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Second Edition

Drug Metabolism Handbook

Concepts and Applications in
Cancer Research

Volume 1

Edited by: **Ala F. Nassar**

Associate Editors: **Paul F. Hollenberg** • **JoAnn Scatina**
Soumen Kanti Manna • **Su Zeng**

Drug Metabolism
Handbook

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Handbook

Second Edition

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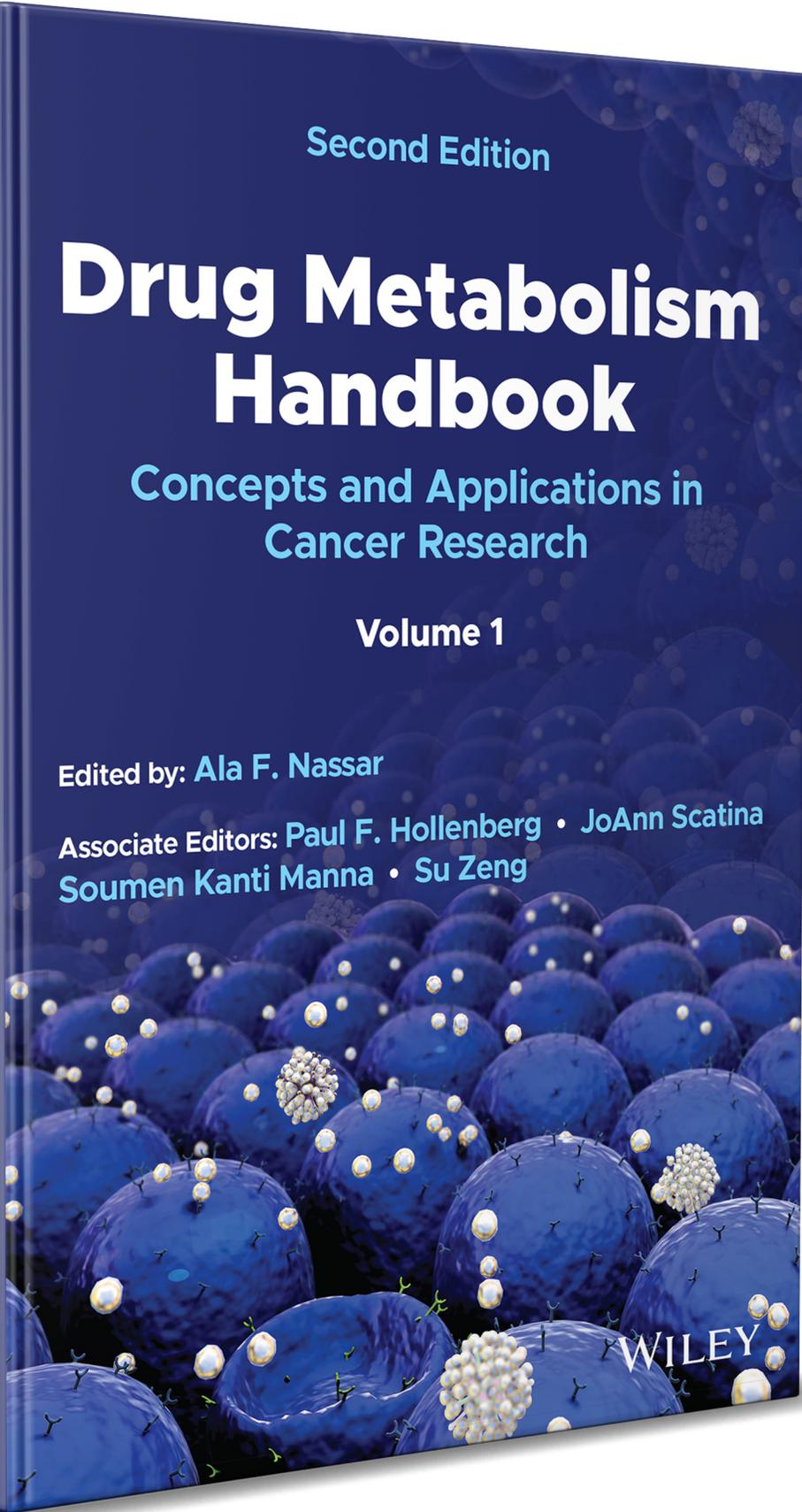
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DRUG METABOLISM HANDBOOK

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CONCEPTS AND APPLICATIONS IN CANCER RESEARCH

Volume 1

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Studies on absorption, distribution, metabolism, and elimination–toxicology (ADME–Tox) have progressed over the years to the point where they now play a major role in drug discovery and development. Until the late 1980s, the primary role of drug metabolism groups in the pharmaceutical industry was to provide ADME–Tox information to support the regulatory package. During the last decade, with the rapid rise in new molecular entities (NMEs) from combinatorial chemistry and high-throughput biological screening, there is an urgent need for the determination of the ADME properties of these NMEs at very early stages in the drug discovery pipeline in order to facilitate the selection of “ideal” drug candidates for further development. Back integration of key studies into the discovery phase has resulted in earlier identification of potential DM/PK and safety liabilities. This information aids in decision making and, in many instances, has been incorporated into criteria for compound advancement into the development phase. Given the need for earlier and more rapid evaluation of a larger number of compounds, drug metabolism scientists have developed and incorporated numerous novel approaches into early drug discovery. These include “humanized” *in vitro*-based cell systems, sophisticated automation, higher-throughput ADME assays and screens, ultrasensitive analytical technologies, and computational models in order to accelerate the examination of the drug metabolism pathways of their NMEs. The success of this approach is evident, as the number of failures due to DM/PK liabilities has dramatically decreased. Clearly, there is a growing need for improving and expanding education of students as well as current practitioners involved in investigations in these areas. The needs for continuing education in the rapidly expanding and dynamic area of ADME–Tox studies are not being met at the university level, and oftentimes this is being taught in a piece-meal fashion on the job in pharmaceutical industries.

Therefore, the goal of this book is to provide a systematic approach for the education of students at the university level, as well as younger researchers and scientists changing fields in the pharmaceutical industry to improve their knowledge of drug metabolism by presenting in-depth coverage of the drug disposition process, pharmacokinetic drug–drug interactions, theory, and evaluation approaches and improving the decision-making process used for the structural modification of drug candidates to reduce toxicity. ADME–Tox experts in the field from both industry and academia have joined forces and offered their time to write this book, introducing students to modern concepts and practices of ADME–Tox. This book provides basic training in the areas of drug metabolism and disposition, including training programs for students as well as new employees in the pharmaceutical industry. Mastery of the material in this text will allow them to apply state-of-the-art research tools to *in vitro* and *in vivo*

metabolism studies and contribute greatly to their abilities to perform pharmaceutical research in support of industrial, academic, and regulatory agency needs. One emphasis of the current edition – as evident from the title – is to improve our understanding of drug metabolism and discovery in the context of cancer. Metabolic reprogramming, which is a hallmark of cancer, is a target of several existing and experimental drugs. This book will discuss the nature of metabolic reprogramming in cancer and its cross-talk with drug metabolism. It will also present strategies and tools for elucidation of heterogeneity in drug disposition and metabolism in tumors as well as for therapeutic personalization.

This textbook consists of five parts. Part I provides an introduction to drug metabolism. Part II presents the *in vitro* and *in vivo* technologies used to investigate the metabolism of drugs and drug candidates. Part III presents an important area of drug–drug interaction. Part IV discusses the toxicity of drugs and their metabolites. Part V of this volume provides an up-to-date series of chapters on the applications of drug metabolism in cancer. This book provides a unique and useful approach for all those involved in drug discovery and development, and for clinicians and researchers in drug metabolism, pharmacology, and clinical pharmacology.

The editors and contributing authors greatly appreciate the commitment of the publishers to make this book available to our scientific colleagues in developing countries to enhance their knowledge in the area of ADME-Tox and to help them in furthering their careers in this very important area of research. Finally, we thank our many colleagues worldwide who have contributed to the development of the knowledge and techniques described in this book. We feel very fortunate to be able to participate in an area of scientific pursuit in which cooperation and collaboration between investigators in industry, academic institutions, and regulatory agencies is so strongly encouraged and highly valued. *Drug Metabolism Handbook* is a comprehensive reference devoted to the current state of research on the impact of various disease states on drug metabolism. The book contains valuable insights into mechanistic effects and examples of how to accurately predict drug metabolism during these different pathophysiological states. Each chapter clearly presents the effects of changes in drug metabolism enzymes and drug transporters on the pharmacokinetics, disposition, and potential toxicity of NMEs.

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August 2022

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PART I

INTRODUCTION

Historical Perspective

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1.1 CONTROVERSIES SPANNING PAST, PRESENT, AND FUTURE

Two major issues have been debated throughout the history of drug metabolism, and are still disputed to some degree. One is the name itself, the other is the physiological purpose of “drug” metabolism. In the 1800s and early 1900s, the generally agreed purpose of these reactions was reflected in the most widely used name, *detoxication mechanisms*. However, *detoxication* became widely recognized as a misnomer because not all parent compounds were toxic and not all metabolites were less or nontoxic. A better term was not invented until the 1950s when the term “drug metabolism” was coined. While handy, this term was still not entirely valid, and it needed silent agreement that “drug” be not restricted to medicinal compounds (Bachman and Bickel, 1985–86). Thus, *xenobiotic metabolism* became popular starting in the 1970s, especially in circles studying carcinogens and environmental compounds. Xenobiotic, by definition, included all compounds foreign to the organism, not just medicinal ones. However, even in the early 1900s many examples were already known of metabolism of endogenous compounds, for example, steroids undergoing glucuronidation. These early examples of endogenous substrates were generally dismissed because they typically occurred at much higher concentrations than normally present, so-called “supraphysiological” concentrations. While none of these three terms could be considered ideal, in 1947 R.T. Williams concluded that the field of detoxication included “... all those metabolic processes not specifically covered by the main streams of fat, carbohydrate and protein intermediary metabolism.” (Williams, 1947). Williams went on to explain that, “Detoxication is, in fact, the study of the metabolism of organic compounds other than lipids, carbohydrates, proteins and closely related natural compounds, although the lines of demarkation between these