Investigations into Idiosyncratic Drug-Induced Hepatotoxicity and Chronic Proliferation of Cancer Cells using a Label-free Method

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Hepatic toxicity has accounted for 15 of the 47 drugs withdrawn from the market in the last two decades. More specifically, Drug Induced Liver Injury (DILI) is the major cause of acute liver failure in the USA and Europe and is one of the main reasons for regulatory actions. DILI is classified as intrinsic (or dose-dependent) or as idiosyncratic. A prominent example of idiosyncrasy is acetaminophen (paracetamol), with a variable time of onset and not directly dependent on dose. We present a non-invasive DILI assay approach based on impedance measurements in monocyte-derived hepatocyte-like (MH) cells from MetaHeps®.

Although improvements have been made to cellular and animal models to predict intrinsic (dose-dependent) DILI, it is almost impossible to predict idiosyncratic DILI. MH cells have been developed as a tool to investigate long-term hepatotoxicity, metabolism and drug interactions. Furthermore, patient-derived MH cells could provide a tool for diagnosis or exclusion of idiosyncratic DILI, and provide the causative agent in polymedicated patients. MH cells were used on a 96-well screening system that monitors changes in impedance or cell monolayer resistance. Once the monolayer is exposed to a cytotoxic agent, the impedance changes and measurements of toxicity can be quantified long-term. Cells are monitored under physiological conditions for temperature, humidity and CO₂. We investigated the hepatotoxic effects of paracetamol on MH cells when exposed for 24 and 48 hours. In agreement with other standard toxicity assays, such as the lactate dehydrogenase release assay, low doses of paracetamol caused transient toxicity and ‘adaptation’ was observed. At higher doses, hepatotoxic effects of paracetamol could be reversed upon washout after 24 hours, but continued exposure caused increased hepatotoxicity.

In addition to hepatotoxicity, another validation of the principle is shown for chronic proliferation of cancer cells. Traditional cell proliferation assays involve labeling cells of interest with compounds that become reduced in the environment of metabolically active cells, or by incubating cells with radioactive labels. In this study, murine mammary carcinoma cells (H8N8 and H8N8 T3.2) were used and changes in impedance, and therefore confluency, were used as a measure of toxicity. Intrinsic (dose-dependent) effects of the standard clinical treatment regimen cyclophosphamide, doxorubicin and 5-fluouracil could be identified consistent with other methods of live cell analysis systems. Therefore, the utilized 96-well impedance system in combination with murine mammary carcinoma cells provides a novel tool for investigating therapy resistance of cancer cells in vitro.