Special Interest Groups

Special Interest Groups 1
New Approaches to Infectious Keratitis

Organizers

Yoshitsugu Inoue
Fuculty of Medicine Tottori University, Yonago, Tottori, Japan
Yu-Feng Yao
Zhejiang University, School of Medicine, Hangzhou, Zhejiang, China

231: SIG1-1

Immune Privileged Role of Indoleamine 2,3-dioxygenase 1 in Corneal Endothelial Cells Exploited by Herpes Simplex Virus Type 1

Speaker: Dai Miyazaki [1]
1. Division of Ophthalmology and Visual Science, Tottori University Faculty of Medicine, Yonago, Tottori, Japan.

Herpes simplex virus type 1 (HSV-1) is one of the leading corneal pathogens and causes blinding endothelial dysfunction of the cornea. The purpose of this study was to determine an unrecognized strategy used by HSV-1 to modulate the host immune responses. We examined the transcriptional responses of human corneal endothelial cells (HCEn) lining an immune privileged site, the anterior chamber, of the eye. Indoleamine 2,3-dioxygenase 1 (IDO1) is strongly expressed in HCEn cells after HSV-1 infection which was dependent on stimulation of toll like receptors. Previously recognized role of IDO1 upon HSV-1 infection was to restrict viral replication. We present evidence that argues against an anti-viral role for IDO1. When HCEn cells were examined for an antigen presenting function, HSV-1-primed HCEn cells stimulated the proliferation of allogeneic $CD4^+$ T cells as a recall response which was manifested by IL-10 secretion. Co-cultures of $CD4^+$ T cells with HSV-1-primed HCEn cells activated $FOXP3^+$ $IL\text{-}10^+$ $CD4^+$ regulatory T cells (Tregs). The role of IDO1 was examined by determining whether it modulated the immune response by activating Treg. When IDO1 was over-expressed in HCEn cells, the activation of Treg was promoted by HCEn cells, and IDO1 silencing of HCEn cells reduced the HCEn-mediated Treg activation. We conclude that IDO1 is exploited for viral immune escape by regulating the $CD4^+$-mediated arm of acquired immunity.

Commercial Relationships: Dai Miyazaki, None
Support: Grant-in-Aid 20592076, 21592258, 25462755, and 25670734 for Scientific Research from the Japanese Ministry of Education, Science, and Culture

232: SIG1-2

Novel method to diagnose and treat Acanthamoeba keratitis

Speaker: Takashi Suzuki [1]
1. Department of Ophthalmology, Ehime University, Graduate School of Medicine, Toon, Ehime, Japan.

Acanthamoeba spp. keratitis (AK) is a severe and sight-threatening ocular infection, and diagnostic tools are needed to confirm AK. Diagnosis of AK by microscopic examination, culture, and polymerase chain reaction (PCR) has several limitations (sensitivity, specificity, rapidity, or necessity of advanced skills and special equipment). We developed a rapid immunochromatographic (IC) test kit using fluorescent silica nanoparticle for detection of Acanthamoeba and confirmed the efficacy for diagnosis of AK. The IC kit consists of a test strip, extracted liquid, and fluorescent silica nanoparticle binding Acanthamoeba antibody. To perform a test, a sample treated with extracted liquid and fluorescent silica nanoparticle are mixed, the mixed liquid is delivered by drops at the edge of the test strip, and fluorescent emission is observed with a fluorescent scope for detection after 30 minutes reaction. The IC kit could detect at least 5 trophozoites and 40 cysts per sample in vitro, and did not show cross-reaction with other pathogens such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Candida albicans*. Patients suspected AK were tested the IC kit and PCR amplifying Acanthamoeba DNA to detect the presence of Acanthamoeba in corneal scraping, and their results were found to be positive by both the IC kit and PCR. Thus the IC test kit using fluorescent silica nanoparticle is efficacy for diagnosis of AK.

Another problem for AK is that there are few effective drugs for treatment of AK, and we need a novel treatment for AK. We evaluated the killing effect of methylene blue (MB) mediated photodynamic therapy (PDT) on pathogenic Acanthamoeba. MB-PDT suppressed respiratory activity of trophozoites and cysts on a MB-concentration dependent manner at total light doses of $10.8J/cm_2$. Moreover MB-PDT had synergistic effects with polyhexamethylene biguanide. In future, PDT using photosensitizer could be useful treatment for AK.

Commercial Relationships: Takashi Suzuki, Furukawa Electric Co., Ltd (F)
Support: KAKENHI: Grants-in-Aid for Young Scientists B, 25861635

233: SIG1-3

New Insights in the Diagnosis of Fungal and Parasitic Keratitis

Speaker: Savitri Sharma [1]
1. Jhaveri Microbiology Centre, L V Prasad Eye Institute, Hyderabad, Telangana, India.

Going by their prevalence in eye infections fungi are indeed important organisms to deal with. Corneal infection is the most frequent fungal infection, however, fungi may affect the orbit, lids, lacrimal apparatus, conjunctiva, and sclera. The diagnosis of fungal infections requires the clinician to (i) establish the presence of ophthalmic pathology (ii) obtain tissue in which the fungus is visualized; and (iii) isolate the responsible fungus. For almost all specimens, the use of blood/chocolate agar and Sabouraud dextrose agar containing gentamicin/

chloramphenicol is recommended. Cycloheximide must never be used in these media as many saprophytic fungi constitute ocular pathogens. Other media such as potato dextrose agar may be included to enhance sporulation, which aids in identification. It is important to determine the significance of the growth from ocular samples since saprophytic fungi are encountered as pathogens. Molecular biology has come to be a useful tool for rapid detection and identification of fungal species especially in intraocular infections. Methods based on detection and analysis of the internal transcribed spacer (ITS)-5.8S ribosomal DNA (rDNA), 18S rDNA or 28SrDNA regions are currently proving to be powerful tools for rapid and precise laboratory diagnosis. It is not uncommon to find non-sporulating fungi among ocular fungal pathogens. DNA sequencing is being increasingly employed to achieve identification in such cases.

The eye is a favorite place for many parasites-both protozoa and helminths. All parts of the eye are susceptible and source of infection can be external or blood borne. External infection would include *Acanthamoeba* keratitis, subconjunctival cysticercosis, subconjunctival dirofilariasis, phthyriasis, ophthalmomyasis, onchocerciasis etc. Diagnosis of parasitic infection depends on the clinical features, direct visualization, serology and PCR. Fungi and parasites form interesting aspect of the microbial world of the eye.While conventional microbiological techniques remain the gold standard for the laboratory diagnosis of fungal and parasitic keratitis, confocal imaging and molecular biology techniques have found a prized place in the rapid and reliable detection and identification of organisms.

Commercial Relationships: Savitri Sharma, None

234: SIG1-4

Clinical Efficacy of Systemic Vitamin C supplementation on Reducing Corneal Opacity Resulting from Infectious Keratitis

Speaker: Seong-Jae Kim [1] Yongwun Cho [1]

1. Department of Ophthalmology, Gyeongsang National University, School of Medicine, Jinju, Gyeongsangnam, Korea (the Republic of).

Infectious keratitis remains a sight-threatening disease despite the development of potent new antibiotics and diagnostic techniques. Even with intensive antibiotic treatment, corneal damage can occur as a result of inflammatory processes caused by infection or scarring related to the healing process. The scarring that accompanies the resolution of infectious keratitis leaves many eyes visually impaired or blind. Thus, it is logical to employ strategies to reduce or prevent scar formation. Topical corticosteroids may seem like an obvious choice for this purpose, but their use is controversial. Some investigators advocate using topical corticosteroids along with antibiotics to reduce immune-mediated tissue damage and scarring. The Steroids for Corneal Ulcers Trial (SCUT) investigated the safety and efficacy of corticosteroids in the treatment of bacterial corneal ulcers. In SCUT, corneal scarring resulting from bacterial keratitis was noted to improve over time with corticosteroid treatment: the density of the scar-related opacity improved, leading to a concurrent improvement in vision.[7] However, corticosteroids may also significantly slow the process of corneal wound healing, prolong infection, and predispose to stromal thinning and perforation. Therefore, treatments to reduce corneal scar formation without adverse effects, such as delayed re-epithelialization or perforation, are sought.

Corneal wound healing is a complex process, involving cellular changes and signaling molecules from cells of every layer of the cornea. Furthermore, a major component of the corneal haze in wound healing is due to changes in the composition and configuration of the extracellular matrix (ECM) and corneal neovascularization. Experimentally, vitamin C has been shown to play a role in synthesizing parallel arrays of extracellular matrix fibrils in cultured human keratocytes. Ascorbic acid is also known to be involved in the suppression of corneal neovascularization via its antioxidant effects and ability to enhance collagen synthesis. Therefore, we speculated that administration of vitamin C may help reduce corneal opacity caused by infectious keratitis.

The therapeutic effects of vitamin C were explored by Linus Pauling, who was the first to introduce the concept of high doses of vitamin C for the treatment of various conditions, from the common cold to cancer. Since then, high doses of vitamin C have been widely used in the treatment and prevention of diabetes, atherosclerosis, the common cold, cataracts, glaucoma, macular degeneration, stroke, heart disease, cancer, and other conditions.

The purpose of the present study was to determine whether oral (3 g/day) or intravenous (20 g/day) vitamin C supplementation during hospital admission reduces corneal opacity resulting from infectious keratitis.

Clinical data were collected at admission, discharge, and last follow-up visit. These data included age, gender, previous medical history including visual acuity, previous ocular history, intraocular pressure, location of corneal ulcer, and culture results from corneal specimens. Best corrected visual acuity (BCVA) was converted into logarithm of the minimal angle of resolution format (counting finger, 2.3; hand movements, 2.6; light perception, 3.0; no light perception 3.6). The size of the corneal lesion was measured using anterior segment photographs; all photographs were taken at the same magnification. The size of the corneal opacity was determined by point to point using the *Image J program* (version 1.27, National Institutes of Health, United States). The opacity size was divided by the size of the whole cornea to facilitate comparisons.

The main finding of the current study is that systemic supplementation of vitamin C (oral or intravenous) effectively decreased the size of corneal opacities resulting from infectious keratitis. Furthermore, intravenous vitamin C was more effective than oral vitamin C in decreasing the corneal opacity size. As well, the reduction in corneal opacity size due to vitamin C treatment was greater when hypopyon was present and when the patient was younger than 60 years old.

Commercial Relationships: Seong-Jae Kim, None; Yongwun Cho, None

Support: This work was supported by biomedical research institute fund (GNUHBRIF-2014-0003) from the Gyeongsang National University Hospital.

235: SIG1-5

Novel Deep Anterior Lamellar Keratoplasty for the recovery from infectious keratitis

Speaker: Yu-Feng Yao [1]

1. Department of Ophthalmology, Sir Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China.

We have developed a novel technique to perform deep anterior lamellar keratoplasty (DALK), in name of Yao's DALK technique, in which a pocketing exposure of Descemet membrane was initially created by forceps hooking, followed by viscoelastic injection through the pocket to fully detach stroma from Descemet membrane, facilitating total stromal removal with exact exposure of Descemet membrane in of full-bed. In this report, we applied Yao's DALK technique to treat severe infectious keratitis, such as bacterial and fungal keratitis. The surgery enables to achieve triple purposes simultaneously including eradicating infection, tectonically reconstructing corneal structure and recovering corneal clarity with rehabilitation of visual acuity in severe infectious keratitis. The surgical technique and clinical results after surgery will be presented.

Commercial Relationships: Yu-Feng Yao, None

Support: Supported in part by the key project grant from the Science and Technology Department of Zhejiang province, China (No. 2011C13029-2), in part by the key project of Medical Scientific Research Foundation of Zhejiang province, China (No. 2012ZDA026, and No. 2013ZDA012).

Special Interest Groups 2
Primary Angle Closure Disease

Organizers

Ching Lin Ho
Glaucoma Service Singapore National Eye Centre/Duke-NUS Graduate Medical School Singapore, Singapore, Singapore
Tetsuya Yamamoto
Gifu University Graduate School of Medicine, Gifu, Gifu, Japan

236: SIG2-1

Detection via anterior segment OCT

Speaker: Mingguang He [1, 2]
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.

Anterior segment optical coherence tomography (AS-OCT) is a high resolution, rapid and noninvasive imaging tool for the anterior segment diseases such as angle closure and angle closure glaucoma. This talk will focus on the quantitative measurements with AS-OCT, summarize key findings from studies and discuss their implications on clinical practice.

Commercial Relationships: Mingguang He, Takagi (F), Optovue Inc. (F), Carl Zeiss Meditec (F)
Support: Fight for Sight (grant no. 1655) (United Kingdom), Sun Yat-sen University 5010 Project Fund (grant no. 2007033)(China), the Richard Desmond CHaritable Foundation (via Fight for Sight UK), Major International (Regional) Joint Research Project (grant no. 81420108008).
Clinical Trail: ISRCTN45213099

237: SIG2-2

Lens Extraction as a Surgical Option for PAC

Speaker: Yasuo Kurimoto [1, 2]
1. Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan. 2. Institute of Biomedical Research and Innovation, Kobe, Japan.

Angle closure in primary angle closure/glaucoma (PAC/G) arises from abnormalities in the relative or absolute sizes and/or positions of the anterior segment structures. Therefore, in principle, anatomical modification with surgical intervention is necessary to resolve the angle closure. Laser peripheral iridotomy (LPI) has long been considered the "gold standard" of first-line treatment, based on the understanding that pupillary block is the predominant causative mechanism of the angle closure. After the introduction of UBM, however, a number of studies have revealed that the angle closure is caused by multiple mechanisms, including non-pupillary block mechanisms such as plateau iris configuration. LPI has no curative effect on non-pupillary block mechanisms, and several studies have reported that LPI alone is not as effective as was generally believed to cure PAC/G. In contrast, lens extraction eliminates the pupillary-block mechanism and the lens-related mechanisms, and attenuates the plateau iris mechanism. As a single procedure, no treatment seems to be as effective in the elimination of the angle-closing mechanisms as is lens extraction. Actually, lens extraction is effective to cure the residual angle closure after LPI in PAC/G, and is superior to LPI as an initial treatment for PAC/G. It seems strange that LPI still remains the first-line treatment of PAC/G in spite of the new global consensus that the angle closure is caused by multiple mechanisms and the effect of LPI is limited. Lens extraction is the best reasonable treatment for the angle closure, and can be the first-line treatment for PACG present day.

Commercial Relationships: Yasuo Kurimoto, None

238: SIG2-3

Treatment options for acute primary angle closure

Speaker: Ching Lin Ho [1]
1. Glaucoma Service Singapore National Eye Centre, Duke-NUS Graduate Medical School Singapore, Singapore, Singapore.

Acute primary angle is an ocular emergency. Delays in effective treatment can result in severe visual loss. Conventional treatment with medications and laser iridotomy has a track record of efficacy. Argon laser iridoplasty and anterior chamber paracentesis have been described as options to rapidly reduce intraocular pressure and achieve clearing of corneal edema. Clinical trials have shown the efficacy and safety of cataract extraction compared to laser iridotomy. Filtration surgery may be required in refractory cases or in advanced acute on chronic angle closure glaucoma. The different treatment options and their roles are discussed.

Commercial Relationships: Ching Lin Ho, None

239: SIG2-4

Drug-induced secondary angle closure

Speaker: Janey L. Wiggs [1]
1. Ophthalmology, Harvard Medical School, Boston, MA, United States.

Angle closure glaucoma can develop secondary to pathological processes that produce uveal effusions. A wide variety of conditions can cause secondary angle closure glaucoma by this mechanism including inflammation (posterior scleritis and Vogt-Koyangi-Harada disease), anatomic abnormalities (persistent fetal vasculature), and drug reactions, most notably bilateral angle-closure secondary to Topiramate. Additionally, a number of other pharmacologic agents also induce bilateral angle-closure glaucoma including the 'sulfa' class of medications. At the Mass Eye and Ear Infirmary we have collected 8 cases of bilateral angle closure secondary

to topiramate use as well as 20 challenged controls. Using this cohort we have investigated the etiology of this condition using genetic and clinical approaches. Our results suggest that this is a complex process that involves age, duration of drug use, and possibly genetic factors.

Commercial Relationships: Janey Wiggs, None

Special Interest Groups 3
Asian Eye Genetics Consortium (AEGC) and eyeGENE International
In conjunction with NEI-NIH

Organizers
Gyan "John" Prakash
National Eye Institute, National Institutes of Health, Bethesda, MD, United States
Takeshi Iwata
Tokyo Medical Center, National Hospital Organization, Meguro, Tokyo, Japan
Calvin CP Pang
The Chinese University of Hong Kong, Kowloon, Hong Kong

240: SIG3-1
Asian Eye Genetics Consortium: Building Bridges between Developed and Developing Worlds

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

Study Group: Genetics

The US National Eye Institute (NEI) at National Institutes of Health (NIH) has recently initiated and helped in launching a new initiative, Asian Eye Genetics Consortium (AEGC). The goal is to identify novel genes or to find mutant frequency in Asia and help in sharing novel information through common information network. The new initiative to support research collaboration is expected to accelerate genetic research studies in the Asian region. The initiative will help in our understanding of biology of eye diseases. Newly available technologies to analyze genome sequence have been established and well tested in several parts of the world. These technologies can be adapted to Asian population to quickly catch up with the genetic studies. AEGC has brought together leading geneticists and eye disease researchers from the US, Japan, India, China, Australia, Singapore, Saudi Arabia, Sri Lanka, and other Asian countries.
Commercial Relationships: Gyan Prakash, None
Clinical Trail: Not Applicable

241: SIG3-2
Asian Eye Genetics Consortium, Genetic research programs covering the entire Asia

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

Study Group: Asian Eye Genetics Consortium

Asian Eye Genetics Consortium (AEGC) was established in April, 2014 by researchers working on patients in Asia affected by various eye diseases associated with gene mutations. The idea of AEGC came to us when we performed a whole exome analysis on inherited retinal diseases in Japanese population. This study resulted with only 17% of pedigree associated with known gene mutations previously reported. Among these mutations number of them is likely to originate in continent of Asia.
AEGC will mainly focus on Mendelian Eye Diseases of patients in Asian countries including Australia and United States. The whole exome analysis or whole genome analysis will be performed for each pedigree to identify disease causing gene mutations. New or highly associated genetic variants will be shared among AEGC member for quick confirmation in other countries.
Online pedigree registration system for research purpose and genotype-phenotype database system for clinical purpose will be setup at the National Institute of Sensory Organs (NISO). EyeGene database currently functional at the National Eye Institute, NIH will be considered as a model for genotype-phenotype database in local language.
Animal models and iPS cells will be collaboratively established and shared for development of diagnostic and therapeutic purpose. We hope to speed up the gene identification process for individual pedigree with the new generation technology. Information and new membership for AEGC will be available at the AEGC website (http://aegc.asia).
Commercial Relationships: Takeshi Iwata, None
Support: Japanese Ministry of Health, Labour and Welfare, Japanese Ministry of Education, Culture, Sports, Science and Technology and the National Hospital Organization of Japan.

242: SIG3-3
Ophthalmic Genetic Studies in India and Pakistan

Speaker: Fielding (James F) J. Hejtmancik [1]
1. Molecular Ophthalmic Genetics Section Ophthalmic Genetics and Visual Function Branch, National Eye Institute, National Institutes of Health, Rockville, MD, United States.

Study Group: Asia Eye Genetics Consortium (AEGC)

The population of the Indian subcontinent including India and Pakistan has been a rich source for identifying genes causing or contributing to ophthalmic disease. A combination of linkage analysis, homozygosity mapping, and DNA sequencing are highly effective in identifying the genetic causes of Mendelian diseases in this population. However, the genetic causes of less than 50% of congenital cataract and retinal degeneration families currently have been identified, so that this population continues to provide a rich resource for identifying novel genes contributing to Mendelian ophthalmic diseases. Similarly, the large patient populations and high quality of care provide an ideal environment for studying the genetic contributions to multifactorial ophthalmic diseases with a complex inheritance. Examples of both types of studies

and a summary of current progress will be covered.
Commercial Relationships: Fielding (James F) Hejtmancik, None

243: SIG3-4

Ethnicities and Allelic Frequencies in Eye Diseases

Speaker: Calvin CP Pang [1]
1. Department of Ophthalmology & Visual Sciences, The Chinese University of Hong Kong, Kowloon, Hong Kong.

Ethnic variations in prevalence are well documented in many eye diseases. There are also diversities in frequencies in genes alleles known to be associated with specific eye diseases, affecting occurrences and clinical presentations. This presentation will present updated information and discuss the issues concerned.
Commercial Relationships: Calvin CP Pang, None

244: SIG3-5

eyeGENE®: A history and a look at its achievements. How can Asian countries participate in eyeGENE® International?

Speaker: Santa Tumminia [1]
1. National Eye Institute, National Institutes of Health, Bethesda, MD, United States.

The eyeGENE® Network is a medical genetics initiative created by the National Eye Institute (NEI), a part of the U.S. National Institutes of Health, to facilitate research into the causes and mechanisms of inherited eye diseases. This is accomplished through a model partnership between the U.S. federal government, eye health care providers, molecular diagnostic laboratories, private industry, vision community scientists and affected individuals.
The Network has three essential elements. Eye health care providers submit a patient's blood sample and receive a DNA evaluation for diagnosis and genetic counseling. Affected individuals contribute their blood and clinical information to a protected, de-identified registry. They may elect to be notified of their eligibility to participate in research activities or clinical trials testing investigational therapies. Researchers have access to de-identified DNA samples and clinical information to investigate genotype/phenotype relationships and the causes of eye disease.
The eyeGENE® Network currently includes over 400 registered clinical organizations from the U.S. and Canada, and is testing ~100 genes for over 35 inherited eye disease categories. To date, the Network has received over 5400 samples from individuals with rare inherited eye diseases.
eyeGENE® has been successful and continues to expand. The popularity of the Network has led to great interest from affected individuals, clinicians, and genetic testing facilities outside of the original scope of the eyeGENE® Network; i.e. the international clinical and research vision communities. Since 2008, eyeGENE® has been the recipient of repeated requests from around the world to allow international participation. Since eyeGENE® promises to facilitate research in inherited eye conditions leading to better treatments, world-wide participation is a natural step towards that goal as it would increase the data available to researchers and foster involvement of patients, physicians, and researchers in eye disease genetics on a much larger scale. We have begun to make progress towards international expansion. To participate in eyeGENE® International, each international member must form its own coordinating center that acts much like the eyeGENE® Coordinating Center. Each member organization will diagnostically screen their own patients for the genetic cause(s) of their disease. This will lead to a biospecimen repository, patient registry and database which could be de-identified, yet harmonized with the eyeGENE® database for maximum potential benefits to patients, clinicians and researchers in the international vision community.
eyeGENE® and eyeGENE® International have the opportunity to provide a rich intellectual resource that creates important collaborations and partnerships between clinical expertise, molecular expertise, institutions, and sample collections, which are necessary to form the multidisciplinary teams required for current investigations in human genetics and genomics and the development of gene-based personalized medicine. It is easy to imagine that the role and value of eyeGENE® and eyeGENE® International will continue to grow as advances in targeted gene-based therapies develop.
Commercial Relationships: Santa Tumminia, None
Clinical Trail: NCT00378742

Special Interest Groups 4
Mechanism of Retinal Degeneration

Organizers
Bo Lei
First Affiliated Hospital of Chongqing Medical University, Chongqing, China
Mineo Kondo
Mie University Graduate School of Medicine, Tsu, Mie, Japan

419: SIG4-1

Stargardt Disease with Foveal Sparing Phenotype

Speaker: Kaoru Fujinami [1,2]
1. Ophthalmology/Laboratory of Visual Physiology, National Hospital Organization, Tokyo Medical Center/National Institute of Sensory Organs, Meguro, Tokyo, Japan. 2. Ophthalmology, Keio University, School of Medicine, Shinjuku-ku, Tokyo, Japan.

Stargardt macular dystrophy (STGD) is an autosomal recessive disorder caused by mutations in the ABCA4 gene. Most cases typically present with central visual loss within the first 2 decades of life and during the course of the disorder there is macular atrophy with yellow-white flecks. However, STGD is associated with a variable phenotype and severity, which has confounded attempts to comprehensively examine genotype-phenotype correlations. A cohort of STGD patients who had better visual acuity compared to 'typical' STGD patients and who showed sparing of the fovea on funduscopy was first reported in 2003 (Rotenstreich *et al.* Ophthalmology 2001). There are also reports describing patients with 'late-onset' STGD, including individuals with foveal sparing (FS) who harbour *ABCA4* variants (Westeneng-van Haaften *et al.* Ophthalmology 2012). However, the clinical and genetic characteristics of FS-STGD have not been fully understood. Here, the distinctive clinical findings and molecular genetic characteristics of 40 patients with FS-STGD will be present, which assists genetic counselling and may help in the appropriate selection of patients for therapeutic clinical trials for *ABCA4*-related retinal disease.

Commercial Relationships: Kaoru Fujinami, None

420: SIG4-2

Activation of Liver X Receptor Prevents Inner Retinal Degeneration Induced by N-methyl-D-aspartate

Speaker: Bo Lei [1]
1. Ophthalmology, First Affiliated Hospital of Chongqing Medical University, Chongqing Key Laboratory of Ophthalmology, Chongqing Eye Institute, Chongqing, China.

Liver X receptors (LXRs) are best known for their role in regulating lipid transport and metabolism. Nowadays, accumulating studies have described new functions of LXRs including regulation of inflammation and neurodegeneration. Here, we show that activation of LXR β and its target gene ABCA1 with a LXR agonist significantly prevented the inner retinal degeneration induced by NMDA.

Commercial Relationships: Bo Lei, None
Support: NNSF of China grants (81271033, 81470621), Chongqing Key Laboratory of Ophthalmology, and National Key Clinical Specialties Construction Program of China.

421: SIG4-3

Mechanism of paraneoplastic retinopathy with retinal ON bipolar cell dysfunction

Speaker: Shinji Ueno [1]
1. Department of Ophthalmology, Nagoya University Graduate School of Medicine, Nagoya, Japan.

The paraneoplastic retinopathies (PRs) are a group of eye diseases characterized by a sudden and progressive dysfunction of the retina caused by an antibody against a protein in a neoplasm. Evidence has been obtained that the transient receptor potential melastatin 1 (TRPM1) protein was one of the antigens for the autoantibody against the ON bipolar cells in PR patients.
However, it has not been determined how the autoantibody causes the dysfunction of the ON bipolar cells. We hypothesized that the antibody against TRPM1 in the serum of patients with PR causes a degeneration of retinal ON bipolar cells. To test this hypothesis, we injected the serum from the PR patient, previously shown to contain anti-TRPM1 antibodies by westerblot, intravitreally into mice and examined the effects on the retina.
We found that the electroretinograms (ERGs) of the mice were altered acutely after the injection, and the shape of the ERGs resembled that of the patient with PR. Immunohistochemical analysis of the eyes injected with the serum showed immunoreactivity against bipolar cells only in wild-type animals and not in TRPM1 knockout mice,consistent with the serum containing anti-TRPM1 antibodies. Histology also showed that some of the bipolar cells were apoptotic by 5 hours after the injection in wild type mice, but no bipolar cell death was found in TRPM1 knockout mice, . At 3 months, the inner nuclear layer was thinner and the amplitudes of the ERGs were still reduced. These results indicate that the serum of a patient with PR contained an antibody against TRPM1 caused an acute death of retinal ON bipolar cells of mice.

Commercial Relationships: Shinji Ueno, None
Support: Grant-in-Aid for Scientific Research (B) (#23791977) from the Ministry of Education, Culture, Sports, Science and Technology, Japan

422: SIG4-4

Comprehensive approach to the retinal ganglion cell changes in optic chiasmal compression

Speaker: Tae Kwann Park [1]

1. Department of Ophthalmology , Soonchunhyang University Hospital, Bucheon, Gyeonggi-do, Korea (the Republic of).

Compressive lesion of the optic chiasm produces visual field (VF) defects typically causing bitemporal hemianopsia and leads to retinal nerve fiber layer (RNFL) loss in the nasal and temporal sectors of the optic nerve. To evaluate structural and functional changes of retinal ganglion cells (RGCs) and RNFL in the patients with chiasmal compressive lesions, various kinds of diagnostic modalities, including OCT, VF, and electrophyiological tests. In this presentation, VF recovery and changes of RGCs after chiasmal decompression will be discussed. The correlation between diagnostic parameters taken pre- and postoperatively will also be reported. Furthermore, prognostic value of OCT and photopic negative response will be suggested.

Commercial Relationships: Tae Kwann Park, None
Support: National Research Foundation of Korea (NRF) Grant 2013R1A1A2009899

Special Interest Groups 5
Corneal Endothelial Health and Disease

Organizer

Shigeru Kinoshita
Kyoto Prefectural University of Medicine, Kyoto, Kyoto, Japan

423: SIG5-1

The scientific foundation of DMEK for treatment of endothelial disorders

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

Endothelial dysfunction due to Fuchs corneal dystrophy or pseudophacic bullous keratopathy represents 40% of all keratoplasties performed in Europe and most parts of the Americas. Two major advancements on the therapy have been made: DSAEK and DMEK, the later representing transplantation of Decements membrane (DM). While we have shown that DMEK renders better outcome than DSAEK the surgical technique still lacks a standardized approach the interaction between stroma and DM is ill defined. Here we will present data which can be used to make DMEK surgery more standardized in the future. We have evaluated the anatomy and biochemistry of DM and its interaction with the stroma. Also we present data regarding the success of tissue preparation, tissue implantation, graft adhesion, migration of endothelial cells after transplantation as well as development of vision and higher order aberration. Also we will touch upon the probability of graft rejection after DMEK.

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

424: SIG5-2

Effect of Topography on Corneal Endothelial Cell Behaviour

Speaker: Jodhbir S. Mehta [1,2]
1. Singapore National Eye Centre, Singapore, Singapore. 2. Singapore Eye Research Institute, Singapore, Singapore.

The human corneal endothelium plays an important role in sustaining corneal transparency.
Human corneal endothelial cells have limited regenerative capability in vivo. Consequently, endothelial dysfunction can occur following corneal endothelial trauma or inherited diseases. To restore endothelial function, corneal transplantation is needed. However, there is a worldwide shortage of donor corneas, motivating development of tissue-engineered graft alternative using cultivated endothelial cells. To induce in vitro cell proliferation, much effort has been made to improve culture conditions and to mimic native extracellular microenvironment. We incorporated topographical and biochemical cues in our in vitro culture of human corneal endothelial cell line B4G12 (HCEC-B4G12) and hypothesized that manipulation of extracellular environment can modulate cell proliferation, morphometry, and phenotype. The topographies tested were nanopillars, microwells, and micropillars on polydimethylsiloxane (PDMS) while the biochemical factors were extracellular matrix protein coatings of fibronectin-collagen I (FC), FNC® Coating Mix (FNC), and laminin-chondroitin sulfate (LC).
Cellular morphometry, Na+/K+-ATPase and ZO-1 gene and protein expression were analyzed 3 days after cells formed confluent monolayer. Cell circularity on all patterns and coatings was above 0.78. On all coatings, cell area was the lowest on micropillars. Coefficient of variation of cell area was the lowest on nanopillars LC coating. With FC coating, micropillars induced better cellular outcome as the cells had greatest circularity, smallest cell area, and highest Na+/K+-ATPase and ZO-1 gene and protein expression. On LC coating, nanopillars resulted in lowest CV of cell area and highest ZO-1 gene expression. Thus, HCEC-B4G12 morphometry and phenotype can be improved using different topographical and biochemical cues.
Commercial Relationships: Jodhbir Mehta, None
Support: TCRP NMRC

425: SIG5-3

Development of a bioengineered corneal endothelial cell sheet to fit the corneal curvature

Speaker: Nobuyuki Shima [1] Masahiro Yamaguchi [2] Shiro Amano [3,4] Satoru Yamagami [1]
1. Department of Ophthalmology, The University of Tokyo, Bunkyo-ku, Tokyo, Japan. 2. Juntendo University School of Medicine, Tokyo, Japan. 3. Inoue Eye Hospital, Tokyo, Japan. 4. Miyata Eye Hospital, Ehime, Japan.

Corneal endothelial cells (CECs) have been found to proliferate *in vitro*, raising the possibility that CEC grafts could be developed by tissue engineering techniques. Several approaches have been tried for the transplantation of cultured CEC, such as injection of a cell suspension, or cell sheet transplantation. The former method could be difficult to apply clinically because it raises safety issues such as the problem of achieving selective attachment of the cells to Descemet's membrane without distribution to other organs. We thus selected the cell sheet transplantation method, which is similar to some techniques used for corneal transplantation, i.e., DSAEK and DMEK.
We tried various CEC sheet transplantation techniques for bullous keratopathy models. We used various scaffolds, because CEC sheet without a scaffold was too fragile to be practical for transplantation. We also developed a CEC sheet transplantation device using a commercially available IOL injector. Viscoat was effective

for protecting CEC from damage due to air exposure after transplantation. Transplanted CEC sheet maintained cell density more than 2800 cells/mm^2 and expression of CEC markers were as similar as donor CEC.
So far, flat sheets have been reported as candidates of scaffolds for CEC transplantation. However, a flat sheet sometimes becomes wrinkled at the peripheral area of corneal posterior surface after transplantation. These wrinkles caused CEC sheet detachment from the posterior surface of the cornea. We therefore evaluated the feasibility of using spherically curved gelatin hydrogel sheet (SCGS) as a scaffold for cultured CEC. After transplantation, the SCGS did not show wrinkling and adhered tightly to the posterior corneal surface. In a monkey or a rabbit model of bullous keratopathy, transplanted CEC-SCGS sheets showed good adhesion to the posterior corneal surface, with subsequent improvement of corneal edema and transparency.
More recently, we have developed a new CEC culture method, which enabled us to obtain CECs expressing much higher levels of progenitor markers. In vitro pomp function analysis of the CEC sheets revealed that the new method showed much higher pomp function than usual culture methods. We are preparing for clinical trial of CEC-SCGS sheet transplantation and we hope that our sheets will quickly improve visual acuity after transplantation for bullous keratopathy.
Commercial Relationships: Nobuyuki Shima, None; Masahiro Yamaguchi, None; Shiro Amano, None; Satoru Yamagami, None
Support: knowledge cluster initiative grant from the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) and adaptable and seamless technology transfer program through target-driven R and D, JST (A-STEP)

426: SIG5-4

Cell Therapy for the Treatment of Corneal Endothelial Dysfunction

Speaker: Naoki Okumura [1, 2]
1. Department of Biomedical Engineering, Doshisha University, Kyoto, Kyoto, Japan. 2. Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan.

Tissue engineering-based therapy for treating corneal endothelial dysfunction has been anticipated. In this presentation, I will present our recent findings associated with a novel cell culture protocol, as well as our findings that modulation of CEC adhesion properties via a Rho kinase inhibitor enables the transplantation of CECs in the form of a cell suspension. In addition, I will provide an update on the clinical application status of a cell-based therapy for treating corneal endothelial dysfunction.
Commercial Relationships: Naoki Okumura, Senju (P), JCR pharma (P), Doshisha university (P)
Support: The Highway Program for Realization of Regenerative Medicine from MEXT
Clinical Trail: UMIN000012534

Special Interest Groups 6
Retinal Development and Regeneration

Organizers
Takahisa Furukawa
Institute for Protein Research, Osaka University, Suita, Osaka, Japan
Masayo Takahashi
Center for Developmental Biology, RIKEN, Chuo, Kobe, Japan

585: SIG6-1

Differentiation of retinal precursor cells from human embryonic stem cell

Speaker: Jung Hyun Park [2,1] Hyeong Gon Yu [1]
1. Ophthalmology, School of Medicine, Seoul National University, Seoul, Korea (the Republic of). 2. Ophthalmology, Seoul Paik Hospital, Inje University, Seoul, Korea (the Republic of).

Human embryonic stem cells are one of the source for retinal pigment epitheliums (RPEs) and photoreceptors. We had derived precursors for RPEs and photoreceptors under the defined condition via the generation of cell masses of neural precursors, which we call spherical neural masses (SNMs). The derived cells had been characterized and transplanted into the retina of retinal degeneration rat model.

Commercial Relationships: Jung Hyun Park, None; Hyeong Gon Yu, None
Support: This work was supported by Basic Science Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Science, ICT & Future Planning(2014R 1A1A 100230)

586: SIG6-2

Regeneration therapy for retinal degeneration

Speaker: Michiko Mandai [1]
1. Laboratory for Retinal Regeneration, RIKEN Center for Developmental Biology, Kobe, Hyogo, Japan.

Now that by the introduction of sefl-organizing diffrentiation of retinal tissue from ES/iPS cells, reconstruction of photoreceptor layer by transplantation is one possible therapeutic option for end stage retinal degeneration.Here we would like to introduce our work using mouse ES/iPS derived retinal tissues transplanted into the subretinal space of progressive retinal degeneration model, rd1. iPS and ES cells both efficiently differentiated into retinal tissue and the younger tissues corresponding to the embryonic developmental stage of 17 or younger efficiently developed structured photoreceptor layers after transplantation even in the severly degenerated environment. These structured grafts could also develop outer segments with strong rhodopsin expression, indicating the full maturation of transplanted photoreceptors. The immunohistochemical observation of these photoreceptors in the structured graft also suggested a possible synaptogenesis between the host bipolar cells and graft photoreceptor cells. Our work suggested 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)

587: SIG6-3

Retinal development and retinitis pigmentosa

Speaker: Shinichi Fukuda [1]
1. Department of Ophthalmology, Institute of Clinical Medicine University of Tsukuba, Tsukuba, Ibaraki, Japan.

Retinitis pigmentosa (RP) is a group of inherited eye disorders and over 100 genes are identified as responsible. Typical gene therapy involves delivery of an expression cassette to mutant cells, which tends to suffer from transgene silencing, aberrant transcriptional regulation and insertional mutagenesis. An alternative strategy is gene targeting repair, allowing for normal regulation of gene expression from the endogenous locus. Such treatments (e.g. oligonucleotides) might be ideal, however, they have been confronted with several problems for actual clinical use; difficulties for selective delivery of drugs to target cells and the low efficiency.
Recently, gene targeting repair using adeno-associated virus (AAV) came to a promising alternative in non-ocular disease. In vitro approach utilizes iPS cells which were induced from patients with genetic diseases, and those cells were transplanted back to the patients again after their mutations were corrected by AAV. Here we propose idea of new treatment of RP potential patients in their childhood, as cell division of human photoreceptor occurs in fetal period and AAV can overcome problems of drug delivery.

Commercial Relationships: Shinichi Fukuda, None

588: SIG6-4

Atp6ap2/(pro)renin receptor is associated with cell polarity required for laminar formation during retinal development in mice

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

Six types of neurons (rod and cone photoreceptors, horizontal, bipolar, amacrine, and ganglion cells) and one type of Müller glial cells in the developing mouse retina originate from common multipotent progenitor cells in a highly conserved order, in which specific transcription-regulatory factors control cell fates. Retinal progenitor cells, initially composed of a single layer, extend processes to both apical and basal regions of the neuroepithelium. Photoreceptors at the apical side generate adherens junctions with Müller glial cells, and these cells are

connected by cadherins at adherens junctions that play critical roles in photoreceptor cell shape and retinal tissue integrity. The partitioning defective 3 homolog (Par3)-Par6-atypical protein kinase C (aPKC) λ complex (i.e., the Par-aPKC system) interacts with adherens junctions for the establishment and maintenance of cell polarity during retinal development.

Atp6ap2, also called (pro)renin receptor [(P)RR], is known to bind with prorenin causing the dual activation of tissue renin-angiotensin system (RAS) together with RAS-independent intracellular signaling pathways (i.e., receptor-associated prorenin system), and contributes to the molecular pathogenesis of end-organ damage such as inflammation and angiogenesis [Kanda A, et al., Diabetologia. 2012]. Recently, we found that Atp6ap2 interacts with Par3, and contributes to laminar formation during retinal development in mice. We propose that this cellular activity associated with the Par-aPKC system, besides the v-ATPase function and tissue RAS activation, is the third biological role of Atp6ap2/(P)RR.

Commercial Relationships: Atsuhiro Kanda, None
Support: Matching Program for Innovations in Future Drug Discovery and Medical Care, Takeda Science Foundation, Mishima Saiichi Memorial Ophthalmic Research Japan Foundation, Suzuken Memorial Foundation, and a grant-in-aid from the Ministry of Education, Science and Culture of Japan (A.K. #24791823).