

Preface

Cancer chemotherapy can be traced in the 1940s when mustine (the prototype nitrogen mustard anticancer chemotherapeutic drug) was injected into a patient with non-Hodgkin's lymphoma, resulting in a dramatic reduction in tumor masses [1]. Thereafter, we witnessed the discovery and the important application of several new drugs, such as methotrexate [2], 6-mercaptopurine (6-MP), vincristine (vinca alkaloid), and aminopterin (folic antagonists) [3]. Then the concept of combination chemotherapy was introduced in 1965 by James Holland, Emil Freireich, and Emil Frei, who administered methotrexate, vincristine, 6-mercaptopurine, and prednisone, together referred as the POMP regimen, which resulted in long-term remission in children with acute lymphoblastic leukemia (ALL). This combination approach was extended to the lymphomas by Vincent T. DeVita and George Canellos in the late 1960s, when it was found that nitrogen mustard, vincristine, procarbazine, and prednisone—known as the MOPP regimen—could cure patients with Hodgkin's and non-Hodgkin's lymphoma. Thereafter, new drugs were discovered, including taxanes, camptothecins, platinum-based agents, nitrosoureas, anthracyclines, and epipodophyllotoxins [4]. The successes of combination chemotherapy suggested that all cancers could be treated provided the correct combination of drugs at the correct doses and correct intervals were established. However, while chemotherapeutic drugs were effective with minimal knowledge of underlying mechanisms of action, new studies began to unravel the genetic nature of cancer and the development of targeted therapies.

Targeted therapies include monoclonal antibodies, cell-mediated immunotherapy, gene immunotherapy, and the development of inhibitors interfering with survival antiapoptotic signaling pathways in cancers. While these novel approaches have significantly improved the outcome of many cancer patients, there remains a major problem in the development of cancer resistance to conventional and novel cytotoxic therapies. Further, since most cytotoxic therapies mediate their activities by inducing programmed cell death, or apoptosis, tumor cells develop mechanisms to resist apoptosis and thus acquire a phenotype of cross-resistance to most cytotoxic stimuli. Therefore, there is an urgent need to unravel the underlying mechanisms of resistance at the biochemical and genetic levels and the development of agents that can reverse resistance, directly or in combination with other cytotoxics. The objective of this book is to select novel approaches developed to reverse tumor cell resistance to chemo/immuno/radio-therapy and the use of various sensitizing agents in combination with various cytotoxics [5]. This volume is by no means exhaustive of this subject matter, but primarily introduces several current approaches that have been developed by established investigators in the field. The volume is arbitrarily divided into several main topics, recognizing that the contents of several chapters in one topic can overlap with other topics.

There are several contributions on tumor cell sensitization based on approaches to target cell surface receptors and how such targeting agents sensitize tumor cells to apoptosis. Dr. Vollmers

and colleagues describe the use of monoclonal antibodies as sensitizing agents to reverse epithelial cancers to apoptosis. Dr. Penichet and colleagues developed monoclonal antibodies directed against the overexpressed transferrin receptor on tumor cells. They also genetically engineered a fusion protein that was found to be cytotoxic and also sensitizes tumor cells to various chemotherapeutic drugs. Dr. Bonavida and colleagues discuss the FDA-approved chimeric anti-CD20 mAb, rituximab, and its ability to sensitize drug-resistant B-NHL to apoptosis by various chemotherapeutic drugs. They describe rituximab-mediated inhibition of several anti-apoptotic and constitutively activated signaling pathways and that are responsible for chemosensitization. Dr. Sakai and colleagues examine the role of the TRAIL death receptor, DR5, and its upregulation by various agents, leading to sensitization of TRAIL-resistant tumor cells to TRAIL-induced apoptosis. It is noteworthy that TRAIL and agonist DR4/DR5 mAbs are currently being tested in phases I and II clinical trials for various cancers. Dr. Murphy and colleagues used proteasome inhibitors to sensitize tumor cells to immune-mediated apoptosis.

Several contributors describe their findings by targeting constitutively activated cell survival pathways in cancer. Dr. Kerbel and colleagues describe the use of anti-angiogenic inhibitors as chemosensitizing agents, with particular emphasis on metastatic disease. Dr. McCubrey and colleagues describe the constitutively activated cell survival pathways, namely, the Raf/MEK/ERK and PI3/AKT pathways, and the use of cell membrane-permeable small-molecular-weight inhibitors that target these pathways and can be used as chemosensitizing agents. Drs. Rosato and Grant describe the use of histone deacetylase inhibitors in combination with other agents for the reversal of tumor cell resistance. Dr. Sorokin describes the role of eicosanoids in the regulation of tumor cell resistance to apoptosis and the various means to target these lipids in order to reverse chemoresistance.

There are several contributions that investigate targeting of transcription factors as sensitizing agents. Dr. Chatterjee and colleagues examine the relationship between the transcriptional regulation of survival pathways and inhibition of these pathways, and shifting the balance to reverse resistance.

They describe the roles of Raf kinase inhibitory protein (RKIP) as apoptotic and signal transducer and activator of transcription (STAT3) as antiapoptotic and describe the opposing effects of these two gene products. Dr. Gambari describes novel RNA-DNA-based strategies as chemosensitizing agents by targeting selected mRNAs with antisense oligonucleotides or small interfering RNAs (siRNA) or targeting transcription factors with decoy oligonucleotides. Drs. Maina and Domo examine the beneficial effect of combining inhibitors of *p53* as sensitizing agents when used in combination with conventional chemo- and radio-therapies to reverse resistance. Dr. Bonavida and colleagues examine the role of various inhibitors, such as nitric oxide (NO) donors, as sensitizing agents leading to inhibition of the transcription factors NF- κ B and Yin Yang1 (YY1). Inhibition of these transcription factors upregulates death receptors (FAS, DR5) and sensitizes tumors cells to FAS ligand and TRAIL-induced apoptosis. Dr. Aggarwal and colleagues used several natural products that inhibit NF- κ B and sensitize tumor cells to both chemotherapy and radiation.

Due to the fact that the apoptotic pathways are dysregulated in cancer, and primarily there is overexpression of antiapoptotic gene products or underexpression of apoptotic gene products, sensitizing agents that can regulate these gene products and interfere with apoptotic pathways may reverse resistance when used in combination with other cytotoxics. Several contributors used such approaches. Dr. Johnson examines the application of inhibitors of the Bcl-2 family as chemo- and radio-sensitizers. These studies were undertaken both in vitro and in vivo for their potential clinical application. Dr. Johnston and colleagues also used the strategy of interfering with the dysregulated apoptotic pathways in cancer and describe various means to interfere with antiapoptotic pathways by using, for example, antisense and siRNA as sensitizing agents. Dr. Li and colleagues discuss the use of peptides and peptide mimetics as sensitizing agents and their possible application in clinical trials as a new approach for cancer therapy. Dr. Mayo and colleagues discuss the utility of nonpeptide mimetics to sensitize tumor cells when used in combination with subtoxic doses of chemotherapy and radiation. Drs. Sarkar and Lee discuss the effects of

combining isoflavones and conventional therapeutics. Isoflavones and derivatives exert many effects on cancer cells, such as regulating several survival pathways and apoptotic pathways. Drs. Schwenzer and Förster discuss antisense oligonucleotides and siRNA applications in therapy and their use in ongoing clinical trials.

The approach of tailored customizing therapy for individual cancer patients requires a thorough understanding of the genetic makeup of the patient and its cancer and the pharmacogenetics of drugs. Drs. Efferth and Wink discuss the pharmacogenetic approach to compare monogenetic disease with a more complex disease such as cancer. These studies open the way to design personalized custom-tailored therapy. Also, Drs. Stivala and her colleagues discuss the importance of how genetic abnormalities may influence the response to treatment. They also discuss current strategies to integrate pharmacogenetics into the development of anticancer drugs.

Clearly, this volume represents a broad overview of the field of cancer sensitization and introduces several novel approaches that can be used to reverse cancer resistance through the application of a variety of sensitizing agents. Readers are also encouraged to read several reviews on related topics. As editor, I wish to thank all of the contributors, without whom this book could not have been realized. In addition, I acknowledge the administrative and

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