pharmacological processes and to complement experimental data for non-accessible steps in the pharmacological causal chain. With the help of two examples, it is illustrated, what level of physiological detail, state-of-the-art models can represent, how predictive these models are and how mechanism-based approaches can be combined with empirical correlation-based concepts.

Keywords
Mechanism based · PK/PD · Systems biology · Systems pharmacology · Translational

1 Introduction

Along the whole life cycle of a pharmacotherapy – from discovery through clinical development to use of a marketed pharmaceutical product – a profound understanding of the efficacy and safety of the pharmaceutical concept is the basis of responsible decision making. This understanding provides the rationale for informed development decisions and the choice of the right treatment for patient groups and eventually individual patients.

Drug responses can only be understood if the whole causal chain from drug application to drug response or adverse event is considered. The most essential steps in this chain are systemic drug exposure, tissue exposure, target engagement, pharmacodynamic (PD) responses, and finally pharmacological response (Fig. 1).

While systemic drug exposure (i.e., systemic PK) and systemic PD and TD markers can be measured via blood sampling, responses in tissue are usually not experimentally accessible in humans and are a significant challenge in preclinical animal models. Consequently, most PK/PD assessments have to deal with a gap in the information available about the causal chain. A common fallback is the measurement and analysis of PD and TD markers secreted into systemic circulation instead or the measurement of markers in blood cells as surrogate tissue. Unfortunately, both settings may result in erroneous interpretations. Measurements in surrogate tissue are outside the causal chain and eventually arising correlations with pharmacological responses or side effects do not necessarily translate. Measurements of secreted markers are impaired by secretion from other tissues other than those of interest resulting in a similar risk of reduced translatability. In any case, links between PD or TD readouts and pharmacological responses are less reliable if they are indirect or if they rely on empirical correlations only.

The relevance of these theoretical considerations has been addressed by a number of publications on R&D productivity in pharmaceutical industry (Cohen 2008; Empfield and Leeson 2010; Cartwright et al. 2010; Gabrielsson et al. 2011; Paul et al. 2010). An impressive analysis was recently presented by Morgan and colleagues (2012). In an analysis of 44 drug development projects in phase II of clinical development at Pfizer, the authors could demonstrate that in projects in which certainty about target exposure and engagement and pharmacodynamic response was not given prior to phase II, the likelihood of failure was very high