A rapid 3D in vitro screening-based discovery approach for selecting and prioritizing NASH drug candidates

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Methods & Technology

Using proprietary Maus® 3D plateau technology for 3D cell culture (Figure 1), we produced 3D liver tissue micromodels using human primary cell types relevant for NASH disease induction and progression: PlmK, HEC, and HSC (Figure 2). To recapitulate NASH pathogenesis in these micromodels we treated for 14 days with media containing high sugars, FFA, and LPS (Figure 2B). Lipid accumulation was assessed using Nile Red staining and high content imaging. To measure tissue glycemic levels, GlycoTriglyceride (GTG) (Profesa) was used. Human Magnetic Luminex Assay (RAD Systems) was used for cytokine/chemokine secretion measurements. Procollagen type-I and III secretion was measured using Procollagen type-I (ProC1) and Procollagen type-III (ProC3) ELISA (QinLab). TIMP-1 was measured by Sierra Pharmaceticals Inc. using Mass Spectroscopy. Collagen III deposition was visualized by Sirius Red staining and phenotypically quantified by high-resolution Fibroscan software (Phosphor). Gene expression analysis was determined by RNA-seq analysis. InSphero’s proprietary INsight® analysis platform was used for data visualization. Data analysis was done using an analytical pipeline developed internally using R. Differential expression analysis (DEA) and pathway analysis (PA) were executed as implemented in DESeq R library and GSEA R library, respectively.

Recapitulation of Pathophysiological Hallmarks of NASH Using Quantitative Endpoints

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