Drug Management of Prostate Cancer
Prostate cancer is the most common noncutaneous malignancy and the second leading cause of cancer deaths among men in the United States. It is a critical public health problem and remains incurable in the metastatic setting with mortality that usually occurs as a result of castration-resistant disease.

Since Huggins and Hodges’ report of the dramatic clinical effects of suppressing serum testosterone levels in men with advanced prostate cancer in 1941, hormone therapy (also called androgen deprivation therapy [ADT]) has become widely accepted as the mainstay of therapy for the treatment of advanced prostate cancer. ADT combined with radiation therapy is a standard of care in the treatment of men with locally advanced prostate cancer on the basis of evidence that shows improved survival. The role of ADT in the management of prostate cancer is controversial in that it is also used for other prostate cancer states (such as in men with biochemical recurrence after radical prostatectomy or lymph node metastases) even though the clinical effects of hormone therapy in these other settings have not been definitively proven to be beneficial. Hence the first part of this volume will focus on the role of hormone therapy in the management of advanced prostate cancer and address the controversies relevant to the role of ADT, including the time to initiate ADT, optimum duration of ADT, the benefits of combined androgen blockade, the role of intermittent ADT, and the benefits of secondary hormonal therapies.

In men whose cancer is no longer responding to hormone therapy, the treatment paradigm is shifted toward chemotherapy and other investigational options. In 2004, two landmark trials using docetaxel-based chemotherapy demonstrated for the first time a survival benefit in metastatic, castration-resistant prostate cancer. Research has revealed several distinct mechanisms of castration-resistant disease that may converge in patients with disease progression on ADT. Many approaches are currently being evaluated to improve the treatment of this condition and these findings have identified several potential targets for therapeutic intervention. These include drugs that are more active or less toxic chemotherapy agents; drugs that induce androgen deprivation; drugs that target the androgen receptor and/or androgen synthesis; drugs that target specific pathways, including angiogenesis and tyrosine kinase inhibitors, endothelin antagonists and matrix metalloproteinase inhibitors; and immunologic approaches. Many of these agents seem promising and the rationale and efficacy of these emerging therapies remain to be validated in future clinical trials.

In light of a growing array of existing and novel treatment options, this book was undertaken to capture the multidisciplinary care approach to the drug management of prostate cancer in order to optimize survival and quality of life for the patients. At this unique juncture in the treatment of prostate cancer, current standard and investigational treatment options for this disease are discussed, including hormone therapy and chemotherapy as well as rapidly evolving therapies in phase II/III trials involving antiangiogenic therapies, immunomodulatory agents, and nuclear receptor targets. It is divided into seven sections, preceded by an introduction that discusses the cell biology and molecular targets of prostate cancer. Part I describes the role of androgens and androgen deprivation therapy in prostate cancer and the several types of hormone therapy used to treat advanced prostate cancer, including luteinizing hormone-releasing hormone agonists and antagonists, and anti-androgens. Androgen receptor biology and the pharmacogenetics of the androgen
metabolic pathway are also presented. Part II discusses the role of chemotherapy in prostate cancer including standard and investigational approaches as well as the clinical pharmacology and pharmacogenetics of these agents. Part III introduces the concept of angiogenesis in prostate cancer by discussing the principles of anti-angiogenic therapy, investigational angiogenesis inhibitors, and the pharmacogenetics of angiogenesis. Part IV focuses on the pathophysiology of prostate cancer bone metastasis and the agents used at this stage of the disease process. Part V continues on to describe the role of immunotherapy for advanced prostate cancer including immunotherapeutics and vaccine approaches. In Part VI, chemoprevention strategies for prostate cancer are discussed. The last section of the book, Part VII, looks at the overall drug and technological development efforts and challenges in prostate cancer.

As such, this book is a comprehensive, concise summary of the pharmacological treatments of prostate cancer detailing knowledge of both conventional and emerging drug therapies. The chapters describe state-of-the-art information that will be appropriate for medical students, physicians in training, physicians, scientists, and members of the pharmaceutical industry. As advances in understanding the biology of prostate cancer and the mechanisms of castration-resistant disease continue over the next decade, novel drug discovery and development efforts will translate into emerging treatment paradigms in the therapeutic management of prostate cancer.

Lastly, we would like to thank our colleagues for providing their timely and important chapters. Our task of compiling this book was made easy by their high-quality contributions.

William D. Figg
Cindy H. Chau
Eric J. Small
Preface ................................................................................................................ v

Contributors ........................................................................................................ xi

1. Cell Biology of Prostate Cancer and Molecular Targets ......................... 1
   Martin E. Gleave, Michael E. Cox, and Yuzhuo Wang

Part I. Hormone Therapy

2. Luteinizing Hormone-Releasing Hormone and its Agonistic, Antagonistic, and Targeted Cytotoxic Analogs in Prostate Cancer ................................................................. 27
   Andrew V. Schally and Norman L. Block

3. Nuclear Receptor Coregulators: Promising Therapeutic Targets for the Treatment of Prostate Cancer ................................................................. 41
   Hannelore V. Heemers and Donald J. Tindall

4. Androgens and Prostate Cancer ................................................................. 53
   Douglas K. Price and Ann W. Hsing

5. Androgen Receptor Biology in Prostate Cancer ........................................ 61
   Edward P. Gelmann

6. Androgen Receptor Antagonists ................................................................. 71
   Howard C. Shen, Mary-Ellen Taplin, and Steven P. Balk

7. 5-Alpha Reductase Inhibitors in Prostate Cancer ..................................... 83
   Zoran Culig

8. Adrenal Androgen Synthesis Inhibitor Therapies in Castration-Resistant Prostate Cancer ................................................................. 91
   Terence W. Friedlander and Charles J. Ryan
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Author(s)</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Androgen Deprivation Therapy</td>
<td>Nima Sharifi</td>
<td>101</td>
</tr>
<tr>
<td>10</td>
<td>Pharmacogenetics of the Androgen Metabolic Pathway</td>
<td>Francine Zanchetta Coelho Marques, Juergen K.V. Reichardt</td>
<td>109</td>
</tr>
<tr>
<td></td>
<td><strong>Part II. Chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Mitoxantrone</td>
<td>Patricia Halterman, Nicholas J. Vogelzang, Oscar B. Goodman Jr.</td>
<td>125</td>
</tr>
<tr>
<td>12</td>
<td>Docetaxel</td>
<td>Courtney K. Phillips, Daniel P. Petrylak</td>
<td>133</td>
</tr>
<tr>
<td>13</td>
<td>Beyond Docetaxel: Emerging Agents in the Treatment of Advanced Prostate Cancer</td>
<td>Jonathan Rosenberg</td>
<td>147</td>
</tr>
<tr>
<td>14</td>
<td>Platinum Agents in Prostate Cancer</td>
<td>Ashley Brick, Junyang Niu, Jiaoti Huang, William K. Oh</td>
<td>153</td>
</tr>
<tr>
<td>15</td>
<td>Clinical Pharmacology and Pharmacogenetics of Chemotherapy in Prostate Cancer</td>
<td>Tristan M. Sissung, William D. Figg</td>
<td>163</td>
</tr>
<tr>
<td>16</td>
<td>Microtubule Targeting Agents</td>
<td>Antonio Tito Fojo, David E. Adelberg</td>
<td>179</td>
</tr>
<tr>
<td></td>
<td><strong>Part III. Angiogenesis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Principles of Antiangiogenic Therapy</td>
<td>Cindy H. Chau, William D. Figg</td>
<td>197</td>
</tr>
<tr>
<td>18</td>
<td>Bevacizumab in Advanced Prostate Cancer</td>
<td>Aymen A. Elfiky, William Kevin Kelly</td>
<td>207</td>
</tr>
<tr>
<td>19</td>
<td>Thalidomide and Analogs</td>
<td>Erin R. Gardner, Giuseppe Di Lorenzo, William D. Figg</td>
<td>215</td>
</tr>
<tr>
<td>20</td>
<td>Investigational Angiogenesis Inhibitors</td>
<td>Jeanny B. Aragon-Ching, William Dahut</td>
<td>225</td>
</tr>
<tr>
<td>21</td>
<td>Pharmacogenetics of Angiogenesis</td>
<td>Guido Bocci, Giuseppe Pasqualetti, Antonello Di Paolo, Francesco Crea, Mario Del Tacca, Romano Danesi</td>
<td>233</td>
</tr>
</tbody>
</table>
Part IV. Bone Metastasis

22. Pathophysiology of Prostate Cancer Bone Metastasis ......................................... 245
   Evan T. Keller and Christopher L. Hall

23. Radiopharmaceuticals .......................................................................................... 255
   Oliver Sartor and Damerla R. Venugopal

24. Bisphosphonates for Prevention and Treatment of Bone Metastases .................. 267
   Philip J. Saylor and Matthew R. Smith

25. Endothelin Receptors as Therapeutic Targets in Castration-Resistant Prostate Cancer ........................................................ 277
   Joel B. Nelson

26. Calcitriol and Vitamin D Analogs ........................................................................ 287
   Ana R. Jensen, Russell Z. Szmulewitz, Tomasz M. Beer, and Edwin M. Posadas

Part V. Immunotherapy

27. Cancer Immunology, Immunotherapeutics, and Vaccine Approaches .................. 305
   Ravi A. Madan, James L. Gulley, Jackie Celestin, Philip M. Arlen, and Jeffrey Schlom

28. Sipuleucel-T (APC8015): Active Cellular Immunotherapy for Advanced Metastatic Castration-Resistant Prostate Cancer ........ 321
   Celestia S. Higano and Mark W. Frohlich

29. GM-CSF Gene-Transduced Prostate Cancer Vaccines: GVAX ......................... 329
   Lalit R. Patel and Jonathan W. Simons

30. CTLA-4 Blockade for Prostate Cancer Treatment ............................................. 343
   Andrea L. Harzstark and Lawrence Fong

Part VI. Prevention

31. Prostate Cancer Chemoprevention Strategies ................................................. 351
   Howard L. Parnes, Margaret G. House, and Joseph A. Tangrea

32. Diet and Prostate Cancer Incidence, Recurrence, and Progression Risk ............ 363
   June M. Chan and Erin L. Richman
33. **Inflammation as a Target in Prostate Cancer** ........................................ 375
   Marshall Scott Lucia, James R. Lambert, Elizabeth A. Platz,
   and Angelo M. De Marzo

Part VII. Drug Development

34. **Challenges for the Development of New Agents in Prostate Cancer** ................................................................. 389
   Ajjai S. Alva, Deborah A. Bradley, and Maha Hussain

35. **FDA Approval of Prostate Cancer Treatments** ........................................ 399
   Yang-Min Ning, Ramzi N. Dagher, and Richard Pazdur

36. **Applications of Proteomics in Prostate Cancer** ................................. 407
   Mitchell Gross, Edward Macrohon Nepomuceno, and David B. Agus

**Erratum** ............................................................................................................. E1

**Index** .................................................................................................................. 419
Contributors

David E. Adelberg
Medical Oncology Branch, National Cancer Institute, Bethesda MD, USA

David B. Agus
USC, Westside Prostate Cancer Center, Keck School of Medicine of USC, Beverly Hills, CA, USA

Ajjai S. Alva
Doctor, Hematology/Oncology Department, University of Michigan, Ann Arbor MI, USA

Jeanny B. Aragon-Ching
Department of Medicine, George Washington University, Washington, DC, USA

Philip M. Arlen
Attending Physician Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda MD, USA

Steven P. Balk
Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston MA 02215, USA

Tomasz M. Beer
Associate Professor of Medicine, Grover C. Bagby Endowed Chair for Prostate Cancer Research Medicine/Hematology and Medical Oncology, Oregon Health & Science University, Portland OR, USA

Norman L. Block
Clinical Director of the Endocrine, Polypeptide, and Cancer Institute, Pathology, Urology, Oncology Miami Veterans Affairs Medical Center, Jackson Memorial Hospital, University of Miami Hospital, University of Miami, Miami FL, USA

Guido Bocci
Assistant Professor Division of Pharmacology and Chemotherapy, Department of Internal Medicine, University of Pisa, Pisa, Italy

Deborah A. Bradley
Assistant Professor of Medicine Department of Internal Medicine, University of Michigan, Ann Arbor MI, USA
Ashley Brick  
Clinical Research Coordinator Genitourinary Oncology,  
Dana-Farber Cancer Institute, Boston, MA USA

Jackie Celestin  
Internal Medicine, University of Connecticut, Farmington, CT USA

June M. Chan  
Epidemiology and Biostatistics, Urology, University of California,  
San Francisco, CA, USA

Cindy H. Chau  
Medical Oncology Branch, Center for Cancer Research,  
National Cancer Institute/NIH, Bethesda, MD, USA

Michael E. Cox  
Associate Professor UBC Department of Urologic Sciences, The Vancouver  
Prostate Centre, Vancouver General Hospital, University of British Columbia,  
Vancouver BC, Canada

Francesco Crea  
Student Division of Pharmacology and Chemotherapy,  
Department of Internal Medicine, University of Pisa, Pisa, Italy

Zoran Culig  
Department of Urology, Innsbruck Medical University, Innsbruck, Austria

Ramzi N. Dagher  
VP Worldwide Regulatory Strategy, Global Research and Development,  
Pfizer, Inc., New London CT, USA

William Dahut  
Chief Genitourinary Research Section Medical Oncology Branch, CCR, NCI, NIH  
Clinical Center, National Cancer Institute, Bethesda MD, USA

Romano Danesi  
Division of Pharmacology and Chemotherapy, Department of Internal Medicine,  
University of Pisa, Pisa, Italy

Angelo M. De Marzo  
Department of Pathology, Bunting Blaustein Cancer Research,  
The Johns Hopkins University School of Medicine, Baltimore MD, USA

Mario Del Tacca  
Full Professor Division of Pharmacology and Chemotherapy,  
Department of Internal Medicine, University of Pisa, Pisa, Italy

Giuseppe Di Lorenzo  
Medical Oncology, AOU Federico II, Napoli, Italy

Antonello Di Paolo  
Division of Pharmacology and Chemotherapy, Department of Internal Medicine,  
University of Pisa, Pisa, Italy
Aymen A. Elfiky
Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute,
Brigham and Women’s Hospital, Harvard Medical School, Boston MA, USA

Alireza Farabishahadel
Department of Internal Medicine, University of Nevada School of Las Vegas,
Las Vegas NV, USA

William D. Figg
Medical Oncology Branch, Center for Cancer Research,
National Cancer Institute, National Institute of Health, Bethesda, MD, USA

Antonio Tito Fojo
Experimental Therapeutics Section, Medical Oncology Branch,
Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

Lawrence Fong
Associate Professor Department of Medicine, Division of Hematology/Oncology,
University of California San Francisco, San Francisco CA, USA

Terence W. Friedlander
Department of Medicine, Division of Hematology/Oncology,
University of California San Francisco Medical Center, San Francisco CA, USA

Mark W. Frohlich
Sr. Vice President, Clinical Affairs and Chief Medical Officer
Dendreon Corporation, Seattle WA, USA

Erin R. Gardner
SAIC-Frederick, Inc., Clinical Pharmacology Program, National Cancer Institute,
Frederick MD, USA

Edward P. Gelmann
Division of Hematology/Oncology, Herbert Irving Comprehensive Cancer Center,
Columbia University, New York, NY, USA

Martin E. Gleave
UBC Department of Urologic Sciences, The Vancouver Prostate Center,
Vancouver General Hospital,
University of British Columbia, Vancouver, BC, Canada

Oscar B. Goodman
Jr., Assistant Professor Clinical Oncology, Nevada Cancer Institute,
Las Vegas NV, USA

Mitchell Gross
Director of Experimental Therapeutics Louis Warschaw Prostate Cancer Center,
Cedars-Sinai Medical Center, Los Angeles CA, USA

James L. Gulley
Laboratory of Tumor Immunology and Biology, Medical Oncology Branch,
National Cancer Institute, Bethesda, MD, USA
Christopher L. Hall  
Research Investigator Department of Urology, University of Michigan, 
Ann Arbor MI, USA

Patricia Halterman  
Clinical Pharmacy, Nevada Cancer Institute, Las Vegas, NV, USA

Andrea L. Harzstark  
Department of Medicine, Division of Hematology/Oncology, 
University of California San Francisco, San Francisco, CA, USA

Hannelore V. Heemers  
Department of Urology, Rosewell Park Cancer Institute, Buffalo, NY 14263, USA

Celestia S. Higano  
University of Washington, Seattle Cancer Care Alliance, Seattle, WA, USA

Margaret G. House  
Nurse Consultant Division of Cancer Prevention, Department of Health and 
Human Services, National Cancer Institute, Rockville MD, USA

Ann W. Hsing  
Senior Investigator Division of Cancer Epidemiology and Genetics, 
National Cancer Institute, National Institutes of Health, Bethesda MD, USA

Jiaoti Huang  
Professor Pathology Department, UCLA David Geffen School of Medicine, 
Los Angeles CA, USA

Maha Hussain  
Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI, USA

Ana R. Jensen  
Sections of Hematology/Oncology, Department of Medicine, 
University of Chicago, Chicago IL, USA

Evan T. Keller  
Department of Urology, University of Michigan, Ann Arbor, MI, USA

William Kevin Kelly  
Solid Tumor Oncology, Department of Medical Oncology, Associate Director of 
Translation Research, Jefferson Kimmel Cancel Center, Thomas Jefferson 
University, Suite 314, Philadelphia, PA 19107, USA

James R. Lambert  
Assistant Professor Pathology Department, 
University of Colorado Denver, Aurora CO, USA

Marshall Scott Lucia  
Department of Pathology, University of Colorado, Denver, Aurora, CO, USA

Ravi A. Madan  
Assistant Clinical Investigator Laboratory of Tumor Immunology and Biology, 
Medical Oncology Branch, National Cancer Institute, Bethesda MD, USA
Francine Zanchetta Coelho Marques  
Plunkett Chair of Molecular Biology (Medicine) Anatomy Department, The University of Sydney, Sydney NSW, Australia

Joel B. Nelson  
Department of Urology, University of Pittsburgh, Pittsburgh, PA, USA

Edward Macrohon Nepomuceno  
Fellow in Medical Oncology and Hematology Olive View, Department of Medicine, UCLA Medical Center, Sylmar CA, USA

Yang-Min Ning  
Office of Oncology Drug Products, The U.S. Food and Drug Administration, Silver Spring MD, USA

Junyang Niu  
Professor Pathology Department, Anhui Provincial Hospital, Hefei, Anhui Province, China

William K. Oh  
Division of Hematology and Medical Oncology, Dana-Farber Cancer Institute, New York, 10029 NY, USA

Howard L. Parnes  
Prostate and Urologic Cancer Research Group, NCI-Division of Cancer Prevention, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

Guiseppe Pasqualetti  
Post-doctoral Fellow Division of Pharmacology and Chemotherapy, Department of Internal Medicine, University of Pisa, Pisa, Italy

Lalit R. Patel  
Research Coordinator Prostate Cancer Foundation, Santa Monica CA, USA

Richard Pazdur  
Director Office of Oncology Drug Products, The U.S. Food and Drug Administration, Silver Spring MD, USA

Daniel P. Petrylak  
Columbia University Medical Center, New York, NY

Courtney K. Phillips  
Assistant Professor of Urology Urology Department, Mount Sinai School of Medicine, New York NY, USA

Elizabeth A. Platz  
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore MD, USA

Edwin M. Posadas  
Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL 60637, USA

Douglas K. Price  
Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
Juergen K.V. Reichardt  
Plunkett Chair of Molecular Biology (Medicine),  
The University of Sydney, Sydney, NSW, Australia

Erin L. Richman  
Nutrition Department, Harvard School of Public Health, Boston MA, USA

Jonathan Rosenberg  
Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute,  
Boston, MA, USA

Charles J. Ryan  
Department of Medicine, University of California San Francisco,  
San Francisco CA, USA

Oliver Sartor  
Departments of Medicine and Urology, Tulane Medical School,  
New Orleans, LA, USA

Philip J. Saylor  
Department of Medicine, Division of Hematology/Oncology,  
Massachusetts General Hospital Cancer Center, Boston, MA, USA

Andrew V. Schally  
Department of Veterans Affairs, VA Research Services, Veterans Affairs Medical  
Center, Miami FL, USA, and Division of Hematology/Oncology and Division of  
Endocrinology,  
Departments of Pathology and Medicine, Miller School of Medicine,  
University of Miami, Miami, FL, USA

Jeffrey Schlom  
Chief Laboratory of Tumor Immunology and Biology,  
Center for Cancer Research, National Cancer Institute,  
National Institutes of Health, Bethesda MD, USA

Nima Sharifi  
Division of Hematology/Oncology, University of Texas Southwestern Medical  
Center, Dallas, TX, USA

Howard C. Shen  
Research Fellow Department of Medicine, Bth Israel Deaconess Medical Center,  
Harvard Medical School, Boston MA, USA

Jonathan W. Simons  
Prostate Cancer Foundation, Santa Monica, CA, USA

Tristan M. Sissung  
Medical Oncology Branch, Center for Cancer Research, National Cancer Institutes,  
National Institute of Health, Bethesda MD, USA

Matthew R. Smith  
Associate Professor Division of Hematology/Oncology, Department of Medicine,  
Massachusetts General Hospital Cancer Center, Harvard Medical School,  
Boston MA, USA
Russell Z. Szmulewitz
Instructor Sections of Hematology/Oncology, Department of Medicine,
University of Chicago, Chicago IL, USA

Joseph A. Tangrea
Program Director Department of Health and Human Services,
National Cancer Institute, Rockville MD, USA

Mary-Ellen Taplin
Associate Professor of Medicine  Lank Center for Genitourinary,
Oncology, Harvard Medical School, Dana-Farber Cancer Institute,
Boston MA, USA

Donald J. Tindall
Professor Department of Urology Research,
Mayo Clinic, Rochester MN, USA

Damerla R. Venugopal
Section of Hematology-Oncology, Department of Medical Oncology,
Tulane Medical School, New Orleans LA, USA

Nicholas J. Vogelzang
Professor, Director Medical Oncology, Nevada Cancer Institute,
University of Nevada School of Medicine, Las Vegas NV, USA

Yuzhuo Wang
Senior Scientist The Vancouver Prostate Centre, Vancouver General Hospital,
University of British Columbia, Vancouver BC, Canada