How brain cells make up their minds

Only 1 out of every 10 brain cells is a neuron, the star of the brain. Cells known as glia make up the rest of the ensemble. Granted, glia are important. They guide young neurons into making proper connections. They nourish neurons, insulate them, clean up after them, and may even chat with them. But clearly, glia form the supporting cast for neurons.

Two research groups, working independently, have now found a genetic switch that determines whether immature brain cells in fruit flies go on to fame as neurons or accept more mundane roles as glia. Both groups have found a gene, called *glial cells missing,* or *gcm*, that turns on briefly in most of the developing nerve cells that become glia. If the researchers force *gcm* to turn on in immature cells that would normally become neurons, those cells change their minds and become glia.

Both groups tracked down the gene by identifying mutations that generated fruit flies with aberrant central and peripheral nervous systems. "The nervous system was perturbed because almost all the glia were missing," says Corey S. Goodman, a Howard Hughes Medical Institute investigator at the University of California, Berkeley. Goodman's group and a second group, headed by Yoshiki Hotta of the University of Tokyo, discuss the new gene in the Sept. 22 CELL.

Goodman and his colleagues believe that the protein encoded by *gcm* turns on other genes that help shape an immature brain cell into a glial cell. They plan to look for those genes. Though vertebrate glia perform duties that insect glia do not, investigators will probably find a similar genetic switch in developing human brain cells, says David J. Anderson of the California Institute of Technology in Pasadena.

Gene therapy's ups . . .

The recent roller-coaster ride of gene therapy's fortunes continues, with peaks and valleys occurring almost monthly. In September, two studies reporting failures in treating cystic fibrosis and muscular dystrophy unleashed a torrent of media hand wringing over the future of the technique. The pendulum swung back this month with the publication of three studies that demonstrate success in treating an immune disorder—though how much success is unclear.

The apparent good news comes from three efforts designed to help people with an inherited genetic defect that prevents them from making an enzyme called ADA. This usually fatal enzyme deficiency poisons the body's T cells, the specialized cells in the blood that mobilize part of the immune system's protective response against infection.

In 1990, in the first gene therapy experiment ever attempted in humans, researchers began treating two ADA-deficient girls. First, the investigators removed some of the girls' T cells and grew them in the laboratory. Then, they added working versions of the ADA gene into this population of T cells and began regular infusions of the altered immune cells back into the children. Both girls today appear healthy, have immune cells that make ADA, and possess functioning immune systems, report R. Michael Blaese of the National Institutes of Health's National Center for Human Genome Research in Bethesda, Md., and his colleagues in the Oct. 20 SCIENCE.

In the same issue, a collaboration of three research groups from Italy details a similar success story in two other children. In addition to injecting relatively short-lived T cells into their patients, the Italian group injected ADA-engineered bone marrow cells. Marrow cells can provide a permanent supply of ADA-making immune cells.

In a third report, detailed in the October NATURE MEDICINE, Blaese and his colleagues discuss another strategy. They identified three fetuses that had inherited broken ADA genes. When the babies were delivered, the investigators obtained stem cells, similar to bone marrow cells, from blood in the umbilical cords. They added functional ADA genes to those cells and injected them into the babies 4 days after birth. The babies appear to have a permanent population of normal immune cells.

In all three efforts to cure ADA deficiency, the children treated now seem healthy. The effectiveness of the gene therapy remains open to question, however. That's largely because the patients also received regular injections of the ADA enzyme itself. Withholding that proven treatment would have been unethical, but the enzyme injections cloud any assessment of the gene therapy's impact, explain investigators.

"They're probably getting biological changes that help the patients, but you can't prove it, " says Ronald G. Crystal of the New York Hospital–Cornell Medical Center in New York City.

. . . and downs

A few years ago, investigators found the broken gene that causes cystic fibrosis, the fatal disease that has since attracted the interest of many in the gene therapy field. By introducing working copies of the cystic fibrosis gene into the lungs of patients, physicians hoped to correct the mutation and prevent the mucus secretions that lead to infections in the lungs. According to animal studies and test-tube experiments with human cells, the most promising delivery vehicle for those genes was an adenovirus, a virus that infects lung cells.

In the most thorough test of this strategy in humans so far, however, investigators have found that adenoviruses are extremely inefficient at shuttling the cystic fibrosis gene into nasal cells with characteristics similar to those of lung cells. The viruses successfully delivered their cargo to less than 1 percent of nasal cells, report Michael R. Knowles of the University of North Carolina at Chapel Hill and his colleagues in the Sept. 28 NEW ENGLAND JOURNAL OF MEDICINE. Higher doses of the adenovirus did not help: They simply irritated the patients' noses, the researchers note.

Gene therapy researchers argue that they are constantly developing better gene-carrying viruses and should be able to overcome these problems. "It's important to remember that gene therapy is truly in its infancy and that the current tools are quite crude," Jeffrey M. Leiden of the University of Chicago wrote in an accompanying commentary.

That same issue of the journal contained more bad news on gene therapy. Genetically engineered muscle cells injected once a month for 6 months into the biceps of 12 boys with Duchenne muscular dystrophy did not restore any of the strength stolen by the disease, report investigators from Ohio State University in Columbus and the North East Wales Institute in Clywd. Researchers had hoped that by injecting the gene for a skeletal muscle protein called dystrophin into the boys' muscle cells, they could make up for the genetic defect that robs Duchenne patients of this protein.

The mixed results presented in the last 2 months are neither surprising nor discouraging for a field that is barely 5 years old, concludes Ronald G. Crystal of the New York Hospital–Cornell Medical Center in New York City. Investigators have shown that they can insert genes into humans, though inconsistently, and that those genes can function, he says. Studies such as the ADA experiments show conclusively that gene therapy can provoke in the body biological responses appropriate to the disease targeted. But Crystal acknowledges that no one has unarguably cured a disease yet.

"Gene therapy is based on solid science. And gene therapy is going to work. And it is going to revolutionize how we treat patients. When that will occur and in what form it will occur we don't know," says Crystal.

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