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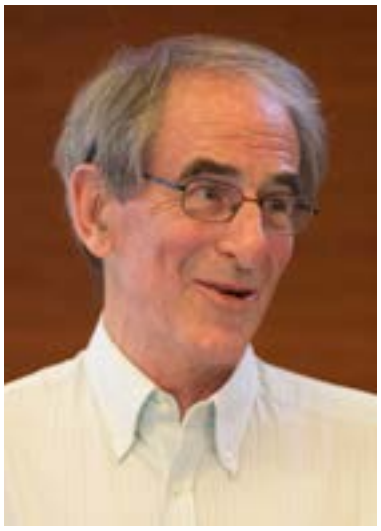
5th Biennial International

Symposium on AMD




October 12-13, 2018
Boston, MA

eye.hms.harvard.edu/amd

HARVARD MEDICAL SCHOOL | DEPARTMENT OF Ophthalmology

AGE-RELATED MACULAR DEGENERATION
CENTER OF EXCELLENCE

Notes

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5th Biennial International

Symposium on AMD

October 12-13, 2018

The Starr Center
185 Cambridge Street, 2nd Floor
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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Organizing Committee

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Co-director, Harvard Ophthalmology AMD Center of Excellence
Director, Howe Laboratory, Mass. Eye and Ear
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David Glendenning Cogan Professor of Ophthalmology, Harvard Medical School
Chair, Department of Ophthalmology, Harvard Medical School
Chief of Ophthalmology, Mass. Eye and Ear
and Massachusetts General Hospital

Welcome

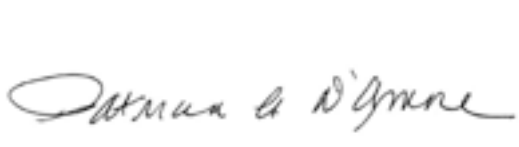
Dear Colleagues,

Welcome to the 5th Biennial International Symposium on AMD. We are very pleased that you have joined us, and we are confident that you will find your time well spent.

As has been our format from the first symposium, a significant proportion of the meeting time will be dedicated to discussion, including a 40-minute panel discussion at the end of each session. We also know that the discussions continue on through the breaks, meals, and the gala dinner.

Another hallmark of this meeting is the inclusion of experts from outside vision research, who are working in areas that we believe are relevant to AMD. This year, you will hear from leaders in metabolomics, epigenetics, and microRNAs.

Please enjoy the meeting and know that your presence is an important contribution to its success.



Patricia A. D'Amore, PhD, MBA

Deeba Husain, MD

Ivana K. Kim, MD

Thursday, October 11

6:00 - 8:00 pm	**Welcome Reception** Mass. Eye and Ear Lank Family Dining Room, 7th Floor 243 Charles Street, Boston, MA

Friday, October 12

7:00 - 8:00 am	**Breakfast and Registration** Starr Center 185 Cambridge Street, 2nd Floor, Boston, MA
8:00 - 8:05 am	**Welcome and Introduction: Joan W. Miller, MD** Harvard Ophthalmology, Mass. Eye and Ear, and Mass General Hospital
8:05 - 8:30 am	**Opening Address: Anthony P. Adamis, MD** Genentech *A Short history of AMD drug development*
8:30 - 10:25 am	**BIOMARKERS**
	Moderator: Deeba Husain, MD Harvard Ophthalmology, Mass. Eye and Ear
8:30 - 8:50 am	**Emily Y. Chew, MD** National Eye Institute, National Institutes of Health *Biomarkers of AMD: dark adaptation, function, and imaging*
8:55 - 9:15 am	**Jessica A. Lasky-Su, ScD** Harvard Medical School, Brigham and Women's Hospital *The utility of metabolomics in an integrative omic era*
9:20 - 9:40 am	**Anders M. Naar, PhD** University of California, Berkeley *Targeting of miR-33 in age-related macular degeneration*
9:45 - 10:25 am	***Panel Discussion***
10:25 - 10:45 am	**Break** Starr Center Breakout Space
10:45 am - 12:40 pm	**VASCULAR**
	Moderator: Demetrios Vavvas, MD, PhD Harvard Ophthalmology, Mass. Eye and Ear
10:45 - 11:05 am	**Barbara Braunger, MD, PhD** University of Regensburg, Germany *Deletion of endothelial TGF-ß signaling promotes choroidal neovascularization*

11:10 - 11:30 am	**Robert J. D'Amato, MD, PhD** Harvard Ophthalmology, Boston Children's Hospital *Identification of novel angiogenesis regulating genes by genome association studies in mice*
11:35 - 11:55 am	**Richard F. Spaide, MD** Vitreous Retina Macula Consultants of New York, New York University *New insights into mactel2 and type 3 neovascularization from optical coherence tomography angiography imaging*
12:00 - 12:40 pm	***Panel Discussion***
12:40 - 1:40 pm	**Lunch** Starr Center Breakout Space
1:40 - 3:35 pm	**INFLAMMATION**
	Moderator: Kip M. Connor, PhD Harvard Ophthalmology, Mass. Eye and Ear
1:40 - 2:00 pm	**Andrew D. Dick, MD** Bristol Eye Hospital, University of Bristol *Immunotherapy regulating immune responses through metabolic sensing*
2:05 - 2:25 pm	**Goldis Malek, PhD** Duke Eye Center, Duke University School of Medicine *Rethinking nuclear receptors as therapeutic targets for AMD*
2:30 - 2:50 pm	**Aparna Lakkaraju, PhD** University of California, San Francisco *Intracellular complement activation in the retinal pigment epithelium*
2:55 - 3:35 pm	***Panel Discussion***
3:35 - 3:55 pm	**Break** Starr Center Breakout Space
4:00 - 5:15 pm	**EPHRAIM FRIEDMAN LECTURE**
4:00 - 4:10 pm	**Introduction to Lecture: Evangelos S. Gragoudas, MD** Harvard Ophthalmology, Mass. Eye and Ear
4:10 - 4:15 pm	**Speaker Introduction: Joan W. Miller, MD** Harvard Ophthalmology, Mass. Eye and Ear, and Mass General Hospital
4:15- 5:15 pm	**François C. Delori, PhD** Harvard Ophthalmology, Schepens Eye Research Institute of Mass. Eye and Ear *Fundus autofluorescence*
6:00 - 10:00 pm	**Gala Dinner at the Boston Museum of Science** *By registration only*

Saturday, October 13

7:00 - 8:00 am	**Breakfast** Starr Center Breakout Space
8:00 - 8:10 am	**Welcome Back** Ivana K. Kim, MD Harvard Ophthalmology, Mass. Eye and Ear
8:10 - 9:20 am	**TRAINEE RAPID FIRE SESSION**
8:10 - 8:20 am	**Introduction: Ivana K. Kim, MD** Harvard Ophthalmology, Mass. Eye and Ear
8:25 - 8:30 am	**Christin Hanke-Gogokhia, PhD** Weill Cornell Medical College *Indian hedgehog (Ihh) secreted by adult choroid endothelial cells regulates choroidal homeostasis and immune response*
8:35 - 8:40 am	**Shuntaro Ogura, MD, PhD** Johns Hopkins University School of Medicine *A novel rat model for mast cell involvement in geographic atrophy and an ex vivo assay for evaluating drug efficacy to quiesce mast cells*
8:45 - 8:50 am	**Jonathan B. Lin, PhD/MD Candidate** Washington University School of Medicine *Macrophage microRNA-150 promotes pathological angiogenesis as seen in age-related macular degeneration*
8:55 - 9:00 am	**Stuart McKeown, PhD** Queen's University Belfast *Endothelial colony forming cell modulation of the choroidal vasculature*
9:05 - 9:10 am	**Katy B. Ebrahimi, MD** University of Pennsylvania Health System *Outer plexiform layer remodeling in aging and age-related macular degeneration*
9:15 - 9:20 am	**Laura Lores-Motta, PhD** Radboud University Medical Center *Genome-wide association study reveals variants in CFH and CFHR4 associated with systemic complement activation: implications in age-related macular degeneration"*
9:20 -9:45 am	**Break** Starr Center Breakout Space

EPIGENETICS

Moderator: Margaret M. DeAngelis, PhD
University of Utah

9:45 - 10:05 am

Trygve O. Tollefsbol, PhD, DO
University of Alabama at Birmingham
Epigenetics of aging and cancer: a nutritional perspective

10:10 - 10:30 am

Myles Brown, MD
Harvard Medical School, Dana-Farber Cancer Institute
Defining the functional epigenome

10:35 am - 10:55 am

Li-Huei Tsai, PhD
Massachusetts Institute of Technology
Transcriptomic analysis of at single-cell resolution in neurodegeneration

11:00 - 11:40 pm

Panel Discussion

11:40 - 12:40 pm

Lunch
Starr Center Breakout Space

MITOCHONDRIA

12:40 - 2:35 pm

Moderator: Scott W. Cousins, MD
Duke University

12:40 - 1:00 pm

Deborah A. Ferrington, PhD
University of Minnesota
Mitochondrial dysfunction in the retinal pigment epithelium promotes AMD pathology

1:05 - 1:25 pm

Zoltan Ungvari, MD, PhD
University of Oklahoma Health Science Center
Role of mitochondrial oxidative stress in cerebromicrovascular aging

1:30 - 1:50 pm

Magali Saint-Geniez, PhD
Harvard Ophthalmology, Schepens Eye Research Institute of Mass. Eye and Ear
Metabolic control of RPE phenotype

1:55 - 2:35 pm

Panel Discussion

CLOSING REMARKS

2:40 - 3:20 pm

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

NIH-Sponsored Travel Award Recipients

Fiona Cunningham
PhD Student
Queen's University Belfast
Ireland

Katy B. Ebrahimi, MD
Instructor
University of Pennsylvania Health System
Pennsylvania

Ankur Gupta, MD
Spect, Inc.
California

Christin Hanke-Gogokhia, PhD
Ophthalmology Fellow
Weill Cornell Medical College
New York

Jonathan B. Lin
MD/PhD Candidate
Washington University School of Medicine
Missouri

Stuart McKeown
MD/PhD Candidate
Queen's University Belfast
Ireland

Laura Lorés de Motta, PhD
Postdoctoral fellow
Radboud University Medical Center
Netherlands

Shuntaro Ogura, MD, PhD
Postdoctoral Research Fellow
Johns Hopkins University School of Medicine
Maryland

Ravi Parikh, MD
Retina Fellow
Mass. Eye and Ear
Boston

Irum Perveen, PhD
Assistant Professor
Shaheed Zulfiqar Ali Bhutto Medical University
Islamabad

Magali Ridano, PhD
Postdoctoral Fellow
National University of Córdoba
Argentina

Roy Schwartz, MD
Specialty Doctor (Department of Medical Retina)
Moorfields Eye Hospital
London

Notes

Abstracts of Talks

Biomarkers

Biomarkers of AMD: Dark adaptation, function, and imaging

Emily Chew, MD

ABSTRACT: he pathogenesis of AMD is still not well understood and clinical trials require significant duration of time to evaluate clinically meaningful changes. It is important to evaluate biomarkers for the purposes of understanding the pathobiology and for potential surrogate outcome measures that could help expedite clinical trials. Data from two longitudinal studies supported by the NEI demonstrate the difference in dark adaptation in persons with AMD and the changes for documented on spectral-domain optical coherence tomography (SD-OCT). A subset of participants was followed longitudinally in the Age-Related Eye Disease Study 2 (AREDS2) demonstrated important SD-OCT factors that predicted the onset of geographic atrophy (GA). The Dark Adaptation Study evaluated 150 participants ranging from no AMD to advanced AMD in one eye. The dark adaptation was performed using a prototype of the AdaptDx dark adaptometer (MacuLogix, Hummelstown, PA). After dilation, the participant was asked to focus on a fixation light and photoflash producing an 82% focal bleach centered at 5o on the inferior visual meridian was performed, and threshold measurements were made at the same location with a 1.7o diameter, 500-nm wavelength circular test spot. Threshold measurements were continued in a stair-case fashion until the patient's visual sensitivity recovered to be able to detect a dimmer stimulus intensity of 5X10-3 cd/m2 (a decrease of 3 log units), or until a maximum test duration of 40 minutes. We have baseline and longitudinal data. The outcome measure of the rod intercept time (RIT) obtained at baseline showed an increased RIT that was associated significantly with increasing AMD severity, increasing age ($r = 0.34$; $P = 0.0002$), decreasing BCVA ($r = 0.54$; $P < 0.0001$), pseudophakia ($P = 0.03$), and decreasing subfoveal choroidal thickness ($r = 0.27$; P ¼ 0.003). Study eyes with reticular pseudodrusen (RPD) (15/116 [13%]) had a significantly greater mean RIT compared with eyes without RPD in any AMD severity group ($P < 0.02$ for all comparisons), with 80%reaching the DA test ceiling. Impairments in DA increased with age, worse visual acuity, presence of RPD, AMD severity, and decreased subfoveal choroidal thickness. Longitudinal data on this cohort are being evaluated currently. The AREDS2 ancillary study of the SD-OCT showed reflective substructures of the drusen could be divided into various forms. The presence of these reflective drusen substructures were associated with (1) greater macular drusen volume at baseline ($P < 0.001$), (2) development of preatrophic changes at year 2 ($P = 0.001$ to 0.01), and (3) development of macular GA ($P = 0.005$) and preatrophic changes at year 3 ($P = 0.002$ to 0.008), but not development of CNV. Optical coherence tomography reflective drusen substructures may be a clinical entity helpful in monitoring AMD progression and informing mechanisms in GA pathogenesis. The AREDS2 ancillary study of the SD-OCT also showed the importance of hyperreflective foci (HF) and their distribution throughout the retina. The number and location of HF were scored in SD-OCT scans of all 299 eyes. The change in transverse (horizontal) and axial (vertical) distribution of HF in the macula were evaluated with pairwise signed-rank tests. Two-year inner retinal HF migration was determined by the change in HF-weighted axial

distribution (AxD) score calculated for each eye. The correlation of HF with SD-OCT features of AMD progression was evaluated with logistic regression analysis. In 299 study eyes, the 2-year increase in the number of HF (P=0.001) and the AxD (P=0.001) per eye represented longitudinal proliferation and shift to inner retinal layers, respectively. Eyes with geographic atrophy (GA) at 2 years were correlated with the presence of baseline HF (P=0.001; odds ratio [OR], 4.72; 95%confidence interval [CI], 2.43–9.80), greater number of baseline HF (P=0.001; OR, 1.61 per HF; 95% CI, 1.32–2.00), and greater baseline AxD (P=0.001; OR, 1.58 per AxD point; 95% CI, 1.29 –1.95). Proliferation and inner retinal migration of SD-OCT HF occurred during follow-up in eyes with intermediate AMD. These characteristics were associated with greater incidence of GA at year 2; therefore, SD-OCT HF proliferation and migration may serve as biomarkers for AMD progression. We also conducted a retrospective cross-sectional study of 325 eyes from 164 subjects who underwent EDI-OCT for the Age-Related Eye Disease Study (AREDS) 2 Ancillary Spectral Domain OCT study. Choroidal thickness was measured by semi-automated segmentation of EDI-OCT images from 1.5 mm nasal to 1.5 mm temporal to the fovea. Multivariate linear regression was used to evaluate the association of subfoveal choroidal thickness or average choroidal thickness across the central 3-mm segment with systemic and ocular variables. Choroidal thickness measurements were compared between eyes with no AMD (n = 154 ie, controls), intermediate AMD (n= 109), and advanced AMD (n - 62). Both subfoveal and average choroidal thick-nesses were associated with age (P < .001) and refractive error (P < .001), but not other variables tested. Mean average choroidal thickness was significantly reduced in advanced AMD as compared with control eyes (P = .008), with no significant difference between advanced and intermediate AMD eyes (P =0.152) or between intermediate AMD and control eyes (P = .098). When adjusted for age and refractive error, central choroidal thickness may not be significantly influenced by AMD status based on AREDS categorization. However, reticular pseudo drusen were not evaluated in this study. These findings are in agreement with the recently proposed classifications of GA. Two consensus meetings (Classification of Atrophy Meeting [CAM]) on conventional and advanced imaging modalities used to detect and quantify atrophy due to late-stage non-neovascular and neovascular age-related macular degeneration (AMD) and to provide recommendations on the use of these modalities in natural history studies and interventional clinical trials. The OCT parameters are an important aspect of this classification.

Biomarkers

The utility of metabolomics in an integrative omics era

Jessica Lasky-Su, ScD

ABSTRACT: Metabolomic profiling has the distinct advantage of being a marker of either mechanisms leading to disease or an established disease process that incorporates both genetic and environmental exposures, making this a promising approach to detect a composite measure of multiple disease influences. In this talk we demonstrate the translational utility of metabolomics through the utilization of multiple omic data types. Inflammatory mediators play a key, but not fully understood, role in the pathogenesis of asthma; with metabolites derived from omega-6 and omega-3 fatty acids of particular importance. FADS2 (fatty acid desaturase 2) encodes a crucial rate-limiting enzyme within these unsaturated fatty acid pathways, and has been linked to asthmatic phenotypes. Metabolomics, which captures both genetic and environmental influences and current phenotype, is ideally suited to explore the downstream functional implications of genetic variants in FADS2 on asthmatic phenotypes. The Childhood Asthma Management Program is a randomized clinical trial investigating the long-term effects of inhaled treatments for asthma in children. Blood samples from 375 participants with asthma were submitted for mass-spectrometry based metabolomic, transriptomic and genome-wide profiling. A metabolite Quantitative Trait Loci analysis (mQTL) was performed using the R package matrixeQTL, to identify metabolites whose abundance was associated with a functional variant in FADS2; rs968567. Mediation analysis was conducted to determine whether the genetic burden of disease severity in asthma was mediated through alterations in the levels of these metabolites. Rs968567 [C>T] was shown to be associated with increased expression of FADS2; (p=6.6x10-14); with multiple lung function metrics, including Brochodialator response (p=0.013) and with 67 metabolites, the majority of which were omega-6 or omega-3 derived fatty acids, and which were themselves associated with asthmatic lung function. Mediation analysis revealed that archidonate (p<2x10-16); Eicosapentaenoate (p<2x10-16); Docosapentaenoate (p=0.06) and Docosahexanoate (p=0.07) were mediating the relationship between the FADS2 variant and Bronchodilator response, although only a proportion of the change attributable to rs968567 was explained by these metabolites. This study leverages population-wide integrative-omic data to demonstrate variants near FADS2 may act as mQTLs driving differential abundance of key inflammatory mediating metabolites that influence asthma severity. The balance of omega-3 versus omega-6 fatty acid conversion regulated by FADS2 in the alpha-linoleic acid pathway is crucial for the resolution of inflammation and dampening of airway hyperresponsiveness. However, mediation analysis suggests that FADS2 may also be exerting its genetic influence on asthma through its role in the regulation of other metabolic pathways.

Biomarkers

Targeting of miR-33 in AMD

Anders M. Näär, PhD

ABSTRACT: AMD, a prominent cause of blindness in the elderly, is associated with the progressive accumulation of cholesterol and other lipids and cellular debris in the eye. AMD also has strong genetic links to genes involved in controlling cellular and circulating cholesterol/lipids, such as the cholesterol efflux pump ABCA1, the cholesterol trafficking protein CETP, and the hepatic lipase LIPC. However, the molecular underpinnings of aberrant cholesterol/lipid metabolism in the aging eye and links to aging-related retinal damage has remained opaque. We have for many years investigated molecular mechanisms governing cholesterol/lipid homeostasis. Our recent studies have uncovered novel and critical roles for small regulatory non-coding RNAs termed microRNAs in the control of cholesterol/lipid metabolic circuits, with potentially important implications for AMD. We initially identified the miR-33 family of microRNAs as key regulators of ABCA1 and cholesterol efflux in a number of cell types, and we and others have demonstrated that miR-33 antisense oligonucleotides represent promising therapeutic modalities to ameliorate abnormal cholesterol homeostasis in mice fed a Western-type diet, and in obese and diabetic non-human primates (Najafi-Shoushtari et al. Science 2010; Rottiers et al. Science Translational Medicine 2013). We have now found that miR-33 also represents a key regulator of cholesterol/lipids and inflammation in the retina of Western-type diet-fed ageing mice and non-human primates. Retinal miR-33 levels are increased in ageing mice, whereas levels of its target ABCA1 are reciprocally decreased. Once-weekly subcutaneous injection of potent antisense oligonucleotides targeting miR-33 in aged mice or non-human primates fed Western-type diets resulted in decreased cholesterol accumulation and improved retinal pigment epithelium morphology and decreased inflammation, without discernable deleterious effects. Together, these studies indicate that miR-33 may represent an attractive therapeutic target for the treatment of AMD.

Vascular

Deletion of endothelial TGF-β signaling promotes choroidal neovascularization

Barbara Braunger, MD, PhD

ABSTRACT: The molecular pathogenesis of choroidal neovascularization (CNV), an angiogenic process that critically contributes to vision loss in AMD is unclear. To identify the role of TGF-β signaling for CNV formation, we generated mice with a conditional deletion of the TGF-β type II (TβRII) receptor which is essential for TGF-β signaling. We generated a series of mutant mouse models with induced conditional deletion of TGF-β signaling in the entire eye, the retinal pigment epithelium (RPE) or the vascular endothelium. To activate Cre recombinase, mice were treated with tamoxifen or doxycycline eye drops either as newborns or at the age of 3 weeks. The successful deletion of TβRII was confirmed by real time RT-PCR, Western blotting and immunohistochemistry. Retinal/choroidal structure and function were studied by light and transmission electron microscopy (TEM), immunohistochemistry, FITC-dextran perfusions, fluorescence angiography, CLARITY imaging, real time RT-PCR, and electroretinography. Deletion of TGF-β signaling in the entire eye of newborn mice resulted in a significant upregulation of retinal Vegf-a, Fgf-2, Angpt2 and Igf expression levels, and markers for reactive microglia such as Cd68, iNos and Tnf-α. At the age of 6 weeks, CNV was detected by CLARITY imaging of the eyes of isolectin B4 injected animals and on meridional sections of dextran perfused eyes. Deletion of TGF-β signaling in the entire eye of three-week-old mice did not cause obvious changes of the retinal vasculature. However, CNV were still observed. TEM analyses showed the thickening of the Bruch's membrane (BM) and fine fibrillar extracellular material between the basal lamina of the choriocapillaris and the elastic layer of BM. At the age of 6 months, ERG analyses showed functional deficits, and marked degenerative changes of the retinae were observed. While the specific deletion of TGF-β signaling in the RPE caused no obvious changes, specific deletion in vascular endothelial cells caused CNV and a phenotype quite similar to that observed after the deletion in the entire eye. Impairment of TGF-β signaling in the vascular endothelium of the eye is sufficient to trigger CNV formation. Our findings highlight the importance of TGF-β signaling as key player in the development of CNV and indicate a fundamental role of TGF-β signaling in the pathogenesis of AMD.

Vascular

Identification novel angiogenesis regulating genes by genome association studies in mice

Robert D'Amato MD, PhD

ABSTRACT: Angiogenesis plays a key role in ocular diseases such as diabetic retinopathy and macular degeneration. Evidence from our lab indicated that the ability to respond to angiogenic stimuli is controlled by genetic variation. We have used genome wide association studies in inbred mice to map the quantitative trait loci responsible for differences in angiogenic response. We then used both expression analyses and a zebrafish model system to verify the gene candidates. These genes are novel and studies to elucidate their role in the regulation of angiogenesis are ongoing.

Vascular

New insights into MacTel2 and type 3 neovascularization from optical coherence tomography angiography imaging

Richard F. Spaide, MD

ABSTRACT: Evaluation of vessels as they descend into the retina, MacTel2 and Type 3 neovascularization being salient examples, are challenging to understand with ocular imaging. Fluorescein angiography has poor ability to resolve vessels deeper than the superficial vascular plexus. Conventional optical coherence tomography (OCT) angiography is viewed in en face modes, which renders vertically coursing vessels small in cross-section. More recently B-scan structural OCTs with flow overlay can show specific planes in cross-section. Appreciation of the course of vessels is possible, but does require creating a mental picture of the vessels from many individual scans. Volume rendering can use all the available information to create three-dimensional representations of vessels. Combined with projection artifact removal, the newer imaging modalities can create representations of descending and deeper vessels without problematical artifacts. These capabilities have improved our ability to image MacTel2 and Type 3 neovascularization, which share some similarities. MacTel2 has vessels that descend to the outer retina, and has been recently shown, can form retinal choroidal anastomoses often without any lateral subretinal proliferation. Eyes with Type 3 disease have hemorrhage and edema not necessarily contiguous with areas of neovascularization. The macular findings such as hemorrhage, telangiectasis, and edema may be related, in part, to increased cytokine levels, particularly vascular endothelial growth factor, and not necessarily the neovascularization itself.

Inflammation

Immunotherapy regulating immune responses through metabolic sensing

Andrew Dick, MD

ABSTRACT: Active immune responses are integral to the health of all tissues and are mediated through both canonical immune cells and many cell types capable of eliciting immune responses. Essential also is an ability to raise immune responses against frank pathogen insults. Despite the sensing systems we have recently understood, including Pattern Recognition Receptors (PPRs), we now have increasing understanding of immunometabolism where changes in intracellular metabolic pathways influence immune function of cells. With respect to AMD, there is a chronic and persistent insult to the outer retina/RPE with consequential biochemical and metabolic changes. Thus, cells adapt to maintain cell function and health, respond to protect to cell function and retain viability and maintain mitochondrial health. In addition, and in face of chronic insult, immune responses adapt their threshold to regulate over action, and particularly so in microglia and macrophages. In support of such mechanisms, we will discuss the role of receptor-ligand regulation of microglia and macrophage responses and the changes in immunometabolism that regulates cell function through cytokines, such as IL-4 and IL-33.

Inflammation

Intracellular complement activation in the retinal pigment epithelium

Aparna Lakkaraju, PhD

ABSTRACT: Abnormal complement activity is strongly associated with the pathogenesis of AMD. Yet, drugs that directly block key components of the complement pathway such as C3 activation have failed in clinical trials. This could be due in part to the intriguing discovery that intracellular C3 determines cell fate by modulating metabolism and inflammation via mTOR (mechanistic target of rapamycin) activation. Therefore, normalizing C3 activity, rather than blocking it, might be a more effective therapeutic approach. Here, using human donor tissue and disease models, we demonstrate that age-related and pathological accumulation of lipofuscin increases ceramide at the apical surface of the retinal pigment epithelium (RPE), and causes aberrant formation of early endosomes due to inward budding and fusion. These enlarged endosomes internalize the complement protein C3 into the RPE, resulting in the intracellular generation of C3a fragments. Increased C3a in turn activates mTOR, a regulator of critical metabolic processes such as autophagy. An FDA-approved drug that decreases ceramide corrects endosomal defects, decreases C3a levels and prevents mTOR activation in the RPE. Our studies establish how organelle dynamics modulate complement activity in the RPE, and identify ceramide as a drug target for macular degenerations.

Inflammation

Rethinking nuclear receptors as therapeutic for targets for AMD

Goldis Malek, PhD

ABSTRACT: Nuclear receptors are transcription factors that control a myriad of biological and disease processes. A subset of these receptors is activated by lipids and have been shown to play a vital role in chronic diseases such as diabetes, atherosclerosis, coronary heart disease, inflammatory skin disorders, and obesity. These diseases share common pathogenic mechanisms with retinal diseases, including AMD and diabetic retinopathy. Recently, we completed a nuclear receptor atlas of human retinal pigment epithelial cells, cells vulnerable in all clinical sub-types of AMD. We identified several candidate receptors that may be important in disease initiation and progression. In this presentation, we will review the impact of these signaling pathways on retinal function, morphology, and AMD-related pathogenic pathways, including lipid metabolism, inflammation, angiogenesis, and fibrosis. Furthermore, we will discuss the therapeutic potential of targeting these signaling pathways on pathobiology associated with the different clinical sub-types of AMD.

Epigenetics

Defining the functional epigenome

Myles Brown, MD

ABSTRACT: Endocrine therapies that prevent the production of sex steroid hormones or that block their transcription factor receptors are mainstays of breast and prostate cancer treatment. Epigenomic profiling approaches have allowed the identification of genes regulated by the steroid hormone receptors and the cis-regulatory targets bound by the receptors across the genome, their cistromes. We have used CRISPR-Cas9 knockout screens to explore the functional cistromes driving the growth of breast and prostate cancer cells by investigating the essentiality of FOXA1 and CTCF binding sites. We found that essential FOXA1 binding sites act to orchestrate the expression of nearby essential genes and bear the hallmarks of active enhancers that bind essential lineage-specific transcription factors. In contrast, CRISPR screens of the CTCF cistrome revealed two classes of essential binding sites. The first class of essential CTCF binding sites act like FOXA1 sites as enhancers to regulate the expression of nearby essential genes. A second class of essential CTCF binding sites was identified at TAD boundaries and display distinct characteristics. Using regression approaches we developed a model to predict the functional cistrome of a transcription factor with high accuracy. This model for FOXA1 cis-element dependence correctly predicts non-coding variants associated with cancer risk and progression identified in genome-wide association studies and may provide an approach to understanding germline risk variants associated with other diseases.

Epigenetics

Epigenetics of aging and cancer: a nutritional perspective

Trygve Tollefsbol, PhD, DO

ABSTRACT: Interest in aging and cancer epigenetics has arisen from the fact that epigenetic processes affect many aspects of aging and tumor formation. The reversibility of epigenetic changes is an important aspect of their potential in approaches for slowing aging and age-related diseases as well as preventing cancer. We coined the term “epigenetics diet” only 6 years ago based on numerous studies delineating the impact of bioactive dietary compounds on changes in the epigenome. There is aberrant gene expression due to epigenetic changes during aging and in all cancer types, so an approach to slowing age-related diseases would be to use these bioactive dietary compounds as a means of neutralizing epigenomic aberrations. Although many of these phytochemicals are efficacious alone or in combination, some are only efficacious at considerably high doses not achievable by diet alone. Combinatorial studies are important to enhance our understanding of the interactions between various epigenomic-modifying dietary compounds. Compounds that display antiaging or anticancer properties by themselves may act in an additive, synergistic, or even antagonistic manner in combination. The epigenetic mechanisms for these interactions are not fully understood, and are an area of increasing interest for the studies of the epigenetics diet. For instance, we have found that both (-)-epigallocatechin-3-gallate (EGCG) from green tea and sulforaphane (SFN) from cruciferous vegetables are able to down-regulate telomerase in breast cancer cells. This occurs through epigenetic modifications of the promoter region of *hTERT*, the gene that encodes the catalytic subunit of telomerase. Since telomerase promotes tumor formation and is active in about 90% of cancers, this epigenetic inhibition of its catalytic subunit gene may have considerable potential in cancer prevention. Telomerase is also important in aging and age-related diseases. In addition, our studies indicate that these bioactive dietary compounds are able to convert estrogen-receptor (ER)-negative breast cancer cells to ER-positive breast cancer cells treatable with tamoxifen or to prevent the formation of highly lethal ER-negative breast cancer. This occurs through epigenetic modifications of the *ERalpha* gene in response to EGCG and SFN. The components of the epigenetic diet are effective both *in vitro* and *in vivo* and also appear to be more effective when administered early in life. On the horizon for studies on the epigenetics diet are additional combinatorial approaches, studies on the effects of the epigenetics diet on the gut microbiome and aging as well as cancer prevention and early-life analyses of the impact of the epigenetics diet on age-related diseases.

Epigenetics

Transcriptomic analysis of at single-cell resolution in neurodegeneration

Li-Huei Tsai, PhD

ABSTRACT: Transcriptomic analyses of human postmortem Alzheimer's disease (AD) brains have revealed global changes in gene expression patterns that are characterized by the downregulation of genes associated with synaptic function, learning and memory, and the upregulation of adaptive as well as innate immune response genes. However, since the brain is a complex system built from many different functionally specialized cell types, ensemble-based approaches measuring gene expression from bulk populations of cells can only report population averages that may not reflect the responses of individual cells. Moreover, during neurodegeneration, cell type composition changes over time, which further confounds the analysis and interpretation of transcriptional changes of various cell types. Recent advances in high-throughput single-cell RNA sequencing technology allow us to determine how the different cell types and their subclasses in the brain are affected by AD. We previously conducted single-cell RNA-sequencing to determine the phenotypic heterogeneity of microglia during the progression of neurodegeneration in a mouse model. In this model, we identified multiple disease stage-specific microglia cell states that are not present in the healthy brain. Specifically, we identified two molecularly distinct reactive microglia phenotypes that are typified by modules of co-regulated type I and type II interferon response genes, respectively. Currently, we are conducting massive single nucleus profiling of postmortem human prefrontal cortex samples with low versus high amyloid pathology from the ROS-MAP cohort. We have identified human brain cell types that exhibit pathology-, cognitive function-, and gender-specific transcriptomic signatures. These data provide unprecedented insight into cellular networks most vulnerable to the presence of AD pathology.

Mitochondria

Mitochondrial dysfunction in the retinal pigment epithelium promotes AMD pathology

Deborah Ferrington, PhD

ABSTRACT: The dry form of AMD, also known as Atrophic AMD, is characterized by the death of the retinal pigment epithelium (RPE) and photoreceptors. Strong experimental evidence from studies of human donors with AMD supports the emerging hypothesis that defects in RPE mitochondria drives the pathology associated with Atrophic AMD. Data supporting this hypothesis have shown donors with AMD exhibit (i) disrupted RPE mitochondrial architecture and decreased mitochondrial number and mass, (ii) altered content of multiple mitochondrial proteins, and (iii) increased mtDNA damage that correlates with disease severity. To directly test the hypothesis that mitochondrial dysfunction occurs with AMD, we evaluated RPE bioenergetics in primary RPE cultures from donors with or without AMD using the Seahorse Extracellular Flux Analyzer. Our results show that RPE from donors with AMD had reduced mitochondrial function compared with age-matched control donors. These results are consistent with the idea that RPE mitochondrial dysfunction contributes to AMD pathology.

Mitochondria

Metabolic control of RPE phenotype

Magali Saint-Geniez, PhD

ABSTRACT: Functional maturation depends on the induction of a specific metabolic program able to support the energetic requirements of specialized tissues. Conversely, metabolic dysregulation can drive cellular reprogramming and transdifferentiation. While establishment and maintenance of retinal pigment epithelial cells (RPE) phenotype is crucial to retinal homeostasis, the molecular mechanisms governing RPE metabolic and functional maturation are unknown. We have previously shown that PGC-1α, a core regulator of oxidative metabolism, promotes RPE mitochondrial function and resistance against pathogenic oxidative stress. To further investigate the relationship between PGC-1α, oxidative metabolism and RPE phenotype, we characterized the functional consequences of PGC-1α loss of function in vitro and in vivo. We showed that mitochondrial dysfunction and oxidative damage secondary to PGC-1α deficiency lead to severe autophagic defect promoting mesenchymal transition. In a mouse model of RPE specific PGC-1α deletion, RPE metabolic dysfunction and dedifferentiation is associated with severe photoreceptor degeneration and choriocapillaries atrophy reminiscent of the changes observed in atrophic AMD patients. Our findings identify PGC-1α as an essential molecular link between oxidative metabolism and RPE functional maturation, and highlight the critical role of oxidative metabolism and mitochondrial health in controlling RPE phenotype.

Mitochondria

Role of mitochondrial oxidative stress in cerebromicrovascular aging

Zoltan Ungvari, MD, PhD

ABSTRACT: Moment-to-moment adjustment of cerebral blood flow via neurovascular coupling has an essential role in maintenance of healthy cognitive function. In advanced age cerebromicrovascular, endothelial dysfunction impairs neurovascular coupling, likely contributing to age-related decline of higher cortical functions. New data will be presented that in aged laboratory rodents neurovascular coupling and endothelium-dependent cerebromicrovascular dilation can be rescued, which represents a potential therapeutic target for the promotion of healthy brain aging. In particular, the potential role of mitochondrial oxidative stress in neurovascular dysfunction will be discussed. Our findings show that treatment of aged mice with the cell permeable, mitochondria-targeted antioxidant peptide (SS-31) improves neurovascular coupling responses by increasing NO-mediated cerebromicrovascular dilation, which is associated with significantly improved spatial working memory, motor skill learning and gait coordination. These findings are paralleled by the protective effects of SS-31 on mitochondrial production of reactive oxygen species and mitochondrial respiration in cultured cerebromicrovascular endothelial cells derived from aged animals. Thus, mitochondrial oxidative stress contributes to age-related cerebromicrovascular dysfunction, exacerbating cognitive decline. We propose that mitochondria-targeted antioxidants could be considered for pharmacological cerebromicrovascular protection for the prevention/treatment of age-related vascular cognitive impairment.

Invited Participant Biographies

Anthony Adamis, MD

Global Head of Ophthalmology, Immunology and Infectious Diseases, Genentech/Roche and Adjunct Professor of Ophthalmology and Visual Sciences, University of Illinois College of Medicine

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Dr. Adamis is Senior Vice President and Global Head of Ophthalmology, Immunology, Infectious Disease & Metabolism Clinical Science at Genentech, a member of the Roche Group. He is best known for his co-discovery of the role of vascular endothelial growth factor (VEGF) in ocular disease. Conducted at Harvard in the 1990's, this research led to his sharing the António Champaulimaud Vision Award in 2014. In 2000, Dr. Adamis co-founded Eyetech Pharmaceuticals, which developed and obtained FDA approval for the first anti-VEGF drug in ophthalmology (pegaptanib for wet AMD; 2004). At Genentech, he led the teams that developed the first FDA-approved drugs for diabetic macular edema, diabetic retinopathy, branch and central retinal vein occlusion, and myopic choroidal neovascularization (ranibizumab, anti-VEGF), as well as temporal arteritis (tolicizumab, anti-IL6R). Since the advent of anti-VEGF drugs, the rates of blindness from wet AMD have dropped by half around the world. Dr. Adamis received his MD with Honors from the University of Chicago. He completed his ophthalmology residency at the University of Michigan and his fellowship at the Mass. Eye and Ear. His research training in vascular biology was with Dr. Judah Folkman at Boston Children's Hospital.

Barbara Braunger, MD, PhD

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Dr. Braunger studied human medicine at the University of Ulm, Germany, where she conducted her MD thesis in the Department of Human Genetics at the University of Ulm and received her medical degree in 2005. She started her clinical training in Ophthalmology from 2005 to 2007 at the University of Erlangen, Germany. In 2007, she moved to the Department of Anatomy and Embryology at the University of Regensburg, Germany, where she earned her PhD followed by a postdoctoral research phase. In 2013, she was appointed group leader and received her habilitation degree in 2014. The same year she joined the laboratory of Patricia D' Amore at the Schepens Eye Research Institute at Mass. Eye and Ear for a sabbatical term. In 2017, Dr. Braunger became Associate Professor of Anatomy at the University of Wuerzburg, Germany. Dr. Braunger's research interests focus on the understanding of the molecular mechanisms leading to neurodegenerative and vascular pathologies in the retina as seen in patients suffering from retinitis pigmentosa, diabetic retinopathy, retinopathy of prematurity or AMD. Her main topic during the last years has been the in depth characterization of the functional role of neuroprotective factors like transforming growth factor beta (TGF-β) and their influence on the developing retina, as well as in the adult eye. Dr. Braunger has developed mice models for intraocular vascular diseases such as diabetic retinopathy and AMD and could recently demonstrate that TGF-β signaling in endothelial cells is critically required to prevent the formation of choroidal neovascularization. Dr. Braunger is the recipient of several awards and honors, including the Retina Förderpreis, the ProRetina macula prize, and the Young Investigator Award of the Anatomical Society.

Myles Brown, MD

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Dr. Brown is the Emil Frei III Professor of Medicine at Harvard Medical School and Director of the Center for Functional Cancer Epigenetics at the Dana-Farber Cancer Institute. His research focuses on the understanding of steroid hormones and their receptors in hormone-dependent cancers. He earned his undergraduate degree from Yale University and his MD from the Johns Hopkins University School of Medicine. He completed training in internal medicine at the Brigham and Women's Hospital while doing research with David Livingston at the Dana-Farber. He went on to complete training in medical oncology at the Dana-Farber and postdoctoral research with Phil Sharp at MIT. Following the completion of his training, he joined the faculty of the Dana-Farber and Harvard Medical School. From 2002-2010, he served as Chief of the Division of Molecular and Cellular Oncology at the Dana-Farber. In 2010, together with Shirley Liu, he founded the Center for Functional Cancer Epigenetics at the Dana-Farber. Dr. Brown has been recognized by numerous awards and honors, including election to the National Academy of Sciences and the American Academy of Arts and Sciences.

Emily Chew, MD

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Dr. Chew received her medical degree and her ophthalmology training at the U. of Toronto, School of Medicine, in Toronto, Canada. She completed her fellowship in Medical Retina at the Wilmer Eye Institute, the Johns Hopkins Medical Institutes and the U. of Nijmegen, the Netherlands Her research interest includes phase I/II clinical trials and epidemiologic studies in retinovascular diseases such as AMD, diabetic retinopathy, ocular diseases of von Hippel-Lindau Disease, and others. She worked extensively in large multi-centered trials headed by the staff of DECA, including the Early Treatment Diabetic Retinopathy Study, the Age-Related Eye Disease Study, and the Age-Related Eye Disease Study 2, which she chairs. She also chairs the Actions to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study in participants with type 2 diabetes, working in collaboration with colleagues at the National Heart, Lung, and Blood Institute/NIH. Dr. Chew is the director of the clinical program in the Macular Telangiectasia Project (Mac Tel Project), which is an international study conducted in 22 clinics in 7 countries along with several basic science laboratories.

Kip Connor, PhD

Assistant Professor in Ophthalmology, Mass. Eye and Ear, Harvard Medical School Epigenetics Session

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Dr. Connor is an Assistant Professor of Ophthalmology at Harvard Medical School, Mass. 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 AMD 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 Dr. Connor's laboratory specializes in is the study of neuroimmunity in ocular development and disease. The laboratory is committed to understanding the role of the immune system in neovascular and neurodegenerative disease pathologies of the retina and identifying new potential therapeutic targets for these diseases. While the majority of the labs work takes place at Mass. Eye and Ear), the flagship academic center for the Harvard Medical School Department of Ophthalmology, it extends nationally and internationally through collaborations with worldwide leaders in the fields of complement biology, lipidomics, and neuro-immunology, along with partnerships with industry. 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 hublike 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

Professor of Ophthalmology, Professor in Immunology, Vice-chair, Research, Department of Ophthalmology, Duke Ophthalmology, Duke University School of Medicine

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Scott W. Cousins, MD is currently the Robert Machemer, MD, Professor of Ophthalmology and Immunology, Vice Chair for Research, Medical Director of the Duke Campus Practice 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 a retina-trained ophthalmologist who specializes in the diagnosis and treatment of macular diseases, especially AMD, diabetic retinopathy, and retinal vascular diseases. Dr. Cousins 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 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 the role of toxicant-induced RPE mitochondrial dysfunction. Other members of his research group investigate the mechanisms of treatment-resistant neovascular AMD, mechanisms of vascular leakage and blood-based biomarkers to predict macular disease progression. Dr. Cousins has published over 150 peer-reviewed manuscripts and book chapters addressing topics of research or clinical care of retinal disease, especially AMD. Dr. Cousins has received numerous scientific awards, including the prestigious Alcon Research Foundation Clinician Scientist Award. He has served as a member of many scientific review committees, as a member of the NEI

Advisory Council, and as president of AUPO Scientific Directors Council. Dr. Cousins is 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.

Patricia A. D'Amore, PhD, MBA

Director, Howe Laboratory Associate Chief of Basic and Translational Research, Mass. Eye and Ear Director of Research, Ankeny Scholar of Retinal Molecular Biology, Schepens Eye Research Institute of Mass. Eye and Ear, Charles L. Schepens Professor of Ophthalmology Professor of Pathology, Co-Director of AMD Center of Excellence Vice-Chair of Basic and Translational Research, Department of Ophthalmology, Harvard Medical School

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Dr. D'Amore earned her PhD in Biology from Boston University, completed a postdoctoral fellowship in physiological chemistry and ophthalmology at Johns Hopkins Medical School, and earned an MBA from Northeastern University. She is a Research Associate in Surgery and a long-standing member of the Program in Vascular Biology at Boston Children's Hospital. She is a Gold Fellow of ARVO. She is a committed teacher and mentor and is the recipient of the A. Clifford Barger Excellence in Mentoring Award from Harvard Medical School and the Everett Mendelsohn Excellence in Mentoring Award from Harvard University. In 2016, she was awarded the William Silen Lifeteime Achievement in Mentoring Award from HMS. In 2018, she received the Barbara J. McNeil Faculty Award for Exceptional Institutional Service from HMS and the Harvard School of Dental Medicine. An international expert in the field of angiogenesis, Dr. D'Amore has published more than 160 peer-reviewed papers and 64 reviews, as well as being editor or co-editor of four books. She is the recipient of numerous awards and honors, including the Alcon Research Institute Award, the Cogan Award from ARVO, the Rous-Whipple Award from the American Society of Investigative Pathology, the Endre A. Balazs Award from the International Society for Eye Research, and the Proctor Medal from ARVO. For her contributions to the development of anti-angiogenic therapy for retinal disease, Dr. D'Amore was a co-recipient of the 2014 António Champalimaud Vision Award, the highest distinction in ophthalmology and visual science. Most recently, she was elected as a Fellow of American Academy of Arts & Sciences, Medical Sciences. Dr. D'Amore's current research focuses on understanding the development and stabilization of the microvasculature. She is also investigating the pathogenesis of AMD, with a focus on inflammation.

Robert D'Amato MD, PhD

Judah Folkman Chair in Surgery Director, Center for Macular Degeneration Research Boston Children's Hospital and Professor of Ophthalmology, Harvard Medical School

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Dr. 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 determinants of angiogenic responsiveness within inbred mouse strains, he hopes to further understand the factors that regulate ocular angiogenesis in humans.

Margaret M. DeAngelis, PhD

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Dr. DeAngelis is currently a tenured 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 (Drs. Ivana Kim and Joan 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 AMD (RORA, ROBO1, CYP24A1) and then replicated these findings in diverse patient populations. We demonstrated that RORA, an intracellular target of cholesterol, interacted with other established AMD genetic risk factors (ARMS2/HTRA1) thus furthering the development of a unifying hypothesis underlying AMD pathophysiology. Our 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 our group to study diseases, including AMD and glaucoma has enabled us to employ and develop multi-omic approaches, including RNASeq, allele specific expression, epigenetic, and statistical/bioinformatic tools to delineate disease mechanism. This is done in an effort to develop appropriate therapeutic targets for these devastating forms of blindness. As an example, work from our laboratory identified Vitamin D pathway genetic risk variants in AMD that resulted in clinical trials for AMD. 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. She is a mentor and advisor to undergraduate, graduate, medical students, fellows, and junior faculty. Dr. DeAngelis has over 75 peer-reviewed publications, book chapters, and reviews. She serves on several editorial boards, and 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.

Francois Delori, PhD

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Dr. Delori primarily studies the retinal pigmented epithelium (RPE) lipofuscin in aging, age-related macular degeneration (AMD), and Stargardt disease. As a biophysicist, he has developed a new technique to quantify retinal autofluorescence from images acquired with scanning laser ophthalmoscopes. This modality allows him to study the distribution of lipofuscin at and around pathological tissue (drusen, geographic atrophy, and hyperpigmentation), follow the progression of disease, and monitor the effect of treatment designed to decrease lipofuscin accumulation. Dr. Delori also has introduced a novel method to measure the optical density of macular pigment and is currently working on methods to measure the light transmission of the ocular media.

Andrew Dick, MD

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Prof. Dick is qualified in medicine and also has a degree in Biochemistry (BSc (Hons)) from the University of London. During his medical education, he spent time as an MRC-sponsored research associate in Biochemistry with Professor Coleman in Yale. Following training in internal medicine and MRCP, he entered ophthalmology residency and also earned his postgraduate research degree, MD in Immunology in 1993 at the University of Aberdeen with Professor John Forrester. He underwent an MRC Post-Doctoral Fellowship to work with Dr. Jon Sedgwick at the Centenary Institute of Cancer Medicine and Cell Biology in Sydney, Australia. His clinical expertise is in inflammatory disorders of the eye, medical retina and vitreoretinal surgery. His research spans the fundamental, basic, and translational science conduit to early phase trials in inflammation as related to autoinflammatory, autoimmune, and degenerative retinal disease. Prof. Dick is a Fellow of the Academy of Medical Sciences in the UK for his significant contribution to research and scholarship. He was awarded the Alcon Research Institute Research annual award in 2011. Prior to becoming director of Europe's largest Vision Science and Ophthalmology centre, the UCL-Institute of Ophthalmology, he was Director of Research for the Faculty of Medicine and Dentistry at University of Bristol. He has previously been editor of *British Journal of Ophthalmology*, president of European Vision and Eye Research, and Master of Oxford Ophthalmological Congress. He is currently the vice president of ARVO.

Deborah Ferrington, PhD

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Dr. Ferrington is currently a Professor and Director of Research in the Department of Ophthalmology and Visual Neurosciences (OVNS) at the University of Minnesota, where she holds the Elaine and Robert Larson Endowed Vision Research Chair. Prior to joining the OVNS in 1999, Dr. Ferrington earned a BS degree in Biological Sciences and MD degree in Secondary Science Education from the University of Pittsburgh. She graduated from the University of Kansas with a PhD in Biochemistry and completed her postdoctoral studies at that institution studying how aging affects the degradation of oxidized proteins. Dr. Ferrington has graduate faculty appointments in the Department of Biochemistry, Molecular Biology, and Biophysics and in the Gerontology Minor Program, and is a member of the Stem Cell Institute at the University of Minnesota.

Evangelos S. Gragoudas, MD

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Dr. Gragoudas is presently the Charles Edward Whitten Professor of Ophthalmology at the 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 written or 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 has been 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 Joan W. Miller, MD, 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. Joan Miller, Tony Adamis, Pat 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 AMS. This award is considered the "Nobel Prize" in Vision Research. He has received numerous honors and awards: Academy Honor Award of American Academy of Ophthalmology; Retina Research Foundation prize of the Jules Gonin Lectureship; Research to Prevent Blindness Senior Scientific Investigators 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 ARVO.

Deeba Husain, MD

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Deeba Husain received her MD from Jawaharlal Nehru Medical College, Aligarh, India. She joined the Department of Ophthalmology at Mass. Eye and Ear to conduct post-doctoral research in photodynamic therapy and age-related macular degeneration with Gragoudas, MD and J.W. Miller, MD. She subsequently completed ophthalmology residency training at Harvard Medical School in 2001, followed by subspecialty training as a vitreoretinal fellow at Mass. Eye and Ear in 2003. She then worked at Boston University School of Medicine, where she served as Director of the Retina Service and Director of the retina fellowship training program. She joined MEEI in 2013 as full time faculty at the Retina Service of MEE, director of MEE Retina Consultants and Lecturer in Ophthalmology at HMS. Her Research focus is translational research in diseases of the retina with emphasis of age related macular degeneration.

Ivana K. Kim, MD

Evangelos S. Gragoudas Distinguished Scholar in Retina Research, Retina Service, Massachusetts Eye and Ear Infirmary, Co-Director, HMS Ophthalmology AMD Center of Excellence, Associate Professor of Ophthalmology, Harvard Medical School

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Dr. Ivana Kim is a graduate of Harvard Medical School and completed her ophthalmology residency and vitreoretinal fellowship at the Massachusetts Eye and Ear Infirmary. She maintains a busy clinical practice including surgical and medical retina, with a focus on age-related macular degeneration (AMD) and uveal melanoma. She has served as 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 Miller which initially involved studying the genetics of AMD utilizing a cohort of extremely discordant sibling pairs. In addition to confirming previously established genetic risk factors for AMD, they described novel associations in genes such as RORA, ROBO1, and CYP24A1. Current studies include deep sequencing to identify rare variants and analyses of ethnically diverse populations. More recently, Dr. Kim has participated in the phenotypic characterization of other ethnic cohorts from the US and abroad as well as evaluation of donor eyes collected by Dr. DeAngelis. Additionally, Dr. Kim contributes to the ongoing work at Mass Eye and Ear led by Dr. Deeba Husain and Dr. Miller investigating imaging and metabolomic biomarkers of AMD.

Aside from AMD, Dr. Kim's research also involves studying the molecular genetics and biomarkers of uveal melanoma in hopes of identifying particular pathways that could serve as targets for new drug therapies.

Aparna Lakkaraju, PhD

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Research in the Lakkaraju laboratory builds on fundamental insights from retinal cell biology to develop effective therapies for inherited and age-related macular degenerations (AMD), which affect millions of people worldwide and have limited therapeutic options. We focus on the retinal pigment epithelium (RPE), which performs numerous functions indispensable for vision and is a key site of injury in macular degenerations. Using state-of-the-art live-cell imaging, mouse models of disease, and novel genetic tools we investigate mechanisms that regulate cellular clearance, mitochondrial dynamics, RPE-photoreceptor communication, and immune privilege in the retina. We are also evaluating the potential of clinically approved drugs as promising therapeutics for macular degenerations.

Jessica Lasky-Su, ScD

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Dr. Lasky-Su is an Associate Professor in Medicine and associate statistician at Harvard Medical School and Brigham and Women's Hospital. Over the last 19 years she has focused on the analysis of genetics, genomics, and metabolomics data of various complex diseases with a primary focus on asthma over the last 15 years. The accumulation of these efforts has resulted in a productive track record of over 120 original research articles. Her ongoing R01 proposals—"The Integrative Metabolomics of Asthma Severity" (PI, R01HL123915), "Mechanistic insights into asthma pathogenesis through the integration of asthma genes, risk exposures, and metabolomics" (PI, R01HL141826), and Department of Defense grant, "Metabolomics of lead exposure and its role in respiratory disease"—has enabled her to develop a metabolomics research program at the Channing Division of Network Medicine that has been highly successful and synergistic in nature, as it has drawn together a diverse group of investigators across many institutions. She also serves in leadership capacities in a variety of consortiums, including currently acting as the chairman of the Consortium of METabolomic Studies (COMETS).

Goldis Malek, PhD

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Dr. Malek, earned her BS and BA in Biology and Psychology from the University of South Florida and her PhD in Vision Science and Physiological Optics from the University of Alabama at Birmingham, during which time she developed an interest in studying the pathology and cellular mechanisms underlying retinal diseases. She completed her postdoctoral studies at Duke University in the Department of Ophthalmology. Since 2007, she has been at Duke University where she holds Associate Professor appointments in the Departments of Ophthalmology and Pathology. She has a strong background in cell biology and a broad understanding of retinal and retinal pigment epithelial cell function in health and disease, including the pathology and pathogenic mechanisms involved in dry and wet AMD, an aged disease characterized by accumulation of extracellular debris, cellular degeneration/apoptosis, and angiogenesis/neovascularization. Dr. Malek's current research focuses on identifying and defining the mechanisms of action of nuclear receptors, a large superfamily of transcription factors, in aging and AMD. To date, her lab has identified several lipid, steroid hormone and toxin-activated nuclear receptors which may play a role in disease initiation and progression using genetic and pharmacological methods, both in *in vitro* models of retinal pigment epithelial and choroidal endothelial cells as well as in *in vivo* models. Her work has also focused on examining the therapeutic potential of targeting these receptors. Most recently, she demonstrated that activating the aryl hydrocarbon receptor ameliorates the severity of experimental choroidal neovascularization. Her work is currently funded by the National Eye Institute. Dr. Malek's laboratory research efforts have received a number of awards and recognitions, including an Alcon Research Institute Young Investigator Award, Edward & Della Thome Memorial Foundation AMD Research Award, Carl and Mildred Reeves Foundation Award, and Research to Prevent Blindness Sybil B. Harrington Scholar Award. She is active in the vision science community and serves as an Editorial Board Member for *Current Eye Research*, *Journal of Ocular Pharmacology and Therapeutics*, and *Molecular Vision*. She is a scientific grant review member for NIH and several

foundations. She has served on several committees within ARVO and ISER, including the Annual Meeting Program Committee, Animals in Research Committee, Communications Committee, and WEAVR.

Anders M. Näär, PhD

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Dr. Näär is a Professor of Cell Biology at Harvard Medical School and the Mass General Hospital Cancer Center. He earned a BS degree in biochemistry/biotechnology from the University of Lund, Sweden, in 1988, and a PhD in Molecular Pathology with Michael G. Rosenfeld at UC San Diego/HHMI in 1995, studying nuclear hormone receptor mechanisms of gene regulation. He was a postdoctoral research fellow with Robert Tjian at UC Berkeley/HHMI, where he discovered the human Mediator transcriptional co-activator complex. In 2001, Dr. Näär accepted an Assistant Professor position at the Department of Cell Biology, Harvard Medical School and the Mass General Hospital Cancer Center, and was promoted to Associate Professor in 2009, and Professor with tenure in 2012. A major focus of his lab is to understand transcriptional and microRNA regulatory mechanisms controlling cholesterol/lipid and energy homeostasis to guide novel therapeutic strategies for the treatment of cardiovascular disease, obesity, Type 2 diabetes, non-alcoholic fatty liver diseases (NAFLD/NASH), and AMD.

Magali Saint-Geniez, PhD

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Dr. 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 of Mass. Eye and Ear to pursue postdoctoral training in the laboratory of Patricia A. D'Amore, PhD, MBA. 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 of Mass. Eye and Ear 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, computational modeling, and molecular and metabolic biology.

Richard F. Spaide, MD

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Dr. Spaide is a specialist in retinal diseases. He has published more than 300 articles in peer-reviewed journals ad nearly 50 book chapters, as well as edited several books. He is a graduate of Muhlenberg College and Jefferson Medical College in Philadelphia. He completed his Ophthalmology Residency at St. Vincent's Hospital and Medical Center in New York and his Retina Fellowship at the Manhattan Eye, Ear, and Throat Hospital. He is in private practice at the Vitreous, Retina, Macula Consultants of New York. His major research interests include macular diseases, retinal surgery, and ocular imaging. Past highlights in his published papers include indocyanine angiography, fundus autofluorescence, characterization of central serous chorioretinopathy, application of mechanical engineering principles to macular hole formation, development of concepts concerning oxidative damage and characterization of lipid peroxides in Bruch's membrane, combination therapy for AMD, and development of new methodologies to image the retina and choroid. His current research interests include multimodal imaging, optical coherence tomography angiography, and new computer-based rendering techniques to visualize retinal anatomy. Dr. Spaide has been cited in multiple Who's Who and Best Doctors lists. He has received many awards: the Richard and Linda Rosenthal Foundation Award in the Visual Sciences, Prix Soubrane de la Recherche en Ophthalmologie, Award of Merit from the Retina Society, Henkind Award, Coscas Award, Nataraja Pillai Award from the Vitreoretinal Society of India, W. Richard Green MD Award, George Theodossiadis Award from the Greek Retinal Society, Founders Award from the American Society of Retinal Surgeons, Life Achievement Honor Award from the American Academy of Ophthalmology, Simon Gratz Award from Thomas Jefferson University, the Roger Johnson Award in Macular Degeneration Research, and the Gass Medal from the Macula Society. He has also received first place in two consecutive biennial Maculart competitions in Paris for medical images with artistic merit. He is on the editorial board of several journals, an associate editor of the journal *Retina*, and a former executive editor of the *American Journal of Ophthalmology*.

Trygve Tollefsbol, PhD, DO

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Dr. Tollefsbol is an UAB Professor of Biology and Senior Scientist in the UAB Comprehensive Cancer Center, the Comprehensive Center for Healthy Aging, the Nutrition Obesity Research Center, and the Comprehensive Diabetes Center as well as Director of the UAB Cell Senescence Culture Facility. He earned doctorate degrees in Molecular Biology and Osteopathic Medicine and trained with National Academy of Science members and a Nobel Laureate at Duke University and the University of North Carolina. Dr. Tollefsbol have published over 130 peer-reviewed papers, many of which have appeared in leading journals. His studies on epigenetics, cancer, and nutrition have been covered in *Reader's Digest*, *Newsweek*, *Women's Health* magazine, *Shape* magazine, AICR Newsletter, A*ARP The Magazine*, *More* magazine, and Nutrition Action HealthLetter (collectively >40 million readers). He has been featured as an Investigator in the Spotlight by the NIH [*Nutrition Frontiers* 5 (2), 3, 2014] as well as a Scientist in the Spotlight by *ScienceNow*. Dr. Tollefsbol is an associate editor for *Frontiers in Genetics*, a contributing editor of *Lewin's GENES* classic textbook, and founding and lead editor for Elsevier's *Translational Epigenetics Series*. Over 30 of his publications have received international accolades, such as best paper, press release and featured on the journal homepage. He has been ranked among the top three authors in the field of cancer epigenetics for idea exchange. Dr. Tollefsbol has given numerous invited scientific presentations worldwide, and his research has been highlighted in leading science news venues, such as *eScience News* and *ScienceDaily*. He has published 15 scholarly books on topics related to his research. He has been investigating epigenetic mechanisms in cancer, aging, and nutrition for more than 25 years. Dr. Tollefsbol has trained over 50 scientists, including 7 PhD or MD/PhD junior faculty, 13 postdoctoral fellows, and 31 graduate students.

Li-Huei Tsai, PhD

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Prof. Tsai is the Director of the Picower Institute for Learning and Memory at the Massachusetts Institute of Technology, a Picower Professor of Neuroscience, and an Associate Member of the Broad Institute. She earned her PhD from University of Texas Southwestern Medical Center in Dallas and completed postdoctoral training at Cold Spring Harbor Laboratories and Mass. General Hospital. Prof. Tsai became Assistant Professor of Pathology at Harvard Medical School and was promoted to tenure Professor at Harvard in 2002. She relocated to Massachusetts Institute of Technology in 2006. She was an Investigator of the Howard Hughes Medical Institute from 1997 to 2013. Prof. Tsai is also a Fellow of the American Association for the Advancement of Science, a member of the National Academy of Medicine, and an Academician of the Academia Sinica in Taiwan. Prof. Tsai is interested in elucidating the pathogenic mechanisms underlying neurological disorders that impact learning and memory. She takes a multidisciplinary approach to investigate the molecular, systems, and circuit basis of neurodegenerative disorders. Recent contributions include the identification of chromatin remodeling as a means to regulate memory gene expression and enhance cognitive function during neurodegeneration. Her lab also conducts epigenomic analysis of mouse and human Alzheimer's disease (AD) brain samples and has identified important contributions of dysregulated immune response genes in AD. Currently, the Prof. Tsai's lab uses induced pluripotent stem cell (iPSCs) derived from human subjects to model AD and large scale imaging, optogenetics, and in vivo electrophysiology to study the brain circuitry affected by AD. Recently, she and her colleagues invented a non-invasive sensory stimulation technology that proved effective in reducing AD pathology on animal models.

Zoltan Ungvari, MD, PhD

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Dr. Ungvari is Professor of Geriatric Medicine and Donald W. Reynolds Chair of Aging Research at University of Oklahoma Health Sciences Center, Oklahoma City. He earned his MD degree and a PhD in Pathology from Semmelweis University, Hungary, in 1996 and 2001, respectively. In 1999, he joined New York Medical College first as an American Heart Association postdoctoral fellow, then Assistant Professor. He rose through the academic ranks serving as Associate Professor from 2006. In 2009, Dr. Ungvari was recruited to the Reynolds Oklahoma Center on Aging of the University of Oklahoma HSC to his current post. He is an internationally recognized expert in the field of cerebrovascular aging and microvascular pathophysiology. His research focuses on the microvascular contributions to age-related cognitive decline and developing new therapies for this devastating condition. His laboratory is a fertile training ground for junior faculty, postdoctoral fellows, and graduate and medical students. Dr. Ungvari has published over 190 papers in peer-reviewed journals. He is active in several national and international research organizations and funding agencies. He participates in review committees at the NIH and the American Heart Association. He is a member of the Program Committee of the Microcirculatory Society and the Program Committee for the upcoming Brain 2019 conference. He is an advisor to the Vascular Cognitive Impairment Program of the University of Szeged and a member of the International Advisory Board of the University of Pecs, Hungary. Dr. Ungvari is currently associate editor for the American Journal of Physiology-Heart and Circulatory Physiology and for the Journal of Gerontology:Biological Sciences and deputy editor for GeroScience. He is a Fellow of the Gerontological Society of America and the American Heart Association. He has received the Nathan Shock Lecture Award (NIA), the August Krogh Award (Microcirculatory Society) and Established Investigator Award (AHA). His work has been consistently funded by the NIH and the AHA since 2004.

Demetrios Vavvas, MD, PhD

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Dr. Vavvas completed his BSc (First Class Honors) in Biology/ Neurosciences from McGill University. He received MD/PhD training (cum laude) in Medicine/Physiology at Boston University School of Medicine and ophthalmology training at Mass. Eye and Ear/Harvard Medical School, where he also served as chief resident and director of the eye trauma service. He completed his vitreoretinal fellowship at Mass. Eye and Ear, where he also served as the vitreoretinal chief fellow. Dr. Vavvas has been studying neurodegeneration and neuroprotection in animal models and his lab 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 detachment and other retinal degenerations. He has actively investigated the role of AMPK and its activators in vascular homeostasis and leakage as well as synapse integrity with aging and the role of autophagy regulation in drusen formation. He was the first to describe use of small gauge vitrectomy for complications of cataract surgery and intraocular foreign bodies. He is active in clinical studies of AMD and Retinal Detachment and has completed a physician-sponsored Investigational New Drug approved phase I-II study for dry AMD and high-dose statins, showing for the first time the potential for reversal of certain high-risk characteristics. He has also shown the pharmacogenetic interaction between vitamin supplementation and conversion to neovascular AMD. Along with Drs. Loewenstein and Eliott, he co-organizes the annual Mass. Eye and Ear Vitrectomy Course, now in its 9th year. Dr. Vavvas has received many awards, including the Research to Prevent Blindness Physician Scientist Award, the Alcon Research Institute, Young Investigator Award, and the ARVO Foundation/Pfizer Ophthalmics Carl Camras Translational Research Award.

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