

correcting macular degeneration with gene therapy:

Canine Models and Human Implications

By Nora Laberee



Left to Right: William Beltran, DVM, PhD; Gustavo Aguirre, VMD, PhD; Karina Guziewicz, PhD; Artur Cideciyan, PhD; Samuel Jacobson, MD, PhD. (Photo credit: John Donges, School of Veterinary Medicine)

Researchers at the University of Pennsylvania recently achieved gene therapy success for treating macular degeneration in dogs. Drs. Artur Cideciyan and Samuel Jacobson of the Perelman School of Medicine, and Drs. Karina Guziewicz, William Beltran, and Gustavo Aguirre of the School of Veterinary Medicine, led the Penn team of researchers responsible for this discovery. Their work was published in March 2018 in *Proceedings of the National Academy of Sciences*.

The therapy targets Best disease, an inherited form of vitelliform macular degeneration that causes blindness.

The term macular degeneration refers to eye conditions in which the central part of the retina, called the macula, is slowly damaged. Individuals with macular degeneration lose their central vision, making reading and recognition of faces and objects difficult, and interfering with daily life activities.

Best disease begins in children and young people and results from a mutation in the *BEST1* gene. The earliest expression of disease causes the foveal retinal cells located at the center of the macula to be separated from their support cells. The fovea is a small but very important

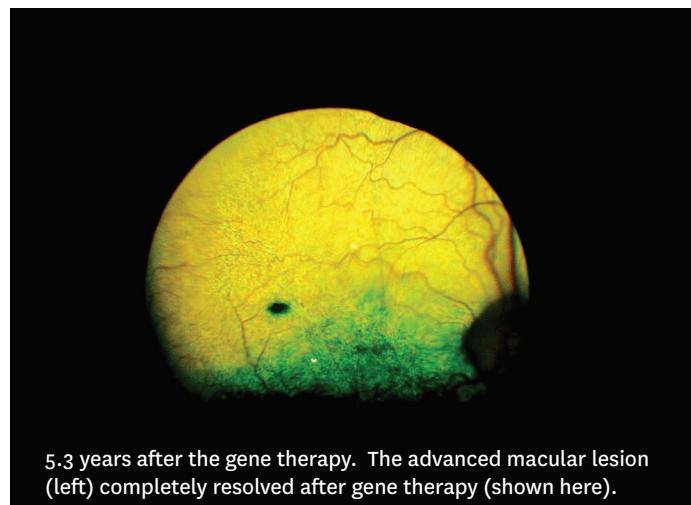
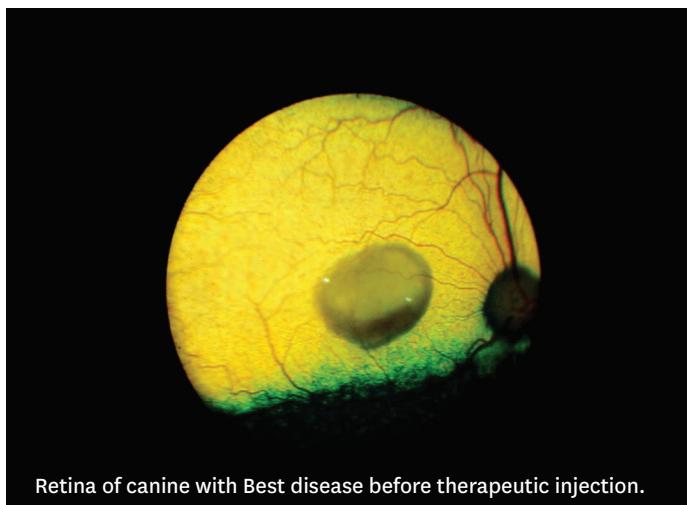
area of tightly packed cone photoreceptors responsible for high resolution vision – a feature thought to be found only in primates. But previous research led by Dr. Beltran, Professor of Ophthalmology and Director of the Division of Experimental Retinal Therapies (ExpeRTs) at Penn's School of Veterinary Medicine, showed that dogs and humans have similar foveas.

Even more, mutations in the *BEST1* gene also cause macular degeneration in dogs. "Not only is it the same gene mutation causing this disease in both dogs and humans," said Dr. Cideciyan, Research Professor of Ophthalmology at Penn Medicine, "but the foveal similarities between the two are remarkable. This was discovered collaboratively, with Penn Vet School and Penn Medicine working together."

By using non-human models with such similar foveas to humans, the researchers are more confident that their canine results are significant for individuals with Best

disease. "Mouse models do not recapitulate the human disease in the same way," said Dr. Guziewicz, Research Assistant Professor of Ophthalmology at Penn Vet School. A crucial difference between mouse and canine models is that dogs cannot be genetically engineered to have the disease; to study canines with Best disease, researchers must find dogs who are already suffering from this form of macular degeneration.

The researchers used a harmless virus to introduce a healthy copy of the *BEST1* gene in the dogs with Best disease, at various stages of the disease. The results have been astounding. The researchers corrected mild and severe lesions, and they were able to observe the gene therapy reconnecting the two retinal cell layers that are separated due to the *BEST1* gene mutation. "On the molecular level, we observed a remarkable restoration of structure between photoreceptors and their support cells, essential for preservation of vision," said Dr. Guziewicz. The treated



dogs have remained disease free for as long as six years.

"Here is one more example of how our longstanding collaborative team of Scheie Eye Institute and Penn Vet's vision scientists and ophthalmologists, harnesses the value of canine models to decipher the mechanisms of retinal diseases and validate novel strategies for treating blindness," said Dr. Beltran.

"This is a new and exciting discovery, with a long history involving key discoveries by many investigators trying to understand and treat macular degeneration," said Dr. Jacobson, Professor of Ophthalmology and Director of the Center for Hereditary Retinal Degenerations.

"This project has been taking shape for decades," added Dr. Aguirre, Professor of Medical Genetics and Ophthalmology at Penn Vet. Dr. Aguirre has been studying retinal disease and gene therapy since the 1970's, and Dr. Jacobson since the 1980's. For the past several years, the researchers have focused on the mechanisms of Best disease.

The researchers also involved human patients with the *BEST1* mutation in the current study, to examine the

similarities between humans and dogs with Best disease. Using novel retinal imaging and vision-testing strategies, they found microscopic separation of retina from its support cells in human patients, which was associated with slowing of adaptation of vision to dark conditions. This suggests that the mechanism of disease through the separation of cell layers is similar in canines and humans, and further supports the evidence that humans could benefit from this new treatment.

The gene therapy developed for Best disease is the result of years of research, and has tremendously exciting implications for the future. While there is work still to be done before the therapy moves to human trials, the collaborative efforts of these Penn Medicine and Veterinary Medicine researchers have garnered sight-saving results so far, and they are hopeful this will translate to humans, too.

Additional authors on this paper include Penn Vet's András M. Komáromy, Valérie L. Dufour, Simone Iwabe, Gordon Ruthel, and Brian T. Kendrick; Penn Medicine's Małgorzata Swider and Alexander Sumaroka; University of Florida's Vince A. Chiodo and William W. Hauswirth; and University of Toronto's Elise Héon.