International Retinal Research Foundation

2019 Annual Report

The IRRF 2019 Annual Report

Sandra Blackwood, Editor
Photos: Sandra Blackwood
David Epstein
Design: Robert Weathers

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IN 2019, THE IRRF BOARD OF DIRECTORS APPROVED EIGHT GRANTEES FOR UP TO TWO YEARS OF FUNDING.

The **International Retinal Research Foundation (IRRF)** provides financial assistance for vision research to scientists in every corner of the world, while focusing on discovery of causes, preventions and cures of macular degeneration and diabetic retinopathy. This support is vital to the ongoing work, which will affect the lives of many individuals and further scientific knowledge.

PROJECT TITLE: PKM2 metabolic reprogramming to prevent photoreceptor death in a preclinical model of macular degeneration

Cagri G. Besirli, MD, PhD
Assistant Professor,
Ophthalmology and
Visual Sciences
University of Michigan,
Ann Arbor, Michigan USA

$100,000 for one year

Dr. Besirli's area of practice is gene therapy for inherited retinal diseases. Other areas include disease and surgery of the retina and vitreous, including retinal detachment, diabetic retinopathy, age-related macular degeneration, retinal vascular disease, ocular trauma, ocular inflammation, macular and submacular surgery. He is also involved in medical and surgical management of acquired and inherited pediatric retinal disorders, including retinopathy of prematurity (ROP), familial exudative vitreoretinopathy (FEVR), Coats' disease.

Dr. Besirli's research focuses on the characterization of pathways critical for cell death during retinal stress, including retinal detachment and macular degeneration. Primary focus is given to the identification of individual proteins that regulate intracellular checkpoints important for retinal cell death or survival, with the ultimate goal of developing new therapeutic agents for clinical use.

Dr. Besirli's IRRF-supported study involves a hypothesis that metabolic reprogramming of photoreceptors (PR), by modulating PKM2 (the key regulatory enzyme of glycolysis, pyruvate kinase muscle isozyme 2) will enhance survival of PRs during outer retinal stress secondary to AMD.

PROJECT TITLE: Pathogenic neovascularization in diabetic retinopathy and age-related macular degeneration: the role of monocyte-derived pro-angiogenic cells

Willem Dik, PhD
Erasmus Medical Center
Department of Immunology
Rotterdam, The Netherlands

$103,500 for one year

Dr. Dik's research focuses on identification of cellular and molecular mechanisms underlying (chronic) inflammatory processes and related tissue and organ dysfunction, with the specific aim to use this information to guide the development of (novel) protective measures to be used in the clinic. Previously, a strong focus has been on ocular disease as proliferative vitreoretinopathy (PVR), uveitis, and Graves' ophthalmology. Various types of patient tissue have been used in the studies, which made extensive use of in-vitro approaches (stimulation of retinal endothelial cells or retinal pigment epithelial cells with ocular fluids, serum, plasma, or specific growth factors).

Dr. Dik's IRRF-supported research aims to determine for both diabetic retinopathy (DR) and AMD: 1) distinctive phenotypic features of monocytes in peripheral blood; 2) the capacity of peripheral blood monocytes to differentiate into pro-angiogenic cells A(PAC); 3) the angiogenic functionality of PAC differentiated from blood monocytes.

PROJECT TITLE: Role of photoreceptors in local inflammation and pathological angiogenesis in diabetic retinopathy

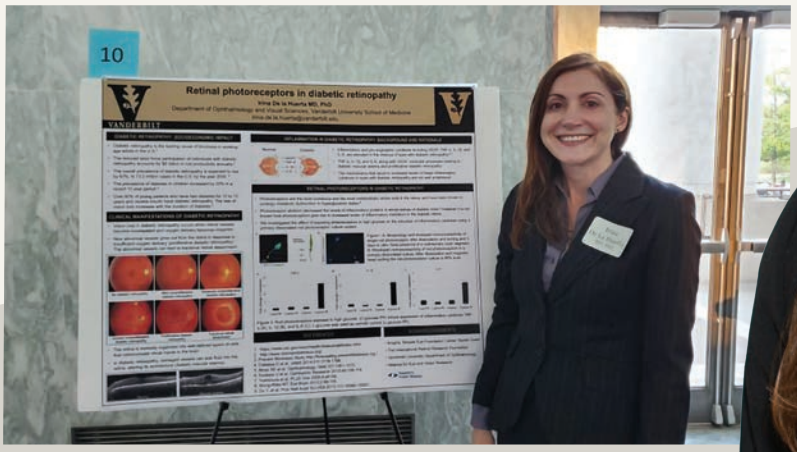
Irina De la Huerta, MD, PhD
Department of Ophthalmology and Visual Sciences
Vanderbilt Eye Institute,
Vanderbilt University
Nashville, Tennessee USA

$100,000 for one year

Dr. De la Huerta obtained her undergraduate degree magna cum laude from Harvard University. Following her medical degree, she received her PhD in Neuroscience from Harvard. She completed her ophthalmology residency at the University of California, San Francisco, and her two-year specialty fellowship in adult and pediatric vitreoretinal surgery at the William Beaumont Hospital. Dr. De la Huerta is the recipient of numerous awards, including the Hogan-Garcia Award for best scientific paper at UCSF, the John Harvard Scholar Award, and the Harvard University Certificate of Distinction in Teaching. In 2019, Dr. De la Huerta was honored as an Emerging Vision Scientist at AEVR's (Association for Eye and Vision Research) 5th Annual reception on Capitol Hill in Washington, D. C. She is a member of the American Academy of Ophthalmology, the Association for Research in Vision and Ophthalmology (ARVO) and the American Society of Retina Specialists.

Dr. De la Huerta's IRRF-supported study will utilize a novel photoreceptor primary dissociated culture system to investigate the hypothesis that photoreceptors under hyperglycemic conditions contribute to local inflammation and pathological angiogenesis.

Dr. De la Huerta presented her work at the 2019 National Association for Eye and Vision



PROJECT TITLE: Non-canonical roles of DNA damage signaling proteins in photoreceptor neuron morphogenesis and degeneration

Rodrigo Martins, PhD
Associate Professor, Institute of Biomedical Sciences
Federal University of Rio de Janeiro, Brazil

$52,250 for one year

Dr. Martins earned his degree in biological sciences from the Federal University of Rio de Janeiro (UFRJ). He also holds an MSc in Biophysics and a Doctor of Science, both from UFRJ. His post-doctoral training in Developmental Biology and Tumorigenesis was received at St. Jude Children's Research Hospital. His main scientific interests are molecular mechanisms of cell cycle control and DNA damage signaling during central nervous system (CNS) development and degeneration.

Dr. Martins IRRF-support research will involve using a novel animal model to describe the molecular basis of cilia-based pathology observed in neuronal cells leading to retinal degeneration.

PROJECT TITLE: Investigating VEGF:VEGFR2 and CXCL8/Interleukin-8:CXCR1/2 Interactions in Diabetic Retinopathy

Dr. Padovani-Claudio's laboratory focuses on finding new treatments for diabetic retinopathy, a leading cause of vision loss and blindness. Due to the growing incidence of obesity and diabetes in the pediatric population an increase in the prevalence of complications associated with diabetic retinopathy is expected. Her research centers on understanding processes that promote inflammation and vascular growth in the retina, and on repurposing existing drugs developed to target these processes in non-ocular systems to prevent, abort or revert them in diabetic retinopathy. She hopes that repurposing such drugs will bypass the costly, lengthy, and risky drug development process and accelerate the translation of her research to effective therapies for patients with blinding conditions.

Dr. Padovani-Claudio's IRRF-supported grant will involve investigating the CXCL8/Interleukin 98 pathway in animal models and also in human patients as an effective potential therapy for patients. She postulates that targeting this chemokine signaling may help patients who fail anti-VEGF therapy.

Dolly Ann Padovani-Claudio, MD, PhD
Assistant Professor of Ophthalmology and Visual Sciences
Vanderbilt Eye Institute
Nashville, Tennessee, USA

$100,000 a year for two years

PROJECT TITLE: Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic Manifestations (RVCL-S), a Vascular Eye Model

Dr. Terwindt is an Associate Professor of Neurology at Leiden University Medical Center, whose special interest is headache and cerebral hereditary angiopathies (CHA). She diagnoses more than 1500 new headache patients a year and aims to combine scientific and clinical work. She introduced a semi-automated questionnaire system (LUMINA and LUCA), and is currently developing other interface tools.

Dr. Terwindt's IRRF-supported study intends to identify retinal imaging markers of disease progression in participants with and without the mutation leading to RVCL, a rare monogenetic microvasculopathy that affects the retina, the brain and other organs. The proposal builds on her world expertise on this condition, first identified by her group.

Gisela Terwindt, MD, PhD, Leiden University Medical Center, The Netherlands

$100,000 for one year

PROJECT TITLE: Understanding Usher Syndrome and Retinitis Pigmentosa Through Investigating the Periciliary Membrane Complex in Photoreceptors

Jun Yang, PhD, Associate Professor of Ophthalmology & Visual Sciences University of Utah, Moran Eye Center

$100,000 a year for two years

Dr. Yang received her B.S. in 1989 from Nankai University, her PhD in 2001 from University of Massachusetts and completed a postdoctoral fellowship in 2001-2006 at Harvard Medical School.

The research in Dr. Yang's laboratory focuses on the disease mechanisms and therapeutic treatments for retinal degenerative diseases using mouse models. Her research group investigates the biological functions of genes whose mutations are known to cause human retinal diseases. Using mouse models, the group also studies how to treat diseases by means of gene therapy. The ongoing research projects in her laboratory are to understand three things: 1. How defects in the multiple protein complex at the periciliary ridge complex in photoreceptors cause retinal degeneration in Usher Syndrome type II, which is a disease with both vision and hearing loss; 2. The biological functions of the ciliary rootlet, a cytoskeletal structure, in photoreceptors and how its defects cause retinal degeneration; 3. How calcium homeostasis is maintained in photoreceptor synaptic terminals and whether it is involved in retinal degeneration.

Dr. Yang's IRRF-supported research will focus on the identification of protein interactions associated with the proteins, when mutated, known to cause two different types of autosomal recessive retinal degeneration caused Usher 2A and autosomal recessive retinitis pigmentosa due to two proteins, ADGRV1 and USH2A.

PROJECT TITLE: Homeostatic Mechanisms Promoting Retinal Output and Vision During Photoreceptor Degenerative Disease

Dr. Vinberg works to understand mechanisms in the retina that enable vision over a wide range of light intensities and colors, and how these mechanisms are affected in major blinding diseases including age-related macular degeneration (AMD) and diabetic retinopathy. The Vinberg Laboratory uses state-of-the-art electrophysiology and molecular/cell biology tools to study fundamental molecular/cellular and disease mechanisms, mainly in the photoreceptor and retinal pigment epithelium cells from mice, primates and donor human eyes.

Dr. Vinberg's IRRF-supported study outlines a plan to explore the mechanisms of compensatory changes that occur in the inner retina following outer retinal degenerations by using in-vitro as well as in-vivo models of outer retinal degenerations.

Terms:

IN-VITRO: A process performed or taking place in a test tube, culture dish, or elsewhere outside a living organism.

IN-VIVO: A process performed or taking place in a living organism.

Frans J. Vinberg, PhD
Assistant Professor of Ophthalmology & Visual Sciences
The Vinberg Laboratory, John A. Moran Eye Center, University of Utah

$99,750 a year for two years

The Association for Research in Vision and Ophthalmology, Inc. (ARVO) was founded in 1928 in Washington, DC by a group of 73 ophthalmologists. The Association's membership today numbers about 12,000 with some 45% of members residing in over 75 countries outside the United States. ARVO is considered the most respected eye and vision research organization in the world. The membership is multidisciplinary and consists of both clinical and basic researchers. This meeting allows scientists to come together to share information and to exchange knowledge, while providing a highly charged environment that serves as a catalyst for learning. The annual meeting is held in a different city every year, giving international visitors an equal opportunity to attend. The 2019 meeting was held in Vancouver, British Columbia, Canada.

(Above) Sandra Blackwood, IRRF Executive Director, signs a letter to Congress advocating more funding for the National Eye Institute, while visiting the National Association for Eye and Vision Research (NAEVR) booth in the Exhibit Hall.

(Above) Monica Jablonski, PhD, University of Tennessee Health Science Center, Memphis, Tennessee, USA, talks with colleagues at ARVO, Vancouver, BC, Canada. Dr. Jablonski is the recipient of the Research to Prevent Blindness/IRRF Catalyst Award for Innovative Research Approaches for Age-related Macular Degeneration for her proposal, New AMD models mined from the BXD family of mice.

The ARVO Foundation for Eye Research funds novel research, education and outreach initiatives of ARVO. The mission is to serve as a global catalyst for innovation, workforce development and collaboration in the field of vision research, while funding the next generation of eye and vision researchers.

(Above) Paul Sternberg, Jr., MD, serves as the ARVO Foundation Board of Governors Chair until 2023. In addition to Dr. Sternberg's responsibilities as the Professor and Chairman of the Department of Ophthalmology and the Vanderbilt Eye Institute, he also serves as the IRRF Director of Research Funding.

The UAB Connections support group provides a unique clinical service that can help both patients and their families adjust to the challenges of living with an eye disease

The UAB Connections meetings are led by licensed mental health facilitators who teach patients and their families evidence-based coping and compensatory strategies designed to enhance their quality of life, community integration, and independence. A range of topics are covered such as eye health, strategies to compensate for vision loss, patient-doctor communication tips, medication adherence, vision research, and family caregiver adjustment. Additionally, once a month social and recreational activities are held by UAB Connections within the community as well as outreach activities to raise awareness about eye diseases and low vision and to learn strategies they can use to adapt services for people with low vision. For example, Dr. Laura Dreer and Ms. Molly Cox (expert group facilitators) conducted a Dinner in the Dark event , a blindfolded dining experience to simulate vision loss, at a local restaurant. Based on attendee feedback ratings, the event was a tremendous success in educating community leaders, eye health care providers, trainees, and support group family members in terms of enhancing their knowledge about low vision and adjustment to an eye disease or eye injury.

UAB Connections educational meetings are offered on the first Tuesday of every month from 10:30am to 1:00pm at the UAB Callahan Eye Hospital. For more information on making referrals, partnering on activities, learning more about the group, or donating to help continue to carry out the activities necessary for conducting the group, please contact Ms. Molly Cox at (205) 488-0788 or mollycox@uabmc.edu

UAB Connections, along with ongoing medical and surgical treatments for vision, can help treat the "whole person." Additionally, it is an innovative, state-of-the-art service not often incorporated into ophthalmology departments. Group members report greater knowledge and control over their eye health, confidence, overall well-being and quality of life. UAB Connections would not be possible without the generous support of our donors and we would like to thank the International Retinal Research Foundation for their financial contribution, which funds the group and helps make a lasting impact on our support group members and their families.

Convening of Private Vision Research Funding Foundations

For the sixth year, Research to Prevent Blindness (RPB) organized a convening of Private Vision Research Funding Foundations with federal agencies that support vision research and vision loss prevention research and vision surveillance, as well as approve new ophthalmic drugs and devices. With a theme of The Eye as a Window to Overall Health, the event featured keynote presentations on the use of visual imaging to diagnose and monitor the progression of various diseases and the use of Artificial Intelligence (AI) in ophthalmology. Attendees also gave updates on collaborations between the participating foundations. International Retinal Research Foundation (IRRF) Executive Director, Sandra Blackwood attended and acted as facilitator for one of the sessions.

RPB/IRRF Catalyst Award for Innovative Research Approaches for Age-Related Macular Degeneration (AMD)

2019 marked the fifth year of collaboration between the International Retinal Research Foundation (IRRF) and Research to Prevent Blindness (RPB) in which our collective resources were used to support focused research into the causes and possible cures for age-related macular degeneration (AMD). The American Macular Degeneration Foundation (AMDF) joined RPB and IRRF in establishing four more catalyst awards in 2019. These Catalyst Awards for Innovative Research Approaches for AMD will provide up to $300,000 per award, payable over 3 years.

The grants are as follows:

RPB/IRRF Catalyst Award for Innovative Research Approaches for AMD

MONICA M. JABLONSKI

Monica M. Jablonski, PhD, FARVO, Professor, University of Tennessee Health Science Center, will develop polygenetic models of AMD in order to better study disease pathogenesis and test innovative therapies.

RPB Catalyst Award for Innovative Research Approaches for AMD

KEVIN L. SCHEY

Kevin L. Schey, PhD, Professor, Vanderbilt University School of Medicine, will develop a novel method of identifying early-stage AMD by correlating molecular and clinical information via a machine learning approach.

ABOUT THE INTERNATIONAL RETINAL RESEARCH FOUNDATION:
The International Retinal Research Foundation (IRRF) provides financial support for vision research to scientists in every corner of the globe, while focusing on discovery of causes, preventions and cures of macular degeneration and diabetic retinopathy. In addition to research funding, IRRF supports training fellowships, public awareness programs, and promotes the exchange of scientific findings. To do this, IRRF must maximize every dollar. Forming partnerships and collaborations with outstanding institutions has made it possible to effectively achieve a collective impact, which will positively affect the lives of many individuals and further scientific knowledge in the vision research community. Learn more at www.irrf.org.

The Catalyst Awards are aimed at researchers who are working on novel approaches to AMD research that has translational relevance or potential. A wide range of applications were considered from promoting a new understanding of AMD and to developing new treatments, including research related to both dry and wet forms of AMD. Assistant professor through full professor from any U.S. academic medical center and any relevant department were eligible to apply. However, the proposed research could not be funded – previously or at the time of application – by others, including government agencies/institutions, non-profits and private funders.

RPB and IRRF launched the first version of the Catalyst Awards in 2014, which focused on supporting novel stem cell-based approaches to AMD. In 2017, RPB and IRRF again joined together to launch the current version of the Catalyst Awards. This collaboration has been a very positive experience and the combining of our respective resources has allowed us to extend a significant award, and we feel confident that worthy recipients have again been selected. The IRRF welcomes the added participation of the American Macular Degeneration Foundation as this will further extend the impact of these awards.

RPB/AMDF Catalyst Award for Innovative Research Approaches for AMD

SABINE FUHRMANN

Sabine Fuhrmann, PhD, Associate Professor, Vanderbilt University Medical Center will examine the potential of retinal pigment epithelium (RPE) cells to regenerate in mature mammalian eyes via specific signaling pathways.

RPB/AMDF Catalyst Award for Innovative Research Approaches for AMD

APARNA LAKKARAJU

Aparna Lakkaraju, PhD, Associate Professor, University of California, San Francisco, School of Medicine, will study RPE cell damage (a known precursor to AMD), with the goal of lerning about the mechanisms that initiate RPE damage and, subsequently, AMD.

Research to Prevent Blindness

ABOUT RESEARCH TO PREVENT BLINDNESS:
Research to Prevent Blindness (RPB) is the leading nonprofit organization supporting eye research directed at the prevention, treatment, or eradication of all diseases that damage and destroy sight. RPB also supports efforts to grow and sustain a robust and diverse vision research community. RPB has awarded more than $368 million in research grants to the most talented vision scientists at the nation's leading medical schools. As a result, RPB has been associated with nearly every major breakthrough in the understanding and treatment of vision loss in the past 59 years. Learn more at www.rpbusa.org.

ABOUT THE AMERICAN MACULAR DEGENERATION FOUNDATION:
The American Macular Degeneration Foundation is a patient-centered foundation that supports potentially game-changing AMD research, education and advocacy in order to improve quality of life and treatment outcomes for all those affected by AMD. Learn more at www.macular.org.

CELL PRESS: Structure of the Decorated Ciliary Doublet Microtubule

(October 31, 2019, Cell 179, 909-922)

Authors: Meisheng Ma[1], Mihaela Stoyanova[2], Griffin Rademacher[3], Susan K. Dutcher[2], **Alan Brown**[3], and Rui Zhang[1].

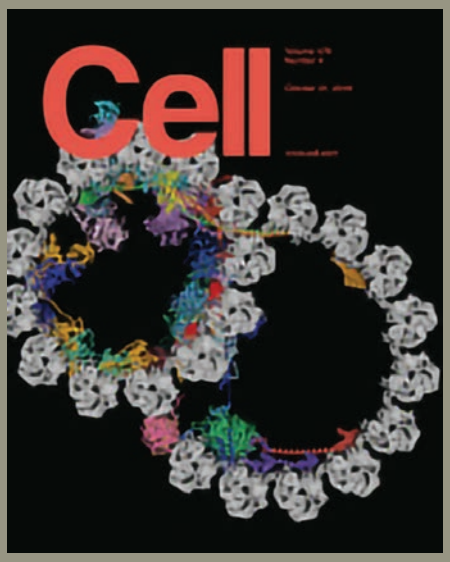
1. Department of Biochemistry and Molecular Biophysics, Washington University in St. Louis, School of Medicine, St. Louis, MO, USA

2. Department of Genetics, Washington University in St. Louis, MO, USA

3. Department of Biological Chemistry and Molecular Pharmacology, Blavatnik Institute, Harvard Medical School, Boston, MA, USA

IN BRIEF: Visualizing axonemal microtubules and the proteins that decorate them, on the outside and inside, points to how the underlying periodic architecture supports cilia function.

SUMMARY: The axoneme of motile cilia is the largest macromolecular machine of eukaryotic cells. In humans, impaired axoneme function causes a range of ciliopathies. Axoneme assembly, structure, and motility require a radially arranged set of doublet microtubules, each decorated in repeating patterns with non-tubulin components. Single-particle cryo-electron microscopy is used to visualize and build an atomic model of the repeating structure of a native axonemal doublet microtubule, which reveals the identities, positions, repeat lengths, and interactions of 38 associated proteins, including 33 microtubule inner proteins (MIPs). The structure demonstrates how these proteins establish the unique architecture of doublet microtubules, maintain coherent periodicities along the axoneme, and stabilize the microtubules against the repeated mechanical stress induced by ciliary motility. This work elucidates the architectural principles that underpin the assembly of this large, repetitive eukaryotic structure and provides a molecular basis for understanding the etiology of human ciliopathies.



This study was conducted with IRRF support – Alan Brown, PhD, 2018 and 2019. Dr. Brown is a member of the faculty of the Department of Biological Chemistry and Molecular Pharmacology at Harvard Medical School in Boston. He holds a B.Sc. in Biochemistry from the University of Warwick, Coventry, UK; and a PhD in Biochemistry from the University of Cambridge, Cambridge, UK.

Proceedings of the National Academy of Sciences (PNAS) of the United States of America

Human complement factor H Y402H polymorphism causes an age-related macular degeneration phenotype and lipoprotein dysregulation in mice.

Michael Landowski, Una Kelly, Mikael Klingeborn, Marybeth Groelle, Jin-Dong Ding, Daniel Grigsby and **Catherine Bowes Rickman**.

PNAS February 26, 2019 116 (9) 3703-3711

To read the entire article go to: https://doi.org/10.1073/pnas.1814014116

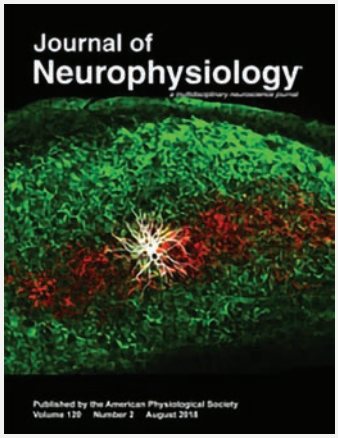
This study was conducted with IRRF support through an RPB/IRRF Catalyst Award for Innovative Research.

SIGNIFICANCE: The complement factor H (CFH) Y402H polymorphism (rs1061170) imparts the strongest risk for age-related macular degeneration (AMD), the leading cause of blindness in the elderly. Popular thinking holds that the CFH H402 variant increases complement activation in the eye, predisposing susceptibility to disease. However, clinical trials of complement inhibitors in AMD patients have failed. This study provides an explanation showing CFH variant-specific differences in the presentation of AMD-like pathologies. The study also shows that aged mice expressing the human H402, but not Y402 variant, (*i*) develop AMD-like symptoms and (*ii*) display differences in their systemic and ocular lipoprotein levels, but not in their complement activation, after diet. These findings support targeting lipoproteins for the treatment of AMD.

A Professor of Ophthalmology and Associate Professor in Cell Biology with tenure at Duke University School of Medicine, Dr. Bowes Rickman is currently receiving funds as a recipient of a Research to Prevent Blindness (RPB)/International Retinal Research Foundation (IRRF) Catalyst Award for Innovative Research Approaches for AMD. The RPB/IRRF Catalyst Awards provide seed money for high-risk/high-gain vision science research, which is innovative, cutting-edge and demonstrates out-of-the box thinking. Research related to both dry and wet forms of AMD are supported by this award.

Dr. Bowes Rickman's current studies involve the molecular mechanisms underlying the development of age-related macular degeneration, with a focus on development and studies of animal models of AMD, AMD pathogenesis and pre-clinical studies of novel therapies for AMD, and she has a strong track record of productive research in this field.

Dopamine D1 receptor activation contributes to light-adapted changes in retinal inhibition to rod bipolar cells



Michael D. Flood, Moore-Dotson JM and **Eggers ED**, University of Arizona.

Journal of Neurophysiology (15 AUG 2018, Vol 120, Issue 2)

To access this article: www.physiology.org/doi/full/10.1152/jn.00855.2017

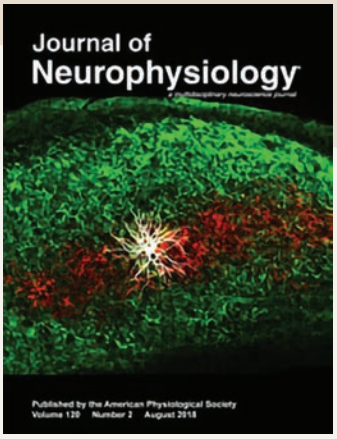
This study conducted with IRRF support, Erika Eggers.

SIGNIFICANCE: Dopamine modulation of retinal signaling has been shown to be an important part of retinal adaptation to increased background light levels, but the role of dopamine modulation of retinal inhibition is not clear. This team previously showed that light adaptation causes a large reduction in inhibition to rod bipolar cells, potentially to match the decrease in excitation after rod saturation. This study determined how dopamine D1 receptors in the inner retina contribute to this modulation. It was found that D1 receptor activation significantly decreased the magnitude of inhibitory light responses from rod bipolar cells. Whereas D1 receptor blockade during light adaptation partially prevented this decline. To determine what mechanisms were involved in the modulation of inhibitory light responses, the effect of D1 receptor activation on spontaneous currents and currents evoked from electrically stimulating amacrine cell inputs to rod bipolar cells was measured. D1 receptor activation decreased the frequency of spontaneous inhibition with no change in event amplitudes, suggesting a presynaptic change in amacrine cell activity in agreement with previous reports that rod bipolar cells lack D1 receptors. Additionally, it was found that D1 receptor activation reduced the amplitude of electrically evoked responses, showing that D1 receptors can modulate amacrine cells directly. These results suggest that D1 receptor activation can replicate a large portion but not all of the effects of light adaptation, likely by modulating release from amacrine cells onto rod bipolar cells.

Erika Eggers, PhD
is an assistant professor at the University of Arizona and received IRRF funding for her study, Testing the role of dopamine as a potential treatment for diabetic retinal dysfunction.

NA3 glycan: a potential therapy for retinal pigment epithelial deficiency

Sumana R. Chintalapudi, XiangDi Wang; XiaoFei Wang; Yunfeng Shi, Mehmet Kocak; Mallika Palamoor; Raven N. Davis; T.J. Hollingsworth; **Monica M. Jablonski**.

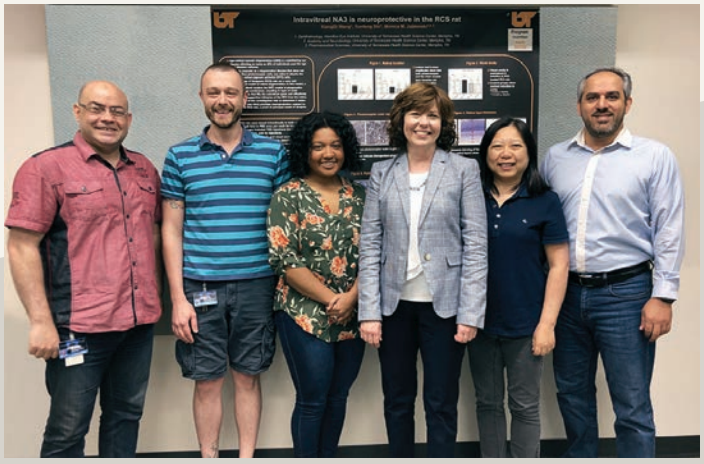


ABSTRACT: Atrophic age-related macular degeneration (AMD) is the most common type of AMD, yet there is no United States Food and Drug Administration (FDA)-approved therapy. This disease is characterized by retinal pigment epithelial (RPE) insufficiency, primarily in the macula, which affects the structure and physiology of photoreceptors and ultimately, visual function. In this study, we evaluated the protective effects of a naturally derived small molecule glycan therapeutic – asialo-, tri-antennary complex-type N-glycan (NA3) – in two distinct preclinical models of atrophic AMD. In RPE-deprived Xenopus laevis tadpole eyes, NA3 supported normal retinal ultrastructure. In RCS rats, NA3 supported fully functioning visual integrity. Furthermore, structural analyses revealed that NA3 prevented photoreceptor outer segment degeneration, pyknosis of the outer nuclear layer, and reactive gliosis of Müller cells (MCs). It also promoted maturation of adherens junctions between MC and photoreceptors. Our results demonstrate the neuroprotective effects of a naturally derived small molecular glycan therapeutic-NA3-in two unique preclinical models with RPE insufficiency. These data suggest that NA3 glycan therapy may provide a new therapeutic avenue in the prevention and/or treatment of retinal diseases such as atrophic AMD.

Dr. Jablonski is an IRRF-supported scientist at the University of Tennessee – Memphis.

Dr. Chintalapudi is the 2019 Charles D. Kelman, MD Postdoctoral Scholar.

You may access this article: https://febs.onlinelibrary.wiley.com/doi/full/10.1111/febs.15006.



Left: Monica Jablonski and team members in University of Tennessee – Memphis labs

Collaboration Leads to Innovation

BY LISA C. BAILEY

> *"It's the divide-and-conquer idea," **Maria Grant, M.D., Eivor and Alston Callahan, M.D.**, Endowed Chair in Ophthalmology (University of Alabama at Birmingham), says of her collaborative research in diabetic retinopathy. "You can't do everything yourself. We're a small- to medium-size lab, and my collaborators across the country are in the same situation. So you split up the workload to make it manageable. It's a much more efficient way to have people doing what they do well to contribute to a project."*

The focus of Grant's most recent research is primarily on understanding basic mechanisms responsible for the pathogens in the development of diabetic retinopathy. "We are particularly interested in trying to understand how the bone marrow and the cells that produce that bone marrow, a process called hematopoietesis, is influenced in diabetes and how that affects the retina," she says. Her collaborators on this particular research include Julia Busik, Ph.D., professor in the Department of Physiology at Michigan State University; Moshe Levi, M.D., professor in the Department of Biochemistry and Molecular &Cellular Biology at Georgetown University; and Qiuhong Li, Ph.D., associate professor in the Department of Ophthalmology Research at the University of Florida. In her lab at UAB, Grant works with six graduate students, four post-docs, and three senior scientists.

"Most recently we've not only focused on the bone marrow interactions with the eye," Grant says, "but also how the gut and the gut microbiome regulate metabolism and immune function in neuroendocrine pathways and how they influence development of diabetic eye disease." According to Grant, the gut microbiome is deregulated in diabetes. "We studied the intestinal microbiome in the context of both Type 1 and Type 2 diabetes," she says, "and we've found that it has an essential role. We've also used the idea of intermittent fasting to influence it, and we were able to show that we could prevent diabetic retinopathy. We found that intermittent fasting generated high levels of a particular neuroprotective bioacid called TUDCA, and we showed that in a paper we published in Diabetes last year. We're continuing our research along those lines."

Grant and her team are now applying some of the things they learned in diabetic retinopathy to atherosclerosis. “Atherosclerosis regression doesn’t occur in diabetic patients,” she says. “We’re trying to understand the mechanism for that, and we believe that it’s gut related and related to swings in blood sugars. Having a leaky gut occasionally or getting bacteria in the blood isn’t necessarily a bad thing. The body usually does an amazing job of cleaning things up and getting rid of the bacteria. But in diabetes this keeps happening many times during one day, and we were able to show that intermittent fasting could reduce that.”

The relationships among her collaborators have been very important in the progress of the research. “It’s important to have a really good collaborative team that is supportive,” she says. “It helps to have someone to talk to and someone to help you deal with the highs and the lows. There are a lot of discouraging times and rejection, and we keep each other encouraged.” She adds, “It also makes the science much more fun—a most important factor in keeping it going.”

Reprinted from the UAB 2019 Annual Report. The Eivor and Alston Callahan, MD, Endowed Chair in Ophthalmology was created through a gift from The International Retinal Research Foundation, Birmingham, Alabama, USA

Maria Grant, M.D.

IRRF Commitment of $2.5 million to the University of Alabama at Birmingham Over the Next Five Years Leads to Innovation

The University of Alabama at Birmingham (UAB) Department of Ophthalmology and Visual Sciences, located at the UAB Callahan Eye Hospital in Birmingham, has experienced unprecedented growth over the past several years, and IRRF support has become a major component of that trajectory. The department ranked sixth in the country for National Institutes of Health (NIH) funding in 2017, advancing to fifth in 2018. This growth was catalyzed by the Vision of Excellence (VOE) investment made possible by the partnership among the International Retinal Research Foundation, the EyeSight Foundation of Alabama and the UAB School of Medicine.

"As a critical founding partner in the VOE endeavor, the International Retinal Research Foundation's support has been integral to our continued success. The Eivor and Alston Callahan, MD Endowed Chair in Ophthalmology helped us recruit nationally renowned Maria Grant, PhD to UAB, and IRRF has also been supportive of the research efforts of Dr. Christine Curcio, as well as patient outreach by supporting Dr. Laura Dreer and Dr. Dawn DeCarlo in the Low Vision Clinic. We are extremely grateful for this partnership," reported Chris Girkin, MD, Chairman, UAB Department of Ophthalmology and Visual Sciences.

The gift will be paid over five years in $500,000 increments, representing a major funding commitment to provide research and programmatic support for the UAB Department of Ophthalmology and Vision Sciences. "Forming partnerships and collaborations with outstanding institutions has made it possible to effectively achieve a collective impact. For this reason, our support of the UAB Department of Ophthalmology and Visual Sciences over the years has proved to be a wise investment producing impactful and worthwhile results." – Sandra Blackwood, IRRF Executive Director.

Above: Christopher Girkin, MD, MSPH, FACS, Chairman and EyeSight Foundation of Alabama Endowed Chair.

2019 Alston Callahan, AMD Postdoctoral Scholar Recipient

During her first year as a postdoctoral fellow at University of Washington's School of Medicine, Dr. Sridhar has garnered 'attention as a rising star,' according to Dr. Thomas Reh. "Dr. Sridhar is exceptionally motivated and very bright. She has only been in my lab for just over one year, but has already made great progress on several projects involving retinal organoids," says Reh. He went on to explain that Dr. Sridhar applied to his lab to further develop her knowledge of neural retinal development and to develop the retinal organoid system to fully reflect normal fetal human embryogenesis, which he describes as an ambitious goal.

The goal of Dr. Sridhar's proposal is to build fovea-like organoids from human pluripotent stem cells (hPSCs). Sridhar explained that given their pluripotent nature, hPSCs serve as a unique and novel tool to allow access to early stages of retinal development.

Dr. Sridhar is joint first author, along with Thomas A. Reh and Akina Hoshino, on a paper recently published, which demonstrates for the first time that the epigenetic aging clock already tracks chronological age in fetal tissue and organoids. She is also preparing two additional manuscripts on single cell RNAseq analysis of fetal human retina and retinal organoids. "This is a remarkable accomplishment," comments Dr. Reh, "typically it takes several years for a new postdoctoral fellow to submit a single report for publication, yet Dr. Sridhar already has most of the data for three publications."

ABSTRACT: Epigenetic changes have been used to estimate chronological age across the lifespan, and some studies suggest that epigenetic "aging" clocks may already operate in developing tissue. To better understand the relationship between developmental stage and epigenetic age, we utilized the highly regular sequence of development found in the mammalian neural retina and a well-established epigenetic aging clock based on DNA methylation. The results demonstrate that the epigenetic age of fetal retina is highly correlated with chronological age. Also established, epigenetic aging progresses normally in vitro, suggesting that epigenetic aging is a property of individual tissues. This correlation is also retained in stem cell-derived retinal organoids, but is accelerated in individuals with Down syndrome, a progeroid-like condition. Overall, the results suggest that epigenetic aging begins as early as a few weeks post-conception, in fetal tissues, and the mechanisms underlying the phenomenon of epigenetic aging might be studied in developing organs.

To view this article in its entirely, please follow the link, or scan: www.Nature.com/articles/s41598-019-39919-3

Akshayalakshmi Sridhar, PhD
University of Washington
Seattle, Washington

Project title: ***Building fovea-like retinal organoids from human pluripotent stem cells.***

Synchrony and asynchrony between an epigenetic clock and developmental timing. Akina Hoshino[1], Steve Horvath[2], **Akshayalakshmi Sridhar**[1], Alex Chitsazan[3], & Thomas A. Reh[1]

1Department of Biological Structure, University of Washington, Seattle, WA, 98195, USA. **2**Human Genetics and Biostatistics, David Geffen School of Medicine, University of California Los Angeles, Gonda Research Center, Los Angeles, CA, 90095-7088, UAS. **3**Department of Biochemistry, University of Washington, Seattle, WA, 98195, USA.

SCIENTIFIC REPORTS
nature research

2019 Charles D. Kelman, MD Postdoctoral Scholar

Sumana R. Chintalapudi, PhD
Boston Children's Hospital
Boston, Massachusetts

Project title: ***Evaluation of the role of Myosin 1d in choroidal angiogenesis.***

Dr. Chintalapudi received her Bachelor's degree in Biochemistry/Zoology from St. Xavier's College (India), Master's degree in Biomedical Genetics from VIT University (India) and PhD in Vision Neuroscience at Hamilton Eye Institute, University of Tennessee Health Science Center (UTHSC), Memphis, Tennessee, USA. While at UTHSC, Dr. Chintalapudi worked on systems genetics of glaucoma using genetic reference populations. After graduating in 2016, she did a postdoctoral fellowship at The Jackson Laboratory, investigating the eye as a biomarker for Alzheimer's disease. Currently, Dr. Chintalapudi is working in Dr. Robert D'Amato's laboratory, Boston Children's Hospital and is investigating novel targets for differential angiogenic responses using genetic approaches and model organisms..

In her application to the IRRF, Dr. Chintalapudi provided background for her proposed study. "The overwhelming cause of severe vision loss in age-related macular degeneration (AMD) patients is choroidal neovascularization (CNV), the growth of abnormal blood vessels beneath the retina. The mechanisms responsible for this process have been deduced to angiogenesis, the sprouting of new blood vessels from pre-existing vasculature, and vasculogenesis, the recruitment, proliferation and incorporation of bone marrow-derived progenitor cells into nascent vasculature. The ocular angiogenic balance varies between individuals and this variation is in large part genetically determined."

During her year of investigation as the IRRF Kelman Postdoctoral Scholar, Dr. Chintalapudi will work to discover genetic traits that correlate with ocular angiogenesis, which is essential in identifying individuals prone to AMD, as well as in discerning signaling cascades that underlie disease pathophysiology.

Dr. D'Amato says of Dr. Chintalapudi, "Sumana is a highly gifted scientist who is one of the best to come through my laboratory."

2019 Loris and David Rich, MD Postdoctoral Scholar

Jason M. Miller, MD, PhD
Kellogg Eye Center
University of Michigan
Ann Arbor, Michigan

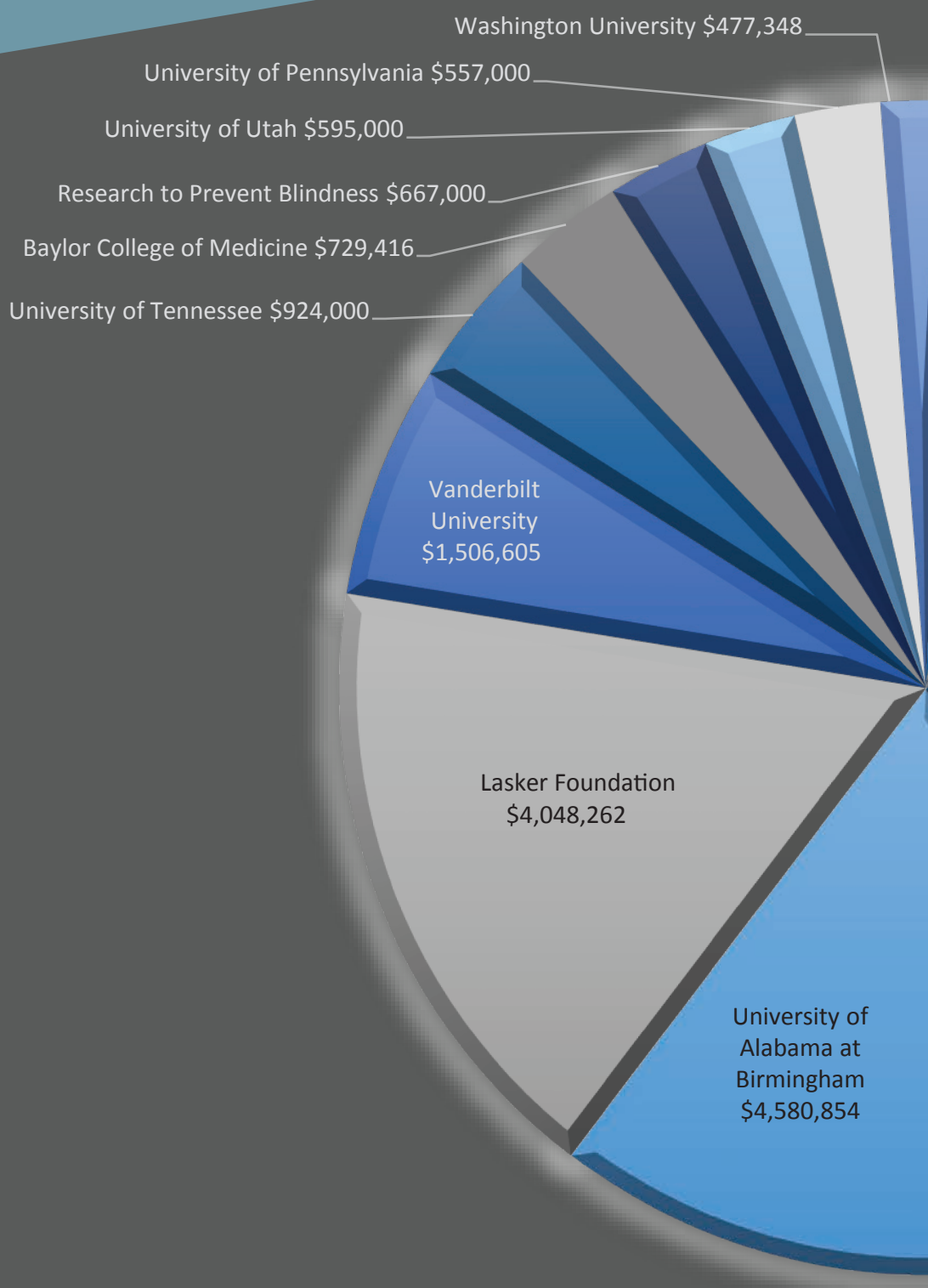
Project title: ***mTor-Independent Activation as a Therapeutic for Lipid-Rich Pathology in Dry Age-Related Macular Degeneration***

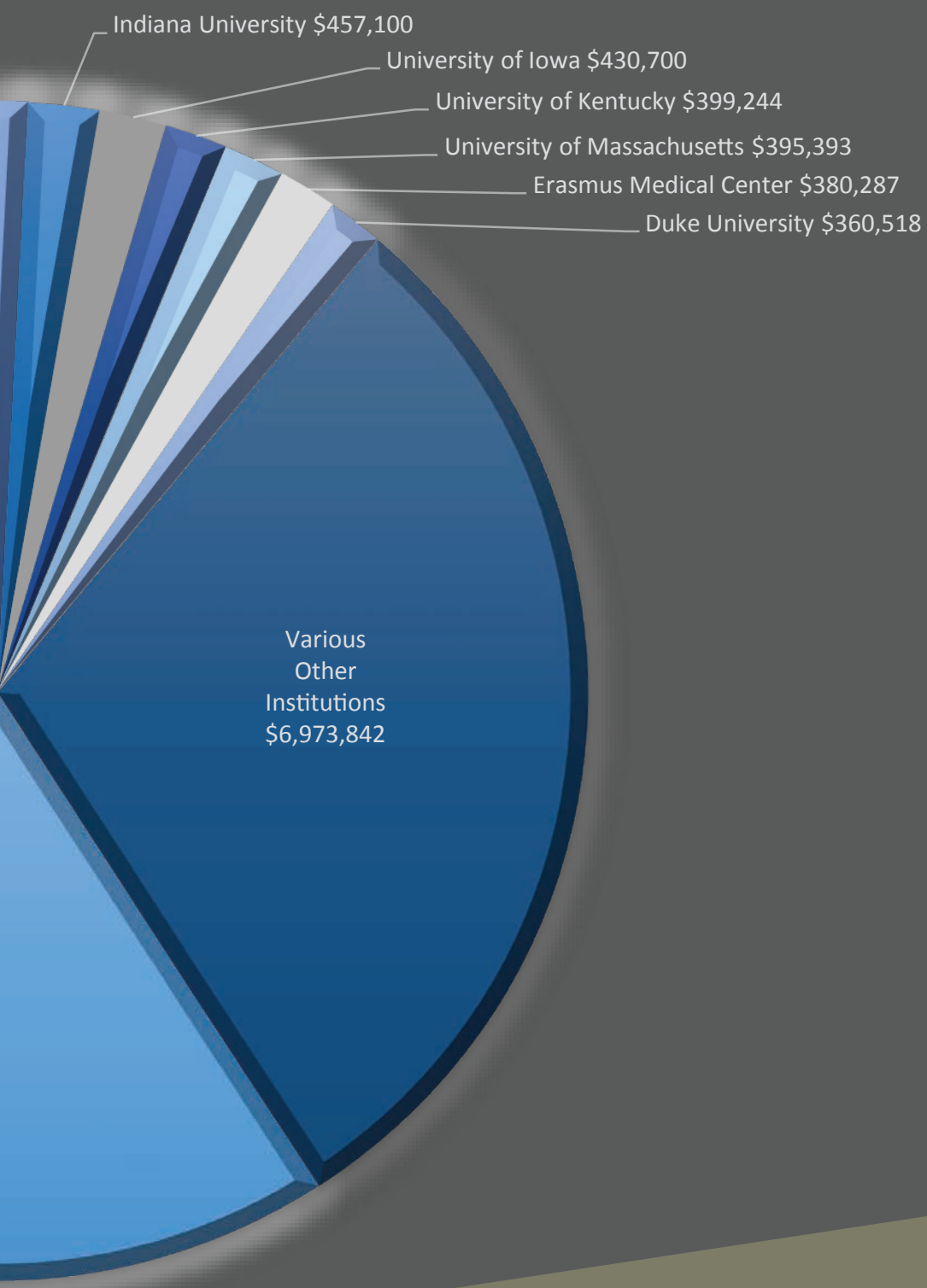
Dr. Miller completed his undergraduate degree in biology at Stanford University, where he was active in development of microsurgical devices with the Department of Ophthalmology. He completed his MD and PhD graduate work at University of California, San Francisco (UCSF), where he developed primary neuronal culture models of Huntington's disease under the mentorship of Steve Finkbeiner at the UCSF-affiliated Gladstone Institute of Neurological Disease. An internal medicine internship at Kaiser Permanente Oakland followed. Seeking to combine his post-graduate medical and scientific training, Dr. Miller became the inaugural awardee for the University of Michigan Kellogg Eye Center's Pre-Residency Research Fellowship. This fellowship allows for establishment of an independent research program prior to joining the ophthalmology residency. After completing this fellowship in 2016, he joined the residency program in July that year.

Dr. Miller's research program, which seeks to establish primary retinal pigment epithelial (RPE) culture models of dry AMD as a platform for testing therapeutic interventions, continues during residency through the help of lab members he trained during the fellowship.

As the IRRF Loris and David Rich, MD Postdoctoral Scholar, Dr. Miller will work to identify small molecule activators of autophagy in RPE that do not directly target the mTOR pathway and are already FDA-approved compounds or that interact with protein targets actively under pharmacologic development.

The International Retinal Research Foundation Grants 1998 – Present





Grand Total All Years $23,482,569

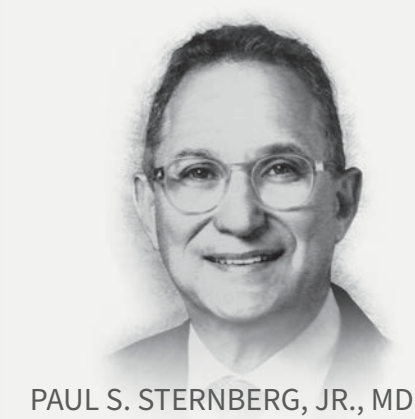
Various Institutions Include all grants of $300,000 or less

THE IRRF BOARD OF DIRECTORS

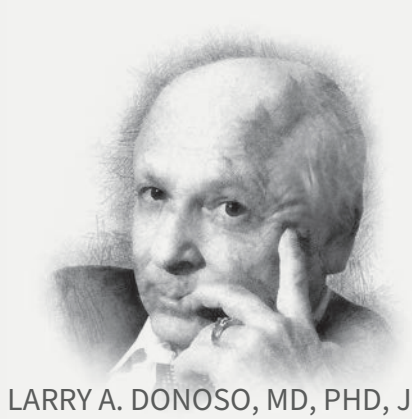
MICHAEL A. CALLAHAN, MD,
has served as President since 2004 and gives generously of his time. Since 1998, Dr. Callahan has held a faculty position as Professor of Ophthalmology in the Department of Ophthalmology at the University of Alabama at Birmingham (UAB), and teaches the intricate surgical procedures of phacoemulsification and intraocular lens insertion. In addition, Dr. Callahan lectures on ophthalmic plastic surgery. Dr. Callahan is also very involved in providing ophthalmic care in the U.S. and countries worldwide, where medical care is not readily available.

JOHN S. PARKER, MD,
serves as Vice President while devoting himself to private ophthalmology practice and teaching responsibilities in the UAB Department of Ophthalmology where he trains ophthalmology residents and donates time and expertise caring for indigent patients. Dr. Parker has served as Director of the Corneal Service and as Director of the Residency Training Program in the UAB Department of Ophthalmology.

V. HUGO MARX, III,
serves as Treasurer and has been a member of the IRRF Board since 2004. Mr. Marx operates several corporations, which represent various industries, including health care, investment banking and venture capital. Through his numerous businesses, Mr. Marx has provided charitable donations as medical supplies, food and support items used in multiple, extreme emergency situations in and outside the U.S.



PAUL S. STERNBERG, JR., MD,
serves as Director of Research Funding for the Foundation in addition to his many other responsibilities at Vanderbilt University in Nashville, Tennessee, where he is Associate Dean for Clinical Affairs and Assistant Vice Chancellor for Adult Health Affairs at the Vanderbilt School of Medicine. He also serves as professor and chairman of the Department of Ophthalmology and the Vanderbilt Eye Institute. With a special interest in age-related macular degeneration, Dr. Sternberg oversees a cell biology and biochemistry laboratory that carries out studies into the causes of the disease.



LARRY A. DONOSO, MD, PHD, JD,
serves as Emeritas Director of Research Education and continues to provide advice to the Foundation Board. Dr. Donoso has over four decades of bench and clinical research experience, which adds an important component to the combined talents of the IRRF Board of Directors. Holding degrees in chemistry, experimental biology, biochemistry/biology, medicine and law, allowed Dr. Donoso to serve as Scientific Director when the Foundation was newly formed and served as a steadfast member of the board for 17 years.

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HOW YOU CAN HELP...

Today's scientists play a crucial role in the universal struggle against debilitating eye diseases, but financial funding is needed to facilitate and sustain their efforts. As of year-end 2019, the IRRF had granted more than $23 million in support of scientific investigations targeting all structures of the human eye, with emphasis on finding the causes, prevention and cure of degenerative diseases. If you would like to help with this challenge, please send your tax deductible contribution to:

The International Retinal Research Foundation, Inc.
Attn.: Sandra Blackwood, MPA, Executive Director
1720 University Boulevard
Birmingham, AL 35233 www.irrf.org