McPherson Eye Research Institute
UNIVERSITY OF WISCONSIN–MADISON

InSights

Published each semester

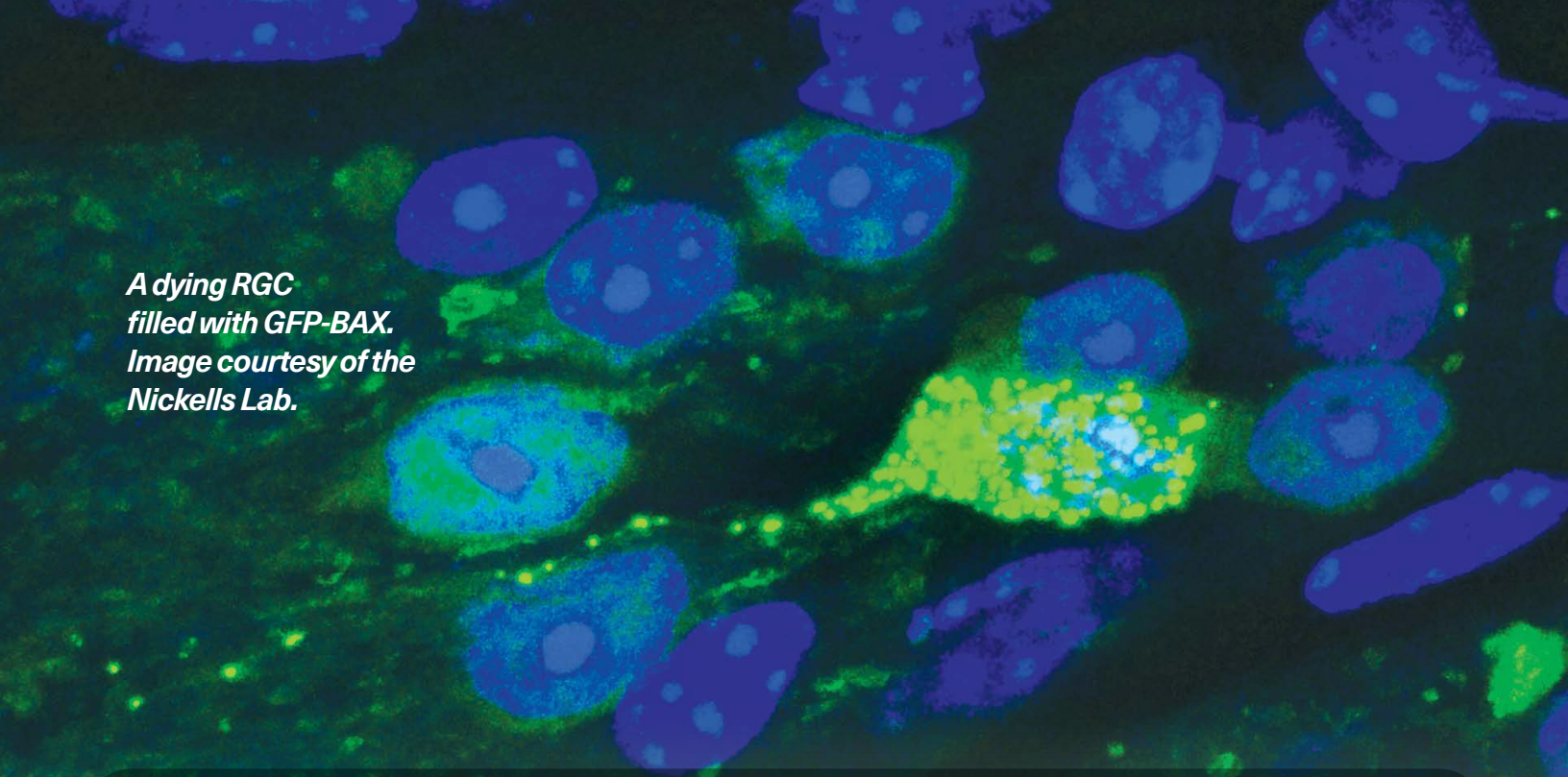
SPRING *2022*

Fighting Glaucoma Head-On

Glaucoma, one of the most common eye diseases of the aging human population, is characterized by degeneration of the optic nerve due to irreversible loss of retinal ganglion cells (RGCs). The only treatments currently available for glaucoma act to lower intraocular pressure, which is a prominent risk factor for the disease. But while lowering eye pressure is effective at slowing the progression of glaucoma in most cases, it does not directly address the death of RGCs. Moreover, many affected individuals continue to lose vision despite achieving normal eye pressures.

Rob Nickells' lab has been working to directly halt the degeneration of damaged RGCs by studying the pathology that is activated in these cells at the molecular level. Using animal models of glaucoma, they found that a critical part of the cell death process (called **apoptosis**) is controlled by the interaction of a particular group of proteins. By genetically altering one of these proteins, called BAX, they could virtually halt the process of RGC death indefinitely in mice with glaucoma.

Before BAX begins to signal for a cell to die, it undergoes a two-step activation process. First, inactive (or latent) BAX proteins are drawn ("**translocated**") to the surface of organelles called mitochondria. In the second step, translocated BAX protein changes its shape, allowing it to insert itself into the surface of the mitochondria. This second step marks the point of no return in cell death. Inserted BAX molecules create holes in the mitochondria that disrupt this organelle's critical function, which is to provide energy to the cell. Simultaneously, BAX proteins initiate a cascade of events that quickly degrade the remaining parts of the cell.



A dying RGC filled with GFP-BAX. Image courtesy of the Nickells Lab.

The Nickells group has shown that the transition from step one (translocation) to step two (shape change) may take several days to occur—and in some cases, the first step in the process can be reversed, allowing RGCs to survive. These observations offer a window of opportunity to therapeutically intervene in the BAX activation process to prevent the loss of these critical cells. What would such a therapeutic intervention look like? We've all heard that "offense wins games, but defense wins championships." One promising option is to bolster the cell's natural defense mechanisms against BAX activation.

In healthy RGCs, BAX is involved in an intricate dance with a partner called BCLXL—a member of the same gene family—which antagonizes BAX and prevents cell death. BCLXL removes BAX from the surface of the mitochondria and sends it back into the cytoplasm, where it remains harmless. However, BAX has allies, too. During cell death, BAX is aided by "BH3-only" proteins, which block the protective function of BCLXL and help BAX accumulate on the mitochondria. Based on these findings, a therapeutic that is capable of shifting the balance in this tug-of-war by decreasing the influence of BAX or increasing the influence of BCLXL should increase the number of RGCs that ultimately survive.

Excitingly, early tests in the Nickells Lab bear out this hypothesis. The lab created a virus that introduces extra copies of the BCLXL gene into RGCs. RGCs treated with the virus increased their production of BCLXL protein—enough to inhibit BAX activation ***even in the presence of helper BH3-only proteins***. Treatment of mice with this BCLXL gene therapy has shown a dramatic lessening of glaucoma-related damage in mice. **In the next step**, the Nickells Lab will collaborate with another McPherson ERI member, Dr. Gillian McLellan, to test this treatment in eyes that are more similar to the human eye. Their hope is to bring this exciting RGC-saving technology to patients to protect vision when other treatments fail.

FROM THE DIRECTOR

Dear Friends of the McPherson ERI,

Fixing a problem usually requires a good understanding of both its cause and the tools needed to repair or prevent the damage it inflicts. In science and medicine, all too often we lack critical knowledge in these areas and thus remain in the dark about how best to treat a disease.

This edition of *InSights* provides prime examples of how McPherson ERI researchers are striving to restore and protect sight by examining the root causes of blinding diseases and developing new therapeutic tools to treat them. These projects, led by Dr. Rob Nickells' lab (on the cover) and Dr. Raunak Sinha (interior), reflect the wide range of strategies being tested in the Institute to address vision problems that continue to plague humankind.

The Nickells lab has uncovered key steps in glaucoma that lead to the death of retinal ganglion cells, including the protein components that fight for or against this cell death process. By manipulating the balance of these components using therapeutic tools they created, his team is working to halt the loss of retinal ganglion cells and preserve sight for patients with glaucoma.

But what tools are available to fix the damage once cells are terminally lost? Dr. Sinha's team of investigators recently showed that lab-grown cone photoreceptors have the potential to respond to blue, red, and green light nearly as well as cones located in the very center of adult primate retinas. These results provide a huge boost of confidence for the Institute's efforts to hone stem cell-based "tools" to replace photoreceptors in retinitis pigmentosa, Usher syndrome, and macular degeneration, among other conditions.

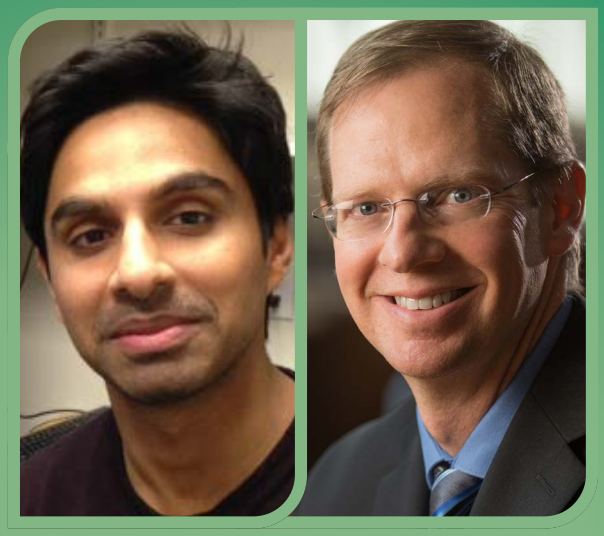
Of course, not every strategy is going to succeed at fixing its targeted problem, which means continued innovation is essential. By lifting the veils of disease and building cutting-edge therapeutic tools, our dedicated research teams are pushing forward to make a difference in the lives of the people we serve.

Thank you for your help and interest,

RRF Emmett A. Humble Distinguished Director, McPherson ERI
Sandra Lemke Trout Chair in Eye Research

Seeing the Light

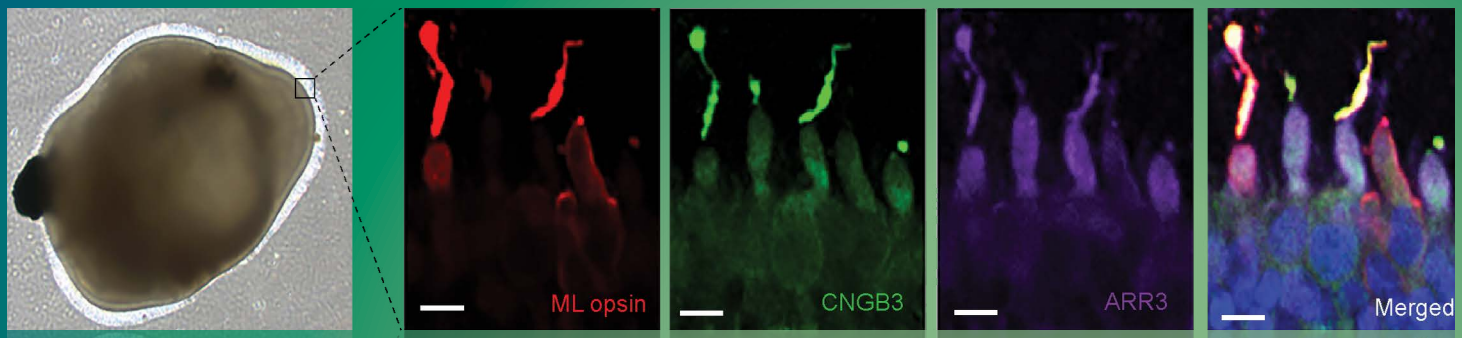
A new landmark study finds photoreceptor cells from retinal organoids can replicate key functions of vision.



Two McPherson ERI researchers have shown for the first time that retinal cone photoreceptors derived from human pluripotent stem cells are capable of the complex process of detecting light, and of converting that signal to electrical waves. Their results, recently published in the journal *Cell Stem Cell*, could unlock new therapeutic avenues for treating vision loss, with lab-grown retinal organoids serving as replacement sources for human photoreceptor cells.

Photoreceptor cells—rods and cones—are key to vision. Both types are found in the retina, with rods handling dim light and peripheral vision and cones handling brighter light, color, and high acuity vision. In lab-grown retinal organoids, the cone photoreceptors are similar to cones in the primate fovea, a specialized area of the eye responsible for high-definition vision. "The retinal organoids grown in our lab look remarkably similar to real human retinas," says David Gamm, MD, PhD, director of the McPherson Eye Research Institute. "They've got the correct cell types and the necessary sub-cellular structures to function appropriately. But it remained uncertain whether they could adequately replicate the fundamental function of the retina, which is to detect light."

Enter neuroscientist Raunak Sinha, PhD, the McPherson ERI's David and Nancy Walsh Family Professor in Vision Research. The Sinha lab studies how neural circuits operate in the retina, most particularly in the fovea. In a collaboration between the UW–Madison Department of Neuroscience and Department of Ophthalmology and Visual Sciences as well as the McPherson Eye Research Institute, Sinha and Gamm looked at cone photoreceptors from retinal organoids that were allowed to mature in the lab for roughly eight months to ensure uniformity. Using advanced electrophysiological techniques to analyze electrical activity, the researchers were able to demonstrate robust, color-specific light responses in the organoid



A mature retinal organoid (left) and its cone photoreceptors (labeled in red, green, and purple to confirm expression of important cone proteins). Images courtesy of the Sinha and Gamm Labs.

cones. Additionally, the lab-cultured cells functioned on par with cones present in the normal primate fovea. "The cells responded in a remarkable fashion," Gamm says, "and could differentiate between red, green and blue light, just like in normal human cones."

The ramifications of the study are huge. "For diseases like macular degeneration where cones in the central-most part of the retina die, causing blindness, there are currently no treatment options," says Sinha. "But with the advent of stem cell technology, you can make these stem cells grow into three-dimensional mini retinas containing cones that can replicate the physiology and function of foveal cones."

Sinha and Gamm have now turned their efforts toward improving the retinal organoids' light-evoked electrical responses, and bringing them closer to the performance of actual human fovea. In addition, the collaborative team led by Sinha and Gamm—which includes researchers Aindrila Saha and Beth Capowski—is using organoids derived from patients to model retinal degenerative diseases in a dish. "These patient-derived retinal organoids are helping us understand how different retinal diseases affect photoreceptor function, and how gene therapy could be used to treat patients," Sinha says.

Gamm adds, "The more we can push retinal organoids to perform at a high level in a [cell culture] dish, the more confidence we have that they may help patients with blinding disorders."

Adapted from an article by Chris Malina

McPHERSON ERI NOTES

SPRING 2022

Van Vreede and Brandt Gifts will fund studies in age -related macular degeneration (AMD) and retinitis pigmentosa (RP)

Generous gifts from Appleton donors **Roger and Lynn Van Vreede**, as well as the **Robert A. Brandt Macular Degeneration Fund**, will fund new pilot grants in 2022 for research in two McPherson ERI disease focus areas. The Van Vreedes and the Brandt estate will each fund a pilot grant for AMD, to be awarded after a competitive review process. Roger and Lynn Van Vreede have funded multiple McPherson ERI endeavors in recent years, and the majority of their gift of $150,000 will be used to fund grants for research in AMD and RP. The gift from the estate of the late Robert A. Brandt, who received his BA and two Master's Degrees from UW-Madison, will be used to fund a second AMD research award.

Graduate student award provided to McPherson ERI trainee Mohan Ji

The 2021 **David G. Walsh Graduate Student Support Initiative (GSSI) Award** was given in December 2021 to McPherson ERI and Department of Psychology investigators 1 **C. Shawn Green, PhD**, and 2 **Emily Ward, PhD**, to support the thesis work of 3 **PhD candidate Mohan Ji**. The award, funded by the David G. Walsh Research Fellowship Fund, provides $12,000 for graduate student tuition. Ji's research focuses on understanding key aspects of human visual perception and their roles in determining evolutionary fitness. The McPherson ERI is grateful to the Walsh family and other Walsh Fund donors for their investment in trainee vision researchers.

McPherson Endowed Lecture

Artificial Intelligence and Data Science for Eye Care: Perspectives from the National Eye Institute

featuring

Dr. Michael F. Chiang

Director of the National Eye Institute at the National Institutes of Health

Artificial intelligence and data science have the potential to change the landscape of clinical care and research in ophthalmology. This talk will discuss the promises and challenges in this field, as well as ways in which the National Eye Institute hopes to work with the scientific community to address those challenges.

June 23, 2022

Reception - 3:00 PM

Lecture - 4:00 PM

Health Sciences Learning Center (HSLC)
Room 1306 - 750 Highland Ave., Madison WI

Generously supported by the McPherson Eye Research Institute Lectureship Fund

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