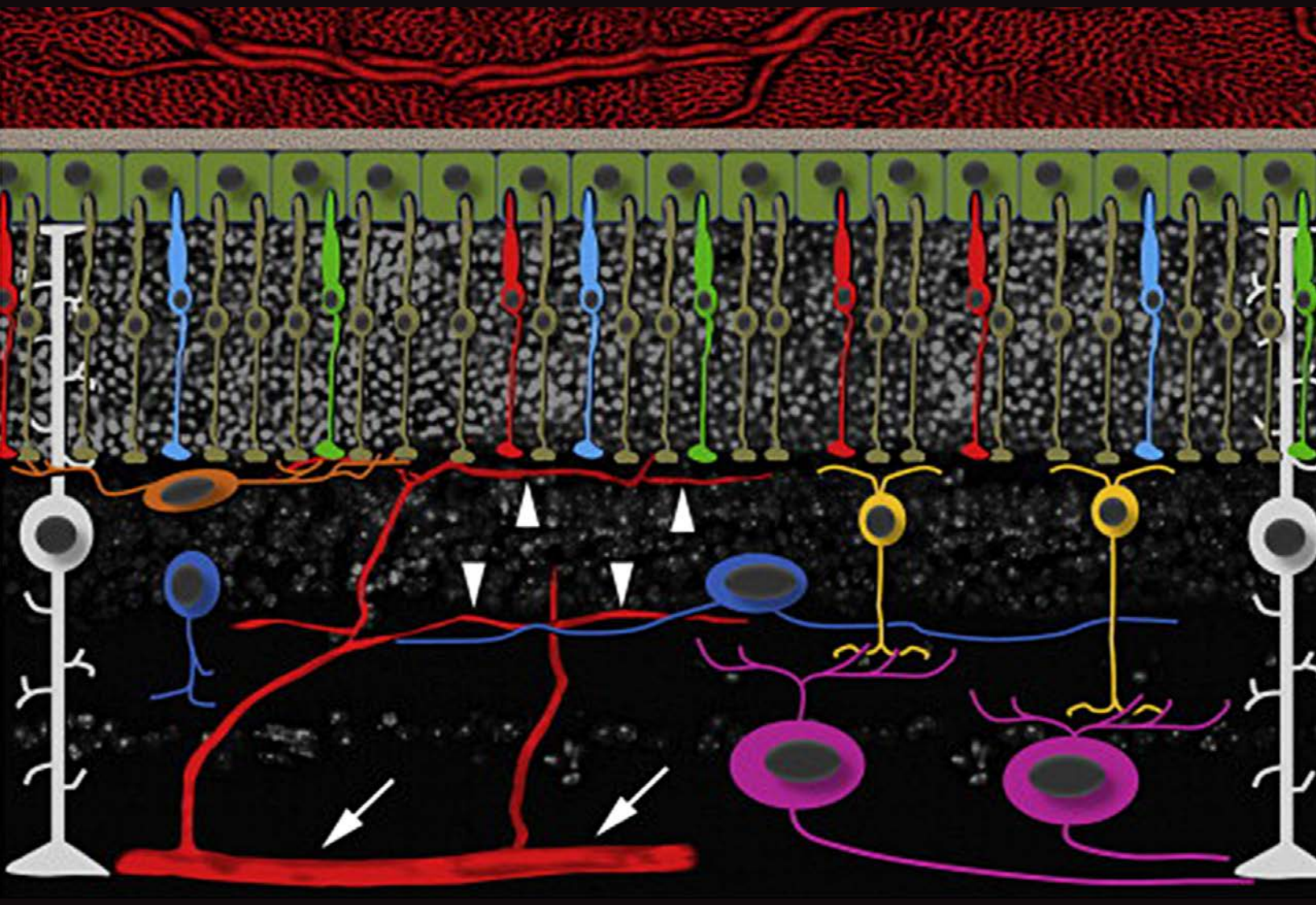
2014 Annual Report



A schematic representation of the organization of the retina and of its blood supply. Read the story on page 2.

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International Retinal Research Foundation

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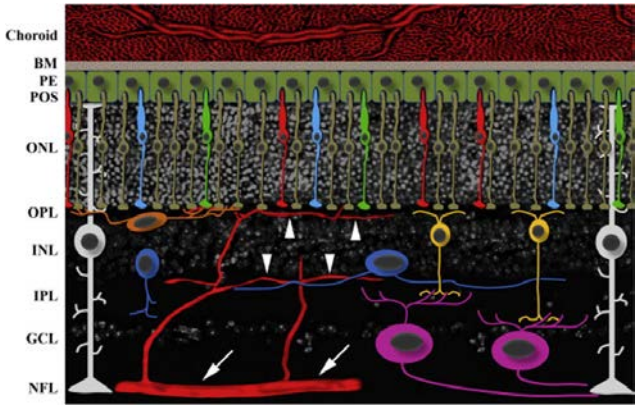
Cover Photo:



The retina can be divided into two portions, relative to the blood supply that they receive (photo above). The outer retina includes the outer nuclear layer, formed by the cell bodies of the photoreceptors, and the layer of the photoreceptor outer segments. This portion of the retina is avascular, and the photoreceptors obtain oxygen and nutrients from choroidal vessels, which are separated from the retina by the retinal pigment epithelium (RPE) and the Bruch's membrane. Fenestrations of the choroidal capillaries facilitate diffusion and transport to the photoreceptors. The inner retina includes the outer plexiform layer (OPL), the inner nuclear layer (INL), the inner plexiform layer (IPL), and the ganglion cell layer (GCL), which ganglion, amacrine, bipolar and horizontal cells, as well as their neuronal processes, are located. This portion of the retina receives its blood supply from the retinal vessels entering at the optic nerve head, traveling along the surface of the retina, and forming branches that arborize into the intermediate and deep capillary beds (Fruttiger, 2007 and Stahl et al., 2010).

Schematic representation of the organization of the retina and of its blood supply. Retinal neuronal cells include: i) rod (brown) and cone (red, green and light blue) photoreceptors, localized to the outer nuclear layer (ONL), whose axons contact both horizontal and bipolar cells in the outer plexiform layer (OPL) and whose external segments (photoreceptor outer segments – POS) closely interact with the cells of the pigment epithelium (PE); ii) horizontal cells (orange), localized to the outermost portion of the inner nuclear layer (INL), whose processes arborize into the OPL, iii) bipolar cells (yellow), localized in the INL, whose dendrites contact the photoreceptor terminals in the OPL and whose axons arborize at two distinct levels in the IPL, contact6ing ganglion cell dendrites; iv) amacrine cells (dark blue), localized to the inner portion of the INL, whose processes form wide or narrow arborizations in the inner plexiform layer (IPL); ganglion cells (pink), localized in the ganglion cell layer (GCL), whose dendrites arborize at two distinct layers in the IPL, and whose axons run in the nerve fiber layer (NFL) towards the optic nerve head. In addition to neuronal cells, the retina also contains Müller glial cells (white), whose processes span the entire retinal thickness. The blood supply to the inner retina is supplied by vessels entering at the optic nerve head and running on the retinal surface near the NFL, (arrows). Their branches form an intermediate capillary bed at the border between the IPL and the INL (downward arrowheads), and a deep capillary bed located at the level of the OPL (upward arrowheads). The outer retina receives oxygen and nutrient supply from the capillaries of the choroid, which are separated from the PE and from the retina by the Bruch's membrane (BM).

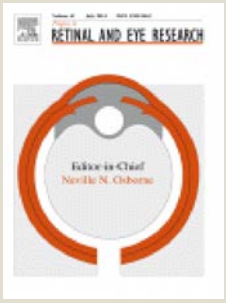
◀Access this article

Progress in Retinal and Eye Research, "The β-adrenergic system as a possible new target for pharmacologic treatment of neovascular retinal diseases"

Retinal neovascular pathologies, such as diabetic retinopathy, retinopathy of prematurity (ROP) and age-related macular degeneration, may be treated with intravitreal injections of drugs targeting vascular endothelial growth factor (VEGF), the main inducer of neoangiogenesis; however further improvements and alternative strategies are needed. In the last few years, an intense research activity has focused on the β-adrenergic system. The results indicate that, in different experimental models, a decrease of the β-adrenergic function may result either in reduction or in exacerbation of the vascular changes, thus suggesting possible dual effects of β-adrenoreceptor (β-AR) modulation depending on the experimental setting. In in vivo models of proliferative retinopathies, most of the data point to a strong inhibitory role against vascular changes exerted by the blockade of specific β-ARs. In particular, the β2-AR seems to be the mostly involved in these responses, and the β1-/ β2-AR blocker propranolol results highly effective in inhibiting both the increase of VEGF expression caused by a hypoxic insult and the consequent neovascular response. These observations have prompted clinical trials in preterm infants with ROP, where oral administrations of propranolol produced positive results in terms of efficacy, although safety problems were also reported. In addition, the possibility of using topical propranolol administrations in the form of eye drops opens new potential routes of drug administration in humans. A further point that should be considered is that there are data demonstrating significant antiapoptotic effects exerted by β-ARs, therefore if β-AR blockers were used to inhibit aberrant neovascularization, there may be a burden to pay in terms of impaired neuronal viability.

Progress in Retinal and Eye Research, *"The β-adrenergic system as a possible new target for pharmacologic treatment of neovascular retinal diseases,"* Giovanni Casini, **Massimo Dal Monte,** Irene Fornaciari, Luca Filippi, Paola Bagnoli, Department of Biology, University of Pisa, Italy. (June 2014 – Although this article is in press, final citation details as volume and/or issue number has not been added.) **This study was conducted with IRRF support. – Massimo Dal Monte**

(Photo above: Massimo Dal Monte, PhD, University of Pisa, Italy)



UPDATE:

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Prevention of retinal light damage by zinc oxide combined with rosemary extract

Molecular Vision
Biology and Genetics in Vision Research

PUBLISHED SCIENCE: Molecular Vision, "Prevention of retinal light damage by zinc oxide combined with rosemary extract," **Daniel T. Organisciak,** R. M. Darrow, C.M. Rapp, J.P. Smuts, D. W. Armstrong, J.C. Lang. (June 2013, v19,1433-1445) **This study was conducted with IRRF support –** Dr. Daniel Organisciak**.**
(Photo above: Dr. Daniel T. Organisciak)

Zinc oxide effectively reduces visual cell loss in rats exposed to intense visible light and is known to slow the rate of disease progression in advanced stages of age-related macular degeneration. The goal of this study was to determine the efficacy of zinc oxide in combination with novel and well-established antioxidants in an animal model of light-induced oxidative retinal damage. a detergent extract of rosemary powder and then exposed to intense visible light for 4-24 hours. Another group of animals received zinc oxide combined with rosemary oil diluted with a mixture of polyunsaturated fatty acids and a third group was given an antioxidant mineral mix containing zinc oxide, as recommended by the Age Related Eye Disease Study group's first clinical trial (AREDS1).

It was found that in the rat model of acute retinal light damage, zinc oxide combined with a detergent extract of rosemary powder or rosemary oil is more effective than treatment with either component alone and significantly more effective than an AREDS mixture containing a comparable dose of zinc oxide. Light-induced oxidative stress in animal models of retinal degeneration can be a useful preclinical paradigm for screening novel antioxidants and for testing potential therapeutics designed to slow the progression of age-related ocular disease.

In the second year of the funding, October 2013 – September 2014, we found that long term environmental light intensity is a major effector of photoreceptor cell survival, following acute photo-oxidative stress, and of retinal protein and gene expression. Higher levels of light in the environment lead to the loss of opsin from cone cells, with modest effects on the cone cell protein called arrestin (mCAR). This may result from a shortening of the opsin containing cone outer segments, without loss of the entire cone photoreceptor. Acute intense light exposure also leads to the loss of rod and cone cell opsins and arrestins, but unlike long term environmental light, the loss of visual cells in this case is largely irreversible. Antioxidants can prevent photoreceptor cell death and the more effective an antioxidant is, the greater the rate of visual cell survival. In the original AREDS study zinc oxide accounted for about 70% of the benefit, thus we sought to enhance the less effective antioxidant fraction of the AREDS formulation. Toward this goal, we fed AREDS, or AREDS plus rosemary to rats daily for six weeks and then treated them with intense white light. In this study the protective efficacy of AREDS against photo-oxidative visual cell damage was enhanced by rosemary supplementation as well as by the major rosemary component carnosic acid. Chronic administration of rosemary, or of its individual antioxidants, may be a useful adjunct to the therapeutic benefit of AREDS in slowing the loss of photoreceptor cells and the progression of AMD to advanced disease.

◀ Access this article

Investigative Ophthalmology & Visual Science, "The Role of Thrombin in Proliferative Vitreoretinopathy"

Investigative Ophthalmology & Visual Science, *"The Role of Thrombin in Proliferative Vitreoretinopathy,"* Jeroen Bastiaans, Jan C. van Meurs, Verena C. Mulder, Nicole M.A. Nagtzaam, Marja Smits-te-Nijenhuis, Diana C. M. Dufour-van den Goorbergh, P. Martin van Hagan, Herbert Hooijkaas, and **Willem A. Dik,** Department of Immunology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands. (July 2014, vol. 55, No. 7) **This study was conducted with IRRF support – Willem A. Dik.**

Proliferative vitreoretinopathy (PVR) is an inflammatory fibrotic disorder that can develop after rhegmatogenous retinal detachment, and is the most common failure of retinal detachment repair. Proliferative vitreoretinopathy development is characterized by the formation of subretinal, intraretinal, and/or epiretinal fibroproliferative membranes that cause the retina to detach due to the contractile properties of myofibroblasts that are abundantly present in these membranes. Retinal pigment epithelial (RPE) cells contribute to the formation of these fibroproliferative membranes through the secretion of cytokines and growth factors, proliferation, and dedifferentiation into extracellular matrix-producing myofibroblasts.

Current knowledge of the underlying pathobiological processes in PVR is still limited. Vitreous of patients with established proliferative vitreoretinopathy contains elevated levels of thrombin, which induces the production of proliferative vitreoretinopathy-associated cytokines, and growth factors by RPE. The purpose of this study is to determine the role of thrombin in the development of proliferative vitreoretinopathy (PVR).

Dr. Dik's research group: Sita Virakul, Willem Dik, Jeroen Bastiaans, Nicole Nagtzaam, Department of Immunology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands.

Christine A. Curcio, PhD is Awarded Matching Funds for the Ludwig von Sallmann Prize

Birmingham, Ala.

The International Retinal Research Foundation (IRRF) provided funds to match the Ludwig von Sallman Prize awarded to Christine A. Curcio, PhD, University of Alabama at Birmingham, Department of Ophthalmology, at the 2014 International Society for Eye Research meeting in San Francisco. The von Sallman Prize carries a $50,000 cash award for the recipient and with the additional $50,000 from the IRRF, Dr. Curcio will invest in and accelerate the next phase of research on age-related macular degeneration, through technology development and staff/student training. Dr. Curcio and her lab are focusing on histological and ultrastructural validation of clinical imaging technologies focused on the retinal pigment epithelium (RPE), a cell central to age-related macular degeneration. These include spectral domain and polarization sensitive optical coherence tomography and total and hyperspectral autofluorescence. With continued access to pathology specimens through the Alabama Eye Bank, Curcio will build the Project MACULA website into a global resource for RPE pathobiology. "This is especially fitting because the IRRF was an important contributor to the original eye repository and website development," said Curcio recently.

Ludwig von Sallmann was a distinguished international ophthalmologist and ophthalmic investigator who served on the staff of Vienna, Peking and Columbia Universities and the Ophthalmology Branch of the former National Institute of Neurological Diseases and Blindness at the National Institutes of Health. His wife, Henrietta von Sallmann, established a trust fund to award, in his memory, a cash prize every two years to an individual who has distinguished himself/herself by making a significant contribution to vision research and ophthalmology.

Left, Dr. Curcio; and Sandra Blackwood, IRRF Executive Director

The Ludwig von Sallmann Prize is one of four International Prizes that are awarded in even years at the Biennial Meeting of the International Society for Eye Research.

Vision Research Funding Partnership: Imagining the Possibilities

Washington, D. C.

The International Retinal Research Foundation and nearly two dozen colleagues from organizations committed to the advancement of eye research convened on September 17, 2014, in Washington, D. C. to discuss vision research funding and a role for funder collaboration in preventing, treating, and curing vision disorders. The meeting was hosted by Research to Prevent Blindness and its president, Brian F. Hofland, PhD. This meeting was an important first step toward collaborations.

Taking into account organizations' unique priorities, the participants acknowledged that a collective effort based on shared interests could impact vision research and outcomes for patients. Consensus began to build in several areas, including:

- Advancing the public health agenda, to address vision problems of the aging U.S. populations
- Encouraging funder partnerships (private/private; public/private), to leverage resources and enable research that no single funder could undertake alone
- Coordinating and supporting advocacy, to raise the profile of vision research, increase federal funding for eye research, and drive education of policymakers and the public. Federal funding is a far greater resource than all private funding taken en masse.
- Supporting interdisciplinary research from within and outside vision research, to promote and accelerate innovation

The convening ended with an expressed interest in exploring collaborative potential.

From left: Arthur Makar (Fight for Sight); Jeff Todd (Prevent Blindness); and Sandra Blackwood (International Retinal Research Foundation)

Partnering for Collective Impact:

In these times of smaller budgets and dwindling donations, the non-profit area is under intense pressure to maximize every dollar. Therefore, more and more foundations are partnering and forming collaborations for what is being called "collective impact." In 2014, the IRRF accepted an invitation to partner with Research to Prevent Blindness (RPB), to advance knowledge about age-related macular degeneration (AMD) through novel stem cell research. **RPB/IRRF & Sybil B. Harrington Catalyst Awards for Stem Cell Research Approaches for Age-Related Macular Degeneration (the Catalyst Awards)** were given to three leading researchers. Each has received $250,000 over four years with research related to both dry and wet forms of AMD supported by these awards.

At a press conference, RPB President Brian F. Hofland, PhD told reporters, "The concept for these partnership grants evolved out of a significant gift that we received from an anonymous donor who wanted us to focus on stem cell research and AMD. It came with the condition that we would find matching funding. We found a valuable partner in the ***International Retinal Research Foundation*** very quickly for two of the awards, and one was matched with bequest money received from the Sybil Harrington Estate – a generous family that is committed to health-related research on several fronts. We are especially encouraged that this all came together at a key time in the field of stem cell research, and we are hopeful that these three awards together will be a catalyst for breakthroughs in this area."

There is also a collaborative learning component that will have the three researchers work together and

These Catalyst Awards will provide seed funding for high-risk/high-gain innovative, cutting-edge vision science research conducted by:

David M. Gamm, MD, PhD; RPB/IRRF Catalyst Awardee, University of Wisconsin School of Medicine, whose goal is to optimize transplanted retinal pigmented epithelium cell survival based on an innovative hypothesis. Gamm is a leader in the retinal pigment epithelium (RPE) stem cell transplantation field. Cell survival is critical to the success of RPE transplantation as a therapy for retinal degenerative diseases. To learn more about Dr. Gamm's research, go to:

www.ophth.wisc.edu/faculty/dgamm

Research to Prevent Blindness

share information on areas of mutual interest and overlap, according to Dr. Hofland.

'We are incredibly excited about the potential impact on AMD stem cell therapies that could result from this partnership," added Sandra Blackwood, Executive Director, IRRF. "RPB and IRRF both seek to accelerate vision science discoveries that could lead to life-changing treatments for patients who have lost sight. By pooling our resources we can better meet the needs of the scientists who are doing the actual heavy lifting."

These Catalyst Awards will provide seed funding for high-risk/high-gain innovative, cutting-edge vision science research conducted by:

Budd A. Tucker, PhD; RPB/IRRF Catalyst Awardee, University of Iowa Carver College of Medicine, whose main objective is to produce outer retinal cell grafts (grown from fibroblasts taken from a patient's own skin) on biodegradable scaffolds and deliver the cell scaffolds into an eye. This work could solve two problems facing cell transplantation methods today: immune response, and the enormous loss of cells that occurs following bulk injection of stem cells into the eye. Dr. Tucker heads up the Tucker Stem Cell Laboratory at the Iowa Carver College of Medicine. To learn more about Dr. Tucker's research, go to:

www.medicine.uiowa.edu/tuckerlab/

Akiko Maeda, MD, PhD; RPB Sybil B. Harrington Awardee, Case Western Reserve University, who proposes to test the validity of induced pluripotent stem cell (iPSC)-derived retinal 3D-optic cups as platforms for individualized drug screening for AMD patients. The combination of stem cell and pharmacologic approaches greatly increases the potential for translation of the concepts under investigations into treatments for patients. To learn more about Dr. Maeda's research, go to:

www.case.edu/med/ophthalmology/BasicResearch/AkikoMaedaResearchPage

Alliance for Eye and Vision Research (AEVR) Releases Attitudinal Survey: Vision and Blindness Fact Sheet

AEVR released the results of a new poll ***The Public's Attitudes about the Health and Economic Impact of Vision Loss and Eye Disease***, and a new Vision and Blindness fact sheet at a September 18 National Press Club event in Washington, D. C. The poll commissioned by Research!America and conducted by Zogby Analytics, was sponsored by a grant from Research to Prevent Blindness (RPB). The most rigorous poll conducted to-date of attitudes about vision and vision loss among ethnic and racial groups, including non-Hispanic Whites, African Americans, Hispanics, and Asian Americans highlighted several important findings:

- A significant number of Americans across all racial lines rate losing their eyesight as having the greatest impact on their daily life, affecting independence, productivity, and quality of life.
- When asked what disease or ailment is the worst that could happen, African Americans ranked blindness first, followed by HIV/AIDS; Hispanics and Asians ranked cancer first and blindness second; while non-Hispanic Whites ranked Alzheimer's disease first, followed by blindness.
- A significant number across all racial lines were aware of the impact of genetics on vision and the impact of lifestyle factors, such as excessive sunlight/UV radiation. Fewer were aware of other lifestyle factors, such as obesity and smoking.
- Knowledge about specific eye diseases was uneven. More than half of all groups had heard of cataracts and glaucoma but fewer were aware of diabetic eye disease and AMD.
- America's minority populations are united in the view that not only is eye and vision research very important and needs to be a national priority, but many feel that the current annual federal funding of $2.10 per person, per year is not enough and should be increased.

The Release Panel, shown left to right: Karla Zadnik, OD, PhD (Ohio State University College of Optometry); James Tsai, MD (New York Eye and Ear Infirmary/Mount Sinai Health System); NEI Director Paul Sieving, MD, PhD; Neil Bressler, MD (Wilmer Eye Institute/Johns Hopkins University School of Medicine; and moderator Michelle Miller (CBS News)

Capitol Hill Education: Early Detection Can Lead to Better Outcomes

Left to Right: Arthur Makar, Fight for Sight; Torrey DeKeyser, EyeSight Foundation of Alabama; Dawn George, Macula Vision Research Foundation; Sandra Blackwood, The International Retinal Research Foundation; Tom Brunner, Glaucoma Research Foundation.

After the release of the poll results regarding the impact of vision loss and eye disease, a Congressional Briefing was held at the National Press Building that focused on how vision research is addressing the challenges presented by aging eye disease prevalence and cost. It is estimated that the current $145 billion annual cost of vision disorders in 2014 will grow to $717 billion by year 2050, driven primarily by the aging of the population. Age-related macular degeneration (AMD) is the leading cause of blindness and low vision overall, especially in the 60-plus population, and will become increasingly prevalent as the population continues to age. This presents significant challenges to vision researchers.

Access the report ▶

The Lasker/IRRF Initiative for Innovation Restoring Vision to the Blind

"The notion that restoring vision to the blind is possible has long been thought to be fanciful. However, beginning as far back as the 1960s vision scientists began to investigate the possibility of restoring vision to the blind by activating neurons in the visual pathways beyond the eye, namely in the visual cortex. These early experiments showed that it is possible to elicit visual sensations in humans by electrically stimulating neurons in the visual cortex." The introduction, by John E. Dowling, PhD, to the latest publication from the Lasker/IRRF Initiative for Innovation in Vision Science: Restoring Vision to the Blind begins with the above sentence. Each of the eight chapters of the report is devoted to a specific topic including visual prostheses, optogenetics, gene therapy, stem cells, endogenous regeneration, neuroprotection, vision aids and endpoints. The chapters describe them in detail with indications as to what the major questions are that need to be addressed and how to go about finding the answers.

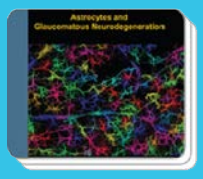
This latest report is the result of the third Initiative of the Albert and Mary Lasker Foundation and the International Retinal Research Foundation, a partnership that represents a 10-year collaboration. Recently published in a special issue of the Association for Research in Vision and Ophthalmology (ARVO) journal, ***Translational Vision Science & Technology (TVST)***, the report discusses the dialogue among key leaders in retinal degeneration, ocular genetics, electrophysiology and sensorimotor research, molecular biology, neuro-ophthalmology, nanotechnology and regenerative medicine in a series of workshops and a plenary session that took place over a two-year period.

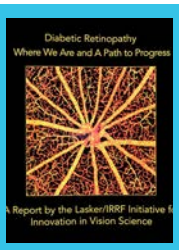
Principal topics of this subject were identified for the two summer sessions held at Woods Hole, MA in the summer of 2013 and the follow-up session at the Howard Hughes Medical Institute (HHMI) Janelia Farm Research Institute in Ashburn, VA in 2014.

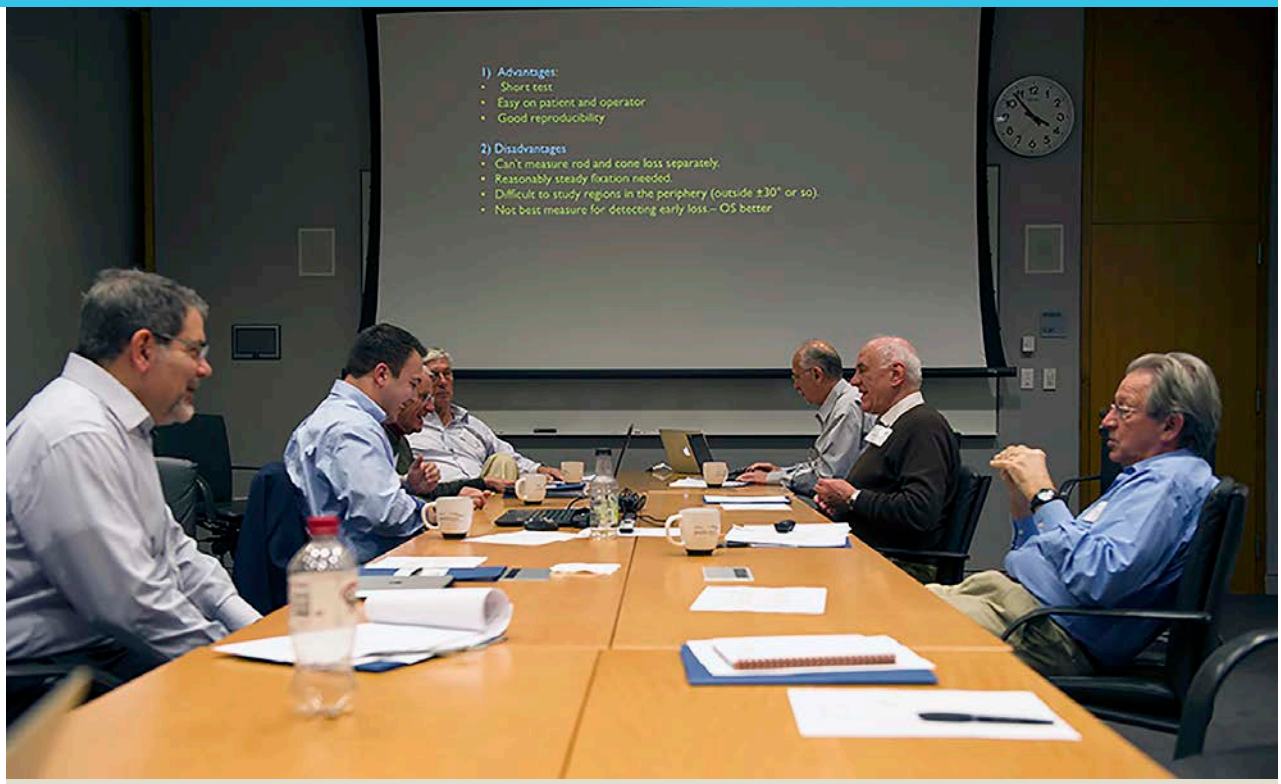
You may read this latest report by following this link:
http://tvst.arvojournals.org/issues.aspx?issueid=933682#issueid=933682

A hard copy of the report is available by request to Sandra Blackwood at
sblackwood@irrfonline.org

in Vision Science:







Since 2009, the Lasker/IRRF Initiative for Innovation in Vision Science has focused on topics deemed critical, with an emphasis on bringing together basic and clinical vision scientists from a cross-section of disciplines and specialties to facilitate collaborations. The first Initiative concentrated on Astrocytes and Glaucomatous Neurodegeneration, following a basic format of two targeted sessions held at Woods Hole, MA and a follow-up of the entire group at HHMI's Janelia Farm Research Institute in Ashburn, VA. The second Initiative, Diabetic Retinopathy: Where We Are and a Path to Progress, followed the same format.

A hard copy of both reports is available by request to Sandra Blackwood at:

sblackwood@irrfonline.org

Research Scientists Who Received IRRF Support in 2014

Yan Chen, PhD; University of Texas-Galveston. Functional Interplay between Phagocytic and Autophagic Pathways in the Retinal Pigment Epithelium.

Timothy Corson, PhD; Indiana University. Mechanistic and therapeutic studies of a novel pharmacotherapy for age-related macular degeneration.

Willem Dik, PhD; Erasmus MC, University Medical Center Rotterdam. Role of Thrombin in PVR; the effect of fibrinogen cleavage products in retinal pigment epithelial cell activation.

Steve K. Fisher, PhD; University of California-Santa Barbara. Creating Brainbow Astrocytes, A New Tool for Studying Retinal and Optic Nerve Astrocytes.

Bradley Gelfand, PhD; University of Kentucky. Iron-induced ALU RNA Stability and Toxicity in Geographic Atrophy.

David Hicks, PhD; Institut des Neuroscience Cellaires et Intégratives, Strasbourg, France. Novel Animal Models of Human Visual Pathophysiology; Rod and Cone Specific Gene Profiles in the Sudanian Unstriped Grass Rat Arvicanthis Ansorgei.

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.

Claudio Punzo, PhD; University of Massachusetts. Modulation of the mTOR pathway: A novel approach to extend vision in dry age-related macular degeneration.

Wenbo Zhang, PhD; University of Texas-Galveston. Interaction of Notch and Wnt pathway in diabetic retinopathy.

Lihong Zhao, PhD; The Jackson Laboratory, Bar Harbor, Maine. Genetic Modifiers of Enhanced S-cone Syndrome.

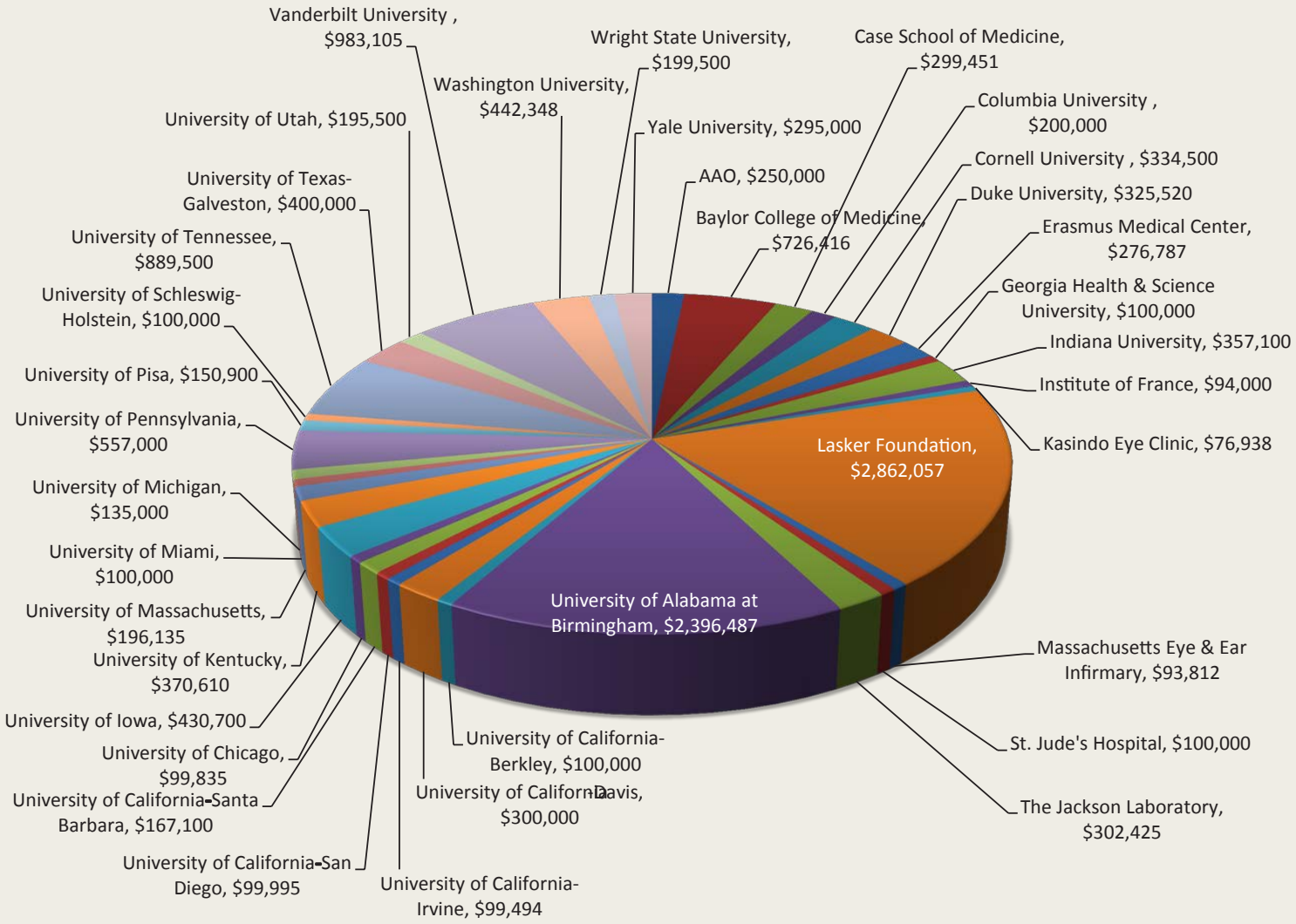
Postdoctoral Scholars Funded in 2014

Jennifer Dulle, PhD; University of Michigan. Regulation of crystalline neuroprotective function in the retina during diabetes: Impact on retinal ganglion cell death.

Alexander Meadway, PhD; University of Alabama at Birmingham. In vivo high-resolution adaptive optics spectroscopy of subretinal drusenoid deposits in age-related macular degeneration.

Charles Wright, PhD; University of Kentucky. The role of DICER 1 neovascular AMD.

The International Retinal Research Foundation Grants
1998 – Present



Grand Total All Years $16,085,105

Various Institutions Include all grants less than $75,000

The Year of AGAM

Birmingham, Ala.

2014 was definitely the Year of Agam at the Callahan Eye Hospital, named for founder Alston Callahan, MD, in Birmingham, Alabama. In 1976, Yaacov Agam, the internationally acclaimed Israeli artist, came to Birmingham at the invitation of Dr. Alston Callahan to personally oversee the dedication festivities for the installation of Agam's creation, ***Complex Vision***. Over the years, the 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 to save what has become a Birmingham icon. All three entities owe their existence, in part, to Alston Callahan, making the decision an easy one.

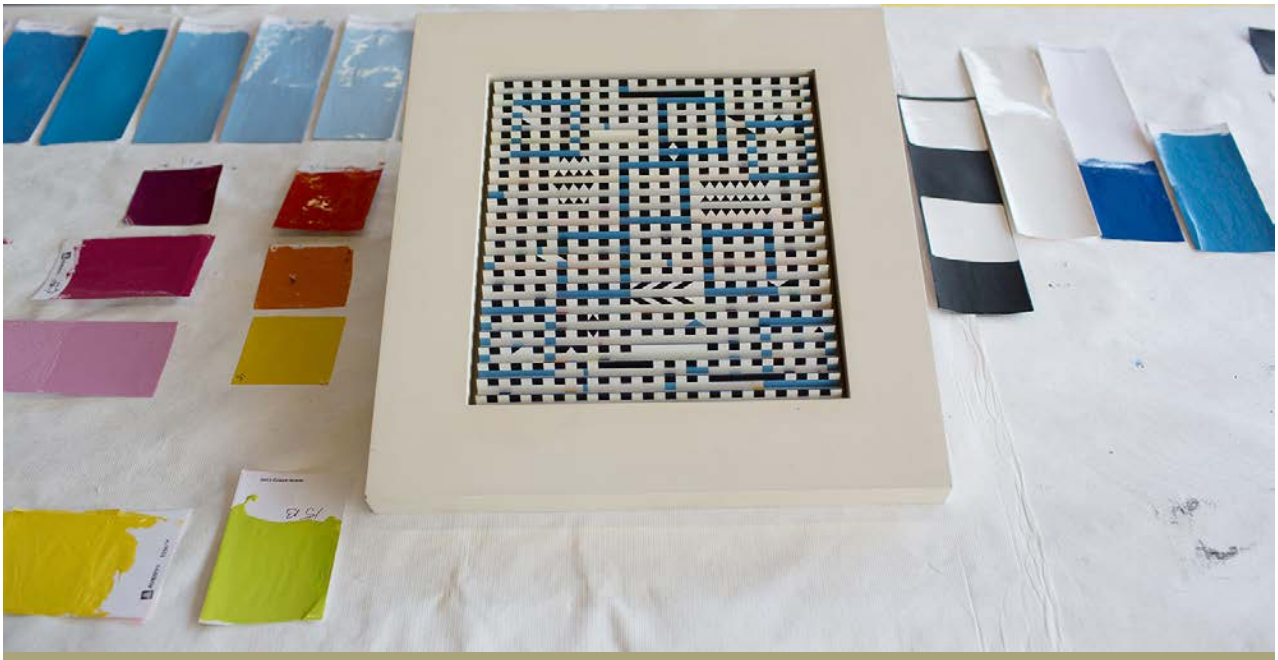
A sense of community prevailed as a couple of locally owned and operated Birmingham businesses came together to perform the preliminary services before the panels could be removed. Many of the workmen remembered when the sculpture was erected, and soon began relating their own impressions of that event. "We had never seen anything like it, but knew something very important was happening," said one, and "My Dad would drive up and down University Boulevard and we kids would watch as the sculpture changed," remarked another. Although the memories were individual, all expressed their excitement over being a part of this monumental undertaking.

After 38 years, the space behind Complex Vision had become home to many insects (including spiders) and birds. Before the dismantling process could begin, the birds were chased away and exterminators were brought in to treat the area. To protect patients and public from any escaping fumes, a large plastic tarp had to be secured over the entire sculpture. As the day was extremely windy, the job proved to be both tedious and dangerous.

After several hours of fighting the wind, the tarp was finally in place so that the back space could be treated for poisonous insects.

Once removed, the panels were packed in individual crates for transport to West Palm Beach, Florida, where they were stripped and prepared for a new finish. Mr. Agam flew from Paris to Florida to oversee the project and to add new color combinations. Once Agam was satisfied with the overall pattern, the application of colors was begun according to his instructions.

The piece is expected to return home in 2015.



A maquette created in 1976 by Agam for Ruth and Marvin Engel, the original donors of Complex Vision, was used to match colors for the restoration, and was generously loaned to the project by William 'Bill' Engel, son of Ruth and Marvin.

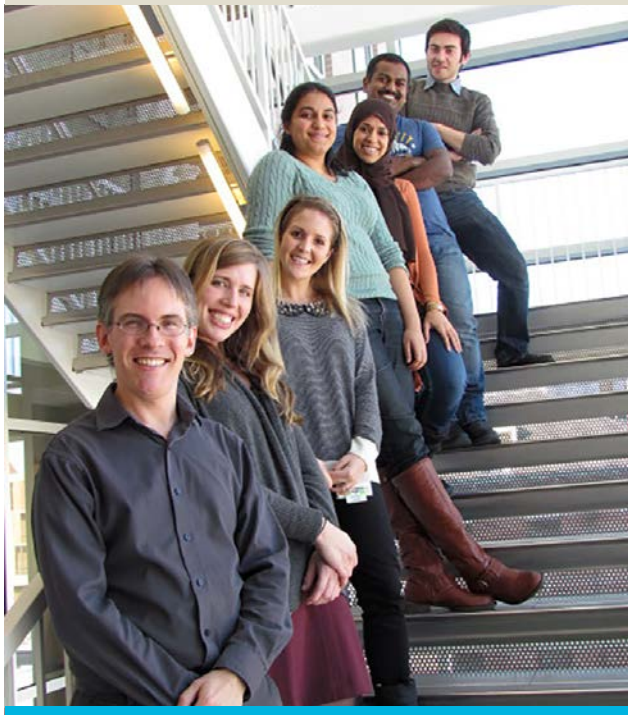
Michael A. Callahan, MD, IRRF President; artist Yaacov Agam; Brian Spraberry, President and CEO of the UAB Callahan Eye Hospital listen as Mr. Agam explains his approach to color selection.

Mr. Agam and Sandra Blackwood, IRRF Executive Director.

Access the report ▶

Synthesis and Mechanistic Studies of a Novel Homoisoflavanone Inhibitor of Endothelial Cell Growth

Plos One, ***"Synthesis and Mechanistic Studies of a Novel Homoisoflavanone Inhibitor of Endothelial Cell Growth,"*** Halesha D. Basavarajappa, Bit Lee, Xiang Fei, Daesung Lim, Breedge Callaghan, Julie A. Mund, Jamie Case, Gangaraju Rajashekhar, Seung-Young Seo, Timothy W. Corson, Department of Pharmacology and Toxicology, Indiana University School of Medicine, Indianapolis, Indiana. (April 2014, vol. 9, Issue 4) **This study was conducted with IRRF support – Timothy W. Corson.**



Corson Lab Group. Timothy Corson in foreground.

ABSTRACT

Preventing pathological ocular angiogenesis is key to treating retinopathy of prematurity, diabetic retinopathy and age-related macular degeneration. At present there is no small molecule drug on the market to target this process and hence there is a pressing need for developing novel small molecules that can replace or complement the present surgical and biologic therapies for these neovascular eye diseases. Previously, an antiangiogenic homoisoflavanone was isolated from the bulb of a medicinal orchid, Cremastra appendiculata. In this study, the team presented the synthesis of a novel homoisoflavanone isomer of this compound. The compound, SH-11052, has antiproliferative activity against human umbilical vein endothelial cells, and also against more ocular disease-relevant human retinal microvascular endothelial cells (HRECs). Tube formation and cell cycle progression of HRECs were inhibited by SH-11052, but the compound did not induce apoptosis at effective concentrations. SH-11052 also decreased TNF-α induced p38 MAPK phosphorylation in these cells. Intriguingly, SH-11052 blocked TNF-α induced IκB-α degradation, and therefore decreased NF-κB nuclear translocation. It decreased the expression of NF-κB target genes and the pro-angiogenic or pro-inflammatory markers VCAM-1, CCL2, IL8, and PTGS2. In addition SH-11052 inhibited VEGH induced activation of Akt but not VEGF receptor autophosphorylation. Based on these results it is proposed that SH-11052 inhibits inflammation induced angiogenesis by blocking both TNF-α and VEGF mediated pathways, two major pathways involved in pathological angiogenesis. Synthesis of this novel homoisoflavanone opens the door to structure-activity relationship studies of this class of compound and further evaluation of its mechanism and potential to complement existing antiangiogenic drugs.

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