Resistance to Targeted Anti-Cancer Therapeutics 21
Series Editor: Benjamin Bonavida

Ana C. Xavier
Mitchell S. Cairo *Editors*

Resistance to Targeted Therapies in Lymphomas

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Resistance to Targeted Anti-Cancer Therapeutics

Volume 21

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Preface

Lymphomas are a complex group of hematological malignancies that have distinctive etiology, epidemiology, clinical behavior, and response to therapy. For decades, multidrug chemotherapy and/or radiation therapy constituted sole backbones to treat those patients. However, the development of resistance to conventional therapy, due to a multitude of genetic, epigenetic, metabolic mechanisms among others, has contributed to hinder the therapeutic success in a significant proportion of patients.

More recently, remarkable advancements in the lymphoma field, with better understanding of lymphoma cell biology and its microenvironment, have contributed to the development of biologic or "targeted" agents and consequent rapid expansion of the therapeutic landscape. These agents are usually designed and developed based on specific target molecules present in key tumor or microenvironmental cells that once blocked or deregulated can lead to cell death, cell differentiation, or immune system recognition. Many clinical studies have focused on testing targeted agents as monotherapy or in combination with conventional chemotherapy with the goal of improving outcomes or reducing acute or long-term complications associated with therapy. Unfortunately, despite the well-thought rational behind each targeted agent development, transient or unsatisfactory responses to those new therapies are commonly described, suggesting the development of tumor-related or host-related treatment resistance as a culprit to treatment failure. In this book, we will review different classes of targeted drugs that have been developed, approved, or are under investigation in the field of lymphoma therapy. Our focus is to provide a comprehensive review of the mechanisms of action or clinical response of several targeted agents and to discuss mechanisms of tumor-related or host-related resistance and potentially how to overcome resistance. This understanding is crucial considering the dismal outcomes of patients with relapsed or refractory lymphomas. Collectively, the chapters offer a unique opportunity to review, understand, and reflect on the recent successes and pitfalls of the modern lymphoma therapy era.

Birmingham, AL, USA — Ana C. Xavier
Valhalla, NY, USA — Mitchell S. Cairo

Aims and Scope

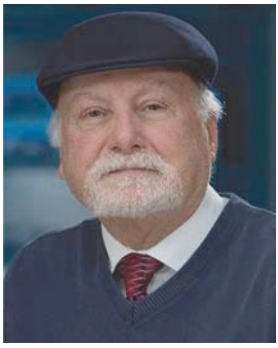
For several decades, treatment of cancer consisted of chemotherapeutic drugs, radiation, and hormonal therapies. Those were not tumor-specific and exhibited several toxicities. During the last several years, targeted cancer therapies (molecularly targeted drugs) have been developed, consisting of immunotherapies (cell-mediated and antibody) drugs or biologicals that can block the growth and spread of cancer by interfering with surface receptors and with specific dysregulated gene products that control tumor cell growth and progression. These include several FDA-approved drugs/antibodies/inhibitors that interfere with cell growth signaling or tumor blood vessel development, promote the cell death of cancer cells, stimulate the immune system to destroy specific cancer cells, and deliver toxic drugs to cancer cells. Targeted cancer therapies are being used alone or in combination with conventional drugs and other targeted therapies.

One of the major problems that arise following treatment with both conventional therapies and targeted cancer therapies is the development of resistance, preexisting in a subset of cancer cells or cancer stem cells and/or induced by the treatments. Tumor cell resistance to targeted therapies remains a major hurdle, and, therefore, several strategies are being considered in delineating the underlining molecular mechanisms of resistance and the development of novel drugs to reverse both the innate and acquired resistance to various targeted therapeutic regimens.

The new series "Resistance of Targeted Anti-cancer Therapeutics" was inaugurated and focuses on the clinical application of targeted cancer therapies (either approved by the FDA or in clinical trials) and the resistance observed by these therapies. Each book will consist of updated reviews on a specific target therapeutic and strategies to overcome resistance at the biochemical, molecular, and both genetic and epigenetic levels. This new series is timely and should be of significant interest to clinicians, scientists, trainees, students, and pharmaceutical companies.

Los Angeles, CA, USA — Benjamin Bonavida

Series Editor Biography



Dr. Benjamin Bonavida, Ph.D. (Series Editor), is currently Distinguished Research Professor at the University of California, Los Angeles (UCLA). His research career, thus far, has focused on basic immunochemistry and cancer immunobiology. His research investigations have ranged from the mechanisms of cell-mediated killing, sensitization of resistant tumor cells to chemo-/immunotherapy, characterization of resistant factors in cancer cells, cell-signaling pathways mediated by therapeutic anticancer antibodies, and characterization of a dysregulated NF-κB/Snail/YY1/RKIP/PTEN loop in many cancers that regulates cell survival, proliferation, invasion, metastasis, and resistance. He has also investigated the role of nitric oxide in cancer and its potential antitumor activity. Many of the above studies are centered on the clinical challenging features of cancer patients' failure to respond to both conventional and targeted therapies. The development and activity of various targeting agents, their modes of action, and resistance are highlighted in many refereed publications.

Acknowledgments

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About the Editors

Ana C. Xavier Dr. Ana C. Xavier is an Associate Professor at the Division of Hematology/Oncology, Department of Pediatrics, University of Alabama at Birmingham (Birmingham, Alabama). She received her medical degree from the University of Sao Paulo, Brazil, and completed her pediatric residency at the Medical University of South Carolina and Pediatric Hematology/Oncology Fellowship Training at the Wayne State University. She is Board Certified in Pediatrics and Pediatric Hematology/Oncology and currently serves as Associate Program Director of the Pediatric Hematology/Oncology Fellowship Program at the University of Alabama at Birmingham. She has authored numerous peer-reviewed manuscripts in highly reputed international journals and has presented several abstracts at various national and international conferences. She holds memberships with the American Academy of Pediatrics, American Society of Hematology, American Society of Pediatric Hematology/Oncology and Children's Oncology Group. Her clinical practice includes both pediatric oncology, and her research interest focuses on the treatment of pediatric patients with lymphoma.

Mitchell S. Cairo Dr. Cairo is currently the Associate Chairman and Professor (with tenure) in the Department of Pediatrics at New York Medical College (NYMC). His additional current leadership positions include being the Chief of the Division of Pediatric Hematology, Oncology, and Stem Cell Transplantation, Program Director of the Adult and Pediatric BMT Program, Director of the Childhood and Adolescent Cancer and Blood Disease Center, Medical and Scientific Director of the GMP Cellular and Tissue Engineering Laboratory at Westchester Medical Center (WMC), Medical Director of the WMC Hematotherapy Program, and Co-chair of the WMC Cancer Committee. His additional academic appointments include being a Professor of Medicine, Pathology, Microbiology and Immunology, Cell Biology and Anatomy, and Public Health at NYMC. Briefly, his past education includes his undergraduate studies at the University of Wisconsin, Madison, WI, graduating in 1972 with a BA and election to Phi Beta Kappa. He received his medical school training at the University of California, San Francisco (USCF), graduating in 1976 with an election to Alpha Omega Alpha (AOA). He trained as a Pediatric Resident at the UCLA Harbor General from 1976 to 1978 under the mentorship of Joseph St. Geme, MD, and then a Chief Residency in Pediatrics from 1978 to 1979 at the UCSF under the mentorship of Melvin Grumbach, MD. He completed a Pediatric Hematology-Oncology Fellowship as an American Cancer Society Fellow at Indiana University from 1979 to 1981 under the mentorship of Robert Baehner, MD. He joined the Faculty of Children's Hospital of Orange County (CHOC) in 1982 and established the BMT/Stem Cell Transplant Program there in 1985 as Director of Blood and Marrow Transplantation. Also, at CHOC, he was the Principal Investigator (PI) for Children's Cancer Group and PI of the Cord Blood Collection Center and Cord Blood Transplant Center under an NHLBI award. In 1997, he was recruited to Georgetown University where he became a Professor of Pediatrics, Medicine, and Pathology, Chief of the Division of Stem Cell Transplantation and Cellular and Gene Therapy, Director of the Adult and Pediatric Bone Marrow Transplantation Program at the Lombardi Cancer Center, and Medical Director of the NHLBI Cord

Blood Collection Center and Cord Blood Bank. In 2000, he was recruited to Columbia University and was a Professor of Pediatrics, Medicine, and Pathology, Director of the Division of Blood and Marrow Transplantation, Member of the Executive Committee of the Department of Pediatrics, Medical Director of the National Marrow Donor Unrelated Transplant Program, Chief of the Division of Pediatric Blood and Marrow Transplantation, and Member of the Executive Steering Committee of the Morgan Stanley Children's Hospital of New York-Presbyterian Hospital. In 2011, he was recruited to NYMC and WMC. He has over 410 peer-reviewed publications, over 1200 national and international abstract presentations, and over 50 book chapters and edited 2 textbooks. He is on the Editorial Board of *British Journal of Hematology*, *Blood Reviews*, and *Cell Transplantation* and Past Editorial Board Member of *Bone Marrow Transplantation* and *Experimental Hematology*. He is a regular NCI Reviewer for PPG and Spore applications. He has been a Member of the CCG/COG Bone Marrow Transplantation, now Cell Therapy Committee, for the last 20 years. He was the Chair of the ISCT Immuno-Gene Therapy Committee and currently is the ISCT North America Vice President Elect and Past Co-chair of the CIBMTR Cellular Therapy Committee. He is also a long-standing Member of the PBMTC Executive and Steering Committee and is an International Leader in the Biology and Treatment of Childhood and Adolescent Lymphomas and Leukemias, Stem Cell Transplantation, Developmental Therapeutics, Experimental Hematopoiesis and Immunology, Tumor Immunology and Biology, and Stem Cell Biology and Regenerative Therapy. He was a Pioneer in the use of cord blood stem cells for treating pediatric malignant and nonmalignant disease and the use of cord blood stem cells for potential regenerative therapy and haploidentical stem cell transplantation for patients with sickle cell disease. He is a Member of a number of national and international societies related to both Pediatrics and Hematology/Oncology/Stem Cell Transplantation, including elected to the Society of Pediatric Research (SPR) and the American Pediatrics Society (APS), and Member of AAP, ESPR, and hematology and oncology and stem

cell transplantation societies such as ASH, ASCO, ASBMT, CIBMTR, AAI, ISEH, AACR, ASPHO, SIOP, PBMTC, and COG. In summary, he has been an International Leader in basic, translational, and clinical research in childhood, adolescent, and young adults with emphasis in stem cell transplantation, stem cell biology, lymphoma, tumor immunology, and developmental therapeutics.