



目前，恶性肿瘤免疫疗法还处于初期，但存在巨大潜力

恶性肿瘤免疫疗法—— 真将成为“变革者”吗？

您知道吗？

1,375

项涉及恶性肿瘤免疫疗法的试验在 clinicaltrials.gov 网站¹上发布

介绍

通常，恶性肿瘤的治疗方法包括手术、化学疗法或者放射疗法。然而，通过应用一种被称为免疫疗法的治疗方法，已产生出一些令人振奋的突破。这一疗法已很好地应用于诸如风湿性关节炎、过敏性哮喘等一些其他疾病的治疗当中。许多资料目前都将免疫疗法喻为治疗恶性肿瘤的“变革者”^{2,3} 我们将就此展开讨论。

¹ See <https://clinicaltrials.gov/ct2/results?term=cancer+immunotherapy>; accessed 25 July 2017

² See BBC health; 9 October 2016; 'Immunotherapy cancer drug hailed as 'game changer'; <http://www.bbc.com/news/health-37588541>

³ See Ravulapati S, MD, et al.; 'Immunotherapy in Squamous Cell Skin Carcinoma: A Game Changer?'; © 2017 Elsevier; [http://www.amjmed.com/article/S0002-9343\(17\)30011-6/fulltext](http://www.amjmed.com/article/S0002-9343(17)30011-6/fulltext)

免疫疗法不只是一种治疗，而是利用免疫系统抗击疾病的许多种治疗方法的总称。恶性肿瘤是一种顽疾，它可以逃避、或者利用免疫系统生长甚至扩散。就像识别细菌或病毒那样，免疫疗法可以激发免疫系统对恶性肿瘤发起攻击。

发展史

恶性肿瘤免疫疗法发展成为一种可选治疗方法最早可追溯至 19 世纪，美国医生威廉·B·科利 (William B Coley) 向肿瘤注射活的灭毒细菌 (科利毒素) 以激发免疫系统应答、攻击肿瘤细胞。不幸的是，科利毒素的作用机理尚未被理解透彻，许多患者因治疗反应而死亡。随着手术、放射疗法以及化学疗法最终成为治疗恶性肿瘤的标准，科利毒素逐渐被人淡忘。

进入 20 世纪以后，T 细胞 (免疫系统的一部分) 被发现可以直接攻击肿瘤细胞、以及受细菌或病毒感染的细胞。20 世纪 70 年代，重组白介素-2 被发现有助于 T 细胞的产生。这一发现在针对转移性恶性肿瘤⁴ 的治疗中显现出效果。但直到 1997 年，首例单克隆抗体才被美国 FDA 批准用于治疗恶性肿瘤、非霍奇金淋巴瘤⁵。

⁴ See Rosenberg SA, et al. Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. *N Engl J Med.* 1985;313(23):1485-1492

⁵ See Targeted Oncology; 21 August 2014; 'A Brief History of Immunotherapy'; <http://www.targetedonc.com/publications/special-reports/2014/immunotherapy-issue3/a-brief-history-of-immunotherapy>

在最近的十年中，关于分子学路径及其伴随基因信号功能的认识获得重大进展。这使得针对不同恶性肿瘤的多种更为有效的新免疫疗法得以发展。

恶性肿瘤免疫疗法的种类

单克隆抗体

这些人造的抗体由一种抗体的多个拷贝组成，可以通过多种不同的方式⁶起作用：

1. **粘附**：他们拥有粘附于特定肿瘤细胞的能力，协助免疫系统识别肿瘤细胞、并发动攻击。
2. **封闭**：免疫系统通过检查位点分子发挥作用，阻止健康细胞过度活跃和损伤。一些肿瘤细胞可以产生大量的这类分子受体，导致免疫系统中攻击恶性肿瘤的 T 细胞被抑止。单克隆抗体可以封闭检查位点的分子受体，包括 PD-1、PD-L1 和 CTLA-4。他们还可以封闭肿瘤细胞赖以生存和分裂增殖的生长因子受体分子。
3. **运载**：他们可以运载特异性杀灭恶性肿瘤的药物或放射物质直接作用于肿瘤细胞。

肿瘤疫苗⁷

疫苗通常被认为可以保护人体免患疾病，事实上已有疫苗被应用于预防特定病毒⁸ 所致的恶性肿瘤。不过同样也存在免疫疗法疫苗，可以协助免疫系统对已被确诊的恶性肿瘤进行应答。当这些疫苗被注射入人体后，它们所含有的抗原可以激活 T 细胞、或产生出靶定恶性肿瘤的抗体。

溶瘤病毒疗法⁹

这一疗法是将转基因病毒注射进肿瘤。病毒一旦进入肿瘤细胞，它就会开始自我复制致使细胞破裂或凋亡。此时释放出抗原，进一步激活免疫系统反应。体内任何包含有相同抗原的肿瘤细胞都会被靶定，健康细胞得以留存。

其他非特异性免疫疗法¹⁰

非特异性免疫疗法虽然不特定靶向肿瘤细胞，但仍可以单独应用或者作为增强免疫系统抗击恶性肿瘤其他疗法的补充。

伴随诊断

治疗仅仅是患者整体护理当中的一部分。现在，医学专家们使用伴随诊断设备（体外或成像工具）获取信息并应用于诸如免疫疗法等的治疗方法，安全而有效地防范潜在风险或副作用。这些设备和工具可用于恶性肿瘤治疗的所有阶段，通过识别往后有可能因治疗的受益或受害、并监测反应，进行各种调整以便尝试提升效果¹¹。

乐观的理由

据报道，那些看似无法治愈的恶性肿瘤患者已得到完全缓解¹²。目前针对多种恶性肿瘤的免疫疗法已经获得批准、或正处于评估当中^{13,14}。这些令人振奋的免疫疗法举措在 2016 年被美国临床肿瘤学协会（ASCO）评为“年度进步”¹⁵。研究人员还在研究是否使用免疫疗法结合手术或放疗治愈更多早期的疾病患者¹⁶。

将免疫疗法有效应用于恶性肿瘤治疗的实例之一是治疗恶性黑色素瘤。黑色素瘤是最致命的皮肤恶性肿瘤，在过去 30-40

⁶ See Cancer Research UK; Last review 27 November 2014; 'Monoclonal Antibodies'; <http://about-cancer.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/biological-therapy/types/monoclonal-antibodies>

⁷ Cancer.net; Approved April 2017; 'Understanding Immunotherapy' <http://www.cancer.net/navigating-cancer-care/how-cancer-treated/immunotherapy-and-vaccines/understanding-immunotherapy>

⁸ See American Cancer Society; Last revision 8 August 2016; 'Cancer Vaccines'; <https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/cancer-vaccines.html>

⁹ See footnote 7

¹⁰ See footnote 7

¹¹ See US Food and Drug Administration; last update 10 October 2016; <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407297.htm>

¹² See Bosely S; 4 February 2016; 'The closest thing yet to a cure for terminal cancer?'; <https://www.theguardian.com/science/2016/feb/04/revolutionary-drug-immune-system-advanced-cancer>

¹³ See Grady D; 12 July 2017; 'F.D.A. Panel Recommends Approval for Gene-Altering Leukemia Treatment'; <https://www.nytimes.com/2017/07/12/health/fda-novartis-leukemia-gene-medicine.html>

¹⁴ See National Cancer Institute; 30 May 2017; 'FDA Approves Immunotherapy Drugs for Patients with Bladder Cancer'; <https://www.cancer.gov/news-events/cancer-currents-blog/2017/approvals-fda-checkpoint-bladder>

¹⁵ See Vose, J.M, Clinical Cancer Advances 2016: Annual Report on Progress Against Cancer © 2016, American Society of Clinical Oncology; <http://ascopubs.org/doi/full/10.1200/jco.2015.65.8427>

¹⁶ See Patel, J, MD; 8 November 2016; '9 Things to Know About Immunotherapy and Lung Cancer'; <http://www.cancer.net/blog/2016-11/9-things-know-about-immunotherapy-and-lung-cancer>

年间其发病率一直在持续上升。在过去 30 年中，达卡巴嗪一直是黑色素瘤的标准治疗方案，即便该疗法并没有显示出对于改善整体生存率存在明显的帮助¹⁷。在 2011 年，Ipilimumab（一种单克隆抗体）被美国 FDA 批准用于治疗晚期黑色素瘤，其他的一些免疫疗法也随后获得批准。这包括 3 种检查点抑制剂、1 种溶瘤病毒、3 种细胞因子疗法和 1 种联合治疗¹⁸。然而，由于恶性黑色素瘤的侵袭特性，患者仍存在明显的身故风险。免疫疗法存在效果，但生存率的增加还仅仅以几个月而不是以几年来衡量，2 年生存率通常还是低于 30%¹⁹。

风险

虽然免疫疗法的副作用比放疗或化疗更小，但是这类治疗方法仍存在一些问题。绝大部分的副作用风险低，比如简单皮肤反应之类的过敏反应。然而，其他的一些情况就需要进行及时的治疗，例如肠道和肺部的炎症、或影响到内分泌系统的问题。有报道称，一些患者的死亡导致了试验被叫停²⁰。

一些批评人士认为，药商希望通过广撒网的方式找寻治疗恶性肿瘤的灵丹妙药，大量的试验正在进行当中、却没有对此提供足够和充分的护理与关注。阻碍联合免疫疗法发展的潜在障碍是医疗体系的开支，一位患者一项免疫疗法的费用每年超过 10 万美元²¹。到 2022 年，检查点抑制剂的销售预计将达到 300 亿美金²²。

对保险业的影响

保险公司需要紧跟恶性肿瘤治疗的发展，并做出适应的举措。某些市场已经开发出相关的保险产品，协助处理高额治疗费

用和其他相关费用，包括住院/门诊治疗、日常生活费用和收入津贴。

随着针对各种恶性肿瘤新疫苗的研制并且投入预防，恶性肿瘤的整体发病率可能会下降，其结果将会是一些保险产品可能会变得更便宜。此外，随着恶性肿瘤生存率的提高，存在晚期恶性肿瘤治疗病史且可投保的人群数量或许会有相当大的增加。因此应进行定期研究，确保提供恰当的产品以及能够准确反映实际的死亡率和发病率风险的定价。

结论

在本文一开始便已提出问题：恶性肿瘤免疫疗法是否将成为“变革者”。目前，恶性肿瘤免疫疗法还处于初期，但存在巨大潜力。虽然这一疗法已获得了一些值得注意的成功，但显著的效果还只局限在一小部分被诊断特定恶性肿瘤的患者当中，并且副作用问题仍有待解决。将免疫疗法与其他治疗方法结合起来，并应用辅助诊断可能是未来改善恶性肿瘤患者生存的关键。

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¹⁷ See Bhatia, S. MD, et al.; Treatment of Metastatic Melanoma: An Overview; ©2009 Oncology Journal; <http://www.cancerresearch.org/cancer-immunotherapy/impacting-all-cancers/melanoma>

¹⁸ See Wolchok, J, M.D., Ph.D; 'What Makes Immunotherapy a Promising Treatment for Melanoma?'; <https://www.cancerresearch.org/cancer-immunotherapy/impacting-all-cancers/melanoma>

¹⁹ See Robert C, et al.; 'Ipilimumab plus dacarbazine for previously untreated metastatic melanoma'; ©2011 N Engl J Med 2011; 364:2517-2526; <http://www.nejm.org/doi/full/10.1056/NEJMoa1104621>

²⁰ See Kenilworth, N.J.; July 5 2017; 'Merck Provides Further Update on Three Multiple Myeloma Studies Evaluating KEYTRUDA® (pembrolizumab) in Combination with Pomalidomide or Lenalidomide'; <http://www.businesswire.com/news/home/20170705006004/en/>

²¹ See Pietrangolo, A; 12 October 2016; 'The Value and Cost of Immunotherapy Cancer Treatments'; <http://www.healthline.com/health-news/value-and-cost-of-immunotherapy#1>

²² See Herper M; May 11 2017; Has Merck Lucked Into A \$10 Billion Drug?; <https://www.forbes.com/sites/matthewherper/2017/05/11/has-merck-lucked-into-a-10-billion-drug/#861f15288c8c>

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