Gen 3- 2019 ISCC Research Project Abstract

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INTESTINAL NICHE IN HOMEOSTASIS AND EPITHELIAL REGENERATION

The intestinal epithelium exhibits a remarkable capacity of self-renewal which reflects the activity of multi- potent intestinal stem cells (**ISCs**) that divide and differentiate to produce the different cell types that comprise the intestinal epithelium. Control of ISC activity is thought to be mediated by factors produced by other cells that reside either in the stromal layer surrounding the intestinal crypt, by cells in the adjoining epithelium, and by the microbiome that resides in the small intestinal lumen. These factors create an environment called the "stem cell niche". Our past work and preliminary findings indicate that epithelial WNTs, stromal myofibroblasts and monocytes, and commensal derived factors are all components of the ISC niche. This renewal application seeks support to continue to collaborate in the Intestinal Stem Cell Consortium (**ISCC**) to extend our previous work defining the role of epithelial, stromal, and luminal intestinal factors that regulate ISC proliferation to acquire knowledge to regenerate and rebuild the human intestine. Gaining a molecular understanding of the role that these cells and factors play in the niche will be essential to consider when building intestine. Our proposed studies within the goals of the ISCC are follows: Goal 1: define essential niche components that contribute to intestinal epithelial homeostasis by (a) determining what microbial communities inhabit the human intestinal crypt and what their role is in regulating the ISC and (b) evaluating how intestinal myofibroblasts and monocytes affect proliferation and lineage differentiation of ISCs. Goal 2: determine niche components that are altered following injury and evaluate whether they play a role in epithelial regeneration by (a) dissecting the molecular signaling pathways in damaged epithelium that stimulate the ISC through WNT3, and (b) determining the specific role of human WNT2B in ISC–induced regeneration. The **mission** of the ISCC is to characterize the minimal, required niche cells and factors that support ISC in health and disease, using an integrated, multidisciplinary team science approach. Our proposed research complements and synergizes with the other eight projects of the ISCC to achieve the ultimate goal of developing both humoral and tissue therapy for gastrointestinal diseases via modulation of factors that comprise the ISC niche. Combining and sharing our skills and resources will allow rapid advancement of ISC biology and application of new knowledge to repair and build an intestine.

Public Health Relevance Statement:

Damage to the intestinal epithelium is a hallmark of many diseases of the GI track including infections, radiation, chemotherapy, and inflammatory bowel diseases. Induction of proliferation of the intestinal stem cell is the central point of all healing or regenerative processes. The proposed work will focus on harnessing epithelial, stromal and commensal factors to induce intestinal stem cell activation thus facilitating epithelial repair.