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:
Microfluidic GI Tract Modules with Three-Dimensionally Shaped Membranes. To simulate the oral uptake of drugs and substances with μCCAs, we have developed a microfabricated gastrointestinal tract model that consists of an on-chip membrane and apical and basolateral fluidic chambers (Figure 2). The membrane can be shaped so that intestinal villi are recreated when epithelial cells (Caco-2) and mucous-producing cells (HT-29) are co-cultured to confluence on the membrane [4]. We showed that key aspects of the intestinal epithelium such as tight junctions developed on the villi shaped membranes [4].

Development of a Twelve-Organ Chamber μCCA. Micro cell culture analog (μCCA) devices are physical representations of physiologically-based pharmacokinetic models (PBPK). To better represent the PBPK model, we expanded our device design to include twelve tissue compartments, representing ten organs (Figure 3). The twelve chambers were scaled from an average male organ sizes by a factor of 105. Since cells will be seeded with matrigel to create a 3D microenvironment, each chamber was designed with a height of 150 µm for matrigel-cell at the bottom and medium flow above. The estimated in vivo volumetric flow...
rate at each organ was scaled down so that physiological residence times were maintained. In addition, the flow pattern was considered as a hydraulic circuit, treating the flow rate as the current, the drag as the resistor, and the pressure drop as the applied voltage. For each channel, the hydraulic diameter was calculated and the Reynolds number was obtained (typically smaller than 1). The pressure drop across each stream was adjusted and maintained approximately to be 500 Pascal based on the hydraulic diameter and flow rate. Finally, the pressure drop across the distributor and the exit triangle is calculated using the Ergun equation, with the assumptions for the pillars in the distributor as baffles. The shear stress for each channel was less than 1.8 dyn/cm².

**Measuring Contractile Forces Generated by Muscle Cells within µCCAs.**

Microcantilevers are widely used devices allowing for the measurement of bending moment due to physical stress applied on the beam structure. The application of such sensors has previously been mainly in gas and chemical vapor sensing but more recently, they were also used in biochemical detection as a mass sensor to determine the concentration of biological agents.

Our group is developing this technology to determine contractile forces generated by muscle cells that are cultivated on a cantilever arrays. The stress generated by myotube contractions can be followed in a detection chamber by a photodetector, allowing the measurement of the deflection of the bridge. Cantilevers are a good alternative to study muscle cell dysfunction and allow the extraction of several physiological parameters of interest like contractile force, refractory period and tetanic contraction [3].

The cantilever array was fabricated on silicon-on-insulator (SOI) wafers. Dimension and geometry were defined by contact photolithography and total backside etching was achieved to release the cantilever using DRIE etching. Cantilever characteristics were determined using a scanning electron microscope to confirm the thickness, length and width of the bridges (Figure 4).

**References:**

