McPherson
Eye Research Institute
UNIVERSITY OF WISCONSIN–MADISON

InSights

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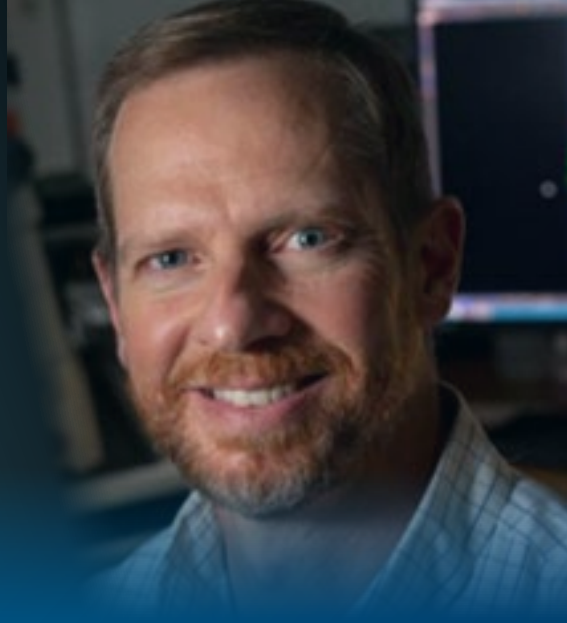


From the Director

DEAR FRIENDS OF THE MCPHERSON ERI,

We often feature collaborative projects in *InSights*, and there's a good reason. Although we've all seen "Eureka!" moments portrayed by single individuals in movies and books, most meaningful advances don't emanate from solitary events or people. Even Nobel Prize winners usually start their acceptance speeches with lengthy acknowledgements of the many dedicated scientists who helped them achieve their breakthrough.

In this issue, we trace the steps that brought together a half-dozen McPherson ERI labs for a common goal—developing better technologies and therapeutics to combat inherited forms of blindness. These vision researchers began exchanging ideas and sharing resources over 10 years ago, and earlier this year those efforts resulted in a $29 million NIH grant to advance a novel form of gene editing to cure two degenerative retinal disorders, Best disease and Leber congenital amaurosis. You will also read in this issue about our core group of researchers that study vision in UW-Madison's Department of Kinesiology, and who benefit from similar collaborative synergies.

At the McPherson ERI, we really do believe that our whole is much greater than the sum of our parts. Our scientists thrive when they work together, inspiring each other in countless ways through formal research interactions or informal conversations walking across campus. It also helps that our researchers are fun, interesting, and kind people, as are our advisors and the many people who support our work. It was fitting that the Institute's Mandelbaum & Albert Family Vision Gallery highlighted many of these individuals this past summer as part of Alan Attie's project entitled ***The Soul in Things***. You'll see some of those images in the pages ahead. I hope you enjoy this issue of ***InSights***, and thank you for your interest.

DAVID M. GAMM MD, PHD
RRF Emmett A. Humble Distinguished Director, McPherson ERI
Professor, Department of Ophthalmology & Visual Sciences
Sandra Lemke Trout Chair in Eye Research

LAUNCHING THE
Trout AMD Project

McPherson ERI scientists were pleased to celebrate the launch of the Trout AMD Project with a community symposium on AMD in Appleton on Saturday, September 23rd. Close to two hundred attendees heard an update on AMD research at the McPherson ERI from UW-Madison's David Gamm, Amitha Domalpally, Aki Ikeda, and Michael Altaweel, and Dr. Kapil Bharti from the National Eye Institute presented the inaugural Sandra Lemke Trout Lecture.

The event, held at Lawrence University's Music-Drama Center, was introduced by Appleton Mayor Jake Woodford and Lawrence University President Laurie Carter, and attendees were warmly welcomed by Sandra Trout. There was a lively Q & A following the talks, and the morning marked an outstanding start to a project that will accelerate new therapies for age-related macular degeneration.

L-R, Drs. Amitha Domalpally, Aki Ikeda, and Michael Altaweel; Dr. Aki Ikeda; Dr. Kapil Bharti; and Dr. Michael Altaweel.

New Trainee Members in Vision Research

McPherson ERI is proud of its trainee members, who will carry vision research years into the future. Thus far in 2023, these trainee members have joined the Institute….

SEHRISH AFSHEEN

Graduate student, Pediatrics

In the laboratory of Dr. Bikash Pattnaik, Sehrish Afsheen studies the functional association of potassium channels with retina cells and the effect of anti-epileptic drugs on these channels.

JIN-WOO CHO PHD

Research Associate, Electrical and Computer Engineering

Working with Dr. Mikhail Kats, Jin-Woo Cho focuses on infrared optics, in particular optical components and structures that emit and modulate thermal radiation. Infrared (thermal) vision can discern information which is less accessible to human vision than "visible" cameras.

MINA GAFFNEY

Graduate student, Biomedical Engineering, Marquette University and the Medical College of Wisconsin

Mina Gaffney's graduate study, mentored by Drs. Joseph Carroll & Robert Cooper, revolves around exploring visual function in individuals with disruptions to their photoreceptor mosaic using AOSLO-based techniques.

JOSEPH KREIS

Graduate student, Cell Biology, Neurobiology, and Anatomy, Medical College of Wisconsin

A student in the Neuroscience Doctoral Program at MCW, Joseph Kreis studies the use of non-invasive retinal imaging methods to observe retinal disease, in Dr. Joseph Carroll's lab.

ANDREW SCHULTZ

Graduate student, Molecular and Cellular Pharmacology Training Program

While pursuing a PhD in pharmacology, Andrew Schultz is researching the role of excitatory neurotransmission and calcium signaling in retinal computation, in Dr. Raunak Sinha's lab.

WHITNEY STEVENS-SOSTRE PHD

Postdoctoral researcher, Ophthalmology and Visual Sciences

As a postdoc in Dr. Mrinalini Hoon's laboratory, Dr. Stevens-Sostre's work will focus on the mechanisms of circuit establishment and function in the mammalian retina using structural, functional, and genetic tools.

RUTH WOEHLKE

Graduate student, Biomedical Engineering

In Dr. Robert Cooper's lab, Ruth Woehlke's work is aimed at increasing the image quality and accessibility of their adaptive optics scanning light ophthalmoscope (AOSLO).

XUTING YANG

Graduate student, Materials Science and Engineering

Xuting Yang works on visible- and near-infrared photonic research for applications in quantum sensing in Dr. Jennifer Choy's research group.

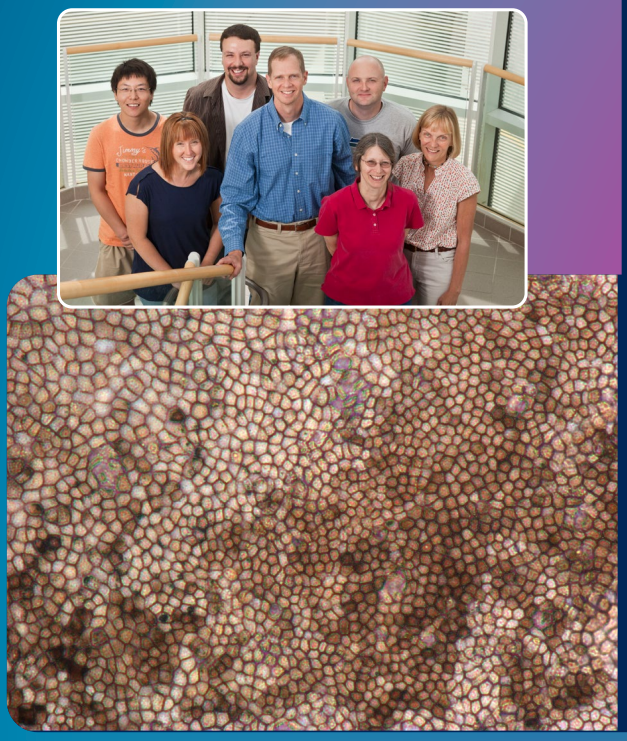
Gene Editing for Retinal Disease

Anatomy of a Collaboration

Earlier this year, the National Institutes of Health announced that a team of researchers from the McPherson Eye Research Institute was awarded a 5-year, $29 million NIH grant to launch the CRISPR Vision Program—a new initiative to advance treatments for two devastating blinding diseases, Best disease and Leber congenital amaurosis.

These hereditary diseases, evident at birth in LCA, or from an early age with Best disease, currently have no cure. The UW-Madison team will use their recent advancements in nanoparticle delivery systems, automated analytical methods, retinal stem cell biology, and CRISPR gene-editing technology to bring new therapies to clinical trials.

We will follow the progress of this collaboration over the coming years. Meanwhile, we thought it worthwhile to look back at the many steps that have led to this point.



HUMAN RETINA CAN BE MADE FROM STEM CELLS IN THE LAB

In 2009, David Gamm's lab reports on generating 3D retinal tissues and cells from human pluripotent stem cells. In the years since, this has allowed his lab to model dozens of retinal diseases in a dish, with further implications for regenerative medicine and the treatment of retinal diseases using stem cell-based approaches.

Top: Gamm Lab members, circa 2009; Left: Lab-grown RPE cells. Images courtesy of the Gamm Lab.

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BEST DISEASE "IN A DISH"

In 2013, David Gamm and Bikash Pattnaik show. using patient-derived stem cells. that Best disease can be mimicked in cell culture (i.e., a Petri-like dish). Their paper contributed valuable insights into the cause and potential treatments of this inherited macular degeneration, which robs people of their central vision.

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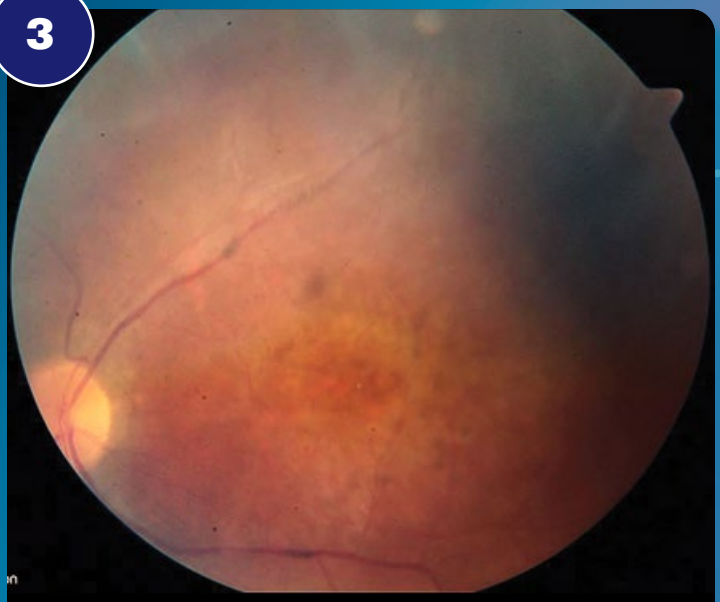

UNDERSTANDING THE CAUSE OF LCA16

In 2015, Bikash Pattnaik's lab announces successful development of new laboratory tools to study a childhood-onset blinding disease, Leber Congenital Amaurosis (LCA16), that results from dysfunction of a particular gene in retinal pigment epithelial (RPE) cells. The ability to understand the genetic basis of LCA16 opens the door to potential gene-editing therapies.

4

A BETTER METHOD FOR GENOME EDITING

In 2018, Kris Saha's lab and David Gamm's lab report on a new method for seamless genome editing for human pluripotent stem cells. The technique enables the isolation of genetically corrected cell populations without introducing "collateral" genetic damage in as little as 2 weeks.

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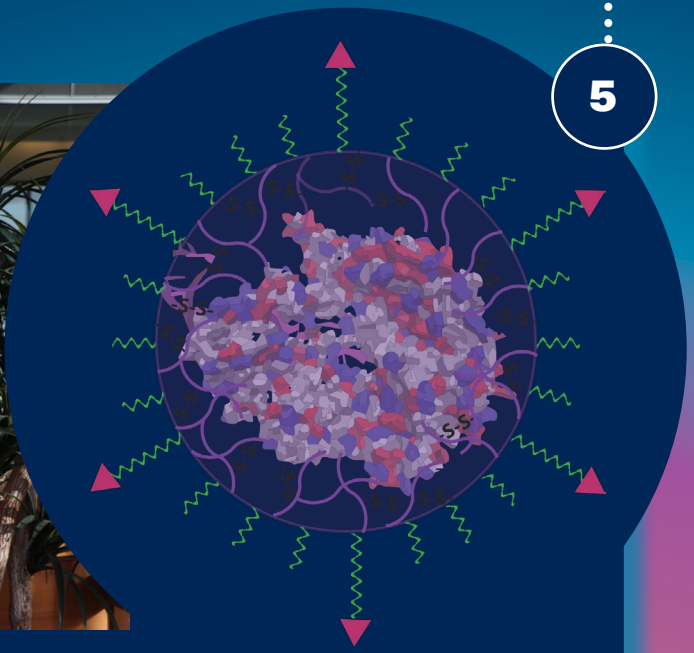

DELIVERING THE PACKAGE

Finding the most effective methods to deliver gene-editing therapies has been a multi-step process. In 2018, **Dr. Sarah Gong**, along with Drs. Pattnaik and Saha, reported the use of versatile nanometer (1 billionth of a meter)-sized particles (i.e., nanoparticles) to deliver gene therapies, including genome editing machinery, to retinal cells. In the following years, these collaborators demonstrated that they could generate even smaller biodegradable nanocapsules capable of genetically editing cells in living creatures. These nanotechnology platforms permit precise and safe delivery of gene-modifying molecules to the correct cells in the eye without the use of viruses.

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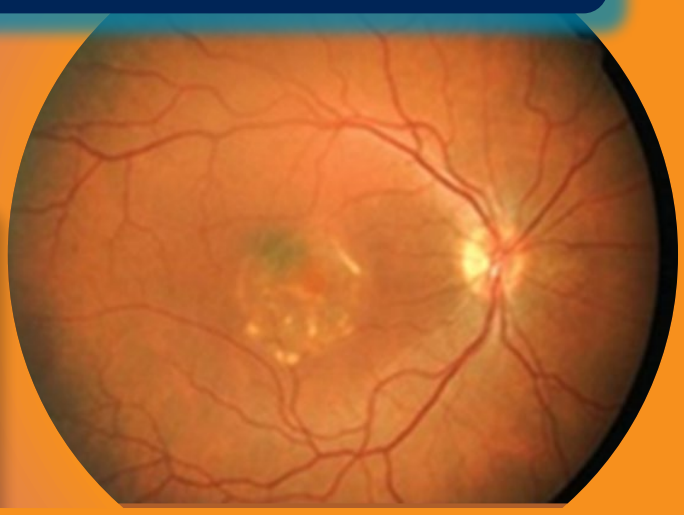
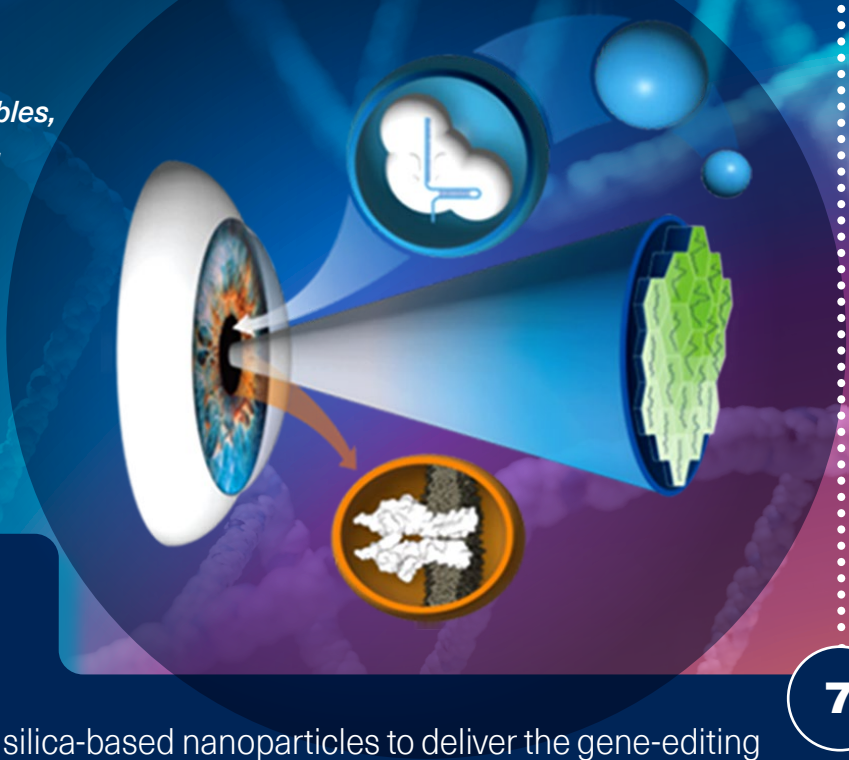
TARGETING BEST DISEASE

In 2020, the Gamm, Pattnaik, and Saha labs corrected Best disease in patient stem cell-derived RPE cells through two methods of gene therapy---first by overwhelming broken copies of the BEST1 gene with many normal copies, then by using CRISPR-Cas9 gene editing to destroy the mutant gene copy. Their work paves the way for personalized gene therapy approaches for Best disease.





This image represents lipid microbubbles, which were injected into a mouse eye, carrying a genome editor to precisely correct a potassium ion channel gene defect. After treatment, the channels were functional and visual function was restored.

Illustration by Adam Steinberg.

A SUCCESSFUL GENE EDIT FOR LCA16

2023: Using Gong-lab engineered, silica-based nanoparticles to deliver the gene-editing CRISPR nucleotide (or "base") editor to retinal cells, the McPherson ERI team was able to repair a gene mutation that causes the childhood blinding disease LCA16. The proof-of-concept study restored the function of a protein that controls the flow of potassium ions in retinal tissue and allows light-detecting cells to work properly. The approach worked in RPE cells grown in the Gamm lab that were derived from stem cells of a patient with Leber congenital amaurosis (LCA), as well as in a mouse model generated by the Pattnaik lab that mimics the disease.

Bikash Pattnaik led a team including scientists and engineers from UW–Madison, Harvard, and MIT that published the study in the ***Journal of Clinical Investigation***. The innovative technique distinguishes the work from a more typical method used in gene editing. Since the gene editing method known as CRISPR/Cas9 was discovered in 2012, using a modified virus has become the norm for delivering gene-editing components into cells. However, the use of viruses for these types of therapeutics has disadvantages in its degree of precision, potential for inflammation, and the possibility of unpredictable side effects.

The Gong lab modified their nanoparticles using synthetic chemistry to enable their uptake in specific retinal cell types. Plus, because they are synthetic, nanoparticles lower the risk of immune system responses that accompany standard viral methods. Another advantage of the team's technique is the specificity of the newer CRISPR-based "base" editing strategy. "The rapid pace of genetic diagnosis development has enabled accuracy in identifying disease-causing mutations, and we used base editing to correct a specific error in the DNA sequence of patients, overcoming several challenges through the collaborative team science approach," said research associate Meha Kabra, who works in the Pattnaik lab.

LCA is relatively rare, but the research team expects that its new nanoparticle-packaged CRISPR technology will be able to treat many other inherited eye diseases, too. "Our goal was to design a package that will carry CRISPR base editors to the retina for a wide range of therapeutic purposes," said Bikash Pattnaik.

"Typically, drug development can take more than 30 years," Pattnaik continues. "But with a collaborative approach that brings together people with different expertise and resources, we can cut this timeline significantly." He says that this work, which demonstrates the feasibility of repairing genetic defects in ion channel proteins, is a critical first step toward restoring the sight of affected young patients.

Adapted from an article by Sharon M Van Sluijs, Department of Pediatrics

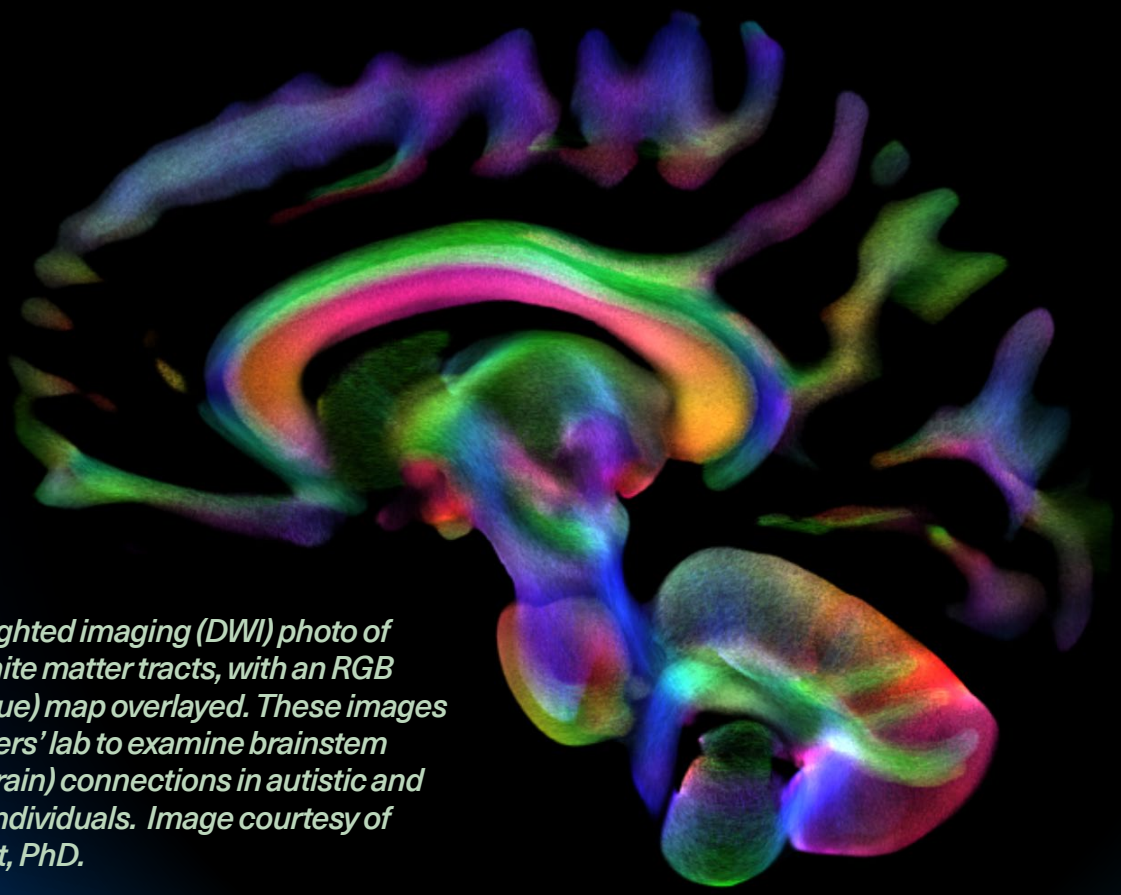
L-R, Pattnaik Lab members Bikash Pattnaik, PhD; Meha Kabra, PhD; and Pawan Shahi, PhD

The next five years… McPherson ERI scientists will continue to investigate new pathways for advancing gene editing for Best disease and LCA.

GOALS INCLUDE:

- **Dr. Gong plans to further refine** her lab's nanoparticle delivery systems for higher editing efficiency and, together with Waisman Biomanufacturing in Madison, develop a manufacturing process appropriate for testing these formulations in humans.
- **The team will work with** retina surgeon Dr. Mike Nork to evaluate the safety and efficiency of the treatment before starting human clinical trials.
- **In a parallel effort,** researchers will collaborate with Spotlight Therapeutics, a California-based company that uses a custom CRISPR-based platform called TAGE (Targeted Active Gene Editors), which may hold important advantages over other gene-editing approaches.
- **The Gamm lab is producing** millions of patient stem cell-derived retinal cells to serve as testing platforms for the team's cutting-edge therapeutics.
- **Rather than develop nanoparticles one-by-one** for each different mutation that causes Best disease or LCA16, the team will explore more efficient approaches to balance safety with speed in advancing these exciting therapies.

Advances taking place at the McPherson ERI reflect and support national research priorities. In 2021, ***Nature*** highlighted the NIH Somatic Cell Genome Editing program, which Kris Saha co-led. This is a collaborative effort to advance genome editing technologies across the nation, with broad implications for medicine and biotechnology—and the McPherson Eye Research Institute was the only team selected to work on eye diseases. Our team will continue to lead this effort in the coming years.



Diffusion weighted imaging (DWI) photo of the brain's white matter tracts, with an RGB (red-green-blue) map overlayed. These images allow Dr. Travers' lab to examine brainstem (and whole-brain) connections in autistic and non-autistic individuals. Image courtesy of Olivia Surgent, PhD.

Movement and Sight

Kinesiology and the McPherson ERI

The McPherson Eye Research Institute exists to bring together researchers from different disciplines to study vision, preserve and restore eyesight, and maximize our visual abilities. That's a broad mandate, and it takes a lot of people from many fields of research to accomplish. Certain fields may be more obvious than others, such as ophthalmology, biomedical engineering, or neuroscience, but a host of other disciplines also focus on vision and impact our lives in profound ways. The Department of Kinesiology, whose researchers focus on the study of human body movement, is the home of three McPherson ERI scientists whose work has a strong vision component.

We tend to take our capacity to move for granted, but it follows from a complex series of inputs and reactions. Indeed, we need to gather and process a vast array of data every second from many sensory systems to efficiently move and interact with objects in our dynamic environments. The research conducted in **Andrea Mason's Human Motor Behavior Lab** strives to understand how people use visual and haptic (touch) feedback to plan and perform both simple and complex movements. For instance, how do people combine the movements of their upper and lower body when reaching to pick up objects while walking?

L-R, Brittany Travers, PhD; Andrea Mason, PhD; and Kristen Pickett, PhD.

Over the past decade, research projects in the Motor Behavior Lab have involved children (both neuro-typical and neuro-divergent) and adults in order to determine how the planning and performance of these coordinated movements change across the lifespan. As you might expect, vision is integral to these changes. Dr. Mason's lab has also compared performance in natural environments, where there is an abundance of accurate sensory feedback, to those in virtual environments, where differences in feedback can alter performance.

Brittany Travers' Motor and Brain Development Lab focuses on the intersection between sensorimotor skills and neurobiology in autistic individuals from childhood into adulthood. Motor (i.e., movement) development serves as a window into the neuroanatomy of autistic individuals, and motor differences can greatly impact their daily lives (including their occupations). Travers' lab studies whether it is possible to compensate for these motor differences in order to enhance autistic individuals' quality of life. For example, in a randomized-controlled trial, her group has tested how a multi-week videogame regimen that provides visual biofeedback can improve standing balance (and can also lead to structural brain changes in autistic individuals).

The Travers Lab studies motor differences in a variety of ways, including grip strength and whole-body motion. Visuo-motor integration—using visual information to execute effective movements—is a key focus of attention. Identifying how circumstances and movements differ in autistic individuals has guided the lab into the understudied territory of the brainstem. Using advanced neuroimaging optimized to study the brainstem, they are able to better understand how this area contributes to sensorimotor differences and other core features of autism.

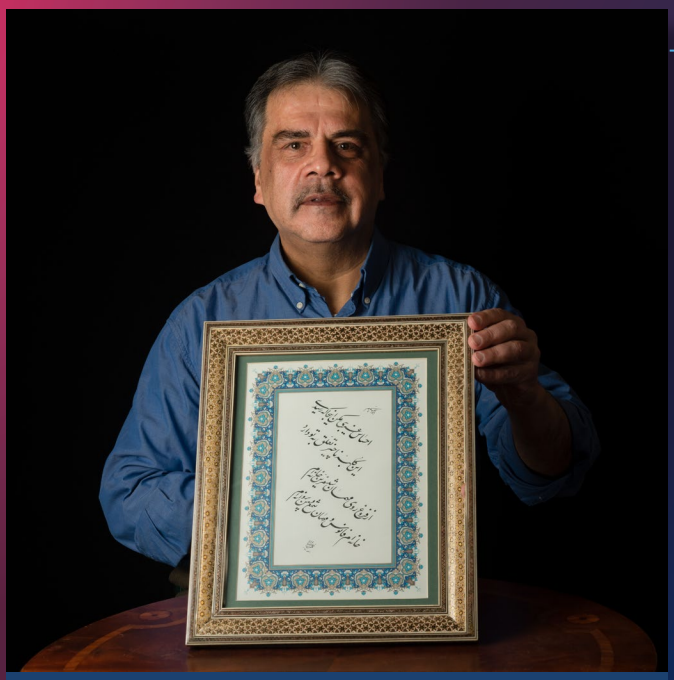
Kristen Pickett's Sensory Motor Control Lab (SMIL) is focused on shaping meaningful health outcomes for older individuals, especially those with Parkinson disease and their family caregivers, using community-guided, innovative, and implementable research. Dr. Pickett's lab focuses on health disparities experienced by individuals in rural areas, which are often best addressed with some form of telehealth or remotely delivered intervention. Telehealth can hold obstacles for some older adults, however, as it often requires accommodations for those with visual limitations. Her lab considers how providers can effectively address these challenges. Dr. Pickett's lab has a particular interest in human gait and falls—a leading cause of injury in older adults. The lab group is working to facilitate sustainable behavioral changes that allow safer in-home participation in daily activities, a goal that will become even more critical as the population ages.

Together, Drs. Mason, Pickett, and Travers are working to understand the unique motor challenges associated with autism. Collaborative research over several years has examined how the complexity of visual motor tasks (for example, grasping objects while walking) may affect autistic adolescents differently than their non-autistic peers. In a recent report (Mason, Pickett, Padilla and Travers; 2022), the group showed that autistic youth who exhibit certain gait patterns during simple assessments of motor ability may have greater difficulty with tasks requiring more complex visuo-motor coordination. By understanding this link, these vital vision researchers are working to help autistic individuals adapt better to the many activities of daily living—dressing, cooking, cleaning, and organization—that will increase safety and autonomy.

The Soul in Things

Photographer Alan Attie's portraits, which were on display in the McPherson ERI's Albert & Mandelbaum Family Vision Gallery throughout Summer 2023, capture his sitters' relationships with objects that hold special meaning to them. The variety of objects, and the range of responses, "have been deeply personal and many have been deeply moving," as Attie notes in his artist's statement. "Ultimately," he says, "this project is about love." We were gratified to be able to include some of the McPherson Eye Research Institute's researchers and friends in Attie's series. Dr. Attie, who is also the Jack Gorski Professor of Biochemistry at UW-Madison, is thoroughly familiar with basic research, and oversees a lab focusing on the genetics of diabetes.

McPherson ERI friends are shown on these pages, along with brief excerpts from their subject statements. To see the complete exhibit along with the full subject statements—not to be missed!—go to **www.alanattiephotography.com/soulinthings.**

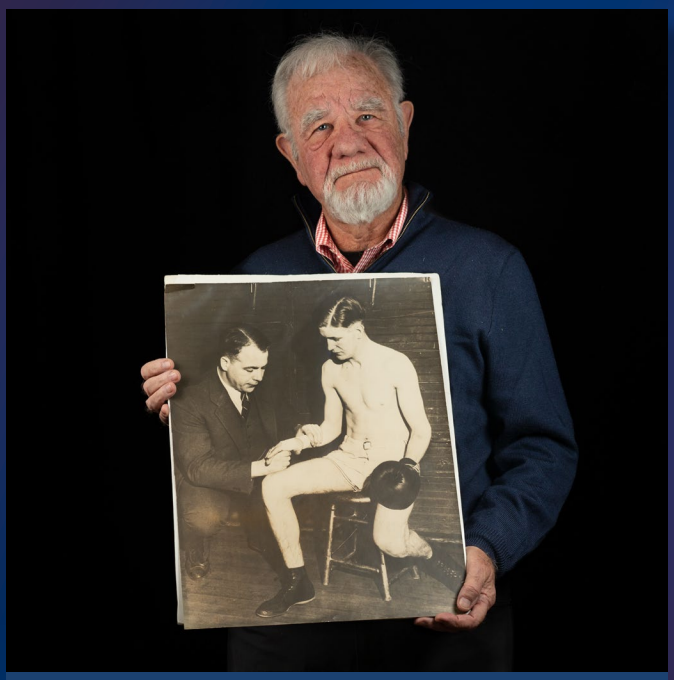


Nader Sheibani, Professor, Department of Ophthalmology and Visual Sciences, with an Iranian poem, written in classical Farsi: "I have been inspired by poems from Iranian poets, which have shaped our culture over the years. I am always deeply touched by many of these poems, and I feel they have had a strong impact on the person I have become."

Gillian McLellan, Veterinary Ophthalmologist and vision scientist, with her 1977 copy of ***The Albatross Book of Verse***: "I was surprised to find poems written by Robert Burns. These works were easy and familiar to me, some I already knew by heart. For the teenage me, Burns' inclusion in this anthology lent credibility to his work and, importantly, lent credibility to my community."

Marshall Flax, Orientation & Mobility Specialist, with a mask used during radiation therapy: "I see my mask as a thing that helped make me really miserable, and at the same time, a thing that saved my life."

Andrea Mason, Chair of the Department of Kinesiology, UW-Madison, with one of her late father's golf clubs: "I loved the times that I was able to play golf with my dad. I always wanted to prove to him that I had inherited some of his gift for movement. Seeing the delight on his face when either one of us hit a great shot is one of my fondest memories."



David Walsh, lawyer and McPherson ERI Advisory Board member, with a picture of his father, John Walsh: "My father was the most influential person in my life. Dad was a world class amateur boxer, having won over 100 fights, including twice winning the National Golden Gloves Championship."

Dick Dubielzig, Veterinary Ophthalmology Pathologist, with a blue whale eyeball: "As the largest eyeball in our collection, this strikingly beautiful specimen is the one I've chosen to represent my abiding passion for eyes and the ongoing adventure that is exploring vision."

Rose Barroilhet, retired Director of Space Management, UW-Madison, and McPherson ERI Advisory Board Chair, with her late mother's teapot: "My first memories are of my mother pouring tea out of this pot. I was brought to her bedroom early each morning to have my cocoa and breakfast, while she sang me Spanish nursery rhymes and told me stories of family history."

Akihiro Ikeda, Professor, Department of Medical Genetics, with his go-to cooking pot: "About 30 years ago, I was in search of a cooking utensil durable and reliable enough for my kitchen...it has been an everyday companion since then. I've lost count of the dishes that this pot has helped me create, each one adding a new flavor to our family's history."

All images courtesy of Alan Attie.

On display until January 10th, 2024

At year's end, please support research on vision loss at the McPherson Eye Research Institute!

FOR MORE INFORMATION

Visit **vision.wisc.edu/giving**, or contact Michael Chaim at **608-320-9347** or **chaim@wisc.edu.**

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T (608) 265-4023 **E** info@vision.wisc.edu **W** www.vision.wisc.edu

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