PART I

INTRODUCTION TO SYSTEMS BIOLOGY IN APPROACH

CHAPTER 1

Introduction to Systems Biology in Drug Discovery and Development

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Summary

Over the last several decades, medical and biological research has opened vast windows into the mechanisms underlying health and disease in living systems. Integrating this knowledge into a unified framework to enhance understanding and decision making is a significant challenge for the research community. Efficient drug discovery and development requires methods for bridging preclinical data with patient data to project both efficacy and safety outcomes for new compounds and treatment approaches. In this book we present the foundations of systems biology, a growing multidisciplinary field applied specifically to drug discovery and development. These methods promise to accelerate time lines, to reduce costs, to decrease portfolio failure rates, and most significantly, to improve treatment by enhancing the workflow, and thus the competitiveness, of pharmaceutical and biotechnology organizations. Ultimately, these improvements will improve overall health care and its delivery.

SYSTEMS BIOLOGY IN PHARMACOLOGY

Discovering a new medicine is a multistep process that requires one to:

- Identify a biochemically based cause–effect pathway (or pathways) inherent in a disease and its pathophysiology

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- Identify those cells and molecular entities (e.g., receptors, cytokines, genes) involved in the control of those pathways (typically termed *targets*)
- Identify an exogenous entity that can manipulate a molecular target to therapeutic advantage (typically termed a *drug*)
- Identify, with some level of specificity, how manipulation modulates the disease effects (termed the *mechanism of action* of the drug)
- Identify that segment of the patient population most likely to respond to manipulation (typically through the use of appropriate surrogates termed *biomarkers*)

Given these challenges, pharmaceutical drug discovery and development is an extremely complex and risky endeavor. Despite growing industry investment in research and development, only one in every 5000 new drug candidates is likely to be approved for therapeutic use in the United States (PhRMA, 2006). In fact, approximately 53% of compounds that progress to phase II trials are likely to fail, resulting in amortized costs of between $800 million and $1.7 billion per approved drug (DiMasi et al., 2003; Gilbert et al., 2003; Pharmaceutical Research and Manufacturers of America, 2006). Clearly, the crux of the problem is the failure rate of compounds, especially those in late-stage clinical development. To solve this problem, one must clearly identify the most appropriate compound for the most appropriate target in the most appropriate subpopulation of patients, and then dose those patients as optimally as possible. This philosophy forms the cornerstone of the "learn and confirm" model of drug development suggested by Sheiner in 1997.

For example, to address these three issues specifically, the Center for Drug Development Science at the University of California–San Francisco has developed a set of guidelines for applying one particular *in silico* technology, biosimulation, to the drug development process (Holford et al., 1999).

These guidelines define a three-step process. During step 1, the most relevant underlying biology describing the pathophysiology of the disease is characterized, as are the pharmacokinetics of any candidate compound aimed at its treatment. In step 2, the various clinical subpopulations expected to receive the compound are identified and characterized, including measures of interpatient variability in drug absorption, distribution, metabolism, and excretion, and compound-specific pharmacodynamics are established. Once steps 1 and 2 are complete, this information is used in step 3 to simulate and thus design the most efficient clinical trial possible.

We believe that the general principles outlined above should not be restricted to only one methodology (i.e., biosimulation) but should be extended to the entire spectrum of *in silico* technologies that make up the generic discipline called *systems biology*. Systems biology is a rapidly developing suite of technologies that captures the complexity and dynamics of disease progression and response to therapy within the context of *in silico* models. Whether these models and their incumbent analytical methodologies represent explicit physi-

ological models and dynamics, statistical associations, or a mix thereof, *en suite* they provide the pharmaceutical researcher with access to the most pertinent information available. By definition, that information must be composed of those data that best characterize the disease and its pathophysiology, the compound and its mechanism of action, and the patient populations in which the compound is most likely to work. With the advance of newer and faster assay technologies, the gathering of those data is no longer the rate-limiting process it once was. Rather, technologies capable of sampling the highly complex spaces underlying biological phenomena have made the interpretation of those data in the most medically and biologically reasonable context the next great hurdle in pharmaceutical drug discovery and development.

To address these challenges adequately, the pharmaceutical or clinical researcher must be able to understand and characterize the effects of diverse chemical entities on the pathways of interest *in the context of the biology they are meant to affect*. To accomplish that, research scientists and clinicians must have at their disposal the means to acquire the most pertinent and predictive information possible. We believe that systems biology is a particularly attractive solution to this problem. It formally integrates knowledge and information from multiple biological sources into a coherent whole by subjecting them to proven engineering, mathematical, and statistical methodologies. The integrated nature of the systems biology approach allows for rapid analysis, simulation, and interpretation of the data at hand. Thus, it informs and optimizes the pharmaceutical discovery and development processes, by formalizing, and testing, the most biologically relevant family of acceptable hypotheses *in silico*, thereby enabling one to reduce development time and costs and improve the efficacy of novel treatments.

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