Predicting human liver toxicity using in vitro measures: Can past failures lead to future success?

Leslie Z. BENET

Department of Bioengineering and Therapeutic Sciences, Schools of Pharmacy and Medicine, University of California San Francisco

Drug-induced liver injury (DILI) remains a major safety concern; it occurs frequently; is idiosyncratic; cannot be adequately predicted; and a multitude of underlying mechanisms have been postulated. Many experimental approaches to predict human DILI have been proposed utilizing in vitro screening such as inhibition of mitochondrial function, hepatobiliary transporter inhibition, reactive metabolite formation, and cellular health, but achieving only minimal success. We have shown that none of the multitude of hypothesized and investigated predictive markers does any better than just avoiding extensively metabolized, poorly soluble compounds, so-called Biopharmaceutics Drug Disposition Classification (BDDCS) Class 2 drugs. Yet, this is not a useful restriction as more than 1/3 of approved drugs are BDDCS Class 2 compounds. Once a clinically relevant dose is known, studies have shown total administered dose (> 50 mg) to be correlated with higher predictability of DILI. It would be best to have a predictive DILI methodology early in drug development, long before the clinical dose is known. We hypothesize that many of the deficiencies of the high-throughput screens employed based on in vitro measures of hepatocyte toxicity can be overcome with long-enduring metabolically competent hepatocyte co-cultures. The long-enduring status has the potential to allow formation of active metabolites and/or accumulation of intracellular toxic substances in hepatocytes due to inhibition of relevant efflux transporters, as well as giving sufficient time for the hepatotoxicity to manifest.