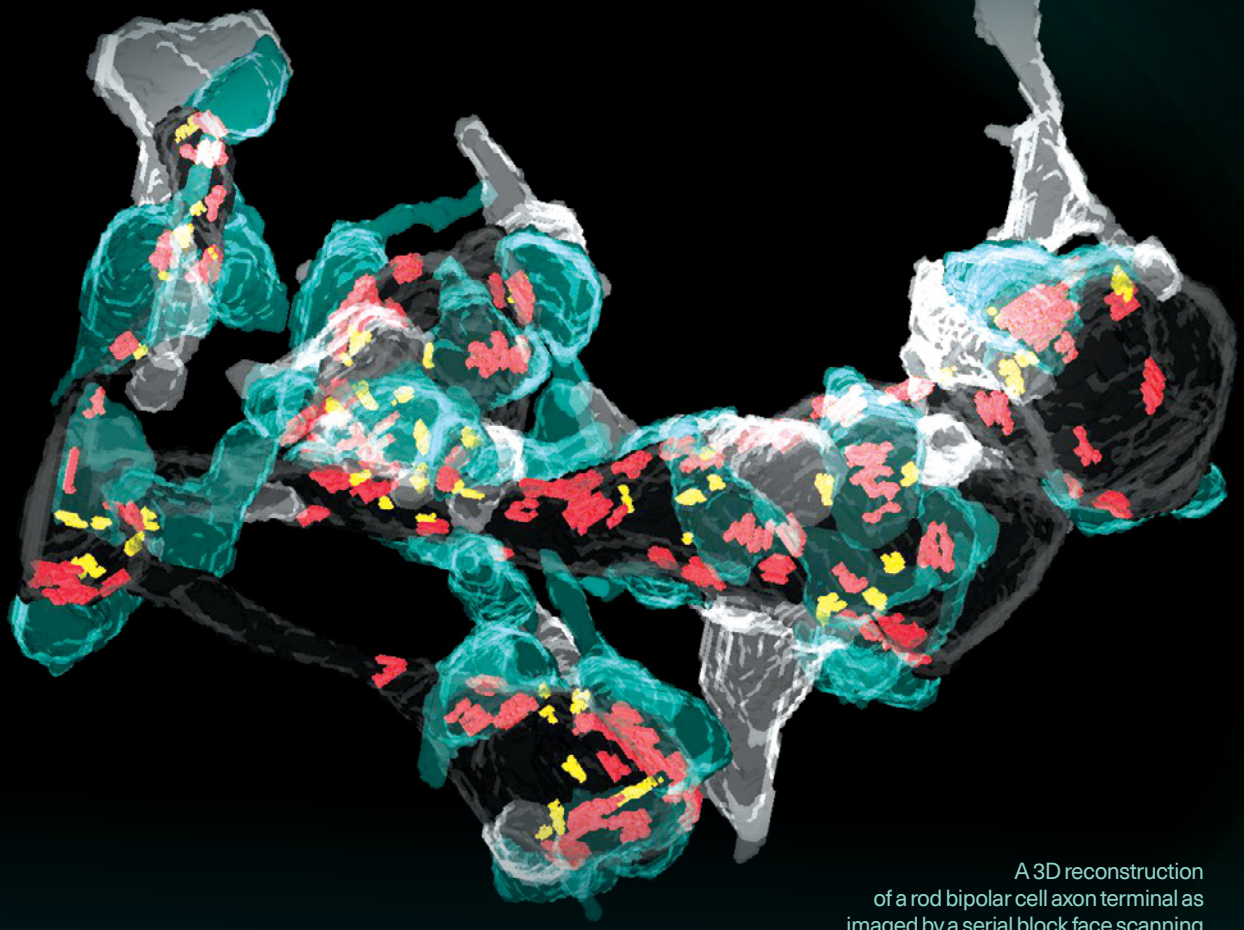
McPherson
Eye Research Institute
UNIVERSITY OF WISCONSIN–MADISON

InSights

Published each semester

FALL *2020*



A 3D reconstruction of a rod bipolar cell axon terminal as imaged by a serial block face scanning electron microscope. All synaptic sites (excitatory: yellow; inhibitory: red) and synaptic partners (green; silver) are shown in relationship to the rod bipolar cell terminal (dark gray). Image rendered from Sinha et al., Neuron 2020.

Remodeling neurons in the diseased retina

WITH MRINALINI HOON, PHD.

Photoreceptors are sensory neurons in the retina that convert light to electrical signals. To create vision, these signals are first transferred through secondary retinal neurons called bipolar cells, and then exit the retina to higher brain centers via long-range retinal neurons called retinal ganglion cells. It is a complex pathway that is disrupted in many types of retinal diseases, including inherited retinal degenerations (RD) like retinitis pigmentosa, which causes vision loss through death of photoreceptors.

Left, Julie Wallin; right, Mrinalini Hoon, PhD.

The Hoon Lab, led by Mrinalini Hoon, PhD, Assistant Professor of Ophthalmology and Visual Sciences, is interested in understanding how secondary retinal neurons — the bipolar cells — are altered during degeneration of photoreceptors, their primary input partner. Bipolar cells connect with other retinal neurons at specialized junctions called 'synapses'. As photoreceptors start to die, bipolar cells change their cellular architecture, synaptic connectivity, and functional response to visual cues. Understanding this process is essential to understanding changes throughout the degenerating retinal circuit and devising new drug-based strategies to restore its function.

Retinal photoreceptors come in two main types: cones that are responsive to bright light and communicate color vision, and rods that are sensitive to dim light and process signals for night vision. These photoreceptor types signal to specific and different downstream neurons. The Hoon lab targets these specific 'rod' vs 'cone' pathway neurons and their associated synaptic junctions using an array of highly sophisticated models and techniques to correlate structure and function, including high-resolution confocal microscopy, serial block face electron microscopy, and single cell electrophysiology. These approaches allow her lab to examine circuit changes on a "cell-by-cell" and "synapse-by-synapse" basis, a critical capability given the complexity of the retina.

Julie Wallin, a research associate in the Hoon lab, is using this precision approach to understand the microscale changes in rod and cone bipolar cell profiles and synaptic connectivity upon photoreceptor loss during RD. Using a method that enables visualization of specific retinal bipolar neurons in RD models, Julie has shown that rod bipolar cells remodel their processes (the dendritic branches and axon terminals that reach out to other cell types) as photoreceptors die, but cone bipolar cells are more resistant to remodeling their structure. Julie and the Hoon Lab team also identified specific inner retinal synaptic connections on bipolar cell axon terminals that are lost during RD. Understanding these alterations will unveil new targets for therapeutic interventions, perhaps allowing the reversal of vision loss and the restoration of visual function.

From the Director

Dear Friends of the McPherson ERI,

Important things come in very small packages, especially when it comes to understanding the complexities of our visual system and treating the diseases that threaten it. William Blake wrote of seeing the world in a grain of sand, a concept that has certainly been embraced by modern science and medicine. Devices of the smallest size, such as the photoreceptor-laden microscopic scaffolds described herein, hold immense promise in treating blinding diseases. And advances in imaging methods allow us to examine the most minute features and components in the eye — such as the junctures between retinal neurons studied in Mrinalini Hoon's lab — which also provide knowledge needed to develop new therapies. It is important to remember, in this year more than most, that the small and unseen can also be used to make our lives better.

Our year-end report and calendar, which you will receive quite soon, will explore other areas of McPherson ERI research and accomplishments in 2020. For now, please enjoy this more compact glimpse at some of our work. Thank you for your interest, and I truly hope that this finds you well.

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

Patching Injured Retinas

McPherson ERI researchers partner with DOD to develop stem cell therapy for service members with combat-related eye injuries.

From left: Joe Phillips, PhD; Shaoqin Gong, PhD; Zhenqiang Ma, PhD; Kapil Bharti, PhD. Not pictured: Richard Blanch, MBChB, PhD, MRCS

Dr. David Gamm's lab has been actively moving photoreceptor replacement therapies towards the clinical trial stage in recent years. Their work received a strong boost this past summer with a grant for more than $5 million from the Department of Defense, which will fund development and testing of an imicroscopic retinal patch to treat United States military personnel blinded in combat.

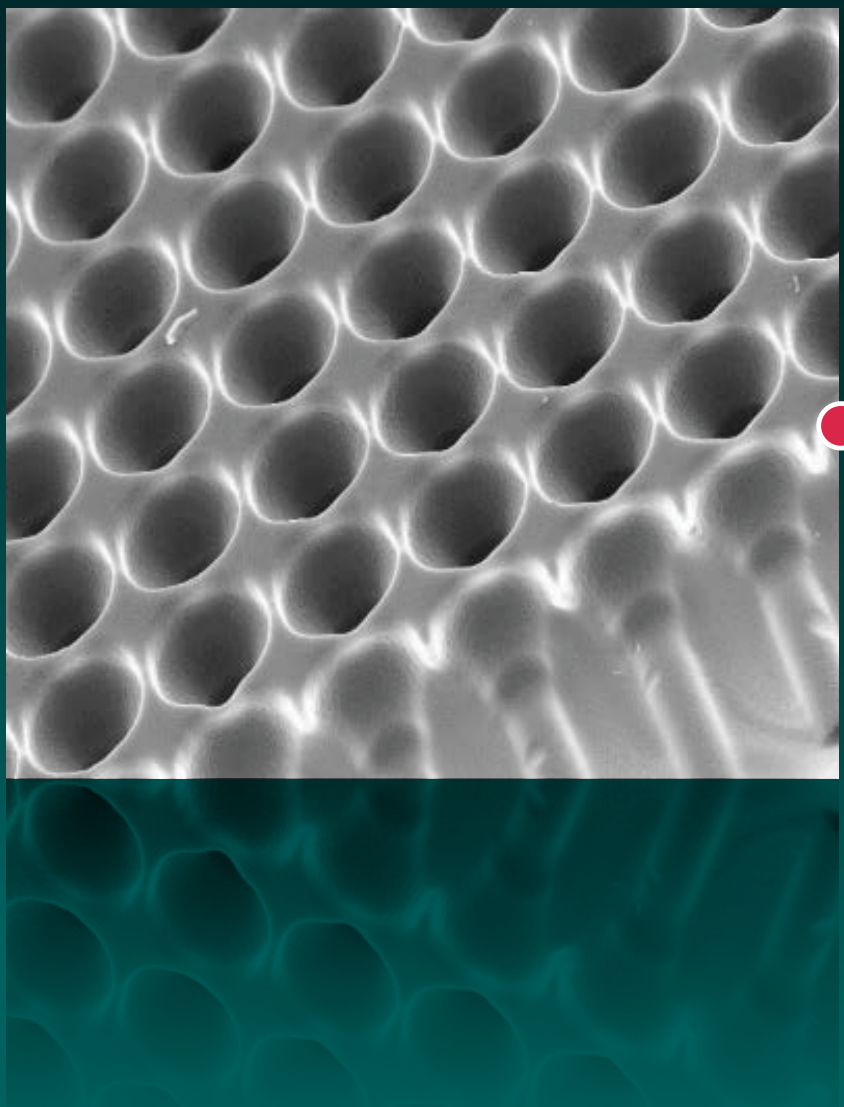
The new project, titled ***Outer Retina Reconstruction for Combat Afflictions***, or ORRCA, is a collaboration between the McPherson Eye Research Insitute at UW–Madison, the UW School of Medicine and Public Health and the UW College of Engineering, the U.S. National Eye Institute, the University of Birmingham, UK, and the British Army. Led by Dr. Gamm, Director of the McPherson ERI and Professor of Ophthalmology and Visual Sciences at the UW School of Medicine and Public Health, the project will develop a transplantable patch to restore vision to members of the armed forces injured by blasts or lasers.

"This is an incredibly exciting project to be a part of," Dr. Gamm said. "The collaboration between vision researchers at UW, the National Eye Institute, and in the U.K., along with our partnership with Opsis Therapeutics here in Madison, is critical to making this work happen."

Gamm enlisted Waisman Center Scientist Joe Phillips, PhD, along with the labs of long-standing collaborators Shaoqin Gong, PhD, Professor of Biomedical Engineering, and Zhenqiang Ma, PhD, Professor of Electrical and Computer Engineering, both at UW-Madison, to assist with various aspects of the research. The UW team will collaborate with Kapil Bharti, PhD, of the National Eye Institute and Richard Blanch, MBChB, PhD, MRCS, an ophthalmologist and researcher at the University of Birmingham, England. Blanch is also a lieutenant colonel in the British Army.

The DOD grant will fund development of the patch in four phases. Dr. Gamm and his team will work with Opsis Therapeutics to develop human photoreceptors, cells in the eye receptive to light sources, and retinal pigment epithelium, or RPE, a cell layer that underlies and assists photoreceptors, using human induced pluripotent stem cells (iPSCs).

Concurrently, the labs of Dr. Gong and Dr. Ma will generate biodegradable, micro-molded scaffolds (the patch) that allow the photoreceptor cells to organize in the most effective possible way, before transplanting them to the correct spot in the retina. From there, the Bharti and Blanch groups will generate testing systems for the patch that mimic the types of laser and blast injuries that are becoming more common in modern warfare. Development of surgical delivery techniques and functional testing will take place using the Yucatan pig, which has a similar eye structure to humans. If the technology shows promise in the Yucatan pig, it will allow the researchers to pursue clinical trials in humans, according to Dr. Gamm.

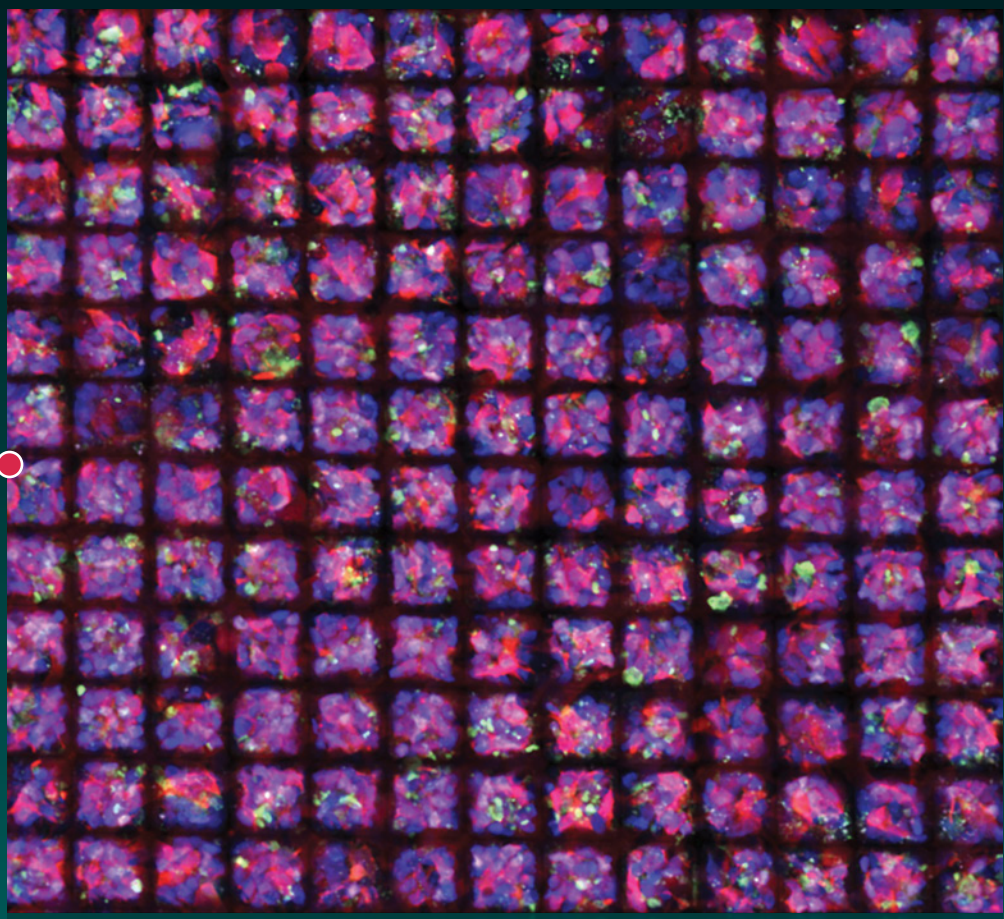


Microscopic image of a “wineglass” design photoreceptor scaffold. Image courtesy of the Ma Lab.

Military personnel often face blast injuries, as well as shockwaves or bright light from explosions. These types of trauma can damage photoreceptors and RPE, leading to permanent partial or total vision loss. When a photoreceptor dies, it has no ability to regenerate. “This patch would, in theory, replace the dead photoreceptors or RPE, and give the person another chance to see,” Dr. Gamm said.

In later life, many veterans (like many in the larger public) develop macular degeneration, a deterioration of their central vision that should also be amenable to the same strategy that Gamm is testing for combat-wounded service men and women. “Photoreceptors and RPE cells die as a result of many types of retinal diseases and injuries,” said Dr. Gamm. “This technology could one day not only help restore sight to those who are injured while serving our country, but to their loved ones back home as well.”

Article courtesy of Andrew Hellpap.



Human pluripotent stem cell-derived photoreceptors (cell bodies labeled in red, nuclei labeled in blue) grown on a biodegradable scaffold designed to replace cells lost to retinal degenerative diseases. This image has been magnified 20x with a confocal microscope to visualize rod (lavender) and cone (green) photoreceptors. The scaffolds are thinner than a sheet of office paper and can fit on a fingertip. Image courtesy of Allison Ludwig, Gamm Lab.

Expanding Our Vision Grants: New Support for Researchers

The McPherson ERI's Expanding Our Vision (EOV) grant program was started this year to provide awards of up to $10,000 to researchers performing vision-related research in visual communication, visual cognition, visual perception/performance, data visualization, development of novel imaging techniques for the visual system, computer sciences, and/or bioinformatics. Research in these areas is essential for understanding the intricacies of human vision and for enhancing our ability to visualize cells and processes in the eye, and to analyze large and complex datasets.

Five projects were awarded EOV grants in October 2020:



Andrea Mason (Kinesiology) and **Leigh Ann Mrotek & Robert Scheidt** (Biomedical Engineering, Marquette University)

- *Impact of visual cue saliency during bimanual visually guided reach-to-grasp*

Ari Rosenberg (Neuroscience)

- *Hierarchical cortical processing of three-dimensional visual motion.*

Sushmita Roy (Biostatistics & Medical Informatics)

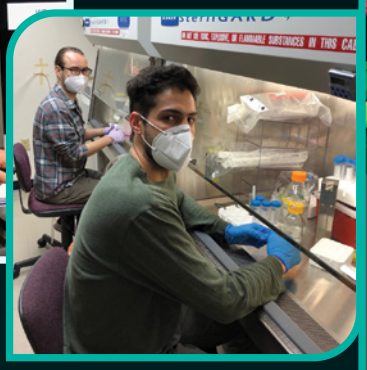
- *Computational approaches for characterizing cell type dynamics in human retinal tissue.*

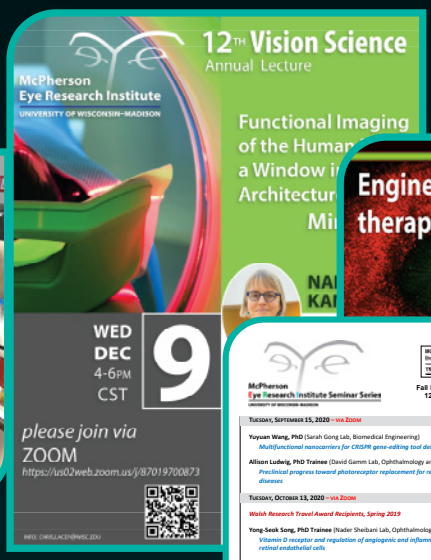
Karen Schloss (Psychology)

- *Understanding dimensional structure underlying color-concept associations to advance visual communication.*

Andreas Velten (Biostatistics & Medical Informatics)

- *Measuring ocular retroreflectance for remote ocular diagnostics.*





McPherson ERI events have gone online this fall.

Ikeda Lab members Aki Ikeda (top) and Richard Shipman and Sam Grindel (right).

COVID-19 and the McPherson ERI

COVID-19 has posed challenges to the McPherson ERI this year, as it has to the University as a whole. But like many challenges, it provided opportunities to enhance efficiency and spur innovation. Over the past year, the Institute has become even more nimble and adaptable — necessity being the mother of invention, of course. McPherson ERI member labs shifted to only performing essential laboratory activities for a few months, which allowed us to focus on grant applications and planning for future research. Over time, labs carefully increased their level of activity while conforming to the well-thought out university guidelines to optimize the safety of all.

Other McPherson ERI operations have also adapted. Our seminars, lectures, and other programs have moved online (including a highly successful Vision Research Update in July). Cycle for Sight 2021 will move ahead as **Cycle for Sight *Plus*** (how's that for staying positive?), with more flexibility and outdoor options. Details will be announced soon. We will continue to adapt as circumstances warrant, keeping our eye on the goal — the continuance of critical, world-leading vision research.

Please remember that gifts to the McPherson ERI through December 31st, 2020 — up to $100,000 — will be matched by Roger & Lynn Van Vreede!

More at **vision.wisc.edu/giving**

Stay tuned for information about Cycle for Sight *Plus*, Spring 2021!

T (608) 265-4023 **E** info@vision.wisc.edu **W** www.vision.wisc.edu **A** McPherson Eye Research Institute | 9431 WIMR | 1111 Highland Avenue | Madison WI 53705

Newsletter design: Malin Nordlund www.malinnordlund.com