McPherson Eye Research Institute
UNIVERSITY OF WISCONSIN–MADISON

InSights

Published each semester

SPRING *2021*

MRI image of estimated neural pathways in the brain, colored to indicate the axes along which information flows. Photo credit: Rosenberg Lab.

Building the Visual World

ARI ROSENBERG'S LAB PUZZLES OUT HOW WE SEE IN 3D

Our overall perception of the world is often fundamentally different from what individual sensors, like those in our eyes and ears, detect. In some striking situations, such as visual illusions found in the works of M.C. Escher, the distinction between our perception and what we understand to be reality is obvious and apparent. More often, the difference escapes immediate awareness. For example, our perception of the world as three-dimensional (3D) is robust and compelling, and one would clearly call it "reality." Ultimately, however, it is a construct of the brain and, therefore, an illusion. We know this because our eyes can only detect two-dimensional (2D) projections of our surroundings, like a movie on a screen. This discrepancy between sensation and perception raises a quintessential neuroscience question: How do we perceive what we cannot sense?

Determining how the brain turns ambiguous sensory signals into robust perceptions can provide insights into psychiatric and neurodevelopmental disorders, as well as inspire novel approaches to artificial intelligence and computer vision systems. To gain headway on this problem, Dr. Ari Rosenberg's lab uses 3D vision as a model system. Visual perception requires the brain to take a pair of 2D retinal images and "reverse engineer" the most likely 3D real-world scene. The Rosenberg lab investigates how this is achieved using a multifaceted approach combining behavioral experiments, electrophysiological recordings, neuroimaging, and neural network modeling. Their work has deepened our understanding of how parallel, hierarchically organized neural pathways achieve 3D perception from 2D retinal input.

Rosenberg's lab has discovered different cortical networks responsible for estimating the **static** (position and orientation) versus **dynamic** (direction and speed) 3D features of objects. Both pathways perform 3D "stereoscopic" triangulation by comparing the left and right retinal images (similar to how a position on earth can be triangulated using satellites). Likewise, they both interpret r etinal images using an "internal model" of the 3D-to-2D projective geometry that describes how the 3D world projects onto the 2D retinae. For example, parallel lines in the world (such as railroad tracks) converge in a 2D projection, and the rate of convergence can be used to infer 3D orientation. (These "perspective" signals are why paintings can elicit sensations of depth). Stereoscopic and perspective signals are individually ambiguous, but by combining them the visual system resolves uncertainties in the sensory information conveyed by the eyes.

The Rosenberg lab has made great progress in elucidating the neural transformations that turn 2D retinal images into 3D perceptions, but this is just one facet of how the group seeks to understand how the brain creates robust perceptions of a world that is only indirectly sensed. A next step is to determine how the visual system is calibrated to ensure successful interactions with the world. It is likely that this occurs via feedback of "action errors," such as when you reach too far for a cup of water and knock it over, but more research will tell.

By studying how sensory information is represented and transformed for us to perceive what we cannot sense, Ari Rosenberg's group will be able to provide insights into how alterations in neural processing give rise to disorders of sensation and perception, thus facilitating potential therapies and also furthering the development of computer vision and artificial intelligence.

Dear Friends of the McPherson ERI,

This issue of *InSights* provides yet more examples of how McPherson ERI investigators are undeterred by the enormous complexity of the eye and visual system—both in health and disease. But the work they do also resonates outside of the eye to other organs and tissues. Dr. Ari Rosenberg studies how the brain "sees" in 3D, a vexing question that has implications not only for vision disorders, but also for disciplines where understanding pathways of perception is crucial, such as artificial intelligence and computer vision. Dr. Bikash Pattnaik's $7.7 million grant, aimed at the correction of disease-causing "nonsense mutations" in the retina, could potentially lead to treatments for up to 15% of all inherited diseases in the retina and throughout the body. Drs. Pattnaik and Rosenberg are excellent representatives of the Institute, which was established in the belief that paradigm-changing research will occur through collaborations across departments, institutions, and scientific and medical disciplines.

One way that we encourage collaborative research is through supporting our researchers at every stage of their careers. Awards provided through our Grant Summit Program bolster highly promising federal grant proposals, often returning 50 to 300 times the award investment. The Kenzi Valentyn Vision Research Awards support important work done by trainee researchers in vision labs across the Institute. Our new Graduate Student Support Initiative (GSSI) awards provide additional opportunities to support the next generation of great vision researchers. If you would like to support these and other research initiatives (and feel good doing it), please consider walking, running, cycling, or exercising in another way during Cycle for Sight Plus this year—see below for further details.

Wishing you the best,

David M. Gamm, MD, PhD
RRF Emmett A. Humble Distinguished Director
Sandra Lemke Trout Chair in Eye Research

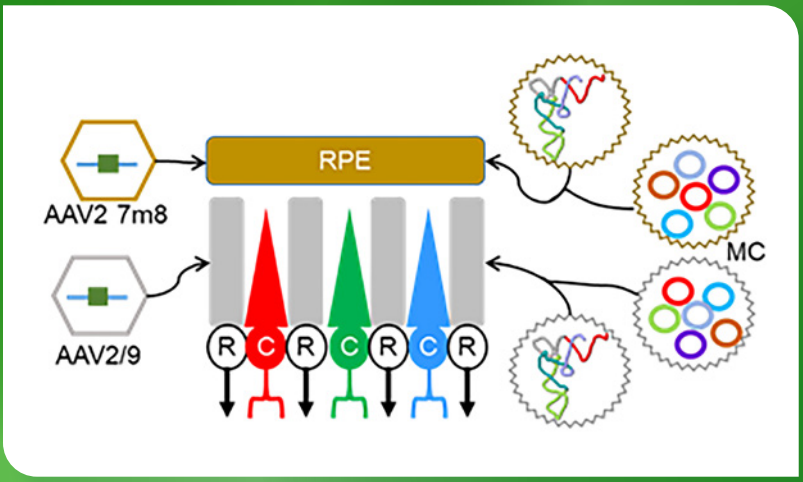
Bikash Pattnaik, PhD
David Gamm, MD, PhD
Sarah Gong, PhD
Christopher Ahern, PhD

No-Nonsense Therapy for the Eye

Gene-based therapies have been praised for their potential to treat or perhaps cure disease and restore function to a variety of bodily systems. However, the enormous complexity of the human genome (the sum total of all of a person's DNA), both in size and function, dictates that no single type of gene therapy will be able to treat all forms of genetic disease. Instead, gene therapies need to be tailored in some respect to the specific gene or gene defect (called a mutation) to be fixed. Each of these possible "fixes" carries a unique set of strengths and limitations that depend on what needs to be repaired and when and where that repair needs to occur during the genetic "decoding" process.

To explain why it's important to understand all of this complexity when designing therapeutics, let's discuss basic genetics. Biological information is permanently stored within every cell as DNA, but when that information is actively needed to build proteins and help the cell survive and function, a go-between—RNA—is called upon. But RNA is much more than a passive supporting molecule. Indeed, research has shown that it may have an active role in causing certain diseases, as well as in potentially treating them.

Of course, biology can't be that simple! As it turns out, RNA comes in multiple forms, two of which we will talk about here. Messenger RNA (mRNA), as the name conveys, delivers the genetic blueprint encoded by the DNA, while transfer RNA (tRNA) brings together the individual building blocks, or amino acids, that ultimately get stitched together to make a protein. Think of them as workers on a production line, each with a different job. Sometimes, a glitch in the system



An illustration of tRNA being delivered to rods (R) and cones (C) or RPE cells by various modes. AAV2.7m8 and AAV2/9 are two types of viral gene delivery. On the right are tRNA molecules encapsulated as biomolecules or DNA mini-circles (MC). Image credit: Pattnaik Lab.

causes a premature "work stoppage"—this specific type of glitch is called a nonsense mutation. A nonsense mutation literally causes the insertion of a genetic signal called a "stop codon," which abnormally shortens the protein. If this protein is needed for vision, blindness results.

Fortunately, a group of McPherson ERI investigators, along with colleagues at the University of Iowa, have a strategy to overcome nonsense mutations, which will be further developed and tested with the aid of a $7.7 million grant from the National Eye Institute. Their plan involves the production of specially engineered tRNA molecules that have the capacity to convert the premature stop codon to a usable amino acid, thus allowing a full and normal protein to be made. The complementary expertise of these researchers, led by **Bikash Pattnaik, PhD** (UW–Madison Department of Pediatrics), brings together human stem cell technology and animal models of human blindness to optimize their approach to treat diseased retinal pigment epithelium and photoreceptors. In addition to Dr. Pattnaik, an expert retina physiologist, the team includes McPherson ERI members **David Gamm, MD, PhD**, an expert in retinal disease modeling using human stem cells, and **Sarah Gong, PhD**, an expert in nanoparticle-mediated drug delivery. They will collaborate with University of Iowa investigator **Christopher Ahern, PhD**, the inventor of engineered tRNA technology.

The combined UW–Madison and Iowa team will focus on diseases caused by nonsense mutations in genes that code for proteins called ion channels. Faulty or absent ion channels can lead to a range of blinding diseases such as Leber congenital amaurosis (LCA), retinitis pigmentosa (RP), or Best disease. However, the team's ultimate goal is to develop therapeutic drugs that can correct nonsense mutations in all genes, regardless of what type of protein is affected. Success in this endeavor would have tremendous implications not only for restoring sight, but for restoring cell function throughout the body. That's because nonsense mutations are responsible not only for 15% of genetically inherited retinal diseases, but for the same percentage of all inherited human disease. Therefore, the benefits of making sense out of nonsense would be dramatic indeed.

Dr. Michael Altaweel Named to New Monroe E. Trout Chair

Michael Altaweel, MD, was named the first Monroe E. Trout Chair in Vision Research in January 2021. Dr. Altaweel, who joined the UW–Madison School of Medicine and Public Health faculty in 2000, is co-director of the Fundus Photograph Reading Center and the director of the Vitreoretinal Fellowship, a program that mentors trainees from around the US. Over the last 20 years, his involvement as an investigator in many clinical trials has changed the standard of care for the delivery of therapeutic agents to the eye. He has a strong interest in gene and stem cell therapies for the retina, and he is currently collaborating with stem cell programs at UW–Madison and the National Eye Institute. The Monroe E. Trout Chair is the third research chair at the Institute endowed by Dr. Monroe and Sandra Trout of Appleton, WI.

MCPHERSON ERI RESEARCHERS RECEIVE ACADEMIC, PROFESSIONAL HONORS

- In January, **Bikash Pattnaik, PhD** (Associate Professor, Dept. of Pediatrics and McPherson ERI/RRF M.D. Matthews Professor) received the Gerard B. Odell Award from the Department of Pediatrics, which honors a faculty researcher for outstanding research accomplishments.
- Two McPherson ERI scientists were recently elected to the American Institute for Medical and Biological Engineering (AIMBE) College of Fellows. **Kevin Eliceiri, PhD** (Professor, Dept. of Medical Physics and Dept. of Biomedical Engineering, and RRF Walter H. Helmerich Associate Director, McPherson ERI) and **David Gamm, MD, PhD** (Professor, Dept. of Ophthalmology and Visual Sciences, Sandra Lemke Trout Chair in Eye Research, and RRF Emmett A. Humble Distinguished Director, McPherson ERI) were selected in AIMBE's class of 2021. The AIMBE College of Fellows is comprised of the top two percent of medical and biological engineers in the country.

NEW DAVID G. WALSH AWARD SUPPORTS GRADUATE STUDENT RESEARCH

Two initial **David G. Walsh Graduate Student Support Initiative (GSSI) awards** were given in December 2020 to McPherson ERI graduate students. The awards, funded by the David G. Walsh Research Fellowship Fund, gives $12,000 each to two McPherson ERI members to support graduate students in their labs. This year's GSSI Award recipients were **Ari Rosenberg, PhD** (Dept. of Neuroscience), in support of PhD candidate **Lowell W. Thomson,** and **Nader Sheibani, PhD** (Dept. of Ophthalmology and Visual Sciences), in support of PhD candidate **Yong-Seok Song**. The McPherson ERI is grateful to the Walsh family and other Walsh Fund donors for their investment in training the newest crop of vision researchers.

Ari Rosenberg, PhD, Lowell W. Thomson, Nader Sheibani, PhD, Yong-Seok Song.

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Exercise for **Vision Research**
with your **TEAM**,
or on your **OWN**!

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Registration is now open!

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VISION RESEARCH NEEDS YOUR HELP

Cycle for Sight supports researchers who work to prevent, treat and cure blinding diseases at the McPherson Eye Research Institute at UW-Madison, Wisconsin's leading vision research institute.

This year, Cycle for Sight is more flexible than ever. Instead of gathering together indoors, teams and individuals will choose their own time, location, and type of exercise during the Cycle for Sight period. The McPherson ERI will help coordinate any team activities, with communication led by your team captain. You can still sign up with your team or as an individual.

Participants and supporters are encouraged to raise funds, which go toward vision research at UW-Madison.

More than 100,000 Wisconsinites deal with blindness or substantial vision loss. Please join us in exercising - indoors or outdoors - to help raise funds to combat vision loss!