2015 ANNUAL REPORT

International Retinal Research Foundation

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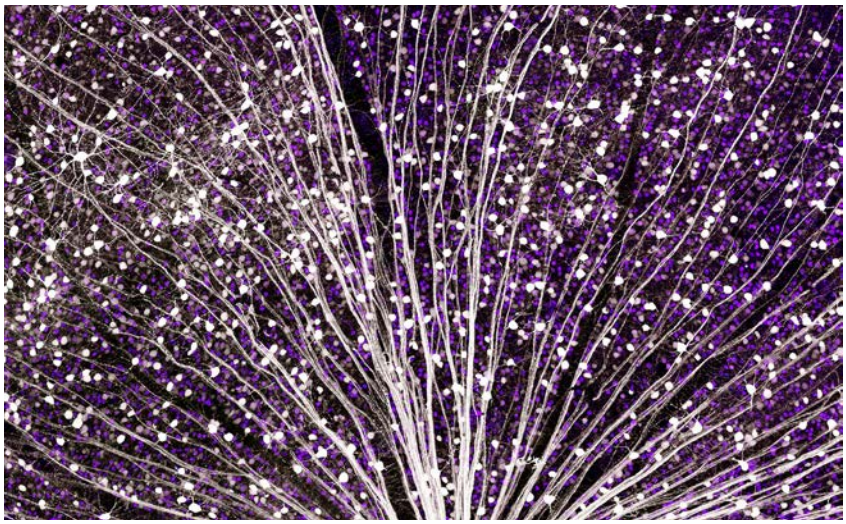
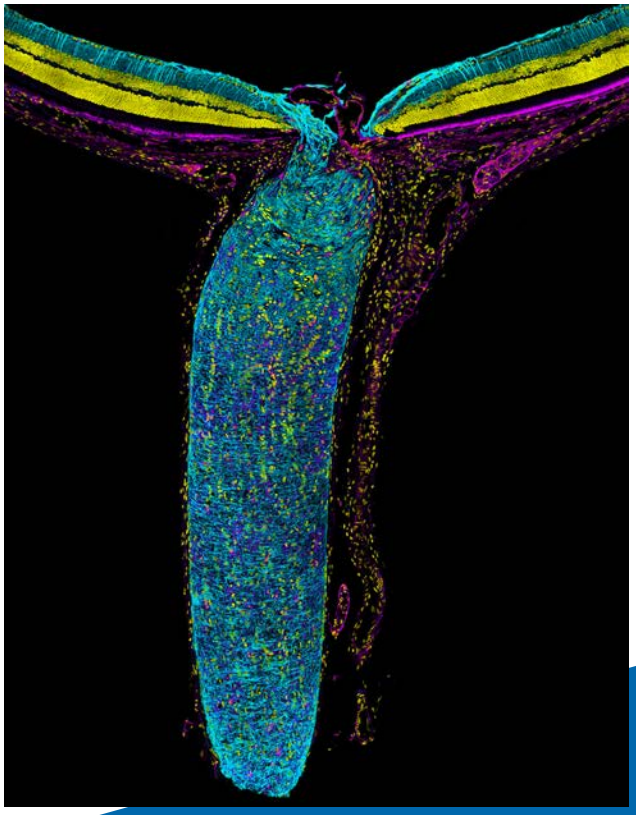
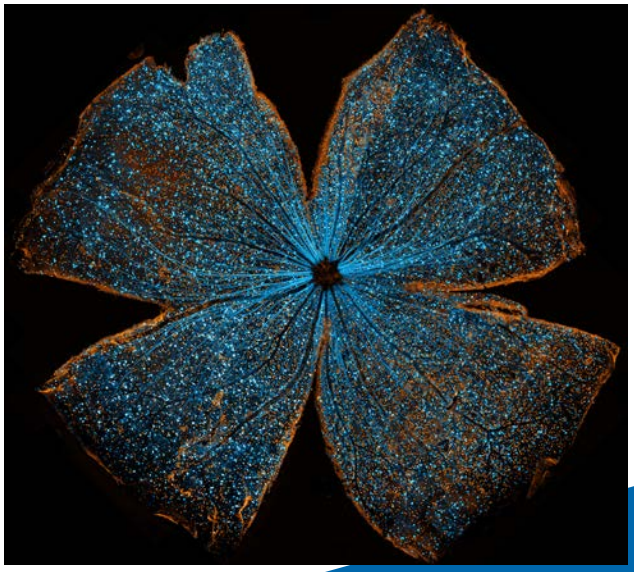


About The Cover Photo

Photo by: Keun-Young Kim, Won-Kyu Ju and Mark H Ellisman

Mouse retina with retinal ganglion cells highlighted by expression green fluorescent protein [GFP (light blue)] and counter stained with Brn3a antibody (orange) to mark the cell nuclei. Note that GFP expression highlights the cell bodies and axons of retinal ganglion cells.





Contents

2015 Lasker Awards, September 2015

In 2008, the **International Retinal Research Foundation** entered into a ten-year partnership with the Albert and Mary Lasker Foundation. Part of this collaboration was to establish the Lasker/IRRF Initiative for Innovation in Vision Science, but another component is to offer support for the annual Lasker Awards that honor outstanding scientists and healthcare advocates who have made a difference in the world of science and medicine. 2015 marked the 60th year these prestigious Awards have been given to recognize the contributions of scientists, physicians, and public servants who have made major advances in the understanding, diagnosis, treatment, and prevention of human disease. The IRRF is proud to be part of this program.

The 2015 Albert Lasker Basic Medical Research Award honored two scientists for their discoveries concerning the DNA-damage response, a mechanism that protects the genomes of all living organisms. **Evelyn M. Witkin** (Rutgers University) established its existence and basic features in bacteria.

Stephen J. Elledge (Brigham and Women's Hospital) uncovered its molecular pathway in more complex organisms. The details of the two systems differ dramatically, yet they share an overarching principle. Both coordinate the activity of a large number of genes whose products shield creatures from potentially lethal harm.

The 2015 Lasker-DeBakey Clinical Medical Research Award honored **James P. Allison** (University of Texas MD Anderson Cancer Center), who discovered and developed a monoclonal antibody therapy that unleashes the immune system to combat cancer. By blocking a protein that normally restrains the body's natural ability to attack tumor cells, Dr. Allison devised a fundamentally new strategy for treating malignancies. Because this approach targets immune cells rather than specific tumors, it holds great promise to thwart diverse cancers.

Allison's work has already benefited thousands of people with advanced melanoma, a disease that typically used to kill people in less than a year. The therapy he conceived has delivered recoveries that last for a decade or more.

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International Retinal Research Foundation

2015 LASKER AWARDS

The 2015 Lasker-Bloomberg Public Service Award

The 2015 Lasker-Bloomberg Public Service Award honored Médecins Sans Frontiéres (Doctors Without Borders) (MSF) for bold leadership in responding to the recent Ebola outbreak in Africa and for sustained and effective frontline responses to health emergencies. Undeterred by grim and demanding circumstances, its employees and volunteers have worked steadily for decades to fulfill the organization's mission. Last year, it undertook a monumental task – a duty that rightly belongs to the international community, not an outfit that is funded primarily by individual donors.

Since 1971, MSF has provided medical assistance and humanitarian aid to the world's neediest citizens, the organization delivers drugs, healthcare, and other essential resources to people who suffer from crises of war, healthcare, and other essential resources to people who suffer from crises of war, famine, natural disasters, and infectious disease. It reaches vast numbers of people in troubled areas, in part because it remains politically neutral.

For more information: laskerfoundation.org

Portions of this article were reprinted with permission from the Lasker Foundation.
Photo credits: Lasker Foundation and Larry Donoso, MD, PhD.

Joanne Liu, International President of MSF, and staff at the Ebola treatment center in Kailahun, Sierra Leone)

Access the publication ▶

Lasker/IRRF Initiative for Innovation in Vision Science

The Initiative dedicated to Restoring Vision to the Blind finished up with an online journal published in Translational Vision Science and Technology (TVST) as a special edition, following an independent print version of the report that had been produced earlier.

Additionally, the partners hosted a Special Interest Group (SIG) at the 2015 Association for Research in Vision and Ophthalmology (ARVO) meeting held in Denver, Colorado in May. The SIG created much attention and was attended by more than 400 national and international vision scientists who had come to attend the ARVO meeting. The forum highlighted the Initiative's work to assess technical hurdles that must be addressed in order to advance research in amblyopia and put forward proposals for innovative strategies to accelerate research aimed at restoring photoreceptor function in blind eyes.

The next study topic for the Initiative is amblyopia. This condition, commonly known as "lazy eye," is a vision development disorder in which an eye fails to achieve normal visual acuity, even with prescription glasses or contact lenses. It is a major cause of visual loss in children, affecting 2 – 3% of people worldwide. During the summer of 2015, two workshops involving a total of 50 participants identified critical knowledge gaps in the variety of abnormalities causing the vision deficits that characterize amblyopia. Right: Lasker/IRRF Initiative on Amblyopia, July 2015, summer workshop, Woods Hole, Massachusetts. (Photo credit: Larry A. Donoso, MD, PhD.)

To acces the original publication, Restoring Vision to the Blind, The Lasker/IRRF Initiative for Innovation in Vision Science: www.laskerfoundation.org/media/filer_public/f0/10/f010f4b7-ff5e-492d-ba6c-ced1734cf107/irrf_15.pdf

◀ Access this article

PUBLISHED SCIENCE:

Experimental Eye Research

"Acetyl-11-keto-β-boswellic acid reduces retinal angiogenesis in a mouse model of oxygen-induced retinopathy"

Matteo Lulli, Maurizio Cammalleri, Irene Fornaciari, Giovanni, Casini, Massimo Dal Monte. (April 2015, v 135, 67-80) **This study was conducted with IRRF support – Dr. Massimo Dal Monte.**

Although therapies directed toward vascular endothelial growth factor (VEGF) represent a significant step forward in the treatment of proliferative retinopathies, further improvements are needed. In the last few years, an intense research activity has focused around the use of herbal and traditional natural medicines as an alternative for slowing down the progression of proliferative retinopathies. In this study, the antiangiogenic effects of acetyl-11-keto-β-boswellic acid (AKBA), one of the active principles derived from the plant *Boswellia serrata*, used in Ayurvedic systems of medicine, was investigated. The team studied the antiangiogenic properties of AKBA using the mouse model of oxygen-induced retinopathy (OIR), which mimics the neovascular response seen in human retinopathy of prematurity. It was observed that AKBA reduced proliferation, migration and tube formation in human retinal microvascular endothelial cells (HRMECs) stimulated with exogenous VEGF, while it reduced migration and tube formation in untreated HRMECs. Taken together, the results demonstrate the antiangiogenic effects of AKBA in a model of pathologic neovascularization, providing a rationale for further investigation of AKBA as a promising therapeutic agent to reduce the impact of proliferative retinopathies.

International Retinal Research Foundation

Research Scientists Who Received IRRF Support in 2015

Ashay Bhatwadekar, PhD; Indiana University. Müller Cell Dysfunction in Diabetic Retinopathy.

Frans P.M. Cremers, PhD; Radboud University Medical Center. The Netherlands. Identification of Novel Human Retinal Dystrophy Genes by Sequence Analysis of Genes Mutated in Mammalian Models with Non-Syndromic Visual Impairment.

Erika D. Eggers, PhD; University of Arizona, Tucson. Testing the Role of Dopamine as a Potential Treatment for Diabetic Retinal Dysfunction.

Denise M. Inman, PhD; Northeast Ohio Medical University. Disruption of Mitochondrial-related Vesicular Traffic by E50K Optineurin.

Yun Z. Le, PhD; University of Oklahoma. Therapeutic Potential of Reducing Lipid Deposition in Geographic Atrophy.

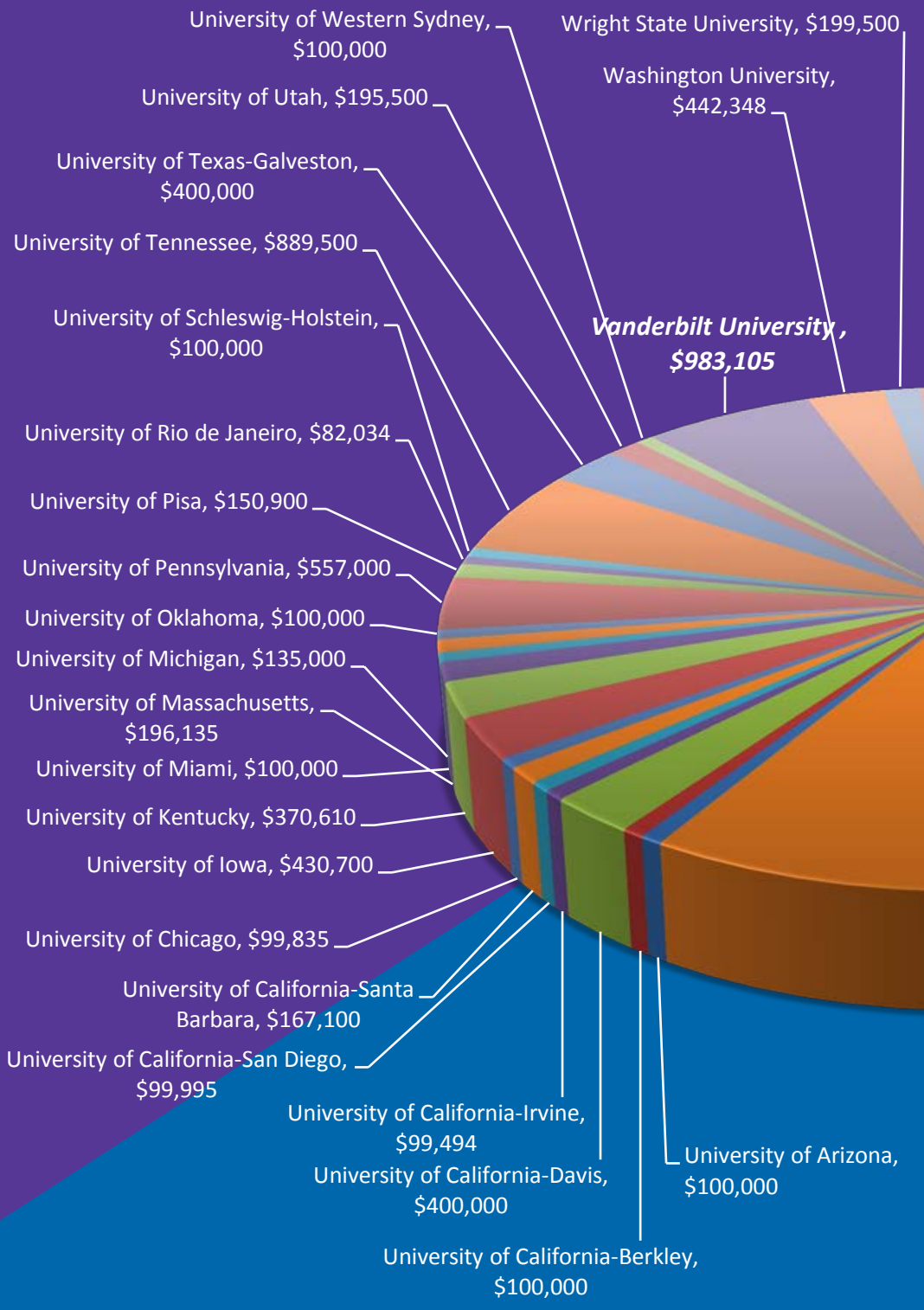
Rodrigo A. P. Martins, PhD; Cidade Universitária, Rio de Janeiro, Brazil. Smc1 and the Cohesion Complex in Retinal Development and Disease: A New Mouse Model of Photoreceptor Degeneration.

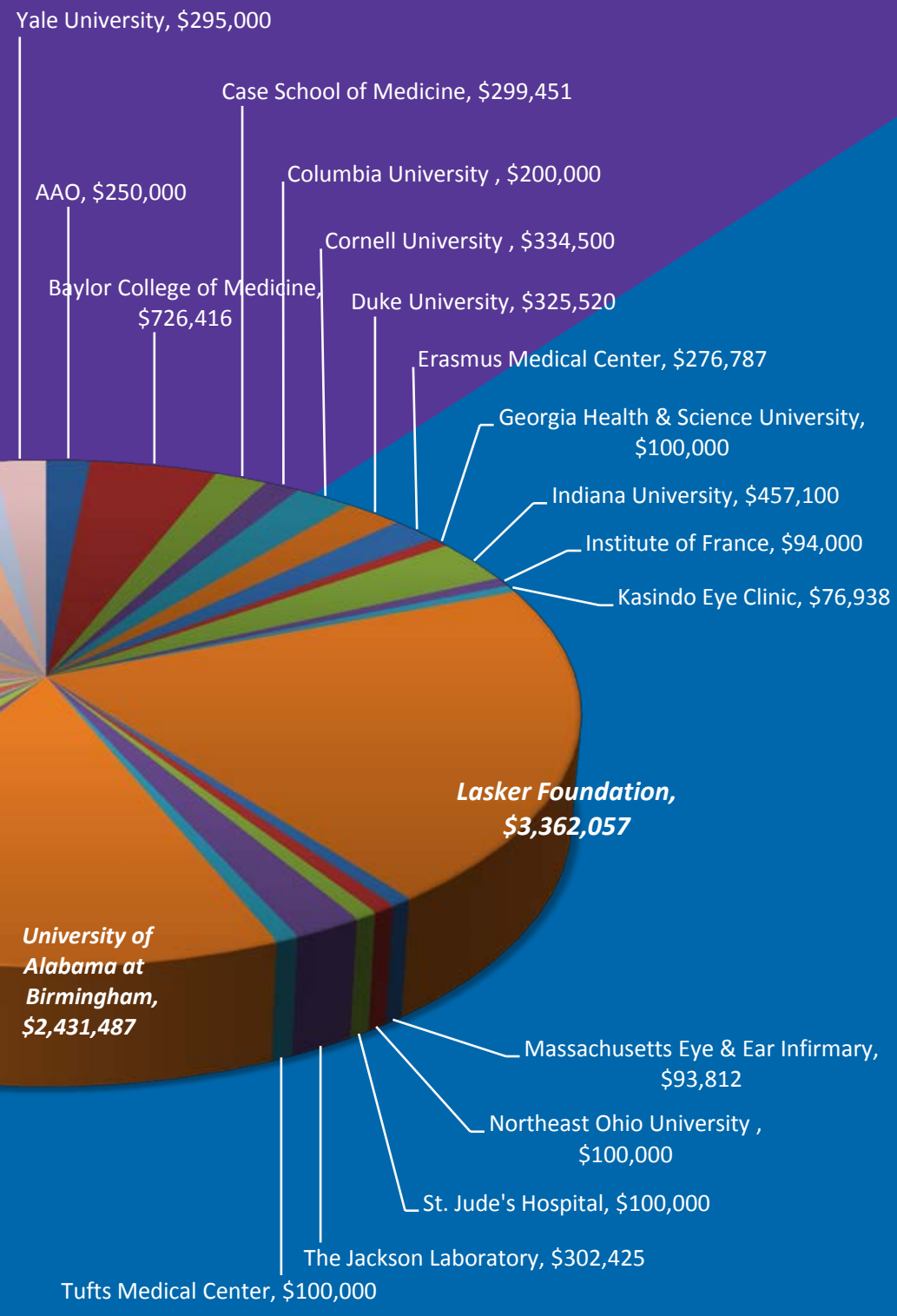
Ala Moshiri, MD, PhD; University of California-Davis. In vivo Monitoring of the Retinoid Cycle of Vision in the Mammalian Retina Using Novel Optogenetic Sensors and Advanced Adaptive Optics Imaging Technology.

Michael O'Connor, PhD; Western Sydney University, Penrith, Australia. Defining the Molecular Pathways Regulated by Endogenous BEST1 in Best Disease.

Johanna Seddon, MD; Tufts Medical Center, Boston, MA. Evaluation of Macular Degeneration Sub-Phenotypes as Biomarkers for Progression and Treatment.

The International Retinal Research Foundation Grants 1998 – Present

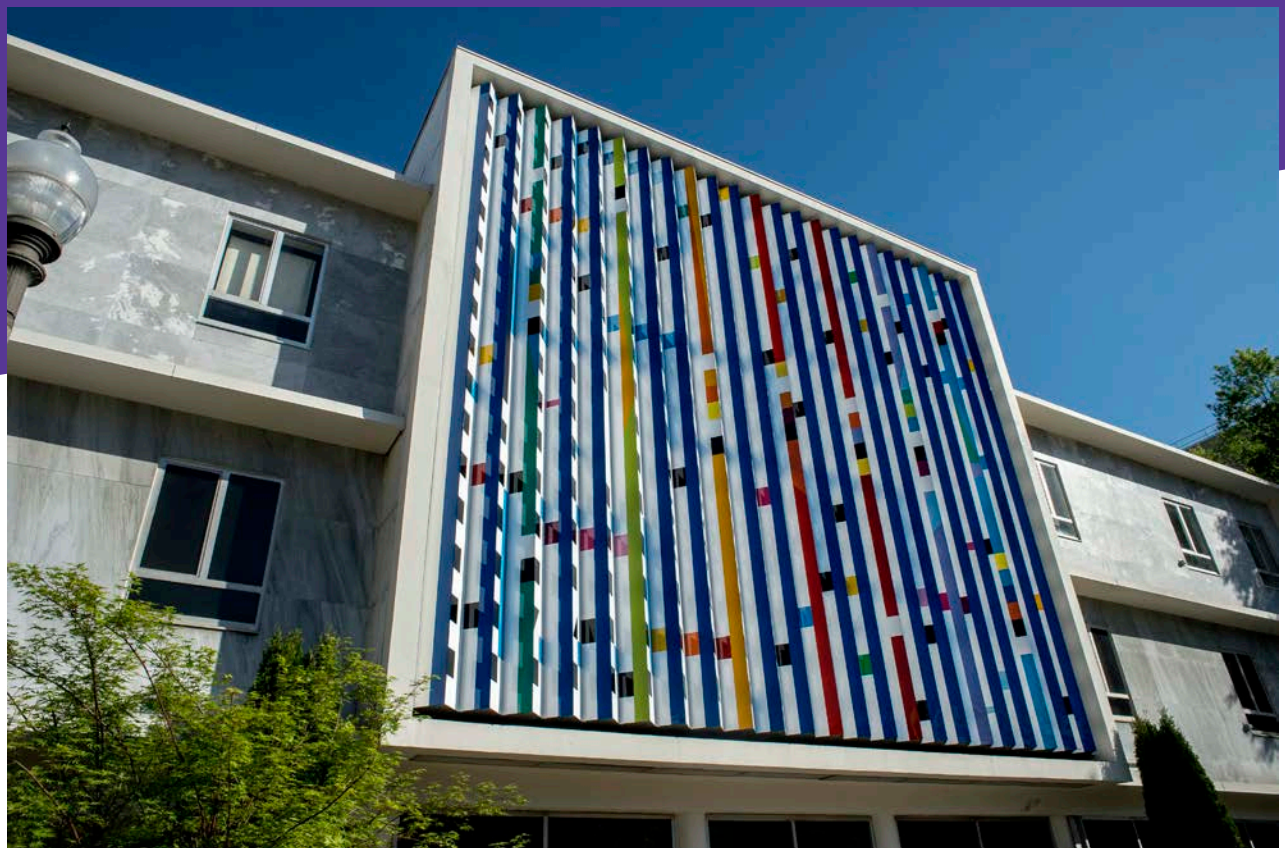




Grand Total All Years $16,085,105

Various Institutions Include all grants less than $75,000

Complex Vision Comes Home



After nearly two years of planning, fund-raising and renovation, Complex Vision has finally returned to its former position on the front of the UAB Callahan Eye Hospital. In July, Yaacov Agam, the internationally renowned Israeli artist, came from Paris to personally oversee the dedication celebration and to resign and date the piece.

The "Agam," as it is sometimes called, was first dedicated in 1976 in honor of Mr. and Mrs. William P. Engel and Mr. and Mrs. E.N. Salomon by their children, Ruth and Marvin Engel, who in large part funded the first project. Over the years, the iconic sculpture had sustained substantial environmental damage and it was feared that if a restoration did not take place, it would be lost to the elements. A partnership was formed between the International Retinal Research Foundation, the EyeSight Foundation of Alabama, and the UAB Callahan Eye Hospital, all of whom owe their existence, in part, to Alston Callahan, to save what has become the symbol of the Hospital that bears Dr. Callahan's name. "This is here not only for the patients but also for the community," Brian Sprayberry, President of the Hospital remarked. "It's part of the culture of the Eye Hospital. This piece has become synonymous with who we are as a hospital and as part of UAB Medicine."


Agam
ABROMS // ENGEL
INSTITUTE for the VISUAL ARTS

◀ Access the article

Providing Developmental Support Through Partnerships

NCBI

Articles of note include:

Enliven: Clinical Ophthalmology Research, "Rods, Dark Adaptation, and the Development of diabetic Retinopathy," David J. Ramsey, MD, PhD, and G. B. Arden, BSc, MBBS, FRC Ophthal. PhD. To access this article, go to:

www.enlivenarchive.org/clinical-ophthalmology-research-001

National Center for Biotechnology Information, National Institutes of Health, "Hypoxia and Dark Adaptation in Diabetic Retinopathy: Interactions, Consequences, and Therapy," Ramsey, DJ, Arden GB.

The International Retinal Research Foundation (IRRF) is partnering with the Fight For Sight Foundation (FFS) based in New York to provide funding to junior faculty members who are developing their independent scientific skills. These Grants-in-Aid are administered by FFS and are important funding sources that allow recipients to go on to successfully compete for larger, multi-year awards from the NIH or other governmental and private sources. The IRRF co – sponsored two such awards in 2015 – David J. Ramsey, MD, PhD, Tufts University School of Medicine and Sara Ross, PhD, University of Pittsburgh.

David J. Ramsey received his MD and PhD degrees from the University of Illinois at Chicago in 2008. He completed his residency in Ophthalmology at the Wilmer Eye Institute of the Johns Hopkins School of Medicine in 2012, followed by a combined medical/surgery fellowship in vitreoretinal diseases at the Massachusetts Eye and Ear Infirmary in 2014. Dr. Ramsey is a senior staff physician at the Lahey Clinic & Medical Center, a teaching hospital for Tufts University School of Medicine.

FIGHT FOR SIGHT

Access the article ▶

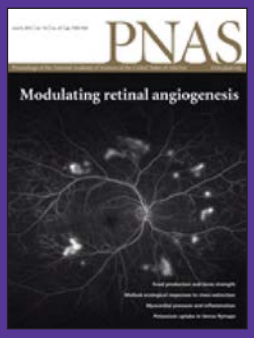
Sarah E. Ross, PhD, is an Assistant Professor at the University of Pittsburgh in the Department of Neurobiology. She received her PhD from the University of Michigan before going on to a postdoctoral fellowship at Harvard Medical School. Dr. Ross's research interest is the functional organization of spinal somatosensory circuits. The spinal cord plays a critical role in processing somatosensory information – touch, temperature, pain and itch. The Ross Laboratory is interested in characterizing these spinal microcircuits, since the dysfunction of these neural circuits can lead to pathological conditions of chronic pain and itch.

The Ross Laboratory uses molecular genetic approaches to identify and modulate populations of neurons in the retina as an entry point to understand how visual input is processed. The Ross lab is using strategic immunohistochemical labeling in combination with confocal imaging to describe the anatomy and identify molecularly distinct subpopulations of interest.

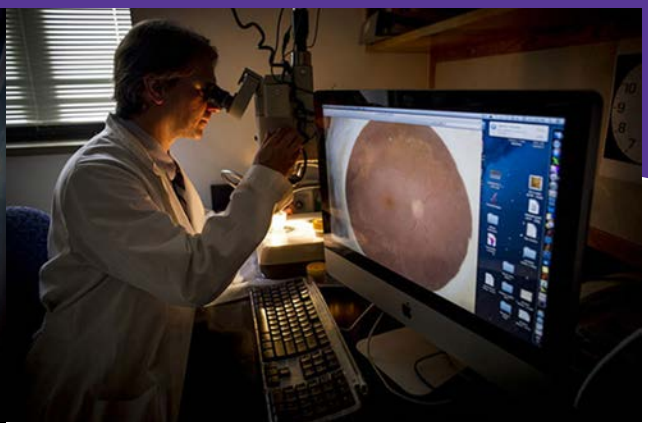
PNAS (Proceedings of the National Academy of Science)

"Transcription factor PRDM8 is required for rod bipolar and type 2 OFF-cone bipolar cell survival and amacrine subtype identity," **Cynthia C. Jung, Denize Atan, David Ng, Lynda Ploder, Sarah E. Ross, Martin Klein, David G. Birch, Eduardo Diez, and Roderick R. McInnes. (June 2015, vol. 112, No.23)**

Significance: Knowledge of the molecules that guide retinal interneuron formation is incomplete. This study showed that PRDI-BF1 and RIZ homology domain containing 8 (PRDM8) is required for the development of rod bipolar cells and OFF-cone bipolar subtypes as well as amacrine cell identify. Although bipolar cells were specified PRDM8-null mice, rod bipolar cell differentiation was impaired, leading to their death and near absence from adult retina. This defect disrupts postphotoreceptor signal transduction, as shown by nonprogressive b-wave deficits in electroretinograms. These findings suggest PRDM8 as a candidate gene for human congenital stationary night blindness. They also establish PRDM8 as a component of the regulatory network governing bipolar cell development and amacrine cell diversity, aiding efforts to generate these essential interneurons in vitro.



To learn more about the work at the Ross Laboratories, go to **www.rosslab.neurobio.pitt.edu/**



Eye site offers new insight on age-related macular degeneration

NOVEMBER 12, 2015

By Megan Yeatts and Matt Windsor

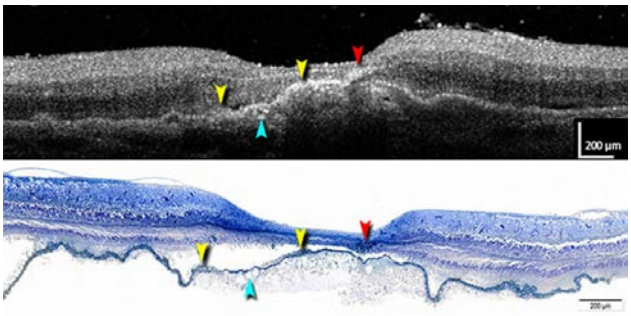
Over the past 14 years, Christine A. Curcio, Ph.D. (pictured above), a professor in the UAB School of Medicine's Department of Ophthalmology, has collected images from hundreds of donor eyes in her search for the basic mechanisms underlying age-related macular degeneration. AMD is the leading cause of severe vision loss and legal blindness in Americans age 60 or older, affecting up to 15 million people in the United States today and almost 200 million people worldwide by 2020. As the population ages, those numbers will only increase. AMD occurs when the central portion of the retina, known as the macula, deteriorates. But the exact cause is unknown, and new treatments are desperately needed.

A few years ago, Curcio realized that the images and tissues she had collected, if properly annotated, classified, and made widely available, could prove invaluable to researchers and clinicians alike. It wasn't as easy as uploading the photos to Facebook. The process took four years, and along the way, Curcio and her team, particularly research associate Jeffrey Messinger, DC, had to develop new naming systems to achieve the level of precision they were after. But the result, an open-access website known as Project MACULA (Maculopathy Unveiled by Laminar Analysis), has been a resounding success, leading to several notable discoveries that have advanced understanding of the disease.

Sharing knowledge

At the close of the 2000s, a high-powered new technology called optical coherence tomography (OCT) was becoming widely available to practicing ophthalmologists. It can provide detailed cross-sectional views of all the layers of the retina and the blood vessels behind it. OCT was so powerful, Curcio said, that clinicians "were now able to see the same structures" as basic researchers with their tissue samples. Curcio recognized that high-quality, accurately annotated lab images of eyes with and without AMD could serve as an invaluable roadmap — helping clinicians interpret the patient images they were seeing with the new machines. "AMD is a degenerative disease that is laid out in delicate tissue layers, and if you know the microscopic histology, it is possible to see almost all of it in OCT," Curcio said. Connecting the microscopic world with patient images from the clinic can lead to "better diagnoses, more efficient clinical trials for new treatments and eventually better experimental model systems to test new ideas," she added.

With seed money from philanthropic foundations, and a subsequent grant from the National Eye Institute, Curcio started Project MACULA. Her team catalogued 142 donor eyes: 82 with AMD and 60 controls. Each was tagged with critical information — such as exact measurements of the thickness of each tissue layer, along with a glossary and



A comparison of optical coherence tomography (OCT) and histology on the same eye allows Project MACULA users to identify the cells on a microscope image (bottom) that are responsible for the hyper-reflective spots seen in the OCT (top, red, yellow), plus examine the contents of drusen, AMD's specific lesion (teal). "From this kind of analysis, we've learned that the retinal pigment epithelium is highly migratory in AMD," Curcio said. "Finding out what these cells are doing is now a research priority, and with OCT, they can be observed in living people."

references — and both laboratory and OCT images. The site officially launched in 2013.

In the process of systematically reviewing the histology, Curcio's team made major discoveries about the pathology of AMD — including a natural history of the principal lesions associated with the disease, known as drusen; the first major description of a new, drusen-like lesion, and the first comprehensive description of the neurodegeneration of AMD involving photoreceptors and the retinal pigment epithelium, which supports the photoreceptors. These findings have led to numerous peer-reviewed journal articles and invitations to major clinical meetings. "Leading ophthalmologists want this information to develop guidelines for trials," for example, Curcio explains. "This is putting the right tools into the hands of the right workforce."

"Having the histologic images available has helped me in interpretations and integration of multimodal imaging in the clinic," agreed Richard Spaide, M.D., a renowned specialist in the diagnosis and treatment of retinal diseases who practices at Vitreous-Retina-Macula Consultants of New York. He has collaborated with Curcio on Project MACULA since 2009, co-authoring several well-cited papers that link clinical presentation on OCT with anatomical features seen in histologic images. "As with anything in science, there is plenty we don't know," Spaide said. "So when a subtle finding is recognized in an imaging modality in the clinic, it is helpful to go back to the known histology to put the new finding into some kind of perspective."

Creating collaborations

Project MACULA has also had the desired effect of fostering important collaborations to advance knowledge about AMD, with the ultimate goal of developing new treatments and cures, Curcio said.

For example, Curcio and collaborator Dwight Stambolian, M.D., Ph.D., associate professor of ophthalmology and genetics at the University of Pennsylvania, recently submitted a funding request to add genetics to the equation. They propose obtaining a new set of donor eyes and uploading one eye from each pair to Project MACULA and sending the other to Stambolian's team for comprehensive and robotic sequencing of RNA. Since AMD is a bilateral disease, affecting both eyes, this would create links in understanding of AMD from genetic variation to cells to clinical presentation.

"Connecting changes on the cellular level with changes in gene expression will hopefully allow us to develop new targets for new drug therapies," said Curcio. "Since Project MACULA also links those changes with clinical images, it will also show physicians how these changes are presenting in the patient so they know when to start treatment, or in some cases, what does not need to be treated." This information advances the goal of personalized medicine for individual patients, Curcio adds.

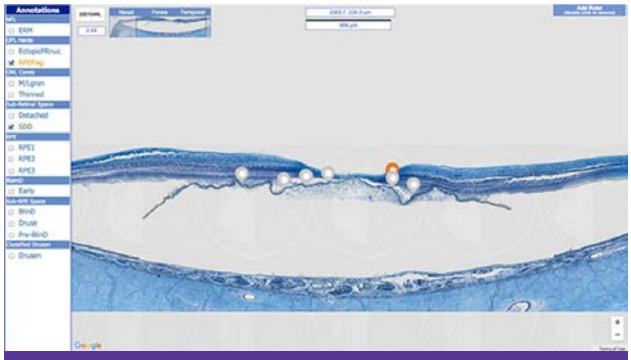
Tissue, technology and other support

The project would not have been possible without several key partners, Curcio points out. "High-quality tissue made discoveries possible at Project MACULA," she said. "Very few people are blessed with a resource like the Alabama Eye Bank, a highly productive eye bank that is able to obtain lots of tissue rapidly and thus meet our research needs." Another invaluable contributor was the UAB Department of Computer and Information Sciences. Associate Professor Kenneth R. Sloan, Ph.D., his students and CIS staff provided the expertise and resources to create and host the Project MACULA site, Curcio notes.

The project also owes much to private funding partners such as the Birmingham-based International Retinal Research Foundation (IRRF), Curcio adds. Initial awards from the IRRF and the Edward N. & Della L. Thome Memorial Foundation allowed Curcio to purchase a large number of donor eyes from the Alabama Eye Bank, which formed the nucleus of Project MACULA. Another IRRF award supported the collection of pilot data that Curcio used to secure a large grant from the National Eye Institute, which funded Project MACULA's creation.

"It isn't possible to obtain large federal grants without first collecting pilot data," said Curcio. "Without the funding support of IRRF during the early stages, Project MACULA would have never gotten off the ground."

"We saw Project MACULA as an extraordinary opportunity to expand AMD histopathology in hopes of translation to better clinical interpretations of this degenerative disease," said Sandra Blackwood, executive director of the IRRF. "This resource is serving as a valuable catalyst to both bench and clinical science."



Users can reveal detailed annotations for each of the microscope and OCT images contained on the Project MACULA site.

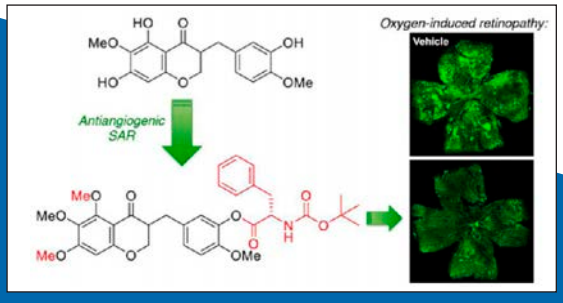
◀ Access this report

Synthesis and Biological Evaluation of Novel Homoisoflavonoids for Retinal Neovascularization

ABSTRACT

Eye diseases characterized by excessive angiogenesis such as wet age-related macular degeneration, proliferative diabetic retinopathy, and retinopathy of prematurity are major causes of blindness. Cremastranone is an antiangiogenic, naturally occurring homoisoflavanone with efficacy in retinal and choroidal neovascularization models and antiproliferative selectivity for endothelial cells over other cell types. The Corson Lab group undertook a cell-based structure-activity relationship study to develop more potent cremastranone analogues, with improved antiproliferative selectivity for retinal endothelial cells. Phenylalanyl-incorporated homoisoflavonoids showed improved activity and remarkable selectivity for retinal microvascular endothelial cells. A lead compound inhibited angiogenesis in vitro without inducing apoptosis and had efficacy in the oxygen-induced retinopathy model in vivo.

Dr. Corson was supported by IRRF for two years, 2014 - 2015. In addition to the above referenced paper, ***Synthesis and Mechanistic Studies of a Novel Homoisoflavanone Inhibitor of Endothelial Cell Growth,*** was published in 2014 in the journal Plos One. Also published in 2014 was, ***The first synthesis of the antiangiogenic homoisoflavanone, cremastranone,*** included in the journal Organic & Biomolecular Chemistry. Dr. Corson reported further findings of IRRF-supported work at the 2015 annual meeting of the Association for Research in Vision and Ophthalmology (ARVO).



To read more about Timothy Corson, PhD and the Corson Lab, visit: www.glick.iu.edu/corson

Journal of Medicinal Chemistry

"Synthesis and Biological Evaluation of Novel Homoisoflavonoids for Retinal Neovascularization"

Helesha D. Basavarajappa, Bit Lee, Hyungjun Lee, Rania S. Sulaiman, Hongchan An, Carlos Magaña, Mehdi Shadmand, Alexandra Vayl, Gangaraju Rajashekhar, Eun-Yeong Kim, Young-Ger Suh, Kiho Lee, Seung-Yong Seo, and Timothy W. Corson. Department of Ophthalmology, Indiana University School of Medicine, Indianapolis.

(June 2015, vol. 58)

This study was conducted with IRRF support — Timothy W. Corson.

Corson Lab Group. Timothy Corson front right.

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The IRRF 2015 ANNUAL REPORT

Sandra Blackwood, Editor
Photos: Sandra Blackwood
Larry Donoso, MD, PhD
Design: Robert T. Weathers

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How You Can Help...

Today's scientists play a crucial role in the universal struggle against debilitating eye diseases, but they need financial funding to facilitate and sustain their efforts. Since 1998, the IRRF has granted more than $16 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:

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