The expanding palette of immunotherapy research

The advent of immunotherapy has revolutionized the cancer field, but it is not without its challenges. In this issue, we launch our Series on Cancer Immunotherapy presenting commissioned Reviews and opinion pieces on the latest advances and efforts to expand the palette of immunotherapies and their clinical translation.

Despite the explosion of the cancer immunotherapy field over the past decade, the idea of harnessing the power of the immune system against cancer is far from new. The origins of immunotherapy can be traced to the end of the nineteenth century and the work of William Coley, who, starting in 1891, used first live and later attenuated bacteria to treat patients with sarcoma. Despite reporting some striking results, his work was received with skepticism by the nascent cancer research field that more readily embraced radio- and chemotherapy. Paul Ehrlich's theory of immune surveillance to suppress tumor growth was met with similar skepticism when it was first proposed in 1909. Half a century would pass before the theory was revisited by Macfarlane Burnet and Lewis Thomas, as improved technology and an increasing understanding of biology gave traction to the tumor immunology field. In subsequent decades, painstaking fundamental and translational research would lead to milestones in clinical immunotherapy, such as the approval, by the US Food and Drug Administration, of interferon-α in 1986, followed by that of interleukin-2 and the monoclonal antibody rituximab in the 1990s and of the first therapeutic vaccine against cancer in 2010, to culminate in approval of the first immune checkpoint inhibitors and chimeric antigen receptor (CAR) T cell therapy in the past decade.

The growth of the field in recent years is astonishing: there are currently dozens of approved immunotherapies and thousands of ongoing clinical trials. This expanded immunotherapy palette includes immune checkpoint inhibitors, adoptive cell therapies, vaccines, cytokines and oncolytic virus therapies that have been proven effective against a number of cancers, alone or in combination with other treatments. However, longstanding hurdles remain to be overcome if immunotherapies are to reach a wider population of patients. Among these hurdles are potentially serious immune-related adverse effects and the variable and/or limited efficacy and response rates that are influenced not only by cancer type, tumor heterogeneity, microenvironment, immunogenicity, and strength of the immune system of individual patients, but also by the development of resistance to immunotherapy. Added to these limitations is the difficulty in predicting efficacy and response and thus the pressing need for more and better biomarkers and clinical trial designs.

Part of the massive growth of the immunotherapy field over the past decade reflects the concerted drive by researchers across disciplines to address these challenges and break new scientific ground. As a result, the spectrum of immunotherapy research today spans preclinical discovery science, translational and clinical work. Among the areas that meet at the immunotherapy nexus are cancer immunology and biology, tumor and immune multi-omics profiling, technology development and computational science, chemical and cell engineering, drug development and testing. Some of the key priorities for this interdisciplinary community are to gain a deeper understanding of the immunotherapeutic response and resistance, to identify new immunotherapeutic targets and modalities, to expand efficacy to more tumor types, including hard-to-treat cancers, to improve the means of identifying and predicting response, resistance and toxicities, and to achieve a more effective exploration of treatment synergies.

To provide expert insights into this fast-moving field, we are pleased to launch in this issue our Series on Cancer Immunotherapy, consisting of specially commissioned Review, Perspective, News and Comment articles, and accompanied by a collection of relevant primary research articles published in *Nature Cancer*. Readers can access the series through its dedicated website, which will be updated as new content is published.

We launch the Series with a Review and a Viewpoint that touch on distinct but crucial topics. In their Review, Ignacio Melero and colleagues discuss immunotherapy combinations by presenting the current status of this area of translational and clinical research and outlining a roadmap for the effective prioritization and testing of promising combinations[1]. Separately, in a Viewpoint, Valsamo Anagnostou, Alberto Bardelli, Timothy Chan and Samra Turajlic engage in a thoughtful discussion on the tumor mutational burden as a biomarker for tumor immunotherapy and share their distinct views on its advantages, limitations, technical challenges and potential broad utility across more patient populations[2]. Accompanying these newly published pieces is a Perspective by Daniel Wells and colleagues on the roles of bystander T cells in tumors and their potential to be targeted therapeutically[3]. In a separate Review, Eugene Hwang et al. delve into the current landscape of cancer immunotherapies for the hard-to-treat setting of pediatric brain tumors[4]. Finally, in their Review, J. Joseph Melenhorst and colleagues provide a deep dive into the current status of CAR T cell therapies, the challenges that remain to be surmounted and strategies for improving CAR T cell engineering to achieve efficacy beyond hematological malignancies[5]. Upcoming pieces will focus on cancer vaccines and ways to improve their clinical development, and the latest knowledge on T cell antigens and strategies for their therapeutic utilization, with further foundational research and clinical topics covered in future articles.

Through our selection of commissioned and primary research articles, we aim to provide an up-to-date and unique view of the evolving palette of cancer immunotherapy and the ways its salient areas are interconnected through the underlying biology and immunology, mechanistic and therapeutic synergies, technological and clinical advances and challenges. We hope our readers enjoy this Series, and we are deeply thankful to our authors and referees for their efforts and contributions. ❐

Published online: 28 June 2022
https://doi.org/10.1038/s43018-022-00410-0

References
1. Sanmamed, M. F., Berraondo, P., Rodriguez-Ruiz, M. E. & Melero, I. *Nat. Cancer* https://doi.org/10.1038/s43018-022-00401-1 (2022).
2. Anagnostou, V., Bardelli, A., Chan, T. & Turajlic, S. *Nat. Cancer* https://doi.org/10.1038/s43018-022-00382-1 (2022).
3. Meier, S. L., Satpathy, A. T. & Wells, D. K. *Nat. Cancer* **3**, 143–155 (2022).
4. Hwang, E. I. et al. *Nat. Cancer* **3**, 11–24 (2022).
5. Milone, M. C. et al. *Nat. Cancer* **2**, 780–793 (2021).