Preface

A new era of anti-cancer therapeutics has emerged with significant objective clinical responses, prolongation of survivals, and even cures. These have been the result of the successful introduction of monoclonal antibodies (mAbs) directed against surface-bound membrane antigens on cancer cells. More than 20 mAbs have been approved for human use targeting a range of different cancers. The observed successes achieved by such antibodies against cancers stem from their high levels of specificity, long biological half lives, ability to recruit host effector cells, synergy with conventional drugs, and minimal toxicity. However, a major drawback of mAbs therapeutics, like any other therapeutics, is that a subset of patients does not initially respond and another initially responding subset develops resistance to further treatments. At the present time, there are no effective therapies for these subsets of cancer patients. Clearly, it is imperative that analyses of underlying mechanisms responsible for resistance will be required to develop and generate new targeted therapies that overcome the resistance. In addition, it will be possible to determine a priori whether a patient will be susceptible to response or not and which will allow oncologists to make proper decisions for treatment of the cancer patient at the individual level.

This volume titled, *Resistance to Immunotherapeutic Antibodies in Cancer: Strategies to Overcome Resistance* has been developed with the objective of highlighting up-to-date information on several investigations that deal with various mechanisms of resistance to anti-cancer mAbs therapeutics as well as those that deal with novel approaches to overcome resistance. The reviews in this volume are written by highly qualified, established, and experienced leaders in the field of resistance to anti-cancer mAbs.

This volume consists of 10 reviews that cover a wide range of topics on resistance. A summary highlighting each chapter is briefly presented. Dr. Dumontet's review titled, *Resistance to Anticancer Antibodies: From Mechanism to Solutions* discusses the importance of finding closed links between preclinical observations and the clinic. These links are imperative to unravel various mechanisms of resistance for the benefit of the patients. He raises the important point that not a simple mechanism of resistance will be found in a cancer patient type but multiple mechanisms will work in concert, due primarily to the heterogeneity of the cancer in question. As an example, he discusses $HER2^{+}$ breast cancer response to

trastuzumab and how to identify both biomarkers to predict an optimal response and gene products that regulate resistance for novel targeted therapies. Dr. Ferrone's review titled, *Tumor Antigen-Specific Monoclonal Antibody-Based Immunotherapy, Cancer Initiating Cells and Disease Recurrence* discusses an important facet of resistance, namely, the intrinsic resistance of a small subgroup of cancer initiating cells (CICs) that are primarily responsible for mAb resistance, relapse, and metastasis. He presents several examples of mAbs that do not affect CICs, however, the use of combination therapies with drugs/radiation and inhibitors of the CIC signaling pathways resulted in significant killing of CICs but not all. He suggests the development of additional targeted therapies and combination to completely eliminate CICs. Dr. Cragg's review titled, *Overcoming Resistance to Therapeutic Antibodies by Targeting Fc Receptors* discusses the clinical finding demonstrating the important role of Fc gamma receptors (FcγRs) polymorphism and response to mAb therapeutics. Due to the number of various FcRs with activating or inhibitory functions, their biology is very complex indeed. Noteworthy, while the role of FcγRs expression by cytotoxic effector cells was primarily reported for the observed polymorphism, however, new findings show that FcRs on both the cancer cell and the effector cell participate in determining the therapeutic efficacy of the monoclonal antibody in question. Several novel strategies are provided to circumvent the unresponsiveness of resistance with the aim to develop more successful mAb therapeutics. Dr. Hernandez-Ilizaliturri and Dr. Czuczman's review titled, *Understanding the Mechanisms of Resistance to Rituximab: Paving the Road for the Development of Therapeutic Strategies to Overcome Rituximab Resistance* discusses the clinical problem of cancer patients resistance to rituximab (antiCD20 mAb) therapy. They discuss several reported mechanisms of resistance that have been observed in cancer patients, including surface receptors and intracellular hyperactivated survival pathways. Their approach to determine potential underlying mechanisms of rituximab-resistance has been to develop preclinically rituximab-resistance lymphoma cell lines. These have been analyzed for their therapeutic phenotypes and molecular properties compared to the parental wild-type cells. Such approaches are clearly important to identify new biomarkers of resistance for both prognostic and novel therapeutics. Dr. Bonavida's review titled, *Tumor Resistance to Antibody-Mediated Immunotherapy and Reversal of Resistance: Rituximab as Prototype* discusses several studies that investigated cell-mediated signaling by rituximab on B-Non-Hodgkin's lymphoma cell lines and which demonstrated the inhibition of several intracellular pathways (example NFκB, p38 MAPK, Raf/ERK/MEK, and PI3K/Akt) leading to inhibition of cell growth and inhibition of anti-apoptotic gene products. In addition, this review discusses the chemo-immunosensitization-mediated by rituximab when used in combination with chemo-immunotherapeutic drugs and various mechanisms of sensitization. Like the above studies by Dr. Hernandez-Ilizaliturri and Dr. Czuczman, the potential mechanism of rituximab resistance has been analyzed by generating rituximab-resistant clones in vitro and their general molecular profiles were compared to wild-type cells. While the resistant clones were unresponsive to rituximab treatment alone or in combination with drugs, however,

intracellular intervention inhibiting the hyper-activated survival pathways by various inhibitors resulted in the reversal resistance to cytotoxic drugs. The analysis with the resistance clones yielded several candidate targets of potential prognostic and therapeutic values. Doctors Saridaki and Souglakos's review titled, *Resistance to the Anti-EGFR Therapy, Beyond KRAS, in Patients with Metastatic Colorectal Cancer* discuss the role of mutation profiles in the treatment decision in patients with metastatic colorectal cancer. They critically reviewed the underlying mechanisms of resistance to anti-EGFR mAbs and their relationship to various mutations. The reported studies are aimed to identify novel biomarkers that may be useful to select cancer patients who will respond favorably to anti-EGFR mAbs. Dr. Hersey and colleagues' review titled, *Overcoming Resistance of Melanoma to Immunotherapy with Monoclonal Antibodies Against Checkpoint Inhibitors* discusses the poor clinical response in melanoma patients following treatment with monoclonal antibodies against checkpoint inhibitors on T cells such as Ipilimumab (anti-CTLA-4) and PD1 (programmed death receptor-1). They discuss various mechanisms of resistance to immunotherapy including changes in the microenvironment, regulation of T-cells infiltration into melanoma tumors and suggest mechanisms to augment T-cell infiltration into the tumors. They also discuss the important role of NF-κB activation as a key regulator of anti-tumor immune resistance. Dr. Fulda's review titled, *Strategies to Overcome TRAIL Resistance in Cancer* discusses the mechanism that underlies the resistance of cancer cells to TRAIL/agonist antibodies directed against TRAIL receptors DR4 or DR5 currently under clinical investigation. She discusses several mechanisms conferring resistance to TRAIL such as the impairment of various members of the TRAIL signaling apoptotic pathways. These include signaling by death and decoy receptors that result in both the activation and the inhibition of apoptosis, the aberrant expression of anti-apoptotic gene products and the regulation of caspases. She implies that a better understanding of the mechanisms that regulate the sensitivity to resistance to TRAIL-apoptosis should lead to the successful application of TRAIL and agonist monoclonal antibodies as new therapeutics in the treatment of cancer.

The above chapters discuss several limitations by the use of therapeutic monoclonal antibodies. The next two chapters discuss the new engineered monoclonal antibody-conjugates as the new generation of antibody therapy. Dr. Smider's review titled, *Unnatural Amino Acid Antibody Conjugates as Next Generation Biologics* discusses the first approved monoclonal antibody against solid tumors, namely, trastuzumab (anti-HERT2$^+$ mAb; herceptin) in 1998 for the treatment of HERT2$^+$ overexpressing metastastatic breast cancer. He reviews several mechanisms of resistance to trastuzumab. He discusses the use of novel antibody-conjugates as novel therapies to overcome resistance. For example, unnatural amino acids were used to create the site specifically linking protein–protein dimers, such as antibody-toxin conjugates and bispecific antibodies. The antibody-drug conjugate, trastuzumab-DM1, has shown biological activity and clinical efficacy in HERT2$^+$ breast cancer and other applications have also been discussed. Dr. Rabuka's review titled, *Antibody-Drug Conjugates: Can Coupling Cytotoxicity and Specificity Overcome Therapeutic Resistance?* discusses the

exquisite selected antibody-drug conjugates (ADCs) for the target antigen and that kill cells at very low concentrations with little effect on normal tissues. This review presents the general properties of ADCs and their mode of action and how they can revert resistance to antibody therapeutics. The development of Mylotarg, gemtuzumab ozogamicin, was approved in 2000 and consists of an anti-CD33 mAb conjugated with a DNA-damaging agent, calicheamicin, for the treatment of $CD33^{+}$ leukemia. There are currently 20 new ADCs in clinical studies that should provide information about their therapeutic efficacy and their ability to reverse resistance.

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