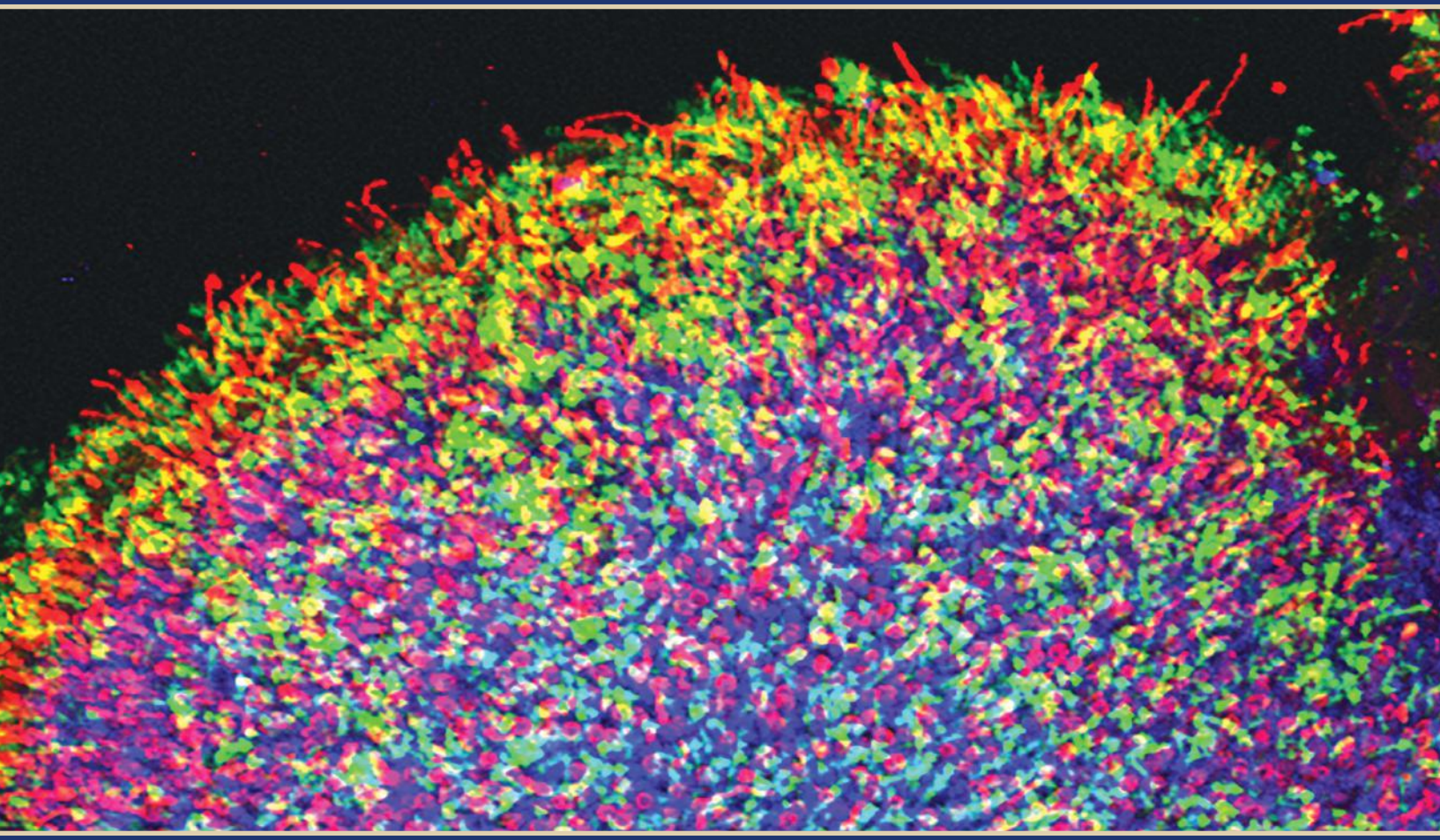
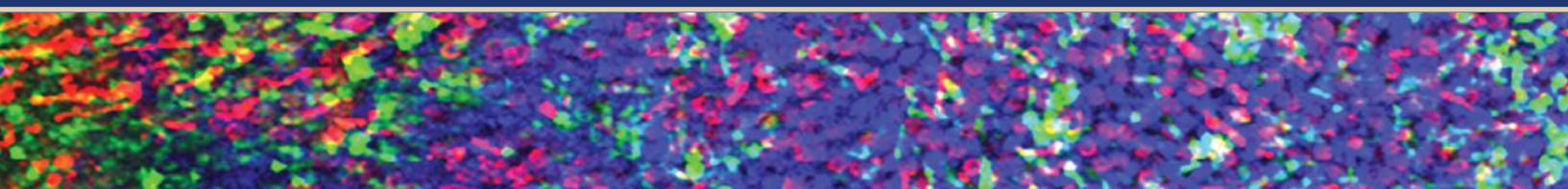
RETINA RESEARCH FOUNDATION



ANNUAL REPORT 2021

FUNDING PROGRAMS IN RESEARCH AND EDUCATION
TO REDUCE RETINAL BLINDNESS WORLDWIDE



Annual Report 2021

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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.

President's Message

Dear Friends,

Throughout the 52 years that RRF has sponsored programs in retina research, the nature of the research has changed, but the ultimate goal has not. We fund research that seeks to understand the miraculous retina, to preserve its function and enable sight when dysfunction or damage would dictate otherwise. Today, these efforts encompass a wide range of project aims, from identifying the genetic causes of inherited retinal diseases to understanding how to replace aging or damaged retinal cells, and many others, research that could not have been imagined when we started.

With our focus on retina, RRF continues to fulfill an important and necessary position in vision research. Our organization is innovative and we have been extremely successful in funding groundbreaking research. In this spirit, we are pleased to share with you highlights from one of RRF's most dynamic and impactful years to date. The basic research program expanded, both in scope and the level of funding provided. The advancements taking place are astounding and were shared extensively through publications in high-impact scientific journals and at scientific meetings. Over the years, RRF programs have expanded to include research awards for career achievement by established scientists, research chairs and professorships, educational programs for ophthalmologists, advanced subspecialty training for promising clinicians from developing countries, and travel grants for young scientists to attend scientific meetings. All are programs designed to share greater understanding of retinal diseases with vision researchers and practitioners throughout the world in an effort to provide novel, more advanced clinical treatments to patients.

In 2021, we forged a new collaborative partnership and revised our efforts with others. In many respects, it has been a very good year, but it has also been a year of departures, as we lost friends who have been involved with our organization for decades. We are fortunate that they remembered RRF in thoughtful ways because, and I quote our Chairman Emeritus, Dr. Frank Eggleston, "It's all about saving sight, that's why [we're] here." Dr. Eggleston was instrumental in our organization's leadership for 20 years. His sentiments are shared by many of you who continue to support RRF year after year. Our success is built upon your continued interest in the work we do, and with your assistance, as of the end of 2021, RRF has directed over $38 million to retinal research. As we look forward, we are encouraged, and we will not waiver in our commitment to realizing our ultimate goal of ending blindness caused by retinal diseases.

With appreciation,

Alice McPherson M.D.

Research Program Overview - 2021

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 2021, 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
- Yingbin Fu, PhD – Dana and Gil Petri Research Project
- Rui Chen, PhD – Manning Research Project
- Graeme Mardon, PhD – Miller Research Project
- Richard Hurwitz, MD – Wilson Research Project

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

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

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

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

University of Utah, John Moran Eye Center, Salt Lake City, UT
- Wolfgang Baehr, PhD – Humble 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

Bascom Palmer Eye Institute, University of Miami, Miami, FL
- Hong Yu, 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, Tuscon, AZ
- Erika D. Eggers, PhD – Basic Research Project

RRF Cox Macula Society Research Grant – administered by The Macula Society
Prithvi Mruthyunjaya, MD, MHS – Byers Eye Institute, Stanford University Medical Center, Palo Alto, CA

Research Chairs – Ongoing Proven Research Projects

Baylor College of Medicine, Houston, TX
Ching-Kang Jason Chen, PhD – RRF Research Chair

University of Wisconsin, Madison, WI
Kevin W. Eliceiri, PhD – Helmerich Chair, Associate Director, McPherson Eye Research Institute
Nader Sheibani, PhD – RRF Research Chair
David Gamm, MD, PhD – Humble Distinguished Directorship, McPherson Eye Research Institute
Krishanu Saha, PhD – Murfee Chair, McPherson Eye Research Institute
Melissa Skala, PhD – Albert Chair, McPherson Eye Research Institute

Research Professorships – Ongoing Proven Research Projects

University of Wisconsin, Madison, WI
Olachi Mezu-Ndubuisi, MD, OD – 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

RRF Award of Merit – presented by The Retina Society
Douglas A. Jabs, MD, MBA, MS – Johns Hopkins Bloomberg School of Public Health and School of Medicine, Baltimore, MD

RRF Pyron Award – presented by American Society of Retina Specialists (ASRS)
Cynthia A. Toth, MD – Duke University School of Medicine, Durham, NC

CL Schepens MD/AAO Award – presented by American Academy of Ophthalmology (AAO) and in the spirit of Schepens International Society (SIS)
Mark S. Humayun, MD, PhD – USC Roski Eye Institute, Los Angeles, CA

RRF Gonin Lecturer – presented by Club Jules Gonin – will be awarded in 2022

Gonin Medal – presented by International Council of Ophthalmology (ICO) – will be awarded in 2022

RRF Kayser International Award – presented by International Society for Eye Research (ISER) – will be awarded in 2022

Paul Kayser/RRF Global Award – presented by Pan-American Association of Ophthalmology (PAAO) – will be awarded in 2023

International Fellowships – Advanced Subspecialty Training

RRF Helmerich International Fellowships – presented by Ophthalmology Foundation (OF) and administered by International Ophthalmological Fellowship Foundation e. V. (IOFF)
Juan Manuel Lopez, MD – from Argentina to CHU Creteil, Paris, France
Perpetua Odugbo, MD – from Nigeria to University of California, Los Angeles (UCLA), Los Angeles, CA

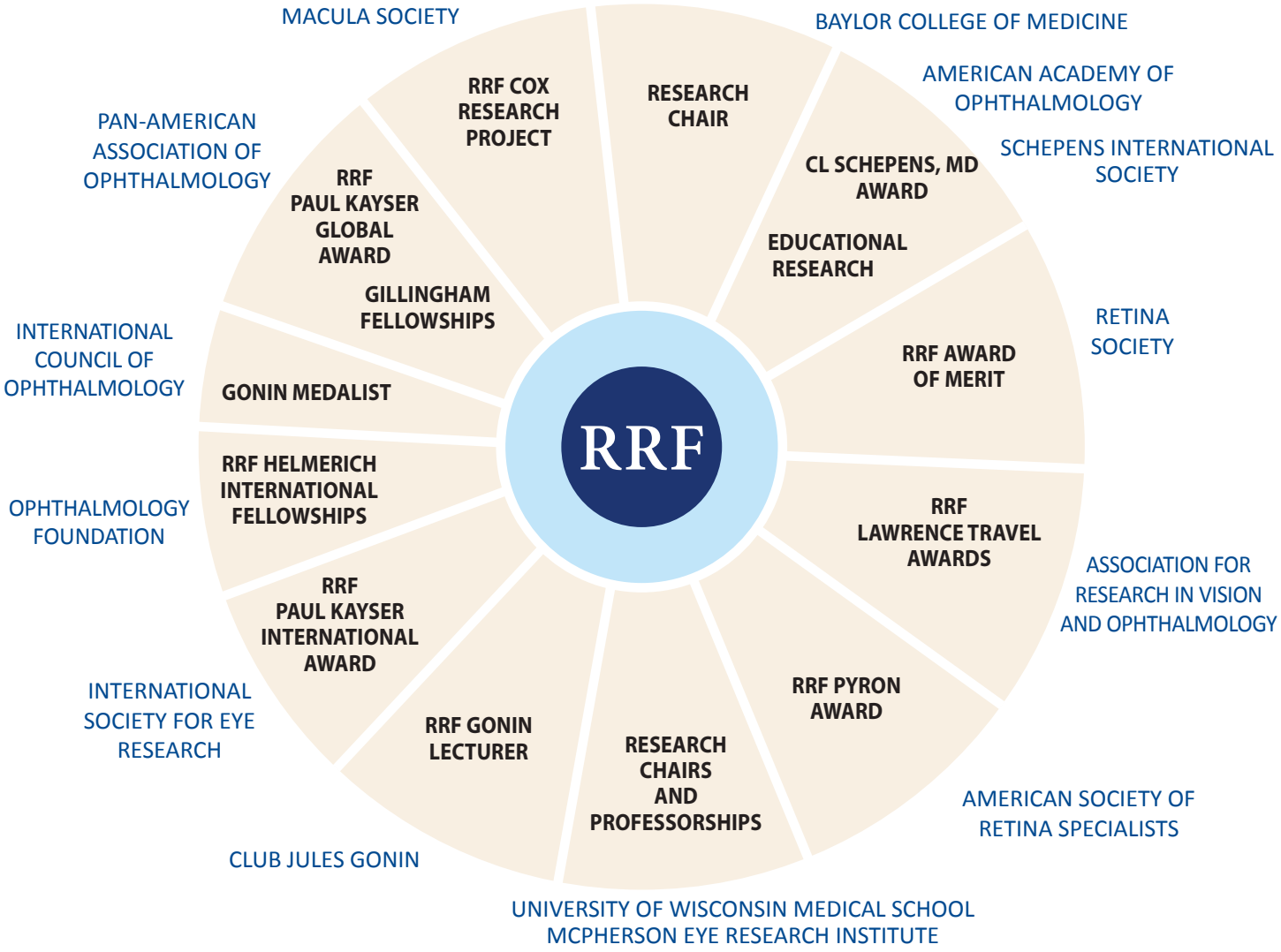
Gillingham Pan-American Fellowships – administered by Pan-American Association of Ophthalmology (PAAO)
Mariana Matioli da Palma, MD – from Brazil to the Oregon Health and Science University (OHSU), Portland, OR
Estephania Feria Anzaldo, MD – from Mexico to Bascom Palmer Eye Institute, Miami, FL

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)
126 virtual travel scholarships awarded in 2021

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 : 47

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
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 : 65

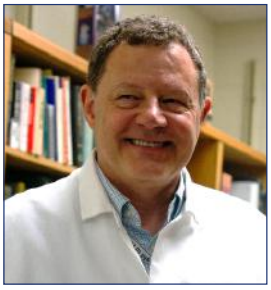
Bascom Palmer Eye Institute	Miami, FL
Beaumont Eye Institute/Hospital	Royal Oak, MI
Byers Eye Institute/Stanford University	Palo Alto, CA
California Institute of Technology	Pasadena, CA
Carver College of Medicine	Iowa City, IA
Case Western Reserve University	Cleveland, OH
Casey Eye Institute	Portland, 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
Georgia Regents University	Augusta, GA
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 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 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 2021, a total of 19 RRF pilot study research projects were funded in Texas and throughout the country. Conducted at leading research institutions, 10 ongoing projects are named in recognition of individuals who have generously supported the mission of our organization. Pilot studies are experimental, basic science studies designed to investigate previously unstudied or understudied retinal disease causes in an effort to break new ground, and advance scientific knowledge. Findings may lead to future ongoing studies. RRF affiliated vision researchers contributed significantly to the body of knowledge with 29 publications submitted or published in high-impact, peer review journals.

Named Basic Research Projects

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

The goal of Dr. Brandt's research is to devise strategies to improve the transduction efficiency of viral vectors designed for ocular gene delivery. In 2021, his lab identified several inflammasome genes whose expression was elevated following gene delivery vector challenge of macaque retina tissue and two human retinal cell lines. Dr. Brandt's lab team also tested the effect of knockdown of two host cell restriction factors, and proteasome inhibition, on viral vector transduction efficiency in a human Muller cell line and found efficiency was increased (Exper. Eye Res. 2021, 204:108436). A link between activation of a key cellular transcription factor, and knockdown of these host cell restriction factors, was also identified. His lab also explored the role of TAK1 kinase activation in restriction of viral vectors in a human Muller cell line.

Dr. Brandt, Sarah Ferguson, and Aaron Kolb discuss the results of an assay for vector transduction of muller cells lacking TRIM5-alpha.

Joe M. and Eula C. Lawrence Research Project

Timothy W. Corson, PhD
Department of Ophthalmology
Indiana University School of
Medicine
Indianapolis, IN

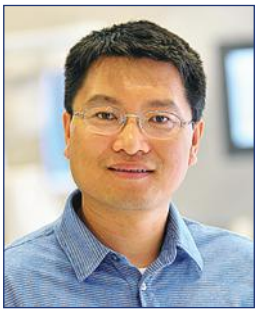
Localization and lipid modulation of soluble epoxide hydrolase in choroidal neovascularization

Dr. Corson's long-term goal is to find new therapeutic approaches for combating ocular neovascularization, the abnormal blood vessel growth seen in diseases like wet age-related macular degeneration. Specifically, the goal of his 2021 project was to determine exactly which cells in the eye express an enzyme identified to be important for abnormal new blood vessel growth, soluble epoxide hydrolase (sEH), and to ascertain the effect on fatty acids when sEH is depleted, to guide therapeutic development. He used a new technique to unambiguously show the retinal cell types producing sEH.

During previous years of RRF funding, Dr. Corson's lab developed a potent chemical called SH-11037, and tested this in combination with standard anti-VEGF therapy. This chemical targeted sEH within the cells, and the lab showed that sEH is present at high levels in human and mouse eyes with AMD-like features. The team also found that known sEH inhibitors can block new blood vessel growth in the eye and characterized the molecular mechanism of how SH-11037 inhibits sEH, including identifying factors that increase its levels in the eye. Assessing their library of novel chemicals, they found candidates that perform as well as SH-11037 at blocking sEH, helping to build a "structure activity relationship" for blocking sEH function. Dr. Corson's research showed differential expression in sEH between the sexes, and found that depletion of sEH with a genetic tool his lab developed reduced inflammatory signals. In 2021, Dr. Corson resolved a controversy on which cells express sEH in the eye, revealing retinal pigment epithelium (RPE) as a major source of this protein.

The Corson Laboratory Team

W.O. Manning Research Project

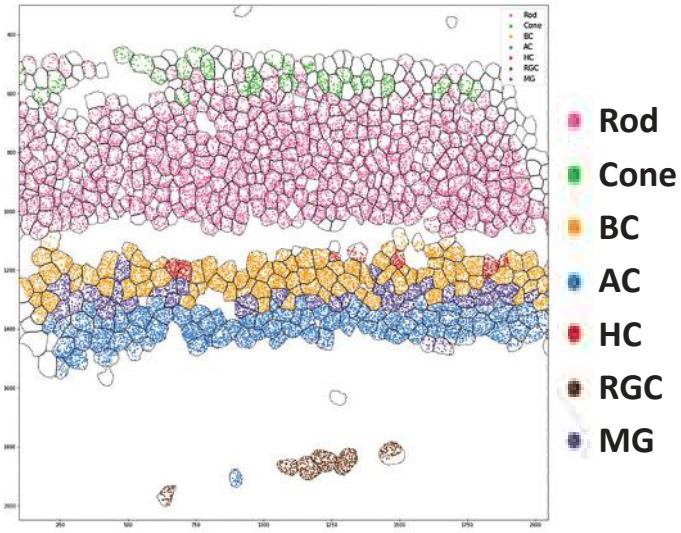


Rui Chen, PhD
Department of Molecular and Human Genetics
Baylor College of Medicine
Houston, TX

Identification and functional analysis of genes involved in retina diseases

Dr. Chen is interested in deciphering the genetic causes of inherited retinal diseases to develop specialized treatments, including gene and drug therapy. He chooses to study Leber congenital amaurosis (LCA) because it is one of the most common causes of hereditary visual impairment in infants and children, and is responsible for more than 5% of all retinal dystrophies. Many different genes or genetic mechanisms can cause LCA, making accurate molecular diagnosis essential for the administration of appropriate treatment interventions. Additionally, LCA shares many common molecular mechanisms with other retinal dystrophies such as Retinitis Pigmentosa and rare Bardet-Biedl Syndrome, so understanding the causes of LCA provides valuable knowledge of these other retinal degenerative diseases as well. Once novel genes are discovered, Dr. Chen's laboratory performs functional analysis of these genes using model organisms, which is the first step in the process of establishing not only reagents for treatment but also for improving the clinical ability to accurately diagnose these genetic diseases.

In 2021, Dr. Chen made progress in both aspects of his research. He completed panel sequencing for all of his and his collaborators' patient cohorts as well as performed whole exome sequencing for 300 patients whose initial sequencing did not identify a good genetic candidate. These efforts identified a novel disease gene TLCD3B, a discovery that Dr. Chen shared in a publication in Genetics in Medicine. In addition, his team completed the gene therapy study distinguishing two isoforms of the disease gene, REEP6, research that resulted in a second publication in Molecular Human Genetics. Finally, animal models were generated for the newly identified TLCD3B and CWC27. Successful gene-augment therapy has been conducted for the Tlcd3b animal model, laying the foundation for future therapeutic development. Dr. Chen shared his research findings with the vision community through a total of five publications.



Retina Spatial Map: Single Cell Spatial Atlas of the Retina

The Chen Laboratory Team

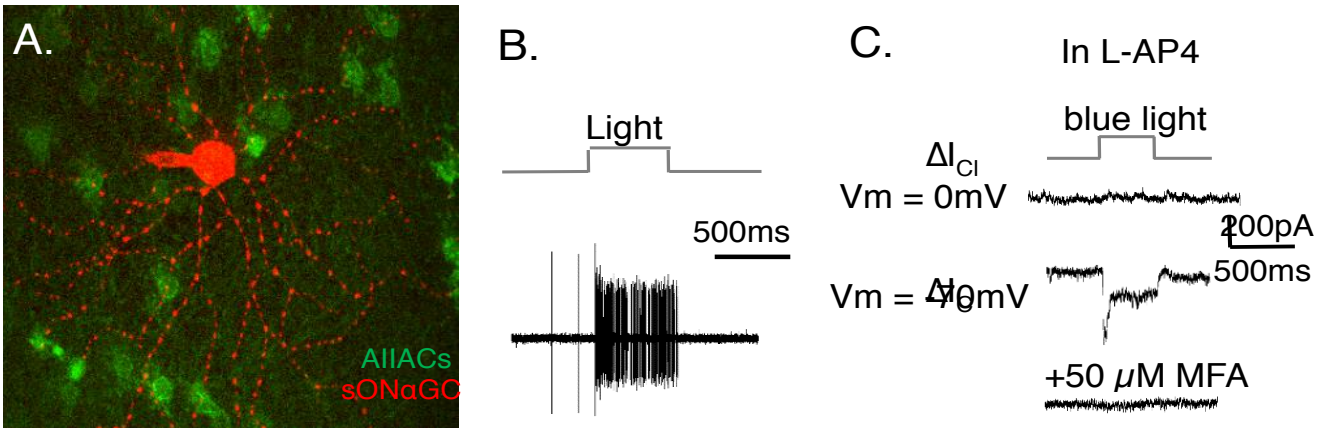
Paul Kayser Research Project

Samuel Wu, PhD

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

Pharmacological and genetic mechanisms underlying retinal cell death in glaucoma and age-related macular degeneration (AMD)

Dr. Wu's research project is to study cellular and genetic mechanisms underlying retinal dysfunction and degeneration in glaucoma and age-related macular degeneration (AMD). By using the newly developed 8-patch electrode recording and the multi-electrode array systems, his lab has employed new analytic tools for studying retinal synaptic connectivity and spatiotemporal receptive field properties of retinal ganglion cells (RGCs). In 2021, Dr. Wu's lab published four papers in top international journals. These publications report their new discoveries on how rod and cone signaling pathways mediate light responses in retinal bipolar cells, and how dysfunction of photoreceptors, bipolar cell and amacrine cell synapses affect degeneration in various forms of retinal and brain diseases. Dr. Wu's research team plans to continue to study synaptic connectivity in normal and disease retinas. They will focus on how AII amacrine cells mediate RGC function and identify targets for drug and gene therapies for treating RGC dysfunction in glaucoma and AMD.



Effects of channel rhodopsin (ChR2)-elicited AIIAC depolarization on ΔIC and ΔICl of a sustained ON alpha ganglion cell (sONaGC). A. sONGC morphology revealed by Alexa Fluor 594 (red). AIIACs are labeled with ChR2 (green). B. light-evoked spike responses recorded under the loose patch configuration. C. blue light activation of ChR2 in AIIACs elicits a large inward cation current (ΔIC) at -70 mV in the sONGC in the presence of L-AP4 which suppress photoreceptor-ON-BC synapses but not the ON BC-ONGC synapses. The ΔIC was blocked by 50 µM MFA, supporting the notion that AIIAC depolarization spreads via gap junctions to ON BCs.

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, diagnostics, and treatments for human retinal diseases that cause congenital blindness. His research team has been studying a causative gene associated with congenital blindness, named SPATA7, which encodes a novel adaptor protein whose mechanism of function is poorly understood. A detailed understanding of SPATA7 function in the eye could have broad implications.

The Mardon lab often uses the mouse as a model system to study the function of conserved genes required for normal retinal development. In the past year, Dr. Mardon completed work on the mouse Spata7 gene and made a significant breakthrough concerning this retinal disease gene.

In particular, he found that Spata7 is not only required for the establishment of the connecting cilium in the mouse retina, but it is also required for the maintenance of that structure in adults. This work represents a major step forward in designing therapeutics for inherited blindness, and findings will be submitted for publication in the coming year.

Emmett A. Humble Research Project

Wolfgang B. Baehr, PhD
Department of Ophthalmology
and Visual Sciences
John Moran Eye Center
University of Utah
Salt Lake City, UT

INPP5E, phosphoinositides and retinal degeneration

Dr. Baehr is interested in understanding mechanisms leading to retina disease and in developing gene-based therapies to address photoreceptor degeneration. In 2021, Dr. Baehr's research focused on the role of INPP5E in the development of disease in photoreceptors. INPP5E is an inositol phosphatase that when mutated causes Joubert Syndrome with Leber congenital amaurosis. Dr. Baehr's laboratory generated a mouse model in which INPP5E was deleted during embryonic development in retina and produced a novel model for INPP5E–LCA. Deletion of INPP5E interrupts axoneme extension and disc membrane elaboration leading to failure of photoreceptor outer segment formation. A manuscript entitled, "Deletion of the phosphatase INPP5E in the murine retina impairs photoreceptor axoneme formation and prevents disc morphogenesis," was published in the Journal of Biological Chemistry in 2021.

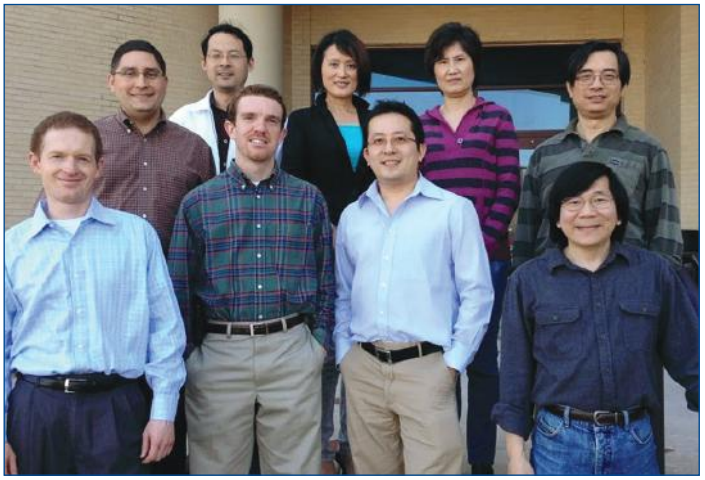
Adolphe G. and Josephine Roberts Gueymard Research Project

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

Proper function of the retina depends on an adequate supply of retinal blood flow, and dysfunction of the retinal microcirculation may lead to disease development. The goal of Dr. Kuo's research project is to identify the mechanisms responsible for the microvascular pathogenesis of diabetic retinopathy and to develop pharmacologic strategies for the prevention and treatment of this sight-threatening disease. Dr. Kuo previously demonstrated that in the diabetic retina, the synthesis of vasoconstrictor/inflammation agent endothelin-1 (ET-1) from endothelin-converting enzyme (ECE) is elevated, and the vascular signaling molecule RhoA kinase (ROCK) and arginase enzyme are upregulated. The current project's hypothesis is that activation of ECE/ROCK/arginase contributes to microvascular dysfunction by increasing microvascular constriction and reducing venous drainage. Using a pig model, which resembles circulation within the human eye, Dr. Kuo is investigating vascular signaling pathways in the initiation and development of diabetic retinopathy.

Although research activity continued to be impacted by the widespread infection of COVID-19, Dr. Kuo's laboratory persevered with their research plan, and their findings yielded three publications. Dr. Kuo documented that activation of stress kinase p38 and sodium-hydrogen exchanger-1 cause enhanced venular constriction to ET-1. Results suggest that treatments targeting these vascular signaling molecules in early diabetes may lessen retinal complications and prevent vascular retinopathy development. The research team also demonstrated that the retinal blood flow is dysregulated before the development of neural retinal dysfunction in type 2 diabetes. It is suggested that retinal blood flow dysregulation likely leads to neural dysfunction and that treatment of blood flow deficiency in early diabetes can be critical before the establishment of overt neurovascular pathology.



Kuo's retinal research team (Dr. Kuo, front row, far right)

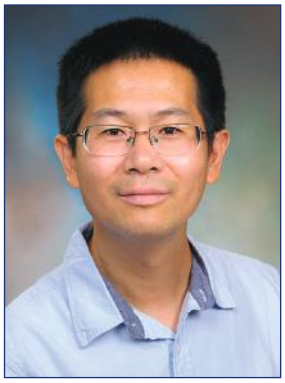
Mary Ellen Wilson Research Project

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

Immune consequences of gene therapy for ocular disorders

Dr. Hurwitz hypothesizes 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. Previously, he 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. Subsequently, Dr. Hurwitz's lab has been exploring the contribution of another vitreous component, the large hyaluronan-binding proteoglycan versican. In addition, they have investigated the G1 and G3 domains of versican, using expression constructs that span the known functional elements that may affect transgene expression. These constructs may be useful in designing more efficient vectors and delivery systems to optimize gene therapy outcomes and to limit toxicities, including immune consequences. Dr. Hurwitz and his research team have 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.

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

Impaired blood supply to the retina causes ischemic retinopathies that results in retinal vessel regression or vascular occlusion. Found to occur in various diseases, such as diabetic retinopathy, retinopathy of prematurity, and retinal vascular occlusion, these conditions affect a large population of patients and often result in irreversible vision loss due to the development and growth of abnormal new vessels. This process is referred to as retinal neovascularization. These abnormal vessels are leaky and fragile, resulting in vitreous hemorrhage, epiretinal or subretinal fibrosis, and tractional retinal detachment. At present, therapies for retinal neovascularization are limited, not always effective, and have considerable side effects. The goal of Dr. Zhang's project is to develop a novel, effective and inexpensive approach to selectively kill abnormal blood vessels in the retina without affecting normal blood vessels.

To this end, Dr. Zhang uses single-cell RNA sequencing technology (scRNAseq) to investigate the heterogeneity of endothelial cells in ischemic retinopathy and identify and characterize the features of putative endothelial cells for neovascularization. His research has identified 77 candidate molecules that could be potentially used as biomarkers for neovascular endothelial cells or as targets for the intervention. Two manuscripts based on data generated from RRF support have been published in a high-impact journal, Acta Neuropathol Commun, and one abstract was presented as a poster during the ARVO annual conference in May, 2021. Dr. Zhang's poster was awarded an ARVO Retina Research Foundation/Joseph M. and Eula C. Lawrence Travel Grant.

Dana and Gil Petri Research Project

Yingbin Fu, PhD

Cullen Eye Institute
Baylor College of Medicine
Houston, TX

A novel treatment strategy for age-related macular degeneration by targeting cholesterol transport

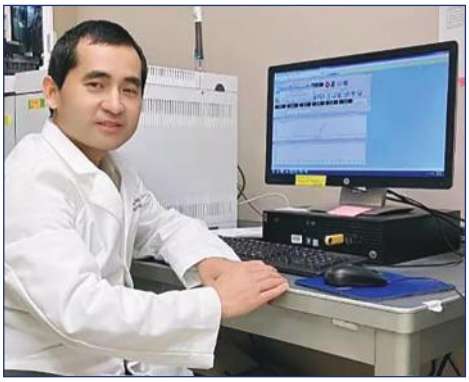
Age-related macular degeneration (AMD) is a major cause of blindness in the elderly. Choroidal neovascularization, the growth of abnormal leaky blood vessels beneath the retina, the wet type AMD, underlies 80-90% of legal blindness due to AMD. Up to one-fourth of patients have poor responses to currently available anti-VEGF treatment, and the long-term outcomes are suboptimal even among responders. The objective of Dr. Fu's project is to develop a highly innovative and effective AIBP/anti-VEGF combination therapy for wet AMD by targeting three critical components involved in CNV pathogenesis: VEGF, endothelial cells, and macrophages.

In 2021, with his collaborators, Dr. Fu successfully developed the first rabbit AMD model of anti-VEGF resistance. This is an important step toward preparing for an Investigational New Drug Application (IND) from the FDA and moving this important novel therapy into the clinic. The development of the first large mammalian AMD model of anti-VEGF resistance for a wide range of preclinical studies is highly significant. Importantly, Dr. Fu filed an international patent application for his studied combination therapy.

In September, Dr. Fu and collaborators received a $4.6 million Audacious Goal Initiative Grant award (1U24EY033272) from the NIH to advance stem cell therapy for various forms of retinal degeneration, including retinitis pigmentosa and AMD.

Dr. Zhao Zhang, a post doctoral research associate from the Fu lab, is examining the phenotype of an animal model of age-related macular degeneration using the Phoenix Mioron IV retinal imaging system.

Basic Research Projects



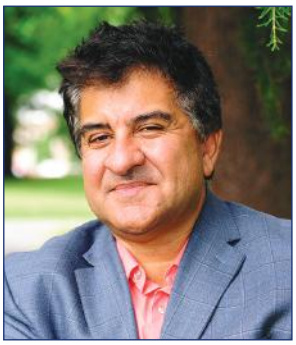
Jianhai Du, PhD
Department of Ophthalmology
West Virginia University School of Medicine
Morgantown, WV

Nutritional strategies in age-related macular degeneration

The goal of Dr. Du's project is to study the role of proline catabolism, the breaking down of this complex molecule into simpler ones that releases energy, in the healthy and diseased retina, and to develop nutritional approaches to treat age-related macular degeneration.

In 2021, Dr. Du's laboratory made significant progress in both aspects of his research. They proposed to investigate the role of proline transport in retinal metabolism and health in vivo. They found that the retinal pigment epithelium (RPE) specific proline transporter, SLC6A20A is important for retinal energy metabolism and visual function. These findings will contribute important preliminary data for Dr. Du's NIH grant application. In addition, Dr. Du proposed to determine the role of dietary proline in retinal metabolism and its protection of age-related visual decline. He discovered that RPE could utilize dietary proline to produce multiple crucial amino acids to nourish the neural retina, including glutamate, aspartate and serine. Significantly, the research team found that mice fed with proline-free diets for eight months show decreased visual function, suggesting that proline is important to maintain retinal metabolism and function. Some of Dr. Du's findings were presented at ARVO 2021 and published in Bio Protocol.

The Du Laboratory Team



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

CD5L-mediated autophagocytosis in RPE cells

The conclusion of 2021 brings Dr. Giorgianni's research project investigating the function of CD5L in the development of age-related macular degeneration (AMD) into its third year. He has discovered that patients affected by AMD have circulating auto antibodies in their blood that can attack and damage proteins present in the eye. One of these targeted proteins, CD5L, facilitates the degradation of metabolites that are toxic to the eye, especially those derived from oxidized low-density lipoproteins (OxLDL), thus potentially preventing damage to the retinal pigment epithelium (RPE). Accumulation of OxLDL is believed to contribute to the pathogenesis of AMD. Dr. Giorgianni has carried out studies to demonstrate the function of CD5L in the RPE and its role in the degradation of OxLDL. Dr. Giorgianni's findings, published in the International Journal of Molecular Sciences, will promote further understanding of the molecular mechanisms that lead to AMD and could provide new leads for the development of new therapeutic strategies.

Milam Brantley, MD, PhD
Department of Ophthalmology & Visual Sciences
Vanderbilt University
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.

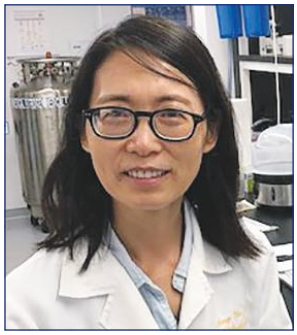
Dr. Brantley's data thus far suggest that treatment of retinal endothelial cells with arginine and citrulline leads to increased nitric oxide synthase activity and nitric oxide production. Arginine and citrulline in combination also reduce arginase-1 expression. His research has also shown that citrulline and arginine-induced angiogenesis, the growth of new blood vessels, is inhibited in the presence of an Akt inhibitor, suggesting that citrulline and arginine promote angiogenesis via the Akt signaling pathway. Lastly, Dr. Brantley demonstrated that citrulline plus arginine alters the association of Claudin-5 to the endothelial cell membrane, suggesting the mechanism by which citrulline and arginine increases retinal endothelial cell permeability.

James Monaghan, PhD
Biology Department
Northeastern University
Boston, MA

Analysis of notch signaling-mediated cell fate determination during regeneration of the neural retina

The cells of the mammalian retina do not regenerate, and in humans, this may progressively lead to retinal disease and possibly the complete loss of vision. Dr. Monaghan's research interests surround the process of regeneration that has been observed in the Mexican axolotl salamander. Since the salamander is able to replace or restore damaged or missing cells, tissues, organs, and even entire body parts to full function, Dr. Monaghan's aim is to uncover the specific mechanisms that control the birth of neurons and supporting glial cells in a regenerating salamander retina.

Dr. Monaghan's findings from the 2021 funding period have confirmed that the Notch signaling pathway plays a critical role in retinal regeneration. His research shows that Notch controls regeneration of photoreceptor neurons, and that two of its effector genes are expressed differentially in a regenerating retina. Dr. Monaghan's team has also found that the axolotl retina likely regenerates from the cells of the retinal pigmented epithelium, identifying for the first time the retinal stem cell population in this animal model.



Hong Yu, PhD
Department of Ophthalmology
Bascom Palmer Eye Institute,
University of Miami
Miami, FL

Modification of mitochondrial DNA using targeted CRISPR/ Cas9

Mutations in mitochondrial DNA lead to a spectrum of neurodegenerative diseases for which no effective treatment exists. Dr. Yu has chosen to focus on ATP6T8993G, one of the most severe mitochondrial gene mutations and responsible for Maternally Inherited Leigh Syndrome (MILS) and Neurogenic muscle weakness, Ataxia, and Retinitis Pigmentosa (NARP). These diseases are notorious for causing death and blindness in children and young adults.

Gene editing provides a promising treatment for these disorders; however, tools that exist for mtDNA manipulation are limited and inefficient. Dr. Yu's research seeks to overcome these limitations by developing and validating a novel genetic delivery system to facilitate a precise modification of mtDNA in stem cells. During the 2021 grant period, Dr. Yu successfully delivered CRISPR-Cas9 components into mitochondria by using a mitochondrial targeting system, which facilitated a successful mtDNA editing into a NARP cybrid cell line, a cytoplasmic hybrid of enucleated cells with mutated mtDNA and normal cells without mtDNA. The data generated from Dr. Yu's work contributed to a NIH R01 application.

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

Development of mutation-independent gene therapy approaches for CEP290-LCA

The overarching goal of Dr. Seo's research program is to develop generic and effective gene therapy strategies for large therapeutic genes. To this end, Dr. Seo has selected the CEP290 gene, which is the leading cause of Leber congenital amaurosis (LCA), a hereditary retinal dystrophy that causes severe vision loss in early childhood. In 2021, Dr. Seo generated an array of split CEP290 constructs with high-affinity peptide pairs to facilitate the re-joining of N- and C-terminal halves of CEP290. He tested their functionality in CEP290 mutant cells and generated a set of short promoters that drive transgene expression at various levels in mouse retinas. These promoters will be used in dual AAV vectors for moderate- to low-level transgene expression. In addition, Dr. Seo developed new strategies to improve the reconstitution efficiencies of the split constructs either at the DNA or protein levels. Successful completion of this study will not only move us forward to the cure of CEP290-LCA but also provide a framework for the development of gene therapy vectors targeting other large gene-associated genetic diseases.

Vladimir Kefalov, PhD
Department of Ophthalmology
and Visual Sciences
University of California, Irvine
Irving, California

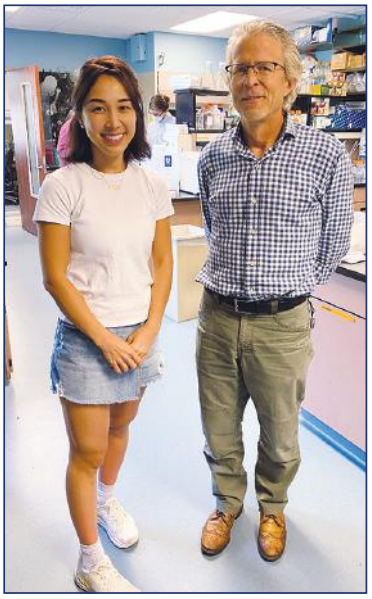
Understanding how the G90D and G90V rhodopsin mutations cause blindness

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 – congenital stationary night blindness (CSNB), and retinitis pigmentosa (RP), respectively. After generating mutant mice carrying the two rhodopsin mutations, Dr. Kefalov and his team analyzed their visual function and found that both G90D and G90V rhodopsin mutations cause suppressed scotopic light responses in four-month-old mice. The rod-driven responses from younger two-month-old mutant animals were similarly reduced, suggesting that this functional deficit is not caused by progressive retinal degeneration but rather by the abnormal function of the mutant rhodopsin. These findings will be presented at the 2022 ARVO meeting in Denver and, encouragingly, are consistent with the human phenotype associated with the G90D and G90V mutations.

Andrius Kazlauskas, PhD
Department of Ophthalmology and Visual Sciences
University of Illinois at Chicago
Chicago, IL

Hyperglycemia-induced mitochondrial adaptation

The fact that diabetic retinopathy typically develops only after a long duration of diabetes constitutes evidence, but not proof, of an endogenous system that protects the retina from the deleterious effects of diabetes. The Kazlauskas lab is developing experimental approaches to investigate this putative protective system. Using primary human retinal endothelial cells, they discovered that prolonged exposure to hyperglycemia (HG) induced mitochondrial adaptation (HIMA). This process involves clearance of dysfunctional mitochondria by a process called mitophagy. Cells that had undergone HIMA acquired resistance to death induced by diabetes-related insults such as oxidative stress, which is one of the drivers of diabetic retinopathy. These findings provide additional evidence for an endogenous protective system and reveal that it functions by inducing adaptation of cells within retinal vessels. Such adaptation is a plausible mechanistic explanation for why diabetic retinopathy does not develop coincident with the onset of diabetes.

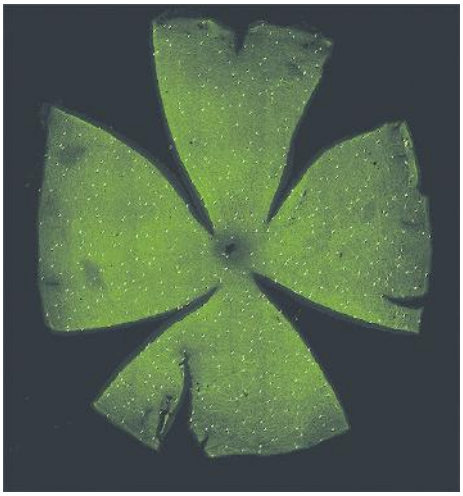


Anara Serikbaeva, PhD student and Andrius Kazlauskas in the Kazlauskas Lab. The RRF-funded project is the basis of A. Serikbaeva's PhD thesis research.

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

Investigation and modulation of inner retinal dysfunction in diabetes

Dr. Eggers's objective is to identify treatment targets to limit diabetic retinal neuronal dysfunction. Diabetic humans and animal models show retinal neuron problems, especially in the dim light-activated rod pathway, beginning before late-stage diabetic retinopathy blood vessel problems. Dr. Eggers is an expert in rod pathway signaling and will determine if this pathway is vulnerable to diabetic damage, and identify the mechanism of dysfunction to develop targeted therapeutics to prevent the neuronal progression of vision loss. Using electrical recordings of retinal neuron's response to light, she will determine if reduced retinal dopamine is responsible for these retinal functional changes. During the initial year of Dr. Eggers's project, she found that one type of dopamine receptor has reduced capability to modulate responses to light in the diabetic retina without reduced expression. This suggests that retinal dopamine signaling pathways are affected in early diabetes. However, the continued receptor presence and function, suggest that dopamine supplementation could be a viable treatment option.



Full retinal image of tyrosine hydroxylase (TH) staining, showing dopaminergic amacrine cells.

2021 RRF Pilot Grant Research Publications

The 19 researchers that RRF supported in 2021 published 29 manuscripts in high-impact, peer-reviewed journals. Science grows and advances by constantly being challenged, revised and expanded. It is through publication that research is disseminated to others and the collection of knowledge is expanded. Publication makes scientific researchers and practitioners with similar interests aware of new knowledge in the field and it helps to advance knowledge and its application. Disseminating breakthrough research through publication is essential to RRF's mission and a factor is determining the ongoing support of our vision researchers. **A complete 2021 publication listing can be found on our website:** retinaresearchfnd.org.

Macula Society Grant Recipient

The RRF Margaret and Mills Cox Macula Society Research Project

Prithvi Mruthyunjaya, MD, MHS
Byers Eye Institute, Stanford University Medical Center
Palo Alto, CA 94303

Aqueous Humor Proteomic analysis to detect targetable diagnostic biomarkers in uveal melanoma

As the Director of Ocular Oncology at the Byers Eye Institute, Dr. Mruthyunjaya's clinical interests lie in the multi-disciplinary, vitreoretinal approach to ocular tumors and simulating conditions, and complex vitreoretinal disorders. He manages both adult and pediatric ocular cancers with a focus on novel therapeutics, intraocular biopsy, and vision-saving strategies to reduce treatment toxicity. He has authored over 125 papers in peer reviewed journals and trained over 45 retina fellows.

Dr. Mruthyunjaya's research interests span three main areas: novel therapeutic strategies to treat intraocular tumors, enhanced imaging of retinal and oncologic disease, and improving patient outcomes through collaborative research networks. A proponent of multi-disciplinary research teams, he is currently working on a micro bubble drug delivery system in model systems of retinoblastoma as well as multi-centered trials of tumor antigen targeting chemotherapy for ocular melanoma. He is interested in new surgical techniques to safely obtain tumor biopsy samples and enhance detection yield. Intraocular imaging with wide-field techniques and latest generation OCT technology has provided novel insights into the early diagnosis of ocular tumors including lymphoma, melanoma, and retinoblastoma. Finally, he actively engages in collaborative networks to advance research and therapies for patients, and one such group he conceived, the Ocular Oncology Study Consortium, was a collaboration between 13 international ocular oncology centers to tackle important questions in the role of tumor genetics, reducing radiation toxicity and tumor biopsy. Dr. Mruthyunjaya will share his research findings at the 2023 annual meeting of The Macula Society.

Research Chairs and Professorships

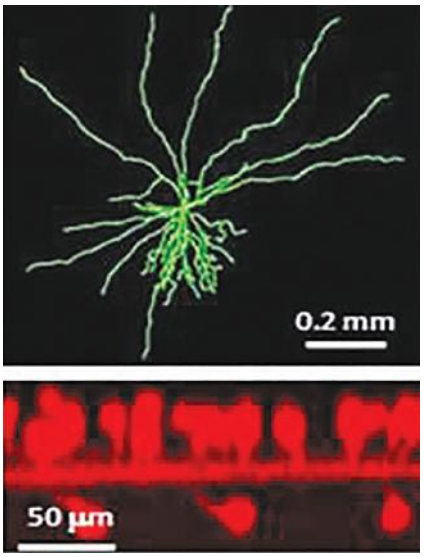
Six academic chairs and three professorships are supported by RRF at nationally recognized research institutions in Houston, Texas, and Madison, Wisconsin. These vision scientists conduct original retina research that has the potential to increase understanding of the retina or retinal diseases. The projects provide inspiring research opportunities for young vision scientists, and benefit from opportunities to collaborate with top researchers within related academic disciplines.

RRF Research Chair

Ching-Kang Jason Chen, PhD
Departments of
Ophthalmology, Biochemistry
and Molecular Biology,
Neuroscience
Baylor College of Medicine
Houston, TX

Transducin- and Melanopsin-Independent Phototransduction

The Chen laboratory in 2021 takes on the initiative of working on a poorly understood neuronal group of the retina called the wide-field amacrine cell (WAC). Unlike its narrow-field and mid-field counterparts, the WAC sends far-reaching dendrites to different parts of the retina, and because the area covered by its dendrites far surpasses the areas surveyed by contemporary connectomic studies, exactly how many WAC types exist, their presynaptic and postsynaptic partners, and their functions in the retina still elude our understanding. The Chen laboratory has discovered that a previously described WAC called TH2-AC can be uniquely labeled in a commercial mouse line, and by using an optogenetic approach has identified eight retinal ganglion cell types as TH2-AC's postsynaptic partners. Moreover, by removal of a TH2 AC-specific protein named trophoblast glycoprotein, the Chen laboratory has revealed that TPBG is required for normal TH2-AC dendritic morphology, as well as for one of TH2-AC's functions in modulating retinal contrast detection. Usually by knocking out a gene, a function carried out by the targeted gene is disabled and results in a "loss-of-function" phenotype. In the case of the trophoblast glycoprotein gene, its inactivation surprisingly leads to enhanced contrast detection to a specific spatial range of light stimuli. Under the auspices of RRF and administratively well-preserved in the Ophthalmology Department, an investigator-initiated research proposal seeking federal support to study the function of trophoblast glycoprotein in the TH2-AC and the role of TH2-AC in retinal contrast detection has been submitted and reviewed favorably by the NIH Biology and Development of the Eye Study Section. This highly original research proposal will also attempt targeted cell ablation in developing and adult retinas to study other functions the TH2-AC might play in mammalian vision.



Upper: Virtually reconstructed dendritic morphology of a mouse TH2-AC showing the short and long dendrites, the latter of which reach far beyond its cell body.

Lower: Confocal image of a cross section of a DATCre/Ai9 mouse retina showing the dendritic stratification level in the inner plexiform layer.

Dr. Tim Stout, Director, Cullen Eye Institute and Chair, Department of Ophthalmology, Baylor College of Medicine, with Dr. Jason Chen, Dr. Alice McPherson and Dr. Sam Wu at the Retina Research Program Laboratories funded in part by RRF for four decades.

Walter H. Helmerich Chair

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

Computational Imaging of the Cellular Microenvironment

Dr. Eliceiri's research interests are in the areas of developing 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 the Wisconsin Reading Center on deep learning approaches for fundus images that can use less annotated datasets.

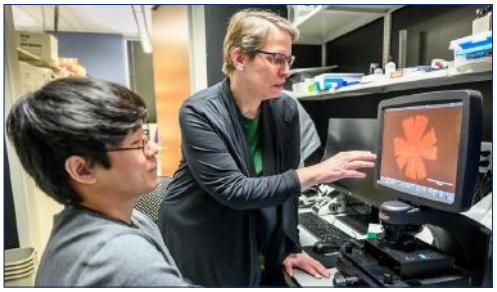
Members of the Eliceiri lab and collaborators at an imaging retreat

RRF Research Chair

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

Adenosinergic Signaling and Ocular Vascular Homeostasis

Dr. Sheibani showed TrkB receptor agonist, 7,8-dihydroxyflavon, provides no protection against retinal ischemic damage. He also reported caffeine mitigates choroidal neovascularization by tampering inflammatory and angiogenesis activities. He was involved with reporting the important role of NAMD receptor in homocysteine mediated AMD. He recently reviewed the impact of hypoxic-ischemic encephalopathy on retinal neurovascular integrity and function. He also reported the importance of alterations in VEGF164a isoforms expression in ischemic retinopathy. He showed that the retinas from juvenile mice, like neonates, are susceptible to neurovascular degeneration after hypoxic-ischemic injury. He demonstrated the lack of thrombospondin-1 (TSP1) expression in retinal endothelial cells or mononuclear phagocytes recapitulate the phenotypes he reported in mice globally lacking TSP1. *Reported in: PLoS One (Dec. 2021), Front Cell Dev Biol (Oct. 2021), Int J Mol Sci (Aug. 2021), J Ophthalmic Vis Res (July 2021), Pediatr Res (July 2021), Sci Rep (June 2021), Front Cell Dev Biol (April 2021).*



Dr. Sheibani's graduate student Yong-Seok Song (left) and Dr. Christine Sorenson (right) examining retinal vasculature integrity in a wholemount from a line of transgenic mice. (Photos by Althea Dotzour / UW–Madison)

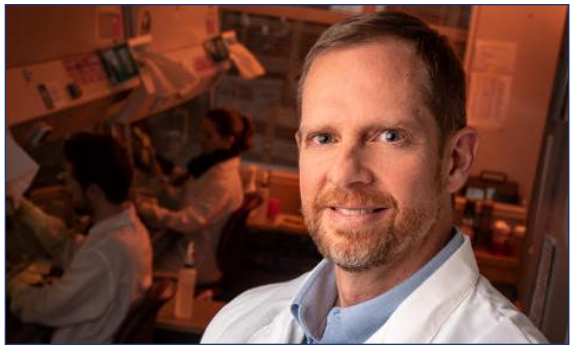
Kathryn and Latimer Murfee Chair

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

Bioengineering of Novel Cell and Gene Therapies for the Retinal Disorders

The goal of Dr. Saha's lab is to develop new, personalized therapies and human disease models using novel biomaterials and genetic engineering techniques. His lab has developed an array of engineering approaches that seek to generate new cells, organoids, and tissues from patient samples, as well as a suite of gene-editing technologies to knockout, correct, or insert transgenes into human cells. One area of focus is developing gene-editing therapies that would correct the genome within the cells of the retina and restore sight or prevent its loss. In the eye, genome editors are capable of affecting many cell types, including rod and cone photoreceptors and nerves. Dr. Saha investigates the beneficial and adverse effects from such treatments by identifying changes in the genetic sequence of photoreceptor cells after treatment. By knowing the result of the changes, this ensures that only safe genome editors move forward in the development process and ultimately avoids adverse events in patients who may be treated with genome-editing therapeutics.

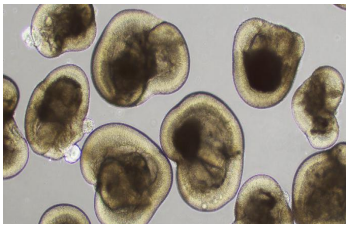
Emmett A. Humble Distinguished Directorship

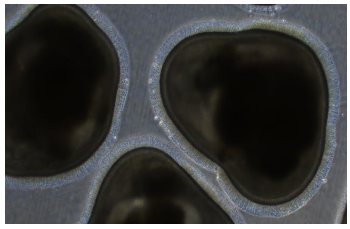


David M. Gamm, MD, PhD
Distinguished Director, McPherson Eye Research Institute
Department of Ophthalmology and Visual Sciences
University of Wisconsin, Madison, WI

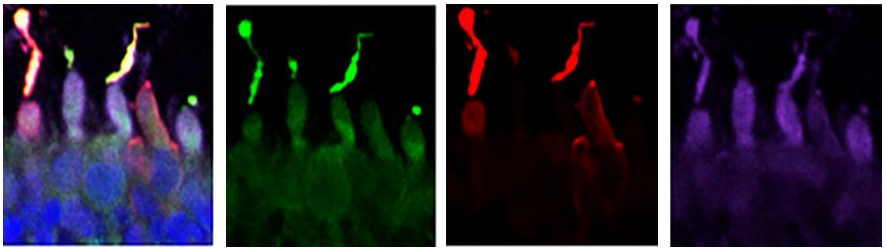
Modeling and Treating Retinal Disease with Human Induced Pluripotent Stem Cells (hiPSCs)

Dr. Gamm pioneered the use of human induced pluripotent stem cells (hiPSCs) to generate 3-dimensional retinal organoids in a laboratory dish, which he uses to model human retinal diseases and test drug and gene therapies. This past year, his lab modeled Leber congenital amaurosis, retinitis pigmentosa, and Best disease, among multiple other active projects. He is also employing his technology to generate clinical-grade photoreceptors and retinal pigment epithelium (RPE) cells on an industrial scale in conjunction with Opsis Therapeutics (Madison, WI), with the goal of treating patients with late-stage retinitis pigmentosa and age-related macular degeneration. In 2021, Dr. Gamm and collaborators discovered that hiPSC-derived cone photoreceptors can function in manner similar to nonhuman primate foveal cones. In addition, they determined the optimal developmental time window for hiPSC-cones to extend axons and make connections with other cells. Together, these findings accelerate their efforts to bring photoreceptor replacement therapies to clinical trials.





Gamm lab retinal organoids: Brightfield microscopic image of young, "stage 1" retinal organoid derived from hiPSCs.
Gamm organoids with outer segments: Brightfield microscopic image of mature, "stage 3" retinal organoids derived from hiPSCs that display light-detecting outer segments on their surfaces.



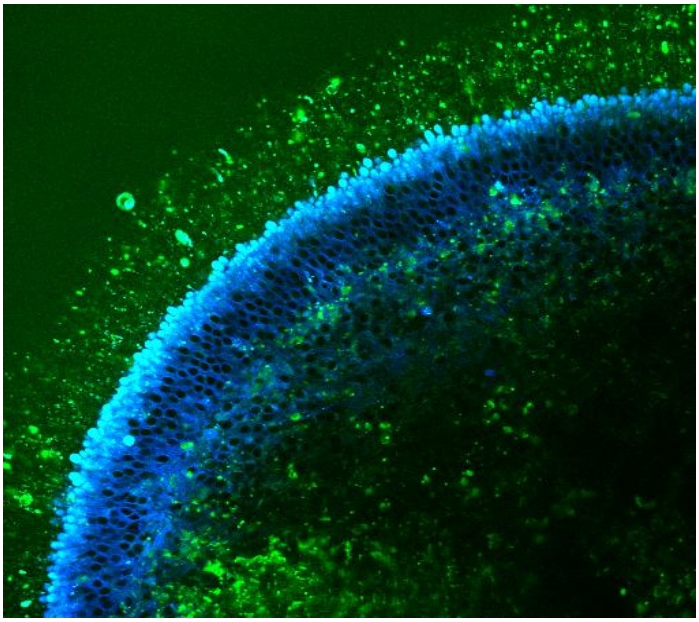
Cone figure: Images of hiPSC-derived cones showing expression of different cone outer segment proteins (CNGB3 in green, M/L opsin in red, and Arrestin 3 in violet). Gamm lab.

Daniel M. Albert Chair

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

Optical imaging of retinal cell function

Dr. Skala's lab develops new optical imaging methods to monitor cell function in the retina, using sources of contrast already present in cells. These methods provide high resolution, biochemical information and are especially well suited for human use. Recently, her lab has developed fluorescence techniques to monitor visual cycle dynamics in human stem-cell derived photoreceptor cells, and to monitor melanin levels in humans with new optical molecular tomography technologies. These tools are now in use to assess gene editing therapies in the retina, and to monitor early changes that precede vision loss in retinal diseases.



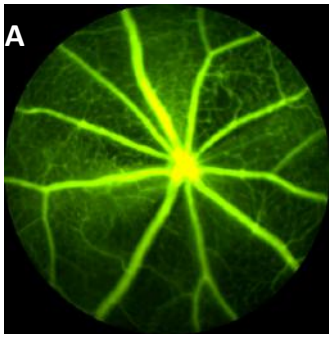
Autofluorescence imaging of human stem-cell derived photoreceptor cells. This imaging technique takes advantage of fluorophores already present in the cells, such as retinoids, to monitor visual cycle dynamics in living cells.

Edwin and Dorothy Gamewell Professor

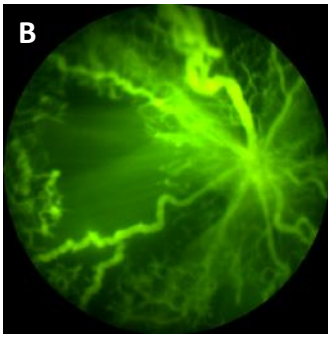
Olachi J. Mezu-Ndubuisi, MD, OD
McPherson Eye Research Institute
Department of Pediatrics
Department of Ophthalmology
University of Wisconsin
Madison, WI

Investigating Pro and Anti-angiogenic Therapies for Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a condition of abnormal retinal vascularization in premature infants exposed to supplemental oxygen, characterized by dysregulation of vascular endothelial growth factor (VEGF). Current ROP therapies are limited in efficacy due to systemic toxicities, therefore ROP remains one of the leading causes of childhood blindness worldwide. An enhanced understanding of mechanisms of VEGF dysregulation during ROP is vital to developing effective therapies. Dr. Mezu-Ndubuisi's research established in vivo (live) retinal imaging techniques in a mouse model of oxygen-induced retinopathy (OIR), which showed unique long-term vascular, structural and functional phenotypes that correlate with histopathologic evidence of neuroglia dysfunction. Her laboratory demonstrated that despite high endogenous VEGF expression during OIR, there was reduced angiogenic activity. She showed differential expression of VEGF isoforms, pro-angiogenic VEGFA164a and antiangiogenic VEGFA164b, during OIR. Dr. Mezu-Ndubuisi is currently investigating the efficacy of innovative pro- and anti-angiogenic treatments for ROP, while avoiding systemic toxicity.

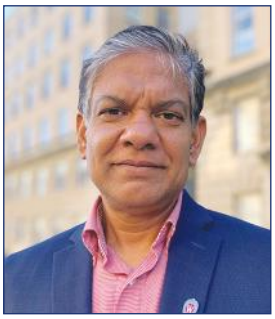


Uniform blood vessels in a 19-day old mouse raised in room air.



Abnormal vessels in a 19-day old mouse exposed to hyperoxia.

M.D. Matthews Research Professor



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

Vision Loss due to Ion-Channelopathy

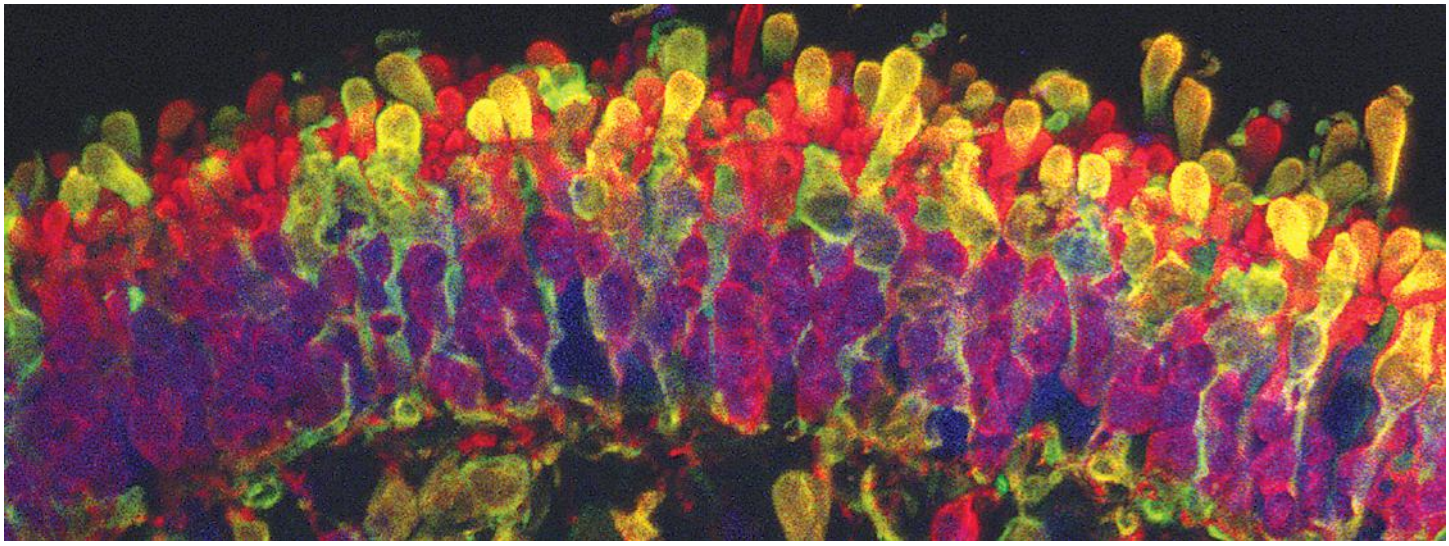
Genetic eye diseases are the predominant, leading cause of blindness across all ages, from infants to adults. Dr. Pattnaik's research focus is on the basic biology that governs ion channel function, molecular mechanisms of disease and novel therapies, and diagnostic use of visual function tests. Key discoveries include the discovery of novel gene defects that cause blindness due to mutations in an inwardly rectifying potassium channel (Kir7.1). This protein is present in the retinal pigment epithelium (RPE) within the retina that helps with the diffusion of potassium across the cell. To model LCA16 blindness, Dr. Pattnaik's team used both induced pluripotent stem cells (iPSC) derived RPE cells from a Leber Congenital Amaurosis patient and in mice with Kir7.1 knock-down. Dr. Pattnaik's lab has developed a gene-therapy treatment for patients that is in advance stage clinical translation through Hubble Therapeutics. Using a particular nonsense mutation disease model, Dr. Pattnaik's lab is pursuing small molecule drugs, or biological molecules such as DNA or RNA that can be targeted to RPE cells as other possible treatments for pediatric blindness caused by defects in both the RPE cells and also the photoreceptors.

Rebecca Meyer Brown Professor

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

Alterations in the Inner Retinal Circuitry after Loss of Photoreceptor Input.

Loss of photoreceptor input is a hallmark of several blinding diseases. By combining genetic approaches with single-cell electrophysiology and high-resolution light and electron microscopy, the Hoon Lab is studying how second order neurons that rely on photoreceptor input alter their morphology and connectivity after loss of photoreceptor input. By contrasting conditions where photoreceptors degenerate versus conditions where photoreceptor signaling is perturbed without actual loss of photoreceptors, the Hoon Lab is delineating which connections within the inner retinal circuitry rely on afferent activity from photoreceptors and which need the physical presence of photoreceptors to remain functional. Interestingly, these connection types can be disparate. Knowledge about alterations in the inner retinal circuitry after loss of photoreceptor input will unveil new therapeutic targets that can be leveraged to re-instate visual function in a degenerating circuit.



Capowski-Gamm lab retinal organoid-photoreceptor image: Immunocytochemistry image of retinal tissue grown in a laboratory dish from hiPSCs. Rods are shown in yellow and cones in red.

These awards are presented to renowned scientists in recognition of their lifetime achievement.

The Award of Merit in Retina Research

Douglas A. Jabs, MD, MBA
Johns Hopkins Bloomberg
School of Public Health
and School of Medicine
Baltimore, MD

Uveitis Management: What Have We Learned from Clinical Trials?

In being chosen for the Award of Merit, Dr. Jabs gave the Charles L. Schepens Lecture at the 54th Annual Scientific Meeting of The Retina Society in Chicago held in September. His lecture reviewed treatment advances in uveitis management resulting from recent clinical trials.

Dr. Jabs is the Director of the Center for Clinical Trials and Evidence Synthesis at the Johns Hopkins University Bloomberg School of Public Health. Prior to his current position, he was the founder of the Division of Ocular Immunology and Uveitis at Wilmer Eye Institute, also at Johns Hopkins University School of Medicine.

Dr. Jabs is an internationally recognized expert in the evaluation and management of patients with uveitis and related immune-mediated ocular disorders, with a long track record in clinical trials, cohort studies and translational research. Dr. Jabs has served as the chair of numerous NIH-funded multi-center, national and international, randomized, comparative effective trials and of long-term prospective cohort studies. He has authored over 320 peer-reviewed journal articles and over 45 book chapters.

RRF Pyron Award for Outstanding Achievement in Retina Research

Cynthia A. Toth, MD
Duke University School
of Medicine
Durham, NC

Retinal OCT at 29: Forever Young and for the Young

Dr. Cynthia Toth was recognized as the 2021 Pyron Award recipient during the ASRS Annual Meeting, held in October in San Antonio, TX where she presented the 26th annual RRF Gertrude D. Pyron Award lecture. Dr. Toth received the honor in recognition of her research in optical coherence tomography (OTC) that has led to integration of OCT imaging into retinal surgery clinical practice and advancement of OCT imaging in pediatric retina treatment.

As a vitreoretinal surgeon and clinician-scientist at Duke University, Dr. Toth is Vice Chair of Clinical Research and Director of Physician-Scientist Development for Duke Eye Center. Following completion of her fellowship, where she pursued research in optical coherence tomography (OCT) retinal imaging, she joined the Duke Faculty.

Dr. Toth succeeded Dr. Robert Machemer in developing macular translocation surgery and as director of the surgical instrument prototyping laboratory. She applied her surgical expertise to complex adult and pediatric vitreoretinal conditions, and many of her surgical technologies translated to clinical use. Dr. Toth transformed the laboratory to the Duke Advanced Research in SD/SS OCT Imaging (DARSI) Laboratory, and co-founded the Duke Reading Center. Her individual and multi-center research leadership has been funded by NIH, Foundations and Industry. With her colleagues in biomedical Engineering, she was the first to integrate OCT imaging into use in retinal surgery and has taken image-guided ocular microsurgery to the next level to improve surgeon performance. Her research has also been the genesis for the field of retinal OCT imaging in infants and young children, and enabled FDA approval of the first handheld system for infant OCT imaging.

The majority of Dr. Toth's 285-plus peer-reviewed publications, chapters and book, advance the understanding and use of OCT imaging and investigational imaging devices to guide diagnosis and clinical and surgical management. Dr. Toth's many contributions have been recognized by her peers with numerous awards, including the 2013 RRF Award of Merit in Retina Research.

Charles L. Schepens, MD/AAO Award

Mark S. Humayun, MD, PhD
USC Roski Eye Institute
University of Southern California (USC)
Los Angeles, CA

Advanced Retinal Implants

The 2021 RRF Charles L. Schepens, MD/AAO Award was given to Mark S. Humayun, MD, PhD. He delivered the Schepens Lecture during the proceedings of the Retina Subspecialty day at the American Academy of Opthalmology's annual meeting held in New Orleans in November.

Dr. Humayun is the Cornelius J. Pings Chair in Biomedical Sciences, professor of ophthalmology, biomedical engineering, and integrative anatomical sciences, director of the University of Southern California (USC) Ginsburg Institute for Biomedical Therapeutics, and co-director of the USC Roski Eye Institute.

Dr. Humayun considers the development of advanced implants for retinal diseases to be his major contribution to the field of visual sciences. He developed the first FDA-approved artificial retina, Argus II, for sight restoration. The advanced bioelectronic implant uses controlled electrical pulses to stimulate the remaining retinal neurons in the setting of total photoreceptor loss. It has restored partial sight to totally blind patients with retinitis pigmentosa enabling them to see large letters and objects. Future improvements will enhance the resolution and develop a visual cortical bioelectronic implant for patients who do not have a viable optic nerve. Dr. Humayun is also the inventor of a bioengineered scaffold with stem cell derived retinal pigment epithelium (RPE). This implant is positioned subretinally and is for patients with advanced, dry macula degeneration and assists with re-establishing host photoreceptor function by providing a healthy layer of RPE.

In completed phase1/2a clinical trials, the results show an unprecedented gain in visual acuity following implantation in very advanced legally blind (20/200 or worse) patients.

Dr. Humayun is an internationally recognized pioneer in vision restoration. He holds more than 125 issued patents, and has authored over 250 peer-reviewed publications. For his extraordinary contributions, Dr. Humayun was awarded the U.S.'s highest technological achievement award, The National Medical of Technology and Innovation by President Barack Obama in 2016. Dr. Humayun has previously received the 2009 RRF Award of Merit, given by The Retina Society, and the 2020 RRF Pyron Award for outstanding achievement in retina research, given by ASRS.

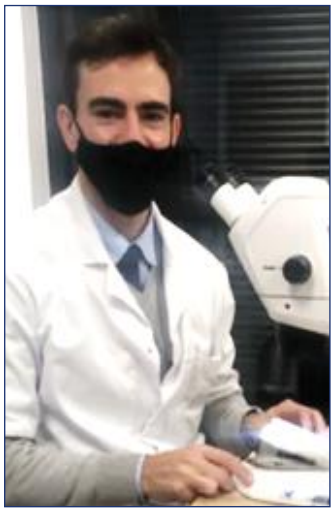
Four RRF established awards were not bestowed in 2021. The Gonin Lecturer given in collaboration with Club Jules Gonin and the Gonin Medal given in conjunction with the International Council of Ophthalmology will both be awarded in 2022. The Paul Kayser/RRF Global Award, given in conjunction with Pan-American Association of Ophthalmology (PAAO) will be awarded in 2023. The Paul Kayser International Award given in conjunction with the International Society for Eye Research (ISER) will be awarded in 2023.

RRF funds two international fellowship programs, 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. 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.

In 2021, RRF pivoted to a new partnership with the Ophthalmology Foundation (OF), an organization whose core leadership has been involved with the fellowship program from the outset, and their partner, International Ophthalmological Fellowship Foundation (IOFF). This collaboration will ensure the continuity of the program and provide a high-quality experience for recipients of the RRF Helmerich International Fellowship Program.



During 2021, Helmerich fellow, **Dr. Juan Manuel Lopez** trained in Medical Retina at the Intercommunal Hospital of Creteil/Paris under supervision of Professor Eric Souied, and his fellowship will continue through to November, 2022.

"My sincere thanks to Professor Alice R. McPherson for being the founder of this wonderful program, and for generating resources and helping ophthalmologists reach their professional dreams of obtaining excellent training opportunities with the best ophthalmologists in the world. The Intercommunal Hospital of Creteil is of the highest level, at the forefront of scientific and technological knowledge, and my fellowship has far exceeded my expectations. This fellowship will help shape my career and contribute to my professional development. I hope to be able to diagnose diseases at an early stage and provide patients with multiple treatment options, including cutting-edge therapy. I also hope to pass on my experience and knowledge to the next generation of ophthalmologists in Argentina. Thank you for helping young ophthalmologists evolve and find their dreams."

Dr. Juan Manuel Lopez

Helmerich Fellow

Dr. Perpetua Odugbo from Nigeria, is receiving a glaucoma fellowship at the Jules Stein Eye Institute, University of California, Los Angeles (UCLA), under the supervision of Dr. Joseph Caprioli.

Dr. Odugbo participates in weekly glaucoma conferences during which pertinent topics on glaucoma are presented, and has completed a microsurgical training program during which she was able to insert an iStent for the first time. Dr. Odugbo also has commenced her first research project, which will focus on risk factor analysis of glaucoma progression in African-Americans.

Dr. Odugbo's fellowship slightly delayed in starting, will continue until April, 2023.

International Fellowships

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.

Mariana Matioli da Palma, MD from Brazil, was accepted for an Ophthalmic Genetics Fellowship at the Casey Eye Institute in Oregon Health & Science University (OHSU), Portland, Oregon.

Dr. Matioli da Palma is pursuing a PhD in ocular genetics.

Her experience at the Casey Eye Institute provided a wide array of learning opportunities. Her experiences are representative of the training similarly received by the prior 64 recipients of the Gillingham Pan-American Fellowships.

Dr. Matiolo's mentor, Dr. Mark Pennesi, MD., PhD, is a world-renowned specialist in the field of ocular genetics whose research focuses on developing treatments for inherited retinal diseases. Under his guidance, she learned about all aspects of her chosen specialty, from providing patient care to conducting clinical trials. Dr. Matiolo also learned about ophthalmic genetics and ocular immunology from assistant professor Dr. Paul Yang, MD, PhD. She attended a wide variety of challenging cases with difficult diagnoses, including congenital diseases and inherited disorders with immunomodulatory responses to learn how to manage inherited eye diseases.

Dr. Paul Yang and Dr. Matioli during a challenging and great clinic day.

Dr. Matioli followed Dr. Andreas Lauer in the operating room to learn about the surgical aspects of gene therapies in clinical trials, and Dr. J. Peter Campbell, a pediatric retina specialist to learn about research projects on retinopathy of prematurity and pediatric retinal disease imaging.

Dr. Matiolo enjoyed her clinic days with patients, her exposure to numerous ocular cancer research projects, and her interaction with international fellows from India and Taiwan. All experiences contributed to her knowledge of ophthalmology practices and cultures around the world.

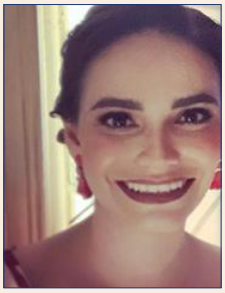
Dr. Matoli and her husband

"The experience with patients was rewarding . . . everything was wonderful. I was lucky to be able to participate in research projects,…prepare manuscripts that [were] approved, and have one of the best experiences in my academic career. We can't stop learning. We need to continually pursue better education. Thank you to the Pan-American Ophthalmological Foundation and the Retina Research Foundation for this award."

Mariana Matioli da Palma, MD

Dr. Andreas Lauer, Dr. Brittni Scruggs, and Dr. Matioli before a gene therapy surgery.

Dr. Matioli and Dr. Mark Pennesi, an inspiring professor.



Gillingham Fellow

Estephania Feria Anzaldo, MD from Mexico, was accepted for a Retinopathy of Prematurity (ROP) and Pediatric Retina Fellowship at Bascom Palmer Eye Institute, Miami, FL USA, with Dr. Audina Berrocal.

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.

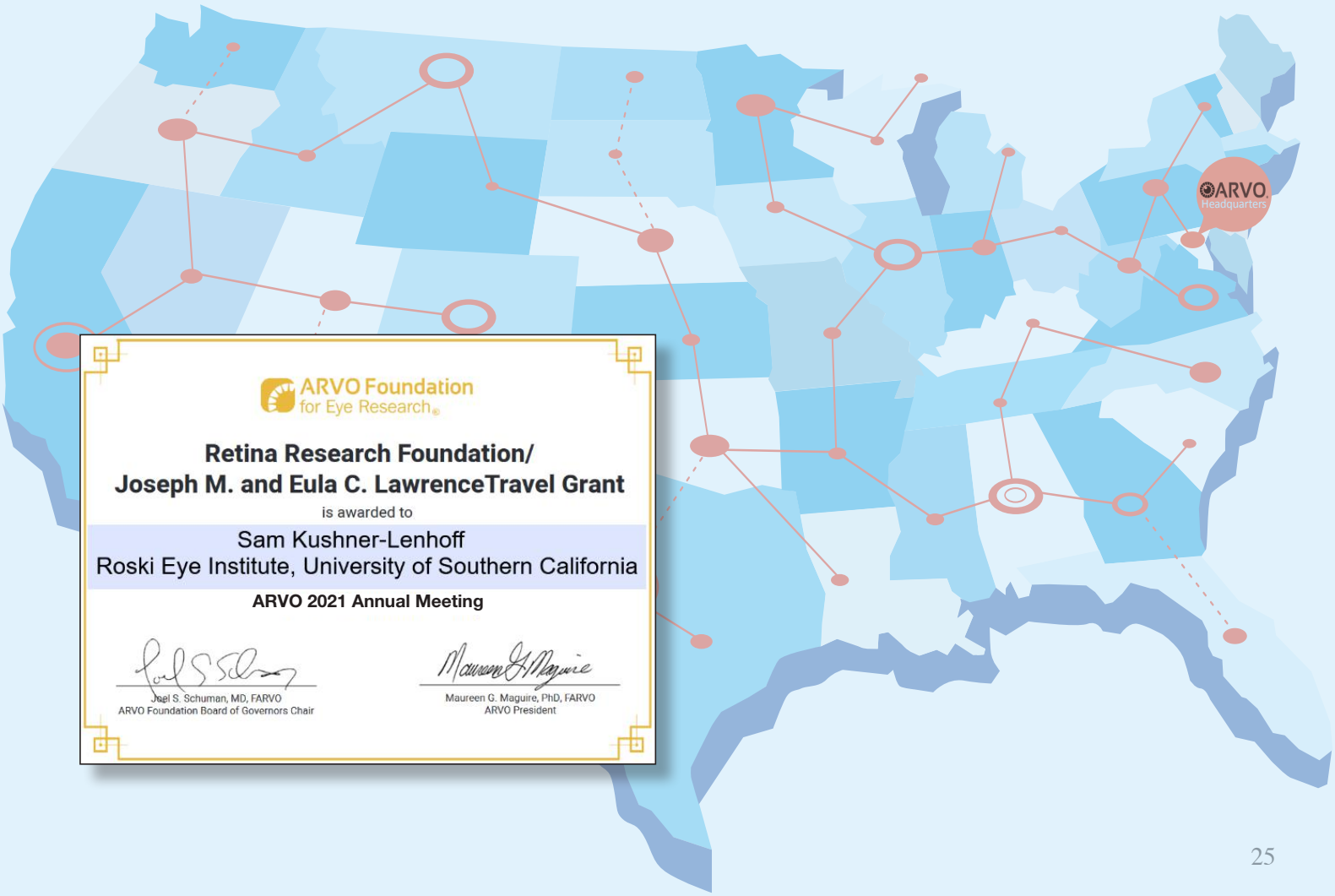
American Academy of Ophthalmology Educational Trust Fund

In collaboration with the American Academy of Ophthalmology, this educational program provides ophthalmologists with 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. The funding level for this educational effort in 2021 was $50,000, and made possible the development of new retina case study materials on retinal hemorrhages, and updates to basic and clinical science courses on retina and vitreous. These resources are available to clinicians as part of AAO's CME activities on the One® Network.

RRF Lawrence Travel Scholarships

In 1992, a gift from Joe M. and Eula C. Lawrence provided funding for the creation of the Lawrence Travel Scholarship program. Administered by the Association for Research in Vision and Ophthalmology (ARVO), the program provides travel-expense scholarships to young vitreoretinal scientists for attending ARVO's annual meeting and participating in presentation of their scientific works. The opportunity to present their papers or posters and to interact with their research peers is important to their career development and quickens the pace of research progress.

The ARVO meeting was held virtually in 2021, and RRF sponsored 126 virtual travel grants. Hailing from many of the country's most prestigious research institutions, these young scientists participated in a virtual poster hall, with the ability to browse the latest research by scientific section, author, title, or by key words within an abstract or poster. RRF heard from many of the grant recipients how stimulating and thought provoking they found it to learn about the research of others, providing further confirmation of the importance of disseminating eye and vision research knowledge through this program.



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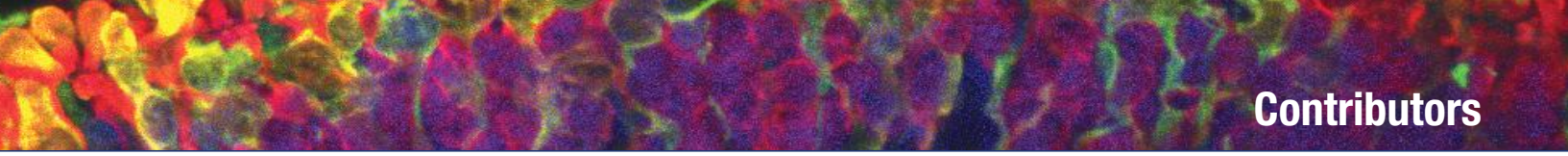

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RETINA RESEARCH FOUNDATION
COMBINED STATEMENT OF FINANCIAL POSITION

December 31, 2021
(with summarized financial information as of December 31, 2020)

	General Funds			Endowment Funds			2021	2020 Total
	Without Donor Restrictions	With Donor Restrictions	Total	Without Donor Restrictions	With Donor Restrictions	Total	**Total All Funds**	All Funds (Memorandum Only)
Assets								
Cash and cash equivalents	$ 1,092,035	$ 162,000	$ 1,254,035	$ -	$ 455,281	$ 455,281	**$ 1,709,316**	$ 3,299,592
Contributions receivable	13,550	150,000	163,550	-	-	-	**163,550**	146,137
Investments	2,976,085	-	2,976,085	5,741,640	64,139,340	69,880,980	**72,857,065**	61,413,280
Furniture and equipment, net of accumulated depreciation of $11,100	14,749	-	14,749	-	-	-	**14,749**	14,932
Intangible assets	12	-	12	-	-	-	**12**	12
Other assets	10,209	-	10,209	-	-	-	**10,209**	15,235
Total assets	$ 4,106,640	$ 312,000	$ 4,418,640	$ 5,741,640	$ 64,594,621	$ 70,336,261	**$ 74,754,901**	$ 64,889,188
Liabilities and net assets								
Accounts payable	$ -	$ -	$ -	$ -	$ 81,976	$ 81,976	**$ 81,976**	$ 65,171
Grants payable	150,000	-	150,000	-	-	-	**150,000**	200,000
Total liabilities	150,000	-	150,000	-	81,976	81,976	**231,976**	265,171
Net assets	3,956,640	312,000	4,268,640	5,741,640	64,512,645	70,254,285	**74,522,925**	64,624,017
Total liabilities and net assets	$ 4,106,640	$ 312,000	$ 4,418,640	$ 5,741,640	$ 64,594,621	$ 70,336,261	**$ 74,754,901**	$ 64,889,188

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

For the year ended December 31, 2021
(with summarized financial information for the year ended December 31, 2020)

	General Funds			Endowment Funds			2021	2020 Total
	Without Donor Restrictions	With Donor Restrictions	Total	Without Donor Restrictions	With Donor Restrictions	Total	**Total All Funds**	All Funds (Memorandum Only)
Revenues								
Contributions	$ 318,712	$ 277,500	$ 596,212	$ 25,327	$ 1,318,281	$ 1,343,608	**$ 1,939,820**	$ 1,695,110
Investment income, net	71,582	-	71,582	126,060	1,394,741	1,520,801	**1,592,383**	1,391,432
Realized and unrealized gains on investments, net	339,648	-	339,648	652,380	7,270,844	7,923,224	**8,262,872**	3,808,634
Mineral interest income and other income	11,237	-	11,237	-	-	-	**11,237**	9,214
Income transferred from Endowment Fund investments	1,714,322	77,000	1,791,322	(147,204)	(1,644,118)	(1,791,322)	**-**	-
Net assets released from restrictions - satisfaction of program restrictions	122,500	(122,500)	-	-	-	-	**-**	-
Total revenues	2,578,001	232,000	2,810,001	656,563	8,339,748	8,996,311	**11,806,312**	6,904,390
Expenses								
Program services								
Research projects and grants	1,749,132	-	1,749,132	-	-	-	**1,749,132**	1,969,509
Supporting services								
Management and general	158,272	-	158,272	-	-	-	**158,272**	167,240
Total expenses	1,907,404	-	1,907,404	-	-	-	**1,907,404**	2,136,749
Changes in net assets	670,597	232,000	902,597	656,563	8,339,748	8,996,311	**9,898,908**	4,767,641
Net assets, beginning of year	3,286,043	80,000	3,366,043	5,085,077	56,172,897	61,257,974	**64,624,017**	59,856,376
Net assets, end of year	$ 3,956,640	$ 312,000	$ 4,268,640	$ 5,741,640	$ 64,512,645	$ 70,254,285	**$ 74,522,925**	$ 64,624,017

In Memoriam

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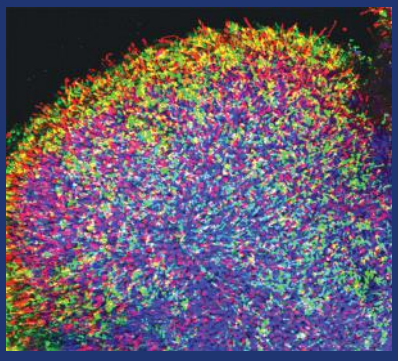
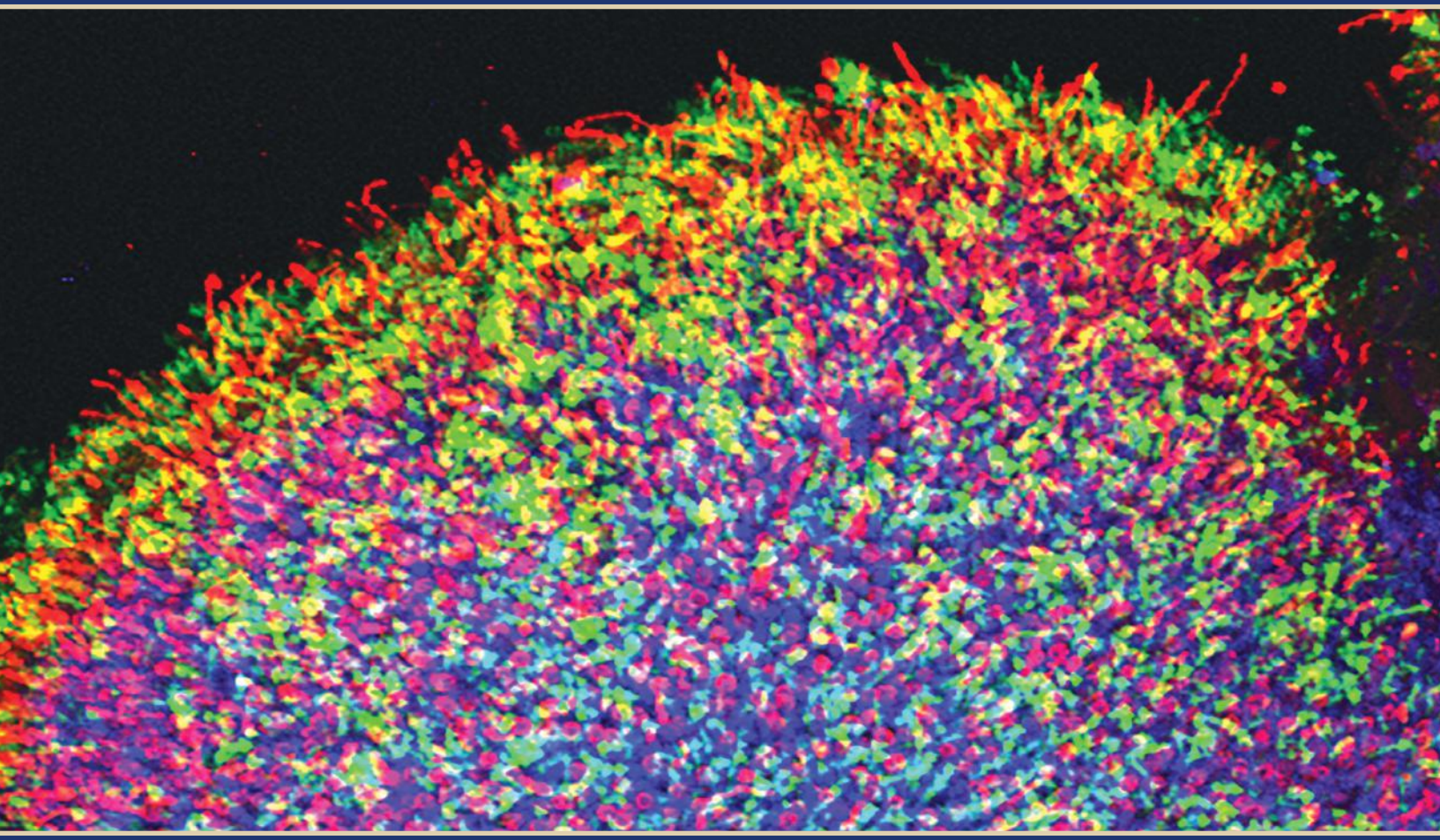


An image of an iPS cell-derived retinal organoid with rod and cone photoreceptors on the surface in yellow, green and red.



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