Body in a Cube: A Multi-Organ Microphysiological System with Near-Physiological Amounts of Blood Surrogate

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Animal experiments are essential when ascertaining a new drug's safety before trying it in clinical trials with humans patients. However, animals do not fully replicate human physiology and metabolism, causing a large number of drugs to pass tests with animals, but fail in humans.[1] Multi-organ microphysiological devices (MPS) can mimic the human metabolism and provide insightful information about a new drug candidate's toxicity profile.[2] To fully realize the potential of role of MPS in the drug development process however, such systems must replicate key aspects of the human metabolism such as functional organ volume ratios, fluid volume, and fluid residence times.

We have, developed an MPS with four physiologically scaled organ chambers (GI tract, liver, kidney, and bone marrow, see Fig. 1) and, unlike any other MPS published to date, with near-physiological amounts of blood surrogate. The organ chambers and blood volume were scaled by a factor of 73,000, using average functional organ volumes of a 73 kg male person, and bringing the blood surrogate volume to 80 µL. The system was operated by recirculating for 80 µL of cell culture medium among the four organ chambers for 72 h. Physiological fluid flow rates were achieved by tailoring the hydraulic resistances of the microfluidic channels feeding into each organ chamber. Drug exposure with two drugs, acetaminophen and troglitazone, caused liver damage in the system within 24 h, evident by a reduction in urea synthesis in the liver tissue as well as by the release of aspartate aminotransferase (AST), a marker for compromised cell membranes in the liver and GI tract (Fig. 2 and 3). The system is suitable for testing acute primary and secondary toxicities of small molecule drugs.

1) Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review, D.B. Fogel, Contemp Clin Trials Commun. 2018 Sep; 11: 156–164.
2) Developing Microphysiological Systems for Use as Regulatory Tools – Challenges and Opportunities, M.E. Andersen et al., ALTEX. 2014; 31(3): 364–367.

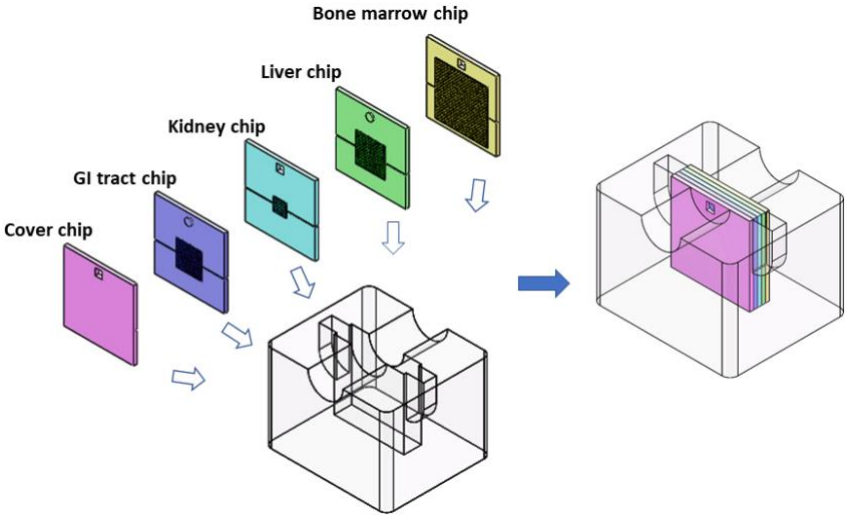

Figure 1: Body Cube: The MPS consists of four organ chips, each with its own microfluidic channels designed to create physiological flow rates when operated via gravity. The chips are combined with each using a cube-shaped holder. Once the chips are aligned next to each other, they are connected via the common reservoirs in the holder, fluid recirculation among all organ chambers is possible.

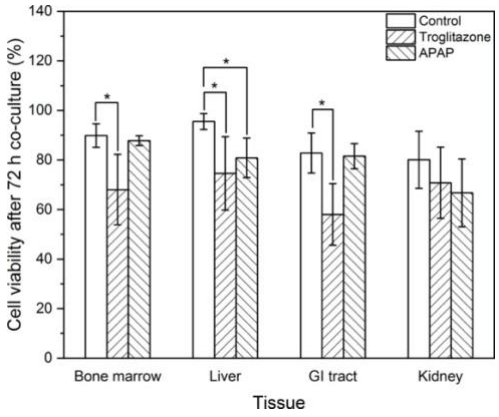

Figure 2: Acute Toxicity Test: Troglitazone and Acetaminophen (APAP) cause the expected decrease in liver cell viability after 72 h of exposure to the drugs.

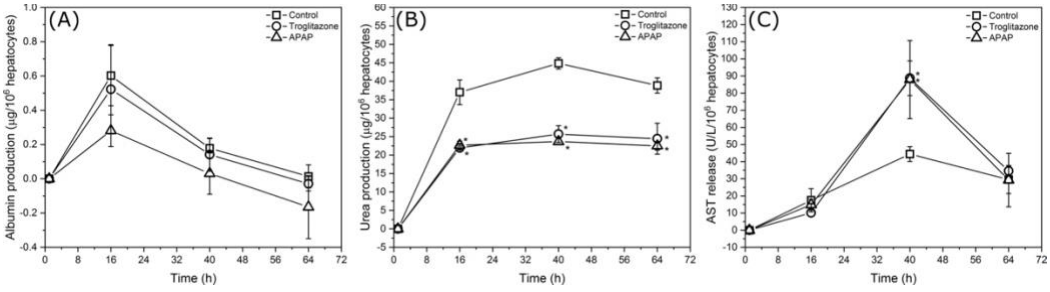

Figure 3: Albumin, urea and AST production: Both drugs cause a decrease in urea production in liver cells. Both drugs also cause an increase of the soluble liver and GI tract cell death marker AST, when measured at the 24 h timepoint.