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Technology Offer

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A predictive 3D multi-scale model of bile flux in the liver lobe

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Background

Cholestatic liver diseases are a heterogeneous group of disorders resulting from genetic, metabolic and congenital defects, as well as DILI (drug-induced liver injury, a leading cause of attrition during drug development).

Current diagnostic techniques for DILI and cholestasis are based on the detection of serum markers and imaging methods such as computer tomography. However, these have a low resolution and only provide a limited understanding of the underlying disease etiology. Therapeutic options are limited to urodeoxycholic acid treatment of early cholestasis, and liver transplantation for late stages. This is primarily due to the poor understanding of the underlying disease etiologies.

Technology

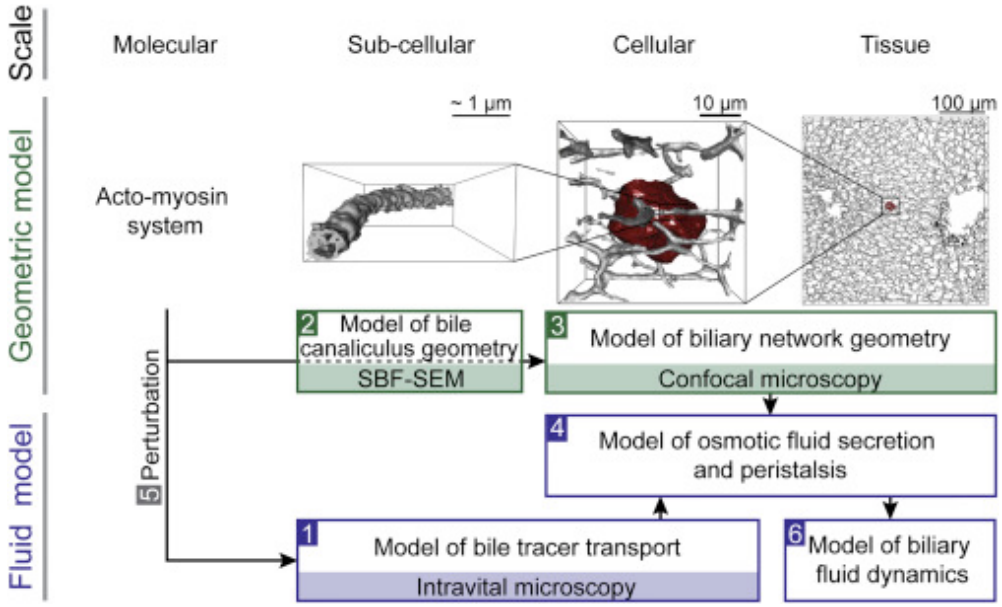
Our scientists have developed the first predictive 3D multi-scale model that simulates bile flow from the sub-cellular level to the tissue level. The model integrates structural and functional properties of the mouse liver lobule determined from high-resolution confocal, intravital and serial block-face scanning electron microscopy, as well as image analysis techniques.

An important new finding of this model is that osmotic pressure alone is insufficient to explain bile flow, and that bile canaliculi contractility is an additional key component. Moreover, using Acetaminophen as an example, our scientists demonstrated the precision of the model, that enabled detection of phenotypes that had previously only been detected for toxic doses of Acetaminophen in liver tissue.

It is also expected to be translatable to human liver; functional tests of bile acid clearance using fluorescent bile tracers, as previously tested in patients, may offer a strategy to calibrate this model to human biliary fluid dynamics.

The imaging and image analysis approaches used are based on a working pipeline that reaches medium throughput, making this model suitable for clinical and pharmacological studies.

Strategy of a Multi-Scale Model of Biliary Fluid Dynamics



The model was developed by integration of geometric (green) and fluid dynamic (blue) models from different scales. Bile canaliculi (BC) network organization: the actomyosin system (molecular scale) is a central component of the subapical cortex of hepatocytes (shown in red) that form BC (shown in gray) from their apical membrane (subcellular scale). These build continuous belts in between neighboring hepatocytes (cellular scale) and a ramified tubular network throughout the liver (tissue scale).
Modeling strategy: biliary transport properties were estimated from intravital microscopy of a bile tracer in a (sub)cellular model of bile transport (step 1). Next, geometric BC properties were quantified from 3D models of the single BC (step 2) and BC network (step 3) using serial block-face scanning electron (SBF-SEM) and confocal microscopy. Based on these experimental measurements, parameters of bile flow were determined in a model of osmotic fluid secretion and biliary peristalsis (step 4) using molecular perturbation of the actomyosin machinery (step 5). The model result was applied to simulate biliary fluid dynamics at the tissue level (step 6).

We are now looking for either a licensing partner, or a collaboration partner to further develop this project.

Publication

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Patent Information

The PCT application was filed on February 20, 2018.