



The International Symposium on
Ocular Pharmacology and Therapeutics

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11th ISOPT *Clinical*

June 19-22, 2014, Reykjavik, Iceland

Scientific Program



DETECT and INJECT

- Vitreomacular traction (VMT), including macular hole, can be progressive and may put patients at risk of central vision loss¹⁻⁴
- To date, there have been only two options (1) Watch and wait; (2) Vitrectomy



INTRODUCING

JETREA® (ocriplasmin) Intravitreal (IVT) Injection

The first pharmacologic treatment for vitreomacular traction (VMT) in adults, including when associated with macular hole of diameter $\leq 400 \mu\text{m}$ ¹

- In clinical trials, a single injection of JETREA® (ocriplasmin) Intravitreal (IVT) Injection was shown to resolve VMT and to help close macular hole as compared to placebo²
- 26.5% of patients treated with JETREA® achieved resolution of VMT at Day 28 (vs 10.1% with placebo)²
- 40.6% of patients treated with JETREA® with full-thickness macular hole (associated with VMT) achieved closure of macular hole of diameter $\leq 400 \mu\text{m}$ at Day 28 (vs 10.6% with placebo)²

 ThromboGenics®


a Novartis company

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Date of preparation: May
JET/OCR: HCP 059/03/13(AL) (A)

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JETREA▼
(ocriplasmin)
Concentrate for solution
for injection, 0.5mg/0.2ml

REFERENCES: 1. JETREA Summary of Product Characteristics. ThromboGenics NV, Belgium; January 2013. 2. Stalmans P, Benz MS, Gandorfer A, Kampik A, et al. Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular hole. *N Engl J Med.* 2012;367(7):606-615. 3. Carrero JL. Incomplete posterior vitreous detachment: prevalence and clinical relevance. *Am J Ophthalmol.* 2012;153(3):497-503. 4. Schneider EW, Johnson MW. Emerging nonsurgical methods for the treatment of vitreomacular adhesion: a review. *Clin Ophthalmol.* 2011;5:1151-1165.

Brief Summary – Please refer to the JETREA® SmPC for full prescribing information

JETREA® 0.5 mg/0.2 ml concentrate for solution for injection (ocriplasmin) Prescribing Information (Refer to full Summary of Product Characteristics (SmPC) before prescribing).
Presentation: Type I glass vial containing 0.2ml concentrate for solution for injection (excipients: mannitol, citric acid, sodium hydroxide (pH adjustment), water for injections). After dilution with 0.2ml of sodium chloride 0.9% solution for injection, 0.1ml of the diluted solution contains 0.125mg ocriplasmin. **Indication(s):** Treatment of vitreomacular traction (VMT) in adults, including when associated with macular hole of diameter less than or equal to 400 microns. **Posology and method of administration:** Adults, including the elderly: Intravitreal injection of 0.125 mg (0.1 ml of the diluted solution) to the affected eye once only as a single dose. **Children and adolescents:** Not recommended. **Hepatic and renal impairment:** No dosage adjustment necessary. **Contraindications:** Hypersensitivity to ocriplasmin or any of the excipients. Active or suspected ocular or perocular infections. **Warnings and precautions:** Proper aseptic injection techniques must always be used and patients should be monitored for any side effects such as, but not limited to, intraocular inflammation/infection and elevation in IOP. Transient increases in IOP including transient blindness and non-perfusion of the optic nerve have been seen within 60 minutes of injection of JETREA. Patients should be instructed to report symptoms of intraocular inflammation/ infection or any other visual/ ocular symptoms without delay. Concurrent administration to both eyes or repeated administration in the same eye is not

recommended. Clinical data is not available on concomitant use with VEGF-inhibitors. Treatment is not recommended in patients with large diameter macular holes (>400microns), high myopia, aphakia, history of rhegmatogenous retinal detachment, lens zonule instability, recent ocular surgery or intraocular injection (including laser therapy), proliferative diabetic retinopathy, ischaemic retinopathies, retinal vein occlusions, exudative age-related macular degeneration (AMD) and vitreous haemorrhage. There is potential for lens subluxation or phacodonesis. Exercise caution if treating patients with non-proliferative diabetic retinopathy, history of uveitis or significant eye trauma. Ocriplasmin efficacy is reduced in patients with an epiretinal membrane or a diameter of VMA > 1500microns. Due to potential increase in tractional forces, there is a risk of occurrence of new or enlarged macular holes. There is a risk of significant but transient loss of visual acuity during the first week after the injection. **Interactions:** Formal studies have not been performed. Systemic interactions are not anticipated. Administration in close temporal association in the same eye with other medicinal products is not recommended as this may affect the activity of both products. **Pregnancy and lactation:** Do not use unless the clinical benefit outweighs the potential risks. **Fertility:** No fertility data are available. **Effects on ability to drive and use machines:** If visual disturbances occur, wait until vision clears before driving or operating machinery. **Undesirable effects:** Very common: Vitreous floaters, eye pain, conjunctival haemorrhage. Common: Visual acuity reduced, visual impairment, vision blurred, retinal haemorrhage,

vitreous haemorrhage, retinal tear, retinal detachment, intraocular pressure increased, macular hole, macular degeneration, retinal degeneration, macular oedema, retinal oedema, retinal pigment epitheliopathy, metamorphopsia, vitreous adhesions, conjunctival oedema, eyelid oedema, vitritis, anterior chamber cell, anterior chamber flare, iritis, photopsia, conjunctival hyperaemia, ocular hyperaemia, vitreous detachment, retinogram abnormal, eye irritation, dry eye, foreign body sensation in eyes, eye pruritus, ocular discomfort, photophobia, chromatopsia. **Uncommon:** transient blindness, lens subluxation, scotoma, visual field defect, diplopia, hyphaema, miosis, pupils unequal, corneal abrasion, anterior chamber inflammation, eye inflammation, conjunctival irritation. Prescribers should consult the SmPC in relation to the side effects. **Overdose:** Clinical data are limited. If an overdose occurs, close monitoring is recommended. **Incompatibilities:** Must not be mixed with other medicinal products except for the specified diluent. **Special Precautions for Storage:** Store frozen at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$. Unopened product in the original carton protected from light has been demonstrated for up to 8 hours when stored below 25°C . Do not refreeze a vial once it has been thawed. **MA Number(s):** EU/1/13/819/001. Further information available from the MA holder: ThromboGenics NV, Gaston Geenslaan 1, B-3001 Leuven, Belgium. Please note that the product is registered in Iceland but not yet marketed.

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Chairs: **B.D. Kuppermann**, USA & **J. Mones**, Spain

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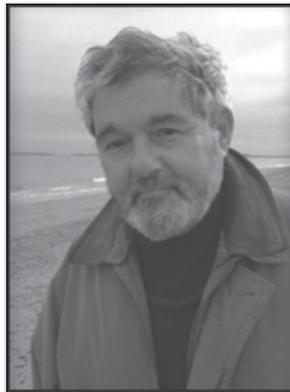
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*The ISOPT Retina section is devoted to
Prof. Ephraim Friedman
1930 -2011*



A friend
A humanist mentor
A relentless explorer on the pathogenesis of AMD
A sculptor



www.ephraimfriedman.com

Thursday, June 19, 2014

Afternoon Sessions – Hall A

14:00-15:30	Diabetic Macular Edema Chairs: <u>Albert J. Augustin</u> , Germany & <u>Michaella Goldstein</u> , Israel	Hall A
14:00	Subthreshold MicroPulse Laser for Diabetic Macular Edema: Basic Science and Clinical Results <u>Jose A. Cardillo</u> , Brazil	
14:13	Aflibercept for DME <u>Patricia Udaondo</u> , Spain	
14:26	Steroid Implants for DME <u>Baruch D. Kuppermann</u> , USA	
14:39	Combination Therapy for Diabetic Macular Edema <u>Albert J. Augustin</u> , Germany	
14:52	Guidelines for the Use of Laser, Anti-VEGF, or Steroids in DME <u>Michaella Goldstein</u> , Israel	
15:05	Anti-VEGF Treatments for Diabetic Macular Edema: Comparison of Phase III Randomized Controlled Clinical Studies <u>Baruch D. Kuppermann</u> , USA	
15:18	Diabetic Macular Edema Case Discussion Panel: <u>Michaella Goldstein</u> , Israel	
15:30-16:00	Coffee Break	Exhibition Hall
16:00-17:30	The New Era of Steroid Therapy for Uveitis Chair: <u>Francine Behar-Cohen</u> , France	Hall A
16:00	Injectable Steroids/Non-Steroid Options <u>Simon R.J. Taylor</u> , UK	
16:10	The Barrier to Inject – Keeping the Risk/Benefit Equation Right <u>Yan Guex-Crosier</u> , Switzerland	
16:20	Differentiating the New Injectable Steroids <u>Francine Behar-Cohen</u> , France	
16:30	The Conundrum of Steroids or VEGF Inhibitors for Retinal Indications <u>Sofia Androudi</u> , Greece	
16:45	Discussion	
17:30	Welcome Reception	Exhibition Hall

Thursday, June 19, 2014

Afternoon Sessions – Hall B

14:00-14:45	New Therapeutic Options for Retinal Diseases Chair: <u>Francine Behar-Cohen</u> , France	Hall B
14:00	Derivation of Traceable and Transplantable Photoreceptors from Embryonic Stem Cells <u>Yvan Arsenijevic</u> , Switzerland	
14:10	iPSCs: What can we Hope? How to Use Them? <u>Olivier Goureau</u> , France	
14:20	Developing New Drugs and Delivery Systems for the Treatment of Inherited Retinal Degeneration: The DRUGSFORD Project <u>François Paquet-Durand</u> , Germany	
14:30	Gene Delivery to the Retina: Choice for a Vector and a Route of Administration <u>Francine Behar-Cohen</u> , France	
14:40	Q&A	
14:45-15:30	Pharmacology in Neuro-Ophthalmology Chair: <u>Hana Leiba</u> , Israel	Hall B
14:45	Botulinum Toxin <u>Fion Bremner</u> , UK	
14:55	Optic Neuritis <u>Hana Leiba</u> , Israel	
15:05	Medical Treatment to Anterior Ischemic Optic Neuropathy <u>Nitza Cohen-Goldenberg</u> , Israel	
15:15	Neurophthalmological Side Effect of Medical Treatment <u>Klara Landau</u> , Switzerland	
15:30-16:00	Coffee Break	Exhibition Hall
16:00-17:30	Anterior Segment Imaging Chair: <u>Penny Asbell</u> , USA	Hall B
16:00	Imaging in Ocular Surface Disease <u>Penny A. Asbell</u> , USA	
16:10	Boston Keratoprosthesis Multicenter Study: Retention and Vision <u>Joseph B. Ciolino</u> , USA	
16:20	In Vivo Histology of Amniotic Membrane Integration in the Human Cornea <u>Berthold Seitz</u> , Germany	
16:30	Inflammation (Confocal) in Dry Eye Disease <u>Pedram Hamrah</u> , USA	
16:40	UV Crosslinking of Donor Corneas to Prevent Keratolysis <u>Joseph B. Ciolino</u> , USA	
16:50	Correlations of Real Time Tear Film Metrology to Subject Symptomology <u>James Aquavella</u> , USA	
17:00	Imaging of the Ocular Surface with Ultra High Resolution Optical Coherence Tomography (UHR-OCT) <u>Victor K. Perez</u> , USA	
17:10	Devices for the Anterior Segment in the US: Reality vs. Myth <u>Malvina B. Eydelman</u> , USA	
17:20	Q&A Panel	
17:30	Welcome Reception	Exhibition Hall

Friday, June 20, 2014

Morning Sessions – Hall A

08:00-09:00 **Cases** **Hall A**
Chair: Eric H. Souied, France

Mystery Case

Eric H. Souied, France

Management of Macular Edema Secondary to Retinitis Pigmentosa

Paolo Lanzetta, Italy

About Angioid Streaks

Gerard Mimoun, France

Some Unusual Cases for Macular Hole Surgery

Albert J. Augustin, Germany

Mystery Case

Francesco Boscia, Italy

You Don't Know JAK

Elias Reichel, USA

Young Maculopathy

Johanna M. Seddon, USA

Mystery Case

Marc Labetoulle, France

A Typical Case of Neovascular AMD

Michaella Goldstein, Israel

A Case Mimicking Neovascular AMD

Shiri Shulman, Israel

09:00-10:30 **Dry AMD** **Hall A**
Chairs: Jordi Mones, Spain & Elias Reichel, USA

09:00 **Pathophysiology of Dry Age Related Maculopathy**

Francesco Boscia, Italy

09:10 **New Approaches to Screening for AMD**

Michaella Goldstein, Israel

09:20 **The Role of Imaging in the Management of Dry AMD**

Gisele Soubrane-Daguet, France

09:30 **The Role of Genetic Testing in the Management of AMD**

Itay Chowers, Israel

09:40 **The TOGA Study: A Phase II/III Study Evaluating the (T)reatment with (O)RACEA (doxycycline) for (G)eographic (A)trophy**

Elias Reichel, USA

09:50 **The Complement System in Dry AMD MAHALO and Others**

Jordi Mones, Spain

10:00 **Alprostadiol for Dry Age Related Macular Degeneration (AMD)**

Albert J. Augustin, Germany

10:10 **Complement Inhibition Using Gene Therapy for AMD**

Elias Reichel, USA

10:20 **Multimodal Functional and Morphological Aspects of Reticular Pseudodrusen**

Eric H. Souied, France

10:30-11:00 **Coffee Break** **Exhibition Hall**

Friday, June 20, 2014

Morning Sessions – Hall A

11:00-11:45	Industry Sponsored Session Severe Dry Eye Disease: Facing the Treatment Challenges Chair: Gysbert van Setten , Sweden	Hall A Page 41
<hr/>		
11:45-12:30	Dry AMD Cont. Chairs: Jordi Mones , Spain & Elias Reichel , USA	Hall A
<hr/>		
11:45	Toward Personalized Medicine in AMD Eric H. Souied , France	
12:05	Case Discussion: How to Follow, Imaging Options, When to Start Nutraceuticals, Role of Complement, Role of Genetic Testing Panel: Francesco Boscia , Italy, Itay Chowers , Israel, Jordi Mones , Spain & Elias Reichel , USA	
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12:30-13:30	Industry Sponsored Lunch Session Ocriplasmin Intravitreal Injection: The Real-World Experience	Hall A Page 41

Friday, June 20, 2014

Morning Sessions – Hall B

08:30-10:30	Infection Chair: <u>Irina Barequet</u> , Israel	Hall B
08:30	Is Tigecycline the Next New Ocular Antibiotic? <u>Eric G. Romanowski</u> , USA	
08:40	The Use of Predatory Prokaryotes to Control Human Ocular Pathogens <u>Robert Shanks</u> , USA	
08:50	Adenoviral Keratoconjunctivitis: Diagnosis and Treatment <u>Penny A. Asbell</u> , USA	
09:00	Clinical Characteristics and Outcomes of Patients with Keratitis Admitted to an Israeli Departments of Ophthalmology <u>Fabio Lavinsky</u> , Brazil	
09:10	Ointment or Eye Drops for Prophylaxis in Corneal Erosions? Comparison of Chloramphenicol Eye Drops vs. Ointment in an Experimental Model <u>Irina Barequet</u> , Israel	
09:20	Microbiological, Chemical, and Mathematical Analysis of Alexidine-Polyethylene Interaction: Implications for the Fusarium Keratitis Epidemic of 2004-2006 <u>John D. Bullock</u> , USA	
09:30	The Comparison of Validated PCR to Culture Isolation for the Detection of Acanthamoeba from Ocular Samples <u>Regis P. Kowalski</u> , USA	
09:40	Development of a Novel Diagnostic Method and Treatment for Acanthamoeba Keratitis <u>Takashi Suzuki</u> , Japan	
09:50	Delayed Course of Acanthamoeba Keratitis <u>Berthold Seitz</u> , Germany	
10:00	Acanthamoeba Infections Related to Contact Lenses <u>Malvina B. Eydelman</u> , USA	
10:10	Discussion	
10:30-11:00	Coffee Break	Exhibition Hall
11:00-11:45	Industry Sponsored Session Severe Dry Eye Disease: Facing the Treatment Challenges Chair: <u>Gysbert van Setten</u> , Sweden	Hall A Page 41
11:45-12:30	Industry Sponsored Session Steroids in the Management of Macular Edema Chairs: <u>Baruch D. Kuppermann</u> , USA & <u>Paolo Lanzetta</u> , Italy	Hall B Page 41
12:30-13:30	Industry Sponsored Lunch Session Ocriplasmin Intravitreal Injection: The Real-World Experience	Hall C Page 41

Friday, June 20, 2014

Morning Sessions – Hall C

08:00-09:15	Microinvasive Glaucoma Surgery (MIGS) Techniques Chairs: <u>Malvina Eydelman</u> , USA & <u>Kuldev Singh</u> , USA	Hall C
08:00	Introduction <u>Malvina B. Eydelman</u> , USA	
08:03	The Patient Population that May Benefit from Minimally Invasive Glaucoma Surgical (MIGS) Procedures <u>Kuldev Singh</u> , USA	
08:10	Non-Implantable and Canal Based Implantable MIGS Procedures <u>Paul Harasymovycz</u> , USA	
08:22	Suprachoroidal and Subconjunctival Implantable MIGS Procedures <u>Steve D. Vold</u> , USA	
08:34	Regulation of MIGS Devices in the U.S. <u>Malvina B. Eydelman</u> , USA	
08:46	MIGS - Defining Safety with New Devices <u>Richard K. Parish</u> , USA	
09:00	Panel Discussion: Safety, Efficacy and Composite Endpoints <u>Malvina B. Eydelman</u> , USA, <u>Kuldev Singh</u> , USA, <u>Richard K. Parrish II</u> , USA & <u>Steven D. Vold</u> , USA	
09:15-10:30	Inhibition of Diabetic Retinopathy Chair: <u>Arup Das</u> , USA	Hall C
09:15	Adrenergic Receptors and Diabetic Retinopathy <u>Timothy Kern</u> , USA	
09:30	Stem Cell Therapy for Diabetic Retinopathy <u>Alexander V. Ljubimov</u> , USA	
09:45	Targeting the Arginase/Polyamine Pathway as a Novel Therapy <u>Ruth Caldwell</u> , USA	
10:00	Protective Effect of PPAR Alpha in Diabetic Retinopathy <u>Jian-Xing Ma</u> , USA	
10:15	Transport and Microglial Uptake of Dendrimers in Normal and Ischemia Reperfusion Retina <u>Gerard Luttj</u> , USA	
10:30-11:00	Coffee Break	Exhibition Hall
11:00-11:45	Industry Sponsored Session Severe Dry Eye Disease: Facing the Treatment Challenges Chair: <u>Gysbert van Setten</u> , Sweden	Hall A Page 41
11:45-12:30	Glaucoma: Imaging, Agents, Drug Delivery Chair: <u>Barrett Katz</u> , USA	Hall C
11:45	Imaging of the Lamina Cribosa <u>Gadi Wollstein</u> , USA	
12:00	Outflow Drugs: What Does the Future Hold? <u>Paul Kaufman</u> , USA	
12:10	Pressure Lowering Agents: What is on the Horizon? <u>Brian Levy</u> , USA	
12:25	Q&A	
12:30-13:30	Industry Sponsored Lunch Session Ocriplasmin Intravitreal Injection: The Real-World Experience	Hall A Page 41

Friday, June 20, 2014

Afternoon Sessions – Hall A

14:00-14:45	Retinal Imaging Chair: <u>Gisele Soubrane-Daguet</u> , France	Hall A
14:00	Imaging of the Retina in OCT: Is it Reliable? <u>Vas Sadda</u> , USA	
14:10	Images of the Choroid: Is it Useful? <u>Gisele Soubrane-Daguet</u> , France	
14:20	Imaging of the Retinal Vessels: With which Means? <u>Nagahisa Yoshimura</u> , Japan	
14:30	SD-OCT of the Nerve Fiber Layer – OCT for Non-Ophthalmologists <u>Albert J. Augustin</u> , Germany	
14:30	Q&A	
14:45-15:30	Nutrition Antioxidants and Genes Chair: <u>Johanna Seddon</u> , USA	Hall A
14:45	Shedding Light on Fundus Autofluorescence and RPE Lipofuscin <u>Janet Sparrow</u> , USA	
14:55	Protective Effect of Glutathione S-Transferase Pi Isoform (GSTP1) Expression in RPE and in Young and Aging Retina <u>Wen-Hsiang Lee</u> , USA	
15:05	Circulating Omega-3 Fatty Acids and Neovascular Age-Related Macular Degeneration <u>Bénédicte Merle</u> , France	
15:13	CFH and ARMS2 Genotypes and Oral Supplementation with Docosahexaenoic Acid for Neovascular Age-Related Macular Degeneration <u>Eric H. Souied</u> , France	
15:20	Omega-3 Fatty Acids and Fat Intake, Genetic Susceptibility and Progression to Geographic Atrophy <u>Johanna M. Seddon</u> , USA	
15:25	Discussion <u>All Speakers</u>	
15:30-16:00	Coffee Break	Exhibition Hall
16:00-17:30	Retinal Vein Occlusion Chairs: <u>Francesco Boscia</u> , Italy & <u>Patricia Udaondo</u> , Spain	Hall A
16:00	Aflibercept for Retinal Vein Occlusion <u>Paolo Lanzetta</u> , Italy	
16:15	Steroids for RVO <u>Patricia Udaondo</u> , Spain	
16:30	Laser for RVO <u>Francesco Boscia</u> , Italy	
16:45	Clinical Markers of Inflammation and Exudation in ME due to RVO <u>Albert J. Augustin</u> , Germany	
17:00	RVO Case Discussion Moderator: <u>Patricia Udaondo</u> , Spain Panel: <u>Paola Lanzetta</u> , Italy, <u>Albert J. Augustin</u> , Germany & <u>Francesco Boscia</u> , Italy	

Friday, June 20, 2014

Afternoon Sessions – Hall B

14:00-15:30	Drug Delivery I Chairs: <u>Robert Gurny</u> , Switzerland & <u>Francine Behar-Cohen</u> , France	Hall B
14:00	An Overview of Delivery Technologies for the Long-term Delivery of Macromolecules to the Back of the Eye <u>Ann Daugherty</u> , USA	
14:30	Non-viral Gene Therapy: Where are We? <u>Francine Behar-Cohen</u> , France	
14:45	In Vitro Testing of Drug Transport in the Eye <u>Randy Mrsny</u> , UK	
15:00	Prodrugs of Cyclosporine: Pros and Cons <u>Robert Gurny</u> , Switzerland	
15:15	Microparticulate Drug Delivery Systems for the Treatment of Chronic Ophthalmic Diseases <u>Maria Rocio Herrero-Vanrell</u> , Spain	
15:30-16:00	Coffee Break	Exhibition Hall
16:00-17:30	Drug Delivery II Chairs: <u>Diane Tang-Liu</u> , USA & <u>Maria Rocio Herrero-Vanrell</u> , Spain	Hall B
16:00	Recent Advances in Gene Therapy <u>Yvan Arsenijevic</u> , Switzerland	
16:15	Long Acting Delivery of Antibody Therapeutics to the Back of the Eye <u>Robert F. Kelley</u> , USA	
16:30	Macromolecule Delivery to the Posterior Segment: Recent Advances <u>Diane Tang-Liu</u> , USA	
16:45	Nanoparticle Delivery for Ocular Disease <u>Kim Brazzell</u> , USA	
17:00	New Concept to Treat Herpes Simplex Keratitis and Uveitis: Iontophoretic Delivery of Water-soluble, Biolabile Aciclovir Prodrugs into Ocular Tissue <u>Yong Chen</u> , Switzerland	
17:15	Topical Ocular Delivery of Drugs to the Back of the Eye – Current Trends <u>James Chastain</u> , USA	

Friday, June 20, 2014

Afternoon Sessions – Hall C

14:00-15:30	Allergic Conjunctivitis Chair: <u>Esen K. Akpek</u> , USA	Hall C
14:00	Ocular Allergy Introduction: Magnitude of the Problem <u>Esen K. Akpek</u> , USA	
14:05	Vernal Keratoconjunctivitis: A Case-Based Presentation <u>Bennie Jeng</u> , USA	
14:20	Deciphering the Immunopathogenesis of Ocular Allergy <u>Michael Stern</u> , USA	
14:35	Vernal Keratoconjunctivitis: Update on Clinical and Immunological Findings <u>Andrea Leonardi</u> , Italy	
14:50	Atopic Keratoconjunctivitis: Update on Treatment <u>Esen K. Akpek</u> , USA	
15:05	Case Discussion Moderator: <u>Esen K. Akpek</u> , USA	
15:30-16:00	Coffee Break	Exhibition Hall
16:00-17:30	Ocular Surface Disease - Mechanisms of Action Chair: <u>Penny A. Asbell</u> , USA	Hall C
16:00	Lids, Lipids, and Dry Eyes: Clinical Overview <u>James McCulley</u> , USA	
16:10	The Cytology in Ocular Surface Disease Diagnosis <u>Pasquale Aragona</u> , Italy	
16:20	Immunopathogenic Mechanisms in Dry Eye Disease <u>Reza Dana</u> , USA	
16:30	Cold Sensation and Dry Eye <u>Jesus Merayo-Llolves</u> , Spain	
16:40	Biomarker and Clinical Importance in Dry-Eye <u>Franz Grus</u> , Germany	
16:50	Molecular Biomarkers of Eye Disease <u>Roger Beuerman</u> , Singapore	
17:00	The Role of Ocular Surface Epithelia in Dry Eye Syndrome <u>Stefano Barabino</u> , Italy	
17:10	Autologous Serum in the Treatment of Ocular Surface Conditions <u>Bennie Jeng</u> , USA	
17:20	Learning Immune Lessons for Dry Eye Pathology and Treatment from Graft vs. Host Disease <u>Victor K. Perez</u> , USA	

Saturday, June 21, 2014

Morning Sessions – Hall A

08:45-09:30	Technologies: Drug Delivery & Diagnostics Chairs: <u>Jose A. Cardillo</u> , Brazil & <u>Einar Stefánsson</u> , Iceland	Hall A
08:45	Microsphere Drug Delivery <u>Jose A. Cardillo</u> , Brazil	
08:55	Cyclodextrin Nanoparticles Optimize Eye Drops for Anterior Segment and Retinal Drug Delivery <u>Gauti Jóhannesson</u> , Sweden	
09:05	Retinal Oximetry in Diabetic Retinopathy and Retinal Vein Occlusions <u>Sveinn Hakon Hardarson</u> , Iceland	
09:15	Risk Stratification in Diabetic Retinopathy <u>Olafur Palsson</u> , Iceland	
09:25	Q&A	
09:30-10:30	Anti-VEGF Chairs: <u>Paolo Lanzetta</u> , Italy & <u>Zohar Yehoshua</u> , USA	Hall A
09:30	A Review of Controversial Safety Topics in AMD, RVO and DME Patients Treated with Anti-VEGF Agents <u>Baruch D. Kuppermann</u> , USA	
09:42	Ocular Side Effects of Intravitreal Anti-VEGF Therapy <u>Zohar Yehoshua</u> , USA	
09:54	Choosing Anti-VEGF Therapy for Wet Age-Related Macular Degeneration <u>Paolo Lanzetta</u> , Italy	
10:06	Panel Discussion Moderator: <u>Baruch D. Kuppermann</u> , USA Panel: <u>Zohar Yehoshua</u> , USA, <u>Paolo Lanzetta</u> , Italy & <u>Peter Kaiser</u> , USA	
10:30-11:00	Coffee Break	Exhibition Hall
11:00-12:30	Wet AMD Chairs: <u>Peter Kaiser</u> , USA & <u>Baruch D. Kuppermann</u> , USA	Hall A
11:00	Synopsis of Comparison Studies: CATT, IVAN, MANTA, GEAFFAL <u>Zohar Yehoshua</u> , USA	
11:10	Pazopanib Eye Drops for the Treatment of Neovascular AMD <u>Baruch D. Kuppermann</u> , USA	
11:20	Integrin Peptide Therapy: The First Wet AMD Experience <u>Peter Kaiser</u> , USA	
11:30	Fovista Combination Therapy for Neovascular AMD <u>Jordi Mones</u> , Spain	
11:40	New Drugs in Development for Wet AMD <u>Peter Kaiser</u> , USA	
11:50	Discussion: <u>Paolo Lanzetta</u> , Italy, <u>Jordi Mones</u> , Spain, <u>Peter Kaiser</u> , USA, <u>Baruch D. Kuppermann</u> , USA & <u>Zohar Yehoshua</u> , USA	
12:30-13:30	Industry Sponsored Lunch Session From Research to Clinic: What do We Understand about Wet AMD	Hall A Page 42

Saturday, June 21, 2014

Morning Sessions – Hall B

08:15-09:00	European Association for Vision and Eye Research Session (EVER) Chairs: <u>Constantin Pournaras</u> , Switzerland & <u>Einar Stefánsson</u> , Iceland	Hall B
08:15	Oxygen Distribution in Health and Diseased Eyes <u>Constantin Pournaras</u> , Switzerland	
08:25	Retinal Oximetry with a Scanning Laser Ophthalmoscope <u>Jona Valgerdur Kristjansdottir</u> , Iceland, Iceland, Iceland	
08:35	Retinal Oximetry in Glaucoma <u>Olof Birna Olafsdottir</u> , Iceland	
08:45	Retinal Oximetry: Status and Challenges <u>Sveinn Hakon Hardarson</u> , Iceland	
08:55	Q&A	
09:00-09:45	Uveitis Studies Endpoints Panel Chair: <u>Christoph Deuter</u> , Germany	Hall B
09:00	Introduction <u>Christoph Deuter</u> , Germany	
09:10	Uveitis Endpoints - The Clinical and Regulatory Strategy for the Approval of Retisert <u>Brian Levy</u> , USA	
09:20	Panel: <u>Talin Barisani-Asenbauer</u> , Austria, <u>Ron Neumann</u> , Israel, <u>Francine Behar-Cohen</u> , France, <u>Marc De Smet</u> , The Netherlands & <u>Brian Levy</u> , USA	
09:45-10:30	Treating Uveitis Guided by Clinical Suspicion Chair: <u>Yosuf El-Shabrawi</u> , Austria	Hall B
09:45	Herpes Uveitis/Keratitis <u>William Ayliffe</u> , UK	
09:55	Behcet Vasculitis <u>Christoph Deuter</u> , Germany	
10:05	VKH <u>Massimo Accorinti</u> , Italy	
10:15	Discussion	
10:30-11:00	Coffee Break	Exhibition Hall
11:00-12:30	Glaucoma, the CNS and Intracranial Pressure: First Cousin? Chair: <u>Barrett Katz</u> , USA	Hall B
11:00	Glaucoma as an Optic Neuropathy - How is it like Other Optic Neuropathies? <u>Anthony Arnold</u> , USA	
11:15	What Pseudotumor Cerebri Treatment Can Teach Us about Glaucoma Therapy <u>Barrett Katz</u> , USA	
11:30	Brain Changes in Glaucoma: Implications for Diagnosis and Treatment <u>Yeni H. Yucel</u> , Canada	
11:45	Cerebral Blood Flow in Glaucoma <u>Alon Harris</u> , USA	
12:00	Case Discussion <u>Barrett Katz</u> , USA	
12:30-13:30	Industry Sponsored Lunch Session From Research to Clinic: What do We Understand about Wet AMD	Hall A Page 42

Saturday, June 21, 2014

Morning Sessions – Hall C

08:30-10:30	Dry Eye Treatment and Clinical Trials Chair: Penny A. Asbell, USA	Hall C
08:30	What is Clinical Implication of Slit Lamp Diagnosed MGD? <u>James McCulley</u> , USA	
08:40	Haematic Derivates in Ocular Surface Disease <u>Jesus Merayo Lloves</u> , Spain	
08:50	3 Year Retrospective on Intense Pulse Light for Dry Eye Disease <u>Rolando Toyos</u> , USA	
09:00	Early Diagnosis of Sjogren's Syndrome <u>Penny A. Asbell</u> , USA	
09:10	Tear Osmolarity and Osmoprotection in Dry Eye <u>Pasquale Aragona</u> , Italy	
09:20	Novel Ophthalmic Formulations of Liposomes Loaded with Anti-inflammatory Drugs and Omega-3 Fatty Acids for Dry Eye Treatment <u>Maria Rocio Herrero-Vanrell</u> , Spain	
09:30	The Impact of Controlled Adverse Environmental Challenges to the Process of Expedited Drug Introduction <u>James Aquavella</u> , USA	
09:40	Boston Type 1 Keratoprosthesis in Patients with Severe Dry Eye <u>Esen K. Akpek</u> , USA	
09:50	Pitfalls in Dry Eye Clinical Trials <u>Michael Goldstein</u> , USA	
10:00	DREAM: Dry Eye Assessment and Management Clinical Trial <u>Penny A. Asbell</u> , USA	
10:10	Q&A	
10:30-11:00	Coffee Break	Exhibition Hall
11:00-12:30	Wound Healing on the Ocular Surface Chair: Penny A. Asbell, USA	Hall C
11:00	Fibrosis in the Mouse Cornea following Sterile Mechanical Trauma or Infection <u>Roger Beuerman</u> , Singapore	
11:12	Corneal Wound Healing with Neurotrophic Factors <u>Jesus Merayo Lloves</u> , Spain	
11:24	Growth Factors and Interleukins in Amniotic Membrane Suspension AMS <u>Berthold Seitz</u> , Germany	
11:36	Topical NSAIDS in Dry Eye Disease - 3 Year Retrospective <u>Rolando Toyos</u> , USA	
11:48	A Drug Eluting Contact Lens <u>Joseph B. Ciolino</u> , USA	
12:00	Rationale for the Treatment of Ocular Surface Diseases with Targeted Biotherapeutics <u>Eric Furfine</u> , USA	
12:12	Discussion	
12:30-13:30	Industry Sponsored Lunch Session From Research to Clinic: What do We Understand about Wet AMD	Hall A Page 42

Saturday, June 21, 2014

Afternoon Sessions – Hall A

14:00-15:30	Retinal Degeneration Chairs: <u>Isabelle Audo</u> , France & <u>Henry J. Klassen</u> , USA	Hall A
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14:00	Extending Cone Survival and Function in Retinal Degenerations <u>Isabelle Audo</u> , France	
14:15	Retinal Progenitor Cell Transplantation for Treatment of Retinal Degeneration <u>Henry J. Klassen</u> , USA	
14:30	Next Generation Sequencing for Retinal Degeneration <u>Isabelle Audo</u> , France	
14:45	Stem Cells as Therapeutic Agents for Retinal Degeneration: Clinical Trials <u>Henry J. Klassen</u> , USA	
15:15	Gene Therapy for Stargardt Disease <u>Isabelle Audo</u> , France	

15:30-16:00	Coffee Break	Exhibition Hall
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16:00-17:30	Innovation Chair: <u>Ron Neumann</u> , Israel	Hall A
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16:00	Conduct of Early Feasibility- First in Human Studies in the US <u>Malvina B. Eydelman</u> , USA	
16:10	Initial Clinical Evaluation of Safety, Tolerability and Pharmacodynamics of AMA0076, a ROCK Inhibitor for the Treatment of Glaucoma <u>Jack Elands</u> , Belgium	
16:20	Double-Masked, Randomized, Dose-Response Study of AR-13324 Ophthalmic Solution Compared to Latanoprost in Patients with Elevated Intraocular Pressure <u>Brian Levy</u> , USA	
16:30	Mucosal Penetrating Products <u>Kim Brazzell</u> , USA	
16:40	Extended Release Injectable Therapeutics <u>Michael J. O'Rourke</u> , USA	
16:50	RNAi Based Therapies for Ocular Conditions <u>Covadonga Paneda</u> , Spain	
17:00	The Ophthalmic Squeeze Dispenser (OSD): A Flexible Multi-Dose Solution for Unpreserved Eye Drops <u>Degenhard Marx</u> , Germany	
17:10	Targeted Biologics in Posterior Chamber Ocular Disorders <u>Eric Furfine</u> , USA	
17:20	Q&A	

Saturday, June 21, 2014

Afternoon Sessions – Hall B

14:00-14:45	A Clinical Guide to the Transition to Biologics Chair: <u>Talin Barisani-Asenbauer</u> , Austria	Hall B
	Introduction - Clinical Guide to the Transition to Biologics <u>Talin Barisani-Asenbauer</u> , Austria	
	Use of Biologics in Pediatric Population <u>Sofia Androudi</u> , Greece	
	Special Considerations in Pregnant/Lactating Women <u>Talin Barisani-Asenbauer</u> , Austria	
	Management of PTS with Other Ocular/Systemic Conditions <u>Manfred Zierhut</u> , Germany	
	Monitoring Efficacy and AEs <u>Marc De Smet</u> , The Netherlands	
	Discussion	
14:45-15:30	Hot Topics – Inflammation 2014 Chair: <u>Esen K. Akpek</u> , USA	Hall B
14:45	Comparative Risk of Conventional Immunosuppressive Drugs vs. Biologics <u>Jennifer E. Thorne</u> , USA	
14:55	Macular Edema: Pathogenesis and Treatment <u>Manfred Zierhut</u> , Germany	
15:05	Gene Polymorphisms in HLA B27 Associated Uveitis and Intermediate Uveitis <u>Yosuf El-Shabrawi</u> , Austria	
15:15	Discussion <u>Esen K. Akpek</u> , USA	
15:30-16:00	Coffee Break	Exhibition Hall
16:00-17:30	Innovation Chair: <u>Ron Neumann</u> , Israel	Hall A Page 29

Saturday, June 21, 2014

Afternoon Sessions – Hall C

14:00-15:30	Therapy for Retinal & Choroidal Angiogenesis Chair: <u>Arup Das</u> , USA	Hall C
14:00	Preclinical Studies of Soluble EphB4-HAS as a Therapeutic in Neovascular ARMD <u>David Hinton</u> , USA	
14:15	Targeting VEGF-Signaling in Specific Retinal Cell Types to Safely Inhibit Retinal Neovascularization <u>Mary E. Hartnett</u> , USA	
14:30	Arachidonic Acid Metabolites as Pharmacotherapeutic Targets for Retinal Neovascularization <u>John S. Penn</u> , USA	
14:45	Gene Therapy for Diabetic Retinopathy <u>Bala Ambati</u> , USA	
15:00	Discussion <u>Arup Das</u> , USA	
15:30-16:00	Coffee Break	<i>Exhibition Hall</i>
16:00-17:30	Innovation Chair: <u>Ron Neumann</u> , Israel	Hall A Page 29

Sunday, June 22, 2014

Morning Sessions – Hall A

08:00-10:30	Retina Free Papers Chairs: <u>Paolo Lanzetta</u> , Italy & <u>Jordi Mones</u> , Spain	Hall A
08:00	Full-field- 3D OCT- based Update on Pathophysiology and Apparent Treatment of Diffuse Diabetic Macular Edema <u>Avinoam Ophir</u> , Israel	
08:08	Full-field- 3-D OCT is Essential for Successful Grid Laser for Diffuse Diabetic Macular Edema (DDME) <u>Avinoam Ophir</u> , Israel	
08:16	Gap Junction Channel Blockers – Saving Sight by Reducing Vascular Leak <u>Ilva Rupenthal</u> , New Zealand	
08:24	Aripiprazole Associated Retinopathy: Multimodal Imaging Findings <u>Céline Faure</u> , France	
08:32	Dexamethasone Intravitreal Implant (Ozurdex®) in Refractory Diabetic Macular Edema. Clinical Practice <u>Félix Manco Lavado</u> , Spain	
08:40	Nepafenac 0,1% Ophthalmic Suspension as Treatment of Chronic Macular Disorders <u>Vladimir Poposki</u> , Spain	
08:48	Phase 2 Study of Conbercept, a Recombinant VEGF Receptor, Treatment of Macular Edema Secondary to Retinal Vein Occlusion (RVO) <u>Xiaoling Liu</u> , China	
08:56	Half-fluence Versus Half-dose Photodynamic Therapy in Chronic Central Serous Chorioretinopathy <u>Chiara M. Eandi</u> , Italy	
09:04	Long-Term Results of Rheohaemapheresis Treatment of Age-Related Macular Degeneration <u>Hana Langrova</u> , Czech Republic	
09:12	Conbercept for Treatment of Wet Age-Related Macular Degeneration (AMD) <u>Bo Lei</u> , China	
09:20	Comparative Study of Free Lutein and Lutein Ester of the Macular Pigment Optical Density for Japanese Individuals <u>Akihiro Ohira</u> , Japan	
09:28	Improvements in Visual Function following Resolution of Vitreomacular Traction with Ocriplasmin <u>Paolo Lanzetta</u> , Italy	
09:36	The INJECT Study: a Non-interventional, Multicentre, Worldwide Study in Patients Treated with Ocriplasmin <u>Rahila Zakir</u> , UK	
09:44	Imaging of Retinal Hypoxia <u>Ashwath Jayagopal</u> , USA	
09:52	Intravitreal Anti-VEGF Therapy Associated with LASER Photocoagulation for the Treatment of Proliferative Sickle Retinopathy in 5 Patients <u>Brigitte Girard</u> , France	
10:00	Intravitreal Aflibercept Decreases the Volume of Vascularized PEDs Better than Frequent Retreatment with Intravitreal Bevacizumab or Ranibizumab <u>Zohar Yehoshua</u> , USA	
10:10	Q&A	
10:30-11:00	Coffee Break	Exhibition Hall

Sunday, June 22, 2014

Morning Sessions – Hall A

11:00-12:30	Retina Free Papers Chairs: Francine Behar-Cohen , France & Akihiro Ohira , Japan	Hall A
11:00	Complement Factor H Treatment is as Effective as Anti-VEGF against Choroidal Neovascularization in a Rat Model of Neovascular AMD <u>Frederic Mascarellj</u> , France	
11:08	Human Dental Pulp Stem Cells can Differentiate into Retinal Cells <u>Samin Hong</u> , South Korea	
11:16	Sigma Receptor 1 Mediates Cytokine Release and NFkB Translocation in Retinal Müller Glial Cells Suggesting a Role in Neuroprotection <u>Sylvia Smith</u> , USA	
11:24	Bio-Compatible Hyaluronic acid as a Coating Strategy to Improve Intravitreal Delivery of Gene Nanomedicines to the Retina <u>Thomas F Martens</u> , Belgium	
11:32	Effects of Dexamethasone on Müller Glial Cells over the Course of Blood Retinal Barrier Breakdown <u>Audrey Giocanti</u> , France	
11:40	Lineage Negative BMCs Induce Regeneration Promoting Effects in Pterygopalatine Artery (PPA) Ligation Model of Ischemic Retinal Injury in Mouse <u>Akshay Anand</u> , India	
11:48	Q&A	

Sunday, June 22, 2014

Morning Sessions – Hall B

08:00-10:30	Anterior Free Papers Chairs: <u>Regis Kowalski</u> , USA & <u>Shmuel Levartovsky</u> , Israel	Hall B
08:00	5-Year Relapse-free Follow-up Following Antibiotic Treatment of a B-cell MALT Lymphoma of the Conjunctiva in a 13-year Old Child <u>Helmut Hoeh</u> , Germany	
08:10	Ranizibumab for the Treatment of Early Pterygium Recurrences <u>Linda Rose</u> , USA	
08:20	Prospective study of Autologous Serum Eye Drops (ASED) confirms sustained benefits in Keratoconjunctivitis Sicca and Non-Healing Corneal Ulcers <u>Phillip Mondy</u> , Australia	
08:30	Pharmacological Validation of an Inflammation-based Murine Model of Dry Eye <u>Andy Whitlock</u> , USA	
08:40	Clinical Experiences with Heparan Sulphate Mimetics Eyedrops in the Persistent Epithelial Defects Therapy <u>Monika Udziela</u> , Poland	
08:50	Pre-Treatment with Non-steroid Anti-inflammatory Drugs as a Possible Success-Factor of Femtosecond Laser Cataract Surgery <u>Zoltan Zsolt Nagy</u> , Hungary	
09:00	Treatment of Corneal Ulcers in Ocular Surface Inflammation <u>Sihem Lazreg</u> , Algeria	
09:10	Artificial Tear Containing both Isotonic Glycerol and Sodium Hyaluronate Decreases Conjunctivochalasis in a Three Months Long Trial <u>Huba Kiss</u> , Hungary	
09:20	Role of Azithromycin in the Treatment of Children Meibomian Gland Disease <u>Sihem Lazreg</u> , Algeria	
09:30	Efficacy and Safety of Azithromycin 1.5% Eye Drops (Azyter®) in Patients with Moderate to Severe Chronic Blepharitis <u>Serge Doan</u> , France	
09:40	Evaluation of Nucleic Acid Amplification Testing (Gen-Probe® Aptima®) (NAAT) for Chlamydia trachomatis from Ocular Samples <u>Regis Kowalski</u> , USA	
09:50	Pharmacological Correction of Presbyopia: A preliminary Study <u>Shmuel Levartovsky</u> , Israel	
10:00	Treatment of Epidemic Keratoconjunctivitis with Povidone Iodine <u>Shmuel Levartovsky</u> , Israel	
10:10	Q&A	
10:30-11:00	Coffee Break	Exhibition Hall

Sunday, June 22, 2014

Morning Sessions – Hall B

11:00-12:30	Glaucoma Free Papers	Hall B
11:00	The Prevalence of Ocular Surface Disease Among Patients on Topical Glaucoma Drug Therapy: A Systematic Review of the Literature <u>Mohammad (Nima) Mohammad-Shahi</u> , Canada	
11:10	Extracellular Matrix and Glial Alterations in an Autoimmune Glaucoma Model <u>Stephanie Joachim</u> , Germany	
11:20	Whole Bovine Lens Culture to Assess the Ocular Toxicity of Single Dose and Multiple-Dose Treatments of Benzalkonium Chloride <u>Jacob Sivak</u> , Canada	
11:30	Adenosine A2A Receptor Blockade and Caffeine Prevent Retinal Neuroinflammation and Retinal Ganglion Cell Death <u>António Francisco Ambrósio</u> , Portugal	
11:40	Activation of Liver X Receptor Alleviates Ocular Inflammation in Experimental Autoimmune Uveitis <u>Bo Lei</u> , China	
11:50	Q&A	

E-Posters

Correlations between the Inflammatory Marker HLA-DR and Other Signs and Symptoms in Dry Eye Disease in Three Phase III Studies

Mourad Amrane, France

Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) Prevents Monosodium Glutamate (MSG) Induced Functional Disturbances in the Mouse Retina

Tamas Atlasz, Hungary

Evaluation of Inflammatory Markers following Use of Systane Balance or Systane Gel in Patients with Dry Eye

Penny A. Asbell, USA

Evaluation of Symptomatic Relief of Dry Eye Symptoms Following Systane Balance or Systane Gel Use

Penny A. Asbell, USA

HP-B-Cyclodextrin – Brinzolamide Complexes: New Formulation Approaches to Enhance Bioavailability and Solubility

Dimitrios Bikiaris, Greece

Chitosan Nanoparticles Loaded With Timolol Drug for Ophthalmic Drops

Dimitrios Bikiaris, Greece

Effect of Topical Azithromycin on Symptoms, Clinical Signs, and Ocular Surface Inflammation in Patients with Meibomian Gland Dysfunction

Stefano Barabino, Italy

Ophthalmic Vascular Tone: Role of NO, CO and H₂S

Claudio Bucolo, Italy

Vascular Stem Cell Therapy of the Diabetic Retina with COMP-Ang1 and Endothelial Progenitor Cells

Judd Cahoon, USA

Intravitreal Ranibizumab Injections with and without Pneumatic Displacement for Treating Submacular Hemorrhage Secondary to Neovascular Age-Related Macular Degeneration

Han Joo Cho, South Korea

John Dalrymple a Surgeon, Pathologist, and Ophthalmologist, and his Work 'The Anatomy of the Human Eye'

Savvas Diafas, Greece

In Vitro Activation of Steroid Receptors in Corneal Epithelial Cells Using a Novel Anti-inflammatory Liposomal Formulation

Yolanda Diebold, Spain

Effect of Two Different Types of Suturing Technique on Astigmatism after Penetrating and Deep Anterior Lamellar Keratoplasty

Naeima M. Elzlitni, Libyan Arab

PACAP Protects the Human Retinal Pigment Epithelial Cells Against Hyperglycaemic and Hypoxic Conditions

Eszter Fabian, Hungary

Potential of Frequency-Doubling Technology for Predicting Future Visual Field Loss for Perimetrically Normal Eyes of Open-Angle Glaucoma Patients

Xiang Fan, China

Unusual Eye Symptoms of Giant Prolactinoma

Hana Fidranska, Czech Republic

Inhibition of Corneal Inflammation Following Keratoplasty by Birch Leaf Extract

Carsten Gründemann, Germany

Association of Vitamin D Status and Open-angle Glaucoma

Samin Hong, South Korea

Moraxella Keratitis Review of 10 Cases

Hidenori Inoue, Japan

Efficacy of Cationorm® Preservative-free Cationic Emulsion Versus Vismed® (0.18% Sodium Hyaluronate) in Moderate to Severe Dry Eye Disease (DED) Patients

Dahlia Ismail, France

Cannabinoid Receptor 2: A Novel Immunosuppressive Target in Experimental Proliferative Vitreoretinopathy

Melanie Kelly, Canada

Human Origin RGD-Containing Recombinant Protein EGT022 Reduces Vascular Leakage through Pericyte Recruitment

Han-Soo Kim, South Korea

Structural Change after Macula-off Rhegmatogenous Retinal Detachment Repair

Hyoung-Seok Kim, South Korea

Intravitreal Ranibizumab for Acute Central Serous Chorioretinopathy

Moosang Kim, South Korea

Expression of MicroRNAs and Targeted MicroRNAs in Fibroblast of Pterygium

Ungsoo S. Kim, South Korea

E-Posters

Antiviral Efficacy of HSV1-Specific Meganucleases in a Mouse Model of Relapsing Herpes Keratitis

Marc Labetoulle, France

Versatility of Cationic Emulsion in Dry Eye Relief

Frederic Lallemandj, France

Design and Synthesis of Functional Lipidic Biomaterials for the Encapsulation and Triggered Release of Drugs in Ocular Applications

Ehud M. Landau, Switzerland

Is Blepharitis Associated with Pathogenesis and/or Progression of Keratoconus?

Shmuel Levartovsky, Israel

Corneal Pocket Technique for Corneal Tattoo

Shmuel Levartovsky, Israel

Chronic Caffeine Treatment Protects Oxygen-Induced Retinal Neovascular Damage in a Mouse Model of Proliferative Retinopathy

Xiaoling Liu, China

Twelve-Month Efficacy and Safety Profile of Ranibizumab versus Laser Photocoagulation in Patients with Diabetic Macular Edema (RE-DES Study)

MI López-Gálvez, Spain

Effects of Early Hyperglycaemia on the Retinal Structure of OIR Rats

Barbara Mammel, Hungary

Management of Biological Material (Mehran, Bio-lent) for Treatment and Avoid Retinal Pathology and Postoperative Complication after Scleral Buckling Surgery in Retinal Detachment

Mehran Masoudnaseri, Ukraine

Development of New Anti-VEGF Therapy by Kinase Inhibitor

Satoshi Morooka, Japan

Intravitreal Dexamethasone Implant for Management of Macular Edema Associated with Retinitis Pigmentosa

Mario Neves, Portugal

Retinal Remodeling under Conditions of Organotypic 3D Culturing in vitro and Retinal Damage in vivo in High and Low Vertebrates

Yulia Novikova, Russia

The Response to Dexametasone Implants (Ozurdex) +/-Photocoagulation in Patients with Naïve or Refractory Diffuse Diabetic Macular Edema (DDME)

Begona Pina-Marin, Spain

A Randomised Cross Over Comparison of Trehalose/Hyaluronate Eye Drops and Standard Treatment: Patient Satisfaction in the Treatment of Dry Eye Syndrome

Juan Carlos Pinto-Bonilla, Spain

Possibility in Pathogenic Therapy of Myopic CNV

Marina Prokopieva, Russia

The Use of a Preservative-Free, Hypotonic Solution of 0.15% Sodium Hyaluronate for Mild to Moderate Dry Eye

Christine Purslow, UK

LipiView-Diagnostic & Meibomian Gland Evaluator (MGE) As basic for optional treatment of the Meibomian Gland Dysfunction (MGD)

Volker Rasch, Germany

Investigating the Retinoprotective Effects of PACAP Fragments, Secretin and Glucagon in Ischemic Retinopathy

Dora Reglodi, Hungary

Photodynamic Therapy - A New Therapeutic Approach for Superficial Eyelid Basal Cell Carcinoma

Renata Ricarova, Czech Republic

Combined Intravitreal Ranibizumab and Laser Treatment for Retinal Angiomatous Proliferation

Timur Shaimov, Russia

Retrospective Comparison of Outcomes of Trainee-Performed Trabeculectomy versus Tube Shunt Surgery

Robert Sharpe, USA

The Placebo Effect in Glaucoma Medication Clinical Trials

Robert Sharpe, USA

Adipose-MSCs Revert VIP, NIC and ATRA Effects on Dying RPE Cells

Girish Kumar Srivastava, Spain

Functional Characteristic of the Myopic Extrafoveal Retina

Bistra Stoimenova, Bulgaria

A Deca-peptide Inhibits Retinal Neovascularization by Down-regulation of VEGF and Up-regulation of PEDF in OIR Mouse

Li Su, China

E-Posters

Protective Effects of Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) in Different Models of Retinal Injuries

Andrea Tamas, Hungary

Effects of Oral Propranolol on a Juxtapapillary Capillary Hemangioma: A Single-subject Pilot Study

Hirotaaka Tanabe, Japan

The Development of Clinical Pharmacist Mode in Ophthalmology Department

Qiwen Tang, China

Experimental Use of Poly lactic-co-glycolic Acid for Visualizing Vitreous Body During Cataract Surgery in Animal Models

Takahiro Uda, Japan

Difficulties of Therapeutic Management in Several Polish Patients with Corneal Inflammations Suspected of Acanthamoeba Infection

Monika Udziela, Poland

Proteome Analysis of Tears from Wild and the PACAP-Deficient Mice

Alexandra Vaczy, Hungary

PACAP Administration can Ameliorate Vascular Changes in Retinopathy of Prematurity

Timea Kvarik, Hungary

Narrow Spectrum Kinase Inhibitors (NSKIs) Potently Inhibit Inflammatory Cytokines in Both in vitro and in vivo Inflammatory Eye Models

Claire Walshe, UK

Evaluating the Therapeutical Outcomes in Retinal Capillary Hemangioblastoma (RCH) in Von Hippel-Lindau Syndrome (VHL) by Color Doppler Imaging (CDI) - A Case Report

Jaromir Wasyluk, Poland

H-RN, A Novel Antiangiogenic Peptide Derived from Hepatocyte Growth Factor Inhibits Inflammation Through PI3K/AKT/IKK/NF- κ B Signal Pathway

Xun Xu, China



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- ➔ Visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM).

Note: Before prescribing, consult full prescribing information.

Presentation: Vial: Ranibizumab. Each vial contains 2.3 mg of ranibizumab in 0.23 mL solution. **Pre-filled syringe:** Ranibizumab. Each pre-filled syringe contains 1.65 mg of ranibizumab in 0.165 mL solution.
Indications: ♦ Treatment of neovascular (wet) age-related macular degeneration (AMD) ♦ Treatment of visual impairment due to diabetic macular edema (DME) ♦ Treatment of visual impairment due to macular edema secondary to retinal vein occlusion (branch RVO or central RVO) ♦ Treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM) ♦ **Dosage:** ♦ The recommended dose is 0.5 mg (0.05 mL) given as a single intravitreal injection. The interval between two doses should not be shorter than 1 month. **AMD, DME, RVO:** ♦ Patients should be monitored monthly for visual acuity ♦ Treatment is given monthly and continued until maximum visual acuity is achieved, confirmed by stable visual acuity for three consecutive monthly assessments performed while on Lucentis® treatment. Treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to wet AMD, DME or macular edema secondary to RVO and continued until stable visual acuity is reached again for three consecutive monthly assessments ♦ Lucentis and laser photocoagulation in DME or in branch RVO: Lucentis has been used concomitantly with laser photocoagulation in clinical studies. When given on the same day, Lucentis should be administered at least 30 minutes after laser photocoagulation. Lucentis can be administered in patients who have received previous laser photocoagulation. **CNV secondary to PM:** Treatment is initiated with a single injection, further treatment is recommended if monitoring reveals signs of disease activity ♦ The frequency of monitoring should be determined by the treating physician ♦ Lucentis must be administered by a qualified ophthalmologist using aseptic techniques. Broad-spectrum topical microbicide and anaesthetic should be administered prior to the injection ♦ Not recommended in children and adolescents ♦ **Contraindications:** Hypersensitivity to ranibizumab or to any of the excipients, patients with active or suspected ocular or periocular infections, patients with active intraocular inflammation ♦ **Warnings/Precautions:** ♦ Intravitreal injections have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Therefore proper aseptic injection techniques must be used. Patients should be monitored during the week following the injection to permit early treatment if an infection occurs ♦ Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of Lucentis. Sustained IOP increases have also been reported. Intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately ♦ There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. A numerically higher stroke rate was observed in patients treated with ranibizumab 0.5 mg compared to ranibizumab 0.3 mg or control, however, the differences were not statistically significant. Patients with known risk factors for stroke, including history of prior stroke or transient ischemic attack

should be carefully evaluated by their physicians as to whether Lucentis treatment is appropriate and the benefit outweighs the potential risk ♦ Available data do not suggest an increased risk of systemic adverse events with bilateral treatment ♦ As with all therapeutic proteins, there is a potential for immunogenicity with Lucentis ♦ Lucentis has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole ♦ There is limited experience with treatment of patients with prior episodes of RVO and of patients with ischemic branch RVO (BRVO) and central RVO (CRVO). In patients with RVO presenting with clinical signs of irreversible ischemic visual function loss, treatment is not recommended ♦ Should not be used during pregnancy unless the expected benefit outweighs the potential risk to the fetus. For women who wish to become pregnant and have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child; use of effective contraception recommended for women of child-bearing potential; breast-feeding not recommended ♦ Following treatment patients may develop transient visual disturbances that may interfere with their ability to drive or use machines. Patients should not drive or use machines as long as these symptoms persist ♦ **Interactions:** No formal interaction studies have been performed ♦ **Adverse reactions:** ♦ **Very common adverse reactions are:** intraocular inflammation, vitritis, vitreous detachment, retinal hemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival hemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperemia, eye pruritus, intraocular pressure increased, nasopharyngitis, headache, arthralgia ♦ **Common adverse reactions are:** retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of the retinal pigment epithelium, retinal pigment epithelium tear, visual acuity reduced, vitreous hemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, cataract, cataract subcapsular, posterior capsule opacification, punctate keratitis, corneal abrasion, anterior chamber flare, vision blurred, injection site hemorrhage, eye hemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eyelid edema, eyelid pain, conjunctival hyperemia, stroke, influenza, urinary tract infection, anemia, anxiety, cough, nausea, allergic reactions (rash, pruritus, urticaria, erythema) ♦ **Uncommon adverse reactions are:** blindness, endophthalmitis, hypopyon, hyphema, keratopathy, iris adhesions, corneal deposits, corneal edema, corneal striae, injection site pain, injection site irritation, abnormal sensation in eye, eyelid irritation ♦ **Serious adverse events** related to intravitreal injections included endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract.

* observed only in the DME population

Packs and prices: Country specific.

Legal classification: Country specific.

Please find the full prescribing information in the Novartis booth



Friday, June 20, 2014

Morning Sessions – Hall A

11:00-11:45	Santen Sponsored Session Severe Dry Eye Disease: Facing the Treatment Challenges Chair: <u>Gysbert van Setten</u> , Sweden	Plenary
11:00	Welcome <u>Gysbert van Setten</u> , Sweden	
11:05	Pathogenetic Considerations and Implications on Simplified Decision Making in Dry Eye Disease <u>Marc Labetoulle</u> , France	
11:15	Stepwise Approach to Anti-Inflammatory Treatment of Dry Eye Syndrome <u>Pasquale Aragona</u> , Italy	
11:25	Effects of Ciclosporin on Corneal Involvement in Patients with Severe Dry Eye Disease <u>Andrea Leonardi</u> , Italy	
11:35	Present and Future Perspectives in the Treatment of Dry Eye Disease <u>Gysbert van Setten</u> , Sweden	
11:45-12:30	Allergan Sponsored Session Steroids in the Management of Macular Edema Chairs: <u>Baruch D. Kuppermann</u> , USA & <u>Paolo Lanzetta</u> , Italy	Hall B
11:45	Therapeutic Targets in Macular Edema <u>Baruch D. Kuppermann</u> , USA	
11:55	Risk Factors & Statistics, Influence on Outcomes <u>Albert J. Augustin</u> , Germany	
12:05	Who are the Patients? Trials vs. Real Life <u>Patricia Udaondo</u> , Spain	
12:15	Panel Discussion: Trial vs. Real Life Outcomes <u>Albert Augustin</u> , Germany, <u>Patricia Udaondo</u> , Spain, <u>Paolo Lanzetta</u> , Italy & <u>Gisele Soubrane</u> , France	
12:25	Close and Sum Up <u>Baruch D. Kuppermann</u> , USA & <u>Paolo Lanzetta</u> , Italy	
12:30-13:30	Alcon Sponsored Lunch Session Ocriplasmin Intravitreal Injection: The Real-World Experience	Plenary
12:45	Real-world Data on the VMA, VMT and Macular Hole Patients: A Retrospective, Observational Study <u>Peter Stalmans</u> , Belgium	
13:00	The Patient Experience with Ocriplasmin: Safety Profile from Pivotal Trials and Post-Marketing <u>Baruch D. Kuppermann</u> , USA	
13:15	From the Pivotal Trials of Ocriplasmin to the Real-World Outcomes: The Importance of Patient Selection <u>Peter Kaiser</u> , USA	

Saturday, June 21, 2014

Morning Sessions – Hall A

12:30-13:30	Bayer Sponsored Lunch Session From Research to Clinic: What do We Understand about Wet AMD	Plenary
<hr/>		
12:45	Epidemiology and Genetics of Wet AMD <u>Fridbert Jonasson</u> , Iceland	
12:55	Pathophysiology of Wet AMD <u>Einar Stefansson</u> , Iceland	
13:00	Managing Wet AMD <u>Paolo Lanzetta</u> , Italy	
13:10	Clinical Experience: A Focus on Aflibercept <u>Faruque Ghanchi</u> , UK	
13:20	Q&A <u>All Speakers</u>	



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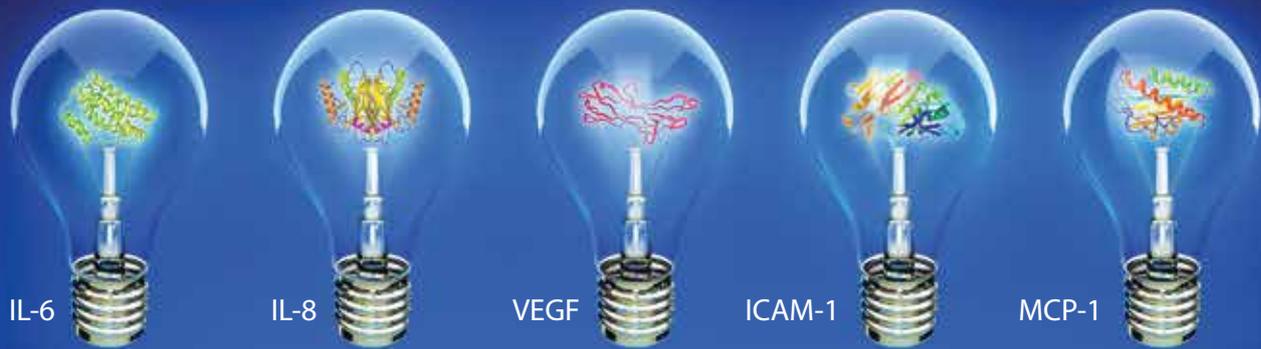
11th ISOPT *Clinical*

June 19-22, 2014, Reykjavik, Iceland

Abstracts



TARGETING THE MEDIATORS OF INFLAMMATION¹



Delivering efficacy in the clinical setting²⁻⁵

Ozurdex[®]
(dexamethasone intravitreal
implant) 0.7mg

These images are for illustrative purposes only and do not represent inflammatory mediator levels in the eye.

OZURDEX (Dexamethasone 700 micrograms intravitreal implant in applicator)

Abbreviated Prescribing Information

Presentation: Intravitreal implant in applicator. One implant contains 700 micrograms of dexamethasone. Disposable injection device, containing a rod-shaped implant which is not visible. The implant is approximately 0.46 mm in diameter and 6 mm in length. **Indications:** Treatment of adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO). Treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis. **Dosage and Administration:** Please refer to the Summary of Product Characteristics before prescribing for full information. OZURDEX must be administered by a qualified ophthalmologist experienced in intravitreal injections. The recommended dose is one OZURDEX implant to be administered intravitreally to the affected eye. Administration to both eyes concurrently is not recommended. Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk. Patients who experience and retain improved vision should not be retreated. Patients who experience a deterioration in vision, which is not slowed by OZURDEX, should not be retreated. There is only very limited information on repeat dosing intervals less than 6 months. There is currently no experience of repeat administrations in posterior segment non-infectious uveitis or beyond 2 implants in Retinal Vein Occlusion. Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs. Single-use intravitreal implant in applicator for intravitreal use only. The intravitreal injection procedure should be carried out under controlled aseptic conditions which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). The patient should be instructed to self-administer broad spectrum antimicrobial drops daily for 3 days before and after each injection. Before the injection, the periocular skin, eyelid and ocular surface should be disinfected and adequate local anaesthesia should be administered. Remove the foil pouch from the carton and examine for damage. In a sterile field, open the foil pouch and gently place the applicator on a sterile tray. Carefully remove the cap from the applicator. Once the foil pouch is opened the applicator should be used immediately. Hold the applicator in one hand and pull the safety tab straight off the applicator. Do not twist or flex the tab. With

the bevel of the needle up away from the sclera, advance the needle about 1 mm into the sclera then redirect toward the centre of the eye into the vitreous cavity until the silicone sleeve is against the conjunctiva. Slowly press the actuator button until an audible click is noted. Before withdrawing the applicator from the eye, make sure that the actuator button is fully pressed and has locked flush with the applicator surface. Remove the needle in the same direction as used to enter the vitreous. Immediately after injecting OZURDEX, use indirect ophthalmoscopy in the quadrant of injection to confirm successful implantation. Visualisation is possible in the large majority of cases. In cases in which the implant cannot be visualised, take a sterile cotton bud and lightly depress over the injection site to bring the implant into view. Following the intravitreal injection patients should continue to be treated with a broad spectrum antimicrobial. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Active or suspected ocular or periocular infection including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases. Advanced glaucoma which cannot be adequately controlled by medicinal products alone. Aphakic eyes with rupture of the posterior lens capsule. Eyes with Anterior Chamber Intraocular Lens (ACIOL) and rupture of the posterior lens capsule. **Warnings/Precautions:** Intravitreal injections, including OZURDEX can be associated with endophthalmitis, intraocular inflammation, increased intraocular pressure and retinal detachment. Proper aseptic injection techniques must always be used. Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between two and seven days following the injection. Patients must be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay. All patients with posterior capsule tear, e.g. those with a posterior lens, and/or those who have an iris defect (e.g. due to iridectomy) with or without a history of vitrectomy, are at risk of implant migration into the anterior chamber. Other than those patients contraindicated where OZURDEX should not be used, OZURDEX should be used with caution and only following a careful risk benefit assessment. These patients should be closely monitored for any signs of implant migration. Corticosteroids should be used cautiously in patients with a history of *ocular herpes simplex* and not be used in active *ocular herpes simplex*. The safety and efficacy of OZURDEX administered to

both eyes concurrently have not been studied and is not recommended. OZURDEX is not recommended in patients with macular oedema secondary to RVO with significant retinal ischemia. OZURDEX should be used with caution in patients taking anti-coagulant or anti-platelet medicinal products. **Interactions:** No interaction studies have been performed. Systemic absorption is minimal and no interactions are anticipated. **Pregnancy:** There are no adequate data from the use of intravitreally administered dexamethasone in pregnant women. OZURDEX is not recommended during pregnancy unless the potential benefit justifies the potential risk to the foetus. **Lactation:** Dexamethasone is excreted in breast milk. No effects on the child are anticipated due to the route of administration and the resulting systemic levels. However OZURDEX is not recommended during breast feeding unless clearly necessary. **Driving/Use of Machines:** Patients may experience temporarily reduced vision after receiving OZURDEX by intravitreal injection. They should not drive or use machines until this has resolved. **Adverse Effects:** RVO In clinical trials the most frequently reported adverse events were increased intraocular pressure (IOP) (24.0%) and conjunctival haemorrhage (14.7%). Increased IOP with OZURDEX peaked at day 60 and returned to baseline levels by day 180. Elevations of IOP either did not require treatment or were managed with the temporary use of topical IOP-lowering medicinal products. The following adverse events were reported: Very common ($\geq 1/10$): IOP increased, conjunctival haemorrhage* Common ($\geq 1/100$ to $< 1/10$): Ocular hypertension, vitreous detachment, cataract, subcapsular cataract, vitreous haemorrhage*, visual disturbance, vitreous opacities* (including vitreous floaters), eye pain*, photopsia*, conjunctival oedema*, anterior chamber cell*, conjunctival hyperaemia*, headache Uncommon ($\geq 1/1,000$ to $< 1/100$): Retinal tear*, anterior chamber flare* Headache. **Uveitis** In clinical trials the most frequently reported adverse events in the study eye were conjunctival haemorrhage (30.3%), increased IOP (25.0%) and cataract (11.8%). The following adverse events were reported: Very common: Increased IOP, cataract, conjunctival haemorrhage* Common: Retinal detachment, Myodesopsia, vitreous opacities, blepharitis, sclera hyperaemia*, visual impairment, abnormal sensation in the eye*, eyelid pruritis, migraine. (*Adverse reactions considered to be related to the intravitreal injection procedure rather than the dexamethasone implant). Please refer to Summary of Product Characteristics for full information on side effects. **Marketing Authorisation number:** EU/1/10/638/001 **Marketing Authorisation Holder:** Allergan Pharmaceuticals Ireland, Castlebar Road, Westport, Co. Mayo, Ireland. **Date of Preparation:** May 2013.

Adverse events should be reported to your local Allergan office and to your Regulatory Authority

References: 1. Nehme A & Edelman J. Invest Ophthalmol Vis Sci. 2008;49(5):2030-2038. 2. Pommier S & Meyer F. Realites Ophthalmologiques 2012; 195. 3. Augustin A. et al. Poster presented at EVER 2012, October 10-13; Nice, France. 4. Querques L. et al. Ophthalmol. 2013;229:21-25. 5. Rostron E. et al. Poster presented at North of England Ophthalmological Society (NEOS) Summer Meeting 2013, June 12; Chester, UK.

Date of Preparation: May 2014 EU/0200/2014e

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ophthalmology

Subthreshold MicroPulse Laser for Diabetic Macular Edema: Basic Science and Clinical Results

Jose A. Cardillo

State University of São Paulo, Hospital de Olhos de Araraquara, Ribeirão Preto, Brazil

The subthreshold modality avoids thermal damage to retinal tissues. Proper parameters are of paramount importance. In a prospective, double-masked trial in 123 patients with DME, we compared the anatomic effects of modified ETDRS focal/grid thermal 532-nm laser photocoagulation vs subthreshold 810-nm diode micropulse laser photocoagulation using either a normal density or high-density treatment pattern. At 1 year, the high-density subthreshold group had the most improvement in best corrected visual acuity (BCVA), followed by the modified ETDRS group. No improvement was seen with the normal-density subthreshold treatment. The high-density group also showed the greatest reduction in central macular thickness (CMT) as measured by optical coherence tomography (OCT). This study demonstrates that when new technologies are introduced, it is vital to consider whether previous parameters and practices are appropriate or must be modified to make the new treatment work optimally. With subthreshold treatment in this study, the higher-density grid application produced the best outcomes. Although the reduction of laser intensity with subthreshold reduces the negative effects of thermal coagulation, it also requires a compensatory increase in treatment density. This is one of the reasons we have spent considerable time and effort refining and optimizing the parameters for this new laser modality.

Aflibercept for DME

Patricia Udaondo

La Fe University Hospital of Valencia, Spain

Different intravitreal anti-vascular endothelial growth factor (VEGF) medications have been used for the management of diabetic retinopathy and diabetic macular edema (DME) with satisfactory results and good safety profiles. Aflibercept, a new anti-VEGF agent with a different mechanism of action compared with prior therapies, has recently emerged. The results of aflibercept Phase II and III studies show its efficacy for the treatment of DME and its binding affinity for VEGF which is substantially greater than that of either bevacizumab or ranibizumab leads to a potentially longer duration of action in the eye and allows for less frequent dosing.

Steroids for the Treatment of Diabetic Macular Edema

Baruch D. Kuppermann

Gavin Herbert Eye Institute, University of California, Irvine

Introduction: There is a growing body of evidence demonstrating the importance of the role of inflammation in the development of DME.

Methods: A review of the literature evaluating the role of inflammation in the development of DME, as well as a review of selected randomized controlled clinical trials evaluating the safety and efficacy of various steroids and steroid based drug delivery systems for the treatment of DME.

Results: A review of the literature and clinical trial results shows the following key findings. Retinopathy progresses with time, and is associated with changes in the amounts of multiple cytokines relative to VEGF. In the FAME evaluating the fluocinolone acetonide (Iluvien) implant for the treatment of DME, the clinical response of the chronic (greater than 3 years duration of DME) versus non-chronic (less than 3 years duration of DME) treatment and control groups to intermittent laser, anti-VEGF and intravitreal steroids was significantly different. Steroids showed an enhanced response in the chronic groups, whereas laser and anti-VEGF showed a preferential response in the non-chronic group. In RIDE and RISE trials evaluating monthly intravitreal ranibizumab for the treatment of DME, the control populations showed a lack of response upon conversion to monthly anti-VEGF injections at the time of crossover 24 months into the study.

Conclusions: Multiple studies have demonstrated elevated expression of a range of inflammatory cytokines in DMO and RVO. Evaluation of clinical responses to anti-VEGF therapy provides insights into the significance of VEGF in mediating retinal vascular disease. These data are consistent with a shift, or transition, in the distribution of cytokines such that in chronic DME, VEGF expression may be less important than in less chronic DME.

Combination Therapy for Diabetic Macular Edema

Albert J. Augustin

Department of Ophthalmology, Klinikum Karlsruhe, Karlsruhe, Germany

Numerous medical and surgical treatments of diabetic macular edema (DME) are available. However, there are many limitations such as refractory, recurrent DME, ideal regimen, appropriate numbers of injections and the choice of injection intervals. To overcome those limitations, various therapeutic options using combination strategies are under investigation. Theoretically, with several anti-VEGF drugs and steroids as well as photocoagulation there are many combinations available thus making prospective randomized trials very difficult.

In this report we will focus on more popular combinations and compare them to monotherapies. Examples are intravitreal bevacizumab injection versus combination treatment consisting of bevacizumab and macular photocoagulation. Intravitreal bevacizumab injection was also compared to a combination with intravitreal triamcinolone acetonide (IVTA) versus macular laser photocoagulation as a primary treatment for diabetic macular edema. Macular grid photocoagulation after intravitreal triamcinolone acetonide for diffuse diabetic macular edema is another possible combination therapy for DME.

Several authors demonstrated that laser photocoagulation following IVTA is more effective than IVTA monotherapy for diffuse DME. Combination therapy required fewer additional treatments and resulted in a lower recurrence rate than IVTA monotherapy. Several authors evaluated the effectiveness of pars plana vitrectomy (PPV) with removal of the internal limiting membrane (ILM). The strategy offers promising results. However, a longer follow-up is needed to assess the effects of this treatment.

The results of the major most recent trials will be presented.

Guidelines for the Use of Laser, Anti-VEGF, or Steroids in DME

Michaella Goldstein

Tel Aviv, Tel Aviv Medical Center, Israel

Cumulating evidence based on the results of several clinical trials on diabetic macular edema has resulted in a fine shift in focus of the treatment of this vision-threatening stage of diabetic retinopathy from containment and stopping the disease progression to improving the vision of affected patients.

3 year follow up results of the DRCR protocol I showed an improvement of +9.7 letters in the ranibizumab 0/5 mg + deferral laser vs +6.8 letters in the ranibizumab 0/5 mg + prompt laser. 2 year follow up results of the BOLT trial have shown that patients treated in the Bevacizumab arm gained on average 8 letters compared to a loss of 0.5 letters in the laser arm. In the VIVID trial roughly 50% of eyes treated with Aflibercept 2 mg either every 4 or 8 weeks gained 10 letters in vision, and in the VISTA trial nearly 60% of treated eyes showed a 10 letters improvement.

Long acting slow release intravitreal steroids have also shown treatment benefit. In the MEAD trial patients were treated with Dexamethazone implant 350 or 700 microgram compared with sham + laser. The 3 year results showed a 15 letters improvement in vision in 22% of Dexamethazone treated eyes. Fluocinolone implant (Iluvien) has been proven as well with 22% of eyes treated with 0.2 microgram/day gaining 15 letters in vision compared to 18.9% in the sham group.

An overview of the current recommendations of various working groups of retina specialists experts shows a common trend towards translating the clinical dilemmas into an individualized approach, leaving far behind the outdated ETDRS standard of the focal/grid laser.

The Barrier to Inject – Keeping the Risk/Benefit Equation Right

Yan Guex-Crosier

Department of Ophthalmology, University of Lausanne, Jules Gonin Eye Hospital, Fondation Asile des Aveugles, Lausanne, Switzerland

Corticosteroids remain the mainstay of therapy of uveitis. Drops of prednisolone acetate 1% are currently used in the therapy of anterior uveitis. But the effect of corticosteroids drops is limited to achieve sufficient intraocular concentration in the posterior segment of the eye. To avoid systemic side effects of corticosteroids, several routes of administration have been used such as posterior subtenon or intraocular injections. Triamcinolone acetate (TA), a glucocorticoid with a fluorine in the ninth position has been extensively used with various dosage from 1 to 25mg. The highest complication rate being observed with the highest dosage. Increased intraocular pressure (IOP) occurs in 30% to 50% of cases with a rise of IOP up to 6 months after injection, leading to filtering surgery in about 1% of cases. Cataract progression is observed in up to 50% of cases after a two years follow-up. But direct intraocular injections are also associated with several ocular complications such as pseudo-uveitis, endophthalmitis, lens damage, retinal detachment. Several studies have shown that preservative in the vehicle suspension of TA could affect the rabbit's retina. Rate of sterile endophthalmitis has been reported from 0.87 to 7.3% after TA injection. Inflammatory reaction seems to be related either to the drug or its vehicle. When repeated injections are performed the cumulative risk of injection must be considered.

Anti-VEGF Treatments for Diabetic Macular Edema: Comparison of Phase III Randomized Controlled Clinical Studies

Baruch D. Kuppermann¹, Beiyong Ding², Ivo Stoilov³

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²Biostatistics, Genentech, Inc, South San Francisco, California, USA

³US Medical Affairs Ophthalmology, Genentech, Inc, South San Francisco, California, USA

Background: Comparison across clinical studies is limited by differences in baseline characteristics. Among phase 3 studies of ranibizumab (RESTORE, DRCR.net Protocol I, RISE, and RIDE), bevacizumab (BOLT), and aflibercept (VIVID and VISTA), inclusion criteria were similar except RESTORE and Protocol I allowed baseline VA up to 20/32 whereas other studies capped vision at 20/40.

Methods: To produce a patient population with comparable inclusion/exclusion criteria and baseline VA, subgroup analysis was conducted including patients in Protocol I with baseline VA of 20/40 or worse.

Results: Across studies, most visual and anatomic improvement occurred during the first year of treatment, with generally stable vision in second and third years despite mean annual injections as low as 2-4 in PRN arms. Subgroup analysis of Protocol I year 1 data (VA 20/40 or worse, n=581, 68% of study eyes) yielded baseline ETDRS letter score ≈57 (comparable to RISE/RISE, VIVID/VISTA and BOLT). The average number of injections was 8.1 for ranibizumab+prompt laser and 8.9 for ranibizumab+deferred laser. Mean BCVA gains from baseline, +11.7 letters (prompt laser) and +11.5 letters (deferred laser), were greater than in the full study population (9 letters) and comparable to RISE, RIDE, VIVID, and VISTA. Among subgroup subjects, 43% (prompt) and 34% (deferred) gained ≥15 letters from baseline, similar to patients in RISE, RIDE, VIVID, and VISTA.

Conclusions/Discussion: VA gains were comparable across trials when adjusted for baseline BCVA. Smaller VA gains in the Protocol I full study population compared with RISE/RIDE and VIVID/VISTA are potentially related to ceiling effect.

Differentiating the New Injectable Steroids

Min Zhao¹, Elodie Bousquet^{1,2}, Francine Behar-Cohen^{1,3}

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Since the first off-label intravitreal injection of Triamcinolone acetonide (TA) (Kenalog[®]), many studies have evaluated different formulations of TA. More recently, implants releasing either dexamethasone (Dex) or fluocinolone acetonide (FA) have been registered for macular edema of various origin. Are the different injectable steroids identical in their efficacy/ toxicity/ specificity/ mechanisms of action? How to choose the optimal steroid?

Methods: The dose and pharmacokinetics of different steroid formulations were compared using literature data analysis. Using retinal cell cultures, retinal rat explants and in vivo rat experiments, we compared the effect of different steroids on cytokines and on ion and water channel expression and distribution.

Results: Glucocorticoids effects on macular edema may result from a combination of mechanisms, including of ocular barriers restoration and activation of drainage mechanisms in retinal pigment epithelial cells and retinal glial Müller cells. The different glucocorticoids do not exert equivalent effect on these different mechanisms. Ocular toxicity of the different formulations and chemical compounds are also not identical.

Conclusions: The differential clinical effects observed with the different new glucocorticoids formulations may be explained by their differential mechanisms of action, that in the future, should be taken into account for optimal use of glucocorticoids in the treatment of retinal diseases.

The Conundrum of Steroids or VEGF Inhibitors for Retinal Indications

Sofia Androudi

Assistant Professor, University of Thessalia, Larissa, Greece

VEGF is suspected to play a role in the loss of vascular integrity in the eye and is known to be induced by inflammatory cytokines, such as interleukin-1 and interleukin-6, which have been found to be elevated intraocularly in uveitis patients.

In addition, fine and associates demonstrated that aqueous vascular endothelial growth factor (VEGF) concentrations are significantly higher in those uveitis patients with CME than those without CME. Therefore, inhibition of inappropriate VEGF activity is a potential new approach to treatment of CME in uveitic population.

In the last few years anti-VEGF therapy has changed the paradigm in the treatment of neovascular age-related macular degeneration. Besides, its potential use in the treatment of diabetic retinopathy and other possible proliferative vascular disorders has also shown promise. Intravitreal ranibizumab appears to be a safe and effective treatment leading to an increase in visual acuity and regression of uveitis-associated CME in patients refractory or intolerant of standard steroid therapy.

Off-label use of bevacizumab has also shown similar benefit but long-term and clinical trial results do not exist. Some of the potential questions in the use of anti-VEGF are recurring cost, possible long-term effect on physiological function of VEGF and determination of endpoint of treatment.

Systemic corticosteroids are the most potent and rapidly acting therapy for autoimmune and inflammatory diseases. They remain the mainstay of first-line therapy for severe ocular inflammatory diseases. Therapeutic principals that can be adopted to help minimize the side effects of corticosteroids include: use the lowest effective dose for the shortest period of time, always consider alternative topical and local therapy, use steroid sparing drugs early in the course of treatment, and using a corticosteroid preparations with less systemic side effects. The longer acting steroids that can be used in the eye have major advantages over triamcinolone which has been the main intravitreal steroid available for use in uveitis, usually used for treating refractory macular edema. We will focus on the most recent steroid drugs available for local delivery and discuss the data of the most recent clinical studies.

iPSCs: What can we Hope? How to Use Them?

Olivier Goureau

Institut de la Vision, INSERM U968; Sorbonne Universités, UPMC-Paris 6, UMR5968; CNRS UMR7210, Paris, France

Rescuing the degenerated retina in retinal diseases, such as inherited retinopathies or age-related macular degeneration (AMD) is a major challenge for which specific cell replacement is one of the most promising approaches. Human induced pluripotent stem (iPS) cells have the ability to be expanded indefinitely in culture and could be used as an unlimited source of retinal cells. Recent data have shown that following various manipulations, human iPS cells can give rise to retinal cells, particularly photoreceptors and retinal pigmented epithelial (RPE) cells (1,2). Innovative 3D protocols have been developed with human iPS cells, which generate self-organizing optic cup, optic vesicle-like or neural retina-like structures (3-5). These protocols allowed the generation of retinal progenitor cells that can be further differentiated into photoreceptors precursors, a potentially transplantable cell population. Regarding, RPE cells that could be transplanted in case of AMD, pilot studies to assess the safety and feasibility of the transplantation of autologous iPS-derived RPE cells should start within the next two years.

The differentiation of iPS cells would not only facilitate cell replacement therapy, but could also be used in disease modelling as a research tool for studying pathogenesis. The generation of mutated iPS cells, that recapitulate defined pathogenic steps at the molecular level, offer opportunities for quantitative modelling of the disease mechanism and drug screening.

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Derivation of Traceable and Transplantable Photoreceptors from Mouse Embryonic Stem Cells

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Retinal degenerative diseases resulting in the loss of photoreceptors are a major cause of blindness. Recently, different groups validated the possibility to reactivate dormant retinal circuits of degenerating retinas using retinal prosthesis, gene therapy, and cell replacement therapy. Photoreceptor replacement therapy may be feasible since transplanted photoreceptors, collected directly from the developing or the adult retina, have been shown to restore some visual function in mice affected by retinal degeneration. Because the developing retina is not a suitable source of renewable photoreceptors, we focused on embryonic stem cells (ESC) for their capacity to generate retinal progenitors and photoreceptor cells in vitro. In this study, we derived a new transgenic ESC line in which the reporter gene, the Crx-GFP transgene, is expressed in both post-mitotic immature and mature photoreceptors, and assessed the extent to which this protocol recapitulates photoreceptor development in vitro. Various oxygen concentrations were tested at different development stages to improve photoreceptor production. As observed during retinogenesis, the optimized 3D-retina induction protocol allows the production of GFP-positive photoreceptors between 12 and 14 days of culture reaching the peak of birth between day 18 and 20 of culture. Similarly the intensity of the GFP signal and their alignment increased over time. We observed that hyperoxic condition improved photoreceptor survival only when present from photoreceptor differentiation onset. Up to 10 layers of photoreceptors can be formed in each in vitro-generated retina. In addition, we proved that transplantation of ESC-derived photoreceptors is feasible. No appearance of tumor formation was detected after transplantation of sorted photoreceptor cells. Many Crx-GFP-positive cells show the presence of outer-segments, ribbon synapses, and light signal transduction pathway proteins. These experiments show the feasibility to reliably generate a large quantity of integration-competent photoreceptors from ESC. A further characterization of the transplanted photoreceptors to reveal their capacity to mediate light stimuli is underway.

Developing New Drugs and Delivery Systems for the Treatment of Inherited Retinal Degeneration: The DRUGSFORD Project

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Dysregulation of cGMP is a pathological hallmark of many forms of inherited retinal degeneration (RD), affecting photoreceptors; the sensory cells of the retina. The aim of the EU-funded DRUGSFORD consortium is to produce new drugs for the treatment of RD, using cGMP-signalling as a common target. These drugs are combined with an innovative liposomal drug delivery system (G-Technology) to allow for efficient drug transfer to the photoreceptors of the retina.

Towards this goal, two companies have teamed up with three academic research groups focussed on retinal degeneration: the German company BIOLOG specializes on development of cyclic nucleotide based drugs targeting cGMP-signalling; the Dutch company to-BBB technologies B.V. develops its proprietary G-Technology to deliver drugs across the blood-brain and blood-retina barriers (BBB, BRB, resp.); the groups of V. Marigo (Modena, Italy), P. Ekström (Lund, Sweden), and F. Paquet-Durand (Tübingen, Germany) have a strong and joint collaborative track record of studying photoreceptor degenerative mechanisms as well as on testing and evaluating drug treatment effects.

So far DRUGSFORD has produced over 150 novel compounds. These were tested in a step-wise fashion in four different assay systems of rising complexity. Importantly, a first formulation based on G-Technology was identified that resulted in a significant rescue of photoreceptors in the rd1 mouse model. Improved photoreceptor survival in this very severe animal model represents an important achievement, and consequently the consortium jointly decided to select this compound in its liposomal formulation as the first lead to be developed towards Phase I clinical testing.

In summary, DRUGSFORD addresses cGMP signalling as a new common target for the treatment of RD. The consortium has produced new cyclic nucleotide compounds, with unique and highly target specific properties and has adapted and developed a new liposomal drug delivery technology for efficient delivery to retinal photoreceptors.

Gene Delivery to the Retina: Choice for a Vector and a Route of Administration

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Background: Gene therapy is one of the ongoing developments with highest potential of success for the treatment of retinal diseases. Clinical experience has demonstrated feasibility and efficacy.

Choosing which vector for which gene delivery to which types of cells to achieve the optimal level of protein expression in the appropriate location, with minimal toxicity, remains amongst the main challenges.

In this presentation we will review the different types of vectors used in clinical and pre clinical studies and their routes of administration. Other routes of administration such as supra choroidal delivery will be discussed.

Levels of protein and their site of production will be also discussed taking into account the various indications proposed for gene therapy development.

Botulinum Toxin

Fion Bremner

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Botulinum neurotoxins (BnT) are proteins derived from the Gram-positive anaerobic bacteria *Clostridium botulinum*. They cause reversible blockade of transmission at cholinergic neuromuscular and neuroeffector junctions by binding to the presynaptic nerve endings and preventing the release of acetylcholine. They were first developed for clinical use as an ophthalmic treatment for strabismus over 30 years ago. Since then BnT has proved effective as treatment for a number of other ophthalmic conditions (e.g. dystonia, lagophthalmos, inappropriate lacrimation) as well as being used in many other medical specialties (neurology, urology, gastroenterology, orthopaedics, dermatology etc). In this talk I will briefly consider the various different uses of BnT in clinical ophthalmology and discuss current controversies.

Treatment of Optic Neuritis

Hana Leiba

Kaplan Medical Center, Israel

Optic neuritis is an inflammation of the optic nerve. It affects mainly young adults and has many causes. Treatment is aimed initially to treat the acute disease and thereafter to prevent further deterioration either in a chronic or a relapsing – remitting course.

Clinically, the disease is divided into typical and atypical forms; typical optic neuritis is associated with MS while the atypical form is associated with other immune mediated conditions. The differential diagnosis is extensive. Thus, efforts are carried to diagnose each case and provide the appropriate treatment.

Due to the current developments in understanding the pathophysiology of the disease, data is accumulating regarding possible treatments.

An update on these developments will be given.

Medical Treatment to Anterior Ischemic Optic Neuropathy

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Nonarteritic anterior ischemic optic neuropathy (NAION) is characterized by acute, monocular, painless visual loss with optic disc swelling. The etiology is unknown, assumed to involve ischemic insult followed by inflammatory reaction. As the mechanism is not clear, the treatment of NAION remains very limited and disappointing. The current attitude is to control and correct risk factors. Several treatments have been suggested but yet in randomized clinical trials, none have demonstrated to be effective in recovering visual loss. Aspirin does not seem to improve vision while owing to the limited evidence supporting steroid treatment to treat acute NAION this latter treatment remains largely debated. Based on the compartment syndrome theory, a surgical decompression study was conducted and failed. Medical decompression by anti VEGF drugs was reported to improve visual outcome in few cases. The recent use of animal models enables the demonstration of the mechanism of the tissue insult in NAION and the examination of various drugs for possible neuroprotection. These studies will be discussed as will the horizon of new treatments.

Neurophthalmological Side Effect of Medical Treatment

Klara Landau

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A large number of commonly used medical treatments may cause side effects affecting the visual system and it is beyond the scope of this talk to cover them all. Focus will thus be given to side effects that may lead to irreversible visual loss (both visual acuity and visual fields) due to retinal toxicity, optic neuropathies or raised intracranial pressure with post-papilledema optic atrophy. The medications with neuro-ophthalmic side effects that will be presented include Vigabatrin for treatment of intractable epilepsy, the antiarrhythmic substance Amiodarone, as well as anti-acne medications such as Tetracyclines and Vitamin A preparations.

The proposed pathophysiological mechanisms will be presented, followed by recommendations for monitoring and management. A special focus will be given to the latest data published in the literature as some of the presented aspects remain to be hypothetical and controversial.

Imaging in Ocular Surface Disease

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Dry Eye disease (DED) is a common, multifactorial disease that causes discomfort, visual disturbance, and tear film instability. While mild DED may be bothersome, severe DED can cause chronic pain and fluctuating vision. Diagnosis of DED is often subjective, and symptoms may be confounded by standard clinical practices such as using anesthetic drops, stains, and illumination. Oculus Keratograph may offer clinicians standardized conditions to noninvasively and objectively measure many DED endpoints – tear break up time, tear meniscus height, meibomian gland dropout, lipid layer, tear film dynamics, and bulbar hyperemia. Keratograph may help to clearly evaluate structural and functional abnormalities as well as signs of inflammation. Studies have shown significant correlation between Keratograph tear break up time measurements and break up time with fluorescein as well as between tear meniscus height and slit lamp examination. The lipid layer and tear film dynamics may be observed in real time. No drops are needed and infrared light is used for illumination, eliminating the effect of bright light and staining drops on measurements. Documentation of these minimally invasive objective metrics may allow for demonstration of treatment effects and disease progression.

Boston Keratoprosthesis Multicenter Study: Retention and Vision

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Objective: To report the retention and visual outcomes of the Boston Keratoprosthesis Type 1.

Methods: Forms reporting preoperative, intraoperative, and postoperative parameters were prospectively collected and subsequently analyzed at a central data collection site.

Results: A total of 300 eyes of 300 patients who underwent implantation of the Boston keratoprosthesis type device between January 2003 and July 2008 by 19 surgeons at 18 medical centers. 33.3% of eyes (n=100) had hand motions acuity and 14.3% (n=43) had only light perception. After an average of 17.1 ± 14.8 months, visual acuity improved significantly (p<0.0001) to a mean final value of 0.89 ± 0.64 (20/150). There were also fewer eyes with hand motions acuity (8.5%; n=24; p=0.263) and significantly fewer with light perception (6.7%; n=19; p<0.0001), although 3.1% (n=9) progressed to no light perception. Multivariate analysis demonstrated three independent predictors of final visual outcome: chemical injury was associated with better final vision (p=0.0012), whereas aniridia (p=0.03) and AMD (p<0.0001) were associated with poorer vision. During the study period, 21 (7%) eyes failed to retain the device; the reasons for keratoprosthesis loss include sterile keratolysis (9), fungal infections (8), dense retroprosthetic membranes (3), and bacterial endophthalmitis (1). Multivariate analysis demonstrated 3 independent risk factors for keratoprosthesis loss: autoimmune disease, ocular surface exposure requiring a concomitant tarsorrhaphy, and number of prior failed penetrating keratoplasties.

Conclusions: The Boston keratoprosthesis type 1 seems to be a viable option for eyes that are not candidates for penetrating keratoplasty (PK).

In Vivo Histology of Amniotic Membrane Integration in the Human Cornea

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Background and Purpose: In therapy resistant deep corneal ulcers a multilayer of amniotic membrane transplantation (AMT) will often result in a faster and stable closure of the epithelial defect. For visual rehabilitation a penetrating keratoplasty (PKP) may be required in the quiet interval after AMT. Histological assessment of the excised specimens proved that various surgical techniques of AMT (Patch, Graft, Sandwich = Graft(s) + Patch) will result in various integrations patterns of the AM in the human cornea (intraepithelial, subepithelial or even stromal integration) (1). The purpose of this study was to assess whether the integration pattern of AM can be visualized by means of a noncontact anterior segment (AS) OCT in vivo.

Patients and Methods: In 3 patients with ulcerative necrotizing stromal keratitis of herpetic origin an AMT with two, three or even five graft layers was performed, one to six months before PKP. Immediately before PKP we performed high resolution AS-OCT (SS 1000 CASIA, Tomey) and compared these results with the histological picture of the excised cornea. Corneal specimens were stained with hematoxylin-eosin und PAS.

Results: The AS-OCT displayed an intact epithelium above the AM grafts as clearly delineated hyporeflexive layer of 30 to 66 µm thickness. The area of the AM layers could be distinguished from the surrounding corneal host stroma because of a different pattern of light reflexion. The relation of the thickness of the AM tissue in comparison to the total corneal thickness after re-establishment of the anterior corneal curvature ranged between 23% and 61%. Depending on the time period after AMT, some of the individual AM layers could be distinguished in vivo due to clefts in between. Using the AS-OCT we were able to distinguish subepithelial from stromal integration of AM in the host cornea - in accordance with the histological findings.

Conclusions: These findings suggest that - in contrast to common contention - besides epithelial healing, biomechanical stability of corneas with deep ulcers or even descemetocelles may be re-established after multilayer AMT by stromal integration. The high resolution AS-OCT may be useful for noncontact follow-up examinations after AMT for deep corneal ulcers. Typically, slit-lamp examination shows a more or less opaque "scar" after AMT, but AS-OCT may elucidate integration patterns of AM in the human cornea ("in vivo histology") as an indicator for biomechanical stability. (1) Resch MD, Schlötzer-Schrehardt U, Hofmann-Rummelt C, Sauer R, Kruse FE, Beckmann MW, Seitz B: Integration patterns of cryopreserved amniotic membranes into the human cornea. Ophthalmology 2006; 113:1927-1935

Inflammation (Confocal) in Dry Eye Disease

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Purpose: Recent studies have shown the role of immune changes in the pathogenesis of dry eye disease

(DED). Clinical examination alone cannot detect these immune changes in various levels of DED severity. Thus, a sensitive test is needed to quantify the immune response. The purpose of this study is to evaluate the changes in corneal immune dendritic cells (DC) in different levels of DED severity.

Methods: This retrospective study included 150 patients with DED and 52 age-matched controls.

The images obtained by in vivo confocal microscopy (IVCM) from central cornea were analyzed for DC density and morphology (cell size, number of dendrites, and DC field). Clinical severity of DED was graded (levels 1-4) based on Dry Eye Workshop (DEWS). Clinical severity of DED was then correlated with IVCM parameters.

Results: Compared with corneal DC density in the control group (26.0 ± 3.7 cell/mm²), significant increases in corneal DC density were observed in all levels of DED (P<0.001), with 87.2 ± 10.4 cell/mm² in level 1 (mild), 92.9 ± 9.6 cell/mm² in level 2 (moderate), 105.8 ± 18 cell/mm² in level 3 (severe), and 95.8 ± 20.32 cell/mm² in level 4 (severe). The differences among corneal DC densities in various levels of DED were not statistically significant. In contrast to corneal DC density, in morphologic parameters there were no significant differences in DC size, number of dendrites and field area between the control group (63.8 ± 4.1 μ m², 2.9 ± 0.1 per DC, 247.5 ± 22.8 μ m², respectively) and level 1 (mild) DED (90.2 ± 3.7 μ m², 3.03 ± 0.1 per DC, 319.8 ± 20.7 μ m², respectively). However, these morphologic parameters showed statistically significant increases in DED levels 2-4 compared with the controls (P<0.05).

Conclusions: Although inflammation plays a major role in the pathogenesis of DED, only a subset of patients shows increased corneal immune cells. This may explain variable success rates of anti-inflammatory therapy in otherwise clinically similar patients. While corneal DC density is increased in mild DED (level 1), DC morphological changes increase in more severe disease, signifying increased activation. These parameters may aid in therapeutic decision-making, and reversal of these differential changes may be used to evaluate the efficacy of anti-inflammatory treatment in DED. By assessing corneal immune response in DED, IVCM may be used to complement clinical examination, stratifying patients for clinical trials and guide treatment.

Correlations of Real Time Tear Film Metrology to Subject Symptomatology

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Background: The main impediments to the development of evidenced based therapy for dry eye disease have been the lack of correlation of subject symptoms with clinical diagnostic testing, as well as the absence of standardized, non-invasive, objective testing modalities.

Methods: We utilized our unique tear film metrology technologies, deployed in multimodal fashion in a controlled environment, to validate subjective responses in real time to geometric and temporal changes in tearfilm components within a blink cycle.

Results: The utilization of these methods for objective data collection can produce statistically significant correlations with heterogeneity and percent of ocular surface coverage associated with individual symptoms.

Conclusions: With ongoing investigation there is the prospect to reproducibly associate at least one subjective symptom to clinically relevant findings in individuals with dry eye disease.

UV Crosslinking of Donor Corneas to Prevent Keratolysis

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Purpose: To develop a modified ex vivo corneal crosslinking method that increases stromal resistance to enzymatic degradation for use as a carrier for the Boston keratoprosthesis.

Methods: Ex vivo crosslinking of human corneas was performed using Barron® artificial anterior chambers. The corneas were de-epithelialized, pre-treated with riboflavin solution (0.1% riboflavin/20% dextran) and irradiated with ultraviolet A (UVA) light ($\lambda=370$ nm, irradiance=3mW/cm²) for various durations. The combined effect of UVA and gamma (γ) irradiation was also assessed using the commercially available γ -irradiated corneal donors. The corneas were then trephined and incubated at 37 degrees Celsius with 0.3% collagenase A solution. The time to dissolution of each cornea was compared across treatments.

Results: De-epithelialized corneas (no UV light, no riboflavin) dissolved in 5.8 ± 0.6 hours. Crosslinked corneas demonstrated increased resistance to dissolution, with a time to dissolution of 17.8 ± 2.6 hours ($p < 0.0001$). The corneal tissues' resistance to collagenase increased with longer UVA exposure, reaching a plateau at 30 minutes. Crosslinking both the anterior and posterior corneas did not provide added resistance when compared to crosslinking the anterior corneas only ($p>0.05$). γ -irradiated corneas dissolved as readily as de-epithelialized controls regardless of whether they were further crosslinked (5.6 ± 1.2 hours) or not (6.1 ± 0.6 hours) ($p=0.43$).

Conclusions: Collagen crosslinking of the de-epithelialized anterior cornea surface for 30 minutes conferred optimal resistance to in vitro keratolysis by collagenase A.

Imaging of the Ocular Surface with Ultra High Resolution Optical Coherence Tomography - (UHR-OCT)

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Direct access to the target organ is an advantage that we have as investigators of vision sciences and ophthalmologists. Our group has dedicated time in the development of high resolution imaging of the ocular surface using optical coherence tomography to evaluate the ocular surface. Using an UHR-OCT that has been adapted to image the anterior segment, we have been able to delineate the corneal epithelium with a resolution of 3 μ m.

Data from these studies demonstrate that in contrast to normal individuals, patients with dry eye have a significant amount of microscopic irregularities, that correlate with symptoms and can be modified with treatment. Moreover, we have developed a corneal irregularity map that provides information of not only the central cornea surface, but also the para-central and peripheral regions as well. The use of anterior segment UHR-OCT provides a unique and novel tool to evaluate and diagnose disorders of the ocular surface.

Devices for the Anterior Segment in the US: Reality vs. Myth

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Advances in imaging devices to assess anterior segment are improving our understanding of ocular pathology. Over the past decade, there has been a significant increase in the number of premarket submissions for imaging devices received by the FDA which has been accompanied by a significant rise in the use of ocular imaging devices in the US clinical practice. Appropriate use of anterior segment imaging devices can enhance patient care, while inaccurate classification or misinterpretation of results can lead to a delay in diagnosis or unnecessary treatment and associated patient anxiety, increased costs, and risks associated with unnecessary treatments. Discussion of the benefits, limitations, and future directions of these technologies is aimed to enhance proper use of anterior segment imaging technologies in clinical practice as well as stimulate further advances in their development and evaluation.

Pathophysiology of Dry Age Related Maculopathy

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Purpose: Age-related macular degeneration (AMD) is the leading cause of legal blindness in elderly individuals in the developed world, affecting 30-50 million people worldwide. The pathophysiology and risk factors for AMD are complex, and the symptoms manifest in multiple related but distinct forms.

Methods: An analysis of the literature was carried out, to find the role of different pathogenetic mechanisms leading to the development of dry AMD.

Results: Dry AMD is a multifactorial disease involving a complex interplay of genetic, environmental, metabolic, and functional factors. Besides smoking, hypertension, obesity, and certain dietary habits, a growing body of evidence indicates that inflammation and the immune system may play a key role in the development of the disease. However, the genetic component is thought to be the main precondition for this disease.

Main genetic polymorphisms associated with risk of AMD development and progression were found to be genes that regulate inflammation especially in complement factor H gene (1q31 locus) and 10q26 locus (PLEKHA1/ARMS2/HTRA1).

Conclusions: The aim of this article is to review and delineate how the different and already known pathogenetic mechanisms can be networked in the development of dry AMD.

New Approaches to Screening for AMD

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Over the last decade, a revolution has occurred in the treatment for AMD. However, some patients still experience permanent vision loss due to late diagnosis followed by late treatment. Recent clinical trials such as CATT, have shown an association between the time to treatment and the final visual outcome. Early detection and treatment of AMD significantly reduces the risk of permanent vision loss. With the newly developed preferential hyperacuity perimetry device, patients are able to screen for anatomical changes and early development of choroidal neovascularization from home with higher sensitivity and specificity than the standard Amsler grid.

1520 patients participated in the AREDS 2 HOME study. The aim of the study was to compare the change in VA from baseline to time of incident CNV in eyes monitored regularly with the PHP device (ForseeHome) compared with the standard of care.

Results from the AREDS 2 HOME Study demonstrate the device's efficacy in screening for AMD. Eyes that were monitored with the standard care lost a median of 9 letters compared to eyes monitored with the PHP that lost only 4 letters at the time of incident CNV. This 5 letter difference was both clinically relevant and statistically significant. Among participants who used the device at the recommended frequency, the proportion maintaining 20/40 or better visual acuity was 94%.

Imaging in Dry AMD

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Ocular imaging technologies enable to follow changes in the RPE, photoreceptors, and choriocapillaris quantitatively as the disease progresses. Detection of GA can be achieved with a number of different imaging techniques, including color fundus photography, fluorescein angiography, indocyanine green angiography, short- and long-wavelength fundus autofluorescence (FAF), near-infrared reflectance, spectral-domain optical coherence tomography and adaptive optics-scanning laser ophthalmoscopy. Color photography has been used previously to the clinical widespread use of autofluorescence imaging. Fundus Autofluorescence (FAF) identifies the RPE disturbances at the junctional zone of GA between the very low FAF signals and the perilesional nonatrophic retina. FAF allows the measurement of the surface of the absent RPE. Its prognostic relevance has resulted in the FDA approval as primary outcome measure in clinical trials to assess GA progression rate. Spectral-domain OCT (SD-OCT) reveals morphological disturbances of the outer retinal layers and a hyporeflectivity in the choriocapillaris. New softwares permit the measurement of the volume of the missing choriocapillaris in addition to that of the dead RPE. These data, when correlated with the known histopathology of AMD, may provide useful measures of treatment efficacy that are likely to be more sensitive and reproducible than conventional end points such as visual acuity and rate of enlargement of geographic atrophy.

The Role of Genetic Testing in the Management of AMD

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Background: Major insights were obtained in recent years into the genetic factors which underlie Age Related Macular Degeneration (AMD). Both common and rare variants in over 20 different genes involved in several biological pathways were associated with risk for developing the disease. These discoveries enabled to uncover the role of inflammation in general and the alternative complement system in particular in the pathogenesis of the disease.

The fact that genetic variants account for the majority of the risk for developing AMD and the variability in response to treatment among patients incite hope that genetic testing may help in diagnosis of AMD and personalized treatment guidance alike.

Methods: Review of literature.

Results: Recent research revealed that genetic testing by themselves are insufficient for the diagnosis of the disease or prediction of the risk for its progression. Currently, algorithms which incorporate genetic testing in addition to other parameters are being developed to aid in these tasks. There are contradicting findings regarding the association of genetic variants with treatment outcome in non-neovascular and neovascular AMD.

Conclusions: While genetic testing may serve as a clinical tool in the context of AMD in the future, it mostly serve as a research tool at this point of time. It is also valuable as a surrogate for clinical trials. Further research is required to evaluate its role in the setting of a clinic.

The MAHALO Phase II Results: Lampalizumab (Anti-factor D) in Patients with Geographic Atrophy

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Purpose: Genetic variations and complement hyperactivity are implicated in the pathogenesis of age-related macular degeneration (AMD). Lampalizumab (formerly identified as FCFD4514S and anti-factor D) is an antigen-binding fragment that targets complement factor D, a rate-limiting enzyme in the alternative complement pathway and potential therapeutic target for geographic atrophy (GA) secondary to AMD. The MAHALO Phase II study assessed the safety, tolerability and evidence of activity of lampalizumab in patients with GA.

Methods: The MAHALO Phase II study enrolled 129 patients aged 60–89 years with GA secondary to AMD in the absence of choroidal neovascularization. Patients were randomized 2:1:2:1 to lampalizumab 10 mg or sham, administered monthly or every other month. The sham arms were pooled for the analyses. The primary endpoint was change in GA area from baseline to month 18 as assessed by confocal scanning laser ophthalmoscopy-fundus autofluorescence imaging. In an exploratory analysis, we also evaluated the relationship between established genetic polymorphisms associated with AMD and GA characteristics and lampalizumab treatment response.

Results: One hundred twenty-three patients received at least 1 sham or lampalizumab treatment and had at least 1 post-baseline primary efficacy measurement (sham pooled, n=40; lampalizumab monthly, n=42; lampalizumab every other month, n=41), which satisfied pre-specified criteria for evaluation. A 20.4% reduction in GA progression was reported in the all-comer lampalizumab monthly arm relative to the pooled sham arm. This positive treatment effect was observed at month 6 through month 18. Furthermore, a 44% reduction in GA progression was observed in a subpopulation treated monthly with lampalizumab and positive for the complement factor I (CFI) biomarker; 57% of the collected samples in MAHALO were CFI biomarker-positive. Lampalizumab demonstrated an acceptable safety profile in the Phase II study; there were no deaths and no ocular or systemic serious adverse events suspected to be study drug-related.

Conclusions: MAHALO is the first study to show a positive treatment effect in reducing GA progression through complement inhibition. The positive effect observed following monthly lampalizumab treatment was further magnified in the CFI biomarker-defined subpopulation. Our data suggest that the CFI biomarker appears to be both prognostic for GA progression and predictive for lampalizumab treatment response.

The TOGA Study: A Phase II/III Study Evaluating the (T)reatment with (O)RACEA (Doxycycline) for (G)eographic (A)trophy

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TOGA is a prospective, randomized, double-masked, placebo-controlled study evaluating the efficacy of daily oral administration of ORACEA[®] compared with placebo control on the rate of change in area of GA as measured by the change in area of GA.

This study consists of a six-month Observation Period followed by a 24-month Treatment Period. 286 subjects will be randomized at 25 investigational centers in the United States to either ORACEA[®] or placebo for 24 months. The TOGA Study is powered to detect a 30% difference in the mean yearly rate of change in the area of GA between the ORACEA[®] group and the placebo group as a function of sample size and the bivariate correlation between the yearly rate of change in the area of GA and the baseline area of GA. The primary outcome measure is the rate of enlargement in the area of GA in the study eye during the Treatment Period, as assessed by fundus photography.

Alprostadil for Dry Age Related Macular Degeneration (AMD)

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Purpose: To assess efficacy and safety of intravenous alprostadil infusion in patients with dry AMD.

Methods: Prospective, randomized, multi-center study. Patients were treated with intravenous infusion of either 60 µg alprostadil or placebo over three weeks. Main efficacy outcomes were mean differences in BCVA from baseline assessed in ETDRS lines immediately, 3 months and 6 months after treatment.

Results: In the Full Analysis Set a mean difference of 0.89 ± 0.537 ETDRS lines according to ANCOVA resulted in the alprostadil group (n=16) and a mean difference of -0.05 ± 0.578 in the placebo group (n=17) 3 months after end of treatment.

Thus, effectiveness of alprostadil infusion was numerically superior to placebo treatment by a mean of 0.94 lines after 3 months (1.51 lines after 6 months). These findings were more pronounced in the Per Protocol Set. Safety results were in line with the good safety profile of alprostadil.

Conclusion and further projects: A numerical treatment effect in favor of alprostadil was visible, which lasted until the end of Follow-up. These results provide further evidence that alprostadil probably has a therapeutic effect in the treatment of dry AMD and justify further clinical studies.

Within future studies on the effect of alprostadil in dAMD inclusion criteria will be dry AMD (dAMD) in at least one eye including geographic atrophy (GA), whereas patients with high conversion risk to neovascular AMD (e.g. large soft drusen) should be excluded from the study. Defining the best clinical trial endpoint for showing efficacy in the shortest period of time is still difficult in investigating dAMD. As patients with early stages of dry AMD, but sometimes even in the late atrophic stages, can maintain good central visual acuity until the disease progresses to involve the foveal center, it might require a long time (or large patient populations) to detect differences in visual acuity outcomes. Therefore in addition to BCVA the evaluation of secondary efficacy parameters is important.

Complement Inhibition Using Gene Therapy for AMD

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Membrane attack complex (MAC), the terminal product of the complement cascade, deposits in the retinal pigment epithelium (RPE) and choriocapillaris and may be a critical factor for the development of AMD. CD59 (protectin) prevents the formation of MAC. CD59 prevents MAC deposition and damage to RPE cells and reduces the growth of choroidal neovascularization (CNV) in a murine laser CNV model. Delivery of soluble CD59 to the retina by a gene therapy approach using adeno-associated virus type 2 may delay or prevent progression to late stage AMD.

Toward Personalized Medicine in AMD

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Since the description of associations between genetic polymorphisms and AMD, the role of genetic factors in the occurrence of AMD is commonly admitted. Smoking and body mass index are important environmental factors associated with an increased risk of AMD while the burden of genetic factors leads to attributable risk estimates up to 60%. Prediction models based on known genetic and environmental factors associated with AMD have been recently established. Seddon et al. described a model showing that the risk of developing exudative AMD in the second eye may vary between 20 and 90% at 3 years, depending on environmental and genetic factors. It is predictable that genes involved in these diverse steps would differ, and that genes involved in the occurrence of AMD would not be the same than genes involved progression of the disease or genes involved in therapeutic responses.

Correlations between some genes and AMD phenotypes have been reported. Recent studies revealed that the severity of AMD could be more specifically associated to ARMS2. Indeed, earlier age of onset, higher rates of progression and bilateralism of the CNV have been observed with carriers of the at-risk alleles of this gene.

The next step of such correlations goes from the degree of response to treatment to therapeutic protocols adjusted to the genotype, the rationale being that genetic profile of an AMD patient could lead to customized treatment strategies. Genetic factors which modulate the response to anti-VEGF therapies are currently difficult to identify. A wide range of therapeutic response is observed, from severe decrease of vision to spectacular improvement of vision. Several factors had been supposed to be associated to therapeutic response such as the subtype of choroidal neovascularization, environmental factors, tachyphylaxis or genetic background. Considering the anti-vascular epithelial growth factor (anti-VEGF) response, it is possible that genes involved in the occurrence of AMD would differ from genes involved in the response to anti-VEGF treatments. This hypothesis may lead to customized treatments based on genetic profiles. Several other therapeutic approaches are emerging, involving different mechanisms, as vascular endothelial growth factor trap-eye. It could also be hypothesized that different genes could modulate the response to different therapeutic target and exert a different influence on the curative response. This approach has been effective for antineoplastic drugs, cardiovascular drugs and drugs used for infectious diseases. Genomics should lead to major developments in the field of AMD through modulation of preventive approaches, customized follow-up of patient and customized therapeutic approaches by using the genetic profile of each patient. Prospective studies are however needed to validate these concepts and to apply them in the everyday clinical practice.

Multimodal Functional and Morphological Aspects of Reticular Pseudodrusen

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Purpose: In 1990 we described reticular pseudodrusen as a peculiar yellowish pattern in the macula of age-related macular degeneration AMD patients. More recently, using spectral domain optical coherence tomography (SD-OCT), we and others demonstrated that discrete collections of hyperreflective material located not under but above the retinal pigment epithelium (RPE), were associated with reticular pseudodrusen. Zweifel et al suggested that the hyperreflective material as visualized by SD-OCT could be graded by the thickness of the accumulation above the RPE, and proposed a defined grading system of 3 stages and we recently proposed a 4th stage, suggesting that reticular pseudodrusen are dynamic pathologic structures. Here our purpose was to analyze choroidal changes associated with reticular pseudodrusen by indocyanine green angiography (ICGA) and enhanced-depth-imaging spectral-domain optical coherence tomography (EDI SD-OCT).

Methods: Twenty-two consecutive patients (22 eyes) with reticular pseudodrusen, and without medium/large drusen, underwent ICGA and EDI OCT. Twenty-one age and sex matched subjects (21 eyes) with early age-related macular degeneration (AMD), and without pseudodrusen, also underwent EDI OCT.

Results: Mean age of patients with reticular pseudodrusen and with early AMD was 82.5±0.9 and 79.3±4.4 year-old, respectively (p=0.9), and 59.0% and 76.2% were women, respectively (p=0.7). On ICGA, reticular patterns appeared as hypofluorescent, not overlying the large choroidal vessels. Areas of iso/hyperfluorescence on ICGA, occurring adjacently to reticular patterns, appeared on OCT as subretinal deposits. The mean subfoveal choroidal thickness was significantly reduced in the group with reticular pseudodrusen compared with the control group (174.6±10.1 and +241.4±16.5, respectively; p<0.001). At all measurement points but the 3000-µm superior to the fovea, the choroidal thickness of eyes with reticular pseudodrusen appeared thinner than that of the control group. Interestingly, the choroid of eyes with reticular pseudodrusen appeared thicker at 3000-µm superior to the fovea compared with all other measurement points.

Conclusions: We showed that the reticular patterns appeared as hypofluorescent lesions on ICGA, closely abutting, but not overlying the large choroidal vessels. In eyes with reticular pseudodrusen, EDI OCT revealed an overall thinned choroid.

Is Tigecycline the Next New Ocular Antibiotic?

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Introduction: Tigecycline is a glycycline antibiotic indicated for treatment of systemic infections. RPX-978 is a topical ophthalmic formulation of tigecycline in development. The goals of the study were to determine: 1) the in vitro activity of tigecycline against multiple clinically relevant ocular pathogens; and 2) compare the efficacy of 0.5% tigecycline to topical vancomycin using a methicillin-resistant *Staphylococcus aureus* (MRSA) keratitis model.

Methods: In vitro: Broth dilution MICs were determined for 110 clinical conjunctivitis isolates based on incidence at the UPMC Eye Center. MICs were also performed on 26 keratitis isolates of *Pseudomonas aeruginosa* and 10 endophthalmitis isolates each of MRSA, MSSA, methicillin-resistant and susceptible coagulase-negative *Staphylococcus*. A total of 176 isolates were tested. In vivo: The corneas of 32 rabbits were intrastromally injected with 1000 CFU of MRSA. Rabbits were separated into 4 groups: 1) tigecycline 0.5%; 2) vancomycin, 3) 5% saline; and 4) no treatment (baseline CFU). Four hours after MRSA challenge, topical treatment of one drop every 15 minutes for 5 hours was initiated. One hour after treatment, the corneas were harvested for CFU.

Results: In vitro: Tigecycline demonstrated excellent MICs for Gram-positive isolates with MIC90 0.5 mg/ml for all species. Tigecycline demonstrated unexpected MICs for Gram-negative isolates with MIC90 8.0 mg/ml for all species. In vivo: Tigecycline and vancomycin demonstrated 99.9% reductions in MRSA compared to baseline CFU (P<0.05).

Conclusions: Tigecycline demonstrated broad spectrum in vitro activity against clinically relevant ocular pathogens. Topical tigecycline was equally efficacious as vancomycin in this MRSA keratitis model.

The Use of Predatory Prokaryotes to Control Human Ocular Pathogens

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Antibiotic resistant microorganisms are an increasing cause for concern in hospitals around the world. In an attempt to find innovative approaches to eradicate antibiotic resistant bacteria, we tested whether predatory bacteria could successfully kill clinical keratitis isolates of *Pseudomonas aeruginosa* and *Serratia marcescens* in vitro. The cytotoxic and inflammatory effect of predatory bacteria on a human corneal cell line was also measured. Predatory bacteria *Bdellovibrio bacteriovorus*, strains HD100 and 109J, and *Micavibrio aeruginosavorus* ARL-13 were used. These are non-pathogenic Gram-negative, obligatory parasites that feed on other Gram-negative bacteria. 10^8 CFU of fluoroquinolone-resistant and susceptible ocular isolates of *P. aeruginosa* and multidrug resistant strains of *S. marcescens* were mixed with 10^8 CFU of predatory bacteria. After 24 and 48 hours surviving bacteria were enumerated. Human corneal limbal epithelial cells (HCLE) were challenged with $\sim 10^9$ CFU of predatory bacteria or 2×10^7 CFU of *P. aeruginosa*; HCLE viability and cytokine concentrations were measured at 4 and 24 hours. *B. bacteriovorus* predatory bacteria reduced *S. marcescens* isolates ($n=9$) CFU by 2-4 logs. *B. bacteriovorus* and *M. aeruginosavorus* predatory bacteria reduced fluoroquinolone-resistant *P. aeruginosa* isolates ($n=9$) CFU by up to 5 logs, and fluoroquinolone-susceptible isolates up to 4-logs. Whereas predatory bacteria were lethal to ocular pathogens, little cytotoxic or inflammatory effect was observed when high doses of the predators were exposed to a human corneal cell line. This work highlights the potential use of predatory bacteria as biological based agent for eradicating antibiotic-resistant ocular infections.

Clinical Characteristics and Outcomes of Patients with Keratitis Admitted to an Israeli Departments of Ophthalmology

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Purpose: To describe the clinical characteristics and outcomes of patients with keratitis admitted to The Goldschleger Eye Institute, Sheba Medical Center, Tel Aviv University, Tel Hashomer, Israel.

Methods: A retrospective cross-sectional study was conducted, in which the medical records of patients with keratitis admitted in a 3-year period were reviewed.

Results: Keratitis was diagnosed in 276 patients admitted to our department (51% males and 48.9% females). The mean age was 39.29 ± 22.30 years. The hospital length of stay ranged from 1 to 65 days (mean 5.69 ± 5.508). Fortified antibiotics were still used at discharge in 72% of the cases. Overall visual acuity improved significantly from the time of admission to the 1st-week follow up visit showing a $p < 0.001$ on the Wilcoxon signed ranks test. Contact lens wearing was present in 36.1% of the patients, although there was no significant relation with severity of the presentation and visual outcome ($p < 0.05$). The degree of hypopyon and cells in the anterior chamber was significantly related to the hospital length of stay (r spearman = 0.31; $p < .001$ and r spearman = 0.21; $p < 0.01$, respectively) as well as to a worse visual outcome (r spearman = 0.32; $p < 0.01$ and r spearman = 0.18; $p = 0.01$, respectively). Of all patients, 2.3% required an urgent therapeutic penetrating keratoplasty, and 1% underwent evisceration. There was no enucleation.

Conclusion: Treating keratitis aggressively and assuring patient compliance is imperative for a good final visual outcome. Inpatient treatment may have a positive impact on this outcome.

Key Words: Cornea, Keratitis, Bacterium, Fungal, Prognosis

Adenoviral Keratoconjunctivitis: Diagnosis and Treatment

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Adenovirus (Ad) is the most common cause of infectious conjunctivitis; by persisting on surfaces for weeks, it can spread epidemically. Adenoviral conjunctivitis can cause severe ocular morbidity lasting up to 3 weeks. About 30-50% of patients with Ad develop persistent morbidity including subepithelial infiltrates. Clinical accuracy of differentiating viral from bacterial conjunctivitis is approximately 50% due to variable/overlapping signs and symptoms. The gold standard for diagnosis is cell culture or polymerase chain reaction (PCR), however, these tests are expensive and take time for results. A disposable, 10-minute immunoassay done in the office has a sensitivity of 90% and specificity of 96%. Since antibiotics are ineffective, testing will help avoid inappropriate use of antibiotics and allow rapid recommendation for isolating contagious patients. Currently no approved Ad specific antiviral treatment exists. Tissue culture efficacy testing of ganciclovir ophthalmic gel (approved for HSV) demonstrated antiviral activity against Ad-5; testing Ad conjunctivitis in a rabbit model demonstrated that ganciclovir did not alter clinical signs of conjunctivitis but did clear Ad virions about 1 week sooner than in control eyes. Further research is needed to understand the potential role of ganciclovir and other Ad ocular infection treatments.

Summary: Rapid in office diagnosis likely will help both patients and clinicians diagnose and determine treatment for Ad ocular infections. Treatment for viral conjunctivitis is at this time largely supportive although promising antiviral therapeutics are currently under investigation. Unnecessary antibiotics use in patients with viral conjunctivitis leads to increased ocular allergy, toxicity, and healthcare costs.

Ointment or Eye Drops for Prophylaxis in Corneal Erosions? Comparison of Chloramphenicol Eye Drops vs. Ointment in an Experimental Model

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Purpose: To compare effect of chloramphenicol eye drops or ointment, high concentration hyaluronic acid, or no treatment on re-epithelialization of corneal erosions in an experimental model.

Methods: Uniform 6mm corneal erosions, were created in 23 rabbit eyes. The rabbits were randomized to 4 treatment groups: 1. chloramphenicol eye drops, group 2. chloramphenicol ointment, 3. hyaluronic acid 2.3%; 4. untreated. Treatment was administered every 8 hours until re-epithelialization. Eyes were photographed every 8 hours with a cobalt blue-filtered light with fluorescein drops until re-epithelialization. The area of the erosion at each time-point was analyzed.

Results: There were no significant differences re-epithelialization of the corneal erosion among the 3 treatment groups ($p < 0.05$). The time was significantly shorter for the control untreated group ($p = 0.005$).

Conclusion: The use of chloramphenicol in the form of eye drops or ointment for prophylaxis in corneal erosions has similar effect on the healing speed of the erosion. Both forms of the antibiotic and high concentration hyaluronic acid had a slowing effect on the healing of the erosion when compared to no treatment. Therefore, the decision to treat erosions with eye drops or ointment can be based on the patient's comfort.

Microbiological, Chemical, and Mathematical Analysis of Alexidine-Polyethylene Interaction: Implications for the Fusarium Keratitis Epidemic of 2004-2006

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Background: Our previous studies indicated that alexidine permeates into the walls of heated ReNu plastic bottles, thereby diminishing its concentration within the solution.

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Methods: Using liquid chromatography-mass spectroscopy (LCMS), alexidine levels were measured in heated/unheated ReNu bottles stored for various time periods. These data were compared with data derived from Fourier transform infrared (FTIR) spectroscopy absorptions of methanol extract evaporate residues of formerly alexidine fluid-exposed bottle walls.

Results: FTIR studies showed that there was approximately 3.1 times more alexidine in the wall of the heated than in the room temperature-stored bottle. The LCMS study showed that there was approximately 3.0 times more alexidine in the walls of the heated bottles. Alexidine levels correlated closely with timed and dilution microbiological studies.

Conclusion: Alexidine levels correlated closely with previously performed microbiological and FTIR studies, strongly suggesting alexidine-plastic interaction as the pharmaceutical failure mechanism of the worldwide Fusarium keratitis event of 2004-2006.

The Comparison of Validated PCR to Culture Isolation for the Detection of Acanthamoeba from Ocular Samples

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Introduction: The diagnosis of acanthamoeba keratitis is commonly ascertained with a combination of clinical presentation, isolation in culture, observation on stained material, and confocal microscopy. Our institution has validated PCR to detect acanthamoeba DNA from ocular samples to complement testing.

Methods: The laboratory records of patients with a differential of acanthamoeba keratitis were reviewed (May 2012 to June 2013), without recording patient identifiers, for 1) acanthamoeba culture isolation and 2) acanthamoeba DNA detection by PCR. For acanthamoeba isolation, corneal samples were planted on non-nutrient agar (Noble Agar) overlaid with Enterobacter aerogenes and monitored for growth over 7 days. Validated PCR for acanthamoeba DNA was processed at the Division of Molecular Diagnostics, UPMC, Pittsburgh, PA.

Results: Culture isolation and PCR were processed on 77 patients. Of these, 65 (84%) were (culture-neg, PCR-neg); 7 (9%) were (culture-pos, PCR-pos); 2 (3%) were (culture-neg, PCR-pos); and, 3 (4%) were (culture-pos, PCR-neg). Culture and PCR were statistically equivalent for detecting acanthamoeba from corneal samples ($p=1.0$, McNemar's). Eleven (14%) of the (culture-neg, PCR-neg) corneal samples were positive for other pathogens (4 *Pseudomonas aeruginosa*, and one each of *MRSA*, *Klebsiella pneumoniae*, *Moraxella lacunata*, *Fusarium*, *Aspergillus*, *Candida albicans*, and HSV).

Conclusions: The present study indicates no real advantage of PCR over culture isolation for acanthamoeba detection. Our laboratory data suggests that although acanthamoeba is the primary suspect in specific cases of severe persistent keratitis, other pathogens such as bacteria, fungus, and virus must still be considered as part of the differential diagnosis. Our plan is to continue to use PCR as part of a complementary test for the support of acanthamoeba keratitis.

Development of a Novel Diagnostic Method and Treatment for Acanthamoeba Keratitis

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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/cm². Moreover MB-PDT had synergistic effects with polyhexamethylene biguanide. In future, PDT using photosensitizer could be useful treatment for AK.

Delayed Course of Acanthamoeba Keratitis

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Background: Acanthamoeba keratitis is a rare but potentially disastrous entity and until now by far not completely understood.

Patient and Methods: A 35-year-old male presented with corneal ulceration on the left eye with a history of treatment for many months. At the first visit in our Department we saw an elliptically shaped ulcerative stromal keratitis with circular corneal neovascularization and an organized hypopyon /hyphaema. The best-corrected visual acuity (BCVA) was light perception. The patient had used contact lenses for many years. Under the suspicion of herpetic keratitis due to a positive "dendrite" the patient had undergone antiviral therapy for 6 months in two different hospitals. Our PCR-based diagnosis was Acanthamoeba keratitis.

Results: We performed elliptical penetrating excimer laser keratoplasty à chaud (8.0x7.0 mm/8.1x7.1 mm) with simultaneous cryotherapy of the midperipheral cornea. The topical therapy was polyhexamethylene biguanide, propamidine isoethionate, neomycin and steroids. A repeat elliptical excimer laser keratoplasty (8.5x7.5 mm/8.6x7.6 mm) with simultaneous amniotic membrane patch and lateral tarsorrhaphy was performed 2 months later due to melting of the graft with positive Seidel test. After successful surgery of the mature cataract the BCVA was 20/25 with a clear corneal graft.

Conclusions: In a patient with positive contact lens history acanthamoeba keratitis should always be considered as differential diagnosis to herpes simplex virus keratitis in the early course of the disease. PCR and/or histological diagnosis and adequate medical triple therapy should be started early. The potential role of photodynamic therapy of the cornea as an adjunctive treatment modality as well as early results of the German Acanthamoeba Keratitis Registry will be discussed.

Acanthamoeba Infections Related to Contact Lenses

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Acanthamoeba keratitis (AK) is a rare and sight threatening corneal infection that is caused by the trophozoite stage of the ubiquitous Acanthamoeba organism. Due to its ability to encyst during periods of environmental adversity, they are able to withstand extreme conditions including high temperature, high salinity, and are chlorine resistance. These factors contribute to the prevalence of infection. Despite many attempts to characterize the pathogenicity of infection, risk factors for infection are not well understood and cases of AK persist.

In 2007, cultures from 138 patients that tested positive for AK resulted in the voluntary recall of a multipurpose solution suspected to be associated with this outbreak. In addition, a consensus method to test solution efficacy against Acanthamoeba has not been developed. Poor contact lens hygiene as well as a lack of premarket disinfection efficacy testing may contribute to infection.

FDA held a workshop in 2009 to discuss possible microbiological approaches for disinfection efficacy testing against Acanthamoeba. The strain type, life cycle stages, growth method, and encystment techniques were all important factors determined to be important in the development of a protocol to test for efficacy. The FDA subsequently engaged in research to further define factors to consider when developing an Acanthamoeba protocol.

Results demonstrated that at least two different strains in cyst form would be appropriate for disinfection efficacy testing. In addition, the organism presents more of a challenge when grown on agar seeded with bacteria and encysted by the starvation method. These data and data from the Centers for Disease Control describing AK investigations were presented at a general issues panel meeting held on May 13th, 2014.

The FDA plans to hold another workshop September 12, 2014 for all interested parties to discuss parameters in disinfection efficacy for Acanthamoeba in hopes of agreeing upon one universal protocol that will satisfy all concerns.

Suprachoroidal and Subconjunctival Implantable MIGS Procedures

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The CyPass Micro-Stent (Transcend Medical, Inc., Menlo Park, CA, USA) and iStent Supra (Glaukos Corporation, Laguna Hills, CA, USA) are devices used to treat glaucoma that are implanted via an ab interno approach into the supraciliary space. Both devices enhance uveoscleral outflow to lower IOP. The preliminary clinical results have been promising from both efficacy and safety standpoints among patients with mild to moderate open-angle glaucoma in the setting of cataract surgery. Enrollment of the CyPass pivotal US IDE trial was completed in March 2013. Enrollment for the pivotal US IDE trial of the iStent Supra is currently ongoing.

The InnFocus MicroShunt (InnFocus, Inc., Miami, FL, USA) and XEN Gel Stent (AqueSys, Inc., Aliso Viejo, CA, USA) are novel subconjunctival-space technologies developed to potentially replace trabeculectomy as the filtration surgery of choice for glaucoma surgeons. The InnFocus MicroShunt is made of an inert, biostable material utilized successfully in coronary artery stents called poly(styrene-block-isobutylene-block-styrene), or "SIBS." The XEN Gel Stent is a porcine collagen-derived, gelatin implant that is soft and flexible when hydrated. It is noninflammatory and designed to potentially mitigate the problem of implant migration. Early postoperative results are encouraging for both subconjunctival devices. The ongoing pivotal US IDE trial for the InnFocus MicroShunt compares both its safety and efficacy to trabeculectomy outcomes. The XEN Gel Stent is currently undergoing evaluation in an US FDA 510(k) protocol to assess its efficacy and safety in refractory glaucoma patients.

The Patient Population that May Benefit from Minimally Invasive Glaucoma Surgical (MIGS) Procedures

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While trabeculectomy and drainage device implantation remain the standard glaucoma surgical procedures for patients who fail to achieve adequate intraocular pressure (IOP) lowering with medications and laser trabeculoplasty, new options have emerged for those who are not refractory to medical therapy, but develop cataract requiring surgical intervention.

Several such MIGS procedures can be easily combined with phacoemulsification cataract surgery, an operation that has been demonstrated to provide sustained lowering of IOP in several prospective studies. The IOP lowering following cataract surgery makes it necessary to have a comparator group undergoing cataract surgery alone when assessing the IOP lowering achieved with combined cataract and MIGS procedures. As combined cataract surgery and trabeculectomy remains the commonly preferred option for patients with moderate to advanced glaucoma uncontrolled with IOP lowering medications who also have coexistent visually disabling cataract, combined cataract and MIGS surgery is generally considered only for patients who have mild to moderate glaucomatous disease, often with IOP well controlled on medical therapy, and may benefit from a reduced postoperative dependence on such medications following cataract surgery. Phacoemulsification cataract surgery alone remains an alternate option for these latter "low risk" patients.

The utility of MIGS procedures is measured by the expected greater IOP lowering seen relative to cataract surgery alone weighed against any incremental risks of such additional glaucoma surgery.

While MIGS procedures may, in the future, be used without adjunctive cataract surgery, efficacy supporting such stand alone use has not as yet been demonstrated in a completed well designed prospective study.

MIGS - Defining Safety with New Devices

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Minimally invasive glaucoma surgery (MIGS) has been proposed to achieve intraocular pressure (IOP) lowering with less morbidity and greater safety than the current standard procedure, trabeculectomy.

Three adverse outcomes that define potential safety issues in glaucoma surgical procedures will be discussed: high postoperative IOP, hypotony (very low postoperative IOP), and visual field loss.

Adrenergic Receptors and Diabetic Retinopathy

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Guanine nucleotide triphosphate-binding protein (G protein)-coupled receptors (GPCRs) form a large superfamily of membrane proteins that transduce extracellular stimuli into intracellular second messengers through activation of G proteins, including the subtypes Gs, Gi, and Gq. Diabetes is known to induce oxidative stress in multiple tissues including the retina.

We investigated the contribution of several GPCRs and their downstream signaling pathways to superoxide generation by retina and retinal cells. Focusing initially on ARs and 5-HT₂Rs, we found that pharmacologic manipulation of these receptors regulated superoxide generation by immortalized retinal photoreceptor cells exposed to elevated glucose. Moreover, pharmacologic inhibition of either the α 1-AR or downstream NADPH oxidase (both components of the Gq-regulated signaling pathway) reduced the diabetes-induced increase in retinal oxidative stress, expression of pro-inflammatory proteins, and the resulting degeneration of retinal capillaries.

These results identify α -adrenergic receptors and their downstream pathways as novel therapeutic targets to reduce retinal superoxide generation and the histopathology of diabetic retinopathy.

Stem Cell Therapy for Diabetic Retinopathy

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Diabetic retinopathy (DR) is a vision-threatening diabetic complication primarily affecting retinal vasculature, although some manifestations are related to neuropathy. DR appears to be a multifactorial disease with an epigenetic component. Because of this, monotherapies for proliferative DR and macular edema including gene therapy have not been efficient enough. It becomes clear that only combination therapy could provide the cure. Because DR entails pericyte dropout and ensuing capillary closure with endothelial cell death, endothelial progenitor cell (EPC) replacement therapies recently emerged. Grant's group showed that diabetic capillary damage could be repaired by circulating bone marrow-derived CD34⁺ EPCs. These cells are dysfunctional in diabetics, largely due to oxidative stress. Fortunately, the function of diabetic EPCs can be restored by increasing eNOS expression, or by decreasing NADPH oxidase-dependent ROS production, or by TGF- β 1 inhibition. Adipose stromal stem cells have been tried in streptozotocin-induced diabetic nude rats. Intravitreal injections of these cells improved "b" wave amplitude, decreased retinal vascular leakage and numbers of apoptotic cells, and decreased proinflammatory gene expression. Induced pluripotent stem cells (iPSC) from CD34⁺ cord blood cells directed to vascular lineage could home and incorporate into acellular capillaries in the diabetic ischemia-reperfusion model. Studies in progress are using iPSC technology to normalize diabetic corneal stem cells to counteract poor wound healing in diabetic keratopathy. These approaches could provide safe and efficient autologous stem/progenitor cell therapies able to counteract the vascular damage in DR. Similar strategies could potentially be used to combat diabetic neuropathy in the eye as well.

Targeting the Arginase/Polyamine Pathway as a Novel Therapy

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Diabetic retinopathy (DR) is associated with early neurovascular damage. However, conventional therapies target clinically significant macula edema and neovascularization, which occur later. Intra-ocular injections of anti-VEGF show promise in reducing retinal edema, but the effects are usually transient and repeated injections increase risk of intraocular infection. Laser photocoagulation can control pathological neovascularization, but may impair vision and in some patients the retinopathy continues to progress. Moreover, neither treatment targets early stage disease or promotes repair. We are investigating the urea hydrolase enzyme arginase as a novel therapeutic target. Arginase metabolizes L-arginine to form polyamines and proline. Excessive arginase activity reduces the L-arginine supply for nitric oxide synthase (NOS), uncoupling NOS and causing it to produce superoxide and less NO. NO and superoxide react, forming the toxic oxidant peroxynitrite. Polyamine oxidation further increases oxidative stress, whereas proline increases collagen production, contributing to fibrosis. Our studies indicate that neurovascular injury during retinopathy are associated with increased arginase expression/activity, decreased NO, enhanced polyamine oxidation and elevated oxidative stress. Furthermore, we have found that the cytosolic isoform arginase 1 is involved in vascular endothelial dysfunction whereas the mitochondrial isoform arginase 2 is involved in neurovascular injury. Thus, we suggest that activation of the arginase pathway causes neurovascular dysfunction by altering NOS function, inducing polyamine oxidation, thereby reducing NO and increasing oxidative stress, all of which contribute to the retinopathic process. Targeting this pathway may offer a new therapy for DR.

Protective Effect of PPAR Alpha in Diabetic Retinopathy

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Peroxisome proliferator-activated receptor- α (PPAR α) is a nuclear hormone receptor that functions as a transcription factor regulating the expression of a number of genes involving lipid metabolism. Two independent clinical studies have reported that fenofibrate, a PPAR α agonist, has robust therapeutic effects on microvascular complications of diabetes including diabetic retinopathy (DR) in type 2 diabetic patients. Previously, we have shown that fenofibrate ameliorated DR through a PPAR α -dependent mechanism in type 1 diabetes models, and the drug target is present in the retina. Recently, we have studied the expression and function of PPAR α in the retina. Immunostaining demonstrated that PPAR α is expressed in multiple cell types in the retina. In both type 1 and type 2 diabetes models, expression of PPAR α was significantly down-regulated in the retina. Furthermore, high glucose medium was sufficient to down-regulate PPAR α expression in cultured retinal cells. To further investigate the role of PPAR α in DR, diabetes was induced in PPAR α knockout (KO) mice and wild-type (WT) mice. Diabetic PPAR α KO mice developed more severe DR, as shown by analyses of retinal vascular leakage, leukostasis, pericyte loss, capillary degeneration, retinal neuron apoptosis and over-expression of inflammatory factors, compared with diabetic WT mice. In addition, activation of PPAR α using fenofibrate and over-expression of PPAR α both significantly alleviated diabetes-induced retinal vascular leakage and retinal inflammation in the retina of diabetic rats. Furthermore, PPAR α over-expression inhibited endothelial cell migration and proliferation and prevented retinal neuron apoptosis under hypoxia. These findings revealed that PPAR α is a protective factor in the retina and represents a promising drug target for DR treatment.

Transport and Microglial Uptake of Dendrimers in Normal and Ischemia Reperfusion Retina

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Microglial activation occurs in many diseases of the retina including viral infection, diabetes, and retinal degeneration. It was shown previously that hydroxyl-terminated polyamidoamine (PAMAM) dendrimers are taken up and retained in microglia during retinal degeneration. The purpose of this study was to develop a nanoparticle formulation that targets activated retinal microglia and can be delivered safely intravenously as well as intravitreally. The dendrimers were conjugated to Cy5 (D-Cy5) and were evaluated by intravenous (femoral vein) or intravitreal injection in normal BALB/c mice and in a murine model of ischemia/reperfusion (I/R). Uptake of the dendrimer by microglia was determined with immunofluorescence using rabbit Iba-1 antibody with Cy3-goat anti-rabbit secondary antibody (microglia) and GSA lectin-FITC (blood vessels and microglia). Clearance of the D-Cy5 from the normal eyes appeared almost complete by 24 hours after injection. In eyes with activated microglia after I/R injury, the D-Cy5 appeared to be retained by microglia (IBA+) up to 21 days after intravenous administration. The nontoxic PAMAM dendrimers appeared to be an excellent drug delivery system to activated microglia. This approach may yield an intravenous dendrimer-based therapy to decrease inflammation in diseases associated with retinal microglia activation like age-related macular degeneration.

Outflow Drugs: What Does the Future Hold?

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Background: The glaucomas are the leading global cause of irreversible blindness. Glaucoma prevalence is increasing as the population ages. Small molecule topical eye drop therapy is the most common first treatment option for elevated intraocular pressure (IOP).

Methods: Organ culture, cell culture and in vivo studies, including clinical trials, were performed. Physiology (e.g. IOP, aqueous humor formation and outflow determinations), morphology (e.g., light and electron microscopy) and molecular biology techniques (e.g. fluorescent labeling,) were used to study the effects of small molecules and gene transfer on human, non-human primate, and pig tissues and eyes.

Results: The newest class of compounds in glaucoma therapeutics (e.g. myosin light-chain kinase inhibitors, rho kinase inhibitors, caldesmon and derivatives of marine macrolides (e.g. latrunculins)) aims to increase conventional or trabecular outflow by directly targeting the extracellular matrix (ECM) and the actin cytoskeleton of the trabecular meshwork (TM). Several of these compounds are in clinical trials. New iterations of fixed dose combination drugs, with multiple mechanisms, targeting the TM and CM are in development. Other compounds in the glaucoma therapeutics pipeline include prostanoid EP2 and EP4, nitric oxide, adenosine (A1, A2A, A3) and Wnt signaling agonists. Gene transfer techniques can produce robust and long-term (2 years) expression of reporter genes in the primate outflow pathway in vivo, with low immunogenicity.

Conclusions/Discussion: Most glaucoma patients will be prescribed multiple topical drops of varying classes of compounds to control their disease. There continues to be a need for novel therapeutics and long-term therapeutic strategies such as gene therapy.

Imaging of the Lamina Cribosa

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Background: The lamina cribrosa (LC) has been widely implicated as a key structure in the pathogenesis of glaucoma. Using optical coherence tomography (OCT) we characterized the 3-dimensional microarchitecture of healthy LC in-vivo and assessed the glaucomatous changes in that region.

Methods: Healthy and glaucoma subjects were scanned with 1) a multimodal retinal imaging system (Physical Sciences Inc, Andover, MA) which includes adaptive optics spectral-domain OCT (AO-SDOCT) and AO confocal scanning laser ophthalmoscopy (AO-CSLO) or 2) a swept-source (SS-) OCT. Dense raster scans were acquired from the optic nerve head region and the microarchitecture of the LC was measured using a semi-automated segmentation analysis.

Results: Eighteen healthy subjects were scanned with the AO-SDOCT. Peripheral LC had smaller pore diameter and beam thickness compared to central lamina, leading to higher pore density and lower connective tissue volume fraction in the periphery. Regional differences were also noted between quadrants and within the lamina depth. 19 healthy and 49 glaucomatous eyes were scanned with SS-OCT, showing statistically significant higher beam thickness to pore diameter ratio and pore diameter standard deviation in glaucomatous eyes. Several LC microarchitecture parameters demonstrated significant relationships with visual field mean deviation.

Discussion: the 3-dimensional microarchitecture configuration of the LC needs to be taken into consideration when evaluating its involvement in glaucoma.

Pressure Lowering Agents: What is on the Horizon?

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Purpose: Glaucoma is a disease of the optic nerve in which the only clinically modifiable risk factor is intra ocular pressure, regardless of the magnitude. Despite the current medical and surgical interventions, epidemiological studies indicate that progression of the disease for various reasons continues in a large segment of the treated population. The purpose of this presentation is to look at treatments in development to meet the unmet needs of the current treatment paradigms.

This presentation will present strategies of selected treatments currently in development, technologies that are meant to fill the current void, discuss the challenges inherent in these development programs and also look at what is beyond the lowering of IOP.

Imaging of the Retina in OCT: Is it Reliable?

Vas Sadda

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Automated retinal thickness measurements for optical coherence tomography (OCT) devices have dramatically impacted the conduct of clinical trials and clinical practice. These measures are now routinely used as entry criteria and secondary endpoints in clinical trials, and are important for assessing treatment response as well as for determining the need for therapy. Despite their ubiquitous use there are many factors which may affect the reliability of these measurements.

These factors include errors in automated segmentation, motion artifact, angle of incidence effects, OCT signal strength, scan density, regional variation, inter-individual variation, and diurnal changes. A detailed understanding of these factors including their frequency, manifestations and ease of detection, and magnitude of effect, are crucial to understand in order to confidently interpret and utilize OCT-based measurements.

Imaging of the Choroid: is it Useful?

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The choroid plays a vital role in the health of the outer retina. Measurements of choroid using optical coherence tomography show altered thickness in aging and macular disease. The choroidal thickness so far has been measured manually perpendicularly from the outer edge of the hyperreflective retinal pigment epithelium (RPE) to the inner sclera (choroid-sclera junction) at 500 microns interval from the fovea using the SD-OCT software. Subfoveal choroidal thickness was reported in normal to range from 191 ± 74.2 to 354 ± 111 microns depending on the instrument used.

Myopia, Retinitis pigmentosa and a number of inherited disorders present a thin choroid. In contrast, increased choroidal thickness has been demonstrated in patients with acute CSR (range, 439–573 μm), even in both eyes in cases with unilateral CSCR; Choroidal thickness may assist in the differentiation of CSR from other causes of serous retinal detachment;

Polypoidal choroidal vasculopathy (PVC) eyes have a thicker subfoveal choroid ($293 \pm 72.3 \mu\text{m}$).

There are many conflicting reports regarding AMD. However, most studies report a thinner choroid than that of normal controls and more importantly even in exudative AMD.

Choroidal thickness measurement could help differentiate the challenging cases. The most frequent challenge is the diagnosis between PVC, or CSR or AOFVD complicated with choroidal neovascularization and exudative AMD

Imaging of the Retinal Vessels: With which Means?

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Background: Imaging of the retinal vessels attracted almost no attention in the era of time-domain OCT. Even with wide use of spectral-domain OCT (SD-OCT), not enough information is available on images of retinal vessels. The purpose of this presentation is to show how much clinically relevant information can be obtained on retinal vessels by SD-OCT.

Methods: SD-OCT images of retinal vessels and arteriovenous (AV) crossing in normal subjects and those from branch retinal vein occlusion (BRVO) were analyzed. Also, age- and hypertension-dependent changes in retinal vessel diameter and wall thickness were analyzed.

Results: In normal retinal vessels, an hour-glass shaped images to show blood flow were obtained. In non-perfused vessels, this hour-glass pattern was lost. In AV crossing with arterial overcrossing, retinal veins run as deep as near the retinal pigment epithelium. Even in cases of BRVO, the lumens of the veins were preserved contrary to the previous belief. Retinal vessel wall thickness and caliber can be measured by using SD-OCT and age- and hypertension-dependent changes were observed.

Conclusions: SD-OCT is useful to know retinal vessel changes in many retinal vascular disorders. Future studies may show usefulness of retinal vessel imaging as a parameter to represent systemic microangiopathy.

SD-OCT of the Nerve Fiber Layer – OCT for Non-Ophthalmologists

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Optical coherence tomography (OCT) is an emerging imaging technology with applications in biology, medicine, and the investigation of many materials. Attractive features include high cellular-level resolution, real-time acquisition rates, and spectroscopic feature extraction in a compact noninvasive instrument. OCT can perform "optical biopsies" of tissue, producing images approaching the resolution of histology without having to resect and histologically process tissue specimens for characterization and diagnosis. Ophthalmology was the first clinical application for OCT, and subsequently, OCT has become well established in our specialty. More recently OCT of the nerve fiber layer and ganglion cell layer became a valuable tool for neurologists. It may serve as both, a technique for the early detection of disorders and as a technique for non-invasive follow-up of treatments. In this presentation the advantages of the OCT-technology for other specialties such as neurology will be discussed in detail.

Shedding Light on Fundus Autofluorescence and RPE Lipofuscin

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Fundus autofluorescence originates from RPE lipofuscin, a mixture of fluorophores with spectral features that reflect the bisretinoid constituents that have been characterized as lipofuscin fluorophores. Using a quantitative method that employs an internal fluorescent reference mounted in the Spectralis HRA+OCT (Heidelberg Engineering), we have detected the expected increase in fundus autofluorescence in ABCA4-related retinal disease but not in Best vitelliform macular dystrophy. RPE bisretinoid lipofuscin form in photoreceptor cells due to reactions of vitamin A aldehyde and are deposited secondarily in RPE as components of phagocytosed outer segment. By way of understanding the adverse effects of these bisretinoid compounds we have shown that they are photo-sensitive chromophores that generate reactive forms of oxygen; they also undergo photooxidation and photodegradation.

The photo-cleavage products of A2E consists of a complex mixture of aldehyde-bearing fragments that includes the small dicarbonyls methylglyoxal and glyoxal [Wu, 2010 #1582] that are responsible for damaging modifications of proteins – advanced glycation end-products (AGEs). We have also shown that lutein and zeaxanthin can protect against A2-PE/A2E photooxidation without appreciable consumption of the carotenoid by chemical reaction.

Circulating Omega-3 Fatty Acids and Neovascular Age-Related Macular Degeneration

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Purpose: To assess the associations of serum, red-blood cell membranes (RBCM) and dietary long-chain n-3 polyunsaturated fatty acids (LC-PUFAs) with neovascular age-related macular degeneration (AMD).

Methods: We included 290 patients of the Nutritional AMD Treatment 2 Study (NAT2) with neovascular AMD in one eye and early AMD lesions in the other eye and 144 normal vision controls without AMD. Dietary intake of seafood was estimated a food frequency questionnaire. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) composition in serum and RBCM were determined by gas chromatography from 12h-fasting blood samples and was expressed as percentages of total fatty acids profile. Logistic regressions estimated associations of neovascular AMD with dietary intake of seafood and circulating n-3 LC-PUFAs.

Results: Dietary oily fish and seafood intake were significantly lower in AMD patients than in controls.

After adjustment for all potential confounders (age, gender, CFH Y402H, ARMS2 A69S, and ApoE4 polymorphisms, plasma triglycerides, hypertension, hypercholesterolemia and family history of AMD), serum EPA was significantly associated with a lower risk for neovascular AMD (OR=0.41 (0.22-0.77); p=0.005). Analysis of RBCM revealed that EPA and EPA+DHA were significantly associated with a lower risk for neovascular AMD (OR=0.25 (0.13-0.47); p<0.0001 and OR=0.52 (0.29-0.94); p=0.03, respectively).

Conclusions: RBCM EPA and EPA+DHA, as long term biomarkers of n-3 dietary PUFA status, were strongly associated with neovascular AMD and may represent an objective marker identifying subjects at high risk for neovascular AMD, whom may most benefit from nutritional interventions.

Protective Effect of Glutathione S-Transferase Pi Isoform (GSTP1) Expression in RPE and in Young and Aging Retina

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Background: GSTP1, a zeaxanthin-binding protein in human macula, is an intracellular detoxification enzyme that scavenges reactive electrophiles. We demonstrated that GSTP1 is decreased in human AMD retina compared to normal controls. We showed that GSTP1 levels parallel survival of human retinal pigment epithelial (RPE) cells exposed to UV light, and GSTP1 over-expression protects them against light damage. Here we determined the developmental time course of GSTP1 expression in young and aging murine retina and in response to light challenge.

Methods: BALB/c mice (age post-natal day 20, 1 month, and 2 months) and BALB/cBy mice (age 2 months, 12 months, and 24 months) were exposed to 1000 lux white fluorescent light for 24 hours and compared to age-matched controls under normal light condition. Retinal GSTP1 levels in these mice were analyzed by Western blot and immunohistochemistry.

Results: GSTP1 levels in young murine retina increased from post-natal day 20, 1 month, and 2 months of age and also increased upon light exposure. In contrast, GSTP1 decreased with increasing age at age 2 months, 12 months, and 24 months. With light challenge, GSTP1 expression initially increased at age 2 months then decreased and plateaued at age 12 months and 24 months compared to controls.

Conclusions/Discussion: GSTP1 in murine retina increases with developmental maturity and decreases with aging. Light challenge induces GSTP1 at younger age but declines with aging. GSTP1 induction may be a protective response to light-induced oxidative damage, and this protective response may decline with aging.

CFH and ARMS2 Genotypes and Oral Supplementation with Docosahexaenoic Acid for Neovascular Age-Related Macular Degeneration

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Purpose: To investigate whether genotype could influence response DHA-supplementation in the occurrence of choroidal new vessels (CNV). The NAT2 study was a randomized, placebo-controlled, double-blind, parallel, comparative study.

Methods: 250 patients aged 55 to 85 years with early lesions of age-related maculopathy and visual acuity better than 0.4 LogMAR units in the study eye and neovascular age-related macular degeneration (AMD) in the fellow-eye. Patients were randomly assigned to receive either 840mg/day DHA and 270mg/day EPA from fish oil capsules or the placebo (olive oil capsules) for 3 years.

Results: Patients bearing CT or CC (risk alleles) genotype for CFH gene had higher risk to develop CNV in the study eye but this association was not significant (HR=0.97 (0.54-1.76) and 1.29 (0.69-2.40) respectively). Concerning ARMS2 polymorphism, patients bearing GT or TT (risk alleles) genotype had higher risk to develop CNV in the study eye, but these associations did not reach statistical significance (HR=1.68 (0.91-3.12); 1.78 (0.90-3.52), respectively). An interaction was observed between CFH genotype and supplementation with DHA (CC; p=0.02). We showed a protective effect of DHA supplementation only among patients with the CFH homozygous non-risk (TT) genotype. In this group occurrence of CNV was 38.2% in placebo group versus 16.7% in DHA group (p=0.008).

Conclusions: These results may imply that a genetic predisposition to AMD conferred by the CFH genotype limits the benefits provided by DHA supplementation and could partly explain the limited benefit of DHA supplementation for occurrence of CNV in NAT2 or ARED52 studies.

Omega-3 Fatty Acids and Fat Intake, Genetic Susceptibility and Progression to Geographic Atrophy

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Purpose: To investigate associations between dietary omega-3 fatty acids and fat intake, genes related to age-related macular degeneration (AMD) and progression to geographic atrophy (GA).

Methods: Among 2,531 individuals, eyes without advanced AMD were evaluated for progression to GA. Data on smoking, body mass index and diet were collected at baseline. Omega-3 fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]), omega-6 fatty acids, monounsaturated, saturated, polyunsaturated, and total fat were adjusted for sex and calories and divided into quintiles (Q). Eight single nucleotide polymorphisms in 7 genes (CFH, ARMS2/HTRA1, CFB, C2, C3, CFI, and LIPC) were assessed. Cox proportional hazards models were used to test for associations between incident GA and lipids and interaction between fat intake and genotypes.

Results: Increased intake of DHA was significantly associated with reduced risk of progression to GA in models with behavioral factors (model A) plus genetic variants (model B) (P trend = 0.01 and 0.03, respectively). Total omega-3 long chain polyunsaturated (DHA + EPA) fatty acid intake was significantly associated with reduced risk of progression in model B (P trend = 0.02). Monounsaturated fat was associated with increased risk in model A (P trend = 0.05). DHA intake was significantly associated with reduced risk of GA among those with the ARMS2/HTRA1 homozygous risk genotype (hazard ratio [HR] Q5 vs Q1, 0.4; P = 0.002; P for interaction between gene and fat intake = 0.05).

Conclusions/Discussion: Increased intake of omega-3 fatty acids is associated with reduced risk of GA and may modify genetic susceptibility for progression to GA.

Steroids for RVO

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It has been demonstrated that inflammation plays an important role in the development of macular edema secondary to vein occlusion. Thanks to the GENEVA trial, a big phase III study, it was proven the efficacy and safety of the sustained release dexamethasone intravitreal implant (Ozurdex®) in the treatment of macular edema secondary to vein occlusion but the results in terms of visual acuity were not as good as they could be in real practice and steroids appeared to be not as good therapy as anti-VEGF and it is, among other things, because of the long mean duration of the edema of the patients included. We analyze our four years experience and good results with the dexamethasone implant in patients with macular edema secondary to vein occlusion.

Aflibercept for Retinal Vein Occlusion

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Background: Retinal vein occlusions remain the leading cause of vision loss second only to diabetic retinopathy in patients with retinal vascular diseases. In addition to treating systemic disease, local therapy remains a mainstay for managing these patients. Laser treatment has demonstrated a statistically significant benefit over the natural course of the disease, particularly in patients with branch retinal vein occlusion, but a more limited efficacy for central retinal vein occlusion. Alternative treatment strategies have evolved including anti-VEGF therapies. Aflibercept is a soluble decoy receptor, engineered by fusing VEGF receptor (VEGFR) 1 and VEGFR2 to the Fc portion of human immunoglobulin G-1 (IgG-1), allowing it to bind all isoforms of VEGF-A, VEGF-B, and placental growth factor (PlGF). The aim of the present study is to summarize the evidence available regarding the outcomes of intravitreal aflibercept in patients with macular edema due to CRVO.

Methods: The safety and efficacy of intravitreal aflibercept in the treatment of macular edema following CRVO were assessed in two randomized, multicenter, double-masked, sham-controlled studies: COPERNICUS and GALILEO. A total of 358 patients were enrolled in the two studies. Patients were randomly assigned in a 3:2 ratio to either 2 mg aflibercept or sham injections. After six monthly injections, patients continued to receive aflibercept treatment during weeks 24 to 52 only if they met pre-specified retreatment criteria. Patients in the placebo group of the COPERNICUS study were switched to pro-re-nata aflibercept at week 24, whereas placebo-treated patients of the GALILEO study were switched to pro-re-nata aflibercept at week 52.

Results: In the COPERNICUS study, at week 100, 49% of patients receiving aflibercept 2 mg gained at least 15 letters of BCVA from baseline. Visual acuity improved, on average, by 13 letters. Central retinal thickness decreased on average by 390 µm. Mean number of injections during the 100 week follow-up period was 12.

In the GALILEO study, at week 52, 60% of patients receiving aflibercept 2 mg gained at least 15 letters of BCVA from baseline. Visual acuity improved, on average, by 16.9 letters. At week 76 mean visual acuity improvement was +13.7 letters. Central retinal thickness decreased on average by 389 µm. Mean number of injections during the 76 week follow-up period was 9.8.

A randomized, controlled prospective study is currently enrolling to test aflibercept in patients with BRVO.

Conclusions: Aflibercept shows benefits for the treatment of visual impairment caused by macular edema following CRVO.

Laser for RVO

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Purpose: To evaluate, in intravitreal therapy era, the therapeutic role played by laser photocoagulation in management of both BRVO and CRVO as monotherapy and/or in association with intravitreal therapy.

Methods: An analysis of the literature was carried out, to find if laser photocoagulation can still be considered an effective treatment for RVO.

Results: MGL applied to discrete areas of leakage can be useful as monotherapy in eyes with macular edema secondary to BRVO as shown in the Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) study. MGL was shown to result in similar visual acuity gains when compared with steroid monotherapy, but with fewer complications. BRVO combination therapy may have the added advantage of limiting toxicity and/or lessening the treatment burden as smaller doses or less frequent treatments, with similar results. Combination therapy may also be used to increase efficacy in patients who are not adequately responsive to monotherapy. In either situation, the benefit of combined treatments is due to the synergistic effects achieved. Studies of anti-VEGF/MGL combination therapy published to date have shown mixed results. In some, the combination clearly outperformed standalone anti-VEGF treatment in achieving better anatomical and visual outcomes. In others, impressive anatomical improvements were not matched by gains in vision. In published studies in which injection frequency was tracked, however, combination laser/anti-VEGF treatment resulted in a reduced need for anti-VEGF injections.

Conclusion: MGL did not improve patients vision in the CVOS, although it did reduce macular leakage. Makes sense to re-evaluate the potential utility of MGL applied in combination with intravitreal agents for CRVO. Unfortunately, only a small number of studies exploring RVO combination therapies have been published to date. Laser in addition to intravitreal anti-VEGF therapy is an often-used combination in clinical practice.

An Overview of Delivery Technologies for the Long-term Delivery of Macromolecules to the Back of the Eye

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The introduction of clinically and commercially successful macromolecular drug therapies for treating posterior eye diseases has spurred the discovery and development of long acting delivery technologies for chronic administration. The objectives for technologies delivering protein containing formulations to the back of the eye are to decrease the frequency of the requisite intravitreal injections as well as to reduce the treatment burden of a patient population that is generally advanced in age.

Such delivery technologies must overcome challenges unique to posterior eye administration in order to be successful.

An overview of the various general classes of ocular delivery technologies classes designed to provide multiple month delivery to the back of the eye will be presented, along with an experientially-based approach to evaluating these exciting and promising technologies.

In Vitro Testing of Drug Transport in the Eye

Randy Mrsny, Hanne Kinnunen
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Therapies for several previously untreatable ocular diseases have now been demonstrated to incite benefit in patients. The clinical benefit of these therapies where biopharmaceutical agents have been injected into the vitreous humor of the eye has validated specific targets in the eye and led to a plethora of new approaches involving novel medicines and sustained delivery technologies to reduce the frequency of these injections into the vitreous humor. One critical aspect involved in the successful development of these new medicines and technologies involves their initial interactions with the mostly a-cellular environment of the vitreous humor of the human eye. We have established a novel in vitro system to model dynamic changes experience by a medicine or sustained delivery material as the local environment transitions from that used to stabilize the injected material to that of the conditions of the human vitreous humor. A series of studies demonstrating the nature and function of this in vitro model to assess early events associated with injections into an artificial vitreous humor will be presented.

Non-Viral Gene Therapy: Where are We?

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Conflicting interests for this talk: Founder of Eyevensys, SA and inventor of patents used in this presentation.

Background: Growing interest in gene therapy is focusing on the use of various viral vectors (AAV and lentivirus) for the treatment of ocular diseases, including non-monogenic retinal diseases requiring sustained release of therapeutic proteins, like AMD or diabetic retinopathy, with encouraging results.

Purpose: To propose an alternative strategy to viral vector gene delivery for the sustained production of secreted therapeutic proteins for the treatment of ocular disease.

Material and Methods: Various plasmid backbone encoding soluble receptors for VEGF and TNF- α were electroporated into ciliary muscle cells of rats, rabbits, monkey and human eyes. Efficacy was evaluated on various rat models of intraocular inflammation and choroidal neovascularization.

Using optimized plasmid and device design, we designed a simplified method for procedure in patients.

Results: Sustained release of therapeutic levels of various proteins was achieved leading to efficient results in various animal models.

Conclusion: Non-viral vector gene delivery might be option for a scalable and more controlled release of therapeutic proteins for the treatment of non-monogenic retinal diseases.

Prodrugs of Cyclosporine: Pros and Cons

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CyA is a highly lipophilic drug challenging to be formulated as an eye drop. A CyA-prodrug panel was generated and a selection was made according to solubility, ocular irritation, bioconversion and ocular distribution (Lallemand et al. 2005). The chemical structures of CyA and the selected prodrug are illustrated in Fig 1. Once in contact with the eye, the ester bound at the end of the prodrug chain is cleaved by esterases, generating a cascade of chemical intermediates that rapidly lead to the release of CyA (see Fig 1).

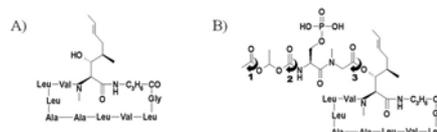


Fig. 1: Chemical structures of A) cyclosporine A and B) the prodrug. Numbered arrows illustrate the bioconversion cascade.

The pros of the presented approach are linked to the use of the freely soluble prodrug instead of the practically insoluble CyA, making possible the formulation of highly concentrated, aqueous and transparent CyA-based eye drops. Additionally, the prodrug displays a number of interesting features:

- i) Excellent ocular tolerance,
- ii) Rapid esterase-based bioconversion into CyA after contact with tears and ocular tissues,
- iii) Ability to accumulate in ocular tissues and iv) higher permeation capacity and lower risk of systemic complications compared to conventional CyA formulations (Rodriguez-Aller et al., 2012 and 2013).

The cons of such a strategy are related to two main facts. First, a prodrug is considered as a new chemical entity (NCE) by regulatory authorities and requires a comprehensive characterization, including complete safety profiling. Besides, the stability of the prodrug formulation requires additional investigations linked to its shelf-life and storage conditions.

Microparticulate Drug Delivery Systems for the Treatment of Chronic Ophthalmic Diseases

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Pathologies affecting the back of the eye are becoming more prevalent due to the increase in society longevity. A successful therapy of these diseases requires effective concentrations of the drug that must be maintained during a long period of time. Although the periocular route is attracting more attention, intravitreal injections are still the most employed. However, despite the advantages of the administration of the drug close to the target site, intravitreal injections are associated with non-desired effects. The administration of drug-loaded biodegradable microspheres offers an excellent alternative to multiple administrations, since they are able to deliver the active substance in a controlled fashion. Moreover, contrary to larger devices, injection of microspheres is performed without the need of surgical procedures.

Additionally, as most of retinal diseases are multifactorial, microspheres especially promising because they can include more than one therapeutic molecule. Personalized therapies can be easily achieved by adjusting the amount of microspheres to be administered according to the patient's needs. In contrast to devices made from non-biodegradable polymers, PLA and PLGA microspheres disappear from the site of injection after releasing the drug and are well tolerated after periocular and intravitreal administration in animals and humans. Furthermore, under the technological point of view, the properties of microspheres can be improved with additives. Preliminary studies have demonstrated that low amounts of therapeutic molecules released from biodegradable microspheres resulted effective for the treatment of chronic diseases affecting the back of the eye.

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Recent Advances in Gene Therapy

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Ocular diseases are promising candidates for gene therapy thanks to the identification of a growing number of genes causing visual impairment as well as to the particularity of the eye as an accessible organ easy to monitor. The existence of many animal models for inherited ocular diseases also accelerated the application of gene transfer into the eye. The main illustration of this phenomenon is the clinical trials for RPE65-affected patients that are proposed now using AAV vectors. After evidence of the absence of adverse effects following AAV-RPE65 injection in the subretinal space of patients, younger affected patients were treated to determine if such approach can improve vision.

The trials occurring in different clinical centers all showed an amelioration of visual functions. However, several problems still need to be solved. In certain patients, a loss of thickness in the foveal area suggests either that the surgical procedure may be deleterious for the patients or that the level of the chromophore is insufficient to support cone survival. In general, the studies of Jacobson et al. revealed that the degeneration is still progressing. Another important observation showing discrepancy with the preclinical studies of RPE65 deficiency in dogs is the absence of detectable ERG after the gene transfer probably indicating a very low level or availability of the chromophore. Regarding all the clinical trials, no dose effects were observed. The possible reasons of these hurdles will be discussed as well as an alternative approach using lentiviral vectors.

Long Acting Delivery of Antibody Therapeutics to the Back of the Eye

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Anti-VEGF therapies have proven effective for treatment of wet age-related macular degeneration (AMD).

Due to a relatively short half-life of antibody therapeutics in the eye, maximal clinical benefit involves frequent intravitreal injection. Pharmacokinetic studies suggest that diffusion and molecular charge contribute to the vitreal clearance of antibodies. Sustained release formulations and implanted devices are being explored for long-acting delivery of antibodies to the eye. Considerations for molecule selection and formulation to facilitate these strategies will be discussed.

Nanoparticle Delivery for Ocular Disease

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Nanotechnology involves the manipulation of matter at the atomic and molecular scale. This rapidly growing area has significantly impacted various fields, including medicine. It has enabled enhanced medical imaging, more sensitive diagnostics, targeted drug delivery, non-viral gene delivery and tissue regeneration.

Nanotechnology has made its way into pharmaceuticals to significantly improve the delivery and efficacy of drugs in a number of therapeutic areas, with several nanoparticle-based products currently on the market. In recent years there has been increasing evidence that nanotechnology can help overcome many of the ocular delivery barriers, allowing enhanced penetration and duration of delivery to various ocular tissues, including the back of the eye, and delivery of genes to ocular tissues without the need for viral vectors. A number of examples of enhanced drug delivery via nanoparticles will be presented as well as a review of some of the companies now working to apply nanotechnology to the better treatment of ocular disease.

New Concept to Treat Herpes Simplex Keratitis and Uveitis: Iontophoretic Delivery of Water-soluble, Biolabile Aciclovir Prodrugs into Ocular Tissue

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Background: Poor delivery of aciclovir (ACV) limits efficacy in the treatment of ocular HSV infections. Biolabile charged amino acid ester prodrugs of ACV (ACV-X, where X=Gly, Trp, Arg) with good aqueous solubility might increase local ACV bioavailability since they should be superior candidates for delivery by ocular iontophoresis.

Methods: A series of ACV prodrugs were synthesized, characterized and their stability investigated. Transport studies were performed using Franz cells. ACV-X formulations, Zovirax® (3% ACV) or saturated ACV solution (2 mg/ml) were loaded into the donor compartment in the presence or absence of current. Permeation of ACV/ACV-X and deposition in porcine ocular tissue were quantified by UHPLC-MS/MS.

Results: Transcorneal permeation of ACV after application of 50 mg Zovirax® or 0.4 ml saturated solution for 60 min was below the LOQ (10 pmol/ml). Anodal iontophoresis (0.5 mA·cm⁻²) for 5 min of ACV-Gly (9 mM, 0.4 ml) followed by passive diffusion for 55 min, resulted in significant transcorneal permeation of ACV (released after ACV-Gly hydrolysis) and ACV-Gly (7.2±1.8 and 3.1±1.3 nmol·cm⁻², respectively). Furthermore, 11.7- and 3.1-fold increases in corneal ACV deposition were observed over Zovirax® and saturated ACV solution; there was negligible ACV-Gly deposition. After 30 min transscleral iontophoresis (1.0 mA·cm⁻²) of ACV-Arg or ACV-Trp (9 mM, 0.4 ml), total permeation of ACV and prodrug (ACV-X) was 128.0±35.5 (~60% ACV) and 96.6±16.0 nmol·cm⁻² (~2% ACV), for ACV-Arg and ACV-Trp cf. saturated ACV solution (16.9±2.5 nmol·cm⁻²).

Conclusions: Iontophoretic delivery of biolabile ACV-X prodrugs could be used to significantly enhance ocular bioavailability of ACV.

Topical Ocular Delivery of Drugs to the Back of the Eye – Current Trends

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Background: Drug treatment of ocular posterior-segment disease, e.g. wet age-related macular degeneration, has come to involve intravitreal injection as standard-of-care. While effective, there remains the potential for complications, and typically the patient must return to the physician's office every month or two for treatment. An obvious alternative is non-invasive topical ocular administration, and there is mounting evidence that this can achieve pharmacologically-relevant concentrations at the back of the eye. The data and current trends are reviewed with regard to the extent and possible mechanism of topical drug distribution to the back of the eye. Specific cases are provided, e.g. betaxolol (beta blocker) and nepafenac (NSAID).

Methods: Studies were conducted in rabbit, monkey and human. Dosing in smaller species was typically unilateral, leaving the fellow eye untreated, allowing one to differentiate drug delivered locally versus drug absorbed into the systemic circulation and redistributed. Following single or multiple topical instillation, animals were euthanized and ocular tissues collected at various time points. In humans, studies were conducted in blind painful eyes scheduled for enucleation. Samples were analyzed by liquid chromatography coupled with tandem mass spectrometry, or other appropriately sensitive method.

Results and Conclusion: Betaxolol distributed locally to the retina in both monkeys (121 ng/g) and humans (71.4 ng/g). Nepafenac and active metabolite, amfenac, distributed locally to the retina in rabbits (22.4-164 ng/g nepafenac; 6.5-20.5 ng/g amfenac) and monkeys (74-93 ng/g nepafenac; 0.7-4.5 ng/g amfenac). These results are consistent with evidence of clinical efficacy following topical ocular dosing. The current body of evidence demonstrates that certain drugs can distribute to the back of the eye at pharmacologically relevant concentrations following topical ocular administration. One possible mechanism involves anterior-to-posterior and outside-in concentration gradients.

Ocular Allergy Introduction: Magnitude of the Problem

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Severe ocular allergy is an uncommon but significant form of ocular surface disease characterized by chronic inflammation of the cornea, conjunctiva, and eyelids. Symptoms of ocular allergy include sensitivity to light, itching, burning, tearing, and red/inflamed eyelids. The pathogenesis of ocular allergy is poorly understood with involvement of both type 1 as well as type 4 hypersensitivity reactions. Although ocular allergy is a chronic disease, symptoms may worsen during particular seasons, especially summer or winter, or with exposure to allergens such as dust, animal dander, or certain foods. Due to its chronic and symptomatic nature, severe ocular allergy is likely to impact patients' health-related quality of life. Decreased vision and even blindness can result from chronic cicatrizing conjunctivitis and corneal involvement in the form of chronic superficial punctate keratitis persistent epithelial defects, neovascularization, scarring and thinning, and keratoconus. Treatment includes combinations of oral and topical antihistamines and mast cell stabilizers, which are usually effective in controlling only mild disease. Severe cases of ocular allergy are treated with chronic topical calcineurin inhibitors including cyclosporine and tacrolimus. Topical corticosteroids, which can lead to the development of cataracts or glaucoma, should be avoided. Systemic immunomodulators are usually spared for severe vision threatening cases.

Vernal Keratoconjunctivitis: A Case-Based Presentation

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Vernal keratoconjunctivitis (VKC) is one of several forms of allergic eye disease, but it is one of them that can lead to vision loss if not treated appropriately. VKC is a type I hypersensitivity reaction, and it classically affects boys more often than girls in the first decade of life. Although it generally subsides by the late teens to early 20's, 6% of patients can have vision-threatening consequences including corneal scarring from shield ulcers or steroid-induced glaucoma. Treatment consists of topical high-potency corticosteroid drops, as well as topical mast cell stabilizers and antihistamines. Systemic therapy may also be necessary to control VKC.

Deciphering the Immunopathogenesis of Ocular Allergy

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Dry eye and allergic conjunctivitis are the most prevalent ocular surface diseases, occurring independently, and in some cases coexisting in the same patient.

Despite stark differences in the proposed etiologies, ocular surface irritation is the primary reason patients seek an ophthalmologist. Dry eye disease is a Th1/Th17-driven autoimmune disease defined by localized inflammation and tissue destruction that results in ocular discomfort, fatigue and chronic pain, accompanied by blurred and fluctuating vision. By contrast, the most common forms of allergic conjunctivitis (seasonal and perennial) are considered classic Th2-driven diseases, defined by ocular surface irritation, redness, edema and excessive tearing. To study the impact of allergy and dry eye on the ocular surface inflammatory response, mice were sensitized/challenged with short ragweed pollen (SRW; Th2 stimulus) to induce allergic conjunctivitis and/or exposed to desiccating stress (DS; Th1/Th17 stimulus) to generate experimental dry eye.

Mice with allergic conjunctivitis, and subsequently exposed to DS, displayed a significant increase in the number of inflammatory cells infiltrating the conjunctiva compared to SRW-sensitized/challenged allergic mice. When allergic conjunctivitis was induced in IFN- γ KO mice, a significant reduction in conjunctival inflammatory cell infiltrate (77% decrease in eosinophils; 35% decrease in neutrophils) was observed relative to wild-type mice with ocular allergy. The absence of IFN- γ was associated with a reduction in vascular adhesion molecule-1 (VCAM-1) on the vascular endothelium, suggesting that this classic Th1 cytokine acts as a gatekeeper by regulating inflammatory conjunctival cell infiltration. Moreover, these data suggest that ocular allergy may exacerbate the severity of ocular surface inflammation and pathology in dry eye patients.

Atopic Keratoconjunctivitis: Update on Treatment

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Atopic keratoconjunctivitis (AKC) is an uncommon, chronic ocular surface disorder in the context of atopic dermatitis. Ocular involvement is seen in 25-40% of patients with atopic dermatitis. Treatment of atopic keratoconjunctivitis (AKC) is challenging and should be multi-prong. Associated herpetic and staph infections of for example conjunctiva, lids and cornea should be addressed separately. Traditionally, the mainstays of anti-inflammatory therapy included a combination of antihistamines, mast cell stabilizers, and corticosteroids.

Corticosteroids are effective in controlling the acute flares of AKC. However, as much as two-thirds of patients managed with a combination of oral antihistamine, topical mast cell stabilizer, and intermittent topical steroid regimen eventually developed significant keratopathy and subsequent vision loss.

Therefore, complete suppression of flare-ups is key in the long-term management of AKC. More recently, other modalities of therapy have been introduced, such as orally administered cyclosporine (CsA). CsA is a hydrophobic, cyclic, polypeptide calcineurin inhibitor purified from the fungus *Tolyposcladium inflatum*. CsA is known to selectively inhibit T lymphocytes by blocking the expression of the interleukin-2 receptor. It also blocks the release of inflammatory mediators from mast cells and eosinophils which is a great advantage in the treatment of atopic conditions. Several previous, short-term studies demonstrated efficacy of topical CsA as a useful steroid-sparing agent in the treatment of AKC. Tacrolimus is also a calcineurin inhibitor which is most commonly used in the field of atopic dermatitis. A few previous studies showed that a combined topical cyclosporine and tacrolimus seems to prevent flare ups of AKC.

In resistant cases, particularly with extensive atopic dermatitis with or without asthma, use of biologics such as efalizumab (anti CD11a-LFA-1), Daclizumab (anti IL-2) and omalizumab (anti IgE) should be considered.

Vernal Keratoconjunctivitis: Update on Clinical and Immunological Findings

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Vernal keratoconjunctivitis (VKC) is an unusually severe sight-threatening allergic eye disease, occurring mainly in children. Conventional therapy for allergic conjunctivitis is generally not adequate, therefore persistent inflammation can lead to permanent visual loss. Children with VKC present with severe ocular signs and symptoms, corneal inflammation associated with tissue remodelling and fibrosis, resulting in potential scarring and corneal opacities. The pathogenesis involves a variety of factors, including environmental allergens, climate, and genetic predisposition. VKC is considered an IgE- and Th2-mediated allergic reaction with additional, not well-defined, perhaps non-specific hypersensitivity responses. In fact, only 50% of patients present a clearly defined allergic sensitization. Multiple mediators, cytokines, chemokines, growth factors, proteases and enzymes are over-expressed in VKC. Their combination may create the different clinical phenotypes seen in these patients. Interestingly, many of the over-expressed proteins detected by proteomic techniques, have anti-inflammatory properties suggesting that regulatory mechanisms are up-regulated to limit and control the extent or effects of pro-inflammatory cytokine as a consequence of local immune reaction. Understanding inflammation in ocular allergy may provide indication for a rational treatment of these diseases and future potential therapeutic approaches including immuno-modulators, such as cyclosporine and tacrolimus.

Lids, Lipids, and Dry Eyes: Clinical Overview

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Purpose: To assess the association between different types of chronic blepharitis, changes in Meibomian secretions, and underlying causes of aqueous deficient dry eyes.

Setting: Ophthalmology Faculty Practice Referral Clinic in an academic setting, UT Southwestern Medical School, Dallas, Texas.

Methods: Patients with chronic blepharitis were classified using the published classification system of McCulley. Lid and conjunctival cul-de-sac aerobic and anaerobic cultures were done. Frequently recovered bacteria were assessed for production of lipolytic exoenzymes. In depth lipid biochemical analysis of individual patients meibomian sections was done. The presence of associated aqueous deficient dry eyes (ADDE) was clinically determined. Tear evaporative rate was measured with an evaporimeter. Meibography was done to assess anatomical meibomian gland changes.

Results: The only statistically significant bacterial recovery was of *Staphylococcus Aureus* (SA) in the Staphylococcal and Mixed Staphylococcal/Seborrhic groups. Coagulase Negative Staph (CNS) and SA were found to frequently produce lipolytic exoenzymes capable of breaking down meibomian gland secretions. Chemical analysis of meibum revealed a complex of nonpolar and polar lipids with a statistically significant decrease in patients with ADDE of sphingomyelin and phosphatidylethanolamine. All patients with ADDE demonstrated excessive aqueous tear evaporation and meibomian gland drop out compared to normals. (80/100)

Conclusion: Patients with chronic blepharitis with associated aqueous deficient dry eyes did not have an identifiable bacterial pathogen, but did have evidence of bacterial lipolytic exoenzyme activity with a decreased in critical polar lipids with associated excessive aqueous tear evaporation and meibomian gland drop out.

The Cytology in Ocular Surface Disease Diagnosis

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The diagnostic assessment of the ocular surface disorders can include the study of corneal-conjunctival disorders. Several types of biological material can be harvested with different techniques: pipetting to obtain cells from tears; scraping or imprinting for the corneal-conjunctival epithelium. The tear cytology is indicated in the diagnosis of inflammatory and infectious diseases. Samples, obtained by glass microcapillaries, can be harvested from the tear menisci. Scraping, instead, is indicated for the diagnosis of infectious (e.g. Acanthameba, Chlamydiae, etc.) or neoplastic diseases. It consists in obtaining samples of corneal-conjunctival epithelium using a platinum spatula (Kimura spatula) or brushes. Finally, the corneal-conjunctival imprinting is the most widely used technique for obtaining epithelial tissue. This technique is used to diagnose epithelial squamous metaplastic changes, inflammatory markers expression, limbal stem cell deficiency, and as an aid in the diagnosis of epithelial tumors.

On impression cytology samples can be applied histochemical and immunohistochemical methods to study the epithelial morphology, the expression of markers or cytological constituents such as cytokeratins. Furthermore, also the use of molecular biology methods can be used to evaluate the expression of molecules such as HLA-DR, transglutaminase 2, metalloproteinases. However, the use of these methods is still dedicated to trials more than to clinical practice.

The study of cytology is a useful, easy to perform diagnostic method that allows a better understanding of the ocular surface conditions and gives the possibility to monitor the effects of ocular surface therapy.

Immunopathogenic Mechanisms in Dry Eye Disease

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Immune mechanisms play a critical role in the pathogenesis and amplification of dry eye disease (DED). In particular, CD4+ IL-17-secreting T helper-17 (Th17) cells play a principal function in mediating the pathogenic mechanisms that induce epithelial damage in DED. But is the immune response generated after desiccating stress merely a consequence of surface dryness? Or, as we have hypothesized, can surface dryness actually cause chronic autoimmune epitheliopathy even after termination of desiccation? Recently, we have shown that mice in whom DED was induced, continue to exhibit ocular surface disease for many months, even when placed in a normal-humidity environment and despite normal to supra-normal tear secretion (Chen Y et al, Mucosal Immunology 2013). In these "chronic DED" mice, the disease is mediated primarily by effector memory Th17 (CD4+CD62L-CD44^{hi}IL-17A+) cells, which can even be adoptively transferred to other (healthy) animals to induce DED. This short presentation will provide an overview of T cell-mediated immune mechanisms in DED, and also highlight the failure of T regulatory cells in controlling ocular surface inflammation in DED.

Cold Sensation and Dry Eye

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Purpose: In this study we suggest the relationship between cold and dry eye sensation. Our purpose is determine the effect of ageing on the number, morphology and electrophysiological properties of corneal cold sensory nerve axons and their influence on basal tearing rate in an animal model.

Methods: TRPM8-EYFP mice of different ages (3, 6, 9, 12, 18 and 24th months) were studied. Basal tearing was measured in anesthetized animals, using phenol red threads. Corneal nerves expressing EYFP protein and neuronal class III beta-tubulin were identified in whole mount corneas using immunocytochemical techniques. Density of subbasal nerve branches and epithelial terminals was measured in the peripheral and central regions of the cornea. Trigeminal ganglion (TG) corneal neurons, labelled with fast blue applied onto the cornea in anesthetized mice, were identified in TG sections using immunofluorescence and counted. Extracellular electrical activity of single sensory nerve endings of the corneal surface was recorded in excised and superfused eyes.

Results: In 3-months mice, TRPM8+ subbasal nerve fibers represent 22,4% of the total number of sub-basal nerve branches; most of them were beaded axons finally ramifying in the uppermost epithelium as a cluster of beaded nerve terminals. Less abundant, longer and narrower fibers lacking beads and ending as a single or double bulbous terminal branch were also found. The total number of TRPM8+ subbasal nerve filaments and epithelial terminals decreased non-linearly with age. 3-months mice had 37% of low-threshold (30.5°C) cold sensitive fibers showing high background activity and vigorous firing responses to cooling. They were reduced to 26% in 24 months-old mice. Contrarily, cold sensitive fibers with a high cooling threshold (30.5°C), very low frequency background activity and weak responses to cooling was 17% in 3 months-old mice and 40% in 24 months-old mice. Basal tearing values also decreased with age (3months= 1.9± 0.2 mm; 24months= 1.3 ± 0.2 mm) varying in parallel with the number of TRPM8 subbasal branches and epithelial terminals.

Conclusions: Reduction in the number and branching pattern of corneal low-threshold cold sensitive fibers with age seems to be associated with a lowering of the tearing rate, thus supporting the hypothesis that sensory input from ocular surface cold thermoreceptors contributes to the maintenance of basal tearing.

Biomarker and Clinical Importance in Dry-Eye

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The composition of proteins and peptides in tears plays an important role in ocular surface diseases like dry eye. The paper will focus on the definition of biomarker and will give a critical state-of-the-art analysis of the relevance of tear film proteomics and immunoproteomics in the diagnosis of disease and the problems of translating it into clinical routine and will reveal biomarkers, which are correlated with dry-eye, but also other ocular diseases such as glaucoma related ocular surface problems. Beside of new treatment options, these biomarkers could serve in future to optimize treatments in individual patients in personalized medicine.

Molecular Biomarkers of Eye Disease

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Purpose: The tears constitute the extra-cellular fluid of the ocular surface and with components from the blood, epithelial cells, lacrimal gland and Meibomian glands reflect and signal normal and pathological processes to the ocular surface. It was hypothesized that qualitative and quantitative changes could be found that would be useful for diagnosis and treatment of both pathologies.

Methods: Tears were collected using Schirmer's strips, iTRAQ together with nanoLC-MS/MS was used to quantitatively compare the tear proteomic profiles among patient groups in keratoconus, KC, and lacrimal gland tumor, LGT. Gene expression of LGT tissues was examined using cDNA microarray (Affymetrix Gene 1.0 ST array). ELISA, Immunofluorescent staining and transmission electron microscopy (TEM) were used to confirm the proteomic results.

Results: In total, over 1000 tear proteins (1% false discovery rate) were identified from the whole study KC patients. Quantitative proteomic results from a group of up-regulated and down-regulated proteins (ratio for KC/control 1.5, or 0.67) revealed a positive correlation between several tear proteins (LCN1, PLA2G2A, SCGB2A1, MSLN and CRYAB) and KC clinical grades (Grade I, II and III). IN LGT, iTRAQ quantitative proteomics results of tears showed that markedly reduced levels of LG secreted proteins (LCN-1, LYZ, LFT, PIP and PRR4, ect.) and elevated MMP-9 level in tears from malignant LGT compared to two other groups. iTRAQ results of LG tissues also showed that these LG secreted proteins are down-regulated in malignant LGT. TEM showed largely decrease of the number of secretory granules in malignant LGT tissues. ELISA (~100 fold higher in malignant LGT) and immunofluorescent staining results confirmed proteomics results. There is a strong correlation among lacrimal-preferred genes, lacrimal gland secreted proteins in lacrimal gland tissues and tear fluids.

Conclusions: Identifying molecular biomarkers in patients tears, it would be feasible to stratify patients based on the results and use these objective measures as a response to treatment.

Autologous Serum in the Treatment of Ocular Surface Conditions

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The use of autologous serum has been gaining widespread popularity as a treatment for various conditions of the ocular surface, most notably for dry eyes and persistent corneal epithelial defects. Numerous studies have recently demonstrated its safety and efficacy in these conditions compared to conventional treatment modalities. Despite these convincing results, barriers to widespread use continue to exist as ophthalmologists must adhere to local regulatory guidelines for its production and distribution. Continued studies will better define the optimal methods of production of serum as well as the ideal indications for its use.

The Role of Ocular Surface Epithelia in Dry Eye Syndrome

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Background: Dry eye syndrome (DES) is a frequent disease that affects the ocular surface system. Most of research studies have focused on tear film and the way to replace it. The aim of the round table held in Rome in 2013 was to review the role of corneal and conjunctival epithelia in DES.

Methods: A round table of five European dry eye experts was organized to review the relationship between ocular surface epithelia and tear film, corneal wound healing mechanisms, corneal nerve changes, inflammatory and immunological modifications in normal and DES conditions. Also, possible treatments to improve epithelia health were reviewed.

Results: Corneal and conjunctival epithelia play a pivotal role in DES pathogenesis and in general in all ocular surface diseases. Diagnostic tests such as lissamine green staining should be routinely used to demonstrate epithelia changes, as well as confocal microscopy and detection of markers of inflammation. So far we have limited therapeutic tools in our hands to directly improve epithelia conditions.

Conclusion: DES is an important disease with a complex pathogenesis, review of existing data integrated by common research efforts could be an interesting approach to improve our knowledge and to develop new treatments.

Learning Immune Lessons for Dry Eye Pathology and Treatment from Graft vs. Host Disease

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Graft-versus-host disease (GVHD) is a potentially blinding condition that affects allogeneic hematopoietic stem-cell transplant (HSCT) survivors. Allo-reactive donor T-cells are essential for the development of GVHD, but their role in ocular GVHD (oGVHD) hasn't been demonstrated. Here we examine immunological and ocular changes using a clinically-relevant MHC-matched, minor-antigen mismatched transplantation model of systemic and oGVHD. After high-dose TBI, C3H.SW mice were transplanted with T-cell depleted bone marrow (TCD-BM) alone or together with T-cells from B6 mice. Clinical score composite monitored GVHD weekly and ocular surface staining Mice that received BM and T-cells from B6 mice developed evidence of systemic GVHD by day 21 as opposed to controls. Beginning at day 28, C3H.SW mice that receive BM+T-cells develop oGVHD characterized by donor T-cell recruitment, and the development of corneal staining, ulceration and loss of goblet cells. These findings support a critical role for donor T-cells in the ocular immune response. Understanding kinetics and pathways will provide targets for the prevention and treatment of oGVHD.

Microsphere Drug Delivery

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Addressing the relative short half-life of most medications in their free form for intravitreal use, a variety of controlled (sustained)-release drug systems have been studied enthusiastically since the latter half of the 1980s. These systems are capable of delivering drugs over longer time periods than conventional formulations and may add rational to the pharmacologic strategy of treating chronic retinal diseases. Growing evidence is indicating the usefulness of biodegradable microspheres for vitreoretinal drug delivery; offering an excellent alternative to lessen the risk associated with multiple intravitreal injections. These erodible devices have the inherent advantage over the non-erodible systems in that they gradually disappear from the site of implantation. In addition, microspheres have also the benefit over larger devices in that they can be delivered by a simple injection, and as a result, fulfilling most of the requirements for an ideal intravitreal-delivery carrier system. Our clinical experience with the use of PLGA-microspheres targeting diabetic macular edema in humans, as well as, a new and optimized Avastin liposomal formulation for the treatment of choroidal neo vascularization will be presented in detail.

Retinal Oximetry in Diabetic Retinopathy and Retinal Vein Occlusions

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Animal studies, limited invasive human studies and indirect evidence suggest that hypoxia is a major factor in both retinal vein occlusions and diabetic retinopathy. Recent non-invasive retinal oximetry studies have also found abnormal oxygenation in both diseases.

Retinal oximetry utilizes the colour of blood to measure the oxygen saturation in retinal blood vessels. Retinal venous saturation has been found to be lower in eyes affected by central retinal vein occlusions (CRVO), compared to the healthy fellow eye in the same patient. It is also interesting that the venous saturation in CRVO is quite variable and further studies are needed to determine if variable oxygen saturation correlates with variable clinical outcome.

Several studies have shown that retinal vessel oxygen saturation is elevated in patients with diabetic retinopathy, which may seem to contradict prior evidence of retinal hypoxia. However, high retinal vessel oxygen saturation may co-exist with retinal tissue hypoxia. More specifically, high vessel oxygen saturation may reflect poor distribution of oxygen from the vasculature to the tissue.

Cyclodextrin Nanoparticles Optimize Eye Drops for Anterior Segment and Retinal Drug Delivery

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We have developed a drug delivery platform that is based on cyclodextrin nanoparticles. The nanoparticles deliver small lipophilic molecules to both the anterior and posterior segments of the eye in significant concentrations. Several drugs have been tested in the platform and two drugs have been tested in clinical studies. These are the anti-inflammatory drug dexamethasone and the intraocular pressure lowering drug dorzolamide.

Nanoparticulated γ -cyclodextrin dexamethasone (DexNP) has been shown to significantly reduce macular edema and improve visual acuity in patients with diabetic macular edema. This can be explained by increased concentration and extended mucoadhesion of DexNP on the surface of the eye when compared to the commercial dexamethasone eye drop (Maxidex[®]).

Nanoparticulated γ -cyclodextrin dorzolamide (DorzNP) given once daily was compared to the commercial dorzolamide (Trusopt[®]) administered three times per day in a phase I clinical study. After 24 hours, the intraocular pressure lowering effect was comparable between the two drugs. However, this indicated long-lasting effect of DorzNP could not be explained by differences in drug concentration in tear fluid.

The initial human results indicate that dorzolamide may not be as suitable to the cyclodextrin nanoparticle suspension drug delivery platform as dexamethasone and further studies are needed. Dexamethasone on the contrary appears to fit the drug delivery platform well with the consequence of high drug concentration and extended mucoadhesion of DexNP with sustained effect of dexamethasone in the posterior segment of the eye. This opens the door to non-invasive treatment of dexamethasone for retinal diseases.

Risk Stratification in Diabetic Retinopathy

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Purpose: To use individualized risk assessment and information technology to make diabetic eye screening more focused and economical; as well as to improve patient education and motivation.

Methods: A mathematical algorithm calculates the risk for progression to sight threatening diabetic retinopathy from clinical risk factors. The algorithm resides in computer software and is also available on the Internet and as a mobile application.

Results: The algorithm and software assists healthcare providers motivating key behavioral changes amongst patients through education, interaction and individualized clinical information. It identifies high and low risk patients and allows optimal screening intervals to be determined according to the patient's clinical profile and risk. Validation studies in Denmark, England, Spain and The Netherlands show that diabetic eye screening can be performed with 50-60% fewer visits than the annual tradition, without compromising patient safety. This reduces costs by more than 50%.

Conclusion: Risk assessment and information technology improves economy of diabetic eye screening. Patient education and motivation is improved and the screening is individualized and more focused with this approach.

A Review of Controversial Safety Topics in AMD, RVO and DME Patients - Treated with Anti-VEGF Agents

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Background: This summary examines several safety topics with the use of anti-VEGF agents for the treatment of age-related macular degeneration (AMD), retinal vein occlusion (RVO) and diabetic macular edema (DME).

Methods: Systemic safety findings with ranibizumab, aflibercept and bevacizumab in patients treated for AMD, RVO and DME have been evaluated. Data to be reviewed include arterial thromboembolic events, effects of anti-VEGF drugs on systemic anti-VEGF levels, endophthalmitis risk, and geographic atrophy.

Results: Previously presented or published data is variable as it relates to the differential risk of arterial thromboembolic events with ranibizumab, aflibercept or bevacizumab. The risk of endophthalmitis has varied across the three drugs. Several studies looking at the rates of geographic atrophy between the agents have provided inconclusive results.

Conclusions: A review of controversial topics in ocular and systemic safety of current anti-VEGF agents for the treatment of AMD, DME and RVO will be presented.

Ocular Side Effects of Intravitreal Anti-VEGF Therapy

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Intravitreal injection enables highly targeted drug therapy, maximizing therapeutic drug delivery to the posterior pole while minimizing systemic toxicity. With the increasing use of intravitreal anti-VEGF agents in the treatment of neovascular age-related macular degeneration (AMD), diabetic macular edema, retinal vein occlusion, and various other retinal vascular disorders, intravitreal injection has become the most common ophthalmic procedure performed in the United States. Potential complications include intraocular inflammation, retinal detachment or perforation, traumatic lens damage, intraocular hemorrhage, sustained ocular hypertension, and hypotony. Of all the complications, infectious endophthalmitis remains one of the most devastating complications. In multicenter clinical trials with anti-VEGF therapy the incidence of endophthalmitis per patient has been reported to range from 0.019 to 1.6%. However, the reported rate in recent studies tends to be lower than that in early trials. The rate of endophthalmitis seems to be the same among different anti-VEGF agents, different injection settings, and different geographical locations. Sterile technique and antisepsis with instillation of topical povidone iodine 5% into the conjunctival fornix prior to an intravitreal injection may reduce the risk of endophthalmitis. Sterile inflammation may be difficult to differentiate from infectious endophthalmitis.

The time of presentation, presence of pain, and the severity of clinical findings may be helpful to distinguish between sterile and infectious endophthalmitis. The overall incidence of rhegmatogenous retinal detachment (RRD) after intravitreal injection of anti-VEGF agents is low (0 to 0.67%). In a study on Medicare database, the differences in rates of RRD and retinal tear were not statistically significant between eyes with intravitreal anti-VEGF injection and a matched control group.

Acute rise of intraocular pressure (IOP) after intravitreal injection is injection procedure-related and lasts a few hours at most. Recent studies, however, have reported a significant number of intravitreal anti-VEGF injections is associated with an increased risk for IOP elevation. Patients with pre-existing glaucoma have higher rates of IOP elevation compared with those without pre-existing glaucoma.

There have been several reports of ocular hemorrhage following the use of intravitreal anti-VEGF drugs. Subconjunctival hemorrhage has been reported to occur in nearly 10% of injections, with higher frequency in patients who were receiving aspirin. Anti-VEGF therapy is the mainstay for the treatment of many retinal diseases. Despite its promising efficacy in halting the disease and improving the vision for the patients, intravitreal injection of anti-VEGF agents may be associated with devastating complications.

Choosing Anti-VEGF Therapy for Wet Age-Related Macular Degeneration

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Background: Wet age-related macular degeneration (AMD) is the principal cause of severe vision loss and blindness among people aged over 50 years. The advent of intravitreal vascular endothelial growth factor (VEGF) inhibitors has significantly improved the visual prognosis for patients affected by neovascular AMD. Several biological anti-VEGF agents have been clinically developed, of which ranibizumab, aflibercept and bevacizumab are the most widely used in neovascular AMD therapy.

Methods: Evidence available from prospective, multi-center clinical studies evaluating different treatment schedules and the use of ranibizumab, aflibercept and bevacizumab (ANCHOR, MARINA, PIER, SAILOR, SUSTAIN, EXCITE, CATT, IVAN, VIEW Trials) and from a selective literature search is utilized to generate evidence-based and consensus recommendations.

Results: Ranibizumab and aflibercept are approved by FDA and EMA for the treatment of wet AMD. Bevacizumab is used off-label as intravitreal VEGF inhibitor for the treatment of choroidal neovascularization due to AMD. Intravitreal anti-VEGF agents have been extensively studied in many large randomized clinical trials on neovascular AMD, demonstrating significant improvements either in morphological and functional outcomes. Several trials have shown that anti-VEGF therapy can be administered with various treatment regimens (monthly fixed, flexible, treat and extend) with good efficacy results. A monthly fixed regimen or an individualized approach with monthly monitoring and aggressive retreatment criteria produce a significant visual acuity improvement in patients affected by wet AMD. Findings from the CATT trial suggested that ranibizumab and bevacizumab may have a different systemic safety profile. Moreover, the IVAN study revealed that patients treated with intravitreal injections of bevacizumab showed a significant change in the median serum VEGF levels.

Conclusions: With the advent of anti-VEGF therapy the prognosis of choroidal neovascularization has changed dramatically. Data from large clinical trials suggest that ranibizumab, bevacizumab and aflibercept are effective in patients affected by wet AMD. Further large and randomized studies are needed to evaluate the safety profile of these different drugs.

Synopsis of Comparison Studies: CATT, IVAN, MANTA, GEFAL

Zohar Yehoshua

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Researcher in countries around the world developed and conducted randomized controlled clinical trials comparing head to head ranibizumab to bevacizumab. Comparison of age related macular degeneration treatment trials (CATT) in the USA, the inhibition of VEGF in a age related choroidal neovascularization IVAN, MANTA (Multicenter Anti-VEGF Trial in Austria), and GEFAL (French Evaluation Group Avastin Versus Lucentis), Lucentis compared to Avastin (LUCAS), the bevacizumab and ranibizumab in age related macular degeneration (BRAMD) study, prevention of vision loss in patients with age related macular degeneration by intravitreal injection of bevacizumab and ranibizumab (VIBERA).

CATT, IVAN, MANTA, GEFAL and the LUCAS studies confirmed that there is no difference in visual acuity improvement in patients treated with either drug. CATT trials demonstrated, at both one and two years, ranibizumab and bevacizumab had similar beneficial effects on visual acuity when the dosing regimen was the same. At two years, the mean gains in visual acuity between the two drugs were within 1.4 letters. Collectively, at two years, 60 percent or more of the patients in all groups had 20/40 vision or better. Subtle differences were detected in year two between dosing regimens: the as-needed dosing of either drug at two years produced 2.4 letters less mean gain versus monthly dosing ($p=0.046$). The greatest difference in mean gain in visual acuity was between ranibizumab monthly and bevacizumab as-needed (3.8 letters).

IVAN study, conducted in the United Kingdom, was the first international version of CATT with the treatment groups defined in the same way as CATT. Only a few differences were made in the study design for IVAN; the most notable change was the as-needed groups received 3 monthly loading doses of bevacizumab or ranibizumab and then were reloaded with every episode of recurrence. The IVAN results confirmed the CATT results in both years. Bevacizumab was not found to be noninferior to ranibizumab. The Groupe d'Evaluation Français Avastin versus Lucentis (GEFAL) study—which was conducted in France and followed the study design of both CATT and IVAN—confirmed through the first year similar findings that these 2 larger studies have shown.

Both studies CATT and IVAN showed that the intermittent approach (CATT PRN and IVAN discontinuous) was significantly inferior when compared to monthly treatment.

All four comparative clinical trials (CATT, IVAN, MANTA, GEFAL) demonstrated a statistically significant difference in the risk of systemic SAE by drug, with a potential disadvantage to bevacizumab. Only IVAN and CATT trials contributed to the analysis of SAE and or death by regimen.

Meta-analysis of the comparison studies' data suggested that monthly dosing, regardless of drug, produced higher rates of geographic atrophy (GA) in patients than did prn dosing. Over a 2-year period, 24% of patients treated on a monthly regimen developed GA, while 15% of patients on a prn regimen developed GA.

Pazopanib Eye Drops vs. Ranibizumab Intravitreal Injection for Neovascular AMD

Baruch D. Kuppermann

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Primary Objective: To evaluate if daily-dosed pazopanib eye drops can maintain or possibly improve vision, while reducing the continued need for IVT injections. The pre-specified criteria for success was a 50% reduction in the frequency of injections compared, with placebo. The non-inferiority margin for visual acuity was 5 letters.

Secondary Objectives: To compare safety and tolerability between each pazopanib arm and control arms. To compare retinal anatomical changes between each pazopanib arm and control arms. To evaluate dose-response relationships across five pazopanib treatment arms.

Exploratory Objectives: To evaluate the response to pazopanib and control arms by genetic variations, including the complement factor H Y402H polymorphism.

Study Design: Phase IIb dose-ranging in previously treated pts with NVAMD; Multicenter, multi-country; Randomized, parallel-group; Double-masked, placebo-controlled eye drop arms; 75 pts per arm; Randomized to one drop 5mg/ml TID vs QID, 10 mg/ml BID vs TID vs QID, placebo QID; PRN Ranibizumab IVT from week 4 to 52; Active-controlled using intravitreal (IVT) ranibizumab; Protocol-defined reinjection criteria based upon OCT, fundus photography, and VA assessment. Monthly monitoring with OCT/VA Results: No Baseline Covariate was Associated with a Treatment Effect for Pazopanib Eye Drops; Statistical significance (0.05 level) of the interaction term was not achieved with any of the more than 25 baseline covariates evaluated in a model.

Safety: Adverse events were evenly distributed across treatment arms, and consistent with expectations for this population; Corneal deposits were reported in 2 subjects (both assigned to the highest dose arm (10 mg/mL QID), and were not resolved at completion of the study.

No additional ocular or systemic safety concerns were noted.

Conclusions: Ocular administration of pazopanib solution, with allowance for as-needed ranibizumab, met the non-inferiority margin (5 letters) of maintaining VA at Week 52 compared to monthly and as-needed ranibizumab.

However, pazopanib eye drops did not displace 50% or more of as-needed injections, the pre-specified minimal success criteria to demonstrate efficacy.

Administration of pazopanib eye drops for up to 52 weeks to AMD subjects who were previously managed by and responsive to anti-VEGF IVT injection therapy was generally safe and well tolerated.

Baruch Kuppermann for the Pazopanib Study Team

Wet AMD in the Pipeline

Peter Kaiser

Peter Kaiser
Cleveland, Cole Eye Institute, USA

Anti-VEGF agents have changed the face of treatment for exudative AMD. However, they require frequent intravitreal injections and do not change the disease process. Researchers have looked to other pathways and targets for wet AMD. This lecture will explore these other targets including blocking platelet derived growth factor, squalamine, tubulin inhibitors, integrin antagonists, combrestatin, complement inhibition, and blockade of bioactive lipids. The current stays of clinical trials will be discussed.

Integrin Peptide Therapy: The First Wet AMD Experience

Peter Kaiser

Peter Kaiser
Cleveland, Cole Eye Institute, Ohio, USA

ALG-1001 is a synthetic integrin peptide oligopeptide that interferes with several pathways of the angiogenic cascade, as it can bind to multiple integrin-receptor sites that are known to be involved in both choroidal and preretinal neovascularization. In vitro, ALB-1001 inhibits integrin receptors and in vivo, arrests aberrant blood vessel growth that is mediated by integrins $\alpha v \beta 3$, $\alpha v \beta 5$, and $\alpha 5 \beta 1$. These are sites that are expressed in neovascular ocular tissue in wet AMD as well as diabetic retinopathy. Integrin peptide therapy is an emerging new class of treatment for neovascular eye diseases. Experimental studies showed a statistically significant reduction in choroidal neovascularization (CNV), retinopathy of prematurity (ROP) and vascular permeability, and a small phase I study in patients with diabetic macular edema showed that more than half of cohort (55%) improved 3 lines or more in BCVA with at least a 30% reduction in OCT CMT with ALG-1001 monotherapy. The key criteria for trial inclusion into the first clinical trial of ALG-1001 in wet AMD included a baseline BCVA between 20/50 and 20/320, CNV due to AMD, and patients could not have received prior treatment with anti-VEGF treatment within 45 days of enrollment. The 15 participants who have been enrolled in the trial are a combination of treatment naïve and previously treated.

Fovista Combination Therapy for Neovascular AMD

Jordi Mones

Jordi Mones
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Title: Anti-fibrosis and neovascular growth in neovascular AMD patients treated with dual antagonism of PDGF (Fovista 1.5mg)/VEGF (Lucentis®0.5mg) in a large (n=449 patients) phase 2b, controlled trial.

Methods: A prospective, randomized, controlled Phase 2b clinical trial of 449 patients with wet AMD, subjects received either combination therapy (Fovista™ plus Lucentis®) or monotherapy Lucentis® for 24 weeks.

Results: Fovista™ (1.5mg) "combination therapy" resulted in 62% comparative visual acuity benefit from baseline ($p=0.019$). Retrospective analyses of development of fibrosis and neovascular growth in patients with poor visual outcome were performed. Greater % of patients in the combination therapy arm vs. monotherapy arm experienced improved visual outcome and reduced visual loss (24 weeks). In patients with poor visual outcome and growth of neovascularization was 15% vs. 42.5% in the combination therapy arm vs. monotherapy arm respectively. Threefold reduction of fibrosis was noted in the combination therapy arm vs. monotherapy.

Conclusion: Enhanced visual outcome with dual antagonism of PDGF/VEGF is associated neovascular regression. In addition, PDGF antagonism (Fovista™ 1.5 mg) may also improve longer-term visual prognosis by inhibiting formation of subretinal fibrosis and reducing neovascular growth. Confirmatory phase 3 trials with a sample size of approximately 1900 patients are currently underway.

Oxygen Distribution in Health and Diseased Eyes

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The distribution of PO₂ close to the vitreoretinal interface is heterogeneous, found higher near the arteriolar wall. Preretinal and transretinal PO₂ profiles indicate that O₂ diffusion from the arterioles affects the PO₂ in the juxta-arteriolar preretinal region. Both the preretinal and inner retinal PO₂ recorded far from the vessels remain constant in all retinal areas.

The oxygen tension (PO₂) in the inner half of the retina remains largely unaffected by moderate changes in perfusion pressure. In addition a constant PO₂ is observed during systemic PaO₂ changes induced either by hyperoxia or hypoxia. However, an increase of PaCO₂ (hypercapnia), as well as an intravenous injection of acetazolamide (carbonic anhydrase inhibitor) can both lead to an increase of preretinal PO₂ due to retinal vessels dilatation.

In the case of eyes with experimental branch retinal vein occlusion, PO₂ values, within the inner retinal layers, are indicative of hypoxic conditions, whereas in adjacent unaffected retinal areas the PO₂ remain normal. In diabetic patients undergoing vitrectomy, reports have shown a lowered vitreal POG in the affected retinal areas. Occlusion of the retinal circulation renders most of the inner retina anoxic.

Retinal Oximetry in Glaucoma

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Glaucoma is one of the leading causes of blindness globally, but the pathophysiology of the disease is unclear. One of the main glaucoma theories suggests that ocular blood flow is decreased (ischemia) or poorly regulated in glaucoma which can lead to hypoxia. We have used a non-invasive retinal oximeter to measure oxygen saturation in healthy and glaucoma where the main objective has been to study whether oxygen metabolism in the retina is abnormal in glaucoma. Our results show that in patients with advanced visual field glaucomatous damage, retinal oxygen saturation in venules has consistently been measured higher and arteriovenous difference lower when compared to glaucoma patients with mild visual field glaucomatous damage and healthy individuals. A positive correlation between the changes in arteriovenous difference and structural changes of the optic disc and nerve fibre layer has also been found. Reduced oxygen consumption in retina is consistent with tissue loss in glaucoma. The data suggest therefore that oxygen metabolism is affected in glaucoma and that it could be secondary to neuropathy.

Retinal Oximetry with a Scanning Laser Ophthalmoscope

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Retinal vessel oxygen saturation can be measured non-invasively with the use of a spectrophotometric retinal oximeter, Oxymap T1. The oximeter is based on a conventional fundus camera and acquires images of the fundus using two wavelengths. Specialised computer software, Oxymap Analyzer, calculates oxygen saturation of the retinal vessels using a two-wavelength oximetry algorithm.

Oxymap T1 has been extensively validated and is sensitive to changes in oxygen saturation and vessel diameter. However, Oxymap T1 is limited to 50° field of view, pupils need to be dilated before image acquisition and imaging through cataracts and other ocular opacities can be difficult.

Optomap 200Tx, a scanning laser ophthalmoscope (SLO), can address these limitations and therefore offers some advantages for retinal oximetry. Optomap 200Tx can acquire up to 200° images of almost the entire fundus, without pupil dilation.

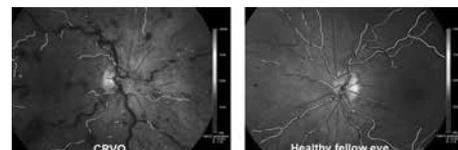
Due to the age-dependent prevalence of many eye-diseases, elderly people are often the group of interest for oximetry. Elderly people do often have cataracts and dilation of pupils is more difficult with increasing age. For this group, an SLO oximetry system would be a better imaging tool. Optomap 200Tx acquires images of the fundus using two laser wavelengths. The resulting two images can be analysed with a two-wavelength oximetry algorithm. Combining the SLO imaging and oximetry image analysis with the Oxymap Analyzer software was tested and proved successful. The SLO oximetry system is sensitive to oxygen saturation and gives repeatable results. The main challenges for further development are large intra- and inter-subject variability.

Retinal Oximetry: Status and Challenges

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Non-invasive retinal oximetry uses the colour of blood to estimate retinal vessel oxygen saturation. Studies, using this technique, have shown altered retinal vessel oxygen saturation in various ocular diseases, such as retinal vessel occlusions, diabetic retinopathy and glaucoma. Disturbed oxygenation may in some diseases be a part of the pathogenesis and in other diseases a consequence of disease processes, such as atrophy. One major aim of retinal oximetry development is to make the technology clinically useful. This may be achieved both by methodological improvement and by more (longitudinal) studies of retinal oxygenation in various diseases. Currently, retinal oximetry is closest to being clinically useful for monitoring of central retinal vein occlusion. The image below shows an oxygen saturation map of a patient with central retinal vein occlusion.



Uveitis Endpoints - The Clinical and Regulatory Strategy for the Approval of Retisert

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Purpose: To discuss the clinical and regulatory strategy for approval of intravitreal fluocinolone acetonide (FA) implants in patients with noninfectious posterior uveitis. Design of the Clinical Program: Prospective, dose-masked, dose-randomized, historically controlled, multicenter trial in patients with unilateral or bilateral disease.

Participants: A total of 278 patients with recurrent noninfectious posterior uveitis were randomized to receive a 0.59-mg (n = 110) or 2.1-mg (n = 168) implant. In patients with bilateral disease, the more severely affected eye received the implant.

Methods: The implant was inserted surgically into the vitreous cavity through a pars plana incision. Follow-up visits were scheduled on day 2, week 1, and then every 4 to 6 weeks through 34 weeks after implantation. Systemic, periocular, and topical therapies were reduced as allowed by the clinical response. Following the 34 week safety and efficacy endpoint, patients were followed for 2 more years.

Regulatory Strategy and Main Outcome Measures: The primary efficacy outcome was a comparison of the recurrence rate in the implanted eye from the 34 weeks before implantation to the 34 weeks after implantation. Visual acuity (VA), need for adjunctive therapy, and safety also were assessed.

Results: Combining both doses, the FA implant reduced the rate of recurrences from 51.4% in the 34 weeks preceding implantation to 6.1% post implantation (P0.0001) in the study eyes. Comparatively, there was a significant increase in the recurrence rate in the fellow non implanted eyes from 20.3% pre implantation to 42.0% post implantation (P0.0001). Visual acuity was stabilized or improved in 87% of implanted eyes and generally was associated with reductions in the area of macular hyper fluorescence. The percentage of eyes that required systemic medications, periocular injections, and topical corticosteroids decreased from 52.9%, 63.0%, and 35.7%, respectively, pre implantation to 12.1%, 2.2%, and 16.5% postimplantation (P 0.0001 in all cases). At week 34, 51.1% of implanted eyes required ocular antihypertensive drops, and 5.8% underwent glaucoma filtering surgery. Lens opacity scores increased by or =2 grades in 19.8% of phakic implanted eyes, and 9.9% required cataract surgery. There were no statistically significant differences in any of the parameters studied for the 0.59-mg implant, compared with the 2.1-mg implant.

Conclusions: The FA implant significantly reduced uveitis recurrences, improved VA, reduced foveal thickness and decreased the need for adjunctive therapy in the studied patient population. The most common side effects included increased intraocular pressure and cataract progression.

Behcet Vasculitis

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Behçet's disease (BD) is a systemic vasculitis of unclear origin. Eye involvement is characterized by an occlusive retinal vasculitis that can result in irreversible visual loss. Several sets of criteria have been developed to establish the diagnosis of BD in a patient based on clinical symptoms. However, sometimes patients present with intraocular inflammation that looks very typical for retinal vasculitis due to BD although other symptoms of this systemic disease are missing. In such a case, treatment with a biologic drug according to the EULAR recommendations should be started even if diagnostic criteria for BD are not fulfilled.

Herpes Uveitis/Keratitis

William Ayliffe

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Herpetic keratitis remains a common problem in clinical ophthalmology.

Most patients resolve with antiviral therapy, some require topical steroids and a few develop severe ulceration and blinding scars. Because of the high incidence of the disease, these rare complications are important. Less well understood are the varieties of intraocular inflammation.

Most uveitis specialists are comfortable with managing acute anterior uveitis due to Herpes, nevertheless recurrent attacks lead to significant pupillary abnormalities that affect quality of vision and glaucoma that can be aggressive. These complications can be very difficult to manage. Particularly severe problems occur in a recently recognized herpetic anterior uveitis in immune-competent people with cytomegalovirus.

The recognition of this condition is important to prevent sight threatening sequelae. The management is different from Herpes Simplex so differentiation at the onset of disease is critical. There are no corneal scars, no posterior synechiae but many have a transient endothelitis and a one or two keratic precipitates only.

These signs associated with a failure to respond to high dose systemic acyclovir should alert the physician to the possibility of CMV uveitis.

VKH

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The diagnosis of Vogt-Koyanagi-Harada disease (VKH), as of many uveitic entities, is based on clinical criteria only. In the acute phase it must be present a bilateral diffuse choroiditis with either focal or bullous subretinal fluid and in the late phase signs of ocular depigmentation, nummular chorioretinal scars with retinal pigment epithelium clumping/migration and recurrent/chronic anterior uveitis, along with a suggestive history of the acute phase. In addition signs of CNS involvement in acute phase (meningismus, tinnitus, dysacusia) and of cutaneous lesions in chronic one (alopecia, vitiligo, poliosis) might be found.

Nevertheless the "sine qua non" criteria to diagnose VKH are: - no history of ocular trauma/surgery; and - no clinical or laboratory evidence of other uveitic entities. Therefore VKH diagnosis seems to be easy when all (or the great majority of) ocular and systemic symptoms are present, but it might be difficult when some of them are lacking, incorrectly reported or inadequately searched. On the other hand a prompt and very aggressive corticosteroids and immunosuppressive therapy is crucial from the early onset of the symptoms to adequately control VKH and to preserve long-term a good visual acuity. Some cases misdiagnosed as VKH will be presented and compared with typical VKH cases in order to highlight the features useful for a correct clinical suspicion. The role for ancillary investigations, such as fluorescein and indocyanine green angiography, will be also discussed for both diagnostic purpose and appropriate follow-up of VKH patients

Glaucoma as an Optic Neuropathy - How is it like Other Optic Neuropathies?

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The optic nerve may be injured by a number of mechanisms, including but not limited to: mechanical deformation of axons; increased surrounding CSF pressure; circulatory insufficiency; inflammation/demyelination; metabolic dysfunction (including mitochondrial disease); and toxicity. The precise mechanism of injury to the retinal ganglion cell (RGC) in glaucoma remains unclear, but probably involves multiple factors.

Documented clinical features include: slowly progressive injury; predilection for arcuate retinal nerve fibers with relative papillomacular sparing; excavation of the optic disc; parapapillary retinal flame hemorrhages associated with focal axonal injury; and absence of optic disc edema. The relative roles of intraocular pressure, optic disc perfusion; CSF pressure, and cribriform plate structure, have not been precisely established. Retinal ganglion cell death involves apoptosis; the role of axoplasmic stasis, alteration of levels of brain-derived neurotrophic factor, and other cell death mechanisms such as excitotoxicity remain unclear as well. Comparison to other optic neuropathies may provide clues to the mechanisms of injury in glaucoma.

Excavation of the optic disc is a common feature of mitochondrial RGC diseases, and also occurs in some cases of compressive, and severe (arteritic) ischemic, injury. Predilection for the arcuate fibers occurs in optic disc drusen, nonarteritic ischemia, and chronic papilledema, but not in inflammatory or mitochondrial diseases. Parapapillary flame hemorrhages occur with ischemia and venous congestion in papilledema, but not with mitochondrial disease or demyelination. Edema of the RGC axons, with or without an extracellular component, is present in ischemia, papilledema, inflammation, and some metabolic (including mitochondrial disease) and toxic processes, but is notably absent in glaucoma. Cell death mechanisms in most other optic neuropathies are incompletely understood.

Critical assessment of similarities and differences between glaucoma and other optic neuropathies may provide insight into mechanisms of injury.

Brain Changes in Glaucoma: Implications for Diagnosis and Treatment

Yeni H. Yucel

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Glaucoma is a neurodegenerative disease of the visual system. In addition to the loss of retinal ganglion cells in the eye, there is injury to major visual pathways of the brain. These central visual system changes are critical to understanding human glaucomatous neural degeneration and disease progression. Compelling neuropathological, neuroimaging and functional evidence regarding brain changes in glaucoma will be presented and their implications for diagnosis will be discussed. In addition to lowering intraocular pressure, pharmacological treatment strategies targeting central visual system degeneration to slow disease progression and prevent vision loss in glaucoma, will be addressed. Finally, the implications of brain changes in glaucoma for regenerative medicine and bionic eye treatment strategies will be discussed.

What Pseudotumor Cerebri Treatment Can Teach Us about Glaucoma Therapy

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Pseudotumor Cerebri is a pressure related phenomenon occurring in a closed cavity that supports neural tissue. It is declared as papilledema, which unfolds into an optic neuropathy. Both glaucoma and pseudotumor are thought to cause embarrassment of anatomy and physiology of retinal ganglion cells expressed as altered appearances of the optic nerve head, changed physiologic integrity of retinal ganglion cells, and, if left untreated, death of those cells. Effects described by Pascal's Law of Fluid Dynamics upon distal optic nerve drive each process. Similarities between pseudotumor and glaucoma are examined and parallels drawn between the results of pressure upon both anatomic integrity and vascular sufficiency of laminar tissues. Both optic neuropathies are managed by medical therapy directed at lowering the inciting fluid pressure – IOP in glaucoma, ICP in pseudotumor. When medical therapy fails in each for whatever reasons, surgery is instigated. In pseudotumor we measure the inciting pressure but once via lumbar puncture to make the diagnosis. After diagnosis, intracranial pressure is not used as a metric of therapeutic success.

In glaucomas pressure is ascertained continually and becomes the compelling metric for therapy rather than the proxy for the disease it actually is. Perhaps glaucoma management could be improved if clinicians monitored neural substrate more, and IOP less. Are Neuro-Ophthalmologists on to something here?

Cerebral Blood Flow in Glaucoma

Alon Harris

Department of Ophthalmology, Eugene and Marilyn Glick Eye Institute Indiana University School of Medicine, Director of Clinical Research, Lois Letzter Professor of Ophthalmology, Professor of Cellular and Integrative Physiology, Indianapolis, Indiana, USA

For decades glaucoma has been associated with vascular diseases such as systemic hyper/hypo-tension, diabetes and migraine. Large population based studies have reported ocular perfusion pressures to be a risk factor for prevalence, incidence and progression of glaucoma while dozens of prospective studies have found low ocular blood flow in glaucoma patients. In addition, some patients with glaucoma show evidence for altered vascular reactivity to stereotyped stimuli, suggesting vasospasm could contribute to the disease process. What is not known is if the contribution of ischemic damage in glaucoma is singular to the retina and anterior optic nerve, or may represent only one aspect of a more generalized ischemic process involving widespread cerebrovascular insufficiency. In this capacity circulatory insufficiency may not be confined within the retina and anterior optic nerve but rather loss of retinal ganglion cells may represent only one manifestation of a more generalized ischemic process that involves the entire cerebral circulation. This presentation will explore the current understanding of ocular and cerebral blood flow research in glaucoma pathophysiology and facilitate discussion on the link between ocular blood flow and cerebral blood flow implications in optic neuropathy. By examining eye and brain interconnectivity to glaucoma through specifically designed prospective studies and mathematical modeling, enhanced screening and novel treatment options may be discovered.

What is Clinical Implication of Slit Lamp Diagnosed MGD?

James McCulley

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Purpose: To assess the evaporative contribution to aqueous tear loss in normals and patients with MGD associated dry eye disease and potential topical anti evaporative preparations.

Methods: 32 eyes of patients with clinical aqueous tear deficiency and associated Meibomian Gland Dysfunction (MGD) had aqueous tear evaporation and tear film break up time (TFBUT) determined at base line, 30 and 60 minutes after installation of an artificial tear containing high concentrations of HP Guar (5x) and one with a lesser concentration of HP Guar (1x) but with an anionic phospholipid in the preparation. Evaporative rates were determined at relative humidity between 25-35% with a specially designed evaporimeter (Oxdata, Portland, Oregon). The impact on tear film breakup time was also determined.

Results: Absolute evaporative aqueous tear loss in normals at baseline was $0.065 \pm 0.022 \mu\text{L}/\text{cm}^2/\text{min}$. and in patients with MGD $0.068 \pm 0.053 \mu\text{L}/\text{cm}^2/\text{min}$. Relative contribution to total aqueous tear loss was $41.66 \pm 23.20\%$ in normals and $57.67 \pm 32.25\%$ in patients with MGD. The HP Guar (5x) artificial tear decreased aqueous tear evaporation at 30 and 60 minutes by 16% and 5% respectively. The HP Guar (1x) with an anionic phospholipid decreased aqueous tear evaporation at 30 and 60 minutes by 14% and 15% respectively. Tear film breakup time improved with both preparations.

Conclusion: Evaporation contributes significantly to aqueous tear loss in normals and patients with MGD, approximately 60% in patients with MGD. Both HP Guar preparations decreased evaporation at 30 minutes after installation however only the anionic phospholipid preparation had a persistent impact at 60 minutes. Both preparations prolonged tear film breakup time.

3 Year Retrospective on Intense Pulse Light for Dry Eye Disease

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Purpose: To determine the clinical benefits of intense-pulsed-light therapy for the treatment of dry-eye syndrome due to meibomian gland dysfunction.

Methods: A retrospective non-comparative interventional case series was conducted of 91 patients presenting with severe dry eye syndrome (eligibility tear breakup time less than 10 seconds). Treatment included intense-pulsed-light therapy and gland expression at a single outpatient clinic over a 30-month study period beginning May 2009. Pre/post tear breakup time data were available for a subset of 78 patients.

For all patients, a specially-developed technique for the treatment of dry eye syndrome was applied as a series of monthly treatments until adequate improvement in dry eye syndrome symptoms by physician-judgment or patient-discontinuation.

Results: Outcomes included change in tear breakup time by Oculus Non Invasive or by Standard Invasive using Fluorescein methods; physician-judged improvement of meibum and lid margin; self-reported patient satisfaction; and adverse events. Physician-judged improvement in dry-eye tear breakup time were found for 68 of 78 (87%) of patients with 7 treatment visits and 4 maintenance visits on average (medians). For the sample of 91 patients, improved meibum and lid margin were found for 94% and 98% of patients, respectively. 93% of patients reported post-treatment satisfaction with dry eye syndrome symptoms. Adverse events - most typically redness or swelling - were found for 13% of patients. No serious adverse events were found.

Conclusions: Study results of intense-pulsed-light therapy treatment for dry eye syndrome are most promising. Further study with a larger sample, treatment comparison groups and randomized controlled trials is warranted.

Haematic Derivates in Ocular Surface Disease

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Purpose: There is increasing evidence of the use of haematic derivates in ocular surface disease such as dry eye and corneal ulcers, but its use in regenerative therapies remain unclear. We analyze the potential use of PRGF-Endoret® as a substitute of xenogeneic sera in corneal cell cultures.

Methods: Plasma rich in growth factors (PRGF) eye drop was obtained using the Endoret (PRGF) kit in Ophthalmology (BTI Biotechnology Institute, S.L., Vitoria, Spain). Briefly, blood was collected from human blood of healthy donors, after informed consent, into 9 mL tubes containing sodium citrate as anticoagulant. Blood was centrifuged at 580g for 8 minutes, whole plasma column was drawn off avoiding the buffy coat, activated with calcium chloride, incubated at 37 degrees for one hour, and finally, the released supernatants were collected by aspiration, filtered and aliquoted and stored at - 80 degrees until use.

Corneoscleral tissue was attained from a local eye bank after penetrant-keratoplasty surgery. Limbal stem cells were obtained from explants of 2-3mm in diameter of the limbal region and cultured in culture medium containing 10% PRGF-Endoret® or 10% of fetal bovine serum for 7 days. Afterwards, cells were fixed in ice-cold methanol and their proliferation was assessed by quantification of the growth area. Immunocytochemistry for p.63 and cytokeratin was also performed in order to check their immunological markers.

Results: Both, PRGF-Endoret® and Fetal Bovine Serum, cell cultures showed a positive expression in p.63 and cytokeratin, however some differences were found between both cultures, while cultures supplemented with Fetal Bovine Serum showed a positive stain for p63 in 73% of the nuclei, PRGF-Endoret® cultures showed a 97% of nuclei stained for p63. Nevertheless, limbal stem cell cultures supplemented with PRGF-Endoret® showed a better growth area in contrast with the ones supplemented with fetal bovine serum. Moreover, there was cellular growth in 80% of the explants cultured in PRGF-Endoret® while only 65% of fetal bovine serum explants had grown.

Conclusions: PRGF-Endoret® seems to improve the cellular growth and, not only maintain the p63 expression, but improve it compared to Fetal Bovine Serum. Therefore, PRGF-Endoret® could be used as a substitute of xenogeneic sera, not only as an allogeneic product but also as an autologous product for the culture and expansion of corneal limbal stem cells.

Early Diagnosis of Sjogren's Syndrome

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Sjogren's disease is a systemic autoimmune disease commonly associated with the loss of salivary gland and lacrimal gland function (present in 30-70 % of cases). Patients may also have a higher risk of developing lymphoma. Diagnosis today for Sjogren's syndrome (SS), based on the revised American European consensus group, includes the following criteria:

- i. Ocular symptoms
- ii. Oral symptoms
- iii. Ocular signs
- iv. Focal sialoadenitis
- v. Salivary gland involvement
- vi. Anti Ro/La antibodies in the absence of head and neck radiation treatment, hepatitis C, AIDS, lymphoma, sarcoidosis, graft versus host disease or anticholinergic drugs.

Diagnosis is based on meeting 3 of 4 objective criteria or 4 of 6 total criteria. However diagnosis of SS can still be difficult, and for many patients it can take years before a diagnosis is reached and treatment can be initiated (estimated time to diagnosis is 4.7 years). In addition, none of the current seriological markers provide an early diagnosis for SS. New research suggests that recently identified antibodies - SP-1, PSP, CA6 - may allow for early diagnosis of SS when Ro and La are still negative. Sampling for these SS biomarkers can now be done in the office by collecting a small sample of blood and sending it to the laboratory for analysis. This in-office testing may lead to an early diagnosis and the opportunity to evaluate early interventions, possibly avoid development of more severe symptoms and signs of SS and improve quality of life.

Tear Osmolarity and Osmoprotection in Dry Eye

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Tear hyperosmolarity is the consequence of both reduced tear production and increased tear evaporation. In dry eye patients it is responsible for the induction of apoptosis and inflammation of the surface epithelia that will contribute to maintain a chronic damage to the ocular surface. Several conditions may induce tear hyperosmolarity, among these environmental and occupational factors. Tear hyperosmolarity can be considered a marker of dry eye and the amelioration of this parameter should be considered by treatments addressing dry eye. Tear hyperosmolarity can be reduced diluting tears by using hypo-osmolar eye drops or using small organic molecules, osmoprotectants, that are used in many cell types throughout the natural world to restore cell volume and stabilize protein function, allowing adaptation to the tear hyperosmolar environment. Osmoprotectants such as erythritol, glycerine, taurine, trehalose and L-carnitine, may directly protect cells against hyperosmolarity and thereby promote the epithelial recovery from the damages induced by hyperosmolarity-driven apoptosis and inflammation.

Novel Ophthalmic Formulations of Liposomes Loaded with Anti-inflammatory Drugs and Omega-3 Fatty Acids for Dry Eye Treatment

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Essential fatty acids, particularly omega-3, have demonstrated to provide beneficial effects for the underlying inflammation in dry eye therapy. Administration of progesterone derivatives with anti-inflammatory properties, such as medroxyprogesterone (mdx), have shown to improve dry eye symptoms. These therapeutic agents can be loaded in liposomal vesicles made of phospholipids similar to the ones present in the lipid layer of the precorneal tear film. Once prepared, liposomes (100 nm size) are dispersed in an aqueous solution of borates, trehalose and hyaluronic acid. Tolerance studies in Human Corneal Inmortalized-Limbal Epithelial Cells (HCLE) rendered cell viability values higher than 80% for short (15min) and long-term (1h and 4h) exposures for the designed formulations. In vitro activation of steroid (glucocorticoid and progesterone) receptors in corneal epithelial cells was observed after treatment with mdx-loaded liposomes. Quality of vision after instillation (50µL) of the novel artificial tear was studied in subjects with occasional dry eye disease. After administration, the TBUT was increased for at least 60 minutes and patients reported no adverse effects. Furthermore, tear osmolarity decreased 7% during the first two hours after administration. The unpreserved ophthalmic formulations based of liposomes can be considered as novel drug delivery systems for dry eye therapy. Support: FIS P113/00516 and P113/00704, UCM Research Group 920415 and RETICS (RD12-0034-003) Oftared.

The Impact of Controlled Adverse Environmental Challenges to the Process of Expedited Drug Introduction

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Background: The process of drug development from concept to marketing has become inordinately lengthy and expensive creating an impediment to the introduction of medication to treat Dry Eye Disease one of the most rapidly increasing cause of ocular morbidity.

Methods: We developed a series of new non invasive and totally objective imaging technologies and deployed them in multimodal fashion in a controlled environment chamber to evaluate ocular surface changes in real time in human subjects.

Results: The utilization of these methods for objective data collection when applied early in the drug selection process can produce statistically significant information with the effect of reducing both time and expenditure associated with the development process.

Conclusions: The ability to derive objective data with statistical significance early in the development of pharmaceutical agents to treat ocular surface disease can result in expediting the concept to marketing process.

Boston Type 1 Keratoprosthesis in Patients with Severe Dry Eye

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Over the past decade the Boston type 1 KPro has emerged as a viable vision rehabilitation procedure for eyes with corneal blindness. Since the United States Food and Drug Administration granted marketing clearance in 1992, the device has undergone multiple design revisions to maximize the outcomes. As of August 2013 8,140 KPros have been implanted worldwide: 5,406 domestically and 2,734. While excellent outcomes have been reported in multiple previous studies, the retention rate is known to be poor in patients with autoimmune ocular surface diseases and severe dry eye. Therefore, Type 2 device is recommended in severe cases of ocular surface diseases particularly from autoimmune etiologies. Unfortunately, this is an uncommonly performed procedure due to the challenging surgical technique as well as a unique complication profile. We report use of novel surgical techniques to salvage a device with significant tissue melt and impending or frank device extrusion, as well as describe a two-step procedure using tarsal or bulbar conjunctival flaps in patients who are predicted to be at risk of poor retention. This approach provides necessary vascular supply to prevent necrosis of the donor and recipient corneal stroma.

Pitfalls in Dry Eye Clinical Trials

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Dry eye disease (DED) represents a significant unmet medical need in the world.

In order to address this unmet need, a number of molecules have been evaluated over the past several years in clinical trials. This review will highlight key learnings from these trials.

Dry eye clinical studies are different than most clinical trials in a number of important ways. First, the placebo response in these trials is typically quite robust. Reasons for the strong placebo response in dry eye trials will be reviewed. In addition, most clinical trials allow for rescue artificial tears, a common treatment used in DED. The impact of this large confounder will be discussed. DED involves subjects with a multitude of different etiologies. It is critically important to identify the target population that is most likely to respond based on the mechanism of action of the drug being tested. In addition, regulatory authorities require an improvement in signs and symptoms of DED. As signs and symptoms do not always correlate, it is important to identify populations of subjects that show an improvement in both signs and symptoms.

Similarly, endpoints chosen need to be consistent with the biology being evaluated and the relevance to clinical improvement in DED patients. Finally, guidelines need to be developed to better define clinically meaningful improvements in signs and symptoms of DED in these patients.

Fibrosis in the Mouse Cornea following Sterile Mechanical Trauma or Infection

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Purpose: The aim of this study was to compare the expression patterns of three important biochemical characteristics of fibrosis-moesin, transforming growth factor (TGF) - β 1 and α -smooth muscle actin (SMA) in the mouse cornea with fibrosis caused by common etiologies-sterile mechanical injury and infection.

Methods: Corneas of 8 week old C57BL6 mice underwent either an anterior keratectomy (AK) wound or infection with *Pseudomonas aeruginosa* (PA), and animals were sacrificed at 2 and 7 days, as well as 2 and 4 weeks after the procedure.

The stroma was isolated and used to monitor the expression and location of moesin, phospho-moesin, and TGF- β 1 by western blotting and immunofluorescence and α -SMA expression.

Results: By western blot analysis, TGF- β 1 and phospho-moesin were not detected in normal corneal stroma. However, after either treatment, TGF- β 1 expression increased, along with phospho-moesin and moesin in the wounded corneal stroma from day 2 to 7, and decreased after 2 weeks. No expression of TGF- β 1 and phospho-moesin was found at PO week 4. Myofibroblasts positive for α -SMA associated with either treatment were detected from day 2 to week 4 and peaked at week 2. Immunostaining data were consistent with western blot data.

Conclusion: The expression patterns of moesin, phospho-moesin, TGF- β 1 and α -SMA in the mouse cornea with fibrosis indicated that the temporal pattern of moesin signaling suggests a role in corneal fibrosis induced by either type of injury. Interfering with the action of moesin is a potential target for interventional strategies to avert corneal fibrosis.

DREAM: Dry Eye Assessment and Management Clinical Trial

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Purpose:

1- To test the effectiveness of Omega-3 supplementation for Dry Eye Disease (DED) in the Primary Clinical Trial.

2- To better understand DED features by observation of a well-characterized group of patients over twelve months.

3- To determine the effects of extended use and discontinuation of Omega-3 supplementation through the Extension Study.

Methods: Primary Trial: Multi-center, double-masked, placebo-controlled, prospective randomized clinical trial with 600 patients at 20 sites. Active (Omega-3) or placebo oral supplements for a year. Subjects selected by OSDI Scores and DED signs. Extension Study: Randomized Withdrawal trial. Subjects recruited from the active group of the Primary Trial and re-randomized to Omega-3 or placebo for another year.

Outcome Measures:

1°Change in OSDI.

2°Changes in signs of DED (corneal and conjunctival staining, TBUT, Schirmer's test) Changes in Quality of life scores Artificial tear use Contrast sensitivity Cost-effectiveness of using Omega-3 Meibomian gland secretion evaluation Exploratory: Keratograph findings: TBUT, Tear Meniscus Height, Redness, Meibography Tear osmolarity Biomarker levels: Tear cytokines, HLA-DR expression.

Results: This is the first NEI funded randomized placebo controlled clinical trial on DED. The outcomes-including biomarkers of inflammation of the ocular surface – will enhance our understanding of DED and its treatment. Trial results will determine the efficacy of Omega-3 and shed light on the role of inflammation in DED. Results are expected in 2015-2016.

Conclusion: DED is a multifactorial disease and the DREAM study will provide significant insights in understanding the role of Omega-3 in treating DED.

Corneal Wound Healing with Neurotrophic Factors

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Purpose: Corneal ulcers remain difficult to treat. Treatment consists of instillation of artificial tears, autologous serum or even growth factors and elimination of toxic agents; however, such treatment may be insufficient. Over the past few years, new types of matrix therapy agents provided encouraging results, accelerating the healing of chronic skin ulcers of diabetic or vascular origin. In the domain of ophthalmology, RGTA (regenerating agent) formulations have been reported to show encouraging results in the treatment of corneal ulcers and dystrophies of various etiologies.

This study purpose is to evaluate the effectiveness of application of CACICOL, regenerative therapy based on heparan sulfate derivatives, in an experimental model of corneal ulcer after photorefractive keratectomy (PRK).

Methods: Mice were subjected to PRK surgery with a 2.0 mm ablation zone on the central cornea and 45 mm of depth on a VISX Star S2 excimer laser. Corneas were treated topically with one drop of CACICOL 1 hour and 48 hours after injury. Control groups received BSS (Balanced Salt Solution) in the same posology. Clinical and histopathological events were evaluated at 1, 2, 3 and 7 days after surgery.

For histological analysis, sections were obtained through the central region of the corneas and used to analyze the general aspect of injured and healed corneas using Hematoxylin and eosin staining. Adjacent sections were used to immunofluorescence analysis using antibodies to Ki67 (proliferation), α SMA (myofibroblast transformation), E Cadherin (assembly of epithelial cells) and neuronal class III β -tubulin (innervation). TUNEL assay was performed to estimate the number of apoptotic cells.

Results: Corneas treated with CACICOL showed a greater degree of transparency compared to BSS treated mice and a higher speed of closure of the wounded area during the first 24 hours. Corneas treated with CACICOL presented a thickness and an epithelial cytoarchitecture, based on E-cadherin labeling, similar to uninjured corneas, indicating a better organized regenerating process. 24 hours after treatment with CACICOL, a marked reduction (~50%) of the apoptotic cell density was observed but CACICOL seemed not to affect the proliferation rate during the wound healing process. Analysis of α SMA profiles in the stroma showed that CACICOL reduced or delayed the presence of myofibroblasts (~58%) in the stroma compared to BSS ($p < 0.001$). Finally we described a putative neuroregenerative effect of CACICOL in corneas submitted to a PRK experimental lesion. Animals treated for 7 days with CACICOL showed an increased epithelial nerve terminal density of 62%.

Conclusions: In a model of laser induced cornea surgical lesions, Heparan sulfate derivatives (CACICOL) topical application could be involved in facilitating the correct assembly of epithelial cells, improving nerve regeneration, avoiding myofibroblast scarring formation or promoting the deposition of newly generated extracellular matrix.

Growth Factors and Interleukins in Amniotic Membrane Suspension AMS

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Purpose: Amniotic membrane suspension (AMS) eye drops were suggested as a potential treatment alternative for therapy resistant corneal epithelial defects. The purpose of this study was to determine the concentrations of growth factors EGF, NGF, VEGF, TGF β 1, FGFb, HGF, KGF and interleukins IL-1 β , IL-6, IL-8 in AMS following different preparation methods and time periods.

Methods: Amniotic membranes of 10 placentas were prepared and thereafter stored at -80°C using the standard method of our LIONS Cornea Bank. Following defreezing, amniotic membrane pieces with a standard size were inserted in a 12-well plate either complete or cut in small pieces, and 2000 μ l DMEM culture medium was added. EGF, NGF, VEGF, TGF β 1, FGFb, HGF, KGF, IL-1 β , IL-6 and IL-8 secretion into the culture medium was determined following 8, 48 and 96 hours and, in a new preparation, following 1, 2, 3 and 4 weeks of incubation using enzyme-linked immunosorbent assay (ELISA).

Results: Secretion of NGF, VEGF, TGF β 1, HGF, KGF and IL-1 β was beyond the detection limit at all the time points. For both complete and small-cut membranes, the concentration of EGF increased from 8 hours to 4 weeks ($p=0.025$), FGFb decreased from 8 hours to 4 weeks ($p=0.018$). In small-cut membranes, IL-6 concentration increased significantly from 8 hours to 1 week ($p=0.012$). From 2 to 4 weeks there was again no significant difference to baseline. In complete membranes, IL-6 concentration decreased significantly from 8 hours to 4 weeks ($p=0.012$). The concentrations of IL-8 over time were similar, but ranged on a higher level than that of IL-6. Comparing complete and small-cut membranes EGF ($p1.95$) and FGFb ($p0.34$) secretion did not differ significantly from baseline at any time point. A significant difference between both preparation methods was shown for the IL-6 concentration after 8 and 48 hours ($p0.001$; $p=0.01$) and in IL-8 concentration after 8 and 96 hours and after 3 weeks ($p=0.02$; $p=0.002$; $p=0.027$).

Conclusion: Containing EGF and FGFb, IL-6 and IL-8, amniotic membrane suspension AMS is a potential non-surgical treatment alternative of therapy resistant corneal epithelial defects. However, the most effective preparation method and the optimal harvesting time point are yet to be determined.

A Drug Eluting Contact Lens

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Objective: To report the development and performance of a drug-eluting contact lens.

Methods: Latanoprost-eluting contact lenses were created by encapsulating latanoprostopoly (lactic-co-glycolic acid films in methafilcon by ultraviolet light polymerization. Release kinetics were evaluated in vitro and in vivo.

Results: In vitro studies showed an early burst of drug release followed by sustained release for one month. The lenses appeared safe in cell culture and animal studies. In vivo, single contact lenses were able to achieve, for at least one month, latanoprost concentrations in the aqueous humor that were comparable to those achieved with topical latanoprost solution, the current first-line treatment for glaucoma.

Conclusions: This contact lens design can potentially be used as a treatment for glaucoma and as a platform for other ocular drug delivery applications.

Topical NSAIDs in Dry Eye Disease - 3 Year Retrospective

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Background: For years Ophthalmologists have been reluctant to use topical NSAIDs in patients with Dry Eye Disease. This reluctance comes from the knowledge that some corneal melts in the late 90's were caused by the use of topical NSAIDs in cataract surgery. In one retrospective study done by Flach et al of 11 patients with corneal melts it was assumed that 2 patients had dry eye because they had punctal plugs. From this one observation a great hesitancy to use any topical NSAIDs in any dry eye patient has happened. Our clinic has used new topical NSAIDs effectively to help dry eye patients improve the signs and symptoms of dry eye.

Methods: A retrospective look at over a 100 confirmed dry eye disease patients with meibomian gland dysfunction who have been on topical NSAIDs (ketorolac, nepafenac, or Bromfenac) once a day for a least a three month period. We documented any adverse events like corneal melts, worsening symptoms, and allergies.

Results: No patients on topical NSAIDs for dry eye experienced a corneal melt. Less than 15 percent of patients reported an allergy or discomfort with the first initial NSAIDs prescribed but were switched to another NSAIDs without any incident. 3 percent of patients stopped using NSAIDs because they reported no significant benefit.

Conclusion: It is safe for MGD DED patients to use topical NSAIDs once a day. A great majority if patients report that using a brand name NSAID provides relief of symptoms.

A prospective study looking to see if a once a day topical NSAID improves the signs of DED is warranted.

Rationale for the Treatment of Ocular Surface Diseases with Targeted Biotherapeutics

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Treatment of ocular surface diseases, such as allergic conjunctivitis (AC) or dry eye disease (DED), have traditionally involved the use of topically applied small molecule drugs, e.g. anti-histamines and mast cell stabilizers for AC and cyclosporin or corticosteroids for DED. These therapies can be efficacious in some of the disease population but not all and can have local, sometimes sight threatening, side effects, for example increasing the risk of glaucoma with steroid use. More recently, with a better understanding of biological pathways, protein therapeutics with high target specificity have transformed the treatment of disease in oncology, inflammation, autoimmunity, metabolic disease, and retinal ophthalmic disease. In ophthalmology, anti-VEGF therapies, have improved vision of patients with wet age-related macular degeneration when previous treatments only partially delayed onset of vision loss. The efficacy of treatments is the result of altering specific target-mediated pharmacology. Dry eye disease (DED) and severe allergic conjunctivitis (severe AC) are ocular surface inflammatory disorders that are mediated by IL-1 (IL-1 β and IL-1 α). IL-1 not only mediates a pathological ocular surface response (sign), but also likely has direct effects on the corneal nerve plexus driving a hyperalgesia resulting in pain and discomfort (symptoms) that drives patients to see their physicians. Specific blockade of IL-1, typically requiring a biologic, is rare in having a prominent role in both the signs (ocular surface damage) and symptoms (pain and discomfort) of DED. IL-1 also may mediate much of inflammatory response in severe AC. A protein therapeutic targeting the IL-1 pathway has the potential to change the treatment paradigm for with a safe and effective treatment of DED and severe AC, both having distinct unmet medical needs.

Extending Cone Survival and Function in Retinal Degenerations

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Inherited retinal dystrophies (IRDs) affect approximately one in every 3000 individuals and are the most frequent inherited forms of human visual handicap. Despite the recent advances in gene therapy, the tremendous genetic heterogeneity of IRDs represents a major obstacle in developing this therapeutic approach in IRDs. In most types of retinitis pigmentosa (RP), the commonest IRD, mutations selectively affect rod but not cone cells. Nevertheless, cones slowly degenerate secondarily to the death of rods, pointing on the crucial importance of cone photoreceptors in human vision. Therefore, extending cone survival represents an alternative approach that can offer sight-restoring treatment for visually impaired and blind people. An attractive candidate for prevention and treatment of retinal degeneration is the protein Rod-derived Cone Viability Factor (RdCVF), which is specifically expressed and secreted by rod photoreceptors.

RdCVF has been shown to directly induce cone survival in animal models of RP with an interesting effect on outer segment preservation, and functional rescue independent of the mechanism and extent of rod degeneration has been documented. Restoring cone function by optogenetic is another innovative approach for treating retinal degeneration. It is based on converting different retinal cell types into "artificial photoreceptors" by genetically targeting them to expressed light sensors. Artificially stimulated retinal activity enabled rd mice to perform visually guided behaviors and restored light responses in human post mortem photoreceptor cells were documented. Restoration of the visual function of optogenetically-transduced "dormant" cones is currently under pre-clinical evaluation, while RdCVF is now in translation as a potential therapeutic agent to save cones and treat a spectrum of degenerative eye diseases.

Next Generation Sequencing for Retinal Degeneration

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Inherited retinal disorders (IRD) are clinically and genetically heterogeneous with more than 150 implicated gene defects and several other to be discovered. Over the past two decades, approaches including linkage and homozygosity mapping, Sanger sequencing, microarray analysis of known mutation were used to investigate the underlying gene defect of IRDs. Despite many advantages, the above-mentioned technologies have limitations in term of time, cost, sensitivity and necessity of requiring "ideal" family structure. With the outcome of next-generation sequencing, high-throughput screening have open the way to unbiased methods to encompass genetic heterogeneity with limited cost. We have previously developed a retinal gene panel applying next generation sequencing (NGS), which was subsequently validated and enhanced to improve the coverage of targeted genomic regions restricting targets to the most relevant genes underlying progressive inherited retinal disorders. We applied this technique to a large IRD cohort and present prevalence of gene defects in this cohort after relevant filtering. Ideal families with no underlying gene defect using this strategy are selected for whole exome sequencing (WES). Doing so, we identified a gene underlying autosomal recessive rod-cone dystrophy (RCD), KIZ, coding for kizuna, a centrosomal protein. Our results on this new finding will be given as an example of the use of WES to identify novel gene defect.

Retinal Progenitor Cell Transplantation for Treatment of Retinal Degeneration

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The isolation of retinal progenitor cells (RPCs) and transplantation to the retina of recipients with retinal degenerations has revealed the therapeutic potential of this approach in the setting of otherwise incurable blinding diseases. The mechanism of action can involve trophic-mediated neuroprotection of host photoreceptors or integration into the host retina and differentiation into retinal cell types such as photoreceptors. Much prior work has been done to distinguish the RPC as a therapeutic candidate of interest. The ongoing project extends this work to the GMP production of human RPCs, formal IND-enabling preclinical studies and upcoming clinical trials. There is much to recommend this approach, including simplicity, safety, and particularly the potential for cell-mediated efficacy in currently untreatable blinding diseases.

Stem Cells as Therapeutic Agents for Retinal Degeneration: Clinical Trials

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After more than a decade of research in animal models, stem cell transplantation is now advancing into early clinical trials in the eye. Multiple programs are now testing a variety of cell types in a number of retinal diseases. In addition, quite a few more programs are on the cusp of entering trials within the next year or so. While it is premature to predict the outcome of these efforts, early indications suggest that safety might not present as large a challenge as originally feared, at least for some of the cell types being tested and under the specific criteria used. There is also room for optimism that evidence of efficacy will emerge from this current burst of activity in the field.

Gene Therapy for Stargardt Disease

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Stargardt disease is the most common cause of macular degeneration and central visual loss in young people. Currently, there is no known effective treatment that can prevent or reverse the vision loss in this disease. The disease is caused by mutations in the photoreceptor-specific ABCA4 gene coding for a protein involved in the active transport of retinoid from the photoreceptors to the underlying retinal pigment epithelium to initiate the visual cycle. Pre-clinical studies on animal model of Stargardt disease have shown effects on subretinal administration of viral vectors containing the human ABCA4 gene upon lipofuscin accumulation, the hall mark of the disease, thus providing evidence of the potential therapeutic efficacy of gene therapy.

Indeed, the first-ever gene-based therapy Phase I/II clinical trial for treatment of Stargardt disease, StarGen™, is currently underway (NCT01367444) at the Casey Eye Institute, Oregon Health & Science University, US and the Centre Hospitalier Nationale d'Ophthalmologie des Quinze-Vingts, Paris, France. We will discuss the principle and issues raised the current trial as well as potential alternative therapies.

Initial Clinical Evaluation of Safety, Tolerability and Pharmacodynamics of AMA0076, a ROCK Inhibitor for the Treatment of Glaucoma

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A First-in-Human (FIH) study with an initial AMA0076 formulation and a subsequent Phase 1b study with optimized formulations were completed. The FIH study was a multicenter, randomized, double-masked, placebo-controlled dose-escalation study with AMA0076 (or matching placebo) applied topically for 28 days in 82 POAG/OHT patients aged 30-85. The Phase 1b study was a single center, randomized, double-masked, placebo-controlled, repeat-dose, 3 period cross over study in which 21 healthy male and female subjects aged 35-65 were randomized. Each treatment period in the Phase 1b study entailed 1 week of BID topical ocular administration (14 active: 7 placebo) with a washout period of 1 week between treatment periods. Safety evaluation in both studies included AE reporting, vital signs, ECG, laboratory, and visual acuity assessments. Both studies also included biomicroscopy, hyperemia grading (according to a standardized photographic scale), and IOP determinations obtained at baseline and end of treatment at the same diurnal timepoints (pre-dose, 2, 4, and 8 hours post-dosing).

AMA0076 was safe and generally well tolerated in both studies. No SAEs were reported. There was no discernible difference in non-ocular AEs or other systemic assessments (vitals, ECG, laboratory) by treatment group in either study. All ocular AEs in both studies resolved without sequelae. At the optimal IOP-lowering dose in each study, all ocular AEs were rated as mild in intensity, with a rate of mild, transient hyperemia in the FIH study and the Phase 1b study of 0% and 28.6%, respectively. In these dose regimens, a decrease in mean diurnal IOP compared to placebo was achieved (p=0.020 and p0.005, respectively).

The optimal dose of AMA0076 demonstrated IOP reduction without significant hyperemia in both clinical studies. No other ROCK inhibitor has demonstrated this finding in the clinic. Therefore, AMA0076, due to its Localized Drug Action, has the potential to optimize the use of ROCK inhibition to lower IOP in patients with glaucoma and ocular hypertension.

Conduct of Early Feasibility- First in Human Studies in the US

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In an effort to encourage medical device innovation in the US and as well as a patient's access to clinical trials and treatments, FDA has released its final guidance on Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies (<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf>).

This guidance outlines two important operating principles regarding the application for and approval of early feasibility study IDEs:

1. FDA's approval of an early feasibility study, including some first-in-human studies, may be based on less nonclinical data than would be expected for other types of studies (e.g., traditional feasibility or pivotal).
2. Implementation of device and clinical protocol modifications should be facilitated during an early feasibility study.

The guidance outlines new emphasis, concepts and approaches:

- a. Emphasis is placed on the unique aspects of the device design and intended patient population.
- b. The concept of 'just in time testing' (JIT), that is, the appropriate type and timing of nonclinical testing needed to justify early feasibility clinical study initiation, is applied when developing and reviewing the Report of Prior Investigations.
- c. Emphasis is placed on appropriate patient selection, clinical mitigation strategies, and informed consent when developing and reviewing the Investigational Plan.
- d. The guidance introduces new approaches for modifying early feasibility studies already underway.
- e. After obtaining clinical information from an EFS, the type of subsequent clinical evaluation (e.g., expansion of the EFS, traditional feasibility, pivotal) will depend on whether changes in the device design are expected, the availability of adequate data to justify the next study, and the purpose of the clinical study.

This guidance and the accompanying program is aimed to encourage early feasibility studies (EFS) in US, provide continuity from early clinical use through pivotal studies to approval in the US and reverse trend of innovation moving outside of the US.

Double-Masked, Randomized, Dose-Response Study of AR-13324 Ophthalmic Solution Compared to Latanoprost in Patients with Elevated Intraocular Pressure

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Purpose: AR-13324 is a new class of ocular hypotensive that inhibits both Rho kinase and norepinephrine transporter to increase trabecular outflow and decrease aqueous production. Study objectives were to evaluate the hypotensive efficacy and ocular and systemic safety of AR-13324 compared to latanoprost.

Methods: Patients with open-angle glaucoma or ocular hypertension were randomized to AR-13324 0.01%, 0.02% or latanoprost, q.d. (PM), for 28 days.

Results: 224 patients were randomized (baseline IOP's 22-36 mmHg). Mean diurnal baseline was 25 to 26 mmHg across groups. On Day 28 mean diurnal IOP decrease from baseline was 5.5, 5.7 and 6.8 mmHg in AR-13324 0.01%, 0.02% and latanoprost respectively (p 0.0001). The difference between AR-13324 0.02% and latanoprost was 1.2 mmHg (p=0.009). In a pre-specified analysis of patients with baselines 26mmHg (n=106) the difference was 0.2 mmHg (p=0.754), demonstrating AR-13324 equivalence to latanoprost due to AR-13324 maintaining efficacy regardless of baseline, while latanoprost lost efficacy at lower baselines. The only safety finding of note for AR-13324 was mild to moderate conjunctival hyperemia.

Discussion: AR-13324 0.02% produced clinically and statistically significant reductions in IOP and was approximately 1mmHg less effective than latanoprost in patients with baseline IOPs in the range of 22 – 36 mm Hg. However AR-13324 0.02% was equivalent to latanoprost in patients with baseline IOPs in the range of 22 – 26 mmHg.

Conclusion: In this 28-day study, AR-13324 was effective and well tolerated in patients with glaucoma and ocular hypertension.

Extended Release Injectable Therapeutics - Small and Large Molecules

Michael J. O'Rourke
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This talk will focus on GrayBug's recent work towards the development of proprietary products based on injectable polymer-based drug delivery systems that provide long-lasting treatment of various diseases that affect vision, including w-AMD and glaucoma. Our ocular neovascularization program is focused on development of the longest-lasting and most effective anti-angiogenic agents in the industry, including regression of choroidal neovascularization. Our lead product, GB-102 for ocular neovascularization including wet-AMD, provides long-term sustained delivery of a single agent that potentially inhibits the action of both VEGF and PDGF and leads to extended efficacy.

Our drug delivery technologies include:

- 1) A biodegradable polymer-drug conjugation technology. Proof-of-concept data for two small molecule drugs have been obtained, including a long-lasting IOP lowering drug for glaucoma and a hypoxia inducible factor 1 inhibitor for potent inhibition of new blood vessels. Results were published in 2013.*
- 2) A biodegradable poly(lactic-co-glycolic acid) (PLGA) based micro and nanoparticle drug delivery system, compatible with delivery of all classes of drugs including small molecules, proteins, peptides, and other biologics. Our technology solves the inflammation problem of PLGA microparticles injected intravitreally utilizing proprietary formulation methods. This technology includes the rare combination of high drug loading and long-term delivery, is designed to keep the particles at the injection site away from the visual axis, and permits drugs to be delivered via small gauge needles.

GrayBug's intraocular controlled-release technologies are aimed at reducing dosing frequency to only 1-3x per year, depending on disease and drug, which is expected to reduce the burden and complications inherent with frequent injections, while improving patient compliance and treatment efficacy.

* T. Iwase et al. *Journal of Controlled Release* 172 (2013) 625-633.

RNAi Based Therapies for Ocular Conditions

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Sylentis is a Spanish biopharmaceutical company focused on developing compounds based on RNA interference for conditions of the anterior segment of the eye. Preclinical and clinical proof-of-concept has been achieved for glaucoma and ocular pain associated to dry eye. SYL040012 is a 21 nucleotide small interference RNA (siRNA) targeting beta 2 adrenergic receptor (ADRB2) and thus reduce production of aqueous humor. SYL1001 is a 19 nucleotide siRNA targeting TRPV1, a well-known nociceptor present in cornea and nerve terminals that innervate the cornea. Application of either siRNA in eye drops to animal models results in rapid absorption and distribution of the compounds into the anterior segment the eye. Very low levels of siRNA are found in systemic circulation or systemic tissues (1ng/g tissue). SYL040012 has shown to reduce IOP in normotensive and hypertensive animal models; and this hypotensive effect is accompanied by reductions of approximately 40% of ADRB2 at the ciliary body. The results of the three clinical trials performed for SYL040012 showed that the siRNA has an excellent tolerance profile and that the dose of 300 ug/eye/day causes a statistically significant reduction in IOP when compared to placebo and to basal values.

SYL1001 was shown to have analgesic effects in the capsaicin induced ocular pain rabbit model. One clinical trial has been completed for SYL1001, in said trial SYL1001 was very well tolerated and no ocular or systemic issues. An additional trial is ongoing in which safety and effect on ocular pain is being compared to placebo.

The Ophthalmic Squeeze Dispenser (OSD): A Flexible Multi-Dose Solution for Unpreserved Eye Drops

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Background: Current knowledge supports the use of unpreserved eye drops for chronic treatments. In Europe, the authorities have recognized the potentially harmful effects of preservatives on the eye. The Ophthalmic Squeeze Dispenser (OSD), a multi-dose device for unpreserved eye drops, is a flexible and safe solution for artificial tears and formulations with active ingredient.

Methods: OSD is designed similar to a common squeeze bottle shape in order to support consumer acceptance and patient compliance. The dispenser uses only mechanical measures to prevent microbial contamination of the product. Key technology is the so called "tip seal technology", in addition to sterile filtration of the venting air. The spring loaded tip seal reliably prevents entrance of microbes into the system. This was demonstrated in various challenging tests, featuring different settings and high microbial burden. The particulars of the tip seal technology however require higher actuation forces compared to conventional, preserved multi-dose droppers. In order to keep the actuation force in an acceptable range, a range of technical options are available, the components of the OSD can easily be adapted to the properties of the formulation. Options are changing the internal flow control, design and material of the spray pin, introduction of a filter protection valve as well as different bottles.

Conclusions: A wide range of artificial tear products are commercially available now in Europe and products containing active pharmaceutical ingredients are under development. The flexible OSD technology provides the basis for a successful development of unpreserved multi-dose eye drops.

Targeted Biologics in Posterior Chamber Ocular Disorders

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The incidence of retinal disease is increasing with our aging population and as a co-morbidity with other diseases such as diabetes. Cytokines and growth factors are important mediators of the processes that drive retinal disease. Protein therapeutics that block VEGF and are administered intravitreally have transformed the treatment of wet age-related macular degeneration (wAMD) and are efficacious in some patients with diabetic macular edema (DME). Clinical studies testing the ability to systemically treat posterior ocular disorders with protein-targeting therapeutics such as anti-IL-17, anti-IL-6 receptor and anti-tumor necrosis factor antibodies have bolstered the idea that the inhibition of cytokines and growth factors may be promising approaches to treating these back of the eye diseases. Levels of cytokines such as IL-6 are elevated in humans with DME and blockade of IL-6 inhibits disease progression in animal models of diabetic retinopathy. As a result, Eleven Biotherapeutics focuses on the design and engineering of biologic inhibitors of signaling through cytokines such as IL-6 and IL-17. These protein-based, cytokine inhibitors are optimized for intravitreal administration and are being developed as treatments for DME and uveitis, respectively.

Comparative Risk of Conventional Immunosuppressive Drugs versus Biologics

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Patients with chronic, sight-threatening uveitis often require long-term systemic therapy in order to suppress the intraocular inflammation, limit structural ocular complications, and preserve visual function. Although a subset of these patients may be controlled on low-doses of daily corticosteroid, many will require additional therapy with immunosuppressive drugs to achieve optimal clinical outcomes, reduce or eliminate the daily dosage of corticosteroid, or both. The numbers of immunosuppressive drugs used in the treatment of uveitis have increased considerably including the use of a growing number of biological drugs. The effectiveness and side effect profiles of conventional immunosuppressive drug and biologics commonly used to treat chronic, sight-threatening uveitis will be reviewed.

Macular Edema: Pathogenesis and Treatment

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For most types of uveitis, macular edema is the major complication. This review will at first present the most important aspects of the pathophysiology of uveitic macular edema. The role of the blood-retina barrier with the physiological water influx will be discussed. Changes of the barriers and of ion channels can then result in extracellular and intracellular macular edema. In the second part strategies against macular edema will be presented, starting with corticosteroids and acetazolamide, finally leading to more experimental, but highly effective drugs like interferon alpha.

Gene Polymorphisms in HLA B27 associated Uveitis and Intermediate Uveitis

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Polymorphism in the promoter part of the genes controlling cytokine or chemokine production may lead to clinically relevant alterations in cytokine expression to a given endogenous or exogenous agent. Thus they may influence disease development and the clinical course of the disease. We determined gene polymorphisms in 114 patients with HLA B27 associated uveitis and 85 patients with intermediate uveitis, to evaluate the role of gene polymorphisms in the MCP-1, TNF alpha, IL-2RA, IL-10 and Vit D gene in these uveitis entities. The genotypes were determined by polymerase chain reaction. Polymorphisms leading to a possible reduction in cytokine or chemokine production were more frequently found in HLA B27 associated uveitis, when compared to controls or intermediate uveitis, were as gene polymorphisms that were associated with a possible increase in the immune response were found more frequently in intermediate uveitis patients.

In conclusion our results suggest that in HLA B27 associated uveitis a possible state of a relative immune deficiency might be pathogenic in this disease entity unlike in intermediate uveitis

Preclinical Studies of Soluble EphB4-HAS as a Therapeutic in Neovascular ARMD

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Background: EphB4 and its ligand, EphrinB2 critically regulate new vessel formation. Inhibition of EphB4-EphrinB2 signaling suppresses angiogenesis. The purpose of this study was to evaluate the effect of intravitreal administration of soluble EphB4 fused to human serum albumin (sEphB4-HSA) on the pathogenesis of laser-induced choroidal neovascularization (CNV).

Methods: Laser-induced CNV was induced in Brown Norway pigmented rats. Four photocoagulation lesions were delivered with a diode green laser (140 mW, 0.05s, 75 microns) to the posterior pole in both eyes. sEphB4-HAS (0.2, 0.6, 2 or 6 micrograms), or vehicle was injected into the vitreous at day 3 and d7 post-laser. Fluorescein angiograms (FA) were evaluated semiquantitatively. CNV volume quantification was performed on retinal flat mounts stained with fluorescein-conjugated isolectin B4 using confocal microscopy at post-laser d14. A yeast two hybrid screen was performed to study the interaction of EphB4 with other proteins. The interactions of EphB4 with candidate interacting proteins were verified in yeast two hybrid system and also using 293T cell co-immunoprecipitation experiments.

Results: Evaluation of CNV lesions revealed that intravitreal sEphB4-HSA injection resulted in a dose-dependent inhibition of leakage on FA, concomitant with a significant reduction in CNV volume, when compared to controls. EphB4 showed interaction with three fibronectin coding clones in the yeast two hybrid screen. The interaction was further confirmed by co-expression of tagged EphB4 and fibronectin.

Conclusions: Intra-vitreous injection of sEphB4-HSA suppresses laser induced CNV. sEphB4-HSA efficacy is considered to be particularly high due to the observed binding to fibronectin that localizes to the vessel wall. The present studies suggest that sEphB4-HSA should be investigated further as a potential new therapy of CNV.

Targeting VEGF-Signaling in Specific Retinal Cell Types to Safely Inhibit Retinal Neovascularization

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Purpose: Despite success in adult retinovascular diseases with agents inhibiting vascular endothelial growth factor (VEGF), safety concerns exist for retinopathy of prematurity (ROP). We adapted a model of ROP to test safety and efficacy from targeted knockdown of Mueller-cell derived VEGF and splice variant VEGF164.

Methods: We created short hairpin RNAs with GFP tags to silence VEGFA (shRNA-VEGF), VEGF164 (shRNA-VEGF164) or control luciferase (shRNA-luc). To target overexpressed VEGFA or VEGF164 in Mueller cells, shRNAs were cloned into a plasmid with a CD44 promoter that was specific to Mueller cells and delivered as 1 μ L subretinal lentivectors into the rat model of ROP at postnatal day (p)8. GFP of transduced cells was visualized in vivo with the Micron fundus camera. At p18 and p25 measurements were: intravitreal neovascularization (IVNV) and percent avascular retina (AVA) in lectin-stained retinal flat mounts; TUNEL positivity and retinal thickness in retinal cryosections; and protein in fresh retinas.

Results: shRNA-VEGFA and shRNA-VEGF164 reduced retinal VEGF at p18 and p25. Compared to shRNA-luc, IVNV was reduced by lentivector shRNA-VEGFA and shRNA-VEGF164 at p18, but only by shRNA-VEGF164 at p25. shRNA-VEGFA caused more TUNEL positive cells at p18 and thinned the outer nuclear layer (ONL) at p18 and p25.

Conclusions: Targeted knockdown in Muller cell-VEGFA or VEGF164 effectively reduced IVNV at p18, but only shRNA-VEGF164 maintained this effect without increasing cell death or thinning the ONL at p25. Future studies are needed to determine the effect of Muller cell knockdown of VEGFA and VEGF164 on retinal structure and function.

Arachidonic Acid Metabolites as Pharmacotherapeutic Targets for Retinal Neovascularization

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Liberation of arachidonic acid from membrane stores by cytosolic phospholipase A2 (cPLA2) allows for its enzymatic conversion by three primary pathways: cyclo-oxygenase (COX), leading to prostanoic acid production; lipoxygenase (LOX), leading to leukotrienes and HETEs; and cytochrome P450 (CYP), leading to epoxyeicosatrienoic acids (EETs). Each of these three families of lipid signaling molecules has its own profile of pleiotropic activities, and all can play roles in regulating angiogenesis. This presentation will place emphasis on the most (COX) and least (CYP) well understood pro-angiogenic signaling pathways involving arachidonic acid metabolites. To date, our comprehensive survey of prostanoids and prostanoic acid receptors has identified PGE2 receptor EP4 as a prominent mediator of retinal angiogenesis. PGI2 and PGD2 also display significant pro-angiogenic activity, but EP4 antagonists clearly demonstrate the predominant role of PGE2/EP4 in the context of retinal disease, distinguishing it from the well-characterized role of PGE2/EP3 in modulating colorectal tumor angiogenesis. Conversely, the role of CYP-derived EETs in tissue angiogenesis has only recently been discovered and very little is known about their pro-angiogenic activity in any tissue. Our present work using the oxygen-induced retinopathy model marks the first attempt to employ chemotherapeutic modification of EET tissue production to understand their roles in retinal angiogenesis. We will present data from chemotherapeutic intervention and genetic manipulation studies related to all three arms of arachidonic acid signaling using well-established models of retinal angiogenesis. Further, we will identify pro-angiogenic arachidonic acid metabolites of relevance to retinal neovascular diseases.

Gene Therapy for Diabetic Retinopathy

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Diabetic retinopathy is the leading cause of blindness in the working-age population. Hyperglycemia induces endothelial damage to retinal vessels creating hyperpermeable vasculature and an ischemic retina. Currently, no therapies exist for stabilizing the vasculature in diabetic retinopathy. Here we show that a single intravitreal dose of adeno-associated virus serotype 2 encoding a stable, soluble form of Ang1 (AAV2.COMP-Ang1) ameliorated structural and functional hallmarks of diabetic retinopathy in the Ins2Akita mouse model of Type 1 diabetes with sustained effects observed through six months. AAV2.COMP-Ang1 increased VE-cadherin expression and decreased VEGF-A expression in the Ins2Akita mouse retina. COMP-Ang1 preserved vascular network area comparable to non-diabetic control levels, despite persistent pericyte dropout. Furthermore, AAV2.COMP-Ang1 therapy prevented retinal thinning and ganglion cell layer dropout. Most importantly, diabetic mice treated with COMP-Ang1 retained near-normal visual acuity and electroretinographic response. AAV2.COMP-Ang1 may be useful in promoting vascular normalization by reducing ischemia and hyperpermeability in diabetic retinopathy.

Full-Field- 3D OCT- based Update on Pathophysiology and Apparent Treatment of Diffuse Diabetic Macular Edema

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Background: The long-term therapeutic efficacy of diffuse diabetic macular edema (DDME) is still relatively poor.

Methods: Summary of recent literature on DDME and OCT by the aid of PubMed.

Results: Evaluating DDME, full-field- 3-D OCT at the area centralis enables imaging of the whole field of interest. It may illustrate a wide area of the posterior hyaloid and its contact site(s) with the retina /ONH in case of incompletely detached posterior hyaloid resulting in extrafoveal traction. We earlier (2010) described that 1/3 of DDME eyes (n=58) were associated with extrafoveal traction. In contrast, B-scans would show one or even several vertical slices of the field, and "cubes" of few SD-OCTs present local images, but association of extrafoveal traction with the diffuse and central edema would commonly be erroneously interpreted.

We further described that tractional phenomena (including vitreofoveal traction and ERM) were detected in more than 75% of DDME eyes, and PPV should then be considered. The multicenter EVRS study (n=870, Dresden 2012: <http://www.evrs.eu/2012-evrs-congress-dresden/>), the only large study comparing PPV with intravitreal anti-VEGF or steroids, indirectly fortified this OCT-based understanding, showing substantial superiority of PPV over the medications.

Furthermore, after excluding extrafoveal traction we treated non-tractional, non-ischemic DDME eyes with central edema by grid laser photocoagulation (2013). After 16 months (mean), 26% (mean) reduction of central edema was achieved in 77% of eyes. Further, causes of recurrent edema were commonly tractional.

Conclusions: Based on full-field- 3-D OCT: A) DDME is typically associated with traction; B) non-tractional DDME responded efficaciously to GLP.

Full-Field- 3-D OCT is Essential for Successful Grid Laser for Diffuse Diabetic Macular Edema (DDME)

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Purpose: We present a group of diffuse DME eyes in which grid laser photocoagulation (GLP) was efficacious after mid-term follow-up. It has been achieved after excluding eyes with extrafoveal vitreous traction, as detected by full-field 3-D spectral-domain optical coherence tomography (FF- 3D-OCT).

Methods: Included in the GLP retrospective study were DDME eyes that had 4-24 months' follow-up. Using FF- 3D-OCT, eyes that had vitreofoveal or extrafoveal traction, epiretinal or Evi membrane, or had been previously treated intravitreally were excluded. 30 analyzed eyes were divided into 3 groups: A) "Classic" DDME that involved the central macula; B) edema did not involve the central macula; C) DDME was associated with macular capillary dropout ≥ 2 disc-diameter (DD).

Results: Group A) 18 "classic" DDME. Following 1.2 GLPs during 15.9 ± 7.4 months, BCVA improved by 1-2 Snellen lines in 44.4% (8/18) and worsened by 1 line in 11% (n=2), and central macular thickness reduced by 26.6% in 77.8% (14/18) of eyes. Failures (n=4) was mainly (n=3) associated with an emergence of extrafoveal traction secondary to new incomplete PVD at months 5-9. B) BCVA improved by 1-2 lines in 2/6 eyes during 11.8 ± 7.3 months' follow-up. C) GLP was of partial benefit in 2/6 eyes (f-up, 8 ± 3.5 months).

Conclusions: The relatively high success rate of GLP in "classic" DDME during mid-term follow-up was possible by avoiding GLP from eyes with extrafoveal vitreous traction, a previously overlooked, common phenomenon in DDME. Unequivocal detection of extrafoveal vitreous traction is frequently possible only by the use of a FF- 3D-OCT.

Gap Junction Channel Blockers – Saving Sight by Reducing Vascular Leak

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Gap junction channels have been implicated in lesion spread following injury, and application of gap junction blockers has been shown to improve healing by preventing vascular disruption and/or restoring vascular integrity. This presentation focusses on the involvement of vascular permeability in ocular inflammatory conditions and highlights the potential of Connexin43 (Cx43) gap junction blockers to preserve vision. Cx43 specific antisense oligodeoxynucleotides were applied to non-healing ocular chemical or thermal burns that had been unresponsive to established best practice clinical management (Ormonde et al. 2012). Following treatment a reduction in inflammation, recovery of the vascular bed and limbal reperfusion were seen and full ocular surface restoration was achieved in all five patients. In glaucoma patients vascular leakage can generally be seen by fluorescein angiography. Using a retinal ischaemia-reperfusion rat model the onset of vascular leak was shown to coincide with increased Cx43 expression correlating with reduced blood flow and areas of vascular disruption (Danesh-Meyer et al. 2012). Intravitreal injection of Cx43 mimetic peptides reduced associated vascular leak which in turn dampened inflammation and subsequently reduced retinal ganglion cell loss. This was particularly evident when using chemically modified peptides with increased stability or peptides packed into polymeric particles to achieve sustained release over prolonged periods. Efficient delivery of gap junction channel blockers has potential to benefit both acute and chronic ocular disorders showing signs of vascular disruption or vessel dropout, including age-related macular degeneration and diabetic macular edema, opening up novel treatment options for these sight threatening diseases.

Dexamethasone Intravitreal Implant (Ozurdex®) in Refractory Diabetic Macular Edema. Clinical Practice

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Purpose: To evaluate the efficacy and safety of Ozurdex® for the treatment of refractory diabetic macular edema (rDME).

Methods: Retrospective, interventional study of patients with rDME treated with Ozurdex®. The primary outcomes were best-corrected visual acuity (BCVA) and central retinal thickness (CRT). The secondary outcomes were intraocular pressure (IOP) and adverse events (AE). Patients were divided into two groups according to the integrity of the inner segment ellipsoid (ISe) band and followed at least 5 months.

Results: 24 eyes of 21 patients were included. 37.5% were vitrectomized eyes. The ISe band was normal in 29.2% and altered in 70.8%. Mean baseline BCVA was 0.61 ± 0.23 logMAR and improved to 0.40 ± 0.19 ($p=0.06$), 0.35 ± 0.16 ($p=0.02$) and 0.48 ± 0.22 ($p=0.35$) at month 1, 3 and 5 in group I. Mean baseline CRT ($467 \pm 90 \mu\text{m}$) decreased to 313 ± 76 ($p=0.04$) and 304 ± 96 ($p=0.04$) during the first and third months but increased to $514 \pm 150 \mu\text{m}$ at month 5. Mean baseline BCVA (0.99 ± 0.52 logMAR) did not show any improvement during the follow up in group II. Mean baseline CRT ($542 \pm 167 \mu\text{m}$) showed similar changes: 314 ± 84 ($p=0.01$), 378 ± 126 ($p=0.02$) and 507 ± 196 ($p=0.14$) at months 1, 3 and 5. In both groups there was a greater CRT decrease in not vitrectomized eyes at months 1 and 3. IOP was stable in both groups. Commonest AE were conjunctival hyperemia and conjunctival hemorrhage.

Conclusions: The treatment of rDME with Ozurdex® improves visual acuity and central macular edema in eyes with normal ISe band but only decreases CRT in eyes with altered ISe, with an acceptable safety profile.

Nepafenac 0,1% Ophthalmic Suspension as Treatment of Chronic Macular Disorders

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Objectives: To evaluate the efficacy of topical nepafenac 0,1% in patients with impaired blood-retinal barrier in the macular area.

Methods: In a prospective pilot study 15 eyes were included; in the first visit and controls complete eye examination was performed (mean follow-up: 79 days). Visual acuity (VA), central thickness (CT) and macular volume (MV) were evaluated. All patients (mean age: 72.7 years) were analyzed before and after the treatment, and later, sub-analysis of two groups was made: A) subjects with diffuse diabetic macular edema - DDME and B) subjects with Irvine - Gass syndrome.

Results: Patients had an initial VA (Snellen) of 0.40 with a final improvement of 0.46 ($p = 0.026$), the CT was reduced from 394.92 to 292 microns ($p = 0.002$) and MV showed a global decrease of 11.26 to 10.65 mm³ ($p = 0.013$). Analyzed sub-parameters of group A (DDME) show that, except in visual acuity ($p = 0.08$), the difference was significant in reduction of CT ($p = 0.01$) and MV ($p = 0.05$). Patients with post-surgical macular edema (group B) had statistically significant differences in VA ($p = 0.02$) and CT ($p = 0.03$) but not in the macular volume ($p = 0.17$).

Conclusions: In our study, nepafenac has proven to be clinically safe and effective treatment, capable of stabilizing the blood-retinal barrier and thereby, reduce macular edema and restore vision. The obtained visual benefit was better in patients with Irvine - Gass syndrome than with DDME.

Phase 2 Study of Conbercept, a Recombinant VEGF Receptor, Treatment of Macular Edema Secondary to Retinal Vein Occlusion (RVO)

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Background: Conbercept, a novel recombinant fusion protein, binds and neutralizes VEGF involved in neovascularization and vascular permeability in retinal vein occlusion.

Methods: In this single arm phase II study, sixty consecutive patients with macular edema secondary to branch RVO (BRVO) (30 patients) or central RVO (CRVO) (30 patients) were enrolled. All subjects received 3 monthly injections of 0.5 mg conbercept, followed by a 6-month PRN (pro re nata) regimen. The changes in best-corrected visual acuity (BCVA) letter score and central retinal thickness (CRT) from baseline, and safety was assessed.

Results: Sixty patients (30 BRVO, 30 CRVO) were enrolled. 59 of subjects had completed the 3 monthly intravitreal injections of conbercept, and 51 of them had completed the 6-month treatment. In BRVO group, BCVA increased with 14.57 letters from baseline (p<0.0001) at month 3, and further improved to 17.53 letters at month 6 (p<0.0001). In CRVO group, BCVA was also improved significantly, with 11.5 and 14.33 letters increased from baseline at month 3 (p<0.0001) and month 6 (p<0.0001) respectively. Meanwhile, central retinal thickness (CRT) was decreased markedly in both group at month 3, with a mean reduction from baseline of 295.53 mm in BRVO group (p<0.0001) and 400.3 mm in CRVO group (p<0.0001). All planned study visits are expected to be completed at the end of April, and 9-month results might be available just before the ISOPT meeting.

Conclusions: Intravitreal injection of 0.5 mg conbercept significantly increased BCVA and decreased central retinal thickness with an acceptable safety profile in RVO patients.

Half-Fluence versus Half-Dose Photodynamic Therapy in Chronic Central Serous Chorioretinopathy

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Purpose: To compare the efficacy and safety of half-fluence versus half-dose photodynamic therapy (PDT) in chronic central serous chorioretinopathy (CSC).

Design: of the study: Multicenter retrospective comparison study.

Methods: Retrospective review of 56 patients affected by chronic CSC, including 28 patients (31 eyes) who received half-fluence PDT and 28 patients (29 eyes) who received half-dose PDT. Best-corrected visual acuity (BCVA), central foveal thickness (CFT) and resolution of subretinal fluid on optical coherence tomography at 1 and 12 months were assessed.

Results: The mean logmar BCVA improved significantly (p<0.001) both in the half-fluence group from 0.187 (±0.187) to 0.083 (±0.164) and in the half-dose group from 0.126 (±0.091) to 0.068 (±0.091) at 12 months, without significant difference between the 2 groups. At 1 month a complete resolution of subretinal fluid was observed in 19 (61.3%) half-fluence treated eyes and in 25 (86.2%) half-dose treated eyes (p=0.04). At 12 months, a complete resolution of sub-retinal fluid was achieved in 26 (83.9%) half-fluence treated eyes and 29 (100%) half-dose treated eyes (p = 0.0529). Nine (29%) eyes in the half-fluence group and 5 (17.2%) eyes in the half-dose group had at least one recurrence of subretinal fluid during the follow-up. Overall there were 15 and 5 recurrences in the half-fluence PDT and half-dose PDT groups respectively (p=0.07). In no eye of both groups atrophy of the RPE was observed in the area of treatment.

Conclusion: Half-dose PDT induced a more rapidly reabsorption of the fluid, a more lasting effect and an equal safety with respect to half-fluence PDT.

Aripiprazole Associated Retinopathy: Multimodal Imaging Findings

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A 47-year old schizophrenic woman complaining of bilateral visual loss was referred for ophthalmic examination. Her RE BCVA was counting finger and her LE BCVA was 20/100. She had not been examined for the 10 previous years, but in her last medical record her RE BCVA was already counting finger and her LE BCVA was 20/30. She had been on neuroleptic drugs (haloperidol and aripiprazole) ever since.

Slit lamp examination was normal except for pigment in her vitreous. RE fundus showed a large area of chorioretinal atrophy. At first sight, nothing obvious was seen on the LE but autofluorescence imaging showed an abnormal repartition of the autofluorescence associated with a vaste but quite fine serous retinal detachment concerning the entire posterior pole.

ERG showed an abnormal response of both scotopic and photopic system. EOG demonstrated no light peak.

Decreasing her dose of aripiprazole allowed almost complete resolution of the serous retinal detachment and better visual acuity.

To date, it is the first report of aripiprazole associated retinopathy. Hypothesis concerning pathophysiology are discussed.

Long-Term Results of Rheohaemapheresis Treatment of Age-Related Macular Degeneration

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Purpose: To evaluate long-term effects of rheohaemapheresis (RHF) treatment of the dry form of age-related macular degeneration (AMD) on anatomical, functional and rheological findings.

Methods: We treated 19 patients (35 eyes) and randomised 18 controls (27 eyes) with AMD with soft drusen. Patients were treated with 8 RHF procedures (cascade filtration of 1.5 plasma volume) within 10 weeks. We evaluated best corrected visual acuity (ETDRS charts), DPED-area (fundusphotography; Visupac software), IS/OS junction status (HD OCT), retinal function (pattern- and multifocal electroretinography).

Results: Baseline mean BCVA of treated patients was 0.74 and 0.71 in the controls. After 42 months, BCVA of treated patients increased slightly to 0.79, whereas it decreased to 0.70 (p = 0.031) in controls. We found a reduction in the size of DPED-area of treated patients from 6.78 ± 3.79 mm² to 4.13 ± 3.84 mm² (p 0,001), whereas it enlarged from 4.09 ± 3.48 mm² to 6.69 ± 4.2 mm² (p = 0,001) in controls. 68.2% of treated patients remained without IS/OS junction defect, IS/OS defects were found in 83% of control eyes. MFERG responses at eccentricities of 5° and 13° were significantly higher in treated patients than in controls after 1.5 and 2.5-years.

Conclusion: Improvement of rheological parameters after RHF contributed to a significant reduction or even the reattachment of DPED and preservation of photoreceptor IS/OS junction integrity in fovea, which is a predictive factor for preservation of visual acuity and stabilization of electrical activity of retina.

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Conbercept for Treatment of Wet Age-Related Macular Degeneration (AMD)

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Aims: Confirm the efficacy of intravitreal 0.5 mg conbercept for wet AMD.

Methods: Randomized, double-masked, multicenter, sham-controlled phase III clinical trial. Patients (≥ 50 years old) with choroidal neovascularization (CNV) secondary to AMD were enrolled, and were randomized 2:1 to conbercept treatment group and sham-injection control group. During the first 3 months, the conbercept group received intravitreal injection of conbercept 3 times monthly; the control group received sham injection 3 times. Then the conbercept group received conbercept every 3 months; the control group received conbercept monthly for 3 times, followed by every 3 months to month 12.

Results: Of 124 enrolled patients, 113 (91.1%) completed the study. At the 3-month primary endpoint, the mean gain in BCVA from baseline in the conbercept group was significantly greater ($P < 0.001$) than the control group (9.2 vs. 2.0 letters). At month 12, the benefit in BCVA of the conbercept group was maintained (+10.0 letters), while that of the control group was significantly improved after treatment compared with baseline (+6.7 letters). Furthermore, the same trends were observed in anatomic outcomes such as central retinal thickness, total lesion area and leakage in the two groups at month 3 and 12. There were no significant safety issues identified during this study.

Conclusions: Conbercept is superior to sham-injection for improving visual acuity. And the improvement can maintain by every 3 months treatment through 12 months.

Improvements in Visual Function following Resolution of Vitreomacular Traction with Ocriplasmin

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Background: A common symptom in patients with vitreomacular traction is impairment to visual function, which can have a negative effect on the patient's vision-related quality of life.¹ The impact of treatment on visual function is, therefore, an important component when evaluating the overall benefit for the patient.

Methods: A post hoc analysis of the ocriplasmin phase III clinical trials evaluated the impact of achieving vitreomacular adhesion (VMA) resolution at Day 28 following ocriplasmin injection (the primary endpoint), on changes in best-corrected visual acuity (BCVA) and the National Eye Institute 25-item visual function questionnaire (NEI VFQ-25).

Results: Of the patients treated with ocriplasmin, BCVA gains of ≥ 2 lines at Month 6 were achieved by 44.7% (55/123) of patients with VMA resolution at Day 28 and 22.0% (75/341) of those who did not meet the primary endpoint ($p < 0.001$). Similarly, ≥ 3 line gains at Month 6 were more frequent in patients who met this endpoint versus those who did not: 20.3% (25/123) and 9.4% (32/341), respectively ($p = 0.002$).

At Month 6, ocriplasmin-treated patients who had achieved VMA resolution at Day 28 reported a mean change from baseline in VFQ-25 composite score of +5.7 compared with +2.6 for those who did not meet the primary endpoint ($p = 0.003$).

Conclusion: Resolution of VMA following treatment with ocriplasmin was associated with an increased likelihood of significant gains in BCVA and improvements in the patient's visual function.

Reference: 1. Okamoto F et al. Invest Ophthalmol Vis Sci 2010;51:744.

Comparative Study of Free Lutein and Lutein Ester of the Macular Pigment Optical Density for Japanese Individuals

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Purpose: To examine whether either free lutein or lutein ester supplementation affects macular pigment concentration/optical density (MPOD) in healthy Japanese individuals.

Methods: Twenty-one healthy volunteers were randomized to either 10 mg of orally administered free lutein or lutein ester daily for up to 3 months. MPOD levels were measured by resonance Raman spectrophotometry (RRS) at baseline and 3 months after the start of supplementation. It was 21 volunteers at the time of the start, but six people fell off three months later and became 15 people. Wilcoxon signed-rank test was used in the study.

Results: MPOD levels measured with each method were correlated significantly at all time points. MPOD(RRS) levels increased 157.3% from baseline at 3 months after free lutein supplementation, but increased to 118.8% with lutein ester group. In the free lutein group, MPOD(RRS) levels significantly increased from baseline at 3 months in individuals. In the lutein ester group, MPOD(RRS) levels was not the statistical significant difference.

Conclusions: MPOD(RRS) levels correlated significantly with each other. In normal healthy Japanese individuals, free lutein supplementation increased MPOD levels within the fovea more effectively than did lutein ester.

The INJECT Study: a Non-interventional, Multicentre, Worldwide Study in Patients Treated with Ocriplasmin

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Background: The efficacy and safety of ocriplasmin in patients with vitreomacular traction (VMT; or symptomatic vitreomacular adhesion), including when associated with a macular hole (MH) of $\leq 400 \mu\text{m}$, was established in the pivotal phase III studies (NCT00781859; NCT00798317). However, clinical trials may not fully reflect the population encountered in clinical practice and often have a limited duration of follow-up.

Methods: The INJECT (INvestigation of JETREA[®] in Patients with Confirmed Vitreomacular Traction) study will evaluate the impact of ocriplasmin on safety, clinical effectiveness, and HRQoL in a real-world setting. This non-randomized, multicentre, worldwide study aims to recruit approximately 1500 patients across around 120 centres, with treatment given according to the approved indication in each country. Demographic information will also be collected. Clinical effectiveness will be evaluated, including resolution of VMT and MH closure, BCVA changes, NEI VFQ-25 outcomes and rate of vitrectomy. Safety evaluations will include slit-lamp biomicroscopy, intraocular pressure, and adverse events with severity and causality assigned at the discretion of each investigator. Three post-baseline visits are recommended, up to a final visit at around 12 months; however, this remains at investigator discretion in accordance with local standards of care. The study is open for enrollment; the first interim analysis is planned for 6 months after enrollment of the first patient, and then at 6–9 month intervals.

Discussion: The INJECT study will build on evidence from the pivotal studies, evaluating the clinical effectiveness and safety of ocriplasmin in a large patient cohort, reflective of everyday clinical practice.

Imaging of Retinal Hypoxia

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Retinal vascular diseases, including diabetic retinopathy and age related macular degeneration, are associated with retinal hypoxia. Therefore, the ability to image hypoxic retinal tissue in vivo would be beneficial for improved clinical management of these diseases. For this purpose, a hypoxia-sensitive fluorescent contrast agent was developed and characterized for imaging of hypoxia in retinal tissue using established cell culture and animal models of retinal vascular disease. To evaluate the utility of this contrast agent for imaging hypoxia, in vitro assays using Human Retinal Microvascular Endothelial Cells (HRMEC) and in vivo studies using mice with oxygen-induced retinopathy (OIR) or laser-induced choroidal neovascularization (LCNV) were performed to determine the hypoxia-associated sensitivity and specificity of this contrast agent. HRMEC conditioned under hypoxia for varying durations of time up to 24 hrs. exhibited dose-dependent fluorescence enhancement due to hypoxia-selective uptake of the contrast agent. In animal models, regions of tissue hypoxia staining positive for pimonidazole hydrochloride were also colocalized with contrast agent uptake, as indicated by in vivo and ex vivo imaging. Contrast agent accumulation in hypoxic tissue was detectable within 2 hrs. post-injection. These studies support the feasibility of imaging hypoxic tissue in vivo using targeted contrast agents in conjunction with readily available retinal fluorescence imaging equipment. Hypoxia-sensitive contrast agents, if clinically translated, may be useful for early detection of retinal vascular diseases and monitoring of therapeutic response in patients.

Intravitreal Aflibercept Decreases the Volume of Vascularized PEDs Better than Frequent

Retreatment with Intravitreal Bevacizumab or Ranibizumab

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Purpose: To evaluate the effects of switching from bevacizumab or ranibizumab to aflibercept in eyes with neovascular AMD requiring frequent retreatment every 4 to 6 weeks.

Methods: A retrospective review was performed on patients with neovascular AMD undergoing anti-VEGF therapy for at least one year with persistent or recurrent macular fluid requiring retreatment every 4 to 6 weeks with intravitreal bevacizumab or ranibizumab prior to the switch to intravitreal aflibercept. Patients were followed for at least 6 months after the switch. All patients were treated using a treat-and-extend strategy, and the treatment interval immediately after the switch was the same as the interval immediately before the switch. Best-corrected visual acuity (BCVA), number of injections, and SDOCT imaging measurements were collected.

Results: A total of 72 eyes of 64 patients with neovascular AMD met the inclusion criteria. The mean duration of anti-VEGF therapy prior to the first aflibercept injection was 44.5 months (range 13.8-104.7). The mean number of total injections was 30.5 for the entire treatment period prior to the switch and 9.9 for the 12 months prior to the switch. The average number of anti-VEGF injections was reduced by 0.58 during the 6 months after the first aflibercept injection compared with the 6 months prior to the first aflibercept injection ($p=0.001$). BCVA increased by 0.5 letters during the 6 months after the switch to aflibercept, which was not statistically different from the 1.0 letter increase during the 6 months before the switch to aflibercept ($p=0.75$). Central retinal thickness (CRT) did improve from 257.4 microns to 239.7 microns during the 6 months after the switch to aflibercept ($p=0.001$). Seventy of the 72 eyes had vascularized retinal pigment epithelial detachments (PEDs). When compared with the change in PED cube-root volume 6 months before the switch (+0.02 mm), the change in PED cube-root volume 6 months after the switch to aflibercept (-0.07 mm) was statistically significant ($p=0.007$).

Conclusions: The volume of vascularized PEDs, the number of injections, and the CRT decreased significantly following the switch to aflibercept in eyes undergoing frequent reinjection using a treat-and-extend treatment strategy.

Intravitreal Anti-VEGF Therapy Associated with LASER Photocoagulation for the Treatment of Proliferative Sickle Retinopathy in 5 Patients

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Sickle cell retinopathy is characterised by occlusion of peripheral retinal vessels, retinal ischemia and development of proliferative retinopathy. This main complication leads to vitreous haemorrhage and retinal detachment, responsible of visual loss. Intravitreal bevacizumab injection is efficient in neovascular glaucoma, off label in neovascular AMD, in diabetic iris and retinal neovascularisation. It has been used in proliferative sickle cell disease with some success (Siqueira et al, 2006; Shaikh, 2008).

Among 45 heterozygote sickle cell patients under laser photocoagulation therapy for proliferative sickle cell retinopathy (PSR), 5 patients Goldberg III and IV, escape the therapeutic schedule and present a worsening of the PSR. Bevacizumab intravitreal injection was proposed and performed. Laser therapy was continued. Clinical follow up was completed by fluorescein angiography if possible.

Dramatic regression of sea fans and neovascularisation was shown at four weeks post injection. Improvement of visual acuity was noted. Scatter laser photocoagulation was still applied to ischemic peripheral retina. This synergic treatment allow the regression of PSR. Although neovascularisation increase at 2 months post injection if laser photocoagulation was not performed. Anti-VEGF intravitreal injection was repeated if necessary, up to 5 in one case. No adverse events were observed in the 2 years of the follow-up. The 5 patients are presented.

Bevacizumab intravitreal injection for the treatment of PSR appears very efficient. No adverse events were noted during all the follow up period unless Babalola reported a secondary hyphaema. Further studies will be needed to assess the place of anti-VEGF therapy in PSR treatment.

Complement Factor H Treatment is as Effective as Anti-VEGF Against Choroidal Neovascularization in a Rat Model of Neovascular AMD

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Age-related macular degeneration (AMD) is a leading cause of irreversible blindness in developed countries. VEGF is the principal angiogenic factor responsible for the development of choroidal neovascularisation (CNV) in the exudative form of AMD. Intravitreal injections of anti-VEGF have become the standard treatment for CNV. Complement factor H (CFH) is required to limit activation of the alternative pathway of the complement system. The T1277C polymorphism in the CFH gene inducing a Tyr (Y) to His (H) substitution in the CFH protein is strongly associated with AMD and poor response to therapy with intravitreal administration of anti-VEGF agents. Therefore, administration of CFH may provide a novel approach for the management of AMD. Therefore, we evaluated the effect of CFH administration in a model of CNV. Recombinant human CFH-Y402 and CFH-H402 proteins were produced and purified. Rats were photocoagulated using diode laser to induce CNV. On the same day, the animals were intravitreally injected with a neutralizing anti-VEGF antibody, CFH-Y402, CFH-H402 or PBS. A unique administration of CFH-Y402 reduced the volume of CNV lesions (by 72%, when injected on the day of CNV induction and by 52% on day 4 after CNV induction). CFH-Y402 was as effective as anti-VEGF, whereas CFH-H402 was ineffective to reduce CNV. We identified genes associated with pro- and anti-angiogenesis as targets of CFH signaling-mediated vascular homeostasis, the disruption of which might underlie CNV. Thus, CFH has a potential therapeutic use for AMD treatment.

Human Dental Pulp Stem Cells can Differentiate into Retinal Cells

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Aim: To investigate how human dental pulp stem cells (hDPSCs) differentiate into retinal cells, especially retinal ganglion cells (RGCs) and glial cells (GCs).

Methods: After dental pulp tissues were isolated from the human molars, hDPSCs were collected by expansion culture. The cells differentiated into retinal cells in specialized media, and their characteristics were evaluated using real-time RT-PCR, Western immunoblots, and immunofluorescence. Then, the GCs differentiated from hDPSCs were cocultured with mouse primary RGCs under oxidative stress. Cell viability and neurite outgrowth ability of mouse primary RGCs cocultured with GCs were assessed by terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) and immunofluorescence.

Results: Undifferentiated hDPSCs had the characteristics similar both to mesenchymal and neural stem cells. In specialized media, the characteristics of differentiated hDPSCs were changed similar to RGCs and/or GCs. When the GCs differentiated from hDPSCs were cocultured with mouse primary RGCs, they significantly attenuated the apoptosis and restored the neurite outgrowth ability of RGCs.

Conclusion: In this investigation, it was revealed that hDPSCs can differentiate into RGCs and GCs. The GCs differentiated from hDPSCs may protect primary RGCs against oxidative stress *in vitro*.

Sigma Receptor 1 Mediates Cytokine Release and NFκB Translocation in Retinal Müller Glial Cells Suggesting a Role in Neuroprotection

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σR1, a non-opioid, non-phencyclidine binding site is considered a molecular chaperone. Its high affinity ligand (+)-pentazocine ((+)-PTZ) affords profound retinal neuroprotection *in vitro* and *in vivo*, by a yet unknown mechanism. Most studies have focused on σR1 effects in neurons; however a common feature of retinal disease is Müller glial cell (MGC) reactive gliosis, which includes cytokine release. Cytokine secretion is accompanied frequently by cytosolic-nuclear translocation of NFκB. In this study we investigated whether (+)-PTZ alters cytokine release by MGC and whether cytosolic-nuclear NFκB translocation is involved. MGC harvested from 5-7 day mice were exposed to 0.1 μg LPS 18 h in presence/absence of 3 μM (+)-PTZ. Inflammatory cytokine release was detected using RayBio mouse inflammation antibody array, which revealed significant release of numerous cytokines in LPS-treated cells compared to controls, including MIP1γ (4-fold), MIP2 (5-fold) and MIP3α (3-fold) and a significant decrease in cytokine secretion by (+)-PTZ-treated cells (compared to LPS-treated): MIP1α (0.1-fold), MIP2 (0.5-fold); MIP3α (0.02-fold). In companion experiments, NFκB sub-cellular localization was determined by immunofluorescence; cells expressing NFκB in nucleus or cytosol/both were quantified. 82.8% of cells incubated with 0.1 μg LPS 15 min localized NFκB to nucleus, 17.2% to cytosol/both. Cells treated with LPS-(+)-PTZ, however, localized NFκB more often to the cytosol/both (65.5%) than nucleus (34.4%), which was similar to controls. The study represents the first investigation asking whether σR1 ligands alter Müller cell function. The data suggest that σR1 may play a beneficial role in decreasing cytokine release by these cells via an NFκB-mediated mechanism.

Bio-compatible Hyaluronic acid as a Coating Strategy to Improve Intravitreal Delivery of Gene Nanomedicines to the Retina

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Background: Delivery of gene nanomedicines to the retinal cells should be possible via intravitreal injection, granted they remain mobile in the vitreous humour and are still able to transfect the retinal target cells. Unfortunately, most nonviral gene nanomedicines have a cationic charge, which we have established to be detrimental for intravitreal mobility. In this study, we investigate hyaluronic acid (HA) as a biocompatible coating strategy to improve intravitreal mobility while retaining the capacity for transfection.

Methods: Ternary polyplexes are formed by electrostatic complexation of plasmid DNA (pDNA) and cationic polymers, with electrostatic coatings of HA of different molecular weights (MW's). These were first evaluated in terms of size, stability, surface charge and the ability to complex pDNA. Furthermore, the mobility of these ternary complexes in vitreous humour was verified with a previously published *ex vivo* model. Finally, we evaluated cytotoxicity, uptake and transfection efficiency on an ARPE19 cell line.

Results: Ternary HA-polyplexes had a negative surface charge and were still able to efficiently complex pDNA. Their hydrophilic and anionic surface provided them with an increased mobility in the vitreous humour. Furthermore, despite the negative surface charge, the HA-coated polyplexes were still able to transfect ARPE19 cells.

Conclusions: Electrostatic coating of polyplexes with HA appears to result in stable, anionic complexes which have an improved mobility in vitreous humour, regardless of the MW of HA used. However, uptake and transfection of ARPE19 cells did show MW-dependence, where a 200 kDa HA-coating was less efficient than 20 kDa or 2000 kDa.

Effects of Dexamethasone on Müller Glial Cells over the Course of Blood Retinal Barrier Breakdown

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Blood retinal barrier breakdown (BRBB) is involved in macular edema formation and intravitreal dexamethasone is used for its treatment. Alterations of Müller glial cells (MGC) may also contribute to edema. One of the functions of MGC is rapid absorption of fluid from retina for maintaining proper homeostasis. This is mediated by water (AQP4) and potassium (Kir4.1) membrane channels. Dystrophin Dp71 a cytoskeleton associated protein has been associated with proper clustering and polarized expression of Kir4.1 and AQP4 in MGC.

We analyzed the effect of intravitreal dexamethasone on expression of Kir4.1, AQP4, Dp71 and inflammatory mediators after post surgical BRBB.

In a post surgical BRBB model in mouse (partial lens surgery), we quantified by qPCR and Western Blot the expression of Kir4.1, AQP4, and Dp71 72 hours after surgery. Same parameters were measured + a single dose of intravitreal dexamethasone. Inflammatory response after surgery was also studied in retina.

BRBB was followed by a down regulation of AQP4 and Dp71 by 30%, and mislocalization of Kir4.1. When dexamethasone was injected, despite no effect on BRBB, expressions of these proteins were preserved at normal levels (= before surgery). Partial lens surgery was also followed by inflammatory changes in the retina.

BRBB involves MGC dysfunction and a certain amount of inflammatory response. Dexamethasone, which is known to act on BRBB and inflammatory processes, appears in our experimental model to play also a key role on MGC function. It preserves the expression and localization of essential transport channels and the protein responsible for their clustering in MGC.

Lineage Negative BMCs Induce Regeneration Promoting Effects in Pterygopalatine Artery (PPA) Ligation Model of Ischemic Retinal Injury in Mouse

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Background: Current treatments available for retinal ischemia are not sufficient to restore the visual functions. Different animal models have been generated to study its pathophysiology and validate therapies. We propose an improvised pterygopalatine artery (PPA) ligation model to study transient retinal ischemia.

Methodology: Age and sex-matched C57BL/6J mice were subjected to PPA ligation. The external carotid artery and the PPA were ligated for 3.5 hours reducing the ocular blood flow analysed by Laser Doppler blood flow meter, fluorescein angiography and ERG. The retinal damage was assessed using histological, molecular, immunohistochemical and electrophysiological techniques. The lineage negative population was purified using magnetic associated cell sorter (MACS). About 100,000 cells were transplanted intravenously after characterising Sca-1, CD34 and CD117 expression by flow-cytometry.

Results: Thinning of retinal layers was observed consequent to retinal ischemia. An increase in GFAP was found when analysed by real-time PCR and IHC. A significant decrease in GFAP expression was observed after 10 days of stem cell transplantation. The expression of Nestin was also found to be increased after 5 and 10 day 10 of transplantation. The expression of various neurotrophic and growth factors was also elevated. The levels of BDNF, FGF2 were also elevated significantly after injury as well as after transplantation of lineage-negative stem cell population.

Conclusions: The lineage negative stem cells derived from mouse bone-marrow exert regeneration promoting effects on ischemic retina.

5-Year Relapse-free Follow-up Following Antibiotic Treatment of a B-cell MALT Lymphoma of the Conjunctiva in a 13-year Old Child

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Medical History: In February 2007, a 13-year old boy presented with a livid tumor in the lower conjunctival fornix of the left eye.

Ophthalmological Findings: The tumor was salmon-coloured, bulging elastic and filled the whole lower conjunctival fornix of the left eye. There was no other pathologic finding in the left eye. Uncorrected visual acuity was 20/20. Intraocular pressure was 12mmHg. There was full motility of the eye.

Treatment: Sample taking was performed in February 2007. Histologically, the tumor presented as an extranodal MALT B-cell lymphoma. DNA-testing for chlamydia trachomatis and chlamydia pneumonia was negative. Systemic treatment with doxycycline (200mg daily) was started.

After six weeks, the tumor became smaller. Azithromycin once a week was added. 18 months after initiation of the treatment, the tumor had completely regressed. A second sample taking in the former tumor area showed tumor-free conjunctiva and subconjunctival tissue. The patient was followed for five more years. There was no relapse of the B-cell lymphoma neither in the orbit nor anywhere else in the body. Chest X-ray, abdomen sonography, MRI of brain and orbit, bone marrow puncture and lumbar puncture was always negative.

Conclusion: We could show that extranodal MALT B-cell lymphomas of the conjunctiva can successfully be treated with antibiotics alone. Studies in adult patients could prove that this type of treatment can be successful in adults, especially if DNA of chlamydia psittaci can be found.

To our knowledge, this is one of only few reports on a child with ocular MALT lymphoma that would successfully be treated with antibiotics alone without positive chlamydia tests, thereby avoiding radiation or chemotherapy.

Ranibizumab for the Treatment of Early Pterygium Recurrences

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Methods: This is a completed phase 1 trial exploring the safety and efficacy of sub-tenon ranibizumab for early pterygium recurrences. Eight subjects were enrolled, given injections of 0.5-2mg of ranibizumab monthly for three doses, and followed for one year. Anterior segment photographs were collected and analyzed by a blinded examiner. The Photoshop Magic Wand tool was used to quantify the presence of conjunctival/corneal blood vessels at the pterygium head in the images. Safety parameters collected included: blood pressure, visual acuity, intraocular pressure, Shirmer's, and tear break up time.

Results: Six out of eight subjects demonstrated a short-term (60 days after the first injection) response to the drug with a visible reduction in vascularity. The quantitative response was highly variable (reduction in vascularity ranged from 32% to 88%). Long-term responses were also analyzed at months 9- 12. Four of the subjects had a persistent reduction in vascularity (range 40-88%) with a full arrest of the impending recurrence. There were no safety concerns raised in any of the subjects. The long-term efficacy of ranibizumab was most marked in subjects that were treated very early in the recurrence (3-5 months post-operatively). The time between surgery and treatment in this study ranged from 3 months to 22 months, and the subjects receiving the drug in a well-established recurrence had the least effective long-term response.

Conclusion: Sub-tenon ranibizumab injections appeared to be safe with a variable efficacy that was most pronounced when recurrences were treated very early (3-5 months post-surgery). In some cases, an impending recurrence treated early will arrest, avoiding consecutive surgery for the patient.

Prospective study of Autologous Serum Eye Drops (ASED) confirms sustained benefits in Keratoconjunctivitis Sicca and Non-Healing Corneal Ulcers

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Aim To confirm prospectively in patients failing other therapies that ASED relieve ocular symptoms at 12 months.

Method Patients newly referred in NSW and Queensland from May 2012 completed surveys (modified and using items from the National Eye Institute Visual Functioning Questionnaire-25¹, Ocular Surface Disease Index, Dry Eye 2001 and Impact of Dry Eye on Everyday Life) that assessed health status, ocular symptoms, visual functioning and quality of life.

From 77 new patients initially screened 47 completed baseline surveys, 42 patients provided survey responses at 2 months and 20 patients completed 12 month follow up by December 2013.

Results between May 2012 and June 2013 47 patients, median symptom duration over 7 years, were enrolled. At 2 months all patients remained on ASED. Symptoms of dryness, ocular pain, grittiness and burning were significantly reduced at 2 and 12 months. ASED were rated highly, median score 7 (0-10 scale), most responding within 1 month. At 12 months 80%, 16/20 were still using ASED 45%, 9 had reduced other therapies with 3 of these ceasing other therapies. At 2 months 22% and 5% at 12 months to date have reported side effects.

Sensitivity to environmental triggers and visual changes were not improved at 12 months despite improvement at 2 months. Quality of life improvements were seen and of the daily living activities cooking was noted to be less problematic.

Summary/ Conclusions Responses to ASED are evident at 2 months and maintained at 12 months.

¹VFQ 25 developed at RAND corporation

Pharmacological Validation of an Inflammation-based Murine Model of Dry Eye

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Background: Several approaches are currently used to model dry eye disease in mice; however, pharmacological validation of these models has proven to be challenging. The T-cell mitogen Concanavalin A (ConA) has been previously utilized in a rabbit model of dry eye to study the potential of anti-inflammatory drugs (Nagelhout 2005). In this study, we validate this ConA model in mice with dexamethasone.

Methods: Female C57 mice were evaluated for baseline corneal staining. Mice with low baseline staining were divided into 3 treatment groups (oral dexamethasone [2 mg/kg/day], oral vehicle, or unchallenged naïve), and pretreated for 3 days prior to ConA challenge. Challenged mice were injected in the lacrimal gland with 100µg/10µL of ConA to induce inflammatory dry eye and placed in Ora's controlled adverse environment (CAE). Mice were evaluated 24 hours following ConA injection for corneal staining.

Results: Unchallenged mice had an average corneal staining score of 3.9. Vehicle-treated mice had an average score of 11.2. In contrast, mice treated with dexamethasone showed a statistically significant decrease in staining (7.7) compared to vehicle.

Conclusions: Our study shows that this murine ConA dry eye model is modifiable by treatment with anti-inflammatory drugs. This finding is significant given that establishing reproducible anti-inflammatory efficacy with steroids in other dry eye models has proven difficult. This study establishes that ConA-induced inflammation in mice, in conjunction with the CAE, can produce an acute form of dry eye disease that is pharmacologically modifiable and applicable for studying novel dry eye drugs.

Pre-Treatment with Non-steroid Anti-inflammatory Drugs as a Possible Success-Factor of Femtosecond Laser Cataract Surgery

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Proper pupil size is important in traditional phacoemulsification, but becomes a crucial factor of successful femtolasar cataract surgery. If the pupil is not wide enough, the femtolasar or the bubbles created by it may hit the iris causing a significant rise in prostaglandin E2 and other cytokines in the aqueous humor. Supporting this view an earlier study Gimbel reported the beneficial effect of non-steroid anti-inflammatory drug (NSAID) eye drops keeping the pupil dilated during phacoemulsification. In a series of publications Bucci and Waterbury reported a decrease in prostaglandin levels after pre-treatments with various non-steroid anti-inflammatory drugs. Our studies were initiated by the observation that two patient groups receiving or not receiving NSAID pre-treatment before femtolasar cataract surgery showed smaller or larger pupils during the surgery, respectively. Prompted by this experience aqueous humor was collected from two age- and gender-matched groups of patients after femtosecond laser pretreatment, receiving or not receiving a pre-treatment of NSAID eye drops (diclofenac) for 1 day, as well as from patients before traditional phacoemulsification, receiving or not receiving NSAID eye drops, and the total prostaglandin, and prostaglandin E2 concentrations of these four patient groups were measured using enzyme-linked immunoassays. Pupil size of the patient groups was also measured both before and after femtolasar treatment, or before traditional cataract surgery. Pre-treatment with NSAID eye drops may be a significant success factor of femtolasar cataract surgery maintaining increased pupil size during and after femtolasar treatment by the inhibition of the liberation of inflammatory prostaglandins during the femtolasar surgery.

Clinical Experiences with Heparan Sulphate Mimetics Eyedrops in the Persistent Epithelial Defects Therapy

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Purpose: To describe treatment efficacy of corneal lesions manifested as recurrent erosions using biodegradable nanopolymer engineered to mimic heparan sulfates (Cacicol 20, Thea Lab).

Material and Methods: 4 patients (4 eyes) with different etiology of corneal persistent epithelial defects (PED) were included in the study. Cases of PED due to neutrophilic degeneration after chronic viral keratitis, history of superficial injury, "map-dot-fingerprint" dystrophy, and toxic exposure after ineffective conventional therapy were treated with Cacicol 20. The corneal lesions were evaluated with slit lamp biomicroscopy, anterior segment optical coherence tomography and in vivo confocal microscopy before and after topical treatment.

Results: In all cases the Cacicol 20 ophthalmic solution was instilled once a week for over one month with a good tolerance. Successful healing of corneal epithelium was noticed after treatment. In the first, third and fourth patient slit-lamp biomicroscopy and confocal microscopy revealed a healthy corneal tissue without any opacities. In the second patient a local, well-demarcated scar within anterior stroma remained.

In all described cases subjective symptoms such as pain and or foreign body sensation were no longer present.

Conclusions: Topical application of heparan sulfate mimetics represents a new therapeutic approach in corneal epithelium defect.

Treatment of Corneal Ulcers in Ocular Surface Inflammation

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Introduction: severe ocular surface inflammation can lead to different diseases and can cause severe corneal involvement.

Patients and methods: 5 cases of ocular surface inflammation with severe corneal ulcers resistant to conventional treatment, all treated with a new matrix therapy agent (cacicol 20%) 1 drop a day every other day for 4 weeks, with biomicroscopic records at D0, D3, D7, D 15 and D30.

Results: patients were aged between 18 to 66 years old, ocular surface inflammation was due to GVHD, severe Sjögren's Syndrome, Atopic keratoconjunctivitis, ocular pterygia and Stevens Johnson syndrome, all ulcers were chronic and rebels to different treatment, at D7 we observed a decrease on VAs pain scale at D15 in all cases a total epithelialization of the ulcers.

Conclusion: CACICOL 20® is a new ophthalmic device, derived from RGTA based matrix therapy (large biopolymers engineered to replace heparan sulfates), which is a revolution in treatment of chronic ulcers, in our cases it has a double effect antalgic and regenerating.

Artificial Tear Containing both Isotonic Glycerol and Sodium Hyaluronate Decreases Conjunctivochalasis in a Three Months Long Trial

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Purpose: Examination of the efficacy of a preservative-free, isotonic glycerol and 0.015% sodium hyaluronate containing artificial tear with special interest to its effect on the conjunctivochalasis.

Patients and methods: A prospective, unmasked, three-months long study with 20 patients enrolled, suffering advanced dry eye disease, representing a high degree of conjunctivochalasis. 16 female and 4 male patients aged 64.0±17.8 years participated in the trial. The degree of conjunctivochalasis (in terms of lid-parallel conjunctival folds (LIPCOF) degree), tear-film breakup time (TFBUT), corneal lissamine staining (Oxford score), and the subjective complaints (OSDI score) were recorded.

Results: The artificial tear caused a significant change in the recorded parameters already after even one month, which became reliable after three months using a power analysis. After three months treatment conjunctivochalasis decreased from a mean (LIPCOF) degree of 2.9±0.4 to 1.4±0.6 on the right, and to 1.4±0.7 on the left eye (pod, os 0.001). The TFBUT increased from 4.8±1.9 seconds on both eyes to 5.9±2.3 seconds on the right and 5.7±1.8 seconds on the left eye (pod=0.004, pos=0.03). The corneal staining reduced significantly (pod0.001) from 1.3±0.6 and 1.4±0.6 to 0.3±0.4 on the right and 0.2±0.4 on the left eye. The OSDI score indicating the subjective complaints of the patients also decreased from a mean value of 36.2±25.3 to 15.6±16.7 (p<0.001).

Conclusion: The regular use of the applied artificial tear decreased the degree of the conjunctivochalasis from the LIPCOF score 3, considered as indication of conjunctival surgery, to 2 or less requiring a conservative therapy.

Role of Azithromycin in the Treatment of Children Meibomian Gland Disease

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Introduction: Meibomian gland disease (MGD) is a common chronic disease of the ocular surface, which can be complicated by severe corneal involvement in children.

Patients and methods: Prospective study conducted between May 2011 and June 2013 on 78 children with MGD. At the first examination, all patients already experienced various ophthalmological treatments without any success leading us to test azithromycin eye drops, a macrolide family with anti-inflammatory properties. The treatment consisted on azithromycin twice a day during 5 days repeated each month for 3 months associated with Dexamethasone eye drops (6 drops a day during one week, the first month) and daily eyelid hygiene (manual or warm glasses) during the all the treatment course. The follow-up visits were performed on D7, D30, D60 and D90 with slit lamp examination (eyelids, BUT, conjunctival and corneal damages) and photography.

Results: 78 children were included, 79.4% had severe corneal complications (neovascularization, ulcers, phlyctenular keratitis). After the first week of treatment, a marked improvement in symptoms was observed in all children probably due to the effect of dexametasone drops, At D60; we observed improvement in corneal signs in 76.8% of cases with a significant decrease of corneal neovessels and phlyctenular keratitis. Associated with azithromycin eye drops, warm glasses showed a better efficacy than manual technic. In 5 cases, in spite of more than 3 months treatment with azithromycin, the results were no conclusive.

Conclusion: Azithromycin associated with eyelid hygiene is a very effective in treatment in children with MGD; furthermore, its ease of use, its very good efficacy and the absence of side effects, makes this therapy a good alternative and choice in this disease.

Efficacy and Safety of Azithromycin 1.5% Eye Drops (Azyter®) in Patients with Moderate to Severe Chronic Blepharitis

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Purpose: To compare the efficacy and safety of azithromycin 1.5% (Azyter®) and placebo eye drops in patients with chronic moderate-to-severe blepharitis.

Methods: This prospective, multicenter, randomized, double-masked, parallel group, phase II pilot study was conducted in 93 chronic moderate-to-severe blepharitis patients. After a 2-week wash-out period with daily eyelid care, patients received azithromycin (AZM) 1.5% or placebo (polyvidone) eye drops for 7 days (2 drops on D1, then one drop daily), followed by a 2-week treatment-free period. This therapeutic scheme was repeated twice. The primary endpoint was the change from D0 to D63 in global ocular discomfort (100-mm visual analogue scale (VAS)). Secondary outcomes included ocular symptoms (irritation, itching, crusting, sticking, light sensitivity, blinking) and signs (margin redness, eyelid swelling, meibomian gland dysfunction).

Results: Mean difference between treatments (AZM - placebo) in global discomfort score was -10.37 mm on D63 (p=0.026). AZM-treated patients also had a lower total symptom score (vs. placebo-treated patients; p=0.005) and a lower score for blepharitis signs (p=0.092). Both treatments were well tolerated.

Conclusions: Azithromycin 1.5% eye drops were effective and safe for the management of moderate-to-severe blepharitis. They appear as a promising therapeutic option, with additional anti-inflammatory activities over the eyelid care.

Evaluation of Nucleic Acid Amplification Testing (Gen-Probe® Aptima®) (NAAT) for Chlamydia trachomatis from Ocular Samples

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Introduction: Chlamydia conjunctivitis may have chronic symptoms with social ramifications. This study presents an evaluation of Gen-Probe APTIMA Combo 2 assay for detection of ribosomal RNA of Chlamydia trachomatis (CT) from ocular samples.

Methods: A battery of 25 true-positive specimens (ocular specimens previously PCR positive for chlamydia) and 20 true-negative specimens (ocular specimens culture-positive for HSV (5), Adenovirus (5), Haemophilus influenzae (5), and Streptococcus pneumoniae (5)) were tested for Chlamydia trachomatis by the Gen-Probe® Aptima®. The 25 chlamydia PCR-positive (obtained May 1994 to May 2012) and 20 true-negative ocular specimens (obtained December 2008 to August 2013) were collected with soft-tipped applicators and placed in Bartels Chlamydia Transport Medium. All specimens were stored at -80°C. Prior to testing; all samples were centrifuged at 13,000 rpm for one hour at 6°C. For each sample, using the APTIMA® Unisex blue swab, a specimen was collected from the conical apex of the storage tube where a pellet was formed. The APTIMA® Unisex swab was placed in a tube of APTIMA® transport medium for testing.

Results: Out of 25 true positive samples, twenty-four (96%) were positive by APTIMA while 20 of 20 true-negatives (100%) tested negative. The test sensitivity and specificity were determined to be: 96% and 100%, respectively.

Conclusions: Gen Probe-APTIMA assay for CT in ocular specimens was optimal for laboratory diagnosis. Validation using more samples is warranted. This study emphasizes the importance of saving excess direct samples for testing validation.

Pharmacological Correction of Presbyopia: A preliminary Study

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Background: A preliminary study of measuring the effect and side effects of PRESBYDROPS in presbyopic patients.

Methods: PRESBYDROPS is composed of low concentration of pilocarpin, non-steroidal anti-inflammatory agent and artificial tears. This combination increases depth of focus for 8 hours, on average. Eighty one patients were treated once to twice a day. Age ranges between 42 to 74 years (mean - 52 years). Exclusion criteria include more than 1 diopter of hypermetropia, myopia or astigmatism as well as other eye disorders.

Results: Pupil diameter was reduced from 3.8 mm to 2.6 after instillation of PRESBYDROPS. Distance uncorrected visual acuity (UCVA) increases from 0.9 (decimal value) to 1.1. Near UCVA increased from 0.36 to 0.65. Depth of focus increased from 1.66 diopters to 2.60 diopters. Adverse effects were: burning (6), nausea (4), temporary headache (4), temporary blurry distance vision (4) and dry eyes (2).

Conclusions: PRESBYDROPS might be considered as a good alternative for the optical correction of presbyopia. It is safe, reversible and it does not have the risks of surgical procedure.

Treatment of Epidemic Keratoconjunctivitis with Povidone Iodine

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Background: We studied the efficacy of a combination Povidone of iodine 0.1% eyedrops and dexamethasone 0.1% eyedrops in the treatment of adenoviral conjunctivitis.

Methods: In a prospective, randomized, controlled clinical trial, patients with recent adenoviral conjunctivitis (diagnosed clinically and confirmed by PCR) were included. Patients were randomly divided into 3 treatment groups: study group - received povidone - iodine 0.1% and dexamethasone 0.1% QID, control 1 group - received dexamethasone 0.1% QID and control 2 group - received lubricating eyedrops (Hypromellose 0.3%) QID. All patients were examined and filled a questionnaire before treatment and on the 3rd, 5th and 7th day of treatment.

Results: We included in the study 78 eyes (26 in each group). Adenovirus type 8 was the most common pathogen (83% of cases). Improvement in symptoms such as red eyes, chemosis, discharge, SPK and pseudomembranes was faster in the study group (p<0.001). Those patients reached a near complete recovery in 5-7 days which was also confirmed by significant reduction in Adenovirus titers by PCR. Improvement was slower in the control 2 group (artificial tears). Subepithelial infiltrates were observed in 44% of the control 1 group, 20% of the control 2 group and in 0% of the study group. The rate of reduction in adenovirus titers was the slowest in control 1 group.

Conclusion: The combination of Povidone iodine 0.1% and dexamethasone 0.1% four times a day can reduce symptoms and expedite recovery in adenoviral keratoconjunctivitis patients.

The Prevalence of Ocular Surface Disease among Patients on Topical Glaucoma Drug Therapy: A Systematic Review of the Literature

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Background: Ocular surface disease (OSD) is common, particularly among the elderly. The general population prevalence has been reported anywhere from 14% to 33% in different studies. Topical glaucoma therapy is thought to cause or exacerbate OSD. This systematic review of the literature aims to assess our current knowledge of the effect of topical glaucoma therapy on the ocular surface.

Methods: We searched OVID Medline and Pubmed from January 1994 to February 2014 using keywords "ocular surface disease", "dry eye", "keratoconjunctivitis", and "glaucoma". Among the search results, we selected English-language publications reporting new data on the prevalence of OSD or one of its surrogate markers among patient on topical glaucoma therapy.

Results: A total of 18 publications were found using the selection criteria mentioned. There was significant variability among these studies in terms of design, the type, number and duration of treatment, and the indices used to assess OSD. Despite the heterogeneity, all studies reported a significantly greater prevalence of OSD, generally ranging from 40 to over 70%, among subjects using topical glaucoma medications compared to their normal controls, or the general population prevalence of OSD. A greater number of medications and longer duration of therapy were associated with higher prevalence and severity of OSD.

Discussion: Topical glaucoma therapy has been shown in a multiple studies to be associated with a greater prevalence of OSD. OSD has in turn been shown to affect patients' quality of life and adherence to treatment. Clinicians must be aware of OSD and its impact on treatment outcomes when treating glaucoma patients with topical medications. Medications that predispose to OSD may have poorer long-term efficacy as they may undermine patient compliance.

Extracellular Matrix and Glial Alterations in an Autoimmune Glaucoma Model

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Background: Glaucoma is characterized by death of retinal ganglion cells (RGCs) and their axons. But its causes are not understood yet. In an autoimmune glaucoma model RGC loss is induced by immunizing with ocular antigens. To gain further knowledge about remodeling of extracellular matrix (ECM) proteins, immunoreactivity against several proteins was evaluated.

Methods: Rats were immunized with optic nerve homogenate (ONA) or S100 protein. The control group received sodium chloride (CO). RGCs were quantified using Brn-3a. Immunoreactivity of tenascin-C, phosphacan, and macroglia was evaluated on retina sections at 7 and 14 days.

Results: At 14 days RGC numbers were comparable in all groups, at 28 days fewer RGCs were observed in ONA and S100 retinas (p<0.05). Interestingly, diverse effects were noted regarding ECM. At 7 days phosphacan reactivity was significantly higher in ONA retinas (p=0.0007). The expression was mainly restricted to Müller glia processes. Phosphacan expression in S100 retinas was not altered (p=0.09). At 14 days phosphacan staining in ONA retinas further increased (p=0.0007). At this point increased expression of macroglia was also noted (p=0.003). S100 retinas were still not affected by phosphacan or macroglia changes (p<0.05). Tenascin-C expression was observed in the nerve fiber and the plexiform layers of the retina. Tenascin reactivity increased in both immunized groups at 7 days (p<0.05), while it went back to control levels later (p<0.05).

Conclusions: Remodeling of the ECM components tenascin and phosphacan occurred shortly after immunization. Up-regulation of phosphacan in macroglia was continuously and exclusively noted in ONA, due to a reactive gliosis. Up-regulation of tenascin early on was accompanied by retinal degeneration.

Whole Bovine Lens Culture to Assess the Ocular Toxicity of Single Dose and Multiple-Dose Treatments of Benzalkonium Chloride

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The toxicity of an ophthalmic chemical is affected by concentration, duration of contact and total dose instilled. The in vitro bovine lens is capable of evaluating both single and multiple-dose exposures over a four day period. Bovine lenses were exposed to benzalkonium chloride (BAK, 0.01%) for 15 min. by submerging the intact lens in a sodium chloride solution. Each lens was then rinsed, placed into fresh medium and incubated at 37°C in a CO₂ incubator. The single-dose group was maintained in culture medium, after initial exposure, for 96 hours. The multiple-dose group was exposed for 15 min. to BAK 24, 48, and 72 hours after initial exposure. On the fourth day of incubation, metabolic activity was assessed using the alamar Blue assay. In addition, the optical quality of the lenses was evaluated using a laser scanner instrument. Single exposure to 0.01% BAK caused metabolic activity of the bovine lens to decrease by 33% (p 0.05) four days after initial exposure. Multiple treatments of BAK caused an even greater drop (73%, p 0.05) in metabolic activity. The laser scanner detected significantly reduced lens optical quality after exposure to single and multiple doses of BAK, when compared to the optics of control lenses (p 0.05). Using this in vitro assay we demonstrate that by measuring the metabolic activity and optical quality of the intact bovine lens, BAK toxicity could be determined both for single and repeat exposures. Repeat exposure to BAK over the course of several days caused increased toxicity.

Activation of Liver X Receptor Alleviates Ocular Inflammation in Experimental Autoimmune Uveitis

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Purpose: To investigate whether a LXR agonist TO901317 (TO90) ameliorates ocular inflammation in experimental autoimmune uveitis (EAU).

Methods: EAU was induced with subcutaneous injection of IRBP161-180 in B10.RIII mice. TO90 (50mg/kg/day) were administered orally for 16 days. The anterior segment was examined and histology was assessed. The levels of LXRs and a NF-κB subunit p65, a LXR target gene ABCA1 in the retina was determined. The pro-inflammatory gene expressions were detected.

Results: Ocular inflammation in EAU mice reached its peak at day 12-14, and gradually regressed thereafter. Western blotting and real-time PCR showed both LXRA and LXRβ were expressed in retina. Expression of LXRA but not LXRβ was upregulated after treatment with TO90 in normal mice (p 0.05). Compared to normals, LXRA was also increased in vehicle and TO90 treated EAU mice (p 0.01). The ABCA1 protein was enhanced in TO90 treated normal mice (p 0.01) and in TO90 treated EAU mice (p 0.01), but was unchanged in vehicle treated EAU mice. Activation of LXRA by TO90 attenuated inflammation and decreased the clinical scores in EAU mice (p 0.05). LXRA activation decreased the expressions of TNF-α, IL-1β, IL-6, MCP-1, IL-17 and IFNγ (p 0.05). Further, TO90 down-regulated NF-κB p65 at protein and mRNA levels (p 0.01).

Conclusion: TO90 activates LXRA and attenuates ocular inflammation in EAU. The alleviation of inflammation could result from inhibition of NF-κB pathway. LXR agonist may be a novel therapeutic agent for uveitis.

Adenosine A2A Receptor Blockade and Caffeine Prevent Retinal Neuroinflammation and Retinal Ganglion Cell Death

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Background: The degeneration of retinal ganglion cells (RGCs) in glaucoma is accompanied by an inflammatory response involving microglia. Blockade of adenosine A2A receptor (A2AR) confers robust neuroprotection in several neurodegenerative conditions involving neuroinflammation. In the CNS, the effects of caffeine are mainly due to the blockade of adenosine receptors. The aim was to evaluate the effect of A2AR blockade and caffeine in the control of retinal neuroinflammation.

Methods: Microglia cell cultures and retinal explants were pretreated with A2AR antagonist (SCH58261, 50nM) and challenged with LPS or elevated pressure. Retinal ischemia was induced by increasing intraocular pressure for 60 min followed by reperfusion (24h or 7 days). Prior ischemia-reperfusion injury (I-R), SCH58261 (100nM, 5μl) was administered intravitreally and caffeine was given in the drinking water (1g/l).

Results: A2AR blockade inhibited LPS-induced expression of TNF and IL-1β and decreased microglia phagocytic efficiency. In retinal explants, A2AR blockade prevented the effects of LPS and elevated pressure on the morphological changes and on the production of NO, TNF and IL-1β. The blockade of A2AR prevented loss of RGCs induced by LPS or elevated pressure. Both SCH58261 and caffeine prevented microglia activation induced by I-R injury. Caffeine also decreased the levels of IL-1β and TNF and retinal cell death induced by I-R.

Conclusions/Discussion: Our results suggest that A2AR blockade and caffeine prevent retinal neuroinflammation and RGCs death, opening the possibility for the use of A2AR antagonists in retinal degenerative diseases involving inflammation, as glaucoma.

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The Placebo Effect in Glaucoma Medication Clinical Trials

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Purpose: To describe the extent of the placebo effect on intraocular pressure (IOP) in glaucoma medication clinical trials and to evaluate techniques employed to reduce the placebo effect.

Methods: Retrospective study review of single and double-masked phase I-III clinical trials with a placebo arm evaluating glaucoma medications that became commercially available in the USA after 1977. Techniques used to reduce the placebo effect included: a second qualifying day to enter the study; an afternoon IOP measurement as a second qualifying baseline; and multiple IOP measures at the same time point.

Results: To evaluate the placebo effect, 23 studies with a total of 1,884 patients evaluating 10 different medications were included. At 8 AM (n=18), mean IOP decrease from baseline for placebo was 2.3 ± 1.6 mmHg (9%) while for the diurnal curve (n=17), mean decrease was 1.4 ± 1.1 mmHg (6%). At 8 AM, 8/18 arms had ≥2 mmHg IOP decrease, and all showed some reduction in IOP. For the diurnal curve, 4/17 studies reduced IOP ≥2 mmHg, and one arm had no placebo effect. For techniques to reduce the placebo effect, 20 studies with 20 placebo arms for 10 different medications were analyzed. No statistical difference among the evaluated study designs was observed for either morning trough or diurnal IOP (p 0.27).

Conclusions: The placebo effect is common in glaucoma clinical trials and could potentially cause confusion to the efficacy of a new medicine. Current techniques employed to limit this phenomenon are no more effective than standard protocol.

Correlations between the Inflammatory Marker HLA-DR and Other Signs and Symptoms in Dry Eye Disease in Three Phase III Studies

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Aim: To investigate the correlations of the inflammatory marker HLA-DR assessed using flow cytometry on conjunctival imprints with clinical signs and symptom-reporting questionnaires commonly used to assess dry eye disease (DED) severity.

Methods: Baseline data were retrospectively collected from 3 clinical trials conducted on moderate to severe DED patients in 9 European countries. 311 patients were included in this analysis (87, 183 and 41 patients). Demographic and baseline DED characteristics were compared to baseline HLA-DR data.

Results: Flow cytometric HLA-DR expression, quantified in arbitrary units of fluorescence (AUF), significantly differentiated with Sjögren status; median values were 71,782 AUF and 45,324 AUF in patients with or without Sjögren syndrome, respectively ($p=0.0024$). The strongest significant correlation was seen with the corneal fluorescein staining (CFS) test ($r=0.30$, $p=0.0001$). Significant negative relationships were also found with Schirmer test ($r=-0.20$, $p=0.0003$) and tear break-up time (TBUT, $r=-0.13$, $p=0.0226$). Similarly, correlations were statistically significant with the total Ocular Surface Disease Index (OSDI) and Visual Analog Scale (VAS) scores ($r=0.12$, $p=0.0426$ and $r=0.14$, $p=0.0176$, respectively). However no significant relationship could be seen between HLA-DR AUF and tear osmolarity ($r=0.08$, $p=0.4987$).

Conclusion: A discrepancy between the symptomatology and the clinical signs of the disease is often observed. Here we found that conjunctival HLA-DR flow cytometry levels significantly correlated not only with clinical signs, such as CFS, Schirmer test and TBUT, but also with the symptom-reporting questionnaires. This is the first evidence that HLA-DR, a marker of ocular surface inflammation, could serve as a surrogate biomarker in the diagnosis of DED.

PACAP Administration can Ameliorate Vascular Changes in Retinopathy of Prematurity

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Premature birth can be associated with a series of disorders affecting future life quality. One of these conditions is a neuromuscular disease of the retina, called retinopathy of prematurity (ROP). Despite striking advances in neonatology ROP still remains the leading cause of vision impairment in childhood. Pituitary adenylate cyclase activating polypeptide (PACAP) and its receptors occur throughout the nervous system, including the retina. The in vivo protective effects of PACAP have been shown in several model of retinal degeneration including diabetic or ischemic retinopathy. Therefore we aimed to study PACAP administration in the well described animal model of ROP, the oxygen induced retinopathy (OIR). Sprague-Dawley rat pups were kept in alternating oxygen concentration for 2 weeks to provoke OIR. Pups were treated either with intravitreal (3x3ul) or intraperitoneal (7x100ul) PACAP injections. After 21 days the rats underwent functional examinations and their eyes were processed to flat mount lectin staining and immunohistochemistry. Quantification of avascular to whole retinal areas showed that PACAP administration decreases the vasoobliterated territory by almost 50 % and there was also a significant reduction in the number of neovascular tufts. These findings were further supported by functional and immunohistochemical examinations. Our results suggest that PACAP can act against retinal vascular changes and reduce the degree of ROP. Supported by MTA-PTE "Lendület" program, the European Union and the State of Hungary, co-financed by the European Social Fund in the framework of TAMOP 4.2.4. A/2-11-1-2012-0001 National Excellence Program, Arimura Foundation, Bolyai Scholarship,

Evaluation of Inflammatory Markers following Use of Systane Balance or Systane Gel in Patients with Dry Eye

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Purpose: To evaluate the change in the tear cytokine concentrations of 4 biomarkers (IFN- γ , IL-1 β , IL-6 & TNF- α) following use of either Systane BALANCE or Systane GEL after 30 days of use in patients with dry eye disease (DED).

Methods: Eligible patients in this single-site, 2-arm, double-masked, randomized study received either BALANCE or GEL, administered 4 times a day for 30 days. Tear cytokine assessments were conducted at baseline and Day 30. The study outcome was a relative change in each tear cytokine concentration from baseline per group.

Results: Fifty-four patients (27 patients/group) were eligible for both safety and intent-to-treat analyses. Patients in the BALANCE and GEL groups had mean ages of 62.3 and 63.8 years, with 37% and 40.7% being males, respectively. After 30 days of either BALANCE or GEL treatment, the mean baseline reduction in tear cytokine concentrations of IFN- γ , IL-1 β , IL-6 & TNF- α in each group were 12.51%, 11.25%, 38.47%, & 23.89% ($p \geq 0.178$), and -30.56%, 6.68%, 6.79%, & -14.22% ($p \geq 0.213$), respectively. There were reductions in all 4 cytokines measured in the BALANCE group and only 2 of 4 cytokines measured in the GEL group; none were statistically significant. Only 1 serious adverse event (AE) was reported in the GEL group, which wasn't considered treatment-related.

Conclusion: This study results showed that both Systane balance and Gel may reduce inflammatory cytokines in patients with dry eyes. A larger study is warranted to further understand the role of lubricants in DED.

Evaluation of Symptomatic Relief of Dry Eye Symptoms Following Systane Balance or Systane Gel Use

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Purpose: To evaluate the ability of either Systane BALANCE or Systane GEL in improving ocular comfort after 30 days use in patients with dry eye.

Methods: Eligible patients in this single-site, 2-arm, double-masked, randomized study received either Systane BALANCE or Systane GEL, administered 4 times a day for 30 days. Study assessments were conducted at 3 different visits (baseline, Day 15 & Day 30). The primary outcome was a change in ocular surface disease index (OSDI) score from baseline for each group.

Results: A total of 54 patients (27 patients/group) were eligible for both safety and intent-to-treat analyses. Patients in the BALANCE and GEL groups had mean ages of 62.3 and 63.8 years, 63% and 59.3% were females; at baseline, the mean OSDI scores were 33.61 and 31.75, respectively. After 30 days of either BALANCE or GEL treatment, the mean change in OSDI scores from baseline were -10.23 ($p=0.021$) and -16.74 ($p=0.001$), respectively. One serious adverse event (AE) was reported in the GEL group, which was not considered treatment-related. A total of 7 patients (2 in the BALANCE & 5 in the GEL groups) experienced 11 adverse events (3 in the BALANCE & 8 in the GEL groups); however, only the AEs experienced by one patient in each group (1 event while on BALANCE and 2 events while on GEL) were considered treatment-related.

Conclusion: This study showed that both Systane products were effective in improving OSDI scores after 30 days of treatment in patients with dry eye.

HP-B-Cyclodextrin –Brinzolamide Complexes: New Formulation Approaches to Enhance Bioavailability and Solubility

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Background: Cyclodextrin (CD) complexation is a technique that is used in pharmaceutical industry, in order to be manufactured novel drug delivery systems which overcome dissolution problems. Brinzolamide (BRI) is a carbonic anhydrase inhibitor which is used to lower intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Its low solubility leads researchers in new formulation approaches to enhance bioavailability.

Aim of this study was to investigate several BRI/HP-b-CD complexes with regard to solubilization and drug delivery and to develop topically effective BRI eye drop HP-b-CD solution.

Methods: Binary complexes of BRI and HP-b-CD were prepared solubilizing the drug in aqueous solution of HP-b-CD at different molecule ratios HP-b-CD:BRI (1:1, 1.5:1, 2:1, 2.5:1, 3:1).

Results and Discussion: The success of inclusion complexation was indicated by FTIR spectroscopy. From the Ap-type phase solubility diagram (Higushi and Connors) it was found that at low HP-b-CD concentration 1:1 complex between BRI and HP-b-CD is formed. However, at higher HP-b-CD concentrations (30-35 mg/ml) one additional cyclodextrin molecule forms the 1:2 complex. For this reason BRI was in amorphous form when its ratio with HP-b-CD was higher than 1:2.5. Dissolution profiles showed that the major quantity of BRI was rapidly released in 20 min followed by slow release. The complexes which express better dissolution rate (~99.99%) were those with molecular ratios 2.5:1. This evidence ascribed to the property of amorphous compounds to dissolve in aqueous solution faster and elevated. Another significant data which the dissolution profile shows is that increasing the amount of CD dissolution rate also increased

Effect of Topical Azithromycin on Symptoms, Clinical Signs, and Ocular Surface Inflammation in Patients with Meibomian Gland Dysfunction

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Background: The aim of this study was to evaluate the efficacy of topical azithromycin to improve symptoms, clinical signs and ocular surface inflammation in patients with MGD.

Methods: Thirty patients with MGD have been enrolled for this double-masked, randomized, pilot study. Diagnosis of MGD and treatment outcomes were assessed by means of OSDI questionnaire, Schirmer I test, tear break-up time (BUT), lissamine green conjunctival staining, fluorescein corneal staining, lid margin hyperemia, meibum quality. Ocular surface inflammation was studied by evaluating HLA-DR expression on conjunctival epithelial cells and pro-inflammatory cytokines in tears. Enrolled patients were divided into 2 groups: study group (n=15) was treated with topical azithromycin (Azyter, Laboratoires Thea) b.i.d. for 3 days and then once a day for 4 days. Control group underwent the same regimen with NaCl 0.9%. Evaluations were performed at day 0, 7, and 21.

Results: A significant improvement of symptoms, BUT, corneal fluorescein staining, meibum quality and lid margin hyperemia was recorded in the study group compared to baseline at day 7 and 21. No significant difference was found for Schirmer test and lissamine green staining. HLA-DR expression was decreased after 7 days of treatment in the study group only. Changes in tear cytokine concentrations were not observed.

Conclusions: Treatment with topical azithromycin for 7 days provides significant improvement in symptoms and signs of MGD that partially persist after 2 weeks. Control of ocular surface inflammation requires a continuous treatment. Larger studies are necessary to confirm these preliminary results.

Chitosan Nanoparticles Loaded With Timolol Drug for Ophthalmic Drops

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Background: In recent years, researchers are focused on the preparation of drug nanoparticles using natural hydrophilic polymers like chitosan (CS) due to its unique properties as mucoadhesive biomaterial. CS nanoparticles are usually prepared by ionic gelation method using tripolyphosphate (TPP) at low pH. Timolol maleate (TIM) is a non-selective beta-adrenergic receptor antagonist indicated for treating glaucoma, heart attacks and hypertension. TIM observe high hydrophilicity. It is well known that very hydrophilic drugs are poorly absorbed because of their inability to cross the lipid-rich cell membranes. The object of this study was to develop nanoparticles of chitosan, for ocular delivery to improve its corneal absorption, as viable alternative to conventional eye drops for management of glaucoma.

Methods: Nanoparticles were prepared by a simple ionic-gelation method at various molar ratios CS/TIM such as 2/1, 4/1 and 7/1.

Results and Discussion: TIM was successfully entrapped into CS nanoparticles prepared by ionic-gelation technique while nanoparticles with mean sizes ranging from 118 to 203 nm were prepared. From XRD patterns of TIM-loaded CS nanoparticles some crystalline peaks in case of 2:1 and 4:1 ratios were found for TIM drug. At 7/1 ratio amorphous inclusions are prepared. The dissolution profile of TIM in simulated organic tears, indicates that release rate is improved. This evidence ascribed to the property of amorphous compounds to dissolve in aqueous solution faster. Drug Release curves initially showed that TIM is rapidly released from the nanoparticles followed by slow release. The initial fast release phase could be due to the rapid dissolution of surface adhered/entrapped drug; in the later phase, the release medium penetrates into nanoparticles and dissolves the entrapped drug.

Ophthalmic Vascular Tone: Role of NO, CO and H2S

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Purpose: To evaluate the vasomotor responses of exogenous carbon monoxide (CO) and hydrogen sulphide (H2S) on isolated rabbit ophthalmic artery and their interaction with endogenous and exogenous nitric oxide (NO).

Methods: ophthalmic artery segments, obtained from albino rabbits, mounted on a wire myograph were challenged with cumulative concentrations of phenylephrine (PE) in the presence or absence of NG-nitro-L-arginine (LNNA) to inhibit production of NO, CO-releasing molecules (CORMs) or the H2S-donor GYY4137. Animals were handled according to the ARVO statement for the use of animals in ophthalmology and vision research.

Results: the maximal vasoconstriction elicited by PE in ophthalmic arteries reached 20-30% of that induced by KCl but was dramatically increased by incubation with LNNA. GYY4137 significantly raised PE-mediated vasoconstriction and reduced relaxation by sodium nitroprusside (SNP); however, GYY4137 depressed PE-induced contractions in the presence of LNNA. CORMs concentration-dependently inhibited PE-induced constriction but were less effective in LNNA treated arteries. In vascular tissues GYY4137 reduced cyclic GMP (cGMP) levels in normal and SNP-treated vessels. CORMs increased cGMP but this effect was strongly reduced by LNNA.

Conclusions: we conclude that both H2S and CO are able to relax isolated ophthalmic artery; however, the effect of H2S is seen only in the absence of endogenous NO and does not involve cGMP generation. In contrast, CO stimulates cGMP in a manner that seems to involve endogenous NO. These findings provided new insights into the complexities of gas interactions suggesting new pharmacological strategy for the treatment of ocular diseases.

Vascular Stem Cell Therapy of the Diabetic Retina with COMP-Ang1 and Endothelial Progenitor Cells

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Background: Diabetic retinopathy (DR) is the leading cause of blindness in the working-age population. Restoring vascular homeostasis and replacing lost endothelial cells could reduce the neurovascular damage that occurs in DR. An important factor lost in diabetic retinopathy is Angiotensin-1 (Ang1), which promotes endothelial survival and stability. Outgrowth endothelial cells (OECs), a specific subtype of endothelial progenitor cell, have the potential to reintegrate into damaged vascular beds and promote reparative angiogenesis. This study's purpose was to determine whether a novel Ang1 analog, COMP-Ang1, could prevent and reverse the structural and functional hallmarks of DR by increasing OEC integration into the diabetic retina.

Methods: Diabetic Ins2Akita mice were treated at 2 months with a single intravitreal dose of adeno-associated virus (AAV2) encoding COMP-Ang1 (AAV2.COMP-Ang1) or control. Four months later retinas were assessed for functional (Evans blue leakage), inflammatory (acridine orange leukography), and structural (confocal microscopy) status. A second cohort of 7 month-old mice (after the onset of DR) were treated with AAV2.COMP-Ang1 and OECs. Three days later retinas were harvested and analyzed with confocal microscopy to assess OEC integration into the retinal vasculature.

Results: AAV2.COMP-Ang1 preserved vascular structure in 6-month-old diabetic mice and decreased vascular leak and leukocyte adhesion. Furthermore, retinal thinning and ganglion cell layer dropout were prevented and treated mice retained near-normal visual acuity and electroretinographic response compared to controls. OEC migration speed, tube formation, and Akt phosphorylation was increased by COMP-Ang1 in a dose-dependent manner *in vitro*. In the second cohort of mice, preliminary results suggest that COMP-Ang1 increases OEC integration into the retinal vasculature compared to control.

Conclusions: AAV2.COMP-Ang1 may be useful in preventing diabetic neurovascular dysfunction. OECs and COMP-Ang1 may play a functional reparative role in diabetic retinopathy and other diabetic microvascular diseases. Future studies will determine whether newly integrated OECs reduce functional deficits in DR.

John Dalrymple a Surgeon, Pathologist, and Ophthalmologist, and his Work 'The Anatomy of the Human Eye'

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John Dalrymple (1803-1852), son of the surgeon William Dalrymple (1772-1847) was a surgeon, a distinguished pathologist and also an ophthalmologist. His work was pioneering as for oncology, regarding the discovery of the albumin known as Bence Jones protein which is often detected in the blood and urine of patients suffering from multiple myeloma. These findings were described in the study 'On the microscope character of motilities ossium'. Also he published two projects focusing on Ophthalmology: "The anatomy of the human eye" (1834) and "Pathology of the human eye" (1852). We examine the first of these treatises, which is presented in this work where the highlights of his scientific integrity become obvious. The writer is also famous for his well known medical sign called 'Dalrymple's point' in the diagnosis of thyroid ophthalmopathy.

Intravitreal Ranibizumab Injections with and without Pneumatic Displacement for Treating Submacular Hemorrhage Secondary to Neovascular Age-Related Macular Degeneration

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Purpose: To evaluate the efficacy of intravitreal ranibizumab with and without pneumatic displacement for the treatment of submacular hemorrhage (SMH) secondary to neovascular age-related macular degeneration (nAMD).

Methods: We retrospectively reviewed the medical records of 93 treatment-naïve patients (93 eyes) with SMH secondary to nAMD. All patients were treated with an initial series of 3 monthly intravitreal ranibizumab injections, followed by as-needed injections. For the patients treated with pneumatic displacement, expansive gas was injected at the time of the first ranibizumab injection.

Results: Twelve months into treatment, the mean logarithm of the minimum angle of resolution (logMAR) of best-corrected visual acuity (BCVA) of all subjects significantly improved from 1.19 ± 0.55 (20/309) at baseline to 0.96 ± 0.39 (20/182, $P = 0.007$). No significant difference in BCVA between ranibizumab monotherapy and combination therapy groups was observed at 12 months. However, the proportion of eyes with ≥ 3 line BCVA improvement was significantly higher in the combination therapy group (57.1%) than in the ranibizumab monotherapy group (37.9%; $P = 0.03$). Among eyes with typical nAMD (39 eyes), the proportion of eyes showing a ≥ 3 -line improvement in BCVA was significantly higher in eyes treated with combination therapy than in eyes treated with ranibizumab monotherapy ($P = 0.02$). This difference was not observed in eyes with polypoidal choroidal vasculopathy (PCV, 54 eyes).

Conclusions: Intravitreal ranibizumab injections with and without pneumatic displacement are viable treatment options for SMH secondary to nAMD. Additional benefits of pneumatic displacement for SMH were only significant in eyes with typical nAMD and not in eyes with PCV.

In Vitro Activation of Steroid Receptors in Corneal Epithelial Cells Using a Novel Anti-inflammatory Liposomal Formulation

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Background: Unpreserved liposome-based formulations were loaded with the anti-inflammatory agent medroxyprogesterone (mdx). We aimed at determining the *in vitro* activation of steroid receptors in corneal epithelial cells after exposure to mdx-loaded liposomes.

Methods: Liposomes (188.90 ± 18.21 nm) composed by phosphatidylcholine, cholesterol and α -tocopherol (8:1:0,08) with (mdx-lipo) or without mdx (blank-lipo) were prepared by the solvent evaporation technique and dispersed with a hypotonic trehalose-borate aqueous solution (dispersion solution) (202.4 ± 0.33 mOsm). Human Corneal Epithelial (HCE) cell line was exposed to dispersion solution, blank-lipo, and mdx-lipo for 1h. A mdx-commercial formulation (Colircusi Medrivas) was used as formulation control. After exposure time, expression of glucocorticoid and progesterone receptors was determined by Western blotting and immunofluorescence. Quantification of nuclear staining was done to measure receptor activation. Cell proliferation and viability were measured after formulation exposure using AlamarBlue[®] and XTT[®] assays, respectively.

Results: Expression of both receptors increased after blank-lipo, mdx-lipo, and Medrivas exposure. However, nuclear staining for both receptors was higher after mdx-lipo exposure than after blank-lipo exposure. Cell proliferation rate significantly decreased 24h after mdx-lipo and Medrivas exposure, and cell viability values were always around 100%.

Conclusions: Exposure of HCE cells to mdx-lipo leads to an activation of glucocorticoid and progesterone receptors and a reduction in proliferation rate. This novel liposome-based formulation, used as unpreserved artificial tears, may be used as anti-inflammatory drug delivery system. Experiments to determine the anti-inflammatory activity of mdx-lipo are ongoing using an *in vitro* model of ocular surface inflammation.

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Effect of Two Different Types of Suturing Technique on Astigmatism after Penetrating and Deep Anterior Lamellar Keratoplasty

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Abstract Aim: To compare the effect of two different suturing technique on astigmatism after penetrating (PKP) and deep anterior lamellar keratoplasty (DALK).

Method: A retrospective study of 71 eyes of 71 patients (52 cases underwent PKP and 19 cases underwent DALK with two types of suturing technique: interrupted and single running) was done. Postoperative uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA) evaluated and astigmatism results measured 6, 12, and 18 months post operatively.

Results: There was no significant difference in the amount of astigmatism between the two types of suturing technique after removal of sutures (at 18 months) in both types of keratoplasty. The interrupted suture group had astigmatism of 6.50 ± 0.75 diopters, while the single running suture group had astigmatism of 5.5 ± 1.0 diopter.

Conclusion: Long term BCVA and post operative astigmatism are similar in both PKP and DALK, regardless of suturing technique.

PACAP Protects the Human Retinal Pigment Epithelial Cells against Hyperglycaemic and Hypoxic Conditions

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Angiogenesis and hypoxia are both playing critical role in many retinal diseases, such as diabetic retinopathy and macular degeneration. Under these conditions the integrity of the pigment epithelial cells is disrupted, thus photoreceptor survival and normal vision become impossible. The retinal pigment epithelial cells are very important elements of the blood retina barrier, and they are known to express different angiogenic factors, such as VEGF (vascular endothelial growth factor), so they most likely important in the process of neovascularisation. PACAP is known to exert retinoprotective effects, against several types of retinal injuries in vivo, including optic nerve transection, retinal ischemia, excitotoxic injuries, UV-A-induced lesion and diabetic retinopathy. We have shown that PACAP activates antiapoptotic pathways and inhibits proapoptotic signaling in retinal lesions in vivo. The aim of the present study was to investigate the possible protective effect of PACAP in hyperglycaemic and hypoxic conditions on ARPE-19 cells. Cells were exposed to 24 h sucrose, CoCl₂ and H₂O₂ treatment. Expression of angiogenic, apoptotic and cell stress markers was investigated by specific arrays, and flow cytometry. Our results showed that sucrose administration increased different proangiogenic factors like VEGF, angiogenin, endothelin while PACAP treatment could decrease most of them. PACAP could also diminish the expression of stress and proapoptotic factors, which were induced upon CoCl₂ and H₂O₂ administration. In summary, our results show that PACAP influences and also regulates angiogenic and apoptotic processes in pigment epithelial cells.

Potential of Frequency-Doubling Technology for Predicting Future Visual Field Loss for Perimetrically Normal Eyes of Open-Angle Glaucoma Patients

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Background: Recent studies indicate standard automated perimetry (SAP) losses sometimes occur before a retinal nerve fiber layer (RNFL) defect is noted. Frequency-doubling technology (FDT) perimetry reportedly detects glaucomatous damage earlier than SAP does. Perimetrically unaffected eyes of glaucoma patients with unilateral visual field (VF) defects are at high risk for developing VF abnormalities on SAP. No studies have evaluated the potential of FDT in such perimetrically unaffected eyes.

Methods: Open-angle glaucoma (OAG) patients with unilateral VF loss detected by SAP were examined with FDT at baseline. VF examinations were followed by a series of SAP examinations administered over 6 years. The SAP test points were matched to the FDT test sectors. The relative risk (RR) of subsequent SAP abnormality corresponding to abnormal FDT sectors in perimetrically normal eyes was calculated.

Results: Forty-eight perimetrically normal eyes of 48 participants had complete data and a qualifying follow-up. Baseline FDT results were abnormal in 69% eyes. Of the eyes with abnormal FDT results, 61% developed abnormal SAP results after 4 to 27 months. Baseline FDT results were also abnormal in 21% of total 912 sectors in perimetrically normal eyes. 24% of abnormal FDT sectors developed SAP abnormality in the SAP-on-FDT sector. The RR of subsequent SAP abnormality corresponding to abnormal FDT sectors was 5.63 (95% confidence interval, 3.54–8.94; P<0.001).

Conclusions: In perimetrically normal eyes of OAG patients, FDT detected VF loss in almost 2 of every 3 of these eyes and also predicted to some extent future VF loss on SAP.

Unusual Eye Symptoms of Giant Prolactinoma

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Background: Prolactinoma is the most common pituitary adenoma, which causes infertility, menstrual irregularity and galactorrhea in women, hypogonadism, erectile dysfunction and gynecomastia in men. The main eye symptom is bitemporal hemianopsia.

We report a case of a patient with the giant prolactinoma and unilateral nasal visual field impairment.

Case Report: The 62 year old man had complained about mild blurred vision and visual field impairment in the right eye for 6 months. The best corrected visual acuity was 0,9 in the right eye and 1,0 in the left eye. There was inferior nasal quadrantanopsia of the right eye, normal visual field of the left eye and symmetrically reduced retinal nerve fibre layer (RNFL) of temporal quadrants in the peripapillary scans of optical coherence tomography (OCT).

Head magnetic resonance imaging (MRI) showed a large pituitary tumour 57x37x42 mm, which was spread in the suprasellar area, and deviated the right optic nerve and the right part of the optic chiasm. Prolactin serum level was more than 150000 mIU/l; testosterone serum level was slightly lower, 7 nmol/l.

The dopamine agonist treatment with daily doses of cabergoline 0,5 mg resulted in complete visual acuity and visual field improvement within one month. At the same time, tumour shrunk by one tenth in the control MRI scan and prolactin level decreased to 60 mIU/l.

Conclusion: The asymmetrically growing tumour exerted pressure on the lateral part of the optic chiasm and optic nerve and caused flattening of temporal quadrants of peripapillary RNFL and unilateral nasal field impairment.

Inhibition of Corneal Inflammation Following Keratoplasty by Birch Leaf Extract

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Background: The objective of this study was to determine the effect of birch leaf (*Betula pendula* Roth) extract (BPE) on corneal inflammation following keratoplasty in the rat model.

Methods: T cells were stimulated *in vitro* in the presence of BPE. Proliferation, activation phenotype and the number of apoptotic/necrotic cells in cell culture were analyzed by flow cytometry. Corneal transplantation was performed between Fisher and Lewis rats. Recipient rats were either treated with cyclosporine A at a low, sub-therapeutic dosage (Low-dose CsA = LDCsA) or received LDCsA in combination with BPE (2x1ml/day). Clinical signs for corneal inflammation and rejection time points were determined. Infiltrating leukocytes were analyzed histologically.

Results: BPE specifically inhibited T cell proliferation *in vitro* by inducing apoptosis. The phenotype was not affected. *In vivo*, BPE significantly delayed the onset of corneal opacification (p0.05). The amount of infiltrating CD45⁺ leukocytes and CD4⁺ T cells (p0.001) was significantly reduced by BPE, whereas infiltration of CD163⁺ macrophages was not significantly different between the two groups. BPE selectively induces apoptosis of activated T cells. Accordingly, BPE-treatment significantly reduces infiltrating T cells and subsequent corneal opacification following keratoplasty.

Conclusion: Our findings suggest BPE as a promising anti-inflammatory drug to treat corneal inflammation.

Association of Vitamin D Status and Open-Angle Glaucoma

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Objective: The present study was conducted to test the hypothesis that lower vitamin D status is associated with greater prevalence of open-angle glaucoma (OAG).

Method: Cross-sectional study. Multivariable logistic regression was performed to examine the relationship between serum 25-hydroxyvitamin D (25(OH)D) and OAG after adjusting for traditional potential confounders. OAG was defined by the criteria of the International Society for Geographical and Epidemiological Ophthalmology.

Results: Multivariable-adjusted odds ratios of OAG across quintiles of decreasing 25(OH)D were 1.26, 1.00 (reference), 1.31, 1.36 and 1.69 (P for quadratic trend 0.01). The odds ratio for the lowest 25(OH)D quintile was significantly higher than that for the second quintile (P 0.01). In addition, we discovered that several factors related to OAG, such as intraocular pressure or vertical and horizontal cup-to-disc ratios, had a significant relationship with 25(OH)D level.

Conclusions: There was a reverse J-shaped association between 25(OH)D levels and the risk of OAG, with significantly elevated risk at lower 25(OH)D. The findings of this research suggest that vitamin D deficiency should be considered as a potential risk factor for the development of OAG.

Moraxella Keratitis Review of 10 Cases

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Purpose: *Moraxella* sp. is one of the major pathogen causing a severe and sight-threatening keratitis. The aim of this work was to analyze the clinical presentation, predisposing risk factors, patients' backgrounds, *in vitro* antimicrobial susceptibility, and treatment period.

Methods: We reviewed 10 culture proven cases of *Moraxella* keratitis, retrospectively, during a 12-year period (from 2003 to 2014) at Ehime University Hospital.

Results: The mean age of the patients with *Moraxella* keratitis was 67 years. Although the ocular conditions included trauma, conjunctivitis, bullous keratopathy, and lagophthalmos, no ocular predisposing factors was identified in six patients. Six patients had diabetes mellitus. In all cases, visual acuities at first visiting were less than 20/200. Eight patients showed the focus with hypopyon. Five cases presented the round or oval shaped focus in the center of cornea, and other five cases showed the irregular or amebic shaped focus in the central or peripheral cornea. *Moraxella* sp. were isolated from cornea scrapping in all patients, and all isolates were sensitive to fluoroquinolone and aminoglycoside. They were treated with combination of fluoroquinolone and tobramycin ophthalmic solution. Although no patients resulted corneal perforation, responses for the treatment in all cases were slow and the mean treatment period was 4.5 weeks.

Conclusion: *Moraxella* keratitis could present in the elder patients with diabetes mellitus in Japan. It shows round, irregular, or amebic shaped focus with hypopyon. Since treatment response for *Moraxella* keratitis could be very slow, we should continue fluoroquinolone and aminoglycoside which has good susceptibility against *Moraxella* sp.

Efficacy of Cationorm® Preservative-free Cationic Emulsion Versus Vismed® (0.18% Sodium Hyaluronate) in Moderate to Severe Dry Eye Disease (DED) Patients

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Background: Cationorm® is a preservative-free cationic emulsion composed of positively-charged lipid nanodroplets which adhere to the negatively-charged ocular surface providing hydration and lubrication while also restoring the lipid layer. Efficacy and safety of Cationorm® were assessed in moderate to severe DED patients.

Methods: DED patients defined by at least 2/7 symptoms of discomfort ≥ 23 (VAS, 0 to 100%) and signs [ocular surface staining (OSS) (i.e. sum of nasal and temporal conjunctiva and corneal staining) score ≥ 4 and ≤ 9 (modified Oxford scale); and either a sum of 3 TBUT measurements ≤ 30 sec. or a Schirmer test ≥ 3 and ≤ 9 mm/5min] were enrolled in a 3-month phase 3, multicenter, investigator masked, parallel-group, randomized study with Cationorm® or Vismed® QID.

Results: 85 patients were enrolled (Cationorm® group: 44, Vismed® group: 41). At Month-1 (primary endpoint), as OSS improvement with Cationorm® was similar to Vismed® (-2.5 \pm 1.3 vs. -1.9 \pm 1.6, respectively), non-inferiority (NI) was demonstrated [95% CI upper bound: -0.15 2 (predefined NI margin), p0.0001].

Total symptoms score of ocular discomfort were significantly better with Cationorm® at Month-1 (difference of 6.77 \pm 3.35, p=0.0469). Investigator global efficacy assessment (p=0.0339) and quality-of-life scores for ocular pain (p=0.013) and driving (p=0.013) were also in favour of Cationorm® at Month-3. No difference between groups in terms of safety was observed.

Conclusion: Cationorm® was demonstrated to be safe and efficient in improving ocular surface damage of patients with moderate to severe DED, with superior relief of ocular discomfort symptoms than Vismed® leading to benefit in the QOL.

Cannabinoid Receptor 2: A Novel Immunosuppressive Target in Experimental Proliferative Vitreoretinopathy

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Introduction: Proliferative vitreoretinopathy (PVR) is a sight-threatening complication of retinal detachment, ocular trauma or inflammation. Cannabinoid receptor 2 (CB2) is expressed on immune cells and activation of this receptor is anti-inflammatory. We examined the role of CB2 in an experimental murine model of PVR using strain control and a genetic knock-out of CB2.

Methods: PVR was induced in CBR2^{-/-} and C57BL/6 mice by intravitreal dispase injection (0.1U; 2ml). At 7 days post-dispase injection, the morphology of the eyes was examined using light microscopy and scored using a clinical grading system. Animals were sacrificed and the eyes enucleated and processed for histological grading. Cytokines were evaluated by ELISA and prostaglandins and related lipids were analyzed using tandem mass spectrometric analysis.

Results: Dispase injection (0.1U; 2 µl) resulted in retinal pathological changes in CB2^{-/-} mice, including retinal folds and choroiditis (inflammation of the choroid), increases in inflammatory markers and exudation. A significant increase (p<0.05) in activated retinal microglia, and elevated levels of prostaglandins and related lipids was also seen in CB2^{-/-} animals. In contrast, only mild or absence of pathology was observed in C57BL/6 animals.

Conclusion: Mice lacking CB2 had increased susceptibility to dispase-induced retinal damage. The retinal pathology in CB2^{-/-} mice was associated with increased activated microglia and elevated levels of prostaglandins and neurotoxic lipids. This data is supportive of an immunosuppressive role for CB2 in inflammatory ocular conditions and suggests that drugs that activate CB2 may be useful in the treatment of ocular inflammatory disease.

Structural Change after Macula-off Rhegmatogenous Retinal Detachment Repair

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Purpose: To evaluate postoperative structural change and identify the difference between scleral buckling and pars plana vitrectomy in macula-off rhegmatogenous retinal detachment repair outcome.

Methods: For this retrospective observational study, 15 patients who underwent scleral buckling and 15 patients who underwent pars plana vitrectomy were involved. We analyzed preoperative and series postoperative spectral domain optical coherence tomography (SD-OCT) and best corrected visual acuity (BCVA).

Results: Foveal subretinal fluid reabsorption took a mean 17.21 ± 9.32 weeks in scleral buckling cases and a mean 5.35 ± 8.76 weeks in pars plana vitrectomy cases. The mean BCVA improvement was 0.53 ± 0.47 logMAR in scleral buckling cases and 0.71 ± 0.64 logMAR in pars plana vitrectomy cases 6 months after surgery. The final BCVA was significantly correlated with integrity of photoreceptor inner segment-outer segment junction in SD-OCT finding.

Conclusions: We observed relatively faster subretinal fluid reabsorption in pars plana vitrectomy cases than scleral buckling cases. Gradual resolution of macular detachment and improvement of inner segment-outer segment disruption on SD-OCT correlated with improvement of BCVA.

Human Origin RGD-Containing Recombinant Protein EGT022 Reduces Vascular Leakage through Pericyte Recruitment

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Purpose: We previously reported the therapeutic effect of EGT022, a human-derived RGD-containing recombinant protein, in oxygen induced retinopathy (OIR) model. To investigate the effect of EGT022 on the blood vessel restoration and maturation further, we examined the effect of EGT022 on pericyte ensheathment to blood vessels in OIR model and vascular leakage in retinas.

Methods: The OIR was induced by 75% oxygen environment and returned to room air followed by EGT022 administration. The pericyte coverage was assessed immunocytochemically using retinal whole mount labeled with endothelial cell or pericyte markers. The reduction of vascular leakage was measured by retinal vessel permeability assay.

Results: EGT022 induced the increase of pericyte coverage on the retinal microvessels dose-dependently in OIR mice. The administration of EGT022 reduced vascular leakage caused by VEGF injection. The pretreatment of EGT022 reduced opaqueness of eye caused by vascular leakage induced by VEGF.

Conclusion: The immunocytochemical staining of OIR shows the poor pericyte-endothelial cell interaction and pericyte drop out. We have demonstrated in this study that EGT022 increases the maturation of blood vessels by recruiting pericyte into damaged microvessels. The recruitment of pericyte to blood vessels stabilizes them and eventually reduces the leakage. Pretreatment of EGT022 induced the reduction of vascular leakage caused by VEGF. The experimental evidences suggest that EGT022 has the potential value to be a novel treatment for retinopathy by maturing blood vessels.

Intravitreal Ranibizumab for Acute Central Serous Chorioretinopathy

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Background: To evaluate the effectiveness of intravitreal ranibizumab injection (IVRI) for acute central serous chorioretinopathy (CSC).

Methods: Patients with symptomatic CSC of less than 3 months were prospectively recruited. Patients (n = 20/group) were randomly assigned to IVRI (0.5 mg/0.05 ml) or observation and followed for 6 months. LogMAR best-corrected visual acuity (BCVA), fluorescein angiography, indocyanine angiography, and central foveal thickness (CFT) were assessed at baseline and at regular follow-ups.

Results: All patients had increased BCVA, decreased CFT, and resolution of the neurosensory detachment. Complete resolution of neurosensory retinal detachment required more time in the observation group (13.0 ± 3.1 vs. 4.2 ± 0.9 weeks; p 0.001). Mean BCVA and mean CFT improved significantly in both groups, but the changes were not significantly different between groups at 6 months.

Conclusions: IVRI for acute CSC might hasten resolution of neurosensory detachment compared to observation alone. At 6 months, BCVA and CFT did not differ between IVRI and observation groups. Further studies are required to determine the long-term benefits of IVRI.

Expression of MicroRNAs and Targeted MicroRNAs in Fibroblast of Pterygium

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Purpose: To screen microRNA (miR) and set up target miRs in the pterygium.

Materials and Methods: Primary fibroblasts were cultured from pterygium and Tenon's capsule. To confirm the culture of fibroblast, we performed immunocytochemistry and western blot analysis. 1733 miRs were screened in the first step using GeneChip® miRNA3.0 Array. Selected secondary targeting miRs that were subsequently analyzed using the following cut-off values; 1) high reproducibility under the repetitive test. 2) base log value of signal more than 7.0 in both controls and fibroblast of pterygium and 3) log ratio between fibroblasts of pterygium and those of normal control 1.0.

Results: In the primary screening test, 887 were upregulated and 846 of 1733 miRs were downregulated in fibroblasts cultured from pterygium as compared to controls. Of 1733 miRs, 4 target miRs met all the established criteria (miR-143a-3p, miR-181a-2-3p, miR-377-5p, and miR-411a-5p). All were upregulated in pterygial fibroblasts compared to controls in the primary screening test and miR-143a-3p showed the highest mean ratio compared to controls.

Conclusions: Four microRNAs including miR-143a-3p, miR-181a-2-3p, miR-377-5p, and miR-411a-5p were upregulated in pterygial fibroblasts compared to control tissue, which may indicate their involvement in the pathogenesis of pterygium.

Versatility of Cationic Emulsion in Dry Eye Relief

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Background: Dry eye relief products provide their efficacy by several mechanisms. The capacity of a product to cover the entire ocular surface whatever the condition of the cornea (injured, dry, wet, etc.) is of great importance in restoring tear film. This property is reflected by the spreading coefficient. This work evaluates and compares the spreading coefficient of several marketed dry eye products.

Methods: Samples of commercially available dry eye products of different types were tested (Cationorm®, Aquarest®, Systane Balance®, Optive®, Refresh® and Vismed®). Spreading coefficients were calculated from surface tension and contact angle scores measured on excised humid rabbit eye, glass plate, teflon plate.

Results: On excised eyes, emulsions, i.e. Cationorm® and Systane Balance® exhibited the highest spreading coefficients. On glass slide results were in the same range to eyes while on Teflon plate spreading coefficients were much lower. Cationorm® remained with the highest coefficient whereas on that surface all the other products exhibited significantly lower spreading coefficients ranging from -55.020 (Systane Balance®) to -101.834 (Vismed®).

Conclusions: On excised eyes, all product except Aquarest perform similarly with emulsions (Cationorm and Systane) having the best spreading property. Teflon™ plate reflects a dry condition with a low mucus content. In those conditions, cationic emulsion (i.e. Cationorm®) and gels (i.e. Aquarest) exhibit the best spreading coefficient. Finally, Cationorm® showed on all types of surface the best spreading coefficient leading to the conclusion that after an instillation a cationic emulsion would spread all over the ocular surface whatever the condition of the cornea.

Antiviral Efficacy of HSV1-Specific Meganucleases in a Mouse Model of Relapsing Herpes Keratitis

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Background: While conventional drugs used in the treatment of infections by Herpes simplex virus type 1 (HSV1) does not reduce the burden of latent virus and therefore the risk of viral reactivation, specific endonucleases (such as méganucleases) could be an issue to reduce the relapsing herpetic keratitis in previously treated tissues.

Methods: Three weeks after subconjunctival inoculation of rAAV (recombinant adenovirus-associated) encoding a meganuclease specific to HSV1 (or the Green Fluorescent Protein, GFP), mice were infected in the lip with a wild type strain of HSV1 (SC16) to induce a latent infection in the trigeminal ganglia (TGs) TG. After 28 days, mice were subjected to a reactivation stimulus (heatshock) and then sacrificed. Corneas and TGs were analyzed for the presence of HSV-1 genome and several viral transcripts (LAT, TK and UL18).

Results: In the corneas, as in TG, mice treated with rAAV encoding meganuclease had more copies of viral genomes (viral load) and LAT, TK and UL18 transcripts (signs of viral replication) than control mice, ie treated with rAAV encoding GFP (p = 0.002 to p = 0.0008), suggesting a significant reduction in the activity of viral replication after herpes reactivation stimulus.

Conclusions: The subconjunctival inoculation of rAAV encoding a specific HSV1 meganuclease in ocular tissues seems to reduce the importance of HSV1 reactivation in TGs (the site of herpetic latency) and corneas. These results suggest that specific HSV1 meganuclease could be tested in therapeutic protocols with the aim of reducing the risk of herpes reactivation in the cornea.

Design and Synthesis of Functional Lipidic Biomaterials for the Encapsulation and Triggered Release of Drugs in Ocular Applications

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A library of novel lipids with designed functionalities was synthesized [1]. These lipids are used as functional additives in host-guest type bicontinuous lipidic cubic phases (LCPs) that exhibit a combination of material properties rendering them highly interesting for various biomaterial applications: they are non-toxic, biodegradable, thermodynamically stable in excess water, and can incorporate active molecules of virtually any polarity and size, retaining them in their active state. The most striking property of LCPs, however, is their optical transparency, making them ideal candidates as ocular drug delivery matrices. Structure, dynamics and properties of these biomaterials will be presented, as well as their applicability as matrices for the encapsulation of active compounds, and their triggered release by chemical [2] and/or photochemical means.

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[2] Nazaruk E, Szlęzak M, Górecka E, Bilewicz R, Osornio YM, Uebelhart P, Landau EM. Design and assembly of pH-sensitive lipidic cubic phase matrices for drug release. *Langmuir*. 2014 Feb 11; 30 (5): 1383-90.

Is Blepharitis Associated with Pathogenesis and/or Progression of Keratoconus?

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Background: An association has been reported between eye rubbing as well as Inflammatory molecules in tears and keratoconus. It is also well known that chronic blepharitis is associated with eye rubbing and chronic ocular inflammation.

Methods: 50 patients aged 18-45 years old with keratoconus and 72 control patients of similar ages and gender were included. The eyelids were checked for presence of scales and foam on the eyelashes and meibomian gland dysfunction test was performed. All patients were asked to fill two questionnaires: the OSDI questionnaire for dry eyes and a questionnaire regarding symptoms, signs and risk factors of blepharitis.

Results: More patients with keratoconus reported suffering from blepharitis as compared with control subjects (24% vs. 2.8%, $p=0.0009$). More KC patients reported rubbing their eyes more than once a day (36% vs. 11.1%, $p=0.002$) as well as red and tired eyes (12% vs 0%, $p= 0.009$). Signs of blepharitis and MGD were found more frequently on external eye examination in the keratoconus group as compared with the control group (Scales: 48% vs. 8.2%, $p0.0001$).

Conclusion: We observed an increased prevalence of blepharitis and dry eye among patients with keratoconus. Mechanical eye rubbing and inflammatory features that accompany chronic blepharitis may play a role in the etiology of keratoconus. Careful follow-up and treatment should be considered.

Corneal Pocket Technique for Corneal Tattoo

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Background: Tattooing of cornea is well accepted technique for achievement of accepted cosmetic results in whitish corneas due to chronic inflammation. I'll describe an easy, efficient and time saving technique of corneal tattoo.

Method: A patient with a blind eye following multiple retinal surgeries applied for cosmetic tattooing of his whitish cornea. During surgery lamellar dissection of cornea through two small peripheral corneal incisions was performed. Tattoo stain was then injected through the small openings. A video clip will show the technique in details.

Results: Tattoo stain was spread evenly across the cornea. Cosmetic results were well accepted.

Conclusion: Corneal lamellar dissection though small opening is recommended for corneal tattooing.

Chronic Caffeine Treatment Protects Oxygen-Induced Retinal Neovascular Damage in a Mouse Model of Proliferative Retinopathy

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Purpose: To evaluate the effects of caffeine on retinal neovascularization (NV) in an oxygen-induced retinopathy (OIR) model.

Methods: Seven-days old C57BL/6J mice were exposed to 75% oxygen for 5 days to induce vaso-obliteration from postnatal day 7 (P7) to P12. At P12, the mice returned to room air to induce retinal neovascularizaion, which was maximal at P17. The nursing mothers were given 1.0 g/L Caffeine solution or water for control, starting from the first day after delivery. Immunostaining, HE staining, and RT-PCR were used to assess retinal nonvascular area and neovascular response.

Results: For the effect of caffeine on vaso-obliteration, 1.0 g/L caffeine-treated OIR group, retinal nonvascular area decreased by 19.98 % at P12 (P0.05), and 47.87% at P17 (P0.05), compared to age-matched OIR control. For the effect of caffeine on vaso-proliferation at P17, not only NV area assessment in flat mount reduced by 44.13%, but quantitative neovascular nuclei counting in cross sections also showed a dramatic inhibition from (86.99±4.52) to (42.88±3.17)(P0.001).

Time course of caffeine administration showed caffeine treatment from P0 to P7, which was equivalently to P0-P17 group, significantly diminished nonvascular area compared to OIR control (10.98±1.64% vs. 17.58±1.41%, P0.05). Caffeine treatment did not affect the superficial, intermediate and deep vascular plexus of C57BL/6 mouse retinal vasculature separately observed under laser scanning microscope.

Conclusions: These finding provides the original experimental evidence that caffeine pretreatment attenuated pathologic but not developmental angiogenesis in the mouse model of OIR.

Twelve-Month Efficacy and Safety Profile of Ranibizumab versus Laser Photocoagulation in Patients with Diabetic Macular Edema (RE-DES Study)

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Objective: To determine whether there were differences in mean change in best corrected visual acuity (BCVA) with ranibizumab 0.5 mg versus laser photocoagulation (LP) in patients with diabetic macular edema (DME) over 12 months.

Methods: This was a multicentre, randomised, open-label controlled trial. Patients were randomly assigned (ratio 1:1) to intravitreal injection of ranibizumab with 3 loading doses and then pro-re-nata treatment or to LP administration. The inclusion criteria were: patients ≥18 years old, diabetes mellitus type 1 or 2, study eye BCVA of 78-25 letters, central retinal thickness (CRT) ≥250 µm, and visual impairment dueto DME.

Results: 83 patients were randomized (40 ranibizumab and 43 LP). The study population was mostly men (59.8%), with a mean (SD) age of 63.5 (9.4) years and BMI of 29.2 (4.2) kg/m². The ranibizumab group showed a trend to a higher BCVA change [8.7 (9.1)] vs LP [4.0 (10.6) letters, $p=0.0778$]. A significantly higher percentage of patients with ranibizumab achieved BCVA73 letters (54%) vs LP (24%, $p=0.0090$) at month 12. CRT at month 1 showed a significant reduction with ranibizumab [-55.2 (62.2) mm, $p0.0001$] but not with LP [-21.9 (82.9) mm, $p=0.3606$]. Almost half the patients in each group had one treatment-emergent adverse event.

Conclusions: Treatment with ranibizumab 0.5 mg showed a better improvement of BCVA than LP at month 12 in patients with DME. A CRT reduction at month 1 in patients treated with ranibizumab was also observed. The safety profile of ranibizumab was consistent with other clinical trials.

Management of Biological Material (Mehran, Bio-lent) for Treatment and Avoid Retinal Pathology and Postoperative Complication after Scleral Buckling Surgery in Retinal Detachment

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Purpose: For treatment and avoid retinal pathology and postoperative complications and improve reattachment retina with Mehran bio -Lent (biomaterial) after scleral buckling.

Methods: Scleral buckle by Mehran bio-lent. that is a piece of biomaterial (trimethyl carbonate) that properties same as silicon material, the sclera toward the middle of the eye. This buckling effect on the sclera relieves the pull (traction) on the retina, which difference is that have 4 pairs of holes in the end of the strip, and on one of its ends there is a split 1*5 mm, the head of the biomaterial can be ahead from the split than fix bio, lent with together on the sclera with nylon Succor After 4-6 mount (after reattachment retina) automat these nylons and biomaterial will be observed, and step by step the eyeball will be as normal size.

Result: Sclera buckling with Mehran bio-lent, surgeon able to control IOP, with regular bio lent, after resolve bio material, avoid of: a- decrease blood circulation, and increase blood pressure. b- choroidea ischemia, and reduced pulse amplitude. c- Change visual axis. d-avoid of glaucoma. e-avoid of rick myopia, strabismus, Astigmatism f-avoid of vitreous hemorrhage. g- to change anterior segment deepness. h-avoid of (IOP) and increase pressures on optical nervous, and avoid of Retina edema, change biochemical process, scleral change diameter, change to microscopic layer retina, avoid vitreous proliferation, internal erosion.

Conclusion: This method helps to provides total retinal attachment to choroidea and help to avoid glaucoma and post operative complication. In scleral buckling surgery.

Development of New Anti-VEGF Therapy by Kinase Inhibitor

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Wet Age-related macular degeneration is characterized by choroidal neovascularization (CNV) concerned with vascular endothelial growth factor (VEGF). The only approved drugs are antibodies to VEGF by intravitreal injection. Intravitreal injection requires tedious procedure so as not to cause complication such as infection. Thus eye drop treatment is desired. However the molecular weight of antibodies is too large for it to become eye drops. We approached this problem by screening small kinase inhibitors that suppress VEGF activity.

Method: We evaluated VEGF protein level in the culture medium after addition of our kinase inhibitor library by ELISA. We added 10 μ M compounds or control (0.1% DMSO) to ARPE-19 cells. The medium was collected 72 hours after the addition of compounds. The compound which inhibited VEGF activity strongest was intravitreally injected to laser CNV model mice immediately after laser photocoagulation. Seven days after laser injury, the mice were perfused with 1mL of 0.5% fluorescein-isothiocyanate (FITC)-labeled dextran. Flat mounts of retinal pigment epithelium (RPE)-choroid complex were obtained and the area of CNV was measured by fluorescence microscopy.

Result: The candidate compounds from invitro kinase assay significantly decreased the VEGF protein levels in the medium of treated cells. The compound which decreased the VEGF protein level most effectively suppressed CNV growth in a dose-dependent manner.

Conclusion Discussion: We screened for drugs which inhibit VEGF secretion and CNV growth. Next, we will try to make the eye drops or ointments of these compounds.

Intravitreal Dexamethasone Implant for Management of Macular Edema Associated with Retinitis Pigmentosa

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Purpose: To report anatomical and functional efficacy of intravitreal dexamethasone implant (Ozurdex[®]) in the management of bilateral refractory cystoid macular edema (CME) associated with retinitis pigmentosa (RP).

Methods: One patient with bilateral CME associated with RP, unresponsive to topical dorzolamide, was offered bilateral intravitreal dexamethasone implant (Ozurdex[®]). Best corrected visual acuity (BCVA) and central macular thickness (CMT), evaluated by Spectral Domain-Optical Coherence Tomography (SD-OCT), were recorded during the seven months follow-up.

Results: 54 year-old woman with bilateral CME presented, at baseline, with BCVA 20/200 in the right eye (OD) and 20/63 in the left eye (OS) as well as CMT of 543 μ m OD and 501 μ m OS, confirmed by SD-OCT. One month after the procedure, BCVA OD was 20/63 and BCVA OS 20/40, as well as CMT OD 181 μ m and CMT OS 176 μ m. At the fourth month, achieved BCVA remained unchanged but bilateral parafoveal intraretinal cysts were evident. At 6 months, CME recurred bilaterally and achieved BCVA returned to near baseline values in both eyes. The patient was reinjected bilaterally and after one month in OS both CMT and BCVA improved. Two weeks after the procedure in OD, CMT improved but BCVA remained unchanged. No ocular or systemic adverse effects were reported during the follow-up period.

Conclusions: Current evidence appears to support the role of chronic inflammatory processes in the pathogenesis of this disease. Anatomical and functional efficacy of intravitreal dexamethasone implant in RP-related CME may offer a valuable treatment option for these patients, with a great improvement of their quality of life.

Retinal Remodeling under Conditions of Organotypic 3D Culturing in vitro and Retinal Damage in vivo in High and Low Vertebrates

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Retinal remodeling is a universal phenomenon accompanies various retinal diseases and manifests in structural and functional changes. These changes occur at the molecular, cellular and tissue levels and involve all cell types of the retina. In our research we used different conditions to induce of retinal remodeling in the eye of low (newt *Pl. waltl*) and high (rat *Wistar*) vertebrates. Method of 3D organotypic culturing of eye tissues in vitro, retinal experimental detachment in vivo, and light-induced retinal damage (LIRD) were applied. Cell type, migration and proliferation were specified by means of immunocytochemistry and specific markers. In all mentioned conditions various modes of retinal remodeling were found. Under conditions of 3D culturing retina of the newt demonstrated the highest ability of reconstruction: proliferation of cells – sources for regeneration, their movement and incorporation into initial retinal structure. In the same experiments with rat retina we observed massive translocation of neuron nuclei and mitosis of non-neuronal cells (macro- and microglia, macrophages, etc.). Complete, artificial detachment of the newt's retina induced a withdrawal of retinal pigment epithelial cells from the layer and penetration by them the inner portion of the retina where they undertook proliferation, radial migration and incorporation into different retinal layers replacing dead neurons. After light induced damage of the rat retina we observed partial elimination of photoreceptor cells, replacement of outer nuclear layer by interneurons of the inner one, and vivid gliotic response. The results can help us in understanding of cellular mechanisms of retinal rescue and regeneration after damaging in vertebrates and human.

The Response to Dexametasone Implants (Ozurdex) +/- Photocoagulation in Patients with Naïve or Refractory Diffuse Diabetic Macular Edema (DDME)

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Background: To show the effect of Dexamethasone-0.7mg implants in refractory and naïve Diffuse Diabetic Macular Edema.

Methods: Prospective study of 76 eyes with Visual Acuities (VA) between 15 and 72 ETDRS letters, central OCT foveal thickness 300 microns. Two groups: 1) Refractory DDME, not responding to conventional treatments, 6 months evolution (40 eyes). 2) Naïve DDME with severe inflammatory component characterized by total macular volume 9mm³ in Topcon OCT-2000-3D (36 eyes). Follow-up: Visits included VA, OCT and ophthalmic examination at 24h, days 7 and 21, and then monthly. Quadrimestral angiographical control. Photocoagulation (PC) allowed complementarily after the first month, and reinjection possible if OCT thickness increased 150 microns compared to the best recorded or VA losses 10 letters.

Results: VA increases and OCT thickness decreases were statistically significant (p<0.05) compared to baseline at days 21 and 7, respectively in both groups. The maximum VA increase occurred 2 months after the injection in both groups: +8.8 letters in refractory group and +13.7 in naïve group. Statistically significant differences were found between both data. The maximum OCT decrease was detected 2 months after the injection in both groups. PC was performed in 47/76 eyes. Transient Intraocular pressure peaks (10 mmHg) were recorded in 6/76 eyes. In 57/76 eyes, a new Ozurdex was needed. Mean time between injections: 4.9 months. Mean follow-up time: 12.7 months.

Conclusions: We have achieved important VA improvements (greater in the naïve group) and OCT thickness in both groups with a satisfactory safety profile.

Possibility in Pathogenic Therapy of Myopic CNV

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Typically myopic CNV - predominantly classic, subfoveal localization, less 1,5 disc diameter in size (3000 µm), detachment the neurosensory retina and retinal pigment epithelium is not expressed [Boiko E.V., Sosnovskiy S.V., 2010, Silva R. Ophthalmologica 2012;228:197-213]. Increased VEGF levels found in myopic CNV provides important, high level evidence of the benefits of ranibizumab for the treatment of myopic CNV [RADIANCE, REPAIR, 2012]. In 2014 LUCENTIS® might be registered in Russia.

Aims: The purpose of treatment is to assess efficacy of ranibizumab for myopic CNV patients.

Methods: 18 patients (21 eyes) with Myopic CNV were cured in Regional therapeutic hospital for War veterans in Chelyabinsk. The mean age from 45 to 78 (63,3±11,2 years). Mean time of observation 26,4±2,7 months. Mean changes in BCVA before treatment 0,14±0,1. Treatment was carried out with the voluntary consent of the patient with the approval of ethical committee. IVV Ranibizumab 0,5 mg: first injection – after the disease proved, retreatment depend on needs (loss of visus, leakage from the CNV based on OCT, FAG). Mean number of injections 2,15±0,89.

Results: Mean time for re-treatment depend on lesion size CNV. If lesion size of CNV before treatment less 1000 µm, mean time for retreatment - 14,1±5,3 months, 1000 – 2000µm, 7,2±3,4months, more than 2000 µm, 5,8±2,4 months.

Summary:

1. Ranibizumab treatment is the most effective type of treatment for myopic CNV leading to progressive improvement in best-corrected visual activity and keeping her stable during long time after treatment.
2. Time for re-treatment depends on lesion size CNV.

A Randomised Cross Over Comparison of Trehalose/Hyaluronate Eye Drops and Standard Treatment: Patient Satisfaction in the Treatment of Dry Eye Syndrome

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The present study compares a novel preparation (Thealoz Duo®) that combines trehalose, an anhydrobiotic disaccharide widespread in single-celled organisms, plants and lower animals, with hyaluronic acid, a similarly widespread polymeric substance associated with water-retentive and lubricative functions, versus a reference treatment Systane®.

17 adult patients with moderate-to-severe dry eye syndrome were recruited and randomized to treatment with Thealoz Duo® or Systane®. Patients were treated for 7 days followed by a 5-day washout period and then crossover to the alternate treatment. Evaluations were undertaken on days 0, 3 and 7 of treatment. The primary efficacy criterion was patient satisfaction assessed on a 0-100 mm visual analogue scale ("What is your global satisfaction concerning your eyes?") and was assessed on days 0 and 7 of treatment. 6 moderate and 11 severe dry eye symptoms were included. VAS improved from 44.5 ± 19.0 mm to 70.2 ± 19.2 mm during Thealoz Duo® treatment and from 47.2 ± 23 to 57.1 ± 19.1 mm during Systane® treatment.

The difference between the two treatments in the change in VAS score from baseline to study end was statistically significant (p=0.043, mixed-effects analysis of covariance). Two secondary efficacy parameters (dry eye symptoms and the impact of their symptoms on work) showed statistically significant advantages for Thealoz Duo® over Systane®.

There were no statistically significant advantages for Systane over Thealoz Duo for any parameter.

No adverse events were reported.

The Use of a Preservative-free, Hypotonic Solution of 0.15% Sodium Hyaluronate for Mild to Moderate Dry Eye

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Background: Hyaluronic acid (HA) is an essential polysaccharide found in many extracellular matrices of human tissues. Its viscoelastic and hydration properties make it an ideal topical lubricant for the ocular surface. The formulation used in this study was Hyabak® (Laboratoires Théa, France), which is also hypotonic to address the increased osmolality of the tear film observed in dry eye.

Methods: Thirty volunteers (8m, 22f, mean age 66.6±9.9yrs) with mild to moderate dry eye symptoms, as assessed by the Ocular Surface Disease Index (OSDI) questionnaire, were recruited. Participants were assessed at baseline and after 10 days of treatment (4 drops per day in both eyes), and the following were recorded: ocular hyperaemia; corneal and conjunctival staining (using grading scales); tear film stability (seconds); ocular comfort (visual analogue scale) and OSDI scores.

Results: Ocular comfort and OSDI scores were significantly improved at day 10 (by 35% and 34% respectively; p<0.001). Average corneal and conjunctival staining decreased by 50% (p<0.001) and 56% (p<0.001), respectively. Ocular hyperaemia was also significantly less 10 days after baseline (range -0.25-1.00 unit change; p<0.001). The increase in tear film stability was statistically significant, but clinically small (+1.1±1.3sec; p<0.001).

Conclusion: Statistically and clinically significant improvements in key clinical indicators of success, including patient comfort, can be seen after only ten days with this preservative-free dry eye treatment.

LipiView-Diagnostic & Meibomian Gland Evaluator (MGE) as Basic for Optional Treatment of the Meibomian Gland Dysfunction (MGD)

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LipiView Interferometer allows to measure the tear film with controlling the lipid layer, the blinking and the eyelid closure. By additional MGE and slit lamp (SL) examination, the functionality of the MG quantitative and qualitative can be examined. With the results the therapy can be planned individually plus the follow up can be done. For an adequate wetting of the eye a sufficient tear film in excellent quality have to be available. In this case the production of the lipids (in the MG) and the distribution with each blink plays a major role. LipiView-System measures the thickness of the tear film lipid layer, the frequency of the blinking and the evaluation of the eyelid closure interferometrically. The standardized expression-test (MGE) at the slit lamp gives informations about the quality of the MG-Secretion (from the MG).

Investigating the Retinoprotective Effects of PACAP Fragments, Secretin and Glucagon in Ischemic Retinopathy

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Pituitary adenylate cyclase activating polypeptide (PACAP) has neuroprotective effects in different neuronal and retinal injuries. Retinal ischemia can be effectively modelled by permanent bilateral common carotid artery occlusion (BCCAO), which causes chronic hypoperfusion-induced degeneration in the entire rat retina. The retinoprotective effect of PACAP38 and VIP is well-established in ischemic retinopathy. However, little is known about the effects of related peptides and PACAP fragments in ischemic retinopathy. The aim of the present study was to investigate the potential retinoprotective effects of different PACAP fragments (PACAP 4-13, 4-22, 6-10, 6-15, 11-15, 20-31) and related peptides (secretin, glucagon) in BCCAO-induced ischaemic retinopathy.

Wistar rats (3-4 months old) were used in the experiment. After performing BCCAO, the right eyes of the animals were treated with PACAP fragments or related peptides intravitreal (100 pM), while the left eyes were injected with saline serving as control eyes. Sham-operated (without BCCAO) rats received the same treatment. Routine histology was performed 2 weeks after the surgery, cells were counted and the thickness of retinal layers were compared. Our results did not reveal retinoprotective effect of the PACAP fragments or related peptides. These results suggest that PACAP 1-38 has the greatest effectiveness in the animal model of ischemic retinopathy.

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Effects of Early Hyperglycaemia on the Retinal Structure of OIR Rats

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In spite of major advances in understanding of the pathogenesis, retinopathy of prematurity (ROP) is still one of the leading cause of childhood blindness in developed countries. Rat pups are applicable to investigate specific role of the factors which are implicated in the pathogenesis of ROP including hyperglycaemia.

The aim of our study was to investigate the effects of streptozotocin-induced hyperglycaemia in the retinal structure of oxygen-induced retinopathy.

Sprague-Dawley rat pups were exposed to alternating oxygen concentration (10%, 50%) for the first 2 weeks of life to induce oxygen-induced retinopathy (OIR). On the second postnatal day pups were treated intraperitoneally with β -cell specific streptozotocin, which caused transient hyperglycaemia. After 21 days the rats underwent (i) functional examinations (electroretinography) and (ii) their eyes were processed to flat mount isolectin staining to visualize the vascular area in the retina.

Quantification of avascular to whole retinal areas showed that hyperglycaemia did not significantly worsen the extent of vasoobliterated territory and there was no significant reduction in the number of neovascular tufts. These findings were further supported by functional examinations.

Our results suggest that – despite of clinical findings – hyperglycaemia does not cause significant vascular alterations in OIR. Further immunohistological analysis need to support the morphological changes of the retina.

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Photodynamic Therapy - A New Therapeutic Approach for Superficial Eyelid Basal Cell Carcinoma

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Introduction: Basal cell carcinoma (BCC) is the most common eyelid malignant tumor, which causes over 90% of eyelid malignancies. Photodynamic therapy (PDT) is successfully used for the treatment of superficial BCC for decades. Topical administration of photosensitizer followed by red light irradiation causes destruction of tumor cells. Eye protection recommended within the irradiation limits the use of PDT for eyelid basal cell carcinoma.

Materials: PDT of the eyelid BCC was performed in a group of seven patients with recurrence of previously excised and histologically verified BCC or new clinically diagnosed superficial eyelid BCC. Methyl aminolaevulinate (MAL) was applied on the BCC and surrounding skin for the three hours incubation time. The anterior segment of the eye was covered with titanium eye shield and the eyelid was illuminated with the total light dose of 40 J/cm² (peak action spectrum 635 nm). The eye shield was then removed and the patient instructed about home measurements. The PDT was repeated once after two weeks. The patients were examined every 3 month during the follow-up period.

Results: The PDT was generally well tolerated, some patients complained of mild pain during the first session which was well controlled by cooling. During the treatment and follow-up the patients presented no eye irritation, infection, functional disorder, skin scarring or recurrence of the basal cell cancer.

Conclusions: PDT of the eyelid BCC proved to be both safe and effective therapy, offering excellent cosmetic results. Larger and long-term clinical trials are needed to evaluate these results.

Combined Intravitreal Ranibizumab and Laser Treatment for Retinal Angiomatous Proliferation

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Background: Retinal angiomatous proliferation (RAP) is the subtype of neovascularization in advanced age-related macular degeneration (AMD). The aim of our study was to assess efficacy of ranibizumab in the combined treatment of patients with RAP.

Materials and Methods: 17 patients (17 eyes) with retinal angiomatous proliferation, stages IIA, IIB and III were examined. Optical coherence tomography was performed to all patients. Intravitreal Ranibizumab was used in all patients up to obtain clinical efficacy. Laser treatment (laser photocoagulation, transpupillary thermotherapy) was performed in 7 patients.

Results: Positive dynamics was observed after the first injection in 11 patients with RAP as increasing the best corrected visual acuity, reducing central retinal thickness, reducing the diameter of intraretinal cysts, decreasing of the extent of pigment epithelium detachment, its height, reducing the extent of neurosensory retinal detachment. The average number of injections was $2,2 \pm 0,59$. No changes were observed in 4 patients, negative dynamics - in 2 patients in the form of reducing the best corrected visual acuity, increasing central retinal thickness, and increasing the diameter of intraretinal cysts. Laser treatment, as a second step, performed in 7 patients in the amount of laser coagulation (5 patients) and transpupillary thermotherapy (2 patients), which resulted in the stabilization process in 4 patients.

Conclusions: Intravitreal injections of ranibizumab in patients with RAP provides clinical effectiveness in 60.45 % of cases, which creates the best opportunity for the laser treatment. Use of combined treatments (Ranibizumab and laser treatment) can lead to the stabilization process.

Retrospective Comparison of Outcomes of Trainee-Performed Trabeculectomy versus Tube Shunt Surgery

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Purpose: To compare outcomes of trabeculectomy (trab) with mitomycin C versus Ahmed valve surgery (valve) performed by residents-in-training.

Methods: Retrospective case review of patients who underwent primary trab or valve surgery performed by a PGY-4 resident from 2005-2012. Intra- and post-operative complications as well as intraocular pressure (IOP), number of medications, visual acuity (VA), and cup-to-disc (C:D) ratio were measured for 1 year.

Results: Of 274 surgeries, 104 met all inclusion criteria. Complication rates were 8.5% and 0% for intra-op and 35.6% and 42.2% for immediate post-op for trab (n=59) and valve (n=45), respectively. Of early complications, 63% were underfiltration and 46% were hyphema for trab and valve, respectively. During post-op months 3-12, 18.6% and 22.2% experienced at least 1 complication predominantly due to cataract in trab and underfiltration in valve group, respectively. Mean pre-op IOP was 24.5 ± 7.1 and 35.2 ± 11.7 mmHg for trab and valve, respectively (p0.1). Significant reductions in IOP and medications were observed in both groups by 1 year (p0.01). One-year mean IOP was 15.3 ± 4.5 and 18.2 ± 8.3 (p=0.06) for trab and valve, respectively. Although number of meds and C:D ratio at 1 year were not statistically different (p0.12), mean VA was poorer in the valve group at 1 year (p0.01).

Conclusion: When performed by senior residents-in-training, both trab and valves are safe and produce significant IOP reductions. Both have similar complication rates, and although most are not serious, they necessitate intensive attending oversight.

Adipose-MSCs Revert VIP, NIC and ATRA Effects on Dying RPE Cells

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Purpose: This work proposes to evaluate drugs, Vasoactive intestinal peptide (VIP), Nicotinamide (NIC) and All trans-retinoic acid (ATRA), effectiveness with adipose-MSCs on degenerating retinal pigment epithelium (RPE), a crucial layer of retina for maintaining retinal structure and functions.

Methods and Materials: ARPE19 cells were grown on bottom of a transwell culture plate for 24 hours for proper adherence (monolayer), treated with $50 \mu\text{g/ml}$ mitomycin C (MMC) for 2 hours followed by washing to remove any residual MMC. Adipose-MSCs were seeded on transwells insert, inserted in each culture well (Co-culture). Alamar Blue (AB) assay was performed at 3 and 5 days. Drugs VIP, NIC and ATRA in a concentration, individually and their combinations (VIP+NIC, VIP+ATRA, NIC+ATRA and VIP+NIC+ATRA), were tested on RPE and in co-culture.

Results: Results showed RPE cells proliferated well for 3 to 5 days but MMC treatment prevented significantly RPE cell proliferation. VIP, NIC and ATRA did not show capacity to revert this MMC effect. Drug combinations showed significantly poor effects than individual drug. However in co-culture adipose-MSCs rescued dying RPE cells. Adipose-MSCs presence with drugs in co-culture showed significant reverting capacity to MMC and drugs effects on RPE.

Conclusions: Adipose-MSCs can revert significantly the effectiveness of VIP, NIC and ATRA on dying RPE cells. Identifying adipose-MSCs secreted factors and testing their combinations with these drugs could be applicable for retinal disease treatments.

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Functional Characteristic of the Myopic Extrafoveal Retina

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Purpose: The purpose of the present study was to determine the luminance difference sensitivity (LDS) in the extrafoveal part of the retinas of myopic subjects.

Method: Forty myopes (mean age 20.2) and twenty emmetropes (mean age 20.1) participated in the study. The spherical equivalent refractive error (SER) of the myopes ranged from -0.75 to -5 D. The LDS, white-on-white, was measured by an Oculus Centerfield Perimeter. Static perimetry with full threshold strategy 4/2 was performed in 92 retinal points in the visual field extending to: 60° nasally, 70° temporally, 55° above and 65° below the horizontal meridian.

The relationship between mean LDS calculated for every stimulated point and eccentricity (measured as the distance in degrees from the fovea centralis) was analyzed with a linear regression model (ANCOVA).

Results: The ANCOVA showed that an increase in the distance from the fovea centralis led to a decrease in the LDS levels. Moreover, the decrease was stronger for myopic subjects – the slope for myopes was significantly lower than the one for emmetropes. The adjusted coefficient of determination was 0.79.

The regression model analyzing the relationship between the LDS and the degree of myopia and eccentricity yielded an adjusted coefficient of determination of 0.5 and the following results. Both explanatory variables influenced negatively the LDS levels of myopic subjects. The estimated coefficients of both variables, absolute value of the SER and distance from the fovea centralis, were negative and significantly different from zero (p-value 0.001).

Conclusions: Myopic subjects exhibit reduced extrafoveal LDS relative to emmetropes and this reduction becomes more pronounced with increasing degree of myopia.

A Deca-peptide Inhibits Retinal Neovascularization by Down-Regulation of VEGF and Up-Regulation of PEDF in OIR Mouse

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A synthetic deca-peptide corresponding to the amino acid sequence Arg54-Trp63 of human tissue-type plasminogen activator (t-PA) kringle 2 domain, named TKII-10, consists of the sequence RNPDGDAPKW. Previous study indicates that TKII-10 inhibits VEGF-induced corneal neovascularization. The purpose of the present study was to investigate the inhibitory efficacy and mechanism of TKII-10 on retinal neovascularization, in an effort to develop a small peptide for clinical application in neovascular retinopathies. In this study, we identified that TKII-10 functioned as a potent angiogenic inhibitor, by inhibiting VEGF-stimulated choroid-retinal endothelial cells (RF/6A) migration and capillary tube formation in a dose-dependent and sequence-dependent manner in vitro. Furthermore, TKII-10 effectively inhibited oxygen-induced retinal neovascularization in mouse. TKII-10 can down-regulate angiogenic stimulator VEGF and up-regulate angiogenic inhibitor PEDF in retinal tissues, leading toward restoration of the balance in angiogenic control. TKII-10 may provide an effective approach for pathological retinal neovascularization therapy.

Protective Effects of Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) in Different Models of Retinal Injuries

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Pituitary adenylate cyclase activating polypeptide (PACAP) is a neuropeptide with widespread distribution and a diverse array of functions. PACAP has very potent neurotrophic and neuroprotective effects in vitro and in animal models of cerebral injuries, such as stroke, Parkinson's disease and traumatic brain injury. PACAP and its receptors also occur in the retina, where the peptide has been shown to have protective effects. The present study gives an overview of the protective effects of this peptide in the retina. In most studies, PACAP was administered intravitreally in most studies and retinas were processed for histological analysis at different times after injuries. The first lesion, where we showed protective effect of the peptide, was glutamate-induced excitotoxicity of neonatal rats. The nearly complete degeneration of the inner retinal layers was markedly prevented by PACAP treatment. Subsequently, we showed similar protective efficacy in chronic retinal hypoperfusion induced by bilateral carotid artery occlusion, UV light-induced damage and diabetic retinopathy. We also showed that endogenous PACAP has similar protective effects using PACAP-deficient mice in a retinal ischemia model, where in lack of PACAP we found increased retinal lesion. The morphological amelioration induced by PACAP is also reflected by functional improvement, as shown by electroretinography. Molecular analysis of PACAP-induced protection has shown that the peptide exerts its protective effects including antiapoptotic, antiinflammatory and antioxidant effects.

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Effects of Oral Propranolol on a Juxtapapillary Capillary Hemangioma: A Single-subject Pilot Study

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Background: Oral propranolol hydrochloride has been reported to be effective in treating infantile hemangiomas. Although some case studies have suggested its efficacy in choroidal hemangiomas, no reports have been published regarding retinal hemangiomas. To our knowledge, this is the first pilot study to describe a case in which oral propranolol was used as a therapeutic approach for a retinal hemangioma.

Methods: This single-subject pilot study was registered with the University Hospital Medical Information Network Clinical Trial Registry in Japan (UMIN000006623). The therapeutic protocol was approved by the Institutional Review Board of Nagoya Medical Center. After informed consent was obtained, a patient with a juxtapapillary capillary hemangioma (JCH) was treated with propranolol at Nagoya Medical Center from February 17 to September 25, 2012. The dose was initiated at 10 mg 3 times/day and was increased monthly by 30 mg/day until the desired effects were observed.

Results: After 1 month of therapy, the patient reported shrinkage of the hemangioma shadow. This good subjective symptom continued until the end of therapy. The height of the tumor (based on the B-mode scan performed at the end of the study) decreased to 91.6% of the initial height. Similarly, compared with baseline, the tumor area (based on fluorescein angiography) was 94.3%, the visual acuity was +0.0 logMAR, and the Humphrey visual field mean deviation was +0.29 dB.

Conclusions/Discussion: Although oral propranolol partially improved the condition of this patient with a JCH, it did not appear to have a critical therapeutic effect.

The Development of Clinical Pharmacist Mode in Ophthalmology Department

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The ophthalmic diseases are always focused on ophthalmic inflammation, cataract, glaucoma, dry eye, vision fatigue and myopia, etc. The medication is usually divided into specific medication (including eye drops, ointment and other ophthalmic formulations) and general medication (including antibiotic, vitamins, steroids, etc). The ophthalmic medication is simpler and dosage is lower, compared to internal and surgical medicine. So the operating mode of ophthalmic clinical pharmacist is seldom explored than the steady development of internal and surgical clinical pharmacist. To explore the operating mode and management mode of ophthalmic clinical pharmacist, by using the experiences of existing and mature ones of internal and surgical clinical pharmacist. Our purpose is to cover all the medication departments in hospital, by commencing with out-patient prescription. The prescriptions assessed regularly and specifically; the medication is assessed in surgery patients; the service information of clinical pharmacist, as well as advices of the prescription to be improved, is feedback to the ophthalmic medical staff by doing lecture; the antibiotic drugs are follow-up; the patients are received medic education. The clinical pharmacist, which is important in management of medical quality, is become the necessary resource to achieve safe, effect, proper, economic and reasonable medication. The reasonable medication and therapy effects is improved, while the adverse drug events and drug-induced disease is decreased, by providing consultant of medication, drug protocol and adverse events.

Experimental Use of Poly lactic-co-glycolic Acid for Visualizing Vitreous Body during Cataract Surgery in Animal Models

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Purpose: To compare the efficacy and safety of poly lactic-co-glycolic acid (PLGA) and triamcinolone acetonide (TA) suspensions in visualizing the prolapsed vitreous body in the anterior chamber after posterior capsule rupture, or disruption of posterior chamber anterior hyaloid membrane (PC-AHM) barrier in eyes without posterior capsule rupture during cataract surgery in animal models.

Method: To evaluate efficacy, TA or PLGA was injected into the anterior chambers of porcine eyes after intentional posterior capsule rupture or making damage at zonule of Zinn. To evaluate safety, TA or PLGA in 0.1 mL suspension was injected into the vitreous of New Zealand white rabbits. Slit lamp examinations, intraocular pressure (IOP), and electroretinogram (ERG) were performed up to 14 days after the injection.

Results: TA and PLGA were equally effective in allowing visualization of the prolapsed vitreous body in the anterior chamber or disruption of PC-AHM barrier in eyes without posterior capsule rupture. Although the granules of TA disappeared two days after the intravitreal injection, a small amount of PLGA remained for 2 weeks. Although mild inflammation of the anterior chamber was observed in all tested eyes one day after injection, it disappeared two days after injection. The amplitude of ERG and IOP on each time point did not differ between TA and PLGA injection group.

Conclusion: PLGA could visualize disruptions of barrier between anterior chamber and vitreous such as rupture of posterior capsule or zonule of Zinn, or AHM tear. In experimental models, no significant side effects were observed after the injection of PLGA in the vitreous.

Difficulties of Therapeutic Management in Several Polish Patients with Corneal Inflammations Suspected of Acanthamoeba Infection

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Background: Acanthamoeba keratitis (AK) is detected with increasing frequency in various parts of the world, including Poland. This progressive, vision-threatening disease is particularly described among contact lens wearers. Other major risk factors predisposing to AK are: damage of cornea epithelial cells, eye surgery and exposure to water containing trophozoites and/or cysts of the amoebae. In this study, we analyze retrospectively several complicated keratitis incidences suspected of amoebic aetiology.

Methods: 7 female patients with severe eye pain, photophobia and corneal inflammation, admitted to our hospital from 2009 to 2013 years were analyzed in terms of the therapeutic management. 4 of them were previously treated in other ophthalmic units with antibacterial and antifungal medications without success. Six of the patients were contact lens users. For proper diagnosis, examinations by the slit-lamp, in vivo confocal microscopy, microbiological and parasitological were performed. Due to AK suspicion, corneal scrapings were taken from all patients. Samples of the scrapings were directly examined microscopically, by PCR technique as well as cultivated in vitro under bacteria-free conditions.

Results: AK has been diagnosed in 6 patients; 5 of them were contact lens wearers. In 3 of the patients, bacterial-fungal-amoebic infections were confirmed and successful medications applied. Generally, the course of disease in these patients with mixed infections was lighter in comparison to this in patients infected with Acanthamoeba only; signs of improvement were visible after 1,5 – 10 months of topical therapy with, among others, propamidine isetionate, chlorhexidine solution and neomycin. In 3 other patients, 2 contact lens users including, the severe course of AK with recurrences occurred and the surgical treatment and prolonged extensive pharmacotherapy were undertaken. The difficulties of therapeutic management correlated with longer time intervals after the proper diagnosis and therapy have been performed.

Conclusion/Discussion: Despite advances in pharmacotherapy, treatment of AK is difficult and often unsuccessful due to, among others, an improper and late diagnosis. Diagnostic mistakes delay appropriate therapy that results in serious corneal deteriorations and prolonged and severe course of this emerging vision-threatening disease. Early proper diagnosis, involving in vivo and in vitro techniques is decisive for therapeutic efficacy, particularly in contact lens users.

Proteome Analysis of Tears from Wild and the PACAP-Deficient Mice

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Pituitary adenylate cyclase activating polypeptide (PACAP) is a pleiotropic and multifunctional neuropeptide distributed throughout the body. The diverse biological actions provide the background for the variety of deficits observed in mice lacking endogenous PACAP. PACAP-deficient mice display several abnormalities, such as completely lost pupillary light reflex, and increased sensitivity to in vitro hypoxia, oxidative stress and excitotoxic insults. However, the proteomic background of these differences observed in PACAP-deficient mice is still not clear. Our aim was to investigate the proteome alterations in the tears of PACAP-deficient mice compared to tear samples from wild type mice. Tear fluid was collected by non-invasive method. Pooled mice tear samples were separated with sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), then the Coomassie-stained bands were cut and digested with trypsin. After digestion, mixtures were analyzed with Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI TOF/TOF). For identification and characterization of proteins we used MASCOT Search Engine software. Furthermore, the peptide samples were subjected to liquid chromatography-mass spectrometry (LC/MS/MS) on AmaZon SL Ion Trap mass spectrometer. This technique was useful for quantitative information about earlier identified proteins. The ratios of proteins showed differences between the tears from PACAP-deficient versus wild type mice.

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Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) Prevents Monosodium Glutamate (MSG) Induced Functional Disturbances in the Mouse Retina

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MSG binds to glutamate receptors and provokes a chronic activation of postsynaptic neurons, thereby exerting excitotoxic effects. We studied the short term functional consequences of MSG treatment in the mouse retina. We investigated whether administration of PACAP1-38, a neuroprotective peptide, could rescue retinal ganglion cells (RGCs) from MSG-induced excitotoxic effects. Spontaneous and light-evoked spikes of RGCs from mice were recorded using a 60-channel multielectrode array. Green light was used to generate full field stimuli. RGCs were also analyzed using the fluorescent Ca²⁺ dye fluo-4. Retinas were treated with MSG or a mixture of MSG + PACAP1-38 or MSG + PACAP1-38 + its antagonist, PACAP6-38. MSG exerted physiologically detectable effects on RGCs at a concentration 10 mM. MSG remarkably elevated the free intracellular calcium [Ca²⁺] concentration and also increased the spontaneous spiking 4-5 minutes after application. Meanwhile, spike correlations between RGC pairs were reduced. However, after 10-15 minutes of MSG application, the spontaneous activity of most RGCs was dramatically reduced. Pretreatment with PACAP1-38 prevented the MSG effects as indicated by little or no change in the spontaneous spiking patterns. Moreover, the Ca²⁺ influx was decreased by PACAP1-38. In addition, MSG blocked the light-evoked responses of all recorded cells but approximately 40% of RGCs were retained following pretreatment with PACAP1-38.

We found that MSG had short term effects on the spontaneous and light-evoked spiking of mouse RGCs. Application of PACAP1-38 rescued RGCs from the short term MSG-induced insults. This work supported by NIH Grant EY017832 to B.V. and EY007360 to S.A.B, PTE-MTA "Lendület" program, the European Union and the State of Hungary, co-financed by the European Social Fund in the framework of TÁMOP 4.2.4. A/2-11-1-2012-0001 'National Excellence Program, Zoltan Magyary Scholarship, Arimura Foundation

Narrow Spectrum Kinase Inhibitors (NSKIs) Potently Inhibit Inflammatory Cytokines in both in vitro and in vivo Inflammatory Eye Models

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Inflammatory eye disease is a major cause of visual impairment. Despite recent advances, corticosteroids (CS) followed by steroid-sparing immunosuppressants remain the mainstay treatment option, but long term use is frequently complicated by cataract and glaucoma. NSKIs are a novel class of small molecule which selectively target key kinases involved in inflammatory signalling cascades. Here, we demonstrate that NSKIs are superior to CS at inhibiting inflammatory cytokines in both in vitro and in vivo inflammatory eye models.

In stimulated primary human retinal endothelial (REC) and epithelial cells (RPE) nanomolar concentrations of NSKI (TOP1106) were more potent than CS in reducing inflammatory cytokine production, as exemplified by IL-6 data in Table 1. Furthermore, in an endotoxin induced uveitis (EIU) model, topical administration of TOP1106 was more potent than CS in reducing inflammatory cytokines, e.g. MCP-1, in the anterior and posterior tissues of the eye, as well as inflammatory cell infiltrate into the aqueous humor (Table 2).

Table 1 IL-6 Release	% Inhibition relative to stimulated untreated control		Table 2 MCP-1 release (pg/ml)		Cell counts (x10 ⁶)
	RPE	REC	Anterior tissue	Posterior tissue	
TOP1106 100 ng/ml	96±1	96±3	Non-diseased control	0±0	4±2
TOP1106 10 ng/ml	97±1	87±5	Vehicle control	421±99	55±13
TOP1106 1 ng/ml	90±6	25±14	TOP1106 1 mg/ml	37±19	9±4
CS 100 ng/ml	78±3	20±4	CS 1 mg/ml	199±76	23±10

These data demonstrate the potential utility of NSKIs in the treatment of inflammatory eye disorders.

Evaluating the Therapeutic Outcomes in Retinal Capillary Hemangioblastoma (RCH) in Von Hippel-Lindau Syndrome (VHL) by Color Doppler Imaging (CDI) - A Case Report

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Aim: The aim of this report was an attempt to apply CDI in monitoring the effects of RCH treatment in patient with VHL in addition to fluorescein angiography (FA), which is the standard traditional invasive method.

Materials and methods: 32 y.o. female reported a sudden loss of vision in the right eye with BCVA=0.3. In the right eye RCH with diameter of 2 DD was found in the lower-nasal sector on the central periphery with a surrounding exudative retinal detachment approaching the macula. Transcleral cryotherapy was applied. At baseline and 3 months after procedure, the blood flow in the pathological vessels of the RCH was assessed using CDI with an 18 MHz probe.

Results: At baseline, the afferent vessel Vamax=11.2cm/s, and in the efferent vessel Vemax=6.4cm/s. At follow-up examination 3 months after cryotherapy CDI did not reveal blood flow in the pathological vessels: Vamax=0 cm/s, Vemax=0 cm/s. FA also didn't show any flow in these vessels nor the leakage from the RCH. The patient's recovered to BCVA=0.9 in the affected eye, and the exudative retinal detachment regressed.

Conclusions: CDI may be an additional valuable tool in monitoring the therapeutic effects of RCHs treatment. To our knowledge this is the first report of implementing CDI in RCHs blood flow imaging. It is not always possible to perform routine FA in patients with poor general condition. CDI offers a non-invasive, faster and cost effective assessment of the therapeutic effects in patients suffering from RCHs in course of VHL disease.

H-RN, A Novel Antiangiogenic Peptide Derived from Hepatocyte Growth Factor Inhibits Inflammation through PI3K/AKT/IKK/NF-κB Signal Pathway

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H-RN, a novel antiangiogenic peptide derived from the kringle 1 domain of hepatocyte growth factor (HGF), consists of the sequence RNPGRGEEGGPW (molecular weight: 1254.34 Da). Emerging evidence indicates that HGF and the kringle domain exhibit anti-inflammatory effects in inflammatory diseases. In the present study, we assessed the anti-inflammatory effect of H-RN in experimental endotoxin-induced uveitis (EIU) and experimental autoimmune uveitis (EAU). The results demonstrated that intravitreal treatment of H-RN concentration-dependently suppressed clinical manifestation, inhibited ocular inflammatory cytokine production and improved histopathologic scores. Moreover, H-RN attenuated the LPS-induced mRNA and protein expression of tumor necrosis factor (TNF)-α and interleukin (IL)-6 in RAW 264.7 cells and inhibited cell migration towards LPS. We also demonstrated that H-RN suppressed TNF-α-induced adhesion molecule expression in HUVECs, including ICAM-1, VCAM-1 and E-selectin, which contributed to its suppressive effect on adherence of U937 cells to endothelial cells. We also demonstrated the possible anti-inflammation mechanism of H-RN. Western blot and immunofluorescence staining analyses revealed that H-RN significantly suppressed LPS-induced phosphorylation of nuclear factor (NF)-κB-p65 at Ser276. Based on examination of upstream pathways, we found that H-RN inhibited PI3K-p85 and AKTSer473 phosphorylation, which may result in the attenuation of LPS-induced IKK complex activation and IκB degradation. Thus, our studies suggest that the H-RN peptide exhibits anti-inflammatory effects in vitro and in vivo and may represent a promising candidate for ocular inflammatory diseases.



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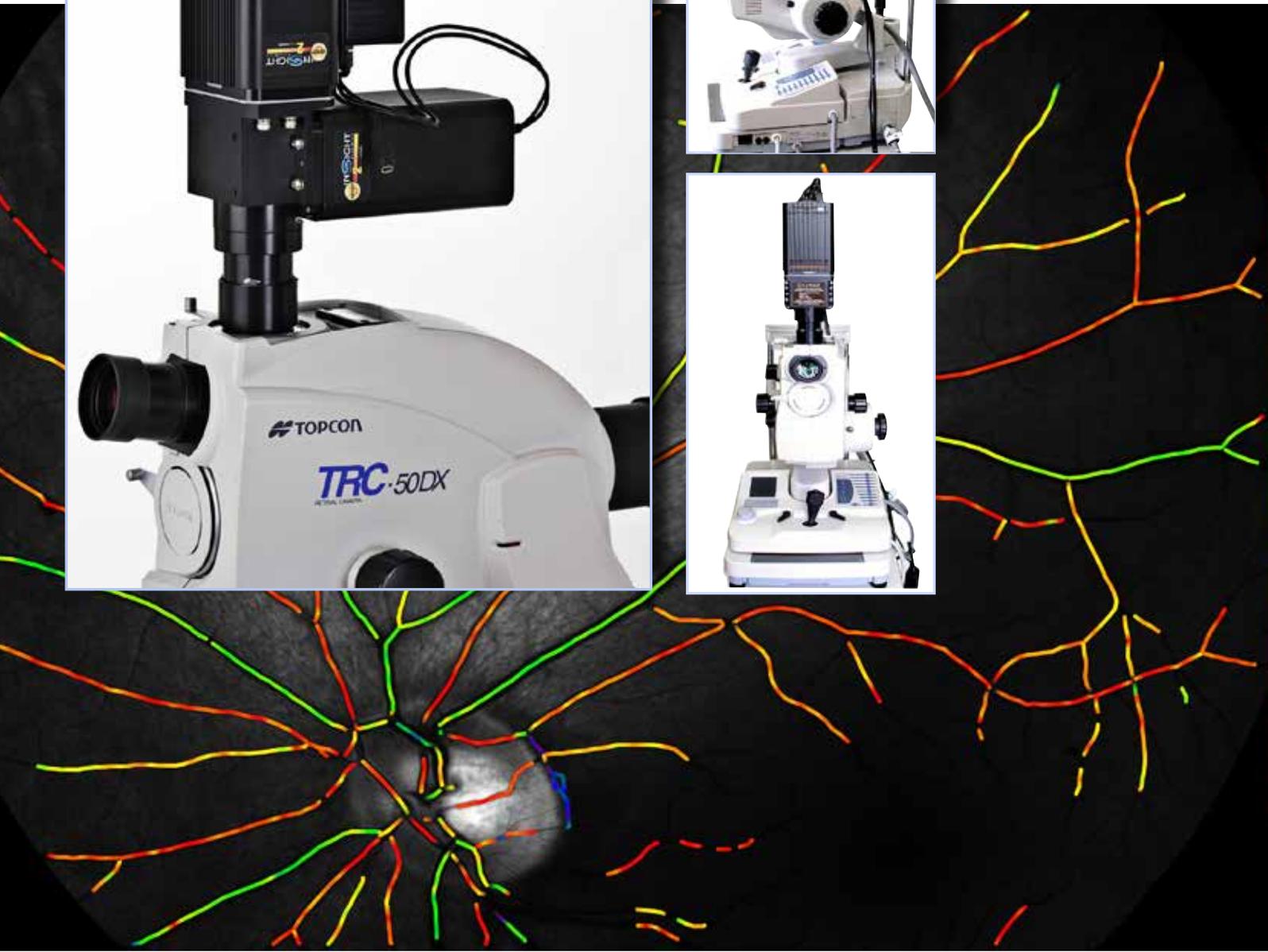
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