

Gen 3-2019 ISCC Research Project Abstract



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NICHE SUPPORT OF HUMAN INTESTINAL STEM CELLS

Intestine development is a highly complex process that involves reciprocal signaling between the intestinal epithelium and the underlying mesenchyme in order to drive the morphogenetic process giving rise to the stereotypical crypt-villus architecture of the fully functional, adult intestine. However, almost nothing is known about the cellular constituents present in the human intestine that comprise the intestinal stem cell (ISC) niche, and even less is understood about how these cells may functionally regulate human ISCs. Improving this gap in knowledge is critical for our understanding of the normal human intestine, and will also lay the groundwork for understanding the molecular and cellular basis of disease and for developing novel therapies aimed at stimulating repair and regeneration. The goal of this proposal is to add fundamental new knowledge of human intestinal biology by interrogating the ISC niche across the human lifespan, from development through adulthood, and to understand how niche cells function to support human ISCs, intestinal maturation and intestinal function.

Public Health Relevance Statement:

The gut epithelium, which is supported by a self-renewing population of intestinal stem cells (ISCs), has the complex task of absorbing nutrients while managing constant bombardment from food and bacterial antigens, acting as the first physical and immunological barrier, and, in the event that the epithelial barrier is compromised or disrupted, the underlying immune system can be triggered, leading to inflammation, damage and disease. Yet, our understanding of the cellular heterogeneity of the human intestine, and the mechanisms by which the human intestinal epithelium is regulated is extremely limited and is largely inferred from animal models. This proposal will leverage recent technological advances in single cell genomic sequencing, along with advances isolating, growing, manipulating and interrogating primary human tissue derived- and pluripotent stem cell-derived organoid models to interrogate niche cells and niche factors that regulate human ISCs.