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Introduction

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INTRODUCTION

The dramatic responses induced by Gleevec^{TM} in patients with chronic myelogenous leukemia and gastrointestinal stromal tumors have generated tremendous excitement and have focused attention on therapies that target molecules that are involved fundamentally in the evolution of a particular cancer. However, the idea of specific, targeted therapy is not a new one, and the treatment of breast cancer provides the oldest example of such a targeted therapy. More than 100 years ago, Beatson demonstrated that estrogen deprivation (by oophorectomy) caused regression of breast cancer. His observations led to the routine use of oophorectomy in the treatment of breast cancer and stimulated investigation of the mechanisms of estrogen function in the pathogenesis of breast cancer. With the understanding of the mechanism of estrogen and estrogen receptor function, drugs that inhibit receptor activation or prevent the production of estrogen have been developed. Today, these hormonal strategies play a central role in the treatment of the majority of patients with breast cancer.

This issue is devoted to therapies that take advantage of molecular targets relevant to breast cancer – so called novel molecular therapies. The chapters selected for this issue are meant to be a sampling of the different approaches being taken to improve upon the current treatment of breast cancer.

The first two chapters review molecular targets that already have been validated as therapeutic targets for breast cancer (i.e., the estrogen receptor and HER-2/neu). That is, therapies directed at these targets have proven efficacy in the treatment or prevention of breast cancer. The first chapter by Fuqua and Cui reviews the role of the estrogen receptor in the pathogenesis and treatment of breast cancer. The authors describe new findings about the estrogen receptor's mechanisms of action, which may provide the basis for better manipulation of the estrogen receptor pathway in the treatment of breast cancer in the future. In the chapter that follows, Zhou, Li, and Hung review HER2/neu signaling pathways and the existing and evolving therapeutic approaches that target either HER2/neu or the downstream pathways.

The remaining chapters discuss a variety of approaches that, as yet, have not been validated as effective therapy for breast cancer. The development of inhibitors of signal transduction pathways downstream of the activated receptor tyrosine kinases (e.g., HER2/neu) is an area of intense activity. Receptor tyrosine kinases initiate a series of signaling events beginning at the membrane, progressing through the cytoplasm and into the nucleus, and culminating in cell cycle progression. Two chapters describe the development of agents that target the cytoplasmic or nuclear phases of signal transduction. Prendergast describes the development of farnesyltransferase inhibitors as inhibitors of Ras. In this chapter, preclinical investigations are described, suggesting that the antitumor activity of farnesyltransferase inhibitors may be mediated by activation of the tumor suppressor effects of RhoB. Data also is presented that suggest that these drugs may act via RhoB to inhibit the

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growth of inflammatory breast cancer cells. Senderowicz presents an overview of the cell cycle, outlines the evidence for aberrations in cell cycle control in cancer patients, and discusses drugs that are being developed to inhibit the cell cycle.

The next chapters review manipulation of protein degradation as an approach to cancer therapy. Protein degradation plays a central role in diverse cellular processes, including signal transduction, transcription, and cell cycle progression. The proteasome, a large multisubunit protein complex, recognizes proteins that have been modified covalently by ubiquitin and degrades them. In the first of these reviews, Neckers describes the development of drugs that inhibit the molecular chaperone, heat shock protein 90. Association of this molecular chaperone is required for the stability and function of many proteins, including proteins important to the pathogenesis of breast cancer (e.g., the estrogen receptor and HER2/neu). Drugs inhibiting the function of the heat shock protein enhance ubiquitin mediated degradation of these proteins and have antitumor efficacy in preclinical trials. In the second of these chapters, Adams describes the development of drugs that inhibit proteasome function. These drugs block ubiquitin mediated degradation of proteins and also have efficacy in preclinical cancer models, including breast cancer. Both classes of drugs are being tested in phase I clinical trials.

Recent work has redefined cancer as an imbalance between proliferation and cell death, rather than simply inappropriate cell growth. The chapter by Cuello, Nau, and Lipkowitz reviews the mechanisms of apoptosis, the dysregulation of apoptosis in the pathogenesis of cancer, and potential ways to induce apoptosis in breast cancer cells.

In the final chapter, Disis summarizes the identification of breast cancer antigens and the development of vaccines. Numerous breast cancer antigens have been identified, and work is in progress to define the most immunogenic antigens. The role of immunotherapy in the treatment of breast cancer most likely will be in the adjuvant or preventive setting.

These chapters present a sampling of both old and new molecularly targeted therapies that are being developed. They represent the beginning of an exciting new era in cancer treatment. However, each new, targeted therapy will need to be validated in preclinical and clinical testing. Furthermore, while the expression of a specific protein or activity of a particular pathway provides an indication of which specific therapy to use, it does not guarantee that therapy targeted to that pathway will be effective. For example, many tumors that express the estrogen receptor do not respond to hormonal manipulations. Similarly, only a fraction of the tumors that have amplification of the HER2/neu gene respond to treatment with Herceptin? (a humaninzed monoclonal antibody directed at HER2/neu). Thus, a thorough understanding of the pathways served by the target and additional information about the molecular phenotype of each tumor will be necessary to truly select those tumors that are most likely to respond to molecularly targeted therapies.