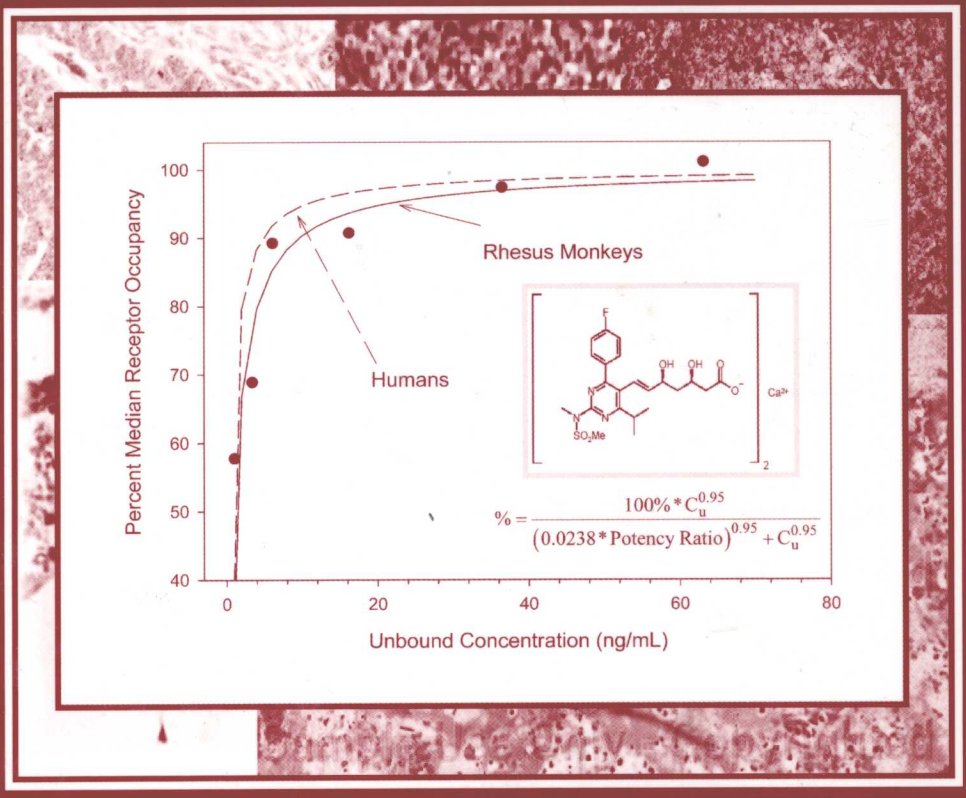
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 152

Preclinical Drug Development



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Preclinical Drug Development

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Foreword

Selection of drug molecules for development from an abundance of potential candidates is a key strategic and risky decision that every company in the business must make routinely. Informative molecule assessment programs will logically facilitate more productive and successful preclinical and clinical development programs, and help guard against unexpected pharmacokinetics or toxicities in clinical testing. Each molecule is unique with its own inherent attributes of efficacy and safety. During the past decade, pharmaceutical scientists have employed standard, as well as breakthrough, technologies in molecular biology and combinatorial chemistry that are customized for a given molecular/therapeutic family in order to significantly increase the rate at which optimal drug candidates progress into preclinical development.

Coincident with the rapid advances in drug molecule discovery, there has been a tremendous expansion in the different scientific domains and skill sets that define preclinical drug development. Experimentally, in vitro predictive methods for assessing tissue permeability, cellular transport and organ toxicity have reduced the number of animals used in preclinical drug development while providing more mechanistic insights into the processes of absorption and disposition, and the safety properties of the molecule. Likewise, the technology and underlying science of pharmacogenomics and toxicogenomics has increased the precision of our understanding of drug metabolism and transport processes at the molecular level and the biological responses that up until now were considered to be imprecise because of random variability or noise. Looking to the future, both drug discovery and preclinical development can anticipate an even faster technology evolution as new quantitative and qualitative technologies that assess biological processes and events become more widely available.

Yet, the work is not done. What remains constant is the need for timely, more predictive and cost effective in vitro and in vivo technologies that enable rapid, more accurate, and information-rich decision making to sustain a healthy and successful development pipeline. It is imperative that candidate drug molecules periodically pass through decision gates predefined by carefully selected criteria as a strategy to terminate drug development as early as possible where appropriate to reduce unexpected late clinical stage failure. Early and appropriate "no-go" decisions, in particular, provide important opportunities for other more viable candidates to move forward in the pipeline.

This textbook has been specifically written to provide medicinal chemists, biologists, pharmacologists, toxicologists, and academic faculty or students who have an interest in the science of drug development with a better understanding of the preclinical drug development process. By understanding the various components and nuances of preclinical drug development, and the criteria for advancing a candidate molecule into development including clinical trials, the likelihood of success—that is, the commercialization of a truly safe and efficacious drug—will be optimized based on good scientific rationale.

The reader is encouraged to consider this text as a starting point, either as a primer or as a refresher on the basic framework for preclinical drug development. The reader is also encouraged to read similar texts that may be focused selectively on more advanced aspects of the individual topics presented in this book.

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Preface

The primary elements of preclinical drug development—product absorption, disposition, and safety—encompass a multitude of diverse disciplines. As such, the preclinical project teams charged with developing a drug candidate are often composed of scientists with expertise in chemistry, biology, pharmacology, pharmacokinetics, and safety. As a team member, you are faced with more questions than answers, technologies that sometimes fall short of demands, the opportunity to improve or even save lives, while always being responsible for the safe and ethical progression of a drug candidate into and through clinical trials. This challenge and the passion for success exist in a team environment where few answers are self evident. As editors, we hope you find this text valuable in generating solutions to the many questions that arise during preclinical drug development.

The scope of this text covers the general elements of preclinical drug development and introduces the reader to these scientific disciplines. Specifically, we introduce you to the framework and rationale for preclinical drug development. You will then find thoughtful discussions on appropriate selection and use of animal models, limits on interpretation of data, and extrapolation of results to potential human outcome. Physiology as it relates to drug absorption, transport, distribution, and elimination is followed by chapters on safety assessment. Liberal use of examples illustrates the application of these principles and technologies. Recognition of the regulatory science and expectations is emphasized.

This text is a starting point for understanding the scientific foundation needed to move a drug candidate into clinical trials and to ensure that the clinical trials proceed efficiently and without unnecessary risk to the patient. You may find additional textbooks that are more focused and advanced on specific scientific disciplines as complementary and we encourage you to learn and develop a practical understanding of drug development. With that

foundation, you will then provide the best value to the decision process; you will optimize the likelihood of developing a safe and effective therapeutic agent.

Completing this project has required significant time, work, and the cooperation of the many chapter authors. We are indebted to those who made these important contributions. We are also indebted to our colleagues and mentors who have served as such great role models. It is not necessary to name you; our admiration and respect for you is evident.

Our employers and supervisors deserve recognition for allowing us to complete this project. Our families deserve special acknowledgment for their strong support and endless patience. Thank you.

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