McPherson Eye Research Institute
UNIVERSITY OF WISCONSIN–MADISON

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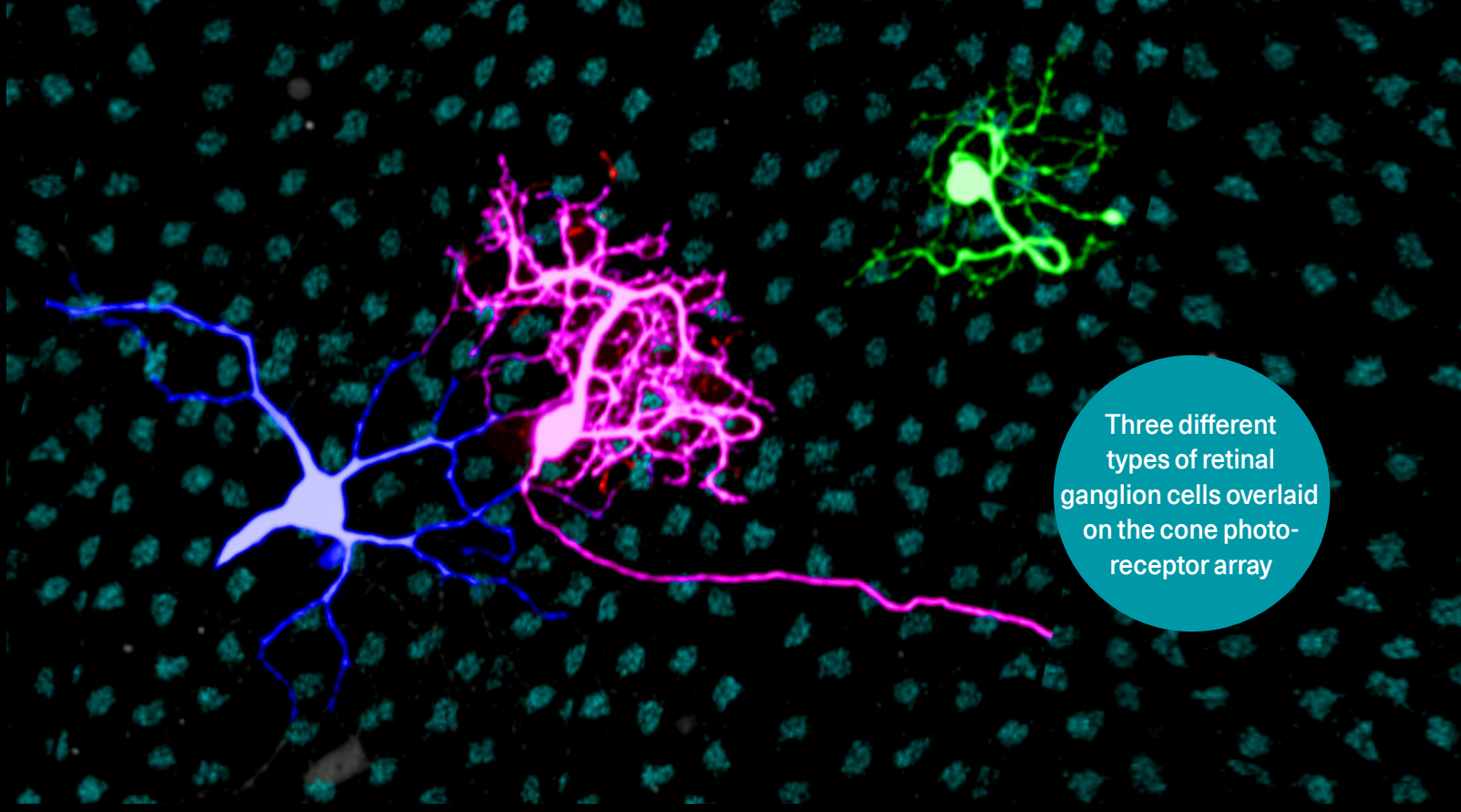
DECONSTRUCTING THE HUMAN FOVEA:

Neurons to High-Definition Vision

WITH PROFESSOR RAUNAK SINHA, PHD

Our everyday visual experience - including your ability to read this text - is dominated by signaling in the fovea. The fovea is a specialized region in the retina that is (almost) unique to primates and is responsible for a detailed visual experience that exceeds the resolution of most other organisms. Most of what we humans see gets to our brain via the fovea, which accounts for approximately half of the retinal output (and hence input to the higher brain centers), while occupying less than 1% of the total retinal surface area. Because our high-definition central vision is critical for interacting with the world around us, retinal diseases that attack the fovea, such as macular degeneration, make it almost impossible to carry out everyday tasks such as reading, writing and driving. Despite its importance, we know very little about how the fovea operates at a cellular level. Understanding how visual signals are processed in the primate fovea is a major area of research in Dr. Raunak Sinha's lab.

In the fovea the first neurons in the visual system called cone photoreceptors form an exquisite 'high definition' pixel array where photons from incident light are converted to electrical signals. This specialized neuronal organization in the fovea together with the downstream neural circuitry is responsible for the high spatial and chromatic resolution of our central vision. A deeper understanding of how the fovea encodes this visual information is a vital step towards devising therapies or engineering prosthetics that can better mimic the fovea. This is challenging, as we currently lack a basic understanding of neural signaling that occurs in the fovea, even in healthy conditions.



Three different types of retinal ganglion cells overlaid on the cone photo-receptor array

Recently, Dr. Sinha overcame the technical limitations associated with electrical recordings in the fovea and provided the first glimpse into how the fragile and inaccessible neurons in the fovea operate at a cellular and synaptic level (Sinha et al., ***Cell*** 2017). Surprisingly, visual signaling in the fovea is specialized and distinct from other regions in the retina starting at the very first neurons of the visual system – the photoreceptors. The Sinha lab is developing new techniques and strategies to perform the first comprehensive evaluation of the neural cell types, their molecular specificity, physiology and connectivity that give rise to diverse foveal visual pathways. Using a combination of functional, anatomical and genetic tools, the Sinha lab will address fundamental aspects of visual processing in the fovea, including phototransduction - the conversion of light to an electrical signal which enables vision. Is this unique in the fovea and if so what is the underlying mechanism? The Sinha lab will also study the diversity of visual pathways in the fovea, and build a wiring map of how foveal neurons are connected.

Vision impairment in macular degeneration is due to the loss of foveal cone photoreceptors. A major effort in the field of human stem cell therapies has been to devise effective photoreceptor replacements for patients with macular degeneration. The Sinha lab is collaborating with Dr. David Gamm's lab to test if the physiology and function of human stem cell-derived retinal neurons, especially cone photoreceptors, are similar to those *in vivo*. This will be an important step to improve stem cell replacement-based therapeutic strategies for treatment of macular degeneration and related forms of blindness. Dr. Sinha is also involved in a collaborative effort with other McPherson ERI members and UW Madison researchers to bring a novel electron microscopy technique to the UW campus for 3-dimensional reconstruction of cellular networks such as the fovea. In the future a deeper understanding of visual processing in the fovea, all the way from genes to neurons to perception, will provide the much needed computational and mechanistic framework for devising therapies for diseases that affect the fovea and our high-definition vision.

Dear Friends of the McPherson Eye Research Institute,

The McPherson Eye Research Institute started with an established core of vision scientists dedicated to collaborative research. It was also understood from the beginning that welcoming new people and new ideas would be vital to the Institute's growth and effectiveness. This issue features a McPherson ERI scientist who is new to UW-Madison, as well as others who are near the beginning of their promising careers in vision research. Each of their unique backgrounds and aspirations expand and deepen our collective capacity to preserve and restore sight. The Institute also incorporates world-renowned researchers already on campus who seek to apply their knowledge and techniques to the cause of protecting sight.

On the cover, you'll read about the work of Raunak Sinha, PhD, who recently joined the Department of Neuroscience and the McPherson ERI at UW-Madison. Dr. Sinha's focus is on the fovea – the tiny area in the center of our retina that provides our most important vision. His work complements research taking place in other member laboratories on age-related macular degeneration, retinitis pigmentosa, diabetic retinopathy, and many other blinding conditions. UW-Madison and the McPherson ERI also recently welcomed Mrinalini Hoon, who joined the Department of Ophthalmology and Visual Sciences to further her groundbreaking investigations into retinal circuitry, which promises to aid our efforts to "re-wire" the retina to treat disease.

Also highlighted in this issue are images from vision science trainees who presented their research at our 10th annual poster session. The Institute is committed to growing the interest and talent needed to further the battle against blindness, and the work of these promising young scientists is inspiring.

We are fortunate in Wisconsin to have the people, environment, and attitude needed to tackle the most challenging issues that threaten vision health. The McPherson ERI puts these powerful pieces together by building, training, and equipping teams to address these challenges head on.

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

Ender Tekin receives research award from Research to Prevent Blindness

Ender Tekin, PhD, Associate Scientist and leader of the AVIATR lab at the Waisman Center and McPherson ERI member, has received a 2018 Low Vision Research Award from Research to Prevent Blindness. The award will fund a new project aimed at improving classroom accessibility for students with low vision. These students, as well as vision-impaired working professionals, suffer from lack of an easily portable and affordable solution to access lecture notes and slides. The Tekin group's proposed solution is a portable device called a ZoomBoard, which uses a camera to capture and broadcast a video stream of the target to be observed (such as lecture slides) to the viewer's mobile devices via easily installed apps. ZoomBoard will offer multiple advantages over existing devices, and will be extensively evaluated in classroom settings.

NEI Audacious Goals Grants awarded to teams featuring Drs. David Gamm, Joseph Carroll

In October, the National Eye Institute announced that two out of five new National Eye Institute Audacious Goals Initiative grants were awarded to teams involving McPherson Eye Research Institute investigators. The funds, awarded "to accelerate the development of regenerative treatments for blindness" in diseases including retinitis pigmentosa and age-related macular degeneration, were given to teams that include Dr. David Gamm at UW-Madison, and Dr. Joseph Carroll at Medical College of Wisconsin in Milwaukee. (Carroll's team includes McPherson ERI investigators Dana Merriman, PhD, UW-Oshkosh, and Daniel Lipinski, MSC, DPhil, Medical College of Wisconsin).

David Gamm's project, in collaboration with Drs. John H. Wolfe and William A. Beltran of the University of Pennsylvania, is entitle "Retinal Disease Models for Translational Photoreceptor Replacement." The study will develop models for surgically implanting replacement adult stem-cell derived photoreceptor cells into living subjects, beginning with blind dogs at the University of Pennsylvania School of Veterinary Medicine. Using technologies developed in the Gamm Lab at UW-Madison, specialized retinal cells will be generated in a dish using cells from adult canines with vision loss. These photoreceptor cells will ultimately be transplanted back into the canine subject's retinas, and in the process, will test effective ways of moving the technology towards human clinical trials.

Dr. Joseph Carroll and his team (which includes Dr. Jacque Duncan, UCSF, as well as his McPherson ERI colleagues) are working to advance translational research into diseases that affect cone photoreceptors, which are responsible for color vision. The goal of their project, entitled "Developing Cone-Dominant Retinal Disease Models as a Resource for Translational Vision Research," is to develop animal models of cone disease, using two mammals with high cone density: the 13-lined ground squirrel and the tree shrew. (Dr. Merriman is known internationally as a leading expert in the 13-lined ground squirrel). In addition to generating these disease models, the Carroll team will evaluate potential stem-cell based treatments, and develop imaging and functional tests to assess cone structure and function.

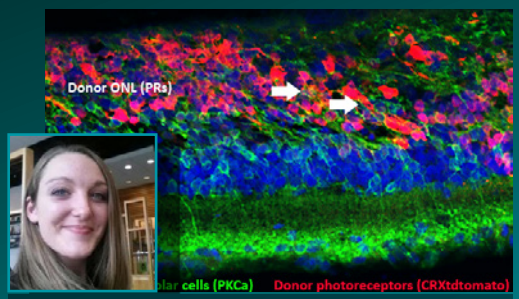
En-Visioning Research

The McPherson Eye Research Institute recently hosted its 10th annual Vision Science Poster Session, where researchers from across the Institute highlight recent findings in their laboratories and research groups.

Posters are a useful and focused way of summarizing a particular experiment or stage in the researcher's work, as well as conveying results to a broader audience. They are most often written and compiled by a graduate student or postdoc in a laboratory, usually summarizing results from multiple researchers. On this page are images from three posters presented this fall which illustrate the value of poster presentations.

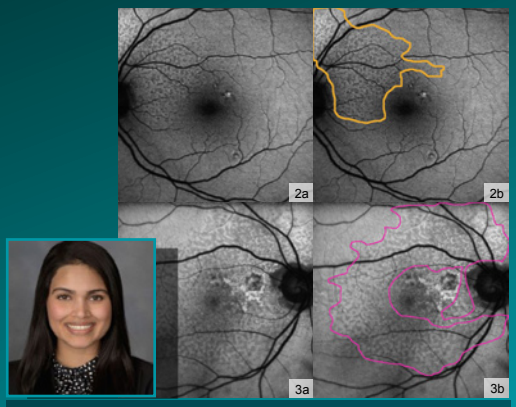
At the poster session, close to 100 McPherson ERI members and colleagues interacted with poster presenters, and a panel of judges chose three as the winner and runners-up for "Best Poster Presentation" awards. Allison Ludwig received the Best Student Presentation Award for her poster, "Comprehensive *in vivo* assessment of human pluripotent stem cell-derived photoreceptor survival & differentiation potential in the S334ter rat model of retinal degeneration" (co-authored with Joe Phillips, PhD, and others in the Gamm Lab). Abhilash Sawant (Raunak Sinha/Mrinalini Hoon labs) and Kazuya Oikawa (Gillian McLellan's lab) won second and third place.

The Institute's David G. Walsh Research Travel Awards, given twice yearly, are an additional opportunity for grad students and postdocs to present posters or papers to fellow researchers – in that case, at conferences in their fields – an important step in disseminating results nationally and internationally.



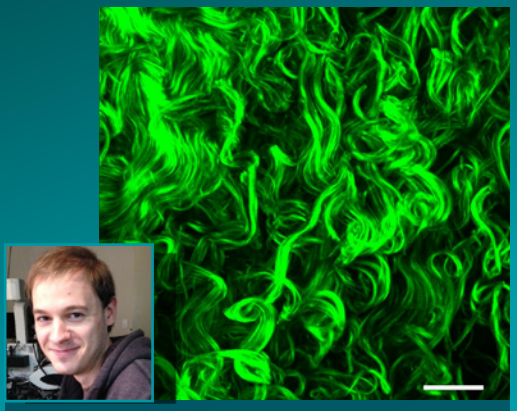
Engrafted donor hPSC-CRX+/tdTomato PRs replacing the host outer nuclear layer at 6 months post-transplant. PKCα+ host bipolar cells extend dendrites into the transplanted PR tissue (arrows).

Posters are most commonly used to highlight discrete research advances, and include supporting images and data. This image, on a poster from DVM/PhD student Allison Ludwig in Dr. David Gamm's lab, highlights human stem cell-derived photoreceptors replacing the photoreceptor layer of the retina six months after transplantation in a rat model of severe photoreceptor loss. The transplanted cells express a red fluorescent marker protein when they begin to differentiate into photoreceptors, making them easier to identify after transplantation. This work is an important step toward developing photoreceptor replacement therapies for patients affected by diseases like retinitis pigmentosa in which photoreceptors are lost over time.



2a. AF image of fundus with a typical example of reticular pseudodrusen. **2b.** RPD area outlined and measured using the lasso tool and measurement analyses in Photoshop CCS 2018 19.1. **3a.** AF image of fundus with reticular pseudodrusen and other pathologic features. **3b.** RPD area outlined and measured (as above), excluding fovea, GA and abnormal AF.

Posters help to clarify and compare research findings in a visually appealing and more readily understood way, as in this poster section by Meghana Agni, MD, Department of Ophthalmology & Visual Sciences. Reticular pseudodrusen (RPD) is a feature seen in age-related macular degeneration. Recent advances in imaging have improved our understanding of RPD. Here we see autofluorescence images of the fundus on the left, with the areas comprising RPD outlined on the right. Dr. Agni and her collaborators aim to describe the characteristics of reticular pseudodrusen by studying fundus autofluorescence images of patients with RPD, taken annually over multiple years.



Scleral Collagen. Changes to collagen architecture can be directly visualized with Second Harmonic Generation microscopy. Changes to collagen architecture in the sclera will manifest in the optical scattering. Scale bar: 50 µm.

Often, a poster points the way towards "future work" in a lab, as in this image from graduate student Ryan Niemeier's poster (Dr. Jeremy Rogers' Biomedical Engineering lab). The entire poster notes how the Rogers Lab uses light scattering in a novel way, as a metric to inform biological processes. (Typically, scattering is minimized in imaging systems to preserve image quality). In the final segment, the goal of better investigating fine structures in the eye is noted – which will be particularly useful for predicting and evaluating the progression of glaucoma, one of the Rogers lab's main research foci.

As 2018 comes to a close, please consider helping the McPherson Eye Research Institute with a gift to support vision research at UW-Madison.

Donate at **vision.wisc.edu/giving**, or contact Michael Chaim, chaim@wisc.edu, 608-265-0690.

Thank you!

And save the date for

Cycle for Sight 2019!

March 9th, 2019

vision.wisc.edu/cycle

SAVE THE DATE

9TH

MAR 2019

Current Exhibition

Mandelbaum & Albert Family Vision Gallery

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