



## RESEARCH NEWS

# DISCOVERING HOW THE RETINA AGES

WITH DR. AKIHIRO IKEDA, DVM, PHD

**Why do age-related diseases occur when people age?** This sounds like a simple question – when else should they occur? But it is a key question which applies to retinal diseases including age-related macular degeneration (AMD), which affects roughly 11 million people in the U.S. and usually leads to loss of central vision. Aging is the largest risk factor for AMD; studies indicate that people over age 60 are at greater risk than those in younger age groups. Dr. Akihiro Ikeda (DVM and PhD), a professor in Medical Genetics and the Associate Director of the McPherson Eye Research Institute, studies the onset and the underlying mechanism of AMD. The Ikeda lab's working hypothesis is that for age-dependent diseases to manifest themselves in an age-dependent manner, there must be tight association between the disease-causing mechanisms and cellular changes that occur with aging. Therefore, it is important to understand how the aging process is regulated at the molecular level, and how the aging process is associated with disease mechanisms.

**Dr. Ikeda and his lab associates** (Sakae Ikeda, DVM, Wei-hua Lee, PhD, Erica Macke, Sarah Lewis & Yuyun Zhu) study age-dependent retinal diseases using a forward genetics approach in mice. This approach is phenotype-driven, starting from observable characteristics in the animal. The advantage of this approach is that it offers the potential of identifying previously unknown genes and molecular pathways affecting age-dependent retinal phenotypes. Specifically, the laboratory aims to identify gene mutations that lead to early onset of aging phenotypes in the mouse retina, as well as to identify genes that cause the difference in the severity of age-dependent retinal abnormalities observed between different mouse inbred strains. Identification of these genes will allow Dr. Ikeda to elucidate the molecular mechanisms causing the age-dependent retinal abnormalities, and therefore, should enhance understanding of age-dependent retinal diseases and aging of the retina.

**Most recently, the Ikeda lab reported** (in *eLife*, one of the top journals in life science) the discovery of a protein that links aging and age-dependent diseases. The molecule, called transmembrane protein 135 (Tmem135), regulates retinal aging; a mutation in the gene encoding this protein results in age-dependent disease. To discover this novel protein and its role in age-dependent retinal diseases, Ikeda and his team studied a mouse model that exhibits retinal abnormalities similar to those seen in normal aged mice, but with earlier onset and faster progression. Interestingly, this accelerated retinal aging in mutant mice is also accompanied by symptoms similar to those observed in human AMD patients. Genetic mapping and positional cloning revealed that a mutation in Tmem135 is the cause behind these retinal symptoms, demonstrating that aging and age-dependent diseases are closely associated with each other at the molecular level.

**The team next discovered that the protein regulates** the size of the mitochondria, an energy-producing organelle that is essential for various metabolic functions of the cell. The regulation of mitochondrial size by TMEM135 determines the sensitivity of cells to environmental stress and the pace of aging in the retina. Functional loss of TMEM135 results in higher sensitivity to such stress, leading to accelerated aging as well as age-dependent pathologies. The Ikeda lab now aims to determine the exact biochemical and molecular functions of TMEM135 in mitochondria as well as molecular pathways affected by defective TMEM135 in the retina, and to examine its roles in the aging process of other tissues and various age-dependent diseases.

**Identification of new genes involved in retinal aging**, such as Tmem135, could potentially lead to development of novel therapeutic approaches including previously-unknown drug therapies. Dr. Ikeda believes that his group's unbiased genetic approach will identify multiple new entry points into the mechanisms controlling aging at the molecular level, providing more targets for therapeutic approaches against age-dependent retinal diseases. In addition to the Tmem135 project, the Ikeda lab is currently working on multiple studies to identify other genes associated with aging of the retina using mouse genetics; more genes equals more ideas for therapy. Their journey opens many exciting pathways forward.

*FROM THE DIRECTOR:*

# Dear Friends of the McPherson Eye Research Institute,

**As an Institute, we often stress the collaborative** nature of our work knowing that the whole is greater than the sum of its parts, especially when it comes to science and medicine. Our researchers generate extraordinary results when they pool their know-how and resources and build on each other's ideas. We never forget, though, that our team efforts are possible only because of the remarkable quality of the individual researchers.

**I am particularly pleased that the work of Aki Ikeda**, Professor of Medical Genetics and one of the Institute's outstanding scientists, is featured on the cover of this issue. Dr. Ikeda, who has served as Associate Director of the McPherson ERI for the past four years, is an insightful and creative "gene sleuth" whose research has led to a better understanding of how the retina ages and - by virtue of that knowledge - hope for keeping it young longer. For these



reasons, we are proud that he will be the first faculty member to hold the Timothy William Trout Professorship in Eye Research, established by Dr. Monroe and Sandra Trout in honor of their younger son, who passed away in May 2016. Dr. Ikeda has devoted much of his career to pursuing not only the causes of normal retinal aging, but also of retinal degenerative diseases such as age-related macular degeneration (AMD). These efforts are in keeping with the founding principles of the Timothy William Trout Professorship, and are critically needed as the number of people with AMD increases.

**AMD research is one of the core pursuits** of McPherson ERI investigators. In addition to the work of Dr. Ikeda, there are many other treatment avenues being explored, including the pharmacologic-based research of Dr. Aparna Lakkaraju (Associate Professor of Ophthalmology and Visual Sciences), which seeks to repurpose existing drugs to slow or reverse AMD. Exciting multi-researcher collaborations are also aimed at combatting AMD. Dr. Lakkaraju and Associate Professors of Biomedical Engineering Kristyn Masters and Pam Kreeger are working to build a tissue-engineered model of the retina in order to simulate AMD more effectively. Additionally, we have a large team of researchers developing stem cell therapies for AMD and other retinal disorders such as retinitis pigmentosa (for comments on retinal stem cell treatments and guarding against false claims please visit our website: [www.vision.wisc.edu](http://www.vision.wisc.edu)).

**One of the most exciting aspects of basic research** is the capacity for a single discovery to lead to advances in multiple areas of medical treatment. Undoubtedly, success in our AMD programs will lead to breakthroughs for other blinding disorders. For example, Dr. Nader Sheibani's research on abnormal blood vessel growth in the eye shows promise not only for wet AMD, but also for diabetic retinopathy – the leading cause of adult blindness in the U.S. Building on wide-reaching opportunities such as these, we strive to make the most of every opportunity to further our overarching goal of preserving and restoring vision for the hopeful patients we serve.

A handwritten signature in red ink that reads "David M. Gamm".

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

# VISION RESEARCH PROGRESSES IN MCPHERSON ERI LABS

**McPherson ERI member** researchers frequently mark the progress of their work with results reported in leading scientific and medical journals. With more than 60 member labs affiliated with the Institute, it is rare that a month goes by without a significant update.

## AMONG THE HIGHLIGHTS FROM THE PAST FEW MONTHS:



A large collaborative team of Institute researchers including **Leandro Teixeira**, **Dick Dubielzig**, **Ian Duncan** (all in Veterinary Medicine) and **James Ver Hoeve** (Ophthalmology and Visual Sciences) showed how specialized optical coherence tomography (OCT) retinal imaging studies can potentially be used as a surrogate marker for progression of multiple sclerosis. This study was published in one of the leading eye research journals, *Investigative Ophthalmology and Visual Science*, and underlines the increasing number of applications that discoveries in the visual system have to other areas and systems in the body.



McPherson ERI Associate Members **Drs. Joseph Carroll** (Medical College of Wisconsin) and **Alf Dubra** (Stanford University), in collaboration with new UW retina specialist and McPherson ERI member **Dr. Kim Stepien**, used advanced adaptive optics imaging of cone photoreceptors to chart the course of photoreceptor degeneration in Best disease (BD), an inherited form of macular degeneration. They succeeded in showing how longitudinal photoreceptor imaging (over a period of two years) can be a powerful tool for understanding retinal disease progression in human subjects and for monitoring responses to emerging therapeutic treatment (published in the journal *Retina*).



**Drs. Nader Sheibani** (Ophthalmology and Visual Sciences) and **Chris Sorenson** (Pediatrics) partnered with McPherson ERI members **Drs. Mahsa Ranji** (Electrical Engineering) and **Carol Hirschmugl** (Physics) at UW-Milwaukee, using an imaging method called “synchrotron Fourier transform infrared (sFTIR) widefield imaging” as a tool to discern early diabetes-induced biochemical changes in retinal cell layers. Their combined efforts show how oxidative stress at the onset of diabetes ultimately contributes to retinal damage (published in *Analyst*). (Oxidative stress – an imbalance between the production of chemically reactive oxygen species and the cells’ ability to neutralize them – has been implicated in the development of a large number of diseases). The conclusions drawn from these studies will help to bridge the gap in our understanding of the molecular and cellular mechanisms that contribute to the pathobiology of diabetic retinopathy.



**Dr. Rob Nickells** (Ophthalmology and Visual Sciences) teamed with McPherson ERI engineer **Dr. Shaoqin (Sarah) Gong** (Biomedical Engineering) to develop a novel intraocular drug delivery system that uses nanotechnology to reduce retinal ganglion cell death in mice with experimental glaucoma (*Journal of Controlled Release*). Dr. Nickells, one of the McPherson ERI’s leading glaucoma researchers, also published a review in *Progress in Retina and Eye Research* discussing the role of specific “programmed cell death” genes (BCL2 genes) in the loss of retinal ganglion cells during glaucoma. This extensive report details his recent efforts to manipulate BCL2 genes to slow the course of this common blinding disease.







## **2016-17 Walsh Research Travel Award Recipients**



With funding from the David G. Walsh Research Fellowship Fund as well as from Cycle for Sight, four McPherson ERI/David G. Walsh Research Travel Awards are given each academic year. These awards assist graduate students and postdocs from MERI members' research groups to attend conferences to present vision-related work and to advance educational and professional development opportunities. The award winners for the current academic year, selected from among a strong and diverse field of applicants, are **Bradley Gundlach, graduate student** (Electrical and Computer Engineering; Mikhail Kats, mentor); **Eric H. Nguyen, postdoctoral researcher** (Ophthalmology and Visual Sciences; Nader Sheibani, mentor); **Gurugirijha Rathnasamy, postdoctoral researcher** (Ophthalmology and Visual Sciences; Aparna Lakkaraju, mentor); and **Seung Heon Yoo, graduate student** (Human Development and Family Studies; Heather Kirkorian, mentor). Each winner will give a presentation at an upcoming McPherson ERI seminar. Congratulations to all!



## **2017 Cycle for Sight update**



**Cycle for Sight, the McPherson ERI's annual spring fundraiser**, was held on March 11th at the Princeton Club West and at two locations on the UW-Madison campus. This year's ride raised more than \$50,000 for vision research by McPherson ERI scientists – the highest donation level in the event's six years. Many of our star teams rode again this year, and it's always a pleasure to see the energy that Blind Take Off, Out of Sight, Team Tiradani, and others bring to the event. Smaller teams from member labs and from the campus and area community are an essential part of the ride as well. This year's ride included the debut of a team from McPherson House, the medical student learning community in the School of Medicine and Public Health named in honor of Dr. Alice McPherson, one of the McPherson ERI's founders.

**The ride was especially memorable** given the presence of Kenzi's Team, which has ridden each year in support of Kenzi Valentyn. Kenzi, the daughter of team captain Nancy Valentyn and her husband Tim, had a neurodegenerative disease which took away her vision, among other health problems. Kenzi Valentyn passed away on March 6th of this year, a few days before the ride. To honor her, family and friends came together to ride on the following Saturday, and they have continued to raise donations for vision research which will compose half of the gifts to this year's ride. The McPherson ERI is proud to dedicate this year's ride to Kenzi Valentyn.

**As Cycle for Sight continues to grow**, we hope that you'll maintain your support and consider hopping on a bike with us (or walking the track at the Princeton Club)! Great people, a vigorous hour's workout, and the chance to advance vision research – what could be better?

# APRIL 27, 2017:

## 5TH ANNUAL MCPHERSON ERI ENDOWED LECTURE

**Dr. José-Alain Sahel**, a world leader in basic and translational retinal research, is our featured lecturer this year. Founder and director of the Institut de la Vision in Paris, he also serves as the chair of Ophthalmology at the University of Pittsburgh Medical Center. In both of these capacities, Dr. Sahel has spearheaded efforts to restore vision to the blind through varied approaches including neuroprotective factors, retinal prosthetics (electronic "chips"), gene replacement therapy, and optogenetics (coercing non-photoreceptor cells to become light-sensitive).

Hear him speak about his research and treatment advances on Thursday, April 27th at 4:30pm, in room 1335 of the UW-Madison Health Sciences Learning Center.



Wisconsin Council of the Blind & Visually Impaired

McPherson Eye Research Institute

### BRIGHT SIGHTS Six Ways of Seeing

An exhibition showcasing works by six Wisconsin artists whose visual impairments inspire and enrich their art:

**Angelynn Brown, Alison Fortney, Ron Wendt, Rosemarie Fortney, Albert Schmlege, and Dan Sullivan (aka D. S. Sully)**

Presented by the  
McPherson Eye Research Institute  
in partnership with the  
Wisconsin Council of the Blind & Visually Impaired

**MANDELBAUM & ALBERT FAMILY VISION GALLERY**

## CLOSING RECEPTION

**THURSDAY, MAY 25TH, 4:30-6:30PM**

9th floor, Wisconsin Institutes for Medical Research  
1111 Highland Avenue, Madison WI 53705

Parking available in UW-Madison lots B2 or B6, and in ramps 75 or 76.  
Contact: Gail Stritt - 608/265/4023 - gstritt@wisc.edu or Michael Chaim - 608/265/0690 - chaim@wisc.edu