A human liver microphysiology platform for studying physiology, drug safety, and disease

February 29 2016

The human body critically depends on the liver to metabolize toxins and synthesize biomolecules necessary for life. In addition to being a site for life threatening diseases, the liver is particularly sensitive to damage induced by xenobiotics and drugs. Lawrence Vernetti, a co-author, puts it this way: "The cost to the drug developer becomes enormous if unexpected liver damage emerges late in drug development. You either stop development of potentially life-saving drugs or face additional expensive human clinical trials."

Liver toxicity and disease is also influenced by liver resident cell types other than hepatocytes and by the microenvironment, such as regions where hepatocytes are known to exist in reduced oxygen conditions. While there are several in vitro human liver models, none of the models provides for long-term chronic exposure studies, while mimicking the physiological conditions created by immune, stellate and endothelial cells, and supporting the detailed detection of early indications of cellular dysfunction by a combination of direct imaging and biochemical readouts.

A study by D. Lansing Taylor and colleagues in the January 2016 Issue (241:1) of *Experimental Biology and Medicine* reports on the development and application of the first generation, Sequentially Layered, Self-Assembly Liver (SQL-SAL) model, a four cell, human organ model constructed in an optically transparent microfluidic chamber. A key feature of the SQL-SAL model is the inclusion of fluorescent protein biosensors which are used for real-time monitoring

of cellular functions such as apoptosis or generation of reactive oxygen species. To establish the predictivity of the model, a Microphysiology Systems (MPS) database that combines the experimental model data with drug-organ interaction data accessed from a variety of public and private databases has been created.

Performance of the SQL-SAL over 28 days was demonstrated by time and dose-dependent changes in liver functions and activation of key toxicity pathways in response to clinically relevant hepatotoxins. Furthermore, hepatotoxins produced immune-cell mediated hepatocellular damage or the deposition of collagen linked to fibrosis concordant with known clinical findings. As D. Lansing Taylor, Director of the University of Pittsburgh Drug Development Institute and the Principle Investigator for the SQL-SAL explains, "The results so far, demonstrate that the 3D, microfluidic, human liver model offers the drug research community a unique platform to test drugs at reasonable costs, early in the development cycle. With further development the SQL-SAL will be constructed using stem cell derived hepatocytes and other cell types from diseased and normal population to produce a powerful new tool to study disease progression and effectiveness of drugs."

Dr. Steven R. Goodman, Editor-in-Chief of *Experimental Biology and Medicine* said "Lans Taylor and his colleagues have developed the SQL-SAL human liver model which is a platform which has the potential to create a paradigmatic shift in the testing of the impact of drugs on normal and diseased liver function."

Provided by Society for Experimental Biology and Medicine