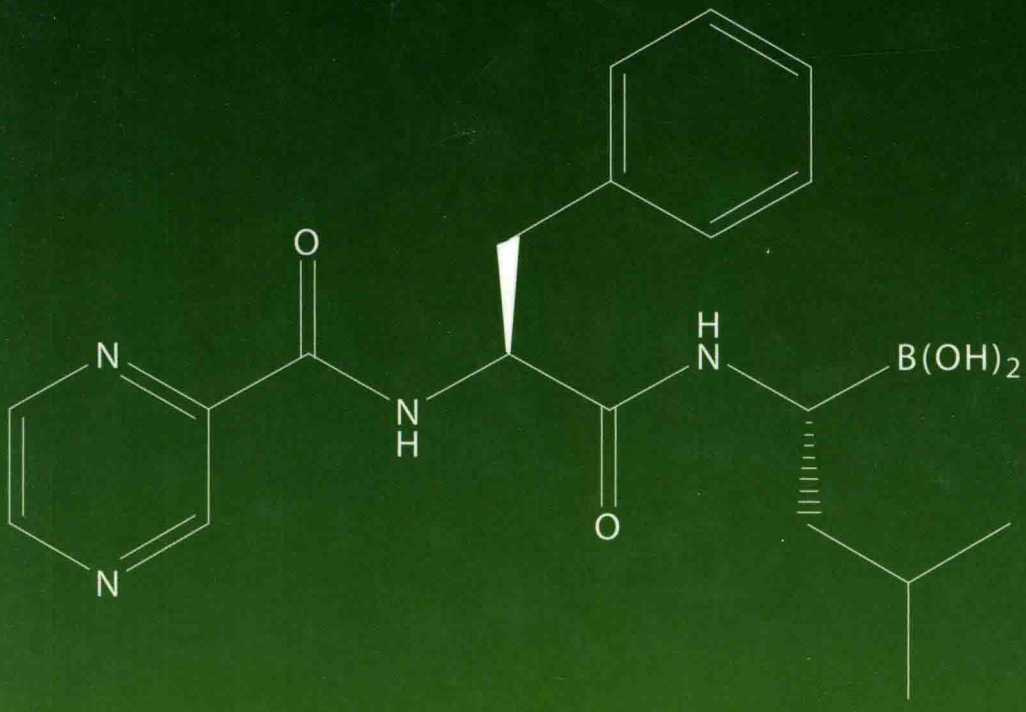
Enzyme Inhibition

in Drug Discovery and Development

THE GOOD AND THE BAD



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PREFACE

Development of pharmaceuticals is a complex science that involves collaborative activities of scientists from several different areas, such as: biochemistry to validate drug targets, medicinal chemistry to synthesize compounds; pharmacology to test the compounds' efficacy; drug metabolism and pharmacokinetics (DMPK) to ensure that the compounds have "drugable" properties, such as appropriate absorption, distribution, metabolism, and excretion (ADME) profiles; formulation science to design appropriate drug products; toxicology to characterize the safety profile in animals and help estimate the safety margin for humans; and last but not least, clinical sciences to ensure adequate pharmacokinetic, efficacy, and safety profiles in humans. Marketing and finance departments are involved right from the start and throughout the process in projecting the market on the basis of the drug's properties and the existing competition. During the costly and lengthy drug development process, the management team continually evaluates the progress of individual programs, sets priorities for development, and allocates resources to maximize the possibility of success given the company's position and market conditions.

Diseases are often associated with the elevation or repression of certain proteins that could be used as drug targets. In general, drug discovery starts by manipulating the drug target proteins (a receptor, kinase, or enzyme) with an agonist or, more commonly, with an antagonist or inhibitor. Such inhibition can generally be termed "good inhibition," because it leads to a desired outcome—that is, suppression of a target and, in turn, a treatment for a disease. More often than not, other proteins unrelated to the target are also inhibited, potentially leading to adverse effects. This additional, unwanted inhibition can be termed "bad inhibition." The inhibited proteins may be receptors,

metabolizing enzymes, drug transporters, and so on. For the purposes of this book, only bad inhibition related to DMPK is covered. Just as good inhibition can lead to bad effects (e.g., related to mechanism-based adverse effects), bad inhibition can have a positive side as well. For example, drugs known to affect nontarget proteins may be used in select cases to cause mixed-type positive effects or in combination with appropriate drugs to complement their shortcomings. These attributes will be discussed in many of the chapters. In this high-throughput era, individual specialities are sometimes too focused on delivering in their own area. An overall understanding of the drug discovery and development process allows each scientist to look beyond his or her specialty at the bigger picture and to mold and integrate his or her research to fill the grand need of the product from all departments' perspectives. The goal of this book is to provide in-depth information to these specialized scientists on the latest science, strategy, and approaches in enzyme inhibition as applied to drug discovery and drug development, as well as to provide value to those who are interested in learning the science of fields other than their own.

This book represents the first of its kind in terms of its inclusion of both pharmacologic and pharmacokinetic aspects of enzyme inhibition, with chapters written by over 50 leading scientists in their fields, from both academia and industry (major pharmaceutical and biotechnology companies). The first part of this book gives an overall review of the drug discovery processes, including chapters on drug discovery strategy, medicinal chemistry, analytical chemistry, drug metabolism, pharmacokinetics, and safety biomarker assessment. The second part of this book discusses the manipulation of drug-metabolizing enzymes and transporters and their mostly adverse consequences, such as drug–drug interactions. The third part of this book reviews the inhibition of several major drug target pathways, such as the GPCR pathway, the NFκB pathway, and the ion channel pathway. This book will allow DMPK scientists to learn and appreciate target biology in drug discovery and, conversely, will allow discovery biologists and medicinal chemists to have a broader understanding of DMPK. It is also intended for readers with a general interest in the field—for instance, students in pharmacology, clinical development staff, those in marketing, and regulatory practitioners, as well as pharmaceutical executives, because it offers the opportunity to learn in a single treatise the basic science of drug discovery and development.

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June 2009

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PART I

DRUG DISCOVERY APPROACHES AND TECHNOLOGIES

1

THE DRUG DISCOVERY PROCESS

GERALD T. MIWA

1.1 INTRODUCTION

The discovery and development of drugs is an inefficient process. Only one of approximately 10,000 compounds synthesized reaches the marketplace, and this requires approximately 10–15 years and $800,000,000 in R&D expenditures (Khosla and Keasling, 2003). The objective of drug discovery should be to identify a compound that will prove to be safe and effective against the intended disease with minimal attrition due to toxicities, inadequate exposure, or unsuccessful translation of target modulation to clinical benefit against the disease. Drug discovery, the process used to select a compound for drug development, is common in most pharmaceutical and biotechnology companies. This process is composed of the following phases: target identification and validation, hit identification, lead optimization, and development candidate nomination (Fig. 1.1).

Target identification and validation is the process used to identify and confirm that the modulation of a biological target will produce a desired therapeutic effect. The methods employed for this phase are mainly biological. The confirmation or validation of the utility of the target in modifying a human disease is critical and remains the greatest potential issue of this phase because of its implication in clinical failures due to inadequate efficacy. Hit identification is the process employed to initially identify molecules that interact with the target. Both biological and chemical methods are used to identify hits. The methods employed, although more comprehensive than in the past, may still not identify all possible hits. Usually, more stringent selection criteria are

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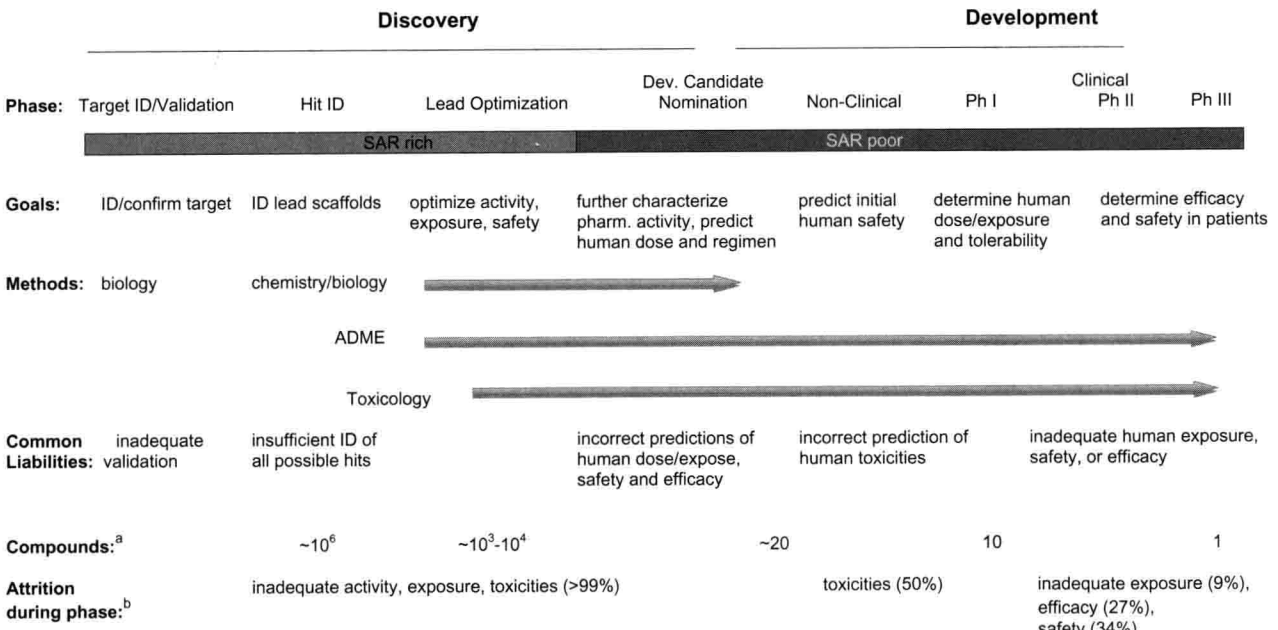

[a] adapted from Khosla 2003

[b] major causes of attrition during a phase and (percentage of total attrition due to these causes), adapted from Kola and Landis 2004

Figure 1.1. Goals and challenges in the processes of drug discovery and development.

implemented to screen hits in order to identify lead compounds that have the potential to improve further with structure modifications. Lead optimization is the chemical structure–activity optimization process that identifies the best possible drug-like molecule. Usually absorption, distribution, metabolism and excretion (ADME) and toxicology assays are added to the biological and chemical methods during lead optimization. Development candidate nomination is the process used to further characterize the potential exposure, efficacy, and safety of the nomination candidate and to judge if the molecule is suitable for drug development. The most common liabilities remaining from this phase are inaccurate predictions of human exposure, safety and efficacy. Although the objectives are common among companies engaged in this process, the methods, issues, and acceptance standards vary. Nevertheless, the best measure for the success of drug discovery is the demonstration of a compound's effectiveness and safety in patients. This chapter describes the elements of the drug discovery process and comments on its successfulness and areas currently under evaluation to improve success.

1.2 TARGET IDENTIFICATION AND VALIDATION

Target identification is the process used to identify potential therapeutic targets amenable to modulation by drug molecules, antibodies, aptamers, or gene modulators such as siRNAs and antisense oligonucleotides. The identification of potential targets for therapeutic intervention by drugs has greatly improved in the past two decades. Prior to the mid-1980s, drug targets were identified by the serendipitous discovery of active agents such as the penicillins and the benzodiazepines, through the symptomatic changes in disease models in animals such as cardiovascular drugs or through activity in suitable *in vitro* systems such as for anti-infective drugs. Biochemical targets were identified through their postulated relevance in pathways thought to be involved in disease processes such as HMG-CoA reductase in cholesterol biosynthesis and coronary heart disease (Tobert, 2003), and the H2-receptor in gastric acid secretion and gastric ulceration. In rare cases, targets could be identified and validated in humans through existing genetic mutations in the human population such as the deficiencies in 5-alpha reductase (Johnson et al., 1986) which led to the 5-alpha reductase inhibitor class of drugs for benign prostatic hypertrophy and propecia.

During the past two decades, greater knowledge and newer biological methods have permitted the mining of patient samples and animal models of diseases to elucidate the probable genes implicated in the disease etiology. Techniques such as gene expression profiling and comparative genomics have been valuable in identifying potential targets. For example, the capability to identify the overexpression of HER2 in the diseased tissues of some breast cancer patients was used to identify HER2 as a new target for metastatic breast cancer and led to the discovery of Herceptin (Chang, 2007).