Prostate Cancer

CURRENT CLINICAL ONCOLOGY

Maurie Markman, MD, SERIES EDITOR

Integrative Oncology: *Incorporating Complementary Medicine into Conventional Cancer Care,* edited by *LORENZO COHEN AND MAURIE MARKMAN, 2008*

Prostate Cancer: *Signaling Networks, Genetics, and New Treatment Strategies,* edited by *RICHARD G. PESTELL AND MARJA T. NEVALAINEN, 2008*

Intraperitoneal Cancer Therapy, edited by *WILLIAM C. HELM AND ROBERT EDWARDS, 2007*

Molecular Pathology of Gynecologic Cancer, edited by *ANTONIO GIORDANO, ALESSANDRO BOVICELLI, AND ROBERT KURMAN, 2007*

Colorectal Cancer: *Evidence-Based Chemotherapy Strategies,* edited by *LEONARD B. SALTZ, 2007*

High-Grade Gliomas: *Diagnosis and Treatment,* edited by *GENE H. BARNETT, 2006*

Cancer in the Spine: *Comprehensive Care,* edited by *ROBERT F. MCLAIN, KAI-UWE LEWANDROWSKI, MAURIE MARKMAN, RONALD M. BUKOWSKI, ROGER MACKLIS, AND EDWARD C. BENZEL, 2006*

Squamous Cell Head and Neck Cancer, edited by *DAVID J. ADELSTEIN, 2005*

Hepatocellular Cancer: *Diagnosis and Treatment,* edited by *BRIAN I. CARR, 2005*

Biology and Management of Multiple Myeloma, edited by *JAMES R. BERENSON, 2004*

Cancer Immunotherapy at the Crossroads: *How Tumors Evade Immunity and What Can Be Done,* edited by *JAMES H. FINKE AND RONALD M. BUKOWSKI, 2004*

Treatment of Acute Leukemias: *New Directions for Clinical Research,* edited by *CHING-HON PUI, 2003*

Allogeneic Stem Cell Transplantation: *Clinical Research and Practice,* edited by *MARY J. LAUGHLIN AND HILLARD M. LAZARUS, 2003*

Chronic Leukemias and Lymphomas: *Biology, Pathophysiology, and Clinical Management,* edited by *GARY J. SCHILLER, 2003*

Colorectal Cancer: *Multimodality Management,* edited by *LEONARD SALTZ, 2002*

Breast Cancer: *A Guide to Detection and Multidisciplinary Therapy,* edited by *MICHAEL H. TOROSIAN, 2002*

Melanoma: *Biologically Targeted Therapeutics,* edited by *ERNEST C. BORDEN, 2002*

Prostate Cancer

Signaling Networks, Genetics, and New Treatment Strategies

Edited by

Richard G. Pestell, MD, PhD

Marja T. Nevalainen, MD, PhD

Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA

Foreword by

Michael Milken, MBA

Prostate Cancer Foundation, Santa Monica, CA

Humana Press

Editors
Richard G. Pestell
Department of Cancer Biology
Kimmel Cancer Center
Thomas Jefferson University
Philadelphia, PA

Marja T. Nevalainen
Department of Cancer Biology
Kimmel Cancer Center
Thomas Jefferson University
Philadelphia, PA

Series Editor
Maurie Markman
MD Anderson Cancer Center
University of Texas
Houston, TX

ISBN 978-1-58829-741-9 e-ISBN 978-1-60327-079-3

Library of Congress Control Number: 2007941659

Cover illustration: Fig. 3, Chapter 17, "Advances in Surgical Intervention of Prostate Cancer: Comparison of the Benefits and Pitfalls of Retropubic, Perineal, and Laparoscopic Radical Prostatectomy," by Jay B. Basillote, Thomas E. Ahlering, and Douglas W. Skarecky.

Printed on acid-free paper

9 8 7 6 5 4 3 2 1

springer.com

Foreword

The minute I walked in the door, I knew something was wrong. My wife waited until I took off my coat and sat down at the kitchen table. "I had some bad news today," Lori began. "Mom has cancer." We talked for hours about what it meant and what we could do to help. It was 1972, only a year after President Nixon had declared "war on cancer," and many of us thought that a concerted national effort could lead to a cure in the same way that President Roosevelt's targeting of polio and President Kennedy's quest to put men on the moon had succeeded.

Over the next 20 years, I acquired an extensive layman's knowledge of cancer in the process of supporting research and seeking effective treatments for my mother-in-law's breast cancer and, later, my father's malignant melanoma, and the cancers of several other close relatives. By 1982, my brother and I had assembled a professional staff to formalize our philanthropy through our family charity, the Milken Family Foundation. Working closely with the foundation's medical and scientific advisors, we became very familiar with the leading-edge work of our grant recipients. We were inspired by the progress of pioneers such as Dennis Slamon in breast cancer, Bert Vogelstein in cancer genetics, Owen Witte in leukemia, Lawrence Einhorn in testicular cancer, and many other recipients of the foundation's cancer research awards.

By the time I was diagnosed with advanced prostate cancer in 1993, I thought I knew a lot about cancer. So the shock of my diagnosis was compounded by the realization that I knew almost nothing about prostate cancer. How could I have spent two decades working with cancer researchers and possess so little knowledge of this disease that had already spread from my prostate to my abdominal lymph nodes? How could I not know that this disease affects one in six American men or that a man is more likely to develop prostate cancer than a woman is to develop breast cancer?

It turned out that I was not alone. The public knew next to nothing about prostate cancer. Articles in the popular press, which so often chronicled the importance of pap smears, mammograms, and smoking cessation, rarely mentioned that little walnut-sized organ surrounding men's urethras. As far as most men were concerned, this disease was something they didn't want to think about. Men seem to be more fatalistic than women and believe they're either living or dying so there's no point in getting tested.

Even more surprising was the lack of interest in the medical community. The National Cancer Institute didn't fund much research on prostate cancer because they received few grant applications. Physician–scientists weren't submitting the applications because there appeared to be little funding available. It was a vicious circle. The field was so moribund that one young investigator was told by his mentor to avoid the "career suicide" of prostate cancer research.

Meanwhile, the pharmaceutical and biotechnology industries weren't allocating enough research funds to cancer drug development because they didn't think the return on the investment would justify the risk. And as I traveled around the country to major academic research centers, I felt a growing sense of frustration, and even anger, when I realized that each of these elite institutions considered the others to be competitors rather than collaborators in cancer research.

After extensive discussions with the heads of these centers and other advisors, I concluded that a new organization was needed to bring focus and a sense of urgency to the field of prostate cancer research. This organization, which would become the Prostate Cancer Foundation (PCF), would need to:

- Identify promising research not being funded by the National Cancer Institute;
- Recruit the best and brightest investigators to energize the field;
- Reduce paperwork requirements and fund projects quickly;
- Require awardees to share the results of their work;
- Help build centers of excellence in prostate cancer and link them digitally;
- Encourage public–private partnerships;
- Pursue a venture-funding model;
- Act with urgency;
- Build public awareness.

The Milken Family Foundation jump-started the process with early funding, but since then, the majority of funds for more than 1400 competitive research awards have been contributed by the public. Awardees gather each year at the PCF's Scientific Retreat to present their findings. Many of them are affiliated with member institutions of the PCF Therapy Consortium comprising eight leading cancer centers that now collaborate on prostate cancer programs.

Over the past 15 years, we've reached several important milestones. The Department of Defense Prostate Cancer Research Program exceeds three-quarters of a billion dollars in cumulative spending. Hundreds of bright young investigators are launching careers in prostate cancer research. Prostate cancer SPORE grants have increased fivefold. Articles about prostate cancer in popular periodicals increased from 2500 in 1993 to nearly 36,000 in 2006. Federal and state government funding of prostate cancer research is 20 times the 1993 level. Major states like New York and California allow taxpayers to check off a donation to prostate cancer research on their tax returns. Institutions

in dozens of countries around the world now participate in PCF collaborations. The latest treatment options are described in a patient guide, and in a separate professional guide, published by the PCF. Millions more men now know about prostate-specific antigen (PSA) tests and DREs. Far more drugs targeting prostate cancer are available or in development than even a few years ago.

None of these achievements would mean much, however, if we weren't keeping more men alive and if they weren't able to enjoy a good quality of life. Fortunately, there's progress here, too. Close to 40,000 prostate cancer patients were dying each year in the early 1990s. With the aging of the baby-boom cohort, that number was expected to increase to as many as 60,000 deaths today. Instead, the number has fallen to below 28,000. The reasons are complex and no one initiative should receive the credit, nor can we be complacent, because without major breakthroughs, death totals could rise again as the first baby boomers move through their seventh and eighth decades.

The work described in *Prostate Cancer: Signaling Networks, Genetics, and New Treatment Strategies*, however, is cause for optimism. The authors of the chapters included here—16 of whom are PCF awardees—are moving quickly on the frontiers of science. They're providing hope that the two million Americans currently living with prostate cancer and the three million projected to join them in the next decade will live long, fulfilling lives.

Building on the lessons of the PCF, we've established a separate organization dedicated to removing the barriers to progress that so often frustrate the efforts of the best researchers in all fields of medicine. This new group, known as FasterCures and headquartered in Washington, D.C., does not fund medical research. Rather, it figures out how we can improve the *process* of research by creating more effective incentives, eliminating unnecessary bureaucracy, improving professional training, linking biobanks, and other steps that shorten the time from idea to bench to bedside. All readers of this book are invited to join us in our effort to make cancer something that our grandchildren will know only by reading history books.

Michael Milken, MBA

Michael Milken, called "The Man Who Changed Medicine" in a 2004 Fortune magazine cover story, is the founder and chairman of the Prostate Cancer Foundation and of FasterCures/The Center for Accelerating Medical Solutions. He has supported medical research for 35 years.

Preface

Prostate cancer remains a major healthcare challenge in the United States. Currently, prostate cancer is the most commonly diagnosed malignancy and the second leading cause of cancer-related deaths in men in the United States. Alternate therapy approaches based on a deeper understanding of prostate cancer are of vital importance. At this time, more than 218,000 new cases of prostate cancer will be diagnosed per year in the United States, and more than 27,000 men will die annually from this disease. We now know that the economic, physical, and psychological burden will be significantly greater for certain groups, including African American men. At this time, an African American man is approximately 2.5 or more times likely to die from prostate cancer than a Caucasian American man. *Prostate Cancer: Signaling Networks, Genetics, and New Treatment Strategies* describes the most current understanding of the molecular mechanisms underlying the onset and progression of prostate cancer. In an attempt to identify new molecular targets for therapy development of prostate cancer, current concepts of steroid receptor and protein kinase signaling pathways are reviewed. In addition, new perspectives in radiation therapy, prediction of therapeutic response, new directions in hormonal treatment, surgical intervention, and targeted therapies are described.

In the opening chapter, new information of histological changes in the prostate associated with cellular atrophy and inflammation provides insight into the pathogenesis of prostate cancer. Chapters 2 through 5 are focused on the key genetic changes involved in prostate carcinogenesis and progression and specific epigenetic abnormalities that accompany prostate cancer progression to advanced disease. The molecular mutations, both low and high penetrant variants, which predispose to and/or modify the response to treatment of prostate cancer, are described. In Chapter 4, Dr. Gelmann focuses on the role of cell cycle control, DNA repair, and oncogenic and tumor suppressor drivers in prostate cancer. In Chapter 5, Drs. Helenius, Waltering, and Visakorpi introduce the role of the somatic genetic changes and the important role of the androgen receptor. Chapters 6 through 9 articulate the role of nuclear hormone receptors in the onset and progression of prostate cancer. We find that the androgen receptor is post-translationally modified not only by phosphorylation but also by acetylation, and these specific post-translational modifications provide new avenues for intervention. In Chapters 8 (Drs. Imamov, Lopatkin, and Gustafsson) and 9 (Drs. Prins and Korach), the authors present an important

and balanced view on the role of both estrogen receptors α and β in prostate tumorigenesis.

Chapters 10 through 13 summarize recent advances in intracellular signaling pathways, including the importance of hypoxia-inducible factor 1, the Ras–MAP kinase pathway, the transcription factors STAT5 and STAT3, and the role of Akt and PI3K kinase signaling in prostate cancer progression. Transcription factor Stat5 as a therapeutic target and prognostic factor of poor clinical outcome is described.

With the goal of identifying key molecular targets for therapeutic stratification and prognostication, Chapters 14 through 20 focus on predictors of clinical outcome and the values of specific molecular targets in the management of prostate cancer. Advances in radiation therapy, hormonal therapy, and surgical intervention are highlighted in Chapters 16 and 17. In Chapter 17, Drs. Basillote, Ahlering, and Skarecky highlight recent data using the Da Vinci Surgical System. In Chapter 18, Drs. Heath and Carducci outline key opportunities given by more than 200 novel agents currently under evaluation in the treatment of prostate cancer. Chapter 19 describes new perspectives in chemotherapy of prostate cancer. In closing, opportunities for early detection and treatment of prostate cancer are outlined by Dr. Gomella and Dr. Valicenti.

As a collective medical community, our responsibility lies with engaging all individuals participating in early detection and valuable preventative measures. We are most grateful for the participation of our colleagues in creating this book for the improvement of the treatment of patients with prostate cancer. We acknowledge and share our gratitude to our patients and families who inspire and guide us on a daily basis.

Richard G. Pestell, MD, PhD
Marja T. Nevalainen, MD, PhD

Contents

Foreword v

Preface ix

Contributors xiii

1. Histopathology and Molecular Biology of Prostate Atrophy: *A Lesion Associated with Inflammation, Prostate Intraepithelial Neoplasia, and Prostate Cancer* 1
Alexander Valdman, Robert B. Jenkins, Fusheng Lan, and Angelo M. De Marzo

2. Epigenetic Gene Silencing in Prostate Cancer 17
Srinivasan Yegnasubramanian and William G. Nelson

3. Inherited Genetic Changes in Prostate Cancer 53
John D. Carpten and Jeffrey M. Trent

4. Prostate Molecular Oncogenesis: *Gene Deletions and Somatic Mutations* 71
Edward P. Gelmann

5. Somatic Genetic Changes in Prostate Cancer: *Androgen Receptor Alterations* 99
Merja A. Helenius, Kati K. Waltering, and Tapio Visakorpi

6. Androgen Receptor in Prostate Cancer Progression 129
Hiroshi Miyamoto, Saleh Altuwaijri, and Chawnshang Chang

7. Epigenetic Modification and Acetylation of Androgen Receptor Regulate Prostate Cellular Growth 147
Michael J. Powell, Shengwen Li, Michael P. Lisanti, Marja T. Nevalainen, Chenguang Wang, and Richard G. Pestell

8. Estrogen Receptor α and β in the Regulation of Normal and Malignant Prostate Epithelium 163
Otabek Imamov, Nikolai A. Lopatkin, and Jan-Åke Gustafsson

9. Estrogen Action in Normal Prostate Epithelium and in Prostate Cancer 181
Gail S. Prins and Kenneth S. Korach

10. Hypoxia-Inducible Factor 1 in the Angiogenesis of Prostate Cancer 209
Jonathan W. Simons

11. Signal Transduction by the Ras–MAP Kinase Pathway in Prostate Cancer Progression 223
Daniel Gioeli, Sarah Kraus, and Michael J. Weber

12. Transcription Factors STAT5 and STAT3: *Survival Factors for Prostate Cancer Cells* 257
Zoran Culig, Richard G. Pestell, and Marja T. Nevalainen

13. Role of PI3K–Akt and PTEN in the Growth and Progression of Prostate Cancer 291
Haojie Huang and Donald J. Tindall

14. New Perspectives in Prediction of Clinical Outcome of Prostate Cancer: *TMPRSS2–ETS Gene Fusion in Prostate Cancer* 309
Mark A. Rubin

15. New Directions in Radiation Therapy of Prostate Cancer: *Brachytherapy and Intensity-Modulated Radiation Therapy* . . . 323
Sean Collins, Donald McRae, Gregory Gagnon, and Anatoly Dritschilo

16. The Current Knowledge of Hormonal Therapy in the Treatment of Prostate Cancer 339
Mario A. Eisenberger

17. Advances in Surgical Intervention of Prostate Cancer: *Comparison of the Benefits and Pitfalls of Retropubic, Perineal, and Laparoscopic Radical Prostatectomy* 355
Jay B. Basillote, Thomas E. Ahlering, and Douglas W. Skarecky

18. Targeted Therapy Trials for Prostate Cancer 383
Elisabeth I. Heath and Michael A. Carducci

19. New Perspectives on Chemotherapy in Prostate Cancer 401
Julia H. Hayes and Philip Kantoff

20. Concluding Remarks: *The Future of Prostate Cancer* 427
Leonard G. Gomella and Richard K. Valicenti

Index 439

Contributors

Thomas E. Ahlering, md, facs • *Division of Urologic Oncology, Department of Urology, University of California Irvine, Orange, CA*

Saleh Altuwaijri, dvm, phd • *Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY; King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia*

Jay B. Basillote, md • *Department of Urology, Richmond University Medical Center, Staten Island, NY*

Michael A. Carducci, md • *Prostate Cancer Program, Chemical Therapeutics, The Sydney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

John D. Carpten, phd • *Division of Integrated Cancer Genomics, Translational Genomics Research Institute (TGen), Phoenix, AZ*

Chawnshang Chang, phd • *George Whipple Laboratory for Cancer Research, Departments of Pathology and Urology, University of Rochester Medical Center, Rochester, NY*

Sean Collins, md, phd • *Department of Radiation Medicine, Lombardi Comprehensive Cancer Center, Georgetown University School of Medicine, Washington, DC*

Zoran Culig, md • *Department of Urology, Medical University of Innsbruck, Innsbruck, Austria*

Angelo M. De Marzo, md, phd • *Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD*

Anatoly Dritschilo, md • *Departments of Radiation Medicine and Oncology, Lombardi Comprehensive Cancer Center, Georgetown University School of Medicine, Washington, DC*

Mario A. Eisenberger, md • *Division of Medical Oncology, Bunting-Blaustein Cancer Research Building, Johns Hopkins University, Baltimore, MD*

Gregory Gagnon, md • *Department of Radiation Medicine, Lombardi Comprehensive Cancer Center, Georgetown University School of Medicine, Washington, DC*

Edward P. Gelmann, md • *Departments of Oncology and Medicine, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC*

Daniel Gioeli, phd • *Department of Microbiology and Cancer Center, University of Virginia Health System, Charlottesville, VA*
Leonard G. Gomella, md • *Department of Urology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*
Jan-Åke Gustafsson, md, phd • *Department of Biosciences and Nutrition, Director of Center for Biotechnology, Karolinska Institute, NOVUM, Stockholm, Sweden*
Julia H. Hayes, md • *Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA*
Elisabeth I. Heath, md • *Department of Medicine and Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, MI*
Merja A. Helenius, phd • *Institute of Medical Technology, University of Tampere and Tampere University Hospital, Tampere, Finland*
Haojie Huang, phd • *Departments of Laboratory Medicine and Pathology, The Cancer Center, University of Minnesota, Minneapolis, MN*
Otabek Imamov, md • *Department of Biosciences and Nutrition, Karolinska Institute, NOVUM, Stockholm, Sweden; Reconstructive Urology Unit, Moscow Institute of Urology, Moscow, Russia*
Robert B. Jenkins, md, phd • *Department of Laboratory Medicine and Pathology, The Mayo Clinic, Rochester, MN*
Philip Kantoff, md • *Division of Solid Tumor Oncology, Lank Center for Genitourinary Oncology, Dana Farber Cancer Institute, Prostate Cancer Program and Prostate Cancer SPORE at Dana Farber Harvard Cancer Center, Harvard Medical School, Dana, Boston, MA*
Kenneth S. Korach, phd • *Environmental Disease and Medicine Program, Laboratory of Reproductive and Developmental Toxicology, NIEHS/NIH, Research Triangle Park, NC*
Sarah Kraus, phd • *Department of Microbiology and Cancer Center, University of Virginia Health System, Charlottesville, VA*
Fusheng Lan, md, phd • *Department of Laboratory Medicine and Pathology, The Mayo Clinic, Rochester, MN*
Shengwen Li, phd • *Department of Cancer Biology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*
Michael P. Lisanti, md, phd • *Department of Cancer Biology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*
Nikolai A. Lopatkin, md, phd • *Academician of Russian Academy of Medical Sciences, Director, Moscow Institute of Urology, Moscow, Russia*
Donald McRae, phd • *Department of Radiation Medicine, Lombardi Comprehensive Cancer Center, Georgetown University School of Medicine, Washington, DC*
Michael Milken, mba • *Prostate Cancer Foundation, Santa Monica, CA*

Hiroshi Miyamoto, md, phd • *Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY*
William G. Nelson, md, phd • *Department of Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Brady Urological Institute, Bunting-Blaustein Cancer Research Building, Baltimore, MD*
Marja T. Nevalainen, md, phd • *Department of Cancer Biology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*
Richard G. Pestell, md, phd • *Kimmel Cancer Center, Department of Cancer Biology, Thomas Jefferson University, Philadelphia, PA*
Michael Powell, bs • *Department of Cancer Biology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*
Gail S. Prins, phd • *Department of Urology, University of Illinois at Chicago, Chicago, IL*
Mark A. Rubin, md • *Department of Urologic Pathology, Brigham and Women's Hospital, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA*
Jonathan W. Simons, md • *Prostate Cancer Foundation, Santa Monica, CA*
Douglas W. Skarecky, bs • *Department of Urology, University of California Irvine, Orange, CA*
Donald J. Tindall, phd • *Departments of Urology and Biochemistry and Molecular Biology, Mayo Clinic College of Medicine, Rochester, MN*
Jeffrey M. Trent, phd • *Translational Genomics Research Institute, Phoenix, AZ*
Alexander Valdman, md, phd • *Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD*
Richard K. Valicenti, md • *Vice Chairman of Clinical Affairs, Department of Radiation Oncology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*
Tapio Visakorpi, md, phd • *Institute of Medical Technology, University of Tampere and Tampere University Hospital, Tampere, Finland*
Kati K. Waltering, msc • *Institute of Medical Technology, University of Tampere and Tampere University Hospital, Tampere, Finland*
Chenguang Wang, phd • *Department of Cancer Biology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*
Michael J. Weber, phd • *Department of Microbiology and Cancer Center, University of Virginia Health System, Charlottesville, VA*
Srinivasan Yegnasubramanian, md, phd • *Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Brady Urological Institute, Bunting-Blaustein Cancer Research Building, Baltimore, MD*