ADVERTISEMENT FEATURE

ORGANOIDS ARE TRANSFORMING GUT SCIENCE

Improved organoid models uncover potential treatments for endocrine-related conditions and reveal new insights into gastrointestinal diseases.

Organoids, three-dimensional lab-grown mini organs, are used to test basic biological theories, help scientists find new drug targets, and even trial a specific patient's responses to particular drugs. But despite their vast potential, organoid models need some fine-tuning. Here, James Wells, developmental biologist and chief scientific officer at the Centre for Stem Cell and Organoid Medicine, Cincinnati Children's Hospital, in the United States, discusses the importance of endocrine cells in health and disease and his lab's recent advances in improving organoid function.

Why create and study organoids?

Around 20 years ago, when first-generation organoids emerged, they were astonishing — but they lacked several key features and functions. Today, researchers are creating more complex and physiologically accurate organoids by incorporating additional cell types that are critical for organ function. For instance, we've added immune cells called macrophages to intestinal organoids to study inflammatory bowel disease. Building on that, personalized organoid diagnostics — where organoids are grown from a patient's own cells — can help pinpoint the underlying causes of their symptoms. Organoid technology could also offer potential for repairing tissues damaged by degenerative gastrointestinal (GI) diseases.

What are you investigating now?

I am interested in rare populations of endocrine cells found in different GI organs, including the stomach, colon, and pancreas. Hormones released by endocrine cells are fascinating regulators, and therefore offer tremendous potential as therapeutics. Little is known about these cell populations in the GI tract, but we are learning more. We know that they secrete pivotal hormones controlling critical aspects of healthy bodily functions, from appetite to interactions between the gut and brain. Five years ago, my lab discovered how endocrine hormones control nutrient absorption, and from this we could improve dietary interventions for chronic malnutrition. Our newest organoid is a fully functional pancreatic organoid that includes the pancreas's intricate ductal networks, and this will enable us to study pancreatitis — a disease for which there are no treatments.

Describe a moment in your lab that led to a key discovery.

Most early published work on human pluripotent stem cells was on two-dimensional monolayers of cells such as hepatocytes or neurons. At that time, we were learning how to turn human pluripotent stem cells into embryonic intestinal cells. A postdoc in my lab, Jason Spence, said he had noticed 'debris' floating around our intestinal monolayer cultures. Despite skimming this debris away, it kept recurring. So, we looked at it under the microscope, and it wasn't debris at all. They were these tiny, three-dimensional structures with very pronounced organization. Around the same time, another lab published the first adult intestinal organoid, created by suspending cells in matrix gel. We put our mysterious structures into a similar gel, and they grew into embryonic and fetal intestinal tissues. For weeks, we had discarded those crucial structures as debris, but as it turns out, we were literally throwing the baby out with the bathwater.

Is there a memorable moment that surprised you?

As we started to take small steps towards building complexity in organoids, we were progressing slowly; adding one cell type here, another there. But a student of mine, Alex Eicher, wanted to take one of our simple stomach organoids and make them much more like an actual stomach. Our first-generation organoid contained only the inner lining — but muscle layers, nerves and other support tissues were missing. Alex added two major cell groups at once, the ones that form the stomach musculature and nervous systems. I was astonished when she brought me the resulting organoid several months later. She had taken a single-layer sheet cake and turned it into a multi-layered showstopper!

The cells had organized themselves independently into complex, layered tissue that was physiologically like a young stomach. Despite all we had done with our early organoids, we hadn't factored in the power of self-organization in mixed cell cultures. It was a game-changing moment, not just for us but for the whole field.

Why is supporting junior scientists important to you?

As a community, we're encountering heightened external pressures that didn't exist before. Mentoring and helping junior scientists thrive is more important than ever. It's vital to help them understand that their chosen career is incredibly challenging, and that even the most experienced scientists, including myself, have faced many difficulties and overcome them.

We also need to improve communication training for young scientists. Learning to explain what you do in lay terms, so that the public can understand and appreciate your work, is a critical skill. In terms of my own research field, it is vital that we train others how to use organoid technologies. Gaps in training could catastrophically impact on our ability to move much of this exciting science forward. If there's a brain drain and an exodus of trainees from the United States, it will have long term knock-on effects, both in discovery-based research and in developing cures.

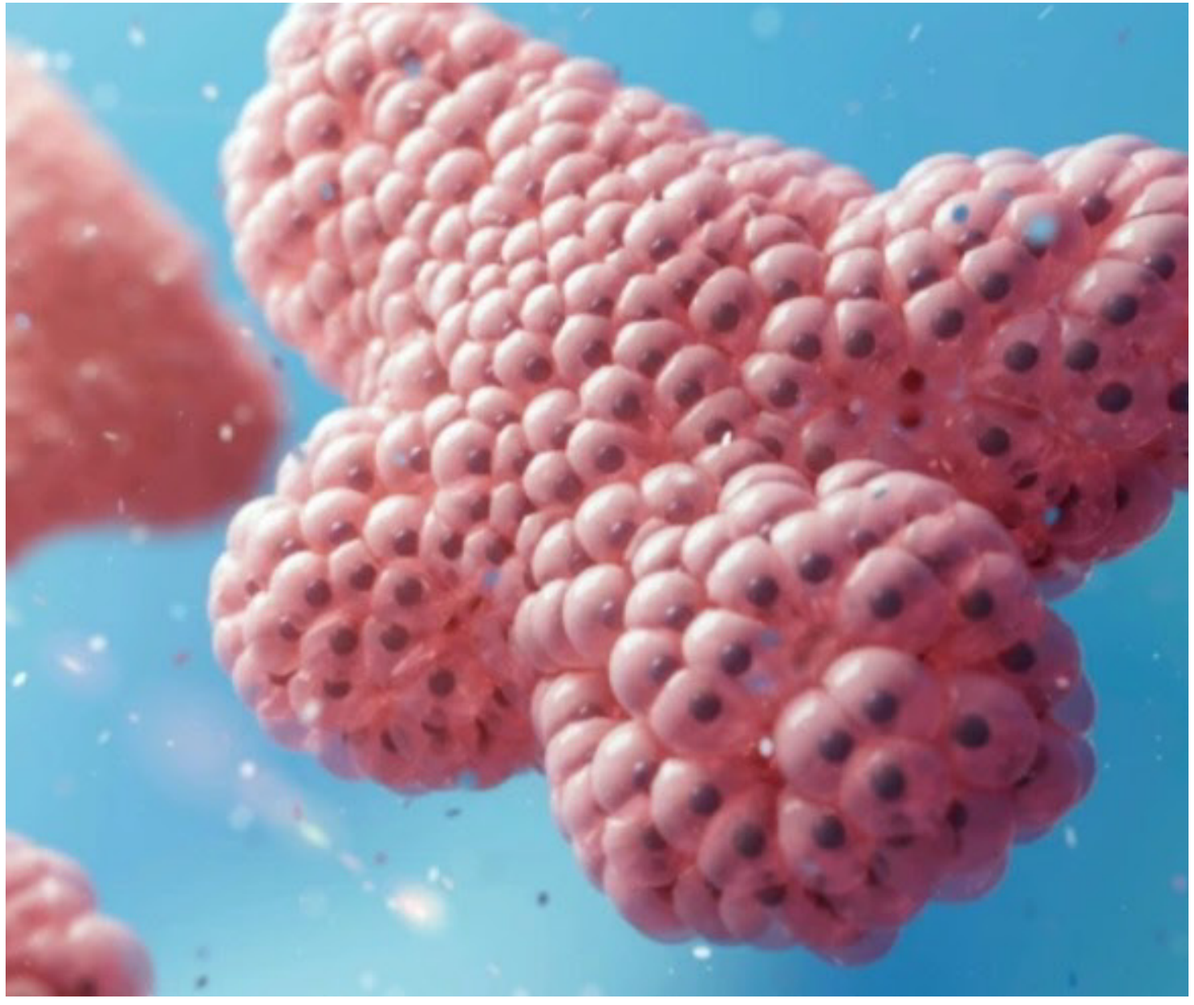

Illustration of lab-grown organoids — miniature 3D models of organs used to study disease and test therapies.
Credit: Thom Leach/ Science Photo Library/ Getty Images