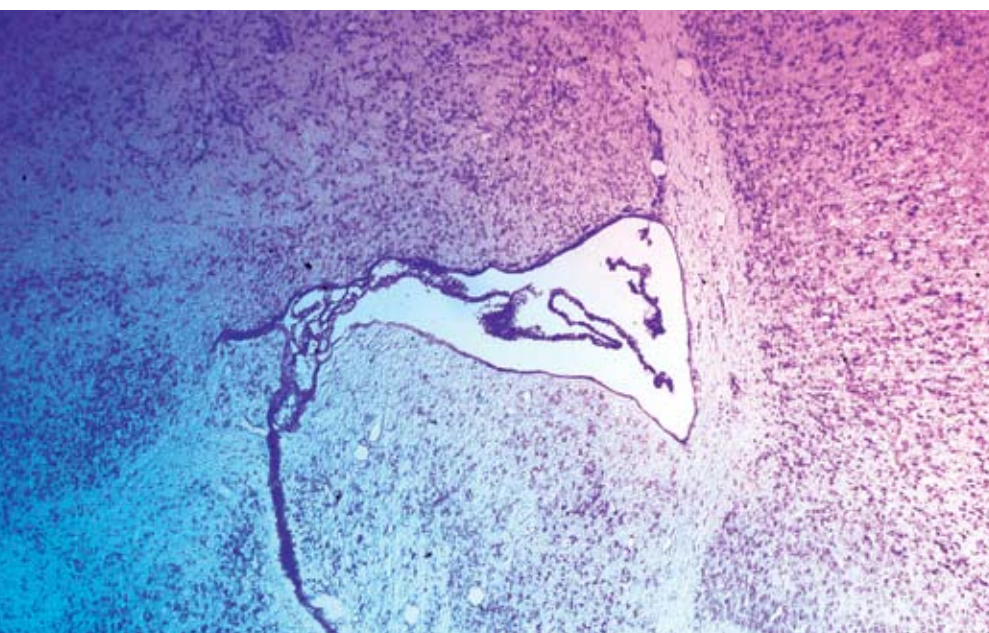
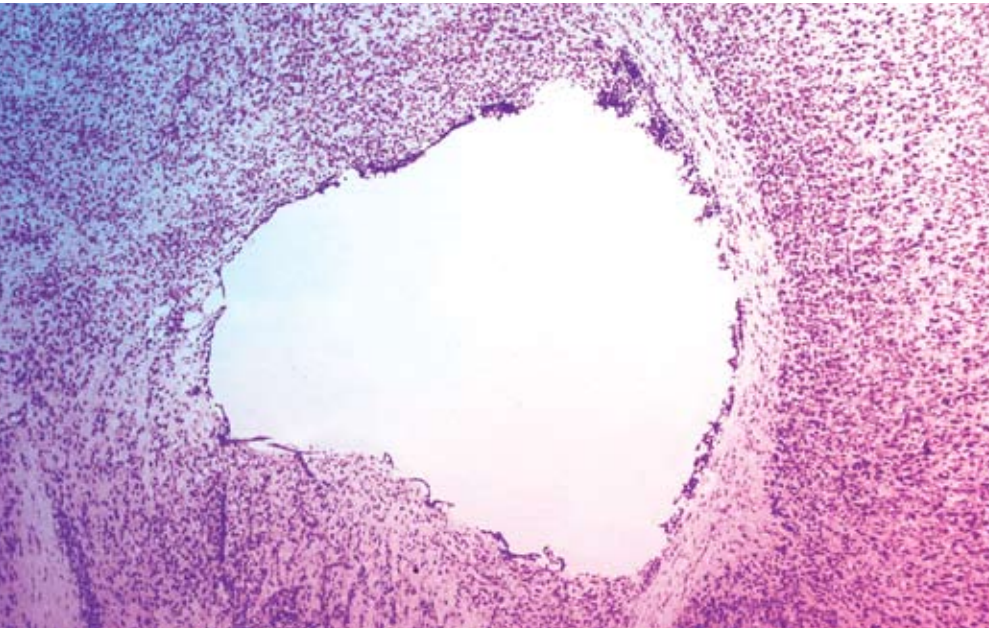


Big Lessons from Small Brains

If a mouse brain can self-repair under certain conditions, can a new stem-cell approach for diseases such as Alzheimer's be far behind?



Top: Stained slice from the brain of a 2-week-old mutant mouse showing a dramatically enlarged lateral ventricle, due to deletions of Numb and Numbl like. **Bottom:** Another mutant mouse, 6 weeks old, reveals substantial self-repair of the lateral ventricle, which is now close to normal size.

AGAINST ALL ODDS, THE FURRY black mouse pup, No. 4302, scurried around its cage. The mouse and its siblings were born with an abnormally large cavity in the brain as a result of a genetic experiment in the joint neuroscience laboratory of Yuh Nung Jan and Lily Y. Jan.

Postdoctoral researcher Chay Kuo had low expectations for the animals' survival, but when he noticed that 4302 was still alive at 4 weeks of age, he investigated further. Kuo made the startling discovery that the neural damage had healed, implying that "the brain has an innate ability to repair that defect," he says.

More specifically, with the help of their collaborators, Kuo and the Jans, both HHMI investigators at the University of California, San Francisco, found that adult stem cells in the brain had responded to the damage by helping to regenerate much of the missing tissue. This finding raises the hope that, if a similar healing mechanism exists in humans, physicians may one day be able to rev it up to treat people with brain disorders such as head trauma, stroke, and neurodegenerative diseases.

The research team's results, reported in the December 15, 2006, issue of *Cell*, are rooted in years of research on the fruit fly, beginning in 1989 when the Jan lab identified a strain of flies without sensory neurons.

These insects lack a gene, called *Numb*, that instructs a progenitor cell to divide and produce a variety of specialized sensory cells such as a neuron and a body-hair cell.

In recent years, the Jan group decided to see whether *Numb* also plays a role in the development of the mammalian brain, particularly in a special niche known to house neural progenitors—stem cells—during embryo growth, after birth, and even into adulthood. This stem cell niche borders a fluid-filled gap called the lateral ventricle and matures into the subventricular zone (SVZ). The biologists identified two equivalent genes, *Numb* and *Numblake*, in mice, and showed in 2002 and 2003 that selectively deleting, or “knocking out,” the pair from the stem cell niche during embryo development caused “a very messed up” brain cortex, says Yuh Nung Jan. Mouse embryos with the mutation had lateral ventricles that were larger than normal.

Kuo joined the Jan lab in the fall of 2002. A newly minted M.D.-Ph.D. from the University of Chicago, he was eager to explore how the brain responds to changes from injury or disease. He particularly wanted to see whether turning off *Numb* and *Numblake* after birth—after the mouse brain has fully formed—might affect subsequent production of neural stem cells. Kuo’s work was largely funded with an HHMI postdoctoral fellowship, along with a grant from the California Institute for Regenerative Medicine.

He set out to create a strain of mice in which he could control *when* the genes were inactivated in the SVZ’s stem cells. After 3 years’ work, Kuo bred the colony that made possible the experiments that led to the brain-repair discovery.

Sitting at his office computer, Yuh Nung Jan pulls up slides of magnified purple-stained slices of mouse brain from Kuo’s mutants. One image, from a 2-week-old pup, shows a triangular hole—a grossly enlarged lateral ventricle. But in another slide, from

a 6-week-old, the gap has shrunk to near normal. Moreover, these mutants, which start out smaller than control mice, catch up in growth and seem to be just fine.

Numb and *Numblake* do more than control neural stem-cell specialization, Jan says. The mouse analyses indicate that these genes also act to maintain junctions between epithelial cells that line the ventricle wall. In mutants without the genes, he says, “the wall sort of disintegrates.”

Then, because some SVZ stem cells escape the gene knockout treatment, says Kuo, those cells are able to trigger the

rebuilding of the wall—although it is not the same as the original—and save the animals.

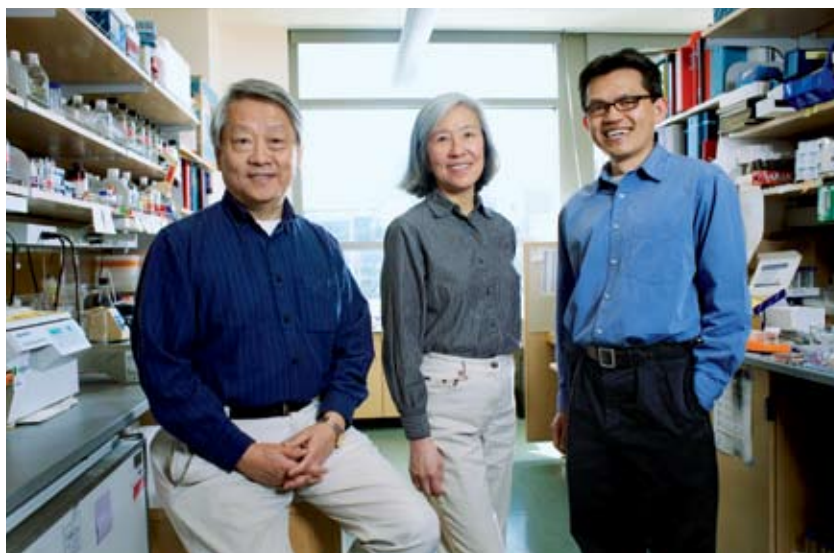
The investigators are now exploring the cellular underpinnings of the lateral-ventricle repair; they are also studying the same stem cells in a mouse model of brain injury. Their aim is to provide an alternative to the scientific community’s current attempts to coax blank-slate embryonic stem cells in the Petri dish to grow into neurons for treatment of conditions like Alzheimer’s disease.

The Jan lab’s work suggests a more direct route: If scientists understood the mechanisms that prompt the body’s existing stem cells to regenerate specific tissue, they might be able to design drugs that enhance that process. “We may be able to coach these cells to do a better job of repairing,” says Kuo.

■ -INGFEI CHEN

“We may be able to coach [these cells] to do a better job of repairing. ”

CHAY KUO



Yuh Nung Jan, Lily Jan, and postdoc Chay Kuo hope that a tissue repair mechanism they found in mice exists in humans.