Mind the Gap

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**Summary** — The unmet needs of biomedical and clinical research are highlighted by reference to drug-induced liver injury (DILI), non-alcoholic fatty liver disease (NAFLD) and its severe form, non-alcoholic steatohepatitis (NASH). Examples in these areas highlight the major limitations of animal models with respect to predicting, examining and managing these clinically significant forms of liver injury. The way in which these knowledge gaps are being bridged by studies involving the use of human tissues and primary cells are described.

**Key words:** animal models, DILI, human primary cells, NAFLD, NASH.

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**Introduction**

A survey of pharmaceutical companies extracted data for 221 separate human toxicities, related to 150 compounds, and found that none of the human hepatotoxities were predictable from the known pharmacological actions of the drugs (1). Indeed, the concordance between animal toxicity and human toxicity (i.e. the ability of animal studies to predict toxicity later observed in humans) is disappointingly poor, and, at 55%, is only slightly better than flipping a coin. Therefore, animal toxicology studies do not appear to contribute effectively to the decision-making process, and arguably not performing any animal studies would offer a similar level of assurance.

Today, a drug that has a potential to cause a serious or life threatening side-effects in one in every 20,000 patients will not gain regulatory approval, or will be withdrawn. A simple power calculation illustrates that, in order to pick up this kind of risk of idiosyncratic hepatotoxicity, 30,000 patients will need to be recruited to an individual clinical trial. This is unrealistic, since the cost of licensing one new product is around $1 billion, and each successful candidate is generally derived from over 4000 candidates, each having been subjected to some level of preclinical drug evaluation. Thus, at the time a drug goes to market, it is likely that, whilst efficacy is virtually certain, safety is only provisional. Furthermore, high levels of drug attrition are significant, not least because of the increasing costs of drug development over the last decade and the likelihood that these costs will be passed on to the patient. This means that some treatments are now beyond the reach of those patients who would benefit from them.

**Liver Toxicity: Case Studies**

Chronic hepatitis B virus (HBV) infection is a prevalent liver condition in Asia. In the early 1990s, a new experimental drug, fialuridine (FIAU) — an antiviral nucleoside analogue (1-[2-deoxy-2-fluoro-β-D-arabinofuranosyl]-5-iodouracil) — was developed in the hope of treating this condition. At first sight, FIAU was successful at halting hepatitis B infection in Hep G2 cells by significantly reducing the levels of viral DNA (2). These effects were confirmed in animals. However, in 1993, patients with chronic HBV infection who had been treated with FIAU for 9.5 to 13 weeks developed signs of severe and, in some cases, fatal hepatotoxicity associated with lactic acidosis and commensurate multiple organ failures (3, 4). Histopathology indicated clear signs of microvesicular steatosis in the liver and pancreas. This is now known to be due to mitochondrial DNA damage, which disturbs electron transport in the mitochondria of patients. This outcome was not seen during preclinical animal studies in mice, rats, woodchucks, dogs and cynomolgus monkeys.

The lessons from FIAU demonstrate that the way in which drug candidates are selected to progress to clinical trials is deficient. Indeed, Figure 1 illustrates how drug-induced liver injury (DILI) continues to be a significant factor in the drug development process, and a common reason for drug withdrawal.

A potential solution to these problems is the earlier use of studies on biopsied human tissues and cells derived from them. In this respect, an interesting case study is that of ximelagatran (Exanta), an anti-thrombin therapy developed to treat patients with adverse reactions to warfarin, or those who are difficult to maintain on warfarin for