Symposium

Symposium 1
New Strategies for Glaucoma Diagnosis and Treatment

Organizers
Calvin CP Pang
The Chinese University of Hong Kong, Kowloon, Hong Kong
Hidenobu Tanihara
Faculty of Life Sciences, Kumamoto University, Kumamoto, Kumamoto, Japan
Takeshi Yoshitomi
Akita University Graduate School of Medicine and Faculty of Medicine, Akita, Akita, Japan

1: SY1-1

Molecular mechanism of axonal damage in glaucoma

Speaker: Masaru Inatani [1]
1. Department of Ophthalmology, University of Fukui, Yoshida, Fukui, Japan.

Disruption of the axonal transport plays a critical role in the molecular mechanism of axonal damage in glaucoma optic neuropathy. We examined whether axonal transport of retinal ganglion cells (RGCs) could be visualized in living RGCs, and whether the disturbance of axonal transport could be detected in axon-damaged RGCs as well as in the optic nerve with high intraocular pressure. For in vitro study, the dynamics of axonal transport was analyzed in cultivated rat RGCs by time-lapse imaging. For in vivo study, the dynamic imaging of axonal transport was evaluated in mice eyes with high intraocular pressure. Time-lapse imaging quantified the density and velocity of the axonal transport in rat cultivated RGCs, as well as the disturbance of axonal transport which was followed by RGC death. Moreover, axonal transport of RGCs in the anterograde as well as retrograde directions was visualized in the living mice eye. We found that the elevation of intraocular pressure in the mice eyes disturbed the axonal transport before the glaucoma optic neuropathy. Our data have confirmed that the axonal transport is disturbed before RGC death and glaucoma optic neuropathy. Dynamic imaging for axonal transport of RGCs might be useful for early detection of glaucoma optic neuropathy.

Commercial Relationships: Masaru Inatani, Pfizer (F), Santen (F), Novartis (F), Alcon (F), Senju (F), Otsuka (F), Kowa (F), HOYA (F), AMO (F), MSD (F), Pfizer (R), Santen (R), Senju (R), MSD (R), Otsuka (R), Novartis (R), Alcon (R), AMO (R), Ueno (R), Bausch & Lomb (R), Ono (R), HOYA (R)
Support: MEXT in Japan #24390395

2: SY1-2

Recovery of retinal ganglion cell function after IOP lowering

Speaker: Jonathan Crowston [1, 2]
1. Department of Ophthalmology, University of Melbourne, East Melbourne, VIC, Australia. 2. Centre for Eye Research Australia, Melbourne, VIC, Australia.

This study will demonstrate recovery of inner retinal function in the mouse eye after acute intracocular pressure challenge. In addition we will present data from 2-human glaucoma cohort studies that deminstrate a similar improvement in inner retinal function using full field electroretinogram in response to intraocular pressure lowering.

Commercial Relationships: Jonathan Crowston, None
Support: NHMRC

3: SY1-3

The role of aquaporin 9 in retinal ganglion cell death in glaucoma

Speaker: Makoto Nakamura [1]
1. Division of Ophthalmology Department of Surgery, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan.

Glaucomatous optic neuropathy is caused by retinal ganglion cell (RGC) death due to yet unidentified mechanisms. Aquaporin (AQP) is a family of transporters of water and other solutes that are located at the plasma membrane and mitochondria. Among 13 isoforms of AQP proteins identified so far, AQP9 belongs to aquaglyceroporin, which transports monocarboxylates such as lactate. Evidence is accumulating that lactate could substitute for glucose as an energy substrate of neurons. Recent studies by us and other groups showed that RGCs express AQP9 and that its expression was reduced in an experimental rodent model of glaucoma and human glaucoma donor eyes. Down-regulation of AQP9 by RNA interference increased death of and reactive oxygen species production in cultured retinal neurons. Replacement of glucose by lactate had a minimal impact on the survival of these cells transfected with control si RNA, whereas the survival of those transfected with AQP9 si RNA was substantially decreased. These lines of evidence indicate that AQP9 plays a critical role of survival of RGCs by transporting the energy substrate lactate and that reduced expression of AQP9 may be involved in RGC death in glaucomatous optic neuropathy.

Commercial Relationships: Makoto Nakamura, None
Support: JSPS KAKENHI (grant number 26462661)

4: SY1-4

Oxidative stresses in glaucoma

Speaker: Masaki Tanito [1]

1. Division of Ophthalmology, Matsue Red Cross Hospital, Matsue, Shimane, Japan.

Oxidative stress may damage trabecular meshwork and retinal ganglion cells; these damages lead to intraocular pressure elevation and optic nerve atrophy, thus association between local oxidative stress and glaucoma pathogenesis has been suggested by various experimental settings and some clinical studies. More recently, involvement of systemic oxidative stress in glaucoma also has been hypothesized by assessing the blood or urine samples obtained from humans. We measured the systemic levels of prooxidants and antioxidants by analyzing the blood biochemistry in patients with glaucoma. Serum levels of oxidant (lipid peroxides, dROM)/ antioxidant (ferric reducing activity, BAP; and thiol antioxidant activity, SH test) status were estimated in 531 Japanese patients with primary open angle glaucoma (PG), exfoliation syndrome (EX), and non-glaucomatous controls (CT). The dROM levels were not statistically different among groups; compared to CT group, the BAP levels were lower in both glaucoma groups, and the SH levels were lower in EX group. After the adjustment for differences in age and sex among groups, lower BAP values correlated significantly with the PG and EX groups. In the whole subjects analysis, the level of BAP negatively correlated with un-treated levels of IOP in both eyes. Lower systemic ferric reducing activity is involved in the pathogenesis of open angle glaucoma possibly through its elevation effect of IOP. As evidenced for age-related macular degeneration, the results support the hypothesis that modification of systemic oxidative stresses can be a therapy for glaucoma also.

Commercial Relationships: Masaki Tanito, None

5: SY1-5

A New Drug Delivery System for Glaucoma Medication

Speaker: Tina Wong [1,2]

1. Department of Glaucoma Singapore National Eye Centre, Singapore Eye Research Institute, Singapore, Singapore. 2. Duke NUS Graduate Medical School, Singapore, Singapore.

While there exists many effective ocular hypotensive medications, they all require patient adherence and correct performance for optimal therapeutic effect. In an effort to improve therapeutics by obviating patient requirements, a new nanomedicine formulation of latanoprost intended for subconjunctival injection has been developed. In ocular hypertensive monkeys, the IOP lowering effect from a single injection of this formulation lowered the intraocular pressure for 120 days and was comparable to daily latanoprost ophthalmic solution. The presentation will share the outcomes of an open-label, pilot first-in-human study evaluating its IOP lowering efficay and safety in patients with POAG and OHT.

Commercial Relationships: Tina Wong, Peregrine Ophthalmic Pte Ltd (I);Peregrine Ophthalmic Pte Ltd (P)
Support: Singapore National Research Foundation under its Translational and Clinical Research Flagship Programme, administered by the Singapore Ministry of Health's National Medical Research Council
Clinical Trail: NCT01987323

6: SY1-6

The Brain and Vision Restoration in Glaucoma: Back to the Future

Speaker: Neeru Gupta [1,2] Yeni Yucel [1,2]

1. Ophthalmology and Vision Sciences, University of Toronto, Toronto, ON, Canada. 2. Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada.

Glaucoma is a blinding neurodegenerative disease with damage to vision pathways extending from the eye to major centeres in the brain. There is evidence that following injury to visual neurons, a window of opportunity for restoration and recovery exists through mechanisms of plasticity. Visual brain damage in experimental and human glaucoma will be reviewed, and novel potential future strategies to restore vision will be presented.

Commercial Relationships: Neeru Gupta, None; Yeni Yucel, None
Support: Canadian Institutes of Health Research

Symposium 2
Ocular Surface and Stromal Biology

Organizers

Shigeru Kinoshita
Kyoto Prefectural University of Medicine, Kyoto, Kyoto, Japan
Friedrich E. Kruse
University of Erlangen-Nuremberg, Erlangen, Germany

31: SY2-1

Mechanisms of Umbilical Mesenchymal Stem Cells in Suppressing Inflammation and Host Immune Rejection

Speaker: Winston W-Y Kao [1]
1. Department of Ophthalmology, University of Cincinnati College of Medicine, Cincinnati, OH, United States.

Novel treatment regimens with human mesenchymal stem cells (UMSC) have been shown to be effective in restoring corneal transparency of congenital and acquired cornea diseases such as *Lum*$^{-/-}$ (lumican null) and *Gusb* (a point mutation of β-galactosidase gene) mice and alkali-burned corneas of wild type mice. The observations suggest UMSC graft can be an effective treatment regimen in ameliorating symptom caused by immune dysfunction, in addition to the capability of UMSC can assume specific phenotypes of cell types in tissue environment dependent manner. In further studies, it is shown that the human UMSC synthesizes and secrets chondroitin sulfate rich glycocalyx that is essential for UMSC ability in modulating inflammation and host immune rejection. This may account for the success of xenograft of human UMSC in treating congenital and acquired corneal diseases.

Commercial Relationships: Winston W-Y Kao, None

Support: NIH/NEI grant EY021768, Ohio Lions Eye Research Foundation

32: SY2-2

Direct conversion of fibroblasts to human corneal epithelial-like cells by defined factors

Speaker: Koji Kitazawa [1, 2] Takafusa Hikichi [2] Takashi Ikeda [2] Takahiro Nakamura [4, 1] Morio Ueno [1] Satoshi Kawasaki [1, 3] Shinji Masui [2] Shigeru Kinoshita [1]
1. Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan. 2. Center for iPS Research & Application, Kyoto University, Kyoto, Japan. 3. Department of Ophthalmology, Osaka University, Osaka, Japan. 4. Doshisha University, Kyoto, Japan.

Corneal epithelium plays a critical role in maintaining the cornea's transparency. The corneal epithelium is maintained by continuous turnover of the corneal epithelial cell (CEC) s, which are supplied by the corneal epithelial stem cells that reside in the periphery of cornea. Severe damage to cornea, such as caused by Stevens-Johnson syndrome, results in depletion of the stem cells, leading to abnormal maintenance of corneal epithelium and to severe reduction of the vision. Allotransplants of cornea fail to restore the deficiency due to immunorejection. Several techniques have been implemented to use autologous cell sources that substitute for corneal epithelium. One approach is to use cultivated oral mucosal epithelial sheet. Although it has provided promising results for physical stabilization of the ocular surface, because of oral mucosal identity this transplantation causes superficial light-scattering and corneal neovascularization that reduce the vision. To overcome these issues, derivation of autologous CECs is required. To this end, here we sought to identify master transcription factor (TF) s in CECs that will allow us to induce these cells through direct reprogramming from human fibroblasts.

Commercial Relationships: Koji Kitazawa, None; Takafusa Hikichi, None; Takashi Ikeda, None; Takahiro Nakamura, None; Morio Ueno, Senju Pharmaceutical Co. (P), Santen Pharmaceutical Co. (P); Satoshi Kawasaki, None; Shinji Masui, None; Shigeru Kinoshita, Santen Pharmaceutical Co. (P), Senju Pharmaceutical Co. (P), Otsuka Pharmaceutical Co. (C), JCR Pharma Co. (P)

33: SY2-3

Ocular surface reconstruction: Focus on the stem cell niche

Speaker: Friedrich E. Kruse [1] Ursula Schloetzer-Schrehardt [1] Johannes Menzel-Severing [1]
1. Department of Ophthalmology, University of Erlangen-Nuremberg, Erlangen, Germany.

Ocular surface reconstruction remains a challenging area in clinical ophthalmology. The integrity of the ocular surface is dependent on the function of corneal epithelial stem cells.

Unilateral stem cell disorders can been treated with limbal autografts. Although these transplants allow long term reconstruction, they involve the risk of inducing stem cell deficiency at the donor site. Ex vivo expansion of cells from a small biopsy of autologous limbal tissue can circumvent such problems. However it is remains controversial if stem cells can be propagated in culture and how they can be maintained on the ocular surface.

The survival of transplanted limbal stem cells depends on functional support of transplanted cells on the ocular surface. In biological systems there is a close interaction between stem cells and their niche cells in the underlying stroma. Here we will present the current understanding of the interaction between limbal stem cells and their underlying stroma. We have performed laser capture micro dissection experiments as well as a large series of immunohistochemical investigation to determine the nature of cell-cell adhesion molecules, extracellular matrix proteins as well as signal transduction molecules in the limbal stem cell niche

Commercial Relationships: Friedrich Kruse, Santen (R), Senju (R); Ursula Schloetzer-Schrehardt, None; Johannes Menzel-Severing, None

34: SY2-4

Bioengineering functional lacrimal gland in vitro

Speaker: Tetsuya Kawakita [1]
1. Department of Ophthalmology, Keio University School of Medicine, Shinjuku, Tokyo, Japan.

The lacrimal gland has a multifaceted role in maintaining a homeostatic microenvironment for a healthy ocular surface via tear secretion.Lacrimal gland dysfunction induced dry-eye disease is one of the most prevalent eye diseases that cause corneal epithelial damage and results in significant loss of vision and a reduction in the quality of life.
We developed a three-dimensional organ-germ culture method for bioengineering lacrimal gland in vitro, and transplaned of this bioengineered lacrimal gland into adult mice with an extra-orbital lacrimal gland defect. Regenerated lacrimal gland transplantation might be an ultimate therapeutic model for severe dry eye disease.
Commercial Relationships: Tetsuya Kawakita, None
Support: Organ Technologies Inc.

35: SY2-5

Squamous Metaplasia of the Ocular Surface Epithelium

Speaker: Zuguo Liu [1, 2]
1. Xiamen Eye Centre of Xiamen University, Xiamen, Fujian, China. 2. Fujian Provincial Key Laboratory of Ophthalmology and Visual Science, Xiamen, China.

Squamous metaplasia occurs when nonsquamous (keratinized) epithelium is replaced by squamous (keratinized) epithelium. It is a common pathologic process that happens in almost all epithelial tissues, including the urothelium and the pulmonary epithelium. It is also a hallmark of a variety of severe ocular surface disorders manifesting dry eye caused by the lack of lacrimal gland secretion such as Sjögren syndrome, and it can be frequently seen in StevensJohnson Syndrome, mucous membrane pemphigoid, chemical/thermal burns, and vitamin A deficiency. The grading of squamous metaplasia correlates well with the severity of this type of dry eye and may lead to severe visual loss or blindness. Squamous metaplasia of the corneal epithelium is well correlated with the loss of corneaspecific keratin K3 and keratin K12 expression, the emergence of epidermis-specific keratin K1 and keratin K10, and such cornified envelope-specific proteins as transglutaminase I,involucrin, filaggrin, and loricrin. Aside from xerophthalmia caused by systemic vitamin A deficiency, which causes squamous metaplasia of ocular surface epithelia in experimental animals and human patients,little is known about the pathogenesis of squamous metaplasia and the signaling pathway involved in this pathologic process. In previous study, we created an ex vivo squamous metaplasia model, and found that p38 MAPK, Wnt and Notch signaling pathway were involved in the pathological process of squamous metaplasia.
Commercial Relationships: Zuguo Liu, None
Support: the National Natural Science Foundation of China (NSFC, No.U1205025, 81270978 and 81330022)

36: SY2-6

Holoclone-type stem cells control corneal homeostasis

Speaker: Takahiro Nakamura [1]
1. Research Center for Inflammation and Regenerative Medicine, Doshisha University, Kyoto, Kyoto, Japan.

Corneal integrity and transparency is indispensable for good vision. Cornea homeostasis is entirely dependent upon corneal stem cells, which are required for complex wound-healing processes that restore corneal integrity following epithelial damage. Here, we found that leucine-rich repeats and immunoglobulin-like domains 1 (*LRIG1*) is highly expressed in the human holoclone-type corneal epithelial stem cell population and sporadically expressed in the basal cells of ocular-surface epithelium. In murine models, LRIG1 regulated corneal epithelial cell fate during wound repair. Deletion of *Lrig1* resulted in impaired stem cell recruitment following injury, and promoted a cell-fate switch from transparent epithelium to keratinized skin-like epidermis, which led to corneal blindness. In addition, we determined that LRIG1 is a negative regulator of the STAT3-dependent inflammatory pathway. Inhibition of STAT3 in corneas of *Lrig1*$^{-/-}$ mice rescued pathological phenotypes, and prevented corneal opacity. Additionally, transgenic mice that expressed a constitutively active form of STAT3 in the corneal epithelium had abnormal features, including corneal plaques and neovascularization similar to *Lrig1*$^{-/-}$ mice. Together, our data indicate that LRIG1 orchestrates corneal-tissue transparency and cell fate during repair, and identify LRIG1 as a key regulator of tissue homeostasis.
Commercial Relationships: Takahiro Nakamura, None
Support: KibanC (23592621)

Symposium 3
Molecular Mechanisms in Diabetic Retinopathy

Organizers
Jeong Hun Kim
Seoul National University College of Medicine, Jongno, Seoul, Korea (the Republic of)
Susumu Ishida
Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan

75: SY3-1

Fight Against Angiogenesis-related Blindness: Beyond Anti-VEGF Antibody Treatment

Speaker: Jeong Hun Kim [1,2] Jin Hyoung Kim [2]
1. Department of Biomedical Sciences & Ophthalmology, Seoul National University College of Medicine, Jongno, Seoul, Korea (the Republic of). 2. FARB Laboratory, Seoul National University Hospital, Seoul, Korea (the Republic of).

From the FDA approval of anti-VEGF antibody to wet-type AMD of choroidal neovascularization, anti-VEGF antibody has been widely used against all kinds of vaso-proliferative retinopathy. Actually, current therapies directed at controlling vascular abnormalities in vaso-proliferative retinopathy target VEGF and can slow the progression of these diseases. While the general role of VEGF in development has been well described, the specific function of locally synthesized VEGF in the eye is incompletely understood. In addition, it should be concerned that VEGF blockade might provoke un-expected off-target side effects. Herein I would like to raise those concerns related anti-VEGF antibody treatment and provide some my recent results to overcome them. For example, targeting factors upstream of VEGF, such as HIFs, may be therapeutically advantageous compared with more potent and selective VEGF antagonists, which may have more off-target inhibitory trophic effects.

Commercial Relationships: Jeong Hun Kim, None; Jin Hyoung Kim, None

Support: the Seoul National University Research Grant (800-20140542), the Seoul National University Hospital Research Fund (03-2014-0260), the Pioneer Research Program of NRF/MEST (2012-0009544), the Bio-Signal Analysis Technology Innovation Program of NRF/MEST (2009-0090895)

76: SY3-2

Inflammation and Oxidative Stress in Diabetic Retinopathy

Speaker: Kousuke Noda [1]
1. Department of Ophthalmology, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan.

Diabetic retinopathy (DR), microvascular complication of diabetes with a complex multifactorial pathogenesis, is a leading cause of acquired blindness among the people of working age in developed countries. The mechanisms underlying the development of DR are not fully understood; however, recent preclinical and clinical studies have revealed that vascular endothelial growth factor (VEGF), a potent angiogenic factor, plays a key role in the pathogenesis of DR and anti-VEGF therapy has emerged as a part of first line treatment in DR, particularly in diabetic macular edema (DME).

Previous studies have elucidated that, in addition to VEGF, a variety of molecules and cellular components also promote the onset and progression of DR. Inflammatory cytokines and leukocyte adhesion molecules are upregulated in eyes with DR and accumulating inflammatory cells disrupt the homeostasis of the vasculature in the diabetic retina. Furthermore, it is also known that oxidative stress is enhanced in ocular tissues of patients with diabetes and associated with microvascular complications in DR. These findings suggest that inflammation and oxidative stress are implicated in the pathogenesis of retinopathy in diabetes.

We have focused on the role of vascular adhesion protein (VAP)-1, leukocyte adhesion molecule expressed at the surface of vascular endothelial cells in mammals, in DR. VAP-1 regulates the extravasation step during leukocyte recruitment. In addition, VAP-1 also has a large homology with semicarbazide-sensitive amine oxidase (SSAO), which oxidizes primary monoamines such as methylamine and aminoacetone, and VAP-1/SSAO converts them to the corresponding aldehydes and ammonia with the release of hydrogen peroxide. Therefore, VAP-1/SSAO is one of the intriguing molecules that presumably participate in the pathogenesis of DR through induction of inflammation and increase of oxidative stress with its adhesive and enzymatic properties.

This presentation provides an overview of the role of inflammation and oxidative stress in DR, and our recent data on the role of VAP-1/SSAO in this sight-threatening disease.

Commercial Relationships: Kousuke Noda, None

77: SY3-3

Alterations in the vitreous proinflammatory cytokine levels after vitrectomy in patients with proliferative diabetic retinopathy

Speaker: Shigeo Yoshida [1]
1. Department of Ophthalmology, Kyushu University Graduate School of Medical Sciences, Fukuoka, Fukuoka, Japan.

Diabetic retinopathy (DR) is a leading cause of blindness in the working age population worldwide. The vision decrease can be caused by either proliferative DR (PDR) or diabetic macular edema (DME). At advanced stages of PDR, neovascularization develops, and blindness can result from the formation of abnormal fibrovascular membrane (FVM) with subsequent intravitreal hemorrhage and tractional retinal detachment.

Evidence has been accumulating that inflammatory processes play a significant role in the pathogenesis of DR.

Several studies including ours have demonstrated that monocyte chemoattractant protein-1 (MCP-1), interleukin 6 (IL-6), interleukin 8 (IL-8), and vascular endothelial growth factor (VEGF) are four major proinflammatory factors that are up-regulated in eyes with DME and PDR. Inflammation is present in the two major causes of impaired vision in diabetes, namely, neovascularization (PDR) and increased retinal vascular permeability in eyes with DME.

Currently, pars plana vitrectomy (PPV) is the only treatment for advanced PDR. To determine the underlying molecular mechanisms that determine the effects of vitrectomy, we have measured the levels of proinflammatory cytokines in vitreous samples from patients with PDR before PPV without an IOL implantation, and also in fluid samples obtained during a secondary surgery for IOL implantation approximately 7 months after the initial vitrectomy after confirming that the activity of retinopathy had calmed down.

We found that the rate of clearance of molecules in vitrectomized eyes was different for different molecules in the vitreous. We detected a significant increase in the intravitreal concentrations of MCP-1 and IL-6, and a significant decrease in IL-8 and VEGF after successful vitrectomy in patients with PDR. In addition, the level of MCP-1 after vitrectomy was significantly correlated with the presence of postoperative DME in vitrectomized eyes. These indicate that the presence of prolonged inflammation in the vitreous even after successful vitrectomy may cause the postoperative DME.

Commercial Relationships: Shigeo Yoshida, None
Support: This work was supported in part by JSPS KAKENHI Grant Numbers 26293374 and 26670757

78: SY3-4

ROCK as a therapeutic target in diabetic retinopathy

Speaker: Shintaro Nakao [1]

1. Department of Ophthalmology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Fukuoka, Japan.

The recent development of new therapeutic agents together with refined surgical interventions could drastically improve the prognosis of diabetic retinopathy (DR). In particular, the therapeutic use of VEGF inhibitors has revolutionized the treatment of DR. However, frequent intravitreal injections are needed for the maximum efficacy and significant adverse events have been reported. Therefore, a better understanding of the pathogenesis of DR is needed to develop effective therapeutic strategies.

The main pathogenesis of DR has been known to be glucose-related microvascular damage including microthrombosis, hyperpermeability and angiogenesis. Furthermore, inflammation has been thought to be the cause of these microvascular damages. Various clinical and experimental data show that anti-VEGF therapy can inhibit hyperpermeability as well as angiogenesis in DR, however, the anti-VEGF therapy could also make the microthrombosis worse in DR.

Rho-associated, coiled-coil-containing protein kinases (ROCKs) is an important molecule in a variety of physiological functions. Previous data have revealed that ROCK could be increased in endothelial cells by elevated glucose levels, in addition, ROCK plays an important role in diabetes. Therefore, we have investigated the role of ROCK in the pathogenesis of DR and its possible utility as a therapeutic target for DR. In this lecture, I would like to present our in vitro and in vivo data of a ROCK inhibitor on the microvascular damage of DR. Furthermore, topical ROCK inhibitor has recently been approved as a therapy for glaucoma patient in Japan. I would like to discuss the possibility of the utility of a ROCK inhibitor as a treatment for additional indication for DR.

Commercial Relationships: Shintaro Nakao, Kowa Company Ltd. (F), Kowa Company Ltd. (P)
Support: JSPS KAKENHI, Grant- in-Aid for Young Scientists (A) No. 25713057
Clinical Trail: JapicCTI-142456

79: SY3-5

Pathophysiology of pericyte-free retinal vessels

Speaker: Akiyoshi Uemura [1]

1. Department of Retinal Vascular Biology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

In diabetic retinopathy, dropout of pericytes from retinal capillary walls has been assumed to be an initial trigger for the subsequent vascular disorders including elevated vascular leakage and neovascularization. However, because of the lack of diabetic animal models that recapitulate human retinopathy, the pathophysiolosy underlying the onset and progression of diabetic retinopathy remains elusive. To tackle this obstacle, we aimed to reproduce retinal vascular abnormalities resulting from pericyte dropout by injecting neonatal mice with anti-PDGFR β antibody that inhibit recruitment of pericytes to developing retinal vessels. Consequently, mouse retinas devoid of pericytes displayed vessel dilation and tortuosity, and progressive hemorrhage and edema, all of which are characteristic features of human diabetic retinopathy. Of interest, comprehensive gene expression analysis in pericyte-free endothelial cells demonstrated that pericyte dropout directly induced inflammatory responses in retinal vessels. Given that high blood glucose can also induce inflammation in retinal vessels, it is plausible that high glucose, pericyte dropout, and inflammation synergistically exacerbate the disease conditions in diabetic retinopathy. In order to break this vicious circle, we are seeking for distinct molecular targets including cytokines and chemokines which are requisite for leukocyte adhesion and infiltration in pericyte-free retinal vessels. We believe that these experimental works will contribute to developing new therapeutic modalities that can halt the progression of diabetic retinopathy.

Commercial Relationships: Akiyoshi Uemura, None
Support: Grants-in-Aid for Scientific Research B and Challenging Exploratory Research from MEXT, Japan.

80: SY3-6

Human retinal mitoscriptome Gene Expression Signature for Diabetic Retinopathy using Human Cadaver Eyes

Speaker: Periasamy Sundaresan [1] Gowthaman Govindarajan [1] Kim Ramasamy [2] Karthick Srinivasan [2]

1. Department of Genetics, Aravind Medical Research Foundation, Aravind Eye Hospital, Madurai, Tamilnadu, India. 2. Department of Retina & vitreous, Aravind Eye Hospital, Madurai, Tamilnadu, India.

Purpose:
Diabetic Retinopathy (DR) is a sight-threatening chronic micro vascular complication of diabetes mellitus and is the leading cause of acquired blindness in adults. Substantial evidence suggests that mitochondria dysfunction plays an important role both in the development of diabetes and DR. In DR, Mitochondrial DNA (mtDNA) is damaged in the retina and its capillary cells in diabetes initiating a vicious cycle of increased superoxide radicals. MtDNA replication and transcription are tightly controlled by nucleus-mitochondria signaling. This subset of transcriptomes, of mtDNA and nuclear origin, can be together called mitoscriptome. The high relevance of energetic to the maintenance of cellular structure and function places mitoscriptome analysis as an important piece of the puzzle in understanding the pathogenesis of DR and diabetes. Therefore the aim of the present study is to obtain the human retinal mitoscriptome gene expression signature for both DR and diabetes using human cadaver eyes which could help us to identify new biomarker in health and disease.

Methodology:
To identify retinal mitoscriptome genes that were differently expressed both in DR and diabetes, the RNA from the neural retinas of five postmortem donors without any history of retinal pathology, six patients retinas with a clinical features of DR and five retinas from diabetic donors without any signs of retinopathy were obtained for differential gene expression, by hybridization of labeled cRNA probes to an agilent human genome microarray 8*15k platform. Representative genes were validated by Taqman realtime quantitative PCR (qPCR).

Results:
Out of the 1100 genes, In the DR as compared to normal control group retinas 59 genes were differentially expressed ($p < 0.05$). Among 59 genes, the levels of 8 showed an increased expression (≥0.6), and 51 were expressed at decreased levels (≤0.6), in the retinas of DR patients compared to the control retinas. In the diabetes 39 genes were differentially expressed ($p<0.05$) as compared to age matched control retinas. In those 39 differentially expressed genes, 8 were up regulated and 31 were down regulated. In the DR retinas as compared to diabetic group 39 genes were shown differentially expression and among that 3 shows up regulation and 36 shows down regulation pattern. Focused qPCR results confirmed the differentially expressed genes both in DR and diabetes as compared to normal group. However, some of the genes were not significantly altered in the qPCR confirmation but did trend towards the same pattern, as observed in the microarray analysis.

Conclusion:
In this study, differentially expressed mitoscriptome genes pattern were observed for both in DR and diabetes which associates several new genes and pathways for the disease mechanism. Further detailed studies were required to study the involvement of these differentially expressed genes in the development of DR. However, the present study established human retinal mitoscriptome gene expression for both DR and diabetes to advance three related goals - Provide target for future biomarker development, Increase knowledge on mitochondrial involvement in the pathogenesis of DR and diabetes and Compare the similarity and difference of retinal mitoscriptome gene expression signature among normal and DR human cadaver eyes.
This is the first study to establish human mitoscriptome gene expression signature for DR and diabetes using human cadaver eye retina. In future, mitoscriptome profile information will likely be useful in developing diagnostic methods and new therapeutic strategies.

Commercial Relationships: Periasamy Sundaresan, None; Gowthaman Govindarajan, None;Aravind Medical Research Foundation (E); Kim Ramasamy, None; Karthick Srinivasan, None
Support: Council of Scientific Industrial Research (CSIR) , Govt.of India

Symposium 4
Science in Corneal and Refractive Surgery

Organizers
Donald Tan
Singapore National Eye Centre, Singapore, Singapore
Shiro Amano
Inoue Eye Hospital/Miyata Eye Hospital, Chiyoda, Tokyo, Japan

7: SY4-1

Update on Deep Anterior Lamellar Keratoplasty

Speaker: Shiro Amano [1]
1. Inouye Eye Hospital, Tokyo, Japan.

Deep anterior lamellar keratoplasty (DALK) is indicated in eyes with corneal opacity or deformity and without endothelial dysfunction including corneal scar, keratoconus, and some kinds of corneal dystrophy. Though DALK has several advantages over penetrating keratoplasty such as no endothelial rejection and slower postoperative endothelial decrease, DALK has not been widely performed. The major reason for this is its technical difficulties in reaching to Descemet's membrane. Several techniques have been reported to efficiently and safely reach to Descemet's membrane. Moreover, the application of femto-second laser to DALK has been reported recently. In this talk, recent updates in DALK will be presented.

Commercial Relationships: Shiro Amano, None

8: SY4-2

Update on DSAEK / DMEK surgery

Speaker: Donald Tan [1, 2]
1. Singapore National Eye Centre, Singapore, Singapore. 2. Duke-NUS Graduate Medical School, Singapore, Singapore.

Descemets stripping automated endothelial keratoplasty (DSAEK) has now replaced conventional penetrating keratoplasty (PK) as the "gold standard" but as we continue to evolve surgical techniques in DSAEK, it is clear that graft outcomes still vary considerably, and may be related to different approaches to donor preparation, insertion, and attachment, which results in varying rates of iatrogenic graft failure, donor dislocation, endothelial cell loss and long term graft survival. At the same time, the perceived need to minimize the stromal component of EK in order to further improve visual outcomes, with ultrathin DSAEK, and the purists' approach to just replace the endothelial layer with descemets membrane endothelial keratoplasty (DMEK) pushes the envelope even further, and more studies comparing DSAEK, ultrathin DSAEK and DMEK are needed.

Commercial Relationships: Donald Tan, Network Medical Products (P), Carl Zeiss Meditec (F), Alcon Labs (F), Bausch & Lomb (F), Allergan (F), Santen (F)
Support: Network Medical Products (patent)

9: SY4-3

The safety issues of phakic IOL

Speaker: Tae-im Kim [1]
1. Department of Ophthalmology, Yonsei University School of Medicine, Seodaemun-gu, Seoul, Korea (the Republic of).

Although the implantation of an ICL offers outstanding advantages, postoperative complications associated with high or low vaulting have been issued by several investigators. ICL vaulting changes continuously with dynamic movement according to lighting conditions or the accommodative status of the eye. Recently, the V4c ICL (CentraFLOW technology, STAAR Surgical Company) was designed with 360-μm central hole to allow for natural flow of the aqueous humor without the need for iridotomy. The V4c ICL has shown comparable clinical outcomes to the conventional V4 ICL. This study aims to compare vaulting changes in eyes implanted with V4c and V4 implantable collamer lenses (ICLs) under differing lighting and accommodative conditions.

Anterior chamber depth (ACD), pupil size and postoperative vaulting were evaluated using a Visante optical coherence tomography system under photopic and mesopic conditions or far focused and 6cm near subject focused state. Refractive errors, keratometry values, axial lengths, intraocular pressures, anterior chamber volumes, and central corneal thicknesses were also recorded.

In different light conditions, no significant differences were noted in ACD in V4c and V4 ICLs. However, significant decreases in vaulting and pupil size were detected under photopic conditions in both groups. And vaulting changes in eyes implanted with V4c ICLs were significantly larger than those in eyes implanted with V4 ICLs. Accommodative state induced decrease of ACD and no change of vaulting.

V4c ICL vaulting decreased more prominently under photopic conditions than did V4 ICL vaulting. Alteration of accommodative state mainly induced decrease of ACD. Therefore, postoperative vaulting under mesopic and photopic conditions should be considered when interpreting the vaulting of eyes implanted with V4c ICLs.

Commercial Relationships: Tae-im Kim, None

10: SY4-4

Corneal crosslinking (m Science m Corneal and Refractive Surgery)

Speaker: Naoko Kato [1]
1. Department of Ophthalmology, Saitama Medical University, Iruma, Saitama, Japan.

Corneal crosslinking (CXL) is a method to halt the progression of keratoconus. CXL was first introduced by Wollensak et al. in 2003 and nowadays has become a standard treatment for progressive keratoconus.

Standard corneal crosslinking, often called the "Dresden protocol", consists of epithelial removal followed by 30

minutes for riboflavin presoaking and another 30 minutes for ultraviolet irradiation. With this procedure, more than 90% of the cases have successful results. However, the Dresden protocol requires more than 1 hour for each procedure.

The unsolved problems with crosslinking are complications such as sterile or infectious keratitis, corneal haze or scarring, or a continued steepening of the cornea. Although many of these complications occur infrequently and can be controlled using medications, limited cases result in a decline in visual acuity. Therefore, CXL is still an invasive procedure, which is accompanied by pain and a transient decline in visual function.

The pathomechanism for postoperative stromal haze has not been identified. We speculate that the corneal haze might be caused by an accumulation of excess extracellular matrices which are related to degenerated or phenotypically altered keratocytes resulting from the ultraviolet irradiation and exposure to oxygen radicals during the procedure.

We have recently started accelerated CXL with 18.0 mW/cm^2 ultraviolet irradiation for 5 minutes. The results of the new accelerated method show effects that are comparable to conventional CXL in terms of halting the progression of keratoconus, but with a clear decrease in the intensity and frequency of post CXL corneal haze. It is our opinion that accelerated CXL is superior due to this reduction in postoperative haze.

Commercial Relationships: Naoko Kato, EyeLens Pte Ltd (F)

Clinical Trail: UMIN000002947

11: SY4-5

Posterior corneal elevation after refractive surgery

Speaker: Vishal Jhanji [1]

1. The Chinese University of Hong Kong, Kowloon, Hong Kong.

This study investigated the change in posterior corneal elevation up to one year after myopic femtosecond assisted-laser in-situ keratomileusis (LASIK) and photorefractive keratectomy (PRK) using swept source optical coherence tomography at baseline and at each postoperative follow-up. The changes in posterior corneal elevation were evaluated at 1 month (B-1), 3 months (B-3), 6 months (B-6) and 12 months (B-12) after surgery. Ninety-eight eyes of 49 patients (62 LASIK, 36 PRK) were included (mean age 35.2 ± 8.5 years). The mean change in posterior corneal elevation values after LASIK and PRK were 4.88 ± 0.47 vs 3.67 ± 0.48 (B-1), 2.42 ± 0.56 vs 3.00 ± 0.47 (B-3), 3.76 ± 0.46 vs 2.76 ± 0.46 (B-6), 2.92 ± 0.46 μ m vs 2.72 ± 0.46 μ m (B-12), respectively. Significant differences in post-LASIK posterior corneal elevation were found between B-1, B-3, B-6 and B-12 ($p \leq 0.001$) whereas posterior corneal elevation did not change significantly between B-3, B-6 and B-12 ($p \geq 0.373$) after PRK. The adjusted forward displacements of the posterior corneal surface were statistically significant throughout the study period after both refractive surgeries ($p < 0.05$).

The findings of this study suggested that there was a mild but significant forward protrusion of the posterior cornea after femtosecond laser-assisted LASIK and PRK. The posterior cornea fluctuated during the first postoperative year after LASIK, while it stabilized as early as 3 months after PRK.

Commercial Relationships: Vishal Jhanji, None

Symposium 5
Recent Topics of Neuro-ophthalmology

Organizers
Hitoshi Ishikawa
School of Allied Health Sciences, Kitasato University, Sagamihara, Kanagawa, Japan
Lin-Chung Woung
Taipei City Hospital, Taipei, Taiwan

37: SY5-1

The origin, pathway and center of pupillary light reflex

Speaker: Ken Asakawa [1]
1. Department of Orthoptics and Visual Science, School of Allied Health Sciences, Kitasato University, Sagamihara, Kanagawa, Japan.

The pupil is constantly affected by various external stimuli that produce a variety of responses, such as pupillary responses to light stimuli (pupillary light reflex) and convergence responses against close visual stimuli (near reflex), among others. In particular, the processes of photoreception via the pupillary light reflex and phototransduction by the rods and cones have been known for over 100 years.
In 1927, Clyde Keeler, published a remarkable paper, entitled: Iris movements in blind mice. Although apparently visual blind, the continued pupil constriction in response to light were shown, and also other light-dependent phenomenon was shown to be preserved, including synchronization of the circadian clock.
Approximately 80 years after Keeler's reports, a novel photoreceptor containing an intrinsically photosensitive visual pigment known as "melanopsin" was found in retinal ganglion cells. These intrinsically photosensitive retinal ganglion cells (mRGC) account for only about 1% of the total number of retinal ganglion cells, but have large cell bodies and an extensively branching dendritic structure with long dendrites. These mRGCs make it possible to detect light over an extensive portion of the retina despite their relatively small number. The nerve terminals of mRGC are found not only in the suprachiasmatic nucleus and the ventrolateral preoptic nucleus but also in the pretectal olivary nucleus; and the mRGC make a contribution to light entrainment in the circadian rhythm, suppression of melatonin production in the pineal gland, and regulation of the pupil diameter to light as their primary roles. The light reaction mediated by mRGC has different sensitivity and color characteristics from that mediated by the rod and cone cells.
The mRGC-mediated light reaction has a selective sensitivity to blue light of a wavelength of about 470 nm, reacts through depolarization to high-intensity light stimulus after a long latent period, and shows a sustained reaction that keeps constricting the pupil even after the light stimulus is discontinued.
On the other hand, the blue light stimulus activates mostly S cones and rods, in addition to any possible activation of mRGCs. The effect on S cones and rods should be considered when the light response to blue light stimulus is evaluated in clinical applications; accordingly, it is still not firmly established whether the obtained response was caused by the mRGCs.
Thus, we performed the morphofunctional evaluations under pharmacological blockade of neurotransmission from rod and cone cells to ON bipolar cells, and also performed the animal experiment in transgenic rabbits with a Pro347Leu rhodopsin mutation.
We conducted the functional evaluation by recording the changes in the pupillary light reflex to red and blue light stimulus and the amplitude of the electroretinography. Morphologically, rod and cone distribution was examined using light and electron microscopy. Immunostaining for the identification of mRGCs was confirmed by injecting a polyclonal antibody.
Here, the recent discovery of an inner retinal photoreceptor is described, along with its histology and physiological properties and the clinical applications of the pupillary light reflex.
Commercial Relationships: Ken Asakawa, None
Support: This study was supported by a grant from Kitasato University School of Allied Health Sciences (Grant-in-Aid for Research Project, No. 2011-1023, 1047). This work was also supported by JSPS KAKENHI, Grant Number 24791871.
Clinical Trail: R000017734

38: SY5-2

Enhanced Depth Imaging (EDI) - OCT in Optic Neuropathies

Speaker: Suntaree Thitiwichienlert [1] Hitoshi Ishikawa [2] Totsuya Ikeda [3] Ken Asakawa [2] Kimiya Shimizu [3]
1. Department of Ophthalmology, Thammasat University Hospital, Pathum Thani, Thailand. 2. Rehabilitation, Orthoptics and Visual Science Course, Kitasato University, Sagamihara, Japan. 3. Ophthalmology, Kitasato University, Sagamihara, Japan.

Evaluation of optic neuropathies involves both structural and functional evaluation of the optic nerve head. In glaucomatous optic neuropathy, the structural evaluation is recognized by a progressive deepening and enlarging of the cup and thinning of the neuroretinal rim. Another important structure is the lamina cribrosa (LC), which the early damage to RGC axons is believed to initiate at this level. The spectral domain OCT (SD-OCT) analyzed the cup shape and retinal nerve fiber layer (RNFL) thickness, but provide unclear visualization of the lamina cribrosa.
With the recently developed technique known as EDI-OCT, the visualization of the deep optic nerve head structures, particular the lamina cribrosa, has been improved.
Several recent papers have studied the laminar thickness using EDI-OCT and Park et al reported decreased laminar thickness in glaucoma and a relationship between laminar thinning and mean deviation of visual field damage.
In non-glaucomatous optic neuropathies, many etiologies

cause interrupt the axoplasmic flow and subsequently lead to damage the retinal ganglion cell axons; however there are no studies about laminar thickness in non-glaucomatous optic neuropathies.
In this respect, the EDI-OCT may enhance the understanding of disease mechanisms that contribute to axoplasmic flow interruption and retinal ganglion cell injury in both glaucomatous and non-glaucomatous optic neuropathies.
In this presentation, we highlight recent advances in EDI-OCT imaging of the LC and address the published experience with EDI-OCT in measurement of laminar thickness in normal subjects, and in patients with glaucomatous optic neuropathy and non-glaucomatous optic neuropathies.
We present the relationship of the laminar thickness with the functional parameters include the mean deviation of visual field in glaucomatous optic neuropathy and the critical flicker frequency response in non-glaucomatous optic neuropathies. The potential gains and limitations of the imaging and clinical significance of such findings has been discussed.
Finally, we share this ability of the EDI-OCT for detecting the change of the laminar thickness and the laminar thickness may be one of useful structural parameter in clinical assessment of optic neuropathies.
Commercial Relationships: Suntaree Thitiwichienlert, None; Hitoshi Ishikawa, None; Totsuya Ikeda, None; Ken Asakawa, None; Kimiya Shimizu, None
Support: Japan Organization for the Prevention of Blindness Grant 18

39: SY5-3

Clinical feature of Leber hereditary optic neuropathy - an update review

Speaker: An-Guor Wang [1, 2]
1. Department of Ophthalmology, Taipei Veterans General Hospital, National Yang-Ming University, Taipei, Taiwan. 2. School of Medicine, National Yang-Ming University, Taipei, Taiwan.

Leber's hereditary optic neuropathy (LHON) is a maternally inherited genetic disease characterized by acute or subacute bilateral visual loss, predominantly affecting young men. This distinctive clinical entity was first described by a German physician, Dr. Theodor Leber, in 1871. LHON was mainly caused by three primary mutations in mitochondrial DNA at position 3460, 11778, and 14484. Its clinical feature and OCT findings will be reviewed in this talk.
Commercial Relationships: An-Guor Wang, None

40: SY5-4

Current Updates in Ethambutol Toxic Optic Neuroretinopathy

Speaker: Erwin D. Palisoc [1, 2]
1. Department of Ophthalmology, Manila Central University College of Medicine, Caloocan city, Philippines. 2. Department of Ophthalmology, Jose R. Reyes Memorial Medical Center, Manila, Philippines.

Ethambutol Toxic Optic Neuropathy (ETON) is relatively common in developing countries particularly in the Philippines because of high incidence of Tuberculosis (TB). It was thought that toxicity is dose and duration dependent. It was reported that ETON typically occurs in 6% of cases at a daily dose of 25 mg/kg, but rarely occur in 15 mg/kg/day. It was also reported that manifestations of ocular toxicity is usually delayed, which usually does not develop until after treatment for at least 1 1/2 months. Variable mean interval between onset of therapy and toxic effects of Ethambutol (EMB) were reported, from 3 to 5 months. Manifestations of toxicity as late as 12 months after initiation of treatment were also reported.
Signs and Symptoms include color reduction, decreased visual acuity and visual field defects. The causes of occurrence are multiple and complex. Risk factors for ETON are old age, pre-existing optic nerve damage such as glaucoma and ischemic diseases like diabetes & hypertension.
Baseline and monthly assessment of visual acuity and color discrimination tests are recommended on patients who are on EMB especially those who exceed the dose of 20 mg/kg/day. History taking & complete ophthalmological examination are essential steps to perform to be able to arrive with a right diagnosis. Physicians must also be vigilant in detecting early the possible adverse effects of EMB in their patients especially with co-morbidities to avoid visual loss to happen. Also, the offending drug must be stopped immediately if symptoms develop. Vitamins and Zinc supplementation can also be given especially in those receiving higher doses of the drug, or in prolonged treatment due to advanced or resistant TB, to prevent the occurrence of toxic neuroretinopathy from Ethambutol intake.
Commercial Relationships: Erwin Palisoc, None

41: SY5-5

Recent development of high-resolution MR imaging for Neuro-ophthalmology

Speaker: Masato Hashimoto [1]
1. Department of Ophthalmology, Sapporo Medical University, Sapporo, Hokkaido, Japan.

High-resolution magnetic resonance imaging (MRI) has rapidly developed and there are various MR sequences in the field of central nervous system. These new techniques have to be adapted in clinical Neuro-ophthalmology. We introduce some of high-resolution MR sequences which become current topics in Neuroradiology.
The high gradient echo techniques such as fast imaging employing steady-state acquisition (FIESTA) have successfully visualized small cranial nerves: oculomotor,

trochlear, abducens and facial nerves. This sequence can demonstrate a very tiny cranial nerve lesion such as neurovascular compression syndrome which has never been clearly delineated on MRI.

Arterial spin labeling (ASL) is a noninvasive MRI technique that uses arterial water as an endogenous tracer to measure cerebral blood flow (CBF). ASL provides reliable absolute quantification of CBF with higher spatial and temporal resolution than other techniques. Time-resolved non contrast enhanced MR angiography with CINEMA (contrast inherent inflow enhanced multi phase angiography) is obtained by performing a segmented readout, at multiple time points after labeling pulse based on ASL.

Commercial Relationships: Masato Hashimoto, None

Symposium 6
What's New in IgG4 Related Ophthalmic Disease

Organizers
Masayuki Takahira
Kanazawa University School of Medicine, Kanazawa, Ishikawa, Japan
Hiroshi Goto
Tokyo Medical University, Shinjuku, Tokyo, Japan

81: SY6-1

Historical overview of IgG4 related disease

Speaker: Mitsuhiro Kawano [1]
1. Division of Rheumatology Department of Internal Medicine, Kanazawa University Hospital, Kanazawa, Ishikawa, Japan.

IgG4-related disease (IgG4-RD) is a newly recognized systemic disease, which can affect almost any organ in our body. Its concept was not established until the 21st century because in the past each organ specific lesion was diagnosed as a separate disease entity, e.g. Mikulicz's disease, autoimmune pancreatitis (AIP), and retroperitoneal fibrosis, and treated by the respective specialists separately. However, a proposal of the concept of AIP by Yoshida et al. opened the door to the discovery of IgG4-RD in 1995. Six years after this proposal, a historic discovery was made by gastroenterologists (Kawa and Hamano), who found very high serum IgG4 concentrations in AIP. Moreover, the following year, histopathological analysis revealed another very important feature of this disease, i.e., abundant infiltration of IgG4-positive plasma cells (IgG4+PC) in the pancreas. In 2003, Kamisawa et al. found that every extra-pancreatic lesion of AIP had IgG4+PC infiltration and therefore proposed the concept of IgG4-related autoimmune disease as a newly discovered systemic disease.
IgG4-RD has an extremely diverse clinical spectrum that is dependent on the combination of involved organ(s), and usually affects several organs synchronically or metachronously. Diagnosis is complicated by the fact that it is sometimes asymptomatic or tends to cause relatively mild clinical symptoms. Imaging study of involved organ(s) reveals solitary or multiple lesions showing diffuse or localized swelling, masses, nodules and/or wall thickening. The most important histopathological feature is marked IgG4+PC infiltration across all affected organs. In addition, IgG4-RD has common histopathological features: dense lymphoplasmacytic infiltrates, characteristic storiform fibrosis, and obliterative phlebitis. Clinical features include a male and middle- or old-age predominance, hyper IgG-emia and elevated serum IgG4 levels. In our experience of 74 cases, frequently affected organs were salivary glands (55%), lacrimal glands and other ophthalmic components (54%), lungs (31%), kidneys (26%), aorta/periaorta (24%), and pancreas (20%). Coexistent autoimmune disease is rare, but rather it has a close association with allergic disorders such as allergic rhinitis and bronchial asthma. Although IgG4-RD is a steroid responsive condition, delayed diagnosis and treatment may result in irreversible fibrosis. In this overview, I will outline this disease with some up-to-date topics of particular interest.
Commercial Relationships: Mitsuhiro Kawano, None
Support: Health and Labour Sciences Research Grants for the Study of Intractable Diseases from the Ministry of Health, Labour and Welfare, Japan

82: SY6-2

Epidemiology and current diagnostic criteria of IgG4 related ophthalmic disease

Speaker: Masayuki Takahira [1]
1. Department of Ophthalmology, Kanazawa University School of Medicine, Kanazawa, Ishikawa, Japan.

The most important issue in diagnosis of IgG4 related ophthalmic disease (IgG4-ROD) is to differentiate it from lymphoma. In a recent epidemiological study of 1,014 cases with orbital lymphoproliferative disorders in Japan, IgG4-ROD accounted for 22%, and IgG4-positive MALT lymphoma consisted of at least 4% of the total. The median age of IgG4-ROD was 62 years and no gender difference was detected. Since the comprehensive diagnostic criteria (Umehara et al, 2011) tends to overestimate, and the consensus diagnostic criteria (Deshpande et al, 2012) seems to underestimate IgG4-ROD, a diagnostic criteria specific for ophthalmic lesions would be desired.
Commercial Relationships: Masayuki Takahira, None

83: SY6-3

Clinical features of IgG4 related ocular diseases

Speaker: David Ta-Li Liu [1]
1. Dennis Lam & Partners Eye Center, Central, Hong Kong.

This is going to be a comprehensive account on the mydriad of clinical manifestations of IgG 4 related ocular diseases.
Commercial Relationships: David Ta-Li Liu, None

84: SY6-4

Differential diagnosis of IgG4 related ophthalmic disease

Speaker: Sunny Shen [1,2] Anita Chan [1,2]
1. Singapore National Eye Center, Singapore, Singapore. 2. Singapore Eye Research Institute, Singapore, Singapore.

Objective: To discuss the differential diagnoses of IgG4 related ophthalmic disease from different perspectives.
Summary of content:
- General approach
- Clinical presentation / Epidemiology
- Radiology
- Histology

Educational goal:
To provide an update in the clinical approach of IgG4 related orbital disease

Commercial Relationships: Sunny Shen, None; Anita Chan, None

85: SY6-5

IgG4 -related ophthalmic disease and systemic evaluations

Speaker: Toshinobu Kubota [1]

1. Department of Ophthalmology, National Hospital Organization Nagoya Medical Center, Nagoya, Aichi, Japan.

IgG4-related ophthalmic disease is a part of systemic IgG4-related diseases which frequently involve IgG4-related lesions in salivary gland, lymphnodes, and sinus. Patients with systemic involvements characterize elevated serum level of IgG4 and also characterize blood eosinophilia and elevated serum level of soluble IL-2 receptor which may reflect systemic immunologic imbalances.
This section focuses on interactive relationships among IgG4-related ophthalmic disease, serum data, and systemic involvements.
Commercial Relationships: Toshinobu Kubota, None

86: SY6-6

Therapeutic strategy for IgG4-related ophthalmic disease

Speaker: Atsushi Azumi [1]

1. Department of Ophthalmology, Kobe Kaisei Hospital, Kobe, Hyogo, Japan.

IgG4-related disease is an inflammatory condition. The lesions are well known to be responsive to drug therapy using corticosteroid. In treating IgG4-related ophthalmic disease (IgG4-ROD), the basic concept is broadly similar, but ophthalmological modification can be sought, because the disease usually requires long-standing corticosteroid administration, resulting in various kinds of distressing side effects. To control IgG4-ROD, the therapeutic dose of corticosteroid is usually less than 5mg of prednisolone (PDL), and no evidence has shown the necessity to start with high dose of PDL. Surgical resection and injection of triamcinolone acetonide is a treatment option when IgG4-ROD affects the lacrimal gland. Other immunosuppressive drugs are expected to induce an earlier recovery.
Commercial Relationships: Atsushi Azumi, None

Symposium 7
Functional Testing of Vision

Organizers
Takashi Fujikado
Osaka University School of Medicine, Suita, Osaka, Japan
Atsushi Mizota
Teikyo University, School of Medicine, Itabashi, Tokyo, Japan

12: SY7-1

Objective evaluation of the ocular functions - strabismus, visual acuity, and others: by using computer-based technologies

Speaker: Jong-Mo Seo [1,2] Woonhee Lee [1] Minwon Seo [1] Jeong-Min Hwang [3]
1. Electrical Engineering and Computer Sciences, Seoul National University, Seoul, Korea (the Republic of). 2. Ophthalmology, Seoul National University Hospital, Seoul, Korea (the Republic of). 3. Ophthalmology, Seoul National University Bundang Hospital, Seognam, Gyeonggi-do, Korea (the Republic of).

The visualization of the clinical status is useful for the objective evaluation of the disease. Thanks to the advancement in imaging technologies and the powerful computer, OCT and other innovative machines are developed and introduced. However, not only high-tech but also low-tech ideas can improve current diagnostic methods and skills. In this talk, basic curiosities in the routine ophthalmologic examination, such as cover-uncover test and Hess-Lancaster test for the strabismus, Snellen chart for the visual acuity and blinking evaluation for the dry eye, will be re-interpreted and re-organized with computer-based technologies. By this way, we can 'see the unseen' in our daily clinic.
Commercial Relationships: Jong-Mo Seo, None; Woonhee Lee, None; Minwon Seo, None; Jeong-Min Hwang, None
Support: This research was supported by the MSIP (Ministry of Science, ICT & Future Planning), Korea in the ICT R&D program 2014

13: SY7-2

Evaluation of ganglion cell layer function by pattern ERG and PhNR

Speaker: Souichi Matsumoto [1]
1. Department of Ophthalmology, Teikyo University, School of Medicine, Itabashi, Tokyo, Japan.

The inner retina integrity is crucial for good visual function. Some visual testings such as the pattern ERG (PERG) and PhNR waveforms of the focal macular ERG (fmERG) have been recently using for evaluation of the function of the retinal ganglion cells on the macular area. We have been performed both the fmERG and the PERG in patients with optic nerve and inner retinal disorders. I will present the results of these two modalities of electrophysiological tests to evaluate the efficacy and the diagnostic usefulness in detecting retinal ganglion cells function.
Commercial Relationships: Souichi Matsumoto, None

14: SY7-3

Evaluation of inner retinal layers by phosphene and OCT in patients with advanced retinitis pigmentosa

Speaker: Takeshi Morimoto [1]
1. Department of Applied Visual Science, Osaka University Graduate School of Medicine, Suita, Osaka, Japan.

Purpose: The success of retinal prosthesis to restore vision depends on the presence of physiologically intact retinal ganglion cells that can transmit visual signals to the brain. Therefore it is important to properly evaluate the degree of retinal integrity for patient selection. The purpose of study to investigate the relationship between the retinal thickness by optical coherence tomography (OCT) and the threshold current to evoke phosphene by transcorneal electrical stimulation (TES) in patients with advanced retinitis pigmentosa (RP).
Methods: Forty three eyes of 24 patients with RP (average age, 64.3 years) were examined. The best-corrected visual acuity (BCVA) ranged from NLP to HM (median, LP). Retinal thickness (RT) was measured by macular cube scan (512 × 128) of Cirrus HD-OCT. Phosphene threshold was obtained when the subject can reliably identify a visual sensation at the center of visual field during TES (10ms/phase,20Hz,20 pulses).
Results: The central phophene was elicited in 24 eyes but was not elicited with current less than 2 mA in 19 eyes. There was no significant difference in BCVA between in a group with central phosphene and in that without central phophene. The average RTs at three areas (center, central subfield, Maximum subfield) were significantly thicker in a group with central phosphene than that without central phosphene (center: 217 ± 75 um vs 128 ± 65 um, $P<0.05$;central subfield: 276 ± 47 um vs 180 ± 81um, $P<0.05$; Maximum subfield: 256 ± 31 um vs 184 ± 67 um, $P<0.05$). Moreover, there were significant correlations between RTs (center and maximum subfield) and central threshold of phosphene.
Conclusions: OCT provides useful information to select a candidate for a retinal prosthesis, and the RTs (center and maximum subfield) proportionally correlate with the central threshold of phosphene. It is necessary to examine patients by both OCT and TES in order to select patients suitable for a retinal prosthesis.
Commercial Relationships: Takeshi Morimoto, None
Support: JRPS2012
Clinical Trail: UMIN000005050

15: SY7-4

The Electrically Evoked Visual Responses and their Usefulness in Retinitis Pigmentosa

Speaker: Marten Erik Brelén [1] Chi Wai Tsang [2] Alvin Young [3] Jean Delbeke [4] Chi Pui C. Pang [1]

1. Department of Ophthalmology and Visual Sciences, Chinese University of Hong Kong, Kowloon, Hong Kong. 2. Hong Kong Eye Hospital, Hong Kong, Hong Kong. 3. Prince of Wales Hospital, Hong Kong, Hong Kong. 4. University of Gent , Gent, Belgium.

Patients who are blind with no light perception due to retinitis pigmentosa (RP) can still have visual sensations evoked by electrically stimulating the visual system. Indeed, the aim of a visual prosthesis is to electrically stimulate the visual pathway downstream from the degenerate photoreceptors in order to recreate a meaningful sense of visual perception. The recording of evoked potentials during electrical stimulation provides objective insight into the events occurring immediately following stimulation. The most basic setup for such an experiment involves surface eye stimulation with electrodes placed on the eyelids. The results from such experiments are discussed in this presentation showing how this can be used to map the size of the electrically inducible visual field and explore inner retinal remodelling. Further experiments using an optic nerve visual prosthesis whilst recording cortical evoked potentials and electroretinograms will also be shown. The results can be used to analyse the timing of cortical generators and source localize these events in the cortex. The practical uses for electrically evoked responses in pre-selecting RP patients for visual prosthesis implantation and monitoring RP patients during visual rehabilitation with a visual prosthesis will be discussed.

Commercial Relationships: Marten Erik Brelén, None; Chi Wai Tsang, None; Alvin Young, None; Jean Delbeke, None; Chi Pui Pang, None

Symposium 8
OCT, Clinical Use and Future

Organizers
Yoshiaki Yasuno
University of Tsukuba, Tsukuba, Ibaraki, Japan
Christopher K. Leung
The Chinese University of Hong Kong, Kowloon, Hong Kong

42: SY8-1

Anterior Segment OCT

Speaker: Donald Tan [1,2]
1. Singapore National Eye Centre, Singapore, Singapore. 2. Duke-NUS Graduate Medical School, Singapore, Singapore.

Anterior segment optical coherence tomography (ASOCT) is a useful adjunctive tool in the diagnosis, medical and surgical treatment of simple and more complex corneal and anterior segment disorders. AS-OCT is now commonly used in the clinic to image the cornea and anterior segment through relatively opaque media, both qualitatively and quantitatively, with the ability to measure corneal thickness in specific areas or quadrants of the cornea, and is especially useful for pre-operative planning for corneal and anterior segment surgery, for assessment of postsurgical complications related to selective lamellar keratoplasty, complex cataract management or post-trauma surgery, and for intraoperative use during DSAEK or DMEK to confirm donor attachment, and during DALK to assess depth of instrumentation and to confirm big bubble formation.
Commercial Relationships: Donald Tan, Network Medical Products (P), Carl Zeiss Meditec (F), Alcon Labs (F), Bausch & Lomb (F), Allergan (F), Santen (F)

43: SY8-2

Latest advances in retinal nerve fiber layer imaging with optical coherence tomography

Speaker: Christopher K. Leung [1]
1. Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Kowloon, Hong Kong.

Optical coherence tomography (OCT) imaging of the retinal nerve fiber layer (RNFL) has become one of the prevailing imaging technologies to detect and monitor glaucoma. With significant improvement in scan speed and scan resolution, spectral-domain OCT is an efficient platform to evaluate progressive RNFL thinning. This presentation summarizes the recent progress of the clinical application of OCT RNFL measurement for the detection of glaucoma and its progression.
Commercial Relationships: Christopher Leung, Carl Zeiss Meditec (F), Alcon (C), Tomey (F), Optovue (F)

44: SY8-3

Deep choridal imaging using optical coherence tomography

Speaker: Yasushi Ikuno [1]
1. Department of Ophthalmology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan.

Thanks to the recent advances of technologies, optical coherence tomography (OCT) has become much faster. The new technology is so-called spectral-domain (SD-) OCT and we appreciate the higher resolution, contrast, and extensive scan, providing more useful, and practical, information for dairy retinal practice. Currently there are 2 modalities to image the choroid on the OCT basis. One is high-penetration OCT using longer wavelength of light source, and the other enhanced depth imaging (EDI). HP-OCT allows you to obtain the choroidal image with longer wavelength (1040 – 1060nm) than commercial machine, which enables higher penetration through the RPE and choroid. In EDI, choroidal signal is maximized by inverting the image to enhance the chorio-scleral interface (CSI), followed by multiple averaging (typically 50x or 100x). This technique is possible in any SD-OCT machine, however Heidelberg OCT (Spectralis OCT®) is mostly used which appreciate better and higher contrasted images by eye-tracking system. Both HP-OCT and EDI has advantages and drawbacks. The choroidal imaging has been found to be effective for several macular diseases such as age-related macular degeneration, polypoidal choroidal vasculopathy, central serous chorioretinopathy, and pathological myopia. In this presentation, the typical choroidal images will be demonstrated, and the current status of choroidal OCT imaging and future direction will be discussed.
Commercial Relationships: Yasushi Ikuno, TOMEY (F), TOPCON (F)

45: SY8-4

Polarization and Dopper ocular imaging

Speaker: Yoshiaki Yasuno [1,2]
1. Computational Optics Group, University of Tsukuba, Tsukuba, Ibaraki, Japan. 2. Computational Optics and Ophthalmology Group, Tsukuba, Japan.

Despite of a history of more than 20 years, optical coherence tomography (OCT) has been utilized only for structural investigation of ocular tissues. OCT is a modality using light as a probe, and light has three quantities to identify itself; amplitude, phase, and polarization. The conventional OCT uses only the amplitude of the probe beam. The question for the next decade is what we see with the phase and polarization. As recently being recognized, the phase of OCT provides Doppler shift information. It, in the eye, provides ocular flow quantification and non-invasive angiography. On the other hand, the birefringence and polarization uniformity

of tissue can be investigated thought the polarization of the probe beam. It finally provides quantitative information on fibrosis and melanin concentration in the eye. In this presentation, we first introduce a new OCT system, so called multifunctional OCT, which is capable of structural, Doppler, and polarization information of posterior eye simultaneously. The discussion is further extended to its clinical values.

Commercial Relationships: Yoshiaki Yasuno, TOPCON Corp. (F), Tomey Corp. (F), Nidek Co. Ltd. (F)

46: SY8-5

Measurement of Retinal Blood-Flow by Doppler-OCT

Speaker: Taiji Nagaoka [1]

1. Department of Ophthalmology, Asahikawa Medical Univeristy, Asahikawa, Hokkaido, Japan.

There have been many clinical studies revealing that measurement of retinal blood flow is important to diagnose and monitor ocular vascular disease. Recently, Optical Coherence Tomography (OCT) has been applied as a novel technique to measure retinal blood flow, namely Doppler OCT. We have confirmed that the newly developed, named as "segmental scanning," Doppler OCT enables accurate and reproducible measurements of retinal blood flow in the retinal arterioles and venules in an *in vivo* cat model and in healthy humans. My presentation will focus on the methodology of our segmental scanning Doppler OCT to measure retinal blood flow and its application to clinical studies in the near future.

Commercial Relationships: Taiji Nagaoka, None

Support: Grant-in-Aid for Scientific Research (B) 25293352 from the Ministry of Education, Science, and Culture, Tokyo.

47: SY8-6

Retinal oximetry using visible-light OCT

Speaker: Hao Zhang [2, 1]

1. Department of Ophthalmology, Northwestern University, Chicago, IL, United States. 2. Department of Biomedical Engineering, Northwestern University, Evanston, IL, United States.

PURPOSE. To explore non-invasive optical imaging methods that can quantify retinal metabolic rate of oxygen (MRO_2).

METHODS. We developed a visible-light OCT (Vis-OCT) to measure both retinal hemoglobin oxygen saturation (sO_2) and retinal retinal flow. The Vis-OCT used a supercontinuum laser as the illumination light source centered at 585 nm. The axial resolution in the retina was 1.3 μm and the A-line rate was 75 kHz. To measure retinal sO_2, we developed a sophisticated inverse algorithm to fit the optical absorption spectrum of the whole blood within the Vis-OCT spectral range. To measure blood flow, we performed double-circular-trajectory scans around the optic disk to obtain the absolute blood velocity. After obtaining the retinal sO_2 and blood velocity, we further measured retinal vessel diameter and calculated the retinal oxygen metabolism rate (MRO_2). To test the capability of Vis-OCT, we imaged wild-type Long-Evans rats inhaling normal air. To introduce oxygen supply deficiency in the choroidal circulation, we mixed pure oxygen with nitrogen and gradually increased the volume fraction of nitrogen in the mixed gas.

RESULTS. The Vis-OCT was able to measure the sO_2 value in every single major retinal vessel around the optical disk as shown in Figure 1. When breathing normal air, the averaged sO_2 in arterial and venous blood in Long-Evans rats was measured to be 95% and 72%, respectively. The total retinal blood flow was 7.6 μl/min. Over a 14-day period, the variations in sO_2 and blood flow measurements were both less than 5% and the variation in MRO2 measurement was less than 8%. We found that when the choroidal circulation supplied less oxygen to the outer retina, the oxygen deficiency was compensated for by increased oxygen extraction from the retinal circulation. The measured increasing oxygen extraction rate from the retinal circulation agrees well with oxygen microelectrode measurements in rodents from terminal studies.

CONCLUSIONS. Vis-OCT is a sensitive tool to measure retinal MRO_2 with a high repeatability. It opens up a new window to investigate several significant blinding diseases, such as diabetic retinopathy and glaucoma, which strongly associate with retinal oxygen metabolic disorders. Vis-OCT also holds promise in clinically identifying biomarkers of these diseases in their early stages.

Commercial Relationships: Hao Zhang, None

Support: NIH 1R01EY019951 and 1R24EY022883; NSF CBET-1055379

Symposium 9
Friendship Makes it Possible! - Vision Van Project
In conjunction with Japan Ophthalmologists Association / Cataract Foundation Japan

Organizers
Shigeru Takano
Japan Ophthalmologists Association, Minato, Tokyo, Japan
Keiichi Kato
Miyagi Ophthalmologists Association, Kurokawa, Miyagi, Japan
Kazuo Tsubota
Keio University School of Medicine, Shinjuku, Tokyo, Japan

87: SY9-1

Vision Van Project Overview

Speaker: Kazuo Tsubota [1]
1. Department of Ophthalmology, Keio University School of Medicine, Shinjuku, Tokyo, Japan.

The Mission Vision Van project had its genesis in the 2011 Great East Japan Earthquake. The Vision Van, a mobile eye clinic, from Miami, Florida, USA arrived in Sendai as an emergency import and was dispatched to the Tohoku disaster area to deliver eye care. The successful treatment of innumerable patients brought widespread accord that a mobile eye care clinic was needed in disaster zones, leading the Japan Ophthalmologists Association to elicit governmental support and produce Japan's own Vision Van. "This mobile clinic can help us serve victims anywhere in Japan," we thought. "And we're now ready to repay others' relief efforts to Japan if something similar happens in Asia." No sooner did the thought occur than when the Philippines was hit by mega-typhoon Yolanda in November 2013, giving us the opportunity to visit and offer assistance. The Japanese Vision Van arrived by ship a few months later and served 2,000 patients in its 10-day rotation by medical team leaders from the Philippines and Japanese volunteers. Through the initial act of friendship from the team at Bascom Palmer Eye Institute in Miami, the Vision Van deployment enormously strengthened the link between ophthalmologists in Japan and the Philippines.
Commercial Relationships: Kazuo Tsubota, None

88: SY9-2

Concept and History of Vision Van

Speaker: Eduardo Alfonso [1]
1. Bascom Palmer Eye Institute, Miami, FL, United States.

Since opening its doors in 1962, Bascom Palmer Eye Institute has been dedicated to providing the finest possible ophthalmic care, finding new ways to treat vision problems and prevent blindness, and educating the physicians and researchers of the future. Bascom Palmer's outreach extends far beyond Miami, Florida USA, to Asia, Africa, Europe and Latin America.
As an integral part of its commitment to community service, in 2004, Bascom Palmer launched the Vision Van, a 12-metre, mobile, self-contained eye clinic that includes a comprehensive examination room, three screening stations and state-of-the-art ophthalmic equipment. Initially conceived as a tool for providing early detection of eye diseases in underserved populations in South Florida, it was soon realized that the Vision Van could travel to areas in need of emergency medical services.
In 2005, the Vision Van and a team of Bascom Palmer's physicians and volunteers, traveled to areas near New Orleans, Louisiana, following the destruction caused by Hurricane Katrina. The Vision Van is uniquely suited for emergency eye care services in an environment where the health care and public works infrastructure is essentially nonexistent.
Immediately following the Tohoku earthquake and tsunami in March 2011, I received an inquiry from my colleague and friend, Professor Kazuo Tsubota, regarding the possibility of borrowing the Vision Van to facilitate eye care delivery in Japan. Within days, the Vision Van was boarded onto a cargo jet for an international rescue mission for ophthalmology to the hard-hit Sendai region. Bascom Palmer was deeply honored to provide resources that enabled Japanese ophthalmologists to better serve those in need.
Commercial Relationships: Eduardo Alfonso, None

89: SY9-3

The Bascom Palmer Eye Institute Vision Van Experience

Speaker: Richard K. Lee [1]
1. Bascom Palmer Eye Institute/ Universitiy of Miami Miller School of Medicine, Miami, FL, United States.

The Bascom Palmer Vision Van (BPVV) is a custom built 40 foot bus that is a mobile eye clinic. The BPVV's purpose is to provide vision screenings in the community throughout South Florida to prevent and/or minimize the impact of preventable eye diseases and irreversible sight threatening diseases, such as glaucoma and age-related macular degeneration. Through our vision screening activities, we also seek to educate the community about eye health and prevention of eye diseases. We screen for eyes diseases at health fairs and community centers and screen thousands of patients a year with volunteer staff and medical students from the University of Miami School of Medicine.
We typically screen for eye diseases in economically depressed regions of South Florida, where access to health care is difficult or enriched for eye diseases. For example, we recently identified that the Afro-Caribbean population in Little Haiti of Miami has a disproportionately high risk for glaucoma at higher eye pressures, greater levels of optic nerve damage, and at earlier ages. Armed this information, we have initiated a telemedicine screening program for eye disease in Little Haiti, emphasizing the

value of bringing eye services to areas with a lack of resources that can be provided by a mobile eye clinic, such as the BPVV.
An extension of the needs a mobile eye clinic can provide is the service the BPVV provided in the aftermath of Hurricane Rita in New Orleans, where the BPVV provided important mobile eye services to a devastated region where the infrastructure for eye care was severely damaged and disrupted. This led to the role of the BPVV in Japan in the Japan Eye Rescue Mission conceived by Dr. Kazuo Tsubota to assist ophthalmologists in providing eye care to people devastated by the Tohoku-Pacific Ocean Earthquake and Tsunami. Flown in the belly of an Antonov 124 cargo plane from Miami to Sendai, the BPVV was used to provide eye care throughput the devastated regions as described by Dr. Toru Nakazawa for approximately six months. The results of this medical mission has been published in news and scientific articles.
We are proud to have been invited to play a role in this great humanitarian endeavor and are especially happy that this collaboration spearheaded by Dr. Kazuo Tsubota has resulted in the Japan Vision Van that has been providing service in Asia and has formed the international bonds that resulted in this symposium.
Commercial Relationships: Richard Lee, None

90: SY9-4

Stories from the U.S. and Japan to the Philippines

Speaker: Toru Nakazawa [1]
1. Department of Ophthalmology, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan.

Japan experienced the Great East Japan Earthquake on March 11th 2011, a magnitude 9.0 quake that lasted for more than 200 seconds. Soon afterwards, an unprecedentedly powerful tsunami with waves more than 40 meters high struck the coast of the Tohoku region. Aftershocks greater than magnitude 7 occurred 8 times, causing local residents to fear that another tsunami. The disaster caused 15,861 people to lose their lives, and 2,939 are still missing.
On the fourth day after the quake, our team at Tohoku University Hospital went to the city of Kesennuma in Miyagi Prefecture and found that the life of the residents was the type of life or death[TH1] . Most survivors were staying in evacuation shelters and needed treatment for chronic diseases, rather than for emergency diseases. They needed glasses and contact lenses to allow them to take part in the response to the emergency and eye drops to treat pre-existing chronic eye diseases. There were no eye doctors in the affected region, and Tohoku University Hospital and the Miyagi Ophthalmologists Association thus cooperated closely to start treatment rounds in the shelters.
Thanks to the dedicated efforts of the team in Miami that operates the Mission Vision Van, we had the chance to use the van to perform eye care for the evacuees from the first month after the earthquake. In the first month, we managed to treat 731 patients, who came to us with such common eye diseases as cataracts, dry eye, conjunctivitis, and glaucoma. Treatment rounds with the Mission Vision Van continued until the end of June 2011, when most private eye clinics in the damaged area had reopened.
Following a request by the Japanese Ophthalmologists Association, the Japanese government provided funding for a Japanese version of the Vision Van. The Japanese Vision Van was completed in March 2013 and has since been used for continuing ophthalmological support in the affected areas of the Japanese coast. Recently, the Japanese Vision Van was also sent to the Philippines following the typhoon in November 2013, and was used by Philippine eye doctors from the 19th to the 28th of February 2014. This activity in the Philippines was commended at the ASEAN+3 meeting.
In this presentation, we would like to tell stories of our experiences during our response to the Great East Japan Earthquake and the support we provided in the Philippines.
Commercial Relationships: Toru Nakazawa, None

91: SY9-5

The Japan Vision Van and the Aftermath of "Typhoon Yolanda"

Speaker: Amelia C. Reyes [1]
1. Eastern Visayas Society of Ophthalmology, Philippine Academy of Ophthalmology, Makat, Philippines.

The Japan Vision Van arrived in Tacloban City, Leyte, Philippines, more than 2 months after the super typhoon Yolanda ravaged Tacloban City and its neighboring towns. It was manned by the eye doctors in the place and has attended to the ophthalmologic needs of 1,923 survivors from Tacloban City and 6 of its neighboring towns in its brief stay. It was a meaningful and successful endeavor for the the people in the Ophthalmology community, and the brains that conceived that idea should be commended.
Commercial Relationships: Amelia Reyes, None

92: SY9-6

Eye Get By with a Little Help from My Friends: A Story of International Cooperation for Disaster Relief and Rehabilitation

Speaker: Harvey Uy [1, 2]
1. Philippine Academy of Ophthalmology, Makati City, Philippines. 2. Pacific Eye and Laser Institute, Makati City, Philippines.

This presentation will describe international collaborative efforts of ophthalmological societies of three countries (Japan, Philippines, USA) to restore eye care services in Typhoon Haiyan ravaged areas in the Philippines. A discussion of the hurdles encountered and eventually surmounted by the project proponents provides a learning experience for those involved or wanting to be involved in international relief efforts. A strong focus will be on ophthalmological aspects of disaster relief.
Commercial Relationships: Harvey Uy, None

Symposium 10
Advances in Drug Delivery
In conjunction with ARVO

Organizers
William Mieler
University of Illinois at Chicago, Chicago, IL, United States
Jennifer J. Kang Mieler
Illinois Institute of Technology, Chicago, IL, United States

16: SY10-1

Overview of Methods of Drug Delivery

Speaker: William Mieler [1]
1. University of Illinois at Chicago, Chicago, IL, United States.

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Commercial Relationships: William Mieler, Genentech (C)

16b: SY10-2

Topical NSAIDs in the Treatment of Posterior Segment Diseases

Speaker: Taiji Sakamoto [1]
1. Department of Ophthalmology, Kagoshima University Graduate School of Medicine and Dental Sciences, Kagoshima, Kagoshima, Japan.

Although anti-VEGF drugs revolutionized the treatment of posterior eye diseases, there are still many burdens for patients and physicians. They include the requirement of frequent injection and the injection itself. There are several commercially available eye-drops of non-steroidal anti-inflammatory drugs (NSAIDs) now. In this presentation, the potential benefit of NSAIDs eye-drops for the treatment of posterior eye diseases will be shown from the point of its pharmacokinetics.

Commercial Relationships: Taiji Sakamoto, Santen (R), Senju (R), Senju (C), Alcon (R)

16c: SY10-3

Present and Future Devices for Intraocular Sustained Drug Delivery

Speaker: Tsutomu Yasukawa [1]
1. Department of Ophthalmology and Visual Science, Nagoya City University Graduate School of Medical Sciences, Nagoya, Aichi, Japan.

Because the eye has a specific environment for pharmacokinetics, topically administration as well as systemic approach cannot easily exhibit drug efficacy on vitreoretinal diseases. One of strategies to overcome these problems may be intraocular drug delivery systems (DDSs). A reservoir-type non-biodegradable implant (named Vitrasert[â]) was first approved in 1996, releasing ganciclovir for the treatment of cytomegalovirus retinitis. Presently, some steroid-releasing devices (Retisert[â], Iluvien[â], and Ozurdex[â]) were commercially available to treat challenging eye diseases such as macular edema and uveitis. However, the development of DDSs for small hydrophilic drugs and large molecules such as proteins are still challenging. New ideas should be employed to develop new DDS devices. Candidates of future DDS devices involve a refillable, non-biodegradable implant, a microelectromechanical systems (MEMS) drug delivery, the encapsulated cell technology, and gelling agents to slow convection of drugs in the vitreous cavity. In this session, I will summarize commercial DDS products and future candidates for intraocular DDSs.

Commercial Relationships: Tsutomu Yasukawa, None

18: SY10-4

A 3-D Intravitreal Injection Device

Speaker: Marten Brelen [1]
1. Department of Ophthalmology and Visual Sciences, Chinese University of Hong Kong, Kowloon, Hong Kong.

Traditionally surgical instruments have been manufactured by a costly and time consuming process which involves developing numerous prototype versions of the device followed by injection molding. This presentation will demonstrate how an ophthalmic surgical instrument can be quickly and inexpensively manufactured by 3D printing. An intravitreal injector device was designed in CAD software (3D Rhino CAD) and then printed in FDA approved nylon plastic using an extrusion deposition printer. The instrument was sterilized by autoclaving and then tested on manikin eyes and 4 rabbit eyes. The animals were examined one day post-op and one week post-op for any complications (including retinal detachments or traumatic cataracts). The process by which instruments manufactured in this manner are certified and used in a clinical trial are also discussed. The instrument has so far proven to be effective and safe at delivering intravitreal injections and allows, for the first time, surgeons to take control of the design and manufacturing of their own instruments.

Commercial Relationships: Marten Brelen, None

17: SY10-5

Sustained Delivery of anti-VEGF agents via microsphere-thermo-responsive hydrogels

Speaker: Jennifer J. Kang Mieler [1]
1. Department of Biomedical Engineering Pritzker Institute of Biomedical Science and Engineering, Illinois Institute of Technology, Chicago, IL, United States.

In this presentation, a novel use of microspheres and hydrogel to deliver pharmacological agent to the posterior segment will be discussed. The presentation will focus on the use of biodegradable microsphere-thermoresponsive hydrogel drug delivery system to delivery anti-VEGF for

an extended delivery.
Commercial Relationships: Jennifer Kang Mieler, None

17b: SY10-6

Polymeric Device for Transscleral Drug Delivery to the Posterior Segment

Speaker: Nobuhiro Nagai [1]
1. Tohoku University, Sendai, Japan.

The design of polymeric system that can deliver multiple drugs to the posterior segment via transscleral administration and its retinal neuroprotective effects against light injury in rats are reported.
Commercial Relationships: Nobuhiro Nagai, 2011-527664 (P), 2011/021594A1 (P)

17c: SY10-7

Neuromodulation Therapy with Microcurrent Stimulation of the Retina

Speaker: Madhaven Jagadeesan [1]
1. Hospital for Sick Children, Toronto, QC, Canada.

My presentation revolves around our work on the effect of neuromodulation therapy (NMT) on genetically and phenotypically characterized inherited retinal degeneration (IRD) patients. In this cohort study, we have compared effect of NMT on phenotypically documented normal controls, *ABCA4* and non *ABCA4* gene defective IRD patients. I would discuss the study design and visual outcome following NMT between cohorts and in individual patients. The adverse effect if any would also be discussed. Further, our work would suggest key criteria in the selection of IRD patients for a successful recovery of vision following NMT.
Commercial Relationships: Madhaven Jagadeesan, None

Symposium 11
The Contribution of the Retinal Circadian System to the Aging of the Retina

Organizer
Gianluca Tosini
Morehouse School of Medicine, Atlanta, GA, United States

48: SY11-1

The retinal circadian clock and melatonin protect photoreceptors from aging

Speaker: Gianluca Tosini [1] Kenkichi Baba [1]
1. Neuroscience Institute and Department of Pharmacology, Morehouse School of Medicine, Atlanta, GA, United States.

Daily rhythms are a ubiquitous feature of living systems. Generally, these rhythms are not just passive consequences of cyclic fluctuations in the environment, but instead originate within the organism. The retina has evolved not only sophisticated mechanisms of light- and dark-adaptation, but also its own local circadian clock to allow anticipation of the regular cycle of the solar day. Several studies have shown that melatonin is the key regulator of the retinal circadian rhythms and dysfunction in the melatonerigic system may also contribute to retinal disease and pathology. Indeed recent studies have shown that removal of melatonin signaling affects photoreceptors and ganglion cells viability during aging. The present talk will focus on the role played by melatonin in retinal circadian functions and how dysfunctions in this system may lead to retinal pathologies.

Commercial Relationships: Gianluca Tosini, None; Kenkichi Baba, None
Support: EY022216

49: SY11-2

Dopamine, Retinal Circadian Clocks, and Visual Function

Speaker: P.Michael Iuvone [1, 2]
1. Department of Ophthalmology, Emory University School of Medicine, Atlanta, GA, United States. 2. Pharmacology, Emory University School of Medicine, Atlanta, GA, United States.

Dopamine is an important neuromodulator in the retina. It modulates multiple dimensions of light-adapted vision. This presentation will describe the roles of dopamine in modulating visual acuity and circadian rhythms of contrast sensitivity, photopic ERG responses, and gene expression in the mouse retina. It will also describe recent studies on the relative roles of CLOCK and NPAS2, two related clock genes, in the regulation of visual function.

Commercial Relationships: P.Michael Iuvone, None
Support: NIH Grants R01EY004864, P30EY006360, and Research to Prevent Blindness

50: SY11-3

Light-dark condition regulates Sirtuins in the retina

Speaker: Yoko Ozawa [1]
1. Department of Ophthalmology, Keio University School of Medicine, Shinjuku, Tokyo, Japan.

Sirtuins (Sirt1-7) are nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylases/ADP-ribosyltransferases that modulate many metabolic responses affecting aging. Here we show that mRNAs of all seven sirtuins are highly expressed in the retina and the sirtuin mRNA profiles in the retina over time were different, under a 12-hr light/12-hr dark cycle (LD condition) and in constant darkness (DD condition), suggesting that sirtuin mRNA levels are affected by light-dark condition. Our observations provide new insights into the metabolic mechanisms of the retina and the sirtuins' regulatory systems.

Commercial Relationships: Yoko Ozawa, Wakasa Seikatsu Co., Ltd (F), NOVARTIS Pharmacetutical Co., Ltd. (F), Alcon Research LTD (F), JINS CO., LTD (F)
Support: JSPS KAKENHI (24592647)

51: SY11-4

The circadian clock and melanopsin: a blue light-sensitive photopigment in mammalian retinal ganglion cells

Speaker: Megumi Hatori [1]
1. Salk Institute for Biological Studies/Department of Ophthalmology, Keio University School of Medicine, Shinjuku, Tokyo, Japan.

The adaptation of behavior and physiology to changes in the ambient light level is of crucial importance to life. These adaptations include the light modulation of neuroendocrine function and temporal alignment of physiology and behavior to the day:night cycle by the circadian clock. These non-image-forming (NIF) responses can function independent of rod and cone photoreceptors but depend on ocular light reception, suggesting the participation of novel photoreceptors in the eye. The discovery of melanopsin in intrinsically photosensitive retinal ganglion cells (ipRGCs) and genetic proof for its important role in major NIF responses have offered an exciting entry point to comprehend how mammals adapt to the light environment. I will talk about the updated stories in melanopsin/ipRGCs research area and the link to the circadian entrainment.

Commercial Relationships: Megumi Hatori, None

Symposium 12
Update on Glaucoma Management
In conjunction with EVER

Organizers
Leopold Schmetterer
Medical University Vienna, Wien, Austria
Gordana S. Megevand
Center Rothschild Foundation, Genéve, Switzerland

93: SY12-1
Structure and Function and their clinical relevance in the new EGS Guidelines

Speaker: Anton Hommer [1, 2]
1. Department of Clinical Pharmacology, Medical University Vienna, Wien, Austria. 2. Hera Hospital, Vienna, Austria.

Individulaized glaucoma treatment aims at providing glaucoma management tailored to the indivvidual needs of the patients. Structural abnormality doesnot necessarily correlate with funcional loss. The aim of the presentation is to diffentiate and balance between the two essential findings of structural and functional loss.
Commercial Relationships: Anton Hommer, None

94: SY12-2
Vascular imaging in Glaucoma

Speaker: Leopold Schmetterer [1]
1. Department of Clinical Pharmacology, Medical University Vienna, Wien, Austria.

The hypothesis that vascular factors are involved in the pathogenesis of glaucoma has been formulated more than 100 years ago. To investigate this hypothesis in more details is, however, a challenge, because measurement of ocular blood flow is difficult. So far a number of techniques was realized including Color Doppler imaging, Laser Doppler Flowmetry, Laser Speckle Flowgraphy and assessment of Pulsatile Ocular Blood Flow, but none of these techniques allows for the measurement of absolute retinal blood flow. Doppler Optical Coherence Tomography (OCT) is a relatively new extension to standard OCT that allows for the quantification of retinal blood flow and the visualization of the retinal and choroidal vasculature. I this presentation the technique is introduced and some results in patents with glaucoma are presented.
Commercial Relationships: Leopold Schmetterer, None
Support: FWF grants APP21570FW and APP21406FW

95: SY12-3
Compliance and its relevance for Glaucoma

Speaker: Gerhard Garhofer [1]
1. Department of Clinical Pharmacology, Medical University Vienna, Wien, Austria.

Adherence to a prescribed drug treatment is an important issue for all drug therapies, especially in chronic diseases such as glaucoma. Sub-optimal treatment results in progressive visual field loss, whereas improving adherence to anti-glaucoma therapy is highly likely to reduce the progression of the disease. However, data from clinical trials indicate that adherence to glaucoma treatment is often poor. In addition, measurement of adherence itself is difficult, because standardized and accurate methods are still not available. Simplifying drop regimens, better education of the patients and tailored therapies may improve adherence to ocular hypertensive therapies. The current talk seeks to summarize our current understanding of the factors influencing patients´ adherence to anti-glaucoma drug therapy. Further, possible methods to increase persistence and adherence will be discussed.
Commercial Relationships: Gerhard Garhofer, None

96: SY12-4
Pulmonary hypertension and Glaucoma

Speaker: Anita Leys [1]
1. Department of Ophthalmology, University Hospital Leuven, Leuven, Belgium.

Thanks to advancement in treatment modalities, the medial survival rate of patientswith pyulmonary arterial hypertension has improved. Unfortunately ocular complications due to the chronically elevated systemic venous pressure become more frequent. Ocular complications have been reported in observational case reports and include: dilated episcleral and conjunctival veins, myopisation, uveal effusion syndrome with intermittent angle closure, exudative retinal detachment, macular edema, venous stasis retinopathy, central retinal vein occlusion, choroidal detachment, delayed choroidal perfusion, open-angle glaucoma and neovascular glaucoma. The departments of pneumology and ophthalmology of UZLeuven initiated a prospective study of 400 patients with pulmonary hypertension with the aim to define risk of sight threatening ocular conditions in these patients. All patients were studied with BCVA, biomicroscopy of anterior and posterior segment, tonometry, colour fundus photography, and in selected patients, additional imaging was performed (OCT-EDI choroidal thickness, autofluorescence, angiography with fluoresceine and indocyaningreen, retina oxymetry). Results will be discussed during the meeting.
Commercial Relationships: Anita Leys, None

97: SY12-5

Glaucoma trearmemt beyond IOP and life style

Speaker: Gordana S. Megevand [1]

1. Center Rothschild Foundation, Genéve, Switzerland.

Evidence based therapy of glaucoma relies on medical treatment, laser and /or surgery. However life style may have an implication on patients suffering from established glaucoma. The presentation will focus on the influence of life style and Alterantive Complementary Therapy and will provide with a review of the recent literature on the topic.

Commercial Relationships: Gordana Megevand, Allergan (C), Alcon (C), Thea (S)

Symposium 13
Molecular Mechanisms in Age-related Macular Degeneration

Organizers
Kyu Hyung Park
Seoul National University, College of Medicine, Jongno, Seoul, Korea (the Republic of)
Yoko Ozawa
Keio University School of Medicine, Shinjuku, Tokyo, Japan

256: SY13-1

Proteomic approaches to gain insight into the molecular pathogenesis of AMD

Speaker: Jeeyun Ahn [1, 2] Se Joon Woo [3, 2] Kyu Hyung Park [3, 2]
1. Department of Ophthalmology, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Jongno, Seoul, Korea (the Republic of). 2. Department of Ophthalmology, Seoul National University, College of Medicine, Seoul, Korea (the Republic of). 3. Department of Ophthalmology, Seoul National University Bundang Hospital, Seongnam, Korea (the Republic of).

AMD is the leading cause of blindness among the elderly worldwide. Compromised integrity of the Bruch's membrane due to aging, oxidative stress, and inflammation as well as genetic susceptibility are known to play a role in the pathogenesis of AMD. Recent application of proteomic analysis techniques to AMD patients have enabled elucidation of novel molecular aspects of AMD and the identification of potential biomarkers associated with AMD. In this talk, we present our results of comprehensive proteomic analysis performed in the plasma of AMD patients. Out of the 320 proteins that were identified, 7 proteins showed significantly differential expression in AMD patient plasma. Construction of a proteo-genomic combination model using known genetic risk factors for AMD, ARMS2 and CFH, yielded satisfactory AUC for discriminating AMD from controls. Usage of such proteomic methods will help us gain insight into new molecular pathogenic mechanisms of AMD and aid early diagnosis as well as timely management by identifying biomarkers for AMD.
Commercial Relationships: Jeeyun Ahn, None; Se Joon Woo, None; Kyu Hyung Park, None
Support: This work was supported by grant from the Korea Health Technology R&D Project, Ministry of Health & Welfare, Korea (A111161).

257: SY13-2

Lipofuscin-related RPE damage in age-related macular degeneration

Speaker: Yasuo Yanagi [1]
1. Department of Ophthalmology, Graduate School of Medicine, The University of Tokyo, Bunkyo, Tokyo, Japan.

Retinal pigment epithelial (RPE) cells, a monolayer of postmitotic cells located between photoreceptors of the retina and choriocapillaris, play multiple vital roles in photoreceptor function and survival, such as photoreceptor outer segment phagocytosis, maintenance of the visual cycle, and supply of nutritional factors, and are possibly associated with the pathogenesis of diverse diseases. Lipofuscin is amassed with age in normal healthy RPE cells, as well as diseased RPE cells. Several clinical observations suggest that excessive lipofuscin accumulation is related to RPE cell damage. It is generally accepted that RPE cell dysfunction due to abnormal lipofuscin accumulation is involved in all key pathological pathways of retinal diseases including Stargardt disease (STGD) and age-related macular degeneration (AMD). Thus, elucidating the molecular mechanisms underlying impaired RPE cell function appears crucial both for improving our understanding of the pathogenesis of retinal disease and for identifying novel targets for prophylaxis and therapeutic intervention. Among more than 25 components of lipofuscin, A2E is the most major fluorophore identified in aged human eyes and is characterized the most intensively. Here we investigated the effects of A2E on RPE cells. Our results elucidated the molecular mechanism of A2E-mediated cytotoxic effects and the pathogenesis of lipofuscin-related retinal diseases at least in part.
Commercial Relationships: Yasuo Yanagi, Novartis Pharmaceuticals (F), Bayer General Healthcare (F), Santen Pharmaceuticals (F)

258: SY13-3

A role of lipid accumulated in Bruch's membrane in the pathogenesis of age-related macular degeneration

Speaker: Tsutomu Yasukawa [1]
1. Department of Ophthalmology and Visual Science, Nagoya City University Graduate School of Medical Sciences, Nagoya, Aichi, Japan.

Age-related macular degeneration (AMD) is considered to be associated with chronic inflammation employing oxidative stress and complement activation as well as vascular endothelial growth factor (VEGF). Integrated evidences from basic researches suggested a role of lipid accumulated in Bruch's membrane in the pathogenesis of AMD. Lipid wall in the Bruch's membrane reduces hydraulic conductivity, likely stagnating VEGF secreted from retinal pigment epithelium (RPE) toward choriocapillaris. Oxidized lipid may result in oxidative stress and complement activation, which attack RPE. We first showed physiological secretion of lipoproteins from RPE cells and concomitant remodeling of the Bruch's membrane by use of a unique 3D spheroid culture (Sato R, Yasukawa T, et al. IOVS 2013;54:1740). In this session, I will discuss physiological functions of RPE, impacts of aging on them, and possible pathogenesis of AMD.
Commercial Relationships: Tsutomu Yasukawa, None

Support: German Research Community (DFG) grant WI 880/9-1 and by a 2006 Grant-in-Aid for Scientific Research No. 18591929 from Japan Society for the Promotion of Science

259: SY13-4

New findings about age-related macular degeneration using polarized RPE cells

Speaker: Hiroto Terasaki [1]

1. Department of Ophthalmology, Kagoshima University Graduate School of Medicine and Dental Sciences, Kagoshima, Kagoshima, Japan.

Retinal pigment epithelial (RPE) cells in situ play important roles in maintaining the homeostasis of the retina and choroid. RPE cells are extensively involved in the pathology of Age-related macular degeneration (AMD) which is a leading cause of blindness in older individuals in developed countries.

The pathophysiology of AMD has been studied in RPE cell cultures, and the results have contributed to our understanding of how RPE cells are involved in it. However, it is difficult to interpret these in vitro data because RPE cells are very plastic, and their properties, e.g., polarization and differentiation, change easily depending on the culture conditions. Thus, the results obtained from studies of cultured RPE cells that are not polarized might not necessarily represent the results obtained from RPE cells in situ.

A new cell culture method was recently developed in our laboratory that produced RPE cells with properties of RPE cells in situ, e.g., matured tight-junction and asymmetrical secretion of VEGF. These RPE cells should then be more suitable for studying the actual mechanism of AMD.

We have been studied different effects of tumor necrosis factor (TNF- α) and thrombin, which are associated with AMD, in polarized and non-polarized RPE cell (Shirasawa et al, Exp Eye Res 2013, Terasaki et al PLoS One 2013, Terasaki et al Curr Eye Res in press). Furthermore, we recently studied the permeability and anti-VEGF effect of anti-VEGF drugs through polarized RPE (Terasaki et al, RETINA in press).

We found that effects of TNF- α and thrombin on RPE were depending upon cellular polarity. Polarized RPE might be good tool to investigate actual in vivo pharmacokinetics of anti-VEGF drugs.

Commercial Relationships: Hiroto Terasaki, Novartis Pharma K.K. (F)

260: SY13-5

The role of SIRT1 in the pathogenesis of age-related macular degeneration

Speaker: Takeshi Yoshida [1]

1. Department of Ophthalmology, Tokyo Medical and Dental University, Bunkyo, Tokyo, Japan.

Age-related macular degeneration (AMD) is a leading cause of blindness in the elderly. The dysregulation of retinal pigment epithelium (RPE) by oxidative stress has been implicated as having an important role in the pathogenesis of AMD. Sirtuin 1 (SIRT1), a histone deacetylase converting enzyme, functions as a NAD+-dependent histone deacetylase. SIRT1 regulates cell senescence, DNA damage repair, and apoptosis and can control longevity in response to caloric restriction in many organisms. Recently, SIRT1 has been shown not only to deacetylate histone but also to target a variety of other factors that are related to oxidative stress response. Therefore SIRT1 may against process of oxidative stress-related disease including AMD. However, it has been still unclear the correlation between pathogenesis of AMD and SIRT1. In the present study, we found that SIRT1 has a strong cytoprotective role through NF-E2-related factor 2 (NRF2) activation and works as an anti-angiogenic factor through an alteration of vascular endothelial growth factor (VEGF) expression in RPE. Our results suggest that the expression of SIRT1 in RPE was strongly associated with the pathogenesis of AMD. Furthermore, we also analyzed the effect of intravitreal administration of an activator of SIRT1, resveratrol, on CNV formation in a laser-induced mouse model, and we found the administration of resveratrol significantly decreased the formation of CNV. Thus, SIRT1 may play an important role in the pathogenesis of AMD, and may be a new therapeutic approach for AMD.

Commercial Relationships: Takeshi Yoshida, None

261: SY13-6

A new therapeutic target in age-related macular degeneration

Speaker: Hiroki Kaneko [1]

1. Department of Ophthalmology, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan.

Neovascular age-related macular degeneration (AMD), also known as wet-AMD, is one of the most common causes of blindness in developed countries. Wet-AMD is characterized by choroidal neovascularization (CNV) developing through Bruch's membrane and into the subretinal space with subsequent damage to the central retina. Currently, the standard treatment for wet-AMD targets vascular endothelial growth factor (VEGF), a key regulator of CNV in patients with wet-AMD. Although anti-VEGF therapy has dramatically changed the therapeutic strategies against wet-AMD, treatments targeting VEGF alone are insufficient as they require repeated injections of anti-VEGF drugs.

We previously reported that genetic depletion of *Hrh4*, histamine receptor H4, and anti-HRH4 chemicals in mice suppressed laser-induced CNV (laser-CNV). In addition, we further explored the therapeutic potential of HRH4-targeted AMD treatment without damaging the physiological condition of the eye.

Here we propose HRH4 as a new therapeutic target for wet-AMD.

Commercial Relationships: Hiroki Kaneko, None

Support: Grant-in-Aid for Young Scientist (A) and a Grant-in-Aid for Challenging Exploratory Research from the Japan Society for the Promotion of Science, Chukyo longevity medical and promotion foundation, Takeda Science Foundation

Symposium 14
Updates on Genetic Epidemiology in Ophthalmology: What's the Next Hope?

Organizers

Tien Yin Wong
Singapore Eye Reseach Institue, Singpore National Eye Center/Duke-NUS Graduate Medical School, Singapore, Singapore
Ryo Kawasaki
Yamagata University Faculty of Medicine, Yamagata, Yamagata, Japan

262: SY14-1

The role of common and rare genetic variants in age-related macular degeneration

Speaker: Ching-Yu Cheng [1, 2]
1. Singapore Eye Research Institute, Singapore, Singapore. 2. Duke-NUS Graduate Medical School, Singapore, Singapore.

The effects of both common and rare genetic variants on human complex diseases, in particular age-related macular degeneration (AMD), will be reviewed. The recent genetic discovery in Asian AMD will be introduced.
Commercial Relationships: Ching-Yu Cheng, None
Support: NMRC CSA/033/2012

263: SY14-2

Gene-environment interaction

Speaker: Terri Young [2, 1] Xiaoyan Luo [1] Pedro Gonzalez [1] Andrei Tkatchenko [3]
1. Duke University, Durham, NC, United States. 2. Ophthalmology and Visual Sciences, University of Wisconsin, Madison, WI, United States. 3. Ophthalmology, Columbia University, New York, NY, United States.

A vision-driven signaling cascade originating in the retina and ultimately leading to scleral wall remodeling directs the postnatal refractive eye development in a process termed emmetropization. The failure of this process, which involves large-scale changes in ocular tissue gene expression, leads to the development of refractive errors. however, the role of microRNAs (miRNAs) in this biological process and particularly in the development of myopic refractive error is largely unknown. In this study we induced form-deprivation myopia in C57BL/6J mice, and determined myopia-associated miRNA expression profiles in the whole eye, retina, and sclera wall tissues using microarray- based assays. We found a total of 80 differentially expressed miRNAs (p-value <0.05; fold change (FC) >=1.5 or FC<=-1.5). Differential expression of identified miRNAs was confirmed using quantitative real-time PCR . We also identified their putative direct targets and potential signaling pathways involved in the development of form-deprivation myopia using miRNA-mRNA interaction network analysis, and information about genes expressed in the mouse and human retina and sclera, as well as genes associated with myopia in humans and animal models. *BMP2* and *RhoA* signaling pathways were among the top identified canonical pathways for differentially expressed miRNAs in the retina; RAR activation and Aryl Hydrocarbon Receptor signaling pathways are among the top identified canonical pathways for differentially expressed miRNAs in the sclera. Our findings highlight an extensive involvement of miRNAs in the regulation of refractive eye development and in the development of myopic refractive error through the regulation of genes in the retina and sclera wall.
Commercial Relationships: Terri Young, None; Xiaoyan Luo, None; Pedro Gonzalez, None; Andrei Tkatchenko, None
Support: NIH, NEI Grant R01 EY014685

264: SY14-3

Epigenetics of Eye Disease: The missing link between genes and environment

Speaker: Alex Hewitt [1]
1. Centre for Eye Research Australia, University of Melbourne, East Melbourne, VIC, Australia.

Epigenetic variations refer to heritable and imprintable genetic modifications which are not attributable to changes in the primary nucleotide sequence within DNA. A vast spectrum of epigenetic changes have been described, including DNA-methylation, histone tail modifications and methylation–acetylation–phosphorylation. The discovery of genetic variants and environmental influences conferring substantial risk for many blinding diseases have been heralded as major breakthroughs; however, the precise mechanisms, whereby these factors epigenetically interplay and ultimately lead to the development or progression of disease, remain to be fully understood. This presentation will describe the our current understanding of the epigenetic mechanisms of common eye disease.
Commercial Relationships: Alex Hewitt, None

265: SY14-4

Copy number variations

Speaker: Paul N. Baird [1]
1. Centre for Eye Research Australia, University of Melbourne, East Melbourne, VIC, Australia.

Copy number variation (CNV) represents one form of genomic rearrangement of the diploid genome. They are typically represented by a deletion of duplication of greater than 1kilobase of genomic DNA and can be rare (<1%) or common (>5%), large (>1Mbp) or multi-allelic (>3 copies). CNVs provide a rich source of genomic diversity and are increasingly being implicated in a number of eye diseases. These include their presence in known high risk gene loci such as the *CFH* gene region on chromosome 1 and the ARMS2 locus on chromosome 10 in age related macular degeneration (AMD). In glaucoma, copy number changes have been identified in the *TBK1* gene in individuals with normal tension glaucoma. CNVs have also

been suggested as associated with the endophenotype of raised intraocular pressure in glaucoma. In cataract there have been putative associations of CNVs with DNA repair genes. These findings all point to an important role for copy numbers in the atiology of a number of eye diseases. Current strategies have typically focused on candidate regions of interest but the use of genome wide association data that is now widely available offers the prospect of identifying many more copy number changes and will likely provide further insight into the genetic mechanisms of both common and rare eye diseases.

Commercial Relationships: Paul Baird, None
Support: NHMRC Senior Research Fellowship 1028444

266: SY14-5

Genome-Cohort studies

Speaker: Nobuo Fuse [1]
1. Tohoku Medical Megabank Organization, Tohoku University, Sendai, Japan.

Study Group: Tohoku Medical Megabank Organization

A prospective cohort study design permits extensive and unbiased characterization of environmental exposures. To reduce the risks of common disease and to monitor the disease incidence, we established prospective genome cohort studies in Miyagi and Iwate prefecture, the Tohoku Medical Megabank Community-Based Study. We also aimed to develop personalized prevention and medicine. In this session, we report the concept and progress of our cohort study in Miyagi area.

We used two types of recruitments. The first one was at the annual health check-up setting, and the second one was volunteer based recruitment at Community Support Centers. We set 7 Community Support Centers in Miyagi prefecture. In Community Support Centers, we asked participants to provide blood, urine sample, and complete detailed questionnaire, and we measured ophthalmological parameters such as central corneal thickness, intraocular pressure, axial length, and fundus examination. Additionally we measured intima-media thickness of carotid, respiratory function, blood pressure, and so on.

Since 2013, Among 38,682 approached individuals, 24,951 (64.5 %) gave their informed consent (until September, 2014), and 6,300 volunteer based recruitment in our study at the community support centers. This prospective cohort study will help clinicians to better understand the relationship between endphenotypes and genetics, and complex interaction of lifestyle and genes in causing a wide range of ocular disorders. And we also created a completed Whole Genome Reference Panel following its completion of whole genome sequencing for 1,000 peoples. Our platform will offer capabilities to perform single nucleotide polymorphism (SNP) searches publicly available with allele frequencies of 5%.

We will report the latest progress of the Tohoku Medical Megabank Community-Based Study in this session.

Commercial Relationships: Nobuo Fuse, None
Support: MEXT Tohoku Medical Megabank Project

Symposium 15
Metamorphopsia

Organizers

Chota Matsumoto
Kinki University Faculty of Medicine, Osakasayama, Osaka, Japan
Se Woong Kang
Sungkyunkwan University School of Medicine, Jongno, Seoul, Korea (the Republic of)

267: SY15-1

Quantification of metamorphopsia

Speaker: Eiko A. Koike [1]
1. Kinki University Sakai Hospital, Sakai, Osaka, Japan.

Background

In cases of macular diseases, metamorphopsia is an important symptom for evaluating visual functions. Amsler charts have been widely used for detecting metamorphopsia. However, it is difficult to quantitatively assess metamorphopsia using Amsler charts. In 1999, we developed a new metamorphopsia chart, M- CHARTS (Inami) to measure metamorphopsia in degree. In this presentation, I will first introduce the method of M-CHARTS, followed by 2 studies. In the first study, we quantified the severity of metamorphopsia in patients with ERM and evaluated the relationship between ERM stage and level of metamorphopsia. We further investigated the correlation between retinal contraction and change in the severity of metamorphopsia in ERM. In the second study, we assessed the correlation between patient's subjective perception and clinical measurements of metamorphopsia obtained by M- CHARTS.

Quantification of Metamorphopsia Using M-CHARTS

In patients with metamorphopsia, a straight line projected onto the retina is recognized as an irregular or curved line. When a dotted line is used and the dot interval changes from fine to coarse, metamorphopsia decreases and finally disappears. Based on this phenomenon, we developed a new chart with 19 dotted lines with dot intervals of 0.2 ° to 2.0° visual angles. While Type (I) has one dotted line on each chart, Type (II) which is designed for patients with central scotoma such as a macular hole has two dotted lines on each chart. The minimum visual angle of the dotted line needed to cause the metamorphopsia to disappear is measured. At first, a vertical straight line (dot interval 0°) on the first chart is shown to the patient, and the patient fixates on a fixation point on the center of the line. If the patient recognizes the straight line as straight, the metamorphopsia score is 0. If the patient sees distortion in the straight line, the following charts that have the dotted lines with intervals from fine to coarse are shown to the patient one after another. When the patient recognizes the dotted line as straight, the visual angle of the dotted line is considered as the patient's horizontal metamorphopsia score (MH). The M-CHARTS are then rotated 90° and the same test is performed using horizontal lines to obtain vertical metamorphopsia score (MV).

STUDY 1: ERM and Metamorphopsia

Study 1A: Quantification of metamorphopsia in patients with ERM

Among visual disturbances reported by patients with ERM, metamorphopsia is one of the most common symptoms. We therefore quantified metamorphopsia in patients with ERM using M-CHARTS.

Subjects and Methods:

Subjects were 47 eyes of 47 healthy participants (29 women; mean age, 56.4 years, range, 23-78 years) and 51 eyes of 51 patients with ERM (31 women; mean age, 64.3 years, range, 44-80 years). The inclusion criteria for the healthy subjects were: corrected visual acuity (VA) of > 1.0, pupil diameter of > 3.0 mm, intraocular pressure of < 21 mm Hg, no ocular and systemic diseases that were likely to affect their visual functions. One randomly selected eye was examined. The inclusion criteria for the ERM patients were: corrected VA of > 0.1, pupil diameter of > 3.0 mm, intraocular pressure of < 21 mm Hg, and no systemic diseases that were likely to affect their visual functions. If ERMs were observed in both eyes, one randomly selected eye was examined. The metamorphopsia scores of the patients with ERM were compared with their ERM stages classified usingscanning laser ophthalmoscope (SLO) images.

Results

In patients with ERM, the metamorphopsia score increased depending on the severity of membrane proliferation classified by SLO images. The MH scores were larger than the MV scores in advanced stages of ERM.

Study 1B: Relationship between retinal contraction and severity of metamorphopsia in ERM

Subjects and Methods:

Subjects were 29 patients (20 women; mean age, 62.1-8.6 years) with ERM who were observed for at least 3 years (mean, 3.55 ± 0.6 years). Diagnosis of ERM was based on SLO results. The inclusion criteria were: corrected VA of > 0.4 (logMAR), a pupil diameter of > 3.0 mm, intraocular pressure of < 21 mm Hg. All the subjects underwent a complete ophthalmic examination every 6 months including measurement of best corrected VA, the M-CHARTS test, slit lamp biomicroscopy, applanation tonometry, dilated funduscopy, fundus photography, examination by SLO, and central 10° standard automated perimetry. MH and MV scores were obtained. To assess horizontal and vertical retinal contraction due to ERM, we used an image-analysis software developed by us to calculate the horizontal and vertical components of changes in the locations of retinal vessels on sequential fundus images, which were taken at baseline and after 3 years of follow-up. We first enhanced the choroidal vessels in the fundus image with a digital color filter and the two fundus images were then composed by matching the optic discs and choroidal vessels. The distance between the center of the optic disc and the fovea was calibrated to be 15 ° (4.02 mm) and the central 20 ° macula area was divided into 25 areas. In each of the 25 areas, two overlapping fundus images were flickered back and forth at a speed of 2 Hz, and the retinal vessels were exactly matched manually. The process was repeated three

times and the average value was used for each area. The movement of the retinal vessels in each of the 25 areas was displayed as a vector and the values of each vector's vertical and horizontal components were recorded in millimeters as the index of retinal contraction. To assess the correlation between retinal vessel movement and degree of metamorphopsia, we performed the analysis with two approaches: first, the relationships between the amount of change in the average of MV and MH, and both the average and maximum of retinal contraction in all 25 areas; and second, the relationships between all horizontal components of the 25 vectors and changes in MV and MH separately, as well as between all 25 vertical components and changes in MV and MH.

Results

A significant ($P < 0.01$) positive correlation between the degree of retinal contraction and metamorphopsia score was observed. In addition, significant positive correlations between horizontal contraction of the retina and the MV score ($P < 0.01$) and between vertical contraction of the retina and the MH score ($P < 0.05$) were also confirmed. No significant correlations were found between change in the metamorphopsia score and change in VA or mean defect.

Conclusion: The results of Study 1A and 1B demonstrated that the M-CHARTS scores can provide useful information for assessment of ERM.

STUDY 2: Patient's Subjective Perception and Clinical Measurements of Metamorphopsia

Purpose:

We examined if the clinical measurement of metamorphopsia by M-CHARTS could truly reflect patient's subjective perception of metamorphopsia in daily life.

Subjects and Methods:

Subjects were 39 patients with ERM (23 women; mean age, 64.1 ± 8.4 years; ERM stage 1: 11 eyes, stage 2: 14 eyes, stage 3, 14 eyes by Nakajima classification), 22 patients with M-hole (10 women; mean age, 63.1 ± 12.1 years; M-hole stage 1: 8 eyes, stage 2: 4 eyes, stage 3: 10 eyes by Gass classification), and 19 patients with AMD (3 women; mean age, 67.6 ± 7.8 years; dry type: 6 eyes, wet type: 13 eyes). Their VA (logMAR) ranged from -0.1 to 0.52 in ERM, 0 to 1.3 in M-hole, and 0 to 0.7 in AMD. We designed a 10-item questionnaire focusing on the symptoms of metamorphopsia and verified its validity with a Rasch analysis.

Results:

Rasch analysis suggested the elimination of one question. The 9-item questionnaire score significantly correlated to the M-CHARTS score in ERM ($r = 0.59$; $P = 0.0004$) but not in M-hole. Patients with a higher questionnaire score also showed a greater change in the M-CHARTS score. Patients with an M-CHARTS score less than 0.5 were hardly affected by metamorphopsia in daily life. Eighty percent of the ERM patients with a MH score greater than the MV score subjectively perceived horizontal metamorphopsia more often. Rasch analysis indicated that the present form of the questionnaire is better suited for moderate to severe cases of metamorphopsia than for mild cases.

Conclusion:

The M-CHARTS can effectively assess the severity of metamorphopsia in patients with macular diseases, particularly with ERM. Moreover, the results well reflect how patients subjectively perceive metamorphopsia, which is one of the most important symptoms in these diseases. Therefore, the M-CHARTS test is an easy-to-use method that can provide useful information for assessment of macular diseases.

Commercial Relationships: Eiko Koike, None

268: SY15-2

Metamorphopsia in epiretinal membrane

Speaker: Fumiki Okamoto [1]

1. Department of Ophthalmology, University of Tsukuba, Tsukuba, Ibaraki, Japan.

Metamorphopsia is one of the most common symptoms in patients with epiretinal membrane (ERM), with 80 - 85% of patients complained of moderate to severe distortion. Visual acuity improves in many patients after successful removal of ERM, but their metamorphopsia could remain for a long period. In addition, changes in metamorphopsia but not the visual acuity were significantly associated with changes in vision-related quality of life which was evaluated using the 25-item National Eye Institute Visual Function Questionnaire after ERM surgery. Therefore, assessing metamorphopsia is of clinical importance.

We quantified metamorphopsia using M-CHARTS, and assessed macular morphologic features using spectral-domain optical coherence tomography (OCT) in patients undergoing ERM surgery, and investigated the relationship between the severity of metamorphopsia and the anatomic features of the macular region. As a result, metamorphopsia was affected by multiple factors, of which inner nuclear layer (INL) thickness had the largest impact on the severity of metamorphopsia as shown by the multiple regression analysis in patients with ERM. On the other hand, Visual acuity had a significant correlation with the degree of the photoreceptor inner and outer segment junction (IS/OS) disruption.

Vitrectomy for ERM improved metamorphopsia, albeit not to a normal level. At 3 months and 6 months postoperatively, metamorphopsia was significantly associated with INL thickness. Multiple regression analysis showed that preoperative INL thickness yielded the highest regression coefficient with postoperative metamorphopsia. Many studies have reported on the association between visual acuity and retinal microstructures in ERM patients. Based on these reports, the outer retinal structure is considered to be a factor that influences visual acuity of ERM patients. In our study, visual acuity was associated with outer retinal layer (ONL+OPL; outer nuclear layer and outer plexiform layer) thickness, disruption of external limiting membrane (ELM) and IS/OS line preoperatively and postoperatively. In contrast, metamorphopsia was found to be associated with inner retina. In addition, preoperative INL thickness was a prognostic factor for postoperative metamorphopsia.

Commercial Relationships: Fumiki Okamoto, None

269: SY15-3

Metamorphopsia of central serous chorioretinopathy

Speaker: Kyoko Fujita [1]
1. Department of Ophthalmology, Nihon University School of Medicine, Chiyoda, Tokyo, Japan.

Central serous chorioretinopathy (CSC) is characterized by serous retinal detachment in the macula. The serous retinal detachment in CSC causes various symptoms, but metamorphopsia is the most common. Metamorphopsia not only produces discomfort for patients but also reduces quality of life. In recent years, photodynamic therapy (PDT) has been reported to be a useful treatment for absorbing the subretinal fluid in the CSC. Therefore, we performed half-dose verteporfin PDT for CSC patients and measured metamorphopsia before and one year after PDT using the M-chart. We demonstrated significantly improved metamorphopsia, though not complete disappearance in many patients. Most notably, those cases with poorer visual acuities before treatment showed no improvement.
The reasons for metamorphopsia occurring in CSC are as yet unknown. Further study is necessary to clarify the mechanism by which metamorphopsia develops in CSC and to as achieve the maximum reduction possible.
Commercial Relationships: Kyoko Fujita, None

270: SY15-4

Metamorphopsia in maular hole

Speaker: Jae Hui Kim [1]
1. Kim's Eye Hospital, Konyang University College of Medicine, Metropolitan, Daejon, Korea (the Republic of).

Metamorphopsia is closely related to quality of vision. Macular hole is a condition that may induce metamorphopsia. Although outcomes of macular hole surgery in terms of visual acuity have been evaluated in numerous articles, few knowledge is available regarding metamorphopsia that occur in macular holes. In this presentation, results of previous studies evaluating metamorphopsia in eyes with macular hole were summarized. In addition, changes in macular microstructures that may possibly be related to metamorphopsia were discussed.
Commercial Relationships: Jae Hui Kim, None

271: SY15-5

Measurement of metamorphopsia: Using 3D display

Speaker: Yun Taek Kim [1]
1. Ewha Womens University, Seoul, Korea (the Republic of).

Metamorphopsia, a hallmark symptom in patients with macular disease, is sometimes overlooked despites its clinical importance.
However, early detection of the onset or progression of metamorphopsia is getting more important as new treatments for macular disorders are coming out. There are several tools for measurement of metamophopsia including Amsler chart, PHP, and M-chart. However, due to low sensitivity for Amsler chart and high false-positive for PHP, evaluation of metamorphopsia is sometimes inaccurate and still difficult.
I hypothesized that the low sensitivity might originate in the absent of the reference. Previous tests employed only one eye at once. It means that an eye should act as the objective and reference simultaneously. Assuming that an eye has a structural abnormaity, the distorted image may not be perceived, because the subject could not find any straight line.
I would like to present a novel method in evaluating metamorphopsia using 3D display. This novel method present lines which are made up of 2 thin lines - one is for the right eye and the other for the left eye. In normal subjects, the lines are perceived as one thick line. If a distortion is perceived from one eye, this image would be compared to that from the other eye, and this disparity may be perceived easily. I would like to present its clinical result and discuss about it.
Commercial Relationships: Yun Taek Kim, Busan Sungmo Hospital Sodam Scholarship Committee (F)
Support: Busan sungmo eye hospital sodam scholarship committee

272: SY15-6

Preferential hyperacuity perimeter as a useful tool for monitoring metamorphopsia

Speaker: So-Hyun Bae [1]
1. Department of Ophthalmology, Kangnam Sacred Heart Hospital, Hallym University School of Medicine, Yeongdeungpo, Seoul, Korea (the Republic of).

Metamorphopsia is a type of visual distortion affecting the contour of objects, often occurring as a result of retinal pathology. Preferential hyperacuity perimeter (PHP) is a useful tool that can quantify the degree of metamorphopsia. PHP is based on the visual function of hyperacuity, that involve sensing the direction of spatial offset of a line or point relative to a reference; the thresholds of hyperacuity are 5-10 times finer than other spatial vision such as visual acuity. Originally, PHP was developed to monitor the progression of neovascular age-related macular degeneration. While, the disarrangement of photoreceptors caused by other retinal diseases also is recorded as distortion or scotoma by PHP, that enables the assessment of metamorphopsia in various retinal diseases such as epiretinal membrane and macular hole.
With regard to the usefulness of PHP, it has been reported to detect metamorphopsia induced by retinal diseases with relatively high sensitivity and specificity, especially in identifying the recent-onset CNV resulting from AMD. PHP quantifies the severity of metamorphopsia covering the central 14 degree of macular field. Serial distortion maps can provide additional information for monitoring the progression or the therapeutic response in retinal diseases. In accordance with this, the author has reported the results of monitoring postoperative metamorphopsia outcomes in the eyes with ERM after surgery. In addition, hyperacuity stimuli of PHP are highly resistant to retinal image degradation induced by opaque media. However, the PHP may be too expensive and the equipment is bulky compared to other devices. The PHP may be influenced

by several factors such as localized spatial discrimination ability of the subject or perceptual adaptation.
In conclusion, the PHP is a useful tool to detect and monitor the metamorphopsia in eyes with various retinal diseases despite of the drawbacks.
Commercial Relationships: So-Hyun Bae, None

Symposium 16
Advances in Eye Research and NEI International Partnerships
In conjunction with NEI-NIH

Organizers
Gyan "John" Prakash
National Eye Institute, National Institutes of Health, Bethesda, MD, United States
Jonathan Crowston
University of Melbourne, East Melbourne, VIC, Australia
Govindasamy Kumaramanickavel
Aditya Jyot Foundation for Twinkling Little Eyes, Mumbai, Maharashtra, India

273: SY16-1
Global Vision Research: NEI's International Agenda

Speaker: Gyan ". Prakash [1]
1. National Eye Institute, National Institutes of Health, Bethesda, MD, United States.

Study Group: Genetics

The US National Eye Institute (NEI) at National Institutes of Health (NIH) is the premier research organization dedicated to conducting and supporting research, training, and other programs with respect to blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight, and specific health problems and needs of the blind. NEI is actively involved in global research and supports unique international opportunities in scientific research on eye disorders. In 2013, NEI supported 57 grants with at least one foreign component in 16 countries in several areas of vision research. There are a number of models that are being used for international research collaborations. The organization is also training more than sixty foreign scientists in its intramural laboratories. NEI has recently initiated and helped in launching a new initiative, Asian Eye Genetics Consortium (AEGC), to identify novel genes or to find mutant frequency in Asia and help in sharing novel information through common information network. The new initiative is expected to accelerate genetic research studies in the Asian region that will help in our understanding of biology of eye diseases.
Commercial Relationships: Gyan Prakash, None

274: SY16-2
Ophthalmology research in the Asia-Pacific region, where we are and where we are going

Speaker: Jonathan Crowston [1]
1. Department of Ophthalmology, University of Melbourne, East Melbourne, VIC, Australia.

The presentation will summarise current strengths and challenges for ophthalmology research within our region and highlight areas for future international collaboration.
Commercial Relationships: Jonathan Crowston, None

275: SY16-3
NISO-NEI collaborative research programs, past and future

Speaker: Takeshi Iwata [1]
1. National Institute of Sensory Organs, Tokyo Medical Center, National Hospital Organization, Megro-ku, Tokyo, Japan.

In April 2014, the National Institute of Sensory Organs (NISO, Japan) and the National Eye Institute (NEI, USA) signed an agreement to strengthen cooperation in vision science and training activities. Prior to this agreement, NISO and NEI have collaborated in number of research projects including glaucoma, age-related macular degeneration and molecular modeling.
Recent project supported by NEI is to explorer the gene(s) responsible for early onset drusen cynomolgus monkey. Funduscopy and histologic examinations were performed on family members in the pedigree and the molecular composition of drusen was analyzed by immunohistochemistry and liquid chromatography mass spectrometry (LC-MS/MS). Drusen in these monkeys showed immune reactivity for apolipoprotein E, amyloid P component, complement component C5, the terminal C5b-9 complement complex, vitronectin, and membrane cofactor protein. LC-MS/MS analyses identified 60 proteins as constituents of drusen, including a number of common components with drusen in AMD, such as annexins, crystallins, immunoglobulins, and complement components similar to human drusen. Careful macula examination of newly born and the whole exome analysis revealed possible digenic mutations for severe drusen. These mutations affect normal function of the retinal pigment epithelial cells, which reduce tight junction and phagocytosis activity.
Recent collaboration with the NEI is to establish Asian Eye Genetics Consortium (AEGC), a consortium mainly focused on genetic study on Mendelian Eye Diseases in Asian countries. The whole exome analysis or whole genome analysis will be performed for each pedigree to identify disease causing gene mutations. New or highly associated genetic variants will be shared among AEGC members.
Commercial Relationships: Takeshi Iwata, None
Support: Japanese Ministry of Health, Labour and Welfare, Japanese Ministry of Education, Culture, Sports, Science and Technology and the National Hospital Organization of Japan.

276: SY16-4

Vision Research Programs in India: past, present and future

Speaker: Radhika Tandon [1]
1. Dr Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, Delhi, India.

The wealth of information available on vision research emerging from Asia is growing at an astounding pace and India itself has made an enriching contribution in this field. Overcoming the burden of blindness is naturally of highest priority for all stakeholders who are however, also acutely aware that investment in fundamental research must go alongside to achieve long term goals and a sustainable success curve.
The Indo-US vision research program is one such initiative of high value as it seeks to bring the best minds together in a truly collaborative spirit to get the maximum benefit of the best available science across the globe. Some of the highly prestigious and admired work includes insight into plasticity of the developing brain, advanced processing of visual information by neural networks, complexities of inheritance of retinal degenerative disorders, better understanding of complex molecular genetics, developing unique animal models, new perceptions in ocular physiology among others.
Keeping in view the local and global disease burden and the need for expanding the frontiers of knowledge while balancing the available resources a short list of key focus areas has been identified which includes but is not limited to diabetic retinopathy, genetics of ophthalmic diseases, tissue engineering and biomaterials in eye diseases, ocular inflammation, innovative and appropriate approaches or technologies. The impact and long term outcome of these measures remains to be assessed objectively in quantitative terms but at the outset past experience can be analyzed to show the results in reality.
Commercial Relationships: Radhika Tandon, None

277: SY16-5

Advances in Eye Research and NEI International Partnerships

Speaker: John McAvoy [1]
1. Save Sight Institute, University of Sydney, Sydney, NSW, Australia.

In my presentation I will discuss the benefits of the visionary policy of NEI to support researchers outside the USA. Back in the 1970s, NEI developed a policy of supporting key research projects in international institutions. This helped promote new and innovative areas of eye research and went hand-in-hand with the development of ARVO from a small local USA meeting into the major international meeting for eye researchers worldwide that it is today.
Commercial Relationships: John McAvoy, None
Support: EY03177

278: SY16-6

Age-related Eye Diseases: Age-realted Macular Degeneration, Glaucoma and Diabetic Retinopathy – The Epidemiology and Genetics

Speaker: Govindasamy Kumaramanickavel [2] Sunita Mohan [1] Radhika Krishnan [1] Sundaram Natarajan [2] Catherine McCarty [3]
1. Aditya Jyot Foundation for Twinkling Little Eyes, Mumbai, Maharashtra, India. 2. Aditya Jyot Eye Hospital, Mumbai, Maharashtra, India. 3. Essentia Institute of Rural Health, Duluth, MN, United States.

Ageing population and related eye diseases like, visual impairment and blindness (VI&B) are a growing health economic burden, globally. The key diseases that cause VI&B are age-related macular degeneration (AMD), glaucoma and diabetic retinopathy (DR). Even though cataract is much more wider a disease burden, there are effective global corrective measures in place today, to combat cataract, however AMD, glaucoma and DR are the rapidly emerging components of VI&B, both in developed and developing coutnries. All three have a genetic background, whereas AMD and DR have lifestyle related envrinormntal influences. Early diagnosis and management are crtical in reducing the morbidity of these diseases in a population.These diseases are widely prevalent in large and also ageing populations around the world. The prevalence and genetics of these diseases would be discussed in detail.
Commercial Relationships: Govindasamy Kumaramanickavel, None; Sunita Mohan, None; Radhika Krishnan, None; Sundaram Natarajan, None; Catherine McCarty, None
Support: World Diabetes Foundation Grant

Symposium 17
Recent Advances in Dry Eye Research

Organizers

Norihiko Yokoi
Kyoto Prefectural University of Medicine, Kamigyo, Kyoto, Japan
Hyo Myung Kim
College of Medicine, Korea University, Seongbuk, Seoul, Korea (the Republic of)

439: SY17-1

Molecular Biomarkers and Personalized Medicine in Ocular Surface Disease

Speaker: Roger Beuerman [1,2]
1. Singapore Eye Research Institute, Singapore, Singapore. 2. Duke-NUS, Singapore, Singapore.

Biomarkers are quantitative end-points which are developed as clinical tools to stratify patients for trials, and can be used for diagnosis and response to treatment. Molecular biomarkers should also provide information regarding the biological basis of the disease, permitting an understanding of the differences in disease between patients. Proteomic biomarkers are increasingluy valuable to provide a link between the underlying genomic profile of a disease which is often difficult to obtain and the disease phenotype. In the eye the tears which are a complex extra-cellular fluid for the cells of the ocular surface have proven to be a rich resource for discovering biomarkers associated with a number of disease states such as dry eye, keratoconus and lacrimal gland cancer.
More often the primary investigative approach for uncoverign molecular biomarkers has been mass spectrometry. In fact, like genomic arrays, mass spectrometry allows an unbiased approach to discovering proteins associated with the disease state. As a quantitative tool this method can achieve a high degree of agreement between laboratories and clinics.
Commercial Relationships: Roger Beuerman, Allergan (C)
Support: NMRC and SingHealth

440: SY17-2

Biomarkers in dry eye disease

Speaker: Kyung Chul Yoon [1]
1. Department of Ophthalmology, Chonnam National University Medical School and Hospital, Gwangju, Gwangju, Korea (the Republic of).

Biomarkers can be used to monitor the disease state an treament reponses in dry eye. Considering poor reliability of symptoms and tear film and ocular surface parameters in dry eye, it is essential to develop biomakers which are key molecules in the pathophysiology of dry eye disease. Known biomarkers in dry eye disease include inflammatory cytokines (interleukin-1 beta, -6, -8, -17, tumor necrosis factor-alpha, and interferon-gamma), matrix metalloproteinase-9, chemokines (CCL3, -4, -5 and CXCL 9, -10, -11, -13), chemokine receptors (CCR5 and CXCR3), HLA-DA, mucins (MUC1, 2, 4, 5AC, 16), protein markers, and tear osmolarity. Recently, oxidative stress markers associated with DNA damage, protein peroxidation, and lipid peroxidation have been considered as new biomarkers in dry eye. In this presentation, biomarkers in the tear film and ocular surface of dry eye will be extensively reviewed and discussed.
Commercial Relationships: Kyung Chul Yoon, None

441: SY17-3

Visual Disturbance in Dry Eye Disease

Speaker: Shizuka Koh [1]
1. Department of Ophthalmology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan.

The last decade in dry eye disease has been remarkable in that visual disturbance were added to the definition of dry eye for the first time in the 2007 DEWS report. Dry eye has been thought of as a chronic, symptomatic ocular surface disease that affects vision in a limited manner, e.g., in advanced or severe cases, since it has been difficult to detect visual or optical changes with standard visual acuity testing in dry eye. In regard to optical function, the instability of a disrupted tear film over the irregular ocular surface of dry eye is thought to be associated with optical disturbances. Recent emerging techniques have enabled us to quantify and show degraded optical quality or visual disturbance in dry eye. The increase in higher-order aberrations is caused by an irregular ocular surface with an unstable tear film. Glare and associated light sensitivity, which might partly be attributed to forward light scattering, are part of the symptomatology of dry eye. Recently, increased ocular forward light scattering in dry eye has been reported. Clinical application of objective optical sampling in dry eye and current understanding of visual disturbance in dry eye will be reviewed in this presentation.
Commercial Relationships: Shizuka Koh, None

442: SY17-4

Recent advances in meibomian gland dysfunction

Speaker: Reiko Arita [1,2]
1. Ophthalmology, Ito Clinic, Saitama, Japan. 2. Ophthalmology, Keio University, Tokyo, Japan.

Study Group: LIME working group

Meibomian gland secrets lipids (meibum) into the tear film and prevent excessive evaporation from the tearfilm. We developed "Non-invasive Meibography", which enables us to observe meibomian gland without any invasive manner and discomfot sensation. The meibography system comprises a slit lamp (BG-4M and DC-4, Topcon) equipped with an infrared transmitting filter and an infrared charge-coupled device video camera. In addition to that,

a mobile pen-shaped meibography system comprises an LED as a light source, a highly sensitive CMOS video camera for acquisition of clear images (Meibom pen, Japan Focus Corparation). Based on the obtained images of meibomian glands, the lost area of the meibomian gland was semi-quantitatively evaluated as meibo-score. Partial or complete loss of meibomian glands was scored for each eyelids from grade 0 (no loss of meibomian gland) through grade 3 (the lost area was more than two-thirds of total meibomian gland are). Since we established the observation method of meibomian gland and the evaluation method, we investigated the alternation of the meibomian gland by aging, meibomian gland dysfunction, aqueous deficient dry eye, contact lens wear, allergic conjunctivitis or anti-glaucomatous eye drops use. Especially, we found that the decreased temperature of tarsal conjunctiva in patients with meibomian gland dysfunction was detected, where the area was coincided to the lesion of lost area of meibomian glands by meibography. In addition to the semi-quantitative evaluation for meibomian gland, we developed the automatic quantification program of meibomian gland area. This method enabled us to evaluate the efficacy of the treatment for meibomian gland dysfunction. In this talk, I am going to review the series of investigations in non-invasive meibography, and present the latest studies about meibomian gland dysfunction.
Commercial Relationships: Reiko Arita, TOPCON (P)

443: SY17-5

Alterations of mucins at the ocular surface in dry eye

Speaker: Yuichi Hori [1]
1. Department of Ophthalmology, Toho University Omori Medical Center, Ota, Tokyo, Japan.

Mucins are large and highly glycosylated hydrophilic glycoproteins present at the mucous membrane in the human body. At the ocular surface, the roles of mucins are; 1) to attract and hold tear fluid due to their hydrophilic character, 2) to lubricate the ocular surface during the eyelid blink, and 3) to provide a barrier to pathogen penetration. In the human ocular surface, at least four membrane-associated mucins, MUC1, MUC4, MUC16, MUC20, are expressed by corneal and conjunctival epithelial cells, a large gel-forming mucin, MUC5AC, is secreted by conjunctival goblet cells, and a small soluble mucin, MUC7 is secreted by lacrimal gland epithelial cells. For years many investigators have reported that the expression of mucins was decreased in the patients with dry eye. Therefore, several drugs /agents which are possible to induce mucin expression or secretion have been investigated as good candidates for treatment of dry eye. Recently, two new eye drops (diquafosol tetrasodium and rebamipide) have been introduced in Japan to treat dry eye. A recent study reported that these eye drops up-regulated expression of a gel-forming mucin and membrane-associated mucins on the ocular surface epithelium. The loss of the hydrophilic mucin on the ocular surface, especially membrane-associated mucins, implies that, even if lacrimal fluid is available, it will not be retained at the ocular surface and leads to shorter breakup time (short BUT type). Our clinical data indicated that these novel secretagogue agents are useful for the patients with the short BUT type dry eye.
Commercial Relationships: Yuichi Hori, Santen Pharmaceutical Co., Ltd (F), Otsuka Pharmaceutical Co., Ltd. (R), Alcon Japan Ltd. (F)
Support: Grants-in-aid for Scientific Research #24592657

Symposium 18
Comparative Effectiveness Research in Ophthalmology

Organizers
Masakazu Yamada
Kyorin University Eye Center, Mitaka, Tokyo, Japan
Yoshimune Hiratsuka
National Institute of Public Health, Wako, Saitama, Japan

444: SY18-1

Overview: How can we assess cost, utility, and effectiveness?

Speaker: Rei Goto [1]
1. Hakubi Center of Advanced Research, Graduate School of Economics, Kyoto University, Sakyo, Kyoto, Japan.

Though preventive services are not covered directly by healthcare insurance, central and regional governments provide various preventive measures in Japan. Due to the inevitable budgetary constraints on healthcare expenditure, decision makers have to prioritize. The role of health technology assessment (HTA) is to provide decision makers with the documentary evidence concerning efficiency of services in terms of both cost and effectiveness. At the current time, the foundations of an official HTA body in Japan are under discussion and research guidelines for HTA are being developed by experts. With regard to assessment of preventive measures for eye diseases, there are several particular technological issues, including modelling methods, indices of effectiveness and the scope of cost. In this presentation, I will give an overview of the HTA situation in Japan and issues for better practice in assessing cost-effectiveness research in this area.

Commercial Relationships: Rei Goto, None

445: SY18-2

Cost-effectiveness in the Treatment of Gluacoma

Speaker: Poemen Pui-Man Chan [1, 2] Emmy Li [1, 2] Clement C. Tham [1, 2]
1. Department of Ophthalmology &Visual Sciences , Chinese University of Hong Kong, Hong Kong, Hong Kong. 2. Hong Kong Eye Hospital, Hong Kong, Hong Kong.

Investigation for the cost-effectiveness of treating different types of glaucoma and "pre-glaucoma status" is important. Over-treatment could lead to undesirable opportunity cost and unnecessary exposure of adverse effects for the patients; whilst under-treating moderate to advance glaucoma could lead to preventable blindness. Numerous reports have investigated the cost-effectiveness of treating ocular hypertension and primary open angle glaucoma. The cost-effectiveness of different treatment modalities and there application at different stages of glaucoma have been extensive studied. We would further discuss the cost-effectiveness of treating normal tension glaucoma and primary angle closure glaucoma. Cost-effectiveness of treating a particular disease depends heavily on the context, and that differs between countries.

Commercial Relationships: Poemen Pui-Man Chan, None; Emmy Li, None; Clement Tham, None
Support: Health an Medical Research Fund (Hong Kong) - KC/KE-12-0162

446: SY18-3

Cost Effectiveness of Treating Patients with Age-Related Macular Degeneration

Speaker: Joshua D. Stein [1, 2]
1. Department of Ophthalmology and Visual Sciences, University of Michigan, Ann Arbor, MI, United States. 2. Institute for Healthcare Policy and Innovation, Ann Arbor, MI, United States.

Anti-VEGF medications have revolutionized the management of neovascular age-related macular degeneration. The two most commonly used anti-VEGF agents are ranibizumab and bevacizumab. These agents are similar in efficacy but differ from one another in several other ways including cost. This presentation will use Markov modelling to describe the cost-effectiveness of ranibizumab and bevacizumab for the treatment of neovascular age-related macular degenration. Sensitivity analyses will be show the impact of varying key parameters in the model and how they impact which of these two interventions confer the most value.

Commercial Relationships: Joshua Stein, None
Support: National Eye Institute K23 Mentored Clinician Scientist Award (1K23EY019511); Grant Number P30DK092926 from the National Institute of Diabetes and Digestive and Kidney Diseases; Research to Prevent Blindness "Physician Scientist" Award; and an unrestricted grant from Research to Prevent Blindness.

447: SY18-4

Diabetic retinopathy

Speaker: Ryo Kawasaki [1]
1. Department of Public Health, Yamagata University Faculty of Medicine, Yamagata, Yamagata, Japan.

Diabetic retinopathy (DR) is prevalent in one third of the people with diabetes, and the number of patietns with DR is emerging in Asian Pacific region. DR is a slowly-progressive disease and asymptomatic in its early stages; DR can be a good candidate for a screening program because it fulfills the necessary conditions for screening.
In Japan, the proportion of those who underwent fundus examinations at regular basis is reported to be 37%, the lowest in the OECD report. There is an urgent need to provide systematic screening program rather than solely dependent on an opportunistic screening. One of the most important conditions for successful screening is to assure such screening program for DR is cost-effective.
We have performed a cost-utility analysis of screening for DR in Japan using a probablistic Markov modeling

reflecting advanced treatment modalities. In our simulation, we found that a DR screening program in Japan is cost-effective, with a potential to reduce blindness and low vision by 16% and 5%, respectively. Our simulation resulted that the incremental cost-effective ness ratio (ICER) as JPY944,981 (US$11,857) per QALY, supporting a strong reason to advocate implementing screening program for DR in Japan. Optimal screening condition may be suggested to screen those aged from 53 to 84 years, at intervals of 3-year or less in this model.
Based on our experience in this simulation study, we believe that we should regulary review the updated epidemiology and treatment standard to reflect flexible screening condition that match to the geographical or health economy contexts.

Commercial Relationships: Ryo Kawasaki, Office Future (C)
Support: Ministry of Health, Labour and Welfare of Japan.

Symposium 19
Cataract: Recent Advances in Etiopathogenic Signaling and Potential Therapies

Organizers
Dhirendra P. Singh
University of Nebraska Medical Center, Omaha, NE, United States
Eri Kubo
Kanazawa Medical University, Kahoku, Ishikawa, Japan

448: SY19-1

Thiol-based redox regulation and signaling in lens epithelial cells

Speaker: Hongli Wu [1,2] Christy Xavier [1] Xiaobin Liu [1]
1. Pharmaceutical Sciences, University of North Texas Health Science Center, Fort Worth, TX, United States. 2. North Texas Eye Research Institute, Fort Worth, TX, United States.

Study Group: Lens (LE)

Purpose: Glutathionylation, the posttranslational modification of protein cysteine residues by the addition of glutathione, has emerged as a key modification required for changing protein structure and function. The activation of nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated redox pathway is an essential cytoprotective response to oxidation. The aim of this study is to examine the role of glutaredoxin-2 (Grx2), the enzyme that reduces glutathionylated proteins, in activating Nrf2 pathway in lens epithelial cells (LECs).

Methods: Primary cultures of LECs were established from the lenses of wild-type (WT) and Grx2-knockout (KO) mice. WT and Grx2 KO cells were incubated in DMEM with or without 100 μM H_2O_2 for 6 h. Cell viability was measured by a colorimetric assay with WST8. Reactive oxygen species (ROS) were labeled using cellrox orange reagent. Nrf2 activation was measured by using a Nrf2 assay kit. The levels of Nrf2 target genes were determined by Western-blot. Nrf2 was pull down with an immunocapture kit and Nrf2 glutathionylation was compared between WT and Grx2 KO LECs.

Results: Grx2 KO cells were more sensitive to oxidative stress as indicated by lower cell viability, higher levels of ROS, and increased protein glutathionylation. Grx2 deletion led to attenuated level of nuclear Nrf2 protein and its target genes including catalase, thioredoxin (Trx), heme oxygenase-1 (HO-1) and NAD(P)H dehydrogenase quinone 1 (NQO1). In addition, deletion of Grx2 caused a marked increase in glutathionylation of Nrf2 upon exposure to H_2O_2. Importing recombinant Grx2, but not its mutated protein could recover Nrf2 activation upon oxidative stress and elevate its downstream genes.

Conclusions: Glutathionylation-deglutathionylation of Nrf2 regulates its transcriptional activity and nuclear translocation. Deletion of Grx2 inhibited Nrf2 activation, thereby causing decreased antioxidant genes expression and increased oxidative damage in LECs. Targeting the Grx2-Nrf2 axis may provide therapeutic strategies for cataracts and other oxidative stress-related ocular diseases.

Commercial Relationships: Hongli Wu, None; Christy Xavier, None; Xiaobin Liu, None
Support: New faculty start-up grant, University of North Texas Health Science Center

449: SY19-2

Prdx6 Mutated at Sumo1 Sites Protects Lens Epithelial Cells by Escaping And Blocking Oxidative Stress-Induced Aberrant Sumoylation Signaling

Speaker: Dhirendra P. Singh [1]
1. Ophthalmology and Visual Sciences, University of Nebraska Medical Center, Omaha, NE, United States.

Aberrant Sumoylation of protein(s) in response to oxidative stress or during aging has been revealed to be involved in pathogenesis and progression of many human diseases. The cytoprotective protein Peroxiredoxin (Prdx) 6 is aberrantly Sumoylated by Sumo (Small Ubiquitin-like Modifier)-1, resulting in loss of Prdx6 expression and protective activity and leading to lens epithelial cell (LEC) death. With this study, Here we provided evidence that oxidative stress-induced aberrant Sumoylation signaling can be reversed by delivering TAT transduction-linked mutant Prdx6 $^{K(Lysine)122/142\ R(Arginine)}$ protein at its Sumoylation motifs. Using aging human or mouse LECs and LECs derived from targeted inactivation of *Prdx6*$^{-/-}$ *gene*, Our experimentation revealed that Aging cells had increased Sumo1 levels and Sumoylation of most proteins. Higher oxidative load aberrantly Sumoylated Prdx6 leading to loss of cellular function and stability. Prdx6$^{K122/142R}$ was more stable with enhance protective activity. *Prdx6*-deficient cells co-overexpressing Sumo1 and wtPrdx6 were more prone to apoptosis than cells with Sumo1 plus Prdx6$^{K122/142R}$. Delivery of TAT-linked-Prdx6$^{K122/142R}$ transduced to LECs and lenses, dramatically enhancing protection against oxidative stress and delaying lens opacity. As whole, the study reveals for the first time the involvement of aberrant Sumoylation signaling in dysregulation of Prdx6 protective activity during oxidative stress and aging leading to pathobiology of cells. The process can be blocked by delivering Prdx6 $^{K122/142R}$. This may well provide a new approach for manipulating proteins to potentiate their activity against the disease linked to oxidative stress and aging.

Commercial Relationships: Dhirendra Singh, None
Support: NEI EY024589 and BrightFocus Foundation, G2014067

450: SY19-3

Autophagy is essential for intracellular quality control and suppression of age-related cataract

Speaker: Hideaki Morishita [1] Satoshi Eguchi [2] Hirotaka Kimura [2] Junko Sasaki [2] Michael L. Robinson [3] Takehiko Sasaki [2] Noboru Mizushima [1]

1. Biochemistry and Molecular Biology, The University of Tokyo, Tokyo, Japan. 2. Medical Biology, Akita University Graduate School of Medicine, Akita, Japan. 3. Zoology, Miami University, Pearson Hall, OH, United States.

Purpose: Autophagy is a major pathway for degradation of cytoplasmic proteins and organelles. We have previously shown that autophagy is constitutively active in the lens, but its function in biology and age-related pathology of the lens has remained unclear

Methods: Autophagy-indicator mouse model (GFP-LC3 mice) was used to monitor autophagy in the lens. Lens-specific knockout mice for Atg5 and Pik3c3 were generated by crossing mice bearing a floxed allele of each gene with MLR10-Cre transgenic mice. Eyes and lenses were examined at embryonic and postnatal stages using histological, immunofluorescent, ultrastructural, and biochemical techniques.

Results: Here we show that autophagy is constitutively activated in the mouse lens especially in differentiating lens fiber cells. Lens-specific deletion of Atg5 (autophagy-related 5), an essential gene for autophagy, results in age-related cataract appearing around 5 months. In Atg5-/- differentiating fiber cells, polyubiquitinated proteins, oxidized proteins, and p62 accumulate in an age-dependent manner, suggesting a defect in intracellular quality control. In the cataractous Atg5-/- lens of 22-month-old mice, almost all crystallins become insoluble, suggesting that autophagy in differentiating fiber cells is important for the quality control of the whole lens. Programmed organelle degradation, a hallmark of fiber cell terminal differentiation, normally occurs in Atg5-/- lens throughout life, indicating that autophagy is not required for lens organelle degradation. We also generated lens-specific Pik3c3/Vps34 knockout mice to investigate the possible involvement of Atg5-independent alternative autophagy, which is proposed to be dependent on Pik3c3, in lens organelle degradation. Although deletion of Pik3c3 causes congenital cataract and microphthalmia, it does not affect lens organelle degradation during the embryonic period. The developmental defect of Pik3c3-/- lens after birth is accompanied by abnormal secondary fiber cell differentiation, which is likely caused by a defect in the endocytic pathways rather than autophagy.

Conclusions: Autophagy is essential for intracellular quality control and suppression of age-related cataract, but not for lens organelle degradation. The function of Pik3c3 in the endocytic pathways is important for lens development after birth and suppression of congenital cataract.

Commercial Relationships: Hideaki Morishita, None; Satoshi Eguchi, None; Hirotaka Kimura, None; Junko Sasaki, None; Michael L. Robinson, None; Takehiko Sasaki, None; Noboru Mizushima, None

Support: Funding Program for Next Generation World-Leading Researchers [grant number LS043], Grants for a research fellowship of the Japan Society for the Promotion of Science for Young Scientists

451: SY19-4

How Do Genetic Modifiers Prevent or Assist Cataract Development

Speaker: Xiaohua Gong [1]

1. Vision Science and Optometry, University of California Berkeley, Berkeley, CA, United States.

Objective: *Gja3* mutations cause variable cataracts in humans and mice. We have investigated what and how genetic modifiers prevent or assist cataractogenesis in Gja3 knockout mice among different mouse strains. We have further tested a hypothesis that beaded intermediate protein CP49 and scaffold protein periaxin function synergistically to influence the development and severity of cataract formation in *Gja3* knockout mice.

Methods: Cataract severity was evaluated by slit-lamp examination and quantified by lens light scattering measurement. SNPs identification was used to determine candidate genes for genetic modifiers. RT-PCR, western blotting and immunohistochemistry were used. High-resolution images of three dimensional lens fibers were collected for examining the molecular and cellular changes.

Results: Periaxin gene on Chr 7 show different amino acid residue substitutions between different mouse strains. Periaxin protein is detected in fiber cell interdigitation and membrane/cytoskeleton of all fibers of lenses at 129 strain, but only in peripheral differentiating fibers of lenses at C57BL/6J strain. A drastic reduction of periaxin protein level was detected in B6 lenses. Morphological data reveal a severe disruption of membrane/cytoskeleton in periaxin-positive inner fibers of 129 *Gaj3-/-* lenses but not in B6 *Gja3-/-* lenses. Presence normal beaded filament protein CP49 can suppress cataract and presence of both B6 periaxin and CP49 can drastically prevent cataract formation in 129 *Gja3-/-* mice.

Conclusion: Periaxin on Chr 7 is a potential genetic modifier. CP49 and periaxin seem synergistically functioning as genetic modifiers to suppress cataract formation in *Gja3-/-* mice by maintaining the stability of membrane-cytoskeleton in lens fiber cells. Intercellular gap junction communication probably regulates the stability and integrity of periaxin-mediated membrane-cytoskeleton in fiber cells. Lifelong lens transparency relies on reciprocal maintenance between intercellular gap junction communication and membrane/cytoskeleton network. [Supported by grants EY013849 from the National Eye Institute.]

Commercial Relationships: Xiaohua Gong, None

Support: NIH Grand EY013849

452: SY19-5

Isomerizations of aspartyl residues in lens crystallins from age-related cataracts

Speaker: Noriko Fujii [1] Takumi Takata [1] Norihiko Fujii [2] Hiroshi Sasaki [3]

1. Radiation Biochemistry and Biological Function Division of Radiation Life Science, Research Reactor Institute, Kyoto University, Sennangun, Osaka, Japan. 2. Teikyo University, Tokyo, Japan. 3. Kanazawa Medical University, Uchinada, Japan.

A cataract is caused by clouding of the eye lens and may lead to blindness. By age 80, more than 90% of people either have a cataract. Although surgical treatment for cataract is a well-established, the mechanism of cataract development is not well understood. It is thought that abnormal aggregates of lens proteins form with age, causing loss of lens clarity and development of the cataract. However, it is not well known what trigger is to induce the formation of abnormal aggregate of the proteins. Lens proteins are composed of soluble α-, β- and γ-crystallins and as long-lived proteins, they undergo posttranslational modifications including isomerization, deamidation and oxidation which induce insolubilization, aggregation and loss of function which may lead to cataracts. Of the post-translational modifications, we have proposed that the appearance of the isomers of aspartyl (Asp) residues, that is L β-, D α- and D β-Asp isomers may be responsible for the change in the higher order structure and contributes to the increase in aggregation, insolublization and disruption of function of lens proteins leading to the formation of cataracts. Because the different side chain orientations by generation of D-form can induce an abnormal peptide backbone and β-linkage of Asp elongates main chain of the protein. The isomization of Asp residues in proteins does not occur uniformly but does so at specific Asp residues on the basis of the sequence context or structural considerations that make the specific residues more susceptible to the reaction than others. It is therefore necessary to determine the nature of the Asp residues at specific sites within particular proteins. However, the detection of D-amino acids in proteins to date has been complex and difficult. In this presentation, we demonstrate 1) the identification of D-Asp sites in lens crystallins, 2) the mechanism of how D-Asp residues spontaneously occur in proteins under physiological conditions, 3) the influence of D-Asp on protein structure and function 4) a new method for the analysis of isomerization of individual Asp residues using LC-MS.

Commercial Relationships: Noriko Fujii, None; Takumi Takata, None; Norihiko Fujii, None; Hiroshi Sasaki, None

Support: A grant (25288075) from the Ministry of Education, Culture, Sports, Science and Technology of Japan

Symposium 20
Basic Research in Ocular Infection and Immunology

Organizers
Soon-Phaik Chee
Singapore National Eye Centre, Singapore, Singapore
Kenichi Namba
Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan

453: SY20-1

Autoimmunity vs autoinflammation in ocular inflammation

Speaker: Yih-Shiou Hwang [1]
1. Department of Ophthalmology, Chang Gung Memorial Hospital, Taipei, Taiwan.

Autoinflammatory diseases (AIDs) have emerged as the new entities, they have been linked to the well-known world of autoimmunity, but with differences. In fact, AIDs and systemic autoimmune diseases (ADs), share some common characteristics: they both start with the prefix "auto" to define a pathological process directed against self; they are systemic diseases (some of them uveitis), frequently involving musculo-skeletal systems; and both include monogenic and polygenic diseases. From the pathogenetic point of view, they are characterized by the chronic activation of immune system, which eventually leads to tissue inflammation in pre-determined genetically predisposed individuals. The specific effectors of the tissue damage are totally different in the two groups of diseases: in AIDs the innate immune system directly causes tissue inflammation, whereas in ADs the innate immune system activates the adaptive immune system which, in turn, is responsible for the inflammatory process.The AIDs vs. ADs roles in Ocular Behcet's disease/uveitis will be discussed in this talk.

Commercial Relationships: Yih-Shiou Hwang, None

454: SY20-2

Immunomodulation in epidemic keratoconjunctivitis

Speaker: Nobuyo Yawata [1, 2]
1. Singapore Eye Research Institute, Singapore, Singapore.
2. Duke-NUS Graduate Medical School/Singapore Institute for Clinical Sciences , Singapore, Singapore.

The conjunctiva is one of the mucosal surfaces that are primary sites of viral infection. The most severe form of virus-induced inflammation within the ocular surface is epidemic keratoconjunctivitis, often caused by group D human adenoviruses (HAdVs). We studied the dynamics of immune response at the human ocular mucosal surface over the course of adenovirus infection. Natural Killer (NK) cells are a first line of defense against viral infection and prime/regulate adaptive immunity. We will discuss how group D HAdVs change expression of immunomodulatory proteins in infected epithelium to escape from ocular surface NK cell anti-viral response.

Commercial Relationships: Nobuyo Yawata, None
Support: NMRC/TA/0010/2012, Agency for Science, Technology and Research (A*STAR) core funding, SERI Pilot Grant R816/11/2011

455: SY20-3

The role of IL-27 in the formation of ocular inflammatory disease

Speaker: Koh-hei Sonoda [1]
1. Department of Ophthalmology, Graduate School of Medicine, Yamaguchi University, Ube-shi, Yamaguchi, Japan.

Purpose: Age-related macular degeneration (AMD) is the most common disease leading to acquired blindness in developed countries. Choroidal neovascularization (CNV) is the foremost cause of AMD, and is thought to be induced by regional inflammation due to age-related conformational changes of the chorioretinal interface. Here we show that interleukin (IL)-27, a member of the IL-6/IL-12 cytokine family, has an angiostatic effect and regulates the development of laser-induced experimental CNV in mice.
Methods: CNV was induced by laser burn in wild-type mice and Epstein-Barr virus-induced gene 3 (*EBI3*) deficient mice, which lack IL-27. Intraocular cytokines were analyzed by real-time PCR and ELISA.
Results: IL-27 expression increased in the damaged choroid, and peaked at the 24 h. IL-27 neutralization induced by inoculating an antagonistic antibody into the vitreous cavity enhanced both vascular endothelial growth factor (VEGF) production and the extent of CNV. By contrast, the administration of recombinant IL-27 reduced VEGF production and the extent of CNV. EBI3-deficient mice also showed more CNV than wild-type mice, and this was reduced by IL-27 supplementation. We additionally investigated the effect of IL-27 on the function of macrophages, which play a critical role in CNV. IL-27 did not affect macrophage migration, but inhibited their VEGF production.
Conclusion: IL-27 appears to regulate CNV, and is a promising candidate target for treating sight-threatening diseases caused by ocular neovascularization

Commercial Relationships: Koh-hei Sonoda, None
Support: Grant-in- Aid ffrom the Ministry of Education, Science, Sports and Culture of Japan (20592080)

456: SY20-4

Mechanisms involved in Vogt-Koyanagi-Harada disease

Speaker: Peizeng Yang [1] Zi Ye [1] Chaokui Wang [1] Shengping Hou [1] Liping Du [1] Jian Qi [1] Aize Kijlstra [2]

1. The First Affiliated Hospital of Chongqing Medical University Chongqing Key Lab of Ophthalmology Chongqing Eye Institute, Chongqing Medical University, Shapingba, Chongqing, China. 2. University Eye Clinic Maastricht, Maastricht, Netherlands.

Vogt-Koyanagi-Harada (VKH) disease is a well known chronic systemic autoimmune disease characterized by a bilateral granulomatous panuveitis, frequently associated with poliosis, vitiligo, alopecia, central nervous system signs and dysacusis. It is one of the most common uveitis entities in China and Japan. The previous studies have shown that IL-23/IL-17 play a crucial role in the development of VKH disease. However, it is not known how this pathway works and which factors are involved in its regulation.

To understand the exact mechanisms involved in VKH disaese, a number of studies were focus on the role of IL-23/IL-17 pathway in VKH disease. The results showed that IL-17 could stimulate the production of IL-6, CXCL8, CCL2 and CCL20 by ARPE-19 cells and compromised the ARPE-19 monolayer barrier function in association with a disrupted distribution of ZO-1 and occludin. We also found that a network of factors modulated IL-23/IL-17 pathway and was therefore involved in the pathogenesis of VKH disease. IL-7, osteopontin and IL-21 could up-regulate IL-23/IL-17, whereas LXR, IL-37, IL-27, VitD3 and IL-25 down-regulated this pathway. A number of cytokines capable of modulating IL-23/IL-17 pathway, including IFN-α, IL-27 and IL-4, were used for the gene treatment of experimental autoimmune uveitis, a classic model for human uveitis, and showed a promising result. Rapamycin, dexamethasone and Berberine exerted their inhibitory effect on VKH disease through down-regulating IL-23/IL-17 pathway. Our study using genome-wide association analysis (GWAS) identified two new loci including IL-23R-C1orf141 at 1p31.2 and ADO-ZNF365-EGR2 at 10q21.3 as risk factors for VKH disease and confirmed the association between HLA genes and this disease. We also identified other 14 genes as risk factors of this disease using candidate gene approach.

Our results suggest that RPE cells may act as target of IL-23/IL-17. A number of molecules may be involved in the VKH disease development through modulating this pathway. Manipulation of this pathway could be potentially as a strategy for the prevention and treatment of this disease.

Commercial Relationships: Peizeng Yang, None; Zi Ye, None; Chaokui Wang, None; Shengping Hou, None; Liping Du, None; Jian Qi, None; Aize Kijlstra, None

457: SY20-5

Immune regulation of ocular inflammatory disease by Foxp3+ regulatory T cells

Speaker: Hiroshi Keino [1]

1. Department of Ophthalmology, Kyorin University School of Medicine, Mitaka, Tokyo, Japan.

Interleukin-2 (IL-2) is one of the most important cytokines for the homeostasis and maintenance of $CD4^+$ $Foxp3^+$ regulatory T cells (Tregs) in the periphery. Recent studies have shown that treatment with exogenous IL-2 or IL-2-anti-IL-2 Ab complex (IL-2 complex) can induce a marked increase in Treg cells in many organs, including the spleen and lymph-nodes (LNs). Here, the role of $Foxp3^+$ Tregs in the development of experimental autoimmune uveoretinitis (EAU) and new treatment strategy using IL-2 complex for EAU are outlined. Finally, the clinical potential of IL-2 complex for the treatment of human refractory uveoretinitis are discussed.

Commercial Relationships: Hiroshi Keino, None

Support: This work was supported by Grant for Scientific Research from Kyorin University, Tokyo, Japan.

Symposium 21
Retinal Imaging

Organizers
Akitoshi Yoshida
Asahikawa Medical University, Asahikawa, Hokkaido, Japan
Gemmy Cheung Chui Ming
Singapore Eye Research Institute, Singapore, Singapore

657: SY21-1

Fundus Autofluorescence in Clinical Practice

Speaker: Tetsuju Sekiryu [1]
1. Department of Ophthalmology, Fukushima Medical University School of Medicine, Fukushima, Fukushima, Japan.

Fundus autofluorescence (FAF) is mainly originalted from the retinal pigment epithelium. FAF is modified by the sensory retina. For these reasons, FAF imaging can provid information about the health and function not just of the retinal pigment epitheium but the sensory retina. So far, FAF has been used as research tools of the retina. Recently, AF imaging is used to help us in the diagnosis, prognosis as well as in expecting the results of the treatment. The following topics will be presented.
1. Basics Science
2. Retinal dystrophy
3. Central serous chorioretinopathy
4. Inflammatory disease

Commercial Relationships: Tetsuju Sekiryu, None

658: SY21-2

Scanning Laser Ophthalmoscope

Speaker: Satoshi Ishiko [1]
1. Department of Medicine and Engineering Combined Research Institute, Asahikawa Medical University, Asahikawa, Hokkaido, Japan.

Scanning laser ophthalmoscope (SLO) provides more detailed fundus image than the fundus camera, with several kinds of light wavelength and apertures. In addition to the SLO fundus monochromatic image, the SLO pseudo-color fundus image can be obtained by the commercially available SLO, the Digital Ophthalmoscope F-10 (Nidek, Gamagori, Japan) and Spectralis (Heidelberg Engineering, Heidelberg, Germany). Furthermore, not only a confocal image but also two kinds of indirect image, so called "dark-field mode" and "retro mode", can be obtained by F-10. In this symposium, I will introduce the clinical application of SLO for the fundus imaging.

Commercial Relationships: Satoshi Ishiko, Nidek (P)

659: SY21-3

Ultra-wide-field imaging in the management of retinal diseases

Speaker: Jaeryung Oh [1]
1. Department of Ophthalmology, Korea University College of Medicine, Seongbuk, Seoul, Korea (the Republic of).

The ultra-wide-field imaging system using a scanning laser ophthalmoscope with an ellipsoid mirror provided improved visualization of peripheral retinal lesion. The ultra-wide-field imaging system provided composite color, green or red light filtered fundus image, fundus autofluorescence, and angiography. A composite color image formed by two laser of different wavelengths covers 200 degree of the retina in one exposure. In addition, Ultra-wide-field fluorescein angiography allows visualization of peripheral retina at the same time-point and improved our understanding of various retinal vascular diseases. The ultra-wide-field imaging system also provided wider field of autofluorescence image than previous systems and extended demarcation of retinal or chorioretinal pathologies outside of macula. Recognizing pros and cons of the imaging system may expand our understanding of various findings on the ultra-wide-field images in eyes with retinal diseases.

Commercial Relationships: Jaeryung Oh, None
Support: Grant from the Korean Health Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A102024).

660: SY21-4

Application of reflectivity-based and motion-based OCT for diagnosis and management of retinal diseases

Speaker: Masanori Hangai [1]
1. Ophthalmology, Saitama Medical University, Iruma, Saitama, Japan.

Optical coherence tomography includes various tissue information of living body, including reflectivity, motion, and polarization. The reflectivity-based OCT B-scan images has been widely used for diagnosis and management of various ocular diseases. Three-dimensional imaging enables to observe the comprehensive structure of the fundus lesions. Speckle-noise-reduction with multiple B-scan averaging allows improved visualization of the individual retinal layers and details of pathological lesions. However, retinal capillaries have not been so clear as to be used for diagnosis or disease management. Recently, motion-contrast technology on OCT allows to selectively visualize retinal and choroidal blood vessels including capillaries. Unfortunately, the area for this technology is much narrower than that of fluorescein angiography. However, motion-contrast OCT enables to visualize each of the 4 retinal capillary networks, which may open a new avenue for understanding pathologies of various retinal

vascular diseases and glaucoma, and management of these diseases on medical therapy.
Commercial Relationships: Masanori Hangai, NIDEK (C)

661: SY21-5

Adaptive Optics Fundus Camera

Speaker: Yasuki Ito [1]
1. Department of Ophthalmology, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan.

Adaptive optics (AO) system is the device that can increase the resolution dramatically. Recently, fundus camera or scanning laser ophthalmoscope (SLO) is used combined with the AO system to improve the resolution. Using these devices, macular cone cells except for the fovea or nerve fiver bundles can be clearly observed. The major differences of the AO fundus camera and AO-SLO is the same as the fundus camera and SLO without AO, i.e. the depth of focus, and the images of AO-SLO are more layer specific than AO fundus camera. On the other hand, the field of view of AO fundus camera is wider than AO-SLO, and the AO fundus camera is more motion-resistant. In addition, AO fundus camera is commercially available and government approved in Japan. Because of its fast technical improvement, AO imaging system will become widely used in near future.
Commercial Relationships: Yasuki Ito, None
Support: Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (C Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (C25462710)

Symposium 22
Molecular Genetics of Eye Diseases

Organizers

Yoshihiro Hotta
Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan
Hyeong Gon Yu
Seoul National University College of Medicine, Jongno-gu,, Seoul, Korea (the Republic of)

662: SY22-1

Molecular genetics of anophthalmia/ microophthalmia

Speaker: Maki Fukami [1]
1. Department of Molecular Endocrinology, National Research Institute for Child Health and Development, Setagaya, Tokyo, Japan.

Anophthalmia and microphthalmia is genetically heterogeneous disorders that occur in approximately 1-2 per 10,000 births. Previous studies revealed that 30-90% of cases with anophthalmia/microphthalmia are associated with non-ocular malformations. Chromosomal abnormalities and single-gene mutations account for 20-25% of cases. Several genes, including *SIX3, HESX1, BCOR, GDF6, FOXE3, OTX2, PAX6, RAX, SOX2* and*VSX2*, have been implicated in the development of anophthalmia/ microphthalmia. Of these, mutations in *SOX2* and *OTX2* have been identified in several patients. In this session, I will review current understanding of molecular basis and clinical characteristics of *SOX2* and *OTX2* abnormalities.

Commercial Relationships: Maki Fukami, None
Support: This work was supported by grants from the Ministry of Health, Labor and Welfare and from Takeda Science Foundation, by Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science, by Grant-in-Aid for Scientific Research on Innovative Areas from the Ministry of Education, Culture, Sports, Science and Technology and by the Grant of National Center for Child Health and Development.

663: SY22-2

Molecular genetics of Miyake's disease

Speaker: Takeshi Iwata [1]
1. National Institute of Sensory Organs, Tokyo Medical Center, National Hospital Organization , Megro-ku, Tokyo, Japan.

Miyake's disease (Occult macular dystrophy, OMD) is an inherited macular dystrophy characterized by progressive loss of macular function but normal ophthalmoscopic appearance. Typical OMD is characterized by a central cone dysfunction leading to a loss of vision despite normal ophthalmoscopic appearance, normal fluorescein angiography, and normal full-field eletroretinogram (ERG), but the amplitudes of the focal macular ERG and multifocal ERG are significantly reduced at the central retina.

Linkage analysis of two affected families was performed by Affymetrix SNP 6.0 array and the SNP High Throughput Linkage analysis system (SNP HiTLink). Coding exons of four protein coding genes in the candidate region were analyzed for sequence variations by direct DNA-sequencing. Immuno-staining for RP1L1 was carried out on frozen sections of normal cynomolgus and paraffin section of normal marmoset. RP1L1 and RP1 were both cloned and expressed in 661W cell line for protein association study.

Genome wide linkage analysis localized the disease locus to chromosome 8p22-p23. Among the 128 genes in the associated region, 22 genes were expressed in the retina, and four candidate genes were selected. Amino acid substitution of R45W in retinitis pigmentosa 1-like 1 (RP1L1) was found in three affected families and W960R in a remaining family. Whole exome analysis was performed to confirm this result. Further analysis of more than 50 Miyake's disease family revealed that R45W and S1199C are the most common mutations and both have not been detected in any controls. Immunohistochemistry of RP1L1 in the retina section of cynomolgus and marmoset monkey revealed expression in the inner segment of rod and cone photoreceptor, supporting a role of RP1L1 in the photoreceptors that, when disrupted by mutation, leads to disease.

Identification of RP1L1 mutations as causative for Miyake's disease has potentially broader implications for understanding the differential cone photoreceptor functions in the fovea and the peripheral retina. Unknown function of RP1L1 is currently under investigation.

Commercial Relationships: Takeshi Iwata, None
Support: Japanese Ministry of Health, Labour and Welfare, Japanese Ministry of Education, Culture, Sports, Science and Technology and the National Hospital Organization of Japan.

664: SY22-3

Mutation analysis of Japanese retinitis pigmentosa patients for various causative genes including EYS and USH2A using multiple methods

Speaker: Shinsei Minoshima [1]
1. Medical Photonics Research Center, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan.

Retinitis pigmentosa (RP) is a highly heterogeneous genetic disease with autosomal recessive (ar), autosomal dominant, or X-linked inheritance. It is known that *EYS* (eyes shut homolog) and *USH2A* genes account for 5–16% and 7–23% arRP cases, respectively, which was reported using mainly Caucasian patients. Meanwhile, Usher syndrome (USH) is an autosomal recessive disorder characterized by hearing loss and RP. The *USH2A* was originally reported as a causative gene for USH type 2 (USH2). We analyzed mutations of *EYS* and *USH2A* in

Japanese ar and isolated non-syndromic RP cases (total 100) as the first analysis. We also analyzed *USH2A* in 19 Japanese USH2 patients. All exons of these genes were analyzed by the Sanger sequencing.
The analysis of *EYS* for 100 RP patients elucidated 7 probable pathogenic mutations from 18 cases. Of them, 12 had a particular insertion mutation c.4957_4958insA and 4 cases had a nonsense mutation c.8868C>A. These 2 mutations were considered frequent mutations in Japanese RP patients. The minimum observed prevalence of *EYS* mutations was 18%, which is higher than previous reports with Caucasian. Next, the RP cases in which *EYS* mutations were not detected (82 cases) were screened for *USH2A*. We found 5 probable pathogenic mutations in 4 patients. The prevalence of *USH2A* was 4%, which was lower than previous reports. Furthermore, the analysis for the *USH2A* in 19 USH2 patients unveiled 23 mutations from 15 cases. Of the 23, 19 of them were novel and a splicing mutation c.8559-2A>G was found in 4 patients. Majority of mutations found in 2 genes of Japanese RP and USH2 patients were novel, and specific frequent mutations for each of them were found, strongly suggesting that mutation spectra of these genes are totally different from Caucasians.
Our recent analysis of the *EYS* using MLPA method to assay the copy number of each exon elucidated a case with an exon deletion and another case with an exon duplication from 9 patients in which only one probable causative mutation had been detected. It is quite possible that more of copy number mutations latently exist in *EYS*, *USH2A* and others of RP and USH2 patients. Currently, we are analyzing mutations of 74 causative genes for RP and Leber congenital amaurosis using next-generation sequencer.
Commercial Relationships: Shinsei Minoshima, None

665: SY22-4

Targeted exome sequencing in Korean with retinitis pigmentosa

Speaker: Hyeong Gon Yu [1]
1. Department of Ophthalmology, Seoul National University College of Medicine, Seoul, South, Korea (the Republic of).

Identification of the causative genes of retinitis pigmentosa (RP) is important for the clinical care of patients with RP. However, the genetic heterogeneity found in sensorineural genetic disorders makes identification of pathogenic mutations challenging. In this talk, high throughput genetic testing using massively parallel sequencing and its application to Korean RP patients will be presented.
Commercial Relationships: Hyeong Gon Yu, Novartis (C)

666: SY22-5

Targeted exome sequencing in Chinese patients with inherited retinal degenerations

Speaker: Zi-Bing Jin [1]
1. Lab for Stem Cell & Retinal Regeneration Division of Ophthalmic Genetics, The Eye Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China.

Inherited retinal dystrophy (IRD) is a leading cause of blindness worldwide. Because of extreme genetic heterogeneity, the etiology and genotypic spectrum of IRD have not been clearly defined, and there is limited information on genotype–phenotype correlations. The purpose of this study was to elucidate the mutational spectrum and genotype–phenotype correlations of IRD. We developed a targeted panel of 164 known retinal disease genes, 88 candidate genes, and 32 retina-abundant microRNAs, used for exome sequencing. A total of 179 Chinese families with IRD were recruited. In 99 unrelated patients, a total of 124 mutations in known retinal disease genes were identified, including 79 novel mutations (detection rate, 55.3%). Moreover, novel genotype–phenotype correlations were discovered, and phenotypic trends noted. Three cases are reported, including the identification of AHI1 as a novel candidate gene for nonsyndromic retinitis pigmentosa. In conclusion, this study revealed novel genotype–phenotype correlations, including a novel candidate gene, and identified 124 genetic defects within a cohort with IRD. The identification of novel genotype–phenotype correlations and the spectrum of mutations greatly enhance the current knowledge of IRD phenotypic and genotypic heterogeneity, which will assist both clinical diagnoses and personalized treatments of IRD patients.
Commercial Relationships: Zi-Bing Jin, None
Support: This work was supported by grants from the National Key Basic Research Program, the National Natural Science Foun- dation of China, and MOST Projects, and was funded in part by a Qianjiang Scholarship and grants from the Qianjiang Talents Project and the Zhejiang Provincial Natural Science Foundation of China.

Symposium 23
New Insight for Retinal Detachment, Damage and Treatment

Organizers
Hiroko Terasaki
Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan
Taiji Sakamoto
Kagoshima University Graduate School of Medicine and Dental Sciences, Kagoshima, Kagoshima, Japan
Demetrios G. Vavvas
Harvard Medical School, Boston, MA, United States

552: SY23-1

Toxic effects of extracellular histones and their neutralization by vitreous in retinal detachment

Speaker: Hiroki Kawano [1] Taiji Sakamoto [1]
1. Department of Ophthalmology, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Kagoshima, Japan.

(Purpose) Histones are DNA-binding proteins and are involved in chromatin remodeling and regulation of gene expression. Histones can be released after tissue injuries, and the extracellular histones cause cellular damage and organ dysfunction. Regardless of their clinical significance, the role and relevance of histones in ocular diseases are unknown. We studied the role of histones in eyes with retinal detachment (RD).
(Methods) Vitreous samples were collected during vitrectomy, and the concentration of histone H3 was measured by enzyme-linked immunosorbent assay. The location of the histones was examined in rat RD models. The release of histones from rat retinal progenitor cells R28 and their effects on R28 and ARPE-19 cells (human retinal pigment epithelium cell line) were evaluated in vitro. In addition, the protective role of the vitreous body and hyaluronan against histones was tested.
(Results) The intravitreal concentration of histones was higher in eyes with RD (mean, 30.9 ± 9.8 ng/ml) than in eyes with macular hole (below the limit of detection, $P < 0.05$). In the rat RD model, histone H3 was observed on the outer side of the detached retina and was associated with photoreceptor death. Histone H3 was released from R28 by oxidative stress. Histones at a concentration of 10 μg/ml induced the production of interleukin-8 in ARPE-19 cells that was mediated through the ERK1/2-, p38 MAPK-dependent pathways, and Toll-like receptor 4. However histones over the concentration of 20 μg/ml were also toxic to cells, vitreous body or hyaluronan decreased the cytokine productions and cytotoxicity of histones by inhibiting diffusion of histones.
(Conclusions) These results indicate that histones are released from damaged detached retina in RD and may modulate the subretinal microenvironment by functioning as damage-associated molecular pattern molecules, thereby inducing proinflammatory cytokines or cell toxicity. In addition, the important role of the vitreous body and hyaluronan in protecting the retina from these toxic effects is suggested.
Commercial Relationships: Hiroki Kawano, None; Taiji Sakamoto, None

553: SY23-2

Biological change in retinal detachment

Speaker: Hiroki Kaneko [1]
1. Department of Ophthalmology, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan.

Retinal detachment (RD) is a disorder in which the sensory retina detaches from the underlying retinal pigment epithelium (RPE). Without rapid and appropriate treatment, RD results in severe vision loss or even blindness.
Inappropriate surgical treatment for RD sometimes causes proliferative vitreoretinopathy (PVR), which is characterized by severe periretinal proliferation of fibrotic cells and refractory RD. To understand the pathogenesis of PVR, the concept of epithelial–mesenchymal transition (EMT) is important. EMT in RD is a process in which RPE cells lose their "epithelial" characteristics such as cell polarity and cell–cell adhesion and instead gain migratory and invasive properties as "mesenchymal" cells. Reducing inflammation associated with surgical treatment may be important for minimizing and preventing PVR.
We previously showed that circulating monocytes accumulate in the subretinal space in RD. We also showed that inflammatory cytokines are detected in high levels in the subretinal fluid in RD. Additionally, we demonstrated some interesting biological changes in PVR after RD.
Commercial Relationships: Hiroki Kaneko, None

554: SY23-3

Retinal and Choroidal Changes after RD surgery

Speaker: Ga Eun Cho [1] Se Woong Kang [1]
1. Department of Ophthalmology, Sunkyunkwan University School of Medicine, Gangnam, Seoul, Korea (the Republic of).

Subretinal fluid (SRF) bleb after rhegmatogenous retinal detachment (RRD) surgery is responsible for delayed recovery, and may exert adverse effects on the final visual outcome. Despite its significance, cause, consequences, and treatment on this SRF bleb remain elusive. Research as well as clinical practice demonstrates that fluid absorption is induced by forces including oncotic pressure gradients, hydrostatic pressure, and retinal pigment epithelial pump. Therefore previous studies on SRF bleb focused on these factors.
RRD treatment using scleral buckling with or without an encircling comprised of cryopexy and/or subretinal fluid drainage and hence choroidal circulation may be impaired. Treatment with vitrectomy and gas tamponade also encompasses retinal photocoagulation which can damage

choroidal circulation.
The introduction of optical coherence tomography (OCT) resulted in multiple reports of SRF bleb after RRD surgery. OCT images show shallow subretinal fluid, even when all retinal breaks are closed and the retina appears fully attached on ophthalmoscopy. Furthermore, visualization of choroid has been enabled by enhanced-depth imaging OCT. By using enhanced-depth imaging OCT, choroidal thickness changes after RRD surgery was investigated in several reports, and they provided indirect information on choroidal vasculature changes.
In this presentation, previous studies on retinal and choroidal changes after RRD surgery will be reviewed focusing on SRF bleb. Also, brief results of ongoing study using indocyanine angiography in eyes which underwent RRD surgery will be presented.
Commercial Relationships: Ga Eun Cho, None; Se Woong Kang, None

555: SY23-4

The protective effects of the proteasome inhibitor bortezomib on ischemia-reperfusion injury in the rat retina

Speaker: Chang-Hao Yang [1]
1. Department of Ophthalmology, National Taiwan University Hospital, Taipei, Taiwan.

The protective effects of proteasome inhibitor bortezomib on ischemia-reperfusion (IR) injury in the rat retina was evaluate. Bortezomib had a neuro-protective effect in retinal IR injury, possibly by inhibiting the activation of NF- κ B related IR insult and reducing the inflammatory signals and oxidative stress in the retina.
Commercial Relationships: Chang-Hao Yang, None

556: SY23-5

New strategies in neuroprotection and regeneration for retinal diseases

Keynote Speaker: Demetrios G. Vavvas [1] Yusuke Murakami [1] Hidetaka Matsumoto [1] Keiko Kataoka [1] George Trichonas [1] Maki Kayama [1] Toshio Hisatomi [3] Hiroko Terasaki [2] Tatsuro Ishibashi [2] Joan Miller [1]
1. Department of Ophthalmology, Harvard Medical School, Boston, MA, United States. 2. Nagoya, Nagoya, Japan. 3. Kyushu University, Fukuoka, Japan.

Apoptosis and necrosis are two major cell death mechanisms. Apoptosis is a highly regulated process involving the caspase family of cysteine proteases. In contrast, necrosis has been considered a passive, unregulated form of cell death; however, recent evidence indicates that some necrosis can be induced by regulated signal transduction pathways, such as those mediated by receptor interacting protein (RIP) kinases, especially when caspases are inhibited or cannot be activated efficiently. This unique mechanism of cell death is termed **programmed necrosis or necroptosis**. In a rodent model of photoreceptor death induced by retinal detachment, we have shown that pro-death ligands and caspases are activated. However, caspase inhibition by Z-VAD fails to prevent the photoreceptor death. Utilizing a combination of morphological, biochemical, genetic, and pharmacological investigations, **we have demonstrated that in addition to caspase-dependent apoptotic pathways, RIP kinase-mediated programmed necroptosis is an essential and redundant mediator of photoreceptor death** after retinal detachment and that in the presence of the pan-caspase inhibitor Z-VAD, necrosis becomes the predominant form of photoreceptor cell loss. It is interesting to note that TUNEL and ultrastructural analyses studies reveal that death of the RPE cells results from necrosis whereas that of the photoreceptors results from apoptosis in animal models of AMD such as the dsRNA induced cell death. In a model of juvenile retinal degeneration we identified that in contrast to rods, which die by apoptosis, cones die by RIP kinases necrosis. In addition data from photoreceptor detachment induced degeneration implicate the infiltrating macrophages and not photoreceptors as a source of RIP3 dependent damaging inflammasomes.
We hypothesize that effective neuroprotection may have been elusive in the past in part because of unrecognized redundancy of cell death pathways. Simultaneous inhibition of RIP kinases and caspases is essential for effective neuroprotection in AMD and other retinal degenerations.
Commercial Relationships: Demetrios Vavvas, None; Yusuke Murakami, None; Hidetaka Matsumoto, None; Keiko Kataoka, None; George Trichonas, None; Maki Kayama, None; Toshio Hisatomi, None; Hiroko Terasaki, None; Tatsuro Ishibashi, None; Joan Miller, None
Support: NEI R21EY023079-01A1 and NEI Grant EY014104 Lions Eye Research Fund; The Yeatts Family Foundation; Macula Society Research Grant award; a Bausch & Lomb Vitreoretinal Fellowship; RPB Physician Scientist Award; Loefller Fund Award

Symposium 24
Epigenetics in Ocular Development and Diseases

Organizers
Sumiko Watanabe
Institute of Medical Science, University of Tokyo, Minato, Tokyo, Japan
Biao Yan
Nanjing Medical University, Nanjing, China

579: SY24-1

The microRNA regulates the lens development and differentiation

Speaker: Eri Kubo [1]
1. Department of Ophthalmology, Kanazawa Medical University, Kahoku, Ishikawa, Japan.

Study Group: LE

Cellular microRNAs (miRNA) are noncoding RNAs of ~21 nucleotides that recognize target mRNAs by base pairing, thereby regulating their expression. The altered expression of specific miRNAs is critical to cell differentiation as well as to the development of several human diseases including cataract. To provide an overview of the breadth of miRNA expression in the lens, we performed microarray analyses to determine miRNA expression profiles in both developing and adult rat lens epithelial cells (LECs). We determined the level of expression of miRNAs and the effects of their levels of expression on gene expression in LECs isolated from developing and cataractous rat lenses, and we assessed the effects of oxidative stress on miRNA expression. Using LECs from rats of different developmental stages and ages, we observed widely varying miRNA expression profiles in rat LECs during development and during aging. Expression of several miRNAs, such as let 7a, let 7b, let 7c, miR 29a, miR 29c, miR 126, miR 204, miR 339-3P, and miR 451, were found to be altered in rat LECs during late embryonic and post-natal development and in adult lenses. The expression of miR 29a, miR 29c, and miR 126 is reduced in cataractous LECs. Treatment of LECs with H_2O_2 increased the expression of miR 29a and 29c at 24 h, but decreased their expression after 48 h. Inhibition of miR 29a and miR 29c induced the expression of tropomyosin (Tpm) 1 α , a cytoskeletal protein highly expressed in tissues with posterior capsular opacification after rat extracapsular lens extraction. Tpm 1 α is also highly expressed in humans with anterior subcapsular fibrosis and severe nuclear cataract and is a target protein for miR 29a and miR 29c, suggesting that oxidative stress is involved in regulating Tpm1 α expression. Taken together, our results suggest that expression of miRNAs pattern may play a major regulatory role in cataractogenesis of rat lenses, and that oxidative stress alters miRNA expression, thereby altering gene expression, in rat LECs.

Commercial Relationships: Eri Kubo, None
Support: JSPS Grants-in-Aid for Scientific Research C26462673

580: SY24-2

Roles of Histone methylation for retinal bipolar cell differentiation

Speaker: Sumiko Watanabe [1]
1. Department of Molecular and Developmental Biology, Institute of Medical Science, University of Tokyo, Minato, Tokyo, Japan.

Network of transcription factors plays critical roles for decision of cells to differentiate/proliferate during organogenesis, and the epigenetic mechanisms may serve in giving competency to the cells. We have been interested in how histone methylation contributes retinal differentiation and maintenance. Di- and tri-methylation of lysine 27 on histone H3 (H3K27me2/3) is a critical gene repression mechanism. We analyzed retina-specific knockout mice of the H3K27me2/3-specific demethylase, Jmjd3, and the methylase, Ezh2 and found that H3K27me3 plays critical roles for maturation of subsets of bipolar cells. We will also discuss about our recent findings suggesting cell lineage specific mechanisms of retinal cell maintenance by H3K27me3 modification.

Commercial Relationships: Sumiko Watanabe, None
Support: a grant-in-aid from the Ministry of Education, Culture, Sports, Science, and Technology of Japan

581: SY24-3

Genomewide DNA methylation analysis of primary human trabecular meshwork cells with dexamethasone stimulation

Speaker: Akira Matsuda [1]
1. Laboratory of Ocular Atopic Diseases, Juntendo University Graduate School of Medicine, Bunkyo, Toko, Japan.

To investigate the roles of epigenetic modification in the pathophysiology of glucocorticoid-induced glaucoma, we carried out genomewide DNA methylation analysis of primary culture trabecular meshwork cells in response to DEX exposure using Illumina 450K methylation chips. To select biological meaningful changes of DNA methylation in response to DEX stimulation, we carried out genomewide gene expression analysis simultaneously. Among the 145 genes with differentially methylated CpG sites, 32 genes (including FKBP5 and SAA1) were showing significant changes of mRNA expression. Differential DNA methylation in TM cells may contribute to the persistent effects with regard to gene expression after DEX exposure.

Commercial Relationships: Akira Matsuda, None
Support: Grants-in-Aid from the Japanese Society for the Promotion of Science (No. 24592652 and No. 21592239)

582: SY24-4

Age-related macular degeneration and DNA methylation

Speaker: Paul N. Baird [1]

1. Centre for Eye Research Australia, University of Melbourne, East Melbourne, VIC, Australia.

A number of well-established risk genes have been identified for Age related macular degeneration (AMD) explaining approximately half of the genetic variability in disease. Other factors therefore contribute to genetic variability in AMD. Epigenetic changes, where gene expression can be modified by an environmental stimulus without a resultant change in DNA sequence may offer one such source of genetic variation. Assessing changes in DNA methylation is the most common route to interrogate a large number of genes at the genome wide level. While overall coverage of methylation sites across the genome on current generation methylation chips is still limited to mainly promoter regions, it has been encouraging that several studies have already identified a number of potentially methylated genes that appear to have a role in AMD. The identified genes currently show limited overlap with known AMD risk genes, although they do implicate some sharing of similar pathways including immune related. Importantly, experimental design, as well as the need to assess temporal changes, the tissue of origin, as well as the functional role of identified changes needs to be considered in the context of identifying epigenetic changes in AMD. Further improvements in genome wide methylation coverage as well as through the use of whole genome bisulphite sequencing are likely to lead to future discoveries in this area. In addition, the discovery of genes exhibiting methylation changes may provide an alternative route for the development of novel therapeutic approaches for treatment.

Commercial Relationships: Paul Baird, None

Support: NHMRC Senior Research Fellowship 1028444

583: SY24-5

Pathogenic role of lncRNA-MALAT1 in endothelial cell dysfunction in diabetes mellitus

Speaker: Biao Yan [1]

1. Nanjing medical university, Nanjing, China.

Study Group: Jing-Yu Liu, Jin Yao, Xiu-Miao Li, Jiang Qin

Long noncoding RNAs (lncRNAs) play important roles in diverse biological processes. Our previous study has revealed that lncRNA-MALAT1 deregulation is implicated in the pathogenesis of diabetes-related microvascular disease, diabetic retinopathy (DR). However, the role of MALAT1 in retinal vasculature remodeling still remains elusive. Here we show that MALAT1 expression is significantly up-regulated in the retinas of STZ-induced diabetic rats and db/db mice. MALAT1 knockdown could obviously ameliorate DR in vivo, as shown by pericyte loss, capillary degeneration, microvascular leakage, and retinal inflammation. Moreover, MALAT1 knockdown could regulate retinal endothelial cell proliferation, migration, and tube formation in vitro. The crosstalk between MALAT1 and p38 MAPK signaling pathway is involved in the regulation of endothelial cell function. MALAT1 up-regulation represents a critical pathogenic mechanism for diabetes-induced microvascular dysfunction. Inhibition of MALAT1 may serve as a potential target for anti-angiogenic therapy for diabetes-related microvascular complications.

Commercial Relationships: Biao Yan, None

Symposium 25
Inflammatory Mechanisms in Diabetic Retinopathy and Other Retiral Degeneration

Organizers
Masaru Takeuchi
National Defense Medical College, Tokorozawa, Saitama, Japan
Susumu Ishida
Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan

669: SY25-1

Role of VEGF as a pro-inflammatory cytokine in diabetic macular edema

Speaker: Susumu Ishida [1]
1. Department of Ophthalmology, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan.

The discovery of vascular endothelial growth factor (VEGF) in 1989 led to significant breakthrough in elucidation of molecular mechanisms in diabetic retinopathy. VEGF proved to be the identical protein with vascular permeability factor (VPF) originally reported in 1983. Retinal edema and neovascularization, both of which are the major abnormalities directly causing vision loss in diabetic retinopathy, are associated with and dependent on its pathological functions as VPF and VEGF, respectively. Moreover, VEGF was shown to be a pro-inflammatory cytokine that stimulates gene expression of various inflammation-related factors including leukocyte adhesion molecules and chemoattractants, which led us to regard diabetic retinopathy to be at least in part as a result of inflammation. Indeed, vitreous samples from patients with diabetic macular edema have been shown to contain multiple proteins suggested to be involved in its pathogenesis. These include monocyte chemotactic protein-1, intercellular adhesion molecule-1, interleukin-6, all of which are known as representative pro-inflammatory molecules. Nowadays, anti-VEGF treatments as well as corticosteroid therapy are thus utilized to suppress the inflammatory pathogenesis of diabetic macular edema. In this presentation, VEGF biology for better understanding of clinical application to diabetic macular edema will be discussed.

Commercial Relationships: Susumu Ishida, None

667: SY25-2

Elevation of Th17-associated cytokines in the vitreous fluids of proliferative diabetic retinopathy

Speaker: Masaru Takeuchi [1]
1. Department of Ophthalmology, National Defense Medical College, Tokorozawa, Saitama, Japan.

Inflammatory process is involved in the pathogenesis of diabetic retinopathy provoking damage of the retinal tissue, and progression of proliferative diabetic retinopathy (PDR) via various systemic and local factors. Several studies have shown that macrophages, which mediate low-grade inflammation in diabetes, produce Interleukin (IL)-1 β , IL-6, IL-8, and tumor necrosis factor α (TNF α) and play pathogenic roles in PDR. T cells are driven by local inflammation and T-helper (Th) cells play a pivotal role as a conductor in acute and chronic immune responses, however the involvement has not yet been elucidated in the progression of PDR. Th cells are generally classified into Th1, Th2, Th17 cells, T regulatory (T reg) cells by cytokines they produce, and their functions are different. Recently, we have found that IL-17A, which is exclusively produced by Th17 cells, are present prominently in the vitreous fluid of PDR patients compared to the serum, and that the vitreous level of PDR is greater than that of epiretinal membrane or macular hole patients. Immune responses via IL-17A are involved in the development of uveitis, which has been demonstrated both in animal models of endogenous uveitis and in human situations. Nevertheless, the vitreous levels of IL-17A in PDR patients were further greater than those of endogenous uveitis. On the other hand, IL-17 (including IL-17A) has been shown to promote angiotensin II-induced hypertension and vascular dysfunction, and to play a role in the pathogenesis of angiotensin II type 1 receptor-induced insulin resistance. In this symposium, I would propose and discuss potential roles of IL-17A in the progression of PDR.

Commercial Relationships: Masaru Takeuchi, None

668: SY25-3

Role of high-mobility group box-1 in the development of diabetic retinopathy

Speaker: Ahmed M. Abu El-Asrar [1]
1. Department of Ophthalmology, College of Medicine, King Saud University, Heidelberg, Saudi Arabia.

The presentation will discuss the following:
1. High-mobility group box-1 and biomarkers of inflammation in the vitreous from patients with proliferative diabetic retinopathy.
2. Expression of high-mobility groups box-1/receptor for advanced glycation end products in proliferative diabetic retinopathy epiretinal membranes.
3. High-mobility group box-1 protein activates inflammatory signaling pathway components and disrupts retinal vascular-barrier in the diabetic retina.
4. The proinflammatory cytokine high-mobility group box-1 mediates retinal neuropathy induced by diabetes.
5. High-mobility group box-1 induces decreased brain-derived neurotrophic factor-mediated neuroprotection in the diabetic retina.

Commercial Relationships: Ahmed Abu El-Asrar, None
Support: Dr. Nasser Al-Rasheed Research Chair in Ophthalmology

668b: SY25-4

Neuro-inflammation in diabetic retinopathy via the renin-angiotensin system activation

Speaker: Toshihide Kurihara [1]
1. Keio University School of Medicine, Tokyo, Japan.

The renin-angiotensin system is classically known as a blood pressure regulator but is becoming well recognized as a proinflammatory mediator. The components of renin-angiotensin system are also produced intrinsically in diverse tissues, making it possible for tissues to respond more dynamically to systemic or local demands. While renin-angiotensin system is important for controlling normal inflammatory responses, ectopic and/or excessive activation of the pathway may cause neural dysfunction as a result of neuro-inflammation, inducing accelerated degradation of some neuronal proteins and activation of pathological glial responses. Chronic inflammation and oxidative stress are risk factors for high incidence vision-threatening diseases such as diabetic retinopathy, age-related macular degeneration, and glaucoma. Visual dysfunction in these diseases is caused by neuronal damage directly or indirectly in the inflammatory cascades. In fact, increasing evidence including results from randomized multicenter clinical trials suggests that inhibition of renin-angiotensin system may actually prevent progression of various ocular diseases. We have previously reported that angiotensin II type 1 receptor blocker (ARB) suppresses retinal neural dysfunction in animal models of acute inflammation or diabetes. Other groups and our own have also reported that ARBs can protect retinal vascular inflammation and neuronal apoptosis. In this session, I will discuss how modulation of renin-angiotensin system may preserve neuronal function and viability while combating ocular diseases such as diabetic retinopathy.

Commercial Relationships: Toshihide Kurihara, None

668c: SY25-5

Role of inflammation in retinitis pigmentosa

Speaker: Yasuhiro Ikeda [1]
1. Ophthalmology, Kyushu University, Fukuoka, Japan.

Retinitis pigmentosa (RP) is a heterogenous group of inherited retinal diseases resulting in adult blindness. Recent basic and clinical studies have suggested the importance of chronic inflammation in the pathogenesis of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and retinal degenerative diseases including RP. We investigated the nature of inflammatory reaction in the eyes of patients with RP and the relationship between inflammation and visual function. We recently demonstrate that: 1) increased levels of a variety of proinflammatory cytokines and chemokines are detected both in aqueous humor and vitreous fluid of patients with RP; 2) a substantial number of inflammatory cells are observed in the vitreous cavity of patients with RP, especially in younger patients; 3) RP patients with a higher number of inflammatory cells show decreased visual function; and 4) aqueous flare is increased in RP patients and negatively correlates with visual function. These findings suggest that chronic inflammation may play a pathogenic role in RP. Therefore, intervention/suppressors of inflammation should be considered as a potential therapy in the treatment of RP.

Commercial Relationships: Yasuhiro Ikeda, None

670: SY25-6

Role of inflammation in age-related macular degeneration

Speaker: Miho Nozaki [1]
1. Department of Ophthalmology and Visual Science, Nagoya City University Graduate School of Medical Sciences, Nagoya, Aichi, Japan.

Age-related macular degeneration (AMD) is a leading cause of legal blindness in most developed nations. The blindness in AMD usually arises from invasion of the retina by choroidal neovascularization (CNV). Although the pathogenesis of CNV has not been understood clearly, inflammatory response is one of major cause of CNV.

Among various inflammatory responses, macrophages are thought to play as pivotal role in pathogenesis of CNV. Macrophages were accumulated in human CNV membrane, and macrophages depletion lead to near-abrogation of laser-CNV and suppression of vascular endothelial growth factor (VEGF) in mice. These data supported that infiltrated macrophages are producer and regulator of VEGF, and manipulation of infiltrated macrophages might be a novel therapeutic approach to treat CNV beyond anti-VEGF therapy. This presentation will explore the role of inflammation in CNV pathogenesis, and new strategies for therapeutic intervention will be discussed.

Commercial Relationships: Miho Nozaki, Sanwa Kagaku Kenkyusho Co., Ltd. (P)

Symposium 26
Recent Topics in Anti-aging in Ophthalmology

Organizers
Nobuyoshi Kitaichi
Health Sciences University of Hokkaido, Sapporo, Hokkaido, Japan
Motoko Kawashima
Keio University School of Medicine, Shinjuku, Tokyo, Japan

671: SY26-1

Aging and oxidative stress in human corneal epithelial cells: protective effects of natural antioxidants

Speaker: Kyung Chul Yoon [1]
1. Department of Ophthalmology, Chonnam National University Medical School and Hospital, Gwangju, Gwangju, Korea (the Republic of).

It has been known that aging is involved in oxidative stress by producing free radicals, and oxidative stress is related with ocular surface diseases including dry eye. Oxidative stress by aging or UV radiation can generate reactive oxygen species and upregulate the expression of proinflammatory cytokines, growth factors, and enzymes mediating prostaglandin and leukotriene biosynthesis, as well as antioxidant enzymes in corneal epithelial cells. We suppose that visible light with short wavelengths may also induce oxidative stress on the corneal epithelium and natural antioxidants can protect oxidative stress. In this presentation, the effects of oxidative stress by irradiation of blue light on human corneal epithelail cells and the impact of ethanol extracts of medicinal plant mixtures having antioxidant and anti-inflammatory effects on induced oxidative stress wil be discussed.

Commercial Relationships: Kyung Chul Yoon, None
Support: Supported by the Ministry of Knowledge Economy and Korea Institute for Advancement of Technology

672: SY26-2

Anti-aging approach for dry eye disease

Speaker: Motoko Kawashima [1]
1. Department of Ophthalmology, Keio University School of Medicine, Shinjuku, Tokyo, Japan.

Dry eye is a multifactorial disorder affecting millions of people, giving severe discomfort and instability of visual function, which deteriorates the quality of life dramatically. Although the etiology is unknown, we believe that unstable tear film is a major component of the pathogenesis of dry eye, which might caused by any disturbance of each layer of the tear film; aqueous tear film, oily tear film, and mucin layer- any of them can produce unstable tear film resulting in the development of dry eye. Especially, we focus on the tear production which is related to aging. Recent progress in the understanding of aging have laid the foundation to a new way of thinking about intervention to the aging process. Since dry eye is accelerated by aging, it might be a good approach for the prevention or treatment of dry eye, if we can interfere with the aging process. From that point of view, oxidative stress is one of the major reasons for aging and age-related functional decline. In this review, I will introduce the clinical dry eye research as well as basic research. Also I will introduce the new approach for the management of dry eye in the future.

Commercial Relationships: Motoko Kawashima, None

673: SY26-3

Accommodation and asthenopia

Speaker: Nobuyoshi Kitaihchi [1, 2]
1. Ophthalmology, Health Sciences University of Hokkaido, Sapporo, Hokkaido, Japan. 2. Ophthalmology, Hokkaido University, Sapporo, Japan.

Computer-related visual and ocular symptoms are one of the most frequently health problems at the present day. It is clinically apparent especially among people of 40 years old or older. Several nutrition factors were investigated in clinical trials for asthenopia / eye strain..

Astaxanthin is found abundantly in the red-orange pigment of marine animals such as salmon, salmon roe, and the shell of crabs and shrimp. It is commonly indicated as antioxidants and immune modulators. It was shown the anti-inflammatory effects on acute uveitis (intraocular inflammation) as well as the inhibition of choroidal neovasculization. Also, astaxanthin eye drops successfully ameliorated the damage of ultraviolet-induced photokeratitis to scavenge reactive oxygen species in animal models.

In humans, accommodation ability of the eye recovered by intake of astaxanthin for 14 days or later. The subjects reported the reduced eye fatigue significantly during the randomized double-blind placebo-controlled study. Laser speckle flowgraphy showed that administration of astaxanthin elevated the choroidal blood flow velocity without any adverse effects in healthy volunteers.

In this session, clinical effects of food factors on accommodation and eyestrain will be presented.

Commercial Relationships: Nobuyoshi Kitaichi, Fuji Chemical (F)

674: SY26-4

Oxidative stress and glaucoma

Speaker: Kenya Yuki [1]
1. Harvard Medical School, Boston Children's Hospital, Boston, MA, Japan.

Aging is a proven risk factor for glaucoma. Oxidative stress is thought to be associated with aging. Superoxide dismutase is an enzyme that catalyzes the superoxide anion. Superoxide dismutase 1 (SOD1) exists in the cytosol. SOD1 knock out mice show a number of aging phenotypes

such as a short-life span, reduced fertility, anemia with auto-antibody, fatty liver, hepatocarcinogensis, hearing loss, skin atrophy, age-related macular degeneration, dry eye, and retinal dystrophy. We have shown that the number of retinal ganglion cells in 24-week-old SOD1 deficient mice are less than that of wild type and retinal ganglion cells of SOD1 deficient mice are more vulnerable to NMDA induced retinal neurotoxicity compared to wild type mice. We have also shown that the serum level of SOD1 is significantly lower in NTG patients compared with age-gender matched controls. In this symposium, I will explain recent studies that reveal the association between oxidative stress and glaucoma.
Commercial Relationships: Kenya Yuki, None

675: SY26-5

Light stress-induced aging of retina and its possible modifications

Speaker: Masaki Tanito [1]
1. Division of Ophthalmology, Matsue Red Cross Hospital, Matsue, Shimane, Japan.

Epidemiological studies suggest a correlation between environmental light exposure and the development/progression of human retinal degenerations such as age related macular degeneration (AMD) and retinitis pigentosa. Light exposure to animals results in selective losses of photoreceptor and retinal pigment epithelial cells; these accompany post-translational modifications of retinal proteins by 4-hydroxynonenal (4-HNE) and 4-hydroxyhexenal, end products of nonezymatic oxidation of n-6 and n-3 polyunsaturated fatty acids (PUFAs), respectively. Levels of PUFAs such as docosahexaenoic acids in photoreceptor outer segments negatively correlate with the susceptibility to light induced retinal degeneration in animals. Thus, the double bonds in long chain PUFAs that are highly enriched in retina could be target substrates to propagate photooxidative stress in photoreceptors, and their oxidation products also are likely to be involved in the light-induced retinal degeneration. Epidemiological studies suggest that prior cataract surgery are a significant risk factor for late-stage AMD, and that an increase in the amount of shorter wavelength blue light reaching the retina after surgery is speculated to be one of the major causes. Macular pigment, an endogenous defense system against retinal pthotooxidative stress, declines with aging, therefor can be a possible surrogate endpoint in assessing retinal aging and AMD development in humans. Cataract surgery with UV-blocking clear intraocular lens (IOL) implantation induces post-surgical decrease in macular pigment level and use of blue-light filtering yellow-tinted IOL retains post-surgical macular pigment level more effectively than clear IOL
Commercial Relationships: Masaki Tanito, None