



InSights

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Getting Ahead of Glaucoma

WITH COLLEEN MCDOWELL, PhD.



By far the best way to defeat any disease is to stop it before it causes a problem, particularly if that problem is permanent. The laboratory of Colleen McDowell – the newly-named William and Phyllis Huffman Research Professor in the Department of Ophthalmology and Visual Sciences – focuses on the molecular pathways associated with the development and progression of glaucoma, in the hope of blocking the disease’s progression before damage arises.

The glaucomas are a diverse group of diseases, affecting 70 million people worldwide, that can lead to blindness through optic nerve damage. One of the major risk factors for the development of glaucoma is an increased pressure inside the eye (high intraocular pressure, or IOP). This occurs when fluid is not removed properly through the drainage structures in the front of the eye, known as the trabecular meshwork (TM). Dr. McDowell’s laboratory aims to understand the processes that regulate the construction and maintenance of these drainage structures, and how changes in the TM prevent proper drainage in the eye. More specifically, her research focuses on the development and regulation of elevated IOP, as well as the effect that elevated IOP has on the survival of retina ganglion cells (RGCs), whose over 1 million axon projections comprise the optic nerve.

To develop novel glaucoma therapies, relevant animal models are required to first understand the mechanisms responsible for glaucoma-related damage to the eye. Mouse models of glaucoma are an excellent choice since scientists can accurately measure their IOP, assess damage to their optic nerve, and readily employ powerful genetic tools. The McDowell Lab has developed a new mouse model of inducible glaucoma by injecting human glaucoma genetic material into the eye.

L-R, Timur Mavlyutov, Tanisha Perlmutter, Colleen McDowell, Philip Mzyk



This model is unique in that it can be used across many different types, or “strains”, of mice, all of which show similar observable characteristics. Furthermore, the damage that occurs in these mice mimics human glaucoma by using similar pathogenic pathways (TGF- β 2) to raise IOP.

Using her new technique, Dr. McDowell successfully raised the IOP in a variety of mouse strains, resulting in the discovery of a unique molecular pathway involved in the development of glaucoma-related damage to the TM. By carefully comparing the different mouse strains that were injected with the human genetic material, McDowell was able to identify a mutation in TLR4 (toll-like receptor 4) that mitigates the high IOP in mice. Excitingly, McDowell’s lab has also identified a new mouse model of glaucoma that sheds light on the signaling that occurs within the cell after TLR4 is activated. Based on these results, McDowell has developed a novel hypothesis that implicates interactions between different cell signaling systems in the process leading to glaucoma.

Projects in Dr. McDowell’s laboratory that directly test this hypothesis include:

- 1.** Post-doctoral trainee Philip Mzyk is using the lab’s mouse model systems, as well as TM cells isolated from human donor eyes, to identify novel molecules that may regulate IOP elevation in glaucoma.
- 2.** Senior Research Assistant Timur Mavlyutov is using advanced imaging techniques to study the fine details and changes that are occurring in the glaucoma-affected TM and optic nerve head.
- 3.** Research Assistant Tanisha Perlmutter is helping to develop several new transgenic mouse strains and characterize their IOP profiles over time to identify new models of glaucoma.

These data are invaluable to the field of glaucoma research because they provide avenues to study damage caused by glaucoma, and also to test novel therapeutics that regulate IOP and minimize retinal ganglion cell and optic nerve damage, thereby preserving sight.

From the Director



Dear Friends,

We are sending this newsletter to you while most of the country – and much of the world – is staying close to home, focused on limiting the spread of COVID-19. That is essential, of course, and I hope that you and your loved ones are taking care of yourselves and staying well. As we navigate these unprecedented times, McPherson ERI investigators, along with our colleagues in other research fields, are doing our part to keep our communities as safe as possible. In addition, we are working diligently and responsibly to ensure that we can “pick up where we left off” when this crisis abates. The strength of this University and of the McPherson ERI has always been rooted in the brilliance, resilience, resourcefulness, and compassion of its people. For that reason, I have no doubt that we will come out the other side more determined and streamlined in our mission than ever before (and perhaps even a bit wiser).

In this issue, we shine a spotlight on several of the McPherson ERI’s glaucoma researchers. Glaucoma causes damage to the 1.2 million retinal ganglion cells whose axons or “wires” comprise the optic nerve (the cable that connects the retina to the brain). Despite numerous advancements over the decades, we still don’t know the underlying causes of the most common forms of glaucoma. To add to the problem, glaucoma is an insidious disease, often going undetected by patients and doctors alike until its later stages. As noted in the adjacent articles, UW-Madison is a world leader in glaucoma research, having attracted a core group of outstanding glaucoma researchers, starting with Dr. Paul Kaufman in the mid-70s. These scientists often work in tandem with clinicians (and some are clinicians themselves) in the Department of Ophthalmology and Visual Sciences to further this critical research.

Although this issue of *InSights* focuses on glaucoma, we continue our fight against many blinding disorders such as retinitis pigmentosa and age-related macular degeneration. Recent additions to the Institute’s roster of endowed research positions from the Trout family – the new Monroe E. Trout Chair in Vision Research and the conversion of the Timothy William Trout Professorship in Eye Research to a full chair level – will bolster the research of two cutting-edge McPherson ERI investigators (including the current Timothy William Trout Professor, Akihiro Ikeda). We’re very grateful to the Trouts, and to Roger and Lynn Van Vreede, whose 2019 year-end donor match drew an exceptional response from many of you.

As we deal with this current challenge in our daily lives, please know that we appreciate your support and interest, and that we will continue moving forward.

Sincerely,

A handwritten signature in black ink that reads "David M. Gamm". The signature is fluid and cursive, with a prominent loop at the end.

David M. Gamm, MD, PhD

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

Glaucoma research

45 years of leadership



When Paul Kaufman arrived at UW-Madison in 1975, there was only one half-day per week glaucoma clinician, and glaucoma research was just beginning

Today, UW-Madison is the home of a major glaucoma research enterprise containing a constellation of stellar research teams. This growth, which Kaufman helped develop over the last 25 years, including his ten years as chair of the Department of Ophthalmology and Visual Sciences, was led by young and mid-career faculty, and has transformed UW-Madison into one of the largest, most prolific glaucoma research centers in the country.

Dr. Kaufman himself leads an influential glaucoma research group, which studies the physiology and pharmacology of ocular fluid drainage, seeking new pathophysiological insights and novel therapeutic approaches to reducing intraocular pressure (IOP). His research has led to (and played a part in) the development of several new glaucoma drugs now on the market. UW-Madison researchers study many different aspects of glaucoma and are also involved in the development of next generation therapies for this blinding condition. Colleen McDowell, featured on this issue's cover, studies the molecular pathways that induce glaucoma, while Gillian McLellan, our *InSights* cover story researcher in Summer 2019, focuses on glaucoma in veterinary patients, including cats and dogs. Three other researchers are profiled here.

L to R: Josh Grosser, Ryan Donahue, Rachel Fehrman (now at MCW), Joel Dietz, and Robert Nickells.



Robert W. Nickells, PhD

Professor & Frederick A. Davis Chair of Ophthalmology,
Department of Ophthalmology & Visual Sciences

Glaucoma is a disease that affects the optic nerve, leading to the death of retinal ganglion cells (RGCs), which collect all the neurosensory signals created by the retina and then send that information to the visual centers in the brain. Rob Nickells' lab is developing a treatment that directly targets the processes that result in RGC death. His research also offers insight on the neuronal cell loss that occurs in nearly all age-related neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. Dr. Nickells strongly believes that what is learned about RGCs will have broad-reaching therapeutic consequences for these afflictions as well.

The Nickells group has been studying how RGCs die for over two decades. They know that there are many complicated and overlapping molecular events that play a role in this process, but their focus is on a pro-death protein called BAX. Interestingly, if the BAX protein is removed from mice, they acquire complete resistance to neuronal death after damage to the optic nerve. Says Dr. Nickells, "With all the complicated molecular biology associated with the pathology of these cells, everything seems to funnel down to the activation of the BAX protein."

His lab has learned a great deal about how BAX works in RGCs, which is essential for developing treatments that target this protein. Great care must be taken, though. BAX may be a cell killer, but it also has a very important role in maintaining the health of critical intracellular structures called mitochondria. These organelles create the energy a cell needs to function. In a dying cell, however, BAX shows a darker side, causing mitochondria to stop functioning and break apart. Therefore, the Nickells lab's strategy is to understand how to reduce the amount of BAX in RGCs just enough to preserve its good function, while preventing it from becoming a bad actor. Ultimately, they hope to develop a therapy that increases the tolerance of RGCs to the damaging influence of elevated IOP. The combined approach of preventing the activation of "bad" BAX and lowering IOP may slow or halt the progression of glaucoma.



Donna Peters, PhD

Professor, Department of Pathology & Lab Medicine

Donna Peters directs a laboratory that studies the causes of primary open-angle glaucoma (POAG) and glaucoma caused by the use of corticosteroids. Clinically, these two types of glaucoma are very similar. Both are age-related diseases in which there is a buildup of resistance to the movement of aqueous humor out of the eye. This buildup causes an increase in IOP, which leads to the degeneration of the optic nerve and irreversible blindness. The restriction in fluid movement is attributed to an increase in the deposition of proteins in the drainage system along with changes in contractile cell forces needed for fluid movement. Central to both of these processes are signaling events mediated by a family of receptors on the surface of cells called integrins.

The Peters Laboratory has shown that an increase in the activity of a specific member of this family of receptors, called $\alpha\beta3$ integrin, may be involved. Their studies have shown that the increased activity of this receptor contributes to both the increase in the deposition of the proteins and the changes in the contractile properties of cells. Currently, her laboratory is looking for ways to control the activity of $\alpha\beta3$ integrin and trying to understand why its activity is increased in glaucoma. Understanding how $\alpha\beta3$ integrin regulates these processes is an important step in identifying new targets to decrease IOP.



T. Michael Nork, MD, MS

Professor, Department of Ophthalmology & Visual Sciences

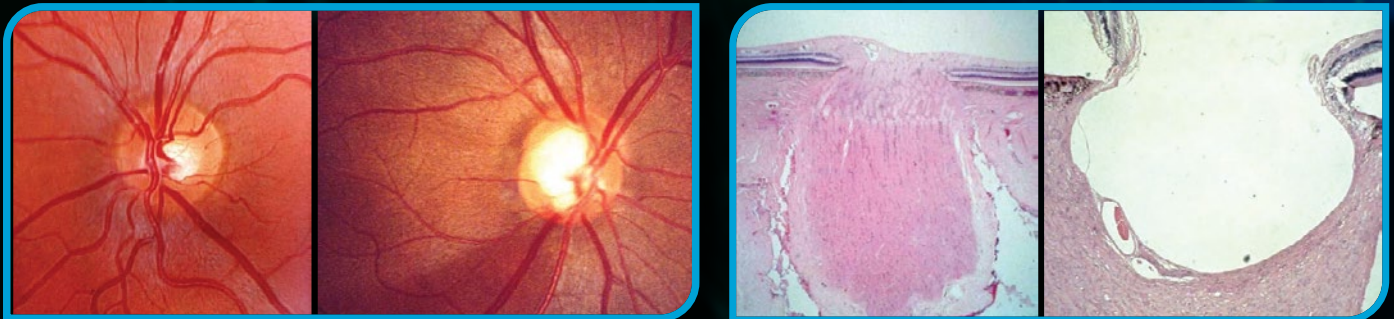
Both vascular and physical mechanisms of optic nerve injury have been proposed as potential causes of glaucoma. Neither of these, however, would account for the characteristic blue-yellow color confusion seen in patients with glaucoma, which is more characteristic of acquired retinal injury than optic nerve dysfunction.

As a retinal specialist with training in ophthalmic pathology, Dr. Nork became intrigued by this disparity. Several years ago, his lab acquired a large number of post-mortem eyes from individuals with and without glaucoma. They found that the cone photoreceptors were markedly swollen, which

is a characteristic of neuronal ischemia (lack of oxygen). Dr. Nork's lab proposed the hypothesis that elevated IOP causes decreased blood flow to the outer retina (rods and cones), resulting in low oxygen levels in the retina and swelling of the cones. The cones then either release or fail to re-uptake the neurochemical known as glutamate, which leads to retinal ganglion cell toxicity.

More recently, Dr. Nork's lab, working with a primate model of glaucoma, has found effects of glaucoma on the functioning of the retinal cones, consistent with their hypothesis. Through close examination of these retinas, they have also found increased glutamate activity. Dr. Nork is currently testing his hypothesis further by injecting a naturally occurring chemical into blood vessels that supply the retinal cones. In preliminary work with rabbits, they have demonstrated the ability to reduce blood flow to the retina in a predictable way without raising IOP. Should this experimental approach prove relevant to the mechanism causing glaucoma, entirely new treatment options might be made available.

These labs are only three among many, all working on methods to treat and, ideally, cure various types of glaucoma. As Paul Kaufman notes, "With the bright, hard-working, well-trained research staff in so many UW labs, we can expect many more new discoveries, leading to novel therapeutics for the world's most common cause of irreversible vision loss and blindness."



Left pair: Image of an optic nerve head from a person without (left) and with (right) glaucoma. (Courtesy of Online Journal of Ophthalmology).

Right pair: Cross section of an optic nerve head from a person without (left) and with (right) severe glaucoma. (Courtesy of Morton Smith, MD.)

McPherson ERI Notes

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Monroe & Sandra Trout, True Visionaries

Trout Family Endowment Gifts Will Support Two New
Endowed Chairs

Monroe and Sandy Trout have been fervent supporters of the McPherson ERI since 2012, when an Institute program at the Trout Museum of Art in Appleton kicked off a close relationship between the Trouts and vision research. Soon after that Appleton event, the Trouts – spurred by Monroe’s struggle with macular degeneration – began to learn more about the extensive work underway by McPherson ERI scientists on that devastating and intractable condition. Service on the McPherson ERI’s Honorary Advisory Board exposed them to regular briefings from a wide range of Institute scientists. All of this led to their establishment of two endowed positions, the Sandra Lemke Trout Chair in Eye Research (held by David Gamm, MD, PhD) and the Timothy William Trout Professorship in Eye Research (held by Akihiro Ikeda, DVM, PhD).

In January, the Trouts deepened their investment in vision research once again by establishing the Monroe E. Trout Chair in Vision Research, a new endowed position that will support outstanding research in age-related macular degeneration. (Their \$1 million gift to establish this Chair will be matched by \$1 million from the newest Morgridge match). The next month, Monroe and Sandy decided (in tandem with the Morgridge match) to double the endowment of the Timothy William Trout Professorship, raising it to the level of a chair. These additions will allow two outstanding researchers to further broaden their important work.

The Trouts are determined to make a difference, as also shown by their September 2019 gift of \$2 million to the Trout Director’s Fund for Vision Research, which supports every aspect of McPherson ERI research and operations. As Monroe told the SMPH Quarterly in 2016, “I have macular degeneration, and I know I might not see the benefits of current research in my lifetime. But we hope we can help researchers find ways to prevent and possibly someday cure a disease which impacts millions of Americans.”

McPherson ERI Notes

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Roger and Lynn Van Vreede, a Matched (and Matching) Pair

Van Vreedes Spur Year-End Giving Through a
Generous and Successful Match Offer

New McPherson ERI Advisory Board members Roger and Lynn Van Vreede have a great deal of experience in encouraging giving. Skilled in business (Roger was the longtime owner of Van Vreede's appliance stores in the Fox River Valley), they have generously donated to many causes, with a particular interest in the environment. They particularly enjoy offering match opportunities in order to encourage giving by others.

In early fall 2019, the Van Vreedes offered to match the McPherson ERI's November and December charitable gifts, up to \$100,000. Inspired by this offer, our donors responded with more than \$120,000 in year-end gifts, well over the Institute's previous year-end giving for that period.

Roger and Lynn were introduced to the McPherson ERI by Monroe and Sandy Trout, good friends and fellow bridge players. The Trouts were aware of the Van Vreedes' experience with macular degeneration. As Roger notes:

"We each have a parent with age-related macular degeneration, and are witnessing the pain and frustration that they are undergoing – the loss of the ability to read easily, to drive, to do so many things that they did without a second thought for so many years. Lynn and I feel that it is critically important to support the scientists who will cure this and other diseases in years to come."

With the addition of Roger and Lynn's match amount, the McPherson ERI's research funding received a fantastic lift in 2019. We begin 2020 grateful for new friends and thankful to all those who responded so generously.

You can support the McPherson ERI at vision.wisc.edu/giving. Thank you!