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Team announces breakthrough for degenerative vision disorder

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A research team, led by John Guy, M.D., professor of ophthalmology at Bascom Palmer Eye Institute of the University of Miami Miller School of Medicine, has pioneered a novel technological treatment for Leber Hereditary Optic Neuropathy (LHON), an inherited genetic defect that causes rapid, permanent, and bilateral loss of vision in people of all ages, but primarily males ages 20-40. Genetic mutations in the mitochondria (part of the cell that produces energy) cause the disorder. Currently, there is no cure for LHON.

However, Guy and his team have successfully modified a virus and used it to introduce healthy genes into the mitochondria to correct the genetic defect. Using experimental models, they have proven that it is both safe and effective to replace mutated genes with healthy ones and that doing so prevents deterioration of the retinal cells that form the optic nerve. This research demonstrates that when efficiently introduced into mitochondria, normal DNA can correct a biochemical defect in cellular energy production and restore visual function.

"A wide range of other factors, including aging, cancer, and Parkinson's disease, are also caused by mutations in the mitochondria," said Dr. Guy. "This new approach shows the vast potential for genetic-therapy applications, while helping to address a significant cause of blindness."

The healthy genes were delivered into the mitochondria via an innovative viral delivery system. Specifically, Guy redirected the adeno-associated virus (a small virus that infects humans but is not known to

cause disease) to the mitochondria rather than to its typical target, the nucleus, where most genes are housed within the cell. He did so via a mitochondrial-targeting sequence (a peptide chain that directs the transport of a protein). This permitted the replacement of the defective mitochondrial gene with a healthy one, which then restored energy production to the affected ocular cells. Two National Institutes of Health/National Eye Institute grants, totaling $6.1 million funded this research, which began in 2007.

"Other research studies have shown that LHON patients who have lost their vision still have some sensitivity to light," said Guy. "This indicated that if you can restore the functioning of those cells through gene therapy, those patients could see again." In conjunction with his research, Guy explored why only about 50 percent of patients with the genetic mutation develop LHON, while others do not.

Known for exploring gene therapy as a potential treatment for diseases of the optic nerve, Guy holds several patents related to mitochondrial gene therapy biotechnology. His next steps will be to investigate incorporating all three genes that cause LHON into a single viral carrier and hopefully receive FDA approval to inject therapeutic genes into patients who have visual loss from mitochondrial disease.

On April 20, 2012, *Proceedings of the National Academy of Sciences* (*PNAS*) published an article by Guy about this recent breakthrough.

Provided by Bascom Palmer Eye Institute