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Researchers grow brain parts to study development, disease

By: MALCOLM RITTER (AP)

NEW YORK (AP) — Dr. Sergiu Pasca, a neuroscientist, used to envy cancer specialists. They could get their hands on tumors for research, while Pasca could not directly study key portions of a living brain.

But these days, Pasca does the next best thing: He grows his own.

In his lab at Stanford University, thousands of whitish balls of human brain tissue float in hundreds of dishes. Each smaller than a pea, they were created from human skin cells, including some from people with autism. Each one carries the DNA of the person it came from, and each organized itself enough to form a part of the brain that interests Pasca.

He is hardly alone. Dozens of labs are growing lumps of human brain tissue for study, a practice that drew notice in 2013 when researchers said they had created "minibrains" that contained multiple major parts of the fetal organ.

Just to be clear: Although brain cells in the lab-grown tissues show some activity, nobody has created fully functioning, adult human brains. The versions reported in scientific journals mimic only one

or more parts of a fetal brain. (An August announcement of a nearly complete brain comparable to a fetal one hasn't been backed up by a journal article yet, and experts are withholding judgment until they can see the details).

Scientists say the technology holds great potential for studying the roots of diseases like autism and schizophrenia, testing possible treatments and tackling basic questions about evolution.

It's part of a larger movement over the past few years to create "organoids," miniature versions of the body's organs or key parts of organs. Goals include studying disease, testing possible treatments and perhaps supplying replacements for transplants. Scientists have made organoids representing the intestine, prostate, kidney, thyroid, retina and liver.

This overall organoid approach "is a major change in the paradigm in terms of doing research with human tissues rather than animal tissues that are substitutes. ... It's truly spectacular," says Arnold Kriegstein, who studies the brain at the University of California, San Francisco.

Organoids "are poised to make a major impact on the understanding of disease, and also human development," he says.

To grow lumps of brain tissue, researchers can call on a technique that helped earn the Nobel prize in medicine in 2012. Virtually all cells of a person's body contain the same lineup of DNA. A skin cell differs from a brain cell because of differences in what genes were turned on, and when, during development. The breakthrough lab technique provides a way to turn skin cells back into blank slates

called iPS cells, a form of stem cell.

These iPS cells can then be turned into any cell of the body, as they respond to nudges from chemical cues they are exposed to.

For years, scientists have used this approach to make brain cells and other cells that lie on the flat surfaces of lab dishes. The new wrinkle is to let the cells grow into three-dimensional clumps instead. They don't need much help to organize themselves.

"They start communicating and signaling with each other," Kriegstein said, specializing "in a way that starts looking like a developing human brain."

But the cells don't get cues from surrounding tissues that help an ordinary fetal brain organize itself, noted Madeline Lancaster of the Medical Research Council Laboratory of Molecular Biology in Cambridge, England. So while the 400 or so tiny "minibrains" floating in dishes at her lab contain many brain parts, she said, those parts are laid out in abnormal patterns.

"They are connecting to each other and the different regions do seem to talk to each other, but not in the way a normal brain would," she said.

Lancaster compares the patchwork layout to an airplane that has one wing on top, a propeller at the back, the cockpit on the bottom and a wheel hanging off the side. "It can't actually fly," she said. But "you can study each of the components individually and learn a lot about them."

A popular region to grow is the cerebral cortex, the wrinkly out layer of the brain that is key for sophisticated thought. The tiny balls of tissue in Pasca's lab were designed to mimic this region because of hints that it's important in development of autism and schizophrenia.

While the effort to learn about disease with the technology is still quite new, some early hints are emerging. Dr. Flora Vaccarino of Yale University grew lumps containing cerebral cortex that were made with DNA from people with autism. She found that a particular kind of brain cell is overproduced, and linked that to overactivity of a particular gene. Vaccarino cautions that she's not claiming this is what causes autism, but Lancaster calls it "really very exciting."

Lancaster studies a rare and devastating disorder in which people are born with small brains because they have too few brain cells called neurons. Her work showed that "minibrains" made with DNA from patients also turned out to be unusually small, and suggested why: The precursor cells that make neurons go to work too early, so they peter out over time and can't fulfill their quota.

That disease, called microcephaly, is a good example of why growing brain tissue can be a better way to study some conditions than studying mouse brains. The genetic mutations that cause the disease in people have little effect when created in mice. The biology of other diseases, like autism and schizophrenia, may also be better mimicked in lab-grown human tissue, experts said.

And even if a disease can be reproduced in mice, their brains are different enough from ours that a treatment that looks good in the

rodent may not work for people, Kriegstein said.

Still, he and others said, the technique probably won't replace mice completely in the lab. Mouse experiments are quicker and cheaper, he said.

Kriegstein also said it's not clear what the lab-grown brain tissue can reveal about illnesses that appear late in life, like Alzheimer's, because it models the fetal brain rather than the aging one. Lancaster said she believes it's still worth a try.

Diseases aren't the only focus. Lancaster and Alysson Muotri of the University of San Diego, California, are tackling the evolutionary question of how our brains develop differently from those of other animals. So far, lumps of brain made with chimp DNA look a lot like their human counterparts at early stages of development, Muotri said.

Lab-grown brain lumps are limited in their growth and development because they lack a blood supply. That brake on maturation helps keep them in a relatively primitive state, which means they are far from posing any ethical questions, researchers say.

"I don't see any philosophical problem yet," Muotri said. But "I don't know what the future holds for us. We may be able one day to recreate the entire brain ... and somehow put memories in there and let those minibrains think. I don't know if that will ever be possible, but it is an interesting possibility."

Hank Greely, who directs the Center for Law and Biosciences at Stanford, says the biggest issue would arise if scientists produce a

brain organoid that could attain something like human consciousness. That's quite unlikely in today's tiny versions, but might be possible down the road, he said.

Kriegstein agreed.

"No one would have thought 10 years ago we'd be able to do what we do now," he said. "Another 10 or 20 years down the road, I have no idea how far along we will be."

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