New Research Reveals Unexpected Biological Pathway in Glaucoma

STUDY IS FIRST TO PINPOINT THE PRECISE ANATOMICAL LOCATION WHERE VISION LOSS APPEARS TO OCCUR IN GLAUCOMA.

SAN DIEGO, CA

Mark H. Ellisman, MA, PhD, Director of the Center for Research in Biological Systems at the University of California San Diego, and Nicholas Marsh-Armstrong, PhD, Assistant Professor at the Johns Hopkins University School of Medicine, Baltimore, Maryland submitted a proposal that was subsequently approved for funding. The IRRF funds, combined with those of the National Eye Institute of the National Institutes of Health, became additional funding for a study principally supported by the Melza M. and Frank Theodore Barr Foundation through the Glaucoma Research Foundation. (continued on page 2)

Astrocytes and Glaucmatous Neurodegeneration

WOODS HOLE, MA

In 2008, the Initiative for Innovation in Vision Science, established by the Albert and Mary Lasker Foundation and the International Retinal Research Foundation, began its mission to identify knowledge gaps in vision research and to apply innovative solutions to develop and promote new clinical treatments of ocular diseases. In 2009, the Initiative convened two workshops in Woods Hole, MA with experts in diseases of the retina and glaucoma along with bench and clinical scientists from other complimentary fields. These combined skills and expertise resulted in the identification and refinement of the main unsolved questions, as well as important areas for further glaucoma research, which may now be experimentally addressed using modern techniques... (continued on page 2)
Astrocytes and Glaucomatous Neurodegeneration

All members from the Woods Hole workshops, as well as scientists with varied backgrounds who could provide additional knowledge, reconvened in March 2009 for a follow-up meeting at the Howard Hughes Medical Institute’s (HHMI) Janelia Farm Research Campus. Astrocytes and Glaucomatous Neurodegeneration, is the resulting publication by the Initiative, which summarizes this comprehensive examination of how astrocytes may play a key role in glaucoma, and outlines innovative approaches that will hopefully advance new methods to diagnose, treat and even prevent this devastating and intractable disease.

Biological Pathway in Glaucoma

The result has been exciting and productive. The study published in the *Proceedings of the National Academy of Sciences* identified a new and unexpected biological pathway that appears to contribute to the development of glaucoma and its resulting vision loss. Prior research suggested that the optic nerve head, the point where the cables that carry information from the eye to the brain exit the eye, plays a role in glaucoma. Researchers also report a series of findings that offer novel insights into cellular and molecular mechanisms operating at the optic nerve head in two mouse models of glaucoma. Most notably, they discovered that at a specific location within the optic nerve head, there is a unique class of cells called astrocytes that demonstrate properties that appear to make them a critical factor in the visual blinding that occurs in glaucoma.

Researchers found abnormal forms of a protein called gamma synuclein that is similar to abnormal forms of alpha synuclein, a related protein known for its key role in cell loss in Parkinson’s disease. This suggests a biological process similar to Parkinson’s disease unfolds in glaucoma at the specific anatomical location pinpointed in this study for the first time. Also discovered at this anatomical location is a surprising process whereby astrocytes remove the debris of neurons, the cells that die in neurodegenerative disorders such as glaucoma. It is likely that this newly discovered process involving removal of the debris of one cell by a neighboring cell is important in glaucoma and Parkinson’s disease, as well as for many neurodegenerative diseases.
The Rotary Club Host Program, a partnership between Rotary Clubs and the American Academy of Ophthalmology (AAO), recognized the 2010 honorees at an International Welcome Luncheon, held in conjunction with the AAO meeting in Chicago last October. Among those in attendance was Lala Ceklic, MD from Bosnia and Herzegovina, the Callahan Visiting Scholar. Dr. Ceklic was hosted by the Roanoke, Virginia Rotary Club and the International Retinal Research Foundation (IRRF) through the recently established Alston Callahan, MD, FACS Endowment Fund.

Dr. Ceklic is an ophthalmologist and chief of the Eye Clinic of Eastern Sarajevo, Bosnia and Herzegovina, and is actively involved in charity programs that provide cataract surgeries for poor and disabled individuals. She was hosted by the Roanoke, Virginia Rotary Club for a week where she shared in professional, educational, cultural and social experiences within the Roanoke area, followed by attendance at the 2010 Joint Meeting of the American Academy of Ophthalmology and the Pan American Association of Ophthalmology. While attending the AAO meeting in Chicago, Dr. Ceklic learned she had been awarded the Helmerich Retina Research Foundation Fellowship Award provided by the International Council of Ophthalmology Foundation.
As people age, their visual acuity, night vision, dark adaptation, and contrast sensitivity deteriorate. This decline results partly from loss of rods, but other processes underlying these phenotypes are poorly understood. To determine whether age-related vision loss in mice is similar to that in humans, photoreceptor electrophysiology, morphology and photopigment levels in old and young mice were compared. Like in humans, visual acuity and contrast sensitivity under bright light were maintained in old mice, indicating that cone function was unimpaired, whereas both measures deteriorated under dim light, indicating rod dysfunction. The number of photoreceptors and the length and width of rod outer segments decreased with age, and responses to light were correspondingly reduced. Increased variance in dark current (reflecting the number of cGMP channels open at rest) in surviving rods accounted for most of their reduced sensitivity. Unlike in humans, however, dark adaptation was unimpaired in old mice; likewise, the visual cycle was unaffected by aging. (Reprinted from The Journal of Neuroscience by permission of the authors.)
IRRF-Supported Scientist Receives Title of Privatdozent

Lübeck, Germany – Martin Rudolf, MD has received the title of Privatdozent (equivalent to a Research Assistant Professor in the United States). After his research fellowship in 2008 with Professor Christine Curcio at the University of Alabama at Birmingham (UAB), Department of Ophthalmology, Dr. Rudolf returned to the Medical University Center Schleswig-Holstein, Lübeck, Germany. Later that same year, he was awarded $100,000 by the IRRF for his proposed study, *In vivo remodeling of Bruch’s membrane by targeting age-related lipid deposition via apolipoprotein mimetics*, based on his fellowship work with Dr. Curcio. The study aims included remodeling of Bruch’s membrane by removing age-related lipid depositions via effective small molecule lipid acceptors. In 2009, Dr. Rudolf founded the Translational ARMD-Research Group Lübeck.
The International Retinal Research Foundation (IRRF) provided an unrestricted Educational Grant to the XIX Biennial Meeting of the International Society for Eye Research (ISER) held in Montreal, July 18-23, 2010. The meeting included 934 participants from 41 countries and brought together leading clinicians and vision researchers from all over the world with the aim of stimulating and promoting international research cooperation. Symposia addressed topics with broad, interdisciplinary interest and were balanced with plenary lectures and poster sessions. Researchers shared their latest findings, technical expertise and experience making this much-anticipated international event a resounding success.

The 2012 meeting of ISER is scheduled to be held in Berlin, Germany.

**Curcio Awarded Prix Soubrane**

PARIS, FRANCE

Christine A. Curcio, PhD, Professor of Ophthalmology, at the University of Alabama at Birmingham (UAB), was awarded the Prix Soubrane de la Recherche en Ophtalmologie for her work on retinal aging and age-related macular degeneration (AMD) at the 6th annual Macula of Paris congress held on January 14. The prize, a limited edition bronze medal, was presented to Dr. Curcio by Gisèle Soubrane, MD, PhD, Professor of Ophthalmology and Chair Emeritus at the University of Paris East-Creteil. Dr. Curcio’s collaborative work with Northwestern University and UAB investigators developed a natural history and biochemical model for the cholesterol deposition occurring behind the retina throughout adulthood, contributing to the principal AMD lesions. This research was funded in part by 2001 and 2004 IRRF grants.
PUBLISHED SCIENCE FINDINGS BROADEN THE FIELD OF KNOWLEDGE AND ARE ESSENTIAL AS A FOUNDATION FOR BREAKTHROUGH DISCOVERIES. IRRF-SUPPORTED SCIENTISTS ARE CONTRIBUTING TO THE RESEARCH FIELD WITH SCHOLARLY ARTICLES THAT ARE CONSTANTLY MOVING FORWARD OUR UNDERSTANDING OF BLINDING EYE DISEASES.

PUBLISHED SCIENCE:


This study was conducted with IRRF support.

Nature, “Altered MTOR Signaling in Senescent Retinal Pigment Epithelium,” Mark E. Kleinman, MD, Judit Z. Baffi, Jayakrishna Ambati, Joshua L. Dunaief, et al. Corresponding author Joshua L. Dunaief, Stellar Chance Labs, University of Pennsylvania; lead authors Jayakrishna Ambati, MD, University of Kentucky; Judit Z. Baffi, MD, PhD, University of Kentucky; Mark E. Kleinman, MD, 2008 Charles D. Kelman MD Postdoctoral Scholar, University of Kentucky. (Published online February 6, 2011) www.nature.com/nature.

This study was conducted with IRRF support.

Investigative Ophthalmology & Visual Science (IOVS), “Altered MTOR Signaling in Senescent Retinal Pigment Epithelium,” Yan Chen, PhD, Jiyang Cai, PhD, Paul Sternberg, MD. Vanderbilt Eye Institute, Vanderbilt University Medical Center, Nashville, TN. (October 2010, Vol. 51, No. 10) www.iovs.org/content/51/10/5314.

full. Dr. Chen, 2007 Alston Callahan, MD Postdoctoral Scholar, has received a National Eye Institute (NIH) K99/ROO transition to independence award for her work on oxidative stress in retinal degeneration.

This study was conducted with IRRF support.
SIG: The Role of Astrocytes and Other Glial Cells in Retinal Function and Glaucoma

FORT LAUDERDALE, FL

The Lasker/IRRF Initiative will sponsor a Special Interest Group (SIG) at the 2011 annual meeting of the Association for Research in Vision and Ophthalmology (ARVO). This SIG is designed to provide an update on the first set of workshops that culminated in the publication of the report *Astrocytes and Glaucomatous Neurodegeneration* in November 2010. A primary focus of the glaucoma initiative was on the possible roles of astrocytes, both positive and negative, on glaucoma pathology. Astrocytes – perhaps of several types – are present in and around the optic nerve head and in the ganglion cell layer. The optic nerve head is believed to be a critical site in the initiation of glaucoma because of the sectorial nature of retinal ganglion cell loss in glaucoma, the evidence for an axonal transport defect at the optic nerve head, and the many changes that occur in astrocytes at that location in glaucoma. Since changes in the optic nerve head are clearly implicated in the etiology of glaucoma, and the ganglion cells are the primary cell type lost in glaucoma, careful consideration of astrocytes as playing a key role in glaucoma is clearly warranted.

THIS SIG HAS BEEN SCHEDULED AS SESSION 139 ON MAY 1, 2011 AT 1:30 PM IN PALM A

**AGENDA**

ARVO Special Interest Group (SIG)

(Session 139)

*The Role of Astrocytes and Other Glial Cells in Retinal Function and Glaucoma*

Sunday, May 1, 2011 1:30-3 PM in Palm A

**PANELISTS**

J. Dowling (Moderator)  *Astrocytes and Neurodegenerative Diseases*

R. Masland  *Structural Responses of Astrocytes to Optic Nerve Damage*

L. Levin  *Glia and Their Role in RGC Death in Glaucoma*

E. Lütjen-Drecoll  *Clinical Pathology of Glia in Glaucoma*

S. John  *Animal Models of Glaucoma*

**PRESENTATION**

N. Marsh-Armstrong  *Myelination Transition Zone Astrocytes*

**GENERAL DISCUSSION**
**SIG: Cholesterol and Lipoproteins in Retinal Health and Maculopathy**

**FORT LAUDERDALE, FL**

Christine A. Curcio, PhD, Department of Ophthalmology, University of Alabama at Birmingham (UAB), has received IRRF funds for the third annual Special Interest Group (SIG) panel, to be held at the 2011 annual meeting of the Association for Research in Vision and Ophthalmology (ARVO). This SIG focuses on *Cholesterol and Lipoproteins in Retinal Health and Maculopathy* and is co-organized by James T. Handa, MD (Wilmer Eye Institute, Johns Hopkins). The large age-related deposition of neutral lipid in Bruch’s membrane of the human eye is related to the formation of drusen, fatty lesions located behind the retinal pigment epithelium in eyes with age-related macular degeneration. IRRF funds enable the participation of outside speakers from cardiovascular medicine, which has decades of laboratory and clinical experience in understanding and treating the effects of cholesterol deposition in vessel walls.

**THIS SIG HAS BEEN SCHEDULED AS SESSION 246 ON MAY 2, 2011 AT 12:00 PM IN GRAND A**

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**AGENDA**

**ARVO Special Interest Group (SIG)**  
(Session 246)  
*Cholesterol and Lipoproteins in Retinal Health and Maculopathy*

Monday, May 2, 2011 at 12:00 PM in Grand A

**PANELISTS**

C. Curcio (Moderator)  
J. Handa  
I. Pikuleva  
P. Bernstein  
A. Stitt  
C. Binder

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**Oxidized LDLs Turn Down the Regulation of Complement**

**Cholesterol Metabolism and P450 Enzymes**

**Very Long Chain Fatty Acids in Human Retina and Choroid**

**AGEs and ALEs in BrM/Choroid**

**Oxidized Lipids, Inflammation, Immunity**

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**GENERAL DISCUSSION**
Due Diligence an Important Part of Foundation Life

WASHINGTON, D.C.

Behind the scenes of supporting groundbreaking research is the day-to-day operations and the rigorous compliance of ever-changing government regulations for non-profit foundations. These duties do not usually make for exciting news, but it is the expertise and diligence of the IRRF staff that keeps the Foundation running. Charlotte Bowers, IRRF Assistant Director of Operations, recently attended a conference hosted by the Association of Small Foundations in Washington, D.C. that provided a line-by-line analysis of the new 990-PF tax form required for all private foundations. The seminar went into detail the many pitfalls and penalties of an incorrect filing. Also stressed were foundation tax planning tips, compliance and enforcement and a brief history of the proposed Excise Tax currently before Congress.

HOMEWOOD, AL

The IRRF participated with Birmingham area individuals and businesses to support the Birmingham VisionWalk held at Homewood Central Park for its 2nd annual run. The 2010 Team IRRF was joined by a couple canine friends making the day even more enjoyable. Sponsorship of local causes allows the Foundation to assist in fund-raising projects that make a positive impact on the Birmingham community.

Left to Right: Michael Fontanello, CPA, Fontanello, Duffield & Otake LLP, San Francisco; Charlotte Bowers, IRRF Assistant Director Operations; Chris Petermann, O’Connor, Davies, Munns & Dobbins, New York.

TEAM IRRF: (Top Left to Right) DyQuan Bowers; Charlotte Bowers; Sandra Blackwood; (Front left to Right) Ashley Sellers; Gunny; Kadyn Bowers; David Sellers and Gypsy.
The above paper demonstrated that claudin-19 is the principal claudin of retinal pigment epithelium (RPE) tight junctions, and without it the outer blood-retinal barrier does not function. Further, a serum-free medium promoted the maturation of hRPE. This medium was designed for co-culture experiments using stem cell-derived RPE and retinal progenitors. This second result gives some insight into the wet form of age-related macular degeneration (AMD). When serum was re-added to the apical, but not the basal, surface of the RPE, the barrier became tighter than normal. This property might reflect a defense mechanism to slow the lateral spread of disease when capillaries invade the subretinal space.

The authors feel they have laid the foundations for understanding RPE/retinal transplantation by exploring the interactions important for forming a blood-retinal barrier, while learning about the effects of subretinal serum and inflammatory cytokines found in retinal disease. Also demonstrated was that RPE-retinal interactions are important for the differentiation/maturation of each tissue. This model will be continued to develop transplantable tissues of superior quality.

As a result of IRRF support, Dr. Rizzolo and staff have obtained funding from the State of Connecticut’s program for stem cell research to continue this project. In addition to the above publication, one manuscript in preparation, and a meeting abstract on the proof of the underlying premise of the project have all been achieved.
BECOME A BENEFACCTOR:
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 $9.3 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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Attn.: Sandra Blackwood, MPA, Executive Director
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