GENE THERAPY FOR CANCER
Cancer Drug Discovery and Development

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The possibility of treating cancer, a disease defined by genetic defects, by introducing genes targeting these very alterations has led to an immense interest in gene therapy for cancer. Although incremental successes have been realized, enthusiasm for gene therapy has declined due to an increasing number of obstacles. These obstacles include vector systems that do not reach systemic metastases, therapeutic genes with redundant mechanisms allowing for cellular resistance, and toxicities in clinical trials leading to premature closure of these studies. Different tactics to overcome or circumvent these obstacles have catalyzed the development of a wide range of gene therapy approaches. Thus far, almost two-thirds of gene therapy trials have focused on cancer. This reflects the concept that gene therapy approaches for the treatment of cancer do not necessarily require long-term expression of the gene as is necessary for the treatment of primary genetic defects like hemophilia or juvenile diabetes. Unlike the treatment of genetic defects, where expression of the corrected gene needs to be strong, permanent and, sometimes regulated, tactics to treat tumors can be based on temporary and locally limited effects. In addition, cancer cells have different properties than normal cells and this allows for targeting gene therapy to specific cells, a major advantage over current antitumor therapies, which are also toxic to normal cells and tissues.

Gene Therapy for Cancer covers the current ideas and technology of gene therapy, as well as the demanding task of bringing it to and applying it in clinical trials. The book is divided into three major parts: (1) Vectors used in gene therapy against cancer, (2) targets and specific approaches for the therapy of cancer, and (3) clinical applications of cancer gene therapy.

The delivery of an antitumor gene, a toxic agent, or an immunostimulating drug selectively to tumor cells is one of the most crucial steps in achieving successful cancer gene therapy. We have dedicated a considerable portion of Gene Therapy for Cancer to a description of the various aspects of gene delivery including vehicles (vectors), their characteristics, and production methods.

Knowledge of the specific strategies and targets for the treatment of cancer has increased dramatically over the past decade. These range from methods that induce immediate cancer cell death through expression of genes that trigger the cell-death program or by reactivating pathways that render mutated cells susceptible to antitumor agents. Additional methods run the gamut from the correction of underlying defects at molecular levels to activation of the immune system or the tumor microenvironment. Understanding the basic underlying oncogenic changes allows for development of vectors engineered to exploit these gene mutations through selective spread of the vector in tumor cells with the specific changes. Background knowledge, technical details, and preclinical and clinical results are provided by specialists in each of these approaches.

Probably more so than in any other antitumor therapy, bringing gene therapy approaches to the clinic is a difficult task burdened by numerous regulations and limited by scarce funding opportunities. We have asked experts in clinical gene therapy trials to discuss the
trials and tribulations of realizing advances in gene therapy at the preclinical level to the benefit of patients with cancer. The readers will gain significant insight into these difficulties and learn how to overcome the obstacles on the way from the laboratory to the bedside. Gene therapy approaches and results that have reached the stage of clinical testing are described by their principal investigators.

With *Gene Therapy for Cancer* we have sought to provide a comprehensive and in-depth view of currently available techniques for cancer gene therapy, including their limitations and the potential for future advances. This should prove to be a valuable resource for both researchers and clinicians in the field. With this approach we hope to provide an opportunity for clinicians and researchers to communicate their perspectives, allowing for increased collaboration and perhaps more rapid advances in this challenging field.

We would like to thank all the specialists who dedicated their valuable time to provide the most important and exciting advances in cancer gene therapy for this book. We are deeply grateful to our families for their continuous support, endless patience, and understanding.

*Kelly K. Hunt, MD*

*Stephan A. Vorburger, MD*

*Stephen G. Swisher, MD*
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CONTRIBUTORS

ROBERT J. AMATO • Scott Department of Urology, Baylor College of Medicine, Houston, TX

DANIEL G. ANDERSON • Chemical Engineering Department, Massachusetts Institute of Technology, Cambridge, MA

GUSTAVO AYALA • Department of Pathology, Baylor College of Medicine, Houston, TX

GLEN N. BARBER • Department of Microbiology and Immunology, University of Miami School of Medicine, Miami, FL

DAVID L. BARTLETT • Division of Surgical Oncology, University of Pittsburgh, Pittsburgh, PA

DORA BOCANGEL • Introgen Therapeutics, Houston, TX

E. BRIAN BUTLER • Department of Radiology, Baylor College of Medicine, Houston, TX

SUNIL CHADA • Introgen Therapeutics, Houston, TX

SRICHARAN CHALIKONDA • Division of Surgical Oncology, University of Pittsburgh, Pittsburgh, PA

DAVID T. CURIEL • Gene Therapy Center, University of Alabama, Birmingham, AL

BINGLIANG FANG • Department of Thoracic and Cardiovascular Surgery–Research, The University of Texas M.D. Anderson Cancer Center, Houston, TX

YUMAN FONG • Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY

JUAN FUEYO • Department of Neuro-Oncology/Research, The University of Texas M. D. Anderson Cancer Center, Houston, TX

TETSUO FUJITA • Scott Department of Urology, Baylor College of Medicine, Houston, TX

DAVID M. GERSHENSON • Department of Gynecologic Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX

STANTON L. GERSON • Division of Hematology-Oncology, Case Western Reserve University School of Medicine, Cleveland, OH

ELIZABETH A. GRIFFIN • Department of Experimental Therapeutics, The University of Texas M.D. Anderson Cancer Center, Houston, TX

GABRIEL N. HORTOBAGYI • Department of Breast Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX

LEAF HUANG • Center for Pharmacogenetics, Department of Pharmaceutical Science, University of Pittsburgh, Pittsburgh, PA

MIEN-CHIE HUNG • Department of Molecular & Cellular Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX

KELLY K. HUNT • Department of Surgical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX