

---

## Preface

The field of cancer therapy is beginning to reap the benefits of our increasing understanding of the molecular basis of cancer. In contrast to conventional surgical interventions or cytotoxic chemotherapy and radiation therapy, a new generation of targeted cancer therapeutics is being specifically directed toward molecular pathways that underlie the malignant phenotype. In this regard, the management of patients with Philadelphia chromosome-positive chronic myeloid leukemia has been profoundly changed by Gleevec<sup>®</sup> (Novartis), a small molecule that specifically inhibits the Bcr-abl tyrosine kinase that is central to the pathogenesis of this disease. Particularly noteworthy is the rapid translation of this molecular targeted agent from the laboratory to clinical trials and thence to regulatory approval. Other novel targeted therapeutics that are currently approved by the FDA for treatment of patients with cancer include Rituxan<sup>®</sup> (Genentech), a humanized monoclonal antibody that binds to the CD20 antigen present on B-cell lymphomas and is currently approved for the treatment of patients with relapsed or refractory low-grade or follicular CD20-positive B-cell non-Hodgkin's lymphoma. The humanized anti-HER-2/neu monoclonal antibody Herceptin<sup>®</sup> (Genentech) is approved for use in patients with metastatic breast cancer that demonstrates overexpression of HER-2/neu. These therapies target specific tumor cell receptors or signaling events that are critical to tumor progression while reducing toxicity to normal cells.

Within this context of targeted molecular interventions with the potential to achieve a much higher level of specificity of action than afforded by conventional drug therapeutics, we can view cancer gene therapy as the transfer of genetic material to the cells of an individual with the goal of eradicating cancer cells. This can be accomplished directly by transferring genetic material into the cancer cells themselves to bring about their destruction, or indirectly, either by stimulating the immune system to recognize and eliminate the cancer cells or by targeting the nonmalignant stromal cells that support the growth and metastasis of cancer cells. Each of these approaches exploits our expanding knowledge of the genetic basis of cancer, thereby allowing rationally targeted interventions at the molecular level. These cancer gene therapy strategies are discussed in the first contributions to *Cancer Gene Therapy*.

Any gene therapy strategy is dependent on the safe and efficient transfer of the therapeutic gene selectively to the target cell. Indeed, one of the main lessons learned from the success of clinical gene therapy trials for monogenic inherited disorders, such as severe combined immunodeficiency and hemophilia, is that therapeutic advances are predicated on improvements in the design of gene delivery vehicles, or vectors. Hence, two chapters focus on the development of vectors for cancer gene therapy, both viral and nonviral, emphasizing how the properties of a given vector favor its application in a particular therapeutic approach.

The recognition of the limitations of replication-defective vectors, which are incapable of delivering therapeutic genes to more than a small proportion of cancer

cells in a 3D tumor mass, has led to the development of a new class of anticancer therapeutic agents, oncolytic replication-competent viruses, which are also described. The safety of oncolytic viruses derives from the restriction of their replication to tumor cells, while sparing normal cells. A number of naturally occurring viruses possess intrinsic selectivity for replication in tumor cells, while advances in the molecular characterization of viruses and cancer cells have enabled other lytic viruses to be genetically engineered to selectively replicate in, and thus destroy, tumor cells.

It is apparent that therapeutic gene delivery designed to eradicate cancer cells in the clinical setting would benefit from noninvasive techniques to monitor the extent of gene transfer and disease regression during the course of treatment. Hence, a chapter describes imaging of cancer gene therapy. After a chapter discussing the lessons learned to date from clinical trials for cancer gene therapy, the final chapter reviews the regulatory guidelines with which future trials should comply.

Thus, the contributions to this book demonstrate that cancer gene therapy strategies are founded on an understanding of the molecular basis of disease that, together with improvements to the safety and efficacy of vectors, will provide a rational basis for their application in the clinic setting. It is anticipated that gene therapy will ultimately take its place in the clinic alongside other targeted molecular inventions for cancer.

*David T. Curiel, MD, PhD*  
*Joanne T. Douglas, PhD*



<http://www.springer.com/978-1-58829-213-1>

Cancer Gene Therapy

Curiel, D.T.; Douglas, J.T. (Eds.)

2005, XII, 490 p., Hardcover

ISBN: 978-1-58829-213-1

A product of Humana Press