Development of an in vitro Human Liver Model for Nonalcoholic Fatty Liver Disease

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There is a great need for a more effective in vitro disease model of nonalcoholic fatty liver disease (NAFLD) for use in high throughput drug screening. It was hypothesized that oleic acid and lipopolysaccharides (LPS) would successfully induce steatosis, or fat accumulation, as well as hepatocyte damage in an optimized in vitro liver model ultimately used to test potential drugs. To first maximize initial steatosis, HepG2 cells, a hepatocyte cell line, were plated (384 well plates) and treated with different initial conditions: oleic or palmitic acid conjugated to either albumin or minimum essential medium (MEM) with 10% fetal bovine serum (FBS), and a media control. Nine different combinations of stressors were added to each plate after a 24 hr incubation period, thus pushing the fattened models into a diseased state with more steatosis as well as hepatocyte damage. High-content imaging was done to quantify disease progression, and the most effective NAFLD model was found to be oleic acid as the initial condition and LPS with oleic acid as the stressors, thus supporting the hypothesis. 3D NAFLD models were then created using the optimized conditions and three types of cells important to NAFLD progression: HepG2 (hepatocytes), LX-2 (hepatic stellate cells), and THP-1 (monocytes). Four different drugs were tested on the model (ploglitazone, obeticholic acid, rosuvastatin, and pentoxifylline) with rosuvastatin appearing most effective at mitigating steatosis. This in vitro NAFLD model can be adjusted to show further disease progression into fibrosis, or liver scarring, and ultimately be used for high-throughput drug screening.

Awards Won: