

A Solution in Sight

Keeping the retina's cone photoreceptors from self-destructing may rely on the neighboring rod photoreceptors. Gene therapy may offer the ultimate remedy.

CONSTANCE CEPKO REMEMBERS THE DAY SHE READ THAT A BRIARD sheep dog had been cured of blindness by gene therapy. The dog, called Lancelot, stopped cowering in corners and acquired the elegant, floating gait of his breed. ¶ It was 2001 and, soon after, Cepko was approached by a family whose son had been born blind. They wanted to fund her research on the retina. “They said, ‘You do basic science; is there anything that someone like you could do to help?’” she recalls.

“It becomes more personal when somebody asks you, ‘What can you do to help children like our son?’”

Cepko, an HHMI investigator, had a head start. The boy’s disorder lay in a spectrum of diseases marked by progressive loss of vision, and some of these diseases were caused by mutations in genes Cepko had been studying in her Harvard Medical School lab. She decided to focus on retinitis pigmentosa, a progressive disease caused by many mutations affecting at least 36 genes. Her group has now discovered that delivering a single gene called *HDAC4* into the retina can save the vision of mice with the disease.

The central portion of the human retina is packed tightly with cells—called cone photoreceptors—which are used for color and high-acuity vision. The periphery of the retina has mostly rod photoreceptors,

which are used primarily to sense dim light at night. In retinitis pigmentosa, the rods die due to genetic defects, causing a loss of night and peripheral vision. Early in the disease, people can still read and recognize faces, but many lose even those abilities as they age because their cones eventually die. In hopes of solving the problem with gene therapy, Cepko wanted to know what was killing the cones.

So Cepko and Claudio Punzo, a post-doctoral fellow in her lab, compared four mouse models of retinitis pigmentosa in

which vision loss occurs at different ages, from three weeks to about 18 months. For each mouse strain, Punzo determined when cones began to die, monitored changes in gene expression, and looked for similarities.

In all four models, as the cones began to die Punzo noted changes in a regulatory switch that senses the availability of nutrients. If nutrient levels drop very low, the switch tells the cell to start digesting itself—a little like burning banisters to heat a house.

The layers of rods and cones normally stay in intimate contact with each other. When the rods die, the cones may lose the connections through which they get food, Punzo and Cepko hypothesize. Or the cones may feel extra pressure from neighboring layers of cells and expend energy to maintain their structures. “Imagine 29



“It becomes more personal when somebody asks you, ‘What can you do to help children like our son?’”

CONSTANCE CEPKO

friends standing around you, holding up a circus tent, and next thing you know they're all gone and you're holding up the tent by yourself," Cepko says. The scientists published their findings in the January 2009 issue of *Nature Neuroscience*.

As Punzo digs deeper into why the cones die, other lab members have been looking for ways to keep the rods alive as well—even nonfunctioning rods might help prevent the death of the cones.

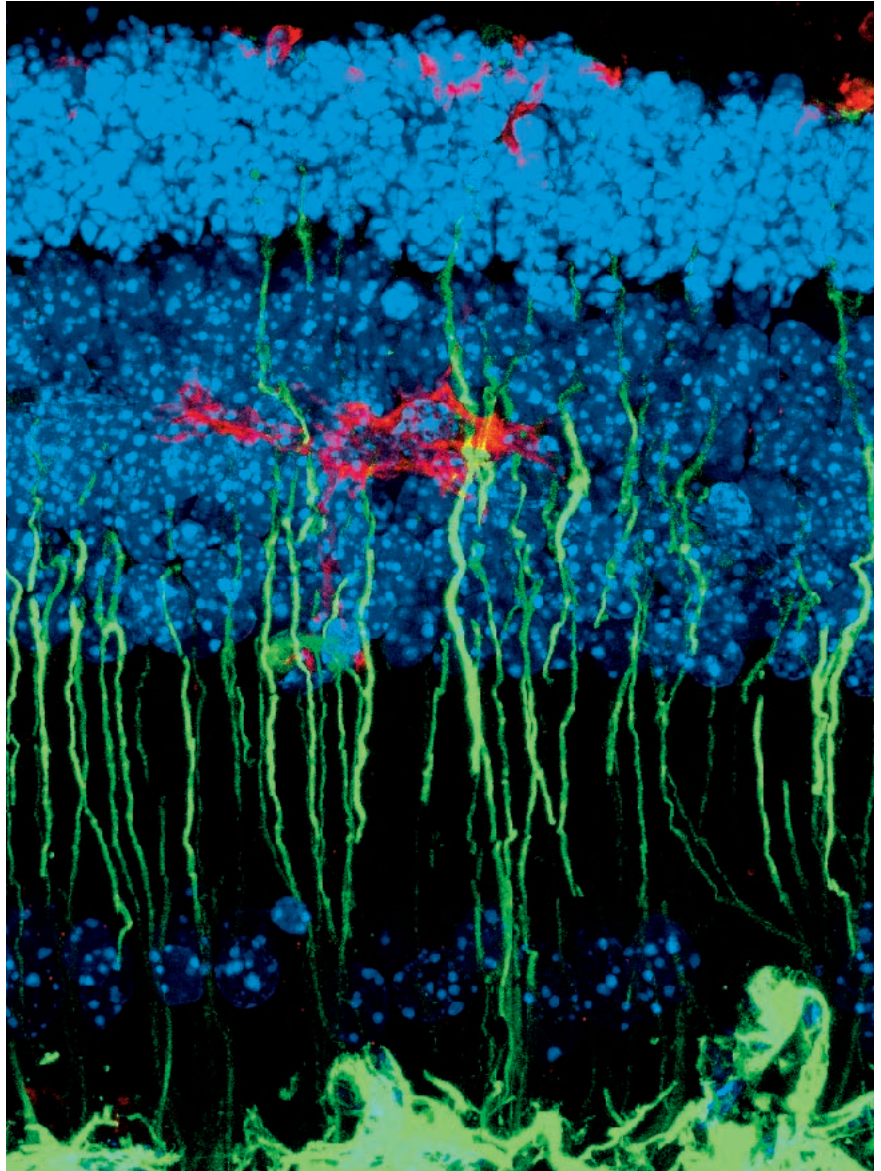
Bo Chen, another postdoctoral fellow, found a potential way to save the rods. Chen found that rods require *HDAC4* to survive during development, so he and Cepko decided to try delivering extra *HDAC4* to the retinas of mice with retinitis pigmentosa. The strain they studied typically loses all rods about three weeks after birth and their cones over the next few months. Using a method previously developed in the lab, Chen deposited *HDAC4* DNA behind the retinas of unconscious mice using a needle a little wider than a hair. He then applied an electric current to enable the DNA to enter the retina. More than two months later, the mice still

retained many of their rods and cones. The results appear in the January 9, 2009, issue of *Science*.

The method Chen used probably would not work on humans—the electric charge might damage parts of the eye. So, he and Cepko are employing the approach used to restore Lancelot's vision: using a harmless virus to deliver the gene to the retina. Eight years after his surgery, the dog can still see. "By just good luck, the virus is still there," Cepko says.

The team packages the *HDAC4* DNA with the virus and delivers it behind the retinas of mice with retinitis pigmentosa; the virus enters the cells on its own.

Cepko is heartened by the work of researchers at the University of Pennsylvania School of Medicine. A year ago, they gave patients with the same genetic defect as Lancelot's—a mutation that causes Leber congenital amaurosis—the therapy that helped the dog. For some of these patients, vision has improved. ■ —OLGA KUCHMENT



Constance Cepko is searching for a way to keep retinal cells alive in patients with a genetic disease that kills off cells important to vision. This cross-section of diseased retina tissue shows supportive cells (green), called Müller glia, and macrophages (red) migrating into the retina (all cells in blue) to remove dying rods.