Cancer Immunotherapy: Advancing and Accelerating Discovery Programs

Abstract

Cancer immunotherapy has emerged as an attractive therapeutic approach. While monoclonal antibodies, cytokines, and vaccines have individually shown some promise, it is likely that the best strategy to combat cancer is to attack on all fronts. Advances in cellular immunology over the past three decades have provided enormous insights into the nature and consequences of interactions between tumors and immune cells that have signaled the beginning of a new era. The characterization of molecular mechanisms controlling the cross-talk between cancer and non-neoplastic somatic cells has expanded the field and understanding of the mechanistic bases of immune-mediated rejection. This knowledge continues to lead to strategies whereby the immune system is being harnessed for treating established malignancies.

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Editorial

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Joseph F Murphy*

Charles River Laboratories, USA

***Corresponding author:** Joseph F Murphy, Charles River Laboratories, 3300 Gateway Center Blvd, Morrisville, NC 27560, USA, Tel: 919 250-2318; Email: joseph.murphy@crl.com

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Introduction

Over the past 3 decades, conceptual and technical advances in the field of immuno-oncology have provided the knowledge and techniques to develop novel immunotherapeutic approaches that are demonstrating real clinical impact. Notably, the most heralded new class of immuno-oncology drugs are the 'immune checkpoint inhibitors', which work by blocking the molecules that switch off immune cells, thus increasing tumor immunogenicity.

Among the immunotherapeutic methods being used in the clinic or explored for therapeutic potential are many that enhance tumor immunogenicity by blocking inhibitory pathways and inhibitory cells in the tumor microenvironment, such as antibodies against cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), programmed death 1 (PD-1) or its ligand programmed death ligand 1 (PDL-1). Similarly, methods that can enhance the specificity of anti-tumor immunity by inducing the expansion of T-cells and antibodies directed to well-defined tumor antigens are being investigated, such as cancer vaccines, potent adjuvants, and immuno-stimulatory cytokines. Even as monotherapies, these approaches have a substantial impact on the treatment of some patients with advanced, previously untreatable, malignancies. These successes provide a rationale to expect that future immunotherapies can transform cancer treatment, improving the prognosis for many patients.

With the increasing success and subsequent interest in cancer immunotherapy, there is a growing need for well-characterized preclinical models. Charles River Laboratories has evaluated the responsiveness of several syngeneic murine tumor models to antibody-based, immune checkpoint inhibitor therapeutics targeting CTLA-4 and PD-1. Our results clearly show a differential response across tumors when these inhibitors were used individually or in combination. This differential allows one to match efficacy with model and expands the portfolio of models available for evaluating combination therapies. Furthermore, we evaluated the efficacy of checkpoint inhibitors in the human RKO colon carcinoma xenograft model in CD34-NSG humanized mice. Results from these studies shows significant tumor growth inhibition in response to checkpoint inhibitor monotherapies associated with activation of cytotoxic lymphocytes and cytokine expression. Findings detailing the benefits of a multidisciplinary approach to cancer immunotherapy efficacy study design and execution can be viewed on the following webinar:

http://register.xtalks.com/Surveys/Questions/SurveyMain.aspx?r=023cad52-baf5-419b-9b6e-89b13746a58f&ma=0

As novel cancer immunotherapy treatments continue to be at the forefront of discovery and development, checkpoint inhibitor treatment remains center stage as immunosuppression associated with cancer has to be overcome to allow better immune-stimulation. Moreover, other targeted and personalized treatment modalities will likely emerge. Central to this effort will be a reliance on appropriate preclinical models, which form the backbone of many immuno-oncology drug discovery programs, particularly with the increasing focus on combination therapy. Different strategies demonstrate varying responses in different populations.

To improve early encouraging clinical results, biomarkers to better select patients that may benefit from immunotherapy are actively sought. It may be that the best results are obtained with vaccines in combination with a variety of antigens or vaccine and antibody combinations. Finally, combination of immunotherapy with conventional treatments (chemotherapy, anti-angiogenic therapy etc.) should further improve this approach, both in its effectiveness and in its clinical indications.