MedicalXpress

New assembly approach generates most complex stomach organoids to date

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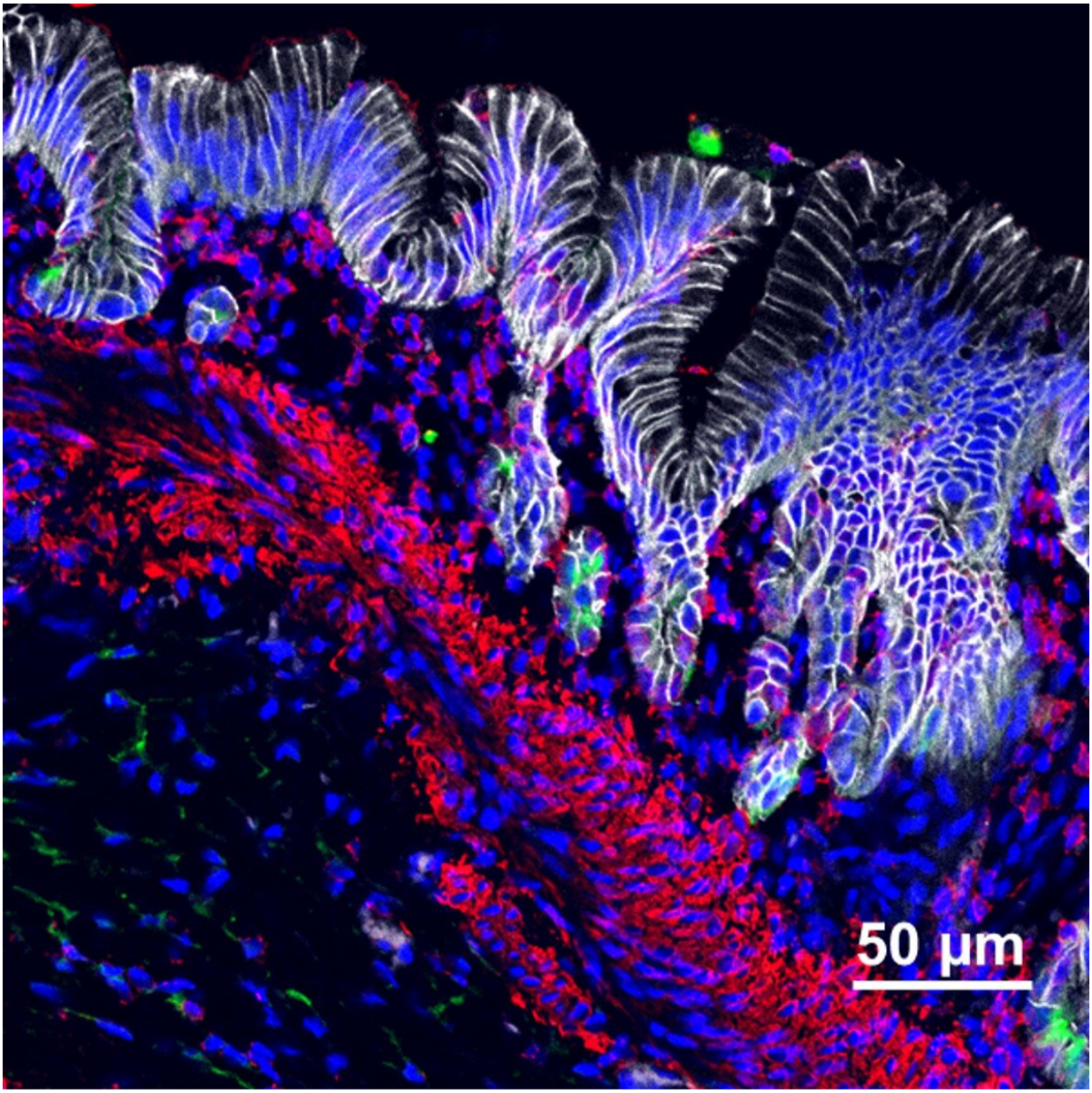


Credit: Cincinnati Children's Hospital Medical Center

In a significant step forward in regenerative medicine, scientists at Cincinnati Children's report success at developing a stomach organoid so sophisticated that it has distinct glands and nerve cells that can control smooth muscle contractions.

The achievement demonstrates that separate layers and portions of complex organs can be grown from separate lines of human pluripotent stem cells (PSCs) and be combined for continued development. And the approach used to produce these multi-layered stomach organoids also can be used to make more-complex versions of other lab-grown organs.

"This advance in tissue engineering is important because we can now assemble complex organ tissues from separately derived components, similar to an assembly line approach," says corresponding author James Wells, Ph.D.

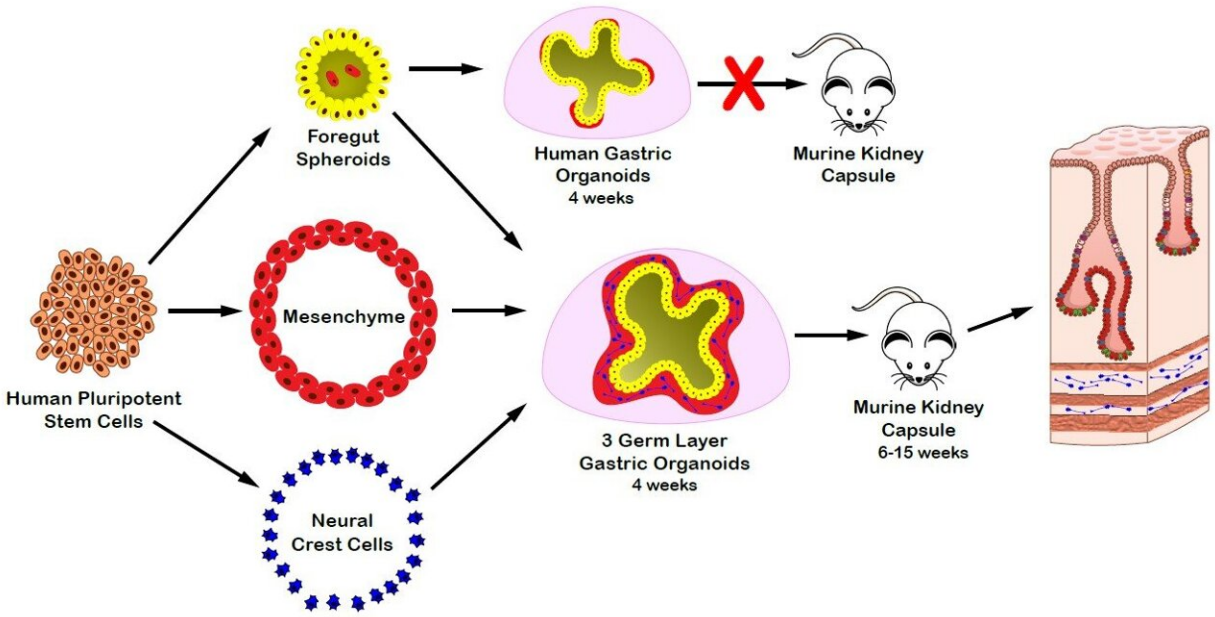
The findings were published Dec. 1, 2021 in *Cell Stem Cell* by Wells and lead author Alexandra Eicher, Ph.D.

Layer-by-layer assembly

Most organoids made so far can form 3D structures involving multiple cell types. In a lab dish, these tiny organs perform real functions that provide new opportunities to study diseases and develop cures. But they typically are missing a variety of cell types that would be needed to produce a full-sized functional organ. Some might not have key nerve fibers, internal blood vessels, or other critical ducts and glands that would be needed to connect the organ to the rest of the body's systems.

This new stomach organoid does not yet have every cell type it needs, but it represents a leap forward.

"We started with cells from the three primary germ layers–enteric neuroglial, mesenchymal, and epithelial precursors–all separately derived from PSCs," Eicher says. "From these we generated stomach tissue that contained acid-producing glands, surrounded by layers of smooth muscle containing functional enteric neurons that controlled contractions of the engineered antral stomach tissue."



Making a Three-Layered Stomach Organoid. Credit: Cincinnati Children's Hospital Medical Center

Importantly, the development of these mini human stomachs was not limited to a thin layer of medium in a lab dish. Once the organoids reached a critical stage (at about 30 days) the team performed

microsurgery to transplant the organoids into a mouse, which provided the blood flow and biological space to allow much more growth.

Instead of spheres of cells that look like dots in a dish, these organoids grew a thousand-fold in volume inside the mice to form mini organs plainly visible to the naked eye.

When viewed under a confocal microscope, with different cell types stained to glow in different colors, these organoids radiate a rainbow of complexity.

In fact, the lab-grown tissue closely resembles naturally grown human tissue at similar stages of development. This new organoid even began developing a Brunner's gland, which secretes an alkaline mucus that protects the duodenum (the top part of the intestine) from the acidity of stomach contents as they begin flowing through.

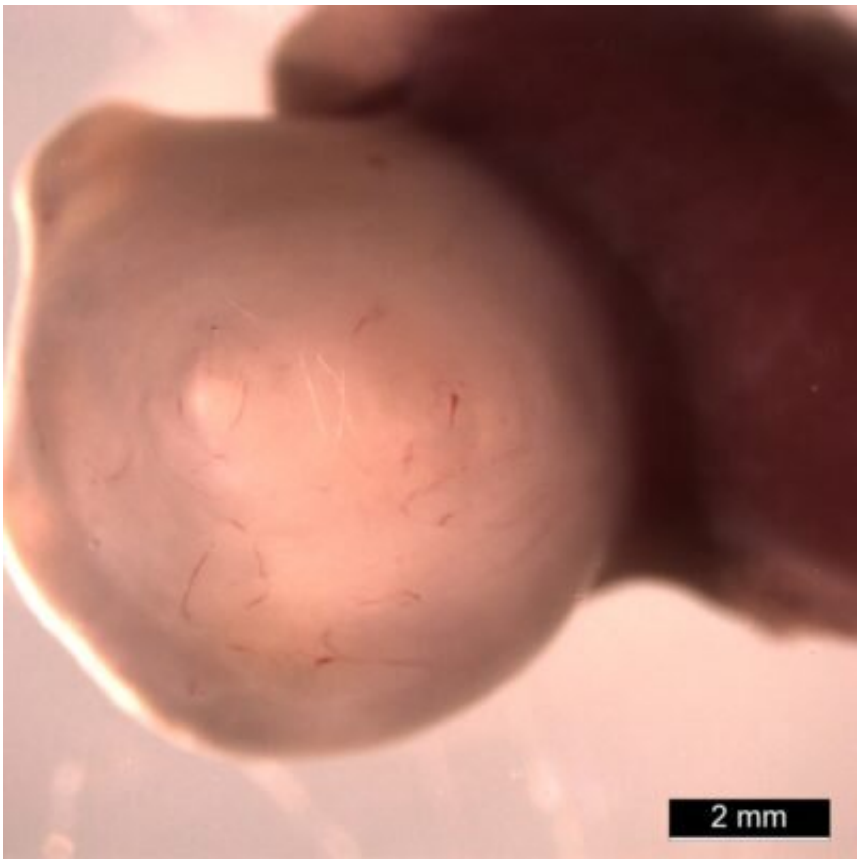
The team also discovered that all these individual components are needed in order to generate stomach tissue with the proper complexity and function. Each component helps guide the proper formation of the other components. For example, the authors found that if they did not add the nerves during the assembly process the stomach glands and muscle did not form properly.

Immediate and long-term potential

In addition to demonstrating a three-layered approach for developing stomach organoids, the team also applied a similar approach to make a more sophisticated esophageal organoid.

At a minimum, these more-complex organoids will serve as useful tools for studying genetic variations and other cell signaling dysfunctions that contribute to gastric diseases—and can serve as improved platforms for

evaluating potential treatments. But there may be even wider-scale impact from these findings.



Credit: Cincinnati Children's Hospital Medical Center

"Given that this technology is broadly translatable to other organs, it is possible that engineered tissue might be a source of material for reconstructing elements of the upper GI tract that are damaged by congenital disorders or acute injuries," Wells says.

While much works remains to develop organoid tissue that would be suitable for transplantation, much progress also has been made.

"Members of this team, with a recent grant awarded from Cincinnati Children's Hospital, are now working to scale up production of therapeutic quality organoid tissues with the goal of transplantation into patients by the end of the decade," Wells says.

Cincinnati Children's has played a leading role in organoid research since 2010 when Wells and colleagues published findings in Nature reporting their first success at developing functional intestinal tissue. In 2019, the medical center launched its Center for Stem Cell and Organoid Medicine (CuSTOM) to further accelerate the work.

Over the years, the growing team has:

- Added nerves to intestinal organoid tissue
- Demonstrated how to mass-produce liver "buds"
- Produced liver organoids for specific disease states
- Grown both major portions of the stomach
- Developed functional esophagus tissue
- Grown a three-organoid system (liver, pancreas, bile ducts)

Next steps

The Helmrath lab at Cincinnati Children's has begun work to expand this line of research beyond mice. While this approach will add important insights at the laboratory level, the research team does not believe that using animals as hosts to continue growing human organs will be the ultimate method for transplanting organoid tissue into human patients.

"Growing full-sized organs for clinical purposes would require GMP (a set of Good Manufacturing Practice regulations established by the U.S. Food and Drug Administration to assure consistency and safety) and that would probably exclude the possibility of using animal hosts to continue growth," Eicher says. "So we would need a way to grow organoids larger

without a host. This would require a way to mimic active nutrient and gas exchange in vitro."

More information: Alexandra K. Eicher et al, Functional human gastrointestinal organoids can be engineered from three primary germ layers derived separately from pluripotent stem cells, *Cell Stem Cell* (2021). DOI: 10.1016/j.stem.2021.10.010

Provided by Cincinnati Children's Hospital Medical Center