ONCOGENOMICS
MOLECULAR APPROACHES TO CANCER

Edited By

Charles Brenner, Ph.D.
Departments of Genetics and Biochemistry
Norris Cotton Cancer Center
Dartmouth Medical School
Lebanon, New Hampshire

David Duggan, Ph.D.
Translational Genomics Research Institute
Phoenix, Arizona

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This book is dedicated to the patients.
CONTENTS

Contributors xi
Preface xv

Section I INTRODUCTION

1 AT THE PRECARIOUS CUSP OF ONCOGENOMICS 3
Charles Brenner

Section II MOLECULAR PROFILING IN CANCER: DNA, RNA, AND PROTEIN

2 GENOME-WIDE SEARCHES FOR MUTATIONS IN HUMAN CANCER 17
Michael R. Stratton, P. Andrew Futreal, and Richard Wooster

3 MOLECULAR CYTOGENETICS: INCREASING RESOLUTION USING ARRAY-BASED CGH 37
Anne Kallioniemi

4 SNPs AND FUNCTIONAL POLYMORPHISMS IN CANCER 57
Penelope E. Bonnen and David L. Nelson

5 EXPRESSION PROFILING OF BREAST CANCER: FROM MOLECULAR PORTRAITS TO CLINICAL UTILITY 77
Therese Sørlie, Anne-Lise Børresen-Dale, Per E. Lønning, Patrick O. Brown, and David Botstein
CLASSIFYING HEREDITARY CANCERS AND PHENOCOPIES OF HEREDITARY CANCERS USING EXPRESSION ARRAYS
Mary B. Daly, Alicia Parlanti, and David Duggan

LINKING DRUGS AND GENES: PHARMACOGENOMICS, PHARMACOPROTEOMICS, BIOINFORMATICS, AND THE NCI-60
John N. Weinstein

TISSUE MICROANALYSIS: PROFILING CANCER STAGES
Michael A. Tangrea and Michael R. Emmert-Buck

PROTEOMICS IN BLADDER CANCER
Julio E. Celis, Irina Gromova, Fritz Rank, and Pavel Gromov

Section III  MODEL SYSTEMS

CHEMICAL AND GENETIC METHODS TO VALIDATE TARGETS IN NONMAMMALIAN ORGANISMS
Tia M. Maiolatesi and Charles Brenner

MOUSE MODELS OF CANCER
Debrah M. Thompson, Louise van der Weyden, Patrick J. Biggs, Yeun-Jun Chung, and Allan Bradley

GENOME-WIDE MODIFIER SCREENS: HOW THE GENETICS OF CANCER PENETRANCE MAY SHAPE THE FUTURE OF PREVENTION AND TREATMENT
Linda D. Siracusa, Karen A. Silverman, Revati Koratkar, Marina Markova, and Arthur M. Buchberg

Section IV  MOLECULARLY TARGETED DRUGS

PROTEIN KINASES AS TARGETS IN CANCER THERAPY: VALIDATED AND EMERGING APPROACHES
Paul Nghiem, Yong-sun Kim, and Stuart L. Schreiber
CONTENTS

14 RAS SUPERFAMILY-DIRECTED COMPOUNDS 317
George C. Prendergast

15 CLINOMICS: POSTGENOMIC CANCER CARE 341
Daniel D. Von Hoff, Haiyong Han, and David Bearss

Section V CONCLUSION

16 ONCOGENOMICS AND THE NCI DIRECTOR’S VISION FOR 2015 361
Andrew C. von Eschenbach

INDEX 365
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CONTRIBUTORS

David Bearss, Montigen Pharmaceuticals, Salt Lake City, Utah

Patrick J. Biggs, The Wellcome Trust Sanger Institute, Hinxton, United Kingdom

Penelope E. Bonnen, Laboratory of Molecular Genetics, Rockefeller University, New York, New York

Anne-Lise Børresen-Dale, Department of Genetics, The Norwegian Radium Hospital, Oslo, Norway

David Botstein, Department of Molecular Biology, Princeton University, Princeton, New Jersey

Allan Bradley, The Wellcome Trust Sanger Institute, Hinxton, United Kingdom

Charles Brenner, Departments of Genetics and Biochemistry and Norris Cotton Cancer Center, Dartmouth Medical School, Lebanon, New Hampshire

Patrick O. Brown, Department of Biochemistry and Howard Hughes Medical Institute, Stanford University, Stanford, California

Arthur M. Buchberg, Department of Microbiology and Immunology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania

Julio E. Celis, Institute of Cancer Biology, The Danish Cancer Society, Copenhagen, Denmark

Yeun-Jun Chung, The Wellcome Trust Sanger Institute, Hinxton, United Kingdom

Mary B. Daly, Fox Chase Cancer Center, Philadelphia, Pennsylvania

David Duggan, Translational Genomics Research Institute, Phoenix, Arizona

Michael R. Emmert-Buck, Pathogenetics Unit, Laboratory of Pathology and Urologic Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

P. Andrew Futreal, Cancer Genome Project, The Wellcome Trust Sanger Institute, Hinxton, United Kingdom

Pavel Gromov, Institute of Cancer Biology, The Danish Cancer Society, Copenhagen, Denmark
Irina Gromova, Institute of Cancer Biology, The Danish Cancer Society, Copenhagen, Denmark

Haiyong Han, Department of Molecular and Cellular Biology, University of Arizona, Tucson, Arizona

Anne Kallioniemi, Laboratory of Cancer Genetics, Institute of Medical Technology, University of Tampere and Tampere University Hospital, Finland

Yong-son Kim, Cutaneous Biology Research Center, Harvard Medical School, Massachusetts General Hospital, Charlestown, Massachusetts

Revati Koratkar, Department of Microbiology and Immunology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania

Per E. Lønning, Department of Medicine, Section of Oncology, Haukeland University Hospital, Bergen, Norway

Tia M. Maiolatesi, Departments of Genetics and Biochemistry and Norris Cotton Cancer Center, Lebanon, New Hampshire

Marina Markova, Department of Microbiology and Immunology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania

David L. Nelson, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas

Paul Nghiem, Cutaneous Biology Research Center, Harvard Medical School, Massachusetts General Hospital, Charlestown, Massachusetts

Alicia Parlanti, Myriad Genetics, Salt Lake City, Utah

George C. Prendergast, Lankenau Institute for Medical Research and Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, Pennsylvania

Fritz Rank, Laboratory of Clinical Pathology, Diagnostic Center, Rigshospitalet, Copenhagen, Denmark

Stuart L. Schreiber, Department of Chemistry and Chemical Biology, Howard Hughes Medical Institute, Harvard University, Cambridge, Massachusetts

Karen A. Silverman, Department of Microbiology and Immunology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania

Linda D. Siracusa, Department of Microbiology and Immunology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania

Therese Sørlie, Department of Genetics, The Norwegian Radium Hospital, Oslo, Norway

Michael R. Stratton, Cancer Genome Project, The Wellcome Trust Sanger Institute, Hinxton, United Kingdom
CONTRIBUTORS

Michael A. Tangrea, Pathogenetics Unit, Laboratory of Pathology and Urologic Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Debrah M. Thompson, The Wellcome Trust Sanger Institute, Hinxton, United Kingdom

Louise van der Weyden, The Wellcome Trust Sanger Institute, Hinxton, United Kingdom

Andrew C. von Eschenbach, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Daniel D. Von Hoff, Departments of Medicine, Pathology and Molecular and Cellular Biology, Arizona Cancer Center, University of Arizona, Tucson, Arizona; Translational Genomics Research Institute, Phoenix, Arizona

John N. Weinstein, Genomics and Bioinformatics Group, Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Richard Wooster, Cancer Genome Project, The Wellcome Trust Sanger Institute, Hinxton, United Kingdom
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The emergence of genomics has changed the way we need to think about cancer in radical ways. When the draft sequence of the human genome was published in 2001, we realized that no one had attempted to assemble the broad expertise to educate working scientists and clinicians, graduate and medical students, advanced practice nurses, genetic counselors, and health educators across all of the cancer-relevant disciplines that have been altered by genomics. We realized that a forward-looking book on cancer prevention, detection, classification, pharmacology, testing, and treatment would span the disciplines of very disparate readers so we would need to begin with an advanced introduction that would allow individuals to gain confidence with the entire scope of the work. The book would devote a number of chapters to molecular profiling of cancer-specific changes at the DNA, RNA, protein and tissue levels with the aims of identifying all of the mutations that occur in malignancies, classifying tumors into a manageable set of functionally different types, and correlating those types with drug sensitivities. The book would provide chapters by experts on model systems—model organisms and cellular and chemical genetic systems—that are increasingly essential for testing hypotheses and treatments. The book would include a section on molecularly targeted drugs to explore the successes, challenges and real-world complications of developing genotype-specific agents. Additionally, the book would feature someone highly experienced in oncology clinical testing to discuss the problems of conducting target-informed trials and a concluding chapter that would set out the expectations for future developments from an authoritative point of view.

Two years ago, bearing our wish-list of contributors ideally suited to write the sixteen chapters that would constitute Oncogenomics, this book’s outline was shepherded through Wiley’s internal and external review process by our able and enthusiastic project editor, Luna Han. Today, we are extremely pleased to present readers a volume written by this dream team of scientists and clinicians. Though we spent considerable effort quilting together their contributions into an enveloping work, the power of the book is clearly in the expertise and the breadth of our contributors. Readers are encouraged to visit the accompanying website, www.wiley.com/go/oncogenomics, for additional resources. Knowing our contributors, we are confident that students will find many of these investigators accessible to discuss experiments and to plan fellowships.

This brings us to the most powerful reason for expending the energy to create the first book on oncogenomics. Novel molecular approaches to cancer prevention, diagnosis, classification, and treatment need to be developed and championed by a new generation of scientists and clinicians who are more interdisciplinary than their mentors. It is our hope that this book will catalyze cross-training such that genomicists will
think about pharmacology, model organism people with think about tumors, clinical oncologists will think about genetics, and all molecularly oriented people will think about cancer prevention.

Year 2004 cancer researchers and clinicians are necessarily wiser than we were in 2001. We are clearer in our understanding that federal and investment dollars will be limited. We know that not all targeted drugs will work as well as Gleevec. And we appreciate that the macro environment—smoking prevalence, healthcare delivery, etc.—will influence greatly the stages at which patients’ tumors will be presented either in community hospitals or in academic health centers and that these factors limit the benefit that will be gleaned from oncogenomics. At the same time, successes breed successes and we are convinced that improvements in cancer outcomes from oncogenomics will lead to an improved environment for public and private healthcare investment, earlier and more extensive applications of molecular diagnostics, and earlier and more effective molecular cancer care.

ACKNOWLEDGMENTS

While taking the opportunity to thank our scientific contributors for producing state-of-the-art chapters for *Oncogenomics*, we also want to hold these individuals and groups out as models of scientific and clinical excellence, whose careers in academia and industry (and frequently both) bear emulation. As the leading figures in molecular profiling, model systems, targeted drugs, and clinical research and care, the book’s contributors have been responsible for revolutionizing their fields. We expect that readers will appreciate the ways in which the contributors opened up their approaches to a wide audience without compromising intellectual precision.

We are grateful to Luna Han at Wiley for the vision to initiate this project and for entrusting it to us. We thank Kristen Hauser and Lisa Van Horn for moving the book through production and all of the people in the service and supply line for ably conducting their work.

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CHARLES BRENNER
DAVID DUGGAN

*Lebanon, New Hampshire*
*Phoenix, Arizona*
*January 2004*
Section I

INTRODUCTION
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AT THE PRECARIOUS CUSP OF ONCOGENOMICS

Charles Brenner

Though “same as it ever was” and “nothing will ever be the same” are clichés, our lives as medical consumers, researchers, and providers are lived in between the clichés. Each day, new cases of cancer are detected by visual and tactile inspection. Each day, researchers consent patients for molecular analysis of tumor samples in the hope of molecular classification and pharmacogenomic profiling. Vast numbers of patients are treated with combinations of the same armaments of cytotoxic compounds that have long been available, while small but increasing numbers are treated with the first gene-based drugs such as Herceptin and Gleevec. The most informed patients seek information from resources made available by the National Cancer Institute and academic medical centers, fueling demand for experimental treatments unavailable from, and in some cases unknown by, community practitioners.

To introduce the first book on cancer genomics—a volume that spans molecular profiling, model systems to discover and validate drug targets, and molecularly targeted cancer pharmacology—an advanced introduction to cancer genetics and cancer pharmacology is provided. Additionally, some of the nontechnological roadblocks to the fruition of oncogenomics are considered. There is tremendous potential for improvements in cancer care to arise from advances in prevention, an improved environment for testing including insurance reimbursement of clinical trials, and hype-free reflection on the words of Hippocrates: “first, do no harm.” The confluence of these streams—where
molecular sciences meet prevention and clinical testing in an environment free from unreasonable expectations—is the leading edge of oncogenomics.

WHAT IS ONCOGENOMICS?

Genetic Changes in Malignant Diseases

Cancer is not a single genetic disease but hundreds of diseases consisting of different combinations of genetic alterations. Several types of genetic alterations contribute to neoplastic transformation. Mutator genes that control the fidelity of genome maintenance and checkpoint genes responsible for quality control in cell division cycles are lost. Oncogenes are activated and tumor suppressor genes are lost.

To consider the types of alterations required to effect neoplastic transformation, it is useful to delineate several of the properties of normal cells. Normal cells correct spontaneously occurring and induced mutations. Normal cells arrest their division cycles when progression would lead to damaged progeny or to mitotic catastrophes. Normal cells divide in harmony with their environments: those in stem cell populations regenerate while terminally differentiated cells in epithelial layers slough off when they are worn out. Normal cells undergo programmed cell death in response to developmental signals and irreparable damage. Normal cells have tightly defined migratory potential.

We are accustomed to considering mutation and selection at the organism level. For example, we know that antibiotic-resistant microbes arise due to the existence of genetic heterogeneity and the survival of those with genes that confer resistance to the challenges to which the microbes are exposed. When the characteristics of normal cells are defined as we have defined them here (arrest, death, limits to migration), it is easy to appreciate that genetic changes leading to the initiation and progression of cancer are a selective process that results in loss of controls (i.e., failure to arrest, failure to die, unlimited migration). Inherited or acquired mutations in DNA repair genes generate the genetic diversity in somatic cells from which subsequent genetic selections occur. Losses of DNA repair genes do not directionally lead to oncogenic alterations: given the vast amount of noncoding DNA in any cell, more mutations are expected to be inconsequential than consequential. However, when a cell acquires the ability to divide more rapidly or evade apoptosis, it generates a clone of cells disencumbered from the rules that keep its neighbors in check. If the immune system does not eliminate such cells, they may survive to accumulate further genetic changes and become malignant.

Our Plastic Genomes: Sporadic versus Hereditary Cancers

I have just described genetic changes in neoplastic transformation in evolutionary terms—i.e., in terms of a population of cells within an individual that accumulate genetic differences in response to selective pressures. The more familiar Darwinian condition—i.e., populations of nonidentical individuals that exhibit different measures of fitness in different environments—is also at work in cancer biology. While all neoplastic diseases involve genetic alterations, most cancer is termed sporadic, while a minority of cases fall into what are termed hereditary syndromes, only some of which have a molecularly known basis.

In sporadic cases, we cannot see clear lines of descent, leading us to believe that the initiating genetic changes occurred within an individual’s somatic cells. In cases
that are classified as hereditary, we can see segregation of disease as a recessive or dominant trait with some measure of penetrance. It would be a mistake to create a sharp dichotomy between sporadic and hereditary cancer. Both the frequency and the consequences of sporadic events in terms of their expression as malignancies are clearly regulated by a variety of inherited factors. Additionally, while an inherited genetic change is necessary for a hereditary cancer syndrome, it is almost certainly not sufficient for malignancy. More insight into this assertion can be gleaned by considering the nature of genetic changes that occur in carcinogenesis.

It was stated at the outset that DNA repair and cell cycle checkpoint genes are lost in cancer, oncogenes are activated in cancer, and tumor suppressor genes are lost. By lowering the fidelity of DNA replication and cell division, losses in repair and checkpoint genes, produce some of the genetic variation from which transforming mutations are selected. Most of the genetic changes that occur in response to losses in fidelity are likely to be inconsequential and selectively neutral: these types of alterations are sometimes termed bystander effects. However, it is the alteration of oncogenes and tumor suppressor genes that contribute to the initiation and maintenance of the transformed phenotype.

**Oncogenes**

We say that oncogenes are *activated* in cancer because the genetic alterations are dominant and give rise to a gain of function at the gene level. An oncogene can become “switched on” by virtue of a single amino acid change, by translocation to a highly active promoter, by producing a constitutively active fusion protein, by producing a truncated protein product that is hyperactive, or by genetic amplification. All of these types of mutations are dominant with respect to the unaltered allele of the oncogene and can contribute to transformation in a heterozygous condition. These types of mutations are almost never inherited, probably because if every cell in the body contained an activating mutation in an oncogene, the embryo would not develop normally. Consequently, we know of no cancer syndromes in which there are adults who are germ-line heterozygous for activated oncogenes. The fact that oncogenes are switched on in cancer makes the oncoprotein products of oncogene mutations rational targets for genotype-specific cancer treatments, as discussed extensively in Chapters 10, 13, 14, and 15.

**Tumor Suppressor Genes**

Tumor suppressor genes, which become *lost* or *inactivated* in the development of cancer, are subject to cancer-associated mutations that are recessive at the gene level. These mutations occur both in sporadic cancer and in inherited cancer predisposition syndromes (Knudson, 1996). Whereas two “hits” are typically required to inactivate such genes in tumors that arise sporadically, if an individual is born heterozygous for such a loss, then only a single change is required in a cell to produce a preneoplastic lesion. The change can be an independent second mutation, an epigenetic change such as DNA methylation that reduces gene expression, or a gene conversion event that produces loss of heterozygosity at the locus. We consider such genetic and epigenetic changes to be preneoplastic because loss of (both copies of) a single tumor suppressor gene is not fully transforming: cancer is a multistage process involving multiple genetic changes.
The fact that tumor suppressor gene mutations are recessive at the gene and single-cell level and can be inherited in a heterozygous state through the germ line creates an additional fact about tumor suppressor gene mutations: when these mutations are followed through generations, they appear dominant at the level of the individual. The reason that a mutation that is loss-of-function at the gene level can be dominant at the organism level is that humans are multicellular organisms who live a long time, and given all of the cell divisions that occur in target tissues, it is not unlikely that a cell will suffer a second hit and produce the preneoplastic genotype. Cancer geneticists are careful to point out that individuals who carry such mutations are dominantly predisposed to get cancer: if the tumor suppressor mutations were dominant at the gene and single-cell levels, every cell that expresses the gene would be aberrant and the individuals could not develop normally. Because tumor suppressor gene mutations are recessive at the gene level, sufficient function is available to allow an individual to develop normally from a heterozygous embryo in order to produce the target organ tissue that may suffer loss of heterozygosity in one or more cells. As discussed in Chapters 10, 12, 13, and 15, cells with losses in checkpoint or tumor suppressor genes might have unique drug sensitivities that would allow them to be molecularly targeted, but—unlike activated oncoproteins—the tumor suppressor proteins themselves will not be cancer drug targets because these proteins are missing from the target tissue.

Penetrance

The final point that needs to be made in an introductory discussion of oncogenomics is that particular cancer-associated mutations bring with them a particular tumor spectrum and an approximate penetrance. For example, being born heterozygous for DNA mismatch repair gene \( MSH2 \) is associated with hereditary nonpolyposis colorectal cancer (HNPCC; Fishel et al., 1993). This syndrome involves predisposition to malignant tumors in the colon, endometrial tissues, stomach, and other sites. While most colorectal cancer is not hereditary and mutations such as \( MSH2-1906G\rightarrow C \) are rare in the general population, they are highly enriched among cancer patients in certain ethnic populations (Foulkes et al., 2002). Based on how deleterious the inherited mutation is, how likely a second hit in the \( MSH2 \) gene is, and how many additional mutations are required to produce tumors (and other interacting genetic and environmental factors), individuals who inherit such a mutation have characteristic likelihoods of developing disease. These averaged likelihoods are termed penetrance. Because colon cancer is relatively common and involves many genetic changes subsequent to reduction of mismatch repair (Vogelstein and Kinzler, 1993), the background level of sporadic colon cancer is high and the penetrance of familial colon cancer is relatively low. A consistently updated resource on the relationship between \( MSH2 \) mutations and HNPCC is maintained at Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov:80/entrez/dispmim.cgi?id=120435).

In retinoblastoma, we encounter a rare tumor that is more typically hereditary and exhibits high penetrance. In high-penetrance retinoblastoma families, individuals are born heterozygous for a deleted \( rb1 \) allele (Friend et al., 1987). During development of the retina, there is sufficient cell division to make loss of heterozygosity events likely during youth. Because an \( rb1^-/rb1^- \) cell does not need a large number of further genetic changes to become malignant, individuals born as \( rb1 \) heterozygotes are almost as likely to suffer bilateral or multifocal retinoblastoma (i.e., two independent tumors)
as they are to escape disease. Thus, such mutations appear dominant in pedigrees with almost complete penetrance. McKusick and his colleagues maintain a comprehensive resource on the genetics and molecular cell biology of retinoblastoma at Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov:80/entrez/dispomim.cgi?id =180200).

**A NEW APPROACH**

**Toward a Molecular Oncology**

From today’s perspective, we know that tumors consist of specific genetic alterations and that cancers are treated with surgery, radiation, and chemotherapy. In the absence of molecular classifications, clinicians have been treating tumors with relatively nonspecific regimens for decades. Though these treatments were not developed specifically to target known genotypes, it has long been appreciated that some patients respond whereas others do not respond to the same treatments. As Von Hoff and co-workers from the Arizona Cancer Center point out in Chapter 15, the earliest molecular classifications of tumors, such as assays of estrogen receptor status for breast and cervical cancer, were followed by the first molecularly correlated and molecularly targeted treatments.

In the “same as it ever was” past, clinicians worked with nothing more than tumor site and size to design treatments. At the precarious cusp at which we find ourselves today, genetic counseling must play a key role in informing patients and family members of what can be done and why they may wish to play a role in well-designed studies. Every author has attempted to make chapters in this book accessible to a diverse target readership population that includes oncologists and oncology nurses, basic and population-based cancer scientists, science journalists, and genetic counselors. The contributors to this volume—all experts in the field of oncogenomics—never opted to dumb the material down in a way that would compromise scientific or medical precision, while thoroughly respecting the multidisciplinary nature of this book.

In the “nothing will ever be the same” future, it has been widely speculated that the molecular profiling technologies described in Chapters 2 through 9 will be used to determine tumor and patient genotypes and genotype-specific treatments will be available for many of the common tumor genotypes. The number of chapters devoted to profiling reflects the need at this early stage of oncogenomics to develop tools to classify the molecular nature of malignant diseases. Chapters 2, 3, and 4 focus on describing DNA changes in tumors, while Chapters 5 and 6 focus primarily on RNA expression changes. Chapter 7 focuses on known cancer cell lines, Chapter 8 focuses on microdissected tissue samples, and Chapter 9 focuses on proteomic analysis.

Cancer researchers seek not only to discover all of the genetic, epigenetic, and phenotypic changes in cancer but to turn these discoveries into molecular targets. Model systems are crucial for genetic and pharmacological validation of candidate diagnostic, preventive, and therapeutic targets. For cancer, model systems are either murine or nonmurine. We review the nonmurine approaches in Chapter 10, and devote Chapters 11 and 12 to complementary approaches to cancer modeling, gene discovery, and target validation in the mouse.

Basic cancer research culminates with drug development and clinical testing. Kinase-directed and Ras superfamily-directed compounds are reviewed in Chapters 13
and 14, respectively. The complexity of cancer as hundreds of different diseases makes clinical testing and clinical care extremely challenging. These issues are reviewed in Chapter 15. In the final chapter, National Cancer Institute Director Andrew C. von Eschenbach makes the case that application of resources to several bottlenecks along the drug development pipeline and exploitation of the fruits of oncogenomics can turn cancer into a manageable condition.

**Molecular Profiling in Cancer: DNA, RNA, and Protein**

In Chapter 2, Stratton and his co-workers describe the Wellcome Trust-Supported Cancer Genome Project (CGP) in its attempt to describe comprehensively every deletion and mutation that has occurred in a reference set of cancer-derived cell lines. This extremely high-tech effort is expected to significantly expand the number of oncogenes, tumor suppressor genes, and cancer-associated mutator and checkpoint genes. Moreover, CGP methods, over the long haul, may allow a patient’s tumor to be comprehensively genotyped at high resolution.

In Chapter 3, Kallioniemi describes how the latest but relatively widely available microarray technologies can be used to detect DNA copy number changes and mRNA expression changes from patient samples. Though Kallioniemi’s methods are not designed to detect single base mutations, they are designed such that they can be replicated in a skilled and well-equipped biomedical laboratory. With the proper training and patient consents, it is not difficult to picture 100 laboratories in the United States succeeding at genotyping via Kallioniemi’s methods upon publication of this book. In contrast, it is difficult to conceive of five places in the world that could realistically take on base resolution whole-genome genotyping in the year 2003.

While Chapters 2 and 3 share the orientation of comparing tumor and normal cells, in Chapter 4, Bonnen and Nelson seek to discern genetic differences between individuals by virtue of identifying single nucleotide polymorphisms (SNPs) that correlate with alterations in cancer incidence. Goals of SNP projects are twofold. First, SNPs are important in cancer gene discovery. Second, SNP-based genotypes are expected to help oncologists stratify patients to improve clinical outcomes. These themes will recur in the Chapter 12 discussion of genetic modifier screens in the mouse.

Editing this volume on the 50th anniversary of the seminal Watson and Crick elucidation of the structure of DNA, we frequently reflected on how cancer biology and molecular biology have grown up together. While the “Central Dogma of Molecular Biology” seems quaintly simplistic in light of current awareness of DNA rearrangements, micro RNAs, RNA catalysis, and protein-based inheritance (among many other antidogmatic developments), the core concepts of gene expression are crucial to the molecular profiling approaches described in Chapters 5 through 9. The critical tool of Chapters 5 and 6 is the mRNA expression microarray whose patterns often reveal the underlying genotype without ever interrogating DNA.

In Chapter 5, Botstein and colleagues discovered a set of less than a thousand genes whose expression patterns allowed classification into five different subtypes of breast cancer. Considering that the clinical standard of diagnostic care is currently estrogen receptor positive versus negative, mechanistic dissection of breast cancer profiles and their correlations with treatment will be extremely important in oncogenic care.

In Chapter 6, Daly and co-workers consider how much genomics has changed genetics. Dr. Daly’s patients include those whose families have a high predisposition
to breast cancer. Recent work has shown that microarray technologies (both for RNA changes and DNA changes) can add a great deal to traditional and molecular genetics in disease classification and risk assessment.

Just as Stratton focused on reference sets of cancer cell lines in Chapter 2, Weinstein, in Chapter 7, focuses on a set of 60 cancer cell lines that are a permanent resource for elucidating the relationships between genome, transcriptome, proteome, and drug sensitivity. Despite the tremendous power of analyses with distributed and well-classified cell lines, there is a need to develop tools to profile DNA, RNA, and protein samples from excised patients' tissues. In Chapter 8, Tangrea and Emmert-Buck describe the state of the art in tissue microanalysis. In Chapter 9, acknowledging the advantages and disadvantages of cell lines and tissues, Celis and co-workers reveal advanced methods to profile expressed proteins in cancer samples.

Model Systems

The chapters on molecular profiling create a dynamic tension regarding potential drug targets in cancer. Whereas the gene discovery efforts described in Chapters 2, 4, 5, 7, 8, and 9 will clearly expand the number of potential cancer targets, the pattern recognition goals of Chapters 3, 5, 6, 7, 8, and 9 imply that substantially fewer than a combinatorial number of genotypes are functionally similar. Essentially every cancer genotype or expression phenotype can be treated as a hypothesis—e.g., that pharmacological targeting of these genotypes and expression phenotypes will reduce cancer incidence or lead to death or redifferentiation of cancer cells. These hypotheses are tested in model systems. In Chapter 10, we review biochemical, cellular, fungal, fly, and fish approaches to validate potential cancer drug targets. In Chapter 11, Bradley and co-workers describe mostly reverse genetic approaches to analyze cancer genotypes in the mouse. By engineering mutations into mice that recapitulate human cancer genotypes, researchers can test human genetic hypotheses in the nearest practical experimental system.

In Chapter 12, Siracusa and co-workers use the mouse for forward genetic screens to find mutations that modify penetrance. It will not escape anyone's notice that the genetic approaches in Chapters 11 and 12 are eminently complementary, as well as complementary with pharmacological approaches. For example, identifying a second mutation that reduces cancer incidence can be followed up with a gene knockout experiment. Targeting an encoded protein with a drug might produce a similar effect pharmacologically.

We note in Chapter 10 that almost the entire history of pharmacology consisted of identifying the target and mechanism of action of compounds that had interesting effects on cells or organisms, while most pharmacology today is target oriented from the start. The combination of genetics and pharmacology has accelerated both successes and failures in cancer targeting. Although failure does not sound good, accelerating failure is important because resources are always limited and in need of prioritization. Moreover, failure to be an effective drug target does not mean failure to provide important insights into molecular, cellular, and organismal biology, all of which are essential for ultimate successes.

Molecularly Targeted Drug Development and Testing

The first two gene-based cancer drugs, Herceptin and Gleevec, are both targeted against oncoprotein kinases. Because many protein kinases are activated in different types of
cancer and biochemical and cellular assays for these enzymes were straightforward to develop, it has been relatively easy to screen for compounds that inhibit oncoprotein kinase functions. In Chapter 13, Schreiber and colleagues describe ways to target protein kinases and study their modes of action using drugs. Just when we feel that the entire oncogenomic and pharmacological enterprise is fully logical and predictable, we read Prendergast’s Chapter 14 on Ras superfamily-directed compounds. It has long been clear that \textit{RAS} genes are activated in cancer and that Ras proteins need to be membrane localized by farnesyltransferase (FT) activity to be transforming. Moreover, FT was targeted for drug development and potent inhibitors (FTI) were developed that reduced anchorage-independent growth of many cancer cell lines. The problem is that cellular FTI activity does not correlate with \textit{RAS} mutation status or with the kinetics of Ras processing inhibition. Thus, the lesson of Chapter 14 is that cell biology is often more complicated than can be anticipated based on genetics.

While it was surprising to discover unanticipated targets for FTIs late in the game, it is essential for as many failures or surprises to occur before drugs get to the clinic. The financial costs involved in clinical testing are such that a company’s ability to raise funds and/or test other drugs may be jeopardized by clinical failures. The human costs can involve not only morbidity and mortality but loss of trust in the medical enterprise, which makes future testing more difficult. Clinical testing is performed in a complicated medical, regulatory, and economic environment that must be navigated by patients and their doctors. In Chapter 15, Von Hoff and colleagues steer us through the rocks with trial designs developed to convince clinicians of the utility of molecularly targeted therapeutics.

Presently, few patients are molecularly profiled and few cancer genotypes are known to be susceptible to molecularly targeted therapies. Living as we do between the “same as it ever was” past and the “nothing will ever be the same” future, we come to the first challenges of oncogenomics.

**THE ROAD AHEAD**

**Challenge 1: Molecular Diagnostics Ahead of Molecularly Targeted Treatments**

What we know about cancer genetics is substantially ahead of genotype-directed molecular pharmacology. The nature of molecular biology and molecular medicine is such that it will always be easier to determine tumor genotypes, gene expression, and protein expression patterns than to treat tumors genotype specifically. As described earlier, mutator, checkpoint, and tumor suppressor genes are lost in cancer while oncogenes are activated. Though the types of alterations that need to be detected are different from gene to gene, every genetic alteration can be detected by multiple methods. The considerations that determine widespread availability of oncogenomic diagnostics are matters of technology (i.e., whether the diagnostics will be based on DNA or cDNA sequencing, hybridization, or antibody methods), intellectual property, and economics.

Therapies will always be more complicated for a variety of reasons. First, though mutator genes are lost in cancer, it is not expected that restoring function will provide effective treatments: This would be akin to closing the barn door of mutagenesis after the horse of oncogenic mutations is out. Second, though restoring checkpoint
and/or tumor suppressor genes has been accomplished in many laboratory-controlled experimental systems, cancer is a disease of escape, and there is no clinically established method to restore a gene to 100% of tumor cells that have a missing gene. As we have discussed, loss of mutator, checkpoint, or tumor suppressor genes might sensitize tumor cells to killing by drugs targeted to other proteins. Even for those oncoproteins that are validated as drug targets and known to be required for maintaining the malignant phenotype, there are few drugs available. Thus, widespread availability of diagnostics in advance of therapeutics runs the risk of offering only negative outcomes such as stress and discrimination.

Although genotype-specific therapies will not come overnight, molecular diagnostics may tell patients and clinicians which of the available therapies are unlikely to bring benefit and might be helpful in promoting lifestyle decisions that are preventive. The utility of molecular diagnostics in ruling out certain treatment regimens is a very significant piece of medicine. Because many of the available cancer chemotherapies involve unpleasant side effects and many individuals do not respond to particular agents, sparing costly and painful treatments to patients unlikely to respond provides a real benefit. It is apparent in these early days of oncogenomic medicine that to reduce ineffective treatments and to improve medical decision making is to “first, do no harm.”

**Challenge 2: Quality of Information in the Age of the Internet**

Because patients make decisions that are irreversible, the quality of information available to physicians and their patients is crucial. In a study from the Rotterdam Family Cancer Clinic, 55% of women with *BRCA1* or *BRCA2* mutations chose to undergo bilateral mastectomies as opposed to frequent screening (Meijers-Heijboer et al., 2001). One cannot be confident of the precise risk reduction in breast cancer associated with radical mastectomy for such women, but figures as high as 90% reduction in risk have been calculated (Hartmann et al., 1999) and widely quoted. Confounding calculations of cancer risk is the fact that the original families used to identify *BRCA1* and *BRCA2* mutations exhibited high penetrance (Begg, 2002). Earlier we attributed penetrance to the severity of an inherited allele coupled to other interacting genetic and environmental factors. Indeed, in the latest study, which calculated the lifetime cancer risk of *BRCA1* and *BRCA2* mutation carriers to be 82%, pregnancy and physical activity were associated with later cancer onset (King et al., 2003).

No statement on cancer risk will be the final word—studies of breast cancer risk and risk reduction continue to be performed and debated in the literature. The problem is that patients who try to be informed are buffeted by the latest press releases. Press releases provide summaries of studies along with punchy and non-peer-reviewed quotes from study authors. Prophylactic mastectomy clearly reduces breast cancer risk: How much it reduces risk and what it costs in physical and psychological well-being vis-à-vis the procedure’s psychological benefits and the procedure’s alternatives are the questions. Because nearly all women that are not *BRCA1* or *BRCA2* mutation carriers appear to overestimate their lifetime cancer risks (Metcalf and Narod, 2002), it is a concern that women may be choosing prophylactic mastectomy based on awareness of cancer among friends and family that is mostly sporadic and entirely unrelated to their own risk.

We live in an environment with a great deal of information available on the Internet and little regulation that would restrain or coordinate access to diagnostic
and prognostic information with preventive or therapeutic options. Because a little knowledge can be a dangerous thing, we need to communicate clearly and carefully to the public and encourage bright people to be trained in genetic counseling.

**Challenge 3: Community Commitment to and Financing of Clinical Testing**

Recent experience with patients infected with HIV suggests that under the right confluence of circumstances a substantial proportion of affected individuals may be willing to volunteer for clinical trials of experimental treatments. However, because homosexual men who were disproportionately infected by HIV were amenable to community organization, and because HIV had essentially no treatment only a few years ago, the fast tracking and degree of community involvement in HIV drug testing may never be equaled in cancer clinical testing. Though the analogy strains on examination, we assert that the epidemic in cancer that most resembles HIV infection is that surrounding lung cancers in present and former smokers. With 150,000 new cases per year in the United States alone and 140,000 deaths per year, there are certainly enough cases to qualify as epidemic. Further, because the vast majority of airway cancer cases are due to the voluntary inhalation of tobacco carcinogens, there is a strong component of unsafe behavior in the etiology of the disease that must be fought prospectively by public health and education. Finally, because smoking is becoming prohibited inside public buildings, the smoking “lifestyle” has become ghettoized during the workweek to segregated spaces—a development that bears a slight resemblance to the demographic fact that many homosexual people live in enclaves. It is conceivable that, as more smokers’ circles are affected by cancer diagnoses and deaths, this community will demand experimental treatments and rally to support clinical testing of cancer drugs.

One problem with genotype-specific medicine is that by limiting the target population for a drug to those with a particular genotype or molecular profile, rather than all of those with tumors in an organ site, it is conceded that only a subset of patients will benefit from new drugs. Though only a fraction of patients respond to the existing cancer chemotherapies, the less specific criteria for prescription provide profits to drug companies. And though much has been said about targeted therapeutics being a new and rational paradigm for drug development, available evidence suggests that research and development costs continue to rise. Thus, smaller and more directed markets and high development costs are likely to lead to high costs of treatment. Groups such as CaPCURE and the Susan B. Komen Foundation have organized effectively to fund early detection programs and research. Legislation that would require health insurers to cover health care costs in approved clinical trials could potentially relieve a major impediment to more rapid and conclusive clinical testing.

**Challenge 4: Hype Harms**

In general, scientists are raised to be cautious in making assertions and predictions. In general, businesspeople responsible for raising start-up capital for biotechnology ventures are substantially less reserved. Though this book is not the place for an analysis of the investment bubble that burst in March 2000, the fallout from oversold promises in networking and biotechnologies did more than hurt people financially. Though scientists are used to failure (we never compute lifetime batting averages on
our hypotheses), patients, doctors, and investors have to be more risk adverse, and once bitten, they are twice shy.

The ethical standards that guide communications about clinical trials must be of the highest order. Drugs must be sufficiently tested preclinically prior to clinical testing and clinical trials must be designed in a manner that optimizes the analytical power behind them. In short, the collapse of the investment bubble of March 2000 and the economic climate that has followed has retaught us that we conduct our work with limited resources that must be prioritized. Of all our resources, the human ones that include the trust and support of the taxpaying, investing, and medical public are the most precious.

Balanced at the cusp of Oncogenomics, I invite the reader to turn the page.

REFERENCES


