Preface

The scientific community has made tremendous strides in understanding the molecular basis of cancer since the pioneering work that culminated in the identification of the first human cellular oncogene in 1978 and tumor suppressor gene in 1987. It is this knowledge of the molecular underpinnings of cancer that has led to the advent of small molecule and antibody therapies targeting proteins that drive carcinogenesis. The preeminent example of these molecular-targeted therapies is imatinib, a selective inhibitor of ABL, KIT, and PDGFR, which is effective for the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors. However, the overall therapeutic response to the molecular-targeted therapies evaluated has been much less than initially hoped. The clinical response of patients to imatinib seems the exception, not the rule. Of the molecular-targeted therapies approved by the Food and Drug Administration, most work on only a subset of patients and ultimately resistance emerges for all molecular-targeted agents. The extensive cross talk between signaling pathways, the multiple mutations, and the genetic plasticity of cancer all contribute to the inherent and acquired resistance to molecular-targeted therapies that leads to the inevitable relapse for patients.

The fundamental hurdle to developing more effective, durable treatments for cancer is overcoming the robustness of cancer. Robustness is the quality of being able to withstand perturbations, coping well with unpredictable variations with minimal loss of functionality. In the case of cancer, this is continued survival and growth. It is important to note that the robustness of the cancer system applies to cancer as a disease and not individual tumor cells. The machinery that maintains cellular and tissue robustness in a healthy individual is hijacked to maintain the dysfunction of cancer, even in response to molecular-targeted therapies that disrupt signaling events that drive carcinogenesis. Thus, responses to molecular-targeted therapies, which are often very dramatic, do not endure.

This book presents examples of the major mechanisms of resistance to targeted agents, new tools for studying the cell signaling network, and emerging fields addressing the mechanism of resistance. The goal is to provide the reader with both an overview as well as a detailed perspective on the mechanisms of resistance to targeted therapeutics. Chapters 1 and 2 of this book address two fundamental mechanisms of resistance to molecular-targeted agents. Chapter 1, “Resistance to

Targeted Therapies As a Result of Mutation(s) in the Target", describes acquired resistance through the acquisition of new mutations within the protein target. This discovery has critical implications for the development of new, molecular-targeted agents that will be effective as second-line treatments for patients with resistance mutations. Alternative mechanisms for resistance include compensatory and redundant signaling events such as the upregulation or preexistence of bypass signaling. In Chapter 2, "The Dynamics of the Cell Signaling Network; Implications for Targeted Therapies", specific examples of compensatory and redundant signaling leading to therapeutic resistance are discussed along with the general implications of the cell signaling network on the design of effective drug treatments.

Not discussed in this book is how multidrug resistance efflux pumps contribute to the resistance of molecular-targeted agents. In general, the same knowledge of how these pumps can facilitate resistance to conventional chemotherapy can be applied to kinase inhibitors. The reader is directed to the book "Multi-Drug Resistance in Cancer" edited by Jun Zhou and published by Springer for in-depth information on this subject. Also not discussed in this book is the potential role of cancer progenitor cells in resistance to molecular-targeted agents. The topic is not without controversy, although the controversy may be largely due to: (1) semantics, (2) the question of how fluid intratumoral cell populations are, and (3) how applicable this concept is to cancers originating from different tissues. The attributes of cancer progenitor cells that facilitate resistance include their rarity, ability to undergo asynchronous DNA synthesis, as well as increased expression in enzymes for DNA repair and antiapoptotic proteins. The reader is directed to the book "Stem Cells and Cancer", edited by Rebecca Bagley and Beverly Teicher, and published by Springer for information on this subject.

The next three chapters (Chapters 3–5) describe cutting edge technologies for evaluating the cell signaling network. Chapter 3, "Cancer Signaling Network Analysis by Quantitative Mass Spectrometry", details advances in both mass spectrometry instrumentation and methodology for identifying and quantifying protein phosphorylation in the cell signaling network. Chapter 4, "Development and Implementation of Array Technologies for Proteomics: Clinical Implications and Applications", describes how tissue and protein microarrays are enabling researchers to assess signaling network activation and broad-scale pathway mapping in a relatively large number of samples, including patient tissue samples where sample material is limited. This section ends with Chapter 5, "Using Phosphoflow to Study Signaling Events of Subpopulations Resistant to Current Therapies", which details how phosphoflow cytometry can be used to study signaling events in cell subpopulations resistant to molecular-targeted therapies. This chapter illustrates how it is now possible to study signal transduction in single cell populations, enabling the study of signaling events in subpopulations of cells that are resistant to targeted therapeutics. These three chapters represent the significant progress in phosphoproteomic research that has occurred in the last decade. Implementing and integrating the approaches described in these chapters will enhance our understanding of cell signaling networks involved in cancer and how cell signaling networks respond to perturbations such as molecular-targeted therapeutics.

These early chapters illustrate the enormous complexity of the problem facing therapeutic resistance. Not only is it difficult to effectively measure changes in the cell signaling network, the network complexity obscures interpretation of such data. One tactic to address this issue is to integrate quantitative experiments with computational modeling. Mathematical modeling of cell signaling and mutation rates provides important insights into how resistance to targeted therapies arises. Such models are uncovering new areas of exploration such as the need for better quantitative tools for measuring patient samples. Importantly, mathematical models also predict the numbers of drug combinations (or targets) required for effective treatment. The application of mathematical modeling found in systems biology is presented in Chapter 6, "Mathematical and Computational Models in Cancer". This highly approachable presentation of this complex subject introduces the reader to how the application of mathematical models can facilitate tracking and interpreting more variables than an individual investigator's cognitive ability can achieve. It also introduces the critical issue that the cancer response to molecular-targeted agents is a multiscale problem not only of many signaling pathways (microscale) but also of different cell and tissue types (macroscale).

Increasingly complex in vitro cancer models and in vivo models of cancer are important tools for studying the mechanism of resistance to targeted therapies. The "gold standard" for the integrated study of micro- and macroscale is the animal model. However, animal models are not without their limitations, since the experimental system chosen may elicit unpredicted escape mechanisms. Chapter 7, "Interrogating Resistance to Targeted Therapy Using Genetically Engineered Mouse Models of Cancer", describes how the engineering of mouse cancer models can be utilized to model molecular-targeted therapies and how in vivo cancers respond to modifications in specific molecular pathways.

Fully addressing the challenge of therapeutic resistance will require incorporating broad-based concepts such as somatic evolution. After all, it is the evolutionary response of the cancer to the molecular-targeted agents that form the basis of resistance. Chapter 8, "Somatic Evolution of Acquired Drug Resistance in Cancer", addresses the role of somatic selection in resistance to targeted therapies and suggests therapeutic modalities that do not impose strong somatic selection pressure.

In our final two chapters, we explore possible ways to inhibit multiple therapeutic targets simultaneously, either with novel therapeutics or combinations of molecular-targeted agents. Chapter 9, "MicroRNA: A Potential Therapy Able to Target Multiple Cancer Pathways", explores the role of miRNAs in cancer and discusses the potential for miRNA-based therapeutic strategies. The discovery of noncoding microRNAs as regulators of development and disease has ushered in a new area of research. MicroRNAs target multiple genes, and therefore are potential therapies for the simultaneous inhibition of multiple oncogenes. Such multitarget therapies will be an important tool for addressing resistance to targeted therapies. It is becoming increasingly clear that, for many cancers, the most effective use of molecular-targeted therapies for cancer will require a combination of several such agents. Our final chapter, Chapter 10, "Rational Combination of Targeted Agents to Overcome Cancer Cell Resistance", describes some of the

ongoing work using combinations of molecular-targeted agents. The argument is that the rational combination of targeted agents, and in particular those that block complementary cell survival or cell cycle regulatory pathways, will be an effective therapeutic strategy.

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I hope that the insights and perspective shared in this book will not only aid in your understanding of the subject matter, but also inspire your science well into the future. Enjoy.

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