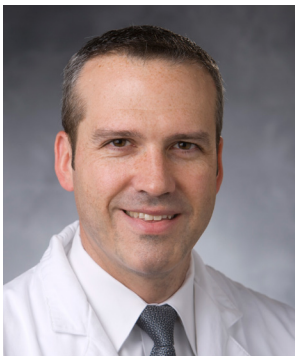
FOREWORD

Towards an integrated understanding of immunotherapy resistance



BRENT A HANKS, MD, PHD, is an Associate Professor of Medical Oncology in the Department of Medicine and Assistant Professor in the Department of Pharmacology and Cancer Biology at Duke University with a dual appointment with the Duke Cancer Institute. Dr Hanks completed his medical degree along with a PhD in tumor immunology while in the Medical Scientist Training Program at Baylor College of Medicine. Dr Hanks went on to complete his internal medicine residency training and his hematology and oncology fellowship training at Duke University. He now manages a basic and translational research lab focusing on understanding biochemical mechanisms of tumor-mediated immune evasion and immunotherapy resistance in cancer. More recently, his lab is also exploring the underlying mechanisms associated with immunotherapy-associated toxicities. In addition to his research efforts, he is also a medical oncologist and manages patients with advanced skin cancers including melanoma and Merkel cell carcinoma. Using an array of experimental techniques, his labs' research goals are to develop novel strategies to enhance the efficacy of checkpoint inhibitor and vaccine immunotherapy while also developing predictive biomarkers to better guide the management of cancer patients with immunotherapeutic agents.

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There are few topics in the field of cancer immunotherapy that are currently more pertinent than resistance as the majority of cancers fail to respond to this treatment modality. Given the broadly recognized implications of understanding the underlying mechanisms of both primary (innate) and secondary (acquired) resistance in drug and biomarker development, this topic is of great interest to many different stakeholders in the field. Accordingly, this issue of Immuno-Oncology Insights addresses several important, yet less mainstream, aspects of the complex and rapidly moving area of immunotherapy resistance by turning its attention towards discussions regarding the resistance of solid tumors to the genetically-engineered T cell therapies. Further consideration is also given to other components of the Cancer Immunity Cycle beyond the T cell, with a focus on the dendritic cell (DC) as an important and generally overlooked node of immunotherapy resistance.

Multiple barriers to the generation of an effective anti-tumor immune response are recognized within the tumor microenvironment (TME). However, the complex interplay between the tumor and the host immune system remains poorly understood. A discussion with Dr Alfonso Quintás-Cardama (TCR^2 Therapeutics) highlights the impressive challenges faced by cytolytic T cells within the TME and what steps can be taken to overcome these barriers. In particular, this discussion provides an interesting overview of a T cell-based platform referred to as TRuCs, or T cell-receptor fusion Constructs, that his group is employing to boost responses to engineered T cells in solid tumors. This is accompanied by further dialogue with Dr Prasad Adusumilli of the Memorial Sloan-Kettering Cancer Center about his group's priorities and approaches for the development of next-generation CAR T cells for overcoming resistance mechanisms in mesothelioma and other metastatic solid tumors. Serving as an excellent backdrop to these discussions, Dr Ingunn Stromnes of the University of Minnesota provides an overview of the current state of and future challenges faced by engineered T cell therapeutics in solid tumors. This includes a summary of TCR-engineered T cells and what measures can be taken to combat against resistance and tumor escape.

When examining the Cancer Immunity Cycle, it quickly becomes apparent, however, that other components of the host immune system are also critical for the generation of an effective anti-tumor immune response. Indeed, recent studies have delineated that the antigen cross-presenting Batf3$^+$ type I DC is essential for the generation of both spontaneous anti-tumor immunity as well as effective tumor antigen-specific cytolytic T cell responses to checkpoint inhibitor immunotherapy. In an opinion piece written by Dr David Munn and colleagues at the Georgia Cancer Center, potential DC-specific targeting strategies are discussed for augmenting responses to the available checkpoint inhibitor therapies. Further insight is given to the development and relevance of dysfunctional DCs in the TME and how select strategies to target common pathways of DC tolerization may be a particularly powerful approach for overcoming immunotherapy resistance and improving clinical outcomes in solid tumor patients.

Finally, I-O Insights reports on a fascinating conversation with Dr Todd Golub of the Broad Institute explaining his view on how genomic approaches can be leveraged in the immuno-oncology space to interrogate resistance mechanisms and provide insight into the design of novel combination regimens. Dr Golub further underscores the importance of engineering improved model systems for investigating immunotherapy resistance and why this is an important step forward for developing the mechanistic understanding necessary for extending clinically relevant responses to a broader population of cancer patients. In addition, as underscored by Dr Adusumilli, improved correlative immunologic data from clinical trials will also be necessary to better understand the impact of therapeutic agents on the tumor immune microenvironment. Additional technologies such as single-cell RNA sequencing, spatial

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transcriptional profiling, and the implementation of various CRISPR/Cas9 genetic screens will also likely play important roles in contributing to a better understanding of immunotherapy resistance.

The complexities of the TME, as discussed here, coupled with intra- and inter-tumor heterogeneity as well as the important, but less studied, aspects of therapeutic sequencing create significant challenges for the future of solid tumor immunotherapy. However, an integrated approach taken by each of the stakeholders in immuno-oncology is poised to continue advancing the field towards a better understanding of the hidden secrets underlying tumor immunotherapy resistance. Further discussion and thoughtful debate as facilitated by *I-O Insights* is expected to play an important role in catalyzing this process.

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AUTHORSHIP & CONFLICT OF INTEREST

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