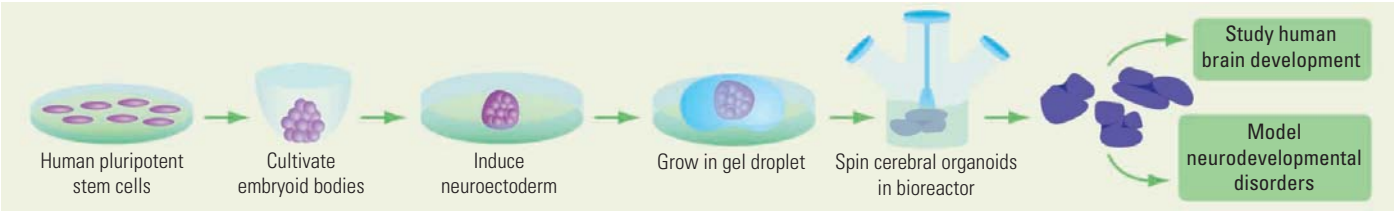

Brain gain. The differentiation process from pluripotent cells to organoid takes about 3 weeks.

example, the scientists used the structures to study microcephaly, a neurodevelopmental disorder in which the head and brain end up much smaller than normal. Rather than starting with ES cells, they took cells from a person with a particular form of the disorder and "reprogrammed" them into so-called induced pluripotent stem (iPS) cells. Mice are a poor model for that form of microcephaly; the specific genetic mutation responsible results in mice with brains that are only slightly smaller than normal. In contrast, organoids derived from the patient's iPS cells were shrunken, and Knoblich's team found a clue to why. Certain precursor cells were maturing earlier than normal, bringing tissue growth to a halt prematurely.

The organoids are probably not yet useful for studying more complex neurodevelopmental conditions such as autism or schizophrenia, because those conditions involve more mature cells and complex cell connections. Lancaster and Knoblich also note that each organoid develops distinctively, resulting in significant differences in composition and structure that make it hard to do controlled experiments.

The researchers are working on ways to grow more consistent organoids—and to incorporate some sort of vascular system so that the cell clusters can grow bigger and presumably develop further. They hope that additional teams will take up and improve the method. Götz and others says they plan to do just that. "For studying the cerebral cortex, this is the best model so far," she says. "People will use it, and time will tell how useful it is."

–GRETCHEN VOGEL

CELL BIOLOGY

NIH Effort Gambles on Mysterious Extracellular RNAs

The versatility of RNA is legendary. Inside the cell it transfers genetic information, acts as an enzyme, and regulates genes. In plants and nematodes, short RNA sequences also act like hormones, carrying messages between cells. Now, a $17 million program of research grants, announced this month by the U.S. National Institutes of Health (NIH), aims to determine whether extracellular RNA (exRNA) has a similar communication role in people—and whether it can be harnessed for diagnosis and treatment of human diseases.

"This is an effort to get a new field going," says Christopher Austin, director of the National Center for Advancing Translational Sciences (NCATS), one of the five NIH centers and institutes participating in the 5-year exRNA initiative.

> ***"This is an effort to get a new field going."***
>
> **—CHRISTOPHER AUSTIN, NCATS**

Conventional wisdom long held that the different varieties of RNA molecules toil mainly within the cells that make them. For more than a decade, however, researchers have seen signs that cells emit RNA molecules that travel throughout an organism and alter the activity of target cells. So far, says molecular biologist John Mattick of the Garvan Institute of Medical Research in Sydney, Australia, scientists have accrued "unassailable" evidence that plant and nematode cells communicate through exRNA.

In humans and other mammals, exRNAs abound in blood, tears, saliva, and every other body fluid. Among the molecules wending through our bodies are messenger RNAs that carry the instructions for making proteins and microRNAs that fine-tune gene activity. The extruded RNA is typically enclosed in membrane-bound capsules such as exosomes (*Science*, 24 June 2005, p. 1862) or accompanied by protein or lipid bodyguards, which protect it from RNA-destroying enzymes.

But definitive data that such exRNAs influence recipient cells have been missing for mammals. "It hasn't been convincingly shown that a small RNA can be active when it enters a different cell," says molecular biologist Michael McManus of the University of California, San Francisco.

Many of the 24 newly funded projects are probing practical uses for exRNA. Some researchers will assess whether exRNAs can serve as biomarkers—molecular indicators that help doctors diagnose illnesses or identify which people are susceptible. A group led by cardiologist Jane Freedman of the University of Massachusetts Medical School in Worcester, for instance, will sift blood samples from nearly 3000 participants in the famous Framingham Heart Study in hopes of learning whether certain exRNAs foretell cardiovascular disease. Even if they are just junk spit out by cells, the molecules may have some diagnostic value.

Other projects will investigate whether exRNA can be harnessed to fight diseases such as cancer, Huntington's disease, and multiple sclerosis. For example, cancer biologists Thomas Schmittgen and Mitch Phelps, of Ohio State University, Columbus, are working to engineer cells to manufacture exosomes that home in on the liver and deliver a specific microRNA that stymies the growth of tumor cells.

McManus is teaming up with plant biologist Olivier Voinnet of the Swiss Federal Institute of Technology in Zurich and colleagues to try to settle the question of whether exRNAs have a biological role in mammals. Voinnet was one of the first researchers to uncover evidence for exRNA signaling in plants more than 15 years ago. No one has so far presented comparable data for humans, he says, but he and his colleagues are willing to be convinced that we use this RNA communication channel. "We are 'positively skeptical' about the whole issue," Voinnet says.

–MITCH LESLIE

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