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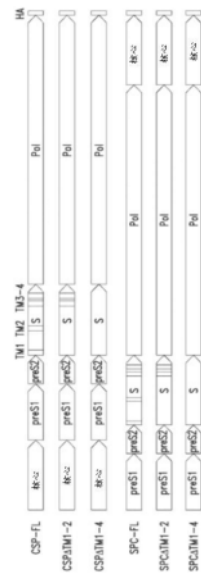
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(54) 发明名称

乙型肝炎病毒疫苗

(57) 摘要

本公开涉及分离的多核苷酸和多肽,以及相关的乙型肝炎病毒 (HBV) 疫苗。本公开还涉及用于表达此类多肽并且可用于HBV疫苗的病毒运载体,以及保护受试者免受HBV感染的方法和治疗受试者中的HBV的方法,所述方法包括施用本文描述的多肽、载体或疫苗。本文还提供了设计和生产HBV疫苗的方法,所述方法包括使用抗原氨基酸序列来设计疫苗抗原以覆盖地理区域内的多样性,所述抗原氨基酸序列有效地覆盖该地理区域中存在的HBV基因型表位。



1. 一种多肽,其由SEQ ID NO: 15所示的氨基酸序列组成。
2. 一种巨细胞病毒 (CMV) 运载体,其包含多核苷酸,所述多核苷酸编码SEQ ID NO: 15的多肽。
3. 根据权利要求2所述的CMV运载体,其中所述CMV运载体是人CMV (HCMV) 运载体或恒河猴CMV (RhCMV) 运载体。
4. 根据权利要求3所述的CMV运载体,其中所述CMV运载体缺少UL82基因。
5. 根据权利要求3所述的CMV运载体,其中所述CMV运载体缺少UL128-UL130基因区域并且缺少UL146-UL147基因区域。
6. 根据权利要求3所述的CMV运载体,其中所述CMV运载体具有完整的UL128-UL130基因区域和完整的UL146-UL147基因区域。
7. 一种组合物,其包含两种或更多种根据权利要求3所述的CMV运载体。
8. 一种乙型肝炎病毒 (HBV) 疫苗,其包含根据权利要求1所述的多肽和药学可接受的载体。
9. 一种乙型肝炎病毒 (HBV) 疫苗,其包含根据权利要求2-6任一项所述的CMV载体和药学上可接受的载体。
10. 根据权利要求1所述的多肽在制备用于治疗HBV的药物中的用途。
11. 根据权利要求2-6中任一项的运载体在制造用于治疗HBV的药物中的用途。
12. 根据权利要求9的疫苗在制造用于治疗HBV的药物中的用途。
13. 根据权利要求1所述的多肽在制备用于保护受试者免受HBV感染的药物中的用途。
14. 根据权利要求2-6中任一项的运载体在制造用于保护受试者免受HBV感染的药物中的用途。
15. 根据权利要求9的疫苗在制造用于保护受试者免受HBV感染的药物中的用途。
16. 根据权利要求1所述的多肽在制备用于在受试者中生成或诱导对HBV的免疫反应的药物中的用途。
17. 根据权利要求2-6中任一项的运载体在制造用于在受试者中生成或诱导对HBV的免疫反应的药物中的用途。
18. 根据权利要求8或9的疫苗在制造用于在受试者中生成或诱导对HBV的免疫反应的药物中的用途。

乙型肝炎病毒疫苗

[0001] 政府利益声明

[0002] 美国政府根据美国能源部与翠德国家安全有限责任公司 (TRIAD National Security, LLC) 之间关于洛斯阿拉莫斯国家实验室 (Los Alamos National Laboratory) 运营的合同号 89233218CNA000001 而享有本发明的某些权利。

[0003] 关于序列表的声明

[0004] 与本申请相关的序列表以文本格式提供以代替纸质副本,并且在此通过引用并入本说明书中。包含序列表的文本文件的名称是 930185_414WO_SEQUENCE_LISTING.txt。文本文件为 186KB, 创建于 2020 年 8 月 21 日, 并经由 EFS-Web 以电子方式提交。

技术领域

[0005] 本主题通常涉及乙型肝炎病毒 (HBV), 特别是涉及 HBV 疫苗。

背景技术

[0006] 乙型肝炎病毒 (HBV) 感染代表了主要的全球健康负担。HBV 感染导致 5-10% 的受感染成年人患慢性肝病, 而围产期传播的比率则相反, 其中 >90% 发展为慢性病。未经治疗的慢性乙型肝炎 (CHB) 感染经常进展为坏死性炎症和持续的肝损伤, 从而导致肝硬化和肝细胞癌 (HCC)。据估计, CHB 会使患 HCC 的风险增加 20 倍并占 HCC 病例的约 54%。HCC 是第三大最致命的癌症形式, 每年诊断出约 800,000 个新病例。高效 (>95%) 预防性疫苗于 1980 年代初实施; 然而, 一旦确定感染, 这些 HBV 疫苗就会失效。尽管广泛使用预防性疫苗, 全世界每年仍有 2.4-3.4 亿慢性 HBV 携带者和超过 780,000 例相关死亡。绝大多数新的 HBV 感染发生在高流行地区, 例如中国、东南亚和撒哈拉以南非洲。HBV 感染通过性、医院或血液传播发生。

[0007] HBV 基因组是 3.2kb 双链 DNA 分子, 其被组织成四个重叠的开放阅读框: 聚合酶 (P 或 Pol)、核心 (C)、表面抗原 (HBsAg) (S) 以及称为 “X” 的基因 (其功能尚未完全了解但与肝癌的进展有关)。Locarnini 等人. *Antivir Ther.* 2010; 15 增刊 3: 3-14。而且, 与显示出高突变率从而导致准种的其他小型慢性病毒 (如 HIV 或 HCV) 不同, HBV 的小型 (3.2kb) DNA 基因组由于重叠的开放阅读框 (ORF) 而在其突变能力方面受到更多限制。虽然宿主内突变有限, 但在全球范围内发现了不同的 HBV 基因型, 在设计治疗法 (例如疫苗) 时需要考虑这些基因型。

[0008] 慢性 HBV 感染的当前护理标准是用抗病毒药和干扰素- α 治疗。

[0009] 迄今为止, 针对 HBV 的治疗性疫苗接种是无效的。有许多潜在的原因。确认感染个体的 HBV 序列有助于确定哪些特定疫苗将提供有效治疗。作为对 HBV 基因组进行测序和检查的协作联盟开发的称为 “HBVdb” 的 HBV 数据库已经确认约 5000 个 HBV 完整基因组。见 Hayer 等人. *Nucleic Acids Res.*, 41: D566-D570 2013, 其全部内容通过引用并入本文。然而, 由于序列的普遍重叠, 并且由于多个序列是从同一患者或从高度紧密的簇中分离出的, HBVdb 已确认的真正独特的总 HBV 完整基因组的数量大致为 3000。由 HBVdb 确认的 HBV 基因组可以分为不同的基因型 (A, B, C, CB, D, DC, DE, E, 以及 F)。基因型的分布在世界人口中各不相同。例如, 在来自亚洲特别是中国的个体的样本中, HBVdb 上可用的数据集序列中有近 75% 包含基

因型B和C。另一方面,欧洲一半以上的HBV感染代表基因型A和D的感染。

[0010] 虽然用抗病毒药和干扰素- α 治疗抑制病毒复制并刺激先天免疫系统,但它们很少清除病毒(每年1-4%)并且患者通常需要终身治疗。此外,随着疾病的进展,个体对这些疗法的反应会变化,并且长期治疗既会导致耐药性突变又会导致广泛的副作用。最有效的直接抗病毒疗法替诺福韦和恩替卡韦价格昂贵并且仅用于使用专家指南和算法的患者子集。随着治疗失败或不使用,肝脏炎症变成慢性,并且损伤和再生成循环可导致纤维化、肝脏结构异常,并可能导致HCC。因此,迫切需要一种有效的免疫疗法,其逐步增加有效的免疫反应,从而导致HBV消除和最终治愈。

[0011] 少数患有慢性HBV的个体将自发清除其感染,如血液中测量的表面抗原的损耗所证明的。该比率低至每年1%,并且使用直接作用的抗病毒剂可得到最低限度的改善。最有效的清除发生在循环表面抗原定量水平低且接受1型干扰素治疗的个体中,这种干扰素具有严重的副作用并且通常耐受性差。

[0012] 治疗性疫苗接种也部分无效,因为清除感染所需的T细胞已经耗尽或耐受,并且不会导致肝脏中HBV的有效清除。因此,需要引出并非由自然感染诱导的,但仍能识别显示在受感染肝细胞表面上的肽序列的T细胞。

[0013] CMV/HBV疫苗提供了一种途径来逐渐增加有效反应从而导致HBV消除和最终治愈。活性肝脏驻留效应器CD8+T细胞(TEM)反应的诱导对于HBV清除至关重要。因此,识别CHB患者肝脏中新表位的持续的HBV特异性效应器CD8+T细胞的诱导应足以控制并最终消除HBV。

[0014] 因此,本领域仍然需要为感染不同HBV基因型的人确认有效的疫苗接种。并且,由于目前可用的针对慢性HBV感染的疫苗无效,因此本领域需要开发一种可用于治疗此类感染的疫苗。还需要设计、制备和测试治疗性HBV疫苗,为临床测试做准备。本文公开的组合物和方法解决了这些需求。

发明内容

[0015] 在某些方面,本公开提供了包含如SEQ ID NO:1-11或SEQ ID NO:14-36中列出的氨基酸序列的多肽。在一些实施方案中,多肽包含两种或更多种如SEQ ID NO:16-36中列出的氨基酸序列。在一些实施方案中,上述多肽,或编码多肽的多核苷酸可用于HBV疫苗。在一些实施方案中,本公开提供了包括包含如SEQ ID NO:1-11或SEQ ID NO:14-36中列出的氨基酸序列的多肽的免疫原性组合物。在更进一步的实施方案中,本公开提供了上述多肽或包含多肽的免疫原性组合物在生成针对HBV的免疫反应,或治疗或预防HBV感染中的用途。

[0016] 在一些实施方案中,本公开提供了包括包含多核苷酸的巨细胞病毒(CMV)运载体的病毒运载体(viral vector),该多核苷酸包含编码如SEQ ID NO:1-36中列出的一种或多种氨基酸序列的序列。在一些实施方案中,多核苷酸编码包含SEQ ID NO:1-11、SEQ ID NO:14-15和SEQ ID NO:24-26中的一项或多项的一种或多种氨基酸序列。在一些实施方案中,对由多核苷酸编码的序列进行排序以改善表达。在一些实施方案中,本公开提供了一种免疫原性组合物,其包含编码多核苷酸的CMV运载体,该多核苷酸包含编码如SEQ ID NO:1-36中列出的一种或多种氨基酸序列的序列。在更进一步的实施方案中,本公开提供了上述运载体或包含运载体的免疫原性组合物在生成针对HBV的免疫反应,或治疗或预防HBV感染中的用途。

[0017] 本文还提供了包含一种或多种HBV表位基共序列抗原(episensus antigen)的免疫原性组合物或疫苗。在一些实施方案中,疫苗的抗原作为多肽提供。在一些实施方案中,抗原由多核苷酸编码。在一些实施方案中,病毒运载体包含多核苷酸。在一些实施方案中,抗原由可由相同或不同启动子表达的两种或更多种多核苷酸编码。在一些实施方案中,抗原由不同的病毒运载体编码。在一些实施方案中,HBV疫苗包含两种或更多种HBV表位基共序列抗原。在一些实施方案中,HBV疫苗包含巨细胞病毒(CMV)运载体和编码一种或多种HBV表位基共序列抗原的多核苷酸。

[0018] 在一些实施方案中,疫苗是预防性疫苗。在一些实施方案中,疫苗是治疗性疫苗。

[0019] 在一些实施方案中,免疫原性组合物或疫苗进一步包含药学上可接受的载体(pharmaceutically acceptable carrier)或赋形剂。

[0020] 在某些方面,本公开提供了一种组合物,例如免疫原性组合物,其包含上述多肽、多核苷酸、运载体或疫苗中的两种或更多种。

[0021] 本文还提供了治疗受试者中HBV的方法,所述方法包含向有此类需要的受试者施用有效量的上述多肽、运载体、疫苗或组合物。本文进一步提供了保护受试者免受HBV感染的方法,所述方法包含向有此类需要的受试者施用有效量的上述多肽、运载体、疫苗或组合物。本文进一步提供了生成针对HBV的免疫反应的方法,所述方法包含向有此类需要的受试者施用有效量的上述多肽、运载体、疫苗或组合物。

[0022] 本文还提供了一些实施方案,其中上述多肽、运载体、疫苗或组合物用于治疗HBV、保护受试者免受HBV感染,或诱导对HBV的免疫反应。

[0023] 本公开还提供了上述多肽、运载体、疫苗或组合物在制备用于治疗HBV感染的药物中的用途。本公开还提供了上述多肽、运载体、疫苗或组合物在制备用于保护受试者免受HBV感染的药物中的用途。本公开还提供了上述多肽、运载体、疫苗或组合物在制备用于生成或诱导针对HBV的免疫反应的药物中的用途。

[0024] 本文提供了包含一种或多种表位基共序列抗原的HBV多肽,所述表位基共序列抗原具有衍生自HBVC、S、P的氨基酸序列,包括全长序列、其区域或其任何组合。

[0025] 本文进一步提供了包含一种或多种药学上可接受的载体和一种或多种表位基共序列抗原的免疫原性组合物或疫苗。本文还提供了包含能够表达一种或多种表位基共序列抗原的运载体的免疫原性组合物或疫苗。在一些实施方案中,HBV表位基共序列抗原包含两种或更多种表位基共序列(episensus sequence)。在一些实施方案中,HBV疫苗是预防性疫苗。在一些实施方案中,HBV疫苗是治疗性疫苗。

[0026] 本公开进一步提供了预防或治疗受试者中HBV感染的方法,所述方法包含向有此类需要的受试者施用有效量的上述免疫原性组合物或疫苗。进一步提供了设计和生产用于受试者的免疫原性组合物或疫苗的方法,所述方法包含对受试者中的HBV病毒进行测序,选择设计用于覆盖受试者中存在的病毒内的多样性的疫苗抗原,以及将疫苗抗原插入运载体中。本文还提供了治疗受试者的HBV感染的方法,所述方法包含向有此类需要的受试者施用有效量的所公开的免疫原性组合物或疫苗。

[0027] 本文还提供了一种诱导效应器记忆T细胞反应的方法,所述方法包含:(a)设计一种或多种表位基共序列抗原;(b)生产包含CMV骨架和编码一种或多种表位基共序列抗原的多核苷酸的免疫原性组合物或疫苗;以及(c)向有此类需要的受试者施用疫苗。

[0028] 在某些实施方案中,本文提供的方法的表位基共序列抗原包含选自SEQ ID NO: 1-11和SEQ ID NO:14-36组成的群组的一种或多种氨基酸序列。

附图说明

[0029] 图1.HBV基因组组织。与显示高突变率从而导致准种的其他小型慢性病毒(例如HIV或HCV)不同,HBV的小型(3.2kb)DNA基因组由于重叠的开放阅读框(ORF)而在其突变能力方面受到更多限制。

[0030] 图2A-2B.3041个HBV序列的全球分布可从HBVdb获得。HBV的基因型在全世界分布。地图上仅显示具有已知采样国家的序列。

[0031] 图3A-3B.亚洲和中国HBV序列分布可从HBVdb获得。在亚洲,尤其是在中国,大约75%的基因型是基因型B和C。

[0032] 图4A-4B.图4A:使用一种、两种和三种表位基共序列对HBV的整个蛋白质组覆盖率。图4A显示单种表位基共序列提供了对HBV基因组的有限覆盖率(上图)。使用两种表位基共序列(中图)或三种表位基共序列(下图)改善了覆盖率。图4B:三种表位基共序列比一种或两种表位基共序列提供更好的覆盖率,如精确9聚体匹配的数量所示。

[0033] 图5A-5C.使用利用全球HBV群体开发的一种、两种或三种表位基共序列时的整个蛋白质组覆盖率。与使用B和C HBV群体开发的表位基共序列相比,利用全球HBV群体开发的两种或三种表位基共序列的使用显著改善了所有主要基因型的覆盖率,同时提供了相当的B和C覆盖率。

[0034] 图6.相对于HBV基因组的四个保守区域,使用两种表位基共序列对HBV的整个蛋白质组覆盖率。用窗口示出了高变区域,其包括29个N-末端氨基酸和P蛋白的N-末端。从进一步分析中去除高变区域。

[0035] 图7A-7B.当一种(图7A)或两种(图7B)表位基共序列用于中国样本、非中国样本和全球样本队列时,潜在T细胞表位(PTE)的覆盖率。X轴表示覆盖百分比。灰色直方图表示1000个随机选择的天然菌株的潜在T细胞表位覆盖率。

[0036] 图8.各种表位基共序列的覆盖率比较。2_ChinaGlobal_Epi(2_CHGL_epi)序列提供了全球样本的0.809(80.9%)的精确全序列覆盖率。2_CHGL_epi序列在中国样本中提供了0.879(87.9%)的精确全序列覆盖率,在非中国样本中提供了0.772(77.2%)的精确全序列覆盖率。

[0037] 图9A-9B.中国样本(图9A,左)、非中国样本(图9A,中)和全球样本队列(图9A,右)中1_D.vac、1_C.ref、1_CH_epi、1_GL_epi、2_CH_epi、2_CHGL_epi和3_GL_epi的保守区域覆盖率比较。图9B描绘了所有主要基因型中1_D.vac、1_GL_epi和2_CHGL_epi的保守区域覆盖率。

[0038] 图10A-10B.与野生型基因型D序列和1_GL_epi序列相比,使用2_CHGL_epi序列的1089个中国HBV序列(图10A)和所有3041个全球HBV序列(图10B)的保守区域覆盖率。基因型D序列被Transgene和GlobeImmune用于疫苗。

[0039] 图11A-11D.图11A和图11B显示了在美国和欧洲为有效表位覆盖而开发的HBV基因型D表位基共序列抗原;抗原构建体在图11A中开始并在图11B中继续。衍生自核心(C)、PreS1和PreS2、表面抗原(S)和聚合酶(P)序列的HBV基因型D表位基共序列抗原按指定顺序

显示。开发衍生自在跨膜(TM)结构域中有缺失的序列或具有相对于HBV中的蛋白质顺序重新排序的抗原的表位基共序列抗原的变体以使聚集最小化并使表达最大化。图11C显示了相同抗原的构建体,每个都包括插入在C-末端处的血凝素(HA)表位标签。图11D显示了如通过SDS聚丙烯酰胺凝胶电泳(SDS-page)测量的抗原的病毒表达,随后是用针对被工程化到每个构建体中的HA表位标签的抗体开发的蛋白免疫印迹。

[0040] 图12A-12B.图12A显示了衍生自PreS1和PreS2、表面抗原(S)、聚合酶(P)和/或核心(C)序列的HBV基因型D表位基共序列抗原。如图所示,抗原中的四种在衍生自P蛋白的序列中有缺失。V5或血凝素(HA)表位标签被工程化到构建体中;V5标签被插入在N'-末端,并且HA标签被插入在C'-末端。图12B显示了如通过SDS-page测量的抗原的病毒表达,随后是用针对被工程化到每个构建体中的V5或HA表位标签的抗体开发的蛋白免疫印迹。

具体实施方式

[0041] I. 定义

[0042] 在整个说明书和权利要求中使用了与描述的方面有关的各种术语。除非另有说明,否则此类术语将被赋予其在本领域中的普通含义。其他具体定义的术语将以与本文提供的定义一致的方式进行解释。

[0043] 如在本说明书和所附权利要求中使用的,单数形式“一种”、“一个”和“该”包括复数指示物,除非内容另有明确规定。因此,例如,提及“一种单元”包括两种或更多种单元的组合等。替代方案(例如,“或”)的使用应理解为表示替代方案中的任一者、两者或其任何组合,并且可以与“和/或”同义地使用。如本文所用,术语“包括”和“具有”作为同义词使用,这些术语及其变体意在解释为非限制性的。

[0044] 如本文在提及诸如量、持续时间等的可测量值时所用的术语“约”意在涵盖从指定值至多±20%的变化,因为此类变化适合于执行所公开的方法。除非另有说明,否则在说明书和权利要求中使用的表达成分、诸如分子量、反应条件等特性的量的所有数字应理解为在所有情况下都被术语“约”修饰。因此,除非有相反的说明,以下说明书和所附权利要求中阐述的数值参数是近似值,其可以根据寻求获得的期望特性而变化。至少并非试图将等效原理的应用限制在权利要求的范围内,每个数值参数至少应根据报告的有效数字的数量并通过应用普通的四舍五入技术来解释。

[0045] 尽管阐述本公开的广泛范围的数值范围和参数是近似值,但在具体实施例中阐述的数值尽可能精确地进行报告。然而,任何数值都固有地包含某些误差,这些误差必然是由于在它们各自的测试测量中发现的标准偏差而导致的。

[0046] 术语“包含”是指权利要求中提及的所述特征、整数、步骤或组分的存在,但不排除一个或多个其他特征、整数、步骤、组分或其群组的存在或添加。术语“基本上由……组成”将权利要求的范围限制为指定的材料或步骤,以及那些不实质影响要求保护的主题的基本和新颖特征的材料或步骤。

[0047] “基本上”一词不排除“完全”;例如,“基本上不含”Y的组合物可以完全不含Y。必要时,本文提供的定义中可以省略“基本上”一词。

[0048] 如上文和整个公开所采用的,术语“有效量”是指要实现关于相关病况、病症或副作用的治疗的期望结果所需要的在剂量和时间段上有效的量。应当理解,组分的有效量将

因患者而异,不仅因所选择的特定疫苗、组分或组合物、给药途径和组分在个体中引起所需结果的能力而异,而且因诸如以下的因素而异:与要缓解的病症病情或严重程度、激素水平、年龄、性别、个体体重、患者的生存状态,以及所治疗的病理状况的严重程度、特定患者同时服用的药物或随后遵循的特殊饮食,以及本领域技术人员将认识到的其他因素,适当的剂量由主治医师酌情决定。可以调整剂量方案以提供改善的治疗反应。有效量也是其中组分的任何毒性或有害作用被治疗上有益的作用所胜过的量。

[0049] 术语“施用”是指直接施用化合物或组合物,或施用将在体内形成等量的活性化合物或物质的前药、衍生物或类似物。

[0050] 术语“受试者”、“个体”和“患者”在本文中可互换使用,并且是指接受了用本文公开的药物组合物进行治疗(包括预防性治疗)的动物,例如人类。如本文所用,术语“受试者”是指人类和非人类动物。术语“非人类动物”包括所有脊椎动物,例如哺乳动物,例如非人类灵长类动物(特别是高等灵长类动物)、绵羊、狗、啮齿动物(例如小鼠或大鼠)、豚鼠、山羊、猪、猫、兔子、牛、马和非哺乳动物,如爬行动物、两栖动物、鸡和火鸡。

[0051] 术语“表位基共序列”是指基于表位的共有序列。它是这样一种序列,其表位尽可能接近地与一组参考天然序列中的表位匹配。通常在更长的天然或疫苗抗原序列的k个字符子序列的情况下,术语“表位”和“潜在表位”是指k个字符的序列(通常k在8-12的范围内)。T细胞可以在免疫反应中识别此类肽。

[0052] 术语“EpiGraph”是指这样一种计算策略,其被开发用于创建提供最佳表位基共序列的序列,或当组合时提供对不同病毒序列群体的最佳覆盖率的一组序列。EpiGraph方法先前被描述于PCT申请号W0 2016/054654A1和Theiler,等人,Sci.Rep.6:33987(2016)中,其全部内容通过引用并入本文。EpiGraph方法产生了成组的人工但完整的抗原,其具有在不同病毒群体中发现的潜在T细胞表位(PTE,通常是9mer肽序列)的最大覆盖率。EpiGraph是相比现有镶嵌疫苗设计方法的下一步。基于图的EpiGraph方法在计算上比使用遗传算法的镶嵌法要强大得多,因而允许通过考虑显著更多的组合来改善PTE覆盖率。EpiGraph和镶嵌方法两者都产生比天然菌株具有更大的T细胞表位多样性覆盖率的蛋白质抗原。与天然菌株或共有免疫原的组合相比,HBV、HIV和HCV镶嵌体引发的细胞免疫反应具有更大的广度和深度。HBV镶嵌体和HIV镶嵌体正处于I期临床试验中。在一些实施方案中,EpiGraph算法用于设计对应于HBV保守区域的“表位基共序列”。

[0053] 术语“表位基共序列”是指使用基于HBV序列群体的EpiGraph算法设计的人工抗原的氨基酸序列。作为HBV序列群体“核心”的表位基共序列是计算得出的提供该群体的最大平均表位覆盖率的序列。“表位基共序列抗原”是包含表位基共氨基酸序列的抗原。

[0054] 如本文所用,术语“治疗”或“疗法”(及其包括治愈性或姑息性在内的不同形式)是指对感染者的治疗。如本文所用,术语“治疗”包括减轻或减少病症、疾病或病况的至少一种不利或负面影响或症状。这种病症、疾病或病况可以是HBV感染。

[0055] 如本文所用,术语“预防”或“预防性”是指防止受试者感染或降低受试者感染例如HBV或相关病毒的风险,或停止传播或降低传播例如HBV或相关病毒的风险。

[0056] “药学上可接受的”是指在合理的医学判断范围内适合与人类和动物的组织接触而不具有过度毒性、刺激性、过敏反应或者其他与合理利益/风险比相称的问题并发症的那些化合物、材料、组合物和/或剂型。

[0057] 如本文所用,术语“疫苗”、“免疫原性化合物”和“免疫原性组合物”可互换使用来指在受试者中诱导免疫反应的化合物或组合物。预防性疫苗提供一定程度的对抗新感染的保护。治疗性疫苗有助于治疗现有感染。

[0058] II. 抗原

[0059] 本文提供了包含衍生自某些HBV群体的序列的多肽。在一些实施方案中,多肽包含如SEQ ID NO:1-11或SEQ ID NO:14-36中列出的氨基酸序列。在一些实施方案中,多肽包含两种或更多种如SEQ ID NO:16-36中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:19或29中列出的氨基酸序列,如SEQ ID NO:16、21、27、28或34中列出的氨基酸序列,以及SEQ ID NO:20、22、23、30、31、33、35或36中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:1中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:2中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:3中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:4中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:5中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:6中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:7中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:8中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:9中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:10中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:11中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:14中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:15中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:24中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:25中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:26中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:3中列出的氨基酸序列和如SEQ ID NO:4中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:5中列出的氨基酸序列和如SEQ ID NO:6中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:7中列出的氨基酸序列和如SEQ ID NO:8中列出的氨基酸序列。在一些实施方案中,多肽包含如SEQ ID NO:9中列出的氨基酸序列、如SEQ ID NO:10中列出的氨基酸序列和如SEQ ID NO:11中列出的氨基酸序列。在任何上述实施方案中,多肽可以进一步包含一种或多种如SEQ ID NO:17和18中列出的氨基酸序列。

[0060] 在一些实施方案中,本公开提供了包含一种或多种上述多肽的免疫原性组合物或疫苗。在某些实施方案中,免疫原性组合物包含一种上述多肽。在其他实施方案中,免疫原性组合物包含两种或更多种上述多肽,其可以作为单一多肽或作为两种或更多种多肽提供。

[0061] 在某些实施方案中,多肽是表位基共序列抗原,其包含使用EpiGraph方法衍生自野生型HBV序列的序列。在EpiGraph算法中,天然序列的特征在于大的节点图,每个节点对应于天然序列中出现的一个表位。当对应的两个表位字符串“一致”(这意味着第一个字符串中的最后k-1个字符与第二个字符串中的前k-1个字符一致)时,定向边连接两个节点。如果两个字符串是一致的,那么它们一起形成一个长度为k+1的字符串。更一般地,通过该节点和边图的路径对应于单个字符串,该单个字符串含有对应于该图中每个节点的k-聚体子字符串。每个节点根据参考集中有多少序列显示对应于该节点的子字符串来加权。

EpiGraph算法使用动态规划方案来找到通过该完整图的路径,该完整图使这些权重的总和最大化并提供最大的覆盖率。

[0062] 在一些实施方案中,表位基共序列抗原衍生自HBV C蛋白。在一些实施方案中,表位基共序列抗原衍生自HBV Pol (P) 或S蛋白,或另一种HBV蛋白。表位基共序列抗原可衍生自全长蛋白质序列、全长蛋白质序列的区域或其任何组合。在一些实施方案中,表位基共序列抗原包含衍生自HBV C、P和S蛋白中的两种或更多种的表位。在一些实施方案中,表位基共序列抗原进一步包含衍生自PreS1结构域或PreS2结构域的一种或多种表位。在一些实施方案中,表位基共序列抗原衍生自HBV的保守区域。在一些实施方案中,表位基共序列抗原衍生自HBV C、S和P中的一种或多种的保守区域。

[0063] 在一些实施方案中,表位基共序列抗原包含衍生自HBV C、P和S蛋白中的两种或更多种的序列,其中序列相对于它们在HBV基因组中的顺序重新排序。表位基共序列抗原内序列的重新排序可以提供更有效或以其他方式改进的抗原体表达。

[0064] 在一些实施方案中,表位基共序列抗原衍生自具有一个或多个突变(例如氨基酸的缺失或取代)的HBV蛋白。在一些实施方案中,突变使野生型蛋白质中存在的至少一种功能灭活。例如,可以通过去除蛋白质N末端的肉豆蔻酰化序列来灭活PreS1,或者通过删除或突变酶活性位点来灭活Pol。在一些实施方案中,一种或多种突变存在于HBV核糖核酸酶H(RNaseH)的活性位点并导致RNaseH活性丧失。示例性突变示于表1中。

[0065] 在某些实施方案中,表位基共序列抗原是使用选定的HBV群体开发的,这产生作为该群体核心的表位基共序列抗原。例如,HBV群体可以是存在于选定地理位置(例如亚洲、北美、南美、欧洲、非洲或澳大利亚)的HBV基因型。在一些实施方案中,表位基共序列抗原是亚洲或更具体是中国的HBV B区域流行病的核心。在其他实施方案中,表位基共序列抗原是亚洲或更具体是中国的HBV C区域流行病的核心。在一些实施方案中,表位基共序列抗原是亚洲或更具体是中国的HBV A区域病的核心。在一些实施方案中,表位基共序列抗原是亚洲或更具体是中国的HBV CB区域流行病的核心。在一些实施方案中,表位基共序列抗原是亚洲或更具体是中国的HBV D区域病的核心。在一些实施方案中,表位基共序列抗原是亚洲或更具体是中国的HBV DC区域流行病的核心。在一些实施方案中,表位基共序列抗原是亚洲或更具体是中国的HBV DE区域流行病的核心。在一些实施方案中,表位基共序列抗原是亚洲或更具体是中国的HBV E区域流行病的核心。在一些实施方案中,表位基共序列抗原是亚洲或更具体是中国的HBV F区域流行病的核心。

[0066] 在其他实施方案中,表位基共序列抗原是北美的HBV多基因型区域流行病的核心。在一些实施方案中,表位基共序列抗原是北美HBV A区域流行病的核心。在一些实施方案中,群体表位基共序列抗原是北美HBV B区域流行病的核心。在一些实施方案中,表位基共序列抗原是北美HBV C区域流行病的核心。在一些实施方案中,表位基共序列抗原是北美HBV CB区域流行病的核心。在一些实施方案中,表位基共序列抗原是北美HBV D区域流行病的核心。在一些实施方案中,表位基共序列抗原是北美HBV DC区域流行病的核心。在一些实施方案中,表位基共序列抗原是北美HBV DE区域流行病的核心。在一些实施方案中,表位基共序列抗原是北美HBV E区域流行病的核心。在一些实施方案中,表位基共序列抗原是北美HBV F区域流行病的核心。

[0067] 在其他实施方案中,表位基共序列抗原是南美洲HBV多基因型区域流行病的核心。

在一些实施方案中,表位基共序列抗原是南美洲HBV A区域流行病的核心。在一些实施方案中,表位基共序列抗原是南美洲HBV B区域流行病的核心。在一些实施方案中,表位基共序列抗原是南美洲HBV C区域流行病的核心。在一些实施方案中,表位基共序列抗原是南美洲HBV CB区域流行病的核心。在一些实施方案中,表位基共序列抗原是南美洲HBV D区域流行病的核心。在一些实施方案中,表位基共序列抗原是南美洲HBV DC区域流行病的核心。在一些实施方案中,表位基共序列抗原是南美洲HBV DE区域流行病的核心。在一些实施方案中,表位基共序列抗原是南美洲HBV E区域流行病的核心。在一些实施方案中,表位基共序列抗原是南美洲HBV F区域流行病的核心。

[0068] 在其他实施方案中,表位基共序列抗原是欧洲HBV多基因型区域流行病的核心。在一些实施方案中,表位基共序列抗原是欧洲HBV A区域流行病的核心。在一些实施方案中,表位基共序列抗原是欧洲HBV B区域流行病的核心。在一些实施方案中,表位基共序列抗原是欧洲HBV C区域流行病的核心。在一些实施方案中,表位基共序列抗原是欧洲HBV CB区域流行病的核心。在一些实施方案中,表位基共序列抗原是欧洲HBV D区域流行病的核心。在一些实施方案中,群体表位基共序列抗原是欧洲HBV DC区域流行病的核心。在一些实施方案中,表位基共序列抗原是欧洲HBV DE区域流行病的核心。在一些实施方案中,表位基共序列抗原是欧洲HBV E区域流行病的核心。在一些实施方案中,表位基共序列抗原是欧洲HBV F区域流行病的核心。

[0069] 在其他实施方案中,表位基共序列抗原是非洲HBV多基因型区域流行病的核心。在一些实施方案中,表位基共序列抗原是非洲HBV A区域流行病的核心。在一些实施方案中,表位基共序列抗原是非洲HBV B区域流行病的核心。在一些实施方案中,表位基共序列抗原是非非洲HBV C区域流行病的核心。在一些实施方案中,表位基共序列抗原是非非洲HBV CB区域流行病的核心。在一些实施方案中,表位基共序列抗原是非非洲HBV D区域流行病的核心。在一些实施方案中,表位基共序列抗原是非非洲HBV DC区域流行病的核心。在一些实施方案中,表位基共序列抗原是非非洲HBV DE区域流行病的核心。在一些实施方案中,表位基共序列抗原是非非洲HBV E区域流行病的核心。在一些实施方案中,表位基共序列抗原是非非洲HBV F区域流行病的核心。

[0070] 在其他实施方案中,表位基共序列抗原是澳大利亚HBV多基因型区域流行病的核心。在一些实施方案中,表位基共序列抗原是澳大利亚HBV A区域流行病的核心。在一些实施方案中,表位基共序列抗原是澳大利亚HBV B区域流行病的核心。在一些实施方案中,表位基共序列抗原是澳大利亚HBV C区域流行病的核心。在一些实施方案中,表位基共序列抗原是非澳大利亚HBV CB区域流行病的核心。在一些实施方案中,表位基共序列抗原是非澳大利亚HBV D区域流行病的核心。在一些实施方案中,表位基共序列抗原是非澳大利亚HBV DC区域流行病的核心。在一些实施方案中,表位基共序列抗原是非澳大利亚HBV DE区域流行病的核心。在一些实施方案中,表位基共序列抗原是非澳大利亚HBV E区域流行病的核心。在一些实施方案中,表位基共序列抗原是非澳大利亚HBV F区域流行病的核心。

[0071] 在其他实施方案中,表位基共序列抗原是所公开疫苗中HBV全局集的核心。

[0072] 在一些实施方案中,HBV表位基共序列抗原是1_CH_epi (SEQ ID NO:1),其使用来自中国的1044个HBV序列开发。在一些实施方案中,HBV表位基共序列抗原是1_GL_epi (SEQ ID NO:2),其使用3041个HBV序列的全球集开发。在一些实施方案中,表位基共序列抗原是

两种或更多种单独的表位基共序列抗原的组合。例如,在一些实施方案中,表位基共序列抗原包含2_CH_epi,其包含使用来自中国的1044个HBV序列(SEQ ID NO:3和SEQ ID NO:4)开发的两种表位基共序列抗原。在一些实施方案中,表位基共序列抗原包含2_CHGL_epi,其包含使用来自中国的1044个HBV序列开发的第一表位基共序列抗原Epi1(SEQ ID NO:5),以及使用3041个HBV序列的全球集开发的第二表位基共序列抗原Epi2(SEQ ID NO:6),其中Epi1已固定在解决方案中。换言之,Epi2是Epi1的补充,是在Epi1已经存在的情况下开发的。在一些实施方案中,表位基共序列抗原包含2_CHGL_epi的修饰形式,其包含Epi3(SEQ ID NO:7)和Epi4(SEQ ID NO:8)。在一些实施方案中,表位基共序列抗原包含3_GL_epi,其包含使用3041个HBV序列的全球集开发的三种表位基共序列抗原(SEQ ID NO:9;SEQ ID NO:10;和SEQ ID NO:11)。在一些实施方案中,表位基共序列抗原包含天然D亚型序列(SEQ ID NO:12),GenBank登录号Y07587。在一些实施方案中,表位基共序列抗原包含天然C亚型参考序列(SEQ ID NO:13),GenBank登录号GQ358158。登录号Y07587和GQ358158的每个参考基因通过引用以其整体并入本文。在一些实施方案中,表位基共序列抗原是SEQ ID NO:14的修饰的基因型D序列。在一些实施方案中,表位基共序列抗原是SEQ ID NO:15的重新排序的基因型D序列。在一些实施方案中,表位基共序列抗原包含一种或多种在SEQ ID NO:16-23和SEQ ID NO:27-36中列出的序列。在一些实施方案中,HBV表位基共序列抗原包含在SEQ ID NO:1-SEQ ID NO:36中列出的序列中的两种或更多种。

[0073] 本文进一步提供了包含一种或多种上述表位基共序列抗原的免疫原性组合物或疫苗。表位基共序列抗原可以作为DNA、RNA或多肽递送。在某些实施方案中,疫苗包含单一抗原。在其他实施方案中,疫苗包含两种或更多种抗原,其可以作为单一多肽或作为两种或更多种多肽提供。在某些实施方案中,疫苗包含为选定的HBV基因型(例如存在于选定地理位置的基因型)提供有效表位覆盖率的表位基共序列抗原。本文提供的疫苗可以是预防性疫苗或治疗性疫苗。在一些实施方案中,疫苗包含一种或多种多肽和药学上可接受的载体或赋形剂。

[0074] 在一些实施方案中,疫苗包含使用来自中国的HBV序列开发的两种表位基共序列抗原。在某些实施方案中,疫苗包括包含SEQ ID NO:3和SEQ ID NO:4中列出的序列的表位基共序列抗原,其可以作为一种多肽或作为两种多肽提供。在一些实施方案中,疫苗包含使用来自中国的HBV序列开发的表位基共序列抗原和使用来自全球集的HBV序列开发的表位基共序列抗原。在某些实施方案中,疫苗包括包含SEQ ID NO:5和SEQ ID NO:6中列出的序列的表位基共序列抗原,其可以作为一种多肽或作为两种多肽提供。在某些实施方案中,疫苗包括包含SEQ ID NO:7和SEQ ID NO:8列出的序列的表位基共序列抗原,其可以作为一种多肽或作为两种多肽提供。在一些实施方案中,疫苗包含使用来自全球集的HBV序列开发的三种表位基共序列抗原。在某些实施方案中,疫苗包括包含SEQ ID NO:9、SEQ ID NO:10和SEQ ID NO:11中列出的序列的表位基共序列抗原,其可以作为一种多肽、作为两种多肽或作为三种多肽提供。

[0075] III. 多核苷酸和运载体

[0076] 在一些实施方案中,本公开提供了编码多肽的多核苷酸序列。多核苷酸可以是DNA或RNA,并且可以编码任何上述抗原。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:1-36中的一种或多种中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸序列被密

码子优化以在特定宿主中表达。

[0077] 在一些实施方案中,多核苷酸编码包含如SEQ ID NO:1-11或SEQ ID NO:14-36中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含两种或更多种如SEQ ID NO:16-36中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码多肽,该多肽包含如SEQ ID NO:19或29中列出的氨基酸序列、如SEQ ID NO:16、21、27、28或34中列出的氨基酸序列和如SEQ ID NO:20、22、23、30、31、33、35或36中列出的氨基酸序列。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:1中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:2中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:3中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:4中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:5中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:6中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:7中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:8中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:9中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:10中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:11中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:14中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:15中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:24中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:25中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:26中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:3中列出的氨基酸序列和如SEQ ID NO:4中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:5中列出的氨基酸序列和如SEQ ID NO:6中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码包含如SEQ ID NO:7中列出的氨基酸序列和如SEQ ID NO:8中列出的氨基酸序列的多肽。在一些实施方案中,多核苷酸编码多肽,其包含如SEQ ID NO:9中列出的氨基酸序列、如SEQ ID NO:10中列出的氨基酸序列和如SEQ ID NO:11中列出的氨基酸序列。在任何上述实施方案中,多核苷酸可进一步编码包含一种或多种如SEQ ID NO:17和18中列出的氨基酸序列的多肽。

[0078] 在一些实施方案中,本公开提供了一种组合物,例如一种免疫原性组合物,其包含两种或更多种上述多核苷酸。

[0079] 在一些实施方案中,本公开提供了包含一种或多种上述多核苷酸的疫苗。在某些实施方案中,疫苗进一步包含药学上可接受的载体或赋形剂。

[0080] 本文进一步提供了包含任何上述多核苷酸的运载体。可以使用的运载体包括但不限于质粒、细菌运载体和病毒运载体。病毒运载体包括巨细胞病毒运载体。用于治疗性疫苗递送的CMV运载体的一个优点是它们可用于引发特定的CD8⁺T细胞反应并诱导更有效和持久的反应。动物模型中已经表明,基于这些病毒运载体的疫苗可以清除病毒感染(Hansen等人,Science 340:1237874(2013)),因此这些方法有望用于治疗性疫苗(另见:Hansen等人,Science 351:714-720(2016))。

[0081] 其他病毒运载体可以包括痘病毒,包括安卡拉牛痘和金丝雀痘;腺病毒,包括5型

腺病毒(Ad5);风疹;仙台病毒;弹状病毒; α 病毒;和腺相关病毒。替代地,疫苗抗原可以作为疫苗的DNA、RNA或蛋白质组分递送。表位基共序列抗原将与基本上任何疫苗抗原递送方式相容。

[0082] 在一些方面,本公开提供基于运载体的免疫原性组合物或疫苗,其中表达运载体用于递送编码本文公开的一种或多种抗原的核酸。例如,表达运载体可以是痘病毒、腺病毒、风疹病毒、仙台病毒、弹状病毒、 α 病毒或腺相关病毒骨架。

[0083] 在一些实施方案中,CMV运载体用于本文公开的组合物和方法。几个方面使慢性HBV感染特别适合通过CMV运载体的免疫治疗干预。

[0084] 首先,具有成熟免疫系统的绝大多数个体容易逐渐增加有效的免疫反应并清除急性感染。由于这种免疫清除主要由产生细胞因子的CD8⁺T细胞介导,因此诱导活性肝脏驻留效应器CD8⁺T细胞(TEM)反应似乎对HBV清除至关重要。因此,在CHB患者的肝脏中诱导持续的效应器HBV特异性CD8⁺T细胞应该足以控制并最终消除HBV。由基于CMV的运载体诱导的TEM频率在接种的恒河猴(RM)的肝脏中特别高(Hansen等人,Nature 473:523-527(2011),补充图1)。

[0085] 其次,与显示高突变率从而导致准种的其他小型慢性病毒(例如HIV或HCV)不同,HBV的小型(3.2kb)DNA基因组由于重叠的开放阅读框而在其突变能力方面受到更多限制(ORF)(图1)。

[0086] 不幸的是,通过传统的疫苗接种方法(例如,基于肽的、基于蛋白质的DNA,甚至涉及DNA和痘病毒运载体两者的异源初免-加强T细胞诱导方案)诱导的T细胞在几个月后在外周不再可检测到,这可能太短而无法完全阻止残留的HBV基因组的存活,而残留的HBV基因组可为病毒反弹潜在地提供来源。相比之下,只有CMV运载体诱导的TEM在循环和肝脏中以高频率持续维持多年(Hansen等人,Nature 2011)。

[0087] 在某些实施方案中,运载体包括人CMV(HCMV)运载体或恒河猴CMV(RhCMV)运载体,其包含HCMV或RhCMV骨架和一种或多种编码抗原的多核苷酸。一种或多种多核苷酸可以编码任何上述抗原。在一些实施方案中,多核苷酸编码两种或更多种上述抗原。在一些实施方案中,载体包含两种或更多种多核苷酸,每种多核苷酸编码一种或多种上述抗原。

[0088] 本公开进一步提供了包含两种或更多种运载体的组合物,每种运载体包含编码一种或多种上述抗原的一种或多种多核苷酸。

[0089] 在一些实施方案中,CMV运载体缺少编码间层蛋白pp71的UL82基因。在一些实施方案中,UL82基因被编码一种或多种上述抗原的一种或多种多核苷酸替代。在一些实施方案中,CMV运载体缺少UL128-UL130基因区域。在一些实施方案中,CMV运载体缺少UL146-UL147基因区域。在一些实施方案中,CMV运载体缺少UL128-UL130基因区域并且缺少UL146-147基因区域。在一些实施方案中,CMV运载体具有完整的UL128-UL130基因区域和完整的UL146-UL147基因区域。UL128-UL130基因区域包括UL128基因、UL130基因以及介于UL128基因和UL130基因之间的任何区域。UL146-UL147基因区域包括UL146基因、UL147基因以及介于UL146基因和UL147基因之间的任何区域。

[0090] 在某些方面,本公开提供了包含上述运载体的免疫原性组合物或疫苗。由CMV运载体引发的免疫反应不受预先存在的抗运载体免疫的影响,因此能够针对不同的抗原连续使用相同的运载体(Hansen等人,Nature Medicine 15:293-299(2009))。部分地,超感染的能

力是由于MHC-I介导的抗原呈递给CD8+T细胞的病毒抑制剂(Hansen等人,Science 328:102-106(2010))。由于几乎整个人类群体,包括大多数CHB患者,都慢性感染HCMV,因此超感染是一个重要特征,无论受体CMV状态如何,都能够使用CMV运载体。CMV运载体具有独特的免疫学。某些修饰的RhCMV/SIV运载体的一个令人惊讶和出乎意料的特征是发现这些运载体引发了CD8+T细胞,该CD8+T细胞不识别被常规MHC-Ia限制性CD8+T细胞响应于SIV感染本身,或响应于任何其他表达SIV抗原的运载体平台而识别的任何表位。尽管如此,CMV运载体引发的CD8+T细胞识别给定抗原内的肽数量的3倍,如PCT/US2016/017373中所示,其全部内容通过引用并入本文(另见Hansen等人,Science 2013,2016)。

[0091] 这种显著广度的根本原因是通过分析100多只动物中给定抗原(CMV、SIV、TB)的单个肽的限制性元件确定的,并证实了CMV运载体的惊人特征:由Rh 68-1运载体诱导的每种肽由通常被CD4+T细胞识别的MHC-II呈递,或者由非多态性MHC-I分子MHC-E呈递,该MHC-E通常与MHC-I衍生肽VMAPRTL (VL9)结合并作为抑制性NKG2A NK细胞受体的配体起作用。(值得注意的是,CD4+T细胞全部都是常规的,即受MHC-II限制。)值得注意的是,菌株68-1RhCMV诱导的CD8+T细胞对覆盖整个抗原的重叠肽库的反应可以通过添加VL9(抑制MHC-E)或不变链衍生性CLIP(抑制MHC-II)完全阻断,从而证实所有CD8+T细胞表位都是“非常规的”(Hansen等人,Science 2016)。虽然在其他传染病和癌症中偶尔观察到MHC-II和MHC-E限制性CD8+T细胞,但此类T细胞在RhCMV免疫动物中的大量存在是前所未有的,并且真正打破了范式。重要的是,RhCMV运载体诱导的MHC-II和MHC-E和MHC-Ia-非典型(下文讨论)限制性CD8+T细胞识别SIV感染的CD4+T细胞,这表明SIV感染的细胞中可发生非常规的抗原呈递,即使SIV无法启动此类反应。由于许多慢性病毒(包括HCV)上调HLA-E,可能作为对NK细胞的防御,这种高度保守的MHC分子代表了免疫治疗的新靶标。(与HCV相比,HBV感染的肝细胞中HLA-E的表达鲜为人知,但在慢性HBV携带者中发现高水平的循环HLA-E)。因此,引发MHC-E限制性CD8+T细胞的能力开启了经由这种高度保守的限制性元件靶向HBV的可能性。

[0092] CMV运载体中基因修饰的特定模式与各种T细胞反应相关联。非常规CD8+T细胞由缺少UL128-UL130基因区域和UL146-UL147基因区域的运载体诱导(Hansen等人,Science 2013,2016,OHSU2346)。相反,由自然RhCMV感染诱导或针对RhCMV(Rh68-1)的UL128-UL130修复版本的CD8+T细胞反应是常规的,即MHC-I受限(Hansen等人,Science 2013)。然而,即使是由UL128-UL130完整运载体引发的常规CD8+T细胞反应仍然比非CMV运载体诱导的那些反应要显著广泛得多(Hansen等人,Science 2013)。此外,这种广泛的常规CD8+T细胞反应完全针对亚显性(“非典型”)表位,因为免疫逃避基因US11阻止诱导识别“典型”(即免疫显性)MHC-I表位的T细胞(Hansen等人,Science 2013)。因此,基因修饰的CMV运载体能够引发四种不同的CD8+T细胞群体,每个群体识别一组非重叠表位并分类如下:1.非常规,MHC-II受限;2.非常规,MHC-E受限;3.常规MHC-I受限、非典型(=亚显性);4.常规,MHC-I受限、典型(=免疫显性)。UL128-UL130和UL146-UL147基因区域的存在或不存在决定了从常规CD8+T细胞到非常规CD8+T细胞的转换,而在其中存在UL128-UL130和UL146-UL147的运载体以及其中不存在UL128-130和UL146-UL147的运载体两者中,在不存在US11的情况下诱导经典CD8+T细胞。

[0093] 在一些实施方案中,本公开提供了一种免疫原性组合物或疫苗,其包含任何上述载体和编码抗原的一种或多种多核苷酸。一种或多种多核苷酸可以编码任何上述抗原。在

一些实施方案中,多核苷酸编码两种或更多种上述抗原。两种或更多种多肽可以由相同或不同的启动子表达。在一些实施方案中,运载体包含两种或更多种多核苷酸,每种多核苷酸编码一种或多种上述抗原。在某些实施方案中,疫苗包含一种或多种上述运载体和药学上可接受的载体或赋形剂。

[0094] III. 治疗方法

[0095] 在某些实施方案中,提供了治疗受试者中HBV的方法,所述方法包括向有此类需要的受试者施用有效量的包含上述多肽、多核苷酸、运载体或组合物中的一种或多种的免疫原性组合物或疫苗。在一些实施方案中,疫苗包含一种或多种抗原或编码抗原的多核苷酸,所述抗原经选择以有效覆盖地理区域内的HBV基因型多样性。在一些实施方案中,疫苗以一种或多种多肽的形式提供。在其他实施方案中,疫苗以一种或多种多核苷酸的形式提供,其可以在重组病毒运载体中提供。在任何上述实施方案中,疫苗可进一步包含一种或多种药学上可接受的载体或赋形剂。

[0096] 在一些实施方案中,提供了在受试者中诱导或生成免疫反应的方法。此类方法包含向有此类需要的受试者施用有效量的包含上述多肽、多核苷酸、运载体或组合物中的一种或多种的免疫原性组合物或疫苗。在一些实施方案中,疫苗包含一种或多种抗原或编码抗原的多核苷酸,所述抗原经选择以有效覆盖地理区域内的HBV基因型多样性。在一些实施方案中,疫苗以一种或多种多肽的形式提供。在其他实施方案中,疫苗以一种或多种多核苷酸的形式提供,其可以在重组病毒运载体中提供。在任何上述实施方案中,疫苗可进一步包含一种或多种药学上可接受的载体或赋形剂。

[0097] 一些实施方案包括治疗受试者中HBV感染的方法,所述方法包括向有此类需要的受试者施用有效量的包含上述多肽、多核苷酸、运载体或组合物中的一种或多种的免疫原性组合物或疫苗。在一些实施方案中,疫苗包含一种或多种抗原或编码抗原的多核苷酸,所述抗原经选择以有效覆盖地理区域内的HBV基因型多样性。在一些实施方案中,疫苗以一种或多种多肽的形式提供。在其他实施方案中,疫苗以一种或多种多核苷酸的形式提供,其可以在重组病毒运载体中提供。在任何上述实施方案中,疫苗可进一步包含一种或多种药学上可接受的载体或赋形剂。

[0098] 本公开进一步提供了保护受试者免受HBV感染的方法,所述方法包括向有此类需要的受试者施用有效量的包含上述多肽、多核苷酸、运载体或组合物中的一种或多种的免疫原性组合物或疫苗。在一些实施方案中,疫苗包含一种或多种抗原或编码抗原的多核苷酸,所述抗原经选择以有效覆盖地理区域内的HBV基因型多样性。在一些实施方案中,疫苗以一种或多种多肽的形式提供。在其他实施方案中,疫苗以一种或多种多核苷酸的形式提供,其可以在重组病毒运载体中提供。在任何上述实施方案中,疫苗可进一步包含一种或多种药学上可接受的载体或赋形剂。

[0099] 一些实施方案包括诱导效应器记忆T细胞反应的方法,所述方法包括确定一种或多种表位基共序列;生成包含运载体的疫苗,所述运载体包含编码一种或多种表位基共序列的一种或多种多核苷酸;以及向有此类需要的受试者施用疫苗。一些实施方案包括诱导效应器记忆T细胞反应的方法,所述方法包括确定一种或多种表位基共序列;生成包含一种或多种抗原的疫苗,所述抗原具有一种或多种表位基共序列的氨基酸序列;以及向有此类需要的受试者施用疫苗。在一些实施方案中,提供了诱导效应器记忆T细胞反应的方法,其

中一种或多种表位基共序列包含1_CH_epi (SEQ ID NO:1);1_GL_epi (SEQ ID NO:2);2_CH_epi,其包含在SEQ ID NO:3和SEQ ID NO:4中列出的氨基酸序列;2_CHGL_epi,其包含在SEQ ID NO:5和SEQ ID NO:6中列出的氨基酸序列;2_CHGL_epi,其包含在SEQ ID NO:7和SEQ ID NO:8中列出的氨基酸序列;3_GL_epi,其包含在SEQ ID NO:9、SEQ ID NO:10和SEQ ID NO:11中列出的氨基酸序列;天然D亚型序列 (SEQ ID NO:12)、天然C亚型参考序列 (SEQ ID NO:13)、SEQ ID NO:14的修饰基因型D序列和SEQ ID NO:15的重新排序的基因型D序列。在一些实施方案中,提供了诱导效应器记忆T细胞反应的方法,其中一种或多种表位基共序列包含在SEQ ID NO:16-23和SEQ ID NO:27-36中列出的一种或多种序列。在一些实施方案中,提供了诱导效应器记忆T细胞反应的方法,其中一种或多种表位基共序列包含SEQ ID NO:1-SEQ ID NO:36中的两种或更多种。

[0100] 一些实施方案包括诱导效应器记忆T细胞反应的方法,所述方法包括生成免疫原性组合物或疫苗,所述免疫原性组合物或疫苗包含编码一种或多种表位基共序列抗原的一种或多种上述多核苷酸;以及向有此类需要的受试者施用免疫原性组合物或疫苗。一些实施方案包括诱导效应器记忆T细胞反应的方法,所述方法包括生成包含一种或多种上述表位基共序列抗原的免疫原性组合物或疫苗,并向有此类需要的受试者施用免疫原性组合物或疫苗。在一些实施方案中,提供了诱导效应器记忆T细胞反应的方法,其中一种或多种表位基共序列包含1_CH_epi (SEQ ID NO:1);1_GL_epi (SEQ ID NO:2);2_CH_epi,其包含在SEQ ID NO:3和SEQ ID NO:4中列出的氨基酸序列;2_CHGL_epi,其包含在SEQ ID NO:5和SEQ ID NO:6中列出的氨基酸序列;2_CHGL_epi,其包含在SEQ ID NO:7和SEQ ID NO:8中列出的氨基酸序列;3_GL_epi,其包含在SEQ ID NO:9、SEQ ID NO:10和SEQ ID NO:11中列出的氨基酸序列;天然D亚型序列 (SEQ ID NO:12)、天然C亚型参考序列 (SEQ ID NO:13)、SEQ ID NO:14的修饰基因型D序列和SEQ ID NO:15的重新排序的基因型D序列。在一些实施方案中,提供了诱导效应器记忆T细胞反应的方法,其中一种或多种表位基共序列包含一种或多种在SEQ ID NO:16-23和SEQ ID NO:27-36中列出的序列。在一些实施方案中,提供了诱导效应器记忆T细胞反应的方法,其中一种或多种表位基共序列包含SEQ ID NO:1-SEQ ID NO:36中的两种或更多种。

[0101] 在任何上述实施方案中,免疫原性组合物或疫苗可以是预防性疫苗或治疗性疫苗。

[0102] HBV疫苗研究的最新突破包括效应器记忆T细胞 (TEM) 诱导疫苗以预防HBV感染的概念。与由传统疫苗方法诱导的中枢记忆T细胞 (TCM) 不同,TEM持续维持在淋巴组织和淋巴外效应器部位,并立即准备好介导抗病毒效应功能,从而在病毒进入的门户和病毒再激活的部位提供持续的免疫保护。诱导和无限维持TEM的最合格的运载体系统衍生自CMV。据推测,由于持续感染细胞中持续的低水平再激活和/或基因表达,CMV维持了TEM维持所需的适量持续、低水平的免疫刺激,而不会引发T细胞衰竭。

[0103] 在某些实施方案中,免疫原性组合物或疫苗可用于治疗性疫苗环境。例如,可以使用k-means聚类策略来设计疫苗,以确认一组6-10个抗原序列,这些抗原序列可以提供感染高度可变病原体 (例如HBV) 的人类群体中的表位的良好覆盖率。在一些实施方案中,对感染受试者的病毒进行测序并且递送提供对感染病毒中表位的良好覆盖率的两种或三种疫苗 (或一种或多种疫苗,其包含两种或三种多肽或编码两种或三种多肽的一种或多种多核苷

酸)。因此,提供了有效的表位覆盖率,同时疫苗和感染菌株之间的表位错配被最小化。

[0104] 提供的某些实施方案包括免疫原性组合物或疫苗,所述免疫原性组合物或疫苗包含缺少某些CMV基因区域的HCMV骨架运载体,以及编码表位基共序列抗原的多核苷酸。在某些实施方案中,HCMV骨架缺少UL128-UL130基因区域(其包括UL128基因、UL130基因和介于UL128基因和UL130基因之间的任何区域)和UL146-UL147基因区域(其包括UL146基因、UL147基因以及介于UL146基因和UL147基因之间的任何区域)。某些实施方案还可包括间层蛋白pp71(UL82)基因的缺失。(美国专利申请公开号2014/0141038;2008/0199493;2013/0142823;以及国际申请公开号W0/2014/138209)。

[0105] 在一些实施方案中,本公开提供了用于治疗HBV感染的任何上述多肽、多核苷酸、运载体、疫苗或组合物。在一些实施方案中,本公开提供了用于保护受试者免受HBV感染的任何上述多肽、多核苷酸、运载体、疫苗或组合物。

[0106] 本公开进一步提供了任何上述多肽、多核苷酸、运载体、疫苗或组合物在制备用于治疗HBV感染的药物中的用途。在一些实施方案中,本公开进一步提供了任何上述多肽、多核苷酸、运载体、免疫原性组合物、疫苗或组合物在制备用于保护受试者免受HBV感染的药物中的用途。

[0107] 施用本文所述的多肽、多核苷酸、运载体、疫苗或组合物的典型途径包括但不限于口服、局部、透皮、吸入、肠胃外、舌下、口腔、直肠、阴道和鼻内。如本文所用,术语“肠胃外”包括皮下注射、静脉内、肌肉内、胸骨内注射或输注技术。在某些实施方案中,施用包含通过选自口服、静脉内、肠胃外、胃内、胸膜内、肺内、直肠内、皮内、腹膜内、瘤内、皮下、局部、透皮、脑池内、鞘内、鼻内和肌肉内的途径施用。

[0108] 根据本发明的某些实施方案的药物组合物被配制为使得其中所含的活性成分在将组合物施用于患者时是生物可利用的。将施用于受试者或患者的组合物可以采取一种或多种剂量单位的形式,其中例如,片剂可以是单一剂量单位,以及本文描述的多肽、多核苷酸、运载体、疫苗或液体形式的组合物的容器可以容纳多个剂量单位。制备此类剂型的实际方法对于本领域技术人员来说是已知的或将是显而易见的;例如,参见Remington:The Science and Practice of Pharmacy,第20版(Philadelphia College of Pharmacy and Science,2000)。在任何情况下,待施用的组合物将包含用于根据本文的教导治疗或预防HBV的有效量的本公开的多肽、多核苷酸、运载体、疫苗或组合物。

[0109] 组合物可以是固体或液体的形式。在一些实施方案中,载体是颗粒状的,因此组合物是例如片剂或粉末形式。载体可以是液体,其中组合物例如是口服油、可注射液体或气雾剂,其可用于例如吸入施用。当意欲用于口服施用时,药物组合物优选为固体或液体形式,其中半固体、半液体、悬浮液和凝胶形式包括在本文视为固体或液体的形式中。

[0110] 作为用于口服施用的固体组合物,药物组合物可以配制成散剂、颗粒剂、压制片剂、丸剂、胶囊剂、口香糖、糯米纸囊剂(wafer)等。这种固体组合物将通常含有一种或多种惰性稀释剂或可食用载体。此外,可以存在以下一种或多种:粘合剂,例如羧甲基纤维素、乙基纤维素、微晶纤维素、黄蓍胶或明胶;赋形剂,例如淀粉、乳糖或糊精;崩解剂,例如海藻酸、海藻酸钠、Primogel、玉米淀粉等;润滑剂,例如硬脂酸镁或Sterotex;助流剂,例如胶体二氧化硅;甜味剂,例如蔗糖或糖精;调味剂,例如薄荷、水杨酸甲酯或橙子调味剂;以及着色剂。当组合物为胶囊(例如明胶胶囊)形式时,除了上述类型的材料之外,它还可以含有液

体载体,例如聚乙二醇或油。

[0111] 组合物可以是液体形式,例如酞剂、糖浆、溶液、乳液或悬浮液。作为两个示例,该液体可以用于口服施用或通过注射递送。当意欲用于口服施用时,除本发明化合物外,优选的组合物还含有甜味剂、防腐剂、染料/着色剂和增味剂中的一种或多种。在意欲通过注射施用的组合物中,可以包括表面活性剂、防腐剂、润湿剂、分散剂、悬浮剂、缓冲剂、稳定剂和等渗剂中的一种或多种。

[0112] 液体药物组合物,无论它们是溶液、悬浮液还是其他类似形式,可以包括一种或多种以下佐剂:无菌稀释剂,例如注射用水;盐水溶液,优选生理盐水、林格氏溶液、等渗氯化钠;固定油,例如可用作溶剂或悬浮介质的合成甘油单酯或甘油二酯、聚乙二醇、甘油、丙二醇或其他溶剂;抗菌剂,例如苯甲醇或对羟基苯甲酸甲酯;抗氧化剂,例如抗坏血酸或亚硫酸氢钠;螯合剂,例如乙二胺四乙酸;缓冲剂,例如醋酸盐、柠檬酸盐或磷酸盐,以及用于调节张力的试剂,例如氯化钠或葡萄糖。肠胃外制剂可以封装在安瓿、一次性注射器,或由玻璃或塑料制成的多剂量小瓶中。生理盐水是优选的佐剂。可注射药物组合物优选是无菌的。用于肠胃外或口服施用的液体组合物应含有一定量的如本文公开的多肽、多核苷酸、运载体、疫苗或组合物,以便获得合适的剂量。

[0113] 组合物可意欲用于局部施用,在这种情况下,载体可适当地包含溶液、乳液、软膏或凝胶基质。例如,该基质可以包含以下一种或多种:矿脂、羊毛脂、聚乙二醇、蜂蜡、矿物油、稀释剂(如水和酒精),以及乳化剂和稳定剂。增稠剂可以存在于用于局部施用的组合物中。如果意欲用于透皮施用,则该组合物可以包括透皮贴剂或离子电渗装置。药物组合物可意欲用于以例如栓剂的形式进行直肠施用,该栓剂将在直肠中融化并释放药物。用于直肠施用的组合物可以含有油质基质作为合适的无刺激性赋形剂。此类基质包括但不限于羊毛脂、可可脂和聚乙二醇。

[0114] 组合物可以包括改变固体或液体剂量单位的物理形式的各种材料。例如,组合物可以包括在活性成分周围形成包衣壳的材料。形成包衣壳的材料通常是惰性的,并且可以选择自例如糖、虫胶和其他肠溶包衣剂。替代地,可将活性成分装入明胶胶囊中。固体或液体形式的组合物可包括与本公开的多肽、多核苷酸、运载体、疫苗或组合物结合并由此有助于化合物递送的试剂。可以以这种能力起作用的合适的试剂包括单克隆或多克隆抗体、一种或多种蛋白质,或脂质体。该组合物可以基本上由可以作为气雾剂施用的剂量单位组成。术语气雾剂用于表示从胶体性质的系统到由加压包装组成的系统的各种系统。可以通过液化或压缩气体或通过分配活性成分的合适泵系统进行递送。气雾剂可以以单相、双相或三相系统递送以便递送活性成分。气雾剂的递送包括必要的容器、活化剂、阀门、子容器等,它们一起可以形成试剂盒。本领域普通技术人员无需过度实验即可确定优选的气雾剂。

[0115] 应当理解,本公开的组合物还涵盖用于多核苷酸的载体分子,如本文所述(例如,脂质纳米颗粒、纳米级递送平台等)。

[0116] 药物组合物可以通过制药领域熟知的方法制备。例如,意欲通过注射施用的组合物可以通过将组合物与无菌蒸馏水组合以便形成溶液来制备,该组合物包含本文所述的多肽、多核苷酸、运载体、疫苗或组合物以及任选地,盐、缓冲剂和/或稳定剂中的一种或多种。可以添加表面活性剂以促进均质溶液或悬浮液的形成。表面活性剂是与分子非共价相互作用以促进分子在水性递送系统中溶解或均质悬浮的化合物。

[0117] 通常,适当的剂量和治疗方案以足量提供治疗和/或预防性益处的量提供组合物。

[0118] 组合物以有效量施用,该有效量将根据多种因素而变化,该因素包括所采用的特定化合物的活性;化合物的代谢稳定性和作用时长;受试者的年龄、体重、一般健康状况、性别和饮食;施用方式和时间;排泄速率;药物组合;特定病况或病症的严重程度;以及接受治疗的受试者。

[0119] 提供以下实施例以更详细地描述本文描述的实施方案。它们旨在说明而非限制实施方案。

[0120] 本文引用的所有文件、专利和专利申请均通过引用并入,并且可用于本文公开的方法和组合物的实践中。

[0121] 实施例

[0122] 实施例1:

[0123] 确认用作治疗性疫苗的表位基共序列抗原

[0124] 使用EpiGraph方法开发针对HBV的表位基共序列抗原,如PCT申请号W0 2016/054654 A1和Theiler,等人,Sci.Rep.6:33987 (2016) (其通过引用完全并入本文)中所述。用于使用EpiGraph算法的工具还可在hiv.lanl.gov/content/sequence/EPIGRAPH/epigraph.html处获得。

[0125] 虽然为每个受试者构建设计疫苗(designer vaccine)是不可行的,但对来自该受试者的病毒进行测序以尝试从疫苗选项的小参考集中获得良好匹配是可行的。基于中国的HBV B基因型试验群体被用来确认可提供治疗效果的疫苗。设计了基于亚洲的参考疫苗集和全球疫苗集,以及更新的基于亚洲的基因型。在C蛋白(减去N-末端上前29个氨基酸)、S蛋白和P蛋白中发现了HBV基因组的保守区域。从考虑中去除P蛋白的N-末端的高度可变区域(参见图6)。

[0126] 与预防性疫苗的情况(其中不知道受试者可能遇到哪些病毒)不同,在治疗性疫苗的情况下,可以获得并匹配感染病毒序列。

[0127] 选择用于免疫原性组合物或疫苗的抗原考虑两个因素:抗原表位应与受试者的感染病毒的尽可能多的表位相匹配,以及抗原与受试者的感染病毒之间的表位错配应为尽可能少,以便疫苗反应尽可能靶向相关表位。

[0128] HBV主要基因型内的系统发育往往几乎没有清晰的结构。相反,它是一个“星暴”,其中外部分支非常长,而基部附近的内部分支非常短,定义不明确。这种结构的一部分可能是由亚型内重组导致。虽然这很难量化,但重组肯定相对频繁地发生,并且与亚型间重组方面所见的类似,它可能是广泛的。鉴于树的结构,简单地使用系统发育树上的聚类来定义可能疫苗的参考集不会那么有效,因为从表位的角度来看,基因型内的关联意义有限。相反,相关措施应考虑序列关系,并应根据天然菌株和推定疫苗设计之间的潜在表位相似性选择参考集。

[0129] 使用氨基酸9-聚体(参见图4A)确认EpiGraph序列,但该方法可以以任何长度的k-聚体作为参考点来使用,其中k是推定的潜在表位长度。在过去的镶嵌工作中,9-聚体的最佳解决方案对于其他接近的长度(8、10、11、12)来说几乎是最佳的,预计EpiGraph方法也是如此。

[0130] 疫苗的表位覆盖率包含:a)一种表位基共序列;b)两种表位基共序列;c)三种表位

基共序列;d) 一种天然HBV基因型序列;以及e) 在图4A-7B中比较了两种天然HBV基因型序列。通常,基于基因型的疫苗提供该基因型的优异覆盖率,但其他基因型的较差覆盖率。图5A-5C中的数据证实,与B和C特异性疫苗相比,二价和三价Global EpiGraph序列显著改善了所有主要基因型的覆盖率,同时提供了可比的B和C覆盖率。例如,如图5A至5C所示,当使用三种表位基共序列抗原时,基因型D覆盖率为约90%,相比之下,对于B或C特异性疫苗甚至B+C特异性疫苗,覆盖率为约50%。

[0131] 实施例2:

[0132] 表位基共序列抗原的瞬时表达

[0133] 使用EpiGraph方法设计成使表位匹配最大化的抗原类似于天然序列,但不再编码天然蛋白质。虽然在构建这些序列时遵循了表达这些人工氨基酸序列的理论指南,但蛋白质可表现出意想不到的表达谱或无法表达稳定的全长蛋白质。

[0134] 为了评估这些序列在哺乳动物细胞情况下的表达谱,使用W02016/054654(其全部内容通过引用并入本文)中描述的方法将编码表位基共序列抗原的多核苷酸合成并克隆用于瞬时转染。简而言之,合成编码构建体的DNA(新泽西州皮斯卡塔韦Genscript)以包含用于质粒运载体(pcDNA3.1和pOri)的相容克隆位点。所有插入物都针对宿主进行了密码子优化。如Kulkarni等人Vaccine(2011)(其全部内容通过引用并入本文)所述,还对每个构建体进行了修饰以消除天然序列的残留酶活性。质粒运载体用相容的核酸内切酶线性化,并用小牛肠磷酸酶处理以防止空运载体的再环化。通过琼脂糖凝胶电泳分离运载体和插入片段以确定消化片段大小并通过PCR纯化试剂盒(Thermo Scientific)进行清洁以用于连接。使用快速连接试剂盒(印第安纳州的印第安纳波利斯的Roche)在室温下以大约为3:1的插入物与载体比率将插入物连接到线性化运载体15分钟,转化到化学感受态大肠杆菌(DH5- α)中并铺在抗生素选择板上。通过限制性消化插入物来筛选来自所得菌落的DNA。

[0135] 含有相对于运载体启动子和poly(A)序列适当取向的每个正确插入物的克隆在液体培养物中生长以用于质粒DNA纯化。在制备脂质体时,在12孔组织培养板中积极生长的亚融合293T或HELA细胞接受500 μ l的新鲜培养基(DMEM 10%FBS)。为了生成含有质粒DNA的脂质体,将250 μ l的无血清培养基与500ng的质粒DNA混合,并将250 μ l的无血清培养基与2 μ l的脂质(Lipofectamine 2000, Invitrogen)混合。在室温下温育5分钟后,将这些溶液合并、混合并温育20分钟。将在此过程期间形成的含有DNA的脂质体(500 μ l)逐滴添加到培养物中并温育12-16小时,之后用新鲜培养基替换转染混合物。再温育一天后,通过刮擦和离心收获培养物。通过抽吸去除上清液,并通过在含有5% SDS和10% 2-巯基乙醇的100 μ l凝胶加载染料中重新悬浮并通过QiaShred柱(加利福尼亚州瓦伦西亚的Qiagen)离心来裂解细胞沉淀。

[0136] 表位基共序列抗原的表达通过SDS聚丙烯酰胺凝胶电泳(SDS-page)和用针对被工程化到每个构建体中的V5或血凝素表位标签的抗体开发的蛋白免疫印迹来证实。简而言之,制备NuPAGE 4-12%Bis-Tris凝胶并加载20-50ug总蛋白并在110-120伏特下电泳90分钟。在30伏特下通过半干法或湿法转移90分钟将分离的蛋白质转移到PVDF膜上。用具有0.1%吐温-20(PBS-T)的10%脱脂奶粉在tris缓冲盐水中的溶液阻断非特异性结合60分钟。将HA(Sigma)或V5(Invitrogen)抗体在5%奶溶液中稀释并与膜一起温育1小时,然后用TBS-T洗涤3次,之后添加1:10000稀释的辣根过氧化物酶结合山羊抗小鼠(Invitrogen)二抗1小时。随后将印迹在TBS-T中洗涤3次,并用酶联化学发光[ECL试剂盒(Thermo-Pierce)]

显色并用数字凝胶成像系统显现。

[0137] 实施例3:

[0138] 将表位基共序列抗原工程化到CMV运载体BAC构建体中并从重建病毒中表达

[0139] 表位基共序列抗原被设计为提供对T细胞表位的良好覆盖率,所述表位代表病毒序列谱和生成它们的HBV基因型。为了最有效地利用这些抗原,编码抗原的多核苷酸已被工程化到CMV运载体中,所述CMV运载体已被证实产生三倍于竞争平台的CD8⁺T细胞谱。CMV运载体的广泛抗原呈递和终生表达谱已证实能够保护和治愈感染SIV的恒河猴。当应用于广泛的预防性疫苗时,与CMV运载体相结合的表位基共序列抗原设计算法可以在基因型内和跨基因型提供甚至更大的HBV覆盖率。

[0140] 使用BAC重组工程与半乳糖激酶和卡那霉素选择将编码被证实在瞬时转染系统中有表达的表位基共序列的多核苷酸转移到CMV骨架。(Warming等人Nucleic Acids Research.2005.33(4):1-12;以及Paredes和Yu Curr Protoc Microbiol.2012.Feb;第14章:单元14E.4;两者均通过引用以其整体并入本文)。此外,衍生自HBV蛋白或蛋白结构域[如核心(C)蛋白、表面抗原(S)蛋白、PreS1结构域、PreS2结构域和聚合酶(P)蛋白]的表位基共序列可以相对于它们在野生型HBV中出现的顺序进行重新排序,如图11A至11B所示,以改善表达。

[0141] 在含有亲本BAC的大肠杆菌菌株SW105的情况下,BAC重组有助于利用温度和代谢物调节的重组酶对大DNA序列进行操作。重组是一个连续的两步过程,其由以下两个步骤组成,步骤1:将带有抗生素抗性基因卡那霉素(kan)的半乳糖激酶(galK)序列插入靶标区域,然后是步骤2:用目标抗原替换galK/kan盒。步骤1在kan中阳性选择后产生含有galK/kan插入物的重组体,而步骤2产生在2-脱氧半乳糖(DOG)中阴性选择后含有目标抗原的重组体。对于这两个步骤,使用与插入位点侧翼的HCMV序列具有长(50+bp)同源臂的引物,通过标准PCR从含有galK/kan盒或目标抗原的模板DNA扩增要插入的序列。

[0142] 为了制备用于galK/kan盒插入(步骤1)的细菌细胞,使5mL培养物在30°C下在2xYT或具有12.5ug/mL氯霉素的极品肉汤(Terrific Broth)中生长过夜,并在第二天早上以1:50稀释。使细菌在30°C下再生长大约2-4小时(达到OD₆₀₀=0.5-0.6),然后通过42°C下摇动15分钟进行热休克以诱导重组酶。在此诱导之后,将细菌沉淀(3000rpm,10分钟,4°C),然后在冰冷的水中洗涤3次。使大肠杆菌细胞具有电感受态以接收PCR产物并具有重组感受态以将序列插入BAC的靶标区域。将纯化的插入物(300ng)与冰上的40μl感受态大肠杆菌结合,移至1mm比色皿,并使用Bio-rad基因脉冲仪Xcell(Bio-rad Gene Pulser Xcell)进行电穿孔。电穿孔后,通过添加5mL培养基稀释细菌,并通过在30°C下摇动2小时使其恢复,之后铺在氯霉素/卡那霉素板上。将板在30°C下温育两天,并通过限制性消化和PCR筛选菌落以进行重组事件。

[0143] galK/kan插入物阳性的BAC构建体进行到第二个步骤,其中galK/kan盒通过与含有目标抗原的PCR片段的重组而被替换。为了制备细菌细胞以在步骤2中替换galK/kan盒,如上所述使细菌生长并进行电穿孔。对于电穿孔恢复,通过添加5mL培养基稀释细菌,并通过在30°C下摇动至少4至4.5小时使其恢复。然后将细胞沉淀(3000rpm,10分钟,4°C)并用1xM9培养基洗涤3次,之后铺在添加了甘油、亮氨酸、生物素、DOG和氯霉素的M63基本培养基板上。然后通过PCR筛选菌落以确认用目标抗原替换galK/kan盒。将阳性克隆在DOG板上重新

划线并分离BAC DNA以通过限制性消化和测序进一步表征。

[0144] 病毒重建:为了再生成病毒,将BAC DNA转移到允许病毒生长的哺乳动物宿主细胞中。简而言之,使用无内毒素的质粒DNA试剂盒将BAC DNA (Macherey-Nagel) 纯化,并转染(16-24ug BAC DNA/T150) 到于37°C在具有5%CO₂下生长在DMEM加1x glutamax和9%FBS中的原代人成纤维细胞的汇合烧瓶中。按照制造商的方案(ThermoFisher) 使用Lipofectamine3000实现转染。第二天,更换培养基,然后每天监测细胞的斑块形成。一旦达到完全的细胞病变效应(CPE),就收获病毒上清液,经由在室温下以2500xg离心5分钟进行澄清,并储存于-80°C下。通过细胞刮刀在DPBS中收获剩余的附着细胞,通过离心(2,500rpm,5分钟) 沉淀并储存于-80°C下。

[0145] 病毒表位基共序列抗原表达:表位基共序列抗原的表达通过SDS聚丙烯酰胺凝胶电泳(SDS-page) 进行测试,然后进行用HBV特异性抗体或针对被工程化到每个构建体中的V5或血凝素(HA) 表位标签的抗体开发的蛋白免疫印迹。简而言之,通过在放射免疫沉淀测定(RIPA) 缓冲液中重新悬浮来裂解细胞沉淀,并使用标准二辛可宁酸测定(BCA) 对蛋白质进行定量。制备NuPAGE 4-12%Bis-Tris凝胶并加载20-50ug总蛋白并在110-130伏特下电泳90分钟。通过半干法或湿法在30伏特下转移90分钟或在15V下转移过夜,将分离的蛋白质转移到PVDF膜上。用具有0.1%吐温-20(PBS-T) 的5%脱脂奶粉在tris缓冲盐水中的溶液阻断非特异性结合60分钟。将一抗在5%奶溶液中稀释并与膜一起温育1小时,然后用TBS-T洗涤3次,之后加入1:10,000稀释的辣根过氧化物酶偶联山羊抗小鼠二抗1小时。随后,将印迹在TBS-T中洗涤3次,并用酶联化学发光[ECL试剂盒(Thermo-Pierce)] 显色并用数字凝胶成像系统显现。

[0146] 实施例4:

[0147] 群体表位基共序列疫苗

[0148] EpiGraph方法最初用于使用CMV运载体产生一组包含编码表位基共序列抗原的多核苷酸的疫苗,然而,也可以使用其他疫苗递送系统。

[0149] 测试了不同表位基共序列抗原和抗原组合的总共58种策略以确定最全面的疫苗治疗。来自dbHBV的HBV样本分为三组:中国样本、非中国样本和全球样本。全球样本包含中国样本和非中国样本的组合。针对天然D和天然C亚型的疫苗用作对照。针对每组测试了具有一种、两种或三种表位基共序列抗原的疫苗。

[0150] 对照包括包含编码以下项的多核苷酸的疫苗:天然D亚型序列(SEQ ID NO:12), GenBank登录号Y07587;以及天然C亚型参考序列(SEQ ID NO:13), GenBank登录号GQ358158。然后将包含编码D和C亚型序列的多核苷酸的疫苗与包含编码以下项的多核苷酸的疫苗进行比较:(a) 1_CH_epi (SEQ ID NO:1), 使用来自中国的1044个HBV序列开发;(b) 1_GL_epi (SEQ ID NO:2), 使用3041个HBV序列的全球集开发;(c) 2_CH_epi, 其包含使用来自中国的1044个HBV序列开发的两种表位基共序列抗原(SEQ ID NO:3和SEQ ID NO:4); (d) 2_CHGL_epi, 其包含两种表位基共序列抗原-第一表位基共序列抗原Epi1 (SEQ ID NO:5), 其使用来自中国的1044个HBV序列开发,以及第二表位基共序列抗原Epi2 (SEQ ID NO:6), 其使用3041个HBV序列的全球集开发,其中Epi1已经固定在解决方案中;(e) Epi7和Epi8(分别为SEQ ID NO:7和SEQ ID NO:8), 其是经修饰以诱导更好表达的Epi1和Epi2的变体;以及(f) 3_GL_epi, 其包含三种表位基共序列抗原(SEQ ID NO:9;SEQ ID NO:10;和SEQ ID NO:

11),使用3041个HBV序列的全球集开发。

[0151] 如图8所示,包含编码使用来自中国的样本开发的第一序列和使用全球集开发的第二序列的多核苷酸的双表位基共序列抗原疫苗提供了~88%的中国序列、~77%的非中国序列以及~80%的全球序列的覆盖率。

[0152] 实施例5:

[0153] 表位覆盖率

[0154] 计算分析包含某些表位基共序列抗原序列的疫苗的HBV表位覆盖率。用于CMV初步测试的疫苗包括:1)单种群体表位基共序列抗原,其是中国基因型流行病的核心;2)提供所有HBV全球样本的覆盖率的单种群体表位基共序列抗原;3)提供来自中国的HBV样本的覆盖率的两种种群体表位基共序列抗原;4)提供所有HBV全球样本的覆盖率的两种种群体表位基共序列抗原;5)提供所有HBV全球样本的覆盖率的三种种群体表位基共序列抗原;以及6)两种种群体表位基共序列抗原:第一种群体表位基共序列抗原,其提供来自中国的HBV样本的覆盖率,以及第二种群体表位基共序列抗原,其提供来自全球集的HBV样本的覆盖率。

[0155] 对照包括包含编码以下项的多核苷酸的疫苗:天然D亚型序列(SEQ ID NO:12), GenBank登录号Y07587;以及天然C亚型参考序列(SEQ ID NO:13), GenBank登录号GQ358158。然后,我们将包含编码D和C亚型序列的多核苷酸的疫苗与包含编码以下项的多核苷酸的疫苗进行比较:(a)1_CH_epi(SEQ ID NO:1),其使用来自中国的1044个HBV序列开发;(b)1_GL_epi(SEQ ID NO:2),使用3041个HBV序列的全球集开发;(c)2_CH_epi,其包含使用来自中国的1044个HBV序列开发的两种表位基共序列抗原(SEQ ID NO:3和SEQ ID NO:4);(d)2_CHGL_epi,包含两种表位基共序列抗原-第一表位基共序列抗原Epi1(SEQ ID NO:5),其使用来自中国的1044个HBV序列开发,以及第二表位基共序列抗原Epi2(SEQ ID NO:6),其使用3041个HBV序列的全球集开发,其中Epi1已经固定在解决方案中;(e)Epi7和Epi8(分别为SEQ ID NO:7和SEQ ID NO:8),其是经修饰以诱导更好表达的Epi1和Epi2的变体;以及(f)3_GL_epi,其包含三种表位基共序列抗原(SEQ ID NO:9;SEQ ID NO:10;和SEQ ID NO:11),使用3041个HBV序列的全球集开发。

[0156] 如图9A至10B中所见,包含2_CHGL_epi的疫苗提供对来自中国的序列的超过80%的精确覆盖率,对不是来自中国的序列的超过75%的精确覆盖率和80%的精确全球覆盖率。这些数据证实,与对照疫苗相比的对所有HBV序列的极高覆盖率。

[0157] 实施例6:

[0158] 第二代HBV表位基共序列抗原

[0159] 对于大多数HBV基因型,核心(C)的HBVN-末端组装结构域(NTD)参与核心颗粒组装,而C-末端结构域参与前基因组/逆转录酶复合物的包装。表面(S)蛋白是单个开放阅读框的产物并通过三个结构域进行区分:PreS1、PreS2和S。聚合酶(P)蛋白表现出DNA依赖性DNA聚合酶和RNA依赖性DNA聚合酶(逆转录酶)活性两者。P蛋白从包壳的前基因组RNA模板复制HBV基因组。P蛋白由4个结构域组成:(1)末端蛋白(TP)结构域,其通过保守的酪氨酸参与蛋白质启动机制;(2)非保守间隔结构域;(3)逆转录酶结构域[RNA依赖性DNA聚合酶(RT)和DNA依赖性DNA聚合酶(活性位点:YMDD保守基序)];以及(4)RNase H结构域(核糖核酸酶H活性)。

[0160] 表位基共序列抗原被设计为提供对T细胞表位的良好覆盖率,所述表位代表生成

它们的病毒序列谱。HBV基因D型的感染是美国和欧洲最普遍的HBV感染之一。包含基因型D表位基共序列(EpiD) 抗原或编码EpiD抗原的核苷酸的治疗性疫苗可对已针对特定基因型进行预筛选的患者有益。本文提供了HBV基因型D表位基共序列抗原(SEQ ID NO:14)的示例,其提供美国和欧洲的HBV基因型的良好覆盖率。在一种变体中,如图11A和11B所示,衍生自核心(C)蛋白、PreS1和PreS2结构域、表面抗原(S)蛋白和聚合酶(P)蛋白的HBV基因型D表位基共序列抗原最初是以它们在HBV基因组中出现的顺序使用:C-S-P(“CSP”)(SEQ ID NO:14),并被重新排序为S-P-C(“SPC”)(SEQ ID NO:15)。通过将EpiGraph方法应用于其中缺失了S蛋白的跨膜结构域1-2或1-4(“CSP Δ TM1-2,” “CSP Δ TM1-4,” “SPC Δ TM1-2,” 或“SPC Δ TM1-4”)的HBV蛋白序列以减少聚集并改善表达,从而生成附加的抗原变体。因此,HBV表位基共序列抗原也可以衍生自包含一种或多种上述变体的HBV蛋白序列。

[0161] 此外,生成衍生自在聚合酶结构域的活性位点中具有突变和/或缺失的P蛋白变体的表位基共序列抗原以降低潜在毒性并提高安全性。例如,在SEQ ID NO:7、8和15中提供了此类表位基共序列抗原的示例。用于开发这些表位基共序列抗原的序列中存在的突变在下表1中提供。也可以使用具有不同突变或缺失的其他P蛋白变体。

[0162] 表1:HBV基因型D中聚合酶的突变修饰

位置	氨基酸	修饰
538-541	YMDD	缺失
689	D	替换为A
718	E	替换为A
737	D	替换为V
777	D	替换为A

[0164] 该表左列的位置是指HBV基因型D中全长聚合酶中的氨基酸数目。YMDD序列是逆转录酶活性位点。(参见Radziwill,等人,J Virol.1990Feb;64(2):613-20,其通过引用以其整体并入本文。)其他4种氨基酸(D、E、D、D)是RNase H活性位点。(参见Tavis等人,PLoS Pathog.2013年1月;9(1):e1003125,其通过引用以其整体并入本文。)

[0165] 衍生自这些变体序列的表位基共序列抗原的表达通过如上所述的SDS-page和蛋白免疫印迹进行测试(图11A至11D)。去除跨膜(TM)结构域不影响表达(图11D)。

[0166] 没有观察到任何EpiD抗原变体的显著聚集。抗原融合蛋白顺序与有效表达有关。SPC重新排序的抗原融合蛋白显示出显著增加的表达。

[0167] HBV表位基共序列抗原可以衍生自以下HBV蛋白或蛋白结构域中的一种或多种:核心(C)蛋白、表面(S)蛋白、PreS1蛋白、PreS2蛋白、S蛋白的跨膜结构域1-4(TM1-4)、决定簇和聚合酶(P)蛋白。表位基共序列抗原可以衍生自具有缺失或突变的各种HBV蛋白和蛋白结构域,和/或表位基共序列抗原可以相对于它们在HBV中的顺序重新排序,以改善表达或活性。为了说明的目的,衍生自HBV亚型D的核心蛋白的表位基共序列在SEQ ID NO:16中提供,衍生自HBV亚型D的PreS1蛋白的表位基共序列在SEQ ID NO:17中提供,衍生自HBV亚型D的PreS2蛋白的表位基共序列在SEQ ID NO:18中提供,衍生自HBV亚型D的表面蛋白(S)的表位基共序列在SEQ ID NO:19中提供,衍生自HBV亚型D的聚合酶(P)蛋白的表位基共序列在SEQ ID NO:20或22中提供,以及衍生自包含表1中所示的突变和缺失的HBV亚型D的聚合酶(P)蛋白的表位基共序列在SEQ ID NO:23中提供。在SEQ ID NO:24中提供衍生自HBV亚型C表面蛋

白(S)、聚合酶蛋白(P)和核心蛋白(C)的表位基共序列的示例,其中抗原序列的顺序为“SPC”。衍生自具有比表1中所示的更大的缺失区域的P蛋白的表位基共序列的示例包括衍生自HBV亚型C表面蛋白(S)、具有氨基酸612-838缺失的聚合酶蛋白(P),以及核心蛋白(C)的表位基共序列在SEQ ID NO:25中提供;以及衍生自HBV亚型D表面蛋白(S)、具有氨基酸601-827缺失的聚合酶蛋白(P),以及核心蛋白(C)的表位基共序列在SEQ ID NO:26中提供。SEQ ID NO:25和26两者都重新排序,从而以“SPC”的顺序提供抗原序列。

[0168] 衍生自具有缺失区域的P蛋白的表位基共序列的其他示例显示在图12A中,并包括P蛋白氨基酸1-200、201-400或401-600的缺失。图12A的构建体的表达数据显示在图12B中。

[0169] 衍生自HBV核心蛋白的表位基共序列的进一步示例在SEQ ID NO:27、28和34中提供。衍生自HBV表面蛋白的表位基共序列的其它示例在SEQ ID NO:29中提供。衍生自HBV的聚合酶蛋白的表位基共序列的进一步示例在SEQ ID NO:30-32和SEQ ID NO:35-36中提供。

[0170] 可以通过与本文公开的序列进行序列比对来确定任何HBV亚型的HBV蛋白和蛋白结构域的序列。例如,HBV的天然D亚型的完整基因组序列在GenBank登录号Y07587(通过引用以其整体并入本文)中提供。P蛋白由GenBank参考基因Y07587的1-1625和2309-3182核苷酸编码。PreS蛋白由GenBank参考基因Y07587的1-837和2850-3182核苷酸编码。S结构域由GenBank参考基因Y07587的157-837核苷酸编码。PreC/C蛋白由GenBank参考基因Y07587的1816-2454核苷酸编码。C蛋白由GenBank参考基因Y07587的1903-2451核苷酸编码。此外,HBV的天然C亚型的完整基因组序列在GenBank登录号GQ358158(通过引用以其整体并入本文)中提供。P蛋白由GenBank参考基因GQ358158的1-1623和2307-3215核苷酸编码。S蛋白由GenBank参考基因GQ358158的1-835和2848-3215核苷酸编码。PreC/C蛋白由GenBank参考基因GQ358158的1814-2452核苷酸编码。C蛋白由GenBank参考基因GQ358158的1901-2452核苷酸编码。

[0171] 实施例7:

[0172] 疫苗测试

[0173] 恒河猴(RM)中测试包含计算设计的表位基共序列抗原的疫苗。预计基于CMV的T细胞反应范围更广,因此覆盖的序列百分比与以前针对其他运载体报道的要高得多。因此,即使动物数量相对较少,也应该有足够的表位反应来评估序列变异对反应的交叉反应潜力的影响。通过使用与疫苗匹配的成组的肽来确定对疫苗的所有反应的数量和幅度。一旦通过仅使用在每只动物中呈阳性的那些肽而确定了靶标肽,就可以确定自然变异对每种疫苗反应肽的影响。测试的自然变体基于参考小图中发现的变体。非参数和计算重采样统计方法被用作评估表位变异对减少幅度或消除识别的影响的主要工具。然而,通过根据需要使用广义线性模型来探索更复杂的相互作用对T细胞反应交叉反应性的影响,将这些分析进行了补充。

[0174] 用于CMV初始测试的疫苗组包括编码以下项的运载体:1)单种群体表位基共序列抗原,其是中国基因型流行病的核心;2)提供所有HBV全球样本的覆盖率的单种群体表位基共序列抗原;3)提供来自中国的HBV样本的覆盖率的两种种群体表位基共序列抗原;4)提供所有HBV全球样本的覆盖率的两种种群体表位基共序列抗原;5)提供所有HBV全球样本的覆盖率的三种种群体表位基共序列抗原;以及6)两种种群体表位基共序列抗原:第一种群体表位基共序列抗原,其提供来自中国的HBV样本的覆盖率,以及第二种群体表位基共序列抗原,其提供来

自全球集的HBV样本的覆盖率,7)使用截短的Po1序列生成的表位基共序列抗原,其提供对HBV C亚型表位(SEQ ID NO:25)的覆盖率,以及8)使用截短的Po1序列生成的表位基共序列抗原,其提供对HBV D亚型表位(SEQ ID NO:26)的覆盖率。对照包括包含编码以下项的多核苷酸的疫苗:天然D亚型序列(SEQ ID NO:12),GenBank登录号Y07587;以及天然C亚型参考序列(SEQ ID NO:13),GenBank登录号GQ358158。

[0175] 最多10个5只恒河猴(RM)队列如下接种 10^6 PFU的HCMV运载体:最多8个队列,每个队列接受上面列出的疫苗1-8中的一种;单个队列接受包含编码天然D亚型的多核苷酸的疫苗;并且单个队列接受包含编码天然C亚型的多核苷酸的疫苗。队列3接受表位基共序列加上不同的定制疫苗运载体,并且队列4接受表位基共序列加上两个定制的疫苗运载体。

[0176] 恒河猴(RM)在第0天和第12周进行皮下接种并纵向跟踪一年。由于HCMV运载体的疫苗接种不受预先存在的抗RhCMV免疫的影响,因此将自然感染RhCMV的动物用于这些实验。流式细胞仪细胞内细胞因子分析(ICS)用于确定CD4⁺和CD8⁺T细胞对单个连续15聚体肽的反应,所述肽包含施用给每只动物的疫苗插入物中的疫苗序列(这将包含疫苗引发的总反应)。然后确定这些表位特异性T细胞是否识别靶标菌株和非靶标菌株两者中的表位变体。对于显示对菌株特异性表位反应的肽,将对“亲本”(疫苗插入序列)肽变体的这些反应的幅度、功能亲合力和功能特征(IFN- γ 、TNF- α 、IL-2和MIP-1 β 产生和CD107外化)进行比较以确定功能交叉反应的程度。在选定的情况下,截断分析用于确认核心表位以进行类似的比较分析。为了确定存在的MHC-II受限CD8⁺T细胞的百分比,“阻断”对MHC-I和MHC-II具有特异性的mAb,以及不变链衍生的MHC-II特异性结合肽CLIP用于抑制PBMC中的流感特异性CD8⁺T细胞反应。

[0177] 尽管已经说明和描述了具体实施方案,但将容易理解的是,可以组合上述各种实施方案以提供进一步的实施方案,并且可以在不背离本发明的精神和范围的情况下在其中做出各种改变。

[0178] 除非另有明确说明,否则在说明书中提及和/或在申请数据表中列出的所有美国专利、美国专利申请公开、美国专利申请、外国专利、外国专利申请和非专利出版物,包括2019年8月29日提交的美国临时专利申请号62/893,546以及2019年11月27日提交的美国临时专利申请号62/941,125,通过引用以其整体并入本文。如果需要,可以修改实施方案的方面以采用各种专利、申请和出版物的概念来提供更进一步的实施方案。

[0179] 根据以上详细描述,可以对实施方案进行这些和其他改变。一般地,在以下权利要求中,所使用的术语不应被解释为将权利要求限制为在说明书和权利要求中公开的特定实施方案,而应被解释为包括所有可能的实施方案以及此类权利要求所享有的等同物的全部范围。因此,权利要求不受本公开的限制。

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[0491]	Thr Pro Val Cys Leu Gly Gln Asn Ser Gln Ser Gln Ile Ser Ser His		
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[0499]	Leu Ile Pro Gly Ser Ser Thr Thr Ser Thr Gly Pro Cys Lys Thr Cys		
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[0501]	Thr Thr Pro Ala Gln Gly Thr Ser Met Tyr Pro Ser Cys Cys Cys Thr		
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[0503]	Lys Pro Thr Asp Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp		
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[0505]	Ala Phe Ala Lys Tyr Leu Trp Glu Trp Ala Ser Val Arg Phe Ser Trp		
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[0515]	Asn Pro His Asn Thr Ala Glu Ser Arg Leu Val Val Asp Phe Ser Gln
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[0517]	Phe Ser Arg Gly Asn Thr Arg Val Ser Trp Pro Lys Phe Ala Val Pro
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[0521]	Ser Leu Asp Val Ser Ala Ala Phe Tyr His Leu Pro Leu His Pro Ala
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[0537]	Leu Gly Ala Lys Ser Val Gln His Leu Glu Ser Leu Tyr Ala Ala Val
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[0539]	Thr Asn Phe Leu Leu Ser Leu Gly Ile His Leu Asn Pro His Lys Thr
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[0541]	Lys Arg Trp Gly Tyr Ser Leu His Phe Met Gly Tyr Val Ile Gly Cys
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[0565]	Tyr Val Pro Ser Ala Leu Asn Pro Ala Asp Asp Pro Ser Arg Gly Arg		
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[0567]	Leu Gly Leu Tyr Arg Pro Leu Leu Arg Leu Leu Tyr Arg Pro Thr Thr		
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[0667]	Met Gln Asp Leu His Asp Ser Cys Ser Arg Asn Leu Tyr Val Ser Leu
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[0675]	Arg Ala Phe Pro His Cys Leu Ala Phe Ser Tyr Met Asp Asp Val Val
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[0677]	Leu Gly Ala Lys Ser Val Gln His Leu Glu Ser Leu Phe Thr Ser Ile
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[0693]	Asn Leu Tyr Pro Val Ala Arg Gln Arg Ser Gly Leu Cys Gln Val Phe
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[0725]	Ala	Ser	Ala	Leu	Tyr	Arg	Asp	Ala	Leu	Glu	Ser	Pro	Glu	His	Cys	Thr
[0726]					35				40				45			
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[0785]	Ala Ser Ala Arg Phe Ser Trp Leu Ser Leu Leu Val Pro Phe Val Gln			
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[0787]	Trp Phe Ala Gly Leu Ser Pro Thr Val Trp Leu Ser Val Ile Trp Met			
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[0803]	Ser Gly Leu Ser Arg Tyr Val Ala Arg Leu Ser Ser Asn Ser Arg Ile			
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[0815]	Ser Tyr Met Asp Asp Leu Val Leu Gly Ala Lys Ser Val Gln His Leu			
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[0821]	Met Gly Tyr Val Ile Gly Cys Tyr Gly Ser Leu Pro Gln Asp His Ile		
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[0839]	Ser Gly Ala Asn Ile Leu Gly Thr Asp Asn Ser Val Val Leu Ser Arg		
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[0849]	Pro Ser Val Pro Ser His Leu Pro Val Arg Val His Phe Ala Ser Pro		
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 [0886] Pro Asp His Gln Leu Asp Pro Ala Phe Gly Ala Asn Ser Asn Asn Pro
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 [0888] Asp Trp Asp Phe Asn Pro Asn Lys Asp His Trp Pro Glu Ala Asn Gln
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 [0894] Ala Ala Pro Pro Pro Ala Ser Thr Asn Arg Gln Ser Gly Arg Gln Pro
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[0926]	Trp Leu Ser Leu Leu Val Pro Phe Val Gln Trp Phe Val Gly Leu Ser		525
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[0930]	Ser Leu Tyr Asn Ile Leu Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe		560
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			605

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[0938]	Pro Asn Leu Gln Ser Leu Thr Asn Leu Leu Ser Ser Asn Leu Ser Trp
[0939]	625 630 635 640
[0940]	Leu Ser Leu Asp Val Ser Ala Ala Phe Tyr His Ile Pro Leu His Pro
[0941]	645 650 655
[0942]	Ala Ala Met Pro His Leu Leu Val Gly Ser Ser Gly Leu Pro Arg Tyr
[0943]	660 665 670
[0944]	Val Ala Arg Leu Ser Ser Thr Ser Arg Asn Ile Asn Tyr Gln His Gly
[0945]	675 680 685
[0946]	Thr Met Gln Asp Leu His Asp Ser Cys Ser Arg Asn Leu Tyr Val Ser
[0947]	690 695 700
[0948]	Leu Leu Leu Leu Tyr Lys Thr Phe Gly Arg Lys Leu His Leu Tyr Ser
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[0950]	His Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro Met Gly Val Gly Leu
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[0952]	Ser Pro Phe Leu Leu Ala Gln Phe Thr Ser Ala Ile Cys Ser Val Val
[0953]	740 745 750
[0954]	Arg Arg Ala Phe Pro His Cys Leu Ala Phe Ser Val Val Leu Gly Ala
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[0957]	770 775 780
[0958]	Leu Leu Ser Leu Gly Ile His Leu Asn Pro Asn Lys Thr Lys Arg Trp
[0959]	785 790 795 800
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[0970]	Ser Pro Thr Tyr Lys Ala Phe Leu Cys Lys Gln Tyr Leu Asn Leu Tyr
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[0972]	Pro Val Ala Arg Gln Arg Ser Gly Leu Cys Gln Val Phe Ala Ala Ala
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[0984]	Ser Ala Leu Asn Pro Ala Ala Asp Pro Ser Arg Gly Arg Leu Gly Leu		
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[1164]	Gln Leu Asp Pro Ala Phe Lys Ala Asn Ser Glu Asn Pro Asp Trp Asp
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[1166]	Leu Asn Pro His Lys Asp Asn Trp Pro Asp Ala Asn Lys Val Gly Ala
[1167]	210 215 220
[1168]	Gly Ala Phe Gly Leu Gly Phe Thr Pro Pro His Gly Gly Val Leu Gly
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[1218]	Asp Val Ser Ala Ala Phe Tyr His Ile Pro Leu His Pro Ala Ala Met			
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[1238]	Trp Gly Tyr Ser Leu His Phe Met Gly Tyr Val Ile Gly Cys Tyr Gly			
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[1426]	Arg Glu Leu Val Val Ser Tyr Val Asn Val Asn Met Gly Leu Lys Ile		
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[1474]	Leu Ile Pro Gly Ser Ser Thr Thr Ser Thr Gly Pro Cys Lys Thr Cys		
[1475]	465	470	475 480
[1476]	Thr Thr Pro Ala Gln Gly Asn Ser Met Phe Pro Ser Cys Cys Cys Thr		
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[1480]	Ala Phe Ala Lys Tyr Leu Trp Glu Trp Ala Ser Val Arg Phe Ser Trp		
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[1618]	Ala Arg Phe Ser Trp Leu Ser Leu Leu Val Pro Phe Val Gln Trp Phe		
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[1620]	Val Gly Leu Ser Pro Thr Val Trp Leu Ser Val Ile Trp Met Met Trp		
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[1622]	Tyr Trp Gly Pro Ser Leu Tyr Ser Ile Leu Ser Pro Phe Leu Pro Leu		
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[1624]	Leu Pro Ile Phe Phe Cys Leu Trp Val Tyr Ile Val Thr Gly Gly Val		
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[1749]	Leu Leu Pro Gly Thr Ser Thr Thr Ser Thr Gly Pro Cys Lys Thr Cys		
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[1751]	Thr Ile Pro Ala Gln Gly Thr Ser Met Phe Pro Ser Cys Cys Cys Thr		
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[1753]	Lys Pro Ser Asp Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp		
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[1761]	Leu	Tyr	Asn	Ile	Leu	Ser	Pro	Phe	Leu	Pro	Leu	Leu	Pro	Leu	Phe	Phe
[1762]					565					570					575	
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			15

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[1941]	Val	Phe	Pro	Cys	Trp	Trp	Leu	Gln	Phe	Arg	Asn	Ser	Lys	Pro	Cys	Ser
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[1943]	Asp	Tyr	Cys	Leu	Ser	His	Ile	Val	Asn	Leu	Leu	Glu	Asp	Trp	Gly	Pro
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[1957]	Leu Val Gly Ser Ser Gly Leu Ser Arg Tyr Val Ala Arg Leu Ser Ser			
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[2394]	Asp Asn Ser Val Val Leu Ser Arg Lys Tyr Thr Ser Phe Pro Trp Leu		
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[2652]															565							570							575																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
[2653]	Gln	His	Gly	Arg	Leu	Val	Phe	Gln	Thr	Ser	Thr	Arg	His	Gly	Asp	Glu																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																			

[2691]	Arg Asn Leu Tyr Val Ser Leu Leu Leu Leu Tyr Lys Thr Phe Gly Arg
[2692]	885 890 895
[2693]	Lys Leu His Leu Tyr Ser His Pro Ile Ile Leu Gly Phe Arg Lys Ile
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[2695]	Pro Met Gly Val Gly Leu Ser Pro Phe Leu Leu Ala Gln Phe Thr Ser
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[2727]	Ser Phe Val Tyr Val Pro Ser Ala Leu Asn Pro Ala Ala Asp Pro Ser
[2728]	1170 1175 1180
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[2739]	Leu Leu Asp Thr Ala Ser Ala Leu Tyr Arg Glu Ala Leu Glu Ser Pro			
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[2741]	Glu His Cys Ser Pro His His Thr Ala Leu Arg Gln Ala Ile Leu Cys			
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[2745]	Asp Pro Ala Ser Arg Glu Leu Val Val Ser Tyr Val Asn Val Asn Met			
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[2778]	Thr Asn Arg Gln Ser Gly Arg Gln Pro Thr Pro Ile Ser Pro Pro Leu		
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[2792]	Thr Ser Leu Asn Phe Leu Gly Gly Ala Pro Thr Cys Pro Gly Gln Asn		
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[2794]	Ser Gln Ser Pro Thr Ser Asn His Ser Pro Thr Ser Cys Pro Pro Ile		
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[2804]	Met Phe Pro Ser Cys Cys Cys Thr Lys Pro Ser Asp Gly Asn Cys Thr		
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[2961]	Lys	Phe	Leu	Trp	Glu	Trp	Ala	Ser	Ala	Arg	Phe	Ser	Trp	Leu	Ser	Leu
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[2967]	Ile Leu Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe Phe Cys Leu Trp					
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[2969]	Val Tyr Ile Pro Leu Ser Tyr Gln His Phe Arg Arg Leu Leu Leu Leu					
[2970]	385		390		395	400
[2971]	Asp Asp Glu Ala Gly Pro Leu Glu Glu Glu Leu Pro Arg Leu Ala Asp					
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[2973]	Glu Gly Leu Asn Arg Arg Val Ala Glu Asp Leu Asn Leu Gly Asn Leu					
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[2975]	Asn Val Ser Ile Pro Trp Thr His Lys Val Gly Asn Phe Thr Gly Leu					
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[2977]	Tyr Ser Ser Thr Val Pro Val Phe Asn Pro His Trp Lys Thr Pro Ser					
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[2979]	Phe Pro Asn Ile His Leu His Gln Asp Ile Ile Lys Lys Cys Glu Gln					
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[2981]	Phe Val Gly Pro Leu Thr Val Asn Glu Lys Arg Arg Leu Gln Leu Ile					
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[2983]	Met Pro Ala Arg Phe Tyr Pro Asn Val Thr Lys Tyr Leu Pro Leu Asp					
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[2985]	Lys Gly Ile Lys Pro Tyr Tyr Pro Glu His Leu Val Asn His Tyr Phe					
[2986]		515		520		525
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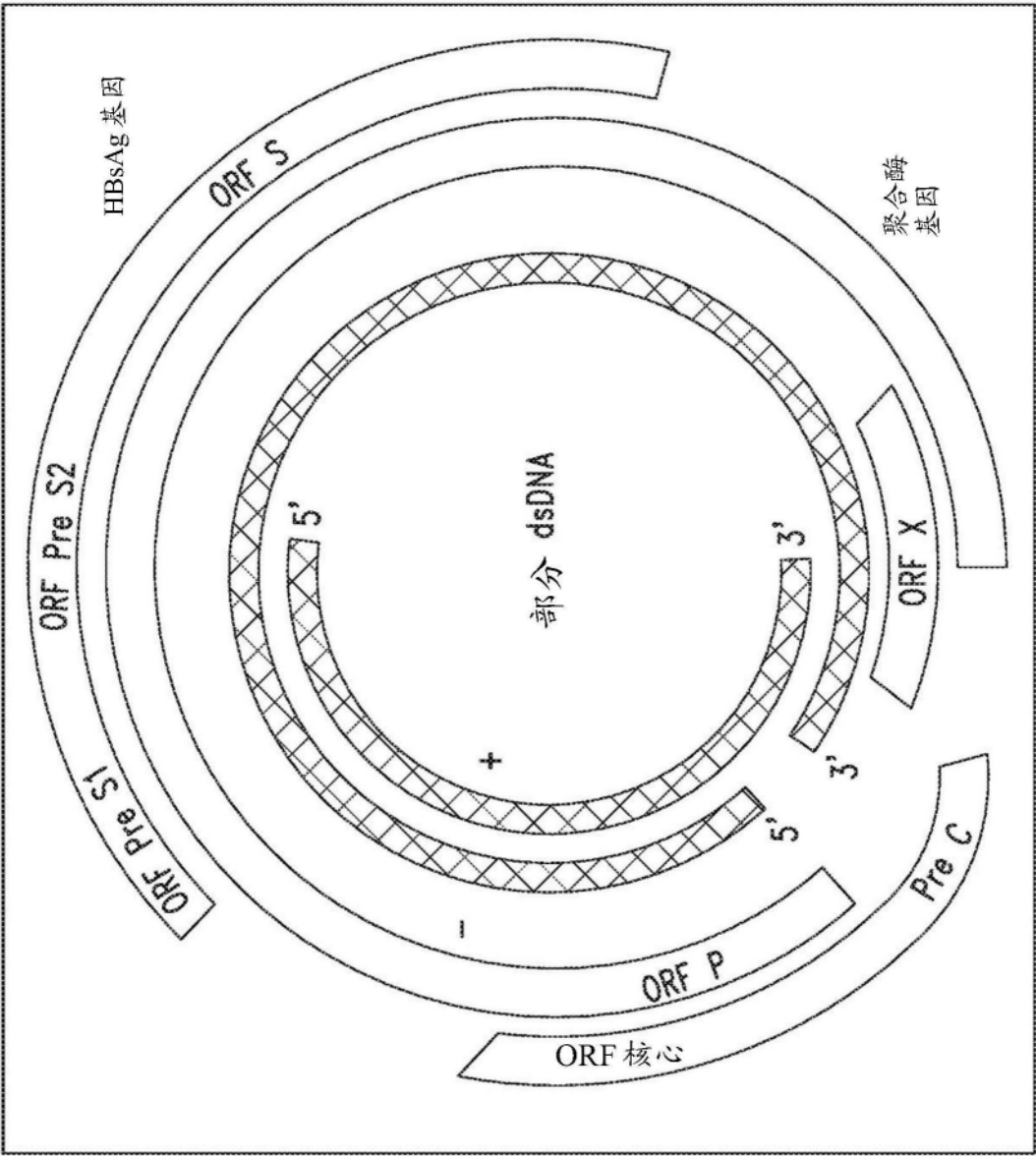


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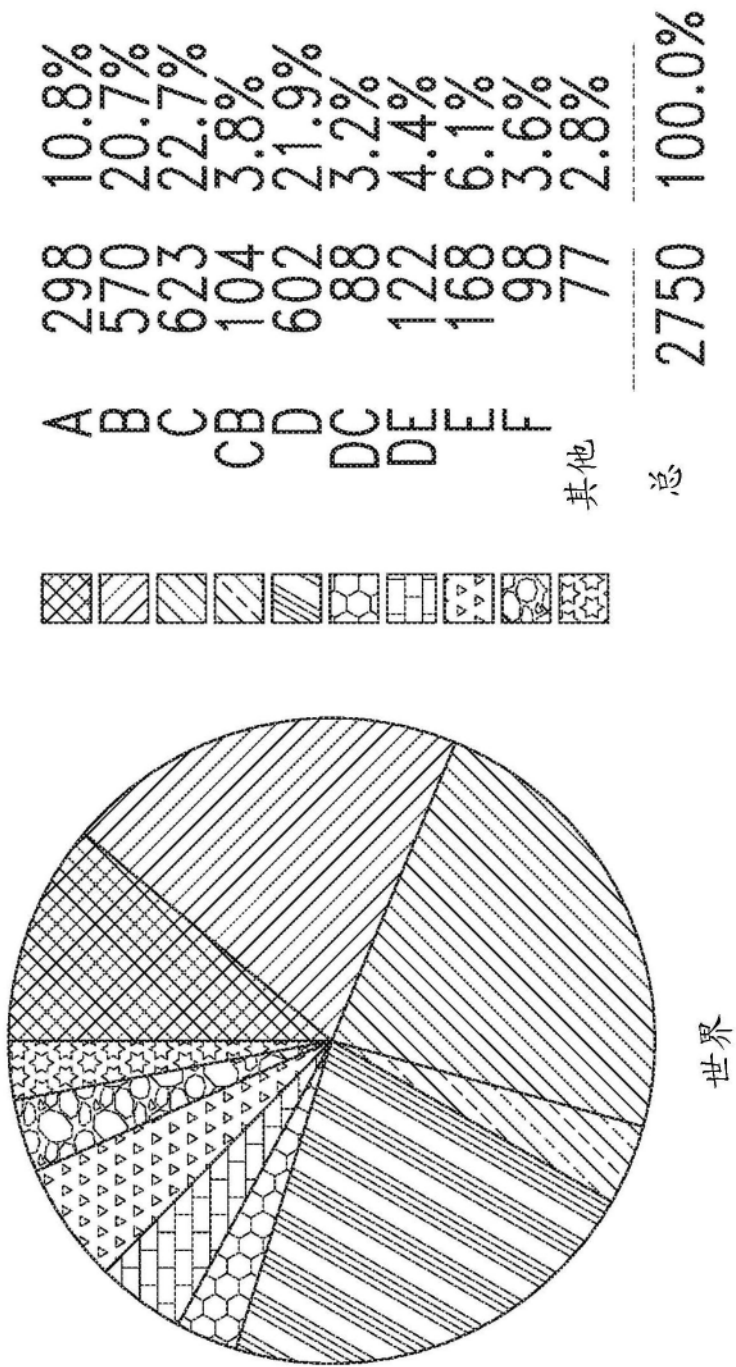


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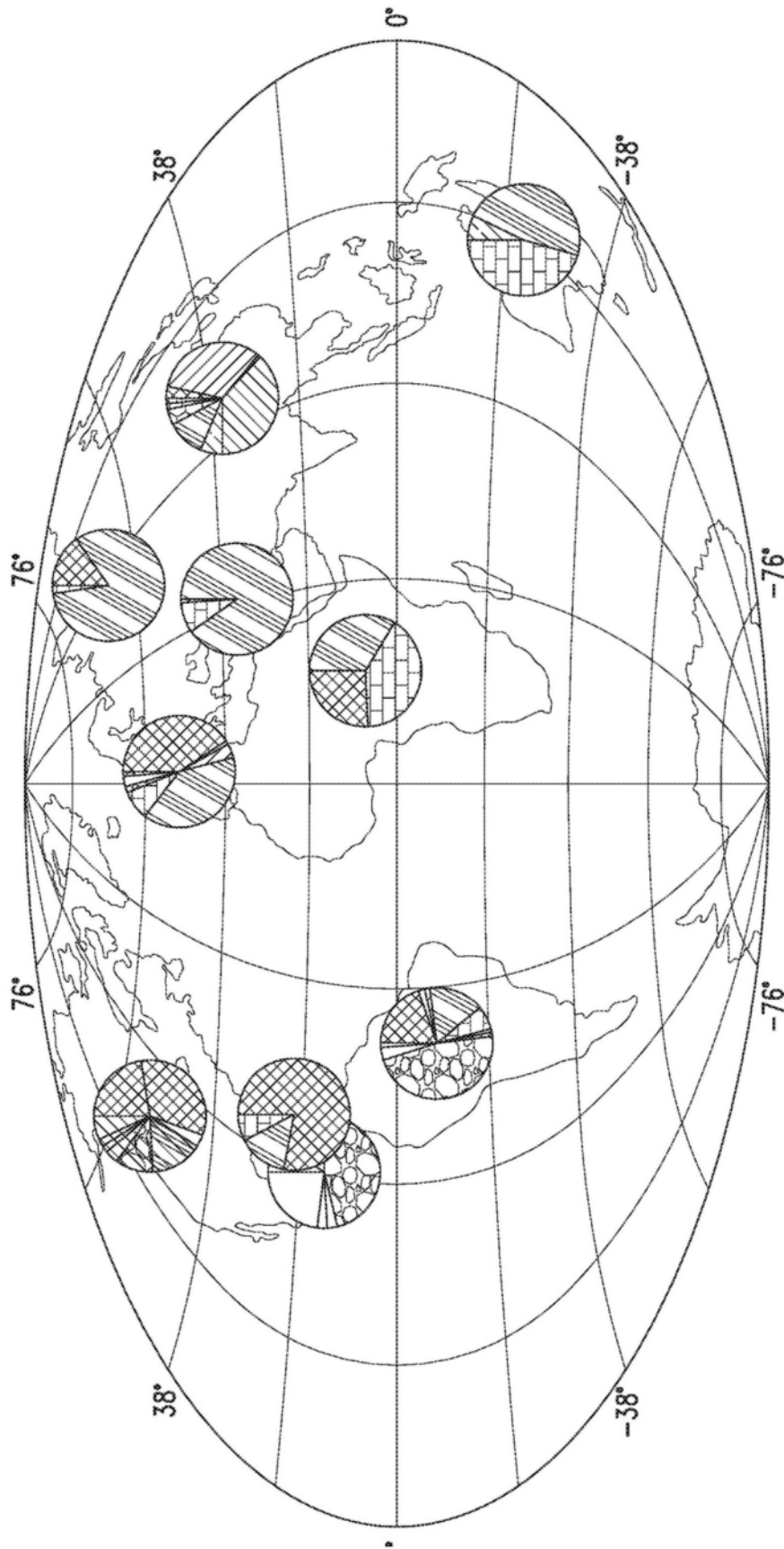
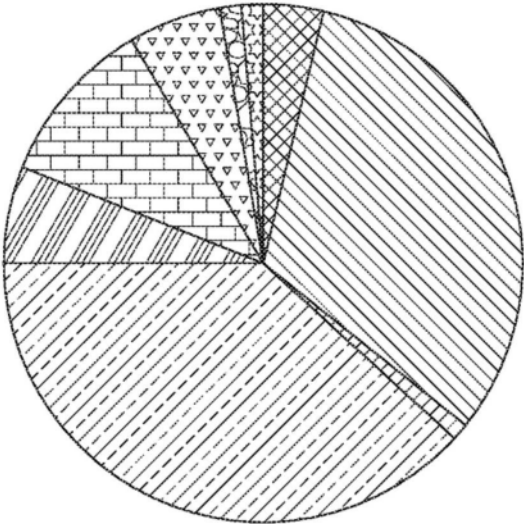
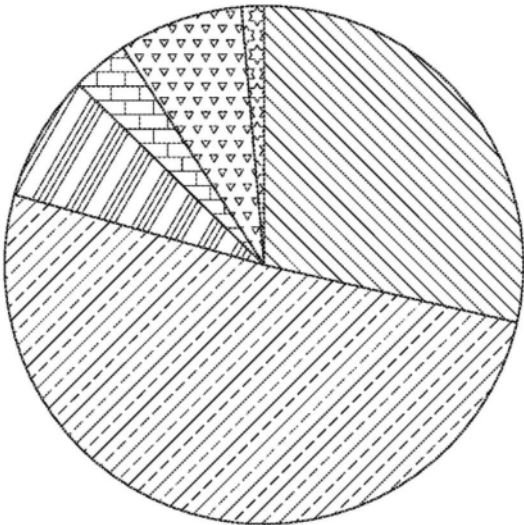


图2B



亚洲

	A	55	3.4%
	B	536	32.8%
	BC	14	0.9%
	C	620	37.9%
	CB	104	6.4%
	D	175	10.7%
	DC	87	5.3%
	DE	22	1.3%
	其他	22	1.3%
总		1635	100.0%



中国

	B	298	28.5%
	C	528	50.6%
	CB	85	8.1%
	D	35	3.4%
	DC	86	8.2%
	其他	12	1.1%
总		1044	100.0%

图3A

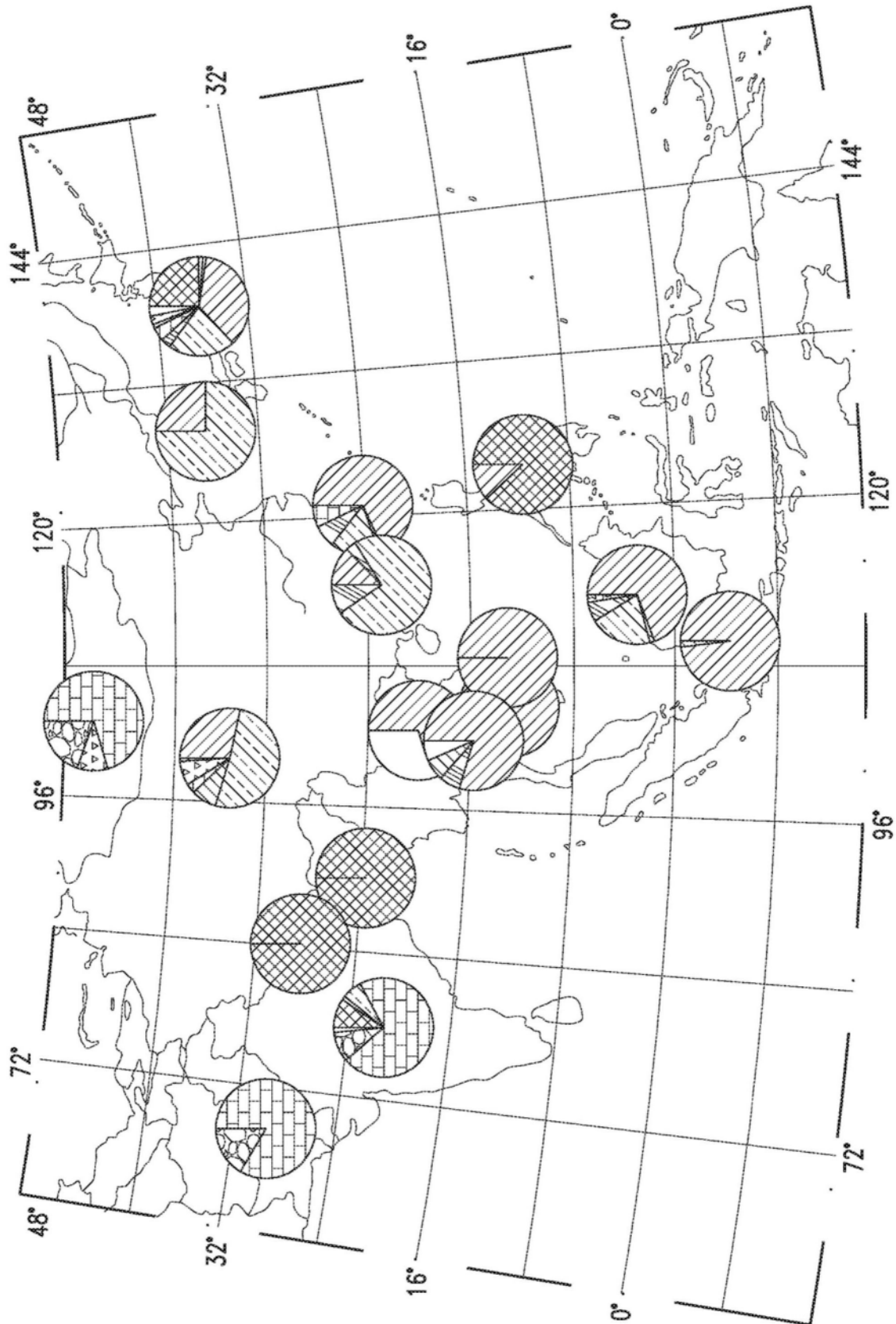


图3B

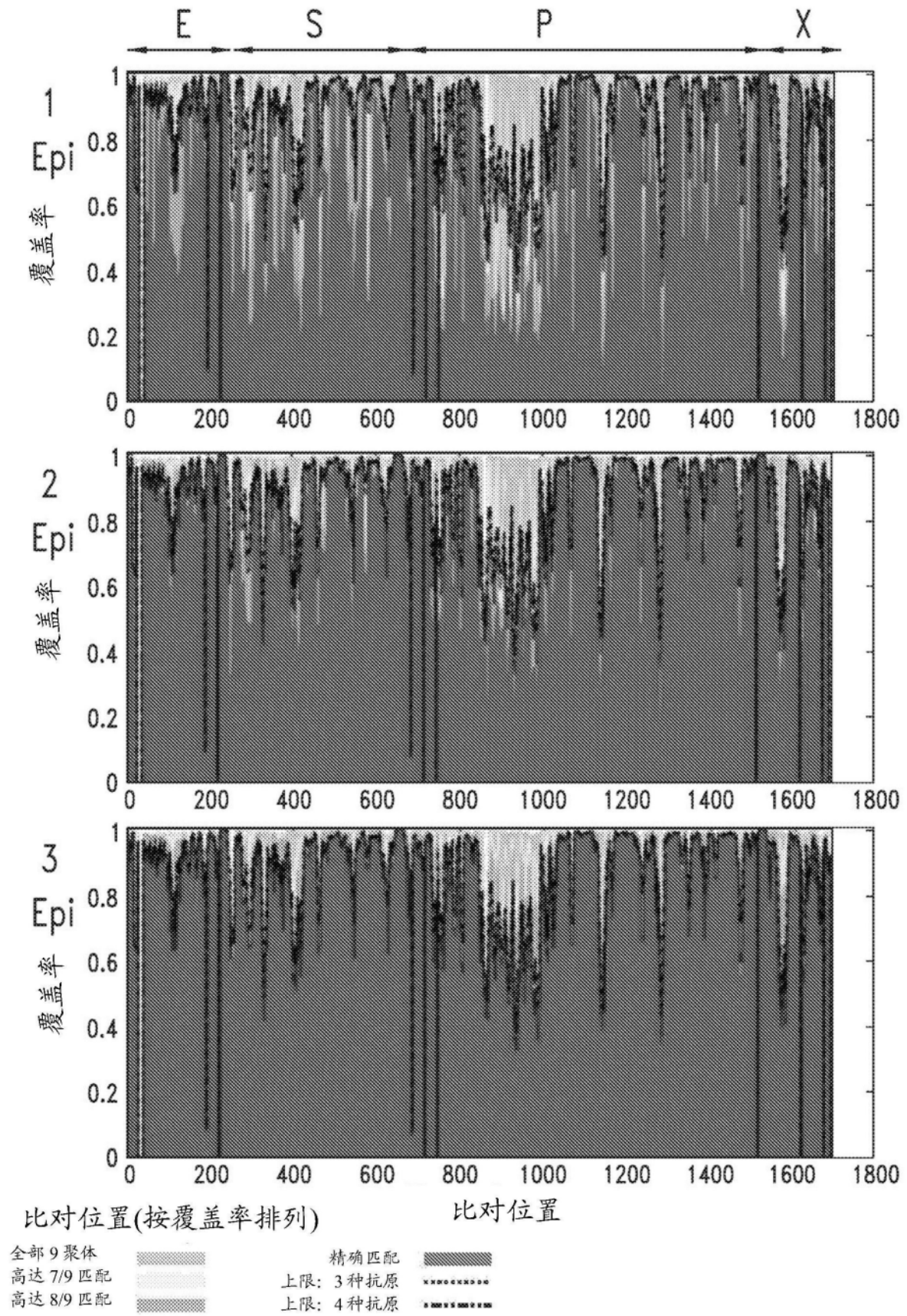


图4A

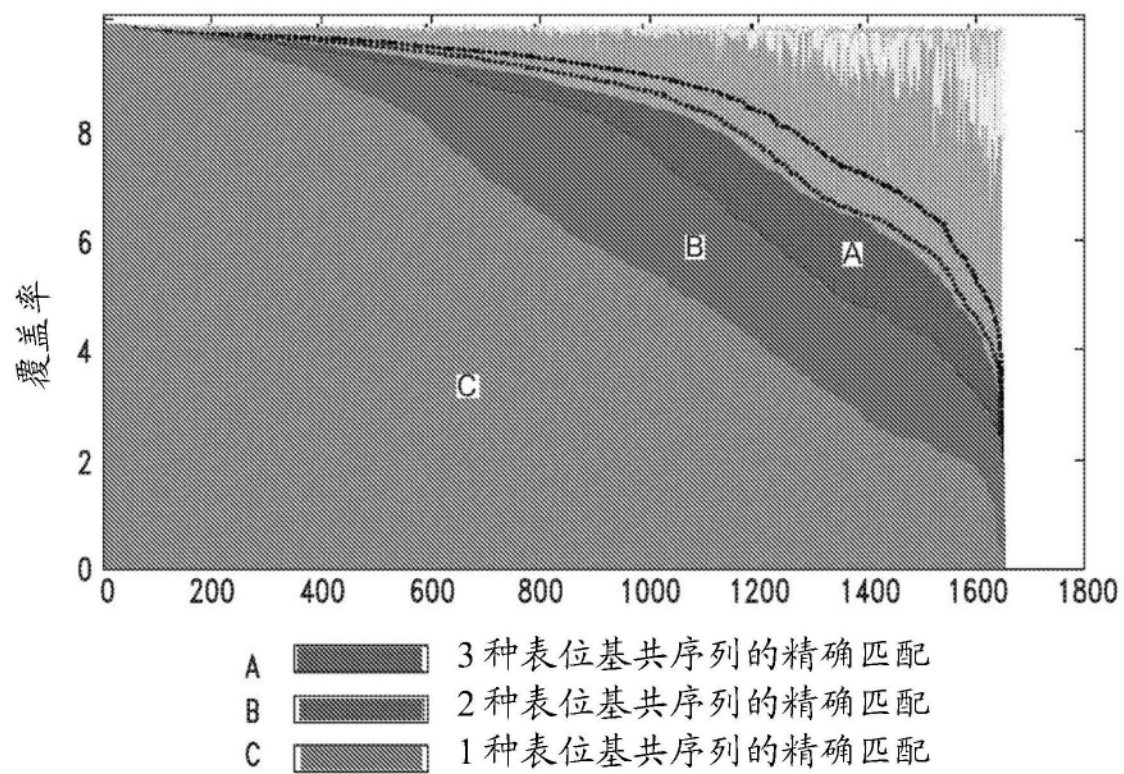


图4B

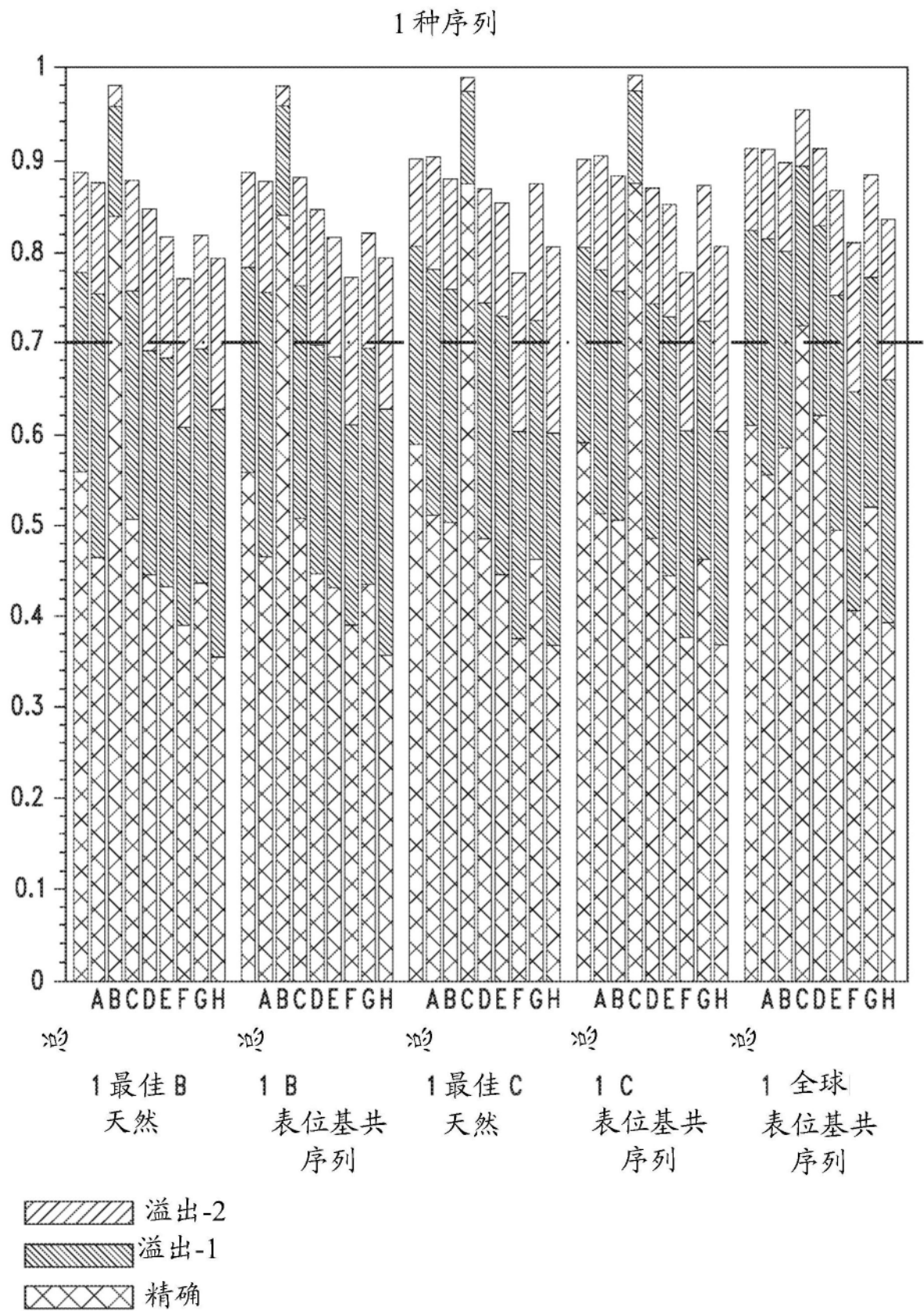


图5A

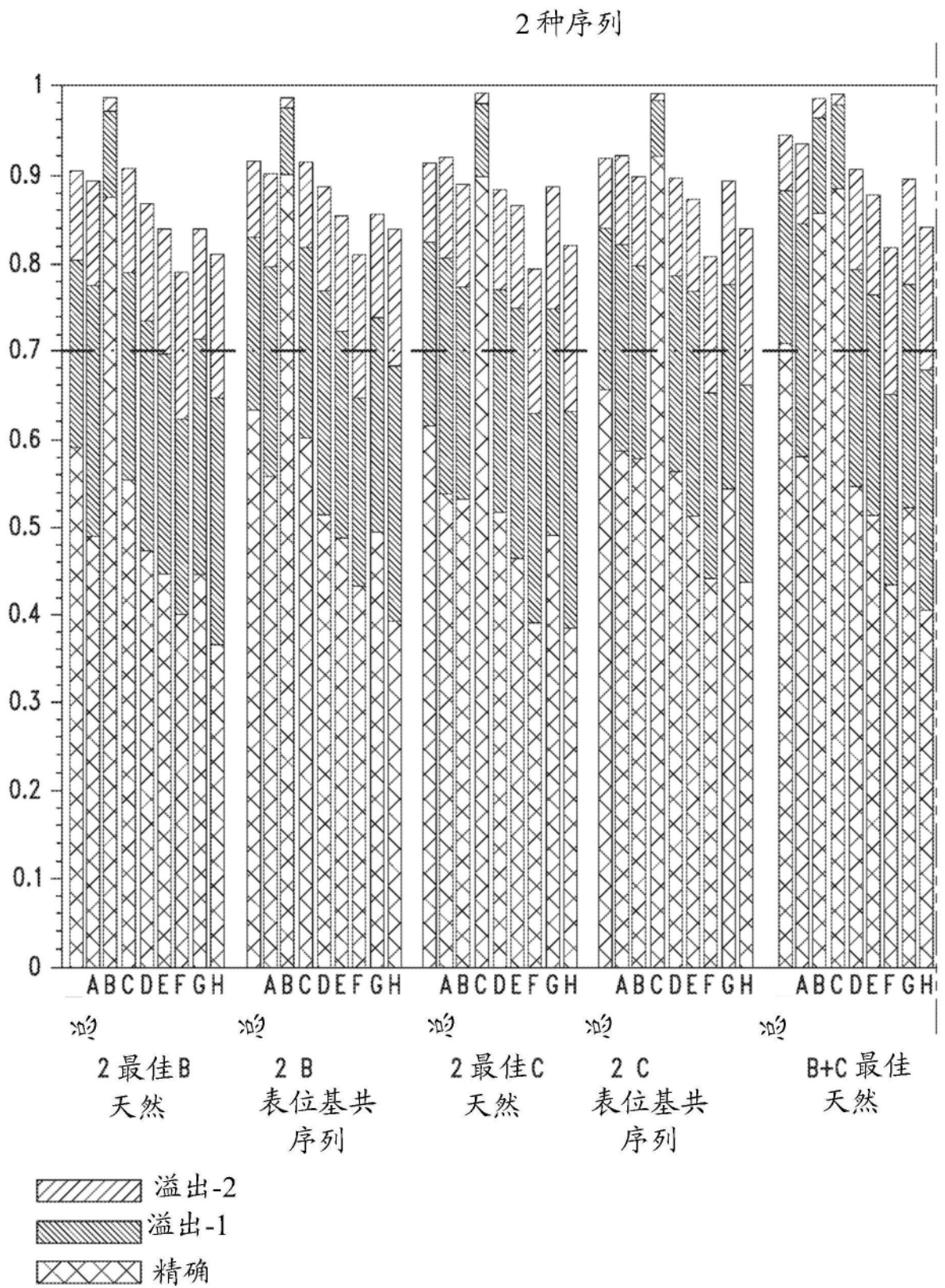


图5B

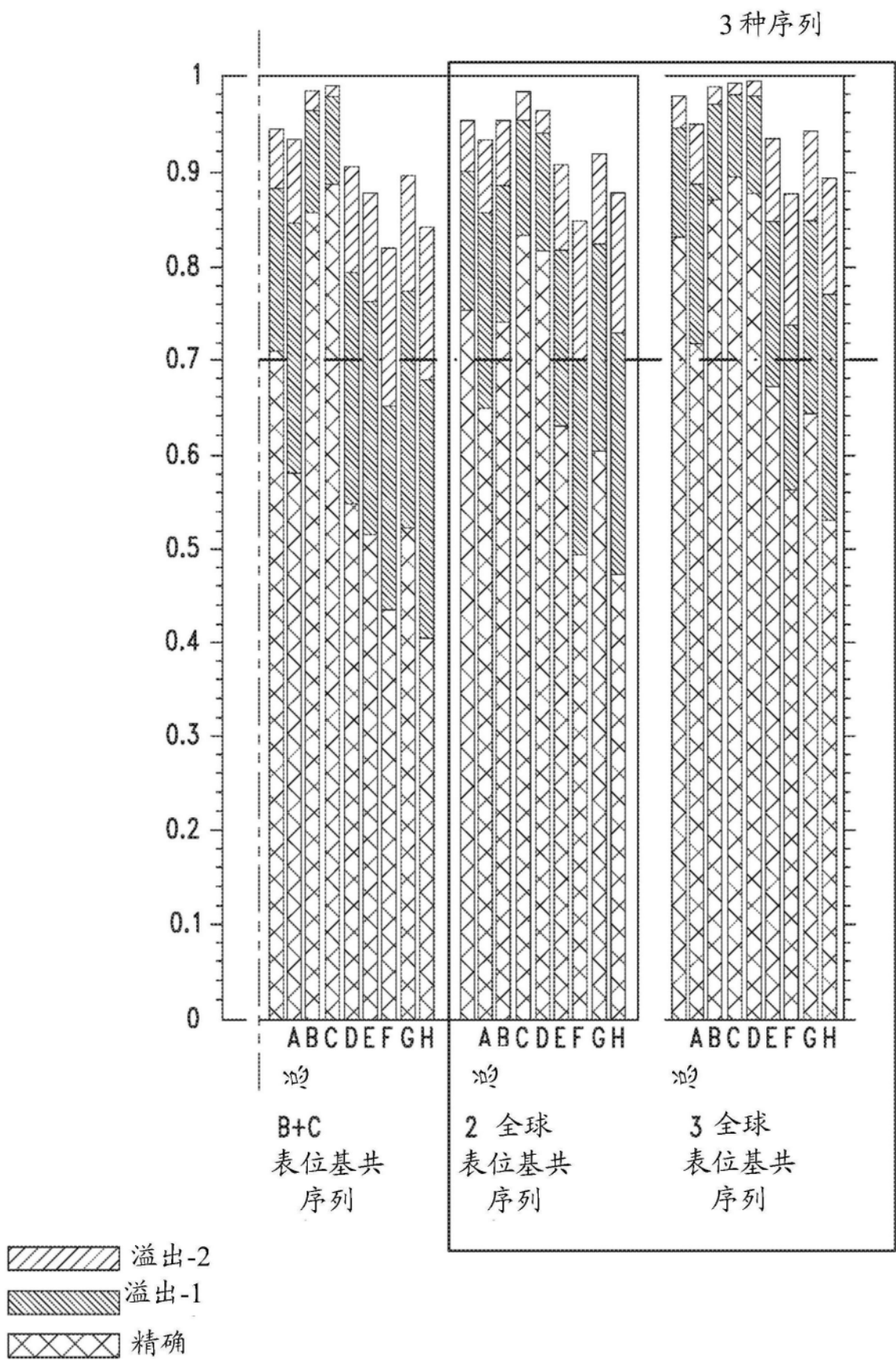


图5C

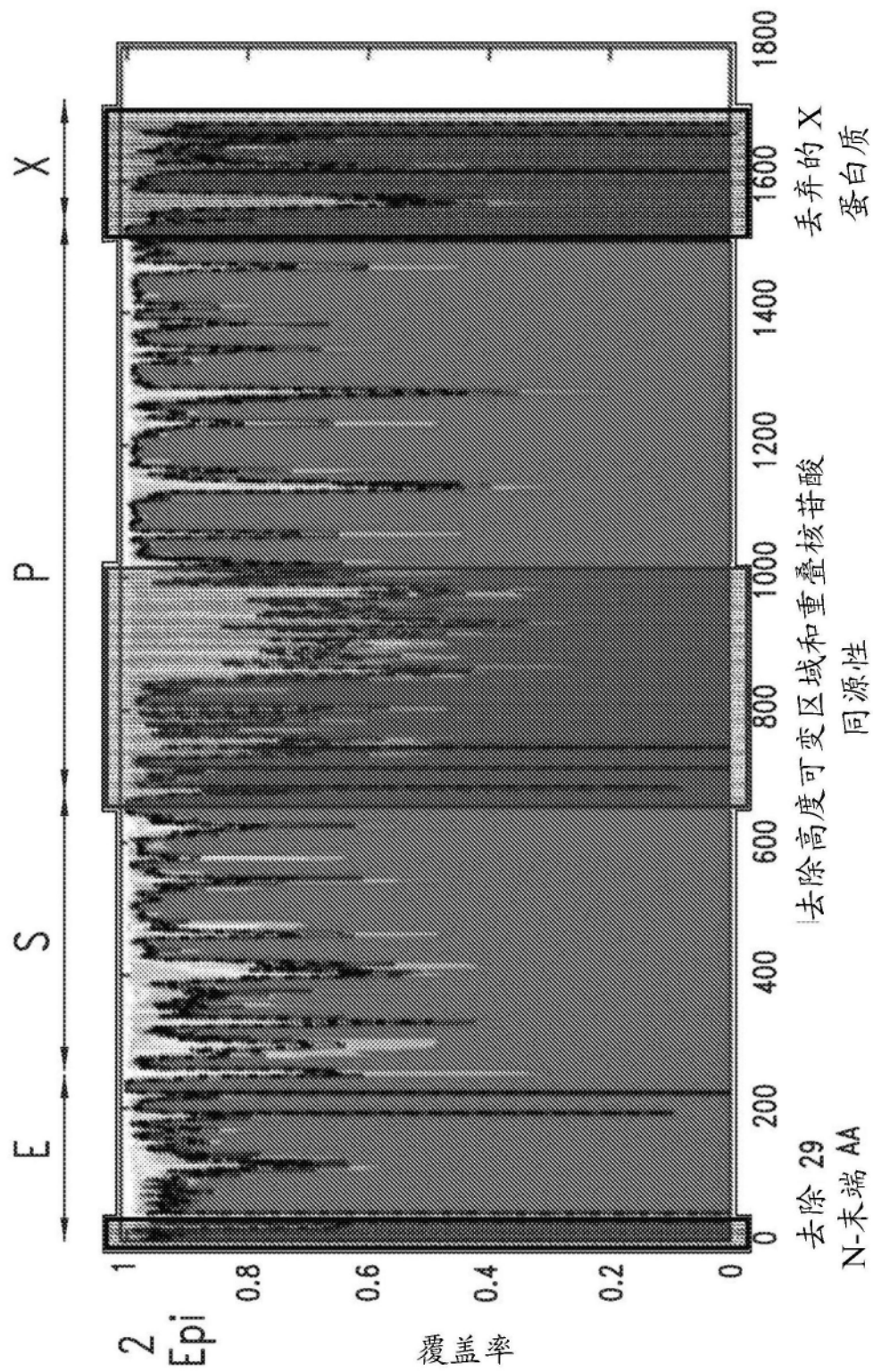


图6

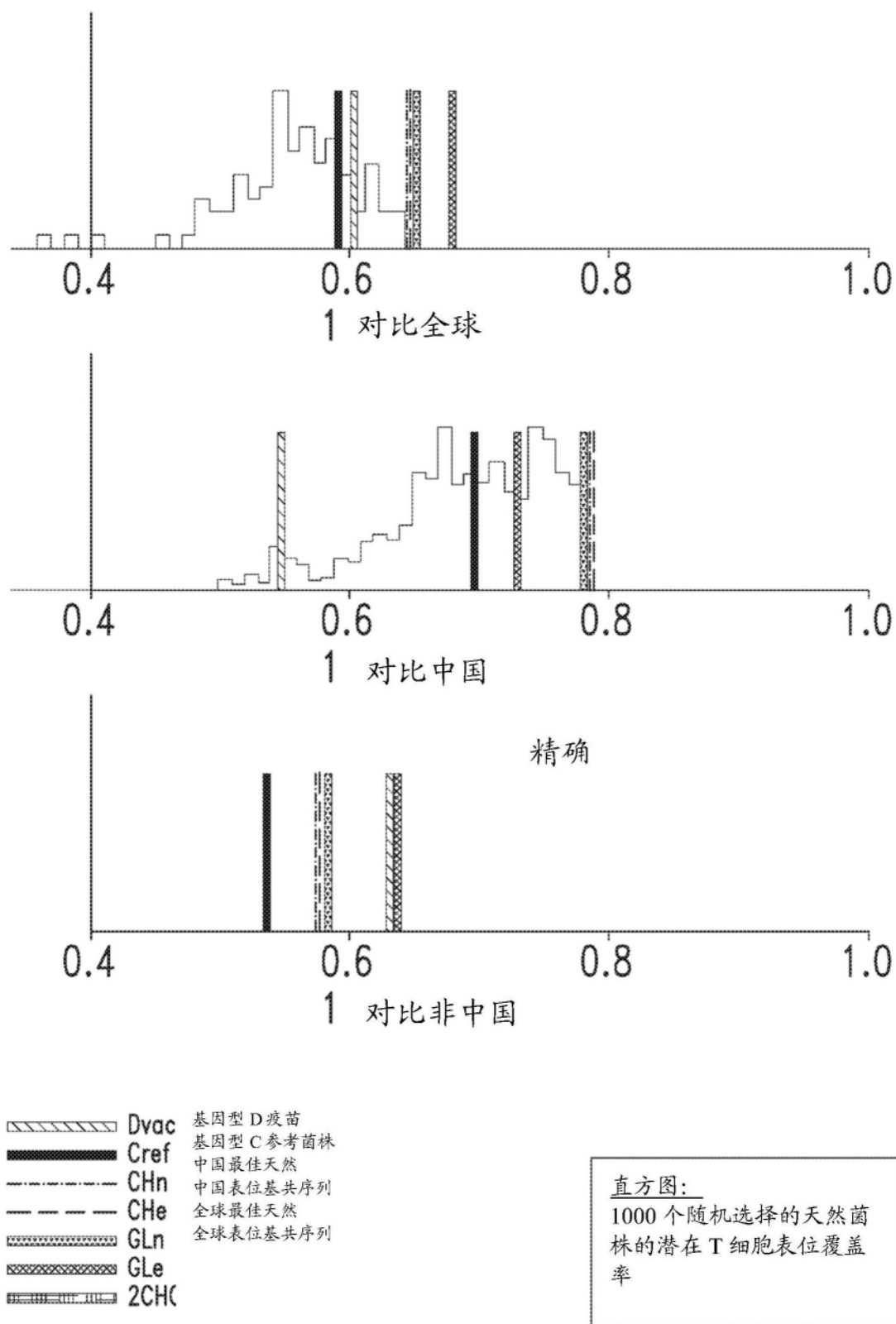


图7A

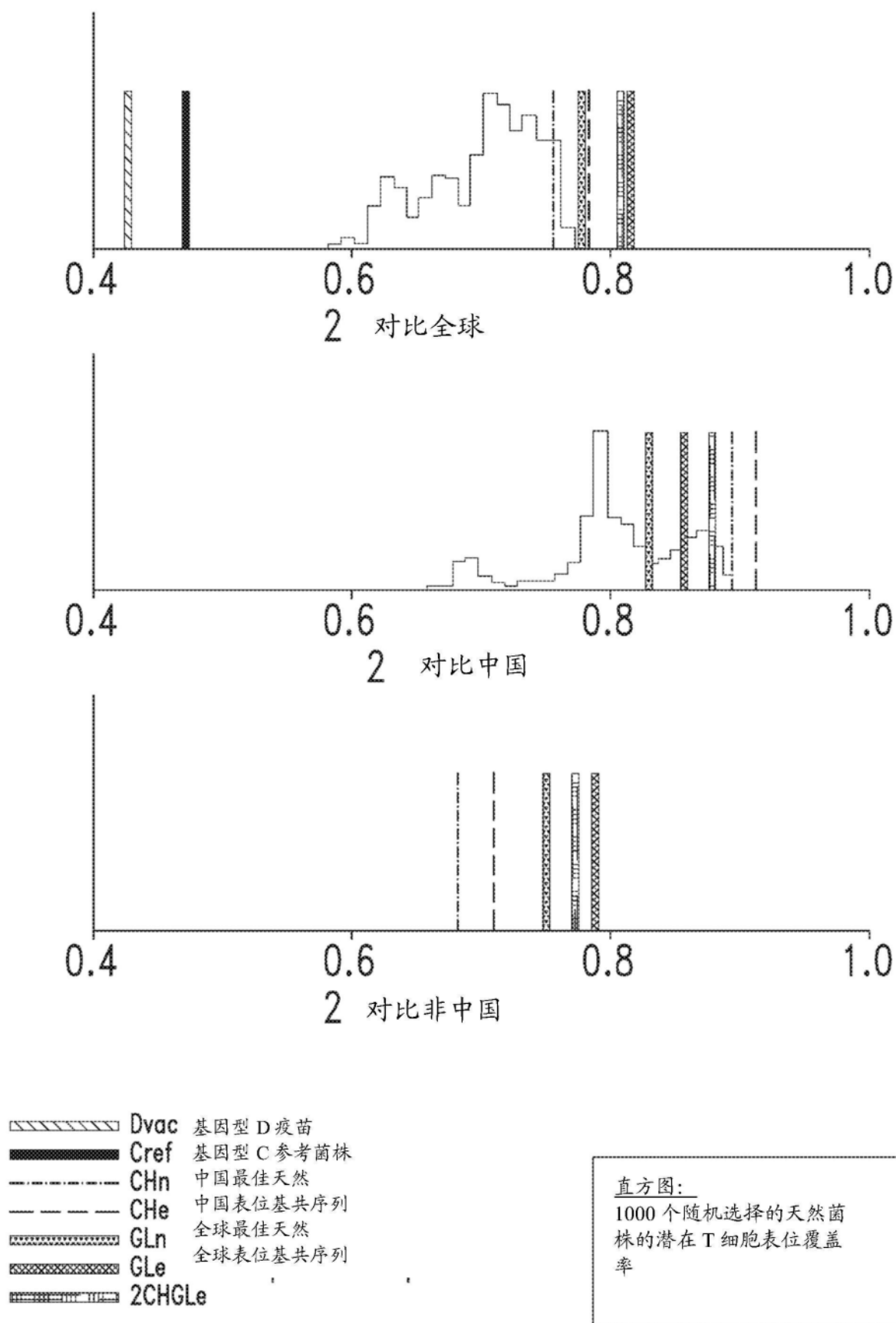


图7B

		参数	中国				非中国				全球			
	疫苗		精确	loff	最稀有 Epi	稀有 计数	精确	loff	最稀有 Epi	稀有 计数	精确	loff	最稀有 Epi	稀有 计数
	1 D_疫苗 (Y07587)		0.548	0.809	0	9	0.633	0.853	1	9	0.603	0.837	1	9
	1 C_疫苗 (GQ358158)		0.696	0.913	0	9	0.536	0.820	1	23	0.591	0.852	1	5
	1 1_中国_Nat	1 最佳天然 中国	0.786	0.929	177	1	0.576	0.825	42	1	0.649	0.861	219	1
E1	1 1_中国_Epi	1;稀有 20; 比对 1; 2 中第 中国	0.788	0.931	215	1	0.577	0.827	97	1	0.650	0.863	320	1
	1 1_中国_Nat	1 最佳天然 全球	0.781	0.927	7	1	0.583	0.828	19	2	0.652	0.823	27	2
C1	1 1_全球_Epi	1;稀有 70; 1 溢出 1; 比对 1; 2 中第 一全球	0.731	0.926	6	2	0.637	0.883	51	2	0.679	0.898	100	1
	2 2_中国_Nat	2 最佳天然 中国	0.894	0.984	2	9	0.681	0.897	0	9	0.755	0.927	2	9
E	2 2_中国_Epi	1;稀有 20; 比对	0.911	0.985	21	3	0.709	0.901	3	3	0.779	0.930	27	3
	2 2_中国_Nat	2 最佳天然 全球	0.829	0.956	0	9	0.749	0.823	1	9	0.777	0.935	1	9
A	2 2_中国_Epi	1;稀有 70;	0.857	0.963	0	9	0.787	0.938	47	3	0.811	0.947	75	3
H	2 2_中国全球_Epi 关于 gen 中国的第 Epi 优 化, 固定, 以及关于全球 的第二 Epi 优化	10110; 稀有, 70; 固定 中国; 比对	0.879	0.971	0	9	0.772	0.930	47	3	0.809	0.944	75	3
D	3 3_中国_Epi	10110; 稀有 15	0.924	0.992	0	65	0.848	0.961	2	1	0.875	0.971	16	10

图8

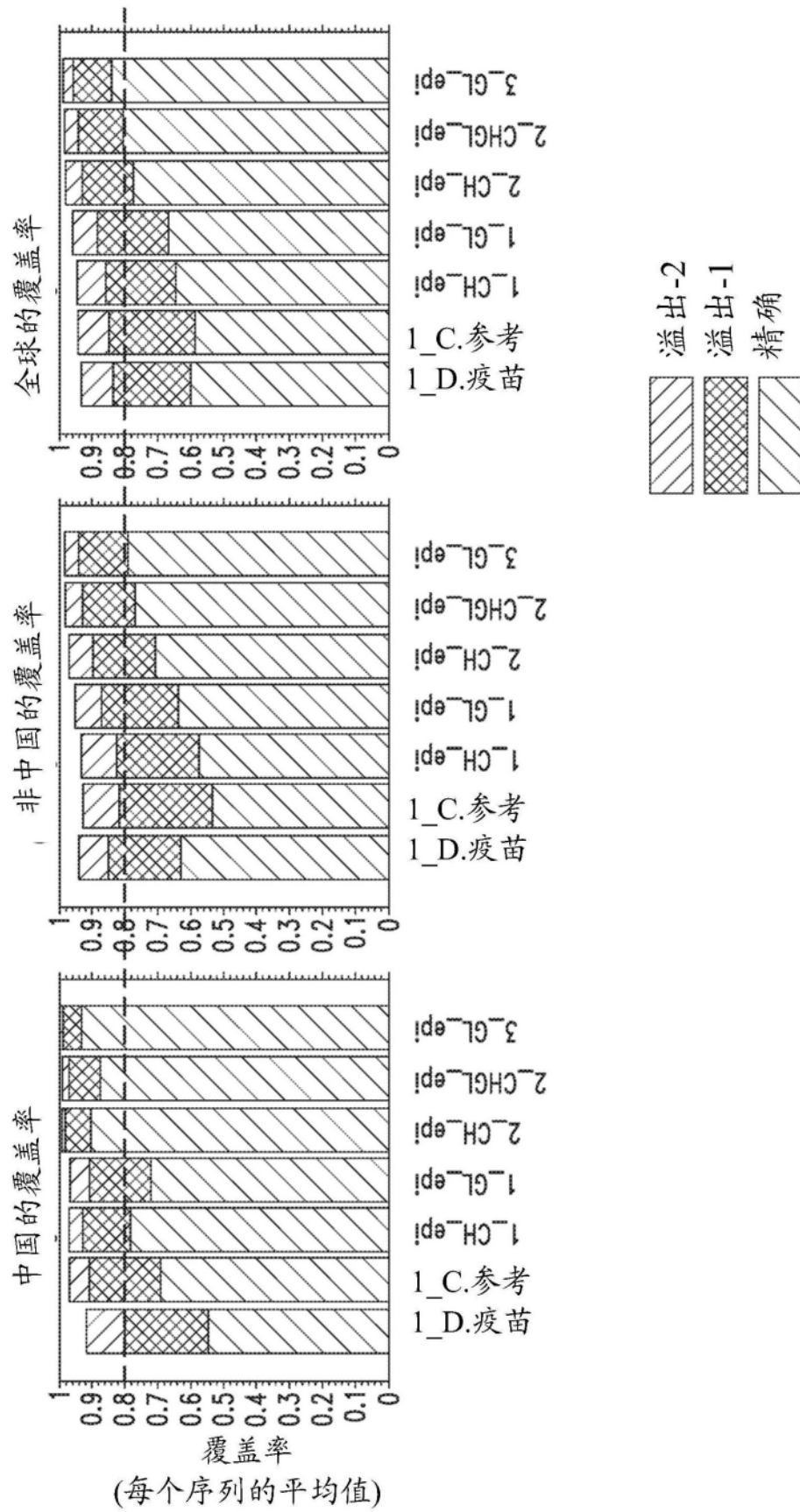


图9A

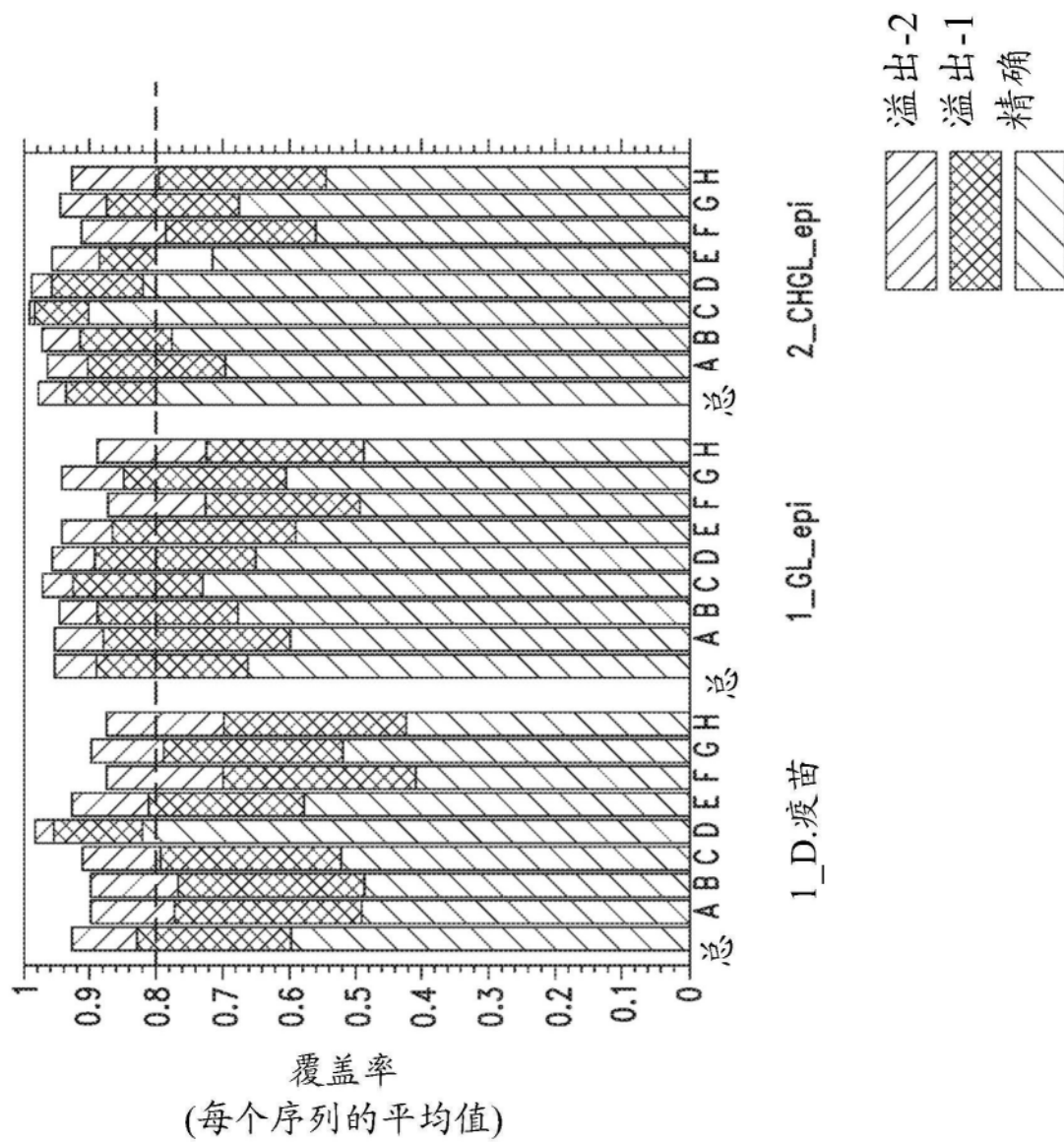


图9B

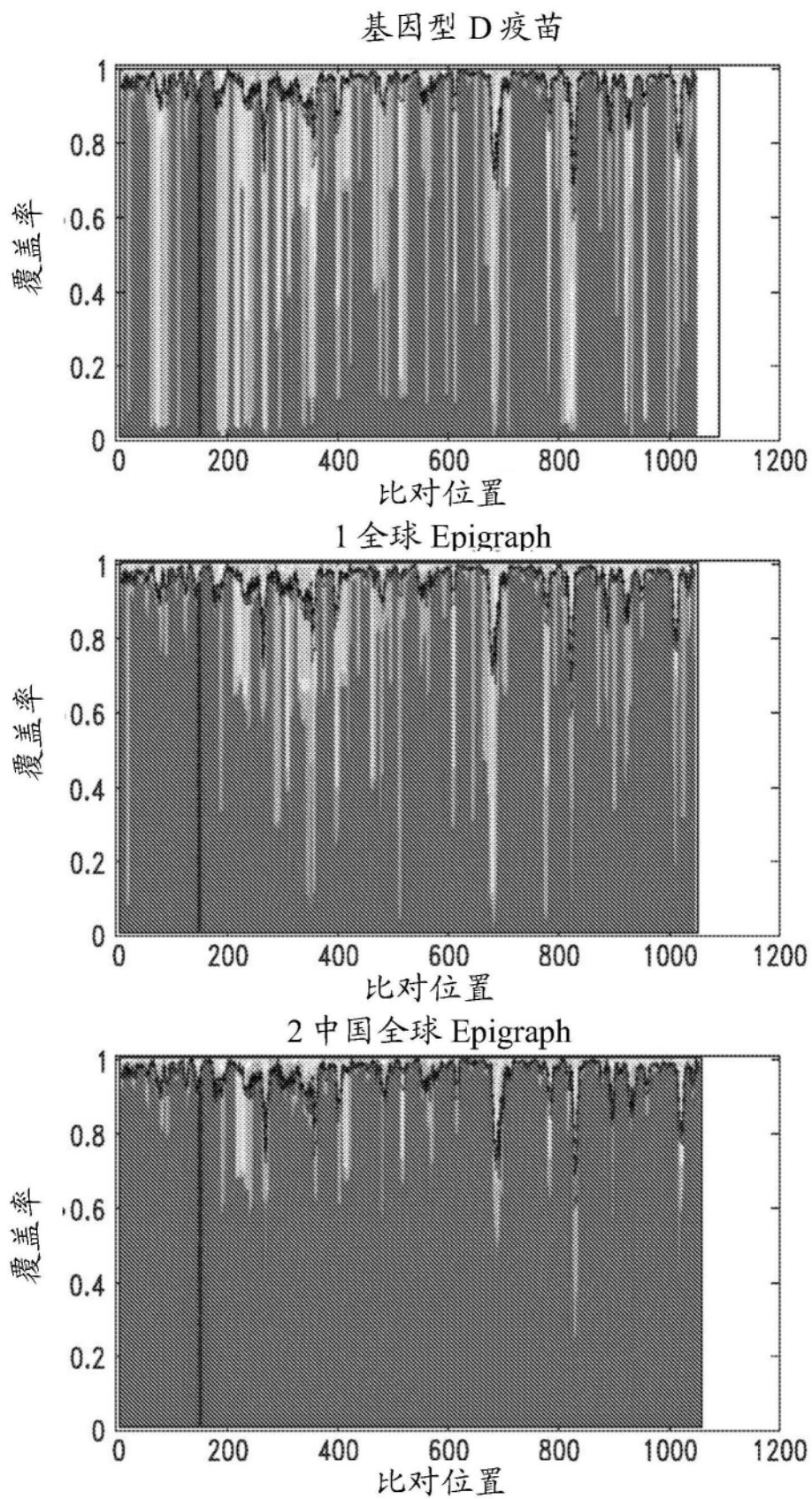


图10A

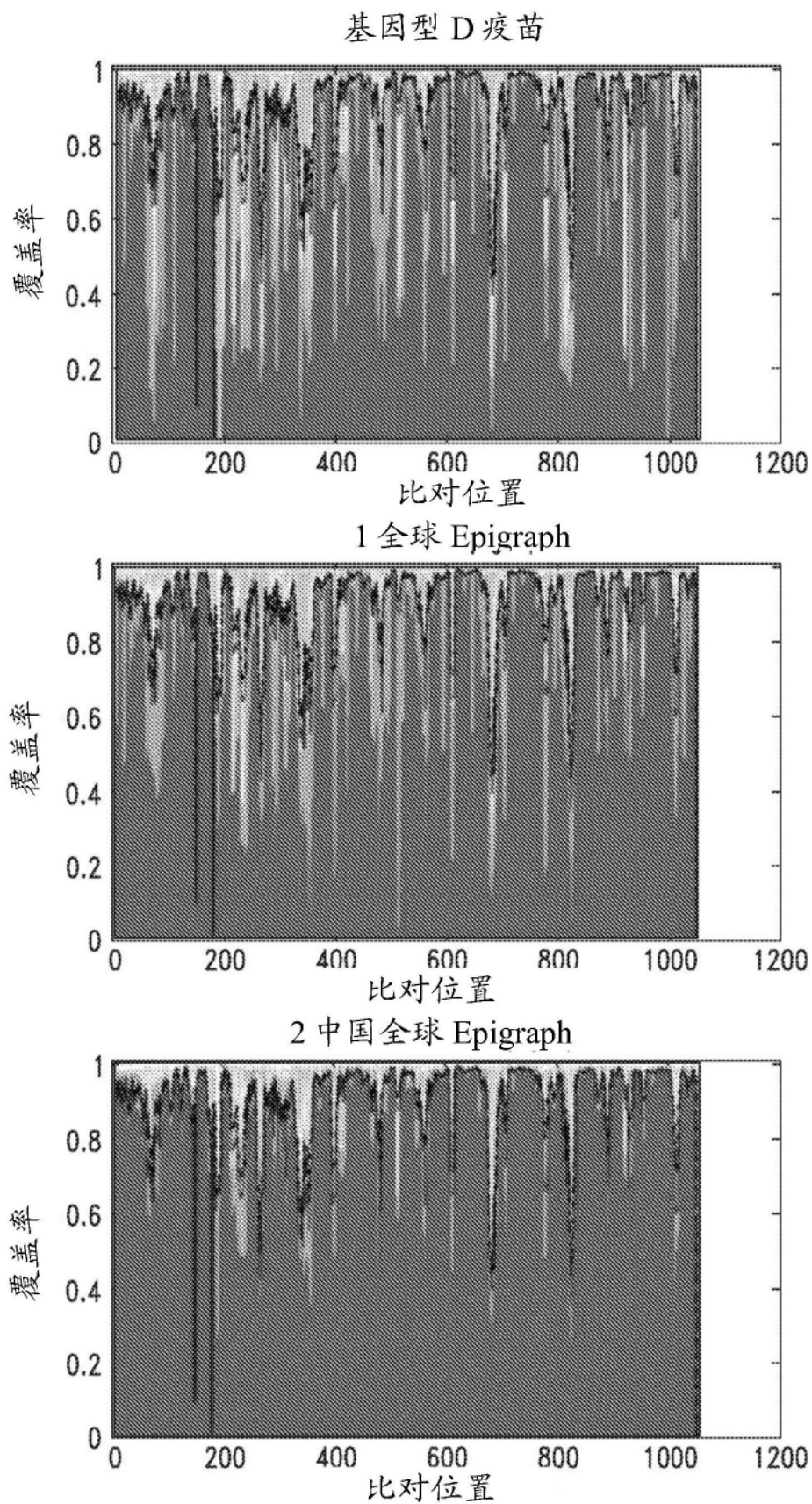


图10B

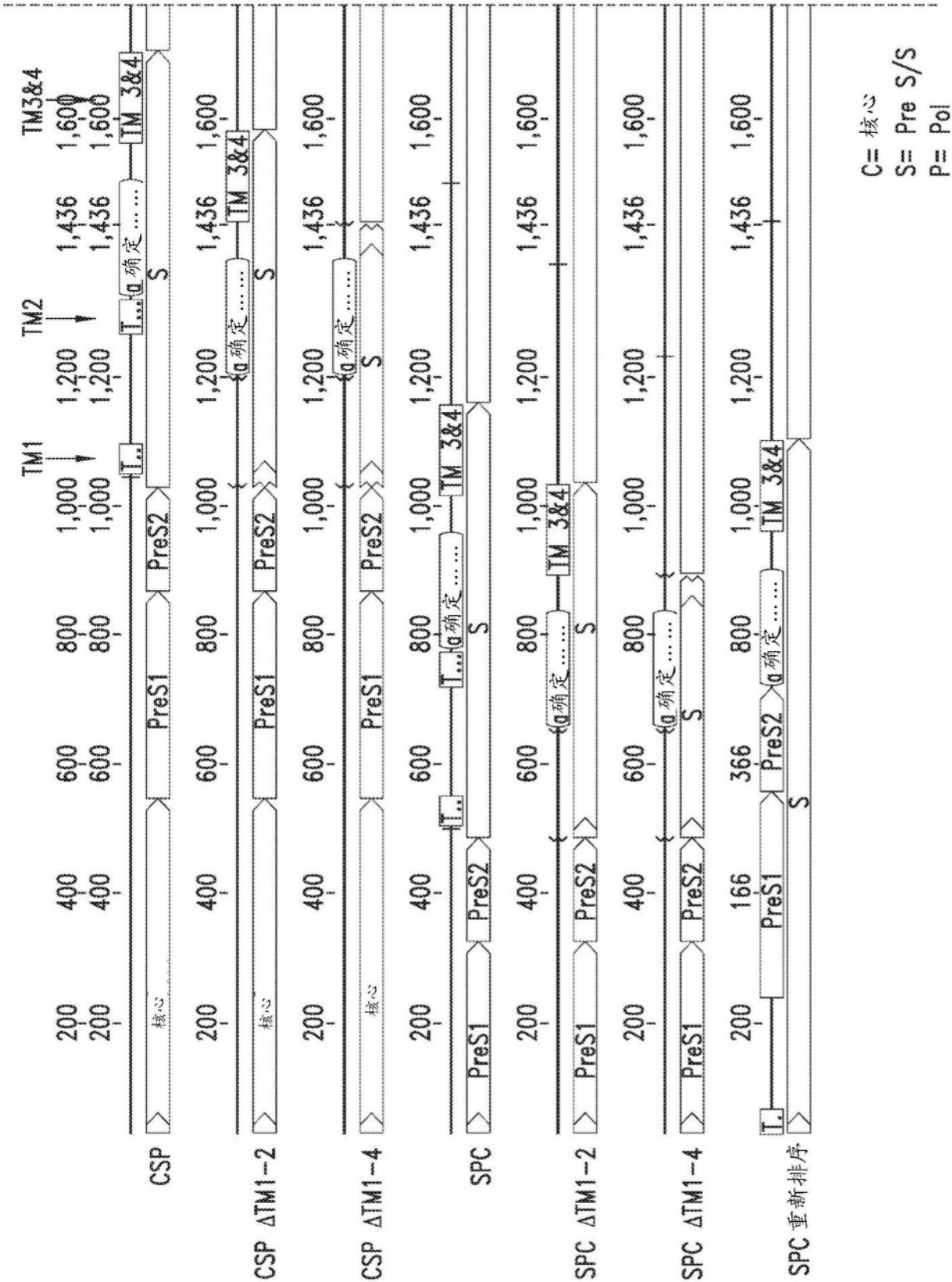


图11A

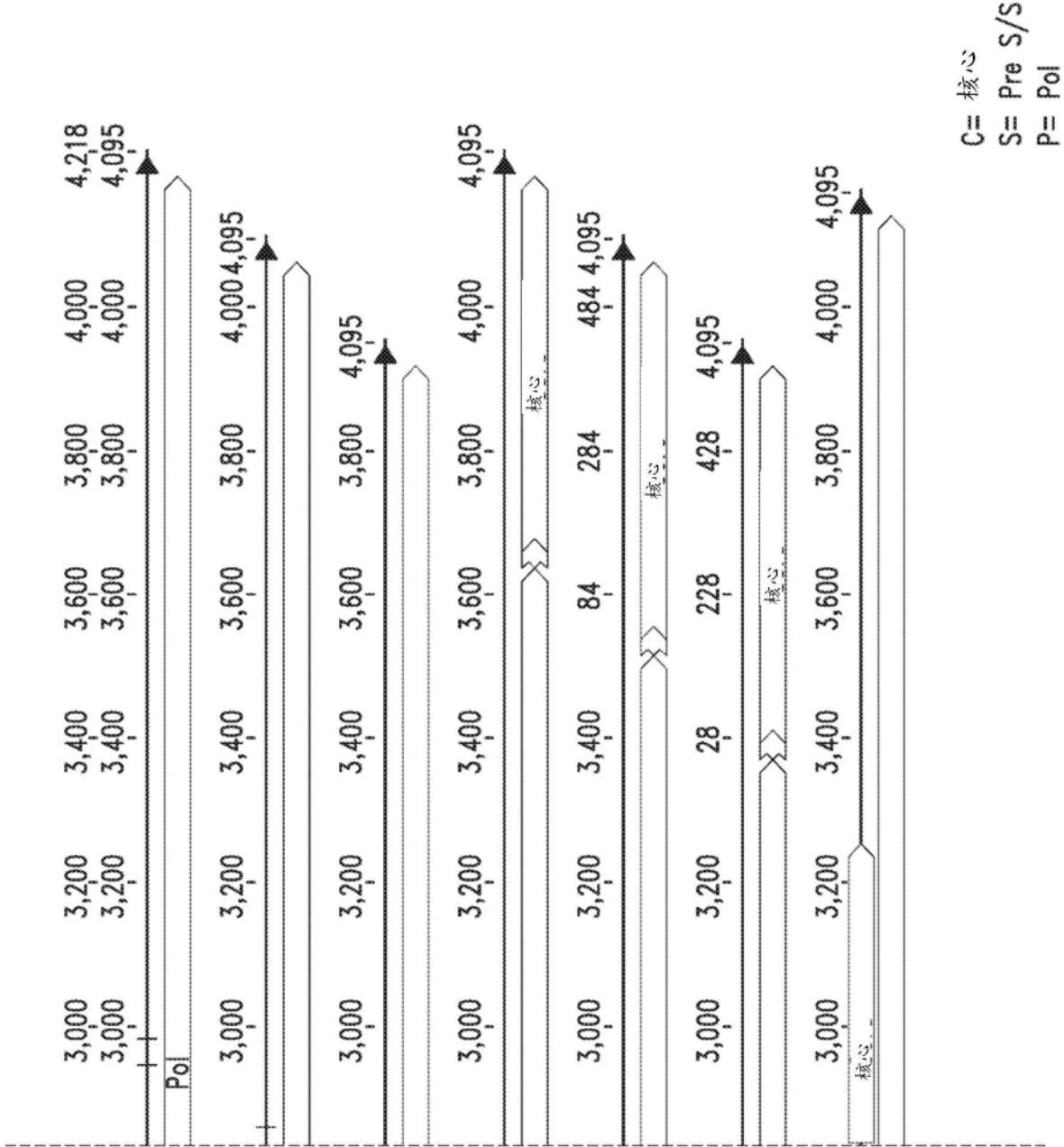


图11B

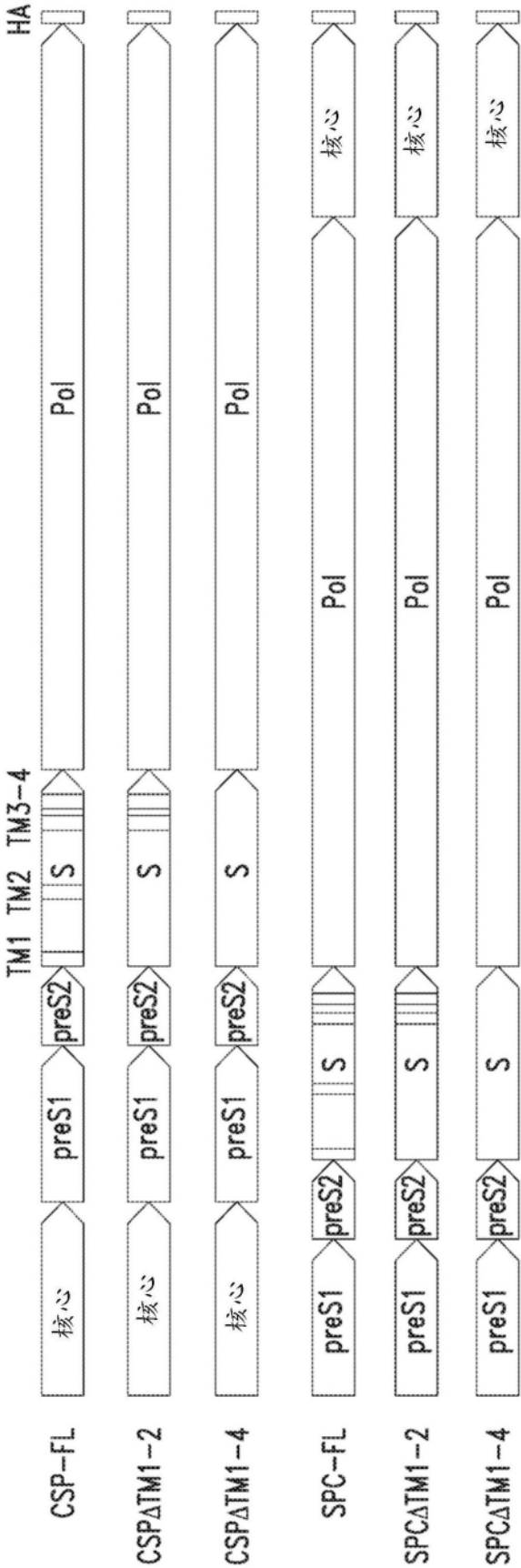


图11C

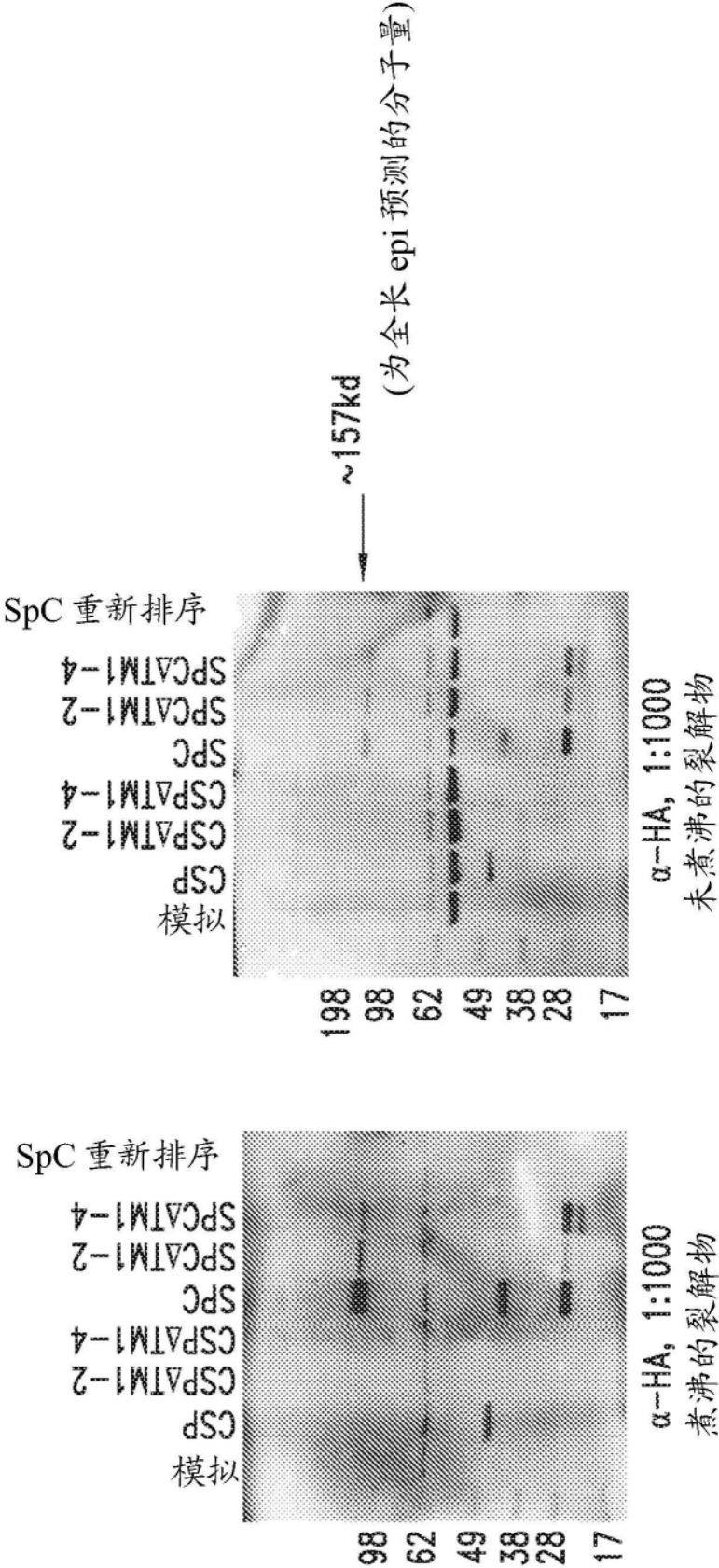


图11D

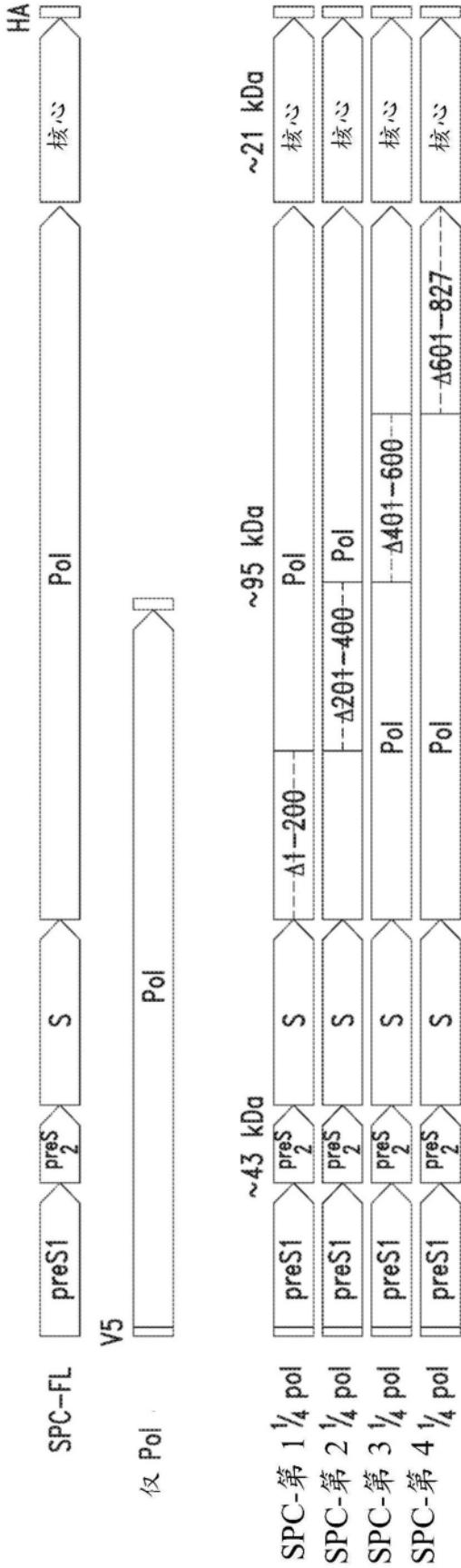


图12A

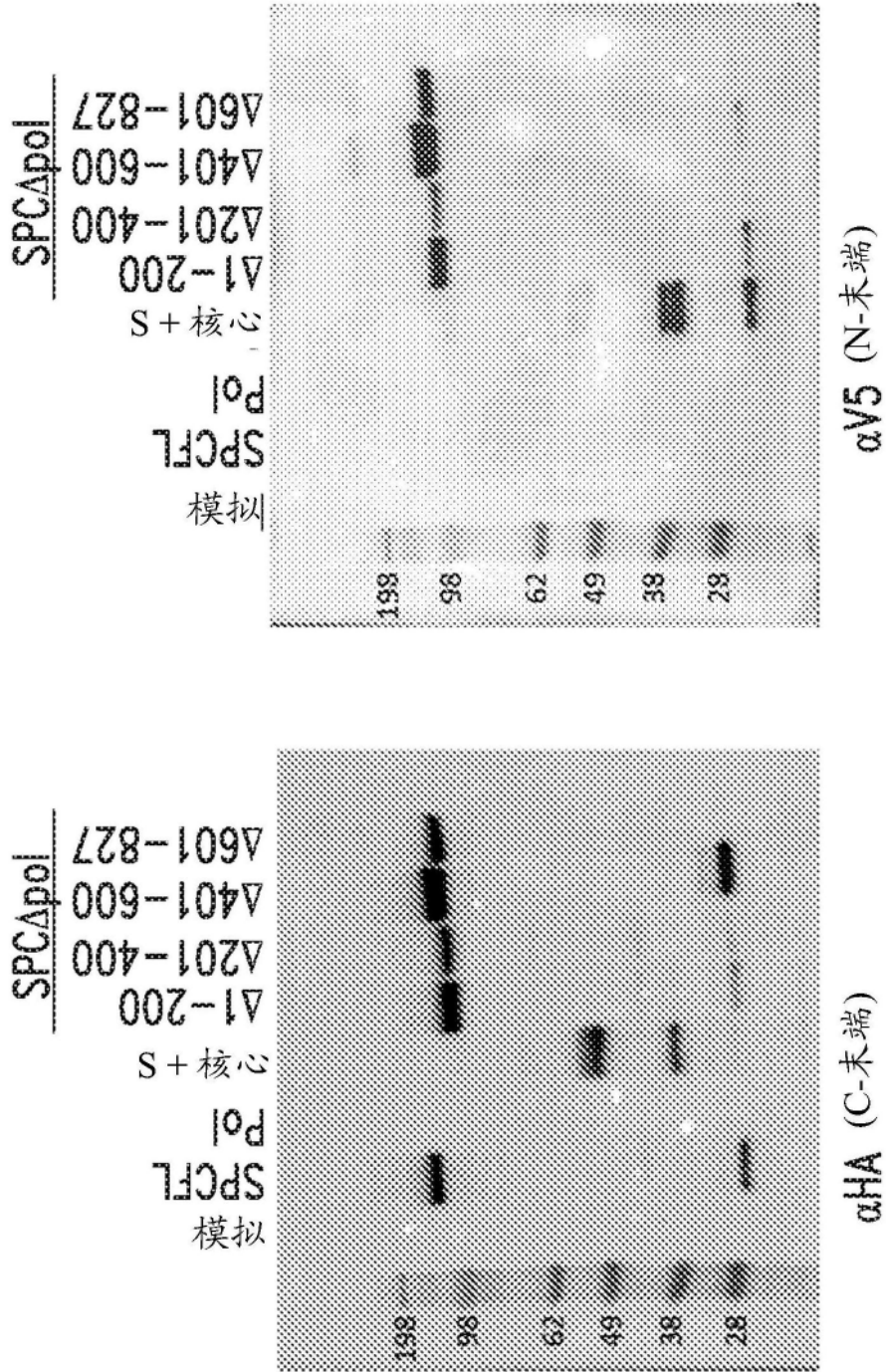


图12B