Title: Precision-Medicine Models for Predicting Immune-Mediated Drug Efficacy and Toxicity
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Extended Abstract:
Historically, therapeutics have been designed and clinically analyzed for the average patient in a one-size-fits-all approach. From the bench, an “average patient” is typically modeled using biochemical, cellular, and animal models representative of a pathophysiology of interest. While these models may consider specific disease-relevant genetics, environments, diets, and microbiomes they often fail to fully represent the diverse populations for those whom a therapeutic is indicated. In an effort to increase both patient representation and disease relevance of models used in drug discovery, we utilize enrolled patients from two disease landscapes (ulcerative colitis and idiosyncratic drug-induced liver injury) to curate biobanks of regenerative *ex-vivo* 3D models for predicting immune-mediated drug efficacy and toxicity.

Ulcerative colitis (UC) is a pharmacologically incurable disease that affects more than 1 million people in the United States. Despite the diverse etiologies of UC, patients are treated in a similar “step-up” manner in which drugs are triaged from least to most expensive with the more expensive and later-triaged drugs being immunomodulators. We have thus far established 4 human colonoid lines from UC patients that express proliferation marker Ki67 at the crypt, show tight barrier integrity through E-cadherin expression, and maintain luminal architecture. We have utilized human colonoids to develop high-content imaging methods in both 2D and 3D imaging formats for morphological profiling of epithelial inflammation that will be used in future studies to quantify patient differential response to pro-inflammatory factors and immunomodulating drugs.

Idiosyncratic drug-induced liver injury (DILI) is a rare-event hepatotoxicity in response to drug treatment that occurs independently of drug dose, duration, or route of administration. Believed to be, in part, mediated by aberrant innate and/or adaptive immunity, we set out to improve upon currently established DILI models by culturing novel human liver organoids (HLOs) from patients who have experienced DILI. HLOs consist of hepatocytes (60%), stellate cells (30%), and tissue resident macrophage Kupffer cells (<1%). When cultured on microfluidic systems (HLO-on-chip), we have previously demonstrated the further maturation of HLOs and more physiological relevance by means of higher albumin production and cytochrome P450 function. To determine the capability of our model to recapitulate idiosyncratic DILI, we performed differential expression and pathway enrichment analysis on scRNAseq data collected from HLOs-on-chip treated with hepatotoxicants to find functional cell activation upon Acetaminophen treatment. These preliminary results are guiding future studies on modeling hepatic stellate-mediated liver regeneration.