MEETING NOTES FROM THE 45TH ANNUAL ARDS MEETING

Following the 44th annual meeting of the Aspen Retinal Detachment Society (ARDS), Retina Today *is privileged to provide a review of the lectures presented by Gary W. Abrams, MD, and Mark S. Humayun, MD, PhD.*

In "Optogenetic Vision Restoration," Dr. Abrams presented the Victor Curtin and Taylor Smith Invited Lecture. Author Jack Stringham, MD, provides background information on the Curtin/Smith Lecture and discusses how a genetic technique for visual restoration is used, essentially, to introduce a gene to create photoreceptors from cells that are not light-sensitive.

In "The Road to Developing Bioelectronics for Ophthalmology," Dr. Humayun presented the Founders Lecture on advances in visual prosthesis. Author Thanos Papakostas, MD, summarizes the lecture with an overview on the history of visual cortical and epiretinal implants and discusses the Argus I and II platforms.

—Timothy G. Murray, MD, MBA

OPTOGENETIC VISION RESTORATION

By Jack Stringham, MD

Taylor Smith, MD, was a legendary eye pathologist and talented vitreoretinal surgeon whose work as both a practitioner and mentor influenced many young ophthalmologists. His disciples included Victor Curtin, MD, a noteworthy surgeon in his own right who helped build the Bascom Palmer Eye Institute in Miami, Fla., along with Edward W.D. Norton, MD. A former mentee of Dr. Curtin, Gary W. Abrams, MD, was honored as the Victor Curtin and Taylor Smith Lecturer at the 45th annual Aspen Retinal Detachment Society (ARDS) meeting.

Dr. Abrams is a professor and former chair of ophthalmology at Wayne State University and the Kresge Eye Institute, as well as a former president of the Association for Research in Vision and Ophthalmology (ARVO) and former chair of the ARVO Foundation. His presentation focused on optogenetics, a promising method for vision restoration that is being developed alongside other approaches such as gene therapy, retina stem cell transplantation, optopharmacology, and stimulation of the retina via retinal implant.

Dr. Abrams spoke about the development of optogenetics to treat diffuse retinal degenerations such as retinitis pigmentosa (RP). Although patients with such conditions are blind due to a substantial loss of photoreceptors, many retain cells in the inner retina—specifically, bipolar and ganglion cells—that remain connected to the visual cortex and largely functional. According to Dr. Abrams, using optogenetics, it may be possible to endow nonphotoreceptor cells such as these with light sensitivity in order to restore partial vision in patients with RP and other diffuse retinal degenerations.

PROMISING RESULTS

Optogenetics is the practice of introducing a gene for a light-sensitive protein into a cell that is not light sensitive, effectively turning it into a photoreceptor cell. The concept of optogenetics was awarded "Method of the Year" in 2010 by *Nature Methods*.[1] The number of publications and researchers in the field is growing,[2-7] and clinical trials in humans have begun.[8-10]

The concept was first described by Boyden and colleagues at the Deisseroth Laboratory at Stanford University,[2] but its roots trace back to the discovery of the photoactive proteins bacterial rhodopsin and halorhodopsin in 1973 and 1982, respectively, at the laboratory of Peter Hegemann in Germany.[3,4] The identification of channelrhodopsin-2 (ChR2) by Nagel et al in 2003, however, made optogenetics a viable possibility.[5]

ChR2 is isolated from green algae, where it is light-sensitive and controls phototaxis. Paired with a viral vector, it can be incorporated into a nonphotoreceptor cell, where it opens a light-sensitive ion channel in the cell membrane, according to Dr. Abrams. By attaching green fluorescent protein, researchers can confirm placement of ChR2 using fluorescent microscopy. The neuron is triggered by blue light to fire an action potential, which effectively turns that neuron into a photoreceptor-like cell. The ganglion cell can then send a signal to the brain that is interpreted there as a vision signal.

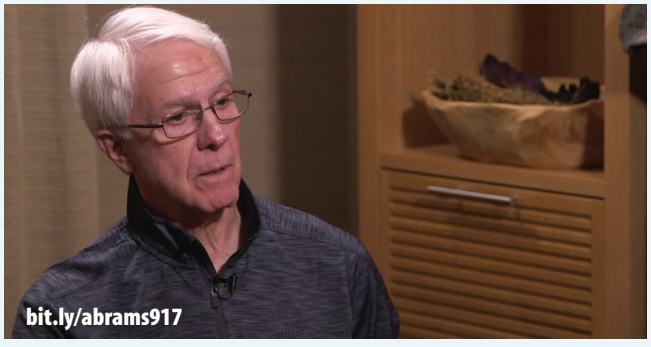
Dr. Abrams cited the work of Zhuo-Hua Pan, PhD, his colleague at Wayne State University, regarded by many as the inventor of optogenetics. Pan and colleagues conducted the first visual restoration experiments in rd1/rd1 mice, which have a retinal degeneration similar to those in humans.[6] They attached the gene for the precursor protein for ChR2, called channelopsin, to a viral vector and introduced it into retinal neurons through intravitreal injection. Dr. Abrams said the researchers were able to record visual evoked potentials (VEPs) from the visual cortices of the implanted mice. When stimulated with 460 nm light, the implanted mice showed a robust response, but unimplanted blind rd1/rd1 mice did not. The Wayne State researchers have also demonstrated a light response after gene transduction in primates.[7]

CHALLENGES AND SOLUTIONS

According to Dr. Abrams, there are several barriers to the success of optogenetics that must be addressed. One is penetration

WATCH IT NOW

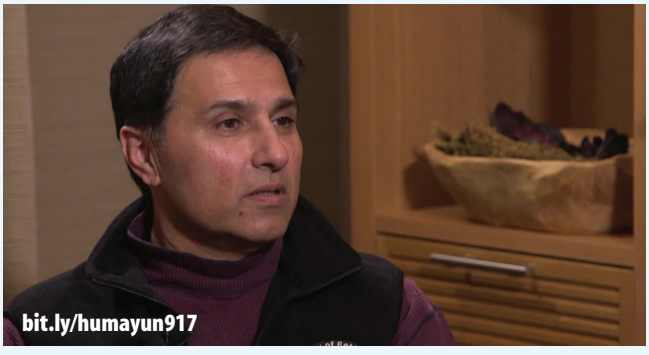
Optogenetic Vision Restoration



Gary W. Abrams, MD, who delivered this year's Victor Curtin and Taylor Smith Lecture, joins Timothy Murray, MD, MBA, for a conversation on optogenetic vision restoration. Dr. Abrams offers a brief overview of how applied optogenetics may one day improve vision in patients with degenerative retinal diseases.

WATCH IT NOW

Retinal Implants: The Next Wave



Mark S. Humayun, MD, PhD, describes a pair of retinal implants that were the cornerstones of his discussions at the Aspen Retinal Detachment Society meeting. Dr. Humayun discusses an implant that enables stem cells to proliferate in the retinal pigment epithelium in patients with geographic atrophy, and also reviews the potential for color vision and digital zoom with the Argus II Retinal Prosthesis (Second Sight) in patients with RP.

of the virus to the human retina. In primate models, transduction was limited to the perifoveal area. He said pharmacologic treatment or surgical peeling of the internal limiting membrane may improve transduction. Another challenge is that severe retinal degeneration is characterized by disorganization and remodeling of all neurons, with a marked reduction in ganglion cells.

Slow kinetics of ChR2, compared with normal ganglion cell firing rates, is another challenge. New engineered versions of channelrhodopsin have faster kinetics, Dr. Abrams said. Similarly, low light sensitivity and limited spectral sensitivity (ChR2 responds only to blue light, which can be toxic to the retina at high intensity) have presented barriers. New engineered and recently discovered natural channelrhodopsin have spectral sensitivities that are shifted toward the red range, so they are safer at higher intensities and more consistent with regular daylight.

Dr. Abrams concluded by highlighting an ongoing phase 1/2a human clinical trial conducted by RetroSense Therapeutics[8] on optogenetic vision restoration in patients with advanced RP.

"In summary," he said, "optogenetics is an exciting advance that has the possibility of restoring vision in blind patients with inherited retinal degenerations. Channelrhodopsins, especially the newer varieties, have kinetics similar to human rhodopsin. Studies in retinal degenerative mice have demonstrated a robust light response in the retina, good cortical responses on VEP, and light-directed behavioral responses. Genes have been introduced into nonhuman primate retinas with evidence of light response." And he closed with a shout-out to Dr. Pan and colleagues at the Ligon Research Center of Vision at Kresge Eye Institute.

1. Method of the year 2010 [editorial]. *Nature Methods*. 2010;8(1).
2. Boyden ES, Zhang F, Bamberg E, Nagel G, Deisseroth K. Millisecond-timescale, genetically targeted optical control of neural activity. *Nat Neurosci*. 2005;8(9):1263-1268.
3. Oesterhelt D, Stoeckenius W. Rhodopsin-like protein from the purple membrane of Halobacterium halobium. *Nat New Biol*. 1971;233(39):149-152.
4. Hegemann P, Steiner M, Oesterhelt D. Isolation and characterization of the retinal-binding component of halorhodopsin. *EMBO J*. 1982;1(10):1177-1183.
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6. Pan ZH, Bi A, Cui J, et al. Ectopic expression of a microbial-type rhodopsin restores visual responses in mice with photoreceptor degeneration. *Neuron*. 2006;50(1):23-33.
7. Ivanova E, Hwang GS, Pan ZH, Troilo D. Evaluation of AAV-mediated expression of Chop2-GFP in the marmoset retina. *Invest Ophthalmol Vis Sci*. 2010;51(10):5288-5296.
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THE ROAD TO DEVELOPING BIOELECTRONICS FOR OPHTHALMOLOGY

An overview of the 2017 ARDS Founders Lecture, given by Mark S. Humayun, MD, PhD

By Thanos Papakostas, MD

As the 2017 Founders Honoree, Mark S. Humayun, MD, PhD, delivered the Founders Lecture at the 2017 ARDS Annual Meeting. Dr. Humayun is best known for his work developing the Argus II Retinal Prosthesis System (Second Sight). He devoted his lecture to reviewing the history of the implant, and he ended with a look ahead at future challenges.

The Argus II is a US Food and Drug Administration (FDA)–approved prosthesis for patients with end-stage RP. Before the Argus, there were other visual prostheses. Visual cortical implants were first developed in the 1970s. In these systems, a camera recorded information, and it was sent through an electrode array directly to the visual cortex.

DESIGN

The Argus features two wearable components—a camera mounted on glasses and a battery-powered video processing unit that is worn on the belt or placed in a pocket. Power and data are sent inductively to the implant, which has no battery. This dedicated wireless inductive link must remain within one inch of the implant. A pattern of stimulation, based on images gathered by the camera, is then transmitted through tiny electrodes to the remaining healthy nerve cells in the retina, which send this information to the brain.

BEGINNING OF THE PROJECT

Dr. Humayun said he started the Argus project in 1987. The first thing he did was examine whether or not there are any retinal cells alive in patients with RP. Conducting a morphometric analysis of postmortem RP eyes, Dr. Humayun and his colleagues found that 30% of the ganglion cells were still there. In a subsequent study with Richard Green, MD, he showed that the inner retina was very much intact, although reorganized.

This discovery led to a short-term test in 1992, in which small electrodes were placed into a conscious patient, so that Dr. Humayun could ask questions of the patient. In 2002, he said, he built the first Argus model from a "hijacked" cochlear implant. The technology went behind the ear, and a cable went into eye to an array of 16 electrodes. This early model provided vital information about how pattern electrical stimulation could be achieved.

APPROVED FOR USE

In 2007, Dr. Humayun's group built the Argus II, which has since received FDA approval and the European CE Mark. More than 200 of these devices have been implanted around the world.

ARGUS I VS ARGUS II

The original Argus had 16 electrodes, and the Argus II has 60. This larger array allows patients to achieve better pattern resolution. In terms of a test such as square localization, Dr. Humayun said, there was no difference between the two devices. However, when detection of motion and grating visual acuity were tested, patients with an Argus II implant performed better than those with an Argus I implant. These tests demonstrated that the use of a larger electrode array can provide better visual function. Packing more electrodes into future versions of the chip may be challenging, however.

During his presentation, Dr. Humayun showed a video of a patient with the Argus II implant reading single letters. He described the Acuboost function of the device, an external signal processing step that allows the patient to enhance visual acuity up to 20/200 with a 16x zoom control.

ARGUS II AND THE VISUAL CORTEX

Dr. Humayun described experiments his group has conducted on the interaction of the Argus II device with the visual cortex. Research has shown that visual deprivation leads to the visual cortex becoming active during nonvisual tasks. His group found that, after extended use of the Argus II device, the visual cortices of implanted patients became less sensitive to tactile stimuli. That is, the Argus II device actually reverse-engineered the brains of these patients back to functioning the way they did before the onset of blindness from RP.

COLOR RECOGNITION

The last topic Dr. Humayun covered was color recognition with the Argus II, which can be modulated by changing the frequency with which the electrodes fire. He concluded by showing an eye tracker his group has built in the lab, which helps to guide patients with macular degeneration to use their remaining useful vision. ■

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