RECENT ADVANCES IN PROSTATE CANCER

Basic Science Discoveries and Clinical Advances

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Editors

Donald J Tindall

Mayo Clinic College of Medicine, USA

Peter T Scardino

Memorial Sloan-Kettering Cancer Center, USA

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CONTRIBUTORS

Cory Abate-Shen, PhD

Departments of Urology and Pathology and Cell Biology
Herbert Irving Comprehensive Cancer Center
Columbia University Medical Center
New York, NY 10032, USA

Elisa Benedettini, PhD

Department of Medical Oncology
Dana-Farber Cancer Institute
Harvard Medical School
Boston, MA 02115, USA

Peter L. Choyke, MD

Molecular Imaging Program
National Cancer Institute
National Institutes of Health
Bethesda, MD 20892, USA

Kimberly B. Dahlman, PhD

Memorial Sloan-Kettering Cancer Center
New York City, NY 10065, USA

Kaustubh Datta, PhD

Assistant Professor

Departments of Urology

Biochemistry and Molecular Biology

Mayo Clinic College of Medicine

Rochester, MN 55905, USA

Angelo M. DeMarzo, MD, PhD

Department of Pathology

Johns Hopkins University School of Medicine

Baltimore, MD 21231, USA

Dayssy Alexandra Diaz, MD

Department of Radiation Oncology

University of Miami/Jackson Memorial Hospital

Sylvester Comprehensive Cancer Center

Miami, FL 33136, USA

James A. Eastham, MD, FACS

Chief, Urology Service

Florence and Theodore Baumritter/

Enid Ancell Chair of Urologic Oncology Department of Surgery

Assistant Attending Surgeon

Division of Urology

Memorial Sloan Kettering Cancer Center

New York, NY 10065, USA

Aymen Elfiky, MD, MA, MPH

Dana-Farber Cancer Institute/

Brigham and Women's Hospital

Harvard Medical School

Boston, MA 02115, USA

Michelangelo Fiorentino, MD, PhD

Center for Oncologic Molecular Pathology

Dana Farber Cancer Institute

Boston, MA 02115, USA

John P. Fitzgerald, MD, MA

Clinical Instructor

Department of Urology

University of Texas Health Science Center at San Antonio

San Antonio, TX 78229, USA

Alejandro S. Godoy, PhD

Department of Urology

Roswell Park Cancer Institute

Buffalo, NY 14263, USA

Bertrand D. Guillonneau, MD

Head, Department of Urology

GH Diaconesses — Croix St. Simon

75012 Paris, France

Amit Gupta, MD, MPH

Department of Surgery (Urology)

Memorial Sloan-Kettering Cancer Center

New York City, NY 10065, USA

John T. Isaacs, PhD

Chemical Therapeutics Program and

Professor of Oncology and Urology

The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Professor in the Cellular and Molecular Medicine Graduate Program

The Johns Hopkins School of Medicine

Professor of Chemical and Biomolecular Engineering

The Whiting School of Engineering

The Johns Hopkins University

Baltimore, MD 21287, USA

William B. Isaacs, PhD

Professor

Urology and Oncology

Johns Hopkins University
School of Medicine
Johns Hopkins Hospital
Baltimore, MD 21287, USA

Michael Ittmann, MD, PhD

Department of Pathology and Immunology
Baylor College of Medicine and
Michael E. DeBakey Department of Veterans
Affairs Medical Center
Houston, TX 77030, USA

Gopa Iyer, MD

Genitourinary Oncology Service
Department of Medicine
Memorial Sloan-Kettering Cancer Center
New York, NY 10065, USA

Philip Kantoff, MD

Chief Clinical Research Officer
Chief, Division of Solid Tumor Oncology
Director of the Lank Center for Genitourinary Oncology
Dana-Farber Cancer Institute/Brigham and Women's Hospital
Professor of Medicine
Harvard Medical School
Boston, MA 02115, USA

Michael W. Kattan, PhD

Professor of Medicine, Epidemiology and Biostatistics
Cleveland Clinic Lerner College of Medicine
of Case Western Reserve University
Chairman, Department of Quantitative
Health Sciences, Cleveland Clinic
Cleveland, OH 44195, USA

Karen Kurdziel, MD

Molecular Imaging Program
National Cancer Institute
National Institutes of Health
Bethesda, MD 20892, USA

Eugene D. Kwon, MD

Professor of Immunology and Urology
Mayo Clinic
Rochester, MN 55905, USA

Vincent P. Laudone, MD

Associate Attending Surgeon
Division of Urology
Co-Director, Robotic Surgery Program
Department of Surgery
Memorial Sloan Kettering Cancer Center
New York, NY 10065, USA

Hans Lilja, MD, PhD

Departments of Clinical Laboratories
Surgery (Urology), and Medicine (GU-Oncology)
Memorial Sloan-Kettering Cancer Center
New York City, NY 10065, USA

Department of Laboratory Medicine, Malmö
Division of Clinical Chemistry
Lund University
University Hospital UMAS
205 02 Malmö, Sweden

Massimo Loda, MD

Department of Pathology
Dana Farber Cancer Institute
Brigham and Women's Hospital, Broad Institute
Professor of Pathology, Harvard Medical School
Boston, MA 02115, USA

Stacy Loeb, MD

Brady Urological Institute
Johns Hopkins Medical Institutions
Baltimore, MD 21287, USA

Wallace L. McKeehan, PhD

Center for Cancer and Stem Cell Biology
Institute of Biosciences and Technology
Texas A&M Health Science Center
Houston, TX 77030, USA

Esther Mena, MD

Molecular Imaging Program
National Cancer Institute
National Institutes of Health
Bethesda, MD 20892, USA

James L. Mohler, MD

Associate Director and Senior Vice President
for Translational Research
Chair, Department of Urology
Roswell Park Cancer Institute
Buffalo, NY 14263, USA

School of Medicine and Biomedical Sciences
State University of New York at Buffalo
Lineberger Comprehensive Cancer Center
University of North Carolina at Chapel Hill

Peter S. Nelson, MD

Human Biology Division
Fred Hutchinson Cancer Research Center
Seattle, WA 98109, USA

William G. Nelson, MD, PhD

Sidney Kimmel Comprehensive Cancer Center
Baltimore, MD 21231, USA

Carvell T. Nguyen, MD, PhD

Fellow, Center for Urologic Oncology
Glickman Urological and Kidney Institute
Cleveland Clinic
Cleveland, OH 44195, USA

Daizo Oka, MD, PhD

Department of Urology
Osaka University Graduate School of Medicine
Osaka 565-0871, Japan

Kathryn L. Penney, ScD

Department of Epidemiology
Harvard School of Public Health
Channing Laboratory
Department of Medicine
Brigham and Women's Hospital
Boston, MA 02115, USA

Alan Pollack, MD, PhD

Department of Radiation Oncology
University of Miami
Sylvester Comprehensive Cancer Center
Miami, FL 33136, USA

Charles L. Sawyers, MD

Chair, Human Oncology and Pathogenesis Program
Marie-Josee and Henry R. Kravis Chair
Memorial Sloan-Kettering Cancer Center
New York City, NY 10065, USA

Howard I. Scher, MD

Chief, Genitourinary Oncology Service
D. Wayne Calloway Chair in Urologic Oncology
Department of Medicine

Sidney Kimmel Center for Prostate and Urologic Cancers
Memorial Sloan-Kettering Cancer Center
New York, NY 10065, USA

Fritz H. Schroeder, MD, PhD
Department of Urology
Erasmus University Medical Centre
Erasmus University Rotterdam
3015 CE, Rotterdam, The Netherlands

Michael M. Shen, PhD
Department of Medicine and Genetics and Development
Herbert Irving Comprehensive Cancer Center
Columbia University Medical Center
New York, NY 10032, USA

David B. Solit, MD
Human Oncology and Pathogenesis Program
Genitourinary Oncology Service
Department of Medicine
Memorial Sloan-Kettering Cancer Center
New York, NY 10065, USA

Andrew J. Stephenson, MD, FACS, FRCS(C)
Associate Professor of Surgery
Case Western Reserve University School of Medicine
Director, Center for Urologic Oncology
Glickman Urological and Kidney Institute
Cleveland Clinic
Cleveland, OH 44195, USA

Melissa Talbert, MD
Department of Urology
University of Texas Health Science Center at San Antonio
San Antonio, TX 78229, USA

Ian Thompson, MD

Director, Cancer Therapy and Research Center
Professor, Department of Urology
University of Texas Health Science Center at San Antonio
San Antonio, TX 78229, USA

Donald J. Tindall, PhD

Professor, Director and Vice Chair of Urologic Research
Carl Rosen Professorship in Urology
Departments of Urology
Biochemistry and Molecular Biology
Mayo Clinic College of Medicine
Rochester, MN 55905, USA

Mark A. Titus, PhD

Department of Urology
Roswell Park Cancer Institute
Buffalo, NY 14263, USA

Matthew K. Tollefson, MD

Assistant Professor of Urology
Mayo Clinic
Rochester, MN 55905, USA

Karim A. Touijer, MD

Assistant Attending Surgeon
Division of Urology
Memorial Sloan Kettering Cancer Center
New York, NY 10065, USA

Lawrence True, MD

Professor of Pathology
Department of Pathology
University of Washington
Seattle, WA 98195, USA

Baris Turkbey, MD

Molecular Imaging Program
National Cancer Institute
National Institutes of Health
Bethesda, MD 20892, USA

Funda Vakar-Lopez, MD

Assistant Professor of Pathology
Department of Pathology
University of Washington
Seattle, WA 98195, USA

Donald J. Vander Griend, PhD

Assistant Professor
Department of Surgery
Section of Urology
The University of Chicago
Chicago, IL 60637, USA

Fen Wang, PhD

Center for Cancer and Stem Cell Biology
Institute of Biosciences and Technology
Texas A&M Health Science Center
Houston, TX 77030, USA

Jianghua Wang, MD

Department of Pathology and Immunology
Baylor College of Medicine and
Michael E. DeBakey Department of Veterans
Affairs Medical Center
Houston, TX 77030, USA

Srinivasan Yegnasubramanian, MD, PhD

Sidney Kimmel Comprehensive Cancer Center
Baltimore, MD 21231, USA

PREFACE

Prostate Cancer is the most common internal cancer in men in the United States and the second leading cause of cancer-related death in men. Prostate cancer incidence has been declining in the United States over the past decade, probably because intense screening with prostate-specific antigen (PSA) and aggressive biopsy techniques have removed many of the prevalent cancers from the population. Mortality rates from prostate cancer have been declining for more than two decades, and age-adjusted mortality rates are 45% below their peak in 1992, most likely as a result of early detection and effective treatment of potentially lethal cancers. The decline in mortality has come at the cost, to some degree, of excess treatment of many indolent cancers that posed little risk to life or health. Despite two multinational screening trials to determine the benefits of widespread PSA testing, the subject remains fraught with controversy. Active surveillance is gaining acceptance as a conservative management strategy in men with low risk cancers, although we are not sure exactly who should qualify for this “watchful waiting” approach or how best to determine when to intervene later if the tumor progresses. Chemoprevention of prostate cancer with 5-alpha reductase inhibitors is a promising way to reduce the incidence of cancer, but the U.S. Food and Drug Administration recently declined to approve these drugs because of concern that they may slightly increase the risk that a man will develop a high grade cancer — a controversial judgment that will require intense investigation to substantiate or refute.

A central factor in prostate cancer initiation, maintenance and progression is the androgen signaling pathway. Androgens play important roles in the development of fusion oncogenes that are important in the initiation of prostate cancer. Androgens also stimulate pathways that are critical in proliferation of cells during the maintenance and progression of prostate cancer. Even after androgen deprivation therapy, prostate cells initiate mechanisms that preserve the activity of the androgen receptor. Other signaling pathways that regulate inflammation, cell cycle, cell survival genomic instability and cell killing play key roles in prostate cancer initiation, maintenance and progression. A critical need for the clinical management of prostate cancer is an ability to distinguish between indolent and aggressive disease beyond Gleason grading. DNA arrays have begun to define genes that are associated with aggressive and non-aggressive tumors. The future looks promising for the validation of such biomarkers that may be useful for prognosis and for directing therapy.

Improved treatment of prostate cancer has benefitted from a better understanding of the cellular mechanisms that contribute to the disease as well as the molecular mechanisms through which drugs act on tumors. In the past five years clinical trials have established the effectiveness of a number of new drugs for advanced prostate cancer, including docetaxel, sipuleucel, carbazitaxel, and abiraterone, which promise to improve the survival of these patients. Docetaxel and carbazitaxel destabilize microtubules, resulting in cell death. Sipuleucel appears to enhance the immune response to prostate cancer.

Abiraterone blocks androgen synthesis not only in the adrenal gland, but in the cancer cells themselves, which seem to develop autocrine mechanisms to synthesize androgens in response to long term androgen deprivation. In addition to advanced surgical and radiation techniques, these drugs will contribute profoundly to improved treatment for prostate cancer and longer survival. Nonetheless, every treatment comes with a potential for adverse side effects.

This book will summarize our current knowledge of prostate cancer, highlighting the key recent advances. It covers our state-of-the-art understanding of risk factors, prevention, detection, prognosis and treatment of this disease. By including both basic scientists and

clinicians as authors, the book will identify the most important recent basic science findings that are being translated into clinical practice, as well as the most promising areas of research that could have the greatest impact on clinical practice in the future. Our understanding of prostate cancer is rapidly evolving. This book should serve as a valuable summary of the current status of the field for the laboratory scientists, the clinician caring for the patient and for those in training who are dedicating their professional efforts to help reduce the burden of suffering and death from this all too common disease.

Donald J. Tindall, PhD

Mayo Clinic College of Medicine

Peter T. Scardino, MD, FACS

Memorial Sloan-Kettering Cancer Center