USE OF ANIMAL MODELS FOR PROJECTION OF CLINICAL DRUG–DRUG INTERACTIONS FOR THERAPEUTIC PROTEINS

EUGENIA KRAYNOV and MARTIN E. DOWTY

6.1 INTRODUCTION

Animal models play an important role in assessing various aspects of a drug candidate during its discovery and clinical development, including anticipated efficacy, pharmacokinetics, and safety. At the same time, there are limitations with animal models in that they do not always reproduce human pathophysiology or disease drivers, pharmacokinetic pathways, or safety mechanisms relevant to humans. Hence the application of animal models must be underpinned by an understanding of the translatability of relevant mechanisms to humans. The most valuable insight into drug–drug interaction (DDI) potential is predicated on a thorough comprehension of the pharmacokinetic (PK) and pharmacodynamic (PD) properties of both interacting drugs and an understanding of their potential to be a DDI victim as well as a perpetrator.

The use of *in vitro* human systems to predict clinical DDIs of small molecules mediated through cytochrome P450 (CYP) metabolism has seen significant value.[1] However, DDI mediated through non-CYP mechanisms requires greater effort to understand *in vitro–in vivo* correlations (IVIVCs). Although the preclinical DDI assessment for therapeutic proteins can theoretically be addressed by using *in vitro* human systems alone, the relevance of the *in vitro* data in the context of a more complex *in vivo* system requires greater validation. *In vivo* animal models can potentially help bridge this gap. However, additional work is needed to address the potential for animal models to provide insight into DDI predictions of therapeutic proteins.

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