Body-on-a-Chip Systems for Drug Development

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Primary CNF Tools Used: VersaLaser Engraver/Cutter tool, ABM contact aligner, SU-8 hot plates, SUEX/ADEX laminator, PDMS casting station, hot press

Abstract:

Organ-on-a-chips are tissue-engineered microsystems that mimic human organs, modeling both structure and function [1]. Human cell-based multi-organ-on-a-chip systems, or body-on-a-chips (BOC), could be a paradigm-shifting technology for drug development [2]. Such microscale biomimetics of human organs with organ-organ interactions hold the promise to simulate human physiology and disease progression, and thus offer more accurate predictions of human responses to therapeutics and provide mechanistic insights into human diseases, while significantly reduce drug development cost and animal usage. Currently, we are developing several BOC systems, which are fabricated with tools at CNF and will be used to study chemotherapeutic toxicity, model cancer cell metastasis, and simulate immune responses.

Summary of Research:

Tumor-Liver-Bone Marrow Chip. A three-organ microphysiological system has been created to study chemotherapeutic toxicity with relevant drug metabolism and hematological side effects. The device contains three chambers for seeding HCT-116 colon tumor spheroids, $HepG_2$/C3A hepatocytes, and HL-60 promyeloblasts encapsulated within 3D hydrogels. Microfluidic channels were etched into a layer of poly (methyl methacrylate) (PMMA) and designed to mimic human blood flow rates [3-5]. The silicone cell culture layer and PMMA channel layer were sandwiched between silicone gaskets and outer PMMA housing pieces. All layers were fabricated using the VersaLaser CO_2 laser cutter at CNF. Utilizing gravity-driven flow on a customized programmable rocker, a common medium is recirculated between the two reservoirs.

Colon-Liver Chip. We have developed a colon-liver dual-organ-on-a-chip system to model colorectal cancer (CRC) liver metastasis. The microphysiological system is based on a pumpless platform [6,7]. Two organ chambers representing colon and liver are interconnected and perfused with gravity-driven flow at physiological perfusion rates. The device is fabricated mainly in PMMA with silicone (gaskets) for sealing. PMMA and silicone sheets are patterned with laser ablation using the VersaLaser CO_2 laser cutter at CNF. The flow dynamics are characterized computationally and experimentally. Flow rates were measured to be within 15% of the designed values. The prototype devices tested with colon and liver cells maintained greater than 85% cell viability.

Using this colon-liver platform, we will incorporate organotypic CRC model and 3D liver constructs and investigate the metabolic stress due to CRC liver metastasis. We will investigate the cellular interaction, differentiation, migration and invasion of primary tumor and metastatic fibroblast tumor microenvironment to evaluate contributing factors in CRC metastasis.

A 5-Compartment Microphysiological System for Drug Screening. We developed a 5-organ BOC system to emulate *in vivo* drug absorption, distribution, metabolism and toxicity, as well as immune responses. The five organ chambers represent bone marrow, inflamed spleen, GI tract, liver and kidney (Figure 1). The 5-Organ Chip consists of five layers: a top cover layer and a bottom

channel layer made of PMMA, a cell chamber layer and a flow dispersion layer made of silicone, and a porous polycarbonate membrane (Figure 1).

The top cover layer and the two silicone layers were patterned using the VersaLaser CO_2 laser cutter at CNF. The bottom PMMA channel layer was fabricated using photolithography and hot embossing. The channel layer pattern was first transferred from a photomask to SUEX epoxy thick dry film using a laminator and standard photolithography technique. A polydimethylsiloxane (PDMS) replica was then created from the SUEX master and was silanized under vacuum overnight. A heat resistant epoxy mold for hot embossing was then created from the silanized PDMS mold using a high-temperature epoxy casting system. The PMMA channel layer was fabricated using a hot press at CNF as shown in Figure 2. The molded PMMA plate was then cut with the VersaLaser to form the channel layer. The assembled device is transparent and allows for real time optical interrogation.

This five-chamber device is being used to study preclinical anti-leishmaniesis drug toxicity and response.

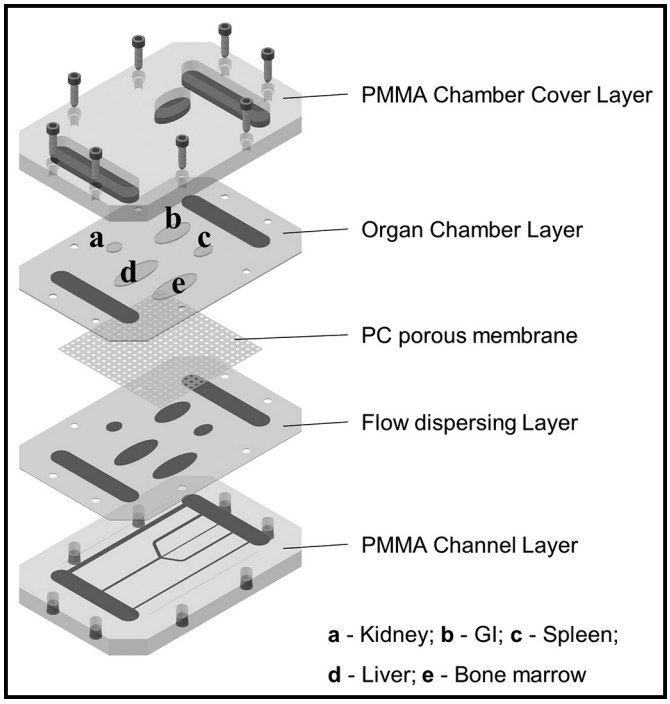

Figure 1: Design of the 5-compartment microphysiological system. Schematic exploded view of the microfluidic platform.

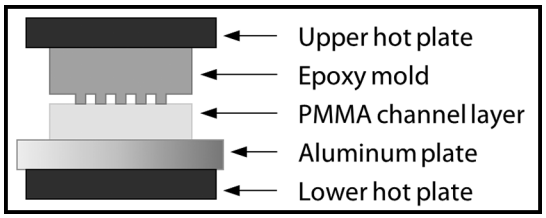

Figure 2: PMMA sheet and epoxy mold assembly for PMMA channel layer fabrication using hot embossing.

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