Dr. Timothy Wang

The intestinal epithelium is rapidly renewed every 3-5 days from both active cycling stem cells, as well as, more quiescent stem cells. The radiation-induced gastrointestinal syndrome (RIGS) results from dose-dependent, cytocidal effects of radiation on intestinal stem cells. Preliminary work from our group has demonstrated using inducible Cre-dependent lineage tracing that Keratin-19 (Krt19) labels intestinal stem cells distinct from Lgr5+ CBCs and located above the +4 region. In contrast to Lgr5+ cells, Krt19+ stem cells are radioresistant and can regenerate the small intestine following 12Gy radiation. In addition, data from our group has shown that both mesenchymal cells and nerves are important in modulating stem cells and contributing to regeneration. Thus, it is our hypothesis that the +4 intestinal stem cell (ISC) marked by Krt19 is critical to the response to radiation injury, and maybe regulated by stromal factors distinct from that for Lgr5+ stem cells. We will explore this hypothesis through three specific aims. (1) What is the hierarchical relationship and characteristics that distinguish Lgr5+ and Krt19+ stem cells. We will use in vivo lineage tracing, in vitro organoids and gene expression studies to explore these distinct stem cell populations. (2) What is the role of neural factors in ISC expansion in response to radiation injury? We will use murine models with altered serotonin and cholinergic signaling to assess the response of ISCs to radiation injury. (3) How do intestinal growth factors regulate ISC regeneration in mice after radiation? We will examine defined intestinal growth factors (such as R-spondin1 and KGF), as well as other candidate niche factors, in the protection and mitigation of RIGS. There are currently no approved medical countermeasures to alleviate the RIGS. Overall, this proposal will investigate the hierarchy, cell fate, and role in regeneration of various ISC populations post-radiation.