FOREWORD

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The evolutionary nature of the cancer immunotherapy revolution

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“Cancer immunotherapy, a field that had too few breakthroughs in the 20th century to inspire the masses, is the hottest topic in oncology.”

First draft submitted 15 May 2017; Accepted for publication 17 May 2017; Published online: 22 August 2017

Cancer immunotherapy, a field that had too few breakthroughs in the 20th century to inspire the masses, is the hottest topic in oncology. From dominating abstracts and presentations at major scientific meetings to a proliferation of articles in the most prestigious journals and even direct-to-consumer advertising, the totality of the shift from full scale denying and denouncing the utility of immunotherapy by the medical oncology community to full-on acceptance has been astonishing. This shift is entirely related to major advances into the understanding of how the immune system works, interacts with tumors and vice versa, and is regulated. Only after this foundation work was established did the clinical development proceed and succeed.

The origins of modern cancer immunotherapy are traced to William Coley, who developed a bacterial toxin designed to stimulate an immune activation that somewhat magically would trigger a tumor-specific response [1]. This approach was never proven to be effective in randomized studies, but yet served as an important proof of principle. The next breakthrough was discovering that T cells were key effectors of a tumor-specific immune response and that a T-cell growth factor, otherwise known as interleukin 2 (IL-2), could further propagate these responses [2,3]. In fact, high-dose IL-2 was FDA-approved in the 1990s for both metastatic renal cell carcinoma and metastatic melanoma; two diseases where traditional therapies such as cytotoxic chemotherapy did not work particularly well [4,5]. During this same era, a number of approaches to prime and direct tumor antigen-specific immunity were designed through a series of vaccines given with a variety of adjuvants. These efforts could almost always be shown to trigger immune responses, typically through *ex vivo* stimulation assays, in some patients but almost never lead to clinical benefit [6].

Through two major breakthroughs in the late 20th century, the way we approach the treatment of patients with solid tumors with immune directed therapy has changed forever. First, the pioneering work of the Surgical Branch at the National Cancer Center (MD, USA), under the leadership of Steven Rosenberg, established standard operating procedures to isolate tumor infiltrating lymphocytes, activate and expand these *ex vivo*, and infuse following conditioning regimens [7,8]. These efforts have either directly or indirectly inspired the development of T cell products with engineered T-cell receptors (TCRs) or chimeric antigen receptors (CARs), which activate specific antigens expressed on tumor cells and direct a potent and specific antigen-specific T cell mediated immunity. Second, the

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identification of immune regulatory elements and agents to disrupt these so-called immune checkpoints has changed the narrative about immunotherapy from being a niche type of treatment for a small number of not particularly common diseases to being the type of therapy that every pharmaceutical and small biotech company must account for, leading to the development of entire immuno-oncology (IO) programs because responses and improved outcomes have been seen in subsets of patients with common malignancies, including lung, breast and colorectal cancer [9,10].

The driving factor for the IO revolution focuses around the finding that B7 homolog 1 (B7-H1; PD-L1), which may be expressed in tumors in response to T cell infiltration, serves as a ligand to the Programmed Death 1 receptor (PD-1), which is expressed in activated T effector cells [9]. When PD-1 and PD-L1 interact, the activated T cells are blocked entry into the tumor. Inhibition of this interaction leads to effective infiltration of activated T cells and ultimately tumor destruction [11]. Remarkably, monoclonal antibodies against PD-1 (pembrolizumab, nivolumab) and PD-L1 (atezolizumab, avelumab, durvalumab) have received regulatory approval in a number of diseases, including melanoma, non-small-cell lung cancer (NSCLC), urothelial bladder cancer (UBC), head and neck squamous cell carcinoma (HNSCC), classical Hodgkin lymphoma and Merkel cell carcinoma, and have shown activity in many others [12–21]. Building upon this work, data with combination therapy with anti-PD-1/PD-L1 agents with anticytotoxic T lymphocyte associated antigen 4 (CTLA4) agents, such as ipilimumab, which was FDA-approved as a single agent in metastatic melanoma in 2011, and tremelimumab, is associated with higher response rates in a number of diseases [22–28].

However, despite the promise of immunotherapy in 2017, a number of limitations prevent the widespread use of these agents for the majority of cancer patients. First, the stark reality is that the majority of patients will not respond to these treatments and cures, to date represented by the rarity of rates of durable

responses lasting at least a few years. Second, few biomarkers to help prospectively select patients for these therapies exist. Third, very little is known about the mechanisms driving primary and acquired resistance to therapy. Fourth, the toxicity of immunotherapy is not trivial and provides a robust challenge, particularly in the development of more effective combinations. Finally, the cost of many of these agents is astronomical and, particularly if at some point these agents become standard for most cancer indications, unsustainable. To say there is more work to be done is a gross understatement.

In this issue of *Future Oncology* entitled “Cancer immunotherapies and the potential for combination”, cancer immunotherapy is the topic and the development of potential combinatorial regimens the focus. With nearly limitless potential combinations and hundreds to thousands of clinical trials ongoing or being planned, it is safe to say this is a broad topic. The papers contained within are thus diverse, both with regard to disease (gastroesophageal adenocarcinoma, colorectal cancer, NSCLC, urothelial cancer, virally-mediated cancers) and types of immunotherapy (peptide vaccines, CAR T cells, anti-PD-1/PD-L1, anti-angiogenic therapy, local therapies, oncogene targeted therapy, chemotherapy, radiation therapy), but by no means representative of the entirety of the field of combination immunotherapy. Rather, what is presented herein is a primer of where the field currently is and where it is going. The future is indeed bright and the challenges are profound but also surmountable.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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