

# Onward and upward for immuno-oncology

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## Introduction

For many decades it has been clear that effectively harnessing the immune system for the treatment of cancer would provide an ideal array of cancer therapies possessing all the properties required to cure many human malignancies safely and effectively. These properties include an exquisite specificity, which enables the immune system to selectively distinguish malignant cells from their normal counterparts, and the availability of a broad range of effector mechanisms to kill tumor targets and overcome the equally broad range of defense mechanisms used by tumors. In addition, the immune system is unique in its ability to adapt to tumor heterogeneity and change because it can itself evolve and alter its specificity and effector function.

## Obstacles to immunotherapy

Unfortunately, exploiting the hypothetical benefits of immuno-oncology has proved to be challenging. Despite the success of tumor-directed monoclonal antibodies (1) and of cellular therapies targeting melanoma (2) and EBV-associated lymphoma (3), immunotherapy as a whole had been considered too complex and too unpredictable to be anything but peripheral to mainstream tumor therapy. Instead, research had increasingly focused on identifying and developing small molecule drugs targeted to tumor-specific molecular lesions. This mindset was epitomized at major cancer meetings by the confinement of most immunotherapy presentations to the last session on the meeting's final day. In short, immuno-oncology was considered "promising", and likely to remain that way forever.

## Transformational events

Two major achievements upended this conventional wisdom.

The first was the development of monoclonal antibodies to immune checkpoints that benefited the patients not by targeting tumor-specific antigens, an approach that could be considered merely another form of targeted drug therapy, but by directly enhancing the function of the immune system itself. When used alone or in combination these checkpoint inhibitor antibodies produced complete and, above all, sustained responses even in patients resistant to conventional therapy (4). The second triumph was the development of chimeric antigen receptor-directed T cells targeted to B cell malignancies (5,6), and the truly miraculous effects these agents could have on even the most advanced and resistant lymphoid malignancies.

It is no exaggeration to say that these two accomplishments have had a transformational effect on how and when future therapies for cancer will be developed. Literally billions of dollars are now being spent developing additional large-molecule and cellular therapeutics for immuno-oncology. All too predictably, a great deal of these funds are being squandered on the development of me-too agents that at best will be marginally differentiated from the competition but will add little to the range or potency of immune therapies. Nonetheless, substantial amounts are being devoted to identifying new targets and mechanisms within the immune system, and to addressing basic obstacles in developing cellular immunotherapy for broader use. It is this latter aspect that may well be most benefited by the upsurge in resource commitment.

## From hand crafted to mass produced

Cellular immunotherapy of cancer has long suffered from a lack of scalable and robust manufacturing processes for producing a uniform product. Until very recently,

manufacture of effective cellular immunotherapeutic agents has been a high skill, low volume industry requiring the artisanal talent of a Michelin-starred chef rather than the minimal manual skills of a burger-flipper. But even when skillfully handcrafted, apparently identical cellular products may function quite differently *in vivo*, due to genetic and acquired variability in the hosts' own immune system and in the tumor and its microenvironment. Thus, it has been exceedingly difficult to produce a standardized cellular immunotherapeutic treatment of predictable potency.

These problems of mass producing a standardized product are not insoluble, but traditional funding mechanisms for academic institutions rarely favor process development over more "innovative" studies, and are even more rarely of sufficient magnitude to allow analysis and manipulation of all the variables essential to understanding and producing standardized cellular products. Consequently, few academic careers can be built in this crucial area, which had been correspondingly neglected. With the involvement of industry, however, the importance of process development is well appreciated, and the skill-sets, experience and funding for standardization, mass production and potency analyses may now all be to hand. Investigators can certainly detect greater integration between industry and academia as cellular immunotherapies are increasingly developed into early stage clinical trials.

### **Compete and collaborate**

The encouraging clinical results that have promoted this essential integration of industry and academia are also leading to the recognition and acceptance that no one immunotherapeutic strategy alone will be capable of consistently eradicating the majority of human cancers. The complexity of the components of malignant disease, and their proclivity for evolving over time and in space mean that strategies reliant on a single point of attack are doomed to fail. Such therapies may produce transient responses but they will not commonly lead to long-term control or eradication, which will instead almost always require combination therapies. Because of the high cost of developing and making cell based therapeutics in particular, their acceptance and widespread use in clinical practice worldwide will only occur once they are shown to substantially prolong high quality life, and even cure the cancer.

Historically, pharma has not favored co-developing combination therapies, but this attitude is now changing, initially with the use of combinations of checkpoint

inhibitors and cell therapies (7). Business models have already emerged that facilitate collaboration in the pre-competitive space of drug development. The implementation of related models in the immuno-oncology competitive space will likely accelerate the development of effective therapies that will in turn help payers, politicians and the public accept the high costs of these potentially curative therapies. Acceptance will be aided by more precise identification of the patients most likely to benefit from these combinations; molecular and cellular analyses of manufactured effector cells, endogenous host cells and tumor phenotype should both predict the probability of success before even beginning treatment, and provide measures of efficacy during therapy, thereby guiding clinicians toward additional interventions that will improve outcome during or following immunotherapy.

### **Nothing succeeds like success**

Of course all the above concerns about effective implementation of high cost/high value combination therapies are contingent on developing treatments that do more than marginally prolong survival with barely tolerable adverse effects. Although immunotherapy of some malignancies has genuinely produced long-term control or cure with excellent quality of life, for the great majority of human cancers we are a long way from this goal. Almost certainly, hematological malignancies will increasingly be managed effectively by immune therapy, extending from B cell leukemias and lymphomas to myeloma, T cell lymphoma and leukemia and myeloid leukemia. In solid tumors, malignancies associated with viruses such as EBV and HPV may also become amenable, as will tumors in which there is expression of a broad array of tumor-associated (neo) antigens. But for many other common human tumors, which possess a broad and ever-changing array of immune evasion mechanisms, there is little doubt that long-term control or cure of disease will require combination therapies of multiple agents, with all the associated challenges of implementation and evaluation described above.

### **Be steadfast and do not fear (8)**

It is often said that the strongest predictor of ultimate success is the will to persevere in the face of adversity. Whatever the challenges ahead, I hope this special issue will provide encouragement and guidance to current and

potential future investigators so that they will persist until immuno-oncology effectively transforms the treatment of malignancy from the harsh present to a more beneficent future.

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### Footnote

*Conflicts of Interest:* The author has equity positions in Tessa pharmaceuticals and in ViraCyte.

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