

## World's First Three-Organoid System Opens Doors for Medical Research and Diagnosis

By themselves, human organoids already provide a sophisticated tool for research. But now, a team of researchers at Cincinnati Children's is growing connected, functioning sets of miniature human liver, pancreas and biliary ducts. Their research, "Modelling human hepato-biliary-pancreatic organogenesis from the foregut–midgut boundary," was published in the journal *Nature* (September 2019).

This advance allows scientists to study how human tissues work in concert. It could begin reducing the need for animal-based medication studies, sharply accelerate the concept of precision medicine, and someday lead to transplantable tissues grown in labs.

"The connectivity is the most important part of a living system," says Takanori Takebe, MD, who led the work. "What we have done is design a method for producing pre-organ, formation-stage tissues so that they can develop naturally. We are maximizing our capacity to make multiple organs much like the body does."

### Merging, morphing spheroids

The early steps of the process were the most challenging. Takebe and his colleagues at Cincinnati Children's started with human skin cells, converting them back into primitive stem cells. Then they guided and prodded those stem cells to form two very early-stage "spheroids" of cells loosely termed the foregut and the midgut.

These spheroids form very early in embryonic development and, over time, merge and morph into the organs that eventually become the digestive tract.

Growing these spheroids in the lab was a complex process that required using the right ingredients at the right time. Once they were mature enough—a timing step that required much work to pinpoint—the team simply placed the spheroids next to each other in a special lab dish. The cells were suspended in a gel to support organoid growth, then placed on top of a thin membrane that covered a carefully mixed batch of growth medium.

From this point, the cells knew what to do. The lab team simply watched as cells from each spheroid

began to transform upon meeting each other at the boundary between the two. They converted themselves, and each other, into more specialized cells that could be seen changing colors thanks to chemical tags the lab team had attached to the cells.

Soon, the merging, changing spheres sprouted into branches leading to new groups of cells that belonged to specific organs. Over a period of 70 days, these cells continued to multiply into more refined and distinct cell types. Ultimately, the mini organoids began processing bile acids as if they were digesting and filtering food.

### A Five-Year Quest

In previous research, Takebe demonstrated a method to produce large supplies of liver "buds," an early-stage form of a liver organoid. He also has grown liver organoids that reflect disease states, including steatohepatitis.

But Takebe says this project is his highest-impact work yet. "We noted this point in organ differentiation some time ago. But it took five years to tune up the culture system to allow this development to occur," Takebe says.

### Practical Applications

In precision medicine, doctors are starting to use genomic data and other information to determine which treatments would work best for patients with serious disease, at what dose, and with the least amount of possible side effects.

A living "gut" of multiple organs would provide a powerful tool for studying exactly how gene variations and other factors affect organ development during pregnancy, and to develop better targeted drugs to



treat conditions after babies are born.

A connected system of “generic” human organoids would offer much more information than having three organoids in disconnected dishes. Growing a set of gut organoids for a specific patient could allow even more precise diagnosis and customized treatment.

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“Current liver regenerative medicine approaches suffer from the absence of bile duct connectivity,” Takebe says. “While much work remains before we can begin human clinical trials, our multi-organoid transplant system is poised to solve this issue and may someday provide a life-long cure for patients with liver diseases.”

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The team already has grown a set of gut organoids that lack the gene *HES1*, one of several known genes that play a major role in triggering biliary atresia. The new study demonstrates how the gut organoids are harmed by the lack of *HES1*. If scientists can find a way to compensate for that genetic variation, they may be able to find a medication or cell transplant that would preserve biliary function in newborns and possibly avoid the need for liver transplants.

Read more about organoid research at [cincinnatichildrens.org/custom](https://cincinnatichildrens.org/custom).

