

RETINA

RESEARCH
FOUNDATION

2017 annual report



Retina Research Foundation Board of Directors



*Dr. Frank Eggleston, Dr. Art Willis,
Dr. Petros Carvounis and Rich Walton*



*Bettie Lee, Dede Weil, Suzanne Miller,
Shara Fryer and Jacque Royce*

Cover photo courtesy of Elizabeth Capowski, PhD
Gamm lab, Waisman Center, University of Wisconsin-Madison

Cross section of a maturing three-dimensional retinal organoid generated from human induced pluripotent stem cells. Cone photoreceptors are shown in green and Muller glia are shown in red.

Retina Research Foundation

Annual Report 2017

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Bettie Lee and Dr. Ben Orman



Ron Webster, Dr. McPherson and Roger Beck



Dede Weil and Jacque Royce



Dr. Jim Key and John Dawson



Malcolm Wooley, Ames Smith and Rich Walton

President's Message



Dear Friends,

We are living in uncertain times – politically, economically and socially – and we may be tempted to become cynical about the prospects for a brighter future. I urge you not to surrender to this temptation, but to always stay hopeful and focused on better days to come.

What can we do today in order to create a better tomorrow? One answer is clearly found in continuing to add to the body of scientific knowledge through support of basic research. The scientific process isn't at the mercy of the ebb and flow of the shifting sands of popular culture, and will ultimately provide many answers to the mysteries of disease and disability that challenge so many today.

Research takes time, in large part due to the nature of the rigorous scientific process. Studies are conducted at leading research institutes and universities under carefully controlled circumstances. These collaborative efforts, by scientists from various disciplines and diverse geographical backgrounds, result in papers that are published in scholarly and peer reviewed journals. This basic science research advances our understanding of both healthy and diseased states at the molecular and cellular level.

The pace of change in our everyday lives is accelerating, and that can leave us off-balance. Popular culture is frantic for instant results and looks only as far ahead as the next fad. We must have confidence in the timeless nature of the scientific process and trust that each discovery lays the groundwork for future discoveries. The knowledge gained will not be lost, and innovations in science bring true benefits to society.

Research goes on forever. As long as mankind has a brain, we will always want to move forward and discover new answers to unsolved problems – everlasting “hope” is a “bottomless bucket!”

With gratitude,

A handwritten signature in black ink that reads "Alice McPherson M.D." in a cursive script.

Alice McPherson, MD
President

Overview of Research - 2017

Retina Research Foundation supports an exemplary variety of programs in retina research around the world. The following is a brief recap of RRF research supported in 2017, which illustrates the wide scope of RRF activities.

RRF Pilot Study Grants – Investigation of New Research Topics

Baylor College of Medicine, Houston, TX

- Samuel Wu, PhD – Kayser Research Project
- Milan Jamrich, PhD – Lawrence Research Project
- Rui Chen, PhD – Manning Research Project
- Graeme Mardon, PhD – Miller Research Project
- Richard Hurwitz, MD – Wilson Research Project

University of Texas MD Anderson Cancer Center, Houston, TX

- Louise C. Strong, MD – Humble Research Project

University of Texas Medical Branch-Galveston, Galveston, TX

- Wenbo Zhang, PhD – Bovay Research Project

Texas A&M Health Science Center, Temple, 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 – Basic Research Grant

University of Utah, John Moran Eye Center, Salt Lake City, UT

- Wolfgang Baehr, PhD – Basic Research Project

Case Western Reserve, Cleveland, OH

- Paul Shin-Hyun Park, PhD – Basic Research Project

RRF Cox Macula Society Research Grant – administered by The Macula Society

- Mary Elizabeth Hartnett, MD – Moran Eye Center, University of Utah, Salt Lake City, UT

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, Assoc. Director, McPherson Eye Research Institute
- Nader Sheibani, PhD – RRF Research Chair
- David Gamm, MD, PhD – Humble Distinguished Director, McPherson Eye Research Institute
- T. Michael Nork, MD – Murfee Chair, McPherson Eye Research Institute
- Christine Sorenson, PhD – Albert Chair, McPherson Eye Research Institute

Overview of Research - 2017

Research Professorships – Ongoing Proven Research Projects

University of Wisconsin, Madison, WI

Jeremy Rogers, PhD – Gamewell Professor, McPherson Eye Research Institute

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

Aparna Lakkaraju, PhD – Brown Professor, McPherson Eye Research Institute

Established Awards – Awards Recognizing Lifetime Achievement

RRF Award of Merit – presented by The Retina Society – Boston, MA – October 6

Michael L. Klein, MD – Casey Eye Institute, Portland, OR

RRF Kayser International Award – presented by International Society for Eye Research (ISER); will be presented again in 2018

RRF Pyron Award – presented by American Society of Retina Specialists (ASRS) – Boston, MA – August 13

Paul A. Sieving, MD, PhD – Director, National Eye Institute, Bethesda, MD

CL Schepens MD/AAO Award – presented by American Academy of Ophthalmology (AAO) and Schepens International Society (SIS) – New Orleans, LA – November 10

Frederick L. Ferris III, MD – National Eye Institute, Bethesda, MD

RRF Gonin Lecturer – presented by Club Jules Gonin; will be presented again in 2018

Gonin Medal – presented by International Council of Ophthalmology (ICO); will be presented again in 2018

Paul Kayser/RRF Global Award – presented by Pan-American Association of Ophthalmology (PAAO) – Lima, Peru – August 9

Jennifer Kang-Mieler, PhD - Illinois Institute of Technology, Chicago, IL

International Fellowships – Advanced Subspecialty Training

ICO – RRF Helmerich International Fellowships – administered by International Council of Ophthalmology Foundation (ICOF)

Linda Espinosa Cernichiaro Amejandra, MD - from Mexico to Bascom Palmer, Miami, FL

Nilufer Yesilirmak, MD - from Turkey to Bascom Palmer, Miami, FL

Gillingham Pan-American Fellowships – administered by Pan-American Association of Ophthalmology (PAAO)

Marcela A. Lonngi, MD - from Colombia to Jules Stein Eye Institute, Los Angeles, CA

Andrea Elizabeth Arriola-López, MD - from Guatemala to Bascom Palmer Eye Institute, Miami, FL

Research Initiatives – Educational and Travel Scholarships

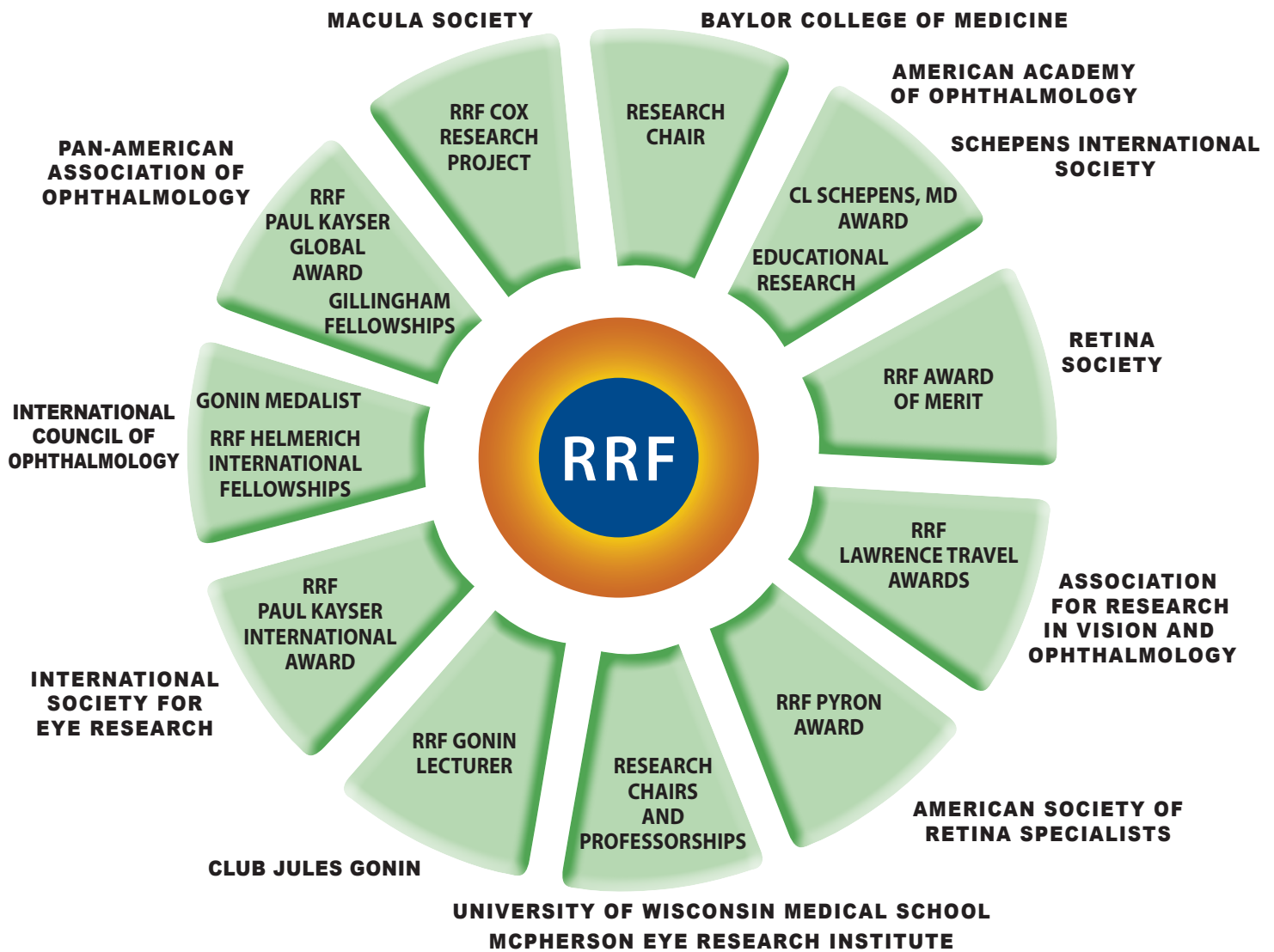
AAO Educational Trust Fund – administered by The Foundation of the American Academy of Ophthalmology (FAAO)

Retina-related educational research programs for clinical and basic science

RRF Lawrence Travel Scholarships – administered by The Association for Research in Vision and Ophthalmology (ARVO)

Twenty-two vitreoretinal scientists representing schools in 16 states traveled to the ARVO Annual Meeting to present their scientific research.

COLLABORATING ORGANIZATIONS



COLLABORATING ORGANIZATIONS	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 SIS Schepens International Society	Charles L. Schepens, MD/AAO Award	2008
ICO/ICOF International Council of Ophthalmology	ICO RRF Helmerich International Fellowships	2009

RETINA RESEARCH SITES

PAST AND PRESENT

TEXAS : 11

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

PAN AMERICAN : 22

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

INTERNATIONAL : 43

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
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
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
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 : 56

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
Case Western Reserve University	Cleveland, OH
Casey Eye Institute	Portland, OR
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	Worcester, 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
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 California	Berkeley, 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 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 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
Wills Eye Hospital	Philadelphia, PA
Wilmer Eye Institute	Baltimore, MD

Research

RRF provided funding for 12 pilot study research projects conducted at leading research institutions. Nine of the projects were named in recognition of generous support through gifts and years of exceptional service to the Foundation. Pilot studies are experimental studies designed “to test the waters” or break new ground. Findings may lead to larger ongoing studies in the future.

Named Basic Research Projects

The Kathryn and Latimer Murfee Macular Degeneration Project



Curtis R. Brandt, PhD

Dept. of Ophthalmology and Visual Sciences
McPherson Eye Research Institute
University of Wisconsin, Madison, WI

Gene therapy for retinal degenerative diseases

The purpose of this project is to determine the mechanism of inflammation triggered by viral gene delivery vector injection in the non-human primate eye. In 2017, Dr. Brandt examined the expression of innate immune receptors, including Toll-like receptors and non-self nucleic acid receptors, as well as components of the inflammasome in non-human primate retina. He continues to examine inflammasome components expressed in non-human primate neural retina tissue and study their role in vector induced inflammation. In addition, he plans to determine whether non-human primate retina tissue expresses host restriction factors, as these proteins can negatively affect viral gene delivery vector transduction efficiency.

Joe M. and Eula C. Lawrence Research Project



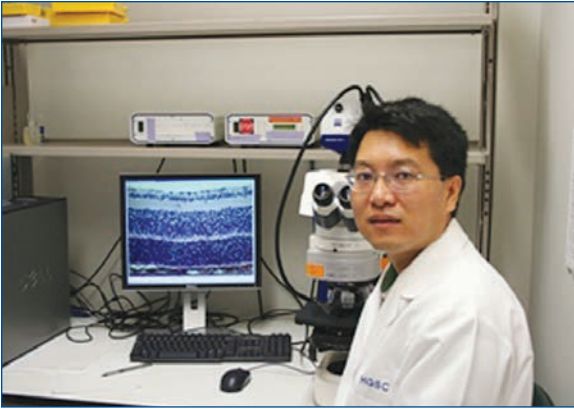
Milan Jamrich, PhD

Dept. of Molecular and Cellular Biology
Baylor College of Medicine, Houston, TX

Function of Rax in the specification, differentiation and survival of vertebrate retinal cells

The goal of this project is to identify genes and processes that are responsible for normal and abnormal vertebrate retinal development, which will lead to a better understanding of eye diseases, and as a result, new diagnostic procedures and treatments will be developed. Rax is a gene that plays a key role in vertebrate eye formation. In 2017, Dr. Jamrich intended to identify the direct target genes of mouse Rax during retinal development. He made a knock-in strain of mouse in which the Rax protein is linked to a tag against which there are antibodies. In order to perform ChIP-seq, he isolated E14 eyes from the Rx/SBP/FLAG knock-in strain of mouse. A company that specializes in ChIP technologies generated a list of potential Rax target genes.

The W.O. Manning Research Project



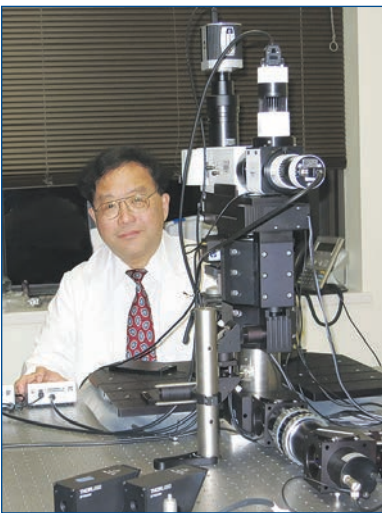
Rui Chen, PhD

Dept. of Molecular and Human Genetics
Baylor College of Medicine, Houston, TX

Identification and functional analysis of genes involved in retina diseases and development

Dr. Chen's long-term goal is to identify and conduct functional characterization of novel disease genes underlying inherited human retinal disorders. Results obtained from these studies can be directly translated into improving molecular diagnosis and form the basis of developing optimal treatment of human eye diseases, including gene therapy. In 2017, Dr. Chen's group completed whole exome sequencing for a cohort of 900 LCA patients recruited worldwide, which led to the identification of several novel disease genes, including REEP6 and CWC27. In addition, mouse models have been established for these novel disease genes. Currently, Dr. Chen's group is characterizing these mouse models for understanding the disease mechanisms and developing new therapeutic approaches.

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 glaucoma and age-related macular degeneration (AMD)

The objective of Dr. Wu's research is to understand mechanisms underlying retinal synaptic dysfunction and cell death in glaucoma and age-related macular degeneration (AMD). He plans to use the newly developed eight-channel patch clamp recording system, which is the most powerful electrophysiological recording apparatus in the world that allows recording of eight retinal cells simultaneously for studying their interconnections and light responses in animal models of glaucoma and AMD. Dr. Wu's lab published five papers and submitted four manuscripts in top international journals in 2017. These publications report Dr. Wu's new discoveries on how rod and cone signaling pathways mediate light responses and receptive fields of various types of retinal ganglion cells (RGC), and how dysfunction of bipolar cell and amacrine cell synapses affect retinal degeneration in glaucoma, AMD and retinitis pigmentosa (RP).

Bertha and I.L. Miller Research Project



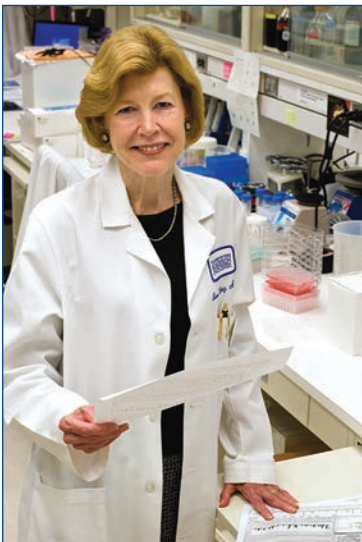
Graeme Mardon, PhD

Depts. of Pathology, Molecular and Human Genetics
Baylor College of Medicine, Houston, TX

Genetic and molecular analysis of retinal development

The long-term goal of this project is to improve our ability to prevent, diagnose, and treat human retinal diseases. Dr. Mardon recently developed animal models for a gene associated with congenital blindness, named *Kcnj13*, which encodes a highly conserved potassium channel protein. In 2017, Dr. Mardon continued to focus on the mouse *Kcnj13* gene and has made significant breakthroughs in his research. He found that conditional loss of *Kcnj13*, specifically in the retinal pigment epithelium in the mouse retina, causes very early loss of photoreceptors, first detectable by 15 days of age, with severe vision defects by 21 days of age. By three months of age, there is complete loss of the photoreceptor layer. Dr. Mardon plans to further characterize his *Kcnj13* mouse models to determine the molecular basis for disease pathology.

Emmett A. Humble Research Project



Louise C. Strong, MD

Dept. of Genetics
University of Texas MD Anderson Cancer Center
Houston, TX

Genetic etiology of retinoblastoma

Dr. Strong's goal is to provide a unique early cancer detection program for individuals with a hereditary cancer predisposition, specifically retinoblastoma and Li Fraumeni syndrome individuals. These tumors are a significant health problem as the most frequent cause of death in hereditary retinoblastoma patients is a second malignant neoplasm. In 2017, Dr. Strong continued to update her registry of hereditary retinoblastoma patients at risk for new non-ocular tumors and noted that most were not aware of the risk and were not undergoing any surveillance. It has been an ongoing aim of this project to maintain the registry of retinoblastoma patients and family members, with the relevant sample and history collection, and to provide sufficient education and guidelines for patients and family members seeking counseling and/or screening. Dr. Strong documents response, interest, barriers to participation, and clinically significant outcomes.

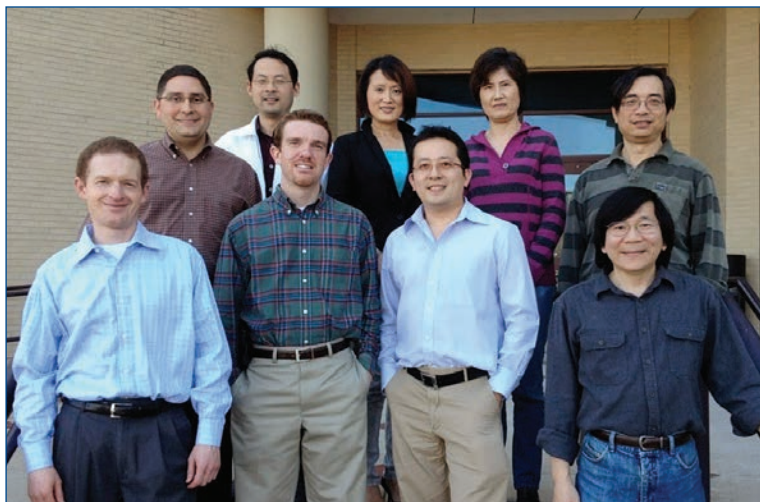
Adolphe G. and Josephine Roberts Gueymard Research Project

Lih Kuo, PhD

Depts. of Medical Physiology, Surgery, and Ophthalmology
Texas A&M Health Science Center, Temple, TX

Activation of endothelin-dependent RhoA/ROCK pathway elicits retinal arteriolar dysfunction in diabetic retinopathy

This project seeks to identify the mechanisms responsible for the initiation and development of diabetic retinopathy and to develop strategies for the prevention and treatment of this disease. Proper function of the retina depends on a sufficient supply of blood to the retina, and the dysfunction of retinal circulation can lead to disease development. Dr. Kuo has found that in the diabetic retina the synthesis of vasoconstrictor/inflammation agent endothelin-1 (ET-1) from endothelin converting enzyme (ECE) is elevated, and the RhoA kinase (ROCK) and arginase signalings are correlatively activated. He hypothesizes that activation of ECE/ROCK/arginase signaling contributes to the retinal vascular disorder and retinopathy. He has established a diabetes pig model, which resembles the human eye pathophysiology, to investigate the mechanism and signaling molecules involved in initiation and development of diabetic retinopathy.



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

Mary Ellen Wilson Research Project



Richard L. Hurwitz, MD

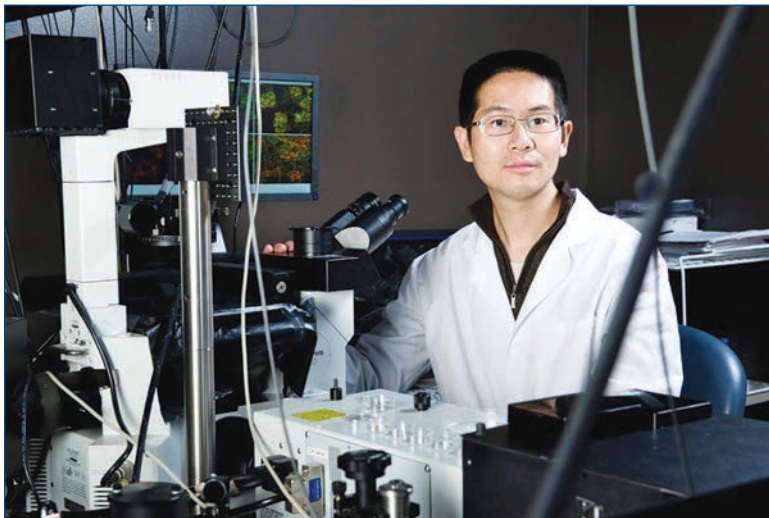
Dept. of Pediatrics, Ophthalmology, Molecular and Cellular Biology
Co-Director, Retinoblastoma Center
Texas Children's Cancer Center
Center for Cell and Gene Therapy
Baylor College of Medicine, Houston, TX

Immune consequences of gene therapy for ocular disorders

Dr. Hurwitz's hypothesis 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. He has 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. Dr. Hurwitz began to explore the contribution of another vitreous component, the large proteoglycan versican, and the initial results of experiments verifying a contribution of the versican G1 domain were published in 2017. The studies included the analysis of biochemical pathways influenced by the G1 domain and may provide useful in designing more efficient vectors and delivery systems to optimize gene therapy outcomes and limit toxicities, including immune consequences.

Research

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

Ischemic retinopathies are caused by impaired retinal blood supply in various diseases such as diabetic retinopathy, retinopathy of prematurity, and retinal vascular occlusion. These conditions often result in irreversible vision loss due to the development and growth of abnormal new vessels after a period of retinal ischemia, a process referred to as retinal

neovascularization. In a mouse model of ischemic retinopathy, Dr. Zhang showed that A2AR expression was significantly increased in retinas and retinal vessels during ischemic retinopathy, which were associated with increase in cAMP production. Dr. Zhang has shown that istradefylline treatment reduced cAMP production, Epac1 activation and retinal neovascularization in ischemic retinopathy. Istradefylline has been approved to treat Parkinson's disease in Japan, and this work supports the possibility of treating ischemic retinopathy by repositioning istradefylline for ophthalmic use.

Basic Research Projects

Timothy W. Corson, PhD

Eugene & Marilyn Glick Eye Institute
Indiana University School of Medicine
Indianapolis, IN

Role of epoxy lipid metabolism in choroidal neovascularization



Dr. Corson (third from left) with his lab group

The overall goal of this project is to develop therapies for diseases like wet AMD by showing how soluble epoxide hydrolase (sEH) is important for abnormal blood vessel growth. In previous years of RRF funding, Dr. Corson's team developed a potent chemical called SH-11037, and found sEH as its cellular target. sEH is present at high levels in human and mouse eyes with AMD-like features. The Corson lab has shown that a substrate (input) of sEH is antiangiogenic, and characterized the molecular mechanism of how SH-11037 inhibits sEH. They showed this inhibition occurs in eye tissue, confirmed that the rod photoreceptor cells are the site of increased sEH in eyes undergoing new blood vessel growth, and found that known sEH inhibitors can block new blood vessel growth in the eye.

Research

Wolfgang B. Baehr, PhD

Department of Ophthalmology and Visual Sciences
University of Utah Health Science Center
Salt Lake City, UT

Therapy in a mouse model of Joubert Syndrome

Dr. Baehr's lab is interested in understanding mechanisms leading to retina disease and developing gene-based therapies for non-syndromic and syndromic ciliopathies, focusing mainly on the retina. This application studies the role of INPP5E, a phosphoinositide phosphatase present in photoreceptors, in pathogenesis of ciliated cells. INPP5E mutations are associated with Joubert syndrome, a syndromic ciliopathy. Common features of Joubert syndrome include ataxia (lack of muscle control), hyperpnea (abnormal breathing patterns), abnormal eye and tongue movements, polydactyly (more than 10 digits) and retinitis pigmentosa. Dr. Baehr studies the consequences of INPP5E deletion, specifically in retina photoreceptors, and devises gene-based therapies to ameliorate or cure disease. A retina-specific knockout has been generated, revealing a rapid degeneration of rods and cones.



Dr. Baehr (second from right) with his lab group



Paul Shin-Hyun Park, PhD

Department of Ophthalmology and Visual Sciences
Case Western Reserve University, Cleveland, OH

A potential neuroprotective role for GPR75 in the retina

GPR75 is an orphan G protein-coupled receptor that is localized in the brain and retina. The function of GPR75 in the retina is currently unknown, but initial studies indicate that this orphan receptor may have important neuroprotective properties. Several mutations in GPR75 have been detected in patients with age-related macular degeneration (AMD), thereby suggesting that defects in GPR75 can contribute to the pathology of this retinal degenerative disorder. The goal of this project is to test the hypothesis that GPR75 has a neuroprotective role in the retina and that defects in the receptor can lead to effects increasing the likelihood of AMD or other retinal degenerative disorders.

Grant Recipient from The Macula Society

The RRF Margaret and Mills Cox Macula Society Research Project



Mary Elizabeth Hartnett, MD

Moran Eye Center, University of Utah
Salt Lake City, UT

Novel Gene Therapy to Regulate Pathologic Neovascularization in AMD

Dr. Hartnett's lab has identified a mechanism for pathologic signaling through vascular endothelial growth factor (VEGF) in retinopathy of prematurity (ROP) that leads to both avascular retina and intravitreal neovascularization. She studies ways to regulate VEGF signaling in order to safely inhibit pathologic neovascularization in both ROP and age-related macular degeneration (AMD).

Dr. Hartnett has over 200 peer-reviewed articles and chapters, and is Editor-in-Chief for the highly acclaimed textbook, *Pediatric Retina*, now in its second edition.

Research Chairs and Professorships

RRF now supports a total of six chairs and three professorships in retina research, which provide funds to vision scientists engaged in original excellent research that has the potential to increase understanding of the retina or retinal diseases.

RRF Research Chair

Ching-Kang Jason Chen, PhD

Depts. of Ophthalmology, Biochemistry and Molecular Biology, Neuroscience
Baylor College of Medicine
Houston, TX

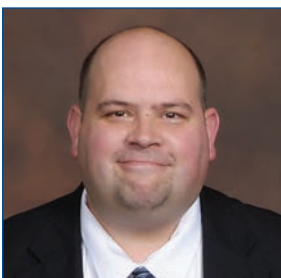
A novel retinal oscillation mechanism in an autosomal dominant mouse model of retinitis pigmentosa

The Chen lab at the Ophthalmology Department of Baylor College of Medicine currently investigates the mechanisms, function and utility of neuronal oscillation in mice where photoreceptor input to inner retinal neurons is disrupted permanently. Because retinal oscillation is synaptically driven, and not all neurons oscillate when deafferentation occurs, determining if and how a genetically marked neuron oscillates thus provides valuable knowledge on upstream synaptic connectivity of such a neuron. This approach is complemented by examining light response properties of similarly marked neurons in wild type mice and in mutant mice with manipulated gene expression. When completed, a catalog of genetically marked inner retinal neurons and their synaptic connections will be at hand to guide future investigations into retinal disease mechanisms as well as potential therapeutic interventions.



Dr. Chen (far right) with his research group

Walter H. Helmerich Chair



Kevin W. Eliceiri, PhD

Associate Director, McPherson Eye Research Institute
Director, Laboratory for Optical and Computational Instrumentation
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 study dynamic cellular processes such as those in the eye non-invasively. The overarching vision is that by applying these technologies to vision studies there will be opportunity to solve fundamental problems in eye and vision research. His current research focuses on the development of novel optical imaging methods and instrumentation for investigating the cellular microenvironment as well as the development of software for multidimensional imaging informatics. Specific interests include developing nonlinear optical approaches for deeper imaging and sensing of the cellular microenvironment, new technologies for metabolic imaging as well as computational algorithms for visualizing large multidimensional datasets with spatial and non-spatial components.

Research Chairs and Professorships

RRF Research Chair

Nader Sheibani, PhD

Department of Ophthalmology & Visual Sciences
University of Wisconsin, Madison, WI

Regulation of ocular vascular development and neovascularization

Dr. Sheibani's work focuses on the mechanisms that regulate ocular vascular homeostasis. He showed vitamin D attenuates retinal neovascularization in a VDR depended manner by inhibiting the proangiogenic activity of pericytes. In collaboration with Dr. Murphy, Dr. Sheibani reported a versatile synthetic alternative to Matrigel for high throughput screening of vascular disrupting agents. In collaboration with Dr. Henkin, he reported the development of a novel nanocarrier for sustained intravitreal delivery of antiangiogenic peptides. In collaboration with Dr. Zhang, he showed metabolic changes in retinal vasculature occurs early during diabetes. He also showed antagonism of β 2-adrenergic receptor suppresses VEGF and IL-6 expression mitigating CNV. Reported in: Plos one (Dec 2017), Nat Biomed Eng (July 2017), IOVS (Oct 2017), IOVS (Feb 2017), and IOVS (Jan 2017).



Dr. Sheibani (front row, third from right) with his research team

Emmett A. Humble Distinguished Directorship



David M. Gamm, MD, PhD

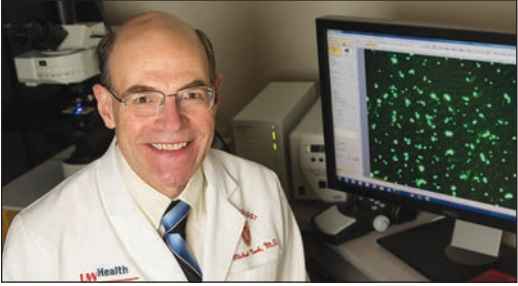
Director, McPherson Eye Research Institute
Department of Ophthalmology & Visual Sciences
University of Wisconsin, Madison, WI

Modeling and treating retinal disease with human induced pluripotent stem cells (hiPSCs)

Dr. Gamm continues to work at the forefront of human pluripotent stem cell (hPSC) technology, which his lab employs to both better understand and develop treatments for retinal degenerative diseases in children and adults. His lab's pioneering stem cell studies on retinitis pigmentosa (RP) and inherited and age-related forms of macular degeneration (AMD) have helped launch projects to advance gene and cell therapies for these largely untreatable conditions. In addition, through his leadership role in Ophis Therapeutics (a subsidiary of FUJIFILM-Cellular Dynamics), Dr. Gamm and his colleagues are working toward clinical trials to test the safety and efficacy of photoreceptor replacement in late stages of RP and AMD.

Research Chairs and Professorships

Kathryn and Latimer Murfee Chair



T. Michael Nork, MD, MS

McPherson Eye Research Institute
Department of Ophthalmology & Visual Sciences
University of Wisconsin, Madison, WI

Functional and Cellular Mechanisms of Ischemic Retinal Injury

The object of Dr. Nork's basic laboratory research has been to understand how an inadequate blood supply (ischemia) to the retina affects its health. Much of his initial and ongoing studies have looked at the ischemic changes that he and others found in the outer retina (rods and cones) in glaucoma and what this might mean for the health of the cells that are most damaged in glaucoma—the retinal ganglion cells. Other retinal diseases such as retinal vascular occlusion are unquestionably the result of reduced retinal circulation. His lab is working with animal models of retinal blood supply restriction and as well as glaucoma. By applying advanced electrophysiologic and histopathologic examination, he hopes to better understand the underlying mechanisms of retinal cellular damage with the long-term goal of developing pharmaceutical and other interventions that might mitigate such injury.

Daniel M. Albert Chair



Christine M. Sorenson, PhD

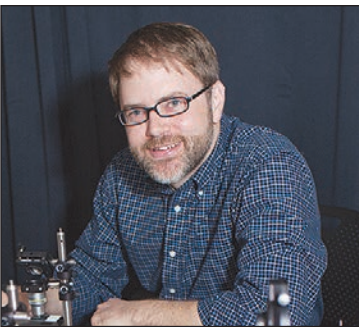
University of Wisconsin Dept. of Pediatrics
McPherson Eye Research Institute
Madison, WI

Apoptosis in retinal vascular development and disease

The focus of Dr. Sorenson's research is to understand the apoptotic and non-apoptotic roles Bcl-2 and Bim play during postnatal retinal vascular development and pathologic neovascularization. She is interested in understanding how the fine-tuned regulation of Bim, Bcl-2 and VEGF expression impacts retinal vascularization and homeostasis. Her studies have novel impact in the design of antiangiogenic therapy.

Photo by Andy Manis

Edwin and Dorothy Gamewell Professor



Jeremy Rogers, PhD

McPherson Eye Research Institute
Department of Biomedical Engineering
University of Wisconsin, Madison, WI

Optical instrumentation and technology platforms for the study and screening of retinal disease

Dr. Rogers develops new imaging tools to aid in the treatment, prevention, and basic research of retinal disease. The ability to image and quantify structure and function of retinal cells in a clinical setting is crucial to advancing treatment and prevention options. Dr. Rogers is developing new imaging technologies that exploit the intrinsic light scattering properties of cells, making these methods suitable for clinical imaging. His laboratory is currently building an Adaptive Optics Scanning Light Ophthalmoscope (AOSLO) that will enable imaging of individual photoreceptors. By developing new imaging methods powered by computational light scattering simulations, he will be able to improve existing instruments and create new methods of imaging cellular function that are needed to develop and monitor future stem cell or gene therapies.

Photo by Todd Brown/Media Solutions

Research Chairs and Professorships

M.D. Matthews Research Professor



Bikash Pattnaik, PhD

McPherson Eye Research Institute
Department of Pediatrics, Ophthalmology & Visual Sciences
University of Wisconsin, Madison, WI

Vision Loss Due to Ion-Channelopathy

Dr. Pattnaik's research focus is on the inherited blindness due to defective inwardly rectifying potassium (Kir7.1) channel present in the retinal pigment epithelium (RPE) cells in the back of the eye. Mutations in the gene *KCNJ13*, that encodes Kir7.1 protein, cause pediatric blindness. Dr. Pattnaik's lab has generated induced pluripotent stem cells (iPSC) derived RPE cells from a Leber Congenital Amaurosis patient with *KCNJ13* mutation. These cells, with a severe reduction in Kir7.1 function, were used to study biology of blindness and test gene and drug-based therapies as patient in-a-dish approach. His goal is to be able to manipulate defective gene in these cells through cutting age gene-editing technology as a possible treatment for pediatric blindness.



Rebecca Meyer Brown Professor

Aparna Lakkaraju, PhD

McPherson Eye Research Institute
Department of Ophthalmology &
Visual Sciences
University of Wisconsin, Madison, WI

Insight into the cellular basis of retinal degenerative diseases

Research in the Lakkaraju laboratory builds on fundamental insights from retinal cell biology to develop effective therapies for inherited and age-related macular degenerations (AMD), which affect millions of people worldwide who have limited therapeutic options. To gain insight into disease mechanisms, her research team investigates critical pathways such as cellular clearance, mitochondrial function, inflammation, and immune privilege in the retina. Using state-of-the-art high-speed live imaging and mouse models of disease, they have recently identified clinically approved drugs that correct multiple dysfunctional pathways in a mouse model of early macular degeneration.



Dr. Lakkaraju (third from right) with her research team

Established Research Awards

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

The Award of Merit in Retina Research



Michael Klein, MD

Casey Eye Institute
Oregon Health & Science University
Portland, OR

Genetics and Age-Related Macular Degeneration

In being chosen for the Award of Merit, Dr. Klein gave the Charles L. Schepens Lecture at the 50th Annual Scientific Meeting of The Retina Society in Boston, MA, which was held in October.

Dr. Klein's clinical practice and research activities have focused on retinal diseases and surgery. He has been a Principal Investigator for several National Eye Institute (NEI) and industry-sponsored clinical trials and is author or co-author of numerous publications dealing with the etiology, natural history, risk factors, clinical-pathologic correlation, and therapy for macular and retinal vascular diseases. In recent years, he has been Principal Investigator of an NEI sponsored study of the genetics of age-related macular degeneration.



Retina Society President Dr. Mark Johnson and Dr. Klein

RRF Pyron Award for Outstanding Achievement in Retina Research



Paul A. Sieving, MD, PhD

Director, National Eye Institute
National Institutes of Health
Bethesda, Maryland

Considerations of Gene Therapy for Retinal Dystrophies

Dr. Sieving presented the RRF Pyron Award lecture at the 35th Annual Meeting of the American Society of Retina Specialists (ASRS), which was held in Boston, MA, in August.

Dr. Sieving is known internationally for studies of human retinal neurodegenerative diseases, termed retinitis pigmentosa. He originated the "NEI Audacious Goals Initiative," a 15-year effort in regenerative medicine to replace photoreceptors and retinal ganglion cells lost from disease. Dr. Sieving continues clinical and research engagement as a tenured Senior Investigator in the NIH Intramural Research Program, and he has published some 260 peer reviewed papers in ocular genetics and the pathophysiology of retinal neurodegenerative diseases.



Dr. Sieving and ASRS President Dr. Mark Humayun

Established Research Awards

Charles L. Schepens, MD/AAO Award



Frederick L. Ferris III, MD

National Eye Institute
Bethesda, MD

*Clinical Trials in Ophthalmology:
Advances in Treating Diabetic Retinopathy*

In being selected for the Charles L. Schepens, MD/AAO Award, Dr. Ferris gave the Charles L. Schepens, MD/AAO Lecture at the Retina Subspecialty Day of the American Academy of Ophthalmologists (AAO) Annual Meeting in New Orleans, LA, on November 10.

Dr. Ferris has been Director of the Division of Epidemiology and Clinical Applications at the National Eye Institute (NEI) since 1994 and was Clinical Director at NEI from 2000 to 2017. He



has participated in many clinical trials during his NEI career; notably, he was Project Officer of the Diabetic Retinopathy Study, Co-Chairman of the Early Treatment Diabetic Study and Chairman of the Age-Related Eye Disease

Study. Dr. Ferris has published 295 manuscripts in peer review journals and is actively involved in AREDS2, CATT, DRCR.net studies and multiple intramural clinical studies at NEI as well as being a senior editor of JAMA-Ophthalmology.



Schepens Award 10th Anniversary:

***Dr. Alice McPherson and Schepens Medalists
Dr. Rick Ferris (2017), Dr. Jerry Shields (2014),
Dr. Mark Blumenkranz (2015), Dr. Harry
Flynn (2016), and Dr. Larry Yannuzzi (2013)***

Paul Kayser / RRF Global Award



Jennifer Kang-Mieler, PhD

Illinois Institute of Technology
Chicago, IL

A novel microsphere-hydrogel ocular drug delivery system for anti-vascular endothelial growth factors (anti-VEGFs)

Dr. Kang-Mieler was chosen as the third Paul Kayser / RRF Global Awardee and delivered the award lecture at the 33rd Pan-American Congress in Lima, Peru, on August 9. Her research interests include translational research such as ocular drug delivery, nitric oxide sensor development, retinal imaging, electroretinography, retinal blood flow and modeling to name few. This award, presented every two years, recognizes outstanding achievement in visual science with preference given in the specialized field of research on the retina and vitreous.

International Fellowships

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

ICO - RRF Helmerich International Fellowships

The International Council of Ophthalmology (ICO), in cooperation with the International Council of Ophthalmology Foundation (ICOF), and Retina Research Foundation, has established two international fellowships with income from an endowment created by Walter H. Helmerich, III. This year two, 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.

Linda Espinosa Cernichiaro Amejandra, MD,



from Mexico, for training in retinopathy of prematurity (ROP) and pediatric retina with Dr. Audina Berrocal at Bascom Palmer Eye Institute, in Miami, FL. Following her training, Dr. Cernichiaro will return to the Asociación para Evitar la Ceguera en México in Mexico City as a member of the medical staff.

Nilufer Yesilirmak, MD,

from Turkey, for training in cornea and external diseases with Dr. Ellen Koo at Bascom Palmer Eye Institute in Miami, Florida. Dr. Yesilirmak will return to Ankara Training and Research Hospital in Ankara, Turkey, as a cornea specialist following her fellowship.



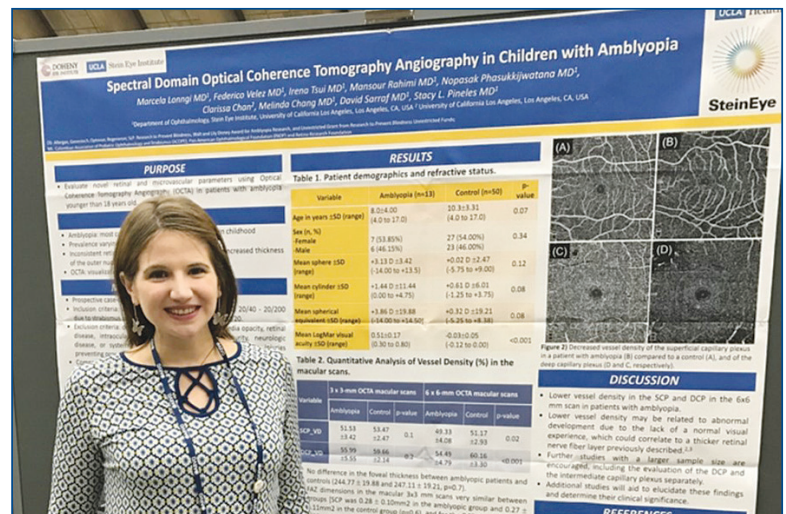
Gillingham Pan-American Fellowships/PAAO

This program is administered for RRF by the Pan-American Association of Ophthalmology (PAAO). Two, six-month fellowships were awarded this year to Latin American ophthalmologists for training at leading institutions in the United States.

Andrea Elizabeth Arriola-López, MD,



from Guatemala City, Guatemala, to Bascom Palmer Eye Institute, Miami, Florida, for training in uveitis with Dr. Thomas Albin and Dr. Eduardo Alfonso.



Marcela A. Lonngi, MD, from Bogotá, Colombia, to Jules Stein Eye Institute, Los Angeles, CA, for training in pediatric ophthalmology and strabismus with Dr. Joseph Demer.

Research Initiatives

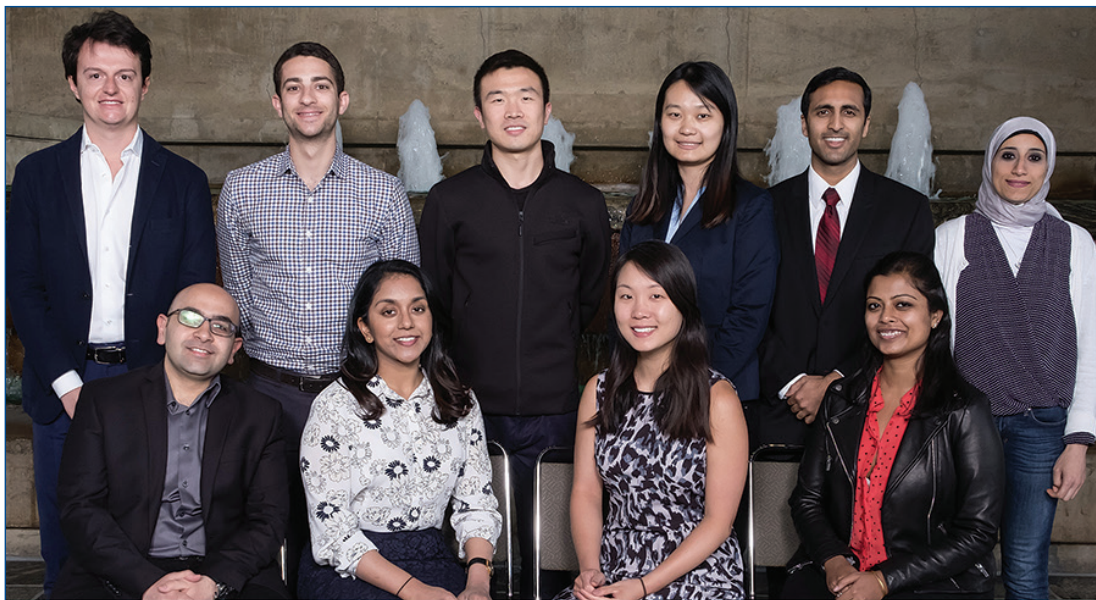
RRF has endowed gifts with earnings applied to translational research and education to bring laboratory knowledge to the clinical level.

American Academy of Ophthalmology Educational Trust Fund

This educational program is administered for RRF by the American Academy of Ophthalmology, and upgrades clinical research skills in the field of retina. The 2017 funding for this program was \$50,000.

RRF Lawrence Travel Scholarships

This program is administered by the Association for Research in Vision and Ophthalmology (ARVO) and is made possible by a gift to RRF from Joe M. and Eula C. Lawrence. A total of \$20,000 was funded to provide travel expenses for young vitreoretinal scientists to attend the ARVO Annual Meeting to present their papers or posters. This year the meeting was held in May in Baltimore, MD.



**ARVO Foundation/Retina Research Foundation/
Joseph M. and Eula C. Lawrence
Travel Grants**

In 2017, twenty-two ophthalmology students were selected from these schools:

University of Texas Medical Branch, Galveston, TX
Louisiana State University School of Medicine, New Orleans, LA
University of Pennsylvania, Philadelphia, PA
Doheny Eye Institute UCLA, Arcadia, CA
Indiana University, Indianapolis, IN
Medical College of Wisconsin, Milwaukee, WI
Vanderbilt University, Nashville, TN
Duke University, Durham, NC
Michigan State University, East Lansing, MI
New York University School of Medicine, New York City, NY

University of Iowa Hospitals & Clinics, Iowa City, IA
National Institutes of Health, Bethesda, MD
University of California, San Diego, CA
University of California, Irvine, CA
Tufts Medical Center, Boston, MA
SUNY, New York City, NY
University of Alabama at Birmingham, AL
Oregon Health and Sciences University, Portland, OR
Warren Alpert Medical School of Brown University, Providence, RI

RRF Board Members Travel to Madison, WI

Eight RRF Board members traveled to Madison, Wisconsin, on April 27 and 28, 2017, for events hosted by McPherson Eye Research Institute at University of Wisconsin-Madison.

The 5th Annual McPherson Endowed Lecture

This year's McPherson Lecturer was Dr. José-Alain Sahel of University of Pittsburgh Medical Center and Institut de la Vision, Pierre et Marie Curie Medical School, Paris. He gave a very well-received talk titled "*Shooting in the Dark: Maintaining cone function in retinal degenerations.*" Dr. Sahel is focused on identifying the mechanisms underlying cone functional loss in blinding diseases so that new therapies can be designed to preserve or restore vision in these patients. A reception and dinner, hosted by McPherson ERI, were held that evening.

Meeting of the McPherson ERI Advisory Board

Dr. David Gamm, Humble Director, McPherson ERI, spoke to the MERI Advisory Board and the RRF Board members about how vision research is changing and how McPherson ERI can maximize its talent and resources to be most effective. He described how scientists of today work in multi-disciplinary teams, share equipment and resources, and have high budget requirements. Federal grants are most desirable because they come with funds for institutional (indirect) support in addition to the research funds.

RRF supports four Chairs and three Professorships at McPherson ERI, and one Chair at the Dept. of Ophthalmology and Visual Sciences, UW-Madison. This trip was an excellent opportunity for RRF Board members to become more familiar with the current research activities of the Institute.



Dr. Alice McPherson and UW-Madison Chancellor Rebecca Blank

Photo credit Todd Brown



RRF Board members attending the McPherson ERI Advisory Board Meeting



Drs. Alice McPherson, José-Alain Sahel, and David Gamm

Photo credit Todd Brown



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RRF 48th Anniversary Luncheon, May 17, 2017



*Arthur "Tim" Garson, Jr, MD
Director, Health Policy Institute
Texas Medical Center, Houston, Texas*

*RRF Lecturer "Texas Medical Center:
What's New and What's Coming?"*



Dr. Frank Eggleston and Dr. Alice McPherson



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RETINA RESEARCH FOUNDATION

COMBINED STATEMENT OF FINANCIAL POSITION

December 31, 2017

(with summarized financial information as of December 31, 2016)

	General Funds			Endowment Funds				2017 Total All Funds	2016 Total All Funds (Memorandum Only)
	Unrestricted	Temporarily		Unrestricted	Temporarily Restricted	Permanently Restricted	Total		
		Restricted	Total						
Assets									
Cash and cash equivalents	\$ 989,490	\$ 112,000	\$ 1,101,490	\$ -	\$ 937,264	\$ -	\$ 937,264	\$ 2,038,754	\$ 6,309,783
Contributions receivable	39,705	5,000	44,705	-	-	10,010	10,010	54,715	31,000
Investments	1,421,686	-	1,421,686	3,498,318	29,296,312	19,641,644	52,436,274	53,857,960	45,661,412
Furniture and equipment, net of accumulated depreciation of \$8,414	20,516	-	20,516	-	-	-	-	20,516	13,495
Intangible assets	12	-	12	-	-	-	-	12	12
Total assets	\$ 2,471,409	\$ 117,000	\$ 2,588,409	\$ 3,498,318	\$ 30,233,576	\$ 19,651,654	\$ 53,383,548	\$ 55,971,957	\$ 52,015,702
Liabilities and net assets									
Accounts payable	\$ -	\$ -	\$ -	\$ -	\$ 68,958	\$ -	\$ 68,958	\$ 68,958	\$ 50,031
Commitments and contingencies									
Net assets	2,471,409	117,000	2,588,409	3,498,318	30,164,618	19,651,654	53,314,590	55,902,999	51,965,671
Total liabilities and net assets	\$ 2,471,409	\$ 117,000	\$ 2,588,409	\$ 3,498,318	\$ 30,233,576	\$ 19,651,654	\$ 53,383,548	\$ 55,971,957	\$ 52,015,702

RETINA RESEARCH FOUNDATION

COMBINED STATEMENT OF ACTIVITIES AND CHANGES IN NET ASSETS

For the year ended December 31, 2017

(with summarized financial information for the year ended December 31, 2016)

	General Funds			Endowment Funds				2017 Total All Funds	2016 Total All Funds (Memorandum Only)
	Unrestricted	Temporarily		Unrestricted	Temporarily Restricted	Permanently Restricted	Total		
		Restricted	Total						
Revenues									
Contributions	\$ 210,291	\$ 150,098	\$ 360,389	\$ -	\$ -	\$ 162,245	\$ 162,245	\$ 522,634	\$ 587,565
Interest, dividend and distribution income	44,437	-	44,437	96,113	1,366,323	-	1,462,436	1,506,873	1,371,724
Realized and unrealized gains on investments, net	93,336	-	93,336	229,670	3,264,853	-	3,494,523	3,587,859	1,697,555
Mineral interest income and other income	19,879	-	19,879	-	-	-	-	19,879	19,447
Change in value of split-interest agreement	-	-	-	-	-	-	-	-	7,963
Income transferred from Endowment Fund investments	1,300,284	75,000	1,375,284	(90,389)	(1,284,895)	-	(1,375,284)	-	-
Net assets released from restrictions - satisfaction of program restrictions	154,098	(154,098)	-	-	-	-	-	-	-
Total revenues	1,822,325	71,000	1,893,325	235,394	3,346,281	162,245	3,743,920	5,637,245	3,684,254
Expenses									
Program services									
Research projects and grants	1,198,740	-	1,198,740	-	-	-	-	1,198,740	1,173,677
Public education	36,000	-	36,000	-	-	-	-	36,000	36,222
Career development and awards	85,731	-	85,731	-	-	-	-	85,731	80,241
Total program services	1,320,471	-	1,320,471	-	-	-	-	1,320,471	1,290,140
Supporting services									
Management and general	103,400	-	103,400	14,578	226,164	-	240,742	344,142	296,696
Fundraising	35,304	-	35,304	-	-	-	-	35,304	12,219
Total supporting services	138,704	-	138,704	14,578	226,164	-	240,742	379,446	308,915
Total expenses	1,459,175	-	1,459,175	14,578	226,164	-	240,742	1,699,917	1,599,055
Changes in net assets	363,150	71,000	434,150	220,816	3,120,117	162,245	3,503,178	3,937,328	2,085,199
Net assets, beginning of year	2,108,259	46,000	2,154,259	3,277,502	27,044,501	19,489,409	49,811,412	51,965,671	49,880,472
Net assets, end of year	\$ 2,471,409	\$ 117,000	\$ 2,588,409	\$ 3,498,318	\$ 30,164,618	\$ 19,651,654	\$ 53,314,590	\$ 55,902,999	\$ 51,965,671

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