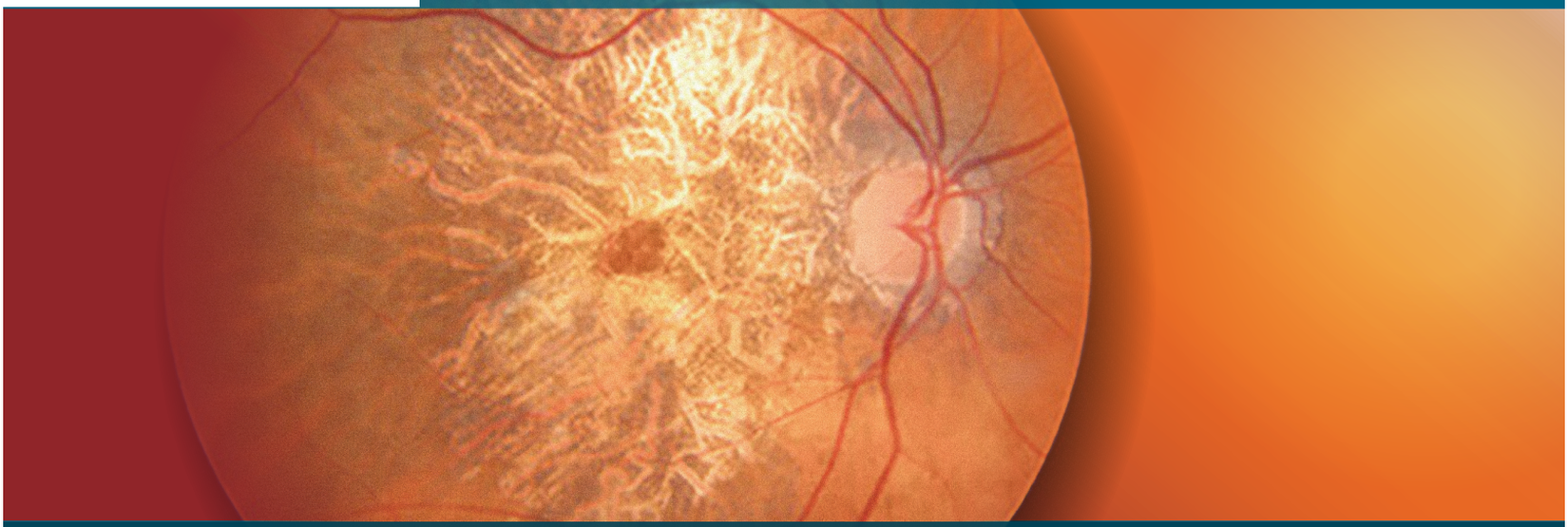
TROUT AMD PROJECT

Annual Update

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

2025



Welcome to our annual Trout AMD Update

Dr. Monroe and Sandy Trout's transformative connection to the McPherson Eye Research Institute was rooted in their desire to combat age-related macular degeneration (AMD), a common cause of permanent central vision loss in older adults. Dr. Trout understood the challenges of AMD firsthand, and as a doctor and pharmaceutical industry pioneer, he was equally aware of the many steps involved in creating a new therapy. But as forward-thinking philanthropists, both Monroe and Sandy Trout also knew that they didn't have to sit on the sidelines and let AMD win. Spurred by Sandy Trout's lifelong regard for her alma mater, the Trouts investigated the University of Wisconsin-Madison's McPherson ERI and determined that it was well-positioned to play a major role in the fight against AMD in coming years. But they didn't stop there – in 2023 they established the Trout AMD Project (TAP), the first program of its kind in the United States.

Monroe and Sandy, in consultation with scientists and clinician-scientists at the McPherson ERI, built the Trout AMD Project to advance research efficiently and thoughtfully until a cure is found. TAP researchers seek to develop more effective therapies through greater knowledge of the causes of AMD, which are still not well understood. Now underway, TAP is making a difference by attracting new AMD researchers and funding them to explore new and exciting ideas to help people afflicted by this devastating disease.

The newsletter in front of you is another facet of the Trout AMD Project. Our goal is to update you on the work that McPherson ERI's AMD researchers are doing and the progress they are making. In these pages, you'll read about a wide range of AMD projects taking place at the Institute and elsewhere, including investigations into the root causes of AMD and efforts to develop therapies to slow, halt, or reverse the progression of the disease. We know that many thousands of people are waiting for treatments for themselves or their loved ones, and this knowledge motivates us to fervently pursue our work every day... and to keep you informed along the way.

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





Dr. Monroe E. Trout

1931-2024

Dr. Monroe Trout, a true friend of the McPherson ERI, passed away on March 4th, 2024, after a short illness. Monroe connected with the Institute following an event held at the Trout Museum in Appleton in 2012 and was an outstanding supporter and advisor in the years since. The Trout AMD Project and four Trout Chairs at the McPherson ERI are testament to his dedication to vision research; certainly, the Trout family's legacy to vision research will live and grow in the Institute forever. Beyond his support for eye research, we delighted in working with Monroe for his good humor, his penchant for envisioning impactful projects, and his over-arching concern for the well-being of others.

He told his extraordinary life story in his autobiography, *Winter Galley*, and captured many of his experiences and passions in his paintings. Monroe lit up whenever he spoke about his family, and his and Sandy's love of children found an outlet in their sponsorship of the PBS Kids Channel at PBS Wisconsin, which was established in honor of their late son Timothy. The Trouts have also supported veterans, numerous schools and universities, the arts, and their Appleton church, among other philanthropic ventures. In his intelligence, integrity, care for others, generosity, and open-heartedness, Monroe exemplified the concept of a life well-lived.

The Trout AMD Project Takes Off

The Trout AMD Project was inaugurated in Appleton with a kickoff event in September 2023, which also included the first annual Sandra Lemke Trout Lecture in AMD.

The talk, given by Kapil Bharti, PhD, was supplemented by a panel of AMD researchers from the McPherson ERI, including Drs. David Gamm, Michael Altaweel, Amitha Domalpally, and Akihiro Ikeda. An enthusiastic audience had the opportunity to ask questions on current and developing therapies for age-related macular degeneration.

The 2nd Annual Sandra Lemke Trout AMD Lecture, given by Goldis Malek, PhD, took place in Madison in September 2024, and was widely viewed both in person and online.











Goldis Malek, PhD (Duke University), at the 2nd annual Sandra Lemke Trout Lecture in 2024.









AMD Research

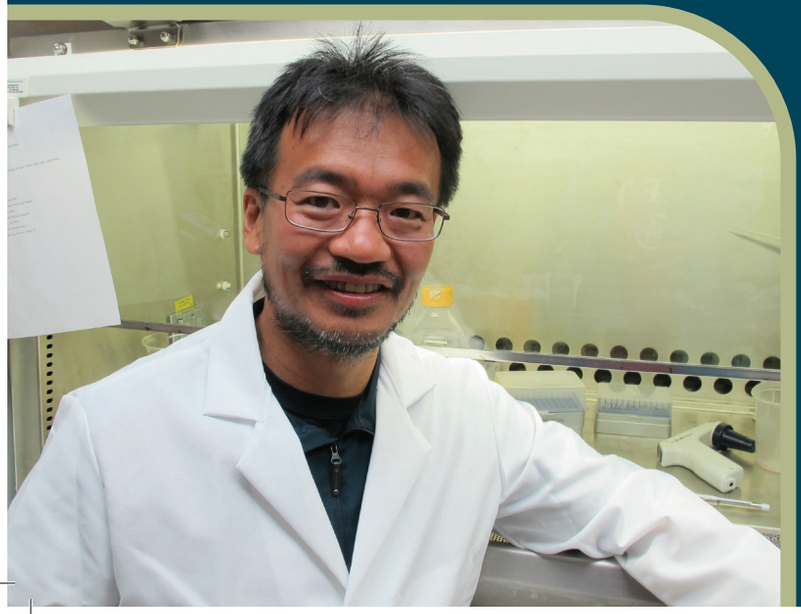
at the McPherson ERI

The effects of age-related macular degeneration can range from slight sight impairment to total loss of central vision. That range means that it is critical to target AMD at every point in its possible trajectory – from prevention, to slowing the disease's progress in its early stages, to developing treatments for advanced AMD. McPherson Eye Research Institute members are researching all of these stages.

AKIHIRO IKEDA DVM, PhD

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

All would agree that preventing the onset of AMD is a critical goal – but to do that, we need to better understand how AMD begins. Research to date highlights processes that are involved with aging of particular cells in the retina. As these cells age, their susceptibility to the onset and progression of AMD increases. Dr. Akihiro Ikeda's team is dedicated to tracking down the molecular causes of retinal aging.



For many years, the Ikeda lab has studied the protein TMEM135, which regulates the manufacturing of docosahexaenoic acid (DHA), an essential fatty acid crucial for retinal health. They are testing whether supplementation of DHA in the diet of *Tmem135* mutant mice can rescue age-related retinal symptoms that are similar to human AMD. *Tmem135* mutant mice treated with DHA supplementation show reduced retinal inflammation and improved maintenance of retinal integrity. This knowledge could potentially be applied to human AMD patients by identifying individuals with low DHA levels in plasma lipid tests and initiating supplementation for those at greatest risk.

While the *Tmem135* and DHA research is exciting, Dr. Ikeda knows that AMD is complex and unlikely to be cured with a single treatment strategy. As such, his lab is always looking for promising new avenues of AMD investigation. Recently, they reported on a project that identified novel human gene variants associated with different diseases. Interestingly, the highest statistical hit for disease association was a deletion affiliated with a gene already linked to AMD, the age-related maculopathy susceptibility 2 *(ARMS2)* gene. The Ikeda Lab is now testing whether this particular genomic deletion influences the production of the protein coded by *ARMS2*, which in turn could affect the onset and progression of AMD.

NADER SHEIBANI PhD

Professor, Department of Ophthalmology and Visual Sciences

It is well-known that multiple factors can influence the development of AMD, but recently the potential contributions of inflammatory processes have taken center stage. Nader Sheibani's lab investigates the role of a particular type of cell, known as a mast cell, in the genesis of AMD. Sheibani's Lab is testing whether mast cells, which are involved in both immune and allergic responses, respond to stress-related stimuli by releasing inflammatory mediators that cause oxidation and inflammation within the retina and choroid. (The choroid is a specialized layer of blood vessels beneath the retina that feeds RPE cells and photoreceptors, the two cell types that degenerate in AMD.) In their laboratory model of dry AMD, these inflammatory mediators interact with and destroy various retinal cell types including RPE cells, which are the first cells to deteriorate in AMD, followed by photoreceptors.



In the coming year, the Sheibani Lab will further investigate the stimuli that activate mast cells and will also determine the role of proteins on the surface of retinal cells that interact with molecules that cause cell stress. The goal of these studies is to identify new targets for drugs that could slow down or stop the progression of AMD.



MICHAEL ALTAWEEL MD

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

Dr. Michael Altaweel is the retinal surgeon tasked with taking the lab-grown replacement photoreceptor and RPE cells, created by the Gamm lab and industry collaborators in Madison, Boston, Japan, and Germany, into the operating room. He led the development of surgical techniques needed to safely and accurately place these photoreceptors and/or RPE cells beneath the center of the retina, where AMD and other retinal degenerative disorders do most of their damage. After numerous practice surgeries, Dr. Altaweel has begun to train retinal surgeons from other investigative sites in the United States who will participate in the upcoming clinical trials. Never one to be fully satisfied, Dr. Altaweel continues to work on subretinal cell implantation techniques, introducing new surgical equipment that may further improve outcomes in future trials.



FREYA MOWAT BVSc, PhD

Associate Professor, Department of Surgical Sciences, School of Veterinary Medicine

Why do some people get AMD, while others – even close relatives – don't? Understanding the individual and combined effects of AMD risk factors will help us to better model the disease and develop effective preventative and/or curative strategies. As it turns out, humans are the only creatures in the world who get AMD. The resulting lack of disease-equivalent animal models has hampered progress in AMD research, since such models are often needed to determine whether a new therapy may have promise in humans. Freya Mowat's lab is bridging this gap by developing a rodent model that can be utilized to study risk factors associated with AMD.

Among AMD risk factors, some – like age, high glycemic diet, and mutations in metabolism genes (for example, the PCG1a gene) – stand out. Dr. Mowat and postdoctoral researcher Dr. David Barnett are initiating a project, funded by the BrightFocus Foundation, to examine the impact of all three of these factors on the retinas of mice. Importantly, the lab has found that mice that have a genetic mutation in PGC1a show early AMD-like changes in the retinal pigmented epithelium – the cell layer that is affected first in humans with AMD.

JEREMY ROGERS PhD

Principal Investigator, Department of Ophthalmology and Visual Sciences

Effective diagnosis and treatment of AMD starts with being able to "see" what is actually taking place in the eye. 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 instruments capable of revealing the structure and function of individual, living retinal cells using an Adaptive Optics Scanning Light Ophthalmoscope (AOSLO). It is a remarkable technology that 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.

Dr. Jeremy Rogers has developed and updated the adaptive optics WAIVS system over the past few years, literally building it from the ground up, with bolts, lenses, and lasers. The instrument is now being used in several animal eye imaging studies, providing opportunities to validate new hardware and software designs and to incorporate these innovations into the human eye imaging system. Already, the WAIVS team has imaged multiple human subjects with retinal deposits known as drusen, one of the early signs of AMD. These tests have led to further refinements of the technology to account for retinal topographic changes that occur during the course of AMD.

The WAIVS team also finished incorporating a prototype visible light stimulus feature into the AOSLO machine, which allows it to function as an Optical Retinogram (ORG). With this advancement, the team can record videos that document and measure the real-time responses of individual photoreceptors in human subjects exposed to various wavelengths of light. They collected their first ORG measurements earlier this year, and are now refining their analytical methods to process the imaging data in a clinic-friendly format. Goals for the near future include improving automation of the method and speeding up the imaging acquisition time to make it faster and easier for both the patient and the examiner.

DAVID 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

Once AMD has reached an advanced stage, the number of severely damaged or destroyed photoreceptors and RPE cells necessitate a radically different approach to restoring sight. Dr. David Gamm's lab has spent almost two decades refining methods to grow bona fide human photoreceptor and RPE cells in a dish from induced pluripotent stem cells (iPSCs). Their goal is to restore vision by implanting these and other cells into the retina to treat a range of clinically advanced degenerative diseases and conditions of the retina.

After eight years working with world-leading stem cell and pharmaceutical industry leaders like Opsis Therapeutics, Fujifilm Cellular Dynamics Inc., FUJIFILM, BlueRock Therapeutics, and Bayer AG, a 12,000-page Investigational New Drug (IND) application was submitted to the FDA in Summer 2024. The IND was approved, setting the stage for an upcoming iPSC clinical trial to replace photoreceptors lost in a range of retinal degenerative diseases – the first of its kind in the world.

This trial is a critical step in the ongoing development of iPSC-based retinal cell therapy products to treat other blinding disorders as well, including AMD. Dr. Gamm believes that such treatments will be effective in time, but that it will be an iterative process requiring careful, independent and unbiased evaluation of safety and efficacy, followed by further refinements and trials. "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 every other technology," Dr. Gamm cautions. "But we are hopeful that the treatment will be safe and have a positive impact on vision."

The Gamm Lab has also initiated a new AMD project that uses iPSCs for a purpose other than transplantation. They are using iPSC-derived human RPE cells to test a new approach to eliminate a factor produced by eyes that leads to abnormal blood vessel formation and conversion of dry AMD to wet AMD. The technique, introduced to their lab by a new postdoctoral researcher, Dr. Celia Bisbach, is capable of selectively eliminating unwanted secreted proteins, and has already been used in cancer treatments.







The staff of the Clinical Eye Research Unit (CERU) in the Department of Ophthalmology and Visual Sciences, including (center) Dr. Mihai Mititelu, CERU's Medical Director. Photo courtesy of DOVS.

AMD Clinical Trials

at UW-Madison

The McPherson Eye Research Institute includes a large contingent of members from UW-Madison's esteemed Department of Ophthalmology and Visual Sciences (DOVS), a national leader in treating and researching eye diseases. Over the last 12 months, the DOVS Clinical Eye Research Unit (CERU) and the DOVS Wisconsin Reading Center (WRC) have been actively participating in several clinical trials focused on dry and wet AMD. McPherson ERI researchers currently work on research that, in the future, will no doubt be tested in additional DOVS clinical trials.

Current AMD trials:

Dry AMD:

- **GALE TRIAL (CERU):** This trial is following patients who participate in the Apellis Gale trial, which tests the use of pegcetacoplan (Syfovre) to treat geographic atrophy (GA), the severe form of dry AMD. Pegcetacoplan is injected into the eye 6 – 12 times a year with the goal of slowing the growth of GA. Enrolled patients are being followed for up to 5 years to provide long-term data on safety and efficacy.
- **HONU NATURAL HISTORY STUDY (CERU):** This is a natural history study of the progression of early AMD to intermediate AMD and follows patients already enrolled in the HONU trial. This 2 year trial includes a number of imaging tests for all participants as well as functional tests that measure the participant's quality of vision.
- **AVICEDA TRIAL (WRC):** Aviceda Therapeutics has developed a novel anti-inflammatory compound for dry AMD that is now being tested in a clinical trial. Participants undergo a microperimetry test to map out their area of vision loss in the center of the retina, allowing investigators to determine if (and how quickly) patients lose visual function over time.
- **COCO GA STUDY (WRC and CERU):** This collaborative trial will test the comparability of 3 imaging systems used to measure GA in patients with advanced AMD. More specifically, it will compare the use of Heidelberg autofluorescence images (the gold standard in measuring the area of GA) to newer ultra-widefield autofluorescence imaging systems. In addition, CERU is testing a novel, non-invasive retinal camera that can detect biomarkers that may prove useful in diagnosing and treating patients with GA.



Wisconsin Reading Center leadership, including (left to right) Ellie Corkery (co-director), Amitha Domalpally, MD, PhD (research director), Barb Blodi, MD (medical director), and Chris Hodges (director of operations). Photo courtesy of DOVS.

Wet AMD:

- **HOME OCT TRIAL (WRC and CERU):** This NEI funded trial is being performed in conjunction with the Diabetic Retinopathy Clinical Network. The purpose of the trial is to assess an at-home retinal imaging system that may facilitate daily diabetic disease monitoring. This trial will investigate whether this system can optimize the frequency of anti-vascular endothelial growth factor (anti-VEGF) eye injections by monitoring an individual patient's retinal health more closely and conveniently.
- **REGENXBIO TRIAL (WRC):** This trial analyzes retinal images from patients undergoing gene therapy for wet AMD in order to reduce their dependence on repeated eye injections of anti-VEGF agents. The gene therapy involves participants undergoing subretinal surgery to inject non-infectious viruses that continuously produce the anti-VEGF medication.
- **PULSAR TRIAL (WRC and CERU):** This trial tested a more concentrated form of Eylea, a newer anti-VEGF agent, which ultimately led to FDA approval for its use in wet AMD patients. Results showed that patients could receive injections of the higher dose of Eylea at an interval of 3 – 6 months rather than 8 weeks.



New Treatments

for Age-related Macular Degeneration

Reprinted from the American Academy of Ophthalmology website, May 23, 2024.

By Susanne Medeiros & Reena Mukamal

For more than a decade, ophthalmologists have treated wet age-related macular degeneration (AMD) with periodic eye injections and dry AMD with antioxidant vitamins. These treatments were groundbreaking, offering hope for the first time that this sight-threatening disease could be slowed, and in some cases stopped or even reversed. This revolution is undergoing an intriguing evolution. So, what will the next decade hold for the nearly 20 million Americans with some form of AMD?

In short, the latest research is varied, vibrant, and suggests a future in which ophthalmologists will have more effective options to protect people from going legally blind from AMD. Here's a rundown of the most promising AMD treatments on the horizon.

NEW TREATMENTS FOR WET AMD

Wet AMD develops when new, abnormal blood vessels grow under the retina and leak blood or other fluids. You lose vision faster with wet AMD than with dry AMD.

In the early 2000s, scientists began creating drugs that interfere with this process. These drugs block a protein called vascular endothelial growth factor (VEGF). Before the creation of these so-called anti-VEGF drugs, people with wet AMD were almost certain to develop severe vision loss or blindness.

Then, in 2005, anti-VEGF drugs broke ground by saving the sight of patients with wet AMD. These drugs — including aflibercept (Eylea), ranibizumab (Lucentis), faricimab (Vabysmo) and bevacizumab (Avastin) — stabilize or improve vision in the vast majority of patients. But they must be injected into the eye on a regular basis.

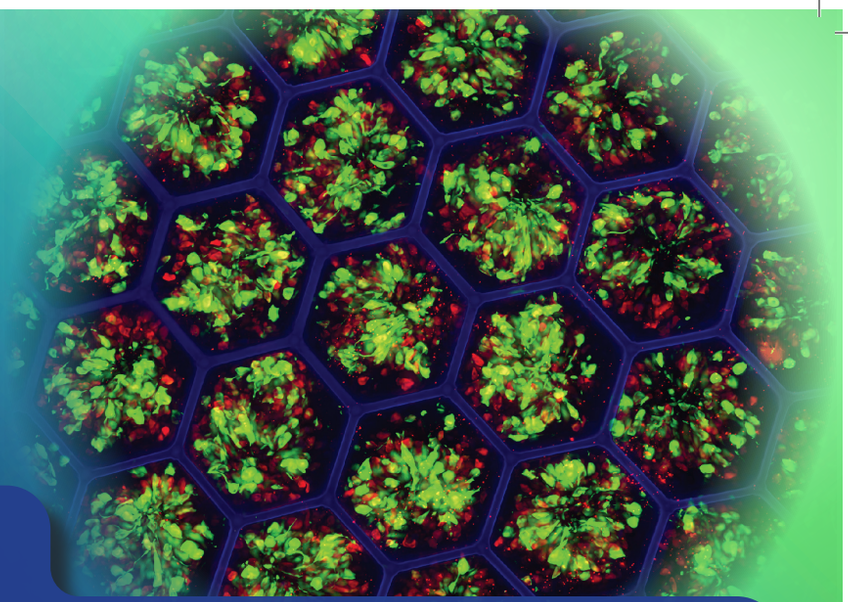
While clinical trials show that anti-VEGF injections have allowed more than 90% of patients to maintain their level of vision, in the real world the percentage is closer to 50%. That's because people aren't being treated as regularly as they should. The problem is most people have needed an injection every month or two to keep their vision. This can be a difficult schedule to maintain for many elderly patients struggling with other maladies and reliant on others to get them to their ophthalmology visits.

Some of the most exciting research today explores alternatives to frequent injections. It's not just about convenience; the hope is that a more consistent treatment will also help people keep more of their vision.

LONGER-LASTING DRUGS FOR WET AMD

A new, higher-dose version of well-established anti-VEGF medicine Eylea may allow patients to go longer in between injections. Eylea HD quadruples the dose of the traditional treatment and can last up to 3 to 4 months as compared to the standard-dose version.

Another new drug that targets two underlying causes of AMD has been FDA approved for both AMD and diabetic macular edema. Faricimab (Vabysmo) targets both VEGF and the protein angiopoietin-2. It's injected into the eye like a typical anti-VEGF treatment, and it may last longer than earlier types of treatments. The latest research suggests most patients can go 3 to 4 months between treatments with Vabysmo.



(Right) Stem cell-derived photoreceptors grown in the Gamm Lab, seeded in honeycomb-patterned scaffolds, with various proteins labeled in green and red. Replacement of damaged cells is one treatment, in this case for advanced AMD, under development at the McPherson ERI. Image taken by Agustin Luz Madrigal, PhD, and Jiahe Jin.

It may also be possible to combine two drugs and hit wet AMD with a double punch. These combos could further improve vision and make injections last longer. Opthea's OPT-302 (Sozinibercept) is currently in clinical trials and has been shown to have better outcomes than anti-VEGF treatments alone.

GENE THERAPY FOR WET AMD

Gene therapy is a promising alternative to ongoing eye injections of drugs such as Eylea, Lucentis, Vabysmo and Avastin. The goal of gene therapy is to provide a 'one-and-done' treatment by helping the eye make its own anti-VEGF medicine. Two different methods are under investigation. One injects the gene therapy underneath the retina in a surgical procedure; the other injects it into the eye just like a routine anti-VEGF treatment and is done in the ophthalmologist's office.

Despite the promise of gene therapy, the long-term effectiveness remains to be seen. Such a treatment is likely to be very expensive and may not be suitable for everyone with wet AMD.

NEW TREATMENTS FOR DRY AMD

About 8 out of 10 people with AMD have the dry form. Dry AMD occurs when parts of the macula thin with age and/or tiny clumps of protein called drusen grow. Patients can slowly lose central vision making it more difficult to retain independence. Depending on severity, dry AMD is considered early, intermediate or late stage.

For people with intermediate disease, a formulation of antioxidant vitamins called the AREDS2 formula can help reduce the risk of vision loss. People with late-stage AMD, also called geographic atrophy (GA), did not have any treatments available until recently. Today, two new therapies are accessible or in early trials for patients with GA. They are offering some hope to patients who previously had none. However, these therapies have special considerations that should be discussed with your retinal specialist.

DRY AMD TREATMENTS THAT TARGET THE IMMUNE SYSTEM

A part of the immune system called the "complement cascade" has long been identified as a culprit in AMD. Two new drugs that target the complement cascade and stop it from attacking the retina have recently been approved by the FDA: Pegcetacoplan (SYFOVRE) and avacincaptad pegol (Izervay). Like currently available treatments for wet AMD, these drugs are injected directly into the patient's eye. While they have been shown to slow the development of geographic atrophy by up to 20%, they do not improve vision.

Additionally, these therapies can cause side effects or complications ranging from mild to severe. Your retinal specialist will discuss these tradeoffs with you and help you determine the best course of treatment.

REPLACING VISION CELLS IN PEOPLE WITH DRY AMD

Another concept under investigation is the possibility of replacing some cells that begin to die in late-stage dry AMD. Stem cells may be able to replace the retinal cells that are killed off by this disease. Doctors are devising ways to transplant these stem cells into the eye. One strategy is to layer the stem cells on thin scaffolds. Another tactic is to put the cells into a fluid suspension that can be injected under the retina. Stem cells have been tested in small clinical trials and they do not have unexpected side effects. It may take about 10 to 15 years for these therapies to be fine-tuned and proven effective in humans.

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Pat and Jay Smith Support Boosts AMD Research at the McPherson ERI

Age-related macular degeneration is a widespread problem, and McPherson ERI AMD research has been supported by many other generous donors, in addition to (and often inspired by) the Trout family. In 2022, Pat and Jay Smith established the Pat and Jay Smith Macular Degeneration Treatment Innovation Program with a $1 million gift to the Institute. The Smith Program addresses critical gaps in our understanding of AMD and applies that knowledge to create more effective therapies. Three major AMD projects have been supported with Smith funds (and are profiled in this report): (1) AMD drug development in Nader Sheibani's lab, (2) stem cell-based AMD model systems and cell-based AMD therapeutics in David Gamm's lab, and (3) advanced imaging of the human retina in health and disease by Jeremy Rogers' lab. The Smiths' interest was spurred by Pat's own experience with age-related macular degeneration, as well as Jay's ongoing service on the McPherson ERI's Advisory Board. We are grateful for their support, and for the support of others who have helped the Institute in these continuing efforts.



Please consider helping our research by donating to the McPherson ERI AMD Fund, either at vision.wisc.edu/giving, or by contacting us at the address or phone number below.

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