Holly Poling
holly.poling@cchmc.org
Graduate Student, University of Cincinnati, Cincinnati Children's Hospital Medical Center
Advisor: Michael Helmrath

All Abstract Authors and Affiliations:
Holly M. Poling 1,2, Nambirajan Sundaram 1, Garrett W. Fisher 1, Akaljot Singh 1, Joseph R. Shiley 3, Kalpana Nattamai 1, Vinothini Govindarajah 1, Alexander R. Cortez 1, Maksym O. Krutko 1,2, Séverine Ménoret 4,5, Ignacio Anegon 4, Magdalena Kasendra 1, James M. Wells 1,6, Christopher N. Mayhew 1,3, Takanori Takebe 1,7, Maxime M. Mahe 1,8, and Michael A. Helmrath 1

1 Center for Stem Cell and Organoid Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, 45219, USA 2 Department of Biomedical Engineering, University of Cincinnati, Cincinnati, OH, 45219, USA 3 Pluripotent Stem Cell Core, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45219, USA 4 Nantes Université, CHU Nantes, Inserm, CNRS, SFR Santé, Inserm UMS 016 CNRS UMS 3556, Nantes, 44035, France 5 INSERM, Centre de Recherche en Transplantation et Immunologie UMR1064, Nantes Université, Nantes, 44035, France 6 Division of Developmental Biology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, 45219, USA
7 Division of Gastroenterology, Hepatology & Nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, 45219, USA 8 Nantes Université, Inserm, TENS UMR1235, The Enteric Nervous System in Gut and Brain Diseases, IMAD, Nantes, 44035, France

Mesenchyme augments the therapeutic capacity of human intestinal organoids in vivo

The fundamental goal of tissue engineering is to functionally restore or improve damaged tissues or organs. Here we address this in the small bowel using an in vivo xenograft preclinical acute damage model. We investigated the therapeutic capacity of human intestinal organoids (HIOs), which are generated from human pluripotent stem cells (hPSCs), to repair damaged small bowel. We hypothesized that the HIO's cellular complexity would allow it to sustain transmural engraftment. To test this, we developed a rodent injury model where, through luminal delivery, we demonstrated that fragmented HIOs engraft, proliferate, and persist throughout the bowel following repair. Not only was restitution of the mucosal layer observed, but significant incorporation was also observed in the muscularis and vascular endothelium. Further analysis characterized sustained cell type presence within the regenerated regions and retention of proximal regionalization. Moreover, electrophysiological studies verified that the regenerated tissue exhibited appropriate

responses to ion transport modulators, demonstrating functional epithelial recovery. No evidence of off-target human cell migration or tumor formation in host tissues was observed. Together, these findings demonstrate the therapeutic importance of mesenchyme for intestinal injury repair and underscore the potential of HIOs as a novel therapeutic strategy for treating severe transmural intestinal injuries.