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Current Approaches to Predictive Toxicology

The package of preclinical toxicology studies conducted on any new pharmaceutical is largely intended to be “predictive”. A series of non-clinical studies is conducted, generally following a tiered approach (*in silico*, *in vitro* and *in vivo*). The studies are designed to identify potential hazards associated with a compound, characterize features such as dose-response, exposure-response, species selectivity, reversibility and availability of early markers, and allow informed risk assessment before administration to humans. However, despite progressive refinement of endpoints in the preclinical studies, it is still not uncommon for “unexpected” findings to occur in clinical studies, or for new hazards to be identified in animal studies late in development, after human studies have started. Some such findings can be worked around if a satisfactory therapeutic index can be derived or a species-specific mechanism can be argued. However, in many cases they can lead to termination of development. In the extreme, human risks may not show themselves till a compound is already on the market, and these can lead to withdrawal of a marketed product. Not only is late attrition of a compound expensive in terms of finance and resource, but also there are huge ethical issues around minimizing risk to human volunteers and patients. Clearly then any advances in methodology that help to give earlier predictions of what might happen in man or in longer term animal studies could contribute to improved efficiency and safety of drug development.

From GSK experience, the commonest organ systems causing safety-related drug attrition are liver and cardiovascular system. Indeed, drug related idiosyncratic liver toxicity is still one of the major causes of acute liver failure cases in man. In this presentation, I therefore focus predominantly on some of the recent advances in methods of evaluating hepatic and cardiac liabilities, and how they fit into tiered approaches and might allow more informed compound screening. For cardiovascular system I will discuss *in vitro* approaches including hERG assay and Lagendorf heart preparations and relationship to *in vivo* effects. For hepatic effects, I will also discuss advances in *in vitro* approaches (cell health assays) and also discuss increased utilization of “omics” technologies on early preclinical *in vivo* studies.

One overarching problem will continue to be early prediction of human dose/exposure at therapeutic doses, and translation of preclinical dose-response

information into the clinical context. Despite advances, therefore, prediction of human risk will remain a complex and necessarily uncertain business.