PREFACE

As genomic techniques allow us a closer and closer look at malignant disease, the ability of cells to respond to chemical and biological insults with remarkable flexibility of phenotype makes it clear that, despite some small successes, there is much to be done to control and eliminate malignant disease. The recruitment of a wide variety of host 'normal' cells into the malignant disease process is critical to disease progression. And so, the difficulties in discovering and/or designing highly effective anticancer therapeutics have been clarified. First, malignant cells can respond with epigenetic, as well as genetic, alterations to escape therapeutic attack. Second, there is a continuum of abnormalities and deregulated behaviors between host "normal" cells and neoplastic cells. To address the resistance of solid tumors to anticancer therapeutics, mechanisms that involve alterations in genetics and epigenetics, cellular biochemistry, properties related to physiology of the solid tumor mass, and alterations in host metabolic and immune status induced by the presence of malignant disease must be considered. Owing to the efforts and expertise of each contributor, *Cancer Drug Resistance* describes the current state of knowledge in these numerous areas and relates to resistance to cancer chemotherapy, radiation therapy, and immunotherapies.

This volume represents a point on the path of the long journey toward understanding the complex interactions between host, tumor, and cytotoxic or immunomodulatory agents. Classically, antitumor therapy sensitivity studies were carried out in tumor-bearing animals. Two observations were made during the course of these early studies. One was that tumors repeatedly treated with a drug could become nonresponsive, that is, resistant to that agent. The other observation was that the pharmacology and pharmacokinetics of drugs were different in tumor-bearing animals compared with normal animals. The advent of cell culture techniques allowed studies of therapeutic resistance to focus on the tumor cell. Critical changes in cellular biochemistry and molecular biology that confer resistance to specific therapeutic agents and treatments have been identified.

Techniques for examining the physiology of solid tumors and host normal tissues have been devised and refined. Abnormalities in solid tumor oxygenation, pH, interstitial pressure, perfusion, and vascular structure have been documented. Evidence continues to support the notion that the abnormal physiology of solid tumors protects these masses from therapeutic attack by chemotherapy, radiation therapy, and biological therapies based on protein molecules that include antibodies, cytokines, and growth factors.

The enormous growth of knowledge in the areas of protein effector molecules, cytokines, growth factors, and hormones has brought the study of therapeutic resistance back to the tumor/host as an interactive system with a new insight. The paracrine and autocrine effects of these secreted peptides, proteins, and small molecules continue to

be elucidated. Defining a relationship between levels of these factors in a host and response of a tumor in that host to cancer therapies is only beginning to be realized.

Cancer Drug Resistance will serve as a resource to scientists of diverse specialties with interests relating to the response of malignant disease to current and experimental therapies.

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