7 Mini-Brains Make New Waves

BY TEAL BURRELL

Clumps of brain cells that are alive and practically kicking — that's what scientists created when they tweaked a method for growing brain tissue in a dish. Meanwhile, another team used a different approach to produce brain waves in similar lab-grown mini-organs.

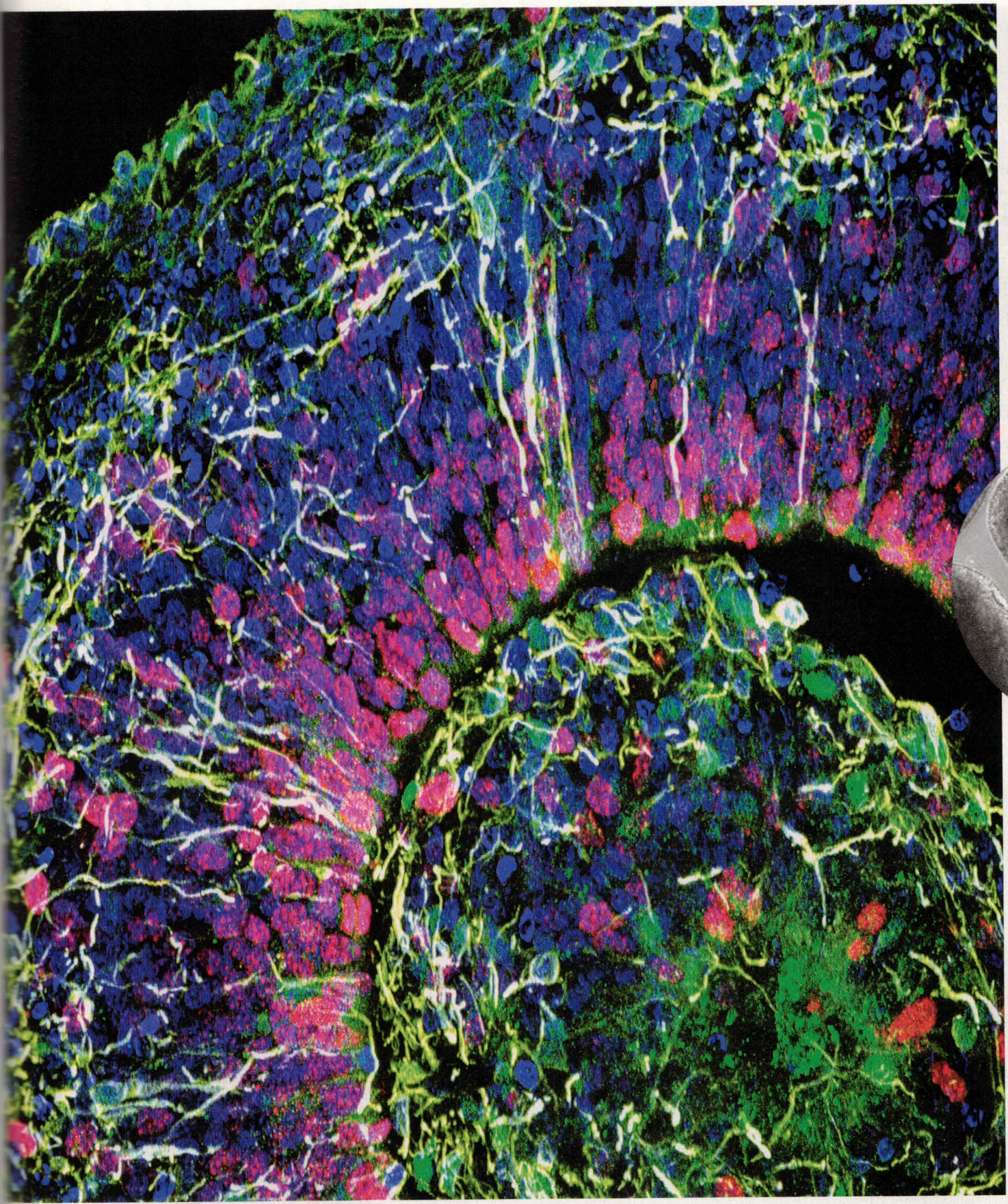
The two papers, published in March in *Nature Neuroscience* and August in *Cell Stem Cell*, modified existing techniques for growing cultures called brain organoids. In organoids, human stem cells are first coaxed into becoming brain cells, which then organize themselves into a three-dimensional structure similar to a developing brain.

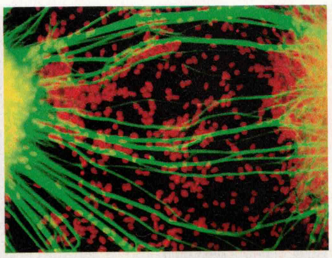
Until now, one limitation of organoids was a lack of blood vessels. This meant cells in the middle of the pencil-eraser-sized blob died without access to oxygen and nutrients.

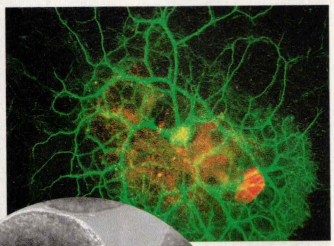
But Madeline Lancaster, a developmental biologist at Cambridge University's Medical Research Council Laboratory of Molecular Biology, and the *Nature Neuroscience* paper's senior author, had an idea: "Why don't we just cut them open?" By making thin slices separated by a membrane, the entire organoid could be exposed to oxygen and nutrients. "Developing brain tissue is quite happy like that," she says.

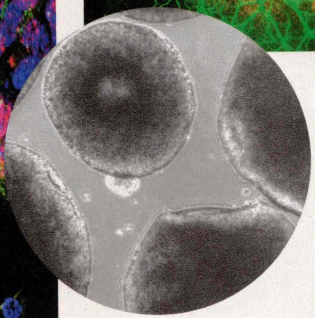
The cells not only stayed alive and healthy, they also formed neural circuits like they would in a developing embryo. Two weeks after the spinal cord and adjoining muscles of a mouse embryo were placed alongside the organoid, the muscles started moving, indicating functional connections grew between the organoid and spinal cord. Lancaster jumped when she first saw the movement. "The individual muscle units have to contract in a coordinated fashion in order for the whole muscle to move," says Lancaster. "To see that actually happening in a dish, that blew me away."

The scientists behind the *Cell Stem Cell* paper took a different route: They spent four years optimizing the concentration and administration of proteins that would help the brain cells grow. Then they grew the organoids on top of electrodes, hoping the









False-color images of brain organoids allow researchers to color code different cells and map their activity (left and top two images). In reality, the organoids are pale and pea-sized (above).

MUOTRI LAB/UC SAN DIEGO (4)

perfected protocol would allow neurons to form networks with detectable electrical activity, like real brains.

After four months of effort, that electrical activity began to increase exponentially. By nine months, it was 100,000 times higher than anything ever recorded outside the body. Next, the team compared the patterns and complexity of the activity with data collected from age-matched preterm babies. By 25 weeks, a computer program struggled to distinguish the organoids' data from the babies' brain waves.

Alysson Muotri, a biologist at University of California, San Diego, and senior author of the paper, was surprised organoids produced complex brain waves without a complete brain or input from the body. It's as if they follow a script. "These early stages of human development are totally genetically encoded," he says. "The brain knows what to do and the information is inside the cells."

Both groups see their new techniques as helpful lab tools to investigate diseases and treatments. Lancaster has her eye on conditions where connections are disrupted, such as spinal cord injury and amyotrophic lateral sclerosis, while Muotri wants to make organoids from the cells of people with epilepsy or autism spectrum disorder to study their altered brain waves.

Now that the lab-grown neurons remain healthier for longer, Lancaster also hopes to examine later stages of brain development. Meanwhile, Muotri is already considering other tweaks. Asked if they can come closer to modeling a real brain in a dish, he says, "If you asked me five years ago, I would say it's impossible. And now I would say it's inevitable."