

# Special Delivery

## destination: the brain

For children with Canavan disease, life may depend on a virus whose payload replaces a mutated gene.

By Anton Zuiker



Michelle Swancey

Lana Swancey with her big brother, Coty.  
Background: an electron micrograph of the AAV virus.

Seven children, a fifty-minute drip, and a thimbleful of genetic elixir: such are the elements of a gene therapy trial that could lead to longer lives for children with the rare Canavan disease.

It all hinges on the work of Jude Samulski, a Carolina scientist who has over the last twenty years tailored a virus that swiftly but harmlessly sneaks into human cells and becomes one with DNA. His lab has fine-tuned adeno-associated virus (AAV) to be a “viral vector,” a minute delivery vehicle that will swap good genes for bad. Conceivably, this gene therapy can allow the body to stop and even reverse the effects of diseases such

as muscular dystrophy, epilepsy, and the neurodegenerative Canavan disease.

Samulski has devoted his career to mastering AAV. (*See Endeavors, Fall 1998.*) With a current Canavan gene therapy trial and one for muscular dystrophy on the way, his commitment to AAV is paying off: labs around the world now use Samulski’s viral vector.

Adeno-associated virus is a non-pathogenic parvovirus discovered as a contaminant in laboratory stocks of adenovirus, itself a candidate for use as a gene therapy viral vector. Because it can’t replicate without genes from “helper” viruses, and because it’s partial to a specific place in human

chromosomes, AAV seems heaven-sent to be a viral vector.

And that’s what the parents of those seven children prayed for this summer.

### Canavan disease

Before Lana Swancey was born, an amniocentesis showed no problems, says her mother, Michelle. And for the first two months little Lana seemed perfect. But then Michelle noticed the baby’s eyes wandering, her arms stiffening, and her head control waning. It took three months for doctors in South Carolina and at Duke University Medical Center to diagnose Canavan dis-

ease, a rare genetic disorder most common to Ashkenazi Jews. Fewer than a thousand children in the U.S. have this disorder, and Canavan disease will likely kill them within a few years of their birth. These children have a mutated gene that prohibits their brains from producing enough of the enzyme aspartoacylase (ASPA).

In healthy brains, ASPA converts n-acetyl-aspartate (NAA) into two other chemicals. Without the regulation of ASPA, NAA accumulates in the central nervous system and begins to corrode the myelin coating of neurons. With neurons increasingly unable to communicate, the brain deteriorates. Canavan children lose their sight and cannot crawl or hold up their heads.

Lana's doctors didn't know much about the disease, Swancey says, and they didn't offer much hope to the family. But a dogged determination to "go chasing moonbeams" led her to Paola Leone, an expert in gene transfer therapy.

Leone is principal investigator for a phase-one safety study testing whether some of Samulski's adeno-associated virus, prepackaged with flawless ASPA genes, can actually reverse the damage to Canavan brains by replacing the flawed genes. It's the only current study using gene therapy in the brain, says Leone, associate professor of molecular genetics at the Robert Wood Johnson Medical School in New Jersey. (In 1998, when Leone worked at Yale University, she and her colleague Matthew During pioneered brain gene therapy, with a test in New Zealand that used a lipid, a type of protein, as a vector to fight Canavan disease.)

In April, a day before Lana Swancey's second birthday, Leone's team of neurosurgeons inserted six fine catheters into the child's brain and in less than an hour carefully pumped 210 microliters of solution bearing about 900 billion genomic particles into specific areas of the brain chosen with minute care. A couple of days later, Lana Swancey left the hospital.

The replacement gene held by the AAV vector—all those billions of genomic particles—melds into the genetic code of neurons within days, Leone says, and will stay with the cells to regulate the conversion of NAA.

"The idea is that gene therapy is forever," Leone says.

By June, Michelle Swancey had noticed a change for the better in Lana. She's much more alert, and much more aware. When Michelle raises Lana's arms up over her head, the child smiles. Before, she screamed in pain. Michelle and her husband, Gary, are filled with hope that these improvements will last.

"Knowing we're not going to bury her—that she'll live past three—is wonderful," Michelle says.

### A viral vector

Leone had turned to Samulski and his team, including Angelique Camp and Scott McPhee, to produce clinical-grade AAV vector for her study. Other academic labs weren't as qualified, she says, and biotech companies would have taken many months longer to produce the billions of virus particles necessary for the small study.

Samulski's lab regularly sends vials of AAV vector to labs in the United States, Australia, Germany, Japan, and other countries. Each package includes a single piece of paper

"The idea is that gene therapy is forever."

vouching for the quality of the material.

The hitch, though, was that while Samulski's lab could produce "research-grade" viral vector easily enough, he needed to methodically produce reams of paperwork to document the production of the same material as "clinical-grade" vector. The difference: \$2,000 for research-grade, \$200,000 for clinical-grade.

No companies are able to provide AAV production as a commercial service, Samulski says. "That's not what universities do for a living, but this is what's required to move this type of technology into the clinic." So the UNC-Chapel Hill Gene Therapy Center and its Human Applications Lab stepped up. And that service was superb, Leone says.

"Jude has the potential, with his knowledge and competence, to create the national gene therapy center," she says. And that's right along the lines of what Samulski seems to want.

"We built this facility specifically to take these rare genetic disorders into the clinic, with the hope that we could complete the loop," Samulski says. He's confident that the Canavan trial will announce to the world that Carolina has a part to play in the development of gene therapy.

Other clinical groups that want to test novel vector technologies, he says, might turn to the Carolina center. Samulski wants to eventually apply to the National Institutes of Health to become a "national vector lab" to make clinical grade adeno-associated viral vectors. (Two such labs exist, at Indiana and Baylor universities, specializing in retroviral and adenoviral vectors, respectively.)

Providing a destination for scientists from institutions with gene therapy trials to prove is satisfying, Carolina researchers say. But they also recognize a greater opportunity.

"The net of it is, we have a good collaborative arrangement here, but we'd like to move to the next level," says Thomas J. McCown, research associate professor of psychiatry.

Last month, McCown published in *Nature Medicine* the results of a study that, he says, is the first successful gene therapy treatment for any basic seizure model in animals. He's using the AAV vector to produce and secrete neuroactive peptides, chemicals that are very effective at blocking seizures.

Epilepsy and seizures affect some 2.5 million Americans—dramatically more than the thousand with Canavan disease. Until the university is able to recruit a clinician to move to UNC-Chapel Hill, any human testing of McCown's seizure therapy must be done elsewhere.

"It's a shame you develop something here and have to hand it off to someone else in another clinic," McCown says.

There's a distinct advantage, say both Samulski and McCown, to being able to sit down with clinician colleagues rather than scrambling to arrange a conference call with distant collaborators or waiting months to years to read about trial results in the scientific journals.

Still, they'll be closely watching Paola Leone's Canavan gene therapy trial. The more smiles it puts on the faces of the parents of those seven children, the more smiles there will be around the Human Applications Lab, where the researchers are already busy planning the next step toward successful gene therapies. **e**