Novel Optogenetic Therapy May Restore Vision After Retinal Degeneration

Researchers have developed an approach to restore vision using a component of green algae.

BY CALLAN NAVITSKY, ASSOCIATE EDITOR

Inherited retinal degenerations that cause partial or total blindness affect 1 in 3000 people worldwide.[1] Drug therapy is available for age-related degenerative diseases such as wet age-related macular degeneration; however, none have been approved for retinal neurodegenerative diseases of genetic origin, such as retinitis pigmentosa (RP).[2] At present, no treatment is available for restoring vision once rods and cones have been lost due to retinal degeneration.

In recent years, developments such as retinal implants and electrical stimulation therapy have been introduced in efforts to address RP. Now, research conducted by Zhuo-Hua Pan, PhD, and colleagues at Salus University, may have the potential to lead to a new treatment option for patients with retinal degenerative disorders—gene therapy.

BREAKTHROUGH RESEARCH

The novel strategy developed by Dr. Pan, a Professor of Anatomy and Cell Biology at Wayne State University School of Medicine, focuses on genetically converting light-insensitive inner retinal neurons into photoreceptor cells, thereby imparting light sensitivity to retinas that lack photoreceptors.

"We took a new strategy for restoring vision by genetically converting the retina's second- or third-order cells to become light sensitive to mimic the function of rods and cones," Dr. Pan wrote in an email to *Retina Today*. "But critical to this strategy, we needed to find certain suitable light sensors that can be easily inserted into these surviving retinal cells."

In November 2003, Dr. Pan learned of the work of Nagel and colleagues,[3,4] who reported the novel properties of an opsin, called channelrhodopsin-2 (ChR2), from green algae. The ChR2 protein in algae is very similar to the photopigments in human photoreceptors, but it acts as a directly light-gated channel and uses a simpler chromophore, all-*trans* retinal. Dr. Pan immediately realized that the ChR2 protein might be the ideal light sensor they had been looking for.

Using an adeno-associated viral vector, Dr. Pan and colleagues introduced ChR2 into retinal ganglion cells of a mouse model of blinding photoreceptor degeneration.[5]

"We showed that the introduced ChR2 protein made the inner retinal neurons become light sensitive," Dr. Pan said. "Furthermore, the ChR2 protein persisted for long periods in these neurons, and the neurons generated signals that were transmitted to the visual cortex of the animals' brains."

This work is part of a relatively new field called optogenetics, the combination of genetics and optics to control events within specific cells of living tissue. This includes the insertion into cells of genes that confer light responsiveness.[6]

INVESTMENTS AND FUNDING

In October 2011, RetroSense Therapeutics LLC announced a license agreement for the novel gene thera-

py approach developed at Wayne State University with the goal of eventually testing the therapy in humans, according to a company news release.

"Channelrhodopsin-based approaches to vision restoration are garnering a great deal of attention from academia and industry right now," RetroSense Therapeutics Founder and CEO Sean Ainsworth said in the news release. "It's a very hot field, and we are quite pleased to be aligned with Dr. Pan and his colleagues who pioneered the approach."

In February 2012, the Foundation Fighting Blindness announced a $250 000 research investment from its affiliate, National Neurovision Research Institute, to RetroSense Therapeutics. The funding supports RetroSense's lab research in preparation for a clinical trial of the gene therapy in 2 to 4 years.

"What Dr. Pan's and RetroSense's work is doing and what the Foundation Fighting Blindness is supporting is taking the surviving ganglion cells and making them into dual-function cells," Stephen Rose, PhD, Foundation Fighting Blindness' Chief Research Officer, said in an interview with *Retina Today*. "In placing ChR2 into the ganglion cells, the cells are now doing
2 things: They are generating the signal that would normally come from the photoreceptor, and then they are transmitting the signal through its normal path back to the brain. This is where the promise of optogenetics in retina is—that you can take individuals who have no light perception and give them light perception by turning those ganglion cells into, if you will, pseudo-photoreceptors."

Although the ChR2-based gene therapy has the potential to restore an individual's light perception, its effect on visual acuity is still undetermined. "What we do not know and what we will not know until work is done in humans is what that means for an individual in terms of visual acuity," Dr. Rose explained. "However, there are 1 million ganglion cells in the retina. Even if we could only turn 30% of those into light-sensing cells, that is still 30 000."

PRECLINICAL WORK AND FUTURE APPLICATIONS

"We are working to modify the properties of ChR2 and other similar light-sensitive molecules in order to better fit the need for vision restoration," Dr. Pan told *Retina Today*. "Also, we will need to find the way to insert these molecules into the right cell types in the right places in order to achieve a better outcome of the restored vision."

To help the company move forward clinically and prepare for a meeting with the US Food and Drug Administration, RetroSense has recently added 2 consultants to its team, a retinal researcher and a clinician. RetroSense is seeking FDA clearance to conduct a phase 1 clinical trial, which could begin in 2013, according to a Wayne State University news release.

Because optogenetic treatments work independently of the genetic defects that cause retinal neurodegenerative diseases, the ChR2-based gene therapy has potential in the treatment of other retinal degenerations in addition to RP, Dr. Pan said. ■

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