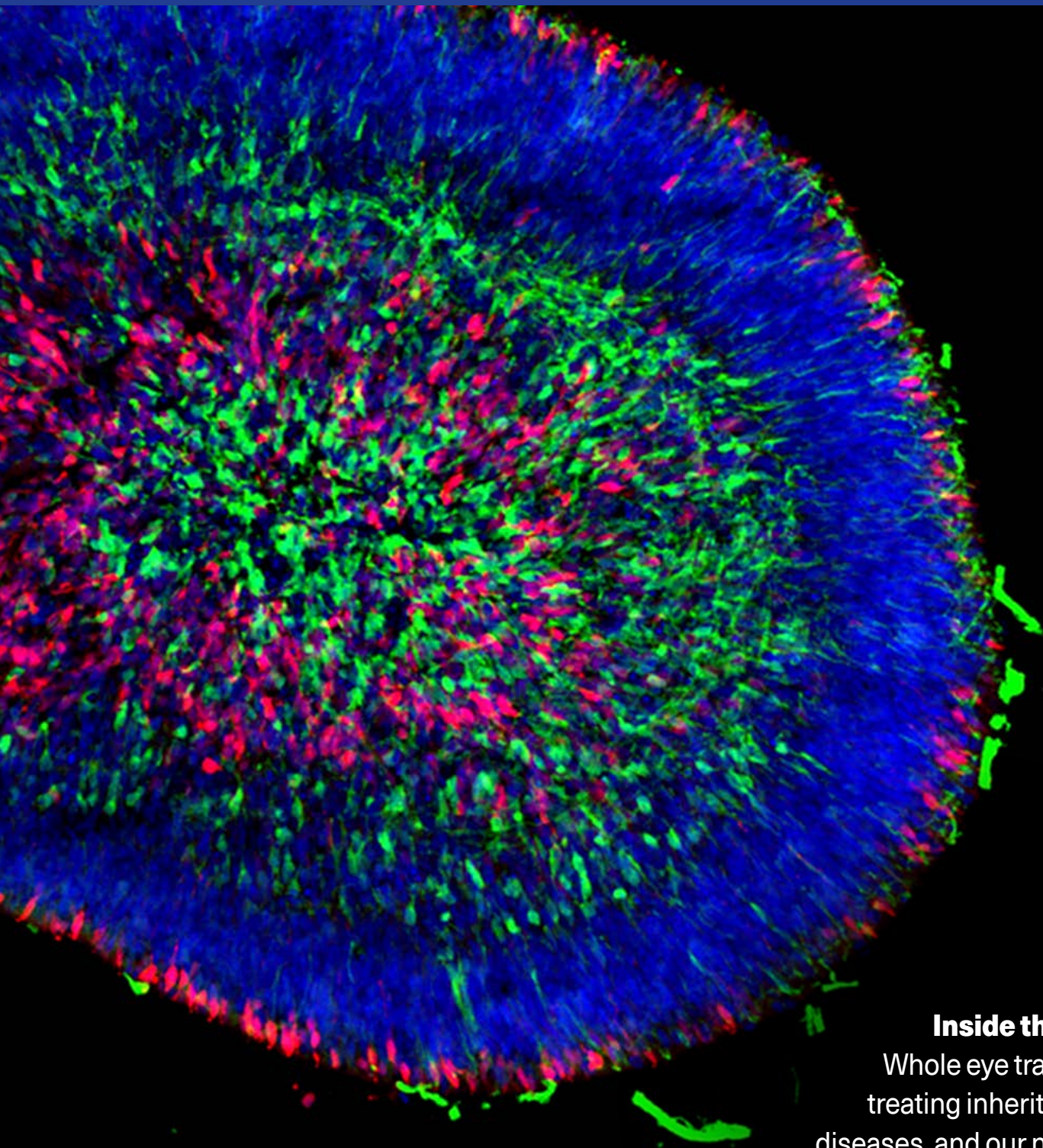




Inside this issue:

Whole eye transplants,
treating inherited retinal
diseases, and our new Grant
Accelerator Program awards.



Cycle for Sight 2025 Signals the Start of Spring!

Thank you to all our participants and donors who made Cycle for Sight 2025 successful once again! This year's ride has raised ~\$73,000, with donations still counting in this year's tally until June 30th. Kenzi's Team was responsible for over half of that this year, with a tally of just under \$40,000. Spinners once again rode in a (newly renovated!) spinning room at Princeton Club West, and other participants walked the track on the Club's lower level.

As in recent years, other teams decided to participate on their own, by hiking at Devil's Lake and along the Baraboo River, walking with their dogs in Madison, and biking with other School of Medicine and Public Health students on campus, among other events. We're pleased that Cycle for Sight serves as an opportunity for supporters to get outside in early spring. Most of all, we're grateful to those teams that exercise with us each year: Blind Take Off, Out of Sight, the Sight O Paths, Team Tiradani, AEI, Opsis Therapeutics, Isthmus Eye Care, our SMPH med school team...and of course, our lab teams, who support the event while working to find new therapies for blinding diseases.

Among other grants, Cycle for Sight supports the Kenzi Valentyn Awards each year. To see our most recent award winners, visit vision.wisc.edu/funding_opportunities/kenzi-valentyn-awards/recipients.





Dear Friends,

There are many vision problems that can be successfully treated with existing devices and therapies, from visual aides to medications to surgical procedures, and one of the missions of McPherson ERI investigators is to make these interventions safer, more effective, and more accessible. However, the outcomes we work hardest to bring to fruition are those that shed light on eye and vision conditions for which there are no treatments—inherited retinal diseases (IRDs), macular degeneration, and advanced forms of glaucoma and diabetic retinopathy, among many others. By understanding the modus operandi of these disorders, we can figure out why they evade traditional treatment approaches and direct our efforts toward the discovery of new therapeutic strategies. While laboratories, including ours, most often use a variety of ‘human-like’ model systems to accomplish this goal, we also know that there is no substitute for the real thing—us.

In this issue of *InSights*, we profile the UW-Madison Department of Ophthalmology and Visual Sciences’ Adult and Pediatric Inherited Retinal Degeneration Clinics, overseen by clinician-researchers who diagnose IRDs, provide counseling, and participate in clinical trials to test new therapies, some of which were developed right here at UW-Madison (including an upcoming stem cell-derived photoreceptor replacement therapy). We also introduce you to an exciting new McPherson ERI project backed by the U.S. Advanced Research Projects Agency for Health (ARPA-H) that seeks to make whole eye transplantation a reality. If this fearless effort doesn’t convince you that there is no problem too big for us, I don’t know what will.

It’s important to note that these promising therapeutic ‘shots on goal’ don’t come out of thin air. They are the result of careful recruitment and support of dedicated and talented researchers. The McPherson ERI’s endowed Grant Accelerator Program (GAP) provides significant seed funding for our scientists to boldly explore new avenues of research and therapeutic development. In this issue, we announce the first cadre of GAP Award recipients who will be reaching for the moon while caring for those still on the ground.

We’re thankful, as always, for your interest.



David M. Gamm, MD, PhD

RRF Emmett A. Humble Distinguished Director, McPherson ERI
Sandra Lemke Trout Chair in Eye Research
Professor, Department of Ophthalmology and Visual Sciences



Stopping Retinal Degeneration

Inherited Retinal Disease Clinics and Research at UW-Madison



All photographs on pp. 4-8 are courtesy of the Department of Ophthalmology and Visual Sciences.

Without a doubt, being told that you or a loved one is losing vision due to an inherited retinal disease (IRD) is difficult, and its impact on the lives of individuals and families can be massive. “We work to give our patients the best available information about their IRD,” says Dr. Kimberly Stepien. “Sometimes individuals have been misdiagnosed or the technology or knowledge at the time of their initial diagnosis simply didn’t exist to give them the information and answers we can today.” Often, the diagnosis comes quite early in life.

IRDs have been diagnosed and managed by UW ophthalmologists for decades. However, the establishment of dedicated IRD clinics for children and adults occurred relatively recently. Pediatric ophthalmologist Dr. Melanie Schmitt helped initiate the Pediatric Inherited Retinal Degenerations Clinic in UW-Madison’s Department of Ophthalmology and Visual Sciences (DOVS) in 2014, and it remains one of only a handful of such clinics in the country, receiving patient referrals both regionally and nationally. Dr. Schmitt’s vision for the IRD clinic began during her fellowship, when she received specific training in IRDs, which can be caused by defects in hundreds of different genes.

In 2016, retina specialist Dr. Stepien arrived at UW-Madison and quickly established the Adult Inherited Retinal Degenerations Clinic. Together, these clinics bring world-class expertise in ocular genetics and compassionate, forward-thinking care to individuals with IRDs across the lifespan. The IRD clinics are also heavily involved in groundbreaking IRD research taking place at UW-Madison and elsewhere, which seeks to develop treatments for these currently incurable disorders.

But a top-notch IRD clinic requires more than specially trained ophthalmologists. Over the years, Dr. Stepien and Dr. Schmitt built a powerful team of subspecialists, genetic counselors, study coordinators, photographers, technicians, social workers and schedulers who provide patients with highly individualized care for their particular IRD.

Patients and their families often begin their IRD experience with a two-to-three-hour consultation that includes a detailed medical and family history (including a family genetic pedigree analysis), a comprehensive ophthalmic exam, and ocular imaging and electrophysiology testing.

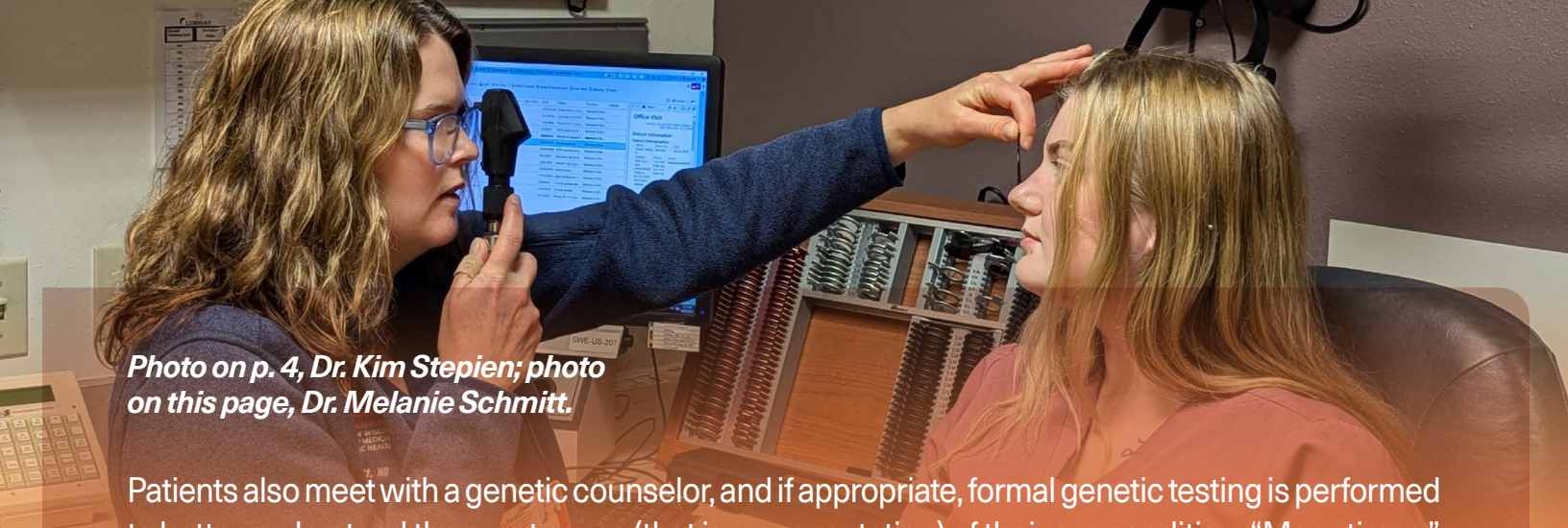


Photo on p. 4, Dr. Kim Stepien; photo on this page, Dr. Melanie Schmitt.

Patients also meet with a genetic counselor, and if appropriate, formal genetic testing is performed to better understand the exact cause (that is, gene mutation) of their eye condition. “Many times,” says Dr. Stepien, “we can provide information that impacts multiple family generations and lets them take more control of their eye health.”

“We also take the time to understand how the patient’s vision changes affect their lives,” notes Dr. Stepien. Referrals are made to a vision rehabilitation specialist, an occupational therapist, or other professionals as needed, and lifestyle recommendations regarding diet, smoking cessation, and light exposure are discussed. A dedicated social worker is also integrated into the clinic, who can help with issues such as transportation needs, food insecurity, and referrals to community resources. “Losing vision profoundly affects an individual, and we work to support them any way we can,” says Dr. Stepien.

Importantly, care in the adult and pediatric IRD clinics is closely linked to rapidly accelerating research on IRDs. Both Dr. Stepien and Dr. Schmitt pursue research in various IRD-focused projects. Dr. Schmitt researches the long-term effects of carbonic anhydrase inhibitors (CAIs) in the treatment of one form of IRD known as X-linked retinoschisis (XLRS). Her findings, published in the journal *Retina* in November 2022, demonstrated an improvement in visual acuity of some XLRS patients after CAI treatment. She has also published reports on other rare conditions, such as Alstrom syndrome. Dr. Stepien is highly involved in the Wisconsin Advanced Imaging of Visual Systems (WAIVS) Lab, which conducts research using novel live imaging instruments that provide incredibly detailed information regarding retinal structure and function in people with IRDs.

UW-Madison’s position at the forefront of clinical trials research for IRDs allows Dr. Schmitt and Dr. Stepien to participate in the process of testing and approving new therapies. Dr. Stepien serves as principal investigator for several IRD clinical trials that test treatments ranging from neuroprotective drugs to gene therapies to upcoming stem cell therapies. If a person is eligible for a trial, study coordinators can connect with the patient during their IRD clinic visit. Patients coming to the IRD clinics are also given the opportunity to enroll in the UW Ocular Genetics Registry, founded by Drs. Stepien and Schmitt in 2017, which ensures that eligible individuals are contacted if clinical trials become available.

“The more we listen to our patients and their families, the better their care experience gets,” says Dr. Stepien. “We want them to get everything they need, which includes in-depth information about current interventions as well as insight into evolving research and treatment strategies.”



Transplant: Advancing the future of vision treatment

Two McPherson ERI and UW-Madison Department of Ophthalmology and Visual Sciences vision researchers are involved in groundbreaking research aimed at curing blindness through human eye transplantation. This is an ambitious goal. To date, there has never been a successful whole human eye transplant for the restoration of vision. The hurdles are numerous, but the possibility continues to tantalize scientists. Research teams across the country, including at the University of Wisconsin-Madison, are hopeful that these new efforts will pave the way for this procedure.

In late 2024, the Advanced Research Projects Agency for Health (ARPA-H), an agency within the U.S. Department of Health and Human Services, announced \$125 million in funding from its Transplantation of Human Eye Allografts program. UW researchers are part of two teams that received those contracts.

David Gamm, MD, PhD and Robert Nickells, PhD—both UW professors—are the lead researchers involved in this cross-institutional work. Dr. Gamm is part of the national team led by researchers at the University of Colorado Anschutz Medical Campus that will focus on developing novel stem cell, gene therapy, and bioelectronic technologies to promote nerve regeneration, as well as refining surgical methods. Dr. Nickells is a member of the team from Stanford University. Their focus is on developing new strategies to promote survival and regeneration of cells of the transplanted eye, donor eye procurement, and performing transplant surgeries.

A Major Challenge

Transplants are not new in the field of ophthalmology. Over 70,000 people in the United States donate their eyes after death each year. However, only parts of the eye, most commonly the cornea at the front of the eye, are used for transplantation. This means that the millions of people blinded by conditions affecting their retina and optic nerve have no options for improvement.

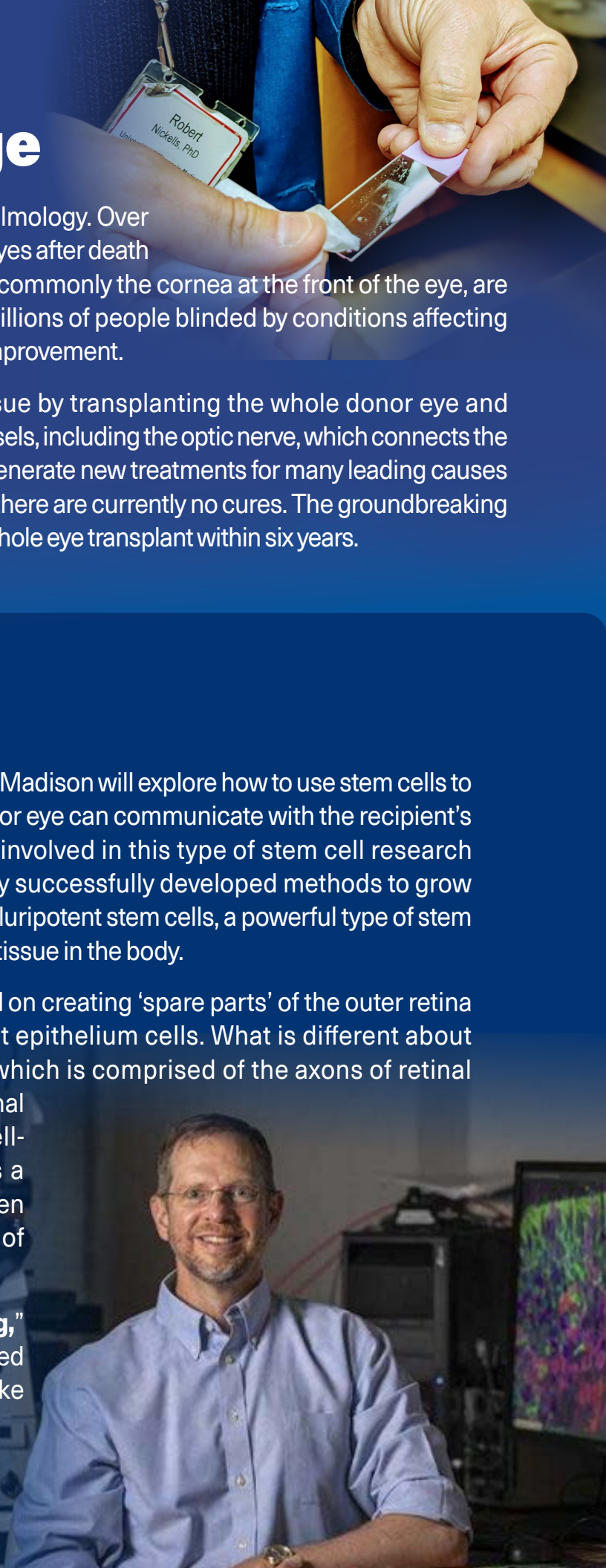
This new initiative aims to address this issue by transplanting the whole donor eye and reconnecting the nerves, muscles, and blood vessels, including the optic nerve, which connects the eye to the brain. If successful, the program will generate new treatments for many leading causes of total blindness in the United States, for which there are currently no cures. The groundbreaking project aims to achieve the goal of a successful whole eye transplant within six years.

The Gamm Lab

Dr. Gamm and his team of researchers at UW-Madison will explore how to use stem cells to repair and reconnect the optic nerve so the donor eye can communicate with the recipient's brain and enable vision. Dr. Gamm has been involved in this type of stem cell research for nearly two decades, and his lab has already successfully developed methods to grow authentic human retinal cells and tissues from pluripotent stem cells, a powerful type of stem cell that can be used to create any type of cell or tissue in the body.

"To date, my lab has primarily been focused on creating 'spare parts' of the outer retina – namely photoreceptors and retinal pigment epithelium cells. What is different about this project is the focus on the optic nerve, which is comprised of the axons of retinal ganglion cells. We are trying to create a neuronal connector, consisting of pluripotent stem cell-derived neurons, that can hopefully act as a circuit coupler to allow communication between the donor eye optic nerve and visual centers of the brain."

"What we are striving for is a huge undertaking," Dr. Gamm added. "But, by leveraging the combined expertise of our partners, we expect to make important advances over the next six years."



A photograph of a man with glasses, wearing a dark lab coat over a light-colored shirt, sitting at a desk in a laboratory. He is looking at a computer monitor. On the desk, there is a laptop, a small green container, and some papers. The background shows a white brick wall and a window with a view of the outdoors.

The Nickells Lab

Dr. Robert Nickells has been studying whole eye transplantation for more than a decade. His team is developing a cold storage solution that keeps the donor eye healthy between recovery and transplantation. They are specifically focused on maintaining the viability of the donor eye and ensuring the health of the retina, the light-sensitive layer at the back of the eye that sends signals to the brain.

“Our goal is to develop a method of preserving donor retinal tissue for up to 24 hours,” Dr. Nickells said. “Over the last several decades, we’ve been studying the biology of what goes on in retinal cells once they become damaged in the hopes of developing treatments to slow down or block this process. When it came to coming up with a cold storage solution, our first thought was to start with what is normally used in the transplant industry for other organs.”

Surprisingly, the team discovered that UW cold storage solution, developed at the University of Wisconsin in the 1970s, was that industry standard.

“While UW solution did fairly well at preserving retinas in our initial studies, we reasoned that we could improve its efficacy by modifying it with supplements that specifically targeted the biochemical pathways that would normally be activated in retinal cells once the donor eye was procured,” explains Dr. Nickells. After testing each supplement individually, the research team came up with a combination that seems to perfectly preserve isolated eyes after prolonged periods in cold storage.

The next step, thanks to the new ARPA-H grant funding, is to examine what happens to the eye, and specifically the highly sensitive retina, once it comes out of cold storage and is warmed up.

“We have some early indications that retinal cells start to regain their function after warming, which is good,” Dr. Nickells continued. “But we also have some indications that the warming process induces a stress response, which may hamper long term survival of the retina after transplantation. Future work may include the addition of further supplements to suppress this stress response.”

“I am honored to be part of this groundbreaking new effort aimed at finding a cure for blindness,” Dr. Nickells added. “The next few years are going to be an exciting time for the field of ophthalmology.”

By Amy Pikalek, lightly adapted with permission and thanks.



Accelerating Research

MERI's Grant Accelerator Program (GAP)
Funds Its First Projects

McPherson ERI's new Grant Accelerator Program aims to light the fuse for innovative research that will protect, restore, or assist vision. GAP awards are intended to promote exploration of new ideas as the first step—which is often to generate critical initial data—that would allow for successful grant applications to external funding organizations. This type of seed funding has been the basis of innumerable transformative discoveries in science, but such funding has traditionally been hard to come by.

With major support from the Estate of Dr. Alice McPherson, alongside generous additional funding from the Van Vreede MERI Greatest Needs Fund, the Robert A. Brandt Macular Degeneration Fund, and additional donors, the McPherson ERI will be able to award a minimum of six \$50,000 awards annually – and in this initial year, we were able to fund seven projects, spanning a range of vision disorders.

Mrinalini Hoon

Associate Professor and RRF
Rebecca Meyer Brown Professor,
Ophthalmology & Visual Sciences, SMPH



Understanding the role of 'ribbons' for establishing connectivity in the mammalian retina. Dr. Hoon's study of a crucial structural component in the majority of retinal synapses has implications for diseases, such as glaucoma, that are associated with the loss of these structures.

Colleen McDowell

Assistant Professor,
Ophthalmology & Visual Sciences, SMPH



A novel mechanism to lower intraocular pressure. Dr. McDowell's lab will test whether a substance called CGRP, released by sensory nerve fibers in the eye, can act as a therapeutic to improve fluid flow and reduce eye pressure.

Freya Mowat

Assistant Professor,
Ophthalmology & Visual Sciences,
SMPH; Surgical Sciences, SVM



The safety and efficacy of repurposed FDA-approved anti-diabetic Thiazolidinediones delivered intravitreally in a mouse model of age-related macular degeneration. TZDs are an already-FDA-approved class of diabetes drugs, with properties that modulate multiple AMD-relevant mechanisms. Dr. Mowat's lab will test the effectiveness of direct intravitreal injection of these drugs on a mouse model with AMD-like symptoms.

Yuhang Zhao

Assistant Professor,
Computer Sciences, SCDIS

Intent-aware Systems to Enhance Low Vision People's Visual Perception.

Dr. Zhao aims to develop systems that will more closely match the specific needs of users of low vision technology; for example, by enhancing magnification where it is needed in a user's field of vision, as determined by their gaze.



Robert Nickells

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

Contralateral astrogliosis after unilateral optic nerve damage. Dr. Nickells' study examines whether damage in one eye causes a neurotoxic reaction in the astrocyte cells in the other eye, a potential risk factor for glaucoma.



Raunak Sinha

Associate Professor, Walsh
Family Professor in Vision
Research, Neuroscience, SMPH

Development of photoreceptor and retinal circuit function responsible for sharp 20/20 vision in primates. Dr. Sinha aims to build up a picture of how sharp vision develops as primates mature in their early years, allowing for a more accurate examination of developmental and degenerative diseases, as well as a strong model of the retina for studying human retinal development.





Amitha Domalpally

Associate Professor, Ophthalmology & Visual Sciences, SMPH; Research Director, Wisconsin Reading Center; Director, A-EYE Research Unit

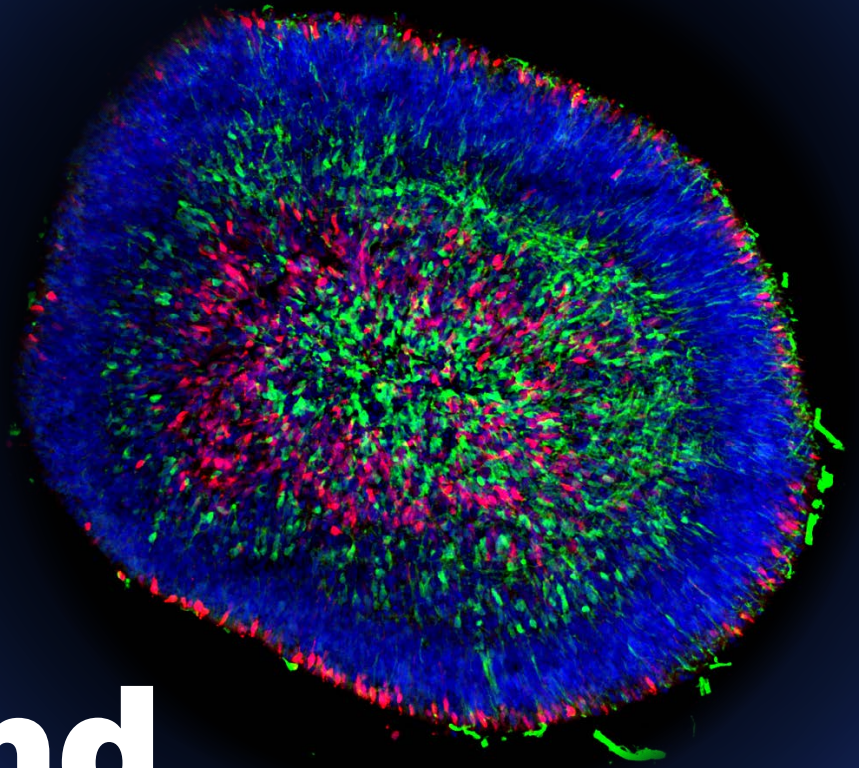
Jeremy Rogers

PI, Ophthalmology & Visual Sciences, SMPH; Director, Wisconsin Advanced Imaging of Visual Systems

Structure and Function in the Progression of Atrophic AMD: Validation of Photoreceptor Damage observed with OCT Using Adaptive Optics and Microperimetry.

Dr. Domalpally and Dr. Rogers are collaborating on a project that will explore the “ellipsoid zone” in the retina—a layer visible on OCT imaging—in more depth and will examine whether the loss of this zone seen in AMD truly correlates with a loss of photoreceptors and functional vision loss.

*Image on the front cover
and on this page of a pig
retinal organoid courtesy
of Kim Edwards, PhD, the
Gamm Lab.*



‘Seq’ and Find

A new way to make pig retinal cells
to advance eye treatments

Inside the human eye, the retina is made up of several types of cells, including the light-sensing photoreceptors that initiate the cascade of events that lead to vision. Damage to the photoreceptors, either through degenerative disease or injury, leads to permanent vision impairment or blindness.

David Gamm has long worked on stem cell replacement therapy using lab-grown photoreceptors as a promising strategy to combat retinal disease. The challenge is that stem cell treatments aimed at replacing photoreceptors need to first be tested in animals. Since human cells are not compatible in other species and are quickly rejected when transplanted, it’s difficult to assess their potential.

“Pig and human retinas share many key features, making pigs ideal for modeling human retinal disease and testing ocular therapeutics,” Gamm says. “By testing ‘human-equivalent’ photoreceptors in pigs, we can get a better sense of what these cells can do if they are not immediately attacked by the host animal.”

In a new study published in *Stem Cell Reports*, the Gamm Lab partnered with researchers at the Morgridge Institute for Research to develop lab-grown pig retinal organoids. They found that pig-derived photoreceptors shared many similarities with those made from human retinal organoids.

“This is the first time that people have made pig retinal organoids,” says Kim Edwards, a recent graduate student in the Gamm Lab (she was awarded her PhD in May 2025) and first author of the study. “And this was the first time that people have done a comparison of human versus another species of retinal organoids.”

Organoids are small tissue clusters—about the size of a large pin head—made up of hundreds of thousands of cells, which allow scientists to replicate the cellular interactions and conditions in a human tissue or organ, but in the controlled environment of a lab dish.

“The photoreceptor cells within human organoids can respond to light and communicate with each other through synaptic connections,” says Gamm. “To determine whether they can connect inside a damaged retina and restore vision, we need to transplant and test them in pigs.”

Stem cells to organoids

Dr. Edwards says that to get quality organoids, it’s important to start with quality stem cells. The lab collaborated with University of Calgary assistant professor Li-Fang “Jack” Chu, formerly a postdoc in Jamie Thomson’s lab at the Morgridge Institute, to obtain the pig pluripotent stem cells.

“Historically, the Thomson Lab has been good at making human induced pluripotent stem cells,” says Ron Stewart, Morgridge investigator in computational biology. “But it turns out that making them for additional species like pig is really challenging. Jack worked it out and is leading the way with his new lab.”

After successfully generating pig induced pluripotent stem cells, the next challenge was to encourage them to differentiate into retinal cells. Edwards began by using the Gamm Lab’s established human organoid protocol to see if it would work using stem cells from pigs. The protocol timing was based on the human gestation period of 40 weeks, but they noted a pig’s pregnancy is only about half that length. So, the scientists thought, what if we use the same protocol, but cut the timing in half?

“We were able to make a lot of retinal organoids from that, which was really exciting,” Edwards says. “It’s a good proof of concept to show that if we’re going to differentiate to a specific cell type, we really need to pay attention to the gestational differences and the inherent differences between the cells.”



Looking deeper into the organoids

Using immunocytochemistry techniques, Edwards and her colleagues characterized proteins associated with specific retinal cells present at early-stage versus late-stage development in both pig and human organoid models. To dig deeper, the Gamm Lab collaborated with computational biologist Beth Moore in the Stewart Computational Biology Group at Morgridge to look at gene expression within the cells using single-cell RNA sequencing (RNA-seq).

“They did a lot of magic using single-cell RNA-seq —things that we didn’t even think were possible,” Edwards says.

The organoids are dissociated into individual cells, and each cell is tagged with a barcode and sequenced individually. The data captured is then used to group similar cells together, giving in-depth insight into the nature of all the cell types found in the organoid, including rod and cone photoreceptors and other cell types such as retinal ganglion cells.

“It’s an unbiased and very comprehensive view of what genes are expressed in each cell type in the organoid,” says Moore. “It’s a different type of marker from the immunochemistry. It’s a different way to come to the same conclusion of identifying different cell types.”



Both Edwards and Moore had to overcome challenges to arrive at these conclusions. First, given the nature of organoids, Edwards needed to optimize their protocols to separate the cells and maintain them prior to sequencing.

“They don’t like to be dissociated and put on a dish, especially the photoreceptors,” says Edwards. “We joke that the photoreceptors work better together, just like people.”

On the data analysis side, Moore explains that each cell gets encapsulated in a droplet that contains the barcode for sequencing. But sometimes, one droplet encapsulates multiple cells, or the droplet might be empty and not contain any cells, which introduces errors in the sequencing data.

“That can really mess up your analysis, especially when you are trying to identify different cell types,” Moore says. Moore developed an analysis pipeline to filter out any unwanted sequences and normalize the data. She then mapped the genes expressed in different clusters, which they could map to specific cell types and compare with the immunocytochemistry results.

Another challenge—the significant difference between pig and human genomes—meant Moore also had to work through a list of known genes in both species and match them with the sequences to map out the different cell types.

“Having that confirmatory data from Beth was really critical for us to feel confident about what we were seeing,” Edwards says.

This work was supported by a grant from the U.S. Department of Defense in collaboration with the National Eye Institute with the aim of exploring cell replacement therapy to treat retinal injuries that commonly occur in the military. The researchers have begun to do transplants in pigs using photoreceptors from the pig organoids to determine whether they establish connections and make synapses with downstream neurons.

“We’re excited to show that you can grow these retinal organoids from different species and that a lot of groups across the world are starting to make them,” says Edwards. “It all starts from having good stem cells.”

Article by Mariel Mohns, Morgridge Institute for Research



Visions of Science: Art from Eye Research

Exhibition dates:

June 19th-September 12th, 2025

Opening reception

Thursday, June 19th

4:30pm to 6:30pm

Mandelbaum & Albert Family Vision Gallery,
9th Floor, Wisconsin Institute for Medical Research,
1111 Highland Ave.



InSights

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