Microfluidic Cell Culture Analog Devices
to Mimic Animal Exposures to Toxins and Drugs

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Abstract:
Our group has developed microfluidic in vitro devices that mimic the response of humans or animals to drugs, toxins, or nanoparticles. Each device, or cell culture analog (CCA), contains an array of pseudo tissues that are interconnected by microfluidic channels [1]. The recirculation of blood surrogate through the microchannels allows us to study tissue-tissue interactions, such as the breakdown of a parent compound in the liver and subsequent transport and reaction in the lung. We combine these in vitro device experiments with physiologically-based pharmacokinetic model simulations to predict toxin and drug dynamics in humans [2].

Summary of Results:
Using μCCAs to Test the Toxicity of Nanoparticles:
We have used micro cell culture analogs (μCCAs) to test the toxicity of nanoparticles. Because of their small size and surface to volume ratio, nanoparticles possess unique properties, which can be utilized in medical applications such as diagnostics and drug delivery [3]. Particles might, for example, carry drugs or alter the absorption of drugs and nutrients that are administered orally. However, little is known of the particle's fate within the body and tissues. We have recently developed a μCCA that combines cell culture models of the liver and the intestinal epithelium of the gastrointestinal tract in a physiologically realistic way (Figure 1) [4]. This model can be used to simulate the oral uptake of nanoparticles and other drugs.

We have used a μCCA that contained a model of the human intestinal epithelium and a model of the liver to simulate the oral uptake of 50 nm carboxylated polystyrene particles. To be able to compare the in vitro results with in vivo results, we also conducted a particle ingestion study with birds. In vitro, intestinal epithelial cells (Caco-2/HT-29/MTX) covered with mucus presents an effective barrier to 90.47% ± 2.85% of the particles over a period of 24 hours. The cell layer allows passage to single particles only. In addition, passing through the intestinal cell layer decreases the surface charge of the particles. At high doses — estimated in terms of possible daily human consumption — both Caco-2/HT-29/MTX and HepG2/C3A cell layers release aspartate transaminase (AST), indicating cellular stress and death. In vivo tests with birds suggest that the percentage of particles that transfer into the systemic circulation at the given concentration is too low to cause liver damage or inflammation, pointing to additional upstream or downstream mechanisms that were not present in the in vitro simulation.
Development of Microfluidic GI Tract Modules:

To obtain more detailed information from simulations with first pass metabolism μCCAs, we have developed a microfabricated gastrointestinal tract model that incorporates an on-chip membrane and integrated electrodes for transepithelial resistance measurements. The transepithelial resistance (TER) of the gastrointestinal epithelium is a measure for the intactness of its barrier function. To simulate the barrier function, gastrointestinal cells are cultured on membranes that allow access to either side (apical and basolateral) of the cell layer. Using GI-tract epithelial cells (Caco-2) and mucous-producing cells (HT-29), co-cultured and grown to confluence on commercially available transwell membranes, we were able to simulate the GI-tract barrier and measure the transepithelial resistance (TER) [4,6]. From experiments with these static cell culture models of the intestinal epithelium, we know that nanoparticles alter the TER. To be able to measure the TER on chip, we have developed microfabricated electrodes and membranes that allow us to include the gastrointestinal tract model on a microfluidic chip that contains the systemic circulation.

In conjunction with the fabrication of flat, porous membranes, we have also developed 3D membranes that simulate the macrovilli characteristic of the GI tract (Figures 3 and 4). These structures increase the potential surface area available for metabolism and provide a more physiological microenvironment, which recent work using collagen-based villi has shown to grow cell monolayers that closely mimic in vivo tissue morphology [7]. Synthetic villi up to 100 µm tall and between 25 and 100 µm wide have been achieved to date. The microfabricated 3D membranes have been shown to sustain long-term growth of the Caco-2 gastrointestinal cell line (Figure 4) and may be easily implemented in an on-chip GI tract module.

References: