Abstract:
We have developed several in vitro systems to predict human and animal responses to chemical exposures. These cell culture analogs (CCAs) are fabricated in silicon or polystyrene, and contain cell culture chambers connected with microfluidic channels. The cell chambers are designed to mimic animal tissues, with chamber size and culture medium flow rate scaled to match corresponding organ size and blood flow. Recirculation of culture medium allows the accumulation and exchange of metabolites between cell types, which is not found in traditional in vitro experiments. These systems provide an experimental platform for evaluating physiologically-based pharmacokinetic (PBPK) models, and potentially increase the understanding of drug and chemical dynamics in the body.

Proof-of-concept experiments using a liver-lung-fat-other tissues CCA have been performed to study the impact of fat tissue bioaccumulation on naphthalene toxicity. Results indicated that inclusion of fat cells in the device significantly reduced toxicity to the lung cells due to sequestering of toxic compounds in the fat cells. We are also modifying this CCA design to facilitate three-dimensional cell cultures and fat mimic materials. The new CCA devices are built in silicon and polystyrene using a developed SU-8 hot embossing technique.

A CCA device containing liver-marrow-“normal” tumor-“resistant” tumor-slowly perfused-other tissues was constructed for studying chemotherapy treatment strategies on multidrug resistant tumor cells. This device has been validated with doxorubicin exposure for both 24 hour-acute toxicity and long term growth reduction to the different cell types. A similar silicon cell culture analog device containing liver-marrow-normal colon-cancerous colon has been fabricated for testing drugs on colon cancer.

A thin silicon nitride membrane with 400 nm pores was fabricated and cultured with endothelial cells/astrocytes to mimic the blood-brain barrier. Additionally, a new CCA of the small intestinal epithelium has been developed by combining micromachining and soft lithography. This intestine device will be characterized by studying the absorption of iron and several pharmaceuticals. Another device to study how potential environmental chemicals with estrogenicities interact with the human endocrine system has been fabricated. We have also developed an in situ fluorescence detection system for use on microdevices to measure real-time fluorescent probes.

Summary:
We have fabricated several different cell culture analog devices for use in risk assessment studies of toxins, and to perform adsorption, distribution, metabolism, elimination and toxicity studies for pharmaceutical evaluation. Proof-of-concept experiments with a lung-liver-fat-other tissues CCA device have clarified the mechanism of lung toxicity from naphthalene exposure, and have shown the importance of fat tissue in mimicking compound distribution in these devices. New CCA devices have been developed to study multi-drug resistant cancer chemotherapy, colon cancer, and transport in the gut.

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

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- Microfabricated cell culture analog devices.
- Chemical and pharmaceutical studies in vitro.
- Metabolite recirculation to target organs.
- Barrier (gut, blood-brain-barrier) transport.

Figure 1, top right: Photograph of a CCA chip for multidrug resistant chemotherapy studies, sized 6.8 cm².

Figure 2, below left: SEM of an ultrathin (10 micron) silicon nitride membrane with astrocytes cultured on bottom, visible penetration of foot processes through pores.

Figure 3, below right: Gluthathione (GSH) reduction (toxicity) in lung and liver cells in CCA w/w out fat when exposed to 50 microgram/mL naphthaquinone.