



First Biennial Symposium on AMD

September 30 - October 2, 2010 • Boston



Cover image: A case of neovascular age-related macular degeneration with central atrophy, possibly due to retinal pigment epithelial tear, and associated subretinal hemorrhage. Ivana K. Kim, M.D.

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Welcome

Dear Colleague,

We are excited to welcome you to our first Biennial Age Related Macular Degeneration Symposium. Great advances have been made in the management of AMD over the past decade, and we are proud that many of these innovations have originated from the Harvard Department of Ophthalmology. Recent progress has brought improved imaging of the retina with ocular coherence tomography and scanning laser ophthalmoscopic angiography, and new therapies for neovascular AMD, most notably photodynamic therapy and anti-VEGF therapy. However, it is clear that we need to further our understanding of the pathogenesis of the disease in order to develop earlier and more effective interventions.

Breakthroughs in the genetics of AMD have moved the focus of investigation to inflammation and complement pathways, yet we do not thoroughly understand the role of the various components and how best to target these complicated systems therapeutically. Similarly, while we recognize overlap between AMD and both cardiovascular and neurodegenerative disorders, we have not elucidated all of the connections.

The goal of this symposium is to bring together experts from ophthalmology and vision research along with experts from the fields of inflammation, complement, neurodegenerative disorders, and cardiovascular disease for a stimulating exchange of ideas and questions. It is our hope that this forum will propel AMD research in new, creative directions and ultimately help the millions of patients afflicted with this blinding disorder.

Thank you for joining us,

Joan W. Miller, M.D., Patricia A. D'Amore, Ph.D., & Ivana K. Kim, M.D

Organizing Committee Co-Chairs

Patricia A. D'Amore, Ph.D.

*Co-Director of Research, Senior Scientist, and
Ankeny Scholar of Retinal Molecular Biology,
Schepens Eye Research Institute
Professor of Ophthalmology and Pathology,
Harvard Medical School*

Ivana K. Kim, M.D.

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Assistant Professor of Ophthalmology,
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Joan W. Miller, M.D.

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

Program

Thursday, September 30, 2010

6:30 - 8:30 PM **Cocktail Reception**
Massachusetts Eye & Ear, 7th Floor

Friday, October 1, 2010

8:00 - 8:15 **8:30 AM- 5:30 PM, Starr Center, 185 Cambridge Street, Boston, MA**
Welcome & Introduction
Joan W. Miller, M.D.
*Henry Willard Williams Professor of Ophthalmology & Chair,
Department of Ophthalmology, Harvard Medical School
Chief of Ophthalmology, Massachusetts Eye and Ear Infirmary and
Massachusetts General Hospital*

8:15 - 8:35 **Pathogenesis of AMD**
Disease mechanisms in atrophic age-related macular degeneration
Alan C. Bird, M.D.
Moorfields Eye Hospital

8:35 - 10:35 **Session 1: RPE/Bruch's membrane/choriocapillaris**

Gerard Luttj, Ph.D., Moderator
Johns Hopkins University School of Medicine

8:35 - 8:55 **The Oil Spill in Aging Bruch's Membrane**
Christine A. Curcio, Ph.D.
University of Alabama at Birmingham

9:00 - 9:20 **Bisretinoids of RPE and Macular Degeneration**
Janet Sparrow, Ph.D.
Columbia University

9:25 - 9:45 **Probing the Molecular Basis of Vascular Barrier Function and
Macromolecular Exchange at the Chorio-Retina Interface**
David T. Shima, Ph.D.
University College, London

9:50 - 10:35

Panel Discussion

Drs. Bird, Curcio, Shima, Sparrow

Moderator's Questions:

1. Autophagy appears necessary for normal turnover of lysosomes. Does decreased autophagy in RPE contribute to autofluorescence? How are increased lipofuscinogenesis and the decreased autophagy connected? Are these changes related to the exocytosis process?
2. Is Drusen formation associated with increased or decreased exocytosis? Or is the problem that exocytosed material can not get through the AMD Bruch's membrane which has poor hydraulic conductivity and increased lipid deposits?

10:35 - 11:00

Break

11:00 - 12:30

Session 2: Animal Models

Robert D'Amato, M.D., Ph.D., Moderator
Harvard Medical School

11:00 - 11:20

Double-stranded RNAs and Geographic Atrophy in AMD

Jayakrishna Ambati, M.D.
University of Kentucky

11:25 - 11:45

Modeling AMD in the Mouse Using an Inflammatory Signal Discovered in Drusen

Joe Hollyfield, Ph.D
Cleveland Clinic

11:50 - 12:30

Panel Discussion

Drs. Ambati, Hollyfield and Demetrios Varvas, M.D., Ph.D., Harvard Medical School

Moderators Questions:

1. What is the best animal model(s) that exist for wet AMD? For dry AMD? Why?
2. What are the limitations of the current animal models for wet AMD? For dry AMD?
3. Which aspects of each form of AMD are most important to be replicated in an animal model?
4. How important is inflammation in wet versus dry AMD? How faithfully do current models replicate this?
5. What role does complement activation play in current models of AMD?

12:30 - 1:45

Lunch

Starr Center Breakout Space

1:45 - 3:00

Session 3: Stem Cells/Tissue Engineering

Richard Masland, Ph.D., Moderator
Harvard Medical School

1:45 - 2:05

Retinal Repair with Stem Cells

Michael J. Young, Ph.D.
Schepens Eye Research Institute, Harvard Medical School

2:10 - 2:30

Differences in Stem Cell Strategies for the Treatment of Dry- and Wet-Age Related Macular Degenerations**Elizabeth Rakoczy, M.Sc., Ph.D.***University of Western Australia*

2:30 - 3:10

Panel Discussion*Drs. Young, Rakoczy and Constance L. Cepko, Ph.D., Harvard Medical School***Moderator's Questions:**

What is the evidence that stem cells can integrate in a functionally significant way into the retinal circuitry?

There is continuing progress in the development of stem cell technology for repairing damaged retinas. It is now certain that transplanted cells can survive in the retinal environment, at least during the span of tests in experimental animals. A leading question is whether or not enough cells can be introduced to be meaningful, and, most importantly, whether or not they form functional synapses and carry out functions that will support vision.

Specific issues:

1. How best to make retinal stem cells ready for transplantation?
2. What is the best place to put them?
3. How long will different cell types survive?
4. Before advancing to therapy, what proof will suffice of integration and function?
5. What is the risk that the cells will de-differentiate in vivo?

3:10 - 3:30**Break****3:30 - 5:30****Session 4: Genetics****Margaret De Angelis, M.D., Ph.D., Moderator***University of Utah*

3:30 - 3:45

AMD: Genetics to Genes and Pathways of Disease Pathogenesis**Anand Swaroop, Ph.D.***National Eye Institute*

3:50 - 4:05

Exome Sequencing as a Discovery Tool for Medical Genetics**Sekar Kathiresan, M.D.***Harvard Medical School*

4:10 - 4:25

Toward the Development of a Neuroprotective Strategy for the Treatment of Atrophic AMD**Donald Zack, M.D., Ph.D.***Johns Hopkins University School of Medicine*

4:25 - 5:30

Panel Discussion*Drs. Swaroop, Catharses, Zack and Hemin Chin, Ph.D., National Eye Institute; Leonard M. Hjelmeland, Ph.D., University of California, Davis; Ivana K. Kim, M.D.**Harvard Medical School; Debra Schaumberg, Sc.D., O.D., M.P.H., Harvard Medical School*

Moderator's Questions:

1. Based on current knowledge in AMD genetics can we predict AMD onset and progression?
2. Some groups are undertaking whole genome sequencing in unrelated case- controls and/or families to find, for example, non-coding RNA's or copy number variation, that may be associated with AMD risk - how can this information help us to uncover disease causality?
3. Some groups are undertaking whole exome sequencing in families in order to identify rare variants that may be associated with AMD risk -how can this information help us to uncover disease causality in a complex disease such as AMD?
4. What if any information would we gain, with respect to AMD causality, from the analysis of ethnically and environmentally diverse populations
5. How can we best validate genetic findings biologically (in vitro or in vivo) in an effort to pinpoint disease causality in AMD?

6:30-9:30 PM Gala Dinner

Taj Boston

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Saturday, October 2, 2010

8:30 AM - 5:30 PM, **Starr Center**

8:00 - 10:00 Session 5: Inflammation I

Anthony P. Adamis, M.D., Moderator
Genentech, Inc.

8:00 - 8:20 **The Alternative Complement Cascade Regulates Pathological Angiogenesis in the Retina**

Kip M. Connor, Ph.D.
Harvard Medical School

8:25 - 8:45 **Does Interaction between Macrophage-Mediated Inflammation and Mesenchymal Cells Regulate Vascular Maturation and Severity in Experimental CNV?**

Scott Cousins, M.D.
Duke University

8:50 - 9:10 **Therapeutic Interventions in The Complement Cascade**

John Lambris, Ph.D.
University of Pennsylvania

9:15 - 10:00

Panel Discussion*Drs. Connor, Cousins, Lambris***Moderator's Questions:**

Genetic data indicate that the complement pathway, and the inflammation associated with its activation, is operative in the pathogenesis of AMD. This panel will explore the mechanistic links between complement, inflammation and AMD by addressing the following questions:

1. At what stage(s) of AMD does the complement pathway play an active pathogenic role?
2. What aspect(s) of complement activation are important in the pathogenesis of AMD; inflammation, opsonization and/or MAC?
3. What is known about the mechanisms of GA initiation/progression? Are the negative CFH genotype/phenotype correlations definitive? Does inflammation play a role in GA?
4. Does inflammation play a role in the onset, progression and/or regression of CNV? Drusen?
5. Does adaptive immunity play a role in AMD?
6. Is an infectious etiology operative in AMD?
7. When does CNV stabilize and become resistant to anti-VEGF therapies? Does inflammation play a role?
8. Is CNV a (mal)adaptive response to choriocapillaris atrophy? If you could pharmacologically regress CNV, would it hasten the formation of geographic atrophy?

10:00 - 10:15 Break**10:15 - 12:15 Session 6: Inflammation II****Patricia A. D'Amore, Ph.D., Moderator***Schepens Eye Research Institute, Harvard Medical School*

10:15 - 10:35

Regulation of NLRP3 and AIM2 Inflammasome Signaling**Eike Latz, M.D., Ph.D.***University of Massachusetts Medical Center*

10:40 - 11:00

Inflammation in Atherosclerosis**Peter Libby, M.D.***Harvard Medical School*

11:05 - 12:15

Panel Discussion*Drs. Latz, Libby and Maria Grant, M.D., University of Florida*

Moderator's Questions:

AMD, atherosclerosis and Alzheimer's are all age-related degenerative diseases. Increasing evidence indicates a role for chronic inflammation in their pathogenesis. The correlation between vascular disease and AMD has led to the suggestion that similar pathogenic processes may be involved. Commonalities among the composition of atherosclerotic deposits, drusen and the plaques that characterize Alzheimer's, support this concept.

This panel discussion will examine the possible links and/or parallels among these pathologies by focusing on the following questions:

1. What are the major similarities between AMD and other age-related degenerative diseases such as atherosclerosis and Alzheimer's?
2. What are the major differences between AMD and other age-related degenerative diseases such as atherosclerosis and Alzheimer's?
3. What is the evidence for a role for inflammation in AMD? In atherosclerosis? In Alzheimer's?
4. What role does inflammation play in AMD? In atherosclerosis? In Alzheimer's? Is it the initiating injury or downstream of some other process?
5. What is the trigger for inflammation in these diseases?
6. Are these local or systemic diseases?
7. What is chronic inflammation? Why does the inflammation not resolve i.e. become chronic?
8. Are there approaches or models being used in the study of atherosclerosis and Alzheimer's that could be applied to the study of AMD?

12:15 - 1:30

Lunch

Starr Center Breakout Space

1:30 - 3:15

Session 7: Neurodegenerative Disease

Lindsay Farrer, M.D., Moderator
Boston University Medical Center

1:30 - 1:50

Neuropathology of Alzheimer Disease
Bradley Hyman, M.D., Ph.D.
Harvard Medical School

1:55 - 2:15

Neuroprotectin D1 (NPD1) is a Sentinel in Early Stages of Age-related Macular Degeneration (AMD) and Alzheimer's Disease (AD)
Nicolas G. Bazan, M.D., Ph.D.
Louisiana State University Health Sciences Center

2:15 - 3:15

Panel Discussion*Drs. Hyman, Bazan, and Lee Goldstein, M.D., Ph.D., Boston University Medical Center***Moderator's Questions:**

1. What clinical and basis research approaches that have lead to a better understanding of neurodegenerative disease (including those covered by the speakers as well as those not covered) may be useful in AMD research?
2. What role, if any, does APP or amyloid beta have in AMD pathogenesis?

Discussion topic: Overlap in biological pathways for AMD and other eye diseases with neurodegenerative disease

3:15 - 3:30

Break

3:50 - 5:00

Session 8: Imaging**Peter J. Bex, Ph.D., Moderator***Schepens Eye Research Institute, Harvard Medical School*

3:30 - 3:45

Imaging Metrics in Dry AMD**Frank Holz, M.D.***University Eye Hospital, Bonn*

3:50 - 4:05

Imaging Microstructural Changes within and beneath the Retina *In Vivo* in non-Advanced AMD**Cynthia A. Toth, M.D.***Duke University Medical Center*

4:10 - 4:25

Adaptive Optics Imaging in Age-Related Macular Degeneration**Mina Chung, M.D.***University of Rochester Medical Center*

4:25 - 5:00

Panel Discussion*Drs. Holz, Toth, Chung, and François C. Delori, Ph.D., Schepens Eye Research Institute, Harvard Medical School***Moderator's Questions**

Recent developments in retinal imaging provide unprecedented non-invasive quantification of human and animal models of AMD, and even simultaneous behavioral assessment of visual function.

This panel discussion will examine the new opportunities opened by in vivo imaging by focusing on the following questions.

1. What additional systems does the field need to link imaging and visual function?
2. What are the imaging limitations for animal models of AMD and what is needed to overcome them?
3. What progression estimates and standards are needed in the field?
4. How can we integrate increasingly high resolution imaging into clinical practice?

5. What image processing methods are available to analyze retinal images and what is needed or being developed for detection and progression/ regression assessment?
6. What are the mechanisms and clinical consequences of the regression of drusen and how can imaging inform our understanding of these processes?
7. What is the relationship between letter acuity improvements following Macugen/ Avastin injections and retinal imaging?
8. While FAOSLO imaging can indirectly assess retinal pigment epithelium, what developments are needed for direct RPE imaging?
9. What are the clinical and technological limitations of the current use of autofluorescence and OCT imaging?

5:00 - 5:30

Closing Summary

Dean Bok, Ph.D.

Jules Stein Eye Institute

Abstracts of Talks

Disease mechanisms in atrophic age-related macular degeneration

Alan C. Bird, M.D.

The structures involved in age-related macular disease are the choroid, Bruch's membrane retinal pigment epithelium (RPE), and photoreceptor cells. Changes in each represent a potential target for treatment.

Choriocapillaris: In young healthy individuals, the choriocapillaris is formed of a sinusoidal complex, which is fenestrated and lacks tight junctions. In one morphometric study, it was found that the density of the choriocapillaris decreases with age in eyes without AMD. In another study, neoprene casts were used to show the change to a tubular vascular system from a sinusoidal system with age. In advanced AMD, loss and narrowing of the choriocapillaris occurs. It is believed that the nature of the choriocapillaris is determined, in part, by the outward constitutive expression of VEGF by the RPE. The changes in the choroid may be due to intrinsic vascular disease or to failure of VEGF expression by RPE or blocking outward diffusion of VEGF from RPE.

Bruch's membrane: Many studies have shown that Bruch's membrane becomes thicker with age. It contains several proteins involved in the complement cascade suggesting that inflammation may play a role in causing cell death. Alternatively the proteins may be oligomerised such they no longer have the biological properties of the monomers. It also contains considerable quantities of lipid and represents a barrier to metabolic exchange between the choroid and RPE.

Retinal pigment epithelium: It has been recognised that the levels of lipofuscin increase with age. Lipofuscin is formed of ethanolamine and vitamin-A. Geographic atrophy is preceded by high levels of lipofuscin as determined clinically as hyperautofluorescence. Lipofuscin is a source of free radicals when exposed to short wavelength light. In addition it interferes with degradation of the phagosome thus reducing the amount of lipid that is available for photoreceptor outer segment renewal. The higher levels of geographic atrophy in Iceland when compared with the rest of Western Europe may be explained by the high intake of vitamin-A in Iceland.

Photoreceptor cells: Both clinical and histopathological studies imply that there is major loss of photoreceptor cells prior to loss of RPE during the evolution of geographic atrophy. It is also apparent that loss of rod photoreceptor cell is much more profound than loss of cones.

The Oil Spill in Aging Bruch's Membrane

Christine A. Curcio, Ph.D.

1. Aging is the largest risk factor for age-related macular degeneration (ARMD). Drusen and basal linear deposits are ARMD-specific lesions. A large age effect confined to BrM, tissue compartment of the lesions, is the deposition of oil red O-binding neutral lipid thought to impair transport to the retinal pigment epithelium (RPE) and retina.
2. Biochemical, histochemical, and ultrastructural methods together show that this lipid can be accounted for by 60 nm diameter particles with ultrastructure and flotation properties resembling lipoproteins.
3. The high enrichment with esterified cholesterol (EC) points to a lipoprotein particle with apolipoprotein B on its surface. ApoB mRNA and protein is expressed in RPE, along with microsomal triglyceride transfer protein, required for its secretion. ApoB secretion has been achieved in human- and rat-derived RPE cell lines.
4. Isolated lipoproteins are rich in the fatty acid linoleate and poor in docosahexaenoate. This points away from one upstream lipid source (outer segments) and towards another (plasma lipoproteins). The cholesterol source is unknown and could be outer segments, plasma lipoproteins, endogenous synthesis, or a combination.
5. With aging, lipoprotein particles accumulate in a thin layer 3-4 deep external to the RPE basal lamina ("Lipid Wall"), the most plausible direct antecedent to basal linear deposit. This is the Oil Spill in BrM.
6. EC and phosphatidylcholine are abundant components of the neutral lipid found in all drusen (Wolter and Falls, 1962; Wang, PLoSOne, 2010). Extractable lipids account for $\geq 40\%$ of druse volume. Membranous debris, the major component of soft drusen, may be lipoprotein-derived debris, as lipid-preserving ultrastructural studies show particles.
7. LDL, an apoB lipoprotein, is a known disease initiator in artery walls, where it is retained and modified, via oxidative and other mechanisms, thereby launching numerous downstream life-threatening events ("Response to retention"). In the eye, an apoB-lipoprotein of intra-ocular origin, perhaps part of lipophilic nutrient delivery and recycling system, could play a similar role. This hypothesis fits well with one stating that BrM lipid hydroperoxide (LHP) deposition can act through inflammation to evoke choroidal neovascularization (Spaide, 2003). LHP are enriched with peroxidized linoleate (Spaide, 1999), the abundant fatty acid of lipoproteins. LHP are potently bio-active, and when injected in animals (Tamai, 2002; Baba, 2010), reliably evoke neovascularization.
8. Borrowing from work in cardiovascular disease, we can convert this hypothesis into rationale for creating new model systems and new diagnostic techniques, preventions, and treatments based on lesion mitigation. Response to the Oil Spill could involve skimmers and dispersants to minimize it directly, "top kill" to slow a putative flow from the RPE, and "bottom kill" to slow the flow by reducing the input lipids through dietary manipulation.

Bisretinoids of RPE and Macular Degeneration

Janet R. Sparrow, Ph.D.

Vitamin A aldehyde-conjugates accumulate as lipofuscin in retinal pigment epithelial (RPE) cells and have been linked to disease processes in some monogenic forms of retinal degeneration as well as in age-related macular degeneration. These bisretinoid constituents of lipofuscin are unique to RPE and in addition to A2E include all-trans-retinal dimer (atRAL dimer), all-trans-retinal dimer-phosphatidylethanolamine (atRAL dimer-PE), all-trans-retinal dimer-ethanolamine (atRAL dimer-E) and a phosphatidyl-dihydropyridine bisretinoid we call A2-DHP-PE. For these bischromophores, absorbance maxima in the visible spectrum are conferred by systems of conjugated double bonds extending along the arms of the molecules and into the six-membered rings. The excitation and emission spectra of these compounds can account for fundus autofluorescence.

Our efforts to understand damaging events initiated by these bisretinoids have revealed that photoexcitation of A2E by wavelengths in the visible spectrum leads to singlet oxygen production and photooxidation of A2E. By employing liquid chromatography (LC) coupled to electrospray ionization mass spectrometry (ESI-MS) together with tandem mass spectrometry (MS/MS), we have demonstrated that A2E undergoes photooxidation-induced degradation and we have elucidated the structures of some of the aldehyde-bearing cleavage products. Given that AMD pathogenesis has been linked to variants in the genes encoding complement factors, it is potentially significant that the bisretinoid compounds of RPE lipofuscin can also activate complement. Therapeutic strategies that target these molecules include antioxidants, inhibitors of complement activation, small molecules that inhibit their formation and gene-based therapy.

Probing the molecular basis of vascular barrier function and macromolecular exchange at the chorio-retina interface

David T. Shima, Ph.D.

Vascular endothelial cells tailor their differentiation programs to meet the particular needs of tissues and organs. Perhaps one of the most fascinating examples occurs during the formation of the vasculature that serves the retina. The inner retinal vasculature is part of the blood-retinal barrier (BRB), strictly regulating access to neural tissue. The vascular supply for the outer retina comes from the fenestrated choriocapillaris, consisting of endothelial cells with numerous pores that allow rapid exchange of nutrients and waste to meet the needs of the RPE and photoreceptors. Additionally, the RPE supplies the second part of the BRB via its barrier function and selective transport.

Little is known about the structural and molecular basis of exchange between the fenestrated choriocapillaris and the RPE/photoreceptors, but it is reasonable to posit that dysfunction of this neurovascular unit contributes to age-related maculopathy. We are developing assays and tools that will help us better understand communication at the chorio-retina interface. We have developed a cell-based model for fenestra formation and have discovered several components that are critical for fenestra biogenesis. We aim to characterize the molecular basis of the fenestral pore and hope to use this knowledge to specifically manipulate fenestra function *in vivo*. We have also developed assays for transport between the choriocapillaris and the RPE *in vivo*, using various fluorescent tracers, and aim to characterize the cellular basis of exchange and alterations that may occur in models of disease.

Double-stranded RNAs and geographic atrophy in AMD

Jayakrishna Ambati, M.D.

The late stage of age-related macular degeneration (AMD) known as geographic atrophy remains an unmet medical need. We have demonstrated that small interfering RNAs (siRNAs) can suppress angiogenesis in numerous model systems via activation of the immune receptor toll-like receptor-3 (TLR3) (Kleinman et al. Nature 2008; Cho et al. PNAS 2009). Subsequently we reported that TLR3 activation by synthetic long double-stranded RNAs (dsRNAs) can induce cell death of human retinal pigmented epithelium (RPE) cells in culture and RPE cell degeneration in mice (Yang et al. NEJM 2008). Here we report the identification of pathological endogenous long dsRNAs specifically in the RPE of human eyes with geographic atrophy. We show that reintroduction of these pathological long dsRNAs induces a geographic atrophy-like phenotype in mice and cell death of human RPE cells in culture, fulfilling molecular Koch's postulates. These findings identify disturbances in dsRNA homeostasis as a potential cause of geographic atrophy and provide a therapeutic rationale for interrupting dsRNA induced cell death.

Modeling AMD in the Mouse Using an Inflammatory Signal Discovered in Drusen

Joe Hollyfield, Ph.D

Introduction: Mice immunized with a hapten (CEP) generated by oxidation fragmentation of docosahexaenoic acid (DHA) adducted to mouse serum albumin (CEP-MSA) shows multiple lesions in the retinal pigment epithelium (RPE) within 3 months of the initial immunization. To follow the persistence of the RPE pathology and the functional consequences of these lesions the following study was performed:

Methods: C57Bl/6 mice, 2-3 months old were immunized with CEP-MSA or MSA controls in complete Freund's adjuvant (CFA) at day 0, followed by challenge at day 10 in incomplete Freund's adjuvant (IFA). A third immunization was given at three months (described in Nature Med. 2009, 14:194). Mice were maintained for an additional 6 months. Scotopic and photopic ERG analysis was performed under anesthesia before sacrifice. Blood was taken for direct ELISA detection of CEP-antibody titer, which was performed in 96-well plates coated with CEP-BSA (100 μ l/well) at 1:1000 dilution in PBS and incubated at 37 °C for 1 hr, using 1% BSA solution as a blank control. One eye from each animal was prepared for routine histology and the other for immunocytochemistry.

Results: CEP-antibody titers were higher in the CEP-MSA immunized mice than in any other group. Both scotopic and photopic ERG amplitudes were reduced by 20-30 percent in the CEP-MSA, and 10-12 percent in the MSA immunized mice when compared to those in non-immunized control animals. Severe focal lesions at the level of the RPE were observed in the fundus of the CEP-MSA immunized mice. These lesions involved a few RPE cells to expansive areas over 200 μ m in length. The photoreceptor layer was thinner over regions with severe pathology, but appeared normal in areas where the RPE is not affected.

Conclusions: These data demonstrate that changes in the RPE in the acute AMD mouse model persist long after the completion of the immunization schedule. The focal changes in photoreceptor density over areas with RPE lesions suggest that the reductions in ERG responses are caused by decreases in photoreceptor density overlying areas of RPE pathology.

Retinal Repair with Stem Cells

Michael J. Young, Ph.D.

My laboratory is directed toward repair of the mature diseased central nervous system, specifically the degeneration that occurs in the retina during disease or injury. We have focused on the use of stem or progenitor cells, which we have isolated from a number of regions of the neuraxis of several different mammalian species. During the last 5 years, work in my lab has established that neural stem or progenitor cells overcome the barrier to morphological integration present in the mature mammalian retina. We have also demonstrated that neural stem cells are an inherently immune privileged tissue, and survive in conventional sites in allogeneic recipients. We have also isolated stem cell from the mouse, pig, and human retina, and shown that such cells are capable of photoreceptor differentiation. We have now embarked upon a series of studies in the pig retina, with the goal of establishing functional connectivity between donor retinal stem cells and the mature, diseased host retina. By using large animals such as the domestic pig, we can take advantage of the availability transgenic donor and hosts, so that we can graft GFP + donor cells into RP porcine recipients, the large eye size that allows traditional pars plana vitrectomy and other retinal surgical techniques; and the ability to evaluate the functional impact of the graft with techniques such as multifocal ERG. This approach will allow us to make important steps toward our goal of functional restoration of vision.

Differences in Stem Cell Strategies for the Treatment of Dry- and Wet- Age Related Macular Degenerations

Elizabeth Rakoczy, M.Sc., Ph.D.

Introduction: Both dry- and wet-ARMD affect the macular region of the retina. However, the etiologies of the two diseases are significantly different and it remains uncertain whether there is a continuous conversion of dry-ARMD into wet-ARMD. Dry-ARMD is associated with the gradual loss of photoreceptors while wet-ARMD is characterized by the growth of abnormal blood vessels into the subretinal space and the sudden loss of vision. Considering these differences the treatment strategies developed for one may be ineffective for the other. However, stem cell-based therapies might offer long term treatments for both conditions. This study aimed to investigate the feasibility of stem cell-based treatment strategies for both dry- and wet-ARMD.

Methods: Bone marrow-derived adult CD90+ Marrow Stromal cells (MSC) were differentiated in vitro or implanted directly in to the eyes of RCS rats. Bone marrow-derived Mesenchymal Precursor Cells (MPC) positive for STRO-1 were expanded. To generate a model of wet-ARMD, CBH-rnu-rats were subjected to laser photocoagulation. STRO-1+MPC were injected into their eyes one day post-photocoagulation. Eyes were analyzed by fundus photography, fluorescein angiography, histology and immunohistochemistry.

Results: CD90+ MSC cells not only differentiated into cells carrying photoreceptor markers in vitro but their subsequent transplantation into the eyes of RCS rats resulted in their differentiation into photoreceptors which were capable of attracting synaptic vesicles. STRO-1+ MPC-injected laser-photocoagulated eyes demonstrated a 70% reduction in the number of laser lesions with fluorescein leakage compared to uninjected laser photocoagulated eyes of CBH-rnu-rats. Light microscopy showed that the thickness of the choroidal neovascular membrane was significantly reduced in the STRO-1+ MPC-injected group of lasered CBH-rnu-rat eyes.

Conclusions: We have shown that depending on the selection markers, bone marrow-derived cells could be used for the treatment either dry- or wet-ARMD.

AMD: Genetics to Genes and Pathways of Disease Pathogenesis

Anand Swaroop, Ph.D.

AMD is caused by interaction of genetic susceptibility variants with environmental factors. To dissect the contribution of genetic variants, we have performed genomewide association study with over 3300 case-controls. In addition to validating reported variants at CFH and ARMS2, we confirmed C2/CFB, C3 and CFI and identified variants near TIMP3 and at four HDL-associated loci. We have recently focused our efforts on elucidating the contribution of ARMS2 versus HTRA1 to AMD susceptibility. We have also initiated studies to identify causal variants at all reported loci. NEI has also taken steps to put together a consortium for meta-analysis of AMD-GWAS data from multiple groups, with a goal to identify all genetic variants associated with AMD.

Exome Sequencing as a Discovery Tool for Medical Genetics

Sekar Kathiresan, M.D.

We sequenced all protein coding regions (the “exome”) in two family members with combined hypolipidemia, marked by extremely low plasma concentrations of low-density lipoprotein (LDL) cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol. Affected individuals were compound heterozygotes for two distinct nonsense mutations in the gene *ANGPTL3* (angiopoietin-like 3). The *ANGPTL3* protein is reported to inhibit lipoprotein lipase and endothelial lipase, thereby increasing plasma triglyceride and HDL cholesterol concentrations in rodents. Our finding highlights a role for *ANGPTL3* in LDL cholesterol metabolism in humans and demonstrates the utility of exome sequencing for identification of novel genetic causes of inherited disorders. Using this study an example, I will highlight the role of exome sequencing as a discovery tool for medical genetics.

Toward the Development of a Neuroprotective Strategy for the Treatment of Atrophic AMD

Donald Zack, M.D., Ph.D.

The last few years have seen impressive gains in the treatment of retinal neovascularization associated with the advanced or “wet” form of age-related macular degeneration (AMD). Unfortunately, however, treatment options for the more common type of AMD, dry or atrophic AMD, remain limited. In an effort to develop novel treatment approaches for atrophic AMD, we have been developing high content screening (HCS) approaches designed to identify novel cytoprotective and neuroprotective molecules that promote photoreceptor and RPE survival, and have been concentrating particularly on compounds that modulate the response of photoreceptor and RPE cells to oxidative damage and endoplasmic reticulum (ER) stress. HCS combines the large-scale capability of directed high throughput screens (HTS), with the complexity of cell-based assays. The benefit of HTS methods is that they can rapidly analyze many thousands of compounds, but on the down side, they usually measure only one or a few biochemical parameters. The advantage of a cell-based, and in particular an image-based assay such as we have been developing, is that it can measure multiple complex phenotypic outputs at the cellular level and thus provide additional information about the activity of candidate molecules. Although these studies are still at an early stage, our screens have successfully identified some molecules that appear to promote photoreceptor differentiation and survival, and we are hopeful that this HCS-based approach will lead to the discovery of small molecules that can be developed into novel treatment approaches to slow down, and ideally halt, the progression of atrophic forms of AMD.

The Alternative Complement Cascade Regulates Pathological Angiogenesis in the Retina

Kip M. Connor, Ph.D.

Introduction: Proliferative ischemic retinopathies (PRs) such as retinopathy of prematurity (ROP) and proliferative diabetic retinopathy (PDR) are the leading causes of blindness in pediatric and working age populations in industrialized countries. These diseases present an inflammatory component in part mediated by the complement signaling cascade. Our current work seeks to elucidate the degree and mode of action by which the alternative complement cascade is involved during oxygen-induced retinopathy (OIR).

Methods: Transgenic mice deficient in alternative complement (Cfd^{-/-}) signaling or containing only a functional alternative complement pathway (C1q/Mbl A/C^{-/-}) along with control mice were used in this study. Proliferative retinopathy was mimicked in an oxygen-induced mouse model where pups were exposed to 75% O₂ from postnatal day (P) 7 to P12 and returned to room air for 5 days. Retinas were collected and analyzed for vessel loss, vessel regrowth, neovascular disease severity and resolution of disease. Immunohistochemistry and laser capture microdissection were used to localize key complement proteins in the retina.

Results: Neovascularization was assessed at P17, P21 and P25 in C57Bl/6, Cfd^{-/-}, and C1q^{-/-}-Mbl A/C^{-/-} mice with OIR and it was determined that loss of the alternative complement signaling cascade increases the severity and duration of retinopathy ($p \leq 0.0001$) in these mice. In whole retina, Cfb mRNA expression was significantly upregulated while Cfh and Cd55 mRNA expression was significantly decreased in OIR vs. normoxia. Cfb was found to coat neovascular tufts that were closely associated with microglia, which was not observed in normal vessels. Additionally, these neovascular tufts produced elevated levels of the chemokines, Ccl3 and Ccl2, leading to recruitment of microglial subpopulations to the site of pathologic vessel growth. Loss of these chemokines leads to a disease phenotype similar to that of the Cfd^{-/-} mice.

Conclusions: The data reported in this study defines a mode of action whereby the alternative complement cascade is protective during retinopathy and mediates the resolution of neovascular tufts during this disease process. Here neovascular tufts down regulate Cd55 allowing for deposition of alternative complement proteins, in turn these tufts secrete chemokines that recruit microglia that aid in the resolution of retinopathy.

1. Connor, K.M., Krah, N., Dennison, R., et al. Quantification of Oxygen Induced Retinopathy in the mouse – A Model of Vessel Loss, Vessel Regrowth, and Pathological Angiogenesis. *Nature Protocols*. 2009; 4(11):1565-73.

2. Connor, K.M., SanGiovanni, JP., Lofqvist, C., et al. Increased dietary intake of omega-3-polyunsaturated fatty acids reduces pathological retinal angiogenesis. *Nature Medicine*. 2007;13(7):868-73.

Does Interaction between Macrophage-Mediated Inflammation and Mesenchymal Cells Regulate Vascular Maturation and Severity in Experimental CNV?

Scott Cousins, M.D.

Scott Cousins, Diego Espinosa-Heidmann, Goldis Malek, Duke Center for Macular Diseases, Duke Eye Center, Durham, NC

In spite of the great success of anti-VEGF agents in the treatment of neovascular AMD, approximately 20% of patients demonstrate resistance to therapy. Our clinical research suggests that choroidal new vessel (CNV) maturation, especially the development of arteriolarization, is a major cause of resistance. In previous research, we have shown that bone marrow-derived mesenchymal progenitor cells seem to be a major regulator of fibrosis and maturation in laser-induced CNV. In this presentation, we will show data to suggest that communication between macrophages and mesenchymal cell types might contribute to maturation. Specifically, we postulate that osteopontin, a macrophage retention factor possibly secreted by mesenchymal progenitors, leads to localization on monocytes near maturing vessels. Conversely, recruited blood-derived macrophages possibly secrete factors such as PDGF, which promote differentiation of mesenchymal progenitors into myofibroblasts and pericytes contributing to fibrosis and vessel maturation, respectively.

Therapeutic Interventions in The Complement Cascade

John Lambris, Ph.D.

Discoveries in the past decades impressively illustrated the two faced nature of the complement system. The rapid detection and elimination of foreign or apoptotic cells represents an essential layer of protection against microbial intruders and contributes to cell homeostasis. On the other hand, excessive activation or insufficient regulation of the cascade is known to contribute to a rapidly growing number of diseases, as e.g. in the case of age-related macular degeneration (AMD). While therapeutic modulation of the complement response has long been recognized as a promising approach for treating such disease states, the way to effective complement-targeted therapeutics has found to be more difficult than initially expected. The recent approval of the first complement-specific drug (Eculizumab) and the initiation of clinical trials with the complement inhibitor Compstatin for the treatment of AMD marked important milestones in the field and fueled the complement-targeted drug discovery engine. I will discuss promising points-of-intervention within the complement cascade and provide an overview over current treatment strategies. I will especially focus on recent achievements in the development of Compstatin, which evolved into a highly promising drug candidate with the potential to improve dry and wet forms of AMD. Novel crystal structures, such as Compstatin in complex with C3, provided long-anticipated insight into the binding mode of the inhibitor and draw a clearer picture on how Compstatin efficiently blocks all initiation and amplification pathways. Detailed thermodynamic studies revealed the importance of individual energy contributions to the binding affinity and showed that previous optimization steps predominantly improved complex stability rather than complex formation. I will introduce novel design approaches for enhancing the inhibitory efficacy and present current strategies to improve the plasma half-life of Compstatin in order to broaden treatment applications and facilitate its use in animal models. Finally, I will present data on the efficacy of compstatin to drusen disappearance in a primate model with early-onset macular degeneration after 6 month of intravitreal injection.

Regulation of NLRP3 and AIM2 Inflammasome Signaling

Eike Latz, M.D., Ph.D.

Innate immunity evolved to recognize microbial infection and to respond to danger signals that appear under disease conditions. The most recently described innate immune receptor family is the Nod-like receptor (NLR) family. The NLR member NLRP3 and the adapter protein ASC form a multi-molecular complex termed the NLRP3 inflammasome. Inflammasomes control the activity of caspase-1, which cleaves and activates the pro-form of the inflammatory cytokines IL-1 β and IL-18. The NLRP3 inflammasome can be activated by various membrane active bacterial toxins (e.g. nigericin, maitotoxin or gramicidin) or after phagocytosis of crystalline materials (e.g. silica, asbestos, monosodium urate or alum). The mechanisms by which the NLRP3 inflammasome is activated by physico-chemical diverse activators are not well understood.

We demonstrate that crystals activate the NLRP3 inflammasome in a process that requires phagocytosis and we found that crystal uptake leads to lysosomal damage and rupture. Furthermore, sterile lysosomal damage is also sufficient to induce NLRP3 activation and inhibition of phagosomal acidification or inhibition or lack of cathepsins impairs NLRP3 activation. These results indicate that the NLRP3 inflammasome can sense lysosomal damage as an endogenous danger signal. Our results demonstrate a novel strategy of immune cells to recognize different classes of stimuli by a common, indirect mechanism.

Cytosolic DNA can also induce caspase-1 activation and release of IL-1 β cytokine family members. DNA delivered into the cytoplasm can activate a NLRP3-independent yet ASC dependent inflammasome. AIM2, a member of the PYHIN protein family, has a pyrin domain and a HIN200 DNA binding domain. We found that AIM2 binds to dsDNA and forms an inflammasome together with ASC leading to caspase-1 activation. These pathways are promising new targets for pharmacological inhibitors with broad clinical significance.

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Inflammation in Atherosclerosis

Peter Libby, M.D.

According to the classical view, atherosclerotic plaques consist of a bland deposit of lipid trapped in a maze of smooth muscle cells and extracellular matrix. Multiple lines of evidence now challenge this notion, and point to inflammation as central to all stages of atherosclerosis including plaque development, disruption, and thrombosis. Atherogenesis begins with activation of the endothelium as shown by surface expression of adhesion molecules that capture blood leukocytes. Many risk factors augment the expression of pro-inflammatory cytokines by cells involved in atherogenesis. Chemoattractant cytokines promote migration of monocytes into the arterial intima and mature into macrophages when stimulated by other cytokines. These phagocytic cells drive many aspects of subsequent atherosclerotic progression, and also contribute to the propensity of plaques to rupture by production of proteases that weaken the fibrous plaque cap, and to thrombosis by production of tissue factor. Such inflammatory processes provide targets for molecular imaging of atherosclerosis under intense evaluation for application to patients. Thrombosis provoked by disrupted atheromatous plaques causes most acute coronary events. A disruption of the physical integrity of the collagenous extracellular matrix of the fibrous cap overlying the atheroma's thrombogenic lipid core causes most fatal coronary thrombi. Inflammation critically regulates the stability of human atherosclerotic plaques. Inflammatory cytokines can elicit the expression by macrophages and smooth muscle cells of enzymes that can weaken the extracellular matrix among them, the matrix metalloproteinases (MMPs) and certain cysteinyl elastases that belong to the cathepsin family. In particular MMP interstitial collagenases can attack the usually protease-resistant interstitial collagen molecule that confers most of the biomechanical strength on the plaque's protective fibrous cap. Experiments in genetically-altered mice have proven the importance in vivo of MMP collagenases in determining the plaque's content of collagen, as well as the organization and architecture of the lesion's collagen. Inflammation regulates both the synthesis of collagen and the enzymes involved in its degradation. Lipid-lowering can reduce inflammation, and collagenase expression, and increase collagen content of experimental atheromata. Inflammation also augments fibrinogen levels, and boosts production of the major inhibitor of fibrinolysis, plasminogen activator inhibitor-1. Thus inflammation not only affects the "solid state" of the plaque, but also the "fluid phase" of the blood in a way that not only favors coagulation but at the same time defeats our endogenous fibrinolytic defenses. Indeed, increasing evidence supports an inextricable intertwining of inflammation and thrombosis. For example, platelets when activated release multiple mediators of inflammation. Thus platelet activation not only contributes to thrombosis, but promotes inflammation. We can now begin to understand the molecular basis of atherothrombosis, and how dysregulation of inflammation controls clinical manifestations of atherosclerotic plaques. Blood biomarkers of the inflammatory response strongly correlate with outcomes in individuals with or without known atherosclerotic disease. Recent clinical trials support the clinical relevance of the inflammation as a driver of atherothrombosis. Apparently well individuals without hypercholesterolemia, but with signs of inflammation (hsCRP > 2mg/L) randomized to a statin showed a marked decrease in cardiovascular events and reduction in all cause mortality. Thus, the growing recognition of the importance of inflammation in atherosclerosis has both theoretical and practical clinical implications. Inflammation in atherosclerosis has now transitioned from being a theory to a practical clinical tool for risk prediction and guiding therapy. The mastery of the biology of inflammation during atherogenesis – its triggers and effectors – opens new opportunities for the development and evaluation of novel therapeutic interventions.

Neuropathology of Alzheimer Disease

Bradley Hyman, M.D., Ph.D.

Alzheimer disease is a neurodegenerative disorder marked by the presence of abnormal protein aggregates both within neurons, neurofibrillary tangles, and in the neuropil, amyloid senile plaques. Marked neuronal loss of a specific subpopulation of neurons occurs. However, current thinking indicates that the fibrillar protein deposits may not be the (most) toxic species, and instead soluble or oligomeric forms may dominate neurodegenerative pathogenesis. Moreover, transgenic mouse models as well as human neuropathological studies suggest that selective vulnerability may be, in part, due to progression transsynaptic degenerative programs. Alzheimers disease may well contain some features that are represented in other neurodegenerative diseases, and AD studies may thereby provide a framework for understanding the broader class of diseases.

Neuroprotectin D1 (NPD1) is a Sentinel in Early Stages of Age-related Macular Degeneration (AMD) and Alzheimer's Disease (AD)

Nicolas G. Bazan, M.D., Ph.D.

Introduction. Among the shared pathophysiological changes in AMD and AD are a non-resolving inflammatory response, amyloid-peptide accumulation, and apoptosis of specific cells. While studying mechanisms of cell survival in neurodegenerations, our laboratory contributed to the discovery of a docosanoid synthesized from DHA (docosahexaenoic acid, an omega-3 essential fatty acid family member enriched and retained in retina and brain), which we dubbed neuroprotectin D1 (NPD1, 10R, 17S-dihydroxy-docosa-4Z, 7Z, 11E, 13E, 15E, 19Z hexaenoic acid). This mediator is a docosanoid because it is derived from the 22C DHA, unlike eicosanoids, which are derived from 20C arachidonic acid, an essential fatty acid not enriched in the nervous system. NPD1 is a neuroprotective lipid mediator synthesized in response to oxidative stress by neurotrophins. Thus we envision NPD1 as one of the very first defenses activated when cell homeostasis is threatened by neurodegenerations.

Methods and Results. We discuss here the significance of NPD1 bioactivity in AD and AMD. 1) NPD1 is drastically reduced in CA1 areas in the early stages of AD as well as in the 3xTg-AD mice that harbor the PS1 (M146V), APP^{sw} and tau (P301L) human transgenes. Therefore we explored the role of NPD1 in cellular models that recapitulate AD pathology. Human neurons/astrocytes challenged by amyloid-oligomer or by overexpressing APP^{sw} (Swedish double mutation APP695^{sw}, K595N-M596L) show that NPD1 downregulates amyloidogenic processing of amyloid-precursor protein, switches off pro-inflammatory gene expression, and promotes neural cell survival. 2) Photoreceptors renew membrane disks containing the phototransduction apparatus and DHA intermittently via shedding of their tips and phagocytosis by retinal pigment epithelial (RPE) cells. At the same time, new membrane disks are made at the base of the outer segments; their length remains constant and cell integrity is maintained remarkably unchanged throughout many decades spite of the fact that photoreceptors are in an oxidative stress-prone environment. We show that phagocytosis of photoreceptor disks promotes (via NPD1 synthesis) specific refractoriness to oxidative stress-induced apoptosis in RPE cells, which in turn fosters homeostatic photoreceptor cell integrity. Disruptions of the sentinel role of NPD1 may participate in macular degeneration and other retinal degenerations. In addition, systemically-administered NPD1 attenuates laser-induced choroidal neovascularization (CNV). Thus NPD1 targets experimental apoptosis and CNV.

Conclusions. Potent anti-inflammatory, anti-amyloidogenic, and anti-apoptotic bioactivities are displayed by NPD1. The anti-amyloidogenic effect is mediated in part through PPAR receptor, while stimulation of the non-amyloidogenic pathway of APP processing is PPAR-independent. NPD1 stimulation of γ -secretase ADAM10 processing coupled to suppression of BACE1-mediated A₄₂ peptide secretion clearly warrants further study, as these dual secretase-mediated pathways may provide effective combinatorial clinical targets in neurodegenerations. Tau hyperphosphorylation is key in AD although its significance is less clear in AMD, whereas in CNV (another NPD1 target) it is critical. These studies allow us to ask mechanistic questions about neurodegenerative diseases as well as explore novel therapeutic avenues for AMD and AD. (Supported by NIH grants from the NEI, NINDS, NCCAM and NCRR, and by the Foundation Fighting Blindness)

Lukiw WJ, Cui JG, Marcheselli VL, Bodker M, Botkjaer A, Gotlinger K, Serhan CN, Bazan NG. A role for docosahexaenoic acid-derived neuroprotectin D1 in neural cell survival and Alzheimer disease. *J Clin Invest.* 115 (2005) 2774-2783.

Bazan NG. Homeostatic regulation of photoreceptor cell integrity: Significance of the potent mediator neuroprotectin D1 biosynthesized from docosahexaenoic acid. The Proctor Lecture. *Invest Ophthalmol Vis Sci.* 48 (2007) 4866-4881.

Imaging Metrics in Dry AMD

Frank Holz, M.D.

Recent developments in imaging technology have contributed to a better understanding in retinal diseases. Fundus autofluorescence (FAF) imaging in vivo using confocal scanning laser ophthalmoscopy (cSLO) has been particularly useful in the context of dry AMD. It allows for precise identification of lesion boundaries in geographic atrophy (GA) and longitudinal quantitative measurements using semi-automated imaging analysis software (RegionFinder). FAF imaging also allows for topographic mapping of lipofuscin distribution in the retinal pigment epithelium (RPE) cell monolayer as well as of other fluorophores that may occur with disease in the outer retina and the subneurosensory space. Excessive accumulation of lipofuscin granules in the lysosomal compartment of RPE cells represents a common downstream pathogenetic pathway in various hereditary and complex retinal diseases, including AMD. It has been shown that excessive lipofuscin levels precede the development of new atrophy and the expansion of preexisting atrophic patches. Based on cSLO FAF phenotyping in the context of the prospective multicenter FAM-Study patterns of abnormal FAF outside the GA patches with either a high and low progression rates were identified and confirmed in the natural history GAP-Study. Consideration of such high-risk characteristics as clinical biomarkers makes clinical trials with pharmacological agents already in clinical development for GA feasible. Implementation of an FAF-based inclusion algorithm has also been accomplished in ongoing interventional trials targeting accumulation of retinal toxins as toxic byproducts of the visual cycle. Simultaneous recordings of confocal SLO-FAF as well as near-infrared reflectance and blue reflectance images together with spectral domain OCT furthermore allows for correlation of tomographic and topographic scans and, thus, for identification of underlying microstructural alterations. When applied in eyes with reticular drusen (RD) the morphologic appearance on SD-OCT was the accumulation of highly reflective material in outer retinal layers, characterized by focal deposits, hyperreflective migrating structures, and regular wavy patterns. The prevalence of RD in 1104 eyes of 552 patients with GA was found to be 62 %, indicating a common phenomenon associated with atrophic AMD. The corresponding morphological substrate in the outer neurosensory retina may reflect a disease process at the level of the photoreceptors in contrast to the biogenesis of other drusen phenotypes located between the RPE and inner aspects of Bruch's membrane. Since RD represent high-risk markers for the progression of AMD, implementation of the cSLO imaging appears prudent for future studies. Overall novel imaging modalities have been shown to be useful with regard to understanding of pathophysiological mechanisms, diagnosis, phenotype-genotype correlation, identification of predictive markers for disease progression, and monitoring of novel therapies in AMD.

Imaging Microstructural Changes within and beneath the Retina In Vivo in non-Advanced AMD

Cynthia A. Toth, M.D.

Introduction: In age related macular degeneration, there are a wide spectrum of phenotypes, rates of progression and late endpoints of disease. Cross-sectional images from a spectral domain optical coherence tomography (SDOCT) high density macular volumes allow for detailed characterization of microstructural alterations in and beneath the retina in the AMD eye. We postulate that some of the SDOCT drusen and retinal characteristics may be imaging biomarkers of disease and may have implications for progression.

Methods: In preliminary studies we used a single SDOCT scan through the center of the fovea or volume scans in a small sample group. In subsequent studies, in collaboration with three other Age-Related Eye Disease Study 2 (AREDS2) sites, we are now studying the range of SDOCT characteristics in several hundred subjects with Category 3 AMD (based on color fundus photographs) in at least one eye over several years.[1]

Results: SDOCT was useful to classify early AMD pathology: first we developed a grading system for evaluating drusen ultrastructure on SDOCT [2], then for the retina overlying drusen, finding photoreceptor layer thinning and loss of the inner segment-outer segment junction over drusen [3], and also for photoreceptor loss at GA margins [4]. These preliminary studies involved limited scans or a small sample group. In the hundreds of baseline eyes designated as Category 3 by color photographs in the A2ASDOCT Study, we define the status of the vitreoretinal interface, intraretinal and subretinal pathology and the frequency of subfoveal geographic atrophy or intra- or subretinal fluid suspicious for advanced AMD. Patterns of drusen and retinal lesions may be associated with fellow eye advanced disease.

Conclusion: Retinal and drusen characteristics, as viewed at the microstructural scale with SD OCT, may reveal early information regarding the pathway of disease progression in an individual. This will be tested in the ongoing longitudinal A2ASDOCT study.

1. AREDS2 Ancillary SDOCT (A2ASDOCT) Study: [clinicaltrials.gov NCT00734487](https://clinicaltrials.gov/ct2/show/study/NCT00734487)
2. Khanifar AA, Koreishi AF, Izatt JA, Toth CA. Drusen Ultrastructure Imaging with SDOCT in AMD. *Ophthalmology*. 2008 Nov; 115(11):1883-90.
3. Schuman SG, Koreishi AF, Farsiu S, Jung SH, Izatt JA, Toth CA. Photoreceptor Layer Thinning over Drusen in Eyes with AMD imaged in Vivo with SDOCT. *Ophthalmology*. 2009 Mar; 116(3):488-96.
4. Bearelyly S, Chau FY, Koreishi A, Stinnett SS, Izatt JA, Toth CA. SDOCT imaging of geographic atrophy margins. *Ophthalmology*. 2009 Sep;116(9):1762-9.

Adaptive Optics Imaging in Age-Related Macular Degeneration

Mina Chung, M.D.

Introduction. Adaptive optics (AO) imaging is a non-invasive technology that provides high-resolution, in vivo images of cells in the human retina. The Fluorescence AO Scanning Laser Ophthalmoscope (FAOSLO) uses cellular lipofuscin fluorescence to produce images of cones and retinal pigment epithelial (RPE) cells simultaneously at the same retinal location. The application of the FAOSLO technique to macular degeneration will be reviewed.

Methods. The FAOSLO simultaneously acquires images of RPE lipofuscin autofluorescence and reflectance from the photoreceptor layer of the human retina. The reflectance images are used for registration of the lower signal autofluorescence images. Image analysis methods provide quantitative metrics including cell density vs eccentricity and mosaic irregularity.

Results. Adaptive optics demonstrates images of the cones, rods, and RPE cells in the human retina in normal subjects and patients with macular and retinal degenerations. AO can detect loss of cone density before it is detectable by standard clinical tests and before vision loss occurs. In patients with AMD, intact photoreceptors are observed overlying small drusen and adjacent to geographic atrophy lesions.

Conclusions: Adaptive optics retinal imaging has the potential to detect the earliest changes in disease and monitor disease progression at the cellular level. Future studies including serial measurements may help to elucidate the cellular sequence of disease in AMD.

Invited Participant Biographies

Anthony P. Adamis, M.D.



Anthony P. Adamis, M.D. is Vice President and Global Head of Ophthalmology at Genentech, a member of the Roche Group. Previously, he co-founded Eyetech (2000) and Jerini Ophthalmic (2007). At Eyetech, Dr. Adamis helped lead the team that obtained FDA approval for the first anti-

VEGF drug in ophthalmology. From 1991 to 2002, Dr. Adamis was on the full time faculty of the Harvard Medical School and was co-director of the Ocular Angiogenesis Laboratory at the Massachusetts Eye and Ear Infirmary. His research is focused on AMD and diabetic retinopathy, as well as ocular drug delivery. Dr. Adamis is best known for his co-discovery of the role of VEGF in ocular disease. He received his M.D. with Honors from the University of Chicago, and completed his ophthalmology residency at the University of Michigan and fellowship in corneal disease at the Massachusetts Eye and Ear Infirmary. His research training in vascular biology was with Dr. Judah Folkman at the Children's Hospital of Boston.

Jayakrishna Ambati, M.D.



Jayakrishna Ambati, M.D. is Professor of Physiology and Professor & Vice-Chair of Ophthalmology and Visual Sciences at the University of Kentucky. He holds the Dr. E. Vernon Smith & Eloise C. Smith Endowed Chair in Macular Degeneration Research. His laboratory has revealed novel mechanisms of

age-related macular degeneration and angiogenesis in numerous publications in *Nature*, *Nature Medicine*, *New England Journal of Medicine*, *JCI*, and *PNAS*. He is the 2010 ARVO Cogan Awardee and the winner of the 2010 Roger H. Johnson Memorial Award for Macular Degeneration Research. He is the first ophthalmologist to win the Doris Duke Distinguished Clinical Scientist Award and the Burroughs Wellcome Fund Clinical Scientist Award in Translational Research. RPB has awarded him its Senior Scientific Investigator Award, Lew R. Wasserman Merit Award, and Physician-Scientist Award. He was elected to The American Society for Clinical Investigation and was the first ophthalmologist to be elected to The

Association of American Physicians. He serves on the Editorial Board of *IOVS* and is an Associate Editor of *Ophthalmology*.

Nicolas G. Bazan, M.D., Ph.D



Nicolas Bazan, M.D. (Tucuman, Argentina) was a postdoc at P&S, Columbia U., and Harvard Medical School. In his first lab, he found that ischemia or seizures increases free docosahexaenoic acid and arachidonic acid (DHA) in the brain. Then he found that: antagonism to the

lipid mediator platelet activating factor (PAF) is neuroprotective; identified synaptic PAF binding; defined PAF regulation of early gene expression and PAF mediation of LTP and memory; the supply of DHA to synapses and photoreceptors is liver-regulated; and Usher's Syndrome patients have blood DHA shortage. He contributed to the discovery of the synthesis and bioactivity of neuroprotectin D1, which arrests apoptosis, and is anti-inflammatory in RPE cells, experimental stroke and Alzheimer's models. Recognitions include: Javits Neuroscience Award, NINDS, NIH (1998); elected Royal Academy of Medicine, Spain (1993, 1996); Endre A. Balazs Prize, International Society of Eye Research (2000); elected fellow, Royal College of Physicians of Ireland, Dublin (1999); and Proctor Medal, highest honor of The Association for Research in Vision and Ophthalmology (2007).

Peter J. Bex, Ph.D.



Peter Bex is an Assistant Professor of Ophthalmology at Harvard Medical School. He completed his Ph.D. at Cardiff University, UK and completed post-doctoral training at the Department of Ophthalmology, McGill University, Canada and at the Center for Visual Science, University of Rochester, NY.

He joined Schepens Eye Research Institute in 2007. He is editor of *Frontiers in Perception Science* and is a member of the Association for Research in Vision and Ophthalmology and the Optical Society of America.

Alan C. Bird, M.D.



After undergraduate studies at Guys Hospital Medical School, Dr. Alan Bird completed junior posts in general Medicine, Surgery and Neurosurgery. After a residency in Ophthalmology at Moorfields Eye Hospital he worked as Senior Registrar at The London Hospital and The Hospital for Nervous Diseases, Queen Square.

This was followed by a Fellowship in neuro-ophthalmology at Bascom Palmer Eye Institute with Dr. Lawton Smith and a brief period with Dr Hoyt in San Francisco.

On returning to London in 1969, Alan Bird was appointed to the Institute of Ophthalmology as Lecturer, and subsequently Senior Lecturer, Reader and Professor, and Consultant at Moorfields Eye Hospital. He changed his main interests from neuro-ophthalmology to retina, and a specialised clinical service was established. This was aided by the conversion of clinical activity in Moorfields Eye Hospital to specialised Services, and the Medical Retinal Service now holds 34 clinics each week, and has 12 Consultants. Over the years a productive multidisciplinary research team developed for the investigation of monogenic retinal disorders and age-related macular disease. Investigative techniques included molecular genetics, electrophysiology, psychophysics, specialised imaging and morphology. Establishment of research programmes was aided by the successful development of the Institute of Ophthalmology, which became a School of University College, London, and the generation by colleagues of research programmes of work in inflammatory eye disease, and retinal vascular diseases. In order to contribute fully to research, he spent a sabbatical period with Dr Dean Bok at UCLA in 1985.

The clinical and research activity in medical retinal diseases has attracted many talented post-residency fellows from all over the world who have added greatly to the research endeavours.

In addition to his work in London he has spent time in Africa undertaking research into river blindness.

The most notable finding was the identification that retinal and optic nerve disease was the main cause of blindness rather than corneal scarring and that the standard treatment of diethyl carbamizine citrate caused rapid onset of blindness. This led to the institution of Ivermectin as the preferred treatment, which has been highly successful. He has also worked in Jamaica recording the retinal changes in sickle cell disease over a 20 year period in a well studied cohort generated by Dr Graham Serjeant.

Dr. Bird has received a number of awards in recognition of his work.

On October 1st 2005 Dr Bird retired from full time clinical practice and was appointed Emeritus Professor at London University and Honorary Consultant, Moorfields Eye Hospital so that research and teaching can be continued.

Dean Bok, Ph.D.



Dr. Dean Bok is the Dolly Green Professor of Ophthalmology and Distinguished Professor of Neurobiology at the University of California, Los Angeles (UCLA) School of Medicine. He earned his Ph.D. degree from UCLA in 1968 and has been a member of the UCLA School of Medicine faculty

since that time. During his tenure, he has served as the Associate Director of the Jules Stein Eye Institute and Vice Chair of the Department of Neurobiology. Dr. Bok is widely recognized for his expertise in the cell and molecular biology of the retinal pigment epithelium (RPE). He and his laboratory group explore interactions that take place between retinal photoreceptors and the retinal pigment epithelium (RPE) in health and disease.

Constance L. Cepko, Ph.D.



Dr. Cepko is Professor of Genetics at Harvard Medical School, an Investigator for the Howard Hughes Medical Institute and Co-Director of the Leder Program in Human Biology and Translational Medicine at Harvard University. She received her PhD degree from the Massachusetts Institute of Technology,

working with Phillip Sharp on the assembly of the adenovirus capsid. She remained at MIT as a Jane Coffin Childs fellow in the laboratory of Richard Mulligan, where she helped develop the technology of retrovirus-mediated gene transduction. Her current research is focussed on the development of the central nervous system, with an emphasis on the retina. She uses genomics technology and other molecular approaches to study both development and diseases of the retina. She is a member of the National Academy of Sciences and the American Academy of Arts and Sciences. Dr. Cepko has served on the Council of the National Eye Institute, as well as on the Bureau of Scientific Counselors of the National Eye Institute.

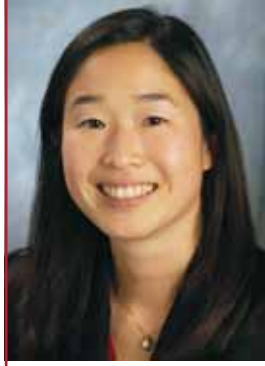
Hemin R. Chin, Ph.D.

Hemin R. Chin is Associate Director of Ophthalmology at the National Eye Institute. In this capacity, Dr. Chin coordinates genetics and genomics initiatives for the institute and takes part in a leadership role in national and international ocular genetics research community. He also continues to actively manage

the research grant portfolio in genetics as Program Director for Ocular Genetics in the Division of Extramural Research.

Dr. Chin received his Ph.D. in neurobiology and physiology from Northwestern University, and completed a two-year training program under a National Research Service Award in molecular neurobiology at the Laboratory of Biochemical Genetics, National Heart, Lung, and Blood Institute, NIH, under the tutelage of Dr. Marshall Nirenberg. Dr. Chin pursued his research in the molecular and genetic mechanisms underlying the structure and functions of neuronal calcium channels in the Laboratory of Neurochemistry, National Institute of Neurological Disorders and Stroke, NIH. He took an extramural program administrator position as Chief of Genetics Basis of Neural Function Program in the Genetics Research Branch at the National Institute of Mental Health (NIMH) before joining NEI to become Director of Ocular Genetics Program. He oversaw NEI Center Core Program for Vision Research from 2006 to 2008, and more recently has served as acting director of Division of Extramural Activities with the responsibility of overseeing Review Branch and Grants Management Branch of the Division of Extramural Research.

Throughout his career, he has been an active member of a number of trans-NIH genomics and genetic initiatives coordinating committees. In recognition of his achievements and contributions to the missions of NIH, Dr. Chin has been given NIH Director's Awards, NIH Merit Award, and the Neuroscience Blueprint Directors' Awards. He has organized numerous international and national symposia and meetings and published over 50 papers and book chapters, and recently co-edited a book, "Methods in Genomic Neuroscience".

Mina Chung, M.D.

Mina Chung, M.D., is an associate professor of ophthalmology at the Flaum Eye Institute and Center for Visual Science at the University of Rochester. She completed medical school at Yale University School of Medicine, ophthalmology residency training at the Doheny Eye

Institute, University of Southern California, and vitreoretinal fellowship at the University of Iowa Hospitals and Clinics. She then served on the faculty of Doheny Eye Institute and Children's Hospital of Los Angeles for 2 years prior to joining the University of Rochester in 2002. Her clinical vitreoretinal practice includes a focus on inherited retinal degenerations. Her research interest is in the application of adaptive optics imaging to the study of macular and retinal degenerations.

Kip M. Connor, Ph.D.

Kip M. Connor received his Ph.D. degree from Albany Medical College in 2005. Kip did his post-graduate studies in the Department of Ophthalmology at Children's Hospital Boston and Harvard Medical School from 2005 to 2010. Here Kip's work addressed the role of dietary intake of omega-3

polyunsaturated fatty acids on disease severity in a mouse model of oxygen-induced retinopathy. In 2010 he was recruited to the Department of Ophthalmology at Massachusetts Eye & Ear Infirmary and Harvard Medical School. Current research collaborations with Dr. Gregory L. Stahl, PhD and John D. Lambris, PhD will address the role of the complement system in ocular angiogenesis.

Scott W. Cousins, M.D.



Scott W. Cousins, M.D. is currently the Robert Machemer, M.D. Professor of Ophthalmology and Immunology, Vice Chair for Research, and Director of the Duke Center for Macular Diseases at Duke Eye Center. He is also the director of the Ophthalmology Site-Based Research Group, which

administrates clinical research 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, 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 clinical trials and innovative therapies for the treatment of macular diseases, especially age-related macular degeneration and diabetic retinopathy.

In his scientific laboratory, Dr. Cousins pursues both NIH-funded research and industry-funded research in various areas of dry and wet macular degeneration. In particular, his laboratory is attempting to develop treatments for dry macular degeneration and improving vision in eyes with wet macular degeneration. His program is also developing blood tests and new imaging technologies for the identification of patients who are at high risk for progressing into complications. 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 age-related macular degeneration. In 2006, Dr. Cousins was awarded the prestigious Alcon Research Foundation Clinician Scientist Award. In 2008, the National Institutes of Health invited Dr. Cousins 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, and the American Association of Immunologists.

Christine A. Curcio, Ph.D.



Christine A. Curcio, Ph.D., received her doctorate from University of Rochester in 1981 and post-doctoral training at Boston University and University of Washington, where she began work on human retina with Anita Hendrickson, Ph.D. Since 1990, she has been on faculty in the Department

of Ophthalmology at the University of Alabama at Birmingham. She serves on the editorial board of IOVS, Current Eye Research, and Progress in Retinal and Eye Research, and is a member of the Board of Scientific Counselors of the National Eye Institute. Her contributions to ARMD research include documenting the early death of rods; discovering, characterizing, and contextualizing the Bruch's membrane lipoprotein (with M. Johnson); formulating a comprehensive theory of ARMD lesion formation highlighting lipoproteins; and characterizing ARMD-specific lesions including sub-retinal drusenoid debris.

Robert D'Amato, M.D., PhD



Robert D'Amato received his B.A, M.D. and Ph.D. from Johns Hopkins University. He completed his Ophthalmology residency at the Massachusetts Eye and Ear Infirmary. After this training, he undertook a postdoctoral research fellowship in the Folkman laboratories. He has been an

independent investigator at Children's since 1994 and is a Professor of Ophthalmology at Harvard Medical School. He currently holds the Judah Folkman Chair in Surgery and leads the endowed Karp Laboratory for Macular Degeneration Research. Noteworthy past research includes the discovery that thalidomide is an angiogenesis inhibitor, which is now FDA approved for cancer. Additionally, his lab discovered a major role of genetics in determining an individual's angiogenic responsiveness. Elucidation of this genetic influence may help us predict and potentially regulate our susceptibility to angiogenesis dependent diseases such as cancer and age related macular degeneration.

Patricia A. D'Amore, Ph.D.



Patricia D'Amore received her Ph.D. in Biology from Boston University in 1977, did a postdoctoral fellowship in Biological Chemistry and Ophthalmology at Johns Hopkins Medical School, and then joined the staff as Assistant Professor of Ophthalmology. In 1981, she moved to the Children's

Hospital in Boston as Assistant Professor where she is still a Research Associate in Surgery and a member of the Program in Vascular Biology. Dr. D'Amore obtained an MBA from Northeastern University in 1987. In 1998, she became Professor of Ophthalmology (Pathology) at Harvard Medical School and a Senior Scientist at the Schepens Eye Research Institute. At Harvard Medical School, she is an Associate Director of the Leder Human and Translational Medicine Graduate Program and Chair of the Scholars in Medicine Committee. In 2004, she was elected to The Academy at Harvard Medical School. Dr. D'Amore is the founder of the Boston Angiogenesis Meeting, which celebrated its 10th annual meeting in 2008. In 2006, she received the A. Clifford Barger Excellence in Mentoring Award from Harvard Medical School. She is currently the Co-Director of Research at Schepens, the Ankeny Scholar of Retinal Molecular Biology, and was recently appointed the Director of the Center of Excellence for Research in Macular Degeneration. She has published 175 peer-reviewed papers and reviews.

Margaret DeAngelis, M.D., Ph.D.



Dr. DeAngelis is currently an Associate Professor at John A Moran Institute, University of Utah School of Medicine. Previously she was an Assistant Professor in the Department of Ophthalmology at Harvard Medical School/Massachusetts Eye and Ear Infirmary. Dr. DeAngelis

focused her career on vision research in 1999 when she received a post-doctoral training grant on macular degeneration as part of the Molecular Basis of Eye Disease program at Harvard Medical School.

Working in collaboration with outstanding retina specialists, Dr. Ivana Kim and Dr. Joan Miller, Dr. DeAngelis recruited a patient population of families to study the genetic and epidemiologic underpinnings of age-related macular degeneration (AMD). As a result Dr. DeAngelis is a Principal Investigator on a competitive renewal from the National Eye Institute to study the molecular genetics of AMD. Dr. DeAngelis has also received funding from private agencies including the Lincy Award, Milton Award, Massachusetts Lion's Award and the Thome Foundation Memorial Award. In addition to studying genetic susceptibility to AMD, her group, utilizing a systems biology based approach is trying to pinpoint disease causality by elucidating key regulatory components in pathways or sets of genes which are implicated in AMD so that appropriate preventive and therapeutic targets can be developed. To that end, her group identified a novel anti-angiogenic AMD associated gene known as RORA. Working with Dr. Debra Schaumberg they demonstrated that RORA was protective against the development of neovascular AMD in 3 diverse patient populations. Moreover, RORA was shown by our groups to interact with other known AMD genetic risk factors thus furthering the development of a unifying hypothesis underlying AMD pathophysiology and hopefully leading to cures for this devastating form of blindness. In collaboration with Dr. Lindsay Farrer and Dr. Gregory Hageman, both genetic association and functional studies on the pathway in which RORA functions are ongoing. The success of this work is the result of building strong collaborations between scientists and clinicians both from outside and within the Harvard community.

François C. Delori, Ph.D.



Dr. Delori is a biophysicist with a field of expertise in light damage to the retina and in noninvasive diagnostic techniques for retinal diseases. By analyzing the nature of the light reflected by the retina, he has obtained quantitative information about many important biological parameters – such

as oxygen levels in retinal blood vessels, speed of blood flow, diffusion of nutrients, and quantities of various 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 RPE as well as new ways to measure the distribution of macular pigment in the neural retina.

Lindsay A. Farrer Ph.D.



Lindsay A. Farrer Ph.D. is Professor of Medicine, Neurology, Ophthalmology, Genetics & Genomics, Epidemiology, and Biostatistics at Boston University Schools of Medicine (BUSM) and Public Health. He is also a board-certified medical geneticist, and Chief of Genetics

and Director of the Molecular Genetics Core Laboratory at BUSM. In collaboration with other laboratories worldwide, Dr. Farrer has localized genes causing a variety of rare and common disorders including Alzheimer disease (AD), age-related macular degeneration (AMD), Wilson disease, Machado-Joseph disease, Waardenburg syndrome, hypertension, sensorineural deafness, and osteoarthritis. Working together with other BU researchers, Dr. Farrer's lab is leading efforts to identify genes influencing severity and expression of sickle cell anemia and α -thalassemia. His group identified a functional genetic variant in the complement factor H gene which accounts for nearly a large portion of the attributable risk for AMD, the leading cause of progressive vision loss and blindness in the elderly. Dr. Farrer's major research focus is Alzheimer disease (AD). Under Dr. Farrer's leadership, the MIRAGE Project, a multi center study of AD funded since 1991 by the National Institute on Aging, has made several important contributions to our understanding of the interactions between genetic and environmental factors for the disorder. This study has a particular emphasis on the genetics of AD in African Americans. This study was the first to demonstrate that genetic factors have a major role in the development of AD. Dr. Farrer co-directed the effort which demonstrated that neuronal sortilin-related receptor SORL1 and other genes involved in protein trafficking are genetically and functionally associated with AD. Dr. Farrer serves on the Executive Committee of the national AD Genetics Consortium and co-directs the data analysis effort for this large NIH-funded project. Currently, his lab is conducting genome wide association studies for AD, AMD and substance dependence. Dr. Farrer is a member of the Steering Committee for the PhenX project, a national effort from the Genome Research Institute at NIH to establish a set of standardized phenotypic measures for genome wide studies.

Lee E Goldstein, M.D., Ph.D.



Dr. Goldstein is Director of the Molecular Aging & Development Laboratory (School of Medicine), the Biophotonics Engineering Laboratory (Photonics Center), and the Translation Core (NIH Alzheimer's Disease Center) at Boston University. He is also Founding Director of the

Boston University Center for Biometals & Metallomics (CBM), the first metallomic imaging mass spectrometry resource of its kind in the nation. Dr. Goldstein is a Phi Beta Kappa graduate of Columbia University. He received medical and doctoral (Neuroscience) degrees from Yale University as an NIH Medical Scientist Training Program Scholar. He completed a clinical fellowship in psychiatry at the Massachusetts General Hospital, Harvard Medical School, where he also conducted postdoctoral research in Alzheimer's disease with Rudolph Tanzi, PhD and Ashley Bush, MD, PhD. In 2001, Dr. Goldstein moved to the Brigham & Women's Hospital as an Assistant Professor in Psychiatry at Harvard Medical School and established his research laboratory as an NIH Beeson Scholar in Aging Research. In 2008, Dr. Goldstein and his team were recruited to Boston University (School of Medicine, College of Engineering, and Photonics Center) and established translational research laboratories spanning the Boston Medical Center and Charles River campuses of Boston University. Dr. Goldstein and his team discovered Alzheimer's disease molecular pathology in the lens of the eye (Lancet, 2003) that define a new disease-linked cataract phenotype and its molecular origin. His laboratory subsequently identified related Alzheimer's disease lens pathology in Down syndrome, thereby establishing the molecular basis of a second cataract phenotype and its link to early-onset Alzheimer's disease associated with this common chromosomal disorder. These findings provide the scientific foundation that are driving the laboratory to develop innovative laser-based ophthalmic technology for very early detection of Alzheimer's disease. Other research thrusts in the Goldstein laboratory include traumatic brain injury, age-related cataracts, radiation biodosimetry, molecular aging, and biometallomics. Dr. Goldstein is a Diplomate of the American College of Neurology & Psychiatry and the recipient of awards from Harvard Medical School, World Congress on Stress Research,

continued next page

Dr. Goldstein continued)

(Alzheimer's Association, American Federation for Aging Research, National Institutes of Health, and the Optical Society of America. Research in the laboratory is supported by the National Institutes of Health, National Science Foundation, US Dept of Energy, NASA, Army Research Laboratory, Alzheimer's Association, American Federation for Aging Research, American Health Assistance Foundation, Ellison Foundation, Boston University, and an anonymous foundation. Dr. Goldstein is a Founding Scientist and Chairman of the Scientific Advisory Board at Neuroptix Corporation, a leading laser diagnostics company in Acton, MA. Contact: lgold@bu.edu

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Maria Grant, M.D.

Dr. Grant received her undergraduate education at University of Florida where she graduated with Highest Honors in Chemistry. She completed Medical School, Internal Medicine Residency and Endocrinology Fellowship at University of Florida, followed by a Research Fellowship in Ophthalmology at Wilmer

Eye Institute prior to joining the faculty at University of Florida in the Department of Internal Medicine. She served as Division Chief of Endocrinology and Metabolism for 7 years until she joined the Department of Pharmacology and Therapeutics as Professor. Currently she also holds joint appointments in the Department of Physiology and Functional Genomics, Ophthalmology and Psychiatry. Dr. Grant's research is currently supported by the National Eye Institute, National Heart Lung and Blood Institute and Florida Department of Health- James and Esther King. She has served on a number of national service panels for the National Institute of Health including study section BPBE and the Governor's Advisory Board for Diabetes. Past research interests have focus on understanding the role of adult, bone marrow derived hematopoietic stem cells, integrins, matrix metalloproteinases and other extracellular matrix and growth factor receptors during physiological and pathological angiogenesis, in particular diabetic retinopathy and AMD. Current interests center on understanding what controls the

differentiation of adult hematopoietic stem cells (HSCs) into endothelial cells or RPE cells so as to promote development of new cell-based therapies to treat multiple degenerative diseases.

Leonard M. Hjelmeland, Ph.D.

Leonard M. Hjelmeland (Larry) is currently a Professor in the Department of Ophthalmology at U.C. Davis, California. After moving to Davis in 1986, Dr. Hjelmeland's career has included chairmanship of the Biological Chemistry Department in the School of Medicine and Special Assistant to the Provost

for academic and infrastructure planning for the Genomics program. He also teaches Biochemistry at both the graduate and undergraduate levels. From 1976 to 1986 Dr. Hjelmeland was appointed under the title of "Expert" first at the NICHD and subsequently at the NEI.

Dr. Hjelmeland received the B.S. and Ph.D. Degrees from Stanford University in 1971 and 1976. Both degrees were awarded for interdepartmental programs in Chemical Physics, Mathematics, Computer Science, and Biophysical Chemistry. Dr. Joshua Lederberg served as Dr. Hjelmeland's Mentor for his advanced degree. Dr. Hjelmeland's current research interests focus on the roles that Epigenetics may play in the pathogenesis of Complex Diseases such as Age-related Macular Degeneration.

Epigenetics is potentially the mechanism through which aging and environmental factors alter nongenetic disease risk.

Joe G. Hollyfield, Ph.D.



Joe G. Hollyfield, Ph.D., is the Llura and Gordon Gund Professor and Director of Ophthalmology Research at the Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio. He received the Ph.D. degree from the University of Texas at Austin and postdoctoral training at the Hubrecht Laboratory, Utrecht, The Netherlands.

Dr. Hollyfield has published extensively in the area of cell and developmental biology of the retina and retinal pigment epithelium in health and disease. He has received awards from the Retina Research Foundation; Research to Prevent Blindness, Inc.; Alcon Research Institute; a Distinguished Alumnus Award from Hendrix College; the Endre A. Balazs Prize from the International Society for Eye Research (ISER); the Proctor Medal from ARVO and the Cless Best of the Best Award from University of Illinois Chicago Department of Ophthalmology. He is Editor-in-Chief of the journal, *Experimental Eye Research*. Dr. Hollyfield currently serves on the Scientific Advisory Boards of The Foundation Fighting Blindness; The Helen Keller Eye Research Foundation; American Health Assistance Foundation Macular Degeneration Review Panel; The South Africa Retinitis Pigmentosa Foundation, Knights Templar Eye Foundation, and Retina International.

of *Der Ophthalmologe*, the official journal of the German Ophthalmological Society. He is a member of the Scientific Advisory Board of the AMD Alliance International, the Macula Society, the American Academy of Ophthalmology (AAO), and the Association for Research in Vision and Ophthalmology (ARVO), among others. He has authored over 200 publications in peer-reviewed journals, is editor/co-editor on several books, and received numerous awards.

Bradley Hyman, M.D., Ph.D.



Dr. Hyman's laboratory studies the anatomical and molecular basis of dementia in Alzheimer's disease and dementia with Lewy bodies. Approaches focus on transgenic mouse models and human neuropathological samples, using advanced microscopy techniques for in vivo longitudinal imaging, direct imaging

on neuropathological processes including cell death, and functional imaging including in vivo assessment of calcium reporters. Quantitative approaches have been developed to apply to clinical pathological and genotype/phenotype analyses. Recent studies have developed the use of multiphoton microscopy for in vivo anatomical and functional imaging in transgenic mouse models of Alzheimer's disease and the utilization of gene transfer techniques to introduce potentially disease-modifying genes into specific cortical regions. We have also developed fluorescence resonance energy transfer (FRET) approaches to allow observation of protein-protein interactions with subcellular resolution, both in vitro and in vivo. These techniques are utilized to examine the alterations that occur in Alzheimer's disease brain, and in mouse models expressing genetic mutants that are linked to Alzheimer's disease.

Frank G. Holz, M.D.



Frank G. Holz is Professor and Chairman of the Department of Ophthalmology at the University of Bonn, Germany. He received his doctoral degree from the Medical School at the University of Heidelberg, Germany, having also trained at the Pritzker School of Medicine at the University

of Chicago. He conducted further research at Moorfields Eye Hospital in London where he passed a Medical Retina and Research Fellowship. He has written widely on retinal diseases with a special interest in AMD and retinal imaging. He is a founding member and co-ordinator of the German Research Council's priority AMD research program. He is the Editor-in-Chief

Sekar Kathiresan, M.D.



Dr. Kathiresan is the current Director of Preventive Cardiology at the Massachusetts General Hospital (MGH) Heart Center, an Assistant Professor of Medicine at Harvard Medical School, and an Associate Member at the Broad Institute. He received his B.A. in history summa cum laude from the

University of Pennsylvania in 1992 and received his M.D. from Harvard Medical School in 1997. Dr. Kathiresan completed his clinical training in internal medicine and cardiology at MGH. He served as Chief Resident in Internal Medicine at MGH in 2002-2003.

Dr. Kathiresan pursued post-doctoral research training in cardiovascular genetics through a combined experience at the Framingham Heart Study and the Broad Institute of MIT and Harvard. In 2008, he joined the research faculties of the MGH Cardiovascular Research Center and the MGH Center for Human Genetic Research.

His research laboratory focuses on: (1) understanding the inherited basis for blood lipids and myocardial infarction; (2) defining the mechanisms by which the newly identified genes impact phenotype; and (3) using these insights to improve preventive cardiac care. In 2010 alone, Dr. Kathiresan and his group have made considerable progress along each of these research goals. He led gene discovery efforts that identified 95 genetic loci responsible for plasma lipid variation in the population (Teslovich, Musunuru, *Nature* 2010) and a gene responsible for extremely low low-density lipoprotein cholesterol in a single family (Musunuru, Pirruccello, Do, *N Engl J Med*, in press). At one new locus for low-density lipoprotein cholesterol and myocardial infarction, he and collaborators defined the causal variant, mechanism and gene responsible for the plasma lipid change (Musunuru, Strong, *Nature* 2010). Finally, he has shown that a multi-locus genetic risk score comprised of 13 myocardial infarction variants can identify 20% of people at about 70% increased risk for future cardiovascular events (Ripatti, *Lancet* in press).

In tandem with his research, Dr. Kathiresan's clinical focus is the primary prevention of myocardial infarction in individuals with a family history of heart attack.

Ivana K. Kim, M.D.



Dr. Ivana Kim is a graduate of Harvard Medical School and completed her ophthalmology residency and vitreoretinal fellowship at Mass Eye and Ear. She is currently an Assistant Professor of Ophthalmology at Harvard Medical School and a member of the full-time staff of the Mass Eye and Ear Retina Service.

She maintains a busy clinical practice including surgical and medical retina, with a focus on age-related macular degeneration and uveal melanoma. She serves as principal investigator for several multi-center as well as investigator-sponsored clinical trials.

Dr. Kim collaborates with Drs. Margaret DeAngelis and Joan Miller in a genetic study of age-related macular degeneration involving extremely discordant sibling pairs. They have collected genetic and epidemiologic data on these sibpairs to study gene-environment interactions, perform candidate gene analyses, and analyze gene expression profiles with the goals of further elucidating the etiology of neovascular AMD and identifying potential biomarkers of the disease.

In addition to studying the genetics of AMD, Dr. Kim also has an ongoing collaboration with Dr. Levi Garraway at the Dana-Farber Cancer Institute to search for oncogenic mutations in uveal melanoma using a high-throughput mass-spectrometry based PCR platform. By defining specific molecular aberrations involved in the malignant transformation of these tumors, they hope to identify particular pathways that could serve as targets for adjunctive chemotherapy.

John D. Lambris, Ph.D.



John D. Lambris, received his Ph.D. in Biochemistry in 1979. He is the Dr. Ralph and Sallie Weaver Professor of Research Medicine in the Department of Pathology & Laboratory Medicine at the University of Pennsylvania, Philadelphia, PA. Using complement as a model system Dr. Lambris applies ideas and methods embodied

in engineering, computer science, physics, chemistry, biomedicine, and other fields to study the structure and functions of the complement system. Dr. Lambris' laboratory was among the first to map the critical sites on C3 responsible for its diverse functions and also to define its complex binding dynamics to various C3 natural ligands, viral proteins, complement receptors, and regulators. His laboratory contributed in the development of complement-based anti-inflammatory therapeutics through the discovery of the first small-size complement inhibitor, termed Compstatin, which has exhibited consistent efficacy for use in a series of in vivo trials and shows great promise for the use in the clinic. His subsequent efforts to develop more potent compstatin analogues have laid the development of a novel platform for peptide-based drug design, integrating both rational and in silico approaches. In a series of in vivo studies the Lambris lab. established an unprecedented association of complement components with non-inflammatory pathways by demonstrating the involvement of complement in the developmental processes, including liver and limb regeneration, hematopoietic development and stem cell engraftment. Dr. Lambris has published over 300 papers in peer-reviewed journals and is the editor of several books and special journal issues. Dr. Lambris is the Founder and Executive Director of Aegean Conferences, an independent, nonprofit, educational organization. He also serves as an Editorial Board Member of several peer-reviewed journals, and has served as the President of the International Complement Society. Dr. Lambris has received research funding from various institutions and agencies including the National Institute of Health (NIH), National Science Foundation (NSF), and American Cancer Society. For further information about Dr. John D. Lambris, visit www.lambris.com

Eicke Latz, M.D., Ph.D.



Eicke Latz, M.D. Ph.D. is an Assistant Professor of Medicine at the University of Massachusetts Medical School, Division of Infectious Diseases and Immunology in Worcester, MA. He is also affiliated with the Institute of Innate Immunity, University Hospital, University of Bonn. He is the author of 66 peer-reviewed publications.

In 2000, he received the Award of the Japanese Society of Surgery, Tokyo National Cancer Center.

Personal Statement

The innate immune system detects invading microbes and responds to danger situations using a set of defined signaling receptors. Inappropriate activation of innate immune receptors is thought to be the basis for many acute and chronic inflammatory diseases. My lab has a longstanding interest in deciphering the molecular mechanisms of innate immune receptor activation. In particular, we are interested in understanding how innate receptors interact with their ligands and how this molecular interaction leads to receptor activation. Recently, we have also focused on the molecular details of RigI activation by RNA and on the mechanisms that lead to the activation of the NLRP3 inflammasome. The NLRP3 inflammasome can respond to a broad range of cellular stressors and to substances that indicate metabolic derangements such as aggregated peptides (A beta peptides that form in Alzheimer's disease), crystals of monosodium urate (forming in gout) or crystals of cholesterol that are found in atherosclerotic plaques. One goal of the research is to translate the molecular understanding of innate immune receptor activation into the generation of molecular tools that could lead to the development of specific diagnostics for inflammatory materials. Another goal is to devise means to pharmacologically interfere with the activation of innate immune receptors in order to develop novel approaches to treat inflammatory diseases such as Alzheimer's disease or atherosclerosis.

Peter Libby, M.D.



Peter Libby, M.D., is the Chief of Cardiovascular Medicine at the Brigham and Women's Hospital in Boston, Massachusetts. He also serves as the Mallinckrodt Professor of Medicine at Harvard Medical School. Dr. Libby directs the D.W. Reynolds Cardiovascular Clinical Research Center at Harvard. His current

major research focus is the role of inflammation in vascular diseases such as atherosclerosis.

Dr. Libby has received numerous awards and recognitions for his research accomplishments. His most recent recognitions include the Lucian Award for Research in Cardiovascular Disease and the International Okamoto Award. His areas of clinical expertise include general and preventive cardiology.

Dr. Libby's professional memberships include the Association of American Physicians, the American Society for Clinical Investigation, and elected honorary memberships in the British Atherosclerosis Society and the Japan Circulation Society. He has served as the President of the Association of University Cardiologists. He also served in many roles as a volunteer for the American Heart Association, including chairman of several research committees and member of the executive committees of the Councils on Arteriosclerosis, Circulation, and Basic Science.

An author and lecturer on cardiovascular medicine and atherosclerosis, Dr. Libby has published extensively in medical journals including *Circulation*, *Journal of Clinical Investigation*, *Proceedings of the National Academy of Sciences*, *New England Journal of Medicine*, and *Nature*.

He is Editor-in-Chief of the Eighth edition of *Braunwald's Heart Disease*. Dr. Libby has also contributed the chapter on the pathogenesis, treatment, and prevention of atherosclerosis to *Harrison's Principles of Internal Medicine*. He has held numerous visiting professorships and has been selected to deliver over 70 named or keynote lectures throughout the world.

Dr. Libby earned his medical degree at the University of California, San Diego, and completed his training in internal medicine and cardiology at the Peter Bent Brigham Hospital (now Brigham and Women's Hospital). He also holds an honorary MA degree from Harvard University, and an honorary doctorate from the University of Lille, France.

Gerard Lutty, Ph.D



Gerard Lutty, Ph.D., received his BS in Zoology (1970) and MS in Microbiology (1980) from Catholic University in Washington, D.C., and his Ph.D. in Cell Biology at Johns Hopkins School of Medicine (1991). He has been a faculty member at Johns Hopkins since 1979 and is currently the inaugural

G. Edward and G. Britton Durrell Professor of Ophthalmology.

Dr. Lutty has demonstrated the mechanisms by which the retinal and choroidal vasculatures develop. He has studied the vaso-obliteration that occurs in oxygen-induced retinopathy (OIR) and the angiogenic processes that follow. He has used his canine OIR model to demonstrate the dangers of anti-VEGF agents in treating OIR but also shown how proper dose and timing of administration can result in complete inhibition of pathological neovascularization and permit normal retinal vascular development.

He has contributed substantially to our understanding of vaso-occlusive and vasoproliferative stages of sickle cell and diabetic retinopathies. He has visualized and quantified the degeneration of RPE and choriocapillaris age-related macular degeneration (AMD) and demonstrated that three endogenous anti-angiogenic factors are reduced or missing in the RPE/Bruch's membrane/choriocapillaris complex in AMD, making this environment permissive for choroidal neovascularization.

Richard H. Masland Ph.D.



Richard H. Masland Ph.D. received his Bachelor's degree from Harvard College and his Doctoral degree from McGill University; He completed his postdoctoral work at Stanford and Harvard Medical Schools. Dr. Masland is the Director of the Howe Laboratory and Associate Chief for Ophthalmology Research at

Massachusetts Eye and Ear Infirmary.

In 2010, Dr. Masland was awarded the Proctor Medal by the Association for Research in Vision and Ophthalmology.

His recent research has been concerned with the neurome of the retina, an ambitious attempt to specify all of the cell types that underlie the retina's processing of information. The assembly of this catalogue, in which several other groups worldwide have now joined him, is fundamental to the understanding of and intervention in retinal disease.

One such intervention is a gene therapy for restoring vision to retinas in which the photoreceptor cells (the cells that sense light) have degenerated. The Masland Laboratory has recently published a proof of principle of this therapy in an animal model, and is now attempting to refine it to the point of clinical usefulness.

Joan W. Miller, M.D.



Dr. Miller was born in Toronto, Ontario, Canada and is a graduate of Massachusetts Institute of Technology and Harvard Medical School. She completed an internship in medicine at Newton Wellesley Hospital and an Ophthalmology residency and a vitreo-retinal fellowship at Massachusetts Eye and Ear Infirmary.

Dr. Miller is the director of Mass. Eye and Ear's Angiogenesis Laboratory and a vitreo-retinal surgeon in the Retina Service at the Infirmary. Dr. Miller's research interests focus on ocular neovascularization, particularly as it relates to age related macular degeneration (AMD) and diabetic retinopathy, including the molecular mechanisms of angiogenesis and neuroprotection, the development of effective therapies, and drug delivery. She and her colleagues at Mass. Eye and Ear pioneered the development of Verteporfin photodynamic therapy (PDT) or Visudyne, the first pharmacologic therapy for AMD which was able to reduce and slow vision loss in patients. The group also identified the importance of vascular endothelial growth factor (VEGF) in neovascular AMD and helped develop anti-VEGF therapies-pegaptanib and ranibizumab-the latter able to improve vision in about one third of patients with neovascular AMD. While these approaches have improved the outlook for patients with AMD, Dr. Miller and her colleagues continue investigations to elucidate the pathophysiology and improve therapies for AMD.

Dr. Miller is the first woman physician promoted to the rank of Professor of Ophthalmology at Harvard Medical School. An internationally recognized expert in the field of macular degeneration, Dr. Miller has published more than 100 peer-reviewed papers, 45 book chapters and review articles, is co-editor of Albert and Jakobiec's Principles and Practice of Ophthalmology, and is a named inventor on six U.S. patents. She has received numerous awards, including the Rosenthal Award and Donald J. Gass Medal of the Macula Society, the Retina Research Award from the Club Jules Gonin, the Alcon Research Institute Award, the ARVO/Pfizer Ophthalmic Translational Research Award, and the Harvard Medical School 2010 Joseph B. Martin Dean's Leadership Award for the Advancement of Women Faculty.

Elizabeth P. Rakoczy, Ph.D.



Elizabeth Rakoczy (University of Western Australia) has been working in the field of retinal degenerations for more than 20 years. She pioneered the concept of secretion gene therapy for wet-ARMD which received approval for a clinical trial. Recently she has been working on stem cell therapies for ARMD. She has published

more than 140 scientific papers and she was one of the “Ten of the Best” award winners in Australia in 2005.

Debra A. Schaumberg, ScD, OD, MPH



Debra A. Schaumberg, Sc.D., O.D., M.P.H. is Associate Professor at Harvard Medical School and the Harvard School of Public Health, and Clinical Scientist at Schepens Eye Research Institute. She is the Director of Ophthalmic Epidemiology in the Division of Preventive Medicine at Brigham and Women’s

Hospital. She is also a Fellow of both the American Academy of Optometry, and the American College of Epidemiology, and a member of the Editorial Board of the journal Archives of Ophthalmology. She is the recipient of numerous research grants including from the National Institutes of Health, the Juvenile Diabetes Foundation, Fight for Sight, Harvard Medical School, and Industry. Dr. Schaumberg has made important contributions to our understanding of the epidemiology of age-related macular degeneration, which focus on the joint roles of environmental and genetic risk factors.

David T. Shima, Ph.D.



David T Shima, Ph.D. is the Rothes Professor of Translational Vision Research at the Institute of Ophthalmology, University College London. He obtained his Ph.D. from Harvard University, Cambridge following studies into the role of Vascular Endothelial Growth Factor (VEGF)

during pathological neovascularization within the eye. After a post-doctoral fellowship at the Imperial Cancer Research Fund in London he was appointed the head of the Endothelial Cell Biology Laboratory and established programs in vascular cell biology, development and disease. In 2002, Prof. Shima moved his laboratory to Boston, USA to join Eyetech Pharmaceuticals, where he established the Eyetech Research Center. The team delivered leads in ocular neovascular disease including E10030, a PDGF-B aptamer which is currently in clinical testing for use in AMD. Prof. Shima was also part of the executive team responsible for the development, approval and commercialization of Macugen®, the first pharmacotherapy for AMD. Once again in the UK, Prof. Shima has established the Translational Vision Research Laboratory at the Institute with the aim of creating a multi-disciplinary environment for exploring fundamental questions in basic vision research coupled with the expertise to help turn new innovations into medical treatments.

Janet R. Sparrow, Ph.D.



Janet R. Sparrow is the Anthony Donn Professor of Ophthalmic Science in the Department of Ophthalmology at Columbia University. She is also Professor in the Department of Pathology and Cell Biology. Research interests include vitamin A aldehyde-derived

compounds that accumulate as lipofuscin in retinal pigment epithelial (RPE) cells and have been linked to recessive Stargardt disease, dominant Stargardt-like maculopathy, Best vitelliform macular degeneration and age-related macular degeneration. These bisretinoid constituents of lipofuscin are unique to RPE. Research is directed toward understanding the composition of RPE lipofuscin, the properties of the constituents of this material, mechanisms by which they form and the adverse effects of these compounds on retina. Studies include the use of animal models and cell culture systems to understand the role of RPE lipofuscin in retinal degenerative disorders, to elucidate conditions that augment the formation of RPE lipofuscin and to investigate RPE lipofuscin pigments as therapeutic targets.

Anand Swaroop, Ph.D.



Anand Swaroop, Ph.D. is Chief of the Neurobiology-Neurodegeneration Repair Laboratory at the National Eye Institute. He has over 18 years experience in eye-related research and administration within academia. Dr. Swaroop obtained his Ph.D. in Biochemistry at the

Indian Institute of Science in Bangalore, India and completed his postdoctoral training at Yale University. He later joined the faculty at the University of Michigan (UM) in 1990 as an assistant professor in the Departments of Ophthalmology and Human Genetics and became full professor in 2000. He also held the Harold F. Falls Collegiate Professorship in Ophthalmology and Visual Sciences from 2003 to 2007. At UM, he was the Coordinator of the Center for Retinal and Macular Degeneration, at the Kellogg Eye Center and a faculty member in Neuroscience, Cellular and Molecular Biology, Center for Organogenesis and the Center for Computational Medicine and Biology. In September 2007, Dr. Swaroop joined the National Eye Institute as Senior Investigator to establish a new program for developing knowledge-based treatment paradigms for retinal diseases.

Using genetic, molecular and biochemical approaches, the Swaroop lab focuses on the development and function of the neural retina, photoreceptor differentiation and mechanism of diseases such as retinal and macular degeneration due to hereditary and environmental factors. In recognition of his leadership, Dr. Swaroop has been the recipient of numerous honors including the Board of Director's award from The Foundation Fighting Blindness for outstanding research in 2006 and the Harrington Senior Scientific Award from Research to Prevent Blindness. In July 2007, he received the highest honor that the University of Michigan Medical School bestows on a faculty, namely the Distinguished Faculty Lectureship Award for his extraordinary research accomplishments and service to the scientific community.

Cynthia A. Toth, M.D.



Dr. Toth received her M.D. from the Medical College of Pennsylvania in 1983. After Ophthalmology Residency at Geisinger Medical Center, she served in as a general ophthalmologist in the US Air Force from 1987-89. After Fellowship in Vitreoretinal Diseases and Surgery at UC Davis in 1991, she became

Chief of the Retina Service at the USAF Medical Center in San Antonio, Texas. Dr. Toth joined the Duke faculty in 1993 and directed the Eye Center Biophysics Laboratory, which she evolved into the Duke Advanced Research in SDOCT Imaging (DARSI) Lab. As Director of Grading for OCT for the Duke Reading Center, Dr. Toth ensures standardized OCT review for multicenter clinical trials. Her research interests for over 18 years include ophthalmic diagnostics such as optical coherence tomography, microsurgical instrumentation and techniques, and quality-of-life outcomes. Her translational research centers on improving the diagnosis, treatment and outcome for adults and children with vitreoretinal disease. vision loss.

Demetrios Vavvas M.D., Ph.D.



Demetrios Vavvas MD, PhD is an Assistant Professor of Ophthalmology at the Retina Service of MEEI. He received his B.Sc. (First Class Honors) from McGill University in 1992 and his combined MD/PhD (Cum laude) in 1999 from Boston University. He completed an internal medicine internship

at the Boston Medical Center in 2000 and his ophthalmology residency and vitreoretinal fellowship at the Massachusetts Eye and Ear Infirmary. He was selected to be Chief Resident and Chief fellow respectively. He has received the Fellow of the year teacher award. In 2007, he joined the retina service as full time staff and became PI at the Angiogenesis laboratory. His clinical interests include improvements in surgical techniques and new applications of small gauge Vitrectomy. His research interest include: neuroprotection/neuroregeneration, non-chemotherapy treatments for ocular cancers, and understanding the role of the cellular energy sensor AMPK in the function of the retina. He has received departmental funds and the Fight for Sight Grant in Aid Award, Boston Area Diabetes and Endocrinology Research Center Pilot grant, and the Alexandros Onassis Scholar Fellowship to support his work.

Michael J. Young, Ph.D.



Michael Young, Ph.D., Associate Scientist at the Schepens Eye Research Institute, received his B.S. degree in behavioral neuroscience from the University of Pittsburgh in 1989. He then received his Ph.D. in anatomy/neuroscience from the University of Cambridge in

1995. Young trained in the laboratory of Prof. Raymond D. Lund. His thesis work involved the study of intracerebral neural and retinal transplantation, and how transplant- and host – derived information is integrated in the central nervous system. A postdoctoral fellowship at the Institute of Ophthalmology, University College, London in 1995 was followed by a two-year postdoctoral fellowship at the Massachusetts Institute of Technology, Department of Brain and Cognitive Sciences.. In 1998, Young joined the Schepens Eye Research Institute as an Investigator in the Minda deGunzburg Research Center for Retinal Transplantation, and an Instructor in the Department of Ophthalmology, Harvard Medical School. He was promoted to Assistant Scientist in 2000, and elected the Director of the Minda deGunzburg Research Center for Retinal Transplantation. In 2001, he was promoted to Assistant Professor in the Department of Ophthalmology, Harvard Medical School. He has since been promoted to Associate Scientist and Associate Professor, and is now the director of the Center for Ocular Regeneration. His research involves the use of stem cells derived from the central nervous system, and neuroretinal transplantation in animal models of retinal degeneration.

Donald Zack, M.D., Ph.D.



Donald J. Zack is currently the Guerrieri Professor of Genetic Engineering and Molecular Ophthalmology at the Wilmer Eye Institute, Johns Hopkins University. He is also a professor in the Departments of Molecular Biology and Genetics, Neuroscience, and the Institute of Genetic Medicine. Dr. Zack graduated

from the Albert Einstein College of Medicine in 1984, where he received a medical degree and a Ph.D. in molecular immunology, under the mentorship of Dr. Matthew Scharff. After a year of internship Dr. Zack completed a three-year residency training program in ophthalmology at the Massachusetts Eye and Ear Infirmary, Harvard University. In 1988 he moved to Johns Hopkins where he pursued specialty training in glaucoma, under the direction of Dr. Harry Quigley, and molecular biology post-doctoral work, under the direction of Dr. Jeremy Nathans. Dr. Zack was appointed Assistant Professor at Hopkins in 1991, Associate Professor in 1997, and Professor in 2001. Dr. Zack's research has implications for understanding the pathogenesis of diseases such as age-related macular degeneration, retinitis pigmentosa, and glaucoma. This increased understanding is forming the basis of efforts to develop new paradigms for the diagnosis, prevention, and treatment of these blinding eye conditions.

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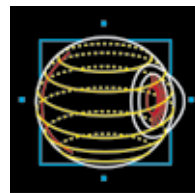
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