McPherson
Eye Research Institute
UNIVERSITY OF WISCONSIN–MADISON

InSights

Published each semester

SPRING *2019*

Imaging Living Cone Photoreceptors

WITH JOSEPH CARROLL, PHD

L-R, Advanced Ocular Imaging Program researchers Jenna Cava, MS, Ben Sajdak, PhD, Hannah Follett, Alex Salmon.

Most of our visual functions – including color vision, high spatial acuity, and nearly all daytime visual tasks – stem from the fovea, the cone-packed pit in the retina's central portion, the macula. Diseases affecting cone photoreceptor structure and function are thus especially devastating. While several innovative therapeutic strategies for restoring cone function are being pursued, their continued development relies on the accessibility of animal models that mimic human retinal anatomy as well as recapitulate the pathophysiology of specific cone disorders. **Joseph Carroll, PhD**, a McPherson ERI member at the Medical College of Wisconsin (MCW) in Milwaukee, is leading an NEI U24 grant with Dr. Jacque Duncan (UCSF), collaborating with McPherson ERI colleagues Dr. Dana Merriman (UW-Oshkosh) and Dr. Daniel Lipinski (MCW) to develop models and treatments of cone disorders in the 13-lined ground squirrel and tree shrew – animals with particularly strong potential to become accessible models for vision research.

Traditional rodent models like mice and rats are poor models for human cone-mediated vision, as their vision has evolved for night-time activity, and they have a uniformly sparse cone

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distribution. 13-lined ground squirrels and northern tree shrews, however, are small, cone-dominant mammals that possess unique "models of nature" with which to study cone structure and function in vivo. The 13-lined ground squirrel goes through annual hibernation, which causes several unusual changes in its cones: the cells' outer segments lose their organized structure, and the cells also remodel their mitochondria, the small "energy factories" within. Both changes are readily reversible when the squirrels come out of hibernation. Having access to this naturally-reversible model of cone degeneration allows researchers to test structural and functional assays in a single animal without inducing any damage. The northern tree shrew's photoreceptor cells (within the cone-dense retina) have massive, more easily studied mitochondria in their inner segments.

To help realize this potential, Dr. Carroll's Advanced Ocular Imaging Program utilizes noninvasive high-resolution retinal imaging tools to study cone structure and function and develop models of cone disorders in these species. The ability to examine the same living retinal structures over time with advancements in optical coherence tomography (OCT) and adaptive optics scanning light ophthalmoscopy (AOSLO) has revolutionized how the retina is studied and is shaping the future of how retinal disease is detected, monitored, and treated. However, many questions remain about the subcellular origin of signals visualized with OCT and AOSLO in health and cone disorders. Dr. Carroll and his colleagues are able to learn more about subcellular (interior) signals of cones by assessing cellular structure of these two species in vivo with OCT and AOSLO; they can subsequently examine cone structure in finer detail with ex vivo microscopy techniques like electron microscopy.

There are immediate benefits to us humans from these studies, too. Animal models offer insights that further our knowledge of what can and is being visualized with OCT and AOSLO. In developing animal models that emulate human disease, Dr. Carroll and his colleagues hope to interpret the subcellular signals of cones across species, which in turn will have exciting potential for the future of disease detection and clinical care.

From the Director

Spring 2019

Welcome to our Spring 2019 *Insights*. In this issue, we highlight two initiatives that advance important new technologies capable of enhancing our knowledge of vision-related diseases and assessing the effectiveness of existing and future treatments. The Wisconsin Advanced Imaging of Visual Systems (WAIVS) project, introduced on this page, seeks to engineer devices that provide exquisitely detailed pictures of the living human retina, with resolution down to individual cells (or even inside cells). This technology will be established and – most importantly – improved upon with the help of our multi-disciplinary team of researchers from the Departments of Biomedical Engineering and Ophthalmology and Visual Sciences, as well as other schools and departments at UW-Madison and beyond. Our collective goal is to accelerate the field of eye imaging and, ultimately, improve patient care. Dr. Joseph Carroll's project, highlighted on the cover, is using advanced imaging technology right now to study cone photoreceptors (responsible for daylight vision) and to assess potential therapeutics for diseases that target these critical light- and color-sensing cells. Together, these two projects highlight our commitment to innovation and our efforts to build a comprehensive "toolkit" needed to detect and beat diseases that threaten our vision.

We're grateful for your interest and help in reaching this goal!

David M. Gamm, MD, PhD

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

Making WAIVS

at UW-Madison

One of the most exciting new projects in vision research at UW-Madison is a groundbreaking group collaboration among the McPherson Eye Research Institute, the Department of Ophthalmology & Visual Sciences, and other UW and national partners. The Wisconsin Advanced Imaging of Visual Systems (WAIVS) Lab, founded in 2018, promises to establish and advance exciting new eye imaging techniques at UW-Madison.

Page through any science magazine, and you'll be amazed at the image quality that is attainable by today's equipment – whether of distant galaxies or within the human body. Imaging techniques developed in recent decades and used to image the eye and retina, such as Optical Coherence Tomography (OCT), have advanced both patient care and basic research immensely. It is a paradox, though, that the more we see, the more we realize how much more there is to see. For instance, we now have the ability to view images of living photoreceptor cells with better clarity than ever before; however, we are only at the starting line when it comes to peering within those cells and understanding the functional relationships of the various cell components. Understanding those relationships is vital to fighting disease and devising better therapies.

The WAIVS project brings together a group of outstanding engineers, basic science researchers, and clinicians who are building an imaging lab featuring an Adaptive Optics (AO) platform. Adaptive Optics is a recently-developed method of eliminating aberrations in images by using dynamic mirrors that correct distortion. The same technology has been used widely in astronomy for improving images from telescopes. WAIVS will have two Adaptive Optics Scanning Laser Ophthalmoscopes (AOSLO) machines housed in dedicated McPherson ERI space in the Wisconsin Institutes for Medical Research (WIMR). One machine will be used for patient research, allowing researchers and clinicians to understand retinal dysfunction on a cellular level in living patients, and also to monitor cellular responses to treatments such as stem cell and gene therapies. In a separate, but nearby space, the other AOSLO machine will be used for building and testing innovative new features for the existing technology that will allow us to "see further". Having the two machines in close proximity will allow for rapid application of imaging breakthroughs.

To better understand **WAIVS**, we'd like you to meet some of its team members:

Dr. Jeremy Rogers (Biomedical Engineering) is the principal UW-Madison investigator responsible for the fabrication and innovation of the AOSLO machines, which are being housed within his lab space in WIMR. He will also oversee advancements in parallel technologies that need to grow with improvements in AOSLO capabilities. With experience in multiple advanced imaging techniques, Dr. Rogers aims to advance AOSLO and other eye and retinal imaging systems to make them as effective as possible.

Alfredo Dubra, PhD (Stanford University, Ophthalmology, ***photo, left***) and **Joe Carroll, PhD** (Medical College of Wisconsin, Ophthalmology, ***photo on cover***) have been at the forefront of building and applying AOSLO technology from its inception, and will collaborate closely in its installation and use at UW-Madison. These AOSLO systems are extraordinarily delicate, and will be constructed on vibration isolation optical tables using a combination of custom-made and off-the-shelf equipment. Drs. Dubra and Carroll will train the UW-Madison team and serve integral roles on the WAIVS team.

Dr. Kim Stepien (Director of the Adult Inherited Retinal Degeneration Clinic, Ophthalmology & Visual Sciences) will direct the use of AOSLO equipment in investigating human ocular diseases, including macular degeneration and inherited retinal conditions such as retinitis pigmentosa. Of great importance is the development of techniques to monitor the effectiveness of new therapeutic approaches, such as gene and stem cell-based therapies, that will be developed and tested at UW-Madison in coming years.

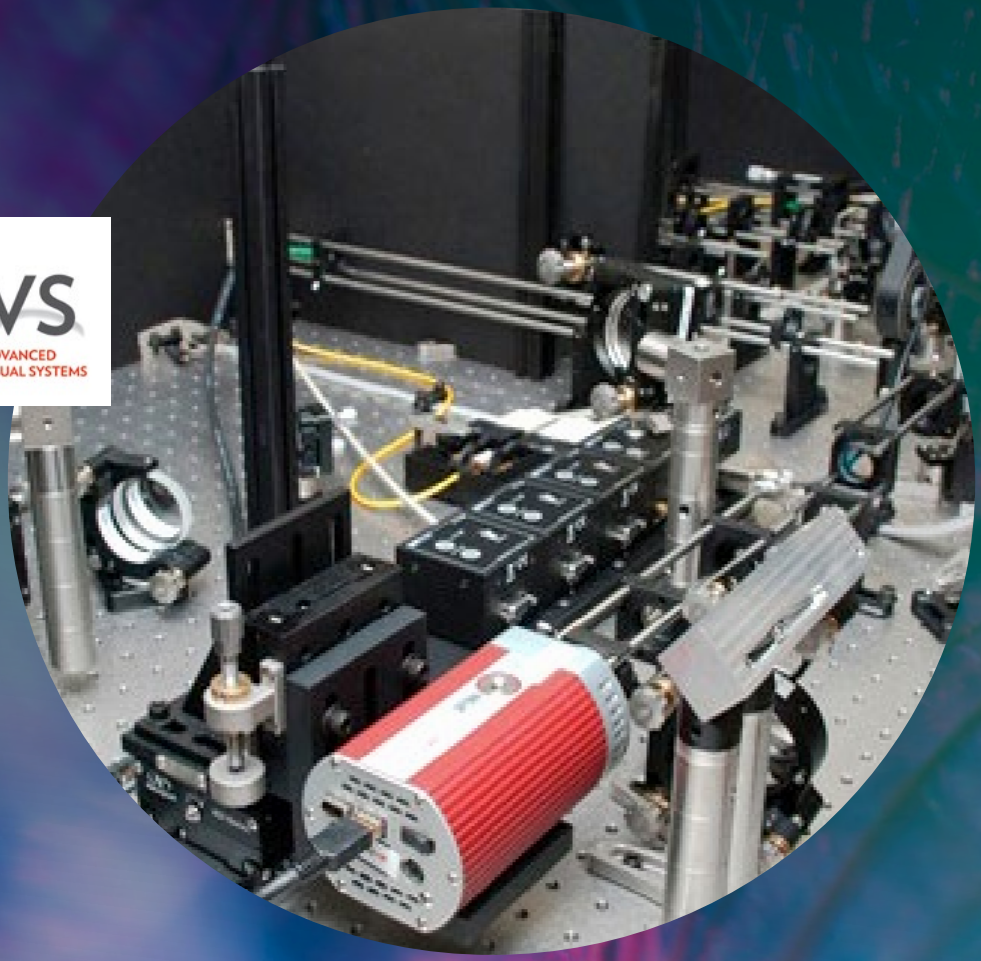
Dr. Barb Blodi (Medical Director, Fundus Photograph Reading Center) will oversee the interface between the WAIVS Lab and the Fundus Photograph Reading Center (FPRC), a unit of the Department of Ophthalmology & Visual Sciences that is world-renowned for its expertise in retinal imaging analysis. The FPRC will help develop standardized Adaptive Optics imaging and grading protocols for image analysis. This is necessary in order for data to be correlated across AO research projects and with other imaging methods.

Dr. David Gamm (Director, McPherson Eye Research Institute) will focus on the potential use(s) of AOSLO imaging in clinical trials for stem cell-based therapies to treat age-related macular degeneration and retinitis pigmentosa.

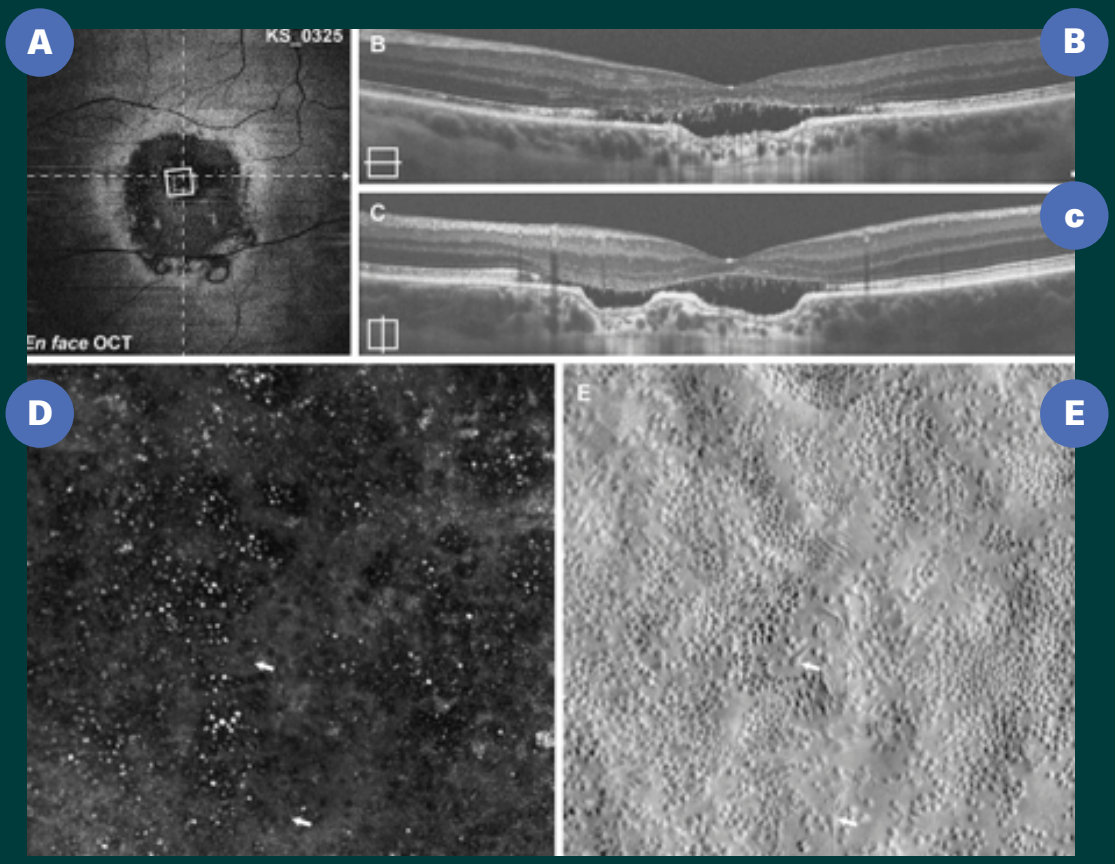


These researchers are a subset of those working to build the WAIVS lab; others include **Kevin Eliceiri, PhD** (Medical Physics; Morgridge Institute for Research; Associate Director, McPherson ERI), **Gillian McLellan, BVMS, PhD** (Ophthalmology & Visual Sciences) and **Melissa Skala, PhD** (Biomedical Engineering; Morgridge Institute for Research). It is truly a cross-campus team whose common goal is to bring state-of-the-art ophthalmic imaging to UW-Madison and combine it with our formidable know-how to make it even more informative and – ultimately – beneficial to patients.

WAIVS
WISCONSIN ADVANCED IMAGING of VISUAL SYSTEMS



What can we see with **Adaptive Optics?**



Optical coherence tomography (OCT), as shown in images **A-C**, has become an invaluable tool for clinical imaging of healthy or diseased retina. OCT provides 3D volumetric images that can then be inspected from different angles. At top, panels **B** and **C** are cross-sections corresponding to the dashed lines in panel **A**.

Despite the clear value of OCT imaging, resolution of OCT remains limited due to imperfections in the lens, cornea, and tear film of the subject. Adaptive Optics solves this limitation, providing "fine focus" with cellular resolution as shown in panel **D** that corresponds to the tiny square in panel **A**.

Even with this resolution, cells can be difficult to visualize using standard confocal contrast. State of the art AOSLO systems like the one being developed at UW-Madison include additional split-detector capabilities as shown in panel **E** to improve contrast and visualization of photoreceptors. In this image, it is possible to see the abnormal morphology of most of the visible photoreceptor cells.

Image adapted from “Photoreceptor Inner Segment Morphology in Best Vitelliform Macular Dystrophy,” Retina. 2017 Apr; 37(4): 741–748.

Cycle for Sight 2019 Raises Over **$50,000** for Vision Research

The McPherson ERI's annual Cycle for Sight fundraiser was held on March 9th, 2019, and drew well over 200 riders and walkers to three Madison sites. The indoor spinning ride raised more than $50,000 for vision research at the Institute. These funds will support a variety of programs, including the Kenzi Valentyn Vision Research Trainee Grants, awarded each year to exceptional grad students and postdocs working in McPherson ERI labs. The McPherson ERI would like to thank all those who have supported Cycle for Sight, now and in past years, including our major sponsors: the MGE Foundation, Opsis Therapeutics, and the Shopko Foundation. The date for Cycle for Sight 2020 will be announced in Fall 2019, and donations can still be made (and pictures viewed!) at **vision.wisc.edu/cycle.**

SAVE THE DATE!

Monday
May 6th
2019

7th Annual McPherson ERI Endowed Lecture

Charles Zuker, PhD

Columbia University

VENUE
DeLuca Forum, Wisconsin Institutes of Discovery

TIME
Reception: 3:00 PM
Lecture: 4:00 PM