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# 肿瘤疫苗的研究进展

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**摘要** 作为一种前景光明的肿瘤治疗方式, 肿瘤疫苗能帮助机体产生针对肿瘤抗原的特异性免疫应答和长期的免疫记忆来治疗肿瘤, 是癌症免疫治疗领域重要的研究方向。目前, 肿瘤疫苗按制剂方式主要可以分为四类, 即细胞疫苗、病毒疫苗、多肽类疫苗和核酸类疫苗。这些疫苗能通过增强机体内抗肿瘤免疫反应而发挥清除肿瘤细胞、抑制肿瘤生长的功能。该综述将对肿瘤疫苗的作用机制、基础研究与临床试验的最新进展进行讨论, 以期为深入理解肿瘤疫苗、开发新型肿瘤疫苗提供有益的参考。

**关键词** 肿瘤免疫治疗; 肿瘤疫苗; mRNA疫苗

# The Advances of Cancer Vaccines

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**Abstract** As a promising means of antitumor treatment, cancer vaccines elicit effective immune response and the long-term immune memory against tumor, and lead an important research direction in the field of cancer immunotherapy. Cancer vaccines can be categorized into four kinds by different formulations: cell-based vaccines, virus-based vaccines, peptide-based vaccines and nucleic acid-based vaccines. These vaccines can inhibit tumor growth by enhancing the antitumor immune response. This review discusses the mechanism of action and recent advances in basic research and clinical trials of cancer vaccines, aiming to inspire the in-depth understanding of cancer vaccines and promote the development of next-generation cancer vaccines.

**Keywords** cancer immunotherapy; cancer vaccines; mRNA vaccines

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长久以来，作为预防传染性疾病的重要治疗策略，疫苗能够诱导机体产生针对特定病原体的免疫应答和免疫记忆，有效保护了人类的生命健康安全。基于疫苗能引起抗原特异性免疫反应、产生长期免疫记忆的特点，针对肿瘤抗原的肿瘤疫苗在恶性肿瘤的预防、治疗、以及清除外科手术后残留的肿瘤细胞方面有着巨大的临床应用价值，这是肿瘤免疫治疗研究领域的重要方向[1]。由于肿瘤病因复杂，针对肿瘤预防的疫苗目前主要是针对病毒相关性肿瘤的病毒疫苗如人类乳头状病毒(human papilla virus, HPV)疫苗，而大部分肿瘤的发病机制并不清楚，发病之前也没有明确的肿瘤抗原，因此尚无成功的预防性肿瘤疫苗。本文所指的肿瘤疫苗主要是治疗性肿瘤疫苗。肿瘤疫苗的相关开创性研究可以追溯到20世纪初Coley毒素(主要成分为灭活的链球菌和沙雷式菌)治疗肿瘤[2]，以及之后OLD等[3]在20世纪50年代发现卡介苗(Bacille-Calmette-Guérin, BCG，减毒的结核杆菌)能够诱导肿瘤消退的报道[2-3]。这些不包含肿瘤抗原的细菌疫苗如何发挥肿瘤治疗作用，目前还并不完全清楚。肿瘤疫苗作为一种转化应用潜力巨大的肿瘤免疫治疗方案，自20世纪80年代以来已有许多临床试验与研究报道[4]。尽管目前只有两种肿瘤疫苗获得批准被用于临床，即用于治疗晚期已转移前列腺癌的Sipuleucel-T疫苗和用于治疗膀胱癌的卡介苗，但近年来随着肿瘤免疫治疗的兴起和技术的进步，已有多种肿瘤疫苗在临床试验中取得了积极的治疗效果，它们能够在病人体内诱导长期的抗原特异性 T细胞免疫反应，降低黑色素瘤和胰腺癌的转移与复发风险，改善患者的预后生存情况[5-9]。图1中列举了近期针对不同癌种的疫苗药物研发情况，其中针对转移性恶性肿瘤的占比最大。因此，肿瘤疫苗是一种前景光明的肿瘤免疫治疗方式，具备良好的临床转化应用价值，值得深入的研究与探索。

肿瘤疫苗一般由三种关键组分组成，即肿瘤抗原、疫苗佐剂和递送系统[10]。肿瘤抗原又可以分为肿瘤相关抗原(tumor associated antigen, TAA)和肿瘤特异性抗原。肿瘤相关抗原通常是在肿瘤中过表达的蛋白如HER2抗原，或者在正常机体中只在早期发育阶段或者特殊组织中表达的抗原如癌胚抗原。而肿瘤特异性抗原是指只在肿瘤细胞上特异表达，而在正常细胞中不表达的抗原，包括肿瘤细胞突变造成的编码序列改变后产生的新抗原(neoantigen)，以及肿瘤相关病毒来源的病毒抗原如HPV来源的E6、E7抗原[11]。由于肿瘤抗原在肿瘤发生发展的过程中已经经历过免疫系统的压力筛选，所以多数肿瘤抗原的免疫原性都很弱，需要配合免疫佐剂(adjuvant)来增强抗原诱导的免疫反应强度。免疫佐剂是疫苗中具备免疫功能的非抗原组分，它能够通过激发有效的固有免疫反应来增强抗原相关的适应性免疫反应的种类和强度，从而提高疫苗疗效。不同佐剂能够影响疫苗诱导的适应性免疫反应，进而为不同疾病的预防与治疗提供对应的有效免疫应答[12]。免疫佐剂可以分为两大类：(1) 具有免疫刺激作用的配体分子，通过结合固有免疫信号通路的模式识别受体如Toll样受体(toll-like receptors, TLRs)、干扰素基因刺激因子(stimulator of interferon genes, STING)、核苷酸结合寡聚化结构域(nucleotide-binding oligomerization domain, NOD)样受体(NOD-like receptors, NLRs)等，引发固有免疫反应；(2) 用作储存抗原或形成递送系统的颗粒佐剂[13]，如氢氧化铝颗粒被广泛用于多种疫苗的佐剂，能够提高抗原在体内的局部浓度和反应强度。有

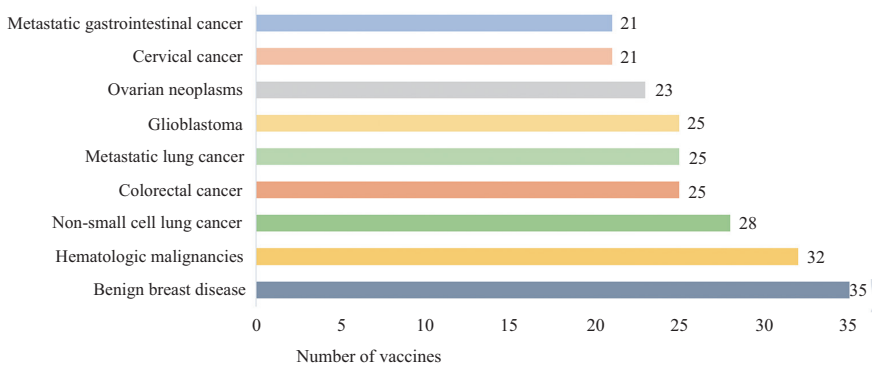


**图1　针对不同癌种的疫苗药物研发情况**

**Fig.1　Distribution of vaccines against different cancer types**

趣的是, 这些颗粒佐剂如氢氧化铝颗粒也能够激活固有免疫受体介导的信号通路如炎症小体反应, 尽管其在疫苗免疫效果中的作用还不完全明确[14]。模式识别受体通常表达在抗原呈递细胞(antigen-presenting cells, APCs), 如树突状细胞(dendritic cells, DCs)上, 能够感知高度保守的病原微生物相关的分子模式物(pathogen-associated molecular patterns, PAMPs)。当具备类似PAMPs结构的佐剂与APCs的模式识别受体相结合后, 这些免疫佐剂能够活化APCs并增强其抗原呈递功能, 从而有助于抗原特异的 T细胞和B细胞的产生, 提高疫苗免疫效果[15-16]。

根据肿瘤抗原的不同表达和制剂形式, 肿瘤疫苗可以进一步分为细胞类疫苗如树突状细胞疫苗、病毒载体疫苗、多肽类疫苗、核酸类疫苗[包括DNA疫苗和信使RNA(messenger RNA, mRNA)疫苗]等[17]。由于抗原存在形式和制备方式的不同, 这些肿瘤疫苗也具备不同的优缺点: 细胞类肿瘤疫苗如树突状细胞疫苗具有良好的体内免疫刺激功能和临床活性, 但需要体外培养细胞, 制备成本高昂; 病毒载体疫苗的免疫刺激功能较为强大, 但制备过程的技术要求较高, 而且需要规避病毒带来的安全风险; 多肽类疫苗安全性和临床活性较好, 但面临着抗原肽合成制备成本高、免疫原性不高的缺点; 核酸疫苗中DNA疫苗制备成本低, 但存在插入基因组造成突变的潜在安全风险; mRNA疫苗制备体系成熟, 能够编码所有类型的肿瘤抗原表位, 体内免疫效果好, 但也存在mRNA易降解和潜在不良反应等问题[18]。本文的后续内容将介绍各种肿瘤疫苗的大致作用机制, 并对不同类型肿瘤疫苗的相关基础研究和临床试验进展进行概述, 以期加深读者对肿瘤疫苗的理解, 为肿瘤疫苗的研究和开发提供有益的参考。

## 1 肿瘤疫苗的作用机制

肿瘤免疫治疗的基本原理是通过激活机体内免疫细胞, 增强固有免疫和适应性免疫系统的功能, 从而提高对肿瘤细胞的免疫杀伤作用来达到治疗肿瘤的目的。作为一种肿瘤免疫治疗方式, 肿瘤疫苗主要通过增强T细胞介导的抗肿瘤免疫反应来发挥作用。注射携带外源性抗原的肿瘤疫苗, 能够帮助引起机体内对肿瘤抗原产生特异性T细胞免疫反应、强化免疫系统对肿瘤细胞的识别与杀伤作用, 从而促进长期的抗肿瘤免疫记忆的产生。图2展示了肿瘤疫苗诱导T细胞发挥抗肿瘤效应的具体作用机制[19]。首先, 肿瘤疫苗注射后, 组织内的抗原呈递细胞能通过摄取疫苗来获得特异的肿瘤抗原, 后者经细胞内蛋白酶体或内体–溶酶体途径被降解后, 释放的抗原表位肽(epitope)与主要组织相容性复合体(major histocompatibility complex, MHC)分子结合, 形成MHC-多肽复合物并转移至细胞膜表面。值得注意的是, MHC-I和MHC-II类分子涉及的抗原呈递机制并不相同。具体而言, 当肿瘤疫苗携带的外源抗原蛋白通过内吞作用进入到APCs细胞内特别是DCs时, 可经蛋白酶体作用被降解为含10~20个氨基酸的多肽, 这些多肽再通过抗原肽转运蛋白进入内质网; 进入内质网的多肽会被进一步消化为含8~10个氨基酸的抗原表位短肽, 这些短肽再与内质网上MHC-I分子结合形成复合物而转运到细胞表面。而外源抗原蛋白进入APCs后, 通过内体–溶酶体途径一步步被降解、加工成抗原表位肽时, 则可以与溶酶体上MHC-II分子结合形成复合物, 同样能转运到细胞膜表面, 参与后续的激活T细胞过程。完成抗原摄取、加工的APCs能够回流到淋巴结内, 其细胞表面的MHC-抗原多肽复合物与幼稚或记忆性$CD4^+$、$CD8^+$ T细

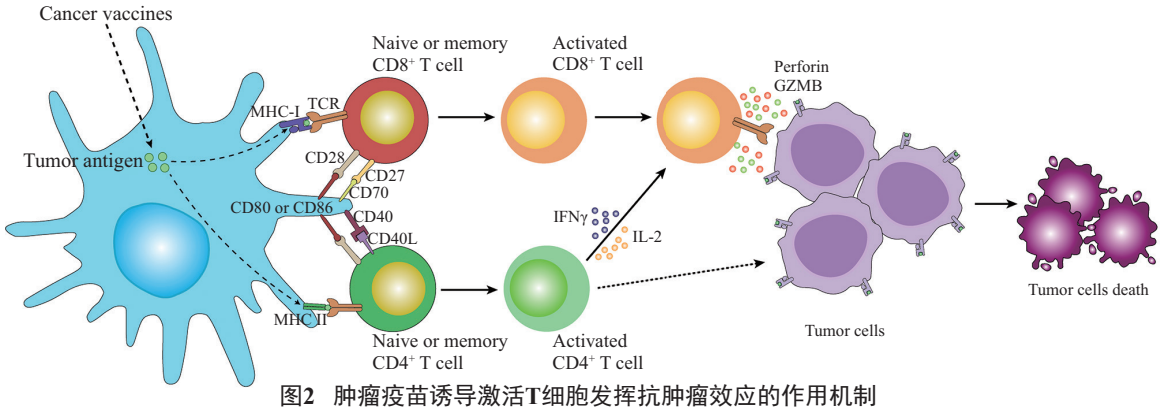


**图2 肿瘤疫苗诱导激活T细胞发挥抗肿瘤效应的作用机制**

**Fig.2 The mechanism by which tumor vaccines induce T cell responses for antitumor activity**

胞表面特异性的T细胞受体(T cell receptor, TCR)结合, 同时APCs表面的共刺激分子CD80/CD86、CD40等也与T细胞上对应的配体CD28、CD40L结合, 从而完成肿瘤抗原特异性T细胞的启动与激活。MHC-I-多肽复合物主要结合$CD8^+$ T细胞表面TCR, 而MHC-II-多肽复合物主要结合$CD4^+$ T细胞表面TCR。由MHC-I分子介导的外源抗原的呈递过程也被称为交叉呈递(cross-presentation)过程, 对于抗原特异性$CD8^+$ T细胞的激活非常重要。活化后的T细胞再经过循环系统转运, 浸润到肿瘤组织内, 通过抗原特异性TCR识别和结合肿瘤细胞后, 释放细胞因子如肿瘤坏死因子α(tumor necrosis factor-α, TNF-α)、γ-干扰素(interferon γ, IFNγ)、颗粒酶B(granzyme B, GZMB)和穿孔素等, 完成对肿瘤细胞的杀伤。$CD8^+$ T细胞是主要负责直接杀伤肿瘤的T细胞, 而$CD4^+$ T细胞除了直接杀伤肿瘤外, 也能够为$CD8^+$ T细胞提供辅助, 如表达CD40L活化树突状细胞和分泌IL-2促进$CD8^+$ T细胞扩增。当肿瘤细胞死亡后, 其释放的肿瘤抗原又可以正向调控抗肿瘤免疫应答这一过程, 促进对肿瘤的清除。此外, 肿瘤疫苗也可以激发B细胞/浆细胞产生肿瘤特异性的抗体, 结合肿瘤细胞引起抗体依赖的细胞介导的细胞毒作用(antibody-dependent cell-mediated cytotoxicity, ADCC)。这些作用机制提示着, 肿瘤疫苗具有强大的免疫保护能力, 能够诱导有效的免疫反应来杀伤肿瘤细胞和清除肿瘤。

## 2 肿瘤疫苗类别与研究进展

### 2.1 细胞类肿瘤疫苗

根据肿瘤抗原的表达方式和制剂形式, 肿瘤疫苗主要分为四类: 细胞类疫苗、病毒类疫苗、多肽类疫苗和核酸类疫苗。细胞类肿瘤疫苗通常由细胞或细胞内组分所制备, 能包含全部的肿瘤抗原, 诱导广泛的抗原相关免疫反应。具体而言, 细胞类疫苗可分为患者自体癌细胞或肿瘤细胞系的全肿瘤细胞疫苗以及负载肿瘤抗原的树突状细胞疫苗。全肿瘤细胞疫苗是一种相对简单的肿瘤免疫治疗方法, 直接将灭活的肿瘤细胞或肿瘤细胞提取物制备为疫苗, 能包含所有的肿瘤相关抗原, 对抑制肿瘤进程有着一定的治疗效果[20]。基于树突状细胞具备的强大抗原呈递能力, DCs疫苗是直接将肿瘤相关抗原导入树突状细胞再回输到病人体内, 使其在体内呈递肿瘤抗原以诱导肿瘤抗原特异性的免疫反应, 是一种有效的肿瘤免疫途径。美国食品药品监督局(Food and Drug Administration, FDA)于2010年批准的前列腺癌疫苗Sipuleucel-T就是一种利用表达前列腺癌抗原前列腺酸性磷酸酶(prostatic acid phosphatase, PAP)的树突状细胞回输患者的细胞疫苗。

在临床试验中, 基于患者自体肿瘤细胞的细胞疫苗往往未表现出有效的抗肿瘤效果, 一种可能的解释为肿瘤细胞或者肿瘤组织裂解物中包含了免疫抑制因子, 对肿瘤抗原引起的免疫反应产生了负面影响[21-22]。因此, 为了增强肿瘤细胞疫苗疗效, 可通过增加肿瘤细胞的免疫原性以提高疫苗的免疫效果。例如, 在肿瘤细胞中表达能促进T细胞存活和记忆T细胞形成的白细胞介素-7(interleukin-7, IL-7)可以促进肿瘤细胞疫苗诱导的$CD8^+$ T细胞抗肿瘤免疫反应[23-24]。此外, 通过不同途径诱导肿瘤的免疫原性死亡也是提高肿瘤细胞疫苗免疫原性的有效方式[25]。有报道称, 溶瘤腺病毒可以通过诱导结肠癌细胞发生免疫原性死亡而增强肿瘤细胞疫苗的免疫效果[26]。肿瘤细胞疫苗与免疫检查点抑制剂如阻断程序性细胞死亡受体1(programmed death-1, PD-1), 细胞毒性T淋巴细胞相关蛋白-4(cytotoxic T lymphocyte-associated antigen-4, CTLA-4)的抗体联合使用也可以显著提高细胞疫苗的疗效[27]。全肿瘤细胞癌症疫苗已进行多项临床试验, 其中一种全肿瘤细胞癌症疫苗GVAX, 由经过基因修饰可表达分泌粒细胞–巨噬细胞集落刺激因子(granulocyte-macrophage colony-stimulating factor, GM-CSF)的胰腺癌细胞系经过辐照制备而成, 在胰腺癌中展现出了一定的临床治疗效果[28-29]。Vigil也是一种来源于肿瘤组织的自体肿瘤细胞疫苗, 在针对晚期卵巢癌患者的II期临床研究结果显示, 与安慰剂组患者相比, 接种疫苗组患者的无复发生存期由8.4个月延长至11.5个月[30]。

树突状细胞作为联接固有免疫系统和适应性免疫系统的桥梁, 可以通过多种机制摄取和呈递肿瘤抗原, 从而引发针对肿瘤的特异性免疫反应。树突状细胞装载的抗原通常来自肿瘤细胞裂解物或肿瘤来源的mRNA、特异性的TAA抗原或编码TAA的mRNA, 甚至整个肿瘤细胞[31]。除了抗原呈递功能外, DCs也具备在淋巴组织和非淋巴组织之间迁移的能力, 能通过分泌细胞因子和趋化因子来控制炎症和影响淋巴细胞归巢, 对长期的抗肿瘤免疫反应有重要影响[32]。大多数树突状细胞疫苗临床试验

中使用离体的单核细胞衍生树突状细胞(monocyte-derived dendritic cells, moDCs)[33], 这些细胞主要由前体单核细胞响应刺激分化而来。虽然通过GM-CSF和IL-4诱导处理可以从外周血中获取大量moDCs[34], 但广泛的疫苗接种研究表明, 临床试验中大多数患者对moDCs疫苗的响应程度不大, 这可能与离体的moDCs发育不健全、淋巴结迁移能力差、激活T细胞效果弱等因素有关[35-36]。体内自然产生的DCs能表达更高水平的MHC分子和趋化因子, 具有更强的抗原提呈和T细胞激活能力, 也可用于树突状细胞疫苗[37-38]。除了moDCs外, 自然产生的DCs还包括经典的DCs(conventional DCs, cDCs)和浆细胞样DCs(plasmacytoid DCs, pDCs)。cDCs中的cDC1细胞亚群具备强大的交叉呈递抗原功能, 对于抗肿瘤免疫反应有重要影响[39]。此外, cDC1还通过表达IFNs、C-X-C基序趋化因子配体9(C-X-C motif chemokine ligand 9, CXCL9)和CXCL10来促进肿瘤中T细胞的浸润[38]。有趣的是, pDCs在病毒感染或疫苗干预后能产生大量I型IFNs, 可以促进cDC1的成熟[32,40]。因此, 这两种DCs亚群细胞联合使用可能具有协同作用[41]。以FMS样酪氨酸激酶3配体(FMS-like tyrosine kinase 3 ligand, FLT3L)处理小鼠骨髓细胞或人的造血干细胞能诱导分化出DCs[42-43], 产生类似于pDC、cDC1和cDC2的细胞亚群, 可以获得足够的DCs以用于制备DCs肿瘤疫苗。此外, 为了进一步提高疫苗的免疫疗效, 树突状细胞疫苗也可以与免疫佐剂、细胞因子等联合使用, 或通过基因编辑改善DCs的功能[44-45]。表1中为部分树突状细胞癌症疫苗的临床试验以及进展, 绝大部分仍然处于临床I期试验。

### 2.2 基于病毒的肿瘤疫苗

基于病毒的肿瘤疫苗具备可以使固有免疫和适应性免疫协同工作以实现有效、持久的免疫反应的优点。基于病毒的肿瘤疫苗分为三种形式: 灭活、减毒或亚单位的致癌病毒疫苗, 溶瘤病毒疫苗和其他病毒载体疫苗。据报道, 大约12%的癌症由病毒感染引起, 其中EB病毒(epstein-barr virus, EBV)、乙肝病毒、丙型肝炎病毒和HPV是常见的癌症相关病毒[46]。病毒灭活疫苗已在包括新型冠状病毒(coronavirus disease 2019, COVID-19)、埃博拉病毒感染等疾病的治疗方面显示出良好的疗效[47-48]。溶瘤病毒疗法能够作为一种新型的肿瘤免疫疗法, 在杀死肿瘤细胞的同时促进抗肿瘤免疫反应。肿瘤细胞被溶瘤病毒感染后, 会产生活性氧(reactive oxygen species, ROS)和细胞因子如IFNs, 促进DCs的成熟并刺激$CD8^+$ T细胞和自然杀伤细胞(natural killer cells, NK细胞); 随后肿瘤细胞裂解, 释放TAA, 从而促进肿瘤抗原特异性免疫反应的产生[49]。包括单纯疱疹病毒、腺病毒、麻疹病毒、牛痘病毒、水疱性口炎病毒等溶瘤病毒的抗肿瘤作用已在多项临床试验中得到证实[50]。溶瘤病毒药物T-VEC(Talimogene Laherparepvec), 是被广泛关注的第一代重组单纯疱疹病毒产品, 用于治疗不可切除的转移性黑色素瘤[51]。瘤内直接注射T-VEC, 能克服血液降低病毒滴度和机体可能中和病毒的缺陷, 诱导肿瘤细胞裂解并促进针对肿瘤远端转移灶的抗肿瘤免疫反应[52-54]。一项T-VEC与新辅助化疗(neoadjuvant chemotherapy, NAC)的II期临床试验表明, T-VEC可以促进三阴性乳腺癌患者对NAC治疗的响应, 使三阴性乳腺癌的治疗取得了令人鼓舞的效果, 2年内无复发的患者比例为89%[55]。除单纯疱疹病毒外, 腺病毒是另一种常用的溶瘤病毒, 它也常被用作基因编辑的载体[56]。腺病毒易于制备, 也常被用于实现基因转导和肿瘤抗原表达。基于腺病毒的癌症疫苗已经在临床前和临床试验中显示出较好的前景[57]。此外, 其他病毒载体如痘苗病毒、慢病毒、腺相关病毒也被用于制备肿瘤疫苗, 其中慢病毒和腺相关病毒具备与腺病毒相似的、能在非分裂细胞中稳定长期表达基因的特性[58-60]。表2中列举了部分病毒相关肿瘤疫苗的临床试验及进展。

### 2.3 基于多肽的肿瘤疫苗

目前, 基于多肽的疫苗是肿瘤疫苗研究领域的热点方向, 这类肿瘤疫苗能作为一种有效的肿瘤免疫治疗方式而在临床试验中取得较好的治疗效果[61]。多肽疫苗中肿瘤抗原是已知或预测的肿瘤抗原表位肽。不过多肽疫苗中抗原肽的免疫原性通常较弱, 很难直接引起强烈的免疫反应并存在免疫耐受的风险。因此, 多肽肿瘤疫苗通常需要加入佐剂以增强多肽抗原引起的免疫反应。与灭活肿瘤细胞疫苗相比, 多肽疫苗能有针对性地引起肿瘤抗原表位肽特异的免疫反应[62]。多肽抗原中存在的抗原表位肽能通过激活细胞毒T淋巴细胞(cytotoxic T lymphocytes, CTLs)和$CD4^+$ T细胞表面特异性受体来激发有效的抗肿瘤免疫反应[63]。

结合MHC-I的肿瘤抗原表位肽通常由8~10个

表1 部分基于树突状细胞肿瘤疫苗的临床试验

Table 1 Selected Dendritic cell-based cancer vaccine trials

| 临床试验注册号 NCT number | 项目名称 Study title | 研究状态 Study status | 入组条件 Conditions | 阶段 Phase |
|---|---|---|---|---|
| NCT05767684 | Neoantigen derived DCs as cancer treatment | Recruiting | Refractory tumor\|solid tumor | Phase I |
| NCT04963413 | RENEW: feasibility of CMV RNA-pulsed dendritic Cells vaccines for the treatment of newly diagnosed glioblastoma patients | Active not recruiting | Glioblastoma | Phase I |
| NCT05882305 | KSD-101 therapy for EBV-associated lymphomas: an exploratory clinical trial | Enrolling by invitation | EBV-associated lymphomas | Early phase I |
| NCT05000801 | Clinical study of DC-AML cells in the treatment of acute myeloid leukemia | Recruiting | Acute myeloid leukemia | NA |
| NCT05635591 | KSD-101 therapy for EBV-associated haematologic neoplasms: an exploratory clinical trial | Enrolling by invitation | EBV-associated haematologic neoplasms | Phase I |
| NCT05317325 | A translational study of tumor antigen-pulsed DC vaccine for ESCC | Not yet recruiting | Esophageal squamous cell carcinoma | Phase I |
| NCT06097793 | KSD-101 therapy for EBV-associated nasopharyngeal carcinoma: an exploratory clinical trial | Not yet recruiting | Nasopharyngeal carcinoma | Early phase I |
| NCT05631886 | Combination of CAR-DC vaccine and ICIs in malignant tumors | Recruiting | Solid tumor, adult\|lymphoma\|EphA2 overexpression\|TP53 R273H\|TP53 R175H\|TP53 R248Q\|TP53 R249S | Phase I |
| NCT05504707 | DecipHER trial - DC1 Tx for early-stage TNBC and ER low positive breast cancer | Suspended | Triple negative breast cancer\|HER2-negative breast cancer | Phase I |
| NCT05631899 | Combination of CAR-DC vaccine and ICIs in local advanced/Metastatic solid tumors | Recruiting | Solid tumor, adult\|EphA2 Overexpression\|KRAS G12V\|KRAS G12C\|KRAS G12D | Phase I |

NA指没有明确的FDA分期信息的临床试验，包括医疗器械或者行为干预的临床试验。

NA (not applicable) is used to describe trials without FDA-defined phases, including trials of devices or behavioral interventions.

表2 部分病毒相关肿瘤疫苗的临床试验

Table 2 Selected virus-associated cancer vaccine trials

| 临床试验注册号 NCT number | 项目名称 Study title | 研究状态 Study status | 入组条件 Conditions | 阶段 Phase |
|---|---|---|---|---|
| NCT03131765 | Dose escalation and cohort expansion study of YS-ON-001 in patients with advanced solid tumors | Recruiting | Cancer | Phase I |
| NCT04410874 | Imvamune vaccine for the treatment of non-melanoma skin cancer | Unknown | Non-melanoma skin cancer\|basal cell carcinoma\|squamous cell carcinoma | Phase I\|phase II |
| NCT05262010 | A phase III clinical trial of a 11-valent recombinant human papillomavirus vaccine (hansenula-polymorpha) in Chinese women aged 9-45 years | Recruiting | HPV infection\|HPV-related carcinoma | Phase III |
| NCT05334706 | A study to assess the reduction of human papillomavirus (HPV) viral infectivity and transmission in HPV-positive women after vaccination with 9vHPV (RIFT-HPV) | Recruiting | Cervical intraepithelial neoplasia grade I/II/III (CIN I/II/III)\|human papillomavirus (HPV) infections\|high-risk HPV\|HPV-16/18 | Phase II |
| NCT03947775 | HPV-SAVE merck sub-study for preventing recurrence of HSIL | Not yet recruiting | Anal intraepithelial neoplasia\|anal cancer\|human papilloma virus | Phase II |

氨基酸构成, 但短肽的免疫原性并不高, 而且可能非特异性结合到非抗原呈递细胞上, 因此目前的研究倾向于使用免疫原性更高的合成长肽制备肿瘤疫苗。与短肽相比, 长肽可以有效地将抗原递送至APCs如DCs, 并避免低免疫原性表位肽带来的潜在免疫耐受[64]。携带肿瘤抗原的长肽被细胞内化后, 一部分可以通过内体途径被降解, 从而装载到MHC-II分子上形成MHC-多肽复合物, 然后被$CD4^+$ T辅助细胞识别; 另一部分也可以进入细胞质或吞噬泡途径, 由MHC-I分子进行交叉呈递, 进一步激活$CD8^+$ T

表3 部分多肽肿瘤疫苗的临床试验

Table 3 Selected peptide-based cancer vaccine trials

| 临床试验注册号<br>NCT number | 项目名称<br>Study title | 研究状态<br>Study status | 入组条件<br>Conditions | 阶段<br>Phase |
|---|---|---|---|---|
| NCT05475106 | Pilot study of neoantigen peptides and leukine for the treatment of neoplasms | Recruiting | Neoplasms | Early phase I |
| NCT05013216 | Mutant KRAS -targeted long peptide vaccine for patients at high risk of developing pancreatic cancer | Recruiting | High risk cancer\|pancreatic cancer | Phase I |
| NCT05741242 | Basket trial of neoantigen synthetic long peptide vaccines in patients with advanced malignancy | Enrolling by invitation | Cancer\|solid tumor | Phase I\|phase II |
| NCT05950139 | Prophylactic cancer peptide vaccine in advanced ALK+ NSCLC | Not yet recruiting | NSCLC stage IV\|ALK fusion protein expression | Phase I\|phase II |
| NCT05025488 | Mutant CALR-peptide based vaccine in patients with mutated CALR myeloproliferative neoplasm | Recruiting | Myelofibrosis\|essential thrombocythemia\|MPN | Phase I |
| NCT05749627 | Using neoantigen peptide vaccine/neoantigen-based DC to treat advanced malignant solid tumors | Recruiting | Advanced malignant solid tumors | NA |
| NCT05283109 | ETAPA I: peptide-based tumor associated antigen vaccine in GBM | Recruiting | Glioma, malignant | Phase I |
| NCT04749641 | Neoantigen vaccine therapy against H3.3-K27M diffuse intrinsic pontine glioma | Recruiting | Diffuse intrinsic pontine glioma | Phase I |
| NCT05843448 | IDO and PD-L1 peptide based immune-modulatory therapeutic (IO102-IO103) in combination with pembrolizumab for BCG-unresponsive or intolerant, non-muscle invasive bladder cancer | Recruiting | High risk non-muscle invasive bladder urothelial carcinoma\|stage 0a bladder cancer AJCC v8\|stage 0is bladder cancer AJCC v8\|stage I bladder cancer AJCC v8 | Phase I |
| NCT05609994 | ViCToRy: vorasidenib in combination with tumor specific peptide vaccine for recurrent IDH1 mutant lower grade gliomas | Not yet recruiting | Low grade glioma of brain | Phase I |
| NCT05721846 | Nivolumab with ipilimumab combined with TGF-15 peptide vaccine and radiotherapy for pancreatic cancer | Recruiting | Pancreatic cancer | Phase I |
| NCT04688385 | Personalized multi-peptide vaccination in CLL patients | Recruiting | Chronic lymphocytic leukemia | Phase I |
| NCT06095934 | Efficacy and safety of neoantigen peptide vaccine in the treatment of advanced NSCLC progressed after EGFR-TKI treatment | Recruiting | NSCLC\|EGFR gene mutation | NA |

NA指没有明确的FDA分期信息的临床试验，包括医疗器械或者行为干预的临床试验。

NA (not applicable) is used to describe trials without FDA-defined phases, including trials of devices or behavioral interventions.

细胞应答[65]。因此, 长肽肿瘤疫苗更有可能诱导持续有效的抗肿瘤活性反应。在一项II期临床试验中, 合成长肽疫苗ISA101与抗PD-1抗体Nivolumab联合治疗对HPV-16阳性的宫颈癌患者表现出良好的治疗效果, 患者对联合疗法的响应率达到33%, 中位总生存期由9.1个月延长为至少17.5个月[66]。此外, 针对HPV-16阳性宫颈癌患者 ($n$=77)进行的ISA101联合标准化疗的I/II期研究表明, ISA101诱导了更强的抗原特异性 T细胞应答[67]。表3中列举了部分基于多肽的癌症疫苗临床试验, 大部分为临床I期, 也有临床II期的试验在开展。

## 2.4 DNA肿瘤疫苗

肿瘤DNA疫苗的肿瘤抗原载体主要是能编码一种或多种肿瘤抗原的质粒, 可诱导固有免疫激活和适应性免疫反应。当DNA疫苗通过注射方式进入机体内后, 疫苗中DNA在APCs细胞内发生转录、翻译, 产生对应的肿瘤抗原, 抗原能通过直接呈递[68]、分泌[69]或凋亡小体[70]等途径加载到MHC-I和MHC-II分子上, 再呈递给$CD8^+$ T和$CD4^+$ T细胞, 进而激活特异性免疫反应。此外, 质粒DNA作为外源物质, 其双链结构可以激活细胞内核酸受体感应信号通路, 诱发固有免疫反应[71]; 而其携带的CpG寡核苷酸序列也可以触发TLR9信号通路, 诱导趋化因子和炎症因子如CXCL10和IL-6的产生, 从而促进疫苗免疫效果[72]。

尽管DNA肿瘤疫苗的相关研究由来已久, 但目前只有少数临床试验证明了DNA疫苗的治疗效果。

在一项编码黑色素瘤相关抗原melan A和gp100的DNA疫苗治疗黑色素瘤患者的临床I/II期试验中, 研究人员将编码抗原的DNA转入moDCs, 并使用炎症因子TNF-α和IL-1β刺激诱导DCs成熟后再对患者进行接种。尽管治疗后在患者体内检测到了抗原特异性T细胞反应, 但实际的患者临床响应率仅为10%, 并且没有产生有效的免疫记忆[73]。值得一提的是, 大多数通过APCs起作用的DNA肿瘤疫苗的临床治疗效果都不够理想, 改善DNA疫苗的设计可能会提高疫苗的效果, 如对DNA表达元件和质粒载体大小的优化能提高抗原转染和表达效率[74], 提高DNA的核转位效率也有助于抗原表达[75], 与佐剂联合使用也可以进一步提升DNA疫苗的免疫原性[76]。在临床试验中, VGX-310是一种针对HPV的DNA疫苗, 近期其治疗宫颈癌前病变的首个III期试验(NCT03185013)取得了积极的治疗结果, 能够引起更高的细胞免疫反应, 降低病人的宫颈切除率; 并且病人在完成治疗后18个月内体内都检测不到HPV16/18病毒[77]。表4中列举了基于DNA肿瘤疫苗的部分处于临床I期和II期试验。

### 2.5 mRNA肿瘤疫苗

近年来, 针对新型冠状病毒COVID-19的mRNA疫苗的巨大成功引起了人们对mRNA疫苗的广泛关注。mRNA疫苗通过将外源合成的mRNA转入到细胞内作为抗原表达的模板, 通过细胞内源的蛋白翻译机制来产生抗原蛋白, 再经过抗原呈递活化T细胞和B细胞来对抗外源病原或者肿瘤[78]。mRNA疫苗技术在问世之初就被用于肿瘤疫苗开发, 然而, 早期的mRNA疫苗受限于mRNA易降解和在体内表达效率低的技术障碍。随着mRNA技术的不断发展, mRNA疫苗的短板如mRNA分子易降解、mRNA递送效率低、免疫原性过强等缺陷正逐渐改善。通过对mRNA疫苗各组分的优化, 可以提高mRNA分子的稳定性和表达效率[79]。2005年, KARIKÓ等[80]发现将假尿苷引入mRNA可以避免宿主细胞对外源mRNA的免疫识别。2008年, KARIKÓ等[81]进一步发现用假尿苷完全替代尿苷的mRNA不仅降低了mRNA的免疫原性, 还可以提高mRNA的稳定性并增强其翻译能力。而去除mRNA分子的非翻译区(untranslated regions, UTR)中高度稳定的二级结构有助于mRNA分子招募核糖体, 从而提高翻译效率[82]。mRNA分子的开放阅读框(open reading frame, ORF)区域密码子的优化对翻译效率也有明显的调节作用, 改变GC含量、替换稀有密码子、避免发夹环等都可以提高翻译效率[83]。含约20%的胞嘧啶的3′端尾部可以帮助mRNA分子不受腺苷酸酶的影响, 并显著提高体内外mRNA的翻译效率、延长mRNA的半衰期[84]。基于RNA的其他载体分子如自我复制的RNA[85]、环状RNA(circular RNAs, circRNA)[86]的应用也显著提高了RNA的稳定性。近期的一项研究开发了一种将短双链RNA(double-stranded RNA, dsRNA)装载到线性mRNA上融合的梳齿状RNA, 可以通过改变dsRNA的长度、序列及数量来控制佐剂效应, 以提高疫苗的安全性和效果[87]。

mRNA疫苗需要能够高效、定向递送mRNA的载体系统[88]。其中脂质纳米颗粒(lipid nanoparticles, LNPs)系统相比其他传统递送载体在生产、免疫原性、避免体内毒性及负载mRNA效率等方面更具优势。另外, LNPs递送系统的发展正被逐步扩展到选择性器官靶向领域, 如LNPs可以将mRNA靶向递送至肝脏以外的其他器官[89-90]。通过调整mRNA疫苗的纳米颗粒大小和表面电荷情况, BioNTech公司开发了一种靶向脾脏的Lipoplex纳米载体, 用于mRNA肿瘤疫苗的递送[40]。甘露糖修饰的LNPs可以通过与细胞膜表面甘露糖受体CD206结合从而靶向APCs[91]。但如何实现mRNA快速、精确且高效的递送仍然是现阶段LNPs递送系统研究的重点和难点问题。此外, LNPs的安全性、免疫刺激作用和对机体代谢的影响等方面也需要更多的研究数据来支撑。基于LNPs递送技术的发展和利用修饰的碱基合成mRNA避免体内抗病毒反应的关键发现, mRNA疫苗最终在预防新冠病毒的应用上取得突破, 快速获得临床批准。对该领域做出革命性贡献的科学家Katalin KARIKÓ和Drew WEISSMAN也获得了2023年诺贝尔生理学和医学奖。

随着测序技术的发展, 通过识别个体肿瘤基因组外显子存在的突变、mRNA异常转录和翻译事件来预测肿瘤特异性新抗原已成为可能[92-94]。肿瘤新抗原具有高度的肿瘤特异性和免疫原性, 对肿瘤疫苗的免疫效果有着决定性影响。目前, 已经有多种基于个性化肿瘤新抗原的mRNA肿瘤疫苗正在进行临床试验, 如表达多个黑色素瘤抗原的mRNA疫苗mRNA-4157联合PD1抗体派姆单抗(pembrolizumab)治疗黑色素瘤患者已进入III期临床试验; 与单独接受派姆单抗治疗的患者相比, 接受mRNA-4157联合

派姆单抗治疗的患者在无复发生存方面的死亡或复发风险降低了约44%[95], 是已知第一个进入III期临床试验的mRNA肿瘤疫苗。此外, BioNTech公司近期也有报道, 利用一种编码CLDN6抗原的mRNA疫苗可以增强Claudin-CAR- T细胞对实体肿瘤的杀伤效果[96]。表5中列举了近3年基于mRNA的部分肿瘤

**表4 部分DNA肿瘤疫苗的临床试验**

**Table 4 Selected DNA-based cancer vaccine trials**

| 临床试验注册号<br>NCT number | 项目名称<br>Study title | 研究状态<br>Study status | 入组条件<br>Conditions | 阶段<br>Phase |
|---|---|---|---|---|
| NCT05743595 | Neoantigen-based personalized DNA vaccine with retifanlimab PD-1 blockade therapy in patients with newly diagnosed, unmethylated glioblastoma | Not yet recruiting | Unmethylated glioblastoma | Phase I |
| NCT06088459 | NWRD06 DNA plasmid for HCC after radical resection | Recruiting | Hepatocellular carcinoma | Phase I |
| NCT03988283 | Neoepitope-based personalized DNA vaccine approach in pediatric patients with recurrent brain tumors | Not yet recruiting | Pediatric recurrent brain tumor | Phase I |
| NCT05455658 | STEMVAC in patients with early stage triple negative breast cancer | Recruiting | Breast cancer \|triple-negative breast carcinoma | Phase II |
| NCT05242965 | A multiple antigen vaccine (stemvac) for the treatment of patients with stage IV non-squamous non-small cell lung cancer | Recruiting | Lung non-squamous non-small cell carcinoma\|stage IV lung cancer AJCC v8 | Phase II |

**表5 部分mRNA肿瘤疫苗的临床试验**

**Table 5 Selected mRNA-based cancer vaccine trials**

| 临床试验注册号<br>NCT number | 项目名称<br>Study title | 研究状态<br>Study status | 入组条件<br>Conditions | 阶段<br>Phase |
|---|---|---|---|---|
| NCT05714748 | Application of mRNA immunotherapy technology in epstein-barr virus-related refractory malignant tumors | Recruiting | Malignant tumors | Phase I |
| NCT05456165 | Study of an individualized vaccine targeting neoantigens in combination with immune checkpoint blockade for patients with colon cancer | TERMINATED | Colonic neoplasms\|colorectal neoplasms | Phase II |
| NCT05938387 | Safety and tolerability of CVGBM in adults with newly diagnosed MGMT-unmethylated glioblastoma or astrocytoma | Recruiting | Glioblastoma | Phase I |
| NCT05949775 | Clinical study of mRNA vaccine in patients with advanced malignant solid tumors | Not yet recruiting | Advanced malignant solid tumors | NA |
| NCT05016622 | Booster dose trial | Recruiting | Cancer | Phase II |
| NCT05981066 | A clinical study of mRNA vaccine (ABOR2014/IPM511) in patients with advanced hepatocellular carcinoma | Recruiting | Advanced hepatocellular carcinoma | NA |
| NCT05799612 | Phase I study of TH1 dendritic cell immunotherapy for the treatment of cutaneous angiosarcoma | Not yet recruiting | Angiosarcoma | Phase I |
| NCT05192460 | Safety and efficacy of personalized neoantigen vaccine in advanced gastric cancer, esophageal cancer and liver cancer | Recruiting | Gastric cancer\|esophageal Cancer\|liver cancer | NA |
| NCT05660408 | Study of RNA-LP (RNA-lipid particle) vaccines for recurrent pulmonary OSA (osteosarcoma) | Not yet recruiting | Pulmonary osteosarcoma | Phase I\|phase II |
| NCT05761717 | Clinical study of mRNA vaccine in patients with liver cancer after operation | Not yet recruiting | Posto perative hepatocellular carcinoma | NA |
| NCT05359354 | Safety and efficacy of personalized neoantigen vaccine in advanced solid tumors | Recruiting | Solid tumor | NA |
| NCT06019702 | Clinical study of personalized mRNA vaccine encoding neoantigen alone in subjects with advanced digestive system neoplasms | Recruiting | Digestive system neoplasms | Phase I |
| NCT05942378 | A study of HRXG-K-1939 and adebrelimab in patients with advanced solid tumors | Not yet recruiting | Advanced solid tumors | Phase I |
| NCT06026774 | Clinical study of personalized mRNA vaccine encoding neoantigen in subjects with resected digestive system neoplasms | Recruiting | Digestive system neoplasms | Phase I |

NA指没有明确的FDA分期信息的临床试验，包括医疗器械或者行为干预的临床试验。

NA (not applicable) is used to describe trials without FDA-defined phases, including trials of devices or behavioral interventions.

疫苗临床试验。总的来说, mRNA肿瘤疫苗是一种前景光明的癌症免疫疗法。

## 3 总结与展望

癌症疫苗是一种前景光明的肿瘤免疫治疗方案, 能诱导机体产生肿瘤抗原特异性的免疫应答和记忆, 对肿瘤的预防与治疗有着巨大的临床应用价值。本综述总结了癌症疫苗的作用机制, 介绍了癌症疫苗的分类、基础研究与临床试验进展, 并总结了不同肿瘤疫苗的优缺点(表6), 希望为理解和开发应用癌症疫苗提供有意义的参考。尽管癌症疫苗的研究由来已久, 但目前临床上仅有少数肿瘤疫苗获得批准使用, 大部分肿瘤疫苗仍处于I/II期临床试验阶段(图3)。如何提高疫苗的治疗效果和适用的肿瘤类型仍然是领域内的难点问题。近年来, 伴随着测序技术的进步, 快速分析并合成针对患者个体特异性的肿瘤新抗原的过程也逐渐成熟, 使得基于肿瘤新抗原的肿瘤疫苗成为领域内的一个重要发展方向。此外, 联合其他疗法如免疫检查点抑制剂等免疫疗法, 以及结合mRNA疫苗技术, 也有望提高癌症疫苗的治疗肿瘤效果, 值得未来更多的研究探索。

**表6 不同肿瘤疫苗的优缺点对比**

**Table 6 The advantages and disadvantages of different cancer vaccines**

| 肿瘤疫苗类型<br>Types of cancer vaccines | 优点<br>Advantages | 缺点<br>Disadvantages |
|---|---|---|
| Whole-tumor-cell vaccines | (1) incorporates the complete spectrum of tumor cell antigens; (2) provokes immune responses against multiple specific antigens; (3) allows for personalization according to the patient's tumor characteristics | (1) requires a sample of the patient's tumor; (2) not suitable for patients from whom adequate tumor tissue cannot be obtained; (3) carries potential risks associated with using entire tumor cells; (4) some patients may not mount an effective immune response |
| Dendritic cell vaccines | (1) customizable based on individual patient tumor features; (2) efficiently activates T cells, eliciting a vigorous immune response; (3) utilizes the patient's own dendritic cells, with a low risk of side effects; (4) provides broad immune protection against multiple antigens | (1) complex and costly preparation; (2) heavily dependent on the patient's intrinsic immune system; (3) limited applicability |
| Viral vector vaccines | (1) rich clinical experience supports rapid optimization of vaccine design; (2) effective for a variety of infectious and non-infectious diseases; (3) induces long-term immune memory | (1) complete viral vectors may pose certain risks; (2) previous exposure to the viral vector may cause an immune response, reducing vaccine efficacy; (3) complex production process |
| Peptide vaccines | (1) precisely targets specific antigens, minimizing non-specific reactions; (2) lacks live pathogens, is degradable, thus safer; (3) no requirement for a cell culture system, enabling simple and rapid production; (4) can enhance immune activation when used with adjuvants or other immunotherapies | (1) peptide segments alone cannot induce a strong immune response; require use with adjuvants or carriers; (2) targets only specific peptide segments, not all antigens; (3) vaccine response may vary significantly among individuals |
| DNA vaccines | (1) more stable than mRNA vaccines, without the need for stringent storage conditions; (2) sustained expression can lead to long-term immune memory; (3) applicable to a variety of infectious and non-infectious diseases; (4) comparatively simple production and lower costs | (1) DNA must translocate into the host cell nucleus, potentially limiting efficiency; (2) potential risk of genomic integration of DNA.<br>Induces a relatively weak immune response; (3) slower clinical advancement without large-scale clinical applications |
| mRNA vaccines | (1) rapid development; (2) no risk of integration into the host genome; (3) activates both humoral and cellular immunity effectively; (4) simplified production process allows for rapid, mass production; (5) facilitates personalized treatment for cancer; (6) capable of encoding multiple tumor antigens concurrently | (1) relative instability necessitates cold chain logistics; (2) potential immune responses to the mrna or its delivery system; (3) technical challenges in synthesizing high-quality mRNA |

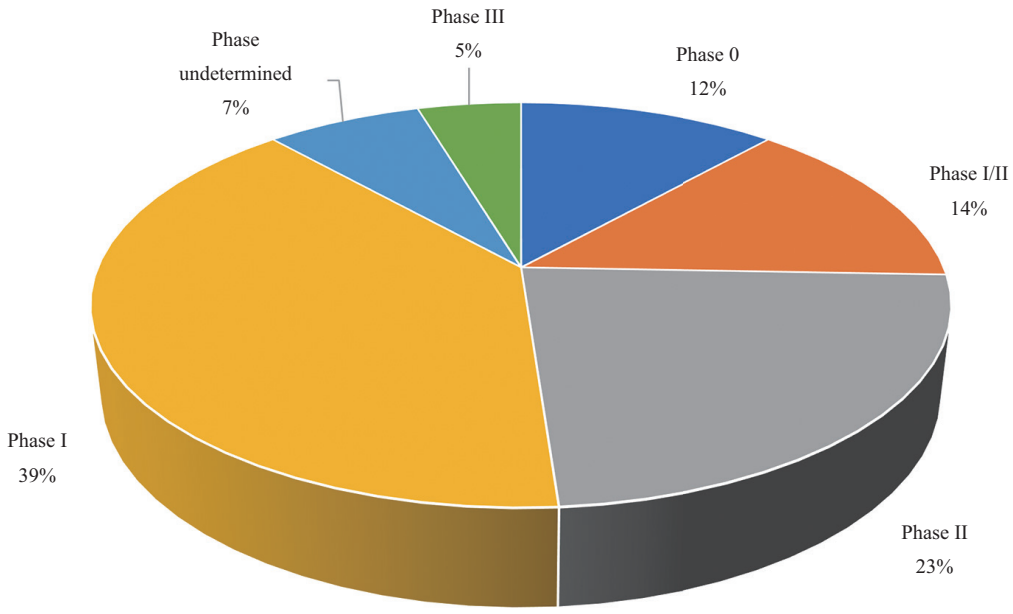


**图3 肿瘤疫苗临床试验阶段分布**

**Fig.3 The current status of tumor vaccine clinical trials**

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