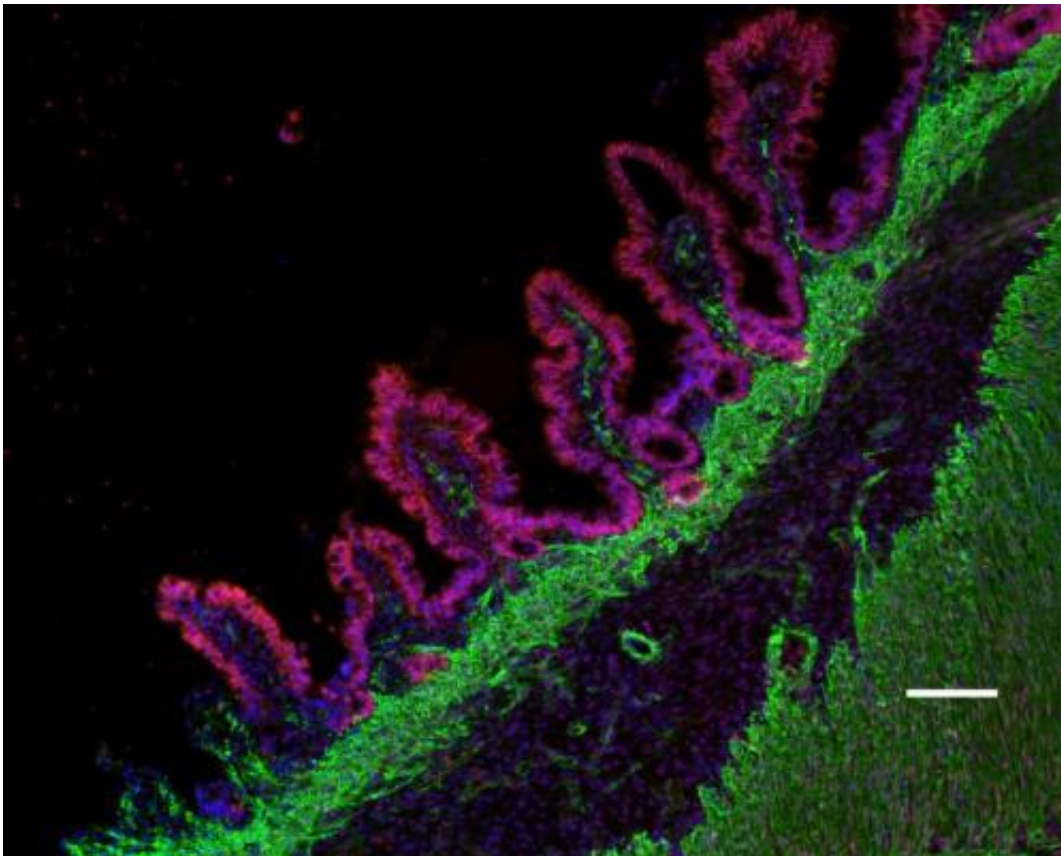


Lab-developed intestinal organoids form mature human tissue in mice

October 19 2014



Immunostaining of engrafted HIO. The tissue is of human origin as stained by human nuclear antigen (red). Muscular layer is stained with alpha-SMA (green). Scale bar: 100um. Credit: Helmraath lab

Researchers have successfully transplanted "organoids" of functioning human intestinal tissue grown from pluripotent stem cells in a lab dish

into mice – creating an unprecedented model for studying diseases of the intestine.

Reporting their results Oct. 19 online in *Nature Medicine*, scientists from Cincinnati Children's Hospital Medical Center said that, through additional translational research the findings could eventually lead to bioengineering personalized human [intestinal tissue](#) to treat gastrointestinal diseases.

"These studies support the concept that patient-specific cells can be used to grow intestine," said Michael Helmuth, MD, MS, lead investigator and surgical director of the Intestinal Rehabilitation Program at Cincinnati Children's. "This provides a new way to study the many diseases and conditions that can cause [intestinal failure](#), from genetic disorders appearing at birth to conditions that strike later in life, such as cancer and Crohn's disease. These studies also advance the longer-term goal of growing tissues that can replace damaged human intestine."

The scientists used induced pluripotent [stem cells](#) (iPSCs) – which can become any tissue type in the body – to generate the intestinal organoids. The team converted adult cells drawn from skin and blood samples into "blank" iPSCs, then placed the stem cells into a specific molecular cocktail so they would form intestinal organoids.

The human organoids were then engrafted into the capsule of the kidney of a mouse, providing a necessary blood supply that allowed the organoid cells to grow into fully mature human intestinal tissue. The researchers noted that this step represents a major sign of progress for a line of regenerative medicine that scientists worldwide have been working for several years to develop.

Mice used in the study were genetically engineered so their immune systems would accept the introduction of human tissues. The grafting

procedure required delicate surgery at a microscopic level, according to researchers. But once attached to a mouse's kidney, the study found that the cells grow and multiply on their own. Each mouse in the study produced significant amounts of fully functional, fully human intestine.

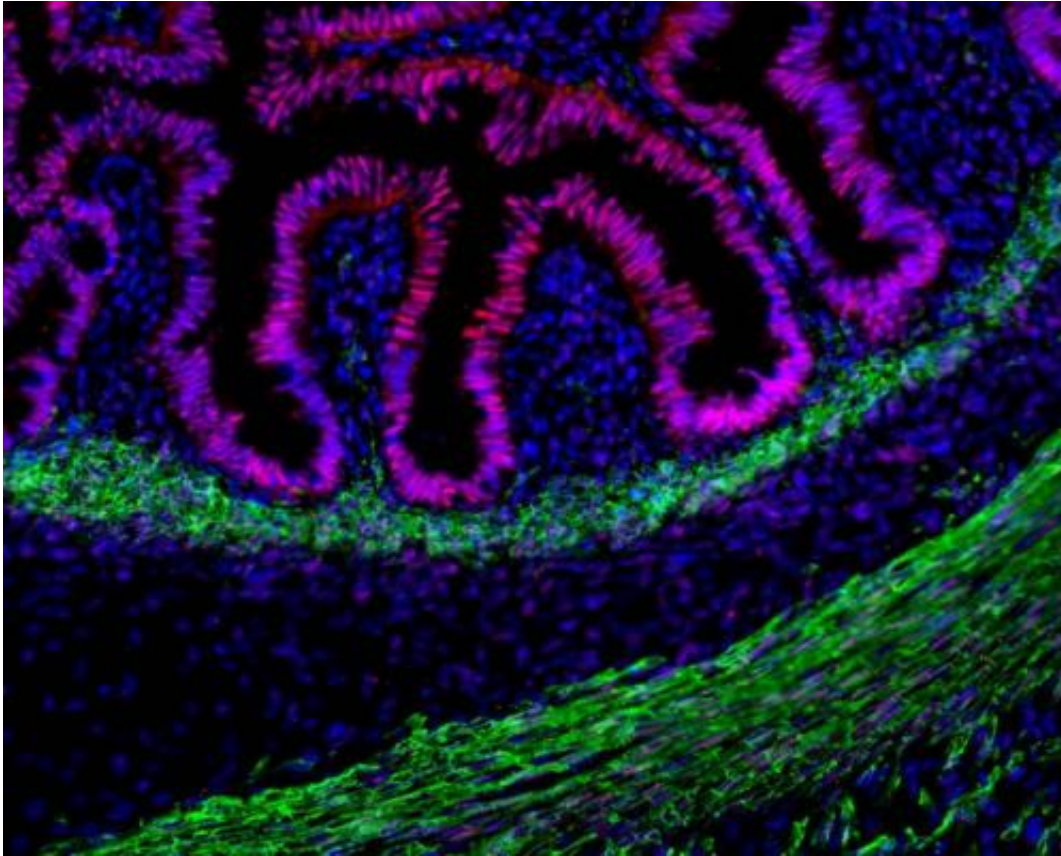
"The mucosal lining contains all the differentiated cells and continuously renews itself by proliferation of [intestinal stem cells](#). In addition, the mucosa develops both absorptive and digestive ability that was not evident in the culture dish," Helmrath said. "Importantly, the muscle layers of the intestine also develop."

What This Means for Patients

The new findings eventually could be good news for people born with genetic defects affecting their digestive systems or people who have lost intestinal function from cancer, as well as Crohn's disease and other related inflammatory bowel diseases (IBD).

One of the advantages of using tissue generated from iPSCs is that the treatment process would involve the patient's own tissue, thus eliminating the risk and expense of life-long medications to prevent transplant rejection.

However, the researchers cautioned that it will take years of further research to translate lab-grown tissue replacement into medical practice. In the meantime, the discovery could have other, more immediate benefits by accelerating drug development and the concept of personalized medicine.



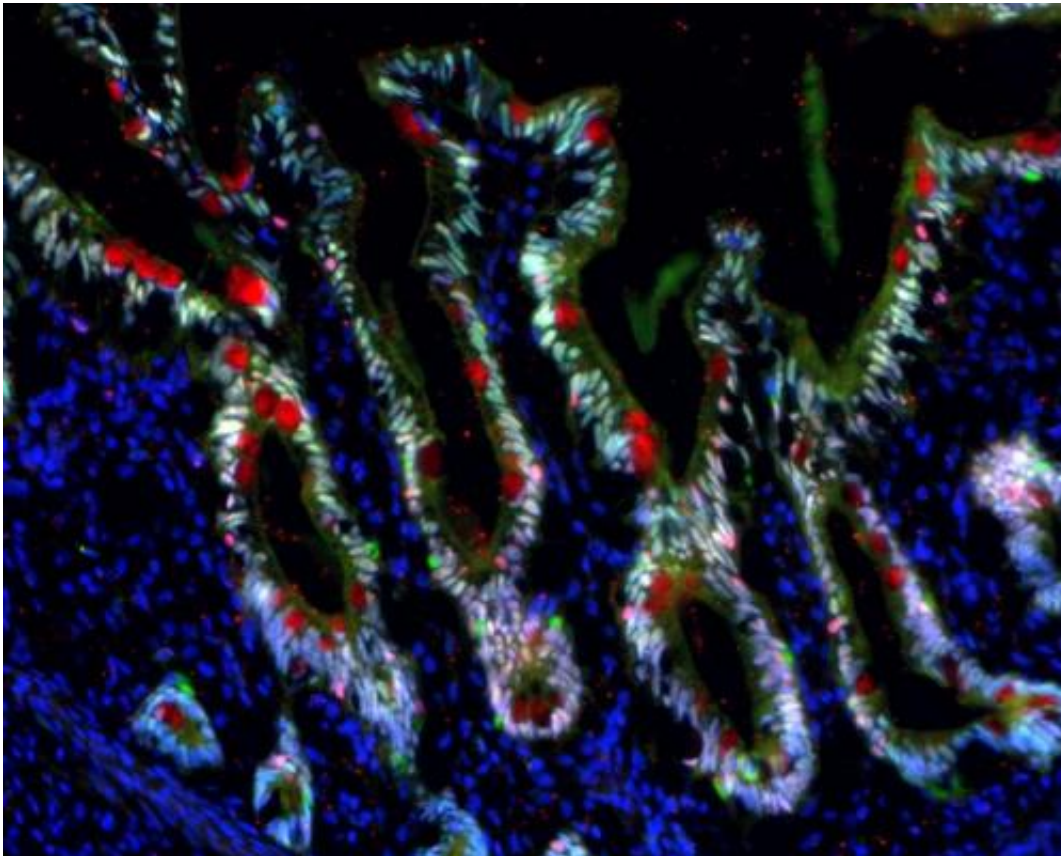
Immunostaining of engrafted HIO. The tissue is of human origin as stained by human nuclear antigen (red). Muscular layer is stained with alpha-SMA (green).
Credit: Helmraath lab

The current process for developing new medications depends on a long and imperfect process of animal testing. Promising compounds from the lab are tested in animals bred to mimic human diseases and conditions. Many compounds that prove effective and safe in mice turn out to be unsuccessful in human clinical trials. Others have mixed results, where some groups of patients clearly benefit from the new drug, but others suffer harmful side effects.

Lab-grown organoids have the potential to replace much of the animal testing stage by allowing early drug research to occur directly upon

human tissue. Going straight to human tissue testing could shave years off the drug development process, researchers said.

The current study in Nature represents the latest step in years of stem cell and organoid research at Cincinnati Children's, much of which has been led by James Wells, PhD, and Noah Shroyer, PhD. Wells is a scientist in the divisions of Developmental Biology and Endocrinology at Cincinnati Children's and director of the Pluripotent Stem Cell Center. Shroyer is a scientist in the divisions of Gastroenterology, Hepatology & Nutrition and Developmental Biology.



Immunostaining of intestinal lineages in transplanted HIO. Credit: Helmraath lab

Wells and colleagues first reported success at growing intestinal organoids in the lab in December 2010. Since then, the team has reported similar success at growing organoids of stomach tissue.

Also collaborating were researchers at the Department of Internal Medicine, University of Michigan (Ann Arbor, Mich.)

More information: *Nature Medicine*. [DOI: 10.1038/nm.3737](https://doi.org/10.1038/nm.3737)

Provided by Cincinnati Children's Hospital Medical Center

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