Preface

After years of disappointments, cancer immunotherapy has finally gained considerable attention due to the development and use of approaches that target T cells, key players in the battle against cancer. In particular, immune checkpoint-targeting antibodies and adoptive T-cell therapies are starting to transform the treatment of advanced cancers. However, despite recent successes, many patients with cancer fail to respond to these treatments. A major challenge now is to identify underlying mechanisms responsible for resistance to cancer immunotherapy in order to overcome them and propose more efficient strategies.

For an effective direct destruction of cancer cells, CD8 T cells must fulfill several functions. First, they should be able to migrate efficiently into and within tumors in order to make contact with malignant cells. Second, they should be able to respond adequately to tumor antigens by releasing cytotoxic granules. In cancer patients, accumulating evidence suggests that responsiveness to tumor antigens is altered and current immunotherapies mainly aim at boosting T-cell activities. But relieving the brake of T-cell suppression will not be effective if lymphocytes are unable to migrate and interact with tumor cells.

The objective of this book titled *Defects in T Cell Trafficking and Resistance to Cancer Immunotherapy* is to focus on this important aspect which has been overlooked for years. The volume starts with a chapter by Stein, Moalli, and Ackerknecht who provide an overview of the main features of T-cell trafficking in basal conditions and during an efficient immune response. T lymphocytes are among the cells in the body that migrate the fastest, and it is now established that these cellular displacements are crucial for T cells to mount a protective immune response. Our understanding of how T cells move in a variety of organs including malignant tumors mainly comes from the two-photon microscopy technique. Loyher, Combadière, and Boissonnas present this powerful approach and discuss the dynamic behavior of T cells within an intact tumor environment.

This volume is also focused on the different obstacles the environment of advanced tumors creates to limit T cells from migrating and making contact with their malignant targets. A specific attention is devoted to defective entry of T cells into tumors and its underlying mechanisms. Fabian and Storkus discuss the unique

characteristics of the tumor-associated vasculature acting as a barrier for T cells. Even when T cells succeed in crossing the tumor vessels, lymphocytes are rarely in contact with tumor cells being instead greatly enriched in the surrounding stroma, composed of non-cancer cells. Over the last few years, different stromal cells and stromal components have been identified as limiting T cells from contacting malignant cells. Pommier and Fearon focus on carcinoma-associated fibroblasts and the negative impact of these stromal cells on T lymphocytes. Apart from detrimental elements, other structures in the tumor stroma that display strong similarities with lymphoid organs favor the trafficking and surveillance activity of T cells. Dubois, Kaplon, Couillault, and colleagues review the current knowledge about these tertiary lymphoid structures and their importance in T-cell antitumor activities.

Finally, a special attention is paid to current and future therapeutic interventions to improve migration of T cells into tumors and thus to enhance the effectiveness of cancer immunotherapy. Several chapters in this book discuss the ideas of modulating a number of components in the lymphocyte migration machinery. Cantor addresses the modulation of integrin functions to improve homing of T cells into tumors. Garetto, Sardi, Morone, and Kallikourdis focus on chemokines and the enforced expression of their receptors on T cells. Finally, Chen, Dotti, and Savoldo explain how the genetic manipulations of chimeric antigen receptor-modified T cells with carefully chosen genes can overcome poor migration and persistence of T lymphocytes into tumors.

The field of cancer immunotherapy has undergone a truly explosive growth in recent years. The development of therapies that target T cells raises hopes for these approaches to become a significant treatment for a variety of cancers. However, in order for these strategies to be fully successful, we need to understand how T cells traffic into and within tumors, how T cells are blocked in these processes, and how these obstacles can be overcome. I believe that this book will help readers to do this.

I would like to thank the authors, who are among the top leaders in their areas of research, for their exceptional contributions. This volume represents one in a book series entitled Resistance to Targeted Anti-Cancer Therapeutics of which Professor Benjamin Bonavida of the University of California, Los Angeles, serves as the series editor (published by Springer Publishing Company). I wish to thank Professor Bonavida for his friendly help and encouragement. Also, I acknowledge the valuable cooperation and coordination with Fiona Sarne, Joy Evangeline Bramble, and Ravishankar Kamalakannan, publishing editors, Cancer Research, Springer Science+Business Media.

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