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## Preface

The cost of drug development continues to climb, reaching in 2014 an estimated \$2.6 billion per approved compound to reach market. A major cost contributor in this exorbitant expense is the number of potential drugs that fail during clinical development. Recently, it has been suggested that this high failure rate can perhaps be addressed, at least in part, by improving preclinical research with a focus on more accurate and imaginative use of animal models and a greater understanding of the role of genetics in drug interactions. Linked with this, and as our understanding of disease biology grows deeper, animal models are growing in sophistication and are increasingly more capable of emulating aspects of human disease. Combined, these developments are having a positive impact in reducing or at least slowing the drug development cost spiral.

It is clear that drug interactions with living organisms are a complex interplay of target and response. This interplay is the direct result of, and is defined by, an organism's genetic makeup plus its environment. In this volume, we present the mouse as a principal tool or, perhaps better stated, reagent. Mouse models can be completely genetically defined and as such can provide clear repeatable phenotypes and experimental data. In this regard, Dr. Michael Festing describes here how using good experimental design plus defined animals is critical to the acquisition of meaningful and reproducible data.

In the development of novel model animals, a major break-through has been in genetic engineering. Systems now exist allowing for simple, efficient, and near universally precise genetic manipulation directly in any organism, including the mouse. These genetic editing tools were first based on Zinc Finger Nuclease (ZFN), then Transcription Activator-Like Effector Nucleases (TALEN), and more recently, the development of a simple and highly efficient system based on Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR). Using these genetic editing tools, it is possible to create novel disease models based on, for example, GWAS data within months. Such tools can also be applied to preexisting models facilitating their sequential genetic modification and hence further development and refinement (Chapter 2, Low et al.). These newly created mouse strains require economic archiving and/or safeguarding against diseases or other disasters which can impact animal rooms and, for this, sperm cryopreservation is a simple solution (Chapter 3, Low et al.).

The creation and use of humanized mice, even with the intrinsic limitations of specific organ systems or proteins, allows fast and direct translation to the human condition. Humanization can be loosely divided into two often overlapping approaches: (1) the addition, modification, and/or replacement of mouse genes with human, thus emulating human conditions, or (2) engraftment of human cells into immunocompromised or often genetically "conditioned" recipients facilitating tissue/cell humanization, for example, hematopoietic stem cells (HSC) or human hepatocytes. Such humanized animals have multiple uses in both disease and drug research, and a few examples are outlined here: Chapters by Brehm, Ploss, Roopenian, and Wiles.

Mouse models can be used in a wide field of disease areas. Here we have included models of type 1 and 2 diabetes (Serreze and Baribault), cardiovascular disease (Howles), skin disorders (Sundberg), cancer (Hannun and Li), neurodegenerative diseases (Janus), neuromuscular

diseases (Burgess), and retinal disorders (Krebs and Chang). Behavioral models also exist, and we outline examples for depression, anxiety (Kalueff), and autism (Sukoff Rizzo). Lastly, there is the growing awareness that *we* are not alone, and that our bodies are ecosystems each of which includes and is impacted by our bacterial flora, collectively known as the microbiome (Kashyap).

This new volume contains a broad review of the use of mouse models in drug discovery and research and is aimed to equip the reader with the overview of possibilities of mice in drug development.

We would like to thank all the contributors, their discussions, and their patience in making this an important volume on mouse models and drug discovery.

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