# Spatial, Single Cell Isolation from Intestinal Crypts

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February 20th, 2015. 11:45 AM, 312 Ell Hall

Cells, tissues, and organs represent a hierarchy of structures which constitute the human body and span a length scale from microns to meters. Cells form the primary building block for tissues and therefore define the form and function of the human body. Often times, it is the precise spatiotemporal arrangement of cells that determines this function. Furthermore, organs undergoing self-renewal, such as the skin and intestinal epithelium, feature a tightly regulated, spatiotemporal arrangement of *multiple* cell types. This gives rise to organ specific, multicellular, subunits featuring a hierarchical cell arrangement. A classic example of such a subunit is the intestinal crypt, which contains differentiated and stem cell types arranged symmetrically around a vertical axis. A key interest in cell and developmental biology is to delineate how the cellular arrangement within tissues like the intestinal crypt gives rise to the form and function of organs. Perhaps, an even more important goal is to learn how cells communicate to maintain and regulate their hierarchy during healthy states but become disorganized in diseased states. The challenge in doing so is because facile methods for isolating viable, single cells from multicellular structures while preserving the cell's spatial location do not exist.

Currently, the predominant single cell isolation techniques are fluorescence activated sorting, micro-pipetting, optical tweezers, serial dilution, and laser micro-dissection[1]. The latter five of the aforementioned techniques can be characterized by low throughput and typically do not lend well to automation. Furthermore, FACS, micro-pipetting, optical tweezers, and serial dilution methods require cells to be in suspension, thereby displacing cells from their original location in intact tissue. Laser micro-dissection utilizes a tightly focused laser to remove target cells and even organelles from intact tissue. Despite being able to remove cells selectively from intact tissue, laser micro-dissection suffers from the preceding drawbacks related to throughput and automation. Additionally, laser micro-dissection requires fixed tissues and lengthy drying procedures thereby introducing a bias into molecular analyses.

A powerful approach for single cell manipulation is microfluidics. Micro fabricated from soft, biocompatible polymers, microfluidics have significantly augmented cell biology. Microfluidic systems have been used for single cell lysis, cellular chemical analyses, rare cell isolation, on-chip perfusion culture systems, and integrating all of the above. These systems have overcome the limits discussed above. For example, miniaturizing analytical systems results in facile parallelization and high throughput[2]. Automated microfluidic systems for cell biology have been demonstrated[2]. In an effort to facilitate studying hierarchical tissue, a microfluidic platform for single cell isolation from intact, viable tissue is proposed. The first of its kind, this device represents a leap forward compared to current cell isolation techniques by combining favorable microfluidic aspects such as high throughput and low cost, with the ability to preserve spatial context post cell isolation. Such a platform is discussed in the context of studying the intestinal stem cell niche. However, the broad impact would be the ability to study any multicellular tissue.

* This work is supervised by Professors Koppes and Murthy, *Northeastern University*, Boston, MA, USA.

References

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