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4th Biennial International Symposium on AMD



October 20-22, 2016

Boston, MA



HARVARD
MEDICAL SCHOOL

DEPARTMENT OF
Ophthalmology



**AGE-RELATED MACULAR
DEGENERATION**
CENTER OF EXCELLENCE





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DEGENERATION
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4th Biennial International
Symposium
on **AMD**

October 20-22, 2016

The Starr Center
185 Cambridge Street
Boston, MA 02114



HARVARD
MEDICAL SCHOOL

DEPARTMENT OF
Ophthalmology

AFFILIATES: Massachusetts Eye and Ear • Massachusetts General Hospital • Boston Children's Hospital
Beetham Eye Institute at the Joslin Diabetes Center • Brigham and Women's Hospital • Beth Israel Deaconess Medical Center
Cambridge Health Alliance • VA Boston Healthcare System • VA Maine Healthcare System

PARTNERS: Aravind Eye Hospital (India) • Shanghai Eye and ENT Hospital, an affiliate of Fudan University (China)

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Co-director, Harvard Ophthalmology AMD Center of Excellence
Director, Howe Laboratory, Mass. Eye and Ear
Associate Chief of Basic and Translational Research, Mass. Eye and Ear
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Associate Professor of Ophthalmology, Harvard Medical School
Co-director, Harvard Ophthalmology AMD Center of Excellence
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Investigator, Angiogenesis Laboratory, Mass. Eye and Ear

Ivana K. Kim, MD

Associate Professor of Ophthalmology, Harvard Medical School
Co-director, Harvard Ophthalmology AMD Center of Excellence
Director, Macular Degeneration Unit, Mass. Eye and Ear

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Joan W. Miller, MD, FARVO

Henry Willard Williams Professor of Ophthalmology, Harvard Medical School
Chair, Department of Ophthalmology, Harvard Medical School
Chief of Ophthalmology, Massachusetts Eye and Ear
and Massachusetts General Hospital

Welcome

Dear Colleagues,

Welcome to the 4th Biennial International Symposium on AMD.

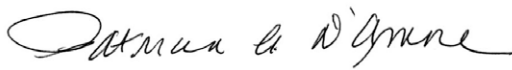
Today, AMD remains the leading cause of blindness among older Americans, and it is ranked among the top three most common causes of visual impairment in the world.

Over the years, we have made great progress in AMD treatment. The last major therapeutic breakthrough led to an entirely new class of anti-VEGF drugs for neovascular AMD. While these advancements dramatically improved the outlook for many patients, our work continues as we strive to better understand the disease pathogenesis and develop new treatment options, particularly for early and atrophic AMD.

The goal of this symposium is to propel innovative AMD research that will ultimately eradicate this blinding disease. Our attendees include prominent scientists and experienced clinicians from multidisciplinary fields whose insights can nurture scientific inquiry and hasten the bench-to-bedside pipeline.

We are excited to have you with us today. Here at Harvard Ophthalmology, we encourage a spirit of open dialogue and collaboration. Thank you in advance for your active participation, which will greatly contribute to the success of this forum and will help us identify novel avenues for future exploration.

We look forward to some stimulating discussions!



Patricia A. D'Amore, PhD, MBA



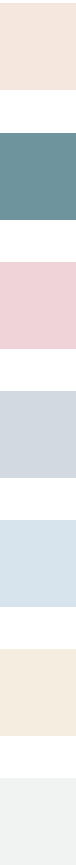
Deeba Husain, MD



Ivana K. Kim, MD



Program



Thursday, October 20

6:00 - 8:00 pm

Welcome Reception
Mass. Eye and Ear
Lank Family Dining Room, 7th Floor
243 Charles Street, Boston, MA

Friday, October 21

7:00 - 8:00 am

Breakfast and Registration
Starr Center
2nd Floor, 185 Cambridge Street, Boston, MA

8:00 - 8:05 am

Welcome: Joan W. Miller, MD
Harvard Ophthalmology, Mass. Eye and Ear, and Mass General Hospital

8:05 - 8:30 am

Opening Address: Ivana K. Kim, MD
Harvard Ophthalmology, Mass. Eye and Ear

8:30 - 10:25 am

AGING

Moderator: Patricia A. D'Amore, PhD, MBA
Harvard Ophthalmology, Schepens Eye Research Institute of Mass. Eye and Ear

8:30 - 8:50 am

Keith Blackwell, MD, PhD
Harvard Medical School Department of Genetics, Joslin Diabetes Center
Redox Signaling, Metabolic Homeostasis, and Aging

8:55 - 9:15 am

James Kirkland, MD, PhD
Mayo Clinic
Aging, Cellular Senescence, and Translation into Clinical Interventions

9:20 - 9:40 am

William Mair, PhD
Harvard T.H. Chan School of Public Health
Pre-mRNA Splicing Homeostasis Predicts Life Expectancy and can be Targeted to Promote Healthy Aging

9:45 - 10:25 am

Panel Discussion

10:25 - 10:50 am

Break
Starr Center Breakout Space

10:50 am - 12:45 pm

RPE BIOLOGY

Moderator: Magali Saint-Geniez, PhD
Harvard Ophthalmology, Schepens Eye Research Institute of Mass. Eye and Ear

10:50 - 11:10 am

Janet Sparrow, PhD
Columbia University
Shining Light on Bisretinoids of Retina

11:15 - 11:35 am	<p>Christine Curcio, PhD UAB School of Medicine <i>Visualizing Retinal Pigment Epithelium Fate in AMD by Histology and Optical Coherence Tomography</i></p>
11:40 am - 12:00 pm	<p>Silvia C. Finnemann, PhD Fordham University <i>The RPE Cytoskeleton: Regulating RPE Function and Potency, and Changes with Age-related Oxidative Stress</i></p>
12:05 - 12:45 pm	<p>Panel Discussion</p>
12:45 - 2:05 pm	<p>Lunch Starr Center Breakout Space</p>
2:05 - 4:00 pm	<p>IMAGING</p> <p>Moderator: François Delori, PhD Harvard Ophthalmology, Schepens Eye Research Institute of Mass. Eye and Ear</p> <p>James Fujimoto, PhD Massachusetts Institute of Technology <i>Ultrahigh Speed Swept Source OCT and OCTA</i></p> <p>Steve Burns, PhD Indiana University <i>Adaptive Optics Retinal Imaging with Multiply Scattered Light</i></p> <p>K. Bailey Freund, MD NYU Langone Medical Center <i>Pachychoroid - A Newly Recognized Risk and Disease Modifier in AMD</i></p> <p>Panel Discussion</p>
4:00 - 4:25 pm	<p>Break Starr Center Breakout Space</p>
4:25 - 5:45 pm	<p>EPHRAIM FRIEDMAN LECTURE</p> <p>Introduction to Lecture: Joan W. Miller, MD Harvard Ophthalmology, Mass. Eye and Ear, and Mass General Hospital</p> <p>Reflections on Ephraim Friedman: Evangelos S. Gragoudas, MD Harvard Ophthalmology, Mass. Eye and Ear</p> <p>Speaker Introduction: Joan W. Miller, MD Harvard Ophthalmology, Mass. Eye and Ear, and Mass General Hospital</p> <p>Robert E. Marc, PhD John A. Moran Eye Center <i>Remodeling in Retinal Degenerations</i></p>
6:45 - 10:00 pm	<p>Gala Dinner at the Liberty Hotel <i>By registration only</i></p>

Saturday, October 22

7:30 - 8:30 am

Breakfast

Starr Center Breakout Space

8:30 - 8:40 am

Welcome Back and Introduction of Travel Awards

Deeba Husain, MD

Harvard Ophthalmology, Mass. Eye and Ear

8:40 - 10:35 am

LIPIDS

Moderator: Deeba Husain, MD

Harvard Ophthalmology, Mass. Eye and Ear

8:40 - 9:00 am

Demetrios Vavvas, MD, PhD

Harvard Ophthalmology, Mass. Eye and Ear

Lipid Treatment in AMD

9:05 - 9:25 am

Margaret DeAngelis, PhD

University of Utah

Genome-Wide Analysis of Allele Specific Expression Demonstrates the Role of Lipid Metabolism in AMD

9:30 - 9:50 am

Gérard Lizard, PhD

INSERM, Universite of Bourgogne

Involvement of Oxysterols in the Physiopathology of Age-related Macular Degeneration

9:55 - 10:35 am

Panel Discussion

10:35 - 10:55 am

Break

Starr Center Breakout Space

10:55 am - 12:50 pm

INFLAMMATION

Moderator: Eric Ng, PhD

Harvard Ophthalmology, Schepens Eye Research Institute of Mass. Eye and Ear

10:55 - 11:15 am

Gökhan Hotamisligil, MD, PhD

Harvard School of Public Health

Endoplasmic Reticulum Function, Proteostasis and Immunometabolic Homeostasis

11:20 - 11:40 am

Steve Elledge, PhD

Harvard Medical School Department of Genetics, Brigham and Women's Hospital

Profiling Immunological History in Humans

11:45 am - 12:05 pm

Scott Cousins, MD

Duke University School of Medicine

Role of Mitochondrial Dysfunction in Experimental Mouse Models of Dry Age-related Macular Degeneration (AMD)

12:10 - 12:50 pm

Panel Discussion

12:50 - 2:05 pm

Lunch
Starr Center Breakout Space

2:05 - 4:00 pm

APPROACHES TO FUTURE TREATMENT

Moderator: Kip M. Connor, PhD
Harvard Ophthalmology, Mass. Eye and Ear

2:05 - 2:25 pm

Lindsay A. Farrer, PhD
Boston University School of Medicine
AMD Genetics – Moving Beyond Disease Associations Toward Novel Therapeutics and Biomarkers

2:30 - 2:50 pm

Sarah Doyle, PhD
Trinity College
The Potential of Immunotherapy for Treating AMD

2:55 - 3:15 pm

Phoebe Lin, MD, PhD
Oregon Health and Science University
Gut Microbial Alterations in Advanced Age-Related Macular Degeneration

3:20 - 4:00 pm

Panel Discussion

4:00 - 4:35 pm

CLOSING REMARKS

4:00 - 4:05 pm

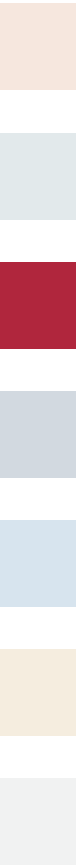
Speaker Introduction: Joan W. Miller, MD
Harvard Ophthalmology, Mass. Eye and Ear, Mass General Hospital

4:05 - 4:35 pm

Robert D'Amato, MD, PhD
Harvard Ophthalmology, Boston Children's Hospital



Abstracts of Talks



Redox Signaling, Metabolic Homeostasis, and Aging

T. Keith Blackwell, MD, PhD

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Senior Investigator, Joslin Diabetes Center

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ABSTRACT: An emerging body of evidence suggests the existence of an exciting new landscape of biological control that is mediated by cysteine (Cys) modifications. The extent and functional versatility of this signaling remain unclear, however. The endoplasmic reticulum (ER) transmembrane protein IRE-1 maintains ER homeostasis by initiating the unfolded protein response (UPR^{ER}). We have determined that IRE-1 has a distinct, unexpected, and conserved redox-regulated function in cytoplasmic homeostasis. When reactive oxygen species (ROS) are produced in the vicinity of IRE-1, a conserved Cys that is located within its cytoplasmic kinase activation loop become sulfenylated (SH to SOH). This modification inhibits the IRE-1-mediated UPRER, and initiates the p38/SKN-1(Nrf2) antioxidant response at IRE-1. This IRE-1/p38 signaling can be triggered by ROS that are produced by mitochondria, by an IRE-1-associated NADPH oxidase in response to stress, or by the ER itself. ER-generated ROS extend *C. elegans* lifespan through this mechanism. This pathway is conserved in human cells, and many AGC-family kinases (AKT, p70S6K, PKC, ROCK1) seem to be regulated similarly.

The data reveal that IRE-1 has an ancient sentinel function as an antioxidant response regulator that protects the cytoplasm, describe a novel ROS sensor for SKN-1/Nrf2, and identify the ER as a source of ROS signals that influence aging. They also define a paradigm whereby cysteine modifications from localized ROS signals may have inhibitory, activating, or neomorphic effects on protein function. Such signals are likely to be of great importance in transducing stress and homeotic signals.

Aging, Cellular Senescence, and Translation into Clinical Interventions

James Kirkland, MD, PhD

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Mayo Clinic

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ABSTRACT: Aging is the leading risk factor for most of the chronic diseases that account for the bulk of morbidity, mortality, and health care expenditures including most forms of visual impairment, diabetes and its complications, atherosclerosis and impaired vascular reactivity, cancers, dementias, chronic lung diseases, bone and joint disease, frailty and sarcopenia, loss of resilience, and many others. Chronological age is the biggest risk factor for many of these diseases. In many cases, aging is a better predictor than all other known risk factors combined. A fundamental mechanism that may contribute to both age-related dysfunction and the pathology underlying chronic diseases is cellular senescence. Senescent cells are at sites of pathology in these conditions and release factors that can cause local and systemic dysfunction. We found that eliminating senescent cells using genetic approaches alleviates age-related phenotypes and diseases in mice. We developed small molecules that selectively eliminate senescent cells, senolytic agents, and agents that impact their inflammatory senescence-associated secretory phenotype (SASP), SASP-protective agents. Here we discuss potential paths to clinical translation. These agents would be transformative if they are successful at delaying, preventing, alleviating, or reversing age-related diseases as a group.

Pre-mRNA Splicing Homeostasis Predicts Life Expectancy and can be Targeted to Promote Healthy Aging

William Mair, PhD

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Harvard T.H. Chan School of Public Health

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ABSTRACT: Aging is driven by a loss of cellular and organismal homeostasis and is the key risk factor for multiple chronic diseases. Therefore, interventions that attenuate or reverse systemic dysfunction seen with age have potential to reduce overall disease risk and prolong healthy years in the elderly. Although loss of protein and transcriptional homeostasis are well-established causes of aging, it remains unclear whether loss of RNA homeostasis and splicing fidelity, key processes in the central dogma of molecular biology, affect longevity. Here we demonstrate that pre-mRNA splicing homeostasis is a biomarker and predictor of life expectancy. We show that dietary restriction promotes longevity via increased pre-mRNA splicing efficiency and identify components of the splicing machinery specifically required for dietary restriction-mediated longevity. Dietary restriction maintains youthful splicing via the TORC1 modulator RAGA-1. Furthermore, splicing factor 1 (SFA-1) is specifically required for both dietary restriction- and TORC1-mediated lifespan extension. Lastly, we demonstrate that deletion of the splicing protein RSP-2, whose expression increases in animals with age, is sufficient to extend lifespan. Together, these data demonstrate that loss of RNA homeostasis is causal to organismal aging, that splicing fidelity is required for dietary restriction and TORC1 longevity, and that altering spliceosome dynamics can prolong lifespan.

Shining Light on Bisretinoids of Retina

Janet R Sparrow, PhD

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ABSTRACT: Research in the laboratory is directed toward understanding the composition of RPE lipofuscin, the structures and properties of the bisretinoid constituents of lipofuscin, the mechanisms by which these compounds form and the adverse effects of these compounds on photoreceptor cells and RPE. Other investigations explore therapies aimed at reducing bisretinoid accumulation. The bisretinoids of retina are the source of fundus autofluorescence. Thus studies also aim to apply an understanding of RPE bisretinoids to clinical interpretations and measurements of fundus autofluorescence in retinal disease. Taken together, efforts in the laboratory contribute to the elucidation of pathology in several retinal disorders including recessive Stargardt disease, retinitis pigmentosa, pattern dystrophies, bull's eye maculopathy and age-related macular degeneration.

Visualizing Retinal Pigment Epithelium Fate in AMD by Histology and Optical Coherence Tomography

Christine A. Curcio, PhD

Professor of Ophthalmology, University of Alabama School of Medicine

EyeSight Foundation of Alabama Vision Research Laboratories
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ABSTRACT: The biophysical basis of reflectivity in optical coherence tomography (OCT) is backscattering towards the detector from organelles (Mie scattering) and via waveguiding, for photoreceptors. The RPE has three cushions of light-scattering organelles (melanosomes, lysosome-derived organelles, mitochondria) that make it a triple reflector in OCT. Three possible fates are death, transdifferentiation to a phenotype not recognizable as RPE, and emigration. Under the hypothesis that the RPE exhibits stereotypic stress responses that can be followed in vivo by OCT, we surveyed RPE morphologies in high-resolution histology of 53 late AMD eyes (geographic atrophy, GA and neovascular AMD) and one direct clinicopathologic correlation of a previously imaged patient. We found many fully pigmented RPE cells in the atrophic zones, cells shedding granules basolaterally, consistent with apoptosis, cells sloughing into the subretinal space and migrating into the retina, and cells subducting under basal laminar deposits in atrophic areas and apparently migrating outward under the non-atrophic zone. Using the descent of the external limiting membrane (ELM) towards Bruch's membrane as the border of atrophy (per S.H. Sarks, 1976) we found that RPE phenotypes worsen and the RPE layer thickens towards this landmark, confirming a progressing dysmorphia that underlies variable autofluorescence in geographic atrophy (Rudolf et al., 2013). In serial eye tracked OCT of drusenoid RPE detachments, the RPE layer can be seen to thicken in advance of hyperreflective foci appearing in the overlying neurosensory retina. This is followed by breakup of the layer, collapse of the detachment, and atrophy of the outer retina. Cells resembling migratory RPE phenotypes express inflammatory markers in other studies. These data converge on a new model of how geographic atrophy proceeds via transdifferentiation and migration of RPE, and provides new insights into the microenvironment confronting replacement cells. A comprehensive and quantitative description of late AMD can inform the study of early AMD by enabling accurate natural history through multimodal clinical imaging and focus on relevant precursor processes in model systems.

The RPE Cytoskeleton: Regulating RPE Function and Potency, and Changes with Age-related Oxidative Stress

Silvia C. Finnemann, PhD

Professor of Cell Biology
Department of Biological Sciences, Fordham University

Center for Cancer, Genetic Diseases, and Gene Regulation
441 East Fordham Road, Bronx, NY 10458
Finnemann@fordham.edu

ABSTRACT: Research in our laboratory aims to identify cellular-molecular mechanisms of photoreceptor outer segment renewal, a fundamental retinal process that is essential for life-long preservation of visual function. It involves diurnal shedding of photoreceptor outer segment tips and their efficient receptor-mediated phagocytosis by the neighboring RPE. Inefficiency of phagocytic digestion with age causes gradual lipofuscin accumulation in the RPE in the human eye, which contributes to RPE dysfunction associated with atrophic age-related macular degeneration. Probing the contributions of the RPE cytoskeleton to RPE phagocytosis in human RPE in culture and in animal models, we recently identified key signaling pathways downstream of RPE surface receptors that govern cytoskeletal regulation. We found that manipulating cytosolic cytoskeletal signaling using pharmacological compounds was sufficient to restore phagocytic function to mutant RPE lacking an essential phagocytic surface receptor in culture and ex situ. Furthermore, the same compounds significantly increased the phagocytic capacity of human donor RPE cells without altering RPE surface receptor expression. However, tweaking cytoskeletal signaling had little effect on RPE function if RPE cells had been exposed to low, sublethal levels of oxidative stress because the RPE cytoskeleton is uniquely susceptible to protein damage through oxidative modification. Altogether, our data suggest that cytoskeletal integrity is a key indicator and master regulator of RPE functionality that may be improved through targeted therapy.

Ultrahigh Speed Swept Source OCT and OCTA

James Fujimoto, PhD

Elihu Thomson Professor of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, Department of Electrical Engineering and Computer Science and Research Laboratory of Electronics

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ABSTRACT: Recent advances in OCT technology have dramatically increased imaging speed. Swept source OCT (SS-OCT) can achieve speeds ~10x faster than current commercial SD-OCT. SS-OCT also enables imaging at longer 1050nm wavelengths compared with SD-OCT at 840nm, providing increased immunity to ocular opacities and improved image penetration to enable choriocapillaris imaging. The ultrahigh imaging speeds achieved by state-of-the-art OCT are important not only for improving retinal coverage, but also for functional OCT imaging. OCT angiography (OCTA) enables three dimensional visualization of retinal and choroidal microvasculature, detecting motion contrast by performing repeated B-scans in the same retinal location, and measuring decorrelation signals, which are generated by moving erythrocytes. OCTA does not require injection of dyes as in fluorescein angiography or indocyanine green angiography and therefore can be performed on every patient visit. However, since OCTA requires repeated scanning, extremely high acquisition speeds are required in order to achieve retinal coverage. OCTA using SS-OCT is especially promising because it enables imaging of the choriocapillaris, detecting flow impairment and atrophy. We summarize OCTA studies in atrophic and exudative AMD using a 400 kHz axial scan rate prototype SS-OCT technology, where OCTA enables visualization of alterations in retinal as well as choriocapillaris vasculature.

Adaptive Optics Retinal Imaging with Multiply Scattered Light

Stephen A. Burns, PhD

Professor, Associate Dean for Graduate Programs
Indiana University School of Optometry

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ABSTRACT: Adaptive Optics Retinal Imaging (AOSLO) is capable of providing cellular resolution imaging of the living human retina. Advances in system configurations and controls have made the technology much more patient-friendly. In recent years we have concentrated on adapting the AOSLO for multiple imaging modalities to provide complementary information on the health of the retina.

We will show how the use of controllable contributions from multiply scattered light allows unique views of the photoreceptors and retinal pigment epithelium (RPE) in outer retinal disease as well as of the vasculature in diabetes and essential hypertension. For the vascular imaging, we see increases in arteriolar wall thickness and, because of the very tight relation between the vessel lumen and wall in normal subjects, this thickening may be an important biomarker for both diabetic and hypertensive remodeling. In addition to changes in the vascular wall there are characteristic anatomical changes in diabetes, including vessel looping, vascular wall irregularity, microcystic changes, and capillary occlusion.

Pachychoroid - A Newly Recognized Risk and Disease Modifier in AMD

K. Bailey Freund, MD

Clinical Professor of Ophthalmology, NYU School of Medicine
Retina Specialist, Vitreous Retina Macula Consultants of New York

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kbfnyf@aol.com

ABSTRACT:

Purpose: To correlate clinical manifestations with multimodal imaging in pachychoroid disorders including central serous chorioretinopathy (CSC), pachychoroid pigment epitheliopathy (PPE), pachychoroid neovascularopathy (PNV), and polypoidal choroidal vasculopathy (PCV).

Methods: Patients with pachychoroid spectrum diagnoses were identified non-consecutively through a review of charts and multimodal imaging including en face OCT and OCT angiography. Each eye was categorized as uncomplicated pachychoroid, PPE, CSC, PNV or PCV.

Results: Choroidal thickness maps confirmed increased thickness under areas of PPE, CSC, type 1 NV (PNV), or polyps (PCV). En face OCT showed dilated outer choroidal vessels in all eyes. In several eyes with chronic disease, focal choriocapillaris atrophy with inward displacement of deep choroidal vessels was noted.

Conclusion: Although clinical manifestations of pachychoroid spectrum disorders vary considerably, these entities share morphologic findings in the choroid, including increased thickness and dilated outer choroidal vessels. En face OCT localizes these changes to disease foci and shows additional findings that may unify our understanding of disease pathogenesis.

Lipid Treatment in AMD

Demetrios Vavvas, MD, PhD

Associate Professor of Ophthalmology, Harvard Medical School
Co-director, Harvard Ophthalmology Ocular Regenerative Medicine Institute
Monte J. Wallace Ophthalmology Chair in Retina at Mass. Eye and Ear

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ABSTRACT: Several gene associations and epidemiological studies have shown lipids to play a central role in age-related macular degeneration (AMD). Cholesterol (esterified and unesterified) constitutes >40% of the druse volume. For this reason, lipid-lowering drugs, such as statins, have been investigated in AMD, but epidemiological studies have yielded conflicting results. A limitation of these studies was the heterogeneity of the disease and non-standardization of statin dosage. We were interested in studying high-dose statins (similar to the levels used in atherosclerosis disease) in a homogeneous group of AMD patients with large lipid rich drusenoid deposits. A pilot, two-center, prospective, phase 1-2 trial using 80 mg atorvastatin was performed. Of the 23 patients finishing the study, none converted to neovascular AMD and 10 showed significant (>50%) reduction in the volume of drusen with visual function recovery. Responders did not differ in a statistically significant way from non-responders in baseline characteristics or the amount of cholesterol reduction. We believe this study gives support to the “oil-spill” hypothesis for AMD and warrants a larger Phase 3 type study.

Genome-Wide Analysis of Allele Specific Expression Demonstrates the Role of Lipid Metabolism in AMD

Margaret M. DeAngelis, PhD

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John A. Moran Eye Center
University of Utah School of Medicine

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margaret.deangelis@utah.edu

ABSTRACT: The identification of allele-specific expression (ASE), utilizing genome wide level transcriptomic data of primary tissues combined with genome wide level genotype data, can be a crucial step in elucidating disease mechanism in complex disease. ASE is a powerful genetic phenomenon for elucidation of disease mechanism in complex disease, not yet done in the field of age-related macular degeneration. AMD is the leading cause of blindness in the aging population for which there is no cure. In this study we carefully characterized the macular retinal pigment epithelium (RPE), choroid, and neural retina in fresh tissue in both eyes from unrelated donors, using postmortem OCT and/or retinal imaging. Whole transcriptome analysis showed that within the macular RPE tissues and separately macular retina tissues, expression was significantly different between different stages of AMD compared to normal age matched controls. ASE analysis identified 78 single nucleotide polymorphisms (SNPs) that showed significantly differential allelic imbalance between disease subtypes. Thirty of these SNPs (38%) are located in coding regions of which 22 are synonymous and 8 are non-synonymous changes. Many of the deleterious changes occur in genes primarily involved in lipid transport and metabolism. Mono-allelic expression was observed for *YPEL2* SNP rs1046037 suggesting the occurrence of methylation and this SNP is located in a region that was previously reported to be methylated in brain. This is the first study to show ASE differences between disease states for a common complex disease. Additionally, our study provides new genetic and epigenetic evidence for the role of lipid metabolism in AMD. Our findings also suggest that ASE may be a valuable tool for a systems-wide genome level approach for bringing precision medicine to the clinic.

Implication of 7-ketocholesterol in the Pathogenesis of Degenerative Diseases: Potential Roles in Age-related Macular Degeneration

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Universit  de Bourgogne Franche Comt , INSERM

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ABSTRACT: The progressive rupture of RedOx homeostasia, which can occur more or less rapidly depending on genetic and environmental factors and life habits, especially nutritional habits, can contribute to lipid peroxidation (cholesterol auto-oxidation and fatty acid degradation leading to oxysterol and aldehyde formation, respectively) subsequently leading to protein modifications, and DNA alterations. The generation of oxysterols (especially those oxidized at C7 such as 7-ketocholesterol (7KC)) and fatty acid degradation products could subsequently favor mitochondrial, lysosomal and peroxisomal dysfunctions, which could in turn amplify oxidative stress, promote cytokine- and non-cytokine-mediated inflammation, and disturb the equilibrium between cell death and cell proliferation. Therefore, similar initial events, resulting from cholesterol and lipid oxidation, could trigger various major age-related diseases including cardiovascular, neurodegenerative, and eye diseases, and cancer. It is therefore supposed that 7KC could constitute an important second messenger in numerous age-related diseases, including age-related macular degeneration (AMD). Indeed, 7KC which is found at enhanced level in oxidized lipoproteins and atheroma plaque, as well as in the plasma and cerebrospinal fluids of patients with various neurodegenerative diseases (X-linked adrenoleukodystrophy (X-ALD), multiple sclerosis, Alzheimer's disease), is also present at elevated levels in abnormal deposits called drusens, which are localized in the Bruch's membrane of the retina of patients with AMD. As 7KC might play important roles in the development of major age-related diseases, such as AMD, it seems important to determine its biological activities, to determine the associated metabolic pathways, and to identify natural or synthetic compounds able to impair its activities, especially its side effects (oxidation, inflammation, lipid metabolism dysfunctions, and cell death induction). We reported that 7KC induces several dysfunctions in various cell types, including retinal epithelial cells, which can contribute to AMD: rupture of RedOx homeostasis associated with overproduction of reactive oxygen species (ROS), enhanced secretion of VEGF and inflammatory cytokines, and mitochondrial and lysosomal dysfunctions, which are involved in 7KC-induced cell death. These different side effects, which can be observed in other cell types (monocytic and nerve cells), can be counteracted in vitro by various natural and synthetic compounds (natural compounds: Vitamins (Vit E, Vit B8 (biotine)), fatty acids (DHA: C22:6 n-3), polyphenols (resveratrol); synthetic compounds: dimethyl fumarate (DMF)). Some of these compounds such as biotine and DMF are currently being evaluated in clinical trials, mainly in neurodegenerative diseases. New therapeutic strategies consisting in inactivating 7KC with particular enzymes are promising. Whereas complex interactions of oxysterols with various compounds can occur in vivo and can modulate their biochemical properties and biological activities, future research on 7KC remains promising to better understand its contribution in ageing processes and age-related diseases, and to identify new treatments.

Endoplasmic Reticulum Function, Proteostasis and Immunometabolic Homeostasis

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ABSTRACT: Proper coordination of cellular metabolism and its integration with immune response is paramount to function of cells, organs, and organisms. The endoplasmic reticulum is the main site for protein and lipid synthesis, trafficking, and the storage of cellular calcium. ER also plays a significant role in adaptation to metabolic fluctuations and their integration to immune response. This dynamic is disrupted in protein folding disorders as well as by metabolic stress of chronic metabolic diseases such as obesity and diabetes in animal models and humans. Restoration of the ER adaptive folding responses by genetic or chemical means improve proteometabolic homeostasis in preclinical models and humans. Therefore, understanding the compositional, structural, and functional regulation of the ER and the mechanisms giving rise to its dysfunction remain limited beyond the canonical unfolded protein response (UPR). We are interested in exploring this aspect of organelle function and understanding both the upstream metabolic signals that influence ER and networks of integration with metaflammation, a novel form of metabolically orchestrated form of inflammation. In recent studies, we discovered interactions between metaflammatory signaling pathways and the unfolded protein response during metabolic stress and pathological interactions between the endoplasmic reticulum and mitochondria that disrupt the function of these organelles. We have also embarked on genetic and chemical screens to identify new targets as well as small molecular entities to exploit ER as a therapeutic platform. Here, I will present evidence integrating metaflammation to organelle function, describe emerging candidates that may provide insights into novel therapeutic aspects of ER biology, and how these targets and mechanisms may be exploited to understand disease pathogenesis and leveraged to design novel and effective preventive and therapeutic strategies.

Profiling Immunological History in Humans

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ABSTRACT: Identifying antibody targets is a critical aspect of immunological analysis. We have developed two methods for genome-wide identification of protein interactions called PhIP-Seq and PLATO. PhIP-Seq takes advantage of a synthetic library of long peptides that cover the coding regions of genomes and display those on the surface of the bacteriophage T7 where they can be affinity purified by antibodies from patients to identify, for examples, autoantibodies for sequencing deconvolution. A second method called PLATO identifies interactions by affinity enrichment of a library of full-length open reading frames displayed on ribosomes, followed by massively parallel analysis using DNA sequencing. Both methods have been used to identify common targets in autoimmune diseases. In this talk, we will describe our attempts to apply this technology to the discovery of antiviral antibodies.

The human virome plays important roles in health and immunity. However, current methods for detecting viral infections and antiviral responses have limited throughput and coverage. To address this we developed VirScan, a high-throughput method to comprehensively analyze antiviral antibodies using PhIP-Seq. We assayed over 108 antibody-peptide interactions in 569 humans across four continents, nearly doubling the number of previously established viral epitopes. We detected antibodies to an average of 10 viral species per person and 84 species in at least two individuals. Although rates of specific virus exposure were heterogeneous across populations, antibody responses targeted strikingly conserved “public epitopes” for each virus, suggesting that they may elicit highly similar antibodies. VirScan is a powerful approach for studying interactions between the virome and the immune system.

Role of Mitochondrial Dysfunction in Experimental Mouse Models of Dry Age-related Macular Degeneration (AMD)

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ABSTRACT: Mitochondrial dysfunction (superoxide overproduction, diminished ATP and other features) has been implicated in causing age-related disorders, including AMD. Our laboratory group is investigating the role of mitochondrial dysfunction in formation of subRPE deposit formation in mouse models of dry AMD. We hypothesize that environmental factors (i.e., high fat diet and exposure to the environmental toxicant, hydroquinone or HQ) induces mitochondrial dysfunction, which, in turn, triggers deposit formation and diminishes photoreceptor function. We have developed an acute mouse model for subRPE deposits based upon subconjunctival injections of HQ, which results in frequency-of-injection dependent accumulation of subRPE deposits precursors in association with induction of mitochondrial dysfunction, specific cytosolic signaling cascades and biochemical mediators of deposits. Treatment with the mitochondria-protective drug, elamipretide (MTP-131) reversed pre-existing HQ-induced mitochondria dysfunction, associated biochemical responses and deposits. Similarly, in the ApoE4 mouse model of deposits, initiation of high fat diet in old mice exacerbated mild pre-existing age-related mitochondria dysfunction, resulting in activation of similar signaling cascades and deposit mediators observed in the acute model. Further, mitochondrial dysfunction, subRPE deposits and diminished ERG responses observed in the ApoE4 deposit model were reversed by elamipretide. Mitochondrial dysfunction may contribute to deposit formation and diminished vision in dry AMD, and mitochondria-targeting drugs may be therapeutic.

AMD Genetics – Moving Beyond Disease Associations Toward Novel Therapeutics and Biomarkers

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ABSTRACT: Genetic studies, including large-scale genome-wide association studies (GWAS), have pinpointed more than 25 distinct loci that likely harbor variants that influence risk of AMD. However, the biological underpinnings of these associations are poorly understood. Moreover, these associations account for no more than one-half of the genetic liability for the disorder. In the absence of good model systems for AMD, experiments involving retinal tissue and RPE obtained from fresh donor eyes that are carefully characterized with respect to AMD are a direct approach to identify novel loci and study the effects of genetic and epigenetic determinants of AMD. Toward this end, joint analysis of genomic, transcriptomic, and methylomic data using bioinformatics approaches can help identify the targets of DNA sequence variants (which may be located elsewhere in the genome) as well as determine the impact of disease risk variants on gene expression and AMD-related pathophysiology in the tissues impacted by AMD. Recognizing that AMD is not one disease (i.e., neovascular, atrophic AMD including dry AMD and geographic atrophy) and the growing number of AMD biological pathways, multiple therapies each targeting a specific disease pathway will be needed. Studies of genes and variants underlying AMD clinical subtypes and endophenotypes (derived perhaps from detailed eye exam) may uncover mechanisms and clues about treatment that are specific to classes of patients. Systems biology approaches which integrate genetics, 'OMICs, biological pathways and detailed clinical and environmental risk factor data can be applied to derive patient subtypes, which can better inform clinical trials and biomarker studies and form the basis of personalized medical approaches. Examples of these approaches from studies of AMD and other disorders will be presented.

The Potential of Immunotherapy for Treating AMD

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ABSTRACT: The IL-1 family of cytokines is a group of complex interleukins with a diverse range of functions that can either overlap or diametrically oppose each other. Two IL-1 family members, IL-1beta and IL-18, are cleaved from immature zymogens into potent mature cytokines by inflammasomes through activation of caspase-1. During investigations into a role for NLRP3 in AMD, we found that one of these cytokines, IL-18, has anti-angiogenic and anti-vascular permeability properties. We have shown that intra-vitreous (IVT) injection of IL-18 can inhibit the formation of choroidal neovascularization in a laser-induced mouse model. Furthermore, IL-18 administered IVT at time of laser-burn can inhibit the formation of grade 4 neovascular lesions in a non-human primate laser-induced choroidal neovascularization model with no apparent adverse effects. To date we have shown that IL-18 can rescue VEGF-induced vascular permeability and appears to specifically downregulate both the production of VEGF itself and the expression of its receptor VEGFR2. We continue to research the mechanisms underlying these properties of IL-18 and are investigating other IL-1 family cytokines for similar functions.

Gut Microbial Alterations in Advanced Age-related Macular Degeneration

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ABSTRACT:

Authors: Phoebe Lin, M.D., Ph.D.; Scott M. McClintic, M.D.; Mohamed Saleh, M.D.; Christina Metea; Kevin Mitio; Jennifer Maykoski; Tammy Martin, Ph.D.; Michael L. Klein, M.D.

Purpose: The collection of microorganisms that co-exist commensally in the human gastrointestinal tract, known as the gut microbiome, has been implicated in many extraintestinal inflammatory diseases likely due to the interaction between the gut microbiota and the vast immune system present in the gut. Many inflammatory factors have been implicated in the pathogenesis of age-related macular degeneration (AMD) including complement pathway proteins and inflammasome components. The purpose of this study was to evaluate the relationship between advanced AMD phenotypes and genotypes and specific alterations in the composition of the gut microbiome.

Methods: Patients aged 18-100 years with advanced AMD (cases: geographic atrophy [GA] and/or choroidal neovascularization [CNV]) and without AMD (controls) were recruited between August 24, 2015 to April 5, 2016 at the Casey Eye Institute. AMD risk allele genotyping was obtained for cases and controls. All subjects were asked to complete a questionnaire detailing their pertinent medical and dietary history, including the use of AREDS supplements. Amplification of the 16S small subunit rRNA gene was performed on DNA extracted from stool, using universal primers 515F/806RB and sequenced on the Illumina MiSeq. The sequences were processed using scripts implemented through the workflow package Quantitative Insights Into Microbial Ecology (QIIME) (v1.9.0). Operational taxonomic units (OTUs) were picked with open reference OTU-picking using uclust against the greengenes reference database (gg_13_8). Differentially abundant OTUs between groups were determined using the Galaxy Linear Discriminant Analysis Effect Size (LEfSe) program with multiple comparisons adjusted p value of < 0.05 considered differentially abundant.

Results: Eighty-five participants with advanced AMD and 49 controls participated in the study. Baseline characteristics differed in terms of age (mean age 82.5 vs. 76.4 years, $p < 0.0001$), use of AREDS (83% vs. 8%, $p < 0.0001$), and the presence of ≥ 1 co-morbidity that might affect the gut microbiota (60% vs. 43%, $p = 0.06$). Other demographics such as gender and concomitant obesity did not differ between cases and controls. Results of the LEfSe analysis revealed 9 differentially abundant bacterial genera among advanced AMD patients compared to controls, of which 5 were more abundant in AMD: Prevotella, Bacteroidales S24-7, Rikenellaceae Alistipes, Synergistaceae, and Enterobacteriaceae. Additionally, GA appeared to be associated with an elevated abundance of Rikenella and Lachnobacteria, among 4 others, or, a decrease in abundance of Butyricoccus and Faecalibacterium. On the other hand the presence of CNVM in AMD was associated with elevated Bifidobacterium. Finally, the CC risk allele of CFH snp rs1061170 was associated with increased Fusobacterium and Lachnobacterium, whereas the ARMS2 TT genotype was associated with increased abundance of 12 different bacteria (including Clostridiales and Lachnospiraceae).

Conclusions: There appears to be a relatively small cohort of gut microbiota associated with advanced AMD phenotypes, some of which may be driven by genotype differences. The confounding effects of age and AREDS supplementation on the microbial differences cannot be excluded. These findings may lead to a novel understanding of the pathogenesis of AMD and potentially reveal new targets for therapeutic modulation of this sight threatening disease.



Invited Participant Biographies



T. Keith Blackwell, MD, PhD



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Dr. Blackwell earned a BS in Chemistry from Duke University and was a student in the MSTP MD-PhD program at Columbia University College of Physicians and Surgeons. He performed his graduate work with Dr. Frederick Alt, studying antigen receptor gene assembly. Subsequently, he completed a postdoctoral fellowship at Fred Hutchinson Cancer Research Center with the late Harold Weintraub, studying protein-DNA recognition. From working on *C. elegans* transcription regulators, Dr. Blackwell became interested in that system, eventually devoting his laboratory to studying stress responses, aging, and metabolic regulatory mechanisms in *C. elegans*. In 1993, Dr. Blackwell joined the Harvard Medical School faculty and, since 2004, has worked at the Joslin Diabetes Center, where he is an Associate Research Director.

Stephen A. Burns, PhD



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Dr. Burns earned a BS in Engineering from Lehigh University and a PhD in Biophysics from the Ohio State University. Currently a Professor of Optometry at Indiana University, Dr. Burns is a fellow of three societies--the Optical Society of America (OSA), the Association for Research in Vision and Ophthalmology (gold), and the American Academy of Optometry. Dr. Burns is a former Chair of OSA's Medical Optics Division (1991) and member of OSA's Board of Directors. He also formerly chaired the ARVO VI program panel and served as Vice Chair of AAO's Visual Science membership committee. He is the past Editor-in-Chief of the *Journal of the Optical Society of America*, and is currently on the Editorial Board of *Vision Research*. Dr. Burns also has served on numerous panels, including the NIH Biology and Diseases of the Posterior Eye Study Section and the FDA's Panel on Ophthalmic Devices.

Dr. Burns' research involves the effects of aging and disease on the human retina. To pursue these research interests he develops state-of-the-art retinal imaging technology using adaptive optics. This technology, derived from astronomy, allows the optical imperfections of the eye (optical aberrations) to be bypassed using modern optical techniques, and his laboratory is able to image individual cells in the living human retina in real time. He uses the technology developed in his lab to investigate the effect of disease on the visual system. In recognition of his contribution to vision science, OSA awarded him the Tillyer Award in 2010.

Kip Connor, PhD



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Dr. Connor is an Assistant Professor of Ophthalmology at Harvard Medical School, Massachusetts Eye and Ear in Boston. He earned his PhD degree from Albany Medical College in 2005 and completed his postgraduate studies in the Department of Ophthalmology at Harvard Medical School, Boston Children's Hospital from 2005 to 2010. As a postdoctoral fellow, his work addressed the effect of dietary intake of omega-3 polyunsaturated fatty acids on disease severity in a mouse model of oxygen-induced retinopathy. In 2010, Dr. Connor was recruited to Mass. Eye and Ear, as a principal investigator. His laboratory currently examines the role of immunity and inflammation using animal models of ocular diseases, such as age-related macular degeneration and retinopathies (diabetic retinopathy and retinopathy of prematurity), as well as neurodegeneration that can occur as a result of retinal detachment.

One major area of investigation in Dr. Connor's laboratory is concentrated on defining the role of the innate immune system in the immunoprivileged retina and how it functions to maintain retinal tissue homeostasis in development and disease. One arm of this work is centered on the role of the complement system in different ocular disease pathologies (vascular pathologies and in neurodegeneration). The complement system is an intricate innate immune surveillance pathway that is able to discriminate between healthy host tissue, diseased host tissue, apoptotic cells, and foreign invaders, while modulating the elimination and repair of host tissue. Consisting of serum and tissue proteins, membrane-bound receptors, and a number of regulatory proteins, the complement system is a hub-like network that is tightly connected to other systems. Within the ocular microenvironment, the alternative complement pathway exhibits low levels of constitutive activation to ensure the intermittent probing of host self cells, which express inhibitors of complement for protection from activation. The other arm of the laboratory's work seeks to assess the role of cytochrome P450 derived lipid biometabolites in their regulation of inflammation during neovascular diseases. To date his laboratory has identified several novel bioactive metabolites involved in the resolution of pathological blood vessel growth, a hallmark of late stage neovascular AMD.

Scott W. Cousins, MD



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Dr. Cousins is the Robert Machemer, MD Professor of Ophthalmology and Immunology, Vice Chair for Research, and Director of the Duke Center for Macular Diseases at Duke Eye Center. As Vice Chair, he oversees all basic science research as well as the Ophthalmology Clinical Research Unit, which administrates both industry-sponsored and investigator-initiated clinical research at the Duke Eye Center. Dr. Cousins is also Medical Director of Hospital-Based Imaging and Procedures for Duke Eye Center.

Dr. Cousins is a retina-trained ophthalmologist who specializes in the diagnosis and treatment of macular diseases, especially age-related macular degeneration (AMD), diabetic retinopathy, and retinal vascular diseases. He is active in both clinical and laboratory research. In his clinical practice, Dr. Cousins is involved in many trials and innovative therapies for the treatment of macular diseases, especially AMD and diabetic retinopathy. He has served as site PI for numerous phase 1-3 clinical trials in AMD, diabetic retinopathy, and other retinal disorders. He has served as a consultant or member of data safety monitoring committees (DSMC) for numerous pharmaceutical and biotechnology startup companies.

In his scientific laboratory, Dr. Cousins pursues both NIH-funded and industry-funded research, which is focused primarily on AMD. In particular, he is studying the pathogenesis of the early form of AMD and working to advance understanding how environmental toxicants and exposures promote dysfunction and injury of the retinal pigment epithelium (RPE) and formation of deposits (drusen) under the RPE. Currently, he is studying RPE mitochondrial dysfunction as a novel paradigm for the development of early AMD. His program is also developing blood tests and new imaging technologies for the identification of patients who are at high risk for AMD and for progression to advanced disease.

Dr. Cousins has published over 100 peer-reviewed manuscripts, book chapters, and other publications addressing topics of research or clinical care of retinal disease, especially AMD. In 2006, Dr. Cousins was awarded the prestigious Alcon Research Foundation Clinician Scientist Award. In 2008, the National Institutes of Health invited him to join the National Advisory Eye Council. Dr. Cousins is also a member of the American Academy of Ophthalmology, the American Society of Retina Specialists, the Retina Society, the Association for Research in Vision and Ophthalmology, the American Association of Immunologists, and the American Medical Association.

In 2010, Dr. Cousins was named one of the "Top 34 Ophthalmologists in the United States" by Becker's ASC Review, a leading source of business and legal news for ambulatory surgery centers. They cited his leadership of the Duke Center for Macular Diseases and his ongoing research in macular degeneration among his distinguishing contributions.

Christine A. Curcio, PhD



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Dr. Curcio is Professor of Ophthalmology, Eminent Scholar in Retina, and Director of the AMD Histopathology Lab at the University of Alabama at Birmingham. Capitalizing on the Alabama Eye Bank as a resource, her research focuses on aging and AMD with emphasis on pathobiology, image validation, and transcriptomics. Dr. Curcio has authored more than 125 journal articles, presented at vision meetings yearly since 1985, and given over 175 invited lectures at major meetings, congresses, and universities in US and international venues. Dr. Curcio serves on the editorial boards of *Investigative Ophthalmology & Visual Science* and *Progress in Retinal and Eye Research* as well as the Disease and Pathology of Visual Study Section. Her research has been funded by the National Eye Institute, National Institute on Aging, Research to Prevent Blindness, International Retinal Research Foundation, Edward N. and Della L. Thome Memorial Foundation, Arnold and Mabel Beckman Initiative for Macular Research, Macula Vision Research Foundation, Macula Foundation, Macula Society, and industry. Scientific contributions include documenting that rods die before cones in aging and AMD (1990-present; with C. Owsley and G.R. Jackson); discovering, characterizing, and contextualizing a large age-related accumulation of lipoprotein particles of intra-ocular origin in human Bruch's membrane that constitutes the largest volumetric pathway in drusen (with M. Johnson, N. Dashti, B.H. Chung, G. Malek, C. Guidry; 1998-2011); characterizing AMD-specific lesions, including basal linear deposits (1999-present) and sub-retinal drusenoid.

Robert D'Amato, MD, PhD



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Robert D'Amato earned his BA, MD, and PhD from Johns Hopkins University. He completed his Ophthalmology residency at Harvard Medical School, and then went on to a postdoctoral research fellowship in the Folkman laboratories from 1992 to 1994. He has been an independent investigator at Boston Children's Hospital, Harvard Ophthalmology since 1994. He is credited with the discovery of the anti-angiogenic class of thalidomide based compounds currently used to treat cancer.

Dr. D'Amato's current research focuses on the genetic control of angiogenesis and the development of new therapeutic agents, especially for the treatment of eye disease. His laboratory is exploring the role of genetics in determining an individual's angiogenic responsiveness. He has found that different strains of inbred mice have an approximately 10-fold range of response to growth factor stimulated angiogenesis in the corneal micropocket assay. These results suggest the presence of genetic factors that control individual angiogenic potential. He recently has completed a genome wide association study in a diverse group of recombinant inbred mouse strains and identified numerous strongly associated candidate genes, which are now being validated. By elucidating the genetic determinates of angiogenic responsiveness within inbred mouse strains, he hopes to further understand the factors that regulate ocular angiogenesis in humans.

Patricia A. D'Amore, PhD, MBA



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Patricia A. D'Amore earned her PhD in Biology from Boston University in 1977, and completed a postdoctoral fellowship at Johns Hopkins Medical School. In 1987, she obtained an MBA from Northeastern University. She is a Research Associate in Surgery and a long-standing member of the Program in Vascular Biology at Children's Hospital Boston. In 2012, she became the Charles L. Schepens Professor of Ophthalmology and in 2013, Professor of Pathology at Harvard Medical School. She is an elected Member of The Academy at Harvard Medical School. She is also a Gold Fellow in the Association for Research in Vision and Ophthalmology (ARVO).

Dr. D'Amore's research concentrates on understanding the regulation of microvascular development and stabilization. Additionally, she is investigating the pathogenesis of age-related macular degeneration (AMD), with a focus on inflammation. As an international expert in vascular growth and development, Dr. D'Amore has been at the forefront of angiogenesis research for over three decades. In collaboration with a group of researchers from Harvard Medical School (HMS) and Mass. Eye and Ear, she contributed to the scientific foundation for anti-VEGF therapies – for this work, the group received the 2014 António Champalimaud Award. Her laboratory also developed a mouse model of oxygen-induced retinopathy, which is widely used for investigations of vascular development and preclinical studies of vascular-targeting agents. She has also revealed important physiological roles of VEGF, yielding insight into the safe use of anti-angiogenic therapies. Her current research interests are two-fold and focus on the role of the endothelial glycocalyx in the regulation of endothelial-leukocyte interactions, and the role of inflammation and lipid handling by the retinal pigment epithelium in the pathogenesis of AMD.

Dr. D'Amore has published more than 150 peer-reviewed papers, 72 reviews, and edited or co-edited four books. She is the recipient of the Alcon Research Award, the Cogan Award from the Association for Research in Vision and Ophthalmology, the A. Clifford Barger Excellence in Mentoring Award from HMS, the Everett Mendelsohn Excellence in Mentoring Award from Harvard University, the Rous-Whipple Award from the Society of Investigative Pathology, the Endre A. Balazs Award from the International Society for Eye Research, and the 2015 Proctor Medal from the Association for Research in Vision and Ophthalmology. Recently, she was a recipient of the 2016 William Silen Lifetime Achievement in Mentoring Award from HMS.

Margaret M. DeAngelis, PhD



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Dr. DeAngelis is currently a Professor at the University of Utah School of Medicine and has focused her career on vision research since 1999, when she received a post-doctoral fellowship training grant on macular degeneration as part of the Molecular Basis of Eye Disease program at Harvard Medical School. Working in collaboration with clinician scientists (including Drs. Ivana Kim and Joan W. Miller) throughout her career, she has recruited, ascertained, and developed large patient populations of both families and unrelated case-controls to study the genetic and epidemiologic underpinnings of both common and rare ophthalmic conditions. Specifically, the DeAngelis group utilizes a systems-biology based approach to pinpoint disease causality. To this end, utilizing both families and then replication in unrelated case-controls to study DNA, gene expression and protein coupled with epidemiological information, her group has identified novel genes and pathways associated with common diseases including age-related macular degeneration (AMD) (*RORA*, *ROBO1*, *CYP24A1*) and then replicated these findings in diverse patient populations. *RORA*, an intracellular target of cholesterol, was shown to interact with other established AMD genetic risk factors (*ARMS2/HTRA1*) thus furthering the development of a unifying hypothesis underlying AMD pathophysiology. The laboratory also continues to recruit and characterize ethnically diverse populations throughout the world in an effort to understand the origin and significance of genetic variation, environmental factors and diseases that co-occur with other blinding eye diseases. The creation of well characterized fresh donor eye repository by Dr. DeAngelis to study diseases including AMD and glaucoma has enabled her laboratory to employ and develop multi-omic approaches, including RNASeq, allele specific expression, epigenetic, and bioinformatic tools to delineate disease mechanism. This is done in an effort to develop appropriate preventive and therapeutic targets for these devastating forms of blindness. Recent work from the DeAngelis lab identifying Vitamin D pathway genetic risk variants in AMD has resulted in clinical trials for age-related macular degeneration. Dr. DeAngelis serves on the senior executive committee/steering committee for the International AMD Genomics Consortium sponsored by NEI/NIH. Dr. DeAngelis is also committed to teaching and mentoring the next generation of scientists and clinician scientists and she is a mentor and advisor to undergraduate, graduate, medical students, fellows and junior faculty. Dr. DeAngelis has over 60 peer reviewed publications, book chapters and reviews. She serves on several editorial boards, national and international grant review panels. Her work has been generously funded by the NEI, ALSAM Foundation, Skaggs Research Foundation, the Bank of America/Thome Memorial Fund, Carl Reeves Foundation, Macular Degeneration Foundation and Center of Aging, Division of Geriatrics, University of Utah.

François Delori, PhD



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Dr. Delori obtained his PhD in physics from Imperial College in London in 1972 and has worked at the Schepens Eye Research Institute since 1980. His interests include the optical properties of ocular tissues, light damage to the retina, and the role of macular pigment and of RPE lipofuscin in age-related retinal degeneration and other retinal degenerations. Dr. Delori's field of expertise is the "noninvasive" testing and imaging of the retina. He uses reflectometry and fluorophotometry to obtain quantitative information about many important biological parameters (oxygen levels in retinal vessels, blood flow, diffusion of nutrients, and quantity of pigments). Dr. Delori has pioneered novel imaging techniques of the retina and has developed advanced optical techniques to study the role of lipofuscin and melanin pigments in the retinal pigmented epithelium as well as new modalities to measure the distribution of macular pigment.

Sarah L. Doyle, PhD



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Dr. Doyle's scientific interests focus on the molecular dialogue associated with how the immune system recognizes injury, reacts, and directs an inflammatory response to resolve insult. Having trained with Professor Luke O'Neill, she is specifically interested in elucidating the cellular mechanisms and signaling events that regulate the effects of Pattern Recognition Receptor (PRR) responses, in particular the TLRs and NLRs of the innate immune system to both pathogen-derived and endogenous damage-associated immunomodulators. During her postdoctoral fellowship, she worked with Professor Terje Espevik's group in NTNU, Norway to learn confocal microscopy techniques, which enabled her to link her work in Trinity on immune cell-signaling with TLR cellular-localization studies. By identifying molecules involved in the signaling pathways initiated upon immune receptor activation and understanding the underlying mechanisms of how signaling intermediates interact in both health and disease, she aims to uncover new targets for therapeutic manipulation. The present understanding of cellular innate immune regulation of retinal diseases is in its infancy, and for the last six years, she has applied her knowledge of inflammation research to the field of AMD with the hope of uncovering novel therapeutic targets that can be rapidly translated into new medicines. To date, she has published basic and translational feasibility studies on the potential for immunotherapy for "wet" AMD in *Nature Medicine* 2012, *Science Translational Medicine* 2014, and *IOVS* 2015. She is presently investigating strategies for the use of immune-modulators in the clinical setting.

Steve J. Elledge, PhD



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Dr. Elledge is the Gregor Mendel Professor of Genetics and Medicine in the Department of Genetics at Harvard Medical School and the Division of Genetics at the Brigham and Women's Hospital and is a Howard Hughes Medical Institute Investigator. He received his BS in chemistry from the University of Illinois in 1978 and his PhD degree in biology from the Massachusetts Institute of Technology in 1983. He is a member of the National Academy of Sciences, National Academy of Medicine, and American Academy of Arts and Sciences. He has been the recipient of many awards including the 2010 Dickson Prize, 2013 Lewis S. Rosenstiel Award for Distinguished Work in the Basic Medical Sciences and the 2013 Gairdner Foundation International Award. In 2015 he received the Abert Lasker Basic Medical research Award. Dr. Elledge's research interests center on the study of proteins that sense and respond to DNA damage and regulate the cell division cycle and cancer. He uncovered what is now known as the DNA Damage Response. More recently Dr. Elledge has developed immunological methods such as VirScan that allow the genome-wide detection of antiviral antibodies from a single drop of patient blood to determine the history of viral exposure.

Lindsay A. Farrer, PhD



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Lindsay A. Farrer is the Boston University Distinguished Professor of Genetics, Chief of the Biomedical Genetics Division, and Professor of Medicine, Neurology, Ophthalmology, Epidemiology and Biostatistics. He is also the Director of the BU Transformative Training Program in Addiction Science and BU Molecular Genetics Core Laboratory. He earned a Bachelor's degree in population biology from the University of North Carolina at Chapel Hill, received his PhD in medical genetics from Indiana University School of Medicine, and completed postdoctoral training at Yale University. Dr. Farrer is a Founding Fellow of the American College of Medical Genetics. He has published more than 350 papers based on his research, which is currently focused on the genetics of several common and complex disorders including age-related macular degeneration (AMD), Alzheimer disease (AD), and substance use disorders (including cocaine, opioids, alcohol, cannabis, and nicotine). His research utilizes many state-of-the-art genomics approaches including genome-wide association studies, next generation sequencing (whole genome, whole exome, and targeted gene), RNA sequencing, and functional experiments in cultured cells and various tissues, such as leukocytes, brain and eye.

Dr. Farrer's research team identified a functional variant in the complement factor H gene, which accounts for as much as 35% of the attributable risk for AMD, the most common cause of blindness in the elderly. Findings from a study he conducted in collaboration with Dr. Margaret DeAngelis using a systems biology approach suggest that distinct *ROBO1* variants may influence the risk of wet and dry AMD, and the effects of *ROBO1* on AMD risk may be modulated by *RORA* variants. Dr. Farrer pioneered genetic studies of AD in African Americans and pre-clinical AD-related changes in the brain. His laboratory was instrumental in the efforts leading to the cloning of the presenilin and nicastrin genes which were subsequently shown to have central roles in AD pathogenesis. His group demonstrated that *SORL1* and other genes involved in protein trafficking are genetically and functionally associated with AD thus establishing intracellular trafficking as one of the major pathways leading to AD. Dr. Farrer's group has shown that genes encoding proteins and subunits for calcium and potassium channels involved in neuronal signaling are strongly associated with addiction to cocaine, opioids, and cannabis. Dr. Farrer has a major role in several large consortium projects. He co-directed data analyses for the International AMD Genetics Consortium leading to the discovery of seven novel AMD susceptibility loci. He also co-directs analyses for the US Alzheimer Disease Genetics Consortium and is a PI of the Alzheimer Disease Sequencing Project.

Silvia C. Finnemann, PhD



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Dr. Finnemann received her diploma and PhD in biochemistry from the Free University of Berlin in Germany and completed postdoctoral training in cell biology at Weill Cornell Medical College in New York, NY. Currently, she is Professor of Cell Biology in the Department of Biological Sciences at Fordham University in the Bronx, NY. Dr. Finnemann's research aims to identify the cellular-molecular mechanisms used by the retinal pigment epithelium (RPE) to support photoreceptor neurons in the healthy mammalian retina and their defects in age or disease. Projects explore animal and cell models that share mechanisms and molecules with those in human retina. Her work has identified central molecular pathways governing outer segment renewal—a fundamental retinal process that is essential for vision and that involves constant collaboration of photoreceptors and neighboring RPE cells. Recent studies from her laboratory have demonstrated circadian phospholipid changes in photoreceptors that occur in part in response to functional interactions with the RPE and that cause synchronized shedding of distal outer segment tips, which in turn triggers ligation of two distinct RPE surface receptors whose downstream signaling pathways synergize to promote shed tip phagocytosis.

K. Bailey Freund, MD

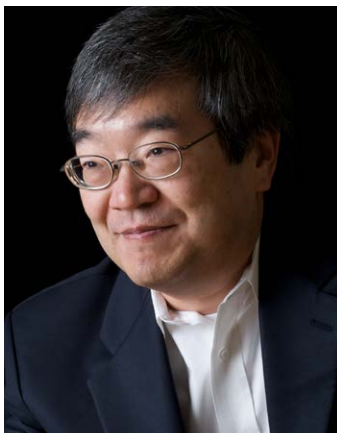


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Dr. Freund specializes in all retinal disorders including macular degeneration, diabetic retinopathy, and retinal vascular diseases and is an expert in difficult-to-diagnose and rare conditions. He has initiated and conducted many clinical trials for treatments for retinal diseases. Dr. Freund is a Clinical Professor of Ophthalmology at New York University School of Medicine. He is a senior partner at Vitreous Retina Macula Consultants of New York. He is an attending surgeon at Manhattan Eye, Ear and Throat Hospital and New York Presbyterian Hospital. Dr. Freund is a member of the Retina Society, Macula Society, and the American Society of Retina Specialists. He is on the Editorial Board of the journal *Retina* and is an Associate Editor for *Retinal Cases & Brief Reports*. He has authored over 260 peer-reviewed scientific manuscripts and has written numerous book chapters. He has received numerous awards including the prestigious Young Investigator Award from the Macula Society. He is a graduate of Williams College and the New York University School of Medicine and completed his residency training in general ophthalmology and fellowship in medical and surgical retina at the Manhattan Eye, Ear, and Throat Hospital. Dr. Freund is also a prominent collector of vintage magic apparatus.

James Fujimoto, PhD



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Dr. Fujimoto is the Elihu Thomson Professor of Electrical Engineering and Computer Science at MIT. His group and collaborators were responsible for the invention and development of OCT. Dr. Fujimoto's group performs research in OCT technology and applications to ophthalmology, endoscopy and oncology. He is a member of the National Academy of Science and National Academy of Engineering.

Evangelos S. Gragoudas, MD



*Charles Edward Whitten Professor of Ophthalmology,
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Dr. Gragoudas is the Charles Edward Whitten Professor of Ophthalmology at Harvard Medical School and Director of the Retina Service at Mass Eye and Ear. A prolific clinician scientist, Dr. Gragoudas has published over 250 articles in peer-reviewed journals and authored more than 100 chapters, reviews, and books. Dr. Gragoudas is considered a world authority on the diagnosis and management of intraocular tumors. He pioneered the use of proton therapy in eye tumors, a treatment modality that has been proven to be extremely successful and is used in many ocular oncology centers around the world. Dr. Gragoudas' second major contribution to Ophthalmology is the use of photodynamic therapy (PDT) for the treatment of AMD. He collaborated with Dr. Joan W. Miller on preclinical studies of PDT and, based on large clinical trials, photodynamic therapy became the first widely used treatment for neovascular AMD. Dr. Gragoudas' third major contribution to Ophthalmology has been his work on ocular angiogenesis and anti-angiogenesis therapy. He worked with a group of ophthalmologists, including Drs. Miller, Tony Adamis, Patricia D'Amore, and others to demonstrate the critical role of vascular endothelial growth factor (VEGF) in ocular neovascularization, and went on to develop therapies targeting VEGF. In 2014 Dr. Gragoudas and his colleagues received the Champalimaud Vision Award for their work on using anti-angiogenesis drug therapy for the treatment of age-related macular degeneration. This award is considered the "Nobel Prize" in Vision Research. Dr. Gragoudas has received numerous honors and awards, including: Academy Honor Award of American Academy of Ophthalmology; Retina Research Foundation prize of the Jules Gonin Lectureship; Research to Prevent Blindness Senior Scientific Investigator Award; Senior Achievement Award of American Academy of Ophthalmology; J. Donald M. Gass Medal of the Macula Society; the Arnall Patz Medal of the Macula Society; and Mildred Weisenfeld Award for Excellence in Ophthalmology from the Association for Research in Vision and Ophthalmology.

Gökhan S. Hotamisligil, MD, PhD



*James S. Simmons Professor of Genetics and Metabolism
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Harvard University, Chan School of Public Health
Director, Sabri Ülker Center for Metabolic Research*

Harvard-MIT Broad Institute, Harvard Stem Cell Institute
Joslin Diabetes Center

Dr. Hotamisligil focuses his research on the genetic basis of common and complex diseases, particularly obesity, diabetes, and heart disease. His research examines the molecular mechanisms of nutrient sensing and response pathways as they relate to immune and metabolic homeostasis. An internationally recognized leader, he has made several seminal contributions to the field. In particular, he defined immunological components of obesity, which led to the emergence of the field of immunometabolism; discovered novel hormones regulating lipid and glucose metabolism; and identified endoplasmic reticulum as a key organelle regulating cellular and organismic metabolism, and its role in obesity, insulin resistance, and diabetes. Dr. Hotamisligil pursues interdisciplinary paths, collaborations, and industry alliances towards development of novel preventive and therapeutic strategies against chronic metabolic diseases. His work has resulted in more than 180 papers which have received over 40,000 citations and resulted in multiple patents. Dr. Hotamisligil has been recognized with many fellowships and awards including Markey, Pew, and AAAS Fellowships, the Outstanding Scientific Accomplishment Award of ADA, Wertheimer Award from IASO, Koç Science Award, Roy Greep Award of Endocrine Society, and the International Danone Prize. He is also a member of the Board of trustees of the Kadir Has University. Dr. Hotamisligil earned his MD from Ankara University, and PhD from Harvard University

Deeba Husain, MD



*Associate Professor of Ophthalmology, Harvard Medical School
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Dr. Husain completed her medical training at Jawaharlal Nehru Medical College, Aligarh, India. Next, she pursued completed postdoctoral research on photodynamic therapy and age-related macular degeneration with Evangelos Gragoudas, MD, and Joan W. Miller, MD, at Mass. Eye and Ear, Harvard Ophthalmology. She subsequently completed an Ophthalmology residency at Harvard and subspecialty training in retina at Mass. Eye and Ear. For 10 years, she worked at Boston University School of Medicine, where she directed the Retina Service and the retina fellowship training program. She joined the faculty at Harvard Ophthalmology in 2013, and is now Associate Professor in Ophthalmology. She also is a full-time member of the Mass. Eye and Ear Retina Service and Director of Mass. Eye and Ear, Retina Consultants. As an Investigator in the Angiogenesis Laboratory, she primarily conducts translational research pertaining to diseases of the retina, with an emphasis on novel biomarkers for age-related macular degeneration.

Ivana K. Kim, MD



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After earning her MD from Harvard Medical School, Dr. Kim completed an ophthalmology residency at Harvard and vitreoretinal fellowship at Massachusetts Eye and Ear. As a retina specialist on the Mass. Eye and Ear Retina Service, she maintains a busy surgical and medical retina practice that focuses on age-related macular degeneration (AMD) and uveal melanoma. She also is a principal investigator for several multi-center—as well as investigator-sponsored—clinical trials involving treatments for AMD, uveal melanoma, and other retinal diseases. Dr. Kim has a long-standing collaboration with Drs. Margaret DeAngelis and Joan W. Miller studying the genetics of AMD utilizing a cohort of extremely discordant sibling pairs. Genetic, biochemical, and epidemiologic data on these sibpairs has been used to investigate gene-environment interactions, perform candidate gene analyses, and analyze gene expression profiles with the goals of further elucidating the etiology of AMD and identifying potential biomarkers of the disease. In addition to confirming previously established genetic risk factors for AMD, they have described novel associations in genes such as *RORA*, *ROBO1*, and *CYP24A1* that may be important in AMD pathogenesis. Current studies include deep sequencing to identify rare variants and analyses of ethnically diverse populations as well as expression analysis in ocular tissues. Aside from AMD, Dr. Kim's research also involves studying the molecular genetics of uveal melanoma in hopes of identifying particular pathways that could serve as targets for new drug therapies.

James Kirkland, MD, PhD



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James L. Kirkland, MD, PhD, is the Director of the Robert and Arlene Kogod Center on Aging at Mayo Clinic and Noaber Foundation Professor of Aging Research. Dr. Kirkland's research is on cellular senescence, age-related adipose tissue and metabolic dysfunction, and development of agents and strategies for targeting fundamental aging mechanisms to treat age-related chronic diseases and disabilities. He recently published the first article about drugs that clear senescent cells – senolytic agents. He is a scientific advisory board member for several companies and academic organizations. He is a member of the National Advisory Council on Aging of the National Institutes of Health, past chair of the Biological Sciences Section of the Gerontological Society of America, and a member of the Board of the American Federation for Aging Research. He holds honorary appointments at Boston University and the University of Groningen in the Netherlands. He is a board certified specialist in internal medicine, geriatrics, and endocrinology and metabolism.

Phoebe Lin, MD, PhD



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Phoebe Lin is an Assistant Professor of Ophthalmology, vitreoretinal surgeon, and uveitis specialist at the Casey Eye Institute in Oregon Health & Science University. She earned a biochemistry degree from Washington University and MD/PhD degrees from the University of Illinois. After completing an ophthalmology residency at the University of California, San Francisco, she went to Duke University for a two-year fellowship in vitreoretinal surgery followed by a one-year uveitis fellowship at the Casey Eye Institute. She is the author of 39 peer-reviewed articles, five chapters, and 28 abstracts on the topics of immunology, ocular inflammation, and retinal diseases. At Casey Eye Institute, she runs a basic science laboratory, investigating novel mechanisms and therapeutics of animal models of uveitis with the support of NEI K08 and RPB CDA funding. She also teaches residents, retina and uveitis fellows, and medical students.

G rard Lizard, PhD



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Dr. Lizard is an INSERM scientist. After seven years as a postdoctoral researcher in pharmaceutical companies (1984-1991), he was recruited as an engineer-researcher by INSERM in 1991. He is currently head of research at INSERM. He was Associate Director of the Team Metabolic Biochemistry and Nutrition (INSERM Research Center 866 - Lipids, Nutrition, Cancer - Dijon) from 2006 to 2012. Since 2012, he is Director of the team 'Biochemistry of the Peroxisome, Inflammation and Lipid Metabolism'. He has strong experiments in the characterization of the side effects (induction of cell death, activation of inflammatory and oxidative processes) triggered by biological agents and chemicals, especially lipids (cholesterol oxide derivatives (oxysterols), fatty acids) on various cellular models, and in cell signalization. He is the co-founding member of ENOR (European Network on Oxysterols Research). He has important experiment in clinical studies as principal or secondary investigator. He is involved in technical transfer in flow cytometry (antigenic analysis, cell cycle analysis, functional tests, multiplexed analyses) towards various INSERM Units, University hospitals (France and abroad), especially Universities of North Africa (Tunisia, Morocco). In the field of flow cytometry, he is now involved in the development of methods in nanotoxicology. He has a strong background in the identification of lipid biomarkers in various age related diseases and neurodegenerative diseases, and is working now on the part taken by the peroxisome in various diseases and ageing processes.

William Mair, PhD



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Ageing is a universal trait that is observed across the evolutionary spectrum. From a public health perspective, the ageing human population and the resultant increase of disease burden suffered by the elderly is becoming a new pandemic that needs addressing in the 21st century. The Mair laboratory studies the basic biology of the ageing process, driven by the central questions: *Why are we more likely to get chronic diseases when we are old than when we are young? What goes wrong in cells and tissues to increase overall risk, and is this decline inevitable or can we reverse it to bring healthy years to the elderly?* Dr. Mair received his BSc (Genetics) and PhD (Biology) from University College London, and carried out his postdoctoral research at The Salk Institute for Biological Studies, La Jolla, CA. He started his own laboratory at Harvard in 2011.

Joan W. Miller, MD



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Dr. Miller is a vitreoretinal specialist in the Retina Service and Co-director of the Mass. Eye and Ear Angiogenesis Laboratory. As a clinician scientist, her clinical and research interests focus on retinal disorders, including age-related macular degeneration (AMD), retinal degenerations, and diabetic retinopathy.

Dr. Miller was among the first to recognize the role of vascular endothelial growth factor (VEGF) in neovascular eye disease. Her work, conducted in collaboration with Dr. Judah Folkman—a noted anti-angiogenesis proponent—as well as several Harvard Ophthalmology colleagues was the principal demonstration of the critical role VEGF plays in ocular neovascularization. Further studies showed that ocular neovascularization could be suppressed with VEGF inhibitors. For her contributions to the development of anti-angiogenic therapy for retinal disease, Dr. Miller was a co-recipient of the 2014 António Champalimaud Vision Award, the highest distinction in ophthalmology and visual science.

Along with Dr. Evangelos Gragoudas, she is credited with the full translational development of photodynamic therapy with verteporfin (Visudyne®), the first AMD treatment approved by the US Food and Drug Administration and international drug regulatory agencies. Dr. Miller and her colleagues continue investigations to elucidate the pathophysiology of vision loss and improve therapies. Current studies include the genetics of AMD, strategies for early intervention in AMD, and neuroprotective therapies for retinal disease.

An internationally recognized expert in the field of macular degeneration, Dr. Miller was elected to the Academia Ophthalmologica Internationalis membership in 2013. In addition to authoring nearly 200 peer-reviewed papers and over 60 book chapters and review articles, she is a named inventor on 11 US patents and seven Canadian patents. The recipient of numerous awards, Dr. Miller has been recognized with the Rosenthal Award, J. Donald M. Gass Medal, and Paul Henkind Memorial Award (all from the Macula Society); the Retina Research Award (Club Jules Gonin); the Alcon Research Institute Award; the ARVO/Pfizer Ophthalmic Translational Research Award; the Suzanne Veronneau-Troutman Award (Women in Ophthalmology); the Pinnacle Award for Achievement in the Professions (Greater Boston Chamber of Commerce); and more.

A graduate of Massachusetts Institute of Technology, Dr. Miller earned her MD from Harvard Medical School (HMS). Following completion of her ophthalmology residency at HMS, Dr. Miller completed a research fellowship and a clinical fellowship in vitreoretinal surgery at Mass. Eye and Ear. During her career, she has achieved many firsts—first female physician to achieve the rank of Professor of Ophthalmology at HMS, first woman to chair HMS Ophthalmology, and first woman appointed Chief of Ophthalmology at both Mass. Eye and Ear and Massachusetts General Hospital. She also became the first woman to receive the Mildred Weisenfeld Award for Excellence in Ophthalmology, one of ARVO's highest honors, which recognizes distinguished scholarly contributions to the clinical practice of ophthalmology.

Yin Shan Eric Ng, PhD



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For more than 15 years, Dr. Ng has conducted research on the molecular regulation of neovascularization—both in normal development and in pathological conditions. In particular, he has been studying the diverse functional roles of the angiogenic growth factor, VEGF, in normal vasculature as well as in pathological angiogenesis in the eye, both in biotech industry and in academia. By applying basic scientific research approaches in a translational research environment, Dr. Ng has applied new insights of VEGF biology into the creation of therapeutic approaches for treating pathological ocular neovascularization. However, this class of new molecular therapeutics for the main causes of vision loss in the developed world is still in its infancy. Anti-VEGF therapies have been an exciting breakthrough in the treatment of neovascular AMD, but they only restore significant vision in a *minority* of patients. Moreover, the application of VEGF antagonists for diabetic retinopathy and other hypoxia-driven retinal pathologies faces further challenges in terms of safety and co-morbidities. Dr. Ng's aim is to develop a program of biomedical research that will help refine the current use of anti-VEGF therapeutics and define new targets for developing the next generation of pharmacotherapies. His current research projects include identifying novel targets for anti-angiogenesis and anti-inflammation in neovascular AMD, diabetic retinopathy, and retinopathy of prematurity.

Magali Saint-Geniez, PhD



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Dr. Magali Saint-Geniez earned her PhD from the University of Toulouse, France where she trained in vascular research at the ISERM laboratory. In 2002, she joined Schepens Eye Research Institute to pursue postdoctoral training in the laboratory of Dr. Patricia D'Amore. At that time, her research focused on the role of VEGF in ocular development and maintenance of retinal homeostasis. She is now an Assistant Scientist at the Schepens Eye Research Institute and Assistant Professor of Ophthalmology at Harvard. Her current research program focuses on the characterization of novel molecular pathways involved in various retinal degenerative diseases. In particular, she is investigating the underlying pathogenic roles of metabolic dysfunction and oxidative damage in photoreceptors and retinal pigment epithelium, and is evaluating the therapeutic benefits of novel metabolic regulators using multidisciplinary approaches, including mouse model generation and molecular and metabolic biology.

Janet R. Sparrow, PhD



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Dr. Sparrow, PhD is currently the Anthony Donn Professor of Ophthalmic Science and Professor in the Department of Pathology and Cell Biology. Research in Dr. Sparrow's laboratory is directed toward understanding the composition of RPE lipofuscin, the structures and properties of the bisretinoid constituents of lipofuscin, the mechanisms by which these compounds form and the adverse effects of these compounds on photoreceptor cells and RPE. Other investigations explore therapies aimed at reducing bisretinoid accumulation. The bisretinoids of retina are the source of fundus autofluorescence. Thus studies also aim to apply an understanding of RPE bisretinoids to clinical interpretations and measurements of fundus autofluorescence in retinal disease. Taken together, efforts in the laboratory contribute to the elucidation of pathology in several retinal disorders including recessive Stargardt disease, retinitis pigmentosa, pattern dystrophies, bull's eye maculopathy and age-related macular degeneration.

Demetrios Vavvas, MD, PhD



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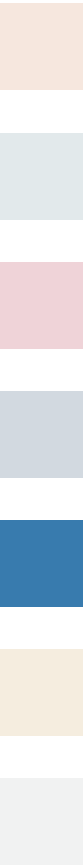
Demetrios Vavvas earned his BSc (First Class Honors) in biology/neurosciences from McGill University and his MD/PhD (*cum laude*) in medicine/physiology at Boston University School of Medicine. Next, he completed an Ophthalmology residency at Harvard, and subsequently served as Chief Resident and Chief Fellow at Mass. Eye and Ear. He joined the Retina Service and Angiogenesis Laboratory at Mass. Eye and Ear, Harvard Ophthalmology as a clinician scientist in late 2007. Since then, he has been studying neurodegeneration and neuroprotection in animal models, and his laboratory has been instrumental in showing redundancy in the cell death pathways involving RIP kinase-mediated cell necrosis and the importance of combinatorial treatment for retinal degenerations. His laboratory also studies the role of energy sensor AMPK in the pathophysiology of the aging eye.





Ephraim Friedman (1930-2011)

Ephraim Friedman Lecture



The 11th Annual Ephraim Friedman Lecture



This lecture honors Dr. Ephraim Friedman (1930-2011), retina specialist and age-related macular degeneration (AMD) researcher. Described by his colleagues as a true Renaissance man, Dr. Friedman was a skilled clinician and surgeon, sculptor, educator, researcher, and administrator.

Drawn to ophthalmology while serving as a captain in the Air Force, Dr. Friedman completed his ophthalmology residency at Harvard Medical School Department of Ophthalmology/Mass. Eye and Ear under Dr. David Cogan in 1961, followed by a research fellowship in the Howe Laboratory of Ophthalmology. As a clinician scientist, Dr. Friedman's scholarly work focused on the circulation of blood in the eye. He developed a vascular model for the pathogenesis of AMD in the late 1960s.

Throughout his career, Dr. Friedman served in leadership positions. He was Dean of Boston University School of Medicine (1970-1974), Dean of Albert Einstein College of Medicine of Yeshiva University (1974-1983), and President of Mass. Eye and Ear (1983-1990). In 2005, Dr. Friedman retired from full-time medicine to spend more time with his family and pursue his artistic passions. Dr. Friedman passed away in June of 2011.

Through this annual lecture, we celebrate Dr. Friedman's extraordinary contributions in teaching, research and service in the field of Ophthalmology and AMD.

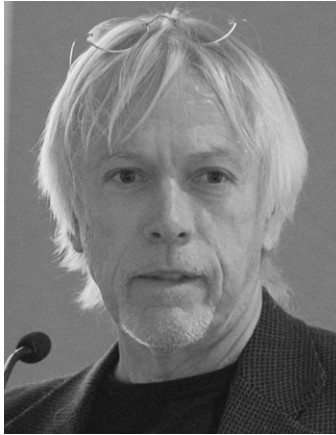
The Ephraim Friedman Lecture is supported by generous gifts from Dr. Friedman's colleagues, friends and family.

"This lecture commemorates the Friedman family hallmark of life-long learning and creates a lasting tribute to a man who gave so much to our profession, our patients and our institution."

– Joan W. Miller, MD

For more information about supporting the Friedman Lecture, please contact Patricia McCabe at 617-573-3303 or via email at patricia_mccabe@meei.harvard.edu

Robert E. Marc, PhD



Calvin and JeNeal Hatch Presidential Endowed Chair in Ophthalmology & Visual Science

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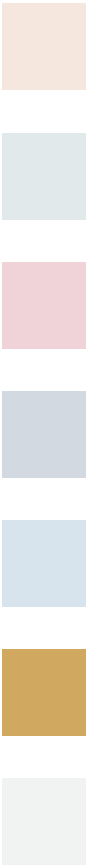
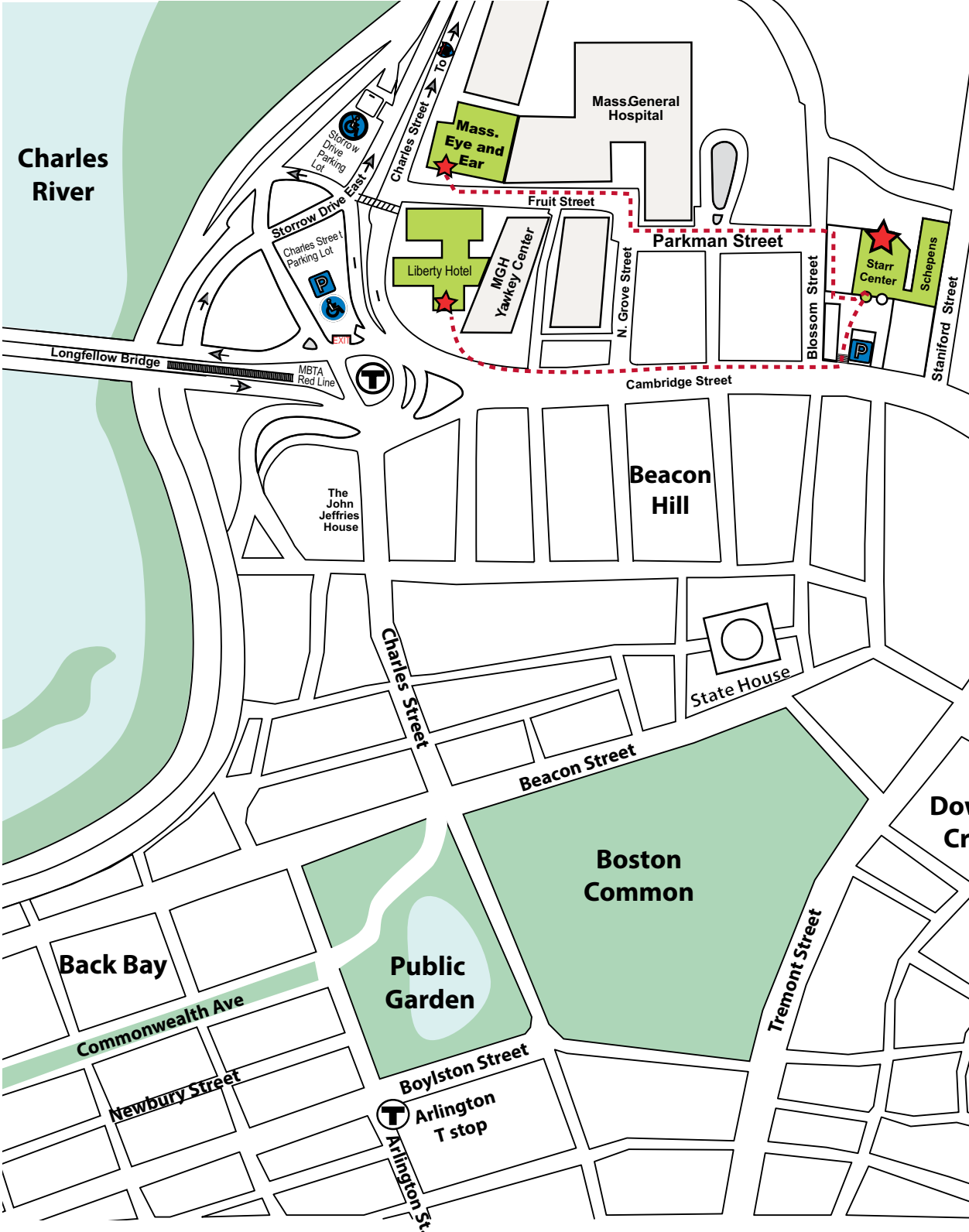
Dr. Marc (b 1949, BSc UT El Paso 1971, PhD UT Houston 1975) is Distinguished Professor of Ophthalmology and the Hatch Presidential Chair in Ophthalmology at the University of Utah. He received the 2014 Kayser Award from the International Society for Eye Research honoring his contributions to retinal neuroscience. Over his 40 year career, he produced the first color maps of cone photoreceptors in the eye, developed molecular and computational tools for tracking retinal neurons, discovered new mechanisms of retinal neurodegenerations, and built the first connectome (the retina's wiring diagram). In 2010, he and Ann Torrence founded Stray Arrow Ranch, Utah's first heritage cider apple orchard.

Remodeling in Retinal Degenerations

ABSTRACT: Remodeling is usually described as a collection of neuroglio-vascular transforms triggered by primary degeneration of retinal photoreceptors. The loss of cone photoreceptors activates a suite of restructuring and pathologic reprogramming events including neuritogenesis, de novo synaptogenesis in microneuromas, neuronal migration, rewiring, altered glial metabolism and progressive neuronal cell death. Using a long-lived transgenic rabbit model (Tg P347L) of autosomal dominant retinitis pigmentosa (RP) to map the progression of remodeling over time scales that overlap with human progression, we now understand remodeling to be a separate disease entity. Remodeling is an unremitting, progressive neurodegeneration that culminates in the complete decimation of the retina. Remodeling is as unremitting as Alzheimer's Dementia (AD), Parkinson's Disease (PD), Amyotrophic Lateral Sclerosis (ALS) and other progressive neurodegenerations. Remodeling manifests an exponential time constant for neuronal loss of $\approx 2y-3y$, resembling the neuronal loss rate in PD. As a group, progressive neurodegenerations are characterized by proteinopathies, especially the intracellular accumulation of a growing list of high-concentration proteins such as α -synuclein, tau proteins, TDP-43, ubiquitin aggregates. We do not yet know whether retinal remodeling involves these specific brain markers, but quantitative small molecule and protein computational molecular phenotyping CMP combined with TEM pathoconnectomics of late stage remodeling retinas reveals neuropil that closely resembles degenerate brain, with dense intracellular aggregates and disrupted protein trafficking. Combined with the loss of glial metabolic regulation, especially the attenuation of glutamate processing, neurodegeneration augurs poorly for the permanent success of any current intervention. Importantly, late stage AMD reveals the same metabolic failures and neurodegeneration as RP.

Notes

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