Plenary Session

Plenary Session 1
AMD in Asians

Organizers

Tien Yin Wong
Singapore Eye Research Institute/ Duke-NUS Graduate Medical School, Singapore, Singapore
Calvin CP Pang
The Chinese University of Hong Kong, Kowloon, Hong Kong

189: PS1-1

AMD in Asians and polypoidal choroidal vasculopathy

Keynote Speaker: Tomohiro Iida [1]
1. Department of Ophthalmology, Tokyo Women's Medical University, Shinjuku, Tokyo, Japan.

Neovascular age-related macular degeneration (neovascular AMD) is a leading cause of legal blindness in elderly patients in developed countries. In Asia, the number of patients with neovascular AMD is not as great as in Western countries. However, the prevalence of AMD in Asia is increasing rapidly. Neovascular AMD in Asian patients has different demographic features compared with that in White patients. In Asian patients, there is a predominance of polypoidal choroidal vasculopathy (PCV), male gender, unilaterality, and absence of drusen in the second eye, with the exception of retinal angiomatous proliferation (RAP). PCV is a disease entity characterized by multiple recurrent detachments of the retinal pigment epithelium and neurosensory retina secondary to leakage and bleeding from choroidal vascular lesions. PCV has characteristic vascular lesions, such as branching choroidal vascular network and polypoidal vascular dilations at the border of the network. Indocyanine green angiography (ICGA) shows the characteristic vascular lesions and is the gold standard for the diagnosis of PCV. Multimodal imaging is useful for understanding the pathophysiology and for individualized treatment in PCV. The activity of PCV could be evaluated by choroidal hyperpermeability on ICGA or thickened choroid on optical coherence tomography. The treatment responses to verteporfin photodynamic therapy or antivascular endothelial growth factor were different in the presence of choroidal vascular hyperpermeability. The purpose of this presentation is to clarify the clinical characteristics of neovascular AMD in Asian patients and to provide additional information for the management of PCV.

Commercial Relationships: Tomohiro Iida, None

190: PS1-2

Update on Imaging in Polypoidal Choroidal Vasculopathy

Speaker: Gemmy Cheung Chui Ming [1,2]
1. Singapore Eye Research Institute, Singapore, Singapore.
2. Singapore National Eye Center, Singapore, Singapore.

Indocyanine green angiography is the gold standard for diagnosing PCV. This lecture will cover the results from comparative studies using different camera systems (such as fundus camera versus cSLO) and using different diagnostic criteria. Additional imaging modes, such as OCT and retromode imaging will also be briefly covered.

Commercial Relationships: Gemmy Cheung Chui Ming, Bayer (F), Bayer (C), Bayer (R), Novartis (C), Novartis (F), Novartis (R), Roche (F), Allergan (R), GlaxoSmithKline (F)
Support: Singapore Eye Research Institute Health Research Endowment fund R893/02/2012; Bayer Global Ophthalmology Award 2012

191: PS1-3

Personalized medicine for age-related macular degeneration

Speaker: Kenji Yamashiro [1]
1. Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, Kyoto, Japan.

Age-related macular degeneration (AMD) is the leading cause of severe visual impairment in industrialized countries among people over 50 years of age. The introduction of anti-vascular endothelial growth factor (VEGF) therapy has revolutionized the treatment of neovascular AMD. However, only 30% of the patients can get significantly improved visual acuity after anti-VEGF treatment.

In Asia, we have more patients with polypoidal choroidal vasculopathy (PCV) than Caucasians. Since the efficacy of anti-VEGF drug is limited for treating PCV, some patients with PCV should be treated with photodynamic therapy (PDT). For the best visual outcome after treatment, we have to chose the best treatment for each patient; anti-VEGF monotherapy, PDT monotherapy, or combination therapy with anti-VEGF drug and PDT. Furthermore, we have to pay attention to the bilaterality of AMD for the best treatment strategy. Patients with high probability of the second-eye involvement have to be treated aggressively and be followed up in short interval.

Recently, genetic studies on AMD suggest that we can predict prognosis and treatment outcome by genotyping patients. For example, ARMS2 gene polymorphism can predict second-eye involvement of AMD. It is also suggested that ARMS2 genotype can predict visual outcome after PDT. As for anti-VEGF treatment, several studies have shown that polymorphisms in CFH, ARMS2, and VEGF gene can predict response of AMD eyes to treatment, while other studies have denied these associations.

We have shown that 10% of unilateral AMD patients with GG genotype in ARMS2 A69S will suffer form the second-eye involvement in 10 years, while more than 50% of patients with TT genotype in ARMS2 A69S will suffer form the second-eye involvement in 10 years. Our genome-wide association study on bilaterality showed that ARMS2 is one of the most important gene to predict bilaterality of AMD. To predict treatment outcome after anti-VEGF

treatment, we performed multi-center prospective study. We enrolled 453 patients with wet AMD and treated all patients with ranibizumab for 12 months. Of the 453 samples, 256 samples were used to discover genes associated with treatment outcome by 2.5M Beadchip genotyping, and the rest of 197 samples were used to replicate the associations. In this session, I would like to talk about our genome-wide association studies and future treatment for AMD.

Commercial Relationships: Kenji Yamashiro, None
Support: MHLW H23-003
Clinical Trail: UMIN000005584

192: PS1-4

Risk factors of AMD in Koreans

Speaker: Kyu Hyung Park [1,2]

1. Department of Ophthalmology, Seoul National University, College of Medicine, Jongno-gu,, Seoul, Korea (the Republic of). 2. Department of Ophthalmology, Seoul National University Bundang Hospital, Seongnam, Korea (the Republic of).

Age-related macular degeneration (AMD) is the leading cause of blindness among the elderly in industrialized countries. AMD is a complex trait influenced by multiple risk factors such as aging, genetic factors, and environmental factors such as smoking, BMI, etc. The prevalence and phenotypes of AMD maybe somewhat different between Asians and Caucasians. In this talk, we present our study on the epidemiologic risk factors of AMD in Koreans based on data from the Korean National Health and Nutrition Examination Survey (KNHANES). We also discuss genetic risk factors of AMD depending on the AMD phenotype in Koreans. Finally, we will share our recent work of proteomic biomarkers which were analyzed in the plasma and aqueous humor of Korean AMD patients. These epidemiologic, genetic and proteomic risk factors, help us to gain further insight on the new patho-physiologic mechanisms of AMD, enabling early diagnosis and aiding the construction of a useful prediction model of AMD in Koreans.

Commercial Relationships: Kyu Hyung Park, None
Support: This work was supported by grants from the Korea Health Technology R&D Project, Ministry of Health & Welfare, Korea (A111161) and the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science, and Technology (2009-0072603).

193: PS1-5

Treatment options in AMD non-responders

Speaker: Marten Erik Brelén [1] Chi Wai Tsang [2] Alvin Young [3] 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.

Anti-VEGF therapy has revolutionized the way we treat patients with neovascular age related macular degeneration (nAMD). New patients presenting with nAMD are routinely told that over 90% of patients will have their vision stabilized whereas one third of patients will have their vision improved. There are still a proportion of patients who don't respond to treatment. Their vision continues to deteriorate and their nAMD isn't stabilized. This presentation will discuss the reasons why patients sometimes don't respond to treatment such as missed PCV (polypoidal choroidal vasculopathy), drug resistance or tachyphalaxis to anti-VEGF and the treatment options available. The advantages of switching monotherapy are presented including which new monotherapies will soon become available and currently undergoing clinical trials. The evidence for combination therapy with PDT with and without intravitreal steroid will also be discussed. Previous work on epimacular brachytherapy will be shown and the results from the large multicenter clinical trials discussed. All the various treatment options will be demonstrated with case examples of patients who did not respond to their initial treatment. The presentation will summarise a logical and easy to follow approach to managing nAMD non-responders.

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

Plenary Session 2
Genome-wide Association Study for Complex Eye Diseases

Organizers

Nobuhisa Mizuki
Yokohama City University School of Medicine, Yokohama, Kanagawa, Japan
Chiea Chuen Khor
Genome Institute of Singapore, Singapore, Singapore

194: PS2-1

Genome-wide association study for Behcet's disease

Speaker: Nobuhisa Mizuki [1]
1. Department of Ophthalmology, Yokohama City University School of Medicine, Yokohama, Kanagawa, Japan.

Behcet's disease (BD) is a chronic systemic inflammatory disorder characterized by four major manifestations: recurrent ocular symptoms, oral and genital ulcers, skin lesions, and (occasional) inflammation in other tissues such as the joint, the vascular system, the gastrointestinal tract, the central nervous system and the epididymis. BD exists worldwide but is more prevalent in countries along the ancient Silk route spanning from Japan to the Middle East and the Mediterranean basin. The etiology of BD remains unclear. However, as in many other inflammatory and/or immune-centered diseases, environmental factors are thought to trigger the symptomatology in individuals that harbor a particular genetic background. The strong association between BD and the *HLA-B*51* allele has been well established. This association indicates that the *HLA-B*51* allele is one of the genetic factors underlying BD. Still, the presence of *HLA-B*51*-negative BD patients suggests that other genetic factor(s) and/or various environmental or infectious agent(s) might also be risk factors for the development of BD. With the exception of the *HLA-B*51* allele, the molecular nature of the "genetic background" of BD has, until recently, remained mostly unknown. A genome-wide association study (GWAS) is an approach that involves rapidly genotyping a dense panel of genetic markers that covers the entire genome and has great power to detect genetic variants that contribute to the risk of developing common and complex diseases. BD susceptibility genes/loci that have been successfully identified by GWASs include *HLA-A*26*, *UBAC2*, *IL10*, *IL23R-IL12RB2*, *STAT4*, *ERAP1*, *CCR1-CCR3*, *KLRK1-KLRC4* and *GIMAP*. Those findings provide new insights into the genetic tendency underlying BD by connecting classically-known findings and allow for clearer interpretation of the etiology and pathophysiology of BD at the molecular level. Thus, findings from genetic studies can provide useful clinical information and open the door to the development of more accurate and reliable diagnostic and treatment approaches for BD. Here I present classically known and recent genetic findings, as well as their possible involvement in the pathogenesis of BD.

Commercial Relationships: Nobuhisa Mizuki, None
Support: Health Labour Sciences Research Grant: JSPS Grants-in-Aid for Scientific Research

195: PS2-2

The genetic basis of Exfoliation syndrome

Speaker: Khor Chiea Chuen [1]
1. Division of Human Genetics, Genome Institute of Singapore, Singapore, Singapore.

Exfoliation syndrome (XFS) is an age-related disease, and constitutes the most common cause of open angle glaucoma world-wide. To better understand the molecular genetics and pathogenesis of XFS, we conducted a genome-wide association study (GWAS) on ≈1500 patients with XFS matched to ≈1200 controls from Japan, and followed up the most significant findings on a further >6000 patients and nearly 20000 controls from 17 countries across 6 continents. Apart from being able to strongly confirm previously published findings at LOXL1, we note strong associations at other locations, suggesting new insights into the disease process of XFS. I will share with you what we have seen so far in this largest to date genetic study on XFS.
Commercial Relationships: Khor Chiea Chuen, None

196: PS2-3

GWAS in myopia: understanding mechanisms of myopia development

Speaker: Christopher Hammond [1]
1. Departments of Ophthalmology and Twin Research & Genetic Epidemiology, King's College London, St Thomas' Hospital, London, United Kingdom.

Study Group: Consortium on Refractive Error and Myopia

GWAS have been instrumental in identifying genes associated with myopia. Two large scale studies of 45,000 subjects each identified common polymorphisms: the international Consortium on Refractive Error and Myopia (CREAM) perfomed a quantitative meta-analysis using population-based studies with spherical equivalent measures, and the 23andMe personal genomics company performed a case-control study with age of onset of spectacle wear as a proxy of severity, and both found remarkably concordant results, with 36 genetic loci explaining ~5% of refractive error variation. Subsequently, a mega-analysis of 167,000 subjects from 23andMe and the CREAM consortium has been performed, and 70 new loci have been identified, now explaining 12% of variation. The genes identified are important in signalling, cell adhesion and other important pathways, and allow us to understand some of the mechanisms involved in failure of emmetropisation. Further studies are needed to look at gene-environment interactions, given the importance of environmental factors causing recent temporal trends of increasing myopia prevalence.
Commercial Relationships: Christopher Hammond, None

197: PS2-4

Genome-wide association study in Asian patients with glaucoma

Speaker: Tin Aung [1, 2]

1. Singapore National Eye Centre & Singapore Eye Research Institute, Singapore, Singapore. 2. Ophthalmology, National University of Singapore, Singapore, Singapore.

Recent research using genome wide association studies (GWAS) has led to the successful identification of genes and genetic risk factors for **primary open angle glaucoma (POAG)**. Other GWAS studies have investigated the genes underlying quantitative traits that are important in POAG such as intraocular pressure, central corneal thickness and optic disc traits. The International Glaucoma Genetics Consortium has been formed in the last few years to increase research and collaboration in this area..

In the past few years, several advances have been made in the genetics of **primary angle closure glaucoma (PACG)**. In 2012, we reported a genome-wide association study (GWAS) identifying three common genetic variants associated with PACG (Vithana EN et al, Nature Genetics 2012). Three new loci for PACG were identified; rs11024102 at PLEKHA7 (per-allele odds ratio (OR) = 1.22, P = 5.33 x 10-12), rs3753841 at COL11A1 (per-allele OR = 1.20, P = 9.22 x 10-10), and rs1015213 located between PCMTD1 and ST18 on Chromosome 8q (per-allele OR = 1.50, P = 3.29 x 10-9). We also conducted a GWAS underlying anterior chamber depth (ACD), a major risk factor for PACG, on a total of 5,308 population-based individuals of Asian descent. Genome-wide significant association was observed at a sequence variant within ABCC5 (rs1401999; per-allele effect size = - 0.045mm, P = 8.17 x 10-9). This loci was associated with an increase in risk of PACG in a separate case-control study (per-allele OR = 1.30, P = 7.45 x 10-9; 3,458 cases vs. 3,831 controls).

Recently, we conducted a GWAS on almost 1500 patients with **exfoliation syndrome (XFS)** matched to 1200 controls from Japan, and followed up the most significant findings on a further 6,500 patients and 19,000 controls from 17 countries across 6 continents. We discovered a significant association between a new locus on chromosome 19 and increased susceptibility to XFS (Odds ratio [OR] = 1.16, P = 1.25 x 10-10). These findings represent the first genetic locus outside of LOXL1 which surpasses genome-wide significance for XFS, and provides new insights into the biology of the disease.

In this talk, an overview of recent advances in glaucoma genetics will be presented and directions for future research will be discussed, in order for attendees to update their knowledge of this rapidly advancing field. These discoveries are critical toward the future development of gene based screening and novel therapeutic approaches based on molecular genetics.

Commercial Relationships: Tin Aung, None

198: PS2-5

GWAS Success in Ophthalmology

Speaker: David A. Mackey [1] Alex Hewitt [1, 2]

1. Lions Eye Institute, University of Western Australia, Crawley, WA, Australia. 2. Centre for Eye Research Australia, Melbourne, VIC, Australia.

Aim

Much progress in our understanding of the genetic profile of many ophthalmic diseases has been made over the last decade. Identification of novel gene associations allows insight into the mechanisms of disease and potentially enables the identification of individuals at increased risk, as well as facilitating the development of new treatments. We highlight key recent discoveries using the genome-wide association study design.

Recent findings

Over the last 2 years, we have seen major international collaborations successfully conduct genome-wide association study to identify genetic pathways associated with eye diseases, such as myopia, age-related macular degeneration and glaucoma. Similarly other studies have identified and confirmed genes associated with ocular biometry or disease-specific endophenotypes.

Summary

Our understanding of the genetic architecture of common eye diseases, such as myopia, age-related macular degeneration and glaucoma, is rapidly expanding. With reducing costs of next-generation sequencing, we expect a transition to large-scale interrogation at the whole exome and genome level, which will enable the identification of rare variants which confer a level of sensitivity and specificity to predict risk that will allow us to further understand, predict and intervene in genetic-based eye diseases.

Commercial Relationships: David Mackey, None; Alex Hewitt, None

Plenary Session 3
Recent Advances in Retinal Basic Research

Organizers
Shibo Tang
Central South University, Changsha, Hunan, China
Yuichiro Ogura
Nagoya City University, Nagoya, Aichi, Japan

199: PS3-1

Recent Advances in Ocular Neovascular Diseases

Speaker: Xuri Li [1]
1. State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-Sen University, Guangzhou, Guangdong, China.

Recent Advances in Ocular Neovascular Diseases will be discussed

Commercial Relationships: Xuri Li, None
Support: State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, China

200: PS3-2

The mechanism of diabetic retinal edema moderated by cell membrane K + channels in retinal Müller cells in diabetic animals

Speaker: Shibo Tang [1] Wei Sun [2] Tao Li [2]
1. Aier School of Ophthalmology, Central South University, Changsha, Hunan, China. 2. Zhongshan Ophthalmic Center, Sun Yat-Sen University, Guangzhou , China.

This presentation will demonstrate the changes of retinal thickness of STZ-induced diabetic SD rats and the relationship between diabetic retinal edema and Kir4.1 channel in retinal Müller cell, by moderating the Kir 4.1 channel. Kir 4.1 protein measured by Western Bolt and Kir 4.1 immunofluorescence decreased at 12W in diabetic rats. Kir 4.1 protein could be inhibited by Barium chloride and the retina thickness was increased; while Pinacidil (Kir 4.1 openner) could stimulate Kir 4.1 protein. The retina thickness was then decreased in this situation. K+ channel is an important pathway of diabetic retinal (macular) edema.

Commercial Relationships: Shibo Tang, None; Wei Sun, None; Tao Li, None
Support: Natinal Nature Science Grant of China 81170865

201: PS3-3

Molecular control of photoreceptor synapse development

Speaker: Takahisa Furukawa [1,2] Rikako Sanuki [1,2]
1. Laboratory for Molecular and Developmental Biology, Institute for Protein Research, Osaka University, Suita, Osaka, Japan. 2. JST, CREST, Suita, Japan.

In vertebrate retinal development, emergence of the outer and inner plexiform layers (OPL and IPL) is closely associated with cell differentiation and maturation. Differentiating retinal neurons extend their neurites toward each other in a coordinated manner to form the OPL and IPL. Although retinal cell differentiation and maturation have been well investigated, there is little information about mechanisms underlying laminar organization of synaptic termini. Photoreceptor cells develop synaptic connection with bipolar and horizontal cells, leading to distinct OPL formation. We found that 4.1-family protein is highly enriched in photoreceptors and localized to the axon side membrane of photoreceptor cells. We investigated OPL formation process by focusing on 4.1 protein function. Our study shows that 4.1 family protein plays an essential role for proper localization of synaptic terminus formed among photoreceptor, bipolar and horizontal cells. Furthermore, our study novel insight into the mechanism and importance of proper synapse location in neural circuit formation.

Commercial Relationships: Takahisa Furukawa, None; Rikako Sanuki, None
Support: JSt, CREST

202: PS3-4

Blue light stress and retinal responses

Speaker: Motohiro Kamei [1]
1. Department of Ophthalmology, Osaka University School of Medicine, Suita, Osaka, Japan.

Purpose: We have reported that chronic photo-oxidative stress can be induced by long-term, low-intensity blue light irradiation, which resulted in developing a choroidal neovascularization (CNV) in mice, and subsequent inflammation was suggested as causative factors for age-related macular degeneration. We now investigate the retinal responses after low intensity blue light irradiation with different exposure patterns.

Methods: Freely moving 2-month-old C57BL/6N mice were kept under normal environment, 500 Lux continuous or cyclic (1, 2 or 3 days' cycling) blue light for 1 or 3 months. Retinal damage was evaluated by histopathologic examination and TUNEL staining. Microglias infiltration was evaluated by immunohistochemistry of Iba-1 and CD45 on cryo-sections and their numbers were quantified on RPE-choroid flat mounts. Expressions of monocyte chemoattractant protein-1(MCP-1) and Interleukin-6 (IL-6) were examined by immunohistochemistry on cryo-sections and their mRNA levels were quantified by quantitative real-time PCR.

Results: Continuous 500 Lux blue light exposure showed obvious hazard to retina, as evidenced by the progressive thinning of the outer nuclear layer (ONL) in histology ($p<0.01$), while no apparent changes were detected in cyclic exposed mice ($p > 0.05$). TUNEL-positive nuclei were observed in a low level in ONL in cyclic exposed mice and their numbers showed no significant differences among these mice ($p > 0.05$), while in continuous exposed

mice, a significant number of TUNEL-positive nuclei occurred in ONL ($p<0.01$). Sub-retinal microglias increased with exposed time ($p<0.05$), which expressed pro-inflammatory cytokines---IL-6. IL-6 mRNA significantly increased in 1 month's continuous exposed mice and all 3 months' exposed mice. MCP-1 predominantly expressed by RPE, and its mRNA level increased in all exposed mice ($p<0.05$).

Conclusions: Low intensity blue light exposure can induce microglial activation and chronic inflammation. Continuous exposure induced thinning of the ONL even with low intensity. Cyclic exposure of low intensity blue light can induce chronic inflammation without severe retinal damage, which may contribute to elucidate the relation between photic stress and AMD.

Commercial Relationships: Motohiro Kamei, None

Support: Ministry of Education, Culture, Sports, Science and Technology (MEXT) #24592670

203: PS3-5

Receptor-associated prorenin system in the pathogenesis of diabetic retinopathy

Speaker: Susumu Ishida [1]

1. Department of Ophthalmology, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan.

The renin-angiotensin system (RAS), a controller of systemic blood pressure (circulatory RAS), plays distinct roles in inflammation and angiogenesis in organs (tissue RAS). Pharmacological blockade of angiotensin II type 1 receptor (AT1R) inhibited the incidence and progression of diabetic retinopathy (DR) in recent clinical trials. We unraveled the molecular mechanisms in which tissue RAS causes retinal inflammation and the critical roles of (pro) renin receptor [(P)RR] in retinal RAS activation. (P)RR binds with prorenin to exert renin activity through the conformational change of the prorenin (for tissue RAS) instead of the proteolysis of the prorenin prosegment (for circulatory RAS). Furthermore, prorenin binding to (P)RR activates RAS-independent signal transduction. The (P)RR-mediated dual activation of tissue RAS and RAS-independent signaling pathways, referred to as the receptor-associated prorenin system (RAPS), was shown to facilitate vascular endothelial growth factor (VEGF)-driven pathogenesis of non-proliferative DR in mice. We further reported that the intravitreal levels of soluble form of (P)RR [s(P)RR], released from neovascular endothelial cells in fibrovascular tissues, increased in the patients with proliferative DR (PDR) and correlated with vitreous prorenin and VEGF levels. This leads to a novel concept for the molecular pathogenesis of tissue RAS in the vitreous (vitreous RAS). Indeed, renin activity levels significantly increased in PDR eyes compared with controls, and correlated with vitreous levels of s(P)RR, prorenin, activated prorenin and VEGF. These data indicate that the vitreous renin activity stems from s(P)RR-mediated non-proteolytic activation of prorenin, and confirm our recent report on the significant roles of (P)RR in the pathogenesis of PDR. Moreover, (P)RR and RAS components were expressed in diabetic fibrovascuar tissues and human retinal cell lines, and the vitreous levels of prorenin and angiotensin II were shown to be elevated in PDR eyes. Importantly, the close link between the vitreous renin activity and VEGF levels validates the pathological concept of vitreous RAS that contributes to the angiogenic activity of DR. Accordingly, in concert with retinal RAPS due to membrane-type (P)RR, vitreous RAS due to s(P)RR is thought to regulate VEGF expression.

Commercial Relationships: Susumu Ishida, None

204: PS3-6

Neuroprotection against oxidative stress in the retina

Speaker: Yoko Ozawa [1, 2]

1. Department of Ophthalmology, Keio University School of Medicine, Shinjuku, Tokyo, Japan. 2. Laboratory of Retinal Cell Biology, Keio University School of Medicine, Tokyo, Japan.

Oxidative stress contributes to the visual function impairment due to the retinal neural degeneration caused by retinal diseases, such as age-related macular degeneration and diabetic retinopathy. Now, to explore the new therapeutic approaches, underlying mechanisms of the pathogenesis should be clarified. In the talk, contribution of oxidative stress in the molecular systems of the retinal neurodegeneration is discussed.

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)

Plenary Session 4
Normal Tension Glaucoma Update

Organizers

Kazuhisa Sugiyama
Kanazawa University Graduate School of Medical Science, Kanazawa, Ishikawa, Japan
Jost B. Jonas
Medical Faculty Mannheim, University Heidelberg, Heidelberg, Germany
Goji Tomita
Toho University Ohashi Medical Center, Meguro, Tokyo, Japan

205: PS4-1

Disc Hemorrhage and NTG

Keynote Speaker: Ki Ho Park [1]
1. Department of Ophthalmology, Seoul National University, Jongno-gu, Seoul, Korea (the Republic of).

The association between optic disc hemorrhage and glaucoma has been studied for many years. Recently, randomized clinical trials have confirmed that disc hemorrhage is a risk factor for development and progression of glaucoma. Disc hemorrhage is more commonly detected in open-angle glaucoma with normal tension than in open-angle glaucoma with high tension. Development of disc hemorrhage possibly is associated with the biomechanical properties of the lamina cribrosa and surrounding tissues, including the intraocular pressure (IOP)-cerebrospinal pressure difference, arterial pressure, and venous pressure.
Disc hemorrhage may be a marker of rapid glaucoma progression, in that localized subclinical structural change predisposes to disc hemorrhage, after which subsequent disease progression is accelerated, and recurrent optic disc hemorrhages are related to rapid structural progression of glaucomatous damage. IOP-lowering therapy can be helpful in halting post-hemorrhage glaucoma progression.
Commercial Relationships: Ki Ho Park, None

206: PS4-2

Clinical feature of primary open-angle glaucoma with myopia

Speaker: Kazuhisa Sugiyama [1]
1. Department of Ophthalmology & Visual Science, Kanazawa University Graduate School of Medical Science, Kanazawa-shi, Ishikawa, Japan.

Primary open-angle glaucoma (POAG) including normal-tension glaucoma (NTG) with myopia, so-called myopic glaucoma, may have both myopic changes and glaucomatous changes, and it is often difficult to clearly distinguish these two pathological changes.
Optical coherence tomography (OCT) imaging of optic nerve head and macula has been widely used in recent years to detect and monitor glaucoma. Myopic glaucoma often demonstrates thinning of macular ganglion cell complex (retinal nerve fiber layer + retinal ganglion cell layer + inner plexiform layer) in the papillo-macular bundle using OCT. Myopic glaucoma patients seem to be susceptible to a visual field defects near the fixation point. The rate of visual field loss progression in POAG patients without myopia was significantly faster than those with high myopia.
Myopic disc changes often demonstrate deformation of lamina cribrosa due to elongation of peripapillary sclera in the X-Y direction by OCT imaging. On the other hand, structural changes in non-myopic glaucomatous eyes are thought to occur due to the pressing force on the lamina cribrosa in the Z direction. Significant lower incidence of disc hemorrhage in myopic glaucomatous eyes was reported as compared to non-myopic glaucomatous eyes. The difference of structural changes in lamina cribrosa between myopic and non-myopic glaucoma may affect the frequency of disc hemorrhage and rate of visual field deterioration.
Myopic glaucoma may have less progressive myopic optic neuropathy in addition to progressive glaucomatous optic neuropathy. As a result, myopic glaucoma may be less progressive visual field damage and less frequent occurrence of disc hemorrhage as compared with non-myopic POAG.
Commercial Relationships: Kazuhisa Sugiyama, None

207: PS4-3

Application of optical coherence tomography in glaucoma management

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

The advent of optical coherence tomography (OCT) has facilitated high resolution imaging of the retinal nerve fiber layer and optic nerve head, providing information relevant to risk assessment, diagnosis and monitoring of glaucoma. Longitudinal studies have demonstrated that progressive optic nerve head changes precede the development of identifiable visual field loss in glaucoma patients. Optic nerve head deformation detected by OCT may well serve as an early biomarker for disease deterioration behavior and that a time window may be available for therapeutic intervention in many patients upon detection of structural optic nerve head changes, before further loss of the visual field and retinal nerve fiber.
Commercial Relationships: Christopher Leung, Carl Zeiss Meditec (F), Tomey (F), Carl Zeiss Meditec (R), Tomey (R)

208: PS4-4

Genetics in normal tension glaucoma

Speaker: Kazuhiko Mori [1]
1. Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto, Japan.

Progress in genetics after Hap map project influenced the

evolution of genome-wide association studies (GWAS) in ophthalmological research field. The discovery of CFH for macular degeneration and LOXL1 for pseudo exfoliation glaucoma was a good example of this success, which was conducted by means of GWAS. Since then, lots of GWAS have been conducted to search for the associated SNPs in primary open angle glaucoma (POAG). Our group also conducted several GWASs for POAG, and clarified the *CDKN2B-AS1* to be mainly associated with normal tension glaucoma.

In this symposium, I would like to overview the background and progress of recent genetics in primary open angle glaucoma including normal tension glaucoma

Commercial Relationships: Kazuhiko Mori, Ocular Instruments (P), Santen (P)

209: PS4-5

Lamina cribrosa in normal tension glaucoma

Speaker: Tae-Woo Kim [1, 2]

1. Department of Ophthalmology, Seoul National University College of Medicine, Jongno-gu,, Seoul, Korea (the Republic of). 2. Seoul National University Bundang Hospital, Seongnam, Korea (the Republic of).

Many of glaucoma patients have normal intraocular pressure. Although clinical studies demonstrated the beneficial effect of intraocular pressure lowering treatment in normal tension glaucoma (NTG) patients, it still remains unclear whether mechanical stress plays a major role in all NTG patients. In addition, there is no method to differentiate NTG patients depending on the pathogenesis (i.e., pressure-dependent or independent).

Previous experimental studies have demonstrated that lamina cribrosa (LC) may be displaced posteriorly after IOP elevation. In line with this finding, recent imaging studies using enhanced depth imaging spectral domain optical coherence tomography (EDI-OCT) have shown that LC displacement might be reversed after IOP-lowering treatment and this reversed LC may be re-displaced in eyes with increased IOP during long-term follow-up. These data together suggest that the LC position is largely dependent upon IOP-derived stress.

Based on the above findings, we hypothesized that assessment of the LC depth in glaucomatous eyes may provide an index for evaluating the magnitude of associated mechanical stress in glaucomatous eyes. Under this hypothesis, our group has measured the LC depth, LC insertion distance both of which are likely associated with mechanical stress given to the ONH. We have found that NTG eyes have deeper LC depth and longer LC insertion distance from the anterior scleral opening level compared to normal healthy eyes. This finding indicates that NTG eyes do suffer from IOP-related mechanical stress. However, there was a substantial overlap in both parameters among healthy controls and NTG eyes, suggesting that the mechanical stress may not be substantial in certain portion of NTG patients. The meaning of these findings and future perspective will be discussed.

Commercial Relationships: Tae-Woo Kim, Topcon (C), Santen (R), Alcon (R), Allergan (R), Pfizer (R)

Support: National Research Foundation of Korea Grant funded by Korean Government (2013R1A1A1A05004781)

210: PS4-6

Blood flow abnormality of optic nerve head in NTG

Speaker: Toru Nakazawa [1]

1. Department of Ophthalmology, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan.

Glaucoma is characterized by optic nerve fiber atrophy and deterioration of the visual field, corresponding to damage to the optic nerve head. The only Evidence-Based, treatable risk factor for open angle glaucoma (OAG) is intraocular pressure (IOP). However, the most common type of OAG in Asia is normal tension glaucoma (NTG), a type of the disease with an unclear pathogenesis. NTG is suspected to be multifactorial and to have IOP-dependent and -independent risk factors, including decreased blood flow, oxidative stress, decreased axoplasmic flow, inflammation, and genetic background. In particular, a number of epidemiological studies have gathered a strong body of evidence suggesting that ocular blood flow is an important potential risk factor for NTG. However, research has been hampered by the lack of instruments capable of easily and reproducibly measuring ocular blood flow.

Recent innovations in laser speckle flowgraphy (LSFG) have allowed us to monitor changes in the microcirculation of the optic nerve head with high reproducibility and speed; LSFG needs only 4 seconds to obtain measurements of NTG patients. LSFG measures mean blur rate (MBR), a parameter obtained from composite maps of blood flow averaged from a single heartbeat, and can provide other blood flow parameters through waveform analysis. Our findings with LSFG have shown that decreased MBR is associated with the severity of glaucoma, and that MBR is significantly correlated with OCT parameters of retinal thickness. Additionally, waveform analysis has enabled us to evaluate the quality of blood flow. Interestingly, we found that changes in LSFG parameters were detectible even in the preperimetric stage of NTG, providing evidence of incipient visual field loss.

In this lecture, we will review recent findings on the role of ocular blood flow in the pathogenesis of NTG and introduce our latest LSFG data on decreased microcirculation in the optic nerve head of eyes with NTG. Thus, we would like to discuss the role of ocular blood flow as an IOP-independent risk factor for patients with NTG, the major type of OAG in Asia.

Commercial Relationships: Toru Nakazawa, None

211: PS4-7

Comparison of visual field defects between HTG and NTG

Speaker: Takeo Fukuchi [1]

1. Division of Ophthalmology and Visual Science, Graduated School of Medical and Dental Sciences, Niigata University, Niigata, Niigata, Japan.

Purpose: To compare visual field defects between high tension glaucoma (HTG) and normal tension glaucoma (NTG). **Methods**: 315 eyes from 315 Japanese treated Open angle glaucoma patients were examined. The mean

deviation, upper and lower total deviation slopes (MDS, UTDS, LTDS) of the Humphrey Field Analyzer were calculated. The cases were classified into 2 groups, HTG (>21 mmHg) and NTG (≦ 21mmHg) by pretreated initial IOP. In addition, the correlation between the MDS and follow-up IOP were examined by HTG and NTG. **Results:** While the average MDS was -0.42 ± 0.50 dB/yr, the average UTDS was -0.42 ± 0.50 dB/yr and the average LTDS was -0.33 ± 0.54 dB/yr. In comparison between HTG and NTG, the UTDS was similar each other but the MDS and LTDS in HTG were lower than those of NTG statistical significantly. The correlation line between the MDS and follow-up IOP was statistically significant in HTG, but not in NTG. The fast progressive group has older patients' age, longer follow-up period, higher mean, highest and lowest IOPs and smaller mean IOP reduction in HTG, and longer follow-up period, larger standard deviation of the mean IOP and larger range of IOP, and higher highest IOP in NTG by comparison with the slow progressive group. **Conclusions**: The progressive rate in lower visual field in HTG might faster than that of NTG. The eyes with faster visual field progression might have the higher follow-up IOP in HTG and the larger IOP fluctuations in NTG.

Commercial Relationships: Takeo Fukuchi, None

212: PS4-8

Pressure relationships in glaucomatous optic neuropathy

Speaker: Jost B. Jonas [1] Ningli Wang [2] Diya Yang [3]

1. Department of Ophthalmology, Medical Faculty Mannheim, University Heidelberg, Heidelberg, Germany. 2. Capital Medical University, Beijing Ophthalmology & Visual Sciences Key Laboratory, China, Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Beijing, China. 3. Capital Medical University, Beijing Ophthalmology and Visual Sciences Key Laboratory, Beijing, China , Beijing Tongren Eye Center, Beijing Tongren Hospital, Beijing, China.

The orbital cerebrospinal fluid pressure (CSFP) represents the true counter-pressure against the intraocular pressure (IOP) across the lamina cribrosa and is, therefore, one of the two determinants of the trans-lamina cribrosa pressure difference (TLCPD). From this anatomic point of view, an elevated TLCPD could be due to elevated IOP or abnormally low orbital CSFP. Both experimental and clinical studies have suggested that a low CSFP could be associated with glaucomatous optic neuropathy in normal-pressure glaucoma. These included monkey studies with an experimental long-term reduction in CSFP, and clinical retrospective and prospective studies on patients with normal-pressure glaucoma. Since the choroidal blood drains via the vortex veins through the superior ophthalmic vein into the intracranial cavernous sinus, anatomy suggests that the CSFP could influence choroidal thickness. A population-based study revealed that thicker subfoveal choroidal thickness was associated with higher CSFP. Since the central retinal vein passes through the orbital CSF space, anatomy suggests that the retinal venous pressure should be at least as high as the orbital CSFP. Other experimental, clinical or population-based studies suggested an association between higher CSFP and higher retinal venous pressure and wider retinal veins. Consequently, a higher estimated CSFP was associated with arterial hypertensive retinopathy (with respect to the dilated retinal vein diameter and higher arterial-to-venous diameter) and with the prevalence, severity and incidence of diabetic retinopathy. Physiologically, CSFP was related with higher IOP. The influence of the CSFP on the episcleral venous pressure and / or a regulation of both CSFP and IOP by a center in the dorsomedial/perifornical hypothalamus may be responsible for this. In summary, the CSFP may be an overlooked parameter in ocular physiology and pathology. Abnormal changes in the CSFP, in particular in relationship to the IOP, may have pathophysiologic importance.

Commercial Relationships: Jost Jonas, Allergan Inc (C), Merck Sharp & Dohme Co., Inc (C), Alimera Co (C), Boehringer Ingelheim Co., (C), Sanofi Co (C), Pfizer Co (C), CellMed AG, Alzenau, Germany (P); Ningli Wang, None; Diya Yang, None

Plenary Session 5
Updates on Standardized Classifications/Severity Scales of Ocular Diseases: a Key for Successful Clinical Research

Organizers
Mingguang He
Sun Yat-sen University, Guangzhou, Guangdong, China
Shih-Jen Chen
Taipei Veterans General Hospital, Taipei, Taiwan

213: PS5-1

Standardized classifications and severity scales of dry eye

Speaker: Kyoung Yul Seo [1] Ji Won Jung [1]
1. Department of Ophthalmology, Yonsei University College of Medicine, Seodaemun-gu, Seoul, Korea (the Republic of).

To validate and review the standardized classifications and severity scales of dry eye, candidate scales are NEI/Industry Workshop classification, the report of the Delphi panel, and 2007 report of the international dry eye workshop (DEWS).
We also review the classification and stage of meibomian gland dysfunction (The international workshop on meibomian gland dysfunction) and the measurement scales for ocular chronic graft-versus-host disease such as the NIH eye scores.
The correlations are evaluated between the classification and severity scales and the concentration of inflammatory tear cytokines.
Commercial Relationships: Kyoung Yul Seo, None; Ji Won Jung, None

214: PS5-2

Standardized classifications and severity scales of myopia and myopic retinopathy

Speaker: Seang-Mei Saw [1]
1. National University of Singapore, Singapore, Singapore.

Myopia is a very important public health problem worldwide and there are several clinical definitions of myopia including SE worse than -0.5 D, SE worse than -0.75 D and -1.0 D. Our study of SCORM children has shown that the definition of SE worse than -0.75 D has the highest accuracy denoted by the Area under the Curve to detect reduced unaided vision due to myopia. Moderate myopia has been defined in the SCORM study as SE worse than -3.0 D. As for high myopia, common definitions include SE worse than -5.0 D, -6.0 D, -8.0 D and -10.0 D. High myopia in adults is associated with visually-disabling pathologic myopia complications. Definitions of myopia include the Avila and Curtin definitions. However, a recent meta-PM international consortium of worldwide studies with fundus photographs graded for pathologic myopia lesions has developed a new "Meta-PM" pathologic myopia classification. There were 5 categories of myopic maculopathy including "no myopic retinal degenerative lesion" (Category 0), "tessellated fundus" (Category 1), "diffuse chorioretinal atrophy" (Category 2), "patchy chorioretinal atrophy" (Category 3), and "macular atrophy" (Category 4). Three additional supplemental features defined as "plus" lesions, namely, lacquer cracks (Lc), myopic choroidal neovascularization (myopic CNV), Fuchs' spot (Fs). Posterior staphyloma (St) was considered as supplemental information. The development of standardized myopia classifications will allow comparisons across studies.
Commercial Relationships: Seang-Mei Saw, None

215: PS5-3

Standardized classifications and severity scales of cataract

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

Cataract grading systems are mainly applied to investigate prevalence, incidence and progression of age-related cataracts and the risk factors are evaluated in epidemiological studies. Cataract grading systems are also used in clinical trials to evaluate the effect of drugs on cataract. Since they are used in clinical practice, it is important that there is a good correlation between cataract grade and visual function.
At present, several grading systems are utilized, including the Oxford Clinical Cataract Classification and Grading System (1986), the Wilmer Cataract Grading System (1988), the Lens Opacities Classification System III (LOCS III) (1993), the Wisconsin Cataract Grading System (1997), the AREDS System for Classifying Cataract (2001), and the WHO Cataract Grading System (2002).
In this symposium, comparison of the above classification systems and an ideal classification system will be discussed.
Commercial Relationships: Hiroshi Sasaki, None

216: PS5-4

Standardized classifications and severity scales of glaucoma

Speaker: Mingguang He [1,2] Xinxing Guo [1]
1. Department of Preventive Ophthalmology Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, Guangdong, China. 2. Centre for Eye Research Australia, University of Melbourne, Melbourne, VIC, Australia.

Glaucoma is a condition in which both structural and functional damage of the retinal ganglion cells are observed, it is the leading cause of irreversable blindness and second leading cause of avoidable blindness in the world. Early detection of the onset and progression of glaucoma and optimal treatment remain the fundamental

goals in the effort to reduce visual disability. This talk reviews the available classifications and severity scales of glaucoma and explores the feasibility in clinical decision making and colleagues communication according to these systems.

Commercial Relationships: Mingguang He, None; Xinxing Guo, None

217: PS5-5

Standardized classifications and severity scales of diabetic retinopathy and age-related macular degeneration

Speaker: Shih-Jen Chen [1,2]

1. Department of Ophthalmology, Taipei Veterans General Hospital, Taipei, Taiwan. 2. School of Medicine, National Yang-Ming University, Taipei, Taiwan.

Since 90% of the visual loss in patients with diabetic retinopathy (DR) can be prevented, it is very important to classify and stage the severity of DR in order to say the same language between the retinal specialists, general ophthalmologists and internist to establish adequate therapy. Classification of diabetic retinopathy was proposed early in the Airlie House symposium in 1968 and then modified by the Early Treatment Diabetic Retinopathy Study (ETDRS). Although this classification was well established with clinical validation, the complexity of the stereo pairs of 7 fields' photographs and multiple grading levels had limit its use in clinics. The international Clinical Disease Severity Scale of DR and diabetic macular edema (DME) was developed and simplified the DR to 5 stages and DME to 3 stages. This classification was widely used today with standard sample photographs. Although still not in consensus for its grading on DME, the optical coherent tomography (OCT) had been a must tool in today's treatment with anti-VEGF. The Wisconsin age-related maculopathy grading system and then the international classification of age-related macular degeneration (AMD), proposed 20 years ago, had made our nomenclature of AMD more universal, screening tool sampler, and data more comparable in the epidemiological studies. Yet the tool, the methods, and the way we looked at our data evolved. Based on these fine classification of drusen, pigment change, geographic atrophy, and neovascularization in every aspect of size, location, area, consistency, and accompanied lesions, the clinical cohort studies of age-related eye disease study (AREDS) had incorporated the status of both eyes of each individual and simplified the clinical classification of AMD according to the drusen size and pigment into 9-step severity scale. Adding the known environmental and genetic risk factors, studies of model in predicting progression of AMD had further shaped the classification of AMD into 5 stages. However, in Asia, there is no consensus on classification of AMD secondary to the prevalent polypoidal choroid vasculopathy. This talk will bring up the history, the present and the future for the classification of DR and AMD.

Commercial Relationships: Shih-Jen Chen, None

Plenary Session 6
Recent Trends in Regenerative Medicine

Organizers
Kohji Nishida
Osaka University Graduate School of Medicine, Suita, Osaka, Japan
Scheffer C. Tseng
TissueTech, Inc., Miami, FL, United States

366: PS6-1

Reprogramming by a Novel Matrix Component HC-HA/PTX3 Purified from Amniotic Membrane

Keynote Speaker: Scheffer C. Tseng [1, 2]
1. R&D Department, TissueTech, Inc., Miami, FL, United States. 2. Ocular Surface Center, Miami, FL, United States.

For more than two decades the surgical procedure of amniotic membrane transplantation has been accepted as a standard procedure for ocular surface reconstruction to deliver anti-inflammatory, anti-scarring, and anti-angiogenic actions to promote epithelial wound healing. For the last decade, we and others have reported that HC-HA/PTX3, which is a novel matrix component that can be biochemically purified from the amniotic membrane as the key component responsible for amniotic membrane's anti-inflammatory, anti-scarring, and anti-angiogenic actions. The HC-HA/PTX3, a complex formed by a covalent linkage between hyaluronan (HA) and HC1 of inter- α -trypsin inhibitor via the catalytic action of TSG-6 is further strongly associated with octomeric PTX3. Our recent research further demonstrated that HC-HA/PTX3 is capable of exerting a potent reprogramming effect of adult differentiated cells. Specifically, our results showed that immobilized HC-HA/PTX3 can, but immobilized HA cannot, reprogram human corneal fibroblasts to neural crest progenitors. In the absence of TGF- β 1, human corneal fibroblasts aggregated on immobilized HC-HA/PTX3 but not HA, and upregulated expression of keratocan and CD34, markers of keratocytes. In the presence of TGF- β 1, human corneal fibroblasts differentiated into myofibroblasts with upregulation of α -SMA and nuclear translocation of pSmad2/3, suggesting the activation of canonical TGF- β signaling when cells were cultured on plastic with or without immobilized HA. In contrast, aggregated human corneal fibroblasts aborted myofibroblast differentiation together with suppression of canonical TGF- β signaling as a result of downregulation of TGF β RII and TGF- β 1 and upregulation of TGF- β 3. Surprisingly, the aforementioned anti-scarring effect of HC-HA/PTX3 was accompanied by upregulation of markers of embryonic stem cells and neural crest progenitors. Such reprogramming was mediated by upregulation of canonical BMP signaling with nuclear translocation of pSmad1/5/8, upregulation of BMP2, 4 and 6, upregulation of BMPR1A, 1B and II, and downstream target genes such as ID1-4. Such reprogramming was further substantiated by demonstrating that the resultant neural crest progenitors could then be differentiated into corneal endothelium. We further gather strong data to show that immobilized HC-HA/PTX3 could also induce such reprogramming of myofibroblasts derived from human conreal fibroblasts after being exposed to TGF- β 1. Collectively, for the first time, our studies show that HC-HA/PTX3 is a unique matrix component from amniotic membrane that can reprogram differentiated/degenerated adult somatic cells without the use of transcription factors.

Commercial Relationships: Scheffer Tseng, TissueTech (E), TissueTech (P)
Support: NIH, NEI, RO1 EY06819, R43/44 EY017497, EY021045, and EY022502

367: PS6-2

Development of stem cell-based therapy for corneal diseases-from tissue stem cell to iPS cell

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

The presentation will cover the recent progress of stem cell therapy for corneal diseases

Commercial Relationships: Kohji Nishida, None

368: PS6-3

Ocular Surface Transplantation: Yesterday, Today & Tomorrow

Speaker: Kenneth Kenyon [2, 1]
1. Harvard Medical School, Boston, MA, United States. 2. Tufts Medical School, Boston, MA, United States.

Although ocular surface transplantation began over 40 years ago with initiation of conjunctival autograft transplantation, predominantly for uniocular chemical injury, it was the recognition of the limbal stem cell (LSC) in the early 1980's which stimulated both definition of LSC deficiency conditions and development of conjunctivo-limbal autograft (CLAU) transplantation. These initial discoveries subsequently evolved to include the kerato-limbal allograft (KLAL) procedure and its variations. Current extensions involve *ex vivo* limbal epithelial transplantation (CLET) and cultured oral mucul membrane transplantation (COMET) to reduce surgical exposure and broaden autologous stem cell sources. Future developments of modified pluripotent LSC and substrates are extremely promising. Such historical perspective affords a sense of exceptional progress commencing with proof of the LSC concept, its extension into expanded sources and improved clinical results, and the impending promise of innovative bioengineering for ocular surface rehabilitation.

Commercial Relationships: Kenneth Kenyon, None

369: PS6-4

Tissue Stem Cells and Pluripotent Stem Cells in Regeneration of the Cornea

Speaker: Shigeto Shimmura [1]

1. Department of Ophthalmology, Keio University School of Medicine, Shinjuku, Tokyo, Japan.

The cornea consists of the epithelium, stroma and endothelium, all of which contain unique cells that are vital for the homeostasis of the cornea. Stem cells for generating all 3 layers of the cornea have been reported both in mice and humans, and studies to apply these cells to the clinic are underway.

Transplantation of cultivated epithelial sheets is an established method for regenerating damaged skin epithelium and corneal epithelium. Both allogeneic donor-derived cells and autologous cells have been used to produce the transplantable epithelial cell sheets. However, since Yamanaka et. al. successfully developed induced pluripotent stem (iPS) cells from somatic cells by forced reprogramming using the transcriptional factors OCT4, SOX2, c-MYC, and KLF4, these pluripotent stem cells have become the focus of intense study. Clinical application of stem cells in the treatment of corneal disease will probably involve both somatic stem cells and iPS cells depending on the disease. For example, since the anterior chamber is an immunologically priviledged site, developing cell therapies from allogeneic pluripotent stem cells (iPSCs) may be less of a challenge compared to other organs. Producing large quantity of iPSC-derived endothelium from a safety-certified iPS clone may reduce therapeutic cost, while solving the problem of donor shortage worldwide. Current developments will be introduced and discussed.

Commercial Relationships: Shigeto Shimmura, US Patent 14/349,961 (P)

Support: Highway Program for Realization of Regenerative Medicine of the Ministry of Education, Culture, Sports, Science and Technology, Japan

370: PS6-5

Retinal regeneration therapy for retinal degenaration using ES/iPS derived retinal tissue

Speaker: Michiko Mandai [1]

1. Laboratory for Retinal Regeneration, RIKEN Center for Developmental Biology, Kobe, Hyogo, Japan.

Now with the introduction of 'self organizing differentiation' of many parts of the body from ES/iPS cells, the transplantation of differentiated retinal tissue emerged as one possible therapeutic strategy for end stage retinal degeneration. We could efficiently and repeatedly differentiate retinal tissues from both mouse ES and iPS cells with an optimized protocol. Further, younger tissues corresponding to the developmental stage of embryonic day 17 or younger subsequently developed structured photoreceptor layers after transplantation with good efficiency even in the severly degenerated host environment. These structured grafts could also develop outer segments with strong rhodopsin expression, indicating the full maturation of transplanted photoreceptors. These photoreceptors in the structured graft were also suggested to form a synaptic contact with host bipolar cells by 3-D immunohistochemical observation. These suggest a possible use of ES/iPS derived retinal tissue for transplantation therapy in retinal degeneration.

Commercial Relationships: Michiko Mandai, None

Support: Centers for Clinical Application Research on Specific Disease/Organ(Type A)

371: PS6-6

Transplantation of Autologous induced Pluripotent Stem Cell-Derived Retinal Pigment Epithelium Cell Sheets for Exudative Age Related Macular Degeneration : A Pilot Clinical Study

Speaker: Yasuo Kurimoto [2, 1]

1. Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan. 2. Institute of Biomedical Research and Innovation, Kobe, Japan.

We started an open-label study of the transplantation of autologous induced pluripotent stem (iPS) cell-derived retinal pigment epithelium cell sheets in patients with exudative age-related macular degeneration. Recently, we have carried out the first ever iPS cell-based transplantation successfully. The primary outcome to be assessed in this study is the safety of the intervention.

In this presentation, I will show the significances and practical details of the ongoing trial.

Commercial Relationships: Yasuo Kurimoto, None

Support: Health Labour Sciences Research Grant

Clinical Trail: UMIN000011929

372: PS6-7

Gene Transfer Driven Regenerative Medicine Approaches For Corneal Endothelial Disorders

Speaker: Rajiv R. Mohan [1, 2]

1. Mason Eye Institute and Vet Med Surgery, University of Missouri-Columbia, Columbia, MO, United States. 2. Ophthalmic Research, Harry S Truman Veterans Memorial Hospital, Columbia, MO, United States.

The development of regenerative medicine for corneal endothelial disorders requires efficacious and safe methods for introducing genes into corneal endothelium *in vitro* and *in vivo*. We established protocols by which genes could be delivered safely and efficiently into corneal endothelial cells *in vitro* and *in vivo* using various AAV serotypes (5, 6, 8 and 9) and nanoparticles, green fluorescent protein (GFP) gene, donor human cornea, C57black mice, and human corneal endothelial cells (HCE). Two microliters of vector were introduced into anterior chamber of the mouse eye utilizing a customized technique that employs Hamilton microinjection syringe system. The amount and area of delivered transgene was quantified by immunofluorescence, ELISA, and qPCR techniques, and the toxicity of vector to HCE was determined with commercial kits measuring change in cellular proliferation, viability, mitochondrial membrane potential, reactive

oxygen species production, and superoxide dismutase and glutathione peroxidase activities. Slitlamp biomicroscopy evaluated the toxic ocular effects of the vector *in vivo*. The combination of vector and delivery techniques led to development of 5 methods to express desired levels of transgene into corneal endothelium *in vitro* or *in vivo*, ranging from 5% to 48% with minimal toxicity. The AAV-based methods provided significantly high and long-term transgene expression, which started on day-3, peaked on day-7 and was detected throughout the 6 months test period without adverse effects. The nanoparticle-based methods showed first transgene expression at 6h, peak levels from 24h to day-10, gradual decline from day-11, and complete disappearance on day-14. Over 90% transgene delivery was into corneal endothelium and 2-10% into iris and trabecular meshwork of the mouse eye *in vivo* by all methods. None of the tested vector methods altered cellular proliferation, viability, total reactive oxygen species stress, mitochondrial membrane potential, and superoxide dismutase and glutathione peroxidase activities significantly. Slit-lamp biomicroscopy revealed no significant inflammation, redness, or opacity in vector-applied mouse eyes.

Commercial Relationships: Rajiv Mohan, None
Support: National Eye Institute, NIH RO1EY17294, Veterans Health Administration Merit Award 1I01BX000357, and Ruth M. Kraeuchi Missouri Endowment Fund

Plenary Session 7
Cell Biology and Pathology of EMT

Organizers
John McAvoy
University of Sydney, Sydney, NSW, Australia
Choun-Ki Joo
College of Medicine, The Catholic University of Korea, Seocho, Seoul, Korea (the Republic of)
Tetsuro Oshika
Faculty of Medicine University of Tsukuba, Tsukuba, Ibaraki, Japan

373: PS7-1

Understanding normal lens cell differentiation processes – will this help prevent PCO and promote lens regeneration after cataract surgery?

Keynote Speaker: John McAvoy [1] Yuki Sugiyama [1] Lucy Dawes [1] Frank J. Lovicu [1]
1. Save Sight Institute, University of Sydney, Sydney, NSW, Australia.

Purpose: During morphogenesis cells become organized into a polarized, spheroidal structure with a monolayer of epithelial cells overlying the apical tips of elongated fiber cells. During growth, epithelial cells proliferate and progeny that shift below the lens equator elongate into new fibers that become polarised/oriented towards the epithelium and undergo directed migration to the poles. This study set out to investigate interactions between epithelial cells and fiber cells in order to better understand mechanisms that underlie their assembly into a polarised spheroidal structure.
Methods: Lens epithelial explant and knockout mouse models were used to study the role of Wnt-Frizzled/Planar Cell Polarity (Wnt-Fz/PCP) signaling in coordinating the directed behavior and ordered assembly of lens fibers.
Results: In explants, FGF -induces epithelial cells to differentiate into fibers and this involves upregulation of Wnt-Fz signaling components. This is accompanied by translocation of Fz and the centrosome/primary cilium to the leading edge (apical tip) of similarly polarised groups of elongating fiber cells that orient towards islands of epithelial cells. Studies with cilia knockout mice indicate that primary cilia have no role in regulating this polarized/oriented behavior; however, evidence from explant studies indicates that this behaviour is in response to epithelial-derived Wnt5A. Explant studies have also revealed a reciprocal interaction where elongated fibers promote proliferation of the associated epithelial cells and recapitulate the Jagged/Notch signaling that has been previously reported to be required for maintaining a proliferating pool of epithelial cells in the lens.
Conclusions: This provides key insights into an FGF-activated mechanism intrinsic to the lens that involves interactions between the Wnt-Fz and Jagged/Notch signaling pathways. This recipriocal epithelial-fiber cell interaction appears to be critical for the assembly and maintenance of the highly ordered three-dimensional architecture that is central to lens function. This information is fundamental to defining the specific conditions and stimuli needed to recapitulate developmental programs and promote regeneration of lens structure and function after cataract surgery.
Commercial Relationships: John McAvoy, None; Yuki Sugiyama, None; Lucy Dawes, None; Frank Lovicu, None
Support: NEI grant, R01EY003177

374: PS7-2

Regulation of RTK signaling in TGF β -induced EMT leading to cataract

Speaker: Frank J. Lovicu [1] Magdalena Wojciechowski [1] Guan Nan Zhao [1] John McAvoy [2]
1. Discipline of Anatomy & Histology Bosch Institute and Save Sight Institute, University of Sydney, Sydney, NSW, Australia. 2. Save Sight Institute, University of Sydney, Sydney, NSW, Australia.

Ocular-derived growth factors play very important roles in lens biology, regulating the normal cellular processes that contribute to lens development, growth and transparency. Many of these growth factors mediate their cell signaling (e.g. Ras-ERK/MAPK) via receptor tyrosine kinases (RTKs), which in turn need to be tightly regulated. Members of the Sef, Sprouty (Spry) and Spred gene families are negative regulators of such pathways and are normally expressed in the lens. Our studies implicate these antagonistic molecules in regulating normal lens cellular processes, and more recently they have been implicated in preventing cataractogenesis. Aberrant changes in lens epithelial cell behavior may lead to an epithelial-to-mesenchymal transition (EMT) that contributes to many forms of fibrotic cataract, including anterior/posterior polar cataracts as well as posterior capsular opacification (PCO). Transforming growth factor β (TGF β) has been shown to induce this EMT, resulting in cataract. We have employed both in vitro (lens epithelial explants) and in vivo (transgenic mice) models to better characterize the mechanisms involved in TGF β -induced EMT leading to cataract. Overexpressing or conditionally deleting Spry in lens cells compromised the integrity of the lens epithelium leading to aberrant TGF β -signaling, EMT and cataract formation. Here we demonstrate how deregulation of these antagonistic molecules influences cellular signaling, promoting the normal lens structure and function, in the process preventing lens pathology.
Commercial Relationships: Frank Lovicu, None; Magdalena Wojciechowski, None; Guan Nan Zhao, None; John McAvoy, None
Support: NHMRC, Australia

375: PS7-3

Transforming growth factor- β induced cytoskeletal rearrangement during epithelial-mesenchymal transition

Speaker: Young Sik Yoo [1] Jong Hwa Jun [1] Choun-Ki Joo [1]
1. Catholic Institute for Visual Science College of Medicine, The Catholic University of Korea, Seoul, Korea (the Republic of).

Transforming growth factor- β (TGF- β) is a multifunctional cytokine that plays a central role during epithelial-mesenchymal transition (EMT) in both lens epithelial cells and retinal pigment epithelial cells. During the EMT, a variety of signaling pathways are activated in these cells, and distinct changes from an epithelial phenotype to a fibroblastoid appearance occur. These changes include cytoskeletal alterations, which are structural modifications that are crucially related to important cellular signaling mechanisms, particularly the regulation of Rho and its downstream effectors that mediate crosstalk with other signaling pathways. In addition, focal adhesion complexes that are connected with cell structural molecules, e.g., actins, contribute to changes in cell morphology during the EMT. In ocular cells, the cytoskeletal changes related to these signaling pathways contribute to ocular pathophysiology and could be potential therapeutic EMT targets.

Commercial Relationships: Young Sik Yoo, None; Jong Hwa Jun, None; Choun-Ki Joo, None

376: PS7-4

Extracellular matrix modulation of TGFb/Smad signaling in EMT

Speaker: Kumi Shirai [1] Shizuya Saika [1]
1. Department of Ophthalmology, Wakayama Medical University, Wakayama, Wakayama, Japan.

Post-cataract surgery fibrosis in lens capsule (PCO), and anterior subcapsular cataract (ASC), are both accompanied with epithelial-mesechymal transition (EMT) of lens epithelium. Prominent features of EMT-related fibrotic lesion in PCO or ASC is the presence of myofibroblasts and accumulation of extracellular matrix (ECM) secreted by the cells. ECM in PCO or ASC contains major fibrous components, i. e., collagen types I and III as well as a number of minor components, i. e., osteopontin and tenascin family members or lumican. Transforming growth factor b (TGFb) -activated Smad signaling plays a critical role in mediating EMT-inducing processes among TGFb signaling cascades. Here we will present the data that indicate TGFb/Smad signal is further modulated by osteopontin and tenascin family members or lumican. In a mouse model of lens injury loss of each of these components attenuated Smad3 activation and delayed the process of lens epithelial cell EMT and formation of fibrotic lesion in the injured lens in vivo. Although TGFb/Smad signal is the main cascade that mediates lens epithelium EMT, crosstalks between Smad and ECM-related signalings are also to be candidates of targets for prevention of PCO and ASC. The data also provides insights to understanding the pathobiology of EMT-related diseases in other non-ocular tissues.

Commercial Relationships: Kumi Shirai, None; Shizuya Saika, None

377: PS7-5

Regulation of EMT and its possibility for suppression of PCO

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

Study Group: LE

The epithelial–mesenchymal transition (EMT) is a crucial event in wound healing and tissue repair in adult tissues. EMT of lens epithelial cells (LECs) has been proposed as a major cause of posterior capsule opacification (PCO) after cataract surgery. The fibroblast growth factor (FGF)-2 and transforming growth factor (TGF)- β 2 families are important in regulating PCO after cataract surgery. FGF has been shown to induce lens fiber differentiation by activating intracellular signaling via the MAPK/ERK1/2 pathway. The tropomyosin (Tpm) family of cytoskeleton proteins is involved in regulating and stabilizing actin microfilaments (F-actin) and is induced by TGF β 2 during EMT in lens. Using an *in vivo* rodent PCO model, we found that Tpm1 α /2 β expression was aberrantly upregulated in remodeling the actin cytoskeleton during EMT of LECs. Here we demonstrate that TGF- β can induce EMT and that long-term exposure to TGF- β elicited the epithelial–myofibroblastic transition (EMyoT). Tpm1 α /2 β expression and stress fiber formation were induced by TGF β 2 and inhibited by FGF2. Addition of FGF2 to TGF- β -treated LECs perturbed EMyoT by reactivating the MEK-Erk pathway, subsequently enhancing EMT. The MAPK inhibitor PD98059 inhibited FGF2-mediated suppression of Tpm1 α /2 β and α -smooth muscle actin (α SMA) in LECs. Overexpression of Tpm1 α /2 β induced the formation of stress fibers and the expression of α SMA. Consequently, normal LECs that have undergone EMT as a result of combined TGF- β and FGF-2 stimulation undergo migration, suggesting that TGF- β and FGF-2 may cooperate with each other and may regulate EMT in LECs during PCO progression. These findings may help clarify the conditions needed to reprogram the actin cytoskeleton during morphogenetic EMT cell proliferation and fiber regeneration in PCO. The balance between FGF-2 and EMT regulation may provide clues to a method of postponing PCO, whereas the balance between Tpm1 α /2 β expression and EMT regulation may inform decisions about treating PCO.

Commercial Relationships: Eri Kubo, ONO PHARMACEUTICAL CO., LTD. (F)
Support: JSPS Grants-in-Aid for Scientific Research C 26462673

378: PS7-6

Conclusive remarks: Epithelial-mesenchymal transition in eye

Speaker: Choun-Ki Joo [1, 2]

1. Department of Ophthalmology & Visual Science, College of Medicine, The Catholic University of Korea, Seocho, Seoul, Korea (the Republic of). 2. Catholic Institute for Visual Science, The Catholic University of Korea, Seoul, Korea (the Republic of).

Lens and retinal pigment epithelial cells would undergo the inappropriate healing process, epithelial-mesenchymal transition (EMT) after various insults on tissues that consist of these cells. This process induce transformation of cellular phenotype from epithelial to fibroblast-like cells, posterior capsule opacification and proliferative vitreoretinopathy in lens epithelial cells and retinal pigment epithelial cells occur, respectively. Recently, our understandings about chief mechanisms, related cytokines and molecules of EMT, are greatly enhanced and attempts for prevention of this process are continuing. Constant exertions to comprehend underlying mechanisms of EMT would provide newer diagnostic approaches and preventions.

Commercial Relationships: Choun-Ki Joo, None

Plenary Session 8
Imaging in Uveitis

Organizers
Sunil Srivastava
Cleveland Clinic, Cleveland, OH, United States
Annabelle A. Okada
Kyorin University School of Medicine, Mitaka, Tokyo, Japan

391: PS8-1

Overview on Imaging in Uveitis: What's Useful and What's Not

Keynote Speaker: Sunil Srivastava [1]
1. Cole Eye Institute, Cleveland Clinic, Cleveland, OH, United States.

Patients with ocular inflammatory diseases and uveitis present unique challenges to physicians. These include diagnosing patients correctly, determining when to initiate therapy and monitoring response to therapy. In all of these cases, ocular imaging provides the information needed to guide the management of uveitis patients. In this presentation, the current use of ocular imaging in the diagnosis and treatment of uveitis patients will be discussed. This includes the use of optical coherence tomography, fluorescein angiography and fundus autofluorescence. In addition, advance imaging software and techniques which could potentially improve the ability of physicians to care for uveitis patients, will also be discussed.

Commercial Relationships: Sunil Srivastava, Santen (C), Optos (C), Zeiss (C), Bioptigen (P), Synergetics (P), Allergan (F), Bausch and Lomb (C), Clearside (F), Novartis (F), Sanofi (F), Regeneron (C)

392: PS8-2

Fluorescein angiography in uveitis

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

Fluorescein angiography (FA) plays an important role in the diagnosis and monitroing of posterior or intermdiate uveitis. While OCT has been widely used in uveitis, FA still remains as a standard for the diagnosis of retinal vasculitis. In this talk, recent development of semiquantitative assessment and wide-field view will be also discussed.

Commercial Relationships: Hyeong Gon Yu, Novartis (C)

393: PS8-3

Indocyanine green angiography in uveitis

Speaker: Kei Nakai [1]
1. Yodogawa Christian Hospital/ Department of Ophthalmology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan.

Indocyanine green (ICG) fluoresces at 830 nm and allows access to the choroidal vascular structures through the retinal pigment epithelium. The molecular weight difference between ICG (775 daltons) and fluorescein (354 daltons) molecules does not account for the specific angiogram pattern. Beside the different wavelength, the difference between these two molecules comes from their binding affinity to proteins. The ICG molecule is nearly completely protein bound and predominantly so to large sized proteins (lipoproteins).

Fluorescein leaks readily from inflamed retinal vessels with minor damage to the blood-retinal barrier and readily impregnates tissues, whereas only major damage to retinal vessels allows ICG to leak.

The ICG molecule is 98% protein bound forming a large macromolecular ICG-protein complex (>58,000 daltons) that extrudes freely through the large fenestrations of the choriocapillaris progressively impregnating the choroidal stroma.

In the choroid, ICG leaks from the fenestrated choriocapillaris. During recirculation, ICG is entrapped in the choroidal tissue as the ICG-protein complex is slowly reabsorbed into the circulation.

Gradual impregnation of the choroid with time causes intermediate and late choroidal background fluorescence.

This choroidal impregnation by ICG is disturbed by choroidal inflammatory lesions, causing areas of decreased or absent fluorescence surrounded by increased fluorescence due to leakage of large choroidal vessels. The slow choroidal impregnation process could be the main parameter studied in ICGA performed for posterior uveitis.

This physiological hyperfluorescence is impaired by two mechanisms producing hypofluorescent ICGA lesions (1) mass effect due to space occupying lesions such as inflammatory granuloma and (2) choriocapillaris non perfusion occuring in inflammatory choriocapillaropathies.

Choroid is the starting point of the inflammation in many diseases including VKH, MEWDS and is participating in the inflammatory diseases such as sarcoidosis, toxoplasmosis, posterior scleritis and more. ICGA is essential to the assessment of the disease involving the choroid.

Especially in VKH, residual hypofluorescent dark dots were observed on ICGA even after the serous retinal detachments resolved and suggested that there might be silent inflammatory activity in a high percentage of patients with VKH despite high-dose immunosuppressive agents.

High-penetration OCT (HP-OCT), which uses a long wavelength (1,040–1,060 nm), allows deeper penetration through these layers and better visualization of the

posterior tissue. This advantage enables observation of the choroidal pathologies.
We used HP-OCT to evaluate the diseases involving choroid and compared the image with ICGA.
Commercial Relationships: Kei Nakai, None

394: PS8-4

Laser speckle flowgraphy in uveitis

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

Laser speckle flowgraphy (LSFG) is a technique that allows for the quantitative estimation of blood flow in the optic nerve head, choroid, retina and iris *in vivo*. LSFG targets moving red blood cells mainly in the choroid using a diode laser (wavelength, 830 nm). Reflected lights from moving erythrocytes produce blurring within the speckle pattern. In the recently modified system, LSFG-NAVI generates mean blur rate (MBR), a relative index of the blood flow velocity and can obtain reproducible data in a short time of approximately 5 seconds.
In Vogt-Koyanagi-Harada (VKH) disease that is one of the representative inflammatory diseases, LSFG revealed that choroidal circulation at the macula increased over time together with improved visual acuity during systemic corticosteroid therapy. Furthermore, we recently investigated the relationship between circulation hemodynamics and morphology in the choroid during systemic corticosteroid therapy for patients with VKH disease.
On the other hand, acute central serous chorioretinopathy (CSC) is recognized as a non-inflammatory disease, and predisposing factors for acute CSC are thought to include increased sympathetic activity, stress-prone personality, and systemic corticosteroid use. LSFG revealed that the macular MBR decreased concurrently with spontaneous regression, suggesting a validity of choroidal blood flow elevation in the pathogenesis of acute CSC.
Although the angiographic features of VKH disease is similar to CSC, including RPE leaking spots together with choroidal hyperpermeability and thickening, the patterns of MBR show quite opposite results in these two diseases. These results can correspond to fundamentally different etiologies between these two clinical entities (i.e., sympathetic vs inflammatory).
LSFG is a useful instrument to find the circulatory disturbance related to various retinochoroidal diseases. This technique can supply quantitative and repeated measurements of choroidal circulation at various intervals during the time course of diseases without any invasions. Thus, LSFG is expected to play a critical role in the diagnosis of diseases and the evaluation of disease activity.
Commercial Relationships: Daiju Iwata, None

395: PS8-5

EDI-OCT in Behcet's disease

Speaker: Min Kim [1] Sung Chul Lee [1]
1. Department of Ophthalmology, Yonsei University College of Medicine, Seodaemun-gu, Seoul, Korea (the Republic of).

Behçet's disease is a chronic, recurrent, inflammatory systemic occlusive vasculitis affecting both arteries and veins in all organs. Its ocular involvement occurs in approximately 70%-90% of patients in the form of anterior uveitis, posterior uveitis, optic neuropathy, and retinal vasculitis. Choroidal involvement in Behçet's uveitis has been previously implicated from histopathologic studies, which reported a diffuse and focal infiltration of the choroid with inflammatory cells. Using fluorescein angiography (FA) and indocyanine green angiography (ICGA), and A-scan echography, several *in vivo* studies have implicated choroidal involvement in Behçet's uveitis.
Recently, enhanced depth imaging optical coherence tomography (EDI-OCT) enabled a non-invasive way to visualize choroidal layers in the living human eye. The use of OCT in Behcet's uveitis also allows visualization of choroidal layer changes. Our study showed that there is a significant choroidal thickening during the active phase of Behcet's uveitis compared to that measured during the quiescent phase in the same eyes. In comparison to the age-matched, sex-matched, spherical equivalent-matched normal group, choroidal thickness was also greater in the quiescent phase of eyes with Behcet's uveitis. The degree of reduction in choroidal thickening is also significantly correlated with improvement in retinal vascular leakage as revealed by fluorescein angiography. Therefore, measurement of choroidal thickness by EDI-OCT may be helpful in evaluating choroidal changes *in vivo*, as well as in monitoring the progression of Behcet's posterior uveitis and response to treatment.
Commercial Relationships: Min Kim, None; Sung Chul Lee, None

396: PS8-6

EDI-OCT in uveitis and scleritis

Speaker: Annabelle A. Okada [1] Hiroshi Keino [1] Takayo Watanabe [1] Makiko Nakayama [1]
1. Department of Ophthalmology, Kyorin University School of Medicine, Mitaka-shi, Tokyo, Japan.

This presentation will review the use of enhanced depth imaging optical coherence tomography (EDI-OCT) to assess choroidal thickness in ocular inflammatory disorders. In particular, EDI-OCT has been used to assist in the diagnosis and management of Vogt-Koyanagi-Harada disease and posterior scleritis. A few representative cases will be shown.
Commercial Relationships: Annabelle Okada, None; Hiroshi Keino, None; Takayo Watanabe, None; Makiko Nakayama, None

Plenary Session 9
Cutting Edge Aging Research

Organizers

Kazuo Tsubota
Keio University School of Medicine, Shinjuku, Tokyo, Japan
Jonathan Crowston
University of Melbourne, East Melbourne, VIC, Australia

544: PS9-1

Autophagy: an intracellular degradation system

Keynote Speaker: Noboru Mizushima [1]
1. Department of Biochemistry and Molecular Biology, Graduate School and Faculty of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan.

Autophagy is one of the major degradation pathways in the cell. In autophagy, intracellular components are sequestered by autophagosomes and then degraded upon fusion with lysosomes. We have shown that autophagy is important for maintenance of the amino acid pool during starvation and neonatal periods, and preimplantation development as an amino acid supplying system, and for intracellular protein quality control to prevent neurodegeneration and tumorigenesis. We also identified a human neurodegenerative disease, in which a core autophagy gene is mutated. Thus, autophagy plays important roles in various physiological and pathological processes.

Using the GFP-LC3 mouse model, we previously suggested that autophagy is constitutively induced in the lens of the eye. To study the role of autophagy in the lens, we generated lens-specific ATG5 knockout mice. Although programmed organelle degradation normally takes place in these lens cells, deletion of Atg5 in the lens results in age-related cataract. These data suggest that autophagy is important for quality control of the lens but not for programmed organelle degradation.

Commercial Relationships: Noboru Mizushima, None
Support: KAKENHI Grants-in-Aid for Scientific Research on Innovative Areas [grant number 25111005]

545: PS9-2

Lifestyle and the ageing optic nerve

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.

Ageing and lifestyle factors alter glaucoma risk. This lecture will cover population data supporting this notion and then discuss recent experimental data showing how ageing and exercise have an impact on retinal ganglion cell recovery after an acute intraocular pressure injury. Put together, these data suggest that the vulnerability of retinal ganglion cells to IOP injury is modifiable.

Commercial Relationships: Jonathan Crowston, None
Support: NHMRC

546: PS9-3

Dry Eye Research from the Aspect of Aging

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

There are many risk factors for dry eye, including aging, video display terminal (VDT) work, smoking tobacco, and inflammation, all of which are related to oxidative stress. The incidence of dry eye increases with age and many adults and the elderly suffer from dry eye in this visually-oriented society. For the prevention and treatment of dry eye, intervening with the aging process shows promising results. Calorie restriction intervention and oxidative stress control are the two major hypotheses to intervene with the aging process. Animals with increased oxidative stress such as SOD1KO mouse and Mev1T mouse have decreased tear volume and develop dry eye. This talk will cover how oxidative stress is related to dry eye in the animal models and show how calorie restriction, exercise, and oxidative stress control can alleviate the dry eye condition.

Commercial Relationships: Kazuo Tsubota, Santen Pharmaceutical Co., Ltd. (F), Santen Pharmaceutical Co., Ltd. (R), Johnson & Johnson Vision Care Co (F), Otsuka (F), Kowa (F), Functional Visual Acuity Meter (P), MediProduct (F), JIN Co., Ltd (F)
Support: Kowa; Otsuka; JIN Co., Ltd.; MediProduct; Johnson & Johnson Vision Care Company; Grant-in-Aid for Young Scientists (B) (22791692) from the Ministry of Education, Culture, Sports, Science and Technology of Japan; Santen Pharmaceutical Co., Ltd.; Wakasa Seikatsu

Plenary Session 10
New Insights into Corneal Cell Biology

Organizers
Shizuya Saika
Wakayama Medical University School of Medicine, Wakayama, Wakayama, Japan
Kyoung Yul Seo
Yonsei University College of Medicine, Seodaemun, Seoul, Korea (the Republic of)

547: PS10-1

Limbal stem cells and niche microenvironments for corneal surface regeneration

Keynote Speaker: Ursula Schlotzer-Schrehardt [1]
Friedrich E. Kruse [1]
1. Department of Ophthalmology, University of Erlangen-Nuernberg, Erlangen, Germany.

Maintenance and regeneration of the corneal epithelium relies on unipotent progenitor cells at the corneoscleral limbus, which are regulated by extrinsic factors from their local microenvironment, the stem cell niche. For ex vivo expansion, limbal stem cells are unfavourably removed from their niche. This lecture provides an overview of current tissue-engineering approaches for corneal surface regeneration that aim at incorporating specific niche components, such as extracellular matrix proteins, growth and signalling factors, or putative niche cells, into the culture systems in order to support maintenance of an undifferentiated phenotype and to improve the therapeutic use of limbal stem cell transplantation.
Commercial Relationships: Ursula Schlotzer-Schrehardt, None; Friedrich Kruse, None

548: PS10-2

UV-induced ocular surface inflammation is related to HMGB1 via reactive oxygen species (ROS)

Speaker: Kyoung Yul Seo [1] Soo Jung Han [1] Sangchul Yoon [1] Jeon-Soo Shin [2]
1. Department of Ophthalmology, Yonsei University College of Medicine, Seodaemun-gu, Seoul, Korea (the Republic of).
2. Department of Microbiology and Immunology, Yonsei University College of Medicine, Seoul, Korea (the Republic of).

High mobility group box 1 (HMGB1) has a dual function as a transcription-enhancing nuclear protein and as a crucial cytokine that regulates inflammation. A pterygium is common ocular surface disease. Although pathogenesis of the disease is unknown, inflammation affected by acute or chronic UV radiation is known to be one of the major causes. This study demonstrated that the secretion of HMGB1 due to UV radiation induces ocular surface inflammation development through UV-mediated ROS production. After treating Chang conjunctival epithelial cells with UV radiation, HMGB1 was translocated from the nucleus to the cytoplasm and eventually to the extracellular space. HMGB1 played a crucial role in UV-induced conjunctival neutrophil infiltration, which subsided when mice were pretreated with the HMGB1 inhibitors sRAGE and HMGB1 A box protein. UV radiation mediated ROS generation in the conjunctival cells of patients with pterygium tissues as well as in UV-treated conjunctival cells in vitro. We demonstrated that exposing conjunctival cells to UV radiation induces ROS generation and HMGB1 secretion. The study confirmed that there is UV-induced inflammation in human pterygium, which is one of the possible explanations for unknown pathogenesis of the disease. We also found that treatment of HMGB1 inhibitors or anti-oxidant inhibits HMGB1 secretion while decreasing UV-induced ocular surface inflammation. Secreted HMGB1 promoted conjunctival inflammation, which can cause ocular surface disease such as pterygium when the condition persists chronically. Our findings revealed new evidence that UV can induce inflammation suggesting a new medical therapeutic target for the ocular surface disease.
Commercial Relationships: Kyoung Yul Seo, None; Soo Jung Han, None; Sangchul Yoon, None; Jeon-Soo Shin, None
Support: This study was supported by grants from the National Research Foundation of Korea (NRF) (MEST) (No. 2011-0017611)

549: PS10-3

Neurotrophic keratopathy: involvement of cation channel receptors in the pathogenesis of

Speaker: Shizuya Saika [1]
1. Department of Ophthalmology, Wakayama Medical University School of Medicine, Wakayama, Wakayama, Japan.

Impairment of trigeminal nerve perception caused by trauma, brain tumor, diabetic neuropathy, etc, potentially disrupts homeostasis of corneal epithelium. Corneal manifestation of the condition names as neurotrophic keratopathy ranges from superficial punctate keratopathy to corneal ulceration, and is refractory to therapeutics. Therapeutic efficacy of topical application of substance P and in insulin-like growth factor was reported by Nishida and his colleagues. We have developed a mouse model of neurotrophic keratopathy by coagulating V1 branch of trigeminal nerve with stereotaxic coagulator. We successfully model severe and less-severe cases of the disease. In our less-severe model, the corneal epithelium is quite normal without additional intervention. However, healing of an epithelial defect was significantly delayed with suppression of expression of cation channel receptors of TRPV1 and TRPA1 in this mouse model. In another series of experiments loss of each of TRPV1 or TRPA1 retards healing of a corneal epithelial defect in mice.

Manipulation of expression pattern of cation channel receptors in trigeminal nerve fibers could be a strategy of treatment of neurotrophic keratopathy.
Commercial Relationships: Shizuya Saika, None

550: PS10-4

The New Cell Surface Markers for Human Corneal endothelial Cells

Speaker: Jodhbir S. Mehta [1, 2]
1. Singapore National Eye Centre, Singapore, Singapore. 2. Tissue Engineering and Stem Cell, Singapore Eye Research Institute, Singapore, Singapore.

Human Corneal Endothelial Cell expansion has become more robust over the last decade. Improvement in cell culture techniques and refinement in the culturing process with respect to greater understanding about corneal endothelial cell biology has allowed this to happen. However, with any culturing system there will be variations with different primary allogeniec tissues as well as cellular heterogeneity following cell expansion. Cellular purity is important for any potential cell therapy process. Inorder to establish cell purity identiifcation of the specific cell type to be transplanted is vital.markers for human corneal endothelial cells have be sparse. the majority of researchers have been using ubiquitiously expressed adhesion or pump markers. The talk will outline the identification of 4 new markers for human corneal endothelial cells that can be used to verify the quality of the cell product before transplantation.
Commercial Relationships: Jodhbir Mehta, UK Network Medical (P), Carl Zeiss Meditec (C), Ziemer (C)
Support: TCRP NMRC

551: PS10-5

Cell-injection therapy as a new therapeutic modality for corneal endothelial diseases

Speaker: Noriko Koizumi [1, 2]
1. Department of Biomedical Engineering Faculty of Life and Medical Sciences, Doshisha University, Kyotanabe, Kyoto, Japan. 2. Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan.

The concept of our new surgical treatment for corneal endothelial dysfunction involves replacing the damaged cell layers with healthy corneal endothelial cells (CECs) cultivated and proliferated in vitro. In 2009, we reported that the selective Rho-associated kinase (ROCK) inhibitor Y-27632 promotes cell adhesion and proliferation and inhibits the apoptosis of primate corneal endothelial cells in culture. Currently, we are developing a cell-injection therapy using cultivated CECs in combination with ROCK inhibitor. We confirmed the efficacy and safety of the cell-injection therapy using both rabbit and monkey models, and we are now moving onto its clinical application.
Commercial Relationships: Noriko Koizumi, Doshisha University (P), Senju Pharmaceutical Co. (P), JCR Pharmaceuticals Co. (P)
Support: Research Center Network for Realization of Regenerative Medicine from JST, Program for the Strategic Research Foundation at Private Universities from MEXT
Clinical Trail: UMIN000012534

Plenary Session 11
Myopia; Genes or Enviroment?

Organizers

David A. Mackey
University of Western Australia, Crawley, WA, Australia
Kyoko Ohno-Matsui
Tokyo Medical and Dental University, Bunkyo, Tokyo, Japan

557: PS11-1

Epidemiology of Myopia

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

Myopia is recognized as one of the most important cause of preventable vision loss. Prevalence of myopia is increasing worldwide, and more emerging in Asian populations. Data suggests that prevalence of myopia in school age children becomes higher at age 7 or older between 1980s and 1990s in Japan. Similar epidemiological data are reported from Taiwan suggesting that this increasing trend continues in 2000s; prevalence of high myopia is also increasing in school age children. Prevalence of myopia and high myopia in adults are high in Asian populations, and the latter is especially so in East Asian countries. Presence of myopia is associated with various ocular comorbidities including myopic maculopathy, glaucoma, and peripheral retinal degeneration, rhegmatogenous retinal detachment and myopic neuropathy. Understanding the etiology and risk factors of myopia and high myopia is an urgent challenge in Asian countries.

Commercial Relationships: Ryo Kawasaki, None

558: PS11-2

Influence of environment

Speaker: Jost B. Jonas [1]
1. Department of Ophthalmology, Medical Faculty Mannheim, University Heidelberg, Heidelberg, Germany.

Development of myopia depends on a magnitude of parameters including genetic factors and environmental parameters. The latter include in particular the time spent outdoors during a viulnerable period in youth. Based on previous studies including the landmark study by Rose, Morgan, Mitchell and colleagues, the talk will discuss various parameters of potential influence for the development and progression of myopia in addition to recent anatomic findings

Commercial Relationships: Jost Jonas, Allergan Inc (C), Merck Sharp & Dohme Co., Inc (C), Alimera Co (C), Boehringer Ingelheim Co., (C), Sanofi Co (C), Pfizer Co (C), CellMed AG, Alzenau, Germany (P)

559: PS11-3

Genetics for myopia, high myopia, and extreme myopia in Japan

Speaker: Masahiro Miyake [1]
1. Department of Ophthalmology, Kyoto University Graduate School of Medicine, Kyoto, Kyoto, Japan.

Study Group: Nagahama study group

Myopia is emerging as a major public health concern in many part of Asia, including Japan. Its prevalence is increasing among younger generation, which would be mainly due to environmental factors. On the other hand, genetic susceptibility to myopia has also been recognized as an important factor for myopia development. In this era of genome-wide association study (GWAS), many myopia-susceptibility genes are detected by international consortium.

We conducted a large scaled community-based cohort study, the Nagahama Study (Nagahama city, Shiga prefecture, Japan), which consisted of ten thousand healthy participants. All of the participants had been extracted their DNA, and 3,712 of them had been genome-scanned using commercially available DNA microarrays (Illumina Inc.). Our group has replicated the contribution of 15 genes to the spherical equivalent, and found a novel susceptibility gene for eyeball size and extreme myopia. Interestingly, this gene showed an interaction with *GJD2*, which is an established susceptibility gene for myopia, enhancing the effect of *GJD2* on spherical equivalent. In addition to the Nagahama cohort, our Kyoto high myopia cohort has revealed several susceptibility genes for high myopia, which include *GJD2*, *RASGRF* and *ZIC2*.

Though many susceptibility genes for myopia and relevant traits are reported, they do not necessarily correspond with each other. Here, we will discuss the similarity and the difference between myopia, high myopia and extreme myopia from the genetical point of view.

Commercial Relationships: Masahiro Miyake, None

Support: the Ministry of Education, Culture, Sports, Science, and Technology of Japan (2006–2012); Grants 19390442, 22791706, and 22791653 from the Japan Society for the Promotion of Science; the Japanese National Society for the Prevention of Blindness; and Takeda Science Foundation (2008–2012).

560: PS11-4

Characterization of genes and gene by environment interactions for myopia in Asian populations

Speaker: Qiao Fan [1]
1. Singapore Eye Research Institute, Singapore, Singapore.

Study Group: CREAM

Myopia, a common refractive error, has been increasing in the last few decades and highly prevalent in Asian

urban areas. As a complex disease, myopia is governed by genetic and environmental factors, and possibly their interplay. By utilizing large numbers of subjects from population-based cohorts and incorporating genome-wide genetic markers and information for environmental factors, we want to address the following questions to understand the etiology of myopia in Asians: 1) whether Asians have different myopia's genetic component compared to Europeans. Specifically, whether there are differences in effects of susceptibility genes for myopia between Asians and Europeans; 2) whether there are any specific interactions between gene and environment (such as education levels, outdoor activities and near work activities) contributing to myopia particularly in Asian adult and paediatric populations. The challenges encountered for gene by environment interaction studies will be also discussed.

Commercial Relationships: Qiao Fan, None

561: PS11-5

Genes and Environment affecting myopia in Australia

Speaker: David A. Mackey [1] Alex Hewitt [1, 2] Seyhan Yazar [1] Maria Franchina [1]

1. Lions Eye Institute, University of Western Australia, Crawley, WA, Australia. 2. Centre for Eye Research Australia, Melbourne, VIC, Australia.

Aim: Identifying gene-environment interactions in myopia is a key next step to translation to prevent myopia. Multiple genes have been identified in GWAS for myopia and some are associated with level of education (a known myopia risk factor). Other environmental factors include reduced time outdoors but this has proven more difficult to standardise for meta-analysis. We reviewed our Australian data to suggest possible markers of outdoor activity.

Method: The Norfolk Island Eye Study (NIES) examined Conjunctival UV Autofluorescence (CUVAF), the twins eye study examined CUVAF in two geographically distinct locations Brisbane (BATS) and Tasmania (TEST), the Raine Eye Health Study (REHS) examined CUVAF and Vitamin D levels, and the Busselton Healthy Aging Study (BHAS) examined reported skin cancer.

Results: In NIES the median total CUVAF was lower in subjects with myopia (mean SE <-1.0D) than participants without myopia: 16.6 mm^2 versus 28.6 mm^2, P<0.001. In the TEST/BATS the level of CUVAF in temperate Tasmania was 28.7 mm^2 compared to subtropical Brisbane 45.2 mm^2 P <0.001. The twins analysis found additive genetic component explained 37% of the variation in CUVAF while 50% was due to the common environment. In the REHS the median area of CUVAF was lower in subject with myopia (mean SE ≤-0.50D) than participants without myopia: 31.9mm^2 versus 47.9mm^2, P<0.001. Also in REHS, myopic subjects had lower serum 25(OH)D3 concentrations compared to subject without myopia: median 67.6 versus 72.5 nmol, P=0.003. In BHAS myopia (mean SE ≤-0.50D) was in 21.6% of non-skin cancer participants and 11.9% in skin cancer participants (P=0.005).

Conclusion: Although historical recall of time spent outdoors may not always be available or accurate other biomarkers of outdoor activity such as CUVAF, Vitamin D and skin cancer are consistently associated with less myopia. These various markers could be used to identify genes associated with the protective effect of outdoor activity and myopia.

Commercial Relationships: David Mackey, None; Alex Hewitt, None; Seyhan Yazar, None; Maria Franchina, None

Support: NHMRC ORIA Telethon