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Genetic Therapy Reverses Nervous System Damage

By Greg Lester

By injecting a therapeutic gene directly into the brain, researchers have treated a naturally occurring genetic disease in cats. This is the first genetic disease affecting the central nervous system to be successfully treated in an animal larger than mice and rats. If this approach can be applied successfully to humans, say the researchers, it might one day treat an entire class of diseases called lysosomal storage disorders, which cause severe, sometimes fatal, disabilities in about one in 5,000 births. The members of the research team from the University of Pennsylvania School of Veterinary Medicine, the Children's Hospital of Philadelphia, and the U.S. Naval Academy published their findings in the March 2005 *Annals of Neurology*.

The animals involved in the study are born with a genetic disorder directly analogous to alpha-mannosidosis, or AMD, an inherited disease in humans that causes severe mental retardation and skeletal abnormalities. Cats with AMD do not live more than six months. Children born with the worst form of the disease rarely survive into their teens.

"Through gene therapy, we replace a 'broken' gene responsible for alpha-mannosidase with the correct, functioning copy, to dramatic results," said **John H. Wolfe**, professor of pathology and medical genetics at the School of Veterinary Medicine and a neurology researcher at Children's Hospital. "The treated cats were markedly improved compared to diseased cats, with better balance and muscle control and fewer tremors."

Although the disease itself is rare, AMD is one of about 50 lysosomal storage diseases, a class of diseases that accounts for a significant portion of the instances of mental retardation in children. Other examples include Tay-Sachs disease, Hunter disease, and Pompe disease. In a lysosomal storage disease, cellular debris accumulates within storage areas of cells called lysosomes. In the case of AMD, children are born with a faulty version of the gene for an enzyme called lysosomal alpha-mannosidase, or LAMAN.

"Shortly after birth, brain tissue is still physically maturing, which means that there is a particularly important window of opportunity for gene therapy in infants," Dr. Wolfe said. "In our study, we could see that gene therapy used during this particular time led to a restoration of damaged neurons, even though the lesions that represent the disease were already extensive."

According to **Charles H. Vite**, lead author of the paper and assistant professor of veterinary neurology at Penn, the treated cats not only demonstrated dramatic clinical improvement, but MRI also revealed that white matter tracks, myelin, in the brain had been largely restored.

"As we move toward the clinical use of this therapy in humans, we must develop and utilize noninvasive methods to monitor the regression of the disease following treatment," Dr. Vite said. "The ability to monitor the improvement in brain myelination in alpha-mannosidosis using imaging allows the clinician to see improvement in brain pathology without the need for brain biopsy."

The large-animal study also demonstrated that only a limited number of injections are necessary to introduce the working LAMAN gene, one of the first steps that will prepare this particular gene therapy for practical use in humans. The gene is transported via a neutralized virus that "infects" cells with the functioning gene. Since the blood-brain barrier would block the virus carrying the gene if it were circulating in the bloodstream, the researchers injected the virus directly into the brain.

"The brain of the cat is much closer in size to the human infant brain compared to mice. Thus we think that it may be possible to achieve similar results in humans with as few as 20 to 30 injections in each of the two hemispheres of the brain," Dr. Wolfe said. "We believe, however, we can further limit the number of injections by the use of strong promoters that could increase the amount of enzyme that comes from corrected cells."

Although encouraged by their findings, the researchers note that any clinical trials in humans might be years in the future.

Video comparing a cat with AMD to one that had been given gene therapy is available at www.mrw.interscience.wiley.com/suppmat/0364-5134/suppmat/2005/57/v57.3.355.html.

Funding for this research was provided by the National Institutes of Health. In addition to Drs. Wolfe and Vite, researchers involved in the study include Joseph G. McGowan; Sumit N. Niogi; Marco A. Passini; **Kenneth J. Drobatz**, associate professor of critical care at the Ryan Hospital; and **Mark E. Haskins, V'69**, professor of pathology and medical genetics. ■

Walter Goodman and Skye Terriers: "Love at First Sight"

In 1936, 14-year-old **Walter Flato Goodman** was vacationing with his family in Paris when he saw his first Skye terrier, and it was love at first sight. When the Goodmans returned to America, a Skye puppy was in tow. Thus Walter's future as a one of the world's most prominent breeder-owner-handlers of Skyes was born.

Since that day, Walter and his terriers have won 99 Best in Show awards and 300 Terrier Group First awards. He is a member of the Westbury Kennel Association, the Westminster Kennel Club, the Palm Beach County Dog Fanciers Association, and The Kennel Club (of England). Walter is President and Chief Steward of the Montgomery County Kennel Club in Pennsylvania, which holds the world's largest annual terrier show. As the Delegate of the Skye Terrier Club of America, he is a member of the Board of Directors of the American Kennel Club. Since 1975, Walter has been approved to judge Best in Show, the Terrier Group, and Junior Showmanship competitions.

Walter has long supported the School; he joined its Board of Overseers in 1986, and, with his associate, Robert A. Flanders, established two irrevocable trusts at Penn. In fall 2003, the School honored Walter by naming its research center the Walter Flato Goodman Center for Comparative Medicine and Genetics, dedicated to clinical and basic research for companion animals with diseases that parallel those in humans. ■

Walter Goodman (left) with his Skye terrier "Evie," who was judged Best in the Terrier Group by Jeremiah O'Callaghan at the 1957 show of the Kennel Club of Philadelphia.