

AMD UPDATE

AGE-RELATED MACULAR DEGENERATION RESEARCH
AT THE MCPHERSON EYE RESEARCH INSTITUTE

2026

Welcome to the second Trout AMD Update



Over the past dozen years, Sandra and the late Monroe Trout of Appleton, Wisconsin, have advanced AMD research at the McPherson ERI and UW-Madison to new heights, founding the Trout AMD Project and endowing four AMD-focused research chairs at the Institute.

The Trouts' commitment was built on a strong foundation, as retinal degenerative diseases have been a focus of McPherson ERI member research since the institute's beginning. There is no question, however, that the resources that Sandy and Monroe dedicated to AMD research have spurred new projects and approaches that are already yielding results and will continue to do so in the coming years.

This year, we are delighted to welcome Dr. Jianhai Du, the inaugural chairholder of the Monroe E. Trout, Jr. Chair in Eye Research, to UW-Madison. Dr. Du's groundbreaking work on retinal metabolism and nutrition holds great promise for uncovering new strategies to maintain and maximize visual function and to blunt or reverse the effects of blinding disorders like AMD. Our team of AMD researchers – and indeed the entire Institute – is eager to collaborate with Dr. Du on exciting new projects that draw upon his internationally renowned skill and expertise.

In this issue, you'll read about work supported directly by the Trouts, as well as by other donors to AMD research, such as Pat and Jay Smith. Our research also benefits greatly from the support of a wide range of donors, many with personal or family experience with AMD. This funding allows the McPherson ERI to develop and initiate promising pilot projects, many of which go on to receive federal and foundation funding – the key to ultimate success. Thank you for your interest and for supporting our efforts to preserve and restore vision.

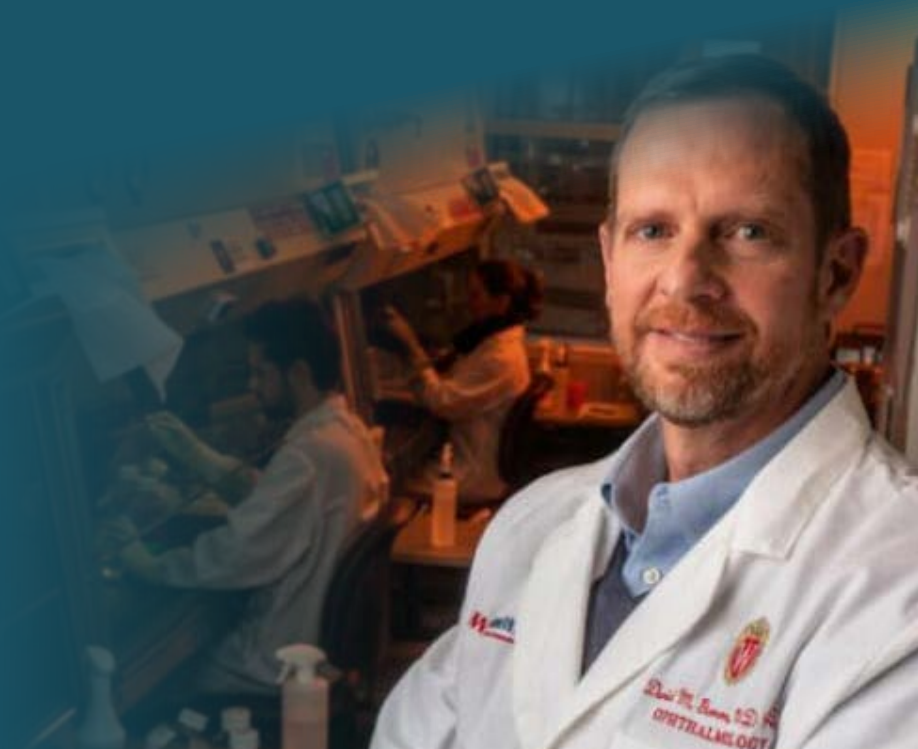


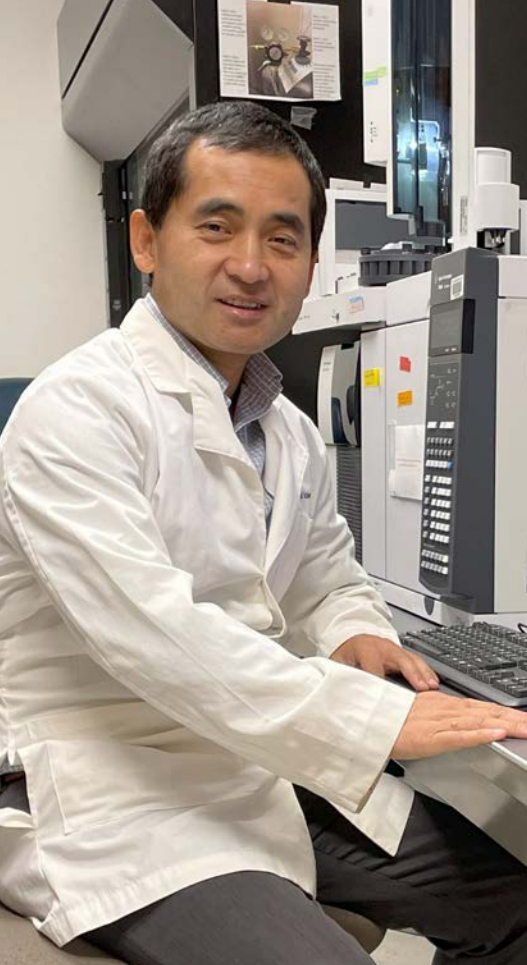
David M. Gamm, MD, PhD

Sandra Lemke Trout Chair in Eye Research

Emmett A. Humble Distinguished Director
of the McPherson Eye Research Institute

Professor, Department of Ophthalmology
and Visual Sciences





A Star Recruit Joins UW-Madison and the MERI Team

In July 2026, Dr. Jianhai Du joined the McPherson ERI and the Department of Ophthalmology and Visual Sciences as the Monroe E. Trout, Jr. Chair in Eye Research, adding another internationally recognized AMD researcher to UW's roster.

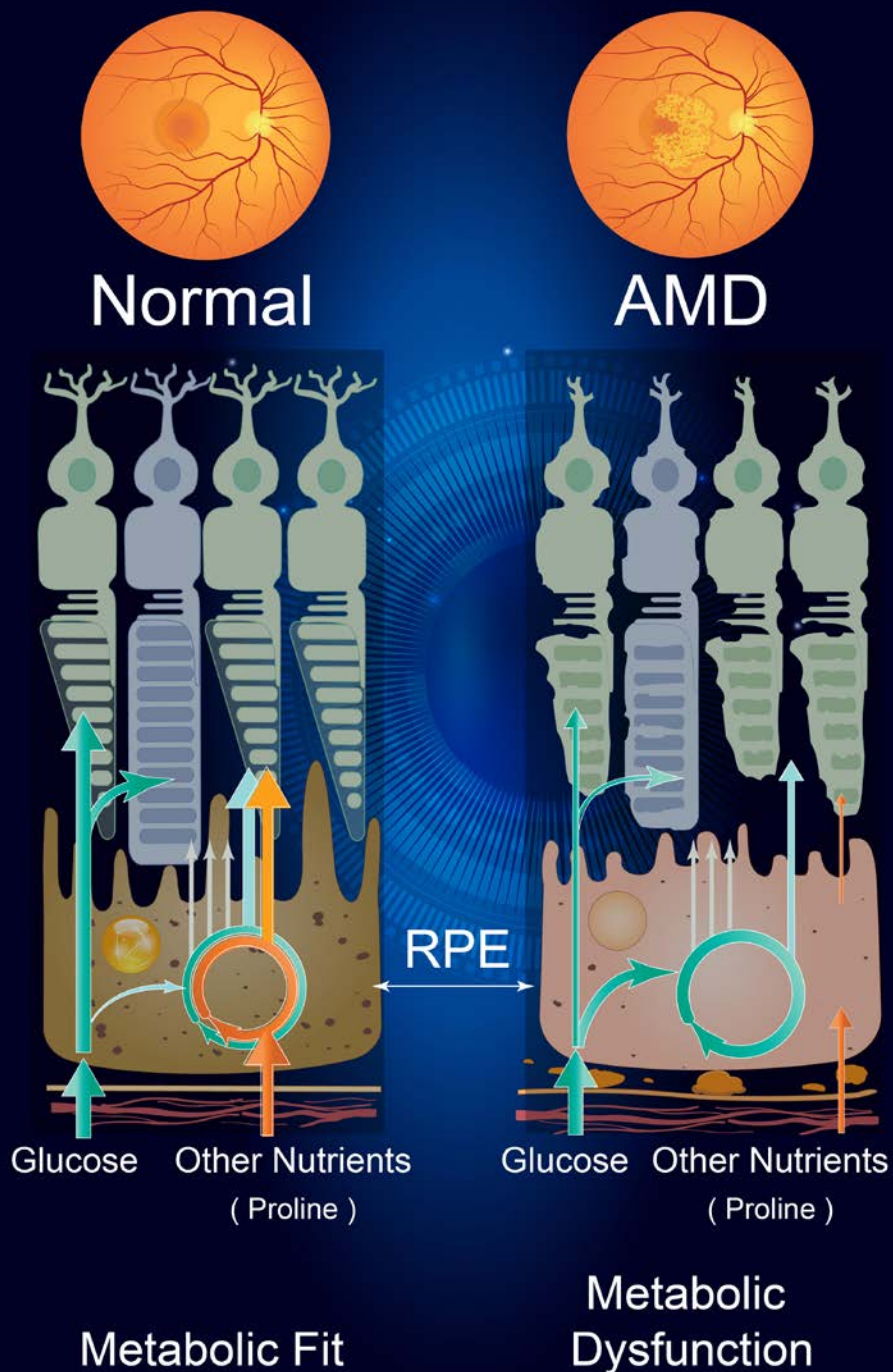
Dr. Du has dedicated his career to understanding how metabolism sustains vision and how its failure contributes to retinal degeneration. During nearly a decade of work at West Virginia University, he pioneered the field of retinal metabolism, building a successful, well-funded research program and collaborating with more than 20 vision research laboratories.

At the center of age-related macular degeneration (AMD) lies a metabolic crisis in the retina. The macula, responsible for sharp and detailed vision, is densely packed with cone photoreceptors. These cells are among the most metabolically demanding cells in the human body, yet they have no direct blood supply. Instead, they rely on neighboring retinal pigment epithelium (RPE) cells for their nutrients and metabolic support. The RPE maintains a highly specialized metabolic ecosystem with photoreceptors by transporting nutrients, producing essential metabolites, recycling byproducts, and clearing cellular waste. When RPE metabolism begins to fail, this ecosystem breaks down, leading to accumulation of lipid (fatty) deposits beneath the RPE, deprivation of nutrients to photoreceptors, and progressive loss of central vision. Understanding how metabolic dysfunction drives AMD is

one of the most urgent challenges in the development of therapies to prevent and treat the disease. Using advanced approaches such as stable isotope tracing and metabolomics, Dr. Du's laboratory has mapped how nutrients are processed and shared within the retina, leading to a new appreciation and understanding of the metabolic communication between RPE cells and photoreceptors.

Dr. Du's work showed that the RPE is not simply a support layer that transport nutrients from the blood to photoreceptors, but an active metabolic hub that uses alternative fuels to spare glucose (sugar) for photoreceptors while producing key metabolites such as glutamate and aspartate. His team identified proline as an important fuel for healthy RPE cells and demonstrated that proline supplementation protects visual function and photoreceptor survival in a mouse AMD model. His research demonstrated that diseased RPE cells lose the metabolic flexibility needed to use alternative fuels, and instead consume more glucose, reducing the nutrient supply available to photoreceptors and worsening metabolic stress in AMD. The Du Lab also discovered that cone photoreceptors in the macula (central retina) have especially high demands for pyruvate and mitochondrial metabolism, and that defects in pyruvate transport lead to visual decline and photoreceptor degeneration. All told, his work has established metabolism as a key driver of retinal health and disease, opening new opportunities to treat AMD by restoring normal metabolism.

At the McPherson Eye Research Institute, Dr. Du will build on this exciting foundation to advance innovative AMD research and develop new approaches for treatment and prevention. His laboratory will develop novel spatial metabolomics platforms to visualize metabolism directly within individual retinal cell types in donor eyes with AMD and in human stem cell-derived retinal organoids. These technologies will reveal how metabolic defects emerge in specific cells and how those changes spread during the course of disease. His team will also create new laboratory models of AMD that are driven by metabolic dysfunction, providing powerful systems to test treatments. Ultimately, Dr. Du aims to translate these discoveries into therapies, including nutritional strategies and gene-based approaches that boost RPE metabolism, restore metabolic support to photoreceptors, and protect central vision for AMD patients.

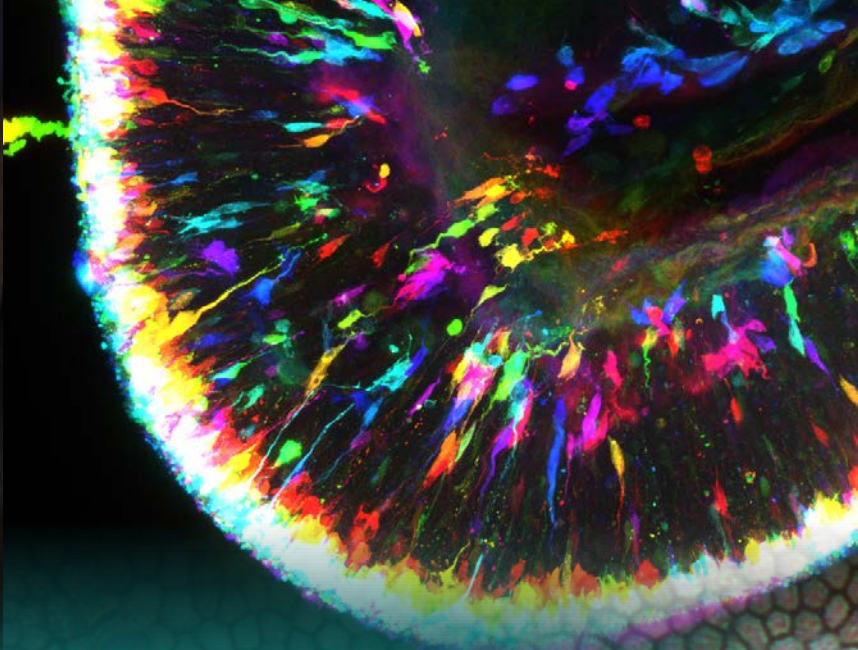


NORMAL

Healthy RPE can use various nutrients, particularly proline, to preserve glucose for the photoreceptors (as shown in the left image, where RPE metabolism is operating correctly).

AMD

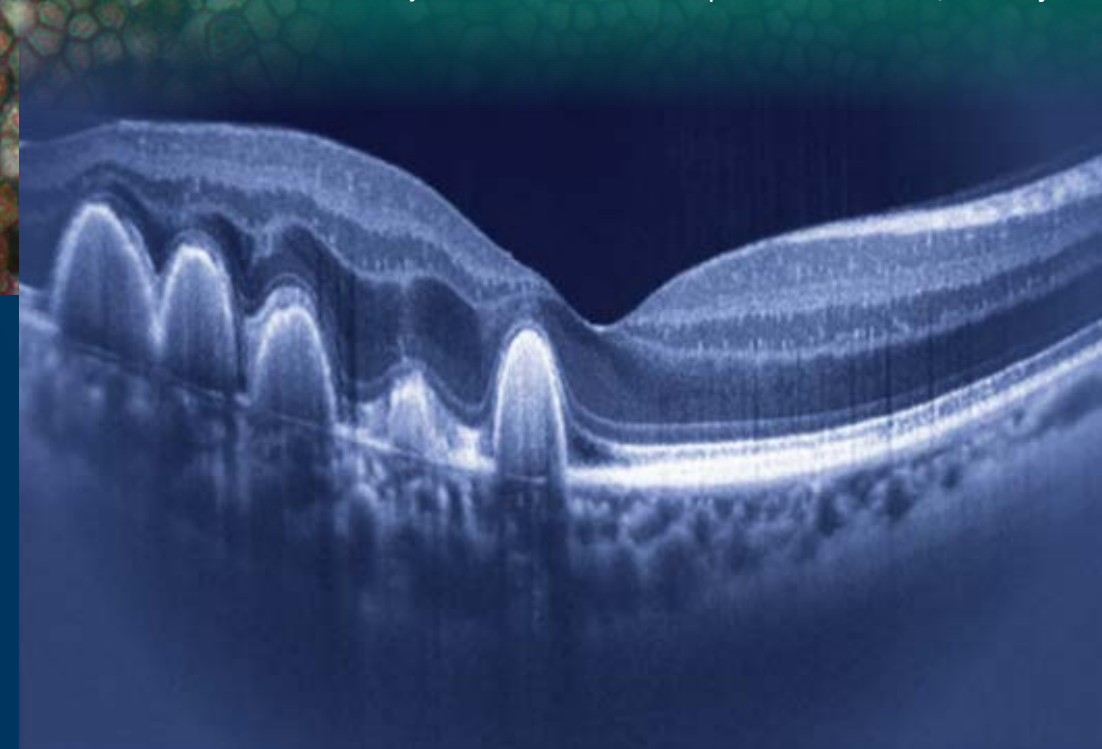
RPE with AMD loses the ability to use proline and relies more on glucose, which disrupts the nutrient supply for photoreceptors and causes metabolic dysfunction (right image).



AMD RESEARCH UPDATES

In the past year, UW-Madison McPherson ERI researchers working on age-related macular degeneration (AMD) advanced their work in areas ranging from diagnostic imaging to adaptive technologies to investigations into the causes of AMD and the development of new or improved treatments. We are pleased to provide updates to you on these activities in the next few pages.

Clockwise from top left: Dr. Monroe Trout; Photoreceptor cells within a retinal organoid (courtesy of Sarah Rempel and Tim Gomez); Sandra Trout; Drusen (the mountain-like projections) adjacent to the fovea of a patient with AMD (courtesy of Joseph Carroll).





JEREMY ROGERS^{PhD}

Principal Investigator, Department of Ophthalmology and Visual Sciences

Standard clinical imaging tools provide exceptional macroscopic (“large scale”) views of the retina, but they do not yet provide the ultrafine, microscopic information needed to evaluate the individual retinal cells (i.e., photoreceptors and retinal pigmented epithelium (RPE) cells) that are affected by AMD.

The Wisconsin Advanced Imaging of Visual Systems (WAIVS) Lab was established by the McPherson ERI and the Department of Ophthalmology and Visual Sciences to develop this ability, and to design and build the next-generation instruments capable of revealing the structure and function of individual, living retinal cells. The primary tool developed, an Adaptive Optics Scanning Light Ophthalmoscope (AOSLO), allows researchers and clinicians to assess the health or dysfunction of retinal cells in people with AMD with a level of precision and detail that is not otherwise possible and to track subtle changes over time. This information is not

only important for accurate disease diagnosis and prognosis, but also for improving therapies and monitoring their outcomes.

Over the past few years, Dr. Jeremy Rogers built and refined the WAIVS AOSLO system, literally from the ground up, with bolts, lenses, and lasers. Excitingly, in the past two years his team has imaged over 100 individuals with a variety of retinal diseases including AMD. AMD is a particularly challenging disease to image at the cellular level with AOSLO, but through innovation that tightly couples the clinical research and optical engineering, the lab has made changes and added key features to the instrument, including eye tracking and the ability to adjust to different pupil sizes (patent pending), which are beginning to enable successful imaging of photoreceptors at the margin of AMD lesions for the first time.

Ongoing technical improvements are key to increasing the lab's ability to harvest the highest quality data from the WAIVS system. For instance, the WAIVS team has incorporated a visible light stimulus feature into the AOSLO machine to enable functional imaging via a new procedure called an Optical Retinogram (ORG). This technology exists at only a handful of institutions worldwide and allows the team to record videos that measure the real-time responses of individual photoreceptors in human subjects exposed to light. This cellular-level monitoring will improve our understanding of the earliest stages of AMD progression and aid the development of new therapies. Moving forward, a pilot study using AOSLO in AMD patients and in partnership with the DOVS A-Eye artificial intelligence group was recently approved, and the team is beginning to collect data from the edges of retinal lesions (termed "geographic atrophy") in patients with AMD.



AKIHIRO IKEDA^{DVM, PhD}

Timothy William Trout Chair in Eye Research, McPherson ERI ☀ Professor, Department of Medical Genetics

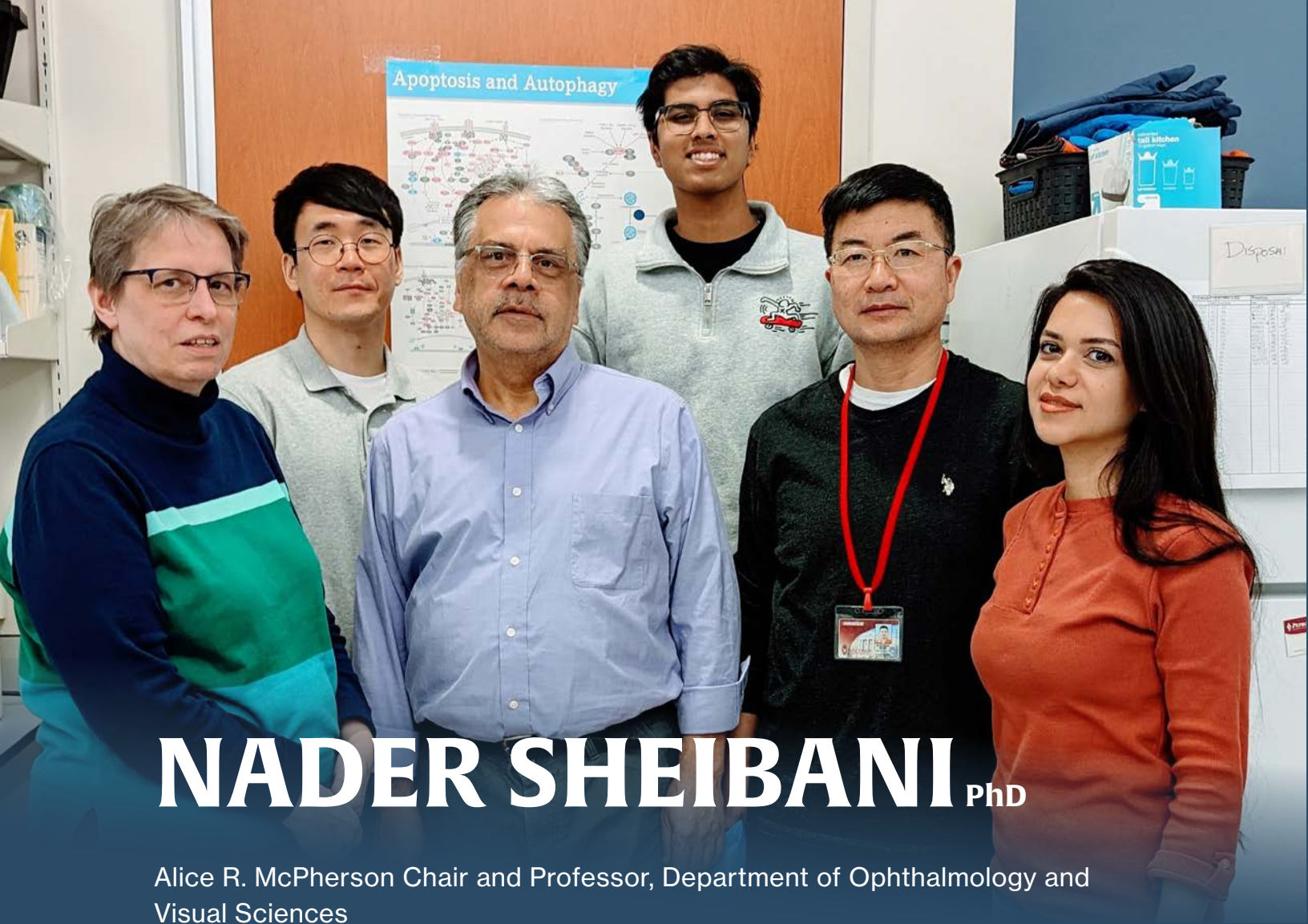
One way of thinking about AMD is as an accelerated aging process – therefore, the more we understand normal retinal aging, the more likely we are to keep our retinas young and healthy for a longer period of time.

Dr. Akihiro Ikeda's team continues to focus on pinning down the underlying molecular causes of retinal aging, which can result in the deterioration of photoreceptor cells and other cell types characteristic of age-related macular degeneration. One highlight of the Ikeda lab's work this past year was the publication of a study demonstrating that two particular proteins, MFN1 and MFN2, are essential for maintaining the unique structure and function of

mitochondria within rod photoreceptor cells. Mitochondria, often referred to as the energy “powerhouses” of cells, are critical to healthy cellular functioning. In their studies, the loss of these two mitochondrial fusion proteins led to faster retinal degeneration and widespread metabolic changes in the retina. These findings provide important insight into how mitochondrial dysfunction contributes to retinal aging and degenerative eye diseases.

In another project, the Ikeda laboratory identified TMEM135 as a key regulator of retinal lipid metabolism. The team found that disruption of this pathway reduces the supply of the essential omega-3 fatty acid DHA, allowing pro-inflammatory omega-6 fatty acids to accumulate in photoreceptor cells. This imbalance increases lipid peroxidation and oxidative stress in photoreceptor cell membranes, ultimately promoting retinal aging. These metabolic changes also activate retinal immune cells called microglia. However, this pathological activation could be significantly reduced with dietary fish oil supplementation. Such discoveries provide new insight into how metabolic dysfunction drives retinal degeneration and are leading to new strategies to prevent age-related eye disease.

Lastly, one of the most exciting developments in the Ikeda lab has been the realization that many pathways involved in retinal aging also influence aging throughout the body. By studying how cells regulate mitochondrial function, lipid metabolism, and inflammatory responses in the retina, they are uncovering mechanisms that may have relevance far beyond vision research, including heart health. This convergence between eye research and general aging biology is opening new opportunities for collaboration and discovery.



NADER SHEIBANI^{PhD}

Alice R. McPherson Chair and Professor, Department of Ophthalmology and Visual Sciences

Increasing evidence points to chronic inflammation as a central driver of disease progression in AMD. Dr. Nader Sheibani's lab investigates the role of mast cells – specialized immune cells that orchestrate inflammatory and allergic responses – in this process.

They are particularly interested in the activity of mast cells in the choroid, a dense layer of blood vessels located immediately beneath the retina that supplies all of the nutrients, oxygen, and other essential materials to (and removes all of the waste products from) the photoreceptors and RPE cells that are affected in AMD. Their studies focus on how stress-associated signals within the aging retina activate choroidal mast cells, in turn triggering the release of inflammatory mediators that increase oxidative stress and inflammation in the retina and choroid. Ultimately, this cascade damages the RPE cells that are critical for maintaining the photoreceptor cells.

The Sheibani lab has identified thrombospondin-1 (TSP1), a naturally occurring “protective” regulator of inflammation and blood vessel growth, as a critical modulator of mast cell function. Over the past several years, the lab’s studies of TSP1 have shown that loss of TSP1 exacerbates inflammation in experimental models of wet AMD (resulting in increased choroidal blood vessel growth and subretinal scarring). They have also demonstrated that TSP1-deficient mice have greater choroidal mast cell activation (concurrent with vascular and RPE and photoreceptor degeneration). Consistent with these findings, mast cells that lack TSP1 cause particularly severe inflammation resulting in tissue injury and disease progression. Together, these studies indicate that augmenting the effects of TSP1 could represent a promising therapeutic avenue. Toward this end, the Sheibani lab is investigating whether peptides that mimic TSP1 can suppress inflammation, protect retinal tissues, slow AMD progression, and preserve vision.

As you might imagine, a greater understanding of this process is critical, and in the coming year, the lab will further examine the mechanisms that maintain or disrupt the critical mast cell balance on which our retinas rely. They will also explore how poor resolution of inflammation contributes to subretinal scarring (also called fibrosis), the leading cause of permanent vision loss in wet AMD. Based on the Sheibani lab’s dedicated work, it is clear that reducing inflammation in the retina and choroid is key to preserving retinal structure, protecting vision, and improving outcomes for the millions of individuals affected by AMD.



DAVID GAMM^{MD, PhD}

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

Age-related macular degeneration is usually a slowly progressive disease that doesn't rob patients of sight all at once. Instead, there is a wide range of vision changes that a person with AMD can experience, and different interventions are needed depending on the stage of the disease.

For early stages, there are vitamin formulations and lifestyle changes that can slow down the progress of AMD in some people, which our researchers continue to study in an effort to rein in the disease. However, at mid- and

late-stages of AMD, photoreceptors and RPE cells are damaged or destroyed irrevocably, and thus more complex approaches to save or restore sight are required.

Over the past 20 years, Dr. David Gamm's lab has developed and refined the ability to grow human photoreceptor and RPE cells in a dish from induced pluripotent stem cells (iPSCs). These replacement cells are the basis of the current CLARICO clinical trial, which targets a wide range of clinically advanced inherited retinal diseases (IRDs). The trial, developed and sponsored through a collaboration among industry leaders like OpSis Therapeutics, Fujifilm Cellular Dynamics Inc., FUJIFILM, BlueRock Therapeutics, and Bayer AG, focused on IRDs as an initial step. The "first-of-its-kind" therapeutic being tested, called OpCT-001, is intended to replace defunct photoreceptors, which are also lost in AMD. But AMD first causes loss of RPE cells; therefore, efforts are now underway to generate RPE from iPS cells, which can be used alone or in combination with OpCT-001 to target mid- or late-stage AMD, respectively.

Timing estimates for future trials are hard to predict and subject to many factors, and Dr. Gamm is careful about overpromising near-term results. "It is important to realize that we are still in the early phases of this technology, and it will get better with time and effort, just like any other promising technology," says Gamm. Even so, he is hopeful that these treatments will be effective in time. "In the long term, we believe that these cell-based treatment strategies can positively impact the lives of individuals with AMD," he notes. "But the rigorous, thoughtful, and cyclical process of trial, evaluation, and refinement is important for understanding where we are with regard to potential risk and benefit."



MICHAEL ALTaweel^{MD}

Monroe E. Trout Chair in Eye Research, McPherson ERI ☀ Professor, Department of Ophthalmology and Visual Sciences

In the past year, Dr. Michael Altaweel and a colleague performed the first retinal surgeries for the CLARICO clinical trial, which is sponsored by BlueRock Therapeutics and designed to evaluate the safety, tolerability, and clinical effects of OpCT-001.

This cell product, developed by Opsi Therapeutics and based on research developed in the Gamm lab, is aimed at replacing damaged photoreceptors with induced pluripotent stem (iPS) cell-derived replacement photoreceptors in a variety of inherited retinal diseases. Dr. Altaweel and his team developed the specific steps and methods of surgery needed to place these cells beneath the center of the retina, and he is also the trainer for other surgeons who are joining this trial across the country.

Dr. Altaweel's team is now preparing for their next therapeutic target: age-related macular degeneration. This is a challenging task that ultimately involves the replacement of multiple cell layers, including the implantation of healthy retinal pigment epithelium (RPE) cells (the cell layer below the photoreceptors, responsible for nourishing the photoreceptor cells). The team has been working in the surgical lab extensively to test different methods of cell delivery. When the trials begin, Dr. Altaweel will again serve both as the lead surgeon and as trainer for colleagues at other clinical trial locations across the U.S.



YUHANG ZHAO^{PhD}

Assistant Professor, Department of Computer Sciences



Vision loss brought on by age-related macular degeneration (as well as many other retinal diseases and conditions) creates many challenges in life, including the need to adapt to new ways of “seeing” and interacting with objects and people.

A recent R01 award from the National Eye Institute (NEI) is enabling a collaborative team of vision researchers from UW-Madison to develop artificial intelligence (AI)-assisted software that will help visually impaired people navigate their environment more quickly and accurately. Dr. Yuhang Zhao, Assistant Professor in the Department of Computer Sciences, is the Principal Investigator for the team. The project, entitled “AI-Assisted Vision: Scene-Aware Augmented Reality Systems to Support Low Vision People in Activities of Daily Living,” will greatly expand our understanding of the challenges and needs of people with diverse visual abilities and then help design and build intelligent interactive systems to assist them.

Researchers will tackle the challenges faced by people with low vision in complex activities of daily living, such as cooking and safely traveling

through a crowded street. For example, with a head-mounted AR (augmented reality) system called CookAR, which recognizes and augments objects (such as kitchen tools) in real time, Zhao and her team can help people with low vision distinguish different components of various tools (such as a knife blade vs. a knife handle), allowing them to use these tools more safely and efficiently.

Dr. Zhao notes that “Low vision is a complex and pervasive condition that affects millions of people in the world, (but) it receives little attention in the technology literature.” The new NEI award will allow Zhao to collaborate with highly experienced colleagues in UW-Madison’s Department of Ophthalmology and Visual Sciences, including Sanbrita Mondal, OD, Chief of Vision Rehabilitation Services. “We plan to involve low vision professionals as well as patients in developing these technologies to ensure they are practical and useful,” explained Dr. Mondal. “In the past, most low vision aids have been developed by sighted researchers. We want to ensure we develop software with the input of low vision users to increase technology usability and acceptance. “

“All of the activities we are focusing on involve constant motion with object interactions. Current low vision aids, like magnifiers, distort users’ natural vision or diminish important details, and thus can’t effectively help with these activities,” said Dr. Zhao. “It is important for us to deeply understand the unique experiences and needs of low vision people and create intelligent assistive technologies that are adaptive to specific contexts and preferences.” To this end, an annual workshop, supported by the research grant, will bring together low vision rehabilitation professionals and patients to promote an ongoing dialogue.

Text adapted from articles from the Departments of Ophthalmology and Visual Sciences and Pediatrics.



CELIA BISBACH_{PhD}

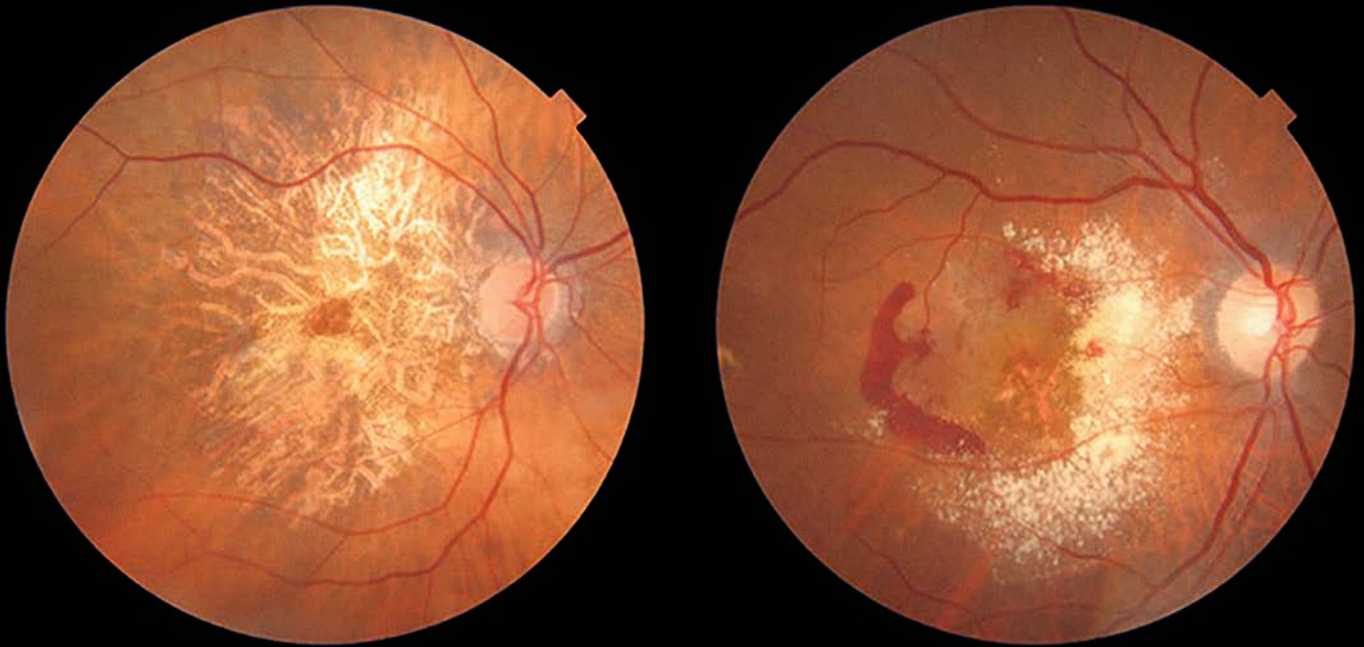
Postdoctoral Researcher, Waisman Center

One of the most common analogies used in discussing age-related macular degeneration is that of a defective garbage disposal, and with good reason. Just as trash accumulates around us in daily life, so our photoreceptor and RPE cells can also accumulate waste and unwanted proteins (in AMD, these trash bags are termed “drusen”).

Sometimes, the retina produces proteins in an attempt to heal itself, but with negative consequences. Such is the case with VEGF, a protein that promotes normal blood vessel growth in many tissues throughout the body, but in the retina can lead to wet AMD and rapid vision loss. Dr. Celia Bisbach, a scientist in the Gamm Lab, has initiated a new AMD project that will hijack the cell's natural "garbage collectors" to remove VEGF in a very precise way. The process, called "targeted protein degradation" (TPD), could lead to a new method for treating wet AMD.

"In many diseases, pathological proteins accumulate in a tissue," Dr. Bisbach explained. "However, if you can trick the protein to jump into one of the cell's waste disposal pathways, you can get rid of it." This approach is widely explored in cancer research, but Dr. Bisbach saw an opportunity to apply it to AMD.

Dr. Bisbach is testing this approach in experiments in the Gamm lab, using induced pluripotent stem cell-derived RPE cells created in a laboratory dish as "subjects" for testing targeted protein degradation in the lab. The technique selectively eliminates VEGF in the areas it is not wanted, thus countering the effects of wet AMD. She hopes that the degraders that she is developing and testing will have benefits over current treatments and provide better long-term outcomes for patients. Looking ahead, Dr. Bisbach hopes to apply the same strategy to dry AMD and inherited retinal conditions like retinitis pigmentosa.



AMD Research Needs Your Help

McPherson ERI's Macular Degeneration Fund was initiated in 2022 with matching gifts from the Trout Family and Dr. Alice McPherson. Since then, many additional donors have contributed to support age-related macular degeneration research in Institute member labs. AMD research is supported by other MERI funds as well, but our dedicated Macular Degeneration Fund is the best route to ensure that your gifts go directly towards developing new therapies and ultimately a cure for this too-common disease. Please help by making a one-time or recurring gift at vision.wisc.edu/giving and click on the button for the McPherson ERI AMD Fund. Or send your gift for the McPherson ERI (specifying the AMD Fund #132580419) to the UW Foundation at:

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