

Ernst Schering Research Foundation Workshop 37
Pharmacokinetic Challenges in Drug Discovery

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Pharmacokinetic Challenges in Drug Discovery

O. Pelkonen, A. Baumann, A. Reichel
Editors

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Preface

The development of new therapeutic agents is an increasingly costly undertaking in which attrition rates at all steps of development are high and the successful outcome uncertain. On the other hand, current advances in *in vitro* approaches and technologies have created a situation in which much knowledge critical for assessment and extrapolation could be, and in fact is being, produced early in the discovery and development process. However, although data are being produced, the transformation into useful knowledge on which to base decisions about the direction of discovery and development is not always self-evident.

It has become increasingly apparent that the pharmacokinetic properties of a drug, i.e. absorption, distribution, metabolism and excretion (ADME), are of the utmost importance for clinical success. Furthermore, interactions have become crucial for the assessment of drugs. Unwanted properties in pharmacokinetics, be they poor absorption, genetic polymorphism in a metabolic enzyme or a transporter, or a potent interaction, could result in failure during clinical trials or withdrawal after registration. A late failure is extremely costly for the industry. Consequently, the pharmacokinetic properties of a drug, especially keeping in mind intended clinical use and goals, should preferably be, many would say must be, elucidated relatively early. This means that elimination characteristics, half-life or clearance, principal metabolites (also whether there is formation of active metabolites), potential interactions and so on, should be screened and appropriate extrapolations and predictions made as early as possible during the drug discovery and development process. It is also important to bear in mind species differences and to put them through a preliminary screening because



The organisers and speakers of the workshop. From left to right, back: M.K. Bayliss, A. Baumann, C. Wienhold, G. Cruziani, B. Wallmark, J. Dixon, G.S.J. Mannens, H. van de Waterbeemd, G. Fricker, A. Reichel, T. Lavé; front: M. Lessl, B. Subramanyam, T.V. Olah, O. Pelkonen, J.H. Lin, A.K. Mandagere

animal toxicology is an integral part of a preclinical dossier and its assessment regarding anticipated human toxicology is an important part of the overall process.

Some other trends in drug discovery and development create additional challenges for ADME screening of drugs. Through combinatorial chemistry and the use of high-throughput (HT) drug target screening, larger numbers of molecules emerge for toxicity and kinetics screening. The ideal scenario is that through an efficient and reliable optimization and selection process, a few carefully evaluated molecules are launched into further development. Efficiency means HTS and reliability means adequate validation, but in reality these partially competing goals have to be reconciled in a productive way, possibly via extensive *in silico* approaches and modelling at the molecular, sub-cellular, cellular, tissue and organism level. All these areas of research

are in such a critical state of development that an integrated overview is needed to develop and apply them optimally in the process of drug discovery.

For these reasons, in early 2000, we decided at Schering AG to arrange a symposium on pharmacokinetic challenges in drug discovery in the Ernst Schering Research Foundation series. The organizers realized that there was a need to bring together experts from both industry and academia to present state-of-the-art information and views on specific aspects of the symposium's topic and to discuss wider implications for the future. The lectures presented during the symposium have now been collected together with the respective discussions as well as the final forum discussion in this volume, which the editors hope will provide useful reading for scientists in the pharmaceutical industry as well as in research institutions and universities interested in drug discovery and development.

Dr. Andreas Baumann, Schering AG, Berlin

Prof. Olavi Pelkonen, University of Oulu

Dr. Andreas Reichel, Schering AG, Berlin

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