McPherson Eye Research Institute
UNIVERSITY OF WISCONSIN–MADISON

InSights

Published each semester

SPRING *2023*

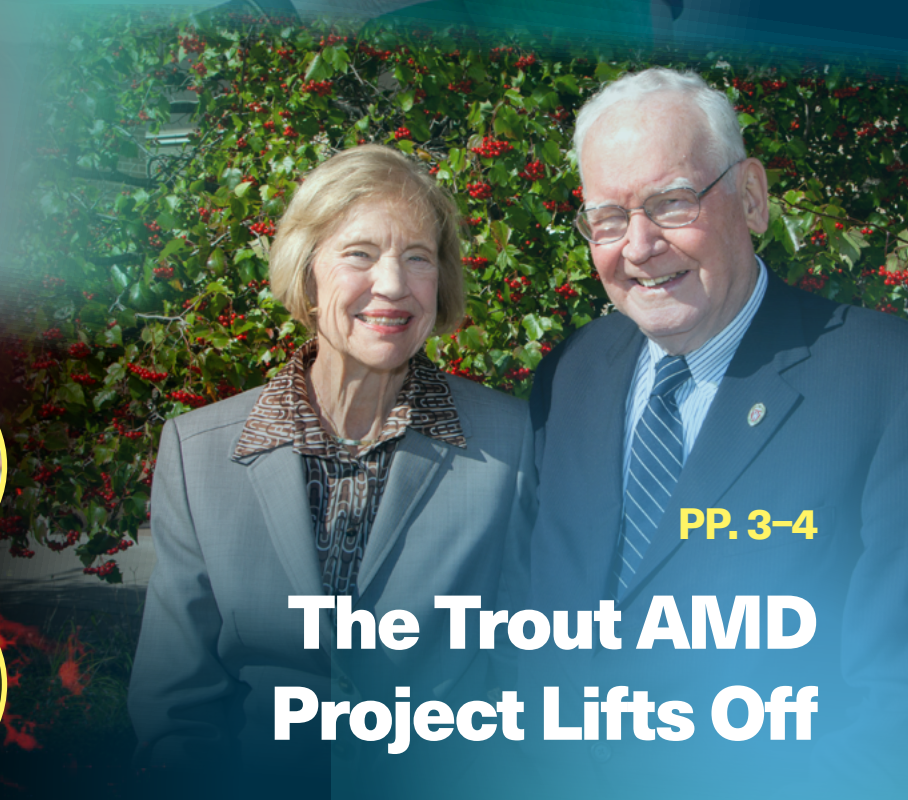
REMEMBERING

Alice McPherson MD

PP. 5–6

PP. 9–17

New Therapies Advance



PP. 3–4

The Trout AMD Project Lifts Off

FROM THE DIRECTOR

Dear Friends of the McPherson ERI,

When someone has lived a life full of meaning and great purpose, we mourn their passing, but we are also given an opportunity to pause and reflect on their life and influence. On January 16th, our co-founder, friend, and advisor, Dr. Alice McPherson, passed away at the age of 96 in Houston. She personified excellence but preferred to celebrate the achievements of others rather than entertain a discussion of her own brilliance and historic achievements. We would like to share with you, on the inside pages, a glimpse into a remarkable career that had—and will continue to have—an immeasurable impact on retina research and therapies worldwide.

Perhaps nothing pleased Dr. McPherson more than hearing how other individuals embraced and supported the effort to cure blinding diseases. Below, you will read about a major McPherson ERI initiative to combat age-related macular degeneration, the Trout AMD Project (TAP), newly established by Dr. Monroe and Sandra Trout through a $5 million donation. TAP is the latest in a series of impactful gifts that will expand and empower our AMD research consortium and fuel our fight against this devastating and highly prevalent disease.

Whether the focus is AMD or one of the many other blinding disorders we have our sights on, translating research to clinical care is an essential goal of the Institute. Sanbrita Mondal, OD (pp. 14-15) exemplifies this determination in her work as Chief of the Vision Rehabilitation Clinic in the Department of Ophthalmology and Visual Sciences. I have witnessed firsthand the extent to which she can help those with vision loss lead full and active lives. Dr. Mondal, and all of the researchers highlighted in these pages—including those involved in a landmark $30 million NEI grant recently awarded to McPherson ERI researchers to develop gene editing therapies for inherited blinding diseases (pp. 9-11)—show how Institute scientists and clinicians are working together to make a difference in people's lives, both now and in the future.

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

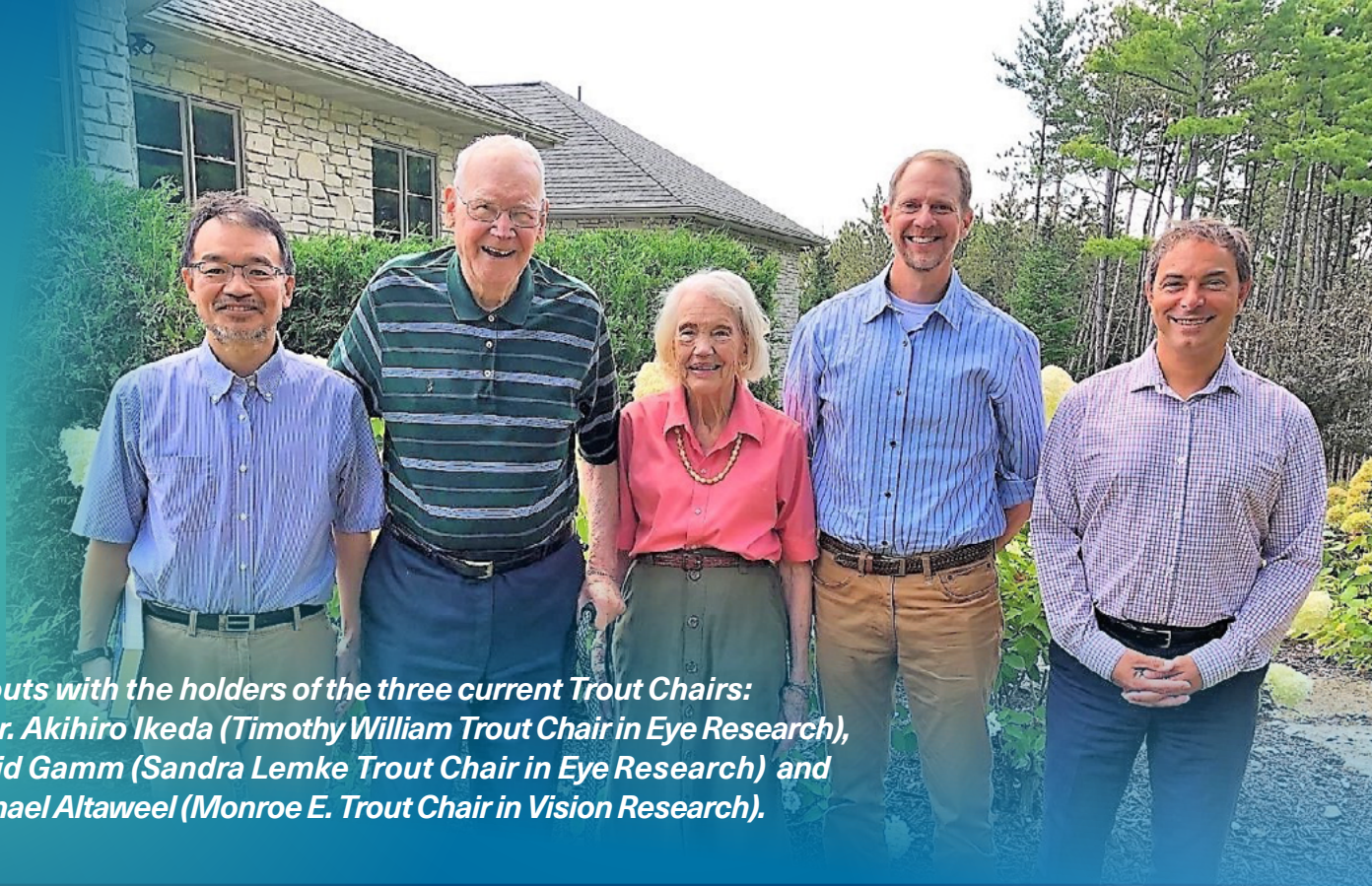
The Trouts with Dean Robert Golden.

TROUT AMD PROJECT

Announcing... the Trout AMD Project (TAP)!

Age-related macular degeneration (AMD) is one of the great health crises of our aging population. The statistics on AMD are staggering. Currently, 15 million people in the U.S. have the disease, and 1.7 million Americans have it in advanced form. 2% of all individuals aged 50-59 have AMD, rising to nearly 30% in individuals over the age of 75. With increasing life expectancies, by 2050 the number of people affected by AMD in the U.S. is expected to double.

For almost ten years, Dr. Monroe and Sandy Trout have targeted AMD with their contributions to the McPherson ERI, including the establishment of three AMD-focused endowed chairs. This year, the Trouts have increased their research investment with the creation of the Trout AMD Project (TAP), a comprehensive initiative that will expand and integrate AMD research at the McPherson ERI. As Dr.Trout noted years ago, "I have macular degeneration, and while I might not see a cure in my lifetime, we want to help researchers find ways to prevent and effectively treat this disease."



The Trouts with the holders of the three current Trout Chairs: (L-R), Dr. Akihiro Ikeda (Timothy William Trout Chair in Eye Research), Dr. David Gamm (Sandra Lemke Trout Chair in Eye Research) and Dr. Michael Altaweel (Monroe E. Trout Chair in Vision Research).

TAP has several components made possible through a $5 million gift, including a fourth Trout endowed chair that will aid in recruiting new AMD researchers, as well as an endowment to directly support AMD research. It will also feature an annual publication to highlight AMD research advances and an annual Sandra Trout Lecture delivered by prominent AMD researchers. TAP will be inaugurated with a September 2023 Trout AMD Symposium in Sandy Trout's hometown of Appleton, WI, where they currently reside.

Dr. David Gamm notes, "Monroe and Sandy understand that continual innovation and open collaboration are needed to address the hurdles that persistently thwart efforts to prevent or treat many forms of AMD. We're fortunate that they are so willing to invest in new ideas like TAP, which is the first of its kind to our knowledge."

The legacy that the Trouts have established at UW-Madison is already remarkable and includes support for Wisconsin Public Television, Wisconsin Public Radio, the Department of Ophthalmology and Visual Sciences, and the Janet Lemke Cancer Fund. With the Trout AMD Project, their generosity will immeasurably impact lives far into the future. As Dr. Gamm noted,

"Monroe and Sandy are exceptionally caring and wise people, and they are determined to make the world a better place in many different ways."

REMEMBERING

A RETINAL RESEARCH PIONEER

Alice R. McPherson MD

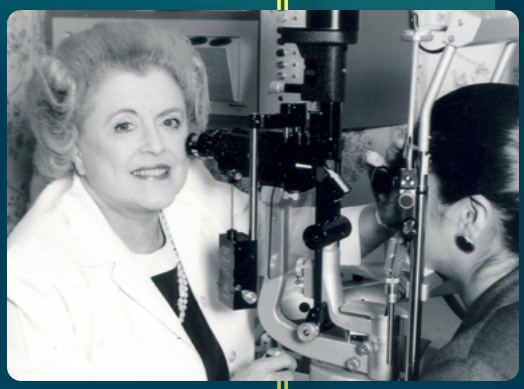
In June 2012, the UW Eye Research Institute was renamed in honor of Alice McPherson, MD, in recognition of her landmark career and dedication to the University of Wisconsin and to vision research. From its inception until very recently, Dr. McPherson was closely involved in establishing and growing the now-McPherson ERI. Dr. McPherson passed away peacefully on the evening of January 16, at the age of 96. With fondness, we look back at the life of one of the UW's finest graduates.

Born in Saskatchewan, Canada, Alice Ruth McPherson spent much of her childhood in Minnesota and Wisconsin. Knowing she wanted to become a physician, she earned her undergraduate and medical degrees and completed an ophthalmologic residency, all at the University of Wisconsin-Madison.

In 1959, she completed a fellowship in retinal diseases and retinal surgery at the Massachusetts Eye and Ear Infirmary at Harvard University Medical School under the supervision of Charles L. Schepens, MD, considered to be the father of modern retinal surgery. She was one of the first fellows of Dr. Schepens and the first-ever female vitreoretinal fellow.

Dr. McPherson's retina expertise led her to become one of the world's leading vitreoretinal specialists and retinal surgeons, and an innovator and early adopter of many ground-breaking procedures. She pioneered treatments for retinopathy of prematurity, and she was an early proponent of photo- coagulation in the treatment of diabetic retinopathy.

She was devoted to students, training over 100 vitreoretinal fellows in her career. In 2015, she established the Dr. Alice R. McPherson Medical Scholarship Fund at the School of Medicine and Public Health, which supports, in perpetuity, each year's outstanding beginning medical students. One of SMPH's four learning communities for first-year medical students is named in honor of Dr. McPherson, and she greatly enjoyed meeting students on visits to Madison.



In 1958, Dr. McPherson married Anthony "Tony" Mierzwa, and they made the decision to move to Houston, Texas. Alongside a professor- ship at the Baylor College of Medicine, Dr. McPherson founded the first retina service in Texas—indeed, in the south. Simultaneously, she became the first full-time female retina specialist in the United States and the world. Dr. McPherson's retina practice spanned more than 70 years. She was devoted to her patients, and they to her.

In 1969, Dr. McPherson founded the Retina Research Foundation (RRF) in Houston, dedicated to the eradication of retinal disease by funding basic science and translational retina research. Under her leadership as President and Scientific Adviser, RRF funded well over 1,000 research grants (worth over $40 million) and helped to launch the careers of many major vision researchers in the United States and abroad.

Dr. McPherson was a founding charter member and later the first female president of the Retina Society, the founding president of the University of Wisconsin Ophthalmology Alumni Association, and the first female chair of the Pan- American Association of Ophthalmology Foundation. She made ophthalmic history as the first woman selected to receive the Jules Gonin Medal, the highest achieve- ment in ophthalmology. Dr. McPherson's Gonin Medal is now on display on the 9th floor of WIMR II.

Dr. McPherson's vision and support were essential to the formation of the McPherson Eye Research Institute. Always keenly interested in the scientific pursuits of the Institute, she was close with the Institute's successive Emmett A. Humble Distinguished Directors, Daniel Albert and David Gamm.

Through her years of involvement with the McPherson ERI, Dr. McPherson traveled frequently to Madison, serving on the Institute's Advisory Board and getting to know many in the McPherson ERI circle.

Dr. McPherson was never one to call attention to herself. As she noted: **"It's all about working together, sharing ideas, educating and inspiring others—men and women alike—to join our mission to save and prolong eyesight."** The measure of her own impact is best summed up in that great old quote from William James: **"The greatest use of a life is to spend it on something that will outlast it."** That, she did.

We will miss her.

Tackling Rare Diseases with Gene Editing

McPherson ERI/WID researchers receive **$30 million** award to treat blindness with new gene editing therapies

Supported by a $30 million grant from the National Institute of Health (NIH), McPherson ERI researchers led by a team at the Wisconsin Institute of Discovery (WID) will be able to test drug therapeutics for two diseases known to cause blindness.

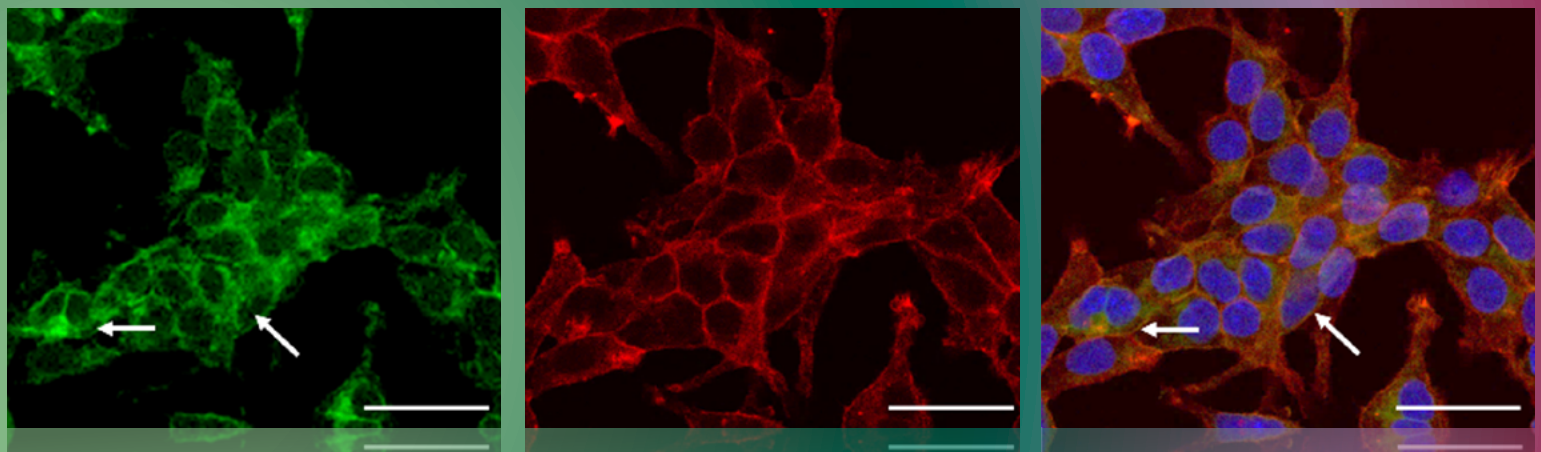
The collaborative project will merge new drug delivery systems with advanced genome CRISPR technology to fuel innovation in treating Best Disease (BD) and Leber Congenital Amaurosis (LCA), both of which are currently untreatable hereditary diseases. The researchers decided to focus on the eye as their starting point due to its self-contained nature, isolation from other organs, accessibility, ease of monitoring, and reduced likelihood of adverse immune reactions.

"Our focus is on two different diseases: LCA, a severe and rare group that affects children and can lead to complete blindness, and BD which affects central vision in older children, teens and adults and has a slower onset," says **David Gamm**, UW–Madison ophthalmology professor and director of the McPherson Eye Research Institute. "By targeting these two diseases, we can gain a broad perspective on the effectiveness of our gene editing therapeutics for many types of genetic disorders of the retina."

Krishanu Saha, an Associate Professor of Biomedical Engineering at WID and a member of NIH's Somatic Cell Genome Editing Consortium, views this grant as a crucial step towards advancing gene editing therapy and drug development on campus.

"The genome editing piece of it is a game changer," Saha says. "The opportunity to execute it in a safe and meaningful way for patients, specifically Wisconsin patients currently diagnosed with one of these diseases, would be a nice fulfillment of why we do the work and why it's publicly funded."

Genome editing involves splicing or cutting DNA at a specific spot and letting it heal, or inserting



Microscopic images of fixing inherited mutations within human cells via genome editing. Red and green mark channel proteins within cells that pump ions within the retina. Blue marks the nucleus containing the genome of each cell. After treating these cells with adenine base editors, a precise fix of the mutation leads to proper localization of the proteins within the cell (shown in some cells with white arrows), which eventually rescues the function of retinal cells. Scale bar: 50 microns.

a DNA template that replaces the cut site. This corrects disease-causing mutations by eliminating or replacing the mutated sequence. Despite significant advancements in CRISPR gene editing technology, it has not yet resulted in useful drug therapies. This is mainly because although CRISPR can modify the DNA of a single cell, treating billions of cells is often necessary for effective treatment. Not so for the retina, where correcting even hundred or thousands of cells may make a meaningful impact on vision.

First, to ensure a therapeutic is safe and effective for patients, a model system is needed to mimic what would happen in a patient, without risking their safety. "This can be done through animal models or lab-grown cell-based systems," says Gamm. "The role of my group is to develop and maintain the induced pluripotent stem cell-based human retina models for testing in the laboratory."

Additionally, most CRISPR technology uses a virus delivery system that is currently hindered by unintended off-target effects, such as reduced effectiveness over time, undesirable immune reactions, and supply chain difficulties. To overcome these limitations, the project aims to leverage nanotechnology to develop novel methods of drug delivery that can effectively transport and utilize CRISPR technology to its intended destination.

One delivery approach will be led by Shaoqin "Sarah" Gong, UW–Madison professor of ophthalmology and visual sciences and biomedical engineering. "Developing a safe and efficient delivery system for the CRISPR genome editor is essential for clinical translation," says Gong. Her work focuses on a new family of nano-scale capsules made of silica that can carry genome-editing tools into target organs or cells around the body and then harmlessly dissolve.

In the past, there have been biosafety issues resulting from prolonged expression of gene editors via viral delivery. However, the silica nanocapsules engineered by the Gong Lab together with the CRISPR gene editors can degrade inside the cell, thereby reducing off-target editing effects. Early studies have shown no adverse events in human cell cultures or mouse models. With U19 grant support, the team aims to optimize the nanocapsule formulations for higher editing efficiency, develop a scale-up manufacturing process, and evaluate biosafety and efficiency in non-human primates. This will lead to a safer and more efficient silica nanocapsule-based ocular gene editing therapy.

Another approach to improving the delivery of genome editing therapeutics involves a partnership with start-up biotechnology company Spotlight Therapeutics. The California-based company will use a multi-prong approach to solving the delivery challenges using proteins and peptides. They will also focus on streamlining the industry side of developing drug therapeutics, from conceptualization to implementation.

"This project could have a potentially durable impact," remarks Saha. "Just trying is a big deal. It's a long road from the design stage of paper and pencil to formulating effective therapeutics with a lifetime impact. It takes lots of investment. The fact that we are piecing together the resources and the people here in Madison makes that really exciting and meaningful."

Another challenge is one of economics. Rare disorders and diseases are not appealing to industry pharmaceuticals because the market cannot sustain the millions of dollars and time it takes to invest in the resources needed to show genome editing therapeutics are safe and effective.

"This grant provides the resources to improve processes that will hopefully lead to the development of a safe patient treatment that will preserve or enhance visual function in a meaningful way.," says Gamm. "These therapeutics are still in the early stages of development, and we expect them to improve over time. It is important to have realistic expectations and to realize that every therapeutic has limitations – blindness is not going to be cured overnight. However, this grant is exceptional because most don't come close to providing the funds necessary to bring multiple complementary teams together to really advance a treatment," Gamm adds.

The grant is set to begin in April and is one of five multidisciplinary grants that the NIH will award in 2023.

Article by Laura C. Red Eagle for WID

L-R: ***Krishanu Saha, Bikash Pattnaik, Shaoqin "Sarah" Gong, David Gamm.***

Closing the Gaps to Restoring Sight

Retinal cells grown from stem cells can reach out and connect with neighbors, according to a new study, completing a "handshake" that may show the cells are ready for trials in humans with degenerative eye disorders.

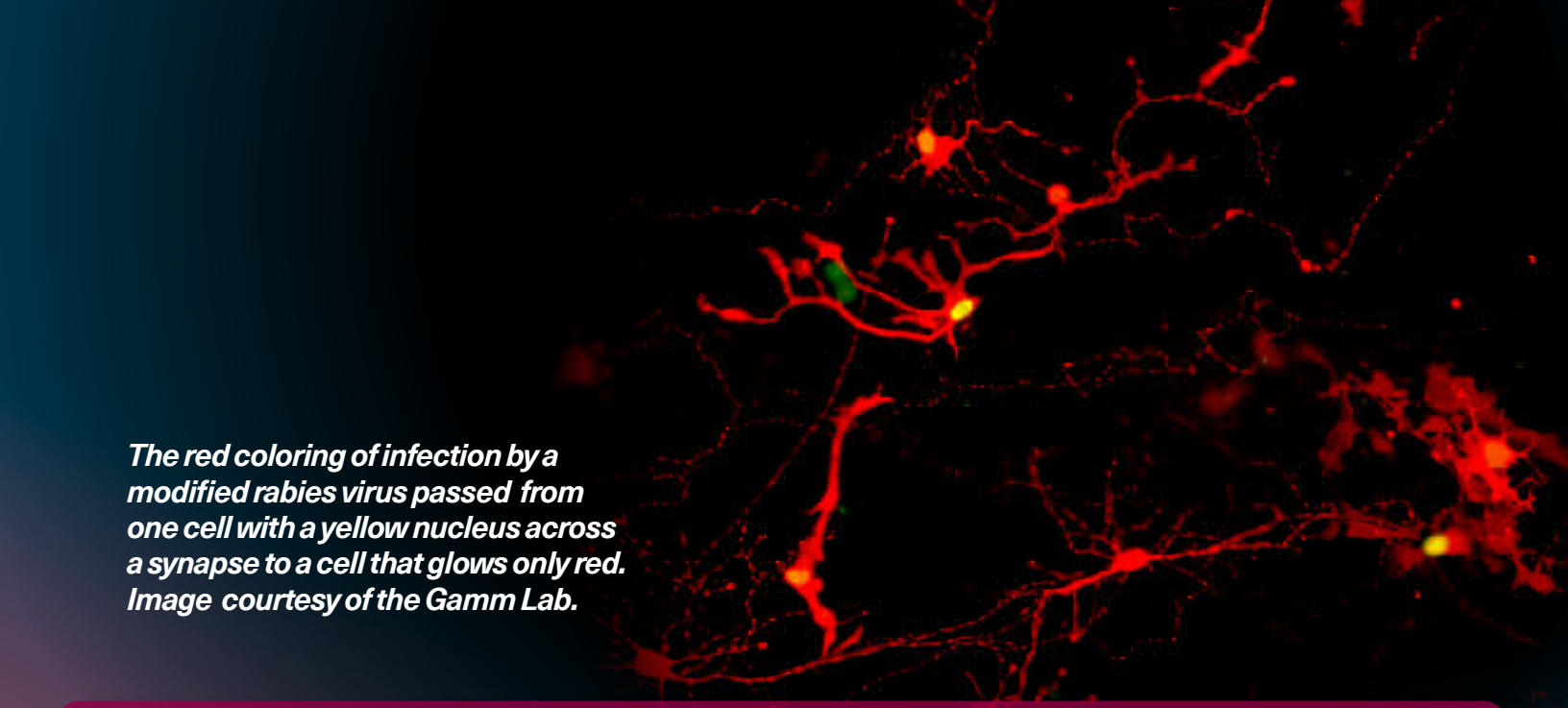
L-R, David Gamm, Xinyu Zhao, Allison Ludwig, Steven Mayerl.

Over a decade ago, researchers in the Gamm Lab developed a way to grow organized clusters of cells, called organoids, that resemble the retina, the light-sensitive tissue at the back of the eye. They coaxed human skin cells reprogrammed to act as stem cells to develop into layers of several types of retinal cells that sense light and ultimately transmit what we see to the brain.

> ***We wanted to use the cells from those organoids as replacement parts for the same types of cells that have been lost in the course of retinal diseases,"*** says David Gamm, ***"but after being grown in a laboratory dish for months as compact clusters, the question remained—will the cells behave appropriately after we tease them apart? Because that is key to introducing them into a patient's eye."***

During 2022, Gamm and UW–Madison collaborators published studies showing that dish-grown retinal cells called photoreceptors respond appropriately to different wavelengths and intensities of light, and that once they are separated from adjacent cells in their organoid, can reach out toward other cells with characteristic biological cords called axons.

> ***The last piece of the puzzle was to see if these cords had the ability to plug into, or shake hands with, other retinal cell types in order to communicate,"*** says Gamm. Cells in the retina and brain communicate across synapses, tiny gaps at the tips of their axons. To confirm that their lab-grown retinal cells have the capacity to replace diseased cells and relay sensory information like healthy ones, they needed to show that they could make these synapses.



The red coloring of infection by a modified rabies virus passed from one cell with a yellow nucleus across a synapse to a cell that glows only red. Image courtesy of the Gamm Lab.

Xinyu Zhao, UW–Madison professor of neuroscience and co-author of the new study, worked with the Gamm lab to probe their cells' ability to form synaptic connections. They did this using a modified rabies virus to identify pairs of cells that had the potential to communicate with one another.

The research team, including graduate students and co-first-authors Allison Ludwig and Steven Mayerl, broke apart the retinal organoids into individual cells, gave them a week to extend their axons and make new connections, exposed them to the virus, and then took a peek. What they saw were many retinal cells marked by a fluorescent color indicating that synapses had successfully formed.

After they confirmed the presence of synaptic connections, the researchers analyzed the cells involved and found that the most common retinal cell types forming synapses were photoreceptors—rods and cones—which are lost in diseases like retinitis pigmentosa and age-related macular degeneration, as well as in certain eye injuries. The next most common cell type, retinal ganglion cells, degenerate in optic nerve disorders like glaucoma.

> ***That was an important revelation for us,"*** says Gamm. ***"It shows the potentially broad impact these retinal organoids could have. Ultimately, it's leading to human clinical trials, which are the clear next step."***

This research, published in the Proceedings of the National Academy of Sciences, was supported by federal grants from the National Institutes of Health, the Department of Defense, the Sandra Lemke Trout Chair in Eye Research, and the RRF Emmett A. Humble Distinguished Directorship of the McPherson ERI.

Adapted from an article by Chris Barncard.

FEATURED RESEARCHER

Sanbrita Mondal OD

Clinical Adjunct Assistant Professor/Senior Research Scientist
Ophthalmology and Visual Sciences Chief of Vision Rehabilitation Services

Cases of low vision and blindness are predicted to more than double by 2050.

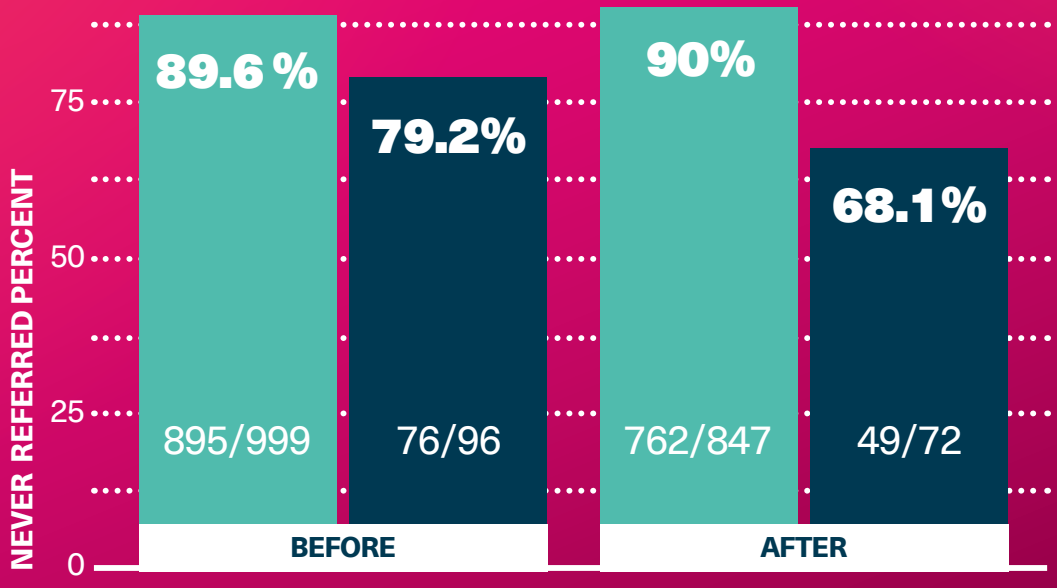
Sanbrita Mondal's work focuses on identifying existing barriers to low vision rehabilitation and implementing a sustainable system to meet the rising demand. Successful rehabilitation involves complex multidisciplinary care—eye care providers, low vision specialists, social work services, and behavioral health. Dr. Mondal's research has revealed that adopting a multidisciplinary service approach increases referrals, but ~90% of patients with moderate (category 1) low vision remain unaware that help is available to them. These forgotten individuals miss out on opportunities to increase their independence with optical and non-optical aids, as well as to get help in coping with and adapting to vision loss.

DR. MONDAL'S CURRENT WORK INCLUDES:

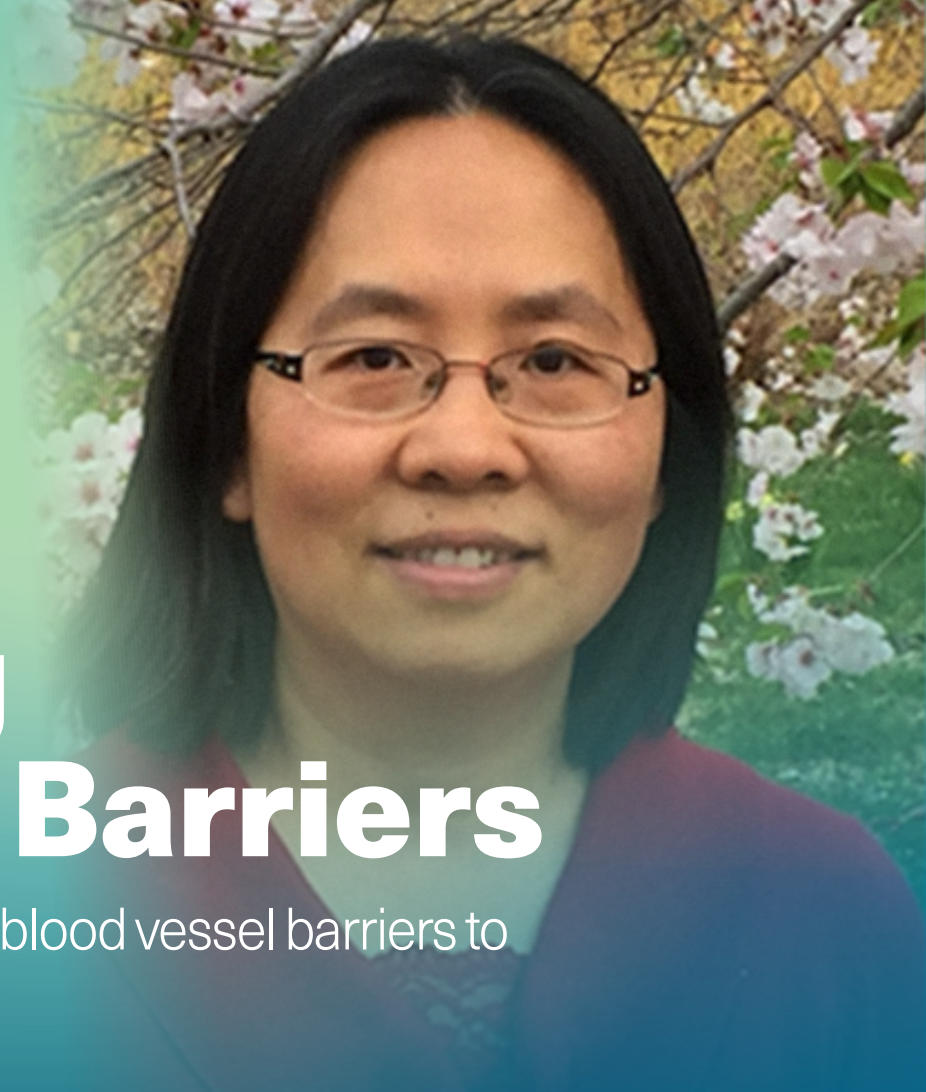
VIVRS, the Vision Impairment and Vision Rehabilitation Service Study, which identifies barriers to low vision services through surveys of relevant stakeholders. This study comes out of the awareness that there is little interaction among these stakeholders, which has created critical gaps in the rehabilitation process. The results of the VIVRS Study will be used to establish best practices and "rehabilitate rehabilitation."

WILVR, the Wisconsin Low Vision Registry and Data Repository, a database that facilitates the use of epidemiological studies of vision impairment to identify where services can be best directed. WILVR captures critical data such as primary ocular disease diagnoses, comorbidities, types of vision loss, intervention timelines, psychosocial effects, adaptation changes, and geographical locations of people with low vision.

Through a collaboration with Yuhang Zhao (Computer Sciences), Dr. Mondal is **designing virtual reality software** for functional vision assessments in a head-mounted display. The intent is to quantify vision loss and to use that information as a tool to initiate vision rehabilitation before an individual's independence is lost substantially.



This chart shows the percentage of patients never referred for vision rehabilitation for each visual acuity category in the better seeing eye (20/70-20/200 vs. 20/200 or worse), before and after the establishment of a low vision rehabilitation program. For patients with low vision, referrals increased substantially after the establishment of the program.



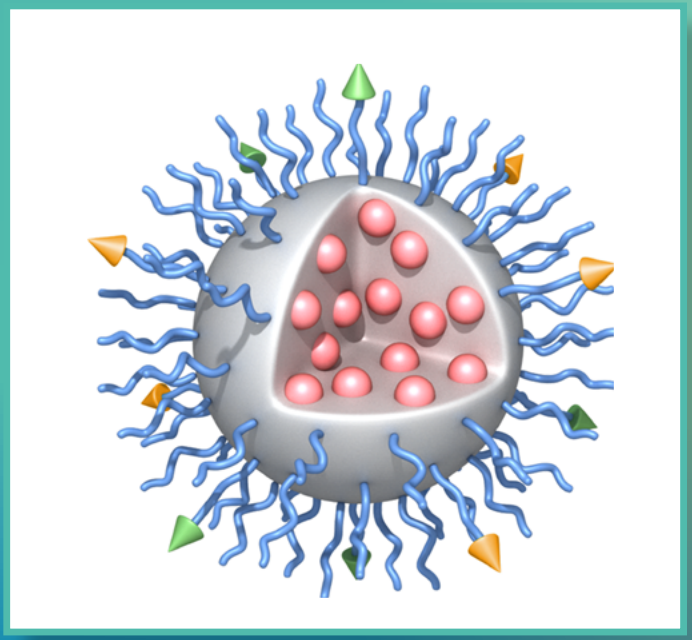
Breaking Through Barriers

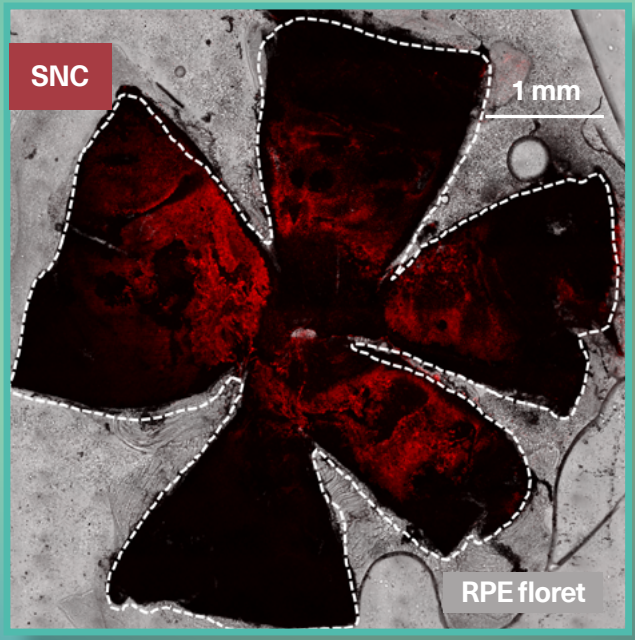
New nanocapsules cross blood vessel barriers to deliver therapies

Dr. Sarah Gong's silica nanocapsule work is essential to the new $30 million genome-editing project noted on pp. 6-7 but is also revolutionary in an additional way. The Gong lab's nanocapsules have been engineered to cross the biological barriers that block most therapeutics from entering both the brain and retina. The techniqaue was first shown to work in mice to deliver gene editing therapy for Alzheimer's disease and will be used to advance therapies for Leber congenital amaurosis (LCA) and Best disease.

Blood vessels in the brain and retina selectively control access to the tissues they course through, screening out toxins and pathogens that may be present in the bloodstream. Unfortunately, these blood vessel barriers also restrict potentially beneficial treatments, like certain gene therapies and pharmaceuticals, from reaching their targets. Injecting therapeutics directly into the brain or the eye is one way to get around these barriers, but it requires more invasive procedures.

"***There is no cure yet for many degenerative brain and retina disorders,***" says Dr. Gong, a UW-Madison professor of ophthalmology and visual sciences and biomedical engineering and researcher at the Wisconsin Institute for Discovery. ***"Innovative delivery strategies may change that by enabling noninvasive, safe and efficient delivery of therapeutics that could halt or reverse these diseases."***





(Left) Schematic illustration of a silica nanocapsule (SNC). (Right) A mouse retinal pigment epithelium layer (outlined with a white dotted line) after efficient delivery of gene editing RNP via silica nanocapsules.

For example, CRISPR-based genome editing is a promising approach for correcting gene mutations that cause disease, but it is only useful if it can access the affected organs and tissues. In a study recently published in the journal ***Advanced Materials***, Gong and her lab members, including postdoctoral researcher and first author of the study Yuyuan Wang, describe a new family of nanoscale capsules made of silica that can carry genome-editing tools into many organs around the body and then harmlessly dissolve.

By modifying the surfaces of the silica nanocapsules, the researchers found the nanocapsules could pass through blood vessel barriers to achieve gene editing in the brains of mice that carry a mutation that is linked to Alzheimer disease. Because the nanocapsules can be administered repeatedly and intravenously, they can achieve higher therapeutic efficacy without risking more localized and invasive methods.

In addition to the work in the eye and brain, this unique technology is also being investigated for the delivery of biologics to other areas of the body, including the liver and lungs. Dr. Gong's ingenuity in bypassing biological barriers could spur a new era of more effective treatments for many of the diseases that continue to plague humankind.

Adapted from an article by Laura Red Eagle, UW News, January 2023

Cycle for Sight 2023

McPherson ERI's annual fundraiser raised $60,000 for vision research grants through April!

You can still support Cycle for Sight 2023 at **give.wiscmedicine.org/cycleforsight**






Please follow the McPherson ERI on

Twitter • @McPherson_ERI » **Facebook** • McPhersonERI