

# CANCER DRUG RESISTANCE

# CANCER DRUG DISCOVERY AND DEVELOPMENT

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*Edited by*

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*For the Beautiful Ones,*

*Joseph and Emily*

# PREFACE

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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.

***Beverly A. Teicher, PhD***

# CONTENTS

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Preface .....	vii
Contributors .....	xiii

## PART I. PHYSIOLOGICAL RESISTANCE

1 The Cycle Between Angiogenesis, Perfusion, and Hypoxia in Tumors <i>Mark W. Dewhirst, Yiting Cao, Benjamin Moeller, and Chuan-Yuan Li</i> .....	3
2 Influence of Tumor pH on Therapeutic Response <i>Chang W. Song, Robert Griffin, and Heon Joo Park</i> .....	21
3 Tumor Oxygenation and Treatment Response <i>Sarah Jane Lunt and Richard P. Hill</i> .....	43
4 Oncogenes and Tumor Suppressor Genes in Therapeutic Resistance: <i>The Role of Evolving Interrelationships Between Cancer Cells and Host Tissues</i> <i>Janusz W. Rak, Brenda Coomber, and Joanne L. Yu</i> .....	67
5 PET Imaging of Response and Resistance to Cancer Therapy <i>David A. Mankoff and Kenneth A. Krohn</i> .....	105

## PART II: BIOLOGICAL RESISTANCE

6 Cancer Stem Cells: <i>Implications for Development of More Effective Therapies</i> <i>Ilia Mantle, Gabriela Dontu, Suling Liu, and Max S. Wicha</i> .....	125
7 Therapeutic Resistance in Leukemia <i>William R. Waud</i> .....	137
8 Tumor Site Implantation and Animal Model Selection in Oncology <i>Anibal A. Arjona and Enrique Alvarez</i> .....	151
9 In Vivo Resistance <i>Beverly A. Teicher</i> .....	161
10 Characteristics of the Metastatic Phenotype: <i>The Melanoma Experience</i> <i>Vladislava O. Melnikova and Menashe Bar-Eli</i> .....	181
11 The Microenvironment and Drug Resistance <i>Patrice J. Morin</i> .....	201



**PART III. BIOCHEMICAL RESISTANCE**

- 12 Glutathione and Glutathione S-Transferases in Drug Resistance  
*Victoria J. Findlay, Danyelle M. Townsend,  
and Kenneth D. Tew* ..... 213
- 13 Metallothioneins in Drug Resistance  
*Faiyaz Notta and D. James Koropatnick* ..... 223
- 14 Molecular Determinants of Intrinsic Multidrug Resistance  
in Cancer Cells and Tumors  
*Elena Monti* ..... 241
- 15 New and Revised Concepts in Multidrug Resistance:  
*Sestamibi, SNPs, Substrates, and Stem Cells*  
*Susan E. Bates, John Deeken, Chaohong Fan,  
and Robert W. Robey* ..... 261
- 16 Cisplatin Resistance: *Molecular Basis of a Multifaceted Impediment*  
*Zahid H. Siddik* ..... 283
- 17 Regulation of the Cellular Pharmacology and Cytotoxicity  
of Cisplatin by Copper Transporters  
*Roohangiz Safaei and Stephen B. Howell* ..... 309
- 18 Resistance to Taxanes  
*Lee M. Greenberger and Deepak Sampath* ..... 329
- 19 CpG Island Methylation and Drug Resistance  
*Jens M. Teodoridis and Robert Brown* ..... 359
- 20 *De Novo* and Acquired Resistance to Antitumor Alkylating Agents  
*Lori A. Hazlehurst and William S. Dalton* ..... 377
- 21 Resistance to Antiangiogenic Agents  
*George W. Sledge, Jr., Kathy D. Miller, Bryan Schneider,  
and Christopher J. Sweeney* ..... 391

**PART IV. THE ROLE OF HORMONES, GROWTH FACTORS, AND ONCOGENES**

- 22 Resistance to Antiestrogens  
*Clodia Osipo and Ruth M. O'Regan* ..... 413
- 23 Mechanisms of Glucocorticoid Actions and Resistance  
in Multiple Myeloma  
*Varsha Gandhi and Beatriz Sanchez-Vega* ..... 435
- 24 Herceptin Resistance  
*Ingrid A. Mayer and Carlos L. Arteaga* ..... 459

---

25	Role of TGF- $\beta$ in Tumor Progression and Metastasis <i>Jan Pinkas and Beverly A. Teicher</i> .....	469
26	p53-Based Immunotherapy of Cancer <i>Albert B. DeLeo</i> .....	491
27	Response and Resistance to Ionizing Radiation <i>Paul Dent, Adly Yacoub, Michael P. Hagan, and Steven Grant</i> .....	507
28	Amplification in DNA Copy Numbers as a Mechanism of Acquired Drug Resistance <i>M. Jim Yen, Ie-Ming Shih, Victor E. Velculescu, and Tian-Li Wang</i> .....	531
<b>PART V. CLINICAL ASPECTS OF RESISTANCE</b>		
29	Cancer Chemotherapy: <i>Clinical Evidence for Drug Resistance</i> <i>Mika A. Sovak and David R. Spriggs</i> .....	543
30	Molecular Profiling in Breast Cancer: <i>Genomic Approaches</i> <i>Toward Tailored Cancer Therapies</i> <i>Kristin Kee and Jeffrey E. Green</i> .....	559
31	Tumor Immune Escape Mechanisms <i>Yi Ting Koh, M. Luz García-Hernández, and W. Martin Kast</i> .....	577
	Index .....	603

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