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Microfluidic Devices for Single-Cell and Organ-Level Studies

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Abstract

The process of developing and testing drug candidates is a slow and costly endeavor. The mainstream technologies such as bulk 2D cell culture techniques have been proven insufficient to capture the pharmacokinetics and pharmacodynamics of drug compounds in humans. Animal models, despite their central role in drug development studies, fall short to predict the human-specific mechanisms of drug clearance and toxicity. In this thesis project, I have designed and evaluated application-specific single-cell and organ-on-a-chip microfluidic platforms for drug and chemical compound testing applications. The fundamental advantage offered by single-cell analysis, is the possibility of capturing the behavior of individual cells which, reveals valuable information on the heterogeneity in a cell population. Simultaneously, creating human-based physiologically relevant organ-mimetic microenvironments for drug metabolism and toxicity is becoming increasingly critical. My thesis work, by taking advantage of experimental approaches, qualitatively and quantitatively validates solutions to address the aforementioned challenges in producing relevant data on drug metabolism and toxicity.

A single-cell analysis platform built with the combination of a 4-inlet microfluidic device, a single-beam optical tweezers setup and an epi-fluorescence microscopy stage was used to study the co-administration of the trivalent form of arsenic, As (III), with a Hog1 inhibitor in yeast. In this work we showed that uptake of sodium arsenite could be regulated in single cells. In the next step, I developed a microfluidic device to facilitate high throughput single-cell studies. The device offered the possibility of studying hundreds of cells in each experiment run. Additionally, diffusion-based flow profiles could be administered in this device thanks to the miniature geometry of the microchannels. To promote the formation of 3D tissue-like structures in a physiologically relevant environment, I tailored a microfluidic device to mimic the geometrical hexagonal structure of a classic liver lobule. In this work I showed that human liver cells could be maintained functional in the microfluidic devices for short-term as well as long-term culture periods.

Keywords: Microfluidics, laminar flow, optical tweezers, fluorescence microscopy, single-cell analysis, heterogeneity, *Saccharomyces cerevisiae*, yeast cells, organ-on-a-chip, liver, liver-on-a-chip, HepG2, hiPSC, hiPSC-derived hepatocytes, drug metabolism, drug toxicity