The Pathology of Retinal Neuro-inflammation

Sunday, May 04, 2014 8:30 AM–10:30 AM
S 230A-D Symposium
Program #/Board # Range: 1–6
Organizing Section: No Organizing Section
Contributing Section(s): Anatomy/Pathology, Glaucma, Immunology/Microbiology, Nanotechnology and Regenerative Medicine, Retinal Cell Biology, Retina, Visual Neuroscience

Program Number: 1
Presentation Time: 8:30 AM–8:49 AM
Genetics and Functional Studies in Retinal Inflammation
Kang Zhang. Zhang Lab-Osler Ln, University of California, San Diego, La Jolla, CA.

Presentation Description: AMD is a multi-factorial disease that involves interaction of genetic and environmental influences. Allelic variants of genes encoding members of the alternative complement pathway, including CFH, and C3 strongly influence an individual’s risk of developing AMD. We and others demonstrated that HTRA1 gene strongly impacts AMD risk (Dewan, et al, Science 2006; Yang et al, Scence, 2006; Jones, PNAS, 2012). We showed that variations in CFH, HTRA1, and C3 contribute to a majority of the genetic risk for AMD and are strongly predictive of advanced AMD (Chen, et al, Arch Oph, 2010). Oxidative stress plays an important role in AMD. We and others show that CFH genotype influences AMD risk by modulating oxidative stress, inflammation, and abnormal angiogenesis. The CFH risk allele confers higher complement activation and cell lysis activity. In addition, we show that e-Jun N-terminal kinase 1 (JNK1) plays a key role in linking oxidative stress, inflammation, macrophage recruitment, apoptosis, and VEGF production in laser induced CNV model and demonstrate that pharmacological JNK inhibition offers a unique and alternative avenue for prevention and treatment of AMD. The recent advances in genetics and translational studies inflammation in AMD and other retinal diseases provides new mechanistic understanding and bold great promise for next generation therapies (Zhang, et al, Nature Review Drug Discovery, 2012).

Commercial Relationships: Kang Zhang, Acucela (C)
Support: NEI/NIH, RPB

Program Number: 2
Presentation Time: 8:49 AM–9:08 AM
Review of cellular targets for diabetic retinopathy, and their relation to animal models
Timothy Korn. 1Medicine, Case Western Reserve University, Cleveland, OH; 2Stokes Veterans Admin Hospital, Cleveland, OH.

Presentation Description: The presentation will discuss molecular targets that have been demonstrated to affect lesions of diabetic retinopathy, and will interpret the findings in the context of the animal models that were used in those studies.

Commercial Relationships: Timothy Korn, None
Support: EY00300, EY02938

Program Number: 3
Presentation Time: 9:08 AM–9:27 AM
Inflammasome in age-related macular degeneration
Jayakrishna Ambati. E300 Kentucky Clinic, University of Kentucky, Lexington, KY.

Presentation Description: The inflammasome, a multiprotein immune complex, has been implicated in the pathogenesis of age-related macular degeneration (AMD), a leading cause of blindness worldwide. This presentation will discuss current cellular, molecular, and translational concepts of the inflammasome in AMD.

Commercial Relationships: Jayakrishna Ambati, Allergan (R), iVeena (S), Regeneron (R), Teva (R), University of Kentucky (P)
Support: NIH/NEI, DDCF, BF, Ellison Medical Foundation, RPB, FFB

Program Number: 4
Presentation Time: 9:27 AM–9:46 AM
Neuro-inflammation in uveitis: Retinal protection by alpha A crystalline/microRNA 146a
Narsing A. Rao. Ophthalmology, Doheny Eye Institute, Los Angeles, CA.

Presentation Description: Uveitis, an intraocular inflammation is a major cause of blindness due to retinal photoreceptor damage resulting from generation of inflammatory mediators and mitochondrial oxidative stress. We have earlier reported a novel finding of selective alpha A crystallin up regulation in the photoreceptors during the early phase of experimental uveitis model (EAU) and human uveitis, sympathetic ophthalmia at the sites of the oxidative stress in the retina, mainly in the photoreceptors cells. Moreover systemic administration of alpha A during the EAU development resulted in amelioration of the inflammatory process by down regulation of the TLRs, Th1- and Th17 cytokines required for induction and perpetuation of the inflammation. Such effects prevented retinal damage in EAU.

Crystallins, the major structural proteins of the eye lens, consist of three distinct families: alpha, beta and gamma. The two alpha-crystallins, alpha A and beta, are the principal members of the small Hsp family of molecular chaperones and are known to be expressed in multiple tissues, including retina, brain, heart, kidney, spinal cord, and lungs. Althoughalpha A- and beta-crystallin have related amino acid sequence, unlike beta, alpha A crystallin plays a critical role in the protection of the photoreceptors in EAU. MicroRNAs (miRNAs) are increasingly recognized to play an important role in the posttranscriptional regulation of gene expression and can target genes of inflammatory cytokines involved in induction of uveitis. EAU animals treated with alpha A crystallin revealed up regulation of select few miRNAs and novel bioinformatics analyses combined with validated microRNA targets revealed that among upregulated microRNAs, microRNA 146a targets both innate and adaptive immune/inflammatory genes. Further in-vivo and in-vitro studies showed that alpha A crystallin upregulates microRNA146a through a transcription factor NFkB. Interestingly systemic or local intravitreal delivery of miRNA146 results in abrogation of the neuro-inflammation in EAU and preservation of the retina.

Commercial Relationships: Narsing A. Rao, None
Support: EY 017347

Program Number: 5
Presentation Time: 9:46 AM–10:05 AM
Neuro-inflammation in glaucoma
Gulgun Tezel. Ophthalmology & Visual Sciences, University of Louisville, Louisville, KY.

Presentation Description: This presentation will highlight molecular pathways and regulation of glial neuro-inflammatory responses in glaucoma and discuss immunomodulatory treatment strategies for neuroprotection.

Commercial Relationships: Gulgun Tezel, None

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ROP blindness worldwide: phenotypes in the 3rd epidemic

Presentation Time: 10:05 AM–10:24 AM
Program Number: 6
Novel drug delivery systems for treating retinal neuroinflammation
Rangaramanujam Kannan. Ophthalmology, Wilmer Eye Institute, Johns Hopkins University, Baltimore, MD.

Presentation Description: As highlighted in this symposium, retinal neuroinflammation, mediated by activated microglia, plays a key role in the pathogenesis of photoreceptor and retinal pigment epithelial cell loss in age-related macular degeneration and retinitis pigmentosa. The impact of inflammation on retinal degeneration can be through many different mechanisms. Therefore, targeted, sustained attenuation of activated microglia and neuroinflammation may be a powerful strategy to arrest retinal degeneration and provide neuroprotection. We explore nanomedicine approaches to address this, using tree-like nanostructured polymers, called dendrimers. We have shown that hydroxyl-terminated polyamidoamine (PAMAM) dendrimers have an intrinsic ability to selectively localize in activated microglia in the brain [1] and retina [2], and provide sustained intracellular delivery of therapeutics. The talk will highlight the role of nanomedicine, especially dendrimers, in developing versatile, targeted drug delivery platforms for addressing retinal neuroinflammation [3].

REFERENCES:

Commercial Relationships: Rangaramanujam Kannan, None

102 ROP: Evolving Phenotypes and Emerging Treatments
Sunday, May 04, 2014 8:30 AM–10:30 AM
Hall SB Symposium

Program #/Board # Range: 7–12
Organizing Section: No Organizing Section

Contributing Section(s): Clinical/Epidemiologic Research, Eye Movements / Strabismus / Amblyopia / Neuro-Ophthalmology, Retinal Cell Biology, Retina, Visual Neuroscience

Program Number: 7
Presentation Time: 8:30 AM–8:50 AM
ROP blindness worldwide: phenotypes in the 3rd epidemic
Graham Quinn. ‘Pediatric Ophthalmology, Children’s Hospital of Philadelphia, Philadelphia, PA; ‘Ophthalmology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA.

Presentation Description: ROP blindness is found throughout the world except in countries with very high infant mortality rates where premature infants do not survive. It is thus an important cause of blindness in prematurely born children and has emerged as an epidemic in middle income and low income countries as neonatal care systems improve and survival of increasingly immature babies increases. Though no preventable at our current state of knowledge, it is a treatable disorder and when the severe forms are recognized and treated appropriately, sight in the vast majority of children is preserved. Systems for detection and treatment are a priority in countries as more premature babies survive.

Commercial Relationships: Graham Quinn, None
Support: NEI U10 EY017014

Program Number: 8
Presentation Time: 8:50 AM–9:10 AM
Prevention of ROP: Mechanisms of lipid metabolites and IGF-1 in ROP
Lois Smith. 1Ophthalmology, Boston Children’s Hospital, Boston, MA; 2Ophthalmology, Harvard Medical School, Boston, MA.

Presentation Description: Omega 3 long chain polysaturated fatty acids have been shown to help prevent neovascular ROP through PPAR gamma and TNF alpha. Further aspects of the mechanisms will be discussed. Replacement of IGF-1, missing after preterm birth, is also effective in helping to prevent retinopathy in animal models and is now in clinical trials for infants with ROP.

Commercial Relationships: Lois Smith, None
Support: NIH grant EY 017017

Program Number: 9
Presentation Time: 9:10 AM–9:30 AM
Mechanisms of Oxygen Stresses in ROP
John S. Penn. Vanderbilt Eye Institute, Vanderbilt Eye Institute, Nashville, TN.

Presentation Description: Commercial Relationships: John S. Penn, None
Support: EY07533, Research to Prevent Blindness, Inc., Reeves Foundation

Program Number: 10
Presentation Time: 9:30 AM–9:50 AM
Promoting Vascular repair in prematurity to prevent ROP
Maria Grant. Pharmacology and Therapeutics, University of Florida, Gainesville, FL.

Presentation Description: The World Health Organization estimates approximately 12.9 million babies worldwide are born prematurely (~37 weeks gestation) every year. Ninety-two percent of these births take place in developing countries and, as access to neonatal intensive care increases across these nations, so will the rise of retinopathy of prematurity (ROP). An estimated 50,000 children are blinded by the disease across the globe. An increase in the incidence of ROP in the developed world is occurring as extremely premature infants (22-24 weeks gestation) are now surviving. The higher-than-normal levels of oxygen required to protect infants from damage to their brains result in a down-regulation of hypoxia-induced VEGF, the stimulus for normal vascular development. Loss of VEGF expression effectively results in “delayed retinal vasculization” relative to neuronal maturation.

Endothelial progenitor cells (EPCs), a small, but critically important population of vascular stem/progenitor cells derived from the bone marrow or peripheral blood play a major role in vascular development in the infant and in blood vessel maintenance and regeneration in the adult. There are several well characterized EPCs populations that are distinguished based on surface markers or behavior in culture. EPCs injected directly into the eye or through systemic delivery have potential to repair damaged retinal blood vessels in animal models of retinal diseases. In this presentation, the possible use of EPCs populations will be presented. Intravitreal administration of specific EPCs populations, by directly incorporating into the newly forming vasculature and by providing paracrine support to the developing vessels, may correct the down-regulation of hypoxia-induced VEGF and provide a stimulus for normal vascular development.
development and neuronal maturation. Use of EPCs for treatment of early stages of ROP in infants may offer a major benefit to the welfare of premature infants.

**Commercial Relationships:** Maria Grant, None

**Support:** EY012601-11, EY007739-21, EY018358 and DK 090730

**Presentation Description:** This presentation will review current strategies for optimal ROP screening as well as the state-of-the-art in interventions to mitigate the impact of ROP.

**Commercial Relationships:** Antonio Capone, FocusROP LLC (I), Pediatric Retinal Imaging Systems LLC (I)

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**Presentation Description:** The cornea is a uniquely accessible tissue for post-transcriptional and genomic modification therapy. Knockdown of VEGF-A using shRNAs expressed by plasmids can successfully suppress neovascularization induced by alkali injury or suture injury as well as inhibit cornea transplant rejection. With respect to inherited corneal dystrophies, causative gene mutations and potential therapeutic strategies will be outlined and overviewed.

**Commercial Relationships:** Balamurali Ambati, None

**Support:** VA Merit Award

**Program Number:** 1225

**Presentation Time:** 5:39 PM–5:58 PM

**Next generation sequencing in inherited retinal disease**

**Eric Pierce.** Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, MA.

**Presentation Description:** Proliferative vitreoretinal diseases such as proliferative diabetic retinopathy(PDR) and vitreoretinopathy (PVR) is a severe, vision-threatening disorder characterized by the fibro(vascular) membrane formation that leads to tractional retinal detachment. There has been no effective therapeutic approach other than vitrectomy surgery. In this study, DNA microarray analysis of the fibro(vascular) membranes revealed significant up-regulation of peristin. We also found increased peristin expression in the vitreous and retinal pigmented epithelial (RPE) cells from fibrous membranes of PDR and PVR patients. In vitro, peristin increased proliferation, adhesion, migration, and collagen production in RPE cells through integrin αV-mediated FAK and AKT phosphorylation. Peristin blockade suppressed migration and adhesion induced by TGFβ2 and PVR vitreous. In vivo, peristin inhibition had the inhibitory effect on progression of experimental PVR in rabbit eyes without affecting the viability of retinal cells. These results identified peristin as a pivotal molecule for fibro(vascular) membrane formation as well as a promising therapeutic target for PDR and PVR.

**Commercial Relationships:** Shigeo Yoshida, None

**Support:** Grants-in-Aid for Scientific Research from Japanese Government 23592574

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**Program Number:** 1224

**Presentation Time:** 5:20 PM–5:39 PM

**Molecular Genetics in Cornes Disease: Use of RNA interference and Potential Future Targets for Gene Therapy, presented by the 2014 Ludwig von Ballmann Clinician-Scientist Award Recipient Balamurali Ambati.** Ophthalmology, University of Utah, Salt Lake City, UT.

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**Program Number:** 11

**Presentation Time:** 9:50 AM–10:10 AM

**Current Screening and Treatments in ROP**

**Antonio Capone.** 1Partner, Associated Retinal Consultants, Royal Oak, MI; 2Ophthalmology, Oakland University-William Beaumont Hospital School of Medicine, Auburn Hills, MI.

**Presentation Description:** We have shown that ROP has its onset during ages at which photoreceptor structure and function are developing rapidly. Thereafter, ROP has a persistent effect on the retina and its function. In the rat model, the status of early photoreceptor function forecasts the vascular status at maturity, and control of retinal vascular and neural development share the same molecular pathways. In infants with a history of ROP, there are significant deficits in both rod photoreceptor and rod mediated post-receptor function regardless of whether the ROP was mild and resolved spontaneously or severe and required treatment. Years later, rod function remains abnormal in both mild and severe ROP, as does rod driven post-receptor function in severe ROP. Post-receptor function, however, becomes normal in mild ROP, likely due to intra-laminar re-organization of neural circuitry after early infancy. The situation is different in the late maturing central retina. Abnormalities of the intra retinal vascular supply and abnormalities of cone driven post-receptor activity remain decades after acute mild ROP had resolved. The implications of these data for vision and for management of former preterms will be discussed.

**Commercial Relationships:** Anne Fulton, None

**Support:** NIH grant EY 10597

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**Program Number:** 12

**Presentation Time:** 10:10 AM–10:30 AM

**Retinal and Visual Development in ROP**

**Anne Fulton.** Ophthalmology, Children’s Hospital of Boston, Harvard, Boston, MA.

**Presentation Description:** We have shown that ROP has its onset during ages at which photoreceptor structure and function are developing rapidly. Thereafter, ROP has a persistent effect on the retina and its function. In the rat model, the status of early photoreceptor function forecasts the vascular status at maturity, and control of retinal vascular and neural development share the same molecular pathways. In infants with a history of ROP, there are significant deficits in both rod photoreceptor and rod mediated post-receptor function regardless of whether the ROP was mild and resolved spontaneously or severe and required treatment. Years later, rod function remains abnormal in both mild and severe ROP, as does rod driven post-receptor function in severe ROP. Post-receptor function, however, becomes normal in mild ROP, likely due to intra-laminar re-organization of neural circuitry after early infancy. The situation is different in the late maturing central retina. Abnormalities of the intra retinal vascular supply and abnormalities of cone driven post-receptor activity remain decades after acute mild ROP had resolved. The implications of these data for vision and for management of former preterms will be discussed.

**Commercial Relationships:** Anne Fulton, None

**Support:** NIH grant EY 10597

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**Presentation Description:** Gene expression profiling of epiretinal membranes from patients with proliferative diabetic retinopathy and proliferative vitreoretinopathy

**Shigeo Yoshida.** Ophthalmology, Kyushu University Graduate School of Medical Sciences, Fukuoka-shi, Japan.

**Presentation Description:** Proliferative vitreoretinal diseases such as proliferative diabetic retinopathy(PDR) and vitreoretinopathy (PVR) is a severe, vision-threatening disorder characterized by the fibro(vascular) membrane formation that leads to tractional retinal detachment. There has been no effective therapeutic approach other than vitrectomy surgery. In this study, DNA microarray analysis of the fibro(vascular) membranes revealed significant up-regulation of peristin. We also found increased peristin expression in the vitreous and retinal pigmented epithelial (RPE) cells from fibrous membranes of PDR and PVR patients. In vitro, peristin increased proliferation, adhesion, migration, and collagen production in RPE cells through integrin αV-mediated FAK and AKT phosphorylation. Peristin blockade suppressed migration and adhesion induced by TGFβ2 and PVR vitreous. In vivo, peristin inhibition had the inhibitory effect on progression of experimental PVR in rabbit eyes without affecting the viability of retinal cells. These results identified peristin as a pivotal molecule for fibro(vascular) membrane formation as well as a promising therapeutic target for PDR and PVR.

**Commercial Relationships:** Shigeo Yoshida, None

**Support:** Grants-in-Aid for Scientific Research from Japanese Government 23592574

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**Program Number:** 1227

**Presentation Time:** 6:17 PM–6:36 PM

**Molecular genetic prognostic methods in uveal melanoma**

**Sarah E. Coupland.** Dept of Molecular and Medical Cancer Medicine, University of Liverpool, Liverpool, United Kingdom.

**Presentation Description:** Uveal Melanoma (UM), the most common primary intraocular cancer in adults, is fatal in almost 50% of patients, because of metastatic spread involving the liver. Chemotherapy of metastases has limited success and disseminated disease is fatal in most patients <2 years of diagnosis. Clinical, histopathological and genetic risk factors for UM metastasis are documented. UM is characterised by frequent non-random gross chromosomal changes, the most common being monosomy 3 and gain of 8q, both of which are strong predictors for metastasis. The purposes of this presentation are to review: a) described genetic
abnormalities of UM, and relate these to hypotheses regarding tumour development and dissemination; b) current methods used in UM prognostication.

METHODS: A literature review of publications addressing UM genetic changes has been undertaken, concentrating particularly on more recent ones describing mutations in GNAQ, GNA11, BRCAl-associated protein 1 (BAP1), SF3B1, EIFAX, and CNKSR3. The author’s experience in using fluorescence in situ hybridisation (FISH) and multiplex ligation-dependent probe amplification (MLPA) in routine clinical prognostication of UM will be presented. It will be discussed in relation to other molecular methods currently used, including array comparative genomic hybridization (aCGH), array single nucleotide polymorphism (aSNP) analysis and gene expression profiling (GEP)-based kits.

RESULTS: While reliable genetic methodologies for predicting metastatic disease from UM are being regularly employed, exciting reports have recently described gene mutations in UM that may aid our understanding of their pathogenesis and the process of dissemination in these tumors. The detection of gene mutations at differing stages of tumor development, offers a deeper insight into the biology of UM development and progression that may ultimately yield useful druggable targets at different stages.

CONCLUSIONS: UM research is increasingly benefiting from technological advances in molecular pathology, allowing us to detect micrometastases earlier and leading us closer in our search for the "magic bullet" in better treating this dire disease.

Commercial Relationships: Sarah E. Coupland, None

Program Number: 1228
Presentation Time: 6:36 PM–6:55 PM
Genome-wide association studies in glaucoma

Presentation Description: Genome-wide association studies (GWAS) have identified susceptibility genes and functional non-coding regions underlying many complex ocular diseases, including adult-onset forms of glaucoma. This presentation will discuss the overall GWAS approach and review advances in the genetics of adult-onset glaucoma, including quantitative endophenotypes. Pathway analyses and gene-based analyses (including rare variants) based on GWAS meta-analyses have suggested potential therapeutic targets, and these and other translational investigations will be presented.

Commercial Relationships: Janey L. Wiggs, Merck (R), NIH/NEI (F)
Support: NIH/NEI R01 EY022305, NIH/NEI R21 EY022766, NIH/NEI P30 EY014104

Program Number: 1229
Presentation Time: 6:55 PM–7:14 PM
Ocular Infections: Morphology to Molecular Diagnosis
Geeta K. Vemuganti. School of Medical Sciences, University of Hyderabad, Hyderabad, India

Presentation Description: Ocular infections pose huge challenge to the clinicians and continue to be an important cause of visual morbidity In developing countries. While microbiologic investigations remain the mainstay of diagnosis, it is not always easy to make specific diagnosis based on traditional staining and culture techniques. The new challenges in diagnosis is the emergence of new pathogens that affect ocular tissues, atypical clinical presentation of known infections, changing patterns of surgical and medical treatment that affect the diagnosis and clinical outcome. In addition to a detailed clinical, morphological, culture sensitivity studies, the tools now available for diagnosis are genotyping for identification of species. The molecular tools of diagnosis include polymerase chain reaction for single or multiplex PCR for diagnosis of various ocular infections eg fungal infection, bacterial infection of cornea and vitreous. Apart from contributing to routine diagnosis, these tools contribute to other identification of specific genetic constitution for further sub classification, identification of newer infections, evaluating for resistant strains, establishing a cause effect relationship between an infectious agent and cancer, and also in trouble shooting for the source of infection during breakdown of sterility measures in clinical setting or laboratory practice.. Some of the well protocols that are in practice are for identification of fungal infections, bacterial infections, mycobacterial, viral keratitis, microsporidal infections. Availability of new kits now make it possible to do these tests on minimal amount of sample as well as archived samples.

Commercial Relationships: Geeta K. Vemuganti, None

385 Where Are the Women? Exploring Roles in ARVO
Tuesday, May 06, 2014 5:30 PM–7:00 PM
S 320AB Symposium
Program #/Board # Range: 4007–4013
Organizing Section: No Organizing Section

Program Number: 4007
Presentation Time: 5:32 PM–5:40 PM
Approach to the gender gap at the institutional level
Lynn K. Gordon. UCLA, Los Angeles, CA.

Commercial Relationships: Lynn K. Gordon, None

Program Number: 4008
Presentation Time: 5:40 PM–5:48 PM
Approach to the gender gap at an organizational level
Hugh R. Taylor. University of Melbourne, Melbourne, VIC, Australia.

Commercial Relationships: Hugh R. Taylor, None

Program Number: 4009
Presentation Time: 5:48 PM–5:56 PM
Approach to the gender gap at the country level
Sarah E. Coupland. Univ of Liverpool/Sydney Jones Library, Liverpool, United Kingdom.

Commercial Relationships: Sarah E. Coupland, None

Program Number: 4010
Presentation Time: 6:06 PM–6:14 PM
How are we doing at ARVO? Membership at ARVO
Francis S. George. ARVO, Rockville, MD.

Commercial Relationships: Francis S. George, None

Program Number: 4011
Presentation Time: 6:14 PM–6:22 PM
How are we doing at ARVO? Meetings at ARVO
Gayle Claman. ARVO, Rockville, MD.

Commercial Relationships: Gayle Claman, None

Program Number: 4012
Presentation Time: 6:32 PM–6:42 PM
The way forward how should ARVO promote women’s leadership: The argument for and against quotas
David S. Williams. UCL, Los Angeles, CA.

Commercial Relationships: David S. Williams, None

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501 Ocular Circulation: Technologies and Applications

**Program Number:** 5414  
**Presentation Time:** 8:30 AM–8:45 AM

**Quantification of ocular blood flow**

*Leopold Schmetterer.* ‘Clinical Pharmacology, Medical University of Vienna, Vienna, Austria; 3Center of Medical Physics and Biomedical Engineering, Medical University of Vienna, Vienna, Austria.

**Presentation Description:** The eye has a complex blood supply enabling adequate delivery of oxygen and nutrients to the ocular tissues. Inadequate blood supply leads to ischemia and/or hypoxia resulting in tissue damage. The degree and nature of damage is, however, strongly dependent on the degree of ischemia. As such researches have tried to measure blood flow in the eye since many decades. This is, however, technically demanding. In addition, interpretation of the measurements requires a profound knowledge of what is exactly measured. Whatever a technique measures the data have to be carefully validated. In the recent years several techniques that assess total retinal blood flow have been realized. Before such techniques are applied to the situation in clinical studies careful validation is mandatory, which is not easy in the absence of a gold standard technique.

**Commercial Relationships:** Leopold Schmetterer, None

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**Program Number:** 5415  
**Presentation Time:** 8:45 AM–9:00 AM

**Optical coherence tomography angiography**

*Yali Jia.* Oregon Health & Science University, Portland, OR.

**Presentation Description:** The leading causes of blindness such as diabetic retinopathy, age-related macular degeneration, and glaucoma are all associated with impaired circulation. Examination of ocular circulation is critical for the assessment of these eye diseases. Therefore, non-invasive ocular angiography would be a powerful methodology for understanding and diagnosing these eye diseases.

Currently, the most widely used technique for examining ocular circulation abnormalities is fundus fluorescein angiography (FA). This is an invasive procedure. It requires dye injection which might cause nausea and anaphylaxis. In addition, FA cannot distinguish choroidal vessels from retinal vessels or detect the lamina cribrosa perfusion deep inside the optic nerve head (ONH). Other existing non-invasive imaging techniques, such as scanning laser Doppler flowmetry and scanning laser speckle flowmetry are also limited to 2D imaging of the superficial perfusion. Optical coherence tomography (OCT) generates cross-sectional images by measuring the echo time delay and magnitude of backscattered light. It has achieved micrometer-level axial resolution in cross-sectional retinal imaging. Currently OCT has been a necessary part of the standard of care for retinal diseases, and increasingly so for glaucoma and anterior segment surgeries as well. However, conventional structural OCT cannot provide the blood flow information directly. Doppler OCT has been used to obtain precise measurements of total retinal blood flow calculated from the Doppler frequency shift of backscattered light. While appropriate for large vessels around the disc, Doppler OCT is not sensitive enough to accurately measure the low velocities of small vessels.

We have recently developed a new 3D ocular angiography using optical coherence tomography. The algorithm is called split-spectrum amplitude-decorrelation angiography (SSADA). By splitting the full OCT spectrum into several narrower bands, SSADA reduces OCT axial resolution and consequently reduces its susceptibility to axial motion noise. These changes enable improved detection of the flow signal, which in the ocular fundus is predominantly in the transverse dimension. With a ~3 second scan using our 100 kHz swept-source OCT prototype, SSADA provides a high-quality 3x3x3 mm 3D angiogram. By selecting the maximum value along the axial (Z) direction or by slicing the angiographic volume at each layer, 3D OCT angiography can produce different types of X-Y projection angiograms for retinal, choroidal, and ONH circulation. In this presentation, the system and theory of OCT angiography and its application on both glaucoma and retinal stuides will be demonstrated.

**Commercial Relationships:** Yali Jia, Optovue, Inc. (P)

**Support:** NIH grant 1R01 EY023285-01

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**Program Number:** 5416  
**Presentation Time:** 9:00 AM–9:15 AM

**Autoregulation of ocular circulation in glaucoma**

*Alon Harris.* Ophthalmology, Indiana University, Indianapolis, IN.

**Presentation Description:** The most widely investigated pressure-independent physiological processes contributing to glaucomatous optic neuropathy is an insufficient supply of ocular circulation and/or faulty vascular regulation and vasospasm. For decades glaucoma has been associated with vascular diseases such as systemic hyper/hypo-tension, diabetes and migraine and dozens of prospective studies have found low ocular blood flow in glaucoma patients. Many large population based studies have reported ocular perfusion pressures to be a risk factor for prevalence, incidence and progression of glaucoma. The contribution of ischemic damage in glaucoma may be local, confined within the retina and anterior optic nerve, or may represent only one aspect of a more generalized ischemic process involving widespread cerebrovascular insufficiency. The exact relationship of blood flow disturbances to glaucoma progression remains insufficiently described; however pilot evidence has begun to suggest an association is present in some individuals. Certain groups of individuals may be at elevated risk for glaucoma due to vascular insults including patients of African descent and patients with diabetes. This presentation will explore the past, present and future direction of ocular blood flow research in glaucoma management and facilitate discussion on the link between ocular blood flow deficits and optic neuropathy. By examining ocular blood flow deficits and their interconnectivity to glaucoma through specifically designed prospective studies and mathematical modeling the understanding of glaucoma pathophysiology and future screening and novel treatment options may be enhanced.

**Commercial Relationships:** Alon Harris, Adom (I), Alcon (R), Allergan (R), Biolight (I), MSD (R), Nano Retina (I), Ono (C), OxiMap (I), Science Based Health (C), Sucampo Pharmaceuticals (C)

**Support:** NIH IR21EY022101-01A1

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Adaptive Optics (AO) compensates ocular aberrations leading to scattered light from a focused beam. Pupils were not dilated. (AOSLO, rtx1, Imagine Eyes, France) was used to produce 4 x


PURPOSE: to measure wall-to-lumen ratio WLR of retinal vessels proposed as early signs of vascular damage in arterial hypertension. culminating in an increased wall-to-lumen-ratio WLR. Increased decreased lumen diameter and a thickening of the arteriolar wall inward remodeling. Eutrophic inward remodeling represents a leads to chronic vasoconstriction of small arteries and eutrophic inward remodeling. The mechanisms of hem- and lymphangiogenesis, their clinical relevance and new strategies for therapeutic intervention in different corneal diseases are outlined.

Commercial Relationships: Gerard A. Lutty, None

Support: AHAF, Beckman Foundation, and NIH Grants EY-016151 and EY001765

Ocular blood flow in diabetic retinopathy
Taiji Nagaoka. Ophthalmology, Asahikawa Medical University, Asahikawa, Japan.

Presentation Description: My presentation will focus on recent technological advances of ocular blood flow and their application to the clinical studies on diabetic retinopathy.

Commercial Relationships: Taiji Nagaoka, None

Support: Supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology in Japan (C-18591904 and B-25293352)

Angiogenesis in corneal diseases
Claus Cursiefen. Dept of Ophthalmology, University of Cologne, Kолн, Germany.

Presentation Description: The role of pathologic blood and lymphatic vessel outgrowths in corneal and ocular surface diseases is discusses. The mechanisms of hem- and lymphangiogenesis, their clinical relevance and new strategies for therapeutic intervention in different corneal diseases are outlined.

Commercial Relationships: Claus Cursiefen, Allergan (C), Gene Signal (C), Novaliq (C)

Support: DFG Cu 47/4-1

Remodelling of Retinal Vessels in Arterial Hypertension

Presentation Description: Background: Elevated blood pressure leads to chronic vasoconstriction of small arteries and eutrophic inward remodeling. Eutrophic inward remodeling represents a decreased lumen diameter and a thickening of the arteriolar wall culminating in an increased wall-to-lumen-ratio WLR. Increased wall-to-lumen ratios in biopsies of subcutaneous vessels were proposed as early signs of vascular damage in arterial hypertension. PURPOSE: to measure wall-to-lumen ratio WLR of retinal vessels using Adaptive Optics Scanning Laser Ophthalmoscopy (AOSLO). METHODS: Adaptive Optics Scanning Laser Ophthalmoscope (AOSLO, rtx1, Imagine Eyes, France) was used to produce 4 x 4 degree high resolution images of retinal vessels by recording scattered light from a focused beam. Pupils were not dilated. Adaptive Optics (AO) compensates ocular aberrations leading to image resolutions of 2 μm. Wall-to-lumen ratio WLR of retinal arterioles was calculated after measuring the distances of the vessel lumen and the vessel wall thickness of parapapillary vessels. Mean and standard deviation of 5 consecutive measurements of vessel lumen and vessel wall thickness were calculated. WLR was calculated by WLR = total wall/ lumen. In addition retinal digital photographs of 45 degree were taken by a digital non-mydriatic fundus camera (KOWA NM-45, nonmyd-alpha). Pupils were not dilated. Arterio-venous ratio AVR of retinal vessels were calculated by a semiautomatic system. PATIENTS: We examined 47 right eyes of 47 (21 male and 25 female) ocular healthy subjects. The mean age was 47,7 ± 17,4 years. Eleven subjects reported arterial hypertension. An age-adjusted-WLR was calculated from ocular and systemic healthy subjects (n=16; mean age= 36,9 ± 17,9 years) with a body-mass-index BMI lower than 25 and no sign of arterial hypertension, diabetes, or elevated levels of cholesterol. RESULTS: Intraobserver variability was 6% and 2% in measuring distances of vessel wall thickness, and vessel lumen inclusive the vessel wall thickness, respectively. Mean of vessel diameter, vessel wall thickness, and WLR were 149,0 ± 30,6 μm, 19,1 ± 5,5 μm, and 0,29 ± 0,06, respectively. The vessel wall thickness was significantly associated with the vessel diameter (r=0,715; p<0,01). Wall-to-lumen ratio WLR correlated inversely with generalized arteriolar narrowing AVR (r= - 0,414; p<0,01) and significantly with age (r= 0,769; p<0,01). Patients with arterial hypertension showed a significantly higher age-adjusted WLR than normotensive controls (0,31 ± 0,03 μm vs. 0,27 ± 0,03 μm). Age-adjusted WLR correlated significantly with BMI (r= 0,306, p<0,05). CONCLUSIONS: Adaptive Optics Scanning Laser Ophthalmoscope AOSLO allowed the measurement of the wall-to-lumen ratio WLR of retinal vessels. Retinal arteriolar WLR was significantly increased in patients with retinal microangiopathy, elder age, arterial hypertension and increased BMI.

Commercial Relationships: Georg Michelson, None

502 Genetics and the Pathophysiology of AMD: From SNPs to Disease Modeling
Thursday, May 08, 2014 8:30 AM–10:30 AM
Hall SB Symposium
Program #/Board # Range: 5421–5426
Organizing Section: No Organizing Section
Contributing Section(s): Biochemistry/Molecular Biology, Clinical/ Epidemiologic Research, Genetics, Physiology/Pharmacology, Retinal Cell Biology, Retina, Visual Neuroscience

Overview of the current state of AMD genetics
Johanna Seddon. Ophthalmology, Tufts University School of Medicine, Boston, MA.

Presentation Description: Commercial Relationships: Johanna Seddon, Arctic Dx (F), Genentech (F), Tufts medical Center (P)
Support: Genentech & Arctic Dx

Program Number: 5421
Presentation Time: 8:30 AM–8:50 AM

Presentation Description: Genetic variation at a locus on chromosome 10q26 has been consistently associated with age-related
macular degeneration (AMD) and represents one of the two strongest genetic effects being identified in AMD. This locus is associated with both types of advanced AMD in most, if not all populations examined. It appears that variants in the locus confer an even greater risk of choroidal neovascularization (CNV) than of geographic atrophy (GA).

At least three genes are located within the bounds of the locus: pleckstrin homology domain containing family A member 1 (PLEKHA1), age-related maculopathy susceptibility 2 (ARMS2) and high-temperature requirement A serine peptidase 1 (HTRA1), all of which are associated with AMD. The most significantly associated haplotype includes single nucleotide polymorphisms (SNP) rs10490924 (amino acid change A69S) in ARMS2 and rs11200638 in the promoter of HTRA1. Due to the strong linkage disequilibrium (LD) across this region, statistical genetic analysis alone is incapable of distinguishing the effect of an individual gene in the locus. HTRA1 protein is known as a secreted protease that degrades numerous extracellular matrix proteins. Animal modeling studies have shown that overexpressing HTRA1 induces AMD-like pathological changes in mice. However, all three possible consequences of HTRA1 expression (up-regulated, not-changed or down-regulated) have been correlated with the AMD-associated variants in the literature. Overexpressing HTRA1 in mouse retinal pigment epithelium (RPE) may not accurately model the expression of HTRA1 in AMD-affected human eyes. HTRA1 thus has not been conclusively established as the susceptibility gene in the locus. ARMS2 is only annotated in genomes of humans and high primates. The basic biology of ARMS2 remains largely unclear. The transcripts, including a novel splice variant, of ARMS2 have been detected in human retinas. However, it has yet to decide whether the associated variants accelerate the degradation of ARMS2 transcripts in the retina. On the other hand, the significantly associated coding variant A69S could potentially change the function of ARMS2, implicating it as a plausible candidate for AMD.

In summary, uncertainty remains in regards to which gene is responsible for the linkage and association of this locus with AMD. Further functional studies are essential to identifying the susceptibility gene(s) in the locus.

Commercial Relationships: Gaofeng Wang, None
Support: NIH (2R01EY012118-11)

Program Number: 5423
Presentation Time: 9:10 AM–9:30 AM
The influence of CFH genotype and age-related changes in Bruch’s membrane on AMD pathogenesis
Anthony J. Day. Faculty of Life Sciences, The University of Manchester, Manchester, United Kingdom.

Presentation Description: The dysregulation of complement has been implicated as having an important role in the pathogenesis of Age-related Macular Degeneration (AMD), based on both biochemical and genetic studies. In this presentation I will describe how the common Y402H polymorphism of complement factor H (CFH), a negative regulator of the complement system, affects the specificity of this protein for a number of ligands. In particular, this tyrosine to histidine amino acid change in the CFH protein sequence alters CFH’s ability to bind to sites within Bruch’s membrane, which are composed of complex sugar molecules that belong to the heparan sulfate (HS) family of glycosaminoglycans. The disease-associated 402H form of CFH only binds to rare HS structures whereas the 402Y variant has a much broader specificity. Evidence suggests that this inherent biochemical difference in the 402H variant impairs the binding of CFH within the Bruch’s membrane, thereby compromising the regulation of complement within this extracellular matrix (ECM). Previously, we have suggested that this could lead to local chronic inflammation at the interface of the Bruch’s membrane and retinal pigment epithelium (RPE), and thus, contribute to the formation of drusen (which are comprised of RPE cellular debris and complement activation products). More recently we have found that there is an age-related reduction in the overall amount (and change in composition) of HS in human Bruch’s membrane. Our data indicate that alterations in the levels of specific proteoglycan core proteins, as well as in HS biosynthesis/turnover, likely contribute to this pronounced (and significant) reduction. Importantly, these age-associated changes in ECM structure are likely to exacerbate the poor binding seen for the 402H variant of CFH to the Bruch’s membrane and could represent a ‘tipping point’ for loss of immune homeostasis in the eye. Therefore, this may explain why the pathology of AMD does not usually develop until the 6th decade of life since it requires an age-related change in HS structure in combination with an allelotype of CFH that has a restricted HS specificity.

Commercial Relationships: Anthony J. Day, None
Support: Medical Research Council Grants G0900592 & K004441; Fight For Sight Grant 1866.

Program Number: 5424
Presentation Time: 9:30 AM–9:50 AM
Future directions in AMD Genetics
Michael Gorin. ¹Dept of Ophthalmology, Jules Stein Eye Institute - UCLA, Los Angeles, CA; ²Human Genetics, David Geffen School of Medicine - UCLA, Los Angeles, CA.

Presentation Description: Family-based linkage and association studies as well as candidate gene and genome-wide case-control association studies have been spectacularly successful in identifying common genetic variants in a number of genes and metabolic pathways that contribute towards the risk of developing age-related macular degeneration. More recent efforts include the detection of rare variants and searching for gene-gene and gene-environmental interactions. Future efforts will include the integration of molecular genetic testing with early disease phenotyping to achieve improved predictive value for testing for early AMD detection to guide preventive therapies. Genetics will continue to be used to attempt to establish subgroups of AMD that are distinctive in their manifestations and responses to therapies. There is an ongoing need to establish the biological bases of the genetic associations that have already been found and to develop pathway-based models for disease pathogenesis that can be developed and explored within animal models and provide new targets for therapy. Such models will play a key role in the investigation of tissue-specific epigenetic processes that may be AMD modifiers. Additional challenges will include the evaluation of the genetics of the human microbiome and how these gene-environmental interactions may also influence the natural history and management of AMD.

Support: NIH grant EY09859, Harold and Pauline Price Foundation, Research to Prevent Blindness

Program Number: 5425
Presentation Time: 9:50 AM–10:10 AM
CFH genotype and choroidal vascular disease in AMD
Robert Mullins. ¹Ophthalmology and Visual Sciences, University of Iowa, Iowa City, IA; ²The Stephen A Wynn Institute for Vision Research, Iowa City, IA.

Presentation Description: We will discuss recent findings related to how high risk SNPs in the CFH gene affect the aging posterior pole. We have studied eyes from genotyped patients and found that

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the membrane attack complex of complement (MAC) is increased in eyes homozygous for the risk allele. Moreover, eyes with high risk genotypes show increased loss of choriocapillaris vasculature, but have preserved RPE integrity. These findings are consistent with the notion that CFH functions in part to protect the choriocapillaris from MAC-mediated injury and that choriocapillaris pathology due to MAC is an early event in AMD pathogenesis. Implications for therapy in early and advanced AMD will be discussed.

Commercial Relationships: Robert Mullins, None
Support: NIH grants EY017451, EY016822

Program Number: 5426
Presentation Time: 10:10 AM–10:30 AM
Exploring the role of complement in AMD via opportunistic clinical scenarios
Andrew Lotery. 1Ophthalmology - Eye Unit, Southampton General Hospital, Southampton, United Kingdom; 2Clinical Neurosciences, University of Southampton, Southampton, United Kingdom.

Presentation Description: This presentation will describe what insights we have gained by studying the effect of systemic complement modulation through liver transplantation. In addition it will evaluate the role of complement in treatment response to therapy for choroidal neovascularization. Thus it will be of interest to individuals wishing to design complement therapies for the treatment of age related macular degeneration.

Commercial Relationships: Andrew Lotery, Novartis (C), Novartis (F)
Support: TFC Frost Charitable Trust, Brian Mercer Trust, Gift of Sight Appeal