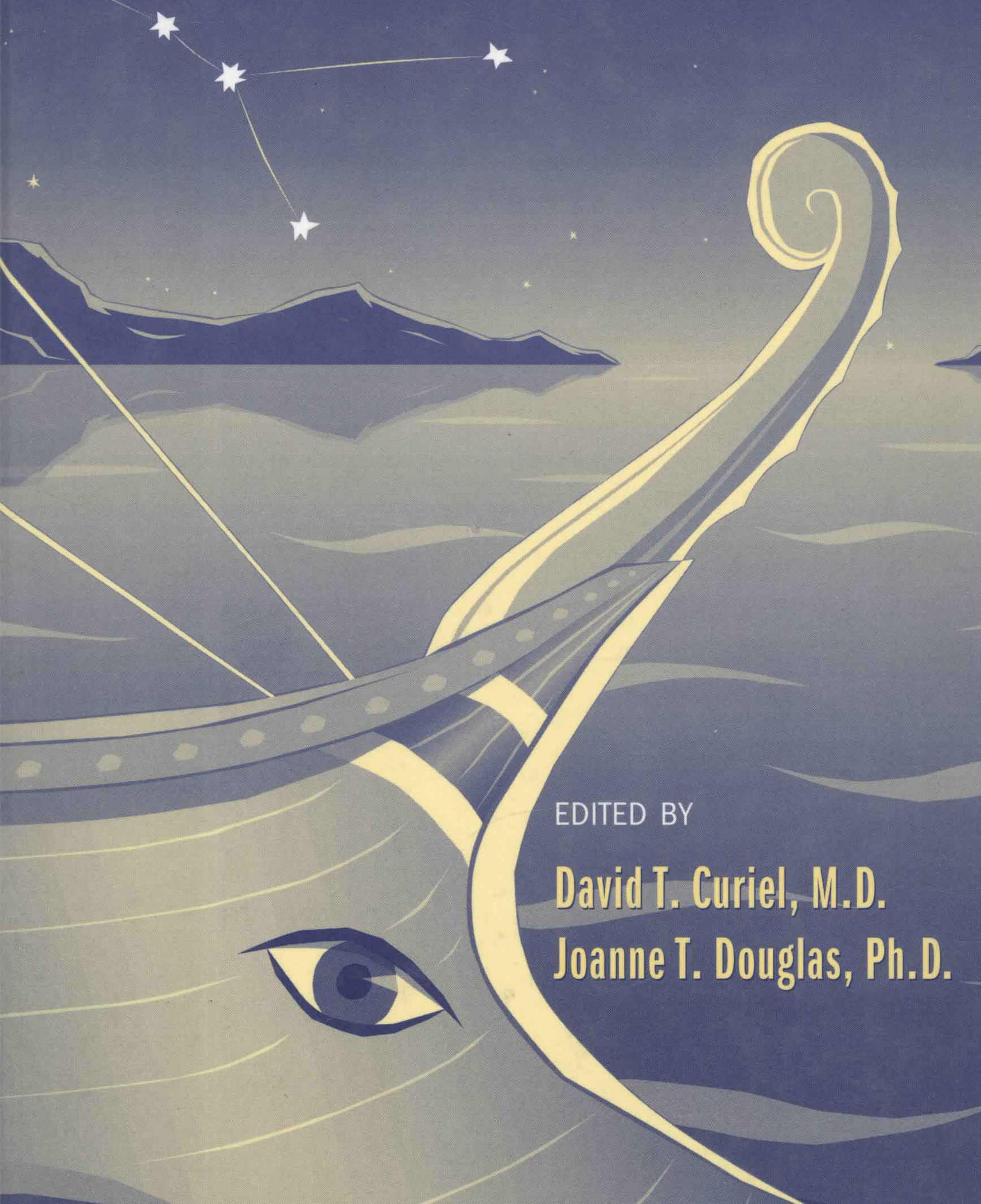
VECTOR TARGETING *for Therapeutic Gene Delivery*



EDITED BY

David T. Curiel, M.D.
Joanne T. Douglas, Ph.D.

Vector Targeting for Therapeutic Gene Delivery

Edited by

DAVID T. CURIEL

JOANNE T. DOUGLAS

Division of Human Gene Therapy
Departments of Medicine, Pathology and Surgery,
and the Gene Therapy Center
The University of Alabama at Birmingham

WILEY-LISS

A JOHN WILEY & SONS, INC., PUBLICATION

This book is printed on acid-free paper. ♾

Published by Wiley-Liss, Inc., Hoboken, New Jersey.

Published simultaneously in Canada.

Library of Congress Cataloging-in-Publication Data:

Vector targeting for therapeutic gene delivery/edited by David T. Curiel, Joanne T. Douglas.
p. cm.
Includes bibliographical references and index.
ISBN 0-471-43479-5 (cloth:alk. paper)
1. Gene therapy. 2. Gene targeting. 3. Genetic vectors. I. Curiel, David.
II. Douglas, Joanne T.

RB155.8 V434 2002
616′.042—dc21

2002071310

Printed in the United States of America.

10 9 8 7 6 5 4 3 2 1

PREFACE

The basic mandates for gene therapy were formulated before the existence of any practical basis for the application of the concept. In this regard, early proponents of genetic therapy defined the basic criteria to be met prior to actual implementation of any human gene therapy approach. Specifically, it was required that the therapeutic gene be efficiently delivered to the relevant target cells, that the gene be expressed at an appropriate level, and that both of these ends be achieved with an acceptable margin of safety. It was thus implicit even at the earliest stage of field conceptualization that targeted gene delivery would need to be accomplished.

Despite this recognition, the earliest human gene therapy approaches proceeded without explicit attention to targeting per se. From the vector standpoint, the earliest issues addressed were related to achieving basic efficacy parameters needed to make practical gene therapy feasible. In the context of nonviral vectors, exploitation of nonspecific cellular transport processes provided the basis of genetic transduction. These methods were inefficient and, by their very design, nontargeted in intent. As an alternative, viral vectors were developed that incorporate a heterologous transgene within the viral genome and exploit the relatively more efficient processes of viral infection of a target cell. Such virus-mediated delivery, however, was restricted by the native tropism of the parent virus.

Early generations of vector systems thus prioritized the development of efficient gene delivery. By virtue of the design logic for both nonviral and viral approaches, specific targeting capacities were not embodied. In fact, the situation predicated vectors having tropism capacities frequently at odds with cell-specific targeting goals. Recognition of these limits led to initial gene therapy approaches whereby target cells could be modified ex vivo. In this schema, cell-specific transduction was achieved by a priori selection and isolation of target cells, followed by vector-mediated transduction. This schema implicitly recognized the limitations of available vector systems for achieving targeting goals. Unfortunately, only a few diseases are amenable to ex vivo gene therapy interventions, reflecting the limited repertoire of parenchymal cells that can be manipulated via extracorporeal methods. These considerations thus highlight the degree to which vector limitations, specifically limitations in vector targeting, restricted the practical implementation of the range of candidate gene therapies.

The goal of extending the range of gene therapy disease targets was fostered by the development of vector systems capable of in vivo gene delivery. In this regard, the capacity of various viral vector systems to achieve in situ gene transfer allowed the conceptualization of gene therapy approaches unconstrained by extracorporeal modifications. On this basis, gene therapy approaches for a variety of inherited and acquired disorders advanced to animal model systems and human clinical trials. Consideration of the results of these various in vivo gene therapy approaches defined the limitations of current vector systems and thereby established the clear rationale for targeting strategies.

In many respects, cancer gene therapy has illustrated key issues with respect to targeting, reflecting the fact that antitumor strategies frequently involve the delivery of toxin genes. In this scenario, the consequences of ectopic, nontargeted delivery would be manifested most prominently as therapy-related toxicity. Thus, the early clinical trials for cancer provided key insights as to the requirements for targeting and potential gains therein. In this regard, the obvious lack of targeting capacity of available vectors mitigated against approaches for disseminated neoplastic disease. Such diseases would have required tumor-selective gene delivery following systemic vector administration. The lack of any vector with such attributes meant it was necessary to address disease contexts in which targeting stringency was not such a paramount consideration. To this end, tumors localized to natural body compartments (central nervous system, thoracic cavity, peritoneal cavity) appeared to offer the ideal scenario—a space-confined tumor allowing vector concentration and containment. Thus, initial in vivo anticancer gene therapy approaches were endeavored for glioma, pleural mesothelioma, and peritoneal carcinomatosis.

The results of these trials were highly disappointing. First, extremely low levels of tumor cell transduction were achieved. Thus, despite apparent vector efficacy in model system studies, target cell transduction rates following in vivo gene delivery were limited. Secondly, ectopic gene delivery occurred in various in vivo delivery schemas, irrespective of theoretical vector containment based on anatomic aspects. Further, ectopic gene deliveries were associated with vector-related toxicities. Thus, whereas the overall profile of anticancer gene therapy has suggested an acceptable safety/toxicity profile, the occurrence of suboptimal target transduction rates might logically predicate advanced dosing schemas, a strategy countermanded by the observed phenomenon of ectopic gene delivery. In vivo gene delivery, even in the optimized scenario of compartment-based models, therefore exhibits all of the limitations invoked as countervailing systemic delivery schemas—limited tumor cell transduction and ectopic gene delivery. These considerations thus clearly establish the universal applicabilities that might derive from targeting, irrespective of delivery route.

The very recent aspect of these findings explains the only recent development, and application, of targeting for gene therapy applications. In this regard, the basic ideas of retargeting vectors for selective gene delivery have been previously studied as a means to improve vector efficiency per se, as in the context of receptor-mediated conjugate vectors. In other words, the idea of targeting to improve gene therapy outcomes has been most generally recognized as a consequence of these disappointing results in human clinical trials. However, basic field paradigms have only been recently established. Further, the actual translation of targeting paradigms into the clinical context has awaited these key proof-of-principle studies whereby direct gene therapy gain via targeting has been established.

For selected viral and nonviral vector systems it has now been demonstrated that targeting strategies can allow targeted, cell-specific gene delivery. However, this has largely been demonstrated only in in vitro proof-of-principle studies. A much smaller subset of studies has demonstrated the capacity to alter vectors in the context of in vivo gene delivery schemas. Such studies have also allowed demonstration of valid functional gene therapy endpoints including increased target cell transduction for enhancement of phenotype correction and mitigation of vector-mediated toxicities. Such powerful results have predicated consideration of translating such approaches into the clinical context to validate the human therapeutic uses embodied in these targeting approaches.

The unfortunate demise of a young man in a human clinical gene therapy trial represented a field landmark. In addition to the obvious field setback provoked, basic limits inherent in current vector systems became apparent. Although a temporary retrenchment in clinical activities could have been predicted, in fact, the longer term effects have been to positively radicalize the field and regulatory agencies with respect to considering vector redesign as of paramount importance to the field. Further, the positive findings in three recent human trials (for X-linked severe combined immunodeficiency, hemophilia B, and ischemic heart disease) have been generally recognized to have been gained via vector improvements. Thus, the formula that vector gain equals gene therapy gain has clearly been established. On this basis, recognition of the need for vector targeting strategies has allowed recent approval by the National Institutes of Health Recombinant DNA Advisory Committee of a variety of human clinical trials that embody targeting principles. The use of tropism-modified viral vectors represents a fundamental paradigm shift of the basic concept of exploitation of viruses for gene therapy applications. The realization of direct gene therapy gains to these trials—that is, an improved therapeutic outcome and/or a reduction of treatment-associated toxicities—will constitute a critical validation of the targeting principle with wide implications for the field.

It is against this historical background that this book has been conceptualized. The first and second sections focus on transductional targeting strategies designed to achieve the selective delivery of the therapeutic gene by both nonviral and viral vectors, respectively. The third section discusses the alternative, but complementary, approach of transcriptional targeting, in which the therapeutic gene is placed under the control of transcriptional regulatory sequences activated in the disease cells but not in normal cells and therefore target expression selectively to the tumor cell. Any transductional targeting approach mandates ligands that can be exploited to achieve cell-specific gene delivery. Therefore, the fourth section is dedicated to the consideration of a variety of strategies that can be employed to define appropriate cellular targeting moieties. Finally, it is becoming increasingly recognized that therapeutic gene delivery in the clinical setting could greatly benefit from strategies to monitor the extent of gene expression. Accordingly, the last section of the book is dedicated to this topic. Whereas the gains of targeting have begun to become apparent in model systems, it is clear that additional, and profound, gains may yet be realized by further endeavors of this type. However, the true gains have yet to be defined in the ultimate context—human clinical gene therapies.

DAVID T. CURIEL
JOANNE T. DOUGLAS

CONTRIBUTORS

W. FRENCH ANDERSON, M.D., Gene Therapy Laboratories and the departments of Surgery and Biochemistry, Keck School of Medicine of the University of Southern California, Los Angeles, California

JOZEF ANNÉ, Ph.D., Laboratory of Bacteriology, Rega Institute, K.U. Leuven, Belgium

DAVID C. ANSARDI, Ph.D., Replicon Technologies Incorporated, OADI Technology Center, Birmingham, Alabama

QING BAI, Ph.D., Department of Molecular Genetics and Biochemistry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

ANDREW BAIRD, Ph.D., Selective Genetics, Inc., San Diego, California

JORGE R. BARRIO, Ph.D., UCLA School of Medicine, Los Angeles, California

MICHAEL A. BARRY, Ph.D., Center for Cell and Gene Therapy, Department of Molecular and Human Genetics, Baylor College of Medicine, and Department of Bioengineerng, Rice University, Houston, Texas

ROBERT W. BEART, JR., M.D., The Department of Surgery, Keck School of Medicine of the University of Southern California, Los Angeles, California

KATIE BINLEY, Ph.D., Oxford BioMedica (UK) Ltd, Medawar Centre, Oxford, United Kingdom

ANDREA BLEDSOE, Ph.D., Department of Microbiology, University of Alabama at Birmingham, Birmingham, Alabama

ABRAHAM BOUT, Ph.D., Crucell Holland BV, Leiden, The Netherlands

HILDEGARD BUNING, Ph.D., Genzentrum Ludwig-Maximilians-Universitat Munchen, Munchen, Germany

EDWARD A. BURTON, M.D., Ph.D., Department of Clinical Neurology, University of Oxford, Oxford, England

ROBERTO CATTANEO, Ph.D., Molecular Medicine Program, Mayo Foundation, Rochester, Minnesota

ESTHER H. CHANG, Ph.D., Department of Oncology, Georgetown University Medical Center, Lombardi Cancer Center, Washington, D.C.

SIMON R. CHERRY, Ph.D., UCLA School of Medicine, Los Angeles, California

CHARLES N. COBBS, M.D., Department of Surgery, University of Alabama at Birmingham, Birmingham, Alabama

DAVID T. CURIEL, M.D., Division of Human Gene Therapy, Departments of Medicine, Pathology and Surgery and the Gene Therapy Center, The University of Alabama at Birmingham, Birmingham, Alabama

PATRICK S. DAUGHERTY, Ph.D., Department of Chemical Engineering, University of California at Santa Barbara, Santa Barbara, California

PAMELA B. DAVIS, M.D., Ph.D., Division of Pediatric Pulmonology, Rainbow Babies and Childrens Hospital, Case Western Reserve University School of Medicine, Cleveland Ohio

JOHN DILEO, M.S., Center for Pharmacogenetics, Department of Pharmaceutical Sciences, University of Pittsburgh School of Pharmacy, Pittsburgh, PA

DAVID DINGLI, M.D., Molecular Medicine Program, Mayo Clinic, Rochester, Minnesota

JOANNE T. DOUGLAS, Ph.D., Division of Human Gene Therapy, Departments of Medicine, Pathology, and Surgery, and the Gene Therapy Center, The University of Alabama at Birmingham, Birmingham, Alabama

STEFAN DÜBEL, Ph.D., Institut für Molekulare Genetik, Universität Heidelberg, Germany

MARIO FERNANDEZ, Ph.D., ICRF Mol Oncology Unit, London, United Kingdom

THEODORE FRIEDMANN, M.D., Center for Molecular Genetics and Department of Pediatrics, UCSD School of Medicine, La Jolla, California

SANJIV S. GAMBHIR, M.D., Ph.D., UCLA School of Medicine, Los Angeles, California

JOSEPH C. GLORIOSO, Ph.D., Department of Molecular Genetics and Biochemistry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

WILLIAM F. GOINS, Ph.D., Department of Molecular Genetics and Biochemistry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

ERLINDA M. GORDON, M.D., Gene Therapy Laboratories and the Department of Pediatrics, Keck School of Medicine of the University of Southern California, Los Angeles, California

HIDDE J. HAISMA, Ph.D., Department of Therapeutic Gene Modulation, University Center for Pharmacy, University of Groningen, The Netherlands

FREDERICK L. HALL, Ph.D., Gene Therapy Laboratories and the Department of Surgery, Keck School of Medicine of the University of Southern California, Los Angeles, California

MICHAEL HALLEK, M.D., Genzentrum Ludwig-Maximilians-Universitat Munchen, Munchen, Germany

ANTHEA L. HAMMOND, Ph.D., Molecular Medicine Program, Mayo Foundation, Rochester, Minnesota

MENZO J. E. HAVENGA, Ph.D., Crucell Holland BV, Leiden, The Netherlands

HARVEY R. HERSCHMAN, Ph.D., UCLA School of Medicine, Los Angeles, California

LEAF HUANG, Ph.D., Center for Pharmacogenetics, Department of Pharmaceutical Sciences, University of Pittsburgh School of Pharmacy, Pittsburgh, PA

CHERYL A. JACKSON, Ph.D., Department of Physiological Optics, University of Alabama at Birmingham, Birminghan, Alabama

LISA K. JOHANSEN, Ph.D., Department of Microbiology, University of Alabama at Birmingham, Birmingham, Alabama

SAMUEL C. KAYMAN, Ph.D., Laboratory of Retroviral Biology, Public Health Research Institute, New York, New York

JÜRGEN KLEINSCHMIDT, Ph.D., Deutsches Krebsforschungszentrum, Forschungs-schwerpunkt Angewandte Tumorvirologie, Heidelberg, Germany

ROLAND E. KONTERMANN, Ph.D., Vectron Therapeutics AG, Marburg, Germany

PHILIPPE LAMBIN, M.D., Ph.D., Department of Radiation Oncology, RTIL/U.H. Maastricht, The Netherlands

WILLY LANDUYT, Ph.D., Department of Radiation Oncology, Laboratory of Experimental Radiobiology, K.U. Leuven, Belgium

DAVID LAROCCA, Ph.D., Selective Genetics, Inc., San Diego, California

NICK LEMOINE, Ph.D., ICRF Mol Oncology Unit, London, United Kingdom

BRANDI LEVIN, B.A., Department of Pathology and Kaplan Comprehensive Cancer Center, New York University Medical Center, New York, New York

SONG LI, M.D., Ph.D., Center for Pharmacogenetics, Department of Pharmaceutical Sciences, University of Pittsburgh School of Pharmacy, Pittsburgh, PA

QIANWA LIANG, Ph.D., UCLA School of Medicine, Los Angeles, California

FENG LIU, Ph.D., Center for Pharmacogenetics, Department of Pharmaceutical Sciences, University of Pittsburgh School of Pharmacy, Pittsburgh, PA

ZHENG MA, M.D., Ph.D., Center for Pharmacogenetics, Department of Pharmaceutical Sciences, University of Pittsburgh School of Pharmacy, Pittsburgh, PA

DUNCAN C. MACLAREN, Ph.D., UCLA School of Medicine, Los Angeles, California

GIANDHAM MAHENDRA, Ph.D., Department of Pathology, The University of Alabama at Birmingham, Birmingham, AL

MAJID MAHTALI, Ph.D., GIANDHAM MAHENDRA, Ph.D., Deltagen Europe S. A., Leiden, The Netherlands

DANIEL MERUELO, Ph.D., Department of Pathology and Kaplan Comprehensive Cancer Center, New York University Medical Center, New York, New York

ATSUSHI MIYANOHARA, Ph.D., Center for Molecular Genetics and Department of Pediatrics, UCSD School of Medicine, La Jolla, California

CASEY D. MORROW, Ph.D., Department of Cell Biology, University of Alabama at Birmingham, Birmingham, Alabama

ROLF MÜLLER, Ph.D., Institute of Molecular Biology and Tumor Research, Philipps-University, Marburg, Germany

DIRK M. NETTELBECK, Ph.D., Division of Human Gene Therapy and Gene Therapy Center, University of Alabama at Birmingham, Birmingham, Alabama

SANDRA NUYTS, M.D., Laboratory of Bacteriology, Rega Institute and Department of Radiation Oncology, Laboratory of Experimental Radiobiology, K. U. Leuven, Leuven, Belgium

MATTHEW T. PALMER, B.S., Department of Cell Biology, University of Alabama at Birmingham, Birmingham, Alabama

CHRISTINE PAMPENO, Ph.D., Department of Pathology and Kaplan Comprehensive Cancer Center, New York University Medical Center, New York, New York

M. BRANDON PARROTT, B.S., Department of Immunology, Baylor College of Medicine, Houston, Texas

JEAN D. PEDUZZI, Ph.D., Department of Physiological Optics, University of Alabama at Birmingham, Birmingham, Alabama

ALEKSANDR PEREBOEV, M.D., Ph.D., Division of Human Gene Therapy, Departments of Medicine, Pathology, and Surgery and The Gene Therapy Center, The University of Alabama at Birmingham, Birmingham, AL

MICHAEL E. PHELPS, Ph.D., UCLA School of Medicine, Los Angeles, California

KATHLEEN F. PIROLLO, Ph.D., Department of Oncology, Georgetown University Medical Center, Lombardi Cancer Center, Washington, D.C.

RICHARD K. PLEMPER, Ph.D., Molecular Medicine Program, Mayo Foundation, Rochester, Minnesota

SELVARANGAN PONNAZHAGAN, Ph.D., Department of Pathology and The Gene Therapy Center, The University of Alabama at Birmingham, Birmingham, Alabama

DONNA C. PORTER, Ph.D., Replicon Technologies Incorporated, OADI Technology Center, Birmingham, Alabama

MARTIN ULRICH RIED, Ph.D., Genzentrum Ludwig-Maximilians-Universitat Munchen, Munchen, Germany

PETRA ROHRBACH, Ph.D., Institut für Molekulare Genetik, Universität Heidelberg, Germany

MARIANNE G. ROTS, Ph.D., Department of Therapeutic Gene Modulation, University Center for Pharmacy, University of Groningen, The Netherlands

STEPHEN J. RUSSELL, M.D., Ph.D., Molecular Medicine Program, Mayo Clinic, Rochester, Minnesota

ISABELLA SAGGIO, Ph.D., Department of Genetics and Molecular Biology, University of Rome “La Sapienza” and Parco Scientifico Biomedico di Roma, S. Raffaele, Italy

NAGICHETTIAR SATYAMURTHY, Ph.D., UCLA School of Medicine, Los Angeles, California

NANCY SMYTH TEMPLETON, Ph.D., Center for Cell and Gene Therapy, Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas

SATOSHI TAKAHASHI, M.D., Center for Gene Therapy, Baylor College of Medicine, Houston, Texas

YADI TAN, Ph.D., Center for Pharmacogenetics, Department of Pharmaceutical Sciences, University of Pittsburgh School of Pharmacy, Pittsburgh, PA

JAN THEYS, Ph.D., Department of Radiation Oncology, RTIL/U.H. Maastricht, The Netherlands

TATSUSHI TOYOKUNI, Ph.D., UCLA School of Medicine, Los Angeles, California

LIEVE VAN MELLAERT, Ph.D., Laboratory of Bacteriology, Rega Institute, K.U. Leuven, Belgium

RONALD VOGELS, Ph.D., Crucell Holland BV, Leiden, The Netherlands

THOMAS J. WICKHAM, Ph.D., GenVec, Inc., Gaithersburg, Maryland

LIANG XU, M.D., Ph.D., Department of Oncology, Geogetown University Medical Center, Lombardi Cancer Center, Washington, D.C.

SHAHRIAR YAGHOUBI, B.S., UCLA School of Medicine, Los Angeles, California

JOHN A. T. YOUNG, Ph.D., McArdle Laboratory for Cancer Research, University of Wisconsin-Madison, Madison, Wisconsin

ASSEM G. ZIADY, Ph.D., Department of Pediatrics at Rainbow Babies and Childrens Hospital, Case Western Reserve University School of Medicine, Cleveland, Ohio

CONTENTS