

Project Number: U01DK85507-01

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Awardee Organization: Stowers Institute for Medical Research

Title: Isolation and Characterization of Intestinal Stem Cells

Abstract Text:

DESCRIPTION (provided by applicant): The small intestine provides a most elegant system for the study of adult stem cells -- cells which hold great promise for regenerative medicine. Genetic studies have revealed several key signaling pathways that play a role in the regulation of intestinal stem cells (ISCs). This has provided important insight into understanding the capacity of ISCs for renewal and self-repair and differentiation into multiple intestinal cell types. However, further progress is impeded by the inability to isolate and transplant ISCs for advanced study either in vivo (within living tissue) or in vitro (within a controlled environment outside of a living organism). This research project proposes to address this barrier to ISC research, including the development of novel and reliable methods for ISC isolation, in vitro culture, and in vivo functional characterization. ISC isolation will be accomplished by using fluorescent label protein and other membrane surface proteins to sort and verify cells by genes known to be expressed in intestinal stem cells. In vitro culture will be accomplished by adding key factors that are important for supporting ISC proliferation into Matrigel or 3-dimensional culture of crypt sphere. Functional characterization will be accomplished by injecting isolated ISCs into the irradiated crypt sphere and then transplanting the chimeric sphere to an in vivo microenvironment to characterize ISC survival, self-renewal, proliferation, and lineage commitment. If this goal can be achieved, it will open avenues not only for advancing the study of ISC behavior, but also for treating intestinal disorders in which ISC-driven tissue regeneration is essential and for screening drugs to target on cancer stem cells. The ability to identify and isolate and characterize ISCs is critical for therapeutic advancements, especially tissue replacement, and for understanding cancer development, prevention and cure.

PUBLIC HEALTH RELEVANCE: The cost of digestive diseases in the U.S. collectively exceeds \$85 billion in direct and \$23 billion in indirect expenses. Evidence indicates intestinal stem cells (ISCs) are involved in many cases -- from Crohn's to colitis to cancer. This research will increase knowledge of ISC biology, which can be applied to enhance treatment efficacies, improve patient outcomes, and ultimately, impact the public health burden of digestive diseases