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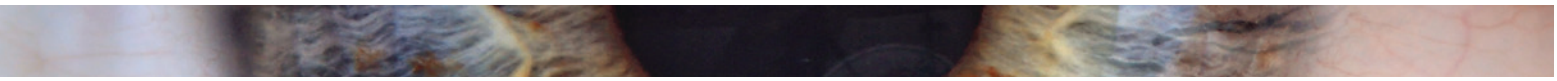

Inside This Edition

Viruses, Gene Therapy, and Retinal Disease

Leah Byrne, PhD, assistant professor in the Department of Ophthalmology and assistant professor of bioengineering in the Swanson School of Engineering at the University of Pittsburgh, specializes in the study and application of gene-based approaches to treat inherited retinal dystrophies. Dr. Byrne's research specifically investigates the use of viral vector-mediated methods in animal models to deliver gene therapies to the retina and to edit or alter the aspects of the genome responsible for inherited retinal diseases. Dr. Byrne's viral vector research has largely focused on developing and testing novel adeno-associated viral (AAV) vectors for genetic therapy delivery.

Dr. Byrne is a neuroscientist by training. She completed her PhD in neuroscience at the University of California, Berkeley in 2011, followed by a postdoctoral fellowship as a Ruth L. Kirschstein NRSA Postdoctoral Fellow at the Helen Wills Neuroscience Institute at Berkeley and the School of Veterinary Medicine at the University of Pennsylvania.

As a postdoctoral researcher, Dr. Byrne engineered next-generation AAV viruses for retinal gene therapy, and she developed high-throughput methods for directed evolution of viral vectors. This research remains a focus of her work and that of the Gene Therapy for Retinal Disease Laboratory she directs at the University of Pittsburgh School of Medicine.

Using Viruses to Alter Retinal DNA

Inherited diseases of the retina affect roughly 2.5 million people worldwide or about 1 in 3,000. "There is a broad spectrum of inherited retinal disease, driven by an even broader spectrum of mutations in more than 200 genes. For the overwhelming majority of these retinal disorders, we have no treatments. These diseases will cause people to lose their vision. My research seeks to develop gene-modifying therapies and delivery methods that can prevent or correct disease after it occurs," says Dr. Byrne.

Continued on Page 4

Adaptive Optics and Its Clinical Implications for the Study and Understanding of Ocular Diseases

Adaptive optics (AO) is a set of technologies that allows optical system imperfections or limitations to be corrected. Adaptive optics technologies involve two aspects: a method for measuring imperfections or aberrations in an optical system (telescope, camera, the human eye) and a method for correcting the imperfections or distortions. Since there are no perfect optical systems, adaptive optics technologies are a way to circumvent some of the natural limitations inherent in an optical system.

Adaptive optics platforms were first developed by the U.S. Department of Defense decades ago for ground-based surveillance systems designed to monitor spy satellite activities in space. The first application of AO technology to study the human eye was achieved in the lab of David R. Williams, PhD, at the University of Rochester in New York. Adaptive optics is a revolutionary approach in the study of the human eye, one that has and will continue to be transformative in the understanding of the eyes' structural characteristics and disease pathogenesis.

AO and Eye Disease — New Research

Using adaptive optics technologies to study anatomical structures within the eye at the cellular level and disease processes within the eye for conditions like macular degeneration and glaucoma are the focal points of research for **Ethan A. Rossi, PhD**, director of the Advanced Ophthalmic Imaging Lab in the Department of Ophthalmology at the University of Pittsburgh School of Medicine.

Dr. Rossi joined the Department in 2016 as an assistant professor of ophthalmology. He also holds a secondary appointment as assistant professor in the Department of Bioengineering at the University of Pittsburgh Swanson School of Engineering and is a faculty member of the McGowan Institute for Regenerative Medicine at the University of Pittsburgh.

Dr. Rossi completed his PhD in vision science at the University of California, Berkeley, followed by postdoctoral fellowships at Berkeley along with the University of Rochester in Dr. Williams' lab, where he studied age-related macular degeneration (AMD) and developed improved techniques to image the cells of the retinal pigment epithelium (RPE), a layer of cells at the back of the eye that is crucial for vision, using adaptive optics.

Dr. Rossi's work at its core is devoted to understanding the cellular organization and characteristics of the human retina in both the normal eye and in the presence of disease. His work and that of his collaborators have made significant advances over the last decade in the ability to image and study the layers and structural aspects of the human retina.

During his postdoctoral work, Dr. Rossi collaborated with the optics and imaging company Canon Inc. to design and develop new technologies for the commercial use of adaptive optics in ophthalmoscopy. This work led to more than a dozen patent applications, with Dr. Rossi being either a sole inventor or co-inventor on several, one of which was recently issued.

Transformative Technologies

Adaptive optics technologies can be applied to various types of cameras or optical systems for imaging internal structures of the eye. This technological approach allows for two distinct areas of scientific research, both of which are part of Dr. Rossi's ongoing studies.

On the one hand, AO allows for sophisticated and detailed high-resolution imaging of living eye structures at cellular and microscopic levels. On the other hand, AO allows for the presentation of stimuli to the retina in a manner that is not possible through normal optical systems. This research is leading to new findings of the visual processing capabilities of the retina and the brain.

Dr. Rossi's research explores both of these lines of investigation to probe the structural nature of the eye and how diseases that afflict it manifest in such areas as the RPE, or how disease states alter and damage components of the human visual system, such as the rods and cones.

"Because of the inherent limitations imposed by the optics of the human eye, we have not known the full potential of the human retina and brain to process visual stimuli. With adaptive optics, we can bypass these normal limitations and deliver visual stimuli that are of higher resolution than the visual system has ever experienced. This allows us to study how the retina and brain sample and process these stimuli," says Dr. Rossi.

More Than Just AO

While a significant portion of Dr. Rossi's past and current work is devoted to using AO to study retinal disease, his lab uses an extensive repertoire of technologies and conventional imaging modalities to study the eye.

"The use of AO has been central in my research, but it is one technology among many to help us understand and measure retinal structure and visual function, and the pathological states of diseased ocular structures. Our lab also uses conventional imaging and visual function testing tools, including visual psychophysics, to better understand how structure is related to function in the eye — a highly critical area for our overall understanding of disease processes. I have an incredible affinity for the science, technology, and engineering aspects of my work, but we are not tied to a particular technology. If another technology comes along that can better help us answer the questions we have related to structure, function, or disease processes, we will incorporate it into our

studies. Ultimately, our goal is to definitively know how a disease manifests, propagates, and impairs vision, and to better understand the mechanism of the damage process if it has started so that we can develop ways to intervene to prevent vision loss or make repairs to restore visual function."

Imaging Breakthroughs With Retinal Ganglion Cells and the RPE

Dr. Rossi's past research has led to several significant breakthroughs in the ability to image structural components of the retina. In 2013, Dr. Rossi's research group showed the ability of AO to image RPE cells in vivo in retinas with age-related macular degeneration. Imaging findings from the study proved to correlate highly with AMD changes in the retina as seen through postmortem histology exams. "The real clinical benefit of this technology is its ability to provide us with longitudinal observational power to see and characterize the changes and progression of AMD in the living retina — in human subjects over very short timescales at the level of single cells," says Dr. Rossi.

More recently, in 2017, Dr. Rossi and colleagues published findings of a study designed to image in vivo aspects of the retinal ganglion cells.

Retinal ganglion cells, among other inner-retinal neurons, are among the most challenging classes of cells in the retina to image. The difficulty lies in the almost-complete transparency of these cells. Because light must pass through all of the layers of the retina to reach the photo-receptors (rods and cones) positioned at the back of the eye, evolutionary processes have made the intervening cells clear to allow for this light transmission.

"If you think about it, it makes perfect sense from a design standpoint. However, in order to image something, it has to scatter light and reflect it toward the imaging device. Since the retinal ganglion cells are virtually transparent, they scatter or reflect very little light, so traditional imaging systems cannot see them," says Dr. Rossi.

Dr. Rossi and colleagues developed a technique to enhance the contrast of the retinal ganglion cells — and other inner-retinal cellular components — and do it in vivo without using fluorescent tracers or levels of light that could cause damage to the subject's eye. Their findings were published in 2017 in the *Proceedings of the National Academy of Sciences* under the title "Imaging Individual Neurons in the Retinal Ganglion Cell Layer of the Living Eye."

Since then, Dr. Rossi, along with collaborator Nils Loewen, MD, PhD, in the Department of Ophthalmology at the University of Pittsburgh, has secured a new grant from the BrightFocus® Foundation to perform in vivo imaging studies of the retinal ganglion cells in the presence of glaucoma.

"Most of my past research has involved studies related to AMD. This new grant is helping to expand our laboratory's work into the world of glaucoma research where we hope to visualize some of the earliest changes occurring in the retinal ganglion cells in patients with glaucoma, and again, monitor and characterize those changes longitudinally to trace the disease process at the cellular level," says Dr. Rossi.

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UPMC at AAO 2018

The American Academy of Ophthalmology (AAO) annual meeting was held October 27-30 in Chicago, Illinois. The conference brought together a global community of innovators in the art and science of ophthalmology. Conference content included game-changing research, techniques, and technologies. UPMC physicians and researchers attended and were well-represented with poster presentations, panels, lectures, and abstracts. The full list of presentations and abstracts can be found at **UPMCPhysicianResources.com**.

José-Alain Sahel, MD, director of the UPMC Eye Center, presented the following preliminary data from the PRIMA French feasibility trial at AAO 2018:

"First Results of Photovoltaic Vision Restoration in Atrophic Dry Age-related Macular Degeneration."

"Photovoltaic Restoration of Central Vision in Atrophic Dry AMD."

AAO selected the first clinical results of PRIMA to be presented during the late-breaking developments session during the Retina subspecialty day program on October 26th. This session is attended by most of the thought leaders and specialists in retina research. The selection for presentation by the subspecialty course directors at AAO 2018 also is a recognition of the high level of interest in efforts to address a significant unmet need for treatment of advanced atrophic dry age-related macular degeneration (dry-AMD) and significant potential of the PRIMA wireless photovoltaic subretinal implant and first human experience. Additionally, Dr. Sahel's paper, "PA075 Photovoltaic Restoration of Central Vision in Atrophic Dry AMD" was voted best at the Retina, Vitreous Original Paper session.

The full set of six-month interim results of the study for all five patients is expected by the end of 2018. This will enable the design of the protocol for the larger multi-centric European pivotal study to commence in 2019, which is required for the CE-mark.

Viruses, Gene Therapy, and Retinal Disease *Continued from Page 1*

Because viruses at a fundamental level infect host cells, transfer their DNA, and replicate themselves, harnessing the molecular power of what a virus does naturally may prove to be an effective means for altering defective or damaged genes or gene sequences responsible for various inherited retinal disorders.

Be it for retinal diseases, cancer, metabolic disorders, or brain disorders such as Parkinson's disease, viral vector-mediated delivery of gene therapies is making progress, but significant obstacles still must be overcome.

As Dr. Byrne points out, these barriers to effective gene therapy delivery include overcoming diseases driven by large genes, those of a dominant inherited nature, and how to understand and overcome genetic mutations that drive diseases that occur in noncoding regions of the genome devoted to retinal development.

A possible technique for overcoming some of these barriers to effective treatment options is a process known as directed evolution. Dr. Byrne uses this technique that essentially can speed up the natural process of viral evolution but in a highly controlled manner in the laboratory. This technique can allow for more rapid creation of viral models to test in the lab.

Dr. Byrne's lab also is investigating the use of CRISPR/Cas9 technology to develop novel gene editing approaches to create new molecular targets and therapies that can reprogram aspects of the genome responsible for retinal disease.

Recent Awards, Grants, and Speaking Engagements

In 2017, Dr. Byrne served as an associate scientific advisor for the journal *Science Translational Medicine,* and she was named as an Emerging Vision Scientist by the National Alliance for Eye and Vision Research. Dr. Byrne also was a 2017 recipient of a Career Development Award from the Research to Prevent Blindness (RPB) organization. Dr. Byrne's grant from RPB is for the "creation of a flexible method of gene and protein delivery in the retina through a modular system of small viruses."

In April 2018, Dr. Byrne was invited to give a University of Pittsburgh Senior Vice Chancellor's Research Seminar lecture. Dr. Byrne's presentation dealt with viral vector-mediated gene delivery for retinal disease.

More recently Dr. Byrne was awarded an individual investigator grant from the Foundation Fighting Blindness. Her grant, "Designing Optimal Viral Gene-Delivery Systems for Retinal Diseases," will continue to support her research to engineer viruses capable of delivering therapeutic genes to the retina. Dr. Byrne's work seeks to create a group of viral promoters and capsids for each of the different cell types in the retina and make these tools available to other researchers in the field to spur on and speed up the search for curative therapies.

For Further Reading

Dr. Byrne's recent publications include:

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Age-Related Macular Degeneration: New Targets for Novel Therapies From the Glia Research Laboratory

Age-related macular degeneration (AMD) is the most common cause of visual impairment in older adults over the age of 60. There are no effective treatments available to stop the progression of the disease and no cure once it manifests (although treatments aimed at neovascularization in the wet form of the disease can slow progression, more than 90 percent of AMD in the United States is of the dry type). Gaps still exist in the understanding of the pathophysiology and mechanisms responsible for activating and driving the progression of disease.

The Glia Research Laboratory in the Department of Ophthalmology, led by **Debasish Sinha, PhD**, is exploring how the mechanistic traits and role of the retinal pigmented epithelium (RPE) and its corresponding cellular lysosome functions, specifically autophagy and phagocytosis changes and dysregulation. These processes are controlled by signaling pathways arising from the protein complex known as mTORC1 — the mechanistic (or mammalian) target of rapamycin complex 1.

Dr. Sinha is the Jennifer Salvitti Davis, MD, Chair in Ophthalmology Research, and a professor of ophthalmology, cell biology, and developmental biology at the University of Pittsburgh School of Medicine. As principal investigator in the Glia Research Laboratory, Dr. Sinha's primary research goal is to better understand the mechanisms that regulate autophagy and phagocytosis in the lysosomes of the RPE cells, the dysregulation of which is a factor in the early stages of development of AMD.

The RPE and AMD

The RPE is a single layer of cells between the retina and the choroid. The RPE is critical to the health of the photoreceptors in the retina. Photoreceptors continually grow new outer segments. As these outer segments are renewed, the terminal portions become damaged and are released into the space between the photoreceptors and RPE. The RPE cells must engulf this material and digest it through phagocytosis. Phagocytosis recycles the constituent molecules from the damaged photoreceptor portions back to the retina so the photoreceptors can manufacture new outer segments.

Autophagy, a process in which damaged proteins or organelles within the cell are collected, degraded, and removed, is also critical in RPE cells.

"We know that when the RPE lose these functions they not only can die, but they also can damage the photoreceptors, leading to loss of vision if the process continues unchecked," says Dr. Sinha.

Early stages of AMD are characterized by the accumulation of drusen between the RPE and the retina, and dysregulation and degeneration of the RPE drive this accumulation of drusen due to changes in the processes of autophagy and phagocytosis in the RPE lysosomes responsible for removing damaged cellular materials.

"The RPE cells are responsible for, among other things, protecting the photoreceptors from damage. It is when these processes go awry that early AMD damage begins to accrue," says Dr. Sinha.

AMD and mTORC1

The mechanistic target of rapamycin complex — mTORC1 — is responsible for a variety of protein translational processes in the human body, mainly related to aspects of growth and metabolism. Because mTORC1 regulates several processes, targeting it directly by modifications or inhibitory processes can lead to severe toxicities and unintended consequences. Because of the systemic nature of mTORC1, a potential way to avoid these toxicities is to stimulate or stabilize the signaling pathway itself without exogenous molecules.

Dr. Sinha's work focuses on the unique proteins that regulate the assembly of the mTORC1 signaling pathway in the RPE cells. These proteins play an important role in the complex process of recruiting mTORC1, which is known to be a negative regulator of autophagy, to the lysosomal surface of the RPE where it influences lysosomal function.

"This is a novel approach to rejuvenating lysosomal function of the RPE that could circumvent the side effects and toxicities that result from directly targeting mTORC1 to develop therapeutic targets in AMD. One of our research priorities is to identify upstream and downstream targets to modulate mTORC1 activity. In theory, this would allow us to regain control over or otherwise regulate autophagy in the lysosome of the RPE cells," says Dr. Sinha.

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ABOUT THE UPMC EYE CENTER

The UPMC Eye Center is a leader in the diagnosis and treatment of eye diseases and disorders, and is helping to advance the field through extensive research.

- UPMC is investing $2 billion to build three new specialty hospitals in Pittsburgh, including one specializing in vision. The UPMC Vision and Rehabilitation Hospital, which is anticipated to open in 2021, will be designed for the many patients in the Pittsburgh region and beyond who need physical rehabilitation and those who have diseases of the eye or vision impairment. Clinicians, researchers, educators, and industry partners will come together in this new hospital to accelerate the process of translating research into innovative treatments for patients.

- Seeing more than 80,000 patients annually, the UPMC Eye Center provides state-of-the-art testing, including electrophysiology and psychophysics services, to diagnose eye, retinal, and optic nerve disorders.

- The Department of Ophthalmology has one of the top basic and clinical research programs in the country. As a leader in National Eye Institute funding, the Department's research focuses on ocular immunology, infectious disease, molecular genetics and molecular biology of retinal disease, glaucoma, regenerative ophthalmology, and advanced diagnostic imaging technology development.

- The Louis J. Fox Center for Vision Restoration is the world's first comprehensive program dedicated to ocular regenerative medicine. Researchers at the Fox Center and the University of Pittsburgh continue to develop innovative solutions, such as bioengineering of ocular tissue, stem cell and gene therapy approaches, and novel drugs or drug delivery systems.

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