Body-on-a-Chip Systems for Studying Liver Metastasis

CNF Project Number: 731-98

Principal Investigator(s): Michael L. Shuler, Harold G. Craighead

User(s): Ying Wang, Paula Miller, Vivek Sitaram Jadhav

Affiliation(s): Nancy E. and Peter C. Meinig School of Biomedical Engineering, Robert Frederick Smith School of Chemical and Biomolecular Engineering; Cornell University

Primary Source(s) of Research Funding: National Center for Advancing Translational Sciences, National Science Foundation, National Institutes of Health

Contact: mls50@cornell.edu, hgc1@cornell.edu, ying.wang@cornell.edu, pgm6@cornell.edu, vj76@cornell.edu

Primary CNF Tools Used: VersaLaser engraver/cutter tool, ABM contact aligner, SU-8 hot plates, SUEX/ADEX laminator, PDMS casting station, hot press, ObJet30 Pro 3D printer

Abstract:

Our organ-on-a-chip devices are physiological tissue-engineered microsystems that mimic human organs, structurally and functionally [1]. Human cell-based multi-organ on-a-chip systems, could be used for drug development [2], simulate human physiology and disease progression. The organ-organ interactions 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 microphysiological 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:

Here, we describe two unidirectional metastatic devices to study colon cancer metastasis and the human liver sinusoidal vasculature for colon cancer extravasation. The both devices have unidirectional flow; colon-liver chip is "pumpless" using a rocker platform for fluid (blood surrogate) unidirectional recirculation and the liver sinusoidal vascular chip is a gravity-driven single pass microfluidic platform.

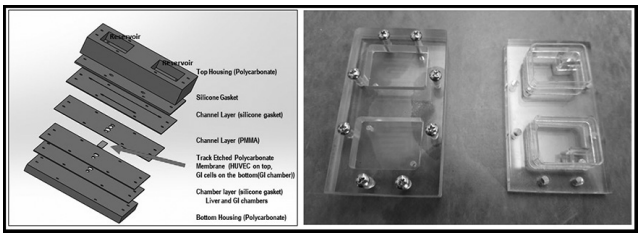

Figure 1: Design of the two-chamber unidirectional device for liver metastasis. Schematic view and actual photographs of the assembled frames.

Colon-Liver Chip:

We have modified our original dual-organ-on-a-chip system to model colorectal cancer (CRC) liver metastasis. This microphysiological system is based on a pumpless platform [3,4]. Two organ chambers representing colon and liver are interconnected and perfused with gravity-driven flow at physiological perfusion rates [5]. The frame was milled out of a polycarbonate sheet with silicone gaskets to help seal the device. Microfluidic channels, chambers and medium reservoirs were patterned with laser ablation into a poly(methyl methacrylate) (PMMA) sheet and/or silicone sheets using the VersaLaser VLS3.60 Cutting and Engraving CO_2 Laser (Universal Laser Systems, Scottsdale, Arizona) at CNF. The flow dynamics were 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 to 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 [Fig.1].

Liver Sinusoidal Vascular Chip:

We have designed and constructed a gravity-driven microfluidic platform for modeling the human liver sinusoidal microenvironment and investigating the extravasation of liver metastatic colorectal cancer (CRC) cells. The frame was fabricated in poly(methyl methacrylate) (PMMA). PMMA layers of desired thickness were patterned using a CO_2 laser (VersaLaser VLS3.50), and were bond together using a hot press at CNF after a 15 min UV/Ozone (Samco UV and Ozone stripper) exposure. Also, flow-through microfluidic channels and chambers were patterned with laser ablation into silicone sheets using the VersaLaser. A propeller stirring device was designed in Inventor to overcome the issue of settling, attachment and aggregation of CRC cells in the feed reservoirs. The propeller stirring device was fabricated using the ObJet30 Pro 3D printer at CNF.

The stirring device was driven by a small stir bar on a magnetic stirrer. We have tested different propeller designs, the positioning in the reservoir, and the stirring speed, to optimize stirring scheme that produced minimal cell aggregation while preserving maximal cell viability. We are currently focusing on characterizing the phenotype of liver sinusoidal endothelial cells in our microfluidic model and comparing CRC cell interactions with human liver sinusoidal endothelial cells versus human umbilical vascular endothelial cells [Figure 2].

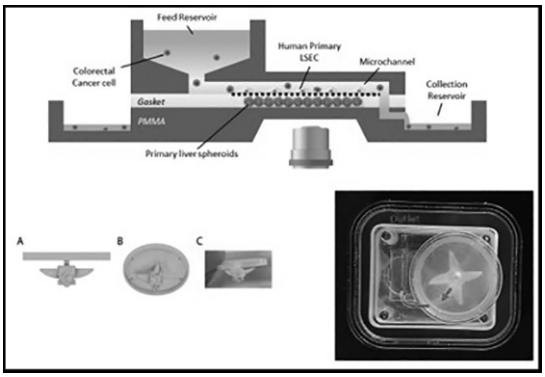

Figure 2: Design of the human liver sinusoidal vasculature for colon cancer extravasation. Schematic views of the device and the propeller stirring device with actual photographs.

References:

[1] Wang YI, Carmona C, Hickman JJ, Shuler ML. Multiorgan Microphysiological Systems for Drug Development: Strategies, Advances, and Challenges. Adv Healthc Mater;7:1701000. doi.org/10.1002/adhm.201701000.2 (2018).

[2] Sung JH, Wang YI, Narasimhan Sriram N, Jackson M, Long C, Hickman JJ, et al.Recent Advances in Body-on-a-Chip Systems. Anal Chem;91:330-51. doi.org/10.1021/acs.analchem.8b05293.3 (2019).

[3] Price PS, Conolly RB, Chaisson CF, Gross E a, Young JS, Mathis ET, Tedder DR. Modeling interindividual variation in physiological factors used in PBPK models of humans. Crit Rev Toxicol.;33(5):469-503. doi:10.1080/713608360 (2003).

[4] Brown RP, Delp MD, Lindstedt SL, Rhomberg LR, Beliles RP. Physiological Parameter Values for Physiologically Based Pharmacokinetic Models. Toxicol Ind Health.;13(4):407-484. doi:10.1177/074823379701300401 (1997).

[5] Forrester DW, Spence VA, Walker WF. The measurement of colonic mucosal.submucosal blood flow in man. J Physiol.;299(1):1-11. doi:10.1113/jphysiol.1980.sp013106 (1980).