

## Department of Ophthalmology

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### General Summary

The main research interest of our department is the pathophysiology of the visual processing system. The following topics are the subjects of basic and clinical studies: color vision, ocular oncology, histopathology, biochemistry, eye movement, neuro-ophthalmology, corneal and refractive surgery, cataract, glaucoma, electrophysiology, diabetes, vitreoretinal diseases, and uveitis.

### Research Activities

#### *Color vision defects and genetic analysis of retinal diseases*

1. We performed genetic testing of 26 male subjects with X-linked red/green color-vision deficiencies. The genotypes of the L and M visual pigment genes were determined with the polymerase chain reaction. Diagnoses of 11 protans and 15 deutans were made. All 13 dichromats had no difference in absorption maxima, whereas 85% (11 of 13 subjects) of anomalous trichromats had some separation in absorption maxima. However, no distinctive genotypes were found to distinguish severe (dichromacy and severe anomalous trichromacy) from mild (mild anomalous trichromacy) forms. Our results suggest that genetic testing is beneficial for distinguishing dichromacy from anomalous trichromacy.
2. We performed clinical and molecular genetic analysis of various inherited retinal diseases, such as retinitis pigmentosa and macular and cone dystrophies. We identified causative mutations in these diseases. To clarify disease haplotypes, results of haplotype analysis with mutations were compared between family members and control subjects.
3. We investigated the involvement of various genetic factors in Japanese patients with age-related macular degeneration, which is a common cause of blindness in the elderly in industrialized countries. More than 500,5688 single nucleotide polymorphisms of the entire genome were genotyped with Affymetrix Human Mapping Arrays and TaqMan assay. We are now analyzing the data to determine which single nucleotide polymorphisms are involved in Japanese patients with age-related macular degeneration.

#### *Ocular oncology and histopathology*

1. Ocular findings associated with systemic malignant tumors were reviewed. The clinical features of metastasis to the orbit and the choroid and of adnexal and ocular

malignant lymphoma and paraneoplastic syndrome were explained in detail. The preoperative evaluation, operative techniques, and management of complications in orbitotomy were described in a book.

2. We reported an unusual case of malignant solitary fibrous tumor arising in the orbit.

### *Biochemistry*

1. We investigated the protective effect of pigment epithelium—derived factor-loaded nanoparticles (PEDF-NPs) against photoreceptor degeneration in P23H transgenic rats. Immunocytochemistry did not show greater opsin preservation in PEDF-NP—treated retinas than in blank NP-treated retinas but did show a significantly higher number of photoreceptors. The results suggest that intravitreal injection of PEDF-NPs does not prevent photoreceptor degeneration in the P23H rat retina.

2. We evaluated the effects of intravenously administered methoxy polyethylene glycol-(D, L-lactide) (PLA-PEG) (stealth) nanoparticles (NPs) encapsulating betamethasone phosphate (BP) on experimental autoimmune uveoretinitis (EAU) in Lewis rats. The cy7-stealth NPs accumulated in the retina and choroid of rats with EAU and remained during the subsequent 3-day period. Furthermore, systemically administered BP-stealth NPs reduced in 1 day the clinical scores of rats with EAU, which were maintained for 2 weeks, and decreased the histological scores. In addition, the expression of inflammatory cytokines was reduced with this treatment. In conclusion, systemically administered BP-stealth NPs inhibit the development of EAU due to the targeting and the sustained release of steroids.

### *Eye movement*

Binocular summation on the visual cortex was explored by comparing cortical responses of binocular and monocular visual stimulation by means of functional magnetic resonance imaging (fMRI). Two different checkerboard stimuli were used. The binocular condition demonstrated signal intensities markedly higher than those in the monocular condition. Two stimuli demonstrated different binocular summation ratios and different increasing signal intensities. These results suggest that the binocular summation processes of these 2 visual stimuli differ in the visual cortex.

### *Neuro-ophthalmology*

1. Endothelin (ET)-1 is a potent vasoconstrictor peptide, and increased ET-1 levels have been described in diseases associated with vascular dysregulation. The pathogenesis of nonarteritic anterior ischemic optic neuropathy (NAION) is poorly understood but may involve vascular dysregulation and vasoconstriction of the nutrient vessels supplying the optic nerve head. To clarify the possible pathophysiological role of ET-1 in the development of NAION, we examined plasma ET-1 levels in patients with NAION. We found increased plasma ET-1 levels in patients with NAION. Our data indicate that elevated plasma ET-1 may be an important risk factor in the development of NAION and suggest that an ET-receptor antagonist might offer a new therapeutic approach to this disease.

2. The assessment of the pupillary reflex in patients with diabetes and the diagnosis of

ocular torticollis were reviewed. Articles on the treatment for neuroretinitis, the differential diagnosis of anisocoria, and the surgical technique of blepharoptosis were published. Neuro-ophthalmological examination in the fields of otorhinolaryngology and neurosurgery was described in books. Brief outlines of neuro-ophthalmology and general ophthalmology were included in textbooks for students of medicine and pharmacology.

3. We reported a case of optic neuropathy with severe visual loss that was detected during the follow-up of a patient with systemic lupus erythematosus. Early corticosteroid pulse therapy was effective in the treatment of severe optic neuropathy associated with systemic lupus erythematosus. We reported the features of optical coherence tomography of retinal lesions in neuro-ophthalmologic disorders and the clinical findings of anti-aquaporin 4 antibody-positive optic neuritis.

#### *Cornea and refractive surgery*

The cornea group at The Jikei University chooses the most appropriate method of corneal surgery by discussing the various options with each patient. We replace only those corneal components that are actually damaged. Photorefractive keratectomy is effective for cases of surface corneal opacity, and automated lamellar therapeutic keratoplasty (ALTK) is also effective for cases of corneal stroma opacity. We also perform Descemet's stripping automated endothelial keratoplasty for corneal endothelium dysfunction.

We have adapted several new treatments for all diseases, such as dry eye, corneal infection, corneal injury, hereditary corneal disease, allergic corneal disease, and keratoconus. ALTK, in which a microkeratome is used to make a lamellar flap, was performed in several cases of corneal opacity. We found that ALTK allows earlier suture removal and induces less astigmatism than does conventional lamellar keratoplasty.

We studied the clinical outcomes of secondary implantation of iris-clip intraocular lens for aphakic eyes for 5 years postoperatively. Clinically significant complications were not found with specular microscopy or a laser flaremeter.

#### *Glaucoma*

1. We compared the effectiveness of Humphrey Matrix perimetry, scanning laser polarimetry with variable corneal compensation (Zeiss GDx scanning laser polarimeter), and optical coherence tomography (Zeiss Stratus OCT 3000) for the early detection of glaucoma. We found that the detection precision of Humphrey Matrix perimetry was equal to those of these optical imaging devices and that pattern standard deviation was the most effective variable.

2. We evaluated the shape and structure of blebs after the trabeculectomy from various angles. We examined risk factors causing leaking bleb and overhanging bleb in relation to operative method and postoperative management.

3. We investigated the effect of ocular optical system aberrations in perimetry, especially for peripheral vision measurement. In peripheral vision, there were astigmatism and coma aberrations, and the point images that were projected onto the retina differed

with the measurement site. These findings suggest that the aberration affects the results of threshold measurements in the peripheral vision.

### *Electrophysiology*

We are performing electroretinography (ERG) to evaluate functional retinal disorders in hereditary retinal degeneration diseases.

The ERG waveforms are recorded as response waves from retinal cells, such as ganglion, amacrine, bipolar, and photoreceptor cells. On the ERG, we use 3 types of machines to obtain full-field, multifocal, and color ERGs. The full-field ERG is recorded according to an international standard, and the responses from cone and rod cells can be separated. The multifocal ERG reflects mainly cone function in the central 30-degree area of the retina which shows mainly cone function, and can record 61 elements. The color ERG records responses separately from long-, middle-, and short-wavelength cones.

In the future, we will evaluate waveforms recorded from full-field ERG, which can be more fully analyzed with a personal computer program. Moreover, as we extract a waveform from a single type of retinal cell, we will be able to investigate retinal disorders at a more detailed level.

### *Diabetes and vitreoretinal diseases*

We have used 23-gauge and 25-gauge transconjunctival vitrectomy systems for macular hole, epiretinal membrane, macular edema and rhegmatogenous retinal detachment. The 25- and 23-gauge sutureless vitrectomy techniques decrease surgical trauma and improve patients' postoperative comfort. The 25- and 23-gauge instrumentation is effective for a variety of vitreoretinal surgical indications. Although the infusion and aspiration rates of the 25- and 23-gauge instruments are lower than those of the 20-gauge high-speed vitrectomy system, the use of 25- and 23-gauge transconjunctival vitrectomy systems may effectively reduce operative times of select cases that do not require the full capability of conventional vitrectomy.

To evaluate the clinical efficacy of the 7-mm intraocular lens (Eternity, Santen Pharmaceutical Co., Ltd.) for combined pars plana vitrectomy, phacoemulsification, and intraocular lens implantation, we observed the visibility of the retina during vitrectomy and measured the depth of anterior chamber preoperatively and postoperatively with the Pentacam (Oculus Optikgeräte GmbH).

We are planning to evaluate changes in regular and irregular corneal astigmatism after 25-gauge and 23-gauge transconjunctival sutureless vitrectomy.

### *Uveitis*

1. A novel therapy with a chimeric antibody against tumor necrosis factor alfa for Behçet disease

Intravenous infliximab significantly decreased the frequency of ocular attacks and improved visual acuity. In addition, we found that intraocular surgery can be performed effectively and safely to improve the vision of patients receiving infliximab therapy for Behçet disease.

## 2. A case of ocular toxocariasis with neuroretinitis

Ocular toxocariasis is usually associated with a history of *Toxocara canis* infection and causes various ophthalmic manifestations, including chronic endophthalmitis, posterior pole granuloma, and peripheral granulomatous inflammatory mass. Neuroretinitis is a rare manifestation of ocular toxocariasis. Oral prednisolone was effective in inhibiting local inflammatory and immunologic responses.

### *Visual neuropsychology*

#### 1. Two temporal channels in human V1 identified with fMRI

We measured responses to spatial uniform (Ganzfeld) luminance changes in the human visual cortex by means of fMRI. We attempted various temporal modulation stimuli without a spatial contrast pattern and found that the blood oxygen level—dependent signal consisted of transient and sustained channel responses that had been reported in previous psychophysical studies. By identifying these 2 independent channels with linear model analysis, we revealed that the relative contribution of these channels varies with the eccentricities across V1.

#### 2. The objective visual field map with fMRI

We developed a software program to analyze visual field maps obtained with fMRI. To evaluate the usefulness of this analysis, we planned an experiment with hemifield visual stimuli and succeeded in drawing a pseudohemianopic visual field map.

#### 3. Neural plasticity of area V1

We used fMRI to assess abnormal V1 signals in patients with juvenile macular degeneration. These signals have been interpreted as indicating cortical plasticity. Subjects viewed a stimulus passively or performed a stimulus-judgment task. During passive viewing, there were large unresponsive V1 regions. We refer to these regions as the lesion-projection zones. In patients with juvenile macular degeneration, we observed highly significant responses in the lesion-projection zones while they performed a task. These task-dependent signals can be explained by hypotheses that have very different implications for V1 plasticity. We propose that these responses were driven by feedback signals by the task demands. Deletion of retinal feed-forward inputs may unmask pre-existing task-dependent feed-back signals that are ordinarily suppressed.

### *Low vision*

We used two methods to measure the visual acuity of patients with low vision and brain injury and examined the degree of divergence. Each eye's visual acuity was measured with both Teller Acuity Cards and Landolt Rings. We further examined the degree of visual field loss. The visual acuity measured with Teller Acuity Cards was significantly better than that measured with Landolt Rings for patients with brain injury and eccentric viewing.

We reported on children of school age who visited the low-vision clinic at Kanagawa Rehabilitation Hospital and on those who were supported by a home for visual disabilities.

## Publications

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