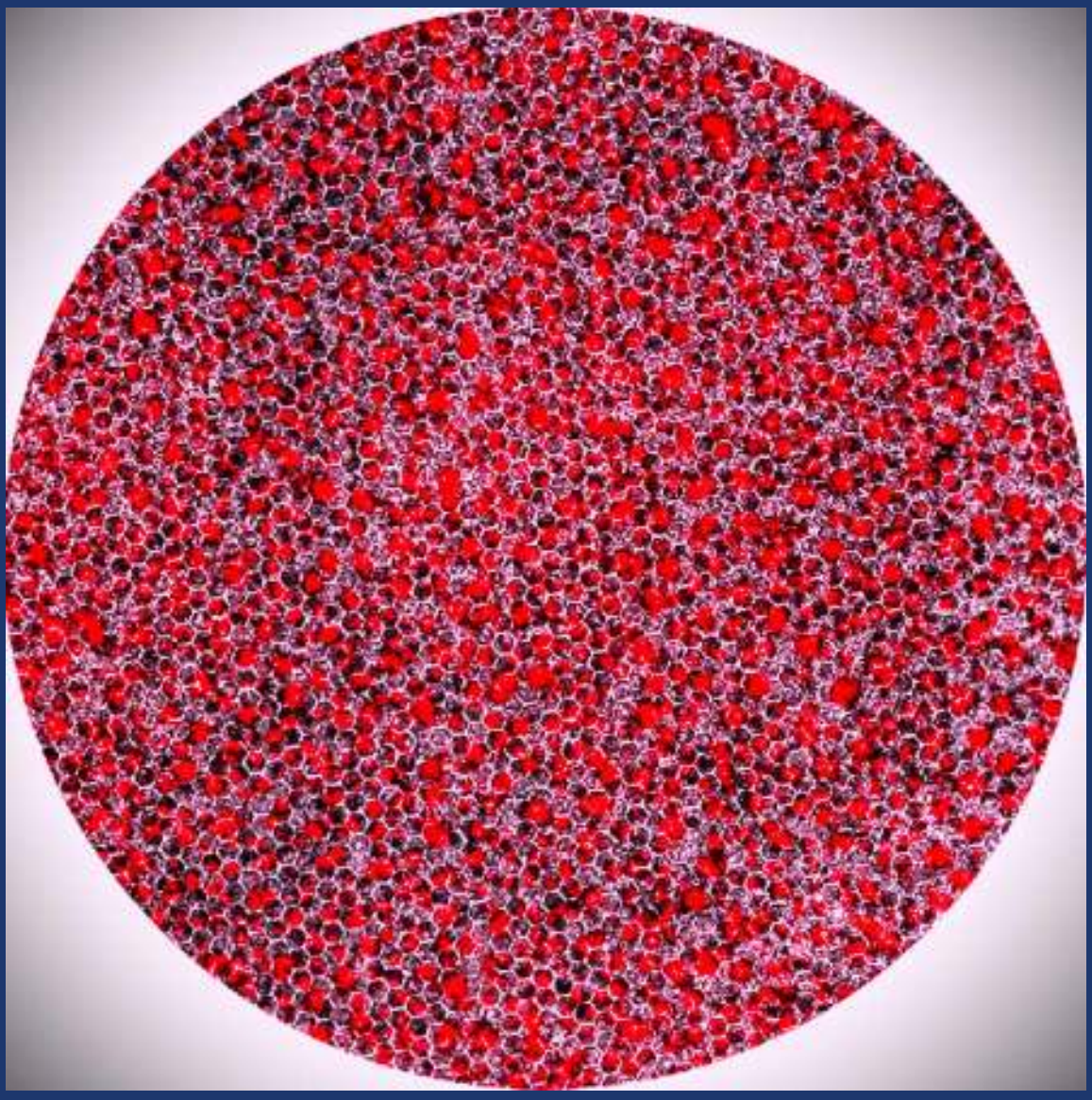
RETINA RESEARCH FOUNDATION



ANNUAL REPORT 2023

FUNDING PROGRAMS IN RESEARCH AND EDUCATION
TO REDUCE RETINAL BLINDNESS WORLDWIDE

Annual Report 2023

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Established in 1969

The mission of the Retina Research Foundation is to reduce retinal blindness worldwide by funding programs in research and education.

Cover image courtesy of UW-Madison, Gamm Laboratory

President's Message

Dear Friends,

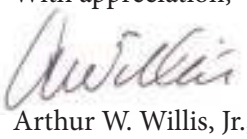
Fifty-two years ago, in 1972, when I moved to Houston to begin my retina specialty training under Dr. Alice McPherson, I could not have foreseen that I would be writing to you today on behalf of such a consequential and impactful research organization. That was also the year that the Foundation's articles of incorporation were amended to reflect a new name to more accurately convey its mission, and the Retina Research Foundation (RRF) that we know today was established. Reflecting on my long professional collaboration and close friendship with Dr. McPherson, combined with my firsthand knowledge of her deep passion and commitment to funding retinal research, has led me to no other possible calling than one of service to RRF's mission, initially as a scientific advisor, later as a managing director and officer, and now as I am most honored to serve, as the bearer of her scientific and philanthropic mantle as the second president of this fine organization, following the end of her truly remarkable life this past January.

With the support of donors like you, the RRF research program has grown from the first pilot study grant of $30,000 made in 1973 to Dr. Donald Kilpatrick of the Cullen Eye Institute at Baylor College of Medicine for his studies on the mechanisms of action of the photoreceptor membrane, to fund over $42.2 million in retina research as of the end of December, 2023. Subsequently, total research funding has increased to over $43 million. One of the objectives of the RRF's basic research grant program is to function as a funding bridge for novel and innovative vision research concepts, too nascent to attract other major, significantly larger funding sources. RRF has been extremely successful in this regard, and to date, it has provided initial funding for many important achievements, including: effective laser treatment of diabetic retinopathy; the use of VEGF inhibitor drugs in the treatment of wet macular degeneration and other retinal disorders; the initial exciting success of gene therapy in treating a genetic form of retina degeneration and in conferring light sensitively on retinal cells other than photoreceptors; the continuing improvements of imaging, including optical coherence tomography for visualizing the retina at the cellular level; and the success of in vitro growth of retinal cells and their possible use for retina cell replacement therapies. As a retina specialist and surgeon, it is gratifying to see how this research progress, funded in part by RRF, has translated into innovative treatments and therapies for patients. Helping prevent vision loss due to retinal disease is our ultimate goal.

The rate of discovery is only accelerating, and RRF is committed to continuing to fund stimulating research that leads to future vision saving discoveries. The proof of this is shared on the pages that follow, where RRF affiliated researchers report on their progress made in the past year, and we share the extent of our Foundation's activities in 2023. I hope you will be as impressed as I am by the progress being made.

Dr. McPherson emphasized many times in her discussions with me and others that vision disorders and blindness remain widespread, particularly among people in their older years, and most of these conditions are caused by retinal disease. She said it best, "*The only hope of reducing blindness is through research*." To this end, RRF has established a precedent for maintaining independence from all institutions regarding its governance and programs, a policy that still guides the Foundation's operations today. Our work is supported by our community, locally in Houston and extending across the U.S. and the globe. RRF continues to dedicate all of its resources and programs to improving retina care through research, and it is the support of RRF donors that makes this progress possible. So in closing and on behalf of the Board of Directors of Retina Research Foundation, I thank you for your continuing interest and support. Without you, RRF would not exist, and a world without RRF, I find hard to imagine. More good work remains to be done.

With appreciation,



Arthur W. Willis, Jr., MD
President

Dr. Art Willis and Dr. Alice McPherson

Research Program Overview - 2023

Retina Research Foundation supports an exemplary variety of programs in retina research all around the world. The following is a brief overview of RRF research supported in 2023, which illustrates the wide scope of the Foundation's activities.

RRF Pilot Study Grants – Investigation of New Research Topics

Baylor College of Medicine, Houston, TX
- Samuel Wu, PhD – Kayser Research Project
- Rui Chen, PhD – Manning Research Project
- Yingbin Fu, PhD – Dana and Gil Petri Research Project
- Richard Hurwitz, MD – Wilson Research Project
- Graeme Mardon, PhD – Miller Research Project

Texas A&M Health Science Center, Bryan, TX
- Lih Kuo, PhD – Gueymard Research Grant

University of Texas Medical Branch-Galveston, Galveston, TX
- Wenbo Zhang, PhD – Bovay Research Project

University of Wisconsin, Madison, WI
- Curtis Brandt, PhD – Murfee Macular Degeneration Project

Indiana University, Indianapolis, IN
- Timothy Corson, PhD – Lawrence Research Project

West Virginia University School of Medicine, Morgantown, WV
- Jianhai Du, PhD – Basic Research Project

University of Tennessee, Memphis, TN
- Francesco Giorgianni, PhD – Basic Research Project

Vanderbilt University, Nashville, TN
- Milam Brantley, MD, PhD – Basic Research Project

Northeastern University, Boston, MA
- James Monaghan, PhD – Basic Research Project

Institute for Vision Research Center, University of Iowa, Iowa City, IA
- Seongjin Seo, PhD – Basic Research Project

University of California, Irving, Irving, CA
- Vladimir Kefalov, PhD – Basic Research Project

University of Illinois at Chicago, Chicago, IL
- Adrius Kazlauskas, PhD – Basic Research Project

University of Arizona, Tucson, AZ
- Erika D. Eggers, PhD – Basic Research Project

University of Kentucky, Lexington, KY
- Ann C. Morris, PhD – Basic Research Project

Augusta University, Medical College of Georgia, Augusta, GA
- Ming Zhang, MD, PhD – Basic Research Project

Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA
- Kinga Bujakowski, PhD – Basic Research Project

University of Texas at Austin, Austin, TX
- Jeffrey M. Gross, PhD – Basic Research Project

University of California, San Francisco (UCSF), San Francisco, CA
- Alex J. Smith, PhD – Basic Research Project

University of Wisconsin-Madison, Madison, WI
- Christine M. Sorenson, PhD – Basic Research Project

University of Michigan, Ann Arbor, MI
- Eric Weh, PhD – Basic Research Project

Schepens Eye Institute, Harvard Medical School, Boston, MA
- David M. Wu, MD, PhD – Basic Research Project

RRF Cox Macula Society Research Grant – New Clinical Research Project

Administered by The Macula Society

Francesco Bandello, MD, San Raffaele Scientific Institute, University Vita-Salute, Milan, Italy

Research Chairs – Ongoing Proven Research Projects

University of Wisconsin, Madison, WI

Nader Sheibani, PhD – RRF Research Chair

David Gamm, MD, PhD – Humble Distinguished Director, McPherson Eye Research Institute

Kevin W. Eliceiri, PhD – Helmerich Chair, Assoc. Director, McPherson Eye Research Institute

Krishanu Saha, PhD – Murfee Chair, McPherson Eye Research Institute

Melissa Skala, PhD – Albert Chair, McPherson Eye Research Institute

Baylor College of Medicine, Houston, TX

RRF Research Chair – nation-wide search in progress

Research Professorships – Ongoing Proven Research Projects

University of Wisconsin, Madison, WI

Sarah Gong, PhD – Gamewell Professor, McPherson Eye Research Institute

Bikash Pattnaik, PhD – Matthews Professor, McPherson Eye Research Institute

Mrinalini Hoon, PhD – Brown Professor, McPherson Eye Research Institute

Established Awards – Awards Recognizing Lifetime Achievement and Ongoing Research

RRF Award of Merit – presented by The Retina Society

SriniVas Sadda, MD – Doheny Eye Institute, University of California, Los Angeles (UCLA), Los Angeles, CA

RRF Pyron Award – presented by American Society of Retina Specialists (ASRS)

Eugene De Juan, MD – University of California, San Francisco (UCSF), San Francisco, CA

CL Schepens MD/AAO Award – presented by American Academy of Ophthalmology (AAO) and in the spirit of Schepens International Society (SIS)

Emily Y. Chew, MD, PhD – National Eye Institute, National Institutes of Health, Bethesda, MD

Paul Kayser/RRF Global Award – presented by Pan-American Association of Ophthalmology (PAAO)

Ranjeer Muni, MD, PhD -- University of Toronto, Ontario, Canada

RRF Kayser International Award – presented by International Society for Eye Research (ISER) – will be awarded in 2024

RRF Gonin Lecturer – presented by Club Jules Gonin - will be awarded in 2024

Gonin Medal – presented by International Council of Ophthalmology (ICO) - will be awarded in 2026

International Fellowships – Advanced Subspecialty Training

RRF Helmerich International Fellowships – presented by Ophthalmology Foundation (OF) and administered by International Ophthalmological Fellowship Foundation e. V. (IOFF)

Daisy Asiama Asare, MD -- from Ghana to Singapore National Eye Center, Singapore, in oculoplastics, orbital and lacrimal surgery

Rolika Bansal, MD -- from India to Wills Eye Hospital, University of Philadelphia, PA in ocular oncology

Gillingham Pan-American Fellowships – administered by Pan-American Association of Ophthalmology (PAAO) – will be awarded in 2024

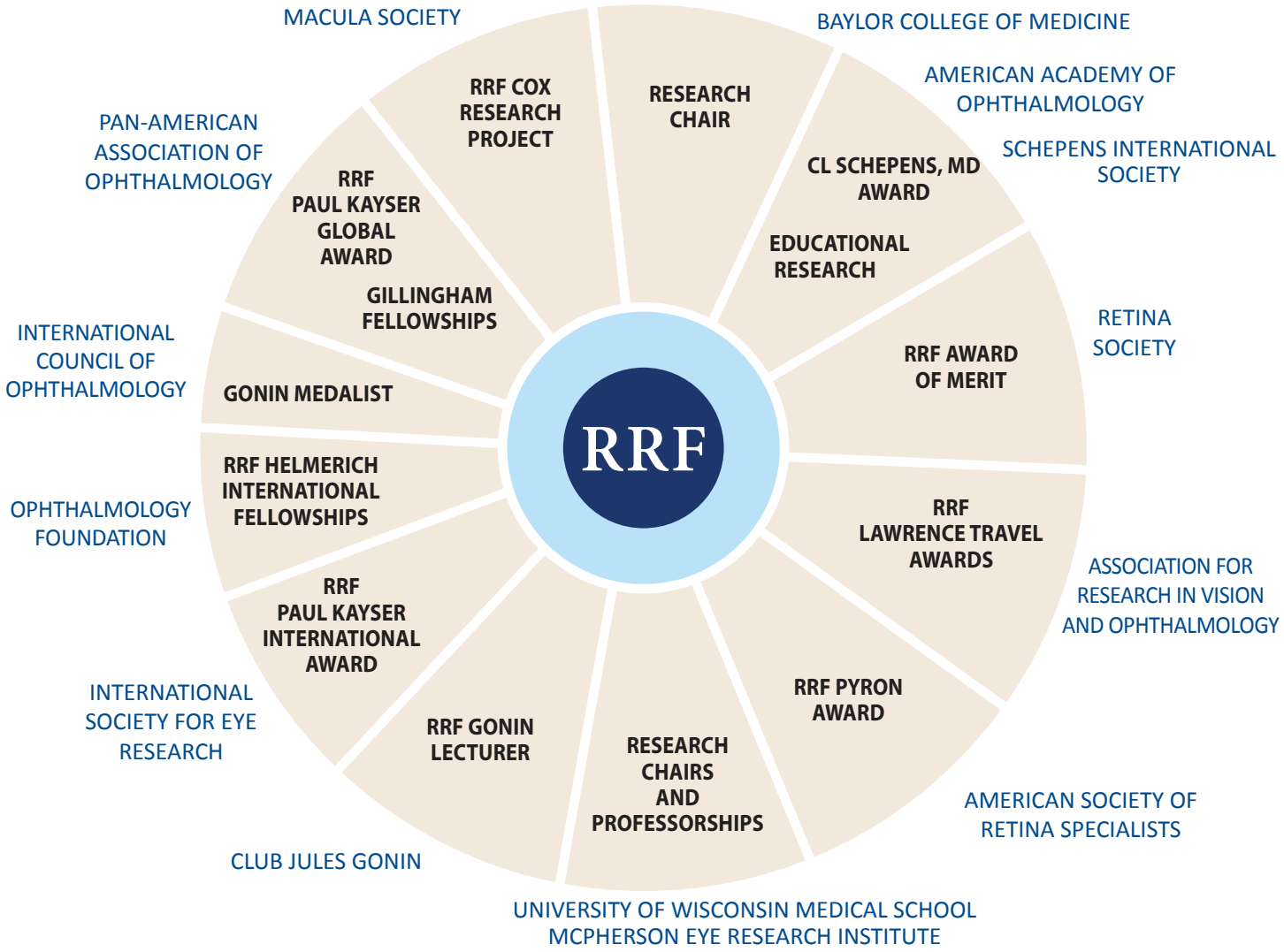
Research Initiatives – Educational and Travel Scholarships

AAO Educational Trust Fund – administered by The Foundation of the American Academy of Ophthalmology (FAAO)

Retina-related educational research programs for clinical and basic science

RRF Lawrence Travel Scholarships – administered by Association for Research in Vision and Ophthalmology (ARVO) – 29 in-person travel scholarships awarded in 2023

Collaborating Organizations



COLLABORATING ORGANIZATION	AWARD	DATE OF FIRST COLLABORATION WITH RRF
RETINA SOCIETY	RRF Award of Merit in Retina Research	1978
ARVO Assoc. for Research in Vision and Ophthalmology	RRF Lawrence Travel Awards	1984
ISER International Society for Eye Research	RRF Paul Kayser International Award	1986
ASRS American Society of Retina Specialists	RRF Pyron Award	1988
PAAO Pan-American Association of Ophthalmology	Gillingham Pan-American Fellowships Paul Kayser/RRF Global Award	1992 2012
AAO American Academy of Ophthalmology	Educational Trust Fund	1993
MACULA SOCIETY	RRF Cox Research Project	1993
CLUB JULES GONIN	RRF Gonin Lecturer	1996
ICO International Council of Ophthalmology with University of Lausanne and Swiss Ophthalmological Society	Gonin Medalist	1998
BAYLOR Baylor College of Medicine	Research Chair	1998
UW University of Wisconsin School of Medicine and Public Health	Research Chairs and Professorships	1998
MERI McPherson Eye Research Institute	Research Chairs and Professorships	2007
AAO American Academy of Ophthalmology with Schepens International Society	Charles L. Schepens, MD/AAO Award	2008
ICO/ICOF International Council of Ophthalmology	RRF Helmerich International Fellowships	2009
OF Ophthalmology Foundation/IOFF	RRF Helmerich International Fellowships	2021

Retina Research Sites

Past and Present

TEXAS : 11

Baylor College of Medicine
Center for Technology
Houston Advanced Research Center
UT MD Anderson Cancer Center
Southwest Research Institute
Texas A&M Health Science Center
Texas Children's Hospital
Houston Methodist Hospital
University of Houston
University of Texas at Galveston
University of Texas at Houston

PAN AMERICAN : 23

Buenos Aires, Argentina
Curitiba, Argentina
La Paz, Bolivia
Belo Horizonte, Brazil
Recife, Brazil
São Paulo, Brazil
Porto Alegre, Brazil
Santiago, Chile
Bogotá, Colombia
Cali, Colombia
San Juan, Costa Rica
Santo Domingo, Dominican Republic
San Salvador, El Salvador
Port-au-Prince, Haiti
San Lorenzo, Honduras
Aguascalientes, Mexico
Mexico City, Mexico
Nuevo León, Mexico
Asunción, Paraguay
Lima, Peru
San Juan, Puerto Rico
Montevideo, Uruguay
Caracas, Venezuela

INTERNATIONAL : 48

Al Shifa Trust Eye Hospital	Rawalpindi, Pakistan
Aravind Eye Hospital	Madurai, India
Asahikawa Medical College	Asahikawa, Japan
Beijing Institute of Ophthalmology	Beijing, China
Bern University Hospital	Bern, Switzerland
Centre for Eye Research	Melbourne, Australia
Copenhagen University	Copenhagen, Denmark
Eskisehir Osmangazi University	Eskisehir, Turkey
Eye & Laser World Center	Giza, Egypt
Eye Foundation Hospital	Lagos, Nigeria
Ghent University Hospital	Ghent, Belgium
Hospital Fondation Rothschild	Paris, France
Institut de la Vision	Paris, France
Intercommunal Hospital of Crèteil	Crèteil, France
Jimma University	Jimma, Ethiopia
Jules-Gonin Eye Hospital	Lausanne, Switzerland
Kasindo Eye Clinic	E. Sarajevo, Bosnia & Herzegovina
Keio University	Tokyo, Japan
L V Prasad Eye Institute	Hyderabad, India
Lariboisiere Hospital	Paris, France
Lidcombe Hospital	Sydney, Australia
Lund University	Lund, Sweden
Magrabi ICO Cameroon Eye Institute	Yaounde, Cameroon
Mashhad University Medical Services	Mashhad, Iran
Melles Cornea Clinic	Rotterdam, Netherlands
McGill University/Montreal General Hospital	Montreal, Canada
Moorfields Eye Hospital	London, England
Osaka Medical School/Osaka University	Osaka, Japan
Research Institute of Ophthalmology	Cairo, Egypt
Royal College of Ophthalmologists	Edinburgh, Scotland
Sadguru Netra Chikitsalaya Eye Hospital	Satna, India
Sankara Nethralaya Eye Hospital	Chennai, India
Singapore National Eye Center	Singapore
Siriraj Hospital	Bangkok, Thailand
St. Thomas Hospital	London, UK
Sussex Eye Hospital	Brighton, UK
Tehran University of Medical Sciences	Tehran, Iran
Toronto Western Hospital	Toronto, Canada
University of Bonn	Bonn, Germany
University of Cambridge	Cambridge, England
University of Iceland	Reykjavik, Iceland
University of Oxford	Oxford, England
University of Paris	Paris, France
University of Erlangen-Nuremberg	Erlangen, Germany
University of Leipzig	Leipzig, Germany
University of Regensburg	Regensburg, Germany
University of Tübingen	Tübingen, Germany
Western General Hospital	Edinburgh, Scotland

NATIONAL : 67

Augusta University College of Medicine	Augusta, GA
Bascom Palmer Eye Institute	Miami, FL
Beaumont Eye Institute/Hospital	Royal Oak, MI
Byers Eye Institute/Stanford University	Palo Alto, CA
California Institute of Technology	Pasadena, CA
Carver College of Medicine	Iowa City, IA
Case Western Reserve University	Cleveland, OH
Casey Eye Institute	Portland, OR
Charles Retina Institute	Germantown, TN
City College of New York	New York, NY
Cleveland Eye Clinic/Cole Eye Institute	Cleveland, OH
Columbia University	New York, NY
Cornell University Medical College	Ithaca, NY
Dean McGee Eye Institute	Oklahoma City, OK
Duke Eye Center/University Medical School	Durham, NC
Emory University Eye Center	Atlanta, GA
Eye Tech Pharmaceuticals	Worchester, MA
Greater Baltimore Medical Center	Baltimore, MD
Harvard Medical School	Boston, MA
Indiana University	Indianapolis, IN
Johns Hopkins University Medical School	Baltimore, MD
Joslin Diabetes Center	Baltimore, MD
Jules Stein Eye Institute	Los Angeles, CA
Kellogg Eye Center/University of Michigan	Ann Arbor, MI
Kresge Eye Institute	Detroit, MI
Massachusetts Eye & Ear Infirmary	Boston, MA
Massachusetts Institute of Technology	Boston, MA
McPherson Eye Research Institute	Madison, WI
Medical University of South Carolina	Charleston, SC
National Eye Institute	Bethesda, MD
Northeastern University	Boston, MA
Northwestern University	Evanston, IL
Rockefeller University	New York, NY
Schepens Eye Research Institute	Boston, MA
Sheie Eye Institute	Philadelphia, PA
Shiley Eye Center, UC San Diego	La Jolla, CA
St. Joseph's Hospital	Baltimore, MD
Tulane University Medical School	New Orleans, LA
Thomas Jefferson University	Philadelphia, PA
University of Alabama at Birmingham	Birmingham, AL
University of Arizona	Tuscon, AZ
University of Buffalo/SUNY	Buffalo NY
University of California	Berkeley, CA
University of California	Irvine, CA
University of California	Los Angeles, CA
University of California	San Francisco, CA
University of Colorado	Aurora, CO
University of Florida	Gainesville, FL
University of Illinois at Chicago	Chicago, IL
University of Iowa	Iowa City, IA
University of Kansas Medical College	Kansas City, KS
University of Kentucky	Lexington, KY
University of Miami Medical School	Miami, FL
University of Nebraska HSC	Omaha, NE
University of Pennsylvania	Pittsburgh, PA
University of Rochester	Rochester, NY
University of Southern California	Los Angeles, CA
University of Tennessee	Memphis, TN
University of Utah, John A. Moran Eye Center	Salt Lake City, UT
University of Washington	Seattle, WA
University of Wisconsin Medical School	Madison, WI
Vanderbilt University	Nashville, TN
Washington University	St. Louis, MO
Weill Cornell Medicine	New York, NY
West Virginia School of Medicine	Morgantown, WV
Wills Eye Hospital	Philadelphia, PA
Wilmer Eye Institute	Baltimore, MD

Research

In 2023, RRF funded 25 pilot studies, including six newly added projects. Pilot studies are experimental, basic science studies, conducted at leading research institutions that are designed to investigate novel lines of inquiry into the causes of retinal diseases in an effort to obtain new understanding and to advance scientific knowledge. The hope is that these studies lead to future ongoing projects and, ultimately, new therapies. Nine established projects are named in recognition of individuals who have generously supported the RRF mission. During the year, RRF affiliated vision researchers contributed to the body of knowledge through publication of an impressive 25 manuscripts, submitted to or published in high-impact, peer review journals. For researchers having a publication accepted in a high-impact journal, this result broadens their research findings visibility and may possibly increase citations by other researchers. The impact factor is a measure of the journal's influence and relevance within the scientific community, and a higher impact factor generally signals broader interest and attention.

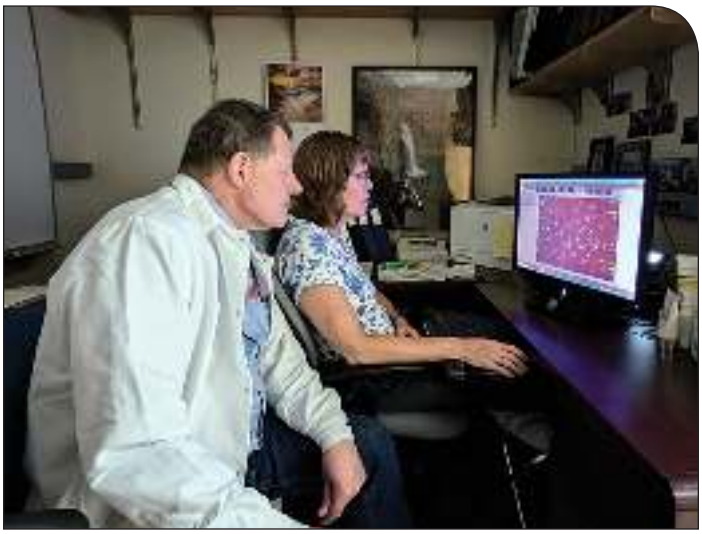
The Kathryn and Latimer Murfee Macular Degeneration Project

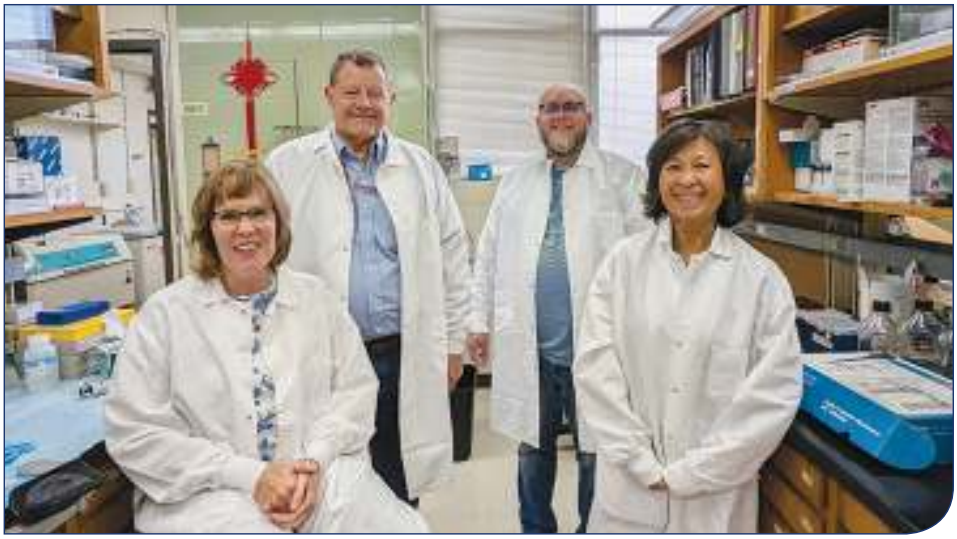
Curtis R. Brandt, PhD
Department of Ophthalmology and Visual Sciences
McPherson Eye Research Institute
University of Wisconsin
Madison, WI

Gene Therapy for Retinal Degenerative Diseases

Dr. Brandt's research project goals are to understand the innate immune response to gene delivery vectors (GDVs) and to reduce the impact of host cell restriction factors on viral vector transduction efficiency in order to improve gene therapy for human ocular diseases. In 2023, his laboratory team completed and published their studies on RNA sensor protein expression in neural retina tissue. They identified a mitochondrial sensor protein that restricts viral GDV transduction in human Mueller cells, results, which were published in *Experimental Eye Research*.

Dr. Brandt also completed an analysis of the effect of viral GDV transduction on RNA and DNA sensor gene expression in human retinal cell lines. The team explored whether small molecule transcription factor activators and inhibitors altered transduction efficiency of viral GDVs in retinal cells. Initial experiments investigating the inflammatory response of human retinal organoids to AAV detected changes in gene expression and secretion of proteins that may contribute to inflammation during ocular gene therapy.





The Brandt laboratory team.

W.O. Manning Research Project

Rui Chen, PhD
Department of Molecular and Human Genetics
Baylor College of Medicine
Houston, TX

Identification and Functional Analysis of Genes Involved in Retina Diseases

Dr. Chen's research goal is to improve the ability to prevent, diagnose, and treat human retinal diseases accomplished by the identification and functional characterization of newly discovered disease genes underlying the diseases. Since many human eye disease genes are involved in normal eye development, the Chen laboratory utilizes animal model systems to study retinal development. Results from these studies deepens our knowledge about human retinal disease and forms the basis of developing optimal treatments.

Dr. Chen has completed panel sequencing for over 7,000 patients with inherited retinal diseases, successfully diagnosing the majority of them; however, about 20% remained unsolved. Performing whole genome sequencing (WGS) on the remaining over 1,000 patients has identified new gene mutations that were previously missed. With a molecular diagnosis, patients are more likely to be eligible for therapeutic clinical trial enrollment. One of the most recent disease genes found, named UBAP1L, with results published in Genetics in Medicine.

Dr. Chen's lab performed functional studies of TLCD3B, a gene his lab previously identified that is associated with inherited retinal disease. The team profiled ceramide in the Tcld3b mutant retina, and as expected, they observed that the level of C16-C20 ceramide is significantly reduced compared to control. These significant results were published in Genetics in Medicine. Dr. Chen also tested the potential interaction between canonical CerS and Tlcd3b by evaluating whether the retina Tlcd3b mutant phenotype can be rescued by overexpression of canonical CerS. Findings suggest that the Tlcd3b retina phenotype can be partially rescued by CerS with the best rescue observed for CerS5. The team further investigated the phenotype and interaction between CerS with Tlcd3b. Increasing evidence suggests that maintenance of the ceramide profile is critical for retinal function and supports the role of ceramide as a mediator of photoreceptor dysfunction or cell death from ceramide accumulation and deficiency contexts. The manuscript describing these results was published in the journal, *Disease Models & Mechanisms*.

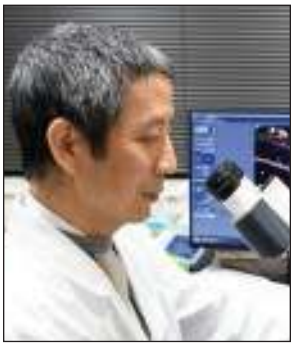
Joe M. and Eula C. Lawrence Research Project

Timothy W. Corson, PhD
Department of Pharmacology and Toxicology
Indiana University School of Medicine
Indianapolis, IN

Development of a Retinal Pigment Epithelium-specific Soluble Epoxide Hydrolase Deletion Model

Dr. Corson's long-term goal is to find new therapeutic approaches for age-related macular degeneration (AMD), a disease characterized by abnormal blood vessel growth ("wet" AMD) and retinal pigment epithelium (RPE) dysfunction ("dry" AMD). The specific goal of the 2023 project was to explore soluble epoxide hydrolase (sEH), an enzyme identified to be important for abnormal new blood vessel growth and more recently, for inflammation. To do this, Dr. Corson's team developed a mouse model in which sEH can be specifically "turned off" in the RPE cells where it normally is highly expressed. Importantly, sEH loss did not cause obvious defects in the eye. This work builds upon previous years' research, during which Dr. Corson found sEH as a target of SH-11037, a chemical his laboratory developed that blocks blood vessel growth. The team showed that sEH is present at high levels in human and mouse eyes with AMD-like features. Further, they found that sEH inhibitors can block new blood vessel growth in the eye. They characterized the molecular mechanism of how SH-11037 inhibits sEH, and identified factors that increase its levels in the eye. Dr. Corson's team assessed their library of novel chemicals to build a "structure activity relationship" for blocking sEH function. Findings showed differential expression in sEH between the sexes, found that depletion of sEH with an in-house developed genetic tool reduces inflammatory signals, and revealed RPE as a major source of this protein. Dr. Corson further explored whether sEH regulates the permeability of blood vessels in culture, finding that sEH inhibition can decrease leakiness of blood vessels. Dr. Corson's research findings related to this project were shared with the scientific community through three published articles in 2023.

Dana and Gil Petri Research Project



Yingbin Fu, PhD
Department of Ophthalmology
Baylor College of Medicine
Houston, TX

A Novel Treatment Strategy for Age-related Macular Degeneration by Targeting Cholesterol Transport

Age-related macular degeneration (AMD) is a major cause of blindness in the elderly. Choroidal neovascularization (CNV or wet AMD), the growth of abnormal leaky blood vessels beneath the retina, underlies 80-90% of legal blindness due to AMD. Up to half of patients have suboptimal responses to the current anti-vascular endothelial growth factor (VEGF) treatment. VEGF is a signaling protein that promotes the growth of new leaky blood vessels under the eye. The objective of Dr. Fu's ongoing project is to develop a highly innovative and effective AIBP/apoA-I/anti-VEGF combination therapy for wet AMD by targeting three critical components: VEGF, endothelial cells, and macrophages.

Because Dr. Fu's prior research shows that macrophages, a type of white blood cell that helps eliminate foreign substances by engulfing foreign material and initiating an immune response, play an important role in drug resistance in AMD. In 2023, he proposed to perform a comprehensive gene profile analysis of macrophages from an anti-VEGF resistant model versus the control to decipher the underlying mechanism. This resulting information will be important to the design of clinical trials to test the improved efficacy and safety of the new combination therapy.

Comparison data of the gene expression profiles of infiltrated ocular show that different macrophage metabolic reprogramming may be responsible for anti-VEGF resistance. This study is highly significant because it has the potential to lead to the discovery of new targets for combating anti-VEGF resistance. Furthermore, Dr. Fu's data suggest a new function of AIBP in inhibiting arteriolar CNV, which is characterized by the presence of large-caliber vessels, vascular loops, and profound leakage, which plays a key role in anti-VEGF resistance. Dr. Fu's significant findings were shared through his published articles in four high-impact journals in 2023.

Dr. Fu, center, and members of his lab.

Mary Ellen Wilson Research Project

Richard L. Hurwitz, MD
Department of Pediatrics
Baylor College of Medicine
Houston, TX

Immune Consequences of Gene Therapy for Ocular Disorders

The hypothesis of Dr. Hurwitz's project is that gene therapy protocols for both ocular and non-ocular disorders can be optimized based on understanding how the unique ocular environment influences the efficacy of the gene therapy treatment.

The Hurwitz team previously published an association of the vitreous component hyaluronan with the enhanced expression of potentially therapeutic genes transferred by adenoviral vectors. Hyaluronan alone does not account for the entire effect observed. Versican is a component of vitreous that binds hyaluronan and is made up of three domains called G1 and G3, separated by a chondroitin-binding domain. The effects of these domains have been examined using expression constructs that span the known functional elements that may affect transgene expression. G1 and G3 have been shown to have a complex interplay in regulating gene expression. G1 also delivers hyaluronan to the cell surface where it further enhances gene expression. These constructs may be useful in designing more efficient vectors and delivery systems to optimize gene therapy outcomes and limit toxicities, including immune consequences.

Dr. Hurwitz has also been exploring the potential of using microwafers loaded with nanoparticles to deliver therapeutic drugs or genes directly to the eye without the need for surgery or injections. He has shown that chemotherapeutic agents can be delivered locally to the eye and treat retinoblastoma in a murine model of the disease.

Adolphe G. and Josephine Roberts Gueymard Research Project

Lih Kuo, PhD
Department of Medical Physiology
Texas A&M University Health Science Center
Bryan, TX

Activation of Endothelin-dependent RhoA/ROCK Pathway Elicits Retinal Microvascular Dysfunction in Diabetic Retinopathy

This project seeks to explain the mechanisms that are responsible for the microvascular pathogenesis of diabetic retinopathy and to develop strategies and related tools for the prevention and treatment of the sight-threatening disease.

Proper function of the retina depends on an adequate blood supply to the retinal tissue, while dysfunction of the retinal microcirculation could lead to disease development. Dr. Kuo has found that in the diabetic retina, the synthesis of vasoconstrictor/inflammation agent endothelin-1 (ET-1) from vascular endothelin converting enzyme (ECE) is elevated, corresponding to the activation of RhoA kinase (ROCK) and arginase enzymes. He hypothesizes that ECE/ROCK/arginase signaling contributes to microvascular dysfunction and leads to ischemia underlying the development of retinopathy. Using a pig model, which resembles the human eye's circulation, Dr. Kuo's laboratory investigates vascular signaling pathways in the initiation and development of diabetic retinopathy with the goal of developing pharmacological strategies for disease prevention and treatment.

Throughout 2023, Dr. Kuo discovered that early diabetes causes a significant reduction in retinal blood flow before the development of pathological retinopathy. This flow deficiency is associated with impaired endothelium-dependent nitric oxide-mediated vasodilation in ophthalmic arteries "feeding" the retina's microcirculation. Dr. Kuo also found that ophthalmic vessels exhibited a 100-fold increase in sensitivity to ET-1 with age, which could contribute to retinal tissue ischemia due to impaired vasodilation and augmented vasoconstriction under hyperglycemic insults. In contrast to retinal circulation, the blood flow to the brain is normal during the progression of diabetes, suggesting that retinal circulation is more susceptible to diabetic insults. It appears that retinal blood flow dysregulation might lead to neural dysfunction in the retina during diabetes progression and that treatment of blood flow deficiency in early diabetes can be critical before the establishment of overt neurovascular pathology. Dr. Kuo's research is the first report in the field to mechanistically explain the clinically observed reduction of retinal blood flow in early diabetes and manuscripts detailing the results are in development.

Bertha and I.L. Miller Research Project

Graeme Mardon, PhD
Departments of Pathology
Molecular and Human Genetics
Baylor College of Medicine
Houston, TX

Genetic and Molecular Analysis of Retinal Development

Dr. Mardon's long-term objective is to improve prevention and treatment for human retinal diseases. To that end, he uses the *Drosophila* eye as a powerful animal model system for deciphering conserved molecular mechanisms of retinal cell fate determination and development.

The mammalian *Onecut* gene family is required for normal eye development and function but little is known about the mechanisms by which these genes act. Importantly, Dr. Mardon created loss-of-function mutations in the highly conserved *Drosophila onecut* gene and discovered that *onecut* is absolutely required for normal response to light (see figure), reaching a major research breakthrough concerning this important retinal gene. This work represents a major step forward in the understanding of basic mechanisms of retinal cell fate determination and is currently being prepared for publication.

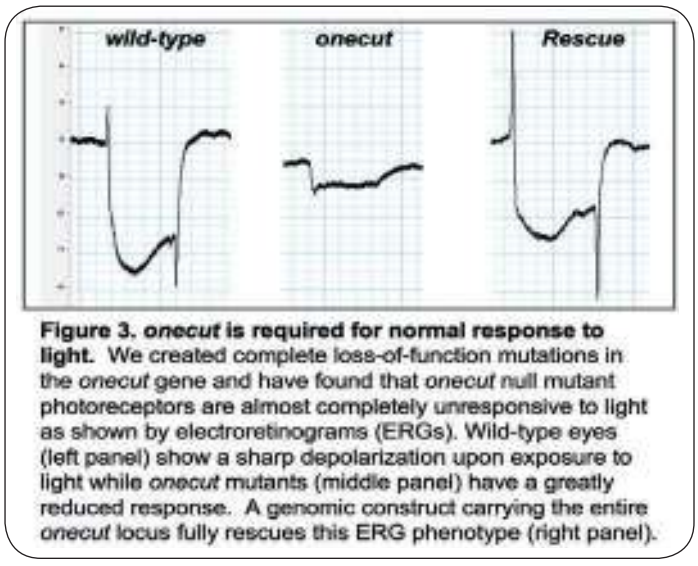


Figure 3. *onecut* is required for normal response to light. We created complete loss-of-function mutations in the *onecut* gene and have found that *onecut* null mutant photoreceptors are almost completely unresponsive to light as shown by electroretinograms (ERGs). Wild-type eyes (left panel) show a sharp depolarization upon exposure to light while *onecut* mutants (middle panel) have a greatly reduced response. A genomic construct carrying the entire *onecut* locus fully rescues this ERG phenotype (right panel).

The Paul Kayser Research Project

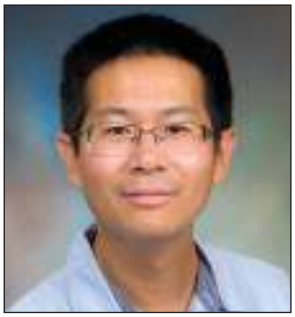
Samuel Wu, PhD
Cullen Eye Institute,
Neurosensory Center
Baylor College of Medicine
Houston, TX

Pharmacological and Genetic Mechanisms Underlying Retinal Cell Death in Age-related Macular Degeneration (AMD) and Glaucoma

Dr. Wu's research in 2023 was very successful. By using the novel 8-patch electrode recording system, developed by his laboratory and used for the first time in retinal research, his lab has successfully developed novel analytic tools for studying retinal synaptic connectivity and spatiotemporal receptive field properties of ganglion cells in normal, AMD and glaucomatous retinas. They study the morphology and synaptic inputs of various types of retinal ganglion cells (RGCs) and identify targets for drug and gene therapies for treating RGC dysfunction in glaucoma and AMD.

In March, Dr. Wu attended the 2023 International Society for Eye Research (ISER) meeting in Australia to belatedly receive his 2020 Retina Research Foundation Paul Kayser International Award in Retina Research and to present a research poster. In May, his lab attended the annual ARVO meeting in New Orleans and presented two posters. Dr. Wu was invited to present seminars to ophthalmology departments at Yale University (June 21), Columbia University (June 22) and Stanford University (July 21). Moreover, as the Director of the Baylor Vision Research Training Program, Dr. Wu was awarded a new, five-year National Eye Institute T32 grant. His group has completed four lines of research projects, four papers have been published, and two manuscripts are in press for publication.

Harry E. Bovay, Jr. Research Project



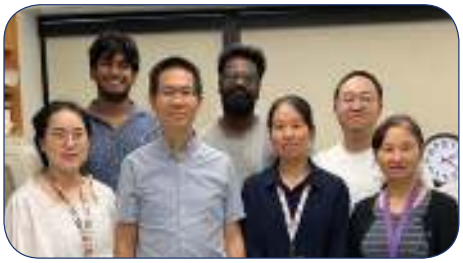
Wenbo Zhang, PhD
Department of Ophthalmology
& Visual Sciences
University of Texas Medical
Branch at Galveston
Galveston, TX

Novel Therapy for Retinal Neovascularization

Inadequate blood supply, ischemia, in the tissue of the retina causes diseases such as diabetic retinopathy, retinal vascular occlusion and retinopathy of prematurity. These diseases affect a large and diverse population of patients, including approximately 14,000 premature infants who develop some degree of retinopathy of prematurity out of the 3.9 million premature infants born in the U.S. each year. After a period of retinal ischemia, often the result is irreversible vision loss due to the development and growth of abnormal new vessels. This process is referred as retinal neovascularization. At present, therapies for ischemic retinopathy mainly target retinal neovascularization, and the treatments are limited, not always effective, have considerable side effects, and are expensive. Dr. Zhang's goal is to develop a novel, effective and inexpensive approach to treat ischemic retinopathy.

In 2023, the Zhang lab explored the ER stress/PERK pathway in retinal neovascularization in a mouse model of ischemic retinopathy (OIR model) and found that phosphorylated PERK (p-PERK) was only upregulated during retinal ischemia but not immediately after vessel degeneration and p-PERK was mainly increased in the ganglion cell layer (GCL), inner nuclear layer (INL), and neovessels. Moreover, the team identified a novel role of Epac1 in mediating the injury of retinal inner neurons in ischemic retinopathy. Additionally, they studied five genes (Synpo, Upp1, Ch25h, Csrp1, Pfkp) that are likely involved in retinal neovascularization. The team determined the roles of these genes in angiogenesis using in vitro tube formation assay, but did not find any of them played a significant role in this process and therefore, did not further investigate their roles in retinal neovascularization in vivo.

Dr. Zhang published one manuscript in IOVS; presented three abstracts during the ISER February, 2023 conference and presented two abstracts ARVO's annual conference on May, 2023.



The Zhang lab at UTMB - Galveston.

Basic Research Projects

Milam A. Brantley, Jr., MD, PhD
Department of Ophthalmology & Visual Sciences
Vanderbilt University Medical Center
Nashville, TN

The Cellular Mechanisms By Which Arginine and Citrulline Promote Vision-Threatening Diabetic Retinopathy

The purpose of Dr. Brantley's project is to understand precisely how arginine and citrulline, two essential amino acids, alter the cells in the retina that are specifically involved in Diabetic Retinopathy (DR). His research aim is to determine exactly how arginine and citrulline function in retinal endothelial cells to cause retinopathy, and how they may be used to modify current treatments for DR. These studies will help to develop new ways of treating, or even preventing, diabetic retinopathy.

Dr. Brantley's progress in 2023 is based upon previous years' data, which showed that citrulline and arginine induce an angiogenic response in retinal endothelial cells by activating eNOS, an essential mediator of retinal angiogenesis, to produce nitric oxide (NO) with no effect on arginase activity. Additionally, Dr. Brantley demonstrated that inhibiting eNOS blocks citrulline and arginine-induced angiogenesis. His team showed that citrulline and arginine phosphorylate eNOS-activating signaling molecules AMPK and Akt, with a manuscript of partial data in revision at *Investigative Ophthalmology and Visual Science (IVOS)*. His team further demonstrated that citrulline and arginine activate signaling molecules downstream of VEGFR in the VEGF signaling pathway, that AMPK inhibition blocks citrulline and arginine-induced angiogenesis without limiting NO production, and that citrulline plus arginine does not increase protein or gene expression of transporters LAT1 or CAT1.

Jianhai Du, PhD
Department of Ophthalmology and Visual Sciences
West Virginia University School of Medicine
Morgantown, WV

Target NAD Degradation in Age-related Macular Degeneration

Dr. Du's project aims to study how NAD+ , a critical molecule controlling metabolism, breaks down in both healthy and diseased retina and retinal pigment epithelium (RPE). Dr. Du wants to understand if stopping this breakdown can protect the retina from degeneration.

Significant progress was made in the initial year of this new area of research. Dr. Du found that NAD+ primarily breaks down in the RPE layer in both mice and humans and that this process differs by gender. Dr. Du's laboratory also developed methods to quantify the metabolic flux of NAD+ breakdown in vivo in mice. By deleting CD38, a key enzyme in NAD+ breakdown, the team was able to increase the levels of NAD+, NADH, NADPH, glutathione and ATP in the RPE. Furthermore, deleting CD38 protects oxidative damage and glial activation in the the AMD-like mouse model suggests that targeting NAD+ degradation could be a promising approach. Dr. Du's findings were presented at the ISER 2023 conference and he published two papers related to this project in the scientific journals, *Investigative Ophthalmology and Visual Science (IVOS)* and the *Journal of Biological Chemistry (JBC).*

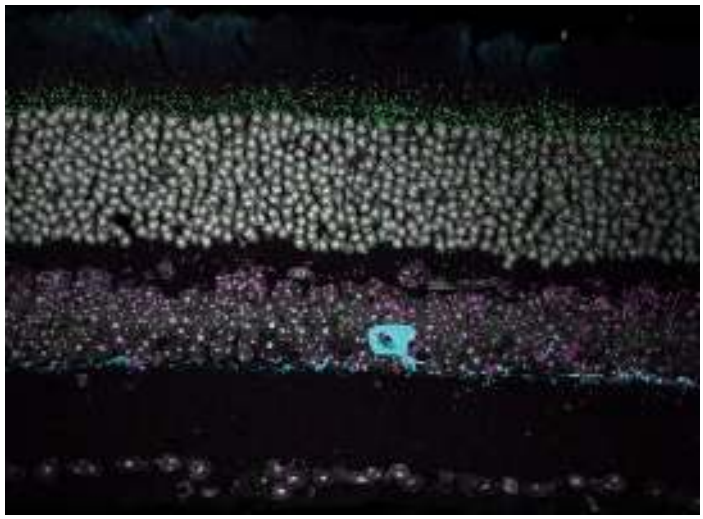
Dr. Du and members of his lab.

Erika D. Eggers, PhD
Department of Physiology & Biomedical Engineering
University of Arizona
Tucson, AZ

Investigation and Modulation of Inner Retinal Dysfunction in Diabetes

Visual deficits in the function of dim light-activated rod pathways are some of the earliest identifiable retinal problems experienced by diabetic patients. Electrical recordings from retinas show dysfunction in the inner retina and these deficits are tied to the development of serious diabetic retinal problems. Dr. Eggers has shown that deficits in the light response of neurons in the inner retina, which are part of the dim light rod pathway, are not due to cell death, but to some unknown mechanism. Dopamine, a neurotransmitter and hormone, is released by dopaminergic amacrine cells to allow the retina to adapt to increasing levels of background light. Diabetic retinas have been found to have low dopamine levels, and perhaps, supplementation of dopamine can reduce inner retinal deficits in diabetes. Drawing from her extensive expertise in rod pathway signaling for this project, Dr. Eggers will determine if this pathway is specifically vulnerable to diabetic damage and identify the mechanism of dysfunction in order to develop targeted therapeutics for prevention of the neuronal progression of vision loss.

In 2023, using the *in vitro electroretinogram (*ERG), Dr. Eggers' team completed studies showing that both dopamine D1 and D4 receptors are less sensitive in the diabetic retina, with the resulting data presented at ARVO and the abstract published in *Investigative Ophthalmology and Vision Science (IOVS)*. Additionally, the methodology for measuring dopamine release from the diabetic retina using HPLC-mass spectrometry was finalized and used to collect preliminary data that confirmed dopamine release is lower in the diabetic retina. Dr. Eggers' research also was published in the *2023 Annual Review of Vision Science*.



Diabetic mouse retina slice showing a dopaminergic amacrine cell (cyan), Drd 2 mRNA (magenta), Drd4 mRNA (green) and nuclei (white).

Francesco Giorgianni, PhD
Department of Pharmaceutical Sciences
University of Tennessee Health Science Center
Memphis, TN

CD5L-mediated Autophagocytosis in RPE Cells

Dr. Giorgianni has discovered that patients affected by age-related macular degeneration (AMD) have antibodies circulating in their blood that can attack and damage proteins present in the eye. One of these targeted proteins, CD5L, might be important for the removal of compounds that are toxic to the eye. Dr. Giorgianni's research project investigating the function of CD5L in the retinal pigment epithelium (RPE), as related to the development of age-related macular degeneration (AMD), has now completed its fourth year. He believes that CD5L carries toxic compounds, especially those derived from cholesterol, and facilitates their degradation, thus preventing their accumulation and damage to the RPE.

Dr. Giorgianni is working to prove that the presence of CD5L inside the RPE cells accelerates the degradation of a compound, derived from cholesterol, called OxLDL. He also will identify other proteins that combine with CD5L to degrade toxic OxLDL by leveraging analytical tools like the mass spectrometer that can identify and quantify proteins. These findings will expand the understanding of the cellular mechanisms that lead to AMD, and could provide new leads for the development of novel therapeutic strategies.

Dr. Sarka Beranova
Assoc. Prof. and co-investigator on Dr. Giorgianni's project.

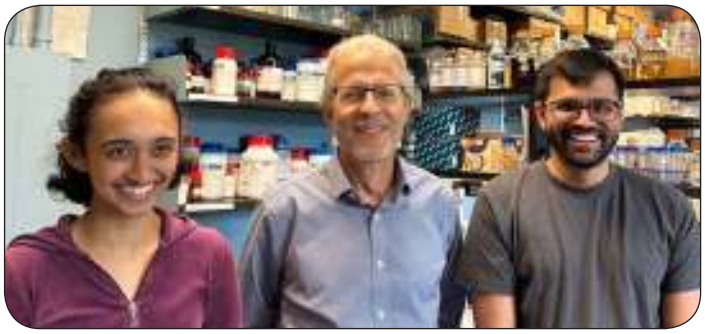
Andrius Kazlauskas, PhD
Departments of Ophthalmology and Visual Sciences, Physiology and Biophysics
University of Illinois Chicago
Chicago, IL

Hyperglycemia-induced Mitochondrial Adaptation

About one-third of people with diabetes have diabetic retinopathy (DR), a complication that can lead to blindness. DR usually appears many years after the onset of diabetes, eventually developing in 80% of people with either type 1 or type 2 diabetes. This is concerning, especially since DR is a major cause of blindness in working-age people, and thereby impacts productivity and increases healthcare costs. The number of people afflicted with DR is expected to rise with the ever-increasing number of individuals who develop diabetes. Dr. Kazlauskas refers to resilience to DR (RDR), which is the long delay from the onset of diabetes mellitus (DM) to the development of DR, is a well-known clinical phenomenon and exciting research opportunity because RDR is not well understood.

To explore the RDR phenomenon, Dr. Kazlauskas created mouse and human cell models of RDR. Using the mouse RDR model he found that diabetes instructs retinal blood vessels to engage a defense system against diabetes-driven death. As the duration of diabetes increases, this defense deteriorates and cells within the vasculature of the retina begin to die. Such blood vessels are dysfunctional and therefore unable to support the needs of the neural retina. The collective consequence of these changes is DR, the progressive accumulation of damage to the retina.

Dr. Kazlauskas used the cell-based model of RDR to investigate the nature of this defense system. His group discovered that elevated glucose (the hallmark of diabetes) not only damages cells within blood vessels, but also boosts their capacity to repair such damage. As long as the rate of repair exceeds the rate a damage, cells remain healthy in the face of high glucose. Ongoing research is focused on why the defense eventually fails. Such information will enable development of new therapeutic approaches to indefinitely delay the onset of DR. These findings were published in the June, 2023 issue of the *International Journal of Molecular Science*.

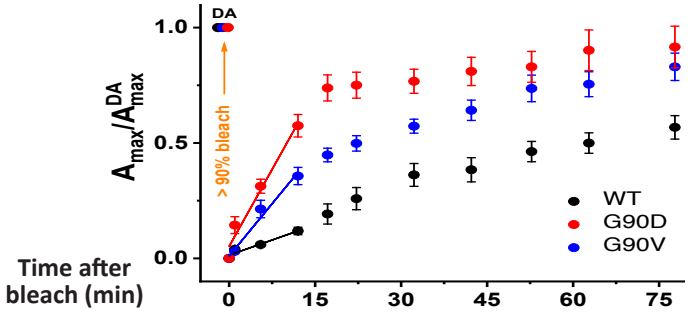


Members of the Kazlauskas lab who are supported by RRF. From left: Trupti Potdukhe, MS (PhD graduate student), Andrius Kazlauskas, PhD, Manav Gandhi, MS (PhD graduate student).

Vladimir Kefalov, PhD
Department of Ophthalmology
University of California, Irvine
Irving, California

Understanding How the G90D and G90V Rhodopsin Mutations Cause Blindness

The purpose of Dr. Kefalov's project is to identify the molecular mechanism by which two similar mutations in the visual pigment rhodopsin, Glycine 90 to Aspartate (G90D) and Glycine 90 to Valine (G90V), cause distinct visual disorders. Initial studies found that the G90D and G90V mutations altered distinctly the stability of metarhodopsin, resulting in very different Meta II decay rates for the two mutants. To investigate the functional significance of this altered rhodopsin stability and decay, the Kefalov team investigated the kinetics of rod dark adaptation of WT, G90D and G90V homozygous mice using in vivo ERG recordings. Following a >90% bleach, the amplitude of rod a-wave recovered to 50% of its pre-bleached level in 63 min for WT rods; 22 min for G90V rods; and 10 min for G90D rods. Thus, both mutations greatly accelerate the regeneration of rhodopsin in vivo, while also producing phenotypes distinct from each other. This accelerated dark adaptation indicates a higher-than-normal phototoxicity in the mutant rods, and might help explain their progressive degeneration, which perhaps surprisingly appears to be more severe in the G90D compared to the G90V rods.



Accelerated rod dark adaptation in rhodopsin G90 mutant mice *in vivo*. Recovery of averaged (mean ± SEM) normalized scotopic ERG maximal a-wave amplitudes (A_{max}) in the dark after bleaching > 90% of rhodopsin in WT (n = 8), G90D (n = 13), and G90V (n = 12) mutant mice. Initial rates of the recovery determined from linear fits yielded 0.009 min^{-1} (WT), 0.044 min^{-1} (G90D), and 0.030 min^{-1} (G90V).

James Monaghan, PhD
Biology Department
Northeastern University
Boston, MA

Stem Cell Fate Determination During Axolotl Retina Regeneration

Dr. Monaghan researches the Mexican axolotl salamander to understand the molecular mechanisms that drive axolotl regeneration of retinal cells. Mammalian retinas do not regenerate. Greater knowledge of the unique mechanisms the axolotl uses that enable this regeneration may ultimately lead to strategies for the restoration and replacement of damaged or missing human retinal cells and tissues.

Previously, using the model of complete retinectomy, Dr. Monaghan's lab described the histology of retina regeneration, completed the first transcriptomic analysis and multiplexed imaging of gene expression, and confirmed that the Notch signaling pathway plays a critical role in retina regeneration. The next phase of the project that is currently underway is to expand this knowledge to study multiple injury types, including chemical injury and optic nerve transection, to identify unique stem cell sources that drive regeneration and compare their findings to their previous discoveries.

Dr. Monaghan's grant supported the work of a first-year graduate student, Nicole Calder. She will continue to work on this project throughout her PhD studies.

Ann C. Morris, PhD
Department of Biology
University of Kentucky
Lexington, KY

Retinal Damage and Regeneration in the African Spiny Mouse (Acomys cahirinus): A Novel Mammalian Model for Translational Research

It is commonly believed that the ability to regenerate neurons in vertebrates is an exclusive property of non-mammalian species such as fish and amphibians. However, in recent years, spiny mice (Acomys) have become the focus of intense research for their enhanced wound repair and regenerative ability in many tissues, raising the question of whether these mammals might regenerate retinal neurons in response to damage. The purpose of Dr. Morris' project is to test the hypothesis that the spiny mouse possesses the capacity to regenerate retinal neurons in response to damage, and to take the first steps in determining the underlying biological mechanism -- this would be the first demonstration of natural regenerative ability in the retina of any mammal.

In 2023, Dr. Morris and her team further explored how the spiny mouse (Acomys) retina responds differently to acute injury compared to the common laboratory mouse (Mus). Data indicates that although there is an increase in inflammation in both species just after injury, in the spiny mouse this does not lead to fibrotic scarring in the retina as it does in Mus. Dr. Morris hypothesizes that this is due to differences in signaling from the retinal microglia, which promote an environment permissive for regeneration in Acomys but not in Mus. Dr. Morris also discovered that there is a second wave of cell proliferation in the spiny mouse retina after damage that is associated with the recovery of the lost retinal neurons.

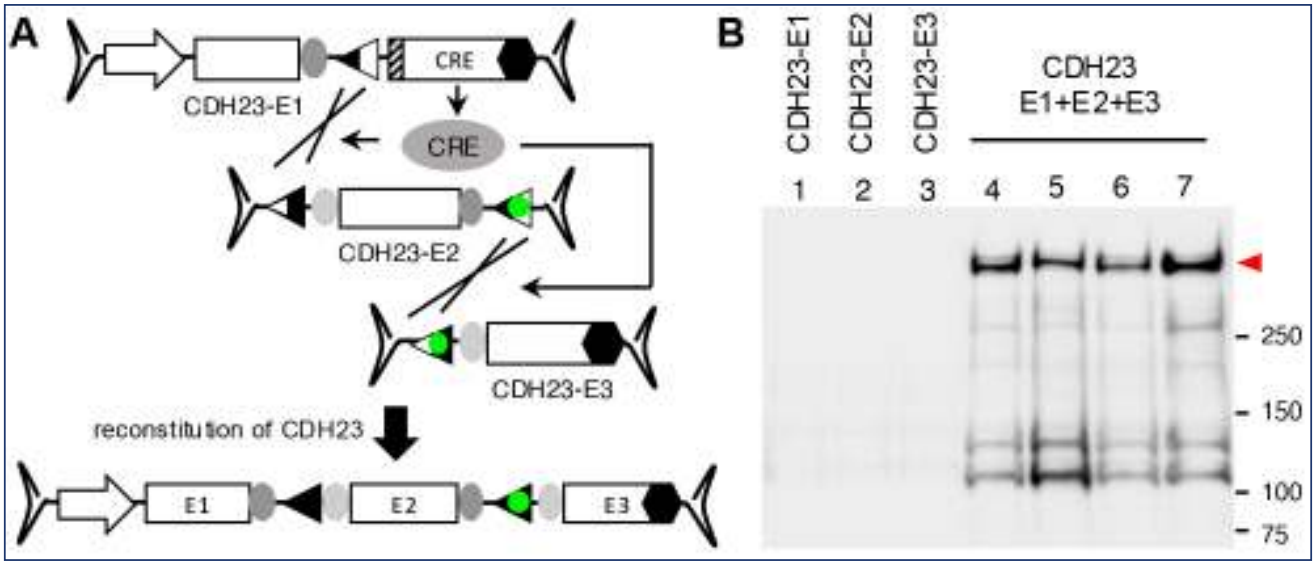
Two graduate students working on Dr. Morris' project: Jess Bills and Dara Buendia Castillo, and their favorite model organism, the spiny mouse.

Seongjin Seo, PhD
Department of Ophthalmology and Visual Sciences
Institute for Vision Research Center, University of Iowa
Iowa City, IA

Novel Dual AAV Approaches to Treat ABCA4-associated Retinal Degeneration

The ultimate goal of Dr. Seo's research is to develop highly efficient, adeno-associated virus (AAV)-based large gene delivery systems for retinal gene therapy. While AAV is a safe and efficient gene delivery vehicle, its main drawback is the limited packaging capacity. In 2023, Dr. Seo focused on developing gene therapy vectors to treat ABCA4-associated retinal degeneration, responsible for 95% of the incidence of Stargardt disease, the most common inherited retinal disease, and PCDH15 (USH1F) and CDH23 (USH1D) associated with Usher Syndrome. Dr. Seo established three approaches to deliver large genes using AAV and compared their reconstitution efficiencies in cultured mammalian cells for ABCA4 gene therapy vectors. One approach utilizes gp41 split intein-mediated protein trans-splicing to re-join protein fragments. The second approach utilizes a pair of high-affinity polypeptides (SpyTag and SpyCatcher) that form a covalent bond upon binding. The third uses the CRE/lox DNA recombination system to facilitate the reconstitution of therapeutic genes.

Following Dr. Seo's preliminary study in Abca4 knockout rats, he opted for the protein-level reconstitution methods for ABCA4. Dr. Seo also identified two distinct phenotypes in Abca4 knockout rats, which serve as valuable indicators for evaluating the therapeutic efficacies of the gene therapy vectors. Furthermore, the team created gene therapy vectors for USH1D and USH1F utilizing these three approaches. After assessing the reconstitution efficiencies in 293T cells, Dr. Seo determined that the CRE/lox-mediated DNA reconstitution system is the most efficient choice for these genes.



CRE-lox-mediated reconstitution of *CDH23* delivered via tripartite AAV vectors.
(A) Schematic representation: The 10,065-bp *CDH23* DNA sequence is divided into three segments (E1, E2, and E3) and delivered to target cells using tripartite AAV-*CDH23* vectors. CRE recombinase facilitates the reconstitution of the full-length *CDH23* in treated cells.

(B) Experimental validation: Tripartite AAV-*CDH23* vectors were administered to mouse eyes, and full-length CDH23 protein production was confirmed by immunoblotting. The red arrowhead indicates the full-length CDH23 proteins, produced only when all three AAV vectors were co-delivered. Each lane corresponds to an individual eye, with protein size markers displayed on the right.

Ming Zhang, MD, PhD
Department of Cellular Biology & Anatomy
Medical College of Georgia, Augusta University
Augusta, GA

The Roles of RIP Kinase 3 in the Development of AMD-like Pathologies During Cytomegalovirus Ocular Latency

Dr. Zhang's research seeks understanding of the underlying causes that contribute to the development of AMD, which remain uncertain but are highly correlated with cell immunological/inflammatory mechanisms in the various tissue layers of the retina. *Receptor-interacting protein (RIP) kinases* have been identified as modulators of inflammatory responses and play an important role in these tissues' specific innate immunity, autophagy and death-inducing processes. Dr. Zhang's studies are the first to explore a possible viral cause of AMD occurring as a result of an inactive, past ocular viral infection.

In 2023, Dr. Zhang tested the hypotheses that RIP3 contributes to the death and/or degeneration of ocular cells/tissues and development of AMD–like pathologies via the production of inflammatory factors, activation of cell death pathways, and via cross-talk among cell death, autophagy and LC3-associated phagocytosis (LAP) using mouse models of murine cytomegalovirus (MCMV) ocular latency.

His studies significantly show that latent ocular MCMV infection, as a result of systemic neonatal MCMV infection, is associated with development of retinal and choroidal pathologies with some features of human-AMD, upregulation of immune and inflammatory responses and downregulation of multiple neuroretinal signaling pathways. RIP3 related cell death signaling pathways are also activated and contribute to the degeneration of photoreceptors, RPE, and choroidal capillaries. A manuscript based on these results was published in March, 2023 in the International Journal of Molecular Science.

Further, although MCMV DNA and mRNA transcripts of several MCMV latency-related genes were detected in eyes and extraocular tissues of both RIP3+/+ and RIP3-/- mice at both 12 and 18 months following systemic neonatal MCMV, the mean retinal thickness was significantly lower in eyes of latently infected RIP3-/- mice, compared to eyes of latently infected RIP3+/+ mice. Retinal thickness is used as a measure of disease activity.

Dr. Zhang's specific MCMV animal models now extend for six generations ensuring his team can feel confident that their results are due to the genetic variables being specifically targeted and not some other cause.

Dr. Jinxian Xu, a post-doctoral research fellow from the Zhang lab, is examining the age-related macular degereration (AMD) like pathologies is an animal model of cytomegalovirus ocular latency using Envisu R2210 optical coherence tomography (SD-OCT) retinal imaging system

Basic Research Projects Receiving Initial Funding in 2023

Kinga Bujakowska, PhD
Ocular Genomics Institute
Massachusetts Eye and Ear Infirmary, Harvard Medical School
Boston, MA

Modeling EYS Associated Retinitis Pigmentosa in Human iPSC Derived Retinal Organoids

Mutations in the Eyes Shut Drosophila homolog *(EYS)* gene are the leading cause of retinitis pigmentosa (RP) in Asia and one of the five most mutated RP genes in the U.S. and Europe. Despite the high prevalence of this disease, little is known about the role of EYS in the retina and the molecular mechanism of the EYS-associated disease. To address this knowledge gap, Dr. Bujakowska is using CRISPR-Cas9 genome editing to establish human induced pluripotent stem cell (iPSC) lines harboring EYS frame shift mutations, thus yielding EYS knockout (EYS KO) cellular models and subsequently, Dr. Bujakowska also used CRISPR-Cas9 genome editing to establish iPSC lines harboring bi-allelic *EYS* frame shift mutations, thus yielding EYS knockout (EYS KO) cellular models to study the pathophysiology of the EYS - associated disease. Her team is in the process of retinal organiod (RO) differentiation from these engineered iPSC lines to study the pathophysiology of the EYS-associated disease.

In 2023, Dr. Bujakowska's laboratory established a robust RO differentiation protocol from human iPSCs. The team used the ROs to study expression and localization of EYS and different stages of development. The principal objective was to elucidate the precise subcellular localization of EYS within retinal organoids and compare it to the native placement in the human retina. Findings from this study were presented in a poster titled "EYS Expression in Human iPSC-Derived Retinal Organoids" at ARVO's 2023 conference.

Dr. Kinga Bujakowska (center) and lab members.

Jeffrey M. Gross, PhD
Department of Molecular Biosciences
University of Texas at Austin
Austin, TX

A Proteomic Analysis of Mitochondria-ER Contact Sites in Muller glia and the Potential Role of Metabolomic Changes in Regulating Intrinsic Retinal Regeneration

The overarching goal of Dr. Gross' research is to understand the molecular underpinnings of Muller glia-dependent retinal regeneration. In the 2023 grant period, the Gross laboratory focused on a previously unexplored aspect of the regenerative process – how metabolic changes facilitate Muller glia activation, reprogramming and regenerative responses, specifically how changes in mitochondria-ER contact sites in Muller glia regulate pro-regenerative responses.

Dr. Gross hypothesizes that mitochondria-ER contact sites change during the injury and regenerative response in Muller glia and that this plays a critical role in retinal regeneration.

His experiments utilize innovative and state-of-the-art transgenic and proteomic techniques to identify changes in the protein composition of mitochondria-ER contact sites during the injury and regenerative responses. His results will be significant because the proteins and metabolites identified may potentially serve as foundations for the development of new therapeutic approaches aimed at stimulating intrinsic regeneration in the retina. Dr. Gross' preliminary data identified enriched proteins associated with Muller glia reactivity and metabolic activity in injury-responsive samples. In parallel, using RNA-sequencing of the same Muller glia populations, transcripts encoding proteins that function to during metabolism or to modulate metabolic processes were the most significantly upregulated in injury-responsive Muller glia. These data strongly support the hypothesis that retinal injury modulates metabolic activity in Muller glia.

Alex J. Smith, PhD
Department of Ophthalmology
University of California San Francisco
San Francisco, CA

Measuring Fluid Clearance Pathways in Retinal Edema

Retinal edema is a serious condition that can distort vision and if left untreated, can cause blindness. To better understand the causes underlying this condition, Dr. Smith's proposes to apply novel imaging techniques, which were developed in his laboratory, to measuring brain fluid transport to the retina. These techniques will be used to measure the routes of fluid clearance from the retina and to determine if there are specific structural barriers to clearance. Specifically, Dr. Smith is testing to determine if the water channel protein, aquaporin-4 regulates fluid clearance in a mouse model of diabetic retinal edema, since aquaporin-4, is thought to be important for fluid clearance from the brain. Results of these experiments will identify new pathways and molecular targets for therapeutics designed to accelerate retinal fluid clearance.

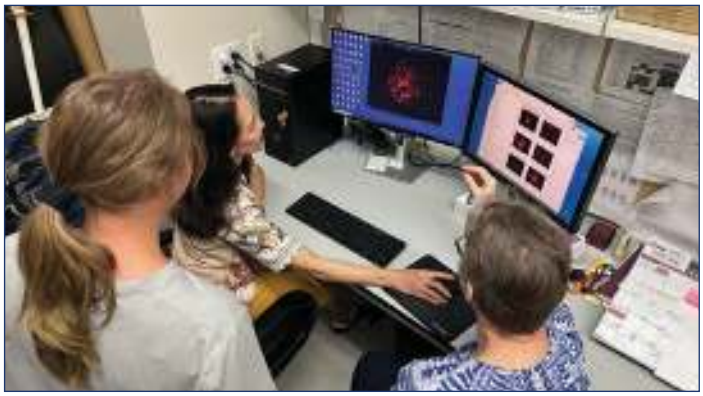
In 2023, Dr. Smith demonstrated that spaces surrounding blood vessels in the retina play a key role in removing fluid from the retina and that these spaces connect the central regions of the retina with the surface. Dr. Smith did not find evidence for a role of the glial water transporter aquaporin-4 in regulating fluid transport along these pathways in the healthy eye, and his team is currently completing studies to determine if aquaporin-4 regulates fluid movement in the diabetic eye. Dr. Smith's findings were published in the journal, *Fluids and Barriers of the CNS*.

Christine M. Sorenson, PhD
Department of Pediatrics
University of Wisconsin School of Medicine and Public Health
Madison, WI

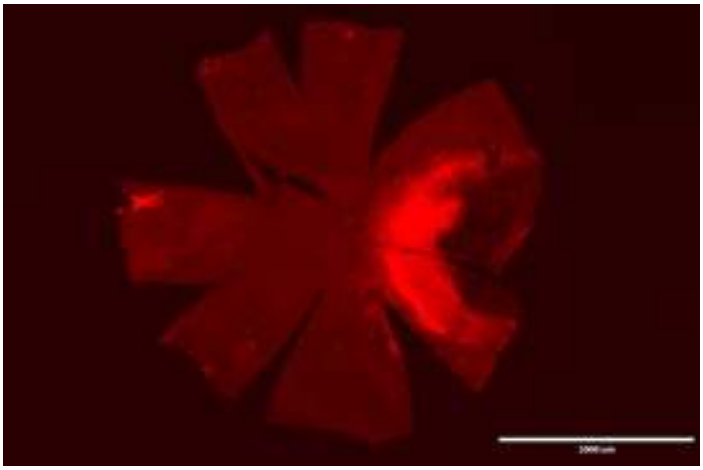
Treatment and Prevention of PVR and Retinal Detachment

The purpose of Dr. Sorenson's project is to improve vision outcomes for proliferative vitreoretinopathy (PVR) patients by preventing or decreasing scar formation.

Retinal detachment (RD) is a vision-threatening condition that requires surgical treatment. RD is accompanied by inflammation that can lead to PVR in up to 20% of patients. Since unchecked inflammation is a driving force in PVR, removal of unhelpful cells that fuel inflammation would be an important treatment in RD patients. Dr. Sorenson's laboratory studies Bcl-2, a protein that prevents cells from dying. Increased Bcl-2 activity can cause cells to live longer than they should, contributing to persistent inflammation, new vessel growth and scarring. The innovation of her project is that it investigates whether increasing the clearance of cells that enhance inflammation, by decreasing Bcl-2 activity, improves vision outcomes for PVR patients by decreasing or reversing scar formation. A better understanding of the critical role Bcl-2 plays in this process may lead to treatments to decrease scar formation and reverse the scars that have already formed for PVR and other eye diseases where scar formation is a major problem.



Dr. Sorenson with lab members Kelsey Johnson and Yayuk Darjatmoko.



Retinal detachment (RD) is a vision threatening condition that requires surgical treatment. RD is accompanied by inflammation that can lead to proliferative vitreoretinopathy (PVR). Here we used a mouse model of PVR to examine scar formation in the retina. The dark red areas are the scarred area in the retina.

Eric Weh, PhD
Department of Ophthalmology
and Visual Sciences
University of Michigan
Ann Arbor, MI

Developing a Novel Treatment to Prevent Vision Loss due to Recurrent Retinal Toxoplasmosis

Vision loss due to infection with the common *Toxoplasma gondii* (*Tg*) parasite is a result of ocular toxoplasmosis. People can get the infection from eating raw or undercooked meat, unpasteurized dairy products, or contaminated vegetables. People can also contract this infection after handling contaminated soil or cat litter without washing their hands before eating. The infection can also be transmitted from mother to baby during pregnancy. Fortunately, most patients with a normal immune system do not require medical treatment. Unfortunately, a fraction of patients will develop ocular toxoplasmosis causing vision loss. Even worse, the disease tends to progress with time as the infection will spontaneously resolve and then recur, further eroding vision. Some patients are at a higher risk of recurrent ocular toxoplasmosis, including those who are older than 40, patients in whom both eyes are affected, patients born with congenital toxoplasmosis, patients whose central vision is affected or patients with large disease lesions. There are currently no treatments available to prevent the recurrence of ocular toxoplasmosis, which means that patients with this disease are likely to continue to experience worsening vision.

Dr. Vernon Carruthers

To help identify promising new therapies to prevent recurrence of ocular toxoplasmosis, Dr. Weh has teamed up with Dr. Vernon Carruthers at the University of Michigan to develop and test new drugs that can selectively kill *Tg* parasites and prevent disease. Previous work by Dr. Carruthers has identified a new protein target that is critical for *Tg* parasite survival during long-term infection. Dr. Carruthers and Dr. Weh have been working together to design and test drugs that can be injected directly into the eye to kill *Tg* parasites at the site of infection. This method, called intra vitreal injection, is used daily in ophthalmology clinics to treat diseases such as Age-related Macular Degeneration (AMD). By killing the *Tg* parasites in the eye when ocular toxoplasmosis occurs, Dr. Weh and Dr. Carruthers believe they will be able to prevent patients from experiencing recurring ocular toxoplasmosis and preserve their vision.

Throughout 2023, Dr. Weh was able to test several candidate drugs for toxicity to the eye. All the compounds tested were found to be safe for the eye, which is a critical step in advancing this novel therapeutic strategy. Dr. Weh, in collaboration with Dr. Carruthers, tested three different compounds in the first characterized mouse model of ocular toxoplasmosis to determine if they could kill parasites following intra vitreal injection. Their results in some cases show a promising trend towards a decrease in the number of parasites remaining in the eye after injection, indicating that targeting the Cathepsin L protein is a viable strategy for preventing vision loss. These studies have laid the groundwork for identifying the properties of drugs targeting Cathepsin L which are important for killing *Tg* parasites. Dr. Weh and Dr. Carruthers are continuing their work to design and develop more potent version of these drugs to more robustly target the Cathepsin L protein to eradicate ocular toxoplasmosis.

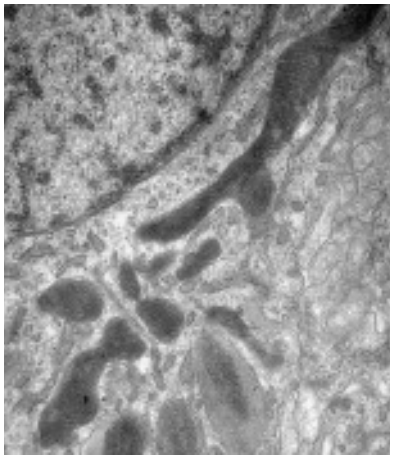
Weh lab from left: Pariyamon (Pha) Thaprawat, Heather Hager, MS, Tracey L. Schultz, Dr. Eric Weh.

David Wu, MD, PhD
Mass Eye and Ear / Schepens Eye Research Institute
Department of Ophthalmology
Harvard Medical School
Boston, MA

Lactate and Its Role in RPE Mitochondrial Function

Dr. Wu seeks to understand how the retinal pigment epithelium (RPE), the cell type in the eye central to the pathology of age-related macular degeneration (AMD), becomes more vulnerable to damage as the metabolism of the eye changes with age.

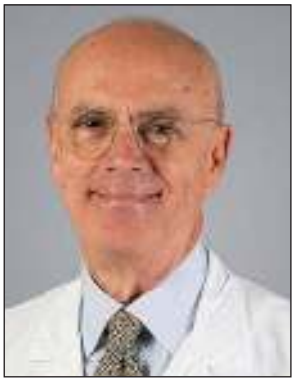
During 2023, Dr. Wu was able to initiate the study of a specialized model of RPE – the iPSC-RPE (induced pluripotent stem cell) in his laboratory. This important model has the advantages of being able to be grown from a specific patient, thus incorporating the patient's own intrinsic background genetic risks into research for the causes of retinal disease. Dr. Wu's team learned that a normal metabolite that may decline with aging – lactate – may play a central role in modulating the function of the mitochondria of the RPE. The mitochondria are the cell's "energy factories," and disturbances in their function is known to occur as part of the progression of AMD worsens. Dr. Wu is studying how lactate can modulate the structure, numbers, and energy production capacity of the mitochondria. This is important because better mitochondria function leads to a healthier cell. Studying this in cells derived from patients may allow us to have a better understanding of the disease in individuals, and identify new therapies that reduce the rate of progression of AMD.



A high magnification (30,000x) transmission electron microscope image of an iPSC-RPE cell showing the mitochondrial powerplants as well as the adjacent organelles (nucleus, endoplasmic reticulum, and pigment granules). Dr. Wu is studying the ultrastructure of the mitochondrial for clues on how AMD progresses.

Macular Society Grant Recipient

The RRF Margaret and Mills Cox Macula Society Research Project



Francesco Bandello, MD
Department of Ophthalmology
University Vita-Salute, Ospedale San Raffaele
Milan, Italy

From Diagnostics to Prognosis and Response Prediction: Integrating Imaging with Genetics in Patients with Retinal Vein Occlusion

Francesco Bandello is Professor and Chairman of the Department of Ophthalmology at the University VitaSalute, Milan, Italy. He is a member of the Academia Ophthalmologica Internationalis and the Vice President of Academia Ophthalmologica Europea. He has been a peer reviewer for National Institutes of Health grant applications. Professor Bandello's scientific interests include the study of new therapeutic agents for the inhibition of angiogenesis in cases of proliferative diabetic retinopathy and age-related macular degeneration (AMD), biomarkers in AMD, and the correlation between systemic and ophthalmic vascular diseases. He is also interested in the application of medical robotics and bioengineering for study of the retina and cardiovascular disease, and use in surgical technique training to improve surgical precision and performance leading to improved patient safety.

Professor Bandello has been the principal investigator in several clinical trials concerning diabetic retinopathy and AMD. He is co-author of nine books and has published 651 articles in journals listed on PubMed relating to retinal diseases, diabetic retinopathy, AMD, and fluorescein and indocyanine green angiographies of different retinal vascular disorders. Dr. Bandello will share his research project findings at the 2025 annual meeting of the Macula Society.

The academic chairs and professorships that RRF supports are located at nationally recognized vision research institutions in Houston, Texas, and Madison, Wisconsin. Often in collaboration with fellow researchers in related academic disciplines, these scientists conduct their own original retina research, with the potential to dramatically increase the understanding of the retina and/or retinal diseases, while also supervising departmental programs that provide research opportunities for young vision scientists and students to pursue their interests and to receive academic training within established investigative laboratories.

RRF Research Chair

Nader Sheibani, PhD
Department of Ophthalmology
and Visual Sciences
University of Wisconsin
Madison, WI

Pathophysiology of Eye Diseases with Neovascularization

Dr. Sheibani showed that vitamin D receptor regulates the angioinflammatory phenotype of retinal endothelial cells. His team found CYP1B1 expression in retinal endothelial cells is vital in regulating iron levels, whose deficiency results in increased iron levels and oxidative stress. Adenosine

The Sheibani lab at University of Wisconsin - Madison

receptors are important regulators of inflammatory and neurodegenerative processes. They showed these receptors are expressed in eyes with both wet and dry AMD, whose changes could contribute to AMD. Dr. Sheibani was involved with investigating the role of inflammatory processes in diabetic retinopathy. His team showed artesunate mitigates choroidal neovascularization in mice. Using network analysis and deep learning techniques, they reported a molecular network for detection and treatment of AMD. They reviewed the role of mast cells in AMD. *Reported in: Cells (Jan 23), Int J Mol Sci (Jan 23), J Ophthalmic Vis Res (Feb 23), Diabetologia (Nov 23), Exp Eye Res (Nov 23), Pharmaceuticals (Nov 23), Cells (Dec 23).*

Walter H. Helmerich Chair

Kevin W. Eliceiri, PhD
Associate Director, McPherson
Eye Research Institute
Departments of Medical Physics
and Biomedical Engineering
University of Wisconsin
Madison, WI

Open Source Computational Imaging of Cellular Microenvironments

Dr. Eliceiri's research interests are in the areas of developing open source optical and computational approaches to non-invasively study dynamic cellular processes like those in the eye. His current research focuses on the development of novel optical imaging methods and instrumentation for investigating the cellular microenvironment, and the development of open-source software for multidimensional imaging informatics. Specific interests include developing label free optical approaches for deeper imaging and sensing of the cellular microenvironment, new technologies for metabolic imaging, as well as technologies for multi-scale and multimodal imaging. Recently, his group has been collaborating with computer scientists on deep learning approaches for smart imaging of cellular metabolism. As well his group is very engaged in community building efforts such as BioImaging North America, which tries to build and bridge imaging expertise across Canada, Mexico and the U.S.

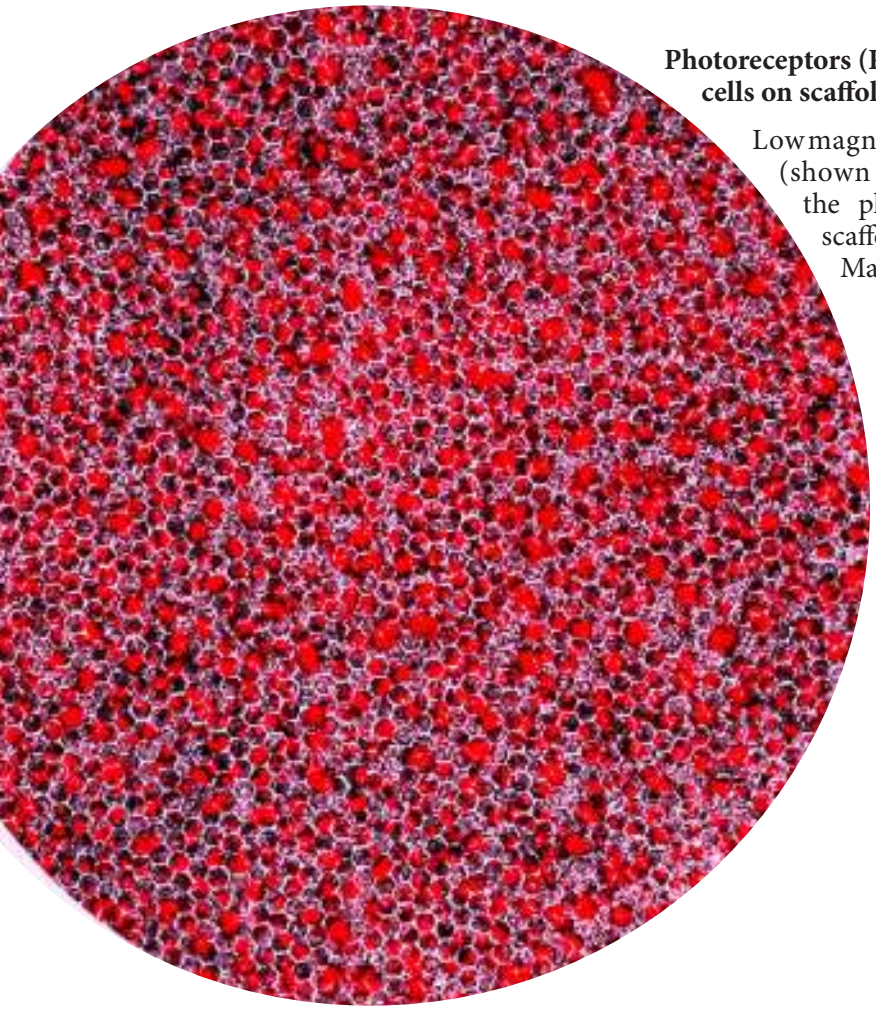
Dr. Eliceiri, seventh from left, at the C-MITIE retreat. Dr. Eliceiri is a member of the leadership team for C-MITIE's quantitative imaging efforts.

Emmett A. Humble Distinguished Directorship

David M. Gamm, MD, PhD
Director, McPherson Eye Research Institute
Department of Ophthalmology and Visual Sciences
University of Wisconsin
Madison, WI

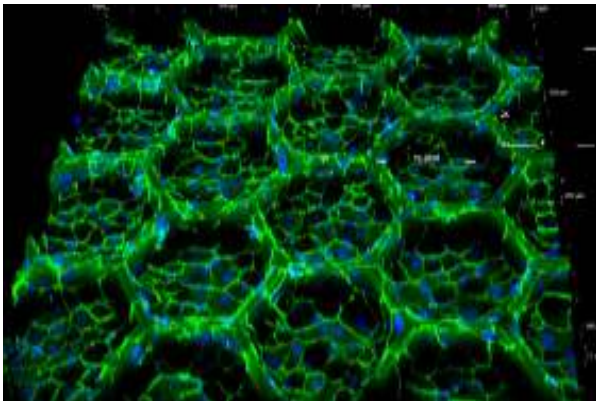
Modeling and Treating Retinal Disease with Human Induced Pluripotent Stem Cells (hiPSCs)

Dr. Gamm employs hiPSC technology to generate retinal organoids, which he uses to model human retinal diseases and develop gene- and cell-based therapies. In 2023, his lab expanded its collaborative studies on Leber congenital amaurosis, Best vitelliform macular dystrophy, and multiple types of retinitis pigmentosa, with the goal of advancing gene augmentation and editing therapies to treat these conditions. In conjunction with Dr. Chris Ahern at the University of Iowa, they also tested promising new technologies to overcome "nonsense" gene mutations, which cause a large percentage of inherited retinal conditions. Lastly, Dr. Gamm and other scientists at UW-Madison published a paper describing a novel, biodegradable scaffold that can accurately and reproducibly deliver hiPSC-derived photoreceptors or photoreceptors plus RPE cells to the subretinal space in an effort to replace cells lost in late stage retinal degenerative diseases.



Photoreceptors (PRs) and Retinal Pigment Epithelium (RPE) cells on scaffold:

Low magnification image of human iPSC-derived photoreceptors (shown in red) and RPE cells (darkly pigmented cells beneath the photoreceptors) grown together on the "honeycomb" scaffold shown in the accompanying image. Lee, Xie, Luz-Madrigal et al. *Bioactive Materials* 2023.



RPE on scaffold:

High magnification image of human iPSC-derived RPE cells (outlined in green) grown on a biodegradable, biocompatible, scaffold with a "honeycomb" design. Lee, Xie, Luz-Madrigal et al. *Bioactive Materials* 2023.

Kathryn and Latimer Murfee Chair

Krishanu Saha, PhD
McPherson Eye Research Institute
Departments of Biomedical Engineering and Pediatrics
Wisconsin Institute for Discovery
University of Wisconsin
Madison, WI

Bioengineering of Novel Cell and Gene Therapies for the Retinal Disorders

In 2023, Dr. Saha's lab made significant strides in advancing CRISPR-based therapies for retinal diseases. The team successfully demonstrated the potential of non-viral CRISPR-Cas9 delivery systems to target and correct genetic mutations through base editing. Additionally, genome-wide screening identified several new genes affecting correction efficiency. They also engineered genome editors controllable by an approved drug. We have engaged the FDA on a platform approach to CRISPR drugs, collaborating with the NIH Somatic Cell Genome Editing Consortium. These breakthroughs, published in high-impact journals and presented at conferences, bring us closer to developing effective treatments for inherited retinal disorders.

Dr. Saha and research team in the laboratory.

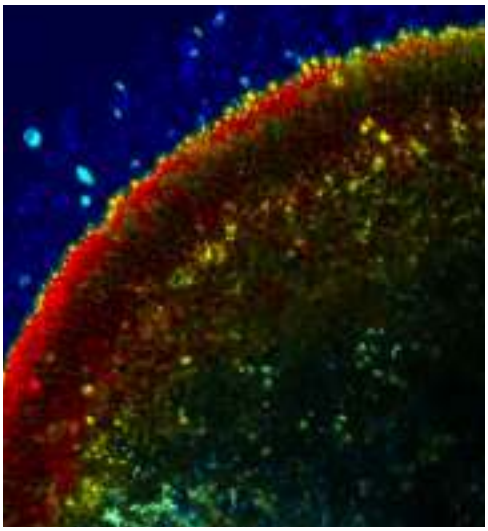
Daniel M. Albert Chair

Melissa Skala, PhD
McPherson Eye Research Institute
Morgridge Institute for Research
Department of Biomedical Engineering
University of Wisconsin
Madison, WI

Molecular Imaging of Light Response in the Retina

Light response in the retina involves molecular changes in vitamin A compounds, known as retinoids. Dr. Skala's laboratory has developed an imaging technique to capture these molecular changes in stem-cell derived human photoreceptors in culture. Imaging was tested with light exposure in 3D retinal organoids to confirm molecular changes in retinoids with time. These imaging techniques rely on molecules already present in cells, so the native state of living cells can be observed. Therefore, the imaging techniques are attractive for monitoring photoreceptor function in drug development and regenerative medicine applications.

In 2023, Dr. Skala applied these imaging techniques to investigate off-target effects of gene editing therapies in the eye in collaboration with Dr. Kris Saha and Dr. David Gamm.



Upon light exposure, stem cell-derived retinal organoid photoreceptors convert all-trans retinaldehyde (AT-RAL) to all-trans retinol (AT-ROL). This fluorescence lifetime image shows AT-ROL (red) production in the photoreceptor inner segments and outer nuclear layer following light exposure, with AT-RAL (blue) in the outer segments. Image is ~500x500µm.

RRF Research Chair at Baylor College of Medicine, Houston, TX

Following the departure of vision researcher, Ching-Kang Jason Chen, PhD, at the end of 2022, a nationwide search for a candidate to hold the RRF Research Chair at Baylor College of Medicine is being conducted and was still ongoing at the end of 2023. Dr. Chen was the first recipient of the chair and held the position from 2013 to 2022.

Edwin and Dorothy Gamewell Professor

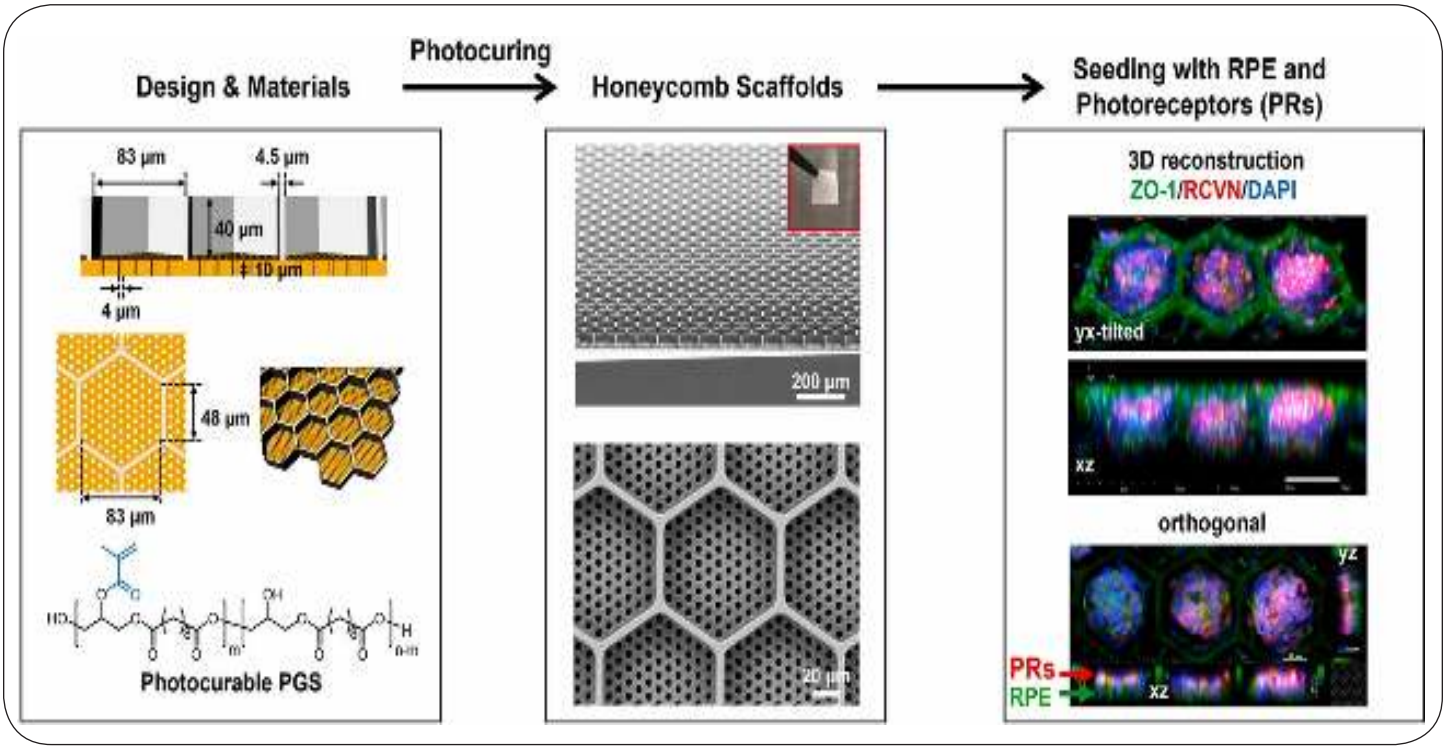
Shaoqin "Sarah" Gong, PhD
McPherson Eye Institute
Department of Ophthalmology and Visual Sciences
Wisconsin Institute for Discovery
University of Wisconsin
Madison, WI

Ocular Gene and Cell Therapy

Dr. Gong's lab focuses on the design, synthesis, and optimization of innovative biomaterials for a wide range of biomedical applications, with a particular emphasis on ocular gene therapy and cell therapy. In collaboration with the laboratories of Dr. David Gamm and Dr. Jack Ma, Dr. Gong has developed multiple generations of tissue engineering scaffolds specifically designed for the delivery of photoreceptors (PR) and/or retinal pigment epithelium (RPE) cells. These advanced scaffolds aim to provide a promising approach for treating blindness by facilitating the targeted delivery and integration of therapeutic cells into the retina.

Terri Young, MD, MBA; Sarah Gong, PhD; David Gamm, MD, PhD at Dr. Gong's Investiture Ceremony. Photo courtesy of UW - Madison

Micromolded honeycomb scaffold design to support the generation of a bilayered RPE and photoreceptor cell construct - ScienceDirect



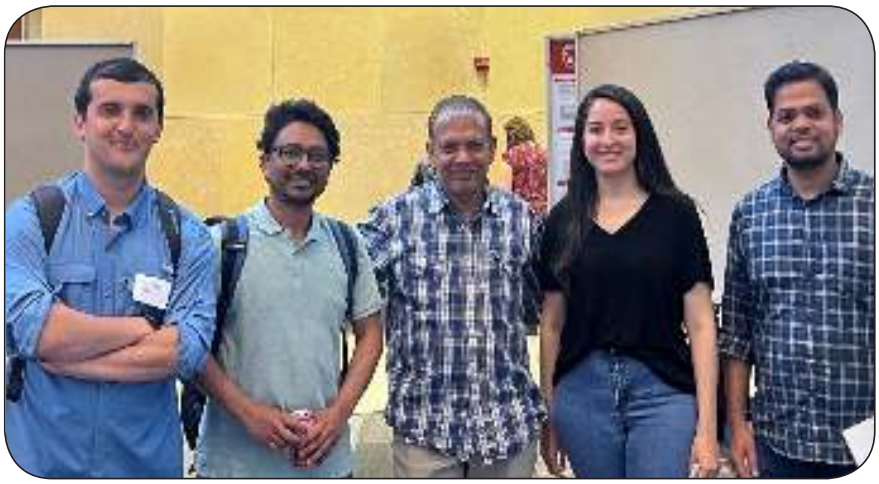
The honeycomb 3D-microstructured biodegradable scaffolds robustly support the seeding of human pluripotent stem cell-derived RPE and PRs, either separately or as a dual cell-layered construct. These advanced, cost-effective, and versatile scaffolds can significantly accelerate retinal cell transplantation efforts, offering great promise for the treatment of age-related macular degeneration and other retinal degenerative diseases.

M.D. Matthews Research Professor

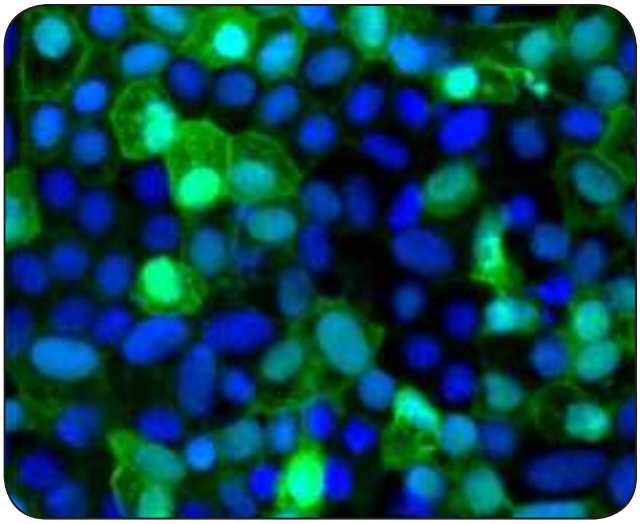
Bikash R. Pattnaik, PhD
McPherson Eye Research Institute
Department of Pediatrics, Ophthalmology and Visual Sciences
University of Wisconsin
Madison, WI

Treatment for Rare Diseases That Challenge Healthcare

Inherited retinal degeneration is a group of genetic disorders that cause progressive vision loss due to the degeneration of cells in the retina. Common forms of inherited retinal degeneration include retinitis pigmentosa, Leber Congenital Amaurosis (LCA), and Best Disease, which lead to severe visual impairment or blindness and can manifest from infancy to adulthood. Channelopathies are the ultrarare to rare forms of these disorders caused by defects in ion channels, which are proteins that regulate the flow of ions across cell membranes. Ion channels are critical for maintaining the proper electrical activity for retinal cells to function correctly. Mutations in genes encoding ion channels can disrupt this activity, leading to retinal degeneration. Bikash Pattnaik's research has been instrumental in understanding the molecular mechanisms underlying these channelopathies. For example, his studies on LCA and Best Disease have identified specific mutations in ion channels that lead to these conditions. His work includes developing gene editing techniques, like CRISPR, to correct these genetic defects and restore normal retinal function. The research team employs various advanced techniques, including patient-derived induced pluripotent stem cells and genetically engineered mouse models, to study the physiology of retinal cells and develop potential therapeutic strategies. This multidisciplinary approach aims to pave the way for new treatments that can halt or reverse the progression of inherited retinal degeneration.



Pattnaik lab (above) presents diseased human-induced pluripotent (hiPSC) retinal pigment epithelium (RPE) cells that express the potassium channel (in green at right) after treatment.



Rebecca Meyer Brown Professor

Mrinalini Hoon, PhD
McPherson Eye Research Institute
Department of Ophthalmology and Visual Sciences
University of Wisconsin
Madison, WI

Impact of Photoreceptor Input Loss on Retinal Connections

Photoreceptors are primary retinal neurons that transduce light to electrical signals and transmit this signal to downstream retinal neurons via specialized connection junctions. Diseases that impact the survivability or activity of photoreceptors lead to blindness. The Hoon lab is determining the structure and function of retinal connections in genetic models with photoreceptor degeneration and in conditions when photoreceptor activity is impaired to understand how the composition and function of retinal connections is altered when photoreceptor input is perturbed. By combining 3D light and electron microscopy with transcriptomics and single cell electrophysiology, the Hoon lab is uncovering the differential impact of photoreceptor input loss on the diverse types of retinal connections, thereby revealing the underlying mechanisms contributing to visual dysfunction. These studies will reveal the identity of retinal connection types that could be amenable to therapeutic strategies aimed at restoring visual function in photoreceptor disease conditions.

Some members from the Hoon Lab research team (Dr. Hoon: *third from left*).

These awards are presented to renowned physician scientists in recognition of their lifetime achievement. RRF's mission is global in scope, and in 2023, four international awards were given.

Three RRF established awards were not bestowed in 2023. The Paul Kayser International Award, given in conjunction with the International Society for Eye Research (ISER) will be awarded in October, 2024; the Club Jules Gonin Lecturer, given in conjunction with Club Jules Gonin will be awarded in May, 2024 and the Gonin Medal will be awarded in 2026.

The Award of Merit in Retina Research

SriniVas R. Sadda, MD
Doheny Eye Institute
University of California at Los Angeles (UCLA)
Los Angeles, CA

Charles L. Schepens Lecture: *Insights into Pathophysiology of AMD Revealed by High-Resolution Imaging*

The Award of Merit in Retina Research was established in 1978 by RRF to recognize outstanding vision scientists whose research contributes significantly to new knowledge about the retina and retinal diseases or disorders. As the 2023 recipient of the award, Dr. SriniVas R. Sadda gave the Charles L. Schepens Lecture at the Retina Society's 56th Annual Scientific Meeting held in New York City in October.

Dr. Sadda is the Director of Artificial Intelligence & Imaging Research at the Doheny Eye Institute, and Professor of Ophthalmology at the University of California – Los Angeles (UCLA) Geffen School of Medicine. He is the immediate past President of the Doheny Eye Institute.

Dr. Sadda's research interests include retinal image analysis, advanced retinal imaging technologies, and clinical trial endpoint design. His research has been continuously funded by the National Institutes of Health for numerous years, including a current R01 grant from the National Eye Institute. He has authored more than 700 peer-reviewed publications and 20 book chapters, and has given over 450 presentations worldwide.

In 2023, Dr. Sadda serves as the president of the Macula Society and as president-elect for the Association for Research in Vision and Ophthalmology (ARVO). He received his medical degree from Johns Hopkins University, where he also completed ophthalmology residency. Further, Dr. Sadda completed fellowships in neuro-ophthalmology and medical retina at the Wilmer Eye Institute, Johns Hopkins University.

RRF Pyron Award for Outstanding Achievement in Retina Research

Eugene de Juan, Jr., MD
University of California at San Francisco (UCSF)
San Francisco, CA

Lecture: *The Road Less Traveled*

The RRF Pyron Award, given by the American Society of Retina Specialists (ASRS) was created by RRF to recognize outstanding vision scientists whose work contributes to knowledge about vitreoretinal disease. Dr. Eugene de Juan was presented with the Pyron Award at the ASRS annual meeting of the in Seattle WA at the end of July. Notably, Dr. de Juan is a former president of the society having served in that capacity in 2005-2006.

Dr. de Juan is the Jean Kelly Stock Distinguished Professor of Ophthalmology at the University of California, San Francisco, a position he has held since 2005. Also in 2005, Dr. de Juan established ForSight Labs, a serial ophthalmic company incubator that has helped develop 12 companies to date. He is the inventor or co-inventor of nearly 100 products. Dr. de Juan holds 150 U.S. patents and has more than 150 other patent applications pending. He is the founder/director of 20 companies with eight exits, six partnered programs, and six venture capital/angel-funded entities. Dr. de Juan has co-authored more than 250 peer-reviewed publications and 10 textbooks.

Dr. de Juan completed his retina fellowship at Duke University and his ophthalmology residency at the Wilmer Eye Institute, Johns Hopkins University. He completed his medical degree and internship at the University of South Alabama in Mobile.

Paul Kayser/RRF Global Award

Rajeev H. Muni, MD, PhD
The University of Toronto
Toronto, Canada

Lecture: *Bacillary Layer Detachment and Associated Abnormalities in Rhegmatogenous Retinal Detachment*

The Paul Kayser/RRF Global Award is given every two years in conjunction with the biennial congress of the Pan-American Association of Ophthalmology (PAAO). The award recognizes outstanding achievement in visual science through significant contributions to knowledge about improving vision and prevention of blindness. Dr. Rajeev Muni presented his lecture during the XXXV Pan-American Congress in March 18, 2023 in Buenos Aires, Argentina.

Dr. Muni is a vitreoretinal surgeon affiliated with St. Michael's Hospital, Hospital for Sick Children and the Kensington Eye Institute in Toronto, Canada, and he is the Vice-Chair of Clinical Research in the Department of Ophthalmology and Vision Sciences, University of Toronto.

Dr. Muni leads an active clinical research program and has a keen interest in randomized clinical trials, particularly in vitreoretinal surgical conditions. Dr Muni and his team conducted the PIVOT randomized trial comparing pneumatic retinopexy versus pars plana vitrectomy for rhegmatogenous retinal detachment repair, which demonstrated superior functional outcomes for patients undergoing pneumatic retinopexy. Dr. Muni has also been instrumental in novel research assessing the integrity of retinal reattachment with various surgical approaches using multimodal imaging and has published extensively on this topic in the highest impact journals in the field. Specifically, Dr. Muni and his team have demonstrated for the first time that photoreceptor recovery can vary with surgical technique. He has also demonstrated that the risk of unwanted anatomic outcomes such as retinal displacement and outer retinal folds vary with surgical technique, with these outcomes being more common following vitrectomy compared to pneumatic retinopexy. Dr. Muni and his team have also characterized the specific sequence of morphological changes that occur in humans in vivo with retinal detachment and retinal reattachment using the latest multimodal imaging. Most recently, Dr. Muni and his team have greatly expanded on our understanding of the pathophysiology of outer retinal corrugations and secondary macular hole in rhegmatogenous retinal detachment. His group has been the first to describe bacillary layer detachment (BALAD) and associated abnormalities in rhegmatogenous retinal detachment. Dr. Muni has over 115 peer-reviewed publications.

Buenos Aires, Argentina

Photos courtesy of PAAO

Charles L. Schepens, MD/AAO Award

Emily Y. Chew, MD
National Eye Institute, National Institutes of Health
Bethesda, MD

Schepens Lecture: *Macular Telangiectasia type 2: Tale of Global Private and Public Collaboration*

The 2023 RRF Charles L. Schepens, MD/AAO Award was given to Emily Y. Chew, MD. She delivered the Schepens Lecture during the morning proceedings of the Retina Subspecialty day at the American Academy of Ophthalmology's annual meeting held in San Francisco, CA on November 3, 2023.

From left: Dr. Julia Haller, Dr. Arthur Willis, Dr. Emily Chew, Dr. Joan Miller.

Dr. Chew is the Director of the Division of Epidemiology and Clinical Applications at the National Eye Institute (NEI), National Institutes of Health (NIH), and she is also the Chief of the Clinical Trials Branch. She received her medical degree and her ophthalmology training at the University of Toronto, School of Medicine. She completed her fellowship in medical retina at the Wilmer Eye Institute, the Johns Hopkins Medical Institutes and the University of Nijmegen, the Netherlands.

Dr. Chew has conducted clinical trials and epidemiologic studies in retinovascular diseases such as age-related macular degeneration (AMD), diabetic retinopathy, the leading causes of blindness. She led large, randomized trials, including the Age-Related Eye Disease Study (AREDS), AREDS2, and the Actions to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. She has conducted clinical trials in rare retinal diseases such as the international Macular Telangiectasia Project (Mac Tel Type 2 Project) and the recent study of belzutifan for von Hippel Lindau disease. She also collaborates with colleagues at the National Library of Medicine (NLM/NIH) utilizing artificial intelligence/deep learning on the detection and progression of AMD and other ocular diseases.

Dr. Michael Chiang, Director of the National Eye Institute/NIH, Dr. Emily Chew, Dr. Steven McLeod, CEO, American Academy of Ophthalmology (AAO).

Dr. Chew and family.

International Fellowships

RRF funds two programs of international fellowships, one a 12-month fellowship and the other, a six-month fellowship.

RRF Helmerich International Fellowships

Since 2009, RRF has offered two international fellowships with income from an endowment created by Walter H. Helmerich, III and his family. The 12-month fellowships provide advanced subspecialty training for young ophthalmologists from developing countries who are recommended by the head of a teaching or public service institution and are committed to returning to a position at a teaching institution or public service hospital in their home country following the fellowship. During 2023, two physicians received training as Helmerich International Fellows. The application process for these fellowships is highly competitive and the selected candidates are ambitious and specifically clear about what they hope to achieve through the experience and the skills and expertise they hope to bring to patients in their home countries following the conclusion of their fellowship.

Traveling from Ghana to Singapore

Dr. Daisy Asiama-Asare was awarded an IOFF-RRF Helmerich Fellowship at the Singapore National Eye Center, where she will serve in the oculoplastic division and complete a fellowship in oculoplastics, orbital and lacrimal surgery.

In her application, Dr. Asiama-Asare wrote: "I wish to learn all there is to know in an oculoplastic fellowship. During my residency training, it always broke my heart to see patients having to wait months before seeing an oculoplastic surgeon because of the scarcity of this subspecialty. It was sad sometimes to see that some lesions were cancerous and an earlier intervention could have saved a life. My country often has fire outbreaks, and the moment it affects the eye, it takes years to have reconstruction even for children. In this regard, I want to learn reconstructive and functional oculoplastics, orbital oncology and surgery, tear duct surgeries, cosmetic oculoplastic surgeries and if possible non-surgical cosmetic procedures. In addition to all of this, I am also motivated because, Ghana as a country is a key referral center to other smaller West African countries. During my training, I saw patients from other sub-Saharan African countries like Liberia, Togo, Benin and Burkina Faso, seeking oculoplastics surgical intervention in Ghana, and I am determined because I know that my skill will not be just for my hospital, my city or my country, but also for Africa as a whole.

The University of Ghana Medical Center is one of Ghana's first quaternary centers. The main aim of the hospital is to have trained fellows that meet world class standards to boost the country's medical care capacity. Being offered the position of the head of department to help build the eye unit was challenging as a specialist but going through a fellowship training would give me both the confidence and the proper medical qualification to maintain that position and form a world class unit. I will also be more equipped with the capacity to train residents in the field of ophthalmology and oculoplastics. Furthermore, another practical implication for this fellowship training in my professional development is that I can become one of the key directors involved in eye care both in my hospital and country and it will be great to have a female serve as a mentor to other females.

I have many plans upon my return. First on my list is to help start training for ophthalmologists interested in the field of oculoplastics. Currently, Ghana does not offer subspecialty training in oculoplastics, partly because we do not have enough trainers. A fellowship in this subspecialty gives me the ability and qualification to start the training in my facility and also train others in other teaching hospitals. Ghana has no properly set up medical simulation center for training. Fortunately, my hospital is one of the first to set up a simulation center. I would help equip one for ophthalmology where residents can be able to learn. This would be ground breaking in my country in the field of ophthalmology. Again, setting up a telemedicine consultation is also key on my list. Other ophthalmologists in other districts in Ghana or even other Sub-Saharan African countries can use this application, where we can consult with them on cases of oculoplastics so that people who are far, or in the deep villages who need oculoplastic care, can have them or have an initial life-saving intervention before referral if need be. My home institute would also be one of the main referral and training centers in the field of oculoplastics."

University of Ghana Medical Center

Traveling from India to the U.S.

Dr. Rolika Bansal from Hyderabad, India, where she is employed by the Center of Sight, was awarded an IOFF-RRF Helmerich Fellowship for a one-year fellowship in ocular oncology at Wills Eye Hospital affiliated with the University of Philadelphia under supervision of Dr. Carol Shields, chief of the ocular oncology program and a world-renowned ocular oncologist who has worked extensively on ocular melanoma and retinoblastoma.

In her application, Dr. Bansal shared her goals for her experience, and wrote: "Learning the best of techniques and absorbing knowledge from my mentors while multi-tasking is the aim, as it will help me in taking care of my patients, efficiently and with expertise. A blend of the two components of research and clinical skills in the field of ocular oncology with an overview of oculoplasty is mandatory for gaining appropriate knowledge and expertise to ensure flawless patient care. Such well-crafted programs under the preceptorship of the pioneers in the field, give us the golden opportunity of learning and honing our skills.

I strongly believe that if one has good mentors right from the beginning, then the basic principles and approach towards research and academics become refined and stay pure. The mentor-mentee relationship is synergistic and as a budding specialist in my field, I would like to fill the lacunae in my research and clinical skills by learning the elements of professional and personal growth from my mentors with a pragmatic approach. With the IOFF-RRF Helmerich fellowship program for one year, I am hoping to learn the elements of clinical and research work along with management and teaching skills.

In our country, we have people from different strata of the society and I wish to build a center, affordable for all, with state-of-the-art patient care and advanced diagnostic modalities with precise surgical skills that I am hoping to imbibe during my tenure of fellowship and thereafter. There is scarcity of provisions to the patients requiring ocular oncology and oculoplasty services in my region (Northern India - Jaipur, Rajasthan), and over the time I wish to build a tertiary care setup in order to help the patients while providing services and comfort in their vicinity along with spreading awareness as very little is known to people about our sub-specialty. In the future, I aspire to put the knowledge gained from my mentors in providing high quality of research and training in my sub-specialty and by bridging the national and international gaps. Learning is a slow and constant process and I wish to continue doing research work throughout my professional career as it keeps us updated. I am hoping to train and teach more refined specialists later in my career. If the roots of experience and knowledge are pure and precise, then one is able to get the best out of themselves in every way."

Graduation ceremony, Wills Eye Hospital from left; Dr. Carol L. Shields, Dr. Rolika Bansal, Dr. Sara E. Lally

Dr. Bansal with colleagues and medical students from across the globe at the Wills Eye Conference.

Gillingham Pan-American Fellowships

A collaboration with the Pan-American Association of Ophthalmology (PAAO), the RRF Gillingham Fellowships program offers two, six-month fellowships to Latin American ophthalmologists for training at leading institutions in the United States or Canada.

Initiated in 1992 by RRF's founder, Dr. Alice McPherson, and made possible through the legacy of W.J. Gillingham, the fellowship program aims to nurture the next generation of ophthalmic leaders from Latin and South America. Annually, up to two deserving scholars who have secured a position in an accredited training program in the U.S. or Canada, are awarded these fellowships.

In 2023, in furtherance of RRF's commitment to advancing ophthalmic education and research, funding for this international educational program was doubled, increasing the annual scholarship amount from $10,000 to $20,000. Nearly 60 Gillingham fellowships have been awarded over the last 30 years, to provide recipient ophthalmologists educational assistance while they receive medical specialty training to improve their patient care treatements and research capabilities in their home country.

Stewardship of endowed gifts enables RRF to generously fund programs in translational research and education, disseminating basic research laboratory knowledge to practicing ophthalmologists and vision scientists worldwide

American Academy of Ophthalmology Educational Trust Fund

In collaboration with the American Academy of Ophthalmology (AAO), this educational program provides ophthalmologists with high-quality educational resources needed to enhance their clinical research skills in the field of retina, and empower them with knowledge of the latest advancements necessary to treat patients more effectively. RRF provides $50,000 annually to this educational effort, and in 2023, made possible the development of a new retina rotation -- resident learning plan, which provides essential education for residents in the retina rotation, and a *Core Ophthalmic Knowledge for Retina* CME course on the diagnosis and management of retinal disorders encountered in everyday practice. "Core ophthalmic knowledge" is defined as necessary clinical knowledge expected of all ophthalmologists regardless of practice area. RRF also supported the *Basic and Clinical Science Course Section 12, Retina and Vitreous*. These resources are available to clinicians as part of AAO's CME activities on the One® Network, the Academy's global platform for ophthalmic education.

RRF Lawrence Travel Scholarships

A portion of the corpus of Joe M. and Eula C. Lawrence's bequest to RRF has provided ongoing funding for the Lawrence Travel Scholarship program since 2002. The original concept agreed upon by RRF and the Association for Research in Vision and Ophthalmology (ARVO) was the first of its kind in the country, and established travel-expense scholarships for young retina research scientists to attend the annual ARVO meeting to present their work. Applying for a travel scholarship has now become an essential milestone in the professional development of many young researchers, across many different vision disciplines. The experience provides an opportunity to interact, both in person and online with fellow scientific colleagues and thereby, exponentially expand one's exposure to new research concepts and findings presented by the global vision research community.

The 2023 ARVO meeting was held in New Orleans in April, and RRF sponsored 29 travel grants. Hailing from the country's most prestigious research institutions, these young scientists participated in poster presentations with the additional ability to browse the latest research online by scientific section, author, title, or by key words within an abstract or poster. RRF grant recipients shared how stimulating and thought provoking they found the experience of presenting their research and learning about the research of others, further signaling the importance of travel scholarships to professional development and the dissemination of vision research data and knowledge.

McPherson Eye Research Institute Pays Tribute to Dr. Alice R. McPherson

In May, members of the RRF Board of Directors traveled to Madison, Wisconsin, to take part in events hosted by the McPherson Eye Research Institute at the University of Wisconsin-Madison. The trip was all the more poignant because Dr. David Gamm, RRF Emmett Humble Distinguished Director of the Institute, gave a lovely and moving tribute to Dr. McPherson, his mentor and friend, as part of a special celebration honoring Dr. McPherson, following her death on January 16, 2023.

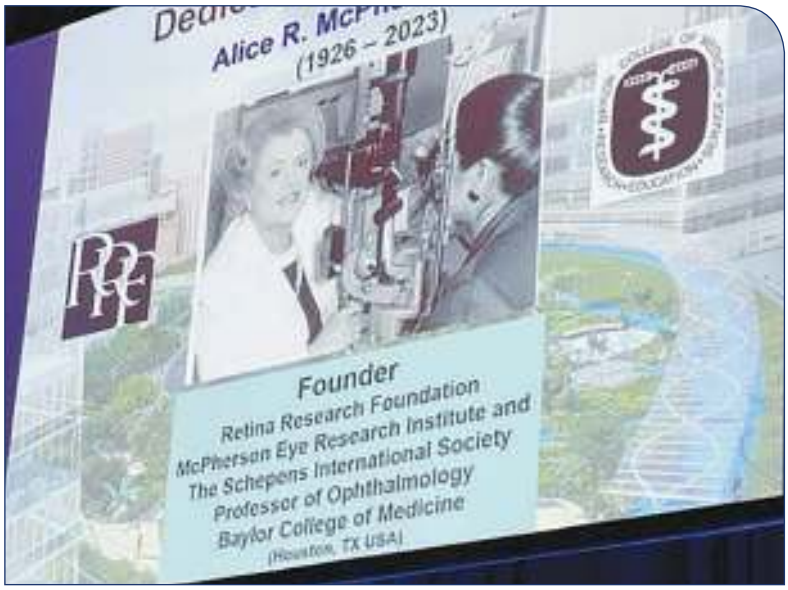
RRF Board members attended the 11th annual Alice R. McPherson Lecture and Dinner, attended the McPherson ERI Advisory Board spring meeting, and toured numerous research laboratories of RRF endowed chairs and professorships at the McPherson ERI, University of Wisconsin-Madison.

Patricia A. D'Amore, PhD, MBA, Charles L. Schepens Professor of Ophthalmology and Vice Chair of Basic and Translational Research, Harvard Medical School, was the invited lecturer. She spoke on the topic of: "Ocular Angiogenesis: Biology, Pathology, & Translation," and provided insights from her research on the abnormal growth of new blood vessels in the retina and how understanding the pathogensis of these disorders has been central to the development of effective therapies.

From left: Dr. Mrinalini Hoon, Dr. David Gamm

At the McPherson ERI Advisory Board meeting, RRF members had the opportunity to hear firsthand about the progress being made by researchers, including David Gamm, MD, PhD and RRF Rebecca Meyer Brown Professor, Mrinalini Hoon, PhD, who shared an update on her most recent work related to the mechanisms that alter inner retinal connections in photoreceptor diseases.

Dr. David Gamm introducing the Alice R. McPherson lecture.



RRF Board Directors John Dawson and Rich Walton

2023 Collaboration Partnership Highlight
Pan-American Association of Ophthalmology

From left: John Dawson, RRF Chairman,
Teresa Bradshaw, PAAO Executive Director

RRF has maintained a strong collaboration with the Pan-American Association of Ophthalmology (PAAO) since 1992. Working together, our two organizations promote high quality educational opportunities for young Latin American Ophthalmologists through the Gillingham Fellowships, and recognize innovation in ophthalmic clinical and basic science research aiming to improve vision and prevent blindness with the Kayser Global Award, which is given every two years.

In September, Teresa Bradshaw, PAAO's executive director, visited with the RRF Board to provide an update on our partnership programs, both historical and contemporary. She presented the board with the inaugural award of the Dr. Bronwyn Bateman PAAO Award for Women's Leadership in Ophthalmology and Vision Research that was posthumously awarded to Dr. Alice McPherson in 2023.

In November, RRF attended PAAO's Circle of Vision Luncheon held each year at the AAO annual meeting, where special tribute was paid to Dr. McPherson for her many years of leadership and support of PAAO.

RRF Board from left: John Dawson, Malcolm Wooley, Dr. Petros Carvounis, Mac Jensen, Dr. Art Willis, Patricia Boyd, Dr. Ben Orman, Teresa Bradshaw, PAAO, Joe Royce, Rose Cullen, Ron Girotto, Larry Washington, Rich Walton,
Not pictured RRF Board Members: Lynn Bernard, Lewis Gissel, Nancy Japhet, Bettie Lee, Bruce Mack, Kathy Orton.

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RETINA RESEARCH FOUNDATION
COMBINED STATEMENT OF FINANCIAL POSITION

December 31, 2023
(with summarized financial information as of December 31, 2022)

	General Funds			Endowment Funds				2022 Total
	Without Donor Restrictions	With Donor Restrictions	Total	Without Donor Restrictions	With Donor Restrictions	Total	**2023 Total All Funds**	All Funds (Memorandum Only)
Assets								
Cash and cash equivalents	$ 689,163	$ 80,856	$ 770,019	$ -	$ 646,549	$ 646,549	**$ 1,416,568**	$ 1,205,560
Promises to give	12,446	50,000	62,446	-	54,000	54,000	**116,446**	220,100
Investments	3,288,842	-	3,288,842	5,522,597	61,970,140	67,492,737	**70,781,579**	63,246,508
Furniture and equipment, net of accumulated depreciation of $12,474	13,414	-	13,414	-	-	-	**13,414**	14,101
Intangible assets	12	-	12	-	-	-	**12**	12
Other assets	8,686	-	8,686	-	-	-	**8,686**	6,651
Total assets	$ 4,012,563	$ 130,856	$ 4,143,419	$ 5,522,597	$ 62,670,689	$ 68,193,286	**$ 72,336,705**	$ 64,692,932
Liabilities and net assets								
Accounts payable	$ -	$ -	$ -	$ -	$ 76,607	$ 76,607	**$ 76,607**	$ 71,176
Grants payable	50,000	-	50,000	-	-	-	**50,000**	100,000
Total liabilities	50,000	-	50,000	-	76,607	76,607	**126,607**	171,176
Net assets	3,962,563	130,856	4,093,419	5,522,597	62,594,082	68,116,679	**72,210,098**	64,521,756
Total liabilities and net assets	$ 4,012,563	$ 130,856	$ 4,143,419	$ 5,522,597	$ 62,670,689	$ 68,193,286	**$ 72,336,705**	$ 64,692,932

RETINA RESEARCH FOUNDATION
COMBINED STATEMENT OF ACTIVITIES AND CHANGES IN NET ASSETS

For the year ended December 31, 2023
(with summarized financial information for the year ended December 31, 2022)

	General Funds			Endowment Funds			2023	2022 Total
	Without Donor Restrictions	With Donor Restrictions	Total	Without Donor Restrictions	With Donor Restrictions	Total	**Total All Funds**	All Funds (Memorandum Only)
Revenues								
Contributions	$ 158,000	$ 132,200	$ 290,200	$ -	$ 179,000	$ 179,000	**$ 469,200**	$ 541,812
Investment income, net	87,969	-	87,969	133,308	1,502,654	1,635,962	**1,723,931**	1,549,250
Realized and unrealized gains (loss) on investments, net	366,121	-	366,121	620,610	7,020,699	7,641,309	**8,007,430**	(9,829,049)
Mineral interest income and other income	18,822	-	18,822	-	-	-	**18,822**	30,242
Income transferred from Endowment Fund investments	1,991,023	53,700	2,044,723	(166,067)	(1,878,656)	(2,044,723)	-	-
Net assets released from restrictions - satisfaction of program and timing restrictions	222,544	(222,544)	-	-	-	-	-	-
Total revenues	2,844,479	(36,644)	2,807,835	587,851	6,823,697	7,411,548	**10,219,383**	(7,707,745)
Expenses								
Program services								
Research projects and grants	2,309,379	-	2,309,379	-	-	-	**2,309,379**	2,103,112
Supporting services								
Management and general	221,662	-	221,662	-	-	-	**221,662**	190,312
Total expenses	2,531,041	-	2,531,041	-	-	-	**2,531,041**	2,293,424
Changes in net assets	313,438	(36,644)	276,794	587,851	6,823,697	7,411,548	**7,688,342**	(10,001,169)
Net assets, beginning of year	3,649,125	167,500	3,816,625	4,934,746	55,770,385	60,705,131	**64,521,756**	74,522,925
Net assets, end of year	$ 3,962,563	$ 130,856	$ 4,093,419	$ 5,522,597	$ 62,594,082	$ 68,116,679	**$ 72,210,098**	$ 64,521,756

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