Body-on-a-Chip Systems for Drug Development and *in vitro* Interactions

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Primary CNF Tools Used: VersaLaser Engraver/Cutter tool, Samco UV and ozone stripper, hot press, Objet30 Pro 3D Printer, ABM contact aligner, SU-8 hot plates, SUEX/ADEX laminator, PDMS casting station, DRIE system

Abstract:

Organ-on-a-chips are microsystems that through tissue-engineering can model human organs, representing both structure and function [1]. Human cell-based multi-organ on-a-chip systems can be used for drug development [2], studying metastasis and chemotherapy. The microscale biomimetics of human organs with organ-organ interactions can be used to model human physiology and disease progression, and thus offer more accurate predictions of human responses to therapeutics and provide mechanistic insights into human diseases. Also, these models can significantly reduce drug development cost and animal usage [3-5]. Currently, we are developing several microfluidic systems, which are fabricated with tools at Cornell NanoScale Facility (CNF) and will be used to study chemotherapeutic toxicity, model cancer cell metastasis, and simulate immune responses.

Summary of Research:

Single-Pass Chip. We have designed and modified a gravity-driven microfluidic model for studying the extravasation of circulating tumor cells (CTC) through endothelium (either primary human liver sinusoidal endothelial cells (LSEC) or human umbilical cord endothelial cells (HUVEC)) into a chamber with HepG2 C3A (liver cells). The frame of this device is made from PMMA layers patterned using a CO_2 laser (VersaLaser VLS3.50), and bonded together using a hot press after a 15 min UV/Ozone (Samco UV& Ozone stripper) exposure at CNF. The propeller stirring lid of the device is fabricated using the Objet30 Pro 3D Printer from the CNF. Clear silicone sheets are also patterned with laser ablation using the VeraLaser CO_2 laser cutter. The stirring is driven by a small stir bar on a magnetic stir plate. This device allows for a continuous operation up to 24 hours while maintaining a constant concentration of CTC and evaluate of the capability of CTC (large and small clusters) from various sources to enter into the liver chamber. [Fig.1]

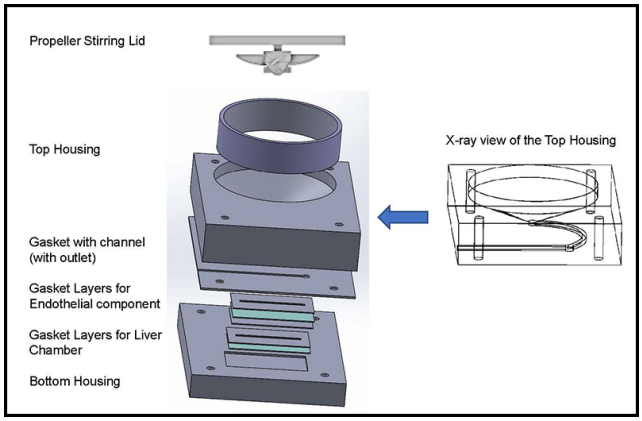

Figure 1: Design of the single pass colorectal/liver metastatic device. Schematic of the single pass device.

Unidirectional Chip Devices. We have two unidirectional chip devices (two-chamber and three-chamber chips) for studying the metastasis and drug effects. Chambers are interconnected and perfused with gravity-driven flow at physiological perfusion rates [3-5]. The flow dynamics are characterized computationally and experimentally. Our pumpless gravity-driven flow is created by using a customized programmable rocker where a common media is recirculated between the two reservoirs. Flow rates were measured to be within 15% of the designed values [6,7]. The prototype devices are initially tested for viability where the goal is to maintain a viability greater than 85%.

Two-Chamber Unidirectional Chip. We have developed and modified our original colon-liver two-chamber unidirectional chip system to model CTC liver metastasis. This two organ system interconnects colon and liver

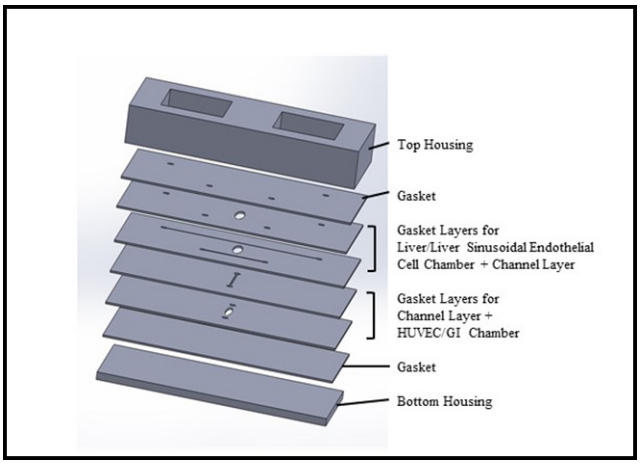

Figure 2: Design of the two-chamber unidirectional chip device. Schematic of the two-chamber unidirectional chip.

chambers. The frame of the modified device is milled out of a polycarbonate (PC) sheet at the Cornell University Olin Hall Machine Shop. Clear silicone sheets are patterned with laser ablation using the VersaLaser CO_2 laser cutter to create the chambers, channels and used for sealing the device. For this device, microfluidic channels were etched into silicone gaskets and designed to mimic human blood flow rates [3-5]. Using this colon-liver platform, we are able to incorporate organotypic CTC model into the colon chamber and create a 3D liver construct by incorporating liver cells in a hydrogel into the liver chamber. Here, we are investigating the ability of CTC from various sources to metastasize to the liver chamber. We will investigate the cellular interaction, differentiation, migration and invasion of primary tumors to evaluate contributing factors in CTC metastasis. [Figure 2]

Three-Chamber Unidirectional Chip. A three-organ microphysiological system (tumor-liver-bone marrow chip) [8] that was initially create to study chemotherapeutic toxicity with relevant drug metabolism and hematological side effects is now being used to study metastasis. We modified this device by changing the biological components of the chambers. First, normal colon cells with colon cancer organoids are plated in the colon chamber, HepG2/C3A hepatocytes (in hydrogel) are plated in the liver chamber and then the third chamber (no cells) is used as a control. For this device, 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. Using this three-chamber platform, we incorporate organotypic CTC model and 3D liver constructs to investigate the metabolic stress due to CRC liver metastasis. We will investigate contributing factors in CTC metastasis by evaluating cellular interaction, differentiation, migration, invasion of primary tumor, metastatic fibroblast tumor microenvironment, and CTC selectivity. [Figure 3]

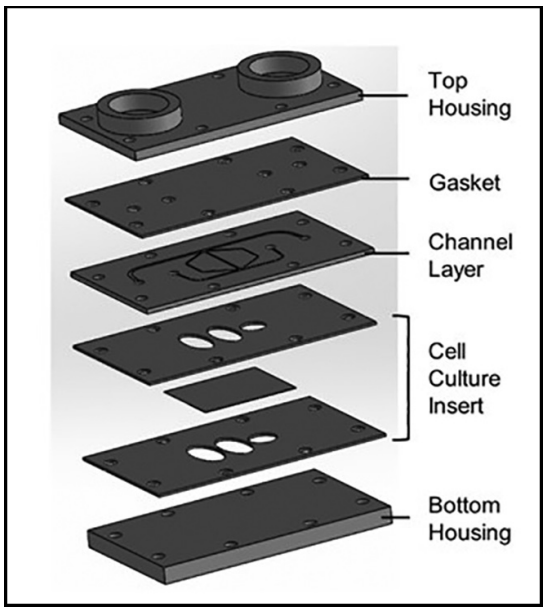

Figure 3: Design of the three-chamber unidirectional chip device. Schematic of the three-chamber unidirectional chip.

Micromechanical Cantilevers for Cell Motion Transduction. New processes were explored for fabricating silicon micromechanical cantilevers for transduction of cell motion. Process development, including addressing issues of uniformity of devices, continues.

References:

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