000、35000、40000、45000bp或更多bp的连续或非连续的核苷酸。本领域普通技术人员将理解与核酸互补的核酸序列和核酸的变体也落入本申请的范围内。在另外的实施方案中,本发明的核酸序列可以是分离的、重组的和/或与异源核苷酸序列融合,或在DNA文库中。

[0103] 在一些方面。本发明提供用于产生scVACV的多核苷酸,其中VACV选自以下株:Western Reserve、克隆3、Tian Tian、Tian Tian克隆TP5、Tian Tian克隆TP3、NYCBH、NYCBH克隆Acambis 2000、Wyeth、Copenhagen、Lister、Lister 107、Lister-LO、Lister GL-ONC1、Lister GL-ONC2、Lister GL-ONC3、Lister GL-ONC4、Lister CTC1、Lister IMG2(Turbo FP635)、IHD-W、LC16m18、Lederle、Tashkent克隆TKT3、Tashkent克隆TKT4、USSR、Evans、Praha、L-IVP、V-VET1或LIVP6.1.1、Ikeda、EM-63、Malbran、Duke、3737、CV-1、Connaught Laboratories、Serro 2、CM-01、NYCBH Dryvax克隆DPP13、NYCBH Dryvax克隆DPP15、NYCBH Dryvax克隆DPP20、NYCBH Dryvax克隆DPP17、NYCBH Dryvax克隆DPP21、VACV-IOC、安卡拉绒毛膜尿囊痘苗病毒(CVA)、改良的安卡拉痘苗病毒(MVA)和MVA-BN。在一个优选实施方案中,scVACV来源于株NYCBH克隆Acambis 2000或ACAM2000。

[0104] 在一方面,本发明提供用于产生合成嵌合痘苗病毒(scVACV)的多核苷酸。在一个具体实施方案中,scVACV基因组可以基于关于VACV株NYCBH克隆ACAM2000描述的公开的基因组序列(GenBank登录号AY313847;Osborne JD等Vaccine.2007;25(52):8807-32)。本发

明各个方面显示了使用本发明的方法,来自痘苗病毒(VACV)株WR的发夹环可以连接到VACV基因组株NYCBH克隆ACAM2000的末端以产生功能性scVACV颗粒。在一些实施方案中,使用本发明的方法,来自痘苗病毒(VACV)株ACAM2000的末端发夹环可以连接到VACV基因组株NYCBH克隆ACAM2000的末端,以产生功能性scVACV颗粒。scVACV基因组可以分成9个重叠片段,如本发明工作实施例中所述和表1中所示。在一些实施方案中,VACV基因组可以分成2、3、4、5、6、7、8、9、10、11、12、13、14或15个重叠片段。在一些实施方案中,整个基因组可以作为一个片段提供。片段大小如表1中所示。在一些实施方案中,VACV基因组可以分成2、3、4、5、6、7、8、9、10、11、12、13、14或15个重叠片段。在一些实施方案中,整个基因组可以作为一个片段提供。片段大小如表1中所示。本发明各方面的多核苷酸包含与SEQ ID NO:1-9至少65%、70%、75%、80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%或100%相同的核酸序列。在一些实施方案中,本发明的分离的多核苷酸包含这些序列的变体,其中此类变体可以包括错义突变、无义突变、复制、缺失和/或添加。SEQ ID NO:13和SEQ ID NO:14描述了VACV(WR株)末端发夹环的核苷酸序列。SEQ ID NO:19和SEQ ID NO:20描述了VACV(ACAM2000株)末端发夹环的核苷酸序列。在一些实施方案中,末端发夹环包含与SEQ ID NO:13或与SEQ ID NO:14至少70%、75%、80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%或100%相同的核酸序列。在一些实施方案中,末端发夹环包含与SEQ ID NO:19或与SEQ ID NO:20至少70%、75%、80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%或100%相同的核酸序列。

[0105] 在其他实施方案中,scVACV基因组是基于选自以下的VACV株所选择的病毒株:Western Reserve(Genbank登录号NC 006998;Genbank登录号AY243312)、CL3(Genbank登录号AY313848)、Tian Tian(Genbank登录号AF095689.1)、Tian Tian克隆TP5(JX489136)、TP3(Genbank登录号KC207810)和TP5(Genbank登录号KC207811)、NYCBH、Wyeth、Copenhagen(Genbank登录号M35027)、NYCBH克隆Acambis 2000(Genbank登录号AY313847)、Lister 107(Genbank登录号DQ121394)Lister-LO(Genbank登录号AY678276)、改良的安卡拉痘苗病毒(MVA)(Genbank登录号U94848;Genbank登录号AY603355)、MVA-BN(Genbank登录号DQ983238)、Lederle、Tashkent克隆TKT3(Genbank登录号KM044309)和TKT4(KM044310)、USSR、Evans、Praha、LIVP、Ikeda、IHD-W(Genbank登录号KJ125439)、LC16m8(AY678275)、EM-63、IC、Malbran、Duke(Genbank登录号DQ439815)、3737(Genbank登录号DQ377945)、VACV-IOC(Genbank登录号KT184690和KT184691)、CV-1、Connaught Laboratories、CVA(Genbank登录号AM501482)、Serro 2病毒(Genbank登录号KF179385)、Cantaglo病毒分离株CM-01(Genbank登录号KT013210)、Dryvax克隆DPP15(Genbank登录号JN654981)、DPP20(Genbank登录号JN654985)、DPP13(Genbank登录号JN654980)、DPP17(Genbank登录号JN654983)、DPP21(Genbank登录号JN654986)。

[0106] 在一方面,本发明提供分离的多核苷酸,其包含与参考wtVACV基因组序列的全部或一部分至少90%相同(例如至少91%、92%、93%或94%相同)、至少95%相同(例如至少96%、97%、98%或99%相同)或100%相同的核苷酸序列。在一些实施方案中,本发明的分离的多核苷酸包含参考序列的变体,其中此类变体可以包括错义突变、无义突变、复制、缺失和/或添加。在一些实施方案中,本发明的分离的多核苷酸可以包含参考多核苷酸分子(例如,参考wtVACV基因组)的至少5、6、7、8、9、10、20、30、40、50、60、70、80、90、100、200、

300、400、500、600、700、800、900、1000、2000、3000、4000、5000、6000、7000、8000、9000、10000、15000、20000、25000、30000、35000、40000、45000bp或更多bp连续或非连续的核苷酸。

[0107] 本申请还涵盖与本文公开的多核苷酸序列中任一互补的多核苷酸。多核苷酸可以是单链(编码或反义)或双链,并且可以是DNA(基因组或合成的)或RNA分子。RNA分子包括mRNA分子。另外的编码或非编码序列可以但不一定存在于本发明的多核苷酸中,并且多核苷酸可以但不必连接至其他分子和/或支持材料。

[0108] 如果两个序列中的核苷酸或氨基酸序列在如下所述进行最大对应性比对时是相同的,则两个多核苷酸或多肽序列被认为是"相同的"。两个序列的比较典型地如下进行:通过将序列在比较窗口上比较以鉴定和比较局部区域的序列相似性。本文所用的"比较窗口"是指至少约20个连续位置、通常30至约75或40至约50个连续位置的区段,其中在两个序列进行最佳比对时,序列可以与具有相同数量的连续位置的参考序列比较。多核苷酸或变体也可以或备选地与本发明提供的多核苷酸基本上同源。此类多核苷酸变体能够在中等严格条件下与本发明的多核苷酸(或其互补序列)杂交。

[0109] 适当的"中等严格条件"包括在5X SSC、0.5%SDS、1.0mM EDTA(pH 8.0)的溶液中预洗涤;在50℃-65℃、5X SSC下杂交过夜;接着在65℃下用含有0.1%SDS的2X、0.5X和0.2X SSC中每一种洗涤两次,每次20分钟。

[0110] 如本文所用,"高度严格条件"或"高严格性条件"如下:(1)使用低离子强度和高温进行洗涤,例如在50℃下使用0.015M氯化钠/0.0015M柠檬酸钠/0.1%十二烷基硫酸钠;(2)在杂交过程中在42℃下采用变性剂,诸如甲酰胺,例如具有0.1%牛血清蛋白/0.1%Ficoll/0.1%聚乙烯吡咯烷酮/50mM磷酸钠缓冲液pH 6.5以及750mM氯化钠、75mM柠檬酸钠的50%(v/v)甲酰胺;或(3)在42℃下使用50%甲酰胺、5x SSC(0.75M NaCl、0.075M柠檬酸钠)、50mM磷酸钠(pH 6.8)、0.1%焦磷酸钠、5x Denhardt氏溶液、超声处理的鲑鱼精子DNA(50μg/ml)、0.1%SDS、和10%硫酸葡聚糖,其中在42℃下在0.2x SSC(氯化钠/柠檬酸钠)中以及在55℃下在50%甲酰胺中洗涤,接着进行由55℃下的含有EDTA的0.1x SSC组成的高严格性洗涤。本领域技术人员将知晓如何根据需要调节温度、离子强度等以适应诸如探针长度等的因素。

[0111] 本发明的多核苷酸可以使用化学合成、重组方法或PCR获得。化学多核苷酸合成的方法是本领域公知的,并且无需在这里详细描述。本领域技术人员可以使用本文提供的序列和商业DNA合成仪供应商来产生所需DNA序列。

[0112] 为使用重组方法制备多核苷酸,包含所需序列的多核苷酸可以插入适当载体中,并且接着可以将载体引入适当宿主细胞中进行复制和扩增,如本文进一步描述。可以通过本领域已知的任何方式将多核苷酸插入宿主细胞。通过直接摄取、内吞作用、转染、F-接合或电穿孔引入外源多核苷酸来转化细胞。一旦引入,外源多核苷酸可以作为非整合载体(诸如质粒)保持在细胞内或整合到宿主细胞基因组中。如此扩增的多核苷酸可以通过本领域公知的方法从宿主细胞分离。参见例如,Sambrook等,1989。

[0113] 备选地,PCR允许DNA序列复制。PCR技术是本领域公知的并且描述于美国专利号4,683,195、4,800,159、4,754,065和4,683,202以及PCR:The Polymerase Chain Reaction,Mullis等编辑,Birkauswer Press,Boston,1994中。

[0114] 可以通过在适当的载体中使用分离的DNA并且将其插入适当的宿主细胞中来获得RNA。当细胞复制并且DNA转录为RNA时,可随后使用本领域公知的方法分离RNA,例如,如上文Sambrook等,1989中阐述。

[0115] 在其他实施方案中,本发明的核酸还包括在高度严格条件下与SEQ ID NO:1-9中所述的核苷酸序列或其互补序列杂交的核苷酸序列。本领域普通技术人员将容易理解,可改变促进DNA杂交的适当严格性条件。例如,可以在约45℃下在6.0x氯化钠/柠檬酸钠(SSC)下进行杂交,随后在50℃通过2.0x SSC洗涤。例如,洗涤步骤中的盐浓度可以选自50℃下约2.0x SSC的低严格性至50℃下约0.2x SSC的高严格性。另外,洗涤步骤中的温度可以从室温(约22℃)的低严格性条件增加至约65℃的高严格性条件。可以改变温度和盐两者,或者温度或盐浓度可以保持恒定而改变另一变量。在一个实施方案中,本发明提供了在室温下在6x SSC的低严格性条件下杂交随后在室温下在2x SSC下洗涤的核酸。

[0116] 由于遗传密码中的简并性而不同的分离的核酸也落入本发明一些方面的范围内。例如,许多氨基酸通过多于一种三联体来指定。指定相同氨基酸或同义密码子(例如,CAU和CAC是组氨酸的同义密码子)的密码子可以引起不影响蛋白氨基酸序列的“沉默”突变。本领域技术人员将理解,由于天然等位基因变异,编码特定蛋白的核酸的一个或多个核苷酸(可达核苷酸的约3-5%)的这些变异可以存在于给定物种的成员中。任何和所有这些核苷酸变异和产生的氨基酸多态性都在本申请的范围内。

[0117] 本发明一方面另外提供用于克隆本发明的多核苷酸的重组克隆载体和表达载体。本发明的一方面进一步提供包含多核苷酸分子或重组载体的转化宿主细胞,和从其衍生的新毒株或细胞系。

[0118] 宿主细胞可以是细菌细胞、酵母细胞、丝状真菌细胞、藻类细胞、昆虫细胞或哺乳动物细胞。在一些实施方案中,宿主细胞是大肠杆菌。已经开发了专用于这些宿主细胞中每一种的各种各样的不同载体,包括噬菌体、高拷贝数质粒、低拷贝数质粒和穿梭载体等,并且这些中的任一种可以用于实施本发明。

[0119] 适当的克隆载体可以根据标准技术构建,或者可以选自本领域可用的大量克隆载体。尽管所选择的克隆载体可以根据意欲使用的宿主细胞而改变,但是适用的克隆载体通常具有自我复制的能力,可具有特定限制性核酸内切酶的单一靶标,和/或可以携带可用于选择含有载体的克隆的标记物的基因。适当的实例包括质粒和细菌病毒,例如pBAD18、pUC18、pUC19、Bluescript(例如pBS SK+)及其衍生物、mp18、mp19、pBR322、pMB9、ColE1、pCR1、RP4、噬菌体DNA和穿梭载体如pSA3和pAT28。这些和许多其他克隆载体可从商业供应商如BioRad、Stratagene和Invitrogen获得。

[0120] 为了帮助选择用本发明的克隆载体转化或转染的宿主细胞,载体可以改造以进一步包括用于报告基因产物或其他选择标记物的编码序列。如上所述,此类编码序列优选与调节元件编码序列可操作关联。用于本发明的一些方面的报告基因是本领域公知的并且包括编码绿色荧光蛋白、荧光素酶、xylE和酪氨酸酶等的那些基因。编码选择标记物的核苷酸序列是本领域公知的,并且包括编码赋予抗生素或抗代谢物抗性的基因产物或提供营养缺陷需要的基因产物的核苷酸序列。这些序列的实例包括编码对氨苄青霉素、红霉素、硫链丝菌肽或卡那霉素等的抗性的那些序列。

[0121] 含有目标多核苷酸的载体和/或多核苷酸本身可以通过多种适当方式中任一种引

入宿主细胞中,包括电穿孔,使用氯化钙、氯化铷、磷酸钙、DEAE-葡聚糖或其他物质的转染;微弹轰击(microprojectile bombardment);脂质体转染;和感染(例如当载体是诸如痘苗病毒的传染性因子时)。引入载体或多核苷酸的选择将通常取决于宿主细胞的特征。

[0122] 本发明的一个方面进一步提供包含多核苷酸分子或重组载体的经转化的宿主细胞,和从其衍生的新的毒株或细胞系。在一些实施方案中,用于实施本发明的宿主细胞是大肠杆菌细胞。可以典型地使用大肠杆菌菌株,诸如例如大肠杆菌TOP10或大肠杆菌BL21(DE3)、DH5α等,其可获自美国典型培养物保藏中心(ATCC)(10801University Blvd.,Manassas,Va.20110,USA)和商业来源。在一些实施方案中,可以使用其他原核细胞或真核细胞。在一些实施方案中,宿主细胞是选自以下的属的成员:梭菌属(Clostridium)、发酵单胞菌属(Zymomonas)、埃希氏菌属(Escherichia)、沙门氏菌属(Salmonella)、沙雷氏菌属(Serratia)、欧文氏菌属(Erwinia)、克雷伯氏菌属(Klebsiella)、志贺氏菌属(Shigella)、红球菌属(Rhodococcus)、假单胞菌属(Pseudomonas)、芽孢杆菌属(Bacillus)、乳杆菌属(Lactobacillus)、肠球菌属(Enterococcus)、产碱菌属(Alcaligenes)、类芽孢杆菌属(Paenibacillus)、节杆菌属(Arthrobacter)、棒杆菌属(Corynebacterium)、短杆菌属(Brevibacterium)、裂殖酵母属(Schizosaccharomyces)、克鲁维酵母属(Kluyveromyces)、耶氏酵母属(Yarrowia)、毕赤酵母属(Pichia)、假丝酵母属(Candida)、毕赤酵母属(Pichia)或酵母属(Saccharomyces)。这样的转化的宿主细胞通常包括但不限于微生物,诸如用重组噬菌体DNA、质粒DNA或粘粒DNA载体转化的细菌或用重组载体转化的酵母等。优选的真核宿主细胞包括酵母细胞,但是哺乳动物细胞或昆虫细胞也可以有效地利用。适当的宿主细胞包括原核生物(诸如大肠杆菌、枯草芽孢杆菌(B.subtillis)、变铅青链霉菌(S.lividans)或谷氨酸棒杆菌(C.glutamicum))和酵母(诸如酿酒酵母(S.cerevisae)、裂殖酵母(S.pombe)、巴斯德毕赤酵母(P.pastoris)或乳酸克鲁维酵母(K.lactis)))。

[0123] 在一方面,本发明还包括scVACV的基因组、其重组体或其功能部分。病毒基因组的功能部分可以为编码蛋白或其部分(例如结构域,表位等)的基因组的一部分,包含调节元件或调节元件的组件(诸如启动子、增强子、顺式或反式作用元件等)的部分。该病毒序列可以用于鉴定或分离病毒或其重组体,例如通过使用PCR、杂交技术或者通过建立ELISA测定。

[0124] 本发明的药物组合物

[0125] 一方面,本发明涉及包含本发明的scVACV和药学上可接受的载体的药物组合物。

[0126] 术语“药学上可接受”是指被联邦政府或州政府的管理机构批准或者在美国药典或其他公认的药典中列出适用于动物和更具体地适用于人类。术语“载体”是指与药物组合物(例如,免疫原性或疫苗制剂)一起施用的稀释剂、佐剂、赋形剂或媒介物。也可以使用盐水溶液和右旋糖水溶液和甘油溶液作为液体载体,特别是用于注射液。适当的赋形剂包括淀粉、葡萄糖、乳糖、蔗糖、明胶、麦芽、大米、面粉、白垩、硅胶、硬脂酸钠、甘油单硬脂酸酯、滑石、氯化钠、脱脂奶粉、甘油、丙烯、二醇、水、乙醇等等。适当的药学载体的实例描述于E.W.Martin的“Remington’s Pharmaceutical Sciences”。制剂应当适合给药方式。

[0127] 在一些实施方案中,本发明的药物组合物可以通过标准给药途径施用。许多方法可以用于将制剂引入受试者中,这些包括但不限于鼻内、气管内、口服、皮内、肌内、腹膜内、静脉内、结膜和皮下途径。

[0128] 例举性用途

[0129] 预防或治疗致病性痘病毒感染

[0130] 在一些实施方案中,本发明的合成嵌合痘苗病毒(scVACV)可以用于免疫接种或触发或增强受试者对致病性痘病毒感染的免疫反应。在另一个实施方案中,scVACV可用于触发或增强针对痘苗病毒的免疫反应。在另一个实施方案中,scVACV可用于触发或增强针对天花病毒的免疫反应。在另一个实施方案中,scVACV可用于触发或增强针对猴痘病毒的免疫反应。在另一个实施方案中,scVACV可用于预防、控制或治疗受试者中一种或多种致病性痘病毒感染,诸如用于治疗天花病毒感染。在一些实施方案中,scVACV选自以下痘苗病毒的株:Western Reserve、克隆3、Tian Tian、Tian Tian克隆TP5、Tian Tian克隆TP3、NYCBH、NYCBH克隆Acambis 2000、Wyeth、Copenhagen、Lister、Lister 107、Lister-LO、Lister GL-ONC1、Lister GL-ONC2、Lister GL-ONC3、Lister GL-ONC4、Lister CTC1、Lister IMG2(Turbo FP635)、IHD-W、LC16m18、Lederle、Tashkent克隆TKT3、Tashkent克隆TKT4、USSR、Evans、Praha、L-IVP、V-VET1或LIVP 6.1.1、Ikeda、EM-63、Malbran、Duke、3737、CV-1、Connaught Laboratories、Serro 2、CM-01、NYCBH Dryvax克隆DPP13、NYCBH Dryvax克隆DPP15、NYCBH Dryvax克隆DPP20、NYCBH Dryvax克隆DPP17、NYCBH Dryvax克隆DPP21、VACV-IOC、安卡拉绒毛膜尿囊痘苗病毒(CVA)、改良的安卡拉痘苗病毒(MVA)和MVA-BN。在优选实施方案中,scVACV来源于株NYCBH克隆Acambis 2000或ACAM2000。

[0131] 一方面,本发明的scVACV可用于免疫原性制剂,例如疫苗制剂。制剂可以用于预防、控制、中和、治疗和/或改善致病性痘病毒感染。免疫原性制剂可以包括活scVACV或灭活scVACV。scVACV可以通过本领域技术人员公知的方法灭活。常见方法使用福尔马林和加热进行灭活。在一些实施方案中,免疫原性制剂包括活疫苗。可以使用常规方法来实现这种活免疫原性制剂的生产,所述方法包括在细胞培养物中繁殖scVACV和随后进行纯化。例如,scVACV可以在BHK、BGMK、BRL3A、BSC-40、CEF、CEK、CHO、COS、CVI、HaCaT、HEL、HeLa细胞、HEK293、人骨骼骨肉瘤细胞系143B、MDCK、NIH/3T3、Vero细胞等中培养,这可由本领域技术人员来确定。

[0132] 一方面,本发明的scVACV可用于预防、控制或治疗天花。在另一方面,本发明的scVACV可用作疫苗来预防已经暴露、潜在暴露或处于暴露于天花风险下的个体或群体中的天花。本发明各方面的scVACV可用于产生新的天花疫苗的国内储备。在一些实施方案中,本发明的scVACV可以预防性地施用于防卫人员、急救人员等。

[0133] 在一个实施方案中,包含本发明的scVACV的组合物用作天花疫苗。一方面,根据本发明的方法产生的本发明的scVACV将具有小空斑表型。通常,小空斑表型被认为是反映减毒。因此,根据本发明的各种方法产生的scVACV提供了对现有天花疫苗的安全替代。在一些实施方案中,疫苗对于免疫抑制的受试者(例如HIV患者、进行化疗的患者、进行癌症治疗的患者、风湿病或自身免疫病患者、正在进行或已经接受器官或组织移植的患者、具有免疫缺陷的患者、儿童、孕妇、患有特应性皮炎、湿疹、银屑病、心脏病的患者和使用免疫抑制剂的患者等)可安全给药,所述受试者可患有来自现有天花疫苗的严重并发症,和因此禁用现有的天花疫苗。在一些实施方案中,疫苗可以与一种或多种抗病毒治疗组合使用以抑制病毒复制。在一些实施方案中,疫苗可以与brincidofovir治疗组合使用以抑制病毒复制。在一些实施方案中,疫苗可以与替韦立马(tecovirimat)/SIGA-246治疗组合使用以抑制病毒复制。在一些实施方案中,疫苗可以与无环核苷磷酸酯(西多福韦(cidofovir))、无环核苷或

膦酸酯的口服烷氧基烷基前药(brincidofovir或CMX001)组合使用。在一些实施方案中,疫苗可以与痘苗免疫球蛋白(VIG)组合使用。在一些实施方案中,疫苗可以在先前已经用来源于VACV、VARV或HPXV的肽或蛋白抗原免疫的受试者中使用。在一些实施方案中,疫苗可以在先前已经用杀死或灭活的VACV免疫的受试者中使用。在一些实施方案中,疫苗可以在先前已经用复制缺陷的/缺陷型VACV病毒毒株MVA(改良的安卡拉痘苗病毒)免疫的受试者中使用。在一些实施方案中,包含本发明的scVACV的疫苗制剂可以包含活的或灭活的scVACV。

[0134] 在一个实施方案中,将包含本发明的scVACV的组合物用作天花疫苗。scVACV可以基于选自以下的VACV株:ACAM2000(Genbank登录号AY313847)、Western Reserve(Genbank登录号NC 006998;Genbank登录号AY243312)、CL3(Genbank登录号AY313848)、Tian Tian(Genbank登录号AF095689.1)、Tian Tian克隆TP5(JX489136)、TP3(Genbank登录号KC207810)和TP5(Genbank登录号KC207811)、NYCBH、Wyeth、Copenhagen(Genbank登录号M35027)、NYCBH克隆Acambis 2000(Genbank登录号AY313847)、Lister 107(Genbank登录号DQ121394)Lister-LO(Genbank登录号AY678276)、改良的安卡拉痘苗病毒(MVA)(Genbank登录号U94848;Genbank登录号AY603355)、MVA-BN(Genbank登录号DQ983238)、Lederle、Tashkent克隆TKT3(Genbank登录号KM044309)和TKT4(KM044310)、USSR、Evans、Praha、LIVP、Ikeda、IHD-W(Genbank登录号KJ125439)、LC16m8(AY678275)、EM-63、IC、Malbran、Duke(Genbank登录号DQ439815)、3737(Genbank登录号DQ377945)、CV-1、Connaught Laboratories、CVA(Genbank登录号AM501482)、Serro 2病毒(Genbank登录号KF179385)、Cantaglo病毒分离株CM-01(Genbank登录号KT013210)、Dryvax克隆DPP15(Genbank登录号JN654981)、DPP20(Genbank登录号JN654985)、DPP13(Genbank登录号JN654980)、DPP17(Genbank登录号JN654983)、DPP21(Genbank登录号JN654986)和IOC(Genbank登录号KT184690和KT184691)。在一个实施方案中,用作天花疫苗的scVACV是基于株ACAM2000(Genbank登录号AY313847)。在一个实施方案中,用作天花疫苗的scVACV是基于株VACV-IOC(Genbank登录号KT184690和KT184691)。在一个实施方案中,用作天花疫苗的scVACV是基于株MVA(Genbank登录号U94848;Genbank登录号AY603355)。在一个实施方案中,用作天花疫苗的scVACV是基于株MVA-BN(Genbank登录号DQ983238)。在一些实施方案中,包含本发明的scVACV的疫苗制剂可以包含活的或灭活的scVACV。

[0135] 在一些实施方案中,包含本发明的scVACV的组合物用作针对VACV感染、MPXV感染或CPXV感染的疫苗。

[0136] 在一些实施方案中,本发明的scVACV可以设计成表达异源抗原或表位,并且可以用作针对此类抗原和/或表位的来源生物体的疫苗。

[0137] 本发明的免疫原性制剂(例如疫苗)包含有效量的scVACV和药学上可接受的载体。术语“药学上可接受”是指被联邦政府或州政府的管理机构批准或者在美国药典或其他公认的药典中列出适用于动物,和更具体地适用于人类。术语“载体”是指与药物组合物(例如,免疫原性或疫苗制剂)一起施用的稀释剂、佐剂、赋形剂或媒介物。也可以使用盐水溶液和右旋糖水溶液和甘油溶液作为液体载体,特别是用于注射液。适当的赋形剂包括淀粉、葡萄糖、乳糖、蔗糖、明胶、麦芽、大米、面粉、白垩、硅胶、硬脂酸钠、甘油单硬脂酸酯、滑石、氯化钠、脱脂奶粉、甘油、丙烯、二醇、水、乙醇等。适当的药学载体的实例描述于E.W.Martin的“Remington’s Pharmaceutical Sciences”。制剂应当适合给药方式。具体制剂也可以取决

于scVACV是活的还是灭活的。在一些实施方案中,纯化的本发明的scVACV可以冻干以备以后使用或者可以立即制备在药物溶液中。scVACV也可以在使用或不使用辅剂或载体的情形稀释在生理学上可接受的溶液如无菌盐水中。

[0138] 一方面,本发明的免疫原性制剂(例如疫苗)可以通过划痕施用于患者。疫苗也可以通过任何其他标准给药途径施用。许多方法可以用于引入免疫原制剂(例如疫苗),这些包括但不限于鼻内、气管内、口服、皮内、肌内、腹膜内、静脉内、结膜和皮下途径。在鸟类中,方法可以进一步包括后鼻孔接种。作为肠胃外给药的备选方式,本发明一方面还包括用于农业目的的大规模给药途径,诸如通过饮用水或喷雾。备选地,可以优选通过其天然感染途径引入本发明的scVACV。在一些实施方案中,本发明的免疫原性制剂作为注射液、表达疫苗的可消费转基因植物、缓释凝胶或可植入包封组合物、固体植入物或核酸施用。免疫原性制剂也可以在乳霜、乳液、软膏、皮肤贴剂、锭剂或口服液诸如混悬剂、溶液剂和乳剂(水包油或油包水)中施用。用于活的复制性天花疫苗的可接受给药途径是经皮划痕,其在疫苗接种位点处产生持续数天的病毒排出病变。该病变是疫苗接触传播至个体的潜在来源,所述个体可能禁忌接受活疫苗。因此,免疫原性制剂的肌内给药可以提供优势。在一个优选实施方案中,scVACV ACAM2000是肌内给药。在另一个优选实施方案中,给药是通过经皮划痕。肌内给药也可以用于其他合成嵌合正痘病毒,诸如合成嵌合马痘病毒(scHPXV)。在肌内给药的情形中,重要的是使用具有正确长度的针头以到达肌肉块,且不渗透至皮下组织。当施用肌内注射剂时,针头应以90°角度插入。

[0139] 在某些实施方案中,本发明的免疫原性制剂(例如疫苗)不导致完全保护免受感染,但相比于未治疗的受试者,导致较低滴度或减少数量的病原体(例如致病性痘病毒)。在某些实施方案中,给药本发明的免疫原性制剂导致相对于未治疗受试者的病原体滴度的0.5倍、1倍、2倍、4倍、6倍、8倍、10倍、15倍、20倍、25倍、50倍、75倍、100倍、125倍、150倍、175倍、200倍、300倍、400倍、500倍、750倍或1,000倍或更大的减少。降低病原体的滴度、数目或总负荷的益处包括但不限于感染症状的严重程度降低以及与感染相关的疾病或病症的持续时间减短。

[0140] 在某些实施方案中,本发明的免疫原性制剂(例如疫苗)不导致完全保护免受感染,但与未治疗的受试者相比,导致症状数目减少或症状强度降低,或发病率降低或死亡率降低。

[0141] 在各种实施方案中,将本发明的免疫原性制剂(例如疫苗)或通过本发明的scVACV产生的抗体与用于预防感染(例如,致病性痘病毒感染)的一种或多种其他疗法(例如,抗病毒或免疫调节疗法)组合施用于受试者。在其他实施方案中,将免疫原性制剂或通过本发明的scVACV产生的抗体与用于治疗感染(例如,致病性痘病毒感染)的一种或多种其他疗法(例如,抗病毒或免疫调节疗法)组合施用于受试者。在还有的其他实施方案中,将免疫原性制剂或通过本发明的scVACV产生的抗体与用于控制和/或改善感染(例如,致病性痘病毒感染)的一种或多种其他疗法(例如,抗病毒或免疫调节疗法)组合施用于受试者。在具体实施方案中,将免疫原性制剂或通过本发明的scVACV产生的抗体与用于预防天花的一种或多种其他疗法(例如,抗病毒或免疫调节疗法)组合施用于受试者。在另一个具体实施方案中,将免疫原性制剂或通过本发明的scVACV产生的抗体与用于治疗天花的一种或多种其他疗法(例如,抗病毒或免疫调节疗法)组合施用于受试者。在一些实施方案中,疫苗可以与一种或

多种抗病毒治疗组合使用以抑制病毒复制。在一些实施方案中,疫苗可以与brincidofovir治疗组合使用以抑制病毒复制。在一些实施方案中,疫苗可以与替韦立马/SIGA-246治疗组合使用以抑制病毒复制。在一些实施方案中,疫苗可以与无环核苷磷酸酯(西多福韦(cidofovir))、无环核苷或膦酸酯的口服烷氧基烷基前药(brincidofovir或CMX001)组合使用。在一些实施方案中,疫苗可以与痘苗免疫球蛋白(VIG)组合使用。在一些实施方案中,疫苗可以在先前已经用来源于VACV、VARV或HPXV的肽或蛋白抗原免疫的受试者中使用。在一些实施方案中,疫苗可以在先前已经用杀死或灭活的VACV免疫的受试者中使用。在一些实施方案中,疫苗可以在先前已经用复制缺陷的/缺陷型VACV病毒毒株、MVA(改良的安卡拉痘苗病毒)免疫的受试者中使用。

[0142] 本领域技术人员公知的任何抗病毒剂都可以用于本发明各方面的制剂(例如疫苗制剂)和方法中。抗病毒剂的非限制性实例包括抑制和/或减少病毒与其受体连接、病毒至细胞中的内化、病毒复制或病毒从细胞中释放的蛋白质、多肽、肽、融合蛋白抗体、核酸分子、有机分子、无机分子和小分子。具体地,抗病毒剂包括但不限于阻断胞外病毒成熟的抗病毒剂(替韦立马/SIGA-246)、无环核苷磷酸酯(西多福韦(cidofovir))、无环核苷或膦酸酯的口服烷氧基烷基前药(brincidofovir或CMX001)或痘苗免疫球蛋白(VIG)。在一些实施方案中,抗病毒剂包括但不限于核苷类似物(例如,齐多夫定(zidovudine)、阿昔洛韦(acyclovir)、更昔洛韦(gangcyclovir)、阿糖腺苷(vidarabine)、碘苷(idoxuridine)、三氟尿苷(trifluridine)和利巴韦林(ribavirin))、膦甲酸(foscarnet)、金刚胺(amantadine)、金刚乙胺(rimantadine)、沙奎那韦(saquinavir)、茚地那韦(indinavir)、利托那韦(ritonavir)、α-干扰素和其他干扰素和AZT。

[0143] 剂量和给药方案可以由本领域技术人员根据待治疗的受试者的需要来确定。本领域技术人员可以考虑诸如受试者的年龄或体重、所治疗的疾病或病症的严重性和受试者对治疗的反应的因素。在一些实施方案中,本发明的组合物例如根据需要或每天给药。剂量给药可以在不同时间段进行。例如,给药方案可以持续1周、2周、3周、4周、5周、6周、7周、8周、9周、10周、11周、12周或更久。在一些实施方案中,给药方案将持续1个月、2个月、3个月、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、12个月或更久。

[0144] 在一些方面,本发明的scVACV还可以用于产生适用于被动免疫疗法、诊断或预后免疫测定等的抗体。产生抗体的方法是本领域公知的。抗体可以在用于免疫疗法中之前进一步修饰(例如,嵌合、人源化等)。

[0145] 溶瘤剂

[0146] 本发明中使用的“溶瘤病毒”或“溶瘤剂”被认为是典型地能够通过感染肿瘤细胞杀死所述肿瘤细胞(非抗性)的任何病毒。

[0147] 一方面,本发明的合成嵌合痘病毒(scVACV)可以用作在癌细胞中选择性复制和杀死癌细胞的溶瘤剂。在另一方面,本发明涉及一种用于诱导受试者中溶瘤反应的方法,包括向所述受试者施用包含本发明的scVACV的组合物。快速分裂的细胞(诸如癌细胞)通常比未分裂细胞更容易感染痘病毒。痘病毒的许多特征,诸如在人体内的安全性、高滴度储液生产的容易性、病毒制剂的稳定性和在肿瘤细胞中复制后诱导抗肿瘤免疫性的能力使得痘病毒成为理想的溶瘤剂。根据本发明的各种方法产生的scVACV可以包含使得它们适合于治疗癌症的一个或多个修饰。因此,在一方面,本发明提供在癌细胞中诱导死亡的方法,该方法包

括将细胞与分离的scVACV或包含本发明的scVACV的药物组合物接触。一方面,本发明提供一种治疗癌症的方法,该方法包括向有需要的患者施用治疗有效量的本发明的scVACV。另一方面包括本文所述的用于治疗癌症或诱导肿瘤性病症死亡的scVACV或组合物。另一方面包括本文所述的scVACV或组合物在肿瘤性病症细胞(诸如癌细胞)中诱导死亡或治疗肿瘤性病症(诸如癌症)的用途。在一些实施方案中,将痘病毒溶瘤疗法与一种或多种常规癌症疗法(例如,手术、化疗、放疗、热疗和生物/免疫疗法)组合施用。在特定实施方案中,溶瘤病毒是scVACV NYCBH株、克隆Acambis 2000或ACAM2000。

[0148] 使用本申请的方法,可以容易地引入一个或多个所需的基因和从scVACV基因组中缺失一个或多个不希望有的基因。在一些实施方案中,用作溶瘤剂的本发明的scVACV被设计来表达转基因以增强它们的免疫反应性、抗肿瘤靶向性和/或效力、细胞至细胞扩散和/或癌症特异性。在一些实施方案中,设计或工程化改造本发明的scVACV来表达免疫调节基因(例如GM-CSF或阻断TNF功能的病毒基因)。在一些实施方案中,设计本发明的scVACV以包括表达减弱毒力的因子的基因。在一些实施方案中,本发明的scVACV被设计或工程化改造来表达治疗剂(例如hEPO、BMP-4、针对特定肿瘤抗原或其部分的抗体等)。在一些实施方案中,本发明的scVACV已经设计或工程化改造来包含gmCSF基因。在一些实施方案中,本发明的scVACV已经经修饰以减毒。在一些实施方案中,本发明的scVACV经设计或工程化改造来缺乏病毒胸苷激酶(TK)基因。在一些实施方案中,本发明的scVACV经设计或工程化改造来缺乏核糖核苷酸还原酶基因。在一些实施方案中,本发明的scVACV经设计或工程化改造来缺乏痘苗生长因子基因。在一些实施方案中,本发明的scVACV经设计或工程化改造来缺乏血凝素基因。

[0149] 一方面,本发明的scVACV适用于治疗各种各样的肿瘤性病症和/或癌症。在一些实施方案中,癌症类型包括但不限于骨癌、乳腺癌、膀胱癌、宫颈癌、结直肠癌、食管癌、神经胶质瘤、胃癌、胃肠癌、头颈癌、肝癌诸如肝细胞癌、白血病、肺癌、淋巴瘤、卵巢癌、胰腺癌、前列腺癌、肾癌、皮肤癌诸如黑素瘤、睾丸癌等或可以治疗的任何其他肿瘤或瘤前病变。

[0150] 在另一个实施方案中,所述方法另外包括检测施用的scVACV在肿瘤性病症或癌细胞和/或在施用本文所述的分离的或重组病毒或组合物的受试者的样品中的存在。例如,可以在施用本文所述的scVACV或组合物之前和/或在施用本文所述的scVACV或组合物之后测试受试者,以评估例如感染的进展。在一些实施方案中,本发明的scVACV包括检测盒,并且检测施用的嵌合VACV的存在包括检测由检测盒编码的蛋白。例如,其中检测盒编码荧光蛋白,使用将荧光可视化的方法对受试者或样品成像。

[0151] 在一方面,本发明的溶瘤制剂包含有效量的本发明的scVACV和药学上可接受的载体。术语“药学上可接受”已经在以上前面部分中解释。

[0152] 在一些实施方案中,本发明的组合物在痘病毒治疗设施中施用。在某些方面,痘病毒治疗设施是如下设施,其中需要用本发明的组合物或方法免疫接种或治疗的受试者可以在使他们与不打算进行免疫或治疗的其他受试者或可能被受治疗的受试者潜在感染的其他受试者(例如,护理人员和家庭成员)隔离的环境中进行免疫或治疗。在一些实施方案中,不打算进行免疫或可能被受治疗的受试者潜在感染的受试者包括HIV患者、正在进行化疗的患者、正在进行癌症、风湿病症或自身免疫病症治疗的患者、正在接受或已经接受器官或组织移植的患者、具有免疫缺陷的患者、儿童、孕妇、患有特应性皮炎、湿疹、银屑病、心脏病

的患者和使用免疫抑制剂的患者等。在一些实施方案中,痘病毒治疗设施是正痘病毒治疗设施。在一些实施方案中,痘病毒治疗设施是天花治疗设施。

[0153] 在一些实施方案中,包含scVACV的本发明的组合物由天花不良事件方面的专家施用。在一些实施方案中,天花不良事件包括但不限于疫苗性湿疹、进行性痘疹、疫苗接种后脑炎、心肌炎和扩张型心肌病。

[0154] 用于重组基因表达的病毒载体

[0155] 一方面,本发明的合成嵌合痘病毒(scVACV)可以工程化改造成携带异源序列。异源序列可以来自不同痘病毒种或来自任何非痘病毒来源。一方面,异源序列是选自任何非痘病毒来源的抗原性表位。如本申请中使用的非痘病毒来源是指与痘病毒不同的生物体。在一些实施方案中,重组病毒可以表达一种或多种来自非痘病毒来源的抗原表位,包括但不限于恶性疟原虫(Plasmodium falciparum)、分枝杆菌(mycobacteria)、炭疽芽孢杆菌(Bacillus anthracis)、霍乱弧菌(Vibrio cholerae)、MRSA、弹状病毒、流感病毒、黄病毒科的病毒、副粘病毒、肝炎病毒、人类免疫缺陷病毒、或来自引起出血热的病毒(诸如汉坦病毒(hantaviruses)或丝状病毒,即埃博拉或马尔堡病毒)。在另一方面,异源序列是来自不同痘病毒种的抗原性表位。这些病毒序列可以用于修饰scVACV的宿主谱或免疫原性。

[0156] 在一些实施方案中,本发明的scVACV可以编码表达治疗性核酸(例如,反义核酸)或治疗性肽(例如,具有所需生物学活性的肽或蛋白)的异源基因/核酸。

[0157] 在一些实施方案中,异源核酸序列的表达优选地但非排他性地处于痘病毒启动子的转录控制之下。在一些实施方案中,异源核酸序列优选插入病毒基因组的非必需区域中。用于将异源序列插入痘病毒基因组中的方法是本领域技术人员已知的。在一些实施方案中,异源核酸通过化学合成引入。在例举性实施方案中,异源核酸可以克隆到本发明的scVACV的VACV105/J2R基因座中。

[0158] 本发明一方面的scVACV可以用于将异源核酸序列引入靶细胞,该序列是与靶细胞同源或异源。将异源核酸序列引入靶细胞中可用于体外产生由所述序列编码的异源肽或多肽和/或完整病毒。在一个实施方案中,该方法包括用本发明的scVACV感染宿主细胞;在适当条件下培养感染的宿主细胞;和分离和/或富集通过宿主细胞产生的肽、蛋白和/或病毒。本领域技术人员公知用于培养scVACV-感染的宿主细胞以便表达异源肽或多肽的适当条件,并且根据所用的宿主细胞而改变(参见例如,Molecular Cloning:A Laboratory Manual,第二版(Sambrook等,1989))。

[0159] 应当理解,已经描述的本申请的实施方案仅仅阐明本申请的原理的一些应用。基于本文提供的教导,本领域技术人员可以在不背离本申请的真实精神和范围的情况下进行许多修改。

[0160] 以下实施例被阐述为代表本申请。这些实施例不应解释为限制本发明的范围,因为这些和其他等同实施方案鉴于本公开内容、附图和后附实施方案将是显而易见的。

实施例

[0161] 实施例1.病毒基因组的重叠片段的选择和设计

[0162] 含有VACV WR株发夹和双链体序列的合成嵌合VACV ACAM2000(scVACV ACAM2000-WR DUP/HP)

[0163] scVACV基因组的设计是基于先前描述的VACV ACAM2000的基因组序列[GenBank登录号AY313847](Osborne JD等Vaccine.2007;25(52):8807-32)。基因组分成9个重叠片段(图1)。这些片段经设计以使得它们与各个相邻片段共有至少1.0kbp的重叠序列(即同源性),以提供同源重组将驱动全长基因组组装的位点(表1)。这些重叠序列提供足够的同源性以在共转染片段之间准确地进行重组(Yao XD,Evans DH.Journal of Virology.2003;77(13):7281-90)。

[0164] 表1:本研究使用的VACV ACAM2000基因组片段。描述了在VACV ACAM2000基因组[GenBank登录号AY313847]内的大小和序列。

[0165]

片段名称	大小(bp)	序列
GA_LITR ACAM2000	18,525	SEQ ID NO:1
GA_FRAG_1 ACAM2000	24,931	SEQ ID NO:2
GA_FRAG_2 ACAM2000	23,333	SEQ ID NO:3
GA_FRAG_3 ACAM2000	26,445	SEQ ID NO:4
GA_FRAG_4 ACAM2000	26,077	SEQ ID NO:5
GA_FRAG_5 ACAM2000	24,671	SEQ ID NO:6
GA_FRAG_6 ACAM2000	25,970	SEQ ID NO:7
GA_FRAG_7 ACAM2000	28,837	SEQ ID NO:8
GA_RITR ACAM2000	17,641	SEQ ID NO:9

[0166] 为辅助这些片段的亚克隆,AarI和BsaI限制位点在所有片段(除了两个ITR编码片段以外)中被沉默突变。在这些区域含有对于高效DNA复制和多联体解析度重要的核苷酸序列特异性识别位点的情况下,在这两个ITR-编码片段中BsaI限制位点不被突变。

[0167] 将在痘病毒早期晚期启动子的控制下的YFP/gpt盒引入胸苷激酶基因座中,使得VACV ACAM2000(VACV ACAM2000 YFP-gpt::105)的再激活在荧光显微镜下容易可视化。Gpt基因座也提供了使用药物选择来选择再激活的病毒的潜在工具。

[0168] 传统地,末端发夹难以克隆和测序,因此VACV ACAM2000基因组的公布序列不完整并不出人意料。在检查公布的VACV ACAM2000株的极末端区域之后,ACAM2000和非常充分表征的VACV WR株(Genbank登录号#AY243312)之间似乎存在一些差异(图2)。在WR株中,存在紧接着共价闭合发夹环的下游的70bp串联重复序列,该发夹环位于VACV基因组的末端5'和3'端处。这些之后接着是两个125bp重复序列和八个54bp重复序列(图2A)。然而,在公布的VACV ACAM2000序列中,仅鉴定了四个54bp重复序列(图2B)。在(使用Illumina)测序之后证实在VACV ACAM2000的野生型分离株中存在70bp、125bp和54bp的重复序列,表明当前公布的ACAM2000的序列是不完整的。由于Illumina读数的较短读数长度(<300核苷酸),所以本发明人不能准确确定哪个实际的ACAM2000基因组序列是该~3kbp形式。替代地,本发明人决定重建从末端发夹至刚好在C23L基因的终止密码子前具有与VACV WR类似序列的VACV ACAM2000病毒(图2)。这包括125bp和54bp串联重复序列两者,尽管其未包括在公布的ACAM2000序列中,但在执行wtVACV ACAM2000的新一代Illumina测序时检测到了它们。在修饰的VACV ACAM2000左侧和右侧ITR片段的5'端处,还包括NheI限制位点,其允许将70bp串联重复序列直接连接至ITR端(在实施例2中讨论)。wtVACV ACAM2000的F和S末端发夹环序列分别显示在图9以及SEQ ID NO:20和19中。

[0169] 含有VACV ACAM2000株发夹和双链体序列的合成嵌合VACV ACAM2000(scVACV ACAM2000-ACAM2000 DUP/HP)

[0170] scVACV基因组的设计是基于先前描述的VACV ACAM2000的基因组序列[GenBank登录号AY313847](Osborne JD等Vaccine.2007;25(52):8807-32)。基因组分成9个重叠片段(图1)。这些片段经设计以使得它们与各个相邻片段共有至少1.0kbp的重叠序列(即同源性),以提供同源重组将驱动全长基因组组装的位点(表1)。这些重叠的序列提供足够的同源性以在共转染片段之间准确地进行重组(Yao XD,Evans DH.Journal of Virology.2003;77(13):7281-90)。

[0171] 为辅助这些片段的亚克隆,AarI和BsaI限制位点在所有片段(除了两个ITR编码片段以外)中被沉默突变。在这些区域含有对于高效DNA复制和多联体解析(concatemer resolution)重要的核苷酸序列特异性识别位点的情况下,在这两个ITR-编码片段中BsaI限制位点不被突变。

[0172] 将在痘病毒早期晚期启动子的控制下的YFP/gpt盒引入胸苷激酶基因座中,使得VACV ACAM2000(VACV ACAM2000 YFP-gpt::105)的再激活在荧光显微镜下容易可视化。Gpt基因座也提供了使用药物选择来选择再激活的病毒的潜在工具。

[0173] wtVACV ACAM2000的F和S末端发夹环序列分别在图9和SEQ ID NO:20和19中显示。

[0174] 实施例2

[0175] 将VACV WR F和S末端发夹环连接至VACV ACAM2000右侧和左侧ITR片段上

[0176] 合成与VACV WR株相同的70bp重复片段(图2C;SEQ ID NO:10)。在70bp串联重复片段的5'和3'末端处包括SapI和NheI限制位点,以促进分别连接到VACV WR发夹序列和VACV ACAM2000右侧和左侧ITR片段上。在VACV WR末端发夹环可以连接到70bp串联重复片段上之前,必须使用通过IDT技术合成的双链体序列将环延长另外58bp(图3A)。这是由于额外序列紧接在多联体解析位点的下游,在VACV株WR中发现的第一个70bp重复序列之前。双链体序列通过合成两个单链DNA分子来产生,该两个单链DNA分子在一起退火时将产生在5'端具有5'-TGT突出端和在3'端具有5'-GGT突出端的双链体DNA(图3A;SEQ ID NO:11和SEQ ID NO:12)。由于VACV WR F和S末端发夹环在它们的末端环处产生3'-ACA突出端,所以58bp双链体连接至发夹以生成与VACV WR株中发现的直至70bp重复序列的开始处的序列看起来相同的~130bp末端发夹环(图3B)。将该发夹/双链体片段凝胶纯化,然后随后连接到70bp重复片段的SapI消化的末端上。用SapI消化70bp串联重复片段产生三碱基突出端(5'-CCA),其与末端发夹/双链体结构中的5'GGT突出端互补。将70bp串联重复与F末端发夹/双链体结构(图4,泳道4)或S末端发夹/双链体结构(图4,泳道5)以相对于70bp串联重复片段的~5-倍摩尔过量、在DNA连接酶存在下混合。与仅有70bp的反应(图4,泳道3)相比,这在DNA电泳凝胶中产生上移,指示末端发夹/双链体被成功地连接到70bp串联重复片段(图4)。

[0177] 该末端发夹/双链体/70bp串联重复片段随后连接到70bp ACAM2000左侧或右侧ITR片段(先前已经在它们的末端进行修饰从而包括NheI限制位点)上。当消化该片段时,5'-CTAG突出端保留在它们的5'末端。在70bp串联重复片段的3'末端,使用NheI位点将该片段直接连接至VACV ACAM2000 DNA片段的LITR和RITR区。在消化VACV ACAM2000左侧和右侧ITR片段后,使用DNA连接酶,以1:1摩尔比在16℃过夜,将S末端发夹/双链体/70bp串联重复片段或F末端发夹/双链体/70bp串联重复片段分别连接到左侧或右侧ITR片段。随后在65℃

使DNA连接酶热失活,之后转染到休普氏纤维瘤病毒(SFV)-感染的BGMK细胞中。

[0178] 将VACV ACAM2000 F和S末端发夹环连接到VACV ACAM2000右侧和左侧ITR片段上

[0179] 合成与VACV ACAM2000株相同的70bp重复片段。在70bp串联重复片段的5'和3'末端包括SapI和NheI限制位点,以便于分别连接到VACV ACAM2000发夹序列和VACV ACAM2000右侧和左侧ITR片段上。在VACV ACAM2000末端发夹环可以连接到70bp串联重复片段上之前,环必须使用通过IDT Technologies合成的双链体序列延长另外58bp。这是由于额外序列紧接在多联体解析度位点的下游,在VACV株ACAM2000中发现的第一个70bp重复序列之前。双链体序列通过合成两个单链DNA分子来合成,所述两个单链DNA分子在一起退火时将产生在5'端具有5'-TGT突出端和在3'端具有5'-GGT突出端的双链体DNA分子(SEQ ID NO:21和SEQ ID NO:22)。由于VACV ACAM2000F和S末端发夹环在它们的末端环上产生3'-ACA突出端,所以将58bp双链体连接到发夹上以产生~130bp末端发夹环。将该发夹/双链体片段凝胶纯化,然后随后连接到70bp重复片段的SapI消化的末端上。用SapI消化70bp串联重复片段产生三碱基突出端(5'-CCA),其与末端发夹/双链体结构中的5'GGT突出端互补。将70bp串联重复与F末端发夹/双链体结构或S末端发夹/双链体结构以相对于70bp串联重复片段的~5-倍摩尔过量、在DNA连接酶存在下混合。与仅有70bp的反应相比,这在DNA电泳凝胶中产生上移,指示末端发夹/双链体被成功地连接到70bp串联重复片段。

[0180] 该末端发夹/双链体/70bp串联重复片段随后连接到ACAM2000左侧或右侧ITR片段(先前已经在它们的末端进行修饰从而包括NheI限制位点)上。当消化该左侧或右侧ITR片段时,5'-CTAG突出端保留在它们的5'末端。在70bp串联重复片段的3'末端,使用NheI位点将该片段直接连接至VACV ACAM2000 DNA片段的LITR和RITR区。在消化VACV ACAM2000左侧和右侧ITR片段后,使用DNA连接酶,以1:1摩尔比在16℃过夜,将S末端发夹/双链体/70bp串联重复片段或F末端发夹/双链体/70bp串联重复片段分别连接到左侧或右侧ITR片段。随后在65℃使DNA连接酶热失活,之后转染到休普氏纤维瘤病毒(SFV)-感染的BGMK细胞中。

[0181] 实施例3.制备VACV ACAM2000重叠DNA片段

[0182] 使用限制酶I-SceI将表1中每个VACV ACAM2000重叠DNA片段克隆到GeneArt提供的质粒中。在将这些合成的DNA片段转染到BGMK细胞中之前,用I-SceI消化质粒,并将产物在凝胶上运行以证实DNA片段被成功地线性化(图5)。在37℃消化2小时后,将反应物随后在65℃热灭活。将样品保存在冰上或在4℃直至形成末端发夹/双链体/70bp串联重复/ITR片段(如上所述)。

[0183] 实施例4.从化学合成的dsDNA片段中再激活

[0184] SFV株Kasza和BSC-40最初获自美国典型培养物保藏中心。Buffalo绿猴肾(BGMK)细胞获自G.McFadden(University of Florida)。BSC-40和BGMK细胞在37℃在5%CO_2中在补充有L-谷氨酰胺、非必需氨基酸、丙酮酸钠、抗生素和抗真菌剂(antimycotics)和5%胎牛血清(FCS;ThermoFisher Scientific)的最低基本培养基(MEM)中繁殖。

[0185] 在休普氏纤维瘤病毒-感染的细胞中scVACV ACAM2000-WR DUP/HP或scVACV ACAM2000-ACAM2000 DUP/HP的再激活

[0186] 将Buffalo绿猴肾(BGMK)细胞培养在含有MEM的60mm组织培养皿中直至它们达到大约80%汇合。细胞用休普氏纤维瘤病毒(SFV)在无血清MEM中以0.5的MOI在37℃感染1小时。接种物更换3ml含有5%FCS的温热MEM,并返回至培养箱另外一小时。同时,如下设定转

染反应。在37℃大约2小时后,将线性化VACV ACAM2000片段基于包含VACV ACAM2000基因组的每个片段的长度以摩尔当量转染(使用脂染胺(Lipofectamine)2000)到SFV-感染的BGMK细胞中。尝试不同的总DNA量,并且5、6和7.5μg的DNA能够成功地从这些重叠DNA片段中再激活ACAM2000。复合物在室温温育10分钟,然后滴加到先前用SFV感染的BGMK细胞中。感染后大约24小时,培养基用新鲜的含有5%FCS的MEM替换。将细胞在37℃培养另外3-4天(总共4-5天)。

[0187] 通过将感染的细胞刮到细胞培养基中和进行三次冷冻和解冻循环,以回收病毒颗粒。将粗提物在无血清MEM中稀释10^{-2},将4ml接种物铺板在BSC-40细胞的9-16个150mm组织培养板上,以回收再激活的scVACV ACAM2000 YFP-gpt::105。感染后1小时,将接种物更换含有5%FCS和0.9%Noble琼脂的MEM。在倒置显微镜下观察到黄色荧光空斑,挑取单个空斑以进一步分析。将scVACV ACAM2000YFP-gpt::105空斑使用黄色荧光选择进行空斑纯化三次。

[0188] 在4天后,收获含有SFV和VACV ACAM2000克隆两者的感染的平板,接着三次冷冻解冻循环以释放病毒,然后系列稀释和铺板到BSC-40细胞上,其与SFV病毒相比优先促进VACV ACAM2000病毒的生长。进行三轮空斑纯化,接着在10-150mm组织培养板中扩增病毒储液。病毒随后从这些细胞裂解并在36%蔗糖垫层上分离,接着在24%-40%蔗糖密度梯度上进一步纯化。从这些纯化的基因组中分离基因组DNA,并且进行下一代Illumina测序,以证实合成的病毒基因组的序列。

[0189] 实施例4.与野生型ACAM2000病毒相比的生长性质

[0190] 在猴肾上皮(BSC-40)细胞中进行分离的合成嵌合VACV ACAM2000-WR DUP/HP、scVACV ACAM2000-ACAM2000 DUP/HP和野生型VACV ACAM2000病毒的体外多步生长曲线。细胞以0.03的感染复数感染,在指定时间(3h、6h、12h、21h、48h和72h)收获病毒,并且在BSC-40细胞上滴定病毒。图6中显示的数据代表三次独立实验。如图6中所示,在72小时时段内,scVACV ACAM2000-WR DUP/HP和wtVACV ACAM2000病毒以不可区分的生长动力学生长。

[0191] scVACV ACAM2000-WR DUP/HP(YFP-gpt标记物)、scVACV ACAM2000-ACAM2000 DUP/HP(YFP-gpt标记物)、scVACV ACAM2000-WR DUP/HP(无标记物)(YFP-gpt标记物用J2R基因序列替换)、scVACV ACAM2000-ACAM2000 DUP/HP(无标记物)(YFP-gpt标记物用J2R基因序列替换)和wtVACV ACAM2000的生长曲线之间的比较显示这些病毒的生长性质与wtACAM2000 VACV相比没有统计学差异(图7)。

[0192] 实施例5.通过PCR和限制片段分析证实scVACV ACAM2000-WR DUP/HP YFP-gpt::105基因组序列

[0193] 在使用蔗糖梯度离心纯化分离的基因组DNA上进行通过限制消化随后脉冲场凝胶电泳(PFGE)进一步分析scVACV ACAM2000YFP-gpt::105基因组(Yao XD,Evans DH.Methods Mol Biol.2004;269:51-64)。纯化两个独立的scVACV ACAM2000-WR DUP/HP克隆加上VACV_WRΔJ2R对照(它们中J2R基因序列已经用YFP-gpt标记物替换)和wtVACV ACAM2000对照(VAC_ACAM2000),然后保持不被消化、用BsaI、HindIII或NotI和PvuI消化。来自scVACV ACAM2000-WR DUP/HP和wtVACV ACAM2000的分离的基因组DNA用BsaI和HindIII消化。由于scVACV ACAM2000基因组中的大多数BsaI位点已经被沉默突变,所以在BsaI消化后观察到大部分完整的~200kbp片段(图8,泳道8和9)。这不同于wtVACV ACAM2000和wtVACV WR对照

(VAC_WRΔJ2R)基因组,当用BsaI处理时,所述基因组已经充分消化(图8,泳道6和7)。为了证实scVACV ACAM2000-WR DUP/HP基因组仍然可以用另一种酶消化,将这些基因组用HindIII消化,其从scVACVACAM2000-WR DUP/HP克隆产生许多条带(图8,泳道12和13)。为了证实在ITR区域内的70bp串联重复元件的存在,将基因组DNA用NotI和PvuI消化(图8,泳道14至17)。

[0194] 在wtVACV WR对照(VAC_WRΔJ2R)样品中,检测到在约3.6kbp处的条带(用星号标记),其包含在VAC的WR株中所有的70bp串联重复。鉴于VACV WR株用作设计ITR重复元件的合成的模板,预期在NotI/PvuI处理的scVACVACAM2000克隆中检测到一些与WR株中观察到的接近相同大小的条带。当比较两个scVACV ACAM2000-WR DUP/HP克隆时,观察到该区域大小的区别,提示并非所有70bp重复被掺入每个重建的基因组中(图7,泳道16和17)。鉴于其他人已经显示这些重复元件可以在细胞培养物中在选择压力下可以扩大和收缩,这并非出人意料的(Paez和Esteban(1988).Virology;163(1):145-54)。

[0195] 总之,scVACV ACAM2000-WR DUP/HP YFP-gpt::105基因组的体外分析提示:从化学合成的DNA片段再激活VACV ACAM2000-WR DUP/HP是成功的,scVACV ACAM2000-WR DUP/HP病毒在体外表现类似于wtVACV ACAM2000病毒。

[0196] 实施例6.通过全基因组序列分析证实scVACV ACAM2000YFP-gpt::105基因组序列

[0197] 将两个scVACV ACAM2000-WR DUP/HP克隆和两个scVACV ACAM2000-ACAM2000 DUP/HP克隆测序。使用字长为35或61的CLC基因组工作站(版本11)从头组装Illumina读数。随后将组装的重叠群(contigs)导入Snapgene软件并与基于GeneArt提供的合成片段预期的scACAM2000序列的参考序列比对。

[0198] 对于scVACV ACAM2000-WR DUP/HP的克隆1,重叠群1是16,317bp并且对应于大部分ITR区域(除了串联重复序列以外)。重叠群2是167,020bp,并且与基因组的中心保守区域(核苷酸位置19,467至186,486)比对。对于scVACV ACAM2000-WR DUP/HP的克隆2,重叠群3是16,322bp并且对应于大部分ITR区域(除了串联重复序列以外)。重叠群1是167,020bp并且与基因组的中心保守区域(核苷酸位置19,467至186,486)比对。在克隆2的重叠群的核苷酸位置136791处具有单核苷酸取代(C至A)。这对应于在scACAM2000基因组序列中的核苷酸位置156,256,并且导致VAC_ACAM2000_177(A41L)中从Asp至Tyr的氨基酸改变。

[0199] 对于scVACV ACAM2000-ACAM2000 DUP/HP的克隆1,重叠群1是167,020bp并且与基因组的中心保守区域(核苷酸位置19,469至186,488)比对。重叠群2是16,150bp并且对应于大部分ITR区域(除了串联重复序列以外)。当该重叠群映射至Snapgene中的参考基因组时,在位置2633至3417和核苷酸位置15,175至15220观察到序列中的缺口。第一缺口区域对应于54bp重复区域并且其最可能是由于使用从头组装工具不能准确组装这些区域。将原始Illumina读数直接映射到参考基因组并不在任一区域中导致任何缺口。对于scVACV ACAM2000-ACAM2000DUP/HP的克隆2,重叠群1是16,075bp并且对应于大部分ITR区域(除了串联重复序列以外)。重叠群2是167,078bp并且与基因组的中心保守区域(核苷酸位置19,469至186,546)比对。在来自核苷酸位置15,176至15,220的重叠群2中观察到一个缺口。然而,将原始Illumina读数直接映射到参考基因组并不在该区域中导致任何缺口。scVACV ACAM2000-ACAM2000 DUP/HP的测序的克隆都没有在基因组的任何位置显示任何其他核苷酸突变。

[0200] 还将Illumina读数映射到CLC基因组中的参考图谱。Illumina读数以分别针对scVACV ACAM2000-WR DUP/HP的克隆1和2的1925和2533的平均覆盖度以及分别针对scVACV ACAM2000-ACAM2000DUP/HP的克隆1和2的2195和1602的平均覆盖度来覆盖参考序列全长。

[0201] 总体上,测序数据证实体外基因组分析数据并且证实在SFV-感染细胞中成功地再激活了scVACV ACAM20000-WR DUP/HP和scVACV ACAM2000-ACAM2000 DUP/HP。

[0202] 实施例7.去除YFP/gpt选择标记物

[0203] 在再激活scVACV ACAM2000 YFP-gpt::105后,可以移除在胸苷激酶基因座中的yfp/gpt选择标记物。

[0204] 实施例8.在末端发夹和ITR中双链体区内各种VACV株之间的核苷酸序列变化

[0205] 图9显示VACV WR株、ACAM 2000、Dryvax和Copenhagen株中直接在多联体解析位点下游的“双链体”区中的核苷酸序列变化。相比于WR株,可看到在wtACAM2000、Dryvax DPP15、TianTan和Copenhagen株之间,序列变化是4个核苷酸取代和3个核苷酸缺失。

[0206] 实施例9.在小鼠鼻内模型中或通过尾部划痕法测定毒力

[0207] 在该研究中测定scVACV ACAM20000-WR DUP/HP和scVACV ACAM2000-ACAM2000 DUP/HP的毒性效应。对于该实验,对6组Balb/c小鼠施用3种不同剂量的在实施例1-7中描述的scVACV ACAM20000-WR DUP/HP和scVACV ACAM2000-ACAM2000DUP/HP,并与PBS对照组以及wtVACV(WR)对照组和wtVACV ACAM2000对照组比较(总共12个治疗组)。该实验中包括在研究持续期间没有接受任何治疗的3只另外的小鼠。在整个实验中,在预定点对所有小鼠进行血液取样,并且将所述另外的小鼠用作血清分析的基线。

[0208] 在接种Balb/c小鼠之前,所有病毒株在BSC-40细胞(非洲绿猴肾)中培养,通过胰蛋白酶消化收获,在PBS中洗涤,通过杜恩斯(dounce)匀浆从细胞中提取,通过超速离心经由36%蔗糖垫层纯化,再悬浮于PBS中并滴定,使得终浓度为10^7PFU/ml至10^9PFU/ml。

[0209] 基于使用已知VACV疫苗病毒株(包括Dryvax和IOC)的先前研究(Medaglia ML,Moussatche N,Nitsche A,Dabrowski PW,Li Y,Damon IK,等,Genomic Analysis,Phenotype,and Virulence of the Historical Brazilian Smallpox Vaccine Strain IOC:Implications for the Origins and Evolutionary Relationships of Vaccinia Virus.Journal of virology.2015;89(23):11909-25;Qin L,Favis N,Famulski J,Evans DH.Evolution of and evolutionary relationships between extant vaccinia virus strains.Journal of virology.2015;89(3):1809-24),选择用于本研究的剂量(10^5PFU/剂量、10^6PFU/剂量和10^7PFU/剂量)。

[0210] 病毒通过鼻内或通过尾部划痕法施用。关于细节参见以下实施例10和11。

[0211] 实施例10.确定通过鼻内接种施用scVACV是否赋予针对致死性VACV-WR攻击的免疫保护

[0212] 由于体重减轻被用作小鼠中毒力的测量,因此以5x 10^3PFU的剂量鼻内施用wtVACV(WR株),其导致大约20-30%的体重减轻。还以10^7PFU/剂量鼻内施用VACV Dryvax克隆DPP15,使得该公知的天花疫苗的毒力可以直接与合成版本的scVACV ACAM20000-WR DUP/HP和scVACV ACAM2000-ACAM2000 DUP/HP相比。小鼠购自Charles River Laboratories,且在收到后在病毒施用之前使其适应环境至少一周。

[0213] 各小鼠在麻醉下同时通过鼻内注射接受施用的单剂量的病毒(~10μl)。每天监测

小鼠的感染迹象(诸如,肿胀、排泄或其他异常情况)持续30天的时间段。在病毒施用后每天专门监视每只小鼠的体重减轻。根据University of Alberta的动物健康护理设施方案,对除其他发病因素以外的体重减轻超过25%的小鼠实行安乐死。

[0214] 即使在测试的最高剂量的scVACV ACAM20000-WR DUP/HP和scVACV ACAM2000-ACAM2000 DUP/HP下,Balb/c小鼠可以没有明显疾病迹象。VACV株(巴西天花疫苗株IOC)中之一,在一些情况下,在10^7PFU下不引起疾病(Medaglia ML,Moussatche N,Nitsche A,Dabrowski PW,Li Y,Damon IK,等,Genomic Analysis,Phenotype,and Virulence of the Historical Brazilian Smallpox Vaccine Strain IOC:Implications for the Origins and Evolutionary Relationships of Vaccinia Virus.Journal of virology.2015;89(23):11909-25)。由于难以制备滴度超过10^9PFU/mL的纯化储液,因此测试比该剂量更高的剂量是不实际的。

[0215] 病毒接种后三十天,随后通过鼻内接种用致死剂量的VACV-WR(10^6PFU/剂量)攻击小鼠。如上所述密切监视小鼠的感染迹象。每日称重小鼠,对除其他发病因素以外的体重减轻超过25%的小鼠实行安乐死。预期在施用致死剂量的VACV-WR之前用PBS接种的小鼠在接种后7-10天内显示显著的体重减轻和其他发病因素的迹象。用VACV-WR致死性攻击后约14天,将所有小鼠实行安乐死,并收集血液以通过标准空斑减少测定来证实血清中VACV-特异性中和抗体的存在。

[0216] 实施例11.确定通过尾部划痕法施用的scVACV是否赋予针对致死性VACV-WR攻击的免疫保护

[0217] 在开始尾部划痕法步骤之前将免疫活性Balb/C小鼠麻醉。在尾巴底部处,使用25号针头的尖端在1-2cm长度上进行一系列15-20个划痕/刺破。将3-5μL体积的不同病毒施加到划痕位点。

[0218] 麻醉小鼠直至病毒有机会吸收到划痕位点中。在28天的时间段每日监视小鼠的体重减轻的迹象。划痕后~8-10天在尾部划痕位点形成脓疱(已知为“获得”)。

[0219] 病毒接种后二十八天,随后通过鼻内接种用致死剂量的VACV-WR(10^6PFU/剂量)攻击小鼠。如上所述密切监视小鼠的感染迹象。每日称重小鼠,对除其他发病因素以外的体重减轻超过25%的小鼠实行安乐死。预期在施用致死剂量的VACV-WR之前用PBS接种的小鼠在接种后7-10天内显示显著的体重减轻和其他发病因素的迹象。用VACV-WR致死性攻击后约14天,将所有小鼠实行安乐死,并收集血液以通过标准空斑减少测定来证实血清中VACV-特异性中和抗体的存在。

[0220] 所有未接种疫苗的动物在病毒攻击后7天内由于该致死剂量的VACV WR而死亡。

[0001] 序列表

[0002] <110> EVANS, DAVID

[0003] NOYCE, RYAN

[0004] LEDERMAN, SETH

[0005] <120> 合成嵌合痘苗病毒

[0006] <130> 104545-0031-WO1

[0007] <140>

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[0009] <150> 62/665,973

[0010] <151> 2018-05-02

[0011] <160> 22

[0012] <170> PatentIn version 3.5

[0013] <210> 1

[0014] <211> 18525

[0015] <212> DNA

[0016] <213> 痘苗病毒

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[3696] atcagaaaga ggtttaatat ttttgtgaga ccatcgaaga gagaaagaga taaaactttt 1380
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[3698] taaaactttt ttacgactcc atcagaaaga ggtttaatat ttttgtgaga ccatcgaaga 1500
[3699] gagaaagaga taaaactttt ttacgactcc atcagaaaga ggtttaatat ttttgtgaga 1560
[3700] ccatcgaaga gagaaagaga taaaactttt ttacgactcc atcagaaaga ggtttaatat 1620
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[3703] atcagaaaga ggtttaatat ttttgtgaga ccatcgaaga gagaaagaga taaaactttt 1800
[3704] ttacgactcc atcagaaaga ggtttaatat ttttgtgaga ccatcgaaga gagaaagaga 1860
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[3706] gagaaagaga taaaactttt ttacgactcc atcagaaaga ggtttaatat ttttgtgaga 1980
[3707] ccatcgaaga gagaaagaga taaaactttt ttacgactcc atcagaaaga ggtttaatat 2040
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[3712] taaaactttt ttacgactcc atcagaaaga ggtttaatat ttttgtgaga ccatcgaaga 2340
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[3714] ccatcgaaga gagaaagaga taaaactttt ttacgactcc atcagaaaga ggtttaatat 2460
[3715] ttttgtgaga ccatcgaaga gagaaagaga taaaactttt ttacgactcc gctagcgaag 2520
[3716] aatagggata acagggtaat 2540
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[3718] <211> 61
[3719] <212> DNA
[3720] <213> 痘苗病毒
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[3725] <211> 61
[3726] <212> DNA
[3727] <213> 痘苗病毒
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[3730] c 61
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[3732] <211> 157
[3733] <212> DNA
[3734] <213> 痘苗病毒
[3735] <400> 13
[3736] acatttttt ctagacacta aataaaatat ttaaaatata atattaatgt actaaaactt 60
[3737] atatattatt aatttatcta actaaagtta gtaaattata tatataattt tataattaat 120

[3738] ttaattttac taattttatt tagtgtctag aaaaaaa 157

[3739] <210> 14

[3740] <211> 157

[3741] <212> DNA

[3742] <213> 痘苗病毒

[3743] <400> 14

[3744] acatttttt ctagacacta aataaaatta gtaaaattaa attaattata aaattatata 60

[3745] tataatttac taactttagt tagataaatt aataatatat aagttttagt acattaatat 120

[3746] tatattttaa atattttatt tagtgtctag aaaaaaa 157

[3747] <210> 15

[3748] <211> 58

[3749] <212> DNA

[3750] <213> 痘苗病毒

[3751] <400> 15

[3752] gtgacccatg actgtaggaa actctagagt gtaagaaaga tcgatcgctt tatagaga 58

[3753] <210> 16

[3754] <211> 58

[3755] <212> DNA

[3756] <213> 痘苗病毒

[3757] <400> 16

[3758] gtgaccaacg accgtaggaa actctagagg gtaagaaaaa tcaatcgctt tatagaga 58

[3759] <210> 17

[3760] <211> 58

[3761] <212> DNA

[3762] <213> 痘苗病毒

[3763] <400> 17

[3764] gtgaccaacg accgtaggaa actctagagg gtaagaaaaa tcaatcgctt tatagaga 58

[3765] <210> 18

[3766] <211> 58

[3767] <212> DNA

[3768] <213> 痘苗病毒

[3769] <400> 18

[3770] gtgaccaacg accgtaggaa actctagagg gtaagaaaaa tcaatcgctt tatagaga 58

[3771] <210> 19

[3772] <211> 154

[3773] <212> DNA

[3774] <213> 痘苗病毒

[3775] <400> 19

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[3777] tgtattatta atttatctaa ctaaagttag taaattatat acataatttt ataattaatt 120

[3778] taattttact atttatttag tgtctagaaa aaaa 154

[3779] <210> 20

[3780] <211> 154

[3781] <212> DNA

[3782] <213> 痘苗病毒

[3783] <400> 20

[3784] acatttttt ctagacacta aataaatagt aaaattaaat taattataaa attatgtata 60

[3785] taatttacta actttagtta gataaattaa taatacataa attttagtat attaatatta 120

[3786] tattttaaat atttatttag tgtctagaaa aaaa 154

[3787] <210> 21

[3788] <211> 61

[3789] <212> DNA

[3790] <213> 痘苗病毒

[3791] <400> 21

[3792] tgtgtgacca acgaccgtag gaaactctag agggtaagaa aaatcaatcg ctttatagag 60

[3793] a 61

[3794] <210> 22

[3795] <211> 61

[3796] <212> DNA

[3797] <213> 痘苗病毒

[3798] <400> 22

[3799] tggtctctat aaagcgattg atttttctta ccctctagag tttcctacgg tcgttggtca 60

[3800] c 61

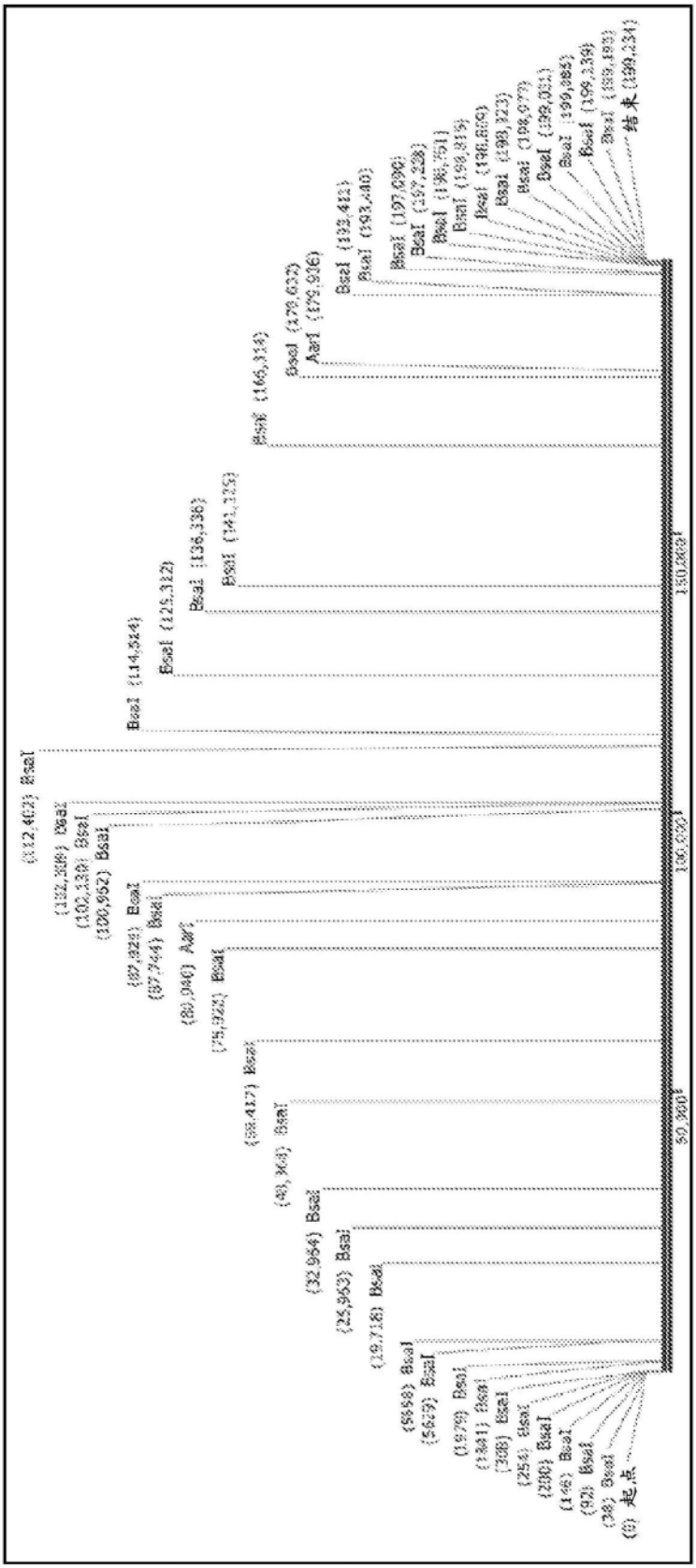

(0) 起点
(92) Bsal
(146) Bsal
(200) Bsal
(254) Bsal
(308) Bsal
(1841) Bsal
(1979) Bsal
(5679) Bsal
(5958) Bsal
(18,718) Bsal
(25,963) Bsal
(32,964) Bsal
(40,368) Bsal
(58,417) Bsal
(75,922) Bsal
(80,046) Aarf
(87,744) Bsal
(87,928) Bsal
(100,952) Bsal
(102,330) Bsal
(122,386) Bsal
(132,402) Bsal
Bsal (114,544)
Bsal (125,312)
Bsal (136,336)
Bsal (141,125)
Bsal (166,314)
Bsal (179,632)
Aarf (179,936)
Bsal (193,411)
Bsal (193,440)
Bsal (197,090)
Bsal (197,228)
Bsal (198,751)
Bsal (198,815)
Bsal (198,859)
Bsal (198,923)
Bsal (198,977)
Bsal (199,051)
Bsal (199,085)
Bsal (199,339)
Bsal (199,493)
结束 (199,231)
50,000
100,000
150,000

图1A

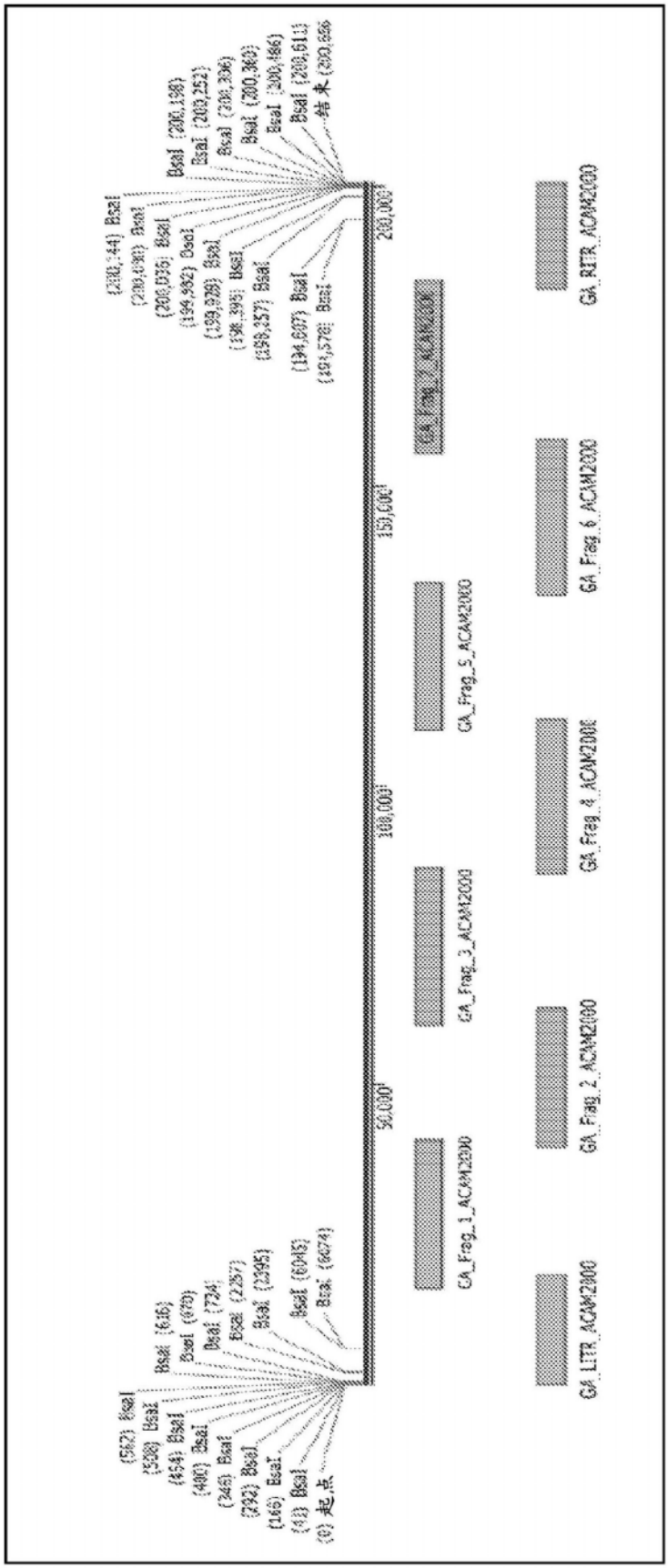

(0) 起点
(13) BsaI
(166) BsaI
(232) BsaI
(246) BsaI
(407) BsaI
(454) BsaI
(508) BsaI
(562) BsaI
BsaI (6074)
BsaI (6043)
BsaI (2395)
BsaI (2257)
BsaI (734)
BsaI (670)
BsaI (616)
50,000
100,000
150,000
200,000
(193,578) BsaI
(194,607) BsaI
(198,393) BsaI
(199,938) BsaI
(199,982) BsaI
(200,036) BsaI
(200,098) BsaI
(200,144) BsaI
结束 (200,856)
BsaI (200,611)
BsaI (200,486)
BsaI (200,360)
BsaI (200,306)
BsaI (200,252)
BsaI (200,198)
GA_LTR_ACAM2000
GA_Frag_1_ACAM2000
GA_Frag_2_ACAM2000
GA_Frag_3_ACAM2000
GA_Frag_4_ACAM2000
GA_Frag_5_ACAM2000
GA_Frag_6_ACAM2000
GA_RTR_ACAM2000

图1B

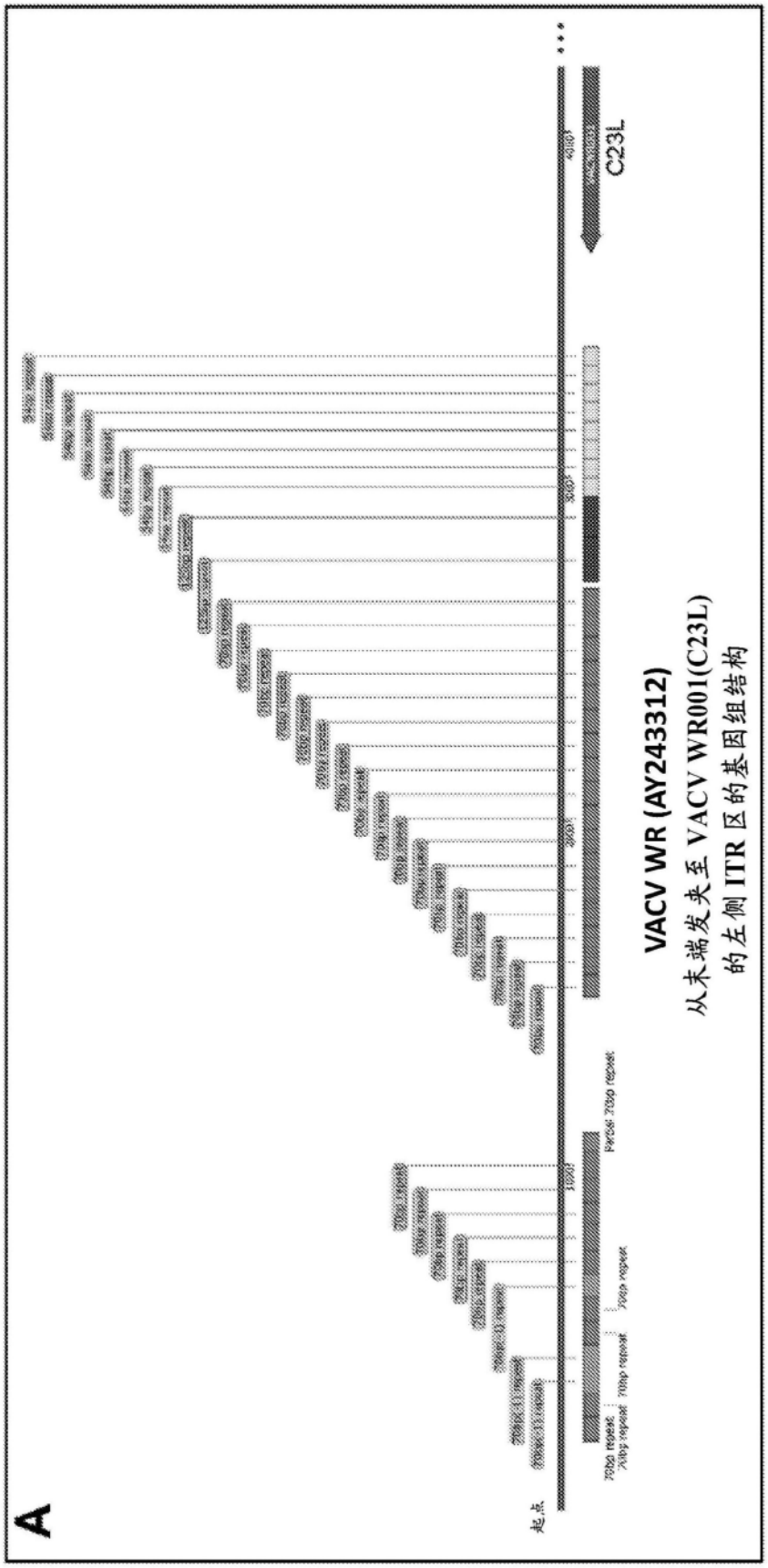

A
VACV WR (AY243312)
从末端发夹至 VACV WR001(C23L)
的左侧 ITR 区的基因组结构
C23L
起点
Partial 2336 repeat
70bp repeat
70bp repeat
70bp repeat
70bp repeat

图2A

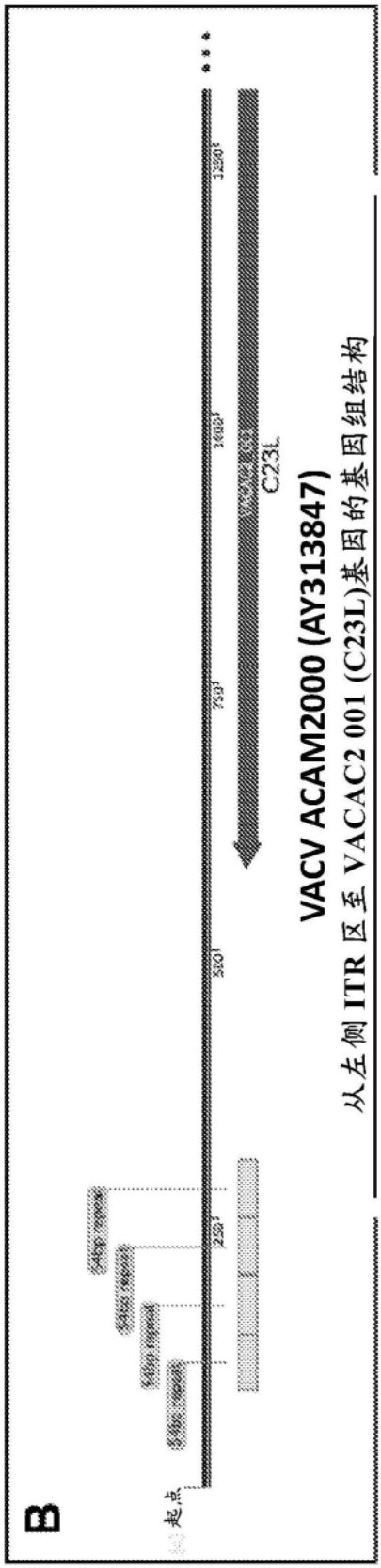

B
起点
C23L
VACV ACAM2000 (AY313847)
从左侧 ITR 区至 VACAC2 001 (C23L)基因的基因组结构

图2B

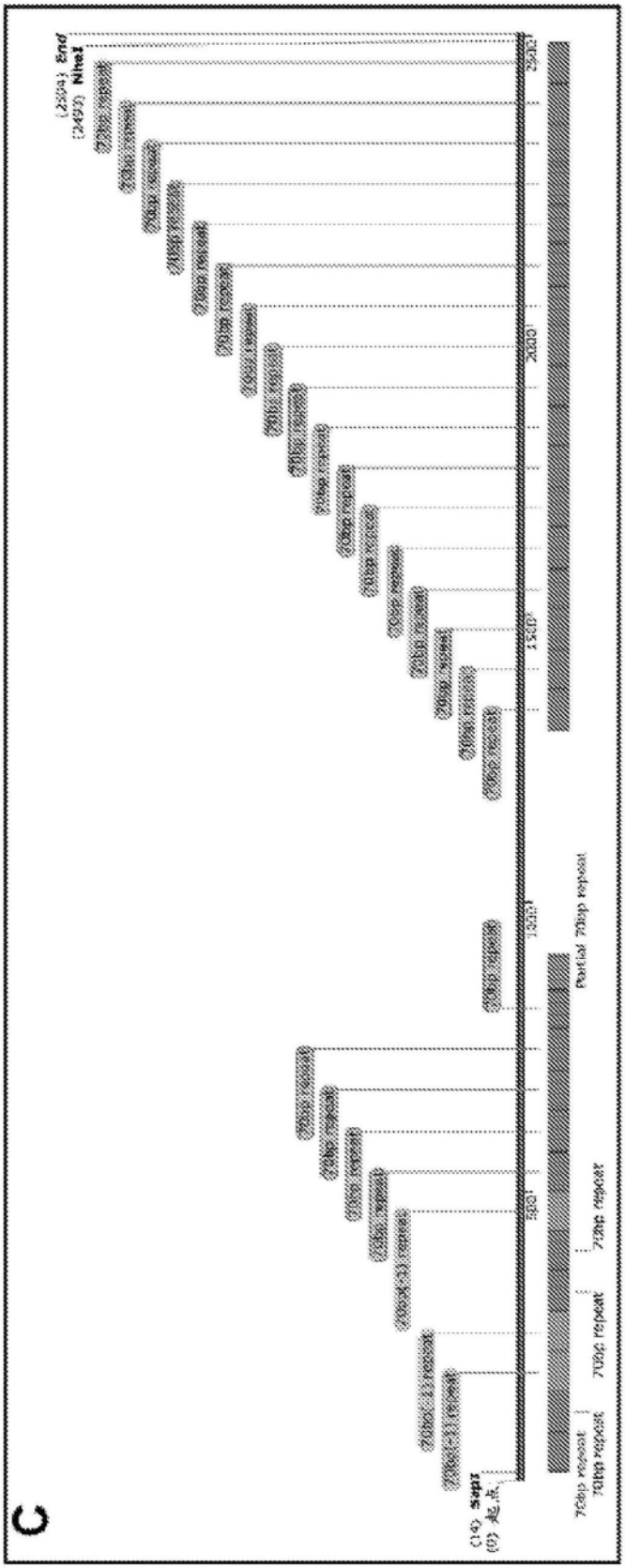


图2C

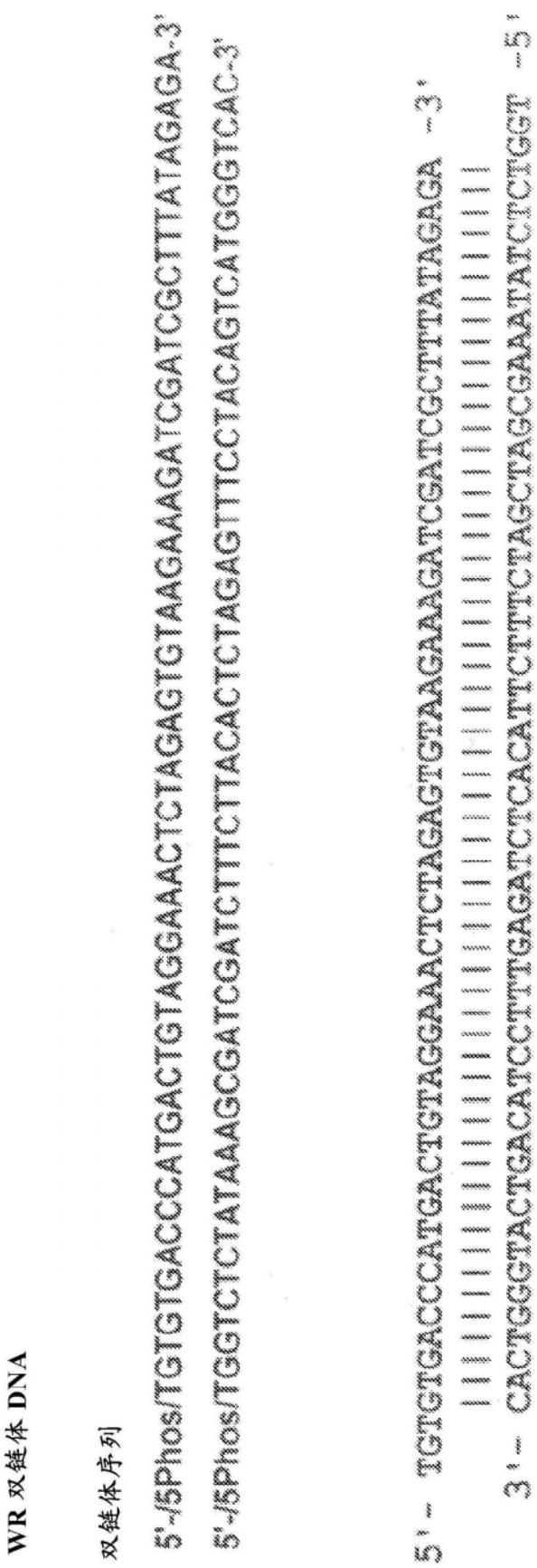

WR 双链体 DNA
双链体序列
5'-/5Phos/TGTGTGACCCATGACTGTAGGAAACTCTAGAGTGTAAGAAAGATCGATCGCTTTATAGAGA-3'
5'-/5Phos/TGGTCTCTATAAAGCGATCGATCTTTCTTACACTCTAGAGTTTCCTACAGTCATGGGTCAC-3'
5' - TGTGTGACCCATGACTGTAGGAAACTCTAGAGTGTAAGAAAGATCGATCGCTTTATAGAGA -3'
3' - CACTGGGTACTGACATCCTTTGAGATCTCACATTCTTTCTAGCTAGCGAAATATCTCTGGT -5'

图3A

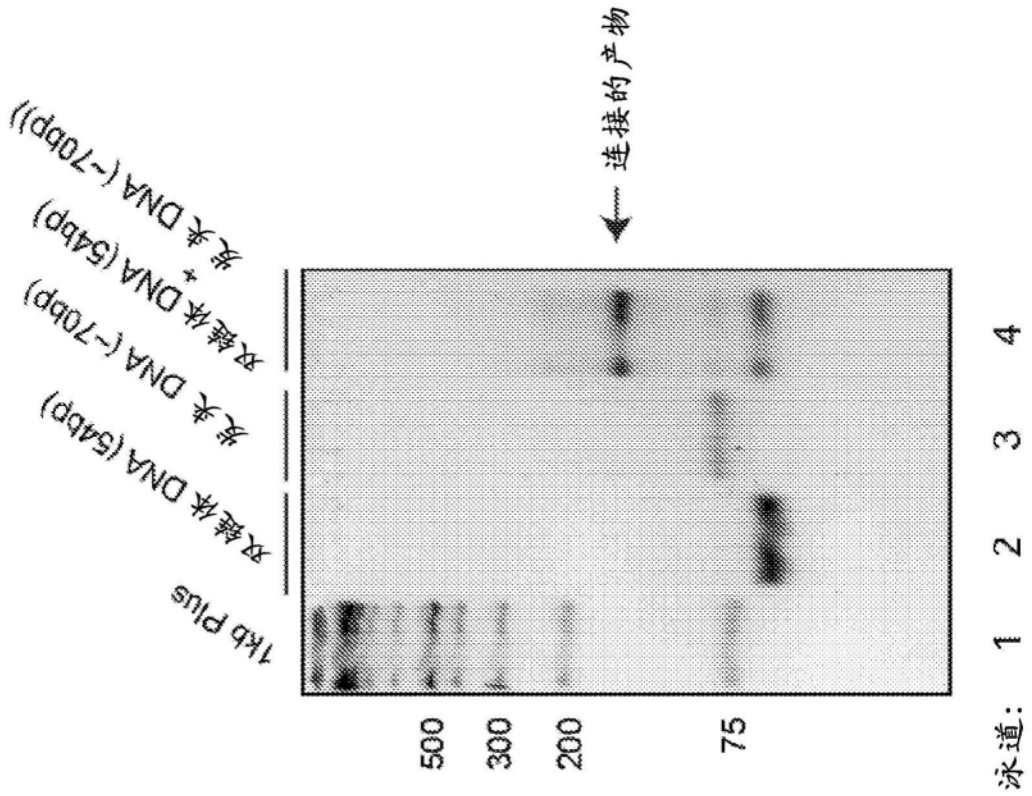

连接的产物
泳道:
1
2
3
4
500
300
200
75
1kb Plus
双雄体 DNA (54bp)
单头 DNA (~70bp)
双雄体 DNA (54bp) + 单头 DNA (~70bp))

图3B

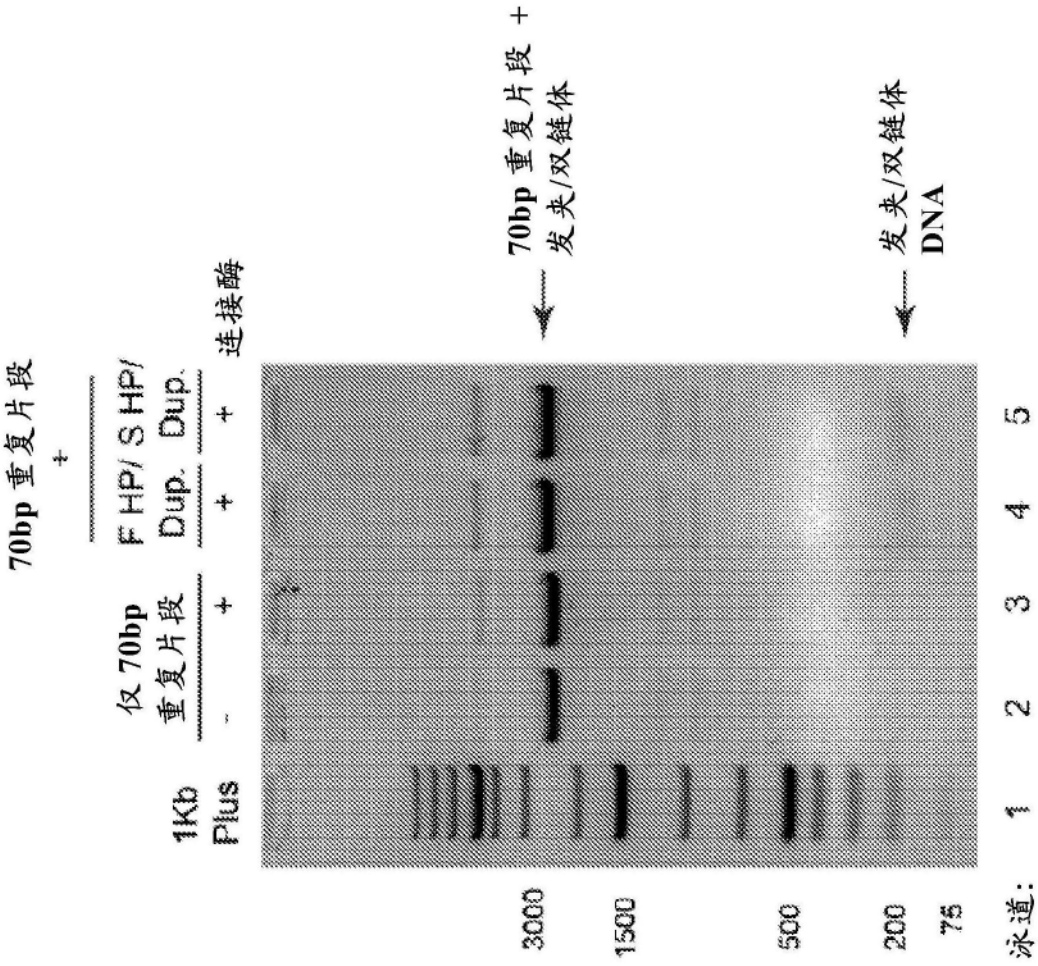

70bp 重复片段
+
1Kb Plus
仅 70bp 重复片段
F HP/ S HP/ Dup. Dup.
连接酶
70bp 重复片段 + 发夹/双链体
发夹/双链体 DNA
3000
1500
500
200
75
泳道: 1 2 3 4 5

图4

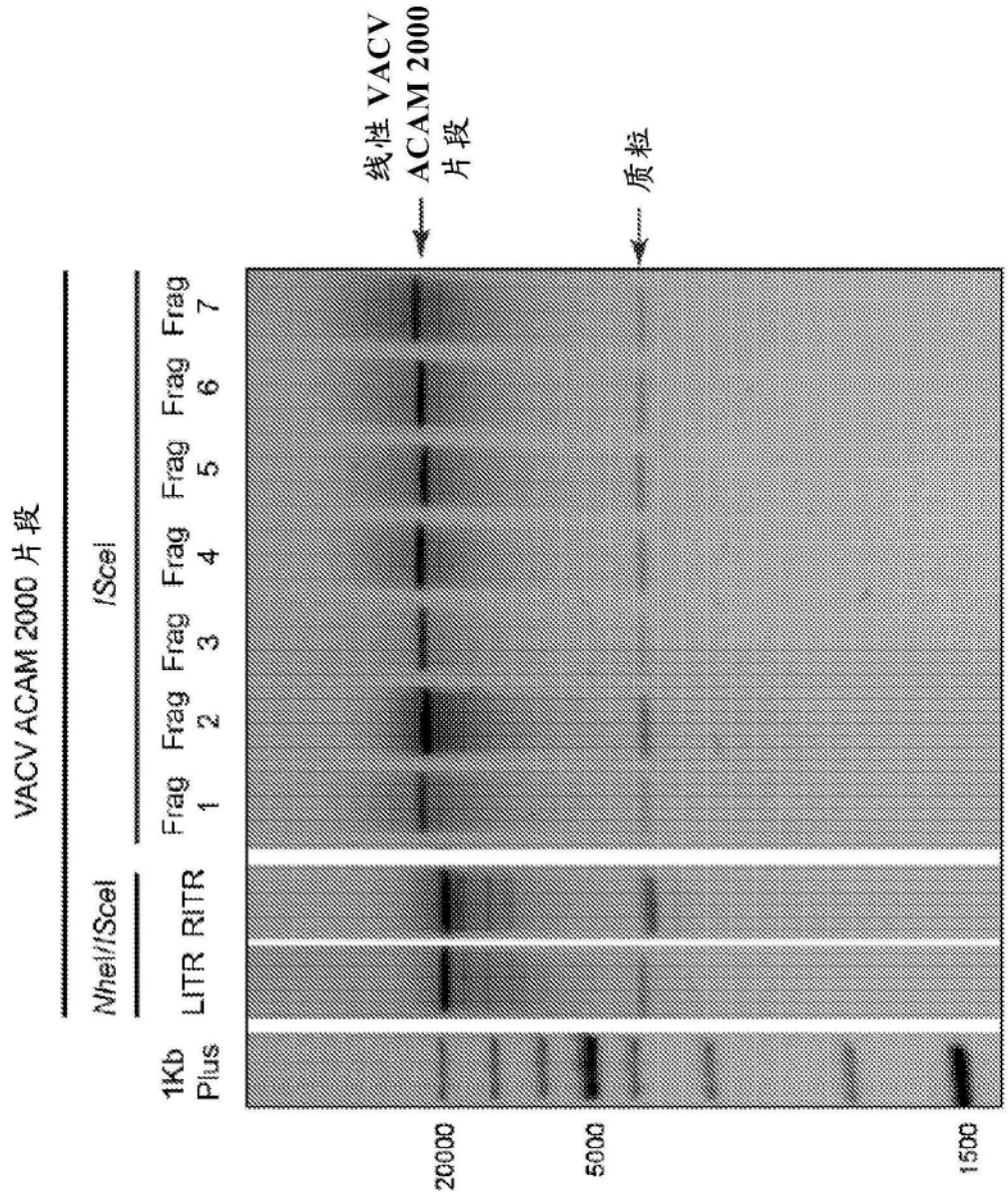

线性 VACV
ACAM 2000
片段
质粒
VACV ACAM 2000 片段
NheI/ISceI
ISceI
1Kb Plus
LITR
RITR
Frag 1
Frag 2
Frag 3
Frag 4
Frag 5
Frag 6
Frag 7
20000
5000
1500

图5

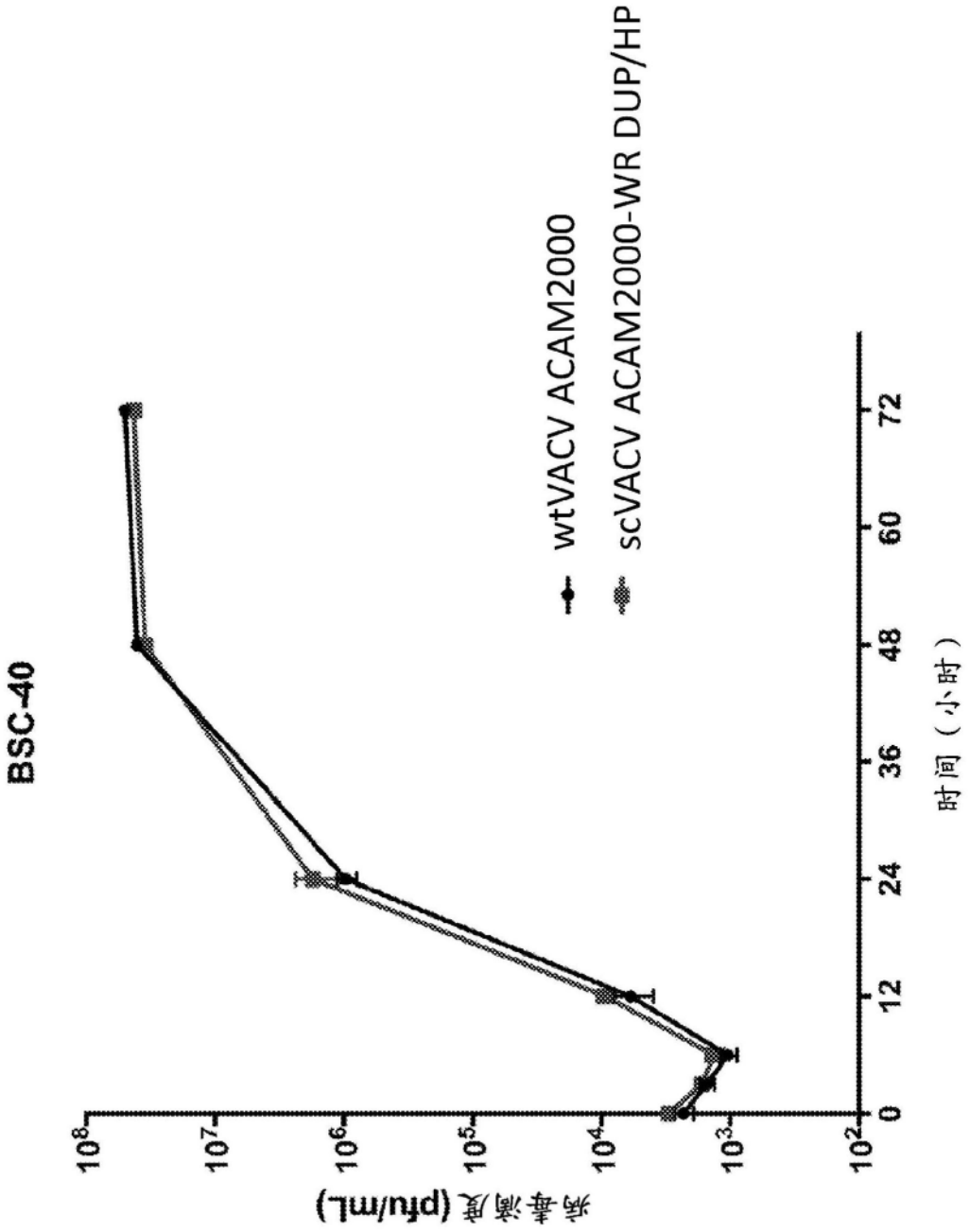

BSC-40
wtVACV ACAM2000
scVACV ACAM2000-WR DUP/HP
病毒滴度 (pfu/mL)
时间（小时）
10^8
10^7
10^6
10^5
10^4
10^3
10^2
0
12
24
36
48
60
72

图6

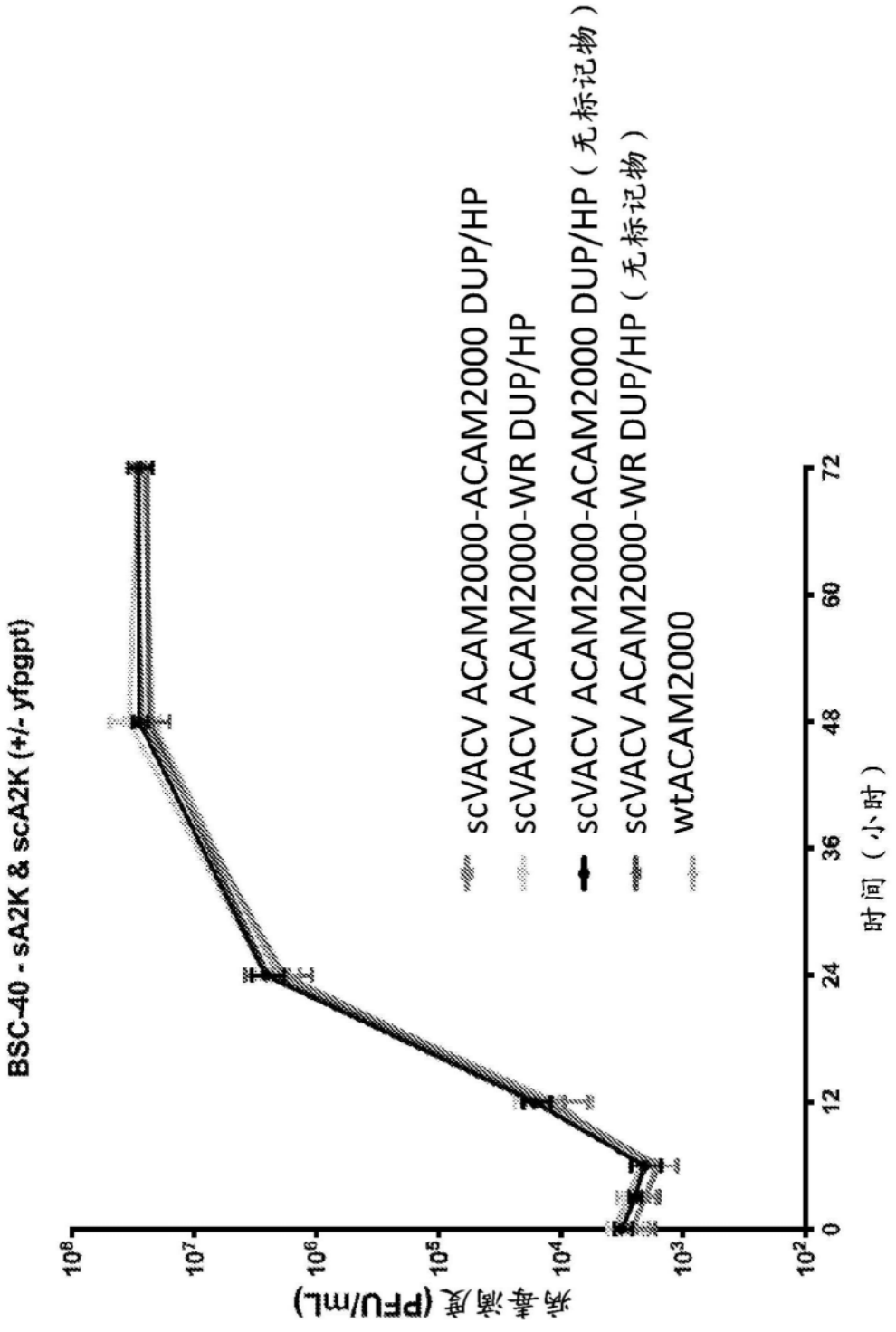

BSC-40 - sA2K & scA2K (+/- yfpgpt)
scVACV ACAM2000-ACAM2000 DUP/HP
scVACV ACAM2000-WR DUP/HP
scVACV ACAM2000-ACAM2000 DUP/HP（无标记物）
scVACV ACAM2000-WR DUP/HP（无标记物）
wtACAM2000
病毒滴度 (PFU/mL)
时间（小时）
10^8
10^7
10^6
10^5
10^4
10^3
10^2
0
12
24
36
48
60
72

图7

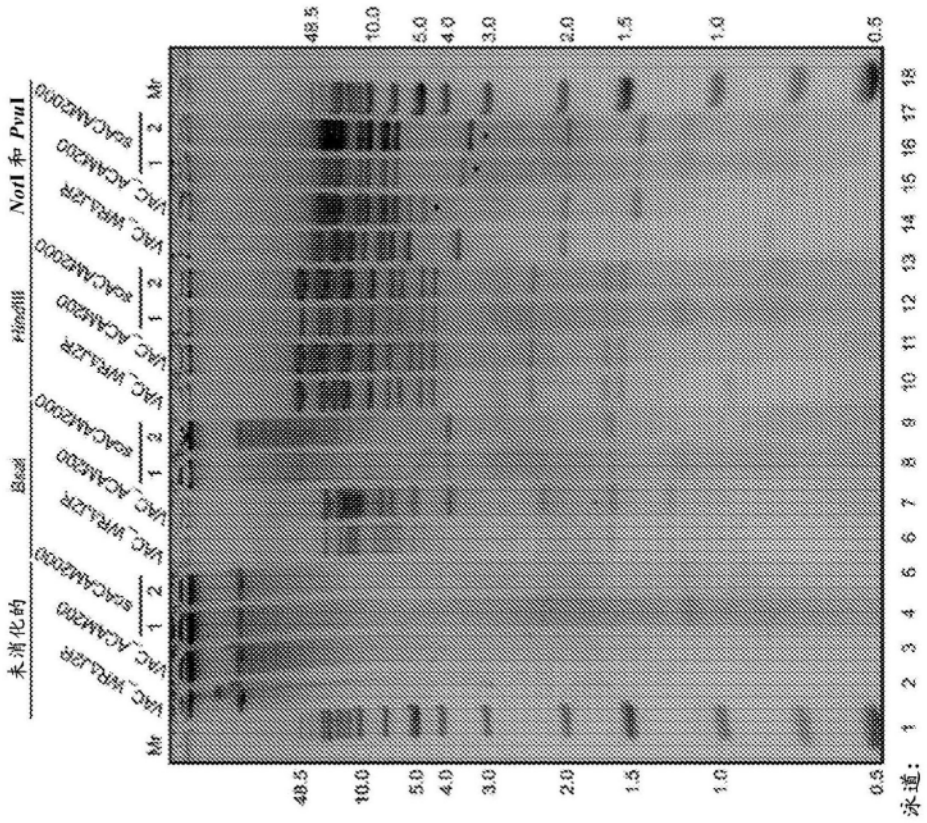

未消化的
BssHII
HindIII
NotI 和 PvuI
Mr
VAC_WRA_IZR
VAC_ACAM209
sCACAM2000
泳道:
48.5
10.0
5.0
4.0
3.0
2.0
1.5
1.0
0.5

图8

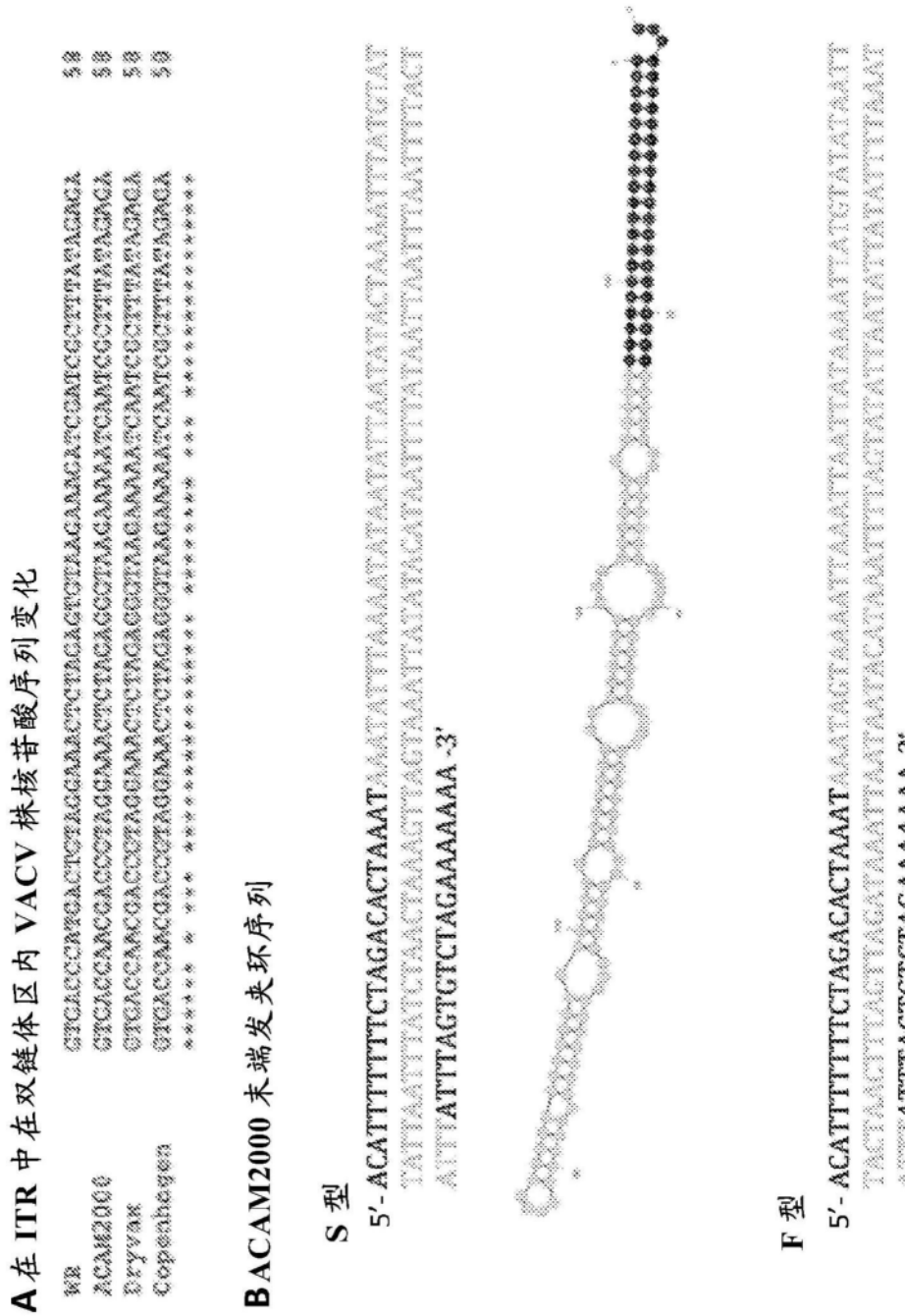

A 在 ITR 中在双链体区内 VACV 株核苷酸序列变化
WR GTCACCCATCCACTCTAGGAAACTCTACAGTCTTAGAAACATCCATCCCTTTATAGACA 58
ACAM2000 GTCACCAACCACCCTAGGAAACTCTACAGCCTTAGAAAACATCAATCCCTTTATAGACA 58
Bryvax GTCACCAACCACCCTAGGAAACTCTACAGCCTTAGAAAAACTCAATCCCTTTATAGACA 58
Copenhagen GTCACCAACCACCCTAGGAAACTCTACAGCCTTAGAAAAACTCAATCCCTTTATAGACA 58
B ACAM2000 末端发夹环序列
S 型
5'- ACATTTTTTTTCTAGACACTAAATTAAATATTTAAAATATAATTAATATACTAAAATTTATGTAT
TATTAATTTATCTAACTAAGTTAGTAAATTATATACATAATTTTATAATTTAATTTTACT
ATTTATTTAGTGTCTAGAAAAAAA -3'
F 型
5'- ACATTTTTTTTCTAGACACTAAATTAAATAGTAAAAATTAATTATAAAATTATGTATATAATT
TACTAACTTTAGTTAGATAAATTAATTATACATAAATTTTAGTATATTAATATTATTTAAAT
ATTTATTTAGTGTCTAGAAAAAAA-3'

图9