Testing Drugs on Mini-Yous, Grown in a Dish

In a lab in the Netherlands, Jeffrey Beekman is testing drugs on people with cystic fibrosis—sort of. He's not giving the patients themselves any medicine; instead, he's building small replicas of their organs using their own cells. He's creating miniature versions of them in a dish.

Cystic fibrosis, an incurable, life-shortening genetic disorder, is caused by mutations in a single gene called CTFR. These genetic faults lead to unusually thick mucus and other bodily fluids, which clog a patient's airways and pancreas. There's no cure, but a new drug called Kalydeco can help people breathe more easily by rectifying the problems caused by CTFR mutations. When the U.S. Food and Drug Administration approved Kalydeco, in 2012, it was billed as the year's "most important new drug" by Forbes.

But Kalydeco doesn't work for everyone with cystic fibrosis. The disease can be caused by almost 2,000 different mutations in the CTFR gene, which vary considerably in their effects. Some cause mild symptoms in just one organ, others trigger full-blown cystic fibrosis. On its own, Kalydeco can treat people with eight of these mutations, who account for 5 percent of the 85,000-strong patient pool. When given with another drug, Orkambi, it might also help the 45 to 50 percent of patients with the most common mutation, F508del.

Not bad, but that still leaves a lot of people without options, especially if their mutations are very rare. To see if drugs like Kalydeco and other CFTR-modulators can help these underserved patients, doctors would need to run clinical trials. But that's almost impossible, says Beekman, because there are so few of these patients, and they're scattered throughout the world.

His solution was to build organoids—three-dimensional mini-organs that are grown in the lab from stem cells. Over the last 8 years, scientists have built organoids of retinas, stomachs, livers, kidneys, and even brains. These blobs recapitulate many of the complex features of their parent organs, so you can use them to study how those organs form normally, and how that process goes awry in genetic disorders.

The crucial thing about organoids is that they are *personalized* blobs. They're made from an individual's cells, so they have all the same mutations that person has. They're not just brains and stomachs in a dish, but *your* brain and *your* stomach in a dish. And scientists can use them to predict not just how people will cope with a new drug, but how *you specifically* will respond.

You can see why Beekman was interested. By making organoids from the cells of cystic

fibrosis patients, he could check if their particular CFTR mutations would benefit from Kalydeco and other drugs, without having to do a single injection.

Postdoc Johanna Dekkers painlessly collected cells from the rectums of 71 cystic fibrosis patients and, within four weeks, had grown them into little spherical rectal organoids. (Many people think of cystic fibrosis as a disease of lungs and airways, but it affects the gut too.) Then, she put them through a simple test.

The CFTR gene creates a small pump that shuttles chloride salts in and out of cells, which in turn controls the flow of water. (That's why this gene affects the thickness of mucus and other bodily fluids.) So, if you make rectal organoids and chemically activate their chloride pumps, fluid should accumulate within them, causing them to swell. If the pumps are missing or broken thanks to mutations in the CFTR gene, nothing happens. And if drugs like Kalydeco can fix these problems, the blobs should swell again. The degree of restored swelling reveals how well the drugs work.

First, the team confirmed that the amounts of swelling seen in organoids with well-studied CFTR mutations match the responses that actual patients with those mutations have shown in clinical trials. The technique had merit.

Next, the team picked two people with rare CFTR mutations, whose organoids responded well to Kalydeco. "Nothing was published on these mutations," says Beekman. "We didn't know anything about them. But we did organoid testing and got a large effect." So they tried both patients on the drug.

After a month, the level of chloride salts in their sweat—a classic marker of cystic fibrosis severity—"were clearly moving into the healthy range," says Beekman. One of the patients showed huge improvements in their breathing, although the other, whose lungs were already severely damaged, did not. "We were probably a bit too late there," says Beekman. "But when we just asked the patients how they felt, they had more energy and they were doing better."

"The beauty of this model is that you don't really need to understand what the mutations do," says Beekman. CFTR mutations can cause problems in at least six different ways, from creating faulty chloride pumps, to not creating the pumps at all. Thanks to organoids, you don't need to know which of these faults is at play. You can skip straight to finding a solution.

"It's fantastic progress," says Jane Davies from Imperial College London, who works on treatments for cystic fibrosis. "What remains to be confirmed in the longer term is how predictive [the organoids are] for meaningful clinical outcomes."

Amy Firth from the University of Southern California added that it would be important

to test organoids built from the cells lining the lung, as these are the main site affected by mutations in CFTR. “Rectal cells, however, are a readily accessible source, which are readily expandable and efficient in organoid generation,” she adds.

There are other limitations. With a lab-grown blob of cells, “you can just drown them in drugs,” says Beekman. The organoids can’t tell you whether the drugs will actually reach the right tissue in real life, or how quickly they act. So Beekman now wants to tweak his team’s laboratory tests, so that the organoids’ responses best reflect what will happen in an actual body. He also wants to look at a wider range of mutations, and to work out why people with the same mutations often respond very differently to the same drug.

In the meantime, the 71 patients who took part in this study might benefit from it for years to come. Their cells have been frozen and stored in biobanks. Whenever a new drug is released, they can be thawed, grown into organoids, and tested again.