

ISCC Research Project Abstracts



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REGULATION OF ACTIVELY PROLIFERATING AND QUIESCENT INTESTINAL STEM CELLS

The tremendous regenerative capacity of the intestine, with epithelial turnover every 5-7 days, is mediated by the carefully orchestrated activity of intestinal stem cells (ISC). The recent identification of molecular markers for ISCs, combined with in vivo lineage tracing and in vitro primary organoid culture methodologies has revolutionized ISC biology. The resultant wealth of findings have showcased ISCs as a robust general paradigm for stem cell behavior and have elicited a next generation of studies exploring the ISC niche, interrelationships and interconversion of actively cycling versus quiescent ISC populations, and translational applications of ISC transplantation. Accordingly, the current application is a continuation of our prior 5 year project for the NIDDK Intestinal Stem Cell Consortium (ISCC), and is responsive to RFA-DK-13-012, Intestinal Stem Cell Consortium Research Projects (U01), seeking to "define conditions controlling proliferation and differentiation of intestinal stem cells", "determine the developmental lineage of characterized populations of stem cells in the small intestine" and "methods for expanding and grafting stem cells back into the intestine". Here, we build upon our preliminary data from the prior cycle with novel reagents and methodologies. Aim 1 explores R-spondins as regulators of Lgr5+ ISC symmetric cell division combining adenovirus-mediated gain- and loss-of-function approaches with in vivo lineage tracing, and pursuing mechanistic and niche localization studies. In Aim 2, interrelationships between diverse cycling and quiescent ISC populations will be investigated by RNA-Seq, and novel lineage relationships of Bmi1+ ISC will be explored. Aims 3 and 4 explore translational aspects of ISC biology, with Aim 3 utilizing organoid culture to evaluating the effects of R-spondins on colon cancer stem cells, and Aim 4 attempting the phenotypic correction of a Mendelian intestinal epithelial defect by ISC transplantation. Overall, these studies describe an integrated approach to ISC biology and translation that is highly responsive to RFA-DK-13-012, Intestinal Stem Cell Consortium Research Projects (U01), with implications for stem cell biology, and intestinal disease pathogenesis and therapy.