

# MOUSE MODELS OF CANCER

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## A LABORATORY MANUAL



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A LABORATORY MANUAL

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#### **General Safety and Hazardous Material Information**

This manual should be used by laboratory personnel with experience in laboratory and chemical safety or students under the supervision of such trained personnel. The procedures, chemicals, and equipment referenced in this manual are hazardous and can cause serious injury unless performed, handled, and used with care and in a manner consistent with safe laboratory practices. Students and researchers using the procedures in this manual do so at their own risk. It is essential for your safety that you consult the appropriate Material Safety Data Sheets, the manufacturers' manuals accompanying equipment, and your institution's Environmental Health and Safety Office, as well as the General Safety and Disposal Cautions in Appendix B for proper handling of hazardous materials in this manual. Cold Spring Harbor Laboratory makes no representations or warranties with respect to the material set forth in this manual and has no liability in connection with the use of these materials.

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Appropriate sources for obtaining safety information and general guidelines for laboratory safety are provided in the General Safety and Hazardous Material Information Appendix of this manual.

## Preface

It has been about 25 years since the first mouse models of cancer were introduced. These were transgenic models primarily based on the forced expression of viral oncogenes in specific tissue sites where they produced cancer phenotypes. Although these relatively straightforward transgenic models have since largely been superseded by more sophisticated ones, these pioneering models established the basic premise that genetically engineered mice could be induced to develop cancer and had the potential to be *in vivo* models for studying human cancer. Indeed, in part because mice rarely develop cancer spontaneously, genetically engineered mice remain the model of choice for studying cancer phenotypes *in vivo*.

Following these early transgenic models, the next wave of genetically engineered mouse models (GEMMs) was based on the germline loss of function of tumor-suppressor genes—particularly models based on loss of function of *p53* and *Rb*. Analyses of these models have contributed to the mechanistic understanding of the tumor-suppressor functions of these genes and confirmed their role in inhibition of tumorigenesis *in vivo*. However, analyses of the phenotype of these germline tumor-suppressor models also raised questions about the spectrum of cancer phenotypes in mice and why they differ so significantly from human cancer. Additionally, because these models were based on germline events, they more closely model hereditary rather than sporadic cancer, which is a relatively smaller subset of cancer phenotypes. Nonetheless, despite these limitations, the important lessons from these loss-of-function germline mouse models, together with the gain-of-function transgenic models, prompted cancer biologists to invest in the generation of GEMMs that recapitulate a wide range of cancer phenotypes.

Nowadays, most GEMMs are based on conditional and often inducible exogenous expression of wild-type or mutant oncogenes or deletion of tumor-suppressor genes in specific tissue compartments and individual cell types. Often the constructs used to generate these models include reporter alleles for *in vivo* imaging. Thus, these “next-generation” models have enabled more sophisticated investigations of the consequences of gain or loss of function of genes for cancer phenotypes and the specific tracking of these events using imaging approaches.

Moreover, in addition to these advances, new technologies have emerged as alternatives to traditional cancer modeling in mice, including retroviral and lentiviral-mediated gene delivery (e.g., the TVA system), introduction of transposable elements for gene insertion, and introduction of short hairpin RNAs to “knock down” rather than “knock out” gene function. Cumulatively, these new technologies have advanced the sophistication of the models and their capabilities for analyses of cancer phenotypes such that some of the genetic complexity of human cancer can be recapitulated and interactions of tumor cells with the microenvironment studied. Moreover, these engineered models are now being complemented by allograft and xenograft models, which enable the analysis of mouse and human cancer following implantation of relevant tissues into immunodeficient hosts. Because these various approaches for modeling cancer in mice are largely complementary, in practice it has been advantageous to perform analyses in various model systems, because each have their own unique advantages and limitations. Finally, in recent years a major effort has been to exploit mouse models not only to study the biology of tumor phenotypes but also as preclinical tools to investigate new potential therapies for treatment and prevention of cancer and for the identification of biomarkers.

In considering these major advances in the evolution of mouse models of cancer and their many applications for understanding the biology of the disease and the development of new treatment paradigms, our goal in developing this book was to highlight the major advances that have been made that have led to the current state of research, while also providing a guide for implementation of these approaches. As such, the book is divided into three parts and appendices. The chapters in

the first part of the book review the history of mouse models, focusing on those that established the feasibility of using mice to study cancer *in vivo* and provided the foundation for current approaches. As such, these are mostly review chapters with few linked protocols.

The chapters in the second part of the book describe state-of-the-art mouse models and provide protocols for the development of these models. Here we have included chapters not only on genetically engineered mice but also on complementary approaches for engrafting mouse and human tissues into mouse hosts. Relevant protocols for development of these types of models are included in this part.

The chapters in the third part of the book are focused on analyses of many aspects of tumor biology in these mouse models, including their pathological and histological assessment. Reflecting what we envision to be the importance of mouse models for advancing our understanding of new treatments for cancer therapy and prevention, throughout the book the use of mouse models for preclinical investigations is emphasized, as also evidenced by the inclusion of a series of chapters in Appendix A that specifically address the use of mouse models for preclinical investigations.

Finally, we would like to thank the many scientists who have contributed to this book. We are very grateful for their enthusiasm, hard work, and attention to detail in preparing this book, which can serve as a resource for technicians, graduate students, postdocs, and any investigator engaged in the study of cancer in mice. We would also like to thank the NCI Mouse Models of Human Cancer Consortium and particularly Pier Paolo Pandolfi for organizing the Appendices A on Applications for GEMMs in Clinical Research. Special thanks also go to Kaaren Janssen, Maryliz Dickerson, Richard Sever, and Kathleen Bubbeo at Cold Spring Harbor Laboratory Press for helping to make this book a reality.

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