Preface

The landmark studies by Gordon and Ruddle in the early 1980s (Gordon et al. 1980; Gordon and Ruddle 1981) demonstrating that the mouse genome could be permanently altered through transgenesis ushered in a remarkable era in biotechnology that has expanded the landscape of molecular biology and functional genomics. Methods to alter the mouse genome have become increasingly sophisticated during the past three decades. Beginning with the initial technique of pronuclear injection of embryos and their transfer into foster recipient female mice, the mouse genome can be modified through homologous recombination to alter a gene in every cell of the animal or only in a subset of targeted cell types at different stages of development. Methods whereby genes or noncoding RNAs can be inducibly expressed or repressed have added the important dimension of more precise temporal control to regulating the expression of transgenes in the animal.

This book provides important overviews regarding the state-of-the-art of mouse modeling related to cancer research written by leaders in the field. The generation of genetically engineered mouse models (GEMMs) of cancer has become increasingly refined to the point where genetic lesions identified in human tumors can be introduced alone or in relevant combinations to recapitulate oncogenic processes that drive cancer formation and progression in humans. The challenge now is to harvest the value of these models for preclinical testing of novel therapeutic strategies to ultimately advance the treatment of cancer in patients.

Part I of the book is devoted to methodologies to generate GEMMs. Chapter 1 provides a general overview of the techniques used to manipulate the mouse genome. Chapter 2 provides detailed expositions on the use of the cre-lox system to conditionally alter a gene and methods for the inducible expression of a gene. The use of the very powerful recombineering approach is discussed in Chapter 3. This technique allows for the introduction of precise alterations in bacterial artificial chromosomes (BACs) and opens up the ability to manipulate very large segments of chromosomal DNA. This has simplified both the replacement of altered genes back into the germ line through homologous recombination and the generation of constructs that contain the authentic regulatory elements distributed over a genetic locus in order to express genes in a manner that exactly recapitulates endogenous expression of that locus.
Forward genetic screens have proved very powerful in identifying genetic interactions that may lead to tumor progression and the use of insertional mutagenesis is described in Chapter 4. Chapter 5 delineates the application of the novel TVA system to target somatic expression of individual or multiple transgenes that has provided important insights into cooperativity between oncogenic pathways. As described in Chapter 6, the use of the chemical carcinogen ENU has been particularly useful as a mutagen to develop rodent models of cancer.

While hundreds of GEMM cancer models have been developed, it is critical that they be thoroughly evaluated on multiple levels to determine in what ways they do or do not represent subtypes of human cancer. Part II of the book explores how various approaches are used to compare mouse models of cancer with human tumors. Morphologic and biomarker studies remain the most important method for diagnosing, staging, and predicting outcome for human patients. Much effort has gone into performing cross-species pathology analyses between human tumors and their counterparts arising in GEMMs. These important comparisons are highlighted in Chapter 7. As high-throughput genomic studies have demonstrated, human cancers arising in the same organ that have similar morphologic appearances may be quite different on a molecular level. Clearly, no single mouse model will represent multiple subtypes of human cancer, but particular GEMMs may be excellent models for a certain subtype of cancer. Identifying such models, therefore, is in keeping with the concept of “personalized medicine,” and will be key in their use for understanding key biologic distinctions between tumor subtypes and for developing new therapeutics. Relevant mouse models are now being evaluated using high-throughput genomic approaches and are being compared to similar studies performed on human tumors. Chapter 8 discusses how this has been performed using methods to determine copy number alterations in the genomes of GEMMs. Chapter 9 summarizes advanced molecular cytogenetic techniques with a special emphasis on their use in visualizing chromosomal translocations—the hallmark of hematological malignancies—and the study of mechanisms by which they arise. Gene expression profiling has provided important insights into how particular GEMMs may cluster together with particular subtypes of human cancer and is reviewed in Chapter 10. As expounded in Chapter 11, advances in \textit{in vivo} imaging modalities have greatly advanced the ability to follow tumor progression in a living animal in real time and to determine how tumors respond to particular therapies without sacrificing the animal. These technologies parallel many aspects of how tumors are assessed and followed in human patients, making such studies in mice highly translational to the clinic.

Part III of the book provides several important examples of how mouse modeling has shed new insights into molecular mechanisms and biologic processes that are fundamental to tumor development. An important example of how normal differentiation programs are related to tumor development is discussed in Chapter 13. Chapter 14 presents an overview of how the functions of p53 and pRB have been dissected using mouse models and how this relates to loss of function of these key tumor suppressor genes in many human cancers. Several genes and pathways have been identified as being involved in human colorectal cancers and have been manipulated in GEM models to generate gastrointestinal tumors. The variety of such
models and the pathways they represent are presented in Chapter 15. This is followed by Chapters 16 and 17 that describe how modeling in the mouse has shed light on the involvement of the Src family members and signaling pathway and maspin expression on regulating metastatic tumor progression. While GEMMs have been developed primarily to manipulate the genome at the DNA level, epigenetic regulation of the genome is increasingly recognized as a major determinant of development, differentiation, and oncogenesis. Understanding the epigenome has been advanced by important studies in mouse models as highlighted in Chapter 18.

The transforming growth factor β (TGFβ) family is composed of a large and complex set of ligands and receptors whose roles in normal tissue homeostasis and tumor formation have been a great challenge to understand. Chapter 19 describes various approaches in GEMMs have provided important insights into the function of this family of genes in cancer biology. Much of the complexity of how the TGFβ family operates is due to its cross talk between multiple cell types. The vital interplay between epithelial tumor cells and their neighboring stromal components is now recognized as fundamental to the development and progression of cancer. How GEMMs have contributed to our knowledge about stromal–epithelial cross talk that influences the development of tumors is presented in Chapter 20. The critical role of the immune system in participating in cross talk with tumor cells is expanded in Chapter 21.

Part IV of the book focuses on how GEM models are being exploited to improve cancer prevention and preclinical testing of novel therapeutic approaches. Unfortunately, the use of GEMMs for drug development has been seriously hampered by intellectual property issues related to the patents, which were awarded to the development of the “Oncomouse” (Stewart et al. 1984). However, academia, biotechnology companies, and the pharmaceutical industries have recognized the value of these models for preclinical applications and in some cases, the preclinical studies in GEMMs have motivated the development of clinical trials in patients. There is a growing trend to utilize many of these models for preclinical testing, although their value for predicting response in patients remains to be shown in many cases. Chapter 22 provides a concise historical perspective of preclinical testing using non-GEM animal models, human cell lines, and xenografts up to the recent use of GEMMs for testing drug therapies. Applying genomic approaches to identify new drug targets, particularly in the context of specific genetic alterations in a tumor, is discussed in Chapter 23. An important use of GEMMs has been to test approaches for cancer prevention. As described in Chapter 24, prevention trials in GEMMs have led to important understandings of how some agents work and to new clinical trials. Interesting approaches using inducible oncogene systems in GEMMs led to the concept of “oncogene addition,” as discussed in Chapter 25. This has underscored the hope that by identifying a pathway or pathways that are the “Achilles heel” of tumor survival, genes critical for tumor maintenance can be functionally identified and targeted for therapeutic intervention.

Chapters 26 and 27 provide excellent examples of how GEMMs have been utilized for testing novel therapies for tumors of the CNS and hematological malignancies. A perspective on how the pharmaceutical industry envisions the incorporation of GEMMs into research and drug development is discussed in Chapter 28.
This book covers many important topics related to the generation, validation, and use of GEM models for advancing our knowledge of the molecular biology of cancer and how GEMMs may be used for translational research. Nonetheless, we realize that many important topics and the outstanding work of many other investigators who have shaped the field of mouse modeling could not be included in this book due to space constraints. We are most grateful to all of those who have contributed to this effort which we feel will further educate students, teachers, investigators, and mouse modelers about the tremendous value gleaned from GEM models utilized in cancer research. We are convinced that the comprehensive and systematic analysis of sophisticated mouse models will provide critical information which ultimately will benefit cancer patients.

Many of the advances described in this book were greatly influenced by the support of the National Cancer Institute for the Mouse Models of Human Cancer Consortium (MMHCC) that was initiated by Dr. Richard Klausner when he was director of the NCI. Many of the advances in cancer modeling and the infrastructure to support this enterprise are the results of the MMHCC initiative through the efforts of the Program Director, Cheryl Marks and Division Director, Dinah Singer. The scientific cancer and mouse modeling community are indebted to their foresight and dedicated efforts.

Bethesda, MD, USA

Jeffrey E. Green

Thomas Ried

References


Genetically Engineered Mice for Cancer Research
design, analysis, pathways, validation and pre-clinical
testing
Green, J.E.; Ried, Th. (Eds.)
2012, XX, 632 p., Hardcover
ISBN: 978-0-387-69803-8