

Gen 3-2019 ISCC Research Project Abstract



Timothy C. Wang, M.D.
Principal Investigator; Voting SC Member
Columbia University Health Sciences



Chandan Guha, M.B.B.S., Ph.D.
Principal Investigator; (Voting) SC Member
Albert Einstein College of Medicine



Samuel Asfaha, M.D., Ph.D., FRCPC
Co-Investigator; Non-Voting SC Member
University of Western Ontario



Kelley Yan, MD, PhD
Co-Investigator; Non-Voting SC Member
Columbia University Health Sciences

UNDERSTANDING STEM CELL HETEROGENEITY AND NICHE FUNCTION IN INTESTINAL REGENERATION AFTER IRRADIATION

The radiation-induced gastrointestinal syndrome (RIGS) results from dose-dependent, cytotoxic effects of radiation on intestinal crypt cells. There are currently no approved medical countermeasures to alleviate the RIGS. While active Lgr5⁺ stem cells are efficiently ablated, regeneration emerges from reserve, quiescent progenitor/stem cells that are radioresistant. The exact relationship between these two progenitor populations (radioresistant and radiosensitive) remains undefined, and more information is needed to develop therapies for RIGS and other disorders. An unbiased approach is critically needed to fully characterize the diversity of cells in normal and regenerating intestine, independent of prior knowledge or purification assays. Work from our lab and the ISCC has demonstrated a key role for the stromal mesenchyme and other niche cells in modulating ISC homeostasis and regeneration, but a comprehensive regulatory model does not exist. Matrix proteins are also part of the niche, and we have been able to grow both enteroids and human intestinal organoids in tissue-specific hydrogels. Our investigators and collaborators have developed novel R-spondin and Wnt agonists for in vivo delivery but the optimal combinations for treatment of RIGS have not been defined. Thus, a full understanding of the cross-talk signals between ISCs and niche cells, and models for stimulating or replacing intestinal ISCs, is needed for advances in therapy for RIGS. In collaboration with other members of the ISCC, we are proposing two specific aims. **Aim 1. How does the heterogeneity of intestinal crypt cells and adjacent stromal cells change after radiation?** We will analyze highly pure crypt epithelial cells and stromal cells using a novel multiplex scRNA-seq platform before and after radiation, and apply computational tools (metaVIPER) to develop a hierarchical structure and regulatory model. **Aim 2. Can therapy with niche factors or stem cells be used to mitigate radiation or inflammatory injury to the intestine?** We will study novel combinations of factors to mitigate RIGS, and then use tissue-specific hydrogels and novel factors and cells to grow in vitro and transplant in vivo human intestinal organoids to treat colitis and radiation proctitis. Overall, this proposal will use novel technology developed at Columbia/Einstein to advance collaboratively the ISCC mission to regenerate the human intestine.

Public Health Relevance Statement:

In this study, we will advance the mission of the ISCC to rebuild the human intestine by pursuing both computational approaches based on scRNA-seq data, and laboratory approaches that test mitigating agents in radiation-induced intestinal injury and tissue engineering approaches that employ novel tissue-specific hydrogel preparations. Together, we aim to leverage niche factors to promote intestinal regeneration.