McPherson Eye Research Institute
UNIVERSITY OF WISCONSIN–MADISON

InSights

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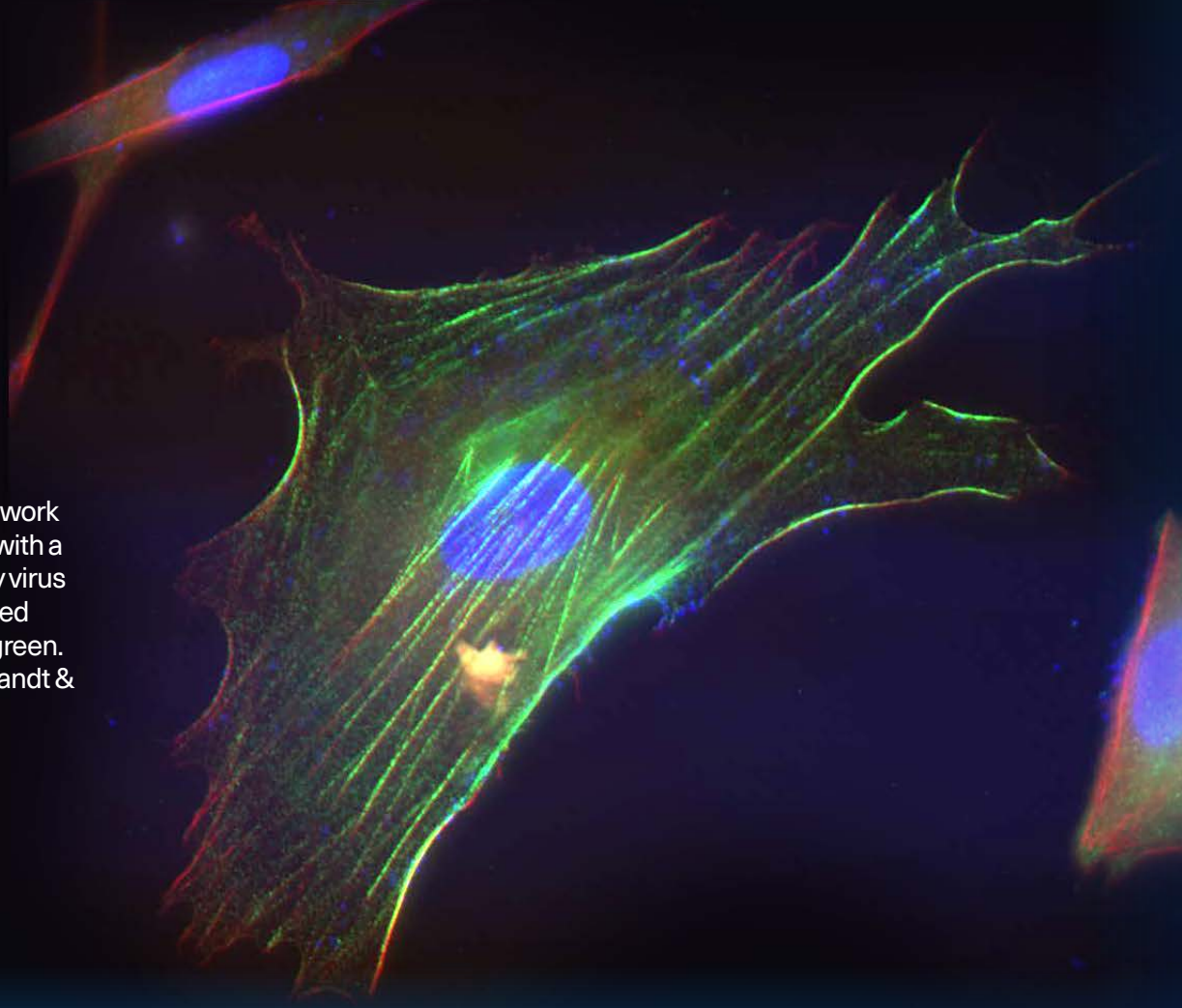
Viruses That Work for Us

WITH CURTIS BRANDT, PHD

With FDA approval of a gene therapy (Luxturna™) for one rare type of retinitis pigmentosa, we have entered into a new era of treatments for ocular diseases. Multiple clinical gene therapy trials are underway, some within UW-Madison's Clinical Eye Research Unit in the Department of Ophthalmology and Visual Sciences. However, there are issues regarding side effects and therapeutic effectiveness of ocular gene delivery that still need to be addressed. Curtis Brandt's laboratory tackles a variety of these issues.

Most gene therapy efforts rely on the use of viruses, which are nature's original gene delivery systems. Although these delivery viruses are genetically disabled and don't cause disease, they still contain viral components. Every cell in our bodies has developed multiple mechanisms to block virus infections or trigger inflammatory processes (called "uveitis" in the eye) that shut the virus down, which in the case of gene therapies can reduce the treatment effect. The Brandt laboratory has been looking at these inflammatory processes and has found that different types of delivery viruses (called vectors) trigger pro-inflammatory processes in different ways. The lab works on the induction of uveitis with the goal of finding a way to blunt these responses.

Another impediment for ocular gene delivery is that the viral vector must be delivered in tiny volumes of fluid at very high concentrations. Why do we need such concentrated virus? In addition to pro-inflammatory systems that detect virus components, every cell in the body makes resistance factors. These intrinsic factors act directly on the viral gene therapy particles to eliminate them and their beneficial effects.



Human trabecular meshwork (HTM) cells transduced with a feline immunodeficiency virus (FIV) vector. The expressed viral protein is shown in green. Image courtesy of the Brandt & Kaufman labs.

One large and diverse group of resistance factors are known as TRIM proteins. Some TRIM proteins are expressed in the cell when viral particles are first detected, whereupon they direct the particles to proteasomes. The proteasomes digest and eliminate the viral particles, minimizing the gene therapy's effectiveness. In collaboration with Dr. Paul Kaufman's group, which is developing gene therapies for glaucoma, the Brandt lab recently reported that treatment with a proteasome inhibitor significantly increased the efficiency of gene delivery in cells that help regulate pressure in the front part of the eye.

The next step was to determine whether reducing the activity of certain TRIM proteins could also improve efficiency of gene delivery to retinal cells in the back of the eye. Indeed, the Brandt lab found that suppressing production of these proteins using a gene editing approach enhanced viral-mediated gene delivery in at least one type of retinal cell, paving the way for future studies aimed at optimizing retinal gene therapies.

Biology is never that simple, however. The Brandt lab's studies also found that TRIM proteins are important for cell survival, so they need to be knocked down—but not completely out. They are currently investigating how to achieve this critical balance in their overarching quest to improve the safety and efficacy of viral gene delivery vectors in the treatment of a wide range of ocular diseases.

Dear Friends of the McPherson ERI,

Scientists invest heavily in the cultivation of future generations of talent, perhaps because we know that a research career, while incredibly rewarding, harbors many challenges that will test the resolve of even the most confident among us. Young scientists must be supported and mentored in the early stages of their careers if discovery is to continue. In this edition of InSights, we're proud to feature four outstanding trainee researchers alongside one of the McPherson ERI's most experienced scientists and mentors, Dr. Curtis Brandt.

Dr. Brandt is an exemplar of the groundbreaking work taking place at UW-Madison. His lab utilizes viruses as delivery vehicles for beneficial gene therapies, which has immense potential for treating many vision disorders. But recent events show why we need careful, persistent, and insightful scientists like Dr. Brandt ensuring that these therapeutic viruses are both effective and safe.

All established McPherson ERI principal investigators need talented trainee researchers (for example, graduate students and post-doctoral scientists) if our laboratories are to make progress. The young scientists featured herein are a small but impactful sample of the approximately 35 trainee members in the McPherson ERI who are already making their mark in different areas of vision research. We are grateful to them, and to you for your support of the Institute.

Enjoy, and I wish you well.

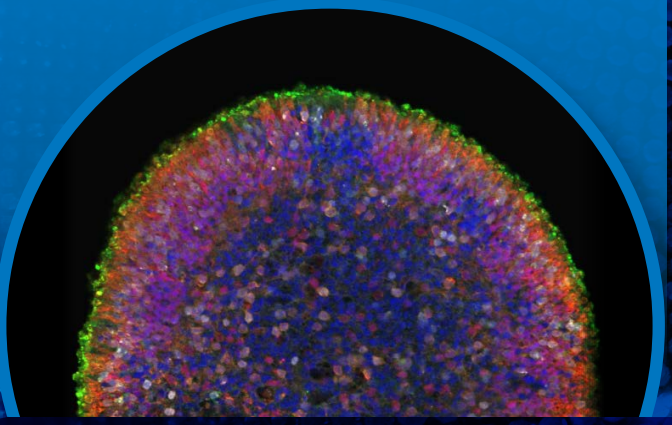
David M. Gamm, MD, PhD
RRF Emmett A. Humble Distinguished Director
Sandra Lemke Trout Chair in Eye Research

VISION RESEARCH, THE NEXT GENERATION

The McPherson Eye Research Institute has an abundance of Principle Investigators (PIs) who lead their namesake labs.

These labs would be considerably less effective without the essential work performed by trainee researchers—graduate students, postdocs, and undergraduate researchers who perform the experimental work and often pursue promising new leads. In doing so, they learn the methods and skills that allow them to one day establish their own laboratories. Here are four outstanding recent trainee members.

A stem cell-derived human retinal organoid, with photoreceptors labeled in red and green. Image courtesy of the Gamm Lab.



Ben Sajdak

PHD

Ben Sajdak learned, in training with MERI researcher Dana Merriman at UW–Oshkosh, that certain animal traits point to new pathways for treating human disease. For example, cone photoreceptors in ground squirrels become inactive and lose their normal structure and function during hibernation, but completely return to normal within hours after the squirrels come out of hibernation. As the new Director of Emerging Animal Models at the biotech startup Fauna Bio, Sajdak will investigate how evolved disease resistance in animals like the hibernating ground squirrel can be applied to treat human disease.

In graduate school, under the guidance of MERI members Joseph Carroll and Alfredo Dubra, Sajdak worked on adaptive optics (AO), which can be applied to study the cells of the retina in living patients and animals. These interests merged in his dissertation work. As a recent 3-year Morgridge Postdoctoral Fellow, Sajdak helped launch the Wisconsin Advanced Imaging of Visual Systems (WAIVS) initiative, bringing AO imaging to UW–Madison and boosting researchers' ability to study retinal disease progression and treatment strategies in patients.

Allison Ludwig

Allison Ludwig is a dual DVM/PhD candidate who recently completed her dissertation research in the laboratory of MERI Director David Gamm. In collaboration with the laboratories of McPherson ERI members Sarah Gong and Jack Ma, her thesis research focused on developing retinal patches to treat diseases like macular degeneration. These retinal patches contain and organize stem cell-derived photoreceptors intended to replace the damaged cells.

Together with McPherson ERI member Xinyu Zhao and trainee member Steven Mayerl, Ludwig has also recently developed a method for studying new connections among stem cell-derived retinal neurons in a dish. As she works to complete her veterinary degree at UW–Madison's School of Veterinary Medicine, Ludwig plans to continue to find new ways to accelerate development of safe and effective cell therapies for retinal degenerative diseases.

Melissa Schoenlein

Melissa Schoenlein is a PhD student in the Department of Psychology and the Wisconsin Institute for Discovery (WID) at UW–Madison. She investigates how people learn and reason with regard to colors; in particular, how people form associations between colors and concepts through experiences in the world, and what environmental and cognitive factors influence this process. Schoenlein also studies how these color-concept associations interact with other kinds of biases to influence people's interpretations of information visualizations.

As a member of the Virtual Environments group in the WID, Melissa is involved in the UW Virtual Brain Project, which creates 3D narrated lessons about perceptual systems of the human brain. She helps design the lessons, tests their effectiveness in the lab and in the classroom, and assists with demonstrations at community events, such as the Wisconsin Science Festival and Saturday Science. Schoenlein is eager to continue pursuing research, engaging with the community, and instilling excitement for science through teaching.

Aindrila Saha

Aindrila Saha is a third-year graduate student in the Cellular and Molecular Biology program at UW–Madison, working in Raunak Sinha's neuroscience lab. Her work builds on the fact that the vertebrate retina provides an excellent model system to study synaptic transmission and neural processing. Saha's PhD thesis research focuses on the mechanism of photoreceptor signaling at the connection between photoreceptor and bipolar cells, which is crucial to understanding sight.

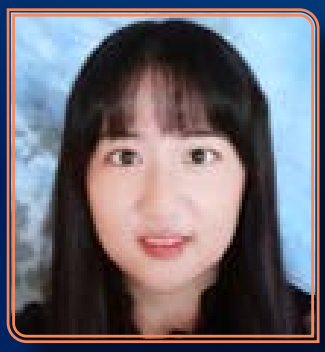
Saha also works with the Gamm lab to characterize photoreceptor function in human stem cell-derived -3D retinal organoids. Her distinguished training thus far has included her master's degree work in India at NISER, Bhubaneswar, where she studied how altered exposures to light and dark conditions affect the physiology, behavior, and gut microbiota in mice. While an undergraduate, Saha was a Khorana scholar in Baron Chanda's neuroscience lab at UW–Madison as well as an Undergraduate Scholar at the Janelia Research Campus in David Clapham's laboratory. She plans to continue her work on understanding the cellular and circuit mechanisms that govern visual functions.

McPHERSON ERI

NOTE

Kenzi Valentyn Vision Research Grants, Fall 2021

Four trainees were awarded Kenzi Valentyn Vision Research Grants this fall for a variety of vision studies—from the prevention of viral ocular disease (Ziyun Ye, Ophthalmology and Visual Sciences) to the cause of onset blindness in dogs (Jennifer Heyward, Comparative Biomedical Sciences); and from the effects of the neurotransmitter GABA in retinal neurons (Jenny Nagy, Cellular & Molecular Pathology) to understanding inferred mappings for colormap data visualizations (Clementine Zimnicki, Psychology). The Institute is glad to support trainees in all areas with the Kenzi Valentyn and other research awards.




L–R: Ziyun Ye, Jennifer Heyward, Jenny Nagy, Clementine Zimnicki.

Walking for Family

Eight-year-old Audrey Olsen was determined to do something to support her uncles, both of whom have Usher Syndrome Type 2C, a condition that leads to loss of vision and hearing. Audrey looped in her brother Charlie, her parents, Molly Walsh and Jeff Olsen, and her grandparents, David and Nancy Walsh—and the result was their first annual Walk for Sight, held on July 24th in their own neighborhood. 130 neighbors and other friends turned out for the walk, which raised approximately $22,000 for vision research (including therapies for Usher Syndrome and other retinal degenerative diseases in development at the McPherson ERI). One loop of the walk was done with participants wearing opaque visors (accompanied by a guide), to experience the outdoors without sight. We're very grateful for the time and initiative put in by Audrey and her entire family!

You can support the McPherson ERI at vision.wisc.edu/giving. **Thank you!**