

# Preface

The last decade has seen a loss of confidence in the big pharma model for the development of new drugs. Despite unprecedented development costs, only about 10% of molecules entering Phase I were registered as drugs between 1991 and 2000 (Kola and Landis 2004). More concerning for the industry is that a significant proportion of the molecules failed in late phase development, after major investments already had been made. Two problems dominated these late stage failures: lack of efficacy and unanticipated safety risks.

Several reasons for this high attrition are suggested by the observation that critical issues related to efficacy often were not answered early in development. For example: Does the molecule reach its target? Is there evidence for the desired pharmacological effect *in vivo*? What is the dose-response relationship? In cases in which some of this information was established in preclinical models, the models did not necessarily reflect the critical biology in humans or for the human disease. Drug development needs to incorporate approaches for more direct *in vivo* pharmacology in humans.

In addition, because so much of the safety evaluation either relies on short term outcomes in humans or preclinical studies using high compound concentrations, more slowly developing pathologies or pathologies idiosyncratic to humans or particular populations can escape detection until large numbers of patients are treated for long periods in Phase III studies. Better ways of bridging between pre-clinical toxicology and clinical toxicology studies are needed. More sensitive measures for toxicology are desired in clinical studies. Safety assessment also can benefit from *in vivo* physiological measures in humans.

The primary limitations of conventional clinical development for many current major disease targets (e.g., in CNS, metabolic and cardiovascular indications) relate to requirements for long periods of evaluation and the modest sensitivity of usual, clinically based measures of outcome. While these clinical measures of outcome may have ecological validity in terms of ultimate clinical impact, they typically are only indirectly related to pharmacology and rarely address toxicology in particular. A compelling new approach to addressing this challenge is the aggressive application early in development of experimental medicine approaches designed to test specific pharmacological or toxicological hypotheses. Using biochemical, structural, or physiological measures that report on changes reflecting distribution or

direct consequences of drug action, the kinds of critical questions posed above can begin to be answered translationally in a coordinated strategy extending from pre-clinical to clinical studies. The translational element involves initial qualification of biomarkers in preclinical experiments, where they can be related directly to a broad range of well-accepted outcomes. When combined with patient populations in which the disease mechanisms are well characterized, the interaction between pharmacology and disease mechanisms can be elucidated more powerfully in shorter studies with more precisely defined and sensitive measures of response.

Such short term biomarker measures of drug distribution of pharmacological response may or may not be predictive of ultimate clinical response for any indication. However, they constitute direct tests of the fundamental hypotheses that are driving development of a molecule. Strict criteria for progression can be defined, making proof of pharmacology a critical part of a decision to progress development from early stages.

While some may argue that there are many examples of useful drugs with activity in disease that was not well predicted by the initial pharmacological hypothesis, set against this is the sad prior (for a rigorous, Bayesian view of drug development): most molecules will fail to make suitable drugs. The prior probability of not developing a potentially important therapeutic molecule because of failure at an early, direct test of pharmacology is therefore low.

*Imaging in CNS Drug Discovery and Development* provides a primer to the emerging potential of imaging as a general biomarker particularly for CNS drug development. The Editors have gathered together an internationally respected group of experts. Both academic and industry leaders are included. Together, they have produced a unique volume introducing the major tools, approaches, and challenges.

Important themes of integration run through the book. The selection of chapter topics emphasizes the need to integrate clinical and preclinical investigations of pharmacology. Preclinical investigations provide a fundamentally important way of relating imaging measures directly to conventional pharmacological and neurobiological response indices. It is not just through biomarker qualification that preclinical imaging provides an important tool to drive more effective clinical investigations. Preclinical studies also provide an opportunity to more completely define response relations and to push the range of such studies over a broader range, providing hypotheses that can later be explored in human toxicologically focused investigations. Preclinical imaging also allows the similar measures used for candidate selection to be applied to the initial proof of pharmacology in humans. At the same time, applications of imaging to preclinical investigations address the three R's of *reduction*, *refinement*, and, by extension to the clinical studies, an emphasis on *replacement* of use of animals by human experimental medicine in drug development.

A second theme addressed very directly in the concluding section of the book is the importance of integration of imaging and other biomarker information to provide multivariate measures of response. The neurobiology of disease and related neuropharmacology are complex. There is increasing evidence that multivariate

approaches provide new ways of enhancing precision of outcome measures and sensitivity. Computational power now should not be limiting. It is imperative that we use the full range of data available more effectively.

Applications of imaging to drug development have been growing rapidly in number over the last few years. In this exciting environment, it would not be possible to create a volume that remains fully current with the state-of-the-art. The Editors therefore have included chapters from experts providing paradigmatic examples that establish a “blueprint” for a way forward. Key therapeutic areas that illustrate the major problems have been identified. The use of functional imaging-based measures to objectify subjective experience is described in the chapter on pain, illustrating how sensitivity to the range of responses to a complex illness can be captured powerfully by imaging. The description of initial studies with post-traumatic stress disorder highlights the role of imaging in diseases of mind. Examples also are chosen from disorders in which there is a more complete understanding of disease neurophysiology, such as addiction and anxiety, illustrating how knowledge of the underlying cognitive systems can be coupled with imaging to drive stronger pharmacological hypotheses. Finally, the discussion of plasticity highlights one of the most important characteristics of noninvasive imaging approaches: the potential to follow the dynamics of change over time.

Recent commentators have looked to major changes in industry structure as a solution to the problems of innovation and high attrition in pharma. *Imaging in CNS Drug Discovery and Development* is part of a fundamentally optimistic alternative future scenario: the idea that drug development can be made better by becoming smarter. Implicitly, the Editors make a strong case that, using a science-based strategy, the paradigm for drug development can be improved. All of us must hope that this promising path forward will have a substantial impact on getting better medicines to the right patients more quickly. This volume contributes substantially to accelerating this grand experiment.

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## Reference

Kola I, Landis J (2004) Can the pharmaceutical industry reduce attrition rates? *Nat Rev Drug Disc* 3:711–715

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