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Early Drug Development

Bringing a Preclinical Candidate to the Clinic

Volume 73
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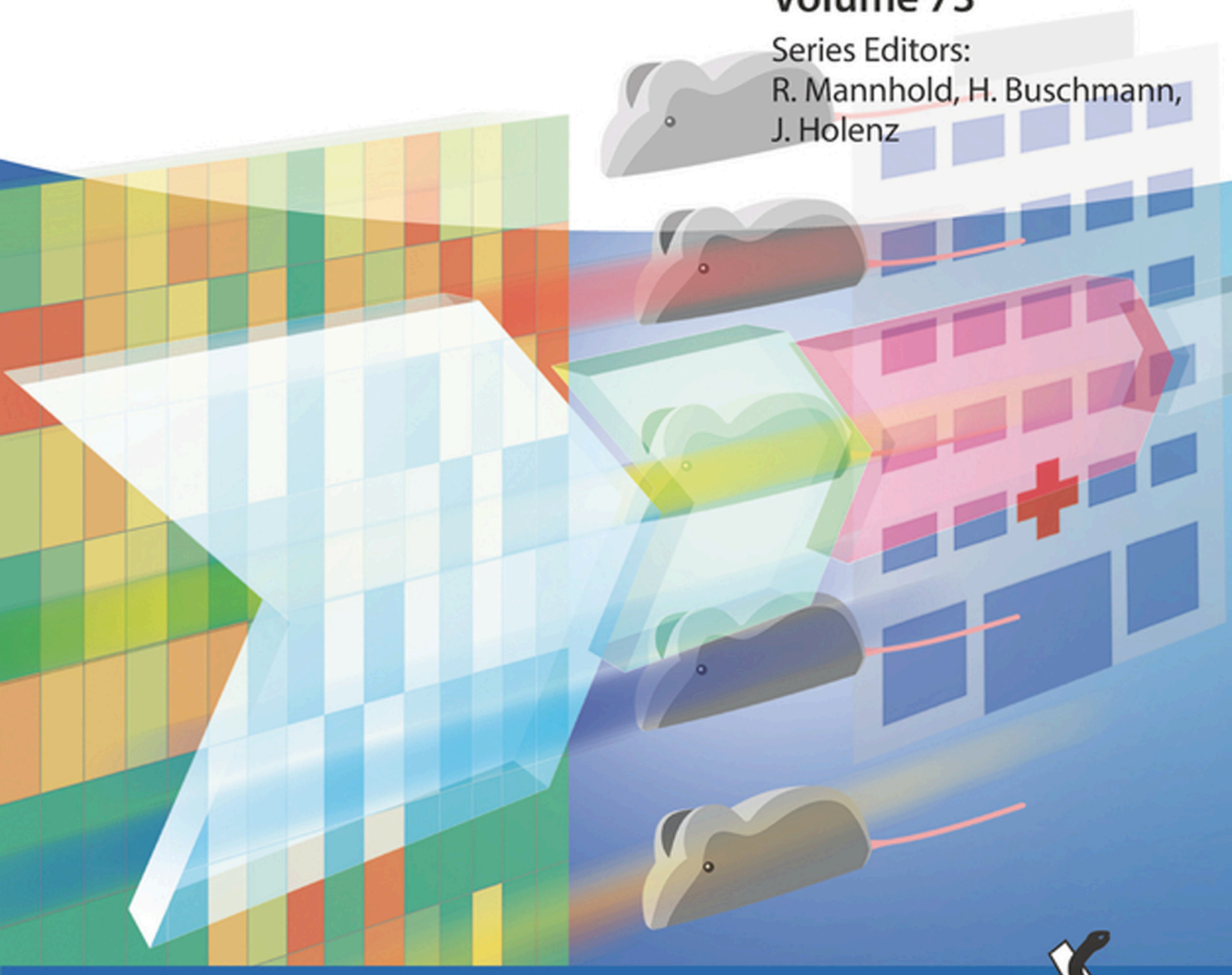
R. Mannhold, H. Buschmann,
J. Holenz



Methods and Principles in Medicinal Chemistry

Early Drug Development

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Volume 1

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Volume 2

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Preface

Modern research in drug discovery and development (DDD) resulted in enormous progress in understanding disease-underlying mechanisms on a molecular level via systems biology strategies and in developing advanced methodological tools [1]. Regrettably, however, this progress did not translate into higher rates of successful approvals for new chemical entities (NCEs). Only one out of 5000–10 000 NCEs is approved, and only one out of nine compounds in clinical development reaches the market [1].

To counteract this unsatisfactory situation and to reduce the number of late-stage failures of clinical candidates, current pharma research dedicates an increased attention to a particular step in the DDD path: the early or preclinical drug development step [1–3] that comprises all activities aimed at bringing optimized lead structures to first-in-human trials considering pharmacological and toxicological characterization as well as GLP and GMP activities according to regulatory guidelines. The goal is to optimally filter out "detrimental" compounds at a very early state of the process and thereby to increase success rates.

In the introduction of this book, Fabrizio Giordanetto gives an overview of the general early drug development (early DD) workflow. In four follow-up sections, the sequential steps of early DD are described in detail, focusing on the availability of the drug substance according to GMP guidelines and the solid phase characterization, the availability of the drug product after preformulation work, the prediction of PK/PD, and the *in silico*, *in vitro*, and *in vivo* prediction of drug safety. All sections include several case studies to further exemplify the respective early DD steps under consideration. Finally, strategic aspects of patenting are addressed.

Drug substance: Drug substance is defined as an active ingredient intended to furnish pharmacologic activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the body; it does not include intermediates used in the synthesis of such an ingredient. Chapters in this section particularly concern process chemistry including route-finding and up-scaling environmental aspects such as green chemistry and costs of goods.

Drug product: The drug product is defined as the finished dosage form, often comprising the drug substance formulated with inactive ingredients optimized for the intended application route with a suitable ADME profile. Drug formulation and their delivery into the human body represent a central