

Patient-specific  
pluripotent stem  
cell-derived RPE



## Genetic Nano-surgery inside the eye

WITH PROFESSOR KRISHANU SAHA, PHD

**A vast array of vision disorders** can be traced to genetic causes, and we now know many more of these disease-causing genes thanks to advances in sequencing the human genome. New tools in bioengineering called “**genome editors**” have recently been developed to precisely repair these genes. This editing involves directly changing the sequences in the maternal and paternal copies of the genome within cells. One of the newest classes of genome editors is called CRISPR (shorthand for clustered interspaced short palindromic repeats). These editors were first identified within bacteria found in yogurt and have now been engineered to work in human cells. CRISPR has taken the biomedical research community by storm since 2012, and is now being developed for applications in the eye. In the labs of Dr. Saha and other McPherson Eye Research Institute members, CRISPR editors are being packaged into extremely small particles, called nanoparticles, in order to treat and perhaps cure vision disorders.

**Genomic medicine entered the clinic** over thirty years ago with viral gene augmentation therapies. These strategies introduced corrected copies of the disease-causing gene within cells, without changing the maternal and paternal copies. After a lengthy development process encumbered by significant safety challenges during clinical trials, these strategies have been approved by the FDA. Luxturna, a viral gene therapy by Spark Therapeutics, was approved in Fall 2017 for a rare retinal disorder called Leber’s congenital amaurosis. However, one size does not fit all. For some disease-causing genes, these therapeutic strategies can be very effective, but for others, they are limited – especially in cases where the maternal and paternal copies of the gene cause significant stress and other dysfunction within the cell. In these cases, genome editing could be more effective. The Saha, Gamm, and Pattnaik labs within the McPherson Eye Research Institute are working with patient-derived retinal tissues to directly compare the genome editing versus the viral approach for several inherited blinding disorders.

**Efficient delivery of the genome editor** to the right cells within the eye is a key challenge. The Saha lab has developed new strategies to package the genome editing machinery into nanoparticles that are amenable for injection into the eye. Dr. Saha’s lab packaged the Cas9 - the ‘molecular scissor’ component of the CRISPR system - with the template that encodes the sequence for repair. Using this strategy, 10 times more precise gene editing with these nanoparticles was demonstrated versus the state-of-the-art approaches used elsewhere in the field.

**Dr. Saha is now leading a collaborative project** (supported by a 2018 WARF 2020 award) to extend and further customize these CRISPR nanoparticles for subretinal injection in the eye, targeting the retinal pigment epithelium, (RPE), the layer of cells that critically supports the photoreceptors within the retina. He has established collaborations with McPherson Eye Research Institute members to develop stem-cell based and mouse models of inherited disorders, as well as novel biomaterials for safe delivery of these genome editors. Additional research is needed to determine the efficacy of these approaches before moving into patients. In the future, this approach has great potential to be precisely tailored to an individual’s genotype, thus opening the door for precision genomic medicine in the eye.



# Dear Friends of the McPherson Eye Research Institute,

**The top priorities of our more than 60** Principal Investigators (PIs) and their many research associates are to better understand how our eyes and visual brain centers work, and to use that knowledge to advance new therapies for vision-related diseases. There are, however, other important goals that we pursue as an Institute, such as fulfilling our education mission.

**Within the McPherson ERI**, we focus on helping to develop younger vision researchers. These investigators – undergraduates, graduate students, and PhDs engaged in post-doctoral research – are essential to the operation of every McPherson ERI lab. Many of these trainees will ultimately start their own labs, moving vision research forward along new (and often unforeseen) paths. But to be successful, they need, and look for, opportunities for support – both from a financial standpoint as well as opportunities for special training, mentoring, and collaborations. The McPherson ERI assists them in multiple ways, including:

- Vision Research Trainee Grants, awarded to two trainees annually and funded from Cycle for Sight proceeds, which give young investigators the chance to develop their grant-writing skills and – if they're successful – to fund a small project.
- David G. Walsh Research Travel Awards, awarded to four grad students or postdocs annually to enable them to present research results at national conferences.
- Trainee research presentation opportunities include our MERI-at-a-Glance forums and our annual Vision Science Poster Session.
- Classroom learning opportunities, such as Adam Steinberg's tutorial on creating effective scientific preparations, and our Vision Science in a Nutshell lecture series.

These and other methods allow beginning researchers to learn and develop key skills, and make important connections to more experienced researchers.

**At the same time, the McPherson ERI's mission** mandates that we share our research with the community – and for that, educational outreach is essential. Institute researchers often bring their work to the interested public. Just last month, four members gave an update to an Appleton audience on age-related macular degeneration, and other researchers participated in our annual animal vision event. We've also brought our education mission to public schools for the past 7 years, developing and teaching a lesson on vision to 8th grade students in the Madison Metropolitan School District. We are counting on a handful of those 8th graders to become interested enough in science – and perhaps in vision science – to carry our research forward in the years to come.

**We appreciate your help in all of this – and hope that you're enjoying the summer.**

## **David M. Gamm, MD, PhD**

RRF Emmett A. Humble Distinguished Director, McPherson ERI  
Sandra Lemke Trout Chair in Eye Research

# Saving Cents for Vision

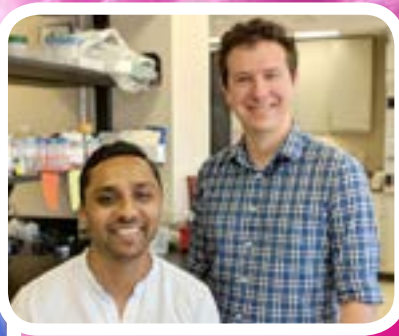


**Every gift to the McPherson Eye Research Institute** helps to advance vision research, and many gifts come with a story worth sharing. When Immaculate Heart of Mary Catholic School in Monona was looking for a new recipient of funds from its “Penny War” fundraiser, Principal Callie Meiller thought of her longtime friend, John Walsh. Walsh – a business attorney with Axley in Madison (and a talented stand-up comic, who took first place out of 116 comics at the Comedy Club on State’s annual Madison’s Funniest Comic Competition this year) – is legally blind from an inherited disease called Usher syndrome, which also affects hearing. (His older brother, Mike, has the same condition, although his vision loss is not quite as advanced as John’s). Callie thought that John, a friend since they were in the same class at Edgewood High School (they went to homecoming together as sophomores), would enjoy talking to the kids and could propose a vision-related recipient for the Penny War funds. She asked him to speak to an assembly of the school’s approximately 140 students, 3 year-olds through 8th graders.

**John Walsh, whose family has long supported** vision research and the McPherson Eye Research Institute, not only agreed to speak to the school; he offered to match the funds that the children raised for the Institute. In his talk to the “kiddos,” as John calls them, he told them where the Penny Wars money was going, and how it helps people like him. It was different from his occasional talks to older audiences – “there was less description of genetics and research, and more about the concept of relying on friends and family for help, and treating people with respect.” The questions were wide-ranging, although John – the stand-up comic peeking through – noted that they were “mainly about how often I hit my head on stuff.” Callie Meiller recalls other questions, about whether John could drive – what he can actually see – and why canes are white and red.

**Over the following two weeks,** the students collected \$367.89, almost entirely in pennies, in a bucket in the school’s office. The collection, which has been donated to the Institute and matched by John’s gift, helps the students understand that (as Meiller puts it) “service projects are a normal thing for our school – part of our faith is wanting to serve others.” It’s a good lesson in friendship, too, and we’re grateful to be part of this story.





**LEFT:** Tom Lawler & Dr. Julie Mares

**TOP:** Dwani Patel & Dr. Daniel Lipinski

## Vision Research Trainee Grants Awarded to McPherson ERI Graduate Students

**Thomas Lawler and Dwani Patel** are the 2018 recipients of the McPherson ERI's **Vision Research Trainee Grants**. These one-year grant awards of \$3000 each are funded by the Institute's annual Cycle for Sight event and awarded by the Research and Leadership Committees. They were established to give trainees experience writing grant applications, to augment their professional development, to advance vision research in McPherson ERI member groups by funding trainee research, and to encourage the next generation of vision scientists. Four grants have been awarded since the program's inception.

**Thomas Lawler** is a graduate student in the Integrated Program in Nutritional Sciences, working with Professor Julie Mares' lab group (Ophthalmology and Visual Sciences). His project will explore "**The association between early life exposure to carotenoids lutein and zeaxanthin and macular pigment optical density in adulthood.**" Lawler hypothesizes that breastfeeding in the first six months may increase macular pigment level in adulthood, and will explore whether this early life exposure to the carotenoids lutein and zeaxanthin (L/Z) reduces the risk for age-related eye disease later in life. If confirmed, such findings would support the development of recommendations concerning breastfeeding and the consumption of L/Z by lactating mothers.

**Dwani Patel**, an MD/PhD graduate student in Professor Daniel Lipinski's lab in the Department of Cell Biology, Neurobiology and Anatomy at the Medical College of Wisconsin, will advance understanding of diabetic retinopathy by "**Utilizing laser speckle contrast imaging (LSCI) to detect pre-clinical markers of retinal vascular dysfunction in diabetic rat models.**" This non-invasive imaging technique can measure the real-time functional dynamics of blood flow in two cell types crucial for maintaining retinal microvascular homeostasis – endothelial cells and retinal pericytes – thus providing an early glimpse at the effects of cell stress on retinal blood vessels. Patel's study would also be the first to enable quantification of the in vivo efficacy of gene therapy in rodent models of early diabetic retinopathy.

## Spring 2018 McPherson ERI/ David G. Walsh Research Travel Award Recipients



**McPherson ERI/David G. Walsh Research Travel Awards** provide funds for McPherson ERI-related graduate students and postdocs to attend conferences to present vision-related work, an important step in their educational and professional development. Twenty-two trainees have received these research travel awards since 2011. Both Spring 2018 award recipients attended the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting in Honolulu in May. **Pawan Kumar Shahi**, a postdoctoral researcher mentored by Bikash Pattnaik (Pediatrics), presented a poster titled "Rescue of Kir7.1 function by gene augmentation in LCA16 patient derived iPSC-RPE cells." **Divya Sinha**, a postdoctoral researcher mentored by David Gamm (Waisman Center & Ophthalmology and Visual Sciences), gave an invited talk in the mini-symposium *Targeting Mitochondrial Dysfunction in Retinal Disease* – sharing her stem cell work on "Mitochondrial integrity and function in hPSC-derived RPE." Drs. Shahi and Sinha will speak at an upcoming McPherson ERI seminar.

TUESDAY, OCTOBER 16, 2018

# 10th Annual Vision Science Poster Session

## 3:00pm – 5:30pm Poster Session

Atrium, Health Sciences Learning Center (HSLC)  
750 Highland Ave, UW-Madison  
Registration opens late August

## 5:45pm Distinguished Guest Lecture

HSLC Room 1325

***OMG, I did not see that!***

***The science of missing what is right in front of your eyes***

### Jeremy M Wolfe, PhD

- Professor of Ophthalmology & Radiology | Harvard Medical School
- Visual Attention Lab | Department of Surgery | Brigham & Women's Hospital



MANDELBAUM & ALBERT FAMILY VISION GALLERY

## CURRENT EXHIBITION



Please support the McPherson ERI anytime at [vision.wisc.edu/giving](http://vision.wisc.edu/giving).  
We greatly appreciate your help in advancing vision research!